

Archives of Hematology and Blood Transfusion

Research Article

Comparative Safety of Weight-Based versus Fixed-Dose Anticoagulation in Antiphospholipid Syndrome

Fabry T^{1*}, Ilavsky K² and Chudik D³

¹Department of Transfusion Medicine and Blood Banking, Guadiana Institute of Hematologic Oncology, Montenegro

²Department of Coagulation Medicine, Volga Institute of Clinical Hematology, Bosnia and Herzegovina

³Department of Laboratory Hematology, Maas Institute of Myeloproliferative Disease Research, Portugal

*Address for Correspondence: Terezia Fabry, Department of Transfusion Medicine and Blood Banking, Guadiana Institute of Hematologic Oncology, Montenegro; E-mail: terezia.fabry@guadiana.edu

Received: 10 March 2022; Accepted: 14 June 2022; Published: 2 September 2022.

Citation of this article: Fabry T, Ilavsky K, Chudik D (2022) Comparative Safety of Weight-Based versus Fixed-Dose Anticoagulation in Antiphospholipid Syndrome. Arch Hematol Blood Transfus, 4(1): 01-06. DOI: [10.5281/zenodo.22818754](https://doi.org/10.5281/zenodo.22818754)

Copyright: © 2022 Terezia Fabry, et al. This is an open access article distributed under the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Antiphospholipid syndrome (APS) confers a high risk of recurrent thrombosis, and secondary prevention has relied on INR-titrated vitamin K antagonist (VKA) therapy, which implicitly absorbs body-weight variability through its monitored endpoint.

Objective: To synthesize evidence on anticoagulation intensity, direct oral anticoagulant (DOAC) performance, and weight-based versus fixed-dose strategies for long-term anticoagulation in APS.

Methods: Narrative review of randomized trials of warfarin intensity, randomized DOAC-versus-warfarin trials in thrombotic APS, a patient-level meta-analysis of DOAC failures, and weight-based dosing evidence from other thrombotic indications.

Findings: Trials show no benefit of high-intensity over moderate-intensity warfarin in standard-risk APS, while fixed-dose rivaroxaban produced an unacceptable excess of arterial thrombosis (12% versus 0%) in triple-positive patients in TRAPS, replicated in an independent trial and a meta-analysis showing roughly sixfold higher recurrence odds with DOACs in triple-positive disease.

Conclusions: Monitored, INR-titrated VKA therapy remains the safest strategy for triple-positive thrombotic APS, and extrapolation from the thrombosis literature supports weight-conscious dosing at the extremes of body weight.

Keywords: antiphospholipid syndrome; anticoagulation; warfarin; direct oral anticoagulants; thrombosis recurrence

1. Introduction

Antiphospholipid syndrome (APS) is defined by the combination of vascular thrombosis or recurrent pregnancy morbidity with persistently positive lupus anticoagulant, anticardiolipin, or anti-beta2-glycoprotein I antibodies, a construct formalized by the Sapporo criteria and refined in the 2006 Sydney revision [1] and again in the 2023 ACR/EULAR classification, which added a weighted clinical and laboratory domain structure and an explicit high-risk antibody profile [2]. Lupus anticoagulant assays are vulnerable to interference from the very anticoagulants used to treat the disease, which is why the ISTH Scientific and Standardization Committee has issued repeated technical guidance on testing patients already on warfarin or a direct oral anticoagulant (DOAC) [3]. Once the diagnosis is secure, the question that dominates long-term management is deceptively narrow: how intensely, and with what agent, should these patients be anticoagulated to prevent recurrent thrombosis without trading one vascular catastrophe for a hemorrhagic one.

