Direct Oral Anticoagulants vs Vitamin-K Antagonists in Thrombotic Antiphospholipid Syndrome: Meta-analysis of Randomized Controlled Trials

Monday | January 30, 2023 | 12:00pm – 1:00pm EST

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Disclosures & Notification of Support

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Behnood Bikdeli
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- Consulting expert (on behalf of the plaintiff) for a litigation related to two brand models of IVC filters

Antiphospholipid Antibody Syndrome: Definition

- A systemic autoimmune disorder characterized by recurrent venous/ arterial micro/**macro** thrombosis and/or obstetric morbidity in the setting of persistent presence of at least one of the three following antiphospholipid antibodies (aPL):

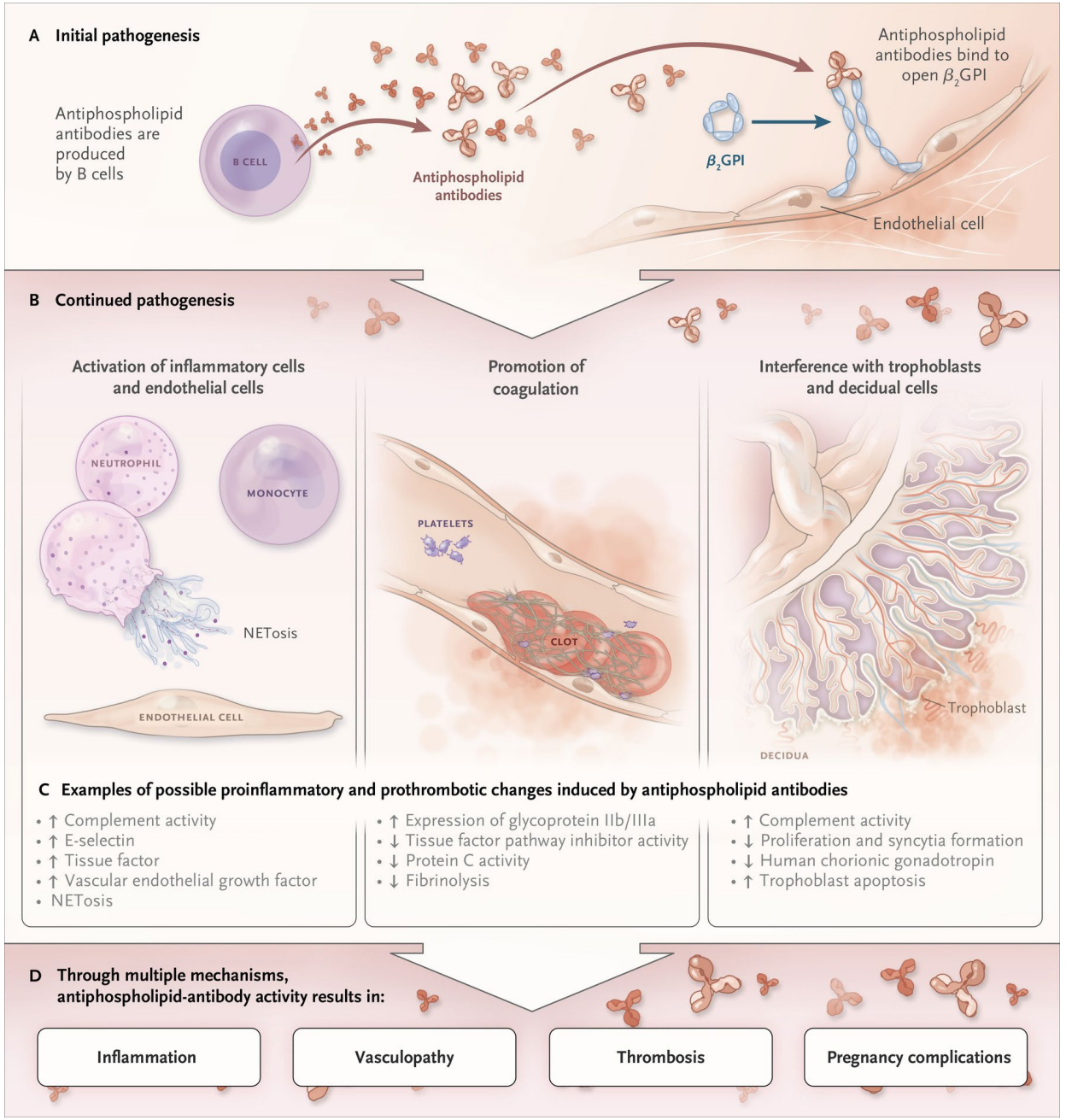
I. Lupus anticoagulant (LA) testing using a method that detects aPL interference in phospholipid-dependent functional clotting assays (e.g., aPTT or dilute Russell viper venom time).

II. An immunoassay (ELISA) for anti-β2 glycoprotein I (anti-β2GP I) antibodies (IgM or IgG).

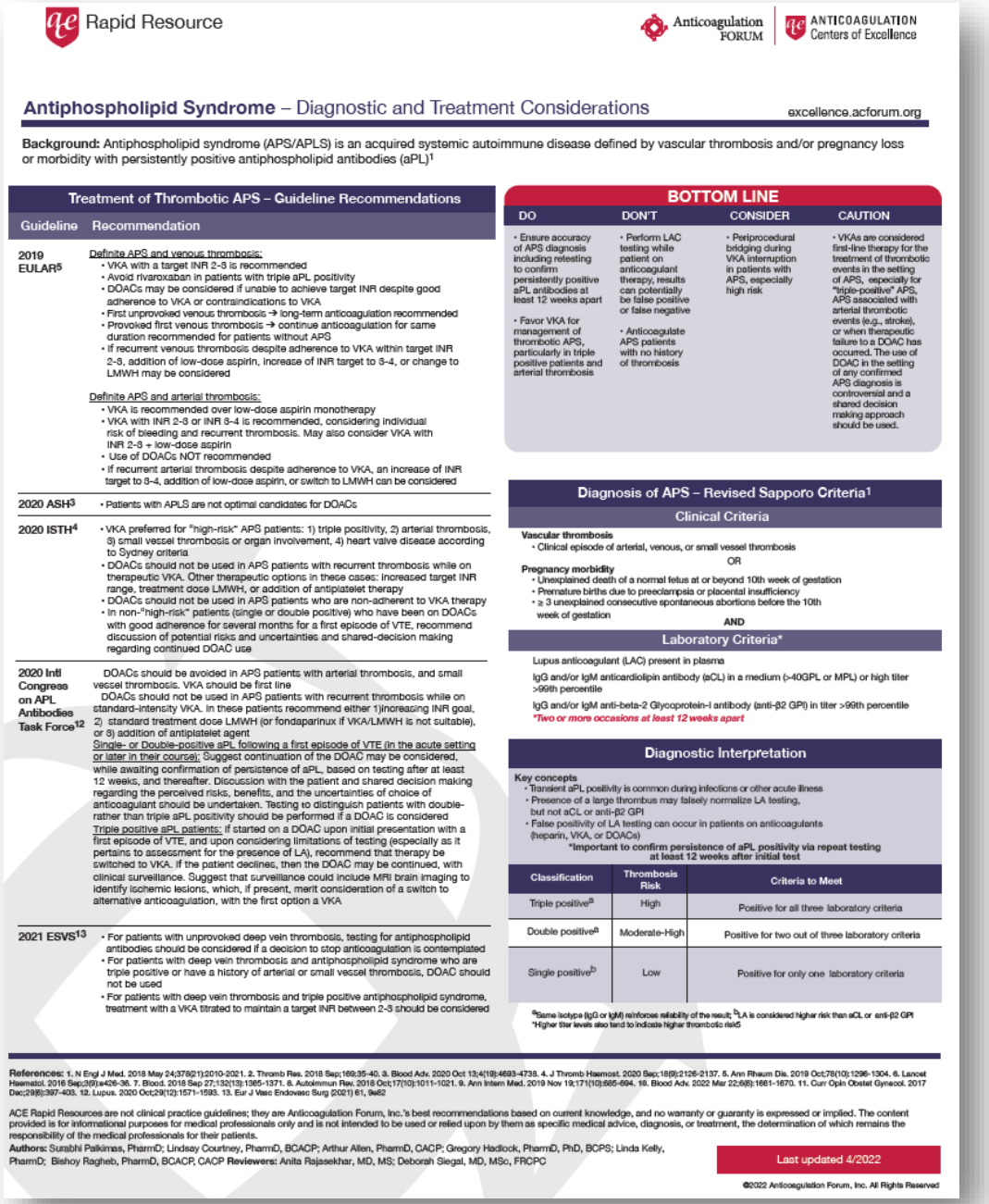
III. An immunoassay (ELISA) for anticardiolipin (aCL) antibodies (IgM or IgG).

Results should be confirmed in ≥2 occasions, at least 12 weeks apart

Devreese KMJ, et al. ISTH Criteria for APS. J Thromb Haemost 2018; 16: 809–13.



Garcia DA, Erkan D. N Engl J Med 2018; 378:2010-2021



Rapid Resource

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

Antiphospholipid Syndrome – Diagnostic and Treatment Considerations

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Background: Antiphospholipid syndrome (APS/APLS) is an acquired systemic autoimmune disease defined by vascular thrombosis and/or pregnancy loss or morbidity with persistently positive antiphospholipid antibodies (aPL)[1]

Treatment of Thrombotic APS – Guideline Recommendations

Guideline	Recommendation
2019 EULAR[5]	Definite APS and venous thrombosis: • VKA with a target INR 2-3 is recommended • Avoid rivaroxaban in patients with triple aPL positivity • DOACs may be considered if unable to achieve target INR despite good adherence to VKA or contraindications to VKA • First unprovoked venous thrombosis → long-term anticoagulation recommended • Provoked first venous thrombosis → continue anticoagulation for same duration recommended for patients without APS • If recurrent venous thrombosis despite adherence to VKA within target INR 2-3, addition of low-dose aspirin, increase of INR target to 3-4, or change to LMWH may be considered Definite APS and arterial thrombosis: • VKA is recommended over low-dose aspirin monotherapy • VKA with INR 2-3 or INR 3-4 is recommended, considering individual risk of bleeding and recurrent thrombosis. May also consider VKA with INR 2-3 + low-dose aspirin • Use of DOACs NOT recommended • If recurrent arterial thrombosis despite adherence to VKA, an increase of INR target to 3-4, addition of low-dose aspirin, or switch to LMWH can be considered
2020 ASH[3]	• Patients with APLS are not optimal candidates for DOACs
2020 ISTH[4]	• VKA preferred for "high-risk" APS patients: 1) triple positivity, 2) arterial thrombosis, 3) small vessel thrombosis or organ involvement, 4) heart valve disease according to Sydney criteria • DOACs should not be used in APS patients with recurrent thrombosis while on therapeutic VKA. Other therapeutic options in these cases: increased target INR range, treatment dose LMWH, or addition of antiplatelet therapy • DOACs should not be used in APS patients who are non-adherent to VKA therapy • In non-"high-risk" patients (single or double positive) who have been on DOACs with good adherence for several months for a first episode of VTE, recommend discussion of potential risks and uncertainties and shared-decision making regarding continued DOAC use
2020 Intl Congress on APL Antibodies Task Force[12]	DOACs should be avoided in APS patients with arterial thrombosis, and small vessel thrombosis. VKA should be first line DOACs should not be used in APS patients with recurrent thrombosis while on standard-intensity VKA. In these patients recommend either 1)increasing INR goal, 2) standard treatment dose LMWH (or fondaparinux if VKA/LMWH is not suitable), or 3) addition of antiplatelet agent Single- or Double-positive aPL following a first episode of VTE (in the acute setting or later in their course): Suggest continuation of the DOAC may be considered, while awaiting confirmation of persistence of aPL, based on testing after at least 12 weeks, and thereafter. Discussion with the patient and shared decision making regarding the perceived risks, benefits, and the uncertainties of choice of anticoagulant should be undertaken. Testing to distinguish patients with double- rather than triple aPL positivity should be performed if a DOAC is considered Triple positive aPL patients: If started on a DOAC upon initial presentation with a first episode of VTE, and upon considering limitations of testing (especially as it pertains to assessment for the presence of LA), recommend that therapy be switched to VKA. If the patient declines, then the DOAC may be continued, with clinical surveillance. Suggest that surveillance could include MRI brain imaging to identify ischemic lesions, which, if present, merit consideration of a switch to alternative anticoagulation, with the first option a VKA
2021 ESVS[13]	• For patients with unprovoked deep vein thrombosis, testing for antiphospholipid antibodies should be considered if a decision to stop anticoagulation is contemplated • For patients with deep vein thrombosis and antiphospholipid syndrome who are triple positive or have a history of arterial or small vessel thrombosis, DOAC should not be used • For patients with deep vein thrombosis and triple positive antiphospholipid syndrome, treatment with a VKA titrated to maintain a target INR between 2-3 should be considered

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Ensure accuracy of APS diagnosis including retesting to confirm persistently positive aPL antibodies at least 12 weeks apart • Favor VKA for management of thrombotic APS, particularly in triple positive patients and arterial thrombosis	• Perform LAC testing while patient on anticoagulant therapy, results can potentially be false positive or false negative • Anticoagulate APS patients with no history of thrombosis	• Periprocedural bridging during VKA interruption in patients with APS, especially high risk	• VKAs are considered first-line therapy for the treatment of thrombotic events in the setting of APS, especially for "triple-positive" APS. APS associated with arterial thrombotic events (e.g., stroke), or when therapeutic failure to a DOAC has occurred. The use of DOAC in the setting of any confirmed APS diagnosis is controversial and a shared decision making approach should be used.

