APPENDIXES

Appendix A: Exact Search Strings

PubMed® search strategy (November 23, 2011)

Table A-1. PubMed search terms for KQ 1: Screening for PAH

Set #	Terms	Results
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))	**23114**
#2	"Echocardiography"[Mesh] OR echocardiogram[tiab] OR echocardiography[tiab] OR TTE[tiab] OR TEE[tiab] OR echo[tiab]	**144853**
#3	(sensitive[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "sensitivity and specificity"[MeSH Terms] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR "diagnosis"[MeSH Terms] OR "diagnosis"[Subheading] OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms] OR cross-sectional[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	**5494431**
#4	#1 AND #2 AND #3 English, Publication Date from 1995 to 2011	**1142**
#5	"Natriuretic Peptides"[Mesh] OR "Uric Acid"[Mesh] OR "Troponin"[Mesh] OR "Nitric Oxide"[Mesh] OR "dimethylarginine"[Supplementary Concept] OR "fibrin fragment D"[Supplementary Concept] OR "Serotonin"[Mesh] OR "von Willebrand Factor"[Mesh] OR "Thrombomodulin"[Mesh] OR "Selectins"[Mesh] OR "C-Reactive Protein"[Mesh] OR "Isoprostanes"[Mesh] OR "Interleukins"[Mesh] OR "Endothelin-1"[Mesh] OR "Cyclic GMP"[Mesh] OR (Natriuretic[tiab] AND Peptides[tiab]) OR (Natriuretic[tiab] AND Peptide[tiab]) OR "Uric Acid"[tiab] OR "Troponin"[tiab] OR "Nitric Oxide"[tiab] OR "dimethylarginine"[tiab] OR "d-dimer"[tiab] OR "Serotonin"[tiab] OR "Willebrand Factor"[tiab] OR "Thrombomodulin"[tiab] OR "Selectins"[tiab] OR "Selectin"[tiab] AND R[All Fields] AND "C-Reactive Protein"[tiab] OR "Isoprostanes"[tiab] OR Isoprostane[tiab] OR "Interleukins"[tiab] OR "Interleukin"[tiab] OR "Endothelin-1"[tiab] OR "Cyclic GMP"[tiab] OR cgmp[tiab] OR (soluble[tiab] AND ligand[tiab]) OR (endothelial[tiab] AND dysfunction[tiab]) OR "Biological Markers"[Mesh] OR (biological[tiab] AND (marker[tiab] OR markers[tiab])) OR biomarker[tiab] OR biomarkers[tiab]	**722243**
#6	#1 AND #5 AND #3 English, Publication Date from 1995 to 2011	**515**
#7	#1 AND #2 AND #5 English, Publication Date from 1995 to 2011	**126**

Table A-2. PubMed search terms for KQ 2: Management of PAH

Set #	Terms	Results
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))	**23114**
#2	"Echocardiography"[Mesh] OR echocardiogram[tiab] OR echocardiography[tiab] OR TTE[tiab] OR TEE[tiab] OR echo[tiab]	**144853**
#3	#1 AND #2 English, Publication Date from 1995 to 2011	**1776**
#4	(clinical[tiab] AND decision[tiab]) OR (clinical[tiab] AND decisions[tiab]) OR (decision[tiab] AND making[tiab]) OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR management[tiab] OR "treatment outcome"[MeSH Terms] OR outcome[tiab] OR outcomes[tiab] OR "Patient Care Management"[Mesh] OR treatment[tiab] OR therapy[tiab]	**4598101**
#5	#3 AND #4 English, Publication Date from 1995 to 2011	**908**

Set #	Terms	Results
#6	"Natriuretic Peptides"[Mesh] OR "Uric Acid"[Mesh] OR "Troponin"[Mesh] OR "Nitric Oxide"[Mesh] OR "dimethylarginine"[Supplementary Concept] OR "fibrin fragment D"[Supplementary Concept] OR "Serotonin"[Mesh] OR "von Willebrand Factor"[Mesh] OR "Thrombomodulin"[Mesh] OR "Selectins"[Mesh] OR "C-Reactive Protein"[Mesh] OR "Isoprostanes"[Mesh] OR "Interleukins"[Mesh] OR "Endothelin-1"[Mesh] OR "Cyclic GMP"[Mesh] OR (Natriuretic[tiab] AND Peptides[tiab]) OR (Natriuretic[tiab] AND Peptide[tiab]) OR "Uric Acid"[tiab] OR "Troponin"[tiab] OR "Nitric Oxide"[tiab] OR "dimethylarginine"[tiab] OR "d-dimer"[tiab] OR "Serotonin"[tiab] OR "Willebrand Factor"[tiab] OR "Thrombomodulin"[tiab] OR "Selectins"[tiab] OR "Selectin"[tiab] AND R[All Fields] AND "C-Reactive Protein"[tiab] OR "Isoprostanes"[tiab] OR Isoprostane[tiab] OR "Interleukins"[tiab] OR "Interleukin"[tiab] OR "Endothelin-1"[tiab] OR "Cyclic GMP"[tiab] OR cgmp[tiab] OR (soluble[tiab] AND ligand[tiab]) OR (endothelial[tiab] AND dysfunction[tiab]) OR "Biological Markers"[Mesh] OR (biological[tiab] AND (marker[tiab] OR markers[tiab])) OR biomarker[tiab] OR biomarkers[tiab]	**722243**
#7	#1 AND #6 English, Publication Date from 1995 to 2011	**1296**
#8	#7 AND #4 English, Publication Date from 1995 to 2011	**615**
#9	#1 AND #2 AND #6 English, Publication Date from 1995 to 2011	**126**
#10	#1 AND (#2 OR #6) English, Publication Date from 1995 to 2011	**2946**
#11	(sensitive[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "sensitivity and specificity"[MeSH Terms] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR "diagnosis"[MeSH Terms] OR "diagnosis"[Subheading] OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms] OR cross-sectional[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	**5494431**
#12	#1 AND (#2 OR #6) AND (#3 OR #11) English, Publication Date from 1995 to 2011	**2176**

Table A-3. PubMed search terms for KQ 3: Monotherapy vs. Combination Therapy for PAH

Set #	Terms	Results
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))	**23114**
#2	"prostaglandins"[MeSH Terms] OR "prostaglandins"[tiab] OR "prostaglandins"[tiab] OR "prostanoid"[tiab] OR "prostanoids"[tiab] OR "epoprostenol"[MeSH Terms] OR "epoprostenol"[tiab] OR "prostacyclin"[tiab] OR "treprostinil"[Supplementary Concept] OR "treprostinil"[tiab] OR "iloprost"[MeSH Terms] OR "iloprost"[tiab] OR "Receptors, Endothelin/antagonists and inhibitors"[Mesh] OR (("endothelins"[MeSH Terms] OR "endothelins"[tiab] OR "endothelin"[tiab]) AND (antagonist[tiab] OR "antagonists"[tiab] OR "inhibitors"[tiab])) OR "bosentan"[Supplementary Concept] OR "bosentan"[tiab] OR "ambrisentan"[Supplementary Concept] OR "ambrisentan"[tiab] OR "phosphodiesterase inhibitors"[MeSH Terms] OR ("phosphodiesterase"[tiab] AND "inhibitors"[tiab]) OR "phosphodiesterase inhibitors"[tiab] OR "phosphodiesterase inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[tiab] OR "phosphoric diester hydrolases"[MeSH Terms] OR ("phosphoric"[tiab] AND "diester"[tiab] AND "hydrolases"[tiab]) OR (("phosphodiesterase"[tiab] OR "phosphodiesterases"[tiab]) AND (inhibitor[tiab] OR "antagonists and inhibitors"[Subheading] OR "antagonists"[tiab] OR "inhibitors"[tiab] OR antagonist[tiab])) OR (pde5[tiab] AND (inhibitor[tiab] OR "antagonists and inhibitors"[Subheading] OR "antagonists"[tiab] OR "antagonist"[tiab] OR "inhibitors"[tiab] OR "inhibitors"[tiab])) OR pde5i[tiab] OR "sildenafil"[Supplementary Concept] OR "sildenafil"[tiab] OR "tadalafil"[Supplementary Concept] OR "tadalafil"[tiab] OR "Vasodilator Agents"[Mesh:noexp] OR "Vasodilator Agents "[Pharmacological Action]	**494538**

Set #	Terms	Results
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	**2150794**
#4	#1 AND #2 AND #3 English, Publication Date from 1995 to 2011	**1633**
#5	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	**4339051**
#6	#1 AND #2 AND #5 English, Publication Date from 1995 to 2011	**1826**

Embase® search strategy (January 6, 2012)

Platform: Embase.com

Table A-4. Embase search terms for KQ 1: Screening for PAH

Set #	Terms	Results
#1	'pulmonary hypertension'/exp OR "idiopathic pulmonary hypertension":ab,ti OR "pulmonary arterial hypertension":ab,ti OR "pulmonary artery hypertension":ab,ti OR "pulmonary hypertension":ab,ti OR pah:ab,ti OR ipah:ab,ti OR pph:ab,ti	**72699**
#2	'echocardiography'/exp OR echocardiography:ab,ti OR echocardiogram:ab,ti OR echo:ab,ti OR TEE:ab,ti OR TEE:ab,ti	**210689**
#3	('sensitivity and specificity'/exp OR diagnosis:de OR diagnostic:de OR 'screening'/exp OR 'cross-sectional study'/exp OR sensitive:ab,ti OR sensitive:ab,ti OR sensitivity:ab,ti OR specificity:ab,ti OR diagnosis:ab,ti OR diagnostic:ab,ti OR diagnosed:ab,ti OR screening:ab,ti OR screen:ab,ti OR cross-sectional:ab,ti OR likelihood:ab,ti) NOT 'editorial'/exp OR 'letter'/exp OR 'case report'/exp	**2177583**
#4	#1 AND #2 AND #3	**2154**
#5	#1 AND #2 AND #3 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py	**493**
#6	'natriuretic factor'/exp OR 'uric acid'/exp OR 'troponin'/exp OR 'nitric oxide'/exp OR '6 n,n` dimethylarginine'/exp OR 'serotonin'/exp OR 'von Willebrand factor'/exp OR 'C reactive protein'/exp OR 'isoprostane derivative'/exp OR 'interleukin derivative'/exp OR 'endothelin 1'/exp OR 'cyclic GMP'/exp OR 'thrombomodulin'/exp OR 'selectin'/exp OR 'biological marker'/exp OR "Natriuretic Peptides":ab,ti OR "Natriuretic Peptide":ab,ti OR "Uric Acid":ab,ti OR Troponin:ab,ti OR "Nitric Oxide":ab,ti OR dimethylarginine:ab,ti OR d-dimer:ab,ti OR Serotonin:ab,ti OR "Willebrand Factor":ab,ti OR Thrombomodulin:ab,ti OR Selectins:ab,ti OR Selectin:ab,ti OR "C-Reactive Protein":ab,ti OR Isoprostanes:ab,ti OR Isoprostane:ab,ti OR Interleukins:ab,ti OR Interleukin:ab,ti OR Endothelin-1:ab,ti OR "Cyclic GMP":ab,ti OR cgmp:ab,ti OR "soluble ligand":ab,ti OR "biological marker":ab,ti OR "biological markers":ab,ti OR biomarker:ab,ti OR biomarkers:ab,ti OR "endothelial dysfunction":ab,ti OR fibrin fragment:de	**334018**
#7	#1 AND #6 AND #3	**1375**
#8	#7 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py	**316**

Set #	Terms	Results
#9	#1 AND #2 AND #3 AND #6 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py	**119**

Table A-5. Embase search terms for KQ 2: Management of PAH

Set #	Terms	Results
#1	'pulmonary hypertension'/exp OR "idiopathic pulmonary hypertension":ab,ti OR "pulmonary arterial hypertension":ab,ti OR "pulmonary artery hypertension":ab,ti OR "pulmonary hypertension":ab,ti OR pah:ab,ti OR ipah:ab,ti OR pph:ab,ti	**72699**
#2	'echocardiography'/exp OR echocardiography:ab,ti OR echocardiogram:ab,ti OR echo:ab,ti OR TEE:ab,ti OR TEE:ab,ti	**210689**
#3	'treatment outcome'/exp OR 'clinical decision making'/exp OR 'decision making'/exp OR 'patient care'/de OR (clinical:ab,ti AND decision:ab,ti) OR (clinical:ab,ti AND decisions:ab,ti) OR (decision:ab,ti AND making:ab,ti) OR management:ab,ti OR "treatment outcome":ab,ti OR outcome:ab,ti OR outcomes:ab,ti OR treatment:ab,ti OR therapy:ab,ti OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'evidence based medicine'/exp	**5995640**
#4	#3 NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)	**5297119**
#5	#1 AND #2 AND (#3 OR #4)	**2702**
#6	#5 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py	**557**
#7	'natriuretic factor'/exp OR 'uric acid'/exp OR 'troponin'/exp OR 'nitric oxide'/exp OR '6 n,n` dimethylarginine'/exp OR 'serotonin'/exp OR 'von Willebrand factor'/exp OR 'C reactive protein'/exp OR 'isoprostane derivative'/exp OR 'interleukin derivative'/exp OR 'endothelin 1'/exp OR 'cyclic GMP'/exp OR 'thrombomodulin'/exp OR 'selectin'/exp OR 'biological marker'/exp OR "Natriuretic Peptides":ab,ti OR "Natriuretic Peptide":ab,ti OR "Uric Acid":ab,ti OR Troponin:ab,ti OR "Nitric Oxide":ab,ti OR dimethylarginine:ab,ti OR d-dimer:ab,ti OR Serotonin:ab,ti OR "Willebrand Factor":ab,ti OR Thrombomodulin:ab,ti OR Selectins:ab,ti OR Selectin:ab,ti OR "C-Reactive Protein":ab,ti OR Isoprostanes:ab,ti OR Isoprostane:ab,ti OR Interleukins:ab,ti OR Interleukin:ab,ti OR Endothelin-1:ab,ti OR "Cyclic GMP":ab,ti OR cgmp:ab,ti OR "soluble ligand":ab,ti OR "biological marker":ab,ti OR "biological markers":ab,ti OR biomarker:ab,ti OR biomarkers:ab,ti OR "endothelial dysfunction":ab,ti OR fibrin fragment:de	**334018**
#8	#1 AND #7 AND #4	**3496**
#9	#8 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py	**791**
#10	#1 AND #2 AND #7 AND #4	**553**
#11	#1 AND (#2 OR #6) English, Publication Date from 1995 to 2011	**134**

