ANTICOAGULANTS

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Disclosure Statement

☑ I have nothing to disclose

OBJECTIVES

- Determine when to start Warfarin if ever
- Determine when a thrombolytic work-up is needed
- Choose the appropriate DOAC
- Determine the duration of DVT treatment (fit to fly)

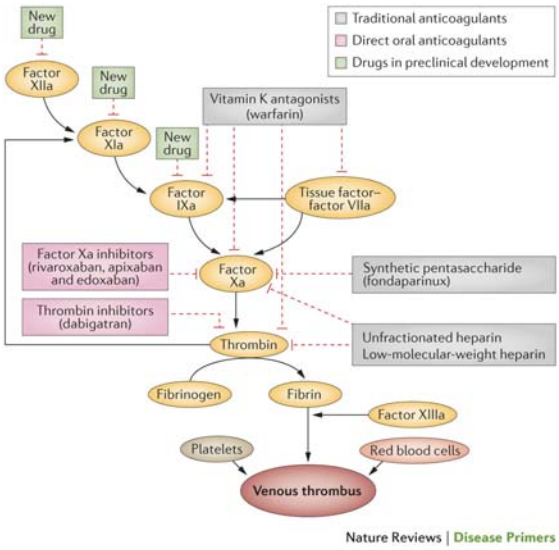
Burden of Thrombosis

- Venous Thromboembolism (VTE)
  - Affects 100,000 Canadians and cause 10,000 deaths per year
  - Substantial morbidity/mortality
  - 1 in 4 people worldwide are dying from conditions caused by thrombosis
- Atrial fibrillation
  - 0.1 % in < 55 yo, 9% in > 80 yo
  - Ischemic stroke: RR↑ x 4-5
  - Accounts for 15% of strokes (30% in > 80 yo)
  - Strokes: 545/100,000/year (Medicare, USA)
  - Only about 40% of AF requiring stroke prophylaxis are anticoagulated

ANTICOAGULANTS

- Parenteral
  - Unfractionated heparin
  - Low molecular weight heparins
  - Fondaparinux
  - Danaparoid
  - Argatroban
- Oral
  - Warfarin
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Figure 2 The coagulation cascade and existing and emerging anticoagulant drugs



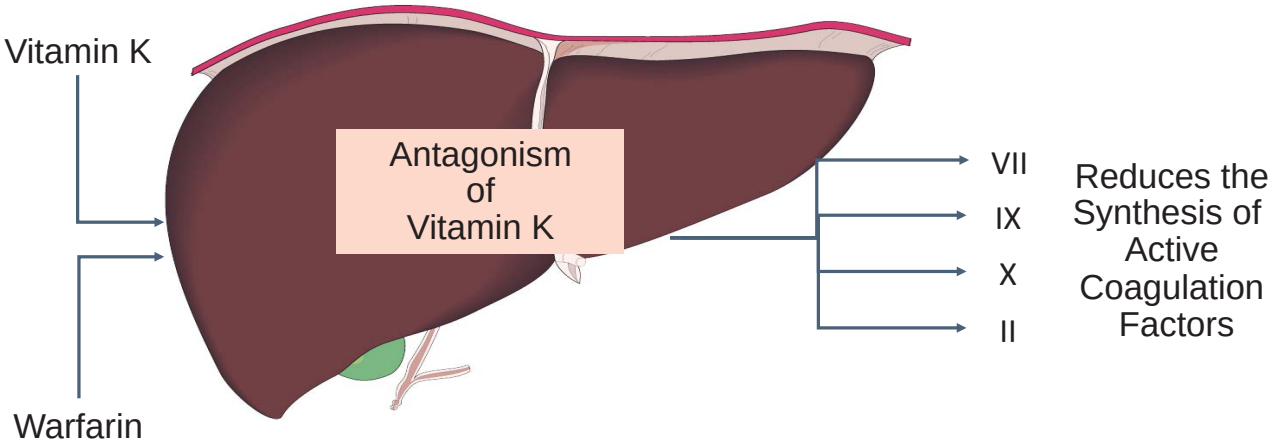
Wolberg, A. S. *et al.* (2015) Venous thrombosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.6

Indications for Warfarin

Is Warfarin becoming obsolete?

