National Institute for Health and Care Excellence

Final

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[A] Managing pulmonary hypertension and cor pulmonale

NICE guideline NG115

Evidence review

December 2018

Final

This evidence review was developed by the NICE Guideline Updates Team

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Managing pulmonary hypertension and cor pulmonale

Review question

What are the most clinically and cost-effective therapies for managing complications (pulmonary hypertension and cor pulmonale) in people with stable chronic obstructive pulmonary disease (COPD)?

Introduction

The aim of this review question was to determine the effectiveness of different approaches to managing pulmonary hypertension and cor pulmonale secondary to COPD.

Pulmonary hypertension (PH) is a common complication of COPD that is associated with a worse disease prognosis, including an increased risk of exacerbations, reduced exercise capacity and reduced survival. PH is defined as raised pressure in the arteries on the right side of the heart that take blood to the lungs. PH can occur alone or as a result of other diseases that affect the heart or lungs such as COPD. Pulmonary artery hypertension is defined in this guideline as a mean pulmonary artery pressure of 25mm Hg or more. Pulmonary hypertension is usually a marker of more severe lung disease and over time this can develop into cor pulmonale.

Cor pulmonale is impairment in the structure and function of the right side of the heart caused by a chronic lung disease with renal fluid retention due to hypoxia/hypercapnia. This typically presents with swollen ankles and lower legs.

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

Table 1 PICO table – managing pulmonary hypertension and cor pulmonale

Population	People diagnosed with COPD, and with pulmonary hypertension or cor pulmonale
Interventions	Any relevant interventions, including: • Smoking cessation • Statins or other lipid modifying drugs • Bosentan • Phosphodiesterase-5 (PD-5) inhibitors (including sildenafil) • Beta blockers • Non-invasive ventilation
Comparator	• Each other • No intervention
Outcomes	• Mortality • Hospital admissions, re-admissions and bed days • Exacerbations • Breathlessness • Orthopnoea • Ankle swelling • Arterial oxygen partial pressure • Resting oxygen saturation • Exercise capacity/exercise tolerance

	• Change in FEV1 (% predicted) • Adverse events: all, serious, treatment discontinuation • Quality of life • Resource use and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. In particular, the minimally important differences (MIDs) used in this review are summarised in Table 5 in appendix B. These were selected based on the literature with input from the committee.

Subgroup analyses specified in the review protocol were not carried out for this review because the majority of included studies did not report data for the categories of interest in an accessible format.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the 2010 NICE COPD guideline (CG101). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews of RCTs identified 3,014 references (no date limit was used as the previous guideline recommendations were not based on a systematic literature review). Additional references were added from the old guideline (13), the surveillance report (1) and from a systematic review (1, see below) to give a total of 3,029 references.

These were screened on title and abstract, with 50 papers ordered as potentially relevant systematic reviews or RCTs. RCTs were excluded if they did not meet the criteria of enrolling people with COPD and either cor pulmonale or pulmonary hypertension at baseline.

Seventeen papers were identified after full text screening: 3 systematic reviews (SRs) and 14 RCTs. Since the SRs were judged to be of low quality and partially applicable, they were only used as a source of primary references. One additional reference was identified in this manner and, as a result, 15 RCTs were included in this review.

For pulmonary hypertension there were 4 RCTs evaluating phosphodiesterase inhibitors, 4 RCTs evaluating statins, 2 RCTs evaluating nifedipine plus 1 RCT each for treatment with bosentan, losartan, nitric oxide and pentoxifylline. Only 1 RCT, using oxygen therapy, was identified for cor pulmonale.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches, which included articles up to February 2018, returned 3,100 references in total for all the questions included in the update, and these were screened on title and abstract. No additional relevant references were found for this review question.

This process of study identification is summarised in the diagram in appendix D.

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G. The references of individual included studies are given in appendix K.

Excluded studies

Details of the studies excluded at full-text review are given in appendix I.

Summary of clinical studies included in the evidence review

The included RCTs are summarised in Table 2 and Table 3.

Table 2 RCTs - pulmonary hypertension

Short Title	Interventions	Population	Outcomes
Azithromycin			
Wang (2017)	• Simvastatin: 20mg/day plus azithromycin 0.25g/day • Simvastatin: 20mg/day	• COPD diagnosis- criteria not stated • Pulmonary arterial hypertension with mean arterial pressure of not less than 25 mmHg by right cardiac catheterization at rest or no less than 30 mm Hg with activity • Sample size: 86 • Intervention: 43 Control: 43 • Mean age: years (SD) • 71.5 (8.2)	• Partial pressure of arterial oxygen (PaO_2) • 6 minute walk distance (metres)
Bosentan			
Valerio (2009)	• Bosentan: 125mg twice a day • Placebo	• COPD diagnosis - American Thoracic Society criteria and Global Initiative for Chronic Obstructive Lung Disease guidelines • Pulmonary arterial hypertension with mean pulmonary arterial pressure >25mmHg determined using right heart catheterization. Patients were monitored for a month and those with persistent pulmonary hypertension were included in the study. • Sample size:40 • Intervention: 20 Control: 20 • Mean age: years (SD) 65.5 (14.0)	• 6 minute walk distance (metres) • FEV1 (%) • Partial pressure of arterial oxygen (PaO_2) • Mean pulmonary arterial pressure (mPAP, in mmHg) • Health-related quality of life: St. George's Respiratory Questionnaire (SGRQ). • Adverse events • Exacerbations per patient • Breathlessness: MRC and WHO scales

Short Title	Interventions	Population	Outcomes
Losartan			
Morrell (2005)	• Losartan: 25mg/day for 1 week, then dose increased to 50mg/day, providing the patient's systolic blood pressure remained ≥ 100 mmHg. The dose could be down titrated once (to 25 mg) if necessary • Placebo	• COPD diagnosis- criteria not stated • Pulmonary arterial hypertension with transtricuspid pressure gradient (TTPG) ≥ 30 mmHg and sitting systolic blood pressure ≥ 100 mmHg • Sample size: 40 • Intervention: 20 Control: 20 • Mean age: years (SD) 67.0 (7.9)	• 10 m shuttle walk test • Health-related quality of life: St George's Hospital Respiratory Questionnaire) (SGRQ) and Patient Health Survey (SF-36). • Adverse events
Nifedipine			
Saadjian (1988)	• Nifedipine: 10mg/ every 8hrs (30mg/day) • No intervention- routine treatment for COPD	• COPD diagnosis- criteria not stated • Pulmonary arterial hypertension with mild PAH -mean pulmonary artery pressure >20 mmHg (control mean 29.3±2.8, intervention 31.7±2.3) determined using right heart catheterization. • Sample size: 20 • Intervention: 10 Control: 10 • Mean age: years (SD) 62.0 (2.3)	• Partial pressure of arterial oxygen (PaO_2) • Mean pulmonary arterial pressure (mPAP, in mmHg) • Adverse events • Ankle oedema
Vestri (1988)	• Nifedipine:10mg three times a day • No intervention - routine treatment for COPD	• COPD diagnosis - American Thoracic Society criteria • Pulmonary arterial hypertension > 20 mmHg at rest, (mPAP Intervention 31.3 mmHg (SD 2.2), control 29.6 mmHg (1.4)). Determined using right heart catheterization. • Sample size: 60 • Intervention: 30 Control: 30	• Partial pressure of arterial oxygen (PaO_2) • Breathlessness • Mortality • Hospitalisation (days) • Ankle oedema

Short Title	Interventions	Population	Outcomes
		• Mean age: years (SD) 63.3 (1.5)	
Nitric oxide			
Vonbank (2003)	• Oxygen and Nitric oxide Pulsed inhalation of 50ml oxygen and 20parts per million NO • Oxygen	• COPD diagnosis - American Thoracic Society criteria • Pulmonary arterial hypertension with mean pulmonary artery pressure of ≥ 25 mmHg determined using right heart catheterization • Sample size: 40 • Oxygen alone: 20 Oxygen and NO: 20 • Mean age: years (SD) 61.6 (8.2)	• Partial pressure of arterial oxygen (PaO_2) • Mean pulmonary arterial pressure (mPAP, in mmHg) • Mortality
Pentoxifylline			
Fallahi (2013)	• Pentoxifylline: 400mg three times daily or 200mg for patients also receiving Theophylline. • Placebo	• COPD diagnosis- criteria not stated • Pulmonary arterial hypertension with systolic pulmonary artery pressure >40 mmHg by echocardiography • Sample size:28 • Intervention: 15 Control: 13 • Mean age: years (SD) 65.5 (10.3)	• 6 minute walk distance (metres) • Oxygen saturation (%) • Pre- and post-test breathlessness (Borg Score)
Phosphodiesterase 5 inhibitors			
Blanco (2013)	• Sildenafil plus pulmonary rehabilitation programme: Sildenafil (20mg) three times daily plus a pulmonary rehabilitation programme starting a week later. This consisted of exercise training sessions on a cycloergometer three	• COPD diagnosis - Global Initiative for Chronic Obstructive Lung Disease guidelines • Pulmonary arterial hypertension with systolic pulmonary arterial pressure (PAP) >34 mmHg or mean PAP ≥ 25 mmHg in patients who had previously been subjected to right heart catheterisation. Determined using echocardiography. • Sample size:60 • Intervention: 29 Control: 31	• 6 minute walk distance (metres) • Cycle endurance time (seconds) • Oxygen saturation (%) • Health-related quality of life: St. George's Respiratory Questionnaire (SGRQ) and Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) • Adverse events • Exacerbations • Mortality

Short Title	Interventions	Population	Outcomes
	times a week for 12 weeks. • Placebo plus a pulmonary rehabilitation programme	• Mean age: years (SD) 65.5 (8.8)	
Goudie (2014)	• Tadalafil: 10mg/day • Placebo	• COPD diagnosis - American Thoracic Society criteria and European Respiratory Society criteria • Pulmonary arterial hypertension with >30 mmHg right ventricular systolic pressure or pulmonary acceleration time <120 ms. PAP determined using echocardiography. • Sample size: 120 • Intervention: 60 Control: 60 • Mean age: years (SD) 69.0 (7.5)	• 6 minute walk distance (metres) • FEV1 (%) • Mean pulmonary arterial pressure (mPAP, in mmHg) • Health-related quality-of-life: Minnesota Living With Heart Failure Questionnaire (MLHFQ), St George's Respiratory Questionnaire (SGRQ), Short Form 36 Health Survey (RAND version 1) (SF-36) • Adverse events
Rao (2011)	• Sildenafil: 20 mg three times a day Placebo	• COPD diagnosis - Global Initiative for Chronic Obstructive Lung Disease guidelines • Pulmonary arterial hypertension with pulmonary artery systolic pressure of >40mmHg mPAP determined using echocardiography • Sample size: 37 • Intervention: 17 Control: 20 • Mean age: years (SD) 62.3 (7.5)	• 6 minute walk distance (metres) • Mean pulmonary arterial pressure (mPAP, in mmHg)
Vitulo (2017)	• Sildenafil: 20mg three times daily	• COPD diagnosis - Global Initiative for Chronic Obstructive Lung Disease guidelines	• 6 minute walk distance (metres) • FEV1 (%) • Partial pressure of arterial oxygen (PaO_2) • Mean pulmonary arterial pressure (mPAP, in mmHg)

Short Title	Interventions	Population	Outcomes
	• Placebo	• Pulmonary arterial hypertension with mPAP ≥ 35mm Hg in the case of FEV1 < 30% of predicted value after bronchodilator, and mPAP ≥ 30 mmHg for a FEV1 > 30% of predicted value after bronchodilator. Determined using right heart catheterisation. • Sample size: 28 • Intervention: 18 Control: 10 • Mean age: years (SD) 65.6 (8.1	• Health-related quality-of-life: Medical Outcomes Study 36-item Short Form Health Survey (SF-36) • Adverse events
Statins			
Arian (2017)	• Atorvastatin: 40mg/day No intervention-routine treatment for COPD	• COPD diagnosis - American Thoracic Society criteria • Pulmonary arterial hypertension with systolic pulmonary arterial pressure of >25 mmHg by echocardiography • Sample size: 42 • Intervention: 21 Control: 21 • Mean age: years (SD) 64.7 (9.4) (for the 34 people who completed the trial)	• Mean pulmonary arterial pressure (mPAP, in mmHg)
Lee (2009)	• Pravastatin: 40mg/day • Placebo	• COPD diagnosis - American Thoracic Society criteria • Pulmonary arterial hypertension determined by routine echocardiogram- systolic pulmonary artery pressure ≥ 35 mmHg. • Sample size: 65 • Intervention: 32 Control: 33 • Mean age: years (SD) 71.5 (7.0) for the 53 people that completed the trial.	• Naughton exercise stress test • FEV1 (%) • Systolic pulmonary arterial pressure (mmHg) • Breathlessness (Borg Score)

Short Title	Interventions	Population	Outcomes
Moosavi (2013)	• Atorvastatin: 40mg/day • Placebo	• COPD diagnosis - American Thoracic Society criteria • Pulmonary arterial hypertension > 40 mmHg, method unclear • Sample size: 45 • Split between study • Intervention: 24 Control: 21 • Mean age: years (SD) 66.4 (12.4)	• 6 minute walk distance (metres) • FEV1 (%) • Systolic pulmonary arterial pressure (mmHg)

Table 3 RCTs - cor pulmonale

Short Title	Interventions	Population	Outcomes
MRC Working party (1981)	• Oxygen: For at least 15hrs a day • No intervention - routine treatment for COPD	• Chronic bronchitis or emphysema with irreversible airways obstruction • One of more episodes of heart failure with ankle oedema • Sample size: 87 • Intervention: 42 Control: 45 • Mean age: years (SD) 57.7 (no SD data provided)	• Mortality • Rate of change in FEV1 • Rate of change in PaO_2

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies and appendix G for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which all were excluded on title and abstract for this review question.

