NHS England

Evidence review: Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension (CTEPH)

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1. Introduction

Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (raised blood pressure in the lungs). Symptoms include chest pain, shortness of breath, fatigue, dizziness and inability to exercise. It develops because blood clots in the lungs (pulmonary emboli) fail to resolve, leaving narrowed and blocked pulmonary arteries. For diagnosis, this must persist despite at least 3 months of effective blood thinning medications (anticoagulation).

Epidemiology

In the general population, the incidence of CTEPH is estimated to be approximately 5 cases per million people per year. (Delcroix 2016a). Most patients have a known history of massive or recurrent acute pulmonary embolism. It is estimated that between 0.6 to 4.8 % of people who have an acute pulmonary embolism develop CTEPH within the next 2 years. (Leopold 2016)

Usual treatment for patients with CTEPH

The treatment of choice is surgery to remove the clots (pulmonary endarterectomy), which can be curative. However, 20-40% of patients with CTEPH have inoperable disease, due to comorbidities or the distal location of the clots. Patients with inoperable CTEPH have an unmet clinical need. They have a worse life expectancy and poorer quality of life compared to those patients who undergo surgery, despite pulmonary vasodilator treatment.

Treatment options for patients with inoperable disease are limited:

- Exercise training has been found in small before and after studies to improve exercise capacity and quality of life in patients with inoperable CTEPH. (Nagel 2012, Fukui 2016) Concern about safety and tolerability has limited its use in routine care for patients with inoperable CTEPH. (Fukui 2016)
- Conventional medical treatments to reduce pulmonary vascular resistance (diuretics, digitalis and chronic oxygen therapy) have little effect and do not affect the underlying disease processes in CTEPH. (Pepke-Zaba 2016)
- Patients with CTEPH may be treated with medications used against pulmonary arterial hypertension such as prostacyclin analogs (epoprostenol, beraprost, iloprost), endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan) and phosphodiesterase-5 inhibitors (sildenafil). Small uncontrolled trials of these medications in CTEPH have had mixed results. (Pepke-Zaba 2016) A randomized controlled trial of bosentan in 157 patients with CTEPH (BENEFiT) found improved pulmonary vascular resistance at 16 weeks among patients receiving bosentan compared to patients receiving placebo, but 6 minute walk distance was not significantly different. (Mathai 2016)
- Riociguat, a guanylate cyclase stimulator, is the first drug to be licensed for use in inoperable or persistent recurrent CTEPH. The main evidence of efficacy of riociguat against CTEPH is derived from one randomized placebo-controlled trial of 261 patients, CHEST-1, which was followed by a 2-year extension, CHEST-2. (Ghofrani 2013, Simonneau 2016) The detailed results of these trials are described below.

Prognosis of inoperable CTEPH

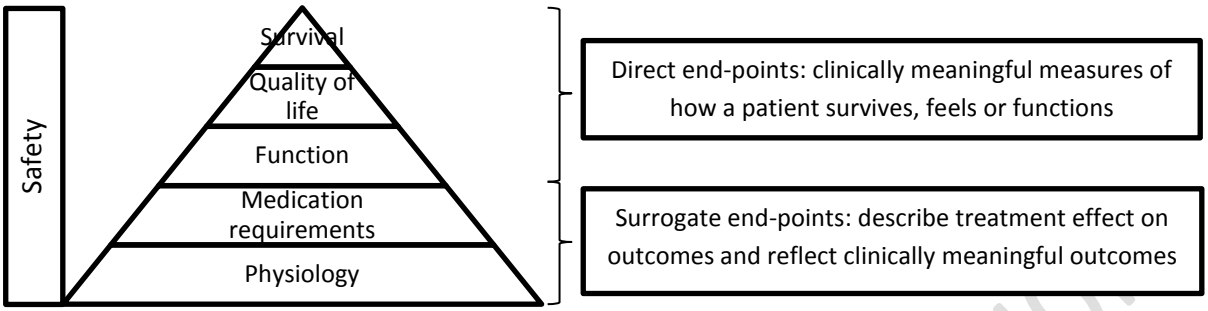
Compared with the general population, patients with CTEPH report a reduced quality of life, and increased rates of depression and anxiety. (Mathai 2016) If left untreated, CTEPH often leads to right heart failure and ultimately death:

- The International CTEPH Registry followed 275 newly diagnosed patients who were not operated upon. Survival at 1, 2, and 3 years was 88% (95%CI 83 – 91), 79% (95% CI 74 – 83) and 70% (95% CI 64 – 76) years. (Delcroix 2016b)
- Among the 237 patients who entered the CHEST-2 trial to receive riociguat, 2 year survival was 93% (95% CI 89-96). However, these were patients selected by virtue of having completed the 16 week CHEST-1 trial, and so may have had better survival than unselected patients. (Simonneau 2016)
- In a Spanish registry of 391 patients with CTEPH 2007-2013, five-year survival was 64.9% among the 68.8% of patients not treated with surgery. (Escribano-Subias 2016)

Measuring outcomes in CTEPH

For this review, a hierarchy of outcomes was used to classify and describe the end points reported in studies of patients with CTEPH (Figure 1).

Figure 1: Hierarchy of outcomes in CTEPH



Survival and quality of life

Survival and validated measures of quality of life were considered the most clinically meaningful outcomes.

Function and exercise capacity

6 minute walk distance (6MWD) is the distance that a patient can walk in 6 minutes, resting as needed. This indicates the extent to which shortness of breath and fatigue affect patients in their daily lives. Improvement in 6MWD has also been found to be associated with higher quality of life among patients with CTEPH. (Mathai 2016, Urushibara 2015) It is also an indicator of prognosis. Among 237 patients with inoperable CTEPH in the CHEST-2 trial, 6MWD was associated with 2 year survival (p=0.02). (Simonneau 2016)

Functional class describes the extent to which exercise-related symptoms limit a patient's activity. A functional class of IV is associated with a nearly five-fold increase in mortality among non-operated patients with CTEPH (HR 4.76, 95% CI 1.76 – 12.88, P=0.0021). (Delcroix 2016)

Table 1: WHO functional classification for pulmonary hypertension

Class	WHO classification (adapted from the New York Heart Association classification for heart failure)
I	No limitation of usual physical activity. Ordinary physical activity does not cause symptoms
II	Mild limitation of physical activity. Comfortable at rest. Normal activity causes undue shortness of breath, fatigue, chest pain or presyncope.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes shortness of breath, fatigue, palpitations or presyncope.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure may be present at rest.

Cardiopulmonary exercise testing assesses the performance of the heart and lungs during maximal exercise, using non-invasive monitoring. A variety of protocols and monitoring techniques can be used.

Medication requirements

A patient no longer requiring long-term oxygen therapy or other medications after BPA is a surrogate marker for symptom improvement, and may also be expected to have a direct impact on quality of life.

Physiology

Physiological changes in pulmonary haemodynamics offer a wide array of surrogate outcomes which mark changes in disease progress, and are expected to be reflected in patient symptoms and prognosis. The main physiological outcomes from each study are included in section 7, Evidence Summary Table. To simplify comparison across studies, the report will focus on two physiological indicators. Both of these indicators are well-reported and are statistically associated with prognosis.

- Pulmonary vascular resistance (PVR) represents the resistance to blood flow offered by the pulmonary vasculature. Among patients with CTEPH, reduced PVR has been found to be associated with higher quality of life (Urushibara 2015) and to predict mortality of medically-treated patients with CTEPH. (Saouti 2009). Post-surgical PVR has also been found to predict long-term survival among patients with CTEPH following surgery in large observational studies (Cannon 2016, Mayer 2011).
- N-terminal pro b-type natriuretic peptide (NT-pro BNP) is a protein produced by the walls of the heart. It is a marker of cardiac strain, and levels are elevated by heart failure. It was associated with 2 year survival of patients with inoperable CTEPH in the CHEST trial (p=0.02) (Simonneau 2016).

The CHEST trial of riociguat for inoperable CTEPH

Riociguat is the only treatment currently licensed for patients with inoperable CTEPH. NHSE has published a routinely commissioned policy on riociguat, which contains detailed information on its effectiveness and safety. The main evidence of efficacy of riociguat against CTEPH is derived from one trial, CHEST-1, which was followed by a 2-year extension, CHEST-2.

CHEST-1 was a randomised controlled trial which compared riociguat to placebo over 16 weeks for 261 patients across 89 centres. The results at 16 weeks showed some improvement in 6 minute walk distance, functional class, pulmonary haemodynamics and NT-pro BNP for patients receiving riociguat compared to patients receiving placebo (Table 2). Changes in quality of life were more equivocal. (Ghofrani 2013)

During the 16 week trial, there were two deaths among 173 patients (1%) in the riociguat group (from heart failure and acute renal failure). The death from acute renal failure was considered to be related to the study drug. This compares to 3 deaths among the 88 patients in the placebo group (3%). (Ghofrani 2013)

Serious adverse events in the riociguat group included right heart decompensation, vaginal bleeding and overdose of study drug (attempted suicide). There was a high risk of discontinuation: 13/173 patients assigned to riociguat (8%) did not tolerate the drug sufficiently to finish the 16 week treatment, although a high discontinuation was also seen in the placebo group, in which 5/88 (6%) did not complete treatment. (Ghofrani 2013)

237 patients from the CHEST-1 study entered the CHEST-2 open-label extension study, in which all patients received riociguat. The primary endpoints were safety and tolerability. At 2 years, overall survival was 93% (95% CI 89–96) and clinical worsening-free survival was 82% (77–87). Serious adverse events were seen in 129 patients (54%), and a further 14 (6%) discontinued riociguat therapy because of adverse events. (Simonneau 2016)

Table 2: Outcomes of CHEST-1 16 week trial of riociguat vs placebo

Outcome	Placebo			Riociguat			Difference (95% CI)*	P value
	n	baseline (mean ±SD)	change (mean ±SD)	n	baseline (mean ±SD)	change (mean ±SD)		
6 minute walk distance (metres)	88	356 ±75	-6 ±84	173	342 ±82	39 ±79	46 (25 to 67)	<0.001
WHO functional class	87	0 in class I, 25 in class II, 69 in class III, 2 in class IV	13 (15%) moved to lower class, 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	3 in class I, 55 in class II, 107 in class III, 8 in class IV	57 (33%) moved to lower class, 107 (62%) stayed in same class, 9 (5%) moved to higher class	-	0.004
Quality of life (EQ-5D score)†	87	0.66 ±0.25	-0.08 ±0.34	172	0.64 ±24	0.06 ±0.28	0.13 (0.06 to 0.21)	<0.001
Quality of life (LPH score)‡	86	46 ±23	-2 ±19	170	41 ±22	-7 ±19	-6 (-10 to -1)	0.1
Pulmonary vascular resistance (dyne.sec.cm^5)	82	779 ±401	23 ±274	151	791 ±432	-226 ±248	-246 (-303 to -190)	<0.001
Cardiac output (litres/minute)	83	4 ±1	-0.03 ±1.07	155	4 ±1	0.8 ±1.1	0.9 (0.6 to 1.1)	<0.001
NT-pro BNP (pg/ml)	73	1706 ±1567	76 ±1447	150	1508 ±2338	-291 ±1717	-444 (-843 to -45)	<0.001

* least squares mean difference on the basis of an analysis of the modified intention-to-treat population with missing values imputed
† Scores on the EuroQol Group 5-Dimension self-report questionnaire (EQ-5D) range from -0.6 to 1.0, with higher scores indicating a better quality of life.
‡ Scores on the Living with Pulmonary Hypertension (LPH) questionnaire range from 0 to 105, with higher scores indicating a worse quality of life.

Balloon pulmonary angioplasty

Balloon pulmonary angioplasty (BPA) aims to reduce pulmonary hypertension by dilating narrowings in the pulmonary arteries.

The procedure is usually done under local anaesthetic and light sedation, with the patient fully anticoagulated. A standard right heart catheterization is performed through the right internal jugular vein or right femoral vein. The narrowed or blocked vessels are identified using selective pulmonary angiography. A balloon catheter is then advanced over a guidewire, and the balloon is inflated to dilate the arteries and restore pulmonary blood flow. Several narrowings may be treated in one session. To reduce the risk of complications, a limited number of segments of lung are usually treated in one session and several sessions are usually required. These are performed at 2-8 week intervals.

Use of BPA for inoperable CTEPH in practice

Although most of the published research is from Japan, BPA is beginning to be used to treat patients with inoperable CTEPH in other countries. For example, there are conference reports of 75 BPA sessions for 21 patients in Spain (Velázquez 2016) and 79 BPA sessions among 32 patients in Poland (Darocha 2015).

Papworth General Hospital is conducting a pilot project in providing balloon pulmonary angioplasty for patients with inoperable CTEPH in the UK, funded by the Papworth Hospital Charitable Funds. Between October 2015 and October 2016, 33 BPA procedures were performed on 10 patients at Papworth Hospital with no major complications. Functional improvement has been observed in the patients' conditions, together with clinically meaningful reductions in their pulmonary vascular resistances (PVR).

Ongoing research into BPA for CTEPH

There is an ongoing clinical trial (RACE) for a randomized open label trial of riociguat versus balloon pulmonary angioplasty in non-operable chronic thromboembolic pulmonary hypertension (ClinicalTrials.gov identifier NCT02634203). The study aims to enroll 124 patients, and is due to complete recruitment in September 2019. The primary outcome measure is change from baseline in pulmonary vascular resistance at 26 weeks. Secondary outcomes will include 6 minute walking distance, WHO functional class, BNP, Borg dyspnoea score and clinical worsening (death, lung transplantation, hospitalization due to PH or start of PAH specific treatment).

