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[Intervention Review]

Anticoagulation therapy versus placebo for pulmonary hypertension

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ABSTRACT

Background

Elevation of pulmonary pressure is no longer a rare disease, given its multifactorial etiology. However data on the actual incidence of this condition are still limited, and controversies regarding its management are ongoing. Use of anticoagulation in the management of pulmonary hypertension is based on the presence of in situ thrombosis in the patient with pulmonary arterial hypertension (PAH) and on retrospective evidence of clinical benefit. Current practice is dependent mostly on expert opinion and individualised experience. The real benefit of its use in different types of pulmonary hypertension is still debatable, and the therapeutic target of the international normalised ratio (INR) among treated patients remains inconclusive. Adverse outcomes associated with anticoagulants are significant and can include fatal haemorrhage. Justification for the use of this intervention requires critical evaluation of randomised controlled trials.

Objectives

1. To evaluate the effectiveness of, and potential adverse events associated with, anticoagulation in the management of pulmonary hypertension (PH).
2. To evaluate the effective therapeutic INR in pulmonary hypertensive patients receiving anticoagulants (North American centres 1.5 to 2.5, European centres 2.0 to 3.0).

Search methods

We identified trials through searches of the following databases.

Cochrane Airways Group Trials Register; Cochrane Central Register of Controlled Trials (CENTRAL), part of *The Cochrane Library*; MEDLINE (Ovid); EMBASE (Ovid); CINAHL (EBSCOhost); Clinical trials.gov and the World Health Organization (WHO) trials portal. The trial search date was 28 March 2014.

Selection criteria

We planned to include only randomised controlled trials. Participants with PH with co-morbidities including medical conditions requiring long-term anticoagulation were to be included. We also planned to include trials comparing any anticoagulant with placebo.

Data collection and analysis

Review authors (IE and HE) independently appraised all identified citations to establish their relevance for inclusion in the review. IE and HE independently screened the titles and abstracts of all identified potential studies for inclusion.

Main results

No eligible trials were identified for inclusion in this review.

Authors' conclusions

No eligible studies were identified for inclusion in this review. Although our review of available non-randomised studies shows beneficial effect, this finding should be interpreted with caution since there are likely to be biases associated with their design and our methods were not designed to identify, appraise and summarise evidence from them. So that better decisions can be made regarding the effectiveness of this intervention, well-designed randomised controlled trials are needed.

PLAIN LANGUAGE SUMMARY

Blood thinners for pulmonary hypertension

Background

The heart has four chambers: two upper and two lower chambers. The lower right chamber, also known as the right ventricle, pumps blood through the pulmonary artery to the lungs, where the blood receives oxygen. Pulmonary hypertension occurs when pressure in the pulmonary arteries is increased to above normal (8 to 25 mmHg). When this happens over time, inflammation of the pulmonary artery occurs. The arteries may then become stiff and tighten. These changes make it difficult for the heart to pump blood to the lungs. The heart becomes weaker as it tries to push against this pressure; the resulting disturbance to blood flow can lead to blood clots. These clots can travel to the lungs, which can worsen the person's condition and may result in death.

People with pulmonary hypertension may complain of tiredness, chest pain and shortness of breath during normal activities like walking and running, which may progress to affect all physical activities. Prospects of survival depend on several factors, but pregnancy is strongly associated with poor survival.

Treatment of this disease is multi-faceted and includes rehabilitation, psychosocial support and surgical and medical treatment. Medical treatment includes the use of blood thinners such as warfarin, heparin, fondaparinux, argatroban, dabigatran, apixaban and rivaroxaban. Blood thinners work by preventing the formation of clot. The blood thinner of choice, warfarin, needs close monitoring with daily to weekly laboratory testing to maintain the therapeutic target; this monitoring may be difficult to keep up with. The major side effect of blood thinners is bleeding, which can manifest as easy bruising, bleeding in the digestive tract and bleeding into the brain; severe cases can be fatal.

Review question

We set out to evaluate the effectiveness of blood thinners in the treatment of pulmonary hypertension. No eligible studies (randomised controlled trials) were found. Review of other studies (non-randomised controlled trials) shows the effectiveness of this intervention. However, these findings should be interpreted with caution because of the low quality of evidence provided by these studies.

Conclusion

No randomised evidence is available. We decided to look at the results of other studies (non-randomised control trials). They provide only poor quality evidence of effectiveness of this intervention, and the results should be interpreted with caution. We are uncertain as to how far the results of studies with this design can be believed, and our own approach was not designed to properly look for them and incorporate them in our systematic review. This review therefore highlights the need for appropriately designed randomised controlled trials.

BACKGROUND

Description of the condition

Pulmonary hypertension (PH) is defined as an increase in pulmonary arterial pressure (PAP) greater than or equal to 25 mmHg at rest as assessed by right heart catheterisation (D'Alonzo 1991). It is a progressive disease that can be fatal if untreated, although the rate of progression is highly variable. Available data show that the normal mean PAP at rest is 14 ± 3 mmHg with an upper limit of normal of approximately 20 mmHg (Badesch 2009; Kovasc 2009).

