REVIEW

Restarting Antithrombotic Drugs After Gastrointestinal Bleeding: An Unresolved Issue of Everyday Clinical Practice

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Abstract

With the evolution in cardiovascular disease understanding and the application of advanced interventional therapies, antithrombotic medication has become the cornerstone of the medical management of cardiovascular patients. However, as older and new trials have confirmed, these drugs carry a substantial risk for hemorrhagic complications, especially from the gastrointestinal (GI) tract, which are accompanied by a significant mortality risk. In case of such an event, the clinician must decide whether to discontinue or not the medication and for how long, and he is called to balance the potential risk of thrombosis and recurrent bleeding. In this brief review, we present the studies which address this issue in order to elicit practical conclusions. (***Rhythmos*** 2017;12(3): 45-49).

Key Words: atrial fibrillation; mechanical valves; anticoagulation; oral anticoagulants; antithrombotic therapy; thromboembolism; gastrointestinal bleeding

Abbreviations: GI = gastrointestinal; GIB = gastrointestinal bleeding

Introduction

The benefits of antithrombotic therapy in atrial fibrillation, mechanical heart valves and secondary prevention of cardiovascular disease both in the clinical setting of acute coronary syndromes and stable ischemic heart disease are well established and the relevant drugs are officially recommended. [1-5] Even more so are the potential risks of intense antithrombotic therapy in terms of gastrointestinal (GI) bleeding (GIB). In the recent large trials of the novel anticoagulants, in patients with atrial fibrillation, the incidence of GIB in the warfarin arms ranged between 0.8-1.2%/year, while it was increased in the treatment arms, exceeding 2%. [6-9] Anti-platelet medications are associated with a GIB incidence of 1-2.5% roughly, as concluded by the studies which evaluated the conventional and novel agents, while antiplatelet combinations incur additional risk. [10-14] Moreover, GIB can carry a mortality risk of 2-4% up to over 25% for lower and upper GI tract respectively, depending on the severity of the hemorrhage and the patient comorbidities. [15,16] The bleeding risk when using antithrombotics is a known and acceptable hazard, as the benefits of therapy regarding the prevention of thrombotic events outweighs the potential harm from the hemorrhagic complications. However, the management of bleeding in the face of established indication of antithrombotic drug use is particularly problematic, especially because despite the frequency of this complication, there are very limited data in the literature to help us out.

Antiplatelets and GI bleeding

The consequences of stopping or temporarily interrupting antiplatelet therapy after a GIB event has been addressed in a few studies, almost exclusively with regard to aspirin. No data are available concerning the management of newer agents such as prasugrel or ticagrelor. Derogar et al studied retrospectively 118 patients on low dose aspirin, treated for gastric ulcer bleeding. Those who discontinued their therapy had a 6-fold increased risk of death or cardiovascular event in the first 6 months, a finding most prominent among patients with cardiovascular comorbidities. Patients who resumed aspirin therapy did so after a median interval of one week (33%) or immediately at discharge (67%). Rebleeding rates were too low in both groups and no statistical analysis is provided. [17]

In a similar but prospective trial, 156 patients with peptic ulcer bleeding taking low dose aspirin were randomly assigned to receive aspirin 80 mg/day or placebo immediately after successful endoscopic hemostasis for a period of 8 weeks. All participants were administered IV infusion of proton pump inhibitors followed by oral use. Recurrent hemorrhage occurred in 10.3% and 5.4% in treatment and control groups respectively, a difference statistically insignificant (hazard ratio 1.9, [CI, 0.6 to 6.0]), while the aspirin arm showed reduced all-cause mortality both at 30 days (hazard ratio, 0.2 [CI, 0.05 to 0.90]) and at 8 weeks (hazard ratio, 0.2 [CI, 0.06 to 0.60]). Of note, deaths due to GIB were recorded within the first 5 days after the index event, while mortality in the placebo group was distributed throughout the entire 8-week time span. [18]