There are many national registries for patients with pulmonary hypertension, including patients with CTEPH. Large registries which have registered as clinical trials studying outcomes of BPA for CTEPH include:

- The International CTEPH Registry is an international prospective, observational multicentre disease registry, which will collect data in chronic thromboembolic pulmonary hypertension (CTEPH) patients. ClinicalTrials.gov identifier: NCT02656238. Its objectives include evaluating new therapeutic approaches in CTEPH. It has recruited 1000 patients from America, Europe and Asia and aims to report 3 year outcomes in 2020. https://www.cteph-association.org/
- The US CTEPH Registry is a national multicentre prospective observational study of the clinical course and treatment of patients diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH), WHO Group IV Classification for Pulmonary Hypertension in the United States. ClinicalTrials.gov identifier: NCT02429284. Its objectives include evaluating the outcomes and predictors of outcomes of nonsurgical therapy in patients with CTEPH. In October 2016 the registry had enrolled 357 subjects and was recruiting further. The study aims to report on 4 year outcomes in 2020. http://www.usctephregistry.com/

2. Summary of results

8 studies from 7 centres were included in this review. All were observational case-series, including between 20 to 103 patients, which compared outcomes before and after BPA.

Direct outcomes

The best available estimate of survival was based on 68 patients, of whom 66 (97%) were alive at one year following BPA. No studies were found which described the effect of BPA for inoperable CTEPH on quality of life. Consistent evidence was found from all studies demonstrating an improved function (or reduced symptoms of heart failure) following BPA compared to prior to BPA. The average improvement in the distance walked in 6 minutes ranged from 46 to 100 metres across the studies, and consistent improvements in functional classification and exercise testing were also reported.

Indirect outcomes

Changes in the requirement for medication was not systematically reported. All studies reported an improvement in physiological markers of heart failure or pulmonary hypertension after balloon pulmonary angioplasty compared to before. Reductions in average pulmonary vascular resistance ranged from 31% to 61% across the studies, while reduction in average brain natriuretic peptide ranged from 10% to 50%. Follow up time periods ranged from immediately after the final BPA session to 14 months later.

Safety

There were 5 deaths around the time of the procedure, among the 281 patients (2%) in the 6 included studies which reported complications. The main complications reported were: injury to the pulmonary artery with the guidewire during BPA, which may cause serious bleeding or death; and pulmonary oedema (fluid on the lungs) following reopening of the narrowed pulmonary arteries. Pulmonary oedema causes shortness of breath and a fall in oxygen levels of the blood, and patients may require artificial ventilation.

Limitations

No studies were found which compared BPA to best medical treatment (riociguat). There was little data on survival, and none on quality of life or long term outcomes. All studies were observational comparisons of patient outcomes after BPA compared to before BPA, which are more vulnerable to bias than randomised trials of treatment with a separate comparison group.

3. Methodology

The report aimed to identify and assess the evidence comparing the effectiveness and safety of balloon pulmonary angioplasty (BPA) with best medical treatment (riociguat) for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

The Medline, EMBASE and Cochrane databases were searched for any clinical trials or observational studies that reported pre-specified outcomes of BPA for human patients with non-operable CTEPH using pre-specified inclusion and exclusion criteria. In additional a clinical trials registry and the NICE website were searched for relevant studies or review. Full details of the search strategy are available in section 9 (literature search terms). The study outcomes are described in the background, and were chosen in discussion with a clinical specialist. Exclusion criteria included:

- Only papers published from 2011 onwards were included.
  The first reports of BPA for treating inoperable CTEPH had high complication rates (Feinstein 2001). The modern era of BPA for CTEPH has introduced safer procedures, including determining the size of the balloon for each lesion using additional imaging such as ultrasound or CT, and limiting the number of lesions and lobes treated in each session to reduce the risk of reperfusion injury. (Mizoguchi 2012) The review was therefore limited to the last 5 years to capture data from the modern era of BPA for CTEPH.
- Only papers which reported results for 20 or more patients were included.
  The BPA procedure is technical, with a learning curve. Including single case reports or small case series might have included poorer outcomes obtained from patients with unusual circumstances (warranting case reports) or centres who have not completed a learning curve. The threshold of 20 patients is arbitrary, but equivalent to that applied to PEA centres conducting pulmonary endarterectomy by the European Society of Cardiology (Galiè 2009).
- Conference abstracts were excluded due to difficulty in assessing methods and quality.
- Non-English language articles would have been excluded due to lack of translation facilities, unless they were thought to add substantially to the English language evidence base. The search and abstract review included non-English language articles, and no potentially eligible articles were identified for consideration.

Full details of the search are available in section 10 (search strategy). In brief, 506 deduplicated abstracts were screened, and 126 selected for full text review. The reference lists of evidence reviews and eligible studies were screened and this identified no new eligible studies. 24 eligible studies were identified which fulfilled the search criteria. These are described in section 11 (evidence selection).

The 24 papers all originated from 7 centres, and there was a high degree of overlap of patient populations. Several papers reported updated outcomes on the same (or a cumulatively growing) cohort of patients over time. Reporting the outcomes from all 24 papers would have been misleading, as the results were not independent: the same patient's outcome might be included in the results for several papers. For this reason, only the paper which described the largest and most representative patient cohort for each centre was included. The selection of the largest most recent papers in this review will tend to exclude papers which have longer follow up periods. One additional paper was therefore included for the long-term survival outcomes only, as a supplement to the main paper for that study group.

Some papers of the same cohort of patients over time varied in the outcomes they reported. The selection of which secondary outcome to report in each paper may have been influenced by whether the result was considered notable. Supplementing the main report with additional minor outcomes reported in one paper and not another therefore risks over-reporting positive results. The review did not pick out additional minor outcomes from these papers, due to this risk of selective reporting bias.

The review aimed to identify studies which compared the outcomes of BPA for those of best medical treatment (riociguat). No direct comparisons were available, and so results of the only randomised controlled study of riociguat vs placebo (CHEST) were provided as a comparison where relevant.

4. Results

Overall results summary

Eight studies from 7 centres were included in this review. All were observational case-series, with cohort sizes from 20 to 103 patients, which compared outcomes before and after BPA. No studies compared BPA to best medical treatment (riociguat). Follow up periods ranged up to 14 months.

Direct outcomes

The best available estimate of survival was based on 68 patients, of whom 66 (97%) were alive at one year following BPA. No studies were found which described the effect of BPA for inoperable CTEPH on quality of life. Consistent evidence was found from all studies demonstrating an improved function (or reduced symptoms of heart failure) following BPA compared to prior to BPA. The average improvement in the distance walked in 6 minutes ranged from 46 to 100 metres across the studies, and consistent improvements in functional classification and exercise testing were also reported.

Indirect outcomes

Changes in the requirement for medication were not systematically reported. All studies reported an improvement in physiological markers of heart failure or pulmonary hypertension after balloon pulmonary angioplasty compared to before. Reductions in average pulmonary vascular resistance ranged from 31% to 61% across the studies, while reduction in average brain natriuretic peptide ranged from 10% to 50%.

Safety

Periprocedural mortality was 5/281 (2%) in the 6 included studies which reported complications. The main complications reported were pulmonary artery wire perforation and reperfusion pulmonary oedema.

A description of each outcome is available in section 1 (background). More detailed results for each outcome are described and discussed in section 8 (grade of evidence table).

Survival

Three included studies reported the proportion of patients who survived a period of follow-up after balloon pulmonary angioplasty. The most robust result that 66/68 patients (97%) were alive at one year after BPA (Mizoguchi 2012). Direct comparisons to survival of patients treated with riociguat were not available.

Quality of life

No studies were found which described the effect of BPA for inoperable CTEPH on quality of life.

Function

6 minute walk distance (6MWD) is the distance in metres a patient walks in 6 minutes.

All but one study reported 6MWD and all found an average improvement, which ranged from 46m to 100m, over follow up periods up to 14 months.

Table 3: 6 minute walk distance (6MWD) before and after balloon pulmonary angioplasty (BPA)

Study	6MWD (m)		Follow up assessment point	P value
	Pre BPA	Post BPA		
Broch 2016	Not reported	Not reported		
Kinutani 2016	303±[92]	394 [±124]	Immediate	<0.01
Yamasaki 2016	391 [±75]	437 [±68]	Unclear: immediate or 3 months	<0.0001
Aoki 2016	390 (286-484)	490 (411-617)	6 months	<0.01
Fukui 2015	405 [±111]	501 [±109]	Mean 3 weeks	<0.001
Inami 2014a	360 (281-430)	420 (350-510)	Median 14 months	<0.001
Mizoguchi 2012	296 [±108]	368 [±83]	Immediate	<0.01.

mean[±SD] or median (IQR)

Functional class (WHO or NYHA) is a description of how symptoms of heart failure affect a patient's activities, classes I-IV where IV is most severe, see page 5 for the classes in full).
Five studies reported functional classification. All found an average improvement, with fewer patients in the more severe classes (III and IV) and more patients in the less severe classes (I and II), over follow up periods up to 1 year.

Table 4: Functional classification before and after balloon pulmonary angioplasty (BPA)

Study	Functional class		Follow up assessment point	P value
	Pre BPA	Post BPA		
Broch 2016	2.9 [±0.5]	1.9 [±0.5]	3 months	<0.001
Kinutani 2016	0/8/16/4 (0/29/57/14)	16/11/1/0 (57/39/4/0)	Immediate	p<0.01
Yamasaki 2016	Not reported	Not reported		
Aoki 2016	0/12/11/1 (0/50/46/4)	5/19/0/0 (24/76/0/0)	6 months	0.04
Fukui 2015	2.6	2.1	Mean 3 weeks	<0.001
Inami 2014a	Not reported	Not reported		
Mizoguchi 2012	0/0/49/19 (0/0/72/28)	17/49/0/0 (25/72/0/0)	1 year	

Mean [±SD] or number in class I/II/III/IV (% in each class)

Fukui (2015) reported an improvement in exercise duration and peak VO2 assessed in *cardiopulmonary exercise testing* at 3 weeks following BPA compared to prior to treatment.

Medication requirements

Change in medication requirements were reported by three studies. In addition, Broch (2016) reported that medications were held constant during the study to reduce confounding of the BPA treatment effect.

- Home oxygen therapy requirement was reduced in the two studies which reported this, (from 79% to 54% immediately after BPA, p=0.01, (Aoki 2016); from 100% to 62% at one year follow up, (Mizoguchi (2012)).
- Pulmonary hypertension therapy changes were reported in 2 studies by drug prescription rather than by treated patient, and combination therapy was not consistently reported. It was unclear whether the number of patients requiring medication changed or whether patterns of medication shifted. The clearest report was that of 14 patients treated with oral pulmonary hypertensive therapies, 1 patient discontinued an endothelin-receptor antagonist (7%) while 13 remained unchanged over follow up (mean 3.5 months) in the study by Fukui (2015).

Physiology

All studies reported an improvement in the average pulmonary vascular resistance (PVR) and/or brain natriuretic peptide (BNP) after BPA, over follow up periods up to 14 months. Average PVR reductions ranged from 31% to 61%, and some post-BPA averages approached normal values for PVR (<250 dyne sec/cm^5). Average BNP reductions ranged from 10% to 50%.

Table 5: Pulmonary vascular resistance (PVR) before and after balloon pulmonary angioplasty (BPA)

Study	PVR (dyne sec/cm^5 unless stated)		Follow up assessment point	P value
	Pre BPA	Post BPA		
Broch 2016	612 [±282]	375 [±221]	3 months	<0.001
Kinutani 2016	574 (317)	258 (171)	Immediate	<0.01
Yamasaki 2016	639 (224)	411 (123)	Mean 88 days	<0.001
Aoki 2016	517 (389-696)	268 (239-345)	6 months	<0.01
Fukui 2015	755 (345)	N/A *	N/A	N/A
Inami 2014a	8.7 Wood units (6.1-13.3)	2.7 Wood units (2.0-4.2)	Median 14 months	<0.001
Mizoguchi 2012	942 (367)	327 (151)	1 year	<0.01

mean[±SD] or median (IQR)

* pulmonary wedge pressure could not be measured post BPA in this study to obtain PVR

Table 6: Brain natriuretic peptide (BNP) before and after balloon pulmonary angioplasty (BPA)

Study	BNP (pg/ml)		Follow up assessment point	P value
	Pre BPA	Post BPA		
Broch 2016	791	237	3 months	0.001
Kinutani 2016	160 [±233]	26 [±31]	Immediate	<0.01
Yamasaki 2016	67 [±61]	34 [±30]	Mean 88 days	<0.05
Aoki 2016	112 (49-199)	28 (15-58)	6 months	<0.01
Fukui 2015	142 [±198]	25 [±11]	Immediate or 3 months (unclear)	<0.01
Inami 2014a	95 (42-270)	34 (16-59)	Median 14 months	<0.001
Mizoguchi 2012	330 [±444]	35 [±55]	1 year	<0.01

mean[±SD] or median (IQR)

Safety

All but one study reported peri-procedural safety. Peri-procedural mortality was 5/281 (2%) among patients included in the studies which reported complications. The main complications reported were:

- Reperfusion pulmonary oedema. Patients may require ventilator support; the condition may be fatal.
- Pulmonary artery wire perforation, which may cause serious bleeding or death.

Table 7: Peri-procedural complications reported for balloon pulmonary angioplasty

Study	N	Severe reperfusion pulmonary oedema	Wire perforation	Peri-procedural deaths
Broch 2016	32	1, fatal	Not reported	2 deaths (reperfusion oedema, acute pulmonary embolism)
Kinutani 2016	29	Desaturation requiring NIPPV in 13 sessions (15% of sessions).	5 (6% of sessions)	1 death prior to BPA, from central venous catheter-associated sepsis related to pre-BPA epoprostenol administration.
Yamasaki 2016	20	Not reported	Not reported	Not reported
Aoki 2016	24	No reperfusion lung oedema requiring mechanical ventilation	"No severe lung bleeding"	No peri-procedural deaths
Fukui 2015	25	No severe reperfusion pulmonary edema requiring invasive ventilation	"No major complications"	No peri-procedural deaths
Inami 2014a	103	Ventilation required after 9/350 sessions (3%)	Dissection in 35/350 sessions (10%). 2 required stent or coil; 1 fatal.	1 death at 2 days (wire perforation): perioperative mortality 1% (1/103).
Mizoguchi 2012	68	4 patients needed intratracheal intubation, 2 needed percutaneous cardiopulmonary support.	5 patients, 2 needed emergency transcatheter coil embolization.	1 (reperfusion pulmonary injury)

5. Discussion

The results are discussed for each outcome, grouped to reduce repetition where similar interpretations apply. This is followed by a summary of the strengths and limitations, overall pattern of results, recommendations for future research and conclusions.

