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Full Length Article

Anaemia as an independent key risk factor for major haemorrhage in patients treated with vitamin K antagonists: Results of the SCORE prospective cohort

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ABSTRACT

Introduction: Risk scores for the prediction of haemorrhage are poorly predictive of major bleeding. The aim of this study was to refine the estimation of bleeding risk by identifying one or several parameters of prognostic significance among these algorithms.
Materials and methods: The SCORE study was a prospective, multicentre cohort study conducted in France in 2009–2010. Patients were eligible if they had received vitamin K antagonist (VKA) for any therapeutic indication for at least 3 months. The primary outcome was the occurrence of major bleeding at 1-year follow-up.
Results: In total, 962 patients were included in this study and evaluated at 1 year. The incidence of major bleeding at 1-year follow-up (Kaplan–Meier method) was 2.9% [95% confidence interval (CI) 1.9–4.2]. The rate of major bleeding was 8.2% (95 CI 3.4–16.2) per year in patients classified as high risk by at least four scores. In a multivariate Cox analysis, of the risk factors for the different scores, only anaemia <100 g/l at inclusion was strongly associated with risk of major bleeding (hazard ratio 6.1, 95% CI 2.7–13.8, $P < 0.0001$). Through an induction tree analysis performed to identify a common parameter in the majority of scores, anaemia was found to be the main predictor of correct classification as high risk by at least four scores (55% of patients classified as high risk by at least four scores vs 3.3% in the absence of anaemia).
Conclusion: Anaemia with haemoglobin <100 g/l is the most important predictor of high risk of bleeding in patients treated with VKA.

1. Introduction

Major bleeding is a complication of anticoagulant therapy. Vitamin K antagonists (VKA) are associated with an incidence of major bleeding of 2–7.2%, and a case-fatality rate of 13.4% [1]. When confronted with the estimation of bleeding risk, physicians tend to do no better than expected by chance. The estimated risk–benefit balance sometimes overestimates the risk and leads to underprescription of VKA, or fails to identify those at high risk who would benefit from close monitoring [2]. Several consensus guidelines have proposed the use of risk stratification models to assist physicians with the evaluation of a patient's risk of bleeding [3,4]. However, several restrictions have been reported regarding the use of such scores [5]. First, these scores classically classify patients into three categories (i.e. low, intermediate and high risk). As bleeding scores were developed to help clinicians make decisions regarding the use of anticoagulants, it is sometimes difficult to make a clear decision for patients in the intermediate-risk group, especially given the overlap in the rate of major bleeding in this group with the low- and high-risk groups [6,7]. Second, although some bleeding risk scores have been validated to discriminate between low and moderate/high risk [8], several recent reports have shown that the different scores are poorly predictive of major bleeding [6,9,10], especially in

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the elderly [7,11], and agreement between different scores has been shown to be low to moderate.

Therefore, the aim of this study was to refine the estimation of bleeding risk by identifying one or several parameters of prognostic significance in these algorithms to help in the evaluation of bleeding risk.

2. Methods

2.1. Study design

The SCORE study was a prospective, multicentre (Grenoble-Alpes University Hospital, Voiron General Hospital and Mutualité Clinic, all in the Grenoble area of France) cohort study that included consecutive patients treated by VKA for any therapeutic indication for a period of at least 3 months, and who had received therapeutic education from the hospital city network [12]. All patients gave their informed consent to participate in the study. Patients were excluded if they were aged <18 years, they had not participated in a VKA teaching programme, informed consent could not be obtained, they were unable to speak French adequately, or they were currently taking part in another study with direct oral anticoagulants (VKA arm). The study was approved by the Ethical Committee of the University Hospital of Grenoble, and collected data were registered and protected according to French law.

For all enrolled patients, a trained educational and study nurse collected baseline demographic information and clinical parameters allowing the calculation of bleeding risk scores at study inclusion using a standardized questionnaire. These parameters included age; treated hypertension; diabetes; excessive fall risk (including neuropsychiatric disease and recent falls); active malignancy; reduced platelet count (<75 g/l) or function; severe anaemia (<100 g/l); liver disease (AST/ALT ≥3 × N); chronic kidney disease (creatinine clearance <30 ml/min); alcohol abuse (>21 drinks/week for men and >14 drinks/week for women); medication (>3); and history of stroke, myocardial infarction, or brain or gastrointestinal bleeding. The questionnaire was validated by a physician. For any missing data, the patient or physician was contacted to retrieve the information. Follow-up at 1 year was undertaken using a standard questionnaire addressed to the general practitioner. In case of no response, the investigator made direct contact via telephone.

