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Anticoagulation in the Liver Transplant Candidate and Perioperative Management

Patrick Northup, MD, MHS, FAASLD
Director, Health System Clinical Hepatology
Medical Director, Adult Liver Transplantation
Professor of Medicine and Surgery
NYU Langone Transplant Institute

NYU Langone Health Transplant Institute

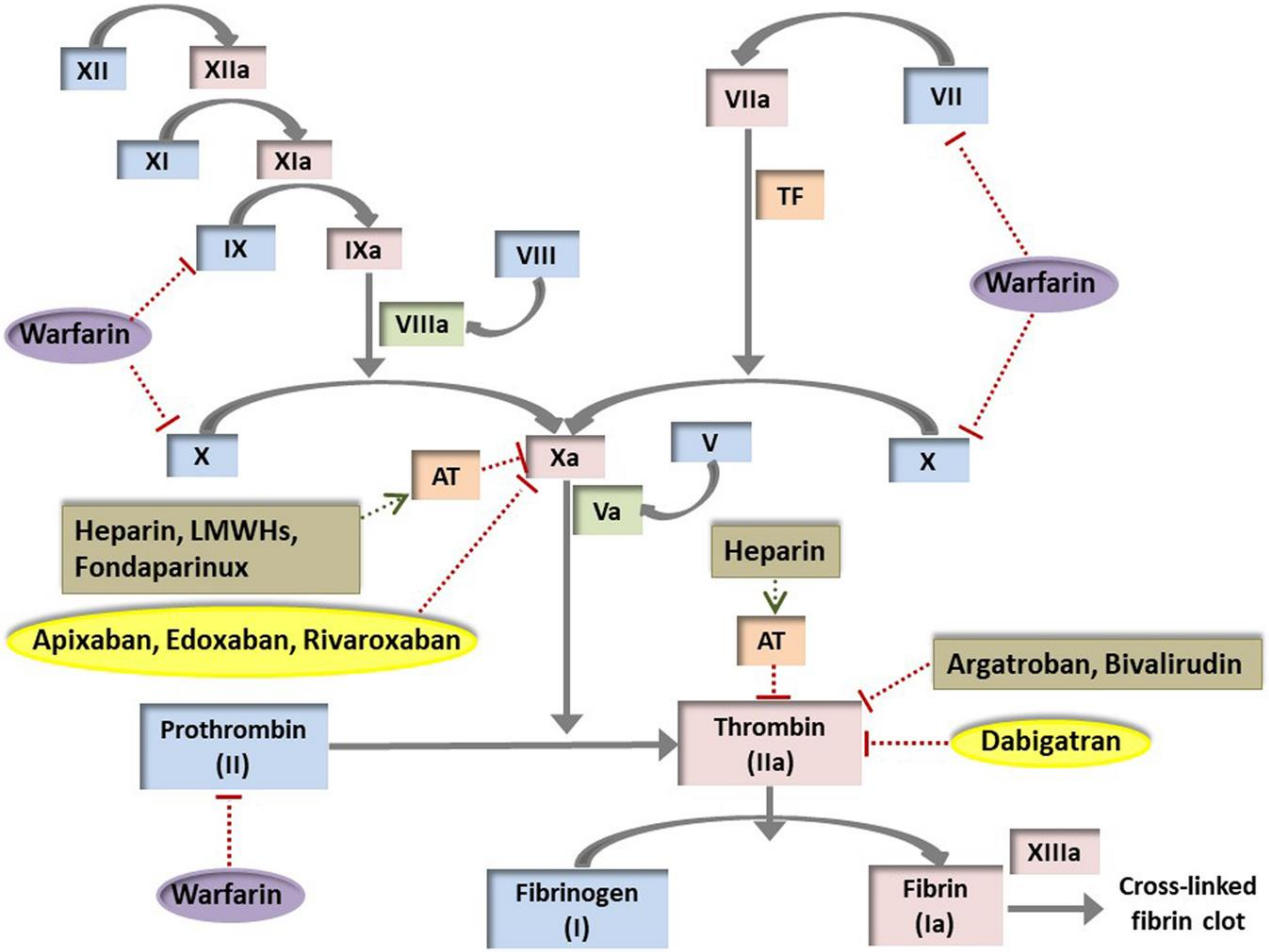
Overview

- Anticoagulation options
- Cirrhosis and DOAC
- Monitoring and reversal
- Postoperative VTE prophylaxis

