

Current management of oral anticoagulation



**E.Papadakis, Hematologist,
Thrombosis and Hemostasis Clinic,
Ob/Gyn Hematology
Genesis Hospital**



The Ideal Anticoagulant

- i. pos administration, od or bid
- ii. Highly efficacious
- iii. Predictable Pharmacokinetics
- iv. Bleeding risk free
- v. No need to monitor
- vi. Wide therapeutic margins
- vii. Without dose adjustments
- viii. No food/drug interactions
- ix. Without plasma protein binding
- x. Inhibition of Coagulation factors both in bound (thrombus) and unbound (plasma) forms

Historical development of anticoagulant treatment



• 1940s



• 1990s



• 1930s

• 1980s

• 2008



Vitamin K Antagonists

- Approved in 1954, VKAs (warfarin, coumadin) for more than one-half of a century, **had been the mainstay of therapy** for thrombotic diseases. Given the established safety profile of VKAs, as well as the efficacy in reducing the risk for fatal pulmonary embolism and recurrent thrombosis, they represented the gold standard
- There are **several shortcomings** associated with VKAs:
 1. they require monitoring
 2. the metabolism of the drug is affected by diet and other medications
 3. they have a defined bleeding risk of 5% to 6% per year.

Direct Oral Anticoagulants

- DOACs have revolutionized anticoagulation management in both stroke prevention and venous thromboembolism (VTE) treatment/prevention.
- Clinical trials and secondary real-world data have shown that DOACs have similar efficacy and, in some cases, improved bleeding safety profiles compared with vitamin K antagonists
- Popularity of DOACs is constantly increasing around the world, whereas that of warfarin has exhibited a constant and inexorable decline

(G. Lippi et al. *Ann Transl Med* 2017;5(16):322, google trend data)

DOACs- Direct pos anticoagulants, novel option, simple single drug approach

LMWH-UFH s.c.

„Conventional“ treatment

Vitamin K Antagonist

„Switching“

LMWH-UFH s.c.

Dabigatran/Pradaxa® (150 mg BID)

LMWH-UFH s.c.

Edoxaban (60 or 30 mg OD)

„Single-drug approach“

Rivaroxaban/Xarelto® (15 mg BID for 3 weeks, followed by 20 mg OD)

Apixaban/Eliquis® (10 mg BID for 1 week, followed by 5 mg BID)

acute

subacute/intermediate

chronic/long-term

Phase of DVT/PE

Oral Anticoagulant prescription trends: AF

Table 2. The use of OACs in patients with diagnosed AF in different regions (2015–2018).

Region	OAC	VKA	NOAC
Europe [32]	84.9%	59.1% of OAC	40.9% of OAC
The UK [37]	75.0%	41.1% of OAC	58.8% of OAC
The USA [92]	60.7%	57.3% of OAC	42.5% of OAC
Korea [93]	50.6%	50% of OAC	50% of OAC

OAC – oral anticoagulation; VKA – vitamin K antagonist, NOAC – non-vitamin K antagonist.

Oral Anticoagulant prescription trends: VTE

BRIEF REPORT



Direct oral anticoagulants and warfarin for venous thromboembolism treatment: Trends from 2012 to 2017

Pamela L. Lutsey PhD¹ | Rob F. Walker MPH¹ | Richard F. MacLehose PhD¹ |
Alvaro Alonso MD² | Terrence J. Adam MD³ | Neil A. Zakai MD⁴

- ❖ **137.203** VTE patients 56.7 ± 16.3 years old και M/F 1:1.
- ❖ Warfarin was the preferred modality for **98.7%** of patients in the start of 2012. By the end of 2017 warfarin prescription drops at **17.5%**.

LUTSEY ET AL.



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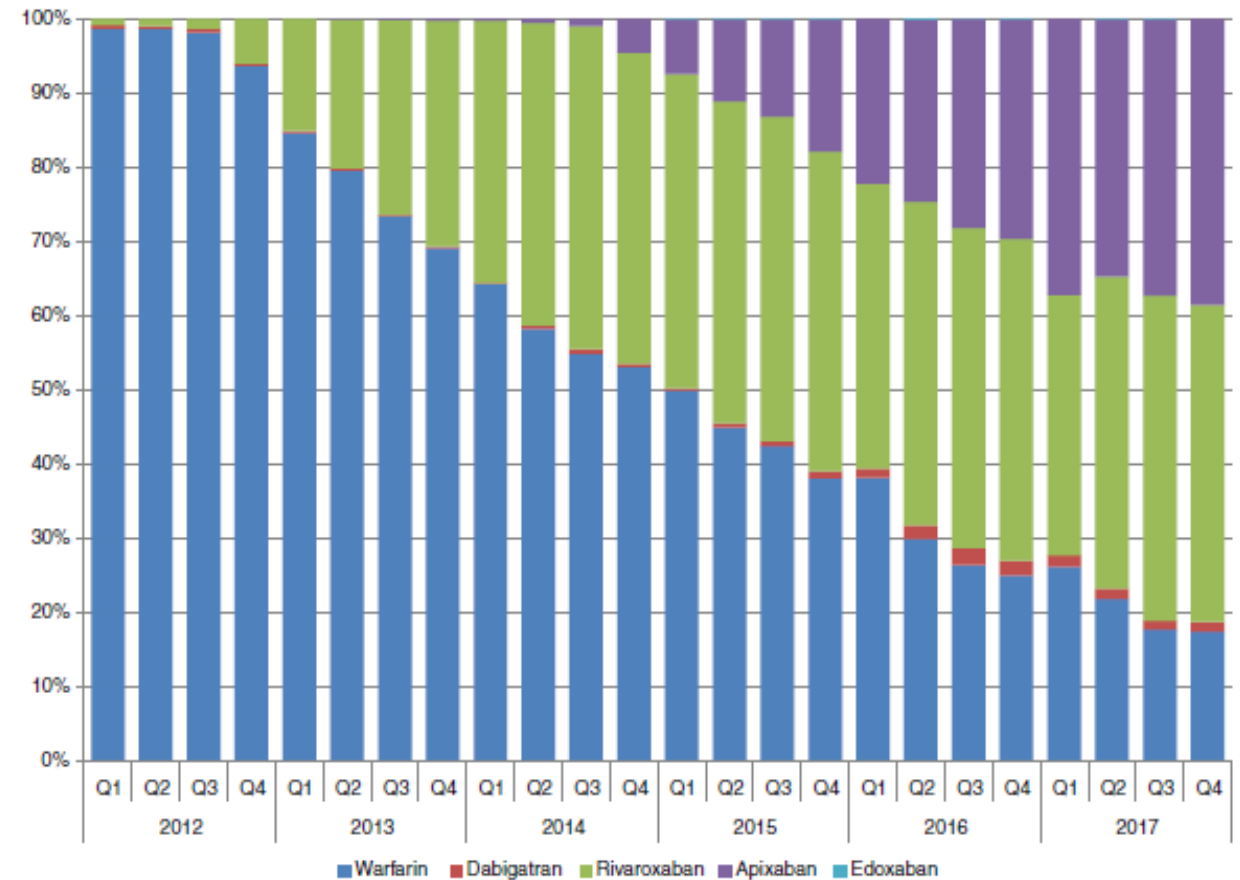


FIGURE 2 Temporal trends in oral anticoagulants prescribed for the primary treatment of venous thromboembolism from 2012 through 2017

Oral Anticoagulant prescription trends: VTE

Table 4 Secondary outcomes—safety, tolerability, efficacy

	Total popula- tion (N=214)	Enoxaparin (n=77)	Warfarin (n=66)	DOAC (n=71)	DOAC vs. enoxaparin p value	DOAC vs. warfarin p value
Safety						
Total bleed events	25 (11.7)	8 (10.4)	9 (13.6)	8 (11.3)	0.913	0.876
Major bleeds	9 (4.2)	3 (3.9)	4 (6.1)	2 (2.8)	0.650	0.672
Minor bleeds	16 (7.5)	5 (6.5)	5 (7.6)	6 (8.5)	0.683	0.851
Tolerability						
Total discontinuations	53 (25)	26 (33.8)	16 (24.2)	11 (15.4)	0.010	0.198
Efficacy						
Total thromboembolic events	23 (10.7)	9 (11.7)	10 (15.2)	4 (5.6)	0.185	0.110
Recurrent DVT	13 (6.1)	6 (7.8)	7 (11)	—	0.005	0.029
Recurrent PE	6 (2.8)	2 (2.6)	3 (4.3)	1 (1.4)	1.000	0.352
Ischemic stroke	4 (1.9)	1 (1.3)	—	3 (4.2)	0.350	0.246

All values expressed as n, % unless otherwise specified

DVT deep vein thrombosis, *PE* pulmonary embolism

Approved indications for DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
A-fib stroke ppx	✓	✓	✓	✓	ppx in Med Pts
Acute VTE treatment	✓*	✓	✓	✓*	
Extended VTE treatment	✓	✓	✓	✗	
Post-op VTE ppx	✓	✓	✓	✗	

*following parenteral anticoagulation after 5-10 days

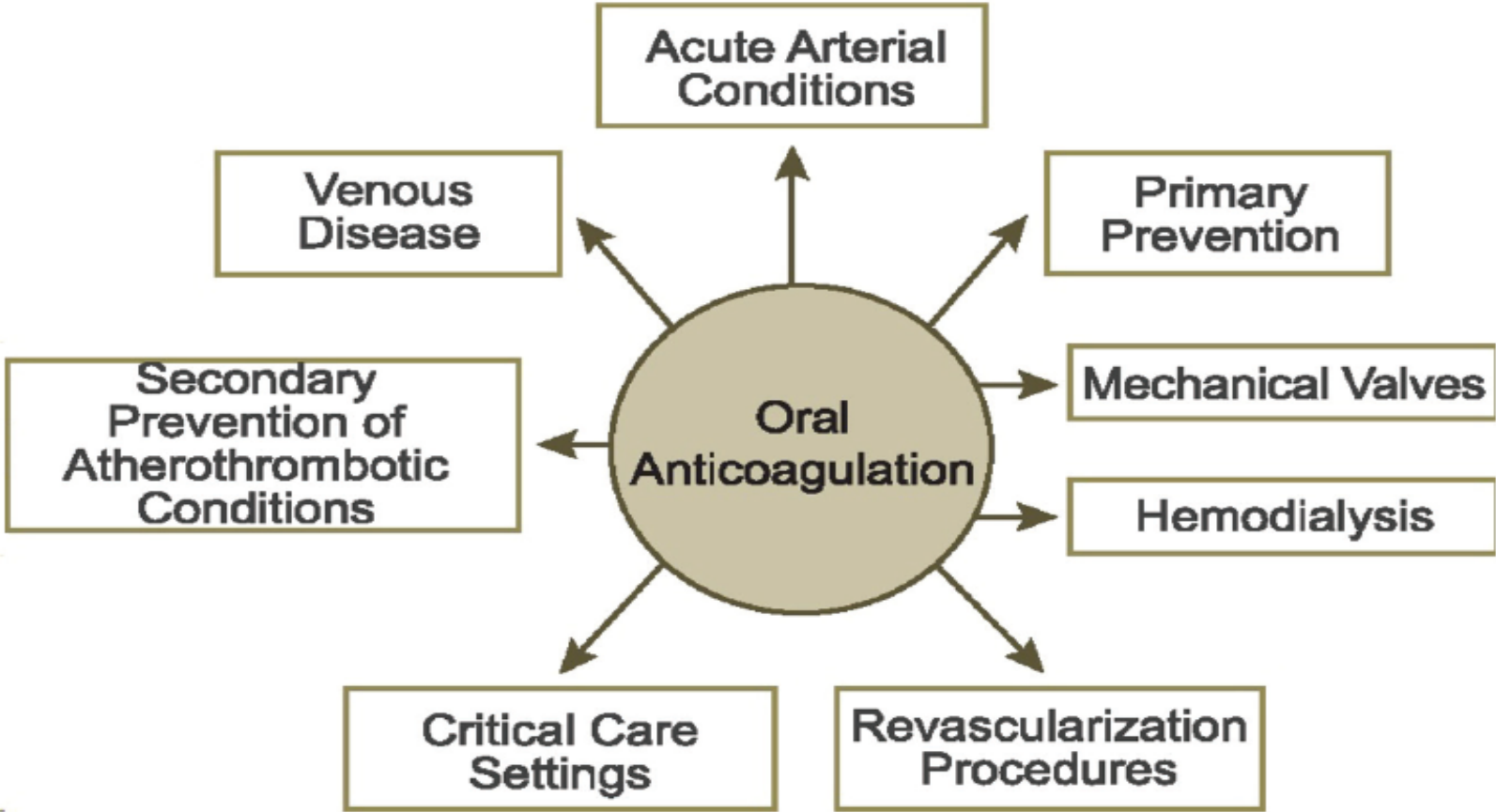


Figure 1. Clinical settings for oral anticoagulation. Clinical questions about the management of the NOACs exist in each of these settings.

Current management of oral anticoagulation

➤ Selection of Anticoagulant

- Unusual sites
- Antiphospholipid Syndrome, HIT
- CAT, Special Populations
- Patient preferences, Cost

➤ Duration Of Anticoagulation

- Unprovoked VTE
- Hormone related VTE

Selection of Oral Anticoagulant

- **2020 ESC Guidelines**, DOACs are the preferred treatment option for stroke prevention among patients with AF
- **CHEST 2021 2nd update to the 9th edition**: DOACs over VKA as treatment-phase (first 3 months) anticoagulant therapy and extended-phase anticoagulation with a DOAC
- **CHEST 2021 2nd update to the 9th edition**: oral Xa inhibitor over LMWH for the initiation and treatment phases of therapy (all cancers???)
- **CHEST 2021 2nd update to the 9th edition**: for extended-phase anticoagulation, we suggest the use of reduced-dose apixaban or rivaroxaban

Gray zones: VTE in unusual sites & special populations

- **VTE pathophysiology** in thrombotic APS and HIT is complex encompassing **cellular and/or complement activation**. In the above clinical entities we observe high prevalence of arterial thrombosis and VTE relapse rates in anticoagulated patients.
- In **4% of cases** VTE is located at splanchnic, CNS, renal and ovarian vasculature. Thrombosis in the above sites collectively are known as **VTE-AL (atypical location)**. VTE-AL management is supported by large relative studies and few existing guidelines are based mainly on expert opinion.

Gray zones: DOACs for VTE in unusual sites & special populations

- **Cerebral Venous Thrombosis** : no CVT patients were included in the large phase 3 studies
- **SVT** : DOACs are used without significant scientific background. In all prospective DOACs studies patients with moderate-severe liver failure were excluded.
- There are no large studies for DOACs in states of high thrombotic risk like **APS or HIT**.