PH was previously classified as primary pulmonary hypertension, now called idiopathic pulmonary arterial hypertension (IPAH), or secondary PH (Rich 1998). The World Health Organization (WHO) classified PH into five groups on the basis of etiopathogenesis (Simoneau 2009).

Group 1 PAH is pulmonary arterial hypertension (PAH). This group consists of sporadic IPAH, heritable IPAH and PAH due to diseases that localise to small pulmonary muscular arterioles. These diseases include connective tissue diseases, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia, persistent pulmonary hypertension of the newborn, pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis. Drug-induced PAH (including anorexigens) and toxin-induced PAH are also considered to belong to group 1 PAH.

Group 2 PH is pulmonary hypertension due to left heart disease. PH due to systolic dysfunction, diastolic dysfunction or valvular heart disease is included in this group. Group 3 PH is pulmonary hypertension due to lung disease or hypoxaemia. This group includes PH caused by chronic obstructive pulmonary disease, interstitial lung disease, pulmonary disease with a mixed restrictive and obstructive pattern, sleep-disordered breathing and alveolar hypoventilation disorders. Group 4 PH is chronic thromboembolic pulmonary hypertension. This group includes PH due to thromboembolic occlusion of the proximal or distal pulmonary vasculature. Group 5 PH is pulmonary hypertension with unclear, multi-factorial mechanisms.

Although the prevalence of group 1 PAH in the general population is estimated to be five to 15 cases per one million adults (Humbert 2006; Ling 2012), a paucity of data can be found on prevalence among other groups of PH.

The prognosis of PH depends on various factors. The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk score is used to predict disease progression. Poor prognostic indicators include age at initial presentation > 50 years (Peacock 2007), male sex and ≥ 60 years (Marcus 2008), persistent (WHO) functional class III or IV pericardial effusion and elevated right atrial pressure (Paulus 2007; Torbicki 2007). One-, three- and five-year survival rates are 84%, 67% and 58%, respectively, with a median survival of 3.6 years (Thenappan 2007). Pregnancy is noted to be associated with 30% to 50% mortality in patients with PAH (Bedard 2009).

Description of the intervention

Recently, treatment of PH has undergone an extraordinary evolution. Management of PH is multi-faceted and includes rehabilitation, psychosocial support and surgical and medical treatment.

Background medical therapy includes diuretics, oxygen and anti-coagulants. In a select group of patients with proven vasoreactivity, calcium channel blockers, for example, nifedipine and diltiazem, can be used. Specific PAH medical therapy comprises endothelin receptor antagonists, for example, ambrisentan and bosentan; phosphodiesterase-5 inhibitors, for example, sildenafil and prostanooids, for example, epoprostenol. Balloon atrial septostomy, septal defect closure and lung transplantation or heart-lung transplantation are the surgical interventions used in advanced cases.

It is generally accepted that anticoagulation is indicated in patients with IPAH (Barst 2009; Galie 2009; McLaughlin 2009), hereditary PAH, drug-induced PAH (Barst 2009; Galie 2009) and chronic thromboembolic PH. Anticoagulants include warfarin, heparin, fondaparinux, argatroban, dabigatran, apixaban and rivaroxaban, but the anticoagulant of choice is warfarin. The target international normalised ratio (INR) in patients with IPAH varies from 1.5 to 2.5 (in most North American centres) to 2.0 to 3.0 (in European centres) (Galie 2009). The starting dose of warfarin is 2 to 5 mg daily, which can be increased until the target INR is achieved. The half-life is 20 to 60 hours and is highly variable depending on the rate of clotting factor catabolism. Warfarin is usually taken once a day by mouth, with or without food, at around the same time every day. It is metabolised in the liver and excreted by the kidneys. Warfarin is also prescribed for selected patients with atrial flutter, atrial fibrillation, prosthetic (replacement or mechanical) heart valves and venous thrombosis. However, the purpose of this review is to evaluate the effects of warfarin and other anticoagulants in the treatment of PH.

Some medications used in the treatment of PH have a significant interaction with warfarin. Concomitant use of epoprostenol (Ogawa 2005) or sitaxsentan (Widlitz 2005) and warfarin increases the risk of bleeding, and bosentan decreases the anticoagulant effect of warfarin (Murphy 2003).

