Dabigatran beyond Atrial Fibrillation

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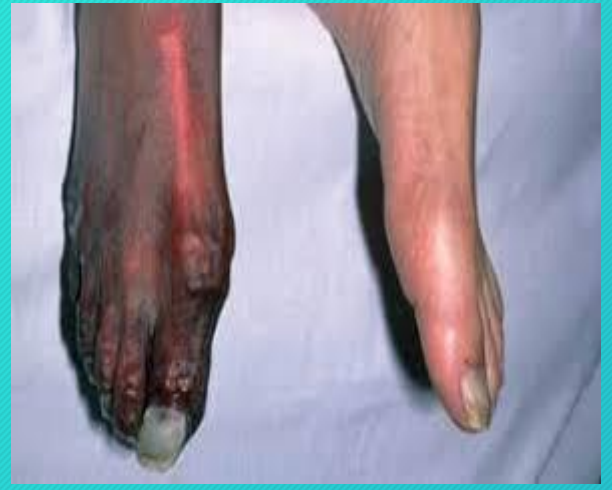
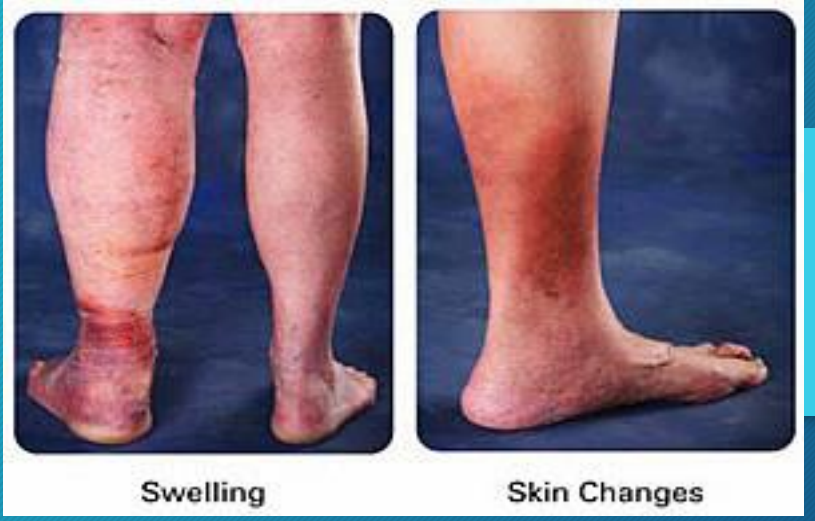
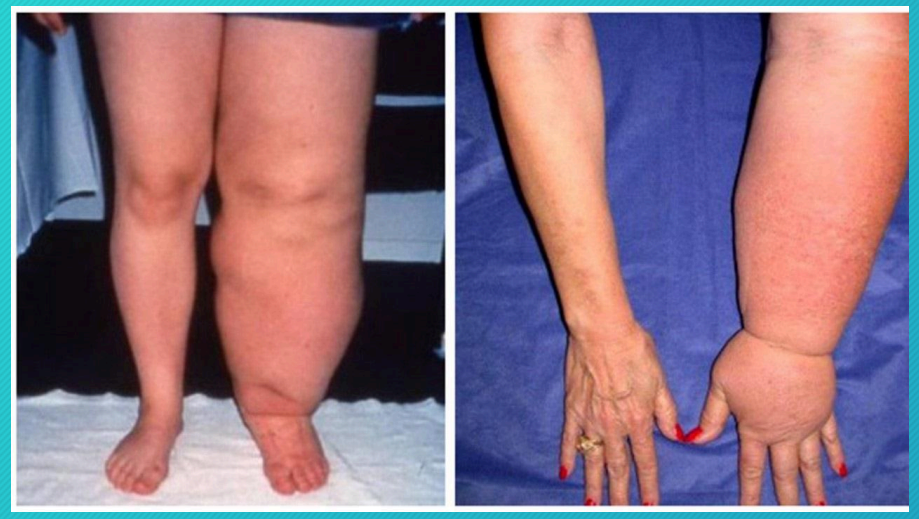
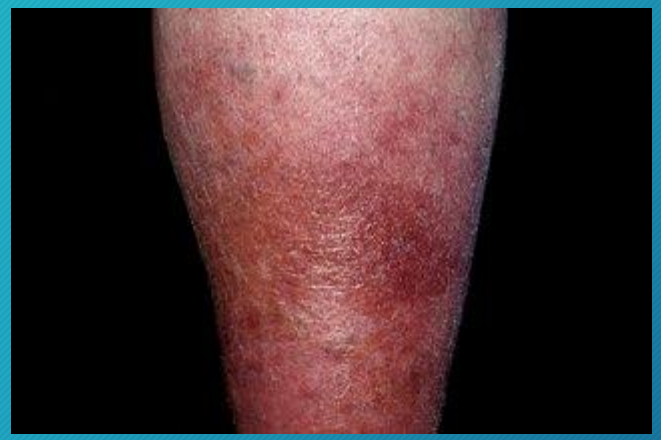