That question has a dosing dimension that is easy to overlook because so much of the APS anticoagulation literature is organized around drug class (vitamin K antagonist versus DOAC) rather than dose-selection strategy. Standard warfarin management, whether targeted to an INR of 2.0-3.0 or 3.0-4.0, is inherently weight-agnostic in its endpoint: the dose is titrated to a measured anticoagulant effect regardless of body size, and heparin bridging during initiation is classically weight-based by nomogram [4]. DOACs, by contrast, are typically fixed-dose by label, with only coarse adjustment for renal function or extremes of body weight, and ISTH guidance on DOAC use in obesity flags that pharmacokinetic data above roughly 120 kg or a body mass index above 40 kg/m are sparse [5]. APS patients occupy an uncomfortable middle ground: many carry prothrombotic and cardiovascular comorbidity that correlates with higher body weight, yet the pivotal trials

that would let a clinician choose a dosing philosophy were designed to compare drug classes at fixed intensities, not to compare weight-adjusted with fixed-intensity regimens directly. This review synthesizes the anticoagulation-intensity, DOAC-failure, and weight-based dosing literature bearing on that gap, and explains why the field has, in practice, settled on a monitored, weight-informed vitamin K antagonist strategy for the highest-risk APS phenotype.

2. Classification and thrombotic risk stratification in APS

Risk within APS is not uniform, and the anticoagulation-intensity question cannot be separated from how a patient is risk-stratified at diagnosis. Triple positivity for lupus anticoagulant, anticardiolipin antibodies, and anti-beta2-glycoprotein I antibodies identifies the subgroup with the highest recurrence hazard: in a prospective cohort of 160 patients with a first thrombotic event followed for a mean of 6 years, the cumulative incidence of a new thrombotic event was 44.2% in triple-positive patients compared with a much lower rate in single- or double-positive patients, and the hazard ratio for recurrence associated with triple positivity exceeded 3 [6]. The Global Anti-Phospholipid Syndrome Score (GAPSS), derived from four independent APS cohorts, formalized this stratification into a points-based tool incorporating antibody profile, hyperlipidemia, hypertension, and antibody isotype, and higher GAPSS values tracked with both first thrombotic events and recurrence risk across derivation and validation cohorts [7]. The practical consequence is that "APS" is not a single anticoagulation-intensity problem: a single-positive, low-titer patient with a provoked venous event and a triple-positive patient with an unprovoked arterial stroke are different management problems wearing the same diagnostic label. The 14th International Congress on Antiphospholipid Antibodies task force recommended long-term, often indefinite, anticoagulation for unprovoked thrombosis with persistent high-risk

antibody profiles [8], and EULAR's 2019 recommendations echo indefinite vitamin K antagonist therapy as the default for thrombotic APS with INR targets set by risk category [9].

3. Standard-intensity vitamin K antagonist therapy

The intensity question for warfarin was addressed directly by two randomized trials that remain the foundation of current practice. Crowther and colleagues randomized 114 APS patients with prior venous thromboembolism to a target INR of 2.0-3.0 versus 3.0-4.0 and found no difference in recurrent thrombosis, with 3 recurrences among 56 patients in the moderate-intensity arm versus 6 among 58 in the high-intensity arm over a mean follow-up of about 2.7 years, while major bleeding occurred numerically more often in the high-intensity group [10]. The Italian WAPS trial reached a concordant conclusion in a population enriched for arterial as well as venous events: 109 patients were randomized to high-intensity warfarin (INR 3.1-4.5) or conventional treatment (INR 2.0-3.0 with or without low-dose aspirin), and the high-intensity strategy showed no advantage in preventing recurrent thrombosis, with comparable major bleeding between arms [11]. These findings revised an earlier, smaller retrospective signal from Khamashta and colleagues, whose 1995 cohort of 147 patients had reported recurrence far more frequent below an INR of 3.0, a result that had driven high-intensity practice for nearly a decade before the two randomized trials narrowed that inference for standard-risk venous APS [12]. The evidence-based consensus that emerged, reaffirmed in subsequent guideline synthesis, is that moderate-intensity warfarin (INR 2.0-3.0) suffices for a first venous event, while a target of 3.0-4.0, or added low-dose aspirin, is reserved for arterial thrombosis or recurrence on adequately dosed moderate-intensity therapy [13]. None of these foundational studies stratified therapy by body weight; INR titration by its nature absorbs interpatient pharmacokinetic variability, including weight, which is precisely the property that later made vitamin K

antagonists difficult to displace with fixed-dose alternatives.