- NO
- Low cost
- Still preferred agent for:
  - mechanical valves
  - advanced renal failure?
  - heart failure (low EF) and prior TE
  - rheumatic mitral valve disease
  - high risk thrombophilias (APS triple positive)
  - LV thrombus

Warfarin: Mechanism of Action



Source: Ansell J et al., Council on Clinical Cardiology. *American Heart Association,* Management of Oral Anticoagulant Therapy, www.americanheart.org/downloadable/heart/3491_Mgt.ppt

UpToDate: Current indications for Warfarin use

- Atrial Fibrillation
- Acute Coronary Syndrome
- Heart Failure
- Prosthetic Heart Valve
- Stroke
- Deep Vein Thrombosis
- Pulmonary Embolism
- Antiphospholipid Syndrome

ORIGINAL ARTICLE

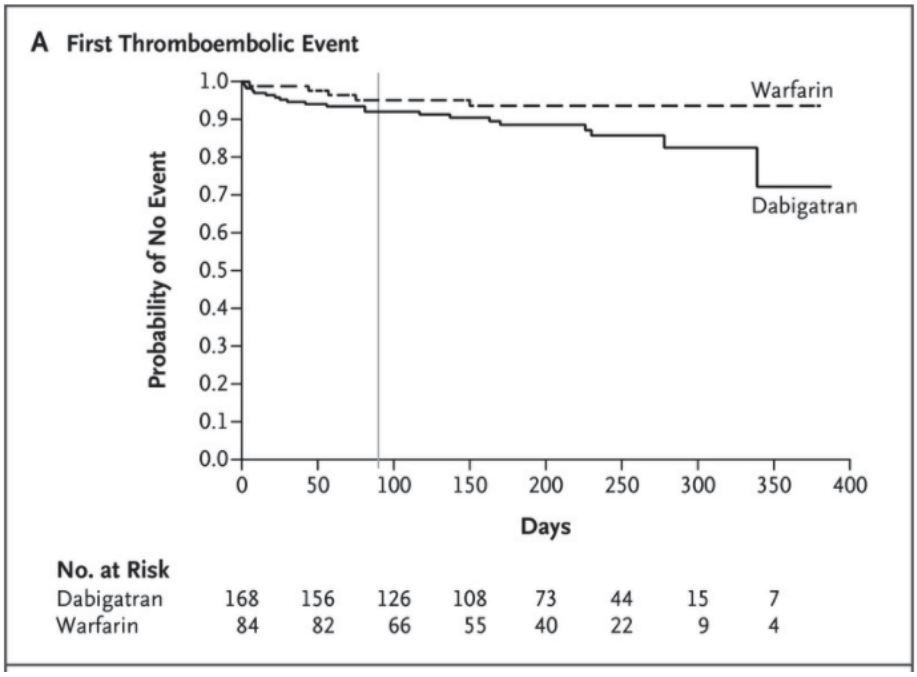
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D.

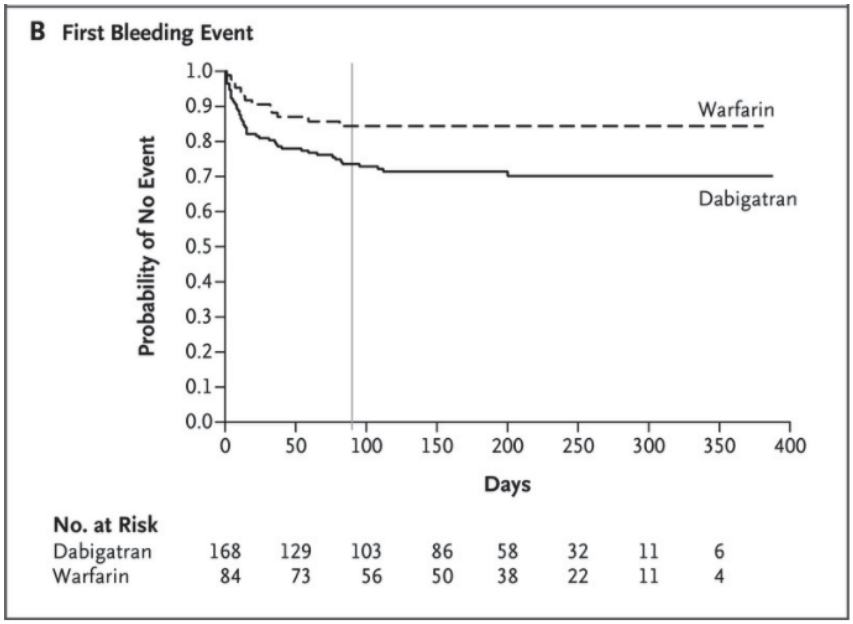
Table 4. Adjudicated Efficacy and Safety Outcomes in the Initial and Extended Trials in the Intention-to-Treat Population.*