Anticoagulation options

Mechanism of Action

- Warfarin VKA
- LMWH and UFH
- Dabigatran (II) and DOAC (X)



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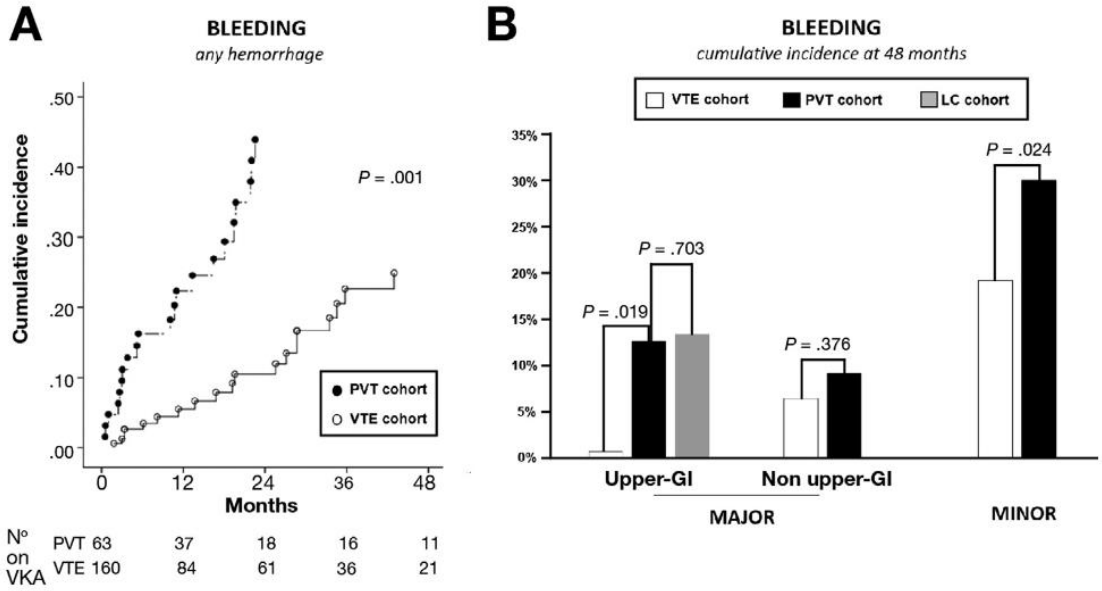
Cross B, et al., *Pharmacogenomics J* **24**, 7 (2024)

VKA / Warfarin in Cirrhosis

VKA Concerns

- Cirrhosis progression causes decreasing levels of VK dependent coagulation factors
- Therapeutic window is very narrow in cirrhosis
- Warfarin is heavily albumin bound
- Patients with CKD have increasing risks of bleeding