Summary of studies included in the economic evidence review

No economic evidence as identified for this review question.

Economic model

Economic modelling was not prioritised for this review question.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B.

Pulmonary hypertension

Phosphodiesterase inhibitors

- Low to moderate quality evidence from up to 3 RCTs reporting data from up to 172 people with COPD and pulmonary hypertension found improvements in pulmonary artery pressure at 12-16 weeks follow-up in people offered a phosphodiesterase 5 inhibitor compared to placebo.
- Very low to moderate quality evidence from up to 2 RCTs reporting data from up to 183 people with COPD and pulmonary hypertension could not differentiate mortality, FEV1, partial pressure of arterial oxygen, 6 minute walk test results, numbers of exacerbations, quality of life, or adverse events at 12-16 weeks follow-up between people offered a phosphodiesterase 5 inhibitor or placebo.

Statins

- Moderate to high quality evidence from up to 3 RCTs reporting data from up to 123 people with COPD and pulmonary hypertension found improvements in systolic pulmonary artery pressure, the Borg breathlessness score and treadmill test results at 6 months follow-up in people offered a statin compared to placebo.
- Low to moderate quality evidence from up to 2 RCTs containing up to 89 people with COPD and pulmonary hypertension could not differentiate FEV1 or 6 minute walk test results at 6 months follow-up between people offered a statin or placebo.

Nifedipine

- Low quality evidence from up to 2 RCTs reporting data from up to 61 people with COPD and pulmonary hypertension found improvements in the levels of breathlessness but worsening in levels of oxygen saturation at 12-18 months follow-up in people offered nifedipine compared to no intervention.

- Very low evidence from up to 2 RCTs reporting data from up to 61 people with COPD and pulmonary hypertension could not differentiate mean pulmonary artery pressure, partial pressure of arterial oxygen, mortality, hospitalisation days or rates of ankle oedema at 12-18 months follow-up between people offered nifedipine or no intervention.

Losartan

- Very low to low quality evidence from 1 RCT reporting data from up to 40 people with COPD and pulmonary hypertension could not differentiate partial pressure of arterial oxygen, mortality, the number of adverse events and adverse events leading to discontinuation of treatment, the distance covered in the shuttle walk test, breathlessness after exercise or quality of life at 48 weeks between people offered losartan compared to placebo.

Pentoxifylline

- Low to high quality evidence from 1 RCT reporting data from up to 20 people with COPD and pulmonary hypertension found there was no meaningful difference in pre-exercise Borg breathlessness scores at 12 weeks in people offered pentoxifylline compared to placebo, and could not differentiate the distance covered during the 6 minute walk test, the post-exercise Borg breathlessness score, or pre- and post-exercise oxygen saturation.

Bosentan

- Low quality evidence from 1 RCT reporting data from 32 people with COPD and pulmonary hypertension found improvements in mean pulmonary artery pressure at 18 months in people offered bosentan compared to placebo.
- Very low quality evidence from 1 RCT reporting data from 32 people with COPD and pulmonary hypertension could not differentiate FEV1, partial pressure of arterial oxygen, the distance covered during the 6 minute walk test, quality of life or the WHO breathlessness scale at 18 months between people offered bosentan or placebo.

Nitric oxide

- Moderate quality evidence from 1 RCT reporting data from 32 people with COPD and pulmonary hypertension found an improvement in mean pulmonary artery pressure at 6 months follow-up in people offered oxygen and nitric oxide compared to oxygen alone.
- Very low to low quality evidence from 1 RCT reporting data from up to 40 people with COPD and pulmonary hypertension could not differentiate partial pressure of arterial oxygen or mortality at 6 months follow-up between people offered oxygen and nitric oxide or oxygen alone.

Azithromycin

- Low quality evidence from 1 RCT reporting data from 86 people with COPD and pulmonary hypertension found improvements in partial pressure of arterial oxygen and in the distance covered during the 6 minute walk test at 6 months follow-up in people offered azithromycin and simvastatin compared to simvastatin alone.

Cor pulmonale

Long term oxygen therapy

- Low quality evidence from 1 RCT reporting data from 59 people with COPD and cor pulmonale found improvements in partial pressure of arterial oxygen at 3 years follow-up in people offered long term oxygen therapy compared to no oxygen.
- Very low quality evidence from 1 RCT reporting data from up to 87 people with COPD and cor pulmonale could not differentiate FEV1 or mortality at 3 years follow-up between people offered long term oxygen therapy to no oxygen.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Improvements in quality of life or functional outcomes such as the 6 minute walk test were prioritised during discussions as these were agreed to be important outcomes for people with COPD. The committee noted that although most included studies measured pulmonary haemodynamic outcomes such as systolic pulmonary artery pressure (systolic PAP), mean pulmonary artery pressure (mPAP) and oxygen saturation, these outcomes were not likely to be important to people with COPD in the absence of functional improvements. The committee agreed however that it was still important to report these haemodynamic outcomes, since if a significant difference in quality of life or functional ability were found with a treatment, these outcomes could help to determine the mechanism behind that improvement, which could have implications for practice.

The committee agreed with the minimally important differences (MIDs) for the St. George Respiratory Questionnaire quality of life outcome measure and 6 minute walk distance used by Blanco (2013) and noted that in the case of mortality any statistically significant change in effect (i.e. where the 95% CI does not cross 1) would be important.

The quality of the evidence

The committee agreed that certain studies were at high risk of bias due to a lack of blinding of participants and/or investigators, and that this was particularly pronounced in the studies that involved an intervention versus usual care instead of a placebo (both nifedipine trials and Arian (2017)). In other cases (Rao 2011, Valerio 2009, Vestri 1988) there was a high or unclear risk of bias due to the potential for selective reporting. This was due to the omission of outcomes that were mentioned in the methods section or the limited number of outcomes presented.

The committee noted that there was an issue with selective reporting bias due to missing data of several types. In some of the included trials this consisted of missing outcomes or participants. In the case of Blanco (2013) it was not possible to include a large part of the data in the meta-analysis as it was presented as medians rather than means and standard deviations. In addition, Chogtu (2016) was excluded at the data extraction stage due to the inadequate presentation of processed results - the results presented implied implausible standard errors and it was not possible to check these due to the absence of raw data. Finally, several potentially relevant RCTs identified by Chen (2015) were excluded as they were not available in English.

The committee noted that the overall quality of evidence was poor in some cases due to inconsistencies between results from different trials looking at similar outcomes

(e.g. treadmill test versus 6 minute walk distance for the trials looking at statins). The committee noted the small sample sizes used in the included trials, and the resulting small evidence base, reduced confidence in the effect sizes as they were associated with large confidence intervals. It discussed the large trials available for statins for other diseases and noted the small evidence base for statins for pulmonary hypertension secondary to COPD.

The committee noted that the measurement of PAP was less accurate if it was determined indirectly using an echocardiogram rather than by right heart catheterisation. It decided that this issue was sufficient to warrant downgrading of this outcome for imprecision in the case of a single study using this intervention, or where more than one third of a meta-analysis used this method to determine PAP. The committee also commented that the differences in PAP as identified by echocardiogram in many of these trials are within the boundary of error for this test (about 5 mmHg) and so these results may be statistically significant but are not necessarily clinically meaningful.

Benefits and harms

The committee agreed not to recommend losartan and pentoxifylline for pulmonary hypertension (PH) secondary to COPD based on the lack of evidence of a significant positive effect from these treatments.

The committee noted that although treatment with nitric oxide, bosentan and phosphodiesterase 5 inhibitors improved pulmonary artery pressure, this was not associated with an improvement in any of the functional outcomes that were important to people with COPD, and thus improvement in this outcome alone was insufficient for them to recommend use of these interventions for people with pulmonary hypertension secondary to COPD.

The committee noted that pravastatin improved the relevant patient outcomes of breathlessness and treadmill walking time/heart rate. However, a trial of atorvastatin found no effect on the 6 minute walking test distance. The committee agreed that this was the more usual test for exercise tolerance and commented that the increase in treadmill walk time of 370 seconds in Lee (2009) seemed particularly high based on their experiences of these tests. They commented that it was mechanistically implausible that statins would have such a large impact. They also agreed it was appropriate to treat statins as a class, both based on the evidence from other indications and from the lack of heterogeneity detected in the evidence between pravastatin and atorvastatin.

The committee noted that although nifedipine improved levels of breathlessness, there was no effect on other patient relevant outcome such as mortality, hospitalisation days or rates of ankle oedema, and the evidence was of low to very low quality. Due to the conflicting evidence and the resulting level of uncertainty surrounding the benefits of statins and nifedipine, the committee agreed the evidence base was not strong enough to recommend these interventions. The committee agreed that it was also appropriate to consider the evidence presented in Wang (2017) within the prophylactic antibiotic review question of the 2018 guideline update, as the intervention in this paper was an antibiotic, azithromycin.

The committee agreed that there was insufficient high-quality evidence to allow them to recommend any of the above treatments for use in people with PH secondary to COPD. The committee noted that although there were no specific harms from treatment identified in the trials, all of these drugs would be associated with a risk of adverse events and there would therefore need to be clear evidence to justify their use.

The committee were concerned that recommending that treatments are not offered would disincentivise research in this area. In particular, they noted that the existing small scale trials do not rule out the possibility of positive effects from these interventions. They chose to make a recommendation that the treatments should only be used in the context of an RCT to highlight the need for larger, well-designed trials using these drugs and other possibly beneficial interventions. The committee also made a research recommendation to reflect this lack of evidence, but agreed that none of the treatments were sufficiently promising to be prioritised for further research over the others.

The committee noted that people may have been prescribed these treatments for other indications or for PH prior to COPD diagnosis, and these people should remain on their current medication unless otherwise indicated. The committee were careful to word the recommendation to only apply to people with pulmonary hypertension caused by COPD to reflect this.

The committee agreed there was no robust evidence that long-term oxygen therapy leads to survival gains in people with COPD and cor pulmonale. They noted that it was now considerably less common for people to first present with COPD and cor pulmonale, and therefore people with COPD would usually have already been identified as having chronic hypoxaemia and have been started on long-term oxygen therapy before cor pulmonale is identified. However, if a person did present for the first time with COPD and cor pulmonale the focus of treatment would be optimal treatment for their underlying COPD.

The committee also agreed that people with cor pulmonale who would benefit from long term oxygen were likely to meet the other criteria for considering long term oxygen given in the guideline. Therefore, in the absence of any strong evidence that these people should be treated differently, they agreed it was appropriate that people with COPD and cor pulmonale should be offered optimal treatment for their COPD (following the other recommendations in this guideline), and this may involve long-term oxygen therapy if they meet the standard criteria for people with COPD. The committee included a reference to the relevant section of the long- term oxygen recommendations to make this clear.

The 2010 guideline contained a list of interventions that were not recommended for the management of cor pulmonale (angiotensin-converting enzyme inhibitors, calcium channel blockers, alpha-blockers and digoxin). In the absence of any new evidence suggesting these interventions are effective, the committee agreed it was appropriate to keep this recommendation.

Cost effectiveness and resource use

No economic evidence was identified for this review question and economic modelling was not prioritised. The committee agreed that in the absence of any robust clinical evidence the interventions were clinically effective, it was not possible to justify the opportunity costs that would result from the NHS investing in prescribing them.

Other factors the committee took into account

The committee noted that it would have been useful to assess the benefits of these interventions for pulmonary hypertension secondary to COPD in patients who were former versus current smokers, but there was insufficient evidence to allow this analysis to be conducted.

Appendix A – Review protocols

Review protocol for managing pulmonary hypertension and cor pulmonale

Field (based on PRISMA-P)	Content
Review question	What are the most clinically and cost-effective therapies for managing complications (pulmonary hypertension and cor pulmonale) in people with stable COPD?
Type of review question	Intervention
Objective of the review	To determine the effectiveness of approaches to managing pulmonary hypertension and cor pulmonale in people with COPD
Eligibility criteria – population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria) and with pulmonary hypertension (mean pulmonary artery pressure of ≥25 mm Hg) or cor pulmonale.
Eligibility criteria – interventions	Any relevant interventions, including: • Any relevant interventions, including: • Smoking cessation (stratification of analysis by intensity of smoking cessation support) • Statins or other lipid modifying • Bosentan • Phosphodiesterase-5 (PD-5) inhibitors (including sildenafil) • Beta blockers • Non-invasive ventilation
Eligibility criteria – comparators	• Each other • No intervention (placebo, usual care, no treatment)
Outcomes	• Mortality • Hospital admissions, re-admissions and bed days • Exacerbations

	• Symptoms including breathlessness (e.g. Borg dyspnoea score, Modified MRC scale for dyspnoea) orthopnoea and ankle swelling • Arterial oxygen partial pressure (PaO2) • Resting oxygen saturation (SaO2) • Exercise capacity/ exercise tolerance (e.g. 6 minute walking distance, 6MWD, treadmill test and the shuttle walk test) • Change in FEV1, rate of change in FEV1 • Adverse events: all, severe, treatment discontinuation • Quality of life (e.g. St. George's respiratory questionnaire, SGRQ, overall score) • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other exclusion criteria	• Trials of less than 12 weeks duration (to ensure trials looking at acute effects (e.g. on exercise) are excluded and confine search to trials looking at longer term effects of interventions, as recommended by the committee.) • Non-English language publications
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Trials that recruited patients with at least one COPD exacerbation in the 12 months before study entry • Heart disease • Heart failure • Obesity • Sleep apnoea • Multimorbidities (including COPD with asthma, bronchopulmonary dysplasia, bronchiectasis, anxiety or depression) Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent

	reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C Main Searches: • Cochrane Database of Systematic Reviews – CDSR (Wiley) • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley) • Database of Abstracts of Reviews of Effects – DARE (Wiley) • Health Technology Assessment Database – HTA (Wiley) • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) • PubMed The search will not be date limited as the 2004 recommendations were not based on a systematic literature search. Economics: • NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid)

	The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017.
Identify if an update	Update of 2004 COPD guideline question: In patients with stable COPD what therapies can be used to manage pulmonary hypertension? The guideline also contains recommendations on the management of cor pulmonale, but it is not clear which specific review question these link to.
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables)
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by

	the NICE Guideline Updates Team and chaired by Damien Longson (until September 2017) and Andrew Molyneux (from September 2017) in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process, they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 4. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 4 Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 5. For other mean differences where no MID is given below the line of no effect is used.

