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Measures of vitamin K antagonist control reported in atrial fibrillation and venous thromboembolism studies: a systematic review

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ABSTRACT

Objective: To aid trialists, systematic reviewers and others, we evaluated the degree of standardisation of control measure reporting that has occurred in atrial fibrillation (AF) and venous thromboembolism (VTE) studies since 2000; and attempted to determine whether the prior recommendation of reporting ≥2 measures per study has been employed.

Design: Systematic review.

Search strategy: We searched bibliographic databases (2000 to June 2013) to identify AF and VTE studies evaluating dose-adjusted vitamin K antagonists (VKAs) and reporting ≥1 control measure. The types of measures reported, proportion of studies reporting ≥2 measures and mean (±SD) number of measures per study were determined for all studies and compared between subgroups.

Data extraction: Through the use of a standardised data extraction tool, we independently extracted all data, with disagreements resolved by a separate investigator.

Results: 148 studies were included, 57% of which reported ≥2 control measures (mean/study=2.13 ±1.36). The proportion of time spent in the target international normalised ratio range (TTR) was most commonly reported (79%), and was frequently accompanied by time above/below range (52%). AF studies more frequently reported ≥2 control measures compared with VTE studies (63% vs 37%; p=0.004), and reported a greater number of measures per study (mean=2.36 vs 1.53; p<0.001). Observational studies were more likely to provide ≥2 measures compared with randomised trials (76% vs 33%; p<0.001) and report a greater number of measures (mean=2.58 vs 1.63; p<0.001). More recent studies (2004–2013) reported ≥2 measures more often than older (2000–2003) studies (59% vs 35%; p=0.05) and reported more measures per study (mean=2.23 vs 1.48; p=0.02).

Conclusions: While TTR was often utilised, studies reported ≥2 measures of VKA control only about half of the time and lacked consistency in the types of measures reported. A trend towards studies reporting greater numbers of VKA control measures over time was observed over our review time horizon, particularly, with AF and observational studies.

Strengths and limitations of this study

- This large systematic review (N=148 studies) adds to the existing literature by providing updated results and new data regarding the frequency and consistency of vitamin K antagonists (VKA) control measure reporting.
- While the previous review by Fitzmaurice *et al* included studies of all VKA indications; ours evaluated atrial fibrillation (AF) and VTE studies only.
- Unlike previous reviews, our systematic review examined VKA control measure reporting over time and differences in reporting between AF and VTE studies and randomised trials and observational studies. In addition, we explored the way in which VKA control measures are concomitantly reported in studies.

INTRODUCTION

Adjusted-dose vitamin K antagonists (VKAs) are frequently used, and are the standard-of-care anticoagulants that most new oral anticoagulants for the prevention of thrombotic events in patients with atrial fibrillation (AF) and following venous thromboembolism (VTE) are compared with.[1–10] VKAs have substantial evidence from clinical trials supporting their efficacy, and their use is endorsed by multiple national guidelines[11 12]; however, they are often underused due to difficulty in maintaining the international normalised ratio (INR) in the narrow therapeutic range (often 2.0–3.0).[13 14]

Fitzmaurice *et al*[15] performed a systematic review of studies published between 1995 and 1999 in order to evaluate the manner in which VKA control was reported and to provide recommendations for reporting of VKA control measures (parameters used to summarise the level of anticoagulation). Their review found that a wide range of measures had been used in the literature, but

with little consistency between studies. Since studies also suggest different VKA control measures (eg, percentage of time spent in range, proportion of tests in range, point prevalence) used in the same population can result in different conclusions regarding the quality of VKA control,[16–18] researchers recommended ≥2 VKA control measures be reported per study.

In order to aid researchers (eg, clinical trialists and systematic reviewers) and other end users, we performed a systematic review to assess the degree of standardisation in VKA control measure reporting that has occurred in AF and VTE studies since the publication of the paper by Fitzmaurice *et al*; and to determine whether their recommendation of reporting ≥2 control measures has been widely employed.

METHODS

A systematic review of MEDLINE, CENTRAL and EMBASE (from 2000 to June 2013) was conducted to identify published studies (English full-text randomised controlled trials, prospective cohort studies or retrospective analyses) including at least one dose-adjusted VKA treatment arm and reporting a minimum of one VKA control measure in adult patients being treated for AF or VTE as their primary reason for anticoagulation. Our search strategy for MEDLINE (PubMed) is provided in online supplementary appendix 1. Studies were excluded if they included <50 patients or planned to treat patients for <3 months. Manual backwards citation tracking of references from identified studies and review articles was also performed to identify additional relevant studies. All citations were screened by two independent investigators (ESM and J-SS) with discrepancies resolved by a third investigator (CIC).

Through the use of a standardised data extraction tool, we independently extracted all data (ESM, J-SS and JH), with disagreements resolved by a separate investigator (CIC). Collected study-level data included: study identifier and year of publication; indication(s) for VKA therapy; sample size; study design (prospective, retrospective or randomised study); duration of VKA treatment; mean age of participants; and the type(s) of VKA used. The types of VKA control measures reported were also extracted from each study. These included (but were not limited to): percentage of time in range (target international normalised ratio (TTR), calculated using Rosendaal's linear interpolation method[19]), below and/or above range, TTR in an extended range (ie, 1.8–3.2) and extreme ranges (ie, <1.5 and/or >5.0); proportion of INR measurements in range (PINRR), below and/or above extreme range; mean/median INR; mean/median VKA dose; frequency of INR monitoring (number of INR measures per patient over the course of the study); INR variability; INR monitoring interval (number of days between each INR measure); point prevalence (eg, the proportion of patients in range and/or out of range, proportion of patients in range >50% of time or proportion of patients with ≥50% of INR measures <3.0); number of VKA dosage changes; INR measure after a previously subtherapeutic or supratherapeutic INR; proportion of patients with ≥1 INR measure below range after reaching an adequate INR; number of days until the next INR measure after an extreme measure; proportion of days with treatment stability (two consecutive INR measures in range); days to reach a therapeutic INR; mean time until stable and minimum and maximum INR values per patient.

The types of measures reported were summarised and displayed using tables and figures, and the proportion of studies reporting ≥2 measures along with the mean number of measures per study (±SD) were reported for all identified studies. We also compared these same end points between select study subgroups (primary indication for anticoagulation (AF vs VTE); study design (randomised trial vs observational study); and year of publication (2000–2003 vs 2004–2013)). The year categorisations were chosen based on the year of publication of the review by Fitzmaurice *et al*.[15] Finally, in order to assess the concomitant use of VKA control measures within studies, a diagram depicting per study measure linkages was created.

Between-group comparisons were made using χ^2 tests (or Fisher's exact tests, where appropriate) for categorical data and unpaired t tests for continuous data. A p value of <0.05 was considered statistically significant in all situations. Statistical analysis was performed using SPSS V.17.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Of the 5301 citations initially identified, 1119 full-text articles were reviewed for inclusion. A total of 148 studies met all inclusion and exclusion criteria and were included in the analysis (figure 1, table 1).[1–9 18 20–157] Of note, 112 VKA studies were excluded from our systematic review because they did not report a VKA control measure although study participants were receiving a VKA for AF or VTE as their primary reason for treatment for greater than 3 months.