In the Danish study, more than 4500 patients with atrial fibrillation on antithrombotics were included after a GI bleeding event and 3409 were followed up from day 90 for a median of two years. The antithrombotic drugs were restarted in 73% and 55% of them received one or two antiplatelet agents. All-cause mortality was lower in the group of participants who restarted one antiplatelet agent (hazard ratio 0.76, CI 0.68 to 0.86) compared with those not resuming therapy. Thromboembolism was also reduced in association with restart of one antiplatelet agent (hazard ratio 0.76, CI 0.61 to 0.95). Antiplatelet medication did not increase hemorrhagic complications. [19]

Kim et al also examined retrospectively 72 patients who suffered a GIB event, while on antiplatelet (80%) or anticoagulant agents. Forty patients stopped the

antithrombotic drugs and 32 resumed or never interrupted therapy. Mean follow up duration was 26 months. Thrombotic events were significantly more in the discontinuation group patients who had a history of ischemic heart disease or cerebral infarct (P=0.001) but not in those without (P=0.635). Recurrent bleeding was equally observed in both groups. Mortality differences were also insignificant (p=0.581) but the absolute number of deaths was too low. [20]

In a different setting, low dose aspirin withdrawal preoperatively in order to avoid hemorrhagic complications, has been associated with cardiovascular events and the time of occurrence is of particular interest since acute cerebral events happen at 14.3 ± 11.3 days, acute coronary syndromes at 8.5 ± 3.6 days and acute peripheral arterial syndromes at 25.8 ± 18.1 days after aspirin discontinuation. In the same metaanalysis uninterrupted aspirin therapy increased the frequency of bleeding complications 1.5 times, but it did not affect their severity in non- intracranial surgery. [21]

Anticoagulants and GI bleeding

Anticoagulant management in case of GIB has been somewhat more investigated. In the Danish study, 22% of the patients who resumed therapy received one anticoagulant and 11% received a combination of anticoagulant and one antiplatelet drug. All-cause mortality and thromboembolic events were significantly lower in both cohorts that continued therapy [HR 0.39 (0.34-0.46) and 0.41 (HR 0.32-0.52) respectively]. Major bleeding was higher in those receiving a single anticoagulant [HR 1.37 (1.06-1.77)], while it hardly missed statistical significance in the double therapy group [HR 1.44 (1.00-2.08)]. Recurrent GI bleeding did not differ between patients who resumed any therapy and those who did not. [19]

Lee et al studied retrospectively 58 patients on warfarin, admitted due to non-variceal upper GI bleeding, and compared them with controls taking aspirin as secondary prevention from ischemic heart disease. Mean follow up duration was 9 months. All participants received the standard medical and interventional or surgical therapy. Thirty-six subjects from the warfarin group (62%) ceased therapy and 6 of them suffered a thromboembolic event between the 21st and 75th day of follow up, significantly more compared with the aspirin group. Recurrent bleeding was also more frequent in patients on warfarin with the hemorrhages occurring within the first 14 days. [22]

In another retrospective study, 442 patients with GIB while on warfarin were followed up for 3 months. Therapy was resumed in 260 of them (58.8%) with a median interruption interval of 4 days and it resulted in lower risk for thrombosis (HR 0.05; 95% CI, 0.01-0.58) and death (HR, 0.31; 95% CI, 0.15-0.62), without significantly increasing the risk for recurrent GIB (HR, 1.32; 95% CI, 0.50-3.57), except for those restarting therapy within the first 7 days. Patients who did not interrupt warfarin for more than 14 days, exhibited no thrombosis. [23] Similar results were reported by Qureshi et al who examined the records of 1329 patients with atrial fibrillation on warfarin presenting with major GIB. Almost half of them restarted anticoagulant therapy (49%). Warfarin resumption was associated with lower risk of thromboembolism (HR 0.71, CI 0.54 to 0.93, p= 0.01) and mortality (HR 0.67, CI 0.56 to 0.81, p <0.0001) without affecting recurrent GIB (HR 1.18, CI 0.94 to 1.10, p=0.47). When the analysis included the time of restarting therapy in days post the index event, it was shown that resuming warfarin 7 days compared with 30 days after the hemorrhagic episode was related with a reduced mortality (HR 0.56, 0.33-0.98, p=0.04) and a trend towards reduced thromboembolism, with no difference in recurrent bleeding. [24]