Table 5 Identified MIDs

Outcome	MID	Source
Borg breathlessness score	2 units	Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg

Outcome	MID	Source
	(-2, +2)	Scale, and Visual Analog Scale. J COPD 2005; 2: 105–110.
6 minute walk distance	26m (-26, +26)	Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J (2011); 37: 784–790.
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. For other relative risks, where no MID was specified, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 6.

Table 6 Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.

GRADE criteria	Reasons for downgrading quality
	Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (one corresponding to meaningful benefit; one corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one MID, and twice if it crossed both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following five conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence sta tements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- We state the evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology ‘up to’ in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement.

Deviations from review protocol

Two additional measures, not specified in the original protocol, were included in the outcomes analysed in this question, as they were agreed to be specific measures of the level of pulmonary hypertension (systolic pulmonary arterial pressure and mean pulmonary arterial pressure). These outcomes were downgraded for imprecision if they were obtained using echocardiography instead of right heart catheterisation, due to the high margins of error in this measurement approach. Downgrading was carried out in the case of a single study or where more than one third of the weight in a meta-analysis used this method to determine pulmonary artery pressure, PAP.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 7.

Table 7 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 8.

Table 8 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Main searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PubMed

Identification of evidence

The population terms have been updated from the original guideline to include potential co-morbidities such as asthma, bronchopulmonary dysplasia and bronchiectasis. These were excluded in the original strategy.

In this update, several lines of the strategy have been focused with the use of the term 'chronic' to reduce retrieval of articles focusing on acute signs or symptoms.

Additional acronyms for COPD have been included and on recommendation from the guideline committee, terms around 'breathlessness' have been added.

Searches were re-run in February 2018 and also included searching Medline epub ahead of print.

Review question search strategy

- What are the most clinically and cost-effective therapies for managing complications (pulmonary hypertension and cor pulmonale) in people with stable COPD?

The MEDLINE search strategy is presented below in Table 9. This was translated for use in all of the other databases.

Table 9 Search strategy

Medline Strategy, searched 28th April 2017 **Database: Ovid MEDLINE(R) 1946 to April Week 3 2017** **Search Strategy:**
1 lung diseases, obstructive/
2 exp pulmonary disease, chronic obstructive/
3 (copd or coad or cobd or aecb).tw.
4 emphysema*.tw.
5 (chronic* adj4 bronch*).tw.
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.

Medline Strategy, searched 28th April 2017 Database: Ovid MEDLINE(R) 1946 to April Week 3 2017 Search Strategy:
7 (pulmonum adj4 (volumen or pneumatosis)).tw.
8 pneumonectasia.tw.
9 *Dyspnea/
10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12 or/1-11
13 exp Hypertension, Pulmonary/
14 ((pulmonary or lung) adj4 hypertensi*).tw.
15 Pulmonary Heart Disease/
16 (cor adj4 pulmonale).tw.
17 corpulmonale.tw.
18 (pulmonary adj4 (cardiac or heart) adj4 (disease* or disorder*)).tw.
19 (chronic* adj3 (anoxemia or anoxia or hypoxi* or hypoxemi*)).tw.
20 (chronic* adj3 oxygen adj3 deficienc*).tw.
21 or/13-20
22 12 and 21
23 animals/ not humans/
24 22 not 23
25 limit 24 to english language
26 limit 25 to (letter or historical article or comment or editorial or news or case reports)
27 25 not 26

Note: In-house RCT and systematic review filters were appended

Study design filters and limits

The MEDLINE systematic review (SR) and Randomized Controlled Trial (RCT) filters were appended to the review question above and are presented below in Table 10. They were translated for use in the MEDLINE In-Process and Embase databases.

Table 10 Study design filters

The MEDLINE SR and RCT filters are presented below.
Systematic Review
1. Meta-Analysis.pt.
2. Meta-Analysis as Topic/
3. Review.pt.
4. exp Review Literature as Topic/
5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
6. (review$ or overview$).ti.
7. (systematic$ adj5 (review$ or overview$)).tw.
8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
9. ((studies or trial$) adj2 (review$ or overview$)).tw.
10. (integrat$ adj3 (research or review$ or literature)).tw.

The MEDLINE SR and RCT filters are presented below.
11. (pool$ adj2 (analy$ or data)).tw. 12. (handsearch$ or (hand adj3 search$)).tw. 13. (manual$ adj3 search$).tw. 14. or/1-13 15. animals/ not humans/ 16. 14 not 15
RCT 1 Randomized Controlled Trial.pt. 2 Controlled Clinical Trial.pt. 3 Clinical Trial.pt. 4 exp Clinical Trials as Topic/ 5 Placebos/ 6 Random Allocation/ 7 Double-Blind Method/ 8 Single-Blind Method/ 9 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. 10 (random$ adj3 allocat$).tw. 11 placebo$.tw. 12 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. 13 or/1-12 14 animals/ not humans/ 15 13 not 14 *Note: analysts requested cross-over studies to be removed.*

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

No date limit was used as the previous guideline recommendations were not based on a systematic literature search.

Health Economics search strategy

Economic evaluations and quality of life data

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and EMBASE to identify relevant evidence and can be seen below in Table 11 . Searches were carried out on 5th May

2017 with a date limit from the previous search of January 2009 – May 2017. Searches were re-run in February 2018.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Table 11 Health economics filters

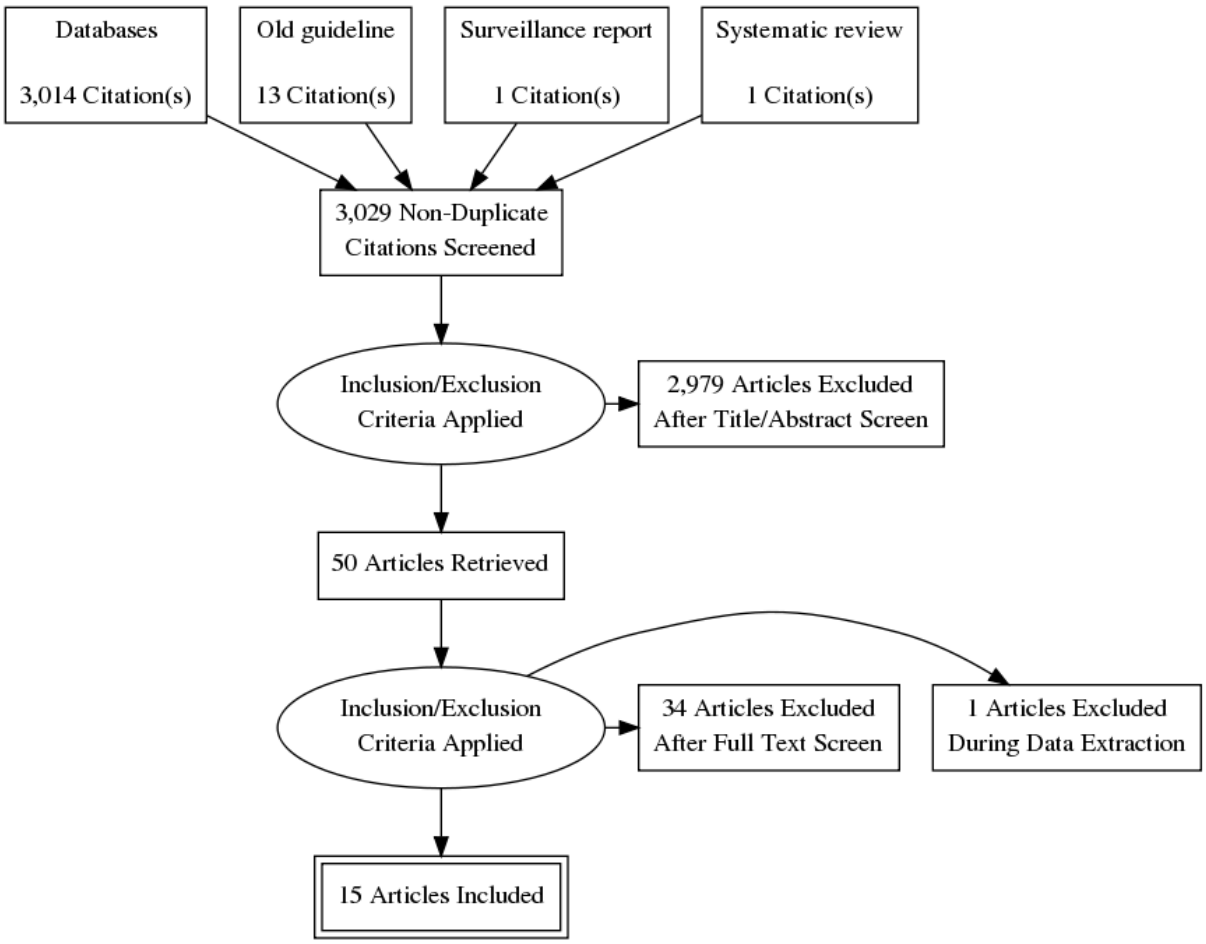
The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
Economic evaluations	
1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/
9	exp Models, Economic/
10	Markov Chains/
11	Monte Carlo Method/
12	Decision Trees/
13	econom$.tw.
14	cba.tw.
15	cea.tw.
16	cua.tw.
17	markov$.tw.
18	(monte adj carlo).tw.
19	(decision adj3 (tree$ or analys$)).tw.
20	(cost or costs or costing$ or costly or costed).tw.
21	(price$ or pricing$).tw.
22	budget$.tw.
23	expenditure$.tw.
24	(value adj3 (money or monetary)).tw.
25	(pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26	or/1-25
Quality of life	
1	"Quality of Life"/
2	quality of life.tw.
3	"Value of Life"/
4	Quality-Adjusted Life Years/
5	quality adjusted life.tw.
6	(qaly$ or qald$ or qale$ or qtime$).tw.
7	disability adjusted life.tw.
8	daly$.tw.
9	Health Status Indicators/

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Pulmonary hypertension

Short Title	Title	Study characteristics	Risk of bias and directness
Arian (2017)	The Effects of Statins on Pulmonary Artery Pressure in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial	**Study type** Randomised controlled trial **Study details** Study location *Iran* Study setting *Vali-Asr Hospital, Birjand, East of Iran.* Study dates *2014* Duration of follow-up *6 months* Sources of funding *Research Committee of Birjand University of Medical Sciences* **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria Pulmonary arterial hypertension *Systolic pulmonary arterial pressure of >25 mmHg by echocardiography.* No previous use of statins	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *No placebo was used in the* study **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Unclear risk of bias *It was unclear how many people were*

		Absence of liver disease **Exclusion criteria** Undergoing treatment for pulmonary hypertension History of heart disease Statin therapy complications Long-term use of systemic corticosteroids Discontinuation of statin therapy during the study **Sample characteristics** Sample size *42* Split between study groups *Intervention: 21 Control: 21* Loss to follow up *34/42 (81%) completed the trial* % female *68% (for the 34 people who completed the trial)* Mean age: years (SD) *64.7 (9.4) (for the 34 people who completed the trial)* **Interventions** Atorvastatin *40mg/day*	*included in each outcome as the paper stated that the number of participants varied slightly due to missing assessments, but did not give numbers. As a result the maximum possible number for each group was used in our analysis.* **Selective reporting** Unclear risk of bias *Very few test outcomes were reported and it was unclear whether additional tests had been carried out and were not presented.* **Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to the risk of performance bias associated with the absence of a placebo, the lack of information provided about the numbers of people associated with the outcome data and an unclear risk of selective reporting.*

		No intervention- routine treatment for COPD **Outcome measure(s)** Mean pulmonary arterial pressure (mPAP, in mmHg)	**Directness** Directly applicable
Blanco (2013)	Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial	**Study type** Randomised controlled trial **Study details** Study location *Barcelona, Spain.* Study setting *Four university hospitals in Barcelona, Spain. The Hospital Clinic of Barcelona carried out the baseline and final measurements, and acted as a co-ordinating centre.* Study dates *August 2008-November 2010* Duration of follow-up *3- months* Sources of funding *Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation. Sildenafil and placebo tablets were donated by Pfizer Inc. but they played no part in the study design, data analyses or manuscript preparation.*	**Random sequence generation** Low risk of bias **Allocation concealment** Low risk of bias **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *The study did not state that the staff assessing the outcome were blind to the intervention leading to a risk of detection bias.*

		Inclusion criteria COPD diagnosis - Global Initiative for Chronic Obstructive Lung Disease guidelines Pulmonary arterial hypertension *Systolic pulmonary arterial pressure (PAP) >34 mmHg or mean PAP ≥ 25 mmHg in patients who had previously been subjected to right heart catheterisation. Determined using echocardiography.* Stable clinical condition free from exacerbations *≥ 4 weeks from last exacerbation* **Exclusion criteria** Pulmonary arterial hypertension with underlying cause other than COPD Ischaemic or mitral or aortic valve diseases Previous use of Sildenafil or other PDE-5 inhibitors History of ischaemic heart disease Inability to exercise on a cycloergometer Treatment with nitrates **Sample characteristics** Sample size *60* Split between study groups *Intervention: 29 Control: 31* Loss to follow up *51/60 (85%) completed trial* % female	**Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low **Directness** Directly applicable