VTE in unusual sites management

J Thromb Thrombolysis (2016) 41:129–143
DOI 10.1007/s11239-015-1308-1



Guidance for the management of venous thrombosis in unusual sites

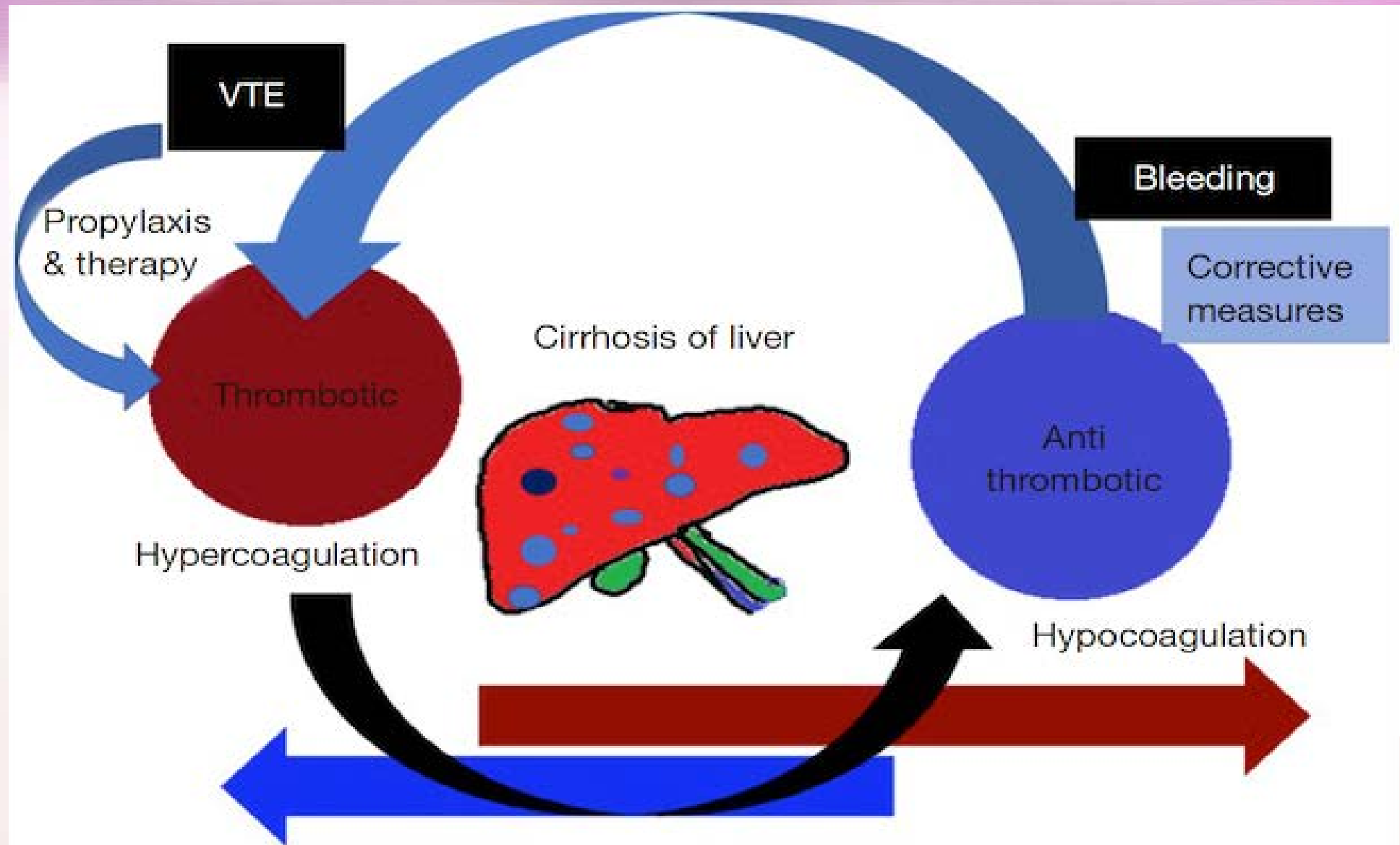
Walter Ageno¹ · Jan Beyer-Westendorf² · David A. Garcia³ · Alejandro Lazo-Langner⁴ · Robert D. McBane⁵ · Maurizio Paciaroni⁶

Table 3 Summary of guidance statements

Question		Guidance statement
(7) Is there a role for the direct oral anticoagulants?	CVT	Given the absence of clinical experience with the use of the direct oral anticoagulants in this setting, there is no evidence for or against their use in clinical practice until additional data from clinical studies will become available. If a decision to use these agents is made, their use should be considered off-label and careful patient counselling and clinical monitoring should follow. Ideally, patients receiving direct oral anticoagulants should be included in prospective cohort studies aimed to fill this knowledge gap
(7) Is there a role for the direct oral anticoagulants?	SVT	Given the absence of clinical experience with the use of the direct oral anticoagulants in this setting, there is no evidence for or against their use in the management of patients with SVT. If a decision to use these agents is made, their use should be considered off-label and careful patient counselling and clinical monitoring should follow. Ideally, patients receiving direct oral anticoagulants should be included in prospective cohort studies aimed to fill this knowledge gap

**A long-long time
ago..... 2016**

Oral anticoagulation in SVT: benefits



DOACs in SVT

Table 2. Studies investigating DOACs in patients with liver cirrhosis.

Author (year)	Study design	Setting	Anticoagulant	Main findings
Intagliata ⁴⁴	Retrospective	39 patients with LC treated for PVT or nonsplanchnic VTE	20 on DOACs (11 apixaban, 9 rivaroxaban) 19 on VKAs (<i>n</i> = 13)/ LMWH (<i>n</i> = 6)	Two major bleedings in the VKAs/LMWH group and one major bleeding in the DOAC group
Yang ⁴¹	Case report	Patient with LC and recurrent PVT	Rivaroxaban	Resolution of PVT after 3 months of Rivaroxaban
Hum ⁴²	Retrospective	LC patients anticoagulated over 3 years for PVT/DVT or stroke prevention in patients with atrial fibrillation	27 patients on DOACs and 18 on VKAs or LMWH	Less major bleedings in the DOACs group (4% <i>versus</i> 28%, <i>p</i> = 0.03). Similar recurrent thrombosis in the two groups
De Gottardi ⁴³	Prospective/survey	36 patients with LC anticoagulated for splanchnic vein thrombosis (75%), deep vein thrombosis (5%), atrial fibrillation (14%) and others (6%)	DOACs: rivaroxaban (83%), dabigatran (11%), apixaban (6%)	1 case of recurrent PVT (DOAC replaced by LMWH) and 5 cases of bleedings (4 minor and 1 major)
DOACs, direct oral anticoagulants; DVT, deep venous thrombosis; LC, liver cirrhosis; LMWH, low molecular weight heparin; PVT, portal vein thrombosis; VTE, venous thromboembolism.				

Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis

Amr Shaaban Hanafy^{a,*}, Sherief Abd-Elsalam^b, Mohammed M. Dawoud^c

^a Internal Medicine Department, Hepatology Division, Zagazig University, Egypt

^b Tropical Medicine Department, Tanta University, Egypt

^c Diagnostic Radiology, Tanta University, Egypt



A.S. Hanafy et al.

Rivaroxaban

Warfarin

Vascular Pharmacology xxx (xxxx) xxx-xxx

Table 2

Outcome after therapeutic anticoagulation in the study and control populations.

Variable	Study group after therapy	Control group after therapy ^a	P
Complete recanalization (n=, onset)	34 (85%, 2.6 ± 0.4 months)	18 (45%, 4.3 ± 1.4 months)	0.001
Partial recanalization (n=, onset)	6 (15%, 6.7 ± 1.2 months)	0	0.001
Ascites (n=)	0 (0%)	9 (41%)	0.001
GIT bleeding	0 (0%)	17 (43.3%)	0.001
Hepatic encephalopathy	0 (0%)	7 (31.8%)	0.003
Intestinal infarction	0 (0%)	2 (9.1%)	0.003
Death	0 (0%)	8 (36.4%)	0.001
Platelets (103/μl)	320 ± 45	213 ± 15	0.02
INR	1.1 ± 0.2	2.4 ± 0.5	0.02
PC %	67 ± 2.3	54 ± 0.9	0.036
Albumin (gm/dl)	3.8 ± 0.4	2.9 ± 0.2	0.02
Total bilirubin (mg/dl)	1.2 ± 0.4	2.4 ± 0.3	0.04
AST (IU/l)	46 ± 12	67 ± 18	0.023
ALT (IU/l)	52 ± 9	60 ± 4	0.03
Creatinine (mg/dl)	0.9 ± 0.4	1.9 ± 0.8	0.02
D.dimer (ng/ml)	234 ± 24.6	456 ± 100	0.004
CTP	6 ± 0.4	9.7 ± 0.8	0.002
MELD	7.5 ± 0.9	24 ± 1.2	0.000

CTP: Child Turcot Pugh, MELD: Model for end stage liver disease.

^a Laboratory values are of the complicated cases in the control group (n = 22).

- 80 pts with chronic HCV and portal vein thrombosis (67 M,13 F) average age 43.2 ± 3.8 yrs.

Management of splanchnic vein thrombosis

Laure Elkrief,^{1,†} Audrey Payancé,^{2,3,†} Aurélie Plessier,^{2,3} Louis d'Alteroche,¹ Maxime Ronot,^{2,4} Valérie Paradis,^{2,5} Dominique Valla,^{2,3} Pierre-Emmanuel Rautou^{2,3,*}



Table 2. Considerations for the choice of anticoagulant to treat splanchnic vein thrombosis and suggestion of doses (adapted from¹⁴⁹).

Considerations	Low-molecular-weight heparin	Vitamin K antagonists	Direct oral anticoagulants			
			Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Liver function						
Child-Pugh class A	No action needed	No action needed Target INR 2-3	No action needed 5 mg <i>twice a day</i>	No action needed 20 mg <i>once a day</i>	No action needed 60 mg <i>once a day</i>	No action needed 150 mg <i>twice a day</i>
Child-Pugh class B	No action needed	Possible Target INR 2-3	Use with caution 2.5 mg <i>twice a day</i>	Use with caution 15 mg <i>once a day</i>	Use with caution 30 mg <i>once daily</i>	Use with caution 110 mg <i>twice a day</i>
Child-Pugh class C	No action needed	Possible Target INR 2-3	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Renal function						
eGFR 30-50 ml/min	No action needed	Possible Target INR 2-3	No action needed 5 mg <i>twice a day</i>	Use with caution 15 mg <i>once a day</i>	Use with caution 30 mg <i>once daily</i>	Use with caution 110 mg <i>twice a day</i>
eGFR <30 ml/min	Use with caution	Possible Target INR 2-3	Use with caution 2.5 mg <i>twice a day</i>	Use with caution 15 mg <i>once a day</i>	Use with caution 30 mg <i>once daily</i>	Contraindicated
eGFR <15 ml/min	Contraindicated	Possible Target INR 2-3	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Other considerations						
Drug-drug interaction Other medication with P-gp protein or Cytochrome 3A4 metabolism	No action needed	No action needed Target INR 2-3	No action needed	Use with caution 15 mg <i>once a day</i>	No action needed	Use with caution 110 mg <i>twice a day</i>
History of peptic ulcer disease with or without gastrointestinal bleeding			No action needed	Use with caution <i>Consider 15 mg once a day</i>	No action needed	Use with caution <i>Consider 110 mg twice a day</i>
Specific consideration		Monitoring may be difficult in patients with liver insufficiency Factor II concentration may be useful in this setting		syndrome No data on pharmacokinetics after TIPS placement		Contraindicated in patients with antiphospholipid

eGFR, estimated glomerular filtration rate; INR, international normalised ratio; P-gp, Permeability glycoprotein; TIPS, transjugular intrahepatic portosystemic shunt.

DOACs in Cerebral Vein Thrombosis, RESPECT-CVT study (dabigatran)

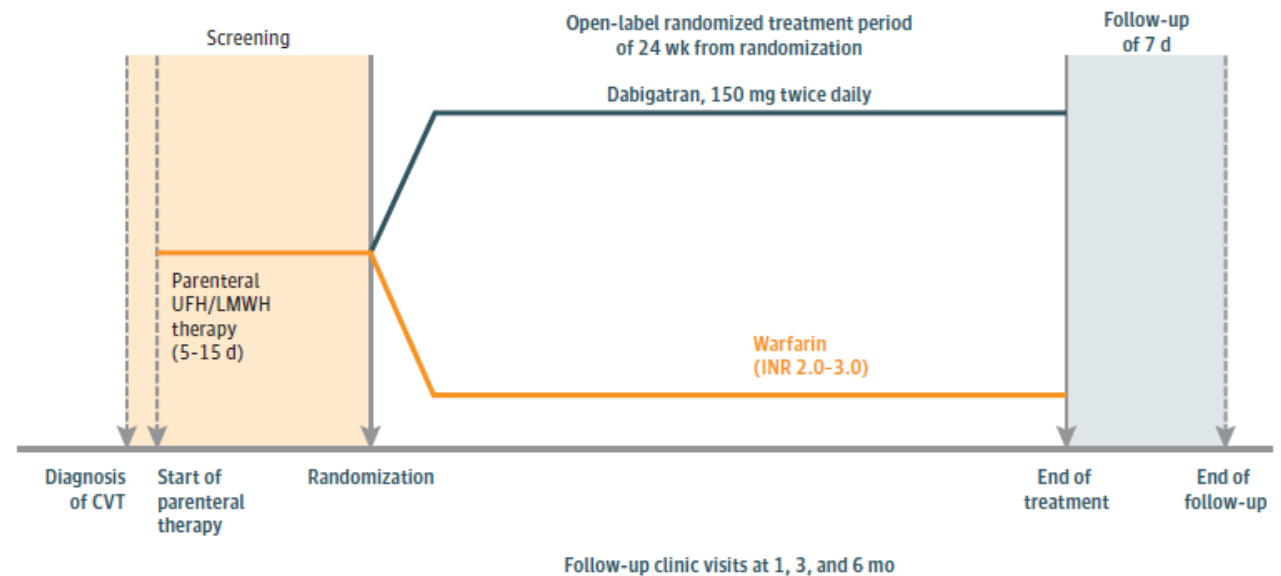
JAMA Neurology | Original Investigation

Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis A Randomized Clinical Trial

José M. Ferro, MD, PhD; Jonathan M. Coutinho, MD, PhD; Francesco Dentali, MD; Adam Kobayashi, MD, PhD; Andrey Alashev, MD, PhD; Patricia Canhão, MD, PhD; Denis Karpov, MD, PhD; Simon Nagel, MD; Laura Posthuma, MD; José Mário Roriz, MD; Jorge Caria, MD; Mandy Frässdorf, PhD; Holger Huisman, MSc; Paul Reilly, PhD; Hans-Christoph Diener, MD, PhD; for the RE-SPECT CVT Study Group

- **Prospective, randomized, multicentric study in 9 countries** (France, Germany, India, Italy, Holland, Poland, Portugal, Russia and Spain)
- **120 patients** with CVT were randomized to receive warfarin or dabigatran

Figure 1. RE-SPECT Cerebral Venous Thrombosis (CVT) Trial Design



INR indicates international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin. Adapted with permission from SAGE Publications, Ltd.¹⁷

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Conclusions

This study showed that the risk of recurrent VTE was low in patients with CVT who received anticoagulant therapy with either dabigatran or dose-adjusted warfarin for 6 months. Anticoagulant therapy was associated with few major or clinically relevant bleeding events, new intracranial bleeds, or enlargement of baseline hemorrhagic lesions. Dabigatran and dose-adjusted warfarin may be safe options to prevent recurrent VTEs in patients with CVT. Because of the limited sample size, we could not demonstrate the noninferiority or superiority of either treatment.

