NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

When a blood clot forms in one of the deep veins in the legs, it is called a deep vein thrombosis. The clot can become loose and be carried in the blood to the lungs. Here, it can block an artery (a blood vessel), which can affect blood flow to the lungs. Blood clots in the lungs may dissolve over time but they do not always dissolve completely, leaving the artery narrowed. This restricts blood flow through the lungs leading to shortness of breath, dizziness, tiredness, chest pain and, eventually, heart failure. In this procedure, a balloon is inserted into an artery in the lungs, through a vein in the neck or groin. The balloon is then positioned at the site of narrowing and inflated to widen the artery. The aim is to improve blood flow through the lungs.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in June 2015

Procedure name

- Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

Specialist societies

- British Cardiovascular Intervention Society

- British Society of Interventional Radiologists
- British Thoracic Society

Description

Indications and current treatment

Chronic thromboembolic pulmonary hypertension is a progressive disease. It is caused by obstruction of the pulmonary arteries (from main to subsegmental levels) by pulmonary emboli that have not resolved but which have become organised. This causes a narrowing of the pulmonary arteries, an increase in the resistance to blood flow and a rise in pressure within the pulmonary arteries (pulmonary hypertension). Progression of pulmonary hypertension may occur in the absence of further pulmonary emboli because of progressive remodelling of unobstructed pulmonary vasculature in response to the haemodynamic changes.

Early symptoms include chest pain, shortness of breath, fatigue, dizziness, peripheral cyanosis and oedema. If left untreated, chronic thromboembolic pulmonary hypertension often leads to right heart failure and ultimately death.

Medical treatment includes anticoagulants to prevent recurrent venous thromboembolism and in-situ pulmonary artery thrombosis. Vasodilators may be used to reduce pulmonary hypertension. Pulmonary endarterectomy (PEA) is a surgical procedure that aims to remove the obstructing thromboembolic material. However, the procedure may not be suitable for all patients.

What the procedure involves

Balloon pulmonary angioplasty (BPA) aims to reduce pulmonary hypertension by dilating stenoses in the main or subsegmental pulmonary arteries. The procedure is usually done using local anaesthetic, with the patient fully anticoagulated. A standard right heart catheterization is done through the right internal jugular vein or right femoral vein. The stenosed and occluded vessels that need treatment are identified using selective pulmonary angiography. Once they are located, a balloon catheter is advanced through the stenosis or occlusion, over a guide wire, and the balloon is inflated to dilate the arteries and restore pulmonary blood flow. Between 1 and 6 segmental or subsegmental arteries are treated during each BPA procedure. The procedure may be repeated after 2–8 weeks until desired haemodynamic measurements are attained.

Heart failure classification

New York Heart Association functional classification system

The New York Heart Association (NYHA) functional classification system is a long-standing, widely-used method of categorising heart failure that relates symptoms to everyday activities and the patient's quality of life. The scoring system consists of 4 categories with higher classes indicating more severe heart failure.

- Class I: no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath) or angina pain.
- Class II: slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
- Class III: marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
- Class IV: the patient is unable to carry out any physical activity without discomfort and has symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. The following databases were searched, covering the period from their start to 25 June 2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with chronic thromboembolic pulmonary hypertension
Intervention/test	Balloon pulmonary angioplasty
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 226 patients from 1 non-randomised comparative study and 7 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

Study 1 Taniguchi Y (2014)

Details

Study type	**Non-randomised retrospective comparative study**
Country	Japan
Recruitment period	2001 to 2013
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**53 patients (29 BPA versus 24 PEA)**
Age and sex	BPA group: mean age, 67 years; sex, 76% (22/29) female PEA group: mean age, 57 years; sex, 71% (17/24) female
Patient selection criteria	Inclusion criteria: patients who were diagnosed with chronic thromboembolic pulmonary hypertension based on medical history, physical examination, chest radiography, echocardiography, computed tomography, lung ventilation-perfusion scintigraphy, right heart catheterisation and pulmonary angiography were included. Operable patients were offered PEA, Inoperable patients were offered BPA Exclusion criteria: not reported
Technique	BPA group: the pulmonary artery was accessed via the right femoral (82.6%) or the jugular vein (17.4%). In cases of severe stenosis, abrupt narrowing, or complete obstruction, a 2.0 mm balloon catheter was used to dilate lesions. Subsequently, lesions were dilated to an appropriate size using 2.0 mm to 9.0 mm balloon catheters, depending on the diameters of the vessels. Between 1 and 6 segmental or subsegmental arteries were treated during each BPA procedure. Each procedure was repeated twice within 2 weeks during one hospital admission. Epoprostenol was used in some patients if their mean pulmonary arterial pressure was over 40 mmHg. Dobutamine was used if the cardiac index was less than 2.0 litre/min/m^2. PEA group: bilateral PEA was done via a median sternotomy. Distant endarterectomy was done with intermittent circulatory arrest for up to 20 minutes while the central temperature was maintained at 16ºC. Patients were given perioperative medical treatment using catecholamines, phosphodiesterase 3 inhibitors, epoprostenol or diuretics until recovery.
Follow-up	**Not adequately defined: varied according to study arm and outcome measure assessed**
Conflict of interest/source of funding	No conflicts of interest were reported.

Analysis

Follow-up issues: Numbers varied according to outcome measure assessed.

Study design issues: The study was done by retrospectively reviewing patients' medical records. Patients who were eligible for surgery had PEA whereas patients who were ineligible for surgery were treated medically for at least 3 months and then had BPA. The main reasons for inoperability were clot inaccessibility (n=13), advanced age (n=6), previous cerebrovascular diseases (n=2), severe chronic obstructive pulmonary disease (n=3), previous PEA (n=2) and coexistence of cancer (n=3). Haemodynamic data were obtained from each group at differing time-points: 1 week after BPA and 2 weeks after PEA. Authors do not report when other outcome measures were assessed in each group.

Study population issues: Significant differences in age and preoperative medication usage were observed between groups. The mean ages of patients in the BPA and PEA groups were 67.3 years and 57.0 years, respectively (p=0.005). The proportions of patients who were using endothelin receptor antagonists and phosphodiesterase-5 inhibitors were significantly higher in the BPA group (p values<0.002). A mean of 2.97 treatment sessions were done in patients from the BPA group. A mean of 2.74 vessels were dilated per BPA treatment.