Table A-6. Embase search terms for KQ 3: Monotherapy vs. Combination Therapy for PAH

Set #	Terms	Results
#1	'pulmonary hypertension'/exp OR "idiopathic pulmonary hypertension":ab,ti OR "pulmonary arterial hypertension":ab,ti OR "pulmonary artery hypertension":ab,ti OR "pulmonary hypertension":ab,ti OR pah:ab,ti OR ipah:ab,ti	**68933**
#2	'prostaglandin'/exp OR 'iloprost'/exp OR 'endothelin receptor'/exp OR 'bosentan'/exp OR 'ambrisentan'/exp OR 'phosphodiesterase inhibitor'/exp OR 'phosphodiesterase'/exp OR 'sildenafil'/exp OR 'tadalafil'/exp OR 'vasodilator agent'/exp or "prostaglandin":ab,ti OR "prostaglandins":ab,ti OR "prostanoid":ab,ti OR "prostanoids":ab,ti OR "epoprostenol":ab,ti OR "prostacyclin":ab,ti OR "treprostinil":ab,ti OR "iloprost":ab,ti OR "bosentan":ab,ti OR "ambrisentan":ab,ti OR ("phosphodiesterase":ab,ti AND "inhibitors":ab,ti) OR "phosphodiesterase inhibitors":ab,ti OR "phosphodiesterase 5 inhibitors":ab,ti OR ("phosphoric":ab,ti AND "diester":ab,ti AND "hydrolases":ab,ti) OR "sildenafil":ab,ti OR "tadalafil":ab,ti OR (("phosphodiesterase":ab,ti OR "phosphodiesterases":ab,ti OR "endothelins":ab,ti OR "endothelin":ab,ti OR pde5:ab,ti) AND (inhibitor:ab,ti OR "antagonists":ab,ti OR "inhibitors":ab,ti OR antagonist:ab,ti))	**593387**

Set #	Terms	Results
#3	'calcium channel blocking agent'/exp OR 'calcium channel blocker':ab,ti OR 'calcium channel blockers':ab,ti OR Amlodipine:ab,ti OR Amrinone:ab,ti OR anandamide:ab,ti OR anipamil:ab,ti OR azimilide:ab,ti OR Bencyclane:ab,ti OR benidipine:ab,ti OR Bepridil:ab,ti OR berbamine:ab,ti OR canadine:ab,ti OR 'carboxyamido-triazole':ab,ti OR caroverine:ab,ti OR cilnidipine:ab,ti OR Cinnarizine:ab,ti OR clentiazem:ab,ti OR Conotoxins:ab,ti OR darodipine:ab,ti OR dauricine:ab,ti OR devapamil:ab,ti OR Diltiazem:ab,ti OR dimeditiapramine:ab,ti OR dotarizine:ab,ti OR efonidipine:ab,ti OR emopamil:ab,ti OR enpiperate:ab,ti OR eperisone:ab,ti OR falipamil:ab,ti OR fantofarone:ab,ti OR fasudil:ab,ti OR Felodipine:ab,ti OR 'fenamic acid':ab,ti OR Fendiline:ab,ti OR Flunarizine:ab,ti OR fosfedil:ab,ti OR gabapentin:ab,ti OR Gallopamil:ab,ti OR Isradipine:ab,ti OR lacidipine:ab,ti OR lamotrigine:ab,ti OR lercanidipine:ab,ti OR Lidoflazine:ab,ti OR 'Magnesium Sulfate':ab,ti OR manidipine:ab,ti OR manoalide:ab,ti OR mepirodipine:ab,ti OR Mibefradil:ab,ti OR monatepil:ab,ti OR naftopidil:ab,ti OR Nicardipine:ab,ti OR Nifedipine:ab,ti OR niguldipine:ab,ti OR niludipin:ab,ti OR nilvadipine:ab,ti OR Nimodipine:ab,ti OR Nisoldipine:ab,ti OR Nitrendipine:ab,ti OR norverapamil:ab,ti OR ochratoxin:ab,ti OR octylonium:ab,ti OR 'omega-Agatoxin':ab,ti OR 'omega-Conotoxin':ab,ti OR 'omega-Conotoxins':ab,ti OR osthol:ab,ti OR oxodipine:ab,ti OR Perhexiline:ab,ti OR pinaverium:ab,ti OR piperidine:ab,ti OR pranidipine:ab,ti OR Prenylamine:ab,ti OR ' risedronic acid':ab,ti OR ryodipine:ab,ti OR sesamodil:ab,ti OR stepholidine:ab,ti OR terodiline:ab,ti OR tetrahydropalmatine:ab,ti OR tetrandrine:ab,ti OR 'tolfenamic acid':ab,ti OR tranilast:ab,ti OR Verapamil:ab,ti OR ziconotide:ab,ti	**203387**
#4	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)	**7703489**
#5	#1 AND (#2 OR #3) AND #4	**5794**
#6	#5 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py	**885**

Cochrane Database of Systematic Reviews (January 10, 2012)

Platform: Wiley

Table A-7. Cochrane search terms for KQs 1 and 2: Screening and Management of PAH

Set #	Terms	Results
#1	MeSH descriptor Hypertension, Pulmonary explode all trees OR (pulmonary hypertension):ti,ab,kw OR (idiopathic pulmonary hypertension):ti,ab,kw OR (pulmonary arterial hypertension):ti,ab,kw OR (pulmonary artery hypertension):ti,ab,kw OR pah:ti,ab,kw OR ipah:ti,ab,kw	**1288**
#2	MeSH descriptor echocardiography explode all trees OR echocardiography:ti,ab,kw OR echocardiogram:ti,ab,kw OR echo:ti,ab,kw OR TEE:ti,ab,kw OR TEE:ti,ab,kw	**5321**
#3	#1 AND #2 AND (Cochrane Reviews, other reviews) AND 1995-2012	**1**

Set #	Terms	Results
#4	MeSH descriptor Natriuretic Peptides explode all trees OR MeSH descriptor Uric Acid explode all trees OR MeSH descriptor Troponin explode all trees OR MeSH descriptor Nitric Oxide explode all trees OR MeSH descriptor Serotonin explode all trees OR MeSH descriptor von Willebrand Factor explode all trees OR MeSH descriptor C-Reactive Protein explode all trees OR MeSH descriptor Isoprostanes explode all trees OR MeSH descriptor Interleukins explode all trees OR MeSH descriptor Endothelins explode all trees OR MeSH descriptor Cyclic GMP explode all trees OR MeSH descriptor Thrombomodulin explode all trees OR MeSH descriptor Selectins explode all trees OR MeSH descriptor Biological Markers explode all trees OR (Natriuretic Peptides):ti,ab,kw OR (Natriuretic Peptide):ti,ab,kw OR (Uric Acid):ti,ab,kw OR Troponin:ti,ab,kw OR (Nitric Oxide):ti,ab,kw OR dimethylarginine:ti,ab,kw OR (d-dimer):ti,ab,kw OR Serotonin:ti,ab,kw OR (Willebrand Factor):ti,ab,kw OR Thrombomodulin:ti,ab,kw OR Selectins:ti,ab,kw OR Selectin:ti,ab,kw OR (C-Reactive Protein):ti,ab,kw OR Isoprostanes:ti,ab,kw OR Isoprostane:ti,ab,kw OR Interleukins:ti,ab,kw OR Interleukin:ti,ab,kw OR (Endothelin-1):ti,ab,kw OR (Cyclic GMP):ti,ab,kw OR cgmp:ti,ab,kw OR (soluble ligand):ti,ab,kw OR (biological marker):ti,ab,kw OR (biological markers):ti,ab,kw OR biomarker:ti,ab,kw OR biomarkers:ti,ab,kw OR (endothelial dysfunction):ti,ab,kw OR (fibrin fragment):ti,ab,kw	**34398**
#5	#1 AND #4 AND (Cochrane Reviews, other reviews) AND 1995-2012	**12**
#6	#1 AND #2 AND #4 AND (Cochrane Reviews, other reviews) AND 1995-2012	**0**

Table A-8. Cochrane search terms for KQ 3: Monotherapy vs. Combination Therapy for PAH

Set #	Terms	Results
#1	MeSH descriptor Hypertension, Pulmonary explode all trees OR (pulmonary hypertension):ti,ab,kw OR (idiopathic pulmonary hypertension):ti,ab,kw OR (pulmonary arterial hypertension):ti,ab,kw OR (pulmonary artery hypertension):ti,ab,kw OR pah:ti,ab,kw OR ipah:ti,ab,kw	1288
#2	bosentan:ti,ab,kw OR ambrisentan:ti,ab,kw OR phosphodiesterase:ti,ab,kw OR sildenafil:ti,ab,kw OR tadalafil:ti,ab,kw OR (vasodilator agent):ti,ab,kw or prostaglandin:ti,ab,kw OR prostaglandins:ti,ab,kw OR prostanoid:ti,ab,kw OR prostanoids:ti,ab,kw OR epoprostenol:ti,ab,kw OR prostacyclin:ti,ab,kw OR treprostinil:ti,ab,kw OR iloprost:ti,ab,kw OR bosentan:ti,ab,kw OR ambrisentan:ti,ab,kw OR sildenafil:ti,ab,kw OR tadalafil:ti,ab,kw OR endothelins:ti,ab,kw OR endothelin:ti,ab,kw OR pde5:ti,ab,kw OR MeSH descriptor Vasodilator Agents explode all trees OR MeSH descriptor Endothelins explode all trees OR MeSH descriptor Prostaglandins explode all trees OR MeSH descriptor Hydrolases explode all trees OR MeSH descriptor Phosphodiesterase Inhibitors explode all trees	40010

Set #	Terms	Results
#3	Amlodipine:ti,ab,kw OR Amrinone:ti,ab,kw OR anandamide:ti,ab,kw OR anipamil:ti,ab,kw OR azimilide:ti,ab,kw OR Bencyclane:ti,ab,kw OR benidipine:ti,ab,kw OR Bepridil:ti,ab,kw OR berbamine:ti,ab,kw OR canadine:ti,ab,kw OR (carboxyamido-triazole):ti,ab,kw OR caroverine:ti,ab,kw OR cilnidipine:ti,ab,kw OR Cinnarizine:ti,ab,kw OR clentiazem:ti,ab,kw OR Conotoxins:ti,ab,kw OR darodipine:ti,ab,kw OR dauricine:ti,ab,kw OR devapamil:ti,ab,kw OR Diltiazem:ti,ab,kw OR dimeditiapramine:ti,ab,kw OR dotarizine:ti,ab,kw OR efonidipine:ti,ab,kw OR emopamil:ti,ab,kw OR enpiperate:ti,ab,kw OR eperisone:ti,ab,kw OR falipamil:ti,ab,kw OR fantofarone:ti,ab,kw OR fasudil:ti,ab,kw OR Felodipine:ti,ab,kw OR (fenamic acid):ti,ab,kw OR Fendiline:ti,ab,kw OR Flunarizine:ti,ab,kw OR fosfedil:ti,ab,kw OR gabapentin:ti,ab,kw OR Gallopamil:ti,ab,kw OR Isradipine:ti,ab,kw OR lacidipine:ti,ab,kw OR lamotrigine:ti,ab,kw OR lercanidipine:ti,ab,kw OR Lidoflazine:ti,ab,kw OR (Magnesium Sulfate):ti,ab,kw OR manidipine:ti,ab,kw OR manoalide:ti,ab,kw OR mepirodipine:ti,ab,kw OR Mibefradil:ti,ab,kw OR monatepil:ti,ab,kw OR naftopidil:ti,ab,kw OR Nicardipine:ti,ab,kw OR Nifedipine:ti,ab,kw OR niguldipine:ti,ab,kw OR niludipin:ti,ab,kw OR nilvadipine:ti,ab,kw OR Nimodipine:ti,ab,kw OR Nisoldipine:ti,ab,kw OR Nitrendipine:ti,ab,kw OR norverapamil:ti,ab,kw OR ochratoxin:ti,ab,kw OR octylonium:ti,ab,kw OR (omega-Agatoxin):ti,ab,kw OR (omega-Conotoxin):ti,ab,kw OR (omega-Conotoxins):ti,ab,kw OR osthol:ti,ab,kw OR oxodipine:ti,ab,kw OR Perhexiline:ti,ab,kw OR pinaverium:ti,ab,kw OR piperidine:ti,ab,kw OR pranidipine:ti,ab,kw OR Prenylamine:ti,ab,kw OR (risedronic acid):ti,ab,kw OR ryodipine:ti,ab,kw OR sesamodil:ti,ab,kw OR stepholidine:ti,ab,kw OR terodiline:ti,ab,kw OR tetrahydropalmatine:ti,ab,kw OR tetrandrine:ti,ab,kw OR (tolfenamic acid):ti,ab,kw OR tranilast:ti,ab,kw OR Verapamil:ti,ab,kw OR ziconotide:ti,ab,kw OR MeSH descriptor Calcium Channel Blockers explode all trees	12915
#4	#1 AND (#2 OR #3) AND (Cochrane Reviews, other reviews) AND 1995-2012	20

Appendix B: Data Abstraction Elements

I. Study Characteristics

- First Author (Last Name) and Year of Publication
- Additional Articles Used in This Abstraction
- Study Sites
  - Single Center; Multicenter; Not reported/Unclear
- Number of Sites
- Geographical Location (Select all applicable geographic regions)
  - US; Canada; UK; Europe; South America; Central America; Asia; Africa; Australia/New Zealand; Not reported/Unclear; Other (Specify)
- Funding Source (Check all that apply)
  - Government; Private Foundation; Industry; Not reported; Other (Specify)
- Enrollment Approach (Check all that apply)
  - Consecutive patients; Convenience sample (not explicitly consecutive); Other (Specify); Not reported/Unclear
- Study Inclusion and Exclusion Criteria
  - Copy/paste inclusion/exclusion criteria as reported in the article
- Study Design
  - RCT; Cohort; Other (describe)
- Study Enrollment/Study Completion
  - Total, Treatment Arm 1, 2, 3, 4
    - Assessed for eligibility (N)
    - Eligible (N)
    - Enrolled/Randomized (N)
    - Completed follow-up (N)
- Subgroup Analysis (Yes/No)
  - If Yes: Describe the subgroups reported
- Key Question Applicability
  - KQ1; KQ2; KQ3
    - 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 plus clinical assessment (e.g., functional class, dyspnea, 6-minute walk test) versus biomarkers plus clinical assessment and (b) echocardiography plus clinical assessment versus echocardiography plus biomarkers and clinical assessment in managing PAH (diagnostic thinking efficacy and therapeutic efficacy) and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes (patient outcome efficacy)?
    - 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?
- Comments

