2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension Supplementary data

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG).

Authors/Task Force Members: Marc Humbert (France), Gabor Kovacs (Austria), Marius M. Hoeper (Germany), Roberto Badagliacca (Italy), Rolf M.F. Berger (Netherlands), Margarita Brida (Croatia), Jørn Carlsen (Denmark), Andrew J.S. Coats (United Kingdom), Pilar Escribano-Subias (Spain), Pisana Ferrari (Italy), Diogenes S. Ferreira (Brazil), Hossein Ardeschir Ghofrani (Germany), George Giannakoulas (Greece), David G. Kiely (United Kingdom), Eckhard Mayer (Germany), Gergely Meszaros (Hungary), Blin Nagavci (Germany), Karen M. Olsson (Germany), Joanna Pepke-Zaba (United Kingdom), Jennifer K. Quint (United Kingdom), Göran Rådegran (Sweden), Gerald Simonneau (France), Olivier Sitbon (France), Thomy Tonia (Switzerland), Mark Toshner (United Kingdom), Jean-Luc Vachiery (Belgium), Anton Vonk Noordegraaf (Netherlands), Marion Delcroix *† (ERS Chairperson) (Belgium), Stephan Rosenkranz *† (ESC Chairperson) (Germany), and ESC/ERS Scientific Document Group

* Corresponding authors: Stephan Rosenkranz, Clinic III for Internal Medicine (Department of Cardiology, Pulmonology and Intensive Care Medicine), and Cologne Cardiovascular Research Center (CCRC), Heart Center at the University Hospital Cologne, Kerpener Str. 62, 50937 Köln, Germany. Tel.: +49-221-478-32356. Email: stephan.rosenkranz@uk-koeln.de; and

Marion Delcroix, Clinical Department of Respiratory Diseases, Centre of Pulmonary Vascular Diseases, University Hospitals of Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 346813. Email: marion.delcroix@uzleuven.be

† The two chairpersons contributed equally to the document and are joint corresponding authors.

Author/Task Force Member affiliations are listed in author information in the full text.

[1] Representing the Association for European Paediatric and Congenital Cardiology (AEPC)

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix in the full text.

ESC subspecialty communities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), and Heart Failure Association (HFA).

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Working Groups: Adult Congenital Heart Disease, Pulmonary Circulation and Right Ventricular Function, Thrombosis.

Patient Forum

Document Reviewers: Markus Schwerzmann (ESC Review Coordinator) (Switzerland), Anh-Tuan Dinh-Xuan (ERS Review Coordinator) (France), Andy Bush (United Kingdom), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Eloisa Arbustini (Italy), Riccardo Asteggiano (Italy), Joan-Albert Barberà (Spain), Maurice Beghetti (Switzerland), Jelena Čelutkienė (Lithuania), Maja Cikes (Croatia), Robin Condliffe (United Kingdom), Frances de Man (Netherlands), Volkmar Falk (Germany), Laurent Fauchier (France), Sean Gaine (Ireland), Nazzareno Galié (Italy), Wendy Gin-Sing (United Kingdom), John Granton (Canada), Ekkehard Grünig (Germany), Paul M. Hassoun (United States of America), Merel Hellemons (Netherlands), Tiny Jaarsma (Sweden), Barbro Kjellström (Sweden), Frederikus A. Klok (Netherlands), Aleksandra Konradi (Russian Federation), Konstantinos C. Koskinas (Switzerland), Dipak Kotecha (United Kingdom), Irene Lang (Austria), Basil S. Lewis (Israel), Ales Linhart (Czech Republic), Gregory Y.H. Lip (United Kingdom), Maja-Lisa Løchen (Norway), Alexander G. Mathioudakis (United Kingdom), Richard Mindham (United Kingdom), Shahin Moledina[1] (United Kingdom), Robert Naeije (Belgium), Jens Cosedis Nielsen (Denmark), Horst Olschewski (Austria), Isabelle Opitz (Switzerland), Steffen E. Petersen (United Kingdom), Eva Prescott (Denmark), Amina Rakisheva (Kazakhstan), Abilio Reis (Portugal), Arsen D. Ristić (Serbia), Nicolas Roche (France), Rita Rodrigues (Portugal), Christine Selton-Suty (France), Rogerio Souza (Brazil), Andrew J. Swift (United Kingdom), Rhian M. Touyz (Canada/United Kingdom), Silvia Ulrich (Switzerland), Martin R. Wilkins (United Kingdom), and Stephen John Wort (United Kingdom)

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1. Abbreviations and acronyms

6MWD	6-minute walking distance
6MWT	6-minute walking test
ABG	Arterial blood gas analysis
AE	Adverse events
ASIG	Australian Scleroderma Interest Group
BNP	Brain natriuretic peptide
BPA	Balloon pulmonary angioplasty
cGMP	Cyclic guanosine monophosphate
CI	Cardiac index/Confidence interval
cMRI	Cardiac magnetic resonance imaging
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
COPD	Chronic obstructive pulmonary disease
CpcPH	Combined post- and pre-capillary pulmonary hypertension
CPET	Cardiopulmonary exercise testing
CT	Computed tomography
CTD	Connective tissue disease
CTEPH	Chronic thrombo-embolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
DLCO	Diffusion capacity for carbon monoxide
DPG	Diastolic pressure gradient
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
EtD	Evidence to Decision
ESV	End systolic volume
FPHR	French Pulmonary Hypertension Registry
FVC	Forced vital capacity
GDT	Guideline development tool
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HFpEF	Heart failure with preserved ejection fraction
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
KQ	Key question
LA	Left atrium/left atrial
LAP	Left atrial pressure
LHD	Left heart disease
LV	Left ventricle/left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEDVI	Left ventricular end-diastolic volume index
LVEI	Left ventricular eccentricity index
MESH	Medical Subject Heading
mPAP	Mean pulmonary arterial pressure
MRI	Magnetic resonance imaging

NO-cGMP	Nitric oxide–cyclic guanosine monophosphate
NPV	Negative predictive value
NT-proBNP	N-terminal pro-brain natriuretic peptide
PA	Pulmonary artery
PAC	Pulmonary artery compliance
$PaCO_2$	Partial pressure of arterial carbon dioxide
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of arterial oxygen
PAP	Pulmonary arterial pressure
PAWP	Pulmonary arterial wedge pressure
PDE5i	Phosphodiesterase 5 inhibitor
$PETCO_2$	End-tidal partial pressure of carbon dioxide
PH	Pulmonary hypertension
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive predictive value
PVD	Pulmonary vascular disease
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
QoL	Quality of life
RA	Right atrium/right atrial
RCT	Randomized controlled trial
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
RHC	Right heart catheterization
RV	Right ventricle/right ventricular
RVEDA	Right ventricular end-diastolic area
RVEDVI	Right ventricular end-diastolic volume index
RVEF	Right ventricular ejection fraction
RVESRI	Right ventricular end-systolic remodelling index
RV-FAC	Right ventricular fractional area change
RVOT AT	Right ventricular outflow tract acceleration time
RV-SD4,	Standard deviation of the times to peak-systolic strain for the four mid-basal right ventricular segments
SAE	Severe adverse event
SaO_2	Arterial oxygen saturation
sGC	Soluble guanylate cyclase
SPAHR	Swedish Pulmonary Arterial Hypertension Registry
sPAP	Systolic pulmonary arterial pressure
SSc	Systemic sclerosis
SV	Stroke volume
SVI	Stroke volume index
TAPSE	Tricuspid annular plane systolic excursion
TPR	Total pulmonary resistance
TR	Tricuspid regurgitation
TRPG	Tricuspid regurgitation pressure gradient
VE/VCO_2	Ventilatory equivalent for carbon dioxide
WU	Wood units

2. Introduction

2.1. Methods for key narrative and Population, Intervention, Comparator, Outcome questions

2.1.1. Question generation, evidence summary, and generation of recommendations

The evidence for practice guidelines was approached in three different ways, combining the different approaches used by the two societies:

(a) Population, Intervention, Comparator, Outcome (PICO) questions: four questions that were considered highly important were formulated in the PICO format and assessed via a full systematic review and application of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach and the Evidence to Decision (EtD) framework. Following the GRADE process, the Task Force made a list of outcomes that are considered important for clinical decision-making, and rated their importance on a scale of 1–9 (mean scores of 7–9 indicating a 'critical outcome', 4–6 indicating an 'important outcome', and 1–3 indicating 'not important outcome').[1] After discussion, consensus was reached about the critical and important outcomes for each PICO question.

Systematic literature searches were designed by information specialists with the input of the clinical experts. The MEDLINE (via PubMed) and Cochrane databases were searched from 1990 onwards to December 2020. Randomized controlled trials (RCTs) were prioritized for inclusion. The retrieved references were screened for inclusion by the PICO leader and one additional Task Force member, if required. PRISMA diagrams were generated reflecting the study selection process. Data from retrieved studies were entered into RevMan v. software. External collaborators created evidence profiles for each PICO question, following the GRADE approach. The certainty of the evidence for each outcome was rated as 'high', 'moderate', 'low', or 'very low'. The certainty of the evidence was initially rated as 'high' if the evidence came from RCTs, and was subsequently downgraded by one or two levels if results from individual studies were at serious or very serious risk of bias,[2] there were serious inconsistencies in the results across studies,[3] the evidence was indirect,[4] the data were imprecise,[5] or publication bias was thought to be likely. The Task Force developed recommendations for the PICO questions using the GRADE Evidence to Decision framework, which considers different factors, such as: the quality of the evidence, balance of desirable and undesirable effects, patient values and preferences, resource use, health equity, acceptability, and feasibility.[6] Each recommendation was rated as 'strong' or 'conditional', following the GRADE principles.[7] Recommendations and their direction and strength were drafted by the PICO leaders, discussed by Task Force members at online meetings, and approved by voting on 19 January 2022.

(b) Key Narrative questions: eight questions that were considered of key importance were formulated and assessed via systematic literature searches and application of the EtD framework. As with PICO questions, systematic literature searches were centralized and designed by information specialists with the input of the clinical experts. The MEDLINE (via PubMed) and Cochrane databases were searched from 1990 onwards to December 2020. For some questions (Key question [KQ]1, KQ2), searches were designed and conducted by individual Task Force members and an information specialist, prior to the centralized searches. In these cases, these acted as the main searches, which were then supplemented with the centralized ones. The results of the searches were screened by Task Force members and described in a narrative way. PRISMA

diagrams were generated reflecting the study selection process. The evidence was not graded using the GRADE approach, but with the usual European Society of Cardiology (ESC) methodology. The usual ESC methodology was followed for making recommendations. However, for these questions, the recommendation-making process was documented using the EtD framework, following European Respiratory Society (ERS) process.[8]

(c) The remaining topics of interest were assessed using the process commonly followed in the ESC Guidelines. Briefly, for each topic, a literature search was undertaken and only peer reviewed, published literature included. Grading tables were then created to describe the level of confidence in the recommendation provided and the quality of evidence supporting the recommendation. These tables were colour-coded for each interpretation.

2.1.2. Presentation of recommendations

For all questions, recommendations are presented using the usual ESC classification. For the PICO questions, recommendations are also presented as 'strong' or 'conditional' following the GRADE process. The overall quality of evidence for every question is also indicated (high, moderate, low, or very low).

3. Definitions and classifications

3.1. Key narrative question #1: Should a new haemodynamic definition of pulmonary hypertension be used?

Chosen parameters were mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), and pulmonary vascular resistance (PVR); 1. Normal values; 2. Prognostic relevance; and 3. Therapy.

3.1.1. The upper limit of normal mean pulmonary arterial pressure and pulmonary vascular resistance

In 2009, a comprehensive, systematic, literature review analysed haemodynamic data obtained by right heart catheterization (RHC) at rest and during exercise from 1187 healthy individuals from 47 studies. The data revealed that in the supine position at rest the normal mPAP is 14.0 $\pm$ 3.3 mmHg and the normal PVR is 0.9 $\pm$ 0.4 Wood units (WU).[9] The current systematic literature review confirmed the main findings of this study and provides a basis for the haemodynamic definitions of pulmonary hypertension (PH). Of special value are studies invasively investigating pulmonary haemodynamics of healthy volunteers who had no symptoms or clinically suspected pulmonary vascular disease (PVD), and who also underwent comprehensive clinical investigations in order to exclude significant left heart or lung disease.[10–26]

3.1.2. Prognostic relevance of mildly increased mean pulmonary arterial pressure and pulmonary vascular resistance

Based on the systemic literature research, there are a handful of studies investigating the prognostic relevance of mPAP, PVR, or PAWP in large patient collectives. In addition, most of the studies used pre-defined cut-offs or the actual thresholds for PH in their analysis, and few studies used an unbiased approach.

Maron and colleagues performed two important analyses, retrospectively investigating the prognostic relevance of mPAP[27] and PVR[28] in >20 000 (and >40 000 in the case of PVR) US veterans undergoing RHC. When treating mPAP and PVR as continuous variables, the mortality hazard increased, beginning at 19 mmHg and 2.2 WU, illustrating a continuum of risk according to mPAP and PVR levels. The prognostic relevance of mPAP $\geq$19 mmHg and PVR $\geq$2.2 WU was confirmed in an independent cohort of >3500 patients.[28]

In other general cohorts of patients undergoing RHC, similar mPAP thresholds were associated with mortality. Assad and colleagues found that after adjusting for clinical covariates, patients with mPAP 19–24 mmHg had impaired survival compared with those with mPAP <19 mmHg.[29] Douschan and colleagues also found that a mildly elevated mPAP is a predictor of mortality, and the first prognostically relevant threshold was found by a tree based analysis at $\geq$17 mmHg.[30] After correcting for age and comorbidities, an mPAP 21–24 mmHg was associated with increased mortality compared with patients with an mPAP $\leq$20 mmHg. Heresi and colleagues also found that an mPAP >20 mmHg was associated with worse survival,[31] and an analysis of the haemodynamic data of 1371 predominantly Black patients undergoing right and left heart catheterization revealed that an mPAP $\geq$20 mmHg was associated with impaired prognosis.[32]

Some recent studies have confirmed a prognostic relevance of mPAP >20 mmHg in specific patient cohorts. Kimura and colleagues found that mPAP independently determined survival in patients with idiopathic pulmonary fibrosis (IPF), and mPAP >20 mmHg proved to be the optimal threshold for predicting the prognosis.[33] Similarly, the mPAP >20 mmHg threshold was prognostically relevant in patients with systemic sclerosis (SSc),[34] and the mPAP $\geq$20 mmHg threshold in patients with connective tissue disease-associated interstitial lung disease (ILD).[35] Patients with SSc and an mPAP 21–24 mmHg more frequently developed an mPAP $\geq$25 mmHg compared with those with an mPAP $\leq$20 mmHg, suggesting that mildly elevated mPAP is associated with frequent progression of PVD.[36,37]

The clinical relevance of PVR $\geq$2 WU was investigated in patients with SSc in a multicentre retrospective study.[38] The data suggested that PVR $\geq$2 WU is associated with clinically significant PVD and reduced survival. In chronic left heart diseases, the prognostic relevance of a pre-defined PVR >3 WU has been confirmed in several studies.[39–41] In a recent study, the clinical development of patients with an mPAP $\geq$25 mmHg (mPAP 27 mmHg [interquartile range (IQR), 25–30]), a PAWP $\leq$15 mmHg, and PVR <3 WU (PVR 2.2 WU [IQR: 1.9–2.7]) receiving pulmonary arterial hypertension (PAH) therapy was evaluated, and adverse outcomes (estimated 1 year and 5 year

survival rates of 98% and 84%, respectively; death attributed to PAH in 33% of patients) were frequently observed, suggesting that even a mild elevation of PVR may be clinically significant.[42]

3.1.3. Upper limit of normal and prognostic relevance of pulmonary arterial wedge pressure

Studies providing PAWP values in healthy controls are heterogeneous. In some studies the values are relatively low, suggesting an upper limit of normal of ≤12 mmHg.[10,20,21,24,25,43–73] Other studies suggest that even healthy subjects may present with a PAWP >12 mmHg.[11–13,16–19,22,23,26,74–91] A PAWP ≥12 mmHg was found to be a strong and independent predictor of both short-term and long-term survival after myocardial infarction, revealing a gradual increase in the 10 year mortality risk.[92] A recent systematic review confirmed that an elevated PAWP is an independent predictor of poor prognosis in heart failure.[93]

See the following sections for the search strategy (13.5) and PRISMA diagram (14.5).

Table S1 Pulmonary arterial hypertension haemodynamic definition used in clinical trials

Drug name/trial name	Author, year of publication	Pulmonary hypertension group included	Specifically mentioned haemodynamic inclusion criteria
Epoprostenol	Rubin *et al. Ann Int Med* 1990[94] Barst *et al. NEJM* 1996[95]	Primary PH	NA
Bosentan/ BREATHE-1	Rubin *et al. NEJM* 2002[96]	Symptomatic, severe PAH (primary or associated with CTD)	mPAP >25 mmHg, PAWP <15 mmHg, and PVR >3 WU
Inhaled iloprost/AIR	Olschewski *et al. NEJM* 2002[97]	Primary PH and selected forms of non-primary PH (appetite suppressant-associated PH, scleroderma-associated PH, inoperable chronic thrombo-embolic PH)	mPAP >30 mmHg, PAWP ≤15 mmHg, and CI 1.5–4.0 L/min/m^2
Treprostinil s.c.	Simonneau *et al. AJRCCM* 2002[98]	Primary PH or PH associated with CTD or associated with congenital systemic-to-pulmonary shunts	mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR >3 WU
2004 ESC Guideline PAH haemodynamic definition: PAH is defined by an mPAP >25 mmHg at rest or >30 mmHg with exercise, by PAWP ≤15 mmHg, and PVR >3 WU.[99]			
Sildenafil/ SUPER	Galiè *et al. NEJM* 2005[100]	PAH (idiopathic, associated with CTD, or occurring after surgical repair of congenital systemic-to-pulmonary shunts that had been performed at least 5 years previously)	mPAP ≥25 mmHg, PAWP ≤15 mmHg
Ambrisentan/ ARIES	Galiè *et al. Circulation* 2008[101]	PAH (idiopathic or associated with CTD, HIV infection, or anorexigen use)	Defined according to current guidelines
Tadalafil/ PHIRST	Galiè *et al. Circulation* 2009[102]	Symptomatic PAH that was idiopathic/heritable or related to anorexigen use, CTD, HIV infection, or congenital systemic-to-pulmonary shunts	mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR ≥3 WU
2009 ESC/ERS Guideline PAH haemodynamic definition: PAH is a clinical condition characterized by the presence of pre-capillary PH (mPAP ≥25 mmHg, PAWP ≤15 mmHg, CO normal or reduced) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thrombo-embolic PH, or other rare diseases.[103,104]			
Macitentan/ SERAPHIN	Pulido *et al. NEJM* 2013[105]	Idiopathic or heritable PAH or PAH related to CTD, repaired congenital systemic-to-pulmonary shunts, HIV infection, or drug use or toxin exposure were eligible for inclusion in the trial	Defined according to current guidelines
Riociguat/ PATENT-1	Ghofrani *et al. NEJM* 2013[106]	Symptomatic PAH (idiopathic, familial, or associated with CTD, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen or amphetamine use)	mPAP ≥25 mmHg, PVR >3.75 WU
2015 ESC/ERS PH Guideline PAH haemodynamic definition: The term PAH describes a group of PH patients (mPAP ≥25 mmHg) characterized haemodynamically by the presence of pre-capillary PH, defined by PAWP ≤15 mmHg and PVR ≥3 WU in the absence of other causes of pre-capillary PH, such as PH due to lung diseases, chronic thrombo-embolic PH, or other rare diseases.[107,108]			
Selexipag/ GRIPHON	Sitbon *et al. NEJM* 2015[109]	Idiopathic or heritable PAH or PAH associated with HIV infection, drug use or toxin exposure, CTD, or repaired congenital systemic-to-pulmonary shunts	PVR ≥5 WU

CI, cardiac index; CTD, connective tissue disease; HIV, human immunodeficiency virus; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

4. Epidemiology and risk factors

No supplementary data for this section.

5. Pulmonary hypertension diagnosis

5.1. Key narrative question #2: Should new echocardiographic probability of pulmonary hypertension approaches be proposed in symptomatic patients with a suspicion of pulmonary hypertension?

Based on the new definition of invasively assessed PH, the estimation of echocardiographic probability should account for increasing sensitivity for detecting mPAP >20 mmHg, to avoid missing cases of evident PH. Nevertheless, the new definition of PH will increase the overlap between healthy subjects and those with suspected PH, which may represent up to 25% of the subjects indicated for echocardiography in the general population.[110] Thus, high specificity and positive predictive value (PPV) are crucial to avoid unnecessary RHC in individuals without PH.

Of note, the association of tricuspid regurgitation (TR) pressure gradient (TRPG) with invasively measured systolic pulmonary arterial pressure (sPAP) is limited at low pressure gradients (TRPG ≤46 mmHg).[111] For this reason, lowering the estimated TRPG cut-off <31 mmHg (TR velocity <2.8 m/s) to screen for the new PH definition results in very low specificity, with unacceptable PPV and moderate accuracy without a substantial increase in sensitivity.[112] Available data do not support the current recommendation on the TRPG threshold for the echocardiographic probability of PH to be changed. A recent study by D'Alto and colleagues validates previous guidelines' strategy as applied for predicting PH or PVD, taking into account the updated haemodynamic definitions of PH.[113]

In this setting, other echocardiographic signs of PH—such as right ventricle (RV)/left ventricle (LV) basal diameter (area) ratio >1.0, flattening of the interventricular septum (LV eccentricity index [LVEI] >1.1), RV outflow tract Doppler acceleration time (RVOT AT) <105 ms and/or mid-systolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/s, inferior vena cava diameter >21 mm with decreased inspiratory collapse, and right atrial (RA) area at end-systole >18 cm^2—significantly increase specificity and overall accuracy for screening of the new definition of PH. Among indirect echocardiographic signs of PH, a pulmonary artery (PA) to aortic root ratio >1 is able to increase accuracy compared with a PA diameter >25 mm (in the absence of aortic or PA pathology). Although normal values for PA diameter are reported to be 18 ± 3 mm (range 9–29 mm),[114] values <29 mm have been observed in up to 25% of patients with PAH or chronic thrombo-embolic PH (CTEPH),[115] while a PA to aortic root ratio >1 is extremely uncommon in healthy subjects (0.008%).[116] Nevertheless, a cut-off for a PA diameter >25 mm has recently been validated.[113]

The tricuspid annular plane systolic excursion (TAPSE)/sPAP ratio, which represents a non-invasive measure of RV–PA coupling, provides additional information for the diagnosis of PH and risk assessment in PAH. A cut-off value of <0.55 mm/mmHg is considered as one measure contributing to the probability of PH (taking into account the updated definition).[117] In patients with PAH, a cut-off of >0.32 mm/mmHg may indicate a low-risk status, whereas a cut-off of <0.19 mm/mmHg may indicate a high mortality risk.[118,119]

Additionally, the TRPG/RVOT AT ratio and the TAPSE/TRPG ratio recently emerged with high discriminatory power when screening for pre-capillary PH (cut-off values 0.37 mmHg/ms and 0.56 mm/mmHg, respectively), providing the highest specificity and accuracy, especially in patients with an mPAP 20–25 mmHg (cut-off values 0.61 mmHg/ms and 0.36 mm/mmHg, respectively).[112] Nevertheless, the overall accuracy of the TRPG/RVOT AT ratio and the TAPSE/TRPG ratio remains suboptimal when screening for pre-capillary PH in patients with low TRPG, even though they were improved and externally validated compared with TRPG alone.

Therefore, the echocardiographic probability of PH should be interpreted in a clinical context, taking into account symptoms and risk factors or associated conditions of PAH and CTEPH. Symptomatic patients with risk factors or associated conditions of PAH and an intermediate echocardiographic probability of PH should be considered for further investigation with cardiopulmonary exercise testing (CPET), to improve the accuracy of the diagnostic algorithm in keeping with the new definition of PH. In this context, the sequential combination of a ventilatory equivalent for carbon dioxide (VE/VCO_2) slope ≥36 in DETECT-positive patients with SSc enabled an increase in the specificity and PPV, reducing the number of unnecessary invasive procedures, without a loss in sensitivity and negative predictive value (NPV; missed diagnoses) in accordance with the new haemodynamic definition.[120] When used in a less sensitive tuned work-up of SSc-associated PAH, end-tidal partial pressure of carbon dioxide ($PETCO_2$) and VE/VCO_2 values, respectively, peak <31.3 mmHg and nadir >35.5, increased specificity and maintained a high NPV for PAH diagnosis.[121] More evidence is required to define the optimal cut-off value to show if accuracy is retained when the new haemodynamic definition is applied.

Larger-scale prospective studies are required to investigate whether CPET would be indicated in symptomatic patients without risk factors or associated conditions for PAH/CTEPH and intermediate echocardiographic probability of PH.

See the following sections for search strategy (13.6), PRISMA diagram (14.6), and Evidence to Decision table (16.5).

5.2. Key narrative question #3: Should screening be offered to guide detection of pulmonary arterial hypertension in systemic sclerosis?

See the following sections for search strategy (13.7), PRISMA diagram (14.7), and Evidence to Decision table (16.6).

6. Pulmonary arterial hypertension (group 1)

Table S2 Imaging-derived variables of prognostic relevance and cut-off values in pulmonary arterial hypertension

	Increased risk	Decreased risk	Ref.
Echocardiography			
Right heart morphology			
RVESRI	≥1.6	NA	122
Δ RVEDA, cm^2	NA	<−2.45	123
RV/LV ratio	>1	NA	NA
Δ RA area, cm^2	NA	<−1.30	123
Δ LVEIs	NA	<−0.12	123
Tricuspid regurgitation, severe	Yes	NA	124
RV systolic function			
TAPSE, mm	≤17	NA	125
TAPSE/sPAP, mm/mmHg	<0.19	>0.55	118
RV-FAC, %	<36.5	NA	126
IVCv, cm/s	≤9	NA	127
RV filling pressure			
Pericardial effusion	Yes	NA	128,129
RV post-systolic strain pattern[a]	2–3	NA	130
RV dyssynchrony[b]			
RV-SD4, ms	>23	≤18	131
Cardiac magnetic resonance			
Heart morphology			
RVEDVI, mL/m^2	>84	NA	132
RVESVI, % pred.	>180 >227	NA	133,134
RV M/V ratio, g/mL	≤0.45	NA	135
LVEDVI, mL/m^2	≤40	>58	132,134
RV function and coupling			
SVI, mL/m^2	≤25	NA	132
RVEF, %[c]	<37	>54	132–134, 136–138
Δ RVEF	NA	>0	137,138
RV SV/ESV	≤0.53	NA	136

IVCv, isovolumic contraction peak velocity at the tricuspid annulus; LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVEIs, LV systolic eccentricity index; pred., predicted; M/V ratio, mass/volume ratio; RA, right atrial; RV, right ventricular; RVEDA, RV end-diastolic area; RVEDVI, RV end-diastolic volume index; RVEF, RV ejection fraction; RVESRI, RV end-systolic remodelling index; RV-FAC, RV fractional area change; RV/LV ratio, RV end-diastolic diameter to LV end-diastolic diameter ratio (measured in the four-chamber apical view); RV-SD4, standard deviation of the times to peak-systolic strain for the four mid-basal RV segments; RV SV/ESV, RV stroke volume/end-systolic volume; sPAP, systolic pulmonary arterial pressure; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.

Δ change in parameter from baseline to 1 year.

[a]RV post-systolic strain pattern: for RV post-systolic patterns, longitudinal strain was considered and the time period from peak-systolic strain to return to baseline point-set for the basal RV free-wall segment was evaluated.

[b]Defined as the standard deviation of the mean value of times to peak-systolic strain for the four mid-basal RV segments.

[c]RVEF-derived cut-offs: increased risk different cut-off values were identified; all were <37%.

6.1. Key narrative question #4: Should a risk-stratification strategy be used to guide treatment in patients with pulmonary arterial hypertension?

Chosen risk-stratification instruments were French invasive, French non-invasive, Swedish Pulmonary Arterial Hypertension Registry (SPAHR)/Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), and Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 score.

The ESC/ERS risk-stratification tool has been validated in a series of retrospective studies at diagnosis, and early and long-term follow-up.[139–143] Accumulating evidence reinforces that changes in risk scores, evaluated by the SPAHR equation/COMPERA, French Pulmonary Hypertension Registry (FPHR), and REVEAL strategies, are influenced by treatment and predict survival and clinical worsening.[139,140,143–146] This supports a goal-orientated treatment approach in PAH, where achieving and/or maintaining a low-risk status is favourable and recommended.[144,147–150] Evidence based on retrospective analyses furthermore displays an intimate association between the use of PAH therapies and improvement in risk score,[147,149–152] supporting a recommendation that risk stratification should be used to guide treatment in patients with PAH. The ESC/ERS 2022 risk assessment and prognostic evaluation model is expanded, being based on 'clinical observations', 'modifiable' variables, and 'patient characteristics', aimed at identifying patients with PAH early in the low-risk zone or those who could be transferred to a low-risk status with treatment. Large, prospective, collaborative studies are encouraged to further improve the ability of risk stratification to guide treatment in patients with PAH, with specific focus on substratifying the large intermediate-risk group, and its use in the elderly or in those with comorbidities. Although determining the superiority and feasibility of the various risk-stratification strategies remains an important task in the future, the major challenge at present is to implement a thorough, multiparametric, risk-stratification approach at all expert PH centres, for PAH patients with different phenotypes, demographics, and comorbidities, as a part of the clinical practice, which is strongly recommended.

See the following sections for search strategy (13.8), PRISMA diagram (14.8), and Evidence to Decision table (16.7).

6.2. PICO question I: Should initial oral double-combination therapy vs. monotherapy be used in symptomatic patients with pulmonary arterial hypertension?

Chosen oral double-combination therapies are endothelin receptor antagonists (ERAs) and phosphodiesterase 5 inhibitors (PDE5is), and monotherapy are ERAs or PDE5is.

See the following sections for search strategy (13.1), PRISMA diagram (14.1), GDT evidence profile (15.1), and Evidence to Decision table (16.1).

6.2.1. Conclusions

The available data support a positive recommendation, despite the low certainty of evidence (a single RCT, small number of events). The primary endpoint of time to death or morbidity event is met (driven by the reduction in hospitalizations). Secondary efficacy endpoints, such as change in exercise capacity (6-minute walking distance [6MWD]) and in cardiac biomarkers (N-terminal pro-brain natriuretic peptide [NT-proBNP]), also favour initial combination therapy. The lack of haemodynamic evaluation is a weakness. There is no safety concern. Finally, the long-term effect on survival is uncertain.

6.2.1.1. Recommendations

For symptomatic patients with PAH, initiating oral double-combination therapy (ERA and PDE5i) rather than monotherapy (conditional recommendation for the intervention, very low-quality evidence) is suggested.

Table S3 Recommendations for efficacy of drug monotherapy for pulmonary arterial hypertension

Recommendations			Class[a]	Level[b]	Ref
Endothelin receptor antagonists	Ambrisentan		I	A	101,153,154
	Bosentan		I	A	96,155,156
	Macitentan		I	B	105,157,158
Phosphodiesterase 5 inhibitors	Sildenafil		I	A	100,159,160
	Tadalafil		I	B	102,161
Guanylate cyclase stimulators	Riociguat		I	B	106,162
Prostacyclin analogues	Epoprostenol	Intravenous	I	A	94,95,163–166
	Iloprost	Inhaled	I	B	97,167
		Intravenous	IIa	C	168–170
	Treprostinil	Subcutaneous	I	B	98,171–173
		Inhaled	IIb	C	174
		Intravenous	IIa	C	175–177
		Oral	IIb	B	178
	Beraprost	Oral	IIb	B	179,180
Prostacyclin receptor agonists	Selexipag	Oral	I	B	109

[a]Class of recommendation.
[b]Level of evidence.

