Eur Respir J 2013; 41: 872–878
DOI: 10.1183/09031936.00039212

Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension

Ivo R. Henkens*, Thomas Hazenoot*,#, Anco Boonstra#, Menno V. Huisman¶ and Anton Vonk-Noordegraaf#

ABSTRACT: Vitamin K antagonists are advised in pulmonary arterial hypertension patients despite a lack of safety data.

We reviewed major bleeding in three classes of pulmonary hypertension patients, all receiving vitamin K antagonists.

Bleeding event rates were 5.4 per 100 patient-years for patients with idiopathic pulmonary arterial hypertension, 19 per 100 patient-years for connective tissue disease related pulmonary arterial hypertension patients and 2.4 per 100 patient-years for chronic thromboembolic pulmonary hypertension patients. Life tables analysis showed that event-free survival was worse in patients with connective tissue disease related pulmonary hypertension than in patients with idiopathic pulmonary arterial hypertension (Wilcoxon=12.8; $p<0.001$), and patients with chronic thromboembolic pulmonary hypertension (Wilcoxon=23.2; $p<0.001$). Patients with idiopathic pulmonary arterial hypertension suffered more events than patients with chronic thromboembolic pulmonary hypertension (Wilcoxon=7.2; $p<0.01$). Major bleeding was independent of age, sex, target international normalised ratio (INR) range, documented INR, vitamin K antagonist type, or right atrial pressure, but was associated with use of prostacyclin analogues.

Major bleeding risk during vitamin K antagonist therapy differs among groups of patients with pulmonary hypertension. Further research regarding optimal anticoagulant therapy is needed, as well as risk–benefit analyses for pulmonary hypertension patients with a higher bleeding propensity.

KEYWORDS: Antithrombotic therapy, connective tissue disease, safety

AFFILIATIONS
*Dept of Cardiology, Leiden University Medical Center, Leiden, #Dept of Pulmonology, VU University Medical Center, Amsterdam, and ¶Depts of Thrombosis and Haemostasis and General Internal Medicine-Endocrinology, Leiden University Medical Center, Leiden, The Netherlands.

CORRESPONDENCE
A. Vonk-Noordegraaf
VU University Medical Center
De Boelelaan 1117
1081 HV Amsterdam
The Netherlands
E-mail: a.vonk@vumc.nl

Received:
March 04 2012
Accepted after revision:
Aug 01 2012
First published online:
Aug 30 2012

Vitamin K antagonists (VKAs) are part of conventional drug treatment for pulmonary hypertension [1]. The observed hypercoagulability in idiopathic pulmonary arterial hypertension (IPAH) patients [2–5], and reported survival-benefit of VKAs in IPAH patients has led to recommendation of administration of VKAs in PAH patients [6], albeit with a class IIa, level of evidence C [6, 7]. This limited level of evidence is due to the lack of prospective comparative trials regarding administration of anticoagulants in PAH patients [7, 8]. Furthermore, clinical studies of systematic anticoagulation in PAH were methodologically limited because of the retrospective nature, lack of randomisation between placebo and anticoagulant drugs, or because of a diverse range of pulmonary hypertension patients [9, 10]. In connective tissue disease related pulmonary arterial hypertension (CTD-PAH) patients, there are no randomised controlled trials on the possible role of VKAs, for which reason the European Society of Cardiology/European Respiratory Society did not make any recommendation on their use in their guidelines [6]. The American College of Chest Physicians guidelines support the use of VKAs in IPAH patients, and advise consideration of their use in CTD-PAH patients, especially when patients have an indwelling catheter for long-term prostanoid treatment [7]. In chronic thromboembolic pulmonary hypertension (CTEPH) patients, a class I, level of evidence C, recommendation is given for VKA administration [6]. Hence, these guidelines suggest that the underlying disease, predisposing to pulmonary hypertension, may influence the outcome of routine administration of VKA [6]. The platelet-inhibiting effect of prostacyclin analogues is widely acknowledged, yet its clinical relevance is still unclear, with respect to concomitant use of VKA [8, 11]. In contrast, sitaxentan interferes with VKA metabolism [12], and has been taken off the market due to increased risk of liver toxicity.

We aimed to investigate the safety of routine administration of VKAs by comparing the incidence of

For editorial comments see page 775.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

major bleeding associated with the use of VKAs in our population of IPAH patients, CTD-PAH and inoperable CTEPH. We chose IPAH and CTD-PAH patients, since these well-defined patient groups constitute the majority of PAH.