II. Baseline Characteristics

- Total, Study Arm 1, Study Arm 2, Study Arm 3, Study Arm 4
    - Patient Population
        - Describe the population for each study arm
    - Number of Subjects
        - N
            - Total
            - Female
            - Male
            - Adults
            - Children
            - Mixed
        - %
            - Female
            - Male
            - Adults
            - Children
            - Mixed
    - Age
        - Mean
            - SD
            - SE
        - Median
            - IQR
    - Ethnicity
        - Hispanic or Latino
            - N
            - %
        - No Hispanic or Latino
            - N
            - %
    - Race
        - Black/African American
            - N
            - %
        - American Indian or Alaska Native
            - N
            - %
        - Asian
            - N
            - %
        - Native Hawaiian or other Pacific Islander
            - N
            - %
        - White
            - N
            - %
        - Multiracial
            - N

        - %
    - Other (Specify)
        - N
        - %
- Baseline Characteristics
    - BMI
        - Mean
            - SD
            - SE
        - Median
            - IQR
    - WHO Functional Class (N)
        - Class I
        - Class II
        - Class III
        - Class IV
    - NYHA Functional Classification (N)
        - Class I
        - Class II
        Class III
        - Class IV
    - PAH Etiology (N)
        - Idiopathic (1.1)
        - Familial (1.2)
        - Collagen vascular disease (1.3.1)
        - Congenital shunts (1.3.2)
        - Portal HTN (1.3.3)
        - HIV (1.3.4)
        - Drugs/toxins (1.3.5)
        - Venous or capillary disease (1.4.x)
        - Pulmonary HTN of newborn (1.5)
        - Thromboembolic (4.x)
        - Other
    - Disease Duration
        - Mean
            - SD
            - SE
        - Median
            - IQR
    - Obesity (e.g. N with BMI>30)
        - Mean
            - SD
            - SE
        - Median
            - IQR
        - N
    - Prior Treatments (N)
        - Calcium channel blockers
        - Diuretics

            - Digoxin
            - Prostanoids
            - Endothelin antagonists
            - Phosphodiesterase inhibitors
            - Anticoagulants
            - Other
        - Left ventricular ejection fraction (LVEF)
            - Mean
                - SD
                - SE
            - Median
                - IQR
        - Other (Specify)
            - Mean
                - SD
                - SE
            - Median
                - IQR
            - N
- Comments

III. Intervention Characteristics

- Study Arm 1, Study Arm 2, Study Arm 3, Study Arm 4
    - Medical Therapy Intervention
        - Amlodipine; Diltiazem; Nifedipine; Verapamil; Epoprostenol; Treprostinil; Iloprost; Bosentan; Ambrisentan; Sildenafil; Tadalafil; Other (Specify); NR/NA
            - Dosage
            - Frequency
            - Duration
                - Administration (oral, inhaled, intravenous, subcutaneous)
    - Describe tests administered
    - Describe biomarkers
    - Describe echocardiographic tests
    - Describe co-treatments
    - Did the study use echocardiography and/or biomarkers?
        - Echocardiography
        - Biomarker(s)
        - Echo + biomarkers
        - NR/NA

IV. Outcomes Definitions

- Time points
    - Time 1
    - Time 2
    - Time 3
    - Time 4
    - Time 5
- Echocardiographic parameters (Check all that apply)
    - Right ventricle (RV) size (any RV linear dimension or area by 2D echo)
    - Right atrium (RA) size (any RA linear dimension or area by 2D echo)

    - Fractional area change (FAC)
    - Tricuspid Annular Plane Systolic Excursion (TAPSE)
    - Systolic excursion velocity (S-prime)
    - RIMP/MPI/Tei Index
    - Systolic pulmonary artery pressure (sPAP)
    - Mean pulmonary artery pressure (mPAP)
    - Tricuspid regurgitant (TR) jet velocity
    - Peak TR velocity
    - Right ventricular outflow tract (RVOT) velocity-time integral
    - Right ventricular ejection fraction (RVEF)
    - Pericardial effusion
    - Other (specify; don't need to include measures of LV function)
- Right-heart catheterization measures (Check all that apply)
    - Mean pulmonary artery pressure (mPAP)
    - Systolic pulmonary artery pressure (sPAP)
    - Diastolic pulmonary artery pressure (dPAP)
    - Pulmonary vascular resistance (PVR)
    - Cardiac output (CO)
    - Other right-heart catheterization measure (specify)
- Biomarkers (Check all that apply)
    - 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
    - Serotonin
    - Other biomarker (specify)
- Clinical outcomes (Check all that apply)
    - Diagnostic thinking efficacy
    - Therapeutic efficacy (e.g. clinician judgment about diagnosis/prognosis, choice of treatment)
    - Dyspnea
    - 6-minute walk change
    - 6-minute walk absolute score
    - Hospitalization
    - Functional class
    - Quality of life (e.g. SF-36, Minnesota Living With Heart Failure [MLWHF], Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR])
    - Right ventricular dysfunction
    - Right heart failure
    - Mortality
    - Progression to right heart failure
    - Other clinical outcomes (specify)
    - Adverse effect – bleeding
    - Adverse effect – bruising
    - Adverse effect – infection
    - Adverse effect – transient ischemic attack from bubble/contrast echocardiogram
    - Adverse effect – liver function abnormalities

    - Adverse effect – headache
    - Adverse effect – flushing
    - Adverse effect – cough
    - Adverse effect – epistaxis
    - Adverse effect – dyspepsia
    - Adverse effect – diarrhea
    - Adverse effect – peripheral edema
    - Adverse effect – nausea
    - Adverse effect – nasal congestion
    - Adverse effect – dizziness
    - Adverse effect – syncope
    - Adverse effect – hypoxia
    - Adverse effect – increased international normalized ratio
    - Adverse effect – increased prothrombin time
    - Adverse effect – line infection
    - Adverse effect – site pain
    - Adverse effect – abrupt catheter occlusion
    - Adverse effect – other (specify)
- Comments

V. KQ 1 Outcomes

- Did the study present other clinical outcomes that will need to be extracted (i.e. bleeding, bruising, etc.)?
- Echo Parameter
        - RV size
        - RA size
        - Fractional area change
        - TAPSE
        - RIMP/MPI/Tei Index
        - sPAP (systolic pulmonary artery pressure)
        - mPAP (mean pulmonary artery pressure)
        - Tricuspid regurgitant jet velocity
        - Peak tricuspid regurgitant velocity
        - RVOT velocity-time integral
        - RVEF
        - Pericardial effusion
    - Echo Parameter Threshold
    - How was this measure calculated?
    - For how many patients was there no test result for this measure?
- Reference standard
        - MPAP (mean pulmonary artery pressure)-RH Cath
        - SPAP (systolic pulmonary artery pressure)-RH Cath
        - dPAP (diastolic pulmonary artery pressure)-RH Cath
        - PVR (pulmonary vascular resistance)-RH Cath
        - CO (cardiac output)-RH Cath
        - CI (cardiac Index)
        - RAP (right atrial pressure)
        - PCWP (pulmonary capillary wedge pressure)
    - Reference Standard Threshold
- Biomarker

        - Natriuretic peptides/BNP
        - Endothelin-1
        - Uric acid
        - Troponin T
        - Nitric oxide
        - Asymmetric dimethylarginine
        - Cyclic guanosine monophosphate
        - D-dimer
    - How was this measure calculated?
    - Biomarker Threshold
    - For how many patients was there no test result for this measure?
- Data presentation
    - Dichotomous/ Continuous/ Both
    - If Dichotomous or Both selected:
        - Echo Alone; Echo + Biomarkers; Biomarkers Alone
            - Test positive
                - Disease Positive – True positive N
                - Disease Negative – False positive N
                - Unclear – N unclear
                - Total – Total N
            - Test negative
                - Disease Positive – False negative
                - Disease Negative – True negative
                - Unclear – N unclear
                - Total – Total N
            - Test uncertain
                - Disease Positive – N positive
                - Disease Negative – N negative
                - Unclear – N unclear
                - Total – Total N
            - Total
                - Disease Positive – N positive
                - Disease Negative – N negative
                - Unclear – N unclear
                - Total – Total N
    - If Continuous or Both selected:
        - Echo Alone; Echo + Biomarkers; Biomarkers Alone
            - Table 1
                - N for Analysis
                - Pearson product-moment correlation (r)
                - r^2
                - Bland-Altman analysis
                - Variability
                    - Standard Error(SE)/ Standard Deviation(SD)/ Other(Specify)
                - p-value between test and reference standard
                - Time interval between test and reference standard
            - Table 2
                - Disease Positive
                    - N Positive

            - Mean
                - SD
                - SE
            - Median
                - IQR
        - Disease Negative
            - N Negative
            - Mean
                - SD
                - SE
            - Median
                - IQR
        - Diagnosis Unclear
            - N Unclear
            - Mean
                - SD
                - SE
            - Median
                - IQR
        - Other
            - N
            - Mean
                - SD
                - SE
            - Median
                - IQR
        - p-value between Test and Reference Standard

VI. KQ 2 Outcomes

- Did the study report other clinical outcomes that will need to be abstracted?(Yes/No)
- Table 1, Table2, Table 3, Table 4, Table 5
    - Timing
        - Baseline
        - Intermediate term >30 days and ≤ 1 year
            - 1 month/ 2 months/ 3 months/ 4 months/ 6 months/ 1 year/ Other (Specify)
        - Long-term > 1 year
            - 2 years/ 3 years/ 4 years/ 5 years/ Other (Specify)
    - Intervention
        - Intervention 1
            - RV size
            - RA size
            - Fractional area change
            - TAPSE
            - RIMP/MPI/Tei Index
            - sPAP (systolic pulmonary artery pressure)
            - mPAP (mean pulmonary artery pressure)
            - Tricuspid regurgitant jet velocity
            - Peak tricuspid regurgitant velocity

            - RVOT velocity-time integral
            - RVEF
            - Pericardial effusion
            - RVSP
            - Natriuretic peptides/BNP
            - Endothelin-1
            - Uric acid
            - Troponin T
            - Nitric oxide
            - Asymmetric dimethylarginine
            - Cyclic guanosine monophosphate
            - D-dimer
        - Describe Intervention 1
        - Intervention 2
            - RV size
            - RA size
            - Fractional area change
            - TAPSE
            - RIMP/MPI/Tei Index
            - sPAP (systolic pulmonary artery pressure)
            - mPAP (mean pulmonary artery pressure)
            - Tricuspid regurgitant jet velocity
            - Peak tricuspid regurgitant velocity
            - RVOT velocity-time integral
            - RVEF
            - Pericardial effusion
            - RVSP
            - Natriuretic peptides/BNP
            - Endothelin-1
            - Uric acid
            - Troponin T
            - Nitric oxide
            - Asymmetric dimethylarginine
            - Cyclic guanosine monophosphate
            - D-dimer
            - NA
        - Describe Intervention 2
    - Comparator
        - Comparator 1
            - RV size
            - RA size
            - Fractional area change
            - TAPSE
            - RIMP/MPI/Tei Index
            - sPAP (systolic pulmonary artery pressure)
            - mPAP (mean pulmonary artery pressure)
            - Tricuspid regurgitant jet velocity
            - Peak tricuspid regurgitant velocity

- RVOT velocity-time integral
- RVEF
- Pericardial effusion
- RVSP
- Natriuretic peptides/BNP
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- Cyclic guanosine monophosphate
- D-dimer
- RH cath-mPAP
- RH cath-sPAP
- RH cath-dPAP
- RH cath-PVR
- RH cath-CO
- Cardiac index (CI)
- Right atrial pressure (RAP)
- Pulmonary capillary wedge pressure (PCWP)
- Dyspnea
- 6 minute walk change
- 6 minute walk (absolute)
- Hospitalization
- Functional class
- Quality of life
- Right ventricular dysfunction
- Right heart failure/progression to right heart failure
- Mortality
- Transplant
- Adverse effect – bleeding
- Adverse effect – bruising
- Adverse effect – infection
- Adverse effect – transient ischemic attack
- Adverse effect – liver function
- Adverse effect – headache
- Adverse effect – flushing
- Adverse effect – cough
- Adverse effect – epistaxis
- Adverse effect – dyspepsia
- Adverse effect – diarrhea
- Adverse effect – peripheral edema
- Adverse effect – nausea
- Adverse effect – nasal congestion
- Adverse effect – dizziness
- Adverse effect – syncope
- Adverse effect – hypoxia
- Adverse effect – increased INR

    - Adverse effect – line infection
    - Adverse effect – site pain
    - Adverse effect – abrupt catheter occlusion
    - Adverse effect – rash
    - Adverse effect – jaw pain
    - Composite outcome (Specify)
- Describe Comparator 1
- Comparator 2
    - RV size
    - RA size
    - Fractional area change
    - TAPSE
    - RIMP/MPI/Tei Index
    - sPAP (systolic pulmonary artery pressure)
    - mPAP (mean pulmonary artery pressure)
    - Tricuspid regurgitant jet velocity
    - Peak tricuspid regurgitant velocity
    - RVOT velocity-time integral
    - RVEF
    - Pericardial effusion
    - RVSP
    - Natriuretic peptides/BNP
    - Endothelin-1
    - Uric acid
    - Troponin T
    - Nitric oxide
    - Asymmetric dimethylarginine
    - Cyclic guanosine monophosphate
    - D-dimer
    - RH cath-mPAP
    - RH cath-sPAP
    - RH cath-dPAP
    - RH cath-PVR
    - RH cath-CO
    - Cardiac index (CI)
    - Right atrial pressure (RAP)
    - Pulmonary capillary wedge pressure (PCWP)
    - Dyspnea
    - 6 minute walk change
    - 6 minute walk (absolute)
    - Hospitalization
    - Functional class
    - Quality of life
    - Right ventricular dysfunction
    - Right heart failure/progression to right heart failure
    - Mortality
    - Transplant
    - Adverse effect – bleeding

