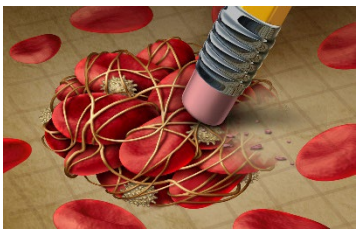
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ



Μεταπτυχιακή Διπλωματική Εργασία

ΚΛΙΝΙΚΑ ΚΑΙ ΕΡΓΑΣΤΗΡΙΑΚΑ ΕΥΡΗΜΑΤΑ ΜΕΙΖΟΝΩΝ ΑΡΤΗΡΙΑΚΩΝ ΘΡΟΜΒΩΣΕΩΝ ΣΤΟ ΑΝΤΙΦΩΣΦΟΛΙΠΙΔΙΚΟ ΣΥΝΔΡΟΜΟ: ΟΜΟΙΟΤΗΤΕΣ ΚΑΙ ΔΙΑΦΟΡΕΣ ΜΕ ΤΟΥΣ ΚΑΘΙΕΡΩΜΕΝΟΥΣ ΚΑΙ ΤΑΞΙΝΟΜΗΤΙΚΟΥΣ ΠΑΡΑΓΟΝΤΕΣ ΑΓΓΕΙΑΚΟΥ ΚΙΝΔΥΝΟΥ

υπό

ΓΕΩΡΓΙΟΥ ΔΡΟΣΟΥ

Ειδικευμένου Εσωτερικής Παθολογίας

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Θρόμβωση και Αντιθρομβωτική Αγωγή»

Λάρισα, 2024

Επιβλέπουσα:

Παρασκευή Κώτση, Επίκουρη Καθηγήτρια, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας

Τριμελής Εξεταστική Επιτροπή:

1. Παρασκευή Κώτση, Επίκουρη Καθηγήτρια, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας
2. Γεωργία Καϊάφα, Αναπληρώτρια Καθηγήτρια, Τμήμα Ιατρικής, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
3. Ελευθερία-Ελμίνα Λευκού, Αιματολόγος, Θεσσαλονίκη

FACULTY OF MEDICINE
SCHOOL OF HEALTH SCIENCES
UNIVERSITY OF THESSALY

MSc COURSE
THROMBOSIS AND ANTITHROMBOTIC TREATMENT

Master of Science Thesis

CLINICAL AND LABORATORY FINDINGS OF MAJOR ARTERIAL THROMBOSIS IN ANTIPHOSPHOLIPID SYNDROME: SIMILARITIES AND DIFFERENCES WITH ESTABLISHED AND CLASSIFICATION CRITERIA VASCULAR RISK FACTORS

by

GEORGIOS DROSOS

Specialist in Internal Medicine

Submitted to fulfil part of the

requirements for the acquisition of the

Diploma of MSc Studies in

“Thrombosis and Antithrombotic Treatment”

Larissa, 2024

Supervisor:

Paraskevi Kotsi, Assistant Professor, Faculty of Medicine, University of Thessaly

Examination Committee:

1. Paraskevi Kotsi, Assistant Professor, Faculty of Medicine, University of Thessaly *(Supervisor)*
2. Georgia Kaiafa, Associate Professor, Faculty of Medicine, Aristotle University of Thessaloniki
3. Eleftheria-Elmina Lefkou, Haematologist, Thessaloniki

Acknowledgements

I would particularly like to thank my Supervisor, Prof. Paraskevi Kotsi, who assigned me the topic of the present thesis. Her unwavering guidance, support and patience were instrumental to the completion of this work.

I would also like to thank all the members and teaching staff of the Master's degree in 'Thrombosis and Antithrombotic Treatment' of the Faculty of Medicine of the University of Thessaly for allowing me to participate in this educational journey and for the generosity and willingness to share their knowledge.

Special thanks to the administrative officers, Ms. Eleni Kletsou and Ms. Vasiliki Spilioti, for responding to all queries with clarity, professionalism and empathy and for providing constant guidance.

Finally yet importantly, I would like to thank my family and friends for their patience and encouragement throughout this project.

