New Oral Anticoagulants Increase Risk for Gastrointestinal Bleeding: A Systematic Review and Meta-analysis

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BACKGROUND & AIMS: A new generation of oral anticoagulants (nOAC), which includes thrombin and factor Xa inhibitors, has been shown to be effective, but little is known about whether these drugs increase patients' risk for gastrointestinal bleeding (GIB). Patients who require OAC therapy frequently have significant comorbidities and may also take aspirin and/or thienopyridines. We performed a systematic review and meta-analysis of the risk of GIB and clinically relevant bleeding in patients taking nOAC. **METHODS:** We queried MEDLINE, EMbase, and the Cochrane library (through July 2012) without language restrictions. We analyzed data from 43 randomized controlled trials (151,578 patients) that compared nOAC (regardless of indication) with standard care for risk of bleeding (19 trials on GIB). Odds ratios (ORs) were estimated using a random-effects model. Heterogeneity was assessed with the Cochran Q test and the Higgins I^2 test. **RESULTS:** The overall OR for GIB among patients taking nOAC was 1.45 (95% confidence interval [CI], 1.07−1.97), but there was substantial heterogeneity among studies (I_2, 61%). Subgroup analyses showed that the OR for atrial fibrillation was 1.21 (95% CI, 0.91−1.61), for thromboprophylaxis after orthopedic surgery the OR was 0.78 (95% CI, 0.31−1.96), for treatment of venous thrombosis the OR was 1.59 (95% CI, 1.03−2.44), and for acute coronary syndrome the OR was 5.21 (95% CI, 2.58−10.53). Among the drugs studied, the OR for apixaban was 1.23 (95% CI, 0.56−2.73), the OR for dabigatran was 1.58 (95% CI, 1.29−1.93), the OR for edoxaban was 0.31 (95% CI, 0.01−7.69), and the OR for rivaroxaban was 1.48 (95% CI, 1.21−1.82). The overall OR for clinically relevant bleeding in patients taking nOAC was 1.16 (95% CI, 1.00−1.34), with similar trends among subgroups. **CONCLUSIONS: Studies on treatment of venous thrombosis or acute coronary syndrome have shown that patients treated with nOAC have an increased risk of GIB, compared with those who receive standard care. Better reporting of GIB events in future trials could allow stratification of patients for therapy with gastroprotective agents.**

Keywords: Anticlotting Agent; Antithrombotic; Comparison; Ulcer.

Gastrointestinal bleeding (GIB) is a serious medical condition that causes considerable morbidity and mortality (5%–15%) and poses an enormous burden on global health care use.[1] The mean hospital costs are reported to range from $2500 to $7300 for upper GIB, $4800 for lower GIB, and around $40,000 for small-bowel bleeding.[2] The expanding indications and increasingly intensive treatment with antithrombotic agents have increased the burden of GIB related to these agents.[3] Antiplatelet agents (eg, aspirin and thienopyridine derivatives) can give rise to GIB by producing ulcers and erosions throughout the gastrointestinal tract. Anticoagulants (ie, vitamin K antagonists [VKA]) and heparins might precipitate bleeding from pre-existing lesions.[4] The relative risk of GIB varies from 1.5 for low-dose aspirin compared with nonuse[5] and more than 5 for the combination of aspirin and VKA.[3] In light of their efficacy, the increased risk of bleeding induced by the therapy is acceptable. Two important limitations of the traditional antithrombotic agents comprise the need for international normalized ratio monitoring with tailored VKA dosing, or subcutaneous administration of low-molecular-weight heparins (LMWH).

New oral anticoagulants (nOAC) (eg, factor IIa [thrombin] or factor Xa inhibitors) have been developed and theoretically lack these limitations.[6–8] These drugs are as effective as current therapy. Some randomized controlled trials (RCTs) reported an isolated higher GIB risk,[9,10] which is potentially fatal, costly, and avoidable. It is therefore important to carefully review the literature on GIB risk attributable to use of nOAC. This is particularly relevant because patients on nOAC often use concomitant low-dose aspirin and/or thienopyridines, which may add substantially to the as yet unknown GIB risk. Furthermore, in contrast with the traditional OAC, no clinically tested antidote is currently available for the novel

Abbreviations used in this paper: ACS, acute coronary syndrome; AF, atrial fibrillation; CI, confidence interval; DVT, deep vein thrombosis; GIB, gastrointestinal bleeding; LMWH, low-molecular-weight heparin; NNH, number needed to harm; NSAID, nonsteroidal anti-inflammatory drug; nOAC, new oral anticoagulants; OR, odds ratio; OS, orthopedic surgery; PE, pulmonary embolism; PPI, proton pump inhibitor; RCT, randomized controlled trial; VKA, vitamin K antagonist.

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agents, hampering therapeutic options in case of GIB.[11] For these reasons, we conducted a systematic review focusing on the risk of GIB of all nOAC. Because not all trials separately reported GIB risk, we also reviewed the evidence on risk of clinically relevant bleeding associated with nOAC use.