Outcome	Population A		Population B		All Patients		Hazard Ratio (95% CI)†	P Value‡
	Dabigatran (N=133)	Warfarin (N=66)	Dabigatran (N=35)	Warfarin (N=18)	Dabigatran (N=168)	Warfarin (N=84)		
	number of patients (percent)							
Death	1 (1)	2 (3)	0	0	1 (1)	2 (2)	0.25 (0.02–2.72)	0.26
Stroke	9 (7)	0	0	0	9 (5)	0	NA	NA
Systemic embolism	0	0	0	0	0	0	NA	NA
Transient ischemic attack	2 (2)	2 (3)	1 (3)	0	3 (2)	2 (2)	0.75 (0.13–4.49)	0.75
Myocardial infarction	1 (1)	0	2 (6)	0	3 (2)	0	NA	NA
Death, stroke, systemic embolism, or myocardial infarction	11 (8)	2 (3)	2 (6)	0	13 (8)	2 (2)	3.37 (0.76–14.95)	0.11
Death, stroke, transient ischemic attack, systemic embolism, or myocardial infarction	12 (9)	4 (6)	3 (9)	0	15 (9)	4 (5)	1.94 (0.64–5.86)	0.24
Valve thrombosis without symptoms	2 (2)	0	3 (9)	0	5 (3)	0	NA	NA
Bleeding								
Any	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)	2.45 (1.23–4.86)	0.01
Major	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.37–8.46)	0.48
Major with pericardial location	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.36–8.45)	0.48

Eikelboom et al, NEJM, 2013, Volume 369 (13): 1206-1214



Eikelboom et al, NEJM, 2013, Volume 369 (13): 1206-1214



Eikelboom et al, NEJM, 2013, Volume 369 (13): 1206-1214

Prosthetic Heart Valves: RE-ALIGN trial

- Conclusion
  - The use of Dabigatran in patients with mechanical heart valves was associated with increased rates of thrombolembolism and bleeding complications as compared with Warfarin thus showing no benefit and excess risk

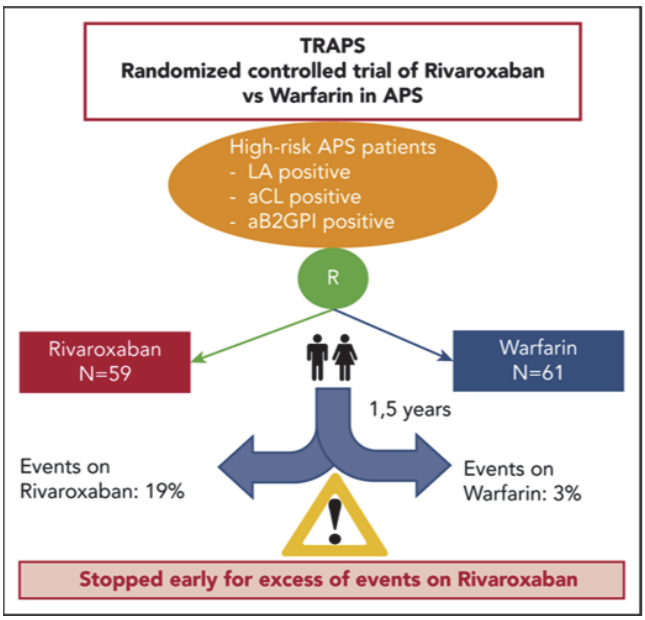
Eikelboom et al, NEJM, 2013, Volume 369 (13): 1206-1214

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

[1]Cardiology Clinic, Thrombosis Centre, Department of Cardiac Thoracic and Vascular Sciences, and [2]Rheumatology Unit, Department of Medicine, University of Padua, Padua, Italy; [3]Rheumatology and Clinical Immunology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; [4]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [5]Section of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [6]Department of Cellular Biotechnologies and Hematology Thrombosis Centre, Sapienza University of Rome, Rome, Italy; [7]Transfusion Medicine, District Hospital, Merate, Italy; [8]Angiology Unit, Department of Internal Medicine, Santa Maria Nuova Hospital, Reggio Emilia, Italy; [9]Hematology Department, San Bortolo Hospital, Vicenza, Italy; [10]Department of Immunohematology and Transfusion Medicine and Hemostasis and Thrombosis Center, Hospital Papa Giovanni XXIII, Bergamo, Italy; [11]A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy; [12]Hemostasis and Thrombosis Center, Laboratory Medicine Department, Azienda Socio-Sanitaria Territoriale, Cremona, Italy; [13]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; and [14]Division of Rheumatology, Department of Clinical Sciences and Community Health, Ospedale Gaetano Pini, University of Milan, Milan, Italy