Περίληψη

Υπόβαθρο. Τα μείζονα αρτηριακά θρομβωτικά επεισόδια (ΜΑΘΕ), όπως το αγγειακό εγκεφαλικό επεισόδιο (ΑΕΕ) και το έμφραγμα του μυοκαρδίου (ΕΜ), αποτελούν σημαντικές αιτίες νοσηρότητας και θνησιμότητας στο αντιφωσφολιπιδικό σύνδρομο (ΑΦΣ). Οι παράγοντες καρδιαγγειακού κινδύνου (ΚΑΚ) που έχουν επικυρωθεί στα γενικά μοντέλα εκτίμησης κινδύνου (ΜΕΚ) όπως τα Systematic Coronary Risk Evaluation-2 (SCORE2), Pooled Cohorts Risk Equation (PCRE) και Second Manifestations of Arterial disease (SMART) συμβάλλουν στην εμφάνιση των ΜΑΘΕ στο ΑΦΣ. Σύμφωνα με τα αναθεωρημένα κριτήρια της Αμερικανικής Εταιρείας Ρευματολογίας και της Ευρωπαϊκής Συμμαχίας Εταιρειών Ρευματολογίας (ACR/EULAR), οι παράγοντες ΚΑΚ οφείλουν να λαμβάνονται υπόψη στην ταξινόμηση του ΑΦΣ. Τα ΜΕΚ για τα υποτροπιάζοντα συμβάντα, όπως τα adjusted Global Antiphospholipid Syndrome Score (aGAPSS) και aGAPSS για την καρδιαγγειακή νόσο ($aGAPSS_{CVD}$), περιλαμβάνουν ανεξάρτητους προβλεπτικούς παράγοντες ΚΑΚ και οι συστάσεις της EULAR για τη διαχείριση του ΚΑΚ στο ΑΦΣ υποδεικνύουν ότι αυτοί οι παράγοντες κινδύνου θα πρέπει να λαμβάνονται αυστηρά υπόψη στην κλινική φροντίδα των ασθενών.

Σκοπός. Η παρούσα διπλωματική εργασία ανασκόπησε τις ομοιότητες και διαφορές μεταξύ των παραγόντων ΚΑΚ που περιλαμβάνονται στα SCORE2, PCRE, SMART, aGAPSS, $aGAPSS_{CVD}$ και τα κριτήρια ταξινόμησης APS, και της συχνότητας, συσχέτισης και αθροιστικής επίδρασης των γενικών και νοσοειδικών παραγόντων ΚΑΚ στα ΜΑΘΕ του ΑΦΣ.

Μέθοδοι. Η ηλεκτρονική βάση δεδομένων Pubmed/MEDLINE αναζητήθηκε για σχετικά άρθρα από την ίδρυσή της έως τον Μάιο 2024. Χρησιμοποιήθηκαν τρεις διαφορετικές αναζητήσεις με τους όρους «αντιφωσφολιπιδικό σύνδρομο», «αρτηριακή θρόμβωση», «εγκεφαλικό επεισόδιο» και «έμφραγμα του μυοκαρδίου». Αποκλείστηκαν εγγραφές που αφορούσαν τη μη αγγλική γλώσσα, μελέτες σε ζώα, μη ενήλικους πληθυσμούς, χαμηλό επίπεδο τεκμηρίωσης, αδυναμία πρόσβασης σε άρθρα πλήρους ανάγνωσης και μη συνάφεια. Οι παράγοντες ΚΑΚ που εξετάστηκαν ήταν το ανδρικό φύλο, η μεγαλύτερη ηλικία, το κάπνισμα, η αρτηριακή πίεση (ΑΠ), η δυσλιπιδαιμία, η παχυσαρκία, ο σακχα-

ρώδης διαβήτης (ΣΔ), η νεφρική νόσος, τα αντιφωσφολιπιδικά αντισώματα (αΦΛ), η αντιθρομβωτική αγωγή, η ανατομική θέση της θρόμβωσης και το ιστορικό θρόμβωσης.