How the intervention might work

PAH is a proliferative vasculopathy characterised by vasoconstriction, cell proliferation, fibrosis and thrombosis. Pathologic findings include intimal hyperplasia and fibrosis, medial hypertrophy and in situ thrombi of the small pulmonary arteries and arterioles (Humbert 2004; Pietra 2004). The pathologic appearance of the small pulmonary arteries and arterioles is qualitatively similar in all patients with group 1 PAH. It is unclear how applicable these mechanisms are to most other types of PH. Current evidence suggests that abnormalities of blood coagulation factors, antithrombotic factors and the fibrinolytic system contribute to a prothrombotic state in patients with IPAH (Johnson 2006a). Patients with PH are at increased risk for intrapulmonary thrombosis and thromboembolism due to sluggish pulmonary blood flow, dilated right heart chambers, venous stasis and immobility. Even a small thrombus can produce haemodynamic deterioration in a patient with a compromised pulmonary vascular bed. The prevalence of vascular thrombotic lesions at postmortem is high in patients with IPAH (Fuster 1984), and histologic evidence of microvascular thrombosis has been found (Bjornsson 1985; Wagenvoort 1980). A previous pathophysiologic review identified several lines of evidence to suggest a relationship between thrombotic arteriopathy and PAH (Johnson 2006a). An anticoagulant is believed to reduce the risk of thrombus formation and embolisation. Anticoagulants like warfarin act by inhibiting the gamma-carboxylation of clotting factors II, V, VII and IX, and endogenous anticoagulants protein C and pro-

tein S. Other anticoagulants function by different mechanisms, for example, argatroban directly inhibits thrombin, whereas fondaparinux directly inhibits activated factor X. Interruption of this coagulation cascade by anticoagulants theoretically should improve survival in patients with PH. This presents a plausible rationale for the use of oral anticoagulation in PH.

Why it is important to do this review

Justification for the use of anticoagulation therapy, as well as its effectiveness and survival benefit, in patients with PH remains uncertain. Current guidelines for anticoagulation with warfarin are based on non-controlled, observational studies along with expert opinion. A recent study found that treatment with warfarin has a low probability of improving survival in systemic sclerosis-associated PAH or IPAH (Johnson 2012a). In a systematic review of seven observational studies that evaluated the effect of warfarin in patients with group 1 PAH, the review authors reported that five studies found a mortality benefit while two studies did not support its effectiveness in IPAH (Johnson 2006). Anticoagulation therapy is not without risk, and risk of major haemorrhage is of greatest concern. The situation is even more grave in patients with increased risk of bleeding, such as those with advanced age; concomitant renal, cardiac or hepatic disease; diabetes (DiMarco 2005); scleroderma (Duchini 1998) and portopulmonary hypertension with severe oesophageal varices (Galie 2009). It is therefore pertinent that we evaluate the effectiveness and potential adverse events associated with anticoagulation in patients with PH.

OBJECTIVES

1. To evaluate the effectiveness of, and potential adverse events associated with, anticoagulation in the management of pulmonary hypertension (PH).
2. To evaluate the effective therapeutic INR in pulmonary hypertensive patients receiving anticoagulants (North American centres 1.5 to 2.5, European centres 2.0 to 3.0).

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs). We also planned to include studies reported in full text, those published as abstracts only and unpublished data. We planned to exclude non-RCTs.

Types of participants

We planned to include all individuals with PH of group 1 through group 5, irrespective of their WHO functional class. PH was defined as an increase in PAP greater than or equal to 25 mmHg at rest as assessed by right heart catheterisation. Patients with PH with comorbidities including medical conditions requiring long-term anticoagulation were also included. No exclusion was based on age, sex or cause of PH.

Types of interventions

We planned to include trials comparing warfarin with placebo, heparin with placebo, argatroban with placebo, fondaparinux with placebo and any other anticoagulant with placebo.

Types of outcome measures

Primary outcomes

1. Mortality.
2. Six-minute walk test.
3. Haemorrhage from anticoagulant use (number of people experiencing one or more events): Bleeding requiring significant intervention will be regarded as a major bleed.

Secondary outcomes

1. Cardiopulmonary exercise testing.
2. Thromboembolism (number of people experiencing one or more events).
3. Pulmonary arterial pressure (PAP).
4. Pulmonary vascular resistance.
5. World Health Organization (WHO) functional class.
6. Adverse events other than haemorrhage: soft tissue necrosis, gangrene, tracheobronchial calcification.

Search methods for identification of studies

Electronic searches

We identified trials by searching the following databases.

1. Cochrane Airways Group Trials Register (all years to March 2014).
2. Cochrane Central Register of Controlled Trials (CENTRAL) 2014, Issue 1, part of *The Cochrane Library*.
3. MEDLINE (Ovid) (1946 to March week 3 2014).
4. EMBASE (Ovid) (1974 to week 12 2014).
5. CINAHL (EBSCOhost) (1937 to March 2014).

Searches were conducted in August 2013 and were updated in March 2014. The strategies used in each database are described in [Appendix 1](#). We handsearched conference abstracts and grey literature through the CENTRAL database. We imposed no restrictions on language or type of publication. We also conducted a search of ClinicalTrials.gov (<http://clinicaltrials.gov>) and the WHO trials portal (www.who.int/ictrp/en/).

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We planned to search for errata or retractions from the included studies.

Data collection and analysis

Review authors (IE and HE) independently appraised all identified citations to establish their relevance for inclusion in the review. Studies were reviewed for relevance on the basis of study design, types of participants, interventions and outcome measures. Disagreements were resolved by discussion. We gave reasons for excluding potentially relevant trials in the table [Characteristics of excluded studies](#).