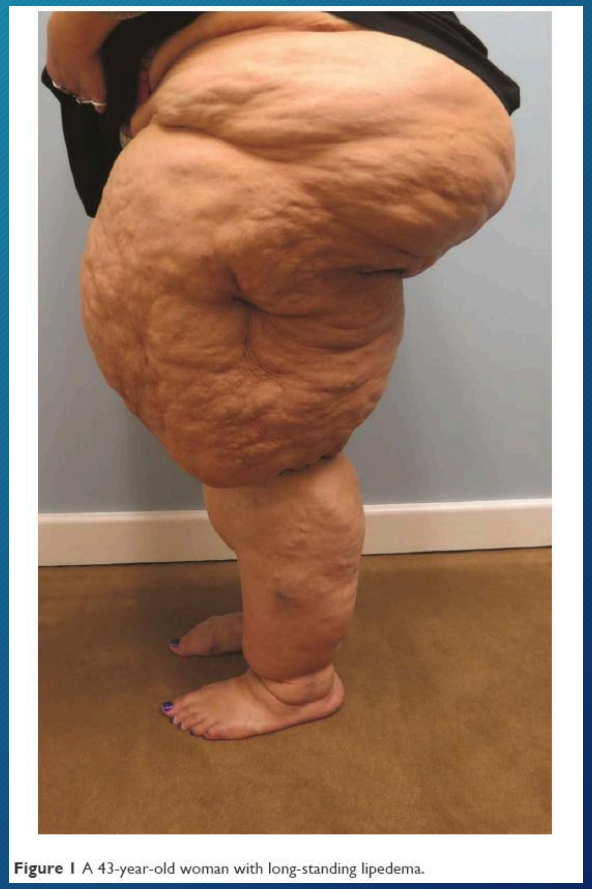


Figure 1 A 43-year-old woman with long-standing lipedema.

Topic will cover

- Pathway of NOAC
- Switching to NOAC from others anticoagulants
- Indications of NOAC
- Reversal of NOAC
- New reversal agent