Other issues: None identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **53 (29 BPA versus 24 PEA); however, numbers varied according to outcome measure assessed**

Haemodynamic data (mean±SD)

Outcome measure	BPA group			PEA group		
	Baseline	1 week Follow-up	p value	Baseline	2 week Follow-up	p value
Mean pulmonary arterial pressure (mmHg)	39.4±6.9	21.3±5.6	<0.001	44.4±11.0	21.6±6.7	<0.001
Right atrial pressure (mmHg)	5.5±5.0	2.6±2.8	0.013	10.2±8.8	6.0±3.8	0.089
Cardiac output (litre/min)	3.47±0.80	4.26±1.15	<0.001	3.35±1.11	4.44±1.58	0.007
Cardiac index (litre/min/m^2)	2.17±0.45	2.69±0.63	<0.001	2.09±0.62	2.83±0.81	0.005
Systolic pulmonary arterial pressure (mmHg)	68.6±13.5	38.1±11.6	<0.001	76.7±19.9	34.6±10.7	<0.001
Diastolic pulmonary arterial pressure (mmHg)	22.1±5.8	10.9±4.6	<0.001	24.4±10.7	12.1±3.5	<0.001
Pulmonary vascular resistance (dyn·S/cm^5)	763±308	284±128	<0.001	781±278	258±125	<0.001
Pulmonary capillary wedge pressure (mmHg)	8.1±3.3	6.9±3.4	0.189	13.1±7.3	8.6±3.4	0.032

- Persistent pulmonary hypertension was reported in 13.8 (4/29) of patients in the BPA group and 16.7% (4/24) of patients in the PEA group.
- The mean post procedural right ventricular systolic pressure changed from 38.4 mmHg to 37.2 mmHg in the BPA group (n=25) at mean follow-up of 1.10 years while the mean right ventricular pressure changed from 29.8 mmHg to 30.9 mmHg in the PEA group (n=18) at mean follow-up of 3.93 years.

NYHA class

Class	% (n/N)			
	BPA group		PEA group	
	Baseline	Follow-up	Baseline	Follow-up
I	0	39.3 (11/28)	0	59.1(13/22)
II	10.3 (3/29)	50.0 (14/28)	12.5 (3/24)	31.8 (7/22)
III	62.1 (18/29)	10.7 (3/28)	54.2 (13/24)	9.1 (2/22)
IV	27.6 (8/29)	0	33.3 (8/24)	0

Other outcome measures

- Mean B-type natriuretic peptide levels decreased from 210 pg/ml to 41 pg/ml in the BPA group (p=0.01) and 263 pg/ml to 74 pg/ml in the PEA group (p=0.022). The follow-up period was not reported.
- In the BPA group, mean 6-minute walking test distance increased from 295 m to 397 m at follow-up (p<0.001). The follow-up period was not reported. No results were reported for the PEA group.

Safety

Patient-based analysis

- In-hospital death, due to infection, was reported in 1 patient from the BPA group. Authors state that the infection was caused by a central venous catheter used for epoprostenol administration. Perioperative death was reported in 2 patients from the PEA group within 16 days of having treatment. Both patients had severe pulmonary hypertension and low cardiac output, which needed constant cardiopulmonary support.

Occurrence of adverse events during <u>treatment sessions</u> (session-based analysis)

Adverse event	% (n/N)	
	BPA	PEA
Reperfusion pulmonary injury		
Severe haemoptysis	3.5 (3/86)	12.5 (3/24)
Haemosputum or desaturation	27.9 (24/86)	12.5 (3/24)
Identified by chest CT	32.6 (28/86)	N/A
Infection		
Ventilator-associated pneumonia	0	8.3 (2/24)
Mediastinitis	0	4.2 (1/24)
Other infections	2.3 (2/86)	4.2 (1/24)
Other adverse events		
Wire perforation	4.7 (4/86)	0
Neurologic complications	0	8.3 (2/24)
Pericardial effusion	0	8.3 (2/24)
Bleeding	0	4.2 (1/24)

Abbreviations used: BPA, balloon pulmonary angioplasty; CT, computed tomography; NYHA, New York Heart Association; PEA, pulmonary endarterectomy

Study 2 Mizoguchi H (2012)

Details

Study type	**Case series**
Country	Japan
Recruitment period	2004 to 2011
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**68 patients**
Age and sex	Mean age, 62 years; sex, 78% (53/63) female
Patient selection criteria	Inclusion criteria: Patients with chronic thromboembolic pulmonary hypertension who were categorised as having WHO class III or IV pulmonary hypertension despite medical therapy were included. All patients had 1 or more of the following features: pouching defects, webs, bands, intimal irregularities, abrupt vascular narrowing or complete vascular obstruction. Furthermore, they were all categorised as inoperable because of the location of thrombi, age or comorbidities. Exclusion criteria: not reported
Technique	All patients had epoprostenol 5 days before BPA to decrease pulmonary arterial pressure. BPA was done via the internal jugular vein (95.6%), the subclavian vein (1.5%) or the femoral vein (2.9%). Clinicians targeted webs or bands, abrupt vascular narrowing or complete vascular obstructions. In most cases, the lower lobe was targeted for the first BPA Session. A 2.0 mm balloon catheter was initially used to dilate lesions. Subsequently, lesions were dilated to an appropriate size using 2.0 mm to 9.0 mm balloon catheters, depending on the diameters of the vessels. The procedure was discontinued when oxygen desaturation was greater than 4% or haemosputum occurred. Target vessels were limited within a unilateral lung until the mean pulmonary arterial pressure decreased to 35 mmHg. After the initial BPA additional sessions were carried out at intervals of 5–14 days. A final BPA session was recommended 12 to 14 weeks after the penultimate BPA procedure.
Follow-up	**Mean follow-up of 2.2 years after last BPA session**
Conflict of interest/source of funding	One author received lecturer fees from pharmaceutical companies

Analysis

Follow-up issues: One patient died 28 days after the third BPA session

Study design issues: None identified.

Study population issues: Before having BPA, 5 patients were having dobutamine because of severe right heart failure. A mean of 4 BPA procedures were done in each patient. The mean number of dilated vessels per session was 3.

Other issues:

- WHO functional assessment classification of pulmonary hypertension:
    - Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
    - Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
    - Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
    - Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **67**

Haemodynamic and biomarker measurements for all patients

	Mean±SD		
Outcome measure	Baseline	Follow-up	p value
Mean pulmonary arterial pressure (mmHg)	45.4±9.6	24.0±6.4	<0.01
Right atrial pressure (mmHg)	8.1±4.4	1.9±1.5	<0.01
Cardiac Index (litre/min/m^2)	2.2±0.7	3.2±0.6	<0.01
Pulmonary vascular resistance (dyn·S/cm^5)	942±367	327±151	<0.01
B-type natriuretic peptide (pg/ml)	330±444	35±5.5	<0.01

WHO functional assessment classification of pulmonary hypertension

- Before BPA, all patients were categorised as having WHO functional class III or IV pulmonary hypertension. After the procedure 95.5% (64/67) of patients were categorised as having WHO functional class I or II and 4.5% (3/67) of patients were categorised as having WHO functional class III pulmonary hypertension.

6-minute walking test distances

- The mean 6-minute walking test distance increased from 296±108 m to 368±83 m at mean follow-up of 2.2 years after last BPA session (p<0.01).

Oxygen inhalation

- The mean rate of oxygen inhalation decreased from 3.0±1.4 litre/min to 1.3±1.0 litre/min at mean follow-up of 2.2 years after last BPA session (p<0.01).