Table 1: Randomized trials of warfarin intensity in antiphospholipid syndrome, showing no benefit of high-intensity targeting over moderate-intensity INR control [10,11,12].

Trial	N	INR arms compared	Recurrence / bleeding finding
[10]	114	2.0-3.0 vs 3.0-4.0	3/56 vs 6/58 recurrence; more bleeding at high intensity
[11]	109	2.0-3.0 (+/- aspirin) vs 3.1-4.5	No recurrence benefit; similar major bleeding
[12]	147 (cohort)	<3.0 vs >=3.0 (retrospective)	Higher recurrence below INR 3.0

4. Evidence against direct oral anticoagulants in triple-positive APS

The appeal of a fixed-dose DOAC strategy in APS was substantial: no INR monitoring, no dietary interaction, and a pharmacokinetic profile that had performed acceptably against warfarin in the general venous thromboembolism population, including extended secondary prevention with dabigatran in the RE-MEDY trial [14]. That appeal collapsed specifically in the highest-risk, triple-positive subgroup. The open-label TRAPS trial randomized 120 triple-positive APS patients with a history of thrombosis to rivaroxaban 20 mg daily or dose-adjusted warfarin (INR 2.0-3.0, or 3.0-4.0 for prior arterial events) and was stopped early for safety: 12% of rivaroxaban-treated patients experienced thromboembolic events, predominantly arterial, compared with none in the warfarin arm, and major bleeding occurred in 7% versus 3% [15]. Two-year follow-up after the trial's closure confirmed durability of that harm signal [16]. The RAPS trial, a mechanistic non-inferiority study in 116 anticoagulated APS patients switched to rivaroxaban versus continued warfarin, was underpowered for clinical outcomes but showed a lower endogenous thrombin potential ratio with warfarin, a biomarker signal foreshadowing the TRAPS findings [17]. The Spanish open-label trial by Ordi-Ros and colleagues randomized 190 thrombotic APS patients to rivaroxaban

or warfarin and reported recurrent thrombosis in 11.6% versus 6.3% over a mean of 3 years, again concentrated in the triple-positive, arterial-event subgroup [18]. Apixaban fared somewhat better in the smaller ASTRO-APS trial, which randomized 48 patients to apixaban 5 mg twice daily or warfarin and reported 3 thrombotic events with apixaban versus none with warfarin, directionally consistent with the rivaroxaban trials though not statistically powered [19]. An international patient-level meta-analysis pooling DOAC-treated APS cohorts found an odds ratio for recurrent thrombosis of approximately 6 in triple-positive patients on a DOAC versus vitamin K antagonist, with excess risk far smaller or absent in single- or double-positive patients [20], and a 2023 meta-analysis of randomized DOAC-versus-VKA trials pooling over 470 patients confirmed significantly higher arterial thrombosis risk with DOACs without a significant bleeding difference [21]. ISTH's 2020 guidance accordingly recommends against DOAC use in triple-positive APS with prior arterial thrombosis, allowing individualized consideration in lower-risk, single-antibody, venous-only phenotypes [22].

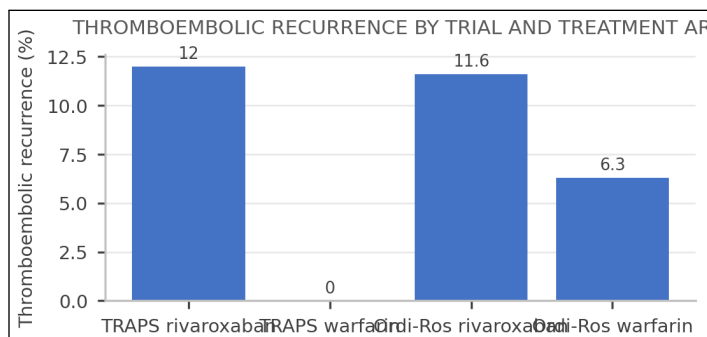


Figure 1: Thromboembolic recurrence rates by treatment arm across randomized DOAC-versus-warfarin trials in thrombotic APS: TRAPS reported 12% recurrence with rivaroxaban versus 0% with warfarin among 120 triple-positive patients [15]; the Ordi-Ros trial reported 11.6% with rivaroxaban versus 6.3% with warfarin among 190 patients [18]; ASTRO-APS reported 3 events with apixaban versus 0 with warfarin among 48 patients [19]; the pooled patient-level meta-analysis found an odds ratio near 6 for recurrence on a DOAC versus warfarin specifically in triple-positive patients [20].

