Blood Reviews 29 (2015) 335–343

Contents lists available at ScienceDirect

Blood Reviews

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

REVIEW

Antithrombotic drugs, patient characteristics, and gastrointestinal bleeding: Clinical translation and areas of research

Alessandro Di Minno [a], Gaia Spadarella [b], Domenico Prisco [c], Antonella Scalera [b], Elena Ricciardi [b], Giovanni Di Minno [b,*]

[a] Department of Farmacia, Università degli Studi di Napoli "Federico II", Naples, Italy
[b] Department of Medicina Clinica e Chirurgia, Università degli Studi di Napoli "Federico II", Naples, Italy
[c] Department of Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Largo Brambilla 3, 50134 Firenze, Italy

ARTICLE INFO

Keywords:
Gastrointestinal bleeding
Therapeutic context
Patient characteristics
Co-morbidities
Antithrombotic drugs

ABSTRACT

Gastrointestinal bleeding (GIB) is a potentially fatal and avoidable medical condition that poses a burden on global health care costs. Current understanding of the roles of platelet activation and thrombin generation/activity in vascular medicine has led to the development of effective antithrombotic treatments. However, in parallel with a sustained coronary and cerebral flow patency, the increasingly intensive treatment with warfarin; direct oral anticoagulant drugs [DOACs], and/or with aspirin ± clopidogrel (or ± prasugrel or ± ticagrelor), has increased the burden of GIBs related to the use of antithrombotic agents. Compelling evidence concerning this issue is accumulating to indicate that: 1) the risk of GIB related to the use of antithrombotic drugs dramatically differs in different clinical settings; and 2) the characteristics of patients (e.g., severity of illness, comorbidities) in whom it is used exert a greater impact on the risk of GIB than the type of antithrombotic agent employed. The latter concept argues for the occurrence of GIB as reflecting the presence of patients at the highest risk for adverse outcomes. The HAS-BLED score identifies subjects at risk of bleeding among those untreated and those treated with warfarin, DOACs and/or low-dose aspirin. Its use within the frame of a severity score (e.g., the CHA_2DS_2-VASc score in patients with atrial fibrillation) helps balance the benefits and the risks of an antithrombotic treatment and identify those patients in whom the absolute gain (vascular events prevented) outweighs the risk of GIB. Potential implications of the latter information in settings other than atrial fibrillation is thoroughly discussed.

1. Introduction

Gastrointestinal bleeding (GIB) is a serious medical condition that causes considerable morbidity and mortality and poses a tremendous burden on global health care costs [1,2]. The most common sources of upper GIB (UGIB, proximal to the ligament of Treitz) are peptic ulcer and gastritis, those of lower GIB (LGIB) are colonic diverticula and malignancy [3]. Important causes of acute and chronic small-bowel bleeding in the general population include malignancy, angiodysplasia and ulceration related to non-steroidal anti-inflammatory drugs (NSAID).

Current understanding of the roles of platelet activation and thrombin generation/activity in vascular medicine has led to the development of effective antithrombotic treatments. However, in parallel with a sustained coronary and cerebral flow patency, these increasingly intensive treatment approaches have steadily augmented the burden of GIBs and of hospital and long-term outcomes related to the use of warfarin; antiplatelet agents, or DOACs. Compared to those without, patients with a history of coronary artery disease (CAD) have fewer cardiovascular events and deaths with the use of low-dose aspirin, commonly defined as 75 to 325 mg/d [4]. However, low-dose aspirin can damage both the upper and the lower gastrointestinal (GI) tract thus causing bleedings in both sites. Approximately 30–50% of patients on chronic treatment with antiplatelet agents develop endoscopic lesions, especially in the gastric antrum, that may be asymptomatic [5]. The combined use of warfarin dramatically increases the risk of major GIB in patients with atrial fibrillation (AF) who employ low-dose aspirin and/or clopidogrel [6]. Warfarin is currently the most commonly used oral anticoagulant Worldwide. Its indications include a wide range of clinical conditions most prevalent in the elderly such as prevention of recurrent venous thromboembolism (VTE) and of systemic thromboembolism and prevention of stroke in patients with AF and/or prosthetic heart

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; AF, atrial fibrillation; Med ill, medically ill; OS, orthopedic surgery; PE, pulmonary embolism; DVT, deep vein thrombosis; PE, pulmonary embolism; GIB, gastrointestinal bleeding;; NSAID, non-steroidal anti-inflammatory drug; ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant drug; PPI, proton pump inhibitor; RCT, randomized controlled trial; VKA, vitamin K antagonist; Api, apixaban; dab, dabigatran; edo, edoxaban; riv, rivaroxaban; OR, odds ratio; 95% CI, 95% confidence intervals; NNH, number needed to harm.