La Mura V, et al. *Clin Gastroenterol and Hepatol* 2018; 16:1146-1152

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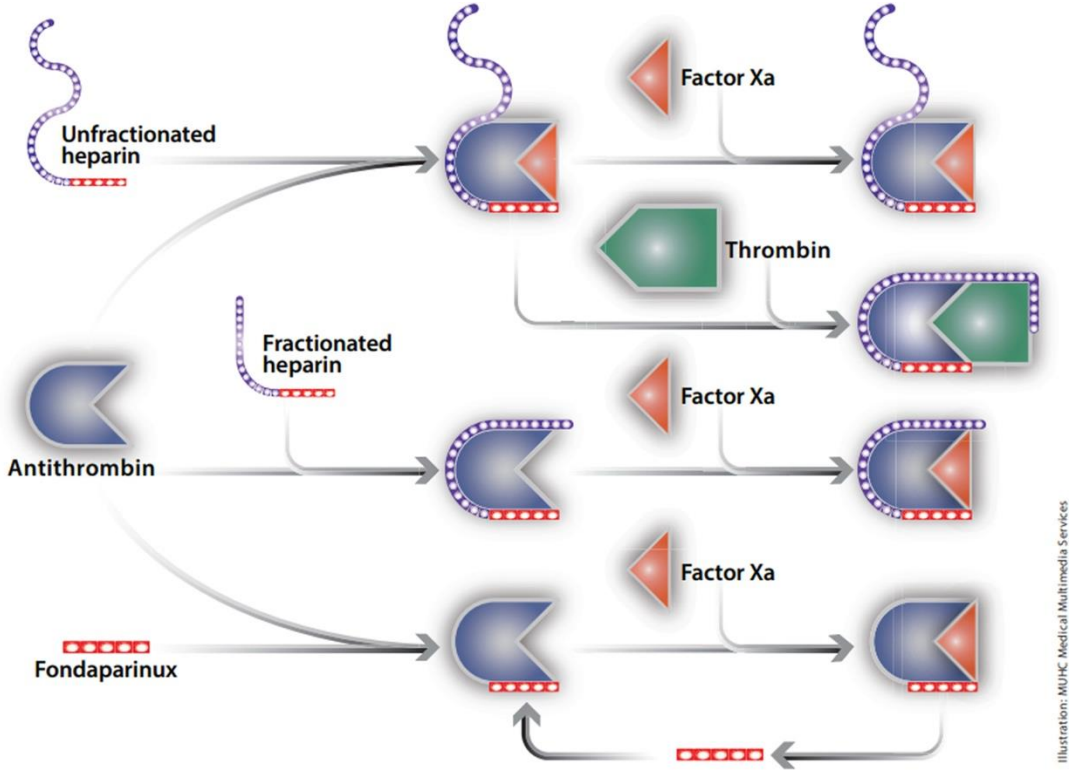
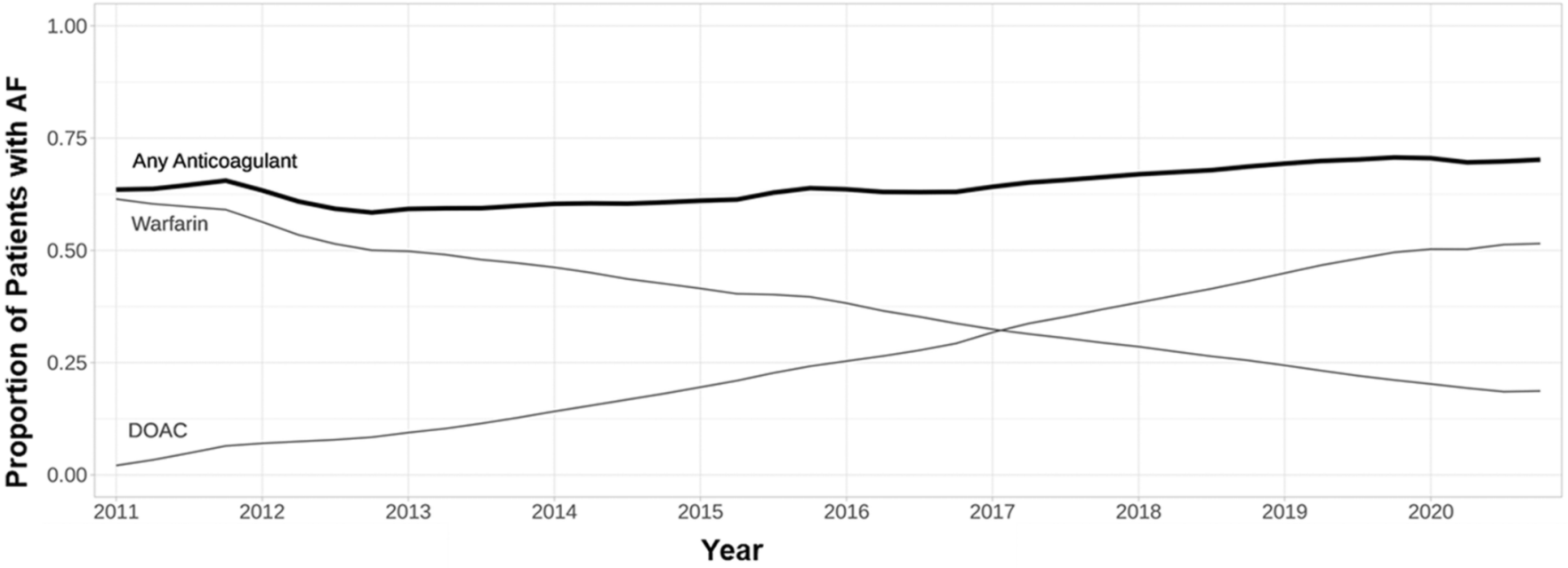
LMWH in Cirrhosis



