Dabigatran must be used carefully: literature review and recommendations for management of adverse events

Abstract: Atrial fibrillation increases the risk of stroke and death. The vitamin-K antagonist warfarin is recommended for patients with atrial fibrillation, but vitamin-K antagonists are cumbersome to use. Therefore, an effective, safe and convenient new anticoagulant is needed. Dabigatran acts by inhibiting free and fibrin-bound thrombin directly. It is an oral anticoagulant that was approved by the US Food and Drug Administration. The oral anticoagulant dabigatran has been used increasingly due to its good tolerance, predictable pharmacokinetics, effective anticoagulant effects, and absence of requirement of coagulation monitoring. However, an increasing prevalence of adverse events has been reported, some of them quite serious. Therefore, we searched and reviewed the literature on dabigatran with regard to adverse events, and proposed solutions to prevent and reduce the chance of adverse events occurring.

Keywords: adverse events, dabigatran, allergic reactions, bleeding, esophageal injury

Introduction
Atrial fibrillation increases the risk of stroke and death. The vitamin-K antagonist warfarin is recommended for patients with atrial fibrillation and who are at risk of stroke, which reduces the risk of stroke and death, but increases the risk of bleeding. Vitamin-K antagonists are cumbersome to use due to: interactions with multiple foods and drugs; a narrow therapeutic range; significant changes in anticoagulant response; a slow onset of action; requirement of frequent testing of laboratory parameters. Patients who receive warfarin have poor compliance and a high prevalence of treatment withdrawal due to the factors mentioned above, so many patients do not receive adequate anticoagulant therapy. Therefore, an effective, safe and convenient new anticoagulant is needed.

Dabigatran acts by inhibiting free and fibrin-bound thrombin directly. It is an oral anticoagulant that was approved by the US Food and Drug Administration in 2010 to prevent embolic events in patients with non-valvular atrial fibrillation. Dabigatran has been used increasingly in clinical practice due to its good tolerance, predictable pharmacokinetics, effective anticoagulant effects, and absence of need of coagulation monitoring. Dabigatran is used as an alternative to warfarin, and it appears to be as effective as warfarin in preventing embolic events in patients with non-hemorrhagic stroke and atrial fibrillation rather than in patients with valve problems.
Despite the many advantages of dabigatran, reports of adverse events have emerged in recent years, such as gastrointestinal discomfort and bleeding. Although patients taking dabigatran have fewer life-threatening hemorrhages, the prevalence of gastrointestinal bleeding was significantly higher than in those who used warfarin. An increasing prevalence of adverse events has been reported, some of them quite serious. Therefore, we searched and reviewed the literature on dabigatran with regard to adverse events (Figure 1).

We searched PubMed, Google scholar and the Chinese National Knowledge Infrastructure using the key words “dabigatran and adverse events”, “dabigatran and side effects” and “dabigatran and induced” from December 2010 to November 2018. Case reports were selected on the adverse events of dabigatran that they described. Twenty-three case reports were reviewed and analyzed, and the clinical features are listed in Table 1.

Adverse events of dabigatran

Bleeding

As with any anticoagulant drug, various types of hemorrhage are common adverse events. Of the cases we reviewed, seven patients developed severe hemorrhage, including three cases of fatal gastrointestinal hemorrhage. Major bleeding was reported to occur in a dose-dependent manner, and this was reported in fewer than 3% of patients during a trial comparing dabigatran with other anticoagulants. Similarly, Connolly et al reported that the prevalence of major bleeding was 2.71% per year in the group receiving dabigatran (110 mg, b.d.) and 3.11% per year in the group receiving dabigatran (150 mg, b.d.), and that the prevalence of life-threatening bleeding in those receiving 110 and 150 mg of dabigatran twice-daily was 1.22% and 1.45%, respectively.

The three patients who died of gastrointestinal bleeding caused by dabigatran were old (mean age=81 years). One of them took only 150 mg of dabigatran once-daily, but this may have been related to the hip arthroplasty that she underwent. These gastrointestinal events may have been due to the dabigatran formulation, which contains granules of tartaric acid to provide an acidic environment. A lower pH is associated with dyspepsia and plays a part in the increased risk of gastrointestinal bleeding. Spontaneous hemopericardium, spontaneous hemothorax and hemorrhagic cystitis occurred separately in three patients. Major bleeding in these anatomic areas is uncommon and has rarely been reported, but it should be documented. Other risk factors of dabigatran-induced gastrointestinal bleeding include concurrent use of ulcerogenic drugs, older age, Helicobacter pylori infection, and previous history of gastrointestinal bleeding. Helicobacter pylori infection and use of NSAIDs are independent risk factors for duodenal ulcer and gastric ulcer and related bleeding. Therefore, we should prevent the combined hemorrhagic effect of dabigatran and Helicobacter pylori, and the patient should be screened for Helicobacter pylori before anticoagulant therapy. In general, these findings also show that the risk of venous thromboembolism and bleeding should be considered before deciding the anticoagulation given to the patient.