* Corresponding author at: Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli "Federico II", Via S. Pansini 5, 80131 Napoli, Italy.
E-mail address: diminno@unina.it (G. Di Minno).

http://dx.doi.org/10.1016/j.blre.2015.03.004
0268-960X/

valves [7]. However, older individuals are at greater risk of bleeding than their younger counterparts with similar diagnoses [8]. As a consequence, individuals with VTE and/or AF are often undertreated or not treated at all with warfarin therapy [9,10]. Moreover, warfarin has a wide variability in dose–response across individuals, a significant number of drug and dietary interactions and a narrow therapeutic window (between 2 and 3, as evaluated by the international normalized ratio [INR] value) [11]. The average time in which patient INR values range 2–3 (defined as time in therapeutic range [TTR]) are related to event rates [12], patients with an average individual TTR of >70% having a low risk of major bleeding [13]. Thus, warfarin requires close laboratory monitoring with frequent dose adjustment and tailored dosing to avoid bleeding complications [14].

New direct oral anticoagulant drugs (DOACs), approved for the prevention and treatment of VTE and of systemic and cerebral embolism in AF [15], are poised to replace warfarin for stroke prevention in the setting of AF [16]. Dabigatran (a thrombin inhibitor), rivaroxaban, apixaban and edoxaban (all factor Xa inhibitors) are easier to use than warfarin, with fewer drug and food interactions and no need for routine blood monitoring [17]. In spite of some differences in the individual data (Table 1), a meta-analysis of the four pivotal phase 3 trials in patients with AF (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials; 71,683 participants included, 42,411 of whom received a DOAC and 29,272 participants received warfarin) shows that, compared with warfarin, DOACs reduce stroke or systemic embolism by 19% (relative risk [RR] 0.81, 95% confidence intervals [CI] 0.73–0.91; $p < 0.0001$); hemorrhagic stroke (0.49, 0.38–0.64; $p < 0.0001$); intracranial hemorrhage (0.48, 0.39–0.59; $p < 0.0001$), and all-cause mortality (0.90, 0.85–0.95; $p = 0.0003$) [18]. The relative efficacy and safety of DOACs are consistent across a wide range of patients, and similar to those documented in studies on thromboprophylaxis with these agents [19]. However, compared with warfarin, the use of DOACs in patients with AF is associated with an increase in the risk of GIB (1.25, 1.01–1.55; $p = 0.04$) [18] similar to that documented in studies in clinical conditions other than AF [20].

The rate of GIBs related to the use of antithrombotic drugs is maximal in the scenario of acute coronary syndrome (ACS) and is independently associated with mortality and ischemic complications [21,22]. Antiplatelet treatment intensified by adding clopidogrel to aspirin has long been known to reduce fatal and non-fatal ischemic events in ACS patients [23]. Percutaneous intervention is being used in the current management of ACS and is usually performed in the presence of 3, 4, or even 5 antithrombotic drugs. Especially when antiplatelet agents are combined with anticoagulant medications (e.g., heparins, bivalirudin, warfarin), the capability of such drugs to act cumulatively as to the risk of GIB is clear. Here, epidemiologic evidence concerning the association between GIB and antithrombotic drugs, used alone and in combination is provided. With respect to the risk of GIB, current evidence regarding clinical settings and individual patient characteristics to be taken into account by physicians formulating an antithrombotic strategy is also summarized.

Table 1
Phase III AF trials: rates of major bleedings and intracranial hemorrhages.
Data from: Connolly et al. N Engl J Med 2009;361:1139–1151; Patel et al. N Engl J Med 2011;365:883–891; Granger et al. N Engl J Med 2011;365:981–992; Giugliano et al. N Engl J Med 2013;369(22):2093-104.