Table S4 Potentially significant drug interactions with pulmonary arterial hypertension-targeted therapies

PAH drug	Mechanism of interaction	Interacting drug	Interaction
Ambrisentan	CYP3A4 induction	Cyclosporine Ketoconazole	Caution is required when co-administering ambrisentan with ketoconazole and cyclosporine
	CYP3A4 induction	Hormonal contraceptives	Ambrisentan slightly decreases the AUC of hormonal contraceptives; not clinically significant
Bosentan[181,182]	CYP3A4 inducer	Sildenafil[183]	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase four-fold. Combination contraindicated
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase two-fold
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increased incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of glibenclamide. Combination contraindicated
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels considerably increase. Combination contraindicated
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease 58%. Need for dose adjustment uncertain

Continued

	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored
	CYP2C9 inducer	Warfarin	Warfarin metabolism increases; may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation, but dose adjustment usually unnecessary
	CYP2C9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable
Macitentan[184]	CYP3A4 substrate	Rifampicin	Rifampicin decreases macitentan levels 79%. Need for dose adjustment uncertain
Selexipag[185]	CYP2C8 substrate	Gemfibrozil	Combination should be avoided as this could lead to high levels of selexipag
	CYP2C8 Substrate	Clopidogrel[186]	Increased levels of selexipag. It is recommended reducing selexipag dosing to half
Sildenafil[187]	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase simvastatin/atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinavir markedly increase sildenafil levels. Co-administration is not recommended
	CYP3A4 inducer	Phenytoin	Sildenafil levels may fall
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase. May not require dose adjustment for a short course
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment
	cGMP	Nitrates Nicorandil Molsidomine[188]	Profound systemic hypotension. Combination contraindicated
Tadalafil	CYP3A4 substrate	Bosentan[189]	Tadalafil exposure decreases 42%, no significant changes in bosentan levels. May not require dose adjustment
	cGMP	Nitrates Nicorandil Molsidomine	Profound systemic hypotension. Combination contraindicated
Riociguat[190]	cGMP	Sildenafil Tadalafil	Hypotension, severe side effects. Combination contraindicated
	cGMP	Nitrates Nicorandil Molsidomine	Profound systemic hypotension. Combination contraindicated

AUC, area under the curve; cGMP, cyclic guanosine monophosphate; CYP, cytochrome P450; HIV, human immunodeficiency virus; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PAH, pulmonary arterial hypertension.
Adapted from the Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland, 2008.[191]

7. Specific pulmonary arterial hypertension subsets

7.1. General classification of paediatric pulmonary hypertension (from 6th World Symposium on Pulmonary Hypertension)

Table S5 Persistent pulmonary hypertension of the newborn and associated disorders

Idiopathic PPHN	Myocardial dysfunction (asphyxia, infection)
Down syndrome	Structural cardiac diseases
Meconium aspiration syndrome	Hepatic and cerebral arteriovenous malformations
Respiratory distress syndrome	NA
Transient tachypnoea of the newborn	Associations with other diseases: Placental dysfunction (pre-eclampsia, chorioamnionitis, maternal hypertension) Metabolic disease Maternal drug use or smoking
Pneumonia/sepsis	
Developmental lung disease	
Perinatal stress	

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Table S6 Congenital post-capillary obstructive lesions

Pulmonary vein stenosis
Isolated
Associated (bronchopulmonary dysplasia, prematurity)
Cor triatriatum
Obstructed total anomalous pulmonary venous return
Mitral/aortic stenosis (including supra/subvalvular)
Coarctation of the aorta

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Table S7 Developmental lung disorders associated with pulmonary hypertension

Bronchopulmonary dysplasia
Congenital diaphragmatic hernia
Down syndrome
Alveolar capillary dysplasia with "misalignment of veins"* (FOXF1)
Lung hypoplasia, acinar dysplasia
Surfactant protein abnormalities
Surfactant protein B deficiency
Surfactant protein C deficiency
ABCA3
TTF1/NKX2-1
TBX4
Pulmonary interstitial glycogenesis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

Table S7 provides a summary of developmental lung disorders that share the common feature of developmental vascular disturbance
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Table S8 Complex congenital heart disease

Segmental pulmonary hypertension
Isolated pulmonary artery of ductal origin
Absent pulmonary artery
Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries
Hemitruncus
Other
Single ventricle
Unoperated
Operated
Scimitar syndrome

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8. Pulmonary hypertension associated with left heart disease (group 2)

8.1. Pathophysiology of pulmonary hypertension and right ventricular dysfunction in group 2 pulmonary hypertension

The pathophysiology of group 2 PH combines several mechanisms (*Figure S1*): (1) an initial passive increase in LV filling pressures; (2)

PA endothelial dysfunction (including vasoconstriction), an early mechanism already observed in cardiac diseases; (3) vascular remodelling, with the development of PVD in some cases; and (4) RV dysfunction and altered RV–PA coupling.

Right ventricular dysfunction is frequent and associated with a worse prognosis in patients with PH-associated with left heart disease (LHD). Afterload-mediated processes account for RV dysfunction in most cases, with RV–PA uncoupling as a marker of disease.[192,193] However, some cardiac diseases (especially heart failure with preserved ejection fraction [HFpEF]) may lead to a distinct feature of RV dysfunction in the absence of PH through various mechanisms, such as reduced pulmonary artery compliance (PAC),[193,194] intrinsic myocardial disease,[195,196] and TR.[193,197–199] In group 2 PH, an elevated PAWP reduces PAC,[193,200,201] which partly explains why a low PAC is associated with a worse outcome. Finally, PAC-mediated RV dysfunction has been shown in patients with heart failure with normal pulmonary arterial pressure (PAP) and PVR.[194]

Description of the haemodynamic mechanisms leading to PH in HFpEF. Elevation of LAP triggers development of PH and leads to:

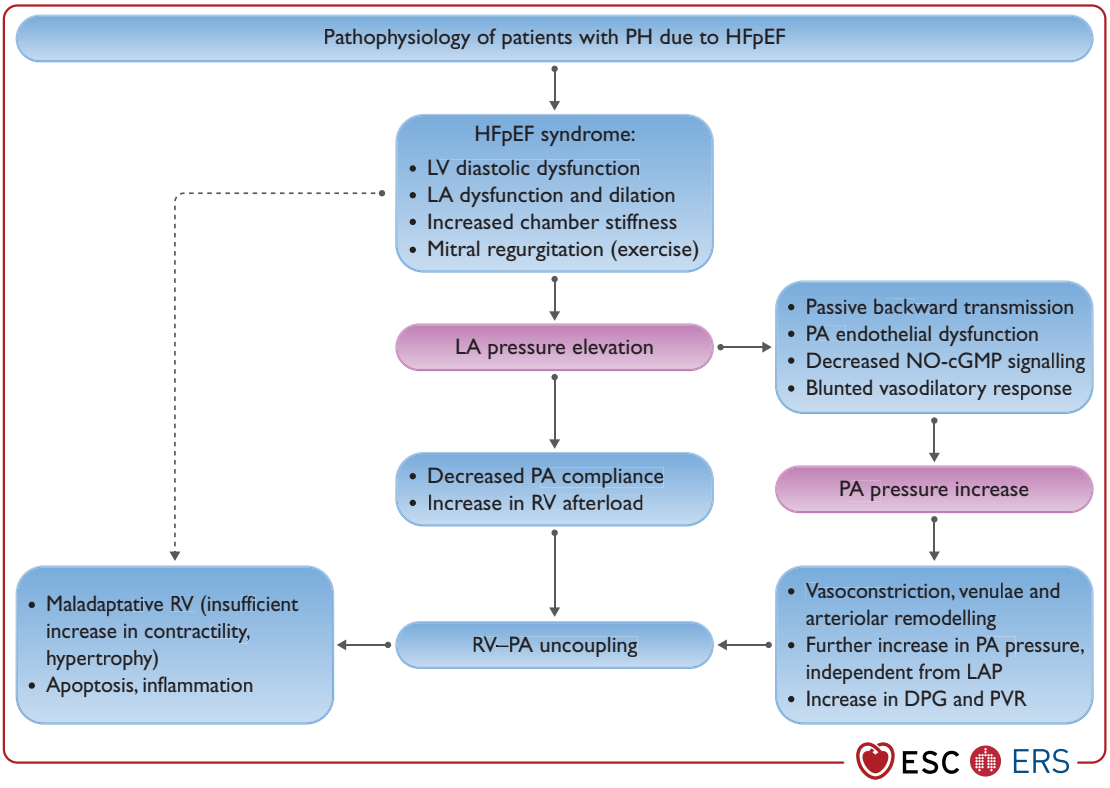

Figure S1 Pathophysiology of pulmonary hypertension due to heart failure with preserved ejection fraction DPG, diastolic pressure gradient; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LAP, left atrial pressure; LV, left ventricular; NO-cGMP, nitric oxide–cyclic guanosine monophosphate; PA, pulmonary artery; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle.

(1) a passive increase in PA pressure; and (2) a decrease in PAC generating a pulsatile increase in RV afterload that is independent from the increase in PA pressure. Right ventricular uncoupling results from a combination of the latter and pulmonary vascular response to the increase in pressure. Endothelial dysfunction may be present before the increase in LAP. A maladaptive RV is common in HFpEF, either in response to an increase in afterload and/or due to direct myocardial insult, leading to RV failure.

8.2. Diagnosis

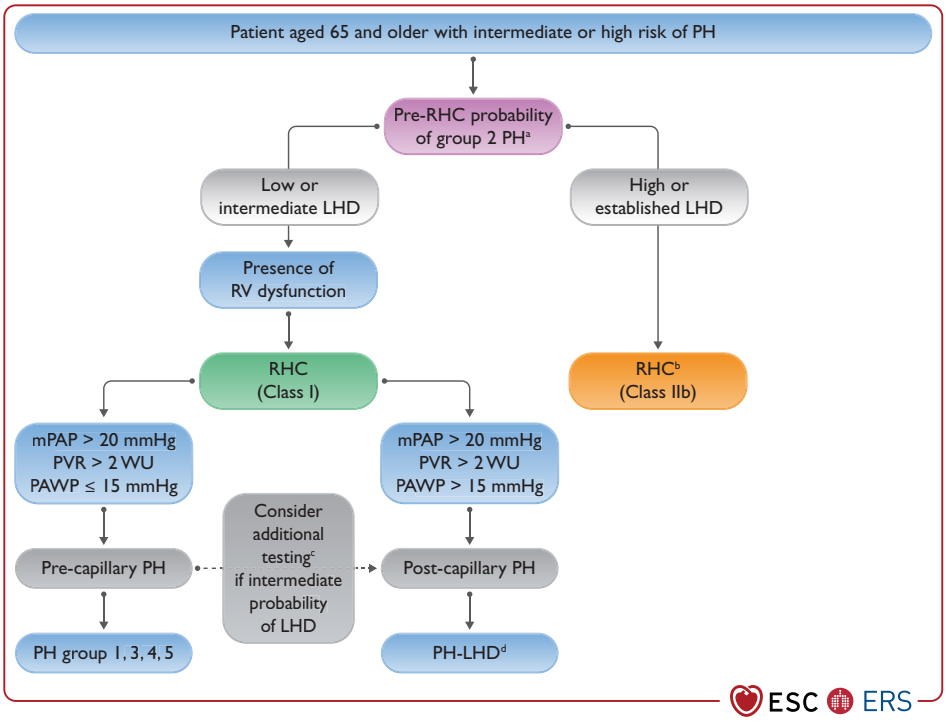

Figure S2 Indications and interpretation of haemodynamic assessment in pulmonary hypertension associated with left heart disease HFpEF, heart failure with preserved ejection fraction; LHD, left heart disease; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; WU, Wood units.

[a]According to probability of LHD as cause of PH (*Table 24*).

[b]RHC may be considered and indicated for prognosis or specific treatment decision purposes, according to the appropriate guidelines.

[c]LVEDP measurement may be indicated if PAWP traces are uninterpretable. Fluid loading test may uncover HFpEF as the cause of PH. Exercise testing may also be considered in experienced centres.

[d]RHC data must be interpreted in the clinical context.

8.3. Key narrative question #5: Should drugs approved for pulmonary arterial hypertension be used in patients with pulmonary hypertension associated with left heart disease?

Chosen drugs are ERAs, PDE5is, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists.

See the following sections for search strategy (13.9), PRISMA diagram (14.9), and Evidence to Decision table (16.8).

8.4. PICO question II: Should phosphodiesterase type 5 inhibitors be used in patients with combined post- and pre-capillary pulmonary hypertension due to heart failure with preserved ejection fraction?

See the following sections for search strategy (13.2), PRISMA diagram (14.2), GDT evidence profile (15.2), and Evidence to Decision table (16.2).

8.4.1. Conclusions

8.4.1.1. Recommendations

The use of a PDE5i in patients with combined post- and pre-capillary PH due to HFpEF is currently not recommended.

9. Pulmonary hypertension associated with lung diseases and/or hypoxia (group 3)

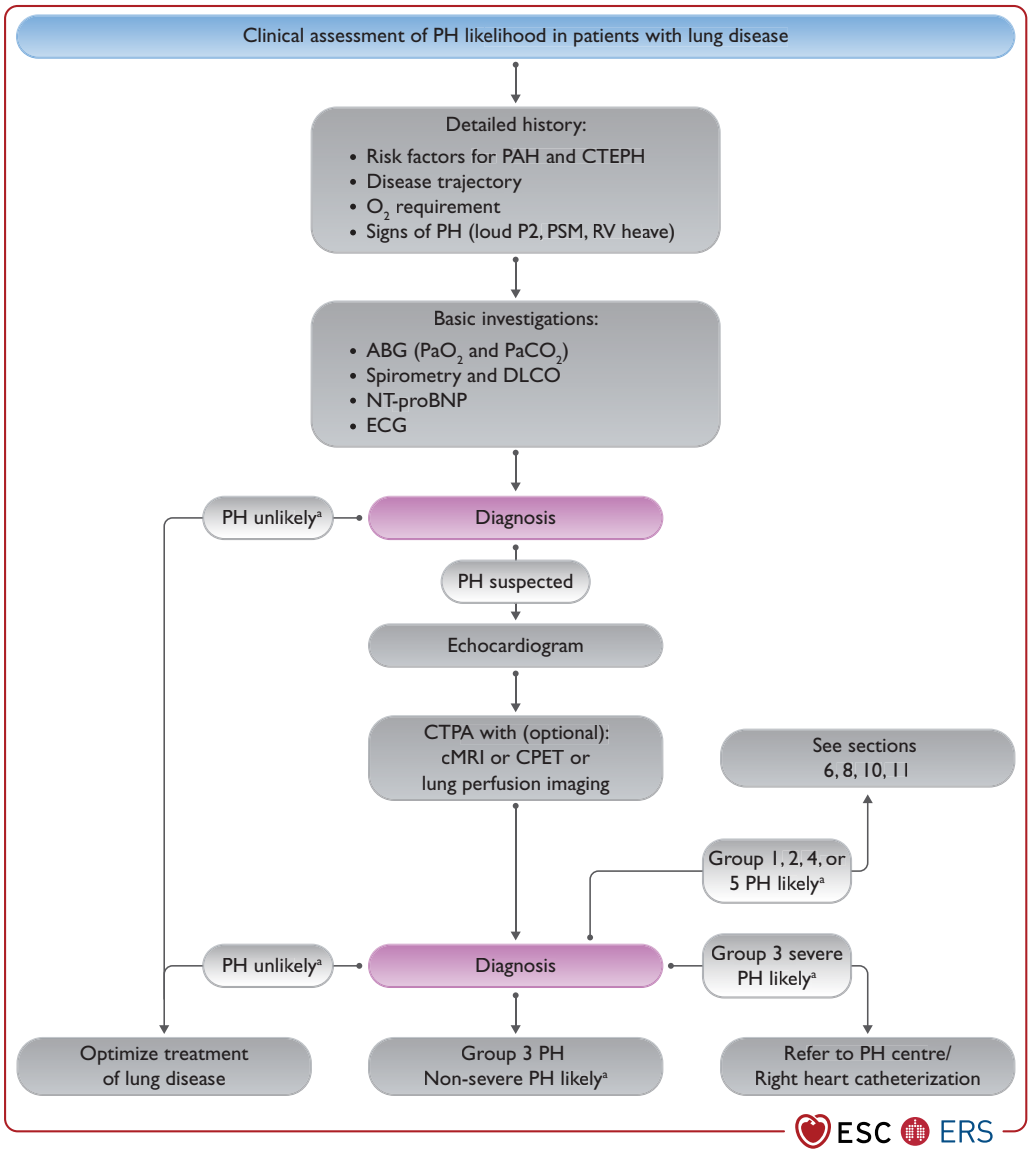

Figure S3 Approach to assessment of suspected pulmonary hypertension in patients with lung disease ABG, arterial blood gas analysis; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; CTEPH, chronic thrombo-embolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; DLCO, lung diffusion capacity for carbon monoxide; ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; O_2, oxygen; P2, second heart sound; PAH, pulmonary arterial hypertension; $PaCO_2$, partial pressure of arterial carbon dioxide; PH, pulmonary hypertension; PaO_2, partial pressure of arterial oxygen; PSM, pan systolic murmur; RV, right ventricular.

[a]Investigations to be integrated with clinical context in a stepwise fashion to assess for the probability and aetiology of PH.

9.1. Key narrative question #6: Should drugs approved for pulmonary arterial hypertension be used in patients with pulmonary hypertension due to chronic obstructive pulmonary disease?

Chosen drugs are ERAs, PDE5is, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists.

See the following sections for search strategy (13.10), PRISMA diagram (14.10), and Evidence to Decision table (16).

9.2. Key narrative question #7: Should drugs approved for pulmonary arterial hypertension be used in patients with pulmonary hypertension due to interstitial lung diseases?

Chosen drugs are ERAs, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists.

See the following sections for search strategy (13.11), PRISMA diagram (14.11), and Evidence to Decision table (16.10).

9.3. PICO question III: Should phosphodiesterase 5 inhibitors be used in patients with severe pulmonary hypertension due to interstitial lung diseases?

See the following sections for search strategy (13.3), PRISMA diagram (14.3), GDT evidence profile (15.3), and Evidence to Decision table (16.3).

9.3.1. Conclusions

9.3.1.1. Recommendations

The use of PDE5is in patients with ILD and non-severe PH is currently not recommended. For patients with ILD and severe PH, individual decision-making is recommended.

10. Chronic thrombo-embolic pulmonary hypertension (group 4)

10.1. Key narrative question #8: Should balloon pulmonary angioplasty or medical therapy be used in patients with inoperable chronic thrombo-embolic pulmonary hypertension?

See the following sections for search strategy (13.12), PRISMA diagram (14.12), and Evidence to Decision table (16.11).

10.2. PICO question IV: Should patients with chronic thrombo-embolic pulmonary hypertension who are considered inoperable but candidates for balloon pulmonary angioplasty receive medical therapy before interventional therapy is initiated?

See the following sections for search strategy (13.4), PRISMA diagram (14.4), GDT evidence profile (15.4), and Evidence to Decision table (16.4).

10.2.1. Conclusions

10.2.1.1. Recommendations

In patients with CTEPH who are candidates for balloon pulmonary angioplasty (BPA), medical therapy should be considered prior to the intervention (conditional recommendation, very low quality of evidence).

11. Pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5)

No supplementary data for this section.

12. Definition of a pulmonary hypertension centre

No supplementary data for this section.

13. Search strategies

13.1. Literature search strategies for PICO I

13.1.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	pulmonary[tiab] AND arter*[tiab] AND hypertensi*[tiab]	32 835
3	1 OR 2	51 442
4	"Combined Modality Therapy"[Mesh]	271 289
5	"combination therapy"[tiab] OR "combined modality therapy"[tiab]	51 186
6	4 OR 5	316 229
7	"Bosentan"[Mesh] OR "Endothelin Receptor Antagonists"[Mesh]	5802
8	"Endothelin Receptor Antagonists"[Pharmacological Action]	5901
9	"ambrisentan"[Supplementary Concept] OR "macitentan"[Supplementary Concept] OR "sitaxsentan"[Supplementary Concept]	553
10	ACT064992[tiab] OR Actelion[tiab] OR Ambrisentan[tiab] OR Bosentan[tiab] OR BSF208075[tiab] OR "endothelin receptor antagonists"[tiab] OR GSK1325760A[tiab] OR Letairis[tiab] OR LU208075[tiab] OR macitentan[tiab] OR opsumit[tiab] Pulmonext[tiab] OR "Ro 470203"[tiab] OR Sitaxentan[tiab] OR Stayveer[tiab] OR Tracleer[tiab] OR Volibris[tiab]	128
11	OR/7-10	6519
12	"Phosphodiesterase 5 Inhibitors"[Mesh] OR "Sildenafil Citrate"[Mesh] OR "Tadalafil"[Mesh] OR "Vardenafil Dihydrochloride"[Mesh]	8411
13	"Phosphodiesterase 5 Inhibitors" [Pharmacological Action]	8485
14	Adcirca[tiab] OR BAY38-9456[tiab] OR Cialis[tiab] OR Desmethylsildenafil[tiab] OR "EC 607-088-5"[tiab] OR GF-196960[tiab] OR Homosildenafil[tiab] OR Hydroxyhomosildenafil[tiab] OR IC351[tiab] OR Levitra[tiab] OR "PDE5I"[tiab] OR "PDE5 inhibitors"[tiab] OR "phosphodiesterase type 5 inhibitors"[tiab] OR Revatio[tiab] OR Sildenafil[tiab] OR Staxyn[tiab] OR Tadalafil[tiab] OR "UK 9248010"[tiab] OR Vardenafil[tiab] OR Viagra[tiab] OR Vivanza[tiab] OR Vizarsin[tiab]	10 426
15	OR/12-14	12 060
16	6 AND 11 AND 15	142

Continued

17	monotherapy[tiab]	52 184
18	11 OR 15	18 015
19	17 AND 18	369
20	3 AND 16 AND 19	46
21	"Animals"[Mesh] NOT "Humans"[Mesh]	NA
22	20 NOT 21	45
23	English[lang]	NA
24	22 AND 23	39
25	1990/1/1:3000/12/31[pdat]	NA
26	24 AND 25	39

13.1.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND arter*:ti,ab AND hypertensi*:ti,ab	2790
3	1 OR 2	3204
4	MeSH descriptor: [Combined Modality Therapy] explode all trees	21 995
5	"combination therapy":ti,ab OR "combined modality therapy":ti,ab	13 687
6	4 OR 5	35 171
7	MeSH descriptor: [Bosentan] explode all trees	190
8	MeSH descriptor: [Endothelin Receptor Antagonists] explode all trees	275
9	ACT064992:ti,ab OR Actelion:ti,ab OR Ambrisentan:ti,ab OR Bosentan:ti,ab OR BSF208075:ti,ab OR "endothelin receptor antagonists":ti,ab OR GSK1325760A:ti,ab OR Letairis:ti,ab OR LU208075:ti,ab OR macitentan:ti,ab OR opsumit:ti,ab Pulmonext:ti,ab OR "Ro 470203":ti,ab OR Sitaxentan:ti,ab OR Stayveer:ti,ab OR Tracleer:ti,ab OR Volibris:ti,ab	899
10	OR/7-9	1072
11	MeSH descriptor: [Phosphodiesterase 5 Inhibitors] explode all trees	382
12	MeSH descriptor: [Sildenafil Citrate] explode all trees	962
13	MeSH descriptor: [Tadalafil] explode all trees	431
14	MeSH descriptor: [Vardenafil Dihydrochloride] explode all trees	174
15	Adcirca:ti,ab OR "BAY38-9456":ti,ab OR Cialis:ti,ab OR Desmethylsildenafil:ti,ab OR "EC 607-088-5":ti,ab OR GF-196960:ti,ab OR Homosildenafil:ti,ab OR Hydroxyhomosildenafil:ti,ab OR IC351:ti,ab OR Levitra:ti,ab OR PDE5I:ti,ab OR "PDE5 inhibitors":ti,ab OR "phosphodiesterase type 5 inhibitors":ti,ab OR Revatio:ti,ab OR Sildenafil:ti,ab OR Staxyn:ti,ab OR Tadalafil:ti,ab OR "UK 9248010":ti,ab OR Vardenafil:ti,ab OR Viagra:ti,ab OR Vivanza:ti,ab OR Vizarsin:ti,ab	3296
16	OR/11-15	3399
17	6 AND 10 AND 16	71
18	monotherapy:ti,ab	21 803
19	10 OR 16	4265
20	18 AND 19	175
22	3 AND 17 AND 20	41

Continued

13.2. Literature search strategies for PICO II

13.2.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	pulmonary[tiab] AND hypertensi*[tiab]	58 338
3	1 OR 2	65 794
4	"Phosphodiesterase 5 Inhibitors"[Mesh] OR "Sildenafil Citrate"[Mesh] OR "Tadalafil"[Mesh] OR "Vardenafil Dihydrochloride"[Mesh]	8411
5	"Phosphodiesterase 5 Inhibitors" [Pharmacological Action]	8485
6	"avanafil"[Supplementary Concept]	59
7	Acetildenafil[tiab] OR Avanafil[tiab] OR Cialis[tiab] OR Desmethylsildenafil[tiab] OR Homosildenafil[tiab] OR Hydroxyhomosildenafil[tiab] OR IC351[tiab] OR Levitra[tiab] OR NCX911[tiab] OR "PDE5I"[tiab] OR "PDE5"[tiab] OR "phosphodiesterase type 5"[tiab] OR Revatio[tiab] OR Sildenafil[tiab] OR Staxyn[tiab] OR Stendra[tiab] OR Tadalafil[tiab] OR "UK 9248010"[tiab] OR Vardenafil[tiab] OR Viagra[tiab]	11 533
8	OR/4-7	12 874
9	"Heart Diseases"[Mesh] OR "Heart Failure"[Mesh]	1 156 314
10	(cardiac[tiab] OR heart[tiab]) AND (disease*[tiab] OR failure[tiab])	538 438
11	9 OR 10	1 374 722
12	"preserved ejection fraction"[tiab]	5068
13	11 AND 12	4990
14	HFpEF[tiab]	3096
15	13 OR 14	5516
16	3 AND 8 AND 15	37

Continued

17	"Animals"[Mesh] NOT "Humans"[Mesh]	NA
18	21 NOT 22	37
19	English[lang]	NA
20	23 AND 24	36
21	1990/1/1:3000/12/31[pdat]	NA
22	25 AND 26	36

13.2.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	MeSH descriptor: [Phosphodiesterase 5 Inhibitors] explode all trees	382
5	MeSH descriptor: [Sildenafil Citrate] explode all trees	962
6	MeSH descriptor: [Tadalafil] explode all trees	431
7	MeSH descriptor: [Vardenafil Dihydrochloride] explode all trees	174
8	Acetildenafil:ti,ab OR Avanafil:ti,ab OR Cialis:ti,ab OR Desmethylsildenafil:ti,ab OR Homosildenafil:ti,ab OR Hydroxyhomosildenafil:ti,ab OR IC351:ti,ab OR Levitra:ti,ab OR NCX911:ti,ab OR "PDE5I":ti,ab OR "PDE5 inhibitors":ti,ab OR "phosphodiesterase type 5 inhibitors":ti,ab OR Revatio:ti,ab OR Sildenafil:ti,ab OR Staxyn:ti,ab OR Stendra:ti,ab OR Tadalafil:ti,ab OR "UK 9248010":ti,ab OR Vardenafil:ti,ab OR Viagra:ti,ab	3344
9	OR/4-8	3443
10	MeSH descriptor: [Heart Failure] explode all trees	9646
11	MeSH descriptor: [Heart Diseases] explode all trees	53 374
12	(cardiac:ti,ab OR heart:ti,ab) AND (disease*:ti,ab OR failure:ti,ab)	64 506
13	OR/10-12	98 071
14	"preserved ejection fraction":ti,ab	964
15	13 AND 14	949
16	HFpEF:ti,ab	754
17	14 OR 15	1087
18	3 AND 9 AND 17	24

13.3. Literature search strategies for PICO III

13.3.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	(pulmonary[tiab] AND hypertensi*[tiab])	58 338
3	1 OR 2	65 794
4	"Phosphodiesterase 5 Inhibitors"[Mesh] OR "Sildenafil Citrate"[Mesh] OR "Tadalafil"[Mesh] OR "Vardenafil Dihydrochloride"[Mesh]	8411
5	"Phosphodiesterase 5 Inhibitors" [Pharmacological Action]	8485
6	"avanafil"[Supplementary Concept]	59
7	Acetildenafil[tiab] OR Avanafil[tiab] OR Cialis[tiab] OR Desmethylsildenafil[tiab] OR Homosildenafil[tiab] OR Hydroxyhomosildenafil[tiab] OR IC351[tiab] OR Levitra[tiab] OR NCX911[tiab] OR "PDE5I"[tiab] OR "PDE5"[tiab] OR "phosphodiesterase type 5"[tiab] OR Revatio[tiab] OR Sildenafil[tiab] OR Staxyn[tiab] OR Stendra[tiab] OR Tadalafil[tiab] OR "UK 9248010"[tiab] OR Vardenafil[tiab] OR Viagra[tiab]	11 533
8	OR/4-7	12 874
9	"Lung Diseases, Interstitial"[Mesh]	57 008
10	(lung[tiab] OR pulmonary[tiab] OR pneumonia*[tiab]) AND (interstitial[tiab] OR idiopathic[tiab] OR fibro*[tiab])	103 277
11	9 OR 10	147 813
12	3 AND 8 AND 11	405
13	"Animals"[Mesh] NOT "Humans"[Mesh]	NA
14	12 NOT 13	384
15	English[lang]	NA
16	14 AND 15	342
17	1990/1/1:3000/12/31[pdat]	NA
18	16 AND 17	342

13.3.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	MeSH descriptor: [Phosphodiesterase 5 Inhibitors] explode all trees	382
5	MeSH descriptor: [Sildenafil Citrate] explode all trees	962
6	MeSH descriptor: [Tadalafil] explode all trees	431
7	MeSH descriptor: [Vardenafil Dihydrochloride] explode all trees	174
8	Acetildenafil:ti,ab OR Avanafil:ti,ab OR Cialis:ti,ab OR Desmethylsildenafil:ti,ab OR Homosildenafil:ti,ab OR Hydroxyhomosildenafil:ti,ab OR IC351:ti,ab OR Levitra:ti,ab OR NCX911:ti,ab OR "PDE5I":ti,ab OR "PDE5":ti,ab OR "phosphodiesterase type 5":ti,ab OR Revatio:ti,ab OR Sildenafil:ti,ab OR Staxyn:ti,ab OR Stendra:ti,ab OR Tadalafil:ti,ab OR "UK 9248010":ti,ab OR Vardenafil:ti,ab OR Viagra:ti,ab	3344
9	OR/4-8	3443
10	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	781
11	(lung:ti,ab OR pulmonary:ti,ab OR pneumonia*:ti,ab) AND (interstitial:ti,ab OR idiopathic:ti,ab OR fibro*:ti,ab)	6424
12	10 OR 11	6828
13	3 AND 9 AND 12	123

13.4. Literature search strategies for PICO IV

13.4.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	"chronic thromboembolic pulmonary hypertension"[tiab] OR CTEPH[tiab]	2331
3	1 OR 2	38 031
4	"Angioplasty, Balloon"[Mesh]	53 390
5	"balloon pulmonary angioplasty"[tiab]	3483
6	4 OR 5	53 527
7	"Drug Therapy"[Mesh]	1 393 014
8	"drug therapy" [Subheading]	2 298 054
9	drug therap*[tiab] OR medical therap*[tiab] OR pulmonary vasodilator therap*[tiab] OR targeted therap*[tiab]	139 797
10	OR/7-9	3 124 966
8	3 AND 6 AND 10	71
9	"Animals"[Mesh] NOT "Humans"[Mesh]	NA
10	8 NOT 9	71
11	English[lang]	NA
12	10 AND 11	67
13	1990/1/1:3000/12/31[pdat]	NA
14	12 AND 13	67

Continued

13.4.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	"chronic thromboembolic pulmonary hypertension":ti,ab OR CTEPH:ti,ab	243
3	1 OR 2	1370
4	MeSH descriptor: [Angioplasty, Balloon] explode all trees	4117
5	"balloon pulmonary angioplasty":ti,ab	24
6	4 OR 5	4138
7	MeSH descriptor: [Drug Therapy] explode all trees	142 349
8	Any MeSH descriptor in all MeSH products and with qualifier(s): [drug therapy - DT]	204 370
9	drug therap*:ti,ab OR medical therap*:ti,ab OR pulmonary vasodilator therap*:ti,ab OR targeted therap*:ti,ab	231 579
10	OR/7-9	404 809
11	3 AND 6 AND 10	8

13.5. Literature search strategies for key narrative question 1

13.5.1. Search strategies (main)

Data sources

The following were searched from 1 January 1946 to 1 November 2020 for English language, peer-reviewed publications: Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. Six different analyses for six different questions were performed.

The first research question looked into the **prognostic relevance of pulmonary vascular resistance**. The following keywords and Medical Subject Heading terms (MESH) were used:

'pulmonary vascular resistance (MESH)', 'total pulmonary resistance', 'PVR', 'TPR', 'total pulmonary vascular resistance', 'mortality (MESH)', 'prognosis', 'outcome', 'death', 'prognos*', 'survival', 'Pulmonary Hypertension (MESH)', 'Pulmonary Artery Hypertension', and 'Pulmonary Arterial Hypertension'.

The second research question was about the **prognostic relevance of mPAP**. The following keywords and MESH terms were used: 'mean pulmonary arterial pressure (MESH)', 'Pulmonary Arterial Pressure', 'mPAP', 'meanPAP', 'mean pulmonary arterial pressure', 'mean pulmonary artery pressure', 'PAPm', 'Pulmonary Artery Pressure', 'Pulmonary Hypertension (MESH)', 'Pulmonary Artery Hypertension', 'Pulmonary Arterial Hypertension', 'mortality (MESH)', 'prognosis', 'outcome', 'death', 'prognos*', 'survival', 'Pulmonary Hypertension (MESH)', 'Pulmonary Artery Hypertension', and 'Pulmonary Arterial Hypertension'.

The third research question included the **prognostic relevance of PAWP**. The following keywords and MESH terms were used: 'pulmonary arterial wedge pressure (MESH)', 'pulmonary wedge pressure', 'pulmonary artery wedge pressure', 'PAWP', 'Pulmonary Capillary Wedge Pressure', 'pulmonary capillary pressure', 'pulmonary artery occlusion pressure', 'PAOP', 'PCWP', 'pulmonary arterial occlusion pressure', 'pulmonary venous wedge pressure', 'PVWP', 'pulmonary venous pressure', 'lung venous pressure', 'mortality (MESH)', 'prognosis', 'outcome', 'death', 'prognos*', 'survival', 'Pulmonary Hypertension (MESH)', 'Pulmonary Artery Hypertension', and 'Pulmonary Arterial Hypertension'.

The fourth research question focused on **normative values of PVR** in healthy subjects measured by RHC. The following keywords and MESH terms were used: 'right heart catheterization (MESH)', 'pulmonary catheter', 'pulmonar* arter* cathet*', 'right heart catheter*', 'right cardiac* cathet*', 'cardiac* cathet*', 'healthy (MESH)', 'health', 'normal', 'normative', 'athletes', 'pulmonary vascular resistance (MESH)', 'total pulmonary resistance', 'PVR', 'TPR', and 'total pulmonary vascular resistance'.

The fifth research question investigated the **normative values of mPAP** in healthy subjects by RHC. The following keywords and MESH terms were used: 'right heart catheterization (MESH)', 'pulmonary catheter', 'pulmonar* arter* cathet*', 'right heart catheter*', 'right cardiac* cathet*', 'cardiac* cathet*', 'healthy (MESH)', 'health', 'normal', 'normative', 'athletes', 'mean pulmonary arterial pressure (MESH)', 'Pulmonary Arterial Pressure', 'Pulmonary Artery Pressure', 'mPAP', 'meanPAP', 'mean pulmonary arterial pressure', 'mean pulmonary artery pressure', and 'PAPm'.