Research Original Investigation

Table 2. Primary and Secondary Outcomes

Outcomes	No. (%) [95% CI]	
	Dabigatran Etexilate (n = 60)	Warfarin (n = 60)
Primary outcome		
Major bleeding or venous thrombotic event (recurrent CVT, DVT of any limb, pulmonary embolism, splanchnic vein thrombosis)	1 (1.7) [0.0-8.9]	2 (3.3) [0.4-11.5]
Secondary outcomes		
All venous thrombotic events	0 [0.0-6.0]	0 [0.0-6.0]
Recanalization: score of occluded veins/sinuses ^a		
Improved	33 (60.0) [45.9-73.0]	35 (67.0) [52.9-79.7]
No change	22 (40.0) [27.9-54.1]	17 (33.0) [20.3-47.1]
Secondary safety outcomes		
Major bleeding event	1 (1.7) [0.0-8.9]	2 (3.3) [0.4-11.5]
Clinically relevant non-major bleeding event	0 [0.0-0.6]	1 (1.7) [0.0-8.9]
Major bleeding or clinically relevant non-major bleeding event	1 (1.7) [0.0-8.9]	3 (5.0) [1.0-13.9]
Any bleeding	12 (20.0) [10.8-32.3]	12 (20.0) [10.8-32.3]
New intracranial hemorrhage or worsening of the hemorrhagic component of a baseline lesion ^b	1 (1.8) [0.0-9.6]	2 (3.8) [0.5-13.0]
New intracranial hemorrhage	0 [0.0-6.4]	2 (3.8) [0.5-13.0]
Worsening of the hemorrhagic component of a baseline lesion	1 (1.8) [0.0-9.6]	0 [0.0-6.7]

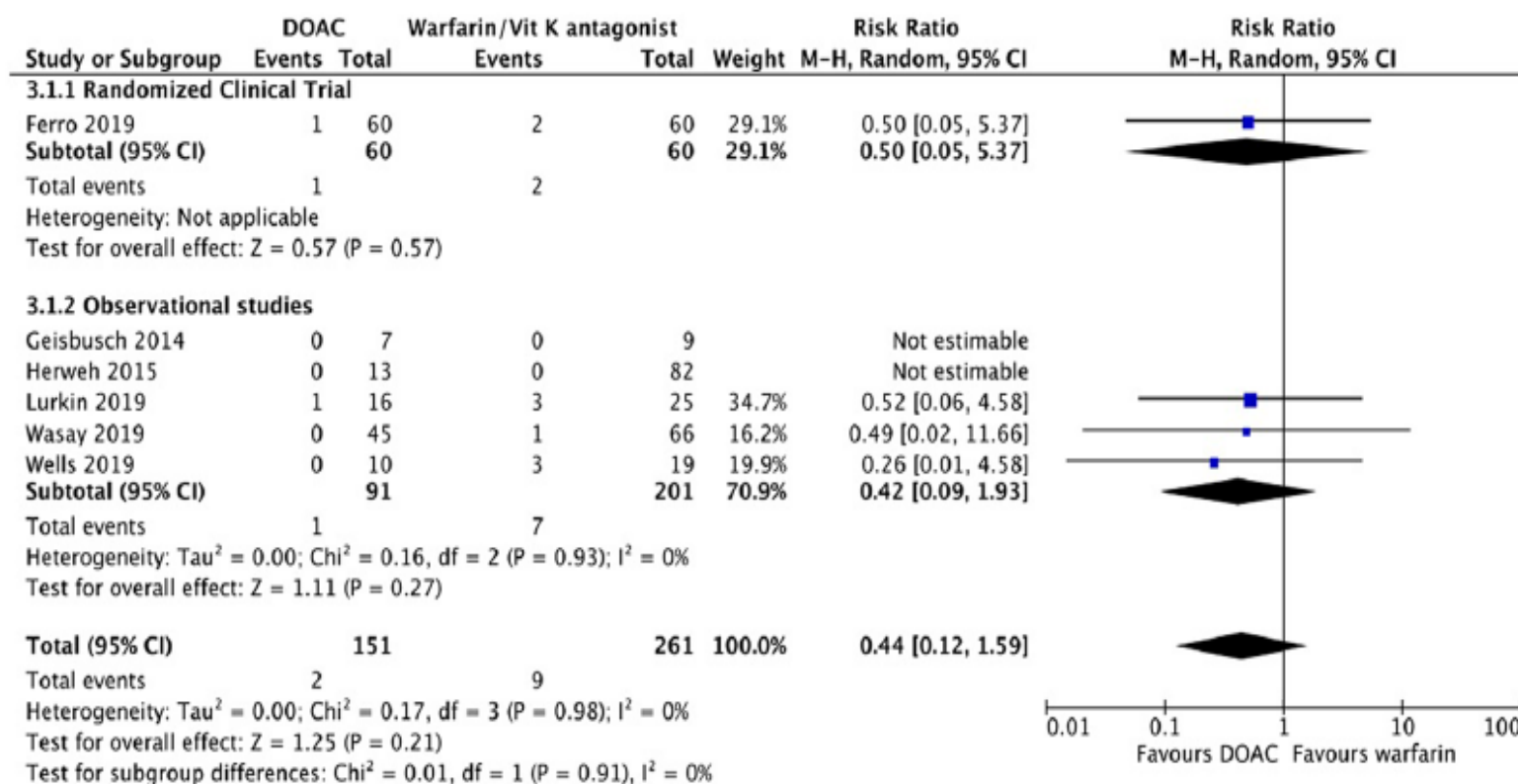
DOACs in CVT



Comparing the efficacy and safety of direct oral anticoagulants with vitamin K antagonist in cerebral venous thrombosis

Grace K. H. Lee¹ · Vanessa H. Chen¹ · Choon-Han Tan² · Aloysius S. T. Leow¹ · Wan-Yee Kong³ · Ching-Hui Sia^{1,4} · Nicholas W. S. Chew¹ · Tian-Ming Tu⁵ · Bernard P. L. Chan⁶ · Leonard L. L. Yeo^{1,6} · Vijay K. Sharma^{1,6} · Benjamin Y. Q. Tan^{1,6}

Fig. 3 Comparing major bleeding events between DOAC and VKA



DOACs in upper extremity DVT

Full Length Article

Rivaroxaban in the treatment of upper extremity deep vein thrombosis: A single-center experience and review of the literature[☆]

Ilya Schastlivtsev^{a,b,*}, Kirill Lobastov^a, Sergey Tsaplin^{a,b}, Irina Kanzafarova^a, Victor Barinov^{a,b}, Leonid Laberko^a, Grigory Rodoman^a, Sergey Zhuravlev^b

^a Pirogov Russian National Research Medical University, 1 Ostrovitianov str., Moscow 117997, Russian Federation

^b Clinical Hospital no.1 President's Administration of Russian Federation, 10 Starovolynskaya str., Moscow 121352, Russian Federation



I. Schastlivtsev, et al.

Table 3

Efficacy and safety of rivaroxaban in the treatment of UEDVT.

	Montiel FS, 2017 [24]	Houghton DE, 2017 [25]	Current study
Number of patients	55	20	30
Duration of therapy	3–6 months	3 months	3–6 months
Recurrent VTE	2.0%	0	0
Major bleeding	0	0	0
CRNM bleeding	2.0%	0	6.7%
Minor bleeding	0	0	6.7%



Rivaroxaban and Apixaban for Initial Treatment of Acute Venous Thromboembolism of Atypical Location

Dawid T. Janczak, MD; Malgorzata K. Mimier, MD; Robert D. McBane, MD; Patrick S. Kamath, MD; Benjamin S. Simmons, BS; Dalene M. Bott-Kitslaar, APRN, CNP; Charles J. Lenz, MD; Emily R. Vargas, MPH; David O. Hodge, MS; and Waldemar E. Wysokinski, MD, PhD

- **Prospective study assessing safety and efficacy of DOACs -rivaroxaban and apixaban- in VTE-AL, collecting data from Mayo Thrombophilia Clinic Registry.**
- **36 Patients with VTE-AL receiving DOACs (2013-17), were compared with 352 typical location VTE patients and 27 VTE-AL patients receiving enoxaparin or warfarin.**
- **VTE relapses and bleeding episodes were similar irrespective of location of VTE and modality of treatment.**

TABLE 2. Location of Venous Thromboembolism of Atypical Location (VTE-AL) Treated With Direct Oral Anticoagulant (DOAC): Rivaroxaban or Apixaban and With Enoxaparin

Vein, n (%)	VTE-AL DOAC (N=38 ^a)	VTE-AL enoxaparin (N=31 ^b)
Splanchnic veins	26 (68.4)	23 (74.2)
Portal	16 (44.4)	13 (56.5)
Mesenteric	8 (22.2)	6 (26.1)
Splenic	2 (5.6)	3 (13.0)
Hepatic	0 (0.0)	1 (4.3)
Ovarian	8 (22.2)	2 (8.7)
Renal	3 (8.3)	5 (21.7)
Cerebral venous sinuses	1 (2.8)	1 (4.3)

^aThirty-eight venous segments of atypical location in 36 patients were treated with DOAC: one patient had thrombosis of portal and mesenteric veins and another one had renal and ovarian vein thrombosis.

^bThirty-one venous segments in 23 patients were treated with enoxaparin: 2 patients had 3 veins involved: splenic, mesenteric, and portal, and another 5 had thrombosis affecting 2 veins: mesenteric and splenic (n=1), renal and ovarian (n=1), portal and hepatic (n=1), renal and portal (n=2).



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TABLE 3. Clinical Outcome in Patients With Acute Venous Thromboembolism (VTE) of Atypical Location (VTE-AL), With VTE of Typical Location (VTE-TL) Treated With Direct Oral Anticoagulants (DOACs): Rivaroxaban and Apixaban and in Patients With VTE-AL Treated With Enoxaparin

Outcome rate per 100 person-years	VTE-AL DOAC (n=36)	VTE-TL DOAC (n=352)	P value	VTE-AL enoxaparin (n=23)	VTE-AL DOAC vs enoxaparin P value
Overall					
VTE Recurrence (n)	2	7	.13	3	.26
Total follow-up person-years	27.4	298.3		12.7	
Recurrence rate (95% CI)	7.3 (0.88-26.3)	2.4 (0.94-4.8)		23.7 (4.9-69.1)	
Major bleed (n)	2	9	.26	3	.31
Total follow-up person-years	27.6	301.9		13.4	
Major bleed rate (95% CI)	7.2 (0.88-26.1)	3.0 (1.4-5.7)		22.4 (4.6-65.4)	
CRNM bleeding (n)	1	25	.38	2	.19
Total follow-up person-years	27.6	287.6		12.8	
Minor bleed rate (95% CI)	3.6 (0.1-20.2)	8.7 (5.6-12.8)		15.6 (1.9-56.3)	
Major or CRNM bleeding (n)	3	33	.95	5	.12
Total follow-up person-years	27.3	287.2		12.7	
Major or minor rate (95% CI)	11.0 (2.3-32.2)	11.5 (7.9-16.1)		39.4 (12.8-91.9)	
Death (n)	6	25	.03	5	.51
Total follow-up person-years	28.0	302.6		13.5	
Death rate (95% CI)	21.5 (7.9-46.7)	8.3 (5.3-12.2)		36.9 (12.0-86.1)	
Patients with cancer only					
VTE Recurrence (n)	2	4	.002	3	.81
Total follow-up person-years	7.9	151.9		12.3	
Recurrence rate (95% CI)	25.4 (3.1-91.8)	2.6 (0.72-6.7)		24.4 (5.0-71.4)	
Major bleed (n)	2	8	.22	3	.76
Total follow-up person-years	8.1	154.3		13.0	
Major bleed rate (95% CI)	24.8 (3.0-89.5)	5.2 (2.2-10.2)		23.1 (4.8-67.4)	
CRNM bleeding (n)	1	17	.72	2	.58
Total follow-up person-years	8.1	147.40		12.42	
Minor bleed rate (95% CI)	12.4 (0.31-69.2)	11.5 (6.7-18.5)		16.1 (2.0-58.1)	
Major or CRNM bleeding (n)	3	24	.55	5	.62
Total follow-up person-years	7.7	146.9		12.3	
Major or minor rate (95% CI)	38.9 (8.0-113.7)	16.3 (10.5-24.3)		40.7 (13.2-95.0)	
Death (n)	6	25	.001	5	.26
Total follow-up person-years	8.4	155.0		13.1	
Death rate (95% CI)	71.4 (26.2-155.3)	16.1 (10.4-23.8)		38.1 (12- 88.8)	

CRNM = clinically relevant nonmajor.

DOACs in thrombotic APS

Table 2: Characteristics and status of completed and recruiting randomised controlled trials of direct oral anticoagulants in thrombotic antiphospholipid syndrome

	RAPS ^[79]	TRAPS ^[7,82]	ASTRO-APS ^[7,83]
Chief Investigator	H Cohen	V Pengo	S Woller
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT
Number of patients	116	536	200
APS subgroups	Previous VTE, target INR of 2.5; no thrombosis >3 m; patients with arterial thrombosis excluded	Triple positive thrombotic APS; arterial, venous, and/or biopsy-proven microthrombosis	Thrombotic APS VTE target INR 2.5; no thrombosis >6 m; definite, likely or historic APS
Intervention	Rivaroxaban 15 mg od vs. warfarin target INR of 2.5	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Apixaban 2.5 mg or 5 mg bd vs. warfarin target INR of 2.5
Primary outcome(s)	Thrombogenesis - endogenous thrombin potential (ETP)	Thrombosis - arterial or venous Major bleeding Death	Thrombosis - arterial and/or venous Bleeding
Duration of recruitment	Jun 14 - Nov 14	Dec 14 - Dec 18	Feb 15 - ongoing
Status	Completed and results published	Ongoing	Ongoing: protocol modified after potential safety signal (see text)

Did not achieve non-inferiority

Use of direct oral anticoagulants in antiphospholipid syndrome.
Cohen H, et al.
JTH 2018 Apr 6. doi: 10.1111/jth.14017.
[Epub ahead of print]

DOACs in thrombotic APS

Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis

Virginie Dufrost^a, Jessie Risse^a, Tatiana Reshetnyak^b, Maria Satybaldyeva^b, Yao Du^c, Xin-Xin Yan^c, Stella Salta^{d,e}, Grigorios Gerotziakas^{d,e}, Zhi-Cheng Jing^c, Ismaël Elalamy^{d,e}, Denis Wahl^a, Stéphane Zuily^{a,*}

Autoimmunity Reviews 17 (2018) 1011–1021

Patient level meta-analysis:

- a) VTE relapse rates in APS patients receiving DOACs
- b) Investigation of factors related with DOACs failures.
 - 47 studies with 447 APS patients under DOACs treatment (rivaroxaban=290, dabigatran etexilate=144 και apixaban=13).
 - **73/447 patients (16%)** presented new thrombotic episode (28 VTE, 31 ATE, 13 microvascular). **Average time** to DOACs failure **12.5 months**.
 - **Triple antibody positivity** was associated with significant 4ply increase in relapse risk (OR=4.3).
 - In patients receiving anti-Xa compounds, history of **arterial thrombosis** was associated increased relapse risk (OR=2.8).

DOACs in thrombotic APS : Guidelines

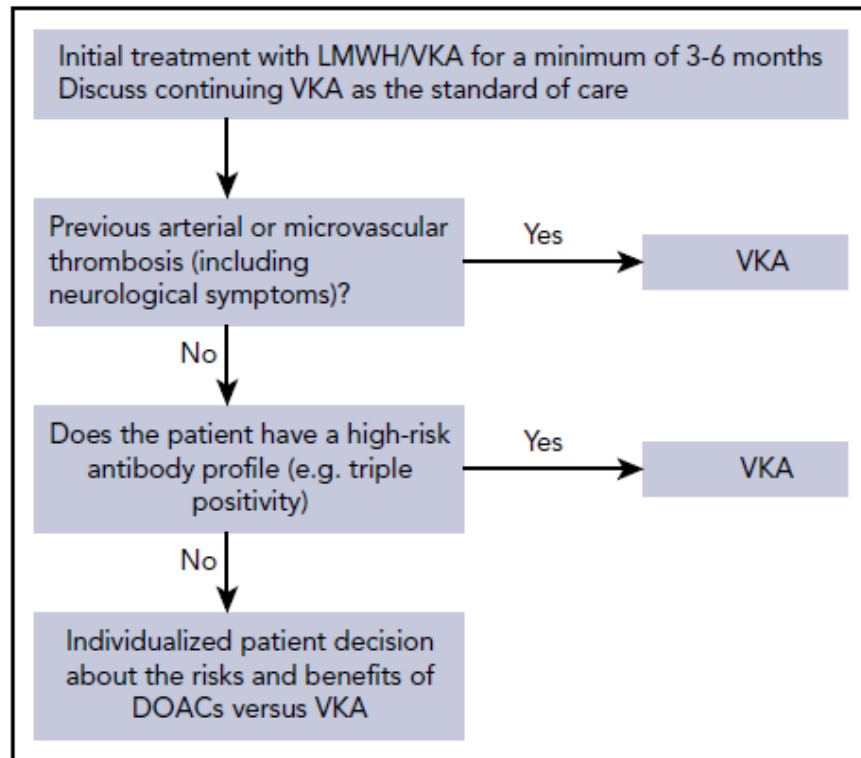


Figure 1. My management approach for confirmed APS and unprovoked VTE.