Pengo et al, Blood, 2018, Volume 132 (13): 1365:1371

Table 4. Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis	7 (12)	0	—	—	7 (12)	0	—	—
Ischemic stroke	4 (7)	0			4 (7)	0		
Myocardial infarction	3 (5)	0			3 (5)	0		
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

Numbers in parentheses denote percentage with respect to total.
—, statistical analysis not applicable.

Pengo et al, Blood, 2018, Volume 132 (13): 1365:1371

TRAPS trial

- Rivaroxaban in high-risk patients with APS was associated with an excess of events compared with Warfarin.

When is a thrombophilia work-up needed?

Risk factors (causes) for the development of venous thrombosis

Inherited thrombophilia
Factor V Leiden mutation
Prothrombin G20210A mutation
Protein S deficiency
Protein C deficiency
Antithrombin deficiency

Other disorders and risk factors
Presence of a central venous catheter
Malignancy
Surgery, especially orthopedic
Trauma
Immobilization
Pregnancy
Oral contraceptives
Hormone replacement therapy
Certain cancer therapies (eg, tamoxifen, thalidomide, lenalidomide, asparaginase)
Heart failure
Congenital heart disease
Antiphospholipid syndrome
Older age (≥65 years)
Obesity
Severe liver disease
Myeloproliferative neoplasms
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome

Prevalence of thrombophilic defects in venous thrombosis

Condition	Prevalence, percent*
Activated protein C resistance (factor V Leiden)	12 to 40¶
Prothrombin G20210A gene mutation	6 to 18¶
Deficiencies of Antithrombin, protein C, protein S	5 to 15
Antiphospholipid antibody syndrome	5 to 10

Note: The lower percentage for each condition is for unselected patients; the higher percentage is for those with first events prior to age 50 or with a history of enous thrombosis in first-degree relatives.
Prevalence restricted to White populations.

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Thrombophilia work-up

- Discuss patient's values and preferences
- Routine evaluation for hypercoagulable disorders in **unselected** patients with a diagnosis of VTE is not warranted
- In **selected** patients:
  - Patients **with** a family history of VTE
    - Documented VTE before age of 45
    - Tested for all 5 inherited thrombophilias (but not APS)

Thrombophilia work-up

- Patients with **no** family history of VTE
  - Young patients (< 45 years of age)
  - Patients with recurrent thrombosis
  - Patients with thrombosis in multiple venous sites or in unusual vascular beds (portal, hepatic, mesenteric, cerebral veins), test for inherited and APS (patients with hepatic and portal vein thrombosis should also be evaluated for JAK-2 mutation and PNH)
  - Patients with history of warfarin-induced skin necrosis are at increased risk of Protein C deficiency (rarely protein S or Factor V Leiden)
  - Patients with arterial thrombosis are at risk of having APS

Thrombophilia work-up

- Major purpose of evaluating for a hypercoagulable state in patients with VTE is the documentation of a biologic risk factor and for genetic counselling/ testing of 1st degree relatives in patients with inherited thrombophilia

Thrombophilia work-up

Benefits

1) Management of conditions that potentially increase risk of a future thrombotic event (ex: thromboprophylaxis in future major surgery)

2) Potential for altered management (ex: avoidance of hormonal contraception, thromboprophylaxis in pregnancy, change from DOAC to Warfarin in triple positive APS)

3) Provision of information (ex: unexplained fetal loss during pregnancy)

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Thrombosis Canada
Thrombose Canada

