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Pulmonary Arterial Hypertension: Screening, Management, and Treatment

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Preface

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Pulmonary Arterial Hypertension: Screening, Management, and Treatment

Structured Abstract

Objectives: Pulmonary arterial hypertension (PAH) is a rare and progressive disease associated with increased pulmonary vascular resistance (PVR) which, if unrelieved, progresses to right ventricular pressure overload, dysfunction, right heart failure, and premature death. PAH is more prevalent in some populations, thereby warranting screening of asymptomatic individuals. This review seeks to evaluate the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the screening, diagnosis, and management of PAH; clarify whether the use of echocardiography or biomarkers affects decisionmaking and clinical outcomes; and determine which medications are effective for treating PAH and whether combination therapy is more effective than monotherapy.

Data Sources: We searched PubMed®, Embase®, and Cochrane Database of Systematic Reviews for relevant English-language comparative studies.

Review Methods: Two investigators screened each abstract and full-text article for inclusion, abstracted data, rated quality and applicability, and graded the strength of evidence. Random-effects models were used to compute summary estimates of effect where several similar studies provided estimates.

Results: Fifty-one studies involving 6980 patients evaluated biomarker tests, echocardiography, or both to screen for PAH. N-terminal pro-B-type natriuretic peptide (NT-proBNP) showed only moderate correlation with right heart catheterization (RHC) hemodynamic measures and a great deal of variability between studies in its diagnostic accuracy and discrimination; however, based on one good-quality prospective cohort study, biomarker testing with NT-proBNP may be useful in ruling out PAH in patients with symptoms suggestive of PAH who have elevated systolic pulmonary artery pressure (sPAP) by echocardiography. No data are available regarding combined echocardiography and biomarker screening in asymptomatic patients at high risk for PAH. Echocardiography estimates of pulmonary artery pressures (sPAP, tricuspid gradient [TG], and tricuspid regurgitant jet velocity [TRV]) and pulmonary vascular resistance (TRV/velocity-time integral of right ventricular outflow tract [VTI_{RVOT}]) demonstrated good accuracy in screening for PAH but varied with the prevalence of PAH in study populations.

Eighty studies involving 7224 patients evaluated biomarker tests, echocardiography, or both to evaluate severity or prognosis and followed progression of disease or response to therapy. B-type natriuretic peptide (BNP) showed only moderate correlation with most RHC measures (mean pulmonary artery pressure [mPAP], PVR, cardiac index, right atrial pressure [RAP]) and clinical measures of disease severity (6-minute walk distance [6MWD]) and showed weak correlation with pulmonary capillary wedge pressure (PCWP), indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Echocardiography-derived sPAP showed strong correlation with RHC-sPAP with a precise effect estimate, although there was a great deal of heterogeneity. Pericardial effusion was the strongest predictor of mortality (summary hazard

ratio [HR] 2.2; 95% confidence interval [CI], 1.42 to 3.41) and may be useful clinically, although the 6 studies contributing data had moderate heterogeneity. Fractional area change (FAC) showed no significant ability to predict mortality.

Thirty-three studies involving 3981 patients assessed the effectiveness of drug treatments for PAH in adults. Few deaths were observed in these limited duration studies, leading to wide CIs and lack of statistical power to detect a mortality difference associated with treatment. All drug classes demonstrated increases in 6WMD when compared with placebo, but comparisons between agents were inconclusive. Combination therapy also showed improved 6WMD compared with single therapy, but the diversity of treatment regimens and the small number of combination therapy trials again make comparisons between specific regimens inconclusive. The odds ratio (OR) of hospitalization was lower in patients taking endothelin receptor antagonists or phosphodiesterase-5 inhibitors compared with placebo (OR 0.34 and 0.48, respectively), while there was no significant reduction in patients taking prostanoids compared with placebo. Combination therapy also reduced hospitalizations compared with single therapy. The impact of treatment on hemodynamic outcomes cardiac index, mPAP, and PVR was inconsistent.

Conclusions: Echocardiography and the biomarker NT-proBNP in combination may be sufficiently accurate to rule out PAH when screening symptomatic patients, but more research is needed regarding their effectiveness for screening asymptomatic populations. With the exception of the presence of pericardial effusion, echocardiography and biomarkers had only low to moderate prognostic value in patients with PAH. Although no treatments demonstrate a consistent mortality reduction, many are associated with improved 6MWD, and some are associated with reduced hospitalization rates. Comparisons of different drug combinations are inconclusive regarding a mortality reduction but suggest an improvement in 6MWD compared with monotherapy.

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Effective Health Care

Pulmonary Arterial Hypertension: Screening, Management, and Treatment

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Background

Epidemiology and Etiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH), is a rare and progressive disease whose prevalence is estimated to be between 15 and 50 cases per million adults.[1] While the pathophysiology is not well understood, both genetic and environmental factors have been found to contribute to changes in the pulmonary vasculature, causing increased pulmonary vascular resistance. This increased resistance, if unrelieved, progresses to right ventricular pressure overload, dysfunction, and ultimately right heart failure and premature death.[2] The causes of PAH are numerous and are listed in Table A, taken from the Third World Symposium on PAH (2003).[3] Before the availability of disease-specific therapy in the mid-1980s, the median life expectancy at the time of diagnosis was 2.8 years.[1,4]

Table A. Clinical classification of pulmonary hypertension[a]

Clinical classification system	
1.	**Pulmonary arterial hypertension**
1.1.	Idiopathic
1.2.	Familial
1.3.	Associated with:
1.3.1.	Collagen vascular disease
1.3.2.	Congenital systemic-to-pulmonary shunts
1.3.3.	Portal hypertension
1.3.4.	Human immunodeficiency virus infection
1.3.5.	Drugs and toxins
1.3.6.	Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
1.4.	Associated with substantial venous or capillary involvement
1.4.1.	Pulmonary veno-occlusive disease
1.4.2.	Pulmonary capillary hemangiomatosis
1.5.	Persistent pulmonary hypertension of the newborn
2.	**Pulmonary hypertension with left-sided heart disease**
2.1.	Left-sided atrial or ventricular heart disease
2.2.	Left-sided valvular heart disease
3.	**Pulmonary hypertension associated with lung diseases and/or hypoxemia**
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Sleep-disordered breathing
3.4.	Alveolar hypoventilation disorders
3.5.	Long-term exposure to high altitude
3.6.	Developmental abnormalities
4.	**Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
4.1.	Thromboembolic obstruction of proximal pulmonary arteries
4.2.	Thromboembolic obstruction of distal pulmonary arteries
4.3.	Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5.	**Miscellaneous**: Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

[a]Adapted from Simonneau et al.[3]

Screening and Diagnosis

There are two separate populations where screening for PAH needs to be considered. First, there are patients with symptoms that raise the suspicion of PAH. The symptoms of PAH can be insidious and nonspecific and may include shortness of breath, fatigue, weakness, chest pain, loss of consciousness, and abdominal distention. Symptoms that are present at rest suggest advanced disease.[1] Since these symptoms are nonspecific, screening may be necessary to help decide whether the patient should undergo a diagnostic workup for PAH, or whether other conditions should be considered. The other population is patients with medical conditions that put them at risk for PAH. In these patients screening tests may be used to identify patients with asymptomatic elevation of pulmonary artery pressures, who might be or more closely monitored for the development of symptoms or progressive disease or offered a diagnostic workup for PAH, and possibly treatment for early disease.

Once screening indicates the possibility of PAH, diagnostic tests are necessary to confirm the presence of elevated right-sided heart pressures and to exclude valvular, primary myocardial, chronic lung disease, thromboembolic, and miscellaneous other causes of pulmonary hypertension (PH). The gold standard for diagnosing PAH is right heart catheterization (RHC), which is generally considered to be a safe procedure. In a retrospective and prospective study by

Hoeper et al.,[5] the rate of serious complications in patients undergoing RHCs for evaluation of pulmonary hypertension was 1.1 percent and included bleeding, vasovagal reactions, systemic hypotension, arterial injury, hypertensive crisis, pneumothorax, and cardiac arrhythmias. The procedure-related mortality was 0.055 percent.[5]

RHC not only confirms the diagnosis of PAH but also provides prognostic hemodynamic information (mean right atrial pressure, pulmonary vascular resistance)[6] to direct treatment decisions. A small subset of patients with PAH, when challenged with a short-acting pulmonary vasodilator, will experience a drop in mean pulmonary artery pressure of at least 10 mmHg (20%) to below 40 mmHg while maintaining cardiac output; this predicts a favorable long-term response to calcium-channel blockers.[1]

Since PAH is a progressive disease, regular reassessment is needed to monitor response to treatment and adjust prognosis. RHC has traditionally been the means by which patients' clinical course is monitored; however, transthoracic echocardiography has emerged as a possible alternative. The number of echocardiographic modalities has increased substantially, providing unique insight into the structure and function of the right heart in patients with pulmonary hypertension.[7] However, this test has not been definitively validated as a substitute for RHC in patients with PAH. Finally, the role of biomarkers has not been fully established in the management and prognosis of PAH. Defining whether biomarkers alone or biomarkers plus echocardiography might be superior to echocardiography alone for informing treatment decisions is a necessary first step in establishing a noninvasive, multifaceted approach to the management of PAH.

Role of Echocardiography

The role of echocardiography in the diagnosis and management of patients with PAH has evolved over time, and has been proposed for screening, assessing prognosis and evaluating response to treatment. Screening high-risk individuals for PAH generally begins with an transthoracic echocardiogram.[8] Echocardiography can estimate the right ventricular systolic pressure and identify other signs of PH including increased right-sided chamber size and wall thickness. Most often, the peak velocity of the tricuspid regurgitant (TR) jet is measured by Doppler and—along with an estimate of right atrial pressure based on inspiratory collapse and size of the inferior vena cava—TR jet is used to estimate the systolic pulmonary artery pressure (sPAP). However, a significant proportion of patients have no measureable TR jet. Estimates are often inaccurate compared with RHC; up to 60 percent of echocardiography estimates were more than 10 mmHg off from RHC measurement in one large multicenter registry of PAH patients.[9] Therefore, although transthoracic echocardiography is the standard screening test for PAH, it is less than completely accurate and there is uncertainty as to which echocardiographic measurements are most useful.

Several studies have investigated the use of echocardiography in establishing prognosis in PAH. In a study of patients with systemic sclerosis (n=155), calculation of the right ventricular systolic pressure (RVSP) using Doppler echocardiography identified 47 patients (36.4%) with RVSP ≥36 mmHg who had decreased 3-year survival rates compared with patients with RVSP <6 mmHg (67% versus 86%, $p < 0.01$).[10] Another study of patients with PAH (n=80) using echocardiography to calculate right ventricular free wall strain found that patients with strain worse than -12.5 percent were associated with increased 6-month disease progression and increased mortality at 1 year (unadjusted hazard ratio 6.2).[11] There remains uncertainty regarding

which echocardiographic measure(s) have prognostic value although TAPSE and pericardial effusion have been proposed.[12]

Traditionally, RHC assessment of hemodynamics is recommended to demonstrate treatment response;[12] echocardiography has been seldom studied in this role.

Role of Biomarkers

Because of the limitations of echocardiography, the potential role of biomarkers in screening for and managing of PAH has been the subject of increasing interest over the last decade. Brain natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP) are two biological substances found in the blood that have been studied as a screening test in patients at risk for PAH and which have been shown to correlate well with the presence of disease.[13,14] Other biomarkers currently under investigation include atrial natriuretic peptide, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin. Several of these biomarkers have been shown to correlate with prognosis and mortality, either alone or in conjunction with other traditional measurements such as the 6-minute walk distance (6MWD) test, functional class assessment, and pulmonary hemodynamics.[15] Select biomarkers may even be superior to traditional testing. Patients with idiopathic and familial PAH were shown to exhibit dysregulation over a broad range of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, when compared with healthy controls, which correlated better with prognosis than 6MWD and pulmonary hemodynamics.[16]

Treatment Strategies

Medications

There has been rapid development and approval of vasodilator medications for PAH over the past three decades. Currently, there are four main classes of medications used to treat PAH:[17]

- Calcium-channel blockers:
  - Amlodipine
  - Diltiazem
  - Nifedipine
- Prostacyclin analogues:
  - Epoprostenol
  - Iloprost
  - Treprostinil
- Endothelin receptor antagonists:
  - Bosentan
  - Ambrisentan
- Phosphodiesterase type 5 inhibitors:
  - Sildenafil
  - Tadalafil

These PAH medications have been shown to improve dyspnea, 6MWD, pulmonary hemodynamics, and functional class. Calcium-channel blockers are associated with long-term (>1 year) improvements in hemodynamics and functional status in about half of the minority of patients who show acute vasoreactivity testing response.[18] The limited usefulness of calcium antagonists—as well as the poor prognosis and diminished quality of life associated with PAH—reinforces the need for new drug therapies and improved delivery of current medications. Limited data suggest that epoprostenol and bosentan may provide a survival benefit; however, this end point has not been studied consistently between the medications.[19] The two medications most recently approved by the U.S. Food and Drug Administration for PAH are inhaled treprostinil, a new delivery system for this prostacyclin analogue, and ambrisentan, a new endothelin receptor antagonist. These new medications were discussed in the Expert Consensus Document on Pulmonary Hypertension released in 2009 by the American College of Cardiology Foundation and the American Heart Association.[19] Since then, however, numerous studies have been published regarding the safety and efficacy of these new medications. Also, more data have been published on the older medications for PAH. These new data may clarify any effect on mortality and gauge the comparative effectiveness of these drugs.

Additionally, combination drug therapy (using multiple drugs with different mechanisms of action) is an important area of research and may be the most promising way to improve clinical outcomes although at higher cost.[2] Combination therapy was addressed in the 2009 ACCF/AHA publication, and several studies have since been published on this topic. In order to optimize PAH care, newer information regarding the latest drugs and combination therapies should be systematically reviewed.[17]

Scope and Key Questions

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). It was designed to evaluate the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the diagnosis and management of PAH in addition to clarifying whether the use of echocardiography and biomarkers affects decisionmaking and clinical outcomes. We also wanted to address which medications are effective for treating PAH and how the newer medications compare with older ones and with each other. Further, there was a need for clarity about whether combination therapy is more effective than monotherapy and what effect monotherapy or combination therapy has on intermediate-term and long-term outcomes.

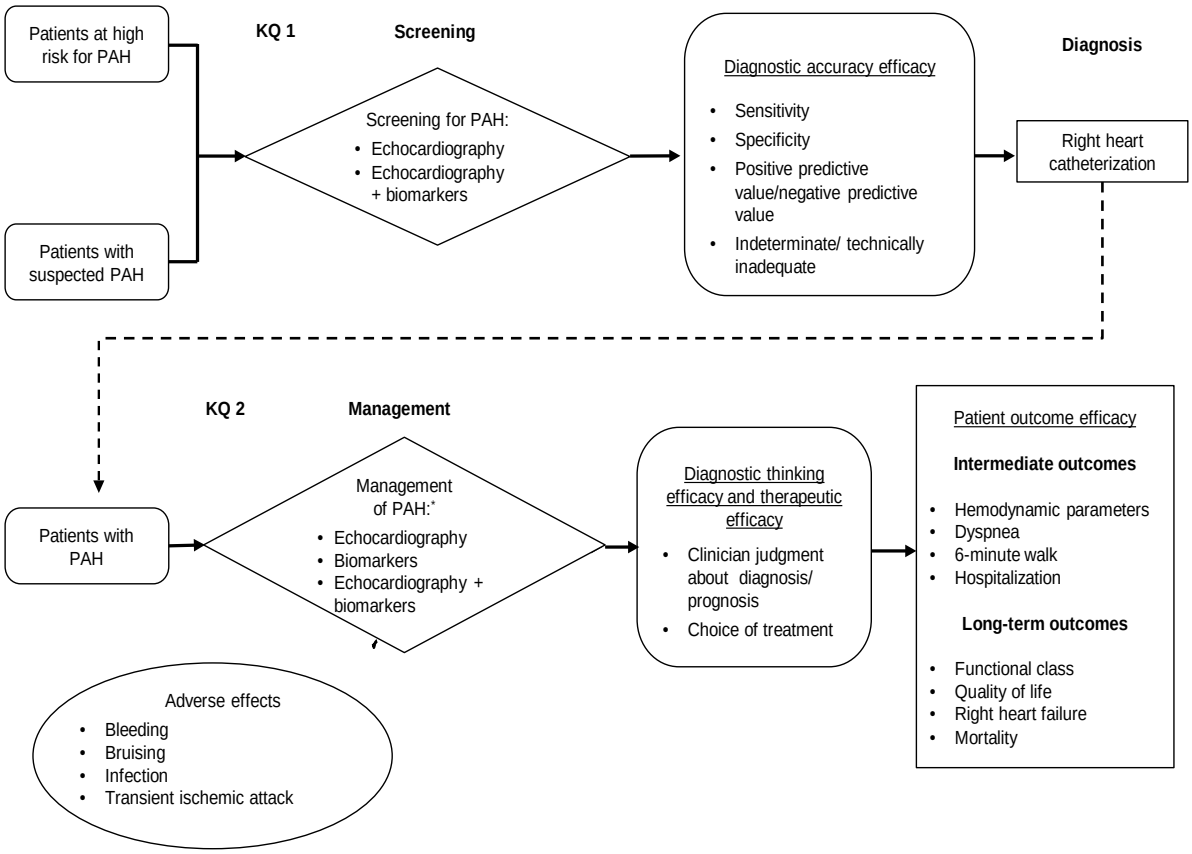
The KQs considered in this comparative effectiveness review were:

- **KQ 1.** For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what is the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?
- **KQ 2.** For patients with PAH, what is the comparative effectiveness and safety of (a) echocardiography versus biomarkers and (b) echocardiography versus echocardiography plus biomarkers in managing PAH and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes?

- **KQ 3.** For patients with PAH, what is the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium-channel blockers, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

Figures A and B show the analytic frameworks for this comparative effectiveness review.

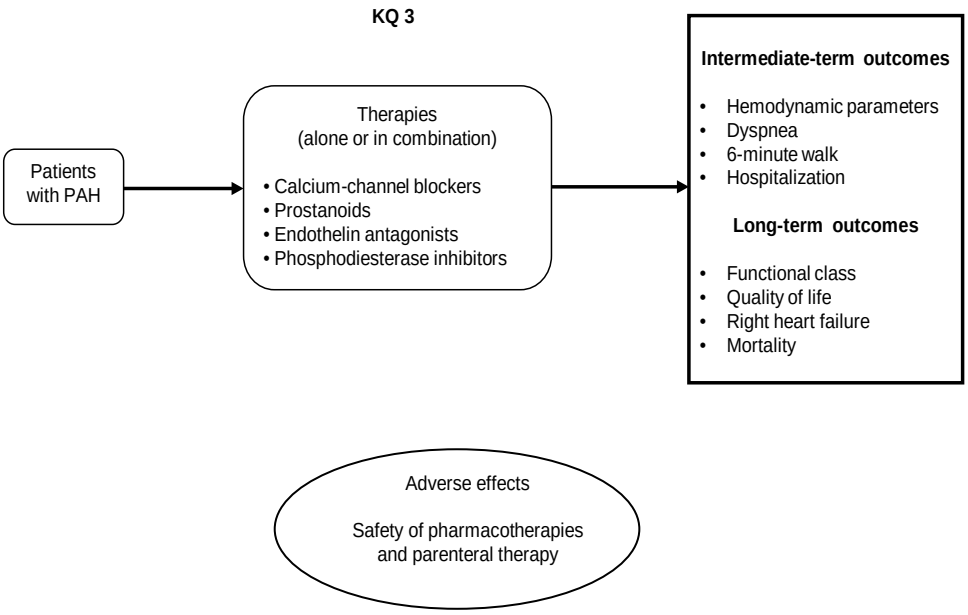
Figure A. Analytic framework for KQs 1 and 2



*In conjunction with routine clinical assessment (functional class, dyspnea, 6-minute walk).

Abbreviations: KQ = Key Question; PAH = pulmonary arterial hypertension

Figure B. Analytic framework for KQ 3



Abbreviations: KQ = Key Question; PAH = pulmonary arterial hypertension

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the *Methods Guide*).[20]

Input from Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing clinicians (pulmonology, cardiology, pathology), patients, scientific experts, and Federal agencies, to help define the Key Questions. The Key Questions were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind and did not contribute to the writing of the report.

Literature Search Strategy

To identify the relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews. We limited the search to English-language studies conducted in adults from 1995 to the present; prior to 1995, newer drug treatments were not available and older echocardiographic and biomarker testing technology is less applicable. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; World Health Organization International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets were requested from the manufacturers of medications and devices and reviewed for relevant articles from completed studies not previously identified in the literature searches.

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in the main report. For KQ 1, the search focused on studies that reported the accuracy of echocardiography, biomarkers or the combination of these tests for diagnosis of PAH in patients suspected of having PAH or asymptomatic patients at high risk for PAH. For KQ 2, the search focused on English-language studies describing data on how echocardiographic or biomarker testing among patients with PAH was related to diagnostic thinking efficacy and therapeutic efficacy (clinician judgment about diagnosis or prognosis or choice of treatment) and patient outcome efficacy (prognosis related to intermediate and long term outcomes, including hemodynamic parameters, dyspnea, 6MWD, functional status, and mortality). For KQ 3, the search focused on studies the effect of pharmacotherapy with prostanoids (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, ambrisentan) or phosphodiesterase inhibitors (sildenafil, tadalafil) on intermediate and long-term outcomes as well as adverse effects in patients with PAH.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the Key Questions. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. Disagreements were resolved by discussion or by a third-party arbitrator, if needed. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners, Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached between the first two investigators.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the *Methods Guide*.[20] To assess methodological quality, we employed the strategy to (a) apply predefined criteria for quality and critical appraisal and (b) arrive at a summary judgment of the study's quality. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor. For studies of diagnostic tests (KQ 1 and KQ 2), we used QUADAS-2,[21] a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing; each domain is rated as high, low, or unclear risk of bias.

Two raters independently evaluated each study and differences were resolved by consensus; if consensus could not be reached, then the item was rated as unclear, and the rationale for each differing assessment was described. Results were described for individual domains. If the distribution of ratings permits, methodological domains were examined for association with effects in meta-analysis.

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting.

Data Synthesis

Quantitative synthesis (i.e., meta-analysis) was done when we found multiple studies of similar design, population, intervention, comparator and outcome that reported sufficient data for analysis. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence. We use meta-analyses both to quantify and to attempt to explain between-study variation as well as to calculate summary estimates. When a meta-analysis was not appropriate we described the reasons, presented data in tabular form and summarized studies either individually or qualitatively.

For sensitivity and specificity data, we used a binomial model to calculate summary estimates of sensitivity and specificity and associated confidence intervals and summary ROC curve using SAS. Sensitivity analyses were conducted using summary receiver operating characteristic meta-analysis using the diagnostic odds ratio with dr-ROC software (Diagnostic Research Design and Reporting; Glenside, PA). For meta-analysis of correlation coefficients and hazard ratios for observational studies, we used a random effects model implemented in SAS (SAS Institute Inc.; Cary, NC). For treatment effects meta-analysis, we used a random effects model meta-analysis implemented in Comprehensive Meta-Analysis Software (Version 2.2.064, Biostat; Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics

(Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited, particularly when the number of studies is small. We present summary estimates and confidence intervals in our data synthesis.

Strength of the Body of Evidence

The strength of evidence for each Key Question was assessed using the approach described in the *Methods Guide*.[22] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate: dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence was assigned after discussion by two reviewers. A grade of insufficient was assigned when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn.

Diagnostic evaluation studies (KQs 1 and 2) are generally indirect, as the link between the test intervention and outcome is mitigated by prognosis, management, and the effectiveness of treatments. As a rule of thumb, we considered correlation coefficients greater than 0.7 as strong evidence of association, 0.40 to 0.69 as moderate evidence, and less than 0.40 as weak evidence. In our summary strength of evidence assessments for KQs 1 and 2, lack of directness was weighed less heavily and risk of bias most heavily. Thus, we allowed high strength of evidence levels despite the lack of directness among these studies.

Applicability

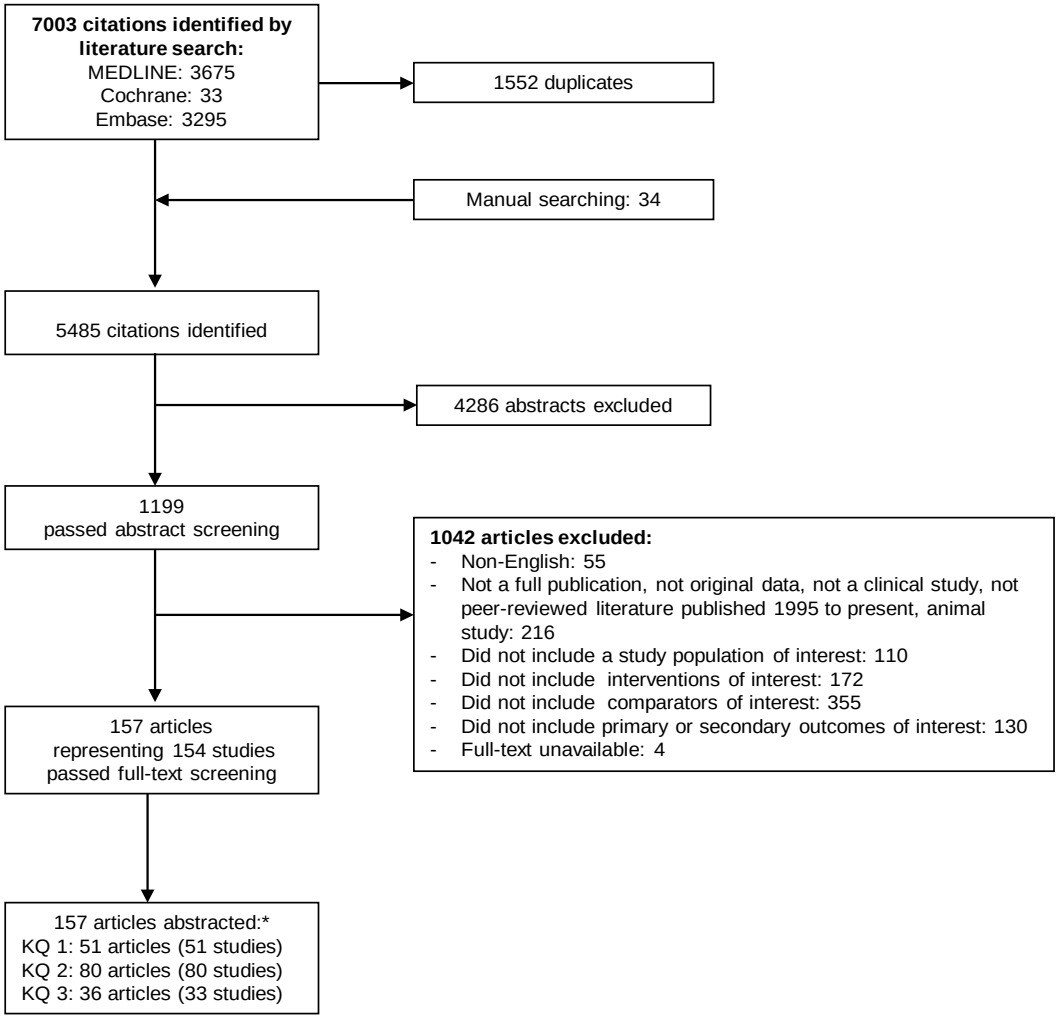
We assessed applicability across our KQs using the PICOTS format as described in the *Methods Guide*.[20,23] We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (such as age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively. Because applicability issues may differ for different users, we reported across a range of potential applicability issues.

In diagnostic evaluation studies, we were particularly concerned with the prevalence of PAH versus PH in the study populations compared, the spectrum of underlying type of PAH, and the assessment of adverse events associated with testing. In PAH drug trials, we were particularly concerned with assessing the severity of illness; use of run-in periods and attrition before randomization; use of surrogate or combined outcome measures; short study duration; reporting of adverse events, in particular including those related to administration or monitoring of treatment; sample size sufficient to assess minimally important differences from a patient perspective; and use of intention-to-treat-analysis.

Results

Figure C depicts the flow of articles through the literature search and screening process. Searches of PubMed®, the Cochrane Database of Systematic Reviews, and Embase® yielded 7003 citations, 1552 of which were duplicate citations. Manual searching identified 34 additional citations, for a total of 5485 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1199 full-text articles were retrieved and screened. Of these, 1042 were excluded at the full-text screening stage, leaving 157 articles (representing 154 unique studies) for data abstraction.

Figure C. Literature flow diagram



Abbreviation: KQ=Key Question
Article counts by KQ do not add to 157 because some studies were included for multiple KQs.

Key Question 1. Screening for Pulmonary Arterial Hypertension

Key Points from the Results chapter are:

- For patients suspected of having PAH with elevated sPAP by echo, additional testing with the biomarker NT-proBNP may identify patients who do not have PAH compared with echo sPAP alone (based on one good-quality prospective cohort study) (low SOE).
- For patients suspected of PAH, echocardiographic estimation of RVSP (or TG) by TRV, sPAP by TRV and RAP, and PVR by TRV/VTI_{RVOT} shows reasonably good accuracy compared with RHC (moderate SOE).
- For both asymptomatic patients at high risk for PAH or symptomatic patients suspected of PAH, natriuretic peptide testing (with either BNP or NT-proBNP) shows highly variable sensitivity and specificity estimates (not simultaneously high) for pulmonary hypertension (PH) or PAH diagnosis (low SOE) and moderate correlation with hemodynamic measures by RHC (moderate SOE).
- There were no studies of the safety of biomarker and echocardiography testing, nor were there any studies of combined echocardiographic and biomarker screening of asymptomatic patients at high risk for PAH (insufficient SOE).

We identified one good-quality study involving 372 patients that compared echocardiography with echocardiography plus biomarkers in patients with suspected PAH, most of whom were symptomatic. There were no other studies directly comparing combinations of echocardiographic and biomarker testing. In order to draw inferences about the comparative effectiveness of other tests, we reviewed the diagnostic accuracy of independent echocardiographic or biomarker testing compared with RHC. By evaluating the relative diagnostic performance of these tests versus a reference standard of RHC or a criterion standard diagnosis, one can impute the comparative effectiveness via indirect comparisons. We describe 50 studies involving a total of 6608 patients that describe the effectiveness of echocardiography or biomarkers in patients with suspected PAH, or in asymptomatic patients at high risk for PAH, as screening modalities before RHC to establish the diagnosis of PAH. Table B summarizes the findings of our review and the strength of evidence (SOE) for the available outcomes of sensitivity, specificity, correlation coefficients, and adverse effects of biomarker and echocardiographic tests. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the main report. Among biomarker studies, natriuretic peptide (BNP, NT-proBNP) was the only biomarker reported in more than one study therefore it is the only biomarker for which we generated a strength of evidence table. Limited data on uric acid, cyclic GMP and endothelin-1 were reported in one study each. Likewise, the echocardiographic estimates of sPAP, and PVR (TRV/VTI_{RVOT}) were the only echocardiographic parameters reported in a sufficient number of studies to support a strength of evidence rating. Limited data on FAC, RA size, RIMP, RV size and TAPSE are described in the main report.

Table B. Summary of strength of evidence and effect estimates for echocardiography versus echocardiography plus biomarkers as screening modalities for PAH (KQ 1)[a]

Test	Sensitivity	Specificity	Correlation with RHC
Echo sPAP with NT-proBNP versus Echo sPAP in symptomatic patients	SOE=Insufficient (1 study, 121 patients) NT-proBNP >80 pg/mL has a low false negative rate compared with RHC reference standard; the serial testing study design did not allow for NT-proBNP testing to improve sensitivity beyond that of echo sPAP alone	SOE=Low (1 study, 121 patients) NT-proBNP ≤80 pg/mL ruled out PAH in 9–16% of patients with elevated echo sPAP ≥36 mmHg	SOE=Insufficient (No studies)
Echo sPAP with NT-proBNP versus Echo sPAP in asymptomatic patients	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)
NT-proBNP compared with RHC	SOE=Low (3 studies, 198 patients) NT-proBNP has variable sensitivity (range, 56% to 100%) for diagnosing PAH; uncertain performance for ruling in PAH	SOE=Low (3 studies, 198 patients) NT-proBNP has variable specificity (range, 24% to 95%); uncertain performance for ruling out PAH	SOE=Moderate (3 studies, 176 patients) Correlation of NT-proBNP and RHC is only moderate (range, 0.43 to 0.72)
TRV/TG/sPAP compared with RHC	SOE=Moderate (15 studies, 1898 patients) Echocardiographic estimate of sPAP showed variable sensitivity ranging from 58% to 100%, with lower prevalence studies finding higher sensitivity	SOE=Moderate (15 studies, 1898 patients) Echocardiographic estimate of sPAP showed variable specificity ranging from 64% to 98%, with lower prevalence studies finding higher specificity	SOE=Moderate (14 studies, 1822 patients) Echocardiographic estimates of sPAP showed moderate to strong correlation (range, 0.38 to 0.96) with RHC and were on average unbiased, but were limited by imprecision and by a significant minority of patients in whom TRV was not measurable
TRV/VTI_{RVOT} compared with RHC	SOE=Moderate (6 studies, 218 patients) Echocardiographic estimate of PVR showed reasonably high sensitivity (range, 89% to 100%) for ruling in PAH	SOE=Moderate (6 studies, 218 patients) Echocardiographic estimate of PVR showed variable specificity (range, 50% to 97%), with better specificity in lower prevalence studies (range, 94% to 97%)	SOE=High (6 studies, 218 patients) Strong correlation between echocardiographic estimates of PVR and PVR by RHC (range, 0.74 to 0.84)

[a]Gray highlights insufficient strength of evidence.
Abbreviations: NT-proBNP=N-terminal pro-B-type natriuretic peptide; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure; TRV=tricuspid regurgitant jet velocity; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

One good-quality study evaluated the diagnostic value of serum NT-proBNP in a noninvasive diagnostic decision algorithm that also used data from electrocardiography and echocardiography. Among 69 patients without RV strain on ECG, serum NT-proBNP level >80 pg/mL had 100 percent sensitivity and 24 percent specificity. Taken in combination with the decision algorithm, and in patients with echocardiographic estimates of sPAP ≥36 mmHg, the presence of RV strain on ECG and serum NT-proBNP >80 pg/mL had a sensitivity of 100 percent and specificity of 19 percent for diagnosis of PAH based on RHC reference standard. By using this decision algorithm to exclude precapillary PH, the investigators concluded that 9 percent of referred patients with elevated sPAP by echocardiography (≥36 mmHg) could avoid undergoing invasive RHC. Excluding patients with RV strain, serum NT-proBNP testing would have avoided RHC in 16 percent of patients.

Twelve studies (5 good quality, 4 fair, and 3 poor) evaluated serum NT-proBNP or BNP in patients both with and without PAH. Sensitivity and specificity estimates among 3 studies that permitted their calculation were highly variable, presumably reflecting differences in study populations because differences in test thresholds did not result in expected direction of change in sensitivity and specificity. Statistically significant correlation coefficients were found between the biomarker level and hemodynamic measures CO, mPAP, PVR, and sPAP

Fifteen studies (5 good, 8 fair, 2 poor) reported the diagnostic accuracy of echocardiographic estimates of pulmonary pressures based on TRV measurement, with or without estimate of RAP, compared with a reference standard diagnosis based on RHC. Summary estimates for sensitivity (0.91; 95% CI, 0.76 to 0.97) and specificity (0.89; 95% CI, 0.82 to 0.94) showed moderate heterogeneity (I^2=61.1%). Studies with lower prevalence of PH (less than 15% of study subjects) showed greater homogeneity than studies with higher prevalence of PH (sensitivity 0.83 [95% CI, 0.67 to 0.92]; specificity 0.86 [95% CI, 0.76 to 0.94]). The eight low prevalence studies (sensitivity 0.91 [95% CI, 0.85 to 0.94]; specificity 0.92 [95% CI, 0.88 to 0.95]) included four studies of liver transplant patients (which had complete verification of test negative subjects) and four studies that had high degree of verification bias.

Six studies (3 good, 2 fair, 1 poor) evaluated the echocardiographic estimation of PVR using TRV/VTI_{RVOT} against RHC diagnosis of elevated PVR. Three of these studies included patients with known PH. Two studies used a threshold for PVR much higher than that used for diagnosis (8 Woods Units versus 2 Woods Units) with the goal of distinguishing more severe PAH; these studies also used a higher test threshold of 0.2 and 0.38 compared with 0.14 to 0.175. Sensitivity ranged from 75 to 94 percent, while specificity ranged from 57 to 100 percent. Because of clinical heterogeneity no meta-analysis was performed.

Six studies correlated TRV/VTI_{RVOT} with PVR by RHC. Correlation coefficients indicated strong correlation ranging from 0.73 to 0.84, with bias ranging from 0 to 6.1, and standard deviations ranging from 1.9 to 4.3 Woods Units.

We found no studies describing safety (or harms) of echocardiography or biomarker testing.

Key Question 2. Management of Pulmonary Arterial Hypertension

Key Points from the Results chapter are:

- No data are available regarding the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers in the management of PAH or patient outcomes (insufficient SOE).
- Systolic pulmonary artery pressure (sPAP) estimated by echocardiography shows good correlation with sPAP from RHC (moderate SOE).
- Serum brain natriuretic peptide (BNP) level shows only moderate correlation with these RHC measures: mean pulmonary artery pressure (mPAP), pulmonary vascular resistance, right atrial pressure, cardiac index, and clinical outcomes such as the 6MWD test (moderate SOE).
- BNP level shows poor correlation with RHC pulmonary capillary wedge pressure (low SOE).
- BNP level alone is not an accurate surrogate marker for disease severity (high SOE).
- BNP level is a poor predictor of mortality (high SOE).
- Fractional area change (FAC) is a poor predictor of mortality (moderate SOE).
- Right atrial (RA) size is a poor predictor of mortality (low SOE).
- Presence of pericardial effusion is the strongest predictor of mortality although there was wide variability in results for this measure (moderate SOE).
- We found no studies addressing diagnostic thinking efficacy, therapeutic efficacy, or harms (insufficient SOE).

We identified 80 unique, observational studies involving a total of 7224 patients that evaluated the use of biomarkers or echocardiographic parameters in the management of PAH or as predictors of patient outcomes. Of these studies, 57 were rated good quality, 21 fair quality, and 2 poor quality. We did not find any studies that assessed the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers as outlined in our original Key Question. Instead, we focus on available studies that evaluate the ability of echocardiography or biomarkers to assess the severity of PAH, to predict events such as lung transplantation or death, or to assess a patient's response to therapy. By evaluating the independent association of biomarkers or echocardiography, one can impute the comparative effectiveness via indirect comparison. The most common biomarker evaluated was BNP (46 studies), followed by uric acid (6), endothelin-1 (4), troponin T (3), nitric oxide (2), cGMP (2) and ANP (1). We found no studies assessing D-dimer or asymmetric dimethylarginine to evaluate their ability to assess severity of disease, response to therapy, or outcome.

Thirty-nine studies evaluated several echocardiographic parameters. These included sPAP (15 studies), RIMP/MPI/Tei (14), RA size (10), pericardial effusion (9), FAC (8), TAPSE (6), RV size (6), mPAP (5), TR jet (3), TRV/VTI_{RVOT} (3), RVEF (2), echocardiography-derived cardiac index (2), and RVSP (2).

For the comparators, we focused on RHC hemodynamics, 6MWD, and functional class (FC) as the gold standards for assessing severity of disease. Thirty-one studies used RHC as a reference test, 13 studies used 6MWD as a reference test, and 8 studies used FC as a reference test.

Thirty-five studies looked at correlation between biomarkers and/or echocardiographic parameters and the comparators. Nineteen studies looked at hazard ratios (HR) for death, two studies looked at HR for a composite outcome of death or lung transplant, and one study looked at HR for lung transplant alone. Seventeen studies evaluated changes in mean values in response to therapy, and two studies evaluated changes in median values in response to therapy. Five studies assessed mean or median change from baseline in response to therapy.

In studies evaluating correlation of the above measures with RHC measures or a commonly used measure of disease severity (6MWD) studies were too underpowered to give reliable results. However, by combining studies looking at the same parameters and performing a meta-analysis we were able to increase the power for seven different comparisons: (1) BNP versus RHC-mPAP, (2) BNP versus RHC-PVR, (3) BNP versus RHC-CI, (4) BNP versus RHC-RAP, (5) BNP versus RHC-PCWP, (6) BNP versus 6MWD, and (7) echocardiography-derived sPAP versus RHC-sPAP. BNP showed only moderate correlation with most RHC measures (mPAP, PVR, cardiac index, RAP) and clinical measures of disease severity (6MWD) and showed weak correlation with PCWP. Most effect estimates were precise (mPAP, PVR, cardiac index, RAP, 6MWD), but estimates for PCWP were imprecise, making it difficult to interpret the clinical importance of the findings for this measure. For the other measures, correlation with BNP was only moderate, indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Echocardiography-derived sPAP showed strong correlation with RHC-sPAP, although there was a great deal of heterogeneity among these studies and only moderate strength of evidence to support the use of this measure.

In studies evaluating the ability of biomarkers or echocardiographic measures to predict mortality, we were able to perform a meta-analysis on four measures. Studies evaluating pericardial effusion, BNP, RA size, and FAC showed fair consistency among hazard ratio estimates. Overall, pericardial effusion was the strongest predictor of mortality and may be useful clinically, though results were not highly precise. BNP, RA size, and FAC showed no significant ability to predict mortality.

The remaining studies that were not included in the meta-analyses were considered to provide insufficient evidence due to small size and poor quality.

The strength of evidence (SOE) ratings for the most commonly reported biomarkers and echocardiographic parameters are summarized in Table C (management of PAH) and Table D (prediction of patient outcomes).