Selection of studies

Two review authors (IE and HE) independently screened the titles and abstracts of all potential studies for inclusion identified as a re-

sult of the search, and coded them as 'retrieve' (eligible or potentially eligible or unclear) or 'do not retrieve.' We retrieved the full-text study reports, and two review authors (JN and CE) independently screened the full text and identified no eligible studies for inclusion. Reasons for exclusion of ineligible studies were noted. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

We identified no eligible studies for inclusion in this review. We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. If eligible studies had been found, one review author (IE) would have extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals and date of study.
2. Participants: total number (N), mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (IE and HE) would have independently extracted outcome data from included studies. We would have noted these in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We would have resolved disagreements by reaching consensus or by involving a third review author (JN). One review author (CE) would have transferred the data to a [Review Manager \(RevMan\) 2012](#) file. We would have double-checked that data were entered correctly by comparing data presented in the systematic review versus those provided in the study reports. A second review author (HE) would have spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

No eligible trials were identified for inclusion in this review. If eligible studies had been found, two review authors (CE and JN) would have independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We would have resolved disagreements by discussion. We would have assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We would have graded each potential source of bias as high, low or unclear and would have provided a quote from the study report, together with a justification for our judgement, in the 'Risk of bias' table. We would have summarised the risk of bias judgements across different studies for each of the domains listed. We would have considered blinding separately for different key outcomes when necessary. When information on risk of bias was related to unpublished data or correspondence with a trialist, we would have noted this in the 'Risk of bias' table.

When considering treatment effects, we would have taken into account the risk of bias for all studies that contributed to a particular outcome.

Assessment of bias in conducting the systematic review

No eligible trials were identified for inclusion in this review. We conducted the review according to the published protocol and reported any deviations from it in the [Differences between protocol and review](#) section of the systematic review.

Measures of treatment effect

No eligible trials were identified for inclusion in this review. If eligible studies had been identified, we planned to analyse dichotomous data as odds ratios and continuous data as mean differences or standardised mean differences. We would have entered presented data as a scale with a consistent direction of effect.

We planned to undertake meta-analysis only when this would be meaningful, that is, when treatments, participants and the underlying clinical question were similar enough (homogeneous) for pooling to make sense. We would have described skewed data reported as medians and interquartile ranges.

When multiple trial arms were reported in a single trial, we planned to include only the relevant arms. If two comparisons (e.g. warfarin vs placebo and heparin vs placebo) were combined in the same meta-analysis, we would have halved the control group to avoid double-counting.

Unit of analysis issues

No eligible trials were identified for inclusion in this review. Studies with similar units of analysis were planned to be grouped together for the purposes of analysis. Studies with different units of analysis would not have been pooled for analysis.

Dealing with missing data

No eligible trials were identified for inclusion in this review. We planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only). When this was not possible and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

No eligible trials were identified for inclusion in this review. We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we would have reported this and would have explored possible causes by performing prespecified subgroup analyses. We planned to

consider an I^2 value of 50% to 90% as reflecting substantial heterogeneity.

Assessment of reporting biases

No eligible trials were identified for inclusion in this review. If we had been able to pool more than 10 trials, we would have created and examined a funnel plot to explore possible small study biases.

Data synthesis

No eligible trials were identified for inclusion in this review. All eligible studies would have been summarised in RevMan. We planned to extract the data and enter all data into RevMan, and all entries would have been rechecked by the review authors. Disagreements would have been resolved by discussion. If no consensus was reached, the Cochrane Airways Review Group would have been contacted. We planned to use a fixed-effect model and to perform a sensitivity analysis using the random-effects model.

Summary of findings table

We identified no eligible trials for inclusion in this review. We planned to create a 'Summary of findings' table using the following outcomes: mortality, six-minute walk test, risk of haemorrhage from anticoagulant use, cardiopulmonary exercise testing, decreased risk of thromboembolism, decreased pulmonary arterial pressure and effect on WHO functional class. We planned to use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the studies contributing data to the meta-analyses for prespecified outcomes. We planned to use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. We planned to justify all decisions to downgrade or upgrade the quality of studies using footnotes, and we would have made comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

No eligible trials were identified for inclusion in this review. Possible sources of heterogeneity in this review would have included type of intervention, for example, various anticoagulant preparations, gender and age of programme recipients.

We planned to carry out the following subgroup analyses.

1. Type of anticoagulant (warfarin, heparin, argatroban, fondaparinux, dabigatran, apixaban, rivaroxaban).

2. Anticoagulant use in relation to different groups of PH (groups 1 to 5).

We planned to use the following outcomes in subgroup analyses.

1. Mortality benefits.
2. Decreased risk of intrapulmonary thrombosis.
3. Serious adverse events (haemorrhage).

We would have used the formal test for subgroup interactions in [Review Manager \(RevMan\) 2012](#).