2.2. Score calculation

The Shireman [13], Kearon [14], OBRI [15], Kuijer [16], HEMMORR2HAGES [17], HAS-BLED [18] and ATRIA [19] scores were calculated for each patient at study inclusion. When information on a parameter was missing (such as CYP 2C9 single nucleotide polymorphisms for HEMORR2HAGES, and the variability of international normalized ratio for HAS-BLED), no point was given, as reported previously [11].

2.3. Outcome

The primary outcome was the occurrence, over a 1-year observation period, of a major bleeding event while receiving VKA treatment, defined by the following criteria: bleeding resulting in haemodynamic instability (systolic blood pressure < 90 mmHg, a decrease of 40 mmHg or signs of shock), bleeding requiring haemostatic intervention, bleeding requiring blood transfusion (>2 units red blood cells), bleeding in a critical area or organ threatening the vital or functional prognosis, external bleeding uncontrollable by usual means, and decreased haemoglobin >20 g/l [20]. Bleeding events were not recorded if they occurred after VKA treatment had ceased. Major bleeding events and death were validated by an independent committee.

2.4. Statistics

Quantitative variables are expressed as medians and interquartile ranges (25th and 75th percentiles). Qualitative variables are expressed as percentages. Sample size was determined to detect a 5% difference in the area under the curve between two scores, for a 5% alpha risk and 80% power. Assuming a 20% loss to follow-up or missing data, 900 patients were recruited.

The incidence of major bleeding was calculated by the Kaplan–Meier method with determination of the 95% confidence interval (CI).

A Cox model univariate analysis was conducted to identify significant risk factors for bleeding among the different scores. Afterwards, a multivariate analysis that integrated parameters from the univariate analysis with $P < 0.20$ was completed using a stepwise approach.

An induction tree analysis was performed to identify a common meta-rule in the majority of scores (i.e. parameters that were the best predictors to classify patients as high risk) [21]. A C4.5 algorithm was used for this purpose, with at least four scores for the same patient and explanatory variables [including 21 risk factors (age, sex, cancer, alcohol abuse, hypertension, ischaemic and haemorrhagic stroke, diabetes mellitus, anaemia, gastro-intestinal haemorrhage, antiplatelet agents, renal and hepatic insufficiency, risk of falls (Up and Go test) or fall during the previous year, low platelet count, myocardial infarction, VKA induction, indication of VKA, and neuropsychiatric disease)] used to explain classification as high risk.

For all analyses, $P < 0.05$ was considered to indicate significance. Analyses were performed at the Clinical Centre of Investigations of Grenoble using STATA Version 12.0 (Stata Corp., College Station, YX, USA) on OSX software. The induction tree was prepared using R Version 3.1.2 (Foundation for Statistical Computing).

3. Results

Between May 2009 and December 2010, 968 patients were included in this study. A total of 962 patients (six patients were lost to follow-up) were followed for 1 year and analysed. Almost all (98.3%) patients were recruited during hospitalization. The population baseline characteristics are depicted in Table 1. During the observation period, 79% of patients were treated with VKA for 180–365 days, and 57.8% of patients were still being treated at 1 year.

At 1-year follow-up, 26 major haemorrhages [14 in the cardiac group and 12 in the venous thromboembolism (VTE) group] were recorded [i.e. 2.86% (95% CI 1.95–4.20) patients-year (intracerebral $n = 5$, gastrointestinal $n = 4$, urinary/genital tractus $n = 5$, deep muscles $n = 3$, pericardic $n = 2$, other $n = 7$)]. The median duration of severe bleeding was 148 days (IQR 59–277) after the initiation of VKA treatment.

In the entire cohort, 66 patients died after 1 year, including eight (30.8%) patients with severe haemorrhage.

3.1. Identification of patients at high risk of major bleeding by scores

Among the cohort, 676 patients [70.3%; 321 (65.2%) and 355 (75.5%) for cardiac and VTE indications, respectively] were not classified as high risk by any of the scores (Table 2). Among them, 15 major bleeds (2.2%) were recorded. Eighty-seven patients (9%) were classified as high risk by a single score, with an incidence of major bleeding in this group of 1.15%. Based on a data-driven approach, the rate of major bleeding was >3% when a patient was classified as high risk by at least four scoring models among the seven tested (Table 2). Therefore, an 8.2% (95% CI 3.4–16.2) incidence of major bleeding was observed at 1 year when a patient was classified as high risk by four or more scores, compared with 2.2% (95% CI 1.3–3.4) if patients were classified as high risk by fewer than four scores. The results were very similar for the entire cohort and for each indication (cardiac or VTE) (Table 3).