Table C. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the management of PAH (KQ 2)

Comparison	Number of Studies (Patients)	Summary Correlation Coefficient Estimate (95% CI)	SOE and Findings
BNP compared with RHC-mPAP	13 (559)	0.41 (0.31 to 0.49)	SOE=Moderate Serum BNP level shows only moderate correlation with mPAP
BNP compared with RHC-PVR	12 (638)	0.49 (0.32 to 0.63)	SOE=Moderate Serum BNP level shows only moderate correlation with PVR
BNP compared with RHC-RAP	11 (600)	0.47 (0.39 to 0.55)	SOE=Moderate Serum BNP level shows only moderate correlation with RAP
BNP compared with cardiac index	9 (509)	-0.47 (-0.59 to -0.34)	SOE=Moderate Serum BNP level shows only moderate correlation with cardiac index
BNP compared with PCWP	5 (319)	0.16 (0.01 to 0.31)	SOE=Low Serum BNP level shows poor correlation with PCWP
BNP compared with 6MWD (absolute)	8 (396)	-0.47 (-0.58 to -0.34)	SOE=Moderate Serum BNP level shows only moderate correlation with 6MWD
Echocardiography-derived sPAP compared with RHC-sPAP	8 (302)	0.79 (0.55 to 0.91)	SOE=Moderate sPAP estimated by echocardiography shows good correlation with sPAP from RHC

Abbreviations: 6MWD=6-minute walk distance; BNP=B-type natriuretic peptide; CI=confidence interval; FAC=fractional area change; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrium; RAP=right atrial pressure; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure

Table D. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the prediction of mortality (KQ 2)

Marker	Number of Studies (Patients)	Summary Hazard Ratio Estimate (95% CI)	SOE and Findings
BNP	9 (632)	1.08 (1.01 to 1.16)	SOE=High BNP level is a poor predictor of mortality
Pericardial effusion	7 (2485)	2.20 (1.42 to 3.41)	SOE=Moderate Presence of pericardial effusion is the strongest predictor of mortality, although there was wide variability in results for this measure
RA size	4 (242)	1.07 (0.99 to 1.14)	SOE=Low RA size is a poor predictor of mortality
FAC	4 (242)	0.99 (0.96 to 1.02)	SOE=Moderate FAC is a poor predictor of mortality

Abbreviations: BNP=B-type natriuretic peptide; CI=confidence interval; FAC=fractional area change; RA=right atrium; RAP=right atrial pressure; SOE=strength of evidence

Key Question 3. Pharmacotherapy for Pulmonary Arterial Hypertension

Key Points from the Results chapter are:

- Evidence comparing monotherapy with combination therapy for PAH permitted a conclusion for only one outcome: improved 6MWD with combination therapy compared with monotherapy (low SOE). For all other outcomes (mortality, pulmonary vascular resistance, mean PAP, and cardiac index), evidence on this comparison was insufficient to permit conclusions.

- In patients treated for PAH with prostanoids, endothelin antagonists, or phosphodiesterase inhibitors, current evidence is inconclusive regarding a reduction in mortality with either monotherapy or combination therapy (insufficient SOE).

- As measured by 6MWD after 12 to 16 weeks of therapy, eight good-quality RCTs support the use of monotherapy with endothelin antagonists (high SOE), phosphodiesterase inhibitors (high SOE), or prostanoids (low SOE) for improving exercise capacity compared with placebo in patients with PAH.

- Eight good-quality and one fair-quality RCTs support a reduction in hospital admissions due to worsening PAH symptoms with the use of either monotherapy or combination therapy, with significant reductions in hospitalizations associated with both endothelin antagonists and phosphodiesterase inhibitors (moderate SOE) compared with placebo or conventional therapy.

- Monotherapy with for PAH is associated with statistically significant improvements in hemodynamic measures such as pulmonary vascular resistance, (four good-quality, one

fair-quality RCTs) mean pulmonary artery pressure (three good-quality, one fair-quality RCT), and cardiac index (four good-quality, one fair-quality RCT) after 12 to 16 weeks of therapy compared with placebo or conventional therapy, but high heterogeneity of published studies precludes the quantifying summary measures of effect that are sufficiently reliable and valid (insufficient SOE).

Among commonly reported adverse events, there is a higher incidence of jaw pain associated with prostanoid treatment compared with placebo (high SOE) and cough associated with prostanoids versus placebo (high SOE). Also, headache was associated with phosphodiesterase inhibitors compared with placebo or conventional therapy (moderate SOE), and flushing was associated with phosphodiesterase inhibitors (moderate SOE) and prostanoids (moderate SOE) compared with placebo or conventional therapy. Twenty-seven RCTs (31 articles) involving 3619 patients evaluated the comparative effectiveness and safety of monotherapy versus combination therapy for PAH. Of these RCTs, 17 (63%) were rated good quality, 9 (33%) fair quality, and 1 (4%) poor quality. Eighteen studies (67%) were funded by industry, one by government, one privately, one by government and private funding, one by private and industry funding, and five did not report funding sources.

The mean patient ages ranged from 28 to 57 years old. Nineteen studies enrolled patients with PAH, three studies enrolled patients with PAH secondary to systemic sclerosis (formerly scleroderma), and two studies enrolled patients with Eisenmenger syndrome. Two studies enrolled a percentage of patients with non-Category 1 PH: chronic thromboembolic pulmonary hypertension (28%), and secondary PAH, PH secondary to lung disease, or chronic thromboembolic pulmonary hypertension (37%).

Eighteen studies compared a single drug versus placebo and included the following drugs: bosentan (6 studies), sildenafil (2), iloprost (2), tadalafil (2), ambrisentan (2), treprostinil (3), and vardenafil (1). Two studies compared epoprostenol with conventional therapy (diuretics, supplemental oxygen, cardiac glycosides, and calcium channel blockers). For the purposes of this analysis, the conventional therapy arms were grouped with the placebo arms. One study was a head-to-head comparison of bosentan and sildenafil. The remaining six studies compared combination therapy with single therapy: (1) intravenous (IV) epoprostenol plus bosentan versus IV epoprostenol plus placebo, (2) sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo, (3) bosentan plus inhaled iloprost versus bosentan, (4) bosentan plus inhaled iloprost versus bosentan plus placebo, (5) bosentan plus tadalafil versus bosentan plus placebo, and (6) aerosolized treprostinil plus bosentan or sildenafil versus bosentan or sildenafil plus placebo. We did not identify any eligible studies published after 1995 that evaluated the safety or efficacy of calcium channel blockers on intermediate-term and long-term patient outcomes.

Most studies (85%) were multicenter trials; two were single-center trials, and four did not report the number of centers. The studies reported the following outcomes: 6 minute walk distance (25 studies), mortality (19), dyspnea (18), right heart catheterization indices (16), functional class (16), hospitalization for worsening PAH (11), quality of life (11), lung transplantation (6), right heart failure or right ventricular dysfunction (4), brain natriuretic peptide (4), and echocardiogram indices (3). Twenty-two studies reported harms or adverse events. Table E summarizes the strength of evidence (SOE) for the key outcomes of mortality, 6MWD, and hospitalization. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) and information on other outcomes are available in the main report.

Table E. Summary of strength of evidence and effect estimates for monotherapy versus combination therapy for PAH (KQ 3)[a]

Intervention	Mortality	6MWD (m)	Hospitalization
Combination vs. monotherapy	SOE=Insufficient (3 studies, 533 patients) No clear differences in mortality (few studies, few deaths lead to wide CIs) OR 0.37 (95% CI, 0.04 to 3.32)	SOE=Low (3 studies, 363 patients) Improved 6MWD with combination therapy compared with monotherapy Mean difference 24.1 (95% CI, 8.2 to 40.0)	SOE=Insufficient (3 studies, 739 patients) Inconclusive benefit (few studies, wide CIs) OR 0.62 (95% CI, 0.28 to 1.37)
Sildenafil vs. bosentan	SOE=Insufficient (1 study, 26 patients)	SOE=Insufficient (1 study, 26 patients) No clear difference in 6MWD between sildenafil and bosentan. Mean difference 16 (95% CI NS; ITT analysis)[b]	SOE=Insufficient (No studies)
Endothelin agonist vs. placebo or standard therapy	SOE=Insufficient No clear differences in morality (few studies, few deaths lead to wide CIs) Bosentan: OR 0.72 (95% CI, 0.14 to 3.60) (3 studies, 411 patients) Ambrisentan: OR 0.33 (95% CI, 0.06 to 1.74) (2 studies, 330 patients)	SOE=High (4 studies, 638 patients) Improved 6MWD with endothelin agonists compared to placebo or standard therapy Mean difference 50.1 (95% CI, 35.0 to 65.3)	SOE=Moderate (3 studies, 606 patients) Reduced risk of hospitalization OR 0.34 (95% CI, 0.17 to 0.69)
Phosphodiesterase type 5 inhibitors vs. placebo or standard therapy	SOE=Insufficient (2 studies, 512 patients)	SOE=High (3 studies, 741 patients) Improved 6MWD with PDE5 therapy compared with placebo or standard therapy Mean difference 37.0 (95% CI, 22.9 to 51.1)	SOE=Moderate (2 studies, 341 patients) Reduced risk of hospitalization OR 0.48 (95% CI, 0.25 to 0.91)
Prostanoids vs. placebo	SOE=Insufficient (6 studies, 971 patients) No clear differences in morality (few studies, few deaths lead to wide confidence intervals) OR (95% CI): Iloprost: 0.70 (0.88 to 6.22) Epoprostenol: 0.25 (0.02 to 3.75) Treprostinil: 0.79 (0.32 to 1.96)	SOE=Low (1 study, 203 patients) Improved 6MWD with prostanoid therapy compared with placebo Mean difference 23.6 (95% CI, 0.3 to 46.9)	SOE=Insufficient (1 study, 235 patients) No clear difference in risk of hospitalization OR 0.43 (95% CI, 0.06 to 3.02)

[a]Gray highlights insufficient strength of evidence.
[b]Completers analysis excluded 1 patient who died on sildenafil and thus favored sildenafil; mean difference 55 m (95% CI, 2 m to 108 m).
Abbreviations: 6MWD=6-minute walk distance; CI=confidence interval; NS=not statistically significant; OR=odds ratio; SOE=strength of evidence

Discussion

Key Findings and Strength of Evidence

We found 1 study involving 372 patients that evaluated the combination of biomarker tests and echocardiography to echocardiography alone to screen for PAH (Key Question [KQ] 1). Based on one good-quality prospective cohort study, biomarker testing with NT-proBNP may be useful in ruling out PAH among those suspected of PH who also have elevated sPAP by echocardiography;[24] however, no data are available regarding combined echocardiography and biomarker screening in asymptomatic patients at high risk for PAH. In the absence of other direct comparative trials, we attempted to address this question by evaluating the efficacy of biomarker and echocardiography independently for screening and diagnosis of PAH. We reviewed 50 studies involving 6608 patients that evaluated biomarker tests, echocardiography, or both, to screen for PAH. The associations between natriuretic peptide testing and PAH diagnosis is insufficiently strong to support its use alone as a screening test in either asymptomatic or symptomatic patients suspected of PAH. Data on biomarker testing were essentially limited to a single test—NT-proBNP—which showed only moderate correlation with RHC hemodynamic measures and showed a great deal of variability between studies in its diagnostic accuracy and discrimination.

We found that echocardiography estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}) demonstrated good accuracy in screening for PAH. In low prevalence populations (<10%), negative predictive value of a normal sPAP is high, suggesting that echocardiography with a low threshold may be an appropriate test in asymptomatic high-risk populations or in patients with symptoms suggesting PAH. (This is shown in studies of liver transplant studies with complete verification).

Our findings suggest that echocardiographic estimation of sPAP is sufficiently accurate to justify its role in screening for PAH in symptomatic patients suspected of having PH. However, this conclusion has several important caveats. First, echocardiography in a small, but significant, number of patients may not produce an estimate of sPAP because of poor-quality Doppler visualization of the tricuspid regurgitant jet. Second, echocardiographic estimates of sPAP often over- or under-estimate pulmonary artery pressure enough to result in misclassification according to PAH diagnostic threshold—hence the selection of a test threshold is critical for the aim of screening. A single test threshold is insufficient to perform with simultaneously high sensitivity and specificity (or PPV and NPV), especially in populations with higher risk or higher prevalence (more symptomatic), where echocardiography cannot be relied upon to exclude pulmonary hypertension if pretest probability is high. In asymptomatic patients at high risk for PH, echocardiography seems to perform with similar sensitivity and specificity; however, these studies suffer from verification bias, which likely inflates both the sensitivity and specificity estimates. Two prospective studies that show approximately 10 percent of asymptomatic patients with systemic sclerosis and normal sPAP develop PH when serially retested with echocardiography are consistent with either misclassification at baseline echocardiographic screening or prospective development of PH. This would suggest that if echocardiographic

screening of asymptomatic patients with a high-risk diagnosis were to be undertaken, then serial testing would be necessary.

We reviewed 80 studies involving 7224 patients that evaluated biomarker tests or echocardiography to diagnose and follow progression of disease as well as response to therapy for PAH (KQ 2). Our review found that BNP showed only moderate correlation with most RHC measures (mPAP, PVR, cardiac index, RAP) and clinical measures of disease severity (6MWD) and showed weak correlation with PCWP. Most effect estimates were precise (mPAP, PVR, cardiac index, RAP, 6MWD), but estimates for PCWP were imprecise, making it difficult to interpret the clinical importance of the findings for this measure. For the other measures, correlation with BNP was only moderate, indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Alternatively, echocardiography-derived sPAP showed strong correlation with RHC-sPAP with a precise effect estimate and may be useful as an alternative to RHC to assess disease severity although there was a great deal of heterogeneity among these studies.

Overall, pericardial effusion was the strongest predictor of mortality and may be useful clinically, though results were not highly precise. BNP, RA size, and FAC showed no significant ability to predict mortality.

Our findings do not support any recommendations for replacing existing measurement tools to assess disease severity, prognosis, or response to therapy. Echocardiography-derived sPAP shows promise as a possible surrogate marker for RHC-sPAP, but whether or not this measure alone is adequate to assess disease severity, prognosis, or response to therapy is unclear.

We reviewed 33 studies involving 3981 patients that assess the effectiveness of drug treatment for PAH in adults. Our review found inconclusive evidence regarding mortality reduction for any of six different drug treatment comparisons: (1) bosentan versus placebo (OR 0.72; 95% CI, 0.14 to 3.68), (2) epoprostenol versus placebo (OR 0.25; 95% CI, 0.02 to 3.76), (3) iloprost versus placebo (OR 0.70; 95% CI, 0.08 to 6.22), (4) ambrisentan versus placebo (OR 0.33; 95% CI, 0.06 to 1.74), (5) treprostinil versus placebo (OR 0.79; 95% CI, 0.32 to 1.96), and (6) combination therapy versus monotherapy (OR 0.37; 95% CI, 0.04 to 3.32). Few deaths were observed in these limited duration studies, leading to wide confidence intervals and lack of statistical power to detect a difference; however, a consistent direction of effect and demonstrated improvements in other outcomes, including functional and hemodynamic measures, support that a mortality reduction might exist.

Increases in 6MWD were observed in trials of all drug classes when compared with placebo; patients receiving endothelin receptor antagonists demonstrated the largest increase (+50.1 meters); however, comparisons between agents are inconclusive. Combination therapy also showed improved 6MWD compared with single therapy; but the diversity of treatment regimens and the small number of combination therapy trials again make comparisons between specific regimens inconclusive.

In patients taking the endothelin receptor antagonists and phosphodiesterase-5 inhibitors, the odds ratio of hospitalization was lower compared with placebo (OR 0.34 and 0.48, respectively), while there was no significant reduction in odds ratio in the prostanoids versus placebo. Combination therapy also reduced hospitalizations compared with single therapy.

The results of hemodynamic outcomes cardiac index, mPAP, and PVR were inconsistent.

In studies reporting adverse effects, we found that phosphodiesterase-5 inhibitors were more likely to cause headache than endothelin receptor antagonists, which were still more likely to cause headache than placebo. Drugs did not significantly differ in their odds of causing dizziness

or diarrhea. Prostanoids were much more likely to cause jaw pain and cough compared with placebo. Adverse event data suggested that phosphodiesterase-5 inhibitors and prostanoids caused more flushing than endothelin receptor antagonists. Phosphodiesterase-5 inhibitors caused more peripheral edema than did the prostanoids or the endothelin receptor antagonists. Our findings are generally consistent with the ESC/ERS guideline recommendation for monotherapy as initial treatment, with combination treatment reserved for patients who have an inadequate clinical response to monotherapy.

Applicability

The principle limitations to applicability of data on the diagnosis of PAH all relate to the patient populations studied. First, the studies may not be applicable to the screening of asymptomatic patients. None of the study populations consisted entirely of asymptomatic patients and, although many studies included some patients without symptoms, they were not reported separately in terms of outcomes. Some studies of populations in whom PAH was suspected failed to adequately describe the basis for a clinical suspicion of PAH, whether symptoms of dyspnea, clinical signs, or other test results, such as diffusion capacity of the lung for carbon monoxide (DLCO), thus also limiting the applicability of these studies for screening symptomatic patients. Second, the spectrum of disease among study populations was often skewed, particularly in case-control studies, by selection criteria that selected from patients with known PAH (cases) and patients known not to have PAH (controls). Such studies usually excluded participants with other conditions that might be confused with PAH such as PH due to left-sided heart failure, thrombotic disease, or chronic obstructive pulmonary disease. Third, participants in many studies had a wide range of disease severity, particularly those cases in case-control design studies, which is a poor match for the question at hand. Other applicability issues identified in the KQ 1 studies were less frequent and judged to be less severe.

Our findings in KQ 2 assessing the prognostic or predictive value of biomarkers and echocardiography may not be applicable to all PAH populations. The greatest concern is that studies in KQ 2 included participants at widely differing points in the natural history of disease and who had widely differing degrees of disease severity. There was also concern that the population was not adequately described to assess applicability, included patients with conditions other than PAH, or in general did not match the review question. Applicability may also be limited by the use of surrogate markers that may not be clinically relevant and insufficient followup time. In a few studies, it was also felt that the intervention arm or cointerventions did not adequately reflect current clinical practice or that the study setting was widely divergent from the current typical U.S. setting. Finally, there is concern that some studies did not provide adequate information about adverse events.

Applicability considerations were somewhat different for KQ 3 than for the Key Questions about screening and management of PAH. Most of the studies included in this review for KQ 3 were RCTs with generally good internal validity. Patient populations, however, differed between studies; variation in eligibility criteria resulted in differences between study populations in severity of illness, underlying etiology of PAH, comorbid conditions, and prior and concurrent treatment. Many different countries were represented, thereby introducing potential differences in clinical practice and care delivery settings relative to current practice in typical settings the U.S. There was also concern that the population was not always adequately described to assess applicability, with few studies exploring potential differences in response to treatment among different patient subgroups.

Research Gaps

The available evidence leaves numerous gaps and areas for potential future research. We used the framework recommended by Robinson et al.[25] to identify gaps in evidence and describe why these gaps exist. Results are as follows:

KQ 1—Screening for PAH

- Patients at elevated risk for PAH, other than systemic sclerosis, have been seldom studied in screening test studies.
  - Consider cohort studies of testing for PH among high risk populations other than systemic sclerosis.
- Relatively few data exist on screening of asymptomatic patients with a combination of echocardiography and biomarker testing.
  - Consider cohort studies that apply echocardiography and biomarker screening in a coordinated or algorithmic way, and studies that verify diagnosis in at least a sample of test-negative patients by RHC or lengthy followup.
  - Future tests of the added value of biomarkers should use well-validated echocardiography parameters as a screening test, including estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}).
- Studies of echocardiography for diagnosis of PH have focused on the association of single measures or parameters at a time rather than an integrated diagnostic assessment based on an entire exam and multiple echocardiographic measures or parameters.
  - Consider studies that evaluate a global echocardiographic assessment based on not only sPAP but also on right heart chamber size wall thickness and function, estimated PVR, and left heart measures.

KQ 2—Management of PAH

- Echocardiographic- and BNP-guided treatment strategies have not been explicitly tested.
  - Consider cohort studies evaluating prognosis as well as treatment trials examining association of baseline echocardiographic parameters and BNP levels to response to treatment.
- Other imaging modalities, such as MRI, have been little studied as an alternative noninvasive test to assess RV function
- Cardiopulmonary exercise testing and exercise echocardiography have relatively few data, uncertain clinical utility, and relationship to PH diagnostic criteria.
  - Consider validation studies to demonstrate prognostic value particularly for patients with normal resting echocardiography but abnormal exercise echocardiography.

KQ 3—Pharmacotherapy for PAH

- Relatively few data exist on the efficacy of treating PAH early in the disease course (WHO functional class I-II).
  - Improved data on efficacy of early PAH would strengthen linkage to efficacy of screening testing.

    - Consider treatment trials in early stage PAH, particularly among patients identified by case finding or screening interventions.

- Relatively few data exist on children with persistent pulmonary hypertension or congenital heart disease.
    - Consider controlled trials in children.

- Few treatment trials address direct comparison of alternative drug treatment particularly for PAH patients early in disease course.
    - Consider trials designed to compare clinical alternative treatments to permit more evidence-based treatment selection such as head-to-head treatment comparisons rather than placebo-control or combination versus monotherapy trials.

- The majority of RCTs thus far have not collected adequate surrogate data and have failed to demonstrate therapeutic gain in terms of definitive endpoints.
    - Consider including biomarker and imaging techniques with conventional clinical outcomes to improve data on validity and responsiveness of surrogate outcomes.

- There are inadequate data on the minimum clinically important change in 6MWD. It is uncertain whether incremental change, absolute distance, or a certain threshold is the most appropriate outcome measure related to 6MWD.
    - Consider studies that can validate change in 6MWD against other measures of prognosis, functional status, and quality of life.

- Few data are available about differences in response to treatment based on patient characteristics from trials.
    - Consider subgroup analysis of treatment efficacy by WHO functional class, underlying etiology, and other patient-level factors.

- Data on the efficacy of combination treatments are limited.
    - Consider more combination treatment trials, in particular trials with clear criteria for starting combination therapy and trials in patients who have not failed monotherapy.

- The duration of controlled trial efficacy data is limited.
    - Consider, particularly for clinically relevant comparisons (e.g., head-to-head treatment or combo versus monotherapy trials), longer term followup studies that retain randomized group comparisons while assessing long-term efficacy.

Conclusions

Echocardiography and the biomarker NT-proBNP in combination may be sufficiently accurate to rule out PAH when screening symptomatic patients, but more research is needed regarding the effectiveness for screening asymptomatic populations. With the exception of the presence of pericardial effusion, echocardiography and biomarkers had only low to moderate prognostic value in patients with PAH. Although no treatments demonstrate a consistent mortality reduction, many are associated with improved 6MWD and reduced hospitalization rates. Comparisons of different drug combinations are inconclusive regarding a mortality reduction but suggest an improvement in 6MWD compared with monotherapy.

Glossary

6MWD	6-minute walk distance
AHRQ	Agency for Healthcare Research and Quality
BID	two times per day
BNP	B-type natriuretic peptide
CI	confidence interval
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	collagen vascular disease
FAC	fractional area change
FC	functional class
HR	hazard ratio
HRQOL	health-related quality of life
IQR	interquartile range
KQ	Key Question
MI	myocardial infarction
mo	month/months
mPAP	mean pulmonary artery pressure
MPI	myocardial performance index
NA	not applicable
NR	not reported
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	odds ratio
PAH	pulmonary arterial hypertension
PADP	pulmonary artery diastolic pressure
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
PPH	primary pulmonary hypertension
PVR	pulmonary vascular resistance
QOL	quality of life
RA	right atrium
RAP	right atrial pressure
RHC	right heart catheterization
RIMP	right index of myocardial performance
RR	risk ratio
RV	right ventricle
RVEF	right ventricle ejection fraction
SD	standard deviation
SEM	standard error of the mean
SOE	strength of evidence
sPAP	systolic pulmonary artery pressure
SSc	systemic sclerosis
TAPSE	tricuspid annular plane systolic excursion

TEP	Technical Expert Panel
TRV	tricuspid regurgitant jet velocity
VSD	ventricular septal defect
VTI_{RVOT}	velocity-time integral of right ventricular outflow tract
yr	year/years

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Introduction

Background

Epidemiology and Etiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH), is a rare and progressive disease whose prevalence is estimated to be between 15 and 50 cases per million adults.[1] While the pathophysiology is not well understood, both genetic and environmental factors have been found to contribute to changes in the pulmonary vasculature, causing increased pulmonary vascular resistance. This increased resistance, if unrelieved, progresses to right ventricular pressure overload, dysfunction, and ultimately right heart failure and premature death.[2] The causes of PAH are numerous and are listed in Table 1, taken from the Third World Symposium on PAH (2003).[1] Before the availability of disease-specific therapy in the mid-1980s, the median life expectancy at the time of diagnosis was 2.8 years.[1,3]

Table 1. Clinical classification of pulmonary hypertension[a]

Clinical classification system	
1.	**Pulmonary arterial hypertension**
1.1.	Idiopathic
1.2.	Familial
1.3.	Associated with:
1.3.1.	Collagen vascular disease
1.3.2.	Congenital systemic-to-pulmonary shunts
1.3.3.	Portal hypertension
1.3.4.	Human immunodeficiency virus infection
1.3.5.	Drugs and toxins
1.3.6.	Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
1.4.	Associated with substantial venous or capillary involvement
1.4.1.	Pulmonary veno-occlusive disease
1.4.2.	Pulmonary capillary hemangiomatosis
1.5.	Persistent pulmonary hypertension of the newborn
2.	**Pulmonary hypertension with left-sided heart disease**
2.1.	Left-sided atrial or ventricular heart disease
2.2.	Left-sided valvular heart disease
3.	**Pulmonary hypertension associated with lung diseases and/or hypoxemia**
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Sleep-disordered breathing
3.4.	Alveolar hypoventilation disorders
3.5.	Long-term exposure to high altitude
3.6.	Developmental abnormalities
4.	**Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
4.1.	Thromboembolic obstruction of proximal pulmonary arteries
4.2.	Thromboembolic obstruction of distal pulmonary arteries
4.3.	Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5.	**Miscellaneous**: Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

[a]Adapted from Simonneau et al.[4]

Screening and Diagnosis

There are two separate populations where screening for PAH needs to be considered. First, there are patients with symptoms that raise the suspicion of PAH. The symptoms of PAH can be insidious and nonspecific and may include shortness of breath, fatigue, weakness, chest pain, loss of consciousness, and abdominal distention. Symptoms that are present at rest suggest advanced disease.[1] Since these symptoms are nonspecific, screening may be necessary to help decide whether the patient should undergo a diagnostic workup for PAH, or whether other conditions should be considered. The other population is patients with medical conditions that put them at risk for PAH. In these patients screening tests may be used to identify patients with asymptomatic elevation of pulmonary artery pressures, who might be or more closely monitored for the development of symptoms or progressive disease or offered a diagnostic workup for PAH, and possibly treatment for early disease.

Once screening indicates the possibility of PAH, diagnostic tests are necessary to confirm the presence of elevated right-sided heart pressures and to exclude valvular, primary myocardial, chronic lung disease, thromboembolic, and miscellaneous other causes of pulmonary hypertension (PH). The gold standard for diagnosing PAH is right heart catheterization (RHC), which is generally considered to be a safe procedure. In a retrospective and prospective study by Hoeper et al.,[5] the rate of serious complications in patients undergoing RHCs for evaluation of pulmonary hypertension was 1.1 percent and included bleeding, vasovagal reactions, systemic hypotension, arterial injury, hypertensive crisis, pneumothorax, and cardiac arrhythmias. The procedure-related mortality was 0.055 percent.[5]

RHC not only confirms the diagnosis of PAH but also provides prognostic hemodynamic information (mean right atrial pressure, pulmonary vascular resistance)[6] to direct treatment decisions. A small subset of patients with PAH, when challenged with a short-acting pulmonary vasodilator, will experience a drop in mean pulmonary artery pressure of at least 10 mmHg (20%) to below 40 mmHg while maintaining cardiac output; this predicts a favorable long-term response to calcium-channel blockers.[1]

Since PAH is a progressive disease, regular reassessment is needed to monitor response to treatment and adjust prognosis. RHC has traditionally been the means by which patients' clinical course is monitored; however, transthoracic echocardiography has emerged as a possible alternative. The number of echocardiographic modalities has increased substantially, providing unique insight into the structure and function of the right heart in patients with pulmonary hypertension.[7] However, this test has not been definitively validated as a substitute for RHC in patients with PAH. Finally, the role of biomarkers has not been fully established in the management and prognosis of PAH. Defining whether biomarkers alone or biomarkers plus echocardiography might be superior to echocardiography alone for informing treatment decisions is a necessary first step in establishing a noninvasive, multifaceted approach to the management of PAH.

Role of Echocardiography

The role of echocardiography in the diagnosis and management of patients with PAH has evolved over time, and has been proposed for screening, assessing prognosis, and evaluating response to treatment. Screening high-risk individuals for PAH generally begins with an transthoracic echocardiogram.[8] Echocardiography can estimate the right ventricular systolic pressure and identify other signs of PH including increased right-sided chamber size and wall thickness. Most often, the peak velocity of the tricuspid regurgitant (TR) jet is measured by

Doppler and—along with an estimate of right atrial pressure based on inspiratory collapse and size of the inferior vena cava—TR jet is used to estimate the systolic pulmonary artery pressure (sPAP). However, a significant proportion of patients have no measureable TR jet. Estimates are often inaccurate compared with RHC; up to 60 percent of echocardiography estimates were more than 10 mmHg off from RHC measurement in one large multicenter registry of PAH patients.[9] Therefore, although transthoracic echocardiography is the standard screening test for PAH, it is less than completely accurate and there is uncertainty as to which echocardiographic measurements are most useful.

Several studies have investigated the use of echocardiography in establishing prognosis in PAH. In a study of patients with systemic sclerosis (n=155), calculation of the right ventricular systolic pressure (RVSP) using Doppler echocardiography identified 47 patients (36.4%) with RVSP ≥36 mmHg who had decreased 3-year survival rates compared with patients with RVSP <6 mmHg (67% versus 86%, $p < 0.01$).[10] Another study of patients with PAH (n=80) using echocardiography to calculate right ventricular free wall strain found that patients with strain worse than -12.5 percent were associated with increased 6-month disease progression and increased mortality at 1 year (unadjusted hazard ratio 6.2).[11] There remains uncertainty regarding which echocardiographic measure(s) have prognostic value although TAPSE and pericardial effusion have been proposed.[12]

Traditionally, RHC assessment of hemodynamics is recommended to demonstrate treatment response;[12] echocardiography has been seldom studied in this role.

Role of Biomarkers

Because of the limitations of echocardiography, the potential role of biomarkers in screening for and managing of PAH has been the subject of increasing interest over the last decade. Brain natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP) are two biological substances found in the blood that have been studied as a screening test in patients at risk for PAH and which have been shown to correlate well with the presence of disease.[13,14] Other biomarkers currently under investigation include atrial natriuretic peptide, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin. Several of these biomarkers have been shown to correlate with prognosis and mortality, either alone or in conjunction with other traditional measurements such as the 6-minute walk distance (6MWD) test, functional class assessment, and pulmonary hemodynamics.[15] Select biomarkers may even be superior to traditional testing. Patients with idiopathic and familial PAH were shown to exhibit dysregulation over a broad range of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, when compared with healthy controls, which correlated better with prognosis than 6MWD and pulmonary hemodynamics.[16]

Treatment Strategies

Medications

The goal of medical treatment for PAH is both to improve patients' symptomatic status and to slow the rate of clinical deterioration. In addition to supportive therapy (diuretics, oxygen, digoxin, oral anticoagulants), specific drug therapy is recommended. There has been rapid development and approval of vasodilator medications for PAH over the past three decades. Currently, there are four main classes of medications used to treat PAH, as shown in the bulleted

list below.[17] Calcium-channel blockers are indicated for the minority of patients who have positive acute vasoreactivity testing and demonstrate a sustained response. Most patients are candidates for treatment with one of the other three classes of medications.

- Calcium-channel blockers:
  - Amlodipine
  - Diltiazem
  - Nifedipine
- Prostacyclin analogues:
  - Epoprostenol
  - Iloprost
  - Treprostinil
- Endothelin receptor antagonists:
  - Bosentan
  - Ambrisentan
- Phosphodiesterase type 5 inhibitors:
  - Sildenafil
  - Tadalafil

These PAH medications have been shown to improve dyspnea, 6MWD, pulmonary hemodynamics, and functional class. Limited data suggest that epoprostenol and bosentan may provide a survival benefit; however, this end point has not been studied consistently between the medications.[18] Calcium-channel blockers are associated with long-term (>1 year) improvements in hemodynamics and functional status in about half of the minority of patients who show acute vasoreactivity testing response.[19] The limited usefulness of calcium antagonists—as well as the poor prognosis and diminished quality of life associated with PAH—reinforces the need for new drug therapies and improved delivery of current medications. Limited data suggest that epoprostenol and bosentan may provide a survival benefit; however, this end point has not been studied consistently between the medications.[18] The two medications most recently approved by the U.S. Food and Drug Administration for PAH are inhaled treprostinil, a new delivery system for this prostacyclin analogue, and ambrisentan, a new endothelin receptor antagonist. These new medications were discussed in the Expert Consensus Document on Pulmonary Hypertension released in 2009 by the American College of Cardiology Foundation and the American Heart Association.[18] Since then, however, numerous studies have been published regarding the safety and efficacy of these new medications. Also, more data have been published on the older medications for PAH. These new data may clarify any effect on mortality and gauge the comparative effectiveness of these drugs.

Additionally, combination drug therapy (using multiple drugs with different mechanisms of action) is an important area of research and may be the most promising way to improve clinical outcomes although at higher cost.[2] Combination therapy was addressed in the 2009 ACCF/AHA publication, and several studies have since been published on this topic. In order to optimize PAH care, newer information regarding the latest drugs and combination therapies should be systematically reviewed.[17]

Scope and Key Questions

Scope of the Review

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). It was designed to evaluate the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the diagnosis and management of PAH in addition to clarifying whether the use of echocardiography and biomarkers affects decisionmaking and clinical outcomes. We also wanted to address which medications are effective for treating PAH and how the newer medications compare with older ones and with each other. Further, there was a need for clarity about whether combination therapy is more effective than monotherapy and what effect monotherapy or combination therapy has on intermediate-term and long-term outcomes.

Key Questions

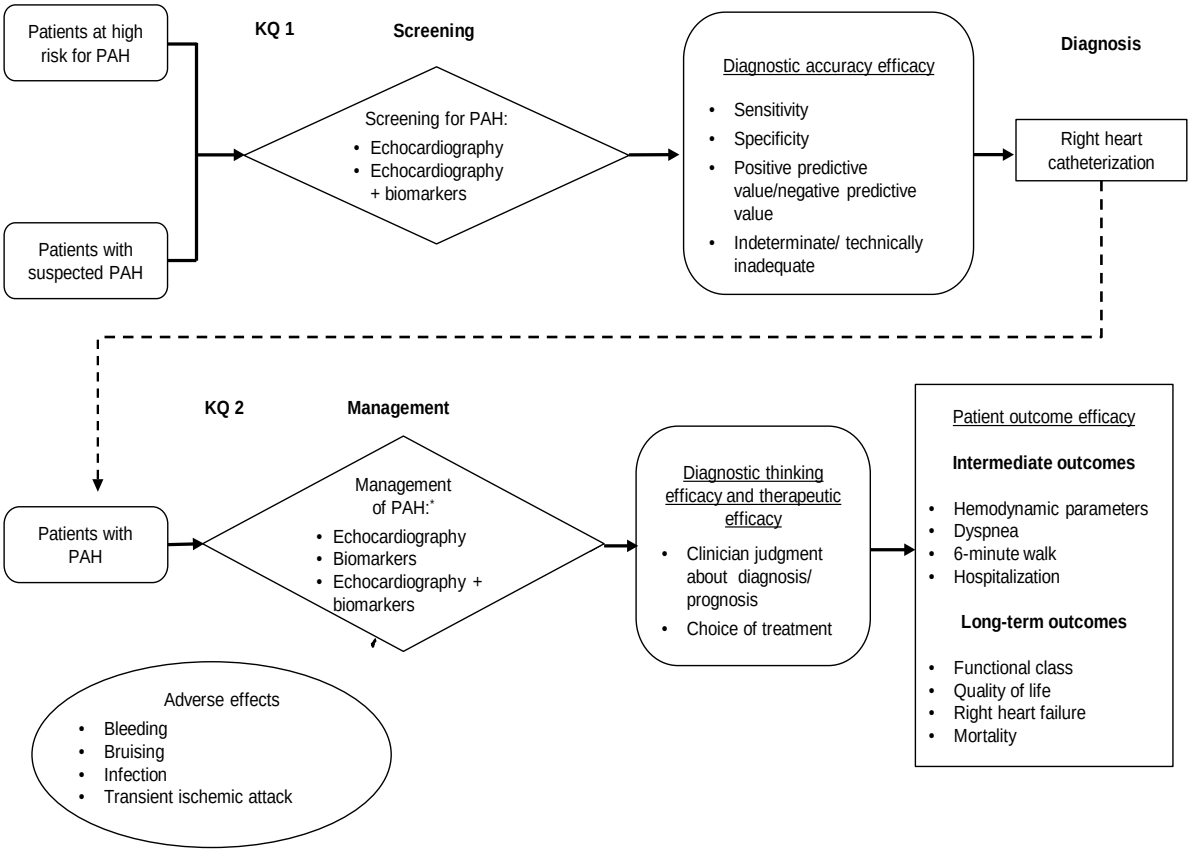
With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods section for details). The KQs considered in this comparative effectiveness review were:

- KQ 1. For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what is the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?
- KQ 2. For patients with PAH, what is the comparative effectiveness and safety of (a) echocardiography versus biomarkers and (b) echocardiography versus echocardiography plus biomarkers in managing PAH and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes?
- KQ 3. For patients with PAH, what is the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium-channel blockers, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

Analytic Framework

Figures 1 and 2 show the analytic frameworks for this comparative effectiveness review.

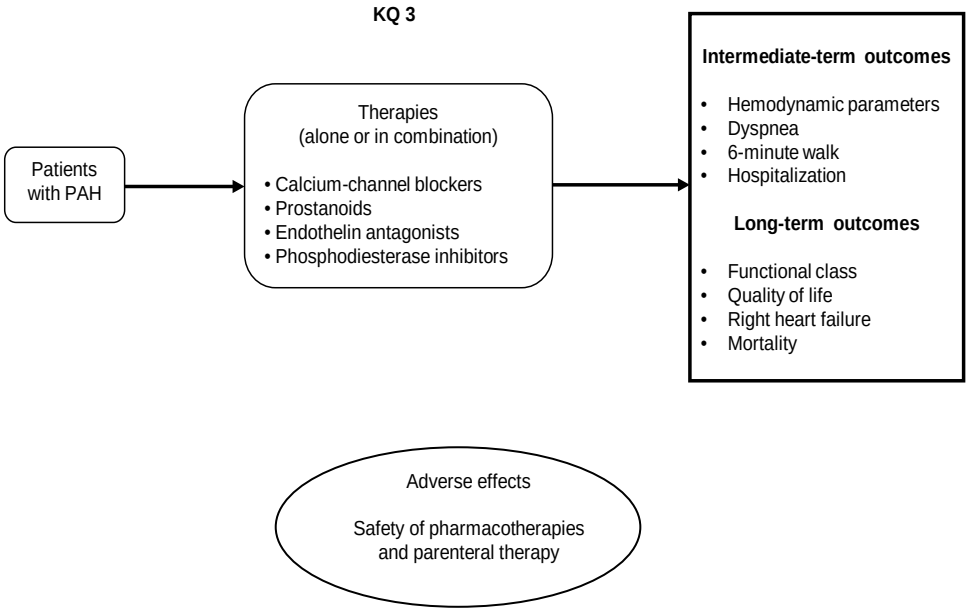
Figure 1. Analytic framework for KQs 1 and 2



*In conjunction with routine clinical assessment (functional class, dyspnea, 6-minute walk).

Abbreviations: KQ = Key Question; PAH = pulmonary arterial hypertension

Figure 2. Analytic framework for KQ 3



Abbreviations: KQ = Key Question; PAH = pulmonary arterial hypertension

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the *Methods Guide*).[20] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[21] All methods and analyses were determined a priori.

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing clinicians (pulmonology, cardiology, pathology), patients, scientific experts, and Federal agencies, to help define the Key Questions. The Key Questions were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind and did not contribute to the writing of the report.

Literature Search Strategy

Sources Searched

Our search strategy used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (Appendix A). We limited the search to English-language studies conducted in adults from 1995 to the present; prior to 1995, newer drug treatments were not available, and older echocardiographic and biomarker testing technology is less applicable. Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed®). We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles was hand-searched and cross-referenced against our library, and additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets were requested from the manufacturers of medications and devices and reviewed for relevant articles from completed studies not previously identified in the literature searches.

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• KQ 1: Patients with suspected pulmonary arterial hypertension (PAH) or asymptomatic patients at high risk for PAH (e.g., patients with a collagen vascular disorder such as scleroderma) • KQs 2 and 3: Patients with PAH	KQ 1: Patients have neither (1) a condition associated with a high risk of undiagnosed PAH (e.g., a collagen vascular disorder) nor (2) signs or symptoms suspicious for PAH. KQ 2 and KQ 3: No patients have PAH
Interventions	• KQ 1 (screening): Echocardiography plus biomarkers including natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide), endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin • KQ 2 (management): o Biomarkers plus clinical assessment (e.g., history, physical exam, functional status) o Echocardiography plus biomarkers plus clinical assessment ▪ KQ 3 (pharmacotherapies): o Calcium-channel blockers (amlodipine, diltiazem, nifedipine, verapamil) o Prostanoids (epoprostenol, treprostinil, iloprost) o Endothelin antagonists (bosentan, ambrisentan) o Phosphodiesterase inhibitors (sildenafil, tadalafil)	Study does not include a comparison of echocardiography or biomarkers for screening, diagnosis, or management of PAH, or does not include a comparison of monotherapy with combination therapy for PAH

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	• KQ 1: Echocardiography vs. echocardiography plus biomarkers • KQ 2: o Echocardiography vs. biomarkers (direct comparison) o Echocardiography vs. echocardiography plus biomarkers (direct comparison) o Echocardiography vs. clinical assessment (indirect comparison) o Biomarkers vs. clinical assessment (indirect comparison) • KQ 3: o One pharmacotherapy versus another pharmacotherapy o Monotherapy versus combination therapy	Study does not include a comparison of echocardiography or biomarkers for screening, diagnosis, or management of PAH, or does not include a comparison of monotherapy with combination therapy for PAH
Outcomes	• KQ 1: Test-associated outcomes: Diagnostic accuracy efficacy (sensitivity, specificity, positive predictive value/negative predictive value); verification by right heart catheterization for test positive patients was required (incomplete verification of test negative patients was allowed) • KQ 2: Efficacy outcomes: o Diagnostic thinking efficacy and therapeutic efficacy (clinician judgment about diagnosis/prognosis, choice of treatment) o Patient outcome efficacy for intermediate-term outcomes (hemodynamic parameters, dyspnea, and 6-minute walk) and long-term outcomes (functional class, quality of life, right heart failure, and mortality) • KQ 3: Effectiveness of pharmacotherapies: o Intermediate-term outcomes such as hemodynamic parameters, dyspnea, and 6-minute walk o Long-term outcomes such as functional class, quality of life, right heart failure or right ventricular dysfunction, and mortality	No primary or secondary outcomes of interest are reported

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes (safety)	• KQs 1 and 2: Adverse effects of echocardiography and biomarkers, such as bleeding, bruising, infection, and transient ischemic attack • KQ 3: Adverse effects of pharmacotherapies (liver function abnormalities, headache, flushing, cough, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion, dizziness, syncope, hypoxia, increased international normalized ratio or prothrombin time) and parenteral therapy (line infection, site pain, abrupt catheter occlusion)	None
Timing	Intermediate-term (≤120 days) and long-term (>120 days)	None
Setting	• Inpatient and outpatient • Specialty (pulmonary, cardiology, rheumatology) and primary care	None
Study design	• Randomized controlled trial, prospective or retrospective observational study, or registry • Original data (or related methodology paper of an included article) for any of the screening or diagnostic tests listed in the KQs, or original data with intermediate-term or long-term outcomes associated with monotherapy or combination therapy for PAH • Relevant systematic review or meta-analysis (used for background only) • All sample sizes	Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series)
Publications	• English-language only • Peer-reviewed article • Published January 1, 1995, to present	Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles will be excluded[b]

Abbreviations: KQ=Key Question; PAH=pulmonary arterial hypertension

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the Key Questions. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, paired researchers independently reviewed the articles and indicated a decision to include or exclude the article for data abstraction. When the paired reviewers arrived at different decisions, we reconciled the difference through review and discussion or through a third-party arbitrator, if needed. Articles meeting eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in the DistillerSR database (Evidence Partners, Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached between the first two investigators. To aid in both reproducibility and standardization of data collection, investigators received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada). Data reported only in graphs were estimated quantitatively using Engauge Digitizer version 4.1 software (www.digitizer.sourceforge.net).