- Active renal excretion limits use to patients with good renal function
- Injectable administration hinders outpatient adherence
- Because of AT deficiency in progressing cirrhosis, anti-Xa assays underestimate true plasma levels of heparins and can lead to iatrogenic bleeding complications. Potze W, et al., *Br J Haematol* 2013; 163(5): 666-73.

Tanguay, Mégane et al. *Res Pract Thromb and Haemostasis*; 6(5): e12773

DOACs vs. Warfarin in Outpatients in the US



Navar AM, *J Am Heart Assoc*. 2022 Nov 15;11(22)

The DOACs

	Dabigatran	Apixaban	Betrixaban (Discontinued)	Edoxaban	Rivaroxaban
Mechanism	Inhibits factor IIa	Inhibits factor Xa	Inhibits factor Xa	Inhibits factor Xa	Inhibits factor Xa
Dosing	BID	BID	Once-daily	Once-daily	Once-daily
Liver disease labeling	Limited experience; no change in exposure in CTP B (n = 12)	<CTP C without significant coagulopathy	Contraindicated in chronic liver disease	Contraindicated in chronic liver disease with coagulopathy	Contraindicated in liver disease with coagulopathy or bleeding risk
CKD adjustment	No	No	Dose reduce for CrCl 15-30 mL/min	Dose reduce for CrCl 15-50 mL/min	No

Adapted from Northup PG, et al., *Hepatology* 2021; 73(1):p 366-413

Cirrhosis and DOACs

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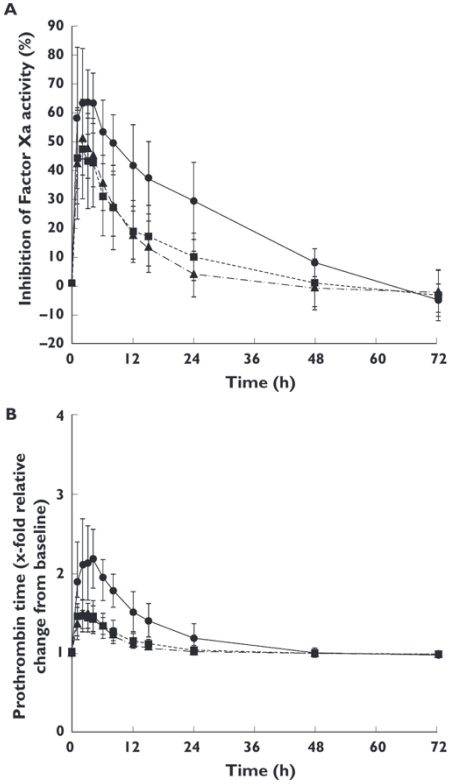
Pharmacokinetics of DOACs in cirrhosis is variable

DOACS vary by hepatic metabolism and renal clearance:

- Dabigatran – LESS systemic exposure with progressive liver disease
- Edoxaban – LESS
- Apixaban – MORE
- Rivaroxaban – MUCH MORE (>200% AUC)



Rivaroxaban

Kubitza D, et al., *British journal of clinical pharmacology*, *76*(1), 89-98.