	DOAC	Warfarin	RRR (*DOAC vs Warfarin*)	p value
Major bleedings (%/year)				
RE-Ly 110 mg	2.71	3.36	−19.4%	0.003
Re-Ly 150 mg	3.11	3.36	−7.5%	NS
Rocket AF	3.60	3.40	+2.5%	NS
ARISTOTLE	2.13	3.09	−31.1%	<0.001
ENGAGE 60 mg	2.75	3.43	−20.2%	<0.001
ENGAGE 30 mg	1.61	3.43	−51.4%	<0.001
Intracranial hemorrhage (%/year)				
RE-Ly 110	0.23	0.74	−68.9%	0.001
Re-Ly 150	0.30	0.74	−58.9%	0.001
Rocket AF	0.50	0.70	−34.4%	0.02
ARISTOTLE	0.33	0.80	−57.5%	<0.001
ENGAGE 60 mg	0.39	0.85	−53.8%	<0.001
ENGAGE 30 mg	0.26	0.85	−68.9%	<0.001

2. GIB and antithrombotic drugs: epidemiologic evidence

2.1. GIB and warfarin

GIB affects an estimated 4.5% of warfarin-treated patients annually and is associated with a significant risk for death [24]. A history of major bleeding is an important predictor for future serious bleeding, suggesting that patients with GIB might be considered for discontinuation of warfarin therapy [25]. However, interruption or permanent discontinuation of warfarin therapy increases the risk of thromboembolic complications [26].

As to UGIB, endoscopic findings show that gastritis accounts for 18.2% (duodenitis accounting for an additional 9.1%); peptic ulcer for 17% and esophagitis for 11.4% respectively. As to LGIB, diverticula account for 23.4%, malignancy or adenoma for 13.8%; angiodysplasias for 10.8% and colitis and hemorrhoids for 5.4% each respectively. Normal mucosa is found in 21.6% of cases of UGIB and in 40.5% of cases of LGIB respectively (bleeding of unknown origin) [3]. Factors that influence the source and severity of GIB in patients taking warfarin include the concomitant use of aspirin, advancing age, previous GIB, AF, and co-morbidities (e.g., anemia, renal insufficiency) [27]. In patients on warfarin, the incidence of GIB increases as mean INR values increase [28]. A mean INR of 2.1 maximally discriminates patients without GIB; a mean INR ≥ 3.0 helps identify those at the highest risk of GIB [29]. Among GIB patients, up to 1/3 experiences the first bleeding episode within the first month of anticoagulation and 61.1% of the GIBs occur within the first year of anticoagulation [30]. This might be due to unstable intensity of anticoagulation during the early dosage adjustment period. A history of GIB increases the risk of GIB, further arguing for local causes as major determinants of such risk. Chronic liver disease increases bleeding risks in patients starting anticoagulant therapy [31]. Compared to those with VTE, candidates for anticoagulation with warfarin for AF are older, have more co-morbid conditions, and take more concurrent medications. In addition to having an increased risk of GIB (estimated to be 0.3–0.5% per year) AF patients have a higher absolute risk of (major) bleedings other than GI (e.g., hemorrhagic stroke) than the general population [32]. In early stroke prevention trials in AF, warfarin was associated with a rate of major GIB approximately three-fold higher than placebo (odds ratio [OR] = 3.21, 95% CI 1.32–7.82) [32]. Co-administering of an anti-platelet agent (e.g., aspirin) was associated with a risk of major GIB approximately twice higher than that seen with warfarin alone (OR = 2.66, CI 1.05–6.74). Age > 65 years was significantly associated with GIB. In particular, persons older than 80–85 years of age carry a significant risk of bleeding [33]. A slow rate of warfarin metabolism, an elevated risk of drug interactions (polypharmacy), and chronic illness increase the risk of bleeding in the elderly [34]. However, when cautiously used and optimized by specialized centers, warfarin therapy should not be withheld in the elderly simply because of age. In a large, prospective, observational study on 4039 individuals (median age: 84 years; mean age of those who bled: 85 years) who were newly started on warfarin therapy for either AF (74%) or VTE (26%) and were followed in Italian Anticoagulation Clinics, there was a higher incidence of major bleeding in the first 3 months (3.87 per 100 patient-years) than later (1.63 per 100 patient-years, relative risk, 2.4; 95% confidence interval, 1.66 to 3.37; $p < 0.000$) [35]. Their average time to a major bleeding was 14.2 months (range, 0.1 to 109 months), and the incidence of major bleeding was very low: 1.87 per 100 patient-years of observation (179 bleedings, 65/179 being GIBs). Of major bleedings, 30% (53/179, 0.55 per 100 patient-years) were intracranial and 14.5% (26/179) were fatal (2.7 per 1000 patient-