Overall, 57% of studies reported ≥2 VKA control measures (mean/study=2.13±1.36; table 2). TTR was the most common measure reported (79%), and in a little more than half of these studies, was accompanied by the proportion of time above and/or below range. Other common metrics (used in ≥20% of studies) included mean/median INR, frequency of INR monitoring, INR testing interval and the proportion of patients in/out of range. Subgroup analysis found AF studies were 1.7-fold more likely than VTE studies (table 3), observational studies were more than twice as likely as randomised trials (p≤0.05 for all comparisons; table 4) and recently published studies were 70% more likely than older studies (2000–2003; table 5) to report ≥2 control measures. Moreover, the AF, observational and later time

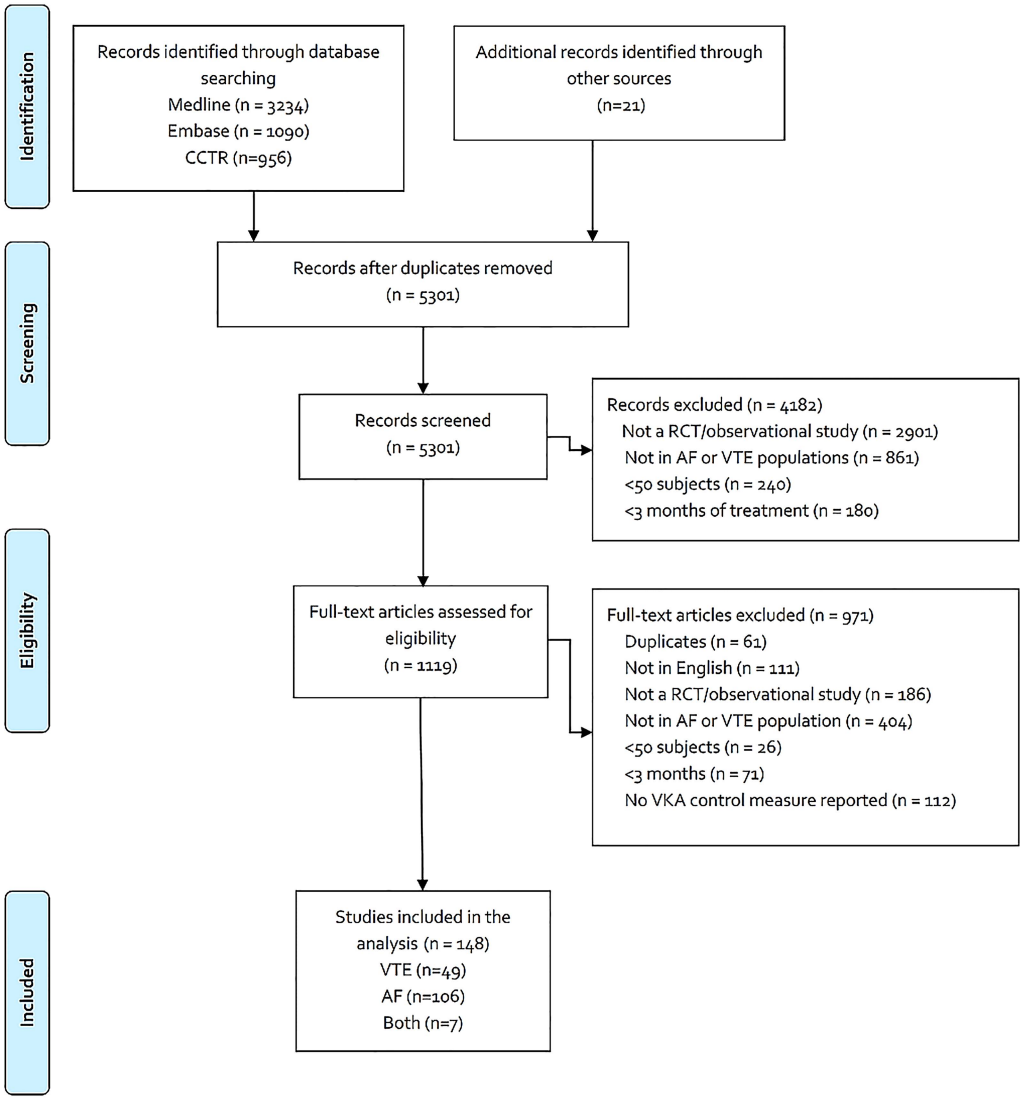

Figure 1 Results of the literature search. AF, atrial fibrillation; CCTR, Cochrane controlled trials register; RCT, randomised controlled trial; VKA, vitamin K antagonist; VTE, venous thromboembolism.

period study subgroups were also more likely to report a greater absolute number of measures per study ($p<0.02$ for all comparisons). When studies that included a new oral anticoagulant (n=30; all published after 2003) were analysed exclusively, only eight (26.7%) reported ≥2 VKA control measures (mean/study=1.37±0.72). At the same time, however, TTR was reported in all but five studies. Finally, AF and observational studies were more likely to report less common metrics, such as extended range time in the therapeutic range, INR testing interval and frequency of INR monitoring ($p<0.05$ for all comparisons).

Our assessment of the concomitant use of VKA control measures in identified studies suggested there was little consistency in their use (figure 2). TTR (the most frequently reported measure overall) was most often reported with mean INR, frequency of INR monitoring and INR testing interval.

DISCUSSION

We performed a systematic review to assess the degree of standardisation of VKA control measures reported in AF and VTE studies since 2000, and to determine the proportion of studies reporting ≥2 control measures. We found that while TTR was frequently reported in identified studies; other measures were more sporadically provided. Our analysis also demonstrated AF studies (compared with VTE studies), observational studies (compared with randomised trials) and more recently published studies (2004–2013) (compared with older ones) were more likely to report ≥2 VKA control measures per study and report a greater absolute number of measures per study. New oral anticoagulant studies utilised TTR quite frequently (>80% of the time), suggesting further standardisation in VKA control measure reporting. Finally, we observed little consistency in the combinations of measures used in identified studies.

Table 1 Studies reporting at least one VKA quality control measure

Study	Disease state	Study design	VKA-treated N	VKA studied	Target INR	TTR, %	PINRR, %	Mean/ median INR	Mean/ median dose	Monitoring frequency	INR variability	INR testing interval, days*	PPIR	Other*
Abdelhafiz and Wheeldon[20]	AF	PD	402	W	2–3	•		•		•	•			
Abdelhafiz and Wheeldon[21]	AF	PD	402	W	2–3	•		•		•	•			
Agnelli *et al*[22]	DVT	RCT	134	W,A	2–3	•								
Agnelli *et al*[23]	PE	RCT	165	W,A	2–3	•								
Agnelli *et al*[24]	DVT	RCT	126	W,A,P	2–3	•								
Agnelli *et al*[7]	VTE	RCT	2704		2–3	•								
Albers *et al*[25]	AF	RCT	1962	W	2–3	•	•						•	
Amiwero *et al*[26]	VTE	RCT	126	W	2–3	•		•					•	
Anderson[27]	AF	RD	87	W	2–3		•			•				
Ansell *et al*[18]	AF	RD	1511	W, A, F	2–3	•	•			•	•	•		•
Aujesky *et al*[28]	PE	RCT	339	W,A,P,F	2–3	•								
Bona *et al*[29]	VTE	PD	98	W	2–3	•								
Boulanger *et al*[30]	AF	RD	6431	W	2–3	•				•		•	•	
Büller *et al*[31]	PE	RCT	2184	–	2–3	•								
Büller *et al*[32]	DVT	RCT	137	W,A,P,F	2–3		•			•				
Büller *et al*[33]	PE	RCT	1595	W	2–3	•								
Burton *et al*[34]	AF	RD	259	W	2–3	•		•		•				
Cafolla *et al*[35]	AF/VTE	PD	871	W,A, other	2–3	•								
Cafolla *et al*[36]	AF	PD	112	W	2–3/ 1.5–2.5	•			•		•			
Campbell *et al*[37]	VTE	RCT	749	W	2–3.5								•	
Cheung *et al*[38]	AF	RD	555	W	1.5–3	•								
Chitsike *et al*[39]	VTE	PD	349	W	2–3	•							•	
Chung *et al*[40]	AF	RCT	75	W	2–3	•								
Coleman *et al*[41]	AF	PD	65	W	2–3	•								•
Connolly *et al*[42]	AF	RCT	3371	–	2–3	•								
Connolly *et al*[43]	AF	RCT	3371	–	2–3	•								
Connolly*et al*[6]	AF	RCT	6022	W	2–3	•								
Copland *et al*[44]	AF	RD	328	W	1.8–3.3				•	•				
Currie *et al*[45]	AF	RD	1513	W	2–3	•	•		•	•	•			•
Daskalopoulos *et al*[46]	DVT	RCT	52	A	2–3				•					
Dimberg *et al*[47]	AF	RD	791	W	2–3	•						•		
Douketis *et al*[48]	VTE	RCT	1021	–	2–3				•					
Easton *et al*[49]	AF	RCT	1643	W	2–3	•								
The Einstein Investigators[49a]	DVT	RCT	1718	W,A	2–3	•								