MATERIALS AND METHODS

Study design

We performed a retrospective analysis of pulmonary hypertension patients treated in the VU Medical Center hospital, Amsterdam, the Netherlands, from 1997 until 2009, and evaluated the safety of routine administration of VKAs (Acenocoumarol and Fenprocoumon). More explicitly, we analysed patients with IPAH, CTD-PAH and CTEPH. The IPAH patients included both sporadic and familiar cases. We combined data from the VU Medical Center and from the specialised anticoagulation clinics, where patients were monitored. We obtained informed consent from patients or their relatives (if the patient was deceased).

Patients

We documented the occurrence of major bleeding, as well as nosebleeding. We did not include patients who refused anticoagulant drug treatment (n=2) in this study. We did not include patients with liver disease (n=2) because of spontaneously prolonged international normalised ratio (INR) values, who were therefore not treated with VKA. We compared groups of patients with IPAH, CTD-PAH and CTEPH for the rate of occurrence of major bleeding.

Patients were prescribed VKA (predominantly acenocoumarol; to a lesser extent fenprocoumon). Drugs prescribed primarily for attenuation of pulmonary vascular resistance were administered according to guidelines and local reimbursement, and included prostacyclin analogues, endothelin-receptor antagonists, and phosphodiesterase-inhibitors.

Data collection and definitions of events

The following information was extracted from the VU Medical Center computerised patients records: sex, age, type of anticoagulation, major bleeding, prothrombin-time measurements (INR) at the time of major bleeding, hospital admissions data and, where applicable, time of death. We documented use of non-steroidal anti-inflammatory drugs (NSAIDs), platelet-inhibiting drugs (aspirin and clopidogrel) and platelet count. We considered bleeding to be major if it was: clinically overt and associated with a fall in haemoglobin of at least 20 $g \cdot L^{-1}$ ($\geqslant$1.2 $mmol \cdot L^{-1}$); resulted in the need for transfusion of at least two units of red cells; involved a critical site; or if it was fatal. Critical sites included the central nervous system, the eye and respiratory tract. We also documented clinically relevant bleeding and subcategorised these accordingly. INR target range was determined by the anticoagulation clinics.

Statistical analysis

We used the SPSS for Windows Software package (Version 16: SPSS Inc, Chicago, IL, USA). We describe the data as mean$\pm$SD or median (interquartile range (IQR)). We plotted one-minus-survival curves based on life tables analysis. We calculated bleeding-free survival time as the time from initiation of VKA treatment until the occurrence of major bleeding. We counted major bleeding only once for each patient for life tables analysis. We investigated the possible influence of age, type of VKA used, and the INR target range on the occurrence of major bleeding, by performing a Cox proportional hazards analysis with a backwards stepwise regression analysis. The relatively small number of patients precluded a direct analysis of influence on bleeding of all possible pulmonary hypertension attenuating drug therapies, and combinations thereof. We therefore chose to limit ourselves to the evaluation of an association between prostacyclin analogues and sitaxentan on bleeding, using cross tabulations with Pearson's Chi-squared test. We compared the last documented INR value before bleeding with the target range INR. We considered a p-value of <0.05 statistically significant.

RESULTS

Patients

A total of 218 PAH patients were available in the database, of whom 198 patients were included in the study: patients diagnosed with IPAH (n=99), CTD-PAH (n=39) and CTEPH (n=60). A total of 20 patients were never prescribed any VKA drug, and were not included in further analyses: IPAH (n=7), CTD-PAH (n=12) and CTEPH (n=1). Four of the latter patients experienced major bleeding events, before consideration of VKA drug prescription. One IPAH patient had recurrent haemoptysis, one CTD-PAH patient had arteriovenous malformation related bleeding and two CTD-PAH patients had major gastrointestinal bleeding, requiring transfusion; one of these during use of acetylsalicylic acid 100 mg once daily. Patient characteristics are described in table 1. Patients with IPAH were generally younger than CTD-PAH patients and CTEPH patients (table 1, $p<0.001$ for both). There was no significant difference between the age of CTD-PAH patients and CTEPH patients (p=0.982). Right atrial pressure was not different between the three patient groups. Mean pulmonary artery pressure was higher in IPAH patients than in CTD-PAH patients (p=0.02). INR target ranges were 2.0–3.0 in 29 patients, 2.5–3.5 in 107 patients and 3.0–4.0 in 53 patients; the choice of a range was irrespective of pulmonary hypertension aetiology. The INR target range was intractable