Survival and quality of life

The best available estimate of survival was based on 68 patients, of whom 66 (97%) were alive at one year following BPA (Mizoguchi 2012). Direct comparisons to survival of patients treated with riociguat were not available. Further available comparisons with results from separate sources are discussed in section 8 (grade of evidence table). These comparisons are limited by a difference in patient status at baseline: it is not clear that patients with the same baseline status are being compared when these patients are in separate cohorts in different settings. With this caveat, the nearest comparison is perhaps that among patients with inoperable CTEPH receiving riociguat in the CHEST-2 extension trial, 2 year survival was 93% (95% CI 89-96).

No studies were found which described the effect of BPA on quality of life. Functional and physiological outcomes (6MWD and PVR) have been found to be statistically associated with quality of life among patients with pulmonary hypertension, and so provide indirect evidence of expected impact of BPA on quality of life. (Mathai 2016, Urushibara 2015) Testimony from UK patients treated at Papworth hospital confirms that the physiological and functional improvements observed following BPA have been accompanied by significant improvements in wellbeing and quality of life.

Short-term mortality will be included as part of a composite outcome of clinical worsening in the RACE trial in which patients from the same population will be randomised to receive either riociguat or BPA. There is potential for more observational reports of survival and quality of life from pulmonary hypertension registries, although as these are observational, the reasons for difference in mortality between the groups may be co-morbidities that also drive selection of treatment choices.

Function and physiology

The results of all studies showed an improvement in function, measuring the experience of heart failure symptoms which affect patients in their day-to-day lives. The average improvement in 6MWD ranged from 46m to 100m across six studies, which is likely to be meaningful to patients. A systematic review found that a change of 45 metres in 6MWD was clinically meaningful among people with chronic heart failure (that is, it exceeded measurement error and was associated with significant changes in either aerobic capacity and/or health-related quality of life). (Shoemaker 2012) The results of changes in average functional classification and in exercise capacity were consistent with a meaningful improvement in symptoms.

All studies reported a sizeable improvement in the physiology outcomes of average pulmonary vascular resistance (PVR) and/or brain natriuretic peptide (BNP) after BPA, over follow up periods up to 14 months. Both pulmonary vascular resistance (a marker of pulmonary hypertension) and brain natriuretic peptide (a marker of right heart strain) are expected to be reflected in patient symptoms and prognosis, but not necessarily in a linear or straightforward relationship. The size of effects observed (in particular that the average PVR was close to normal following BPA in some studies) does support the expectation that these physiological changes would correspond to clinically meaningful changes in the patient's symptoms.

Most of the studies have a small number of patients, and so are vulnerable to overestimation of the size of effects. However, both functional and physiological effects were consistently observed across the studies, and the highest quality study which had a moderately sized cohort of 68 patients reported similar effect sizes to smaller studies (Mizoguchi 2012). All studies were observational before-and-after case series, but the improvements are large enough that they are unlikely to be explained by regression to the mean given the natural history of the condition. There is some scope for studies to have selectively reported the more favourable of 6MWD or functional class – however, most studies report both, which limits the likely extent of selective reporting bias. The universal reporting of physiological outcomes means they are not vulnerable to selective reporting bias. Mizoguchi (2012) found that the improvements were sustained at one year's follow up following BPA but longer term results were not available.

The CHEST-1 trial of riociguat found that 6MWD and physiological markers of disease improved among

patients receiving riociguat over 16 weeks to an extent that would also be expected to be clinically meaningful to patients. It is not straightforward to directly compare these results to studies of BPA, as the baseline condition of patients is likely to differ between the studies, and this will affect the potential physiological improvements. PVR, 6MWD and functional class are pre-specified outcomes of the RACE randomised controlled trial of riociguat vs BPA, which will improve this evidence base.

Currently there is reasonable certainty that patients with CTEPH have improved function/ symptoms of heart failure and physiological markers of pulmonary hypertension and right heart strain in the year following BPA, but there is a lack of evidence of longer-term effectiveness, which will take time to accrue.

Medication requirements

Medication requirements were not identified as a pre-specified outcome for any study, and this outcome is highly vulnerable to selective reporting in which only positive changes may have been reported. It is a question of high uncertainty whether BPA reduces medication requirements for patients with CTEPH. Observational data from CTEPH registries may improve the evidence base for this question in the future. Reporting by patient rather than only by prescription, or clearly identifying combination therapy, could improve the clarity of reporting for this outcome.

Safety

Peri-procedural mortality was 5/281 (2%) among patients included in the studies which reported complications. The absolute risk of serious complications (reperfusion pulmonary oedema and wire perforation) is more difficult to assess given the varying thresholds for reporting these complications across the multiple small studies.

In the context of such a serious and progressive disease, with a major impact on quality of life, the safety profile should be balanced against the potential benefit of treatment. The safety profile of BPA appears comparable to accepted treatments for this condition:

- The peri-procedural mortality is comparable to or better than the peri-operative mortality for pulmonary endarterectomy, depending on the centre: the European Society of Cardiology requires an expert PEA centre to have a peri-procedural mortality of ≤10% (Galiè 2009). However, pulmonary endarterectomy is potentially curative, and so a higher mortality may be acceptable to patients for surgery than BPA.
- The safety and tolerability profile of riociguat in the CHEST-1 trial and CHEST-2 extension showed a high risk of drug discontinuation and adverse events. 8% of patients (13/173) assigned to riociguat did not tolerate the drug sufficiently to finish the 16 week treatment, and a further 14 (6%) discontinued riociguat in the next 2 years due to adverse events. Over two years, serious adverse events occurred in 129 patients (54%) receiving riociguat. (Ghofrani 2013, Simonneau 2016)

There is reasonable certainty that the safety of BPA for patients with CTEPH using modern BPA techniques in experienced centres is acceptable in the context of this disease and the safety profile of accepted treatments.

Strengths and limitations

A number of case series studies were identified, some of which included moderate numbers of patients. Most stated that the patients were identified consecutively, and several had high or complete follow up, limiting the potential for selection bias. In all studies the intervention was described clearly and appeared to be implemented consistently. All studies reported at least one functional outcome of direct relevance to patients, and similar reporting of physiological outcomes allowed the consistency of results across studies to be identified.

These studies have considerable limitations. These are discussed as they apply to each individual result above. Overall, all the studies were observational case-series, comparing patient outcomes after BPA to before BPA. Most were small studies, and thus vulnerable to over-estimation of the size of effect from small numbers. Study quality varied, and for several the reporting of design was unclear, limiting the extent to which bias could be assessed.

Reliance on indirect (surrogate) outcomes

Evidence on the effect of BPA on outcomes which directly describe the patient's quality of life was limited.

However, evidence consistently showed that patients have better function and indicators of physiology after BPA compared to before BPA. These would be expected to translate into better survival and quality of life for patients:

- Both the functional and the physiological outcomes described are associated with quality of life in CTEPH. Improvement in 6MWD has been found to be associated with higher quality of life among patients with CTEPH. (Mathai 2016, Urushibara 2015) Among patients with CTEPH, reduced PVR has been found to be associated with higher quality of life (Urushibara 2015)
- Both the functional and the physiological outcomes described are associated with survival among patients with CTEPH. Among 237 patients with inoperable CTEPH in the CHEST-2 trial, 6MWD was associated with 2 year survival (p=0.02). (Simonneau 2016) A functional class of IV is associated with a nearly five-fold increase in mortality among non-operated patients with CTEPH (HR 4.76, 95% CI 1.76 – 12.88, P=0.0021). (Delcroix 2016) PVR predicts mortality of medically-treated patients with CTEPH. (Saouti 2009). BNP was associated with 2 year survival of patients with inoperable CTEPH in the CHEST trial (p=0.02) (Simonneau 2016).
- This is consistent with the finding in large observational studies that post-surgical PVR predicts long-term survival among patients with CTEPH following surgery (Cannon 2016, Mayer 2011).
- Expert clinical testimony from the clinical working group confirms that these indicators (6MWD, functional class, pulmonary vascular resistance and BNP) are clinically important in practice and that the links between these indicators and improved symptoms, quality of life and survival are supported by biological mechanisms.
- Expert patient testimony from UK patients treated at Papworth hospital confirms that the physiological and functional improvements observed among these patients have been accompanied by significant improvements in wellbeing and quality of life following BPA.

For this rare disease, recruiting patients to studies large enough to study rare outcomes such as mortality may be challenging, and surrogate outcomes with a strong clinical basis are a realistic alternative. Quality of life should be studied in future research wherever possible.

Comparison to medical treatment

There is no direct evidence comparing BPA head-to-head against best medical practice (riociguat). For the proportion of inoperable patients who cannot tolerate riociguat, BPA may be the only evidence-based treatment option. However, for the majority of patients with inoperable CTEPH, riociguat represents the best alternative treatment to BPA.

This evidence gap is unsurprising as riociguat is recently licensed, and so the comparison has only recently become relevant or possible. The CHEST-1 placebo-controlled trial and 2 year extension provide an indication of the effectiveness of medical treatment. The effect of BPA on function and physiology compare well enough to these to suggest equipoise and encourage further study.

To identify which treatment has better outcomes a head-to-head comparison in a randomised trial is required, so that patients with similar characteristics at baseline are compared, and treatment allocation is not influenced by patient factors. The RACE trial will randomise patients to riociguat or BPA, but will still have limitation. The trial will take time (the trial aims to complete recruitment in 2019), and is a small study (aiming to recruit 124 patients), which plans to evaluate an indirect primary outcome (pulmonary vascular resistance) over a short period (26 weeks). The study may not have sufficient power to provide a sufficient evidence base on important outcomes such as survival (which is being measured as part of a composite outcome of clinical worsening) and will not (unless extended) provide data on long term outcomes.

Summary of main findings

There is reasonable certainty that patients with CTEPH have improved function and physiological markers of pulmonary hypertension and right heart strain following BPA in the short term (up to a year), compared to before BPA. These effects were large enough that they are expected to be clinically meaningful to patients, and were consistently observed. Direct evidence about the effect of BPA on survival, quality of life and medication requirements is limited, but the expectation of improvements in these is supported by the strong and consistent improvements in function and physiology, which are known to be clinically important and associated with improved quality of life and prognosis. Evidence of long-term effectiveness is lacking, and there is no direct evidence on the effectiveness of BPA compared to best medical practice (riociguat).

Recommendations for further research

One randomised controlled trial of riociguat vs BPA is ongoing, and is due to complete recruitment in 2019. This will improve the evidence base for treatment decisions among patients with inoperable CTEPH but will not (unless extended) provide data on long term outcomes, and may not have sufficient power to provide a sufficient evidence base on survival, as discussed above.

Additional research is desirable to improve the evidence base for treatment decisions among patients with inoperable CTEPH. A large multi-centre randomised controlled trial of riociguat vs BPA with long-term follow-up would be ideal but would be difficult given the rarity of inoperable CTEPH and the shortage of centres with experience of providing BPA for this condition. The large international registries offer an opportunity for observational studies to build the evidence base for the effect of BPA on under-reported outcomes (including quality of life, changes in medication requirements and long term survival).

All studies should:

- Compare BPA to best medical treatment (riociguat) wherever possible, ideally with treatment randomised to ensure that the patients with similar characteristics at baseline are compared.
- Include long-term survival and validated quality of life measures as pre-specified outcomes, which are of high value to patients.
- Include changes in medication requirements as a pre-specified outcome likely to influence analysis of cost-effectiveness of treatment, and report this by patient not just prescription – or clearly report combination therapy so that reduced medication requirement can be distinguished from altered patterns of combination prescribing.
- Encourage reporting of standardised definitions of complications (for example, reperfusion pulmonary injury categorized by requirement for non-invasive ventilatory support) so that these can be compared and collated across studies.
- Report methods clearly in accordance with relevant guidelines (such as STROBE or CONSORT).

6. Conclusion

CTEPH is a rare but serious disease with a major impact on quality of life and mortality. Surgery is potentially curative, but 20-40% of patients with CTEPH have inoperable disease, due to comorbidities or the distal location of the clots. Patients with inoperable CTEPH have limited treatment options and an unmet clinical need. They have a worse life expectancy and poorer quality of life compared to those patients who undergo surgery, despite pulmonary vasodilator treatment. The best medical treatment available is riociguat, which has shown promising short-term results in one 16-week randomised placebo-controlled trial of 261 patients with a 2-year extension looking at safety and sustained effect.

Balloon pulmonary angioplasty (BPA) is a procedure which aims to reduce pulmonary hypertension by dilating narrowings in the pulmonary arteries. Currently there is reasonable certainty that patients with CTEPH have improved function/ symptoms of heart failure and physiological markers of pulmonary hypertension and right heart strain in the short term (up to a year) following BPA, compared to before BPA. These effects were large enough that they are expected to be clinically meaningful to patients, and were consistently observed. The effect of BPA on survival, quality of life and medication requirements is uncertain. For all outcomes there is a lack of evidence of long-term effectiveness.

There is currently no evidence directly comparing the effectiveness of BPA to riociguat. Observational studies from registries offer opportunities to improve the direct evidence of long term effectiveness and quality of life over time. One randomised trial of riociguat vs BPA is ongoing, which should improve the evidence base for treatment decisions among patients with inoperable CTEPH: but recruitment will take several years, and the trial may still be under-powered to compare the effects on direct patient outcomes such as survival. These limitations are inherent in studies of a highly specialized treatment of a rare disease, and a much stronger evidence base may be difficult to achieve.

7. Evidence Summary Table

<table>
<tr><th colspan="8">Use of Balloon Pulmonary Angioplasty (BPA) vs no comparator

to treat Chronic Thromboembolic Pulmonary Hypertension (CTEPH)</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome type *</th><th>Outcome measures and results</th><th>Applicability and Quality of Evidence Score (columns combined from report template)</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td>Broch (2016)</td>
<td>Consecutive case series with standardised outcome assessment</td>
<td>32 consecutive patients treated with BPA for inoperable CTEPH (n=29) or residual PH post PEA (n=3)

3 month outcomes excluded 4 for lack of echocardiography data and 2 who died early in follow up.