Continued

Table 1 Continued

Study	Disease state	Study design	VKA-treated N	VKA studied	Target INR	TTR, %	PINRR, %	Mean/ median INR	Mean/ median dose	Monitoring frequency	INR variability	INR testing interval, days*	PPIR	Other*
The Einstein Investigators[49b]	PE	RCT	2413	W,A	2–3	•								
Ellis *et al*[50]	AF	RCT	66	T	2–3	•		•	•				•	
Evans *et al*[51]	AF	PD	288	W	2–3	•	•							
Evans *et al*[52]	AF	PD	214	W	2–3	•	•							
Ezekowitz *et al*[53]	AF	RCT	70	W	2–3	•								
Ezekowitz *et al*[54]	AF	RCT	6022	W	2–3	•								
Fiessinger *et al*[55]	VTE	RCT	1249	W	2–3	•								
Ford *et al*[56]	AF	RCT	3665	W	2–3	•	•							
Gadisseur *et al*[57]	DVT	PD	266	A,P	2.5–3.5	•	•							
Gallagher *et al*[58]	AF	RD	18 113	W	2–3	•				•				
Gallagher *et al*[59]	VTE	RD	10 381	W,A,P	2–3	•				•				
Garcia *et al*[60]	AF	RCT	9081	W	2–3	•								
Go *et al*[61]	AF	RD	6320	W	2–3	•				•				
Gomberg-Maitland *et al*[62]	AF	RCT	3624	W	2–3	•								
Granger *et al*[8]	AF	RCT	9081	W	2–3	•								
Hankey *et al*[63]	AF	RCT	7133	W	2–3	•								
Heidinger *et al*[64]	AF/DVT	PD	1375	–	2–3				•					
Ho *et al*[65]	AF	RD	476	W	2–3	•	•						•	
Hokusai-VTE Investigators[65a]	VTE	RCT	4122	W	2–3	•								
Holmes *et al*[66]	AF	RCT	244	W	2–3	•								
Hori *et al*[67]	AF	RCT	108	W	2–3/ 2–2.6	•								
Hori *et al*[68]	AF	RCT	639	W	2–3/ 1.6–2.6				•					
Hutten *et al*[69]	VTE	RCT	1039	–	2–3	•								
Hylek *et al*[70]	AF	PD	472	W	2–3	•				•				
Hylek *et al*[71]	AF	RCT	3665	W	2–3	•							•	
Jacobs *et al*[72]	AF	RD	90	W	2–3	•						•		
Jones *et al*[73]	AF	RD	2223	W	2–3	•	•		•	•		•		
Kalra *et al*[74]	AF	PD	167	W	2–3	•						•		
Kearon *et al*[75]	VTE	RCT	738	W	2–3/ 1.5–1.9	•	•					•		
Kearon *et al*[76]	VTE	RCT	81	W	2–3	•	•							
Kearon *et al*[77]	VTE	RCT	703	W	2–3	•								
Kim *et al*[78]	AF	RD	129	W	2–3	•		•	•	•		•		
Kim *et al*[79]	AF/VTE	PD	646	W	2–3	•								
Kulo *et al*[80]	AF	PD/RD	117	W,A	2–3	•	•	•	•	•				

Continued

Table 1 Continued

Study	Disease state	Study design	VKA-treated N	VKA studied	Target INR	TTR, %	PINRR, %	Mean/ median INR	Mean/ median dose	Monitoring frequency	INR variability	INR testing interval, days*	PPIR	Other*
Kulo *et al*[81]	AF	PD/RD	117	W,A	2–3	•			•	•		•	•	
Kurtoglu *et al*[82]	DVT	PD	246	W	2–3	•								•
Lee *et al*[83]	AF	PD/RD	200	W	2–3	•	•						•	
Lip *et al*[84]	AF	RCT	318	–	2–3								•	
Lopez-Beret *et al*[85]	DVT	RCT	77	A	2–3				•					
Malik and Taylor [86]	AF/VTE	RD	328	W	2–3	•								
Mant *et al*[87]	AF	RCT	488	W	2–3	•	•							
Matchar *et al*[88]	AF	RCT	363	W	2–3	•						•		
Matchar [89]	AF	RCT	363	W	2–3	•						•		
McBride *et al*[90]	AF	PD	324	W	2–3	•								
McCormick *et al*[91]	AF	RD	174	W	2–3	•						•		
Melamed *et al*[92]	AF	RD	906	W	2–3	•				•			•	
Menzin *et al*[93]	AF	RD	600	W	2–3	•				•				
Morgan *et al*[94]	AF	RD	2235	W	2–3	•				•				
Naganuma *et al*[95]	AF	RD	845	W	1.5–2.5	•								
Nakatani *et al*[96]	AF	R	95	W	2–3/ 1.6–2.6	•			•		•	•		
Neree *et al*[97]	AF	RD	395	W,P,A	2–3	•			•	•			•	
Nichol *et al*[98]	AF	RD	1107	W	2–3	•						•		
Nieuwlaat *et al*[99]	AF	RCT	266	–	2–3	•	•					•		
Njaastad *et al*[100]	AF/VTE	RD	936	W	2–3	•								
Nozawa *et al*[101]	AF	PD	156	W	1.6–1.9		•			•	•			•
Obata *et al*[102]	AF	RD	110	W	1.6–2.6	•	•	•		•	•	•		
Ogawa *et al*[103]	AF	RCT	74	W	2–3/ 2–2.6								•	
Okumura *et al*[104]	AF	PD	501	W	2–3/ 1.6–2.6	•		•				•		
Olsson [105]	AF	RCT	1703	W	2–3	•	•							
Olsson *et al*[106]	AF	RCT	83	W	2–3	•								
Ombandza-Moussa *et al*[107]	VTE	RD	81	–	–		•							
Ono and Fujita[108]	AF	PD	63	W	1.5–2.5	•	•					•		
Palareti *et al*[109]	VTE	PD	733	W, A	2–3	•						•		
Palareti *et al*[110]	VTE	PD	297	W, A	2–3	•								
Patel *et al*[1]	AF	RCT	7133	W	2–3	•								
Pengo *et al*[111]	AF	PD	433	W,A	2–3	•	•	•				•		
Pengo *et al*[112]	AF	RCT	267	W	2–3/ 1.5–2.0	•	•					•		
Perez-de-Llano[113]	PE	RCT	50	A	2–3				•					
Perez-Gomez[114]	AF	RCT	479	A	2–3	•	•	•		•		•		

Continued

Table 1 Continued

Study	Disease state	Study design	VKA-treated N	VKA studied	Target INR	TTR, %	PINRR, %	Mean/ median INR	Mean/ median dose	Monitoring frequency	INR variability	INR testing interval, days*	PPIR	Other*
Perez-Gomez[115]	AF	RCT	91	–	2–3	•	•	•		•		•		
Perez-Gomez[116]	AF	RCT	496	–	2–3	•	•	•						
PERSIST Investigators[117]	DVT	RCT	132	W	2–3				•	•				
Petersen *et al*[118]	AF	RCT	67	W	2–3								•	
Poli *et al*[119]	VTE	PD	182	W	2–3	•		•						
Poli *et al*[120]	AF	PD	290	–	2–3	•								
Poli *et al*[121]	AF	PD	783	W	2–3	•		•						
Poli *et al*[122]	AF	PD	780	W	2–3	•		•						
Poli *et al*[123]	AF	PD	578	–	2–3	•	•							
Poller *et al*[124]	AF/VTE	RCT	9148	W, A, P	2–3	•								
Prandoni (Galilei) *et al*[125]	VTE	RCT	720	W	2–3								•	
Prandoni *et al*[126]	DVT	RCT	180	–	2–3								•	
Ridker *et al*[127]	VTE	RCT	255	W	1.5–2		•	•						
Rombouts *et al*[128]	AF	RCT	104	P	2–3.5	•								
Sadanaga *et al*[129]	AF	PD	269	W	1.5–3		•						•	
Samsa *et al*[130]	AF	RD	660	W	2–3	•			•	•		•		
Sarawate *et al*[131]	AF	PD	470	W	2–3	•								
Schulman *et al*[4]	VTE	RCT	1265	W	2–3	•				•				
Schulman *et al*[5]	VTE	RCT	1426	W	2–3	•								
Sconce *et al*[132]	AF	RCT	70	W	2–3	•		•			•			
Shalev *et al*[133]	AF	RD	4408	W	2–3	•			•	•		•		
Shen *et al*[134]	AF	RD	18 867	W	2–3	•				•				
Shen *et al*[135]	AF	RD	8992	W	2–3	•				•				
Sullivan *et al*[136]	AF	RCT	4060	W	2–3	•								
Suzuki *et al*[137]	AF	PD	667	W	1.6–2.6		•							
Tincani *et al*[138]	AF	PD	90	W,A	2–3	•		•						
van Bladel *et al*[139]	PE	PD	86	A	2–3.5	•								
van Dongen *et al*[140]	DVT	PD	244	–	2–3	•							•	
van Geest-Daalderop *et al*[141]	AF	RD	284	A	2–3.5	•								
van Gogh Investigators[141a]	VTE	RCT	2572	W,A	2–3	•								•
Van Spall *et al*[143]	AF	RCT	6022	W	2–3	•				•				
Veeger *et al*[144]	VTE	RD	2304	A	2–3.5	•	•			•		•	•	
Vene *et al*[145]	AF	PD	113	W	2–3		•							
Voller *et al*[146]	AF	RCT	202	–	2–3	•			•	•	•			
Walker *et al*[147]	AF	RD	84	W	2–3	•								•
Weimar *et al*[148]	AF	PD	252	W	2–3							•		•
Weitz *et al*[149]	AF	RCT	250	W	2–3	•								•