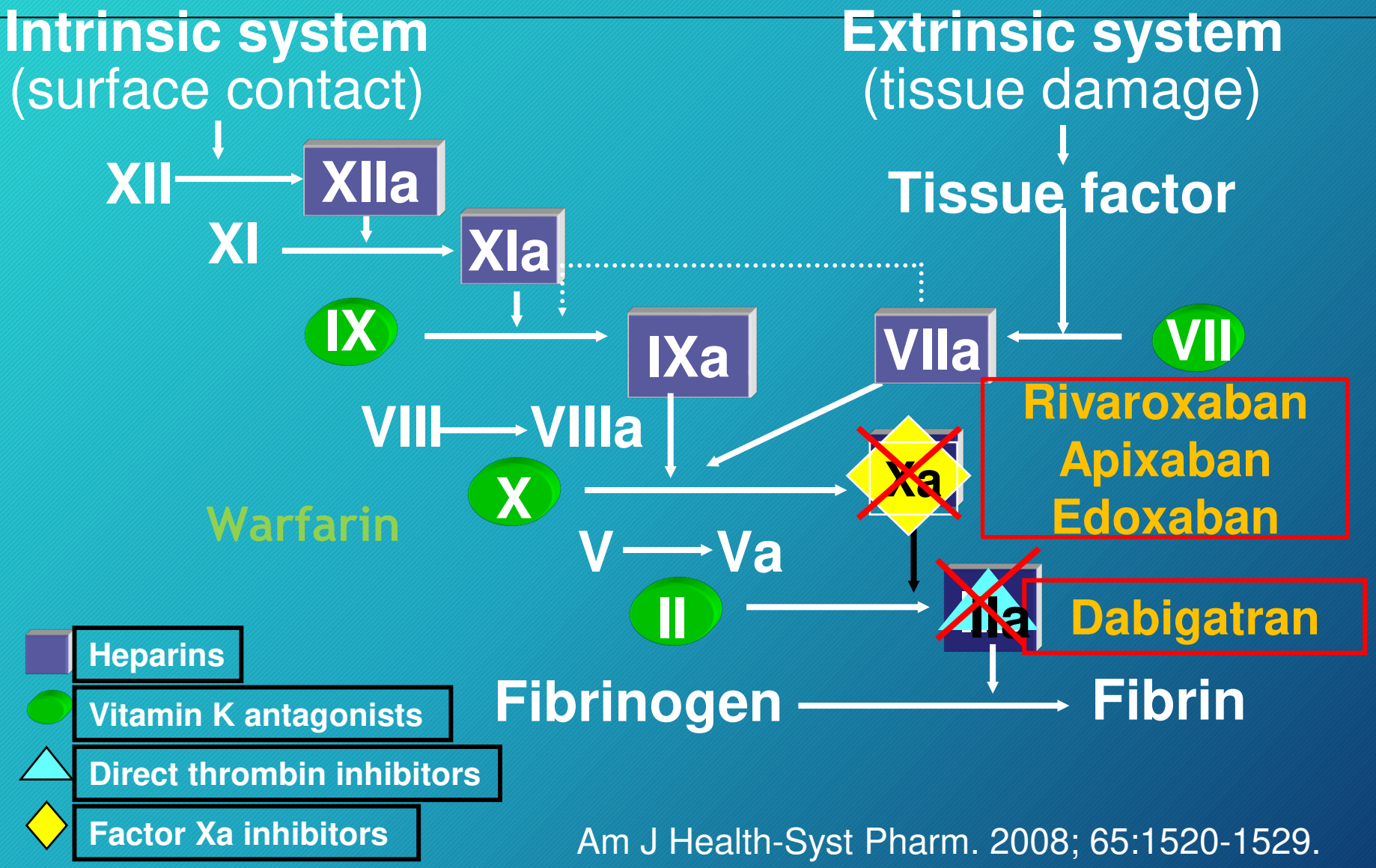
Different names in oral Anticoagulants

- NOAC- Novel oral anti coagulants and Non Vitamin K oral anticoagulants.
- TOAC- Target Specific oral anticoagulants
- DOAC- Direct oral anticoagulants

Why are the NOAC so appealing?

Warfarin	NOACs
Vitamin K Narrow Therapeutic index Many Drugs interactions Delayed Pharmacodynamical index	Not impacted by dietary intake of K More consistent pharmacokinetics Fever drug interaction Relatively quick onset of action Not all require heparin administration prior to use for VTE

Anticoagulants: Mode of Action



Am J Health-Syst Pharm. 2008; 65:1520-1529.

