To thin or Too thin ? Anticoagulation 2019

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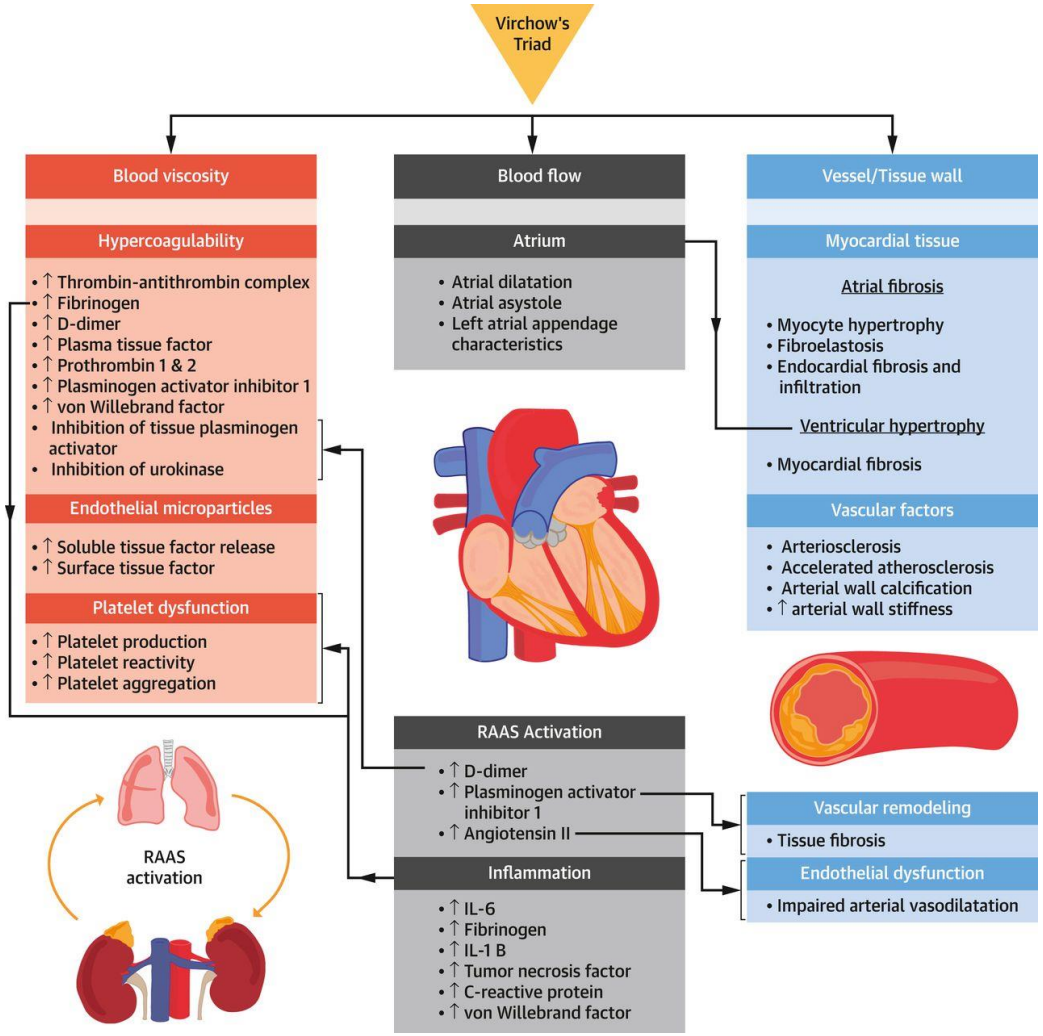
Professor of Medicine

ACOI Annual meeting Oct 2019



Shankar Kumar et al. J Am Coll Cardiol 2019;74:2204-2215

Attributes of The Ideal anticoagulant?

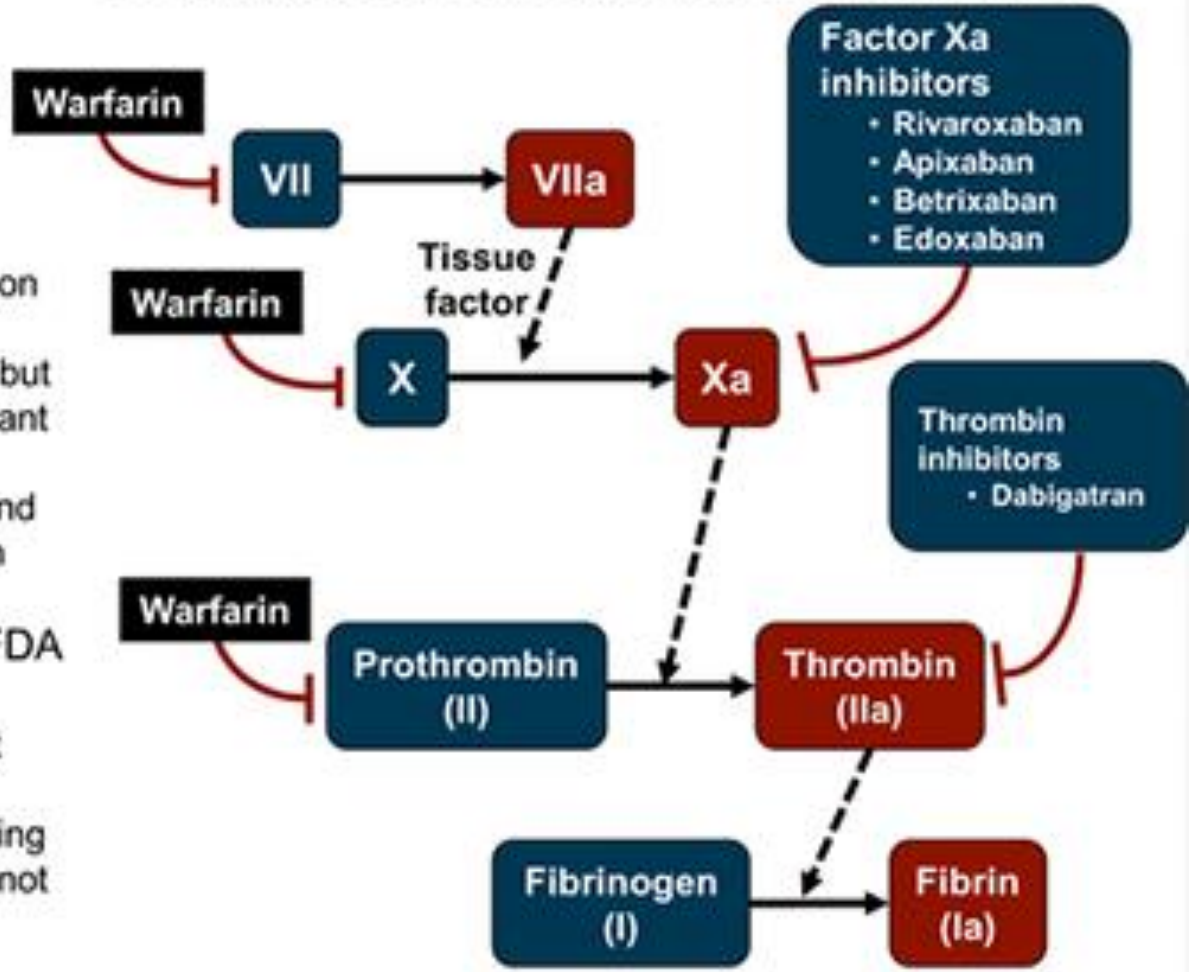
- Oral administration
- Rapid onset/offset of action
- Wide therapeutic range
- Predictable therapeutic effect with fixed dosing
- Well defined pharmacokinetics in renal/hepatic disease
- No food or drug-drug interactions
- No monitoring required(but available)
- Easily reversible
- Cost effective