		10% Mean age: years (SD) *65.5 (8.8)* **Interventions** Sildenafil plus pulmonary rehabilitation programme *Sildenafil (20mg) three times daily plus a pulmonary rehabilitation programme starting a week later. This consisted of exercise training sessions on a cycloergometer three times a week for 12 weeks.* Placebo plus a pulmonary rehabilitation programme **Outcome measure(s)** 6 minute walk distance (metres) Cycle endurance time (seconds) Oxygen saturation (%) Health-related quality-of-life Adverse events Incidence of exacerbations Mortality	
Fallahi (2013)	Effects of pentoxifylline on oxygenation and exercise tolerance in patients with severe chronic obstructive pulmonary disease	**Study type** Randomised controlled trial **Study details** Study location Study setting	**Random sequence generation** Low risk of bias

		Outpatient Pulmonary Clinic at Shiraz Medical Centre Study dates *Not stated* Duration of follow-up *12 weeks* Sources of funding *Not stated* **Inclusion criteria** COPD diagnosis- criteria not stated *Severe to very severe COPD with FEV1 of < 50% of their predicted value.* Pulmonary arterial hypertension *Systolic pulmonary artery pressure >40 mmHg by echocardiography.* **Exclusion criteria** History of ischaemic heart disease Inability to perform the 6-min walk test Systolic blood pressure >180 mmHg or diastolic blood pressure >120 mm Hg Left ventricular dysfunction Exertional dysrhythmias or symptomatic peripheral vascular disease	**Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Unclear risk of bias *5/37 participants were lost to follow-up* **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low

		Sample characteristics Sample size *28* Split between study groups *Intervention: 15 Control: 13* Loss to follow up *20/28 (71%) completed the trial* % female *32%* Mean age: years (SD) *65.5 (10.3)* **Interventions** Placebo Pentoxifylline *400mg three times daily or 200mg for patients also receiving Theophylline.* **Outcome measure(s)** 6 minute walk distance (metres) Oxygen saturation (%) *pre- and post- exercise test* Breathlessness (Borg Score) *pre- and post- exercise test*	**Directness** Directly applicable

Goudie (2014)	Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial	**Study type** Randomised controlled trial **Study details** Study location *Scotland, UK* Study setting *Unspecified centres in Dundee, Perth and Fife.* Study dates *September 2010- September 2012.* Duration of follow-up *12 weeks* Sources of funding *Chief Scientist Office for Scotland* **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria COPD diagnosis - European Respiratory Society criteria Sildenafil test criteria fulfilled *Patients tested with 50mg dose of Sildenafil and observed for 3 hrs. People were included if they were free from clinically significant symptoms, hypotension (systolic blood pressure <90 mmHg) or symptomatic postural hypotension (a decrease of ≥ 20 mmHg in systolic blood pressure drop during 3 min of standing) throughout the test dose observation period.* Pulmonary arterial hypertension *>30 mmHg right ventricular systolic pressure or pulmonary*	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Overall risk of bias** Low

		acceleration time <120 ms. PAP determined using echocardiography. Stable clinical condition free from exacerbations *No exacerbations for at least a month.* Smokers or ex-smokers Age 35-85 years old Post- bronchodilator forced expiratory volume in 1 s < 80% predicted **Exclusion criteria** Treatment with nitrates Treatment with nicorandil or doxazosin Left ventricular dysfunction *< 45%* Pulmonary stenosis Left ventricular outflow obstruction confirmed by echocardiography **Sample characteristics** Sample size *120* Split between study groups *Intervention: 60 Control: 60* Loss to follow up *113/120 (94%) completed the trial* % female *32%* Mean age: years (SD)	**Directness** Directly applicable

		69.0 (7.5) **Interventions** Placebo Tadalafil *10mg/day* **Outcome measure(s)** 6 minute walk distance (metres) FEV1 (%) Mean pulmonary arterial pressure (mPAP, in mmHg) Health-related quality-of-life *Minnesota Living With Heart Failure Questionnaire (MLHFQ), St George's Respiratory Questionnaire (SGRQ), Short Form 36 Health Survey (RAND version 1) (SF-36).* Adverse events	
Lee (2009)	Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension	**Study type** Randomised controlled trial **Study details** Study location *Taiwan* Study setting *A tertiary care medical centre* Study dates	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel**

		Not stated Duration of follow-up *6 months* Sources of funding *Chi-Mei Medical Centre and Department of Health, Taiwan.* **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria *With FEV1 (forced expiratory volume in 1 sec) <80% of predicted values and FEV1/FVC (forced vital capacity) ratio <70%.* Pulmonary arterial hypertension *Determined by routine echocardiogram- systolic pulmonary artery pressure ≥ 35 mmHg.* Stable clinical condition free from exacerbations *≥ 3 months* Age *40-80 years* **Exclusion criteria** Asthma, periodic wheezing, allergic rhinitis, pulmonary embolism Previous treatment with cholesterol lowering agents Improvement in FEV1 >X% of expected values after use of a bronchodilator *>15% increase*	Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low **Directness** Directly applicable

		Sample characteristics Sample size *65* Split between study groups *Intervention: 32 Control: 33* Loss to follow up *53/65 (82%) completed the trial.* % female *22% for the 53 people who completed the trial* Mean age: years (SD) *71.5 (7.0) for the 53 people that completed the trial.* **Interventions** Placebo Pravastatin *40mg/day* **Outcome measure(s)** Naughton exercise stress test FEV1 (%) Systolic pulmonary arterial pressure (mmHg) Breathlessness (Borg Score) *Measured using the Borg scale.*	

Moosavi (2013)	Evaluation of the Effects of Atorvastatin on the Treatment of Secondary Pulmonary Hypertension due to Chronic Obstructive Pulmonary Diseases: A Randomized Controlled Trial	**Study type** Randomised controlled trial **Study details** Study location *Tehran, Iran* Study setting *Rasoule-Akram hospital* Study dates *2009-2011* Duration of follow-up *6 months* Sources of funding *Not stated* **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria *FEV1 (forced expiratory volume in 1 s) < 80% of the predicted values, and a FEV1/FVC (forced vital capacity) ratio < 70%* Pulmonary arterial hypertension *> 40 mmHg, method unclear.* No history of using prostanoids, statins, endothelin antagonists Ability to complete the 6-min walk test Obstructive pattern in pulmonary function test	**Random sequence generation** Low risk of bias **Allocation concealment** Low risk of bias **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** High risk of bias *20% dropout rate in study.* **Selective reporting** Low risk of bias

		Exclusion criteria Pulmonary arterial hypertension with underlying cause other than COPD LDL < 70 mg/dl ALT or AST > 3x upper limit normal **Sample characteristics** Sample size *45* Split between study groups *Intervention: 24 Control: 21* Loss to follow up *36/45 (80%) completed trial* % female *37.8%* Mean age: years (SD) *66.4 (12.4)* Mean duration of COPD in months (SD) *72.0 (12.1)* **Interventions** Atorvastatin *40mg/day* Placebo	**Other sources of bias** Low risk of bias **Overall risk of bias** Low **Directness** Directly applicable

		Outcome measure(s) 6 minute walk distance (metres) FEV1 (%) Systolic pulmonary arterial pressure (mmHg)	
Morrell (2005)	Pilot study of losartan for pulmonary hypertension in chronic obstructive pulmonary disease	**Study type** Randomised controlled trial **Study details** Study location *UK* Study setting *An unspecified hospital clinic.* Study dates *Not stated.* Duration of follow-up *48 weeks* Sources of funding *Merck Sharp & Dohme Ltd. Two of the researchers were employed by Merck Sharp & Dohme Ltd and may own stock/stock options.* **Inclusion criteria** COPD diagnosis- criteria not stated Pulmonary arterial hypertension *Transtricuspid pressure gradient (TTPG) ≥ 30 mmHg and sitting systolic blood pressure ≥ 100 mmHg.* Obstructive pattern in pulmonary function test	**Random sequence generation** Unclear risk of bias *No information provided* **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** Unclear risk of bias *No information provided on whether personnel were blinded, but a placebo was used* **Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** High risk of bias *Large loss to follow-up as 13/40 did not complete the trial*

		FEV1/FVC ≤ 70% Age *50-80 years* **Exclusion criteria** Significant kidney dysfunction Left ventricular dysfunction *Ejection fraction < 35%* Myocardial infarction Recent exacerbation of COPD Concomitant use of vasodilators, Beta- blockers or potassium-sparing diuretics **Sample characteristics** Sample size *40* Split between study groups *Intervention: 20 Control: 20* Loss to follow up *27/40 (67.5%) completed the trial.* % female *52.5%* Mean age: years (SD) *67.0 (7.9)* Mean duration of COPD in months (SD)	**Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Due to the large loss to follow-up of trial participants and a lack of information regarding randomisation and blinding* **Directness** Directly applicable

		100.8 (not stated) **Interventions** Placebo Losartan *25mg/day for 1 week, then dose increased to 50mg/day, providing the patient's systolic blood pressure remained ≥ 100 mmHg. The dose could be down titrated once (to 25 mg) if necessary.* **Outcome measure(s)** 10 m shuttle walk test Health-related quality-of-life *St George's Hospital Respiratory Questionnaire) (SGRQ) and Patient Health Survey (SF-36).* Adverse events	
Rao (2011)	Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial.	**Study type** Randomised controlled trial **Study details** Study location *India* Study setting *Not stated.* Study dates *Not stated.*	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel**

		Duration of follow-up *12 weeks* Sources of funding *Not stated, M/s Cipla Pharmaceuticals provided the drug and identical placebo.* **Inclusion criteria** COPD diagnosis - Global Initiative for Chronic Obstructive Lung Disease guidelines *Severe or very severe COPD.* Pulmonary arterial hypertension *Pulmonary artery systolic pressure of >40mmHg mPAP determined using echocardiography.* Past history of smoking at least 20 packs/year **Exclusion criteria** Pulmonary arterial hypertension with underlying cause other than COPD History of ischaemic heart disease Treatment with nitrates *Use of nitrates or other vasodilators throughout the study period* History of heart disease History of asthma Improvement in FEV1 >X% of expected values after use of a bronchodilator *>12% increase* Recent exacerbation of COPD	Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** High risk of bias *Heart rate, oxygen saturation and breathlessness as per the Borg scale before and after the walk were recorded but not presented.* Low risk of bias *For the PAP and 6MWD test data presented.* **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate

		< 1month Any severe concomitant disease Haemoglobin <12g/dL **Sample characteristics** Sample size *37* Split between study groups *Intervention: 17 Control: 20* Loss to follow up *33/37 (89%) completed the trial.* % female *Not stated.* Mean age: years (SD) *62.3 (7.5)* **Interventions** Placebo Sildenafil *20 mg three times a day. (Patients were using inhaled anti-muscarinic, long-acting beta agonists, inhaled corticosteroids and sustained release theophylline one month before the enrolment in the study and the same medicines were continued during the study for both groups.)*	Due to lack of information about allocation concealment and assessor blinding plus reporting bias for certain outcomes **Directness** Directly applicable

		Outcome measure(s) 6 minute walk distance (metres) Mean pulmonary arterial pressure (mPAP, in mmHg)	
Saadjian (1988)	Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study.	**Study type** Randomised controlled trial **Study details** Study location *France* Study setting *Not stated.* Study dates *Not stated.* Duration of follow-up *18 months* Sources of funding *Not stated.* **Inclusion criteria** COPD diagnosis- criteria not stated *With functional tests showing evidence of serious respiratory impairment (forced expiratory volume in one second (FEY 1) between 20 and 40% of predicted.* Pulmonary arterial hypertension *Mild PAH -mean pulmonary artery pressure >20 mmHg (control mean 29.3±2.8, intervention 31.7±2.3) determined using right heart*	**Random sequence generation** Unclear risk of bias *No information provided* **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *No placebo was used in the* study **Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias

		catheterization. Stable clinical condition free from exacerbations *≥ 2 months* Breathlessness and fatigue after minimal or moderate exertion **Exclusion criteria** Left ventricular dysfunction Treatment with vasodilators, long-acting theophylline, B2 agonists, almitrine, diuretics or digitalis. **Sample characteristics** Sample size *20* Split between study groups *Intervention: 10 Control: 10* Loss to follow up *20/20 (100%) completed the trial.* % female *0%* Mean age: years (SD) *62.0 (2.3)* **Interventions** No intervention- routine treatment for COPD Nifedipine	**Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to the absence of a placebo and a lack of information about randomisation and outcome assessor* **Directness** Directly applicable

		10mg/ every 8hrs (30mg/day) **Outcome measure(s)** Partial pressure of arterial oxygen (PaO_2) Mean pulmonary arterial pressure (mPAP, in mmHg) Adverse events Ankle oedema	
Valerio (2009)	Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease	**Study type** Randomised controlled trial **Study details** Study location *Italy* Study setting *Centre for the Treatment of Chronic Respiratory Insufficiency* Study dates *Not stated* Duration of follow-up *18 months* Sources of funding *Not stated* **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria COPD diagnosis - Global Initiative for Chronic Obstructive Lung	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *Participants were blinded, but medical staff were not because of the severe respiratory failure seen in some patients.* **Blinding of outcome assessment** High risk of bias *Medical staff were not blinded because*