	Warfarin (Coumadin®)	Dabigatran (Pradaxa®)	Rivaroxaba (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Drug Class	Anticoagulant (vitamin K antagonist)	Anticoagulant (direct thrombin inhibitor)	Anticoagulant (factor Xa inhibitor)	Anticoagulant (factor Xa inhibitor)	Anticoagulant (factor Xa inhibitor)
Mechanism of Action	Depletes vitamin K inhibiting factors II, VII, IX, X	Reversible direct thrombin inhibitor (PRODRUG)	Selective inhibition of factor Xa	Selective inhibition of factor Xa	Selective inhibition of factor Xa
Indication	**DVT/PE/AF:** INR 2.0-3.0 2.5-3.5 (mechanical mitral valve)	**DVT/PE/NVAF:** 150 mg BID (CrCl > 30 ml/min) 75 mg twice daily PO (CrCl 15-30 ml/min) Not recommended in CrCl < 15 ml/min	**DVT/PE:** 15 mg BID with food for 3 weeks followed by 20 mg once daily **Orthopedic prophylaxis:** 10 mg once daily **Nonvalvular atrial fibrillation***: 20 mg once daily with food PO; 15 mg once daily for CrCl 15-50 ml/min Can give via NG tube: mix with 50ml water	**DVT/PE:** 10 mg BID followed by 5 mg BID for 6 months **Nonvalvular atrial fibrillation**: 5 mg twice daily PO; 2.5 mg BID if ≥2 of the following: ≥ 80 yo, ≤ 60kg, Cr ≥ 1.5 mg/dL	**DVT/PE/NVAF:** 60 mg/d 30 mg/d: patients with CrCl 30-50 mL/min, weight 60 kg, or concomitant use of PgP inhibitors

Annu Rev Med 2011;62:41-57. Erikkson BI, et al. Clin Pharmacokinet 2009;48:1-22. JAMA 2015;:314: 76-7.

NOAC administration instructions:

Dabigatran (Pradaxa®)	• Swallow whole with or without food • Do not chew or open capsule • Keep in original packaging • Do not transfer capsule to a dose administration aid
Apixaban (Eliquis®)	• Swallow whole with or without food • Can be used in dose administration aids
Rivaroxaban (Xarelto®)	• 10 mg tablet may be taken with or without food • 15 mg and 20 mg tablet should be taken **with food** Can be used in dose administration aids

Images courtesy of MIMS Australia

MEDICATION SAFETY AND QUALITY High-Risk Medicines

Warfarin and NOAC Pharmacokinetics

Characteristics	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Betrixaban	Edoxaban
Molecular weight (Da)	308	628	460	436	452	548
Bioavailability (%)	98	6–7	66	63–79	40–80[a]	50[a]
*t*max (h)	72–120	2–3	1–3	2–4	NR	1–3
*t*1/2 (h)	20–60	7–17	8–15	7–13	5[a]	9–11
Protein binding (%)	99	35	87	95	NR	54
Food effect	Yes	Delayed absorption	No	Delayed absorption	No	No
Dosing regimen	once daily	twice daily	twice daily	once daily	once daily	once daily
Metabolism/elimination	100% liver	80% renal 20% liver	25% renal 75% fecal	1/3 renal 2/3 liver	5% renal 95% liver	35% renal 65% liver
Substrate CYP	2C9, 3A4	No	3A4	3A4, 2J2	No	3A4
Substrate P-gp	No	Yes	Yes	Yes	No	yes
Food interaction	Yes	No	No	No	No	NR

Poulsen *et al.* [2012], Lip *et al.* [2012] and Perez *et al.* [2013] Ther Adv in Drug Safe. 2014;5(1):8-20.

