REVIEW ARTICLE

Dabigatran as anticoagulant therapy for atrial fibrillation

Which patients should receive it, which patients may not need it, and other practical aspects of patient management

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KEY WORDS

new anticoagulants, perioperative anticoagulation, pharmacodynamics, pharmacokinetics

ABSTRACT

In the past decade, antithrombotic therapy research has focused on the development of new oral anticoagulant drugs to replace vitamin K antagonists for stroke prevention in patients with chronic atrial fibrillation, for preventing cardiovascular complications of acute coronary syndromes, and for the prevention and treatment of venous thromboembolism. The most anticipated studies relate to the use of new oral anticoagulants to replace vitamin K antagonists for the prevention of stroke in patients with atrial fibrillation. This review will focus on dabigatran, the first non-vitamin K anticoagulant approved for this clinical indication, and will assess the RE-LY trial (Randomized Evaluation of Long Term Anticoagulant Therapy) findings according to the level of anticoagulation control in warfarin-treated patients. The objectives of this review are: 1) to provide an overview of dabigatran, highlighting clinically relevant properties; 2) to provide a commentary on the study by Wallentin et al. within the context of how the quality of anticoagulation control affects warfarin efficacy and safety; and 3) to consider which patients with chronic atrial fibrillation should receive and which may not need to receive dabigatran.

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Introduction The past decade has been an intense period of research and development of new anticoagulant drugs aimed at replacing and complementing vitamin K antagonists (VKAs) and heparins for stroke prevention in patients with chronic atrial fibrillation, for preventing cardiovascular complications of acute coronary syndromes, and for the prevention and treatment of venous thromboembolism.

The new anticoagulants can be separated into 3 groups based on their target of action: 1) oral direct thrombin (or factor IIa) inhibitors, which include dabigatran etexilate (Pradaxa®) and AZD 0837; 2) oral factor Xa inhibitors, which include rivaroxaban (Xarelto®), apixaban, betrixaban, edoxaban and eribaxaban; and 3) parenteral factor Xa inhibitors, which include idrabiotaparinux (biotinylated idraparinux, a derivative of fondaparinux) and semuloparin. Anticoagulants more familiar to clinicians are VKAs (warfarin, acenocoumarol, phenprocoumon), heparins (unfractionated heparin, low-molecular-weight heparins [LMWHs]), parenteral factor Xa inhibitors (fondaparinux), and parenteral direct thrombin inhibitors (hirudin, lepirudin, argatroban).[1-4]

To place the new anticoagulants in the context of older agents, TABLE 1 compares the pharmacologic properties of the most commonly used older anticoagulants with those of dabigatran, rivaroxaban, and apixaban, which are either currently available or will be soon available for clinical use. TABLE 2 considers a comparison of more practical properties of the older and new anticoagulants. A more detailed discussion of the pharmacologic properties of new oral anticoagulants is provided elsewhere.[1-4]

Among the new oral anticoagulants, rivaroxaban and dabigatran are currently used for prophylaxis against deep vein thrombosis after major orthopedic surgery. To a large extent, they have replaced LMWHs as the dominant thromboprophylaxis

TABLE 1 Pharmacologic properties of older and new anticoagulants

Pharmacologic property	Older anticoagulants				New anticoagulants		
	VKA	UFH	LMWH	fondaparinux	dabigatran	rivaroxaban	apixaban
mode of action	inhibit factors II, VII, IX, X	indirect factor IIa and factor Xa inhibitor	indirect factor Xa inhibitor; partial factor IIa inhibitor	indirect factor Xa inhibitor	direct factor IIa inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor
bioavailability (F_{rel})	100%	100%	100%	100%	6.5%	80%	80%
peak action (t_{max})	4–5 days	IV: immediate SC: 20–60 min	2–4 hours	2–4 hours	1–3 hours	1–3 hours	1–3 hours
elimination half-life ($t_{1/2}$)	36–42 hours	1.0–1.5 hours	3–4 hours	17–21 hours	14–17 hours	9–15 hours	9–14 hours
route of clearance	multiple	reticuloendothelial system	>80% renal	100% renal	100% renal	65% renal	25% renal
involvement of CYP	yes	no	no	no	minor	minor	minor