Esophagitis or esophageal injury

Another adverse event that requires attention is esophagitis or esophageal injury (including esophageal ulcers) induced by dabigatran intake. In 1983, it was estimated that the esophageal injury caused by drugs was only 3.9 cases per 100,000 people per year. In 2016, Toya et al reported that dabigatran use caused ~20% of patients to suffer damage to the esophageal mucosa. However, among
### Table 1 Clinical features of dabigatran-induced adverse events

| Ref. | Author      | Age | Country | Gender | Dosage                  | Adverse events | Main symptoms                                                                 | Treatment                                      | Outcomes |
|------|-------------|-----|---------|--------|-------------------------|----------------|-------------------------------------------------------------------------------|-----------------------------------------------|----------|
| 5    | Jelani Q et al. | 87  | United States | Male   | 150 mg, twice daily    | Spontaneous hemopericardium | Dyspnea on exertion               | Dabigatran discontinued; Pericardiocentesis; Idarucizumab | Improved |
| 6    | Huang J et al. | 83  | China    | Male   | 110 mg, twice daily    | Spontaneous hemotherorax   | Chest pain and dyspnea            | Dabigatran discontinued; Thoracocentesis    | Improved |
| 7    | Otteno H et al. | 82  | United States | Female | Unknown                | Hemorrhagic cystitis       | Pelvic pain, dysuria, frequency, and urgency | Warfarin replaces dabigatran                 | Improved |
| 8    | Carter A et al. | 79  | United Kingdom | Female | 150 mg, once daily    | Gastrointestinal haemorrhage | Abdominal pain and hypotensive shock | Resuscitation                               | Death    |
| 9    | Dumkow LE et al. | 85  | United States | Male   | 150 mg, twice daily   | Gastrointestinal bleeding | Malaise and difficulty breathing  | PCC and FFP                                 | Death    |
| 10   | Cano EL et al.  | 78  | United States | Male   | 150 mg, twice daily   | Fatal Hemorrhage            | Hematochezia, nausea, vomiting, and diarrhea | PRBC, Platelet and PCC                      | Death    |
| 11   | Wychowski MK et al. | 66  | United States | Female | 150 mg, twice daily | Gastrointestinal bleeding | Altered mental status             | PRBC and PCC                                 | Improved |
| 12   | Matsuura H et al. | 84  | Japan    | Male   | Unknown                | Esophagitis                | Progressive dysphagia and odynophagia | Apixaban replaces dabigatran; PPI            | Improved |
| 13   | Fujikawa K et al. | 87  | Japan    | Male   | 220 mg, once daily    | Esophageal injury           | Heartburn and dysphagia           | Apixaban replaces dabigatran; Fasting       | Improved |
| 14   | Yoshimitsu M et al. | 78  | Japan    | Female | Unknown                | Exfoliative esophagitis    | Epigastralgia                     | Drink a sufficient of water; Maintain an upright position | Improved |
| 15   | Shibagaki K et al. | 75  | Japan    | Male   | 110 mg, twice daily   | Esophageal mucosal injury  | None                            | Warfarin replaces dabigatran               | Improved |
| 16   | Izumikawa K et al. | 67  | Japan    | Male   | 150 mg, twice daily   | Esophageal ulcer            | Heartburn                        | Drink a sufficient of water; Maintain an upright position | Improved |
|      |              | 81  | Japan    | Female | 110 mg, twice daily   | Esophageal ulcer            | Chest pain and upper abdominal pain. | Drink a sufficient of water; Maintain an upright position | Improved |
| 17   | Zimmer V et al.  | 90  | Germany  | Female | Unknown                | Exfoliative esophagitis    | Chest pain and odynophagia       | Dabigatran discontinued; PPI                | Improved |
| 18   | Ootani A et al.  | 70  | Japan    | Male   | 110 mg, twice daily   | Esophagitis                 | Retrosternal pain and dysphagia   | Dabigatran discontinued; Rabeprazole      | Improved |
|      |              | 73  | Japan    | Male   | 110 mg, twice daily   | Esophagitis                 | Retrosternal pain and odynophagia | Dabigatran discontinued; Rabeprazole      | Improved |
| 19   | Singh S et al.   | 69  | United Kingdom | Male   | 220 mg, once daily    | Oesophagogastric ulceration | Vomiting and epigastric pain      | Dabigatran discontinued; PPI                | Improved |
| 20   | Patel S et al.   | 59  | United States | Male   | Unknown                | Acute interstitial nephritis | No symptoms with Abnormal laboratory test | Prednisone                                   | Improved |