Sensitivity analysis

We identified no eligible trials for inclusion in this review. If the number of studies and available data had allowed for sensitivity analysis, we would have performed a sensitivity analysis by using one or all of the following strategies.

1. Removing studies with high risk of bias to see whether any effect on the results of the meta-analysis occurred.
2. Reanalysing studies with missing data using a reasonable range of missing values.
3. Reanalysing data using different statistical approaches.

Reaching conclusions

We identified no eligible trials for inclusion in this review. We planned to base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We planned to avoid making recommendations for practice. Our implications for research suggest priorities for future research and outline remaining uncertainties in the area.

RESULTS

Description of studies

See [Characteristics of excluded studies](#). No eligible trials were identified for inclusion in this review.

Results of the search

The electronic literature search identified a total of 3332 references after duplicates were removed. These references were screened by two review authors and were initially assessed on the basis of title and abstract. Following this, the full text of 36 relevant papers was obtained and translated when necessary. We found no studies that met the inclusion criteria. See [Figure 1](#) for the study flow diagram.

Figure 1. Study flow diagram.

Included studies

We identified no eligible trials for inclusion in this review.

Excluded studies

See [Characteristics of excluded studies](#).

Risk of bias in included studies

We identified no eligible trials for inclusion in this review.

Effects of interventions

We identified no eligible trials for inclusion in this review.

DISCUSSION

Treatment of pulmonary hypertension remains a challenging area in clinical medicine. Over several decades of initiation of oral anticoagulation in the management of pulmonary hypertension, no strong clinical evidence of its efficacy has been noted. Although some study authors argue for the use of anticoagulants in the management of idiopathic pulmonary arterial hypertension, greater uncertainty surrounds its effectiveness in other forms of pulmonary hypertension. Thus there is a tradeoff between potential serious adverse events and supposed benefits. For superior decision making regarding this intervention, a systematic review of well-designed randomised controlled trials is essential.

Summary of main results

We set out to perform a critical evaluation of the effectiveness and/or harm of anticoagulation therapy in the management of pulmonary hypertension. We were not able to identify any randomised controlled trials for inclusion in this review.

Overall completeness and applicability of evidence

We identified no eligible RCTs for this review. However we were able to identify some illustrative non-randomised studies. These included non-randomised prospective studies, retrospective studies, reviews of expert opinion, case series and case reports, all of which present low to very low quality of evidence. However, we are about to summarise non-randomised evidence derived from other trials to inform future research. Most of these studies report survival benefit of anticoagulation therapy in the treatment of pulmonary hypertension. In this regard, the studies we describe below should be interpreted with caution.

Summary of non-randomised studies

A new study ([Olsson 2014](#)) from the COMPERA registry, an ongoing pulmonary hypertension registry, included a sample of 1283 participants who were newly diagnosed with pulmonary arterial hypertension since 2007. Eight hundred participants had IPAH, and the remaining participants had other forms of pulmonary arterial hypertension. Sixty-six percent and 44% of participants, respectively, with idiopathic pulmonary arterial hypertension and other forms of PH received anticoagulation therapy. Most participants given anticoagulation were older and had worse functional classes and baseline haemodynamics. Three-year follow-up revealed statistically significant survival benefit among participants with IPAH who were given anticoagulation, despite their increased baseline morbidity. Estimated survival probability at one, two and three years

in the coagulation group was 94.9%, 86.8% and 76.9% compared with 90.9%, 80.9% and 66.3% among the untreated group, respectively (P value 0.006). No survival benefit of anticoagulation use has been noted among participants with other forms of PH. However, it is worthy of note that the average age of participants enrolled in the COMPERA registry is much higher than that of participants enrolled in other registries, raising the possibility of associated co-morbidities, more frequent with aging, that may benefit from anticoagulation.

In another study, 173 participants, predominantly women (144), with PPH or drug-induced PH were retrospectively reviewed ([Frank 1997](#)). Investigators reported significantly better survival time in aminorex-induced, plexogenic pulmonary arteriopathy compared with idiopathic disorders or PPH, independent of anticoagulation. Among participants treated with warfarin, significant improvement in quality of life (improvement in symptoms was seen in 44.8% of the anticoagulated group, and deterioration was noted in 72.2% of the control group), pulmonary pressure and survival benefit, especially in drug (anorexigen)-induced PH, was noted, with long-term survival of 7.5 years versus 3.9 years among untreated participants (P value < 0.001). Participants who received warfarin earlier had 10.9 years' versus 5.9 years' survival compared with participants who received it two years thereafter.

Available prospective studies support the use of anticoagulation in chronic thromboembolic pulmonary hypertension (CTEPH) and PPH. [Romaszkiewicz 2006](#) conducted a prospective analysis of 29 newly diagnosed participants with CTEPH (males nine, females 20) between 37 and 82 years of age who had not been treated with pulmonary endarterectomy and were not receiving anticoagulation. Long-term oral anticoagulation with acenocoumarol at a dose adjusted to recommend an INR between two and three was then initiated, and its efficacy was monitored at the beginning and at the end of one-year follow-up. Investigators suggested that a favourable prognosis after isolated anticoagulation is likely in patients with newly diagnosed CTEPH, mild and moderate baseline pulmonary hypertension and acceptable exercise tolerance. Of 20 participants of New York Heart Association (NYHA) Class III before initiation of anticoagulation, 13 had a lesser class after one year of anticoagulation. A decrease in pulmonary arterial systolic pressure of about 11 mmHg after anticoagulation (P value < 0.001) was also noted. Investigators suggested the necessity for anticoagulation in such patients before pulmonary endarterectomy.