Continued

Table 1 Continued

Study	Disease state	Study design	VKA-treated N	VKA studied	Target INR	TTR, %	PINRR, %	Mean/ median INR	Mean/ median dose	Monitoring frequency	INR variability	INR testing interval, days*	PPIR	Other*
White *et al*[150]	AF	RCT	3587	W	2–3	•				•		•		•
Wieloch *et al*[151]	AF/VTE	RD	15 264	W	2–3	•			•	•				
Willey *et al*[152]	VTE	RD	225	W	2–3	•	•			•				
Wyse *et al*[153]	AF	RCT	4060	W	2–3		•							
Yamaguchi[154]	AF	RCT	115	W	2.2–3.5/ 1.5–2.1		•							
Yamashita *et al*[155]	AF	RCT	129	W	2–3/ 1.6–2.6	•								
Yasaka *et al*[156]	AF	PD	88	W	–		•							
Yousef *et al*[157]	AF	RD	739	W	2–3		•		•	•		•		

*'Other' includes: number of dosage changes; INR measure after a previously subtherapeutic or supratherapeutic INR; proportion of patients with ≥1INR measure below range after reaching an adequate INR; number of days until the next INR measure after an extreme measure; proportion of days with treatment stability (two consecutive INR measures in range); days to reach a therapeutic INR; mean time until stable (6 months within target INR range); minimum and maximum INR values per patient.
– Indicates data not reported.
A, acenocoumarol; AF, atrial fibrillation; DVT, deep vein thrombosis; F, fluindione; INR, international normalised ratio; N, sample size; PD, prospective design; P, phenprocoumon; PINRR, proportion of INR measures in range; PPIR, proportion of patients in range; RCT, randomised controlled trial; RD, retrospective design; T, tecarfarin; TTR, time in therapeutic range; VKA, vitamin K antagonist; VTE, venous thromboembolism; W, warfarin.

We believe the results of our systematic review extend current knowledge regarding the frequency and consistency of VKA control measure reporting in anticoagulation studies, and can serve as a valuable tool for clinical trialists and systematic reviewers. The aforementioned review performed by Fitzmaurice *et al*[15] included only 15 studies across varying indications (not just AF and VTE), making it only a fraction of the size of our own and suggesting that direct comparison between these systematic reviews should be made with caution. Fitzmaurice *et al* found 60% of VKA studies published between 1995 and 1999 reported ≥2 control measures (mean=1.93/study), but with a wide variation in the type of measures reported. TTR (47%), mean/median INR (33%), PINRR (40%) and mean/median warfarin dose (33%) were the most frequently reported VKA control measures identified in their review; however, none of their studies reported point prevalence despite its easy calculation and recommended use at the time.[158]

While our systematic review appears to confirm a number of findings of Fitzmaurice *et al*, our review also suggests that since 2000, additional measures of VKA control—including point prevalence—have become at least to some degree more common in the anticoagulation literature. Moreover, our findings of discrepancies in the number of control measures reported between AF and VTE studies and observational and randomised studies are novel.

There are a number of reasons why reporting multiple measures of VKA control in anticoagulation studies (as originally suggested by Fitzmaurice *et al*) seems wise. First, by reporting multiple measures of control, the likelihood that potentially comparable studies share at least one measure in common is increased. Furthermore, studies suggesting different VKA control measures may yield disparate findings even when utilised in the same patient population.[16–18] In a retrospective cohort study of 633 patients undergoing anticoagulation with a VKA, Schmitt *et al*[17] observed 24%, 24% and 22% absolute differences between TTR and PINRR estimates of INR control and 22%, 26% and 17% absolute differences between TTR and point prevalence (cross-sectional) estimates of INR control after 2-month, 3-month and 6-month time intervals of follow-up, respectively. Moreover, in a randomised trial of 367 patients receiving a VKA, Fitzmaurice *et al*[16] demonstrated up to a 9% variance between TTR, point prevalence and PINRR estimates in the same population. Finally, a retrospective study of 1511 patients performed by Ansell *et al*[18] provided yet more evidence to support population differences in VKA control estimates when different measures are used, demonstrating a 5–10% absolute difference between TTR and PINRR estimates for patients from five different countries.

A final reason for including multiple measures on VKA control in anticoagulation studies is that different VKA control measures have their own unique strengths and weaknesses.[17] While TTR takes into account actual days in the target INR range (typically by assuming

Table 2 Types and frequency of VKA control measures reported in identified studies

Variable	(N=148) n (%)
Number of measures reported (mean±SD)	2.13±1.36
1	63 (42.6)
2	44 (29.7)
3	16 (10.8)
4	13 (8.8)
5	8 (5.4)
6	3 (2.0)
7	1 (0.7)
≥2	85 (57.4)
Percentage of time in range (INR=2–3)	117 (79.1)
Below range (<2)	77 (52.0)
Above range (>3)	77 (52.0)
In extended range (1.8–3.2)	15 (10.1)
In extreme range (<1.5, >5)	19 (12.8)
Proportion of INR tests in range (INR=2–3)	24 (16.2)
Below range (<2)	22 (14.9)
Above range (>3)	20 (13.5)
In extreme range (<1.5, >4)	11 (7.4)
Mean/median INR	38 (25.7)
Mean/median VKA dose	17 (11.5)
Frequency of INR monitoring	38 (25.7)
INR variability	8 (5.4)
INR testing interval	32 (21.6)
Proportion of patients in/out of range*	29 (19.6)
Other†	13 (8.8)

*For example, point prevalence, proportion of patients in range >50% of time or proportion of patients with ≥50% of INR measures <3.0.
†Other measures include: number of dosage changes; INR measure after a previously subtherapeutic or supratherapeutic INR; proportion of patients with ≥1INR measure below range after reaching an adequate INR; number of days until the next INR measure after an extreme measure; proportion of days with treatment stability (two consecutive INR measures in range); days to reach a therapeutic INR; mean time until stable (6 months within target INR range); minimum and maximum INR values per patient.
INR, international normalised ratio; VKA, vitamin K antagonist.

Table 3 Differences in VKA control measures reported between AF and VTE studies

Variable	AF (N=106) n (%)	VTE (N=49) n (%)	p Value*
Number of measures reported (mean±SD)	2.36±1.44	1.53±0.92	<0.001
1	39 (36.8)	31 (63.3)	
2	30 (28.3)	13 (26.5)	
3	13 (12.3)	4 (8.2)	
4	13 (12.3)	0	
5	8 (7.5)	0	
6	2 (1.9)	1 (2.0)	
7	1 (0.9)	0	
≥2	67 (63.2)	18 (36.7)	0.004
Percentage of time in range (INR=2–3)	87 (82.1)	36 (73.5)	0.31
Below range (<2)	53 (50.0)	25 (51.0)	0.96
Above range (>3)	54 (51.0)	24 (49.0)	0.96
In extended range (1.8–3.2)	15 (14.2)	0	0.01
In extreme range (<1.5, >5)	13 (12.3)	6 (12.2)	0.80
Proportion of INR tests in range (INR=2–3)	18 (17.0)	7 (14.3)	0.85
Below range (<2)	16 (15.1)	7 (14.3)	0.91
Above range (>3)	14 (13.2)	7 (14.3)	0.94
In extreme range (<1.5, >4)	11 (10.4)	0	0.05
Mean/median INR	30 (28.3)	8 (16.3)	0.16
Mean/median VKA dose	15 (14.2)	3 (6.1)	0.24
Frequency of INR monitoring	32 (30.2)	7 (14.3)	0.06
INR variability	8 (7.5)	0	0.11
INR testing interval	29 (27.4)	4 (8.2)	0.01
Proportion of patients in/out of range†	20 (18.9)	9 (18.4)	0.88
Other‡	11 (10.4)	2 (4.1)	0.32

