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REVIEW

A review on increasing risk for gastrointestinal bleeding associated with dabigatran

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Abstract

Dabigatran, a reversible direct thrombin inhibitor, is widely used in clinical practice as a therapeutic option due to its unique mechanism of action in comparison to other anticoagulants. Although patients taking dabigatran experience a reduced risk of fatal bleeding, a higher risk of gastrointestinal bleeding (GIB) is associated with dabigatran, and its rational use between anticoagulation and bleeding is challenging for clinicians. To prevent GIB, it is imperative for clinicians to understand the pharmacological characteristics of dabigatran to ensure that its prescription should be avoided in patients with bleeding. In this review, we summarize the mechanism of action and pharmacokinetics of dabigatran and bleeding sites in the gastrointestinal tract in patients treated with dabigatran, as well as discuss the factors that increase the risk of dabigatran-induced GIB, including dose, age, drug interactions, race, genetics and past medical history. Finally, the treatment and prevention of GIB with dabigatran is also discussed. This review will help clinicians choose their drugs and doses more carefully for treating GIB.

Keywords

Dabigatran; Gastrointestinal bleeding; Risk factors; Treatment

1. Introduction

New oral anticoagulants (NOACs) include direct thrombin inhibitors (dabigatran) and coagulation Xa factor inhibitors (rivaroxaban, apixaban and edoxaban). NOACs have several advantages over vitamin K antagonists, including a more rapid onset/offset of pharmacodynamics, lower food/drug influence and predictable anticoagulant effects [1]. Dabigatran is an orally active direct thrombin inhibitor that was first approved for use in patients with nonvalvular atrial fibrillation by the Food and Drug Administration (FDA) in the United States [2]. Compared with the standard anticoagulant warfarin, various advantages, such as more predictable pharmacokinetics, an unnecessitated blood test, and a lower risk of fatal bleeding, have led to the rapid use of dabigatran in anticoagulant therapy [3]. Dabigatran is used to reduce the risk of stroke and transient ischemic attack in patients with nonvalvular atrial fibrillation, prevent recurrences of deep vein thrombosis and pulmonary embolus in patients who have been on parenteral anticoagulation for at least 5 years [4] and treat venous thrombosis following joint replacement surgery [5].

Gastrointestinal bleeding (GIB) is a frequent cause of hospital admission and contributes to hospital morbidity and mortality [6]. Anticoagulation therapy frequently needs to be interrupted because GIB is a severe complication in patients with nonvalvular atrial fibrillation. However, interruption of anticoagulation therapy results in an increased risk of thrombotic events or mortality from all causes [7]. Compared with vitamin K-dependent anticoagulants, the use of dabigatran is associated with a higher risk of GIB in clinical trials (hazard ratio (HR): 1.13, 95% confidence interval (CI): 1.00–1.28) based on a combined systematic review and meta-analysis evaluating bleeding safety [8, 9]. Additionally, high dosages of dabigatran increase the risk ratio of GIB compared to FXa inhibitors in NOACs [10]. Therefore, a balance between bleeding and anticoagulation while using dabigatran in clinical practice is required. Although some studies have confirmed that dabigatran increases the risk of GIB, no systematic review has examined the underlying reasons, which may be related to a majority of internal or external factors. The comparative risk of GIB with dabigatran is associated with different circumstances. Therefore, this review aims to analyze various conditions that induce a high GIB risk for dabigatran.

2. Mechanism of action of dabigatran

Dabigatran is an oral, reversible direct factor II inhibitor that inhibits liberated thrombin [11]. Oral dabigatran etexilate is a prodrug of the anticoagulant drug dabigatran. It functions as an anticoagulant by suppressing thrombin production through the conversion of serum esterase to activate dabigatran [12]. Dabigatran inhibits the action of thrombin by binding to three different domains on the protein, including the active site, exosite 1 and exosite 2. Specific site 1 (S1), proximal site

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2 (S2) and distal site 3 (D3) are active sites of thrombin. Specifically, the basic arginine residue at the substrate's P1 site is provided by aspartate (Asp) 189, located at the base of the S1 pocket. Ionic interactions between the basic functional site and Asp 189 in the S1 pocket allow dabigatran to bind to the active site of the thrombin molecule in a direct and specific way [13]. Dabigatran causes inactivation of thrombin in a dose- and concentration-dependent manner.