Abbreviations: CYP – cytochrome P-450, IV – intravenous, LMWH – low-molecular-weight heparin, SC – subcutaneous, UFH – unfractionated heparin, VKA – vitamin K antagonists

TABLE 2 Clinically relevant properties of conventional and new anticoagulants

Property	Conventional anticoagulants				New anticoagulants		
	warfarin	UFH	LMWH	fondaparinux	dabigatran	rivaroxaban	apixaban
dose regimen (prevention)	variable dose	5000–7500 IU twice daily	fixed dose	fixed dose (2.5 mg daily)	fixed dose (220 mg daily)	fixed dose (10 mg daily)	fixed dose
dose regimen (treatment)	variable dose	variable dose	fixed dose, weight based	fixed dose (7.5 mg daily)	fixed dose (150 mg twice daily)	fixed dose (20 mg daily)	fixed dose
dose reduction in renal insufficiency	none	none	yes	yes	yes	yes	yes
drug interactions	multiple drugs	none	none	none	some drugs	some drugs	some drugs
food interactions	yes	none	none	none	none	none	none
laboratory monitoring	INR	aPTT	anti-factor Xa	anti-factor Xa	TT? ECT?	anti-factor Xa	anti-factor Xa
reversibility	vitamin K	protamine sulphate	protamine sulphate (partial)	none	none	none	none

Abbreviations: aPTT – activated partial thromboplastin time, ECT – ecarin clotting time, INR – international normalized ratio, IU – international units, TT – thrombin time, others – see TABLE 1

agents and are administered for 10 to 14 days after knee replacement and up to 30 days after hip replacement.[5,6] The most anticipated studies relate to the use of new oral anticoagulants to replace VKAs for stroke prevention in patients with chronic atrial fibrillation.[7,8] The focus herein is on dabigatran, which is the first non-VKA approved (in North America in 2010) for this clinical indication. In particular, the study by Wallentin et al.,[9] which aimed to assess the findings of the main RE-LY trial (Randomized Evaluation of Long Term Anticoagulant Therapy) according to the level of anticoagulation control in warfarin-treated patients, will be reviewed.

Against this background, the objectives of this review are: 1) to provide an overview of dabigatran, highlighting clinically-relevant properties; 2) to provide a commentary on the study by Wallentin et al.[9] within the context of how the quality of anticoagulation control affects warfarin efficacy and safety; and 3) to consider in which patients with atrial fibrillation that dabigatran should be first-line therapy and in which patients VKAs may be considered for treatment.

Clinically relevant properties of dabigatran The availability of dabigatran for the long-term anticoagulant management of patients with atrial fibrillation and venous thromboembolism is a major step forward in patient care because its ease of administration, with a fixed oral dose that does not require laboratory monitoring, thereby overcoming many of the drawbacks of VKAs.[7,10] Furthermore, dabigatran does not have the hepatotoxicity associated with its predecessor, ximela-

gatran.[11,12] The key properties of dabigatran are summarized below.

Pharmacologic properties of dabigatran Dabigatran etexilate, a prodrug of dabigatran, is rapidly absorbed in the intestine and is converted to dabigatran in the enterocytes, portal vein, and liver by mechanisms independent of the cytochrome P-450 pathway, thereby accounting for its low drug interaction potential.[13,14] Peak levels are achieved 1.25 to 3 hours after intake with an elimination half-life of 12 to 17 hours.[15-17] Interestingly, the dabigatran drug capsule consists of small (0.8 mm) pellets of a tartaric acid core coated with dabigatran. The tartaric acid creates an acidic microenvironment that allows absorption of dabigatran, independent of gastric pH,[15] but probably also accounts for the 6% to 12% incidence of dyspepsia observed in dabigatran-treated patients.[7,10] Dabigatran elimination is 80% by the renal route, and the remaining 20% elimination is by the biliary route after dabigatran is conjugated to active metabolites in the liver.[15-17]

Potential drug and food interactions Dabigatran should be used cautiously in patients who are receiving certain drugs. Potential dabigatran-drug interactions may occur with amiodarone, which increases the dabigatran area under the curve by 50% to 60%, and in patients who are receiving verapamil, rifampin, tenofivir, quinidine, and clarithromycin.[1] There are no known food interactions with dabigatran.