The sixth research question looked into the **normative values of PAWP** in healthy subjects by RHC. The following keywords and MESH terms were used: 'right heart catheterization (MESH)', 'pulmonary catheter', 'pulmonar* arter* cathet*', 'right heart catheter*', 'right cardiac* cathet*', 'cardiac* cathet*', 'healthy (MESH)', 'health', 'normal', 'normative', 'athletes', 'pulmonary arterial wedge pressure (MESH)', 'pulmonary wedge pressure', 'pulmonary artery wedge pressure', 'PAWP', 'Pulmonary Capillary Wedge Pressure', 'pulmonary capillary pressure', 'pulmonary artery occlusion pressure', 'PAOP', 'PCWP', 'pulmonary arterial occlusion pressure', 'pulmonary venous wedge pressure', 'PVWP', 'pulmonary venous pressure', and 'lung venous pressure'.

Study selection

Prognostic studies were included if: (1) pulmonary haemodynamics were assessed by RHC, with at least one valid measurement at rest and (2) the end-point of prognosis was mortality. Studies on normative data were included if: (1) pulmonary haemodynamics were assessed by RHC, with at least one valid measurement at rest and (2) the study included at least one group of subjects that were claimed as healthy.

Data extraction and quality assessment

Study eligibility and quality were evaluated by two physicians independently. Data extraction was performed by the same physicians using standardized data collection sheets. Disagreements were resolved by consensus.

Outcomes

The primary outcome of interest for the prognostic questions was all-cause mortality. The primary outcome of interest of the normative values was pulmonary haemodynamics in healthy subjects.

Acknowledgements

We thank Dr Katarina Zeder and Gregor Steinrisser for their help in performing the systematic literature review.

13.5.2. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hemodynamics"[Mesh]	690 654
2	hemodynamic*[tiab] OR haemodynamic*[tiab]	185 657
3	1 OR 2	771 723
4	pulmonary[tiab]	567 245
5	3 AND 4	65 576
6	"Hypertension, Pulmonary"[Mesh]	37 397
7	(pulmonary[tiab] AND hypertensi*[tiab])	58 338
8	6 OR 7	65 794
9	"Cardiac Catheterization"[Mesh]	51 836
10	(arter*[tiab] OR cardiac[tiab] OR heart[tiab] OR pulmonary[tiab]) AND catheter*[tiab]	98 496
11	9 OR 10	130 210
12	right[tiab]	551 254
13	11 AND 12	27 174
14	"Arterial Pressure"[Mesh] OR "Pulmonary Wedge Pressure"[Mesh] OR "Vascular Resistance"[Mesh]	51 128
15	"arterial pressure"[tiab] OR "artery pressure"[tiab] OR "mean pulmonary arterial pressure"[tiab] OR "mean pulmonary artery pressure"[tiab] OR "pulmonary arterial pressure"[tiab] OR "pulmonary artery pressure"[tiab] OR "pulmonary vascular resistance"[tiab] OR "pulmonary wedge pressure"[tiab] OR "vascular resistance"[tiab] OR "wedge pressure"[tiab]	96 579
16	14 OR 15	126 089
17	5 AND 8 AND 13 AND 16	2085
18	"Animals"[Mesh] NOT "Humans"[Mesh]	NA
19	17 NOT 18	1926
20	English[lang]	NA
21	19 AND 20	1703

Continued

22	1990/1/1:3000/12/31[pdat]	NA
23	21 AND 22	1566
24	health*[tiab] OR normal*[tiab] OR normative*[tiab]	4 748 751
25	"burden of disease*"[tiab] OR death*[tiab] OR mortalit*[tiab] OR outcome*[tiab] OR prognos*[tiab] OR surviv*[tiab]	4 065 820
26	24 OR 25	7 845 557
27	23 AND 26	982

13.5.3. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hemodynamics] explode all trees	51 982
2	hemodynamic*:ti,ab OR haemodynamic*:ti,ab	30 916
3	1 OR 2	73 224
4	pulmonary:ti,ab	47 656
5	3 AND 4	5472
6	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
7	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
8	6 OR 7	4743
9	MeSH descriptor: [Cardiac Catheterization] explode all trees	1344
10	(arter*:ti,ab OR cardiac:ti,ab OR heart:ti,ab OR pulmonary:ti,ab) AND catheter*:ti,ab	9982
11	9 OR 10	10 585
12	right:ti,ab	27 832
13	11 AND 12	1658
14	MeSH descriptor: [Arterial Pressure] explode all trees	434
15	MeSH descriptor: [Pulmonary Wedge Pressure] explode all trees	380
16	MeSH descriptor: [Vascular Resistance] explode all trees	2060
17	"arterial pressure":ti,ab OR "artery pressure":ti,ab OR "mean pulmonary arterial pressure":ti,ab OR "mean pulmonary artery pressure":ti,ab OR "pulmonary arterial pressure":ti,ab OR "pulmonary artery pressure":ti,ab OR "pulmonary vascular resistance":ti,ab OR "pulmonary wedge pressure":ti,ab OR "vascular resistance":ti,ab OR "wedge pressure":ti,ab	14 614
18	OR/14-17	15 794
19	5 AND 8 AND 13 AND 18	196
20	health*:ti,ab OR normal*:ti,ab OR normative*:ti,ab	410 308
21	"burden of disease*":ti,ab OR death*:ti,ab OR mortalit*:ti,ab OR outcome*:ti,ab OR prognos*:ti,ab OR surviv*:ti,ab	600 251
22	20 OR 21	835 523
23	19 AND 22	115
24	1990-current	NA
25	23 OR 24	114

Continued

13.6. Literature search strategies for key narrative question 2

13.6.1. Search strategies (main)

13.6.1.1. Cardiopulmonary exercise testing in pulmonary hypertension for diagnosis

STEP 1

Entry terms (PubMed):

(Pulmonary hypertension diagnosis) AND (Cardiopulmonary Exercise Testing)

Search results: 1845 journal articles

Search conducted: February 2021

STEP 2

Filters (PubMed):

- Results by years 1996–2021

Search results: 1618 journal articles

Search conducted: February 2021

- ((english[Filter]) AND (humans[Filter]) AND (adult: 19+years[Filter]))

Search results: 1130 journal articles

Search conducted: February 2021

STEP 3

Eligible criteria (abstract and title review):

Inclusion criteria:

- Original articles on PH patients
- Pulmonary hypertension diagnosis based on RHC
- Results from studies with sample size PAH cohorts ≥20 patients
- CPET variables associated with PH diagnosis

Exclusion criteria:

- Results from studies with sample size PAH cohorts <20 patients
- Pulmonary hypertension diagnosis based on echocardiography

Search results: nine journal articles

Search conducted: February 2021

STEP 4

Methodological criteria

- CPET used as a tool in suspected patients for PAH
- Increased accuracy of standard criteria for diagnosis of mPAP >20 mmHg

Search results: two journal articles

Search conducted: February 2021

Supplementary research strategy

Between STEP 2 and STEP 3 supplementary searches were conducted:

- PubMed similar articles function
- References from systematic reviews
- Manual searching for known studies

Search results: three journal articles
Search conducted: February 2021

13.6.1.2. Echocardiography in pulmonary hypertension for diagnosis

Search strategy

STEP 1

Entry terms (PubMed):

((("Pulmonary Hypertension Diagnosis"[Mesh]) OR ("pulmonary hypertension diagnosis") AND "Echocardiography"[Mesh]))

Search results: 6025 journal articles
Search conducted: February 2021

STEP 2

Filters (PubMed):

- Results by years 1996–2021

Search results: 5016 journal articles
Search conducted: February 2021

- ((english[Filter]) AND (humans[Filter]) AND (adult: 19+years[Filter]))

Search results: 3009 journal articles
Search conducted: February 2021

STEP 3

Eligible criteria (abstract and title review):

Inclusion criteria:

- Original articles on PH patients
- Pulmonary hypertension diagnosis based on RHC
- Results from studies with sample size PAH cohorts ≥20 patients

Exclusion criteria:

- Results from studies with sample size PAH cohorts <20 patients
- Pulmonary hypertension diagnosis based on echocardiography

Search results: 67 journal articles
Search conducted: February 2021

STEP 4

Methodological criteria (full manuscript review)

- One or more echocardiographic variable(s) of PH signs, according to the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
- Peak TR velocity
- Right ventricle/LV basal diameter ratio >1.0
- Flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole)
- Right ventricular outflow Doppler acceleration time <105 msec and/or mid-systolic notching
- Early diastolic pulmonary regurgitation velocity >2.2 m/sec
- PA diameter >25 mm
- Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration
- Right atrial area (end-systole) >18 cm^2
- Compared with new methodological criteria for increased accuracy to detect mPAP >20 mmHg

Search results: 0
Search conducted: February 2021

13.6.2. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"pulmonary arterial hypertension"[tiab]	12 889
2	"Echocardiography"[Mesh]	139 477
3	echocardiograph*[tiab]	147 529
4	2 OR 3	199 865
5	"Diagnosis"[Mesh]	8 755 313
6	"diagnosis" [Subheading]	3 668 679
7	probability[tiab] OR diagnos*[tiab]	2 812 268
8	OR/5-7	10 779 000
9	"Cardiac Catheterization"[Mesh]	51 836
10	(arter*[tiab] OR cardiac[tiab] OR heart[tiab] OR pulmonary[tiab]) AND catheter*[tiab]	98 496
11	9 OR 10	130 210
12	right[tiab]	551 254
13	11 AND 12	27 174
14	1 AND 4 AND 8 AND 13	576
15	English[lang]	NA
16	14 AND 15	498
17	1990/1/1:3000/12/31[pdat]	NA
18	16 AND 17	487

13.6.3. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	"pulmonary arterial hypertension":ti,ab	1446
2	MeSH descriptor: [Echocardiography] explode all trees	4188
3	echocardiograph*:ti,ab	11 369
4	2 OR 3	2969
5	MeSH descriptor: [Diagnosis] explode all trees	337 591
6	Any MeSH descriptor in all MeSH products and with qualifier(s): [diagnosis - DI]	52 946
7	probability:ti,ab OR diagnos*:ti,ab	163 468
8	OR/5-7	479 699
9	MeSH descriptor: [Cardiac Catheterization] explode all trees	1344
10	(arter*:ti,ab OR cardiac:ti,ab OR heart:ti,ab OR pulmonary:ti,ab) AND catheter*:ti,ab	9982
11	9 OR 10	10 585
12	right:ti,ab	27 832
13	11 AND 12	1658
14	1 AND 4 AND 8 AND 13	1

13.7. Literature search strategies for key narrative question 3

13.7.1. Search strategies (main)

Ovid SP was used to search MEDLINE on 28 October 2020. Search terms were: 'pulmonary hypertension' or 'pulmonary arterial hypertension' AND 'systemic sclerosis' or 'scleroderma' or 'connective tissue disease' AND 'detection' or 'screening' or 'diagnosis'

13.7.2. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	(pulmonary[tiab] AND hypertensi*[tiab])	58 338
3	1 OR 2	65 794
4	"Scleroderma, Systemic"[Mesh]	21 086
5	((diffuse[tiab] OR limited[tiab] OR systemic[tiab]) AND (scleroderma[tiab] OR sclerosis[tiab])) OR "CREST Syndrome"[tiab]	30 165
6	4 OR 5	37 527
7	screen*[tiab] OR detect*[tiab]	3 065 944
8	3 AND 6 AND 7	480
9	English[lang]	NA
10	8 AND 9	433
11	1990/1/1:3000/12/31[pdat]	NA
12	10 AND 11	427

13.7.3. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	MeSH descriptor: [Scleroderma, Systemic] explode all trees	577
5	((diffuse:ti,ab OR limited:ti,ab OR systemic:ti,ab) AND (scleroderma:ti,ab OR sclerosis:ti,ab)) OR "CREST Syndrome":ti,ab	2055
6	4 OR 5	2152
7	screen*:ti,ab OR detect*:ti,ab	147 955
8	3 AND 6 AND 7	30

13.8. Literature search strategies for key narrative question 4

13.8.1. Search strategies (main)

i.) EMBASE

PAH, 268 results (with filters): 18 January 2021

Search terms: ('pulmonary arterial hypertension' OR 'pulmonary artery hypertension' OR 'pah') AND ('risk assessment'/exp OR 'risk algorithm'/exp OR 'risk score' OR 'risk stratification') AND ('therapy' OR 'prognosis' OR 'survival' OR 'mortality' OR 'outcome' OR 'outcomes') AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [english]/lim AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim

ii.) PubMed

PAH, 191 results (with filters): 18 January 2021

Search terms: ((("Pulmonary Arterial Hypertension"[Mesh]) OR ("pulmonary arterial hypertension" OR "pulmonary artery hypertension" OR "PAH")) AND (((((("Risk Assessment"[Mesh]) OR ("risk assessment")) OR ("risk stratification")) OR ("risk score")) OR ("risk algorithm"))) AND ((((((("Therapeutics"[Mesh]) OR ("Survival"[Mesh])) OR ("Prognosis"[Mesh])) OR ("Mortality"[Mesh])) OR ("outcomes")) OR ("outcome")) AND ((humans[Filter]) AND (english[Filter])) AND ((humans[Filter]) AND (english[Filter]) AND (alladult[Filter]))

13.8.2. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Majr]	29 328
2	(pulmonary[ti] AND hypertensi*[ti])	26 904
3	1 OR 2	33 957
4	"Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension"[tiab] OR COMPERA[tiab] OR (French[tiab] AND (invasive[tiab] OR noninvasive[tiab])) OR "Registry to Evaluate Early and Long-term PAH Disease Management"[tiab] OR "REVEAL 2.0"[tiab] OR "REVEAL Registry"[tiab] OR "REVEAL Risk Score"[tiab] OR "risk assessment "[tiab] OR "risk stratification"[tiab] OR SPAHR OR "Swedish PAH Registry"[tiab]	105 333
5	3 AND 4	343
6	(("Adolescent Medicine"[Mesh] OR "Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])	NA
7	5 NOT 6	332
8	"Animals"[Mesh] NOT "Humans"[Mesh]	NA
9	7 NOT 8	330
10	English[lang]	NA
11	9 AND 10	314
12	1990/1/1:3000/12/31[pdat]	NA
13	11 AND 12	314

13.8.3. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	"Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension":ti,ab OR COMPERA:ti,ab OR (French:ti,ab AND (invasive:ti,ab OR noninvasive:ti,ab)) OR "Registry to Evaluate Early and Long-term PAH Disease Management":ti,ab OR "REVEAL 2.0":ti,ab OR "REVEAL Registry":ti,ab OR "REVEAL Risk Score":ti,ab OR "risk assessment ":ti,ab OR "risk stratification":ti,ab OR SPAHR OR "Swedish PAH Registry":ti,ab	4407
5	3 AND 4	53

13.9. Literature search strategies for key narrative question 5

13.9.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	(pulmonary[tiab] AND hypertensi*[tiab])	58 338
3	1 OR 2	65 794
4	"Heart Failure"[Mesh] OR "Heart Valve Diseases"[Mesh] OR "Ventricular Dysfunction, Left"[Mesh]	365 189
5	((heart[tiab] OR ventricular[tiab]) AND (disease[tiab] OR dysfunction[tiab] OR failure[tiab]))	484 668
6	4 OR 5	617 809
7	left[tiab]	698 310
8	6 AND 7	150 116
9	"Atrasentan"[Mesh] OR "Bosentan"[Mesh] OR "Endothelin Receptor Antagonists"[Mesh]	5883
10	"Endothelin Receptor Antagonists"[Pharmacological Action]	5901
11	"A 192621"[Supplementary Concept] OR "ambrisentan"[Supplementary Concept] OR "BQ 788"[Supplementary Concept] OR "cyclo(Trp-Asp-Pro-Val-Leu)"[Supplementary Concept] OR "macitentan"[Supplementary Concept] OR "ZD4054"[Supplementary Concept]	2205
12	A127722[tiab] OR A147627[tiab] OR A192621[tiab] OR ABT627[tiab] OR Ambrisentan[tiab] OR Atrasentan[tiab] OR Bosentan[tiab] OR BQ-123[tiab] OR BQ-788[tiab] OR BSF208075[tiab] OR "cyclo(D-Trp-D-Asp-Pro-D-Val-Leu)"[tiab] OR "endothelin receptor antagonists"[tiab] OR GSK1325760A[tiab] OR Letairis[tiab] OR LU208075[tiab] OR macitentan[tiab] OR opsumit[tiab] OR "Ro 470203"[tiab] OR Sitaxentan[tiab] OR Tracleer[tiab] OR Xinlay[tiab] OR Zibotentan[tiab]	5558
13	OR/9-12	8350
14	"Phosphodiesterase 5 Inhibitors"[Mesh] OR "Sildenafil Citrate"[Mesh] OR "Tadalafil"[Mesh] OR "Vardenafil Dihydrochloride"[Mesh]	8411
15	"Phosphodiesterase 5 Inhibitors" [Pharmacological Action]	8485
16	"avanafil"[Supplementary Concept]	59
17	Acetildenafil[tiab] OR Avanafil[tiab] OR Cialis[tiab] OR Desmethylsildenafil[tiab] OR Homosildenafil[tiab] OR Hydroxyhomosildenafil[tiab] OR IC351[tiab] OR Levitra[tiab] OR NCX911[tiab] OR "PDE5I"[tiab] OR "PDE5 inhibitors"[tiab] OR "phosphodiesterase type 5 inhibitors"[tiab] OR Revatio[tiab] OR Sildenafil[tiab] OR Staxyn[tiab] OR Stendra[tiab] OR Tadalafil[tiab] OR "UK 9248010"[tiab] OR Vardenafil[tiab] OR Viagra[tiab]	10 470
18	OR/14-17	12 090
19	"Soluble Guanylyl Cyclase"[Mesh]	1147
20	"BAY 58-2667"[Supplementary Concept] OR "riociguat"[Supplementary Concept] OR "SgcA protein, Dictyostelium discoideum"[Supplementary Concept] OR "vericiguat"[Supplementary Concept]	313
21	adempas[tiab] OR cinaciguat[tiab] OR "guanylate cyclase"[tiab] OR riociguat[tiab] OR vericiguat[tiab] OR verquvo[tiab]	7874
22	OR/19-21	8518
23	"Epoprostenol"[Mesh] OR "Iloprost"[Mesh] OR "Receptors, Epoprostenol"[Mesh]	14 245
24	"treprostinil"[Supplementary Concept]	366
25	ciloprost[tiab] OR flolan[tiab] OR orenitram[tiab] OR prostacyclin[tiab] OR remodulin[tiab] OR veletri[tiab] OR ventavis[tiab]	14 391
26	OR/23-25	20 053
27	13 OR 18 OR 22 OR 26	46 639
28	3 AND 8 AND 27	376
29	English[lang]	NA
30	28 AND 29	342
31	1990/1/1:3000/12/31[pdat]	NA
32	30 AND 31	340

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13.9.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	MeSH descriptor: [Heart Failure] explode all trees	9646
5	MeSH descriptor: [Heart Valve Diseases] explode all trees	2132
6	MeSH descriptor: [Ventricular Dysfunction, Left] explode all trees	1988
7	((heart:ti,ab OR ventricular:ti,ab) AND (disease:ti,ab OR dysfunction:ti,ab OR failure:ti,ab))	57 320
8	OR/4-7	60 144
9	left:ti,ab	46 240
10	8 AND 9	14 510
11	MeSH descriptor: [Atrasentan] explode all trees	39
12	MeSH descriptor: [Bosentan] explode all trees	190
13	MeSH descriptor: [Endothelin Receptor Antagonists] explode all trees	275
14	A127722:ti,ab OR A147627:ti,ab OR A192621:ti,ab OR ABT627:ti,ab OR Ambrisentan:ti,ab OR Atrasentan:ti,ab OR Bosentan:ti,ab OR BQ-123:ti,ab OR BQ-788:ti,ab OR BSF208075:ti,ab OR "cyclo(D-Trp-D-Asp-Pro-D-Val-Leu)":ti,ab OR "endothelin receptor antagonists":ti,ab OR GSK1325760A:ti,ab OR Letairis:ti,ab OR LU208075:ti,ab OR macitentan:ti,ab OR opsumit:ti,ab OR "Ro 470203":ti,ab OR Sitaxentan:ti,ab OR Tracleer:ti,ab OR Xinlay:ti,ab OR Zibotentan:ti,ab	1075
15	MeSH descriptor: [Phosphodiesterase 5 Inhibitors] explode all trees	382
16	MeSH descriptor: [Sildenafil Citrate] explode all trees	962
17	MeSH descriptor: [Tadalafil] explode all trees	431
18	MeSH descriptor: [Vardenafil Dihydrochloride] explode all trees	174
19	Acetildenafil:ti,ab OR Avanafil:ti,ab OR Cialis:ti,ab OR Desmethylsildenafil:ti,ab OR Homosildenafil:ti,ab OR Hydroxyhomosildenafil:ti,ab OR IC351:ti,ab OR Levitra:ti,ab OR NCX911:ti,ab OR "PDE5I":ti,ab OR "PDE5 inhibitors":ti,ab OR "phosphodiesterase type 5 inhibitors":ti,ab OR Revatio:ti,ab OR Sildenafil:ti,ab OR Staxyn:ti,ab OR Stendra:ti,ab OR Tadalafil:ti,ab OR "UK 9248010":ti,ab OR Vardenafil:ti,ab OR Viagra:ti,ab	3344
20	MeSH descriptor: [Soluble Guanylyl Cyclase] explode all trees	14
21	adempas:ti,ab OR cinaciguat:ti,ab OR "guanylate cyclase":ti,ab OR riociguat:ti,ab OR vericiguat:ti,ab OR verquvo:ti,ab	415
22	MeSH descriptor: [Epoprostenol] explode all trees	527
23	MeSH descriptor: [Iloprost] explode all trees	224
24	MeSH descriptor: [Receptors, Epoprostenol] explode all trees	9
25	ciloprost:ti,ab OR flolan:ti,ab OR orenitram:ti,ab OR prostacyclin:ti,ab OR remodulin:ti,ab OR veletri:ti,ab OR ventavis:ti,ab	1184
26	OR/11-25	6140
27	3 AND 4 AND 10	141

13.10. Literature search strategies for key narrative question 6

13.10.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	39 397
2	pulmonary[tiab] AND hypertensi*[tiab]	58 338
3	1 OR 2	65 794
4	"Pulmonary Disease, Chronic Obstructive"[Mesh]	57 844
5	"Chronic Obstructive Pulmonary Disease"[tiab] OR COPD[tiab]	67 781
6	4 OR 5	88 997
7	"Atrasentan"[Mesh] OR "Bosentan"[Mesh] OR "Endothelin Receptor Antagonists"[Mesh]	5883
8	"Endothelin Receptor Antagonists"[Pharmacological Action]	5901
9	"A 192621"[Supplementary Concept] OR "ambrisentan"[Supplementary Concept] OR "BQ 788"[Supplementary Concept] OR "cyclo(Trp-Asp-Pro-Val-Leu)"[Supplementary Concept] OR "macitentan"[Supplementary Concept] OR "ZD4054"[Supplementary Concept]	2205
10	A127722[tiab] OR A147627[tiab] OR A192621[tiab] OR ABT627[tiab] OR Ambrisentan[tiab] OR Atrasentan[tiab] OR Bosentan[tiab] OR BQ-123[tiab] OR BQ-788[tiab] OR BSF208075[tiab] OR "cyclo(D-Trp-D-Asp-Pro-D-Val-Leu)"[tiab] OR "endothelin receptor antagonists"[tiab] OR GSK1325760A[tiab] OR Letairis[tiab] OR LU208075[tiab] OR macitentan[tiab] OR opsumit[tiab] OR "Ro 470203"[tiab] OR Sitaxentan[tiab] OR Tracleer[tiab] OR Xinlay[tiab] OR Zibotentan[tiab]	5558
11	OR/7-10	8350
12	"Phosphodiesterase 5 Inhibitors"[Mesh] OR "Sildenafil Citrate"[Mesh] OR "Tadalafil"[Mesh] OR "Vardenafil Dihydrochloride"[Mesh]	8411
13	"Phosphodiesterase 5 Inhibitors" [Pharmacological Action]	8485
14	"avanafil" [Supplementary Concept]	59
15	Acetildenafil[tiab] OR Avanafil[tiab] OR Cialis[tiab] OR Desmethylsildenafil[tiab] OR Homosildenafil[tiab] OR Hydroxyhomosildenafil[tiab] OR IC351[tiab] OR Levitra[tiab] OR NCX911[tiab] OR "PDE5I"[tiab] OR "PDE5 inhibitors"[tiab] OR "phosphodiesterase type 5 inhibitors"[tiab] OR Revatio[tiab] OR Sildenafil[tiab] OR Staxyn[tiab] OR Stendra[tiab] OR Tadalafil[tiab] OR "UK 9248010"[tiab] OR Vardenafil[tiab] OR Viagra[tiab]	10 470
16	OR/12-15	12 090
17	"Soluble Guanylyl Cyclase"[Mesh]	1147
18	"BAY 58-2667" [Supplementary Concept] OR "riociguat" [Supplementary Concept] OR "SgcA protein, Dictyostelium discoideum" [Supplementary Concept] OR "vericiguat" [Supplementary Concept]	313

Continued

19	adempas[tiab] OR cinaciguat[tiab] OR "guanylate cyclase"[tiab] OR riociguat[tiab] OR vericiguat[tiab] OR verquvo[tiab]	7874
20	OR/17-19	8518
21	"Epoprostenol"[Mesh] OR "Iloprost"[Mesh] OR "Receptors, Epoprostenol"[Mesh]	14 245
22	"treprostinil" [Supplementary Concept]	366
23	ciloprost[tiab] OR flolan[tiab] OR orenitram[tiab] OR prostacyclin[tiab] OR remodulin[tiab] OR veletri[tiab] OR ventavis[tiab]	14 391
24	OR/21-23	20 053
25	11 OR 16 OR 20 OR 24	46 639
26	3 AND 6 AND 25	134
27	English[lang]	NA
28	26 AND 27	122
29	1990/1/1:3000/12/31[pdat]	NA
30	28 AND 29	120

13.10.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	5855
5	"Chronic Obstructive Pulmonary Disease":ti OR COPD:ti	15 260
6	4 OR 5	16 651
7	MeSH descriptor: [Atrasentan] explode all trees	39
8	MeSH descriptor: [Bosentan] explode all trees	190
9	MeSH descriptor: [Endothelin Receptor Antagonists] explode all trees	275
10	A127722:ti,ab OR A147627:ti,ab OR A192621:ti,ab OR ABT627:ti,ab OR Ambrisentan:ti,ab OR Atrasentan:ti,ab OR Bosentan:ti,ab OR BQ-123:ti,ab OR BQ-788:ti,ab OR BSF208075:ti,ab OR "cyclo(D-Trp-D-Asp-Pro-D-Val-Leu)":ti,ab OR "endothelin receptor antagonists":ti,ab OR GSK1325760A:ti,ab OR Letairis:ti,ab OR LU208075:ti,ab OR macitentan:ti,ab OR opsumit:ti,ab OR "Ro 470203":ti,ab OR Sitaxentan:ti,ab OR Tracleer:ti,ab OR Xinlay:ti,ab OR Zibotentan:ti,ab	1075
11	MeSH descriptor: [Phosphodiesterase 5 Inhibitors] explode all trees	382
12	MeSH descriptor: [Sildenafil Citrate] explode all trees	962
13	MeSH descriptor: [Tadalafil] explode all trees	431
14	MeSH descriptor: [Vardenafil Dihydrochloride] explode all trees	174
15	Acetildenafil:ti,ab OR Avanafil:ti,ab OR Cialis:ti,ab OR Desmethylsildenafil:ti,ab OR Homosildenafil:ti,ab OR Hydroxyhomosildenafil:ti,ab OR IC351:ti,ab OR Levitra:ti,ab OR NCX911:ti,ab OR "PDE5I":ti,ab OR "PDE5 inhibitors":ti,ab OR "phosphodiesterase type 5 inhibitors":ti,ab OR Revatio:ti,ab OR Sildenafil:ti,ab OR Staxyn:ti,ab OR Stendra:ti,ab OR Tadalafil:ti,ab OR "UK 9248010":ti,ab OR Vardenafil:ti,ab OR Viagra:ti,ab	3344
16	MeSH descriptor: [Soluble Guanylyl Cyclase] explode all trees	14
17	adempas:ti,ab OR cinaciguat:ti,ab OR "guanylate cyclase":ti,ab OR riociguat:ti,ab OR vericiguat:ti,ab OR verquvo:ti,ab	415
18	MeSH descriptor: [Epoprostenol] explode all trees	527
19	MeSH descriptor: [Iloprost] explode all trees	224
20	MeSH descriptor: [Receptors, Epoprostenol] explode all trees	9
21	ciloprost:ti,ab OR flolan:ti,ab OR orenitram:ti,ab OR prostacyclin:ti,ab OR remodulin:ti,ab OR veletri:ti,ab OR ventavis:ti,ab	1184
22	OR/7-21	6140
23	3 AND 6 AND 22	50

Continued

13.11. Literature search strategies for key narrative question 7

13.11.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Hypertension, Pulmonary"[Mesh]	37 397
2	pulmonary[tiab] AND hypertensi*[tiab]	58 338
3	1 OR 2	65 794
4	"Lung Diseases, Interstitial"[Mesh]	57 008
5	(interstitial[tiab] AND lung[tiab]) OR "idiopathic pulmonary fibrosis"[tiab]	30 364
6	4 OR 5	78 946
7	"Atrasentan"[Mesh] OR "Bosentan"[Mesh] OR "Endothelin Receptor Antagonists"[Mesh]	5883
8	"Endothelin Receptor Antagonists"[Pharmacological Action]	5901
9	"A 192621"[Supplementary Concept] OR "ambrisentan"[Supplementary Concept] OR "BQ 788"[Supplementary Concept] OR "cyclo(Trp-Asp-Pro-Val-Leu)"[Supplementary Concept] OR "macitentan"[Supplementary Concept] OR "ZD4054"[Supplementary Concept]	2205
10	A127722[tiab] OR A147627[tiab] OR A192621[tiab] OR ABT627[tiab] OR Ambrisentan[tiab] OR Atrasentan[tiab] OR Bosentan[tiab] OR BQ-123[tiab] OR BQ-788[tiab] OR BSF208075[tiab] OR "cyclo(D-Trp-D-Asp-Pro-D-Val-Leu)"[tiab] OR "endothelin receptor antagonists"[tiab] OR GSK1325760A[tiab] OR Letairis[tiab] OR LU208075[tiab] OR macitentan[tiab] OR opsumit[tiab] OR "Ro 470203"[tiab] OR Sitaxentan[tiab] OR Tracleer[tiab] OR Xinlay[tiab] OR Zibotentan[tiab]	5558
11	OR/9-12	8350
12	"Soluble Guanylyl Cyclase"[Mesh]	1147
13	"BAY 58-2667"[Supplementary Concept] OR "riociguat"[Supplementary Concept] OR "SgcA protein, Dictyostelium	313

Continued

	discoideum"[Supplementary Concept] OR "vericiguat"[Supplementary Concept]	
14	adempas[tiab] OR cinaciguat[tiab] OR "guanylate cyclase"[tiab] OR riociguat[tiab] OR vericiguat[tiab] OR verquvo[tiab]	7874
15	OR/19-21	8518
16	"Epoprostenol"[Mesh] OR "Iloprost"[Mesh] OR "Receptors, Epoprostenol"[Mesh]	14 245
17	"treprostinil"[Supplementary Concept]	366
18	ciloprost[tiab] OR flolan[tiab] OR orenitram[tiab] OR prostacyclin[tiab] OR remodulin[tiab] OR veletri[tiab] OR ventavis[tiab]	14 391
19	OR/23-25	20 053
20	11 OR 15 OR 19	35 938
21	3 AND 6 AND 20	147
22	English[lang]	NA
23	21 AND 22	133
24	1990/1/1:3000/12/31[pdat]	NA
25	23 AND 24	131

13.11.2. Cochrane

Search date: 12 April 2021

Set #	Search strategy	Results
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1194
2	pulmonary:ti,ab AND hypertensi*:ti,ab	4586
3	1 OR 2	4743
4	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	781
5	(interstitial:ti,ab AND lung:ti,ab) OR "idiopathic pulmonary fibrosis":ti,ab	2231
6	4 OR 5	2677
7	MeSH descriptor: [Atrasentan] explode all trees	39
8	MeSH descriptor: [Bosentan] explode all trees	190
9	MeSH descriptor: [Endothelin Receptor Antagonists] explode all trees	275
10	A127722:ti,ab OR A147627:ti,ab OR A192621:ti,ab OR ABT627:ti,ab OR Ambrisentan:ti,ab OR Atrasentan:ti,ab OR Bosentan:ti,ab OR BQ-123:ti,ab OR BQ-788:ti,ab OR BSF208075:ti,ab OR "cyclo(D-Trp-D-Asp-Pro-D-Val-Leu)":ti,ab OR "endothelin receptor antagonists":ti,ab OR GSK1325760A:ti,ab OR Letairis:ti,ab OR LU208075:ti,ab OR macitentan:ti,ab OR opsumit:ti,ab OR "Ro 470203":ti,ab OR Sitaxentan:ti,ab OR Tracleer:ti,ab OR Xinlay:ti,ab OR Zibotentan:ti,ab	1075
11	MeSH descriptor: [Soluble Guanylyl Cyclase] explode all trees	14
12	adempas:ti,ab OR cinaciguat:ti,ab OR "guanylate cyclase":ti,ab OR riociguat:ti,ab OR vericiguat:ti,ab OR verquvo:ti,ab	415
13	MeSH descriptor: [Epoprostenol] explode all trees	527
14	MeSH descriptor: [Iloprost] explode all trees	224
15	MeSH descriptor: [Receptors, Epoprostenol] explode all trees	9
16	ciloprost:ti,ab OR flolan:ti,ab OR orenitram:ti,ab OR prostacyclin:ti,ab OR remodulin:ti,ab OR veletri:ti,ab OR ventavis:ti,ab	1189
17	OR/7-16	2950
18	3 AND 6 AND 17	41

