BMJ Open

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

Elizabeth S Mearns,1,2 Jessica Hawthorne,1 Ju-Sung Song,1 Craig I Coleman1,2

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 al25 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

Correspondence to
Dr Craig I Coleman;
craig.coleman@hhchealth.org

To cite: Mearns ES, Hawthorne J, Song J-S, et al. BMJ Open 2014;4:e005379. doi:10.1136/bmjopen-2014-005379

Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2014-005379).
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, 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), 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. 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 χ² 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). 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 median/mean 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
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.
| 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 | AF            | PD           | 402           | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Abdelhafiz and Wheeldon | AF            | PD           | 402           | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Agnelli et al        | DVT           | RCT          | 134           | W,A         | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Agnelli et al        | PE            | RCT          | 165           | W,A         | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Agnelli et al        | DVT           | RCT          | 126           | W,A,P       | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Agnelli et al        | VTE           | RCT          | 2704          | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Albers et al         | AF            | RCT          | 1962          | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Amiwero et al        | VTE           | RCT          | 126           | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Anderson             | AF            | RD           | 87            | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Ansell et al         | AF            | RD           | 1511          | W, A, F     | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Augesky et al        | PE            | RCT          | 339           | W,A,P,F     | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Bona et al           | VTE           | PD           | 98            | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Boulanger et al      | AF            | RD           | 6431          | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Büller et al         | PE            | RCT          | 2184          | –           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Büller et al         | DVT           | RCT          | 137           | W,A,P,F     | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Büller et al         | PE            | RCT          | 1595          | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Burton et al         | AF            | RD           | 259           | W           | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Cafolla et al        | AF/VTE        | PD           | 871           | W,A, other  | 2–3        | •      | •        | •                | •                | •                   |                |                           |       |        |
| Cafolla et al        | AF            | PD           | 112           | W           | 2–3/1.5   | •      | •        | •                | •                | •                   |                |                           |       |        |
| Campbell et al       | VTE           | RCT          | 749           | W           | 2–3.5     | •      | •        | •                | •                | •                   |                |                           |       |        |
| Cheung et al         | AF            | RD           | 555           | W           | 1.5–3     | •      | •        | •                | •                | •                   |                |                           |       |        |
| Chitsike et al       | VTE           | PD           | 349           | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Chung et al          | AF            | RCT          | 75            | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Coleman et al        | AF            | RD           | 65            | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Connolly et al       | AF            | RCT          | 3371          | –           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Connolly et al       | AF            | RCT          | 3371          | –           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Connolly et al       | AF            | RCT          | 6022          | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Copland et al        | AF            | RD           | 328           | W           | 1.8–3.3   | •      | •        | •                | •                | •                   |                |                           |       |        |
| Currie et al         | AF            | RD           | 1513          | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Daskalopoulos et al  | DVT           | RCT          | 52            | A           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Dimberg et al        | AF            | RD           | 791           | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Douketis et al       | VTE           | RCT          | 1021          | –           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| Easton et al         | AF            | RCT          | 1643          | W           | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |
| The Einstein Investigators | DVT   | RCT          | 1718          | W,A         | 2–3       | •      | •        | •                | •                | •                   |                |                           |       |        |

