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Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review

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ABSTRACT: Thrombotic arteriopathy has been implicated in the pathophysiology of pulmonary arterial hypertension (PAH). However, the role of anticoagulants in the treatment of PAH is uncertain. Through a qualitative systematic review of epidemiological studies, the effectiveness of anticoagulation therapy with warfarin on survival was evaluated in patients with PAH.

MEDLINE (1966 to November 2005), EMBASE (1966 to November 2005), bibliographies of included studies and published reviews were searched without language restriction. Epidemiological studies evaluating the effectiveness of warfarin in PAH were included. Studies had to report mortality as an outcome.

Seven observational studies evaluating the effectiveness of warfarin comprising 488 patients were identified. Five studies support the effectiveness of anticoagulation therapy, whereas two do not.

Data from observational studies suggest that anticoagulation therapy may be an effective intervention in pulmonary arterial hypertension. However, given the methodological limitations and the small number of existing observational studies, a randomised controlled trial is needed in order to definitively address this important clinical issue.

KEYWORDS: Anticoagulation, idiopathic pulmonary arterial hypertension, systematic review, thrombosis, thrombotic arteriopathy, warfarin

Pulmonary hypertension is a devastating condition resulting in significant clinical symptoms, impairment of quality of life and untimely mortality, for which there is currently no cure. Current evidence suggests that abnormalities of blood coagulation factors, antithrombotic factors and the fibrinolytic system contribute to a prothrombotic state in patients with idiopathic pulmonary arterial hypertension (IPAH) [1]. Partly organised vascular thrombosis has been observed in histological studies of IPAH [2]. It has been suggested that the thrombotic pulmonary vascular lesions may be integral aspects of pulmonary vascular remodelling, luminal narrowing and increased vascular resistance, and may contribute to the progression of pulmonary arterial hypertension (PAH).

Given these findings, there may be a role for systemic anticoagulation therapy, with the goals of decreasing the burden of thrombosis and improving outcomes. Many authors have recommended the use of chronic anticoagulation therapy, specifically warfarin, with the intention of improving cardiopulmonary haemodynamics and survival [3–6]. However, these recommendations remain controversial, and there has been a call for further evaluation of the efficacy of anticoagulation therapy in this setting [7], in particular the need for a randomised controlled trial. Through a systematic review of epidemiological studies, the present study synthesises the state of current knowledge regarding the effect of anticoagulation therapy with warfarin on survival in patients with IPAH.

METHODS

Systematic review of anticoagulation in PAH

Inclusion and exclusion criteria

Eligible studies were published observational studies and randomised controlled trials of human subjects evaluating the use of anticoagulation therapy in IPAH that reported death as an outcome. Studies were ineligible if they included individuals aged <18 yrs or with acute/chronic thromboembolic pulmonary hypertension.

Search strategy, methodological assessment and data abstraction

Eligible studies were identified using MEDLINE (1966 to week 1, November 2005; ''pulmonary hypertension'' plus ''warfarin'', ''Coumadin'' or ''anticoagulants'') and EMBASE (1966 to November

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2005; same search) without language restriction. Titles and abstracts were screened to exclude ineligible studies. Included studies were entered into PUBMED and the ''related articles'' tool was used to search for other potentially eligible studies. The bibliographies of included studies and published reviews were also searched. Two reviewers independently abstracted the following data on to standardised forms: study design, patient sample size, aetiology, treatments, and 3- and 5-yr mortality data. The reviewers were blinded to the names of authors, institutions and journals when performing data abstraction. All disagreements were resolved by consensus.

RESULTS

Of the 737 studies identified through a systematic review of the literature, nine observational studies were identified for full review. No randomised controlled trials were identified. One study evaluated the effect of the anticoagulant fraxiparin in patients with IPAH; however, it was excluded as it did not evaluate the end-points of interest [8]. Another study was excluded as it reported duplicate data (fig. 1) [9]. One study reported outcomes in both IPAH and PAH associated with other diseases or things (APAH), in this case anorexigens. Since mortality data were available for the IPAH subset, this study was included in the present review. The remaining studies, comprising 488 patients, are summarised in table 1.

Five studies support the effectiveness of warfarin with regards to survival in IPAH. ROMAN *et al.* [14] reported a retrospective case series of 44 IPAH patients followed in Barcelona (Spain) during the period 1992–2000. The mean (range) systolic pulmonary arterial pressure (P_{pa}) of the cohort was 92 mmHg (43–154). The investigators reported that five patients improved with warfarin and calcium channel blocker (CCB) therapy (diltiazem or nifedipine) [14].