2003-2014 in Oslo, Norway.

Mean age 59 years (SD 12).

All NYHA-FC II-IV.</td>
<td>Balloon pulmonary angioplasty.

Mean 4 sessions (range 1-9).

Maximum 3 lung segments per session, repeated every 5-8 weeks.

Medications fixed from baseline to 3 months.</td>
<td>Primary CE</td>
<td>Survival
26/32 alive and transplant-free after median follow-up of 2.9 years (range 0-12 years).</td>
<td rowspan="4">Applicability: direct. Study focused on people with inoperable CTEPH.

Quality: total 5/10.
Aims and design clearly stated: 1/2 aims and pre-specified outcomes clear, lacks information on extent of planning/protocol vs pragmatic reporting.

Design appropriate 1/2: no comparison group.

Methods clearly described 1/2: procedures clearly described, timing of other outcomes (such as functional assessment) lack detail.

Data adequate for authors' interpretation: 1/2. Authors acknowledge interpretation of effectiveness is limited by data.

Results generalizable: 1/2. Operability criteria subjective, specialised technique with learning curve: outcomes may be centre dependent.</td>
<td rowspan="4"><u>Positives:</u>
• Consecutive patients reported: reduces potential for selection bias.
• Loss to follow up clearly described with reasons: unlikely to be differential.
• Objective outcome measures.
• Consistency of outcomes demonstrated: functional improvement associated with improvement in physiological indices.
<u>Negatives:</u>
• Small cohort.
• No comparison group. Cannot compare to medical treatment.
• Survival data is difficult to interpret. With neither a set period of follow up nor information on the timing of the deaths and distribution of follow up time, expected survival at a defined time point cannot be identified from this.
• Unclear if all available outcome data were reported: earlier report of cohort includes more information on complications and oxygen requirements. Potential for selective reporting of outcomes.
• Inoperability assessment is subjective and technique is skilled: outcomes may not generalise to other centres
• Standardised follow up only 3 months. Cannot assess long term outcomes.</td>
</tr>
<tr>
<td></td><td></td><td></td><td>Primary CE</td>
<td>Function
Pre-BPA and at 3 months after last session, n=26
<table>
<tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>Difference</td><td>P value</td></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td>(95% CI)</td><td></td></tr>
<tr><td>NYHA-FC</td><td>2.9 (0.5)</td><td>1.9 (0.5)</td><td>-1.0 (-12 to -0.8)</td><td><0.001</td></tr>
</table>
</td>
</tr>
<tr>
<td></td><td></td><td></td><td>Secondary CE</td>
<td>Physiology
Pre-BPA and at 3 months after last session, n=26
<table>
<tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>Difference (95% CI)</td><td>P value</td></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td></td><td></td></tr>
<tr><td>mPAP</td><td>44 (11)</td><td>33 (9)</td><td>-11 (-15 to -8)</td><td><0.001</td></tr>
<tr><td>CO</td><td>5.3 (1.6)</td><td>6.2 (1.7)</td><td>0.9 (0.5-1.3)</td><td><0.001</td></tr>
<tr><td>PVR</td><td>612 (282)</td><td>375 (221)</td><td>-237 (-329 to -146)</td><td><0.001</td></tr>
<tr><td>BNP</td><td>791</td><td>237</td><td></td><td>0.001</td></tr>
<tr><td>RV fractional area change %</td><td>26 (10)</td><td>32 (10)</td><td>6 (2-9)</td><td>0.003</td></tr>
<tr><td>TAPSE</td><td>19 5)</td><td>22 (5)</td><td>3 (2-5)</td><td><0.001</td></tr>
</table>
</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td><td>Safety</td>
<td>28-day mortality: 2 deaths (reperfusion oedema and RV failure: acute pulmonary embolism).</td>
</tr>
</table>

<table>
<tr>
<td>Kinutani (2016)</td>
<td>Consecutive case series</td>
<td>29 consecutive inoperable patients with CTEPH

October 2012 – April 2015 in Kobe, Japan

Mean age 65 years (SD 12)

All WHO functional class II-IV.</td>
<td>Balloon pulmonary angioplasty

Mean 3 sessions, SD 1.4

1 week intervals between sessions

During BPA: intravenous ultrasound to select balloon size</td>
<td>Primary CE</td>
<td colspan="2">Function
Pre-BPA and after last session, n=28

<table>
<tr><td></td><td></td><td>Pre BPA</td><td>After</td><td>P value</td></tr>
<tr><td rowspan="4">WHO-FC (n)</td><td>IV</td><td>4</td><td>0</td><td rowspan="4"><0.01</td></tr>
<tr><td>III</td><td>16</td><td>1</td></tr>
<tr><td>II</td><td>8</td><td>11</td></tr>
<tr><td>I</td><td>0</td><td>16</td></tr>
<tr><td colspan="2">6MWD mean (SD)</td><td>303 (92)</td><td>394 (124)</td><td><0.01</td></tr>
</table></td>
<td rowspan="4">Applicability: direct. Study focused on people with inoperable CTEPH.

Quality: total 6/10.

Aims and design clearly stated: 1/2 aims clear, unclear whether prospectively planned or retrospectively pragmatic design.

Design appropriate 1/2: no comparison group.

Methods clearly described 2/2: yes.

Data adequate for authors' interpretation: 1/2. Authors acknowledge interpretation of effectiveness is limited by data.

Results generalizable: 1/2. Operability criteria subjective, specialised technique with learning curve: outcomes may be centre dependent.</td>
<td rowspan="4"><u>Positives:</u>
• Consecutive patients reported: reduces potential for selection bias.
• No loss to follow up.
• Systematic evaluation of objective outcome measures.

<u>Negatives:</u>
• Small cohort.
• No comparison group. Cannot compare to medical treatment.
• Aim is to identify predictors of reperfusion pulmonary injury, not to evaluate BPA effectiveness: outcomes selected accordingly.
• Inoperability assessment is subjective and technique is skilled: outcomes may not generalise to other centres.
• Immediate outcomes only. Cannot assess long term outcomes.</td>
</tr>
<tr>
<td>Secondary CE</td>
<td colspan="2">Physiology
Pre-BPA and after last session, n=28

<table>
<tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>P value</td></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td></td></tr>
<tr><td>mPAP</td><td>34.2 (10.4)</td><td>19.2 (5.7)</td><td><0.01</td></tr>
<tr><td>CO</td><td>4.1 (1.3)</td><td>4.5(1.6)</td><td>0.14</td></tr>
<tr><td>PVR</td><td>574 (317)</td><td>258 (171)</td><td><0.01</td></tr>
<tr><td>BNP</td><td>160 (233)</td><td>26 (31)</td><td><0.01</td></tr>
</table></td>
</tr>
<tr>
<td rowspan="3">Safety</td>
<td>28 day mortality</td>
<td>1 death prior to BPA, from central venous catheter-associated sepsis related to pre-BPA epoprostenol administration.</td>
</tr>
<tr>
<td>Reperfusion pulmonary injury</td>
<td>Haemosputum in 14 sessions (17%), desaturation requiring NIPPV in 13 sessions (15%).</td>
</tr>
<tr>
<td>Wire perforation</td>
<td>5 (6% of sessions)</td>
</tr>
</table>

<table>
<tr>
<td>Yamasaki (2016)</td>
<td>Consecutive case series with standardised outcome assessment

Also recruited 11 healthy volunteers – purpose unclear.</td>
<td>24 patients with inoperable CTEPH

20 patients enrolled (exclusion criteria listed but reasons for individual exclusion not specified)

May 2012 – August 2015 in Fukuoka, Japan

Mean age 62 years (SD 11)

All WHO functional class II-IV.</td>
<td>Balloon pulmonary angioplasty.

Mean 2.7 sessions (SD 1.6).

Pulmonary vasodilators fixed from 1 month prior to end of follow up.</td>
<td>Primary CE

Secondary CE</td>
<td>Function

<table>
<tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>P value</td></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td></td></tr>
<tr><td>6MWD</td><td>391 (75)</td><td>437 (68)</td><td><0.0001</td></tr>
</table>
Physiology

Pre BPA and approximately 3 months post final BPA session (interval to follow up right heart catheterisation 88 ± 50 days, to cardiac MRI 80 ± 49 days).

<table>
<tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>P value</td></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td></td></tr>
<tr><td>mPAP</td><td>42.6 (11.0)</td><td>30.0 (6.6)</td><td><0.0001</td></tr>
<tr><td>CI</td><td>3.1 (0.9)</td><td>3.2 (0.9)</td><td>>0.05</td></tr>
<tr><td>PVR</td><td>639 (224)</td><td>411 (123)</td><td><0.0001</td></tr>
<tr><td>BNP</td><td>66.5 (61.3)</td><td>33.8 (30.0)</td><td><0.05</td></tr>
<tr><td>RVEF</td><td>35.5 (12.1)</td><td>42.4 (11.3)</td><td><0.0001</td></tr>
</table>
</td>
<td>Applicability: direct. Study focused on people with inoperable CTEPH.

Quality: total 5/10.

Aims and design clearly stated: 1/2 aims and prospective design clear, lacks information on reasons for variations from protocol.

Design appropriate 1/2: no relevant comparison group. Purpose of healthy volunteers unclear.

Methods clearly described 1/2: procedures clearly described, timing of other outcome assessments (6MWD) unclear, reasons for exclusions not given.

Data adequate for authors' interpretation: 1/2. Authors acknowledge interpretation of effectiveness is limited by data.

Results generalizable: 1/2. Operability criteria subjective, specialised technique with learning curve: outcomes may be centre dependent.</td>
<td><u>Positives:</u>
• Consecutive patients reported: reduces potential for selection bias.
• Loss to follow up clearly described with reasons: unlikely to be differential.
• Objective outcome measures, with radiologists blinded to patient's clinical information for functional MRI measurements.
• Attempt to standardise timing of outcome with study protocol, although wide range of timings in practice.
• Consistency of outcomes demonstrated: functional improvement associated with improvement in physiological indices.

<u>Negatives:</u>
• Small cohort.
• Reasons for exclusion of 4 patients not stated (although generic exclusion criteria listed) thus cannot assess potential for selection bias.
• No comparison group relevant to this review. Cannot compare to medical alternatives. Purpose of 11 healthy volunteers unclear, but not a relevant comparison group for functional or physiological outcomes in CTEPH for the purposes of this review.
• Wide range of timing of follow up assessments, without reasons presented for variation: possibly correlated to clinical status and thus potential for information bias.
• Inoperability assessment is subjective and technique is skilled: outcomes may not generalise to other centres
• Follow up only 3 months. Cannot assess long term outcomes.
• Complications not reported. Cannot assess safety.</td>
</tr>
</table>

<table>
<tr>
<td>Aoki (2016)</td>
<td>Retrospective consecutive case series with standardised outcome measurement</td>
<td>24 consecutive patients with inoperable CTEPH (1/25 excluded for lung disease)

August 2013 - May 2015 in Sendai, Japan

Median age 70 years [IQR 60–74]

All WHO functional class II-IV.</td>
<td>Balloon pulmonary angioplasty

Mean 4.7 procedures per patient

Balloon size selected using angiography and/or intravascular imaging, including optical coherence tomography

Maximum 3 lobes per session</td>
<td>Primary CE</td>
<td>Function
Before BPA and 6 months after last BPA
<table>
<tr><th></th><th>Pre BPA</th><th>Post BPA</th><th>P value</th></tr>
<tr><td>6MWD median (IQR)</td><td>390 (286-484)</td><td>490 (411-617)</td><td><0.01</td></tr>
<tr><td>WHO-FC I/II/III/IV (%)</td><td>0/12/11/1 (0/50/46/4)</td><td>5/19/0/0 (24/76/0/0)</td><td>0.04</td></tr>
</table>
</td>
<td rowspan="4">Applicability: direct. Study focused on people with inoperable CTEPH.

Quality: total 6/10

Aims and design clearly stated: 1/2. States aims clearly, design partly implied in discussion.

Design appropriate 1/2: no comparison group.

Methods clearly described 2/2: Yes.

Data adequate for authors' interpretation: 1/2. Authors acknowledge limitations but retain strong interpretation of effectiveness.

Results generalizable: 1/2. Operability criteria subjective, specialised technique with learning curve: outcomes may be centre dependent.</td>
<td rowspan="4"><u>Positives:</u>
• Consecutive patients reported: reduces potential for selection bias.
• No loss to follow up.
• Standardised follow up time of 6 months.
• Systematic evaluation of objective outcome measures.