            - Adverse effect – bruising
            - Adverse effect – infection
            - Adverse effect – transient ischemic attack
            - Adverse effect – liver function
            - Adverse effect – headache
            - Adverse effect – flushing
            - Adverse effect – cough
            - Adverse effect – epistaxis
            - Adverse effect – dyspepsia
            - Adverse effect – diarrhea
            - Adverse effect – peripheral edema
            - Adverse effect – nausea
            - Adverse effect – nasal congestion
            - Adverse effect – dizziness
            - Adverse effect – syncope
            - Adverse effect – hypoxia
            - Adverse effect – increased INR
            - Adverse effect – line infection
            - Adverse effect – site pain
            - Adverse effect – abrupt catheter occlusion
            - Adverse effect – rash
            - Adverse effect – jaw pain
            - Composite outcome (Specify)
        - Describe Comparator 2
- Population and N for Analysis
    - Intervention
        - Population
        - N for Analysis
    - Comparator
        - Population
        - N for Analysis
- Result
    - Mean
    - Median
    - Number Patients with Outcome
    - % Patients w ith Outcome
    - Relative Risk (RR)
    - Relative Hazard (HR)
    - Odds Ratio (OR)
    - Risk difference
    - Correlation
    - Other (Specify)
- Variability
    - Standard Error (SE)
    - Standard Deviation (SD)
    - Other (Specify)
- Confidence interval (CI) or Interquartile Range (IQR)
    - 95% CI/ Other % CI (Specify)/ IQR
        - LL (25% if IQR)

            - UL (75% if IQR)
    - p-value between treatment groups
- Describe the diagnostic thinking efficacy
- Describe the therapeutic efficacy
- Comments

VII. Clinical Outcomes

- Outcome reported on this form
    - Dyspnea
    - Six minute walk change
    - Six minute walk (absolute)
    - Hospitalization
    - Functional class
    - Quality of life (SF-36, MLWH, CAMPHOR)
    - Right ventricular dysfunction
    - Right heart failure/progression to right heart failure
    - Mortality
    - Transplant/progression to transplant
    - Adverse effect – bleeding
    - Adverse effect – bruising
    - Adverse effect – infection
    - Adverse effect – transient ischemic attack
    - Adverse effect – liver function abnormalities
    - Adverse effect – headache
    - Adverse effect – flushing
    - Adverse effect – cough
    - Adverse effect – epistaxis
    - Adverse effect – dyspepsia
    - Adverse effect – diarrhea
    - Adverse effect – peripheral edema
    - Adverse effect – nausea
    - Adverse effect – nasal congestion
    - Adverse effect – dizziness
    - Adverse effect – syncope
    - Adverse effect – hypoxia
    - Adverse effect – increased international normalized ratio
    - Adverse effect – line infection
    - Adverse effect – site pain
    - Adverse effect – abrupt catheter occlusion
    - Adverse effect – jaw pain
    - Adverse effect – rash
    - Composite outcome
        - Composite outcome consisted of
    - RV size
    - RA size
    - Fractional area change
    - TAPSE
    - RIMP/MPI/Tei Index
    - sPAP
    - mPAP

    - TR jet velocity
    - Peak TR velocity/RVOT velocity-time interval
    - RVEF
    - Pericardial Effusion
    - RVSP
    - Natriuretic peptides/BNP
    - Endothelin-1
    - Uric acid
    - Troponin T
    - Nitric oxide
    - Asymmetric dimethylarginine
    - c-GMP
    - D-dimer
    - RH cath – sPAP
    - RH cath – mPAP
    - RH cath – dPAP
    - RH cath –PVR
    - RH cath – CO
    - Cardiac Index (CI)
    - Right atrial pressure (RAP)
    - Pulmonary capillary wedge pressure (PCWP)
- Additional/alternate outcome name (if applicable)
- Authors' definition of outcome (if applicable)
- Table 1, 2, 3, 4, 5
    - Timing
        - Baseline
        - Intermediate term > 30 days and ≤ 1 year
            - 1 month/ 2 months/ 3 months/ 4 months/ 6 months/ 1 year/ Other (Specify)
        - Long-term > 1 year
            - 2 years/ 3 years/ 4 years/ 5 years/ Other (Specify)
    - Adjustments
        - Results are not adjusted
        - Age
        - Sex
        - Race/ethnicity
        - Comorbidity(ies) (Specify)
        - Body weight/ BMI
        - Risk factors
        - PAH classification
        - Other (specify all)
    - Group
        - Study Arm 1, 2, 3, 4
    - N for Analysis
    - Result
        - Mean
        - Median
        - Number Patients with Outcome
        - % Patients with Outcome
        - Relative Risk (RR)

        - Relative Hazard (HR)
        - Odds Ratio (OR)
        - Risk difference
        - Other (Specify)
    - Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - Other (Specify)
    - Confidence Interval (CI) or Interquartile Range (IQR)
        - 95% CI/ Other % CI (Specify)/ IQR
            - LL (25% if IQR)
            - UL (75% if IQR)
    - p-value between treatment groups
    - Reference group (for comparisons between treatment groups)
- Comments

VIII. Quality

- Was this an accuracy study? (Yes/No)
    - If Yes:
        - Population (P)
            - Was a consecutive or random sample of patients unrolled? (Yes/No/Unclear)
            - Was a case-control design avoided? (Yes/No/Unclear)
            - Did the study avoid inappropriate exclusions? (Yes/No/Unclear)
            - Could the selection of patients have introduced bias? (Yes/No/Unclear)
        - Interventions (I)
            - Were the index test results interpreted without knowledge of the results of the reference standard? (Yes/No/Unclear)
            - If a threshold was used, was it pre-specified? (Yes/No/Unclear)
            - Could the conduct or interpretation of the index test have introduced bias? (Yes/No/Unclear)
        - Comparators (C)
            - Is the reference standard likely to correctly classify the target condition? (Yes/No/Unclear)
            - Were the reference standard results interpreted without knowledge of the results of the index test? (Yes/No/Unclear)
            - Could the reference standard, its conduct, or its interpretation have introduced bias? (Yes/No/Unclear)
        - Timing (T)
            - Was there an appropriate interval between index test(s) and reference standard? (Yes/No/Unclear)
            - Did all patients receive a reference standard? (Yes/No/Unclear)
            - Did all patients receive the same reference standard? (Yes/No/Unclear)
            - Were all patients included in the analysis? (Yes/No/Unclear)
            - Could the patient flow have introduced bias? (Yes/No/Unclear)
        - Overall study rating (Good/Fair/Poor)
            - If Fair: Describe why the study was given a ‘Fair’ rating
            - If Poor: Describe why the study was given a ‘Poor’ rating
    - If No:

- Was this study randomized? (Yes/No)
    - If Yes:
        - Were study subjects randomized? (Yes/No/Unclear)
        - Was the randomization process described? (Yes/No/Unclear)
        - Was the outcome assessor blinded to study assignment? (Yes/No/Unclear)
        - Were patients blinded to study intervention? (Yes/No/Unclear)
        - Were results adjusted for clustering? (Yes/No/Unclear)
        - Were measures of outcomes based on validated procedures or instruments? (Yes/No/Unclear)
        - Conducted an intent-to-treat analysis? (Yes/No/Unclear)
        - Were all outcomes reported (i.e. was there evidence of selective outcome reporting)? (Yes/No/Unclear)
        - Were incomplete data adequately addressed? (Yes/No/Unclear)
        - Was there adequate power (either based on pre-study or post-hoc power calculations [80% power for primary outcome])? (Yes/No/Unclear)
        - Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared? (Yes/No/Unclear)
        - Were comparable groups maintained? (Yes/No/Unclear)
        - Was there absence of potential important conflict-of-interest? (Yes/No/Unclear)
    - If No:
        - Basic Design
            - Is the study design prospective, retrospective, or mixed? (Prospective/Mixed/Retrospective/Cannot determine)
        - Selection Bias
            - Inclusion/Exclusion Criteria
                - Are the inclusion/exclusion criteria clearly stated (does not require the reader to infer)? (Yes/Partially/No)
                - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/Partially/No/NA)
            - Recruitment
                - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Cannot determine/NA)
            - Baseline characteristics similar or appropriate adjusted analysis
                - Are key characteristics of study participants similar between intervention and control groups? If not similar, did the analysis appropriately adjust for important differences? (Yes/Partially/No/Insufficient reporting to be able to determine/NA)
            - Comparison Group
                - Is the selection of the comparison group appropriate? (Yes/No/Cannot determine/NA)

- Performance Bias
  - Intervention implementation
    - What is the level of detail in describing the intervention or exposure?
      - High; very clear, all PI-required details provided
      - Medium; somewhat clear, majority of PI-required details provided
      - Low; unclear, many PI-required details missing
  - Concurrent/concomitant interventions
    - Did researchers isolate the impact from a concurrent intervention or unintended exposure that might bias the results, e.g., through multivariate analysis, stratification, or subgroup analysis? (Yes/Partially/Not described/NA)
- Attrition Bias
  - Equality of length of follow-up for participants
    - In cohort studies, is the length of follow-up different between the groups? (Yes/No or cannot determine/NA)
  - Completeness of follow-up
    - Was there a high rate of differential or overall attrition? (Yes/No/Cannot determine)
  - Attrition affecting participant composition
    - Did attrition result in a difference in group characteristics between baseline and follow-up? (Yes/No/Cannot determine)
  - Any attempt to balance
    - Any attempt to balance the allocation between the groups? (Yes/No/Cannot determine/NA)
  - Intention-to-treat analysis
    - Is the analysis conducted on an intention-to-treat (ITT) basis, that is, the intervention allocation status rather than the actual intervention received? (Yes/No/Cannot determine/NA)
- Detection Bias
  - Source of information re: outcomes
    - Are clinical outcomes (e.g. hemodynamic parameters, right heart failure or right ventricular dysfunction, and mortality) assessed using valid and reliable measures and implemented consistently across all study participants? (Yes/No/Cannot determine/NA)
    - Are patient-reported outcomes (e.g., symptom scores, quality of life) assessed using valid and reliable measures and implemented consistently across all study participants? (Yes/No/Cannot determine/NA)

            - Are functional capacity outcomes (e.g. 6-minute walk test, functional class) assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Cannot determine/NA)
    - Reporting Bias
        - Are any important primary outcomes missing from the results? (Yes/No/Cannot determine/Primary outcomes not pre-specified)
    - Other risk of bias issues
        - Are the statistical methods used to assess the primary outcomes appropriate to the data? (Yes/Partially/No/Cannot determine)
    - Power and sample size
        - Did the authors report conducting a power analysis or some other basis for determining the adequacy of study group sizes for the primary outcome(s) being abstracted? (Yes/No/NA)
    - Overall rating of the study (Good/Fair/Poor)
        - If Fair: Describe why the study was given a 'Fair' rating
        - If Poor: Describe why the study was given a 'Poor' rating

IX. Applicability

- Population (P)
    - Is there concern that the study population is inadequately described to assess the applicability of this study? (Yes/No)
    - Is there concern that participants are at widely differing points in natural history of disease? (Yes/No)
    - Is there concern that participants have widely differing degrees of disease severity? (Yes/No)
    - Is there concern that the included patients do not match the review question? (Yes/No)
    - Did the study exclude participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD? (KQ1 only) (Yes/No)
    - Did the study include patients with a wide variety of conditions in addition to the target population? (Yes/No)
    - Did the study selectively recruit participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition? (KQ2 and KQ3 only) (Yes/No)
- Intervention (I)
    - Is there concern that the index test, its conduct, or interpretation differ from the review question? (KA1,2) (Yes/No)
    - Is there concern that equipment or operator level of training/proficiency is not widely available? (KQ1, KQ2) (Yes/No)
    - Is there concern that the intervention (active arm) is not similar to that used in routine clinical practice? (Yes/No)
- Comparator (C)
    - Is there concern that the target condition as defined by the reference standard does not match the review question? (Yes/No)

- Outcomes (O)
    - Is there concern that cointerventions/treatments do not adequately reflect routine clinical practice? (Yes/No)
    - If surrogate outcomes were used, is there concern that they are not sufficiently clinically relevant? (Yes/No)
    - Is there concern that outcomes are not measured for sufficiently long duration of treatment? (KQ2, KQ3) (Yes/No)
    - Is there concern that potential adverse events associated with testing (KQ1,2) or treatment (KQ2,3) were not measured or reported? (Yes/No)
- Setting (S)
    - Is there concern that the care delivery setting is widely divergent from the current typical US setting? (Yes/No)
- Did the study have significant issues with applicability? (Yes/No)
- Comments

Appendix C: List of Included Studies

Ajami GH, Cheriki S, Amoozgar H, et al. Accuracy of doppler-derived estimation of pulmonary vascular resistance in congenital heart disease: An index of operability. Pediatr Cardiol. 2011;32(8):1168-74.