TABLE 1 Patient characteristics

	IPAH	CTD-PAH	CTEPH
Age years	46$\pm$16	59$\pm$13	61$\pm$14
Male/female	19/80	7/32	21/39
RAP mmHg	8$\pm$5	8.9$\pm$6.4	9.6$\pm$5.9
Mean PAP mmHg	53$\pm$13	44$\pm$15	46$\pm$11
Fenprocoumon/acenocoumarol	17/82	7/32	14/46
INR target range %			
2.0–3.0	21	9	9
2.5–3.5	53	51	67
3.0–4.0	26	40	24

Data are presented as mean$\pm$SD, n/n or %. IPAH: idiopathic pulmonary arterial hypertension; CTD-PAH: connective tissue disease related pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; RAP: right atrial pressure; PAP: pulmonary arterial pressure; INR: international normalised ratio.

TABLE 2 Incidence of adverse events

	IPAH	CTD-PAH	CTEPH	Total
Subjects	99	39	60	198
Major bleeding	24 (24)	15 (38)	7 (12)	46 (23)
Fatal bleeding	1	0	0	1
Critical site				
CNS related bleeding	0	1	0	1
Intraocular bleeding	2	1	0	3
Haemoptysis	7	1	1	9
Clinically overt bleeding#				
Gastrointestinal bleeding (upper/lower)	5	4	2	11
Gastrointestinal bleeding (non-upper/lower)¶	5	7	2	14
Urogenital bleeding	3	1	0	4
Diffuse large haematomas	1+	0	0	1
Haematoma as a consequence of an intervention	0	0	2	2
Non-major bleeding (all nose bleeding)	11	8	10	29
Any first bleeding	35 (35)	23 (59)	17 (28)	75 (38)

Data are presented as n or n (%). IPAH: idiopathic pulmonary arterial hypertension; CTD-PAH: connective tissue disease related pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CNS: central nervous system (here: subdural bleeding). We counted nosebleeds as minor events, which could occur apart from a major adverse event in the same patient. We counted major adverse events only once for each patient. #: haemoglobin (Hb) drop >20 $g \cdot L^{-1}$ ($\geqslant$1.2 $mmol \cdot L^{-1}$)/transfusion of at least two units of red cells; ¶: average Hb drop was 3.5 (range 2.5–4.9 $mmol \cdot L^{-1}$), no focus was found during routine endoscopy (upper gastrointestinal tract and colon; videocapsule enhanced endoscopy was not performed), and there was intra-abdominal bleeding in two patients; +: one patient developed large, diffuse haematomas with a critical anaemia and was subsequently diagnosed with hairy cell leukaemia.

in nine patients. There were no significant differences in INR target range between the different patient groups.

Bleeding events

A total of 24 major bleeding events occurred in 99 IPAH patients during 448 patient-exposure-years (bleeding rate 5.4 per 100 patient-years), 15 major bleeding events occurred in 39 CTD-PAH patients during 81 patient-exposure-years (bleeding rate 19 per 100 patient-years), and seven events occurred in 60 CTEPH patients during 291 patient-exposure-years (bleeding rate 2.4 per 100 patient-years; table 2). Fatal bleeding occurred in one patient, who experienced a massive sub-pleural haemorrhage 3 months after combined heart/lung transplantation. The other sites of major bleeding events were intracranial (subdural bleeding; one patient), intraocular (three patients), pulmonary (nine patients), gastrointestinal (25 patients) and urogenital (four patients). One patient developed a critical anaemia due to diffuse, large haematomas, and was diagnosed with hairy cell leukaemia. Two patients suffered bleeding as a consequence of an intervention (one groin bleeding after diagnostic heart catheterisation; one bleeding after portacath placement). The subdural bleeding was non-traumatic in a patient with the antiphospholipid syndrome (target INR range 3.0–4.0) and was treated conservatively.

We counted major bleeding only once for each patient, but for clarity we also documented any bleeding event, including non-major bleeding (table 2). Nosebleeding occurred in a considerable number of patients, but there was no patient with nosebleeding requiring blood transfusion (table 2).