5. Weight-based dosing rationale and evidence from other thrombotic indications

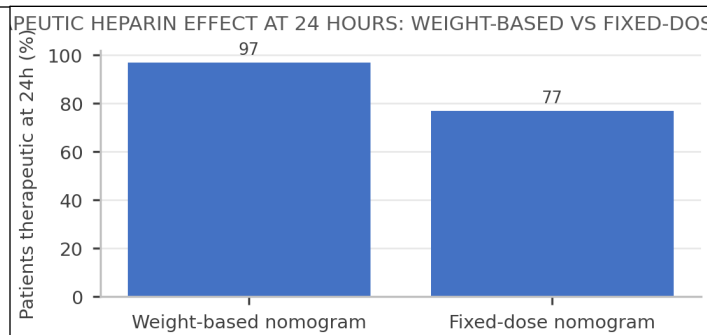


Figure 2: Proportion of 115 patients reaching a therapeutic activated partial thromboplastin time within 24 hours under a weight-based heparin nomogram (97%) versus a fixed-dose 'standard care' nomogram (77%), without an increase in major bleeding under the weight-based protocol [4].

Because no APS-specific randomized trial has directly compared weight-based against fixed-dose anticoagulation, the rationale for a weight-informed strategy is necessarily extrapolated from the broader thrombosis literature, where the principle is well established. The original weight-based unfractionated heparin nomogram, validated by Raschke and colleagues in 115 patients, produced a therapeutic activated partial thromboplastin time within 24 hours in 97% of patients compared with 77% under a fixed-dose "standard care" nomogram, without an increase in major bleeding [4], a finding that has anchored initial anticoagulation dosing broadly, including bridging therapy at warfarin initiation in APS. Warfarin loading itself interacts with patient size and sensitivity: a randomized comparison of 5 mg versus 10 mg loading doses in 98 patients found the lower, more conservative loading dose achieved a therapeutic INR with fewer supratherapeutic excursions, reinforcing that fixed initiation doses perform unevenly across a heterogeneous population and that titration, not a flat starting dose, ultimately controls exposure [23]. The CHEST antithrombotic therapy guideline frames vitamin K antagonist dosing as an INR-titrated, and therefore implicitly weight-adjusted, process, while flagging that DOAC dosing in obese patients rests on limited pharmacokinetic data from trials that enrolled few patients above 120 kg [24]. ISTH guidance on DOAC use in obesity is the most direct statement of the concern: trough

DOAC concentrations trend lower with increasing body weight, and the committee recommended against standard-dose DOAC use above 120 kg or a body mass index above 40 kg/m², favoring monitored vitamin K antagonist therapy in that subgroup [5]. APS patients, who frequently carry metabolic and cardiovascular comorbidity correlating with higher body weight, sit inside the population for which that caution was written, even though no APS-specific DOAC trial reported outcomes stratified by weight, leaving this an inference rather than a directly demonstrated APS finding.

6. Bleeding risk and monitoring practicalities

A weight-informed, INR-titrated vitamin K antagonist strategy carries its own costs, weighed against the thrombotic recurrence signal that drives DOAC caution. Major bleeding rates across the moderate- and high-intensity warfarin trials in APS ran roughly 3-10% depending on intensity and follow-up duration [10,11], and the burden of INR monitoring, dietary vitamin K interaction, and dose instability is a real quality-of-life cost not captured by thrombosis and bleeding endpoints alone. Garcia and Erkan's clinical review frames the treatment decision as exactly this tradeoff: DOACs offer simplicity at the price of unacceptable arterial thrombosis risk in triple-positive patients, whereas vitamin K antagonists offer proven efficacy at the price of monitoring burden and a bleeding rate that rises with intensity [25]. The Cochrane systematic review of antithrombotic strategies for secondary prevention in APS concluded that moderate-intensity warfarin remains the best-supported option for standard-risk thrombotic APS, that high-intensity warfarin or added antiplatelet therapy is not strongly supported outside arterial or recurrent disease, and that DOAC evidence was insufficient, and in the triple-positive subgroup unfavorable, to recommend routine substitution [26]. Arachchillage and Laffan's review emphasizes that bleeding risk interacts with thrombocytopenia, which affects a meaningful minority of APS patients and complicates dosing decisions

