Treatment of Venous Thromboembolism (VTE)

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1

Disclosure

Consultant: Anthos; AstraZeneca; Bayer; Gilead; Perosphere; Regeneron

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Learning Objectives

- Be able to have shared decision-making regarding treating or serial testing for patients with isolated calf vein thrombosis
- Utilize recent guideline-based therapy for VTE
- Know which dose of anticoagulant to use for extended VTE treatment

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3

Treatment of Venous Thromboembolism (VTE)

- Venous thromboembolism (VTE)
  - Extended treatment
  - Cancer
  - Obesity
  - Renal failure
  - Antiphospholipid antibody syndrome
  - Severe inherited thrombophilia
- Deep vein thrombosis (DVT)
  - Isolated calf vein DVT
  - Post-thrombotic syndrome
- Pulmonary embolism (PE)
  - Subsegmental PE

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4

Case

- 42-year-old male with **"non-provoked"** pulmonary embolism
  - **No transient or persistent major risk factors**
- No transient or persistent risk factors
  - No recent surgery, no leg immobilization, no ≥ 3-day hospitalization, no recent long-haul travel
- Has been on full dose apixaban/rivaroxaban (Eliquis/Xarelto) for **6 months**
- No signs of recurrent DVT, feels well, no shortness of breath
- No increase bleeding risk

What Would You Do?

A. Stop anticoagulation, has completed 6 months

B. Continue until 12 months of treatment

C. Continue full dose indefinitely

D. Step down to ½ dose and continue indefinitely

American College of Chest Physicians (ACCP) Guidelines

- In patients with VTE diagnosed in the setting of a major transient risk factor (see text), we *recommend* against offering extended-phase anticoagulation
- In patients with VTE diagnosed in the setting of a minor transient risk factor (see text), we *suggest* against offering extended-phase anticoagulation
- In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), we *recommend* offering extended-phase anticoagulation with a DOAC
- In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, we *suggest* offering extended-phase anticoagulation with a VKA

HENRY FORD HEALTH Stevens SM. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. PMID: 34352278.

7

American College of Chest Physicians (ACCP) Guidelines

- **VTE provoked by a major transient risk factor**
  - (eg, surgery with general anesthesia for greater than 30 min,
  - confinement to bed in hospital [only "bathroom privileges"] for at least 3 days with an acute illness,
  - cesarean section);
- **VTE provoked by a minor transient risk factor**
  - (eg, surgery with general anesthesia for less than 30 min,
  - admission to hospital for less than 3 days with an acute illness,
  - estrogen therapy,
  - pregnancy or puerperium,
  - confinement to bed out of hospital for at least 3 days with an acute illness,
  - leg injury associated with reduced mobility for at least 3 days); and
  - Flight $\geq$ 8 hours
- **VTE that is unprovoked or has persistent risk factors**

HENRY FORD HEALTH Stevens SM. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. PMID: 34352278.

8

American College of Chest Physicians (ACCP) Guidelines

- In patients offered extended-phase anticoagulation, we *suggest* the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban
  - Remark: Reduced dose refers to
    - apixaban 2.5 mg twice daily and
    - rivaroxaban 10 mg once daily
- In patients offered extended-phase anticoagulation, we *recommend* reduced-dose DOAC over aspirin or no therapy and *suggest* rivaroxaban over aspirin
- In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE

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9

RENOVE Trial

- Question: what is the optimal dose of DOAC for extended treatment of VTE?
- Design: RCT, open-label with blinded end point adjudication, (non-inferiority for efficacy and superiority for safety) with hierarchical testing
- Patients: 2768 patients that had completed 6-24 months of uninterrupted full-dose anticoagulation and **candidates for extended treatment** in 47 French hospitals with
  - VTE that was unprovoked, recurrent, had persistent risk or other high-risk factors
  - Patients with cancer and birth control related VTE were excluded
- Intervention: reduced dose apixaban (2.5 mg bid) or rivaroxaban (10 mg qd)
- Comparison: full dose apixaban (5 mg qd) or rivaroxaban (20 mg qd)
- Outcomes:
  - Primary efficacy: symptomatic VTE including fatal or non-fatal PE and proximal DVT
  - Secondary: major bleeding (ISTH), clinically relevant non-major bleeding (not ISTH), and net clinical benefit
- Timeframe: median follow-up 37.1 months

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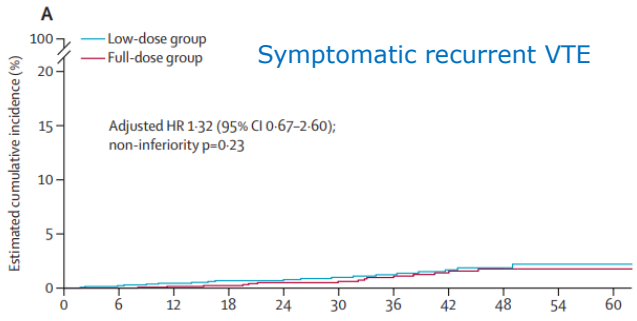
Couturaud F. Lancet. 2025 Mar 1;405(10480):725-735. PMID: 40023651.