Diagnosis of APS – Revised Sapporo Criteria[1]

Clinical Criteria

Vascular thrombosis
- Clinical episode of arterial, venous, or small vessel thrombosis

OR

Pregnancy morbidity
- Unexplained death of a normal fetus at or beyond 10th week of gestation
- Premature births due to preeclampsia or placental insufficiency
- ≥ 3 unexplained consecutive spontaneous abortions before the 10th week of gestation

AND

Laboratory Criteria*

Lupus anticoagulant (LAC) present in plasma

IgG and/or IgM anticardiolipin antibody (aCL) in a medium (>40GPL or MPL) or high titer >99th percentile

IgG and/or IgM anti-beta-2 Glycoprotein-I antibody (anti-β2 GPI) in titer >99th percentile

Two or more occasions at least 12 weeks apart

Diagnostic Interpretation

Key concepts
- Transient aPL positivity is common during infections or other acute illness
- Presence of a large thrombus may falsely normalize LA testing, but not aCL or anti-β2 GPI
- False positivity of LA testing can occur in patients on anticoagulants (heparin, VKA, or DOACs)

*Important to confirm persistence of aPL positivity via repeat testing at least 12 weeks after initial test

Classification	Thrombosis Risk	Criteria to Meet
Triple positive[a]	High	Positive for all three laboratory criteria
Double positive[a]	Moderate-High	Positive for two out of three laboratory criteria
Single positive[b]	Low	Positive for only one laboratory criteria

[a]Same isotype (IgG or IgM) reinforces reliability of the result; [b]LA is considered higher risk than aCL or anti-β2 GPI
*Higher titer levels also tend to indicate higher thrombotic risk5

References: 1. N Engl J Med. 2018 May 24;378(21):2010-2021. 2. Thromb Res. 2018 Sep;169:35-40. 3. Blood Adv. 2020 Oct 13;4(19):4693-4738. 4. J Thromb Haemost. 2020 Sep;18(9):2126-2137. 5. Ann Rheum Dis. 2019 Oct;78(10):1296-1304. 6. Lancet Haematol. 2018 Sep;29(e428-36. 7. Blood. 2018 Sep 27;132(13):1365-1371. 8. Autoimmun Rev. 2018 Oct;17(10):1011-1021. 9. Ann Intern Med. 2019 Nov 19;171(10):685-694. 10. Blood Adv. 2022 Mar 22;6(6):1661-1670. 11. Curr Opin Obstet Gynecol. 2017 Dec;29(6):397-403. 12. Lupus. 2020 Oct;29(12):1571-1593. 13. Eur J Vasc Endovasc Surg (2021) 61, 9e62

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https://acforum-excellence.org/Resource-Center/resource_files/-2022-07-14-081041.pdf

DOAC for APS?

- More convenient
- Less challenges with monitoring and titration especially in APS
- However, the efficacy and safety of DOACs vs VKAs in this setting was unknown

Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

Rivaroxaban: RAPS

- Short-term study of rivaroxaban (20mg/d) vs VKAs (INR: 2-3) in patients who had completed at least 3 months of anticoagulation with VKA: 54 assigned to rivaroxaban and 56 receiving VKAs included in the final analysis

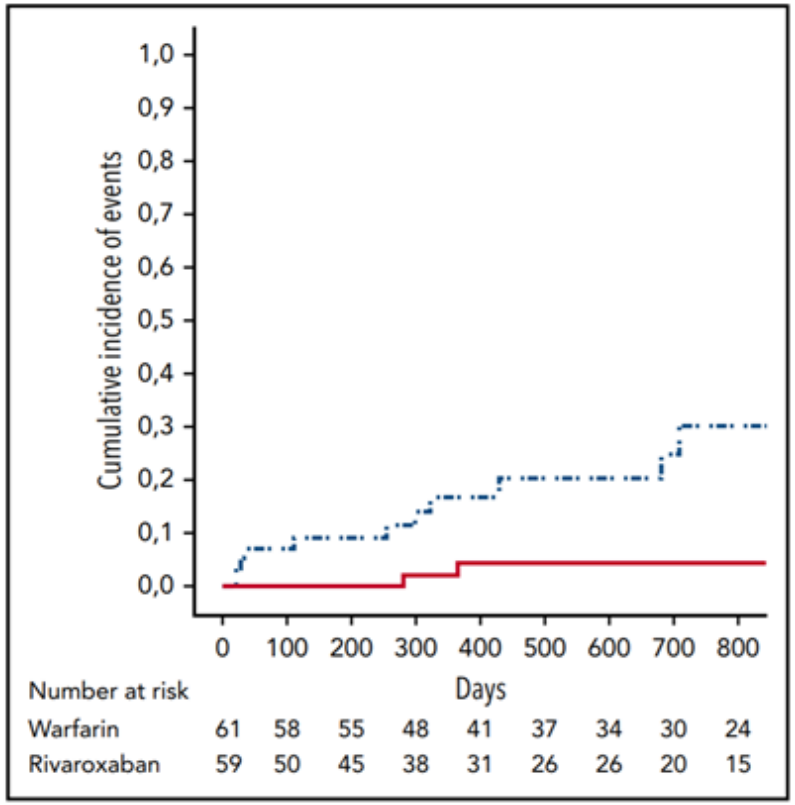
- None of the enrollees had arterial thrombosis or recurrent thrombosis Hx

- At day 42, endogenous thrombin potential was higher in the rivaroxaban than in VKA group (mean 1086 nmol/L per min, 95% CI, 957-1233 vs 548, 484-621; P<0.001). No thrombotic events occurred.

Cohen H, et al. Lancet Haematol 2016; 3: e426–36.

Rivaroxaban: TRAPS

- Patients with triple-positive thrombotic APS randomized to rivaroxaban (20mg once daily) vs VKAs (INR 2.5)
- Terminated prematurely after enrolling 120 patients (59 randomized to rivaroxaban and 61 to warfarin) due to concern for harm
- 4 ischemic strokes and 3 Mis in those assigned to rivaroxaban, none with VKAs
- 4 MBs with rivaroxaban, 2 with VKAs



- The composite primary outcome of thromboembolic events, major bleeding, and vascular death occurred in 13 patients in the rivaroxaban group and in 2 patients in the VKA group (HR, 7.4; 95% CI, 1.7-32.9; P = 0.008)

Pengo V, et al. Blood. 2018; 132: 1365-1371.

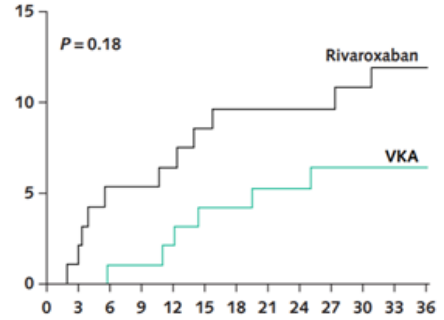
Rivaroxaban: Ordi-ros et al

- 190 patients (95 per group) with thrombotic APS randomized to rivaroxaban (20mg/d) vs VKAs (INR: 2-3)
  Any form of confirmed APS.

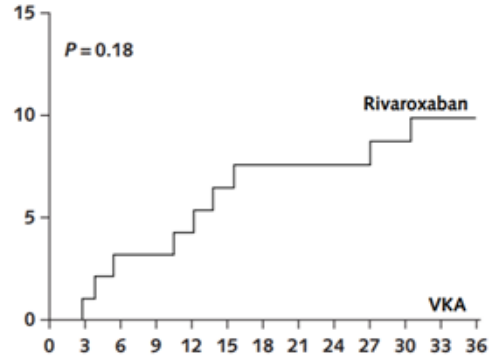
Table 2. Efficacy End Points of Recurrent Thrombotic Events*

Study Population	Events, *n* (%)		Risk Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)‡	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)†				
Per protocol, as treated						
All events	11 (11.6)	6 (6.3)	1.83 (0.71–4.76)	0.21	1.94 (0.72–5.24)	0.190
Arterial events§	10 (10.5)	3 (3.2)	3.33 (0.95–11.73)	0.060	3.52 (0.97–12.79)	0.060
Venous events§	2 (2.1)	3 (3.2)	0.67 (0.11–3.90)	0.65	0.70 (0.12–4.21)	0.70
Stroke	9 (9.5)	0 (0)	19.00 (1.12–321.9)	<0.001	19.97 (1.00–400.0)	0.050
Intention to treat						
All events	12 (12.6)	6 (6.3)	2.00 (0.78–5.11)	0.150	2.10 (0.79–5.59)	0.140
Arterial events	11 (11.6)	3 (3.2)	3.67 (1.06–12.73)	0.040	3.84 (1.07–13.76)	0.040
Venous events	2 (2.1)	3 (3.2)	0.67 (0.11–3.90)	0.65	0.70 (0.12–4.18)	0.69
Stroke	10 (10.5)	0 (0)	21.00 (1.25–353.3)	0.001	20.01 (1.12–431.8)	0.040

Time to Recurrent Thrombotic Event in the Per Protocol Population



Time to Stroke Event in the Per Protocol Population

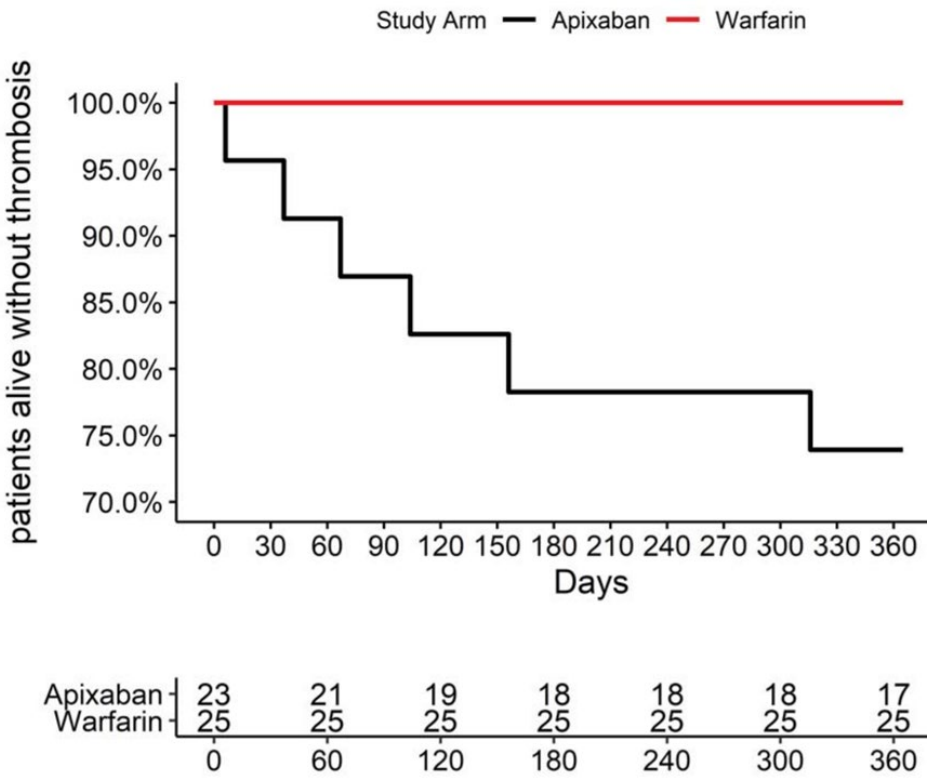


- Non-inferiority not shown.

Ordi-Ros J, et al. Ann Intern Med. 2019; 171: 685-694.