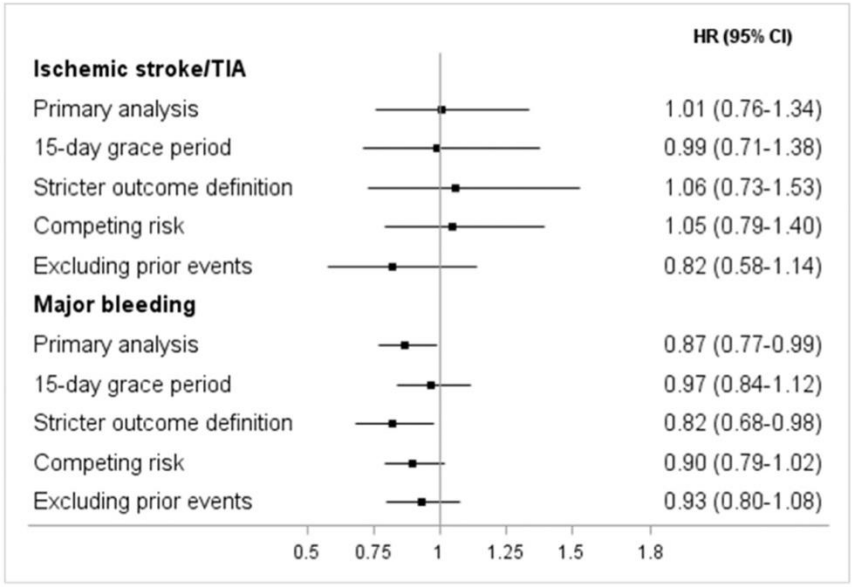
“Chronic liver disease", NVAF, apixaban superior

Clinical outcomes	Exposure to individual direct oral anticoagulants		Warfarin users		
	Events, n	IR/100 PY (IPTW)	Events, n	IR/100 PY (IPTW)	IPTW hazards ratio (95% CI)
Primary study outcomes					
Ischemic stroke/SE					
Apixaban	21	1.5	115	4.0	0.40 (0.19–0.82)
Rivaroxaban	34	3.0	115	4.1	0.76 (0.47–1.21)
Major bleeding					
Apixaban	98	7.9	383	13.6	0.60 (0.46–0.78)
Rivaroxaban	119	10.6	383	13.9	0.79 (0.62–1.0)
Major gastrointestinal bleeding					
Apixaban	60	4.1	248	8.5	0.50 (0.36–0.68)
Rivaroxaban	86	7.8	248	9.0	0.90 (0.67–1.20)

Lawal OD, et al., *Circulation* 2023; 147(10): 782-94

Apixaban vs. Rivaroxaban in Patients with Liver Disease and NVAF

A



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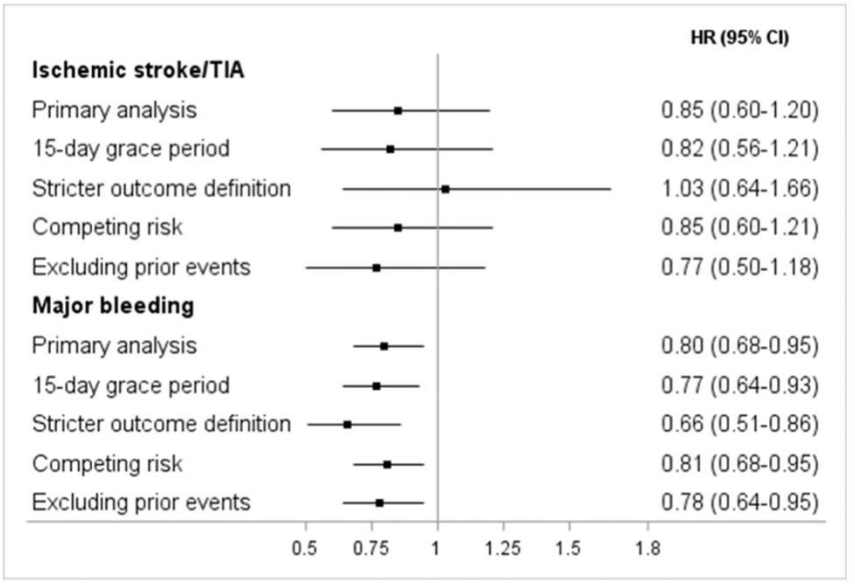

