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Editorial

Gastrointestinal Bleeding in Patients on Non-Vitamin K Oral Anticoagulants Versus Vitamin K Oral Anticoagulants

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Abbreviations

NOACs: Novel Oral Anticoagulants; DOACs: Direct Oral Anticoagulants; OAC: Vitamin K Oral Anticoagulants; GIB: Gastrointestinal Bleeding; Afib: Atrial Fibrillation; DVT/PE: Deep Vein Thrombosis/Pulmonary Thromboembolism

Introduction

Novel oral anticoagulants (NOACs) represents a group of medications: direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) are increasingly favorized over conventional oral anticoagulants (OAC), vitamin K oral anticoagulants such as warfarin. As requested by some authors the term "NOACs", should be restricted to "non-vitamin K oral anticoagulants" while others suggest the term "direct oral anticoagulants" (DOACs) [1]. This tendency for grouping terminology should be adopted as the name implies similar pharmacological actions that inhibit a single target. At the present time, approved indications for NOACs prescription are: non-valvular atrial fibrillation (AFib), postoperative DVT/PE thromboprophylaxis (hip or knee replacement), treatment and prevention of recurrent DVT/PE, acute coronary syndrome and still not officially medically ill patients [1].

Although effective in the prevention and treatment of thromboembolism, NOACs are associated with bleeding complications, as are OACs, but according to the literature data, it seems that NOACs are associated with significantly higher risk for gastrointestinal bleeding (GIB) [1,2].

Why NOACs are preferred over OAK

One of the first indications for NOACs was stroke prevention in patients with atrial fibrillation. Although OACs dramatically reduces the risk for ischemic stroke, their use is often inadequate. In real life in AFib patients OACs are under prescribed (in less than 60% of cases), their safety and efficacy depends on adequate anticoagulation effect, but the time that patients are in therapeutic range is only 63%, then there are known drug-drug interaction, and maybe even more important food interactions. Aspirin monotherapy for stroke prevention in AFib patients does not provide adequate protection, while in the same is associated with a significant increase in bleeding complications. This leads us to NOACs – medications with a favorable risk-benefit profile, resulting in significant reductions in stroke, intracranial hemorrhage and mortality, with similar rates of major bleeding compared to OACs but increased risk for gastrointestinal bleeding (GIB) [3]. When compared with warfarin, dabigatran and rivaroxaban (the most significant amount of data exists for this two NOACs), are associated with an increased risk of GIB only, but not bleeding in other organs including intracranial hemorrhage [1].

Some of advantages of NOACs are rapid onset and offset of action, predictable pharmacodynamics which enables their usage without regular therapeutic monitoring, and fewer food-drug or drug-drug interactions. Although NOACs demonstrated a favorable safety profile, especially considering bleeding complications, it seems that the risk of gastrointestinal bleedings is higher in NOAC treated patients in comparison to OACs [1,2].

Why are NOACs related to increased risk of gastrointestinal bleeding? - Mechanisms of NOAC-related GIB

The pathogenesis of GIB in NOACs is dual, first there is a systemic anticoagulant effect, and then, there is local – topical effect such as inhibition of GI mucosal healing, direct caustic injury and incomplete absorption (with increased topical anticoagulant effect). For example, dabigatran etexilate is specific in his structure with the tartaric acid in his molecule that cause direct caustic injury. When compared with warfarin, dabigatran and rivaroxaban are associated with an increased risk of GIB only [1,4].

The sites of GIB are different for individual NOACs. In contrast to the usual pattern observed with OACs, aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) where upper GIB predominates [5], lower GIB accounted for 53% of major GIB seen in dabigatran users in the RE-LY trial [6]. One possible explanation is the fact that there is incomplete absorption of the active NOACs in the upper GI tract with resulting increased availability of dabigatran to the lower GI tract, and topical effect on intestinal mucosa that leads to bleeding, especially in the presence of pre-existing lesions. On the other hand, the bioavailability of warfarin is more than 95%, and non-absorbed warfarin does not have any topical effect. Upper GIB are more common among rivaroxaban users (76% vs 24% for lower GIB), while the risks of upper and lower GIB were comparable with high-dose edoxaban (60 mg daily) [1].

Other important element for risk of GIB is the dosing [1]. Rivaroxaban and apixaban are administered in active form, and have similar bioavailability, but they differ in the risk of GIB, which may be related to the higher peak level of once-daily dosing of rivaroxaban than the twice-daily dosing of apixaban. Similarly, the once-daily dosing of rivaroxaban may also account for the higher GIB risk observed in the head-to-head comparison of rivaroxaban and dabigatran [7].