In another prospective non-randomised study of 71 participants diagnosed with primary pulmonary hypertension between 1985 and 1991 ([Rich 1992](#)), seven participants were excluded because they were severely ill. The remaining 64 participants were treated with high-dose calcium channel blockers and were further classified on the basis of reduction in pulmonary artery pressure after treatment. A total of 17 participants responded to the calcium channel blocker. Investigators evaluated the effect of concurrent therapy. Warfarin was given to 55% of the study group (47% of responders and 57% of non-responders). Significant survival benefit was noted among participants who received warfarin compared with the non-warfarin group. It is pertinent to note that survival was very prominent among calcium blocker non-responders, with 91%, 62% and 47% survival over one, three and five years, respectively, compared with 52%, 31% and 31%, respectively, of the non-warfarin group. Given the small size and the non-randomised nature of this

study, the risk of bias is high. In addition, participants had already received diuretic and digoxin therapy before receiving warfarin.

Kawut 2005 reviewed 84 participants who were newly diagnosed with pulmonary arterial hypertension between 1994 and 2002 with a median follow-up of 764 days. Participants included 66 individuals with IPAH, 14 with familial PAH and four with PAH related to anorexigen use. Female participants accounted for 81% of the study population, and the mean age of participants was 42 ± 14 years. Ninety-four percent of participants received warfarin. Primary outcome measures were death, lung transplant or survival at one, three and five years. In their univariate analysis of transplant-free survival among treated participants, the hazard ratio was 0.33 with 95% CI 0.12 to 0.90 (P value 0.03). This study reports that lack of warfarin use was associated with a significant increase in mortality. However 39% and 86% of participants received oral calcium channel blocker and digoxin. Thus it may be difficult to attribute this effect solely to warfarin.

Fuster 1984 reviewed a clinical series of 120 participants with primary pulmonary hypertension. Eighty-seven women were included in the study, and the mean age at entry into the study was 34 years. The review authors defined anticoagulated participants as those treated with anticoagulant who commenced therapy within the first year after diagnosis. Univariate and multi-variate analyses showed a beneficial effect of anticoagulation therapy on overall survival in participants with chronic thromboembolic pulmonary hypertension and those with plexogenic pulmonary arteriopathy. At the end of three-year follow-up, percent survival was about 50% compared with about 25% among the non-treated group. However, the review authors noted that the number of study participants was small.

Similarly, **Ogata 1993** studied retrospectively a small number (20) of participants who had primary pulmonary hypertension; seven were treated with vasodilator and warfarin, and the rest served as control with no vasodilator and with no warfarin. Study authors reported significant survival benefit and improvement in haemodynamics among the treatment group. The five-year survival rate is 57% versus 15% among the non-treated group, respectively (P value < 0.05). However, it is unclear whether these improvements were result of vasodilator, warfarin or a synergistic effect.

The rationale for the use of anticoagulation in the management of pulmonary arterial hypertension is based on the thrombophilic predisposition of patients with such disease. The therapeutic INR target to be achieved in participants with pulmonary hypertension treated with warfarin varies from centre to centre (**Galie 2009**). Anticoagulation therapy is associated with bleeding risk, which could be fatal; thus the lowest possible effective INR therapy should be pursued. A prospective study by **Jansa 2011** looked into thrombin generation at different levels of INR in 58 participants with IPAH receiving stable doses of warfarin. A significant reduction in thrombin generation was noted in participants with INR between 1.5 and 2.5 compared with the control group with INR less than 1.5 ($r = -0.709$, P value < 0.001), leading to the conclusion that a low target INR of 1.5 to 2.5 may be sufficiently effective in patients with IPAH. However this study did not ascertain whether additional benefit was seen with INR greater than 2.5.

The adverse effects of anticoagulation in the management of PH were not universally investigated in most studies. However, **Henkens 2013** reviewed bleeding risk among participants with dif-

ferent groups of PH who received anticoagulant. 198 participants were included in the study: 99, 13 and 60 had IPAH, connective tissue disease (CTD)-associated PAH and chronic thromboembolic pulmonary hypertension, respectively. Twenty participants were excluded because they were not treated. Major bleeding events were reported in 448 patient exposure-years (bleeding rate 5.4 per 100 patient-years) in IPAH, 15 in CTD PAH during 81 patient-exposure years (bleeding rate 19 per 100 patient-years) and 7 in CTEPH during 291 patient exposure-years (bleeding rate 2.4 per 100 patient-years). This points out a higher bleeding risk in CTD PAH patients compared with other groups of PH.

