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Review article

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

Felipe Freire da Silva[a], *Jozélio Freire de Carvalho*[b],*

[a] *Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil*
[b] *Centro Médico do Hospital Aliança, Salvador, BA, Brazil*

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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.

* Corresponding author.
  E-mail: jotafc@gmail.com (J.F.d. Carvalho).

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 eletrônicos: 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 ensaio 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.

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-β2 glycoprotein I [anti-β2GPI]).[1,2]

Thrombosis, both venous and arterial, is the most common clinical manifestation and the one that causes more morbidity in APS.[3] Venous thromboembolism is present in about 55% of these patients[4], 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.[1,4,5]

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

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.[8] 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.[9] 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.[7,10–12] 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.[13–19] 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.[20] There is a strong correlation between the intensity of anticoagulation and the incidence of bleeding events. In fact, Levine et al.[21] 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.[21]

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

of these individuals, reducing rates of morbidity and mortality, mainly represented by the frequency of thrombotic events and complications, such as bleeding.

Therefore, the aim of this study was to evaluate which intensity of anticoagulation with warfarin (conventional/MI vs. HI) is associated with greater reduction of thromboembolic events in the treatment of patients with APS. As a secondary endpoint, the risk of bleeding according to the different intensities of anticoagulation will be assessed.

Methodology

Study design

Systematic review of literature and meta-analysis.

Search strategy

A search was performed in electronic databases: PubMed, LILACS and SciELO, covering the period from 1983 (when APS was described) to April 2013. The following key-words were used: treatment, warfarin (Wisconsin Alumni Research Foundation), antiphospholipid syndrome, antiphospholipid antibody syndrome and their respective translations into Portuguese, in different combinations. The references of all selected articles were also evaluated in search for work that was not identified in the initial search. There were no language restrictions.

Inclusion and exclusion criteria

Scientific papers that have the design of a randomized clinical trial (RCT) were selected to assess the use of warfarin for secondary prophylaxis of thrombosis in APS in patients older than 18 years. Any other study type was excluded from this review, as well as subgroup analyzes of randomized clinical trials.

The studies had to: (1) present interventions with warfarin carried out in accordance with the conventional treatment (INR: 2-3) and with high-intensity treatment (INR: 3.1 to 4.5); (2) have each therapy compared with placebo/control group or compared to each other (conventional/MI vs. HI); (3) assess as primary endpoint the occurrence of recurrent thrombotic events and bleeding, and (4) classify bleeding as total, major and minor.

Patients selected for the studies participating in this review should also meet Sapporo[22] and/or Sydney criteria[23] for the diagnosis of APS. The former include laboratory determinations of anticardiolipin of immunoglobulin G (IgG) and/or M (IgM) subtypes, and LAC in patients with arterial/venous thrombosis or episode of fetal loss. Sydney criteria require at least one clinical and one laboratory criterion (involving the presence of anti-β2-GPI IgG and/or IgM subtypes).

Data selection

The two authors of this article conducted a search individually and decided on consensus (according to predetermined methodology) for the selection of items participating in this review.
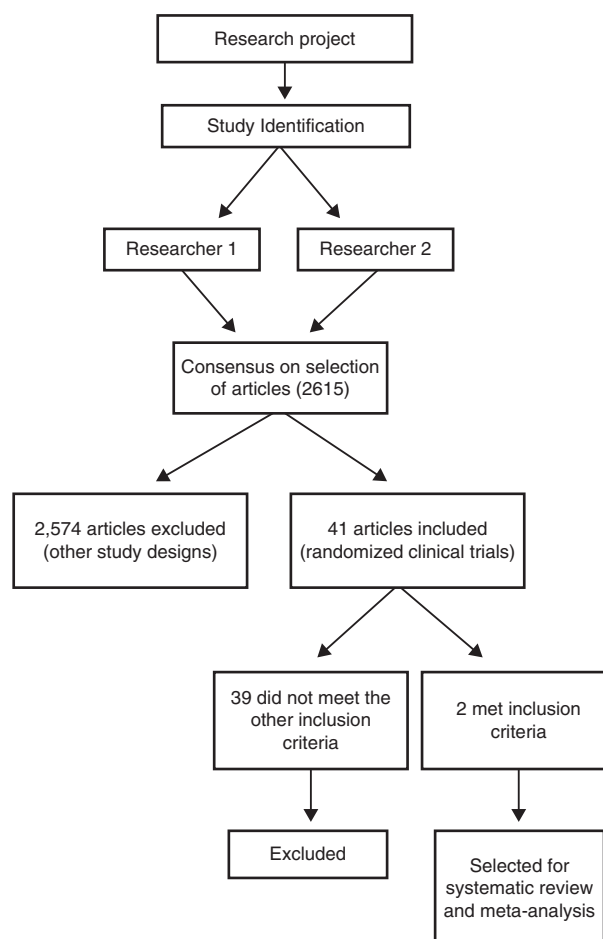

