Target-Specific Oral Anticoagulants:

Should We Switch from Warfarin?

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For many years, vitamin K antagonists (VKAs), such as warfarin, acenocoumarol, phenprocoumon, and fluindione, have been the mainstay of thromboembolic disease management, including the management of venous thromboembolism (VTE) and atrial fibrillation (AF)-related stroke. Warfarin is the most widely used VKA in clinical practice.[1] The VKAs are highly effective in preventing recurrent VTE (with a relative risk [RR] reduction of ~85% compared with placebo) and AF-related stroke (with a RR reduction of 64% compared with placebo, and a 37% RR reduction compared with antiplatelet therapy).[2,3]

The VKAs, however, have substantial limitations that can outweigh these advantages—including certain drug–drug and drug–food interactions, a narrow therapeutic window, and unpredictable anticoagulant effects, all of which necessitate regular laboratory monitoring to evaluate their efficacy and safety.[3] In order to overcome these limitations, target-specific oral anticoagulants (TSOACs), which directly inhibit the activity of coagulation factor Xa (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran), have been developed to replace VKAs.

Effectiveness and Safety of Target-Specific Oral Anticoagulants

In comparison with VKAs, TSOACs have predictable anticoagulant responses (enabling fixed dosing without the need for routine anticoagulation monitoring), fewer food and drug interactions, shorter half-lives, and more rapid onset of action[4] (Table I[4,5]).

On the basis of large human clinical trial evidence and real-world post-marketing surveillance studies, TSOACs have at least the same efficacy and safety as VKAs or low-molecular-weight heparin for approved indications (Table II[6]).

Drug Interactions. The TSOACs have fewer drug interactions than does warfarin, but they are subject to drug–drug interactions via the cytochrome P450 and P-glycoprotein systems: inducers or inhibitors of these factors can change the plasma levels of TSOACs.

P-glycoprotein transporter plays a major role in absorption and renal clearance. Cytochrome P450 (CYP3A4) is necessary for hepatic clearance, which itself has a substantial role in the elimination of rivaroxaban but a minor role in the elimination of apixaban and edoxaban, and no role in the elimination of dabigatran. Amiodarone, dronedarone, ketoconazole, verapamil, quinidine, clarithromycin/rifampicin, St. John's wort, carbamazepine, phenytoin, and phenobarbital are among the agents that exhibit possible drug–drug interaction with TSOACs.[7]

Target-Specific Oral Anticoagulants in Renal Dysfunction. All the TSOACs have some degree of renal excretion (dabigatran, 80%; rivaroxaban, 35%; and apixaban, 25%). Patients with impaired renal function are at risk of TSOAC accumulation and at higher risk of bleeding, so TSOAC doses should be modified on the basis of renal function[8] (Table III[5,8-10]). Among patients with chronic kidney disease (defined as a creatinine clearance [CrCl] ≤50 mL/min), TSOACs showed no significant difference from VKAs, in efficacy or in risk of bleeding.[8] The TSOACs are not recommended for use in patients who are on dialysis or who have AF and end-stage chronic kidney disease.

Management of Bleeding Events. Currently, there is no specific antidote for TSOACs, so recommendations on bleeding management usually arise from experts' opinions or laboratory endpoints. Considering TSOACs' relatively short elimination half-lives, stopping the drug and providing supportive care (such as the transfusion of blood

products) might be sufficient treatment in cases of mild bleeding. In severe bleeding, prothrombin complex concentrates (PCCs), activated PCCs, or recombinant factor VIIa should be used[11] (Fig. 1).

Measurement of Anticoagulant Effects. Although TSOACs do not require routine coagulation monitoring, laboratory testing can be beneficial in some situations like severe bleeding, severe renal impairment,

TABLE I. Current FDA-Approved Indications for Oral Anticoagulants[4,5]

Drug	Indications
Warfarin	• Prophylaxis and treatment of venous thrombosis and its extension, PE; • Prophylaxis and treatment of thromboembolic complications associated with AF or cardiac valve replacement; • Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events
Dabigatran	• Stroke prevention in patients with nonvalvular AF; • Treatment of DVT and PE after 5 to 10 d of parenteral anticoagulation; • Reduction in the risk of recurrence of DVT and PE in previously treated patients
Rivaroxaban	• Stroke prevention in patients with nonvalvular AF; • Prevention of venous thromboembolism in patients undergoing hip or knee replacement; • Acute treatment of DVT/PE; • Secondary prevention of DVT/PE
Apixaban	• Stroke prevention in patients with nonvalvular AF; • Acute treatment of DVT/PE; • Secondary prevention of DVT/PE

AF = atrial fibrillation; DVT = deep vein thrombosis; FDA = U.S. Food and Drug Administration; PE = pulmonary embolism

TABLE II. Randomized Trials Comparing the Efficacy and Safety of Target-Specific Oral Anticoagulants with Warfarin for Stroke Prevention in Patients with Atrial Fibrillation

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%
Creatinine clearance‡												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8	2·2	2·2
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)	NA	65 (51–76)

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. $CHADS_2$=stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction<40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used VKAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. ¶IQRs not available.