Apixaban

- Patients with thrombotic APS, treated for at least 6 months, mostly from Intermountain Medical Center (UT), testing apixaban 2.5mg bid vs VKA (INR 2-3)
- A subsequent protocol amendment increased the dose of apixaban to 5mg bid
- Planned to enroll 200 patients. Ultimately, stopped after enrolling 48 patients (23 assigned to apixaban and 25 to warfarin).
- Arterial thrombosis in 6 patients assigned to apixaban (only 2 were triple positive) and none of patients assigned to VKAs



Woller SC, et al. Blood Adv. Epub Ahead of Print doi: 10.1182/bloodadvances.2021005808.

Continued uncertainty

- None of these studies were large enough to provide definitive evidence
- Uncertainties also existed in subgroups
- A team of investigators decided to conduct a comprehensive systematic review and meta-analysis to generate addition insights

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Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Antiphospholipid Syndromes

Meta-Analysis of Randomized Trials

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DOACs vs VKAs in thrombotic APS SRMA: Methods

- Study protocol developed in advance and registered in PROSPERO (CRD42022268035)
- Search of PubMed, Embase and Cochrane for RCTs through April 9, 2022
- Search of clinicaltrials.gov for identification of ongoing RCTs
- Major exclusions: Non-RCT studies, those with a crossover design, those focused on APS without thrombosis, and clinical trials of pediatric populations

Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

DOACs vs VKAs in thrombotic APS SRMA: Methods

- If the data elements were not available in the published papers, the PIs of the original trials were contacted. Investigators from 3 trials (VP, SCW, and JCH) provided additional data.

- **Main outcomes:** A. Composite of arterial thrombotic events B. VTE

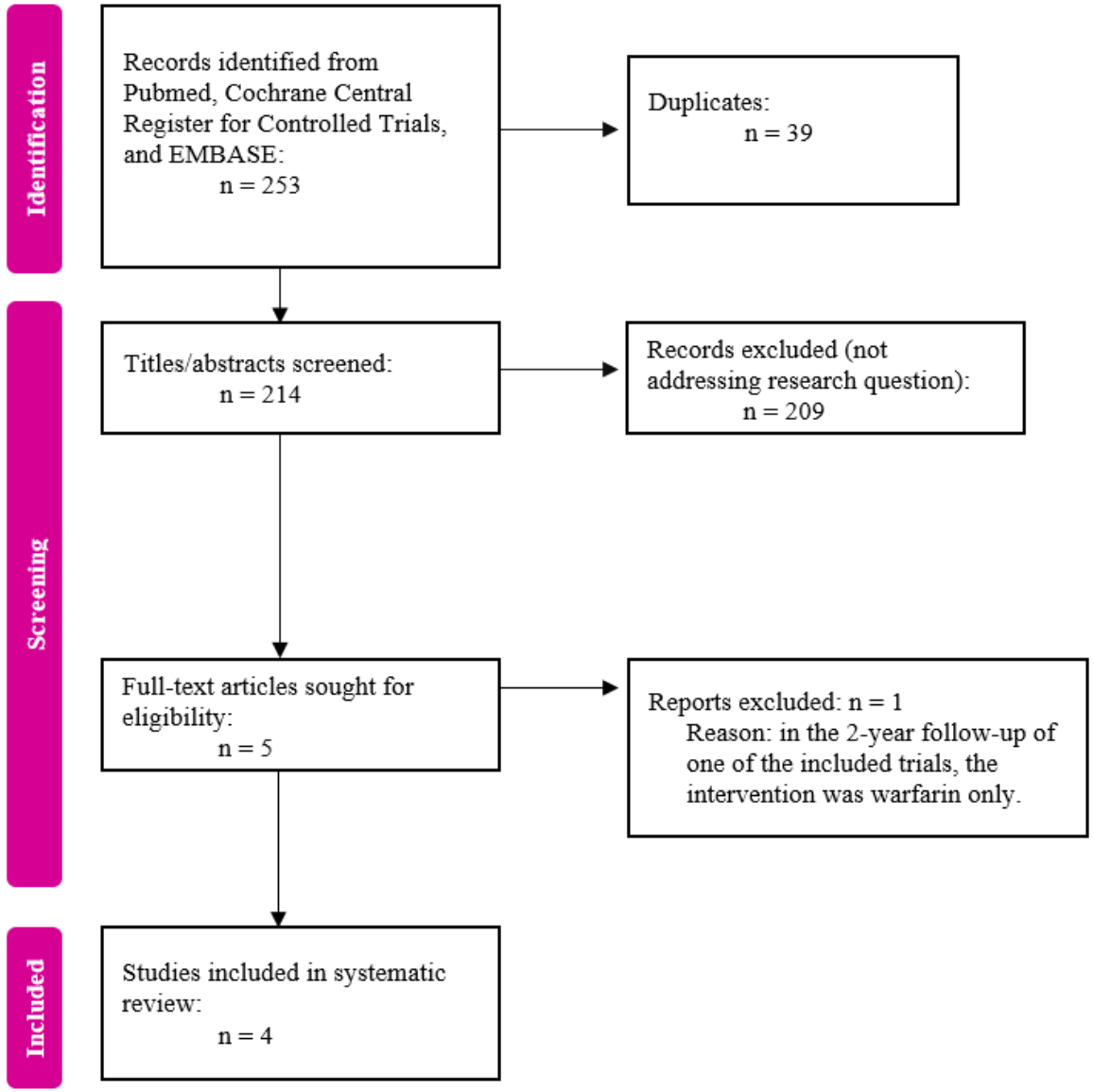
Several additional outcomes explored including any thrombotic event, MI, stroke, bleeding, mortality.

Risk of bias assessment: Cochrane criteria for individual studies, GRADE criteria for outcomes.

Several subgroup analyses pre-specified, including in women vs men, in those with vs without triple-positive APS, and others.

Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

Supplemental Figure 1. PRISMA diagram for study inclusion.



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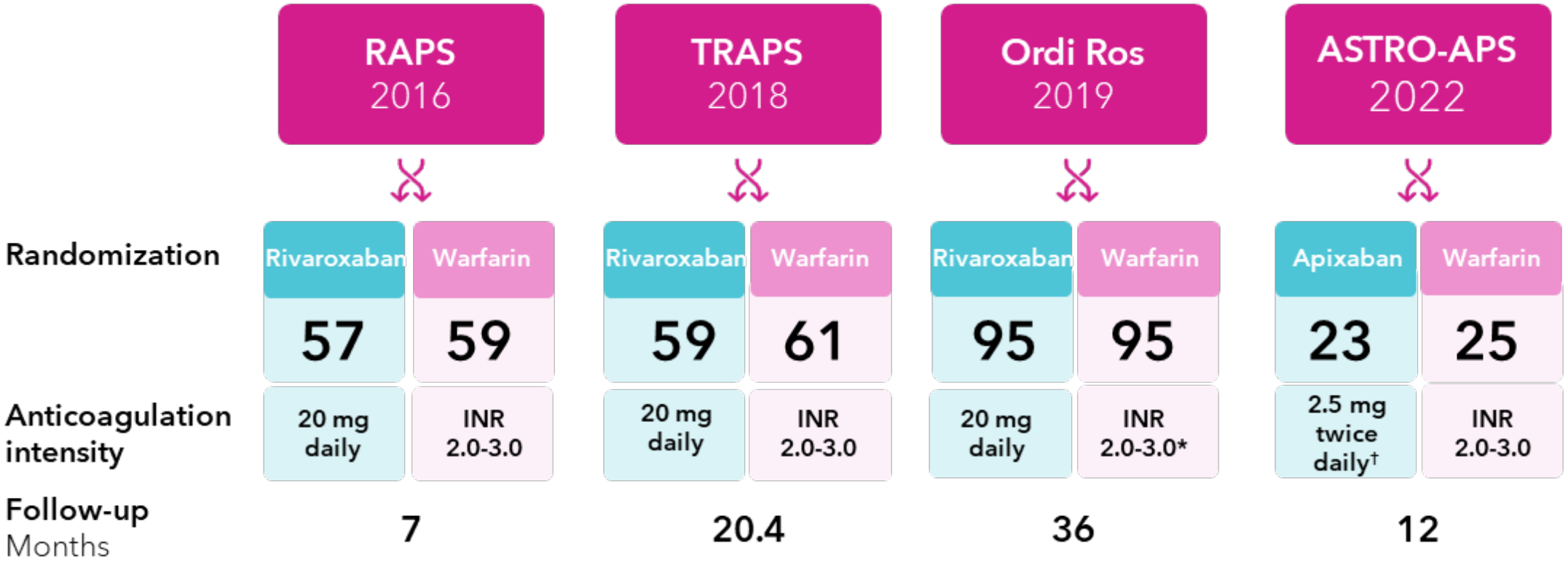
TRIAL DESIGN



*Patients with a history of recurrent thrombosis were assigned to an INR of 3.1 to 4 in the VKA arm

†In ASTRO-APS, after 25 patients were randomized, all patients in the apixaban arm had their dose increased to 5 mg BID

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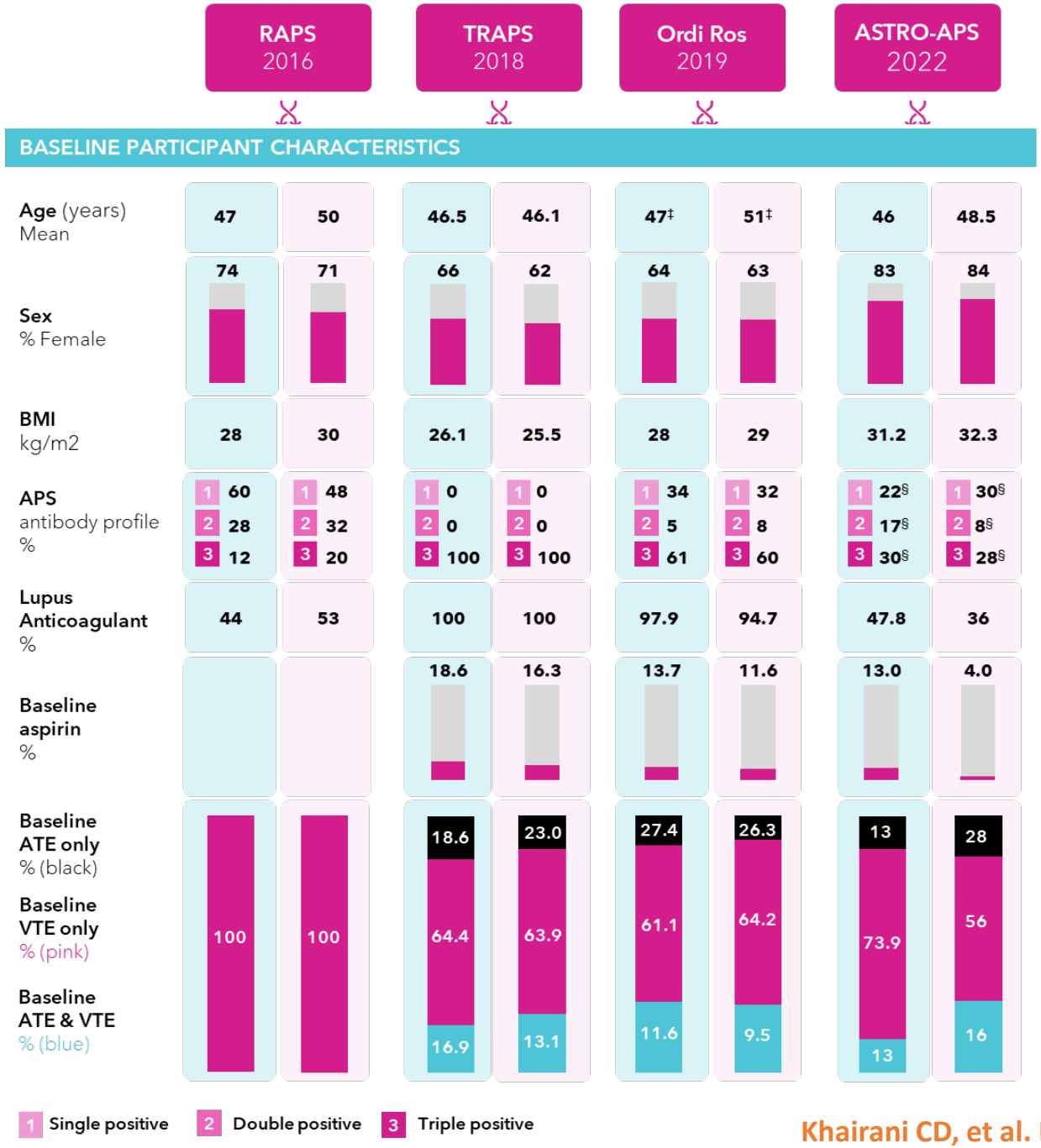