*p Value for the comparison of AF vs VTE.
†For example, point prevalence, proportion of patients in range >50% of time or proportion of patients with ≥50% of INR measures <3.0.
‡Other measures include: number of dosage changes; INR measure after a previously subtherapeutic or supratherapeutic INR; proportion of patients with ≥1INR measure below range after reaching an adequate INR; number of days until the next INR measure after an extreme measure; proportion of days with treatment stability (two consecutive INR measures in range); days to reach a therapeutic INR; mean time until stable (6 months within target INR range); minimum and maximum INR values per patient.
AF, atrial fibrillation; INR, international normalised ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism.

values vary linearly between two measures[19]), its calculation is more complex than other measures; it makes assumptions about INR values between actual tests and can be biased by extreme out-of-range INR values. In addition, while we were not able to assess this in our systematic review because of a lack of consistent reporting, there appears to be variability in what INR values are included in TTR calculations, with some studies excluding INR values occurring during the initiation phase (ie, first week) and/or around temporary interruptions of a VKA.[6 8] PINRR is a simpler measure to calculate than TTR; it requires only one INR measurement per patient and is not influenced by the extent INRs are out of range; nevertheless, it fails to take into account actual days of anticoagulation like TTR and may underestimate control when more frequent INR testing occurs in unstable patients. Point prevalence is perhaps the simplest measure to calculate because it takes only one time point into consideration (a cross-sectional method), and like PINRR, it is not influenced by the extent an INR value is out of range; however, unlike the aforementioned methods, point prevalence takes individual patients into account. Finally, it is worth noting that VKA control measures may tend to stabilise over time, suggesting duration of study follow-up should be considered when interpreting a control measure.

On the basis of the results of our systematic review, we agree with the previous recommendation of Fitzmaurice

Table 4 Differences in VKA control measures reported between randomised trials and observational studies

Variable	Randomised controlled trials (N=72) n (%)	Observational studies (N=76) n (%)	p Value*
Number of measures reported (mean±SD)	1.63±1.08	2.58±1.46	<0.001
1	48 (66.7)	18 (23.7)	
2	12 (16.7)	29 (38.2)	
3	6 (8.3)	10 (13.2)	
4	3 (4.2)	10 (13.2)	
5	3 (4.2)	5 (6.6)	
6	0	3 (3.9)	
7	0	1 (1.3)	
≥2	24 (33.3)	58 (76.3)	<0.001
Percentage of time in range (INR=2–3)	56 (77.8)	61 (80.3)	0.87
Proportion of INR tests in range (INR=2–3)	10 (13.9)	14 (18.4)	0.60
Mean/median INR	14 (19.4)	24 (31.6)	0.09
Mean/median VKA dose	6 (8.3)	11 (14.5)	0.36
Frequency of INR monitoring	8 (11.1)	30 (39.5)	<0.001
INR variability	2 (2.8)	6 (7.9)	0.31
INR testing interval	6 (8.3)	24 (31.6)	<0.001
Proportion of patients in/out of range†	13 (18.1)	16 (21.1)	0.80
Other‡	2 (2.8)	10 (13.2)	0.04

*p Value for the comparison of randomised controlled trials vs observational studies.
†For example, point prevalence, proportion of patients in range >50% of time or proportion of patients with ≥50% of INR measures <3.0.
‡Other measures include: number of dosage changes; INR measure after a previously subtherapeutic or supratherapeutic INR; proportion of patients with ≥1INR measure below range after reaching an adequate INR; number of days until the next INR measure after an extreme measure; proportion of days with treatment stability (two consecutive INR measures in range); days to reach a therapeutic INR; mean time until stable (6 months within target INR range); minimum and maximum INR values per patient.
INR, international normalised ratio; VKA, vitamin K antagonist.

Table 5 Change in VKA control measures reported in studies published between 2000–2003 and 2004–2013

Variable	Studies published in 2000–2003 (N=23) n (%)	Studies published in 2004–2013 (N=125) n (%)	p Value*
Number of measures reported (mean±SD)	1.48±0.79	2.23±1.43	0.02
1	15 (65.2)	51 (40.8)	
2	6 (26.1)	35 (28.0)	
3	1 (4.3)	15 (12.0)	
4	1 (4.3)	12 (9.6)	
5	0	8 (6.4)	
6	0	3 (2.4)	
7	0	1 (0.8)	
≥2	8 (34.8)	74 (59.2)	0.05
Percentage of time in range (INR=2–3)	15 (65.2)	102 (81.6)	0.14
Proportion of INR tests in range (INR=2–3)	4 (17.4)	20 (16.0)	0.89
Mean/median INR	7 (30.4)	31 (24.8)	0.76
Mean/median VKA dose	1 (4.3)	16 (12.8)	0.42
Frequency of INR monitoring	2 (8.7)	36 (28.8)	0.08
INR variability	0	8 (6.4)	0.46
INR testing interval	4 (17.4)	26 (20.8)	0.98
Proportion of patients in/out of range†	1 (4.3)	28 (22.4)	0.09
Other‡	0	12 (9.6)	0.26

*p Value for the comparison of studies published in 2000–2003 vs 2004–2013.
† For example, point prevalence, proportion of patients in range >50% of time or proportion of patients with ≥50% of INR measures <3.0.
‡Other measures include: number of dosage changes; INR measure after a previously subtherapeutic or supratherapeutic INR; proportion of patients with ≥1INR measure below range after reaching an adequate INR; number of days until the next INR measure after an extreme measure; proportion of days with treatment stability (two consecutive INR measures in range); days to reach a therapeutic INR; mean time until stable (6 months within target INR range); minimum and maximum INR values per patient.
INR, international normalised ratio; VKA, vitamin K antagonist.

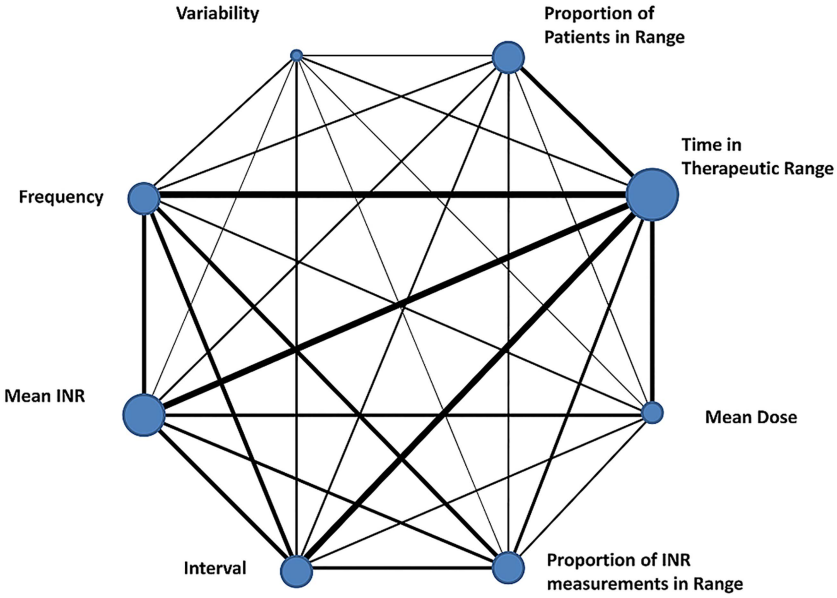

Figure 2 Frequency of concomitant reporting of vitamin K antagonist (VKA) control measures in identified studies. The width of the line is proportional to the number of trials reporting each pair of VKA control measures. Each node is proportional to the total number of times the VKA control measure was reported. INR, international normalised ratio.

et al of reporting at least two measures of VKA control. However, we would like to emphasise that while we recommend multiple measures be reported, we are by no means suggesting that the quantity of measures reported is more important than the quality of the measures. For this reason, we further suggest TTR be one of the measures because of its frequent study in the literature (use in studies and linkage to anticoagulation outcomes).