Oral Anticoagulants in AF[a,b]

A Brief History

- VKAs (eg, warfarin, phenprocoumon): introduced in the 1950s
  - Mechanism of action: inhibit hepatic vitamin K-dependent synthesis of multiple coagulation factors
  - Inexpensive and widely used, but have unpredictable anticoagulant effects
  - Require frequent monitoring and dose adjustment; bridging with parenteral anticoagulant
- NOACs (first approved by the FDA in 2010 [dabigatran])
  - Mechanism of action: interrupt coagulation cascade
  - Do not require routine monitoring
  - Antidotes/reversal agents are not yet widely available

Coagulation Cascade and Anticoagulant Action[c]

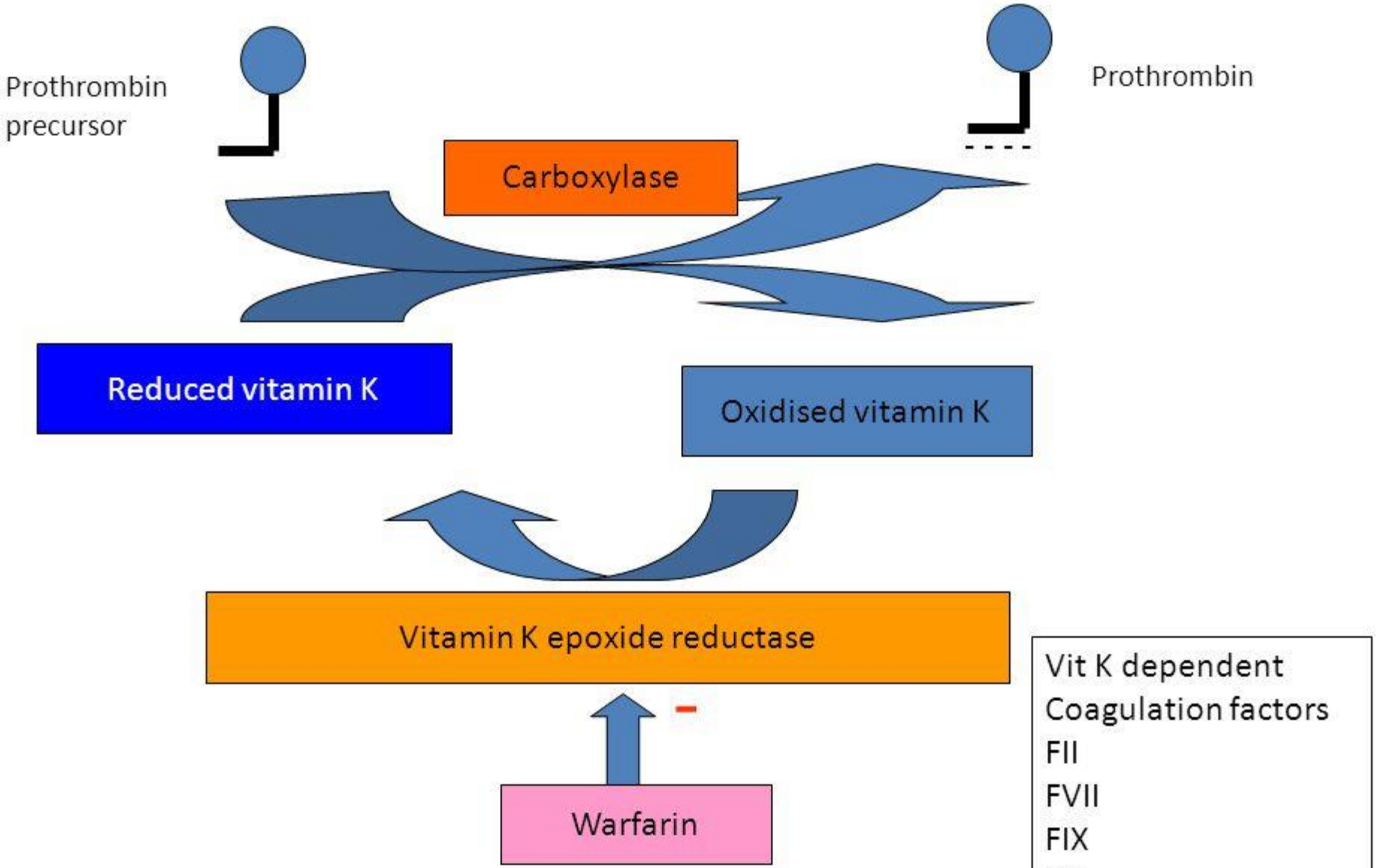


a. Mani H, et al. *Drug Des Dev Ther*. 2014;8:789-798[1]; b. Steinberg BA, et al. *BMJ*. 2014;348:g2116[2]; c. Makaryus JN, et al. *Nat Rev Cardiol*. 2013;10:397-409.[20]

Indications

- Vitamin K antagonists (VKAs)oral vitamin antagonists
- Prevention of arterial and venous thromboembolic events (VTE)
- Safe and effective if a high time in the therapeutic range is achieved
- Challenge in context of drug and food interaction and liver disease
- Thromboembolism (undertreatment)
- Bleeding (overtreatment)

Warfarin Mode of Action



Vit K dependent Coagulation factors
FII
FVII
FIX
FX

Onset of action- >5 days; not until INR >2 for 24hrs

Terminology

- VKA
- INW
- NOAC
- DOAC International Society on Thrombosis and Haemostasis

Barnes GD, Ageno W, Ansell J, Kaatz S. Recommendation on the nomenclature for oral anticoagulants: communications from the SSC of the ISTH: reply. *J Thromb Haemost* 2015;**13**(11):2132–3.

Direct Oral Anticoagulants

1.Indications for using DOAC’s

2. Types of DOACS

3. Half –life and mode of elimination

4.DOACs and organ failure

5. Reduced absorption and enterohepatic recirculation

6.Monitoring of DOAC

Conclusion

attractive options for anticoagulation.