Continued

13.12. Literature search strategies for key narrative question 8

13.12.1. Pubmed

Search date: 12 April 2021

Set #	Search strategy	Results
1	"Angioplasty, Balloon"[Mesh]	53 390
2	"balloon pulmonary angioplasty"[tiab]	348
3	1 OR 2	53 527
4	"Drug Therapy"[Mesh]	1 393 014
5	"drug therapy"[Subheading] OR "therapy"[Subheading]	7266 292
6	"drug therap*"[tiab] OR "medical therap*"[tiab] OR "pulmonary vasodilator therap*"[tiab] OR "targeted therap*"[tiab]	139 797
7	OR/4-6	7 802 736
8	"chronic thromboembolic pulmonary hypertension"[tiab] OR CTEPH[tiab] OR "residual pulmonary hypertension"[tiab]	2385
9	3 AND 7 AND 8	246
10	English[lang]	NA
11	9 AND 10	231
12	1990/1/1:3000/12/31[pdat]	NA
13	11 AND 12	231

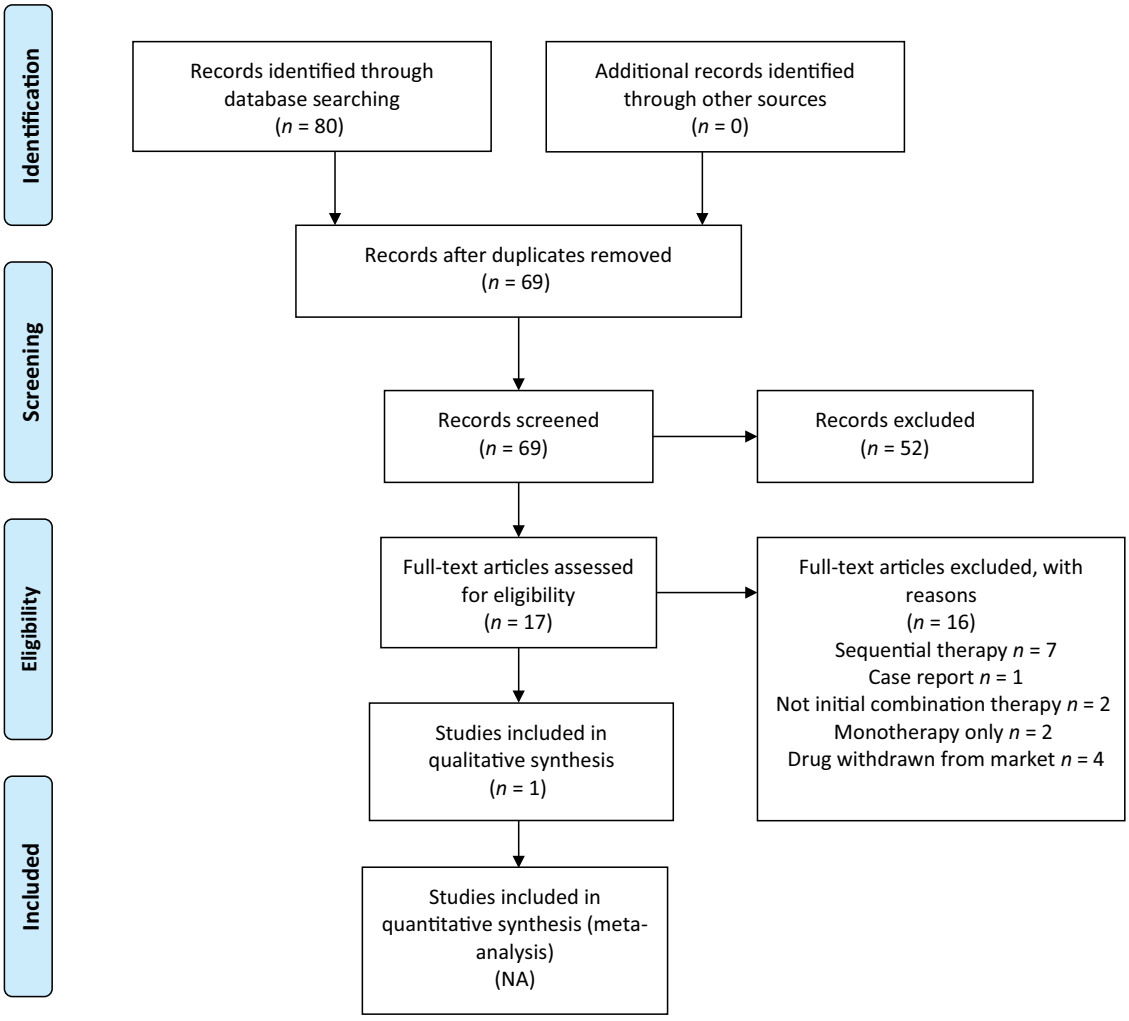
13.12.2. Cochrane

Search date: 12 April 2021

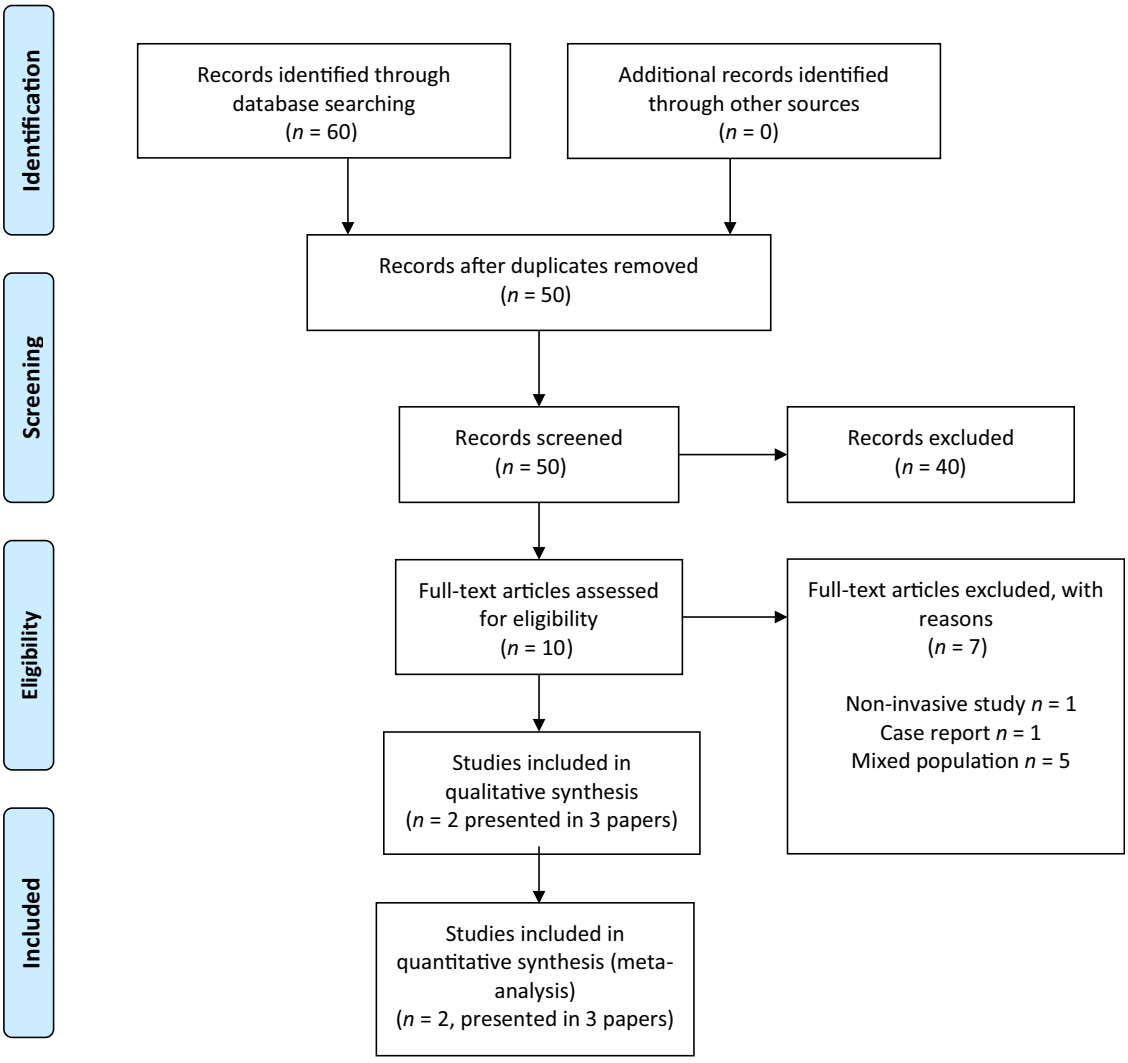
Set #	Search strategy	Results
1	MeSH descriptor: [Angioplasty, Balloon] explode all trees	4117
2	"balloon pulmonary angioplasty":ti,ab	24
3	1 OR 2	4138
4	MeSH descriptor: [Drug Therapy] explode all trees	142 349
5	Any MeSH descriptor in all MeSH products and with qualifier(s): [drug therapy - DT]	204 370
NA	Any MeSH descriptor in all MeSH products and with qualifier(s): [therapy - DT]	94 769
6	"drug therap*":ti,ab OR "medical therap*":ti,ab OR "pulmonary vasodilator therap*":ti,ab OR "targeted therap*":ti,ab	231 579
7	OR/4-6	470 529
8	"chronic thromboembolic pulmonary hypertension":ti,ab OR CTEPH:ti,ab OR "residual pulmonary hypertension":ti,ab	246
9	3 AND 7 AND 8	11

14. PRISMA diagrams

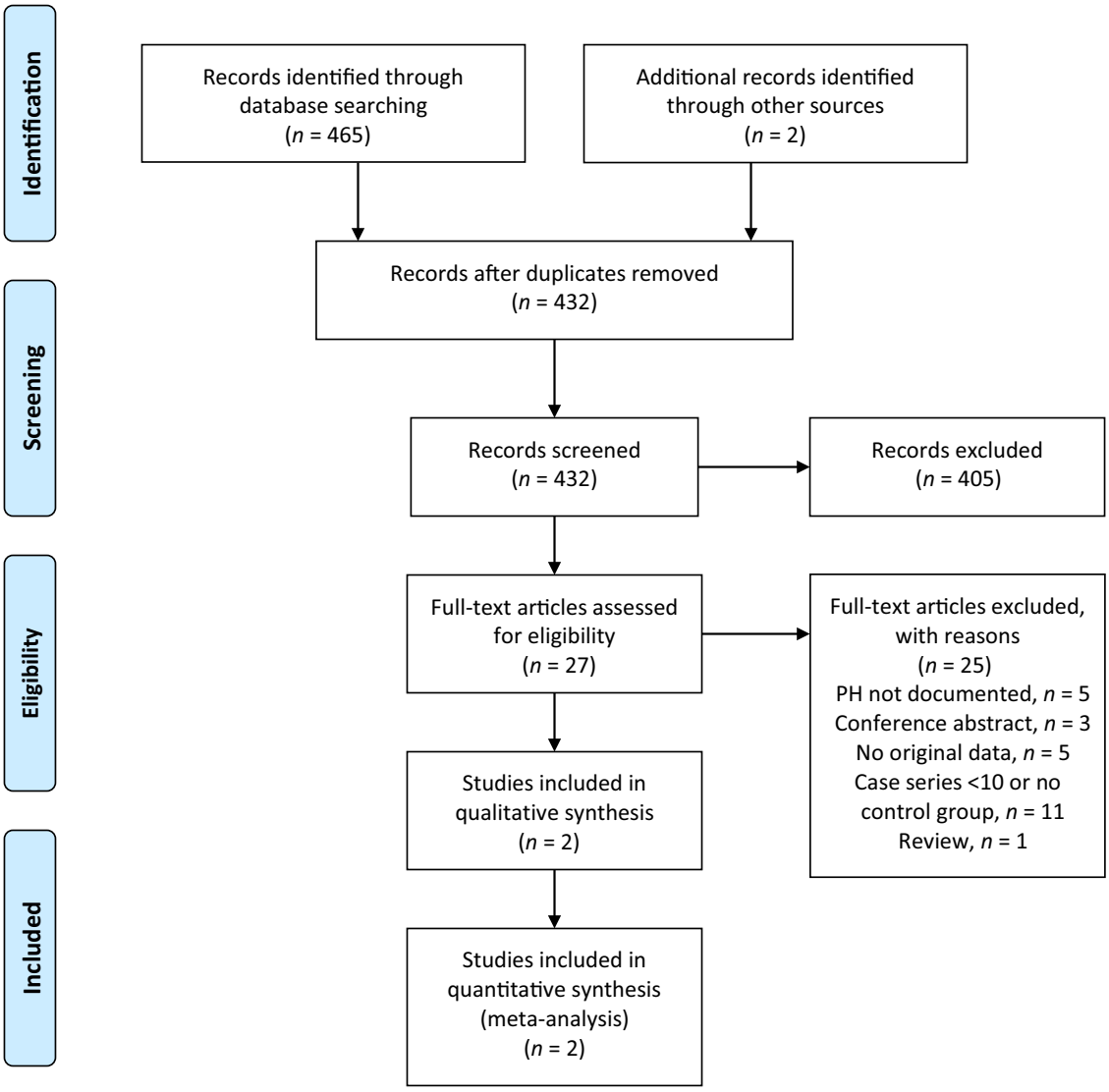
14.1. Prisma diagram PICO I



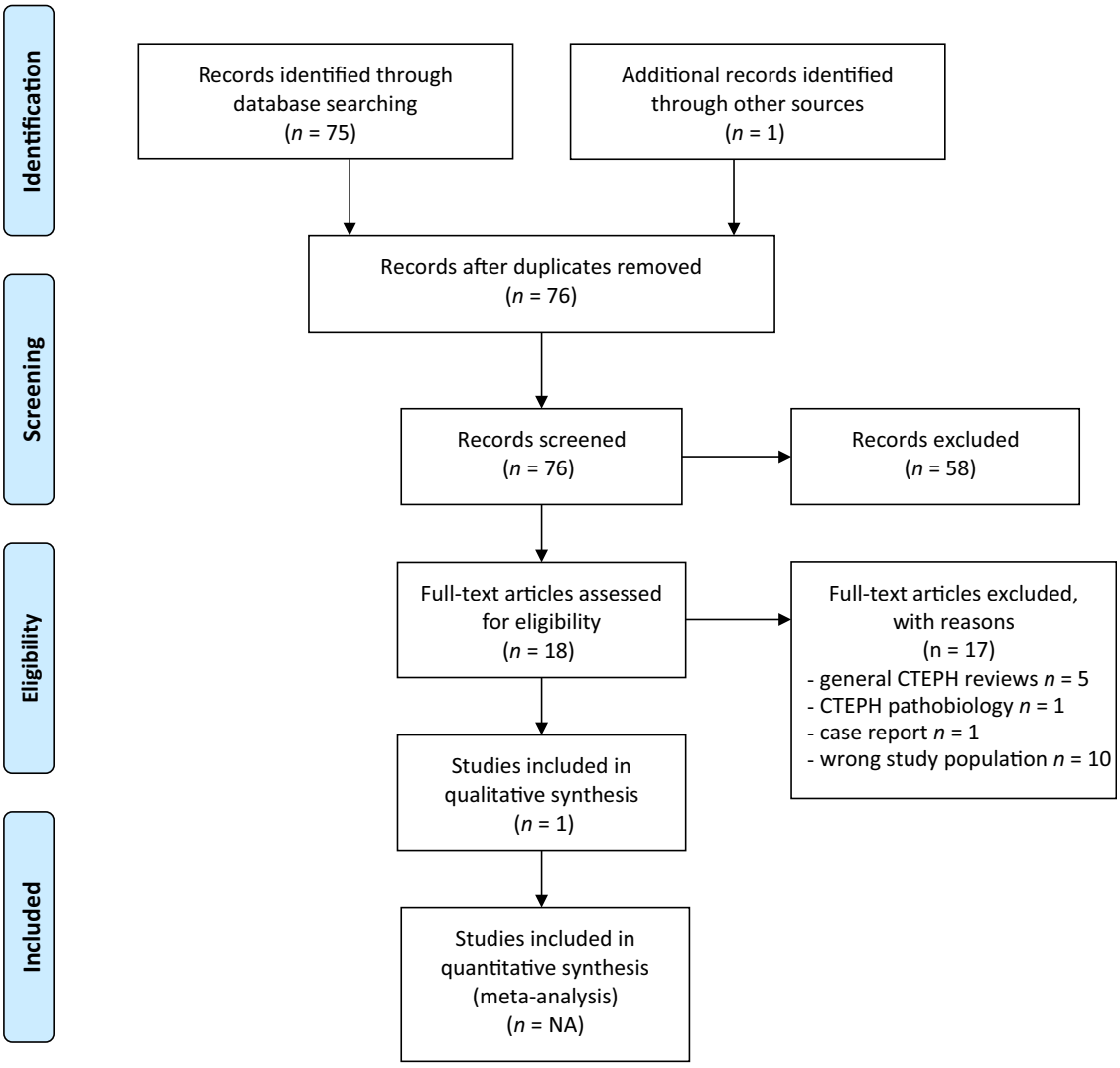
14.2. Prisma diagram PICO II



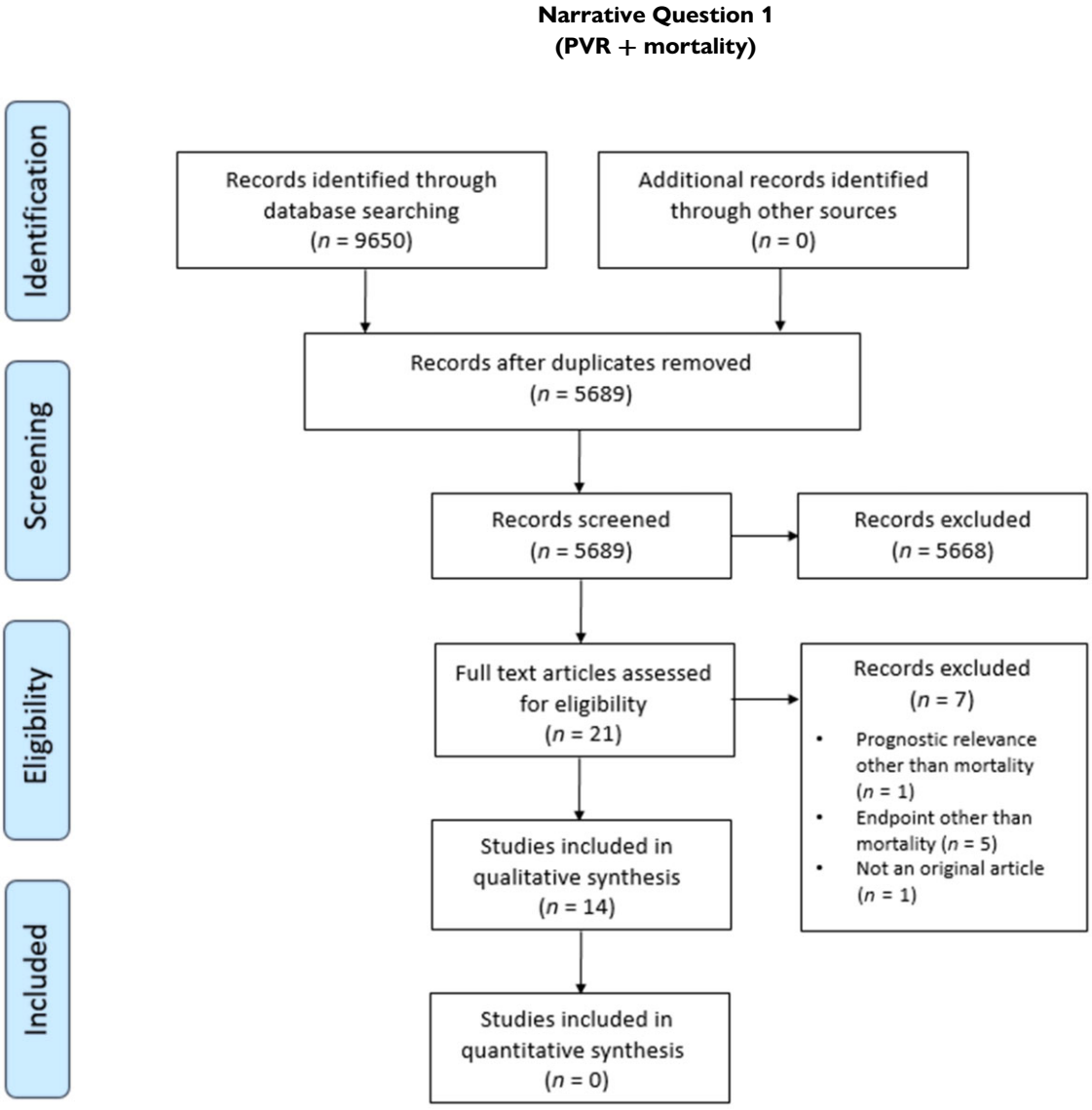
14.3. Prisma diagram PICO III



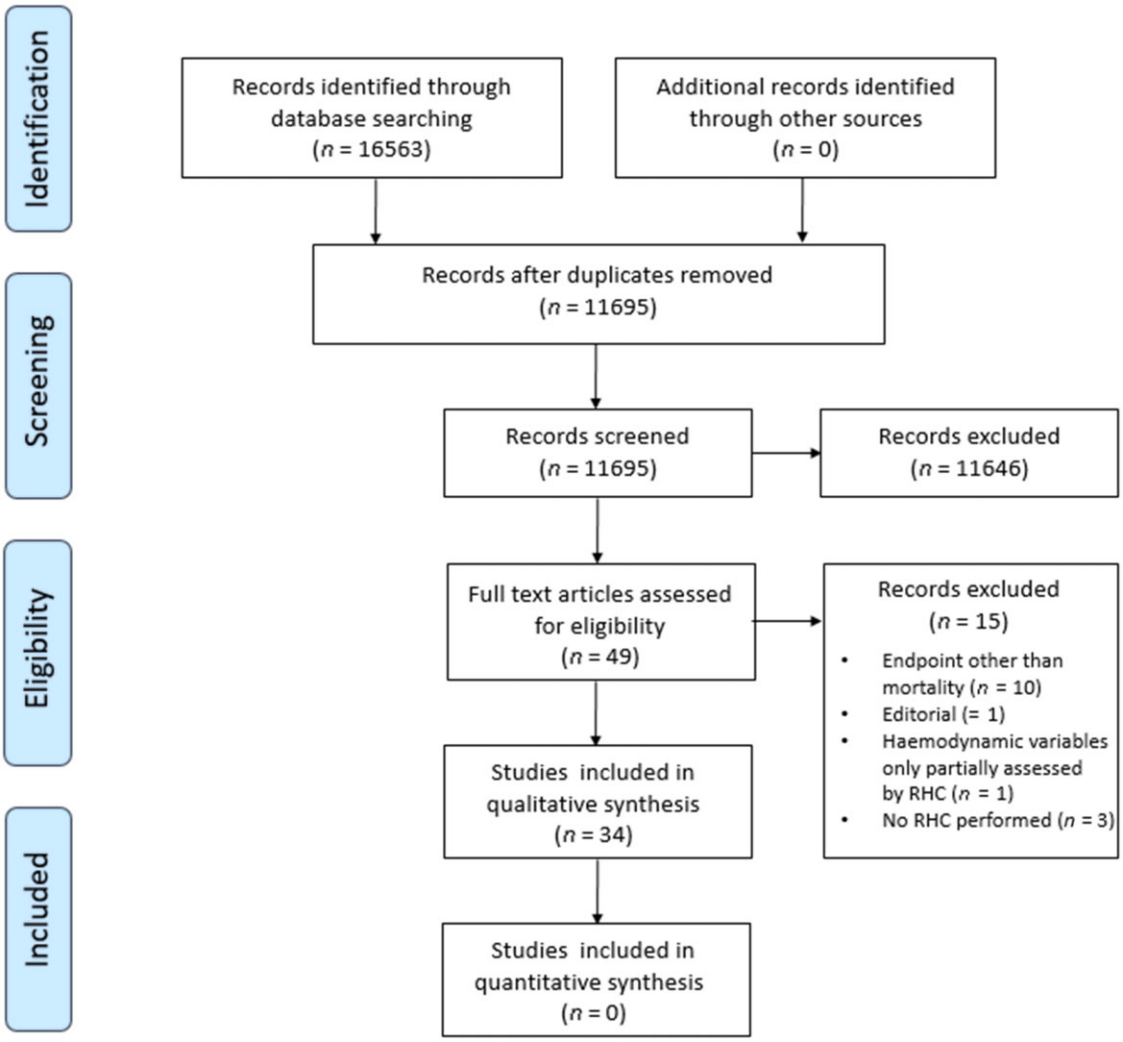
14.4. Prisma diagram PICO IV



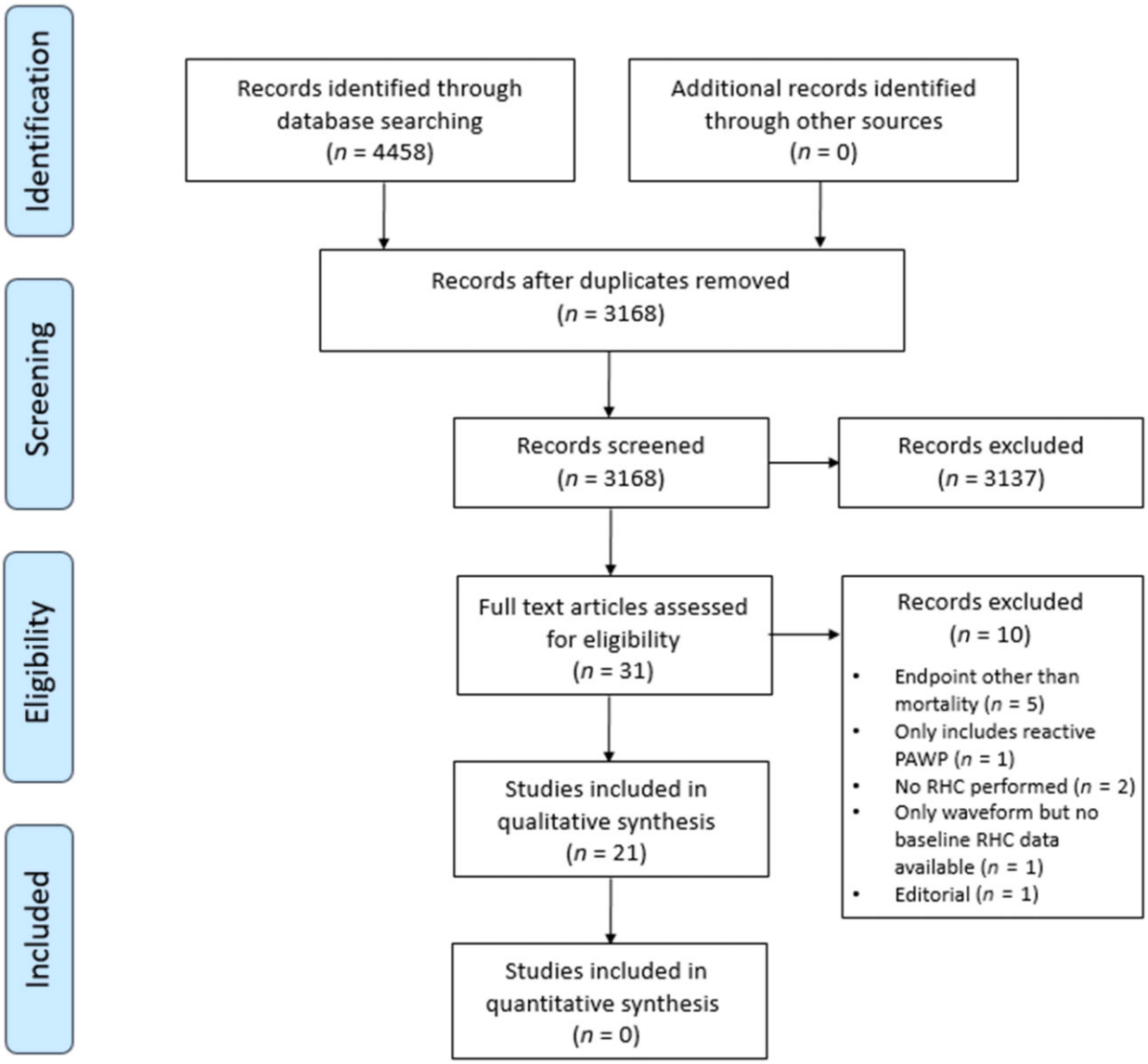
14.5. Prisma diagram key narrative question 1



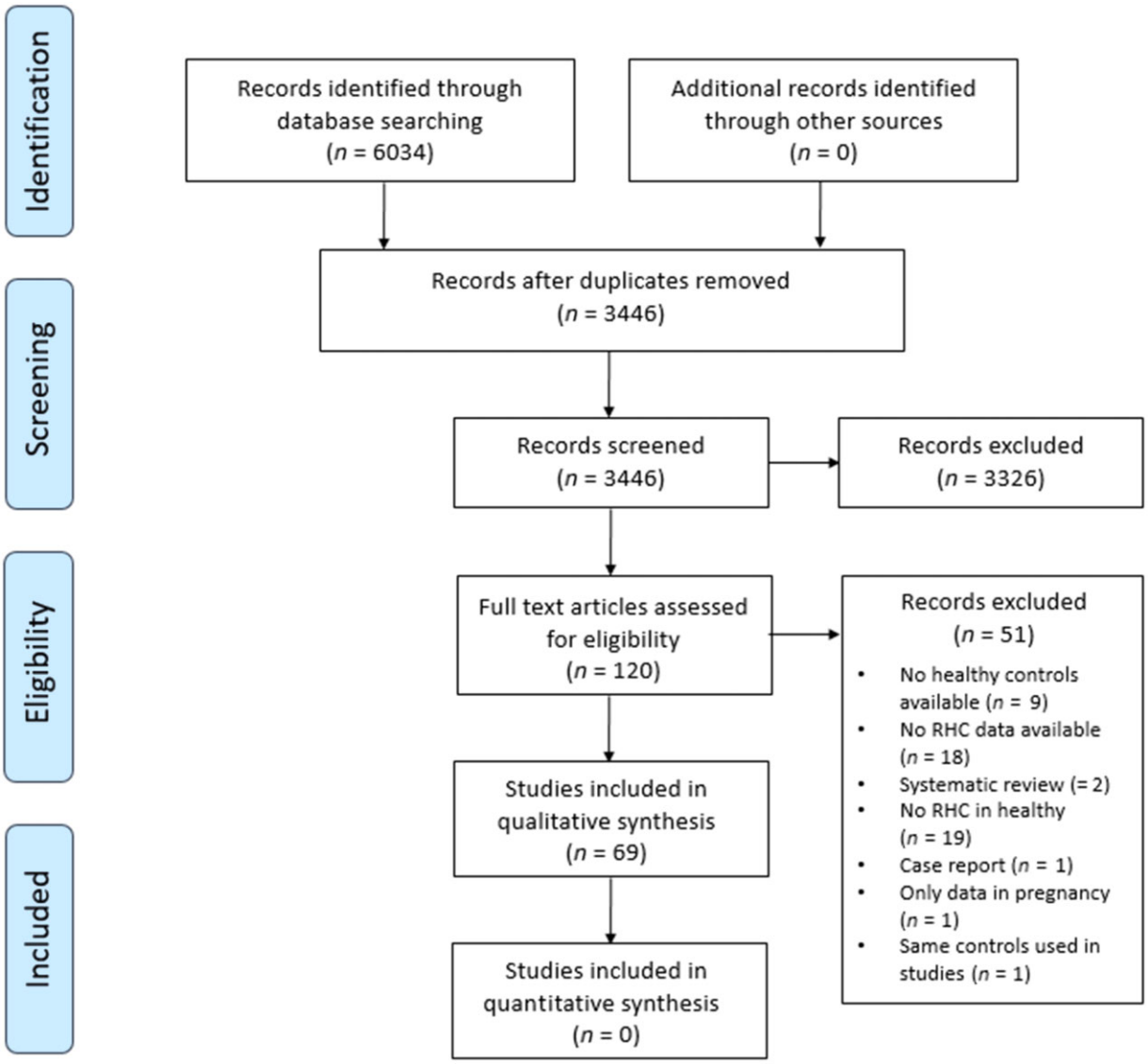
Narrative Question 1
(mPAP + mortality)