There are several limitations of our systematic review worth discussion. First, like any other systematic review, the possibility that we missed eligible studies could exist. However, we consider this risk to be minimal due to our systematic search strategy and manual backwards citation tracking. In addition, the large number of included studies in this review lessens the impact that missed studies might have on our overall conclusions. Next, it is reasonable to question the inclusion of mean/median warfarin dose as a true measure of VKA control, since unlike other measures, it does not consider INR values. However, we opted to include it as a measure in order to stay consistent with the methods of the prior review by Fitzmaurice *et al*.[15] Finally, the possibility that journal word limits may have played some role in the underreporting of VKA control measures should be considered.

CONCLUSIONS

VKA studies lack consistency in the types and combinations of control measures reported. A trend towards studies reporting greater numbers of VKA control measures over time was observed over our review time horizon, particularly, with AF and observational studies. The findings of this systematic review should be taken into consideration by researchers when performing future work in this area.

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REFERENCES

1. Patel MR, Mahaffey KW, Garg J, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.

2. Bauersachs R, Berkowitz SD, Brenner B, *et al*. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
3. Büller HR, Prins MH, Lensin AW, *et al*. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
4. Schulman S, Kearon C, Kakkar AK, *et al*. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–52.
5. Schulman S, Kearon C, Kakkar AK, *et al*. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368:709–18.
6. Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
7. Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.
8. Granger CB, Alexander JH, McMurray JJ, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
9. Büller HR, Décousus H, Grosso MA, *et al*. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
10. Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
11. Fuster V, Rydén LE, Cannom DS, *et al*. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Circulation* 2006;114:e257–354.
12. Kearon C, Akl EA, Comerota AJ, *et al*. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e419S–94S.
13. Bungard TJ, Ghali WA, Teo KK, *et al*. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med* 2000;160: 41–6.
14. Cohen N, Almoznino-Sarafian D, Alon I, *et al*. Warfarin for stroke prevention still underused in atrial fibrillation: patterns of omission. *Stroke* 2000;31:1217–22.
15. Fitzmaurice DA, Kesteven P, Gee KM, *et al*. A systematic review of outcome measures reported for the therapeutic effectiveness of oral anticoagulation. *J Clin Pathol* 2003;56:48–51.
16. Fitzmaurice DA, Hobbs FD, Murray ET, *et al*. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. *Arch Intern Med* 2000;160:2343–8.
17. Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: comparative evaluation of measures of time-in-therapeutic range. *J Thromb Thrombolysis* 2003;15:213–16.
18. Ansell J, Hollowell J, Pengo V, *et al*. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the international study of anticoagulation management (ISAM). *J Thromb Thrombolysis* 2007;23:83–91.
19. Rosendaal F, Cannegieter S, Van Der Meer F, *et al*. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemostas* 1993;69:236–9.
20. Abdelhafiz AH, Wheeldon NM. Results of an open-labeled, prospective study of anticoagulant therapy for atrial fibrillation in an outpatient anticoagulation clinic. *Clin Ther* 2004;26:1470–8.
21. Abdelhafiz AH, Wheeldon NM. Risk factors for bleeding during anticoagulation of atrial fibrillation in older and younger patients in clinical practice. *Am J Geriatr Pharmacother* 2008;6:1–11.
22. Agnelli G, Prandoni P, Santamaria MG, *et al*. Warfarin optimal duration Italian trial investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001;345:165–9.
23. Agnelli G, Prandoni P, Becattini C, *et al*. Warfarin optimal duration Italian trial investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003;139:19–25.
24. Agnelli G, Gallus A, Goldhaber SZ, *et al*. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY59–7939): the ODIXa-DVT (Oral direct factor Xa inhibitor BAY 59–7939 in patients with acute symptomatic deep-vein thrombosis) study. *Circulation* 2007;116:180–7.
25. Albers GW, Diener HC, Frison L, *et al*. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005;293:690–8.
26. Amiwero C, Campbell IA, Prescott RJ. A re-appraisal of warfarin control in the treatment of deep vein thrombosis and/or pulmonary embolism. *Afr Health Sci* 2009;9:179–85.
27. Anderson RJ. Cost analysis of a managed care decentralized outpatient pharmacy anticoagulation service. *J Manag Care Pharm* 2004;10:159–65.
28. Aujesky D, Roy PM, Verschuren F, *et al*. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet* 2011;378:41–8.
29. Bona RD, Hickey AD, Wallace DM. Warfarin is safe as secondary prophylaxis in patients with cancer and a previous episode of venous thrombosis. *Am J Clin Oncol* 2000;23:71–3.
30. Boulanger L, Kim J, Friedman M, *et al*. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. *Int J Clin Pract* 2006;60:258–64.
31. Büller HR, Davidson BL, Decousus H, *et al*. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695–702.
32. Büller HR, Lensing AW, Prins MH, *et al*. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. *Blood* 2008;112:2242–7.
33. Büller HR, Gallus AS, Pillion G, *et al*. Enoxaparin followed by once-weekly idrabiotaparinux versus enoxaparin plus warfarin for patients with acute symptomatic pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial. *Lancet* 2012;379:123–9.
34. Burton C, Isles C, Norrie J, *et al*. The safety and adequacy of antithrombotic therapy for atrial fibrillation: a regional cohort study. *Br J Gen Pract* 2006;56:697–702.
35. Cafolla A, Melizzi R, Baldacci E, *et al*. 'Zeus' a new oral anticoagulant therapy dosing algorithm: a cohort study. *Thromb Res* 2011;128:325–30.
36. Cafolla A, Campanelli M, Baldacci E, *et al*. Oral anticoagulant therapy in Italian patients 80 yr of age or older with atrial fibrillation: a pilot study of low vs. standard PT/INR targets. *Eur J Haematol* 2012;89:81–6.
37. Campbell IA, Bentley DP, Prescott RJ, *et al*. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. *BMJ* 2007; 334:674.
38. Cheung CM, Tsoi TH, Huang CY. The lowest effective intensity of prophylactic anticoagulation for patients with atrial fibrillation. *Cerebrovasc Dis* 2005;20:114–19.
39. Chitsike RS, Rodger MA, Kovacs MJ, *et al*. Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. *J Thromb Haemost* 2012;10:2039–44.
40. Chung N, Jeon HK, Lien LM, *et al*. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost* 2011;105:535–44.
41. Coleman CI, Coleman SM, Vanderpoel J, *et al*. Patient satisfaction with warfarin- and non-warfarin-containing thromboprophylaxis regimens for atrial fibrillation. *J Investig Med* 2013;61: 878–81.
42. Connolly S, Pogue J, Hart R, *et al*. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–12.
43. Connolly SJ, Pogue J, Eikelboom J, *et al*. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;118:2029–37.
44. Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. *Arch Intern Med* 2001;161:2125–8.
45. Currie CJ, McEwan P, Emmas C, *et al*. Anticoagulation in patients with non-valvular atrial fibrillation: an evaluation of stability and early factors that predict longer-term stability on warfarin in a large UK population. *Curr Med Res Opin* 2005;21: 1905–13.
46. Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, *et al*. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg* 2005;29:638–50.