Figure 1 – Flowchart of methodology adopted in the selection of studies included in this review.

Fig. 1 summarizes the methodology followed in this systematic review and meta-analysis for the selection of studies.

Studies qualitative evaluation

The scientific papers selected were also subjected to qualitative evaluation through the application of Jadad scale.[24] Studies that had grade 3 or greater on the Jadad scale were characterized as of good quality. In order to strengthen the assessment of the methodological quality of studies to be included in the review, the scale of Downs & Black was also applied.[25] This method consists of a questionnaire containing 27 items. It evaluates: information, external validity, internal validity - bias, confounding (selection bias) and study power. For each question, the article may receive a score of 0 or 1, with the exception of question 5, which can generate 2 points. Each item can get a maximum of 28 points.

Statistics analysis

For the analysis of dichotomous endpoints some statistical methods are used by the meta-analysis through the Review Manager 5.2 software, by Cochrane.[26] The statistical method

Table 1 – Characteristics of studies evaluating the use of warfarin for secondary prophylaxis of thrombosis in patients with APS, from INR of moderate and high intensity.

Author; year	Type of study	Jadad Scale	Downs & Black Scale	N	Length of follow-up (years)	Age (years)	Female gender
Crowther et al., 2003[30]	Randomized, double blind, multicenter clinical trial	5	21	MI: 58 HI: 56	MI: 2,7 HI: 2,6	MI: 41 (21-81) HI: 43 (20-80)	MI: 41 (70.7%) HI: 27 (48.2%)
Finazzi et al., 2005[31]	Randomized, multicenter clinical trial	3	21	MI: 55 HI: 54	MI: 3,3 HI: 3,5	MI: 41 ± 12.3 HI: 41.1 ± 12.1	MI: 35 (63.6%) HI: 33 (61.1%)

HI, high intensity; MI, moderate intensity; N, number of participants; INR, international normalized ratio; APS, antiphospholipid syndrome.

used was the classical Mantel-Haenszel.[27–29] The fixed-effect model was chosen as analysis model, and the risk ratio as a measure of effect. A p-value of less than or equal to 0.05 was considered as statistically significant, with the adoption of a confidence interval (CI) of 95%.

Results

Two articles met the inclusion criteria for this study. Both are randomized trials that addressed the intensity of warfarin used in the treatment of patients with APS and were published in sequence in the years 2003 and 2005.[30,31]

Both studies, by Crowther et al.[30] and Finazzi et al.,[31] included in this analysis, scored 21 on Downs & Black scale,[25] corresponding to more than 70% of the questions, therefore suggesting studies of good methodological quality. Furthermore, those selected clinical trials had grade 3 or greater on Jadad scale,[24] also classifying the included work as of good quality.

The main characteristics of the studies included in this review, including its methodological evaluations, number of participants, and demographic data are summarized on Table 1.

Although the beginning of data collection was almost simultaneous, the follow-up time was slightly higher in the European study (Finazzi),[31] being held for 3.5 years in the group of HI and 3.3 years for the group with conventional treatment. The Canadian study (Crowther)[30] presented 2.7 and 2.6 years of follow-up, respectively, for groups of MI and HI.

The studies showed a similar number of participants (Crowther et al.[30] = 114; Finazzi et al.[31] = 109), that were properly randomized into two groups: those who received HI warfarin therapy (with an INR of 3-4.5 for Finazzi et al.[31] and of 3.1-4 for Crowther et al.[30]) and those who would be in the MI group with an INR between 2-3. However, the clinical trial by Finazzi et al.[31] was just blind on outcomes evaluation, as opposed to Crowther et al.,[30] which was double-blinded, decreasing potential biases considerably.