		Disease guidelines Pulmonary arterial hypertension *Mean pulmonary arterial pressure >25mmHg determined using right heart catheterization. Patients were monitored for a month and those with persistent pulmonary hypertension were included in the study.* **Exclusion criteria** None reported **Sample characteristics** Sample size *40* Split between study groups *Intervention: 20 Control: 20* Loss to follow up *32/40 (80%) completed the trial* % female *22% female (of the patients completing the study)* Mean age: years (SD) *65.5 (14.0)* **Interventions** Placebo Bosentan	*of the severe respiratory failure seen in some patients.* **Incomplete outcome data** High risk of bias *8/40 participants did not complete the trial* **Selective reporting** High risk of bias *Several outcomes mentioned in the methods are not presented in the results section (including SaO_2, MRC breathlessness scale results).* **Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to a lack of blinding, a high risk of at attrition bias and selective reporting* **Directness** Directly applicable

		125mg twice a day **Outcome measure(s)** 6 minute walk distance (metres) FEV1 (%) Partial pressure of arterial oxygen (PaO_2) Mean pulmonary arterial pressure (mPAP, in mmHg) Health-related quality-of-life *St. George's Respiratory Questionnaire* Adverse events *Exacerbations per patient* Breathlessness *MRC and WHO scales*	
Vestri (1988)	One-year clinical study on nifedipine in the treatment of pulmonary hypertension in chronic obstructive lung disease	**Study type** Randomised controlled trial **Study details** Study location *France* Study setting *Not stated.* Study dates *Not stated.* Duration of follow-up *12 months* Sources of funding	**Random sequence generation** Unclear risk of bias *No information provided* **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *No placebo was used in the study*

		Not stated. **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria *With severe exertional breathlessness, bronchial airflow obstruction and persistent hypoxemia (PaO_2 <80 mmHg).* Pulmonary arterial hypertension *PAH > 20 mmHg at rest, (mPAP Intervention 31.3 mmHg (SD 2.2), control 29.6 mmHg (1.4)). Determined using right heart catheterization.* Stable clinical condition free from exacerbations *> 1 month* No evidence of left ventricular hypertrophy or hemodynamic criteria of left ventricular failure. Nifedipine test criteria fulfilled *Tested with a dose of 10mg nifedipine. Patients who did not suffer a decrease in cardiac output or any other adverse effect in the hour following administration were included in the study.* **Exclusion criteria** None reported **Sample characteristics** Sample size *60* Split between study groups	**Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Unclear risk of bias *Unclear how many people included in the analysis for the following outcomes: breathlessness, hospitalisations, PaO_2.* Low risk of bias *For the ankle oedema and death outcomes as including all participants.* **Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to issues with randomisation, blinding (including the lack of a*

		Intervention: 30 Control: 30 Loss to follow up *41/60 (68%) completed the trial.* % female *6.7%* Mean age: years (SD) *63.3 (1.5)* Mean duration of COPD in months (SD) *155.76 (10.8)* **Interventions** No intervention- routine treatment for COPD Nifedipine *10mg three times a day* **Outcome measure(s)** Partial pressure of arterial oxygen (PaO_2) Breathlessness Mortality Hospitalisation (days) Ankle oedema	*placebo) and a high risk of selective reporting* **Directness** Directly applicable
Vitulo (2017)	Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized	**Study type** Randomised controlled trial	**Random sequence generation** Low risk of bias

	controlled multicenter clinical trial	**Study details** Study location *Italy* Study setting *Seven centres with expertise in the management of COPD and pulmonary hypertension.* Study dates *March 2012-March 2013* Duration of follow-up *16 weeks* Sources of funding *Pfizer provided funding and sildenafil/identical placebo tablets, but was not involved in the study design, data collection or analysis or manuscript preparation. The study was sponsored by Associazione Italiana Pneumologi Ospedaleri.* **Inclusion criteria** COPD diagnosis - Global Initiative for Chronic Obstructive Lung Disease guidelines Pulmonary arterial hypertension *Patients with a baseline systolic pulmonary arterial pressure of ≥ 50 mmHg underwent right heart catheterisation. To ensure significant PH patients were selected with mPAP ≥ 35mm Hg in the case of FEV1 < 30% of predicted value after bronchodilator, and mPAP ≥ 30 mmHg for a FEV1 > 30% of predicted value after bronchodilator.* Stable clinical condition free from exacerbations	**Allocation concealment** Low risk of bias **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low

		Last exacerbation ≥ 4 weeks earlier **Exclusion criteria** Pulmonary arterial hypertension with underlying cause other than COPD Ischaemic or mitral or aortic valve diseases Treatment with nitrates Undergoing treatment for pulmonary hypertension Decompensated heart failure Intolerance to or contraindication for the use of Sildenafil A severe mental disorder preventing informed consent to participate in the study Liver/kidney dysfunction **Sample characteristics** Sample size *28* Split between study groups *Intervention: 18 Control: 10* Loss to follow up *25/28 (89%) completed the trial.* % female *25%* Mean age: years (SD) *65.6 (8.1)*	**Directness** Directly applicable

		Interventions Placebo Sildenafil *20mg three times daily.* **Outcome measure(s)** 6 minute walk distance (metres) FEV1 (%) Partial pressure of arterial oxygen (PaO_2) Mean pulmonary arterial pressure (mPAP, in mmHg) Health-related quality-of-life *Medical Outcomes Study 36-item Short Form Health Survey (SF-36).* Adverse events	
Vonbank (2003)	Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD	**Study type** Randomised controlled trial **Study details** Study location *Austria* Study setting *Not stated.* Study dates *July 1998-January 2000* Duration of follow-up *6 months* Sources of funding	**Random sequence generation** Low risk of bias **Allocation concealment** Low risk of bias **Blinding of participants and personnel** Unclear risk of bias *No information was provided about whether personnel were blinded to the intervention and it was unclear whether*

		Messer Austria. **Inclusion criteria** COPD diagnosis - American Thoracic Society criteria Pulmonary arterial hypertension *Mean pulmonary artery pressure of ≥ 25 mmHg determined using right heart catheterization.* **Exclusion criteria** History of ischaemic heart disease Myocardial infarction *During the 6 month period before the study.* Stroke during the 6 months before the study Acute left heart disease Pulmonary wedge pressure of >13mmHg Atrial fibrillation or flutter **Sample characteristics** Sample size *40* Split between study groups *Oxygen alone: 20 Oxygen and NO: 20* Loss to follow up *31/40 (77.5%) completed the trial.* % female *32.5%*	*participants were able to determine their treatment group.* **Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Due to a lack of information regarding blinding of study participants, staff and assessors.* **Directness** Directly applicable

		Mean age: years (SD) *61.6 (8.2)* Mean duration of COPD in months (SD) *107.2 (63.6)* **Interventions** Oxygen Oxygen and Nitric oxide *Pulsed inhalation of 50ml oxygen and 20 parts per million NO.* **Outcome measure(s)** Partial pressure of arterial oxygen (PaO_2) Mean pulmonary arterial pressure (mPAP, in mmHg) Mortality	
Wang (2017)	Effect of azithromycin in combination with simvastatin in the treatment of chronic obstructive pulmonary disease complicated by pulmonary arterial hypertension	**Study type** Randomised controlled trial **Study details** Study location *China* Study setting *Zhengzhou TCM Hospital* Study dates *August 2013 to October 2014* Duration of follow-up *6 months* Sources of funding	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *Lack of a placebo for patients in the control group and no information regarding blinding of personnel*

		None stated **Inclusion criteria** COPD diagnosis- criteria not stated Pulmonary arterial hypertension *Mean arterial pressure of not less than 25 mmHg by right cardiac catheterization at rest or no less than 30 mm Hg with activity.* Stable clinical condition free from exacerbations Not currently suffering from an acute lung infection. **Exclusion criteria** Pulmonary arterial hypertension with underlying cause other than COPD Primary pulmonary hypertension Liver/kidney dysfunction Asthma or allergic rhinitis Known allergy to simvastatin or azithromycin Pulmonary thromboembolism Severe cardiac abnormality **Sample characteristics** Sample size *86* Split between study groups *Intervention: 43 Control: 43* Loss to follow up *86/86 (100%) completed the trial* % female *40.7* Mean age: years (SD) *71.5 (8.2)* Mean duration of COPD in months (SD)	**Blinding of outcome assessment** High risk of bias *No blinding of outcome assessors described.* **Incomplete outcome data** Unclear risk of bias *Not described* **Selective reporting** High risk of bias *Due to the lack of a data for the breathlessness outcome.* **Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to the lack of blinding of participants, personnel and outcome assessors and the lack of a data for the breathlessness outcome.* **Directness** Directly applicable

		133.2 (64.8) **Interventions** Simvastatin *Simvastatin 20mg/day* Simvastatin and azithromycin *Simvastatin 20mg/day, azithromycin 0.25g once a day* **Outcome measure(s)** 6 minute walk distance (metres) Partial pressure of arterial oxygen (PaO2)	

Cor pulmonale

Short Title	Title	Study characteristics	Risk of bias and directness
Medical Research Council working party (1981)	Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party.	**Study type** Randomised controlled trial **Study details** Study location *UK* Study setting *Centres in Edinburgh, Birmingham and Sheffield.* Study dates *1973- unknown end date* Duration of follow-up *3 years* Sources of funding	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *Absence of a placebo*

		Medical Research Council **Inclusion criteria** Chronic bronchitis or emphysema with irreversible airways obstruction *FEV1 <1.2 litres* Arterial oxygen tension between 40 and 60 mmHg when breathing air at rest One of more episodes of heart failure with ankle oedema. *Resting pulmonary arterial hypertension was not used as an entry criterion.* Arterial blood gas, FEV1 and body weight stable over 2 measurements at least 3 weeks apart. **Exclusion criteria** History of ischaemic heart disease Other concomitant life threatening diseases Fibrotic or infiltrative lung disease Pneumoconiosis (category 2 or more), severe kyphoscoliosis, overt episodes of pulmonary embolism Systemic hypertension *diastolic pressure >100 mmHg under 60 years of age, or > 110 mmHg over 65 years of age.* **Sample characteristics** Sample size	**Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** High risk of bias *Data for rates of change of physiological variables is not presented for the whole data set, just males.* **Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to the lack of information regarding allocation concealment and outcome assessor blinding, the absence of a placebo and selective reporting of data*

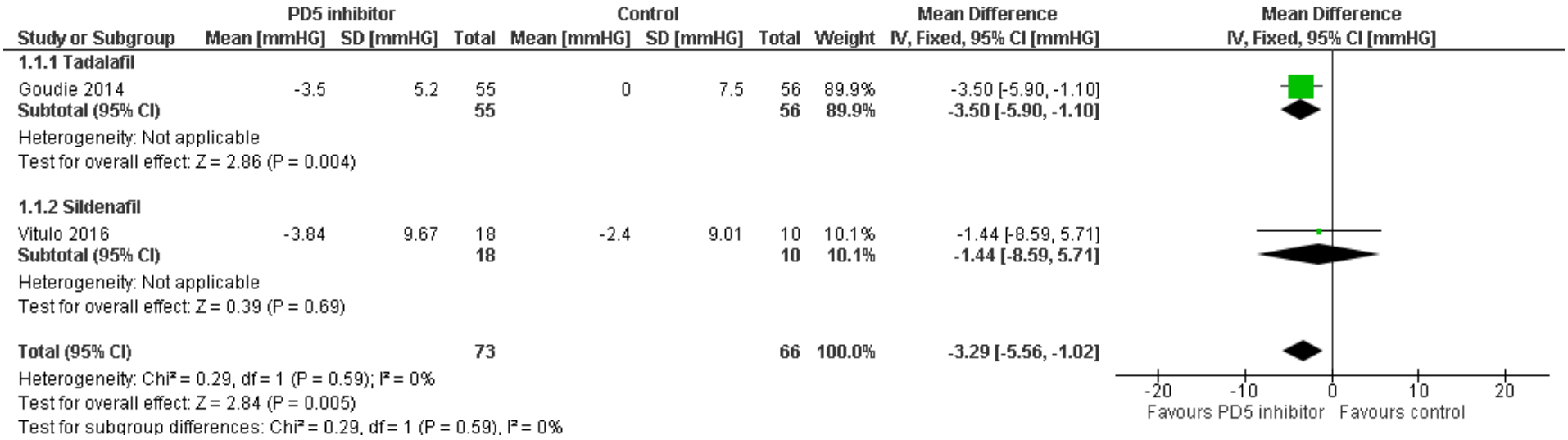
		87 Split between study groups *Intervention: 43 Control: 45* Loss to follow up *86/87 (98.9%) completed the trial.* % female *24.1%* Mean age: years (SD) *57.7 (no SD data provided)* **Interventions** No intervention- routine treatment for COPD Oxygen *For at least 15hrs a day.* **Outcome measure(s)** Mortality Rate of change in FEV1 Rate of change in PaO_2	**Directness** Directly applicable

Appendix F – Forest plots

Pulmonary hypertension

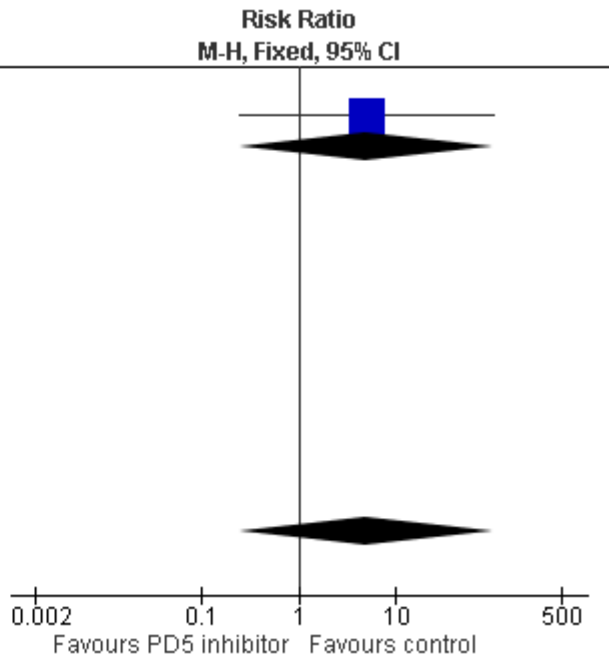
Phosphodiesterase 5 inhibitors

Mean pulmonary artery pressure (mPAP, mmHg)