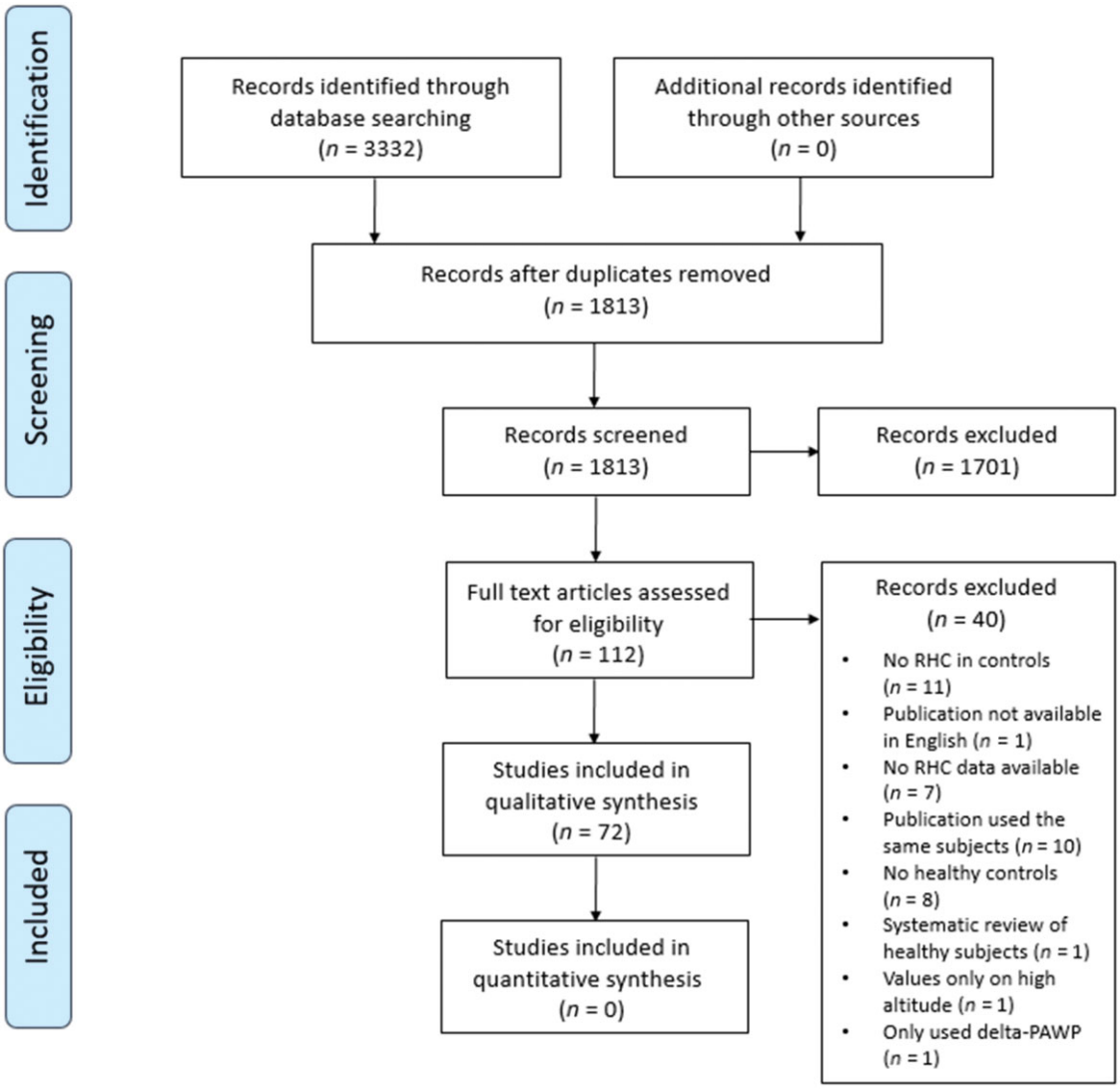
Narrative Question 1
(PAWP + mortality)



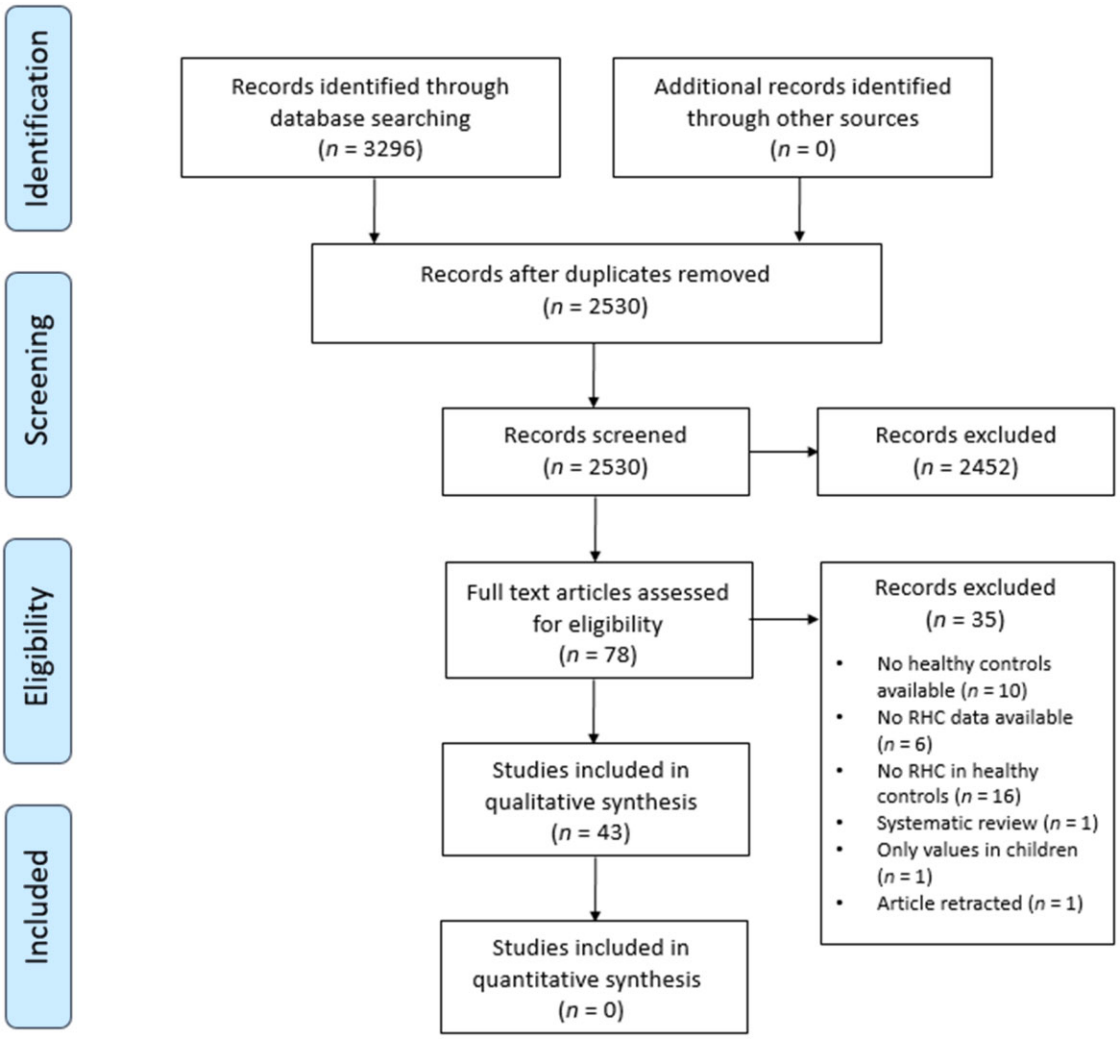
Narrative Question 1
(mPAP + normal values)



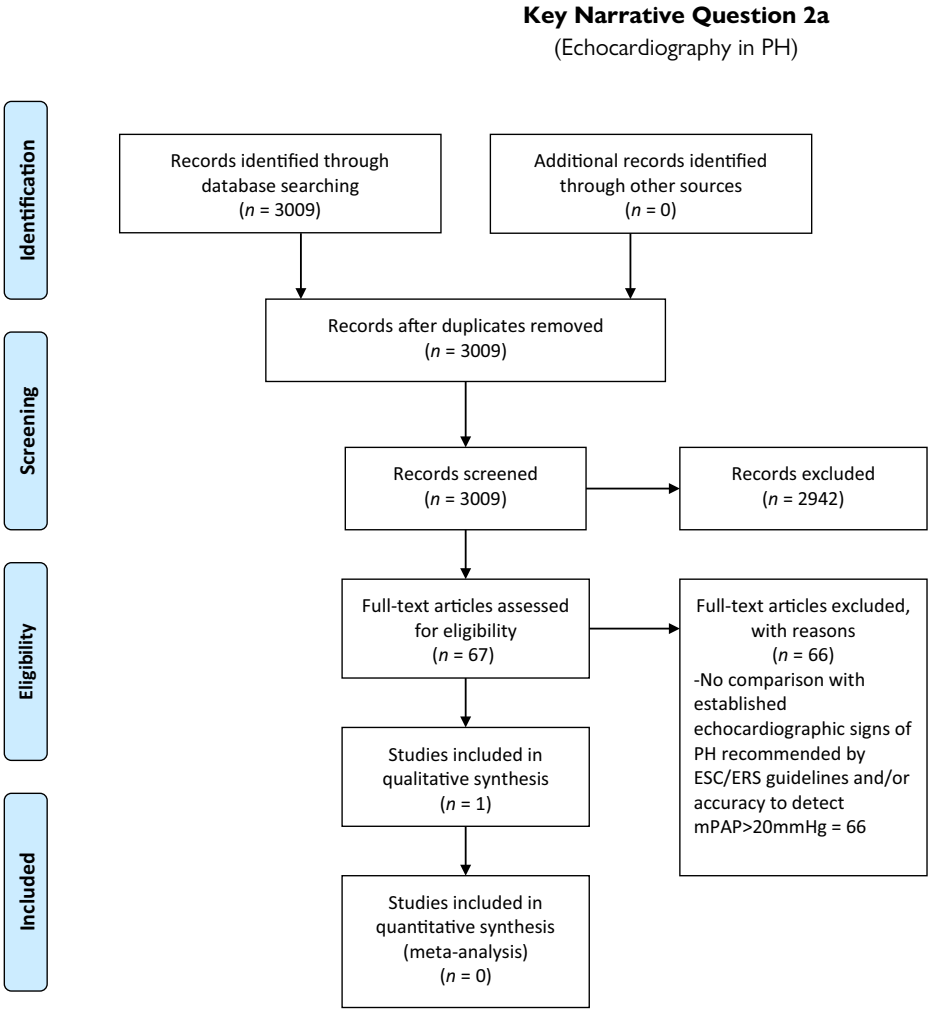
Narrative Question 1
(PAWP + normal values)



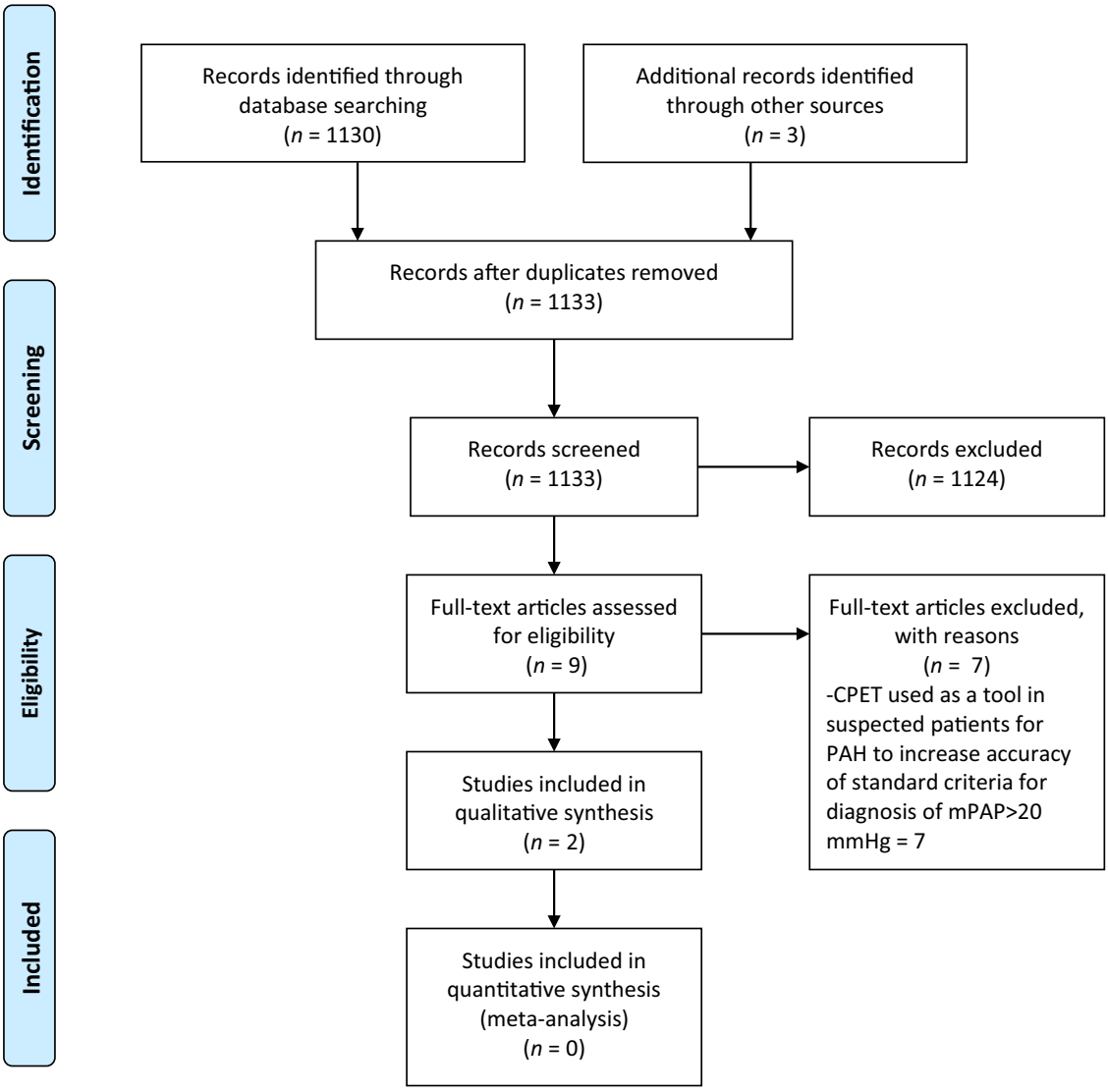
Narrative Question 1
(PVR + normal values)



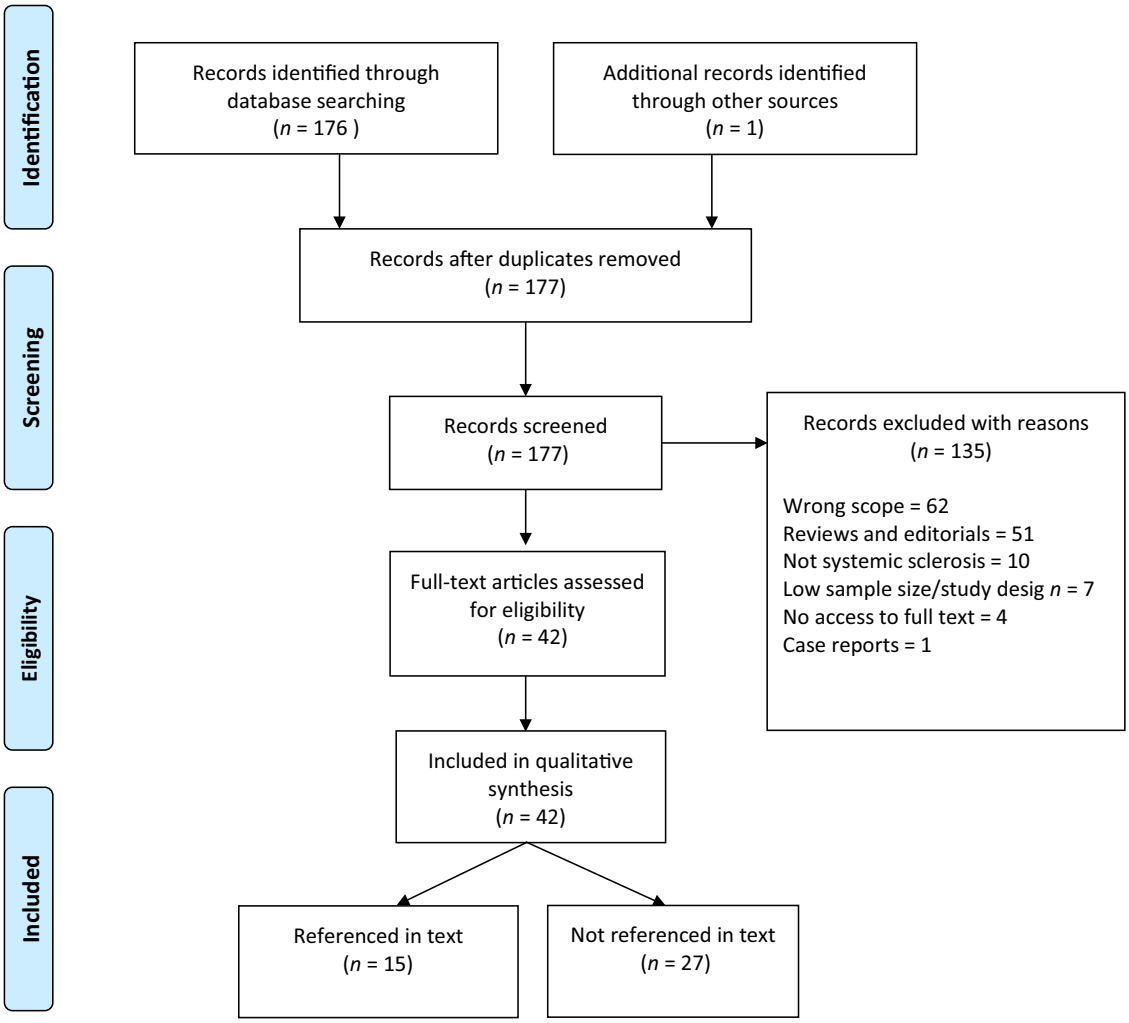
14.6. Prisma diagram key narrative question 2



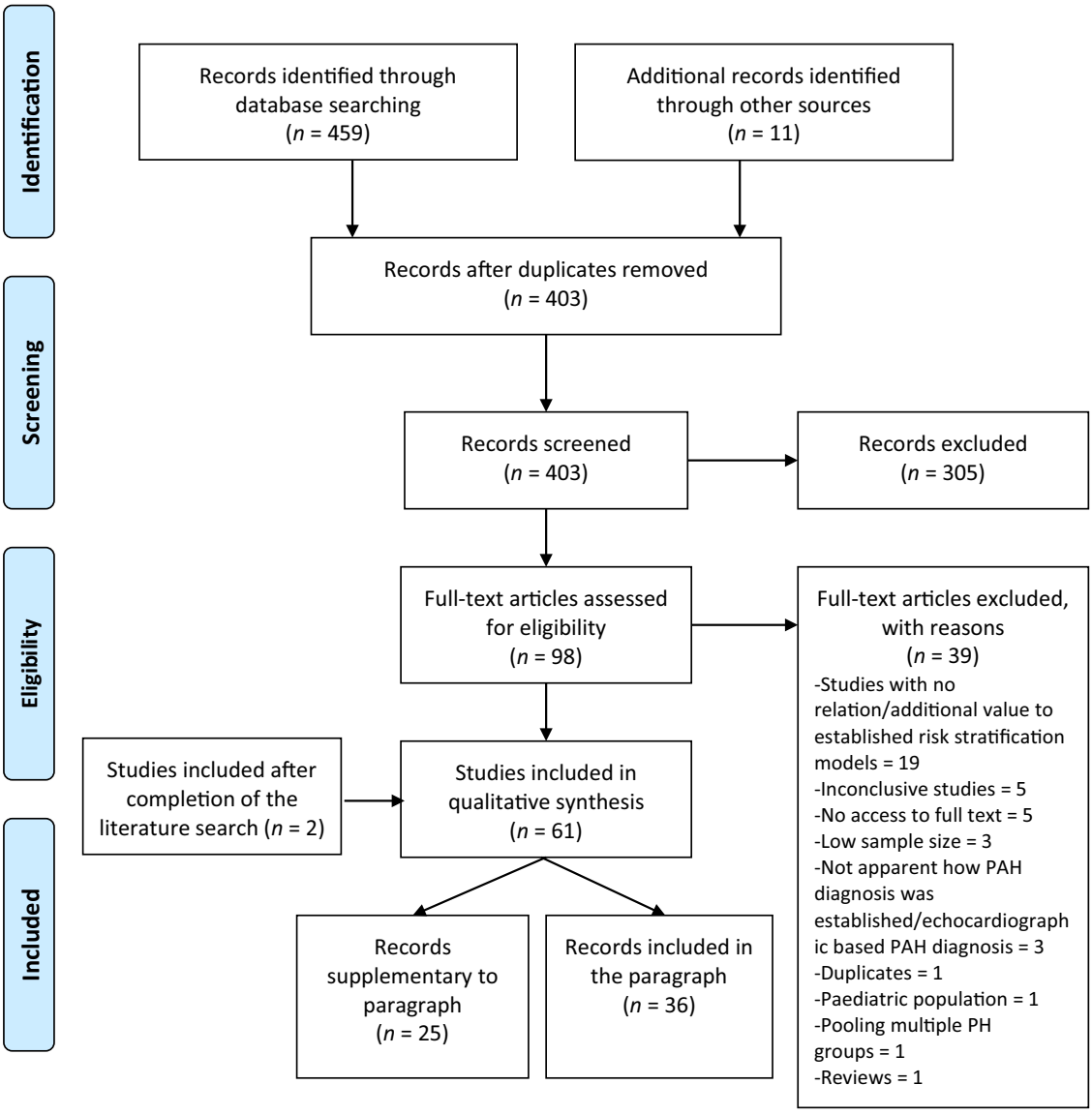
Key Narrative Question 2b
(Cardiopulmonary exercise testing in PH)



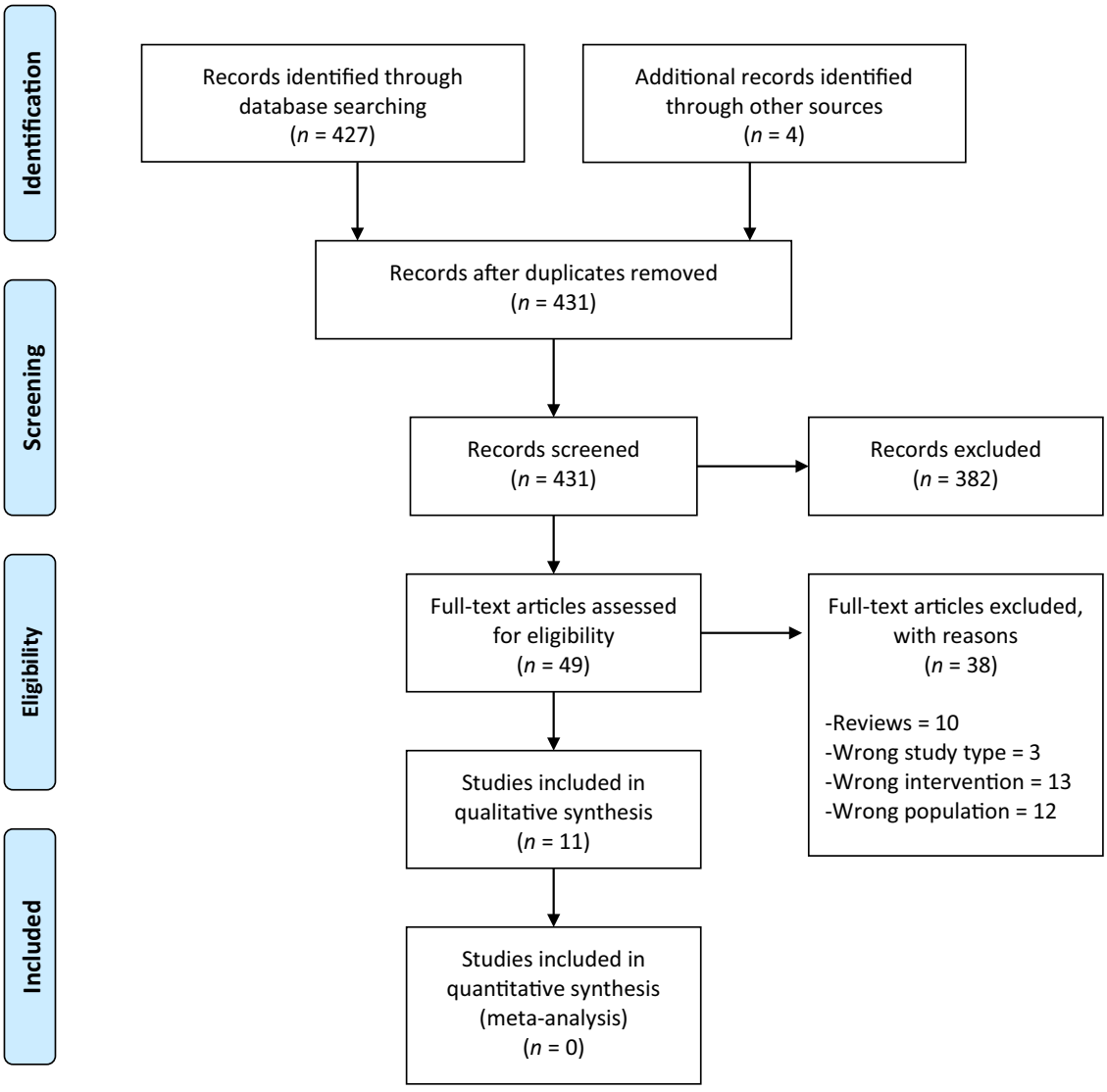
14.7. Prisma diagram key narrative question 3



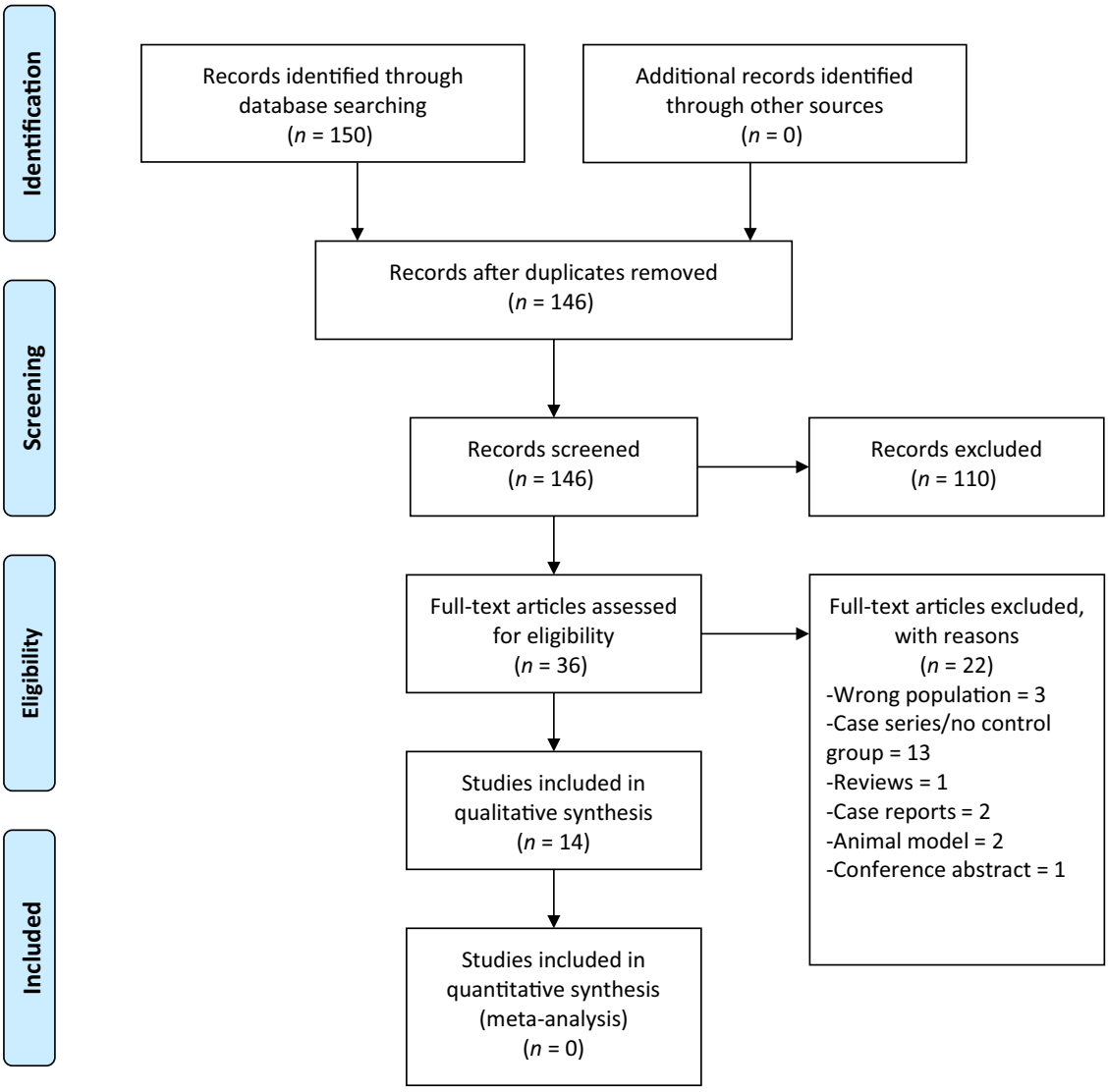
14.8. Prisma diagram key narrative question 4



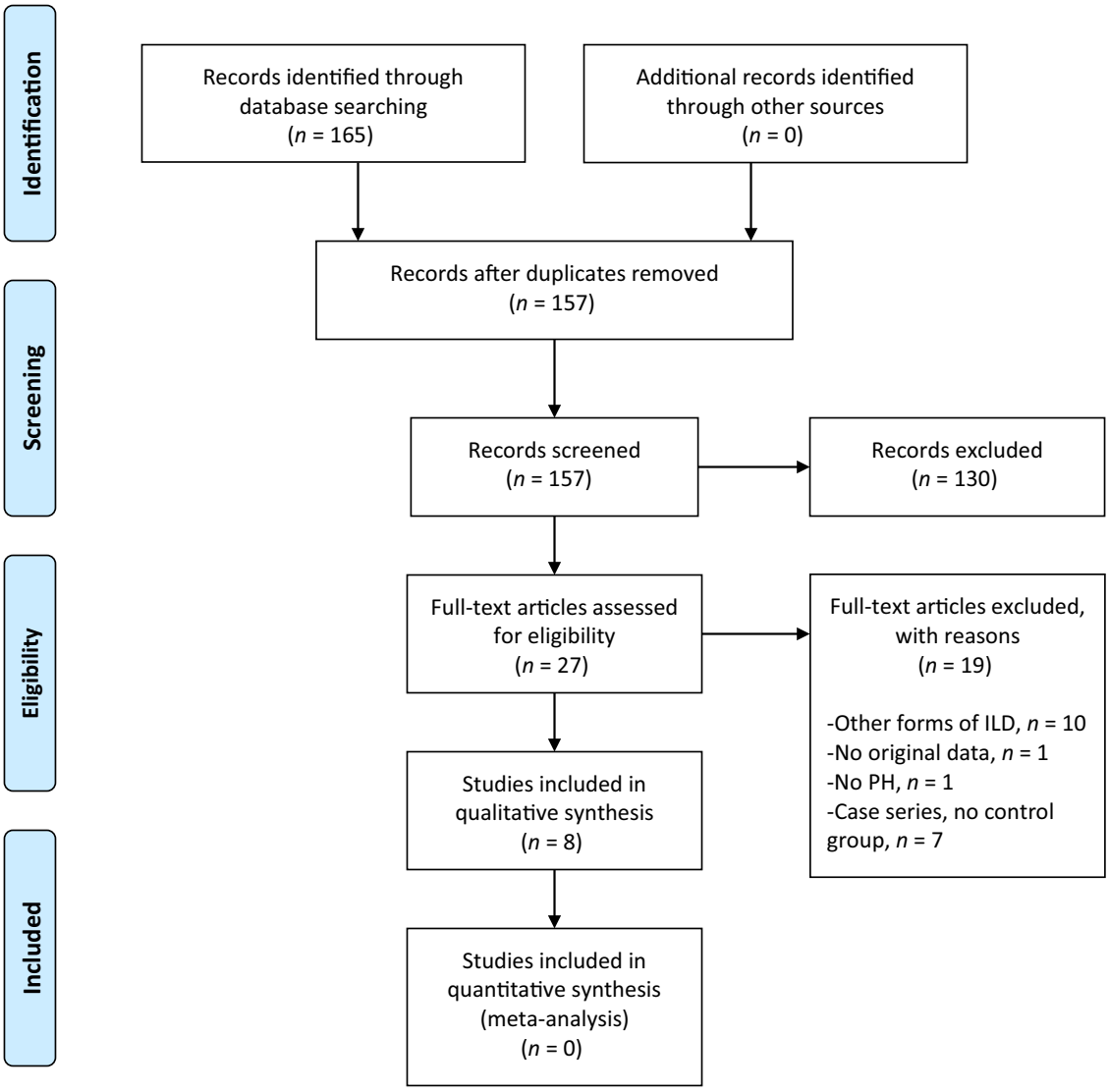
14.9. Prisma diagram key narrative question 5



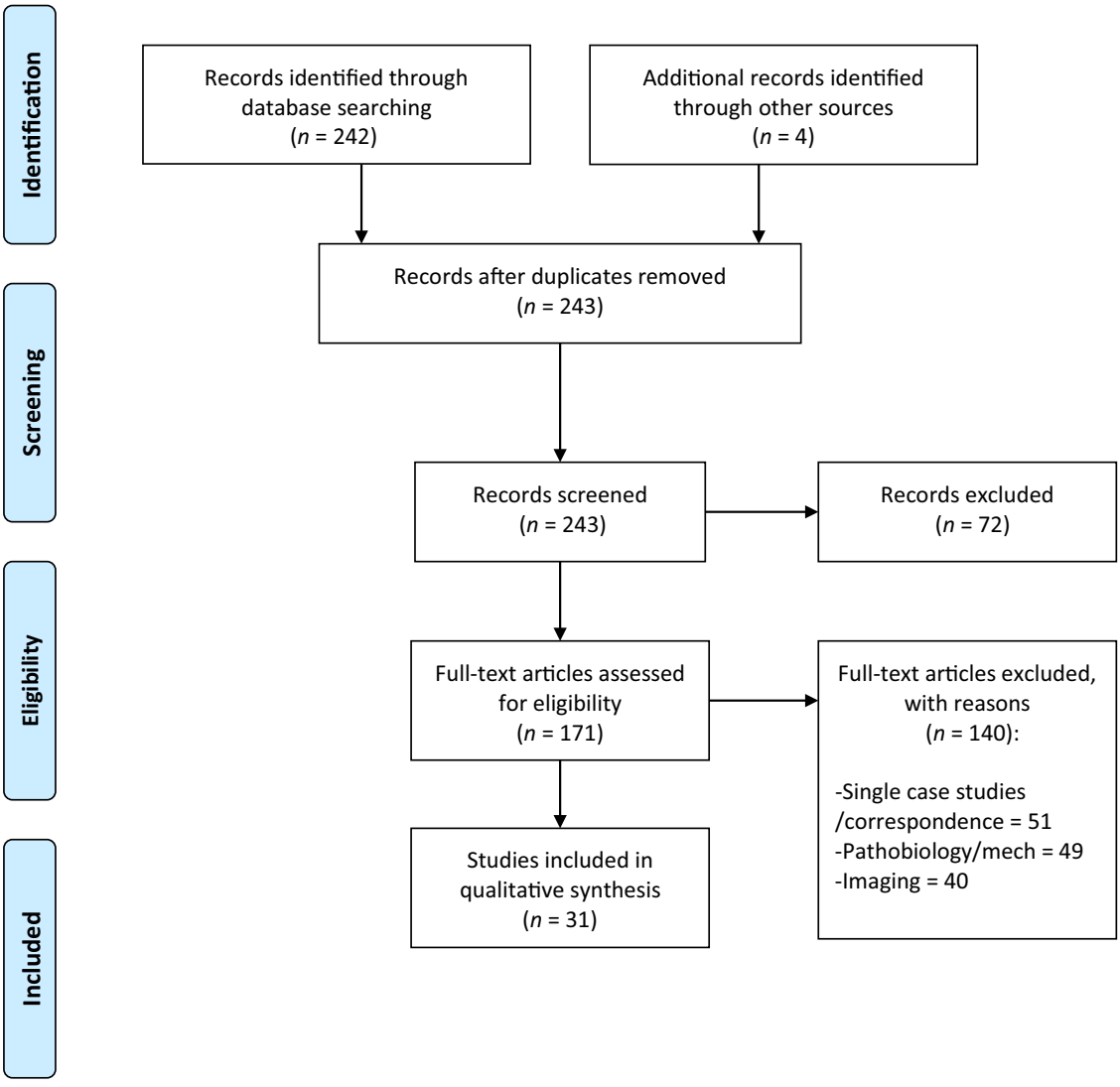
14.10. Prisma diagram key narrative question 6



14.11. Prisma diagram key narrative question 7



14.12. Prisma diagram key narrative question 8



15. Guideline development tool (GDT) evidence profile

15.1. Guideline development tool evidence profile for PICO I

Question: Should initial oral double-combination therapy vs. monotherapy be used in symptomatic patients with pulmonary arterial hypertension?