Dabigatran inhibits coagulation in three different ways, as shown in Fig. 1. First, dabigatran inhibits fibrinogen synthesis by interacting with thrombin to imitate a portion of the fibrin molecular structure [14]. Second, dabigatran inhibits the coagulation cascade by obstructing free thrombin and the activation of coagulation factors V, VIII, XI and XIII by thrombin. Further, some active thrombin, which functions as a hemostatic agent, is also retained due to the partial preservation of tissue factor-induced thrombin synthesis [15]. Finally, dabigatran blocks thrombin activation of protease-activated receptor-1 (PAR-1) to indirectly reduce platelet activation. In addition, dabigatran directly suppresses the expression of P-selectin (CD62P) in the membranes of platelets, which in turn limits platelet activation [16]. Therefore, dabigatran has the potential to be used as both an antithrombotic and antiplatelet drug.

3. Pharmacokinetics of dabigatran and its relationship with GIB

3.1 Absorption

Dabigatran has only 6.5% bioavailability due to the degree of polarization. Hence, dabigatran etexilate, a predrug of dabigatran, has been developed as an orally active anticoagulant to increase bioavailability. Dabigatran is most effectively utilized after being ingested as its inactive precursor, dabigatran etexilate and then rapidly absorbed and hydrolyzed by esterase in the colon, liver and plasma. The plasma concentration of dabigatran reaches its maximum measured concentration at a median time of 1.5–3 h in a dose-dependent manner [17]. In the past, dabigatran etexilate was packaged in capsules with tartrate pellets, which provide an acidic environment as dabigatran distribution and absorption depend on the pH of gastric acid [18]. However, the tartaric acid that is present in dabigatran etexilate may result in bleeding in the gut. This could be related to the fact that tartaric acid granules create an acidic environment in the GI tract, and a lower pH may lead to adverse outcomes in the GI tract, such as GI distress and bleeding. Dabigatran has lower bioavailability and incomplete absorption than warfarin, which may be related to an increased risk of bleeding in the GI tract. GIB could also occur due to pre-existing lesions in the mucosa, such as vascular dysplasia and erosions [19]. According to a previous study, patients treated with dabigatran experienced less life-threatening bleeding than those treated with warfarin. However, a higher risk of GIB was observed among patients consuming dabigatran [20].

3.2 Distribution

The volume of distribution of dabigatran is 60–70 L, which is approximately 0.9–1.0 L/kg, which represents a medium tissue distribution. The drug is almost exclusively extracellular, and approximately 65% of the floating drug is discovered in the plasma [21]. This high extracellular concentration makes it easy to fall to less than 30% of their peak levels in 4–6 h