Advantages DOACs > VKAs

rapid onset and offset of anticoagulant effect

fixed dosing

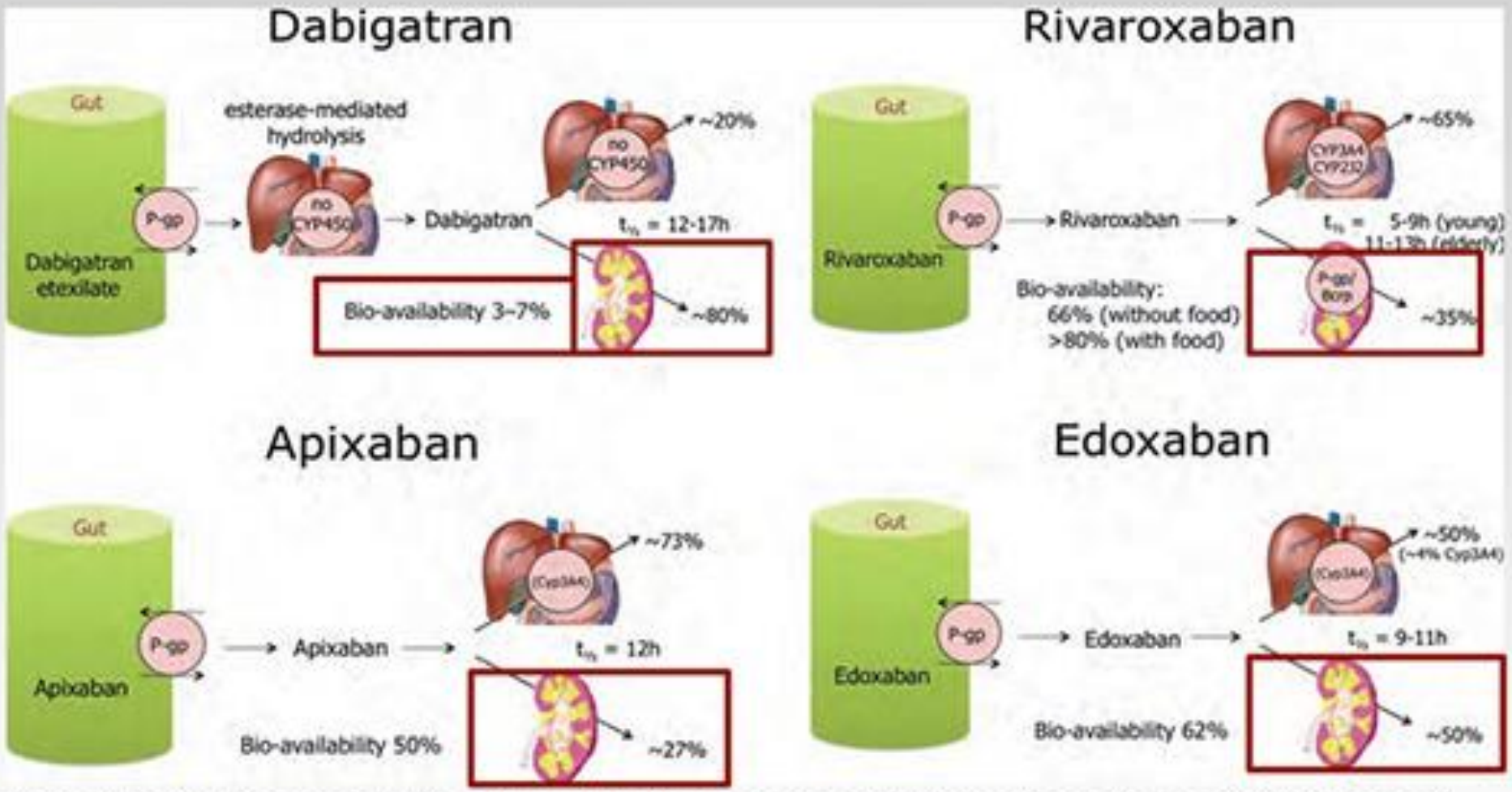
fewer drug and dietary interactions

no monitoring requirement

DOAC Time line

Dabigatran RE-LY 2009	**Pradaxa**
Rivaroxaban Rocket-AF 2010	**Xarelto**
Apixaban Aristotle 2011	**Eliquis**
Edoxaban Engage 2013	**Savaysa**
Betrixaban Apex 2016	**Bevyxxa**

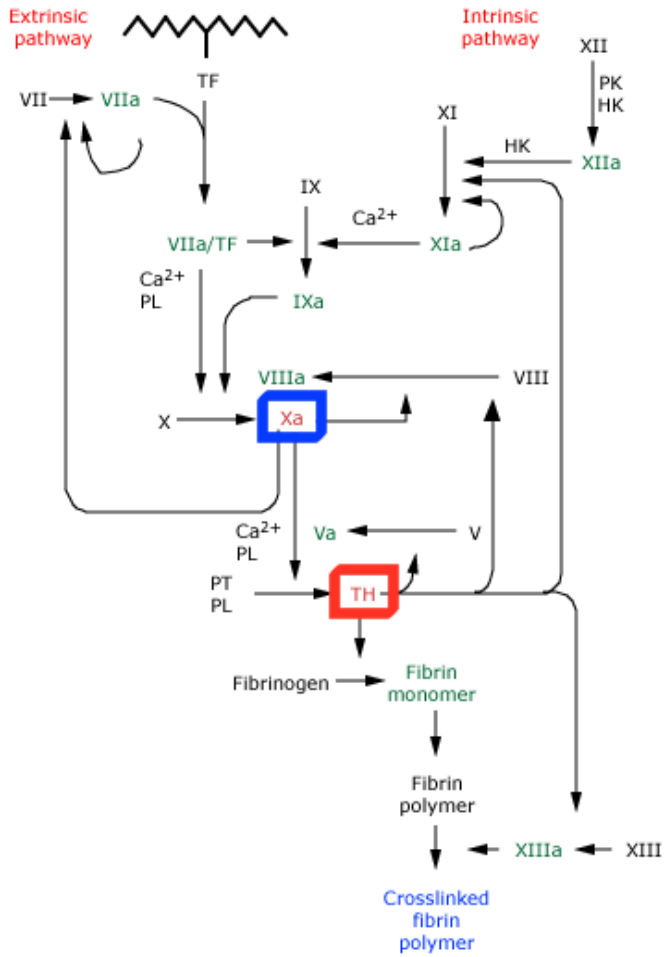
Absorption and Metabolism of NOACs



There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolism /excretion. The brackets around (Cyp3A4) with apixaban indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged

Heidbuchel H, et al. *Europace*. 2013;15:625-651.[23]

Coagulation cascade



Rivaroxaban

Dabigatran

Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors.
HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.
Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:8.