Cautions with dabigatran use Dabigatran use is contraindicated in patients with severe renal insufficiency (creatinine clearance [CrCl] <30 ml/min), and caution should be used with its use in patients with moderate renal insufficiency (CrCl 30–50 ml/min). Although there is no evidence to date that dabigatran is associated with hepatotoxicity, its use is contraindicated in patients with severe liver insufficiency, in part because 20% of its clearance is by hepatobiliary mechanisms.[15-17] Caution should also be used when dabigatran is given to patients who are receiving drugs that affect hemostasis, such as acetylsalicylic acid (ASA) and clopidogrel, because of the established increase in serious bleeding that occurs when antithrombotic drugs are combined.[18]

Effect of quality of anticoagulation control on efficacy and safety The RE-LY study found that compared with warfarin therapy, administered to achieve an international normalized ratio (INR) range of 2.0 to 3.0, dabigatran, 150 mg twice daily, reduced the risk for stroke (including hemorrhagic stroke) without an increase in overall major bleeding, whereas dabigatran, 110 mg twice daily, was noninferior in reducing the risk for stroke but conferred a decreased risk for overall major bleeding.[7] The mean time in therapeutic range (TTR) among warfarin-treated patients was 64%, which is comparable to that observed in other trials assessing long-term warfarin.[11,12,19] In observational studies, TTR varies widely, from <50% to >70%, depending on the clinical setting and expertise of the anticoagulant management provider.[20-22]

Wallentin et al.[9] assessed the RE-LY findings whereby the efficacy and safety of dabigatran, 150 mg and 110 mg, were compared to warfarin according to the TTR, which was assessed based on clinical-center-specific TTR (cTTR) given the wider variability observed with individual patient TTR.[9] The interpretation of the findings may vary depending on whether one adopts a statistical or more clinically oriented perspective. The principal findings, focusing on the primary efficacy outcome of stroke/systemic embolism and the primary safety outcome of major (or serious) bleeding, according to cTTR are presented in **TABLE 3**.

From a statistical perspective, there was no significant interaction of TTR on the efficacy outcome of stroke/systemic embolism ($P = 0.20$), indicating that there was no significant difference in efficacy between dabigatran (at the 110 mg or 150 mg dose) and warfarin. Stated differently, this means that when TTR quartiles are considered collectively, anticoagulant control did not appear to affect the findings between dabigatran and warfarin for the efficacy outcome. In terms of the effect of TTR and major bleeding, there was no significant interaction ($P = 0.50$) of the TTR on the findings between dabigatran, 110 mg, and warfarin, but there was a significant interaction ($P = 0.03$) between dabigatran, 150 mg, and warfarin. Stated differently, this means that TTR quartiles are considered as a group, the control of anticoagulation affected the comparison of major bleeding when warfarin was compared to dabigatran, 150 mg twice daily, but did not affect the comparison of bleeding between warfarin and dabigatran, 110 mg twice daily. Findings on the secondary outcomes of intracranial bleeding and total mortality can also be considered in this manner.

From a more clinical perspective, practicing physicians may be more interested in knowing how the therapeutic benefits and risks of dabigatran compare against a level of anticoagulation control observed in their practice or for an individual patient. For example, some patients may have very poor or very good anticoagulation control and the same can be said for the clinical setting of anticoagulation monitoring because specialized anticoagulation clinics or nomogram-based approaches achieve better anticoagulation control than that attained in an office- or community-based practice. For example, many clinicians (or clinics) may attain TTR for INR levels in the 65%–72% range. If using this benchmark, the findings in **TABLE 3** indicate that dabigatran, 150 mg twice daily, appears to confer improved stroke prevention compared with warfarin

TABLE 3 Incidence of adverse outcomes with dabigatran and warfarin according to the time in therapeutic range