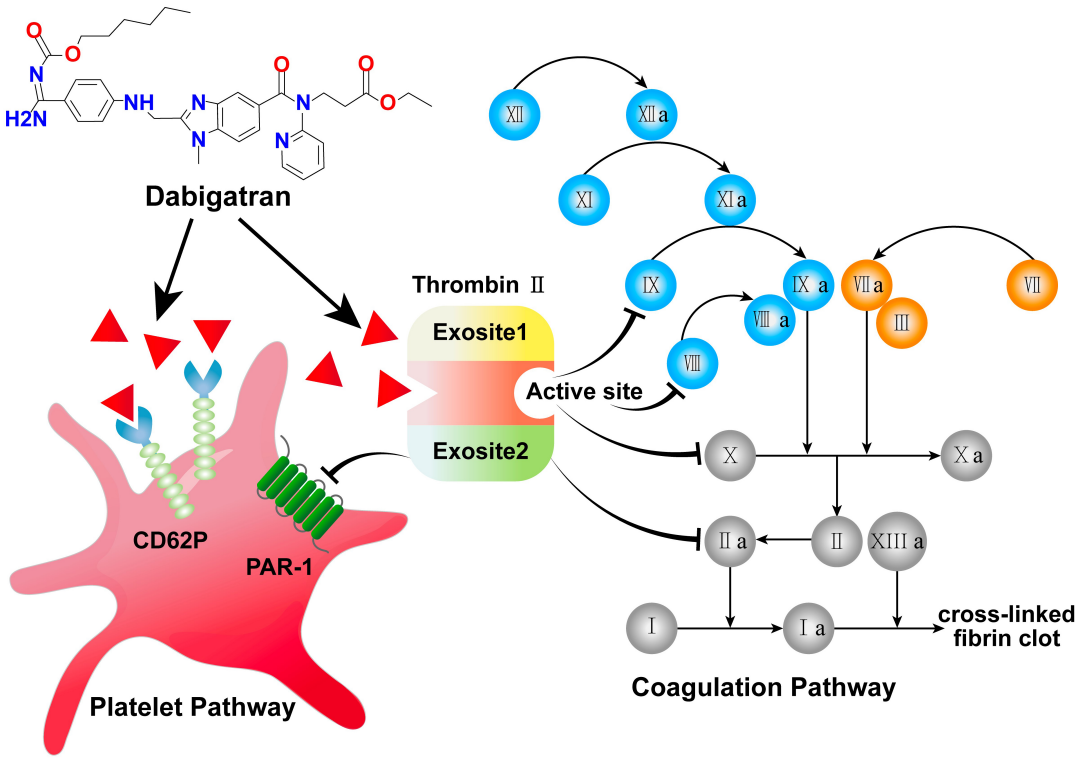

FIGURE 1. Detailed visual description of the coagulation cascade and the sites blocked either directly or indirectly by platelet activation.

[22]. Only 35% of protein bound to dabigatran allows it to be effectively cleared by dialysis [23].

3.3 Excretion

Approximately 80–85% of dabigatran is eliminated *via* glomerular filtration, and the remaining 5–7% is eliminated *via* tubular secretion and absorption [24]. The biliary system only excretes a modest percentage (15–20%), and the urine primarily comprises unmodified dabigatran and trace levels of dabigatran glycosylate [25]. Whereas, the feces contain negligible amounts of dabigatran [26]. Therefore, patients with progressive renal dysfunction are more likely to be exposed to the anticoagulant effects of the medicine and more likely to experience GIB. The half-life of dabigatran in healthy persons is between 12 and 17 h; however, in patients with substantially compromised renal function (creatinine clearance, 30 mL/min), this increases to an average of 27 h. If the predose is not altered, renal dysfunction could lead to increased dabigatran area under the time-concentration curve (AUC) and maximum plasma concentration (C max) by approximately 6- and 2-fold, respectively [27]. Oral administration of dabigatran etexilate is approximately 2.7- and 6-fold higher in patients with moderate renal insufficiency (creatinine clearance of 30–50 mL/min) and severe renal insufficiency (creatinine clearance of 10–30 mL/min), respectively, compared with the patients who do not have renal insufficiency [28]. Another study revealed that the AUC of dabigatran was increased by 1.5, 3.1 and 6.3 times in patients with mild, moderate and severe renal injury, respectively, compared with healthy patients. In addition, the half-life was extended to 15, 18 and 27 h [23].

It is not entirely apparent why dabigatran raises the risk of GIB. However, there are three possible explanations for this phenomenon. First, oral dabigatran is less consumed and is not yet fully absorbed by the gastric mucosa. Consequently, its effect is confined mainly to the superficial tissue of the gastric mucosa. Second, tartaric acid can directly irritate the digestive tract, and the vascular lesions are particularly prone to be influenced by tartaric acid. Third, approximately 80–85% of dabigatran is excreted by the kidneys *via* glomerular filtration. Therefore, loss of renal function results in a continual rise in blood levels of dabigatran, leading to an increase in GIB risk. In conclusion, pharmacokinetics is the primary factor responsible for dabigatran's adverse effects. Clinicians should prescribe dabigatran considering its pharmacokinetics, and pharmacokinetic interactions should be identified to help control the patient's clinical GIB. In addition, long-term research to investigate the pharmacokinetics of dabigatran and its relationship with GIB is required.

4. Different risks of upper or lower GIB caused by dabigatran

GIB in many patients has been reported to be associated with dabigatran, but only a few studies have described the sites of GIB. The findings of a propensity score-matched cohort study reported that treatment with dabigatran is associated with a higher risk of bleeding in the lower GI tract, compared with warfarin [29]. An observational study including 417 patients (208 dabigatran *vs.* 209 warfarin) in Korea demonstrated that the lower GI tract was the most common site of GIB in the dabigatran group compared with the warfarin group (80.0% *vs.* 38.1%, $p = 0.014$), and notably, a history of previous GIB was another risk factor for GIB in the dabigatran group ($p = 0.036$, odds ratio (OR) = 6.3) [30]. Dabigatran is associated with an increased risk of colonic bleeding in patients with membranous atrial fibrillation compared with warfarin, particularly in patients with vascular dysplasia [31]. Another meta-analysis showed that dabigatran use was associated with a significantly lower risk of upper GIB (OR: 0.742, 95% CI: 0.569–0.968) but not lower GIB (OR: 1.208, 95% CI: 0.902–1.619) compared to warfarin, suggesting that dabigatran is more likely to cause lower GIB [32]. In addition, a retrospective review of medical records reported 44 bleeding events (27% of which were severe) in patients treated with dabigatran during the first 2 months after drug release in Australia and New Zealand. Rectal bleeding is the most common bleeding complication of dabigatran treatment, and a higher risk of bleeding is associated with an underlying history of rectal, colonic or diverticular bleeding [33].