Review

14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends

Doruk Erkan ^{a,*}, Cassyenne L. Aguiar ^a, Danieli Andrade ^b, Hannah Cohen ^{c,d}, Maria J. Cuadrado ^e, Adriana Danowski ^f, Roger A. Levy ^g, Thomas L. Ortel ^h, Anisur Rahman ^{c,d}, Jane E. Salmon ^a, Maria G. Tektonidou ⁱ, Rohan Willis ^j, Michael D. Lockshin ^a

2.5. Recommendations for clinicians

The task force recommends that warfarin or other VKA remains the mainstay of anticoagulation in thrombotic APS. Oral direct inhibitors can be considered in APS patients with a first or recurrent VTE occurring off or on subtherapeutic anticoagulation, only when there is known VKA allergy/intolerance or poor anticoagulant control. There are no data to recommend ODI in APS patients with recurrent VTE occurring on therapeutic anticoagulation or with APS-related arterial thrombosis.

Recommendation

EULAR recommendations for the management of antiphospholipid syndrome in adults

Maria G Tektonidou,¹ Laura Andreoli,² Marteen Limper,³ Zahir Amoura,⁴ Ricard Cervera,⁵ Nathalie Costedoat-Chalumeau,⁶ Maria Jose Cuadrado,⁷ Thomas Dörner,⁸ Raquel Ferrer-Oliveras,⁹ Karen Hambly,¹⁰ Munther A Khamashta,¹¹ Judith King,¹² Francesca Marchioni,¹³ Pier Luigi Meroni,¹⁴ Marta Mosca,¹⁵ Vittorio Pengo,¹⁶ Luigi Raio,¹⁷ Guillermo Ruiz-Irastorza,¹⁸ Yehuda Shoenfeld,¹⁹ Ljudmila Stojanovich,²⁰ Elisabet Svenungsson,²¹ Denis Wahl,²² Angela Tincani,² Michael M Ward²³

B. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events. Direct oral anticoagulants (DOACs) could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA).

Treatment of the antiphospholipid syndrome with direct oral anticoagulants
Position statement of German societies
Vasa (2019), 48, pp. 483-486.

Conclusions:

1. Clinical suspicion of APS requires careful diagnostic testing. Because of inadequate diagnostic workup, many patients may not even have an APS, and these patients **could be adequately treated with a DOAC.**
2. Patients with single or double positive antiphospholipid antibodies but without positive LA may have a comparably low thrombotic risk and **may also be treated with a DOAC in venous TE** – sufficient evidence for that conclusion is not yet available but is suggested by the results of meta-analyses.

DOACs in HIT patients

- ✓ HIT constitutes **severe prothrombotic state necessitating promptly effective anticoagulation**
- ✓ DOACs are an attractive option they have rapid onset, they are not affecting protein C levels and they are not antigenic.
- ✓ HIT patients often present renal or hepatic failure, they are treated with CYP3A4 inducers, they present thrombocytopenia $PLTs < 80 \times 10^9/l$ and increased bleeding risk
- ✓ We do not have **readily available laboratory tests** to monitor DOAC treatment.

Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review

Theodore E. Warkentin,¹⁻³ Menaka Pai,¹⁻⁴ and Lori-Ann Linkins^{2,4}

Blood. 2017;130(9):1104-1113

Table 2. Literature review of rivaroxaban for probable HIT (including new patients reported in this article): primary or secondary treatment during acute HIT (groups A₁, A₂, and B)

Study author	Reference	No. of patients	Group			Median platelet count at rivaroxaban start	HIT-associated thrombosis*		Outcome			
			A ₁	A ₂	B		No.	%	Thrombosis		Bleed	
									No.	%	No.	%
Rivaroxaban-Hamilton experience												
Linkins et al	17	12	3	2	7	56	6		1		0†	
This study		10	7	1	2	64	5		0		0	
Rivaroxaban-other (non-Hamilton) centers												
Kopolovic and Warkentin	28	1	0	0	1	30	0		0		0	
Ng et al, Ong et al‡	29, 36	9	9	0	0	64	9		0		0	
Sharifi et al§	30	9‡	0	0	9	90‡	4		0		0	
Hantson et al	31	1	0	0	1	30	1		0		0	
Abouchakra et al	32	1	1	0	0	25	1		0		0	
Sartori et al	33	1	0	1	0	150	1		0		0	
Casan et al	34	1	0	0	1	48	1		0		0	
Samoš et al	35	1	1	0	0	65	1		0		0	
Summary		46	21	4	21	73	29/46	63.0	1/46	2.2	0/46	0

CLINICAL TRIALS AND OBSERVATIONS

Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review

Theodore E. Warkentin,¹⁻³ Menaka Pai,¹⁻⁴ and Lori-Ann Linkins^{2,4}

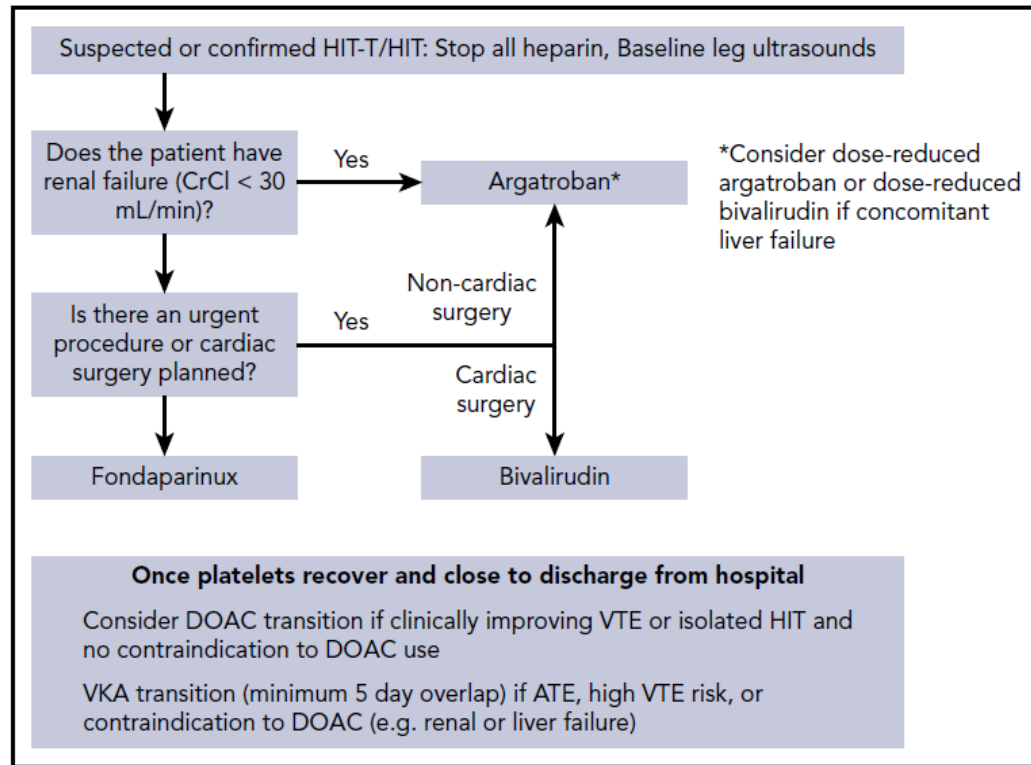
Blood. 2017;130(9):1104-1113

Table 3. Literature review of apixaban or dabigatran for probable acute HIT (including new patients reported in this article): primary or secondary treatment (groups A₁, A₂, and B)

Study author	Reference	No. of patients	Group			Median platelet count at DOAC start	HIT-associated thrombosis*		Outcome			
			A ₁	A ₂	B		No.	%	Thrombosis		Bleed	
									No.	%	No.	%
Apixaban												
Sharifi et al†	30	5	0	0	5	90‡	1		0		0	
Larsen et al	37	1	1	0	0	112	0		0		0	
Delgado-García et al§	38, 39	1	1	0	0	25	1		0		0	
Kunk et al	40	5	0	0	5	111	3		0		0	
Total		12	2	0	10	90‡	5/12	41.7	0/12	0	0/12	0
Dabigatran												
Sharifi et al†	30	6	0	0	6	90‡	2		0		0	
Anniccherico et al	41, 42	1	0	0	1	120	1		0		0	
Mirdamadi§	43	1	1	0	0	32	1		0		0	
Tardy-Poncet et al	44	1	0	0	1	56	0		0		0	
Noel et al	45	1	0	1	0	216	1		1¶		0	
Bircan and Alanoglu§	46	1	1	0	0	52	1		0		0	
Total		11	2	1	8	58	6/11	54.5	1/11	9.1	0/11	0

- ✓ **No immunogenic interaction** between DOACs and HIT antibodies.
- ✓ DOACs unlike AVKs can be readily administered in the **acute phase of HIT**.
- ✓ **DOACs** can be administered as long term anticoagulation **avoiding the transition from parenteral to oral treatment**.

DOACs in HIT patients. Guidelines



Leslie Skeith

CLINICAL GUIDELINES



American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

Management of the acute phase of HIT

Recommendation 3.1. In patients with acute HIT complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT), the ASH guideline panel *recommends* discontinuation of heparin and initiation of a non-heparin anticoagulant (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕○). When a non-heparin anticoagulant is being selected, the ASH guideline panel *suggests* argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC) (conditional recommendation, very low certainty in the evidence about effects ⊕○○○).

VTE treatment and prophylaxis in patients with remote HIT

Recommendation 7.1. In patients with remote HIT who require VTE treatment or prophylaxis, the ASH guideline panel *recommends* administration of a non-heparin anticoagulant (eg, apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or VKA) rather than UFH or LMWH (strong recommendation, very low certainty in the evidence about effects ⊕○○○). **Remarks:** For

DOACs in Cancer Associated VTE

Table 2 Summary of major trials comparing DOACs with LMWH

Trial	VTE recurrence (%)	Major bleeding (%)	Mortality (%)
Hokusai VTE Cancer ³³	8.8 vs 6.5		24.2 vs 24.8
Dalteparin vs edoxaban	Edoxaban		Major bleeding rates were not significantly different, nor was mortality
SELECT			30 vs 25
Dalteparin vs rivaroxaban			Major bleeding were not significantly different, nor was mortality in the rivaroxaban arm. No difference in mortality
ADAM V			10.6 vs 15.9
Dalteparin vs apixaban			No significant difference in bleeding rates or mortality

Note: Six-month survival
Abbreviations: DC

A Pill Instead of a Needle for Cancer-Associated Venous Thromboembolism? YES!

LORI-ANN LINKINS, MD, MSc(CLIN EPI), FRCPC
Associate Professor, McMaster University, Hamilton, ON, Canada

Not a clinic goes by where I don't hear, "don't you have a pill I can take instead of a needle?" from a patient with cancer-associated venous thromboembolism (VTE). The 2017 ASH Annual Meeting brings hope that we are finally able to say "yes" to some of these patients.

LMWH, low molecular weight heparin; VTE, venous thromboembolism.





National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer-Associated Venous Thromboembolic Disease

NCCN.org

Version 1.2019 — February 26, 2019

[Continue](#)



Journal of Thrombosis and Haemostasis, 11: 56–70

DOI: 10.1111/jth.12070

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

ASCO special article

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Nigel S. Key, MB ChB¹; Alok A. Khorana, MD²; Nicole M. Kuderer, MD³; Kari Bohlke, ScD⁴; Agnes Y.Y. Lee, MD, MSc⁵; Juan I. Arcelus, MD, PhD⁶; Sandra L. Wong, MD, MS⁷; Edward P. Balaban, DO⁸; Christopher R. Flowers, MD, MS⁹; Charles W. Francis, MD¹⁰; Leigh E. Gates¹¹; Ajay K. Kakkar, MBBS, PhD¹²; Mark N. Levine, MD, MSc¹³; Howard A. Liebman, MD¹⁴; Margaret A. Tempero, MD¹⁵; Gary H. Lyman, MD, MPH¹⁶; and Anna Falanga, MD¹⁷

2019 by American Society of Clinical Oncology



clinical practice guidelines

Annals of Oncology 22 (Supplement 6): vi85–vi92, 2011
doi:10.1093/annonc/mdr392

Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines

M. Mandalà¹, A. Falanga² & F. Roila³

On behalf of the ESMO Guidelines Working Group*

Isth™
International Society on
Thrombosis and Haemostasis

[Evidence-Based Medicine]

CHEST

CHEST 2016; 149(2):315-352

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report



American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer



New

Initial treatment (first week) for patients with active cancer and VTE. RECOMMENDATION 20. For patients with cancer and VTE, the ASH guideline panel *suggests* DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 21. For patients with cancer and VTE, we *recommend* LMWH over UFH for initial treatment of VTE for patients with cancer (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕○).

RECOMMENDATION 22. For patients with cancer and VTE, the ASH guideline panel *suggests* LMWH over fondaparinux for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

Short-term treatment for patients with active cancer (initial 3-6 months). RECOMMENDATION 23. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕○○).

RECOMMENDATION 24. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over VKA (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 25. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕○).

RECOMMENDATION 26. For patients with cancer and incidental (unsuspected) pulmonary embolism (PE), the ASH guideline panel *suggests* short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 27. For patients with cancer and subsegmental PE (SSPE), the ASH guideline panel *suggests* short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 28. For patients with cancer and visceral/splanchnic vein thrombosis, the ASH guideline panel *suggests* treating with short-term anticoagulation or observing (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 29. For patients with cancer with CVC-related VTE receiving anticoagulant treatment, the ASH guideline panel *suggests* keeping the CVC over removing the CVC (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 30. For patients with cancer and recurrent VTE despite receiving therapeutic LMWH, the ASH guideline panel *suggests* increasing the LMWH dose to a supratherapeutic level or continuing with a therapeutic dose (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 31. For patients with cancer and recurrent VTE despite anticoagulation treatment, the ASH guideline panel *suggests* not using an inferior vena cava (IVC) filter over using a filter (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

Long-term treatment (>6 months) for patients with active cancer and VTE. RECOMMENDATION 32. For patients with active cancer and VTE, the ASH guideline panel *suggests* long-term anticoagulation for secondary prophylaxis (>6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕○○).