10



RENOVE Trial

- Recurrent VTE at 5 years
  - Reduced dose: 2.2%
  - Full dose: 1.8%
  - Non-inferiority **NOT** met
  - Recurrent rates lower than expected
- Major and clinically relevant bleeding
  - Reduced dose: 9.9%
  - Full dose: 15.2%
  - Hazzard ratio 0.61 (0.48-0.79)
- Major bleeding
  - Reduced dose: 2.1%
  - Full dose: 4.0%
  - Hazzard ratio 0.40 (0.22-0.72)

Couturaud F. Lancet. 2025 Mar 1;405(10480):725-735. PMID: 40023651.

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11

Treatment of Venous Thromboembolism (VTE)

- Venous thromboembolism (VTE)
  - Extended treatment
  - **Cancer**
  - Obesity
  - Renal failure
  - Antiphospholipid antibody syndrome
  - Severe inherited thrombophilia
- Deep vein thrombosis (DVT)
  - Isolated calf vein DVT
  - Post-thrombotic syndrome
- Pulmonary embolism (PE)
  - Subsegmental PE

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12

Case

- 63-year-old female with new diagnosis of colon cancer, presented with constipation and no bleeding
- Cancer not resected
- New proximal deep vein thrombosis

Which Anticoagulant?

A. Low molecular weight heparin (LMWH)
B. Warfarin (Coumadin)
C. Apixaban (Eliquis)
D. Rivaroxaban (Xarelto)
E. Edoxaban (Savaysa)

Cancer Associated VTE

- In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) we *recommend*
  - an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban)
  - over low molecular weight heparin (LMWH) for the initiation and treatment phases of therapy

- Remark: Edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in patients with cancer-associated thrombosis (CAT) and a luminal GI malignancy, while apixaban does not
  - Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies

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15

Systematic Review LMWH vs. DOAC in Cancer Associated VTE

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)	RR (95% CI)	Observed risk with LMWH	Anticipated absolute effects: Risk with DOACs*	Anticipated absolute effects: Absolute risk difference
Recurrent VTE	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	0.68 (0.39 to 1.17)	8.3%	5.6%	−2.7% (–5.1 to 1.4)
Major bleeding	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.36 (0.55 to 3.35)	3.5%	4.8%	1.3% (–1.6 to 8.3)
Composite outcome of first recurrent VTE and major bleeding	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	0.86 (0.60 to 1.23)	11.1%	9.5%	−1.6% (–4.4 to 2.6)
Clinically relevant nonmajor bleeding	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.63 (0.73 to 3.64)	6.5%	10.6%	4.1% (–1.8 to 17.2)
All-cause mortality	2607 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	0.96 (0.68 to 1.36)	25.7%	24.7%	−1.0% (–8.2 to 9.3)
On-treatment analyses						
Recurrent VTE (on-treatment)	2440 (3 RCTs)	⊕⊕⊕⊕ HIGH	0.60 (0.38 to 0.95)	8.1%	4.9%	−3.2% (–5.0 to −0.4)
Major bleeding (on-treatment)	2440 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.43 (0.46 to 4.45)	3.2%	4.6%	1.4% (–1.7 to 11.0)
Clinically relevant nonmajor bleeding (on-treatment)	2440 (3 RCTs)	⊕⊕⊕○ MODERATE due to imprecision†	1.93 (0.70 to 5.31)	4.6%	8.9%	4.3% (–1.4 to 19.7)

Mulder FI. Blood. 2020 Sep 17;136(12):1433-1441. PMID: 32396939.

16

Case

- 63-year-old female with colon cancer
- Treated with chemotherapy
- Treated with apixaban for 6 months with no bleeding
- You are extending anticoagulation

Would You Reduce to ½ Dose (2.5 mg bid) Apixaban?

A. Yes
B. No

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EVE Trial

- Question: is apixaban 2.5 mg bid safer than 5.0 mg bid for extended treatment of cancer associate VTE
- Design: randomized double–blind trial
- Patients: 360 cancer associated VTE and treated for 6-12 months
- Intervention: apixaban 2.5 mg bid
- Comparison: apixaban 5 mg bid
- Outcomes:
  - –Primary: major + clinically relevant non-major bleeding (ISTH criteria)
  - –Secondary: recurrent VTE or arterial thromboembolism
- Timeframe: 12 months

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McBane RD 2nd,. J Thromb Haemost. 2024 Jun;22(6):1704-1714. PMID: 38537780.