FUSTER *et al.* [11] reported upon a retrospective cohort of patients diagnosed with IPAH at the Mayo clinic during the period 1955–1977, and followed until 1983 (median follow-up 14 yrs). The mean age at study entry was 34 yrs, and 73% were female. In these patients, many of whom showed severe PAH (mean (range) P_{pa} 64 mmHg (36–120)), 57% showed evidence of chronic organised pulmonary vascular thromboses on autopsy. Exposure to anticoagulation therapy was defined as initiation of warfarin treatment within 12 months of diagnosis. No other PAH-specific therapies were reported. The median (range) time to death from diagnosis was 1.9 yrs (0–16). Although overall survival was poor (only 21% of patients survived 5 yrs), improved 3-yr survival was observed in 78 patients who had received anticoagulant therapy compared with 37 who had not ($p=0.02$). Univariate analysis of the 56 patients who underwent autopsy demonstrated a beneficial effect of anticoagulant therapy ($p=0.04$). In a stepwise multivariate analysis, one of the strongest positive prognostic factors was the use of systemic anticoagulation therapy ($p=0.01$).

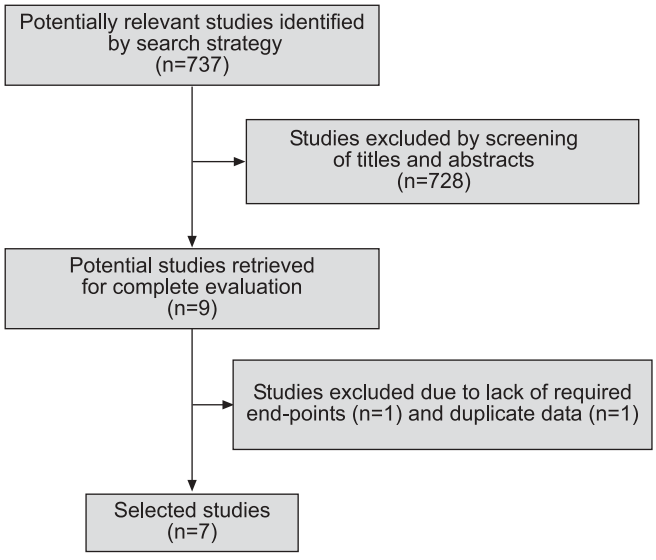

FIGURE 1. Flow diagram showing systematic review protocol.

In a third study, OGATA *et al.* [13] reported a Japanese retrospective cohort study of seven IPAH patients treated with warfarin in conjunction with a vasodilator (isoproterenol 30–45 mg daily or nifedipine 30–40 mg daily), and compared their outcome to that of 13 IPAH patients who were not treated. The warfarin dose was titrated to maintain thrombo test results within the range of 10–25%. Treatment duration was not specified. The mean (range) age at diagnosis was 31.2 yrs (14–56), and 50% of patients were in New York Heart Association Functional Classes II or III. The age at diagnosis was higher in the treatment group than in the control group (39 ± 15.5 *versus* 27.2 ± 12.0 yrs; $p<0.05$); however, there was no difference between groups in terms of duration of symptoms or functional class. Despite similar baseline haemodynamics (baseline mean P_{pa} was 57.5 ± 8.9 *versus* 49.3 ± 5.0 mmHg in the treatment and control groups, respectively), the treatment group showed a reduction in P_{pa} of $19\pm14\%$ ($p<0.05$) and a reduction in pulmonary vascular resistance of $13\pm17\%$ ($p<0.05$). Five-year survival was improved in the treatment group compared with controls (57 *versus* 15%; $p<0.025$).

In a prospective cohort study, RICH *et al.* [15] evaluated the effectiveness of CCBs in IPAH patients referred to the University of Illinois between July 1985 and March 1991, and followed until October 1991. Co-interventions included digoxin (for all CCB recipients), diuretics (for patients with a history of pedal oedema or right atrial pressure of >8 mmHg) and warfarin (for patients with nonuniform blood flow on nuclear lung perfusion scan). In all, 35 of 64 (55%) patients with IPAH received warfarin. Survival, adjusted for baseline haemodynamic variables and response to CCBs, was better in those treated with warfarin than in those not treated with warfarin ($p=0.025$). In a *post hoc* subgroup analysis, there was no significant difference in survival in vasodilator responder patients treated or not treated with anticoagulation therapy. This improvement in survival was found in patients not receiving chronic CCB therapy over the 5-yr follow-up period because of the lack of an acute CCB vasodilator response. In this group of patients, the survival rates at 1, 3 and 5 yrs were 91, 62 and 47%, respectively, with anticoagulation therapy *versus* 52, 31 and 31%, respectively, without anticoagulation therapy.