RECOMMENDATION 33. For patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel *suggests* continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 34. For patients with active cancer and VTE requiring long-term anticoagulation (>6 months), the ASH guideline panel *suggests* using DOACs or LMWH (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

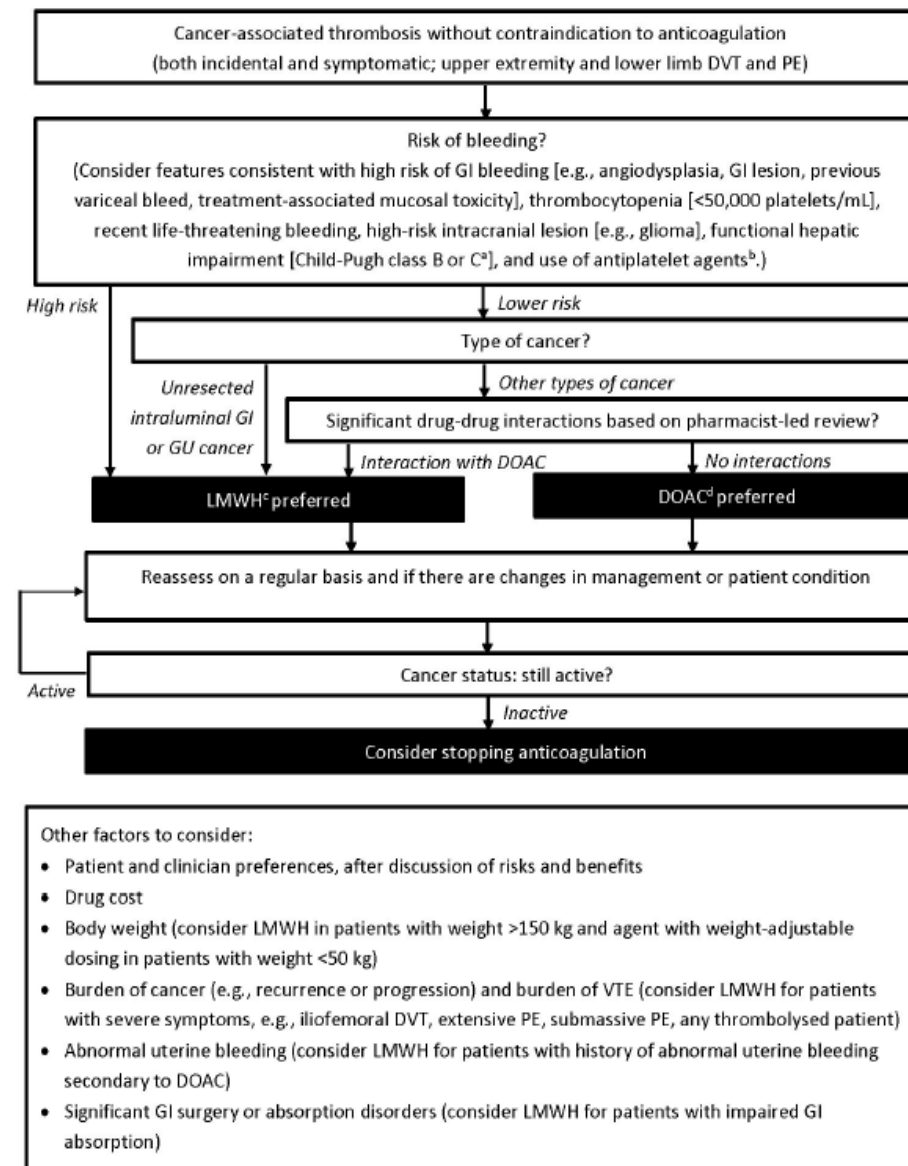
Treatment Algorithm in Cancer-Associated Thrombosis: Updated Canadian Expert Consensus

Marc Carrier ^{1,*}, Normand Blais ², Mark Crowther ³, Petr Kavan ⁴, Grégoire Le Gal ¹, Otto Moodley ⁵, Sudeep Shivakumar ⁶, Deepa Suryanarayan ⁷, Vicky Tagalakakis ⁸, Cynthia Wu ⁹ and Agnes Y. Y. Lee ¹⁰

2021



Figure 1. Patient risk stratification algorithm for anticoagulant therapy in cancer-associated thrombosis. ^a None of the DOACs are recommended for use in patients meeting criteria for Child-Pugh class C, with use of rivaroxaban being contraindicated in patients with hepatic disease (including Child-Pugh class B and C) associated with coagulopathy and having clinically relevant bleeding risk. Apixaban should be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh class A or B), while these patients exhibited comparable pharmacokinetics and pharmacodynamics to healthy controls when treated with edoxaban. ^b Use of antiplatelet agents should be assessed, and discontinuation should be considered in the absence of a strong indication. Shared decision-making with other health care providers is warranted. ^c Currently, dalteparin, enoxaparin, and tinzaparin have randomized controlled trial evidence in cancer-associated thrombosis, with the evidence base being stronger for dalteparin and tinzaparin. Refer to the relevant product monograph for appropriate dosing. ^d Currently, apixaban, edoxaban, and rivaroxaban have randomized controlled trial evidence in cancer-associated thrombosis, with stronger evidence for apixaban and edoxaban. Refer to the relevant product monograph for appropriate dosing. DVT = deep vein thrombosis; PE = pulmonary embolism; GI = gastrointestinal; GU = genitourinary; DOAC = direct-acting oral anticoagulant; LMWH = low molecular weight heparin; VTE = venous thromboembolism.



DOACs in CAT-VTE

LMWH	Optimal	• Frequent emetogenic chemotherapy, nausea and vomiting, difficulty with oral intake • Concerns for GI absorption (feeding tubes, gastric or bowel resections) • Drug—drug interactions with DOAC or VKA • Motivated patient willing to use for extended durations³¹ • Known increased bleeding risk • Recurrent cancer-associated VTE while on anticoagulants^{c88–90}
	Avoid	• Strong aversion to injectable therapy³¹ • Renal insufficiency/fluctuating renal status²³ • Extremes of weight (<50 kg or >150 kg)^b

DOAC	Optimal	• Patient without GI malignancy^{33,34} • Low risk of major bleeding^a • Ease of treatment for patient is a priority³¹ • No strong drug—drug interactions
	Avoid	• Active GI malignancy^{33,34} • History of GI bleeding^{33,34} • Extremes of weight (<50 kg or >150 kg)^b • Renal insufficiency/fluctuating renal status⁶¹

VKA	Optimal	• Any situation in which close anticoagulant monitoring is necessary (eg, multiple prior bleeds) or concern about absorption and metabolism • Advanced chronic kidney disease • Extremes of weight (<50 kg or >150 kg)^b
	Avoid	• Lack of access to dedicated anticoagulation monitoring service with experience caring for cancer patients⁹¹

Personalized approach for CAT-VTE

T	Assess Thromboembolic risk: • AF-related risk (eg, CHA₂DS₂-VASc score) • Cancer-associated risk (eg, Khorana score)
B	Assess Bleeding risk: • Thrombocytopenia (PTL <50,000/μL) • GI/GU cancer, GI comorbidities or toxicity • Recent or evolving intracranial lesions • Recent major bleeding • Severe renal dysfunction (eGFR <30 mL/min/1.73m²) • Bleeding risk scores (HAS-BLED, HEMORR₂HAGES, other?)
I	Assess drug-drug Interactions (P-glycoprotein, CYP3A4): • Anticancer agents • Supportive therapies
P	Assess Patient access and preferences • Access to drugs, drug availability • Patient preference

Tailor-made (TBIP)
approach with

Reassessment on
patients' journey



VTE MANAGEMENT IN OBESITY: Challenges

- Other than weight loss, **no current published recommendations** available to prevent/treat thrombosis in obese patients
- It is established that **obese patients require** significantly higher doses of warfarin to reach INR goals in a timely manner
- **Uncertainty of weight-based** and maximum doses of LMWH
- **DOACs are approved with fixed doses** and obese patients were excluded from the trials to support approval
- **Using anti-Xa levels** with these therapeutic options **are not well established**

VTE MANAGEMENT IN OBESITY:

Summary of Clinical Data

	Phase 3 Studies Comparing DOACs with VKA in VTE		Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)	
	BMI >35 or BW >120 kg	BMI >40	BMI >35 or BW >120 kg	BMI >40
Apixaban	X	X	Similar outcomes ⁶	Similar outcomes ^{5,6}
Dabigatran	X	X	X	X
Edoxaban	X	X	X	X
Rivaroxaban	Similar outcomes ⁷	X	Similar outcomes ^{5,8-10}	Similar outcomes ^{5,9}
Pooled DOAC	Similar outcomes ¹¹	X	Similar outcomes ¹²⁻¹⁶	Similar outcomes ¹²

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

Abbreviations: BMI, body mass index, expressed in kg/m²; BW, body weight; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

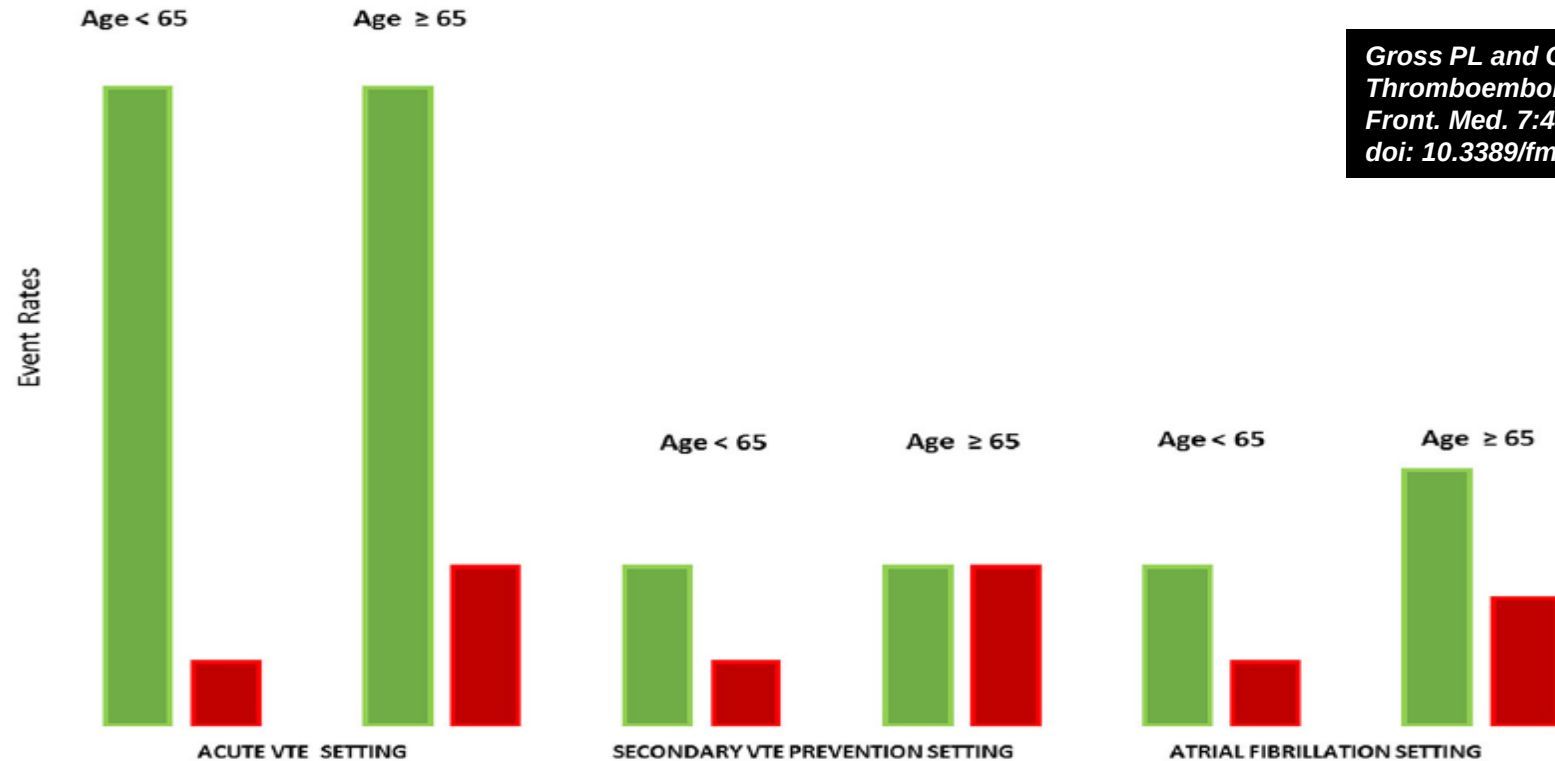
Updated Summary Guidance Statements for use of DOACs for VTE in patients with obesity

- 1) Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m² or weight 120 kg. For patients with BMI > 40 kg/m² or weight >120 kg, we recommend that the individual DOACs should be used as follows:
- 2) For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Less supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.
- 3) For primary prevention of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
- 4) We suggest not to use dabigatran, edoxaban or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m² or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
- 5) We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.
- 6) We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

ORAL ANTICOAGULATION MANAGEMENT IN THE ELDERLY: Challenges

- Prevalent **features that complicate** anticoagulant management in older adults are: non-adherence, falls, chronic kidney disease (CKD), polypharmacy, food-drug, and drug-drug interactions.
- At a prescriber level, concerns about bleeding have led to the underuse and **underdosing of anticoagulants** in this population.
- ! older patients with AF with an additional risk factor for stroke would have to **fall 295 times a year** for the risk of a subdural hematoma to outweigh the reduction in stroke risk with anticoagulant therapy
- Almost **two-thirds of all VTE** events occur in patients over **70 years**
- Prior to the introduction of DOACs, **50% of eligible AF** patients received treatment with a VKA, and only **50%** who received treatment had a **TTR >60%**.

ORAL ANTICOAGULATION MANAGEMENT IN THE ELDERLY: Challenges



Gross PL and Chan NC (2021)
Thromboembolism in Older Adults.
Front. Med. 7:470016.
doi: 10.3389/fmed.2020.470016

FIGURE 2 | The dynamic between thromboembolic and bleeding risks according to age in various settings. The figure shows the dynamic between thromboembolic and bleeding risks according to age and to clinical indications. In the acute VTE setting, without anticoagulant therapy, the risk of recurrent VTE is very high irrespective of age. Although bleeding risk on anticoagulation increases with age, anticoagulant therapy is associated with a net clinical benefit in acute VTE treatment in younger and older patients. In the secondary VTE prevention setting, the risk of VTE recurrence after a treated index event is lower compared to the acute VTE setting and similar in both younger and older patients. Because of higher bleeding risk, the benefit of anticoagulation for secondary VTE prevention is likely reduced in older patients compared with younger patients. Consequently, VTE guidelines are less strong in recommending extended anticoagulation in older patients. By contrast, the risk of cardioembolic stroke in AF rises with age and thus most older patients continue to benefit from anticoagulant therapy despite a higher bleeding risk. Despite the similar definition of major bleeding, the consequence of a venous thromboembolic event and an arterial thromboembolic event are not equal. **Green**, thromboembolic risk in absence of anticoagulant therapy; **Red**, major bleeding risk with anticoagulation.

ORAL ANTICOAGULATION MANAGEMENT IN THE ELDERLY

Table 2. Efficacy and safety of NOACs compared with warfarin in patients with AF aged 75 y or older

Trial acronym	Comparisons	Number of patients ≥75 y	Stroke/SEE HR (95% CI)	Major bleeding HR (95% CI)	Intracranial bleeding HR (95% CI)
RE-LY	DE 150 mg bid vs warfarin	7258	0.67 (0.49-0.90)	1.18 (0.98-1.42)	0.42 (0.25-0.70)
	DE 110 mg bid* vs warfarin		0.88 (0.66-1.17)	1.01 (0.83-1.23)	0.37 (0.21-0.64)
ROCKET-AF	Rivaroxaban daily vs warfarin	6229	0.80 (0.63-1.02)	1.11 (0.92-1.34)	0.80 (0.50-1.28)
ARISTOTLE	Apixaban bid vs warfarin	5678	0.71 (0.53-0.95)	0.64 (0.52-0.79)	0.34 (0.20-0.57)
ENGAGE-AF	Edoxaban 60 mg daily vs warfarin	8474	0.83 (0.66-1.04)	0.83 (0.70-0.99)	0.40 (0.26 -0.62)
	Edoxaban 30 mg† daily vs warfarin*		1.12 (0.91-1.37)	0.47 (0.38 -0.58)	0.31 (0.19-0.49)

bid, twice daily; DE, dabigatran etexilate; SEE, systemic embolic event.