Both studies also showed as limitation the premature discontinuation of clinical care when the HI group had significantly higher rates of thrombotic events compared to the control group.

The RCT by Crowther et al.[30] recruited their patients from tertiary care clinics of rheumatology and thromboembolism and had as one of its inclusion criteria patients with positivity

for aPLs (LAC and/or aCL) and confirmed history of arterial and/or venous thrombosis. On the other hand, the RCT by Finazzi et al.[31] selected their patients from 26 centers in four European countries and Argentina. In line with the Canadian study, their inclusion criteria were similar.

Regarding the characteristics of the population evaluated in the studies included in this review, the average age was similar (Crowther et al.[30] = 42 years; Finazzi et al.[31] = 40,5 years). However, despite the similar percentage of women in the Canadian study[30] there is a major disparity among randomized groups (MI: 71% of women; HI: 48% of women). None of the studies provided information about the patients' color, but probably the majority is certainly white, due to the places where the scientific work was carried out.

When evaluating the study by Crowther et al.,[30] something that called the attention was a large percentage of patients who left the study.[31] There was only 8.2% of this type of loss to follow-up. However, there were no deaths in the first study, except for the European RCT,[31] which reported five deaths.

Analysis of prothrombin time, from INR, to control treatment, was observed in both studies, which showed similar mean values (Crowther et al.[30] = 3.3 HI and 2.3 MI; Finazzi et al.[31] = 3.2 HI and 2.5 MI).

Regarding the main endpoint assessed in this study, the two studies showed similar values, indicating higher frequency of thrombotic events in HI groups (Crowther et al.[30] = 14.2% AI *vs.* 3.6% MI; Finazzi et al.[31] = 11.1% HI *vs.* 5.5% MI).

As a secondary endpoint observed in anticoagulant therapy, the frequency of bleeding was evaluated. Finazzi et al.[31] defined major bleeding as one that required transfusion or surgery, fatal, retroperitoneal or intracranial hemorrhage. All other types of bleeding were classified as minor hemorrhage. Hemorrhage, in total, appeared in 25% of HI vs. 19% of MI in the Canadian study,[30] and in 27.8% of HI *vs.* 14.6% of MI in the European study.[31] The major hemorrhagic event was also assessed separately, being present in 5.3% of HI vs. 6.8% of MI (Crowther et al.[30]) and in 3.7% of HI *vs.* 5.5% of MI (Finazzi et al.[31]). Finally, the presence of minor hemorrhage in the European study[31] was higher in the HI group - 27.8% of HI vs. 10.9% of MI - and was not separately evaluated in the Canadian work.[30]

Table 2 summarizes the main endpoints evaluated in the studies involved in this systematic review.

The comparative analysis of RCTs evaluated, performed in this study, demonstrated an increased thrombotic risk for

Table 2 – Main outcomes evaluated in the studies selected for this review.

Author; year	Thrombotic Event	HR (95% IC)	Minor Hemorrhage	HR (95% CI)	Major Hemorrhage	HR (95% CI)	Total of bleeding	HR (95% CI)	death	HR (95% CI)
Crowther et al., 2003[30]	MI: 2/58 (3.4%) HI: 8/56 (14,2%)	3.1 (0.6-15)	MI: NA HI: NA	NA	MI: 4/58 (6.8%) HI: 3/56 (5.3%)	1 (0.2-4.8)	MI: 11/58 (18.9%) HI: 14/56 (25.0%)	1,9 (0.8 – 4.2)	MI: 0/58 HI: 0/56	NA
Finazzi et al., 2005[31]	MI: 3/55 (5.4%) HI: 6/54 (11.1%)	1.97 (0.49-7.89)	MI: 6/55 (10.9%) HI: 15/54 (27.7%)	2.92 (1.13-7.52)	MI: 3/55 (5.4%) HI: 2/54 (3.7%)	0.66 (0.11-3.96)	MI: 8/55 (14.5%) HI: 15/54 (27.7%)	2,18 (0,92 – 5,15)	MI: 2/55 (3.6%) HI: 3/54 (5.5%)	1.41 (0.23 – 8.47)

HI, high intensity; CI, confidence interval; HR, *hazards ratio*; MI, moderate intensity; NA, not assessed.

those patients who received intervention with HI warfarin compared to the group randomized to conventional anticoagulant treatment. Another finding of the meta-analysis was the higher incidence of minor hemorrhage also in the experimental group, that received warfarin keeping an INR > 3.