<u>Negatives:</u>
• Small cohort.
• No comparison group. Cannot compare to medical treatment.
• Information on medication requirements does not allow comparison of patient numbers
• Inoperability assessment is subjective and technique is skilled: outcomes may not generalise to other centres
• Limited information on complications reported. Cannot assess safety.
• Follow up only 6 months. Cannot assess long term outcomes.</td>
</tr>
<tr>
<td>Primary CE</td>
<td>Treatment required
Before BPA, 19 patients required home oxygen therapy (79%); after BPA this was 13 patients (54%, p=0.01)
Before BPA, 22 patients (92%) were treated with vasodilators, including 7 receiving combination therapy (28%). After BPA, the use of phosphodiesterase-5 inhibitors decreased but the reported data did not allow assessment of whether this represented a decrease in medication requirement or shifting to alternative drugs, as combination therapy post BPA was not described. The number of patients receiving riociguat remained similar (3 patients prior to BPA, 4 after BPA, p=1).</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>Physiology
Before BPA and 6 months after last BPA
<table>
<tr><th></th><th>Pre BPA</th><th>Post BPA</th><th>P value</th></tr>
<tr><td></td><td colspan="2">median (IQR)</td><td></td></tr>
<tr><td>mPAP</td><td>37 (28-45)</td><td>23 (19-27)</td><td><0.01</td></tr>
<tr><td>CI</td><td>2.4 (2.0-2.8)</td><td>2.4 (2.1-2.7)</td><td>0.96</td></tr>
<tr><td>PVR</td><td>517 (389-696)</td><td>268 (239-345)</td><td><0.01</td></tr>
<tr><td>BNP</td><td>112 (49-199)</td><td>27.5 (14.6-58.4)</td><td><0.01</td></tr>
</table>
</td>
</tr>
<tr>
<td>Safety</td>
<td>No peri-procedural deaths, severe lung bleeding or reperfusion lung oedema requiring mechanical ventilation.</td>
</tr>
</table>

<table>
<tr>
<td>Fukui (2015)</td>
<td>Consecutive case series

Partly retrospective, partly prospective</td>
<td>25 consecutive patients with inoperable CTEPH treated with BPA and who also had cardiopulmonary exercise testing before and after BPA

Dates not reported but some overlap reported with study from 2012-2013

Suita, Japan

Mean age 67 years (SD 10)

All WHO functional class II-III.</td>
<td>Balloon pulmonary angioplasty

Mean 3.6 sessions, SD 1.8

Balloon size selected using CT measurements

Maximum 1-2 segments in 1 lobe in first session

Routine non-invasive positive airway pressure ventilation overnight</td>
<td>Primary CE</td>
<td>Function
Mean 3.2 weeks from final BPA (SD 4.0), n=25
<table>
<tr><th></th><th>Pre BPA</th><th>Post BPA</th><th>P value</th></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td></td></tr>
<tr><td>6MWD</td><td>405 (111)</td><td>501 (109)</td><td><0.001</td></tr>
<tr><td>WHO-FC</td><td>2.6</td><td>2.1</td><td><0.001</td></tr>
<tr><td>Exercise duration (seconds)</td><td>389 (84)</td><td>433 (94)</td><td><0.001</td></tr>
<tr><td>Peak VO2 % predicted</td><td>60 .1 (12.6)</td><td>70.9 (10.9)</td><td><0.001</td></tr>
</table>
</td>
<td rowspan="4">Applicability: direct. Study focused on people with inoperable CTEPH.

Quality: total 3/10.

Aims and design clearly stated: 1/2 aims clear, design unclear due to limited methods reporting.

Design appropriate 1/2: no relevant comparison group. Limited reporting of design limits quality assessment.

Methods clearly described 0/2: Limited reporting of methods: in particular it is unclear when outcomes were measured, and whether patients were selected from a larger group.

Results generalizable: 1/2. Operability criteria subjective, specialised technique with learning curve: outcomes may be centre dependent</td>
<td rowspan="4"><u>Positives:</u>
• Consecutive patients reported: reduces potential for selection bias.
• No loss to follow up affecting the outcomes reported for this review.
• Objective outcome measures.
• Consistency of outcomes demonstrated: functional improvement associated with improvement in physiological indices.

<u>Negatives:</u>
• Small cohort.
• Unclear whether cardiopulmonary exercise testing was routine for all patients with BPA for CTEPH, or whether this requirement introduced selection: potential for selection bias cannot be assessed from methods presented
• Timing of cardiopulmonary exercise testing relative to BPA appears to have been variable, which may affect consistency of outcome measurement.
• Unclear whether right heart catheterisation results are from the day post BPA or 3 months after. Methods report measurements at both points, but only one set is reported with timing unspecified. Potential for selective reporting bias, and unclear whether these are immediate or short term outcomes.
• No comparison group relevant to this review.
• Inoperability assessment is subjective and technique is skilled: outcomes may not generalise to other centres.
• Short follow up. Cannot assess long term outcomes.</td>
</tr>
<tr>
<td>Primary CE</td>
<td>Treatment required
Of 14 patients treated with oral pulmonary hypertensive therapies, 1 patient discontinued an endothelin-receptor antagonist (7%). 13 remained unchanged over follow up (mean 3.5 months, SD 1.8).</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>Physiology
Timing of reported outcomes unclear: methods report that measured both day after BPA and 3 months after. n=25
<table>
<tr><th></th><th>Pre BPA</th><th>Post BPA</th><th>P value</th></tr>
<tr><td></td><td colspan="2">mean (SD)</td><td></td></tr>
<tr><td>mPAP</td><td>35.8 (10.3)</td><td>23.0 (5.1)</td><td><0.01</td></tr>
<tr><td>CI</td><td>2.2 (0.5)</td><td>2.5 (0.5)</td><td><0.01</td></tr>
<tr><td>PVR</td><td>755 (345)</td><td>N/A *</td><td>N/A</td></tr>
<tr><td>BNP</td><td>142 (198)</td><td>25 (11)</td><td><0.01</td></tr>
</table>
* pulmonary artery wedge pressure could not be obtained post BPA and therefore PVR not calculated</td>
</tr>
<tr>
<td>Safety</td>
<td>“No deaths or major complications such as severe reperfusion pulmonary edema requiring invasive ventilation”.</td>
</tr>
</table>

<table>
<tr>
<td>Inami (2014a)</td>
<td>Retrospective consecutive case series</td>
<td>103 consecutive patients treated with BPA

No operability criteria described

January 2009 – December 2013 Keio University Hospital & Kyorin University Hospital, Japan

Median age 65 years (IQR 53-72)

All WHO functional class II-IV.</td>
<td>Balloon pulmonary angioplasty 350 sessions.

Median 3 sessions (IQR 2-4)

Median total 11 vessels dilated per patient (IQ 7-17)

BPA ended when Pulmonary Edema Predictive Scoring Index (PEPSI) score* >35.4 from June 2012 onwards

Balloon dilation managed targeted using ratio of distal to proximal pressure across target lesion, using a pressure wire, from January 2013 onwards.</td>
<td>Primary CE</td>
<td>Function
Median time from first procedure to follow up 14 months (IQR 7.6-21.9), n=69
<table><tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>P value</td></tr><tr><td></td><td colspan="2">median (IQR)</td><td></td></tr><tr><td>6MWD</td><td>360 (281-430)</td><td>420 (350-510)</td><td><0.001</td></tr></table></td>
<td>Applicability: unclear. Likely to be mostly direct but no criteria relating to operability are described. It is therefore unclear whether this population is limited to patients with inoperable CTEPH, or may include patients with operable CTEPH. Study focused on people with inoperable CTEPH.

Quality: total 4/10.

Aims and design clearly stated: 1/2 aims clear, design described incorrectly as case-control study.

Design appropriate 1/2: Design aims to compare safety and effectiveness of BPA at the centre over time, and is appropriate for this. No relevant comparison group for effectiveness of BPA against medical therapy.

Methods clearly described 1/2: procedures clearly described, timing of other outcome assessments unclear, reasons for loss of follow up not given.

Data adequate for authors' interpretation: 0/2. Authors draw strong conclusion of effectiveness of local techniques at reducing risk despite small numbers and lack of significant findings when comparing groups or to previous reports.

Results generalizable: 1/2. Centre-specific techniques, specialised technique with learning curve: outcomes may be centre dependent.</td>
<td><u>Positives:</u>
• Moderately sized cohort
• Consecutive patients reported: reduces potential for selection bias.
• Objective outcome measures.
• Separates patients into three groups according to time period of treatment, and compares outcomes across these groups. This allows some assessment for whether outcomes were influenced by change of procedures and learning curve.

<u>Negatives:</u>
• High loss to follow up with reasons not given: high potential for selection bias.
• No operability criteria described, cannot assess whether these patients included patients with operable disease.
• No comparison group relevant to this review.
• Design is described incorrectly as a case-control study. This could be described as a retrospective case series or descriptive cohort study.
• Specific techniques were introduced locally (PEPSI score and pressure-wire guiding): outcomes may not generalise to other centres.
• Short non-standardised follow up. Cannot assess long term outcomes.</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary CE</td>
<td>Physiology
Median time from first procedure to follow up 14 months (IQR 7.6-21.9), n=83
<table><tr><td></td><td>Pre BPA</td><td>Post BPA</td><td>P value</td></tr><tr><td></td><td colspan="2">median (IQR)</td><td></td></tr><tr><td>mPAP</td><td>41 (34-47)</td><td>21 (18-28)</td><td><0.001</td></tr><tr><td>CI</td><td>2.5 (2.1-2.9)</td><td>2.9 (2.4-3.5)</td><td><0.001</td></tr><tr><td>PVR (Wood units)</td><td>8.7 (6.1-13.3)</td><td>2.7 (2.0-4.2)</td><td><0.001</td></tr><tr><td>BNP</td><td>94.5 (41.7-269.5)</td><td>33.7 (15.8-59.2)</td><td><0.001</td></tr></table></td>
<td></td><td></td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Safety</td>
<td>28 day mortality: 1 death at 2 days (wire perforation): perioperative mortality 1% (1/103).

Reperfusion pulmonary injury: Ventilation required after 9/350 (3%) sessions.

Wire perforation: Dissection in 35/350 sessions (10%) of which: 7 had no extravascular leaks; 28 had extravascular leaks and 2 required stent or coil.</td>
<td></td><td></td>
</tr>
</table>

Inami (2014b) included and assessed only for reporting of survival as an outcome	Retrospective consecutive case series	68 patients with CTEPH treated with PTPA January 2009 – April 2013 Keio University Hospital & Kyorin University Hospital, Japan Included inoperable and operable patients from January 2009 Comparison groups: 29 patients medical treatment (14 2000-2008, 15 2009-2013) because BPA not available, unsuitability (e..g serious comorbidity) or refusal of intervention 39 patients treated with surgery (PEA) (38 2000-2008, 1 2009-2013)	Balloon pulmonary angioplasty 213 sessions Mean 2.5 sessions (SD 1.4) BPA ended when Pulmonary Edema Predictive Scoring Index (PEPSI) score* >35.4 from June 2012 onwards Balloon dilation managed targeted using ratio of distal to proximal pressure across target lesion, using a pressure wire, from January 2013 onwards.	Primary CE	**Survival** During the follow up period of mean 14.3 months, (SD 10.4) one patient treated with BPA died, from a peri-procedural complication (wire perforation). This group had a reported 2- year survival of 98.5%. However, the numbers included in follow up were small (17/68 included in the analysis at 20 months). This was not compared to 2 year survival for patients receiving medical treatment. For patients treated with surgery, 2-year survival was 97.4% (no evidence of difference from BPA group p=0.73) but these were not comparable patients (surgical patients were younger than patients in the BPA group but with more severe disease, and were mostly (38/39) treated in an earlier time period of 2000-2008). The paper reported 5 year survival for the interventions group (BPA or PEA 2000-2013) of 98%, and for the medical-only treatment group of 64% over the same period. However, it is not clear whether this estimate includes any patients treated with BPA – as BPA was started in 2009, and the paper was published in 2014, few if any patients treated with BPA will have been eligible to be included in this estimate. Other outcomes: reported instead from Inami (2014a), which includes a larger cohort and reports outcomes for patients treated with BPA separately from patients treated with surgery.	**Applicability:** direct. Study focused on people with inoperable CTEPH. **Quality:** total 4/10 Aims and design clearly stated: 1/2. States aims clearly, design described incorrectly as case-control study and extent of pre-specification unclear. Design appropriate 1/2: Combination of patients treated with BPA and with surgery as a single group results in mixed outcomes which are difficult to interpret. Methods clearly described 1/2: procedures clearly described, follow up and assessment of outcomes less clear. Data adequate for authors' interpretation: 0/2. Authors acknowledge some limitations but still draw strong conclusion on effectiveness of "interventions" (as a combined category of surgery and BPA) vs medical therapy. Results generalizable: 1/2. Specialised technique with learning curve: outcomes may be centre dependent. Survival is reported for a mixed group which includes both patients treated with surgery or with BPA.	<u>Positives:</u> • Moderately sized cohort. • Objective outcome measure. • To check for changes in survival over time, the authors compared the total survival for all included patients (receiving medical treatment, BPA or surgery) in the period 2000-2008 (89%) vs 2009-2013 (95%) and found no evidence of difference (p=0.4). Patients treated in the earlier time period were different (younger, with more severe CTEPH, received surgery not BPA) to patients treated in the later period and a secular effect cannot be excluded. <u>Negatives:</u> • Survival estimates are based on small numbers (17/68 patients were in follow up at 20 months following BPA, and 3/68 patients at 40 months). These data are vulnerable to over-estimation of the size of effect from small numbers. • Some of the loss is explained by patients having procedures too recently to be eligible for 5 year follow up but it unclear how much. Loss to follow up is not described. Survival estimates may also be vulnerable to selection bias from loss to follow up. • Medical treatment group not directly comparable to BPA patients– includes patients treated in an earlier era (2000-2008) and patients not suitable for BPA due to serious comorbidity. • Surgical treatment group not directly comparable to BPA patients. These patients were younger than patients in the BPA group but had more severe disease, and were mostly (38/39) treated in an earlier time period (2000-2008) . • Outcomes for inoperable patients may be different for patients with operable disease but are reported together. • Technique is skilled: outcomes may not generalise to other centres.

<table>
<tr>
<td>Mizoguchi (2012)</td>
<td>Consecutive case series with standardised management and outcome measurements</td>
<td>68 consecutive patients treated with BPA for inoperable CTEPH

Nov 2004 –Sept 2011 in Okayama Japan.

Mean age 62 years (SD 12)

All WHO functional class III or IV, treated with oxygen and >1 pulmonary hypertension-targeted medication</td>
<td>Balloon pulmonary angioplasty

Median 4 sessions (range 2-8).

Median 3 vessels dilated per session (range 1-14).

Pre BPA: epoprostenol.

During BPA: intravenous ultrasound to select balloon size.

Post BPA: ≥24 hours non-invasive positive airway pressure ventilation</td>
<td>Primary CE</td>
<td>Survival

1 year survival 66/68 (97%)</td>
<td rowspan="4">Applicability: direct. Study focused on people with inoperable CTEPH.

Quality: total 6/10

Aims and design clearly stated: 1/2. States aims and consecutive design clearly. Unclear if pre-specified outcomes.

Design appropriate 1/2: no comparison group.

Methods clearly described 2/2: Yes.

Data adequate for authors' interpretation: 1/2. Authors acknowledge interpretation of effectiveness is limited by data.