We designed the data abstraction forms for this project to collect data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes were framed to help identify adverse events, including bleeding, bruising, infection, liver function abnormalities, headache, flushing, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion, dizziness, syncope, increased international normalized ratio or prothrombin time.

Data necessary for assessing quality and applicability, as described in the *Methods Guide*,[20] were also abstracted. Before they were used, abstraction form templates were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Appendix B lists the elements used in the data abstraction forms. Appendix C contains a bibliography of all articles/studies included in this review, organized alphabetically by author.

Quality (Risk of Bias) Assessment of Individual Studies

We evaluated the quality of individual studies by using the approach described in the *Methods Guide*.[20] For studies of diagnostic tests (KQ 1 and KQ 2), we used QUADAS-2,[22] a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing; each domain is rated as high, low, or unclear risk of bias.

Two raters independently evaluated each study and differences were resolved by consensus; if consensus could not be reached, then the item was rated as unclear, and the rationale for each differing assessment was described. Results were described for individual domains. If the distribution of ratings permits, methodological domains were examined for association with effects in meta-analysis.

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting (Table 3).

Table 3. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Included meta-analyses were appraised according to criteria adapted from the PRISMA Statement.[21] Grading was outcome-specific; thus, a given study may have been graded of different quality for two individual outcomes reported within that study. Study design also was considered when grading quality. RCTs were graded as good, fair, or poor. Observational studies were graded separately, also as good, fair, or poor. Appendix D summarizes our assessment of the quality and applicability for each included study.

Data Synthesis

Quantitative synthesis (i.e., meta-analysis) was done when we found multiple studies of similar design, population, intervention, comparator and outcome that reported sufficient data for analysis. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence. We use meta-analyses both to quantify and to attempt to explain between-study variation as well as to calculate summary estimates. When a meta-analysis was not appropriate, we described the reasons, presented data in tabular form, and summarized studies either individually or qualitatively.

For sensitivity and specificity data, we used a binomial model to calculate summary estimates of sensitivity and specificity and associated confidence intervals and summary ROC curve using SAS. Sensitivity analyses were conducted using summary receiver operating characteristic meta-analysis using the diagnostic odds ratio with dr-ROC software (Diagnostic Research Design and Reporting; Glenside, PA). For meta-analysis of correlation coefficients and hazard ratios for observational studies, we used a random effects model implemented in SAS (SAS Institute Inc.; Cary, NC). For treatment effects meta-analysis, we used a random effects model meta-analysis implemented in Comprehensive Meta-Analysis Software (Version 2.2.064, Biostat; Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited, particularly when the number of studies is small. We present summary estimates and confidence intervals in our data synthesis.

Strength of the Body of Evidence

The strength of evidence for each Key Question was assessed using the approach described in the *Methods Guide*.[23] The evidence was evaluated using the four required domains: risk of bias, consistency, directness, and precision (Table 4).

Table 4. Strength of evidence required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates

Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned. This four-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Diagnostic evaluation studies (KQs 1 and 2) are generally indirect, as the link between the test intervention and outcome is mitigated by prognosis, management, and the effectiveness of treatments. As a rule of thumb, we considered correlation coefficients greater than 0.7 as strong evidence of association, 0.40 to 0.69 as moderate evidence, and less than 0.40 as weak evidence. In our summary strength of evidence assessments for KQs 1 and 2, lack of directness was weighed less heavily and risk of bias most heavily. Thus, we allowed high strength of evidence levels despite the lack of directness among these studies.

Applicability

We assessed applicability across our KQs using the PICOTS format as described in the *Methods Guide*.[20,24] We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (such as age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively. Because applicability issues may differ for different users, we reported across a range of potential applicability issues (Appendix D).

In diagnostic evaluation studies, we were particularly concerned with the prevalence of PAH versus PH in the study populations compared, the spectrum of underlying type of PAH, and the assessment of adverse events associated with testing. In PAH drug trials, we were particularly concerned with assessing the severity of illness; use of run-in periods and attrition before randomization; use of surrogate or combined outcome measures; short study duration; reporting of adverse events, in particular including those related to administration or monitoring of treatment; sample size sufficient to assess minimally important differences from a patient perspective; and use of intention-to-treat-analysis.

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in cardiology, radiology, vascular surgery, general medicine, and nursing along with individuals representing stakeholder and user communities, have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final report.

Results

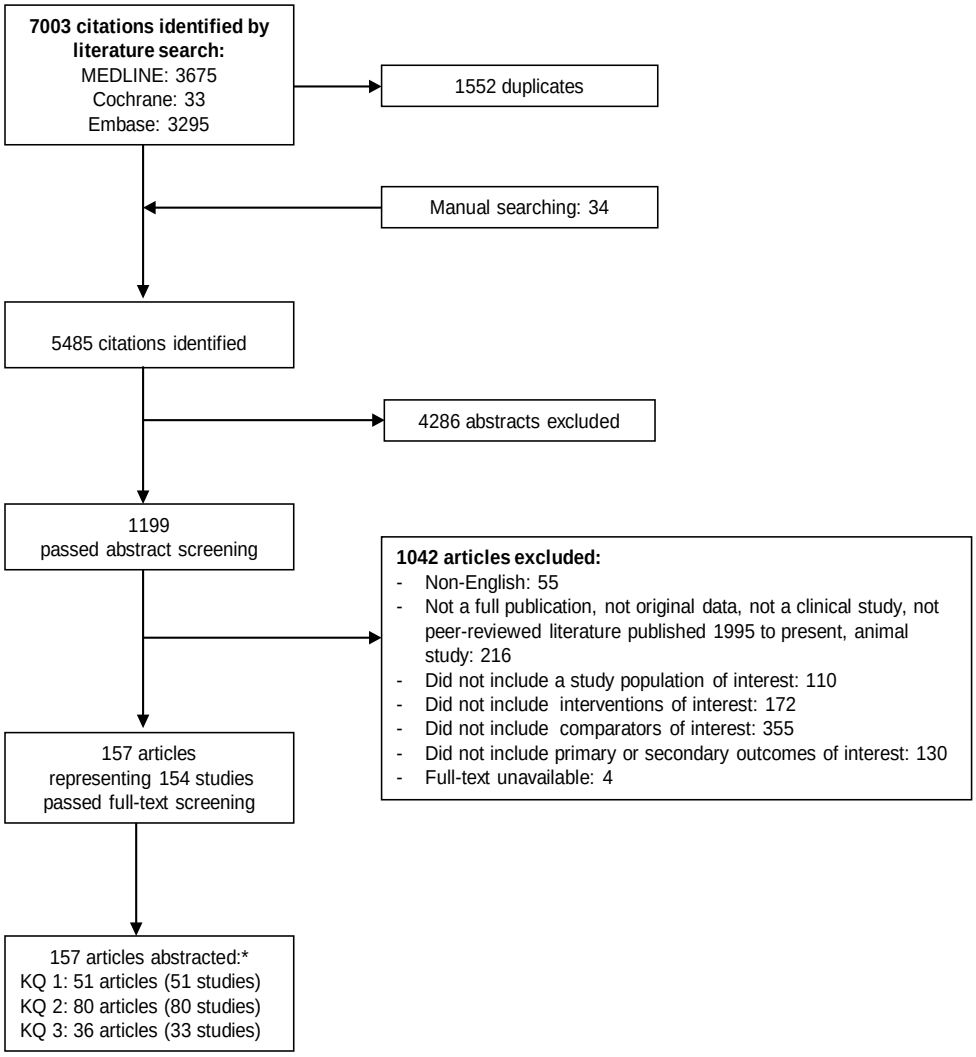
Introduction

In what follows, we begin by presenting the results of our literature searches. The remainder of the chapter is organized by Key Question (KQ). Under each KQ, we begin by listing the key points of the findings, followed by a brief description of included studies and a study characteristics table, followed by a more detailed synthesis of the evidence. We conducted quantitative analyses (i.e., meta-analyses) where possible, as described in the Methods chapter. Results of these analyses are presented graphically in the form of forest plots and in tabular format. A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 3 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, the Cochrane Database of Systematic Reviews, and Embase® yielded 7003 citations, 1552 of which were duplicate citations. Manual searching identified 34 additional citations, for a total of 5485 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1199 full-text articles were retrieved and screened. Of these, 1042 were excluded at the full-text screening stage, leaving 157 articles (representing 154 unique studies) for data abstraction. Appendix C provides a detailed listing of included articles. Appendix E provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 3. Literature flow diagram



Abbreviation: KQ=Key Question
*Article counts by KQ do not add to 157 because some studies were included for multiple KQs.

Key Question 1. Screening for PAH

KQ 1: For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what is the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?

Key Points

- For patients suspected of having PAH with elevated systolic pulmonary artery pressure (sPAP) by echo, additional testing with the biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) may identify patients who do not have PAH compared with echo sPAP alone (based on one good-quality prospective cohort study) (low SOE).
- For patients suspected of PAH, echocardiographic estimation of right ventricular systolic pressure (RVSP) (or tricuspid gradient [TG]) by tricuspid regurgitation jet velocity (TRV), sPAP by TRV and right atrial pressure (RAP), and pulmonary vascular resistance (PVR) by TRV/velocity-time integral right ventricular outflow tract (VTI_{RVOT}) show reasonably good accuracy compared with right heart catheterization (RHC) (moderate SOE).
- For both asymptomatic patients at high risk for PAH or symptomatic patients suspected of PAH, natriuretic peptide testing (with either BNP or NT-proBNP) shows highly variable sensitivity and specificity estimates (not simultaneously high) for pulmonary hypertension (PH) or PAH diagnosis (low SOE) and moderate correlation with hemodynamic measures by RHC (moderate SOE).
- There were no studies of the safety of biomarker and echocardiography testing, nor were there any studies of combined echocardiographic and biomarker screening of asymptomatic patients at high risk for PAH (insufficient SOE).

Description of Included Studies

We identified one good-quality study[25] involving 372 patients that compared echocardiography with echocardiography plus biomarkers in patients with suspected PAH, most of whom were symptomatic. There were no other studies directly comparing combinations of echocardiographic and biomarker testing. In order to draw inferences about the comparative effectiveness of other tests, we reviewed the diagnostic accuracy of independent echocardiographic or biomarker testing compared with RHC. By evaluating the relative diagnostic performance of these tests versus a reference standard of RHC or a criterion standard diagnosis, one can impute the comparative effectiveness via indirect comparisons.

We identified 50 unique studies involving a total of 6608 patients that described the effectiveness of echocardiography or biomarkers in patients with suspected PAH, or in asymptomatic patients at high risk for PAH, as screening modalities before right heart catheterization to establish the diagnosis of PAH.[9,14,26-73] Of these studies, 17 (33%) were rated good quality, 27 (53%) fair quality, and 8 (16%) poor quality. Echocardiographic parameters

evaluated were right ventricular (RV) size, right atrium (RA) size, fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), right ventricular index of myocardial performance (RIMP), myocardial performance index (MPI), Tei index, systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressure (mPAP), tricuspid regurgitation jet velocity (TRV), velocity-time integral right ventricular outflow tract (VTI_{RVOT}), right ventricular ejection fraction (RVEF), right ventricular systolic pressure (RVSP), and pericardial effusion. Biomarkers evaluated were natriuretic peptides, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, and D-dimer.

Study Characteristics

Table F-1 in Appendix F summarizes the patient population, study size, test measures, study objectives, and quality rating for each study relevant to KQ 1. Of these studies, 19 were conducted in Europe (including the United Kingdom),[14,25-29,31,34,35,38-40,45,54,55,57,58,60,66,68,70,71,73] 14 in the United States,[9,32,36,42,44,50-53,56,59,61,65,67] 9 in Asia,[37,46-48,62-64,69,72] 4 in Australia/New Zealand,[30,41,43,49] and 1 in South America.[33] The vast majority of studies included only adults; exceptions were three studies that included only children[44,63,64] and two studies that included both children and adults.[65,69] In studies that reported the sex of participants, a total of 3606 participants were female and 976 were male. Of the included studies, 8 compared biomarker levels, 20 evaluated the diagnostic accuracy of echocardiographic parameters, and 1 assessed the accuracy of echocardiography plus biomarkers as a screening modality in patients with suspected PAH or asymptomatic patients at high risk for developing PAH. BNP and NT-proBNP were the most commonly evaluated biomarkers. The most commonly reported echocardiographic parameters compared with RHC were FAC, mPAP, RIMP, TRV/VTI_{RVOT}, sPAP, TRV, and TAPSE.

Detailed Synthesis

Echocardiography Plus Biomarkers for Screening PAH

We identified only one study (good quality) that gave data on the use of echocardiography and biomarkers in screening patients suspected of having PAH.[25] This study used retrospective data on patients referred for evaluation of precapillary PH to develop a noninvasive diagnostic decision algorithm. This diagnostic algorithm was subsequently tested and validated in a prospective study using data from electrocardiography, serum NT-proBNP, and echocardiography. The goal was to use the aforementioned assessment to distinguish between patients in whom precapillary PH was likely versus those in whom precapillary PH could be excluded with the goal of avoiding unnecessary, invasive RHC procedures. Patients with neither RV strain on ECG (defined as ST-segment deviation and T-wave inversions in leads V1-V3) nor elevated serum NT-proBNP (>80 pg/mL) were considered to have the diagnosis of precapillary PH excluded despite elevated sPAP (≥36 mmHg) by echocardiography.

In 121 patients prospectively evaluated with this algorithm, 44 demonstrated RV strain, which alone had a sensitivity of 66 percent and specificity of 96 percent for identifying patients with precapillary PH. Among the remaining 69 patients, serum NT-proBNP level >80 pg/mL had 100 percent sensitivity and 24 percent specificity. Taken in combination with the decision algorithm, , and in patients with echocardiographic estimates of sPAP ≥36 mmHg, the presence of RV strain on ECG and serum NT-proBNP >80 pg/mL had a sensitivity of 100 percent and specificity of 19 percent for diagnosis of PAH based on RHC reference standard. By using this

decision algorithm to exclude precapillary PH, the investigators concluded that 9 percent of referred patients with elevated sPAP by echocardiography (≥36 mmHg) could avoid undergoing invasive RHC. Excluding patients with RV strain, serum NT-proBNP testing would have avoided RHC in 16 percent of patients.

Biomarkers for Screening PAH

Twelve studies (5 good quality, 4 fair, and 3 poor) evaluated serum NT-proBNP or BNP in patients both with and without PAH.[14,25-27,34,42,58,63,64,68,71,73] Most studies were of natriuretic peptide (serum NT-proBNP or BNP); we found one study each or urinary cGMP[27] and plasma endothelin-1 (ET-1).[64] Two studies evaluated biomarkers at baseline for an association with incident diagnosis of PAH,[26,34] while the remaining studies evaluated concurrent biomarker and reference data.[14,25,42,58,63,68,71,73] Three of these studies were case-control design.[58,68,73] Three studies permitted calculation of sensitivity and specificity (of a prespecified NT-proBNP diagnostic threshold) for diagnosis of PAH (Table 5).[25,58,68] The remaining studies were divided between those reporting biomarker group mean (or median) and standard deviation (or interquartile range) for groups with or without PAH (n=6) and those reporting the correlation between biomarker level and hemodynamic measures from RHC in the form of a correlation coefficient (n=3).[14,42,63]

Table 5. Diagnostic accuracy of biomarkers for PAH

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Allanore, 2008[26] SSc patients with echocardiography sPAP<40 mmHg and no NYHA III/IV symptoms N=101 Good	NT-proBNP	>97th percent-tile for age/sex	mPAP ≥25 mmHg	6	3	16	77	67 (35 to 88)	83 (74 to 89)	8.8%
Bonderman, 2011[25] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372 Good	NT-proBNP	>80pg/mL	mPAP >35 mmHg PCWP <15 mmHg	23	0	35	11	100 (88 to 100)	24 (13 to 39)	33%
Frea, 2011[34] SSc patients with no signs or symptoms of PAH N=76 Fair	NT-proBNP	>97th percent-tile for age/sex	mPAP ≥25 mmHg	1	3	6	28	25 (4.6 to 70)	82 (67 to 92)	10.5%
Simeoni, 2008[58] Known SSc-associated PAH and controls with SSc but no PAH N=20 Poor	NT-proBNP	≥125 pg/mL	mPAP	9	1	3	7	90 (55 to 100)	70 (35 to 93)	50%

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Williams, 2006[68] SSc patients with PAH and controls with SSc but without PAH N=109 Fair	NT-proBNP	>91 pg/mL	mPAP	38	30	2	39	56 (43 to 68)	95 (83 to 99)	62%

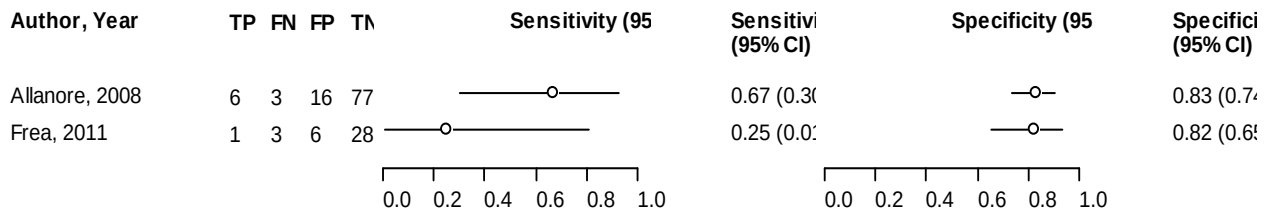
Abbreviations: FN=false negative; FP=false positive; mPAP=mean pulmonary artery pressure; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; PCWP=pulmonary capillary wedge pressure; sPAP=systolic pulmonary artery pressure; TN=true negative; TP=true positive

Predicting Incidence of PAH

Two studies of patients with systemic sclerosis reported NT-proBNP levels measured at baseline among patients subsequently diagnosed with PAH.[26,34] At baseline patients were either without any signs or symptoms suggesting PAH[34] or with no NYHA class II or IV symptoms and echocardiographic estimate of sPAP less than 40 mmHg.[26] In both studies, patients were followed over time for development of symptoms or echocardiographic evidence of elevated sPAP. In followup ranging between 12 mo[34] and 36 mo,[26] approximately 10 percent of patients developed PAH in each study (Table 6).

Mean NT-proBNP levels at baseline were significantly higher among patients subsequently diagnosed with PAH in one study,[26] but not significantly so in the other.[34] This may be related to smaller numbers of patients with PAH or use of a lower mPAP threshold for diagnosis of PAH (25mmHg rather than 35mmHg). Applying a diagnostic threshold based on the 97th percentile by sex and age group in healthy subjects, these two studies found nearly identical specificity, around 83 percent, but sensitivity estimates that are lower with wide confidence limits (Figure 4).

Figure 4. Sensitivity and specificity of NT-proBNP levels for predicting development of PAH

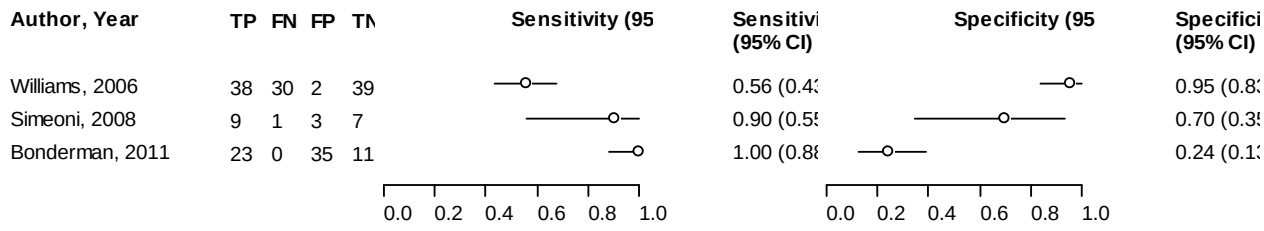


Abbreviations: CI =confidence interval; FN=false negative; FP=false positive; TN=true negative; TP=true positive

Diagnosis of Prevalent PAH

Three studies evaluated NT-proBNP for diagnosing PAH; two studies used a case-control design among patients with systemic sclerosis, comparing cases with known PAH to controls with systemic sclerosis but no PAH (Figure 5).[58,68] The third study included patients referred for evaluation of suspected PAH, but without a specific high-risk diagnosis.[25] Thresholds for NT-proBNP were fairly similar, ranging from 80 to 125 pg/mL, and set relatively low compared with the normal ranges described above. Estimates of the sensitivity and specificity are quite different among these three studies. Differences between sensitivity and specificity estimates among these studies likely stem from the inclusion criteria in the study by Bonderman et al.[25] in which all patients had elevated sPAP (>40 mmHg) by echocardiography, leading to a population with a high proportion of patients who had elevated NT-proBNP levels.

Figure 5. Sensitivity and specificity of NT-proBNP for diagnosis of PAH



Abbreviations: CI =confidence interval; FN=false negative; FP=false positive; TN=true negative; TP=true positive

Six studies reported biomarker levels by PAH diagnosis.[14,25,58,68,71,73] Four studies included patients with systemic sclerosis;[14,58,68,71] one included HIV-positive patients,[73] and one (previously described) included patients referred for suspicion of PAH without a specific high-risk diagnosis.[25] Although serum BNP and NT-proBNP levels were consistently more elevated in patients with PAH than those without PAH in these studies, this was represented by a wide range of mean values between studies (Table 6).

Table 6. Biomarker levels by diagnostic group

Study Population (N) Quality	Biomarker	Reference Diagnostic Criterion for PAH	Patients With PAH		Patients Without PAH		Summary measure
			N	Mean (SD) (pg/mL)	N	Mean (SD) (pg/mL)	Criteria for Verification by RHC
Allanore, 2008[26a] SSc patients with echocardiography sPAP<40 mmHg and no NYHA III/IV symptoms N=101 Good	NT-proBNP	mPAP ≥35 mmHg PCWP ≤15 mmHg	8	413 (304)	93	127 (135)	sPAP>40mmHg, DLCO<50% predicted without pulmonary fibrosis or unexplained dyspnea, negative CT, D-dimer
Bonderman, 2011[25] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372 Good	NT-proBNP	mPAP >35 mmHg PCWP <15 mmHg	64	3648 (6541)	57	1489 (3518)	sPAP≥36mmHg
Cavagna, 2010[14] SSc patients; symptoms not described N=135 Good	NT-proBNP	mPAP >35 mmHg PCWP <15 mmHg	20	189 (44 to 665)[a]	115	84 (39 to 181)[b]	sPAP≥36mmHg
Frea, 2011[34a] SSc patients with no signs or symptoms of PAH N=76 Fair	NT-proBNP	mPAP ≥25 mmHg PCWP ≤15 mmHg	4	211 (134)	34	127 (100)	TRV≥3m/s or sPAP≥40mmHg

Study Population (N) Quality	Biomarker	Reference Diagnostic Criterion for PAH	Patients With PAH		Patients Without PAH		Summary measure
			N	Mean (SD) (pg/mL)	N	Mean (SD) (pg/mL)	Criteria for Verification by RHC
Ghio, 2004[73] HIV and confirmed PAH. Controls with HIV and no known cardiac or pulmonary disease N=93 Fair	NT-proBNP	NR	16	1412 (574 to 2326)[a]	77	29 (7 to 48)[b]	NR (case-control design)
Simeoni, 2008[58] Known SSc-associated PAH and controls with SSc but no PAH N=20 Poor	NT-proBNP	NR	10	198	10	103	NR (case-control design)
Williams, 2006[68] SSc patients with PAH and controls with SSc but without PAH N=109 Fair	NT-proBNP	NR, but PCWP ≤15 mmHg required	68	1474 (2642)	41	139 (150)	NA (case-control design; all patients had RHC)
Cavagna, 2010[14] SSc patients; symptoms not described N=135 Good	BNP	mPAP ≥25 mmHg PCWP <15 mmHg	20	74.5 (29 to 196)[a]	115	30 (18 to 49)[b]	sPAP≥36mmHg, DLCO<50%pred, 20% decrease DLCO in 1 yr in absence of pulmonary fibrosis, or unexplained dyspnea, negative CT

Study Population (N) Quality	Biomarker	Reference Diagnostic Criterion for PAH	Patients With PAH		Patients Without PAH		Summary measure
			N	Mean (SD) (pg/mL)	N	Mean (SD) (pg/mL)	Criteria for Verification by RHC
Elias, 2008[71] SSc patients. Some were symptomatic N=106 Fair	BNP	NR	37	163 (159)	69	33 (23)	sPAP>40mmHg (18/37 patients verified by RHC)

[a]Studies that assessed baseline NT-proBNP as predictors of future development of PAH.
[b]Median interquartile range.
Abbreviations: DLCO=diffusion capacity of the lung for carbon monoxide; mPAP=mean pulmonary artery pressure; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; PCWP=pulmonary capillary wedge pressure; sPAP=systolic pulmonary artery pressure; RHC=right heart catheterization

Three studies examined the correlation between either serum BNP or NT-proBNP levels and hemodynamic parameters measured at RHC. Statistically significant correlations were found between the biomarker level and CO, mPAP, PVR and sPAP; these correlations were of moderate strength for all parameters (Table 7).

Table 7. Correlations of biomarkers with RHC in PAH

Study Population (N) Quality	Biomarker	RHC Parameter	Total N	Correlation (p-value)
Machado, 2006[42] Sickle cell disease N=416 Poor	NT-proBNP	CO	37	-0.43 (0.006)
	NT-proBNP	mPAP	37	0.43 (0.006)
	NT-proBNP	PVR (NR)	37	0.51 (0.001)
	NT-proBNP	sPAP	37	0.59 (0.002)
Cavagna, 2010[14] SSc patients; symptoms not described N=135 Good	NT-proBNP	mPAP	115	0.61 (0.001)
	BNP	mPAP	135	0.72 (0.002)
Toyono, 2008[63] Children with VSD and severe PH N=24 Good	BNP	PVR (Fick)	24	0.56 (0.004)

Abbreviations: BNP= B-type natriuretic peptide; CO=cardiac output; mPAP=mean pulmonary artery pressure; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; sPAP=systolic pulmonary artery pressure; PVR= pulmonary vascular resistance

Echocardiography for Diagnosing PAH

Twenty-one studies assessed echocardiography in evaluating patients suspected of PAH. All studies reported data that compared a single hemodynamic parameter at a time. Fifteen studies (5 good quality, 4 fair, 3 poor) reported the diagnostic accuracy of echocardiographic estimates of pulmonary pressures based on TRV measurement, with or without estimate of RAP, compared with a reference standard diagnosis based on RHC (Table 8).[28,29,31,33,35-39,41,45,49,50,59,60]

Five studies used a variable estimate of RAP (based on IVC size and inspiratory variation or JVP) to calculate sPAP;[28,31,37,39,50] four studies calculated sPAP using a fixed value for RAP;[36,49,59,60] and six studies used TG or TRV.[29,33,35,38,41,45]

Nine of these studies were of patients with systemic sclerosis (or other collagen vascular disease) with suspected PAH based on symptoms.[29,31,35,36,38,39,45,49,59] Four studies evaluated liver transplant candidates;[28,37,50,60] one study included patients with sickle cell disease;[33] and one study had patients referred for evaluation of suspected PAH without a single high risk condition.[41]

Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Pre-valence
Hua, 2008[37] Liver transplant candidates N=105 Good	sPAP $4*TRV^2+RAP$	≥30 mmHg	mPAP ≥25 mmHg (PVR ≥ 240 dyne*sec/cm^5 PCWP <15 mmHg	4	0	18	83	100 (47 to 100)	82 (73 to 89)	3.8%
Torregrosa, 2001[60] Liver transplant candidates N=94 Fair	sPAP $4*TRV^2+10$	≥40 mmHg	mPAP ≥25 mmHg or PVR >120 dynes*s/cm^5	4	1	9	93	80 (28 to 99)	91 (84 to 96)	4.7%
Mukerjee, 2004[45] SSc patients with suspected PAH, symptoms of exercise limitation and reduced DLCO N=137 Fair	TG $4*TRV^2$	≥40 mmHg	mPAP>25mmHg or resting PVR>200 dyne*sec/cm^5 mPAP>30mmHg with exercise	57	42	5	33	58 (47 to 67)	87 (72 to 96)	72%
Phung, 2009[49] SSc patient referred with or without suspicion of PAH; 10% had NYHA III/IV symptoms N=184 Good	sPAP $4*TRV^2+10$	>40 mmHg	mPAP ≥25 mmHg	23	0	18	119	100 (88 to 100)	87 (80 to 92)	14%

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Pre-valence
Pilatis, 2000[50] Liver transplant candidates N=55 Fair	sPAP $4*TRV^2+RAP$	>40 mmHg	mPAP ≥25mmHg	5	3	1	46	62 (24 to 91)	98 (89 to 100)	14%
Steen, 2008[59] SSc patients with suspected PAH based on symptoms or signs N=54 Fair	sPAP $4*TRV^2+10$	>20 mmHg increase over resting	mPAP >25 mmHg (rest) or >30 mmHg (exercise)	21	5	3	25	81 (61 to 93)	89 (72 to 98)	48%
Colle, 2003[28] Liver transplant candidates N=165 Good	sPAP $4*TRV^2+RAP$	≥30 mmHg	mPAP >25 PCWP <15 PVR >120 dynes*s/cm^5	8	2	6	149	80 (44 to 97)	96 (92 to 99)	6.1%
Hsu, 2008[36] SSc patients with dyspnea or other clinical features suggestive of PAH N=49 Good	sPAP $4*TRV^2+10$	>47 mmHg	sPAP>25 mmHg	14	10	1	24	58 (37 to 78)	96 (80 to 100)	49%

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Pre-valence
Denton, 1997[31] SSc patients suspected of PAH, most due to reduced DLCO N=93 Fair	sPAP $4*TRV^2+JVP$	≥30 mmHg	sPAP ≥30 mmHg	19	2	3	9	90 (70 to 99)	75 (43 to 95)	64%
Kovacs, 2010[39] Patients with CVD some with symptoms N=52 Good	sPAP $4*TRV^2+RAP$	>40 mmHg	sPAP >40 mmHg with exercise	11	5	10	18	69 (41 to 89)	64 (44 to 81)	36%
Condliffe, 2011[29] SSc patients with suspected PAH; symptoms not described N=89 Fair	TRV	≥35 mmHg (≥2.96 m/s)	mPAP PVR	42	5	10	10	89 (77 to 96)	50 (27 to 73)	70%
Fonseca, 2012[33] Sickle cell disease; symptoms not described N=80 Fair	TRV	>2.5 m/s	mPAP ≥25 mmHg PCWP ≤15 mmHg	8	0	18	48	100 (69 to 100)	73 (60 to 83)	10.8%

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Pre-valence
Hachulla, 2005[35] SSc patients; some symptomatic N=599 Poor	TRV	≥3 m/s or ≥2.5 m/s with unexplained dyspnea	MPAP ≥25 mmHg rest or ≥30 mmHg with exercise	18	0	15	419	100 (85 to 100)	97 (94 to 98)	4%
Jansa, 2011[38] SSc patients some with dyspnea N=203 Fair	TRV	>30 mmHg (>2.74 m/s)	MPAP ≥25 mmHg PCWP ≤15 mmHg	6	0	10	186	100 (61 to 100)	95 (91 to 98)	3%
Low, 2011[41] Referred for evaluation of suspected or definite PAH, most with symptoms N=200 Poor	TRV	≥36 mmHg (≥3 m/s)	MPAP >25 mmHg PCWP, LAP or LVEDP ≤15 mmHg PVR >3WU	58	0	8	128	100 (95 to 100)	94 (89 to 97)	30%
Dahiya, 2010[30] Referred for evaluation of suspected PH; all patients had dyspnea N=114 Good	TRV/VTI_{RVOT}	>0.16	PVR >2 WU	47	3	2	20	94 (83 to 99)	91 (71 to 99)	69%

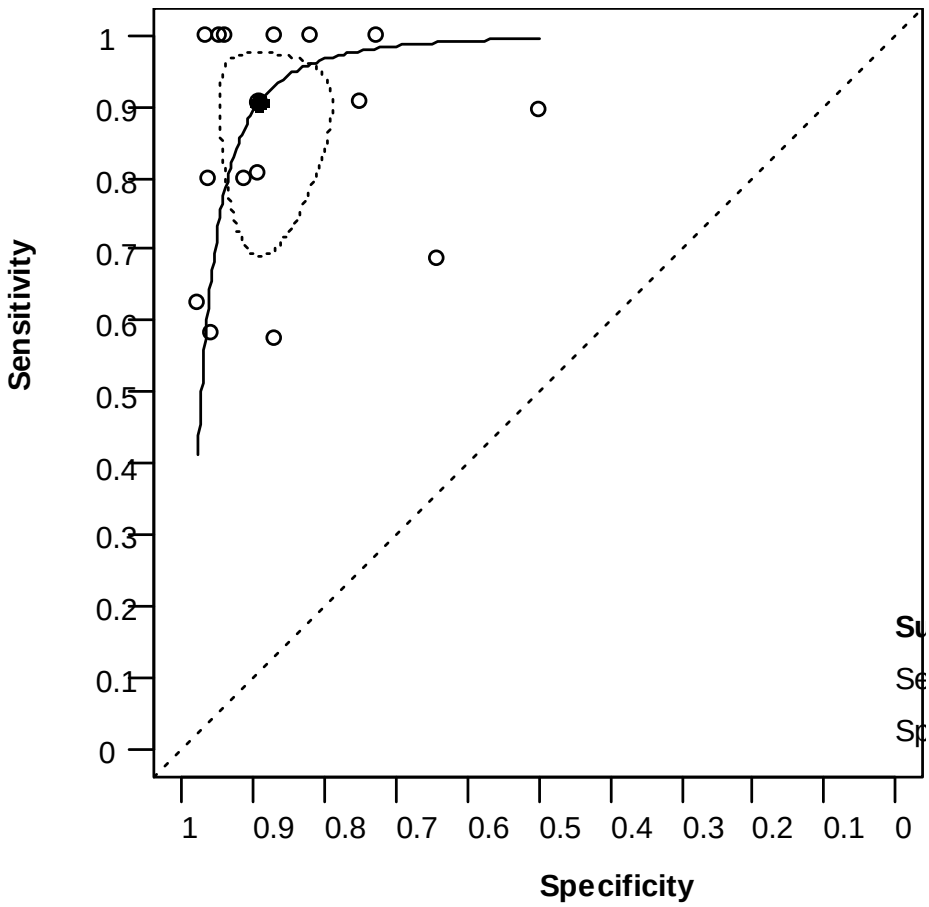
Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Pre-valence
Lindqvist, 2011[40] Patients with PH undergoing RHC N=30 Fair	TRV/VTI_{RVOT}	>0.175	PVR >3 WU	16	2	1	6	88 (65 to 99)	86 (42 to 100)	72%
Rajagopalan, 2009[51] Known pulmonary hypertension N=52 Fair	TRV/VTI_{RVOT}	>0.16	PVR >2 WU	41	4	0	7	91 (79 to 98)	100 (65 to 100)	87%
Roule, 2010[55] Known PH N=37 Good	TRV/VTI_{RVOT}	>0.14	sPAP	28	2	3	4	93 (78 to 99)	57 (18 to 90)	81%
Vlahos, 2007[65] Known or suspected pulmonary hypertension N=12 Fair	TRV/VTI_{RVOT}	>0.38	PVR>8WU	6	2	0	4	75 (35 to 97)	100 (47 to 100)	67%

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Pre-valence
Ajami, 2011[68,69] Children and young adults with congenital heart disease referred for RHC N=20 Good	TRV/VTI_{RVOT}	>0.2	PVR>8WU	9	1	1	9	90 (55 to 100)	90 (55 to 100)	50%

Abbreviations: FAC=fractional area change; FN=false negative; FP=false positive; mmHg=millimeter of mercury; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrium; RIMP=right index of myocardial performance; RV=right ventricle; sPAP=systolic pulmonary artery pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TG=tricuspid gradient; TN=true negative; TP=true positive; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Sensitivity of estimates ranged from 58 to 100 percent, while specificity estimates ranged from 50 to 91 percent. The paired sensitivity and specificity values are show in Figure 6 in receiver operating curve space. The studies with the greatest degree of verification bias (large proportion of test-negative patients with no RHC verification of disease status) tend to have both high specificity and sensitivity estimates. Four studies of liver transplant candidates were the only ones to have complete RHC verification, and these studies had sensitivity estimates from 62 to 100 percent and specificity estimates from 82 to 98 percent.[28,37,50,60]

Figure 6. Summary sensitivity and specificity values for echocardiography sPAP diagnosis of PH



Meta-analysis of the 15 studies yielded summary estimates for sensitivity and specificity close to 90 percent, with confidence region as shown in Figure 7. There was moderate heterogeneity (I^2=61.1%). In an effort to explain the between-study variation, we undertook a sensitivity analysis based on features we suspected might account for variation and that had suitable distributions among the studies. The results of the sensitivity analyses are shown in Table 9.

Figure 7. Sensitivity and specificity of echocardiography sPAP for diagnosis of PAH

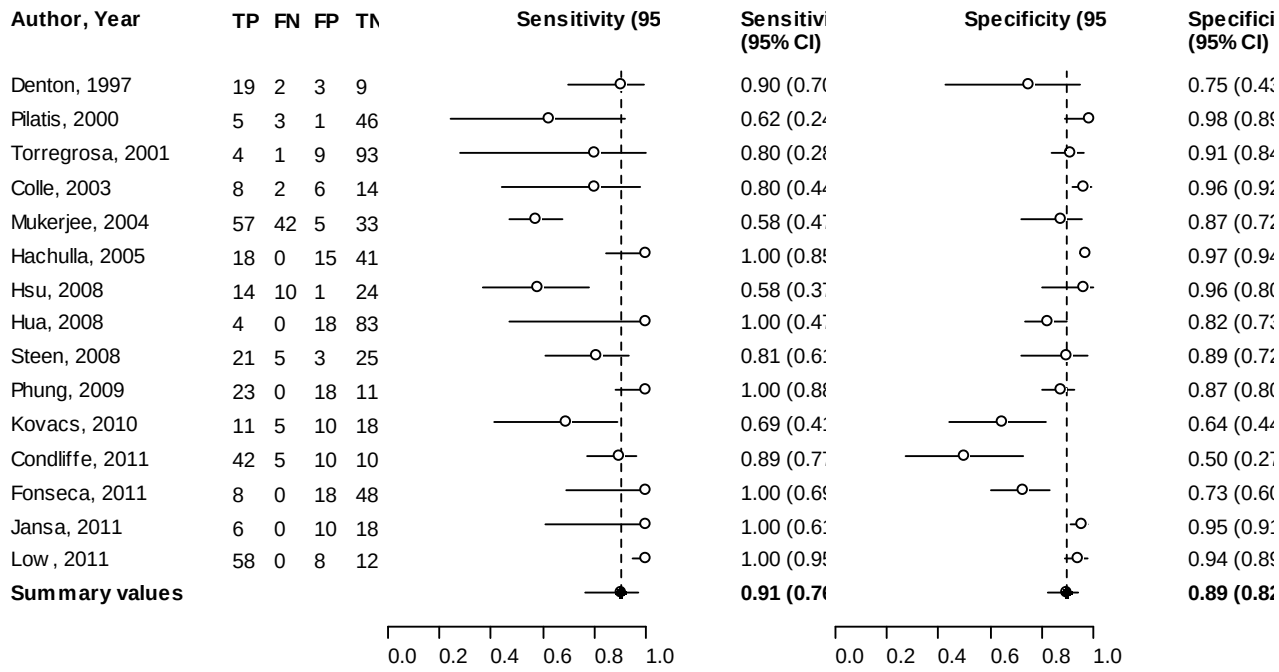


Table 9. Sensitivity analysis of echocardiography sPAP by study characteristics

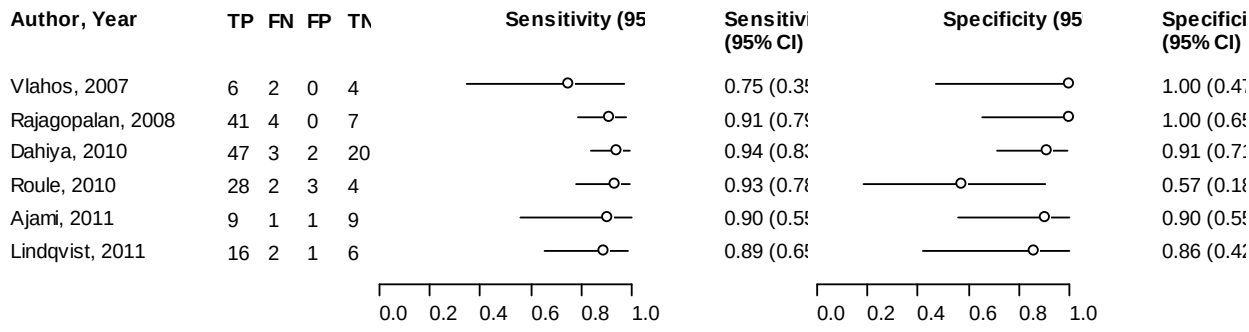
Study Characteristic	Number of Studies (Patients)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	I^2
Prevalence				
Less than 15%	8 (1320)	90.8 (85.2 to 94.4)	92.3 (87.6 to 95.3)	0
15% or more	7 (578)	83.2 (66.8 to 92.4)	86.5 (72.2 to 94.0)	66.1%
Diagnosis				
Liver transplant	4 (432)	79.7 (72.5 to 85.4)	93.8 (91.1 to 95.8)	0
Systemic sclerosis	8 (1154)	87.6 (78.2 to 93.3)	90.1 (82.2 to 94.8)	57.2%
Other (SSD, CVD)	3 (312)	94.2 (0.40 to 100)	80.6 (0.10 to 100)	86.8%
RAP method				
None or fixed	10 (1496)	90.4 (84.4 to 94.2)	90.6 (84.7 to 94.3)	64.5%
Variable	5 (402)	80.6 (63.6 to 90.9)	88.1 (76.4 to 94.9)	62.3%

Abbreviations: CI =confidence interval; CVD=collagen vascular disease; RAP=right atrial pressure; sPAP=systolic pulmonary artery pressure; SSD=sickle cell disease

Studies with lower prevalence of PH (less than 15% of study subjects) showed greater homogeneity than studies with higher prevalence of PH. These eight low prevalence studies included the four studies of liver transplant patients (which had complete verification of test-negative subjects) and four studies that had high degree of verification bias. The studies among liver transplant patients had no important heterogeneity compared with eight studies of systemic sclerosis patients or studies in patients with other diagnoses. The method of correction for RAP (fixed or none versus variable estimate) did not explain between-study heterogeneity.