TTR	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg vs. warfarin	Dabigatran, 150 mg vs. warfarin
	events	events/100 person-years	events	events/100 person-years	events	events/100 person-years	HR (95% CI) [*P* value for interaction][a]	HR (95% CI) [*P* value for interaction][b]
stroke and systemic embolism								
<57.1%	55	1.91	32	1.10	54	1.92	1.00 (0.68–1.45)	0.57 (0.37–0.88)
57.1–65.5%	51	1.67	32	1.04	62	2.06	0.81 (0.56–1.17)	0.50 (0.33–0.77)
65.5–72.6%	40	1.34	31	1.04	45	1.51	0.89 (0.58–1.36)	0.69 (0.44–1.09)
>72.6%	36	1.23	38	1.27	40	1.34	0.92 (0.59–1.45) [0.89]	0.95 (0.61–1.48) [0.20]
major bleeding								
<57.1%	68	2.36	74	2.54	101	3.59	0.65 (0.48–0.89)	0.71 (0.52–0.96)
57.1–65.5%	103	3.38	102	3.33	124	4.13	0.82 (0.63–1.06)	0.81 (0.62–1.05)
65.5–72.6%	84	2.82	113	3.80	101	3.40	0.83 (0.62–1.11)	1.13 (0.87–1.48)
>72.6%	82	2.81	108	3.60	93	3.11	0.90 (0.67–1.21) [0.50]	1.16 (0.88–1.54) [0.03]
intracranial bleeding								
<57.1%	8	0.28	10	0.34	18	0.64	0.43 (0.19–1.00)	0.53 (0.25–1.15)
57.1–65.5%	9	0.30	13	0.42	28	0.93	0.31 (0.15–0.66)	0.45 (0.24–0.88)
65.5–72.6%	4	0.13	7	0.24	20	0.67	0.20 (0.07–0.58)	0.35 (0.15–0.82)
>72.6%	6	0.21	9	0.30	23	0.77	0.27 (0.11–0.66) [0.71]	0.39 (0.18–0.84) [0.89]
total death								
<57.1%	120	4.17	112	3.85	161	5.72	0.73 (0.58–0.92)	0.67 (0.53–0.85)
57.1–65.5%	121	3.97	115	3.75	123	4.09	0.97 (0.75–1.24)	0.92 (0.71–1.18)
65.5–72.6%	95	3.19	108	3.64	110	3.70	0.86 (0.65–1.13)	0.98 (0.75–1.28)
>72.6%	105	3.60	99	3.30	91	3.04	1.18 (0.89–1.57) [0.066]	1.08 (0.81–1.44) [0.052]

a for entire subgroup (dabigatran, 110 mg vs. warfarin)
b for entire subgroup (dabigatran, 150 mg vs. warfarin)

Abbreviations: CI – confidence interval, HR – hazard ratio, TTR – time in therapeutic range for INR, others – see TABLE 2

(hazard ratio [HR] = 0.69; 95% confidence interval [CI]: 0.44–1.09) without an increased risk for major bleeding (HR = 1.13; CI: 0.87–1.48). In patients of clinical setting in which INR control is superior, with TTR >72%, the findings from TABLE 3 suggest that dabigatran, 150 mg twice daily, is comparable to warfarin for stroke prevention (HR = 0.95; CI: 0.61–1.48) and bleeding risk (HR = 1.13; CI: 0.88–1.54). What is also noteworthy is that the rate of intracranial bleeding is lower with dabigatran (with either the 110 mg or 150 mg dose) irrespective of INR control, thereby suggesting that compared with warfarin dabigatran may have a protective effect against intracranial bleeding, a finding that was not observed when ximelagatran was compared with warfarin.[23]

Taken together, the key message appears that dabigatran has clear advantages over warfarin in terms of its efficacy (with the 150 mg dose) and safety (with the 110 mg dose), but that the net therapeutic benefit is attenuated (and possibly nullified) when there is good or excellent anticoagulation control with warfarin (as defined by a TTR >72%).