47. Dimberg I, Grzymala-Lubanski B, Hägerfelth A, *et al*. Computerised assistance for warfarin dosage—effects on treatment quality. *Eur J Intern Med* 2012;23:742–4.
48. Douketis JD, Foster GA, Crowther MA, *et al*. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. *Arch Intern Med* 2000;160:3431–6.
49. Easton JD, Lopes RD, Bahit MC, *et al*. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012;11:503–11.
49a. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
49b. EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
50. Ellis DJ, Usman MH, Milner PG, *et al*. The first evaluation of a novel vitamin K antagonist, tecarfarin (ATI-5923), in patients with atrial fibrillation. *Circulation* 2009;120:1029–35, 2 p following 1035.
51. Evans A, Perez I, Yu G, *et al*. Secondary stroke prevention in atrial fibrillation: lessons from clinical practice. *Stroke* 2000;31:2106–11.
52. Evans A, Perez I, Yu G, *et al*. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? *Stroke* 2001;32:2828–32.
53. Ezekowitz MD, Reilly PA, Nehmiz G, *et al*. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007;100:1419–26.
54. Ezekowitz MD, Wallentin L, Connolly SJ, *et al*. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. *Circulation* 2010;122:2246–53.
55. Fiessinger JN, Huisman MV, Davidson BL, *et al*. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. *JAMA* 2005;293:681–9.
56. Ford GA, Choy AM, Deedwania P, *et al*. Direct thrombin inhibition and stroke prevention in elderly patients with atrial fibrillation: experience from the SPORTIF III and V Trials. *Stroke* 2007;38:2965–71.
57. Gadisseur AP, Christiansen SC, Van der Meer FJ, *et al*. The quality of oral anticoagulant therapy and recurrent venous thrombotic events in the Leiden Thrombophilia Study. *J Thromb Haemost* 2007;5:931–6.
58. Gallagher AM, Setakis E, Plumb JM, *et al*. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;106:968–77.
59. Gallagher AM, de Vries F, Plumb JM, *et al*. Quality of INR control and outcomes following venous thromboembolism. *Clin Appl Thromb Hemost* 2012;18:370–8.
60. Garcia DA, Wallentin L, Lopes RD, *et al*. Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: results from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial. *Am Heart J* 2013;166:549–58.
61. Go AS, Hylek EM, Chang Y, *et al*. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003;290:2685–92.
62. Gomberg-Maitland M, Wenger NK, Feyzi J, *et al*. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. *Eur Heart J* 2006;27:1947–53.
63. Hankey GJ, Patel MR, Stevens SR, *et al*. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;11:315–22.
64. Heidinger KS, Bernardo A, Taborski U, *et al*. Clinical outcome of self-management of oral anticoagulation in patients with atrial fibrillation or deep vein thrombosis. *Thromb Res* 2000;98:287–93.
65. Ho LY, Siu CW, Yue WS, *et al*. Safety and efficacy of oral anticoagulation therapy in Chinese patients with concomitant atrial fibrillation and hypertension. *J Hum Hypertens* 2011;25:304–10.
65a. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
66. Holmes DR, Reddy VY, Turi ZG, *et al*. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374:534–42.
67. Hori M, Connolly SJ, Ezekowitz MD, *et al*. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation—sub-analysis in Japanese population in RE-LY trial. *Circ J* 2011;75:800–5.
68. Hori M, Matsumoto M, Tanahashi N, *et al*. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation—the J-ROCKET AF study. *Circ J* 2012;76:2104–11.
69. Hutten BA, Prins MH, Gent M, *et al*. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000;18:3078–83.
70. Hylek EM, Evans-Molina C, Shea C, *et al*. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007;115:2689–96.
71. Hylek EM, Frison L, Henault LE, *et al*. Disparate stroke rates on warfarin among contemporaneous cohorts with atrial fibrillation: potential insights into risk from a comparative analysis of SPORTIF III versus SPORTIF V. *Stroke* 2008;39:3009–14.
72. Jacobs LG, Billett HH, Freeman K, *et al*. Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: a single-center, retrospective, observational study. *Am J Geriatr Pharmacother* 2009;7:159–66.
73. Jones M, McEwan P, Morgan CL, *et al*. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. *Heart* 2005;91:472–7.
74. Kalra L, Yu G, Perez I, *et al*. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* 2000;320:1236–9.
75. 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;349:631–9.
76. Kearon C, Ginsberg JS, Anderson DR, *et al*. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. *J Thromb Haemost* 2004;2:743–9.
77. Kearon C, Ginsberg JS, Julian JA, *et al*. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA* 2006;296:935–42.
78. Kim JH, Song YB, Shin DH, *et al*. How well does the target INR level maintain in warfarin-treated patients with non-valvular atrial fibrillation? *Yonsei Med J* 2009;50:83–8.
79. Kim YK, Nieuwlaat R, Connolly SJ, *et al*. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study. *J Thromb Haemost* 2010;8:101–6.
80. Kulo A, Mulabegović N, Kusturica J, *et al*. Outpatient management of oral anticoagulation therapy in patients with nonvalvular atrial fibrillation. *Bosn J Basic Med Sci* 2009;9:313–19.
81. Kulo A, Kusturica J, Kapić E, *et al*. Better stability of acenocoumarol compared to warfarin treatment in one-year observational, clinical study in patients with nonvalvular atrial fibrillation. *Med Glas (Zenica)* 2011;8:9–14.
82. Kurtoglu M, Koksoy C, Hasan E, *et al*. Long-term efficacy and safety of once-daily enoxaparin plus warfarin for the outpatient ambulatory treatment of lower-limb deep vein thrombosis in the TROMBOTEK trial. *J Vasc Surg* 2010;52:1262–70.
83. Lee SJ, Shin DH, Hwang HJ, *et al*. Bleeding risk and major adverse events in patients with previous ulcer on oral anticoagulation therapy. *Am J Cardiol* 2012;110:373–7.
84. Lip GY, Rasmussen LH, Olsson SB, *et al*. Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists. *Eur Heart J* 2009;30:2897–907.
85. López-Beret P, Orgaz A, Fontcuberta J, *et al*. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 2001;33:77–90.
86. Malik AK, Taylor AJ. Can warfarin randomized trials be reproduced in 'real life'? Adherence to warfarin guidelines for intensity of anticoagulation in a university-based warfarin clinic. *South Med J* 2000;93:58–61.
87. Mant J, Hobbs FD, Fletcher K, *et al*. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493–503.