Finally, in a recent retrospective cohort study, KAWUT *et al.* [12] evaluated predictors of outcome in IPAH patients. They evaluated 84 consecutive newly diagnosed adult PAH patients

TABLE 1 Observational studies of anticoagulant therapy in idiopathic pulmonary arterial hypertension

First author [ref.]	Study design	Subjects n	Exposure	Outcomes
FRANK [10]	Retrospective cohort	69	Warfarin	No difference in 5-yr survival; nonsignificant survival benefit in warfarin-treated group at 10 yrs
FUSTER [11]	Retrospective cohort	115	Warfarin	Improved 3-yr survival in 78 anticoagulant- *versus* 37 nonanticoagulant-treated patients (p=0.02)
KAWUT [12]	Retrospective cohort	66	Warfarin	Improved transplant-free survival; HR 0.35 (95% CI 0.12–0.99; p=0.05)
OGATA [13]	Retrospective cohort	20	Warfarin plus isoproterenol/ nifedipine	Improved 5-yr survival in anticoagulant group (57 *versus* 15% for controls; p<0.05)
ROMAN [14]	Case series	44	Warfarin	Improvement in five patients
RICH [15]	Prospective cohort	35	Warfarin	Improved survival in subgroup of patients treated with warfarin compared to nonanticoagulant-treated patients (p=0.025)
STORSTEIN [16]	Retrospective cohort	10	Anticoagulant#	No difference in survival between anticoagulant- and non-anticoagulant-treated patients

HR: hazard ratio; CI: confidence interval. #: anticoagulant type not specified.

between January 1994 and June 2002. Eighty-four patients were included in the study, of whom 66 (78%) had IPAH. Of the remainder, 14 (17%) had familial PAH and four (5%) anorexigen-associated APAH. Sixty-eight (81%) were female. The cohort had a mean age of 42±14 yrs and mean (range) P_{pa} of 55 mmHg (48–61). Seventy-nine (86%) patients were treated with warfarin. Multivariate analyses of transplant-free survival indicated that warfarin use was associated with survival (hazard ratio 0.35, 95% confidence interval (CI) 0.12–0.99; p=0.05).

In contrast to the previous studies, two observational studies did not support the effectiveness of anticoagulation therapy in IPAH. STORSTEIN *et al.* [16] reported a retrospective cohort study of 10 IPAH patients treated with anticoagulants and seven not treated with anticoagulants over a 6-yr period. The age of the patients ranged 7–70 yrs and the disease duration ranged 1–22 yrs. Symptom severity ranged from slight dyspnoea on exertion to dyspnoea at rest. Four patients reported a previous history of thrombosis. The baseline mean systolic P_{pa} on cardiac catheterisation ranged 50–125 mmHg. Treatment with anticoagulants (type not specified) was titrated to maintain a prothrombin-proconvertin time in the range of 10–30%. Treatment duration ranged 2–5 yrs. No other PAH-specific medical therapies were described. Of the nine patients who underwent pathological evaluation, four showed pulmonary artery thrombosis in conjunction with arteriopathic changes. Follow-up cardiac catheterisation was performed in four of the anticoagulant-treated patients, and none exhibited a reduction in their P_{pa} during treatment. Six anticoagulant-treated patients died during the study period. The investigators concluded that anticoagulation therapy provided neither a reduction in P_{pa} on cardiac catheterisation nor a difference in survival between groups [16].

In a retrospective cohort study, FRANK *et al.* [10] evaluated the effectiveness of warfarin on survival, P_{pa} and New York Heart Association Functional Class in 173 patients with IPAH or aminorex-associated APAH in Vienna (Austria) and Bern (Switzerland). The nonanticoagulant-treated IPAH group consisted of 45 patients (36 female and nine male). There were 24 anticoagulant-treated IPAH patients (17 female and seven male), with a mean age of 44±11.7 yrs. Among the patients exposed to warfarin, seven were treated immediately after diagnosis, six had their therapy initiated within 1 yr of symptom onset and four within 2 yrs. Co-interventions in both the warfarin-exposed and -nonexposed IPAH and APAH groups included digoxin, diuretics, steroids and α-adrenergic receptor antagonists. The investigators reported improved 5- (63 *versus* 38%) and 10-yr survival (39 *versus* 20%) in warfarin-treated *versus* warfarin-naive APAH patients. However, no difference in 5-yr survival was observed between warfarin-treated and warfarin-naive IPAH patients. A non-significant survival benefit was observed in the warfarin-treated group at 10 yrs [10].