Conversely, several studies have demonstrated that dabigatran increases the probability of upper GIB. Further, patients treated with dabigatran have a relatively high risk of mild and life-threatening GIB, and long-term dabigatran treatment significantly increases the risk of upper GIB [34]. Abraham *et al*. [35] showed more upper GIB events with dabigatran in atrial fibrillation (AF) and non-AF sub-cohorts (1.42 *vs.* 0.86; 2.73 *vs.* 1.37) compared with lower GIB events. Another study reported a higher risk of upper GIB caused by dabigatran than lower GIB in the Hong Kong population in patients with a history of peptic ulcer or GIB [36]. The study by Maruyama conducted at a single Japanese institution reported GIB events in 658 patients taking dabigatran, rivaroxaban or apixaban between April 2011 and November 2015. Their results suggest that upper GIB tends to be more severe than lower GIB. In addition, the study also suggested that the incidence of upper GIB was significantly associated with previous GI ulceration, nonuse of proton pump inhibitors (PPIs), and concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and dual antiplatelet agents. Therefore, previous GIB is a significant risk factor for upper GIB [37].

Although dabigatran medication increases the risk of GIB, the evidence was inconclusive when we specifically examined the risk of upper and lower GIB. The location of GIB in patients might vary substantially due to the individual variances and variability among patients consuming dabigatran. In general, there is significant evidence for the increased risk of lower GI risk associated with dabigatran as well as a higher incidence of adverse events related to colonic hemorrhage. Anti-inflammatory and antiplatelet drugs, as well as a previous history of GIB, have been linked to an increased prevalence of lower digestive tract bleeding. Peptic ulcers are frequently associated with an increased risk of bleeding in the upper GI tract. Although studies have compared the risk of bleeding in the upper and lower tracts, a slight gap in research on the specific sites of GIB still remains. However, further research in this area to guide clinical practice in targeting different sites of

bleeding and administering appropriate measures is required.

5. The risk of GIB increases with increasing age and doses of dabigatran

There are several factors that can influence the occurrence of GIB, particularly the impact of age and dose. In a systematic review analysis, the incidence of GIB was shown to be 23% higher with dabigatran compared with warfarin, and the researchers concluded that the elevated risk of GIB owing to dabigatran may be age-driven, particularly in older patients [38]. Due to the lack of evidence for the efficacy of dabigatran in older patients (>75 years), Avgil-Tsadok conducted a population-based study in Quebec (1999–2013) using an administrative database to assess the efficacy and safety of dabigatran in clinical practice in older patients to determine whether dabigatran was effective and safe for older patients. For determining the occurrence of strokes and bleeding events, users of dabigatran (110/150 mg) were compared with users of warfarin (matching doses). Compared to warfarin, the use of dabigatran was linked with a higher risk of GIB (HR: 1.30, 95% CI: 1.14–1.50) [39]. In addition, Graham *et al*. [40] in a cohort study including older Medicare beneficiaries with nonvalvular atrial fibrillation reported that 150 mg of dabigatran was associated with an increased risk of GIB compared with warfarin in older patients and that the increased risk of major GIB with dabigatran appeared to be limited to women and men aged ≥75 and ≥85 years, respectively. Further, the risk of GIB increases with age; patients at age 76 with atrial fibrillation taking dabigatran (HR: 2.49, 95% CI: 1.61–3.83) and patients with and without atrial fibrillation taking rivaroxaban (HR: 2.91, 95% CI: 1.65–4.81) have a higher risk of GIB than those taking warfarin [35].