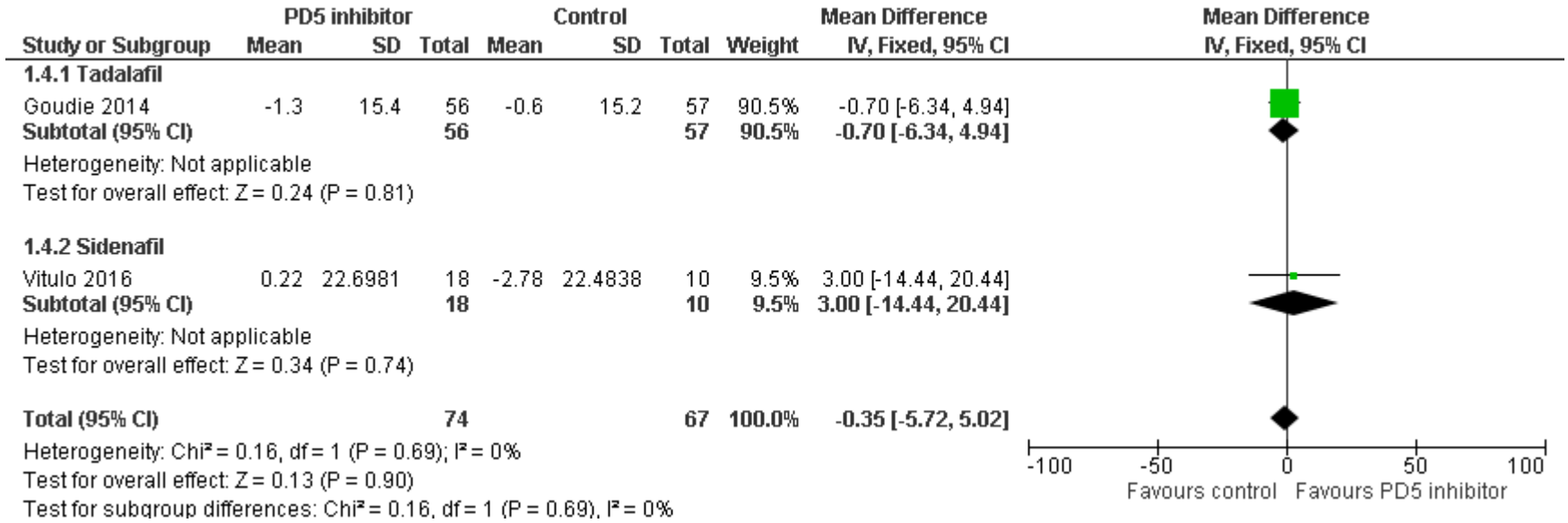


Mortality (number of deaths)

Study or Subgroup	PD5 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Tadalafil						
Goudie 2014	2	60	0	60	100.0%	5.00 [0.25, 102.00]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**5.00 [0.25, 102.00]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
1.3.2 Sidenafil						
Blanco 2013	0	32	0	31		Not estimable
Subtotal (95% CI)		**32**		**31**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**92**		**91**	**100.0%**	**5.00 [0.25, 102.00]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Test for subgroup differences: Not applicable						

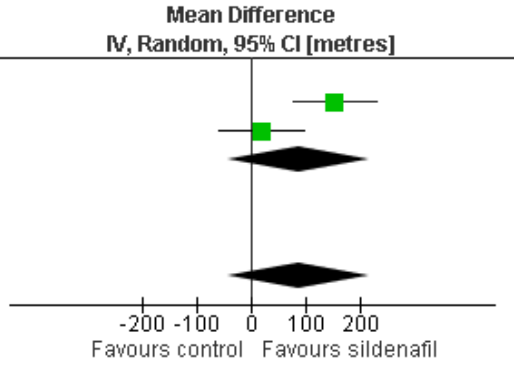


Forced expiratory volume in 1 second (FEV1, % predicted)



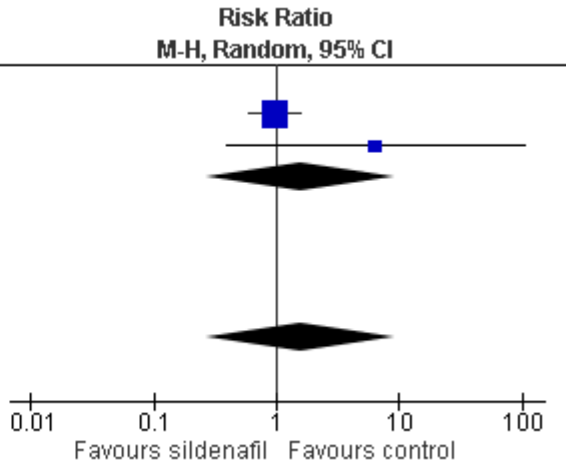
6 minute walk distance (metres)

Study or Subgroup	Sildenafill Mean [metres]	Sildenafill SD [metres]	Sildenafill Total	Control Mean [metres]	Control SD [metres]	Control Total	Weight	Mean Difference IV, Random, 95% CI [metres]
2.3.1 Sildenafil								
Rao 2010	191	127	15	39	87	18	50.3%	152.00 [76.20, 227.80]
Vitulo 2016	8.1	102.67	18	-11.2	101.19	10	49.7%	19.30 [-59.33, 97.93]
Subtotal (95% CI)			**33**			**28**	**100.0%**	**86.08 [-43.96, 216.12]**
Heterogeneity: Tau² = 7251.98; Chi² = 5.67, df = 1 (P = 0.02); I² = 82%								
Test for overall effect: Z = 1.30 (P = 0.19)								
Total (95% CI)			**33**			**28**	**100.0%**	**86.08 [-43.96, 216.12]**
Heterogeneity: Tau² = 7251.98; Chi² = 5.67, df = 1 (P = 0.02); I² = 82%								
Test for overall effect: Z = 1.30 (P = 0.19)								
Test for subgroup differences: Not applicable								



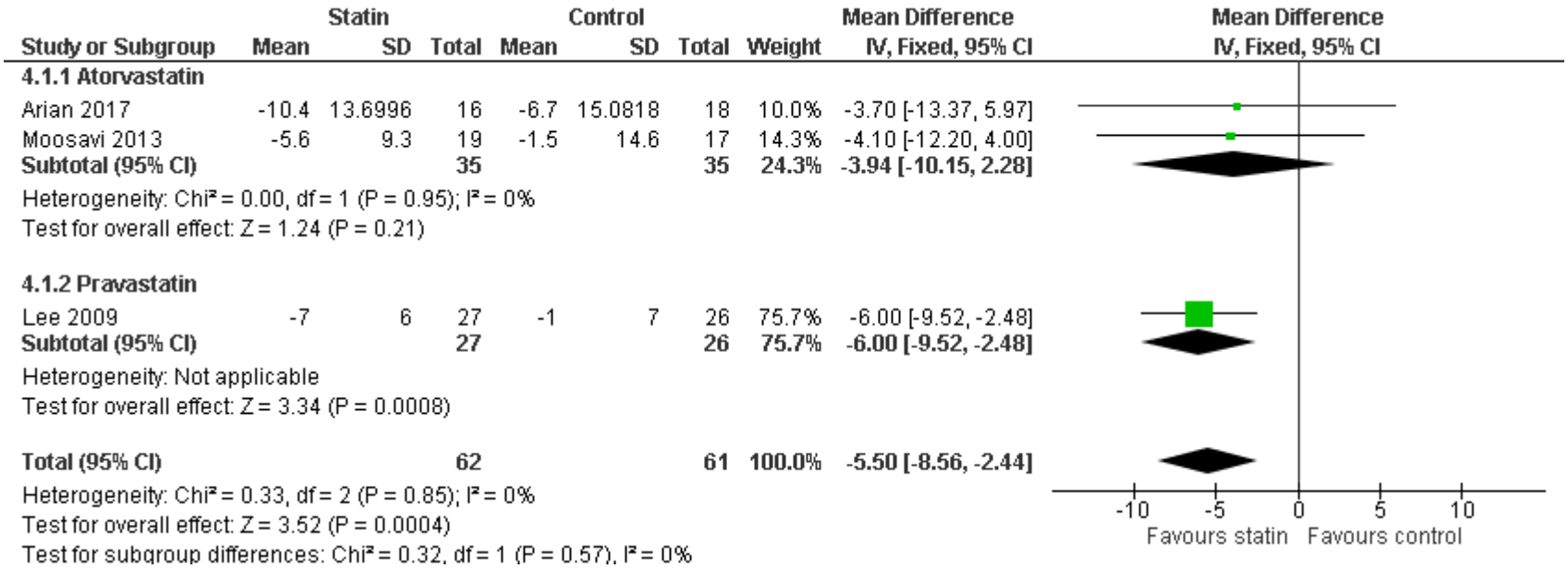
All adverse events

Study or Subgroup	Sildenafill Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Sildenafil						
Blanco 2013	16	32	16	31	73.6%	0.97 [0.60, 1.58]
Vitulo 2016	5	18	0	10	26.4%	6.37 [0.39, 104.54]
Subtotal (95% CI)		**50**		**41**	**100.0%**	**1.59 [0.27, 9.32]**
Total events	21		16			
Heterogeneity: Tau² = 1.04; Chi² = 1.99, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.52 (P = 0.61)						
Total (95% CI)		**50**		**41**	**100.0%**	**1.59 [0.27, 9.32]**
Total events	21		16			
Heterogeneity: Tau² = 1.04; Chi² = 1.99, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.52 (P = 0.61)						
Test for subgroup differences: Not applicable						

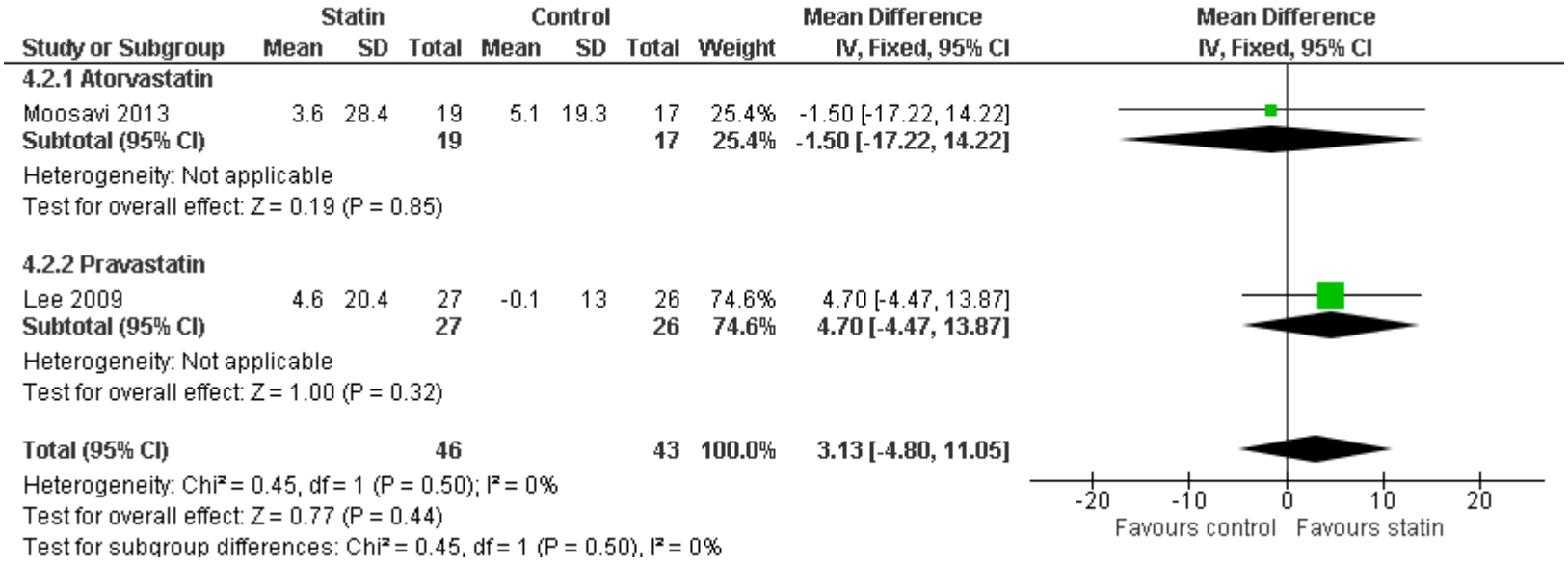


Statins

Systolic pulmonary artery pressure (PAP, mmHg)



Forced expiratory volume in 1 second (FEV1, % predicted

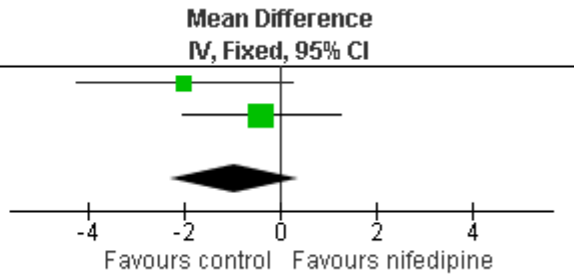


Nifedipine

Partial pressure of arterial oxygen (PaO_2, mmHg)

	Nifedipine			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saadjian 1988	-4.7	2	10	-2.7	3	10	35.1%	-2.00 [-4.23, 0.23]
Vestri 1988	3.2	2.9	19	3.6	2.4	22	64.9%	-0.40 [-2.05, 1.25]
Total (95% CI)			**29**			**32**	**100.0%**	**-0.96 [-2.29, 0.36]**