Αποτελέσματα. Από τις αναζητήσεις στο Pubmed/MEDLINE προέκυψαν 1344 εγγραφές, εκ των οποίων 71 άρθρα συμπεριλήφθηκαν στην ανασκόπηση. Όλοι οι παράγοντες ΚΑΚ που εξετάστηκαν σχετίζονταν με την εμφάνιση ή την υποτροπή των ΜΑΘΕ στο ΑΦΣ. Η τεκμηρίωση ήταν εκτενέστερη και σαφέστερη για κάπνισμα, ΑΠ, δυσλιπιδαιμία, αΦΛ και αντιθρομβωτική αγωγή (ιδίως την αποφυγή των άμεσων από του στόματος αντιπηκτικών). ΑΠ και δυσλιπιδαιμία ενδέχεται να ασκούν διαφορετικές επιδράσεις στο ΑΕΕ και στο ΕΜ, αντίστοιχα. Ο ρόλος των μη κριτηρίων αΦΛ είναι πιο ασαφής σε σύγκριση με τα αΦΛ των κριτηρίων ταξινόμησης. Νεφρική νόσος, παχυσαρκία, ΣΔ και ανατομική θέση/ιστορικό θρόμβωσης ήταν οι λιγότερο μελετημένοι παράγοντες κινδύνου. Οι περισσότερες μελέτες σχετικές με το αντικείμενο της ανασκόπησης δεν διέκριναν μεταξύ αθηροθρομβωτικών και μη αθηροθρομβωτικών συμβάντων. Οι περιγραφές των παραγόντων ΚΑΚ ήταν ετερογενείς ή απουσίαζαν σε σημαντικό αριθμό μελετών, αποκλείοντας μερικώς τις άμεσες συγκρίσεις με τα ΜΕΚ ή τα κριτήρια ταξινόμησης ACR/EULAR.

Συμπέρασμα. Παρατηρήθηκαν κυρίως ομοιότητες μεταξύ των μεμονωμένων παραγόντων ΚΑΚ και εκείνων που περιλαμβάνονται στα ΜΕΚ, παρά με τις κατατομές ΚΑΚ των κριτηρίων ταξινόμησης ACR/EULAR. Η βελτιστοποίηση της καρδιαγγειακής πρόληψης στο ΑΦΣ απαιτεί τυποποίηση των εκθέσεων ΚΑΚ και των αγγειακών εκβάσεων στα ΜΑΘΕ πριν από την περαιτέρω αξιολόγηση των ταξινομητών ΚΑΚ με αποδεδειγμένη κλινική σημασία.

Λέξεις-κλειδιά: Αντιφωσφολιπιδικό σύνδρομο, αρτηριακή θρόμβωση, αγγειακό εγκεφαλικό επεισόδιο, έμφραγμα του μυοκαρδίου, καρδιαγγειακός κίνδυνος.

Abstract

Background. Major arterial thrombotic events (MATEs) such as stroke and myocardial infarction (MI) are important causes of morbidity and mortality in the antiphospholipid syndrome (APS). Cardiovascular risk (CVR) factors such as those validated in the general risk assessment models (RAMs) including the Systematic Coronary Risk Evaluation-2 (SCORE2), the Pooled Cohorts Risk Equation (PCRE) and the Second Manifestations of Arterial disease score (SMART) contribute to the occurrence of MATEs in APS. According to the revised criteria by the American Society of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR), established CVR factors should be accounted for in the classification of APS. RAMs for recurrent events, such as the adjusted Global Antiphospholipid Syndrome Score (aGAPSS) and the aGAPSS for cardiovascular disease ($aGAPSS_{CVD}$), include CVR factors as independent predictors, and the EULAR recommendations for CVR management in APS suggest that these risk factors should be strictly considered in the clinical care of patients.

Objective. The purpose of this thesis was to review the similarities and differences between CVR factors included in SCORE2, PCRE, SMART, aGAPSS, $aGAPSS_{CVD}$ and the APS classification criteria and the frequency, association and cumulative effect of general and disease-specific CVR factors on MATEs in patients with APS.

Methods. The Pubmed/MEDLINE electronic database was searched for relevant articles from its inception to May 2024. Three different search strings that included the terms ‘antiphospholipid syndrome’, ‘arterial thrombosis’, ‘stroke’ and ‘myocardial infarction’ were used. Records pertaining to non-English language, animal studies, non-adult populations, low level of evidence, inability to access full-text articles and non-relevance were excluded. The CVR factors examined were male gender, older age, smoking, blood pressure (BP), dyslipidaemia, obesity, diabetes mellitus (DM), renal disease, antiphospholipid antibodies (aPL), antithrombotic treatment, anatomical site of thrombosis and history of thrombosis.