Use of oral medications

- The proportion of patients who used endothelin receptor agonists decreased from 52% (35/68) to 37% (25/67) at mean follow-up of 2.2 years after last BPA session (p<0.05).
- The proportion of patients who used phosphodiesterase-5 inhibitor decreased from 40% (27/68) to 28% (19/67) at mean follow-up of 2.2 years after last BPA session (p<0.05).

Safety

Death

- Death due to right heart failure was reported in 1 patient 28 days after their third BPA session. A severe pulmonary injury occurred during the BPA session and exacerbated the patient's right heart failure.
- Death due to pneumonia was reported in 1 patient during mean follow-up of 2.2 years.

Occurrence of adverse events during treatment sessions (session-based analysis)

Adverse event	Incidence % (n/N)
Pulmonary artery perforation	1.9 (5/255)
Reperfusion pulmonary injury	
Haemosputum	15.7 (40/255)
Confirmed by chest X-ray or desaturation	14.1 (36/255)
Identified by chest CT	56.9 (145/255)

Abbreviations used: BPA, balloon pulmonary angioplasty; CT, computed tomography; PEA, pulmonary endarterectomy; SD, standard deviation; WHO, World Health Organization

Study 3 Kimura M (2015)

Details

Study type	**Case series**
Country	Japan
Recruitment period	2012 to 2014
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**46**
Age and sex	Mean age, 63 years; sex, 70% (32/46) female
Patient selection criteria	Inclusion criteria: not reported Exclusion criteria: not reported
Technique	Authors state that BPA was done in staged pleural sessions at intervals of 1 to 2 weeks. All patients had right-sided heart catheterisation just before the first treatment session and within 2 weeks after the final session.
Follow-up	**Mean of 5.5 months after last BPA session**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: No patients were lost to follow-up.

Study design issues: Authors stated that the aim of the study was to 'investigate the influence of BPA on renal function in patients with chronic thromboembolic pulmonary hypertension'.

Study population issues: The proportion of patients with NYHA class III or IV heart failure was 84.8% (39/46). Four patients previously had PEA. The mean number of target vessels per patient was 13.5±2.3. A mean of 6.1±2.2 BPA treatments were done in each patient.

Other issues: None identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **46**

Haemodynamic and biomarker measurements for all patients

	Mean±SD		
Outcome measure	Baseline	Follow-up	p value
Mean pulmonary arterial pressure (mmHg)	38.6±10.1	18.6±3.6	<0.001
Right atrial pressure (mmHg)	6.3±3.2	1.8±1.7	<0.001
Cardiac output (litre/min)	3.5±1.0	3.7±0.8	0.257
Pulmonary capillary wedge pressure (mmHg)	8.8±3.2	6.7±3.3	0.001
Pulmonary vascular resistance (dyn·S/cm^5)	765.6±446.1	257.4±91.3	<0.001
Mixed venous oxygen saturation (%)	64.2±8.3	69.3±4.3	0.001
B-type natriuretic peptide (pg/ml)	184.8±340.7	30.5±32.0	<0.001
Creatinine (mg/dL)	0.86±0.26	0.83±0.25	0.073
Estimated glomerular filtration rate (ml/min/1.73m^2)	61.4±18.1	63.7±17.5	0.114

Haemodynamic and biomarker measurements for patients with impaired estimated glomerular filtration rates (defined as lower than the sample median of 57 ml/min/1.73m^2): n=23

	Mean±SD		
Outcome measure	Baseline	Follow-up	p value
Right atrial pressure (mmHg)	7.0±3.7	2.0±1.7	<0.001
Pulmonary arterial pressure (mmHg)	40.4±11.9	19.2±3.5	<0.001
Cardiac output (litre/min)	3.3±1.2	3.6±0.9	0.134
Pulmonary capillary wedge pressure (mmHg)	8.3±3.8	6.7±2.9	0.093
Pulmonary vascular resistance (dyn·S/cm^5)	904.8±541.8	277.0±88.7	<0.001
Mixed venous oxygen saturation (%)	61.4±9.3	69.2±4.4	0.001
B-type natriuretic peptide (pg/ml)	295.1±436.6	40.1±41.7	<0.001
Creatinine (mg/dL)	1.00±0.26	0.94±0.27	0.058
Estimated glomerular filtration rate (ml/min/1.73m^2)	47.0±6.5	51.5±9.6	0.018

Safety

The study did not actively assess the occurrence of adverse events.

Abbreviations used: SD, standard deviation

Study 4 Feinstein JA (2001)

Details

Study type	**Case series**
Country	USA
Recruitment period	1994 to 1999
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**18**
Age and sex	Mean age, 52 years; sex, not reported
Patient selection criteria	Inclusion criteria: patients with chronic thromboembolic pulmonary hypertension, characterised by the presence of a mean pulmonary arterial pressure greater than 30 mmHg and angiographic demonstration of multiple bilateral pulmonary artery obstructions associated with vascular cut-offs and webs were included. Included patients had distal branch pulmonary obstructions with either surgically inaccessible lesions (obstructions beginning primarily in the third-order branches after the main pulmonary artery) or the presence of severe concomitant medical morbidity that precluded surgery.
Technique	BPA was done via conventional right heart catheterisation. Pulmonary artery segments were sequentially dilated in an order chosen to maximally-restore balance in pulmonary blood flow. Lower lobe vessels were preferentially dilated. Balloons sized between 3 mm and 6 mm were inflated to between 75% and 100% of the vessel diameter. Balloons were inflated until the fluoroscopic waist disappeared or until the balloon was fully expanded. Repeat dilation was done if there was less than a 50% increase in angiographic vessel size. Additional pulmonary artery segments were dilated in up to 3 lobes. Authors state that repeat catheterisation at an interval of 6–12 weeks after BPA was recommended for all patients with a resultant mean pulmonary arterial pressure greater than 30 mmHg and residual lesions that were thought to be amenable to BPA.
Follow-up	**Mean of 3 years after last BPA session**
Conflict of interest/source of funding	No conflicts of interest were reported

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: The small sample size may result in low statistical power, leading to overestimates of the treatment effect.

Study population issues: Distal surgically inaccessible lesions were present in 88.9% (16/18) of patients. The remaining patients had proximal disease with severe concomitant medical illness: one patient was morbidly obese whereas the other patient had severe coronary artery disease and chronic obstructive pulmonary disease. The median number of BPA treatments per patient was 3. The mean number of dilated vessels per BPA treatment was 2.3.