Risk of NOAC-related GIB in RCTS as compared to Observational Studies

It seems that there is a difference in reported rates of GIB in randomized clinical trials (RCTS) as compared with data gathered from observational studies.

Holster performed meta-analysis, which included 75081 patients who received either NOACs or standard care [low-molecular-weight heparin (LMWH), OACs, antiplatelet therapy or placebo]. The total incidence of GIB events was 1.5%, with 89% major GIB (a decrease in hemoglobin ≥ 2 g/dL, a transfusion of ≥ 2 units of packed red cells, necessitating intervention including surgery, or fatal bleeding). Overall, patients treated with NOACs had 1.45 odds ratio (OR) for GIB in comparison to standard care receivers [8].

Comparison between different NOACs gives us insufficient data pointing to dabigatran and rivaroxaban as associated with a higher risk of GIB (OR 1.58 and 1.48, respectively), but not apixaban and edoxaban. But, these are no data from head-to-head comparisons, so it is difficult to conclude at this point [1].

The GIB risk is also associated with the indications for which NOACs are used, and that is directly associated with dose that was used and concomitant therapy. The highest risk of GIB is seen in patients with acute coronary syndrome (OR 5.21), in whom NOACs were co-prescribed with antiplatelet agents. GIB risk was not significantly increased in patients receiving NOACs for prevention of VTE after orthopedic surgery and in medically ill patients, which can be explained with the lower dose and shorter duration of the treatment. Among dabigatran receivers only the higher dose (150 mg b.i.d) was associated with a higher GIB risk when compared with warfarin, indicating a dose-related effect. Same effect was present with high-dose edoxaban of 60 mg daily (HR 1.23) [1,4].

He Y., *et al*. performed meta-analyze of observational studies on 117339 NOAC users, either dabigatran or rivaroxaban. The pooled incidence rates of GIB were 4.5 per 100 patient-years and 7.18 per 100 patient-years for dabigatran and rivaroxaban, respectively. Compared with warfarin, dabigatran led to relative risk (RR) 1.21, for GIB, while rivaroxaban did not demonstrate a significant increase in risk [1,9]. In head-to-head comparative observational study for non-valvular AFib rivaroxaban was found to be associated with a higher risk of major GIB compared with dabigatran (150 mg b.i.d) [hazard ratio (HR) 1.40] [4,10].

Contrary to the postulated, the risk of GIB was slightly lower in observational studies when compared with that reported in RCTs. This can be explained: RCTs are recruiting patients with more severe risk profile, while doctors in real life are more careful in selecting patients for NOACs [1].

Observational study of Abraham., *et al*. demonstrated that the risk of GIB associated to NOACs was similar to that for warfarin. Caution should be used when prescribing novel oral anticoagulants to older people, particularly those over 75 years of age. As additional risk factor that have to be taken in consideration when deciding to prescribe NOACs are: patients age (advanced age increases the GIB risk), the amount of comorbidities, especially uncontrolled hypertension, diabetes, congestive heart failure, history of stroke or thromboembolism, previous GIB, or Helicobacter pillory presence, uncontrolled usage of NSAIDs, antiplatelet, steroids and selective serotonin reuptake inhibitors, alcohol consumption, hepatic and renal function and HAS-BLED score [11].

On the other side in the real-life situations doctors are prescribing gastroprotective medications such H2 blockers or proton pump inhibitors. Prevention of NOAC-related GIB includes proper patient selection, using a lower dose of NOACs, especially in patients with liver and renal impairment, correction of modifiable risk factors, and prescription of gastroprotective medications [1].

Conclusion

Compared with warfarin, there is a higher risk of GIB for high-dose dabigatran (150 mg b.i.d), rivaroxaban and high-dose edoxaban (60 mg daily). Reviewing the indications of NOACs and prescribing a particular NOAC on an individual basis are therefore of utmost importance.

Whenever prescribing NOACs, physicians should carefully review the indications and appropriate dosage, as well as balancing the risks and benefits. Patients that have indication for receiving these medications and in the same time have an increased risk of GIB should be advised to undertake preventive measures to reduce the risk of GIB. Prevention of NOAC-related GIB includes proper patient selection, using a lower dose of certain NOACs in patients with renal impairment, correction of modifiable risk factors, and prescription of gastroprotective medications.

Conflict of Interest

I declare no conflict of interest regarding this manuscript.

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