(Continued)
Table 1 (Continued).

| Ref. | Author          | Age | Country       | Gender | Dosage           | Adverse events         | Main symptoms                     | Treatment                              | Outcomes   |
|------|-----------------|-----|---------------|--------|------------------|------------------------|------------------------------------|----------------------------------------|------------|
| 21   | Rochwerg B et al. | 71  | Canada        | Male   | Unknown          | Acute hepatitis        | Progressive painless icterus, fatigue, and anorexia | Dabigatran discontinued               | Improved   |
| 22   | Zaleski M et al. | 52  | United States | Male   | Unknown          | Hyperkalemia           | Unknown                          | Dabigatran discontinued               | Improved   |
| 23   | Stöllberger C et al. | 89  | Austria       | Female | 110 mg, twice daily | Lupus                 | Epistaxis                         | Dabigatran discontinued; Cauterization | Improved   |
| 24   | Mancano M A.    | 71  | United States | Female | 150 mg, twice    | Pustular eruptions    | Itching on palms and feet         | Dabigatran discontinued; Enoxaparin   | Improved   |
| 25   | Eid TJ et al.    | 78  | Caucasus      | Male   | 150 mg, twice    | Rash                  | Diffuse, full-body pruritic rash | Dabigatran discontinued; Diphenhydramine | Improved   |
| 26   | Vega-Molpeceres S et al. | 80  | Spain         | Female | Unknown          | Exanthem               | Itching                           | Dabigatran discontinued; H₂RA        | Improved   |
| 27   | Whitehead H et al. | 20  | United States | Male   | 150 mg, twice daily | Exanthem               | Itching                           | Dabigatran discontinued; Prednisone   | Improved   |

Abbreviations: H₂RA, H₂ receptor inhibitor; PPIs, proton pump inhibitors; PCC, prothrombin complex concentrate; PRBC, packed red blood cells; FFP, fresh frozen plasma.
the cases we reviewed, 10 of 25 patients developed varying degrees of esophagitis or esophageal injury after dabigatran use. Therefore, dabigatran-induced esophagitis may be overlooked in asymptomatic patients who have not undergone endoscopy. Among the 10 patients (four males and six females) we reviewed, the mean age was 77 years and there was no significant difference between the doses of dabigatran used. It has been speculated that the tartaric acid core in dabigatran not only plays a part in gastrointestinal bleeding, but is released after digestion and adheres to the esophagus to damage the esophageal mucosa, and then the damaged esophageal mucosa exfoliates after peristalsis. In older patients, due to reduced activity (sitting or lying down for long periods) and reduced salivary secretion, if the volume of water consumed is low, the lack of a sufficient liquid bolus will increase the possibility of contact by dabigatran with the esophageal mucosa. The mean age of the patients we reviewed was 77 years, so we speculate that advanced age was an important risk factor for dabigatran-induced esophagitis. Clinicians should not ignore the possibility of esophagitis after giving patients dabigatran, especially if patients develop dysphagia, chest pain, upper abdominal pain, or heartburn.

Impairment of function of the liver and kidney
The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial showed that impairment of liver function (an increase in the levels of aspartate aminotransferase or alanine aminotransferase by more than three times the upper limit of the normal range) caused by dabigatran did not occur more frequently than that with warfarin. In the literature that we reviewed, dabigatran-induced acute interstitial nephritis, acute hepatitis, and hyperkalemia were reported. In a phase-II dose-finding trial of dabigatran, Eriksson et al found only mild increases in transaminase levels in the dose ranges tested, but two patients had severe hepatitis (transaminase levels more than five times the upper limit of normal). The cause of liver and kidney dysfunction caused by dabigatran may be because first-pass elimination occurs in the liver and 80% of a given dose is excreted by the kidney. One of the patients in a study experienced hyperkalemia. Hyperkalemia is a potentially fatal side-effect that can occur in patients with altered renal function, and understanding that dabigatran can cause hyperkalemia in this patient population is crucial. Dabigatran can induce hyperreninemic hypoaldosteronism in patients with impaired renal function, which leads to hyperkalemia. Careful monitoring of renal function is recommended if physicians prescribe dabigatran for patients with renal insufficiency.