- See Thrombophilia Testing Algorithm

Choice of appropriate DOACs

	DABIGATRAN (PRADAXA®)	RIVAROXABAN (XARELTO®)	APIXABAN (ELIQUIS®)	EDOXABAN (LIXIANA®)
Clinical Indications and Doses				
Atrial fibrillation (indefinite duration)	150 mg or 110 mg twice daily	20 mg daily	5 mg twice daily	60 mg or 30 mg daily
Acute VTE (3 to 6 months)	150 mg twice daily	20 mg daily (15 mg twice daily for initial 21 days)	5 mg twice daily (10 mg twice daily for initial 7 days)	60 mg daily
VTE prevention after knee or hip replacement surgery (14 to 30 days)	110 mg (initial dose) then 220 mg daily	10 mg daily	2.5 mg twice daily	Not applicable
Key Pharmacologic Properties				
Mechanism of action	Direct factor IIa (thrombin) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Renal clearance	80%	33% (active drug)	25%	50%
Half-life				
Normal to mild impairment (CrCl ≥50 mL/min)	7-17 hours	7-11 hours	8-12 hours	10-14 hours
Moderate renal impairment (CrCl 30-49 mL/min)	17-20 hours	7-11hours	8-12 hours	
Severe renal impairment (CrCl <30 mL/min)	21-35 hours	11-15 hours	12-17 hours	
Onset of action (after oral intake)	1-3 hours	1-3 hours	1-3 hours	1-3 hours
Key Practical Properties				
Food or alcohol interactions	none	none	none	none
Drug interactions	• amiodarone, quinidine, azole antifungals (e.g. ketoconazole), ritonavir increase dabigatran levels • rifampin reduces dabigatran levels	• azole antifungals (e.g. ketoconazole), ritanovir, clarithromycin increase rivaroxaban levels • anticonvulsants (e.g. phenytoin, carbamazepine), rifampin reduce rivaroxaban levels	• azole antifungals (e.g. ketoconazole), ritanovir, clarithromycin likely increase apixaban levels • anticonvulsants (e.g. phenytoin, carbamazepine), rifampin likely reduce apixaban levels	• azole antifungals (e.g. ketoconazole), ritanovir, clarithromycin likely increase edoxaban levels • anticonvulsants (e.g. phenytoin, carbamazepine), rifampin likely reduce edoxaban levels
Antidote	Idarucizumab	Andexanet alfa (not yet approved by Health Canada)	Andexanet alfa (not yet approved by Health Canada)	Andexanet alfa (not yet approved by Health Canada)
Laboratory Measurement of Anticoagulant Effect‡	• aPTT or thrombin clotting time (TCT) • dilute TCT (Hemoclot assay)	• prothrombin time (PT)/INR • anti-factor Xa assay	• PT/INR (has minimal effect) • anti-factor Xa assay	• anti-factor Xa assay

Thrombosis Canada

DOACs: Indications

	Non valvular A Fib	VTE treatment	VTE extended Tx	DVT prophylaxism (knee/hip surgery)
Apixaban Code RAMQ	✓ CV155	✓ CV169 (6 months)	✓ CV170[3] (> 6months)	✓ CV126/17
Dabigatran Code RAMQ	✓ CV155	✓[1]	✓	✓[2]
Edoxaban Code RAMQ	✓	✓[1]	✓	
Rivaroxaban Code RAMQ	✓ CV155	✓ CV157-DVT (6m) CV165-PE	✓	✓ CV126/127

[1] Following 5-10 days of parenteral anticoagulation
[2] Hip surgery only
[3] Idiopathic VTE only for RAMQ

DOACs Dosing: Non Valvular Atrial Fibrillation

		Renal Insufficiency
Apixaban	5 mg bid 2.5 mg bid if two of: > 80 yo, W < 60kg, creat > 133	Clcr > 25 : no adjustement Clcr 15-24 : 2.5 mg bid ?
Dabigatran	150 mg bid 110 mg bid if age > 75, or W < 50 kg or bleeding risk	Clcr > 30 : no adjustement Clcr < 30 : not indicated
Edoxaban	60 mg die 30 mg die if Clcr 30-50, or W < 60, or strong inh P-gp	Clcr > 95 : not indicated Clcr 30-50: 30 mg die Clcr < 30 : not indicated
Rivaroxaban	20 mg die	Clcr 30-49 : 15 mg die Clcr < 30 : not indicated

Always validate dosage with drug monography

DOACs Dosing: DVT and PE

		Renal Insufficiency
Apixaban	10 mg bid x 7 d → 5 mg bid Prevention recurrence: 2.5 mg bid	Clcr > 30 : no adjustment Clcr 15-29 : 2.5 mg bid ? Clcr < 15 : not indicated
Dabigatran	LMWH x 5-10 d → 150 mg bid 110 mg bid if W < 50 kg or increased bleeding risk	Clcr > 30 : no adjustment Clcr < 30 : not indicated
Edoxaban	LMWH x 5-10 d → 60 mg die 30 mg die if Clcr 30-50, or W < 60, or strong inh P-gp	Clcr > 95 : not indicated Clcr 15-50: 30 mg die Clcr < 15 : not indicated
Rivaroxaban	15 mg bid x 3 wks → 20 mg die	Clcr 30-49 : no adjustment Clcr < 30 : not indicated