According to life tables analysis (fig. 1) CTD-PAH patients had worse event-free survival than IPAH patients (Wilcoxon=12.0; $p<0.001$) and CTEPH patients (Wilcoxon=21.5; $p<0.001$). Event-free survival was less in IPAH patients than in CTEPH patients (Wilcoxon=7.2; $p<0.01$). Cox proportional hazards analysis found no significant relationship between major bleeding and age, sex, target INR range, type of VKA drug used, or right atrial pressure (table 3). Target INR range did not influence the occurrence of nosebleeding either. The mean

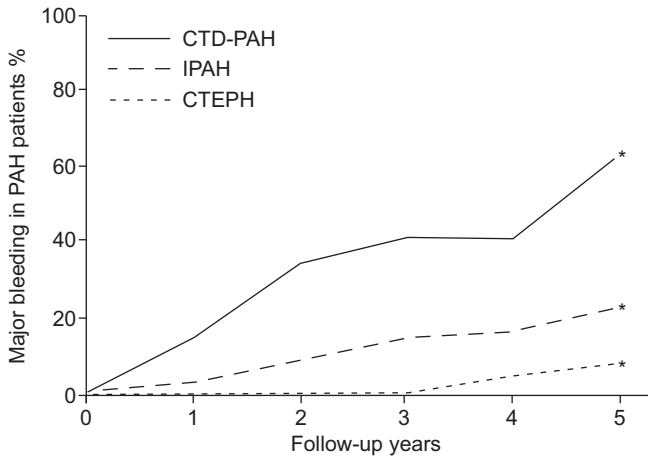

FIGURE 1. Cumulative vitamin K antagonist related major bleeding in pulmonary arterial hypertension patients. Patients with connective tissue disease related pulmonary arterial hypertension (CTD-PAH) experienced worse event-free survival than idiopathic pulmonary arterial hypertension (IPAH) patients (Wilcoxon=12.0; $p<0.001$) and chronic thromboembolic pulmonary hypertension (CTEPH) patients (Wilcoxon=21.5; $p<0.001$). Event-free survival was also less in IPAH patients than in CTEPH patients (Wilcoxon=7.2; $p<0.01$). *: $p<0.05$.

TABLE 3 Cox regression analysis with odds ratios for prespecified variables of potential influence on bleeding

	OR (95% CI)	p-value
Age	1.01 (0.99–1.03)	0.44
Male sex	0.90 (0.44–1.84)	0.77
INR 2.5–3.5	1.16 (0.49–2.76)	0.74
INR 3.0–4.0	0.74 (0.37–1.48)	0.40
Acenocoumarol	1.70 (0.77–3.75)	0.19

INR: international normalised ratio. INR values are compared to the reference category of 2.0–3.0. Acenocoumarol is compared to fenprocoumon.

last documented INR before major bleeding was not different from the mean INR target range (3.4 ± 1.6 *versus* 3.1 ± 0.6; $p=0.19$). In 13 patients the INR at the time of the adverse event was unavailable. For these patients the median number of days between the last documented INR and the occurrence of an adverse event was 7 days (IQR 3–16 days).

The small number of patients using sitaxentan (n=7) precluded a conclusion on safety regarding concomitant VKA drug use, but there was a significant association between the use of prostacyclin analogues as pulmonary hypertension therapy and major bleeding (table 4; Pearson's Chi-squared=15.1; $p<0.01$). We counted just one major bleeding event, a large haematoma after placement of a permanent subcutaneously situated venous catheter used for infusion of epoprostenol, which was treated conservatively. All other bleeding events were unrelated to the prostacyclin administration site or related procedures. NSAID use was documented in five patients, and aspirin use in nine patients. There was no relationship with bleeding. Platelet count was available in 185 patients (93.4%) and was not different between groups of IPAH, CTD-PAH and CTEPH patients, but was related to bleeding (table 5). There were no patients with end-stage renal disease. Several patients had an indication for VKA apart from having pulmonary hypertension (table 6). After the occurrence of major bleeding, physicians discontinued VKA permanently in 13 patients (seven IPAH patients, six CTD-PAH patients). Despite this, subsequent transfusion demanding bleeding occurred in two of these patients. Physicians discontinued VKA temporarily in five patients (five IPAH patients). In these patients three transfusion demanding bleeding events occurred after resumption of VKA. Physicians continued VKA in the remaining 29 patients. In the latter group there were seven subsequent major bleeding events, one of which was gastrointestinal bleeding, and three were haemoptysis. Nosebleeding was documented in four patients. In patients with haemoptysis, embolisation of bronchial arteries was performed. All patients subsequently resumed VKA treatment.