In addition, various studies have revealed that an increased risk of GIB is associated with dabigatran in a dose-dependent manner. For instance, in a clinical trial, the use of dabigatran 110 mg (also known as D110) versus 150 mg (also known as D150) was prospectively examined in an experimental population that included both Vitamin K antagonist (VKA) users and nonusers. According to this finding, the risk of GIB was significantly higher in patients treated with D150 than in those treated with warfarin [41]. A higher percentage of patients experienced GIB at high dabigatran dosage (1.4% for dabigatran 110 mg and 9.9% for dabigatran 150 mg) in another prospective cohort study. Compared to the groups receiving dabigatran 150 mg and warfarin, those receiving dabigatran 110 mg had a considerably reduced rate of GIB and a significantly lower relative risk of GIB (p = 0.002 and p = 0.001, respectively) [42]. In another meta-analysis, dabigatran was associated with somewhat greater risk of GIB compared with warfarin; however, therapy with rivaroxaban and warfarin showed no significant difference in the risk of GIB. In patients with a considerably increased risk of GIB, the findings demonstrate that dabigatran had a dose-dependent impact beginning at 150 mg (risk ratio (RR): 1.51, 95% CI: 1.34–1.70) but not in patients taking 75 or 110 mg [43]. According to a cohort study of Medicare beneficiaries over the age of 65 with nonvalvular atrial fibrillation, dabigatran was also associated with an increased risk of GIB in patients receiving 150 mg of dabigatran twice daily. However, the relationship between 75 mg of dabigatran twice daily and GIB was not significantly different from that of warfarin [40].

Although age and dose have been associated with increased GIB due to dabigatran, the majority of the research has various limitations that prevent researchers from completely ruling out the possibility of these interactions in their analyses due to flaws in the methodology used to collect the large data sets. The most likely explanation for this discrepancy is that the inclusion criteria used for each set of data are slightly different [44]. Moreover, most observational studies also failed to account for the use of over-the-counter aspirin, which could skew the results if there were a difference in aspirin use rates between patients taking dabigatran and warfarin. In addition, the use of PPIs can similarly impact the results of the dabigatran group. For example, a retrospective analysis of 5041 patients indicated that concomitant dabigatran-PPI treatment significantly reduced GIB risk compared with dabigatran without a PPI [45]. Ray *et al*. [46] also revealed that the risk of upper GI tract bleeding hospitalizations (n = 2245) was lower overall (incidence rate ratios (IRR): 0.66, 95% CI: 0.62–0.69) and for dabigatran (IRR: 0.49, 95% CI: 0.41–0.59) (risk difference (RD): −61.1, 95% CI: −74.8–−47.4) when patients were treated with PPI co-therapy compared with treatment without PPI co-therapy. Interestingly, the increase in gastric pH induced by PPI may affect the solubility and absorption of dabigatran [47]. Therefore, a dispute about PPI's association with dabigatran remains unresolved.

6. The risk of GIB increases due to the interaction of dabigatran with other drugs

When compared to other anticoagulants, dabigatran has a low bioavailability of 6.5, which leads to a significant difference in its absorption in the gastrointestinal (GI) tract. Furthermore, the combination of multiple treatments can cause significant drug–drug interactions by affecting the exposure or pharmacological activity of direct oral anticoagulants (DOACs) [48]. Dabigatran is the active component of dabigatran etexilate, which is first absorbed in its ester form before being hydrolyzed to produce dabigatran. Dabigatran etexilate is a substrate of the efflux transport protein P-gp. Hence, dabigatran can interact with powerful inducers or inhibitors of glycoprotein (P-gp) substrates, including P-gp inhibitors (including amiodarone, verapamil, clarithromycin, itraconazole, ketoconazole, nelfinavir and quinidine) and P-gp inducers (including rifampin, St. John's wort and carbamazepine). The concurrent use of potent P-gp inhibitors, such as systemic ketoconazole with cyclosporine or dronedarone, is not only discouraged but also outright forbidden.

6.1 Anti-hypertensive drugs

In a cohort study of patients without a history of kidney disease receiving DOACs, overall GIB rates were higher with dabigatran combined with verapamil or diltiazem compared with amlodipine (or metoprolol) combined with dabigatran

(244.9 *vs.* 158.4 per 1000 person-years; adjusted hazard ratio (AHR) for total GIB: 2.16; 95% CI: 1.30–3.60) [49].

6.2 Anti-arrhythmic drugs

Dronedarone, a Vaughn-Williams class I–IV anti-arrhythmic drug, is a strong inhibitor of P-gp and a moderate inhibitor of CYP3A4 [50]. A retrospective cohort study found an increased risk of GIB when dronedarone and dabigatran were used together compared with dabigatran alone (AHR for GIB: 1.40, 95% CI: 1.01–1.93, $p = 0.04$). However, there was no overall change in the risk of bleeding [51]. The pharmacological effects of dabigatran in conjunction with amiodarone have also been investigated. Patients treated with amiodarone combined with NOAC had a higher risk of severe bleeding than those treated with dabigatran alone; however, GIB was not specifically addressed in this retrospective study of 91,330 patients with atrial fibrillation in Taiwan [52].