Results. The Pubmed/MEDLINE search strings yielded 1344 records, of which 71 unique full-text articles were included in the review. All CVR factors examined were found to be related to the occurrence or recurrence of MATEs in APS. The evidence was more extensive and appeared clearer for smoking, BP, dyslipidaemia, aPL and antithrombotic treatment (particularly avoidance of direct oral anticoagulants). BP and dyslipidaemia may exert different effects on stroke and MI, respectively. The role of non-criteria aPL is more unclear compared to aPL included in the APS classification criteria. Renal disease, obesity, DM, and anatomic site/history of thrombosis were the least studied risk factors. Most studies conducted on the subject of the review did not distinguish between atherothrombotic and non-atherothrombotic events. Descriptions of CVR factors were heterogeneous or missing in a significant number of studies, partially precluding direct comparisons with RAMs or the ACR/EULAR classification criteria.
Conclusion. Similarities were primarily observed between individual CVR factors and risk predictors included in RAMs, rather than with the vascular risk profiles suggested by the ACR/EULAR classification criteria. To optimise cardiovascular prevention in APS, standardisation of CVR exposures and vascular outcomes in MATEs is required prior to further evaluation of CVR classifiers with established clinical importance.

Keywords: Antiphospholipid syndrome; arterial thrombosis; stroke; myocardial infarction; cardiovascular risk.

Table of contents

List of tables

List of figures

List of abbreviations

aCL	antibodies against cardiolipin
ACR	American College of Rheumatology
aGAPSS	adjusted GAPSS
$aGAPSS_{CVD}$	adjusted GAPSS for CVD
Anti-PT/PS	antibodies against PT/PS
Anti-β2GPI	antibodies against β2GPI
aPL	antiphospholipid antibodies
aPL_{pos}	positivity for aPL
APS	antiphospholipid syndrome
ATE	arterial thrombotic event
BP	blood pressure
CAPS	catastrophic APS
CVD	cardiovascular disease
CVR	cardiovascular risk
DM	diabetes mellitus
DOAC	direct oral anticoagulant
EULAR	European Alliance of Associations for Rheumatology
GAPSS	Global APS Score
IgG	immunoglobulin G
IgM	immunoglobulin M
LA	lupus anticoagulant
MATE	major ATE
MI	myocardial infarction
NET	neutrophil extracellular trap
OAPS	obstetric APS
PCRE	Pooled Cohorts Risk Equation
PICO	Population Intervention Comparator Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	phosphatidylserine
PT	prothrombin
RAM	risk assessment model
SCORE	Systematic Coronary Risk Evaluation
SLE	systemic lupus erythematosus
SMART	Second Manifestations of Arterial Disease
TAPS	thrombotic APS
VKA	vitamin K antagonist
VTE	venous thrombotic event
β2GPI	beta-2-glycoprotein I

PART **A**

THEORETICAL BACKGROUND

1. Antiphospholipid syndrome

1.1 Definition and historical aspects

Antiphospholipid syndrome (APS) is a systemic, non-organ-specific autoimmune disease[1-5] that clinically manifests itself primarily as a thrombophilic disorder characterised by venous, arterial and/or microvascular thrombosis or maternal–foetal morbidity in the setting of persistently circulating autoantibodies against cell membrane phospholipids (ie, *antiphospholipid antibodies*, aPL).[2-4] Because these antibodies predominantly target proteins associated with phospholipids, the term 'aPL' (and consequently that of APS) is considered a misnomer.[2 3] The aetiology of APS is unknown and current theories attribute genetic, epigenetic and exposomal effects to the pathogenesis of the syndrome.[2 4 6]

The discovery and characterisation of aPL is closely related to the research into syphilis and systemic lupus erythematosus (SLE).[2 3 5] In 1941, it was discovered that *cardiolipin*, a phospholipid extracted from bovine myocardial tissue, was the antigenic substrate responsible for a positive syphilis screening test using the Wasserman antibody.[2 5] Ten years later, it was found that patients with SLE also tested positive for this test even though they did not have syphilis,[2 3 5] an observation that led to the suggestion that antibodies to cardiolipin (ie, *anti-cardiolipin antibodies*, aCL) could also be a feature of autoimmune disease.[2 3] The *'lupus anticoagulant'* (LA) phenomenon, which is crucial to the pathophysiological and clinical aspects of APS, was also first described in lupus patients in the 1950s.[2 5] In the last decade of the 20th century, a series of studies further clarified that aCL associated with APS actually target a protein cofactor bound to membrane phospholipids, namely *beta-2-glycoprotein I*, which acts as an intermediary to the binding of autoantibodies to phospholipids.[2-5] These antibodies are now referred to as *anti-β2GPI* antibodies (*anti-β2GPI*).