Other issues: None identified

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **18** • The survival rate was 88.9% (16/18) at mean follow-up of 34 months. • The average mean pulmonary arterial pressure decreased from 42 mmHg to 33 mmHg at mean follow-up of 3 years (p=0.002). • The mean cardiac index changed from 2.0 litre/min/m^2 to 2.1 litre/min/m^2 at mean follow-up of 3 years (not significant). • The mean right ventricular pressure decreased from 74 mmHg to 58 mmHg at mean follow-up of 3 years (p=0.004). • The mean ratio of right ventricular pressure divided by systemic pressure decreased from 0.64% to 0.48% at mean follow-up of 3 years (p=0.007). • The mean total pulmonary resistance decreased from 22 WU/m^2 to 17 WU/m^2 at mean follow-up of 3 years (no p value reported). • The mean NYHA class improved from 3.3 to 1.8 at mean follow-up of 3 years (p<0.001) • 6-minute walking test distances increased from 209 yards to 497 yards at mean follow-up of 3 years (p<0.0001).	• Death due to right ventricular failure was reported in 1 patient 7 days after treatment. The patient developed segmental pulmonary oedema in all dilated areas and was having mechanical ventilation. • Death due to recurrent aspiration pneumonia was reported in 1 patient 16 months after their first BPA session. • Perforation of the pulmonary artery in the right lower lobe was reported in 1 patient. This was treated by coil occlusion of the vessel. • Femoral artery pseudoaneurysm was reported in 16.7% (3/18) of patients: these were obese patients who needed femoral arterial access for monitoring during BPA. All were successfully treated by surgical repair or mechanical compression. • Reperfusion pulmonary oedema was reported in 61.1% (11/18) of patients: 4 cases were identified at the time of catheterisation and 7 were identified up to 48 hours after having treatment. All cases were managed with diuretics and oxygen and 3 needed additional mechanical ventilation.
Abbreviation: BPA, balloon pulmonary angioplasty; NYHA, New York Heart Association;	

Study 5 Andreassen AK (2013)

Details

Study type	**Case series**
Country	Norway
Recruitment period	2003 to 2011
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**20**
Age and sex	Mean age, 60 years; sex, 50% (10/20) female
Patient selection criteria	Inclusion criteria: patients between 18 and 75 years who were diagnosed with chronic thromboembolic pulmonary hypertension (confirmed by radiological detection of vascular obstructions) were included. All participants had a mean pulmonary arterial pressure greater than 25 mmHg and a pulmonary capillary wedge pressure less than 12 mmHg. Exclusion criteria: not reported
Technique	The pulmonary artery was accessed via the right femoral vein. Selective catheterisation was done to demonstrate stenosis, occlusions, and reduction of parenchymal opacification after injection of vascular contrast medium. Coronary monorail balloon catheters (1.25–4 mm) and renal monorail catheters (5–7 mm) were positioned over the selected lesion and inflated with a mixture of saline and contrast medium to pressures of 1 to 10 atmospheres for 5–30 seconds. Each BPA procedure was confined to 3 lung segments. Further treatments were done after 6–8 weeks.
Follow-up	**3 months after last BPA session**
Conflict of interest/source of funding	No conflicts of interest were reported

Analysis

Follow-up issues: 2 patients died within 9 days of their first BPA treatment and were excluded from the analysis of efficacy.

Study design issues: The small sample size may result in low statistical power, leading to overestimates of the treatment effect.

Study population issues: Distal pulmonary artery obstructions that were considered surgically inaccessible were found in 80% (16/20) of patients. Thromboembolic risk factors were present in 4 patients: 2 had lupus anticoagulant antibodies, 1 had polycythaemia vera and 1 had protein C and S deficiency. The mean number of BPA treatments per patient was 3.7. The mean number of dilated vessels per patient was 18.6.

Other issues: The cardiopulmonary cardiac test was carried out on an upright electrical braked bicycle ergometer. The initial power was set at 20 watts and the workload was ramped up to 10 w/min. Patients were encouraged to exercise for as long as possible while maintaining 60 revolutions per second on the bike.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **18**

Haemodynamic and biomarker measurements 3 months after last BPA session (mean±SD unless otherwise stated)

Outcome	Baseline	3 months	p value
Mean pulmonary arterial pressure (mmHg)	45±11	33±10	<0.001
Right atrial pressure (mmHg)	6±3	4±3	0.062
Cardiac output (litre/min)	4.9±1.6	5.4±1.9	0.011
Cardiac index (litre/min/m^2)	2.3±1.6	2.8±1.9	0.005
Resting heartrate (beats/min)	77±12	71±12	0.017
Stroke volume (ml)	66±27	77±28	<0.001
Pulmonary capillary wedge pressure	7±3	6±3	0.156
Pulmonary vascular resistance (mmHg/litre/min)	8.8±4.0	5.9±3.6	<0.001
Systemic blood pressure	89±13	85±15	0.463
Oxygen saturation	90±5	93±4	0.004
Mixed venous oxygen saturation	63±6	68±6	<0.001
B-type natriuretic peptide (pmol/L)	194±182	90±119	0.007
Troponin T positive (% [n/N])	60 [12/20]	15 [3/20]	0.001

[a] Proportion of patients who were Troponin T positive

Cardiopulmonary exercise testing 3 months after last BPA sessions (mean±SD)

Outcome	Baseline	3 months	p value
Peak oxygen consumption (ml/Kg/min)	13.6±5.6	17.0±6.5	<0.001
Peak watts	86±54	111±66	0.001
- Peak watts (% of predicted)	53±25	76±31	<0.001
Exercise duration (min)	6.5±3.2	9.2±3.3	0.017
Peak heartrate (beats/min)	133±20	148±28	0.043
- Peak heartrate (% of predicted)	83±14	91±13	0.033
Peak oxygen pulse (ml/beat)	8.8±4.6	11.2±4.8	0.004
- Peak oxygen pulse (% of predicted)	64±17	81±20	0.008
Peak systolic blood pressure (mmHg)	158±31	166±40	0.324
Peak diastolic blood pressure (mmHg)	92±14	89±13	0.571
Ventilator efficiency/carbon dioxide production	41±9	34±8	0.002
Respiratory exchange ratio	1.10±0.07	1.17±0.11	0.021

NYHA class

	% (n/N)	
NYHA class	Baseline	3 months
I	0	22 (4/18)
II	15 (3/20)	61 (11/18)
III	70 (14/20)	17 (3/18)
IV	15 (3/20)	0

Safety

- Death due to acute right ventricular failure was reported in 1 patient within 2 hours after his first BPA session.
- Death due to acute pulmonary embolism was reported in 1 patient 9 days after his first BPA session.
- Death due to chronic right heart failure was reported in 1 patient 15 months after his last BPA session.

Reperfusion pulmonary oedema was reported in 35% (7/20) of patients. All cases were treated by supplementary oxygen therapy and diuretics.

Abbreviations used: BPA, balloon pulmonary angioplasty; NYHA, New York Heart Association

Study 6 Sugimura K (2012)

Details

Study type	**Case series**
Country	2009 to 2011
Recruitment period	Japan
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**12**
Age and sex	Mean age, 58 years; sex, 92% (11/12) female
Patient selection criteria	Inclusion criteria: patients with chronic thromboembolic pulmonary hypertension who had been treated medically for 1 to 3 months were included. Exclusion criteria: not reported.
Technique	BPA was done via conventional right heart catheterisation. Pulmonary artery segments with signs of intravascular webs, filling defects or complete occlusion were selected for balloon dilation. Balloon catheters between 2 mm to 7 mm in size were used to dilate the target lesions to between 50% and 70% of the vessel diameter. Up to 2 lobes were treated during each BPA procedure. Catheterisation was repeated 4–8 weeks intervals until the mean pulmonary arterial pressure became less than 30 mmHg.
Follow-up	**Mean of 12 months after last BPA session**
Conflict of interest/source of funding	Not reported.