Six studies (3 good quality, 2 fair, 1 poor) evaluated the echocardiographic estimation of PVR using TRV/VTI_{RVOT} against RHC diagnosis of elevated PVR (Figure 8).[30,40,51,55,65,69] Three of these studies included patients with known PH.[40,51,55] Two studies used a threshold for PVR much higher than that used for diagnosis (8 Woods Units versus 2 Woods Units)[65,69] with the goal of distinguishing more severe PAH; these studies also used a higher test threshold of 0.2 and 0.38 compared with 0.14 to 0.175. Sensitivity ranged from 75 to 94 percent, while specificity ranged from 57 to 100 percent.

Figure 8. Sensitivity and specificity of TRV/VTI_{RVOT} for diagnosis of PAH



Abbreviations: CI =confidence interval; FN=false negative; FP=false positive; PAH=pulmonary arterial hypertension; TN=true negative; TP=true positive; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Echocardiographic Parameters by Diagnostic Group

Eight studies reported data on the mean (or median) and standard deviation (or interquartile range) for specific echocardiographic parameters for patients with and without PAH (Table 10). Two of these studies reported echocardiographic values at baseline for prospectively identified incident cases of PAH.[26,34] In one study the diagnostic categories distinguished between primary PAH and chronic thromboembolic pulmonary hypertension.[47]

Table 10. Echocardiographic parameter values by diagnostic group

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		p-value
				N	Mean (SD)	N	Mean (SD)	
Ruan, 2007[56] Known PAH and healthy controls N=180 Fair	FAC	NR (case-control design)	NR	70	19 (10)	35	53 (10)	NR
Bonderman, 2011[25] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372 Good	RA size	sPAP ≥36 mmHg	mPAP >35 mmHg PCWP <15 mmHg	64	58.7 (10.9)	57	59.1 (11.5)	0.87
Tei, 1996[61] Known PPH and health controls N=53 Poor	RIMP	NR (case-control design)	NR	26	0.89 (0.25)	37	0.28 (0.04)	<0.001
Elias, 2008[71] SSc patients. Some were symptomatic N=106 Fair	RIMP	sPAP >40 mmHg (18/37 patients verified by RHC)	NR	37	0.41 (0.03)	69	0.37 (0.02)	<0.001

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		p-value
				N	Mean (SD)	N	Mean (SD)	
Bonderman, 2011[25] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372 Good	RV size	sPAP ≥36 mmHg	mPAP >35 mmHg PCWP <15 mmHg	64	44 (9.2)	57	38.2 (6.9)	<0.001
Ruan, 2007[56] Known PAH and healthy controls N=180 Fair	RV size	NR (case-control design)	NR	70	28 (9)	35	14 (6)	NR
Bonderman, 2011[25] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372 Good	sPAP	sPAP ≥36 mmHg	mPAP >35 mmHg PCWP <15 mmHg	64	82.6 (24.3)	57	55.2 (16.3)	<0.001
Ruan, 2007[56] Known PAH and healthy controls N=180 Fair	sPAP	NR (case-control design)	NR	70	73 (6)	35	21 (6)	NR

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		p-value
				N	Mean (SD)	N	Mean (SD)	
Torregrosa, 2001[60]	sPAP	NA (all patients had RHC)	mPAP ≥25 mmHg PVR >120 dyne*sec/cm^5	5	54 (15)	102	36 (5)	<0.001
Fukuda, 2011[72] Patients with known PH N=67 Fair	sPAP	NR (case-control design)	mPAP >25 mmHg	45	67 (23)	22	20 (10)	0.0001
Frea, 2011[34a] SSc patients with no signs or symptoms of PAH N=76 Fair	FAC	TRV≥3m/s or sPAP≥40mmHg	mPAP ≥25 mmHg PCWP ≤15 mmHg	4	41.25 (2.22)	34	43.7 (4.5)	0.29
	RIMP	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP ≥25 mmHg PCWP ≤15 mmHg	4	0.32 (0.16)	34	0.26 (0.07)	0.14
	RV size	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP ≥25 mmHg PCWP ≤15 mmHg	4	35.2 (30)	34	33 (3.5)	0.24
	TRV/VTI_{RVOT}	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP≥25mmHg PCWP≤15mmHg	4	0.157 (0.033)	34	0.122 (0.022)	0.01
Allanore, 2008[26a] SSc patients with echocardiography sPAP<40 mmHg and no NYHA III/IV symptoms N=101 Good	sPAP	sPAP >40 mmHg, DLCO <50% predicted without pulmonary fibrosis or unexplained dyspnea, negative CT, D-dimer	mPAP ≥35 mmHg PCWP ≤15 mmHg	8	38.2 (9.4)	93	31.2 (5.9)	0.001
Frea, 2011[34a] SSc patients with no signs or symptoms of PAH N=76 Fair	TAPSE	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP ≥25 mmHg PCWP ≤15 mmHg	4	23 (1.63)	34	22.3 (2.19)	0.54

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		p-value
				N	Mean (SD)	N	Mean (SD)	
Nakayama, 1998[47b] Patients with known, symptomatic CTEPH or PPH N=35 Fair	mPAP	NA (all patients had RHC)	NR but includes negative V/Q scan	19	41 (10)	16	54 (9)	

[a]Studies that assessed baseline NT-proBNP as predictors of future development of PAH.
[b]Study attempted to distinguish primary PAH from CTEPH (rather than no PAH).
Abbreviations: DLCO=diffusion capacity of the lung for carbon monoxide; mmHg=millimeter of mercury; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrium; RHC=right heart catheterization; RV=right ventricle; sPAP=systolic pulmonary artery pressure; SD=standard deviation; SSc=systemic sclerosis; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Among the echocardiographic parameters at baseline, TRV/VTI_{RVOT} and sPAP showed statistically significant differences at baseline among those who later developed PAH compared with those who did not (Table 11). Other parameters examined, including FAC, RIMP, RV size and TAPSE, failed to show statistically significant differences; however, the number of cases in this study was small (n=4), suggesting this analysis lacks sensitivity. Likewise the number of parameters examined for association is large relative to the number of cases, suggesting the possibility of finding significant associations by chance.

Six studies evaluated concurrent echocardiography measurement with diagnosis of PAH and provide data on five different echocardiographic parameters: sPAP, RIMP, RV size, RA size, and FAC. Three of the studies used a case-control design; two used elevated sPAP by echocardiography to select patients for diagnostic verification; one study verified all participants' diagnosis with RHC. Four studies indicate large differences in echocardiography sPAP between patients with PAH and those without PAH with differences in means ranging from 18 to 52 mmHg. These differences, while highly significant, reflect incorporation bias since the diagnostic classification is based on mPAP, which is highly correlated with sPAP.

RIMP and RV size were reported in two studies each. These parameters were significantly different between patients with PAH or not. RA size, in one study did not show statistically significant differences, while FAC, in a case-control study showed large differences, greatly exceeding standard deviation, between patients with PAH or not.

Accuracy and Precision of Echocardiography Versus RHC

Twenty-five studies reported the correlation and or agreement between echocardiographic measurements and corresponding hemodynamic parameters measured at RHC (Table 11). The correlation coefficient between echocardiography sPAP and RHC sPAP ranged from 0.375 to 0.94. Two studies reported correlation of echocardiography sPAP with both simultaneous and nonconcurrent RHC; in each case, correlations were improved when echocardiography was performed simultaneously with RHC; however, the improvement in correlation was only 0.03 to 0.06.

Bias in measurement was estimated by examining the difference between two tests measured on the same scale using the method of Bland and Altman. In nine studies comparing sPAP values, the average bias varied between a 5.9 mmHg underestimate and an 11.4 mmHg overestimate by echocardiography. The standard deviation of the bias measurements ranged from 1.8 to 30.1, with all but one greater than 7.5. With a standard deviation of this magnitude, one would expect about 80 percent of echocardiography sPAP reading to fall within 10 mmHg of RHC sPAP; however, the large Reveal registry[9] found that only 39.8 percent of echocardiography sPAP estimates were within 10mmHg of same-day RHC-measured sPAP, corresponding to a standard deviation of around 20 mmHg. The remaining 60 percent were approximately equally divided between overestimates (greater than 10 mmHg) and underestimates (more than 10 mmHg).

Four studies reported correlation between echocardiography transtricuspid gradient and sPAP, with estimates ranging from 0.19 to 0.80. The low outlier was a small study of young children with chronic lung disease. One other study found negligible bias, but a large standard deviation of difference between echocardiography and RHC measures.

Six studies correlated TRV/VTI_{RVOT} with PVR by RHC. Correlation coefficients indicated strong correlation ranging from 0.73 to 0.84, with bias ranging from 0 to 6.1, and standard deviations ranging from 1.9 to 4.3 Woods Units.

Two studies reported strong correlations between echocardiography estimates of mPAP with RHC-measured mPAP. Correlation coefficients were 0.88 and 0.91, but increased to 0.95 when echocardiography was simultaneous to RHC. The estimates of bias of a 2 and 5.7 mmHg underestimate improved to a 1.4 mmHg overestimate when echocardiography was performed simultaneously to RHC; the standard deviations of difference between echocardiography and RHC ranged from 0.84 to 7.2.

Low to moderate correlations were observed between RIMP and mPAP, RIMP and PVR, TAPSE and mPAP, FAC and mPAP, FAC and PVR, and TG and mPAP. One study found a strong correlation between TG and PVR.

Table 11. Correlation of echocardiographic parameters with RHC in PAH

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Fukuda, 2011[72] Patients with known PH N=67 Fair	FAC	RV end-diastolic area- RV end-systolic area/RV end-diastolic area x 100%	mPAP	45	-0.47 (0.001)	
			PVR (Fick)	45	-0.46 (0.002)	
Selimovic, 2007[57] Patients with suspected pulmonary vascular disease. 37/42 NYHA III/IV N=42 Good	mPAP	PADP+0.33(PASP-PADP)	mPAP	56 (4)	0.91 (0.04)	-2.0 (7.2)
	mPAP	Simultaneous with RHC	mPAP	20 (0)	0.95 (0.31)	1.4 (5.8)
	sPAP	$4\times TRV^2+RAP$ (5, 10, 15)	sPAP	56 (4)	0.88 (0.3)	-1.7 (12.3)
Tian, 2001[62] Suspected PH based on symptoms N=42 Fair	mPAP		mPAP	42 (0)	0.88(0.0001)	-5.7 (0.84)
Vonk, 2007[66] Connective tissue diseases. One-third NYHA III/IV N=98 Fair	RIMP		mPAP	35 (2)	0.46 (0.01)	

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Fukuda, 2011[72] Patients with known PH N=67 Fair	RIMP		mPAP	45 (0)	-0.21 (0.174)	
Vonk, 2007[66] Connective tissue diseases. One-third NYHA III/IV N=98 Fair	RIMP		PVR (TD)	35 (2)	0.33 (0.08)	
Fukuda, 2011[72] Patients with known PH N=67 Fair	RIMP		PVR (Fick)	45 (0)	-0.26 (0.12)	
Dahiya, 2010[30] Referred for evaluation of suspected PH; all patients had dyspnea N=114 Good	TRV/VTI_{RVOT}		PVR (TD)	50	0.77 (0.001)	1.8 (3.3)
Lindqvist, 2011[40] Patients with PH undergoing RHC N=30 Fair	TRV/VTI_{RVOT}		PVR (TD)	25 (5)	0.78 (0.001)	6.1 (4.0)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Rajagopalan, 2009[51] Known pulmonary hypertension N=52 Fair	TRV/VTI_{RVOT}		PVR (Fick)	52	0.73 (0.001)	0 (4.3)
Roule, 2010[55] Known PH N=37 Good	TRV/VTI_{RVOT}		PVR (TD)	37 (NR)	0.76 (0.0001)	0 (1.9)
Vlahos, 2008[65] Known or suspected pulmonary hypertension N=12 Poor	TRV/VTI_{RVOT}		PVR (Fick)	12 (0)	0.843 (NR)	
Ajami, 2011[69] Children & young adults with congenital heart disease referred for RHC N=20 Good	TRV/VTI_{RVOT}		PVR (Fick)	20 (0)	0.73 (NR)	
Denton, 1997[31] SSc patients suspected of PAH, most due to reduced DLCO N=93 Fair	sPAP	$4 \times TRV^2 + JVP$	sPAP	20 (13)	0.83 (0.001)	11.4 (9.8)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Farber, 2011[9] Patients with PAH N=1883 Fair	sPAP	$4\times TRV^2+RAP$	sPAP	1360 (NR)	0.56 (0.001)	
Hsu, 2008[36] SSc patients with dyspnea or other clinical features suggestive of PAH N=49 Good	sPAP	$4\times TRV^2+10$	sPAP	49 (NR)	0.71 (NR)	
Fisher, 2009[32] Patients undergoing RHC for known or suspected PAH; symptoms not described N=65 Good	sPAP	$4\times TRV^2+RAP$	sPAP	59 (NR)	0.66 (0.001)	-0.6 (20)
Kovacs, 2010[39] Patients with CVD some with symptoms N=52 Good	sPAP	$4\times TRV^2+RAP$	sPAP	28 (9)		0.3 (7.6)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Nogami, 2009[48] Suspected pulmonary hypertension; all patients symptomatic N=29 Good	sPAP	$4\times TRV^2+RAP$ (5, 15)	sPAP	20 (0)	0.86 (0.01)	-5.9 (14.1)
Rich, 2011[53] Patients with both RHC and Doppler echo N=183 Good	sPAP	$4\times TRV^2+RAP$ (5, 10, 15 or 20)	sPAP	160 (X)	0.68 (0.001)	2.2 (18.6)
		with simultaneous RHC	sPAP	23 (X)	0.71 (0.01)	8.0 (8.8)
Roeleveld, 2005[54] Known PH N=47 Fair	sPAP	$4\times TRV^2+RAP$ (5, 10, 15)	sPAP	35 (9)	0.375 (0.026)	-5 (30.1)
		Simultaneous RHC	sPAP	22 (1)	0.94 (0.69)	0.7 (7.8)
Tian, 2011[62] Suspected PH based on symptoms N=42 Fair	sPAP	$4\times TRV^2+RAP$ (4, 10, 14)	sPAP	42 (X)	0.96 (0.0001)	-1.8 (1.8)
Vonk, 2007[66] Connective tissue diseases. One-third NYHA III/IV N=98 Fair	sPAP	$4\times TRV^2+RAP$	sPAP	35 (0)	NR (0.001)	

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Willens, 2008[67] Patients with known PH and elevated sPAP and controls with CHF and elevated sPAP N=47 Fair	sPAP	$4\times TRV^2+RAP$	sPAP	44 (3)	0.75 (0.001)	
Rajagopalan, 2007[52] Known pulmonary hypertension N=52 Fair	sPAP	$4\times TRV^2+RAP$	sPAP	32 (0)	0.87 (0.001)	
Murata, 1997[46] SSc patients. Symptoms not described, but most had reduced DLCO N=135 Fair	sPAP	$4\times TRV^2+ 10$	sPAP	19 (6)	0.41 (NR)	-0.53 (12.1)
Fukuda, 2011[72] Patients with known PH N=67 Fair	TAPSE	Total excursion of tricuspid annulus during systole	mPAP	45 (0)	-0.33 (0.027)	
			PVR (Fick)	45 (0)	-0.49 (0.002)	

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Condliffe, 2011[29] SSc patients with suspected PAH; symptoms not described N=89 Fair	TRV	$4\times TRV^2$	mPAP	70 (0)	0.64 (0.001)	
	TRV	$4\times TRV^2$	PVR (TD)	70 (0)	0.76 (0.001)	
Fisher, 2009[32] Patients undergoing RHC for known or suspected PAH; symptoms not described N=65 Good	TRV	$4\times TRV^2$	sPAP	59 (NR)		-1.8 (18.1)
Fonseca, 2011[33] Sickle cell disease; symptoms not described N=80 Fair	TRV	$4\times TRV^2$	sPAP	26 (0)	0.77 (0.001)	
Mourani, 2008[44] Children under 2 years of age undergoing RHC for chronic lung disease N=25 Fair	TRV	$4\times TRV^2$	sPAP	19 (12)	0.19 (0.43)	

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-value)	Bias (SD)
Mukerjee, 2004[45] SSc patients with suspected PAH, symptoms of exercise limitation and reduced DLCO N=137 Fair	TRV	TG calculated from TRV using “standard templates”	sPAP	137 (NR)	0.67 (NR)	
Roule, 2010[55] Known PH N=37 Good	TRV	$4 \times TRV^2$	sPAP	37 (0)	0.8 (NR)	

Abbreviations: mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; PADP=pulmonary artery diastolic pressure; PASP= pulmonary artery systolic pressure; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RAP=right atrial pressure; RIMP=right index of myocardial performance; RV=right ventricle; sPAP=systolic pulmonary artery pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TG=tricuspid gradient; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Results for these outcomes and comparisons, along with ratings for strength of evidence are shown in Tables 12–15.

Table 12. Summary SOE for KQ 1: echo sPAP with NT-proBNP versus echo sPAP in symptomatic patients

Number of Studies (Subjects)	Domains				Strength of Evidence Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Sensitivity					**SOE=Insufficient**
1 (121)	Moderate	NA	Direct	Imprecise	NT-proBNP >80 pg/mL has a low false negative rate compared with RHC reference standard; the serial testing study design did not allow for NT-proBNP testing to improve sensitivity beyond that of echo sPAP alone
Specificity					**SOE=Low**
1 (121)	Moderate	NA	Direct	Imprecise	NT-proBNP ≤80 pg/mL ruled out PAH in 9–16% of patients with elevated echo sPAP ≥36 mmHg
Correlation					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA
Adverse effects					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA

Abbreviations: CI=confidence interval; NA=not applicable; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure

Table 13. Summary SOE for KQ 1: NT-proBNP compared with RHC

Number of Studies (Subjects)	Domains				Strength of Evidence Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Sensitivity					**SOE=Low**
3 (198)	Moderate	Inconsistent	Indirect	Imprecise	Range 56% to 100% NT-proBNP has variable sensitivity for diagnosing PAH; uncertain performance for ruling in PAH
Specificity					**SOE=Low**
3 (198)	Moderate	Inconsistent	Indirect	Imprecise	Range 24% to 95% NT-proBNP has variable specificity; uncertain performance for ruling out PAH
Correlation					**SOE=Moderate**
3 (176)	Moderate	Consistent	Indirect	Imprecise	Range 0.43 to 0.72 Correlation of NT-proBNP and RHC is only moderate
Adverse effects					**SOE=Insufficient**
0 (0)	Insufficient	Insufficient	Insufficient	Insufficient	NA

Abbreviations: CI=confidence interval; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PAH=pulmonary arterial hypertension; RHC=right heart catheterization; SOE=strength of evidence

Table 14. Summary SOE for KQ 1: TRV/TG/sPAP compared with RHC

Number of Studies (Subjects)	Domains				Strength of Evidence Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Sensitivity					**SOE=Moderate**
15 (1898)	Moderate	Consistent	Indirect	Imprecise	Range 58% to 100% Echocardiographic estimate of sPAP showed variable sensitivity, with lower prevalence studies finding higher sensitivity
Specificity					**SOE=Moderate**
15 (1898)	Moderate	Consistent	Indirect	Imprecise	Range 64% to 98% Echocardiographic estimate of sPAP showed variable specificity, with lower prevalence studies finding higher specificity
Correlation					**SOE=Moderate**
14 (1822)	Low	Inconsistent	Indirect	Imprecise	Range 0.38 to 0.96 Echocardiographic estimates of sPAP showed moderate to strong correlation with RHC and were on average unbiased, but were limited by imprecision and by a significant minority of patients in whom TRV was not measurable
Adverse effects					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA

Abbreviations: CI=confidence interval; PAH=pulmonary arterial hypertension; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure; TG=??; TRV= tricuspid regurgitant jet velocity

Table 15. Summary SOE for KQ 1: TRV/VTI$_{RVOT}$ compared with RHC

Number of Studies (Subjects)	Domains				Strength of Evidence Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Sensitivity					**SOE=Moderate**
6 (218)	Moderate	Consistent	Indirect	Precise	Range 89% to 100% Echocardiographic estimate of PVR showed reasonably high sensitivity for ruling in PAH
Specificity					**SOE=Moderate**
6 (218)	Moderate	Consistent	Indirect	Imprecise	Range 50% to 97% Echocardiographic estimate of PVR showed variable specificity, with better specificity in lower prevalence studies (range, 94% to 97%)
Correlation					**SOE=High**
6 (218)	Low	Consistent	Indirect	Precise	Range 0.74 to 0.84 Strong correlation between echocardiographic estimates of PVR and PVR by RHC
Adverse effects					**SOE=Insufficient**
6 (218)	Insufficient	Insufficient	Insufficient	Insufficient	NA

Abbreviations: CI=confidence interval; PAH=pulmonary arterial hypertension; PVR=??; RHC=right heart catheterization; SOE=strength of evidence; TRV=tricuspid regurgitant jet velocity; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Key Question 2. Management of PAH

KQ 2. For patients with PAH, what is the comparative effectiveness and safety of (a) echocardiography versus biomarkers and (b) echocardiography versus echocardiography plus biomarkers in managing PAH and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes ?

Key Points

- No data are available regarding the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers in the management of PAH or patient outcomes (insufficient SOE).
- Systolic pulmonary artery pressure (sPAP) estimated by echocardiography shows good correlation with sPAP from RHC (moderate SOE).
- Serum brain natriuretic peptide (BNP) level shows only moderate correlation with these RHC measures: mean pulmonary artery pressure (mPAP), pulmonary vascular resistance, right atrial pressure, cardiac index, and clinical outcomes such as the 6MWD test (moderate SOE).
- BNP level shows poor correlation with RHC pulmonary capillary wedge pressure (low SOE).
- BNP level alone is not an accurate surrogate marker for disease severity (high SOE).
- BNP level is a poor predictor of mortality (high SOE).
- Fractional area change (FAC) is a poor predictor of mortality (moderate SOE).
- Right atrial (RA) size is a poor predictor of mortality (low SOE).
- Presence of pericardial effusion is the strongest predictor of mortality although there was wide variability in results for this measure (moderate SOE).
- We found no studies addressing diagnostic thinking efficacy, therapeutic efficacy, or harms (insufficient SOE).

Description of Included Studies

We identified 80 unique, observational studies involving a total of 7224 patients that evaluated the use of biomarkers or echocardiographic parameters in the management of PAH or as predictors of patient outcomes.[6,42,58,68,74-149] Of these studies, 57 were rated good quality, 21 fair quality, and 2 poor quality. Biomarkers evaluated were natriuretic peptides, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, and D-dimer. Echocardiographic parameters evaluated were right ventricular (RV) size, right atrium (RA) size, fractional area change, tricuspid annular plane systolic

excursion (TAPSE), right ventricular index of myocardial performance (RIMP), myocardial performance index (MPI), Tei index, systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressure (mPAP), tricuspid regurgitation (TR) jet, tricuspid regurgitation jet velocity/velocity-time integral right ventricular outflow tract (TRV/VTI_{RVOT}), right ventricular ejection fraction (RVEF), right ventricular systolic pressure (RVSP), and pericardial effusion. We found no studies addressing diagnostic thinking efficacy or therapeutic efficacy.

Study Characteristics

Table F-2 in Appendix F summarizes the study location, patient population, study size, sex ratio, index test, comparator, type of result reported, and the quality for each study relevant to KQ 2. Of the 75 studies that reported sex, there were a total of 2919 women and 1235 men. Of the 74 studies that reported age, 62 studies included adults,[6,58,68,74,75,78-84,86,87,90-94,96-111,114,115,117,118,120-124,127,129-135,137-142,144,146,147,149] 6 studies included children,[77,88,112,119,126,143] and 6 studies included both adults and children.[76,89,95,128,136,148] Study locations included Asia (17 studies), Europe (32), United States or Canada (23), Africa (1), Australia/New Zealand (1), South America (1), multiple geographic locations (3), and unreported or unclear setting (2).

We did not find any studies that assessed the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers as outlined in our original Key Question. Instead, we focus on available studies that evaluate the ability of echocardiography or biomarkers to assess the severity of PAH, to predict events such as lung transplantation or death, or to assess a patient's response to therapy. By evaluating the independent association of biomarkers or echocardiography, one can impute the comparative effectiveness via indirect comparison.

The most common biomarker evaluated was BNP (46 studies), followed by uric acid (6), endothelin-1 (4), troponin T (3), nitric oxide (2), cGMP (2) and ANP (1). We found no studies assessing D-dimer or asymmetric dimethylarginine to evaluate their ability to assess severity of disease, response to therapy, or outcome.

Thirty-nine studies evaluated several echocardiographic parameters. These included sPAP (15 studies), RIMP/MPI/Tei (14), RA size (10), pericardial effusion (9), FAC (8), TAPSE (6), RV size (6), mPAP (5), TR jet (3), TRV/VTI_{RVOT} (3), RVEF (2), echocardiography-derived cardiac index (2), and RVSP (2).

For the comparators, we focused on RHC hemodynamics, six-minute walk distance (6MWD), and functional class (FC) as the gold standards for assessing severity of disease. Thirty-one studies used RHC as a reference test, 13 studies used 6MWD as a reference test, and 8 studies used FC as a reference test.

Thirty-five studies looked at correlation between biomarkers and/or echocardiographic parameters and the comparators. Nineteen studies looked at hazard ratios (HR) for death, two studies looked at HR for a composite outcome of death or lung transplant, and one study looked at HR for lung transplant alone. Seventeen studies evaluated changes in mean values in response to therapy, and two studies evaluated changes in median values in response to therapy. Five studies assessed mean or median change from baseline in response to therapy.

Detailed Synthesis

Evaluation of Prognostic Value of Biomarkers and Echocardiography as Assessed by Correlation With Outcomes With Known Prognostic Ability

Table G-1 in Appendix G outlines the 35 studies that reported the correlation between a biomarker or echocardiographic parameter result and a hemodynamic or clinical outcome. The included studies consisted of a total of 983 patients. Of studies with adults reporting age, the mean age ranged from 37 to 64 years. Two studies evaluating children reported a median age range of 7.0 to 9.3 years. The following were the most common comparisons encountered in the studies and included in our analysis:

- BNP versus RHC-mPAP (13 studies, 559 patients)
- BNP versus RHC-PVR (12 studies, 638 patients)
- BNP versus RHC-RAP (11 studies, 600 patients)
- BNP versus 6MWD (8 studies, 396 patients)
- BNP versus RHC-CI (9 studies, 509 patients)
- Echocardiography-derived sPAP versus RHC-sPAP (8 studies, 302 patients)
- BNP versus PCWP (5 studies, 319 patients)

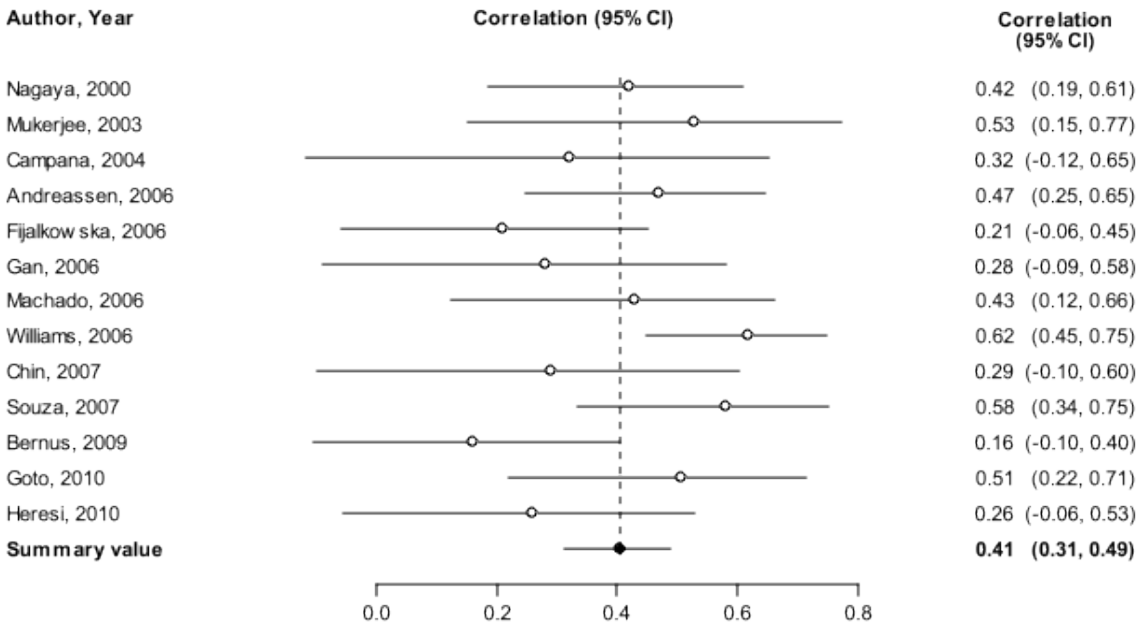
Meta-analysis of Correlation Studies

There appeared to be excessive heterogeneity in correlations that seemed to be explained by temporal differences between noninvasive assessment and outcome measures, whether hemodynamic at RHC or functional assessment. Therefore, we decided to limit our meta-analysis of correlation studies to those assessing correlation between baseline values at a given time. We did not include studies that correlated change in values between two tests due to the small number of these studies. To improve the robustness of the results, we also limited our meta-analysis to those comparisons that were evaluated in at least four studies.

Figure 9 shows the forest plot of the correlation between BNP and RHC-mPAP from 13 studies (559 patients) with values ranging from 0.16 to 0.62. The summary correlation coefficient is 0.41 (95% CI, 0.31 to 0.49), indicating moderate correlation between the two tests. There is evidence of moderate heterogeneity, with a Q-value of 17.7 for 12 degrees of freedom, I^2=32.4%, p=0.12. In these studies, heterogeneity was introduced in part by different study populations. While all studies evaluated patients with PAH, there was a variety of etiologies included with some studies evaluating a specific etiology[42,68,125,129,138] and others assessing a mixture of PAH etiologies.[74,77,83,85,92,97,100,105] In addition, the Bernus study[77] focused on a pediatric population while the others focused on adult populations. Further, studies evaluated different BNP measurements, which may add to heterogeneity. Some studies report results for BNP[77,83,85,100,105,125] and others report results for NT-proBNP.[42,68,74,92,97,129,138] Some studies report log-transformed values[68,77,83,92,125,129,138] and others report non–log-transformed values.[42,74,85,97,100,105] Most studies included patients on a variety of PAH treatments while the Chin study focused on patients treated with epoprostenol.[85] The strength of evidence is moderate

based on most studies with low risk of bias having consistent results of an indirect outcome and precise estimates.

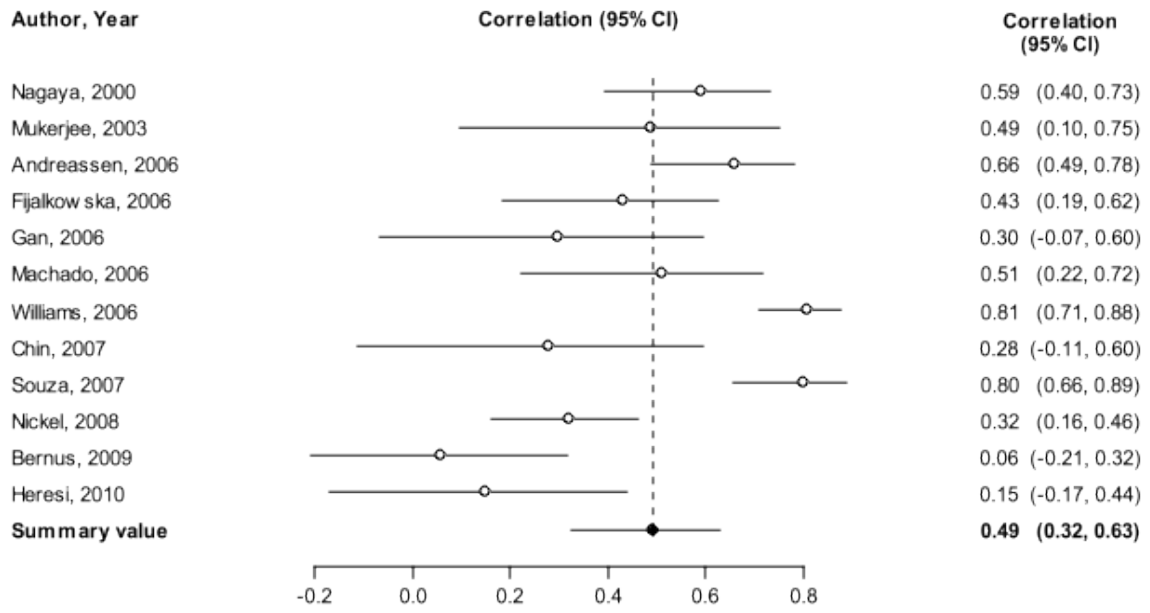
Figure 9. Forest plot for correlation between BNP and RHC-mPAP



Abbreviation: CI=confidence interval

Figure 10 shows the forest plot of the correlation between BNP and RHC-PVR from 12 studies (638 patients) with values ranging from 0.06 to 081. The summary correlation coefficient is 0.49 (95% CI, 0.32 to 0.63), indicating moderate correlation between the two tests. There is evidence of high heterogeneity, with a Q-value of 66.3 for 11 degrees of freedom, I^2=83.4%, p<0.001. In these studies, heterogeneity was also introduced by different study populations with some studies evaluating a specific etiology[42,68,129,134,138,150] and others assessing a mixture of PAH etiologies.[74,77,85,92,97,105] In addition, the Bernus study[77] focused on a pediatric population while the others focused on adult populations. As with the above comparison, studies evaluated different biomarker measurements. Some studies report results for BNP[77,85,105,125] and others report results for NT-proBNP.[42,68,74,92,97,129,134,138] Some studies report log-transformed values[68,77,92,125,129,134,138] and others report non–log-transformed values.[42,74,85,97,105] Further, two studies (Bernus and Gan) reported PVR as an index value[77,97] while the remainder reported absolute PVR value. The strength of evidence is low based on most studies having low risk of bias and studies having inconsistent results of an indirect outcome and precise estimates.

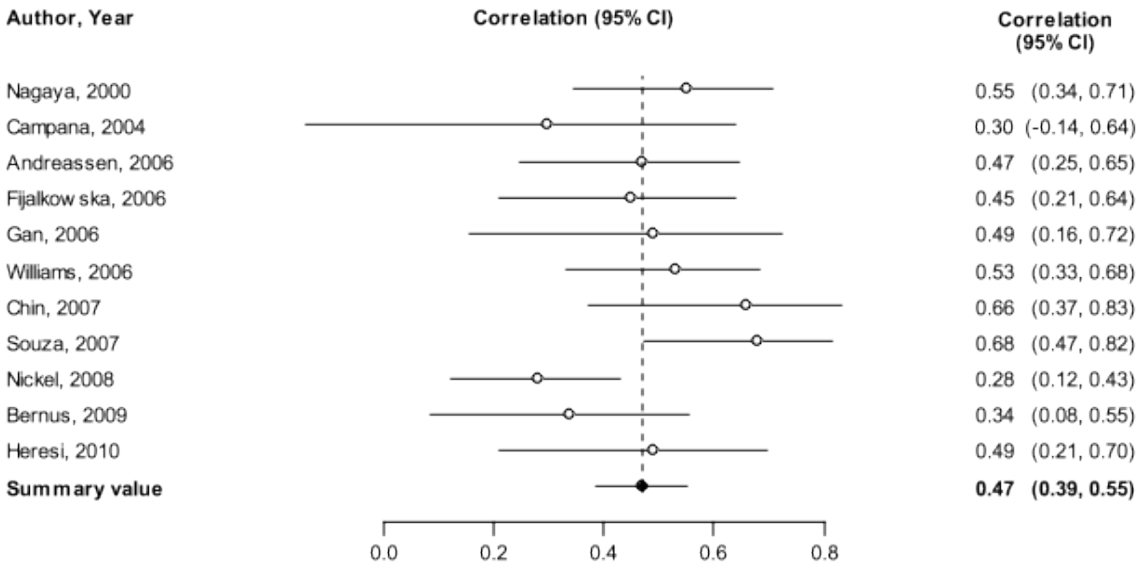
Figure 10. Forest plot for correlation between BNP and RHC-PVR



Abbreviation: CI=confidence interval

Figure 11 shows the forest plot of the correlation between BNP and RHC-RAP from 11 studies (600 patients) with values ranging from 0.28 to 0.68. The summary correlation coefficient is 0.47 (95% CI, 0.39 to 0.55), indicating moderate correlation between the two tests. There is evidence of moderate heterogeneity, with a Q-value of 15.4 for 10 degrees of freedom, I^2=35.2%, p=0.12. In these studies heterogeneity was again introduced by different study populations with a focus on specific PAH etiology in some studies[68,125,134,138] and others evaluating a mixture of PAH etiologies.[74,77,83,85,97,105,151] As with the previous comparisons, one study[77] focused on a pediatric population while the others focused on adult populations. Also as before, studies evaluated different biomarker measurements with some studies report results for BNP[77,83,85,105,125] and others report results for NT-proBNP.[68,74,92,97,134,138] Some studies report log-transformed values,[68,77,83,92,125,134,138] and others report non–log-transformed values.[74,85,97,105] The strength of evidence is moderate based on studies with low risk of bias and studies having consistent results of an indirect outcome and precise estimates.

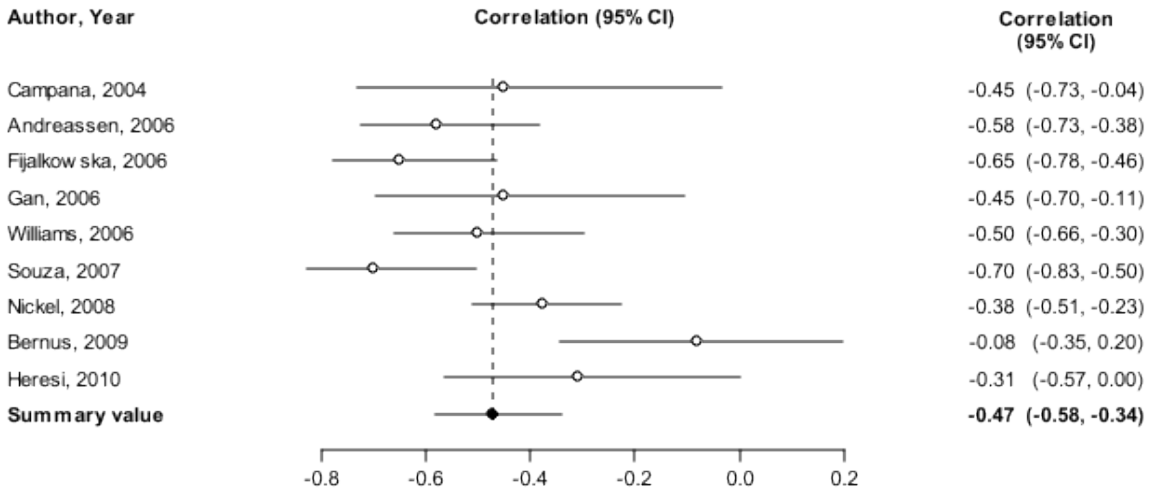
Figure 11. Forest plot for correlation between BNP and RHC-RAP



Abbreviation: CI=confidence interval

Figure 12 shows the forest plot of the correlation between BNP and RHC-CI from 9 studies (509 patients) with values ranging from -0.70 to -0.08. The summary correlation coefficient is -0.47 (95% CI, -0.58 to -0.34), indicating negative moderate correlation between the two tests. There is evidence of moderate heterogeneity, with a Q-value of 22.2 for 8 degrees of freedom, I^2=63.9%, p=0.005. Again, heterogeneity was likely introduced by different study populations. While all studies evaluated patients with PAH, there was a variety of etiologies included with some studies looking at a specific etiology,[68,134,138] and others looking at a mixture of PAH etiologies.[74,77,83,92,97,105] The Bernus study[77] focused on a pediatric population while the others focused on adult populations. Further, studies evaluated different biomarker measurements. Some studies report results for BNP[77,83,105] and others report results for NT-proBNP,[68,74,92,97,134,138] some studies report log-transformed values,[68,77,83,92,134,138] and others report non–log-transformed values.[74,97,105] The strength of evidence is low based on most studies having low risk of bias and studies having inconsistent results of an indirect outcome and precise estimates.