Anticoagulant management of atrial fibrillation: dabigatran or warfarin? Prior to determining which anticoagulant a patient with atrial fibrillation should receive, the clinician can consider their risks for stroke and bleeding. The risk for stroke can be estimated with the $CHADS_2$[24] or CHA_2DS_2-VASc[25] scores, whereas the risk for bleeding can be estimated with the HAS-BLED[26] score (TABLE 4). The most recent treatment guidelines on anticoagulant therapy for atrial fibrillation come from the 2010 European Society of Cardiology (ESC) Task Force for the Management of Atrial Fibrillation.[27] This consensus panel recommends long-term oral anticoagulant therapy (with a VKA or dabigatran) for patients with a CHA_2DS_2-VASc score ≥2 or a $CHADS_2$ score ≥1. The ESC does not specify which anticoagulant (VKA or dabigatran) should be used but comments on the dabigatran dose regimen: 150 mg twice daily in patients at low risk for bleeding (e.g., HAS-BLED score:

TABLE 4 Clinical prediction guides to estimate risk for stroke without VKA therapy and bleeding during VKA therapy[24-26]

Risk factor	Score
$CHADS_2$ score	
congestive heart failure	1
hypertension	1
age ≥75 years	1
diabetes	1
prior stroke or transient ischemic attack	2
CHA_2DS_2-VASc score	
congestive heart failure/left ventricular dysfunction	1
hypertension	1
age ≥75 years	2
diabetes	1
prior stroke or transient ischemic attack or systemic embolism	2
vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
age 64–74 years	1
female sex	1
HAS-BLED score	
hypertension (systolic pressure >160 mmHg)	1
abnormal renal function	1
abnormal liver function	1
age ≥65 years	1
prior stroke	1
prior bleeding	1
labile INRs (e.g., TTR <60%)	1
taking other drugs at the same time (e.g., ASA, NSAIDs)	1
alcohol intake at the same time	1

Abbreviations: ASA – acetylsalicylic acid, NSAIDs – nonsteroidal anti-inflammatory drugs, others – see TABLES 1 and 3

<3); 110 mg twice daily in patients at higher risk for bleeding (e.g., HAS-BLED score: ≥3).

Determining which patients with chronic atrial fibrillation are eligible to receive long-term anticoagulation should receive dabigatran (and, if so, which dose should be prescribed) and, on the other hand, which patients should receive warfarin depends on multiple factors. Perhaps an overarching consideration to address is drug cost because dabigatran is likely to be priced approximately 10-fold higher than warfarin or another VKA. If a patient cannot afford the cost of dabigatran, whether due to lack of drug cost coverage by a third party or personal financial limitations, warfarin would be considered while acknowledging that it may be a less effective option for stroke prevention. Another consideration is whether a patient has incident (newly-diagnosed) atrial fibrillation and is not receiving antithrombotic therapy or if a patient has prevalent atrial fibrillation that is being treated with warfarin, warfarin combined with ASA or ASA alone.

Finally, patients' renal function should be considered. Many patients with atrial fibrillation are elderly and have a natural decline in renal function. The RE-LY study excluded patients with severe renal insufficiency (CrCl <30 ml/min), and there are no studies so far on the safety of dabigatran in patients with moderate renal insufficiency (CrCl 30–50 ml/min). Until such data are available, caution should be used when administering dabigatran in patients with impaired renal function. This issue is particularly relevant in elderly patients as renal function declines but serum creatinine S_{Cr} concentration may only increase slightly (due to a concurrent decrease in muscle mass). Thus, many elderly patients with atrial fibrillation who may be eligible to receive dabigatran may, unknowingly, have impaired renal function. Estimating patients' renal function can be done easily with the Cockroft-Gault equation,[28] as shown below:

$$C_{Cr} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times S_{Cr}} \times (0.85 \text{ if female}),$$

where C_{Cr} is given in ml/min, S_{Cr} in mmol/l, weight in kg.

Patients with incident atrial fibrillation In patients with newly-diagnosed or incident atrial fibrillation, dabigatran, 150 mg twice-daily, should be considered as first-line treatment, given its superior efficacy and comparable safety with warfarin, especially for patients at higher risk for stroke (e.g., $CHADS_2$ score ≥3). If a patient is at higher risk for stroke and is also at higher risk for bleeding (e.g., HAS-BLED score ≥3), dabigatran can be administered at the 110 mg twice-daily dose. A VKA can be considered as a second-line agent and may be more suitable for patients at low risk for stroke ($CHADS_2$ score: 0–2), in which the efficacy advantage of dabigatran may be attenuated due to a lower baseline risk for stroke in such patients. Additional patients who may be considered for VKA therapy are those who are likely to have stable anticoagulant dose requirements with a VKA such as those who have few comorbidities or who are receiving few concomitant drugs that may lead to warfarin-drug interactions.