Results generalizable: 1/2. Operability criteria subjective, specialised technique with learning curve: outcomes may be centre dependent.</td>
<td rowspan="4"><u>Positives:</u>
• Moderately sized cohort
• Consecutive patients reported, no exclusions based on severity of haemodynamics nor age: reduces potential for selection bias
• Loss to follow up low – 100% 1 year follow up for functional outcomes. (87% for haemodynamics)
• Standardised pre, peri and post procedure management.
• Objective outcome measures.
• Functional improvements demonstrated as maintained for a year.
• Dose-response relationship: relative reduction in mean pulmonary artery pressure and absolute change in pulmonary artery pressure between pre and immediately post BPA were both correlated to number of opened segments (P<0.01 for both).

<u>Negatives:</u>
• No comparison group. Cannot compare to medical alternatives.
• Unclear if outcomes were pre-specified: could be selective reporting of outcomes.
• Inoperability assessment is subjective and technique is skilled: outcomes may not generalise to other centres.
• Additional management (e.g. pre-procedure epoprostenol, IV ultrasound) may or may not be required for outcomes.
• Follow up only 1 year. Cannot describe long term outcomes.</td>
</tr>
<tr>
<td>Primary CE</td>
<td>Function
Prior to BPA, all had WHO functional class III or IV. At one year, all were in functional class I or II.

<table>
<tr><th>WHO class</th><th>Pre BPA n</th><th>1 year n</th></tr>
<tr><td>IV</td><td>19</td><td>0</td></tr>
<tr><td>III</td><td>49</td><td>0</td></tr>
<tr><td>II</td><td>0</td><td>49</td></tr>
<tr><td>I</td><td>0</td><td>17</td></tr>
</table>
6MWD
Before BPA 296 metres (SD 108).
Immediately post BPA 368m (SD 83). P<0.01.</td>
</tr>
<tr>
<td>Primary CE</td>
<td>Treatment required
Prior to BPA all required long term oxygen therapy. At one year post-BPA, 26/68 (38%) no longer required oxygen therapy.

Pulmonary hypertension medication at 1 year:
- 4/4 had discontinued long term epoprostenol
- Percentage on other oral medications was reduced from pre-BPA (endothelin receptor antagonist from 52% to 37%, p<0.05: phosphodiesterase-5 inhibitor from 40% to 28% P<0.05)</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>Physiology
Immediate changes in haemodynamics were maintained at 1 year post BPA.

<table>
<tr><th></th><th>Pre BPA</th><th>Post BPA</th><th>1 year</th><th>P value</th></tr>
<tr><td></td><td colspan="3">mean (SD)</td><td></td></tr>
<tr><td>mPAP</td><td>45.4 (9.6)</td><td>24.0 (6.4)</td><td>24.0 (5.8)</td><td><0.01</td></tr>
<tr><td>CI</td><td>2.2 (0.7)</td><td>3.2 (0.6)</td><td>>3*</td><td><0.01</td></tr>
</table>
</td>
</tr>
</table>

					PVR	942 (367)	327 (151)	<400*	<0.01
					BNP	330 (444)	35 (55)	-	<0.01
					* shown graphically				
				Safety	28-day mortality	1 (reperfusion pulmonary injury)			
					Clinical reperfusion pulmonary injury	Haemosputum or desaturation in 41/68 (60%), of whom 4 needed intratracheal intubation and 2 needed percutaneous cardiopulmonary support			
					Pulmonary artery perforation	5 patients, of whom 2 needed emergency transcatheter coil embolization.			
					Other 28-day complications	Interstitial pneumonitis in 1 patient and interstitial nephritis in 2 patients, with suspected cause NSAIDs and radio-contrast medium.			

* Primary or secondary clinical effectiveness (CE), or safety.

BPA, balloon pulmonary angioplasty; CTEPH chronic thromboembolic pulmonary hypertension; IQR, interquartile range; SD, standard deviation; IQR interquartile range boundaries; 95% CI, 95% confidence interval; * PEPSI score: sum total change of pulmonary flow grade scores x baseline PVR [Wood units]; 6MWD, six minute walking distance, metres; mPAP, mean pulmonary arterial pressure, mmHg; CI, cardiac index, L/ m^2; CO, cardiac output, litre/min; PVR, pulmonary vascular resistance, dyne sec/cm^5 unless stated as Wood units; BNP, Brain natriuretic peptide, pg/mL; TAPSE, tricuspid annular plane systolic excursion, mm; RVEF, right ventricular ejection fraction, %.

8. Grade of evidence table

Use of Intervention Balloon Pulmonary Angioplasty (BPA) vs no comparator to treat Chronic Thromboembolic Pulmonary Hypertension (CTEPH)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Survival	Broch 2016	5/10	Direct	Grade B: More than one study of medium quality score (4-6/10) and at least one has direct applicability.	Three included studies reported the proportion of patients who survived a period of follow-up after balloon pulmonary angioplasty. The most robust result was that in the study by Mizoguchi (2012) 66/68 patients (97%) were alive at one year after BPA. Other estimates had methodological weaknesses: • In Inami (2014b), patients treated with BPA had a 2- year survival of 98.5%. However, the numbers included in follow up were small (17/68 were included in follow up at 20 months). These data are very vulnerable to over-estimation of size of effect from small numbers. If the small number in follow-up was partly due to loss to follow-up (rather than procedures more recent than 2 years) this would also be vulnerable to selection bias. • In Broch (2016) the data are difficult to interpret: with neither a set period of follow up nor information on the timing of the deaths and distribution of follow up time, the expected proportion of patients alive at a given time after the procedure cannot be described. The authors report that 26/32 patients (81%) were alive and transplant-free after a median follow-up of 2.9 years (range 0-12 years). Direct comparisons to survival of patients treated with riociguat are not available. • Inami (2014b). did not report 2 year survival for patients receiving medical treatment. For patients treated with surgery, 2-year survival was 97.4% (no evidence of difference from BPA group p=0.73) but these were not comparable patients (surgical patients were younger than patients in the BPA group but with more severe disease, and were mostly (38/39) treated in an earlier time period of 2000-2008). • 2 year survival of patients receiving riociguat in the CHEST-2 extension trial was 93% (95% CI 89–96). However, patients participating in a trial may have better health status than patients included in a clinical case series. The comparison of survival in a trial of riociguat with survival in a case series of BPA may therefore disadvantage BPA survival estimates.
	Inami 2014b	4/10	Direct		
	Mizoguchi 2012	6/10	Direct		

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>

The International CTEPH Registry followed 275 newly diagnosed patients who were not operated upon. Survival at 1, 2, and 3 years was 88% (95%CI 83–91), 79% (95% CI 74–83) and 70% (95% CI 64–76) years. (Delcroix 2016b). These patients may include a mixture of patients treated with BPA, riociguat, or other medications and so this initial report does not offer a clear comparison group for the studies included in this review.

This outcome has a high degree of uncertainty.

Information on short-term mortality is likely to improve over the next few years with reporting of the RACE trial of riociguat vs BPA. More detailed reports from pulmonary hypertension registries will add information, although as these are observational, the reasons for difference in mortality between the groups may be co-morbidities that also drive selection of treatment choices.
Information on long-term survival following BPA compared to riociguat will take longer to accrue.

</td></tr>
<tr><td>Function</td><td colspan="5">The functional outcomes reported were: 6 minute walk distance (6MWD); NYHA or WHO functional class; and cardiopulmonary exercise testing.</td></tr>
<tr><td rowspan="7">6MWD (Function)</td><td>Kinutani 2016</td><td>6/10</td><td>Direct</td><td rowspan="7">Grade B: More than one study of medium quality score (4-6/10) and at least one has direct applicability.</td><td rowspan="7">
6 minute walk distance (6MWD); the distance in metres a patient walks in 6 minutes.

All but one study group reported 6MWD and all found an average improvement, which ranged from 46m to 100m. No single study could be identified as providing the ‘best’ estimate of change in 6MWD. A systematic review found that a change in 6MWD of 45 metres was clinically meaningful among people with chronic heart failure (that is, it exceeded measurement error and was associated with significant changes in either aerobic capacity and/or health-related quality of life). (Shoemaker 2012)
<table>
<tr><th>Study</th><th>6MWD (m) Pre BPA</th><th>6MWD (m) Post BPA</th><th>Follow up assessment point</th><th>P value</th></tr>
<tr><td>Broch 2016</td><td>NR</td><td>NR</td><td></td><td></td></tr>
<tr><td>Kinutani 2016</td><td>303±[92]</td><td>394 [±124]</td><td>Immediate</td><td><0.01</td></tr>
<tr><td>Yamasaki 2016</td><td>391 [±75]</td><td>437 [±68]</td><td>Unclear: immediate or 3 months</td><td><0.0001</td></tr>
<tr><td>Aoki 2016</td><td>390 (286-484)</td><td>490 (411-617)</td><td>6 months</td><td><0.01</td></tr>
<tr><td>Fukui 2015</td><td>405 [±111]</td><td>501 [±109]</td><td>mean 3 weeks</td><td><0.001</td></tr>
</table>
</td></tr>
<tr><td>Yamasaki 2016</td><td>5/10</td><td>Direct</td></tr>
<tr><td>Aoki 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Fukui 2015</td><td>3/10</td><td>Direct</td></tr>
<tr><td>Inami 2014a</td><td>4/10</td><td>Likely direct but unclear.</td></tr>
<tr><td>Mizoguchi 2012</td><td>6/10</td><td>Direct</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Inami 2014a</td><td>360 (281-430)</td><td>420 (350-510)</td><td>median 14 months</td><td><0.001</td></tr>
<tr><td>Mizoguchi 2012</td><td>296 [±108]</td><td>368 [±83]</td><td>Immediate</td><td>P<0.01.</td></tr>
</table>
mean[±SD] or median (IQR); NR, not reported
</td></tr>
<tr><td rowspan="8">Functional class (function)</td><td>Broch 2016</td><td>5/10</td><td>Direct</td><td rowspan="8">Grade B: More than one study of medium quality score (4-6/10) and at least one has direct applicability.</td><td rowspan="8">
Functional class (WHO or NYHA); a description of how symptoms of heart failure affect a patient's activities, classes I-IV where IV is most severe, see page 5 for the classes in full). Five of seven study groups reported functional classification. No single study could be identified as providing the 'best' estimate of change in functional class. All found an average improvement, with fewer patients in the more severe classes (III and IV) and more patients in the less severe classes (I and II).
<table>
<tr><td>Study</td><td>Pre BPA</td><td>Post BPA</td><td>Follow up assessment point</td><td>P value</td></tr>
<tr><td>Broch 2016</td><td>2.9 [±0.5]</td><td>1.9 [±0.5]</td><td>3 months</td><td><0.001</td></tr>
<tr><td>Kinutani 2016</td><td>0/8/16/4 (0/29/57/14)</td><td>16/11/1/0 (57/39/4/0)</td><td>Immediate</td><td>p<0.01</td></tr>
<tr><td>Yamasaki 2016</td><td>NR</td><td>NR</td><td></td><td></td></tr>
<tr><td>Aoki 2016</td><td>0/12/11/1 (0/50/46/4)</td><td>5/19/0/0 (24/76/0/0)</td><td>6 months</td><td>0.04</td></tr>
<tr><td>Fukui 2015</td><td>2.6</td><td>2.1</td><td>mean 3 weeks</td><td><0.001</td></tr>
<tr><td>Inami 2014a</td><td>NR</td><td>NR</td><td></td><td></td></tr>
<tr><td>Mizoguchi 2012</td><td>0/0/49/19 (0/0/72/28)</td><td>17/49/0/0 (25/72/0/0)</td><td>1 year</td><td></td></tr>
</table>
Mean [±SD] or number in class I/II/III/IV (% in each class); NR, not reported
</td></tr>
<tr><td>Aoki 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Fukui 2015</td><td>3/10</td><td>Direct</td></tr>
<tr><td>Inami 2014a</td><td>4/10</td><td>Likely direct but unclear.</td></tr>
<tr><td>Kinutani 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Mizoguchi 2012</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Yamasaki 2016</td><td>5/10</td><td>Direct</td></tr>
<tr><td>Cardiopulmonary exercise testing (function)</td><td>Fukui 2015</td><td>3/10</td><td>Direct</td><td>Grade C: studies of low quality only</td><td>Fukui et al. reported an improvement in exercise duration and peak VO2 assessed in cardiopulmonary exercise testing. The size of improvement achievable will be dependent on the patient status at baseline.</td></tr>
<tr><td>Function summary</td><td colspan="4">Overall interpretation of the physiological outcomes is combined to reduce repetition.</td><td>All studies showed an improvement in function, which has a direct impact on the experience of heart failure symptoms for patients in their day-to-day lives.
• All are observational before-and-after studies, but the improvements are large enough that they are unlikely to be explained by regression to the mean given the</td></tr>
</table>

					natural history of the condition. • Improvements were consistently found, in both main types of outcome (6MWD and functional class). • Mizoguchi (2012) found that the improvement was sustained at one year's follow up but longer term results were not available. • Direct comparison with functional outcomes from best medical treatment (riociguat) were not available. The CHEST-1 trial of riociguat found that over 16 weeks of medical treatment, 6MWD improved among patients receiving riociguat by 46m (95% CI 25 to 67) more than among patients receiving placebo. • There is some scope for studies to have selectively reported the more favourable of 6MWD or functional class – however, most studies report both, which limits the likely extent of selective reporting bias for this outcome. Currently there is reasonable certainty that BPA improves function/ symptoms of heart failure among patients with CTEPH. There is scant evidence on the comparative effectiveness compared to riociguat. 6MWD and functional class are pre-specified outcomes of the RACE randomised controlled trial of riociguat vs BPA, which is expected to report in 2020, which will improve this evidence base.
Medication required	Aoki 2016	6/10	Direct	Grade B: More than one study of medium quality score (4-6/10) and at least one has direct applicability.	A patient no longer requiring long-term oxygen therapy or other medications after BPA is a surrogate marker for symptom improvement, may also be expected to have a direct impact on quality of life, and reduces the long-term cost of treatment. Change in treatment requirements were reported by 3 studies. In addition, Broch (2016). reported that medications were held constant during the study to reduce confounding of the BPA treatment effect. Medication requirements were not identified as a pre-specified outcome for any study, and this outcome is highly vulnerable to selective reporting in which only positive changes may have been reported. • Home oxygen therapy requirement was reduced in the two studies which reported this, (from 79% to 54% immediately after BPA, p=0.01, Aoki 2016; from 100% to 62% at one year follow up, Mizoguchi 2012). • Pulmonary hypertension therapy changes were reported in little detail. It is hard to assess whether the number of patients requiring medication changed or whether patterns of medication shifted as combination therapy was not consistently reported. The clearest report (by patient rather than medication type) was from Fukui (2015), who reported that of 14 patients treated with oral pulmonary hypertensive therapies, 1 patient discontinued an endothelin-receptor antagonist
	Fukui 2015	3/10	Direct		
	Mizoguchi 2012	6/10	Direct		