	Vitamin K Antagonists	FXa Inhibitors			Direct Thrombin Inhibitors	
	Warfarin	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Dabigatran**	**Ximelagatran**
Mode of action	Inhibition of hepatic synthesis of vitamin K-dependent coagulation factors	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of clot-bound and free thrombin (FIIa)	Direct inhibition of thrombin (FII)
Time to peak effect (hours)	72–96	0.5–3	3	1.5	2–3	1.6–1.9
Half-life hours	20–60	5–9 (9–13 in elderly)	8–13	9–11	14–17	4–5
Bioavailability %	100	80	66	50	6.5	20
Recommended therapeutic dose and frequency	Adjusted-dose based on INR; once daily	20 mg; once daily	5 mg; twice daily	30 mg or 60 mg; once daily	150 mg; twice daily	Not available in the U.S.
Monitoring	Required using INR	Not required In case of hemorrhage or renal impairment, FXa-dependent assays may be used[47]	Not required due to predictable pharmacokinetics In hemorrhage or renal impairment, FXa-dependent assays may be used[47]	Not required due to predictable pharmacokinetics	Not required except in subgroups such as patients with renal impairment [48] Ecarin clotting time can be used if needed[49]	Not required
Renal excretion[39]	1% excreted unchanged in the urine	66% renal elimination	50% renal elimination	45% renal elimination	80% renal elimination	Main route of elimination
Interactions	CYP2C9, CYP1A2, CYP3A4 inhibitors Dietary vitamin K[50]	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors[50]	Potent CYP3A4 inhibitors[50]	P-glycoprotein inhibitors[43]	P-glycoprotein inhibitors Proton pump inhibitors[38]	NA
Drug reversal	Vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant FVIIa[51]	FVIIa partially reverses rivaroxaban anticoagulant effect[52] Prothrombin complex concentrate completely reverses its anticoagulant effect[53]	No available antidote	No available antidote	It is partially dialyzable[54]	NA
Precautions	Severe active bleeding, pregnancy, breast feeding, documented hypersensitivity[55] Severe renal impairment (glomerular filtration rate <30 mL/min/1.73m^2)[39]	Severe active bleeding; severe renal impairment[39]	Severe active bleeding; severe renal impairment	Severe active bleeding; severe renal impairment	Severe active bleeding, severe renal impairment[39]	NA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY

- N = 18,113, Follow-up median 2 years, CHADS2 median 2.1, open-label
- Inclusion: Afib on EKG w/in last 6 months, plus at least one: CVA, TIA, LVEF < 40%, NYHA class II or great HF symptoms w/in 6 months and age of at least ≥75 or 65-74 plus DM, HTN, or CAD
- Exclusion: severe heart-valve disorder, stroke w/in 14 days or severe stroke w/in 6 months, increased risk of bleeding, CrCl < 30, liver dx, prenancy
- Randomized to 110 or 150 mg of dabigitran BID vs unblinded warfarin (ASA <100 mg or other antiplatelet agents allowed)
- Primary outcome: stroke or systemic embolization
- Safety outcome: major hemorrhage (reduction of Hgb by 2 g/dL, 2 units of PRBCs, or symptomatic bleeding in critical area)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

ROCKET-AF

- N = 14,264, Follow-up median 1.6 yrs, CHADS2 median 3, double-blind
- Inclusion: Non-valvular Afib by EKG w/ hx of stroke, TIA, or embolism or with at least a CHADS2 ≥ 2
- Randomized to rivaroxaban 20 mg daily or 15 mg daily depending on CrCl vs warfarin
- Primary outcome: stroke and embolism
- Safety end point: major and non-major clinically relevant bleeding

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D.,
Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D.,
David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D.,
for the RE-COVER Study Group*

December 6, 2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

December 2010

Action Points

- The direct oral anticoagulant rivaroxaban did not demonstrate noninferiority to dose-adjusted vitamin K antagonists (VKAs) for secondary prophylaxis in patients with thrombotic antiphospholipid antibody syndrome (APS).
- Note that recurrent thrombotic events in the rivaroxaban group were predominantly arterial, with a high rate of stroke (nine events vs none for those receiving VKAs).

Betrixaban

- Bevyxxa
- Once daily Factor Xa inhibitor
- Extended prophylaxis of venous thromboembolism (VTE)
- Bevyxxa (betrixaban) is indicated for the prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- The recommended dose of Bevyxxa is an initial single dose of 160 mg starting on day 1, followed by 80 mg once daily taken for 35 to 42 days at the same time each day with food.

Betrixaban

- **Warning: Spinal / Epidural Hematoma**
- Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis.

Bevyxxa

- An epidural catheter should not be removed earlier than 72 hours after the last administration of Bevyxxa.
- The next Bevyxxa dose is not to be administered earlier than 5 hours after the removal of the catheter.
- If traumatic puncture occurs, delay the administration of Bevyxxa for 7 hours.
- Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary.

Bevyxxa Use in severe renal impairment

- Patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min computed by Cockcroft-Gault) taking Bevyxxa may have an increased risk of bleeding events.

- Reduce dose of Bevyxxa, monitor patients closely, and promptly evaluate any signs or symptoms of blood loss in these patients.

Bevyxxa

Concomitant P-glycoprotein (P-gp) Inhibitors

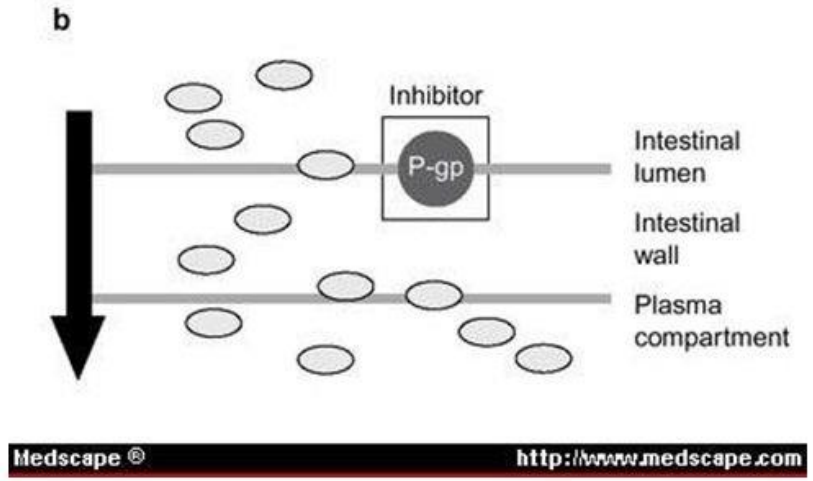
- Avoid use of Bevyxxa in patients with severe renal impairment receiving concomitant P-gp inhibitors.

- Patients on concomitant P-gp inhibitors with Bevyxxa may have an increased risk of bleeding. Reduce dose of Bevyxxa, monitor patients closely, and promptly evaluate any signs or symptoms of blood loss in these patients.ccxcxxx

P-gp inhibitors

- Valspodar
- Quinidine
- Verapamil
- Cyclosporin
- Spironolactone
- Ketoconazole
- Erythromycin

- Amiodarone
- Diltiazem
- Itraconazole



Hansten, PD. Role of P-Glycoprotein and Organic Anion Transporting Polypeptides in Drug Absorption and Distribution: Focus on H1-Receptor Antagonists. Clin Drug Invest 21 (8):587-596, 2001. Posted to Medscape 8/1/01

Bevyxxa Hepatic impairment

- Bevyxxa has not been evaluated in patients with hepatic impairment, because these patients may have intrinsic coagulation abnormalities.