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Appendix D: Quality and Applicability of Included Studies

Table D-1. Quality and applicability for KQ 1 studies

Study	Test Measures	Quality	Limitations to Applicability
Ajami, 2011[1]	• TRV/VTIRVOT	Good	• Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Allanore, 2008[2]	• NT-proBNP, plasma • sPAP	Good	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Index test, its conduct, or interpretation differed from the review question
Bogdan, 1998[3]	• cGMP, urine	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Bonderman, 2011[4]	• NT-proBNP • sPAP • RA size • RV size • TAPSE	Good	• Included patients did not match the review question
Cavagna, 2010[5]	• BNP • NT-proBNP	Good	• Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • None
Ciurzynski, 2011[6]	• Transtricuspid gradient rest/exercise	Good	• None
Colle, 2003[7]	• sPAP	Good	• None
Condliffe, 2011[8]	• Tricuspid gradient	Fair	• None
Dahiya, 2010[9]	• TRV/VTIRVOT	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Denton, 1997[10]	• RV size • sPAP	Fair	• None
Elias, 2008[11]	• NT-proBNP • RIMP/MPI/Tei index	Fair	• None

Study	Test Measures	Quality	Limitations to Applicability
Farber, 2011[12]	• sPAP • RAP	Fair	• None
Fisher, 2009[13]	• sPAP • Transtricuspid gradient	Good	• Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Fonseca, 2011[14]	• TRV • Uric acid	Fair	• None
Frea, 2011[15]	• NT-proBNP • FAC • RIMP/MPI/Tei index • RV size • TRV/VTIRVOT • TAPSE	Fair	• Index test, its conduct, or interpretation differed from the review question
Fukuda, 2011[16]	• FAC • TAPSE • RIMP/MPI/Tei index • sPAP	Fair	• Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Ghio, 2004[17]	• NT-proBNP	Fair	• Target condition as defined by the reference standard did not match the review question
Hachulla, 2005[18]	• TRV	Poor	• None
Hsu, 2008[19]	• sPAP	Good	• None
Hua, 2009[20]	• sPAP	Good	• None
Jansa, 2011[21]	• TRV	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Kovacs, 2010[22]	• sPAP rest and exercise	Good	• None
Lindqvist, 2011[23]	• TRV/VTIRVOT	Fair	• Participants had widely differing degrees of disease severity • Included patients did not match the review question
Low, 2011[24]	• Transtricuspid gradient	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question
Machado, 2006[25]	• NT-proBNP	Poor	• None

Study	Test Measures	Quality	Limitations to Applicability
McLean, 2007[26]	• RV end-diastolic diameter (RVD) • Tpeak (RV tricuspid annular motion by TDI, time from beginning of IC to first Sm peak)	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population • Index test, its conduct, or interpretation differed from the review question • Intervention (active arm) was not similar to that used in routine clinical practice • Cointerventions/treatments did not adequately reflect routine clinical practice
Mourani, 2008[27]	• RA size • RV size • Transtricuspid gradient	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Mukerjee, 2004[28]	• sPAP	Fair	• Index test, its conduct, or interpretation differed from the review question • Potential adverse events associated with testing were not measured or reported
Murata, 1997[29]	• sPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Nakayama, 1998[30]	• sPAP • mPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Potential adverse events associated with testing (KQ1,2) or treatment (KQ2,3) were not measured or reported
Nogami, 2009[31]	• sPAP	Good	• Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population
Phung, 2009[32]	• sPAP	Good	• Study included patients with a wide variety of conditions in addition to the target population
Pilatis, 2000[33]	• RV size • sPAP	Fair	• Target condition as defined by the reference standard did not match the review question • Potential adverse events associated with testing (KQ1,2) or treatment (KQ2,3) were not measured or reported

Study	Test Measures	Quality	Limitations to Applicability
Rajagopalan, 2007[34]	• sPAP • S'	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Rajagopalan, 2009[35]	• TRV/VTIRVOT	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question
Rich, 2011[36]	• sPAP	Good	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Index test, its conduct, or interpretation differed from the review question
Roeleveld, 2005[37]	• sPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Roule, 2010[38]	• TRV • TRV/VTIRVOT	Good	• Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Ruan, 2007[39]	• FAC • RV size • sPAP	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Selimovic, 2007[40]	• sPAP • mPAP	Good	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Simeoni, 2008[41]	• NT-proBNP	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population

Study	Test Measures	Quality	Limitations to Applicability
Steen, 2008[42]	• sPAP rest/exercise	Fair	• Target condition as defined by the reference standard did not match the review question • Surrogate outcomes were not sufficiently clinically relevant
Tei, 1996[43]	• RIMP/MPI/Tei index	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Tian, 2011[44]	• sPAP • mPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Torregrosa, 2001[45]	• sPAP	Fair	• None
Toyono, 2008[46]	• BNP	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Tutar, 1999[47]	• Endothelin-1, plasma	Fair	• Participants had widely differing degrees of disease severity
Vlahos, 2007[48]	• TRV/VTIRVOT	Poor	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Vonk, 2007[49]	• RIMP/MPI/Tei index • sPAP	Fair	• None
Willens, 2008[50]	• sPAP	Fair	• Included patients did not match the review question
Williams, 2006[51]	• NT-proBNP	Fair	• None

Table D-2. Quality and applicability for KQ 2 studies

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Andreassen, 2006[52]	• BNP • Cardiac index • Functional class • RHC-mPAP • RHC-PVR • RHC-sPAP • RAP • Mortality	Low	• None
Barst, 1996[53]	• mPAP	Low	• None
Bendayan, 2002[54]	• Uric acid • 6 minute walk (absolute) • Functional class • Mortality • RHC-CO • RHC-mPAP	Low	• None
Benza, 2010[55]	• BNP >180 • BNP<50 • Pericardial effusion • Mortality	Low	• None
Bernus, 2009[56]	• BNP • Cardiac index • Peak TRV • PCWP • RHC-mPAP • RHC-PVR • Right atrial pressure • RV size • TRV	Low	• None
Bharani, 2007[57]	• sPAP	Moderate	• Intervention (active arm) was not similar to that used in routine clinical practice
Borges, 2006[58]	• RIMP/MPI/Tei index • RV size • 6 minute walk (absolute) • RHC-PVR	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Brierre, 2010[59]	• mPAP • mPAP >= 49 • Pericardial effusion • RIMP/MPI/Tei index • RIMP/MPI/Tei index ≥0.98 • TAPSE • Mortality	Low	• Outcomes were not measured for sufficiently long duration of treatment
Bustamante-Labarta, 2002[60]	• RA size • Survival free from lung transplant	Low	• None
Campana, 2004[61]	• BNP • Cardiac index • FAC • RV size • TAPSE • mPAP • Right atrial pressure • RVEF	Low	• None
Cella, 2009[62]	• RVSP • Nitric oxide • 6MWD (change)	Low	• None
Channick, 2001[63]	• mPAP	Low	• Potential adverse events associated with testing or treatment were not measured or reported
Chin, 2007[64]	• BNP • 6 minute walk (absolute) • PCWP • RHC-CO • RHC-mPAP • RHC-PVR • Right atrial pressure	Low	• None
Dimitroulas, 2007[65]	• BNP	Low	• None
D'Alto, 2010[66]	• BNP	Moderate	• None
Dyer, 2006[67]	• RIMP/MPI/Tei index • RHC-mPAP	Moderate	• None
Elstein, 2004[68]	• BNP • Tricuspid insufficiency	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Fahmy Elnoamany, 2007[69]	• Endothelin-1 • sPAP • RHC-sPAP • RIMP/MPI/Tei Index • RVEF	Moderate	• None
Feliciano, 2005[70]	• RIMP/MPI/Tei index	Low	• None
Fijalkowska, 2006[71]	• BNP • FAC • Pericardial effusion • RA size • RIMP/MPI/Tei index • RV size • Troponin T • 6 minute walk (absolute) • Cardiac index • Functional class • Peak TRV • RHC-mPAP • RHC-PVR • Right atrial pressure • Mortality	Low	• None
Filusch, 2010[72]	• cTroponin T • hsTroponin T • BNP • Mortality • WHO class	Low	• Surrogate outcomes were not sufficiently clinically relevant
Forfia, 2006[73]	• TAPSE • RHC-PVR • Mortality	Low	• None
Friedberg, 2006[74]	• mPAP • BNP • sPAP • RHC-mPAP • RHC-sPAP	Low	• Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population
Galie, 2008[75]	• BNP	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Gan, 2006[76]	• BNP • 6 minute walk (absolute) • Cardiac index • RHC-mPAP • RHC-PVR • Right atrial pressure • RVEF	Low	• None
Ghio, 2010[77]	• FAC • Pericardial effusion • RIMP/MPI/Tei index • sPAP • TAPSE • Mortality	Low	• Study population was inadequately described to assess the applicability of this study • Target condition as defined by the reference standard did not match the review question
Ghofrani, 2002[78]	• BNP • cGMP • RHC-PVR	Moderate	• Surrogate outcomes were not sufficiently clinically relevant •
Goto, 2010[79]	• BNP • sPAP • RHC-mPAP • RHC-sPAP	Low	• Study population was inadequately described to assess the applicability of this study • Participants had widely differing degrees of disease severity • Included patients did not match the review question
Grapsa, 2007[80]	• RIMP/MPI/Tei index • Pericardial effusion • RA size • TRV	Low	• None
Grubstein, 2008[81]	• sPAP • RHC-sPAP	Moderate	• None
Haddad, 2009[82]	• mPAP • sPAP • RHC-mPAP • RHC-sPAP	Low	• None
Hampole, 2009[83]	• BNP • Mortality	Low	• None
Heresi, 2010[84]	• BNP • 6 minute walk (absolute) • Cardiac index • RHC-mPAP • RHC-PVR • Right atrial pressure • Mortality	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Hinderliter, 1997[85]	• FAC • Pericardial effusion • RV size • sPAP • TRV • 6 minute walk (absolute) • Cardiac index • RHC-mPAP • Right atrial pressure • RHC-sPAP	Moderate	• Outcomes were not measured for sufficiently long duration of treatment • Potential adverse events associated with testing or treatment were not measured or reported
Hiramoto, 2009[86]	• BNP • Endothelin-1	Moderate	• None
Ho, 2009[87]	• RIMP/MPI/Tei Index • FAC • BNP • sPAP • RVEF	Low	• None
Homma, 2001[88]	• sPAP • RHC-sPAP	Low	• None
Jacobs, 2009[89]	• BNP	Moderate	• None
Keogh, 2011[90]	• sPAP	Moderate	• None
Knirsch, 2011[91]	• BNP	Low	• Study population was inadequately described to assess the applicability of this study • Study included patients with a wide variety of conditions in addition to the target population • Cointerventions/treatments did not adequately reflect routine clinical practice • Outcomes were not measured for sufficiently long duration of treatment
Lammers, 2009[92]	• BNP • 6 minute walk (absolute) • Functional class	Low	• None
Langleben, 1999[93]	• Endothelin-1	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Leuchte, 2005[94]	• Change in BNP • BNP • Change in : • 6 minute walk (absolute) • Cardiac index • RHC-CO • RHC-mPAP • RHC-PVR • Right atrial pressure	Low	• None
Lorenzen, 2011[95]	• BNP • Uric acid • Mortality	Low	• None
Machado, 2006[25]	• BNP • BNP ≥160, unadjusted ≥160, adjusted log10, adjusted log10, unadjusted • 6 minute walk (absolute) • mPAP • PCWP • RA size • RHC-CO • RHC-dPAP • RHC-PVR • RHC-sPAP • RV size • TRV • Mortality	High	• None
Machado, 2004[96]	• Nitric oxide • sPAP • mPAP • RHC-sPAP	Moderate	• None
Mahapatra, 2006[97]	• RIMP/MPI/Tei Index • RVSP • Mortality	Moderate	• None
Mathai, 2011[98]	• FAC • Peak TRV • Pericardial effusion • RA size • TAPSE • Mortality	Moderate	• None
Mauritz, 2011[99]	• BNP	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
McLaughlin, 2010[100]	• BNP	Low	• None
Michelakis, 2002[101]	• cGMP	Moderate	• Surrogate outcomes were not sufficiently clinically relevant • Outcomes were not measured for sufficiently long duration of treatment • Potential adverse events associated with testing or treatment were not measured or reported
Minniti, 2009[102]	• BNP • TRV	High	• None
Montani, 2007[103]	• Endothelin-1 • Cardiac index • RHC-PVR • Right atrial pressure	Moderate	• Participants were at widely differing points in natural history of disease • Intervention (active arm) was not similar to that used in routine clinical practice
Morishita, 2009[104]	• Pericardial effusion • RA size • RA size • BNP • Functional class	Low	• None
Mukerjee, 2003[105]	• BNP • RHC-mPAP • RHC-PVR	Low	• None
Nagaya, 2000[106]	• ANP • BNP • PCWP • RHC-CO • RHC-mPAP • Right atrial pressure • Mortality • RHC-PVR • Right atrial pressure • RV size	Low	• None
Nakayama, 2007[107]	• BNP	Moderate	• None
Nath, 2005[108]	• Peak TRV • RIMP/MPI/Tei Index • RV size • sPAP • TRV • Functional class	Low	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Nickel, 2008[109]	• BNP • Uric acid • Composite outcome (death or lung transplantation)	Moderate	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Njaman, 2007[110]	• Uric acid • Mortality	Low	• None
Park, 2004[111]	• sPAP • BNP • Clinical event	Moderate	• None
Raymond, 2002[112]	• FAC • Peak TRV • Pericardial effusion • RA size • Mortality • Composite outcome (death or transplantation)	Moderate	• None
Rhodes, 2011[113]	• BNP • 6 minute walk (absolute) • Cardiac index • PCWP • RHC-PVR • Right atrial pressure • Mortality	Low	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Schumann, 2010[114]	• BNP • sPAP	Low	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Sebbag, 2001[115]	• RIMP/MPI/Tei Index • SPAP	Low	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Potential adverse events associated with testing or treatment were not measured or reported
Simeoni, 2008[41]	• BNP	Low	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Soon, 2011[116]	• BNP	Low	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Souza, 2007[117]	• BNP • 6 minute walk (absolute) • Cardiac index • Functional class • RHC-mPAP • RHC-PVR • Right atrial pressure	Low	• None
Takeda, 2010[118]	• BNP • Mortality	Low	• None
Torbicki, 2003[119]	• FAC • BNP • Pericardial effusion • RA size • Troponin T • Mortality	Low	• None
Utsunomiya, 2011[120]	• BNP • RA size • RIMP/MPI/Tei Index • Mortality	Moderate	• None
Utsunomiya, 2009[121]	• RA size • Right atrial pressure • RIMP/MPI/Tei Index	Low	• None
Van Albada, 2008[122]	• Uric acid • Cardiac index • Mortality • RHC-mPAP • RHC-PVR	Low	• Potential adverse events associated with testing or treatment were not measured or reported
Vizza, 2008[123]	• Endothelin-1 • BNP	Low	• None
Voelkel, 2000[124]	• Uric acid • RHC-mPAP • Right atrial pressure	Low	• None
Williams, 2006[51]	• BNP • 10-fold increase from baseline levels	Moderate	• None
Wilkins, 2005[125]	• RV size • Cardiac index • RIMP/MPI/Tei Index • RA size • BNP	Low	• None
Yanagisawa, 2012[126]	• BNP	Low	• None

Study	Index Tests/Comparators	Risk of Bias	Limitations to Applicability
Zafrir, 2007[127]	• RA size • RIMP/MPI/Tei Index • RVEF	Low	• None
Zeng, 2011[128]	• BNP	Low	• None