88. Matchar DB, Samsa GP, Cohen SJ, *et al*. Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: results of the managing anticoagulation services trial. *Am J Med* 2002;113:42–51.
89. Matchar DB. Do anticoagulation management services improve care? Implications of the Managing Anticoagulation Services Trial. *Card Electrophysiol Rev* 2003;7:379–81.
90. McBride D, Brüggenjürgen B, Roll S, *et al*. Anticoagulation treatment for the reduction of stroke in atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. *J Thromb Thrombolysis* 2007;24:65–72.
91. McCormick D, Gurwitz JH, Goldberg RJ, *et al*. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. *Arch Intern Med* 2001;161:2458–63.
92. Melamed OC, Horowitz G, Elhayany A, *et al*. Quality of anticoagulation control among patients with atrial fibrillation. *Am J Manag Care* 2011;17:232–7.
93. Menzin J, Boulanger L, Hauch O, *et al*. Quality of anticoagulation control and costs of monitoring warfarin therapy among patients with atrial fibrillation in clinic settings: a multi-site managed-care study. *Ann Pharmacother* 2005;39:446–51.
94. Morgan CL, McEwan P, Tukiendorf A, *et al*. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. *Thromb Res* 2009;124:37–41.
95. Naganuma M, Shiga T, Sato K, *et al*. Clinical outcome in Japanese elderly patients with non-valvular atrial fibrillation taking warfarin: a single-center observational study. *Thromb Res* 2012;130: 21–6.
96. Nakatani Y, Mizumaki K, Nishida K, *et al*. Anticoagulation control quality affects the D-dimer levels of atrial fibrillation patients. *Circ J* 2012;76:317–21.
97. Neree C. Quality of oral anticoagulation in patients with atrial fibrillation: a cross-sectional study in general practice. *Eur J Gen Pract* 2006;12:163–8.
98. Nichol MB, Knight TK, Dow T, *et al*. Quality of anticoagulation monitoring in nonvalvular atrial fibrillation patients: comparison of anticoagulation clinic versus usual care. *Ann Pharmacother* 2008;42:62–70.
99. Nieuwlaat R, Connolly BJ, Hubers LM, *et al*. Quality of individual INR control and the risk of stroke and bleeding events in atrial fibrillation patients: a nested case control analysis of the ACTIVE W study. *Thromb Res* 2012;129:715–19.
100. Njaastad AM, Abildgaard U, Lassen JF. Gains and losses of warfarin therapy as performed in an anticoagulation clinic. *J Intern Med* 2006;259:296–304.
101. Nozawa T, Asanoi H, Inoue H, *et al*. Instability of anticoagulation intensity contributes to occurrence of ischemic stroke in patients with non-rheumatic atrial fibrillation. *Jpn Circ J* 2001;65:404–8.
102. Obata H, Watanabe H, Ito M, *et al*. Effects of combination therapy with warfarin and bucolome for anticoagulation in patients with atrial fibrillation. *Circ J* 2011;75:201–3.
103. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. The ARISTOTLE-J study. *Circ J* 2011;75:1852–9.
104. Okumura K, Komatsu T, Yamashita T, *et al*. Time in the therapeutic range during warfarin therapy in Japanese patients with non-valvular atrial fibrillation—a multicenter study of its status and influential factors. *Circ J* 2011;75:2087–94.
105. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362:1691–8.
106. Olsson SB, Rasmussen LH, Tveit A, *et al*. Safety and tolerability of an immediate-release formulation of the oral direct thrombin inhibitor AZD0837 in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Thromb Haemost* 2010;103: 604–12.
107. Ombandza-Moussa E, Samama MM, Horellou MH, *et al*. Potential use of D-dimer measurement in patients treated with oral anticoagulant for a venous thromboembolic episode. *Int Angiol* 2003;22:364–9.
108. Ono A, Fujita T. Low-intensity anticoagulation for stroke prevention in elderly patients with atrial fibrillation: efficacy and safety in actual clinical practice. *J Clin Neurosci* 2005;12:891–4.
109. Palareti G, Legnani C, Lee A, *et al*. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. *Thromb Haemost* 2000;84:805–10.
110. Palareti G, Legnani C, Cosmi B, *et al*. Poor anticoagulation quality in the first 3 months after unprovoked venous thromboembolism is a risk factor for long-term recurrence. *J Thromb Haemost* 2005;3:955–61.
111. Pengo V, Legnani C, Noventa F, *et al*. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. *Thromb Haemost* 2001;85:418–22.
112. Pengo V, Cucchini U, Denas G, *et al*. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. *Thromb Haemost* 2010;103:442–9.
113. Pérez-de-Llano LA, Leiro-Fernández V, Golpe R, *et al*. Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. *Blood Coagul Fibrinolysis* 2010;21:744–9.
114. Pérez-Gómez F, Alegría E, Berjón 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;44:1557–66.
115. Pérez-Gómez F, Salvador A, Zumalde J, *et al*. Effect of antithrombotic therapy in patients with mitral stenosis and atrial fibrillation: a sub-analysis of NASPEAF randomized trial. *Eur Heart J* 2006;27:960–7.
116. Pérez-Gómez F, Iriarte JA, Zumalde J, *et al*. Antithrombotic therapy in elderly patients with atrial fibrillation: effects and bleeding complications: a stratified analysis of the NASPEAF randomized trial. *Eur Heart J* 2007;28:996–1003.
117. PERSIST investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis. A Phase II evaluation. *J Thromb Haemost* 2004;2:47–53.
118. Petersen P, Grind M, Adler J, *et al*. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol* 2003;41:1445–51.
119. Poli D, Antonucci E, Ciuti G, *et al*. Anticoagulation quality and the risk of recurrence of venous thromboembolism. *Thromb Haemost* 2007;98:1148–50.
120. Poli D, Antonucci E, Marcucci R, *et al*. Risk of bleeding in very old atrial fibrillation patients on warfarin: relationship with ageing and CHADS2 score. *Thromb Res* 2007;121:347–52.
121. Poli D, Antonucci E, Grifoni E, *et al*. Bleeding risk during oral anticoagulation in atrial fibrillation patients older than 80years. *J Am Coll Cardiol* 2009;54:999–1002.
122. Poli D, Antonucci E, Grifoni E, *et al*. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost* 2009;101:938–42.
123. Poli D, Antonucci E, Marcucci R, *et al*. The quality of anticoagulation on functional outcome and mortality for TIA/stroke in atrial fibrillation patients. *Int J Cardiol* 2009;132:109–13.
124. Poller L, Keown M, Ibrahim S, *et al*. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. *J Thromb Haemost* 2008;6:935–43.
125. Prandoni P, Carnovali M, Marchiori A, *et al*. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med* 2004;164:1077–83.
126. Prandoni P, Lensing AW, Prins MH, *et al*. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004;141:249–56.
127. Ridker PM, Goldhaber SZ, Danielson E, *et al*. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;348:1425–34.
128. Rombouts EK, Rosendaal FR, Van Der Meer FJ. Daily vitamin K supplementation improves anticoagulant stability. *J Thromb Haemost* 2007;5:2043–8.
129. Sadanaga T, Sadanaga M, Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *J Am Coll Cardiol* 2010;55:2225–31.
130. Samsa GP, Matchar DB, Goldstein LB, *et al*. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. *Arch Intern Med* 2000;160:967–73.
131. Sarawate C, Sikirica MV, Willey VJ, *et al*. Monitoring anticoagulation in atrial fibrillation. *J Thromb Thrombolysis* 2006;21:191–8.
132. Sconce E, Avery P, Wynne H, *et al*. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. *Blood* 2007;109:2419–23.
133. Shalev V, Rogowski O, Shimron O, *et al*. The interval between prothrombin time tests and the quality of oral anticoagulants

treatment in patients with chronic atrial fibrillation. *Thromb Res* 2007;120:201–6.
134. Shen AY, Yao JF, Brar SS, *et al*. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007;50:309–15.
135. Shen AY, Yao JF, Brar SS, *et al*. Racial/ethnic differences in ischemic stroke rates and the efficacy of warfarin among patients with atrial fibrillation. *Stroke* 2008;39:2736–43.
136. Sullivan RM, Zhang J, Zamba G, *et al*. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). *Am J Cardiol* 2012;110:1799–802.
137. Suzuki S, Yamashita T, Kato T, *et al*. Incidence of major bleeding complication of warfarin therapy in Japanese patients with atrial fibrillation. *Circ J* 2007;71:761–5.
138. Tincani E, Baldini P, Crowther MA, *et al*. Bleeding rates in patients older than 90 years of age on vitamin K antagonist therapy for nonvalvular atrial fibrillation. *Blood Coagul Fibrinolysis* 2009;20:47–51.
139. van Bladel ER, Agterof MJ, Frijling BD, *et al*. Out of hospital anticoagulant therapy in patients with acute pulmonary embolism is frequently practised but not perfect. *Thromb Res* 2010;126:481–5.
140. van Dongen CJ, Prandoni P, Frulla M, *et al*. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. *J Thromb Haemost* 2005;3:939–42.
141. van Geest-Daalderop JH, Hutten BA, Sturk A, *et al*. Age and first INR after initiation of oral anticoagulant therapy with acenocoumarol predict the maintenance dosage. *J Thromb Thrombolysis* 2003;15:197–203.
141a. van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007;357:1094–104.
142. Buller HR, Cohen AT, Davidson B, *et al*. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007;357:1094–104.
143. Van Spall HG, Wallentin L, Yusuf S, *et al*. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. *Circulation* 2012;126:2309–16.
144. Veeger NJ, Piersma-Wichers M, Tijssen JG, *et al*. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol* 2005;128:513–19.
145. Vene N, Mavri A, Kosmelj K, *et al*. High D-dimer levels predict cardiovascular events in patients with chronic atrial fibrillation during oral anticoagulant therapy. *Thromb Haemost* 2003;90:1163–72.
146. Völler H, Glatz J, Taborski U, *et al*. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). *Z Kardiol* 2005;94:182–6.
147. Walker GA, Heidenreich PA, Phibbs CS, *et al*. Mental illness and warfarin use in atrial fibrillation. *Am J Manag Care* 2011;17:617–24.
148. Weimar C, Benemann J, Katsarava Z, *et al*. Adherence and quality of oral anticoagulation in cerebrovascular disease patients with atrial fibrillation. *Eur Neurol* 2008;60:142–8.
149. Weitz JI, Connolly SJ, Patel I, *et al*. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost* 2010;104:633–41.
150. White HD, Gruber M, Feyzi J, *et al*. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med* 2007;167:239–45.
151. Wieloch M, Själander 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;32:2282–9.
152. Willey VJ, Bullano MF, Hauch O, *et al*. Management patterns and outcomes of patients with venous thromboembolism in the usual community practice setting. *Clin Ther* 2004;26:1149–59.
153. Wyse DG, Waldo AL, DiMarco JP, *et al*. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–33.
154. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. *Stroke* 2000;31:817–21.
155. Yamashita T, Koretsune Y, Yasaka M, *et al*. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J* 2012;76:1840–7.
156. Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. *Intern Med* 2001;40:1183–8.
157. Yousef ZR, Tandy SC, Tudor V, *et al*. Warfarin for non-rheumatic atrial fibrillation: five year experience in a district general hospital. *Heart* 2004;90:1259–62.
158. van den Besselaar AM. Recommended method for reporting therapeutic control of oral anticoagulant therapy. Control of Anticoagulation Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 1990;63:316–17.