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Meta-Analysis to Assess the Quality of International Normalized Ratio Control and Associated Outcomes in Venous Thromboembolism Patients

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ABSTRACT

Introduction: Patients with venous thromboembolism (VTE) frequently require vitamin K antagonists (VKAs) to prevent recurrent events, but their use increases hemorrhage risk. We performed a meta-analysis to assess the quality of international normalized ratio (INR) control, identify study-level predictors of poor control and to examine the relationship between INR control and adverse outcomes in VTE patients.
Materials and Methods: We searched bibliographic databases (1990-June 2013) for studies of VTE patients receiving adjusted-dose VKAs that reported time in range (2.0-3.0) or proportion of INRs in range and/or reported INR measurements coinciding with thromboembolic or hemorrhagic events. Meta-analysis and meta-regression analysis was performed.
Results: Upon meta-analysis, studies found 59% (95%CI: 54-64%) of INRs measured and 61% (95%CI: 59-63%) of the time patients were treated were spent outside the target range of 2.0-3.0; with a tendency for under- versus over-anticoagulation. Moreover, this poor INR control resulted in a greater chance of recurrent VTE (beta-coefficient = -0.46, p = 0.01) and major bleeding (beta-coefficient = -0.30, p = 0.02). Patients with an INR < 2.0 made up 58% (95%CI: 39-77%) of VTE cases, while those with an INR > 3.0 made up 48% (95%CI: 34-61%) of major hemorrhage cases. Upon meta-regression, being VKA-naïve (-14%, p = 0.04) and treated in the community (-7%, p < 0.001) were associated with less time in range, while being treated in Europe/United Kingdom (compared to North America) was associated with (11%, p = 0.003) greater time.
Conclusions: Strategies to improve INR control or alternative anticoagulants, including the newer oral agents, should be widely implemented in VTE patients to reduce the rate of recurrent events and bleeding.

Introduction

Venous thromboembolism (VTE) is the third most common cause of vascular death with an incidence of 1 to 2 cases per 1000 people in the general population [1]. Anticoagulation is usually administered in three different phases including the initial phase (~7 days), long term therapy (up to 3 months) and extended therapy (three months or longer) which can reduce the risk of recurrent VTE but increase the risk of bleeding. Vitamin K antagonists (VKA) are commonly recommended for long term and extended therapy but can be challenging given the narrow international normalized range (INR), high inter-patient variability in response, numerous drug and food interactions, requirement for continual laboratory monitoring and risks of non-adherence [2].

In a previous meta-analysis of INR control by Erkens and colleagues [3], patients with VTE spent as little as 54% of their time in the therapeutic range (TTR); with quality of control being highly dependent on the time-period since the start of treatment. Their informative meta-analysis did not attempt to assess the impact of other potential study-level predictors of quality VKA INR control; particularly those assessed in previous meta-analyses of atrial fibrillation (AF) [4,5] and mixed indications [6,7] studies (e.g., year of study publication, study design, study follow-up duration, INR interpolation method, use of patient self-management, and VKA dosing setting). In addition, the meta-analysis performed by Erkens and colleagues did not attempt to demonstrate

Abbreviations: VTE, venous thromboembolism; VKA, vitamin K antagonist; TTR, time in therapeutic range; PINRR, proportion of INR measurements in range; INR, international normalized ratio; CI, confidence interval; UK, United Kingdom; RCT, randomized controlled trial; ICH, intracranial hemorrhage.

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the presence and magnitude of the relationship between the quality of INR control and major adverse outcomes including major hemorrhage and thrombotic event rates.

Therefore, we conducted a systematic review and meta-analysis/meta-regression of published randomized trials or cohort studies evaluating the quality of VKA management for extended therapy in VTE patients to (1) determine the weighted average proportion of TTR or proportion of INR measurements (PINRR) in the target range of 2.0 to 3.0 (as well as above or below), (2) determine study-level predictors of TTR or PINRR, and (3) to systematically examine the relationship between VKA anticoagulation control and adverse clinical events (major hemorrhage and recurrent thromboembolic events).

Methods

A systematic review of the MEDLINE, CENTRAL and EMBASE (from 1990 through June 2013) bibliographic databases was performed. Our search strategy for Medline is provided in the Appendix A. Two investigators reviewed all potentially relevant citations independently, with disagreement resolved by a third investigator. To be included in our analyses, studies (English full-text randomized controlled trials, prospective cohort studies or retrospective analyses) had to contain at least one dose-adjusted VKA-treated group including at least 50 patients for whom INR control was monitored; be conducted in adult patients being treated for VTE as their primary reason for anticoagulation; and report data on TTR or PINRR or specific INR values at or near (more than 48 hours from the event) the time of a major adverse event (recurrent thromboembolism or major bleed). Studies were excluded if they planned to treat patients for <3-months, used a target INR range other than 2.0 to 3.0 or had an overlapping patient population with another study. Manual backward citation tracking of references from identified studies and review articles was also performed to identify additional relevant studies.