Continued
| Study                      | Disease state | Study design | VKA-treated | 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 |               |              |             |             |            |        |           |                 |                  |                      |                  |                          |           |
| Ellis et al              | AF            | RCT          | 66          | T           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Evans et al              | AF            | PD           | 288         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Evans et al              | AF            | PD           | 214         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Ezekowitz et al          | AF            | RCT          | 70          | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Ezekowitz et al          | AF            | RCT          | 6022        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Fiesinger et al          | VTE           | RCT          | 1249        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Ford et al               | AF            | RCT          | 3665        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Gadisseur et al          | DVT           | PD           | 256         | A,P         | 2.5–3.5    | •      |           |                 |                  |                      |                  |                          |           |
| Gallagher et al          | AF            | RD           | 18113       | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Gallagher et al          | VTE           | RD           | 10381       | W,A,P       | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Garcia et al             | AF            | RCT          | 9081        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Go et al                 | AF            | RD           | 6320        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Gomberg-Maitland et al   | AF            | RCT          | 3624        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Granger et al            | AF            | RCT          | 9081        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Hankey et al             | AF            | RCT          | 7133        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Heidinger et al          | AF/DVT        | PD           | 1375        | –           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Ho et al                 | AF            | RD           | 476         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Hokusai-VTE Investigators | VTE           | RCT          | 4122        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Holmes et al             | AF            | RCT          | 244         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Hori et al               | AF            | RCT          | 108         | W           | 2–3/       | •      |           |                 |                  |                      |                  |                          |           |
| Hori et al               | AF            | RCT          | 639         | W           | 2–3/       | •      |           |                 |                  |                      |                  | 1.6–2.6                 |           |
| Hutten et al             | VTE           | RCT          | 1039        | –           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Hylek et al              | AF            | PD           | 472         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Hylek et al              | AF            | RCT          | 3665        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Jacobs et al             | AF            | RD           | 90          | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Jones et al              | AF            | RD           | 2223        | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Kalra et al              | AF            | PD           | 167         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Kearon et al             | VTE           | RCT          | 738         | W           | 2–3/       | •      |           |                 |                  |                      |                  |                          |           |
| Kearon et al             | VTE           | RCT          | 81          | W           | 2–3        | •      |           |                 |                  |                      |                  | 1.5–1.9                 |           |
| Kearon et al             | VTE           | RCT          | 703         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Kim et al                | AF            | RD           | 129         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Kim et al                | AF/VTE        | PD           | 646         | W           | 2–3        | •      |           |                 |                  |                      |                  |                          |           |
| Kulo et al               | AF            | PD/RD        | 117         | W,A         | 2–3        | •      |           |                 |                  |                      |                  |                          |           |