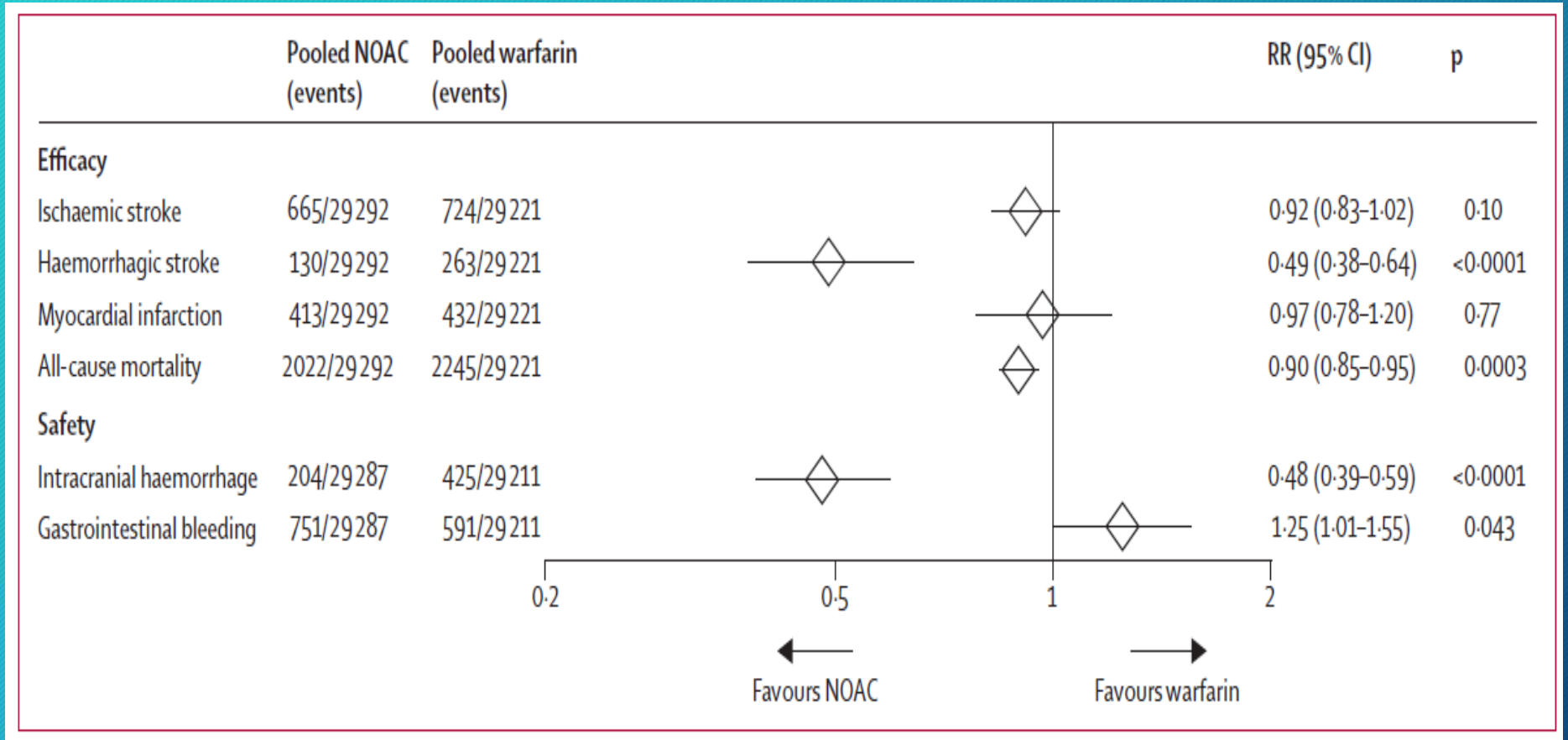
Newer OACs Lab Tests

	Usefulness of lab test	Dabigatran	Rivaroxaban	Apixaban
Lab tests	Strong ↕ Weak	• ECT • TT • aPTT • PT/INR	• Chromogenic anti-Xa • aPTT, PT	• Chromogenic anti -Xa

ECT, ecarin clotting time; TT, thrombin time; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalization ratio.