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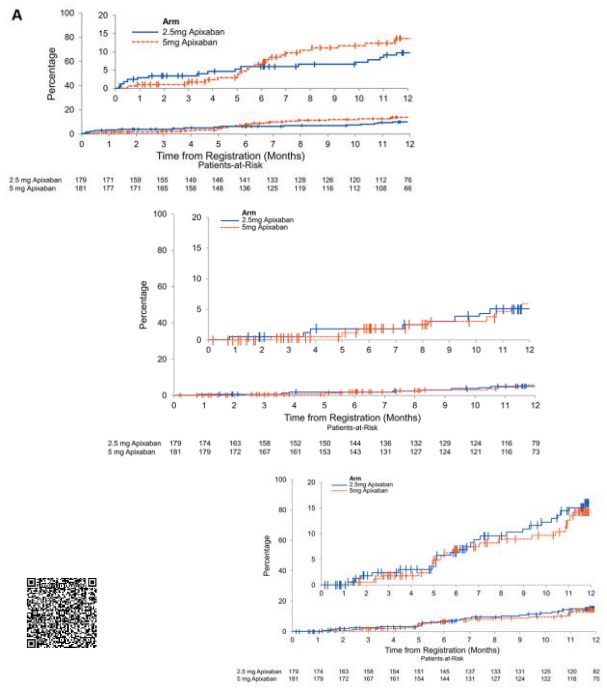

EVE Trial

- Top graph
  - No difference in major + clinically relevant non-major bleeding
    - ~ 10%
    - No difference in major bleeding
- Middle graph
  - No difference in recurrent VTE or new arterial thromboembolism
    - ~ 5%
- Bottom graph
  - No difference in all-cause mortality
    - ~ 12%

McBane RD 2nd,. J Thromb Haemost. 2024 Jun;22(6):1704-1714. PMID: 38537780.

19

API-CAT Trial

- Question: is reduced dose apixaban as effective and safer than full dose in cancer associated VTE?
- Design: RCT, double-blinded
- Patients: 1766 at 121 centers in 11 countries with active cancer
  - proximal DVT or PE (including incidental segmental PE – 1/3 of patients)
  - completed at least 6 months (median 8 months) of treatment
- Intervention: apixaban 2.5 mg bid
- Comparison: apixaban 5.0 mg bid
- Outcome:
  - Primary: fatal or nonfatal recurrent VTE, non-inferiority (margin 2.00)
  - Secondary: clinically relevant bleeding, superiority
- Timeframe: median 11.8 months follow up

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Mahé I. N Engl J Med. 2025 Mar 29. PMID: 40162636.

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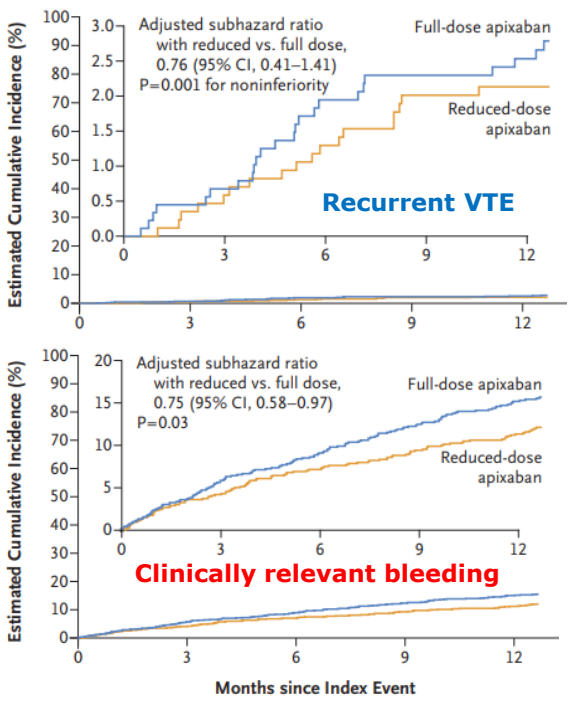

API-CAT Trial

- Recurrent VTE
  - Reduced dose: 2.1% vs. Full dose: 2.8%
  - Non-inferior
- Clinically relevant bleeding
  - Reduced dose: 12.1% vs. Full dose: 15.6%
  - Superior
- Major bleeding
  - Not significantly different
  - However, reduced by ½ including ~ 50% reduction in upper and lower GI bleeding
- Death
  - Reduced dose: 17.7% vs. Full dose: 19.6%
  - Not significantly different

Mahé I. N Engl J Med. 2025 Mar 29. PMID: 40162636.

21

Treatment of Venous Thromboembolism (VTE)

- Venous thromboembolism (VTE)
  - Extended treatment
  - Cancer
  - **Obesity**
  - Renal failure
  - Antiphospholipid antibody syndrome
  - Severe inherited thrombophilia
- Deep vein thrombosis (DVT)
  - Isolated calf vein DVT
  - Post-thrombotic syndrome
- Pulmonary embolism (PE)
  - Subsegmental PE

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Case

- 42-year-old male with non-provoked pulmonary embolism.
  - No transient or persistent risk factors
- No recent surgery, no leg immobilization, no ≥ 3-day hospitalization, no recent long-haul travel
- Was hoping to have bariatric surgery in a couple of months
- Weight 140 kg

Which Anticoagulant?