Continued
| Study                  | Disease state | Study design | VKA-treated N | VKA studied | Target INR | TTR, TINR, PINR, | Mean/median dose | Monitoring frequency | INR variability | INR testing interval, days | PPIR Other* |
|------------------------|---------------|--------------|---------------|-------------|------------|------------------|------------------|----------------------|------------------|--------------------------|--------------|
| Kulo et al            | AF            | PD/RD        | 117 W,A       | 2–3         |            | *                | *                |                      | *                | *                       |              |
| Kurtoglu et al         | DVT           | PD           | 246 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Lee et al              | AF            | PD/RD        | 200 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Lip et al              | AF            | RCT          | 318 –         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Lopez-Beret et al      | DVT           | RCT          | 77 A          | 2–3         |            | *                | *                |                      |                  |                         |              |
| Malik and Taylor       | AF/VTE        | RD           | 328 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Mant et al             | AF            | RCT          | 488 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Matchar et al          | AF            | RCT          | 363 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Matchar               | AF            | RCT          | 363 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| McBride et al          | AF            | PD           | 324 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| McCormick et al        | AF            | RD           | 174 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Melamed et al          | AF            | RD           | 906 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Menzin et al           | AF            | RD           | 600 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Morgan et al           | AF            | RCT          | 2235 W        | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Naganuma et al         | AF            | RD           | 845 W         | 1.5–2.5     | *          | *                | *                |                      |                  |                         |              |
| Nakatani et al         | AF            | R            | 95 W          | 2–3/1.5     | *          | *                | *                |                      |                  |                         |              |
| Nere et al             | AF            | RD           | 395 W,P,A     | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Nichol et al           | AF            | RD           | 1107 W        | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Nieuwlaat et al        | AF            | RCT          | 266 –         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Njaastad et al         | AF/VTE        | RD           | 936 W         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Nozawa et al           | AF            | PD           | 156 W         | 1.6–1.9     | *          | *                | *                |                      |                  |                         |              |
| Obata et al            | AF            | RD           | 110 W         | 1.6–2.6     | *          | *                | *                |                      |                  |                         |              |
| Ogawa et al            | AF            | RCT          | 74 W          | 2–3/1.5     | *          | *                | *                |                      |                  |                         |              |
| Okumura et al          | AF            | PD           | 501 W         | 2–3/1.5     | *          | *                | *                |                      |                  |                         |              |
| Olsson                 | AF            | RCT          | 1703 W        | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Olsson et al           | AF            | RCT          | 83 W          | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Ombandza-Moussa et al  | VTE           | RD           | 81 –          | –            | –          | –                | –                |                      |                  |                         |              |
| Ono and Fujita         | AF            | PD           | 63 W          | 1.5–2.5     | *          | *                | *                |                      |                  |                         |              |
| Palareti et al         | VTE           | PD           | 733 W,A       | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Palareti et al         | VTE           | PD           | 297 W,A       | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Patel et al            | AF            | RCT          | 7133 W        | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Pengo et al            | AF            | PD           | 433 W,A       | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Pengo et al            | AF            | RCT          | 267 W         | 2–3/1.5     | *          | *                | *                |                      |                  |                         |              |
| Perez-de-Llano         | PE            | RCT          | 50 A          | 2–3         | *          | *                | *                |                      |                  |                         |              |
| Perez-Gomez            | AF            | RCT          | 479 A         | 2–3         | *          | *                | *                |                      |                  |                         |              |
| 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                  | AF            | RCT          | 91            | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Perez-Gomez                  | AF            | RCT          | 496           | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| PERSIST Investigators         | DVT           | RCT          | 132           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Petersen et al               | AF            | RCT          | 67            | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Poli et al                   | AF            | PD           | 182           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Poli et al                   | AF            | PD           | 290           | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Poli et al                   | AF            | PD           | 783           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Poli et al                   | AF            | PD           | 780           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Poli et al                   | AF            | PD           | 578           | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Poller et al                 | AF/VTE        | RCT          | 9148          | W, A, P     | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Prandoni (Galilei) et al     | VTE           | RCT          | 720           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Prandoni et al               | DVT           | RCT          | 180           | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Ridker et al                 | VTE           | RCT          | 255           | W           | 1.5–2     | •      | •        |                |                |                      |                |                           |             |
| Rombouts et al               | AF            | RCT          | 104           | P           | 2–3.5     | •      | •        |                |                |                      |                |                           |             |
| Sadanaga et al               | AF            | PD           | 269           | W           | 1.5–3     | •      | •        |                |                |                      |                |                           |             |
| Samsa et al                  | AF            | RD           | 660           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Sarawate et al               | AF            | PD           | 470           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Schulman et al               | VTE           | RCT          | 1265          | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Schulman et al               | VTE           | RCT          | 1426          | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Sconce et al                 | AF            | RCT          | 70            | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Shalev et al                 | AF            | RD           | 4408          | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Shen et al                   | AF            | RD           | 18 867        | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Shen et al                   | AF            | RD           | 8992          | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Sullivan et al               | AF            | RCT          | 4060          | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Suzuki et al                 | AF            | PD           | 667           | W           | 1.6–2.6   | •      | •        |                |                |                      |                |                           |             |
| Tincani et al                | AF            | PD           | 90            | W,A         | 2–3        | •      | •        |                |                |                      |                |                           |             |
| van Bladel et al             | PE            | PD           | 86            | A           | 2–3.5     | •      | •        |                |                |                      |                |                           |             |
| van Dongen et al             | DVT           | PD           | 244           | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| van Geest-Daalderop et al    | AF            | RD           | 284           | A           | 2–3.5     | •      | •        |                |                |                      |                |                           |             |
| van Gogh Investigators       | VTE           | RCT          | 2572          | W,A         | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Van Spall et al              | AF            | RCT          | 6022          | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Veeger et al                 | VTE           | RD           | 2304          | A           | 2–3.5     | •      | •        |                |                |                      |                |                           |             |
| Vene et al                   | AF            | PD           | 113           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Voiler et al                 | AF            | RCT          | 202           | –           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Walker et al                 | AF            | RD           | 84            | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Weimar et al                 | AF            | PD           | 252           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
| Weitz et al                  | AF            | RCT          | 250           | W           | 2–3        | •      | •        |                |                |                      |                |                           |             |
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\textsuperscript{158} 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\textsuperscript{158} 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.