independent of body weight [27]. Catastrophic APS, a rare but rapidly fatal multi-organ thrombotic crisis, sits outside routine dosing-strategy comparison and is managed with combined anticoagulation, corticosteroids, and plasma exchange or immunosuppression under dedicated guidelines [28]. A practical caveat relevant to weight-based reasoning: DOAC-based lupus anticoagulant testing is itself unreliable, so a patient switched to a DOAC for convenience may become undiagnosable on repeat antibody testing, a laboratory-interference problem unrelated to dose [3].

Table 2: Approximate major bleeding rates and monitoring burden by anticoagulation strategy in thrombotic APS, synthesized from randomized and cohort evidence [10,11,15,26].			
Strategy	Major bleeding	Monitoring burden	Recurrence risk in triple-positive APS
Moderate-intensity warfarin (INR 2-3)	~3-6%	Frequent INR checks	Low with adherence
High-intensity warfarin (INR 3-4.5)	~6-10%	Frequent INR checks	Not lower than moderate intensity
Fixed-dose rivaroxaban	~3-7%	None	Unacceptably high (12%) [15]

7. Conclusion

The anticoagulation-intensity and DOAC-failure literature in APS is large and increasingly consistent, but it was not designed to answer a weight-based-versus-fixed-dose question directly, and this review has treated that limitation as a finding rather than papering over it. What the evidence does establish is that INR-titrated vitamin K antagonist therapy, which absorbs weight and other pharmacokinetic variability through its monitored endpoint, remains the standard of care for triple-positive thrombotic APS after two large trials showed rivaroxaban's fixed-dose strategy produced a clinically unacceptable excess of arterial events [15,18] and a patient-level meta-analysis confirmed that excess concentrates specifically in the highest-risk antibody profile [20]. The parallel evidence from weight-based heparin dosing [4], warfarin loading-dose comparisons [23], and ISTH obesity

guidance for DOACs [5] supports extrapolating a weight-conscious approach even without an APS-specific randomized comparison, particularly at the upper extreme of body weight where fixed-dose DOAC exposure is least well characterized. For lower-risk, single- or double-positive, venous-only APS, the incremental value of weight-based reasoning is smaller, and standard moderate-intensity, INR-titrated warfarin without additional adjustment remains adequate under current guidelines [9,26]. Trials that explicitly stratify DOAC and vitamin K antagonist outcomes by body weight, rather than treating dosing strategy and drug class as inseparable, would close a genuine gap in an otherwise mature literature.