Table: **Baseline characteristics of the intention-to-treat populations of the included trials**

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TABLE III. Recommended Doses of Target-Specific Oral Anticoagulants on the Basis of Creatinine Clearance[5,8-10]

Apixaban	Dabigatran	Rivaroxaban
In management of nonvalvular AF and VTE:	**In management of nonvalvular AF:**	**In management of nonvalvular AF:**
CrCl >30 mL/min: 5 mg twice/d except for patients* with any 2 of the following characteristics: age, ≥80 yr; body weight, ≤60 kg; or serum creatinine, ≥1.5 mg/dL	CrCl >30 mL/min: 150 mg twice/d	CrCl >50 mL/min: 20 mg/d with the evening meal
2.5 mg twice/d if co-administered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, ritonavir, and clarithromycin	CrCl 15–30 mL/min: 75 mg twice/d	CrCl 15–50 mL/min: 15 mg/d with the evening meal
CrCl 15–29 mL/min: 2.5 mg twice/d Contraindicated if CrCl <15 mL/min	CrCl <15 mL/min or on dialysis: dosing recommendations cannot be provided	Contraindicated if CrCl <15 mL/min
Prophylaxis of DVT after hip or knee replacement surgery:	**In management of VTE:**	**In management of VTE:**
Initial dose should be taken 12 to 24 hr after surgery.	CrCl >30 mL/min: 150 mg twice/d, after 5–10 d of parenteral anticoagulation	CrCl 30–49 mL/min: 15 mg twice/d with food for the first 21 d; then 20 mg/d with food, for remaining treatment
Hip replacement surgery: 2.5 mg twice/d for 35 d;	CrCl <30 mL/min or on dialysis: dosing recommendations cannot be provided	Contraindicated if CrCl <30 mL/min
Knee replacement: 2.5 mg twice/d for 12 d		**Prophylaxis of DVT after hip or knee replacement surgery:**
		Hip replacement: 10 mg/d for 35 d;
		Knee replacement: 10 mg/d for 12 d

AF = atrial fibrillation; CrCl = creatinine clearance; DVT = deep vein thrombosis; VTE = venous thromboembolism

*The recommended dose of apixaban is 2.5 mg twice/d in these patients

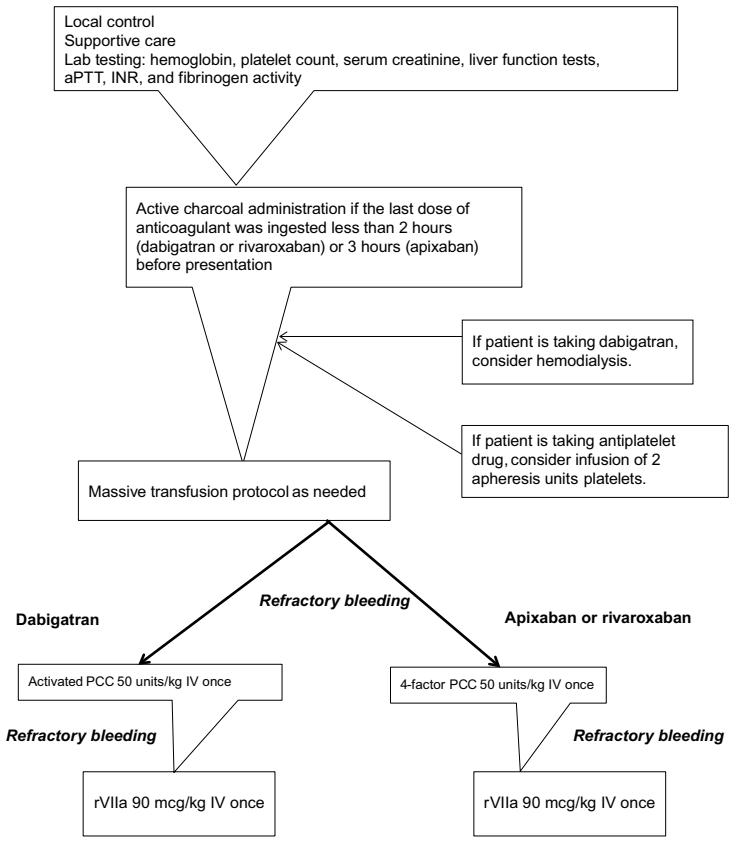

Fig. 1 *Management of bleeding events with target-specific oral anticoagulants.*

Adapted with permission from Biomed Res Int 2014: Baumann Kreuziger LM, et al.[11]