Johnson 2012 found no increase in major bleeding in a subgroup of participants with systemic sclerosis (SSc) PAH who were treated with warfarin compared with the control group, which did not receive warfarin, as would have been expected because of increased vascular lesions in patients with SSc. However major gastrointestinal (GI) bleeding was reported more frequently in participants with IPAH receiving warfarin therapy. This study did not account for minor bleeding and defined major GI bleeding as events necessitating transfusion.

In contrast to the previous studies, the oldest study in this review found no benefit with the use of anticoagulants in the management of PH (**Storstein 1966**). Seventeen participants with PPH comprising 10 women and seven men with an age range of seven to 70 years were enrolled in this prospective study. Only two participants were younger than 18 years of age. Duration of illness was between one and 22 years before enrolment. Ten participants received anticoagulation for two to five years with target prothrombin-proconversion time of 10% to 30%, which was achieved in seven participants. Among the 10 treated participants, six died during follow-up, and the other four had a repeat cardiac catheterisation with no reduction in pulmonary arterial pressure. Investigators concluded that the treatment was not beneficial. The quality of evidence in this study is very low, given the very small number of participants and its non-randomised nature.

Summary of observational evidence

A considerable number of reports provide non-randomised evidence for this intervention, and they suggest an association between the use of warfarin and improved survival. However, the known increased risk of bleeding in those who take warfarin can be reliably balanced only against the possibility of improved survival in randomised trials, as too many confounding factors are present in the observational data to trade off the risks and benefits of treatment.

Quality of the evidence

No randomised controlled trial was identified for inclusion in this review. Most of the studies that we have described were retrospective case series, case reports and observational studies. The limited number of participants included in many of the studies described further compromised the quality of the evidence.

Potential biases in the review process

To search for RCTs, we used a robust and inclusive search strategy. We also followed a published protocol, and two people screened the search to minimise bias and ensure quality.

The non-randomised evidence discussed here was identified by handsearching rather than through a comprehensive literature search. This is a limitation of this review of non-randomised evidence in that the initial electronic search was not intended to include non-randomised trials.

Agreements and disagreements with other studies or reviews

A previous systematic review of this intervention ([Johnson 2006](#)) identified no randomised controlled trials. Review of observational studies found the intervention effective. This is similar to the findings of non-randomised evidence in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Because of the non-existence of randomised controlled trials on anticoagulation versus placebo for the treatment of pulmonary hypertension, benefits and adverse effects associated with the use of this intervention remain unclear.

Implications for research

We identified no eligible studies for inclusion in this review. The absence of RCTs assessing the use of anticoagulation therapy in the

treatment of pulmonary hypertension, which currently has a poor prognosis, advocates for the importance of appropriately designed RCTs to allow superior decisions concerning this intervention. More specifically, this review highlights the need for evaluation of adverse effects associated with this intervention.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Akagi 2008	Retrospective review
Bouvier 1970	Non-randomised controlled trial
Cohen 1986	Case report
Elder 2012	Observational study
Frank 1997	Retrospective study
Fuster 1984	Retrospective study
Gomez-Arroyo 2010	Non-randomised controlled trial
Henkens 2013	Retrospective study
Jansa 2011	Non-randomised controlled trial
Johnson 2006	Systematic review of observational studies

Study	Reason for exclusion
Johnson 2011	Review of expert opinion
Johnson 2012	Chart review
Kawut 2005	Retrospective cohort study
Ogata 1993	Retrospective study
Olsson 2014	Retrospective study
Rich 1992	Non-randomised controlled trial
Romaszkiewicz 2006	Non-randomised controlled trial
Storstein 1966	Non-randomised controlled trial

APPENDICES

Appendix 1. Database search strategies

CENTRAL (The Cochrane Library)

- #1 MeSH descriptor: [Hypertension, Pulmonary] explode all trees
- #2 MeSH descriptor: [Pulmonary Heart Disease] this term only
- #3 pulmonary near hypertensi*
- #4 #1 or #2 or #3
- #5 MeSH descriptor: [Anticoagulants] explode all trees
- #6 anticoagul*
- #7 warfarin
- #8 Coumadin
- #9 heparin*
- #10 dalteparin
- #11 enoxaparin
- #12 nadroparin
- #13 coumarin*
- #14 acenocoumarol
- #15 dicoumarin
- #16 dicumarol
- #17 "Ethyl biscoumacetate"
- #18 phenindione
- #19 phenprocoumon

- #20 argatroban
- #21 fondaparinux
- #22 dabigatran
- #23 apixaban
- #24 rivaroxaban
- #25 {or #5-#24}
- #26 #4 and #25

Cochrane Airways Group Register

#1 MeSH DESCRIPTOR Hypertension, Pulmonary Explode All

#2 MeSH DESCRIPTOR Pulmonary Heart Disease

#3 pulmonary near hypertensi*

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Anticoagulants Explode All

#6 anticoagul*

#7 warfarin

#8 Coumadin

#9 heparin*

#10 dalteparin

#11 enoxaparin

#12 nadroparin

#13 coumarin*

#14 acenocoumarol

#15 dicoumarin

#16 dicumarol

#17 "Ethyl biscoumacetate"