TABLE 4 Influence of pulmonary hypertension (PH) treatment on bleeding

	No bleeding	Major bleeding	Total
Prostacyclin analogues	44	26	70
Sitaxentan	6	1	7
Other PH attenuating medication	105	16	121
Total	155	43	198

Overall, cells were compared for an even distribution of prostacyclin analogues, sitaxentan, and other PH attenuating medication: Chi-squared=15.1; $p<0.01$.

TABLE 5 Platelet count and bleeding

	Platelet cell count per L		
	$>150 \times 10^9$	$>50 \times 10^9$ and $<150 \times 10^9$	$<50 \times 10^9$
IPAH	75 (40)	14 (12)	4 (2)
CTD-PAH	30 (16)	6 (3)	1 (1)
CTEPH	50 (27)	4 (2)	0 (0)
No adverse event	102 (55)	14 (8)	0 (0)
Nosebleeding	26 (14)	0 (0)	0 (0)
Major bleeding	27 (15)	10 (5)	5 (3)

Documentation of platelet count was available in 185 (93.4%) out of 198 patients. Data are presented as n (%). IPAH: idiopathic pulmonary arterial hypertension; CTD-PAH: connective tissue disease related pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension. According to Chi-squared analysis platelet count was not different between IPAH, CTD-PAH and CTEPH patients ($p=0.19$). According to Chi-squared analysis a lower platelet count was related to major bleeding ($p<0.01$).

DISCUSSION

The key finding of this study is that routine VKA administration to patients with different types of pulmonary hypertension was associated with an unequal incidence of major bleeding. CTD-PAH patients had a markedly higher rate of major bleeding complications than IPAH or CTEPH patients.

TABLE 6 Co-indications for vitamin K antagonist (VKA) drugs

Co-indication	IPAH	CTD-PAH	CTEPH
Subjects	99	39	60
None	76	23	0
Supraventricular arrythmia	11	8	0
Recurrent DVT	0	0	0
Pulmonary embolism	2	2	All
Recurrent pulmonary embolism	2	1	All
Cardiac aneurysm or clot	1	0	0
Ischemic heart disease	2	1	0
APLS	1	0	0
>1 indication	4	3	10

Data presented as n. IPAH: idiopathic pulmonary arterial hypertension; CTD-PAH: connective tissue disease related pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; DVT: deep venous thrombosis; APLS: antiphospholipid syndrome.

IPAH patients in turn demonstrated a higher incidence rate of major bleeding than CTEPH patients.

The clinical efficacy and safety of oral anticoagulant therapy has been well established in patients with a high risk of thrombotic complications, such as those with mechanical heart valves or atrial fibrillation [13, 14]. In general, optimal oral anticoagulant therapy intensity (*i.e.* the level at which thromboembolic complications are effectively prevented without excessive bleeding) has been well documented by studying large numbers of patients [15]. In pulmonary hypertension patients the latter has not yet been feasible. However, retrospective reports suggest a better outcome in IPAH patients treated with VKAs [9, 10]. Nevertheless, despite the fact that pulmonary hypertension is a common denominator, IPAH patients, CTD-PAH patients and CTEPH patients constitute very different groups of patients. Hypothetically, CTEPH patients should benefit from life-long anticoagulant therapy, similar to patients with recurrent deep-vein thrombosis or pulmonary embolism, since hypercoagulability as well as impaired clot resolution are considered the root of the disease [16, 17]. In our cohort, major bleeding in CTEPH patients was restricted to two patients suffering from gastrointestinal bleeding, four patients with a transfusion demanding fall in haemoglobin level, without an overt focus of bleeding, and one case of haemoptysis. Overall, the incidence of major bleeding was well within limits reported in large studies with VKAs and lower than in IPAH [18]. A representative overview of bleeding in large groups of patients on VKA for atrial fibrillation or venous thromboembolism is given in table 7. The pulmonary arterial hypertension patients we describe are generally younger, and there is a female to male predominance. There was no difference in mean right atrial pressure between the different groups of patients, hence no hint of a predominance of liver congestion in any of these groups, which could otherwise have explained a higher risk of gastrointestinal bleeding. The occurrence of haemoptysis in patients with pulmonary hypertension is well known, but is hardly ever reported in patients using VKAs for atrial fibrillation or venous thromboembolism (table 7) [26]. Haemoptysis occurred predominantly in IPAH patients. IPAH patients may have an inherently higher risk of haemoptysis due to bronchial artery bleeding, which is most likely unrelated to VKA use [27]. CTD-PAH patients experienced an even larger number of major bleeding events than the two other groups. Patients with CTD-PAH tend to be older than IPAH patients, but in our study age did not explain this high rate of major bleeding. Aspirin and NSAID use was very limited, and did not explain bleeding. Documented platelet counts showed a relationship with bleeding, but the retrospective analysis precludes any statement regarding cause and effect. The high rate of gastrointestinal bleeding in CTD-PAH is likely due to gastrointestinal angiodysplasia [28], increasing the risk for unwanted side-effects of anticoagulant therapy.