The graphs of this meta-analysis results (Forest Plot) addressing the analysis of outcomes - thrombotic events, total bleeding, major bleeding, minor bleeding and death - are illustrated in Figs. 2–6, respectively.

Discussion

This study conducted a meta-analysis of outcomes of thrombosis and hemorrhage of the articles in the scientific literature that evaluated different intensities of anticoagulation in the treatment of thrombosis in patients with APS.

Analyzing the available scientific literature on the subject, it is possible to find observational studies of prospective and retrospective cohort that have been mostly published before the RCTs evaluated in this review and, in general, showed lower rates of recurrent thrombotic events in patients receiving warfarin with INR> 3 compared to those receiving anticoagulant therapy at a lower intensity (INR < 3).[13–19,32]

In fact, the restrospective cohort study by Rosove et al.[14] evaluated 70 patients with APS and concluded that warfarin therapy of intermediate/high intensity may provide greater antithrombotic protection compared to the use of warfarin of low/intermediate intensity. However, this work, besides having a retrospective nature, included patients without diagnostic criteria for APS as the population of study, weakening such scientific evidence. In 1995, Khamashta et al.,[13] retrospectively evaluating 147 patients with APS, also showed, in their study, more efficacy in preventing recurrent thrombotic events in patients receiving warfarin with INR> 3 compared to those treated with anticoagulant therapy of lower intensity.

On the other hand, the prospective study by Ames et al.[33] demonstrated that HI oral anticoagulation in patients with APS was not better than the conventional treatment in the secondary prevention of thrombosis. This work followed, for eight years, 67 patients with APS, 89 with hereditary thrombophilia, and 24 with mitral valve replacement.

Another conclusion obtained from the analysis of observational studies was greater trend to recurrence of thrombotic events of those patients who had arterial events. These individuals would therefore have higher cardiovascular risk and would require a more aggressive therapy. However, the retrospective study that reached this conclusion did not require
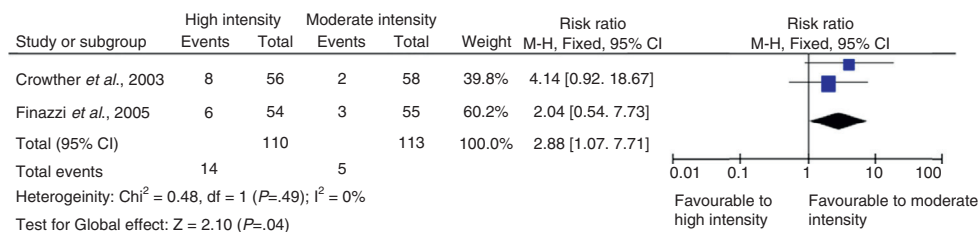

Figure 2 – **Graph of meta-analysis (Forest Plot) for comparative analysis of thrombotic events occurrence.**
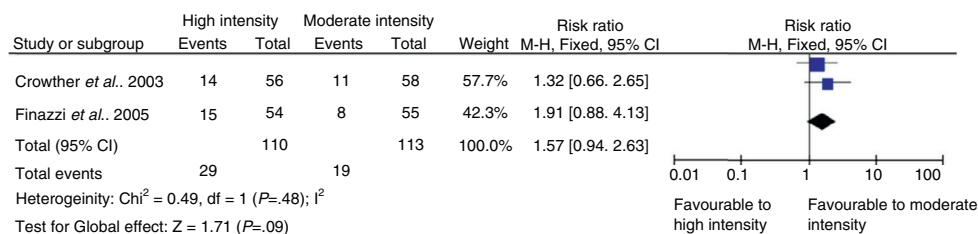