Table D-3. Quality and applicability for KQ 3 studies

Study	Intervention/Comparator	Quality	Limitations to Applicability
Badesch, 2000[129]	• Epoprostenol ≤2 ng/kg, then adjusted • Conventional therapy only	Fair	• None
Barst, 1996[53] Primary Pulmonary Hypertension Study	• Epoprostenol ≤4 ng/kg, then adjusted • Conventional therapy only	Good	• None
Barst, 2010[130] ASSET-1	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Fair	• None
Barst, 2010[130] ASSET-2	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Fair	• None
Barst, 2011[131] STARTS-1	• Low dose sildenafil • Medium dose sildenafil • High dose sildenafil • Placebo	Fair	• None
Bharani, 2007[57]	• Tadalafil 20 mg daily • Placebo 20 mg daily	Fair	• Intervention (active arm) was not similar to that used in routine clinical practice
Channick, 2001[63] Badesch, 2002[132]	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Good	• Potential adverse events associated with testing or treatment were not measured or reported
Fix, 2007[133]	• Epoprostenol 1 ng/kg/min, then titrated to mean dose of 29 ng/kg/min • Non-epoprostenol group	Fair	• None
Galie, 2005[134] Badesch, 2007[135] Rubin, 2011[136] SUPER	• Sildenafil 20 mg TID • Sildenafil 40 mg TID • Sildenafil 80 mg TID • Placebo	Good	• None
Galie, 2006[137] BREATHE-5	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Good	• None

Study	Intervention/Comparator	Quality	Limitations to Applicability
Galie, 2008[138] EARLY	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Good	• None
Galie, 2008[75] AIRES-1	• Ambrisentan 5 mg daily • Ambrisentan 10 mg daily • Placebo	Good	• None
Galie, 2008[75] AIRES-2	• Ambrisentan 2.5 mg daily • Ambrisentan 5 mg daily • Placebo	Good	• None
Galie, 2009[139] Barst, 2011[140] PHIRST	• Tadalafil 2.5 mg daily • Tadalafil 10 mg daily • Tadalafil 20 mg daily • Tadalafil 40 mg daily • Placebo	Good	• None
Hiremath, 2010[141] TRUST	• Treprostinil 4 ng/kg/min, then adjusted • Placebo	Fair	• Study population was inadequately described to assess the applicability of this study • Cointerventions/treatments did not adequately reflect routine clinical practice • Care delivery setting was widely divergent from the current typical US setting
Hoeper, 2006[142] COMBI	• Bosentan 125 mg BID + iloprost (aerosolized) • Bosentan 125 mg	Fair	• None
Hoeper, 2007[143]	• Bosentan 62.5 mg BID x 4 weeks, then 125 mg thereafter • Iloprost (aerosolized) 5 mcg 6x daily	Fair	• None
Humbert, 2004[144] BREATHE-2	• Epoprostenol + bosentan 62.5 mg BID, then 125 mg BID • Epoprostenol + placebo	Good	• None
Jacobs, 2009[89]	• Epoprostenol titrated to 6-8 ng/kg/min after 1 weeks • Treprostinil increased to 10 ng/kg/min after 1 week, then 20 ng/kg/min after 6 weeks	Fair	• None
Jing, 2011[145] EVALUATION	• Vardenafil 5 mg qD, then 5 mg BID • Placebo	Good	• None
McLaughlin, 2003[146]	• Treprostinil 2.5-5.0 ng/kg/min, then adjusted • Placebo	Poor	• None
McLaughlin, 2006[147]	• Bosentan + iloprost (aerosolized) • Bosentan + placebo	Good	• None

Study	Intervention/Comparator	Quality	Limitations to Applicability
McLaughlin, 2010[100] TRIUMPH 1	• Treprostinil (aerosolized) • Placebo	Good	• None
Mukhopadhyay, 2011[148]	• Tadalafil 40 mg daily • Placebo	Fair	• Care delivery setting was widely divergent from the current typical US setting
Olschewski, 2002[149] AIR	• Iloprost (aerosolized) • Placebo	Good	• None
Olschewski, 2010[150]	• Iloprost (aerosolized) • Standard therapy only	Fair	• None
Reichenberger, 2011[151]	• Epoprostenol • Iloprost up to 20 mcg per breath, max 120 mcg total daily dose	Fair	• None
Rubin, 2002[152] Galie, 2003[153] BREATHE	• Bosentan 62.5 mg BID, then 125 mg BID • Bosentan 62.5 mg BID, then 250 mg BID • Placebo	Good	• None
Sastry, 2007[154]	• Sildenafil 25-50 mg TID • Conventional therapy	Fair	• None
Simonneau, 2002[155] Treprostinil Study	• Treprostinil 1.25 ng/kg/min, then adjusted • Placebo	Good	• None
Simonneau, 2008[156] PACES	• Sildenafil 20 mg TID, then up to 80 mg TID • Placebo	Good	• None
Wilkins, 2005[125] SERAPH	• Bosentan 62.5 mg BID, then 125 mg BID • Sildenafil 50 mg BID, then 50 mg TID	Good	• None
Zeng, 2011[157]	• Sildenafil • Conventional therapy	Fair	• None

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Appendix E: List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reason shown in bold. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Non-English language

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Appendix F: Study Characteristics Tables

Table F-1. Study characteristics table for KQ 1

Study	Population Total N	Test Measures	Study Objectives	Quality
Ajami, 2011[1]	Children & young adults with congenital heart disease referred for RHC N=20	TRV/VTI_{RVOT}	Accuracy of TRV/VTI_{RVOT} for diagnosing elevated PVR	Good
Allanore, 2008[2]	SSc patients with echocardiography sPAP<40 mmHg and no NYHA III/IV symptoms N=101	NT-proBNP, plasma sPAP	Screening for prospective development of PAH (Predicting development of PAH in at-risk population)	Good
Bogdan, 1998[3]	PAH patients and controls N=19	cGMP, urine	Test association of PAH with urine cGMP	Poor
Bonderman, 2011[4]	Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372	NT-proBNP sPAP RA size RV size TAPSE	Diagnostic accuracy for distinguishing PAH from secondary PH Precision/calibration of echocardiographic measures	Good
Cavagna, 2010[5]	SSc patients; symptoms not described N=135	BNP NT-proBNP	Screening for PAH Discrimination between PAH or not Reference standard based on echocardiography sPAP screening with RHC verification of positives	Good
Ciurzynski, 2011[6]	SSc patients. Patients with signs or symptoms of heart or lung disease excluded N=71	Transtricuspid gradient rest/exercise	Association with diagnosis of PAH	Good
Colle, 2003[7]	Liver transplant candidates N=165	sPAP	Screening for portopulmonary hypertension	Good
Condliffe, 2011[8]	SSc patients with suspected PAH; symptoms not described N=89	Tricuspid gradient	Discrimination between PAH or not Reference standard=RHC	Fair
Dahiya, 2010[9]	Referred for evaluation of suspected PH; all patients had dyspnea N=114	TRV/VTI_{RVOT}	Diagnostic accuracy, calibration, and precision of echocardiography estimation of elevated PVR	Good
Denton, 1997[10]	SSc patients suspected of PAH, most due to reduced DLCO N=93	RV size sPAP	Diagnostic accuracy, discrimination of echocardiography for diagnosing PAH	Fair
Elias, 2008[11]	SSc patients. Some were symptomatic N=106	NT-proBNP RIMP/MPI/Tei index	Association with diagnosis of PAH	Fair

Study	Population Total N	Test Measures	Study Objectives	Quality
Farber, 2011[12]	Patients with PAH N=1883	sPAP RAP	Accuracy of echocardiography for sPAP and RAP	Fair
Fisher, 2009[13]	Patients undergoing RHC for known or suspected PAH; symptoms not described N=65	sPAP Transtricuspid gradient	Precision/calibration of echocardiography for mPAP, sPAP compared with RHC	Good
Fonseca, 2011[14]	Sickle cell disease; symptoms not described N=80	TRV Uric acid	Screening for PAH Echocardiography screening of TRV with RHC verification of positives	Fair
Frea, 2011[15]	SSc patients with no signs or symptoms of PAH N=76	NT-proBNP FAC RIMP/MPI/Tei index RV size TRV/VTI_{RVOT} TAPSE	Screening for prospective development of PAH (Predicting development of PAH in at-risk population)	Fair
Fukuda, 2011[16]	Patients with known PH N=67	FAC TAPSE RIMP/MPI/Tei index sPAP	Correlation between echocardiography and RHC hemodynamics in patient with elevated mPAP	Fair
Ghio, 2004[17]	HIV and confirmed PAH. Controls with HIV and no known cardiac or pulmonary disease N=93	NT-proBNP	Diagnostic accuracy for NT-proBNP for discriminating HIV-positive PAH patients from HIV-positive controls	Fair
Hachulla, 2005[18]	SSc patients; some symptomatic N=599	TRV	Screening for PAH in at-risk population	Poor
Hsu, 2008[19]	SSc patients with dyspnea or other clinical features suggestive of PAH N=49	sPAP	Diagnostic accuracy for diagnosing PAH	Good
Hua, 2009[20]	Liver transplant candidates N=105	sPAP	Diagnostic accuracy for portopulmonary hypertension	Good
Jansa, 2011[21]	SSc patients some with dyspnea N=203	TRV	Screening for PAH in at-risk population	Fair
Kovacs, 2010[22]	Patients with CVD some with symptoms N=52	sPAP rest and exercise	Screening for PAH in at-risk population	Good
Lindqvist, 2011[23]	Patients with PH undergoing RHC N=30	TRV/VTI_{RVOT}	Accuracy for diagnosis of elevated PVR Precision/calibration of echocardiography estimate of PVR	Fair
Low, 2011[24]	Referred for evaluation of suspected or definite PAH, most with symptoms N=200	Transtricuspid gradient	Diagnostic accuracy for diagnosing PAH	Poor
Machado, 2006[25]	Sickle cell disease N=416	NT-proBNP	Association between biomarker and hemodynamic measures. Diagnosis based on echocardiography screen with partial verification by RHC of some test positives.	Poor

Study	Population Total N	Test Measures	Study Objectives	Quality
McLean, 2007[26]	Referred for echocardiography with adequate TR jet on Doppler, nearly all with symptoms N=108	RV end-diastolic diameter (RVD) time to peak (RV tricuspid annular motion by TDI, time from beginning of IC to first systolic myocardial peak)	Correlation between echocardiography RVD/time to peak and RHC PASP	Poor
Mourani, 2008[27]	Children under 2 years of age undergoing RHC for chronic lung disease N=25	RA size RV size Transtricuspid gradient	Asses echocardiography feasibility, calibration for estimating hemodynamics, and accuracy for diagnosis of PAH	Fair
Mukerjee, 2004[28]	SSc patients with suspected PAH, symptoms of exercise limitation and reduced DLCO N=137	sPAP	Accuracy of echocardiography sPAP at different thresholds for diagnosis of PAH	Fair
Murata, 1997[29]	SSc patients. Symptoms not described, but most had reduced DLCO N=135	sPAP	Precision/calibration of echocardiography for estimating invasive pulmonary hemodynamics	Fair
Nakayama, 1998[30]	Patients with known, symptomatic CTEPH or PPH N=35	sPAP mPAP	Accuracy of echocardiography for discrimination between CTEPH and PPH	Fair
Nogami, 2009[31]	Suspected pulmonary hypertension; all patients symptomatic N=29	sPAP	Precision/calibration of echocardiography for estimating invasive pulmonary hemodynamics	Good
Phung, 2009[32]	SSc patient referred with or without suspicion of PAH; 10% had NYHA III/IV symptoms N=184	sPAP	Accuracy of echocardiography sPAP for diagnosing PAH	Good
Pilatis, 2000[33]	Liver transplant candidates N=55	RV size sPAP	Accuracy of echocardiography for diagnosing portopulmonary hypertension	Fair
Rajagopalan, 2007[34]	Patients with suspected PH. Many symptomatic; mean WHO functional class 2.5 N=32	sPAP S’	Calibration/precision of echocardiography for estimating RHC hemodynamics	Fair
Rajagopalan, 2008[35]	Known pulmonary hypertension N=52	TRV/VTI_{RVOT}	Accuracy of echocardiography for estimating PVR in PH patients	Fair
Rich, 2011[36]	Patients with both RHC and Doppler echo N=183	sPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Good
Roeleveld, 2005[37]	Known PH N=47	sPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Fair

Study	Population Total N	Test Measures	Study Objectives	Quality
Roule, 2010[38]	Known PH N=37	TRV TRV/VTI_{RVOT}	Calibration/precision for estimating RHC hemodynamics at elevated PA pressures Accuracy for diagnosing elevated PVR in PH patients	Good
Ruan, 2007[39]	Known PAH and healthy controls N=180	FAC RV size sPAP	Diagnostic accuracy of echocardiography for discriminating PAH and control patients	Fair
Selimovic, 2007[40]	Patients with suspected pulmonary vascular disease. 37/42 NYHA III/IV N=42	sPAP mPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Good
Simeoni, 2008[41]	Known SSc-associated PAH and controls with SSc but no PAH N=20	NT-proBNP	Diagnostic accuracy of NT-proBNP for discriminating PAH and control patients	Poor
Steen, 2008[42]	SSc patients with suspected PAH based on symptoms or signs N=54	sPAP rest/exercise	Accuracy of rest/exercise echocardiography to diagnose PAH	Fair
Tei, 1996[43]	Known PPH and health controls N=53	RIMP/MPI/Tei index	Association of Tei index with PPH versus normal controls	Poor
Tian, 2011[44]	Suspected PH based on symptoms N=42	sPAP mPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Fair
Torregrosa, 2001[45]	Liver transplant candidates N=94	sPAP	Accuracy for diagnosing portopulmonary hypertension	Fair
Toyono, 2008[46]	Children with VSD and severe PH N=24	BNP	Correlation between BNP levels and invasive PVR	Good
Tutar, 1999[47]	Children with left-to-right shunt and health controls N=23	Endothelin-1, plasma	Association of endothelin-1 levels and pulmonary hypertension	Fair
Vlahos, 2007[48]	Known or suspected pulmonary hypertension N=12	TRV/VTI_{RVOT}	Accuracy of echocardiography for diagnosing elevated PVR	Poor
Vonk, 2007[49]	Connective tissue diseases. One-third NYHA III/IV N=98	RIMP/MPI/Tei index sPAP	Accuracy for diagnosis of PAH or not	Fair
Willens, 2008[50]	Patients with known PH and elevated sPAP and controls with CHF and elevated sPAP N=47	sPAP	Association of sPAP with PH versus CHF	Fair
Williams, 2006[51]	SSc patients with PAH and controls with SSc but without PAH N=109	NT-proBNP	Accuracy for diagnosis of PAH	Fair