Always validate dosage with drug monography

REVIEW

CURRENT OPINION

Direct oral anticoagulants in chronic kidney disease: an update

Thomas A. Mavrakanas[a], David M. Charytan[b], and Wolfgang C. Winkelmayer[c]

Coumadin vs DOACs

Advantages and disadvantages of oral anticoagulants (warfarin versus direct oral anticoagulants*)

	Warfarin	Direct oral anticoagulants*
Dosing	Once-daily dosing may be more convenient	May require more frequent dosing
Dietary restrictions	Need to ensure relatively constant level of vitamin K intake	None. Rivaroxaban should be taken with food when used for atrial fibrillation thromboprophylaxis. Betrixaban should be taken with food when used for VTE prophylaxis.
Monitoring therapy	PT/INR monitoring is required, which entails regular visits to a facility for most patients (point of care devices may be an option for some)	Not required; however, noncompliance will not be as readily apparent
Drug interactions	Many	Rivaroxaban interacts with CYP-3A4 and P-glycoprotein inhibitors; other factor Xa inhibitors interact with P-glycoprotein; dabigatran may be affected by P-glycoprotein inducers or inhibitors
Time in therapeutic range	Approximately 65% based on clinical trials	Expected to be superior to warfarin, although therapeutic ranges have not been established
Reversal agent(s)	Several available (eg, vitamin K, FFP, PCC, rFVIIa)	Idarucizumab is available to reverse dabigatran. Specific reversal agents are not available for direct factor Xa inhibitors but several are in development. Activated charcoal; antifibrinolytic agents; PCC may be used for life-threatening bleeding. Hemodialysis could be used in severe cases for dabigatran (but not rivaroxaban or apixaban).
Monitoring reversal	PT/INR can be used	TT can be used for dabigatran; anti-factor Xa can be used for apixaban
Effect of comorbid conditions		Renal function affects pharmacokinetics; dosing unclear in those with obesity

- "Lack" of laboratory monitoring for DOACs
- Cost effectiveness favoring DOACs for NVAF ?
- DOACs not indicated for mechanical prosthetic valves

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TABLE 2. Choosing Among the DOACs[12,29]

Characteristics	DOAC Option	Rationale for Selection
CrCl <30 mL/min	Apixaban	Other DOACs are more affected by renal impairment than apixaban
All-oral therapy	Rivaroxaban or apixaban	Dabigatran and edoxaban require UFH or LMWH bridging
Dyspepsia or upper GI complaints	Rivaroxaban, apixaban, or edoxaban	Dyspepsia with dabigatran in up to 10% of patients
Recent GI bleed	Apixaban or low-dose edoxaban	More GI bleeding with rivaroxaban, high-dose dabigatran, or edoxaban
Significant CAD	Rivaroxaban, apixaban, or edoxaban	MI appears to be more common in dabigatran compared with VKA
Poor compliance with twice-daily dosing	Rivaroxaban[a] or edoxaban	Apixaban dosing is twice daily. Dabigatran is twice daily, except in patients receiving VTE prophylaxis following THA (once daily).
Concern regarding reversal agent	Dabigatran (idarucizumab)	No reversal agent is available for DOACs aside from dabigatran

CAD indicates coronary artery disease; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; GI, gastrointestinal; LMWH, low-molecular weight heparin; MI, myocardial infarction; THA, total hip arthroplasty; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Rivaroxaban requires twice-daily dosing during initial 21 days of VTE treatment, then becomes once daily.