In a different analysis according to $CHADS_2$ and HASBLED scores, the outcomes of relatively early (15-30 days) restart of anticoagulation were compared with a delayed one (after 30 days). The risk of stroke within 12 months was clearly smaller with earlier re-initiation group in all patients. Recurrent bleeding within three months was twice as high only in patients with a high HAS-BLED score (>3). [25]

Sengupta et al followed prospectively 197 patients with GIB while on anticoagulants. The drugs were discontinued at discharge in 39% of the subjects. Continuation of therapy was associated with decreased major thrombotic episodes within 90 days (HR 0.121, CI 0.006–0.812, P =0.03), while no significant difference was noted with regard to recurrent GIB (HR 2.17, CI 0.861–6.67, P =0.10) or death within the same follow up period (HR 0.632, CI 0.216–1.89, P =0.40). In this study, most participants were taking warfarin (74%), enoxaparin (8%) or unfractionated heparin (6%). Patients on novel oral anticoagulants were included but they represented a small percentage (13% in total). [26]

Table 1. $CHADS_2$ score and annual incidence of stroke

$CHADS_2$ score	Stroke rate (%/year)
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

Table 2. CHA_2DS_2VASc score and annual incidence of stroke

CHA_2DS_2VASc score	Stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Reaching a decision

It is rarely feasible to come to a safe conclusion on the absolute need and timing of antithrombotic therapy re-establishment after a bleeding episode. Each case should be individualized and potential risks should be taken into account. At first, the thrombotic and bleeding risk should be assessed. In patients on antiplatelet medication, clinical conditions constituting a high thrombotic risk include a recent acute coronary event (up to 12 months old), and recent coronary angioplasty and stenting (at least 1 month for bare metal and 6-12 months for drug-eluting stents). The risk is small when the drugs are used for primary prevention. [27] When dealing with atrial fibrillation and anticoagulation is needed, the risk can be stratified according to the $CHADS_2$ and CHA_2DS_2VASc scores as shown on Tables 1 and 2. [28,29] The thromboembolic risk in the presence of mechanical valves depends on both the technical aspects of the prosthesis and the comorbidities of the patient. A rough estimation is provided in Table 3. [5,27,30,31]

The bleeding risk is also a function of the patient's comorbidities and the clinical and laboratory status during the index GI hemorrhagic event. As far as the former parameters are concerned, several scoring systems have been developed to predict the chance of bleeding complications from vitamin K antagonists, but two of them are the most commonly used, the HAS-BLED and the ATRIA scores (Table 4). [32-34] With regard to the latter parameters, the most well-known score for predicting the possibility of recurrent hemorrhage is the Rockall score (Table 5). [35]

The balance between thrombotic and hemorrhagic risk will be the criterion for setting priorities. If bleeding risk is excessive and thrombotic events less likely, antithrombotics will be withheld for a longer period of time. If the thrombotic risk is high instead, the interruption has to be as short as possible. In the studies presented earlier, patients on antithrombotic medication admitted for GI hemorrhage, stopped or temporarily interrupted their drugs and were followed up for a period ranging from 8 weeks to 24 months. Drug interruption lasted between 4 and 30 days roughly. In most of the studies, discontinuation of therapy resulted in an excess of thrombotic episodes and increased mortality, without a significant reduction in bleeding recurrencies. It should be noted, that these results apply the most to patients who need antithrombotics for secondary cardiovascular prevention, or have atrial fibrillation with a clear indication for anticoagulation.