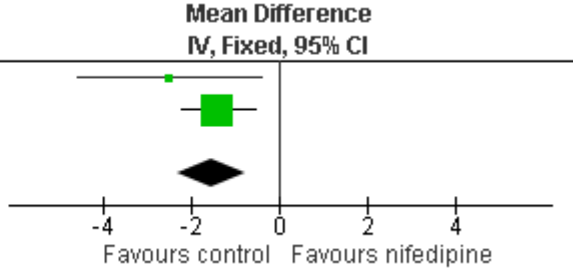
Heterogeneity: Chi² = 1.28, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 1.42 (P = 0.15)



Oxygen saturation (SaO_2, %)

	Nifedipine			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saadjian 1988	-3	2.4	10	-0.5	2.4	10	13.8%	-2.50 [-4.60, -0.40]
Vestri 1988	0.7	1.6	19	2.11	1.05	22	86.2%	-1.41 [-2.25, -0.57]
Total (95% CI)			**29**			**32**	**100.0%**	**-1.56 [-2.34, -0.78]**

Heterogeneity: Chi² = 0.89, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 3.91 (P < 0.0001)



Appendix G – GRADE tables

Pulmonary hypertension

Phosphodiesterase 5 inhibitors (PD5 inhibitors) versus control (placebo or no intervention)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean pulmonary artery pressure (mPAP) – mmHg (lower values favour PD5 inhibitor)										
2	RCT	139	MD -3.29 (-5.56, -1.02)	-	-	Not serious	Not serious	Not serious	Serious[1]	Moderate
Systolic pulmonary artery pressure (PAP) – mmHg (lower values favour PD5 inhibitor)										
1 (Rao 2010)	RCT	33	MD -8.00 (-14.86, -1.14)	-	-	Serious[2]	N/A	Not serious	Serious[1]	Low
Mortality – number of deaths (lower values favour PD5 inhibitor)										
2	RCT	183	RR 5.00 (0.25, 102.00)	Not calculable[3]	Not calculable[3]	Not serious	N/A[4]	Not serious	Serious[6]	Moderate
FEV1 - % predicted (higher values favour PD5 inhibitor)										
2	RCT	141	MD -0.35 (-5.72, 5.02)	-	-	Not serious	Not serious	Not serious	Serious[6]	Moderate
Partial pressure of arterial oxygen (PaO_2) - mmHg (higher values favour sildenafil)										
1 (Vitulo 2016)	RCT	28	MD -1.02 (-11.13, 9.09)	-	-	Not serious	N/A	Not serious	Very serious[7]	Low
Short Form 36 health survey, general health domain (higher values favour sildenafil)										
1 (Vitulo 2016)	RCT	28	MD 9.90	-	-	Not serious	N/A	Not serious	Very serious[7]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(-3.05, 22.85)							
6 minute walk distance – metres (higher values favour sildenafil)										
2	RCT	61	MD 86.08 (-43.96, 216.12)	-	-	Serious[8]	Very serious[9]	Not serious	Very serious[5]	Very low
Modified MRC scale for breathlessness (lower values favour sildenafil)										
1 (Vitulo 2016)	RCT	28	MD -0.60 (-1.27, 0.07)	-	-	Not serious	N/A	Not serious	Very serious[7]	Low
All adverse events– number of events (lower values favour sildenafil)										
2	RCT	91	RR 1.59 (0.27, 9.32)	39.02 per 100	62.05 per 100 (10.54, 100)	Not serious	Serious[10]	Not serious	Very serious[5]	Very low
Exacerbations leading to discontinuation – number of exacerbations (lower values favour sildenafil)										
1 (Blanco 2013)	RCT	63	RR 1.94 (0.38, 9.83)	6.45 per 100	12.52 per 100 (2.45, 63.42)	Not serious	N/A	Not serious	Very serious[5]	Low
Exacerbations leading to hospitalisation – number of exacerbations (lower values favour sildenafil)										
1 (Blanco 2013)	RCT	63	RR 1.45 (0.26, 8.11)	6.45 per 100	9.35 per 100 (1.68, 52.32)	Not serious	N/A	Not serious	Very serious[5]	Low
All exacerbations – number of exacerbations (lower values favour sildenafil)										
1 (Blanco 2013)	RCT	63	RR 0.88 (0.44, 1.77)	35.48 per 100	31.23 per 100 (15.61, 62.81)	Not serious	N/A	Not serious	Very serious[5]	Low
St. George's respiratory questionnaire (SGRQ), total score (lower values favour tadalafil)										
1 (Goudie 2014)	RCT	113	MD -2.64 (-6.43, 1.15)	-	-	Not serious	N/A	Not serious	Serious[11]	Moderate
Short Form 36 health survey (SF36), physical functioning domain score (higher values favour tadalafil)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Goudie 2014)	RCT	113	MD 4.08 (-1.36, 9.52)	-	-	Not serious	N/A	Not serious	Serious[6]	Moderate
Minnesota living with heart failure questionnaire (MHLFQ), total score (lower values favour tadalafil)										
1 (Goudie 2014)	RCT	113	MD -2.31 (-7.06, 2.44)	-	-	Not serious	N/A	Not serious	Serious[6]	Moderate

1. Single study or meta-analysis where the >33.3% of weight came from trials measuring PAP by echocardiography, which is less accurate than the alternative method of right heart catheterization.
2. Study at high risk of reporting bias.
3. No events occurred in the placebo arm of either trial
4. Relative risk could only be calculated for one study, as no events occurred in either arm of the second study
5. 95% confidence interval crosses both ends of a defined MID interval
6. Non-significant result
7. Non-significant result and small sample size
8. >33.3% of weighted data from studies at moderate or high risk of bias
9. i-squared >66.7%
10. i-squared >33.3% and <66.7%
11. 95% confidence interval crosses one end of a defined MID interval

Statins versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Systolic pulmonary artery pressure (PAP) – mmHg (lower values favour statins)										
3	RCT	123	MD -5.50[1] (-8.56, -2.44)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
FEV1 - % predicted (higher values favour statins)										
2	RCT	89	MD 3.13 (-4.80, 11.05)	-	-	Not serious	Not serious	Not serious	Serious[3]	Moderate
Borg breathlessness score following exercise test (lower values favours pravastatin)										
1 (Lee 2009)	RCT	53	MD -2.74 (-3.27, -2.21)	-	-	Not serious	N/A	Not serious	Not serious	High
6 minute walk distance – metres (higher values favour atorvastatin)										
1 (Moosavi 2013)	RCT	36	MD 45.00 (-41.00, 131.00)	-	-	Not serious	N/A	Not serious	Very serious[4]	Low
Treadmill test- exercise time - seconds (higher values favour pravastatin)										
1 (Lee 2009)	RCT	53	MD 370.00 (231.99, 508.01)	-	-	Not serious	N/A	Not serious	Not serious	High
Treadmill test- target heart rate - % (higher values favour pravastatin)										
1 (Lee 2009)	RCT	53	MD 9.00 (3.27, 14.73)	-	-	Not serious	N/A	Not serious	Not serious	High

1. Result does not meaningfully change when study at high risk of bias is excluded.
2. Downgraded as systolic pulmonary artery pressure was measured using echocardiography, a less accurate method than right heart catheterisation.
3. Non-significant result
4. 95% confidence interval crosses both ends of a defined MID interval

Nifedipine versus no intervention

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean pulmonary artery pressure (mPAP) – mmHg (lower values favour nifedipine)										
1 (Saadjian 1988)	RCT	20	MD -2.00 (-4.49, 0.49)	-	-	Very serious[1]	N/A	Not serious	Very serious[2]	Very low
Partial pressure of arterial oxygen (PaO_2) - mmHg (higher values favour nifedipine)										
2	RCT	61	MD -0.96 (-2.29, 0.36)	-	-	Very serious[5]	Not serious	Not serious	Serious[3]	Very low[4]
Oxygen saturation (SaO_2)- % (higher values favour nifedipine)										
2	RCT	61	MD -1.56 (-2.34, -0.78)	-	-	Very serious[5]	Not serious	Not serious	Not serious	Low[4]
Mortality – number of deaths (lower values favour nifedipine)										
1 (Vestri 1988)	RCT	60	RR 0.88 (0.36, 2.11)	26.67 per 100	23.47 per 100 (9.60, 56.27)	Very serious[6]	N/A	Not serious	Serious[3]	Very low
Hospitalisation days (lower values favour nifedipine)										
1 (Vestri 1988)	RCT	41	MD 0.20 (-1.95, 2.35)	-	-	Very serious[6]	N/A	Not serious	Serious[3]	Very low
Ankle oedema– number of events (lower values favour nifedipine)										
1 (Vestri 1988)	RCT	60	RR 9.00 (0.51, 160.17)	Not calculable[8]	Not calculable[8]	Very serious[6]	N/A	Not serious	Very serious[7]	Very low
Breathlessness (lower values favour nifedipine)										
1 (Vestri 1988)	RCT	41	MD -0.53 (-0.65, -0.41)	-	-	Very serious[6]	N/A	Not serious	Not serious	Low

1. Lack of information regarding random sequence generation, allocation concealment and blinding of participants, personnel and outcome assessors.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2. Non-significant result and small sample size 3. Non-significant result 4. Effect size does not meaningfully change when studies at high risk of bias are excluded 5. Both studies were judged to be at high risk of bias due to the lack of information provided for most of the risk of bias assessment domains. 6. Lack of information regarding random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, and possible selective reporting 7. 95% confidence interval crosses both ends of a defined MID interval 8. No events occurred in the placebo arm of the trial										

Losartan versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Partial pressure of arterial oxygen (PaO_2) - kPa (higher values favour losartan)										
1 (Morrell 2005)	RCT	27	MD -0.70 (-1.76, 0.36)	-	-	Serious[1]	N/A	Not serious	Very serious[2]	Very low
Mortality– number of deaths (lower values favour losartan)										
1 (Morrell 2005)	RCT	40	RR 3.00 (0.13, 69.52)	Not calculable[3]	Not calculable[3]	Serious[1]	N/A	Not serious	Serious[5]	Low
Adverse events leading to discontinuation of treatment – number of events (lower values favour losartan)										
1 (Morrell 2005)	RCT	40	RR 0.33 (0.04, 2.94)	15.00 per 100	4.95 per 100 (0.60, 44.10)	Serious[1]	N/A	Not serious	Very serious[4]	Very low
All adverse events– number of events (lower values favour losartan)										
1 (Morrell 2005)	RCT	40	RR 0.21 (0.02, 2.08)	95.00 per 100	19.95 per 100 (1.90, 100)	Serious[1]	N/A	Not serious	Very serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Shuttle walk test – number of shuttle distances completed (higher values favour losartan)										
1 (Morrell 2005)	RCT	32	MD 2.40 (-1.25, 6.05)	-	-	Serious[1]	N/A	Not serious	Serious[5]	Low
Breathlessness after exercise (lower values favour losartan)										
1 (Morrell 2005)	RCT	32	MD 0.70 (-0.47, 1.87)	-	-	Serious[1]	N/A	Not serious	Serious[5]	Low
St. George's respiratory questionnaire (SGRQ), total score (lower values favour losartan)										
1 (Morrell 2005)	RCT	33	MD -5.30 (-11.60, 1.00)	-	-	Serious[1]	N/A	Not serious	Serious[6]	Low

1. Lack of information regarding random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors and a high risk of bias for incomplete outcome data.
2. Non-significant result and small sample size
3. No events occurred in the placebo arm of the trial
4. 95% confidence interval crosses both ends of a defined MID interval
5. Non-significant result
6. 95% confidence interval crosses one end of a defined MID interval

Pentoxifylline versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
6 minute walk distance – metres (higher values favour pentoxifylline)										
1 (Fallahi 2013)	RCT	20	MD 17.00 (-41.29, 75.29)	-	-	Not serious	N/A	Not serious	Very serious[1]	Low
Borg score (pre-test) (lower values favour pentoxifylline)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Fallahi 2013)	RCT	20	MD -0.40 (-1.38. 0.58)	-	-	Not serious	N/A	Not serious	Not serious	High
Borg score (post-test) (lower values favour pentoxifylline)										
1 (Fallahi 2013)	RCT	20	MD -0.40 (-2.31, 1.51)	-	-	Not serious	N/A	Not serious	Serious[2]	Moderate
Oxygen saturation (pre-test) - % (higher values favour pentoxifylline)										
1 (Fallahi 2013)	RCT	20	MD -2.00 (-10.77, 6.77)	-	-	Not serious	N/A	Not serious	Very serious[3]	Low
Oxygen saturation (post-test) - % (higher values favour pentoxifylline)										
1 (Fallahi 2013)	RCT	20	MD -1.00 (-5.47, 3.47)	-	-	Not serious	N/A	Not serious	Very serious[3]	Low

1. 95% confidence interval crosses both ends of a defined MID interval
2. 95% confidence interval crosses one end of a defined MID interval
3. Non-significant result and small sample size

Bosentan versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean pulmonary artery pressure (mPAP) – mmHg (lower values favour bosentan)										
1 (Valerio 2009)	RCT	32	MD -8.00 (-12.52, -3.48)	-	-	Very serious[1]	N/A	Not serious	Not serious	Low
FEV1 - % predicted (higher values favour bosentan)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Valerio 2009)	RCT	32	MD 6.00 (-4.75, 16.75)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Partial pressure of arterial oxygen (PaO_2) - mmHg (higher values favour bosentan)										
1 (Valerio 2009)	RCT	32	MD 7.00 (-0.07, 14.07)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
6 minute walk distance – metres (higher values favour bosentan)										
1 (Valerio 2009)	RCT	32	MD 84.00 (-18.53, 186.53)	-	-	Very serious[1]	N/A	Not serious	Serious[3]	Very low
St. George's respiratory questionnaire (SGRQ), total score (lower values favour bosentan)										
1 (Valerio 2009)	RCT	32	MD 5.00 (-4.01, 14.01)	-	-	Very serious[1]	N/A	Not serious	Very serious[4]	Very low
WHO breathlessness scale (Grade) (lower values favour bosentan)										
1 (Valerio 2009)	RCT	32	MD -0.45 (-1.22, 0.32)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low