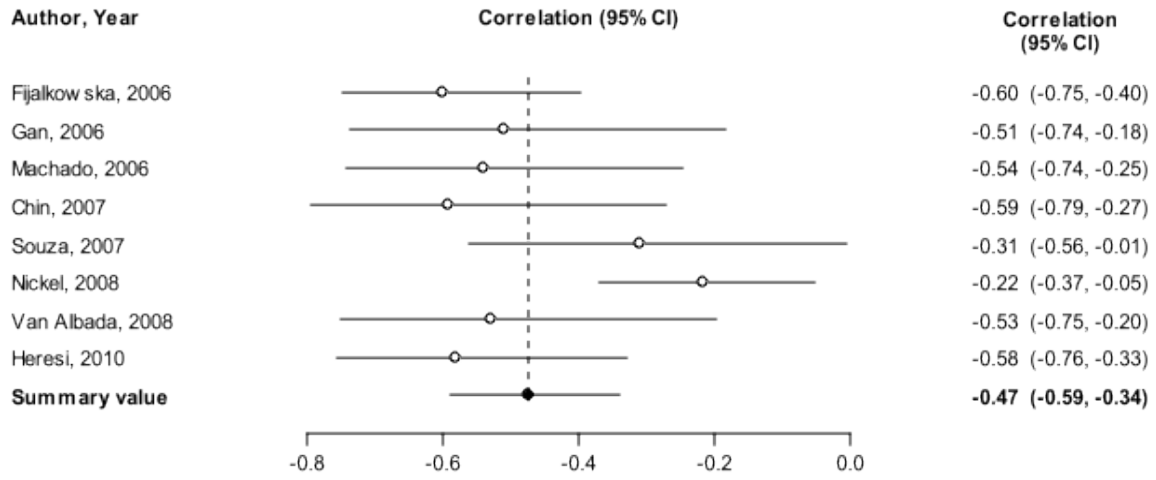
Figure 12. Forest plot for correlation between BNP and RHC-CI



Abbreviation: CI=confidence interval

Figure 13 shows the forest plot of the correlation between BNP and 6MWD from 8 studies (396 patients) with values ranging from -0.60 to -0.22. The summary correlation coefficient is -0.47 (95% CI, -0.59 to -0.34), indicating negative moderate correlation between the two tests. There is evidence of moderate heterogeneity, with a Q-value of 15.4 for 7 degrees of freedom, I^2=54.4%, p=0.032. The above studies included those that focused on a certain etiology of PAH[42,134,138] or a mixture of PAH etiologies.[85,92,97,105,143] The Van Albada study[143] focused on a pediatric population while the others focused on adult populations. Studies evaluated different biomarker measurements. Some studies report results for BNP[85,105] and others report results for NT-proBNP[42,92,97,134,138,143] some studies report log-transformed values[92,134,138,143] and others report non–log-transformed values[42,85,97,105] The strength of evidence is low based on most studies with low risk of bias and studies having inconsistent results of a direct outcome and precise estimates.

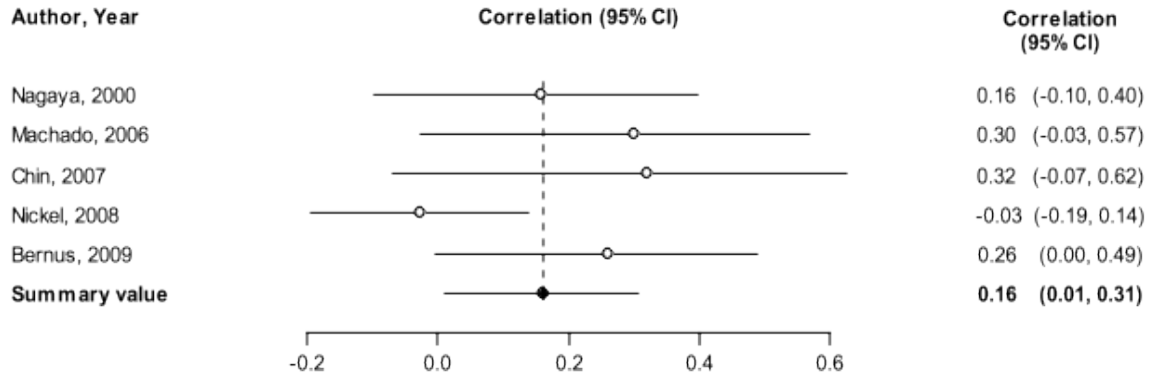
Figure 13. Forest plot for correlation between BNP and 6MWD



Abbreviation: CI=confidence interval

Figure 14 shows the forest plot of the correlation between BNP and RHC-PCWP from 5 studies (319 patients) with values ranging from -0.03 to 0.32. The summary correlation coefficient is 0.16 (95% CI, 0.01 to 0.31), indicating low correlation between the two tests. There is evidence of moderate heterogeneity, with a Q-value of 6.5 for 4 degrees of freedom, I^2=38.0%, p= 0.17. Heterogeneity in this group of studies was also introduced by differing populations with some studies looking at populations with a specific etiology of PAH[42,134] some looking at populations with a mixture of PAH etiologies,[125, 369, 595] and the Bernus study[77] focused on a pediatric population. Studies evaluated different BNP values with some studies reporting results for BNP[77,85,125] and others report results for NT-proBNP[42,134] Some studies report log-transformed values[77,125,134] and others report non–log-transformed values[42,85] There is not enough information in the Rhodes study[134] regarding how variables were measured to adequately explain why this study found a negative correlation between the two markers. The strength of evidence is low based on most studies having low risk of bias and studies having consistent results of an indirect outcome and imprecise estimates.

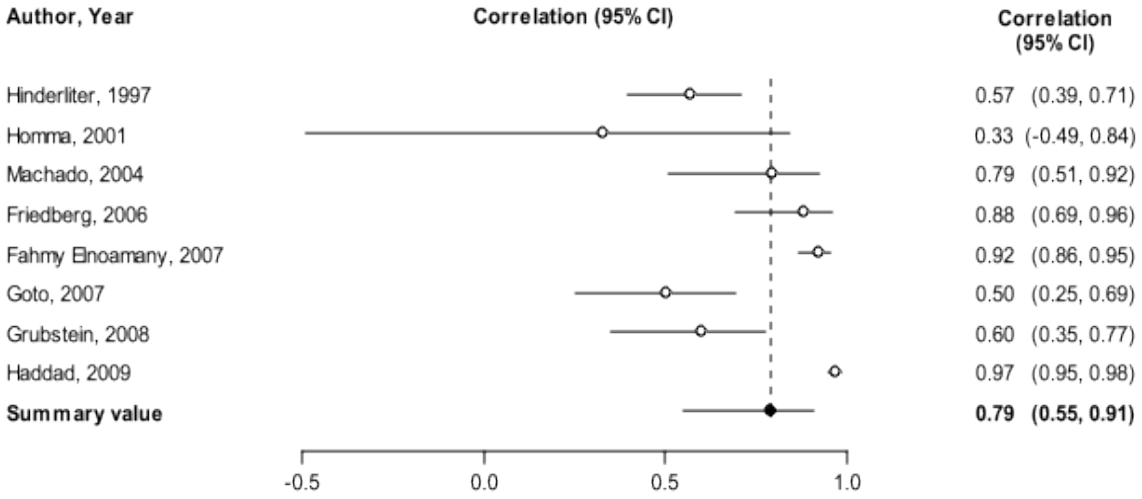
Figure 14. Forest plot for correlation between BNP and RHC-PCWP



Abbreviation: CI=confidence interval

Figure 15 shows the forest plot of the correlation between echocardiography-derived sPAP and RHC-sPAP from 8 studies (302 patients) with values ranging from 0.33 to 0.97. The summary correlation coefficient is 0.79 (95% CI, 0.55 to 0.91), indicating high correlation between the two tests. There is evidence of high heterogeneity, with a Q-value of 93.5 for 7 degrees of freedom, I^2=92.5%, p<0.001. These studies used a variety of methods to estimate sPAP by echocardiography including Bernoulli equation without correction[90,95,116,152] Bernoulli equation plus estimated RAP,[100] Bernoulli equation plus a fixed value for RAP,[106,108] and one study which did not report how sPAP was estimated. In addition, there was variability in timing between the catheterization study and the echocardiography study. In three studies it appears that right heart catheterization and echocardiography were done during the initial evaluation.[103,106,108] In one study the tests were done within 30 days of each other[95] and in another were done within 4 to 9 months of each other.[116] Two studies were retrospective chart reviews which evaluated the most recent catheterization or echocardiography results[100,102] and one prospective study did not specify a time frame between the tests.[92] Most studies included patients with a wide range of disease severity, but the Homma study focused only on patients undergoing evaluation for lung transplantation.[108] The strength of evidence is low based on most studies having low risk of bias and studies having inconsistent results of an indirect outcome and precise estimates.

Figure 15. Forest plot for correlation between echocardiography-sPAP and RHC-sPAP



Abbreviation: CI=confidence interval

Evaluation of Predictive Value of Biomarkers and Echocardiography as Assessed by Hazard Ratios

Table 16 summarizes the 21 studies that reported the association between a biomarker or echocardiographic parameter and a future clinical outcome in the form of a hazard ratio. Studies evaluating a hazard ratio consisted of 4287 patients, with a female-to-male ratio of 1149 to 422 in those studies reporting sex. Mean age ranged from 33 to 61 years. Included studies evaluated hazard ratios for the following outcomes:

Mortality (19 studies with 15 studies reporting mean duration of 2 years; 2 studies reporting median duration of 2 years) evaluating BNP (12 studies), pericardial effusion (7), RA size (5), FAC (5), RIMP/MPI/Tei index (5), TAPSE (4), RV size (2), troponin T (2), peak TRV (2), uric acid (1), mPAP (1), sPAP (1), ANP (1).

- Composite outcome of death or lung transplantation (2 studies with one reporting median duration of 4 years and the other reporting mean duration of 3 years) evaluating BNP (1 study), RA size (1), uric acid (1), peak TRV (1), pericardial effusion (1), FAC (1), RV size (1)

- Lung transplantation (one study with mean duration of 2 years) evaluating RA size

Table 16. Hazard ratio table for KQ 2

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N	Result	95% CI	p-value
Benza, 2010[6] Adults with PAH N=2716 Good	Mean 50.4 (SD 16.8)	Mean followup ~18 mo	Pericardial effusion	Mortality	2105	1.35		0.014
Brierre, 2010[80] Adults with PAH N=79 Good	Median 61.4 (IQR 46.0 to 74.1)	Mean duration 12 mo	mPAP	Mortality	79	3.94	1.34 to 11.5	0.012
			Pericardial effusion	Mortality	79	5.18	1.85 to 14.5	0.002
			RIMP/MPI/ Tei Index	Mortality	79	5.41	1.12 to 26.1	0.035
			TAPSE	Mortality	79	0.84	0.72 to 0.98	0.024
Bustamante-Labarta, 2002[81] Adults with PPH N=25 Good	Mean 37.6 (SD 12.7)	Mean followup 29 mo	RA size (RA area)	Transplant (survival from)	25	1.1		0.0004
Fijalkowska, 2006[92] Adults with PH N=55 Good	Mean 41 (SD 15.1)	Mean followup 770 ± 336 days	FAC	Mortality	55	0.98	0.93 to 1.03	NS
			BNP	Mortality	55	3.0	1.45 to 6.18	0.002
			Pericardial effusion	Mortality	55	3.8	1.46 to 9.93	0.006
			RA size (RA area)	Mortality	55	1.02	0.97 to 1.07	NS
			RIMP/MPI/ Tei index	Mortality	55	1.01	0.34 to 3.01	NS
			RV size (RV diameter)	Mortality	55	1.08	0.99 to 1.17	NS
			cTnT (detectable)	Mortality	55	4.5	1.56 to 12.92	0.005

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N	Result	95% CI	p-value
Forfia, 2006[94] Adults with PH N=63 Good	Mean 55 (SD 15)	Mean followup 19.3 mo	TAPSE	Mortality	63	1.17	1.04 to 1.32	0.006
Ghio, 2010[98] Adults with IPAH N=59 Good	Mean 46.4 (SD 16.1)	Mean followup 52 mo	FAC	Mortality	59	0.004	0.02 to 0.62	0.025
			Pericardial effusion	Mortality	59	0.79	0.18 to 3.4	0.75
			RIMP/MPI/ Tei Index	Mortality	59	2.61	0.52 to 13.03	0.26
			sPAP (transtricuspid gradient)	Mortality	59	0.99	0.98 to 1.02	0.92
			TAPSE	Mortality	59	0.91	0.83 to 0.99	0.026
Hampole, 2009[104] Adults with PH N=162 Good	Mean 53 (SD 15)	Mean followup 2.1 ± 0.8 yr	BNP (log)	Mortality	162	1.62	1.01 to 2.60	0.044
Heresi, 2010[105] Adults with PPH N=40 Good	Mean 44 (SD 14)	23.5 ± 13.5 mo	BNP	Mortality	40	1.20	0.11 to 13.28	0.88

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N	Result	95% CI	p-value
Lorenzen, 2011[115] Adults with PAH N=70 Good	Mean 42 (IQR 48 to 59)	3 mo	BNP (ln)	Mortality	25	1.9	1.2 to 2.9	<0.001
			Uric acid	Mortality	25	1.9	1.5 to 2.6	<0.001
Machado, 2006[42] Patients with sickle cell disease N=230 Poor	Median 33 (IQR 27 to 44)	Median followup 31 mo	BNP (log)	Mortality	230	2.1	1.4 to 2.9	<0.001
Mahapatra, 2006[117] Adults with PH N=54 Fair	Mean 52 (SD 11)	250 person yr	RIMP/MPI/Tei Index	Mortality	54	1.66	1.05 to 2.6	0.04
Mathai, 2011[118] Adults with known or suspected PAH N=50 Fair	Mean 61 (SD 11)	Median followup 15.7 mo	FAC (RVFAC)	Mortality	50	0.99	0.95 to 1.03	0.47
			Peak TRV	Mortality	50	0.58	0.31 to 1.10	0.10
			Pericardial effusion	Mortality	50	1.11	0.75 to 1.64	0.59
			RA size (RA area indexed)	Mortality	50	1.11	1.02 to 1.19	0.01
			TAPSE	Mortality	50	0.87	0.78 to 0.96	<0.01
Nagaya, 2000[125] Patients with PPH N=60 Good	Mean 38 (Range 15 to 69)	Mean followup 24 ± 2 mo	BNP	Mortality	60	6.983	1.923 to 23.357	0.0031
			BNP (log)	Mortality	53	29.310	5.294 to 162.275	0.0001
			ANP (log)	Mortality	53	19.676	3.834 to 100.978	0.0004
			ANP	Mortality	60	4.641	1.347 to 15.986	0.0150

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N	Result	95% CI	p-value
Nickel, 2008[130] Adults with IPAH N=76 Fair	Mean 52 (Range 44 to 63)	Median followup 48 mo	BNP (ln)	Composite outcome (Death or lung transplant)	76	2.62	1.78 to 3.86	<0.001
			Uric acid	Composite outcome (Death or lung transplant)	76	1.56	1.27 to 1.96	<0.001
Raymond, 2002[133] Adults with PPH N=81 Fair	Mean 40 (SD 15)	Mean followup 36.9 ± 15.4 mo	FAC	Composite outcome (Death or lung transplant)	81	0.86	0.57 to 1.28	0.454
			FAC	Mortality	81	0.70	0.39 to 1.25	0.225
			Peak TRV	Composite outcome (Death or lung transplant)	81	1.00	0.77 to 1.30	0.981
			Peak TRV	Mortality	81	0.90	0.62 to 1.31	0.591
			Pericardial effusion	Composite outcome (Death or lung transplant)	81	2.08	1.12 to 3.86	0.017
			Pericardial effusion	Mortality	81	3.89	1.49 to 10.14	0.003
			RA size (RA area indexed)	Composite outcome (Death or lung transplant)	81	1.33	1.06 to 1.66	0.012
			RA size (RA area indexed)	Mortality	81	1.54	1.13 to 2.10	0.005

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N	Result	95% CI	p-value
			RV size (RVED area index)	Composite outcome (Death or lung transplant)	81	1.26	0.95 to 1.66	0.110
			RV size (RVED area index)	Mortality	81	1.34	0.90 to 1.98	0.148
Rhodes, 2011[134] Adults with IPAH N=139 Good	Mean 47.6 (SD 15.8)	2 yr	BNP (square root)	Mortality	139	1.038	1.018 to 1.058	<0.001
Takeda, 2010[139] Adults with PAH N=37 Good	Mean 49 (SD 18)	635 ± 510 days	BNP (log)	Mortality	37	2.79	1.55 to 5.04	0.001
Torbicki, 2003[140] Adults with PAH N=56 Good	Mean 41 (SD 15)	Mean followup 17 ± 8.5 mo	FAC	Mortality	56	0.999	0.94 to 1.06	0.96
			BNP	Mortality	56	1.84	0.89 to 5.45	0.32
			Pericardial effusion	Mortality	56	2.77	0.89 to 8.59	0.08
			RA size (RA area)	Mortality	56	1.03	0.97 to 1.09	0.39
			cTnT (detectable)	Mortality	56	5.47	1.62 to 18.46	0.003
Utsunomiya, 2011[141] Adults with chronic PH	Mean 46 (SD 13)		BNP	Mortality	50			0.006
			RA size (RA end systolic area indexed)	Mortality	50			0.005

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N	Result	95% CI	p-value
N=50 Good			RIMP/MPI/ Tei index	Mortality	50			0.005
Williams, 2006[68] Adults with systemic sclerosis N=109 Fair	Mean 60 (SD 10)	1 yr	BNP (10-fold increase FROM baseline)	Mortality	68	3.82	1.46 to 9.96	0.006
			BNP (10-fold increase IN baseline)	Mortality	68	4.82	1.29 to 18.05	0.002
Yanagisawa, 2012[149] Adults with PAH N=46 Good	Mean 42 (SD 14)	44 ± 26 mo	BNP	Mortality	46	1.00	0.99 to 1.00	NS

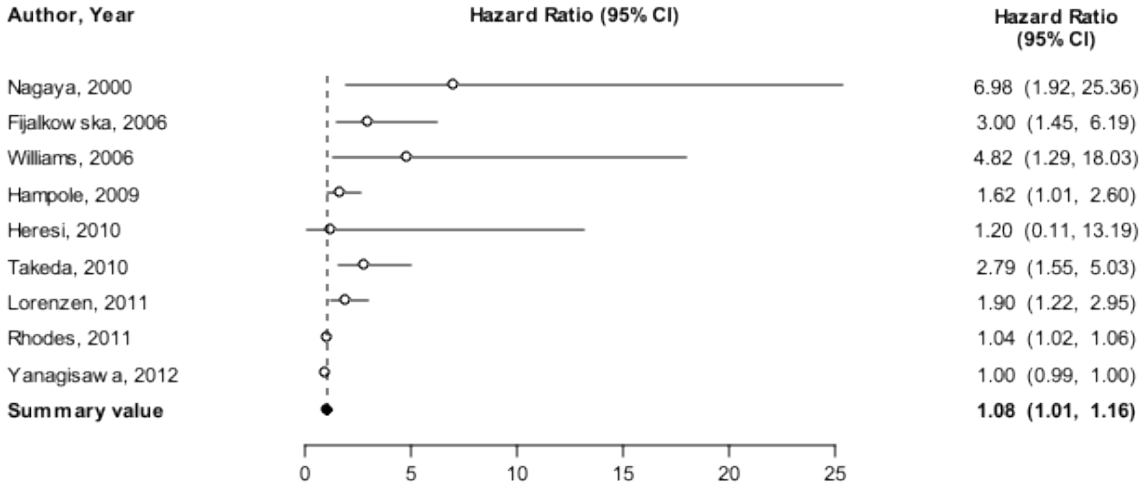
Abbreviations: ANP=A-type natriuretic peptide; BNP=B-type natriuretic peptide ; CO=cardiac output; cTnT=cardiac troponin T; CVD=collagen vascular disease; FAC=fractional area change; IQR=interquartile range; mPAP=mean pulmonary artery pressure; mo=month/months; MPI=myocardial performance index; NR=not reported; PVR=pulmonary vascular resistance; RA=right atrium; RIMP=right index of myocardial performance; RV=right ventricle; SD=standard deviation; SEM=standard error of the mean; sPAP=systolic pulmonary artery pressure; TAPSE=tricuspid annular plane systolic excursion; TRV=tricuspid regurgitant jet velocity; yr=year/years

Meta-analysis of Hazard Ratio Studies

There were too few studies to permit a meta-analysis assessing hazard ratios for a composite outcome. Our analysis focused on those studies that evaluated biomarkers or echocardiographic parameters as predictors of mortality. To improve the robustness of the analysis, we included only index tests that were evaluated in at least four different studies. We also concentrated on univariate hazard ratios as each study that created a multivariate model adjusted for different variables.

Figure 16 shows the forest plot of the hazard ratio for BNP and mortality from 9 studies (632 patients) with values ranging from 1.0 to 6.98. The summary hazard ratio is 1.08 (95% CI, 1.01 to 1.16), indicating that changes in BNP were not associated with mortality. There is evidence of high heterogeneity, with a Q-value of 64.6 for 8 degrees of freedom, I^2=87.6%, p<0.001. Heterogeneity in these studies is likely influenced by the same factors as in the correlation comparisons involving BNP. Studies differed in study population with some looking at populations with a specific etiology for PAH[68,115,134] and others looking at mixed populations[92,104,105,125,139,149] Studies looked at either BNP[105,125,139,149] or NT-proBNP[68,92,104,115,134] One study[68] compared 10-fold increase in BNP level with 5-fold increase in mortality which may explain why this study differs significantly from the overall summary estimate. We could find no obvious reason to explain why the results of the Nagaya study[125] differed so substantially from the overall summary estimate. The strength of evidence is high based on most studies having low risk of bias and studies having consistent results of a direct outcome and precise estimates.

Figure 16. Forest plot for hazard ratio for BNP and mortality

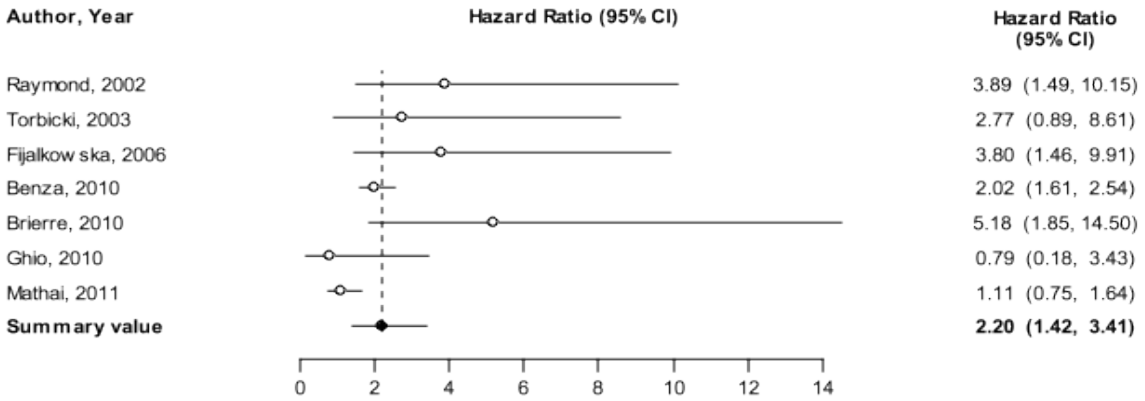


Abbreviation: CI=confidence interval

Figure 17 shows the forest plot of the hazard ratio for pericardial effusion and mortality from 7 studies (2485 patients) with values ranging from 0.79 to 3.89. The summary hazard ratio is 2.20 (95% CI, 1.42 to 3.41), indicating that the presence of pericardial effusion is associated with higher mortality. There is evidence of moderate heterogeneity, with a Q-value of 13.4 for 5 degrees of freedom, I^2=62.6%, p=0.02. The two studies that reported an effect estimate smaller than the summary estimate[98,118] reported the pericardial effusion value as a combined value incorporating both presence and grade or severity. The other four studies reported only presence

of effusion. The strength of evidence is moderate based on most studies having low risk of bias and studies having inconsistent results of a direct outcome and imprecise estimates.

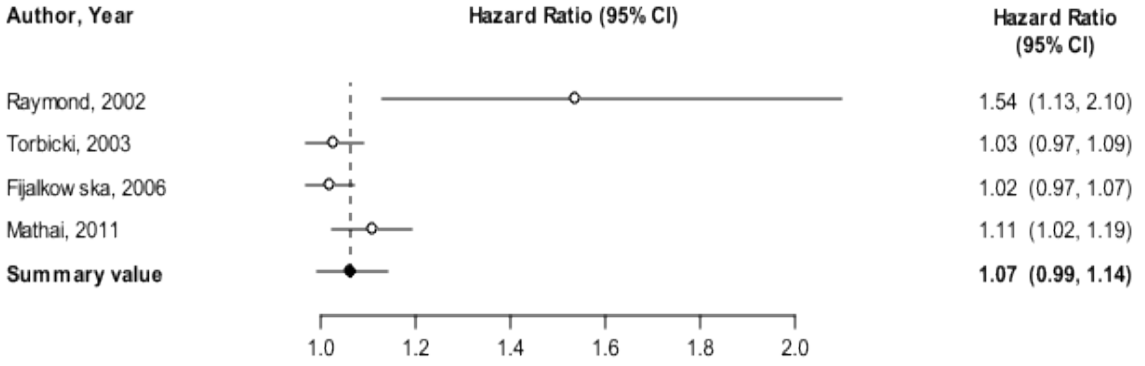
Figure 17. Forest plot for hazard ratio for pericardial effusion and mortality



Abbreviation: CI=confidence interval

Figure 18 shows the forest plot of the hazard ratio for RA size and mortality from 4 studies (242 patients) with values ranging from 1.02 to 1.54. The summary hazard ratio is 1.07 (95% CI, 0.99 to 1.14), indicating that changes in RA size had no influence on mortality. There is evidence of moderate heterogeneity, with a Q-value of 9.3 for 3 degrees of freedom, I^2=67.7%, p=0.026. It is unclear why the Raymond study[133] reports such disparate results as compared with the other three studies. This study does report RA area indexed to patient height, but the Mathai study[118] reports this value in the same way. We could find no other significant differences in the studies to explain the heterogeneity. The strength of evidence is low based on two studies having low risk of bias and two studies having moderate risk of bias and studies having inconsistent results of a direct outcome and imprecise estimates.

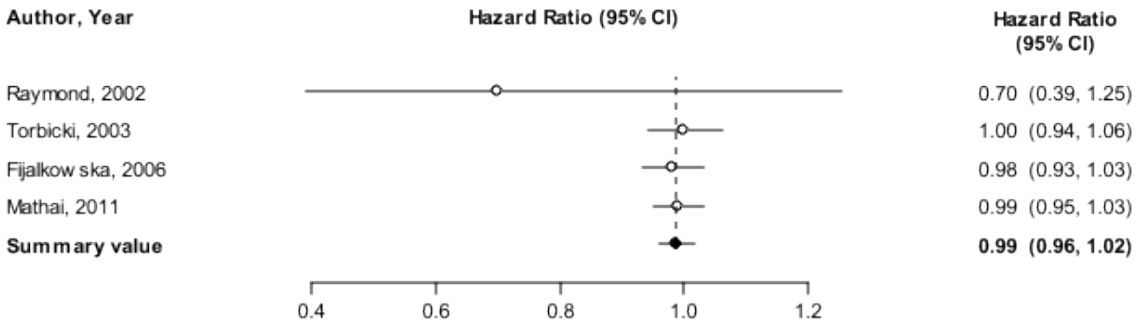
Figure 18. Forest plot for hazard ratio for RA size and mortality



Abbreviation: CI=confidence interval

Figure 19 shows the forest plot of the hazard ratio for FAC and mortality from 4 studies (242 patients) with values ranging from 0.7 to 1.0. The summary hazard ratio is 0.99 (95% CI, 0.96 to 1.02), indicating that changes in FAC had no relationship to mortality. There is evidence of low heterogeneity, with a Q-value of 1.6 for 3 degrees of freedom, I^2=0, p= 0.66. Again, we were unable to determine why the Raymond study[133] showed such disparate results from the other studies. The strength of evidence is high based on studies having low risk of bias and studies having consistent results of a direct outcome and precise estimates.

Figure 19. Forest plot for hazard ratio for FAC and mortality



Abbreviation: CI=confidence interval

Evaluation of Responsiveness of Biomarkers and Echocardiography as Assessed by Changes in Mean or Median Levels in Response to Treatment

In our review, we focused only on those studies that measured mean or median values for biomarkers or echocardiographic parameters measured at two or more different time points or reported as a change from baseline to evaluate whether changes in these measures could serve as a potential surrogate marker for response to therapy. Tables 17–19 show means, medians, and changes in either mean or median from baseline.

- Seventeen studies including 872 patients evaluated changes in mean values in response to therapy for a subset of 758 patients evaluating BNP (9 studies), sPAP (4), RIMP/MPI/Tei index (3), RV size (2), TRV (2), TAPSE (1), FAC (1), nitric oxide (1), endothelin-1 (1) and RA size (1).
- Two studies with a total of 16 patients evaluated changes in median in response to therapy evaluating BNP (2 studies), RIMP/MPI/Tei index (1), sPAP (1), FAC (1), RVEF (1).
- Five studies with a total 455 patients looked at mean or median change from baseline in response to therapy for a subset of 197 patients evaluating BNP (2 studies), RV size (2), mPAP (2), FAC (1), TRV (1), RIMP/MPI/Tei index (1), RA size (1) and cardiac index (1).

- Response to therapy was evaluated for the following drugs: ambrisentan (2 studies), bosentan (9), epoprostenol (9), iloprost (1), sildenafil (1), tadalafil (1), and treprostinil (2).

Due to the small number and heterogeneity of these studies in regard to index test and type of therapy, we were unable to perform meta-analysis on this data. While a few studies found changes in biomarkers or echocardiographic parameters in response to various treatments, there was insufficient data to quantitatively assess overall response or to recommend use of these markers as surrogate outcomes measures.

Of the nine studies that assessed mean values of BNP in response to various therapies (prostanoids, sildenafil, ambrisentan, bosentan, or "standard therapy"), all showed a decrease in BNP levels by approximately half after 3 to 6 months of therapy (Table 17).[83,86,96,109,114,120,123,126] Studies with longer followup times showed that the lower BNP levels remained stable throughout the course of followup.[83,109,126]

Three of the four studies assessing changes in mean sPAP showed decreased values in response to tadalafil after 1 month of followup[78] or epoprostenol after 6 to 24 months of followup.[127,136] One study showed no change in mean sPAP levels for unspecified monotherapy after 18 month followup or combination therapy after 12 months of followup.[111]

In three studies, mean RIMP/MPI/Tei index did not change appreciably over time following treatment with bosentan/iloprost[91] or epoprostenol[127,136] after 5 to 23 months of followup. Two studies showed no change in mean RV size after treatment with epoprostenol for 15 to 23 months of followup.[83,127] Mean TRV decreased slightly in one study after 22 months of treatment with epoprostenol.[127] Another study showed no change in mean TRV over 6 months of treatment with either bosentan or ambrisentan.[123] There was a slight decrease in mean TAPSE value following 15 months of epoprostenol therapy in one study.[83] Separate studies showed no change in mean levels of endothelin-1,[113] FAC,[83] or RA size[128] in response to epoprostenol after 3 months, 15 months, and 24 months followup respectively. In one study, mean nitric oxide level decreased significantly over 1 year of treatment with bosentan.[82]

Table 17. Mean table for KQ 2

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical scenario
Bharani, 2007[78] Adults and children with suspected or symptomatic PAH N=8 Fair	Mean 28 (SD 9.38)	Baseline	sPAP	8	114.12	SD 23.14	Response to tadalafil
		1 mo	sPAP	8	88.75	SD 23.26	Response to tadalafil
Campana, 2004[83] Adults with pre-capillary PH N=22 Good	Mean 50 (SD 11)	Baseline	FAC	22	0.26	SD 0.10	Response to epoprostenol
		Mean followup 15 ± 4 mo	FAC	22	0.23	SD 0.08 p=0.8	Response to epoprostenol
		Baseline	BNP	22	246	SD 162	Response to epoprostenol
		Mean followup 15 ± 4 mo	BNP	22	256	SD 180 p=0.9	Response to epoprostenol
		Baseline	RV size (RV end diastolic diameter)	22	36	SD 7.5	Response to epoprostenol
		Mean followup 15 ± 4 mo	RV size (RV end diastolic diameter)	22	39	SD 7.3 p=0.09	Response to epoprostenol
		Baseline	TAPSE	22	17.3	SD 4.4	Response to epoprostenol
		Mean followup 15 ± 4 mo	TAPSE	22	15.2	SD 4.4 p=0.04	Response to epoprostenol
Cella, 2009[82] Adults with PAH associated with CTD N=18 Good	Mean 53.8 (SD 13.1)	Baseline	Nitric oxide	18	24.05	SD 6.04	Response to bosentan
		1 yr	Nitric oxide	18	13.92	SD 3.40 p<0.001	Response to bosentan

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical scenario
D'Alto, 2010[86] Adults with PAH due to CHD N=32 Fair	Mean 37.1 (SD 13.7)	Baseline	BNP	32	760	SD 943	Response to bosentan + sildenafil
		6 mo	BNP	32	303	SD 366 p=0.008	Response to bosentan + sildenafil
Feliciano, 2004[91] Adults with severe PAH N=11 Good	Mean 42 (SD 18)	Baseline	RIMP/MPI/Tei index	11	0.8	SD 0.6	Bosentan or iloprost
		11.3 ± 7.9 mo	RIMP/MPI/Tei index	11	0.7	SD 0.4 p=0.02 (compared with baseline)	Bosentan or iloprost
Galie, 2008[96] Adults with PAH N=201 Good	NR	Baseline	BNP	394	122.92	95% CI 93.30 to 160.82	Response to ambrisentan 5mg (Aries I)
		12 wk	BNP	394	85.75	95% CI 66.01 to 111.23	Response to ambrisentan 5mg (Aries I)
		Baseline	BNP	394	132.07	95% CI 89.72 to 193.86	Response to ambrisentan10 mg (Aries I)
		12 wk	BNP	394	72.29	95% CI 53.50 to 98.72	Response to ambrisentan10 mg (Aries I)
		Baseline	BNP	394	129.94	95% CI 89.49 to 188.22	Response to ambrisentan 2.5mg (Aries II)
		12 wk	BNP	394	92.68	95% CI 69.43 to 124.84	Response to ambrisentan 2.5mg (Aries II)
		Baseline	BNP	394	89.81	95% CI 58.92 to 137.58	Response to ambrisentan 5mg (Aries II)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical scenario
		12 wk	BNP	394	62.74	95% CI 42.36 to 93.63	Response to ambrisentan 5mg (Aries II)
Jacobs, 2009[109] Adults with idiopathic PAH N=16 Fair	Mean 37.0 (SD 2.8)	Baseline	BNP	11	2830	SEM 818	Response to prostanoids
		Mean followup 37.0 ± 4.4 mo	BNP	11	1574	SEM 447 p=0.049	Response to prostanoids
Keogh, 2011[111] Adults with PAH N=112 Fair	Mean 51.4 (SD 17.8)	Baseline (at start of monotherapy)	sPAP	101	83	SD 23	Response to monotherapy
		Mean followup 18.7 ± 13.4 mo on monotherapy	sPAP	103	86	SD 25	Response to monotherapy
		1 yr after starting combination therapy	sPAP	112	77	SD 22	Response to combo therapy
Knirsch, 2011[119] Children with heart disease N=103 Good	Mean 6.4 (SD 5.2)	Baseline	BNP	4	980.5	SD 994.9	Before treatment in patients with IPAH
		Baseline	BNP	6	665.2	SD 1371	Before treatment in patients with PAH 2/2 CHD
		No followup time specified	BNP	8	25.6	SD 13.2 p<0.05	Response to standardized protocol in patients with IPAH
		No followup time specified	BNP	15	152.9	SD 224.4 p<0.05	Response to standardized protocol in patients with PAH 2/2 CHD

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical scenario
Langleben, 1999[113] Patients with PPH N=18 Good	NR	Baseline	Endothelin-1	11	1.62	SEM 0.35	Response to epoprostenol
		3 mo	Endothelin-1	11	1.84	SEM 0.41	Response to epoprostenol
Leuchte, 2005[114] Adults with PAH N=30 Good	Mean 46.93 (SEM 2.8)	Baseline	BNP	30	45.51	SEM 7.52	Comparison to therapy (nonspecific)
		Mean followup 12.6 ± 1.5 mo	BNP	30	58.2	SEM 11.4	Comparison to therapy (nonspecific)
Minniti, 2009[123] Adults with SCD and PH N=14 Poor	Mean 48.9	Baseline	BNP	14	407	SD 172	Response to bosentan or ambrisentan
		2 mo	BNP	14	286	SD 63	Response to bosentan or ambrisentan
		3 mo	BNP	14	224	SD 46	Response to bosentan or ambrisentan
		Baseline	TRV	14	3.4	SD 0.1	Response to bosentan or ambrisentan
		2 mo	TRV	14	3.4	SD 0.1	Response to bosentan or ambrisentan
		3 mo	TRV	14	3.3	SD 0.1	Response to bosentan or ambrisentan
		6 mo	TRV	14	3.3	SD 0.2	Response to bosentan or ambrisentan

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical scenario
Morishita, 2009[128] Adults and children with PAH N=7 Good	Median 34.6 (Range 15 to 49)	1 mo	RA size (RA area indexed)	7	18.6	SD 10.4	Response to epoprostenol
		3 mo	RA size (RA area indexed)	7	19.4	SD 10.7	Response to epoprostenol
		6 mo	RA size (RA area indexed)	7	14.6	SD 5.4	Response to epoprostenol
		1 yr	RA size (RA area indexed)	7	14.5	SD 5.8	Response to epoprostenol
Nakayama, 2007[126] Patients with PPH N=60 Good	Mean 10.7 (SD 3.5)	3 mo	BNP	27	187.0	SD 221.4	Response to epoprostenol
		1 yr	BNP	27	86.6	SD 133.9	Response to epoprostenol
		2 yr	BNP	27	85.3	SD 206.1	Response to epoprostenol
Nath, 2005[127] Adults with PPH N=20 Good	Mean 46 (SD 11)	Baseline	RIMP/MPI/Tei index	20	0.6	SD 0.3	Response to epoprostenol
		22.7 ± 9.3 mo	RIMP/MPI/Tei index	20	0.6	SD 0.3 p=0.54	Response to epoprostenol
		Baseline	RV size	20	2.1	SD 0.9	Response to epoprostenol
		22.7 ± 9.3 mo	RV size	20	1.8	SD 1.5 p=0.07	Response to epoprostenol
		Baseline	sPAP	20	87	SD 26	Response to epoprostenol
		22.7 ± 9.3 mo	sPAP	20	75	SD 24 p=0.02	Response to epoprostenol
		Baseline	TRV	20	4.2	SD 0.6	Response to epoprostenol
		22.7 ± 9.3 mo	TRV	20	3.8	SD 0.7 p=0.02	Response to epoprostenol

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical scenario
Sebbag, 2001[136] Adults and children with PPH N=16 Good	Mean 43 (SD 16)	Baseline	RIMP/MPI/Tei index	16	0.72	SD 0.22	Response to epoprostenol
		5.9 ± 4.6 mo	RIMP/MPI/Tei index	16	0.64	SD 0.17 p=0.05	Response to epoprostenol
		Baseline	sPAP	16	108	SD 19	Response to epoprostenol
		5.9 ± 4.6 mo	sPAP	16	94	SD 22 p=0.03	Response to epoprostenol
Simeoni, 2008[58] Adults with systemic sclerosis and PH N=20 Good	Median 55 (Range 40 to 70)	Baseline	BNP	10	23.4 pmol/L	Range 11.1 to 38	Response to bosentan
		3 mo	BNP	10	26	Range 4.54 to 144 p=0.953	Response to bosentan
		7 mo	BNP	10	15.7	Range 6 to 79 p=0.600	Response to bosentan

Abbreviations: ANP=A-type natriuretic peptide; BNP=B-type natriuretic peptide ; CO=cardiac output; cTnT=cardiac troponin T; CVD=collagen vascular disease; FAC=fractional area change; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NR=not reported; PVR=pulmonary vascular resistance; RA=right atrium; RIMP=right index of myocardial performance; RV=right ventricle; SD=standard deviation; SEM=standard error of the mean; sPAP=systolic pulmonary artery pressure; TAPSE=tricuspid annular plane systolic excursion; TRV=tricuspid regurgitant jet velocity

The two studies that assessed change in median levels of BNP in response to therapy with bosentan showed decrease by approximately half after 4 to 6 months of therapy (Table 18).[87,110] However, one of these studies showed increasing levels of BNP back toward baseline over 30 months of therapy.[110] One study showed an overall moderate decrease in median RIMP/MPI/Tei index levels over 30 months of therapy but no significant change in median values of sPAP, FAC or RVEF after over 30 months of therapy.[110]

Table 18. Median table for KQ 2

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Median	Variability (Range)	Clinical scenario
Dimitroulas, 2007[87] Adults with PAH associated with scleroderma N=10 Good	Median 58 (Range 39 to 74)	Baseline	Natriuretic peptides/BNP	10	474		Response to bosentan
		20 wk	Natriuretic peptides/BNP	10	238	198-335 (p=0.002 compared with baseline)	Response to bosentan
Ho, 2009[110] Adults with PAH N=6 Good	Mean 33 (NR)	Baseline	RIMP/MPI/Tei index	6	0.85	0.49 to 1.75	Response to bosentan
		6 mo	RIMP/MPI/Tei index	6	0.55	0.22 to 0.81	Response to bosentan
		1 yr	RIMP/MPI/Tei index	6	0.63	0.33 to 1.49	Response to bosentan
		18 mo	RIMP/MPI/Tei index	4	0.70	0.26 to 1.10	Response to bosentan
		2 yr	RIMP/MPI/Tei index	4	0.73	0.62 to 1.08	Response to bosentan
		30 mo	RIMP/MPI/Tei index	4	0.67	0.45 to 1.16	Response to bosentan
		Baseline	sPAP	6	98	50 to 163	Response to bosentan
		6 mo	sPAP	6	103	37 to 142	Response to bosentan
		1 yr	sPAP	6	92	42 to 127	Response to bosentan
		18 mo	sPAP	4	118	28 to 143	Response to bosentan
		2 yr	sPAP	4	118	61 to 136	Response to bosentan
		30 mo	sPAP	4	108	87 to 117	Response to bosentan
		Baseline	Fractional area change	6	22	13 to 28	Response to bosentan
		6 mo	Fractional area change	6	27	15 to 54	Response to bosentan
		1 yr	Fractional area change	6	26	9 to 49	Response to bosentan
		18 mo	Fractional area change	4	35	26 to 53	Response to bosentan
		2 yr	Fractional area change	4	27	16 to 33	Response to bosentan

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Median	Variability (Range)	Clinical scenario
		30 mo	Fractional area change	4	21	19 to 45	Response to bosentan
		Baseline	Natriuretic peptides/BNP	6	224	20 to 169	Response to bosentan
		6 mo	Natriuretic peptides/BNP	6	111	13 to 231	Response to bosentan
		1 yr	Natriuretic peptides/BNP	6	136	5 to 249	Response to bosentan
		18 mo	Natriuretic peptides/BNP	4	215	14 to 352	Response to bosentan
		2 yr	Natriuretic peptides/BNP	4	193	92 to 293	Response to bosentan
		30 mo	Natriuretic peptides/BNP	4	203	81 to 376	Response to bosentan
		Baseline	RVEF	6	30	14 to 35	Response to bosentan
		6 mo	RVEF	6	39	17 to 71	Response to bosentan
		1 yr	RVEF	6	35	15 to 60	Response to bosentan
		1 yr	RVEF	6	32	15 to 83	Response to bosentan
		18 mo	RVEF	4	45	31 to 77	Response to bosentan
		2 yr	RVEF	4	38	20 to 50	Response to bosentan
		30 mo	RVEF	4	28	24 to 62	Response to bosentan

Abbreviations: BNP=B-type natriuretic peptide; mo=month/months; NR=not reported; RVEF=right ventricle ejection fraction; yr=year/years

Five studies assessed mean change from baseline for BNP or various echocardiographic parameters (Table 19). One study evaluated response to therapy with epoprostenol over 3 months and showed mild increase in RV size, decrease in FAC, and minimal decrease in TR jet velocity.[106] Another study evaluated response to 4 months of therapy with bosentan or sildenafil and showed—in response to bosentan—decrease in RV size, minimal increase in CI, minimal decrease in RIMP/MPI/Tei index, increase in RA size, decrease in BNP, and decrease in RV size, and—in response to sildenafil—greater decrease in RV size, RIMP/MPI/Tei index and BNP and decrease in RA size but similar response in CI.[146] One study showed decrease in median levels of BNP in response to treprostinil after 6 weeks with some attenuation of response after 3 months.[121] Two studies showed a decrease from baseline for mean levels of mPAP, one after 3 months therapy with bosentan[84] and the other after 3 months therapy with epoprostenol.[75]

Table 19. Mean/median change from baseline table for KQ 2

Study Population (N) Quality	Age (Variability)	Timing	Result	Index Test	N	Results	Variability	Clinical scenario
Barst, 1996[75] Adults with PPH N=81 Good	NR for cohort	3 mo	Mean change	mPAP	41	-4.8	SE 1.3	Response to epoprostenol
Channick, 2001[84] Adults with PPH or PAH associated with scleroderma N=32 Good	NR for cohort	3 mo	Mean change	mPAP	20	-1.6	SE 1.2	Response to bosentan
Hinderliter, 1997[106] Adults with PPH N=81 Fair	NR for cohort	Baseline	Mean	RV size	38	21.2	SE 0.7	Response to epoprostenol
		Baseline	Mean	Fractional area change	38	19.2	SE 1.2	Response to epoprostenol
		Baseline	Mean	TR jet velocity	36	4.3	SE 0.1	Response to epoprostenol
		3 mo	Median change	RV size	33	0.4		Response to epoprostenol
		3 mo	Median change	Fractional area change	33	-2.2		Response to epoprostenol
		3 mo	Median change	TR jet velocity	32	-0.04		Response to epoprostenol

Study Population (N) Quality	Age (Variability)	Timing	Result	Index Test	N	Results	Variability	Clinical scenario
Wilkins, 2005[146] Adults with IPAH or PAH associated with CTD N=26 Good	NR for cohort	4 mo	Mean change	RV size	12	-3	95% CI -7.5 to 1.5	Response to bosentan
		4 mo	Mean change	Cardiac Index	12	0.3	95% CI 0.1 to 0.4 p=0.01	Response to bosentan
		4 mo	Mean change	RIMP/MPI/Tei Index	12	-0.02	95% CI -0.1 to 0.11	Response to bosentan
		4 mo	Mean change	RA size	12	4	95% CI -16 to 23	Response to bosentan
		4 mo	Mean change	Natriuretic peptides/ BNP	12	-5.9	95% CI -35 to 24	Response to bosentan
		4 mo	Mean change	RV size	13	-8.8	95% CI -16 to -2 p=0.05	Response to sildenafil
		4 mo	Mean change	Cardiac Index	13	0.3	95% CI 0.1 to 0.4 p=0.01	Response to sildenafil
		4 mo	Mean change	RIMP/MPI/Tei Index	13	-0.11	95% CI -0.23 to 0.01	Response to sildenafil
		4 mo	Mean change	RA size	13	-4	95% CI -19 to 12	Response to sildenafil
		4 mo	Mean change	Natriuretic peptides/ BNP	13	-19.4	95% CI -34 to -5	Response to sildenafil
McLaughlin, 2010[121] Adults with PAH N=235 Good	Mean 54 (Range 18-75)	6 weeks	Median change	Natriuretic peptides/ BNP	86	-71	p<0.0003	Response to treprostinil
		3mo	Median change	Natriuretic peptides/ BNP	73	-57	IQR -396.0 to 34.0	Response to treprostinil

Abbreviations: BNP=B-type natriuretic peptide; CI=confidence interval; IQR=interquartile range; mPAP=mean pulmonary artery pressure; mo=month/months; MPI=myocardial performance index; NR=not reported; PVR=pulmonary vascular resistance; RA=right atrium; RIMP=right index of myocardial performance; RV=right ventricle; RVEF=right ventricle ejection fraction; SD=standard deviation; SEM=standard error of the mean; sPAP=systolic pulmonary artery pressure; TAPSE=tricuspid annular plane systolic excursion; TRV=tricuspid regurgitant jet velocity

The strength of evidence (SOE) ratings for the most commonly reported biomarkers and echocardiographic parameters are summarized in Table 20 (assessment of prognostic value) and Table 21 (assessment of predictive value).