- Bevyxxa is not recommended in patients with hepatic impairment.

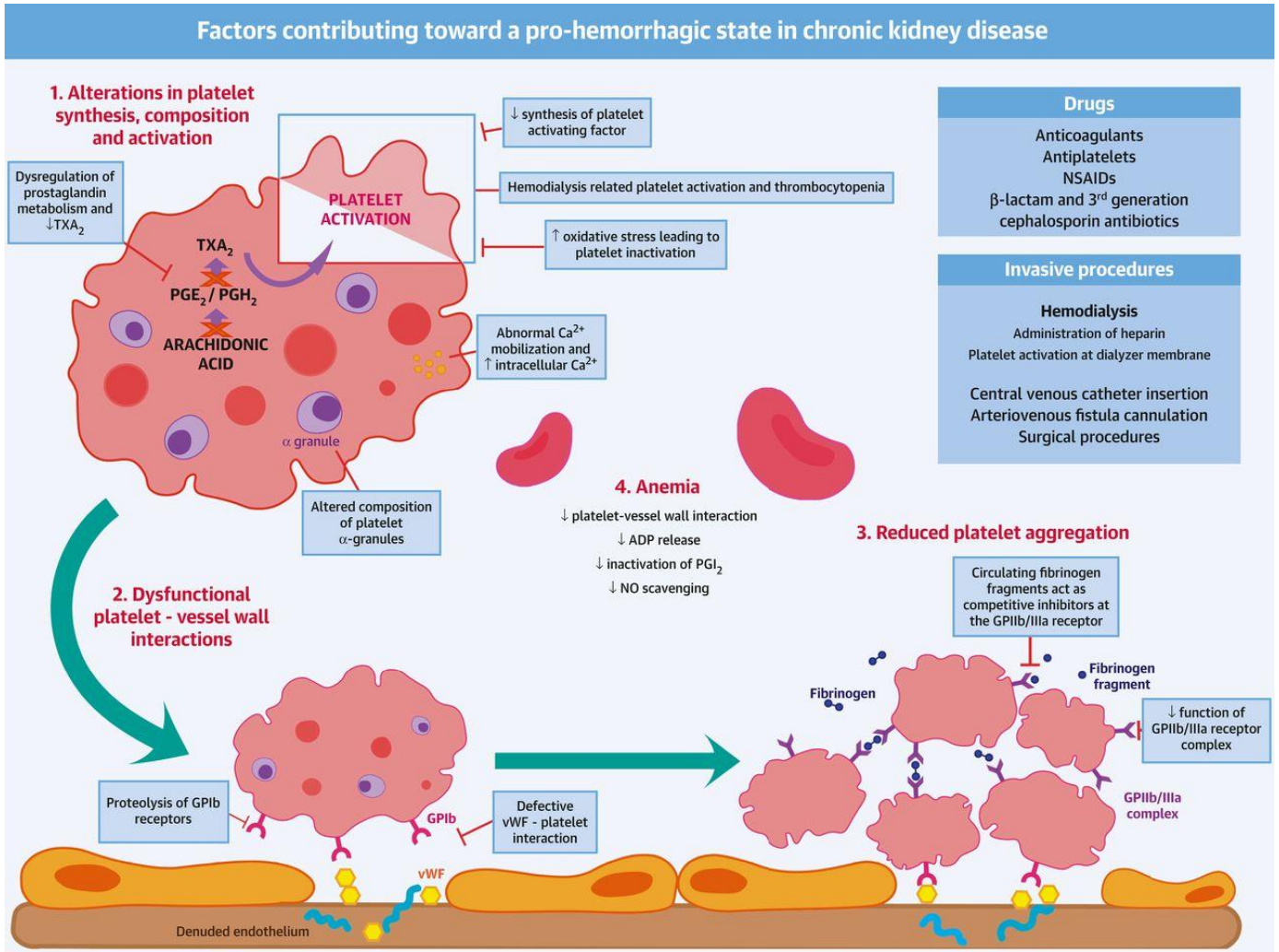
Bevyxxa

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement.

Discontinue Bevyxxa in patients with active pathological bleeding.

There **is no established way to reverse the anticoagulant effect of betrixaban,** which can be expected to persist for **at least 72 hours after the last dose.**



Shankar Kumar et al. J Am Coll Cardiol 2019;74:2204-2215

Table 2: Effect of Direct Oral Anticoagulants on Haemostasis Tests and Drug Concentration Quantification[36,37]

NOAC	Quantification	PT	aPTT	TT
Dabigatran	Dilute TT (DTI assay), ECT, chromogenic anti-IIa assay	Variable depending on reagent	If normal, excludes supratherapeutic concentration	If normal, excludes clinically-relevant concentration
Rivaroxaban	Anti-Xa concentration (calibrated for rivaroxaban)	If normal, excludes supratherapeutic concentration; can be used for crude estimation	Less sensitive than PT	Insensitive
Apixaban	Anti-Xa concentration (calibrated for apixaban)	Insensitive; might have normal PT, despite therapeutic concentration	Insensitive; might have normal aPTT, despite therapeutic concentration	Insensitive
Edoxaban	Anti-Xa concentration (calibrated for edoxaban)	If normal, excludes clinically-relevant concentration	If normal, excludes clinically-relevant concentration	Insensitive

aPTT = activated partial thromboplastin time; DTI = direct thrombin inhibitor; ECT = ecarin clotting time; NOAC = new/novel oral anticoagulant; PT = prothrombin time; TT = thrombin time.