DISCUSSION

The effect of anticoagulation therapy on survival in patients with PAH has long been controversial. To the present authors' knowledge, this is the first qualitative systematic review in the literature examining this issue. A previous pathophysiological review identified several lines of evidence to suggest a relationship between thrombotic arteriopathy and PAH [1]. Abnormalities of the activated clotting system [17–19], impaired fibrinolysis [20, 21], abnormal platelet function [22, 23] and histological evidence of microvascular thrombosis [24, 25] have been associated with animal models and patients with IPAH. Thus, there is a biologically plausible rationale for anticoagulation therapy in these patients, with the goals of preventing progression of disease, decreasing P_{pa}, and improving symptoms and prognosis [1]. However, initial case reports and case series reported conflicting outcomes with regards to the effectiveness of anticoagulation therapy on survival [26–28]. Through the present systematic review, seven observational studies addressing the effectiveness of anticoagulant therapy on survival were identified. One recent case series [14], three retrospective cohort studies [11, 12, 13] and one prospective cohort study [15] have demonstrated a survival benefit of anticoagulation therapy in IPAH patients.

Improved 5-yr (63 *versus* 38%) and 10-yr survival (39 *versus* 20%) has been reported in warfarin-treated *versus* warfarin-naive APAH patients [10]. However, two retrospective cohort studies did not corroborate this finding [10, 16].

Overall, the literature supports a treatment effect of warfarin on survival in IPAH patients. These results suggest that interruption of ongoing thrombosis with effective systemic anticoagulation therapy is associated with a better prognosis, especially for patients with disease not responsive to vasodilators. The available data were insufficient for a formal meta-analysis, and the present results should be interpreted with caution. Many of the studies evaluated patient groups that were heterogeneous with regards to a number of important factors, including age, study location, inclusion of paediatric patients, disease duration and treatment duration. Furthermore, these factors were often not accounted for in the analyses. Due to the heterogeneity of study designs and study populations, pooling the data of these observational studies in a meta-analysis would be inappropriate [29].

A number of methodological concerns affect the validity of the study results. Earlier studies may have suffered from misclassification bias, as they were unable to accurately distinguish IPAH from other causes of PAH. In addition, selection bias and confounding by severity threaten the validity of some of these studies. Many of the studies did not identify how patients were selected for participation in the study. Many studies did not indicate on what basis anticoagulation therapy was given to some patients, and, conversely, on what basis it was withheld from others.

Confounding by severity occurs when the severity of the disease systematically influences exposure. Sicker patients, or those with increased bleeding risk, may not have been prescribed warfarin, and, as a result, the cohort studies may show better outcomes in those patients treated with warfarin therapy, whereas, in reality, this is just a reflection of the fact that sicker patients with a higher risk of death were not given warfarin.

Inconsistencies regarding treatment exposure and use of co-interventions also threaten the validity of the results. Exposure to warfarin was not consistently specified across studies. One study did not clearly identify what type of anticoagulant(s) were used, whereas others did not clearly state whether all patients in the study received the same form of anticoagulation therapy. Finally, the use of co-intervention(s) was not accounted for in the estimates of treatment effect. For example, in the study of OGATA *et al.* [13], survival was improved in patients treated with oral anticoagulant therapy in combination with vasodilators (isoproterenol or nifedipine). However, acute vasoreactivity was not reported in these patients. The effect on survival may be related to vasodilator rather than anticoagulation therapy if some of these patients were considered acute responders. Due to the effects of confounding and bias, these observational studies (individually and together) may produce estimates of associations that deviate from the underlying effect in ways that may systematically differ from chance.

These studies provide insufficient data to form conclusions about the appropriate dose of warfarin. The American College of Chest Physicians Clinical Practice Guidelines recommend a target international normalised ratio (INR) of 1.5–2.5 [4]. Additional research is needed to evaluate the validity of this therapeutic range.