DOACs in Cirrhosis Patients

	n	Percent	Annualized rate
Any bleeding	45	32.6%	25.1%
Major bleeding	11	8.0%	6.2%
Fatal bleeding	0	0%	0%
Central nervous system bleeding	1	0.7%	0.6%
Hemoglobin drop ≥ 2 g/dL or ≥ 2 units PRBC	10	7.2%	6.2%
Clinically relevant non-major bleeding	22	15.9%	12.2%
Minor bleeding	12	8.7%	6.7%
DOAC discontinuation due to bleeding	29	21%	16.5%

"Currently available data suggest that there are no major safety concerns regarding the use of DOACs in patients with Child-Pugh class A cirrhosis. Due to the possibility of accumulation, DOACs should be used with caution in patients with Child-Pugh class B cirrhosis, as well as in patients with creatinine clearance below 30 ml/min. The use of DOACs in those with Child-Pugh class C cirrhosis is not recommended outside study protocols." Baveno VII, de Franchis, et al., J Hepatol 2022

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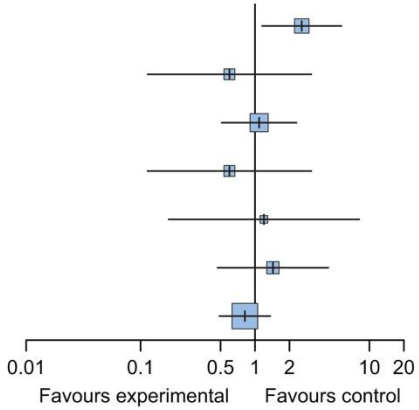
Mort, Northup et al. *Clin Gastroenterol and Hep* 2020

Rivaroxaban safety: Blinded RCT, CIRROXABAN

Adverse events	Rivaroxaban events	Rivaroxaban total	Placebo events	Placebo total	Risk	RR	[95% CI]	Weight (%)
Bleeding	15	41	7	49		2.56	[1.16; 5.67]	19.2
Hepatotoxicity	2	41	4	49		0.60	[0.12; 3.10]	6.2
Infection	10	41	11	49		1.09	[0.51; 2.30]	20.7
Neoplasm	2	41	4	49		0.60	[0.12; 3.10]	6.2
AKI	2	41	2	49		1.20	[0.18; 8.12]	4.7
Pain	6	41	5	49		1.43	[0.47; 4.36]	11.9
Others	15	41	22	49		0.81	[0.49; 1.35]	31.2