Palladino, et. Al., *Am J Hematol* 2012;87(suppl 1):s127-132

NOAC vs Warfarin: Safety/Efficacy



Lancet 2014;383:955-62.

NOAC adverse effects

	Dabigatran	Apixaban	Rivaroxaban
Common	bleeding anaemia nausea dyspepsia gastritis abdominal pain	bleeding anaemia dyspepsia GI bleeding	bleeding anaemia peripheral oedema itch, skin blisters muscle spasm
Infrequent	increased liver enzymes	thrombocytopenia increased liver enzymes	increased liver enzymes
Rare	allergic reactions	allergic reactions	allergic reactions

MEDICATION SAFETY AND QUALITY
High-Risk Medicines

Bleeding risk- Warfarin vs NOAC

- GI bleeds: No statistical difference between warfarin and NOAC
- Intracranial Hemorrhage: 54% relative risk reduction with NOAC Vs Warfarin. Studies favors NOAC over warfarin.
- Total Bleeding: Studies trended towards NOAC than warfarin

Renal Dysfunction Affects NOAC Half-Life

Table 1.
Properties of Target-Specific Oral Anticoagulants[15,16,a]

Property	Dabigatran	Rivaroxaban	Apixaban
Direct factor inhibition	IIa	Xa	Xa
Renal clearance (%)	80	33	25
Half-life in renal impairment (hr)			
CL_{cr} >80 mL/min	14–17	5–9	8–15
CL_{cr} 50–79 mL/min	16.6	8.7	14.6
CL_{cr} 30–49 mL/min	18.7	9.0	17.6
CL_{cr} <30 mL/min	27.5	9.5	17.3
Dialyzable	Yes	Unlikely	Unlikely

Am J Health-Syst Pharm. 2013; 70(Suppl1):S3-11

Perioperative NOAC Discontinuation

Renal function (CLcr ml/min)	Dabigatran		Rivaroxaban		Apixaban	
	Standard risk of bleeding	High risk of bleeding	Standard risk of bleeding	High risk of bleeding	Standard risk of bleeding	High risk of bleeding
>50	24 h	2–4 days	24 h	3 days	24–36 h	3 days
30–50	48 h	4 days	48 h	3 days	48 h	4 days
<30	2–5 days	>5 days	3 days	4 days		

van Ryn *et al.* [2010], Spyropoulos and Douketis [2012] and Baumann Kreuziger *et al.* [2012]. Ther Adv in Drug Safe. 2014;5(1):8-20.

Resumption of Therapy

- Warfarin therapy should generally be resumed:
  - 12 - 24 hours after surgery
    - Unless substantial risk of delayed bleeding or reoperation anticipated
- NOAC therapy should generally be resumed:
  - 24 - 48 hours after a minor procedure
  - 48 - 72 hours after major surgery
- Bridging Therapy: (UFH or LMWH in high risk patients)
  - NOAC should be resumed
    - 1 hr before UFH infusion is discontinued or
    - 10-12 hours after the last scheduled dose of LMWH

Am J Health-Syst Pharm. 2013; 70 (Suppl1):S3-11. J Cardivasc Electrophysiol. 2011(8):948-55.
N Engl J Med 2013;368:2113-24.