Table 20. Summary SOE for KQ 2: assessment of prognostic value

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
BNP compared with RHC-mPAP					**SOE=Moderate**
13 (559)	Low (11) Moderate (1) High (1)	Consistent	Indirect	Precise	0.41 (0.31 to 0.49) Serum BNP level shows only moderate correlation with mPAP
BNP compared with RHC-PVR					**SOE=Moderate**
12 (638)	Low (10) Moderate (1) High (1)	Consistent	Indirect	Precise	0.49 (0.32 to 0.63) Serum BNP level shows only moderate correlation with PVR
BNP compared with RHC-RAP					**SOE=Moderate**
11 (600)	Low (10) Moderate (1)	Consistent	Indirect	Precise	0.47 (0.39 to 0.55) Serum BNP level shows only moderate correlation with RAP
BNP compared with cardiac index					**SOE=Moderate**
9 (509)	Low (8) Moderate (1)	Consistent	Indirect	Precise	-0.47 (-0.59 to -0.34) Serum BNP level shows only moderate correlation with cardiac index
BNP compared with PCWP					**SOE=Low**
5 (319)	Low (4) High (1)	Consistent	Indirect	Imprecise	0.16 (0.01 to 0.31) Serum BNP level shows poor correlation with PCWP
BNP compared with 6MWD (absolute)					**SOE=Moderate**
8 (396)	Low (7) High (1)	Consistent	Direct	Precise	-0.47 (-0.58 to -0.34) Serum BNP level shows only moderate correlation with 6MWD
Echocardiography-derived sPAP compared with RHC-sPAP					**SOE=Moderate**
8 (302)	Low (5) Moderate (3)	Consistent	Indirect	Precise	0.79 (0.55 to 0.91) sPAP estimated by echocardiography shows good correlation with sPAP from RHC

Abbreviations: 6MWD=6-minute walk distance; BNP=B-type natriuretic peptide; CI=confidence interval; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure

Table 21. Summary SOE for KQ 2: assessment of predictive value

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
BNP					**SOE=High**
9 (632)	Low (8) Moderate (1)	Consistent	Direct	Precise	1.08 (1.01 to 1.16) BNP level is a poor predictor of mortality
Pericardial effusion					**SOE=Moderate**
7 (2485)	Low (5) Moderate (2)	Inconsistent	Direct	Imprecise	2.20 (1.42 to 3.41) Presence of pericardial effusion is the strongest predictor of mortality, although there was wide variability in results for this measure
RA size					**SOE=Low**
4 (242)	Low (2) Moderate (2)	Inconsistent	Direct	Imprecise	1.07 (0.99 to 1.14) RA size is a poor predictor of mortality
FAC					**SOE=Moderate**
4 (242)	Low (2) Moderate (2)	Consistent	Direct	Precise	0.99 (0.96 to 1.02) FAC is a poor predictor of mortality

Abbreviations: BNP=B-type natriuretic peptide; CI=confidence interval; FAC=fractional area change; RA=right atrium; RAP=right atrial pressure; SOE=strength of evidence

Key Question 3. Pharmacotherapy for PAH

KQ 3: For adults with PAH, what is the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium-channel blockers, prostanoids, endothelin antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

Key Points

- Evidence comparing monotherapy with combination therapy for PAH permitted a conclusion for only one outcome: improved 6MWD with combination therapy compared with monotherapy (low SOE). For all other outcomes (mortality, pulmonary vascular resistance, mean PAP, and cardiac index), evidence on this comparison was insufficient to permit conclusions.

- In patients treated for PAH with prostanoids, endothelin antagonists, or phosphodiesterase inhibitors, current evidence is inconclusive regarding a reduction in mortality with either monotherapy or combination therapy (insufficient SOE).

- As measured by 6MWD after 12 to 16 weeks of therapy, eight good-quality RCTs support the use of monotherapy with endothelin antagonists (high SOE), phosphodiesterase inhibitors (high SOE), or prostanoids (low SOE) for improving exercise capacity compared with placebo in patients with PAH,

- Eight good-quality and one fair-quality RCTs support a reduction in hospital admissions due to worsening PAH symptoms with the use of either monotherapy or combination therapy, with significant reductions in hospitalizations associated with both endothelin antagonists and phosphodiesterase inhibitors (moderate SOE) compared with placebo or conventional therapy.

- Monotherapy with for PAH is associated with statistically significant improvements in hemodynamic measures such as pulmonary vascular resistance, (four good-quality, one fair-quality RCTs) mean pulmonary artery pressure (three good-quality, one fair-quality RCT), and cardiac index (four good-quality, one fair-quality RCT) after 12 to 16 weeks of therapy compared with placebo or conventional therapy, but high heterogeneity of published studies precludes the quantifying summary measures of effect that are sufficiently reliable and valid.

- Among commonly reported adverse events, there is a higher incidence of jaw pain associated with prostanoid treatment compared with placebo (high SOE) and cough associated with prostanoids versus placebo (high SOE). In addition, headache was associated with phosphodiesterase inhibitors compared with placebo or conventional therapy (moderate SOE), and flushing was associated with phosphodiesterase inhibitors (moderate SOE) and prostanoids (moderate SOE) compared with placebo or conventional therapy.

Description of Included Studies

Study Characteristics

Randomized Controlled Trials

Twenty-seven RCTs (31 articles) involving 3619 patients evaluated the comparative effectiveness and safety of monotherapy versus combination therapy for PAH.[75,78,84,96,121,146,153-176] Of these RCTs, 17 (63%) were rated good quality, 9 (33%) fair quality, and 1 (4%) poor quality. Eighteen studies (67%) were funded by industry, one by government, one privately, one by government and private funding, one by private and industry funding, and five did not report funding sources.

Table 22 summarizes the study, patient population, quality, study size, drugs and comparators, duration and followup, and outcomes for each study relevant to KQ 3. The mean patient ages ranged from 28 to 57 years old. Nineteen studies enrolled patients with PAH,[75,78,96,121,154,155,157,159-164,167,168,171-176] three studies enrolled patients with PAH secondary to systemic sclerosis (formerly scleroderma),[84,153,158,169] and two studies enrolled patients with Eisenmenger syndrome.[156,170] Two studies enrolled a percentage of patients with non-Category 1 PH: chronic thromboembolic pulmonary hypertension (28%),[165] and secondary PAH, PH secondary to lung disease, or chronic thromboembolic pulmonary hypertension (37%).[166]

Eighteen studies compared a single drug versus placebo and included the following drugs: bosentan (6 studies), sildenafil (2), iloprost (2), tadalafil (2), ambrisentan (2), treprostinil (3), and vardenafil (1). Two studies compared epoprostenol with conventional therapy (diuretics, supplemental oxygen, cardiac glycosides, and calcium channel blockers). For the purposes of this analysis, the conventional therapy arms were grouped with the placebo arms. One study was

a head-to-head comparison of bosentan and sildenafil. The remaining six studies compared combination therapy with single therapy: (1) intravenous (IV) epoprostenol plus bosentan versus IV epoprostenol plus placebo, (2) sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo, (3) bosentan plus inhaled iloprost versus bosentan, (4) bosentan plus inhaled iloprost versus bosentan plus placebo, (5) bosentan plus tadalafil versus bosentan plus placebo, and (6) aerosolized treprostinil plus bosentan or sildenafil versus bosentan or sildenafil plus placebo. We did not identify any eligible studies published after 1995 that evaluated the safety or efficacy of calcium channel blockers on intermediate-term and long-term patient outcomes.

Most studies (85%) were multicenter trials; two were single-center trials, and four did not report the number of centers. Study locations included Europe (14 studies, 70%), United States (13), Australia or New Zealand (5), Asia (4), India (3), Israel (3), South America (3), and Mexico (3), Central America (2), and unreported or unclear setting (7). Of the 20 studies reporting study locations, each study had on average 2.5 sites participating.

The studies reported the following outcomes: 6 minute walk distance (25 studies), mortality (19), dyspnea (18), right heart catheterization indices (16), functional class (16), hospitalization for worsening PAH (11), quality of life (11), lung transplantation (6), right heart failure or right ventricular dysfunction (4), brain natriuretic peptide (4), and echocardiogram indices (3). Twenty-two studies reported harms or adverse events.

Table 22. Study characteristics table for KQ 3 (RCTs)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
BOSENTAN				
Individual drug studies				
Channick, 2001[84] Badesch, 2002[153] PPH or PH due to SCD N=32 Good	- Bosentan 62.5 mg BID, then 125 mg BID (N=21) - Placebo (N=11)	12	4, 8, 12, 20, 28	- 6MWD - Dyspnea - Functional class - Transplantation - RHC - Adverse events
Rubin, 2002[154] Galie, 2003[155] BREATHE PAH N=213 Good	- Bosentan 62.5 mg BID, then 125 mg BID (N=74) - Bosentan 62.5 mg BID, then 250 mg BID (N=70) - Placebo (N=69)	12	4, 8, 16	- 6MWD - Dyspnea - Functional class - Mortality - Hospitalization - Echocardiography - Adverse events
Wilkins, 2005[146] SERAPH PAH N=26 Good	- Bosentan 62.5 mg BID, then 125 mg BID (N=12) - Sildenafil 50 mg BID, then 50 mg TID (N=14)	16	16	- 6MWD - Quality of life - Mortality - Right ventricular dysfunction - Echocardiography - BNP
Galie, 2006[156] BREATHE-5 Eisenmenger syndrome N=54 Good	- Bosentan 62.5 mg BID, then 125 mg BID (N=37) - Placebo (N=17)	4	4	- 6MWD - Functional class - RHC - Adverse events

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
Galie, 2008[157] EARLY PAH N=185 Good	- Bosentan 62.5 mg BID, then 125 mg BID (N=93) - Placebo (N=92)	24	24	- 6MWD[a] - Dyspnea[a] - Functional class[a] - Quality of life[a] - Mortality[a] - Hospitalization[a] - RHC[a] - Adverse events[a]
Barst, 2010[158] ASSET-1 SCD with PAH N=14 Fair	- Bosentan 62.5 mg BID, then 125 mg BID (N=6) - Placebo (N=8)	16	16	- 6MWD - Mortality - RHC
Barst, 2010[158] ASSET-2 PH N=12 Fair	- Bosentan 62.5 mg BID, then 125 mg BID (N=5) - Placebo (N=7)	16	16	- 6MWD - Mortality - RHC
Combination drug studies				
Humbert, 2004[159] BREATHE-2 PAH N=23 Good	- Epoprostenol + bosentan 62.5 mg BID, then 125 mg BID (N=22) - Epoprostenol + placebo (N=11)	16	16	- 6MWD - Dyspnea - Functional class - Hospitalization - Right heart failure - RHC - Adverse events

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
SILDENAFIL				
Individual drug studies				
Galie, 2005[160] Badesch, 2007[161] Rubin, 2011[162] SUPER PAH N=278 Good	- Sildenafil 20 mg TID (N=69) - Sildenafil 40 mg TID (N=67) - Sildenafil 80 mg TID (N=71) - Placebo (N=70)	12	4, 8, 12, 52, 156	- 6MWD - Dyspnea - Mortality - Hospitalization - Adverse events - RHC
Barst, 2011[163] STARTS-1 PAH N=234 Fair	- Low dose sildenafil (N=42) - Medium dose sildenafil (N=55) - High dose sildenafil (N=77) - Placebo (N=60)	16	16, >156	- Functional class - Quality of life - Mortality - RHC - Adverse events
Combination drug studies				
Simonneau, 2008[164] PACES PAH N=267 Good	- Sildenafil 20 mg TID + epoprostenol, then up to 80 mg TID + epoprostenol (N=134) - Placebo + epoprostenol (N=133)	16	4, 8, 12, 16	- Dyspnea - Quality of life - Mortality - Hospitalization - Transplantation - Adverse events

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
ILOPROST				
Individual drug studies				
Olschewski, 2002[165] AIR Severe PAH or chronic thromboembolic PH N=203 Good	- Iloprost (aerosolized) (N=101) - Placebo (N=102)	12	4, 8, 12	- 6MWD - Dyspnea - Functional class - Quality of life - Mortality - Transplantation - Right ventricular dysfunction - RHC - Adverse events
Olschewski, 2010[166] IPAH or other PH N=63 Fair	- Iloprost (aerosolized) (N=30) - Conventional therapy only (N=33)	12	12, 104	- 6MWD - Dyspnea - Functional class - Quality of life - Mortality - Right heart failure - RHC - Adverse events
Combination drug studies				
Hoeper, 2006[167] COMBI IPAH N=40 Fair	- Bosentan 125 mg BID + iloprost (aerosolized) (N=19) - Bosentan 125 mg (N=21)	12	6, 12	- 6MWD - Adverse events
McLaughlin, 2006[168] PAH N=67 Good	- Bosentan + iloprost (aerosolized) (N=34) - Bosentan + placebo (N=33)	12	4, 8, 12	- 6MWD - Dyspnea - Functional class - Hospitalization - RHC - Adverse events

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
EPOPROSTENOL				
Individual drug studies				
Barst, 1996[75] Primary Pulmonary Hypertension Study PPH N=81 Good	- Epoprostenol 4 ng/kg, then adjusted (N=41) - Conventional therapy only (N=40)	12	1, 6, 12	- 6MWD - Quality of life - Mortality - Transplantation - RHC - Adverse events
Badesch, 2000[169] PH secondary to SCD spectrum of disease N=111 Fair	- Epoprostenol ≤ 2 ng/kg, then adjusted (N=56) - Conventional therapy only (N=55)	12	1, 6, 12	- 6MWD - Dyspnea - Mortality - RHC - Adverse events
TADALAFIL				
Individual drug studies				
Bharani, 2007[78] PAH N=11 Fair	- Tadalafil 20 mg daily (N=11) - Placebo 20 mg daily (N=11)	4	4	- 6MWD[a] - Dyspnea[a] - Functional class[a] - Echocardiography[a]
Mukhopadhyay, 2011[170] Eisenmenger Syndrome N=28 Fair	- Tadalafil 40 mg daily (N=28) - Placebo (N=28)	6	6	- 6MWD[a] - RHC[a]

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
Combination drug studies				
Galie, 2009[171] Barst, 2011[172] Barst, 2011[172] PHIRST PAH N=406 Good	- Bosentan + placebo (N=45) - Bosentan + tadalafil 20 mg daily (N=45) - Bosentan + tadalafil 40 mg daily (N=42)	16	4, 8, 12, 16	- 6MWD - Functional class - Mortality - Hospitalization - RHC - Adverse events
AMBRISENTAN				
Individual drug studies				
Galie, 2008[96] AIRES-1 PAH N=201 Good	- Ambrisentan 5 mg daily (N=67) - Ambrisentan 10 mg daily (N=67) - Placebo (N=67)	12	4, 8, 12, 48	- 6MWD - Dyspnea - Functional class - Quality of life - Mortality - Hospitalization - BNP - Adverse events
Galie, 2008[96] AIRES-2 PAH N=192 Good	- Ambrisentan 2.5 mg daily (N=64) - Ambrisentan 5 mg daily (N=63) - Placebo (N=65)	12	4, 8, 12, 48	- 6MWD - Dyspnea - Functional class - Quality of life - Mortality - Hospitalization - BNP - Adverse events

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
TREPROSTINIL				
Individual drug studies				
Simonneau, 2002[173] Treprostinil Study PAH N=470 Good	- Treprostinil 1.25 ng/kg/min, then adjusted (N=233) - Placebo (N=236)	12	12	- 6MWD - Dyspnea - Quality of life - Mortality - Transplantation - Adverse events
McLaughlin, 2003[174] PPH N=26 Poor	- Treprostinil 2.5-5.0 ng/kg/min, then adjusted (N=17) - Placebo (N=9)	8	8	- 6MWD[a] - Dyspnea[a] - Adverse events[a]
Hiremath, 2010[175] TRUST PAH N=45 Fair	- Treprostinil 4 ng/kg/min, then adjusted (N=30) - Placebo (N=14)	12	12	- 6MWD - Dyspnea - Functional class - Mortality - Adverse events
Combination drug studies				
McLaughlin, 2010[121] TRIUMPH 1 Severe PAH N=235 Good	- Treprostinil (aerosolized) 18 mcg 4 times daily, gradually increased to 54 mcg+ bosentan/ sildenafil (N=115) - Placebo + bosentan/sildenafil (N=120)	12	6, 12	- 6MWD - Dyspnea - Functional class - Quality of life - Mortality - Hospitalization - Transplantation - BNP - Adverse events

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
VARDENAFIL				
Individual drug studies				
Jing, 2011[176] EVALUATION PAH N=66 Good	- Vardenafil 5 mg qD, then 5 mg BID (N=44) - Placebo (N=22)	12	12, 24	- 6MWD - Dyspnea - Functional class - Mortality - Hospitalization - RHC - Adverse events

[a]Outcome not assessed at 12 or 16 weeks.
Abbreviations: 6MWD=6 minute walk distance; IPAH=idiopathic PAH; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=Primary pulmonary hypertension; SCD=scleroderma

Nonrandomized Comparative Observational Studies

We identified 6 nonrandomized observational studies involving 362 patients. Of these, all studies were rated fair quality studies (Table 23). Three studies were retrospective case series and three were prospective case series. Epoprostenol was evaluated in three studies, iloprost in two studies, and bosentan, sildenafil, and treprostinil were each evaluated in one study. Three studies directly compared two different monotherapies; one study compared bosentan with iloprost, one compared epoprostenol with treprostinil, and 1 compared epoprostenol with iloprost. We do not discuss these nonrandomized comparative studies further in this report because the size and quality of the nonrandomized comparative studies compared poorly to the randomized trial data we identified. Although these studies offer the ability to address the comparative effects of treatments and longer duration of follow-up beyond that reported in the randomized trials, we thought that the limitations of poorly specified comparison (control) treatments and selection bias in treatment allocation combined with a lack of power from small size made these data inconclusive.

Table 23. Study characteristics table for KQ 3 (nonrandomized studies)

Study Study Type Population (N) Quality	Study Arms (N)	Study Review Range	Followup Assessments (Months)	Outcome Measures
Fix, 2007[177] Retrospective case series Porto-pulmonary hypertension N=36 Fair	- Epoprostenol 1 ng/kg/min, then titrated to mean dose of 29 ng/kg/min (N=19) - Non-epoprostenol (N=17)	1998-2005	2-95	- Mortality - RHC - Adverse events
Hoeper, 2007[178] Retrospective case series Porto-pulmonary hypertension and cirrhosis N=31 Fair	- Bosentan 62.5 mg BID x 4 weeks, then 125 mg BID thereafter (N=18) - Iloprost (aerosolized) 5 mcg 6 times daily (N=13)	1999-2004	3, 6, 12, 18, 24, 30, 36	- 6MWD - Functional class - Mortality - Event-free survival - RHC - Adverse events
Sastry, 2007[179] Prospective case series IPAH N=178 Fair	- Conventional therapy (historical control) (N=39) - Conventional therapy + sildenafil 25-50 mg 3 times daily (N=139)	1999-2005	12, 24, 36, 48, 60	- Mortality

Study Study Type Population (N) Quality	Study Arms (N)	Study Review Range	Followup Assessments (Months)	Outcome Measures
Jacobs, 2009[109] Prospective case series IPAH N=16 Fair	- Epoprostenol titrated to 6-8 ng/kg/min after 1 week (N=6) - Treprostinil gradually increased to 10 ng/kg/min after 1 week, then 20 ng/kg/min after 6 weeks (N=10)	2002-2007	4, 6	- 6MWD - Functional class - Mortality - Natriuretic peptides - Adverse events
Reichenberger, 2011[180] Prospective case series IPAH, PAH, portopulmonary hypertension N=24 Fair	- Epoprostenol gradually increased to maximum tolerated dose (N=12) - Iloprost (aerosolized) gradual titration up to 20 mcg per breath, max 120 mcg total daily dose (N=12)	NR	3, 12, 18, 20	- 6MWD - Functional class - Mortality - RHC - Progression to transplant - Adverse events
Zeng, 2011[181] Retrospective case series IPAH N=77 Fair	- Conventional therapy (N=26) - Sildenafil 25 mg 3 times daily (N=51)	2005-2009	12, 24, 36	- 6MWD - Dyspnea - Mortality - RHC - BNP

Abbreviations: 6MWD=6 minute walk distance; BNP=brain natriuretic peptide; IPAH=idiopathic PAH; PAH=pulmonary arterial hypertension; RHC=right heart catheterization

Detailed Synthesis of RCTs

We report on the outcomes of mortality, 6-minute walk distance (6MWD), hospitalization, pulmonary vascular resistance, mean pulmonary arterial pressure, cardiac index, and certain adverse reactions (headache, dizziness, diarrhea, peripheral edema, jaw pain, flushing, cough, and infections) for the following comparative analyses of pharmacotherapies:

- Head-to-head comparisons by individual drug, when available
- Monotherapy versus placebo (or monotherapy plus standard therapy vs. standard therapy alone) by individual drug
- Monotherapy versus placebo (or monotherapy plus standard therapy vs. standard therapy alone) by class of drug
- Combination therapy vs. monotherapy by individual drug

The latter three comparative analyses are reported in tabular and graphic form in a single forest plot for each outcome. We also conducted meta-analyses and reported summary measures for the analyses by individual drug (e.g., studies of bosentan vs. placebo) and class of drug (e.g., prostacyclin-analogues vs. placebo or standard therapy) whenever there were two or more studies with comparable study arms.

We use the term background treatment for cointerventions that are preexisting and applied to both study arms of an RCT in which a second (new) drug is added to one arm (experimental) but not the other (control). Thus, trial of tadalafil plus bosentan versus bosentan (e.g., Galie et al., 2009, PHIRST[171]) would be described as a trial of tadalafil with bosentan background therapy, and can demonstrate the efficacy of combination versus monotherapy; it is also relevant to the efficacy of tadalafil. In our meta-analyses, we would infer efficacy of tadalafil from controlled trials of tadalafil both with and without background therapy.

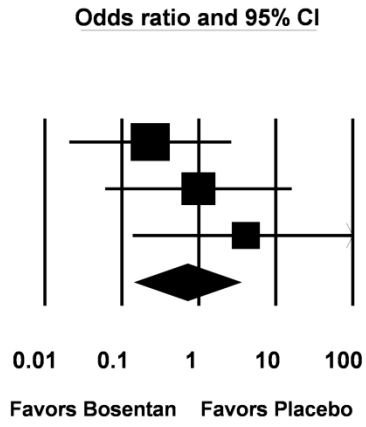
Mortality

A total of 22 RCTs reported the effects of single or combination therapy for PAH on mortality; 4 of these studies reported no deaths (therefore, no OR for mortality could be calculated for these studies).[158,163,167,168] Another study did not clearly define the number of deaths per group.[172] Therefore, 17 studies (14 therapy studies and 3 combination therapy) were included for analysis: 1 study directly compared bosentan with sildenafil,[146] 3 studies compared bosentan with placebo,[154,157,158] 2 studies compared sildenafil with placebo,[160,163] 2 studies compared inhaled iloprost with placebo,[165,166] 2 studies compared IV epoprostenol with conventional therapy,[75,169] 2 studies represented by 1 article compared ambrisentan with placebo,[96] 2 studies compared IV or subcutaneous treprostinil versus placebo[173,175], and 3 studies evaluated combination therapy versus single therapy.[121,159,164] The included studies consist of a total of 2339 patients.

Figure 20 shows the forest plot of the odds ratio for mortality for treatment with bosentan versus placebo from three studies (411 patients). The dosages of bosentan across the trials were similar (62.5 mg BID titrated up to 125 mg BID). The duration of treatment ranged from 16 to 32 weeks. The individual odds ratios range from 0.23 to 4.09, and the summary odds ratio is 0.72 (95% CI, 0.14 to 3.60). The comparative efficacy of bosentan in reducing mortality compared with placebo is inconclusive, given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 20. Forest plot for odds ratio for mortality for bosentan versus placebo

Study name	Acronym	Active drug	Deaths / Total				
			Treated	Control	Odds ratio	Lower limit	Upper limit
Rubin 2001	BREATHE	Bosentan	1 / 144	2 / 69	0.23	0.02	2.63
Galie 2008(I)	EARLY	Bosentan	1 / 93	1 / 92	0.99	0.06	16.05
Barst 2010	Blank	Bosentan	1 / 6	0 / 7	4.09	0.14	120.69
					0.72	0.14	3.60

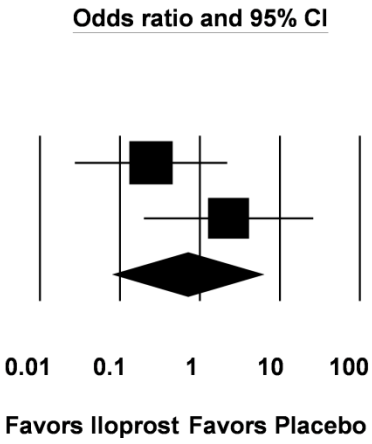


Abbreviations: CI=confidence interval

Figure 21 shows the forest plot of the odds ratio for mortality for treatment with inhaled iloprost versus placebo from two studies (266 patients). Both studies contained patient groups diagnosed with non-Category 1 PH. The duration of therapy was similar (both 12 weeks). The doses of inhaled iloprost were between 2.5 and 5.0 micrograms delivered from six to nine times daily with dosage and schedules individualized based on a predetermined algorithm. The individual odds ratios ranged from 0.24 to 2.29, and the summary odds ratio is 0.70 (95% CI, 0.08 to 6.22). The comparative efficacy of iloprost in reducing mortality compared with placebo is inconclusive, given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 21. Forest plot for odds ratio for mortality for inhaled iloprost versus placebo

Study name	Active drug	Deaths / Total				
		Treated	Control	Odds ratio	Lower limit	Upper limit
Olschewski 2002	Iloprost	1 / 101	4 / 102	0.25	0.03	2.23
Olchewski 2010	Iloprost	2 / 30	1 / 33	2.29	0.20	26.58
				0.70	0.08	6.22

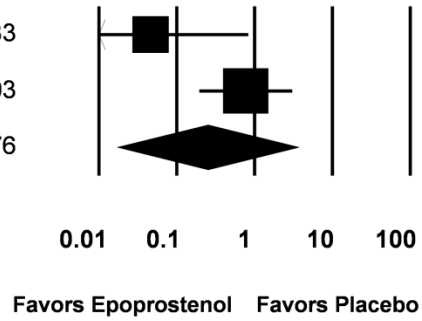


Abbreviations: CI=confidence interval

Figure 22 shows the forest plot of the odds ratio for mortality for treatment with intravenous epoprostenol versus conventional therapy from two studies (192 patients). The duration of therapy was similar (both 12 weeks). The individual odds ratios ranged from 0.05 to 0.77, and the summary odds ratio of 0.25 (95% CI, 0.02 to 3.76). The comparative efficacy of epoprostenol in reducing mortality compared with placebo is inconclusive, given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 22. Forest plot of odds ratio for mortality for intravenous epoprostenol versus placebo

Study name	Active drug	Deaths / Total				
		Treated	Control	Odds ratio	Lower limit	Upper limit
Barst 1996	Epoprostenol	0 / 41	8 / 40	0.05	0.00	0.83
Badesch 2000	Epoprostenol	4 / 56	5 / 55	0.77	0.20	3.03
				0.25	0.02	3.76

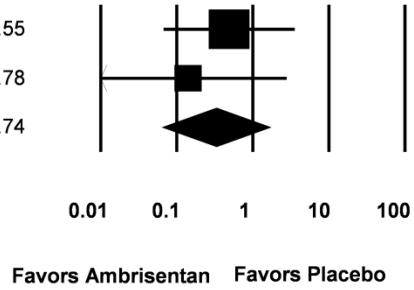


Abbreviations: CI=confidence interval

Figure 23 shows the forest plot of the odds ratio for mortality for treatment with ambrisentan versus placebo from 2 studies (330 patients). The dosages of ambrisentan across the trials ranged from 2.5 mg to 10 mg daily. The duration of treatment was similar (12 weeks) in each study. The individual odds ratios range from 0.14 to 0.49, and the summary odds ratio is 0.33 (95% CI, 0.06 to 1.74). The comparative efficacy of ambrisentan in reducing mortality compared with placebo is inconclusive, given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 23. Forest plot of odds ratio for mortality for ambrisentan versus placebo

Study name	Active drug	Acronym	Deaths / Total				
			Treated	Control	Odds ratio	Lower limit	Upper limit
Galie 2008(II)	Ambrisentan	AIRES-1	2 / 135	2 / 67	0.49	0.07	3.55
Galie 2008(II)b	Ambrisentan	AIRES-2	0 / 63	3 / 65	0.14	0.01	2.78
					0.33	0.06	1.74

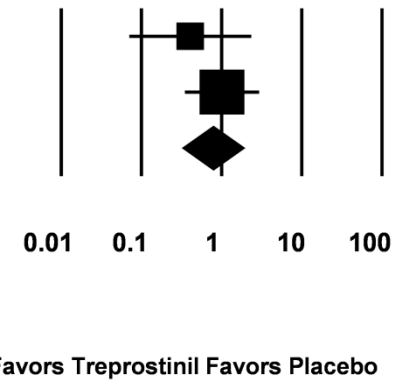


Abbreviations: CI=confidence interval

Figure 24 shows the forest plot of the odds ratio for mortality for treatment with treprostinil versus placebo from two studies (513 patients). The duration of treatment was similar (12 weeks) in each study. The method of infusion was different between the studies (intravenous versus subcutaneous). The individual odds ratios range from 0.41 to 1.01, and the summary odds ratio is 0.79 (95% CI, 0.32 to 1.96). The comparative efficacy of treprostinil in reducing mortality compared with placebo is inconclusive, given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 24. Forest plot of odds ratio for mortality for treprostinil versus placebo

Study name	Active drug	Deaths / Total Treated	Deaths / Total Control	Odds ratio	Lower limit	Upper limit
Hiremath 2010	Treprostinil	3 / 30	3 / 14	0.41	0.07	2.34
Simonneau 2002	Treprostinil	7 / 233	7 / 236	1.01	0.35	2.94
				0.79	0.32	1.96

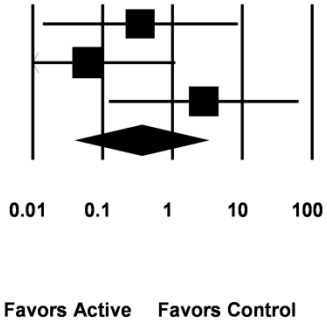


Abbreviations: CI=confidence interval

Figure 25 shows the forest plot of the odds ratio for mortality for treatment with combination therapy versus single therapy from three studies (533 patients). The therapies differed between studies: sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo, bosentan plus IV epoprostenol versus IV epoprostenol plus placebo, bosentan/sildenafil plus inhaled treprostinil versus bosentan/sildenafil plus placebo. The duration of treatment ranged from 12 to 16 weeks. The individual odds ratios range from 0.06 to 2.80, and the summary odds ratio is 0.37 (95% CI, 0.04 to 3.32) The comparative efficacy of combination therapy in reducing mortality compared with single therapy is inconclusive, given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 25. Forest plot of odds ratio for mortality for combination therapy versus monotherapy

Study name	Acronym	Active drug	Background drug	Deaths / Total Treated	Deaths / Total Control	Odds ratio	Lower limit	Upper limit
McLaughlin 2010	TRIUMPH-1	Treprostinil	Bosentan/Sldn	0 / 115	1 / 120	0.34	0.01	8.55
Simonneau 2008	PACES	Sildenafil	Epoprostenol	0 / 134	7 / 131	0.06	0.00	1.09
Humbert 2004	BREATHE-2	Bosentan	Epoprostenol	2 / 22	0 / 11	2.80	0.12	63.59
						0.37	0.04	3.32



Abbreviations: CI=confidence interval

There was little between-study heterogeneity for the studies that reported mortality at 12 to 16 weeks after initiation of therapy, with a Q-value of 11.33 for 13 degrees of freedom, I^2=0, p=0.583. When grouped by drug class, there was little heterogeneity among the 5 studies that evaluated endothelin antagonists and the seven studies that evaluated prostanoids, but there was moderate heterogeneity among the studies involving phosphodiesterase inhibitors, with a Q-value of 2.231 for 1 degree of freedom, I^2=55.2%.

6-Minute Walk Distance

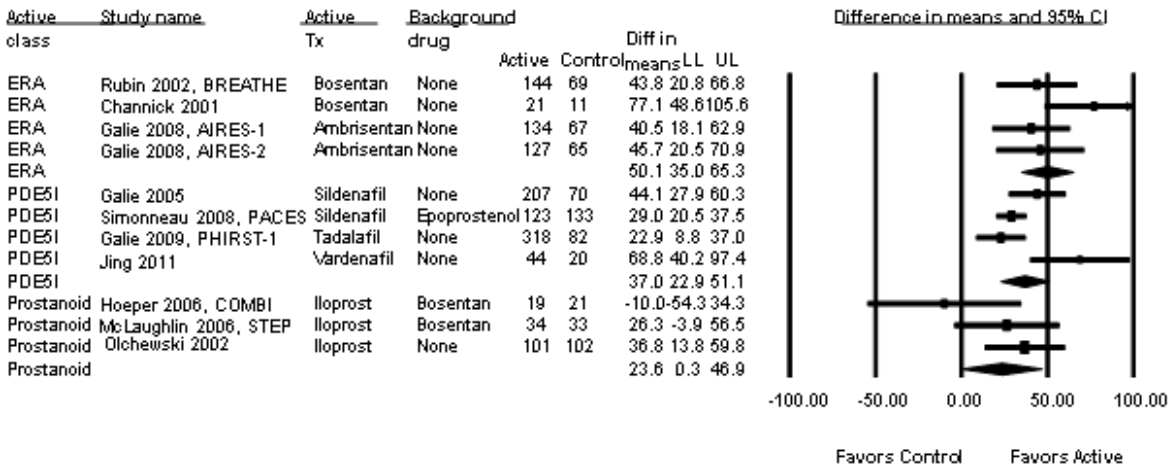
A total of 13 RCTs (12 articles) representing 2116 patients reported the effects of monotherapy or combination therapy for PAH on 6-minute walk distance (6MWD) at 12 or 16 weeks after initiating treatment (Figure 26).[84,96,146,154,160,164,165,167,168,171,176] One study compared bosentan with sildenafil.[146] Two studies compared bosentan with placebo.[84,154] One article reporting the results of two studies compared ambrisentan with placebo.[160] Two studies compared sildenafil with placebo,[160,164] one study compared tadalafil with placebo,[171] one study compared vardenafil with placebo,[176] and three studies compared iloprost with placebo.[165,167,168] Three of the 12 studies evaluated combination therapy versus single therapy: 1 sildenafil study was conducted in patients with epoprostenol as background therapy,[164] and 2 iloprost studies were conducted in patients with bosentan as background therapy.[167,168] Eleven of the 12 studies were rated good quality and one[167] fair quality.

The single small head-to-head comparison of bosentan versus sildenafil showed no statistically significant difference in 6MWD in an intention-to-treat analysis.[146] Meta-analysis of the 12 remaining studies revealed a statistically significant improvement in 6MWD associated with all 3 drug classes, with an overall improvement in between-group 6MWD associated with any treatment of 39.9 m (95% CI, 30.5 to 49.3). There was moderate heterogeneity among these studies, with a Q-value of 29.4 for 10 degrees of freedom, I^2=66%, p=0.001. Endothelin antagonists, as a class, were associated with an improvement in 6MWD of 50.1 m (CI, 35.0 to 65.3), whereas phosphodiesterase inhibitors and prostanoids were associated with improvements of 37.0 m (CI, 22.9 to 51.1) and 23.6 m (CI, 0.3 to 46.9), respectively.

Two good-quality studies[164,168] and one fair-quality study[167] involving 363 patients evaluated changes in 6MWD associated with combination therapy versus monotherapy. One study evaluated the efficacy of sildenafil with epoprostenol as background therapy, and two evaluated

the efficacy of iloprost with bosentan as background therapy. The summary estimate of the difference in means for these 3 studies was 24.1 m (95% CI, 8.2 to 40.0).

Figure 26. Forest plot for effects of therapy by drug class on 6MWD



Abbreviations: CI=confidence interval

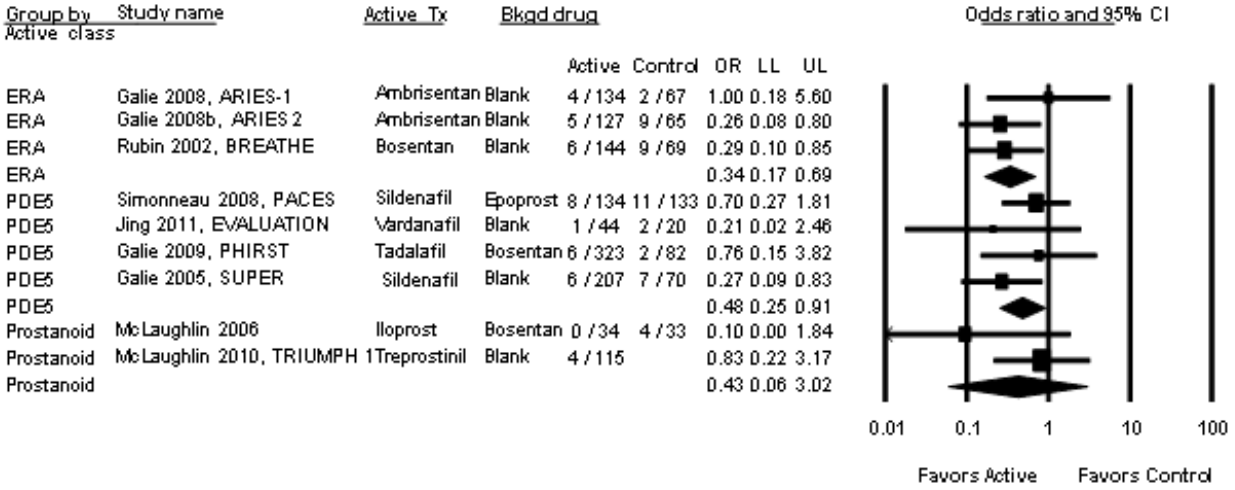
Hospitalization

A total of 9 RCTs (8 articles) representing 1921 patients reported the effects of monotherapy or combination therapy for PAH on hospitalization for worsening of PAH within 12 to 16 weeks after initiating treatment (Figure 27).[96,121,154,160,164,168,171,176] One study compared bosentan with placebo,[154] one article reporting the results of two studies compared ambrisentan with placebo,[160] two studies compared sildenafil with placebo[160,164] (one with epoprostenol as background therapy), one study compared tadalafil with placebo with bosentan as background therapy,[171] one study compared vardenafil with placebo,[176] one study compared iloprost with placebo with bosentan as background therapy[168] and one study compared treprostinil with placebo.[121] Eight of the nine studies were rated good quality and one fair quality.[154] There was low heterogeneity among these studies, with a Q-value of 5.74 for 8 degrees of freedom, I^2=0, p=0.57.