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>while 13 remained unchanged over follow up (mean 3.5 months).
It is a question of high uncertainty whether BPA reduces medication requirements for patients with CTEPH. Observational data from CTEPH registries may improve the evidence base for this question in the future.</td></tr>
<tr><td>Physiology</td><td colspan="5">To simplify comparison across studies, the report focuses on two physiological indicators:
• Pulmonary vascular resistance (PVR) represents the resistance to blood flow offered by the pulmonary vasculature.
• N-terminal pro b-type natriuretic peptide (NT-pro BNP) is a protein produced by the walls of the heart. It is a marker of cardiac strain, and levels are elevated by heart failure.</td></tr>
<tr><td rowspan="7">Pulmonary vascular resistance (physiology)</td><td>Broch 2016</td><td>5/10</td><td>Direct</td><td rowspan="7">Grade B: More than one study of medium quality score (4-6/10) and at least one has direct applicability.</td><td rowspan="7">All studies reported the results of right heart catheterisation (including pulmonary vascular resistance). All studies reported an improvement in the average PVR after balloon pulmonary angioplasty. No single study could be identified as providing the ‘best’ estimate of change in PVR. Average PVR reductions ranged from 31% to 61%, and some post-BPA averages approached normal values for PVR (<250 dyne sec/cm^5). Follow up time periods ranged from immediately after the final BPA session to 14 months later.

Pulmonary vascular resistance before and after BPA (dyne sec/cm^5 unless stated)
<table><tr><th>Study</th><th>Pre BPA</th><th>Post BPA</th><th>Follow up assessment point</th><th>P value</th></tr><tr><td>Broch 2016</td><td>612 [±282]</td><td>375 [±221]</td><td>3 months</td><td><0.001</td></tr><tr><td>Kinutani 2016</td><td>574 (317)</td><td>258 (171)</td><td>Immediate</td><td><0.01</td></tr><tr><td>Yamasaki 2016</td><td>639 (224)</td><td>411 (123)</td><td>Mean 88 days</td><td><0.0001</td></tr><tr><td>Aoki 2016</td><td>517 (389-696)</td><td>268 (239-345)</td><td>6 months</td><td><0.01</td></tr><tr><td>Fukui 2015</td><td>755 (345)</td><td>N/A *</td><td>N/A</td><td>N/A</td></tr><tr><td>Inami 2014a</td><td>8.7 Wood units (6.1-13.3)</td><td>2.7 Wood units (2.0-4.2)</td><td>Median 14 months</td><td><0.001</td></tr><tr><td>Mizoguchi 2012</td><td>942 (367)</td><td>327 (151)</td><td>1 year</td><td><0.01</td></tr></table>mean[±SD] or median (IQR)
* pulmonary wedge pressure could not be measured post BPA in this study to obtain PVR</td></tr>
<tr><td>Kinutani 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Yamasaki 2016</td><td>5/10</td><td>Direct</td></tr>
<tr><td>Aoki 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Fukui 2015</td><td>3/10</td><td>Direct</td></tr>
<tr><td>Inami 2014a</td><td>4/10</td><td>Likely direct but unclear.</td></tr>
<tr><td>Mizoguchi 2012</td><td>6/10</td><td>Direct</td></tr>
<tr><td rowspan="3">Brain natriuretic peptide (physiolog</td><td>Broch 2016</td><td>5/10</td><td>Direct</td><td rowspan="3">Grade B: More than one study of medium quality score (4-6/10)</td><td rowspan="3">All studies reported the results of BNP. All studies reported an improvement in the average after balloon pulmonary angioplasty. No single study could be identified as providing the ‘best’ estimate of change in BNP. Average BNP reductions ranged from 10% to 50%. Follow up time periods ranged from immediately after the final BPA session to 14</td></tr>
<tr><td>Kinutani 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Yamasaki 2016</td><td>5/10</td><td>Direct</td></tr>
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<td>y)</td>
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<tr><td>Aoki 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Fukui 2015</td><td>3/10</td><td>Direct</td></tr>
<tr><td>Inami 2014a</td><td>4/10</td><td>Likely direct but unclear.</td></tr>
<tr><td>Mizoguchi 2012</td><td>6/10</td><td>Direct</td></tr>
</table>
</td>
<td>and at least one has direct applicability.</td>
<td>months later.

BNP before and after BPA (pg/mL)
<table>
<tr><th>Study</th><th>Pre BPA</th><th>Post BPA</th><th>Follow up assessment point</th><th>P value</th></tr>
<tr><td>Broch 2016</td><td>791</td><td>237</td><td>3 months</td><td>0.001</td></tr>
<tr><td>Kinutani 2016</td><td>160 [±233]</td><td>26 [±31]</td><td>Immediate</td><td><0.01</td></tr>
<tr><td>Yamasaki 2016</td><td>67 [±61]</td><td>34 [±30]</td><td>Mean 88 days</td><td><0.05</td></tr>
<tr><td>Aoki 2016</td><td>112 (49-199)</td><td>28 (15-58)</td><td>6 months</td><td><0.01</td></tr>
<tr><td>Fukui 2015</td><td>142 [±198]</td><td>25 [±11]</td><td>Immediate or 3 months (unclear)</td><td><0.01</td></tr>
<tr><td>Inami 2014a</td><td>95 (42-270)</td><td>34 (16-59)</td><td>Median 14 months</td><td><0.001</td></tr>
<tr><td>Mizoguchi 2012</td><td>330 [±444]</td><td>35 [±55]</td><td>1 year</td><td><0.01</td></tr>
</table>
mean[±SD] or median (IQR)</td>
</tr>
<tr>
<td>Physiology summary</td>
<td colspan="3">Overall interpretation of the physiological outcomes is combined to reduce repetition.</td>
<td>The size of effects consistently observed suggests that there is reasonable certainty that patients with CTEPH have improved physiological markers of pulmonary hypertension and right heart strain following BPA.
• Most of the included studies have a small number of patients, and so are vulnerable to overestimation of the size of effects, and so the size of effects estimated may not be reliable.
• With this caveat, the size and consistency of effects observed are unlikely to be explained by regression to the mean, given the natural history of this disease.
• The universal reporting of these outcomes means they are not vulnerable to selective reporting of outcomes.
• No long-term outcomes were available.

There is no evidence on the question as to how improvements in physiological markers of disease compare between BPA and best medical practice (riociguat).
• Patients in the CHEST-1 trial of riociguat vs placebo experienced clinically important reductions in physiological markers of disease, including PVR and BNP. The size of the reductions is affected by the baseline condition of the patients, and so these results cannot meaningfully be compared across studies.
PVR is the primary outcome of the RACE randomised controlled trial of riociguat vs BPA, which is expected to report in 2020, which will improve this evidence base.</td>
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<td>Safety</td>
<td>Broch 2016</td>
<td>5/10</td>
<td>Direct</td>
<td rowspan="7">Grade B: More than one study of medium quality score (4-6/10) and at least one has direct applicability.</td>
<td rowspan="7">All but one study reported peri-procedural safety. No single study could be identified as providing the ‘best’ estimate of safety. The main complications reported were:
• Reperfusion pulmonary oedema: pulmonary oedema following reopening of the narrowed or blocked pulmonary arteries. Mild pulmonary oedema causes shortness of breath: more severe pulmonary oedema causes a fall in oxygenation of the blood. Patients may require ventilation and the condition may be fatal.
• Pulmonary artery wire perforation: injury to the pulmonary artery with the guidewire during BPA, which may cause serious bleeding or death.

<table>
<tr><th>Study</th><th>N</th><th>Severe reperfusion oedema</th><th>Wire perforation</th><th>Peri-procedural deaths</th></tr>
<tr><td>Broch 2016</td><td>32</td><td>1, fatal</td><td>NR</td><td>2 deaths (reperfusion oedema, acute pulmonary embolism)</td></tr>
<tr><td>Kinutani 2016</td><td>29</td><td>Desaturation requiring NIPPV in 13 sessions (15% of sessions).</td><td>5 (6% of sessions)</td><td>1 death prior to BPA, from central venous catheter-associated sepsis related to pre-BPA epoprostenol administration.</td></tr>
<tr><td>Yamasaki 2016</td><td>20</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Aoki 2016</td><td>24</td><td>No reperfusion lung oedema requiring mechanical ventilation</td><td>“No severe lung bleeding”</td><td>No peri-procedural deaths</td></tr>
<tr><td>Fukui 2015</td><td>25</td><td>No severe reperfusion pulmonary edema requiring invasive ventilation</td><td>“No major complications”</td><td>No peri-procedural deaths</td></tr>
<tr><td>Inami 2014a</td><td>103</td><td>Ventilation required after 9/350 (3%) sessions.</td><td>Dissection in 35/350 sessions (10%) of which: 28 had extravascular leaks; 2 required stent or coil; 1</td><td>1 death at 2 days (wire perforation): perioperative mortality 1% (1/103).</td></tr>
</table>
</td>
</tr>
<tr><td>Kinutani 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Aoki 2016</td><td>6/10</td><td>Direct</td></tr>
<tr><td>Fukui 2015</td><td>3/10</td><td>Direct</td></tr>
<tr><td>Inami 2014a</td><td>4/10</td><td>Likely direct but unclear.</td></tr>
<tr><td>Mizoguchi 2012</td><td>6/10</td><td>Direct</td></tr>
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			fatal.	
Mizoguchi 2012	68	4 patients needed intratracheal intubation and 2 needed percutaneous cardiopulmonary support	5 patients, of whom 2 needed emergency transcatheter coil embolization	1 (reperfusion pulmonary injury)

NR: not reported.

There is reasonable certainty that the risk of peri-procedural complications of BPA for patients with CTEPH is low in the modern era, but the risk of serious complications (reperfusion pulmonary oedema and wire perforation) is more difficult to assess given the varying thresholds for reporting these complications across the multiple small studies. These are serious complications which would require evidence of benefit to balance the evidence of harm.

- Peri-procedural mortality appears to be approximately 5/281 (2%) among patients included in the studies which reported complications.
- This is comparable to the peri-operative mortality for pulmonary endarterectomy. However, pulmonary endarterectomy is potentially curative, and so a higher mortality may be acceptable to patients for surgery than BPA.
- The peri-procedural complication rate for BPA cannot meaningfully be compared to 16-week safety of riociguat in the CHEST-1 trial, as a procedural intervention would be expected to have a different profile of safety over time to a medical treatment, and the baseline status of the patients in the different studies may vary by enough to explain the difference in mortality.
- Long term survival data comparing patients randomised to riociguat or BPA in the RACE trial will help to establish the evidence base for the relative safety of these alternative treatments.

9. Literature Search Terms

Search strategy	
Terms to include: Balloon pulmonary angioplasty, Pulmonary endarterectomy Chronic thromboembolic pulmonary hypertension	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	This intervention is for patients with chronic thromboembolic pulmonary hypertension for whom surgery with pulmonary endarterectomy is considered to be unsuitable (because of comorbidities or the distribution of their thromboembolic disease).
I – Intervention Which intervention, treatment or approach should be used?	Balloon pulmonary angioplasty
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	All patients with CTEPH are treated with anticoagulants lifelong to prevent recurrent venous thromboembolism and in-situ pulmonary artery thrombosis. Lifelong pulmonary hypertension targeted therapies are currently the only alternative treatment for those patients not suitable for PEA. Riociguat (Adempas) has recently been licensed for this indication and has funding approved by the Clinical Commissioning Policy A11/P/c.
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* Improved survival Improved quality of life (for example CAMPHOR) Improved functional class and exercise capacity (WHO classification), 6 minute walking test and / or cardiopulmonary exercise test in some cases Improved pulmonary haemodynamics (pulmonary arterial pressure and vascular resistance measured at right heart catheterisation) *Important to decision-making:* Number of patients able to stop expensive pulmonary hypertensive targeted therapies or oxygen Improved right heart function (Nt-pro BNP and echocardiography) Improved right ventricle remodelling on imaging (e.g. selective or computed tomography pulmonary angiography) Peri-procedural morbidity and complications (e.g. reperfusion injury, need for CPAP/ invasive ventilation, ECMO, bleeding complications, renal failure, hospital LOS)
Assumptions / limits applied to search	
Inclusion Criteria	Any clinical trials or observational studies that report outcome of balloon pulmonary endarterectomy for human patients with non-operable chronic thromboembolic pulmonary hypertension. Published within the last 5 years. Reporting results of >= 20 patients who had BPA for inoperable CTEPH.
Exclusion Criteria	CTEPH patients suitable for surgery with pulmonary endarterectomy Conference abstracts will be excluded due to difficulty in assessing methods and quality. Non-english language articles will be excluded unless they are thought to add substantially to the English language evidence base.

10. Search Strategy

((((Balloon OR percutaneous OR transluminal) AND (endarterectomy OR angioplasty)) AND (pulmonary OR pulm*))
OR (BPA OR PTPA))
AND (CTEPH OR pulmonary hypertension OR pulmonary embolism)

Using filters or limits where possible to limit search results to clinical studies of humans published from 2011 onwards.

Literature reviews were extracted for reference searching, and the references of eligible studies were searched.