Pharmacokinetic Comparison of Reversal Agents

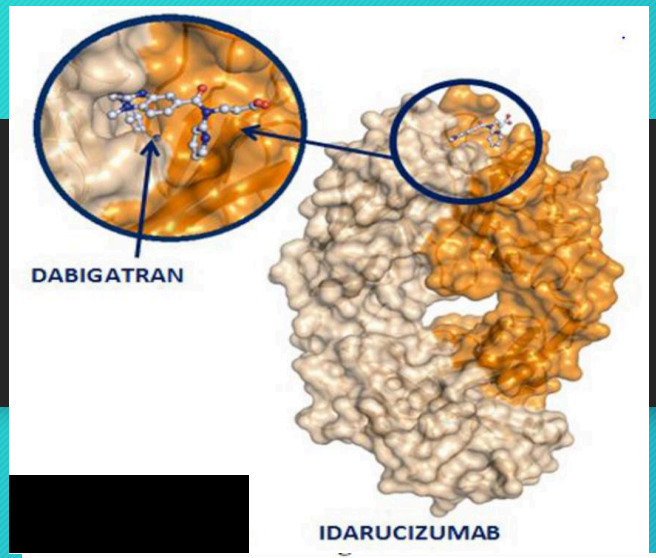
Anticoagulation Reversal Pharmacokinetics			
Agent	Onset	Duration	Rebound of Anticoagulant
Vitamin K	2 – 8 hours	Days for INR	Dose-dependent
FFP	1 – 4 hours	6 hours	4 – 6 hours
PCC	10 – 15 minutes	12 – 24 hours	~ 12 hours
rFactor VIIa	10 minutes	4 – 6 hours	6 – 12 hours

Studies Evaluating NOAC Reversal

	Apixaban	Dabigatran	Rivaroxaban
Activated charcoal	No data	In vitro	No data
Hemodialysis	No data	Human volunteers	No data
Hemoperfusion w/ activated charcoal	No data	In vitro	No data
FFP	No data	Animal model	No data
Activated factor VIIa	In vitro	Animal model/ ex vivo	Animal model/ ex vivo
3-factor PCC	No data	No data	No data
4-factor PCC	In vitro	Human volunteers animal models	Human volunteers
aPCC	In vitro	Animal, ex vivo	Animal, ex vivo, human case reports

Kaata S, Kouides P, Garcia D, et al. *Am. J. Hematol.* 2012; 87: S141-145.

NEW Anticoagulant Antidotes



Agents	Target	Structure	Route	MOA	Pharmacokinetics
Idarucizumab	Dabigatran	Humanized monoclonal antibody fragment	IV	Binds to dabigatran with a high affinity (~350 times greater affinity than thrombin) No binding to thrombin substrates (no procoagulant activity)	Biphasic $t_{1/2}$, ranging from 0.4 hrs to a terminal $t_{1/2}$ of 4.3 hrs
Andexanet alfa	Direct and indirect FXa inhibitors	Modified recombinant form of FXa	IV	Binds to FXa inhibitors with affinity similar to that of native FXa	Terminal $t_{1/2}$: ~6 hrs
Aripazine	Universal (oral FXa and FIIa inhibitors, UFH, LMWH, and fondaparinux	Small synthetic molecule	IV	Binds to TSOACs and heparin and reverses the anticoagulant effects	Not available

FIIa = factor IIa; FXa = factor Xa; IV = intravenous; LMWH = low-molecular-weight heparin; MOA = mechanism of action; $t_{1/2}$ = half-life; UFH = unfractionated heparin.

Pharmacotherapy 2015;35(2):198–207

Drugs interaction with Dabigatran

Drugs	Dabigatran
Ketoconazole	Avoid
Erythromycin	Precaution
Clarithromycin	No adjustment
Fluconazole	Avoid
Rifampicin	Avoid
Verapamil	Avoid
Clopidogrel	Caution
Diltiazem	Unknown
Heparin	Avoid
NSAIDs	caution

Why didn’t dabigatran work in some new environment?

- Thrombin Generation:
- Atrial Fibrillation triggered by stasis
- Mechanical valve – triggered by release of tissue factors

Current FDA approved Indications of NOAC

	VTE prevention	VTE treatment	Non Valvular AF	Mechanical valve
Apixaban	Hip and Knee	YES	YES	NO
Dabigatran	Hip	YES	YES	No
Edoxaban	No	Yes	Yes	No
Rivaroxaban	Hip and Knee	Yes	Yes	No
Warfarin	Hip and Knee	Yes	Yes	Yes

75mg/110mg/150mg