Patients with prevalent atrial fibrillation In patients with atrial fibrillation who have been receiving a VKA for at least 2 to 3 months and in whom, by this time, a VKA dosing and INR monitoring pattern typically is established, the choice between continuing with a VKA or switching to dabigatran should be individualized. Continuation of a VKA would be appropriate for patients with excellent anticoagulation control (i.e., TTR >72%), patients at low risk for stroke (e.g., $CHADS_2$ score: 0–2), and patients who prefer to continue VKA therapy. In the later circumstance, some patients may prefer the familiarity of a VKA, especially if they have had good clinical results with years of use or may be reassured by periodic anticoagulant monitoring (in a manner similar to patients who are receiving blood pressure-, glucose-, or lipid-lowering therapies). Furthermore, VKA management is

TABLE 5A Preoperative interruption of dabigatran: an empiric, suggested approach[34]

Dabigatran	Renal function	Aim for no or minimal residual anticoagulant effect at surgery (4–5 drug half-lives separate last dose and surgery)	Aim for mild–moderate residual anticoagulant effect at surgery (2–3 drug half-lives separate last dose and surgery)
$t_{1/2}$ = 12–17 hours	normal or mild impairment (creatinine clearance >50 ml/min)	last dose: day –3 before surgery (skip 4 doses)	last dose: day –2 before surgery (skip 2 doses)
$t_{1/2}$ = 12–17 hours	moderate impairment (creatinine clearance 30–50 ml/min)	last dose: day –4 to day –5 before surgery (skip 6–8 doses)	last dose: day –3 before surgery (skip 4 doses)

TABLE 5B Postoperative resumption of dabigatran: an empiric, suggested approach[34]

Minor surgery or procedure (low bleeding risk)	Major surgery (high bleeding risk)
resume on day after surgery (24 hours postoperative), 150 mg twice daily	resume 2 days after surgery (48 hours postoperative), 150 mg twice daily[a]

a for patients at high risk for thrombmoembolism consider a reduced dose of dabigatran (e.g., 110–150 mg once daily) on the evening after surgery and on the following day (day +1) after surgery

becoming increasingly simplified by standardized and/or computer-based VKA dosing algorithms, which provide excellent anticoagulation control with minimal INR monitoring.[29,30]

On the other hand, dabigatran has advantages for VKA-treated patients in whom anticoagulation control has been problematic, either due to inability to attain stable INR levels or suboptimal compliance with INR testing. Furthermore, dabigatran would be preferred over VKAs in patients at high risk for stroke or those who have had a prior stroke, systemic embolism, or transient ischemic attack while receiving VKA therapy.

Practical aspects of managing patients receiving dabigatran Although the RE-LY trial provides information relating to the efficacy and safety of dabigatran in all patients and in patient subgroups, there are at least 3 issues that will arise in everyday clinical practice and will be briefly addressed herein.

Laboratory monitoring of dabigatran Dabigatran causes a dose-dependent and short-lived (1–4 hours after administration) prolongation in the activated partial thromboplastin time (aPTT) and prothrombin time (PT), whereas its effect on the INR is less clear.[31,32] Monitoring the anticoagulant effect of dabigatran may involve the thrombin time (TT), which measures the conversion of fibrinogen to fibrin by thrombin (factor II). This test may be too sensitive to distinguish different levels of dabigatran-associated anticoagulant effect and may require modification and calibration against a dabigatran-based standard. Tests such as the aPTT, PT, and INR are unlikely to reliably measure the anticoagulant effect of dabigatran. However, a normal TT is likely to reliably reflect the absence of a significant anticoagulant effect from dabigatran.