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.\textsuperscript{16–18} In a retrospective cohort study of 633 patients undergoing anticoagulation with a VKA, Schmitt et al\textsuperscript{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 estimates in the same population.\textsuperscript{16–18} Another study of 1511 patients performed by Ansell et al\textsuperscript{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.\textsuperscript{17} While TTR takes into account actual days in the target INR range (typically by assuming...
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 et al\(^{68}\).
### 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 ≥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 (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 ≥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 (6 months within target INR range); minimum and maximum INR values per patient.
INR, international normalised ratio; VKA, vitamin K antagonist.
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 under-reporting 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.

Author affiliations

1Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Connecticut, USA
2The University of Connecticut/Hartford Hospital Evidence-Based Practice Center, Hartford, Connecticut, USA

Contributors

ESM and CIC participated in study concept and design, drafting of the manuscript, administrative, technical and material support. ESM, JH, J-SS and CIC participated in acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. CIC participated in study supervision. ESM and CIC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Funding

This study was funded by Janssen Scientific Affairs. The authors maintained full control over the design and conduct of the study; collection, management, analysis and interpretation of the data and preparation and review of the manuscript.

Competing interests

CIC has received honoraria for participation on advisory boards and speaker’s bureaus and has received research funding from Janssen Scientific Affairs, LLC.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

Dataset available from the corresponding author via email.

Open Access

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

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;363:2499–501.

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;360:19–25.

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;361:1113–91.

7. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:981–92.

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 acute 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, Rybicki F, 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, Akai EA, Cornera 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:e415S–945S.

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, Gues 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;160:2345–8.

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, Horrow 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, Wheelon DM. Results of an open-labeled, prospective study of anticoagulation therapy for atrial fibrillation in an outpatient anticoagulation clinic. Clin Ther 2004;26:1470–8.

21. Abdelhafiz AH, Wheelon 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, Goltzhaber SZ, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban: 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, Dicter HD, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690–8.
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.

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.

Hylek EM, Ryan L, Hentz AE, et al. Disparate stroke rates on warfarin among contemporaneous cohorts with atrial fibrillation: potential insights into this risk shift from a comparative analysis of SPORTIF III versus SPORITF V. Stroke 2008;39:3009–14.

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.

Jones M, McEwan P, Morgan CL, et al. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of anticoagulation therapy in Chinese patients with concomitant atrial fibrillation and hypertension. J Thromb Haemost 2012;11:503–9.

Keaor 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;349:831–9.

Keaor 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 2007;5:743–9.

Keaor 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 2000;320:1236–9.

Kim YH, 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.

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.

Kulo A, Mulabegovic M, Kusturica J, et al. Outpatient management of anticoagulant therapy in patients with nonvalvular atrial fibrillation. Bosn J Basic Med Sci 2010;76:2104–9.

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.

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.

Lip GY, Rasmussen LH, Olsson SB, et al. Oral direct thrombin inhibitor AZD0837 for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized, dose-ranging, safety, and tolerability study of four doses of AZD0837 with Ximelagatran. K antagonsists. Eur Heart J 2009;30:2897–907.

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. Vasc Surg 2001;35:377–90.

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.