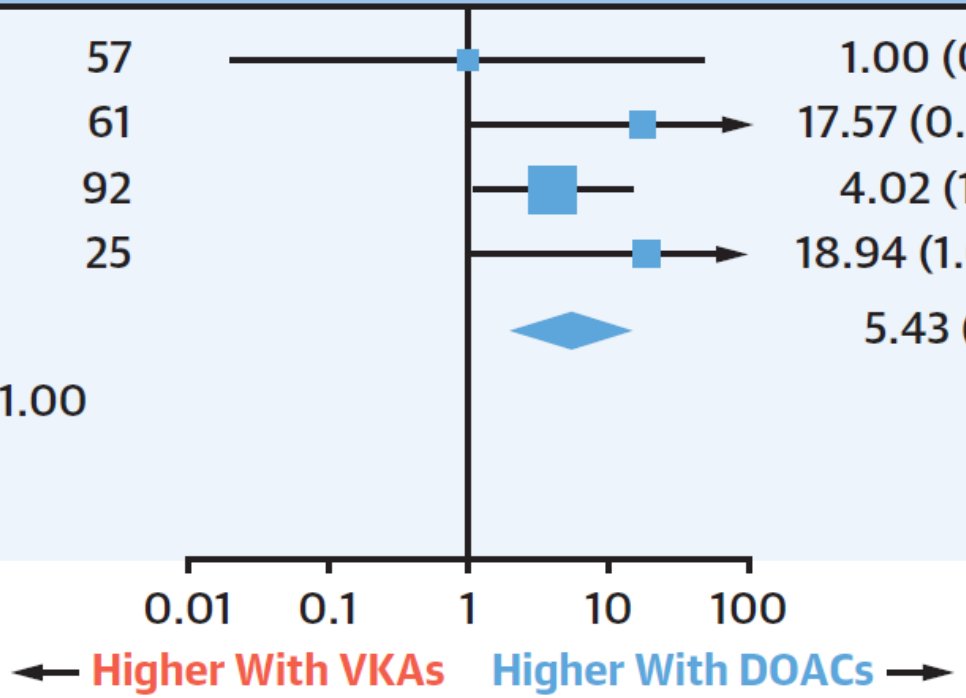
. §In the ASTRO-APS trial, 31% had historical APS in the apixaban group, and 34% had historical APS in the VKA group.

Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

A Composite of Arterial Thrombotic Events

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	7.31
Pengo (2018)	7	52	0	61	17.57 (0.98-315.00)	13.60
Ordi-Ros (2019)	11	84	3	92	4.02 (1.08-14.89)	65.98
Woller (2022)	6	17	0	25	18.94 (1.00-358.35)	13.11
Overall					5.43 (1.87-15.75)	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(3) = 2.24$, $P = 0.52$
Test of $\theta = 0$: $z = 3.12$, $P = 0.00$



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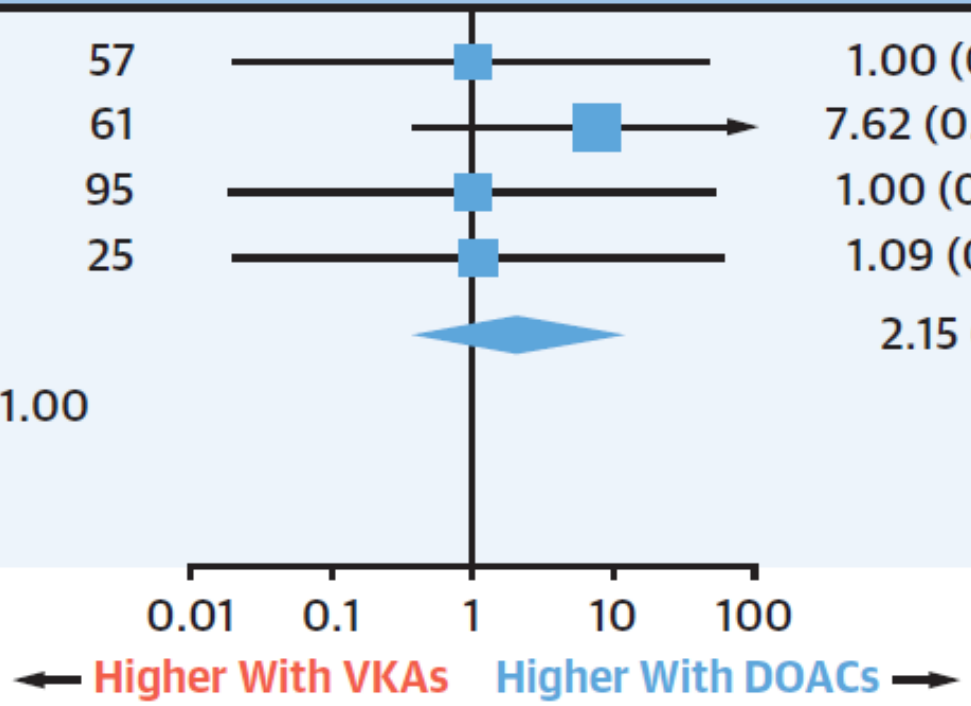
B Myocardial Infarction

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	21.14
Pengo (2018)	3	56	0	61	7.62 (0.39-150.78)	36.76
Ordi-Ros (2019)	0	95	0	95	1.00 (0.02-50.92)	21.21
Woller (2022)	0	23	0	25	1.09 (0.02-56.91)	20.89
Overall					2.15 (0.35-13.11)	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(3) = 1.10$, $P = 0.78$
Test of $\theta = 0$: $z = 0.83$, $P = 0.41$



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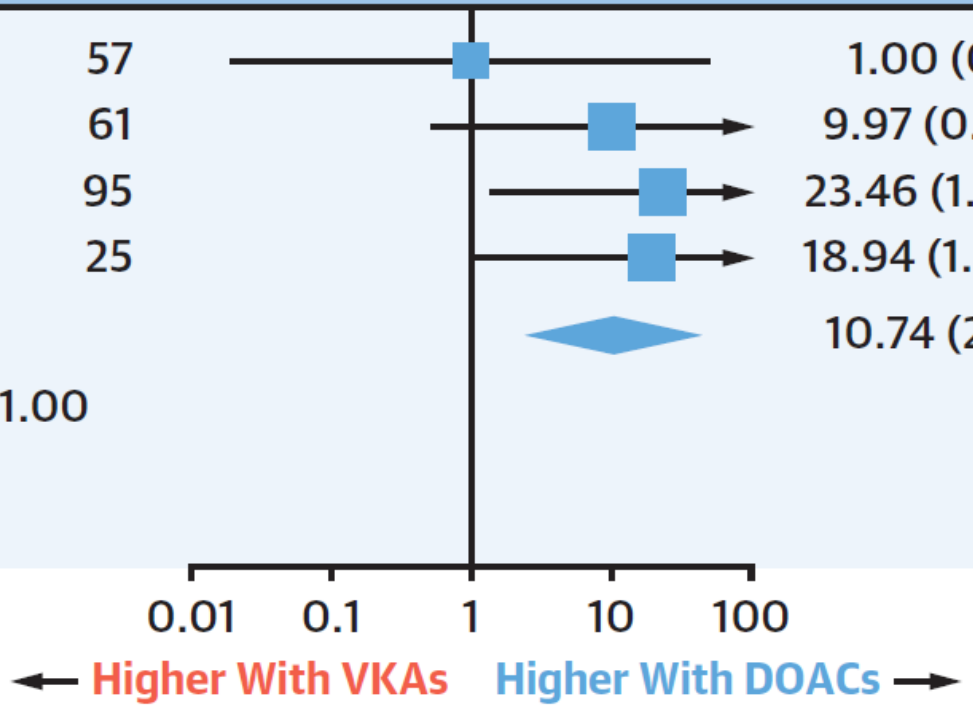
C Stroke

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	15.42
Pengo (2018)	4	55	0	61	9.97 (0.53-189.44)	27.57
Ordi-Ros (2019)	10	85	0	95	23.46 (1.35-406.32)	29.38
Woller (2022)	6	17	0	25	18.94 (1.00-358.35)	27.64
Overall					10.74 (2.29-50.38)	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(3) = 1.83$, $P = 0.61$
Test of $\theta = 0$: $z = 3.01$, $P = 0.00$



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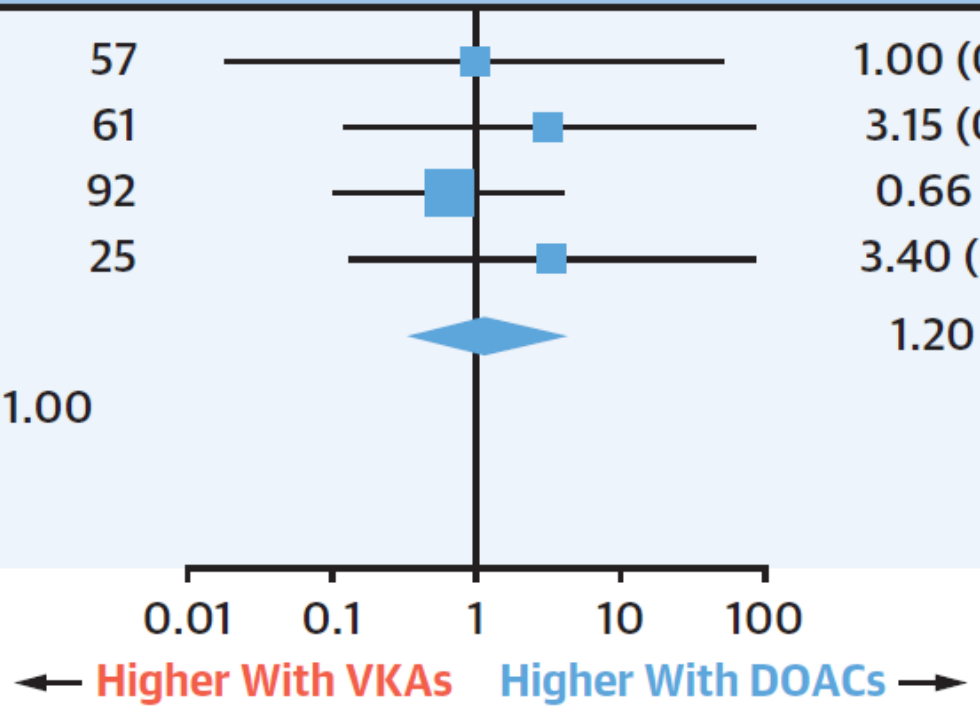
A Venous Thromboembolic Events

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	11.52
Pengo (2018)	1	58	0	61	3.15 (0.13-78.98)	17.21
Ordi-Ros (2019)	2	93	3	92	0.66 (0.11-4.04)	54.37
Woller (2022)	1	22	0	25	3.40 (0.13-87.72)	16.90
Overall					1.20 (0.31-4.55)	

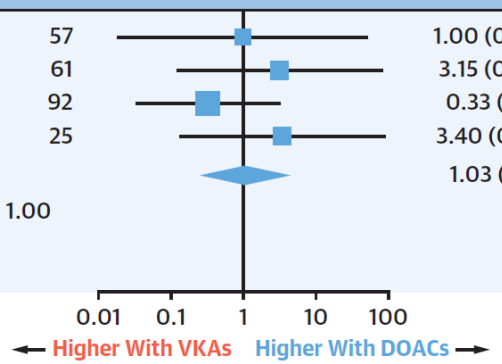
Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(3) = 1.17$, $P = 0.76$
Test of $\theta = 0$: $z = 0.26$, $P = 0.79$



B Deep Vein Thrombosis

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	14.41
Pengo (2018)	1	58	0	61	3.15 (0.13-78.98)	21.53
Ordi-Ros (2019)	1	94	3	92	0.33 (0.03-3.19)	42.91
Woller (2022)	1	22	0	25	3.40 (0.13-87.72)	21.14
Overall					1.03 (0.23-4.57)	

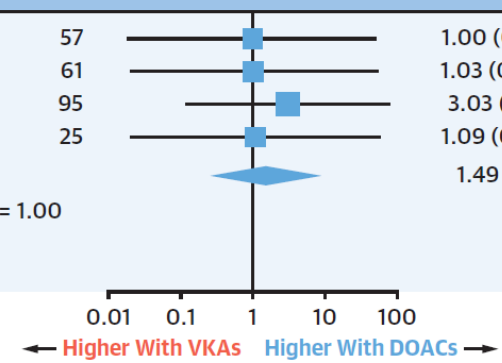
Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: Q(3) = 1.96, $P = 0.58$
Test of $\theta = 0$: z = 0.03, $P = 0.97$