Abbreviations: CHF=congestive heart failure; CTEPH=chronic thromboembolic pulmonary hypertension; CVD=collagen vascular disease; DLCO=diffusion capacity of the lung for carbon monoxide; FAC=fractional area change; 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; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Table F-2. Study characteristics table for KQ 2

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Andreassen, 2006[52] Europe	Adults with suspected chronic precapillary PH N=61 42:19	BNP BNP	Cardiac index Functional class RHC-mPAP RHC-PVR RHC-sPAP RAP Mortality	Correlation Odds ratio	Good
Barst, 1996[53] US/Canada	Adults with PPH N=81 59:22	mPAP		Change in mean from baseline in response to therapy (epoprostenol)	Good
Bendayan, 2002[54] Asia	Adults and children with PAH N=29 25:4	Uric acid	6 minute walk (absolute) Functional class Mortality RHC-CO RHC-mPAP	Correlation	Good
Benza, 2010[55] US	Adults with PAH N=2716 NR	BNP >180 BNP <50 Pericardial effusion	Mortality	HR	Good
Bernus, 2009[56] US	Children with PAH N=78 42:26	BNP	Cardiac index Peak TRV PCWP RHC-mPAP RHC-PVR Right atrial pressure RV size TRV	Correlation	Good
Bharani, 2007[57] Asia	Adults and children with suspected or symptomatic PAH N=8 4:4	sPAP		Change in mean in response to therapy (tadalafil)	Fair

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Borges, 2006[58] Europe	Chronic PAH N=37 24:13	RIMP/MPI/Tei index TAPSE TAPSE RV size	6 minute walk (absolute) RHC-PVR	Correlation Change in mean in response to therapy (bosentan ± beraprost or iloprost)	Good
Brierre, 2010[59] Europe	Adults with PAH N=79 36:43	mPAP mPAP ≥ 49 Pericardial effusion RIMP/MPI/Tei index RIMP/MPI/Tei index ≥0.98 TAPSE	Mortality	HR	Good
Bustamante-Labarta, 2002[60] South America	Adults with PPH N=25 19:6	RA size	Survival free from lung transplant	HR	Good
Campana, 2004[61] Europe	Adults with pre-capillary PH N=22 14:8	BNP Cardiac index FAC BNP RV size TAPSE	mPAP Right atrial pressure RVEF TAPSE	Correlation Changes in means in response to therapy (epoprostenol)	Good
Cella, 2009[62] Europe	Adults with PAH associated with CTD N=18 13:5	RVSP Nitric oxide	6MWD (change)	Correlation Change in mean over time in response to therapy (bosentan)	Good
Channick, 2001[63] US/Europe	Adults with PPH or PAH associated with scleroderma N=32 28:4	mPAP		Change in mean from baseline in response to therapy (bosentan)	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Chin, 2007[64] US	Epoprostenol-treated patients with pulmonary hypertension N=27 19:8	BNP	6 minute walk (absolute) PCWP RHC-CO RHC-mPAP RHC-PVR Right atrial pressure	Correlation	Good
Dimitroulas, 2007[65] Europe	Adults with PAH associated with scleroderma N=10 9:1	BNP		Change in median over time in response to therapy (Bosentan)	Good
D'Alto, 2010[66] Europe	Adults with PAH due to CHD N=32 18:14	BNP		Change in mean in response to therapy (bosentan + sildenafil)	Fair
Dyer, 2006[67] US	Children with IPAH N=12 NR	RIMP/MPI/Tei index	RHC-mPAP	Correlation	Fair
Elstein, 2004[68] Asia	Adults and children with Gaucher disease N=47 27:20	BNP	Tricuspid insufficiency	Correlation with stratified TI values	Good
Fahmy Elnoamany, 2007[69] Africa	Adults with arterial PH with different cardiac pathologies N=53 8:45	Endothelin-1 sPAP	RHC-sPAP RIMP/MPI/Tei Index RVEF sPAP RHC-sPAP	Correlation	Fair
Feliciano, 2005[70] Europe	Adults with severe PAH N=11 9:2	RIMP/MPI/Tei index		Change in mean in response to therapy (bosentan or Iloprost)	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Fijalkowska, 2006[71] Europe	Adults with PH N=55 43:12	BNP FAC BNP BNP Pericardial effusion RA size RIMP/MPI/Tei index RV size Troponin T	6 minute walk (absolute) Cardiac index Functional class Peak TRV Pericardial effusion RHC-mPAP RHC-PVR Right atrial pressure RIMP/MPI/Tei Index RV size Troponin T Mortality	Correlation HR	Good
Filusch, 2010[72] Europe	Adults with PAH N=55 33:22	cTroponin T hsTroponin T BNP	Mortality WHO class	Sensitivity Specificity NPV PPV for prediction	Good
Forfia, 2006[73] US	Adults with PH N=63 52:11	TAPSE TAPSE	RHC-PVR Mortality	Correlation HR	Good
Friedberg, 2006[74] US	Adults and children who had undergone RHC N=112 48:64	mPAP BNP sPAP	RHC-mPAP RHC-sPAP	Correlation	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Galie, 2008[75] US/Europe/Mexico/ South America/ Australia/NZ	Adults with PAH N=201 168:33	BNP		Change in mean in response to therapy (ambrisentan)	Good
Gan, 2006[76] Europe	Adults with PH N=30 22:8	BNP	6 minute walk (absolute) Cardiac index RHC-mPAP RHC-PVR Right atrial pressure RVEF	Correlation	Good
Ghio, 2010[77] Europe	Adults with IPAH N=59 37:22	FAC Pericardial effusion RIMP/MPI/Tei index sPAP TAPSE	Mortality	HR	Good
Ghofrani, 2002[78] Europe	Adults with severe precapillary PH. N=20 (36 tests) NR	BNP cGMP	RHC-PVR Cyclic guanosine monophosphate RHC-PVR	Correlation	Fair
Goto, 2010[79] Asia	Adults with PAH N=46 34:12	BNP sPAP	RHC-mPAP RHC-sPAP	Correlation	Good
Grapsa, 2007[80] UK	Adults with PH N=93 50:43	RIMP/MPI/Tei index	Pericardial effusion RA size TRV	Correlation	Good
Grubstein, 2008[81] Asia	Adults with PH N=38 27:11	sPAP	RHC-sPAP	Correlation	Fair
Haddad, 2009[82] US	Adults with PAH N=51 35:16	mPAP sPAP	RHC-mPAP RHC-sPAP	Correlation	Good
Hampole, 2009[83] US	Adults with PH N=162 126:36	BNP	Mortality	HR	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Heresi, 2010[84] US	Adults with PPH N=40 37:3	BNP	6 minute walk (absolute) Cardiac index RHC-mPAP RHC-PVR Right atrial pressure Mortality	Correlation HR	Good
Hinderliter, 1997[85] Other	Adults with PPH N=81 59:22	FAC Pericardial effusion RV size sPAP RV size FAC TRV	6 minute walk (absolute) Cardiac index RHC-mPAP Right atrial pressure 6 minute walk (absolute) Cardiac index (CI) RHC-mPAP Right atrial pressure 6 minute walk (absolute) Cardiac index RHC-mPAP Right atrial pressure RHC-sPAP	Correlation Correlation Correlation Correlation Change in mean from baseline in response to therapy (epoprostenol)	Fair
Hiramoto, 2009[86] Asia	Adults with PAH N=16 11:5	BNP	Endothelin-1	Changes in mean stratified by % change in ET-1	Fair

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Ho, 2009[87] Asia	Adults with PAH N=6 4:2	RIMP/MPI/Tei Index FAC BNP sPAP RVEF		Changes in median in response to therapy (bosentan)	Good
Homma, 2001[88] US	Adults with PH N=8 5:3	sPAP	RHC-sPAP	Correlation	Good
Jacobs, 2009[89] Europe	Adults with idiopathic PAH N=16 13:3	BNP		Change in mean in response to therapy	Fair
Keogh, 2011[90] Australia/NZ	Adults with PAH N=112 89:23	sPAP		Change in mean in response to therapy (monotherapy vs. combination therapy)	Fair
Knirsch, 2011[91] Europe	Children with heart disease N=103 NR	BNP		Changes in mean in response to therapy (standardized protocol)	Good
Lammers, 2009[92] UK	Children with PH N=50 18:32	BNP	6 minute walk (absolute) Functional class	Correlation	Good
Langleben, 1999[93] US/Canada	Patients with PPH N=18 NR	Endothelin-1		Change in mean in response to therapy	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Leuchte, 2005[94] Europe	Adults with PAH N=30 18:12	Change in BNP BNP	6 minute walk (absolute) Cardiac index RHC-CO RHC-mPAP RHC-PVR Right atrial pressure	Correlation Changes in mean levels over time (no specific therapy)	Good
Lorenzen, 2011[95] Europe	Adults with PAH N=70 48:22	BNP Uric acid	Mortality	HR	Good
Machado, 2006[25] US	Patients with sickle cell disease N=230 138:92	BNP BNP ≥160, unadjusted ≥160, adjusted log10, adjusted log10, unadjusted	6 minute walk (absolute) mPAP PCWP RA size RHC-CO RHC-dPAP RHC-PVR RHC-sPAP RV size TRV Mortality	Correlation HR	Poor
Machado, 2004[96] US	Patients with PAH N=17 17:0	Nitric oxide sPAP	mPAP RHC-sPAP	Correlation	Fair
Mahapatra, 2006[97] US	Adults with PH N=54 41:13	RIMP/MPI/Tei Index RVSP	Mortality	HR	Fair

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Mathai, 2011[98] US	Adults with known or suspected PAH N=50 49:1	FAC Peak TRV Pericardial effusion RA size TAPSE	Mortality	HR	Fair
Mauritz, 2011[99] Europe	Adults with PAH N=198 149:49	BNP		Baseline means only	Good
McLaughlin, 2010[100] US/Europe	Adults with PAH N=235 191:44	BNP		Change in median from baseline in response to therapy (treprostinil)	Good
Michelakis, 2002[101] Canada	Adults with PH N=13 9:4	cGMP		Acute change in mean levels after dose of various vasodilators (iNO, sildenafil, iNO + sildenafil)	Fair
Minniti, 2009[102] US	Adults with SCD and PH N=14 10:4	BNP TRV		Change in mean in response to therapy (ambrisentan)	Poor
Montani, 2007[103] Europe	Adults with PAH N=33 21:12	Endothelin-1	Cardiac index RHC-PVR Right atrial pressure	Correlation	Fair
Morishita, 2009[104] Asia	Adults and children with PAH N=7 6:1	Pericardial effusion RA size RA size BNP	Functional class BNP	Correlation Changes in mean in response to therapy (epoprostenol)	Good
Mukerjee, 2003[105] Europe	Adults with systemic sclerosis N=23 21:2	BNP	RHC-mPAP RHC-PVR	Correlation	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Nagaya, 2000[106] Asia	Patients with PPH N=60 42:18	ANP ANP BNP BNP	PCWP RHC-CO RHC-mPAP Right atrial pressure Mortality PCWP RHC-CO RHC-mPAP RHC-mPAP RHC-PVR Right atrial pressure RV size Mortality	Correlation HR Correlation HR	Good
Nakayama, 2007[107] Asia	Children with IPAH N=31 15:16	BNP		Change in mean in response to therapy (epoprostenol)	Fair
Nath, 2005[108] US	Adults with PPH N=20 16:4	Peak TRV RIMP/MPI/Tei Index RV size RIMP/MPI/Tei Index RV size sPAP TRV	Functional class	Correlation Mean changes over time in response to therapy (epoprostenol)	Good
Nickel, 2008[109] Europe	Adults with IPAH N=76 52:24	BNP Uric acid	Composite outcome (death or lung transplantation)	HR	Fair
Njaman, 2007[110] Asia	Adults with PH N=90 77:13	Uric acid	Mortality	HR stratified by UA levels	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Park, 2004[111] US	Adults with PAH N=20 16:4	sPAP BNP	Clinical event	Mean levels at baseline and over time stratified by patients with event vs patients without event	Fair
Raymond, 2002[112] Not reported/Unclear	Adults with PPH N=81 59:22	FAC Peak TRV Pericardial effusion RA size	Mortality Composite outcome (death or transplantation)	HR	Fair
Rhodes, 2011[113] Europe	Adults with IPAH N=139 98:41	BNP	6 minute walk (absolute) Cardiac index PCWP RHC-PVR Right atrial pressure Mortality	Correlation HR	Good
Schumann, 2010[114] Europe	Adults with PH N=36 17:19	BNP	sPAP	BNP levels stratified by different levels of disease severity	Good
Sebbag, 2001[115] Canada	Adults and children with PPH N=16 13:3	RIMP/MPI/Tei Index SPAP		Changes in mean in response to therapy (epoprostenol)	Good
Simeoni, 2008[41] Europe	Adults with systemic sclerosis and PH N=20 18:2	BNP		Changes in mean in response to therapy (bosentan)	Good
Soon, 2011[116] UK	Adults with PH N=63 42:21	BNP		Determination of most accurate log transformed dichotomous BNP variables to predict events	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Souza, 2007[117] Not reported/Unclear	Adults with IPAH N=42 10:32	BNP	6 minute walk (absolute) Cardiac index Functional class RHC-mPAP RHC-PVR Right atrial pressure	Correlation	Good
Takeda, 2010[118] Asia	Adults with PAH N=37 29:8	BNP	Mortality	HR	Good
Torbicki, 2003[119] Europe	Adults with PAH N=56 43:13	FAC BNP Pericardial effusion RA size Troponin T	Mortality	HR	Good
Utsunomiya, 2011[120] Asia	Adults with PH N=50 39:11	BNP RA size RIMP/MPI/Tei Index	Mortality	HR	Fair
Utsunomiya, 2009[121] Asia	Adults with chronic PH N=50 39:11	RA size	Right atrial pressure RIMP/MPI/Tei Index	Correlation	Good
Van Albada, 2008[122] Europe	Children with PAH N=29 18:11	BNP Uric acid	6 minute walk (absolute) 6 minute walk (change) Functional class Mortality Cardiac index RHC-mPAP RHC-PVR Mortality	Correlation	Good
Vizza, 2008[123] Europe	Adults with PAH associated with CTD N=25 21:4	Endothelin-1	BNP	Correlation	Good