6.3 Antidepressants

Retrospective cohort studies on patients with atrial fibrillation revealed the combined use of DOACs and selective serotonin reuptake inhibitors (SSRIs). Further, the use of bupropion was associated with an elevated risk of bleeding in the digestive tract in patients with atrial fibrillation treated with dabigatran [53].

6.4 Lipid-regulating drugs

Patients diagnosed with atrial fibrillation are frequently prescribed lipid-modifying medications since coronary heart disease (CHD) is highly prevalent in the general population. In a case-control study, Antoniou *et al*. [54] found that simvastatin and lovastatin, when given as endostatin, were nearly 10 times more potent as P-gp inhibitors than hydroxy when compared with dabigatran alone. They also found that patients treated with dabigatran and simvastatin or lovastatin had a higher risk of major bleeding.

6.5 Antibiotics

The widespread use of antibiotics has drawn attention towards the effect associated with the use of dabigatran. A retrospective population-based cohort study was conducted in older adults (age: 77.6 $\pm$ 7.2 years) taking dabigatran in combination with clarithromycin or azithromycin. The Cox proportional risk regression analysis that evaluated the relationship between bleeding and antibiotic use (clarithromycin versus azithromycin) revealed that higher rates of bleeding were associated with the combined use of dabigatran in a large number of patients in advanced age (>66 years) compared with the period of clarithromycin alone. However, GIB alone was not evaluated [55].

Notably, these studies suffer from a number of limitations. First, the difficulties in collecting clinical cases result in the lack of published research investigating dabigatran's interactions with other drugs. Second, many studies do not include information on indicators of renal function, smoking, over-the-counter use of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, and adequacy of blood pressure and diabetes control to exclude errors introduced by the patient's own disease and other medications. Therefore, inherent errors in the statistical analyses cannot be avoided.

7. The risk of GIB increases with other factors

Race is another factor that contributes to an increased risk of GI hemorrhage in patients taking dabigatran. One study found that patients treated with dabigatran in China had a higher risk of GIB (4.2 cases per 100 people) compared to 1.2 cases per 100 people per year in Denmark and 0.6–3.4 cases per 100 people per year in the United States, with lower rates of GIB in Western populations. This can be attributable to genetic differences in the blood clotting rate between Asians and non-Asians [36].

Dabigatran is a prodrug that can be taken orally and is converted to its intermediate metabolite, ethyl dabigatran, through early metabolism by intestinal carboxylesterase (CES)2. The hepatic CES1 enzyme is responsible for the subsequent conversion of ethyl dabigatran to its active form, dabigatran. Adenosine triphosphate (ATP)-binding cassette subfamily B member 1 (ABCB1) is a gene that encodes P-gp, an ATP-dependent drug efflux transport protein that affects the bioavailability of dabigatran etexilate [56]. Moreover, the CES1 and ABCB1 genes play critical roles in dabigatran etexilate metabolism [57]. The CES1 (single nucleotide polymorphism) SNP rs2244613 is associated with a decreased risk of major bleeding (OR: 0.66; 95% CI: 0.43–1.01) and a lower risk of any bleeding in dabigatran-treated patients (OR: 0.67; 95% CI: 0.55–0.82) [58]. A study has confirmed that the CES1 SNP rs8192935 may play an essential role in modulating dabigatran concentrations in a sample of real-world patients with anticoagulation in two Italian outpatient clinics [59]. However, reports on genes associated with GIB are unavailable. Nonetheless, the effect of genes on blood concentration may be one of the factors contributing to the risk of GIB.

8. Prevention and treatment of GIB caused by dabigatran

To prevent GIB while using dabigatran, medical practitioners need to be aware of the risk factors for GIB, risk assessment and reactions to varying degrees of GIB. A summary of the measures that can be taken to prevent and treat GIB associated with dabigatran is presented in Fig. 2. Mostly, the same fundamental rules that are used in the management of any bleeding event are applied for the primary emergency management of bleeding that occurs due to dabigatran. However, there are some peculiarities in the pharmacology of dabigatran that should be noted and applied to the clinical course of treatment. Distinct degrees of GIB require the application of a different spectrum of therapeutic methods. These parameters are mostly outlined in the 2021 practical guidelines for the use of nonvitamin K antagonist oral anticoagulants in patients with atrial fibrillation that were published by the European Heart Rhythm Association [4].