C Pulmonary Embolism

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	22.27
Pengo (2018)	0	59	0	61	1.03 (0.02-52.94)	22.28
Ordi-Ros (2019)	1	94	0	95	3.03 (0.12-75.37)	33.43
Woller (2022)	0	23	0	25	1.09 (0.02-56.91)	22.01
Overall					1.49 (0.23-9.53)	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: Q(3) = 0.28, $P = 0.96$
Test of $\theta = 0$: z = 0.42, $P = 0.68$

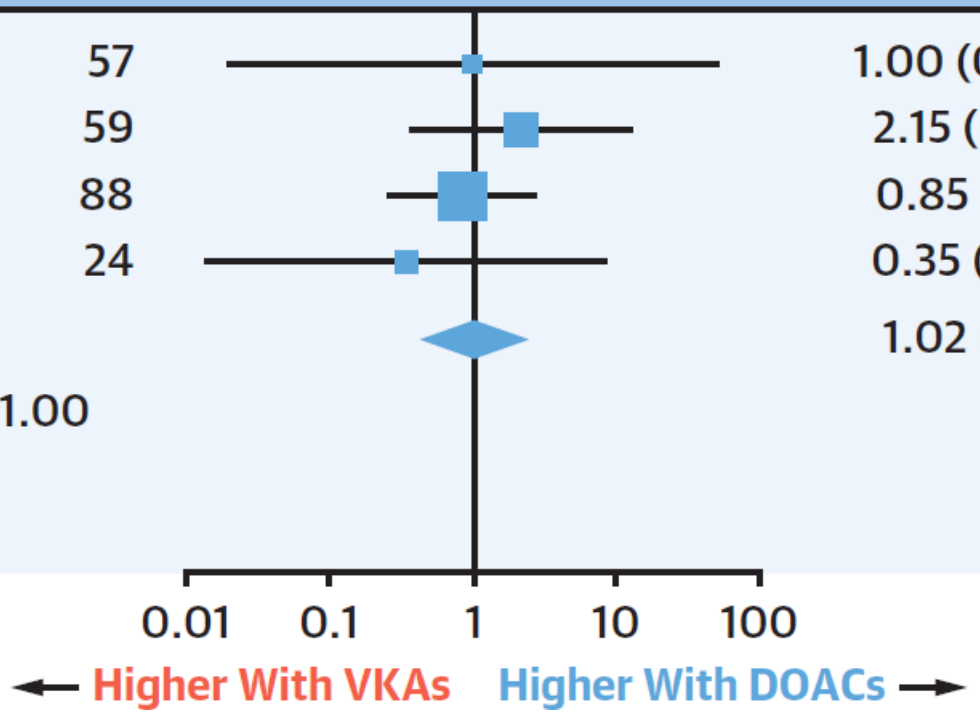


Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

A Major Bleeding

Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	0	57	0	57	1.00 (0.02-51.26)	5.06
Pengo (2018)	4	55	2	59	2.15 (0.38-12.18)	26.01
Ordi-Ros (2019)	6	89	7	88	0.85 (0.27-2.62)	61.50
Woller (2022)	0	23	1	24	0.35 (0.01-8.96)	7.43
Overall					1.02 (0.42-2.47)	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(3) = 1.23$, $P = 0.75$
Test of $\theta = 0$: $z = 0.04$, $P = 0.97$

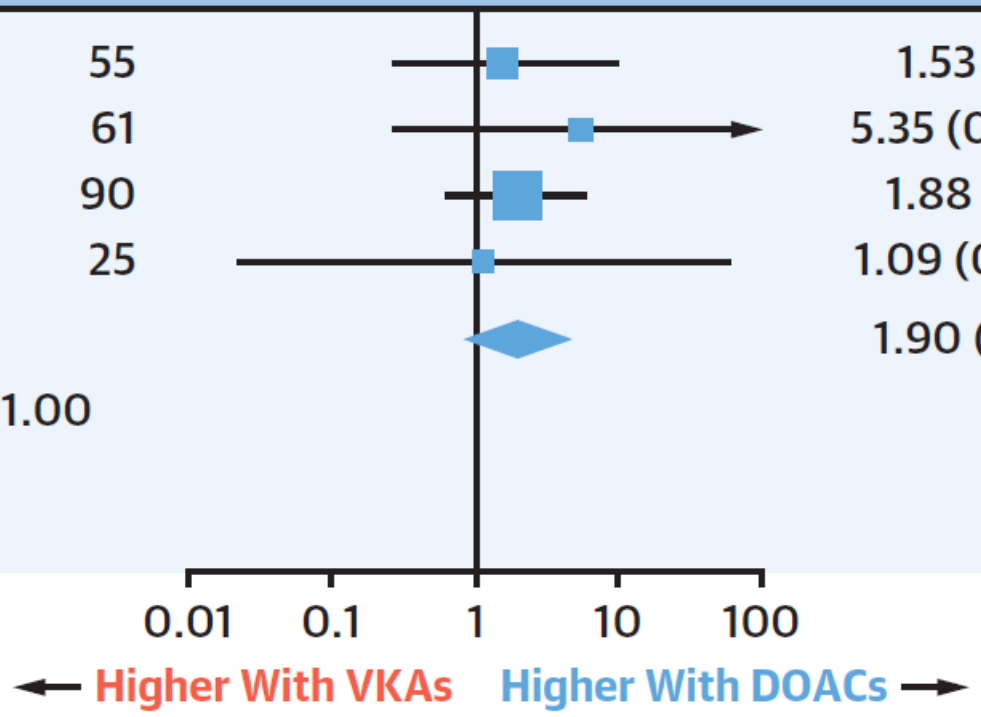


Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

B Clinically Relevant Nonmajor Bleeding

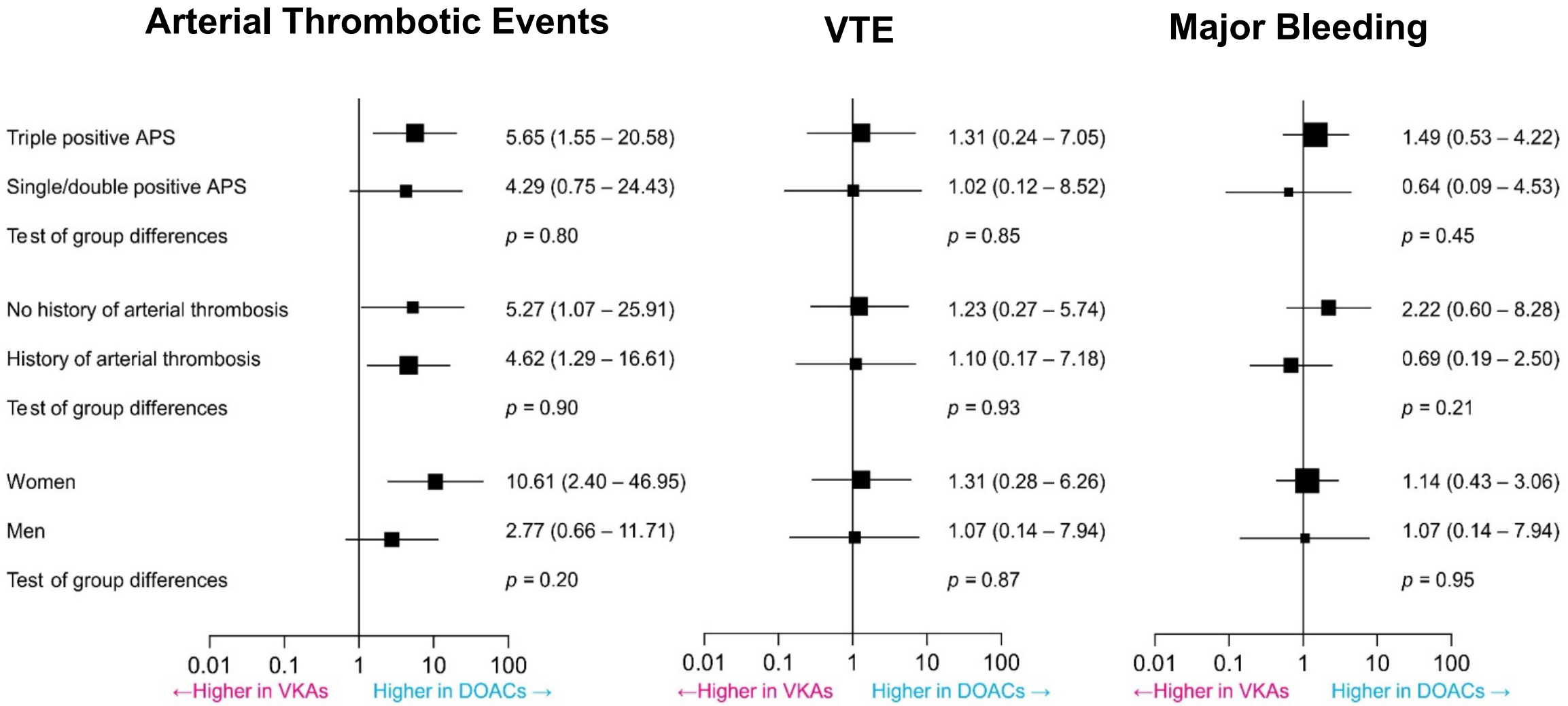
Study (Year)	DOACs Events	DOACs No Events	VKAs Events	VKAs No Events	OR With 95% CI	Weight (%)
Cohen (2016)	3	54	2	55	1.53 (0.25-9.51)	23.94
Pengo (2018)	2	57	0	61	5.35 (0.25-113.78)	8.56
Ordi-Ros (2019)	9	86	5	90	1.88 (0.61-5.85)	62.40
Woller (2022)	0	23	0	25	1.09 (0.02-56.91)	5.10
Overall					1.90 (0.78-4.66)	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(3) = 0.57$, $P = 0.90$
Test of $\theta = 0$: $z = 1.41$, $P = 0.16$



Khairani CD, et al. Bikdeli B. J Am Coll Cardiol. doi: 10.1016/j.jacc.2022.10.008.

Pre-specified subgroup analyses



Risk of Bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
RAPS 2016	+	+	-	+	-	-	-
TRAPS 2018	+	+	-	+	-	-	-
Ordi-Ros 2019	+	+	-	+	-	-	-
ASTRO-APS 2022	+	+	-	+	-	-	-

Note: +, present; -, absent; green, low risk of bias; red, high risk of bias.

GRADE Assessment per outcome

	Certainty Assessment							Patients, n		Effect			
	No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Consideration	DOACs, n/N (%)	VKAs, n/N (%)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Composite of arterial thrombotic events	4	Randomized trials	Not serious	Not serious	Not serious	Not serious	Very strong association	24/234 (10.3)	3/238 (1.3)	OR: 5.43 (1.87-15.75)	5 more per 100 (from 1 more to 15 more)	⨁⨁⨁⨁ High	Critical
Venous thromboembolic events	4	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	4/234 (1.7)	3/238 (1.3)	OR: 1.20 (0.31-4.55)	0 fewer per 100 (from 1 fewer to 4 more)	⨁⨁⨁ Moderate	Important
Major bleeding	4	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	10/234 (4.3)	10/238 (4.2)	OR: 1.02 (0.42-2.47)	0 fewer per 100 (from 2 fewer to 6 more)	⨁⨁⨁ Moderate	Important

Factors contributing to the certainty of evidence include the risk of bias, inconsistency, indirectness, imprecision, publication bias, and the strength of association. [a]Low event rate and wide CI with no clear harm or benefit with the use of direct oral anticoagulants (DOACs). ++++ = high certainty; +++ = moderate certainty.

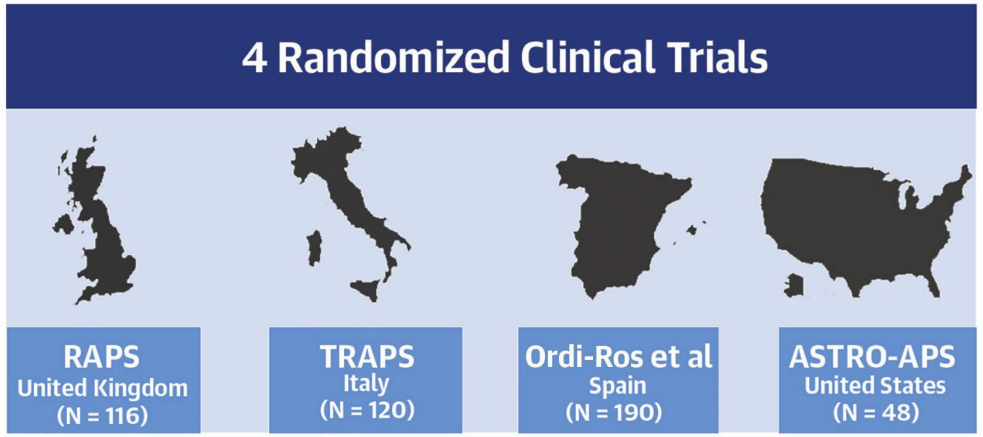
GRADE = Grading of Recommendations, Assessment, Development and Evaluation; VKA = vitamin K antagonist.