A. Low molecular weight heparin (LMWH)
B. Warfarin (Coumadin)
C. Apixaban (Eliquis)
D. Rivaroxaban (Xarelto)
E. Dabigatran (Pradaxa)

Obesity

- …For patients with BMI >40 kg/m2 or weight >120 kg, we recommend …
- For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban.
  - VKA, weight based LMWH (per manufacturers' recommendations), and fondaparinux are also options

	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]

Martin KA. J Thromb Haemost. 2021 Aug;19(8):1874-1882. PMID: 34259389.

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Bariatric Surgery

- 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.

		Surgical Intervention and Anticipated Effect on Absorption		
DOAC	Site of Absorption in Gastrointestinal Tract	Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration[39]	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine[41,42,49]	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dependent on acidic environment [43,44]	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach[43-45]	Possibly reduced	Possibly reduced	Possibly reduced

Martin KA. J Thromb Haemost. 2021 Aug;19(8):1874-1882. PMID: 34259389.

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26

Treatment of Venous Thromboembolism (VTE)

- Venous thromboembolism (VTE)
  - Extended treatment
  - Cancer
  - Obesity
  - **Renal failure**
  - Antiphospholipid antibody syndrome
  - Severe inherited thrombophilia
- Deep vein thrombosis (DVT)
  - Isolated calf vein DVT
  - Post-thrombotic syndrome
- Pulmonary embolism (PE)
  - Subsegmental PE

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27

Case

- 56-year-old on dialysis
- Acute proximal DVT

What Would You Prescribe?

A. Unfractionated heparin drip and warfarin in the usual manner
B. LMWH with renal adjustment and warfarin
C. Apixaban usual starter pack (10 mg bid for 7 days and then 5 mg bid)
D. Apixaban 5 mg bid
E. Apixaban 2.5 mg bid

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Safety and Effectiveness of Apixaban Versus Warfarin for Acute Venous Thromboembolism (VTE) in Patients with End-stage Kidney Disease: A National Cohort Study

- Question: what is the safety and effectiveness of apixaban relative to warfarin in patients on dialysis and acute VTE?
- Design: retrospective large data-set observational study, "intention to treat" with inverse probability of treatment weighting
- Patients: in the United States Renal Data System from 2014 to 2018 with acute VTE
- "Intervention": apixaban 5 mg, 2.5 mg or both. Dosing of 10 mg bid for first 7 days unknown
- "Comparison": warfarin, time in therapeutic INR range unknown
- Outcomes: co-primary of recurrent VTE, major bleeding and all cause mortality
- Timeframe: 6 months

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Ellenbogen MI. J Hosp Med. 2022 Oct;17(10):809-818.. PMID: 35929542.

29

	Total	Apixaban	Warfarin
Number of patients, *N*	11,565	2302	9263
Total major bleeding[a]			
Patients, *N* (%)	1507 (13.0)	238 (10.3)	1269 (13.7)
IPTW and index year adjusted, HR (95% CI)		**0.81 (0.70–0.94)**	Ref.
Fatal major bleeding			
Patients, *N* (%)	297 (2.6)	44 (1.9)	253 (2.7)
IPTW and index year adjusted, HR (95% CI)		0.71 (0.51–1.00)	Ref.
Nonfatal major bleeding			
Patients, *N* (%)	1239 (10.7)	199 (8.6)	1040 (11.2)
IPTW and index year adjusted, HR (95% CI)		0.85 (0.72–1.004)	Ref.
Total clinically relevant nonmajor bleeding			
Patients, *N* (%)	2026 (17.5)	351 (15.3)	1675 (18.1)
IPTW and index year adjusted, HR (95% CI)		**0.84 (0.74–0.94)**	Ref.
Intracranial bleeding			
Patients, *N* (%)	274 (2.4)	41 (1.8)	233 (2.5)
IPTW and index year adjusted, HR (95% CI)		**0.69 (0.48–0.98)**	Ref.
GI bleeding			
Patients, *N* (%)	1160 (10.0)	198 (8.6)	962 (10.4)
IPTW and index year adjusted, HR (95% CI)		**0.82 (0.69–0.96)**	Ref.
Recurrent VTE			
Patients, *N* (%)	736 (6.4)	152 (6.6)	584 (6.3)
IPTW and index year adjusted, HR (95% CI)		0.83 (0.69–1.002)	Ref.
All-cause mortality			
Patients, *N* (%)	1187 (10.3)	231 (10.0)	956 (10.3)
IPTW and index year adjusted, HR (95% CI)		1.06 (0.91–1.24)	Ref.