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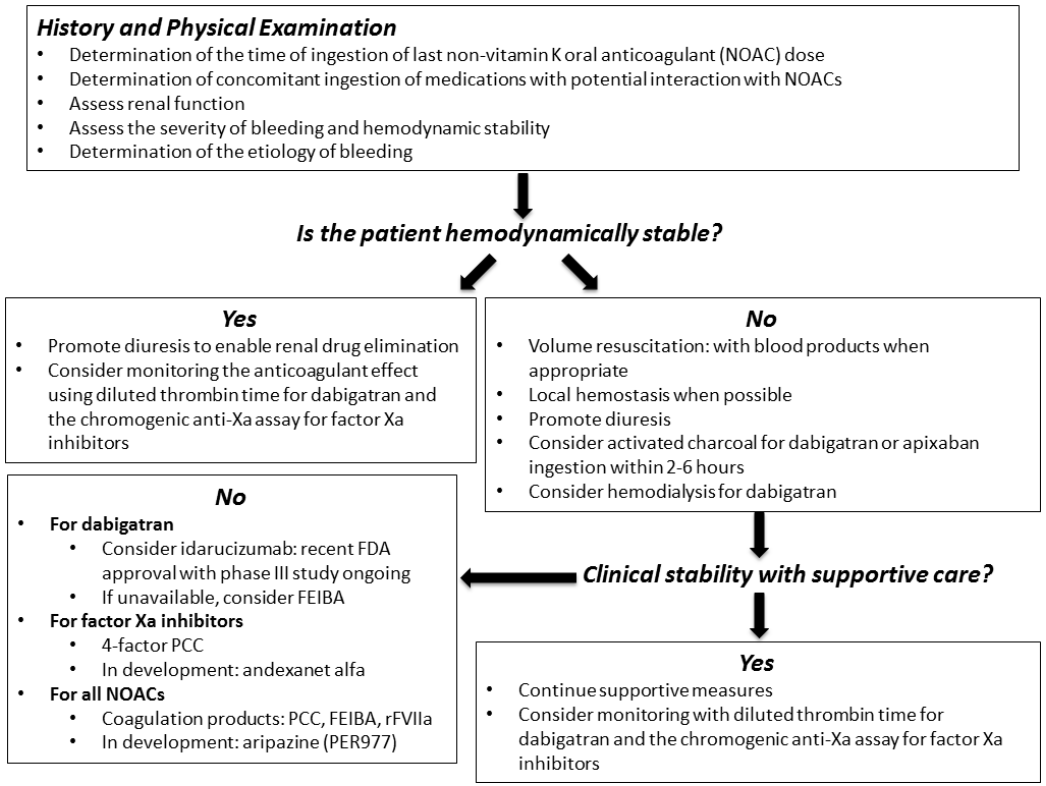
Strategy for managing acute bleeding with DOAC



Atrial fibrillation + PCI

- An edoxaban-based dual regimen was noninferior to standard triple therapy (P2Y12 inhibition, aspirin, and a vitamin K antagonist) on the composite endpoint of major or clinically relevant non-major bleeding over 12 months in patients with atrial fibrillation (AF) who had percutaneous coronary intervention (PCI).
- Note that use of dual antithrombotic therapy did not imply that aspirin should be omitted in the peri-PCI period

Lessons learned from PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI trials:

- An NOAC should be the anticoagulant of choice and used at the dose shown to be effective in regulatory trials of AF
- A VKA-based triple antithrombotic regimen should generally be avoided
- Pending a full assessment of prasugrel or ticagrelor combined with an NOAC, clopidogrel is the P2Y12 inhibitor of choice because it was the most used in the trials
- Dual antithrombotic therapy seems to be the best option for patients with AF who have had PCI when concerns about bleeding prevail over concerns about stent thrombosis

Cost -antidotes

- Andexant $580.00
- 800 mg bolus
- 960 mg infusion
- 3300 mg /100 ml vial

- Idaucizumab
- 4200.00 /dose

Table 3: Recommended Timing of Discontinuation of Direct Oral Anticoagulants Pre-procedure[38]

	CrCl (ml/min)	Half-life (h)	Risk of bleeding (h)	
			Low	High
Dabigatran	≥80	13	24	48
	≥50 to <80		24–48	48–72
	≥30 to <50		48–72	96
Rivaroxaban	≥30	9	24	48
	<30		48	72
Apixaban	≥30	8	24	48
	<30		48	72
Edoxaban	≥30	10–14	24	48
	<30		48	72

CrCl = creatinine clearance using Cockroft–Gault method.

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ANNEXA-4: Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Ongoing, multicenter, prospective, open-label, single-group study. **Not a placebo-controlled trial.**

Included 67 patients from April 2015 to July 2016 who had acute major bleeding

Primary outcomes:

- Percent change in the anti-Xa activity
- Rate of excellent or good hemostatic efficacy 12 hours after the infusion.

Primary sites of bleeding: **GI 33/67 (49%), intracranial 28/67 (42%)**, **other bleeding sites in 6/67 (9%)** which included a nose bleed…

All patients received a bolus followed by a 2-h infusion of the drug.

How ANDEXANET Works

Andexanet has a rapid onset with a ***half-life of approximately 1 hour***.[4] The package insert states 5-7 hours.[1] Based on the phase 2 trials demonstrating *the change in anti-Factor Xa activity* in healthy volunteers, in addition to the safety profile observed in ANNEXA-4, Andexanet received FDA approval on May 3, 2018.

1. *Andexxa (andexanet alfa) [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals, Inc; May 2018.*
2. Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016; 375:1131–1141.

ANNEXA-4: Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Mean (± SD) time from ED presentation to the administration bolus was **4.8 ± 1.8 hours**. (what was everyone doing?).

Clinical hemostasis was evaluated 12 hours after the andexanet infusion, adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis.

Anti-Xa activity **re-elevated at 2 hours post-infusion**. When the infusion is discontinued, andexanet starts to dissociate from the Xa inhibitors resulting in the potential to inhibit FXa.

Thrombotic events occurred in 12/67 (18%)

During the 30-day follow-up, 15% of the patients died.

How it Works

How ANDEXANET Works

Andexanet is a recombinant modified Factor Xa molecule that binds and sequesters the FXa inhibitors, rivaroxaban and apixaban. In addition, Andexanet inhibits the activity of Tissue Factor Pathway Inhibitor (TFPI), increasing tissue factor-initiated thrombin generation.[1]

1.Andexxa (andexanet alfa) [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals, Inc; May 2018.2Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al.

2. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016; 375:1131–1141.

Kcentra Factor IX concentrate

- $2.17/IU cost
- 2500 IU /$5425
- 5000 IU / $10,850 max dose

OAC - Choosing Wisely

Patients with **compliance problems**?

Warfarin(monitoring)

Rivaroxaban or Edoxaban(daily dosing)

Patient with **history of GI Bleeding ?**

warfarin ,Apixaban or Edoxaban(NOT dabigatran, rivaroxaban)

Patient with **Kidney dysfunction**

consider Apixaban or warfarin

Survival?

Apixaban demonstrated an overall survival advantage compared to warfarin

Anticoagulants in Atrial fibrillation:

Adherence among elders reduces stroke risk by **40%**

Takeaway

Persistent adherence to an oral anticoagulant among Medicare beneficiaries with a new Atrial fibrillation diagnosis is tied to a 40% stroke risk reduction.

Why this matters

Sticking with the anticoagulant plan is important among these patients, who tend to drop off in the first year, with only a third making it to 12 months.

Source: ***Am J Cardiovasc Drugs*** *Curated by:* ***Emily Willingham, PhD*** *September 18, 2019*

Anticoagulants in Atrial fibrillation:

Adherence among elders reduces stroke risk by **40%**

Source: ***Am J Cardiovasc Drugs*** *Curated by:* ***Emily Willingham, PhD*** *September 18, 2019*

Key results

Only 35.0% spent the follow-up remaining adherent.

Adherence was tied to reduced stroke risk vs nonuse: aHR, 0.62 (95% CI, 0.52-0.74).