TABLE IV. Effect of Target-Specific Oral Anticoagulants on Coagulation Tests

Test	Dabigatran	Rivaroxaban	Apixaban
Prothrombin time	Increased or unchanged	Increased or unchanged*	Increased or unchanged*
aPTT	Increased	Increased or unchanged	Increased or unchanged
Thrombin time	Increased	—	—
Hemoclot test	Increased	—	—
Ecarin clotting time	Increased	—	—
Anti-factor-Xa activity	—	Increased	Increased

aPTT = activated partial thromboplastin time

*Highly reagent-dependent

Adapted with permission from Can J Cardiol 2013: Liew A, et al.[12]

TABLE V. Switching between Anticoagulant Regimens: Recommendations[7]

Regimen Change	Recommendation
VKA to TSOAC	INR <2: immediate; INR 2–2.5: immediate or next day; INR >2.5: use INR and VKA half-life to estimate time to INR <2.5
TSOAC to VKA	Administer concomitantly until INR is in appropriate range; measure INR just before next intake of TSOAC; retest 24 hr after last dose of TSOAC; monitor INR in first month until stable values (2–3) are achieved
TSOAC to TSOAC	Initiate when next dose is due, except when higher plasma concentrations are expected (for example, during renal impairment)
Aspirin or clopidogrel to TSOAC	Switch immediately, unless combination therapy is needed
TSOAC to parenteral anticoagulant	Initiate when next dose of TSOAC is due

INR = international normalized ratio; TSOAC = target-specific oral anticoagulant; VKA = vitamin K antagonist

emergency or urgent surgery, and overdose. The effects of TSOACs on coagulation assays are summarized in Table IV.[12]

Switching to or from a Target-Specific Oral Anticoagulant. In switching between anticoagulation regimens, the pharmacokinetics and pharmacodynamics of each anticoagulant should be considered, and the patient's coagulation status and renal function should be appropriately evaluated. Table V summarizes current recommendations as applied to various switches.[7]

Use of Target-Specific Oral Anticoagulants in Patients with Atrial Fibrillation. Those patients with nonvalvular AF who should be treated with anticoagulants have a choice among warfarin and the TSOACs, but the level of evidence that supports the use of warfarin (level A) is still higher than that in support of TSOACs (level B). Direct thrombin inhibitor (dabigatran) should not be used in patients with a mechanical heart valve.[13] Switching from warfarin to TSOAC should be considered in cases of drug intolerance, therapeutic failure, and patient preference.[14] Dabigatran and rivaroxaban are U.S. Food and Drug Administration (FDA) pregnancy category C (that is, animal reproduction studies showed adverse effects on the fetus, and there are no adequate and well-controlled studies in human beings); apixaban is FDA pregnancy category B (animal reproduction studies showed no harm to the fetus, but there are no adequate and well-controlled studies in pregnant women).[14]

Conclusion

We conclude that TSOACs are a safe and effective alternative to VKAs in suitable candidates.

References

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133(6 Suppl):160S-198S.
2. Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database Syst Rev 2006;(1):CD001367.
3. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012;126(20):2381-91.
4. Shafeeq H, Tran TH. New oral anticoagulants for atrial fibrillation: are they worth the risk? P T 2014;39(1):54-64.
5. Pradaxa (dabigatran etexilate mesylate) drug - indications and dosage [Internet]. Available from: http://www.rxlist.com/pradaxa-drug/indications-dosage.htm [2014 Aug; cited 2015 Mar 17].
6. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383(9921):955-62.
7. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013;15(5):625-51.
8. Harel Z, Sholzberg M, Shah PS, Pavenski K, Harel S, Wald R, et al. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. J Am Soc Nephrol 2014;25(3):431-42.
9. Xarelto (rivaroxaban film-coated oral tablets) drug - indications and dosage [Internet]. Available from: http://www.

rxlist.com/xarelto-drug/indications-dosage.htm [2014 Aug; cited 2015 Mar 17].
10. Eliquis (apixaban tablets) drug - indications and dosage [Internet]. Available from: http://www.rxlist.com/eliquis-drug/indications-dosage.htm [2014 Mar; cited 2015 Mar 17].
11. Baumann Kreuziger LM, Keenan JC, Morton CT, Dries DJ. Management of the bleeding patient receiving new oral anticoagulants: a role for prothrombin complex concentrates. Biomed Res Int 2014;2014:583794.
12. Liew A, Eikelboom JW, O'Donnell M, Hart RG. Assessment of anticoagulation intensity and management of bleeding with old and new oral anticoagulants. Can J Cardiol 2013;29 (7 Suppl):S34-44.
13. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society [published erratum appears in Circulation 2014;130(23):e270-1]. Circulation 2014;130 (23):2071-104.
14. Abo-Salem E, Becker R. Transitioning to and from the novel oral anticoagulants: a management strategy for clinicians. J Thromb Thrombolysis 2014;37(3):372-9.