It is also important to recognise that anticoagulation therapy using warfarin is not without potential risk. The greatest concern pertains to the risk of major haemorrhage, including gastrointestinal bleeding and intracranial haemorrhage. The risk of these complications in warfarin-treated PAH patients is uncertain. However, large studies of patients treated with warfarin for venous thrombosis or atrial fibrillation reported annual incidence estimates for major haemorrhage of 2–3% [30, 31]. The risk of major haemorrhage increases with advanced age, concomitant renal, cardiac and hepatic disease, and diabetes [30–33]. There is also concern regarding increased risk of gastrointestinal haemorrhage among patients with scleroderma-associated pulmonary hypertension due to the presence of luminal telangiectasia [34]. Many medications have been implicated in potentiation of the effect of warfarin, including azole antibiotics [35, 36], macrolides [37], quinolones [38], selective serotonin reuptake inhibitors [39] and amiodarone [40–42]. Caution should also be exercised with the concomitant use of other PH therapies and warfarin. MURPHEY and HOOD [43] have suggested that bosentan may decrease the anticoagulant properties of warfarin, whereas WIDLITZ *et al.* [44] report an increased prothrombin time/INR in patients taking warfarin and sitaxsentan, requiring significant warfarin dose reduction. OGAWA *et al.* [45] have reported an increased risk of alveolar haemorrhage in patients taking epoprostenol and warfarin. The medications of most concern are those with an inherent risk of bleeding, which further potentiates the risk of haemorrhage with warfarin and attendant monitoring of the INR is not helpful. These include antiplatelet agents and both cyclooxygenase-2-selective and -nonselective nonsteroidal anti-inflammatory drugs. Combination of these drugs with warfarin should be monitored closely [46].

In addition, there is increasing evidence that a therapeutic INR range is difficult to maintain in the long term. In a large population-based cohort study of patients with atrial fibrillation and treated with warfarin, patients were outside the INR target range 32.1% of the time, with 15.4% of INRs being >3.0 [47]. Similarly, in a meta-analysis evaluating the relationship between the INR and major bleeding events among atrial fibrillation patients receiving warfarin, REYNOLDS *et al.* [48] reported that patients spent 13% of the time in the supra-therapeutic range. Furthermore, an INR of >3.0, compared with an INR of $\leqslant 3.0$, was associated with an odds ratio of 3.21 (95% CI 1.24–8.28) for bleeding events. Further research is needed to evaluate whether or not these observations hold true for PAH patients treated with warfarin.

In summary, five observational studies suggest that there is a survival benefit associated with warfarin in the treatment of IPAH, whereas two observational studies do not support this association. As epidemiological studies, these cohort studies suffer from many methodological issues, including selection bias and confounding by indication. The impossibility of accounting for all measured and unmeasured confounding factors in such studies means that conclusions must be

tempered in the absence of a randomised clinical trial. There remains clinical uncertainty regarding the effect of anticoagulation therapy on survival patients with IPAH.

Furthermore, anticoagulation therapy with warfarin is associated with inherent risks.

In order to definitively evaluate the efficacy of anticoagulation therapy with warfarin on survival and ascertain whether or not the clinical benefit outweighs the potential risks, a randomised controlled trial is needed. Proposals for randomised trials to evaluate the efficacy of warfarin in IPAH and scleroderma-associated PAH patients have been developed in both the USA (D. Badesch, Pulmonary Hypertension Center, University of Colorado Health Sciences Center, Denver, CO, USA, personal communication (September 2005)) and Canada (J. Granton, Pulmonary Hypertension Programme, University Health Network, University of Toronto, Toronto, ON, Canada, personal communication (February 2004)). Undoubtedly, clinical trials of rare diseases suffer from many methodological challenges. First is the issue of recruitment of adequate numbers of patients so that there is sufficient power to detect meaningful treatment effects. The second challenge is the fact that one arm may deteriorate faster than another. One innovative design and analytical strategy that may be useful is Bayesian inference. Bayesian inference allows for the reporting of a probability of a treatment effect using the available data [49]. Study data could be analysed in a Bayesian context during interim analyses and inform decision rules for early termination of the study [50]. In this way, fewer patients are needed to address clinically meaningful outcomes. Clinical deterioration would be detected using conventional endpoints, such as 6-min walking distance, functional class and time to clinical worsening. A multidisciplinary group of investigators is currently using consensus methods to identify appropriate outcome measures for clinical trials of scleroderma-associated PAH (D. Pittrow, Dept for Clinical Pharmacology, Medical Faculty, Technical University of Dresden, Dresden, Germany, personal communication (February 2006)). Similar research is required to identify appropriate outcome measures for clinical trials of IPAH. Together, the results of these trials will clarify this important issue.

Conclusion

The literature appears to support a treatment effect of anticoagulation therapy with warfarin on mortality in idiopathic pulmonary arterial hypertension. However, conflicting results and methodological issues regarding previous observational studies demonstrate the need for a randomised controlled trial in order to definitively evaluate the efficacy of warfarin in pulmonary arterial hypertension patients.

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