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Case fatality of bleeding and recurrent venous thromboembolism during, initial therapy with direct oral anticoagulants: A systematic review

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ABSTRACT

Introduction: The frequency and case fatality of venous thromboembolism (VTE) and major bleeding during the initial 3 months of therapy in those treated for symptomatic VTE with either direct oral anticoagulants (DOACs) or vitamin K antagonists (VKA) are important clinically relevant outcomes. We sought to measure it during the initial months of anticoagulation for symptomatic VTE.

Material and Methods: We searched MEDLINE, EMBASE, and CENTRAL to identify studies that enrolled patients with acute symptomatic VTE treated with DOACs or VKA and reported data on bleeding, VTE recurrence and death. Studies were evaluated according to a priori inclusion criteria and critically appraised using established internal validity criteria. Single-proportion random-effects models were used to pool estimates.

Results: Of the 2453 citations retrieved, 5 RCTs that enrolled 24,507 patients were included. The rate of major bleeding was 1.8 (95% CI: 1.3-2.5) and 3.1 (95% CI: 2.4-3.9) per 100 patient-years in DOAC and VKA arms, respectively. The rate of VTE recurrence was 3.7 (95% CI: 2.7-4.7) and 4.1 (95% CI: 3.0-5.4) per 100 patient-years of DOAC and VKA, respectively. The case fatality rate of bleeding was significantly higher in the VKA arms 10.4% (95% CI: 6.6-15.4) compared to DOACs 6.1% (95% CI: 2.7-11.7; p value for difference = 0.029) with no statistical difference between the case fatalities for recurrent VTE. The rate of death from either definite major bleeding or definite recurrent VTE was 0.27 (95% CI: 0.16-0.40) and 0.46 (95% CI: 0.32-0.63) per 100 patient-years for DOACs and VKAs respectively, resulting in a number needed to treat of 875 for DOACs to prevent one death.

Conclusion: DOACs are attractive alternatives to VKAs for initial treatment of symptomatic VTE, with lower frequency and case fatality for major bleeding. However, the incremental safety benefit of DOACs over VKAs is small, with large numbers needed to treat.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with a high rate of morbidity and mortality [1,2]. For decades, vitamin K antagonists (VKAs) have been the mainstay of VTE treatment and prevention [3]. Without adequate anticoagulant therapy, the risk of recurrent VTE is estimated to be 50% in the first 3 months following a new diagnosis [4,5]. In the absence of active bleeding, the risk of major bleeding is usually much smaller in this time period [6]. After 3 months, the risk of recurrent VTE drops off sharply and is estimated to be 3-5% per year for events provoked by transient risk factors and 10% per year for idiopathic events [7,8].

Several direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban have emerged as alternatives to VKAs. Clinical trials have shown each of these agents to be at least as effective and safe as VKAs for the acute treatment of VTE and the secondary prevention of recurrent VTE [9–15]. The benefit of treating VTE with anticoagulant therapy must always be weighed against the risk of bleeding complications. The variable clinical course of recurrent VTE and bleeding complications make balancing the risks and benefits of anticoagulation difficult for clinicians and patients. Nevertheless, mortality is a serious and objective adverse outcome associated with both recurrent VTE and bleeding complications, and therefore a comparison of case fatality associated with recurrent VTE and with major bleeding may help judge the true benefit of anticoagulation. The purpose of this study was to look at patients with acute symptomatic

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VTE who were randomized to receiving DOACs compared to VKAs and estimate the rates and case-fatality of recurrent VTE and major bleeding during the initial months of therapy.

Material and Methods

Studies Identification

We conducted a systematic literature search to identify all randomized controlled trials (RCTs) that included adult patients (≥18 years old) treated with DOACs for acute symptomatic VTE treatment (i.e. not less than 3 months) based on *a priori* protocol available on request. Patients treated for other indications, including joint replacements, atrial fibrillation or acute coronary syndrome were excluded in order to minimize study heterogeneity when comparing safety and efficacy endpoints. The review was reported according to the PRISMA statement [16,17].

Literature Search

We searched MEDLINE, Cochrane Central Register of Controlled Trials and EMBASE databases from inception through December 2013 to identify all published and unpublished literature, in any language, related to our topic. The search strategy included the MeSH terms venous thrombosis and pulmonary embolism. The following terms were also added to the search strategy: recurrent venous thromboembolism, new oral anticoagulants, dabigatran, apixaban, rivaroxaban, edoxaban, warfarin and acenocoumarol. We also screened major Hematology international conferences (American Society of Hematology, International Society of Thrombosis and Hemostasis, and European Hematology Association) for abstracts from their annual meetings from 2010-2013, registries of health technology assessments and clinical trials, and the reference list of retrieved studies for additional studies and unpublished data.