With respect to concomitant pulmonary hypertension attenuating therapy used, we cannot conclude whether sitaxentan had any influence on bleeding, due the low number of patients exposed to this drug. The platelet-inhibiting effect of prostacyclin analogues has long been recognised [29]. The incidence of alveolar bleeding in PAH patients with concomitant use of epoprostenol and VKA has also been reported [11]. Since the use of prostacyclin analogues was lower in our group of patients without major bleeding, we looked for confounders that might explain these findings, other than prostacyclin analogues themselves. As such, we only identified one event related to a chronic intravenous catheter. Patients using epoprostenol may, on average, have had more advanced disease, yet no association with right atrial pressure was found. Major bleeding may, therefore, be associated with prostacyclin analogues through their platelet-inhibiting effect on top of the VKA [29]. The vasodilatory effect of prostacyclin analogues, most apparent in skin and intestines, may both predispose to bleeding, and enhance bleeding once vascular integrity is lost [30, 31].

Preliminary studies evaluating the benefit of pure platelet function inhibitors have so far not led to prospective trials evaluating optimal anticoagulant treatment in PAH patients [32]. Nevertheless, the major bleeding rate in our cohort of IPAH patients, and in CTD-PAH patients especially, not only supersedes that of CTEPH patients, but more importantly, the rate is much higher than reported bleeding rates in larger,

TABLE 7 Overview of major bleeding, central nervous system (CNS) and gastrointestinal (GI) bleeding

Author [ref.]	Year	Type	Study	Age years	Subjects n (male %)	OAC	Target INR	Major bleeding#	CNS %	GI %	Other %
Wieloch *et al.* [19]	2011	AF	National registry	70±12	18 391 (60)	Warfarin	2.0–3.0	2.6 (2.0–3.1)	16	37	47
Friberg *et al.* [20]	2012	AF	National cohort study	74±10	68 306 (59)	Warfarin	NA	1.9	32	NA	68
DiMarco *et al.* [21]	2005	AF	AFFIRM study	70±9	4060 (61)	Warfarin (89%)	2.0–3.0	2.6	23		77
Pérez-gómez *et al.* [22]	2004	AF	NASPEAF	70±7	237 (55)	Acenocoumarol	2.0–3.0	1.8	40	10	50
Nieto *et al.* [23]	2010	VT	RIETE registry	NA	24 395 (NA)	VKA	NA	8.9¶	25	40	35
Linkins *et al.* [24]	2003	VT	Meta-analysis	NA	10 757 (NA)	VKA	2.0–3.0	7.2	9	NA	91
Kearon *et al.* [25]	2003	VT	RCT	57±16	369 (53)	Warfarin	2.0–3.0	0.9 (0.4–3.0)	22	NA	78

OAC: oral anticoagulation therapy; INR: international normalised ratio; AF: atrial fibrillation; VT: venous thromboembolism; RCT: randomised controlled trial; VKA: vitamin K antagonist; NA: not available. #: bleeding rate per 100 patient-years, confidence intervals are provided, where available. ¶: 546 bleeding events were documented in 90 days.

prospective studies [13, 15, 18]. Although we did not find the observed INR target range to be of influence in this respect, one would expect that higher INR target ranges would eventually result in increased bleeding when complications do occur. So far, there has been no consensus on the optimal INR target range for pulmonary hypertension patients [4]. In the Netherlands, patients are dosed with VKA according to local policy in the anticoagulation clinics. Determination of optimal INR intensity will require prospective studies in large numbers of patients.