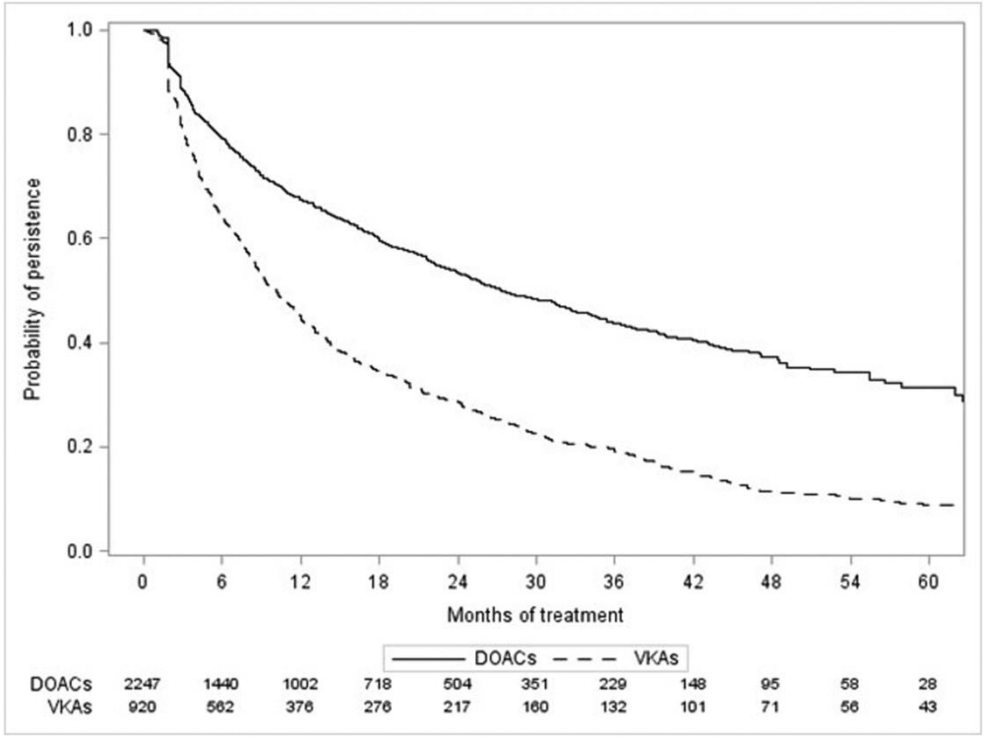


	Placebo (n=49)	Rivaroxaban (n=41)
Child-Pugh class	B = 48 (98%)	B = 38 (92.7%)
	C = 1(2%)	C = 3 (7.3%)

Puente A, et al., J Hepatol Nov 2025; 83(5): 1096-1076

Most Anticoagulation in Patients with Cirrhosis is Discontinued by Year Three

- Adherence to treatment is better with a DOAC compared to VKA
- Most discontinuations are due to minor bleeding
- Time in therapeutic INR is a significant issue in VKA use



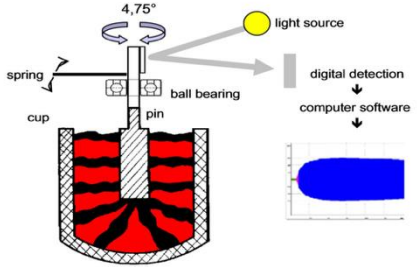
Douros A, et al., *Br J Clin Pharmacol*. 2022; 88(3): 994-1009

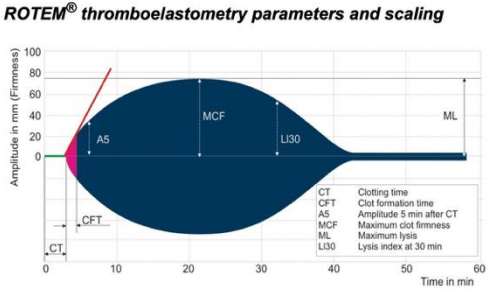
Monitoring and reversal

Routine DOAC monitoring

Routine monitoring is not recommended. BUT in the setting of bleeding or potential toxicity:

DOAC	Test
Dabigatran	• Thrombin time, TEG/ROTEM • Blood drug level (sendout)
fXa Inhibitors	• Anti-Xa, TEG/ROTEM • Blood drug level (sendout)





Connors JM. *Blood* 2018; 132(19): 2009-15

Reversal of Dabigatran for Liver Transplant with Idarucizumab

Reversal of Direct Oral Anticoagulants for Liver Transplantation in Cirrhosis: A Step Forward

TO THE EDITOR:

Direct oral anticoagulants (DOACs) are increasingly used for the treatment and prevention of venous thromboembolism (VTE), including in patients with liver disease. Dabigatran, a factor IIa inhibitor, is approved for treatment of VTE and to reduce the risk of stroke

We present a case of a 60-year-old man with cirrhosis from primary sclerosing cholangitis and hepatocellular carcinoma (HCC) treated with dabigatran 150 mg twice daily (anti-factor IIa) for recurrent lower extremity deep venous thrombosis (DVT) while listed for liver transplant. Prior hepatic decompensation in the past included esophageal variceal bleeding, hepatic encephalopathy, and ascites. At the time of transplant, he had a Model for

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Intagliata, et al., *Liver Transpl*. 2017 Mar;23(3):396-397

Reversal of Apixaban and Rivaroxaban?

Andexanet alfa is approved in the US for rapid reversal of bleeding due to oral FXa inhibitors rivaroxaban and apixaban.