Safety and Effectiveness of Apixaban Versus Warfarin for Acute Venous Thromboembolism (VTE) in Patients with End-stage Kidney Disease: A National Cohort Study

- Major bleeding
  - Apixaban 10.3% vs. warfarin 13.7%
- Clinically relevant non-major bleeding
  - Apixaban 15.3% vs. warfarin 18.1%
- Intracranial bleeding
  - Apixaban 1.8% vs. warfarin 2.5%
- GI bleeding
  - Apixaban 8.6% vs. warfarin 10.4%
- Recurrent VTE (not significant)
  - Apixaban 6.6% vs. warfarin 6.3%
- All-cause mortality (not significant)
  - Apixaban 10.0% vs. warfarin 10.3%

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30

Safety and Effectiveness of Apixaban Versus Warfarin for Acute Venous Thromboembolism (VTE) in Patients with End-stage Kidney Disease: A National Cohort Study

- Fairly similar outcomes
  - Apixaban 2.5 mg vs warfarin
  - Apixaban 5 mg vs warfarin
  - Apixaban 2.5 mg vs apixaban 5 mg except less GI bleeding with 2.5 mg

	Apixaban 2.5 mg Subgroup	Warfarin Cohort
Number of patients, N	933	9,263
Total Major bleeding, HR (95% CI)	**0.68 (0.54-0.85)**	Ref.
Fatal major bleeding	0.75 (0.48-1.18)	Ref.
Non-fatal major bleeding	**0.67 (0.52-0.87)**	Ref.
Total clinically relevant non-major bleeding	**0.78 (0.65-0.93)**	Ref.
Intracranial bleeding	**0.48 (0.27-0.84)**	Ref.
GI bleeding	**0.61 (0.47-0.79)**	Ref.
Recurrent VTE	0.81 (0.62-1.06)	Ref.
All-cause mortality	1.08 (0.87-1.34)	Ref.

	Apixaban 5 mg Subgroup	Warfarin Cohort
Number of patients, N	1,150	9,263
Total Major bleeding, HR (95% CI)	**0.76 (0.62-0.93)**	Ref.
Fatal major bleeding	**0.60 (0.36-0.98)**	Ref.
Non-fatal major bleeding	0.82 (0.66-1.02)	Ref.
Total clinically relevant non-major bleeding	**0.77 (0.65-0.90)**	Ref.
Intracranial bleeding	0.72 (0.45-1.16)	Ref.
GI bleeding	0.87 (0.71-1.08)	Ref.
Recurrent VTE	**0.76 (0.58-0.98)**	Ref.
All-cause mortality	0.98 (0.79-1.21)	Ref.

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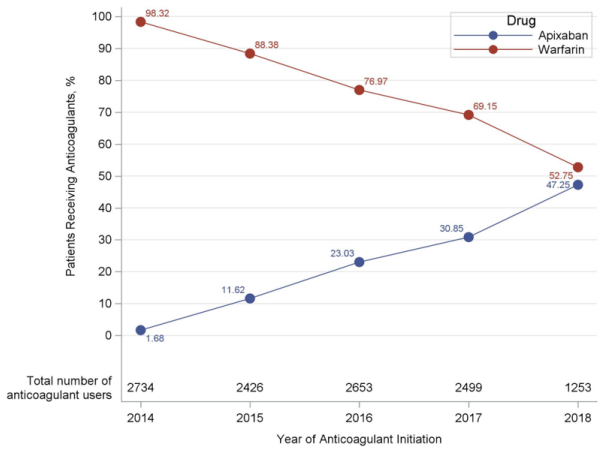
Safety and Effectiveness of Apixaban Versus Warfarin for Acute Venous Thromboembolism (VTE) in Patients with End-stage Kidney Disease: A National Cohort Study



- We don't know best approach for dialysis patients with acute VTE
- Apixaban 5 mg bid or 2.5 mg bid reasonable
- No data on using 10 mg bid for first 7 days
- Heparin drip with warfarin not unreasonable but data suggesting advantage for apixaban long term
- My best guess with apixaban
  - 10 mg bid x 7 days and then 5 mg bid for "big" VTE
  - 5 mg bid for non-high risk recurrence and bleeding
  - 2.5 mg bid for high bleeding risk with/without induction dosing

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  - Post-thrombotic syndrome
- Pulmonary embolism (PE)
  - Subsegmental PE

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33

Case

- 38-year-old female with acute DVT
- No transient or persistent risk factors
- No arterial thrombosis, livedo racemose, pulmonary hemorrhage, nephropathy, myocardial disease, or adrenal hemorrhage
- 1 miscarriage at 9 weeks and no preeclampsia or intrauterine fetal growth restriction

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34

Which Anticoagulant?