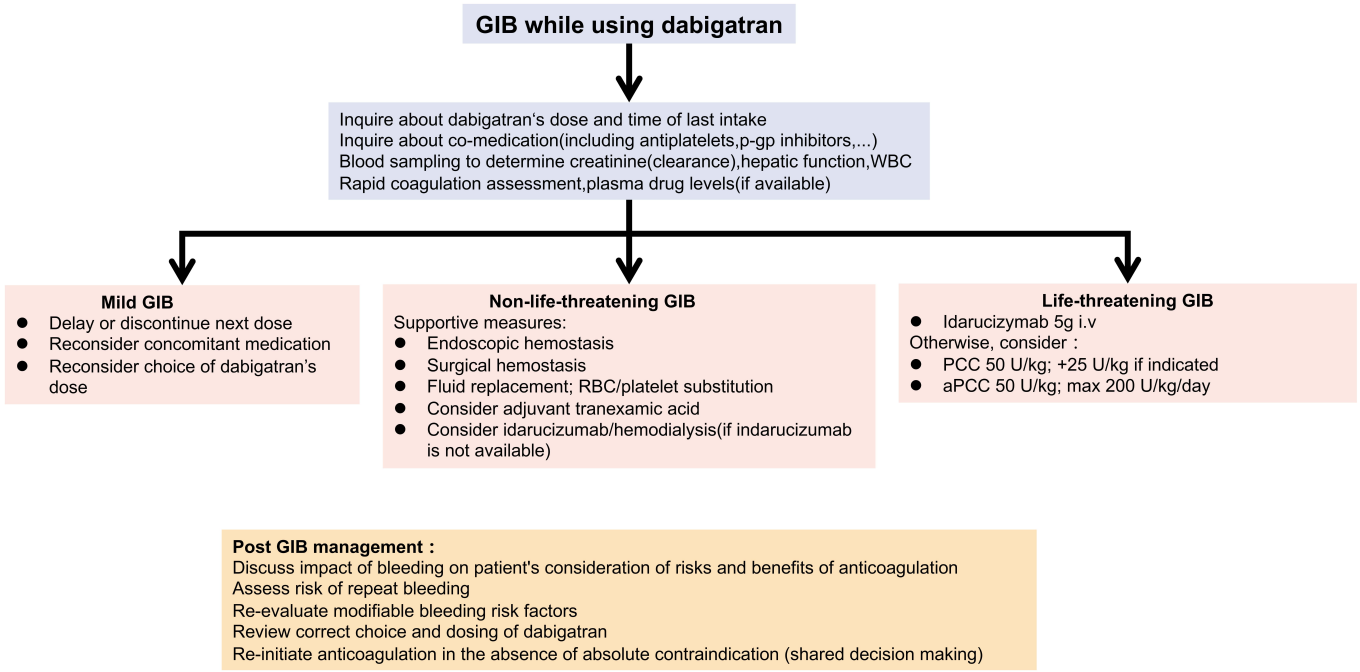

FIGURE 2. Management of gastrointestinal bleeding in patients taking dabigatran. GIB: gastrointestinal bleeding; RBC: red blood cell; WBC: white blood cell; PCC: prothrombin complex concentrate.

8.1 Mild bleeding

Dabigatran has a relatively short half-life compared with warfarin. The blood's ability to clot quickly returns to normal within 2–24 h when treatment with dabigatran is stopped. Coagulation is nearly totally restored in patients who have normal renal function after five half-lives of the drug [60]. Therefore, it is usually possible to control mild occurrences of bleeding by discontinuing the medicine in question or by undergoing endoscopic therapy [61, 62]. The severity of GIB and the patient's hemodynamic status should both be considered when deciding when to perform an endoscopy. Endoscopy can be performed after 12–24 h in patients who do not have severe GIB [63]. The advantages of this delayed approach are the increased effectiveness of endoscopic interventions as the effect of the drug diminishes, improved safety in non-emergency situations, and improved endoscopic visualization due to reduced/stopped bleeding and better colonic cleansing. In contrast, in patients with severe GIB or unstable hemodynamics, emergency endoscopy should be carried out as soon as possible following resuscitation [64]. When repeated endoscopic treatments are unsuccessful, the next course of action could be radiological or surgical intervention.