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Initial oral double combination therapy (ERAs and PDE5is)**	**Monotherapy (ERAs, PDE5is)**	**Relative [95% CI]**	**Absolute [95% CI]**		
Hospitalization												
1[203]	randomized trials	not serious	not serious	not serious	serious[a]	none	10/253 (4.0%)	30/247 (12.1%)	**RR 0.33** [0.16–0.65]	**81 fewer per 1000** [from 102 fewer to 43 fewer]	⊕⊕⊕○ MODERATE	CRITICAL
Unsatisfactory long-term clinical response												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	17/253 (6.7%)	23/247 (9.3%)	**RR 0.72** [0.40–1.32]	**26 fewer per 1000** [from 56 fewer to 30 more]	⊕⊕○○ LOW	CRITICAL
Disease progression												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	10/253 (4.0%)	11/247 (4.5%)	**RR 0.61** [0.28–1.32]	**17 fewer per 100** [from 32 fewer to 14 more]	⊕⊕○○ LOW	CRITICAL
Exercise capacity (assessed with 6-minute walking distance)												
1[203]	randomized trials	not serious	not serious	not serious	serious[c]	none	253	247	–	MD **25.18 m higher** [22.87 higher to 27.49 higher]	⊕⊕⊕○ MODERATE	CRITICAL
Haemodynamic variables - not reported												
–	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT
Cardiac biomarkers (assessed with NT-proBNP level)												
1[203]	randomized trials	serious[d]	not serious	not serious	serious[c]	none	percentage change in geometric mean from baseline to week 24: Combination therapy ($n = 253$): −67.2 Monotherapy-pooled ($n = 247$): −50.4				⊕⊕○○ LOW	IMPORTANT

Continued

Quality of life (assessed with improvement in WHO Functional Class at week 24)												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	94/252 (37.3%)	81/244 (33.2%)	**RR 1.12** [0.88–1.43]	**40 more per 1000** [from 40 fewer to 143 more]	⊕⊕◯◯ LOW	IMPORTANT
Quality of life (assessed with no change in WHO Functional Class at week 24)												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	146/252 (57.9%)	147/244 (60.2%)	**RR 0.96** [0.83–1.11]	**24 fewer per 1000** [from 102 fewer to 66 more]	⊕⊕◯◯ LOW	IMPORTANT
Quality of life (assessed with deterioration in WHO Functional Class at week 24)												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	12/252 (4.8%)	16/244 (6.6%)	**RR 0.73** [0.35–1.50]	**18 fewer per 1000** [from 43 fewer to 33 more]	⊕⊕◯◯ LOW	IMPORTANT
Serious adverse events (including pulmonary hypertension, pneumonia)												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	92/253 (36.4%)	95/247 (38.5%)	**RR 0.94** [0.75–1.19]	**23 fewer per 1000** [from 96 fewer to 73 more]	⊕⊕◯◯ LOW	IMPORTANT
Adverse events leading to discontinuation (including dyspnoea, peripheral oedema)												
1[203]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	31/253 (12.3%)	28/247 (11.3%)	**RR 1.08** [0.67–1.75]	**9 more per 1000** [from 37 fewer to 85 more]	⊕⊕◯◯ LOW	IMPORTANT
Survival												
1[204]	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	29/302 (9.6%)	41/303 (13.5%)	**HR 0.67** [0.42–1.08]	**42 fewer per 1000** [from 76 fewer to 10 more]	⊕⊕◯◯ LOW	NA

CI, confidence interval; RR, risk ratio; MD, mean difference; HR, hazard ratio; WHO, World Health Organization.

Explanations

[a]The small number of events did not meet optimal information size and suggested fragility of the estimate.

[b]The 95% CI included the potential for both meaningful benefit and meaningful harm.

[c]The small sample size suggested fragility of the estimate.

[d]Data were based on observed cases, with no imputation. A number of NT-proBNP samples were lost or could not be analysed. Analysis of NT-proBNP was performed on data from 204 participants in the combination therapy group and 199 in the pooled monotherapy group (99 in the ambrisentan-monotherapy group and 100 in the tadalafil-monotherapy group).

15.2. Guideline development tool evidence profile for PICO II

Question: Should phosphodiesterase type 5 inhibitors be used in patients with combined post- and pre-capillary pulmonary hypertension due to heart failure with preserved ejection fraction?

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phosphodiesterase type 5 inhibitors	No phosphodiesterase type 5 inhibitors	Relative [95% CI]	Absolute [95% CI]		
Mortality (follow-up: 12 weeks)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[a]	none	1/26 (3.8%)	1/26 (3.8%)	**RR 1.00** [0.07–15.15]	**0 fewer per 1000** [from 36 fewer to 544 more]	⊕⊕○○ LOW	CRITICAL
Cardiovascular morbidity (cardiac failure) (follow-up: 12 weeks)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[a]	none	1/26 (3.8%)	0/26 (0.0%)	**RR 3.00** [0.13–70.42]	**39 more per 1000** [from 35 fewer to 112 more][b]	⊕⊕○○ LOW	CRITICAL
Hospitalization/clinical worsening - not reported												
–	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Quality of life (follow-up: 12 weeks; assessed with Kansas City Cardiomyopathy Questionnaire)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[c]	none	26	26	–	MD **17 lower** [22.04 lower to 11.96 lower]	⊕⊕○○ LOW	CRITICAL
Primary safety endpoint (composite: cardiac failure, intestinal infarction, death) (follow-up: 12 weeks)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[a]	none	1/26 (3.8%)	1/26 (3.8%)	**RR 1.00** [0.07–15.15]	**0 fewer per 1000** [from 36 fewer to 544 more]	⊕⊕○○ LOW	CRITICAL
Non-study-specific severe adverse events (pneumonia, vascular pseudoaneurysm, medical device complication, elective surgery, respiratory tract infection) (follow-up: 12 weeks)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[a]	none	3/26 (11.5%)	2/26 (7.7%)	**RR 1.50** [0.27–8.25]	**38 more per 1000** [from 56 fewer to 558 more]	⊕⊕○○ LOW	CRITICAL
Exercise capacity (follow-up: 12 months; assessed with forced expiratory volume in 1 second)												
1[206]	randomized trials	not serious	not serious	not serious	very serious[c]	none	22	22	–	MD **10 % predicted higher** [7.32 higher to 12.68 higher]	⊕⊕○○ LOW	IMPORTANT
Exercise capacity (follow-up: 12 weeks; assessed with peak oxygen consumption)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[a]	none	26	26	–	MD **0.6 mL/min/kg higher** [0.96 lower to 2.16 higher]	⊕⊕○○ LOW	IMPORTANT

Continued

Echocardiography – pulmonary arterial pressure (follow-up: 12 weeks)												
2[205,206]	randomized trials	not serious	serious[d]	not serious	serious[c]	none	48	48	–	MD **17.29 mmHg lower** [19.54 lower to 15.05 lower]	⊕⊕○○ LOW	IMPORTANT
Echocardiography – right ventricular systolic pressure (follow-up: 12 weeks)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[c]	none	26	26	–	MD **2 mmHg higher** [0.29 higher to 3.71 higher]	⊕⊕○○ LOW	IMPORTANT
Echocardiography – tricuspid annular plane systolic excursion (follow-up: 12 weeks)												
2[205,206]	randomized trials	not serious	serious[e]	not serious	serious[c]	none	48	48	–	MD **7.08 mm higher** [6.07 higher to 8.08 higher]	⊕⊕○○ LOW	IMPORTANT
Echocardiography – right ventricular ejection fraction (follow-up: 12 weeks)												
1[206]	randomized trials	not serious	not serious	not serious	very serious[c]	none	22	22	–	MD **54 mL/s higher** [37.53 higher to 70.47 higher]	⊕⊕○○ LOW	IMPORTANT
Echocardiography – cardiac output (follow-up: 12 weeks)												
2[205,206]	randomized trials	not serious	not serious	not serious	very serious[a]	none	48	48	–	SMD **0.07 SD higher** [0.33 lower to 0.47 higher]	⊕⊕○○ LOW	IMPORTANT
Pulmonary vascular resistance (follow-up: 12 weeks)												
2[205,206]	randomized trials	not serious	serious[f]	not serious	serious[c]	none	48	48	—	SMD **0.95 SD lower** [1.43 lower to 0.48 lower]	⊕⊕○○ LOW	IMPORTANT
Biomarkers (N-terminal pro-brain natriuretic peptide) (follow-up: 12 weeks)												
1[205]	randomized trials	not serious	not serious	not serious	very serious[a]	none	26	26	–	MD **327 ng/L higher** [195.73 lower to 849.73 higher]	⊕⊕○○ LOW	IMPORTANT

CI, confidence interval; RR, risk ratio; MD, mean difference; SMD, standardized mean difference.

Explanations

[a]Small sample included and few events did not meet the optimal information size and suggested fragility of the estimate. The 95% CI included the potential for both meaningful benefit and meaningful harm.
[b]Zero events reported in the comparison arm. Manually calculated ARR.
[c]Small sample included and few events did not meet the optimal information size and suggested fragility of the estimate.
[d]Heterogeneity strongly suspected, $I^2 = 99\%$.
[e]Heterogeneity strongly suspected, $I^2 = 96\%$.
[f]Heterogeneity strongly suspected, $I^2 = 97\%$.

15.3. Guideline development tool evidence profile for PICO III

Question: Should phosphodiesterase type 5 inhibitors be used in patients with severe pulmonary hypertension associated with idiopathic interstitial lung diseases?

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phosphodiesterase type 5 inhibitors	No phosphodiesterase type 5 inhibitors	Relative [95% CI]	Absolute [95% CI]		
Mortality - right ventricular hypertrophy (follow-up: 12 weeks)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[c,d]	none	0/9 (0.0%)	1/6 (16.7%)	**RR 0.23** [0.01–4.93]	**128 fewer per 1000** [from 165 fewer to 655 more]	⊕○○○ VERY LOW	CRITICAL
Mortality - right ventricular systolic dysfunction (follow-up: 12 weeks)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[c,d]	none	0/11 (0.0%)	1/11 (9.1%)	**RR 0.33** [0.02–7.39]	**61 fewer per 1000** [from 89 fewer to 581 more]	⊕○○○ VERY LOW	CRITICAL
Mortality - no right ventricular hypertrophy (follow-up: 12 weeks)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[c,d]	none	2/46 (4.3%)	2/56 (3.6%)	**RR 1.22** [0.18–8.31]	**8 more per 1000** [from 29 fewer to 261 more]	⊕○○○ VERY LOW	CRITICAL
Mortality - no right ventricular systolic dysfunction (follow-up: 12 weeks)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[c,d]	none	2/45 (4.4%)	2/51 (3.9%)	**RR 1.13** [0.17–7.72]	**5 more per 1000** [from 33 fewer to 264 more]	⊕○○○ VERY LOW	CRITICAL
Safety (follow-up: 1 day)												
1[208]	randomized trials	serious[e]	not serious	serious[b]	very serious[f]	none	0/8 (0.0%)	0/8 (0.0%)	**RR 1.00** [0.02–45.13]	**0 fewer per 1000** [from 0 fewer to 0 fewer]	⊕○○○ VERY LOW	CRITICAL
Partial pressure of arterial oxygen (PaO2) (follow-up: 1 day; assessed with fibreoptic thermodilution pulmonary artery catheter)												
1[208]	randomized trials	not serious[g]	not serious	serious[b]	very serious[d,h]	none	8	8	–	median difference **12 mmHg higher** [2 lower to 30 higher]	⊕○○○ VERY LOW	CRITICAL

Continued

Exercise capacity - right ventricular hypertrophy (follow-up: 12 weeks; assessed with 6-minute walking distance)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[d,h]	none	56	63	–	MD **78.5 m higher** [24.1 lower to 181 higher]	⊕○○○ VERY LOW	CRITICAL
Exercise capacity - right ventricular systolic dysfunction (follow-up: 12 weeks; assessed with 6-minute walking distance)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	serious[h]	none	56	63	–	MD **99.3 m higher** [22.3 higher to 176.2 higher]	⊕○○○ VERY LOW	CRITICAL
Exercise capacity - no right ventricular hypertrophy (follow-up: 12 weeks; assessed with 6-minute walking distance)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[d,h]	none	56	63	–	MD **19.1 m higher** [18.1 lower to 56.4 higher]	⊕○○○ VERY LOW	CRITICAL
Exercise capacity - no right ventricular systolic dysfunction (follow-up: 12 weeks; assessed with 6-minute walking distance)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[d,h]	none	56	63	–	MD **10 m higher** [27.9 lower to 47.8 higher]	⊕○○○ VERY LOW	CRITICAL
Pulmonary vascular resistance index (PVRI) (follow-up: 1 day; assessed with fibreoptic thermodilution pulmonary artery catheter)												
1[208]	randomized trials	not serious[g]	not serious	serious[b]	very serious[h]	none	8	8	–	median difference **32.5% lower** [54.1 lower to 10.2 lower]	⊕○○○ VERY LOW	IMPORTANT
Mean pulmonary artery pressure (mPAP) (follow-up: 1 day; assessed with fibreoptic thermodilution pulmonary artery catheter)												
1[208]	randomized trials	not serious[g]	not serious	serious[b]	very serious[h]	none	8	8	–	median difference **26% lower** [15 lower to 40 lower]	⊕○○○ VERY LOW	IMPORTANT
Quality of life - right ventricular hypertrophy (follow-up: 12 weeks; assessed with St George's Respiratory Questionnaire)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	serious[h]	none	56	63	–	MD **14.8 points lower** [2.8 lower to 26.8 lower]	⊕○○○ VERY LOW	NA

Continued

Quality of life - right ventricular systolic dysfunction (follow-up: 12 weeks; assessed with St George's Respiratory Questionnaire)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	serious[h]	none	56	63	–	MD **13.4 points lower** [4.2 lower to 22.7 lower]	⊕○○○ VERY LOW	NA
Quality of life - no right ventricular hypertrophy (follow-up: 12 weeks; assessed with St George's Respiratory Questionnaire)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[d,h]	none	56	63	–	MD **3.4 points lower** [7.8 lower to 1 higher]	⊕○○○ VERY LOW	NA
Quality of life - no right ventricular systolic dysfunction (follow-up: 12 weeks; assessed with St George's Respiratory Questionnaire)												
1[207]	randomized trials	serious[a]	not serious	serious[b]	very serious[d,h]	none	56	63	–	MD **3 points lower** [7.6 lower to 1.7 higher]	⊕○○○ VERY LOW	NA

CI, confidence interval; RR, risk ratio; MD, mean difference.

Explanations

[a]The study reported a post hoc subgroup analysis, breaking the randomization from the original trial.

[b]Patients were not reported to have idiopathic interstitial pneumonia.

[c]Small sample with few events; did not meet the optimal information size and suggested fragility of the estimate.

[d]The 95% CI included the potential for both meaningful benefit and meaningful harm.

[e]Intervention not blinded to participants or investigators.

[f]No events reported; did not meet the optimal information size and suggested fragility of the estimate.

[g]Although the intervention was not blinded, the outcomes were physiological measurements and unlikely to be influenced by subjective perception.

[h]Small sample; did not meet the optimal information size and suggested fragility of the estimate.

15.4. Guideline development tool evidence profile for PICO IV

Question: Should patients with chronic thrombo-embolic pulmonary hypertension who are considered inoperable but candidates for balloon pulmonary angioplasty receive medical therapy before interventional therapy is initiated?

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Riociguat+BPA**	**BPA**	**Relative [95% CI]**	**Absolute [95% CI]**		
Pulmonary vascular resistance, Wood units (follow-up: 52 weeks)												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	36	31	-	MD **0.2 higher** [0.39 lower to 0.79 higher]	⊕◯◯◯ Very low	IMPORTANT
6-minute walking distance, metres (follow-up: 52 weeks)												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	36	31	-	MD **5 higher** [41.22 lower to 51.22 higher]	⊕◯◯◯ Very low	CRITICAL
Patients with ≥1 adverse events related to balloon pulmonary angioplasty (follow-up: 26 weeks)[c]												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	10/36 (27.8%)	19/52 (36.5%)	**RR 0.76** [0.40 to 1.44]	**88 fewer per 1000** [from 219 fewer to 161 more]	⊕◯◯◯ Very low	CRITICAL
Patients with ≥1 adverse events and/or severe adverse events related to balloon pulmonary angioplasty (follow-up: 26 weeks)[c]												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	12/36 (33.3%)	32/52 (61.5%)	**RR 0.54** [0.33 to 0.90]	**283 fewer per 1000** [from 412 fewer to 62 fewer]	⊕◯◯◯ Very low	CRITICAL
Patients with ≥1 severe adverse events related to balloon pulmonary angioplasty (follow-up: 26 weeks)[c]												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	5/36 (13.9%)	22/52 (42.3%)	**RR 0.33** [0.14 to 0.79]	**283 fewer per 1000** [from 364 fewer to 89 fewer]	⊕◯◯◯ Very low	CRITICAL

Continued

Patients with ≥1 severe balloon pulmonary angioplasty procedure-related complications (follow-up: 26 weeks)[c]												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	3/36 (8.3%)	18/52 (34.6%)	**RR 0.24** [0.08 to 0.76]	**263 fewer per 1000** [from 318 fewer to 83 fewer]	⨁◯◯◯ Very low	CRITICAL
Mean pulmonary arterial pressure, mmHg (follow-up: 52 weeks)												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	36	31	-	MD **5 higher** [2.11 higher to 7.89 higher]	⨁◯◯◯ Very low	NOT IMPORTANT
Cardiac output, L/min (follow-up: 52 weeks)												
1	randomized trial	very serious[a]	not serious	not serious	serious[b]	none	36	31	-	MD **0.6 higher** [0.02 higher to 1.18 higher]	⨁◯◯◯ Very low	NOT IMPORTANT
Survival, hospitalization, clinical worsening, quality of life, and lung injury - not reported												
–	–	–	–	–	–	–	–	–	-	-	-	-

BPA, balloon pulmonary angioplasty; CI, confidence interval; MD, mean difference; RR, risk ratio.

Explanations

[a]The RACE study was open-label and the allocation of intervention for the extended follow-up study was not randomized.

[b]A single study including 105 patients.

[c]Adverse events related to BPA, severe adverse events related to BPA, and severe BPA procedure-related complications were monitored from study week 1 to 26 in patients allocated to BPA first-line and from study weeks 27–52 in patients allocated to BPA second-line after riociguat (group riociguat+BPA).

The final results of the RACE trial[209] and the ancillary extended 6 month follow-up have not yet been published, but confidential trial results have kindly been shared with the Guideline Panel by the RACE study investigators.

16. Evidence to Decision (EtD) tables

16.1. Evidence to Decision for PICO I

Table S9 Evidence to Decision for PICO I

QUESTION

Should initial oral double combination therapy (ERAs and PDE5is) vs. monotherapy (ERAs, PDE5is) be used for symptomatic patients with pulmonary arterial hypertension?	
Population	Symptomatic patients with pulmonary arterial hypertension (PAH)
Intervention	Initial oral double combination therapy (ERAs and PDE5is)
Comparison	Monotherapy (ERAs, PDE5is)
Main outcomes	Hospitalization; unsatisfactory long-term clinical response; disease progression; exercise capacity; haemodynamic variables; cardiac biomarkers; quality of life; serious adverse events (including pulmonary hypertension, pneumonia); adverse events leading to discontinuation (including dyspnoea, peripheral oedema); and survival
Setting	A single, event-driven, multicentre, randomized, double-blind, phase 3–4 study with time to first event of clinical failure as primary end-point
Perspective	NA
Background	The RCT and its long-term extension were retained for analysis
Conflict of interests	See COI declaration of the whole Task Force

ASSESSMENT

Problem: Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	Early intervention is of major importance in PAH, with late intervention being associated with irreversible damage in the pulmonary circulation. The results of main RCTs with monotherapies showed modest improvements in exercise capacity and haemodynamics, and their effect on long-term outcomes was less well established. Combination therapy with drugs targeting different dysfunctional pathways is an appealing treatment strategy for patients with PAH. It may potentially increase the therapeutic effect of the agents on the mechanisms of the disease and provide additional clinical benefits. Previous clinical studies only investigated sequential add-on combination therapies leading to heterogeneous results in terms of clinical benefit. There is a single treatment strategy trial (AMBITION) comparing dual oral combination therapy (with an endothelin-receptor antagonist, ambrisentan, and a PDE5i, tadalafil) and monotherapy (with ambrisentan or tadalafil).	NA

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ☑ **Large** ○ Varies ○ Don't know	The single RCT (AMBITION) showed a desirable effect with dual oral combination therapy vs. oral monotherapy on the reduction in PAH-related hospitalization and improvement in exercise capacity assessed after 6 months (importance: critical; certainty: moderate). However, the risk of imprecision is serious due to the small number of events, which did not meet optimal information size and suggested fragility of the estimate. Other desirable effects—including reduction in unsatisfactory clinical response and disease progression, reduction in the level of cardiac biomarkers, and improvement in functional class, both assessed after 6 months—had lower certainty. In addition, the effect of initial dual oral combination therapy over monotherapy on survival was uncertain. Finally, the effect of the two strategies (initial dual oral combination	Additional registry data do not support a favourable effect of initial dual combination over monotherapy on survival. Analysis of the association between initial treatment strategy and survival in a large cohort of idiopathic, heritable, and anorexigen-associated PAH, diagnosed between 2006–2018 and enrolled in the French PH Registry ($n = 1611$), did not show any difference in long-term survival between patients initiated with dual combination therapy or monotherapy. A mild improvement in survival was observed with initial combination therapy in the subset of patients at intermediate risk.[210] In addition, despite the increasing use of initial combination therapy from 2010–2019 in patients enrolled in COMPERA ($n = 2531$), 1 and 3 year survival rates did not change over time.[211] Similar results have been observed in a large cohort of patients ($n = 435$) diagnosed at three major centres in Canada.[212]

Continued

	therapy or oral monotherapy) on cardiopulmonary haemodynamics was not assessed in AMBITION.	There is no haemodynamic evaluation from the AMBITION study. However, a favourable effect on cardiopulmonary haemodynamics has been shown with other combinations of an ERA and a PDE5i: French Registry,[213] OPTIMA study,[214] TRITON study.[215] There were no comparisons with monotherapy in those studies. Only historical haemodynamic data are available with oral monotherapies.

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ☑ **Small** ○ Trivial ○ Varies ○ Don't know	Peripheral oedema, headache, and nasal congestion are more common with combination therapy than with monotherapy. However, these undesirable effects are usually easily manageable. The incidence of hypotension, rates of discontinuation, and serious adverse events were similar with either combination therapy or monotherapy.	Initial dual oral combination therapy is considered as safe as monotherapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ☑ **Low** ○ Moderate ○ High ○ No included studies	Low, based on the lowest grading of the critical outcomes. Due to the presence of a single RCT and the small number of events, there was a serious imprecision in the results (did not meet optimal information size and suggested fragility of the estimate). The quality of evidence was low or moderate, depending on the outcome (due to the imprecision). Moderate certainty was observed for hospitalization and 6MWD, which are two major predictors of outcomes in PAH. There was a non-significant trend for improved survival with initial dual combination vs. monotherapy	Additional registry data do not support a favourable effect of initial dual combination over monotherapy on survival. Analysis of the association between initial treatment strategy and survival in a large cohort of idiopathic, heritable, and anorexigen-associated PAH, diagnosed between 2006–2018 and enrolled in the French PH Registry ($n = 1611$), did not show any difference in long-term survival between patients initiated with dual combination therapy or monotherapy. A mild improvement in survival was observed with initial combination therapy in the subset of patients at intermediate risk.[210] In addition, despite the increasing use of initial combination therapy from 2010–2019 in patients enrolled in COMPERA ($n = 2531$), 1 and 3 year survival rates did not change over time.[211] Similar results have been observed in a large cohort of patients ($n = 435$) diagnosed at three major centres in Canada.[212]

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	There are no included studies.	Patient preferences include usually fewer symptoms, better exercise capacity, better overall quality of life, using the most effective medicine rather than the most aggressive medicine. Haemodynamics seem to be less important for patients.

Continued

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ☑ **Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	The single RCT (AMBITION) showed a desirable effect with dual oral combination therapy vs. monotherapy on the reduction in PAH-related hospitalization and improvement in exercise capacity assessed after 6 months (importance: critical; certainty: moderate). However, the risk of imprecision was serious due to the small number of events, which did not meet optimal information size and suggested fragility of the estimate. Other desirable effects—including reduction in unsatisfactory clinical response and disease progression, as well as reduction in the level of cardiac biomarkers and improvement in functional class, both assessed after 6 months—had lower certainty. The effect on survival was also uncertain. Effect on cardiopulmonary haemodynamics was not assessed.	NA

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ☑ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	This was not formally assessed in the single trial.	Initial combination therapy is obviously more costly than monotherapy. The cost of intervention is variable across countries. However, ambrisentan and tadalafil are today generic worldwide and costs of medication are much lower than they were in the past. Reductions in hospitalizations may be associated with savings. The balance between the cost of the drugs and savings in hospitalization costs may differ between health care systems.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ☑ **Low** ○ Moderate ○ High ○ No included studies	There is no pharmaco-economic analysis.	NA

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ☑ **Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	This was not formally assessed in the single trial.	The beneficial effect of initial dual oral combination therapy on the reduction in PAH-related hospitalizations (which represents the highest cost in the care of patients with PAH) may be associated with cost savings. The reduction in hospitalization combined with the reduction in medication costs could be cost-effective. However, the balance between the cost of drugs and savings in hospitalization costs may differ between health care systems.

Continued

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ☑ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no included studies. However, it is not believed that this intervention would have an impact on health equity.	NA

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	There are no included studies.	Stakeholders would likely consider the intervention acceptable due to the large utilization of this approach in clinical practice.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	There are no included studies.	There is no real barrier to feasibility in the general management of PAH (oral drugs).

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	Trivial	Small	Moderate	**Large**	NA	Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**	NA	Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High	NA	NA	No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High	NA	NA	No included studies

Continued

Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	☑	○

CONCLUSIONS

Recommendations
The available data support a positive recommendation, despite the low certainty of evidence (a single RCT; small number of events). The primary end-point of time to death or morbidity event was met (driven by the reduction in hospitalizations). Secondary efficacy end-points such as change in exercise capacity (6MWD) and cardiac biomarkers (NT-proBNP) are also in favour of initial combination therapy. The lack of haemodynamic evaluation is a weakness. There is no safety concern. Finally, the long-term effect on survival is uncertain. Recommendation: For symptomatic patients with pulmonary arterial hypertension, it is suggested to initiate oral double combination therapy (endothelin receptor antagonists and phosphodiesterase type 5 inhibitors) (conditional recommendation for the intervention, low-quality evidence).
Justification
Although the quality of evidence is low, initial oral combination therapy with an ERA and PDE5i achieves important targets such as improvement in symptoms (functional class), exercise capacity, and cardiac biomarkers. The reduction in hospitalizations is an important effect, as it is usually associated with improved survival (not demonstrated in the single RCT).
Subgroup considerations
NA
Implementation considerations
NA
Monitoring and evaluation
NA
Research priorities
Further data on the comparison of initial combination therapy and monotherapy followed by sequential combination therapy if needed would be welcome. If an RCT is difficult to consider, a deep analysis into registries could address this question.

16.2. Evidence to Decision for PICO II

Table S10 Evidence to Decision for PICO II

QUESTION

Should phosphodiesterase type 5 inhibitors be used for patients with combined post- and pre-capillary pulmonary hypertension due to heart failure with preserved ejection fraction?	
Population	Patients with combined post- and pre-capillary pulmonary hypertension due to HFpEF
Intervention	Phosphodiesterase type 5 inhibitors
Comparison	No phosphodiesterase type 5 inhibitors
Main outcomes	Mortality; CV morbidity (cardiac failure); hospitalization/clinical worsening; quality of life; primary safety endpoint (composite: cardiac failure, intestinal infarction, death); non-study specific SAEs (pneumonia, vascular pseudoaneurysm, medical device complication, elective surgery, respiratory tract infection); exercise capacity; echocardiography - PAP; echocardiography - RVSP; echocardiography - TAPSE; echocardiography - RVEF; echocardiography - CO; pulmonary vascular resistance; biomarkers (NT-proBNP).

Continued

Setting	Only placebo-controlled clinical trials reporting invasive haemodynamics were considered for analysis.
Perspective	NA
Background	Data from registries showed that PDE5i are occasionally used to treat patients with HFpEF and PH, despite a class III recommendation in previous guidelines. There are no RCTs on PDE5i that specifically enrolled patients with HFpEF and CpcPH. As additional information, two RCTs in patients with HFpEF and PH were retained for analysis, both being conducted with sildenafil as study drug.
Conflict of interests	See the COI declaration of the whole Task Force.

ASSESSMENT

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	There is clear evidence that HFpEF and PH due to HFpEF are areas of unmet medical need. When present, PH at rest was associated with a worse outcome (see references in the text). In addition, the presence of a pre-capillary component was a strong marker of outcome. Until now, there is no approved therapy for the underlying cause of PH. Although data from registries, case series, or retrospective analysis suggested a benefit from the intervention, there is a need to establish specific therapies through RCTs.	NA

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ☑ **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	There are no RCTs on PDE5i that specifically enrolled patients with HFpEF and CpcPH. Two small RCTs were identified that were performed in patients with HFpEF and PH, with variable haemodynamic profiles: (1) In patients with predominantly an IpcPH profile, sildenafil vs. placebo had no effect on PAPm (primary endpoint), or other haemodynamic and clinical measures. (2) In patients with a predominantly CpcPH profile, sildenafil vs. placebo improved haemodynamics, RV function, and quality of life (QoL) at 6 and 12 months. No data on cardiovascular events (mortality, hospitalizations) are available.[205,206]	In addition, retrospective data from single centre analyses suggest that PDE5i may improve haemodynamics, symptoms, and exercise capacity in selected patients with HFpEF and severe PH (i.e. a pre-capillary component characterized by an increase in PVR >5 WU.[216] In addition, analysis of the prospective registry COMPERA suggested improvements in exercise capacity with PDE5i therapy in patients with HFpEF-PH who also had an elevated PVR (7.0 ± 3.4 WU), albeit to a lesser extent than in patients with PAH.[217] Long-term data on the effects of PDE5i against a comparator on clinical worsening events and survival were not provided in these studies.

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ☑ **Trivial** ○ Varies ○ Don't know	In line with the above desirable effects, there are also no RCTs on PDE5i that specifically enrolled patients with HFpEF and CpcPH with respect to undesirable effects. There is no evidence on the safety, tolerability, and efficacy of PDE5i from RCTs specifically performed in patients with HFpEF-CpcPH. The analysis from the available studies assessing the use of PDE5i in patients with HFpEF and PH did not suggest	There was also no safety signal for PDE5i vs. placebo in an RCT in patients with HFpEF who were not selected for the presence of PH.[218] In a COMPERA analysis,[217] the overall rate of PDE5i withdrawal was higher in patients with PH associated with HFpEF than in patients with 'atypical' and 'typical' idiopathic pulmonary arterial hypertension (18.4%, 13.2%, and 8.8%, respectively), which was partly due to non-specified side effects (5.3%, 3.8%, and 2.6%, respectively).