8. References

1. Miyakis, S., Lockshin, M.D., Atsumi, T., Branch, D.W., Brey, R.L., Cervera, R., et al. (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *Journal of Thrombosis and Haemostasis*, 4(2): 295-306. DOI: [10.1111/j.1538-7836.2006.01753.x](https://doi.org/10.1111/j.1538-7836.2006.01753.x)
2. Barbhaiya, M., Zuily, S., Naden, R., Hendry, A., Manneville, F., Amigo, M.C., et al. (2023) 2023 ACR/EULAR antiphospholipid syndrome classification criteria. *Arthritis & Rheumatology*, 75(10): 1687-1702. DOI: [10.1002/art.42624](https://doi.org/10.1002/art.42624)
3. Devreese, K.M.J., Ortel, T.L., Pengo, V., de Laat, B. (2020) Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*, 18(11): 2828-2839. DOI: [10.1111/jth.13976](https://doi.org/10.1111/jth.13976)
4. Raschke, R.A., Reilly, B.M., Guidry, J.R., Fontana, J.R., Srinivas, S. (1993) The weight-based heparin dosing nomogram compared with a "standard care" nomogram. *Annals of Internal Medicine*, 119(9): 874-881. DOI: [10.7326/0003-4819-119-9-199311010-00002](https://doi.org/10.7326/0003-4819-119-9-199311010-00002)
5. Martin, K.A., Beyer-Westendorf, J., Davidson, B.L., Huisman, M.V., Sandset, P.M., Moll, S. (2016) Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: guidance from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*, 14(6): 1308-1313. DOI: [10.1111/jth.13323](https://doi.org/10.1111/jth.13323)
6. Pengo, V., Ruffatti, A., Legnani, C., Testa, S., Fierro, T., Marongiu, F., et al. (2010) Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *Journal of Thrombosis and Haemostasis*, 8(2): 237-242. DOI: [10.1111/j.1538-7836.2009.03674.x](https://doi.org/10.1111/j.1538-7836.2009.03674.x)
7. Sciascia, S., Sanna, G., Murru, V., Roccatello, D., Khamashta, M.A., Bertolaccini, M.L. (2013) GAPSS: the Global Anti-Phospholipid Syndrome Score. *Rheumatology*, 52(8): 1397-1403. DOI: [10.1093/rheumatology/kes388](https://doi.org/10.1093/rheumatology/kes388)
8. Erkan, D., Aguiar, C.L., Andrade, D., Cohen, H., Cuadrado, M.J., Danowski, A., et al. (2014) 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmunity Reviews*, 13(6): 685-696. DOI: [10.1016/j.autrev.2014.01.053](https://doi.org/10.1016/j.autrev.2014.01.053)
9. Tektonidou, M.G., Andreoli, L., Limper, M., Amoura, Z., Cervera, R., Costedoat-Chalumeau, N., et al. (2019) EULAR recommendations for the management of antiphospholipid syndrome in adults. *Annals of the Rheumatic Diseases*, 78(10): 1296-1304. DOI: [10.1136/annrheumdis-2019-215213](https://doi.org/10.1136/annrheumdis-2019-215213)
10. Crowther, M.A., Ginsberg, J.S., Julian, J., Denburg, J., Hirsh, J., Douketis, J., et al. (2003) A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *New England Journal of Medicine*, 349(12): 1133-1138. DOI: [10.1056/NEJMoa035241](https://doi.org/10.1056/NEJMoa035241)
11. Finazzi, G., Marchioli, R., Brancaccio, V., Schinco, P., Wisloff, F., Musial, J., et al. (2005) A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS).