A. Low molecular weight heparin
B. DOAC
C. Warfarin

Antiphospholipid Syndrome

- In patients with confirmed antiphospholipid syndrome being treated with anticoagulant therapy, we *suggest* adjusted dose VKA (target INR 2.5) over direct oral anticoagulant (DOAC) therapy during the treatment phase

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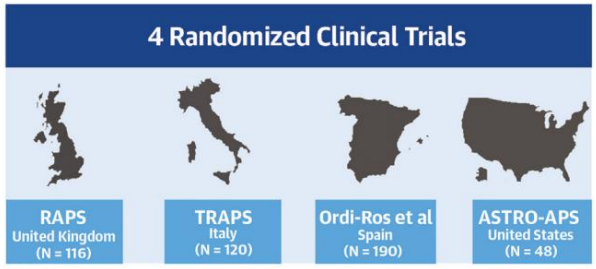
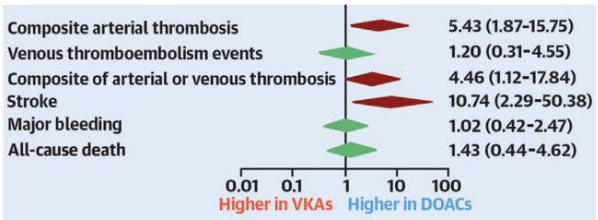
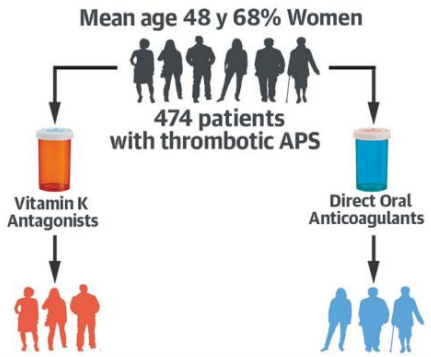
Stevens SM. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. PMID: 34352278.

CENTRAL ILLUSTRATION Use of Direct Oral Anticoagulants vs Vitamin K Antagonists in Thrombotic Antiphospholipid Syndrome







Use of DOACs Compared With VKAs Was Associated With:

- Increased odds of arterial thrombotic events, especially stroke
- No change in the odds of VTE or major bleeding

Results were consistent within subgroups

HENRY FORD HEALTH Khairani CDJ. J Am Coll Cardiol. 2023 Jan 3;81(1):16-30 PMID: 36328154.

37

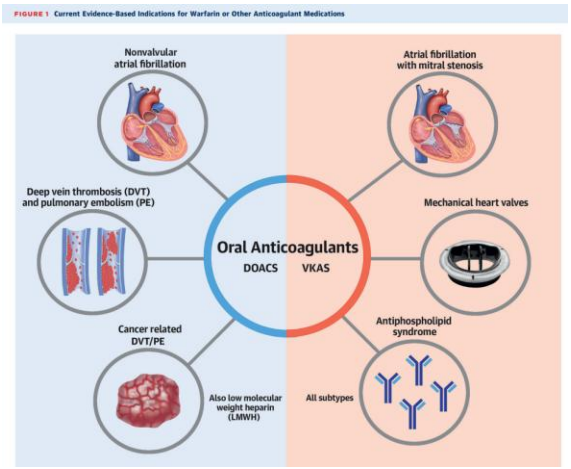
EDITORIAL COMMENT

Warfarin Is the Preferred Therapy for Patients With Thrombotic APS

Back to the Future*

Mark A. Crowther, MD,[a] Aubrey E. Jones, PharmD, MSCI,[b] Daniel M. Witt, PharmD, BCPS[b]

- Editorial suggests not using DOAC for any antiphospholipid syndrome or serology
  - Triple, double or single positive



HENRY FORD HEALTH Crowther MA. J Am Coll Cardiol. 2023 Jan 3;81(1):31-33. PMID: 36328156.

38

Treatment of Venous Thromboembolism (VTE)

- Venous thromboembolism (VTE)
  - Extended treatment
  - Cancer
  - Obesity
  - Renal failure
  - Antiphospholipid antibody syndrome
  - **Severe inherited thrombophilia**
- Deep vein thrombosis (DVT)
  - Isolated calf vein DVT
  - Post-thrombotic syndrome
- Pulmonary embolism (PE)
  - Subsegmental PE

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39

Case

- 26-year-old male with acute DVT
- Positive family history of VTE
- Homozygous for factor V Leiden

How Would You Treat?

A. Direct oral anticoagulant (DOAC)

B. Warfarin with usual low molecular weight heparin (LMWH) bridge

C. LMWH alone

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40

ISTH SCC Communication on Treatment of VTE with Severe Thrombophilia

- Not a guideline because paucity of high-quality data
- Severe thrombophilia include:
  - Deficiency of antithrombin, protein C and protein S
  - Homozygous factor V Leiden and F2 mutation (prothrombin gene 20210a) or combined heterozygous
- 25 studies with 5 cohorts, 4 single-center and 16 case reports

- Our review suggests that **full-dose DOACs have a similar efficacy and bleeding rates to VKAs** in most of those with severe thrombophilia.
- There is very limited evidence of the use of **low-dose DOACs, and they cannot be recommended** at this time.
- Finally, we recommend caution in using DOACs in those with **severe PS deficiency and homozygous AT Budapest 3** as there is evidence of limited efficacy.