Managing patients who require elective surgery/invasive procedure The perioperative management of dabigatran-treated patients has not been established so far because available studies lack perioperative outcomes in dabigatran-treated patients who require elective surgery. Furthermore, it is not clear whether dabigatran can be continued without interruption around the time of minor dental, eye, or skin procedures, as is the case with VKA-treated patients who do not require VKA therapy to be stopped before such minor procedures.[33]

For preoperative management, an anticoagulant should be stopped at a time in advance of surgery so that there is minimal or no residual anticoagulant effect at the time of surgery. Although a small anticoagulant effect at surgery is unlikely to have major bleeding consequences, it may be important in patients who are receiving spinal/epidural anesthesia or who are undergoing cardiac, spinal, or intracranial surgery in whom even minor bleeding may have devastating clinical consequences. With dabigatran, which has a half-life of 12 to 17 hours, the last dose should be given 2 to 3 days (48–72 hours) before surgery, which corresponds to 4 to 5 elimination half-lives. This should ensure no residual anticoagulant effect at the time of surgery. However, for many minor surgeries, stopping dabigatran closer to surgery may allow sufficient hemostasis for surgery to be safely undertaken. In RE-LY, dabigatran-treated patients who required surgery followed an empiric protocol anchored on whether major or minor surgery was being done and the extent of renal insufficiency (TABLES 5A and 5B). Postoperative management is also suggested and is anchored, as with postoperative resumption of other anticoagulants, on the adequacy of postoperative hemostasis.

Managing patients with dabigatran-associated bleeding There is currently no antidote to dabigatran that can be administered to patients who develop serious (major) bleeding during dabigatran therapy. At present, there is no evidence that dabigatran-associated bleeding is associated with more serious clinical consequences than

VKA-associated bleeding. In patients who received ximelagatran, the prototype oral direct thrombin inhibitor, the case-fatality of major bleeding was similar to that in warfarin-treated patients (~9%),[23] and there is no reason that this would not also apply to dabigatran.

Patient management should include, as it does with VKA-associated bleeding, administration of coagulation factor replacement, with either prothrombin complex concentrate (15 ml/kg) or fresh frozen plasma (4 units). The role for recombinant activated factor VII is unclear but it may be considered for life-threatening bleeding that continues despite blood product administration and other hemostatic measures. One additional consideration in dabigatran-treated bleeding patients with prior or newly developed renal failure is that hemodialysis may be needed to remove dabigatran that might have accumulated due to worsening renal function.

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ARTYKUŁ POGLĄDOWY

Dabigatran jako lek przeciwkrzepliwy w migotaniu przedsionków

Którzy chorzy powinni ten lek otrzymać, którzy być może go nie potrzebują i inne praktyczne aspekty postępowania

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antykoagulacja okołooperacyjna, farmakodynamika, farmakokinetyka, nowe antykoagulanty

STRESZCZENIE

W ostatnim dziesięcioleciu badania nad leczeniem przeciwzakrzepowym koncentrowały się na opracowaniu nowych antykoagulantów, które zastąpiłyby antagonistów witaminy K w prewencji udaru mózgu u chorych z migotaniem przedsionków, w prewencji powikłań sercowo-naczyniowych u chorych z ostrymi zespołami wieńcowymi oraz w prewencji i leczeniu żylnej choroby zakrzepowo-zatorowej. Najbardziej oczekiwane badania dotyczą zastosowania nowych antykoagulantów zamiast antagonistów witaminy K w prewencji udaru mózgu u chorych z migotaniem przedsionków. W niniejszym artykule przeglądowym omówiono dabigatran, pierwszy antykoagulant niebędący antagonistą witaminy K zarejestrowany w tym wskazaniu klinicznym, oraz przeanalizowano wyniki badania RE-LY w odniesieniu do stopnia kontroli antykoagulacji u chorych leczonych warfaryną. Cele tego przeglądu są następujące: 1) podsumowanie wiadomości o dabigatranie ze szczególnym uwzględnieniem właściwości istotnych klinicznie; 2) omówienie badania Wallentina i wsp. ze zwróceniem uwagi na to, jak jakość kontroli antykoagulacji wpływa na skuteczność i bezpieczeństwo stosowania warfaryny; 3) rozważenie, którzy chorzy z przewlekłym migotaniem przedsionków powinni otrzymywać dabigatran, a którzy być może go nie potrzebują.

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