*Dabigatran 110 mg is not approved in the United States for stroke prevention in AF.

†Edoxaban 30 mg is not approved in many countries.

ORAL ANTICOAGULATION MANAGEMENT IN CHILDREN: Challenges

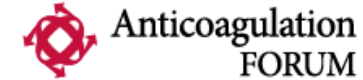
- The incidence of thromboembolic events is **relatively low** in the general **pediatric population**, but it increases in hospitalized children and those who undergo thrombogenic procedures.
- Although evidence regarding DOACs in children with VTE is growing, DOACs were excluded from existing guidelines due to the lack of reliable data at that moment.
- **Standard treatment** recommendations in pediatric patients with VTE include LMWH or UFH, followed by LMWH or AVK.

January 2022, DOACs with the most published pediatric data are rivaroxaban and dabigatran, and both have recent approval for treatment of pediatric VTE by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA).

ORAL ANTICOAGULATION MANAGEMENT IN CHILDREN: Guidelines



Last updated 12/2022



Appropriate Use of DOACs in the Pediatric Population

excellence.acforum.org

BOTTOM LINE

DOAC use in pediatrics is a rapidly evolving area of practice with lack of consensus guidelines at this time due to the newness of clinical data. Current recommendations are based on a critical evaluation of available evidence.

DOACs are an increasingly utilized option for treating and preventing thrombosis in children.

Rivaroxaban and dabigatran are approved for treatment and prevention of VTE in children. Clinical trials using apixaban and edoxaban are underway.

The FDA approved the use of rivaroxaban post-Fontan, but the details of the dose and study population are important to consider (see details below).

While rates of recurrent thrombosis and bleeding in the published DOAC clinical trials were low, the patients enrolled may not reflect the complexity of pediatric patients in clinical practice.

There remains limited data on DOACs in neonates & infants.

Decisions regarding antithrombotic therapy in children are best guided by providers with expertise in pediatric thrombosis.

Considerations for using DOACs in children

Don't use a DOAC in patients who are: critically ill, have prosthetic heart valves, antiphospholipid antibody syndrome, renal failure, and/or significant hepatic dysfunction.

Patient should be tolerating good enteral intake via oral, NG or G-tube.

Need ≥ 5 days of parenteral anticoagulation prior to DOAC for VTE treatment (pediatric regimen).

Check for clinically significant drug interactions.

Have a plan for reversal in case of bleeding or urgent surgery (recognizing the lack of pediatric data for reversal).

Evaluate availability of appropriate drug formulation.

Check for barriers to drug acquisition - insurance coverage.

Black box: Contraindications to DOAC use

- **Mechanical heart valves**
- **Moderate to severe mitral stenosis**
- **Severe renal or hepatic impairment**
- **Pregnancy, lactation**

Apixaban in End Stage Renal Disease/dialysis patients

- Apixaban in ESRD-AF patients, the **RENAL-AF study**-> Randomized controlled study. Stopped prematurely due to enrollment. TTR warfarin-treated patients was 44%. Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism in the study population.
- Single-centre prospective analysis carried out at **Oxford Kidney Unit** to evaluate the efficacy and safety of apixaban when used at the dose of 2.5-mg twice daily (BD) for dialysis patients with NVAf-> Supports **apixaban at a dose of 2.5-mg BD in patients receiving dialysis as an alternative to VKA in NVAf**, longitudinal data on apixaban levels, over a 3-month period, suggest that there is no risk of cumulative exposure.
- Retrospective cohort analysis of **five U.S. claims databases**-> evaluate the risk of recurrent VTE, MB, and CRNMB for apixaban versus warfarin among VTE patients diagnosed with CKD, including ESRD. **29,790 VTE patients with CKD** were selected for analyses. Apixaban was associated with a significantly lower risk of recurrent VTE and MB than warfarin among VTE patients with CKD. CKD stages did not have significant impact on treatment effects for recurrent VTE and MB

1. *Circulation*. 2022;146:1735-1745. DOI: 10.1161/CIRCULATIONAHA.121.054990
2. *eJHaem*. 2023;4:291-293
3. *Thromb Haemost* 2022;122:926-938

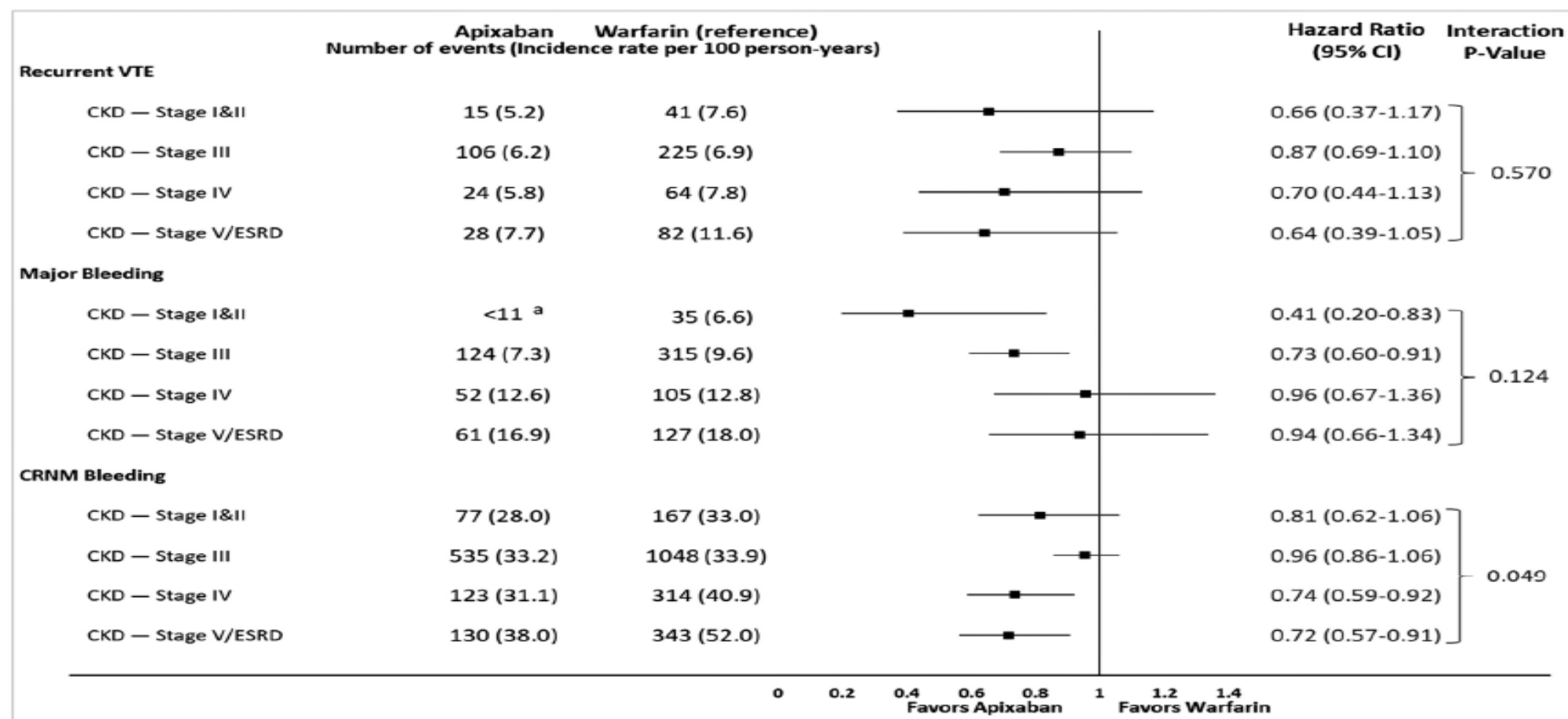


Fig. 3 Risk of recurrent venous thromboembolism (VTE), major bleeding, and clinically relevant nonmajor bleeding among patients with chronic kidney disease prescribed apixaban or warfarin to treat VTE, stratified by CKD stages. The figure shows a forest plot of the risks of recurrent VTE, major bleeding, and CRNMB. The patient population consisted of patients with CKD being treated for VTE with apixaban or warfarin during the study period, stratified by the stage of CKD (stage I/II, stage III, stage IV, stage V/ESRD). The number of events and the incidence per 100 person-years are listed for each outcome, stage, and treatment. Risk is indicated by an HR and 95% CI. The degree of risk is indicated along the x-axis. The *p*-value for interaction indicates the association between CKD stages and treatment effects on a specific outcome. *Black squares* indicate the hazard ratio; *solid black lines* indicate the 95% CI. CI, confidence interval; CKD, chronic kidney disease; CRNMB, clinically relevant nonmajor bleeding; ESRD, end-stage renal disease; HR, hazard ratio; VTE, venous thromboembolism. ^a < 11 used due to agreements with commercial providers to assure privacy for very small number of events; interaction is significant if *p* < 0.10.

Direct Oral Anticoagulants (DOACs)

Pharmacokinetics & Pharmacodynamics

JAm Coll Cardiol Intv 2014;7:1333-51; P&T 2018;43: 85-88.

Property	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
MOA	Direct Thrombin Inhibitor	Direct Xa Inhibitor	Direct Xa Inhibitor	Direct Xa Inhibitor	Direct Xa Inhibitor
Bioavailability	6 – 7%	80%	50%	62%	35%
Tmax	1.5 hours	2 – 4 hours	2 – 3 hours	1 – 2 hours	3 – 4 hours
T½	12 – 14 hours	9 – 13 hours	8 – 15 hours	8 – 11 hours	19 – 27 hours
CPY450 Metabolism	No	Yes	Yes	No	No
Drug Interactions	P-gp	P-gp + CYP3A4	P-gp + CYP3A4	P-gp	P-gp
Dialyzable	Yes	No	No	No	No
Renal Elimination	80%	35%	25%	40%	<10%
Renal Dose Adjust	Yes	Yes	No?	Yes	Yes
Antidote	Yes	Yes	Yes	Yes?	Yes?

CAVUHB Guidance for choice of NOAC



*Licensed antidote available at UHW / UHL for dabigatran

Adapted for C&V UHB from: Camm J. *Am J Med* 2013; Updated 01-06-17

Are all DOACs the same???

Direct comparative effectiveness and safety between non-vitamin K antagonist oral...

Table 2 Results of comparative effectiveness and safety amongst NOACs in patients with AF

Outcome	Rivaroxaban versus Dabigatran		Rivaroxaban versus Apixaban		Apixaban versus Dabigatran	
	Number of studies/patients	Pooled HR (95% CI), <i>p</i> value	Number of studies/patients	Pooled HR (95% CI), <i>p</i> value	Number of studies/patients	Pooled HR (95% CI), <i>p</i> value
Stroke or SE	7/198,445	1.00 (0.91–1.10), 0.97	2/25,217	1.09 (0.96–1.24), 0.19 ^b	2/25,312	0.94 (0.83–1.06), 0.32 ^b
Stroke	4/164,722	1.02 (0.89–1.16), 0.75 ^c	1/13,130	— ^a	1/13,084	— ^a
SE	1/13,121	— ^a	0/0	— ^a	0/0	— ^a
Major bleeding	7/206,623	1.39 (1.28–1.51), < 0.001	7/77,657	1.71 (1.51 – 1.94), < 0.001	6/43,470	0.80 (0.68 – 0.95), 0.01
ICH	4/173,423	1.19 (0.75–1.88), 0.46	1/13,130	— ^a	1/13,084	— ^a
Major GI bleeding	3/141,849	1.26 (1.18–1.36), < 0.001	0/0	— ^a	0/0	— ^a
Myocardial infarction	2/128,728 ^b	0.87 (0.72–1.05), 0.15	0/0	— ^a	0/0	— ^a
All-cause death	4/148,798	1.28 (1.14–1.43), < 0.001	0/0	— ^a	0/0	— ^a

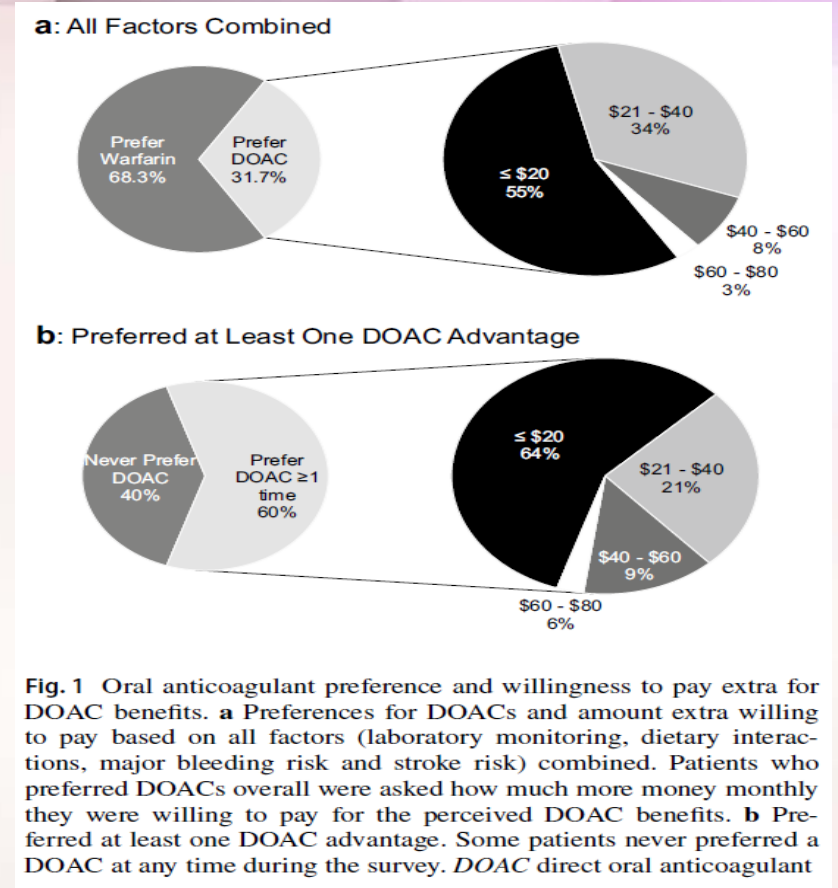
^aNo meta-analysis conducted due to insufficient studies or data available

^bFixed-effects model was used due to only two studies included for analysis

^cData were for ischemic stroke

Current anticoagulant treatment patient preferences, cost

- Patients are willing to **pay more** for potential **DOAC benefits?**
- Utah Health Thrombosis Service were given a one-time electronic survey
- **68% of warfarin** patients preferred to **stay on warfarin**
- Willingness to **pay extra** for DOAC advantages did not exceed **\$20/month** in the majority of survey respondents.
- A recent study demonstrated a monthly median out of pocket cost for DOAC of **\$317** for Medicare Part D beneficiaries, as opposed to **\$8 for warfarin**
- cost is a factor in shared decision-making for oral anticoagulant therapy selection.



Prediction of effective TTR levels: the SAME-TT2R2 score

Table 1

SAMe-TT₂R₂ variables.