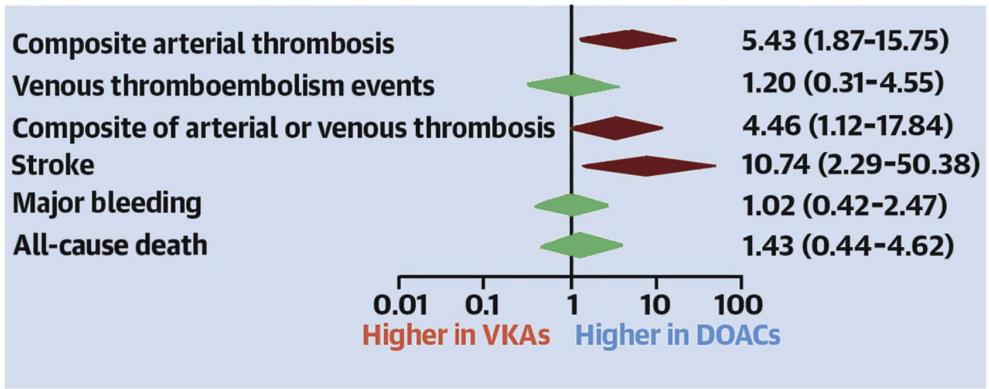
Why are DOACs less effective??

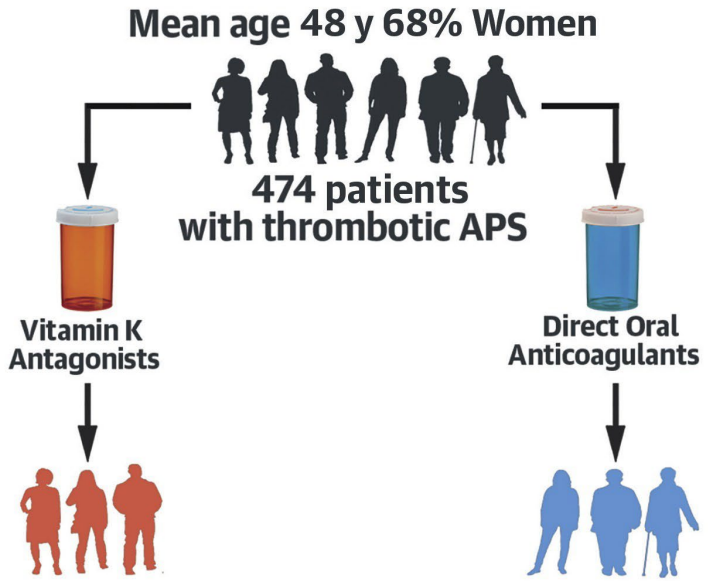
- Adherence is a bigger issue with DOACs (short half life)?
- Unlikely to be the explanation. In the apixaban trial, adherence was 97%
- Blocking the coagulation cascade at multiple points (VKAs) more effective in these cases (similar to mechanical valves, and rheumatic AF)?
- Higher dose of DOACs needed? RISPAS (NCT03684564) is currently randomizing patients to rivaroxaban 15mg bid vs VKAs (INR 3-4)

Bottomline:

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

Khairani CD, et al. J Am Coll Cardiol. 2023;81(1):16-30.

Thank you very much!!

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Anticoagulation Forum

BWH, AHA, YNHH/Yale CORE

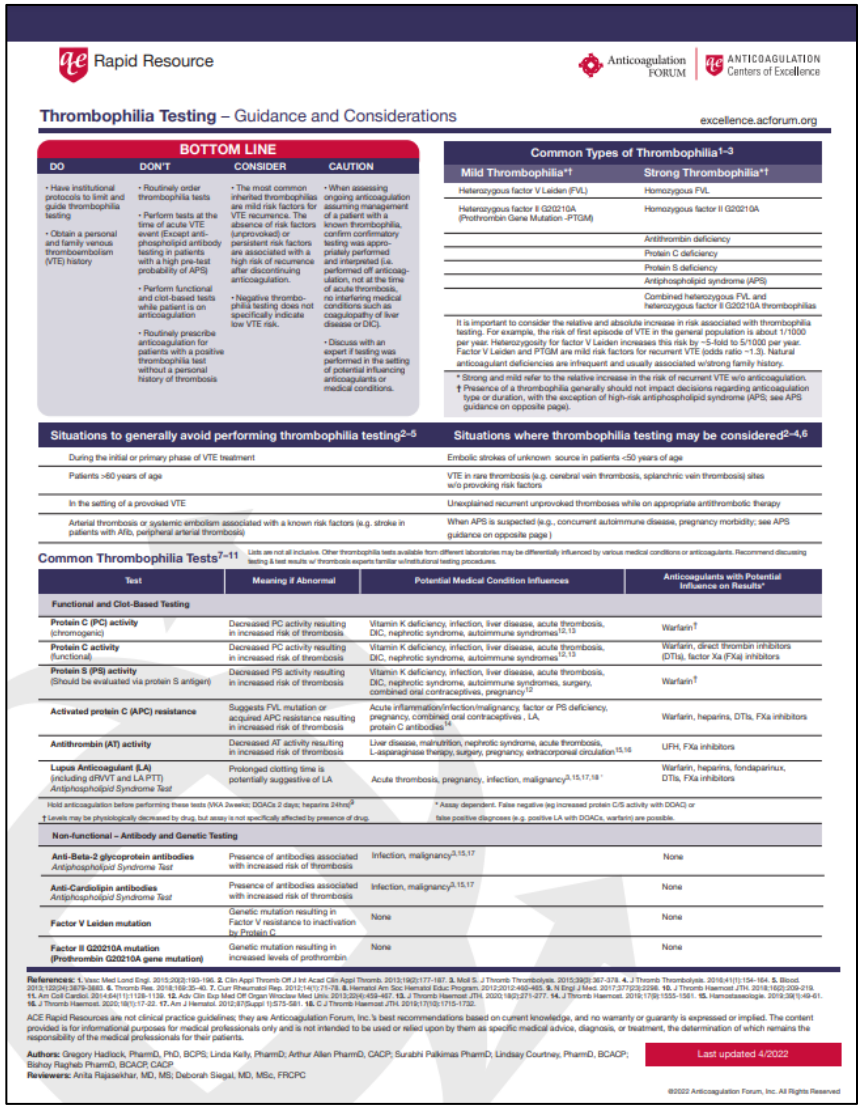
Collaborators, mentors, friends, and family!

Rapid Resource:
Thrombophilia Testing & Antiphospholipid Syndrome

Surabhi Palkimas, PharmD

Anticoagulation FORUM | Webinar

Rapid Resource



Rapid Resource

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

Thrombophilia Testing – Guidance and Considerations

excellence.acforum.org

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Have institutional protocols to limit and guide thrombophilia testing • Obtain a personal and family venous thromboembolism (VTE) history	• Routinely order thrombophilia tests • Perform tests at the time of acute VTE event (Except anti-phospholipid antibody testing in patients with a high pre-test probability of APS) • Perform functional and clot-based tests while patient is on anticoagulation • Routinely prescribe anticoagulation for patients with a positive thrombophilia test without a personal history of thrombosis	• The most common inherited thrombophilias are mild risk factors for VTE recurrence. The absence of risk factors (unprovoked) or persistent risk factors are associated with a high risk of recurrence after discontinuing anticoagulation. • Negative thrombophilia testing does not specifically indicate low VTE risk.	• When assessing ongoing anticoagulation assuming management of a patient with a known thrombophilia, confirm confirmatory testing was appropriately performed and interpreted (i.e. performed off anticoagulation, not at the time of acute thrombosis, no interfering medical conditions such as coagulopathy of liver disease or DIC). • Discuss with an expert if testing was performed in the setting of potential influencing anticoagulants or medical conditions.

Common Types of Thrombophilia[1–3]

Mild Thrombophilia*†	Strong Thrombophilia*†
Heterozygous factor V Leiden (FVL)	Homozygous FVL
Heterozygous factor II G20210A (Prothrombin Gene Mutation -PTGM)	Homozygous factor II G20210A
	Antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
	Antiphospholipid syndrome (APS)
	Combined heterozygous FVL and heterozygous factor II G20210A thrombophilias

It is important to consider the relative and absolute increase in risk associated with thrombophilia testing. For example, the risk of first episode of VTE in the general population is about 1/1000 per year. Heterozygosity for factor V Leiden increases this risk by ~5-fold to 5/1000 per year. Factor V Leiden and PTGM are mild risk factors for recurrent VTE (odds ratio ~1.3). Natural anticoagulant deficiencies are infrequent and usually associated w/strong family history.

* Strong and mild refer to the relative increase in the risk of recurrent VTE w/o anticoagulation.
† Presence of a thrombophilia generally should not impact decisions regarding anticoagulation type or duration, with the exception of high-risk antiphospholipid syndrome (APS, see APS guidance on opposite page).

Situations to generally avoid performing thrombophilia testing[2–5]	Situations where thrombophilia testing may be considered[2–4,6]
During the initial or primary phase of VTE treatment	Embolic strokes of unknown source in patients <50 years of age
Patients >60 years of age	VTE in rare thrombosis (e.g. cerebral vein thrombosis, splanchnic vein thrombosis) sites w/o provoking risk factors
In the setting of a provoked VTE	Unexplained recurrent unprovoked thromboses while on appropriate antithrombotic therapy
Arterial thrombosis or systemic embolism associated with a known risk factors (e.g. stroke in patients with Afib, peripheral arterial thrombosis)	When APS is suspected (e.g., concurrent autoimmune disease, pregnancy morbidity; see APS guidance on opposite page)

Common Thrombophilia Tests[7–11]

Lists are not all inclusive. Other thrombophilia tests available from different laboratories may be differentially influenced by various medical conditions or anticoagulants. Recommend discussing testing & test results w/ thrombosis experts familiar w/institutional testing procedures.

Test	Meaning if Abnormal	Potential Medical Condition Influences	Anticoagulants with Potential Influence on Results*
Functional and Clot-Based Testing			
Protein C (PC) activity (chromogenic)	Decreased PC activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes[12,13]	Warfarin†
Protein C activity (functional)	Decreased PC activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes[12,13]	Warfarin, direct thrombin inhibitors (DTIs), factor Xa (FXa) inhibitors
Protein S (PS) activity (Should be evaluated via protein S antigen)	Decreased PS activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes, surgery, combined oral contraceptives, pregnancy[12]	Warfarin†
Activated protein C (APC) resistance	Suggests FVL mutation or acquired APC resistance resulting in increased risk of thrombosis	Acute inflammation/infection/malignancy, factor or PS deficiency, pregnancy, combined oral contraceptives , LA, protein C antibodies[14]	Warfarin, heparins, DTIs, FXa inhibitors
Antithrombin (AT) activity	Decreased AT activity resulting in increased risk of thrombosis	Liver disease, malnutrition, nephrotic syndrome, acute thrombosis, L-asparaginase therapy, surgery, pregnancy, extracorporeal circulation[15,16]	UFH, FXa inhibitors
Lupus Anticoagulant (LA) (including dRVVT and LA PTT) *Antiphospholipid Syndrome Test*	Prolonged clotting time is potentially suggestive of LA	Acute thrombosis, pregnancy, infection, malignancy[3,15,17,18] *	Warfarin, heparins, fondaparinux, DTIs, FXa inhibitors
Hold anticoagulation before performing these tests (VKA 2weeks; DOACs 2 days; heparins 24hrs)[9]		* Assay dependent. False negative (eg increased protein C/S activity with DOAC) or false positive diagnoses (e.g. positive LA with DOACs, warfarin) are possible.	
† Levels may be physiologically decreased by drug, but assay is not specifically affected by presence of drug.			
Non-functional – Antibody and Genetic Testing			
Anti-Beta-2 glycoprotein antibodies *Antiphospholipid Syndrome Test*	Presence of antibodies associated with increased risk of thrombosis	Infection, malignancy[3,15,17]	None
Anti-Cardiolipin antibodies *Antiphospholipid Syndrome Test*	Presence of antibodies associated with increased risk of thrombosis	Infection, malignancy[3,15,17]	None
Factor V Leiden mutation	Genetic mutation resulting in Factor V resistance to inactivation by Protein C	None	None
Factor II G20210A mutation (Prothrombin G20210A gene mutation)	Genetic mutation resulting in increased levels of prothrombin	None	None

References: 1. Vasc Med Lond Engl. 2015;20(3):193-196. 2. Clin Appl Thromb Off J Int Acad Clin Appl Thromb. 2013;19(2):177-187. 3. Moll S. J Thromb Thrombolysis. 2015;39(3):367-378. 4. J Thromb Thrombolysis. 2016;41(1):154-164. 5. Blood. 2013;122(24):3878-3883. 6. Thromb Res. 2018;168:35-40. 7. Curr Rheumatol Rep. 2012;14(1):71-78. 8. Hematol Am Soc Hematol Educ Program. 2012;2012:465-483. 9. N Engl J Med. 2017;377(23):2298. 10. J Thromb Haemost JTH. 2018;16(2):209-219. 11. Am Coll Cardiol. 2014;64(11):1128-1139. 12. Adv Clin Exp Med Off Organ Wroclaw Med Univ. 2013;22(4):459-467. 13. J Thromb Haemost JTH. 2020;18(2):271-277. 14. J Thromb Haemost. 2019;17(9):1555-1561. 15. Hamostaseologie. 2019;39(1):49-61. 16. J Thromb Haemost. 2020;18(1):17-22. 17. Am J Hematol. 2012;87(Suppl 1):S75-S81. 18. C J Thromb Haemost JTH. 2019;17(10):1715-1732.