Meta-analysis of these 9 studies revealed a statistically significant reduction in hospitalization associated with endothelin antagonists (OR 0.34; 95% CI, 0.17 to 0.69) and phosphodiesterase inhibitors (OR 0.48; CI, 0.25 to 0.91) but not with prostanoids (OR 0.43; CI, 0.06 to 3.02). The summary odds ratio estimate for overall treatment effect across all drug classes and doses was 0.41 (CI, 0.26 to 0.66).

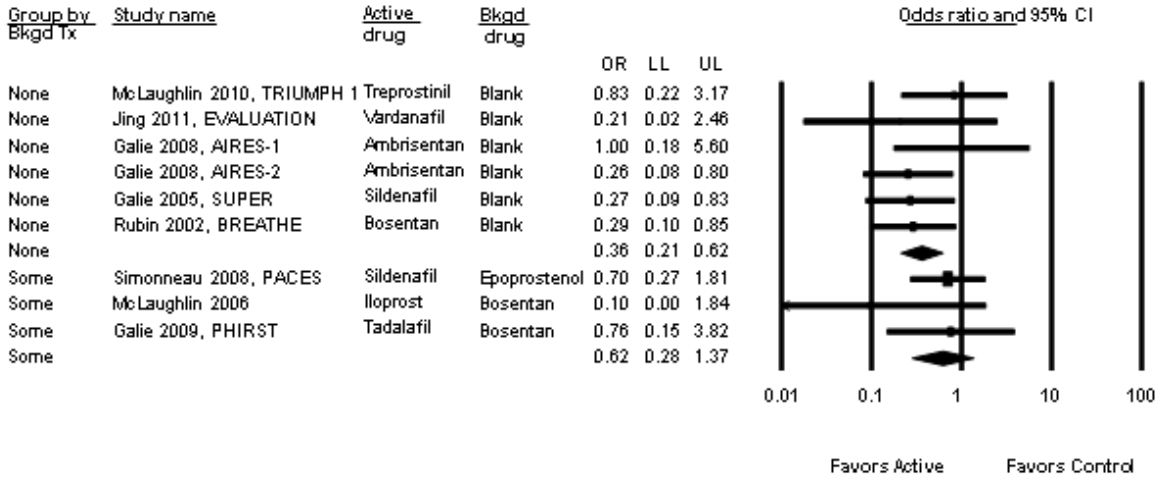
Three good-quality studies[164,168,171] involving 739 patients evaluated hospital admissions due to worsening PAH symptoms associated with combination therapy versus monotherapy (Figure 28). One study evaluated the efficacy of sildenafil with epoprostenol as background therapy, one compared tadalafil with placebo with bosentan as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. The summary estimate of the odds ratios for these three studies was 0.62 (95% CI, 0.28 to 1.37).

Figure 27. Forest plot for effects of therapy by drug class on hospitalization



Abbreviations: CI=confidence interval

Figure 28. Forest plot for effects of monotherapy vs. combination therapy on hospitalization



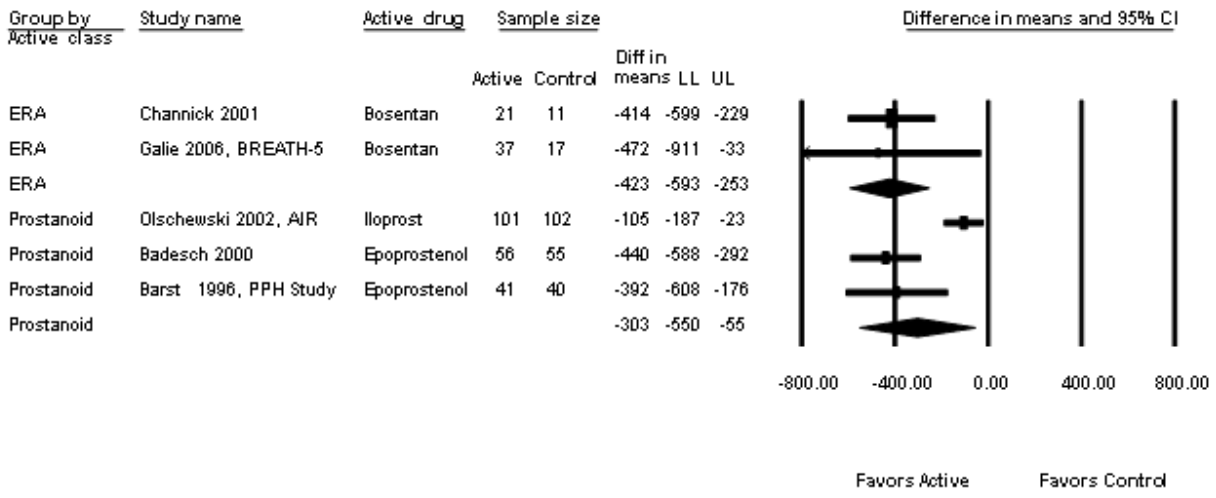
Abbreviations: CI=confidence interval

Pulmonary Vascular Resistance

A total of 5 RCTs representing 481 patients reported the effects of monotherapy or combination therapy for PAH on pulmonary vascular resistance as assessed by right heart catheterization at 12 or 16 weeks after initiating treatment (Figure 29).[75,84,156,165,169] Two studies compared bosentan with placebo,[84,156] one study compared iloprost with placebo,[165] and two studies compared epoprostenol with conventional therapy.[75,169] None of the five studies evaluated combination therapy versus single therapy. Four studies were rated good quality and one fair quality.[169]

Pulmonary vascular resistance was significantly lower in the active treatment arm versus the placebo arm at 12 to 16 weeks in each of these 5 studies. Meta-analysis of all five studies (combining endothelin antagonists with prostanoids, and combining all doses) yielded a summary estimate of -235 mm Hg/liter/min (95% CI, -298 to -172). There was very high heterogeneity among these studies, with a Q-value of 23.6 for 4 degrees of freedom, I^2=83.1%, p<0.001. No studies compared combination therapy with monotherapy using pulmonary vascular resistance at 12 to 16 weeks after initiating treatment as an outcome.

Figure 29. Forest plot for effects of therapy by drug class on pulmonary vascular resistance

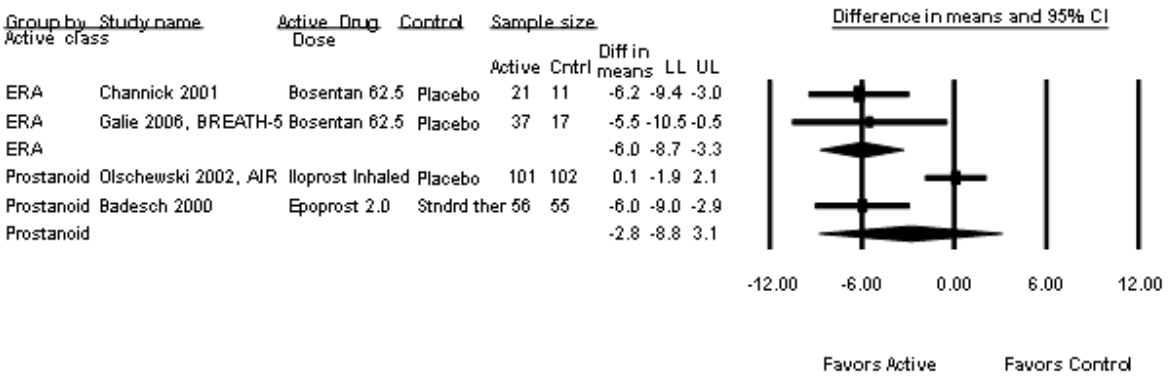


Abbreviations: CI=confidence interval

Mean Pulmonary Artery Pressure

Only 4 RCTs representing 40 patients reported mean pulmonary artery pressure as assessed by right heart catheterization 12 to 16 weeks after initiation of treatment (Figure 30).[84,156,165,169] There was high heterogeneity among these studies, with three rated good quality and one fair quality, with a Q-value of 18 for 3 degrees of freedom, I^2=83.4%, p<0.001. Mean pulmonary artery pressure was significantly lower in the active treatment arm versus the placebo arm at 12 to 16 weeks in 3 of the 4 studies with mean reductions in mPAP ranging from 5.5 to 6.2 mmHg. No studies compared combination therapy with monotherapy using mean pulmonary artery pressure at 12 to 16 weeks after initiating treatment as an outcome.

Figure 30. Forest plot for effects of therapy by drug class on mean pulmonary artery pressure



Abbreviations: CI=confidence interval

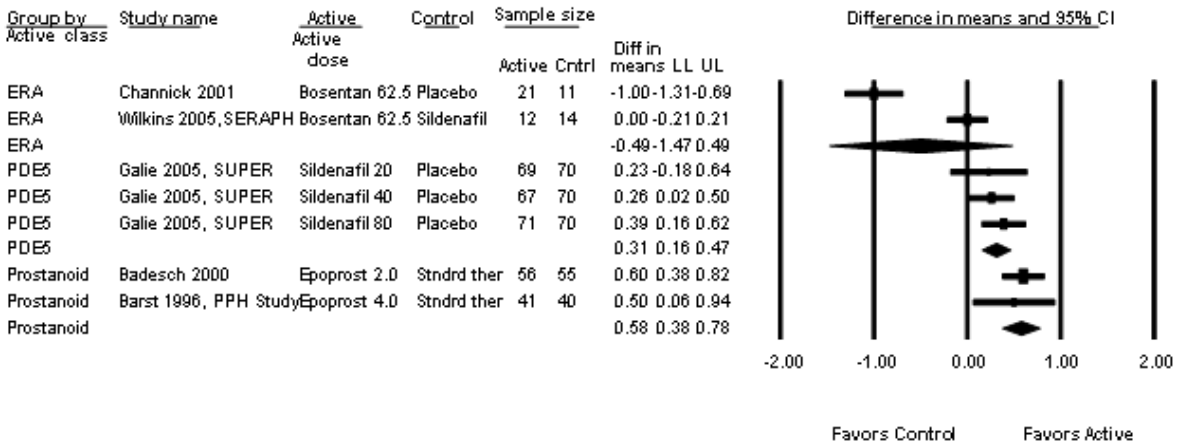
Cardiac Index

A total of 5 RCTs representing 527 patients reported cardiac index assessed 12 to 16 weeks after initiation of treatment (Figure 31).[75,84,146,160,169] One good-quality study compared bosentan with placebo,[84] one good-quality study was a head-to-head trial that compared bosentan with sildenafil,[146] one good-quality and one fair-quality study compared epoprostenol with conventional therapy,[75,169] and one good-quality study compared three doses of sildenafil with each other and with placebo.[160] There was very high heterogeneity among these studies, with a Q-value of 44.3 for 4 degrees of freedom, I^2=91.0%, p<0.001. However, this heterogeneity was confined to differences in studies of bosentan.

The single RCT that compared bosentan to placebo demonstrated a significant improvement in cardiac index of -1.00 (95% CI, -1.31 to -0.69) at 12 weeks, in favor of bosentan, while a study comparing bosentan to sildenafil showed no effect on cardiac index. Meta-analysis of the two epoprostenol studies yielded a summary estimate for improvement in cardiac index of 0.58 L per minute per meter-squared (CI, 0.38 to 0.78) at 12 weeks associated with treatment with epoprostenol versus conventional therapy. One study that compared sildenafil with placebo permitted dose comparisons; each of the 3 doses (20, 40, and 80 mg three times daily) was associated with statistically significant improvement in cardiac index at 12 weeks. Combining the data from all three sildenafil doses yields a summary estimate of an improvement in cardiac index associated with sildenafil versus placebo at 12 weeks, with a trend suggestive of increased effect at higher doses. Because of clinical and statistical heterogeneity in the bosentan studies,

and nonindependence of the dose-comparison estimates of the sildenafil study (due to use of a single common control group), no summary estimate was calculated. No studies compared combination therapy with monotherapy using cardiac outcome at 12 to 16 weeks after initiating treatment as an outcome.

Figure 31. Forest plot for effects of therapy by drug class on cardiac index



Abbreviations: CI=confidence interval

Adverse Events

Adverse events that occurred during the first 12 to 16 weeks after initiation of treatment were reported in 22 of the 27 RCTs that compared an endothelin antagonist, phosphodiesterase inhibitor, or prostanoids to either placebo or conventional therapy. Adverse events were not reported in the single RCT that compared two active therapies.[146] The most commonly assessed and reported adverse events were headache, dizziness, diarrhea, peripheral edema, jaw pain, flushing, and cough.

For these studies, we computed a summary estimate for the odds ratio, with an odds ratio greater than 1.0 indicating a higher incidence of adverse events associated with active treatment, and an odds ratio less than 1.0 indicating a lower incidence of adverse events associated with active treatment. When combination therapy was compared with monotherapy, an odds ratio greater than 1.0 indicates a higher incidence of adverse events associated with monotherapy.

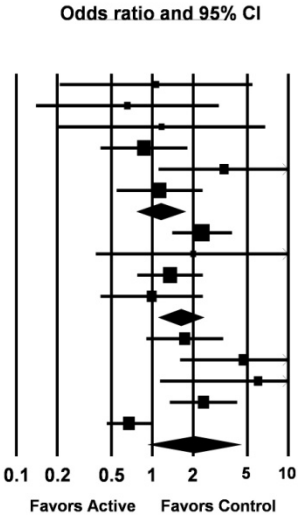
Headache

A total of 15 RCTs (14 articles) representing 2629 patients assessed the incidence of headache within the first 12 to 16 weeks of initiating therapy (Figure 32).[84,96,121,154,156,159,160,163-165,168,173,175,176] Thirteen were rated good quality and two fair quality. There was moderate heterogeneity among these studies, with a Q-value of 36.3 for 14 degrees of freedom, I^2=61.4%, p<0.001. Meta-analysis of 6 good-quality studies of endothelin antagonists involving 780 patients yielded a summary odds ratio of 1.16 (95% CI, 0.77 to 1.77). There was a significantly higher incidence of headache among patients treated with phosphodiesterase inhibitors compared with placebo or conventional therapy (OR 1.63; CI, 1.11 to 2.41). The summary odds ratio associated with prostanoids was somewhat higher at 2.05, but the 95-percent confidence interval includes 1.0 (CI, 0.93 to 4.53).

Three good-quality studies[159,164,168] involving 356 patients evaluated the incidence of headache associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for headache associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 32. Forest plot for effects of therapy by drug class on headache

Group by Active class	Study name	Acitve drug	Bkgd drug	Headache / Total Active	Headache / Total Control	OR	LL	UL
ERA	Channick 2001	Bosentan	None	6 / 21	3 / 11	1.07	0.21	5.44
ERA	Humbert 2004	Bosentan	Epoprostenol	6 / 22	4 / 11	0.66	0.14	3.08
ERA	Galie 2006	Bosentan	None	5 / 37	2 / 17	1.17	0.20	6.75
ERA	Galie 2008 (1)	Ambrisentan	None	25 / 134	14 / 67	0.87	0.42	1.81
ERA	Galie 2008 (2)	Ambrisentan	None	23 / 127	4 / 65	3.37	1.11	10.21
ERA	Rubin 2002	Bosentan	None	30 / 144	13 / 69	1.13	0.55	2.34
ERA						1.16	0.77	1.77
PDE5	Simonneau 2008	Sildenafil	Epoprostenol	76 / 134	44 / 122	2.32	1.40	3.84
PDE5	Jing 2011	Vardanafil	None	8 / 44	2 / 20	2.00	0.38	10.41
PDE5	Galie 2005	Sildenafil	None	95 / 207	27 / 70	1.35	0.78	2.35
PDE5	Barst 2011	Sildenafil	None	23 / 174	8 / 60	0.99	0.42	2.35
PDE5						1.63	1.11	2.41
Prostanoid	Olschewski 2002	Iloprost	None	30 / 101	20 / 102	1.73	0.91	3.31
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	19 / 34	7 / 33	4.70	1.61	13.78
Prostanoid	Hiremath 2010	Treprostinil	None	15 / 30	2 / 14	6.00	1.14	31.53
Prostanoid	McLaughlin 2010	Treprostinil	None	47 / 115	27 / 120	2.38	1.35	4.20
Prostanoid	Simonneau 2002	Treprostinil	None	79 / 233	102 / 236	0.67	0.46	0.98
Prostanoid						2.05	0.93	4.53



Abbreviations: CI=confidence interval

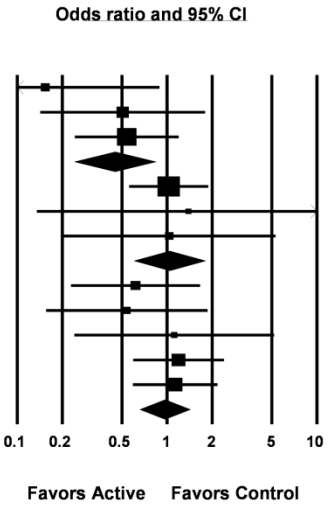
Dizziness

A total of 11 RCTs representing 1872 patients assessed the incidence of dizziness within the first 12 to 16 weeks of initiating therapy (Figure 33).[121,154,156,159,163-165,168,173,175,176] Nine studies were rated good quality and two fair quality. There was little evidence of statistical heterogeneity, with a Q-value of 8.87 for 10 degrees of freedom, I^2=0, p=0.30. With the exception of one small study[159] that reported a higher incidence of dizziness in the in the epoprostenol plus bosentan study arm compared with the epoprostenol plus placebo arm, there were no statistically significant differences in the proportion of patients reporting adverse events between active and control groups across in any of the individual studies, or within drug class.

Three good-quality studies[159,164,168] involving 356 patients evaluated the incidence of dizziness associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for dizziness associated with combination therapy compared with monotherapy because of the high degree of clinical heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 33. Forest plot for effects of therapy by drug class on dizziness

Group by Active class	Study name	Active drug	Bkgd drug	Active	Control	OR	LL	UL
ERA	Humbert 2004	Bosentan	Epoprost	9 / 22	9 / 11	0.15	0.03	0.89
ERA	Galie 2006	Bosentan	None	8 / 37	6 / 17	0.51	0.14	1.79
ERA	Rubin 2002	Bosentan	None	16 / 144	13 / 69	0.54	0.24	1.19
ERA						0.45	0.24	0.85
PDE5	Simonneau 2008	Sildenafil	Epoprost	28 / 134	25 / 122	1.02	0.56	1.88
PDE5	Jing 2011	Vardanafil	None	3 / 44	1 / 20	1.39	0.14	14.25
PDE5	Barst 2011	Sildenafil	None	6 / 174	2 / 60	1.04	0.20	5.28
PDE5						1.04	0.60	1.81
Prostanoid	Olschewski 2002	Iloprost	Blank	7 / 101	11 / 102	0.62	0.23	1.66
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	5 / 34	8 / 33	0.54	0.16	1.86
Prostanoid	Hiremath 2010	Treprostinil	None	7 / 30	3 / 14	1.12	0.24	5.16
Prostanoid	McLaughlin 2010	Treprostinil	None	20 / 115	18 / 120	1.19	0.60	2.39
Prostanoid	Simonneau 2002	Treprostinil	None	21 / 233	19 / 236	1.13	0.59	2.16
Prostanoid						0.97	0.66	1.44



Abbreviations: CI=confidence interval

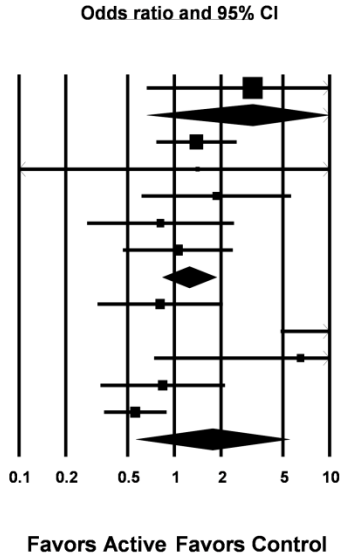
Diarrhea

A total of 11 RCTs representing 2311 patients assessed the incidence of diarrhea within the first 12 to 16 weeks of initiating therapy (Figure 34).[121,159,160,163-165,169,171,173,175,176] Eight studies were rated good quality and three fair quality. Odds ratios showed moderate heterogeneity, with a Q-value of 32.9 for 10 degrees of freedom, I^2=65.6%, p<0.001. Meta-analysis of studies by drug class or by all studies and doses combined did not yield a statistically significant odds ratio.

Three good-quality studies[159,164,171] involving 694 patients evaluated the incidence of diarrhea associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of tadalafil with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for diarrhea associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 34. Forest plot for effects of therapy by drug class on diarrhea

Group by Active class	Study name	Active drug	Bkgd drug	Active	Control	OR	LL	UL
ERA	Humbert 2004	Bosentan	Epoprostt	12 / 22	3 / 11	3.20	0.67	15.38
ERA						3.20	0.67	15.38
PDE5	Simonneau 2008	Sildenafil	Epoprost	34 / 134	24 / 122	1.39	0.77	2.51
PDE5	Jing 2011	Vardanafil	None	1 / 44	0 / 20	1.41	0.06	36.22
PDE5	Galie 2005	Sildenafil	None	21 / 207	4 / 70	1.86	0.62	5.63
PDE5	Barst 2011	Sildenafil	None	12 / 174	5 / 60	0.81	0.27	2.42
PDE5	Galie 2009	Tadalafil	Bosentan	33 / 323	8 / 82	1.05	0.47	2.37
PDE5						1.25	0.84	1.88
Prostanoid	Olschewski 2002	Iloprost	None	9 / 101	11 / 102	0.81	0.32	2.05
Prostanoid	Badesch 2000	Epoprost	None	28 / 56	3 / 55	17.33	4.84	62.11
Prostanoid	Hiremath 2010	Treprostinil	None	10 / 30	1 / 14	6.50	0.74	56.98
Prostanoid	McLaughlin 2010	Treprostinil	None	9 / 115	11 / 120	0.84	0.34	2.11
Prostanoid	Simonneau 2002	Treprostinil	None	36 / 233	58 / 236	0.56	0.35	0.89
Prostanoid						1.77	0.57	5.53



Abbreviations: CI=confidence interval

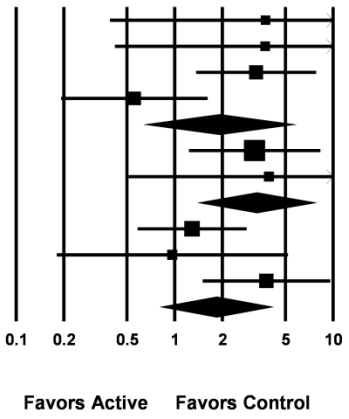
Peripheral Edema

A total of 9 RCTs (8 articles) representing 1880 patients assessed the incidence of peripheral edema within the first 12 to 16 weeks of initiating therapy (Figure 35).[96,156,159,164,165,168,171,173] All nine studies were rated good quality. There was low heterogeneity among these studies, with a Q-value of 12.5 for 8 degrees of freedom, I^2=35.9%, p<0.13. Meta-analysis by drug class yielded statistically significant odds ratios for phosphodiesterase inhibitors (OR 3.32; 95% CI, 1.40 to 7.87) but not for endothelin antagonists (OR 1.93; CI, 0.64 to 5.85) or prostanoids (OR 1.85; CI, 0.81 to 4.21). The overall summary estimate for the odds ratio associated with active therapy across all studies was statistically significant at 2.32 (CI, 1.37 to 3.91).

Three good-quality studies[159,164,168] involving 356 patients evaluated the incidence of peripheral edema associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for peripheral edema associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 35. Forest plot for effects of therapy by drug class on peripheral edema

Group by Active class	Study name	Active drug	Bkgd drug	Edema / Total Active	Edema / Total Control	OR	LL	UL
ERA	Humbert 2004	Bosentan	Epoprostenol	6 / 22	1 / 11	3.75	0.39	35.92
ERA	Galie 2006	Bosentan	None	7 / 37	1 / 17	3.73	0.42	33.07
ERA	Galie 2008	Ambrisentan	None	37 / 134	7 / 67	3.27	1.37	7.80
ERA	Galie 2008	Ambrisentan	None	8 / 127	7 / 65	0.56	0.19	1.61
ERA						1.93	0.64	5.85
PDE5	Simonneau 2008	Sildenafil	Epoprostenol	19 / 134	6 / 122	3.19	1.23	8.29
PDE5	Galie 2009	Tadalafil	Bosentan	15 / 323	1 / 82	3.94	0.51	30.31
PDE5						3.32	1.40	7.87
Prostanoid	Olschewski 2002	Iloprost	None	16 / 101	13 / 102	1.29	0.58	2.84
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	3 / 34	3 / 33	0.97	0.18	5.18
Prostanoid	Simonneau 2002	Treprostinil	None	21 / 233	6 / 236	3.80	1.50	9.59
Prostanoid						1.85	0.81	4.21



Abbreviations: CI=confidence interval

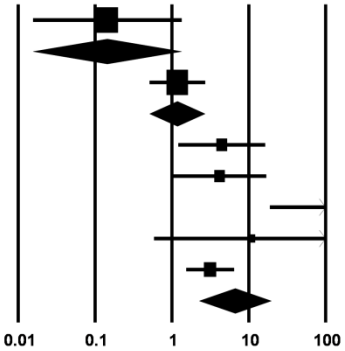
Jaw Pain

A total of 7 RCTs assessed the incidence of jaw pain within the first 12 to 16 weeks of initiating therapy (Figure 36).[159,164,165,168,169,173,175] Five studies were rated good quality and two fair quality. There was high heterogeneity among these studies, with a Q-value of 23.3 for 6 degrees of freedom, I^2=74.3%, p=0.001. Of these, 5 RCTs representing 894 patients compared a prostanoid with placebo or conventional therapy. Meta-analysis of these five studies yielded a summary estimate of the odds ratio of 6.68 (95% CI, 2.28 to 19.62).

Three good-quality studies[159,164,168] involving 356 patients evaluated the incidence of jaw pain associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for jaw pain associated with combination therapy compared with monotherapy because of the high degree of clinical heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 36. Forest plot for effects of therapy by drug class on jaw pain

Group by Active class	Study name	Active drug	Bkgd drug	Active	Control	OR	LL	UL
ERA	Humbert 2004	Bosentan	Epoprost	13 / 22	10 / 11	0.14	0.02	1.34
ERA						0.14	0.02	1.34
PDE5	Simonneau 2008	Sildenafil	Epoprost	14 / 134	11 / 122	1.18	0.51	2.70
PDE5						1.18	0.51	2.70
Prostanoid	Olschewski 2002	Iloprost	None	12 / 101	3 / 102	4.45	1.22	16.28
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	10 / 34	3 / 33	4.17	1.03	16.85
Prostanoid	Badesch 2000	Epoprost	None	42 / 56	0 / 55	325.3	18.9	5609.7
Prostanoid	Hiremath 2010	Treprostinil	None	8 / 30	0 / 14	10.96	0.59	204.67
Prostanoid	Simonneau 2002	Treprostinil	None	31 / 233	11 / 236	3.14	1.54	6.41
Prostanoid						6.68	2.28	19.62



Abbreviations: CI=confidence interval

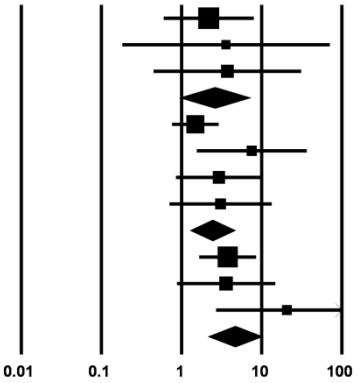
Flushing

A total of 10 RCTs (9 articles) representing 2113 patients assessed the incidence of flushing within the first 12 to 16 weeks of initiating therapy (Figure 37).[96,121,154,160,164,165,168,171,176] All 10 studies were rated good quality. There was low heterogeneity among these studies, with a Q-value of 9.55 for 9 degrees of freedom, I^2=5.8%, p=0.39. Meta-analysis of these studies demonstrates that the incidence of flushing was significantly higher among patients treated with a phosphodiesterase inhibitor (OR 2.46; 95% CI, 1.27 to 4.75) or a prostanoid (OR 4.72; CI, 2.13 to 10.42). The summary odds ratio for flushing associated with treatment with an endothelin antagonist may also be elevated (OR 2.63; CI, 0.94 to 7.40), but the 95-percent confidence interval of this summary estimate includes 1.0.

Three good-quality studies[164,168,171] involving 728 patients evaluated the incidence of flushing associated with combination therapy versus monotherapy. One study compared sildenafil with placebo with epoprostenol as background therapy, one evaluated the efficacy of tadalafil with bosentan as background therapy, and one compared iloprost to placebo with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for flushing associated with combination therapy compared with monotherapy because of the high degree of clinical heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 37. Forest plot for effects of therapy by drug class on flushing

Group by Active class	Study name	Active drug	Bkgd drug	Active	Control	OR	LL	UL
ERA	Rubin 2002	Bosentan	None	13 / 144	3 / 69	2.18	0.60	7.93
ERA	Galie 2008	Ambrisentan	None	3 / 134	0 / 67	3.59	0.18	70.58
ERA	Galie 2008	Ambrisentan	None	7 / 127	1 / 65	3.73	0.45	31.01
ERA						2.63	0.94	7.40
PDE5	Simonneau 2008	Sildenafil	Epoprost	26 / 134	17 / 122	1.49	0.76	2.90
PDE5	Jing 2011	Vardanafil	None	20 / 44	2 / 20	7.50	1.55	36.30
PDE5	Galie 2005	Sildenafil	None	24 / 207	3 / 70	2.93	0.85	10.04
PDE5	Galie 2009	Tadalafil	Bosentan	23 / 323	2 / 82	3.07	0.71	13.28
PDE5						2.46	1.27	4.75
Prostanoid	Olschewski 2002	Iloprost	None	27 / 101	9 / 102	3.77	1.67	8.51
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	9 / 34	3 / 33	3.60	0.88	14.75
Prostanoid	McLaughlin 2010	Treprostinil	None	17 / 115	1 / 120	20.64	2.70	157.87
Prostanoid						4.72	2.13	10.42



Abbreviations: CI=confidence interval

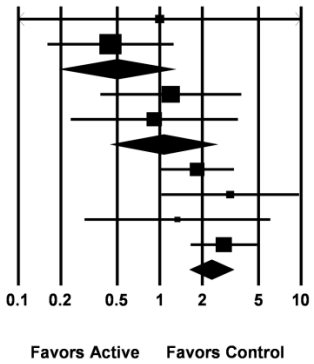
Cough

A total of 8 RCTs representing 1306 patients assessed the incidence of cough within the first 12 to 16 weeks of initiating therapy (Figure 38).[121,154,159,160,163,165,168,175] Six studies were rated good quality and two fair quality. There was moderate amount of heterogeneity among the 8 studies, with a Q-value of 12.6 for 7 degrees of freedom, I^2=44%, p=0.08. Meta-analysis of these studies suggests that there is no difference in incidence of cough associated with endothelin antagonists or phosphodiesterase inhibitors. Prostanoids, however, are associated with a higher incidence of cough compared with placebo or conventional therapy. The summary estimate of the odds ratio associated with prostanoids is 2.34 (95% CI, 1.62 to 3.37).

Two good-quality studies[159,168] involving 100 patients evaluated the incidence of cough associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for cough associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 38. Forest plot for effects of therapy by drug class on cough

Group by Active class	Study name	Active drug	Bkgd drug	Cough / Total Active	Cough / Total Control	OR	LL	UL
ERA	Humbert 2004	Bosentan	Epoprost	2 / 22	1 / 11	1.00	0.08	12.40
ERA	Rubin 2002	Bosentan	None	8 / 144	8 / 69	0.45	0.16	1.25
ERA						0.50	0.19	1.30
PDE5	Galie 2005	Sildenafil	None	14 / 207	4 / 70	1.20	0.38	3.76
PDE5	Barst 2011	Sildenafil	None	8 / 174	3 / 60	0.92	0.23	3.57
PDE5						1.07	0.45	2.57
Prostanoid	Olschewski 2002	Iloprost	None	39 / 101	26 / 102	1.84	1.01	3.35
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	14 / 34	6 / 33	3.15	1.03	9.63
Prostanoid	Hiremath 2010	Treprostinil	None	8 / 30	3 / 14	1.33	0.29	6.04
Prostanoid	McLaughlin 2010	Treprostinil	None	62 / 115	35 / 120	2.84	1.66	4.87
Prostanoid						2.34	1.62	3.37



Abbreviations: CI=confidence interval

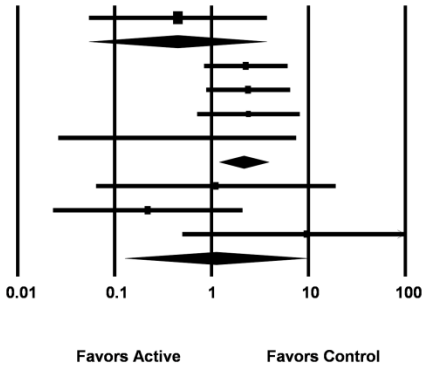
Infections

A total of 8 RCTs representing 1210 patients assessed the incidence of infections within the first 12 to 16 weeks of initiating therapy (Figure 39).[159,163,164,167-169,171,176] Five studies were rated good quality and three fair quality. There was low heterogeneity among these studies, with a Q-value of 8.0 for 7 degrees of freedom, I^2=12.8%, p=0.33. Meta-analysis of these studies yields an overall summary odds ratio estimate of 1.87 (95% CI, 1.07 to 3.25).

Four good-quality studies[159,164,168,171] and one fair-quality study[167] involving 801 patients evaluated the incidence of infections associated with combination therapy versus monotherapy. We did not calculate a summary estimate for the odds ratio for infections associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 39. Forest plot for effects of therapy by drug class on infections

Group by Active class	Study name	Active drug	Bkgd drug	Infection / Total Active	Infection / Total Control	OR	LL	UL
ERA	Humbert 2004	Bosentan	Epoprost	2 / 22	2 / 11	0.45	0.05	3.72
ERA						0.45	0.05	3.72
PDE5	Simonneau 2008	Sildenafil	Epoprost	14 / 134	6 / 122	2.26	0.84	6.07
PDE5	Barst 2011	Sildenafil	None	31 / 174	5 / 60	2.38	0.88	6.45
PDE5	Galie 2009	Tadalafil		27 / 323	3 / 82	2.40	0.71	8.12
PDE5	Jing 2011	Vardanafil	None	1 / 44	1 / 20	0.44	0.03	7.44
PDE5						2.17	1.20	3.94
Prostanoid	Hoeper 2006	Iloprost	Bosentan	1 / 19	1 / 21	1.11	0.06	19.09
Prostanoid	McLaughlin 2006	Iloprost	Bosentan	1 / 34	4 / 33	0.22	0.02	2.08
Prostanoid	Badesch 20000	Epoprost	None	4 / 56	0 / 55	9.51	0.50	181.06
Prostanoid						1.12	0.13	9.87



Abbreviations: CI=confidence interval

Results for these outcomes and comparisons, along with ratings for strength of evidence are shown in Tables 24–30.

Table 24. Summary SOE for KQ 3: mortality

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Combination therapy vs. monotherapy					**SOE=Insufficient**
3 (533)	Low (3)	Inconsistent	Direct	Imprecise	0.37 (0.04 to 3.32)
Sildenafil vs. bosentan					**SOE=Insufficient**
1 (26)	Low (1)	NA	Direct	Imprecise	NA
Bosentan vs. placebo					**SOE=Insufficient**
3 (411)	Low (3)	Inconsistent	Direct	Imprecise	OR 0.72 (0.14 to 3.60)
Iloprost vs. placebo					**SOE=Insufficient**
3 (266)	Low (2) Moderate (1)	Inconsistent	Direct	Imprecise	OR 0.70 (0.88 to 6.22)
Epoprostenol vs. placebo or standard therapy					**SOE=Insufficient**
2 (192)	Low (2)	Inconsistent	Direct	Imprecise	OR 0.25 (0.02 to 3.76)
Ambrisentan vs. placebo					**SOE=Insufficient**
2 (330)	Low (2)	Consistent	Direct	Imprecise	OR 0.33 (0.06 to 1.74)
Treprostinil vs. placebo					**SOE=Insufficient**
2 (513)	Low (2)	Consistent	Direct	Imprecise	OR 0.79 (0.32 to 1.96)

Abbreviations: CI=confidence interval; OR=odds ratio; SOE=strength of evidence

Table 25. Summary SOE for KQ 3: 6MWD

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Combination therapy vs. monotherapy					**SOE=Low**
3 (363)	Low (2) Moderate (1)	Inconsistent	Direct	Imprecise	Mean difference 24.1 (8.2 to 40.0) Favors combination therapy
Sildenafil vs. bosentan					**SOE=Insufficient**
1 (26)	Low (1)	NA	Direct	Imprecise	Mean difference 16 (NS) No significant difference between treatments
Endothelin antagonists vs. placebo					**SOE=High**
4 (638)	Low (4)	Consistent	Direct	Precise	Mean difference 50.1 (35.0 to 65.3) Favors endothelin antagonists
Phosphodiesterase type 5 inhibitors vs. placebo or standard therapy					**SOE=High**
3 (741)	Low (3)	Consistent	Direct	Precise	Mean difference 37.0 (22.9 to 51.1) Favors PDE inhibitors

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Prostanoids vs. placebo					**SOE=Low**
1 (203)	Low (1)	NA	Direct	Imprecise	Mean difference 23.6 (0.3 to 46.9) Favors prostanoids

Abbreviations: CI=confidence interval; OR=odds ratio; SOE=strength of evidence

Table 26. Summary SOE for KQ 3: hospitalization

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Combination therapy vs. monotherapy					**SOE=Insufficient**
3 (739)	Low (3)	Inconsistent	Direct	Imprecise	OR 0.62 (0.28 to 1.37) Inconclusive benefit (few studies, wide CIs
Sildenafil vs. bosentan					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA
Endothelin antagonists vs. placebo					**SOE=Moderate**
3 (606)	Low (2) Moderate (1)	Consistent	Direct	Imprecise	OR 0.34 (0.17 to 0.69) Favors endothelin antagonists
Phosphodiesterase type 5 inhibitors vs. placebo or standard therapy					**SOE=Moderate**
2 (341))	Low (2)	Consistent	Direct	Imprecise	OR 0.48 (0.25 to 0.91) Favors PDE inhibitors
Prostanoids vs. placebo					**SOE=Insufficient**
1 (235))	Low (1)	Inconsistent	Direct	Imprecise	OR 0.43 (0.06 to 3.02) No clear difference in risk of hospitalization between treatments

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio; SOE=strength of evidence

Table 27. Summary SOE for KQ 3: pulmonary vascular resistance

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo					**SOE=Insufficient**
2 (86)	Low (2)	Inconsistent	Direct	Imprecise	NA
Phosphodiesterase inhibitors vs. placebo or standard therapy					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA
Prostanoids vs. placebo					**SOE=Low**
3 (395)	Low (2) Moderate (1)	Inconsistent	Direct	Imprecise	Mean difference -303 (-550 to -55) Favors prostanoids
Combination therapy vs. monotherapy					**SOE=Insufficient**

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
0 (0)	NA	NA	NA	NA	NA

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio; SOE=strength of evidence

Table 28. Summary SOE for KQ 3: mean pulmonary artery pressure

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo					**SOE=Insufficient**
2 (86)	Low (2)	Consistent	Direct	Imprecise	Mean difference -0.05 (-0.12 to 0.02)
Phosphodiesterase inhibitors vs. placebo or standard therapy					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA
Prostanoids vs. placebo					**SOE=Insufficient**
2 (111)	Low (1) Moderate (1)	Inconsistent	Direct	Imprecise	NA
Combination therapy vs. monotherapy					**SOE=Insufficient**
3 (739)	Low (3)	Inconsistent	Direct	Imprecise	NA

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio; SOE=strength of evidence

Table 29. Summary SOE for KQ 3: cardiac index

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Bosentan vs. placebo					**SOE=Insufficient**
2 (58)	Low (2)	Inconsistent	Direct	Imprecise	NA
Epoprostenol vs. placebo or standard therapy					**SOE=Low**
2 (192)	Low (2)	Consistent	Direct	Imprecise	Mean difference 0.58 (0.38 to 0.78) Favors epoprostenol
Sildenafil vs. placebo					**SOE=Insufficient**
1 (277)	Low (1)	NA	Direct	NA	NA
Combination therapy vs. monotherapy					**SOE=Insufficient**
0 (0)	NA	NA	NA	NA	NA

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio; SOE=strength of evidence

Table 30. Summary SOE for KQ 3: adverse events

Number of Studies (Subjects)	Domains				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
PDE inhibitor therapy vs. placebo or conventional therapy: Headache					**SOE=Moderate**
4 (833)	Low (4)	Consistent	Direct	Imprecise	OR 1.63 (1.11 to 2.41) Favors placebo
Combination therapy vs. monotherapy: Headache					**SOE=Insufficient**
3 (356)	Low (3)	Inconsistent	Direct	Imprecise	NA
Combination therapy vs. monotherapy: Dizziness					**SOE=Insufficient**
3 (356)	Low (3)	Inconsistent	Direct	Imprecise	NA
Combination therapy vs. monotherapy: Diarrhea					**SOE=Insufficient**
3 (694)	Low (3)	Inconsistent	Direct	Imprecise	NA
Combination therapy vs. monotherapy: Peripheral edema					**SOE=Insufficient**
4 (761)	Low (4)	Inconsistent	Direct	Imprecise	NA
Prostanoids vs. placebo: Jaw pain					**SOE=High**
5 (894)	Low (3) Moderate (2)	Consistent	Direct	Precise	OR 6.68 (2.28 to 19.62) Favors placebo
Combination therapy vs. monotherapy: Jaw pain					**SOE=Insufficient**
3 (356)	Low (3)	Inconsistent	Direct	Imprecise	NA
PDE therapy vs. placebo or conventional therapy: Flushing					**SOE=Moderate**
4 (1002)	Low (4)	Consistent	Direct	Imprecise	OR 2.46 (1.27 to 4.75) Favors placebo
Prostanoid therapy vs. placebo or conventional therapy: Flushing					**SOE=Moderate**
3 (505)	Low (3)	Consistent	Direct	Imprecise	OR 4.72 (2.13 to 10.4) Favors placebo
Combination therapy vs. monotherapy: Flushing					**SOE=Insufficient**
3 (728)	Low (3)	Inconsistent	Direct	Precise	NA
Prostanoids vs. placebo: Cough					**SOE=High**
4 (549)	Low (3) Moderate (1)	Consistent	Direct	Precise	OR 2.34 (1.62 to 3.37) Favors placebo
Combination therapy vs. monotherapy: Cough					**SOE=Insufficient**
2 (100)	Low (2)	Inconsistent	Direct	Imprecise	NA
Combination therapy vs. monotherapy: Infections					**SOE=Insufficient**
5 (801)	Low (4) Moderate (1)	Inconsistent	Direct	Imprecise	NA

Abbreviations: CI=confidence interval; NA=not applicable; OR=odds ratio; SOE=strength of evidence

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review, we included 51 studies involving 6980 patients that evaluated biomarker tests, echocardiography, or both, to screen for PAH (KQ 1); 80 studies involving 7224 patients that evaluated biomarker tests, echocardiography, or both, to diagnose and follow progression of disease as well as response to therapy for PAH (KQ 2); and 33 studies involving 3981 patients that assessed the effectiveness of drug treatments for PAH in adults.