	Variables	Points
S	Sex – female	1
A	Age < 60 years	1
Me	Medical history > 2 comorbidities ^a	1
T	Treatment medications (e.g. amiodarone)	1
T ₂	Tobacco use	2
R ₂	Race – non-Caucasian	2
	Maximum points	8

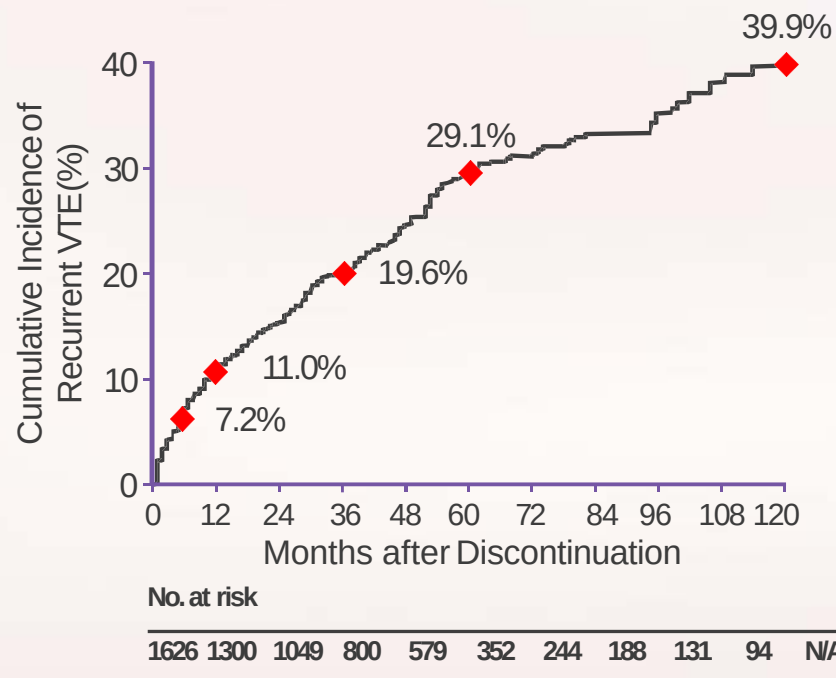
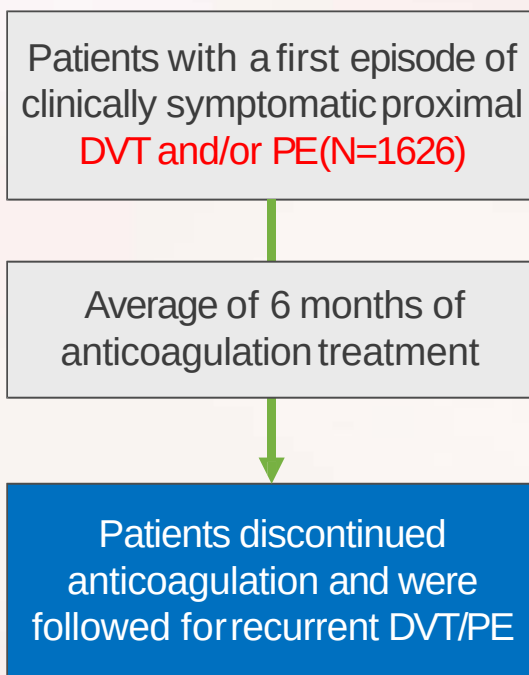
^aMe, one point is allotted if more than two of the following conditions are present: diabetes, hypertension, renal disease or hepatic disease, pulmonary disease, congestive heart failure, coronary artery disease, peripheral vascular disease or previous stroke.

-TTR <60% was more frequent among patients with a **high (>2) versus low (0-1)** SAMe-TT₂R₂ score (63.4% vs 52.3%, p<0.0001).

-high SAMe-TT₂R₂ score (>2) correlated with **increased overall adverse events** driven primarily by increased recurrent VTE rates

-The utility of the SAMe-TT₂R₂ score to guide clinical decision-making remains to be investigated.

Risk of Recurrent DVT/PE Persists Following Discontinuation of Anticoagulation



Prandoni P et al. *Haematologica* 2007; 92:199-205.

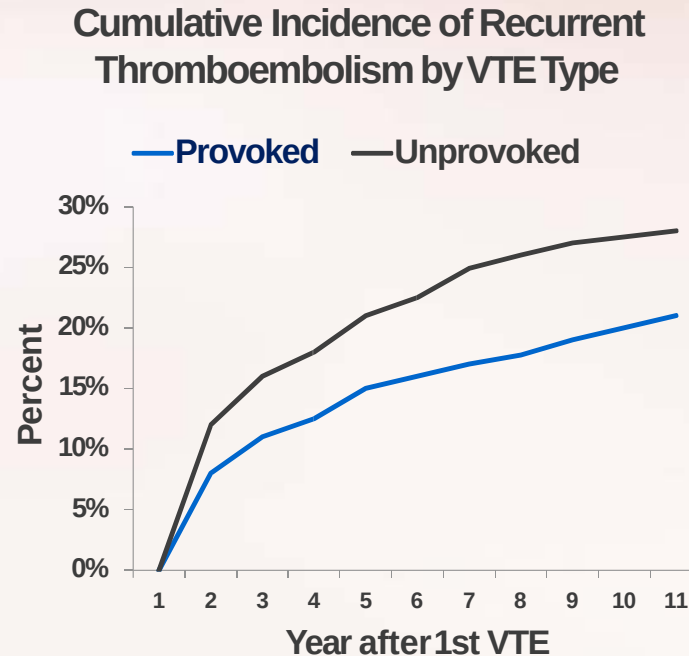
Risk of Recurrent DVT/PE Following Discontinuation of Anticoagulation: Prediction Models

Table 3 Prediction models for recurrent venous thromboembolism

Model name	Vienna prediction model ¹⁶	DASH score ¹⁹	Rodger or men continue and HER DOO2 score ²⁰
Number of patients	929	1,818	646
Design	Prospective cohort study	Patient-level meta-analysis	Prospective cohort study
Predictive variables	Male > female. PE > proximal DVT > distal DVT. Elevated D-dimer after AC	D-dimer abnormal after cessation of AC (2 points). Age ≤50 years (1 point). Sex – male (1 point). Hormonal use at VTE onset (–2 points)	Men continue. Hyperpigmentation (1 point). Edema (1 point). Redness (1 point). D-dimer ≥250 µg/L during AC (1 point). Obesity (BMI ≥30 kg/m ²) (1 point). Old (age ≥65 years) (1 point)
Total score	0 to 350	–2 to 4	0 to 6
Annual risk of recurrence	2%–15% depending on total score (nomogram)	Score of ≤1: 3.1% Score of 2: 6.4% Score of ≥3: 12.3%	Women with score of ≤1: 1.6% Women with score of ≥2: 14.1% Men: 13.7%

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism; AC, anticoagulation; BMI, body mass index; PE, pulmonary embolism.

Role of Prevention of Recurrent VTE



Study	Intervention	Recurrent VTE
PREVENT	Warfarin, INR 1.5-2 vs. placebo	↓64%
ELATE	Warfarin, INR 2-3 vs. INR 1.5-2	↓63%
RE-MEDY	Dabigatran vs. warfarin, INR 2-3	Non-inferior
INSPIRE	Aspirin vs. placebo	↓32%

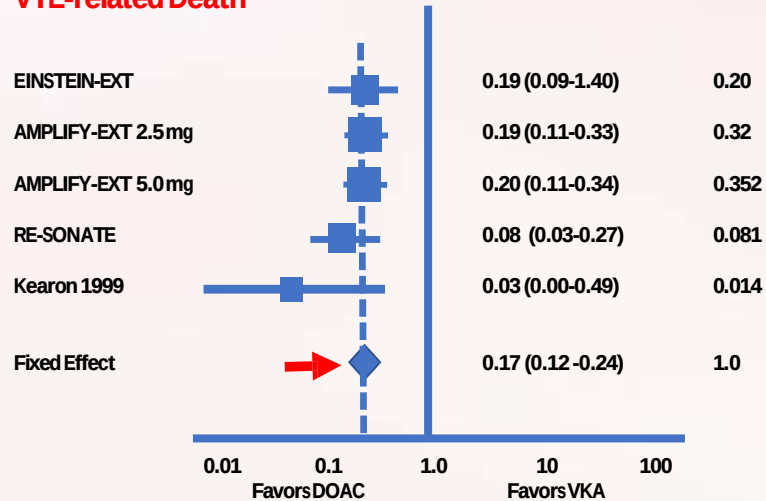
Prolonging anticoagulant therapy leads to a **significant reduction** of recurrence in patients with unprovoked VTE, a **benefit, which is lost** after stopping the anticoagulant treatment.

Martinez C et al. *Thromb Haemost.* 2014; 112: 255-63.
Goldhaber SZ et al. *Circulation.* 2011; 123:664-7. Ridker PM et al. *N Engl J Med.* 2003; 348:1425-34. Kearon C et al. *N Engl J Med.* 2003; 349:631-9. Schulman S et al. *N Engl J Med.* 2013; 368:709-18. Simes J et al. *Circulation.* 2014; 130:1062-71.

Extended VTE Treatment & DOACs: Outcomes

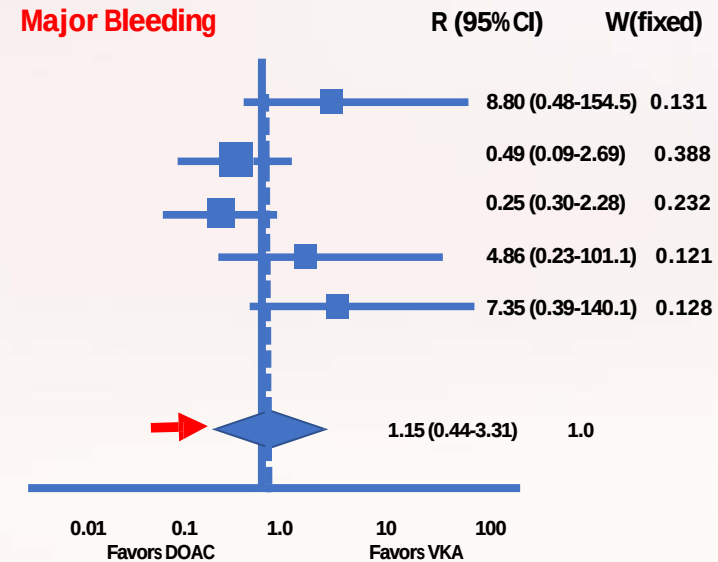
Meta-analysis (n=3,015)

Recurrent VTE, VTE-related Death



83% relative risk reduction of recurrent VTE or VTE-related death (CI: 0.12-0.24, $p < 0.0001$)

Major Bleeding



No significant increase in the risk of major bleeding (CI: 0.40-3.31, $p = 0.38$)

Duration of anticoagulant treatment after VTE event

2021

TABLE 4: SUMMARY OF RECOMMENDATIONS FOR DURATION OF TREATMENT

CATEGORIES OF VTE	DURATION OF TREATMENT
First VTE provoked by a transient risk factor	3 months*
Second VTE provoked by a transient risk factor	Same as for first VTE provoked by a transient risk factor*
First unprovoked VTE† With low or moderate bleeding risk With high bleeding risk	Minimum of 3 months and then reassess. Indefinite therapy with periodic reviews¶‡ 3 months, especially if recurrent VTE risk is relatively lower and/or bleeding risk factors cannot be mitigated
Second unprovoked VTE	Same as for first unprovoked VTE; this is a strong indication for indefinite anticoagulant therapy unless there is a very high bleeding risk¶‡
Isolated distal DVT	3 months*
Central venous catheter(CVC)-associated VTE	3 months*; longer if CVC remains in place
VTE associated with ongoing non-cancer-related risk factors (e.g. paraplegia or other significant immobility, active inflammatory bowel disease, high risk thrombophilia)	Indefinite therapy with periodic reviews or as long as the risk factor persists¶
Cancer-associated VTE	Minimum 3 months, then reassess and continue if active cancer or patient continuing to receive anticancer therapy

Duration of anticoagulant treatment after VTE event



Thrombosis Canada

Thrombose Canada

2021

TABLE 3: ESTIMATED RISK OF RECURRENCE AFTER STOPPING ANTICOAGULATION FOR A FIRST VTE

	1 YEAR AFTER STOPPING ANTICOAGULANTS	5 YEARS AFTER STOPPING ANTICOAGULANTS
Surgical/Major	1-2%	3%
Non-surgical/Minor (e.g. hospitalization, plaster cast immobilization, hormone therapy*, flight of > 8 hours, medical illness with immobilization)	5%	15%

*The risk of recurrence in women with a first VTE associated with estrogen-containing contraceptive use (4% by 5 years off anticoagulation) may be lower than that seen with VTE provoked by other minor risk factors.

2023

American Society of Hematology 2023 Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing

Question 3: In patients with VTE provoked by a non-surgical major transient risk factor, should thrombophilia testing be performed to guide treatment duration?

Recommendation 3. In patients with VTE provoked by a non-surgical major transient risk factor who have completed primary short-term treatment, the ASH guideline panel suggests testing for thrombophilia to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulant treatment in patients with thrombophilia and stopping anticoagulant treatment in patients without thrombophilia (conditional recommendation).

We did not identify direct studies to answer these questions

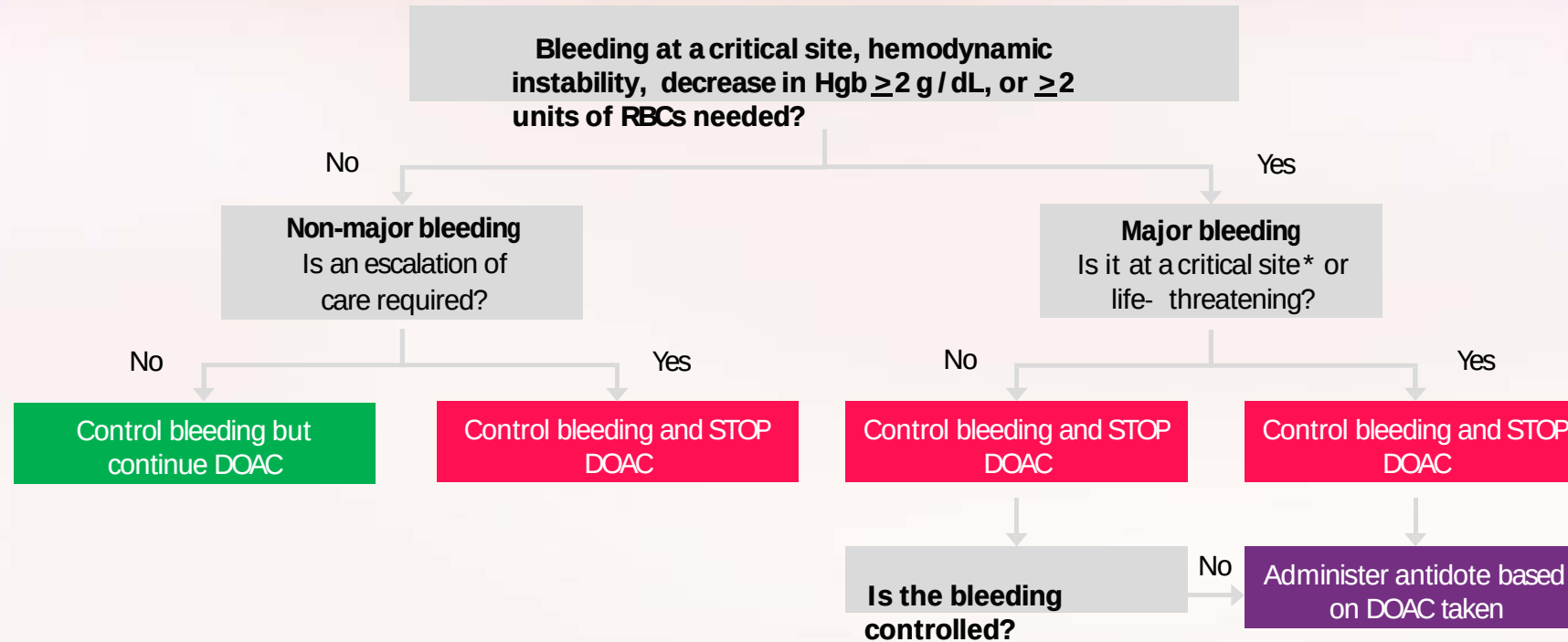
or postpartum, should thrombophilia testing be performed to guide treatment duration?