1. High risk of bias for selective reporting and blinding of participants, personnel and outcome assessors; unclear risk of bias for allocation concealment and outcome data.
2. Non-significant result
3. 95% confidence interval crosses one end of a defined MID interval
4. 95% confidence interval crosses both ends of a defined MID interval

Nitric Oxide versus no intervention

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean pulmonary artery pressure (mPAP) – mmHg (lower values favour nitric oxide)										
1 (Vonbank 2003)	RCT	32	MD -7.60 (-11.56, -3.64)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
Partial pressure of arterial oxygen (PaO_2) - kPa (higher values favour nitric oxide)										
1 (Vonbank 2003)	RCT	32	MD 0.40 (-0.81,1.61)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Mortality - number of deaths (lower values favour nitric oxide)										
1 (Vonbank 2003)	RCT	40	RR 0.33 (0.01, 7.72)	Not calculable[2]	Not calculable[2]	Serious[1]	N/A	Not serious	Serious[2]	Low

1. High risk of bias due to a lack of information regarding blinding of study participants, personnel and assessors.
2. Non-significant result
3. No events occurred in the control arm of the trial

Azithromycin versus no intervention

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Partial pressure of arterial oxygen (PaO_2) (higher values favour azithromycin)										
1 (Wang 2017)	RCT	86	MD 8.43 (6.66, 10.02)	-	-	Very serious[1]	N/A	Not serious	Not serious	Low
6 minute walk distance – metres (higher values favour azithromycin)										
1 (Wang 2017)	RCT	86	MD 83.90 (71.00, 96.80)	-	-	Very serious[1]	N/A	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

1. Study at high risk of bias due to the lack of blinding of participants, personnel and outcome assessors and the lack of a data for the breathlessness outcome.

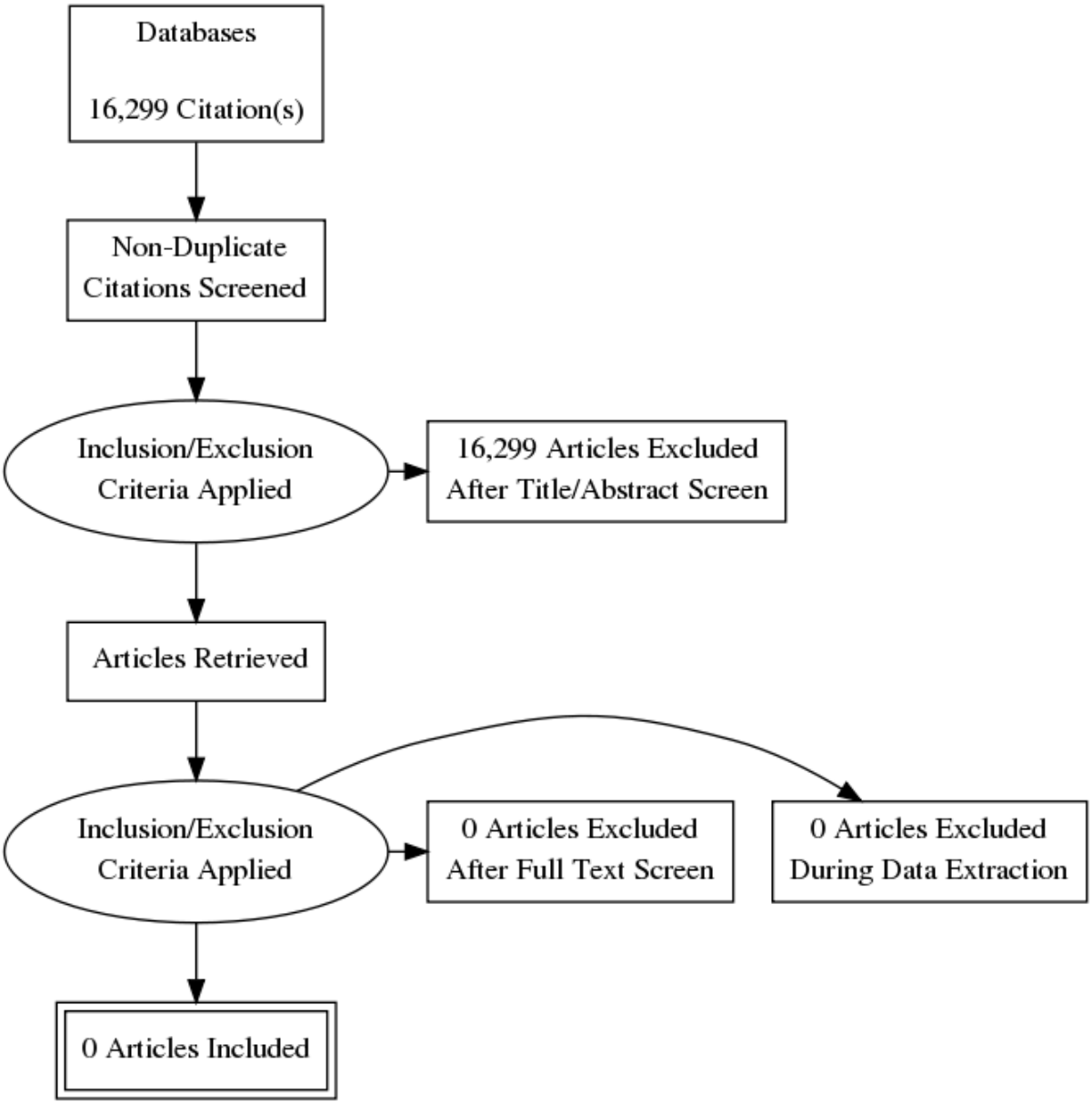
Cor pulmonale

Long term oxygen therapy versus no oxygen

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Rate of change in Partial pressure of arterial oxygen (PaO_2) (higher values favour LTOT)										
1 (MRC 1981)	RCT	59	MD 2.69 (0.49, 4.90)	-	-	Very serious[1]	N/A	Not serious	Not serious	Low
FEV1 (higher values favour LTOT)										
1 (MRC 1981)	RCT	61	MD 0.02 (-0.02, 0.07)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Mortality– number of deaths (lower values favour LTOT)										
1 (MRC 1981)	RCT	87	RR 0.68 (0.46, 1.00)	66.67 per 100	45.33 per 100 (30.67, 66.67)	Very serious[1]	N/A	Not serious	Serious[2]	Very low

1. Issues with selective reporting of data (men only) and blinding of participants, personnel and outcome assessors.
2. Non-significant result

Appendix H – Economic evidence study selection



Appendix I – Excluded studies

Clinical studies

Short Title	Title	Reason for exclusion
Adnot (1988)	The effects of urapidil therapy on hemodynamics and gas exchange in exercising patients with chronic obstructive pulmonary disease and pulmonary hypertension	Study duration <12 weeks
Alkhayat (2016)	Sildenafil citrate therapy for secondary pulmonary arterial hypertension due to chronic obstructive lung disease	Not a relevant study design
Blanco (2010)	Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension	Study duration <12 weeks
Blanco (2013)	Sildenafil treatment to improve the outcomes of pulmonary rehabilitation in COPD: A randomized, controlled trial	Conference abstract
Boeck (2011)	Inhalation of a prostacyclin analog (iloprost) does not improve exercise capacity in COPD with disproportional pulmonary hypertension	Conference abstract
Chogtu (2016)	A prospective, randomized study: Evaluation of the effect of rosuvastatin in patients with chronic obstructive pulmonary disease and pulmonary hypertension	Data not reported in an extractable format. The paper does not present primary data for the outcomes of interest and the CI around the MD for the 6MW test is implausibly small.
Danahy (1979)	Effects of isosorbide dinitrate on pulmonary hypertension in chronic obstructive pulmonary disease	Study duration <12 weeks
Dwivedi (2015)	Assessment of short term effects of sildenafil therapy in patients with secondary pulmonary hypertension	Conference abstract
Elborn (1992)	The effects of flosequinan on hemodynamics and oxygen delivery in cor pulmonale	Study duration <12 weeks
Feuring (2000)	Moxonidine and ramipril in patients with hypertension and obstructive pulmonary disease	Study duration <12 weeks
Goudie (2013)	Do phosphodiesterase 5 inhibitors improve exercise capacity in patients with COPD associated pulmonary hypertension? (3P study)	Conference abstract
Harris (2010)	The effects of sildenafil in pulmonary hypertension secondary to chronic obstructive pulmonary disease	Conference abstract

Short Title	Title	Reason for exclusion
Horita (2014)	Statins reduce all-cause mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis of observational studies.	SR of wrong study type (not RCTs) or SR did not include any relevant RCTs
Kennedy (1984)	Nifedipine inhibits hypoxic pulmonary vasoconstriction during rest and exercise in patients with chronic obstructive pulmonary disease. A controlled double-blind study	Study duration <12 weeks
Lampert (1991)	Disappearance of molsidomine effects on pulmonary circulation of patients with chronic obstructive pulmonary disease after a three week treatment	Study duration <12 weeks
Lee (2004)	Effect of beraprost sodium in patients with chronic obstructive pulmonary disease	Study not reported in English
Liker (1975)	Portable oxygen in chronic obstructive lung disease with hypoxemia and cor pulmonale. A controlled double-blind crossover study	Study duration <12 weeks
Lin (1996)	Comparisons of long-term effects of lisinopril vs nifedipine vs conventional therapy in the treatment of mild-to-moderate hypertension in patients with chronic obstructive pulmonary disease	Study does not contain any of the outcomes of interest
Liu (2015)	Influence of Rho kinase inhibitor fasudil on late endothelial progenitor cells in peripheral blood of COPD patients with pulmonary artery hypertension	Study duration <12 weeks
Nenci (1988)	Effects of dipyridamole on the hypoxemic pulmonary hypertension of patients with chronic obstructive pulmonary disease	Not a relevant study design
Oh (2015)	Effects of trimetazidine on patients with chronic obstructive pulmonary disease and pulmonary hypertension	Conference abstract
Oliver (1996)	Xamoterol improves right ventricular systolic and diastolic function in pulmonary heart disease	Study duration <12 weeks
Park (2013)	Systemic review and meta-analysis of pulmonary specific therapy for exercise capacity in COPD	Full text paper not available
Pourdowlat (2013)	Is there a new indication and route of administration for an old drug in pulmonary hypertension (PH) secondary to COPD? a pilot study	Conference abstract
Prins (2016)	Use of PAH-specific therapy in world health organization group iii pulmonary hypertension: A systematic review and meta-analysis	Conference abstract

Short Title	Title	Reason for exclusion
Salem (2014)	Short term effects of sildenafil citrate therapy in secondary pulmonary hypertension	Study duration <12 weeks
Seibold (1994)	Elderly patients benefit from calcium antagonist therapy	Study not reported in English. Study duration <12 weeks
Sharif-Kashani (2014)	The Effect of Amlodipine and Sildenafil on the NT-ProBNP Level of Patients with COPD-Induced Pulmonary Hypertension	Study does not contain any of the outcomes of interest. Study duration <12 weeks
Sin (2007)	Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients with advanced COPD	Does not contain a population of people with COPD, and cor pulmonale or pulmonary hypertension
Skwarski (1989)	The effects of mexiletine on cardiac arrhythmias in patients with cor pulmonale	Study duration <12 weeks
Wever (1983)	The influence of guanfacine on blood pressure and lung function in hypertensive patients with chronic obstructive lung disease	Study duration <12 weeks
Zielinski (1986)	Captopril effects on pulmonary and systemic hemodynamics in chronic cor pulmonale.	Study duration <12 weeks

Appendix J – Research recommendations

Question	What are the most clinical and cost effective treatments for pulmonary hypertension in people with COPD?
Population	People diagnosed with pulmonary hypertension secondary to COPD
Interventions	Any relevant intervention (including pharmacological treatments, pulmonary rehabilitation and non-invasive ventilation)
Comparator	• Each other • Placebo
Outcomes	• Mortality • Hospital admissions, re-admissions and bed days • Exacerbations • Breathlessness, orthopnoea, ankle swelling • Arterial oxygen partial pressure (PaO2) • Resting oxygen saturation (SaO2) • Exercise capacity/ exercise tolerance (walk test) • Change in FEV1 • Adverse events: all, severe, treatment discontinuation • Quality of life • Resource use and costs
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	Pulmonary hypertension is a common complication of COPD that is associated with a worse disease prognosis, including an increased rate of exacerbations, reduced exercise capacity and reduced survival. Treatment of this complication could improve quality of life for people with COPD.
Relevance to NICE guidance	Moderate-priority: a negative recommendation was made due to the lack of evidence for an effective treatment. This recommendation could be changed if a new treatment was shown to be effective for the outcomes of most interest to people with pulmonary hypertension secondary to COPD or if new evidence supported the use of an existing intervention.
Current evidence base	Although there were a number of studies looking at pharmacological treatments for pulmonary hypertension secondary to COPD, some of these studies had methodological limitations that increased the uncertainty surrounding their results. In addition, there were inconsistencies in the evidence base within some drug classes that further complicated interpretation. No evidence was identified for the effectiveness of non-pharmacological interventions.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with pulmonary hypertension secondary to COPD that intervention studies in this area should be feasible.

Appendix K – References

Clinical evidence - included studies

Pulmonary hypertension - RCTs

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