Continued

	undesirable effects besides the known side effects of PDE5i therapy. Although the certainty of evidence was low, there was no undesirable effect identified within the two RCTs in patients with HFpEF and PH. The intervention appears safe.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○Very low ☑ **Low** ○ Moderate ○ High ○ No included studies	Based on GRADE assessment, see GRADE evidence profile.	The presence of conflicting results obtained in heterogenous populations and the small sample sizes made the overall quality of the evidence low.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No evidence identified.	While there are no data on how patients with PH-HFpEF value major outcomes, there is evidence from HFpEF and other forms of PH that important patient-related outcomes include exercise capacity, breathlessness, QoL, and survival. There is no reason to assume that patients with PH-HFpEF have a different perspective on these outcomes than patients with HFpEF alone or other forms of PH.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ☑ **Does not favour either the intervention or the comparison** ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Although there is no negative safety signal, the current evidence is insufficient to determine the balance of desirable and undesirable effects of PDE5i in patients with HFpEF and PH.	NA

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ☑ **Don't know**	No evidence identified. There is no pharmacoeconomic analysis available.	The costs of the intervention vary between countries but are generally considered moderate. Potential savings through reduction in hospitalizations have not been assessed and therefore cannot be considered.

Continued

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ☑ **No included studies**	No evidence identified. There is no pharmacoeconomic analysis available.	The costs of PDE5is can be obtained from current local price lists.

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **No included studies**	No evidence identified. This has not been formally assessed.	There was no cost-effectiveness analysis in the two studies mentioned above.

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ☑ **Don't know**	No data available.	It is difficult to assess the risk of inequity, given the small number of patients included in RCTs, which makes the subgroup/groups at risk of inequity feasibility.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ☑ **Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	No evidence identified.	Based on the available evidence and given the conflicting data in heterogenous patient cohorts, stakeholders would unlikely consider the intervention acceptable.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	No evidence identified.	Implementation of PDE5i therapy in patients with HHpEF-CpcPH would be feasible if there was sufficient evidence suggesting beneficial effects on patient-relevant outcomes to convince the key stakeholders to introduce and reimburse this treatment. There is no barrier to feasibility in the general context, but RHC would be required to establish the diagnosis. Therefore, feasibility would be restricted to facilities experienced with both PH and HF.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	**Trivial**	Small	Moderate	Large	NA	Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**	NA	Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High	NA	NA	No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
Acceptability	No	**Probably no**	Probably yes	Yes	NA	Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes	NA	Varies	Don't know

TYPE OF RECOMMENDATION: NO RECOMMENDATION ON THE USE OF PDE5i IN PATIENTS WITH HFpEF AND COMBINED POST- AND PRE-CAPILLARY PH

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

TYPE OF RECOMMENDATION: CONDITIONAL RECOMMENDATION AGAINST THE USE OF PDE5i IN PATIENTS WITH HFpEF AND ISOLATED POST-CAPILLARY PH

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	☑	○	○	○

CONCLUSIONS

Recommendation
No recommendation can be given for or against the use of PDE5i in patients with HFpEF and combined post- and pre-capillary PH (no recommendation, no identified evidence). The use of PDE5i in patients with HFpEF and isolated post-capillary PH is not suggested (conditional recommendation, low quality of evidence). For patients with a severe pre-capillary component (e.g. PVR >5 WU), referral to an expert centre for individual decision-making is recommended.
Justification
The following considerations were made: There are no RCTs on PDE5i that specifically enrolled patients with HFpEF and CpcPH. Hence, there are no data from RCTs on the safety, tolerability, and efficacy of PDE5i in this patient population. Harmful effects cannot be excluded, even if the available data from clinical studies, case series, and registries suggest that PDE5i may be safely administered in patients with HFpEF-CpcPH. The additional data identified and included in the GRADE evidence profiles did not enable firm conclusions to be drawn for these specific patient populations. **As a result, a general recommendation cannot be made for the use of PDE5i in patients with HFpEF and CpcPH.** Case series and registry data indicate that physicians occasionally treat patients with HFpEF-CpcPH with PDE5i, especially those with a severe pre-capillary component (e.g. PVR >5 WU). Case series and registry data also suggest that exercise capacity and RV function may improve in some patients with such a haemodynamic profile with PDE5i treatment. **Based on this, it is recommended that such patients (particularly those with echocardiographic signs of a severe pre-capillary component [e.g. PVR >5 WU] and/or predominant right-sided heart failure) are referred to a PH centre for individualized decision-making.** The two identified monocentric RCTs with small sample sizes conducted in patients with HFpEF and PH led to conflicting results with low level of evidence. One study in 52 patients with HFpEF and predominantly IpcPH[205] did not demonstrate a benefit on haemodynamics and exercise capacity after 12 weeks of sildenafil therapy. This was confirmed in a long-term analysis of this cohort. Another study in 44 patients with HFpEF and a predominantly CpcPH haemodynamic profile[206] showed improvements in haemodynamics, RV function, and QoL after 6 and 12 months of sildenafil therapy. Based on these studies, the use of PDE5i in not suggested in patients with HFpEF and IpcPH. The absence of any detectable treatment effect in patients with an IpcPH profile is consistent with the pathophysiological concept that there is no treatable target in the absence of an elevated PVR.
Subgroup considerations
The Task Force acknowledges that, based on the current evidence, a severe pre-capillary component in HFpEF-CpcPH may be defined by a PVR >5 WU, although this threshold needs to be further validated. In the absence of robust evidence, no further considerations on CpcPH subtypes in patients with HFpEF are provided.
Implementation considerations
The Task Force believes that, given the current very low level of evidence, any treatment decision-making in HFpEF-CpcPH should be considered in expert centres after careful evaluation. It is acknowledged that the profile of patients who may benefit from treatment with a PDE5i is currently unknown.
Monitoring and evaluation
Patients with HFpEF-CpcPH should be carefully monitored.
Research priorities
Further evaluation of the safety and efficacy of PDE5i in patients with HFpEF-CpcPH is considered a research priority, as registry data indicate that PDE5i are used in subsets of patients with HFpEF-CpcPH (especially in those with a severe pre-capillary component), despite the absence of robust data. Prospective RTCs are required to inform on the effects of PDE5i, focusing on safety, tolerability, exercise capacity, QoL, and survival. The survival aspect is crucial, which is why short-term studies alone are insufficient to generate the evidence that is needed to inform the key stakeholders on the safety and efficacy of PDE5i in patients with HFpEF-CpcPH. It may be neither feasible nor necessary to demonstrate improved survival if the intervention shows improvements in patient-relevant outcomes such as exercise capacity and QoL, but it will be necessary to demonstrate that there are a no adverse effects on survival.

16.3. Evidence to Decision for PICO III

Table S11 Evidence to Decision for PICO III

QUESTION

Should phosphodiesterase type 5 inhibitors be used for patients with severe pulmonary hypertension due to interstitial lung diseases?	
Population	Patients with severe PH associated with idiopathic interstitial pneumonia.
Intervention	Phosphodiesterase type 5 inhibitors.
Comparison	No phosphodiesterase type 5 inhibitors.

Continued

Main outcomes	Mortality - right ventricular hypertrophy; mortality - right ventricular systolic dysfunction; mortality - no right ventricular hypertrophy; mortality - no right ventricular systolic dysfunction; safety; partial pressure of arterial oxygen (pO_2); exercise capacity - right ventricular hypertrophy; exercise capacity - right ventricular systolic dysfunction; exercise capacity - no right ventricular hypertrophy; exercise capacity - no right ventricular systolic dysfunction; Pulmonary Vascular Resistance Index (PVRI); mean pulmonary arterial pressure (mPAP); quality of life - right ventricular hypertrophy; quality of life - right ventricular systolic dysfunction; quality of life - no right ventricular hypertrophy; quality of life - no right ventricular systolic dysfunction.
Setting	NA
Perspective	NA
Background	Data from registries show that PDE5is are occasionally used to treat patients with PH-ILD, despite a class III recommendation in previous guidelines.
Conflict of interests	See COIs for the Task Force.

ASSESSMENT

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	Registry data indicate that physicians use PDE5is to treat patients with idiopathic interstitial pneumonia (IIP) and PH. There is also data from registries and case series suggesting that PDE5is may be safe in this patient population and that some patients derive clinical benefit.[219] The safety of PDE5is, mainly sildenafil, has been demonstrated in RCTs that enrolled patients with various forms of ILD, but the clinical benefit is unclear, mainly because these trials did not use RHC as entry criteria.	The RISE-IIP study with riociguat, a soluble guanylate cyclase stimulator, in patients with idiopathic interstitial pneumonias, was terminated because of signals increasing a higher risk of clinical worsening events including death.[220] As both PDE5is and riociguat act via the same pathway, it will be critical to obtain survival data with the use of PDE5is.

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ☑ **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Sildenafil given as single dose of 50 mg acutely improved pulmonary vascular resistance and oxygenation in patients with PH associated with pulmonary fibrosis. In patients with ILD and right ventricular dysfunction, exercise capacity may be better preserved and QoL may be improved with sildenafil and placebo.	Most of the available data come from studies that did not include patients with ILD and documented PH. Additional studies that were considered were STEP-IPF[221] and the INSTAGE study[222]; both studies included patients with idiopathic pulmonary fibrosis without documented PH; STEP-IPF did not meet its primary endpoint (increase in 6MWD by ≥20%), but showed improvement in QoL with the use of sildenafil. INSTAGE did not confirm this finding and was negative for all outcome measures. Both studies did not find safety signals of concern. Registry data suggest that some patients with ILD and documented PH may improve exercise capacity with PDE5i therapy, especially when PH is severe.[219] So far, there is no indication that this intervention improves survival of patients with PH-ILD.

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ☑ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	No adverse events were noted with the administration of sildenafil as a single dose of 50 mg in patients with PH-ILD. Adverse events were not reported in the study by Han *et al.*[207]	The potential for undesirable effects of PDE5is in patients with PH-ILD is unclear. Well-known side effects of PDE5is—such as headache, heartburn, and diarrhoea-—have been reported to occur in patients with PH-ILD with a similar frequency as in patients with other conditions. In patients with PH-ILD, long-term administration of PDE5is may have detrimental effects on oxygenation, but this has not been sufficiently explored.

Continued

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
☑ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Very low based on the lowest score for critical outcomes.	There is no evidence on the safety, tolerability, and efficacy of PDE5is from RCTs in patients with PH-ILD.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No evidence identified.	While there are no data on how patients with PH-ILD value major outcomes, there is evidence from other forms of PH that important patient-related outcomes include exercise capacity, breathlessness, QoL, and survival. There is no reason to assume that patients with PH-ILD have a different perspective on these outcomes than patients with other forms of PH.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **Don't know**	The current evidence is insufficient to determine the balance of desirable and undesirable effects of PDE5is in patients with PH-ILD.	NA

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ☑ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No evidence identified.	The costs of the intervention vary between countries but are generally considered moderate.

Continued

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
☑ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	No evidence identified.	The costs of PDE5is can be obtained from current local price lists.

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **No included studies**	No evidence identified.	NA

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ☑ **Don't know**	No data available.	NA

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
☑ **No** ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No evidence identified.	Based on the available evidence, the intervention will not be acceptable for patients, physicians, and payers.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	No evidence identified.	Implementation of PDE5i therapy in patients with PH-ILD would be feasible if there was sufficient evidence suggesting beneficial effects on patient relevant outcomes to convince the key stakeholders to introduce and reimburse this treatment.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	Trivial	Small	**Moderate**	Large	NA	Varies	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial	NA	Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High	NA	NA	No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
Acceptability	No	Probably no	**Probably yes**	Yes	NA	Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	☑	○	○	○

CONCLUSIONS

Recommendations
The use of PDE5i in patients with ILD and non-severe PH is currently not recommended (conditional recommendation against the intervention, very low quality of evidence). For patients with ILD and severe PH, individual decision-making is recommended.
Justification
There is no direct data from RCTs on the safety, tolerability, and efficacy of PDE5is in patients with PH-ILD. The indirect data we included does not allow us to draw firm conclusions. Harmful effects cannot be excluded even if case series and registry data suggest that PDE5is may be safely administered in patients with PH-ILD. Case series and registry data indicate that some patients with PH-ILD are receiving PDE5i therapy, especially those with severe PH (with variable criteria having been used for defining severe PH). Case series and registry data also suggest that some patients with PH-ILD seem to benefit from PDE5i treatment. Given the lack of robust evidence, the Task Force members felt unable to provide a recommendation for or against the use of PDE5is in patients with ILD and severe PH, and recommend that these patients are referred to a PH centre for individualized decision-making. For patients with ILD and non-severe PH, it is not recommended to use PDE5is.

Continued

Subgroup considerations
In the absence of evidence, no further considerations on ILD subtypes are provided.
Implementation considerations
The Task Force believes that, given the current levels of evidence, PDE5i therapy should not be used in most patients with PH-ILD. However, it is acknowledged that there are patients with ILD and severe PH who may benefit from PDE5i treatment. In the absence of robust evidence, this decision should be made individually in PH centres. It is acknowledged that PDE5is are not approved for patients with PH-ILD and that reimbursement will depend on local regulations.
Monitoring and evaluation
Patients with PH-ILD who are being treated with PDE5is should be carefully monitored for efficacy and safety. Such monitoring should include measurements of oxygenation, which may deteriorate with PDE5i treatment.
Research priorities
Further evaluation of the safety and efficacy of PDE5is in patients with PH-ILD is considered a research priority, as registry data indicate that PDE5is are widely used in patients with PH-ILD (especially in those with severe PH), despite the absence of robust data. Prospective RCTs are required, which should inform on the effects of PDE5is, focusing on safety, tolerability, exercise capacity, QoL, and survival. The survival aspect is crucial, which is why short-term studies alone are insufficient to generate the evidence that is needed to inform the key stakeholders on the safety and efficacy of PDE5is in patients with PH-ILD. It may be neither feasible nor necessary to demonstrate improved survival if the intervention shows improvements in patient-relevant outcomes such as exercise capacity and QoL, but it will be necessary to demonstrate that there are a no adverse effects on survival.

16.4. Evidence to Decision for PICO IV

Table S12 Evidence to Decision for PICO IV

QUESTION

Should patients with chronic thrombo-embolic pulmonary hypertension who are considered inoperable but candidates for balloon pulmonary angioplasty receive medical therapy before interventional therapy is initiated?	
Population	Patients with chronic thrombo-embolic pulmonary hypertension who are considered inoperable but candidates for balloon pulmonary angioplasty (BPA).
Intervention	Medical therapy before BPA.
Comparison	BPA without medical pre-treatment.
Main outcomes	Critical outcomes: survival, hospitalization, clinical worsening, exercise capacity, lung injury, and safety. Important outcomes: pulmonary vascular resistance and quality of life.
Setting	Placebo-controlled clinical trials and case series reporting invasive haemodynamics were considered for analysis.
Perspective	NA
Background	NA
Conflict of interests	See the COI declaration of the whole Task Force.

ASSESSMENT

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	There is evidence from an RCT that medical therapy is improving PVR and 6MWT in patients with inoperable CTEPH, but this does not normalize the haemodynamics. There are data from retrospective studies that series of BPA interventions can normalize the haemodynamics, but BPA is associated with periprocedural complications including deaths. Until now, there is no evidence that medical therapy introduced prior to BPA intervention can improve outcome (improved haemodynamics, functional status, and safety during BPA procedures). Although case series or retrospective analysis suggest a benefit from the interventions, there is a need to establish specific therapies through RCTs.	NA

Continued

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ☑ **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Only the RACE RCT[223,224] provided efficacy data for this question. Riociguat therapy before BPA compared with BPA had no significant effect on 6MWD at 52 weeks [mean difference (MD) = 5 metres; 95% CI, –41.22, 51.22; 67 participants; very low certainty] and no significant effect on PVR at 52 weeks (MD = 0.2 WU; 95% CI, −0.39, 0.79; 67 participants; very low certainty). The RACE trial also reported on two additional outcomes that had not been considered critical or important by the Guideline panel: PAP and cardiac output. Given the fact that there were limited data for this question, it was decided a posteriori to also consider these outcomes. Riociguat therapy before BPA compared with BPA resulted in higher mean PAP at 52 weeks (MD = 5 mmHg; 95% CI, 2.11, 7.89; 67 patients; very low certainty) and higher cardiac output (MD = 0.6 L/min; 95% CI, 0.02, 1.18; 67 patients; very low certainty).	In a prospective single-centre study, 36 consecutive patients with inoperable CTEPH were treated with riociguat before BPA.[225] Significant improvements in pulmonary haemodynamics and physical capacity were observed for riociguat treatment, and subsequent BPA interventions yielded further benefits.

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ☑ **Small** ○ Trivial ○ Varies ○ Don't know	Only the RACE RCT[223,224] provided safety data for this question. Riociguat therapy before BPA compared with BPA resulted in lower risk of adverse events (AE) and/or severe adverse events (SAE) related to BPA during 26 weeks (absolute risk = 283 fewer patients with ≥1 AE and/or SAE related to BPA per 1000 patients; 95% CI, from 412 to 62 fewer patients, 88 patients; very low certainty). Riociguat before BPA lowered the risk of SAE related to BPA during 26 weeks (absolute risk = 283 fewer participants with ≥1 SAE related to BPA per 1000 patients; 95% CI, from 364 to 89 fewer patients; 88 patients; very low certainty). Riociguat before BPA was also safer compared to BPA when severe BPA procedure-related complications were analysed during 26 weeks (absolute risk = 263 fewer patients with ≥1 severe BPA procedure-related complications, from 318 to 83 fewer patients; 88 patients; very low certainty). However, there was similar risk of AE related to BPA when comparing riociguat+BPA and BPA (absolute risk = 88 fewer patients with ≥1 AE related to BPA per 1000 patients; 95% CI, from 219 fewer to 161 more patients; 88 patients; very low certainty).	Riociguat initiated prior to BPA may improve the safety of BPA, most likely by optimizing pre-BPA pulmonary haemodynamics.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
☑ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Based on the low level of quality for critical outcomes.	The presence of one RCT, one small size single-centre prospective stud, and one retrospective single-centre study provided limited evidence to the analysed data.[225,226]

Continued

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ☑ **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No evidence on values and preferences from the included study.	Quality of life was measured in a single centre study showing improvement in QoL with BPA. Hug KP, *et al.*[226] Clinical experience from several centres across the world shows functional improvement on top of haemodynamic improvement. Given the diverse populations and practice, the studies retained for analysis provide consistency to support a possible positive recommendation.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ☑ **Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	Although the decrease in PVR at 1 year was similar regardless of the first-line treatment that was used (BPA or riociguat) and there was no significant difference between BPA and riociguat used as first-line therapy for change in 6MWD at 1 year (+46 m vs. +58 m), the incidence of SAE related to BPA was much lower when BPA was preceded by 6 months of treatment with riociguat compared with BPA first line.	Additional clinical worldwide experience shows that BPA is safer after pre-treatment with medical therapy.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ☑ **Don't know**	There is no cost-effectiveness analysis in the included study.	The cost of the intervention is variable between countries.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ☑ **No included studies**	There is no health economic analysis provided in the included study.	See above.

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **No included studies**	There is no cost-effectiveness analysis in the included study.	NA

Continued

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ☑ **Don't know**	There is no evidence from the included trial supporting such analysis.	It is difficult to assess the risk of inequity, given the small number of patients included.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ☑ **Probably yes** ○ Yes ○ Varies ○ Don't know	NA	Given the limiting but encouraging evidence, stakeholders might consider the intervention acceptable.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ☑ **Probably yes** ○ Yes ○ Varies ○ Don't know	NA	There is no real barrier to feasibility in the general context of the management of CTPH. However, as BPA is a highly specialized intervention, feasibility would be restricted to facilities treating CTPH. In other words, this would be unfeasible in all facilities.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large	NA	Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial	NA	Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High	NA	NA	No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**

Continued

Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
Acceptability	No	Probably no	**Probably yes**	Yes	NA	Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	☑	○

CONCLUSIONS

Recommendations
In patients with CTEPH who are candidates for BPA, medical therapy should be considered prior to the intervention (conditional recommendation for the intervention, very low quality of evidence).
Justification
The included evidence suggested that pre-treatment improves pulmonary haemodynamics and safety of the procedure. This was confirmed by the clinical experience of the Task Force members. However, due to the low certainty of the evidence, the recommendation is conditional.
Subgroup considerations
Implementation considerations
Monitoring and evaluation
Research priorities
More RCTs are needed to re-assess haemodynamics and long-term outcomes on bigger populations.

16.5. Evidence to Decision for key narrative question 2

Table S13 Evidence to Decision for key narrative question 2

QUESTION 2 (NARRATIVE)

Should new echocardiographic probability of pulmonary hypertension approaches be proposed in symptomatic patients with a suspicion of pulmonary hypertension?	
Population	Suspected PH.
Intervention	Echocardiography testing.
Purpose of the test	To improve accuracy of the diagnostic algorithm for PH.
Role of the test	To establish the echocardiographic probability of PH based on TR velocity and indirect signs of PH.
Linked treatments	NA
Anticipated outcomes	NA
Setting	NA
Perspective	NA
Background	NA
Subgroups	NA
Conflict of interests	None

ASSESSMENT

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	It is a priority, as the haemodynamic definition of PH has changed.	NA

Test accuracy

How accurate is the test?

Judgement	Research evidence	Additional considerations
○ Very inaccurate ○ Inaccurate ☑ **Accurate** ○ Very accurate ○ Varies ○ Don't know	Echocardiographic criteria for PH probability have high sensitivity and good specificity.	NA

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
☑ **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The introduction of a new haemodynamic definition of PH would not change the sensitivity of the echocardiographic PH probability criteria.	NA

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ☑ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	The introduction of a new haemodynamic definition of PH would reduce the specificity of the echocardiographic PH probability criteria.	NA

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	The certainty of the evidence of test accuracy is moderate based on the four included studies.	Adding new echocardiographic indices among the indirect signs of PH will enable increased specificity, maintaining high sensitivity.

Continued

Certainty of the evidence of test effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects, or burden of the test?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	The burden of the evidence for direct benefits of the test is moderate. No potential adverse effects can be considered, as echocardiography is an easy and non-invasive test.	NA

Certainty of the evidence of management effects

What is the overall certainty of the evidence of effects of management effects that is guided by the test results?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Increasing the specificity and positive predictive value of the test (echocardiographic probability of PH) is crucial to avoid unnecessary RHC in individuals without PH.	NA

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Increasing the specificity and positive predictive value of the test (echocardiographic probability of PH) is crucial to avoid unnecessary RHC in individuals without PH.	NA

Certainty of effects

What is the overall certainty of the evidence of effects of the test?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	The new echocardiographic indirect signs of PH have been investigated in two monocentric studies.	NA

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	Not applicable.	NA

Continued

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ☑ **Favours the intervention** ○ Varies ○ Don't know	Including new echocardiographic indices of indirect signs of PH increases specificity without reducing sensitivity of the test.	As the echocardiographic evaluation is non-invasive, the assessment of new indices should be offered to all patients with suspected PH.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ☑ **Large savings** ○ Varies ○ Don't know	There are no additional costs, as the new indices are measured during the echocardiographic evaluation already scheduled for suspected PH.	NA

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ☑ **No included studies**	Not reviewed as part of this question.	NA

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ☑ **Favours the intervention** ○ Varies ○ No included studies	Not reviewed as part of this question.	The introduction of new echocardiographic indices will increase specificity, maintaining high sensitivity, without increased costs.

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ☑ **Probably increased** ○ Increased ○ Varies ○ Don't know	Not reviewed as part of this question.	Unequal access to echocardiographic testing should not occur, as the test is widely available among centres.

Continued

Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	Not reviewed as part of this question.	The echocardiographic testing is non-invasive and the addition of new simple indices is not time-consuming and may be considered acceptable by practitioners.

Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	The new indices are collected during routine echocardiographic evaluation of the probability of PH and are easy to measure, without significant prolongation of the testing.	NA

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	**Accurate**	Very accurate	NA	Varies	Don't know
Desirable effects	**Trivial**	Small	Moderate	Large	NA	Varies	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial	NA	Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of the evidence of test effects	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of the evidence of management effects	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of the evidence of test result/ management	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of effects	Very low	Low	**Moderate**	High	NA	NA	No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know

Continued

Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	☑	○

CONCLUSIONS

Recommendation
It is recommended not to change the TR velocity cut-off values for estimating the echocardiographic probability of PH. It is recommended to use the echocardiographic probability of PH in the diagnostic algorithm, including the new set of parameters among the indirect signs of PH to improve overall accuracy. Cardiopulmonary exercise testing may also be considered in particular settings to further improve accuracy.
Justification
The new haemodynamic definition of PH would not reduce sensitivity and negative predictive value of the current TR velocity cut-off values for estimating the echocardiographic probability of PH, while the application of new echocardiographic indices of indirect signs would increase the specificity and positive predictive value.
Subgroup considerations
Symptomatic patients with risk factors or associated conditions for PAH and intermediate echocardiographic probability of PH should be considered for further investigation with cardiopulmonary exercise testing, in order to improve the accuracy of the diagnostic algorithm in keeping with the new definition of PH, especially for scleroderma patients.
Implementation considerations
Echocardiographic testing is non-invasive and the addition of new simple indices is not time-consuming and may be considered acceptable by practitioners. Unequal access to echocardiographic testing should not occur, as the test is widely available among centres.
Monitoring and evaluation
NA
Research priorities
Further studies are needed to find new echocardiographic indices of indirect signs of PH, to increase the overall accuracy of the test. Further studies are needed to increase the evidence in favour of the application of the CPET, to increase the accuracy of the echocardiographic probability of PH.

16.6. Evidence to Decision for key narrative question 3

Table S14 Evidence to Decision for key narrative question 3

QUESTION 3 (NARRATIVE)

Should screening be offered to guide detection of pulmonary arterial hypertension in systemic sclerosis?	
Population	Patients with a diagnosis of systemic sclerosis (SSc).
Intervention	Systematic application of a test or tests to guide detection of pulmonary arterial hypertension (PAH).
Purpose of the test	To diagnose PAH in at-risk asymptomatic individuals or individuals who would not otherwise have sought medical attention on account of their symptoms.
Role of the test	To identify patients at risk of PAH for RHC (gold standard test to confirm or refute a diagnosis of PAH).
Linked treatments	Drug therapies for PAH.
Anticipated outcomes	Detection of less severe (haemodynamic) disease compared with patients not screened for PAH. Improved outcomes in patients with PAH who receive treatment at an earlier stage.
Setting	Deployment of screening programme in health care professionals managing patients with SSc; primarily rheumatologists in the secondary care setting.
Perspective	Healthcare professionals with patient involvement.
Background	In SSc, prevalence of PAH is high (5–19%) and the leading cause of death is due to SSc-related organ involvement. Prior to the advent of PAH therapies, patients presented with advanced and severe disease, and prognosis was very poor. Therapies for PAH prevent clinical worsening and improve survival. Patients with less severe disease at diagnosis have improved outcomes compared with those with more severe disease. Earlier treatment would be expected to improve outcomes. The high prevalence of PAH in SSc supports screening of asymptomatic patients and early detection of PAH in those who would not otherwise have sought medical advice.
Subgroups	No specific subgroup analysis. Patients with diffuse and limited disease analysed as a single group.
Conflict of interests	See ESC declaration of interest.

ASSESSMENT

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	PAH is a leading cause of death related to SSc organ involvement. Prior to PAH therapies, SSc-PAH was associated with a poor prognosis with a 3 year survival of 30%.[227] Mortality remains high despite PAH-specific therapy; a meta-analysis reported 1 and 3 year survival rates of 81% and 52%, respectively.[228] Evidence for the practicality of screening to detect less severe haemodynamic disease in SSc was provided by an early detection screening programme in France that combined echocardiography and symptomatic assessment to determine the need for RHC.[229] Compared with a contemporary non-screened cohort they had less severe haemodynamic disease and 1 and 5 year survival of 100% and 73% compared with 75% and 25%, respectively.[230] Limitations included small numbers and lead time, and length-time bias; however, this provides a strong rationale for screening for PAH in SSc. The high prevalence of PAH in SSc and the impact on survival makes screening for PAH in SSc attractive; however, there is concern regarding the limitations of available screening tools.[231]	NA

Test accuracy

How accurate is the test?

Judgement	Research evidence	Additional considerations
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate	A number of tests can be used to screen for PAH. Early screening recommendations for SSc were based on echocardiography alone; however, up to 29% of patients with PAH may be missed using this approach.[232] A number of screening algorithms using a combination of clinical features, echocardiography, lung function, and NT-proBNP to select patients for RHC have been studied. The DETECT study is the only study to perform RHC (the gold standard test for a diagnosis of PAH) in all	NA

Continued

☑ **Varies** ○ Don't know	patients with SSc who were screened for PAH, allowing calculation of a true false negative rate. The DETECT algorithm proposes a two-step approach. In step one, six variables, presence or absence of telangiectasia, forced vital capacity (FVC)%/DLCO%, right axis deviation on ECG, anti-centromere antibody status, serum urate, and NT-proBNP are used to decide the need for echocardiography or proceeding straight to RHC. In step two, the step one prediction score and two echocardiographic variables determine referral to RHC.[232] In this enriched cohort of patients (disease duration >3 years with other and DLCO < 60%), 4% of patients with PAH were missed compared with 29% using echocardiography alone. Using the DETECT algorithm, overall sensitivity was high at 96%, although specificity was significantly lower at 48% and in the population studied PPV 35% and NPV 98%. The downside to the high sensitivity of the algorithm is the high RHC referral rate. Other screening approaches can also be used for PAH. The Australian Scleroderma Interest Group (ASIG) has used an algorithm based on lung function (DLCO < 70% and FVC/DLCO ≥1.8) and/or NT-proBNP > 210 pg/mL to select patients for further testing, including RHC and reported sensitivity, specificity, positive and negative predictive values of 94.1%, 54.5%, 61.5%, and 92.3%, respectively.[233] This combined approach improved diagnostic accuracy compared with use of NT-proBNP or lung function alone. Comparisons between screening approaches have also been performed. A recent study found similar performance for DETECT and ASIG but a higher RHC rate for DETECT;[234] however, caution should be used when interpreting these results due to methodological limitations.	