- Journal of Thrombosis and Haemostasis, 3(5): 848-853. DOI: [10.1111/j.1538-7836.2005.01340.x](https://doi.org/10.1111/j.1538-7836.2005.01340.x)
12. Khamashta, M.A., Cuadrado, M.J., Mujic, F., Taub, N.A., Hunt, B.J., Hughes, G.R. (1995) The management of thrombosis in the antiphospholipid-antibody syndrome. New England Journal of Medicine, 332(15): 993-997. DOI: [10.1056/NEJM199504133321504](https://doi.org/10.1056/NEJM199504133321504)
13. Ruiz-Irastorza, G., Cuadrado, M.J., Ruiz-Arruza, I., Brey, R., Crowther, M., Derksen, R., et al. (2011) Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients. Lupus, 20(2): 206-218. DOI: [10.1177/0961203310395803](https://doi.org/10.1177/0961203310395803)
14. Schulman, S., Kearon, C., Kakkar, A.K., Schellong, S., Eriksson, H., Baanstra, D., et al. (2015) Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. New England Journal of Medicine, 368(8): 709-718. DOI: [10.1056/NEJMoa1113697](https://doi.org/10.1056/NEJMoa1113697)
15. Pengo, V., Denas, G., Zoppellaro, G., Jose, S.P., Hoxha, A., Ruffatti, A., et al. (2018) Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood, 132(13): 1365-1371. DOI: [10.1182/blood-2018-04-848333](https://doi.org/10.1182/blood-2018-04-848333)
16. Pengo, V., Hoxha, A., Andreoli, L., Tincani, A., Silvestri, E., Prisco, D., et al. (2021) Trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS): Two-year outcomes after the study closure. Journal of Thrombosis and Haemostasis, 19(2): 531-535. DOI: [10.1111/jth.15158](https://doi.org/10.1111/jth.15158)
17. Cohen, H., Hunt, B.J., Efthymiou, M., Arachchillage, D.R., Mackie, I.J., Clawson, S., et al. (2016) Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematology, 3(9): e426-e436. DOI: [10.1016/S2352-3026\(16\)30079-5](https://doi.org/10.1016/S2352-3026(16)30079-5)
18. Ordi-Ros, J., Saez-Comet, L., Perez-Conesa, M., Vidal, X., Riera-Mestre, A., Castro-Salomo, A., et al. (2019) Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. Annals of Internal Medicine, 171(10): 685-694. DOI: [10.7326/M19-0291](https://doi.org/10.7326/M19-0291)
19. Woller, S.C., Stevens, S.M., Kaplan, D.A., Wang, T.F., Branch, D.W., Groat, D., et al. (2022) Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. Blood Advances, 6(6): 1661-1670. DOI: [10.1182/bloodadvances.2021005808](https://doi.org/10.1182/bloodadvances.2021005808)
20. Dufrost, V., Risse, J., Reshetnyak, T., Satybaldyeva, M., Du, Y., Yan, X.X., et al. (2018) Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis. Autoimmunity Reviews, 17(10): 1011-1021. DOI: [10.1016/j.autrev.2018.04.009](https://doi.org/10.1016/j.autrev.2018.04.009)
21. Khairani, C.D., Bejjani, A., Piazza, G., Jimenez, D., Monreal, M., Chatterjee, S., et al. (2023) Direct oral anticoagulants vs vitamin K antagonists in patients with antiphospholipid syndromes. Journal of the American College of Cardiology, 81(1): 16-30. DOI: [10.1016/j.jacc.2022.10.008](https://doi.org/10.1016/j.jacc.2022.10.008)
22. Zuily, S., Cohen, H., Isenberg, D., Woller, S.C., Crowther, M., Dufrost, V., et al. (2020) Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: guidance from the Scientific and Standardization Committee of the ISTH. Journal of Thrombosis and Haemostasis, 18(9): 2126-2137. DOI: [10.1111/jth.14935](https://doi.org/10.1111/jth.14935)
23. Crowther, M.A., Ginsberg, J.B., Kearon, C., Harrison, L., Johnson, J., Massicotte, M.P., et al. (1999) A randomized trial comparing 5-mg and 10-mg warfarin loading doses. Archives of Internal Medicine, 159(1): 46-48. DOI: [10.1001/archinte.159.1.46](https://doi.org/10.1001/archinte.159.1.46)
24. Kearon, C., Akl, E.A., Ornelas, J., Blaivas, A., Jimenez, D., Bounameaux, H., et al. (2016) Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest, 149(2): 315-352. DOI: [10.1016/j.chest.2015.11.026](https://doi.org/10.1016/j.chest.2015.11.026)

25. Garcia, D., Erkan, D. (2018) Diagnosis and management of the antiphospholipid syndrome. New England Journal of Medicine, 378(21): 2010-2021. DOI: [10.1056/NEJMra1705454](https://doi.org/10.1056/NEJMra1705454)
26. Bala, M.M., Celinska-Lowenhoff, M., Szot, W., Padjas, A., Kaczmarczyk, M., Swierz, M.J., et al. (2020) Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome. Cochrane Database of Systematic Reviews, 10: CD012169. DOI: [10.1002/14651858.CD012169.pub3](https://doi.org/10.1002/14651858.CD012169.pub3)
27. Arachchillage, D.R.J., Laffan, M. (2017) Pathogenesis and management of antiphospholipid syndrome. British Journal of Haematology, 178(2): 181-195. DOI: [10.1111/bjh.14632](https://doi.org/10.1111/bjh.14632)
28. Legault, K., Schunemann, H., Hillis, C., Yeung, C., Akl, E.A., Carrier, M., et al. (2018) McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. Journal of Thrombosis and Haemostasis, 16(8): 1656-1664. DOI: [10.1111/jth.14192](https://doi.org/10.1111/jth.14192)