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VTE and CANCER (1)

- LMWH vs Coumadin (CLOT and CATCH studies)
  - Recurrent VTE - 9 vs 17% (dalteparin), 7 vs 11% (tinzaparin)
  - Similar bleeding
  - Standard of care became LMWH

- Edoxaban vs LMWH (dalteparin) (Hokusai VTE Cancer Investigators)*
  - Non inferiority for combined end-point of recurrences + major bleeding
    - Fewer VTE recurrences (7.9% vs. 11.3%, P = 0.09) with edoxaban
    - More major bleeding (6.9% vs. 4.0%, P = 0.04), particularly with GI and GU cancers
    - More patients continuing treatment for 12 months (38.3% vs. 29.4%)

** N Engl J Med 2018; 378: 615-24*

VTE and CANCER (2)

- Rivaroxaban vs dalteparin (SELECT-D)*
  - Recurrent VTE (6 months) – 4% vs 11%
  - Major bleedings – (5 vs 3%), GI and GU cancers
  - Clinically relevant non major bleeding - 12% vs 3%

- Apixaban vs dalteparin (CARAVAGGIO)** Best option in GI cancers
  - Recurrent VTE (6 months) – 5.6% vs 7.9%
  - Major bleedings – (3.8% vs 4.0%)
  - Major GI bleeding – 1.9% vs 1.7%
  - Major non-GI bleeding 1.9% vs 2.2%
  - Cancers with high thromboembolic risk such as lung and colorectal were well represented.

* *ash.confex.com/ash/2017/webprogram/Paper104979.html*
** *Agnelli et al, NEJM, 2020; 382:1599-1607*

Abnormal uterine bleeding and Rivaroxaban

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use

Ida Martinelli,[1] Anthonie W. A. Lensing,[2] Saskia Middeldorp,[3] Marcel Levi,[3] Jan Beyer-Westendorf,[4] Bonno van Bellen,[5] Henri Bounameaux,[6] Timothy A. Brighton,[7] Alexander T. Cohen,[8] Mila Trajanovic,[9] Martin Gebel,[2] Phuong Lam,[10] Philip S. Wells,[11] and Martin H. Prins[12]

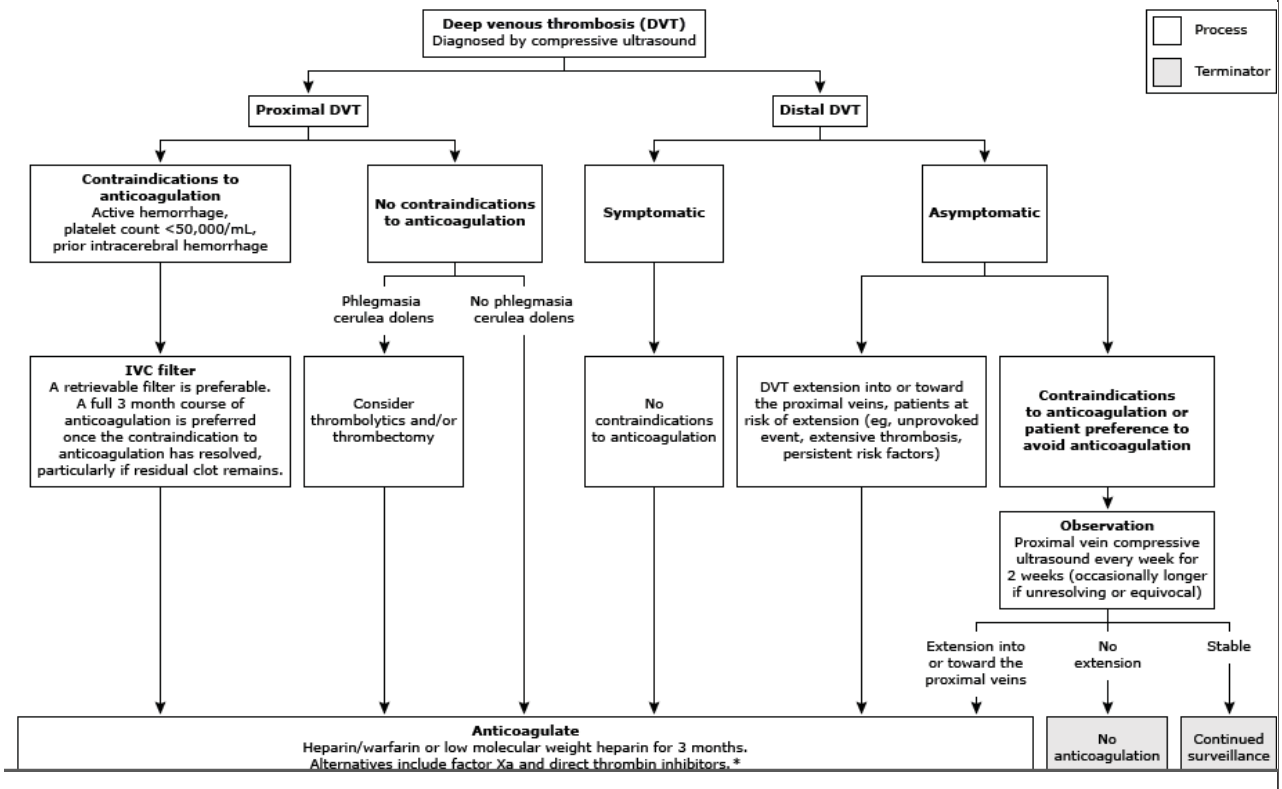
[1]A Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Bayer HealthCare, Wuppertal, Germany; [3]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands; [4]University Hospital "Carl Gustav Carus," Technische Universität Dresden, Dresden, Germany; [5]Department of Vascular Surgery, Beneficencia Portuguesa Hospital, São Paulo, Brazil; [6]University Hospitals and Faculty of Medicine, Geneva, Switzerland; [7]Department of Haematology, Prince of Wales Hospital, Sydney, Australia; [8]Department of Haematology, Guy's and St Thomas' Hospitals National Health Service Trust, London, United Kingdom; [9]Bayer HealthCare Pharmaceuticals, Whippany, NJ; [10]Bayer HealthCare, Ho Chi Minh, Vietnam; [11]Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, ON, Canada; and [12]Maastricht University Medical Center, Maastricht, The Netherlands