Materials and Methods

Study Definitions

The exposure of interest was defined as the (approximated) indication-specific recommended daily dose of the nOAC either by the European Medicines Agency[12] or the Food and Drug Administration[13] for registered nOAC. When nOAC was not registered for the indication for which it was studied, the indication-specific daily dose was defined according to the pharmaceutical manufacturer.

Standard care was defined as either low-molecular-weight heparin, vitamin K antagonist, antiplatelet therapy, or no (additional) therapy/placebo, depending on the (inter)national guidelines regarding antithrombotic therapy for the concerning indication.

The primary outcome of this systematic review was the risk of GIB. GIB was considered as at least one episode of clinically apparent hematemesis (frank blood or coffee-ground material that tested positive for blood), melena, or spontaneous rectal bleeding (if more than a few spots) or endoscopically confirmed bleeding, and was judged as major or clinically relevant nonmajor depending on the severity.[14]

The secondary outcome was the risk of clinically relevant bleeding (encompassing both major bleeding and clinically relevant nonmajor bleeding). Major bleeding and clinically relevant nonmajor bleeding in the included studies were defined by the following: (1) the International Society on Thrombosis and Haemostasis,[15,16] (2) the Thrombolysis In Myocardial Infarction,[17] or (3) an adjustment of the International Society on Thrombosis and Haemostasis definition (see Table 1 for exact definitions).

Data Sources and Searches

A comprehensive literature search was conducted to identify RCTs reporting GIB or clinically relevant bleeding in patients receiving nOAC compared with standard treatment. Medline with PubMed as interface, EMbase, and the Cochrane Central Register of Controlled Trials were searched from inception to July 2012. Medical subject heading terms and keywords used to identify RCTs included "apixaban," "rivaroxaban," "dabigatran," "edoxaban," "betrixaban," "humans," and "randomized controlled trial." No language restrictions were applied. The electronic search strategy was complemented by a manual review of reference lists of included articles. References of recent reviews on nOAC also were examined.[11,18–23]

Study Selection

Search results were combined and duplicates were removed. Studies were first screened based on title and abstract for relevance, after which the full text was reviewed. This was performed independently by 2 reviewers (I.L.H. and V.E.V.). Inter-rater agreement was assessed using the k statistic. Any discrepancies were resolved by consensus, contacting a third author (E.T.T.L.T.). Studies had to meet the following inclusion criteria: (1) the study compared nOAC with the current standard care in a randomized setting; (2) results included bleeding events as a safety outcome; (3) the study was conducted in the target population of the drug and not in healthy volunteers; and (4) it was published as a full-text article. If any of the 4 criteria were not met, the study was excluded. If data from the same study were published in multiple languages, data from the English article were extracted. In case of suspicion of double reporting of the same patient populations, data from the main publication were extracted.

Data Extraction

The included studies were divided by clinical indication of anticoagulant therapy into the following indication groups: (1) prevention of stroke and systemic embolism in patients with atrial fibrillation (AF); (2) prevention of venous thromboembolism after orthopedic surgery (OS); (3) prevention of venous thromboembolism in medically ill patients; (4) treatment of acute deep vein thrombosis (DVT) or pulmonary embolism (PE); and (5) treatment of acute coronary syndrome (ACS). For each included study, we recorded the number of trial participants, follow-up period, and the number of patients who developed the primary safety end points for both treatment arms. The mean age at baseline and the percentage of males were assessed, as well as other characteristics of the study population such as relevant concomitant medications that may affect bleeding risk. This was performed independently by 2 authors (I.L.H. and V.E.V.). Finally, we contacted the main investigator for missing data. Furthermore, given the heterogeneity of the studies, an individual patient data analysis was attempted. All authors were contacted and requested to provide individual patient data. We received responses from 7 of 23

Table 1. Definitions of Bleeding

End point	Sub–end point	Definition
Clinically relevant bleeding	Major bleeding	Acute, clinically overt bleeding accompanied by ≥1 of the following events: a decrease in hemoglobin level of ≥2 g/dL within a 24-hour period; a transfusion of ≥2 units of packed red cells; bleeding at a critical site (ie, intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint (for the studies regarding thromboprophylaxis after surgery), requiring an additional surgery or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding[15,16] In addition to the above, when major bleeding occurred in the gastrointestinal tract (defined by at least one episode of clinically apparent hematemesis, melena, spontaneous rectal bleeding) or when a major bleeding was confirmed by endoscopy, it was defined as (major) GIB[14]
	Clinically relevant nonmajor bleeding	Acute, clinically overt bleeding, such as excessive wound hematoma, bruising or ecchymosis (>25 cm^2), gastrointestinal bleeding, hemoptysis, macroscopic hematuria, gingival bleeding (>5 min), epistaxis (>5 min), or any bleeding leading to hospital admission or discontinuation of the study medication, unscheduled contact with a physician, or discomfort or impairment of activities of daily life, that did not meet the other criteria for major bleeding