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: Patients who had BPA were compared against 39 historical controls who had been treated medically for a mean of 3.9 years: 59% (23/39) of whom were classified as NYHA class II. Only 33% (4/12) of BPA patients were classified as NYHA class II. The small sample size may result in low statistical power, leading to overestimates of the treatment effect.

Study population issues: Two patients previously had residual pulmonary hypertension following pulmonary endarterectomy.

Other issues: None identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **12**

Haemodynamic data (mean±SD)

	Patients treated by BPA			
Outcome measure	Baseline	After medical therapy	After BPA	Historical controls
Mean pulmonary arterial pressure (mmHg)	47.8±11.6	43.2±9.5	24.8±4.9 [ab]	43.4±11.5
Right atrial pressure (mmHg)	7.3±2.3	6±2.7	3.3±1.5 [ab]	4.8±3.6
Cardiac index (litre·ml^{-2}·m^{-2})	2.17±0.35	2.66±0.47 [a]	2.79±0.37 [ab]	2.47±0.64
Pulmonary vascular resistance (dyn·S/cm^5)	971±500	672±236 [a]	310±73 [ab]	848±393

[a] A significant difference was observed between baseline and follow-up measurements (p values<0.05)

[b] A significant difference was observed between measurements taken after medical therapy and measurements taken after BPA

NYHA class: % (n/N)

	Patients treated by BPA			
NYHA class	Baseline	After medical therapy	After BPA	Historical controls
II	33 (4/12)	50 (6/12)	100 (12/12)	59 (23/39)
III	42 (5/12)	42 (5/12)	0	31 (12/39)
IV	25 (3/12)	8 (1/12)	0	10 (4/39)

6-minute walking test distances

- Mean 6-minute walking test distances increased from 288 m to 350 m after medical therapy (not significant). Following BPA, mean 6-minute walking test distances increased to 441 m (p value vs baseline<0.05).

B-type natriuretic peptide

- Mean B-type natriuretic peptide levels improved from 335 pg/ml to 78 pg/ml after medical therapy (p<0.05). Following BPA, mean B-type natriuretic peptide levels improved to 16 pg/m (p value vs baseline<0.05)

Safety

- Mild to moderate haemoptysis was reported in 50% (6/12) of patients.

Abbreviations used: BPA, balloon pulmonary angioplasty; NYHA, New York Heart Association; SD, standard deviation

Study 7 Shimura N (2015)

Details

Study type	**Case series**
Country	Japan
Recruitment period	2009 to 2011
Study population and number	Patients who had residual pulmonary hypertension following PEA n=**9**
Age and sex	Mean age, 55.1 years; sex, 78% (7/9) female
Patient selection criteria	Inclusion criteria: patients with chronic thromboembolic hypertension who had residual pulmonary hypertension (pulmonary arterial pressure ≥25 mmHg and pulmonary vascular resistance ≥3.75 mmHg/litre/min) following 3 months after PEA, were included. Exclusion criteria: not reported
Technique	The pulmonary artery was accessed via the right jugular vein because the majority of patients had an anti-embolic filter in their inferior vena cava. Target lesions were dilated with 1.2 to 9 mm monorail or over-the-wire catheters according to the vessel diameter. Balloons were inflated by hand for 15 to 30 seconds.
Follow-up	**Up to 12 months after last BPA session**
Conflict of interest/source of funding	No conflicts of interest were reported

Analysis

Follow-up issues: No patients were lost to follow-up

Study design issues: Study assessed the additive effect of BPA in patients who had residual pulmonary hypertension following PEA. The small sample size may result in low statistical power, leading to overestimates of the treatment effect. Authors state that the mean time from PEA to BPA was 4.1 years.

Study population issues: None identified

Other issues: None identified

Key efficacy and safety findings

Efficacy

Number of patients analysed: **9**

Haemodynamic and biomarker measurements

Outcome	Mean			
	Baseline	After PEA	Before BPA	6 to 12 months after BPA
Mean pulmonary arterial pressure (mmHg)	52	35 [b]	43 [c]	26 [d]
Systolic pulmonary arterial pressure (mmHg)	83	53 [b]	65 [c]	42 [d]
Cardiac output (litre/min)	3.3	5.2 [a]	3.9 [c]	4.2 [e]
Pulmonary vascular resistance (mmHg/litre/min)	15.6	5.6 [a]	8.1 [c]	4.2 [d]
B-type natriuretic peptide (pg/ml)	197.0	103.5 [b]	49.2 [c]	51.1 [e]

[a] Significant differences were observed between baseline measurements and measurements obtained after PEA (p values<0.05).

[b] No significant differences were observed between baseline measurements and measurements obtained after PEA (p values>0.05).

[c] No significant differences were observed between measurements obtained after PEA and measurements obtained before BPA (p values>0.05).

[d] Significant differences were observed between measurements obtained before BPA and measurements obtained after BPA (p values>0.05).

[e] No significant differences were observed between measurements obtained before BPA and measurements obtained after BPA (p values>0.05).

Safety

- Injury of a vessel accompanied by haemoptysis was reported in 1 patient. This needed a covered stent to stop the bleeding.
- Reperfusion pulmonary oedema was reported in 1 patient. Non-invasive post-pressure ventilation was needed because of hypoxia resistant to supplementary oxygen therapy.

Abbreviations used: BPA, balloon pulmonary angioplasty; PEA, pulmonary endarterectomy

Study 8 Darocha S (2014)

Details

Study type	**Case series (conference abstract)**
Country	Poland
Recruitment period	Not reported
Study population and number	Patients with chronic thromboembolic pulmonary hypertension n=**8**
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: patients for whom pulmonary endarterectomy was unsuitable due to distal localisation of thrombi Exclusion criteria: not reported
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported
Safety Outcomes	The following adverse events were reported in the 8 patients who had BPA; however, no further details were provided. • Haemoptysis was reported in 3 patients. • Dyspnoea was reported in 3 patients. • Reperfusion pulmonary injury was reported in 2 patients. • Desaturation was reported in 3 patients. • Atrial arrhythmia was reported in 1 patient. • Subcutaneous haematoma was reported in 1 patient.
Abbreviation: BPA; balloon pulmonary angioplasty	

Efficacy

Survival

In a case series of 18 patients, the survival rate was 89% (16/18) at mean follow-up of 34 months[4].

Haemodynamic changes

In a non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24), the average mean pulmonary arterial pressure decreased from 39.4 mmHg to 21.3 mmHg in the BPA group at 1-week follow-up ($p<0.001$) and from 44.4 mmHg to 21.6 mmHg in the PEA group at 2-week follow-up ($p<0.001$). In the same study, the mean right atrial pressure decreased from 5.5 mmHg to 2.6 mmHg in the BPA group at 1-week follow-up ($p=0.013$) and from 10.2 mmHg to 6.0 mmHg in the PEA group at 2-week follow-up (not significant). The mean cardiac index increased from 2.2 litre/min/m^2 to 2.7 litre/min/m^2 in the BPA group at 1-week follow-up ($p<0.001$) and from 2.1 litre/min/m^2 to 2.8 litre/min/m^2 in the PEA group at 2-week follow-up ($p=0.005$)[1].