Whereas there have been many randomised trials evaluating the clinical benefit of new drugs attenuating pulmonary hypertension, there has been little attention to a closer evaluation of more conservative therapies. There have been no randomised controlled prospective studies determining the real benefits of treating different classes of pulmonary hypertension patients with VKA in the presence of other PAH specific therapy. The favourable results of VKA in early observational studies along with the overall poor prognosis of pulmonary hypertension patients [9, 10], however, have resulted in widespread use of VKA as a cornerstone of background therapy in pulmonary hypertension patients [33, 34]. Major bleeding events can nevertheless have important deleterious haemodynamic consequences for these patients and, especially, haemoptysis is often life-threatening [11]. The reported high incidence of VKA drug-related major bleeding in IPAH patients, but especially in CTD-PAH patients, warrants a closer look at the safety of routine administration of anticoagulant therapy to PAH patients.

Limitations of this study are its retrospective nature, as well as the patient data being from a single centre. The lack of a direct control group precludes any direct comparison with the observed bleeding indices. Given a relatively small patient number, the number of end-points was also small with inherent confidence limits. Although the poor survival for the CTD-PAH group is common, it precludes an adequate conclusion regarding long-term bleeding risk. Platelet function tests were not performed, therefore the reported platelet count is of limited value. Nevertheless, all data were derived directly from clinical practice, and documentation of all patients included in the study was also carefully recorded by the Dutch anticoagulation clinics.

In conclusion, oral vitamin K antagonist anticoagulation therapy is associated with different rates of major bleeding in different groups of pulmonary hypertension patients. IPAH patients, but CTD-PAH patients especially, appear to be at a markedly higher risk of major bleeding complications than would generally be accepted. Further studies are needed to determine the role of anticoagulant treatment in the standard of care for different groups of patients with PAH.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We conducted this study without external funding and we are very grateful for the help we received from the Dutch anticoagulation clinics, as well as for the patient care provided by them.

Dutch anticoagulation clinics who contributed: Stichting Trombosedienst Alkmaar, Alkmaar; Stichting Trombosedienst Eemvallei, Amersfoort; ATAL Medisch Diagnostisch Centrum, Amsterdam; Trombosedienst Rode Kruis Ziekenhuis, Beverwijk; Stichting Trombosedienst Delft en omstreken, Delft; Stichting Artsenlaboratorium en Trombosedienst, Den Helder; Stichting Regionale Trombosedienst Drechtsteden, Dordrecht; Stichting Trombosedienst Drachten en Omstreken, Drachten; Trombosedienst Neder-Veluwe, Ede Gld; Trombosedienst Scheper Ziekenhuis, Emmen; AntiStollingsCentrum Oost-Nederland ASCON, Enschede; Stichting Regionale Trombosedienst Breda, Etten-Leur; St. Annaziekenhuis, Geldrop Stichting Trombosedienst Gouda, Gouda; Stichting Medische Diagnostiek (Medial), Haarlem; Trombosedienst Ziekenhuis "De Tjongerschans", Heerenveen; Stichting Trombosedienst Oostelijk Zuid-Limburg, Heerlen; Trombosedienst van het Elkerliek Ziekenhuis, Helmond; Stichting Trombosedienst Hengelo en omstreken, Hengelo Stichting Trombosedienst voor het Gooi, Hilversum; Trombosedienst van het Ziekenhuis Bethesda, Hoogeveen; STAT Westfriesland, Hoorn NH; Trombosedienst Friesland Noord, Leeuwarden; Stichting Trombosedienst Leiden e.o., Leiden; Trombosedienst Flevoland, Lelystad; AntiStollingsCentrum Oost-Nederland ASCON, Lichtenvoorde; Stichting Trombosedienst Zeeland, Middelburg; Stichting I.N.R. Trombosedienst, Nijmegen; Trombosedienst NW Veluwe, Nunspeet; Trombosedienst Oldenzaal, Medisch Spectrum Twente, Oldenzaal; Trombosedienst Ziekenhuis Bernhoven, locatie Oss, Oss; Stichting Regionale Trombosedienst 's-Gravenhage e.o., Rijswijk ZH; Trombosedienst Roermond, Roermond; Trombosedienst St. Franciscus Ziekenhuis, Roosendaal; Stichting Trombosedienst & Artsenlaboratorium, Rotterdam; Stichting Trombosedienst 's-Hertogenbosch e.o., 's Hertogenbosch; Stichting Trombosedienst Schiedam e.o., Schiedam; Stichting Trombosedienst Zuid-West Friesland, Sneek; Trombosedienst West-Betuwe/Bommelerwaard, Tiel; Stichting Trombosedienst Midden Brabant, Tilburg; SALTRO, Utrecht; Stichting Trombosedienst Regio Eindhoven, Veldhoven; Trombosedienst Hofpoort Ziekenhuis, Woerden; Stichting Zeister Trombosedienst, Zeist Stichting Trombosedienst Zevenaar e.o., Zevenaar; Gelre Ziekenhuizen, Zutphen Trombosedienst Isala Klinieken, Zwolle.