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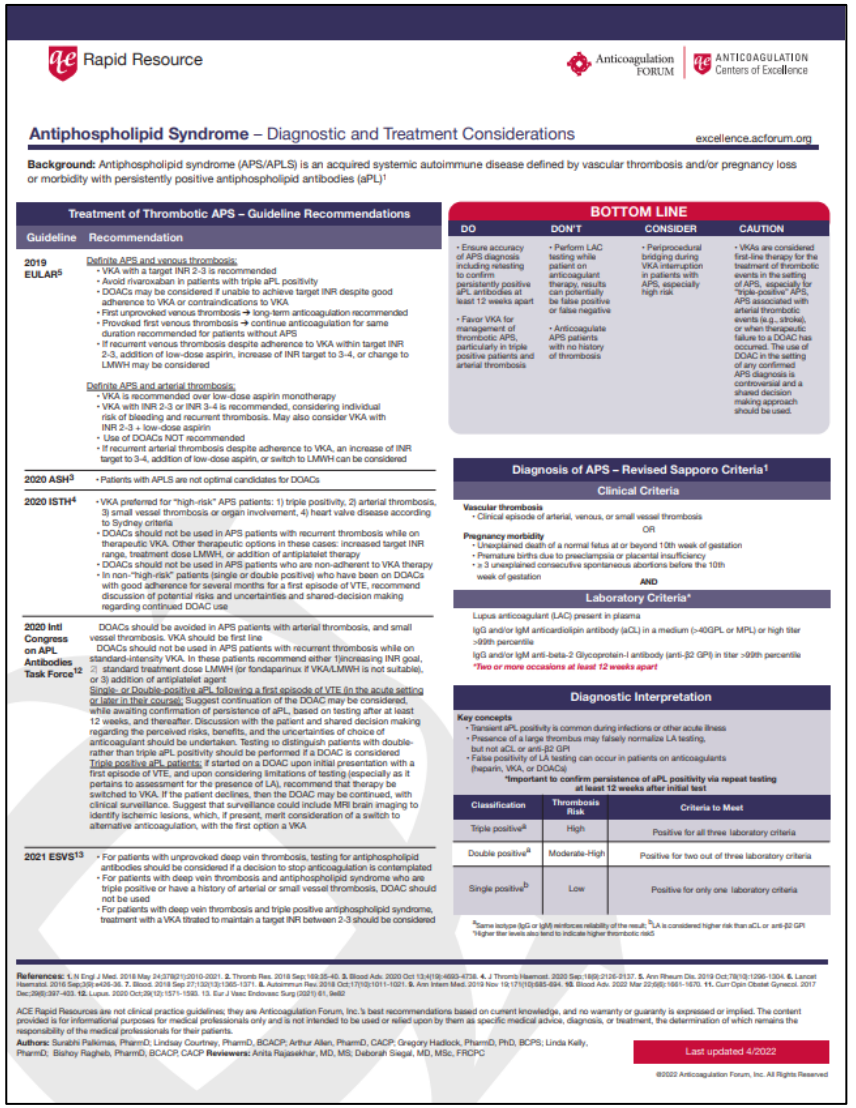

Rapid Resource

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Antiphospholipid Syndrome – Diagnostic and Treatment Considerations

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Background: Antiphospholipid syndrome (APS/APLS) is an acquired systemic autoimmune disease defined by vascular thrombosis and/or pregnancy loss or morbidity with persistently positive antiphospholipid antibodies (aPL)[1]

Treatment of Thrombotic APS – Guideline Recommendations

Guideline	Recommendation
2019 EULAR[5]	Definite APS and venous thrombosis: • VKA with a target INR 2-3 is recommended • Avoid rivaroxaban in patients with triple aPL positivity • DOACs may be considered if unable to achieve target INR despite good adherence to VKA or contraindications to VKA • First unprovoked venous thrombosis → long-term anticoagulation recommended • Provoked first venous thrombosis → continue anticoagulation for same duration recommended for patients without APS • If recurrent venous thrombosis despite adherence to VKA within target INR 2-3, addition of low-dose aspirin, increase of INR target to 3-4, or change to LMWH may be considered Definite APS and arterial thrombosis: • VKA is recommended over low-dose aspirin monotherapy • VKA with INR 2-3 or INR 3-4 is recommended, considering individual risk of bleeding and recurrent thrombosis. May also consider VKA with INR 2-3 + low-dose aspirin • Use of DOACs NOT recommended • If recurrent arterial thrombosis despite adherence to VKA, an increase of INR target to 3-4, addition of low-dose aspirin, or switch to LMWH can be considered
2020 ASH[3]	• Patients with APLS are not optimal candidates for DOACs
2020 ISTH[4]	• VKA preferred for "high-risk" APS patients: 1) triple positivity, 2) arterial thrombosis, 3) small vessel thrombosis or organ involvement, 4) heart valve disease according to Sydney criteria • DOACs should not be used in APS patients with recurrent thrombosis while on therapeutic VKA. Other therapeutic options in these cases: increased target INR range, treatment dose LMWH, or addition of antiplatelet therapy • DOACs should not be used in APS patients who are non-adherent to VKA therapy • In non-"high-risk" patients (single or double positive) who have been on DOACs with good adherence for several months for a first episode of VTE, recommend discussion of potential risks and uncertainties and shared-decision making regarding continued DOAC use
2020 Intl Congress on APL Antibodies Task Force[12]	DOACs should be avoided in APS patients with arterial thrombosis, and small vessel thrombosis. VKA should be first line DOACs should not be used in APS patients with recurrent thrombosis while on standard-intensity VKA. In these patients recommend either 1)increasing INR goal, 2) standard treatment dose LMWH (or fondaparinux if VKA/LMWH is not suitable), or 3) addition of antiplatelet agent Single- or Double-positive aPL following a first episode of VTE (in the acute setting or later in their course): Suggest continuation of the DOAC may be considered, while awaiting confirmation of persistence of aPL, based on testing after at least 12 weeks, and thereafter. Discussion with the patient and shared decision making regarding the perceived risks, benefits, and the uncertainties of choice of anticoagulant should be undertaken. Testing to distinguish patients with double- rather than triple aPL positivity should be performed if a DOAC is considered Triple positive aPL patients: if started on a DOAC upon initial presentation with a first episode of VTE, and upon considering limitations of testing (especially as it pertains to assessment for the presence of LA), recommend that therapy be switched to VKA. If the patient declines, then the DOAC may be continued, with clinical surveillance. Suggest that surveillance could include MRI brain imaging to identify ischemic lesions, which, if present, merit consideration of a switch to alternative anticoagulation, with the first option a VKA
2021 ESVS[13]	• For patients with unprovoked deep vein thrombosis, testing for antiphospholipid antibodies should be considered if a decision to stop anticoagulation is contemplated • For patients with deep vein thrombosis and antiphospholipid syndrome who are triple positive or have a history of arterial or small vessel thrombosis, DOAC should not be used • For patients with deep vein thrombosis and triple positive antiphospholipid syndrome, treatment with a VKA titrated to maintain a target INR between 2-3 should be considered

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Ensure accuracy of APS diagnosis including retesting to confirm persistently positive aPL antibodies at least 12 weeks apart • Favor VKA for management of thrombotic APS, particularly in triple positive patients and arterial thrombosis	• Perform LAC testing while patient on anticoagulant therapy, results can potentially be false positive or false negative • Anticoagulate APS patients with no history of thrombosis	• Perioprocedural bridging during VKA interruption in patients with APS, especially high risk	• VKAs are considered first-line therapy for the treatment of thrombotic events in the setting of APS, especially for "triple-positive" APS, APS associated with arterial thrombotic events (e.g., stroke), or when therapeutic failure to a DOAC has occurred. The use of DOAC in the setting of any confirmed APS diagnosis is controversial and a shared decision making approach should be used.

Diagnosis of APS – Revised Sapporo Criteria[1]

Clinical Criteria

Vascular thrombosis
• Clinical episode of arterial, venous, or small vessel thrombosis
OR
Pregnancy morbidity
• Unexplained death of a normal fetus at or beyond 10th week of gestation
• Premature births due to preeclampsia or placental insufficiency
• ≥ 3 unexplained consecutive spontaneous abortions before the 10th week of gestation
AND

Laboratory Criteria*

Lupus anticoagulant (LAC) present in plasma
IgG and/or IgM anticardiolipin antibody (aCL) in a medium (>40GPL or MPL) or high titer >99th percentile
IgG and/or IgM anti-beta-2 Glycoprotein-I antibody (anti-β2 GPI) in titer >99th percentile
**Two or more occasions at least 12 weeks apart*

Diagnostic Interpretation

Key concepts
• Transient aPL positivity is common during infections or other acute illness
• Presence of a large thrombus may falsely normalize LA testing, but not aCL or anti-β2 GPI
• False positivity of LA testing can occur in patients on anticoagulants (heparin, VKA, or DOACs)
***Important to confirm persistence of aPL positivity via repeat testing at least 12 weeks after initial test**

Classification	Thrombosis Risk	Criteria to Meet
Triple positive[a]	High	Positive for all three laboratory criteria
Double positive[a]	Moderate-High	Positive for two out of three laboratory criteria
Single positive[b]	Low	Positive for only one laboratory criteria

[a]Same isotype (IgG or IgM) reinforces reliability of the result; [b]LA is considered higher risk than aCL or anti-β2 GPI
[c]Higher titer levels also tend to indicate higher thrombotic risk5

References: 1. N Engl J Med. 2018 May 24;378(21):2010-2021. 2. Thromb Res. 2018 Sep;169:35-40. 3. Blood Adv. 2020 Oct 13;4(19):4693-4738. 4. J Thromb Haemost. 2020 Sep;18(9):2126-2137. 5. Ann Rheum Dis. 2019 Oct;78(10):1296-1304. 6. Lancet Haematol. 2016 Sep;3(9):e426-36. 7. Blood. 2018 Sep 27;132(13):1365-1371. 8. Autoimmun Rev. 2018 Oct;17(10):1011-1021. 9. Ann Intern Med. 2019 Nov 19;171(10):685-694. 10. Blood Adv. 2022 Mar 22;6(6):1661-1670. 11. Curr Opin Obstet Gynecol. 2017 Dec;29(6):397-403. 12. Lupus. 2020 Oct;29(12):1571-1593. 13. Eur J Vasc Endovasc Surg (2021) 61, 9e82

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Thrombophilia

- Thrombophilia can increase risk of venous or arterial thrombosis
- Presence of thrombophilia is only one of many elements that determine risk of thrombosis
- Need for thrombophilia testing to inform prevention or treatment decisions is controversial

J Thromb Thrombolysis. 2016;41:154-164

Prevalence and Risk of Thrombosis for Thrombophilia

Thrombophilia	Prevalence	Relative (absolute annualized) risk of Initial VTE	Relative risk of recurrent VTE
FVL (heterozygous)	2 - 7%	3.48 - 5.51 (0.05 - 0.2%)	1.1 - 1.8
FVL (homozygous)	0.06 - 0.25%	6.79 - 19.29 (0.8%)	1.8
PGM (heterozygous)	1 – 2%	2.25 - 3.48 (0.13%)	0.7 - 2.3
PGM (homozygous)	Rare	2.19 - 20.72	Uncertain
FVL & PGM (heterozygous)	0.1%	1.13 - 5.04 (0.42%)	2.7
Protein C deficiency	0.2 - 0.5%	10 (0.4 - 2.3%)	1.8
Protein S deficiency	0.1 - 0.7%	9.6 (0.7 - 3.2%)	1.0
Antithrombin deficiency	0.02%	10 – 30 (1.2 - 4.4%)	2.6
APS	2%	7	1.5 - 6.8