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ☑ **Large** ○ Varies ○ Don't know	Compared with a contemporary non-screened cohort, an early detection programme in France demonstrated that patients detected following screening had less severe haemodynamic disease[229] than non-screened patients and 1 and 5 year survival of 100% and 73% compared with 75% and 25%, respectively, in a contemporaneous non-screened cohort.[230] The DETECT programme confirmed that screening asymptomatic patients was also capable of identifying patients with mild elevation of mPAP 21–24 mmHg.[232]	NA

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ☑ **Small** ○ Trivial ○ Varies ○ Don't know	Screening has emotional and financial impacts, although data for screening for PAH in SSc are very limited. Annual screening for PAH in SSc is currently recommended in asymptomatic patients. The cost is dependent on the approach to screening. There are limited data comparing the cost of screening regimens. A study by Vandecasteele *et al.*[235] compared DETECT vs. three alternative screening approaches and noted that DETECT was the most expensive. The costings, however, appeared very conservative. The cost was EUR224/80/90/112 per patient using the DETECT algorithm/2009 ESC/ERS Guidelines/2015 echo screening/2015 combined screening. Given that patients with SSc frequently develop PAH after many years, a significant number of patients would be expected to be screened >10 times during their lifetime. With significant financial cost, RHC is an invasive test with an albeit relatively low morbidity and mortality, and has significant associated costs. Reducing the number of RHCs recommended using a screening programme would be highly desirable. The DETECT approach recommends RHC in a larger number of patients than other approaches.	NA

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ☑ **High** ○ No included studies	A single study[232] performed RHC in all patients (DETECT), so for other studies the true false–negative rate cannot be calculated. However, this study provides a high level of evidence for test accuracy. A limitation of this study is that the screened population was enriched for patients at increased risk of PAH. This study provides valuable evidence that echocardiography alone missed a large number of patients with PAH when used to screen asymptomatic patients with SSc. This has resulted in removal of the previous recommendations for yearly echocardiography alone to screen for PAH in SSc.	NA

Continued

Certainty of the evidence of test effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects, or burden of the test?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Available data have demonstrated that patients with SSc-PAH can be diagnosed with less severe haemodynamic disease; however, the comparisons are related to contemporaneous cohorts and there is no study evidence randomizing patients to screening or no screening.[230,232] Given the current strength of evidence, undertaking such studies would be challenging.	NA

Certainty of the evidence of management effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Studies have examined how screening for PAH is implemented in patients with SSc. Despite recommendations to annually screen for SSc, data suggest that adherence to screening is moderate overall, although networks of physicians with an interest in SSc have demonstrably higher adherence to screening regimens.[236] A study showed that 35% of patients with SSc had an echocardiogram and 53% had lung function testing in the year prior to PAH diagnosis.[237] A study from Australia showed that <60% of patients underwent annual screening and that RHC was not used in all to confirm the diagnosis of PAH.[238] A number of approaches to improve deployment and adherence to screening regimens have been implemented and the success of these approaches assessed. In Australia, the ASCS used a web-based data collection and decision support for applying a PAH screening algorithm in patients with SSc. Since its introduction, adherence to annual screening has increased from 56% to 89%.[236] However, 30% of patients deemed to be at moderate or high risk of PAH were referred for RHC, predominantly due to preservation of functional class or following referral to a cardiologist or respiratory physician where RHC was not deemed necessary. Patient refusal for RHC occurred in a minority of 2%. These results highlight that a number of factors exist that limit adherence to current international screening recommendations.	NA

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Data for networks of physicians with an interest in SSc show that, despite recommendations to perform RHC in patients at risk of PAH, a significant number of patients do not undergo the gold standard test (RHC) to confirm or refute the diagnosis of PAH (see section above), with less symptomatic or asymptomatic patients less likely to undergo testing, particularly when there are coexisting comorbidities. Limited data are available on how patients are treated when diagnosed with PAH from screening programmes. Data from Mihai *et al.*[239] noted that 24/25 patients with progressive PAH received treatment, whereas 28/32 patients with stable PAH received therapy during 3 years of follow-up after being identified as having PAH from a screening programme.	NA

Certainty of effects

What is the overall certainty of the evidence of effects of the test?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ☑ **High** ○ No included studies	Humbert *et al.* reported better outcomes in screened patients with SSc compared with those with PAH-SSc who were not identified from screening programmes, although this was not a randomized study but rather a comparison with a contemporary cohort.[230] The DETECT study reported on patients observed for 3 years following screening. They presented data on 57 patients with PAH. Patients received therapy for their PAH; despite this, 40% of early diagnosed patients with PAH progressed, with male gender, functional class and pulmonary function tests at	NA

Continued

	diagnosis associated with disease progression.[239] These data support that patients diagnosed with PAH from a screening programme have a high rate of clinical worsening, suggesting that the screening test identifies clinically meaningful disease (i.e. the certainty of effect is high). The improved outcomes of patients identified from screening compared with historical or contemporary cohorts would support a positive impact on long-term outcomes, although the impact of lead time bias could not be excluded.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	There is general acceptance that screening for PAH in SSc is appropriate. The uncertainty pertains to the population to be screened and the frequency with which this should be done.	Screening for PAH is SSc is also endorsed by patient organizations, and the high uptake amongst patients reflects that this approach is generally acceptable. The Scleroderma and Raynaud's UK charity (SRUK) notes 'annual tests are essential to monitor the progression of scleroderma and something you are entitled to as a patient' and 'if any of these tests are not being performed and you feel they should be, tell your doctor…' https://www.sruk.co.uk/scleroderma/annual-tests-scleroderma/

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ☑ **Favours the intervention** ○ Varies ○ Don't know	Screening using the DETECT algorithm in a cohort of patients with SSc enriched for PAH identified a high proportion of patients with PAH (19%). These patients had haemodynamically modest disease 32.5(8) mmHg and PVR 371(226) dynes. Although patients underwent RHC, complication rates were low, with one patient having a haematoma caused by accidental carotid puncture.[232] Given the high rate of subsequent clinical worsening of 40% over 3 years in this cohort,[239] the conclusion is that screening in this population identifies a high proportion of patients with PAH, with modest disease, which is clinically important and undesirable effects were low. Subsequent studies have also demonstrated in other cohorts that DETECT can be deployed to screen for PAH. The evidence strongly favours the intervention (screening).	NA

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ☑ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Investigations to screen for PAH in SSc are clearly identified for a defined population (e.g. DETECT, Coghlan *et al.*[232]) and costings are moderate. Other screening programmes exist where the testing algorithm is also clearly defined.[229,240] However, there are no currently available data on costing a lifetime strategy for screening and early detection approaches for PAH in SSc. Importantly, the data for the optimal interval between screening for PAH in SSc is unknown. Given that risk factors exist for the development of PAH, there has been some discussion as to whether approaches to screening should be based on evaluation of risk factors for PAH.[236] This has resulted in approaches that incorporate the use of risk factors to aid subsequent deployment of investigative/screening strategies for PAH in SSc. Semalulu *et al.* have proposed a simple prediction model integrating symptoms, DLCO, and NT-proBNP that identified subjects at very low probability of PAH, who could potentially forgo further specific testing for PAH.[241] A recent meta-analysis of the use of video capillaroscopy showed that a reduction in capillary density or progression to a severe active/late pattern of vascular involvement is also a risk factor for PAH; however, the clinical utility of incorporating this into current algorithms has not been assessed.[242] Other investigators have identified angiogenic and inflammatory biomarkers, chemokines, microRNAs. and chemokines that may potentially aid decisions regarding subsequent screening	NA

Continued

	intervals, although data are limited and the findings exploratory.[243] For patients meeting criteria for RHC following non-invasive screening, additional non-invasive tests to refine the need for RHC have also been evaluated. Santaniello *et al.* performed CPET in patients identified from the DETECT screening regimen.[244] They postulated that determination of the VE/VCO_2 slope in DETECT-positive patients may reduce the need for invasive procedures such as RHC. Hagger *et al.* and Rajaram *et al.* evaluated magnetic resonance imaging (MRI) in patients with SSc and CTD, and showed that MRI cannot exclude patients with SSc-PAH but can identify patients with a low risk of mortality.[245,246] There is, however, no economic analysis of the cost of implementing either of these approaches in the diagnostic pathway. In summary, the resources required to screen for PAH in SSc and facilitate early detection are dependent on the overarching approach and the frequency with which they are conducted. Appraisal of the current evidence supports the application of DETECT for a defined cohort of patients with SSc and an approach based on a risk assessment for PAH in SSc made pragmatically on a yearly basis for patients ineligible for screening or those who have been screened and did not require further PAH investigation.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Limited published data on screening costs and estimated costs appear conservative.[235] Costs of tests will vary between institutions; however, recommendations regarding testing enables institutions to cost implementation of a screening programme for SSc. Despite the lack of large-scale studies, the proposed screening regimens do allow for costing of the economic impact. See section above.	NA

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ☑ **Varies** ○ No included studies	Limited published data on screening costs and estimated costs appear conservative.[235] Used costs will vary depending on the screening approach. It is believed that there are no data on cost-effectiveness of screening or not screening for PAH in SSc. Given current practice, it is unlikely that a prospective study examining the economic impact of screening vs. not screening for PAH in SSc will be performed. There is the potential, however, to compare the cost-effectiveness of different approaches or to model the cost of screening for PAH in SSc.	NA

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ☑ **Probably increased** ○ Increased ○ Varies ○ Don't know	Given that individuals who are socially and economically disadvantaged may delay seeking medical care, screening and early detection approaches at a population-based level in patients with SSc will probably increase health equity.	NA

Continued

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	Given the high prevalence of PAH, its impact on outcomes and data supporting diagnosis of less severe disease (which appears to be more treatment responsive), screening for PAH in patients with SSc is well accepted within the health care community and is recommended by learned societies[247] and by consensus statements from the international community.[248] Screening is also endorsed by patient organizations and the high uptake amongst patients reflects that this approach is generally acceptable. The Scleroderma and Raynaud's UK charity (SRUK) notes 'annual tests are essential to monitor the progression of scleroderma and something you are entitled to as a patient' and 'if any of these tests are not being performed and you feel they should be, tell your doctor…' https://www.sruk.co.uk/scleroderma/annual-tests-scleroderma/	NA

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	Yes. Published evidence from multiple countries confirms that screening using a number of different approaches is feasible to implement in a real-world setting (i.e. outside the context of a clinical trial).[233,235,236,241]	NA

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate	NA	**Varies**	Don't know
Desirable effects	Trivial	Small	Moderate	**Large**	NA	Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial	NA	Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	**High**	NA	NA	No included studies
Certainty of the evidence of test effects	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of the evidence of management effects	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of the evidence of test result/ management	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of effects	Very low	Low	Moderate	**High**	NA	NA	No included studies

Continued

Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	**Moderate**	High	NA	NA	No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	**Varies**	No included studies
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	☑

Pulmonary arterial hypertension has a high prevalence in SSc and its development negatively impacts QoL. Data support a strong recommendation for screening selected asymptomatic patients with SSc for PAH. Assessing the risk of having PAH is also recommended in patients with SSc who do not meet the criteria for asymptomatic screening, to facilitate early detection.

CONCLUSIONS

Recommendations

1. In adult systemic sclerosis (SSc) patients with >3 years of disease duration, an FVC ≥40%, and a DLCO <60%, the DETECT algorithm is recommended for identifying asymptomatic patients with PAH.

Class I Level B (key references below[232])

2. An annual evaluation of the risk of having PAH is recommended in patients with SSc.

Class I Level B (key references below[240,241,249])

3. In SSc, the risk of having PAH should be evaluated to decide the need for further investigations.

Class IIa Level B (key references below[241])

4. In SSc, evaluation of the risk of having PAH should be based on an evaluation of breathlessness, in combination with either an echocardiogram or lung function testing and NT-proBNP.

Class IIa Level B (key references below[229,233])

5. Hospitals managing patients with SSc should have policies in place to facilitate the risk of having PAH based on the availability of local testing.

Class IIa Level C (key references below[a])

6. Exercise echocardiography, or CPET, or CMR may be used to aid decisions to perform RHC in symptomatic patients with SSc.

Class IIb Level C (key references below[244,245])

Justification

Strong recommendation for screening for PAH in SSc

The prevalence of PAH is high (5–19%) in SSc and the leading cause of death due to SSc-related organ involvement. Screening of asymptomatic patients and early detection of PAH in those who would not otherwise have sought medical advice is practical, detects less severe haemodynamic disease, and, compared with contemporary non-screened cohorts, is associated with improved survival. Screening for PAH is endorsed by organizations supporting people affected by

Continued

SSc. Therapies for PAH are available, of moderate cost, and prevent clinical worsening. Current challenges relate to refining strategies to i) assess for the risk of having PAH; ii) establish the optimal frequency for undertaking screening; iii) reduce the need for invasive testing with RHC to confirm or refute a diagnosis of PAH; and iv) improve cost-effectiveness and acceptability to patients. See text; key references for each recommendation are highlighted below. [a]based on expert opinion.
Subgroup considerations
In adult SSc patients with >3 years of disease duration, an FVC ≥40%, and DLCO <60%, the DETECT algorithm is recommended for identifying asymptomatic patients with PAH.
Implementation considerations
To facilitate screening for PAH in SSc, hospitals managing patients with SSc should have policies in place to aid assessment for PAH.
Monitoring and evaluation
Rheumatology centres should conduct regular audit of screening and early detection approaches for patients with SSc.
Research priorities
Evaluation of the economic impact, acceptability to patients of screening regimens, and approaches to early detection of PAH in patients with SSc. Improved identification of patients at low and high risk of developing PAH using novel biomarkers and approaches. Understand the acceptability of and barriers to screening and early detection of PAH in SSc, in patients and health care professionals. Improved understanding of the incidence of PAH in connective tissues diseases other than SSc and how to improve early detection of PAH in these patients.

16.7. Evidence to Decision for key narrative question 4

Table S15 **Evidence to Decision for key narrative question 4**

QUESTION 4 (NARRATIVE)

Should a risk-stratification strategy be used to guide treatment in pulmonary arterial hypertension?	
Population	Adult (aged ≥18 years) patients with pulmonary arterial hypertension (PAH).
Intervention	Risk stratification instruments (SPAHR/COMPERA, French invasive, French non-invasive, and REVEAL-based scores). KQ4 - Should a risk-stratification strategy be used to guide treatment in patients with PAH? (Chosen risk stratification instruments being French invasive, French noninvasive, SPAHR/COMPERA, and REVEAL-based scores (REVEAL, REVEAL 2.0, REVEAL Lite 2).
Purpose of the test/ KQ4	To assess the value of risk stratification.
Role of the test	To guide treatment in PAH.
Linked treatments	PAH treatments, targeting the endothelin, nitric oxide, and prostacyclin pathways.
Main outcomes	NA
Setting	NA
Perspective	NA
Background	NA
Subgroups	NA
Conflict of interests	NA

ASSESSMENT

Problem

Is the problem a priority? (Is it important to apply multiparametric risk stratification?)

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	According to the 2015 ESC/ERS PH guidelines, there is no single parameter that provides adequate prognostic information in PAH.[247,250] Multiparametric risk stratification is intimately associated with mortality and provides prognostic information.	NA

Test accuracy

How accurate is the test? (How accurate is risk stratification?)

Judgement (concordance statistics)	Research evidence	Additional considerations
○ Very inaccurate (≤0.5) ○ Inaccurate (0.51–0.6) ☑ **Moderately accurate (0.61–0.8)** ○ Accurate (0.81–0.9) ○ Very accurate (>0.9) ○ Varies ○ Don't know	Depending on the risk stratification strategy used, concordance statics for estimated 1 year survival ranged 0.62–0.76,[251] and for transplant free survival >5 years between 0.56–0.70.[252]	Weighting of parameters. Invasive vs. non-invasive as well as modifiable vs. non-modifiable. Additional variables for future refinement of risk stratification and prognostication (echocardiography/ CMRI, CPET, biochemical markers, and patient-reported outcome measures).

Desirable effects

How substantial are the desirable anticipated effects? (What are the advantages of risk stratification?)

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ☑ **Large** ○ Varies ○ Don't know	Risk stratifications provide estimation of short- and long-term outcome.[251,253–257] Most risk assessment strategies are feasible and flexible in terms of available/included parameters.	Although the strategies are somewhat flexible, accuracy may vary depending on the included/available variables and selected strategy.

Undesirable effects

How substantial are the undesirable anticipated effects? (What are the disadvantages of risk stratification?)

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ☑ **Trivial** ○ Varies ○ Don't know	May require invasive assessment. May require many parameters. Consensus on the optimal combination of parameters remain unclear. A large intermediate-risk group (now resolved into low–intermediate and high–intermediate).	Some patients may still have poor prognosis, despite being in a low-risk profile, depending for how long the right ventricle can withstand the high pressure and resistance in the pulmonary circulation. Risk assessment does not currently involve the patient-reported outcome measures.

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy? (What is the evidence on risk stratification in prognostication?)

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Evidence based on large independent retrospective studies (they have validated and provided concordance statistics).[251–255,258] The lack of prospective studies suggests a downgrade from high to moderate evidence.	NA

Continued

Certainty of the evidence of test effects

~~What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?~~

Judgement	Research evidence	Additional considerations
~~○ Very low~~ ~~○ Low~~ ~~○ Moderate~~ ~~○ High~~ ~~○ No included studies~~	NA	NA

Certainty of the evidence of management effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results? (Evidence of KQ4?)

Judgement	Research evidence	Additional considerations
○ Very low ☑ **Low** ☑ **Moderate** ○ High ○ No included studies	Although several studies have demonstrated an intimate relation between the use of PAH treatment and change in risk scores, prospective studies are needed.[259–262]	Low–moderate due to lack of prospective studies.

Certainty of the evidence of test result/management

~~How certain is the link between test results and management decisions?~~

Judgement	Research evidence	Additional considerations
~~○ Very low~~ ~~○ Low~~ ~~○ Moderate~~ ~~○ High~~ ~~○ No included studies~~	NA	NA

Certainty of effects

What is the overall certainty of the evidence of effects of the test? (What is the overall certainty of the evidence of effects of risk assessment?)

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ☑ **High** ○ No included studies	Achieving a low-risk status is consistent with an excellent outcome, supporting a goal-orientated approach.[257,259–261,263]	Some patients may achieve a low-risk profile but may still have a poor prognosis.

Values

Is there important uncertainty about or variability in how much people value the main outcomes? (What patients may value as important, and what they think about using risk stratification to guide treatment. Assumptions?)

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	NA	NA

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison? (If the advantages/benefits of stratification outweigh the disadvantages/risks?)

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the	See *desirable effects* and *undesirable effects* with associated references. In short, the advantages of risk stratification outweigh the trivial disadvantages.	NA

Continued

intervention or the comparison ○ Probably favours the intervention ☑ **Favours the intervention/risk stratification** ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ☑ **Varies** ○ Don't know	NA	It depends on the risk stratification strategy used, as well as patient status (patients with severe PAH require more extensive assessment).

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ☑ **No included studies**	NA	NA

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **No included studies**	NA	NA

Equity

What would be the impact on health equity? (Would applying risk stratification impact health equity?)

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ☑ **Varies** ○ Don't know	NA	Equity depends on the country in which risk stratification is performed, and the health care system, infrastructure, insurances, etc.

Continued

Acceptability

Is the intervention acceptable to key stakeholders? (Is the intervention (risk assessment) acceptable to key stakeholders [clinicians, patients])?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	NA	NA

Feasibility

Is the intervention feasible to implement? (Is there available infrastructure, or a lot of organizations that are needed to implement risk stratification or KQ4?)

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	NA	Most of the parameters are obtainable by means of clinical assessment/imaging/RHC/blood study at diagnosis or follow-up, where invasive and non-invasive parameters are included. However, depending on the infrastructure and country, the availability of expert PH centres could impact the establishment of diagnosis and implementation.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	**Moderately accurate**	Accurate	Very accurate	Varies	Don't know
Desirable effects	Trivial	Small	Moderate	**Large**	NA	Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**	NA	Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	**Moderate**	High	NA	NA	No included studies
Certainty of the evidence of management effects	Very low	**Low**	**Moderate**	High	NA	NA	No included studies
Certainty of effects	Very low	Low	Moderate	**High**	NA	NA	No included studies

Continued

Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

CONCLUSIONS

Recommendations
It is recommended to evaluate disease severity in patients with PAH with a panel of data derived from clinical assessment, exercise tests, biochemical markers, and echocardiographic and haemodynamic evaluations. It is recommended to perform regular follow-up assessments in patients with PAH, depending on their stability, need, risk category, demographics, and comorbidities. Achieving and maintaining a low-risk profile on optimized medical therapy is recommended as a treatment goal in patients with PAH. Achieving and maintaining an intermediate-risk profile on optimized medical therapy is considered as an inadequate status for most patients with PAH.
Justification
See provided document and references in Section 6.2.5: Comprehensive prognostic evaluation and risk assessment in PAH, as well as *Table 16* (recommendations for evaluation of severity of PAH and clinical status on therapy), in which proposed changes are stated.
Subgroup considerations
Implementation considerations
Monitoring and evaluation
Research priorities
Future directions
Consider further substratification of the intermediate-risk group into low–intermediate and high–intermediate.

16.8. Evidence to Decision for key narrative question 5

Table S16 Evidence to Decision for key narrative question 5

QUESTION 5 (NARRATIVE)

Should drugs approved for pulmonary hypertension be used in patients with pulmonary hypertension associated with left heart disease?	
Population	Pulmonary hypertension associated with left heart disease (HFpEF, HFrEF, and valvular heart disease).
Intervention	Pulmonary arterial hypertension approved drugs (ERA: ambrisentan, bosentan, macitentan; PDE5i: sildenafil, tadalafil; soluble guanylate cyclase (sGC): riociguat).
Comparison	For RCTs: placebo (standard of care). For registries: no active comparator.
Main outcomes	Clinical events (death, hospitalization, worsening HF); exercise capacity (6MWT, CPET); haemodynamics (PVR, CO, mPAP); symptoms and quality of life; drug-induced adverse events.

ASSESSMENT

Problem

Is the problem a priority?

Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	Pulmonary hypertension due to left heart disease is the most common cause of PH and is highly prevalent, especially in HF.[264,265] Across the spectrum of left heart disease, PH is associated with more symptoms, worse exercise capacity, and a dismal prognosis.	NA

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	**Research evidence**	**Additional considerations**
☑ **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Five of seven RCTS did not meet their primary end-point of improving haemodynamics (mPAP, PVR), exercise capacity (6MWT), or reduce the rate of clinical events.[205,206,266–269] Two small monocentric studies with sildenafil suggested a benefit in HFrEF and HFpEF. There was an improvement in exercise capacity and haemodynamics that was not confirmed in large RCTs.[206,266]	Several meta-analysis of available RCTs concluded that there was no benefit in any of the outcomes of interest (PVR, 6MWD) and a trend to an increased rate of event in the active group.[271,272] Data from registries were conflicting and suggested that the benefit of intervention is uncertain, with a worse response in patients with PH due to LHD compared with PAH when PAH-approved drugs are used.[217]

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	**Research evidence**	**Additional considerations**
☑ **Large** ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Studies with an ERA (bosentan or macitentan) led to an early adverse event of fluid retention.[267–269] A study with bosentan in HFpEF was interrupted after an interim analysis demonstrated a better response in the placebo group.[269] A study with sildenafil in patients with PH associated with valvular heart disease demonstrated that patients in the active group less frequently met the primary composite endpoint of improvement. In this trial, there was an increased rate of clinical worsening in the sildenafil group.[270]	One meta-analysis of available RCTs suggested a trend in the risk of clinical worsening (death, hospitalizations) in the active groups.[272]

Continued

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	The reported evidence is based on the analysis of available RCTs with the following compounds: bosentan (one study[268]), macitentan (one study[267]), riociguat (one study[273]), and sildenafil (four studies[205,206,266,270]).	Additional evidence is provided by open label registries,[217] single-centre retrospective analysis, and four meta-analyses.[216,274]

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
☑ **Important uncertainty or variability** ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	There is a significant variability of the value of the main outcome, as most studies did not meet their primary endpoint and two were associated with a worse outcome in the active group compared with placebo. The reasons explaining this variability are numerous, including heterogeneity of the populations, different endpoints, and the study sample size.	NA

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
☑ **Favours the comparison** ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Based on the above-mentioned analysis, the balance between the desirable and undesirable effects is in favour of the comparator (i.e. placebo on top of the standard of care for the underlying disorder).	NA

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○Varies ☑ **Don't know**	There is no cost-effectiveness analysis available.	The lack of global benefit, trend to an increased risk of hospitalization, management of side effects, and cost of PAH-approved drugs are associated with a greater mobilization of resources compared with the standard of care.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ☑ **No included studies**	See above.	NA

Continued

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **No included studies**	See above.	Despite the lack of formal cost-effectiveness analysis, the balance of the use of PAH-approved therapies in this context is negative (favours the comparator).

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ☑ **Don't know**	See above.	NA

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
☑ **No** ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	For the reasons mentioned above, the intervention is unacceptable to key stakeholders.	NA

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
☑ **No** ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	At this stage of knowledge, the intervention is unfeasible.	NA

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	**Trivial**	Small	Moderate	Large	NA	Varies	Don't know
Undesirable effects	**Large**	Moderate	Small	Trivial	NA	Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High	NA	NA	No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	NA	NA	NA
Balance of effects	**Favours the comparison**	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
Acceptability	**No**	Probably no	Probably yes	Yes	NA	Varies	Don't know
Feasibility	**No**	Probably no	Probably yes	Yes	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☑	○	○	○	○

CONCLUSIONS

Recommendations
Drugs approved for PAH are not recommended in pulmonary hypertension associated with left heart disease (class of recommendation III – level of evidence A).
Justification
Analysis of the available data does not show a clear benefit of an intervention, which also appeared in the meta-analysis. In addition, serious safety concerns have been identified when ERAs were used in patients with heart failure (HFpEF and HFrEF, with or without PH) and when sildenafil was used in patients with persistent PH after correction of valvular heart disease.
Subgroup considerations
Not applicable.
Implementation considerations
Not applicable.

Continued

Monitoring and evaluation
Not applicable.
Research priorities
There is no doubt that the question of treating PH associated with LHD must not be abandoned; however, several considerations must be taken into account: A better identification in disease mechanisms and pathways leading to PH associated with LHD would help to differentiate appropriate targets for research. Homogenization of the study populations and the PH phenotype should be prioritized, for example: patients with CpcPH, elevated PVR (i.e. >5 WU) with mildly elevated PAWP (i.e. 15–25 mmHg), RV dysfunction or other markers of severity would be a population of great interest. Identification of an appropriate endpoint and outcome metrics are highly desirable, specific to each stage of drug development.

16.9. Evidence to Decision for key narrative question 6

Table S17 Evidence to Decision for key narrative question 6

QUESTION 6 (NARRATIVE)

Should drugs approved for pulmonary arterial hypertension be used in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease? (Chosen drugs are ERAs, PDE5is, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists)?	
Population	Patients with pulmonary hypertension (PH) associated with COPD.
Intervention	Drugs approved for the treatment of pulmonary arterial hypertension (PAH) (i.e. ERAs, PDE5i, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists).
Comparison	Placebo or no use of drugs approved for the treatment of pulmonary arterial hypertension (PAH).
Main outcomes	Survival, hospitalization, clinical worsening, exercise capacity, echocardiography, mPAP, PVR, NT-proBNP, PaO_2, $PaCO_2$, arterial oxygen saturation (SaO_2), oxygen requirement, and safety.
Setting	Specialized PH centres.
Perspective	NA
Background	Drugs approved for PAH are occasionally used to treat patients with PH associated with COPD, although neither the safety nor the efficacy of this approach is fully known.
Conflict of interest	NA

ASSESSMENT

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	High medical need (i.e. high prevalence of PH-COPD). Increased symptom burden and mortality risk with development of PH in patients with COPD. Particularly high mortality risk in patients with COPD who develop severe PH (PVR >5 WU).[275]	NA

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ☑ **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Improvement in PVR by −1.4 WU after 16 weeks in a small ($n = 28$) RCT with sildenafil in patients with COPD and RHC-confirmed PH.[276]	Insufficient data to assess effects of PAH therapies on exercise capacity, QoL, and survival in patients with PH-COPD.

Continued

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ☑ **Don't know**	NA	Insufficient evidence to assess risk and side-effects of PAH medication in patients with PH-COPD.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
☑ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Very few RCTs, a small number of patients, and short observation periods.	Additional signals from registries raising the possibility of clinical improvements and better survival in patients with COPD and severe PH, yet unconfirmed by RCTs.[277]

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
☑ **Important uncertainty or variability** ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Patients with COPD and RHC-documented PH may benefit more from treatment from PAH drugs than those in whom PH is suspected by echocardiography.	NA

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **Don't know**	Balance of effects is unknown.	NA

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ☑ **Varies** ○ Don't know	Registry data suggest that physicians use PAH medication in selected patients with COPD and PH, mostly in those with severe PH. No approval and no reimbursement of PAH medication for PH-COPD.	NA

Continued

Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	NA	NA

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large	NA	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	NA	Varies	**Don't know**
Certainty of evidence	**Very low**	Low	Moderate	High	NA	NA	No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**Don't know**
Acceptability	No	Probably no	Probably yes	Yes	NA	Varies	**Don't know**
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	☑	○	○

CONCLUSIONS

Recommendations
The use of medication approved for PAH is not recommended in patients with COPD and PH.
Justification
There is insufficient evidence to support the use of medication approved for PAH to be recommended in patients with COPD and PH. Safety, tolerability, and efficacy of PAH medication in patients with PH-COPD are unknown.
Subgroup considerations
Registry data raise the possibility that selected patients with COPD and severe PH (PVR >5 WU) may benefit from medication targeting PH, but this has not yet been confirmed by prospective clinical trials.
Implementation considerations
Implementation of treatment would be feasible, provided that solid data support safety and efficacy.

Continued

Monitoring and evaluation
See research priorities below.
Research priorities
1) Evaluation of the safety, tolerability, and efficacy of PAH medication in patients with COPD and severe PH, as defined by PVR >5 WU. 2) In a stepwise approach, PAH medication that proves to be safe and efficacious in patients with COPD and severe COPD should be evaluated in patients with COPD and less severe PH.

16.10. Evidence to Decision for key narrative question 7

Table S18 Evidence to Decision for key narrative question 7

QUESTION 7 (NARRATIVE)

Should drugs approved for pulmonary arterial hypertension be used in patients with pulmonary hypertension associated with interstitial lung diseases? (Chosen drugs are ERAs, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists)?	
Population	Patients with pulmonary hypertension (PH) associated with ILD; ILD restricted to the most common idiopathic interstitial pneumonias (IIPs) (i.e. IPF and fibrotic non-specific interstitial pneumonitis).
Intervention	Drugs approved for the treatment of pulmonary arterial hypertension (PAH) (i.e. ERAs, PDE5is, guanylate cyclase stimulators, prostacyclin derivatives, and prostacyclin receptor agonists.
Comparison	Placebo or no use of drugs approved for the treatment of pulmonary arterial hypertension (PAH).
Main outcomes	Survival, hospitalization, clinical worsening, exercise capacity, echocardiography, mPAP, PVR, NT-proBNP, PaO_2, $PaCO_2$, SaO_2, oxygen requirement, and safety.
Setting	Specialized pulmonary hypertension centres.
Perspective	NA
Background	Drugs approved for PAH are occasionally used to treat patients with PH associated with ILD, although neither the safety nor the efficacy of this approach is fully known.
Conflict of interest	NA

ASSESSMENT

Problem
Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	High medical need (i.e. high prevalence of PH in patients with ILD). Increased symptom burden and mortality risk with development of PH in patients with ILD. Particularly high mortality risk in patients with ILD who develop severe PH (PVR >5 WU).	NA

Desirable effects
How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ☑ **Moderate** ○ Large ○ Varies ○ Don't know	Placebo-corrected improvement in 6MWD by 31 m and lower incidence of clinical worsening events after 16 weeks of treatment with inhaled treprostinil.[278] There is insufficient evidence on safety and efficacy of ERA and PDE5i in patients with PH-ILD.	Effects of inhaled treprostinil on long-term outcomes in patients with PH-ILD unknown.

Continued

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Trivial ☑ **Varies** ○ Don't know	In the abovementioned study, 16 weeks of therapy with inhaled treprostinil was not associated with more adverse events or drug discontinuations due to adverse events than placebo. In patients with IIP and PH, there was a signal of increased mortality with the use of riociguat.[220]	Insufficient evidence to assess risk and side effects of PAH medication in patients with PH-ILD.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ☑ **Low** ○ Moderate ○ High ○ No included studies	Single, short-term trial with inhaled treprostinil in patients with PH-ILD.[278] Mortality signal with riociguat in patients with IIP-PH not statistically significant.[220] Insufficient evidence for ERA and PDE5i in patients with ILD-PH.	NA

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
☑ **Important uncertainty or variability** ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The clinical benefit (PROs, QoL, survival) of any PAH drugs in patients with PH-ILD is unknown.	NA

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ☑ **Varies** ○ Don't know	Given the available evidence, inhaled treprostinil may have favourable effects in patients with PH-ILD. For riociguat in patients with PH-ILD, the available evidence favours the comparison (placebo). For all other PAH drugs, the balance of effects in patients with PH-ILD is unknown	NA

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ☑ **Varies** ○ Don't know	Registry data suggest that physicians use PAH drugs in selected patients with ILD and PH, mostly in those with severe PH. No approval and no reimbursement of PAH medication for PH-ILD.	NA

Continued

Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	NA	NA

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	Trivial	Small	**Moderate**	Large	NA	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	NA	**Varies**	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High	NA	NA	No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	**Varies**	Don't know
Acceptability	No	Probably no	Probably yes	Yes	NA	**Varies**	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	☑	○	○

CONCLUSIONS

Recommendations
Inhaled treprostinil may be considered in patients with ILD who have PH documented by RHC. Riociguat is not recommended for patients with PH-ILD, as this intervention may be associated with increased mortality. Other PAH drugs are not recommended in patients with PH-ILD due to lack of supportive evidence.
Justification
As above.
Subgroup considerations
Registry data raise the possibility that selected patients with ILD and severe PH (PVR >5 WU) have a particularly high mortality risk and may benefit from medication targeting PH, but this has not yet been confirmed by prospective clinical trials.
Implementation considerations
Implementation of treatment would be feasible, provided that solid data support safety and efficacy.

Continued

Monitoring and evaluation
See research priorities below.
Research priorities
1) Studies investigating the use of PAH medication in patients with PH-ILD need to ensure proper phenotyping of patients; this includes RHC at enrolment. 2) Evaluation of the safety, tolerability, and efficacy of PAH medication in patients with ILD and severe PH, as defined by a PVR >5 WU. 3) In a stepwise approach, PAH medication that proves to be safe and efficacious in patients with ILD and severe COPD should be evaluated in patients with ILD and less severe PH.

16.11. Evidence to Decision for key narrative question 8

Table S19 Evidence to Decision for key narrative question 8

QUESTION 8 (NARRATIVE)

Should balloon pulmonary angioplasty or medical therapy be used in patients with inoperable chronic thrombo-embolic pulmonary hypertension?	
Population	Patients with inoperable chronic thrombo-embolic pulmonary hypertension.
Intervention	Balloon pulmonary angioplasty or medical therapy.
Comparison	NA
Main outcomes	Improvement in pulmonary haemodynamics, functional status, exercise tolerance, biomarkers, and QoL.
Setting	NA
Perspective	NA
Background	NA
Conflict of interests	NA

ASSESSMENT

Problem
Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	NA	NA

Desirable effects
How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ○ Large ☑ **Varies** ○ Don't know	Improved pulmonary haemodynamics, exercise tolerance, and biomarkers.	NA

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ☑ **Moderate**	Specifically for BPA,[279] due to periprocedural complications (BPA complication rate is reduced when patients are pre-treated with medical therapy).[209]	NA

Continued

○ Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ☑ **Moderate** ○ High ○ No included studies	Single and multicenter studies for BPA,[280–288] three positive RCTs for medical treatment.[289–291]	See *Recommendation Table 23.*

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ☑ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	BPA-followed medical therapy improves patient haemodynamics, exercise tolerance, and QoL. Data on long-term outcomes are limited but suggestive of improved survival.[280–288] Medical therapy without BPA is improving pulmonary haemodynamics, exercise tolerance, and QoL.[289–291] Long-term data show improved survival.[292]	NA

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ☑ **Favours the intervention** ○ Varies ○ Don't know	Most studies describe benefits with limited complications (BPA) or drug side effects (medical therapy).	NA

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
☑ **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	NA	Drugs are expensive and BPA procedures require hospital stay (costs dependent on the country).

Continued

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ☑ **No included studies**	NA	No economical studies were performed, but Task Force member experience suggests overall benefits of BPA or medical therapy.

Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ☑ **No included studies**	No evidence.	NA

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ☑ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	NA	BPA can be provided in countries where medical therapy is unavailable.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ☑ **Probably yes** ○ Yes ○ Varies ○ Don't know	Improving haemodynamics, exercise capacity, QoL, and survival.	NA

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ☑ **Yes** ○ Varies ○ Don't know	NA	Only for expert CTEPH centres.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large	NA	**Varies**	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial	NA	Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High	NA	NA	No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	NA	NA	NA
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
Resources required	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High	NA	NA	**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**	NA	Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes	NA	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	☑

CONCLUSIONS

Recommendation
Interventional BPA is recommended in patients who are technically inoperable or have proximal disease but carry an unfavourable risk:benefit ratio for pulmonary endarterectomy provided distal obstructions amenable to BPA are present. Riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy. Treprostinil s.c. may be considered in symptomatic patients who have been classified as having inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy. Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH.
Justification
Evidence shows improved pulmonary haemodynamics, exercise capacity, biomarkers, QoL, and long-term survival.
Subgroup considerations
Implementation considerations

Continued

Monitoring and evaluation

Research priorities

There is a need for more RCTs, as current evidence for BPA is predominantly based on retrospective single-centre data.

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