In a case series of 68 patients, the average mean pulmonary arterial pressure decreased from 45.4 mmHg to 24.0 mmHg at mean follow-up of 2.2 years after last BPA session ($p<0.01$). In the same study, the mean right atrial pressure decreased from 8.1 mmHg to 1.9 mmHg at mean follow-up of 2.2 years ($p<0.01$) after last BPA session. The mean cardiac index increased from 2.2 litre/min/m^2 to 3.2 litre/min/m^2 at mean follow-up of 2.2 years after last BPA session (<0.01)[2].

In a case series of 18 patients, the average mean pulmonary arterial pressure decreased from 42 mmHg to 33 mmHg at mean follow-up of 3 years after last BPA session ($p=0.002$). In the same study, the mean cardiac index changed from 2.0 litre/min/m^2 to 2.1 litre/min/m^2 at mean follow-up of 3 years after last BPA session (not significant)[4].

Changes in biomarkers

In the non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24), mean B-type natriuretic peptide levels decreased from 210 pg/ml to 41 pg/ml in the BPA group ($p=0.01$) and 263 pg/ml to 74 pg/ml in the PEA group ($p=0.022$). The follow-up period was not reported[1].

In the case series of 68 patients, mean B-type natriuretic peptide levels decreased from 330 pg/ml to 35 pg/ml at mean follow-up of 2.2 years after last BPA session ($p<0.01$)[2].

In a case series of 20 patients, the proportion of patients who were Troponin T-positive decreased from 60% (12/20) to 15% (3/20), 3 months after last BPA session ($p=0.001$)[5].

Functional activity

In the case series of 18 patients, the mean NYHA class (classes ranged from I to IV: I indicating no limitation of physical activity due to heart failure and IV indicating severe limitation of physical activity due to heart failure) improved from 3.3 to 1.8 at mean follow-up of 3 years after last BPA session ($p<0.001$)[4].

In the case series of 68 patients, all patients were categorised as having World Health Organization (WHO) Class III or IV pulmonary hypertension (marked or severe limitation of physical activity due to pulmonary hypertension). At mean follow-up of 2.2 years after last BPA session, 95.5% (64/67) of patients were categorised as having WHO functional class I or II pulmonary hypertension (no or slight limitation of physical activity due to pulmonary hypertension) and 4.5% (3/67) of patients were categorised as having WHO functional class III pulmonary hypertension[2].

Exercise tolerance

In the non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24), the mean 6-minute walking test distance increased from 295 m to 397 m in the BPA group ($p<0.001$). The follow-up period was not reported. No results were reported for the PEA group[1].

In the case series of 18 patients the mean 6-minute walking test distance increased from 191 m to 454 m at mean follow-up of 3 years after last BPA session ($p<0.0001$)[4].

In a case series of 20 patients, the mean time that patients were able to carry out cardiopulmonary exercise tests increased from 6.5 minutes to 9.2 minutes, 3 months after last BPA session ($p=0.017$). The mean total workload (peak watts) reached during cardiopulmonary exercise testing increased from 86 watts to 111 watts, 3 months after last BPA session ($p=0.001$). The mean peak oxygen consumption during cardiopulmonary exercise testing increased from 13.6 ml/Kg/ml to 17.0 ml/Kg/ml, 3 months after last BPA session [5].

Use of oral medication

In the case series of 68 patients, the proportion of patients who used endothelin receptor agonists decreased from 52% (35/68) to 37% (25/67) at mean follow-up of 2.2 years after last BPA session. In the same study, the proportion of patients who used phosphodiesterase-5 inhibitors decreased from 40% (27/68) to 28% (19/67) at mean follow-up of 2.2 years after last BPA session[2].

Safety

Death

In-hospital death, due to infection, was reported in 1 patient in the BPA group in a non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24). Authors state that the infection was caused by a central

venous catheter used for administering epoprostenol. In the same study, perioperative death was reported in 2 patients in the PEA group within 16 days of having surgery. Both patients had severe pulmonary hypertension and low cardiac output which needed constant cardiopulmonary support[1].

Death due to right heart failure was reported in 1 patient, 28 days after their third BPA session, in a case series of 68 patients. A severe pulmonary injury occurred during the BPA session and exacerbated the patient's right heart failure[2].

Death due to right ventricular failure was reported in 1 patient, 7 days after BPA, in a case series of 18 patients. The patient initially developed segmental pulmonary oedema in all dilated areas and was having mechanical ventilation. In the same study, death due to recurrent aspiration pneumonia was reported in 1 patient, 16 months after their first BPA session[4].

Death due to acute right ventricular failure was reported in 1 patient, within 2 hours of his first BPA session, in a case series of 20 patients. In the same study, death due to acute pulmonary embolism was reported in 1 patient 9 days after his first BPA session. Death due to chronic right heart failure was reported in 1 patient 15 months after his last BPA session[5].

Vessel perforation

Wire perforation (blood vessels not specified) was reported after 5% (4/86) of BPAs and no PEAs in the non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24)[1].

Pulmonary artery perforation was reported after 1.9% (5/255) of BPAs in a case series of 68 patients[2].

Perforation of the pulmonary artery in the right lower lobe was reported in 1 patient in the case series of 18 patients. This was treated by coil occlusion[4].

Pseudoaneurysm

Femoral artery pseudoaneurysm was reported in 16.7% (3/18) of patients in the case series of 18 patients; these were obese patients who needed femoral arterial access for monitoring during BPA. All were successfully treated by surgical repair or mechanical compression[4].

Reperfusion pulmonary oedema

Reperfusion pulmonary oedema was reported in 61% (11/18) of patients in the case series of 18 patients: 4 cases were identified at the time of catheterisation and 7 were identified up to 48 hours after having treatment. All cases were managed with diuretics and oxygen and 3 needed additional mechanical ventilation[4].

Reperfusion pulmonary oedema was reported in 35% (7/20) of patients in the case series of 20 patients. All cases were treated by supplementary oxygen therapy and diuretics[5].

Haemoptysis

Severe haemoptysis was reported after 4% (3/86) of BPAs and 13% (3/24) of PEAs in the non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24)[1].

Mild to moderate haemoptysis was reported in 50% (6/12) of patients in a case series of 12 patients[6].

Other adverse events

Haemosputum or desaturation was reported after 28% (24/86) of BPAs and 13% (3/24) of PEAs in the non-randomised retrospective comparative study of 53 patients treated by BPA (n=29) or PEA (n=24)[1].

In a case series of 8 patients, dyspnoea and desaturation were each reported in 3 patients. In the same study, atrial arrhythmia and subcutaneous haematoma were each reported in 1 patient[8].