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Kovac M. J Thromb Haemost. 2024 Nov;22(11):3322-3329. PMID: 39233011.

41

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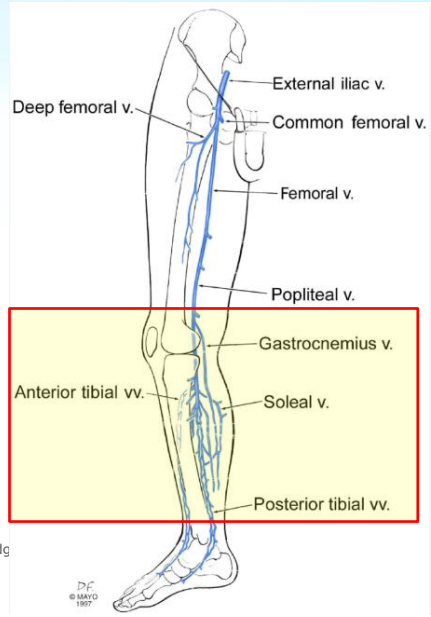
42

Case

- 32-year-old female on birth control pills
- Single calf vein thrombosis



https://www.google.com/search?q=graphic+of+calf+veins&oq=graphic+of+calf+veins&aqs=edg
69i57j0i22i30j0i390i650l5j69i64.4983j0j1&sourceid=chrome&ie=UTF-
8#vhid=GgivRTnVJyyqtM&vssid=3981:1-SZ9Av02lCetM

How Would You Treat?

A. Direct oral anticoagulant (DOAC)
B. Warfarin
C. LMWH
D. No anticoagulation, serial ultrasound and treat if extension

American College of Chest Physicians (ACCP) Guidelines

- In patients with acute isolated distal DVT of the leg: and (i) without severe symptoms or risk factors for extension (see text), we *suggest*
  - serial imaging of the deep veins for 2 weeks over anticoagulation or
  - with severe symptoms or risk factors for extension (see text), we
    - *suggest* anticoagulation over serial imaging of the deep veins

- In patients with acute isolated distal DVT of the leg who are treated with serial imaging, we
  - *recommend* no anticoagulation if the thrombus does not extend
  - *suggest* anticoagulation if the thrombus extends but remains confined to the distal veins
  - *recommend* anticoagulation if the thrombus extends into the proximal veins

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Stevens SM. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. PMID: 34352278.

45

American College of Chest Physicians (ACCP) Guidelines

The following factors may favor choosing anticoagulation:

1. D-dimer is positive (particularly when markedly so without an alternative reason)
2. Thrombosis is extensive (eg, > 5 cm in length, involves multiple veins, > 7 mm in maximum diameter)
3. Thrombosis is close to the proximal veins
4. There is no reversible provoking factor for DVT
5. The patient has active cancer
6. The patient has a history of VTE
7. The patient has inpatient status
8. The patient has COVID-19
9. The patient is highly symptomatic
10. The patient prefers to avoid repeat imaging

The following factors may favor choosing serial imaging:

1. Thrombosis is confined to the muscular veins of the calf (ie, soleus, gastrocnemius)
2. There is a high or moderate risk for bleeding
3. The patient prefers to avoid anticoagulation

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Stevens SM. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. PMID: 34352278.

46

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47

Case

- 62-year-old with proximal (femoral vein) moderately extensive DVT
- Normal BMI and relatively healthy

Would You Prescribe Compression Stockings to Prevent Post-thrombotic (Phlebitis) Syndrome?

A. Yes

B. No

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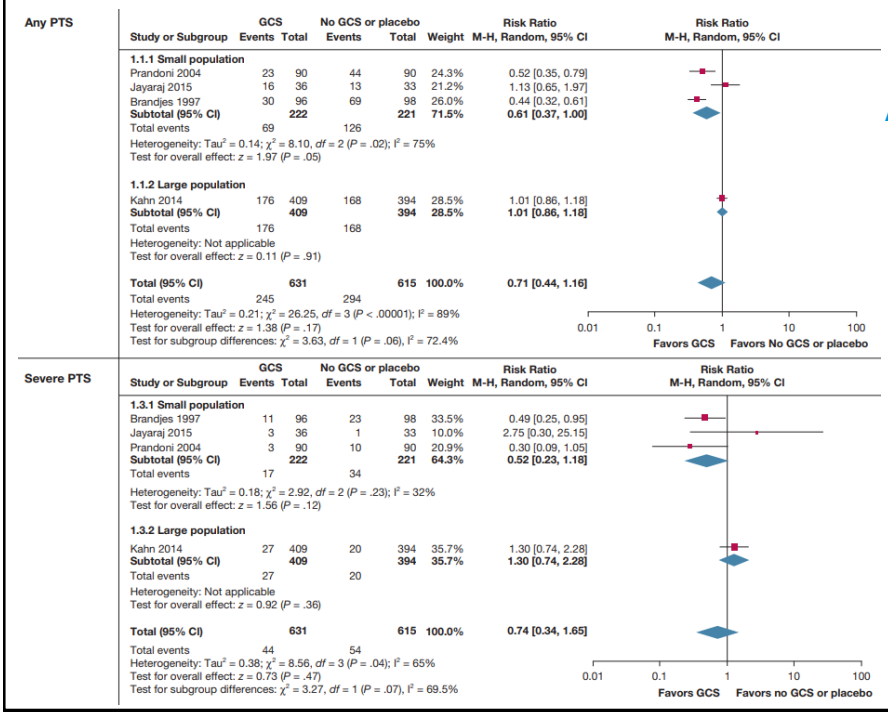
48



