Best Practice & Research Clinical Haematology 26 (2013) 215–224

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

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New oral anticoagulants in elderly patients

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Keywords:
elderly
atrial fibrillation
stroke
venous thromboembolism
anticoagulants
dabigatran etexilate
rivaroxaban
apixaban
vitamin K antagonists

The new oral anticoagulants (NOACs) dabigatran etexilate, rivaroxaban, and apixaban have been extensively studied for prevention and treatment of venous thromboembolic disease and for stroke prevention in atrial fibrillation. Elderly patients have the highest incidence of thrombotic complications but also have the highest risk of anticoagulant associated bleeding. In this review we critically examine the balance between risks and benefits of NOACs compared with vitamin K antagonists in elderly patients enrolled in phase 3 randomized controlled trials for the management of venous thrombosis and stroke prevention in atrial fibrillation. Results show that the favourable balance between risks and benefits of NOACs is preserved in the elderly population.

Introduction

Increasing age is an important risk factor for arterial and venous thromboembolic disease. The risk of ischaemic stroke increases 1.5-fold for every 10 years of age increase [1] with estimated incidences of 14 and 29 per 1000 person-years for people aged 75 to <85 years and people 85 years or over, respectively [2]. The increased incidence is in part explained by the increased prevalence of stroke risk factors in the elderly, such as hypertension, heart failure and atrial fibrillation (AF). While

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http://dx.doi.org/10.1016/j.beha.2013.07.011

AF is uncommon in patients below 65 years of age (<2%), the prevalence is approximately 10% in patients aged 85 years or over [3]. Thereby, almost 25% of ischaemic strokes in patients over 80 years of age is attributable to AF [4]. Oral anticoagulant therapy with vitamin K antagonists (VKA) reduces the risk of ischaemic stroke by 64% in patients with AF, and due to the higher incidence of stroke in the elderly, the absolute risk reduction is higher in elderly than in younger patients [5]. The incidence of venous thromboembolism (VTE) rises similarly with age. The incidence of a first episode of deep vein thrombosis (DVT) or pulmonary embolism (PE) is below 1 per 1000 person-years in people under 50 years of age and rises to 6 per 1000 person-years in patients over 80 years of age [6].

Although VKA therapy is highly effective for prevention and treatment of arterial and venous thromboembolism, anticoagulants can cause bleeding complications. The risk per year of major bleeding in patients treated with VKAs is estimated at 2–3% with another 14% of patients experiencing minor bleeding complications [7]. The risk of anticoagulant associated bleeding is age-dependent and increases by approximately 40% per 10 years of age increase [7]. Concern about the risk of anticoagulant associated bleeding contributes to the underuse of VKAs in patients with AF. Surveys from Europe and North-America have consistently shown that VKAs are used in only 50–60% of patients with AF [8–10] and in only 35% of those 85 or older [8].

New oral anticoagulants (NOACs) are small molecules designed to specifically target individual clotting factors. Due to lower propensity for food and drug interactions, the anticoagulant effects of NOACs compared with VKAs are much more predictable allowing them to be given in fixed doses without routine coagulation monitoring. The direct thrombin inhibitor, dabigatran etexilate, and the direct factor Xa inhibitors, rivaroxaban and apixaban, have undergone extensive testing in phase 3 randomized controlled trials for prevention and treatment of VTE, for stroke prevention in patients with AF and as secondary prevention after acute coronary syndromes [11–26]. In the VTE treatment and AF trials NOACs were either non-inferior or superior to monitored VKA treatment, with similar or reduced rates of major bleeding [13,15,16,19,22–25]. Moreover, in patients with AF, each of the NOACs were associated with a 30–70% reduction in intracranial haemorrhage (ICH) compared with warfarin [15,19,22].

Clinicians have questioned the generalizability of the results comparing NOACs with warfarin to elderly patients at highest risk of thrombosis and of bleeding. Elderly patients generally have more comorbidities and concomitant medication use and a higher prevalence of chronic kidney disease than younger patients. Impaired renal function could lead to increased blood levels of NOACs because these agents are partially renally cleared (dabigatran 80%, rivaroxaban 33%, apixaban 25%), whereas VKAs are 100% non-renally cleared [27–29]. Since NOACs are used at a fixed dose, more variability of the drug blood levels may be expected in the elderly and it is uncertain if this variability may unfavourably alter the balance between risks and benefits of treatment. In a recent case-series of 44 patients with dabigatran associated bleeding complications, 67% of patients were aged 80 years or over, raising concerns about the safety of NOACs in the elderly [30].

In this review we describe the safety and efficacy of NOACs in elderly patients. We focus on subgroup analyses of the phase 3 randomized controlled trials in which the NOACs were compared with VKAs in patients with VTE or AF.

Methods

All phase 3 randomized controlled trials comparing NOACs with VKA therapy for initial and prolonged treatment of VTE and for stroke prevention in AF were included. From these trials, all available analyses for age subgroups were obtained from the original publications of the specific trials, from their online supplements, from congress abstracts and from data product monographs on which the regulatory approval for these drugs was based. Hazard ratios (HRs) and concomitant 95% confidence intervals (95%CIs) of the NOAC vs. VKA therapy for each available age category are presented. Consistency of the HRs among the various age categories was assessed by the *p*-value for interaction between age category and treatment. The interaction was considered statistically significant when the interaction *p*-value was 0.05 or lower. Interaction *p*-values were calculated based on the HRs and 95%CIs in case they were not provided by the publication.