Validity and generalisability of the studies

- Only 1 non-randomised comparative study was identified that compared BPA against PEA. In this study, BPA was done in patients for whom PEA was not suitable[1].
- The longest follow-up period reported was a mean of 3 years after the last BPA session[3].
- None of the identified studies used subjective outcome measures to evaluate the impact of BPA on patients' quality of life.
- In the studies identified, BPA was usually repeated after 2 to 12 weeks until desired haemodynamic measurements were attained.
- Only 1 case series included more than 20 patients[2].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Ultrasound-enhanced catheter-directed thrombolysis for pulmonary embolism. NICE interventional procedure guidance 524 (2015). Available from: https://www.nice.org.uk/guidance/ipg524
- Telemetric adjustable pulmonary artery banding for pulmonary hypertension in infants with congenital heart defects. NICE interventional procedure guidance 505 (2014). Available from: http://www.nice.org.uk/guidance/ipg505

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Six Specialist Advisor questionnaires for Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing trials:

NCT02429284: U.S. CTEPH Registry; Study type, Disease registry; location, United States; estimated enrolment, 750; start date, April 2015; estimated completion date, April 2020

References

1. Taniguchi Y, Miyagawa K, Nakayama K et al. (2014) Balloon pulmonary angioplasty: an additional treatment option to improve the prognosis of patients with chronic thromboembolic pulmonary hypertension. EuroIntervention 10(4):518-25. doi: 10.4244/EIJV10I4A89.
2. Mizoguchi H, Ogawa A, Munemasa M, et al (2012) Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. 5(6):748-55. doi: 10.1161/CIRCINTERVENTIONS.112.971077.
3. Kimura M, Kataoka M, Kawakami T et al. (2015) Balloon pulmonary angioplasty using contrast agents improves impaired renal function in patients with chronic thromboembolic pulmonary hypertension. Int J Cardiol 188:41-2. doi: 10.1016/j.ijcard.2015.04.030.
4. Feinstein JA, Goldhaber SZ, Lock JE et al. (2001) Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 103(1):10-3.
5. Andreassen AK, Ragnarsson A, Gude E et al. (2013) Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Heart (19):1415-20. doi: 10.1136/heartjnl-2012-303549.
6. Sugimura K, Fukumoto Y, Satoh K et al. (2012) Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J 76(2):485-8.
7. Shimura N, Kataoka M, Inami T et al. (2015) Additional percutaneous transluminal pulmonary angioplasty for residual or recurrent pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol 183:138-42. doi: 10.1016/j.ijcard.2015.01.034.
8. Darocha S, Pedowska-Wloszek J, Kilianek L, et al. (2014) The efficacy and safety of the balloon pulmonary angioplasty (BPA) for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) - preliminary results. Proceedings of the European Society of Cardiology 2014 conference, Spain, page 917.

Appendix A: Additional papers on balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Fukui S, Ogo T, Goto Y et al (2015) Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Int J Cardiol. 180:66-8. doi: 10.1016/j.ijcard.2014.11.187.	Case series n=25 Follow-up: mean of 3.2 weeks	The mean systolic pulmonary arterial pressure decreased from 67.4 mmHg to 42.0 mmHg at mean follow-up ($p<0.001$). The mean pulmonary arterial pressure decreased from 35.8 mmHg to 23.0 mmHg ($p<0.001$). The mean right atrial pressure decreased from 3.5 mmHg to 1.3 mmHg ($p<0.001$). Significant improvements in cardiopulmonary exercise test parameters (respiratory exchange ratio, peak workload, peak oxygen consumption, exercise duration, peak heart rate, peak systolic blood pressure, peak diastolic blood pressure, oxygen pulse and recovery half-time) were reported at mean follow-up of 3.2 weeks. Mean 6-minute walking test distances improved from 405 m to 501 m at mean follow-up of 3.2 weeks	Patients were followed up for a mean of 3.2 weeks. Larger case series which reported similar outcome measures (haemodynamic and cardiopulmonary exercise test data) and followed-up patients over longer periods of time are included in table 2.
Kataoka M, Inami T, Hayashida K et al. (2012) Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 5(6):756-62. doi: 10.1161/CIRCINTERVENTIONS.112.971390.	Case series n=29 Follow-up: 6 months	The mean right atrial pressure decreased from 5.4 mmHg to 3.5 mmHg at 6 month follow-up ($p<0.05$). The average mean pulmonary arterial pressure decreased 43.3 mmHg to 30.6 mmHg at 6 month follow-up ($p<0.05$). The mean cardiac output increased by 3.8 litre/min/m^2 to 4.6 litre/min/m^2 at 6-month follow-up ($p<0.05$). Mean B-type natriuretic peptide levels decreased from 306 to 98 pg/ml at 6 months follow-up ($p<0.01$)	The majority of results were displayed graphically, which made data extraction difficult. Furthermore, larger case series which reported similar outcome measures (haemodynamic and cardiopulmonary exercise test data) are included in table 2.
Tsugu T, Murata M, Kawakami T et al. (2015) Significance of echocardiographic assessment for right	Case series n=25	The average mean pulmonary arterial pressure decreased from 38.9 mmHg to 17.6 mmHg ($p<0.001$). The average mean right atrium pressure decreased	Larger case series which reported similar outcome measures (haemodynamic and cardiopulmonary

ventricular function after balloon pulmonary angioplasty in patients with chronic thromboembolic induced pulmonary hypertension. Am J Cardiol. 115(2):256-61. doi: 10.1016/j.amjcard.2014.10.034.	Follow-up: not reported	from 5.4 mmHg to 1.6 mmHg ($p<0.001$). The mean cardiac index increased from 2.3 litre/min/m^2 to 3.2 litre/min/m^2.The mean WHO functional class decreased from 2.9 to 1.2 ($p<0.001$).	exercise test data) are included in table 2.
Fukui S, Ogo T, Morita Y et al. (2014) Right ventricular reverse remodelling after balloon pulmonary angioplasty. Eur Respir J. 43(5):1394-402. doi: 10.1183/09031936.00012914.	Case series n=20 Follow-up: mean of 4 months	The average mean pulmonary arterial pressure decreased from 39.4 mmHg to 27.3 mmHg at mean follow-up of 4 months ($p<0.001$). The mean cardiac index increased from 2.18 litre/min/m^2 to 2.38 litre/min/m^2 ($p<0.05$). The mean WHO functional class decreased from 2.8 to 2.0 ($p<0.001$). Mean 6-minute walk test distances increased from 361 metres to 463 metres ($p<0.001$)	Larger case series which reported similar outcome measures (haemodynamic and cardiopulmonary exercise test data) and followed-up patients over longer periods of time are included in table 2.
Nakamura M, Sunagawa O, Tsuchiya H et al. (2015) Rescue balloon pulmonary angioplasty under veno-arterial extracorporeal membrane oxygenation in a patient with acute exacerbation of chronic thromboembolic pulmonary hypertension. Int Heart J. 56(1):116-20. doi: 10.1536/ihj.14-257.	Case report n=1 Follow-up: 124 days	BPA was carried out in a 41 year old patient with chronic thromboembolic hypertension that failed to respond adequately to pulmonary endarterectomy, due to peripheral thrombi. Right atrial pressure decreased from 18 mmHg to 4 mmHg and mean pulmonary arterial pressure decreased from 50 mmHg to 23 mmHg 124 days after BPA.	Larger studies that reported similar outcome measures are included in table 2
Darocha S, Kurzyna M, Pietura R et al. (2013) Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension.Kardiol Pol.71(12):1331. doi: 10.5603/KP.2013.0343.	Case report n=1 Follow-up: not adequately defined	BPA was carried out in a 43 year old patient with a 2 year history of chronic thromboembolic hypertension. Mean pulmonary arterial pressure decreased from 56 to 33 mmHg. Cardiac output decreased from 6.03 to 4.88 litre/min. Pulmonary vascular resistance decreased 7.96 to 4.35 wood units. Before BPA the patient was classified as having NYHA class III heart failure. After the procedure, the patient was classified as having NYHA class II heart failure.	Larger studies that reported similar outcome measures are included in table 2
Tsuji A, Ogo T, Demachi J et al. (2014) Rescue balloon pulmonary angioplasty in a rapidly deteriorating chronic thromboembolic pulmonary hypertension patient with liver failure and refractory infection. Pulm Circ. 4(1):142-7.	Case report n=1 Follow-up: not adequately defined	BPA was carried out in a 43 year old patient with a 10 year history of chronic thromboembolic hypertension who unable to have pulmonary endarterectomy because they had a respiratory infection. The mean pulmonary arterial pressure decreased from 38 mmHg to 21 mmHg and the he cardiac index increased from 1.08	Larger studies that reported similar outcome measures are included in table 2

