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## Review article

# Intensity of anticoagulation in the treatment of thrombosis in the antiphospholipid syndrome: a meta-analysis



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## ABSTRACT

**Introduction:** Discussion about the intensity of warfarin in patients with antiphospholipid syndrome (APS) remains present in our days.

**Objectives:** To evaluate which intensity of anticoagulation with warfarin is associated with a greater reduction of thromboembolic events in the treatment of patients with APS, as well as assess the risk of bleeding in the different treatment modalities.

**Methodology:** A systematic review of the literature was carried out with search from electronic databases: PubMed, LILACS and SciELO, with the use of the key-words: *treatment, warfarin, antiphospholipid syndrome, antiphospholipid antibody syndrome* and their respective translations into Portuguese, in different combinations. In addition, a meta-analysis with the aid of Review Manager 5.2 software by Cochrane was performed.

**Results:** Only two articles met the inclusion criteria for this study. Regarding the main outcome assessed in this study, the two studies showed similar values, indicating higher frequency of thrombotic events in high-intensity groups. The comparative analysis of the randomized clinical trial evaluated showed an increased thrombotic risk for those patients who received intervention with high-intensity warfarin. Another finding of the meta-analysis was the higher incidence of minor bleeding, also in the experimental group, that received warfarin keeping International Normalized Ratio (INR) > 3.

**Conclusion:** In individuals with APS and prevalence of venous events, the use of moderate intensity (MI) anticoagulation (INR: 2-3) is the most suitable. However, this evidence cannot yet be extended to patients with arterial events, due to the limited representation of this sample of subjects in the two clinical trials included in this meta-analysis.

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## Intensidade da anticoagulação no tratamento da trombose na síndrome antifosfolípide: meta-análise

### R E S U M O

#### Palavras-chave:

Síndrome antifosfolípide  
Trombose  
Hemorragia  
Varfarina

**Introdução:** a discussão sobre a intensidade de varfarina em pacientes com síndrome antifosfolípide (SAF) permanece presente nos dias atuais.

**Objetivos:** avaliar qual intensidade de anticoagulação com varfarina está associada com maior redução de eventos tromboembólicos no tratamento de pacientes com SAF, assim como avaliar o risco de hemorragia nas diferentes modalidades de tratamento.

**Metodologia:** foi realizada uma revisão sistemática da literatura a partir de busca nas bases de dados eletrônicas: PubMed, LILACS e SciELO, sendo utilizadas as palavras-chave: *treatment, warfarin, antiphospholipid syndrome, antiphospholipid antibody syndrome* e suas respectivas traduções para o português, em diferentes combinações. Também foi realizada uma meta-análise com auxílio do programa Review Manager 5.2 da Cochrane.

**Resultados:** apenas dois artigos preencheram os critérios para inclusão neste estudo. Em relação ao principal desfecho avaliado neste trabalho, os dois estudos apresentaram valores similares, demonstrando maior frequência de eventos trombóticos nos grupos de alta intensidade. A análise comparativa dos ensaios clínicos randomizados avaliados demonstrou um risco trombótico aumentado para aqueles pacientes que receberam intervenção com varfarina em alta intensidade. Outro achado da meta-análise foi a maior ocorrência de hemorragia menor também no grupo experimental, que recebeu varfarina mantendo Razão Normalizada Internacional (RNI) > 3.

**Conclusão:** nos indivíduos com SAF e predominância de eventos venosos, o uso de anticoagulação em moderada intensidade (MI) (RNI: 2-3) está mais indicado. Por outro lado, essa evidência ainda não pode ser estendida aos pacientes com eventos arteriais, pela limitada representação dessa amostra de sujeitos nos dois estudos clínicos incluídos nesta meta-análise.

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## Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune condition consisting of thromboembolic and/or obstetric events in the presence of circulating antiphospholipid antibodies (aPLs) in plasma (anticardiolipin antibodies [aCL], lupus anticoagulant [LAC] and anti- $\beta$ 2 glycoprotein I [anti- $\beta$ 2GPI]).<sup>1,2</sup>

Thrombosis, both venous and arterial, is the most common clinical manifestation and the one that causes more morbidity in APS.<sup>3</sup> Venous thromboembolism is present in about 55% of these patients<sup>4</sup>, mainly characterized by deep vein thrombosis (DVT) and pulmonary embolism (PE). The most common arterial thrombotic manifestations are cerebrovascular accident (CVA) and transient ischemic attack (TIA), affecting approximately 50% of patients with APS.<sup>1,4,5</sup>

The treatment of APS that is currently applied includes: (1) antiplatelet agents (aspirin or clopidogrel); (2) low molecular weight heparin and (3) warfarin,<sup>6</sup> thus not differing from the treatment offered to the general population presenting thrombotic event.<sup>7</sup>

In the management of patients on anticoagulant medication, a strict monitoring is essential in order to reach therapeutic doses and do not cause adverse effects.<sup>8</sup> An INR between 2 and 3 presented by patients on warfarin reflects anticoagulant treatment of moderate intensity (MI), which is the most used and recommended in the scientific literature.<sup>9</sup> However, an INR > 3, which represents high-intensity

treatment (HI), is indicated by some previous work as the best option in some cases, in secondary prophylaxis of thrombosis in APS.<sup>7,10-12</sup> Most of these studies is partially based on retrospective cohort suggesting increased risk of recurrent thrombosis in patients on MI warfarin therapy as compared to treatment of HI.<sup>13-19</sup> Therefore, the discussion about the intensity of warfarin for secondary prophylaxis of thrombosis in patients with APS remains present nowadays.

Another controversial issue, when articles comparing the two intensities of warfarin (MI versus HI) in the treatment of patients with presence of aPLs are analyzed, is the occurrence of bleeding, one of the most dreaded complications of anticoagulant therapy that has a frequency of 2%-3% per year (major bleeding), similar to that of patients without APS also undergoing anticoagulation.<sup>20</sup> There is a strong correlation between the intensity of anticoagulation and the incidence of bleeding events. In fact, Levine et al.<sup>21</sup> say that we already have good evidence that the treatment with vitamin K antagonists (eg. Warfarin) with INR between 2-3 is associated with lower rates of bleeding when compared to treatment of major intensity (INR > 3). Thus, when evaluating the reduction of thrombotic events with anticoagulant treatment, the associated risk of bleeding complications should also be considered.<sup>21</sup>

Thus, the mode of use of warfarin in clinical practice is still in debate today, particularly among rheumatologists, hematologists and clinicians who deal with the prevention of recurrent thrombosis in patients with APS. Standardization in this direction would help in the proper management

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