Study Location	Population Total N Female : Male	Index Test(s)	Comparator(s)	Result	Quality
Voelkel, 2000[124] US	Patients with PH N=191 NR	Uric acid	RHC-mPAP Right atrial pressure	Correlation	Good
Williams, 2006[51] UK	Adults with systemic sclerosis N=109 88:21	BNP BNP 10-fold increase *from* baseline levels 10-fold increase *in* baseline levels	Cardiac index RHC-mPAP RHC-PVR Right atrial pressure Mortality	Correlation HR	Fair
Wilkins, 2005[125] UK	Adults with IPAH or PAH associated with CTD N=26 21:5	RV size Cardiac index RIMP/MPI/Tei Index RA size BNP		Change in mean from baseline in response to therapy (bosentan)	Good
Yanagisawa, 2012[126] Asia	Adults with PAH N=46 38:8	BNP	Mortality	HR	Good
Zafrir, 2007[127] Asia	Adults with PPH +/- collagen vascular disease N=29 22:7	RA size RIMP/MPI/Tei Index RVEF	6 minute walk (absolute) Functional class 6 minute walk (absolute) Functional class	Correlation	Good
Zeng, 2011[128] Asia	Adults and children with IPAH N=95 61:34	BNP		Means stratified by survivor/ nonsurvivor	Good

BNP=B-type natriuretic peptide; CTD=connective tissue disease; FAC=fractional area change; iNO=inhaled nitric oxide; IPAH=idiopathic pulmonary hypertension; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; PAH=pulmonary arterial hypertension; PCWP=pulmonary capillary wedge pressure; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrium; RIMP=; RV=right ventricle; SCD=sickle cell disease; sPAP=systolic pulmonary artery pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TRV=tricuspid regurgitant jet velocity

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Appendix G: Correlation Table for KQ 2

Table G-1. Correlation table for KQ 2 (management of PAH)

Study	Age (Variability)	Timing	Index Tests	Comparators	N	Result	p-value
Andreassen, 2006[1]	NR for total cohort	Baseline	BNP	Cardiac index	61	-0.58	<0.001
			BNP	Functional class	61	0.27	0.047
			BNP	RHC-mPAP	61	0.47	<0.001
			BNP	RHC-PVR	61	0.66	<0.001
			BNP	RHC-PVR	17	0.55	0.041
			BNP	RHC-sPAP	61	-0.29	0.028
			BNP	Right atrial pressure	61	0.47	<0.001
Bendayan, 2002[2]	Mean 54.9 (Range 16 to 80)	Baseline	Uric acid	6 minute walk (absolute)	29	-0.35	0.03
			Uric acid	Functional class	29	0.66	0.001
			Uric acid	Mortality	29	0.66	0.001
			Uric acid	RHC-CO	29	0.06	0.72
			Uric acid	RHC-mPAP	29	0.19	0.17
Bernus, 2009[3]	Median 9.3 (Range 5.2 to 14.2)	Baseline	BNP	Cardiac index	52	-0.08	NS
			BNP	Peak TRV	47	0.23	NS
			BNP	PCWP	56	0.26	<0.05
			BNP	RHC-mPAP	57	0.16	NS
			BNP	RHC-PVR	56	0.06	NS
			BNP	Right atrial pressure	56	0.34	p<0.05
			BNP	RV size	42	0.23	NS
Borges, 2006[4]	Mean 56.4 (SD 11)	Baseline	RIMP/MPI/ Tei Index	6 minute walk (absolute)	37	-0.73	0.661
			RIMP/MPI/ Tei Index	RHC-PVR	37	0.172	0.47
			TAPSE	6 minute walk (absolute)	37	0.36	0.028
			TAPSE	RHC-PVR	37	-0.072	0.53

Study	Age (Variability)	Timing	Index Tests	Comparators	N	Result	p-value
Campana, 2004[5]	Mean 50 (SD 11)	Baseline	BNP	Cardiac index	22	r^2=0.2 (negative correlation)	
			BNP	RHC-mPAP	22	r^2=0.1	
			BNP	Right atrial pressure	22	r^2=0.09	
			BNP	RVEF	22	r^2=0.46 (negative correlation)	
			BNP	TAPSE	22	r^2=0.005	
Cella, 2009[6]	Mean 53.8 (SD 13.1)	1 year	Change in RVSP	6 minute walk (change)	18	R2=0.5355	0.0006
Chin, 2007[7]	NR	Baseline	BNP	6 minute walk (absolute)	27	-0.59	0.04
			BNP	PCWP	27	0.32	0.10
			BNP	RHC-CO	27	-0.25	0.19
			BNP	RHC-mPAP	27	0.29	0.14
			BNP	RHC-PVR	27	0.28	0.15
			BNP	Right atrial pressure	27	0.66	<0.001
Dyer, 2006[8]	Mean 9.6 (SD 4.8)	Baseline	RIMP/MPI/ Tei Index	RHC-mPAP	12	0.94	<0.001
		Intermediate	RIMP/MPI/ Tei Index	RHC-mPAP	12	0.90	<0.001
Fahmy Elnoamany, 2007[9]	Mean 55.3 (SD 10.39)	Baseline	Endothelin-1	RHC-sPAP	53	0.94	<0.001
			sPAP	RHC-sPAP	53	0.92	<0.001
Fijalkowska, 2006[10]	Mean 41 (SD 15.1)	Baseline	BNP	6 minute walk (absolute)	55	-0.60	<0.001
			BNP	Cardiac index	55	-0.65	<0.001
			BNP	Functional class	55	0.45	<0.001
			BNP	Peak TRV	55	0.08	NS
			BNP	RHC-mPAP	55	0.21	NS
			BNP	RHC-PVR	55	0.43	<0.001
			BNP	Right atrial pressure	55	0.45	<0.001
Forfia, 2006[11]	Mean 55 (SD 15)	Baseline	TAPSE	RHC-PVR	63	-0.52	<0.0001

Study	Age (Variability)	Timing	Index Tests	Comparators	N	Result	p-value
Friedberg, 2006[12]	NR	Baseline	mPAP	RHC-mPAP	17	0.85	<0.0001
			mPAP	RHC-mPAP	17	0.85	<0.0001
			sPAP	RHC-sPAP	17	0.88	<0.0001
			sPAP	RHC-sPAP	17	0.88	<0.0001
Gan, 2006[13]	Mean 48 (Range 21 to 80)	Baseline	BNP	6 minute walk (absolute)	30	-0.51	0.008
			BNP	Cardiac index	30	-0.45	0.019
			BNP	RHC-mPAP	30	0.28	0.143
			BNP	RHC-PVR	30	0.30	0.122
			BNP	Right atrial pressure	30	0.49	0.008
Ghofrani, 2002[14]	Mean 48.3 (SEM 3.7)	Baseline	ANP	RHC-PVR	20	0.66	<0.0001
			cGMP	RHC-PVR	36	0.139	NS
Goto, 2010[15]	Mean 64.07 (SD 12.28)	Baseline	BNP	RHC-mPAP	46	0.508	0.044
			sPAP	RHC-sPAP	46	0.505	<0.01
Grubstein, 2008[16]	Mean 52 (Range 20 to 80)	Baseline	sPAP	RHC-sPAP	38	0.6	0.001
Haddad, 2009[17]	Mean 49 (SD 11)	Baseline	mPAP	RHC-mPAP	51	0.94	0.90-0.97
			sPAP	RHC-sPAP	48	0.97	0.94-0.98
Heresi, 2010[18]	Mean 44 (SD 14)	Baseline	BNP	6 minute walk (absolute)	40	-0.58	<0.001
			BNP	Cardiac index	40	-0.31	0.07
			BNP	RHC-mPAP	40	0.26	0.10
			BNP	RHC-PVR	40	0.15	0.36
			BNP	Right atrial pressure	40	0.49	0.001

Study	Age (Variability)	Timing	Index Tests	Comparators	N	Result	p-value
Hinderliter, 1997[19]	NR for total cohort	Baseline	FAC	6 minute walk (absolute)	75	0.08	
			FAC	Cardiac index	75	-0.01	
			FAC	RHC-mPAP	75	-0.37	<0.01
			FAC	Right atrial pressure	75	-0.01	
			Pericardial effusion	6 minute walk (absolute)	75	-0.50	<0.01
			Pericardial effusion	Cardiac index	75	-0.40	<0.001
			Pericardial effusion	RHC-mPAP	75	0.22	
			Pericardial effusion	Right atrial pressure	75	0.50	<0.001
			RV size	6 minute walk (absolute)	75	-0.24	<0.05
			RV size	Cardiac index	75	-0.16	
			RV size	RHC-mPAP	75	0.25	
			RV size	Right atrial pressure	75	0.45	<0.001
			sPAP	RHC-sPAP	75	0.57	<0.001
Homma, 2001[20]	Mean 45.0 (SD 10.6)	Baseline	sPAP	RHC-sPAP	8	r^2=0.11	
Leuchte, 2005[21]	Mean 46.93 (SEM 2.8)	Mean followup 12.6 ± 1.5 months	Change in BNP	Change in 6 minute walk	30	-0.74	<0.001
			Change in BNP	Change in cardiac index	30	-0.49	<0.01
			Change in BNP	Change in RHC-CO	30	-0.48	<0.01
			Change in BNP	Change in RHC-mPAP	30	0.54	<0.01
			Change in BNP	Change in RHC-PVR	30	0.55	<0.01
			Change in BNP	Change in right atrial pressure	30	0.78	<0.001
Machado, 2006[22]	NR for total cohort	Baseline	BNP	6 minute walk (absolute)	34	-0.54	0.001
			BNP	PCWP	37	0.30	0.07
			BNP	RA size	211	0.21	0.002
			BNP	RHC-CO	37	-0.43	0.006
			BNP	RHC-dPAP	37	0.37	0.02
			BNP	RHC-mPAP	37	0.43	0.006
			BNP	RHC-PVR	37	0.51	0.001
			BNP	RHC-sPAP	37	0.59	
Machado, 2004[23]	NR for total cohort	Baseline	Nitric oxide	RHC-mPAP	12	0.56	0.054
			sPAP	RHC-sPAP	17	0.794	<0.001

Study	Age (Variability)	Timing	Index Tests	Comparators	N	Result	p-value
Montani, 2007[24]	Mean 43.8 (Range 33.8-56.6)	Baseline	Endothelin-1	Cardiac index	33	-0.47	<0.008
			Endothelin-1	RHC-PVR	33	0.55	<0.05
			Endothelin-1	Right atrial pressure	33	0.46	0.01
Morishita, 2009[25]	Mean 32.6 (Range 15-49)	Baseline	Pericardial effusion	Functional class	7	0.34	<0.05
			RA size	Functional class	7	0.33	NS
Mukerjee, 2003[26]	Mean 57 (Range 34-80)	Baseline	BNP	RHC-mPAP	23	r^2=0.28	<0.05
			BNP	RHC-PVR	23	r^2=0.24	<0.05
Nagaya, 2000[27]	NR for total cohort	Baseline	ANP	PCWP	60	0.22	NS
			ANP	RHC-CO	60	-0.49	<0.001
			ANP	RHC-mPAP	60	0.42	<0.001
			ANP	Right atrial pressure	60	0.55	<0.001
		Baseline	BNP	PCWP	60	0.16	
			BNP	RHC-CO	60	-0.51	<0.001
			BNP	RHC-mPAP	60	0.42	
			BNP	RHC-mPAP	60	0.43	<0.05
			BNP	RHC-PVR	60	0.59	<0.001
			BNP	Right atrial pressure	60	0.55	<0.001
Nath, 2005[28]	Mean 46 (SD 11)	Long-term >1 year	Peak TRV	Functional class	20	0.26	0.29
			Peak TRV	Functional class	20	0.23	0.33
			Peak TRV	Functional class	20	0.38	0.10
Nickel, 2008[29]	Mean 47.6 (SD 15.8)	Baseline	BNP	6 minute walk (absolute)	139	-0.217	0.028
			BNP	Cardiac index	139	-0.378	0.001
			BNP	PCWP	139	-0.027	0.9
			BNP	RHC-PVR	139	0.321	0.006
			BNP	Right atrial pressure	139	0.283	0.008
Souza, 2007[30]	Mean 37 (SEM 2)	Baseline	BNP	6 minute walk (absolute)	42	-0.31	0.052
			BNP	Cardiac index	42	-0.70	<0.001
			BNP	Functional class	42	0.81	<0.001
			BNP	RHC-mPAP	42	0.58	<0.001
			BNP	RHC-PVR	42	0.80	<0.001
			BNP	Right atrial pressure	42	0.68	0.004
Utsunomiya, 2009[31]	Mean 46 (SD 13)	Baseline	RA size	Right atrial pressure	50	0.31	0.03

Study	Age (Variability)	Timing	Index Tests	Comparators	N	Result	p-value
Van Albada, 2008[32]	Median 7.0 (Range 0.1-17.3)	Baseline	BNP	6 minute walk (absolute)	29	-0.527	<0.001
		Long-term >1 year	BNP	6 minute walk (change)	20	-0.63	0.04
		Baseline	BNP	Functional class	29	0.34	0.04
		Long-term >1 year	BNP	Functional class	20	0.72	0.02
		Long-term >1 year	BNP	Mortality	29	9.93	0.002
		Baseline	Uric acid	Cardiac index	16	-0.65	0.007
		Long-term >1 year	Uric acid	Mortality	29	5.93	0.015
		Baseline	Uric acid	RHC-mPAP	16	0.63	0.01
		Baseline	Uric acid	RHC-PVR	16	0.71	0.03
Voelkel, 2000[33]	NR for total cohort	Baseline	Uric acid	RHC-mPAP	191	0.41	<0.0001
			Uric acid	Right atrial pressure	191	0.486	<0.0001
Williams, 2006[34]	Mean 60 (SD 11)	Baseline	BNP	Cardiac index	68	-0.5	<0.0001
			BNP	RHC-mPAP	68	0.62	<0.0001
			BNP	RHC-PVR	68	0.81	<0.0001
			BNP	Right atrial pressure	68	0.53	<0.0001
Zafrir, 2007[35]	Mean 51 (SD 14.7)	Baseline	RA size	6 minute walk (absolute)	29	-0.42	0.02
				Functional class	29	0.39	0.04
			RIMP/MPI/ Tei Index	6 minute walk (absolute)	29	-0.25	0.18
			RVEF	Functional class	29	-0.45	0.019

Abbreviations: ANP=A-type natriuretic peptide; BNP=B-type natriuretic peptide ; CO=cardiac output; CVD=collagen vascular disease; FAC=fractional area change; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NR=not reported; PCWP=pulmonary capillary wedge pressure; 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

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