Figure 3 – **Graph of meta-analysis (Forest Plot) for comparative analysis of total bleeding occurrence.**
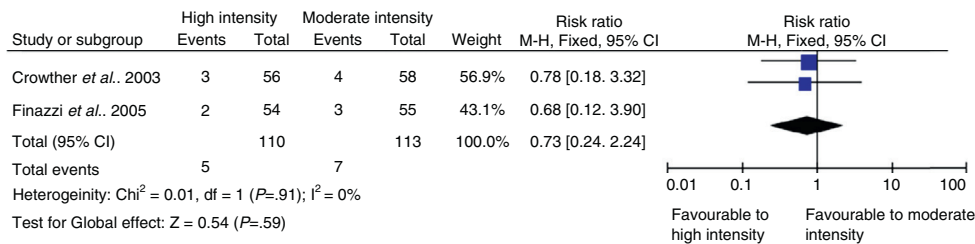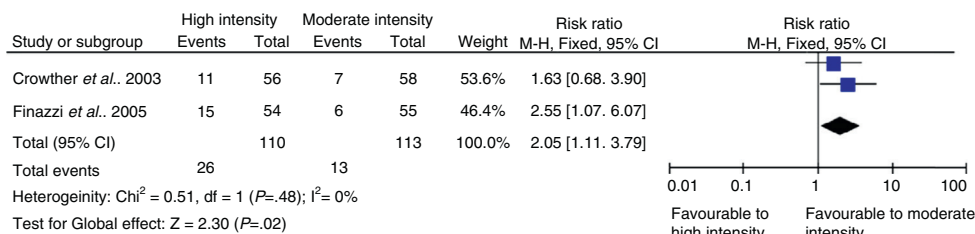
Study or subgroup	High intensity Events	Total	Moderate intensity Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Crowther et al.. 2003	3	56	4	58	56.9%	0.78 [0.18. 3.32]
Finazzi et al.. 2005	2	54	3	55	43.1%	0.68 [0.12. 3.90]
Total (95% CI)		110		113	100.0%	0.73 [0.24. 2.24]
Total events	5		7			

Heterogeinity: Chi^2 = 0.01, df = 1 (P=.91); I^2 = 0%
Test for Global effect: Z = 0.54 (P=.59)

Figure 4 – Graph of meta-analysis (Forest Plot) for comparative analysis of major bleeding occurrence.

Study or subgroup	High intensity Events	Total	Moderate intensity Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Crowther et al.. 2003	11	56	7	58	53.6%	1.63 [0.68. 3.90]
Finazzi et al.. 2005	15	54	6	55	46.4%	2.55 [1.07. 6.07]
Total (95% CI)		110		113	100.0%	2.05 [1.11. 3.79]
Total events	26		13			

Heterogeinity: Chi^2 = 0.51, df = 1 (P=.48); I^2 = 0%
Test for Global effect: Z = 2.30 (P=.02)

Figure 5 – Graph of meta-analysis (Forest Plot) for comparative analysis of minor bleeding occurrence.

Study or subgroup	High intensity Events	Total	Moderate intensity Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Crowther et al.. 2003	1	56	1	58	33.1%	1.04 [0.07. 16.16]
Finazzi et al.. 2005	3	54	2	55	66.9%	1.53 [0.27. 8.79]
Total (95% CI)		110		113	100.0%	1.36 [0.31. 5.93]
Total events	4		3			

Heterogeinity: Chi^2 = 0.5, df = 1 (P=.82); I^2 = 0%
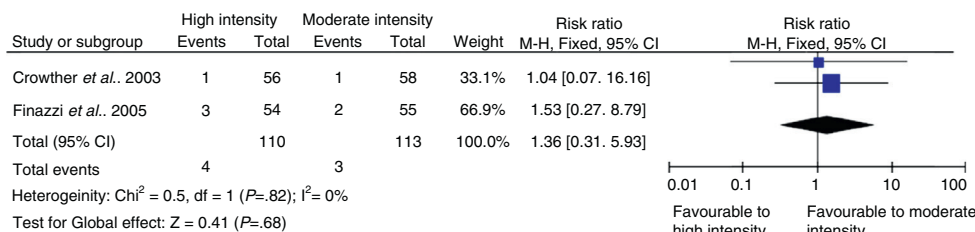Test for Global effect: Z = 0.41 (P=.68)

Figure 6 – Graph of meta-analysis (Forest Plot) for comparative analysis of death occurrence.

the fulfilling of diagnostic criteria for APS as a prerequisite for selection of patients.[17]

Regarding the frequency of bleeding events, the study by Ruiz-Irastorza et al.[15] found similar results of major hemorrhage in rats treated with warfarin according to INR ≥ 3.5. Moreover, the work by Ames et al.,[33] Khamashta et al.,[13] Derksen et al.,[16] Muñoz et al.[18] and Girón-Gonzáles et al.[32] showed higher rates of bleeding in patients treated with HI anticoagulant, with INR rates ranging from 3-7.5 at the moment of bleeding.