	Search terms	Search details	Results
MEDLINE	1. ((((balloon) OR percutaneous) OR transluminal) OR percut*) OR translum* 2. ((pulmonary) OR lung) OR pulmon* 3. (((endarterectomy) OR endarterec*) OR angioplasty) OR angiop* 4. ((#1) AND #2) AND #3 5. ((#4) OR BPA) OR PTPA 6. ((pulmonary hypertension) OR pulmonary embolism) OR CTEPH 7. (#5) AND #6	Searched using Pubmed on 19 October 2016 Filters: published in the last 5 years MESH terms mapped	309 titles and abstracts screened 58 identified for full-text review
EMBASE	1. (balloon OR percutaneous OR transluminal OR percut* OR translum).ti,ab 2. (pulmonary OR lung OR pulmon*).ti,ab 3. (endarterectomy OR endarterect* OR angioplasty OR angiop*).ti,ab 4. (BPA OR PTPA).ti,ab 5. ("pulmonary hypertension" OR "pulmonary embolism" OR CTEPH).ti,ab 6. 1 AND 2 AND 3 7. 6 OR 4 8. 7 AND 5	Searched using HDAS portal on 20 October 2016 Limited to articles published on or after 1 January 2011	317 titles and abstracts screened 120 duplicates of Medline search 68 identified for full-text review
Cochrane	1. ((((balloon) OR percutaneous) OR transluminal) OR percut*) OR translum* 2. ((pulmonary) OR lung) OR pulmon* 3. (((endarterectomy) OR endarterec*) OR angioplasty) OR angiop* 4. ((#1) AND #2) AND #3 5. ((#4) OR BPA) OR PTPA 6. ((pulmonary hypertension) OR pulmonary embolism) OR CTEPH (#5) AND #6	No studies identified. Reviewed 108 studies returned from search #5.	No eligible studies identified.

NICE	Identified Interventional Procedure overview of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension, June 2015.	References searched.	No new studies identified.
Trial registries	chronic thromboembolic pulmonary hypertension	clinicaltrials.gov	55 trials reviewed 1 ongoing trial of BPA vs riociguat identified

11. Evidence selection

- Total number of publications reviewed: 506 deduplicated titles and abstracts screened, 118 full text reviewed, of which 55 were identified as conference abstracts.
- Total number of publications considered relevant: 24
- Total number of publications selected for inclusion in this briefing: 8

The evidence review identified 24 papers which fulfilled the search criteria. As discussed in the section 3 (methodology) these all originated from 7 centres, and there was a high degree of overlap of patient populations. Only the main paper for each centre was selected for inclusion in this evidence review, with one additional paper included for long-term survival outcomes. The 24 papers are summarised in Table 9, below.

Table 8: Rationale for inclusion of eligible papers

	Population included	Main outcomes	Decision and rationale
Okayama Medical Centre, Japan			
● Mizoguchi (2012)	68 consecutive patients November 2004 – September 2011	Before BPA, immediately after and 1 year follow up Function: WHO-FC, 6MWD Medication required Physiology: RHC, BNP Complications	INCLUDED Largest cohort reported for this treatment centre.
Kyushu University, Fukuoka, Japan			
● Yamasaki (2016)	20 inoperable patients May 2012 – February 2016	Before first BPA and after last BPA Function: 6MWD Physiology: RHC, BNP, Cardiac MR imaging	INCLUDED Largest cohort reported for this treatment centre.
Kobe, Japan			
● Kinutani (2016)	28 patients inoperable patients 84 BPA sessions October 2012 – April 2015	Pre and post procedure Function: WHO-FC, 6MWD Physiology: RHC, BNP, pulmonary arterial pressure Complications	INCLUDED Largest cohort reported for this treatment centre excluding learning curve.
● Taniguchi Y, Miyagawa K, Nakayama K, et al. (2014) EuroIntervention 10 pp.518-525.	29 inoperable patients 86 BPA sessions March 2011 – September 2013 Presents 24 patients who had PEA as comparison group	Before and 7 days post final BPA Function: WHO-FC, 6MWD Physiology: RHC, BNP Complications	EXCLUDED Population: Includes learning curve (BPA started March 2011). Majority nested in Kinutani 2016. Novel comparison group: not the relevant comparison group for this review, which is considering patients with non-operable CTEPH.

Oslo University Hospital Rikshospitalet, Norway			
● Broch (2016)	26 inoperable patients 2003-2014	Before first BPA, 3 months after final BPA Function: NYH-FC, cardiopulmonary exercise testing Physiology: RHC, BNP, echocardiography	INCLUDED Largest cohort reported for this treatment centre.
● Andreassen A, Ragnarsson A, Gude E et al. (2013) Heart 99 pp.1415-1420.	20 inoperable patients 73 sessions of BPA January 2003 – August 2011	Before first BPA, 3 months after final BPA Function: NYH-FC, cardiopulmonary exercise testing Medication required Physiology: RHC, BNP, arterial blood gas, Troponin Complications	EXCLUDED Population: nested within Broch 2016
Suita, Japan			
● Fukui (2015)	25 inoperable patients who had BPA and cardiopulmonary exercise testing Dates not reported	Before BPA and at 3 month follow up Function: WHO functional class, 6MWD, cardiopulmonary exercise testing Physiology: RHC	INCLUDED: Largest cohort reported for this treatment centre Patient population: 6 patients from Fukui 2014 Eur Respir J. Quality: Unclear whether selection of patients with cardiopulmonary exercise testing occurred: potential for selection bias cannot be assessed.
● Fukui S, Ogo T, Morita Y, et al. (2014) Eur Respir J 43 pp. 1394-1402.	20 inoperable patients who had BPA and cardiac MR August 2012 – December 2013	Before BPA and 3-6 months after BPA Function: WHO-FC, 6MWD Physiology: RHC, Cardiac MR imaging	EXCLUDED: Smaller study than alternative, similar quality, novel outcome of less relevance to patient experience Patient population: 6 patients from Fukui 2015. Quality: Unclear whether selection of patients with cardiac MR imaging occurred: potential for selection bias cannot be assessed.

Keio University Hospital and Kyorin University Hospital , Tokyo, Japan

● Inami T, Kataoka M, Shimura N, et al. (2015) International Journal of Cardiology 201 pp.35-37.	143 patients 540 BPA sessions Keio and Kyorin January 2009 – June 2015	Immediate Complication: Pulmonary artery injury incidence, outcomes, and causes	EXCLUDED Population: significant overlap with Inami 2014 JACC Cardiovasc Intv. Quality: letter, limited methods. Scope: limited to overview of single outcome. Does not report any outcomes pre-specified as critical to decision for this review.
● Inami (2014a)	103 patients: 83 included in follow up 350 consecutive BPA sessions Keio and Kyorin January 2009 - December 2013	Baseline to follow up (median 14 months) Function: 6 MWD Physiology: RHC, BNP Complications	INCLUDED Largest cohort reported for this treatment centre, reports standard range of outcomes for BPA.
● Inami (2014b)	68 patients had 213 BPA sessions Keio and Kyorin January 2009 – April 2013 (Comparison groups: - 29 patients medical treatment if excluded from BPA eligibility (e.g. co-morbidities) or refused BPA 2000 – April 2013 - 39 patients who had PEA January 2000 – April 2013)	3 month follow up for 54 BPA patients. Survival. Function: NYHA-FC (graphical), 6MWD Physiology: RHC (graphical), BNP Complications	LONG TERM SURVIVAL OUTCOME INCLUDED AS ADDITIONAL OUTCOME Population: nested within Inami (2014a). Novel comparison group: PEA not appropriate comparator for this review. Medical treatment is an appropriate comparator but the comparability of the patient groups is limited: treatment not randomised, (medical group older with longer 6MWD than BPA group) and limited outcomes reported for medical group.
● Yanagisawa R, Kataoka M, Inami T, et al. (2014) International	70 patients 257 consecutive BPA sessions	Before and at follow up shown on graph for both age groups	EXCLUDED Population: nested within Inami (2014a).

Journal of Cardiology 175 pp.285-289.	Keio and Kyorin January 2009 – July 2013	Function: NYHA-FC, 6MWD Physiology: RHC, BNP Length of hospital stay Complications	Quality: Graphical results hard to extract as exact results.
● Inami T, Kataoka M, Shimura N, et al. (2013) JACC: Cardiol Intv 6(7) pp.725-736.	54 patients 140 consecutive BPA sessions Keio and Kyorin January 2009 – May 2012	Before first procedure and after last for 44 patients Function: 6MWD Physiology: RHC, BNP Complications	EXCLUDED Population: nested within Inami (2014a). Quality: varying number of patients included by outcome type. Novel outcomes: none.
● Kataoka M, Inami T, Hayashida K, et al. (2013) Circ Cadiovasc Interv. 5 pp.756-762.	28 patients Keio and Kyorin January 2009 – December 2011	Before first procedure and after last Function: NYHA-FC (graphical) Physiology: RHC, BNP Complications	EXCLUDED Population: nested within Inami (2014a).
● Sueoka J, Kataoka M, Shimura N, et al. (2015) International Journal of Cardiology 201 pp.271-273.	100 patients who had BPA – dates and location not specified. Authors from Keio and Kyorin.	Reported according to presence or absence of anti-cardiolipin antibodies Physiology: RHC (graphical) Complications	EXCLUDED Population: origin not described but authors as for Keio and Kyorin cohort papers. Quality: Letter, very limited methods reported.
● Kimura M, Kohno T, Kawakami T, et al. (2016) International Journal of Cardiology 207 pp.387-389.	66 consecutive patients 446 BPA sessions Keio only November 2012 – October 2015	Before and after (within 2 weeks) of BPA. Physiology: RHC, BNP, Troponin Complications	EXCLUDED Patient population considerable overlap with Inami (2014a). Quality: Letter, limited methods reported
● Takei M, Kataoka M, Kawakami T, et al. (2016a) International Journal of Cardiology 203 pp.1016-1017.	73 patients Keio only BPA November 2012 – July 2015	During and within 2 days of BPA Complications: peri-procedural	EXCLUDED Population: nested in Kimura 2016 (other than minor differences in exclusion criteria), considerable overlap with Inami (2014a). Quality: Letter, limited methods reported

● Takei M, Kataoka M, Kawakami T, et al. (2016b) International Journal of Cardiology 212 pp.190-191.	55 patients consecutive BPA Keio only November 2012 – April 2015	Before and within 2 weeks of BPA Function: WHO-FC Physiology: RHC, BNP, Respiratory indices and blood gas results Complications: peri-procedural	EXCLUDED Population: nested in Kimura 2016, considerable overlap with Inami (2014a). Quality: Letter, limited methods reported
● Tsugu T, Murata M, Kawakami T, et al. (2016) Am J Cardiol 118 pp.1081-1087.	26 patients Keio only BPA November 2012 – January 2015 and followed up ≥6 months Excluded patients with lung disease, left sided heart failure or moderate/severe aortic or mitral valvular heart disease	Before, immediately after and 6 months after BPA Function: WHO-FC, 6MWD Physiology: RHC, BNP, echocardiography, uric acid	EXCLUDED Population: nested in Kimura 2016, considerable overlap with Inami (2014a). Novel outcomes: none identified as critical to decision for this review.
● Kimura M, Kataoka M, Kawakami T, et al. (2015) International Journal of Cardiology 188 pp.41-42.	46 consecutive patients BPA Keio only November 2012 – December 2014	Before and after (within 2 weeks) of BPA Physiology: RHC, BNP, eGFR	EXCLUDED Population: nested in Kimura 2016, considerable overlap with Inami (2014a). Quality: Letter, limited methods reported
● Tsugu T, Murata M, Kawakami T, et al. (2015) Am J Cardiol 115 pp.256-261.	25 patients BPA Keio only November 2012 – May 2014 Excluded patients with lung disease, left sided heart failure or valvular heart disease	Before and after BPA Function: WHO-FC Physiology: RHC, BNP, echocardiography, uric acid	EXCLUDED Population: nested in Tsugu 2016 Novel outcomes: as Tsugu 2016

Tohoku University Hospital, Sendai, Japan			
● Sato H, Ota H, Sugimara K et al. (2016) Circ J 80 pp.1470-1477.	30 consecutive inoperable patients 152 BPA sessions July 2009 – July 2015.	Before and after BPA Function: WHO-FC, 6MWD Medication required Physiology: RHC, BNP, cardiac MR imaging Complications	EXCLUDED Patient population: Overlap with patients in Aoki 2016 and Tatebe 2016. Within this period, Tatebe et al. report 55 consecutive patients. Fewer patients included in this consecutive series despite longer time frame: appears to be due to difference in description of use of dates rather than exclusion criteria. Quality: Includes learning curve: first BPA conducted at institution in July 2009.
● Aoki (2016)	24 consecutive inoperable patients 113 BPA sessions August 2013 – May 2015	Before first BPA and 6 months after last BPA Function: WHO-FC, 6MWD Medication required Physiology: RHC, BNP, respiratory function tests	INCLUDED Largest representative cohort reported for this treatment centre excluding learning curve.
● Tatebe S, Sugimura K, Aoki T, et al. (2016) Circ J 80 pp.980-988.	35 patients from 55 consecutive inoperable patients: excluded 20 patients medicated with antihyperlipidaemic or antihyperglycaemic drugs March 2012 – December 2014	Before and at follow up (mean 474 days) Function: WHO-FC, 6MWD Medication required Physiology: RHC, BNP, metabolic markers (body mass index, HbA1C, fasting blood sugar, lipid profile, full blood count, thyroid function tests, albumin, eGFR, Troponin, ferritin)	EXCLUDED Patient population: Overlap with patients in Sato 2016 unclear. Exclusion criteria reduce the generalisability of the results – less representative cohort than Sato 2016. Quality: Excluded 20/55 patients for taking antiglycaemic or antilipidaemic medications. There is high potential for selection bias (from including or excluding patients according to decisions on treatment status).

WHO-FC, World Health Organization functional class; NYHA-FC, New York Heart Association functional classification; 6MWD, 6 minute walking distance; RHC, right heart catheterisation; BNP, Brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

12. References

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