doi: 10.1086/675643.		litre/Min/m^2 to 2.1 litre/min/m^2, 7 days after the last BPA procedure. Repeat BPA was needed several months (not specified) later because the patient's cardiac index decreased to 1.68 litre/Min/m^2. After treatment the patient's mean pulmonary arterial pressure was 16 mmHg and their cardiac index was 2.4 litre/Min/m^2	
Pitton MB, Herber S, Mayer E et al. (2003) Pulmonary balloon angioplasty of chronic thromboembolic pulmonary hypertension (CTEPH) in surgically inaccessible cases. Rofo. 175(5):631-4.	Case reports (n=2) Follow-up: Up to 13 months	Case 1: Post-interventional haemodynamic assessments demonstrated a decrease in pulmonary vascular resistance right atrial pressure and heartrate, whereas the stroke volume index increased. At 13-month follow-up, further reductions in pulmonary vascular resistance and right atrial pressure. Furthermore, the patient's walking capacity improved from 50 to 400 metres. Case 2: Post-interventional haemodynamic assessments showed an increased cardiac index and a slightly raised pulmonary vascular resistance which was attributable to the large amount of contrast medium used. A chest X-ray done 1 day after treatment revealed a circumscribed haematoma. At 3-month follow-up, further increases in pulmonary vascular resistance and cardiac index were observed. The patient's walking capacity improved from 80 to 500 metres.	Larger studies that reported similar outcome measures are included in table 2

Appendix B: Related NICE guidance for balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

Guidance	Recommendations
Interventional procedures	**Ultrasound-enhanced catheter-directed thrombolysis for pulmonary embolism. NICE interventional procedure guidance 524 (2015).** 1.1 The evidence on ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism raises no major safety concerns over those of catheter-directed thrombolysis (CDT) alone. With regard to efficacy, evidence of any enhancement of thrombolysis over CDT alone is inadequate in quality and quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to do ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) for pulmonary embolism (PE) should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having UE-CDT for PE (see section 7.1). 1.3 NICE encourages further research into ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism. Ideally this should include comparative studies against catheter-directed thrombolysis alone. Patient selection should be documented. The dose of thrombolytic agent used and the duration of thrombolysis should be reported, together with all complications. Outcome measures should include the success of thrombolysis (complete, partial or failed) and long-term sequelae. NICE may update the guidance on publication of further evidence.

	Telemetric adjustable pulmonary artery banding for pulmonary hypertension in infants with congenital heart defects. NICE interventional procedure guidance 505 (2014). 1.1 The evidence on the efficacy of telemetric adjustable pulmonary artery banding shows that the procedure can provide adjustable reduction of pulmonary artery flow in infants with congenital heart defects, but there are uncertainties about which infants will derive benefit from the procedure. The evidence on safety is limited in quantity. Therefore the procedure should only be used with special arrangements for consent, audit or research and clinical governance. 1.2 Clinicians wishing to undertake telemetric adjustable pulmonary artery banding for pulmonary hypertension in infants with congenital heart defects should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that parents and carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Enter details about all infants undergoing telemetric adjustable pulmonary artery banding for pulmonary hypertension associated with congenital heart defects onto the UK Central Cardiac Audit Database and review clinical outcomes locally. 1.3 Patient selection for telemetric adjustable pulmonary artery banding for pulmonary hypertension in infants with congenital heart defects should only be done in paediatric cardiac centres, by a multidisciplinary team experienced in managing infants and children with congenital heart defects. 1.4 Further research should focus on the extended use of telemetric adjustable pulmonary artery banding for ventricular retraining and for its use pending the resolution of ventricular septal defects. Data collection may provide useful information. NICE may review the procedure on publication of further evidence.

Appendix C: Literature search for balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	25/06/2015	Issue 6 of 12, June 2015
Central register of controlled trials (Cochrane)	08/07/2015	Issue 6 of 12, June 2015
HTA database (Cochrane)	25/06/2015	Issue 2 of 4, April 2015
MEDLINE (Ovid)	25/06/2015	1946 to June Week 3 2015
MEDLINE In-Process (Ovid)	25/06/2015	June 24, 2015
EMBASE (Ovid)	25/06/2015	1974 to 2015 week 25
PubMed	25/06/2015	n/a
BLIC (Dialog DataStar)	25/06/2015	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	angioplasty, balloon/
2	balloon occlusion/
3	or/1-2
4	catheterization/
5	catheters/
6	or/4-5
7	3 and 6
8	(Balloon* adj4 (dilat* or cathet* or expand* or inflat* or angioplast* or pulmon* or occlusion*)).ti,ab.
9	BPA.ti,ab.
10	or/8-9
11	7 or 10
12	Thromboembolism/
13	Thrombectomy/
14	or/12-13

15	Pulmonary Embolism/ or Hypertension, Pulmonary/
16	pulmonary artery/
17	or/15-16
18	14 and 17
19	(pulmon* adj4 (narrow or block* or clog* or restrict*)).ti.
20	(pulmon* adj4 (thromb* or emboli* or hypertens*)).ti.
21	thromboemboli*.ti,ab.
22	(Chronic* adj4 (thromboemboli* or pulmon*) adj4 hypertens*).ti,ab.
23	CTEPH.ti,ab.
24	or/19-23
25	18 or 24
26	11 and 25
27	animals/ not humans/
28	26 not 27