- Half life of one hour
- When administered as a continuous infusion, andexanet will block the anticoagulant's ability to inhibit fXa. Andexanet decreases anti-Xa levels within 2-5 minutes
- The reversal of anticoagulation with andexanet persists for ~1 hour after the infusion is completed

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Andexanet pricing?

The published average wholesale price (AWP) is $3300 per 100 mg vial which is consistent with what Portola Pharmaceuticals previously quoted

1 dose = 900 or 1800 mg → each vial contains 100 mg = 9 or 18 vials = AWP $26,400 per dose

Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose			
FXa inhibitor	FXa inhibitor last dose	Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation	
		<8 Hours or Unknown	≥8 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg/unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg/unknown	High dose	

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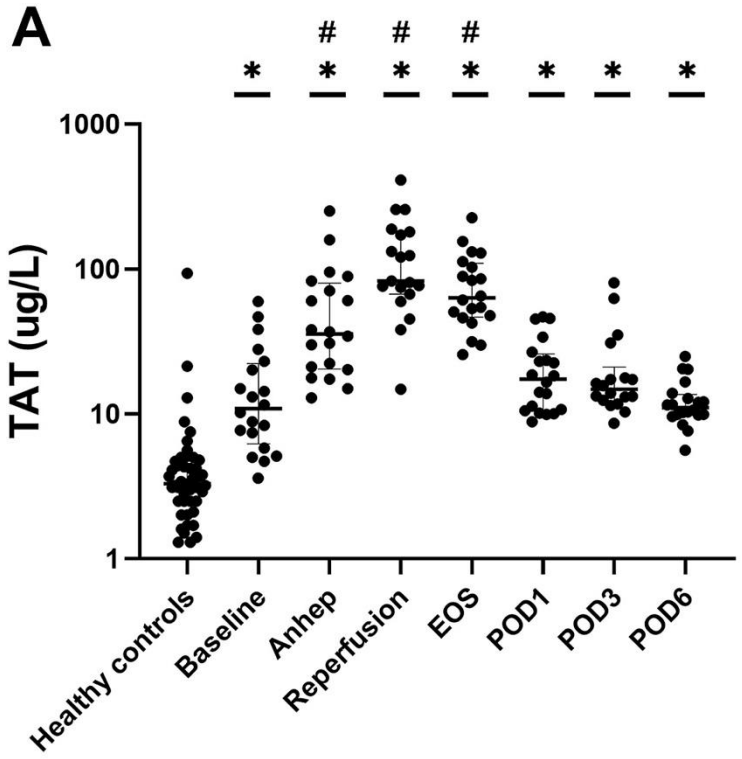
Postoperative VTE Prophylaxis

Activation of Intrinsic Pathway after OLT



- Activation of coagulation was estimated by plasma thrombin-antithrombin (TAT) levels
- Peaked at reperfusion
- Persisted above controls until day 6
- Similar effect seen in partial hepatectomy and Whipple patients

Elvers, Lisman, et al. 2025, *Res and Pract in Thromb Heamostasis*

Posttransplant VTE at NYU: Room for Improvement

Incidence of VTE	22 / 465 (4.7%)
Lower Ext/Upper Ext	10 (45%) / 12 (55%)
Median time to Dx	8 days (50% occurred within 10 days)
Delay in start of Ppx	14 / 22 (64%)
Clot while ON ppx	12 / 22 (55%)

- 73% of DVT patients having platelets under 100 and about 55% having platelets under 50.
- Overall, 9 of 22 patients (41%) met early allograft dysfunction criteria.

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Unpublished internal data 2026

Summary

Summary

- The DOACs are the most used outpatient anticoagulants in the US with a well-defined safety profile
- Patients with cirrhosis have differing metabolism and elimination of the various DOACs
- The DOACs appear safer than warfarin with at least equal efficacy in patients with cirrhosis
- Circumstantial evidence suggests apixaban may be superior in safety profile compared with other DOACs in patients with chronic liver disease
- Posttransplant VTE is possibly related to a persistent hypercoagulable state, especially in early graft dysfunction

Thank you

Patrick.Northup@nyulangone.org

@NorthupHepTXP

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