Recommendation 4. In women with VTE provoked by pregnancy or postpartum who have completed primary treatment, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulant treatment in women with thrombophilia and stopping anticoagulant treatment in women without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⊕○○○).

Remarks:

- According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.

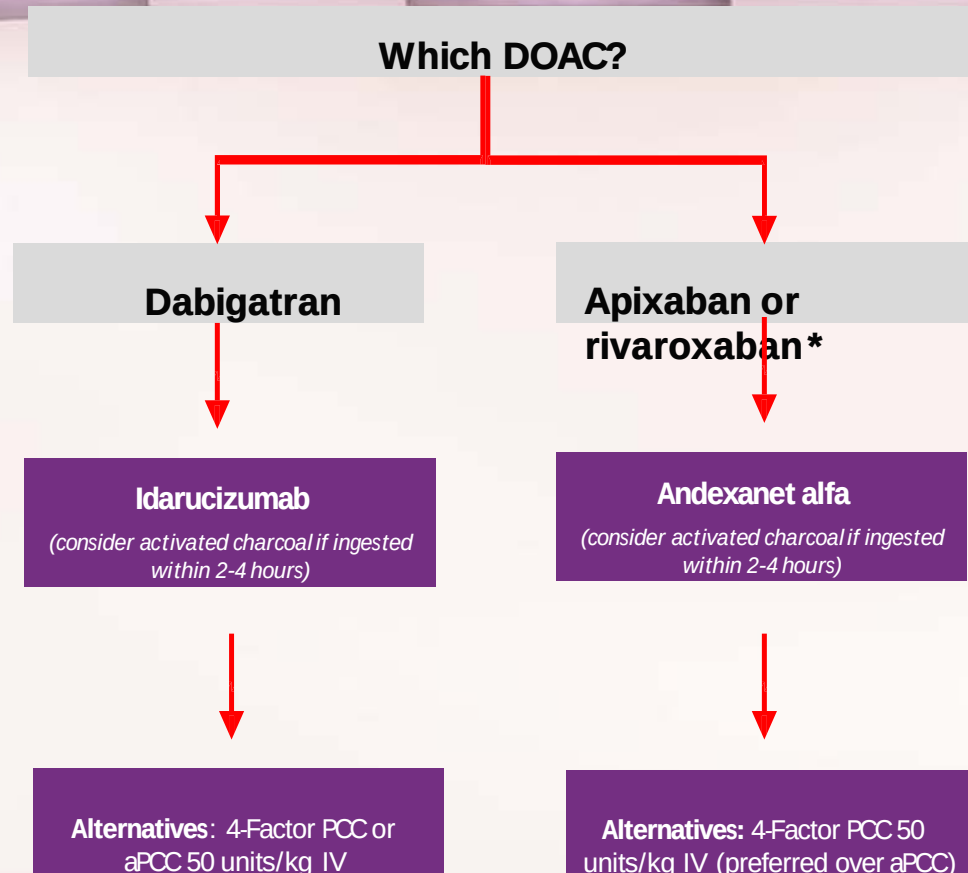
DOACs Bleeding Management Overview



*Critical site bleeds include central nervous system bleeding, pericardial tamponade, airway bleeding, hemothorax, intra-abdominal bleeding, retroperitoneal hematoma, and intramuscular/intra-articular extremity bleeding. Abbreviations: Hgb hemoglobin, RBCs red blood cells

Adapted from *JAm Coll Cardiol*. 2017 Dec 19;70(24):3042-3067

DOAC Reversal Strategies



*Case studies suggest that andexanet alfa may also be effective for reversing edoxaban and betrixaban. Abbreviations: aPCC activated prothrombin complex concentrates, PCC prothrombin complex concentrates. Adapted from *J Am Coll Cardiol*. 2017 Dec 19;70(24):3042-3067

A sunset scene over a body of water. Two suns are visible on the horizon, creating a double-sun effect. The sky is filled with orange and yellow clouds. The water is dark with some ripples.

AVKs

DOACs

Thank you for your attention

Anticoagulation planet

Notable DOAC Drug-Drug Interactions

Category	Examples	Management
P-gp inducers	Barbiturates, phenytoin, carbamazepine, rifampin, St. John's wort	Avoid dabigatran and edoxaban
P-gp inhibitors	Amiodarone, dronedarone*, diltiazem, verapamil, clarithromycin, grapefruit juice, cyclosporine, tacrolimus, ketoconazole*, itraconazole, ritonavir	Use dabigatran and edoxaban with caution; consider avoiding in renal dysfunction
P-gp <u>plus</u> strong CYP3A4 inducers	Barbiturates, phenytoin, carbamazepine, rifampin, St. John's wort	Avoid apixaban and rivaroxaban
P-gp <u>plus</u> strong CYP3A4 inhibitors	Clarithromycin, grapefruit juice, ketoconazole, itraconazole, ritonavir	Avoid rivaroxaban Dose-reduce apixaban, or avoid if already using lower dose
P-gp <u>plus</u> moderate CYP3A4 inhibitors	Dronedarone, diltiazem, verapamil, azithromycin	Use rivaroxaban with caution, especially in renal dysfunction

*Dose-reduce dabigatran or avoid in coexisting renal dysfunction. DOAC direct-acting oral anticoagulant, P-gp p-glycoprotein
Adapted from *JThrombThrombolysis*. 2016 Jan;41(1):206–32.

Table 1. General recommendation for anticoagulation according to AF guidelines over a decade.

AF GUIDELINES	General recommendation for anticoagulation
2018 CHEST [7]	• OAC is recommended for male AF patients with a CHA₂DS₂-VASc score ≥ 1; and in female AF patients with a CHA₂DS₂-VASc ≥ 2. • NOACs are recommended in preference to a VKA for patients with AF who are eligible for NOACs. • Antiplatelet monotherapy is not recommended for stroke prevention in patients with AF • Attention to modifiable bleeding risk factors
2020 ESC [5]	• Shared-decision making • Bleeding risk assessment: attention to modifiable bleeding risk factors and identifying patients at high risk of bleeding • OAC is recommended for male AF patients with a CHA₂DS₂-VASc score ≥ 1; and in female AF patients with a CHA₂DS₂-VASc ≥ 2. • NOACs are recommended in preference to a VKA for patients with AF who are eligible for NOACs. • Switching to a NOAC in patients on VKA with a low TTR. • Antiplatelet monotherapy is not recommended for stroke prevention in patients with AF

AF – atrial fibrillation; OAC – oral anticoagulation; VKA – vitamin K antagonist, NOAC – non-vitamin K antagonist; CHADS₂ – heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, or transient ischemic attack (doubled); CHA₂DS₂VASc – heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, stroke, or transient ischemic attack (doubled), vascular disease, age 65–74 years and female sex; TTR – time in therapeutic range

Why to measure DOACs?

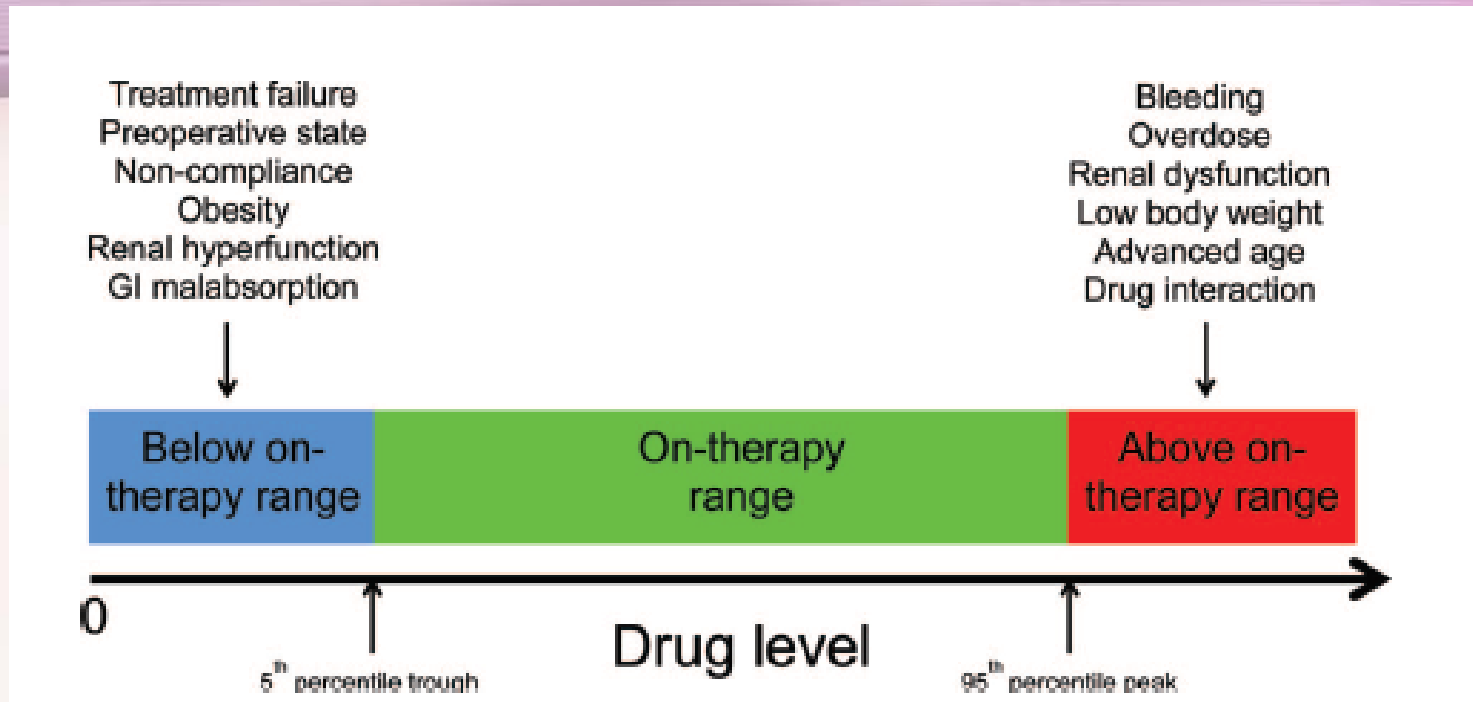


Table 1. Steady-state plasma DOAC concentrations

Drug	Dose, mg	Trough concentration, ng/mL		Peak concentration, ng/mL	
		Median	5 th to 95 th percentile	Median	5 th to 95 th percentile
Dabigatran ²	150 BID	90	31-225	184	64-443
Rivaroxaban ³	20 daily	26	6-87	270	189-419
Apixaban ⁴	5 BID	103	41-230	171	91-321
Edoxaban ⁵	60 daily	22	10-40*	170	120-250*

* Interquartile range.

Monitoring and reversal of direct oral anticoagulants
A. Cuker and D. Siegal. Hematology 2015

When do we need to measure DOACs in urgent situations?

- **Bleeding or recurrence of thrombosis** (to assessing the potential contribution of DOACs)
- **Before an invasive procedure** (elective or **urgent surgery** at risk of bleeding, **thrombolysis**) to make decision about timing of these procedures or to determine whether patients with acute ischemic stroke can safely be given fibrinolytic therapy.
- To select patients who will benefit from **antidote administration** (RE-VERSE AD study; at baseline, 25 patients had a normal aPTT → more sensitive tests than the aPTT are needed to best identify patients who will benefit from idarucizumab and to monitor their response to treatment).
- To monitor the **extent of reversal** achieved when reversal agents are given

Table 1 Summary of NOAC effects on hemostasis assays

Tests	Dabigatran	Rivaroxaban	Apixaban	Comments
(A) Routine assays (screening)				
PT	-/↑	↑/↑↑	-/↑	Different reagents show different sensitivities; in general, order of sensitivity = rivaroxaban, dabigatran, apixaban; only a few reagents sensitive to apixaban
APTT	↑/↑↑	-/↑	-/↑	Different reagents show different sensitivities; in general, order of sensitivity = dabigatran, rivaroxaban, apixaban
TT	↑↑↑	-	-	Very sensitive to dabigatran; insensitive to anti-Xa agents
Fibrinogen	-/↓	-/↓	-/↓	Most von Clauss methods insensitive; occasional von Clauss methods and PT-based methods will show some false loss
dRVVT	↑↑	↑↑	↑↑	Most dRVVT methods sensitive to all agents
(B) Quantifying assays (measuring)				
dTT/DTI	↑↑	-	-	Very sensitive to dabigatran; not affected by anti-Xa agents including rivaroxaban and apixaban
ECT/ECA	↑↑	-	-	Very sensitive to dabigatran; not affected by anti-Xa agents including rivaroxaban and apixaban
PICT	↑↑	↑↑	↑↑	Requires assay modifications to provide sensitivity to all agents; may require different setups for anti-IIa vs. anti-Xa drugs
Anti-Xa	-	↑↑	↑↑	Sensitive to anti-Xa agents (including rivaroxaban and apixaban); insensitive to dabigatran
(C) Drug interference				
PT factors	↓/↓↓↓	↓/↓↓↓	↓/↓↓↓	All PT factors affected, although most sensitive to dabigatran and rivaroxaban; can also yield impression of factor inhibitor
APTT factors	↓↓/↓↓↓	↓/↓↓↓	↓/↓↓↓	All APTT factors affected, although most sensitive to dabigatran and then rivaroxaban; can also yield impression of factor inhibitor
Protein C	-/↑	-/↑	-/↑	Chromogenic tests unaffected; clot-based tests may be affected
Protein S	-/↑	-/↑	-/↑	Antigen-based tests (e.g., LIA) unaffected; clot-based tests affected
Antithrombin	-/↑	-/↑	-/↑	Anti-IIa-based methods affected by dabigatran; anti-Xa-based methods affected by other drugs
APCR	-/↑	-/↑	-/↑	APTT-based assays are mostly affected
LA	↑/↑↑	↑/↑↑	-/↑	LA tests are sometimes affected so that prolongation in screen assays exceed prolongation in confirm assays, leading to high screen/confirm assay ratios, and thus false determination of LA. This is especially true of dabigatran and rivaroxaban
VWF	-	-	-	
TEG	↓/↓↓↓	↓/↓↓↓	↓/↓↓↓	Various parameters affected
LTA	- ^a	-	-	
PFA	-	-	-	
TGA	↓/↓↓↓	↓/↓↓↓	↓/↓↓↓	Various parameters affected
(D) Other				
mPT/dPT	↑/↑↑	↑/↑↑	↑/↑↑	Various modifications of the PT may increase sensitivity to all drugs
ACT	↑/↑↑	-/↑	-/↑	

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Table 4

Interpretation of coagulation assays in DOAC-treated patients. Below on-therapy, on-therapy, and above on-therapy ranges are listed in Table 1 and relate specifically to the doses shown in Table 1.

Test	Dabigatran		Xa Inhibitors	
	Normal	Abnormal/prolonged*	Normal	Abnormal/prolonged*
APTT	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present
PT	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present
TT	Excludes clinically significant levels	Below on-therapy, on-therapy, or above on-therapy levels likely present	Not useful	Not useful
dTT	Likely excludes clinically significant levels	May be used to quantify drug levels	Not useful	Not useful
Ecarin-based assay	Likely excludes clinically significant levels	May be used to quantify drug levels	Not useful	Not useful
Test	Dabigatran		Xa Inhibitors	
	<Lower limit of quantification	Analytical measurement range	<Lower limit of quantification	Analytical measurement range
Anti-Xa assay (UFH/LMWH calibrated)	Not useful	Not useful	Likely excludes clinically significant levels	May be used to estimate drug levels
Anti-Xa assay (DOAC calibrated)	Not useful	Not useful	Likely excludes clinically significant levels	May be used to quantify drug levels

DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

* Alternative etiologies for coagulopathy should also be considered (e.g. disseminated intravascular coagulation, liver injury, etc.)

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