FVL: Factor V Leiden, PGM: Prothrombin gene mutation; APS: Antiphospholipid Syndrome

J Thromb Thrombolysis. 2016;41:154-164

Common Types of Thrombophilia

- Inherited: Genetic mutation affecting amount or function of a protein
  - Loss of function mutations: Antithrombin, Protein C & S
  - Gain of function mutations: Factor V Leiden, Prothrombin gene mutations

Mild Thrombophilia	Strong Thrombophilia
Heterozygous factor V Leiden (FVL)	Homozygous FVL
Heterozygous factor II G20210A (Prothrombin Gene Mutation –PTGM)	Homozygous factor II G20210A
	Antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
	Antiphospholipid syndrome (APS)
	Combined heterozygous FVL and heterozygous factor II G20210A

J Thromb Thrombolysis. 2016;41:154-164

Thrombophilia Testing: Patient Selection

- Patients with family history of VTE

- Patients without family history of VTE that are:
  - Young patients (<45 years)
  - Recurrent unprovoked thrombosis despite antithrombotic therapy
  - Thrombosis in multiple venous/unusual sites
  - History of warfarin induced skin necrosis
  - Arterial thrombosis
  - APS suspected

Thromb Res. 2018;169:35-40
J Thromb Thrombolysis. 2016;41:154-164

Common Thrombophilia Tests

Common Thrombophilia Tests[7–11]

Lists are not all inclusive. Other thrombophilia tests available from different laboratories may be differentially influenced by various medical conditions or anticoagulants. Recommend discussing testing & test results w/ thrombosis experts familiar w/institutional testing procedures.

Test	Meaning if Abnormal	Potential Medical Condition Influences	Anticoagulants with Potential Influence on Results*
Functional and Clot-Based Testing			
Protein C (PC) activity (chromogenic)	Decreased PC activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes[12,13]	Warfarin†
Protein C activity (functional)	Decreased PC activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes[12,13]	Warfarin, direct thrombin inhibitors (DTIs), factor Xa (FXa) inhibitors
Protein S (PS) activity (Should be evaluated via protein S antigen)	Decreased PS activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes, surgery, combined oral contraceptives, pregnancy[12]	Warfarin†
Activated protein C (APC) resistance	Suggests FVL mutation or acquired APC resistance resulting in increased risk of thrombosis	Acute inflammation/infection/malignancy, factor or PS deficiency, pregnancy, combined oral contraceptives , LA, protein C antibodies[14]	Warfarin, heparins, DTIs, FXa inhibitors
Antithrombin (AT) activity	Decreased AT activity resulting in increased risk of thrombosis	Liver disease, malnutrition, nephrotic syndrome, acute thrombosis, L-asparaginase therapy, surgery, pregnancy, extracorporeal circulation[15,16]	UFH, FXa inhibitors
Lupus Anticoagulant (LA) (including dRVVT and LA PTT) *Antiphospholipid Syndrome Test*	Prolonged clotting time is potentially suggestive of LA	Acute thrombosis, pregnancy, infection, malignancy[3,15,17,18] *	Warfarin, heparins, fondaparinux, DTIs, FXa inhibitors
Non-functional – Antibody and Genetic Testing			
Anti-Beta-2 glycoprotein antibodies *Antiphospholipid Syndrome Test*	Presence of antibodies associated with increased risk of thrombosis	Infection, malignancy[3,15,17]	None
Anti-Cardiolipin antibodies *Antiphospholipid Syndrome Test*	Presence of antibodies associated with increased risk of thrombosis	Infection, malignancy[3,15,17]	None
Factor V Leiden mutation	Genetic mutation resulting in Factor V resistance to inactivation by Protein C	None	None
Factor II G20210A mutation (Prothrombin G20210A gene mutation)	Genetic mutation resulting in increased levels of prothrombin	None	None

Hold anticoagulation before performing these tests (VKA 2weeks; DOACs 2 days; heparins 24hrs)[9]

† Levels may be physiologically decreased by drug, but assay is not specifically affected by presence of drug.

* Assay dependent. False negative (eg increased protein C/S activity with DOAC) or false positive diagnoses (e.g. positive LA with DOACs, warfarin) are possible.

Bottom Line for Thrombophilia Testing

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Have institutional protocols to limit and guide thrombophilia testing • Obtain a personal and family venous thromboembolism (VTE) history	• Routinely order thrombophilia tests • Perform tests at the time of acute VTE event (Except anti-phospholipid antibody testing in patients with a high pre-test probability of APS) • Perform functional and clot-based tests while patient is on anticoagulation • Routinely prescribe anticoagulation for patients with a positive thrombophilia test without a personal history of thrombosis	• The most common inherited thrombophilias are mild risk factors for VTE recurrence. The absence of risk factors (unprovoked) or persistent risk factors are associated with a high risk of recurrence after discontinuing anticoagulation. • Negative thrombophilia testing does not specifically indicate low VTE risk.	• When assessing ongoing anticoagulation **or** assuming management of a patient with a known thrombophilia, confirm confirmatory testing was appro-priately performed and interpreted (i.e. performed off anticoag-ulation, not at the time of acute thrombosis, no interfering medical conditions such as coagulopathy of liver disease or DIC). • Discuss with an expert if testing was performed in the setting of potential influencing anticoagulants or medical conditions.

Diagnosis of APS

- Revised Sapporo Criteria

Clinical Criteria		Laboratory Criteria*
Vascular Thrombosis • Clinical episode of arterial, venous, or small vessel thrombosis	AND	Lupus anticoagulant (LAC) present in plasma
Pregnancy Morbidity • Unexplained death of a normal fetus at or beyond 10th week of gestation • Premature births due to preeclampsia or placental insufficiency • >/= 3 unexplained consecutive spontaneous abortions before the 10th week of gestation		IgG and/or IgM anticardiolipin antibody (aCL) in a medium (>40 GPL or MPL) or higher titer >99th percentile
		IgG and/or IgM anti-beta-2 Glycoprotein-1 antibody (anti-β2 GPI) in titer >99th percentile

*Laboratory testing needs to be performed 2 or more occasions at least 12 weeks apart

N Engl J Med. 2018; 378(21):2010-2021

Diagnostic Interpretation

Classification	Thrombosis Risk	Criteria to Meet
Triple Positive	High	Positive for all three laboratory criteria
Double Positive	Medium-High	Positive for two out of three laboratory criteria
Single Positive	Low	Positive for only one laboratory criteria

Key concepts

- ✓Transient aPL positivity is common during infection or acute illness
- ✓Presence of a large thrombus may falsely normalize LAC testing, but not aCL or Anti-β2 GPI
- ✓Falsely positivity of LAC testing can occur in patients on anticoagulants

N Engl J Med. 2018; 378(21):2010-2021

Guideline Recommendation

ASH (2020)

- Patients with APLS are not optimal candidates for DOACs

ISTH (2020)

- VKA preferred for high-risk APS patients
- DOACs should not be used in APS patients with recurrent thrombosis while on VKA
- DOACs should not be used in patients who are non-adherent to VKA therapy
- In "non-high-risk" patients with SDM can consider DOAC therapy

Blood Adv. 2020;4(19):4693-4738
J Thromb Haemost. 2020;18(9):2126-2137

Guideline Recommendation

ESVS (2021)

- Triple positive APS or history of arterial thrombosis, DOACs should not be used
  - VKA with goal INR 2-3 should be considered
- Unprovoked DVT, testing for APS should be considered if a decision to stop anticoagulation is contemplated

Intl Congress on APL Antibodies Task Force (2020)

- VKA first line in APS patients with arterial and small vessel thrombosis
- DOAC should not be used in APS patients with recurrent thrombosis while on VKA therapy

Eur J Vasc Edovasc Surg. 2021;61:9e82
Lupus. 2020;29(12):1571-1593

Bottom Line for APS Management

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Ensure accuracy of APS diagnosis including retesting to confirm persistently positive aPL antibodies at least 12 weeks apart • Favor VKA for management of thrombotic APS, particularly in triple positive patients and arterial thrombosis	• Perform LAC testing while patient on anticoagulant therapy, results can potentially be false positive or false negative • Anticoagulate APS patients with no history of thrombosis	• Periprocedural bridging during VKA interruption in patients with APS, especially high risk	• VKAs are considered first-line therapy for the treatment of thrombotic events in the setting of APS, especially for "triple-positive" APS, APS associated with arterial thrombotic events (e.g., stroke), or when therapeutic failure to a DOAC has occurred. The use of DOAC in the setting of any confirmed APS diagnosis is controversial and a shared decision making approach should be used.

Questions?

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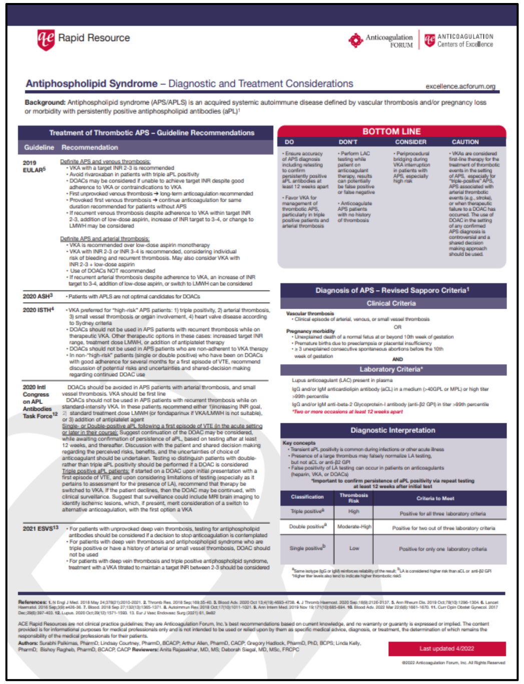

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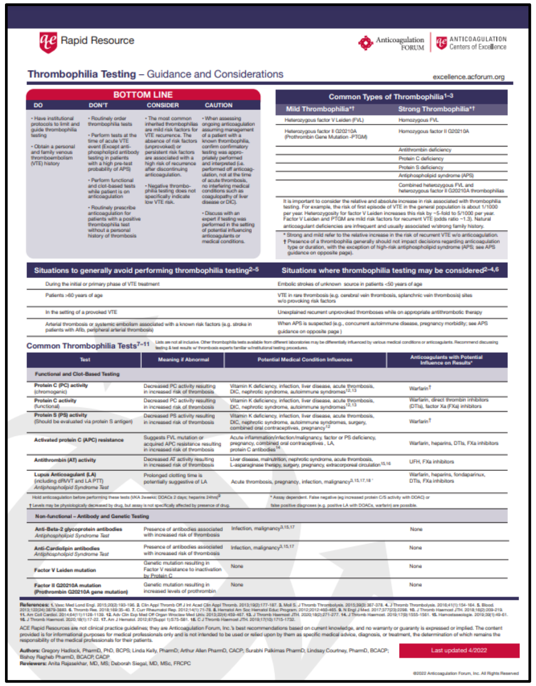

Thrombophilia Testing – Guidance and Considerations

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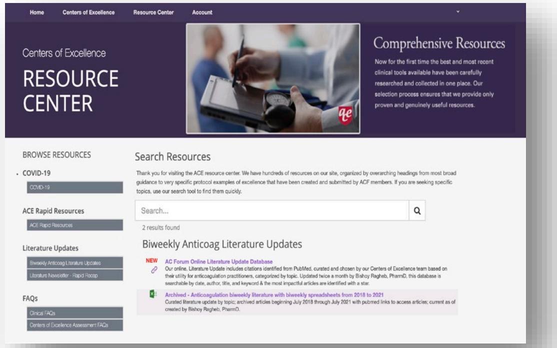

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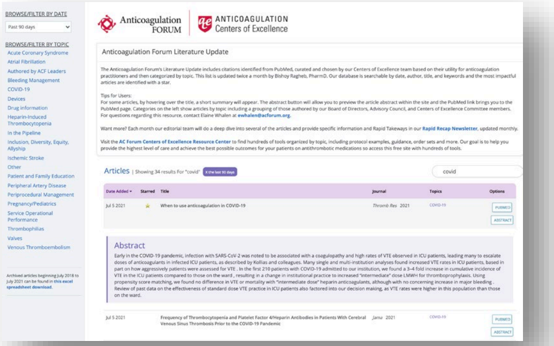

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