American College of Chest Physicians (ACCP) Guidelines

- In patients with acute DVT of the leg, we *suggest* against using compression stockings routinely to prevent post-thrombotic syndrome (PTS)

Stevens SM. Chest. 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. PMID: 34352278.

49

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  - **Subsegmental PE**

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50

Case

- 67-year-old with mild shortness of breath
- Hip replacement 6 weeks ago, ambulating well
- CT with 2 sub-segmental pulmonary emboli
- Normal simplified PESI score, normal troponin
- No cancer
- Lower extremity doppler normal

Would You Anticoagulated?

A. Yes

B. No

Subsegmental PE

- In patients with subsegmental pulmonary embolism (PE) … and no proximal DVT in the legs who have a
  - (i) low risk for recurrent VTE (see text),
    - we *suggest* clinical surveillance over anticoagulation
    - (ii) high risk for recurrent VTE (see text),
      - we *suggest* anticoagulation over clinical surveillance
        - Are hospitalized or have reduced mobility for another reason
        - Have active cancer (particularly if metastatic or being treated with chemotherapy)
        - Have no reversible risk factor for VTE such as recent surgery
        - Are pregnant

Stevens SM. Chest. 2021 Dec;160(6):e545-e608. PMID: 34352278.

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Rapid Recap | Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

February 2024

- Clinical Surveillance vs Anticoagulation Therapy for **Isolated Subsegmental Pulmonary Embolism (ISSPE)**: A Systematic Review of Clinical Outcomes
- Question: is there a difference in recurrent VTE, major bleeding or all-cause mortality at 90 days in patients with ISSPE with anticoagulation vs. surveillance?
- Design: systematic review of 3 prospective and 7 retrospective observational studies
- Patients: single (3 studies) or multiple (7 studies) ISSPE
  - Studies with high-risk patients such as those with malignancy excluded
- "Intervention": anticoagulation
- "Comparison": no anticoagulation and surveillance
- Outcomes
  - Recurrent VTE
  - Major bleeding
  - All-cause mortality
- Timeframe: 90 days

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https://acforum-excellence.org/Resource-Center/resource_files/2148-2024-02-13-195500.pdf

Chin B, Tweedie C. Am Surg. 2024 May;90(5):1089-1097. PMID: 38058129.

53

Clinical Surveillance vs Anticoagulation Therapy for Isolated Subsegmental Pulmonary Embolism: A Systematic Review of Clinical Outcomes

Table 4. 90-Day Outcomes for ISSPE Patients Who Underwent Clinical Surveillance.

Clinical Surveillance Group 90-Day Outcomes

	Author (Year)	Recurrent VTE, n (%)	Major Bleeding, n (%)	All-Cause Mortality, n (%)
Patients with single ISSPE only	Castaner et al (2022)	0 (0%)	0 (0%)	0 (0%)
	Li et al (2022)	1 (3.2%)	1 (3.2%)	3 (9.7%)
	Mehta et al (2014)	0 (0%)	0 (0%)	1 (8.3%)
Patients with single or multiple ISSPE	Dahan et al (2022)	0 (0%)	NR	7 (16.3%)
	Donato et al (2010)	0 (0%)	0 (0%)	0 (0%)
	Eyer et al (2005)	0 (0%)	NR	5 (15.6%)
	Le Gal et al (2021)	8 (3.0%)	2 (.8%)	4 (1.5%)
	Raslan et al (2018)	0 (0%)	NR	4 (44.4%)

167 in 6 studies
266 in Le Gal

Abbreviations: NR = not Reported; VTE = venous thromboembolism; ISSPE = isolated subsegmental pulmonary embolism.

- Incidence of recurrent venous thromboembolism in Le Gal study
  - Single 2.1% (CI, 0.8% to 5.5%)
  - Multiple 5.7% (CI, 2.2% to 14.4%)

Chin B, Tweedie C. Am Surg. 2024 May;90(5):1089-1097. PMID: 38058129.

Le Gal G,. Ann Intern Med. 2022 Jan;175(1):29-35. PMID: 34807722.

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54

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55