KQ 1: Screening for PAH

We found 1 study involving 372 patients that evaluated the combination of biomarker tests and echocardiography to echocardiography alone to screen for PAH (Key Question [KQ] 1). Based on one good-quality prospective cohort study, biomarker testing with NT-proBNP may be useful in ruling out PAH among those suspected of PH who also have elevated sPAP by echocardiography;[25] however, no data are available regarding combined echocardiography and biomarker screening in asymptomatic patients at high risk for PAH. In the absence of other direct comparative trials, we attempted to address this question by evaluating the efficacy of biomarker and echocardiography independently for screening and diagnosis of PAH. We reviewed 50 studies involving 6608 patients that evaluated biomarker tests, echocardiography, or both, to screen for PAH. The associations between natriuretic peptide testing and PAH diagnosis is insufficiently strong to support its use alone as a screening test in either asymptomatic or symptomatic patients suspected of PAH. Data on biomarker testing were essentially limited to a single test—NT-proBNP—which showed only moderate correlation with RHC hemodynamic measures and showed a great deal of variability between studies in its diagnostic accuracy and discrimination.

We found that echocardiography estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}) demonstrated good accuracy in screening for PAH. In low prevalence populations (<10%), negative predictive value of a normal sPAP is high, suggesting that echocardiography with a low threshold may be an appropriate test in asymptomatic high-risk populations or in patients with symptoms suggesting PAH. (This is shown in studies of liver transplant studies with complete verification).

Our findings suggest that echocardiographic estimation of sPAP is sufficiently accurate to justify its role in screening for PAH in symptomatic patients suspected of having PH. However, this conclusion has several important caveats. First, echocardiography in a small, but significant, number of patients may not produce an estimate of sPAP because of poor-quality Doppler visualization of the tricuspid regurgitant jet. Second, echocardiographic estimates of sPAP often over- or under-estimate pulmonary artery pressure enough to result in misclassification according to PAH diagnostic threshold—hence the selection of a test threshold is critical for the aim of screening. A single test threshold is insufficient to perform with simultaneously high sensitivity and specificity (or PPV and NPV), especially in populations with higher risk or higher prevalence (more symptomatic), where echocardiography cannot be relied upon to exclude pulmonary hypertension if pretest probability is high. In asymptomatic patients at high risk for PH, echocardiography seems to perform with similar sensitivity and specificity; however, these studies suffer from verification bias, which likely inflates both the sensitivity and specificity

estimates. Two prospective studies that show approximately 10 percent of asymptomatic patients with systemic sclerosis and normal sPAP develop PH when serially retested with echocardiography are consistent with either misclassification at baseline echocardiographic screening or prospective development of PH. This would suggest that if echocardiographic screening of asymptomatic patients with a high-risk diagnosis were to be undertaken, then serial testing would be necessary.

Table 31 summarizes the findings of our review and the strength of evidence (SOE) for the available outcomes of sensitivity, specificity, correlation coefficients, and adverse effects of biomarker and echocardiographic tests.

Table 31. Summary of strength of evidence and effect estimates for echocardiography vs. echocardiography plus biomarkers as screening modalities for PAH (KQ 1)[a]

Test	Sensitivity	Specificity	Correlation with RHC
Echo sPAP with NT-proBNP versus Echo sPAP in symptomatic patients	SOE=Insufficient (1 study, 121 patients) NT-proBNP >80 pg/mL has a low false negative rate compared with RHC reference standard; the serial testing study design did not allow for NT-proBNP testing to improve sensitivity beyond that of echo sPAP alone	SOE=Low (1 study, 121 patients) NT-proBNP ≤80 pg/mL ruled out PAH in 9–16% of patients with elevated echo sPAP ≥36 mmHg	SOE=Insufficient (No studies)
Echo sPAP with NT-proBNP versus Echo sPAP in asymptomatic patients	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)	SOE=Insufficient (No studies)
NT-proBNP compared with RHC	SOE=Low (3 studies, 198 patients) NT-proBNP has variable sensitivity (range, 56% to 100%) for diagnosing PAH; uncertain performance for ruling in PAH	SOE=Low (3 studies, 198 patients) NT-proBNP has variable specificity (range, 24% to 95%); uncertain performance for ruling out PAH	SOE=Moderate (3 studies, 176 patients) Correlation of NT-proBNP and RHC is only moderate (range, 0.43 to 0.72)
TRV/TG/sPAP compared with RHC	SOE=Moderate (15 studies, 1898 patients) Echocardiographic estimate of sPAP showed variable sensitivity ranging from 58% to 100%, with lower prevalence studies finding higher sensitivity	SOE=Moderate (15 studies, 1898 patients) Echocardiographic estimate of sPAP showed variable specificity ranging from 64% to 98%, with lower prevalence studies finding higher specificity	SOE=Moderate (14 studies, 1822 patients) Echocardiographic estimates of sPAP showed moderate to strong correlation (range, 0.38 to 0.96) with RHC and were on average unbiased, but were limited by imprecision and by a significant minority of patients in whom TRV was not measurable

Test	Sensitivity	Specificity	Correlation with RHC
TRV/VTI$_{RVOT}$ compared with RHC	SOE=Moderate (6 studies, 218 patients) Echocardiographic estimate of PVR showed reasonably high sensitivity (range, 89% to 100%) for ruling in PAH	SOE=Moderate (6 studies, 218 patients) Echocardiographic estimate of PVR showed variable specificity (range, 50% to 97%), with better specificity in lower prevalence studies (range, 94% to 97%)	SOE=High (6 studies, 218 patients) Strong correlation between echocardiographic estimates of PVR and PVR by RHC (range, 0.74 to 0.84)

[a]Gray highlights insufficient strength of evidence.
Abbreviations: NT-proBNP=N-terminal pro-B-type natriuretic peptide; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure; TRV=tricuspid regurgitant jet velocity; VTI$_{RVOT}$=velocity-time integral of right ventricular outflow tract

KQ 2: Management of PAH

Currently, right heart catheterization (RHC) is the gold standard for diagnosing and monitoring progression of PAH. Several biomarkers and echocardiographic parameters have been proposed as potential alternatives to frequent RHC monitoring. In KQ 2 we reviewed studies that evaluated the most commonly studied biomarkers (natriuretic peptides, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, and D-dimer) and echocardiographic parameters (RV size, RA size, FAC, TAPSE, RIMP/MPI/Tei index, sPAP, mPAP, TR jet, peak TR jet, RVOT, RVEF, RVSP or pericardial effusion) to determine the ability of these measures to assess severity of disease, predict mortality or lung transplantation, or assess response to therapy.

In studies evaluating correlation of the above measures with RHC measures or a commonly used measure of disease severity (6MWD) studies were too underpowered to give reliable results. However, by combining studies looking at the same parameters and performing a meta-analysis we were able to increase the power for seven different comparisons: (1) BNP versus RHC-mPAP, (2) BNP versus RHC-PVR, (3) BNP versus RHC-CI, (4) BNP versus RHC-RAP, (5) BNP versus RHC-PCWP, (6) BNP versus 6MWD, and (7) echocardiography-derived sPAP versus RHC-sPAP. BNP showed only moderate correlation with most RHC measures (mPAP, PVR, CI, RAP) and clinical measures of disease severity (6MWD) and showed weak correlation with PCWP. Most effect estimates were precise (mPAP, PVR, CI, RAP, 6MWD), but estimates for PCWP were imprecise, making it difficult to interpret the clinical importance of the findings for this measure. For the other measures, correlation with BNP was only moderate, indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Echocardiography-derived sPAP showed strong correlation with RHC-sPAP, although there was a great deal of heterogeneity among these studies and only moderate strength of evidence to support the use of this measure. In studies evaluating the ability of biomarkers or echocardiographic measures to predict mortality, we were able to perform a meta-analysis on four measures. Studies evaluating pericardial effusion, BNP, RA size, and FAC showed fair consistency among hazard ratio estimates. Overall, pericardial effusion was the strongest predictor of mortality and may be useful clinically, though results were not highly precise. BNP, RA size, and FAC showed no significant ability to predict mortality.

The remaining studies that were not included in the meta-analyses were considered to provide insufficient evidence due to small size and poor quality.

Several studies evaluated mean or median levels of biomarkers or echocardiographic parameters at various points in time or as a change from baseline to evaluate response to therapy. Due to the small number and heterogeneity of these studies, we were unable to perform meta-analysis on this data. While a few studies found changes in biomarkers or echocardiographic parameters in response to various treatments, there was insufficient data to quantitatively assess overall response or to recommend use of these markers as surrogate outcomes measures.

We found no studies addressing diagnostic thinking efficacy, therapeutic efficacy, or safety concerns with echocardiography or biomarkers.

The strength of evidence (SOE) ratings for the most commonly reported biomarkers and echocardiographic parameters are summarized in Table 32 (management of PAH) and Table 33 (prediction of patient outcomes).

Table 32. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the management of PAH (KQ 2)

Comparison	Number of Studies (Patients)	Summary Correlation Coefficient Estimate (95% CI)	SOE and Findings
BNP compared with RHC-mPAP	13 (559)	0.41 (0.31 to 0.49)	SOE=Moderate Serum BNP level shows only moderate correlation with mPAP
BNP compared with RHC-PVR	12 (638)	0.49 (0.32 to 0.63)	SOE=Moderate Serum BNP level shows only moderate correlation with PVR
BNP compared with RHC-RAP	11 (600)	0.47 (0.39 to 0.55)	SOE=Moderate Serum BNP level shows only moderate correlation with RAP
BNP compared with cardiac index	9 (509)	-0.47 (-0.59 to -0.34)	SOE=Moderate Serum BNP level shows only moderate correlation with cardiac index
BNP compared with PCWP	5 (319)	0.16 (0.01 to 0.31)	SOE=Low Serum BNP level shows poor correlation with PCWP
BNP compared with 6MWD (absolute)	8 (396)	-0.47 (-0.58 to -0.34)	SOE=Moderate Serum BNP level shows only moderate correlation with 6MWD
Echocardiography-derived sPAP compared with RHC-sPAP	8 (302)	0.79 (0.55 to 0.91)	SOE=Moderate sPAP estimated by echocardiography shows good correlation with sPAP from RHC

Abbreviations: 6MWD=6-minute walk distance; BNP=B-type natriuretic peptide; CI=confidence interval; FAC=fractional area change; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrium; RAP=right atrial pressure; RHC=right heart catheterization; SOE=strength of evidence; sPAP=systolic pulmonary artery pressure

Table 33. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the prediction of mortality (KQ 2)

Marker	Number of Studies (Patients)	Summary Hazard Ratio Estimate (95% CI)	SOE and Findings
BNP	9 (632)	1.08 (1.01 to 1.16)	SOE=High BNP level is a poor predictor of mortality
Pericardial effusion	7 (2485)	2.20 (1.42 to 3.41)	SOE=Moderate Presence of pericardial effusion is the strongest predictor of mortality, although there was wide variability in results for this measure
RA size	4 (242)	1.07 (0.99 to 1.14)	SOE=Low RA size is a poor predictor of mortality
FAC	4 (242)	0.99 (0.96 to 1.02)	SOE=Moderate FAC is a poor predictor of mortality

Abbreviations: BNP=B-type natriuretic peptide; CI=confidence interval; FAC=fractional area change; RA=right atrium; RAP=right atrial pressure; SOE=strength of evidence

KQ 3: Pharmacotherapy for PAH

The treatment options for PAH currently are based on three main classes of drugs: prostacyclin-analogues (epoprostenol, iloprost, treprostinil), endothelin receptor-antagonists (bosentan, ambrisentan), and phosphodiesterase-5 inhibitors (sildenafil, tadalafil). Few RCTs have been performed to date to fully evaluate the efficacy of these drugs—individually or in combination.

We reviewed 33 studies involving 3981 patients that assess the effectiveness of drug treatment for PAH in adults. Our review found inconclusive evidence regarding mortality reduction for any of six different drug treatment comparisons: (1) bosentan versus placebo (OR 0.72; 95% CI, 0.14 to 3.60), (2) epoprostenol versus placebo (OR 0.25; CI, 0.02 to 3.76), (3) iloprost versus placebo (OR 0.70; CI, 0.08 to 6.22), (4) ambrisentan versus placebo (OR 0.33; CI, 0.06 to 1.74), (5) treprostinil versus placebo (OR 0.79; CI, 0.32 to 1.96), and (6) combination therapy versus monotherapy (OR 0.37; CI, 0.04 to 3.32). Few deaths were observed in these limited duration studies, leading to wide confidence intervals and lack of statistical power to detect a difference; however, a consistent direction of effect and demonstrated improvements in other outcomes, including functional and hemodynamic measures, support that a mortality reduction might exist.

The combination therapy analyzed included three different combinations of drugs: sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo; bosentan plus IV epoprostenol versus IV epoprostenol plus placebo; and bosentan/sildenafil plus inhaled treprostinil versus bosentan/sildenafil plus placebo (more broadly, this is bosentan/Sildenafil plus prostanoid versus prostanoid alone). Our results are similar to a recent meta-analysis by Fox et al.,[182] which found no significant change in mortality with combination therapy compared with single therapy for PAH (OR 0.42; 95% CI, 0.08 to 2.26). Clearly more studies are needed in this area.

In studies evaluating 6MWD, we performed four meta-analyses: (1) endothelin receptor antagonists versus placebo, (2) phosphodiesterase-5 inhibitors versus placebo, (3) prostanoids versus placebo, and (4) combination therapy versus single therapy. Increases in 6MWD were observed in trials of all drug classes when compared with placebo; patients receiving endothelin receptor antagonists demonstrated the largest increase (+50.1 meters); however, comparisons between agents are inconclusive. Combination therapy also showed improved 6MWD compared with single therapy; but the diversity of treatment regimens and the small number of combination therapy trials again make comparisons between specific regimens inconclusive.

In studies evaluating hospitalization, we performed three meta-analyses: (1) endothelin receptor antagonists versus placebo, (2) phosphodiasterase-5 inhibitors versus placebo, and (3) prostanoids versus placebo. In patients taking the endothelin receptor antagonists and phosphodiesterase-5 inhibitors, the odds ratio of hospitalization was lower compared with placebo (OR 0.34 and 0.48, respectively), while there was no significant reduction in odds ratio in the prostanoids versus placebo. Combination therapy also reduced hospitalizations compared with single therapy.

The results of hemodynamic outcomes cardiac index, mPAP, and PVR were inconsistent. In studies using right heart catheterization to follow response to therapy, we performed meta-analyses on the following outcomes: (1) pulmonary vascular resistance, (2) mean pulmonary artery pressure, and (3) cardiac index. Because only 4 to 5 studies reported each outcome, only one meta-analysis was performed grouping all studies together for pulmonary vascular resistance and mean pulmonary artery pressure (active versus control arms), which found modest reductions in both measures in patients treated for PAH. There was no combination therapy meta-analysis performed. Patients receiving epoprostenol and sildenafil experienced an increase in cardiac index compared with placebo (0.58 L/min/m2 versus 0.31 L/min/m2, respectively). No combination therapy meta-analyses were performed due to limited data.

In studies reporting adverse effects, we found that phosphodiesterase-5 inhibitors were more likely to cause headache than endothelin receptor antagonists, which were still more likely to cause headache than placebo. Drugs did not significantly differ in their odds of causing dizziness or diarrhea. Prostanoids were much more likely to cause jaw pain and cough compared with placebo. Phosphodiesterase-5 inhibitors and prostanoids caused more flushing than endothelin receptor antagonists. Phosphodiesterase-5 inhibitors caused more peripheral edema than did the prostanoids or the endothelin receptor antagonists.

The strength of evidence (SOE) ratings are summarized in Table 34.

Table 34. Summary of strength of evidence and effect estimates for monotherapy versus combination therapy for PAH (KQ 3)[a]

Intervention	Mortality	6MWD (m)	Hospitalization
Combination vs. monotherapy	SOE=Insufficient (3 studies, 533 patients) No clear differences in mortality (few studies, few deaths lead to wide CIs) OR 0.37 (95% CI, 0.04 to 3.32)	SOE=Low (3 studies, 363 patients) Improved 6MWD with combination therapy compared with monotherapy Mean difference 24.1 (95% CI, 8.2 to 40.0)	SOE=Insufficient (3 studies, 739 patients) Inconclusive benefit (few studies, wide CIs) OR 0.62 (95% CI, 0.28 to 1.37)

Intervention	Mortality	6MWD (m)	Hospitalization
Sildenafil vs. bosentan	SOE=Insufficient (1 study, 26 patients)	SOE=Insufficient (1 study, 26 patients) No clear difference in 6MWD between sildenafil and bosentan. Mean difference 16 (95% CI NS; ITT analysis)[b]	SOE=Insufficient (No studies)
Endothelin agonist vs. placebo or standard therapy	SOE=Insufficient No clear differences in morality (few studies, few deaths lead to wide CIs) Bosentan: OR 0.72 (95% CI, 0.14 to 3.60) (3 studies, 411 patients) Ambrisentan: OR 0.33 (95% CI, 0.06 to 1.74) (2 studies, 330 patients)	SOE=High (4 studies, 638 patients) Improved 6MWD with endothelin agonists compared to placebo or standard therapy Mean difference 50.1 (95% CI, 35.0 to 65.3)	SOE=Moderate (3 studies, 606 patients) Reduced risk of hospitalization OR 0.34 (95% CI, 0.17 to 0.69)
Phosphodiesterase type 5 inhibitors vs. placebo or standard therapy	SOE=Insufficient (2 studies, 512 patients)	SOE=High (3 studies, 741 patients) Improved 6MWD with PDE5 therapy compared with placebo or standard therapy Mean difference 37.0 (95% CI, 22.9 to 51.1)	SOE=Moderate (2 studies, 341 patients) Reduced risk of hospitalization OR 0.48 (95% CI, 0.25 to 0.91)
Prostanoids vs. placebo	SOE=Insufficient (6 studies, 971 patients) No clear differences in morality (few studies, few deaths lead to wide confidence intervals) OR (95% CI): Iloprost: 0.70 (0.88 to 6.22) Epoprostenol: 0.25 (0.02 to 3.76) Treprostinil: 0.79 (0.32 to 1.96)	SOE=Low (1 study, 203 patients) Improved 6MWD with prostanoid therapy compared with placebo Mean difference 23.6 (95% CI, 0.3 to 46.9)	SOE=Insufficient (1 study, 235 patients) No clear difference in risk of hospitalization OR 0.43 (95% CI, 0.06 to 3.02)

[a]Gray highlights insufficient strength of evidence.
[b]Completers analysis excluded 1 patient who died on sildenafil and thus favored sildenafil; mean difference 55 m (95% CI, 2 m to 108 m).
Abbreviations: 6MWD=6-minute walk distance; CI=confidence interval; NS=not statistically significant; OR=odds ratio; SOE=strength of evidence

Findings in Relation to What is Already Known

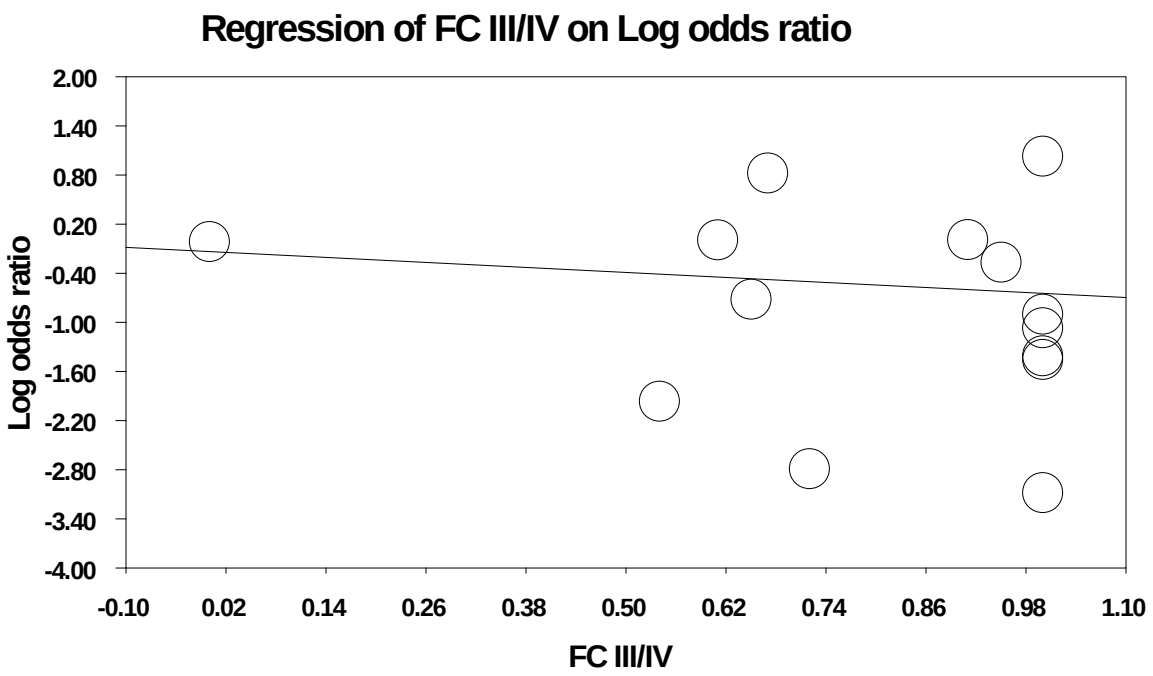
Two previous meta-analyses of echocardiography for diagnosing pulmonary hypertension, focusing solely on sPAP, drew similar conclusions to our review, despite methodological differences, suggesting that our findings are robust. Zhang et al.[183] analyzed six studies, finding a summary sensitivity of 0.82 (95% CI; 0.76 to 0.88) and summary specificity of 0.68 (95% CI, 0.64 to 0.72). These estimates are somewhat lower that our findings. Despite inclusion criteria that seem to be similar, Zhang et al.[183] included fewer eligible studies than our review even taking into account the date range. Another more recent analysis that included more studies had broader inclusion criteria including patients with COPD and heart failure who were not suspected of having PAH.[184] Summary estimates of sensitivity of 0.83 (CI, 0.73 to 0.90) and specificity of 0.72 (CI, 0.53 to 0.85) were closer to our findings. This study found significant heterogeneity and, given larger numbers of included studies, was able to undertake various sensitivity analyses to explore the reasons for heterogeneity; however, none of the characteristics examined—including prospective studies, study year, population (cardiac versus lung), interval between echocardiography and RHC, and method of RAP estimate—revealed a source for the heterogeneity. Both reviews concluded that echocardiography has acceptable accuracy for use as the initial measure of pulmonary pressures in evaluating patients in whom PH is suspected, but not sufficient accuracy to diagnose PH without RHC.

KQ 2 focused on determining whether echocardiographic parameters and/or biomarkers have value in the management of PAH. The current guidelines for diagnosis and treatment of pulmonary hypertension have identified the presence of pericardial effusion, indexed right atrial area, LV eccentricity index, and RV Doppler index (RIMP/MPI/Tei index) as the echocardiographic parameters having the best prognostic value. TAPSE has also been reported to have some prognostic value.[12] Our findings confirm that pericardial effusion was a strong predictor of mortality; however, right atrial size showed no significant prognostic ability. We had insufficient data to evaluate the prognostic value of LV eccentricity index, RV Doppler index or TAPSE. These guidelines have also reported that uric acid, ANP, BNP, and troponin T have prognostic value in PAH. In our review, BNP did show moderate correlation with hemodynamic measures such as RAP and PVR as well as clinical outcomes such as the 6MWD, which have all been reported by the current guidelines to be strong predictors of prognosis, but it showed no significant prognostic value related to overall survival. Prior studies also have attempted to determine an optimal cutoff point for BNP levels to most accurately predict prognosis, but we had insufficient data to make any such determination. We also had insufficient data to determine the prognostic significance of other biomarkers. We did find that echocardiography-derived sPAP correlated strongly with RHC-sPAP, but given that sPAP is considered less important than mPAP in terms of prognostic value for PAH, this correlation may be of limited clinical utility.

For KQ 3, our results are similar to a recent meta-analysis by Fox et al.,[182] which found no significant change in mortality with combination therapy compared with single therapy for PAH (RRR 0.42; 95% CI, 0.08 to 2.26). Our assessment resulted in minor differences that did not impact the conclusions of the study, including a reversal of the effect direction in one study of 6MWD[167] and inability to reproduce the mortality data from another study[172]. Another meta-analysis of similar scope reported a significant effect of prostanoids on mortality.[185] This may be due to inclusion of the sentinel study by Rubin et al.[186] that we excluded because of our date criterion. Other methodological differences that might account for this finding include the use of fixed-effects model meta-analysis in the absence of demonstrated heterogeneity (which results in

narrower confidence intervals). Another finding from this study suggested a relationship between the efficacy of treatment on mortality and functional class severity in individual trials. A meta-regression showed greater reduction in mortality in trials with higher proportions of functional class III or IV patients (R^2=0.51). We reexamined this hypothesis in our set of data, which included several more trials with lower proportions of functional class III or IV patients. We found no significant association (p=0.69) (Figure 40).

Figure 40. Regression of functional class on log odds ratio



Applicability

The principle limitations to applicability of data on the diagnosis of PAH all relate to the patient populations studied. First, the studies may not be applicable to the screening of asymptomatic patients. None of the study populations consisted entirely of asymptomatic patients and, although many studies included some patients without symptoms, they were not reported separately in terms of outcomes. Some studies of populations in whom PAH was suspected failed to adequately describe the basis for a clinical suspicion of PAH, whether symptoms of dyspnea, clinical signs, or other test results, such as diffusion capacity of the lung for carbon monoxide (DLCO), thus also limiting the applicability of these studies for screening symptomatic patients. Second, the spectrum of disease among study populations was often skewed, particularly in case-control studies, by selection criteria that selected from patients with known PAH (cases) and patients known not to have PAH (controls). Such studies usually excluded participants with other conditions that might be confused with PAH such as PH due to left-sided heart failure, thrombotic disease, or chronic obstructive pulmonary disease. Third, participants in many studies had a wide range of disease severity, particularly those cases in case-control design studies, which is a poor match for the question at hand. Other applicability issues identified in the KQ 1 studies were less frequent and judged to be less severe.

Our findings in KQ 2 assessing the prognostic or predictive value of biomarkers and echocardiography may not be applicable to all PAH populations. The greatest concern is that studies in KQ 2 included participants at widely differing points in the natural history of disease and who had widely differing degrees of disease severity. There was also concern that the population was not adequately described to assess applicability, included patients with conditions other than PAH, or in general did not match the review question. Applicability may also be limited by the use of surrogate markers that may not be clinically relevant and insufficient followup time. In a few studies, it was also felt that the intervention arm or cointerventions did not adequately reflect current clinical practice or that the study setting was widely divergent from the current typical U.S. setting. Finally, there is concern that some studies did not provide adequate information about adverse events.

Applicability considerations were somewhat different for KQ 3 than for the Key Questions about screening and management of PAH. Most of the studies included in this review for KQ 3 were RCTs with generally good internal validity. Patient populations, however, differed between studies; variation in eligibility criteria resulted in differences between study populations in severity of illness, underlying etiology of PAH, comorbid conditions, and prior and concurrent treatment. Many different countries were represented, thereby introducing potential differences in clinical practice and care delivery settings relative to current practice in typical settings the U.S. There was also concern that the population was not always adequately described to assess applicability, with few studies exploring potential differences in response to treatment among different patient subgroups.

Implications for Clinical and Policy Decisionmaking

With regard to screening for PH with echocardiography, our findings are generally consistent with the approach used in the ESC/ERS Guidelines,[12,187] which describe a stratification based on echocardiographic TRV or sPAP and other echocardiographic variables suggestive of pulmonary hypertension (PH):

- PH unlikely: TRV ≤2.8 m/s or sPAP ≤36 mmHg and no additional echocardiographic variable suggestive of PH
- PH possible: TRV ≤2.8 m/s or sPAP ≤36 mmHg but with additional echocardiographic variable suggestive of PH or TRV 2.9–3.4 m/s or sPAP 37–50 mmHg
- PH likely: TRV >3.4 m/s or sPAP >50 mmHg

The additional echocardiographic variables include increased velocity of pulmonary valve regurgitation and a short acceleration time of RV ejection into the PA. The guideline noted that RA and RV dilation, abnormal septum shape or function, increased RV wall thickness, and dilated main PA occur late in the course of PH and thus have questionable value in screening.

The guideline specifically recommends against screening to identify mild, asymptomatic PH because of the high frequency of both underestimation and overestimation of pulmonary artery pressures by echocardiography. Hence, the thresholds are set high. This guideline recommends that echocardiography always be performed when PH is suspected. Also recommended is echocardiographic screening of patients who are candidates for liver transplantation and symptomatic patients with liver disease, connective tissue diseases, HIV infection, and lung disease. The only suggestion for screening asymptomatic patients is for patients with the scleroderma spectrum of diseases, in whom screening “may be considered.”

For KQ 2, our findings support using echocardiography or biomarkers in place of existing measurement tools to assess disease severity, prognosis, or response to therapy. Echocardiography-derived sPAP shows promise as a possible surrogate marker for RHC-sPAP, but whether or not this measure alone is adequate to assess disease severity, prognosis, or response to therapy is unclear, and so this evidence is insufficient to support recommendations regarding policy changes in regard to this measurement tool.

Our findings are generally consistent with the ESC/ERS guideline recommendation for monotherapy as initial treatment, with combination treatment reserved for patients who have an inadequate clinical response to monotherapy.

Limitations of the Comparative Effectiveness Review Process

The process of a comparative effectiveness review calls for specifying the scope and methods a priori. In this review, certain decisions made in designing the review resulted in limitations to this report. First, although we did not intend to exclude studies of children, some of the inclusion criteria we established had the effect of eliminating much of the literature on children with PAH. These criteria included the requirement for RHC verification of diagnoses of PAH and, for therapy trials, a minimum followup of 3 months. Studies in children, particularly newborns with PPHN, often omitted RHC and reported outcomes in shorter followup intervals. Second, we anticipated better quality data for the questions about screening and diagnosis (KQ 1) and prognosis (KQ 2) than we actually found.

For KQ 3, certain limitations exist in our search criteria, which may have limited the analysis. First, as with all meta-analyses, there is the potential for bias due to analyzing published studies, which are more likely to have positive results. While we tried to reduce this bias by searching in multiple arenas, the potential for bias still exists. Second, our search focused on studies published between 1995 and present day; however, the sentinel study on epoprostenol[186] was published in 1990 and was therefore excluded by our search. Second, by pooling the lower doses of drug with the higher doses, we may have diluted any treatment effects—either beneficial or harmful—seen in the higher doses. We also may have missed lower doses that were less efficacious as well. Third, our analysis of the 6MWD outcome was hindered by the statistical heterogeneity reported by the studies (mean versus median) as we were not able to compare all the studies that reported this outcome.

Limitations of the Evidence Base

Current evidence has several important limitations that preclude a firm conclusion about the effectiveness of echocardiography and biomarker screening for PAH. First, studies have most often assembled populations that reflect referral-filter bias and which inadequately document the presence of symptoms and signs related to PAH or to an alternative diagnosis such as congestive heart failure (CHF) or pulmonary fibrosis, etc. In such studies, we found that the diagnostic performance of echocardiographic testing varied with PAH prevalence such that higher prevalence was associated with poorer diagnostic performance. We believe this is related to a higher proportion of conditions that may be confused with PAH and which use screening tests that fail to distinguish these conditions (e.g., PCWP >15 mmHg can be easily found at RHC but is difficult to ascertain by echocardiography; BNP can be similarly elevated in CHF and PAH).

Second, the diagnosis of PAH is based on multiple components that include not only pulmonary artery pressure but also the absence of elevated PCWP and elevated PVR. However, nearly all studies of echocardiographic screening relied on the measurement of a single parameter—TRV—as the sole basis for calculation of TG. TG is the principle component for estimation of sPAP and is a key part of estimation of PVR as TRV/VTI_{RVOT}. In theory, the use of ancillary data of a different sort, such as NT-proBNP, is potentially valuable as a diagnostic strategy.

One study that used serial application of echocardiography and biomarker testing (NT-proBNP) suggests that a combination of echocardiography and biomarker testing can work. With a goal of identifying patients with elevated echocardiography sPAP who could safely refrain from RHC, this study applied a low (highly sensitive) threshold for NT-proBNP and also used ECG evidence of RVH. However, this study was small and, like all of the other studies we identified, suffers from inadequate verification of disease status of at least some screening of test-negative patients.

Given the invasive nature of the RHC reference standard test, it is not surprising that many studies, especially those in lower risk screening populations, would shun widespread verification of test-negative patients. However, the selection of test-negative patients for verification when based on other clinical characteristics (such as DLCO measures or symptoms of dyspnea) was often inadequately reported to quantify the bias due to inadequate verification. None of the studies used an alternate reference standard for test-negative patients; however, two studies that sought to prospectively identify predictors of incident PAH provide valuable insight into this problem—suggesting that approximately 10 percent of echocardiography-screened negative SSc patients would meet PAH diagnostic criteria within 6 to 36 months.

The value of a screening test for early diagnosis depends not only on the diagnostic accuracy of the test for diagnosing the target condition but also the consequences of the different outcomes of testing. These consequences include (1) adverse effects of followup testing or treatment of patients with a false-positive screen and (2) outcomes for patients who go undiagnosed or untreated after a false-negative screen balanced against the benefits that accrue to patients with the target condition who may begin treatment earlier as a result of a true-positive screen. In the case of PAH, although we found no indication of harms related to the screening tests themselves, neither did we find information about the harms of subsequent diagnostic evaluation (such as RHC). Also, there are no clear data on benefits of early treatment or harms from delaying treatment. Thus the considerations are limited to the diagnostic accuracy of testing rather than a broader examination of a policy of screening for early identification.

The main focus of KQ 2 was to determine the comparative effectiveness of biomarkers, echocardiographic parameters, or the combination of both to manage PAH and affect diagnostic thinking efficacy, therapeutic efficacy, and patient outcome efficacy. None of the included studies addressed diagnostic thinking efficacy or therapeutic efficacy. Several studies evaluated changes in levels of biomarkers or echocardiographic parameters in response to therapy, but there were too few studies for any particular marker, as well as significant heterogeneity among studies, leading to insufficient evidence to assess patient outcome efficacy. In addition, no studies evaluated the combination of biomarkers and echocardiography in regard to management of PAH. While there were several studies included in the review that evaluated biomarkers, only BNP had a sufficient number of studies to allow meta-analysis. We limited the evaluation of biomarkers and echocardiographic parameters to those most widely studied; however, the literature review did reveal a wide range of other biomarkers and echocardiographic parameters

in a limited number of studies that may be promising in the management of PAH. Further, while studies evaluating echocardiography or using RHC as a comparator reported results for multiple different parameters, it was unclear in the literature which parameters were most clinically relevant.

Additional research is needed to more fully address the questions posed by KQ 2. Future studies need to evaluate how biomarkers or echocardiography affect diagnostic thinking efficacy and therapeutic efficacy. It has been proposed that a measure that combines a biomarker or biomarkers and echocardiography may be a more effective tool in managing PAH, but research is needed to support this theory. More research needs to be done focusing on response to therapy with increased standardization of duration of followup and medication regimens. A greater body of evidence is needed for novel biomarkers and echocardiographic parameters to effectively assess their usefulness in managing PAH. Future studies should focus on echocardiographic parameters and RHC parameters that are most clinically important.

The evidence for KQ 3 had several limitations. First, we found only a small number of RCTs to analyze. This greatly limited our ability to perform the wide range of meta-analyses on which we had planned, and as such there are gaps in the data. Study populations are not comparable from study to study; because sicker patients are more likely to be on prostanoid therapy, the data on the efficacy of oral therapies may appear to be more favorable because they were studied in patients who were less sick.

Research Gaps

The available evidence leaves numerous gaps and areas for potential future research. We used the framework recommended by Robinson et al.[188] to identify gaps in evidence and describe why these gaps exist. Results are as follows:

KQ 1—Screening for PAH

- Patients at elevated risk for PAH, other than systemic sclerosis, have been seldom studied in screening test studies.
  - Consider cohort studies of testing for PH among high risk populations other than systemic sclerosis.
- Relatively few data exist on screening of asymptomatic patients with a combination of echocardiography and biomarker testing.
  - Consider cohort studies that apply echocardiography and biomarker screening in a coordinated or algorithmic way, and studies that verify diagnosis in at least a sample of test-negative patients by RHC or lengthy followup.
  - Future tests of the added value of biomarkers should use well-validated echocardiography parameters as a screening test, including estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}).
- Studies of echocardiography for diagnosis of PH have focused on the association of single measures or parameters at a time rather than an integrated diagnostic assessment based on an entire exam and multiple echocardiographic measures or parameters.

- Consider studies that evaluate a global echocardiographic assessment based on not only sPAP but also on right heart chamber size wall thickness and function, estimated PVR, and left heart measures.

KQ 2—Management of PAH

- Echocardiographic- and BNP-guided treatment strategies have not been explicitly tested.
  - Consider cohort studies evaluating prognosis as well as treatment trials examining association of baseline echocardiographic parameters and BNP levels to response to treatment.
- Other imaging modalities, such as MRI, have been little studied as an alternative noninvasive test to assess RV function
- Cardiopulmonary exercise testing and exercise echocardiography have relatively few data, uncertain clinical utility, and relationship to PH diagnostic criteria.
  - Consider validation studies to demonstrate prognostic value particularly for patients with normal resting echocardiography but abnormal exercise echocardiography.

KQ 3—Pharmacotherapy for PAH

- Relatively few data exist on the efficacy of treating PAH early in the disease course (WHO functional class I-II).
  - Improved data on efficacy of early PAH would strengthen linkage to efficacy of screening testing.
  - Consider treatment trials in early stage PAH, particularly among patients identified by case finding or screening interventions.
- Relatively few data exist on children with persistent pulmonary hypertension or congenital heart disease.
  - Consider controlled trials in children.
- Few treatment trials address direct comparison of alternative drug treatment particularly for PAH patients early in disease course.
  - Consider trials designed to compare clinical alternative treatments to permit more evidence-based treatment selection such as head-to-head treatment comparisons rather than placebo-control or combination versus monotherapy trials.
- The majority of RCTs thus far have not collected adequate surrogate data and have failed to demonstrate therapeutic gain in terms of definitive endpoints.
  - Consider including biomarker and imaging techniques with conventional clinical outcomes to improve data on validity and responsiveness of surrogate outcomes.
- There are inadequate data on the minimum clinically important change in 6MWD. It is uncertain whether incremental change, absolute distance, or a certain threshold is the most appropriate outcome measure related to 6MWD.
  - Consider studies that can validate change in 6MWD against other measures of prognosis, functional status, and quality of life.
- Few data are available about differences in response to treatment based on patient characteristics from trials.

    - Consider subgroup analysis of treatment efficacy by WHO functional class, underlying etiology, and other patient-level factors.

- Data on the efficacy of combination treatments are limited.
    - Consider more combination treatment trials, in particular trials with clear criteria for starting combination therapy and trials in patients who have not failed monotherapy.

- The duration of controlled trial efficacy data is limited.
    - Consider, particularly for clinically relevant comparisons (e.g., head-to-head treatment or combo versus monotherapy trials), longer term followup studies that retain randomized group comparisons while assessing long-term efficacy.

Conclusions

Echocardiography and the biomarker NT-proBNP in combination may be sufficiently accurate to rule out PAH when screening symptomatic patients, but more research is needed regarding the effectiveness for screening asymptomatic populations. With the exception of the presence of pericardial effusion, echocardiography and biomarkers had only low to moderate prognostic value in patients with PAH. Although no treatments demonstrate a consistent mortality reduction, many are associated with improved 6MWD and reduced hospitalization rates. Comparisons of different drug combinations are inconclusive regarding a mortality reduction but suggest an improvement in 6MWD compared with monotherapy.

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Abbreviations

6MWD	6-minute walk distance
AHRQ	Agency for Healthcare Research and Quality
BID	two times per day
BNP	B-type natriuretic peptide
CI	confidence interval
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	collagen vascular disease
FAC	fractional area change
FC	functional class
HR	hazard ratio
HRQOL	health-related quality of life
IQR	interquartile range
KQ	Key Question
MI	myocardial infarction
mo	month/months
mPAP	mean pulmonary artery pressure
MPI	myocardial performance index
NA	not applicable
NR	not reported
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	odds ratio
PAH	pulmonary arterial hypertension
PADP	pulmonary artery diastolic pressure
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
PPH	primary pulmonary hypertension
PVR	pulmonary vascular resistance
QOL	quality of life
RA	right atrium
RAP	right atrial pressure
RHC	right heart catheterization
RIMP	right index of myocardial performance
RR	risk ratio
RV	right ventricle
RVEF	right ventricle ejection fraction
SD	standard deviation
SEM	standard error of the mean
SOE	strength of evidence
sPAP	systolic pulmonary artery pressure

SSc	systemic sclerosis
TAPSE	tricuspid annular plane systolic excursion
TEP	Technical Expert Panel
TG	tricuspid gradient
TRV	tricuspid regurgitant jet velocity
VSD	ventricular septal defect
VTI_{RVOT}	velocity-time integral of right ventricular outflow tract
yr	year/years