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Full Length Article

Safety of warfarin in "high-risk" populations: A meta-analysis of randomized and controlled trials

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ABSTRACT

Introduction: Few data are available about safety of vitamin K antagonists (VKAs) in patients with clinical/demographic characteristics predisposing to an increased risk of bleeding. We performed a meta-analysis to evaluate the safety of VKAs in patients with atrial fibrillation (AF) or venous thromboembolism (VTE) in the following subgroups of "high-risk" patients: elderly patients, patients with low body weight and patients with impaired renal function.

Materials and methods: Major electronic databases were systematically searched to identify randomized controlled trials (RCTs) addressing this issue. Pooled Risk Ratios (RR) and 95% Confidence Intervals (CI) were calculated for each outcome using a random effects model.

Results: Eleven RCTs for a total of 41,015 patients treated with VKAs (25,901 with AF and 15,114 with VTE) were included. We found a significant association between age > 75 years and bleeding in patients receiving VKAs (RR: 1.62, 95%CI: 1.28–2.05; $P < 0.0001$). Moreover, the prevalence of bleeding events under VKAs was significantly higher in patients with low body weight (RR: 1.20, 95%CI: 1.03–1.40; $P = 0.02$) and in those with impaired renal function (RR: 1.59, 95%CI: 1.30–1.94; $P < 0.00001$). Results were confirmed when separately analyzing data on AF and VTE. Regression models showed that treatment duration did not impact on the differences found in the safety profile of VKAs in different settings analyzed.

Conclusions: Results of our meta-analysis suggest an increased risk of bleeding complications in "high-risk" patients. Although all results are significant, other studies focused on this issue are warranted to further validate these results.

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1. Introduction

Vitamin K antagonists (VKAs) have proved to be highly effective in preventing thromboembolic events in patients with non valvular atrial fibrillation (AF) [1,2] as well as in those with an acute venous thrombotic event (VTE) [3]. In recent years, direct oral anticoagulants (DOACs) have been developed, including Factor IIa and Factor Xa inhibitors [4] and a number of trials have shown an overall clinical benefit of DOACs compared with VKAs [5–9]. Among their potential advantages, DOACs include a wider therapeutic window at fixed dosing regimens and minimal and manageable food and drug interactions with no requirement for routine monitoring [4]. However, certain characteristics of patients may modify the effect of treatment with DOACs [10]. Some additional risk factors, such as an age > 75 years, impaired renal function, extreme body weight and congestive heart failure, independently predict both a higher risk of stroke [11] and bleeding [12]. Although a series of substudies and meta-analyses have suggested an acceptable benefit-risk profile of DOACs also in these specific clinical settings [13–23], it has been suggested to preferentially keep using VKAs in these "fragile" patients while waiting for further studies on DOACs. However, only few data are available about safety of VKAs in "high-risk" patients. Thus, the aim of our meta-analysis was to evaluate the risk of bleeding episodes reported in randomized controlled trials (RCTs) on the use of VKAs for the prevention of thromboembolic events in AF and for the treatment of acute VTE.

2. Methods

We searched for studies reporting data on the safety of VKA in patients with AF and in patients with VTE in the following specific subgroups of "high-risk" patients: elderly patients, patients of low body weight and patients with impaired renal function. Medline, ISI Web of

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Science, SCOPUS, Cochrane database and EMBASE databases were searched up to September 2015. Research was supplemented by manually reviewing abstract books from congresses of the ESC, the ISTH, and the ASH (2003–2015) and the reference lists of all retrieved articles. Only RCTs or post-hoc analyses of RCTs were considered, whereas non randomized studies were excluded. Furthermore, studies evaluating patients receiving anticoagulation with drugs other than VKA were not included. The safety outcome was represented by the occurrence of major bleeding and clinically relevant non-major bleeding. In all the included studies, bleeding was defined as major or clinically relevant non-major according to validated criteria [24,25] (Supplemental Table 1a). To better describe how the risk/benefit profile of VKA changes in these specific subgroups of "high-risk" patients, data on the efficacy of VKA were also extracted (i.e. prevention of stroke/systemic embolism in studies on AF patients and prevention of VTE recurrence in studies on acute VTE).

Search results were reported according to PRISMA guidelines [26]. Data about study (year of publication, study type) and patient characteristics (number of subjects studied, mean age, gender, prevalence of low body weight [body weight lower than 50–60 kg], prevalence of kidney disease [creatinine clearance 30–50 ml/min] and treatment duration) were extracted from each selected study. Discrepancy between reviewers was resolved by discussion or by the opinion of a third reviewer, if necessary. The occurrence of bleeding events was evaluated stratifying patients according to age (higher vs lower than 75 years), body weight (normal body weight vs low body weight) and renal function (creatinine clearance 30–50 ml/min vs > 50 ml/min).

Statistical analysis was performed using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration. Pooled Risk Ratios (RR) and 95% Confidence Intervals (CI) were calculated for each outcome using a random effects model.

Statistical heterogeneity was evaluated through the use of Cochran's Q and of I^2 statistics which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [27].

Attributable risk of high-risk states (low body weight, advanced age and impaired renal function) for safety and of efficacy outcomes was calculated as (risk of the outcome in high-risk patients − risk of the outcome in controls) / (risk of the outcome in high-risk patients).