Table 3. Thrombotic risk stratification (for patients with indication for anticoagulants)

Risk	High (>10% / year)	Moderate (4-10% / year)	Low (≤4% / year)
Mechanical heart valve	MV prosthesis Caged-ball or tilting disc AoV prosthesis Recent (within 6 months) stroke or TIA	Bileaflet AoV prosthesis & ≥1 of following risk factors: AF, prior stroke or TIA, HTN, DM, CHF, age >75 y	Bileaflet aortic valve prosthesis without AF and no other risk factors for stroke
AF	$CHADS_2$ score 5-6 CHA_2DS_2VA Sc score 8-9	$CHADS_2$ score 3-4 CHA_2DS_2VASc score 5-7	$CHADS_2$ 0-2 CHA_2DS_2VAS 0-4

AF = atrial fibrillation; AoV = aortic valve; CHF = congestive heart failure; DM = diabetes mellitus; HTN = hypertension; MV = mitral valve; TIA = transient ischemic attack

Table 4. Scoring systems predicting bleeding risk in patients with AF receiving VKAs

HAS-BLED score		ATRIA score	
Clinical parameter	points	Clinical parameter	points
Hypertension	1	Anemia	3
Abnormal renal and liver function (1 point each)	1 or 2	Severe renal disease (GFR < 30 ml/min)	3
Stroke	1	Age >75 years	2
Bleeding	1	Prior hemorrhage diagnosis	1
Labile INRs	1	Hypertension	1
Elderly (e.g. age >65 years)	1		
Drugs or alcohol (1 point each) Drugs or alcohol (1 point each)	1 or 2		
0-1: low risk (<1.5%/year) 2: moderate risk (≈2%/year) ≥3: high risk (>4%/year)		0-3: low risk (<1%/year) 4: moderate risk (1-5%/year) 5-10: high risk (5-17%/year)	

It is also interesting that in most studies, thrombotic complications occurred constantly beyond the 10th day of drug interruption, while recurrent bleeding episodes were noted within the first 7-14 days. Moreover, when the results were analyzed according to the interruption interval, restarting warfarin at 7-21 days carried a mortality benefit, while earlier administration of the anticoagulant was associated with excess rate of rebleeding.[24] Furthermore, following discontinuation of aspirin, coronary syndromes, cerebrovascular and peripheral arterial events occured around the 8th, 14th and 26th day respectively.

Table 5. Estimation of recurrent GI bleeding rates (Rockall score)

Parameter	Score			
	0	1	2	3
Age	<60	60-79	>80	
Hemodynamic instability	No	SBP >100 mmHg HR>100 bpm	SBO <100 mmHg	
Comorbidity	No		Heart failure, Ischemic heart disease	Renal failure Liver failure Metastatic cancer
Diagnosis	Mallory -Weiss	All other diagnoses	GI malignancy	
Evidence of bleeding	None		Blood, adherent clot, spurting vessel	
Score ≤5: risk for recurrent bleeding ≤14.1% and risk of death ≤5.3%; score >5: risk of recurrent bleeding ≥24.1% and risk of death ≥10.8% [35,36]				

Thus, in ***conclusion***, after taking into account the thrombotic and bleeding risk of the individual patient and assess the power of the indication for certain antithrombotic medications, it appears prudent to withhold the drugs for the first 7-14 days to avoid recurrent hemorrhage and to re-institute therapy thereafter to benefit from the reduction in thromboembolism and possibly mortality. Needless to say, all patients should be offered appropriate medical treatment for the GI bleeding with proton pump inhibitors, *H. pylori* eradication, reversal of antithrombotic effect, endoscopic hemostasis and interventional or surgical therapy according to current guidelines. However, important knowledge gaps still exist in the literature. Restarting double antiplatelet or triple antithrombotic medication has not been tested, although it is used in a significant number of patients with coronary artery disease. Novel antiplatelets and anticoagulants have not been used in the relevant trials or they are represented in so small numbers that preclude any conclusions from being drawn. Moreover, the existing data are derived not exclusively, but mostly, from retrospective studies, which limit the value of these data. Hence, more research is needed on the subject, as imperative questions on everyday clinical problems still seek an answer.

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