Partial adherence was also linked to reduced risk, just less so: aHR, 0.74 (95% CI, 0.57-0.95).

Risk decreases did not differ with adherence to an oral anticoagulant vs warfarin: HR, 0.77 (95% CI, 0.56-1.04).

Study design

Analysis of 2013-2016 Medicare claims data for 39,272 patients with a new Afib diagnosis, 2014-2015.

Funding: National Heart, Lung and Blood Institute.

Limitations

Limitations of claims data, including no confirmation that filled prescriptions were actually used.

warfarin

- Mechanical heart valves
- Patient preference
- Cost prohibitive
- Poor renal Function
- ?questionable patient compliance (longer half life, daily dosing
- Ability to monitor are advantages) vs (liability and do you feel comfortable utilizing in non-compliant patient?)

Indications

Stroke prevention in atrial fibrillation(non-valvular)

- dabigatran
- rivaroxaban
- apixaban
- Edoxaban

Treatment of arterial and venous thromboembolic events (VTE)

Thromboprophylaxis following major orthopedic surgery

Prevention atherothrombotic events following acute coronary syndrome(ACS)

- rivaroxaban

rivaroxaban

- Superior to aspirin for prevention DVT post Hip surgery

Table 1: Drug Interactions with Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Increased concentration	Strong p-gp inhibitors: ketoconazole, ciclosporin, tacrolimus, ritonavir, dronedarone Caution with: amiodarone, verapamil, clarithromycin, quinidine, ticagrelor	Strong CYP3A4 and p-gp inhibitors: ketoconazole, ritonavir, dronedarone Caution with: ciclosporin, tacrolimus	Strong CYP3A4 and p-gp inhibitors: ketoconazole, ritonavir, dronedarone	Strong p-gp inhibitors: reduce dose with ketoconazole, ciclosporin, dronedarone Caution with: ritonavir
Reduced concentration	Strong p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates, dexamethasone	Strong CYP3A4 and p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates	Strong CYP3A4 and p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates	Strong p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates, dexamethasone

p-gp = P-glycoprotein.

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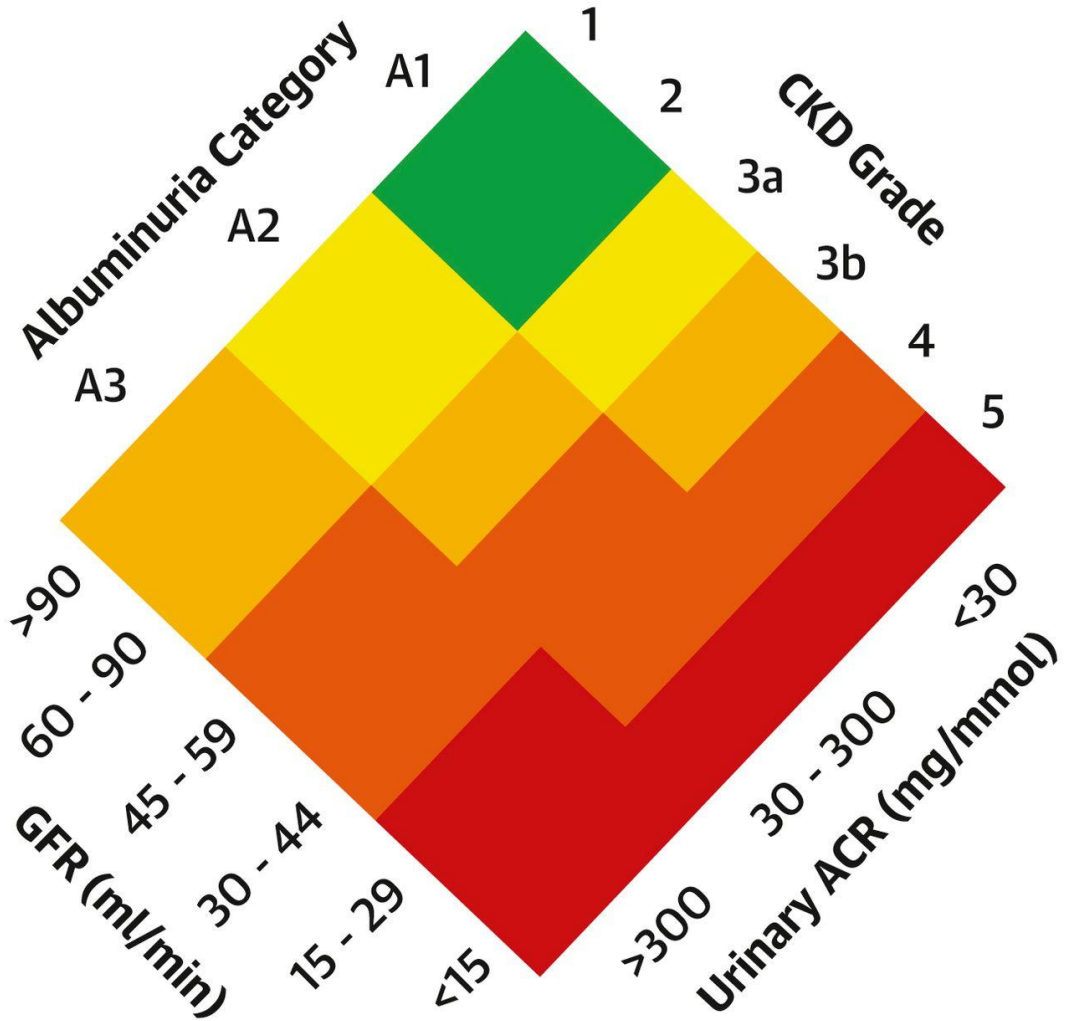
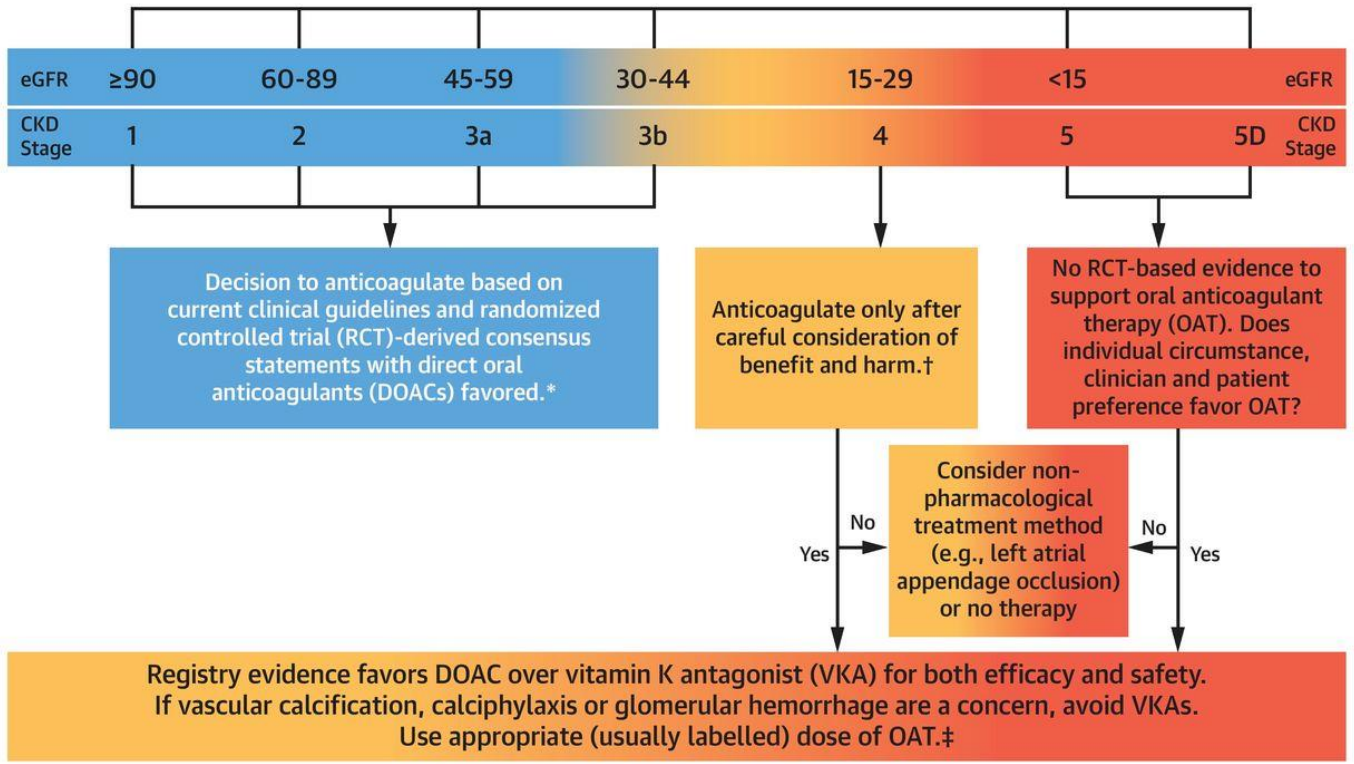