Mani J, Holmes 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.
Palareti G, Legnani C, Lee A, Ono A, Fujita T. Low-intensity anticoagulation for stroke prevention in elderly patients with non-valvular atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. J Thromb Thrombolysis 2007;24:65–72.

McCormick D, Gurwitz JH, Goldberg RJ, et al. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term-care care setting. Arch Intern Med 2001;161:2458–63.

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.

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.

Morgan CL, McEwan P, Tukendorf 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.

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.

Nakatani Y, Mizumaki N, Nishida K, et al. Quality of anticoagulation control among patients with atrial fibrillation. Thromb J 2012;76:317–21.

Nerée 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.

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;42:66–70.

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.

Nijjast AM, Abildgaard U, Lassen JF. Gains and losses of warfarin therapy as performed in an anticoagulation clinic. J Intern Med 2006;259:296–304.

Nozawa T, Asanoi H, Inoue H, et al. Instability of anticoagulation intensity contributes to occurrence of ischaemic stroke in patients with non-therapeutic anticoagulation. Jpn Circ J 2001;65:404–8.

Obata H, Watanabe H, Ito M, et al. Effects of combination therapy with warfarin and bufucolome for anticoagulation in patients with atrial fibrillation. Circ J 2011;75:201–3.

Ogawa S, Shigematsu Y, Kamatke 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.

Okumura K, Komatsu Y, 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.

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.

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 nonvalvular atrial fibrillation. Thromb Haemost 2010;103:604–12.

Ombardza-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.

Ono A, Fujiya 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.

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.

Paiari 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.

Pengo V, Legnani C, Novella F, et al. Oral anticoagulant therapy in patients with nonthrombotic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. Thromb Haemost 2001;85:418–22.

Pengo V, Cucinotti U, Demos 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.

Pérez-de-Llano LA, Leiro-Fernández V, Golpe R, et al. Comparison of tinzaparin and acenocumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. Blood Coagul Fibrinolysis 2007;18:744–9.

Pérez-Gómez F, Alejandra E, Bergeron 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;44:1557–63.

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.

Pérez Iriarte JA, Zamalde 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.

PERSIST investigators. A novel long-acting synthetic factor Xa inhibitor (Sam034006) to replace warfarin for secondary prevention in deep vein thrombosis. A Phase II evaluation. J Thromb Haemost 2004;2:47–53.

Petersen P, Grind M, Adler J, et al. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-ranging, tolerability, and safety study. J Am Coll Cardiol 2003;41:1445–51.

Poll D, Antonucci E, Ciutil G, et al. Anticoagulation quality and the risk of recurrence of venous thromboembolism. Thromb Haemost 2007;98:1148–50.

Poll 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.

Poll 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.

Poll 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.

Poll 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.

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;6:893–43.

Prandoni P, Caravelli 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.

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.

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.

Rombouts EK, Rosendaal FR, Van Der Meer FJ. Daily vitamin K supplementation improves anticoagulant stability. J Thromb Haemost 2007;5:2043–8.

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.

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.

Sarawate CA, Sikirica MV, Willey VJ, et al. Monitoring anticoagulation in atrial fibrillation. J Thromb Thrombolysis 2002;11:191–8.

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.

Shalev V, Rogowski O, Shimon O, et al. The interval between prothrombin time tests and the quality of oral anticoagulants...
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;110:799–802.

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 Fibrolysis 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. Quality of anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007;167:239–45.

142. van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007;357:1094–104.

143. van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007;357:1094–104.

144. 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.

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. Wiech M, Stjälander 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 Acuria. Eur Heart J 2011;32:2282–9.

152. Willey VJ, Bullano MF, Hauch Q, 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;347:182–33.

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 warfarin use in atrial fibrillation. Am J Manag Care 2004;9:182–8.

157. Yousef ZR, Tandy SC, Tudor V, et al. Anticoagulation in atrial fibrillation. Thromb Haemost 1990;63:316–17.