Publication bias was assessed by the Egger's test and represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, as well as Egger's test to address publication bias, over and above any subjective evaluation. A $P < 0.10$ was considered statistically significant [28]. In case of a significant publication bias, the Duval and Tweedie's trim and fill method was used to allow for the estimation of an adjusted effect size [29]. In order to be as conservative as possible, the random-effect method was used to take into account the variability among included studies. We hypothesized that differences among studies in the prevalence of bleeding episodes may be affected by the treatment duration. To assess the possible effect of this variable in explaining the different results observed across studies, we planned to perform a meta-regression analysis after implementing a regression model with the difference in the prevalence of bleeding episodes as dependent variable (y) and the treatment duration as independent variables (x).

3. Results

After excluding duplicates, the search provided 1939 results. Of these studies, 1635 were excluded because they were off the topic after scanning the title and/or the abstract, 254 because they were reviews/comments/case reports or they lacked of data of interest. Other 39 studies were excluded after full-length paper evaluation.

Thus, 11 RCTs for a total of 41,015 patients treated with VKAs (25,901 with AF and 15,114 with a recent VTE) were included in the final analysis (Supplemental Fig. 1a) [30–40]. In detail, we included 11 studies stratifying bleeding according to patient age (11,914 subjects >75 years and 28,337 < 75 years), 8 studies in which stratification was made according to weight (3968 low body weight patients and 18,184 with normal body weight), and 10 studies stratifying bleeding episodes according to renal function (5123 subjects with creatinine clearance (CrCl) 30–50 ml/min and 30,832 with CrCl >50 ml/min). In all studies, patients with a CrCl <30 ml/min were excluded.

3.1. Study characteristics

Major characteristics of the 11 studies included in the meta-analysis are shown in Table 1.

The number of patients varied from 1603 to 9081, the mean age from 54.8 to 73 years, with a proportion of patients ≥75 years ranging from 10.6% to 48.8%. The prevalence of low body weight varied from 1% to 82.7%, while an impaired renal function (i.e. CrCl 30–50 ml/min) was reported in 5.4%–20.5%.

3.2. Age

Eleven studies [30–40] (11,914 subjects with >75 years and 28,337 with <75 years) reported a significant association between age > 75 years and bleeding in patients receiving VKAs (RR: 1.62, 95%CI: 1.28–2.05; $P < 0.0001$, Fig. 1). The heterogeneity among the studies, significant in the overall analysis ($I^2 = 89\%$; $P < 0.00001$), was reduced ($I^2 = 51\%$; $P = 0.04$) after excluding one study [39]. In contrast, no heterogeneity among results from studies on AF and VTE was found ($I^2 = 0\%$; $P = 0.52$).

By separately analyzing AF and VTE, the association between age > 75 years and VKAs-related bleedings was consistently confirmed by the 7 studies [30,32–35,37,38] (2073 patients >75 years and 12,920 < 75 years) on VTE (RR: 1.68, 95%CI: 1.43–1.97; $P < 0.00001$, $I^2 = 25\%$; $P = 0.26$, Fig. 1) and marginally by the 4 studies [31,36,39,40] evaluating 9841 AF patients >75 years and 15,417 with <75 years (RR: 1.46, 95%CI: 0.99–2.15; $P = 0.06$, $I^2 = 95\%$; $P < 0.00001$, Fig. 1).

3.3. Low body weight

Eight studies [30,32–35,37–39] with a total of 3968 low body weight patients and 18,184 with normal body weight, reported a significant association between low body weight and VKA-related bleedings (RR: 1.20, 95%CI: 1.03–1.40; $P = 0.02$, Fig. 2). No heterogeneity was found both in the overall analysis ($I^2 = 0\%$; $P = 0.81$) and among studies on AF and VTE ($I^2 = 0\%$; $P = 0.97$).

Of interest, after excluding the only study on AF [39], a marginally higher prevalence of bleeding events in VTE patients with low body weight was found (RR: 1.20, 95%CI: 1.00–1.45; $P = 0.05$, $I^2 = 0\%$; $P = 0.68$, Fig. 2).

3.4. Creatinine clearance (CrCL)

Ten studies [30–39] evaluated a total of 5123 subjects with CrCl 30–50 ml/min and 30,832 with CrCl >50 ml/min. The prevalence of bleeding events with VKAs was significantly higher in patients with impaired renal function (RR: 1.59, 95%CI: 1.30–1.94; $P < 0.00001$, Fig. 3), with significant heterogeneity among studies ($I^2 = 69\%$; $P = 0.002$). In contrast, no heterogeneity among results from studies on AF and VTE was found ($I^2 = 0\%$; $P = 0.53$).

All results were confirmed both by the 3 studies [31,36,39] evaluating 4097 AF patients with CrCl 30–50 ml/min and 17,983 with CrCl >50 ml/min (RR: 1.69, 95%CI: 1.25–2.29; $P = 0.0007$, $I^2 = 82\%$; $P = 0.004$, Fig. 3), and by the 7 studies [30,32–35,37,38] (1026 patients with CrCl 30–50 ml/min and 12,849 subjects with CrCl >50 ml/min)

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