Myocardial infarction or acute coronary syndrome
A small (but significant) increased risk of myocardial infarction or acute coronary syndrome has been noted when combining safety-outcome data from multiple trials. The RE-LY trial showed that the prevalence of myocardial infarction per year was 0.53% with warfarin, and that the prevalence per year in patients taking 110 mg of dabigatran and 150 mg of dabigatran was 0.72% and 0.74%, respectively. These findings were probably because warfarin provides better protection against coronary ischemic events than dabigatran. In the literature that we reviewed, such adverse events were not reported in any patient. Nevertheless, clinicians should continue to consider the possibility of these severe, harmful cardiovascular effects after dabigatran administration.

Allergic reactions
Five patients developed allergic reactions after taking dabigatran. In addition, one patient developed drug-induced lupus (DIL). Stöllberger and colleagues suggested that a small lipophilic molecule with a molecular weight of 472 Da may play a part in immune side-effects after dabigatran administration. Furthermore, DIL is characterized by high levels of antinuclear antibodies and antihistone antibodies, with no evidence of complement consumption, and circulating immune complexes within the normal range. The RE-LY trial reported that fewer than 0.1% of patients receiving dabigatran reported drug allergies, allergic edema, allergic reactions, or anaphylactic shock. Even though allergic edema and allergic reactions are rare, monitoring and reporting allergic reactions in patients taking dabigatran is important.

Age
Among the patients with adverse events that we reviewed (except for a 20-year-old patient with a dabigatran-induced exanthema), the mean age was 76 (range, 52–90) years. Regardless of whether adverse events are associated with age, more clinical trials are needed to ascertain the relationship between age, dose, and adverse effects to better guide management.
Conclusions and recommendations

The oral anticoagulant dabigatran is used widely. Nevertheless, clinicians cannot ignore the adverse events caused by dabigatran. We recommend the management detailed below for the adverse events caused by dabigatran.

(a) According to the patient’s symptoms, signs and laboratory tests, once the diagnosis of gastrointestinal bleeding is clear, depending on the amount of bleeding, if a small amount of bleeding, in addition to observing clinical changes, the clinicians may consider adding H₂ receptor inhibitor (H₂RA), proton pump inhibitors (PPIs) and mucosal protective agent. In severe bleeding, measures include discontinuation of dabigatran immediately and administration of prothrombin complex concentrate, packed red blood cells, and fresh frozen plasma, the use of specific reversal agents such as idarucizumab for dabigatran, and emergency endoscopic management.

(b) If heartburn, chest pain and upper abdominal pain appear shortly after dabigatran administration, drinking a sufficient volume of water (150 mL or more) and maintaining an upright position for ≥30 mins are useful strategies for relieving symptoms. If necessary, PPIs and H₂RAs can be added. If symptoms persist, dabigatran should be discontinued; apixaban, rivaroxaban and warfarin are alternatives.

(c) If patients have dysphagia, upper abdominal pain, chest pain, retrosternal pain, vomiting, and odynophagia, and their duration is long, clinicians should be alert to the possibility of dabigatran-induced esophagitis or esophageal injury. Endoscopy should be undertaken as soon as possible. Longitudinal exfoliation of the distal esophagus is a characteristic feature of dabigatran-induced esophagitis.

(d) If abdominal pain, anorexia, or fatigue is the main clinical manifestations of dabigatran use, hepatic lesions should be considered after excluding esophageal lesions. Monitoring indicators of liver function are particularly important. If hepatic lesions are present, dabigatran should be stopped and drugs that can protect liver function, such as bicyclol, glutathione, and magnesium isoglycyrrhizinate, should be administered.

(e) Impairment of renal function (including acute interstitial nephritis and hyperkalemia) should be noted, especially hyperkalemia. Discontinuation of dabigatran and laboratory tests is recommended. Hemofiltration and glucocorticoid therapy are feasible if indicated.

(f) As an anticoagulant, dabigatran, may increase the risk of myocardial infarction or acute coronary syndrome. Clinicians should consider the possibility of these severe, harmful cardiovascular effects following use of dabigatran.

(g) Allergic reactions such as rash are not very common and can be treated with antihistamines, and discontinue dabigatran if necessary. DIL due to dabigatran is extremely rare but, if it occurs, dabigatran should be discontinued as soon as possible and autoantibody profiles are helpful for the diagnosis.

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