Two investigators used a common data abstraction tool but independently abstracted all data. If a disagreement arose, it was resolved by a third investigator. The following study-level information was obtained from each eligible study: author identification, year of publication, geographic location of the study (Europe/United Kingdom (UK), Asia, North America, multinational or other), duration of VKA treatment (3 months or >3 months), type of VKA(s) used, TTR interpolation/calculation method, whether patients were utilizing VKA self-management to monitor INR control, whether patients were VKA naïve (<30% of the population receiving a VKA prior to entering the study) or experienced (>70% of the population receiving a VKA prior to entering the study), and the study setting (designated as anticoagulation clinic, randomized controlled trial (RCT), or community/standard practice). The setting was designated using the following definitions: (a) an anticoagulation clinic, if the study took place in an anticoagulation clinic or if the stated role of the study clinicians in patient care was limited to managing anticoagulation; (b) a randomized trial, if random allocation was employed to assign subjects to receive warfarin or another non-warfarin therapy; and (c) all others were classified as community practice. Measures of INR control and data on major adverse outcome occurrence were abstracted from each study including TTR, time spent below and above range, PINRR, proportion of INR measurements below and above range, and clinical outcomes of recurrent VTE and major hemorrhage (including both intracranial hemorrhage (ICH) and extracranial bleeding requiring hospitalization, blood transfusion or surgical treatment, or occurring at a critical anatomical location) and event rates (percent per person-year). INR values at or near the time of major adverse events were also abstracted.

TTR and PINRR for each VKA study group, as well as the time/proportions below and above range for these measures were expressed as an incidence density using a person-time approach. The numerator was calculated as the proportion of time that the group spent within, below or above the INR range or proportion of INR measurements in, below or above range multiplied by person-years of follow-up. The denominator was the total person-years of follow-up for each VKA study group (or the mean/median observation time multiplied by the number of patients in each study group, if person-years of follow-up for the VKA arm(s) in a study was not reported). Ninety-five percent confidence intervals (CIs) were calculated for each incidence density using the Wilson score method without continuity correction. For the purposes of this meta-analysis, all studies were pooled using a random-effects model. Statistical heterogeneity between individual studies was determined using the I^2 statistic, with ranges from 0% to 100%, and a value >50% signifying an important degree of statistical heterogeneity). Publication bias was assessed using the Egger's weighted regression statistic, with a p-value <0.05 suggesting a higher likelihood of publication bias).

In order to determine how study–level factors influenced TTR and PINRR, both subgroup and meta-regression analyses were also performed. Meta-regression allows for the evaluation of effect of any given influencing factor (i.e., study setting) independent of the effect of other independent variable (i.e., prior VKA experience, etc.). A multiple linear mixed method model using both fixed- and ranom-effects was utilized for meta-regression, which was weighted by the inverse of the variance of TTR or PINRR. Fixed-effects were assumed for all study-level factors, including: study design (community vs. anticoagulation clinic/RCT), study year (from 1990-2000, 2001-2007 or 2008-2013), use of self-management or not, and interpolation method (linear or other), prior experience with VKAs (naïve, experienced, mixed/not reported), geographic region (North America, Europe/UK, Asia, multinational, other) and duration of VKA treatment (3 months, >3 months). No hierarchy was used in the model for these covariates.

To evaluate the relationship between INR control and recurrent VTE and major bleeding events, two additional and distinct analyses were undertaken. A weighted least squares linear regression was performed; with major adverse event rates as the dependent variable and TTR as the independent variable; and each VKA arm in the analysis being weighted according to person-years of follow-up (akin to meta-analysis, studies with a greater number of person-years of follow-up received greater weight in the regression analysis). However, as the relationship between TTR and major adverse outcomes may not be strictly linear, subgroup analysis was performed by stratifying studies into categories based upon whether they reported a mean/median TTR < 60% or ≥60%. A TTR of 60% was used as the cut-point for this analysis because it has been identified as the "minimum target TTR" by previous investigators [8]. Lastly, for studies assigning specific INR levels to major adverse events, the proportion of recurrent VTE and major hemorrhagic events outside of the INR range (<2.0 or >3.0, respectively) for each study group was calculated. The numerator was the number of recurrent VTE events below an INR of 2.0 or major hemorrhagic events above an INR of 3.0. The denominator was the total number of events for each study group. Ninety-five percent CIs were calculated for each proportion using the Wilson score method without continuity correction. All studies were pooled using a random-effects model.

All statistical analysis was performed using StatsDirect version 2.7.6 (StatsDirect Ltd., Cheshire, England), SAS, version 9.2 (SAS Institute Inc., Cary, NC) and SPSS 15.0 for Windows (SPSS Inc., Chicago, IL).

Results

We identified 5,326 citations, of which 5,273 were excluded for reasons specified in Fig. 1, resulting in 53 total studies included in the analyses [9–61]. Of the identified studies, 46 reported at least one measure of INR control with a total of 52 VKA study groups, and 16 studies reported an INR measurement at or near the time of an adverse event (9 articles reported both measures and were used in both analyses).

Demographics of the included studies can be found in Table 1. Of the 52 study groups reporting a measure of INR control, 44 reported a TTR