#18 phenindione

#19 phenprocoumon

#20 argatroban

#21 fondaparinux

#22 dabigatran

#23 apixaban

#24 rivaroxaban

#25 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

#26 #4 and #25

MEDLINE (Ovid)

1. exp Hypertension, Pulmonary/
2. Pulmonary Heart Disease/
3. (pulmonary adj5 hypertensi\$).tw.
4. or/1-3
5. exp Anticoagulants/
6. anticoagul\$.tw.
7. warfarin.tw.
8. Coumadin.tw.
9. heparin\$.tw.
10. dalteparin.tw.
11. enoxaparin.tw.
12. nadroparin.tw.
13. coumarin\$.tw.
14. acenocoumarol.tw.
15. dicoumarin.tw.
16. dicumarol.tw.
17. "Ethyl biscoumacetate".tw.
18. phenindione.tw.
19. phenprocoumon.tw.
20. argatroban.tw.
21. fondaparinux.tw.
22. dabigatran.tw.
23. apixaban.tw.
24. rivaroxaban.tw.
25. or/5-24
26. 4 and 25
27. (clinical trial or controlled clinical trial or randomised controlled trial).pt.
28. (randomised or randomised).ab,ti.
29. placebo.ab,ti.
30. dt.fs.
31. randomly.ab,ti.
32. trial.ab,ti.
33. groups.ab,ti.
34. or/27-33

- 35. Animals/
- 36. Humans/
- 37. 35 not (35 and 36)
- 38. 34 not 37
- 39. 26 and 38

EMBASE (Ovid)

- 1. exp pulmonary hypertension/
- 2. (pulmonary adj5 hypertensi\$).ti,ab.
- 3. 1 or 2
- 4. exp anticoagulant agent/
- 5. anticoagul\$.tw.
- 6. warfarin.tw.
- 7. Coumadin.tw.
- 8. heparin\$.tw.
- 9. dalteparin.tw.
- 10. enoxaparin.tw.
- 11. nadroparin.tw.
- 12. coumarin\$.tw.
- 13. acenocoumarol.tw.
- 14. dicoumarin.tw.
- 15. dicumarol.tw.
- 16. "Ethyl biscoumacetate".tw.
- 17. phenindione.tw.
- 18. phenprocoumon.tw.
- 19. argatroban.tw.
- 20. fondaparinux.tw.
- 21. dabigatran.tw.
- 22. apixaban.tw.
- 23. rivaroxaban.tw.
- 24. or/4-23
- 25. Randomized Controlled Trial/
- 26. randomisation/
- 27. Controlled Study/
- 28. Clinical Trial/
- 29. controlled clinical trial/

30. Double Blind Procedure/
31. Single Blind Procedure/
32. Crossover Procedure/
33. or/25-32
34. (clinical\$ adj3 trial\$).tw.
35. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (mask\$ or blind\$ or method\$)).tw.
36. exp Placebo/
37. placebo\$.tw.
38. random\$.tw.
39. ((control\$ or prospectiv\$) adj3 (trial\$ or method\$ or stud\$)).tw.
40. (crossover\$ or cross-over\$).tw.
41. or/34-40
42. 33 or 41
43. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
44. human/ or normal human/ or human cell/
45. 43 and 44
46. 43 not 45
47. 42 not 46
48. 3 and 24 and 47

CINAHL Plus (EBSCO)

- S1 (MH "Hypertension, Pulmonary+")
- S2 (MH "Pulmonary Heart Disease")
- S3 pulmonary N3 hypertensi*
- S4 S1 OR S2 OR S3
- S5 (MH "Anticoagulants+")
- S6 anticoagul*
- S7 warfarin
- S8 Coumadin
- S9 heparin*
- S10 dalteparin
- S11 enoxaparin
- S12 nadroparin
- S13 coumarin
- S14 acenocoumarol
- S15 dicoumarin
- S16 dicumarol
- S17 "Ethyl biscoumacetate"
- S18 phenindione
- S19 phenprocoumon
- S20 argatroban
- S21 fondaparinux
- S22 dabigatran
- S23 apixaban
- S24 rivaroxaban
- S25 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24

S26 S4 AND S25
S27 (MH "Randomized Controlled Trials")
S28 (MH "Double-Blind Studies")
S29 (MH "Random Assignment")
S30 (MH "Placebos")
S31 placebo*
S32 random*
S33 crossover* or cross-over*
S34 clinical* N3 (trial* or study or studies)
S35 (single* or double* or triple*) N3 blind*
S36 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
S37 S26 AND S36

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the writing of this review.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects] [*therapeutic use]; Hypertension, Pulmonary [*drug therapy]; International Normalized Ratio; Placebos [therapeutic use]

MeSH check words

Humans