8.2 Severe life-threatening bleeding

Notably, if the bleeding is severe, activated charcoal, hemodialysis, hemoperfusion and the use of prothrombin complex concentrate may be considered. Activated charcoal can be administered to patients to lessen the intestinal absorption of residual medicine if the last dose of dabigatran is administered within 2 h [65]. However, this possible benefit needs to be evaluated against the damage that endoscopic visualization can subsequently cause. In cases of life-threatening GIB or renal failure, the removal of dabigatran may also be considered *via* hemodialysis or hemoperfusion [66]. Idarucizumab is an antibody fragment that has been humanized and specifically binds to dabigatran. In October 2015, the Food and Drug Administration approved the use of idarucizumab, a drug that can specifically reverse the effects of dabigatran [67]. In December 2015, the European Medicines Agency further approved its use in emergency surgery, emergency treatments or bleeding that is life-threatening or uncontrollable in patients. In the Reversal of Idarucizumab in Patients with Active Dabigatran (RE-VERSE-AD) study, idarucizumab was successfully used in patients with dabigatran hemorrhage or life-threatening bleeding or who required emergency surgery. Idarucizumab completely reversed the anticoagulant activity of dabigatran within minutes in almost all patients and is therefore considered a first-line treatment in such cases [68]. If idarucizumab is not accessible, dialysis is other option for clearing circulating dabigatran. However, initiating and continuing dialysis could be difficult in patients experiencing severe life-threatening conditions. Therefore, dialysis is only suggested in situations where idarucizumab is not easily accessible.

9. Prospect

The most common adverse effect of dabigatran is GIB. Patients suffering from uncontrollable GIB have a risk of losing their lives. The clinician's treatment plan and drug adjustments are based on the location of the GIB, the presence of comorbidities, and the interactions between different drugs. However, we discovered that the research on the relationship between the aforementioned factors and dabigatran-affected GIB is still relatively lacking, and future studies may enrich results in this area to better direct clinical practice. In addition, we believe that more cohort studies employing different statistical

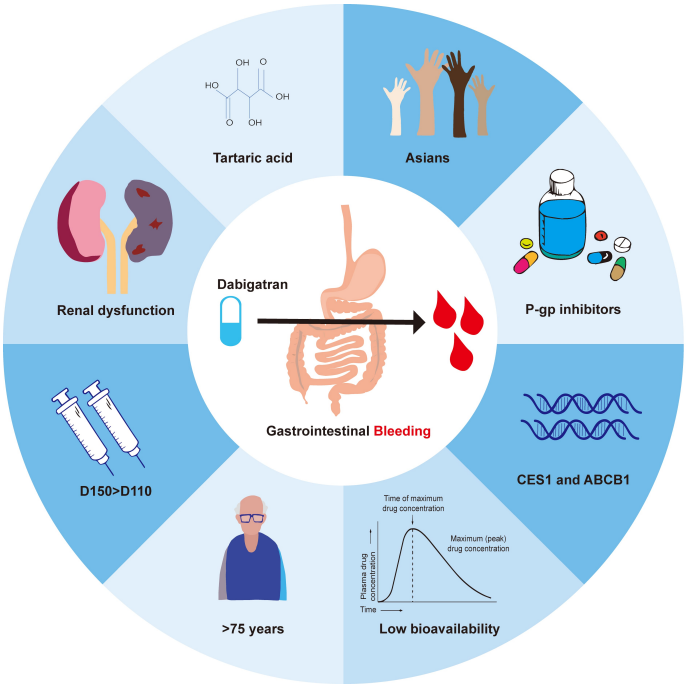

FIGURE 3. Factors that increase the risk of dabigatran-induced gastrointestinal bleeding. Various factors can increase dabigatran-induced GIB, such as tartaric acid, renal dysfunction, age, dose, drug-drug interactions, race, genetics and low bioavailability. CES1: carboxylesterase 1; ABCB1: Adenosine triphosphate-binding cassette subfamily B member 1.

methods to avoid errors and draw more accurate conclusions are required, as the majority of the studies are retrospective, which have inherent drawbacks and unavoidable confounding factors and used different criteria for determining the degree of bleeding. In this review we have discussed the risk factors that could result in GIB due to dabigatran. We believe that this review will help clinicians choose their drugs and doses more carefully during the treatment.

10. Conclusion

Dabigatran, a more recent oral anticoagulant, is thought to be more advantageous for patients who require anticoagulant therapy because of its rapid onset and elimination, definite clinical efficacy, predictable anticoagulant effect and absence of routine coagulation monitoring. However, various factors, including anticoagulation mechanism, pharmacokinetics of dabigatran, age, dose, drug–drug interactions, race and gene are associated with increased risk of GIB (Fig. 3). Patient-specific analysis using dabigatran may help to find a balance between bleeding and anticoagulation.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YWJ—concept, design, supervision, funding, critical review; QSN, GY and PL—data collection and/or processing; QSN and PL—Analysis and/or interpretation, writing; PL and GY—Literature search.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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