Study Selection

We included studies that: I) were randomized controlled trials comparing therapeutic doses of dabigatran, apixaban, edoxaban or rivaroxaban to standard (heparin/VKAs) (target INR 2-3) for treatment of symptomatic VTE for at least 3 months; II) included study population with deep venous thromboembolism, pulmonary embolism or both; III) included a qualifying event (DVT or PE) that was confirmed objectively by the presence of intraluminal defect on venography or venous non-compressibility on duplex ultrasound for DVT [18], and the presence of intraluminal filling defect on pulmonary angiography or a high probability ventilation-perfusion scan for PE [19]; and IV) reported at least one of the following outcomes on anticoagulation: 1) recurrent events defined as symptomatic thromboembolic event that occurred after initiation of VTE treatment and diagnosed objectively by a new intraluminal filling defect on venography or a new non-compressible vein segment on duplex ultrasound for recurrent DVT or by a new intraluminal filling defect on pulmonary angiography or a new high probability ventilation-perfusion lung scan, 2) major bleeding events as defined by ISTH [20] or as per study definition, and 3) mortality caused by bleeding or venous thromboembolic event. Patients receiving additional treatment (e.g., thrombolysis, inferior vena filters) were excluded. Eligible studies were reviewed independently by two reviewers (CW, GA) to assess suitability for inclusion, and all included trials were reviewed to assess agreement in outcome event reporting. Studies considered relevant by one or both reviewers were retrieved and disagreements were resolved by discussion.

Outcome Measures and Data Extraction

Our primary outcome measures were: 1) frequency of major bleeding; 2) frequency of fatal bleeding; 3) frequency of VTE recurrence; and 4) frequency of fatal VTE recurrence (definite and possible). Two reviewers independently abstracted the data describing baseline characteristics, treatment interventions and outcomes. Discrepancies were solved by discussion. Results of intention-to-treat analyses were collected if reported. Because the cause of death in cases with suspected VTE related death is not always objectively confirmed, we reported VTE deaths as definite or possible. Definite fatal recurrent VTE was defined as any VTE diagnosed postmortem, or a new intraluminal-filling defect detected on computed tomography, venography or ventilation perfusion scan, or a high clinical probability of fatal pulmonary embolism as adjudicated by the study investigators immediately before death. Possible VTE deaths included data reported as, "PE cannot be ruled out."

Quality Assessment

Two reviewers independently assessed each study's risk of bias using the 6 domains of the Cochrane Collaboration's tool for assessing risk for in randomized trials [21] and disagreements were resolved by discussion.

Data Synthesis and Analysis

The results of individual studies were combined to determine the following outcomes: (1) the rate of major bleeding; (2) the rate of fatal bleeding; (3) the rate of VTE recurrence; (4) the rate of fatal VTE recurrence (definite and possible). We also calculated the case fatality rate of major bleeding, and recurrent VTE (both definite and possible). The case fatality rate of recurrent VTE was defined as the proportion of all recurrent VTE events (fatal and nonfatal) resulting in death. Fatal bleeding was defined as a major bleeding event directly leading to death or death was reported as "associated with bleeding". The case fatality rate of a major bleeding event was defined as the proportion of all major bleeding events causing or associated with death [22]. All rates were expressed as events per 100 patient-years of anticoagulation to standardize for different follow-up durations across studies [23,24].

Proportions were transformed via the Freeman-Tukey double arcsine method [25,26] before pooling the case fatality rates. We then performed a DerSimonian–Laird random-effects model to pool the transformed rates [27]. After pooling the resulting estimates and their 95% CIs, limits were back-transformed to rates per 100 patient-years of follow-up. The pooled random effect incidence rate ratio (IRR) [28] was used to estimate of the effects of treatment with DOACs. The I^2 statistic was used to estimate total variation among the pooled estimates across studies. An I^2 value less than 25% was considered low-level heterogeneity, 25% to 50% was moderate-level, and greater than 50% was high-level [29]. Statistical analysis was done using StatsDirect statistical software (version 2.8.0).

Results

Study Selection and Patient Characteristics

The literature search yielded 2453 studies (Fig. 1). Of these, 5 RCTs [9,11,13–15] met the inclusion criteria and enrolled 12258 patients for acute VTE treatment in DOAC arms and 12249 patients for VKA arms. Trials evaluated three factor Xa inhibitors (rivaroxaban, n = 4150), (apixaban, n = 2691), (edoxaban, n = 4143) and one direct thrombin inhibitor (dabigatran, n = 1274). The majority of patients (>80%) enrolled in these studies were treated for idiopathic (unprovoked) VTE events and were anticoagulated for a median time of 6.7 months (Table 1). The time from symptoms onset to randomization ranged