Shankar Kumar et al. J Am Coll Cardiol 2019;74:2204-2215

CENTRAL ILLUSTRATION: Proposed Approach to Stroke Thromboprophylaxis in a Patient With Concomitant Chronic Kidney Disease and Atrial Fibrillation



Kumar, S. et al. J Am Coll Cardiol. 2019;74(17):2204-15.

Shankar Kumar et al. J Am Coll Cardiol 2019;74:2204-2215

Age	Normal renal function or CKD stages 1-2	CKD stage 3	CKD stage 4	CKD stage 5D
<75 years	(Extensive RCT data available) Warfarin—adjusted dose Dabigatran 150 mg PO BID Rivaroxaban 20 mg PO daily Apixaban 5 mg PO BID* Edoxaban 60 mg PO daily (Edoxaban is not recommended if CrCl>95 ml/min.)	(Reasonable representation in RCTs) Warfarin—adjusted dose Dabigatran 150 mg PO BID Rivaroxaban 15 mg PO daily Apixaban 5 mg or 2.5 mg PO BID* Edoxaban 30 mg PO daily	(No RCT data) Dabigatran 75 mg twice daily approved by FDA.	(No RCT data) Warfarin-adjusted dose Apixaban 5 mg or 2.5 mg twice daily*
> 75 years	Based on meta-analysis of 10 RCTs ** involving 25,031 patients > 75 years, newer anticoagulants (Dabigatran/Rivaroxaban/Apixaban) equivalent to conventional therapy in efficacy and bleeding risk. In ENGAGE AF TIMI 48 for Edoxaban, 40% patients were ≥ 75 yrs and 17% ≥ 80 years of age.		(No RCT data)	(No RCT data) Warfarin-adjusted dose Apixaban 2.5 mg daily*

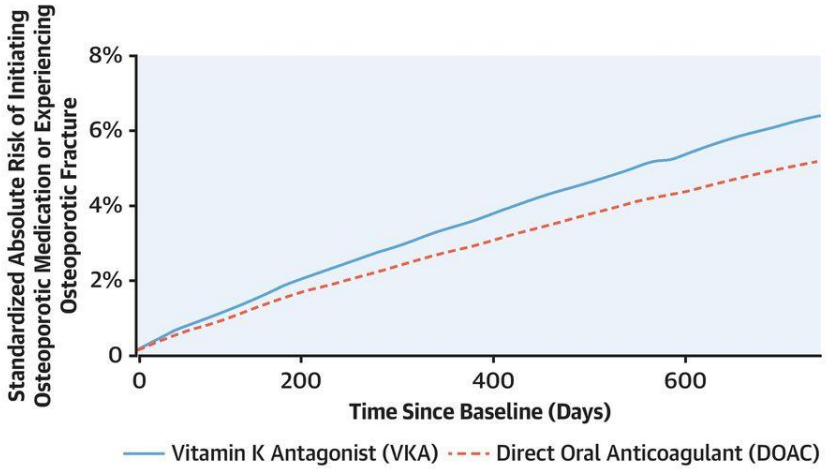
Description:

Legend: RCT = randomized controlled trial; CrCl = creatinine clearance; BID = twice daily.

*Based on the ARISTOTLE trial, FDA label recommends dose of apixaban to be reduced to 2.5 mg twice daily if any two of the following criteria are met: age ≥80 years, creatinine ≥ 1.5 mg/dl or weight ≤ 60 kg.

** Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. *J Am Geriatr Soc* 2014;62:857-64.

CENTRAL ILLUSTRATION: Standardized Absolute 2-Year Risk of Osteoporotic Fractures Among Atrial Fibrillation Patients



	Standardized Absolute 2-Year Risk (95% CI)
Any Fracture	
VKA	3.77% (3.37% to 4.19%)
DOAC	3.09% (2.85% to 3.33%)
Initiation of Osteoporotic Medication	
VKA	3.14% (2.79% to 3.51%)
DOAC	2.44% (2.22% to 2.66%)

Binding, C. et al. J Am Coll Cardiol. 2019;74(17):2150-8.

Casper Binding et al. J Am Coll Cardiol 2019;74:2150-2158

COST

Savaysa	Edoxaban	$332.00/month
Eliquis	apixaban	$473.25/month 5 mg bid
		$473.25/ month 2.5 mg bid
Xarelto	rivaroxiban	$477.30 10 mg /d
		$477.30 20 mg/d
Pradaxa	dabigatran	$266.44

Summary

- Non-inferior for prevention of stroke/embolism in Afib
- Non-inferior for treatment of DVT/PE
- NNT for clinical benefit are large
- Probable reduced hemorrhagic stroke rate
- Reduced rate of fatal bleeding events
- Increased incidence of GI bleeds
- Perhaps increased incidence of MIs with dabigatran
- Cost of drug/year $3000

The End