However, we must be aware of the importance of conducting systematic reviews nowadays, as they minimize potential biases due to their rigid methodology, enabling the gathering of the best scientific evidence that will be the foundation of health care decision-making. The meta-analysis, in its turn, allows better assessment of the evidence found in a literature review and of a possible heterogeneity of the results presented.[34,35] Therefore, this feature allows improving precision and accuracy in the estimate of treatment effect, increasing its statistical power.[35]

One of the advantages of this review was the very restrictive selection criteria, which allowed a more accurate and reliable analysis of results. Thus, there was the exclusion of studies with designs different from that of randomized clinical trials, such as case reports, case series, case-control studies, retrospective, cross-sectional and cohort studies (the latter

was excluded for not allowing the evaluation of interventions).

Another benefit arising from the design of the selected studies is the fact that these are multicenter studies, involving a total of 39 clinical centers, including cities in Europe, Canada, United States and Argentina, which brings external validity to the data found. Furthermore, the study by Crowther et al.[30] presented double-blind design, favoring further recognition of the value of its results.

On the other hand, some important limitations of the evaluated studies should be highlighted. Namely, the study by Finazzi et al.[31] was not double-blind (they used ad hoc committee of clinical experts blinded to the treatment adopted), which favors outcome biases. Moreover, the same work interrupted clinical trial early, because of patients leaving the study due to adverse effects, or patient or physician refusal to keep the protocol.

Another aspect to be considered is that the study by Crowther et al.[30] failed to analyze the effectiveness of warfarin in the first three months after the first thrombotic event in patients involved in the study. This limitation was due to the need, set during the study protocol, to perform two tests for APLs with an interval of three months. Additionally, patients with high risk of bleeding, such as those with prior stroke, thrombocytopenia (<50,000 mm^3) and gastrointestinal bleeding in the past three months, were excluded from this work

in the same way that, in both studies, patients with recurring events, even during the use of anticoagulant prophylaxis, were excluded from clinical trials. Thus, many patients with severe cases of the disease were not included in the studies.

It is surprising to note that, in the study by Crowther et al.,[30] INR targets were not achieved in 43% of the time in patients randomized to the HI warfarin group, what can perfectly explain the higher incidence of thrombosis in this group that was "undertreated". In the study by Finazzi et al.,[31] such information was not found. Another possible explanation for these results would be poor randomization, for example, the biased allocation of subjects, where the most severe ones could have been distributed to the HI group.

A further negative character of both studies is that they were developed intending to demonstrate the superiority of anticoagulant treatment with warfarin in high doses. However, the results presented in the work by Crowther et al.[30] show similarities between both intensities of anticoagulation. Additionally, the study by Finazzi et al.[31] found even worse outcomes in the HI group.

The evidence found in the studies included in this review should be carefully evaluated in patients with arterial thrombosis, since venous thromboembolic events were the prevalent, representing about 70% of cases in both studies. Therefore, a suggestion for future clinical studies in this area is the unique inclusion of patients with arterial events, considering that the results of both previous studies already carried out may be more appropriately applied in patients with venous events.

All the difficulties enumerated should be milded because this is an uncommon disease. In fact, the APS has an estimated prevalence of 40-50 cases per 100,000 people.[36] Thus, the two scientific papers included in this meta-analysis represent the best medical evidence available at the time. And yet, this evidence should be valued as prospective studies with large numbers of participants and presenting appropriate criteria for selection, inclusion and exclusion are unlikely to occur.

In brief, the present meta-analysis compared two different intensities of anticoagulation in APS with thrombotic event and demonstrated that patients on HI warfarin (INR: 3-4) had more thrombotic events (although about 40% of this group were "undertreated") and minor bleeding. This finding provides evidence of usefulness for clinical practice, in the sense that, in individuals with APS and prevalence of venous events, the use of MI anticoagulation (INR: 2.0-3.0) is more appropriate. Moreover, such evidence may not 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. We therefore suggest the conduction of RCTs involving patients with APS and prevalence of arterial thrombosis.

Funding

Conflicts of interest

The authors declare no conflicts of interest.

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