REFERENCES

1 Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1425–1436.
2 Huber K, Beckmann R, Frank H, *et al.* Fibrinogen, t-PA, and PAI-1 plasma levels in patients with pulmonary hypertension. *Am J Respir Crit Care Med* 1994; 150: 929–933.
3 Hoeper MM, Sosada M, Fabel H. Plasma coagulation profiles in patients with severe primary pulmonary hypertension. *Eur Respir J* 1998; 12: 1446–1449.
4 Herve P, Humbert M, Sitbon O, *et al.* Pathobiology of pulmonary hypertension. The role of platelets and thrombosis. *Clin Chest Med* 2001; 22: 451–458.
5 Johnson SR, Granton JT, Mehta S. Thrombotic arteriopathy and anticoagulation in pulmonary hypertension. *Chest* 2006; 130: 545–552.
6 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493–2537.
7 Badesch DB, Abman SH, Simonneau G, *et al.* Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007; 131: 1917–1928.
8 Galie N, Seeger W, Naeije R, *et al.* Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: 81S–88S.
9 Fuster V, Steele PM, Edwards WD, *et al.* Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984; 70: 580–587.

10 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327: 76–81.
11 Ogawa A, Matsubara H, Fujio H, *et al.* Risk of alveolar hemorrhage in patients with primary pulmonary hypertension–anticoagulation and epoprostenol therapy. *Circ J* 2005; 69: 216–220.
12 Pulido T, Sandoval J, Roquet I, *et al.* Interaction of acenocoumarol and sitaxentan in pulmonary arterial hypertension. *Eur J Clin Invest* 2009; 39: Suppl. 2, 14–18.
13 Hylek EM, Skates SJ, Sheehan MA, *et al.* An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996; 335: 540–546.
14 Schulman S. Clinical practice. Care of patients receiving long-term anticoagulant therapy. *N Engl J Med* 2003; 349: 675–683.
15 Hylek EM, Go AS, Chang Y, *et al.* Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003; 349: 1019–1026.
16 Hoeper MM, Mayer E, Simonneau G, *et al.* Chronic thromboembolic pulmonary hypertension. *Circulation* 2006; 113: 2011–2020.
17 Torbicki A, Perrier A, Konstantinides S, *et al.* Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008; 29: 2276–2315.
18 Connolly SJ, Ezekowitz MD, Yusuf S, *et al.* Dabigatran *versus* warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.
19 Wieloch M, Sjalander A, Frykman V, *et al.* Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. *Eur Heart J* 2011; 32: 2282–2289.
20 Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 2012; 125: 2298–2307.
21 DiMarco JP, Flaker G, Waldo AL, *et al.* Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; 149: 650–656.
22 Perez-Gomez F, Alegria E, Berjon J, *et al.* Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol* 2004; 44: 1557–1566.
23 Nieto JA, Solano R, Ruiz-Ribo MD, *et al.* Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost* 2010; 8: 1216–1222.
24 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003; 139: 893–900.
25 Kearon C, Ginsberg JS, Kovacs MJ, *et al.* Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; 349: 631–639.
26 Delcroix M, Naeije R. Optimising the management of pulmonary arterial hypertension patients: emergency treatments. *Eur Respir Rev* 2010; 19: 204–211.
27 Zylkowska J, Kurzyna M, Pietura R, *et al.* Recurrent hemoptysis: an emerging life-threatening complication in idiopathic pulmonary arterial hypertension. *Chest* 2011; 139: 690–693.
28 Duchini A, Sessoms SL. Gastrointestinal hemorrhage in patients with systemic sclerosis and CREST syndrome. *Am J Gastroenterol* 1998; 93: 1453–1456.
29 Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1655–1665.
30 McLaughlin VV, Genthner DE, Panella MM, *et al.* Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998; 338: 273–277.
31 Badesch DB, McLaughlin VV, Delcroix M, *et al.* Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: 56S–61S.
32 Robbins IM, Kawut SM, Yung D, *et al.* A study of aspirin and clopidogrel in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006; 27: 578–584.
33 Provencher S, Sitbon O, Humbert M, *et al.* Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 589–595.
34 Galie N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148–2157.