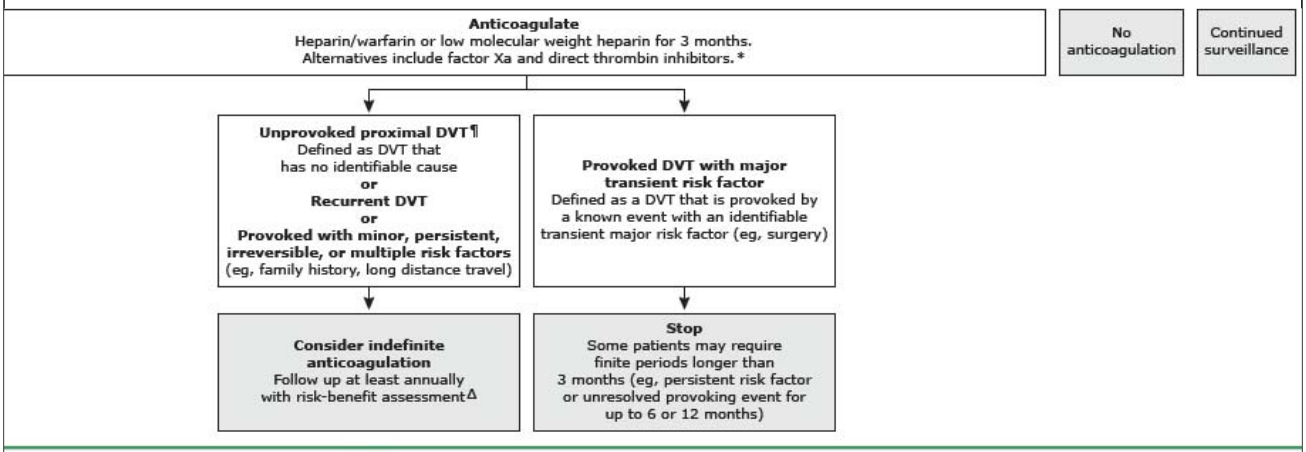
Blood, 2016, 127(11): 1417-25

Abnormal uterine bleeding and Rivaroxaban in pre-menopausal women

- Occurred more frequently with Rivaroxaban than with Enoxaparin or VKAs (HR 2.13, 95% CI, 1.57-2.89)
- ISTH recommendation: avoid Rivaroxaban in pre-menopausal women
- COBRRA study: ongoing trial comparing bleeding risk with Apixaban and Rivaroxaban

Duration of VTE treatment





s algorithm only applies to patients with a **first** episode of DVT.

ease refer to the UpToDate topic on deep venous thrombosis: long-term anticoagulation (3 to 6 months).
atients with an unprovoked distal DVT should receive at least 3 months of anticoagulation. A small proportion may benefit from indefinite anticoagulation. Please
r to the UpToDate topic on rationale and indications for indefinite anticoagulation in patients with venous thromboembolism.
ease refer to the UpToDate topic on rationale and indications for indefinite anticoagulation in patients with venous thromboembolism.

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