The systematic description of APS as a distinct clinical entity occurred in the 1980s.[2 3 5] Originally considered as a disease association to SLE due to the frequent combination of aCL positivity, LA positivity, thrombosis and foetal loss in lupus patients, it was later characterised as a clinicopathological entity that

can occur in the absence of SLE or other autoimmune disorders. Nevertheless, retrospective analyses of the medical histories of culturally relevant people, such as members of the royal families of Great Britain, suggest that the syndrome might have been present as early as the 17th century, with Anne, Queen of Great Britain (1665–1714) possibly being one of the first APS cases in the history of Medicine.[7]

1.2 Pathogenicity of aPL

The capacity of aPL to impart clinical effects underlying the vascular and obstetric morbidity in APS is determined by a number of qualitative and quantitative conditions.[2-4 8 9] *Qualitative* determinants of aPL pathogenicity refer to their antigenic specificity (*type* of aPL – eg, aCL, anti-β2GPI), immunoglobulin class (*isotype* of aPL – IgG, IgM or IgA) and induction of the *in vitro* LA effect. *Quantitative* aspects include their serological concentration (aPL *titre*), number of co-occurring aPL types (single versus multiple aPL positivity) and duration of aPL positivity (*persistence* of positive titres).

To date, a vast number of antigenic targets of aPL have been described.[2 10 11] Among them, antibodies against β2GPI (ie, *β2GPI-dependent* aPL) are considered more pathogenic compared to β2GPI-independent aPL.[2-4 11] Other important antigens associated with clinically relevant aPL include the phospholipids *cardiolipin* and *phosphatidylserine* (PS), as well as the proteins *annexin*, *prothrombin* (PT) and *complement* components.[5 10 11] These antigenic targets can induce production of aPL directly (eg, aCL) or as protein–phospholipid complexes (eg, anti-β2GPI, anti- PT/PS). Antibodies of the *IgG class* appear to have a higher pathogenic potential than IgM or IgA aPL.[4 9] The *LA test* is a functional assay that assesses the prolongation of phospholipid-dependent coagulation reactions in the presence of aPL (particularly anti-β2GPI and/or anti-PT/ PS).[2 3 6 10] A positive LA test is highly specific for APS in the absence of other acquired coagulation inhibitors that may produce similar laboratory findings.

Higher aPL titres are associated with an increased risk of adverse clinical events due to aPL positivity (aPL_{pos}).[3 4 8 9] Titre cut-offs are established according to the presence of at least a two-fold to four-fold increase in aCL and/or anti-β2GPI titres above the 99th percentile, which corresponds to the definition of

'moderate-titre' and 'high-titre' aPL, respectively.[6 12] *Double positivity* for any two of aCL, anti-β2GPI or LA, as well as *triple positivity* for all of these aPL, have been associated with a high risk of thrombosis and pregnancy complications in APS.[2 4 8] *Persistent positivity* for any type of aPL also has significant implications for the diagnosis, classification and prognosis of APS.[8 9]

The above considerations are of clinical importance because aPL can be detected in a large number of clinical conditions, including infectious disease, malignancies, immune-mediated disorders and even in otherwise healthy individuals, without signifying a risk condition or indicating APS as the cause of a thrombotic or obstetric event.[2-4 9] Indeed, transient, low-titre IgM β2GPI-independent aCL can accompany many acute infections, but this type of aPL profile should not be considered *a priori* pathogenic in relation to APS.[2 4 9]

1.3 Descriptors of APS

APS has been described using various disease attributes, including clinical manifestations and association with an index disease.[2-4] *Thrombotic* APS (TAPS), *obstetric* APS (OAPS), and *catastrophic* APS (CAPS) are routinely used descriptions and can be considered *de facto* accepted in the nomenclature applied to the syndrome.[2 6 9] *Primary* APS (PAPS) was described as a nosological entity in the late 1980s and refers to the presence of clinical and laboratory findings indicative of APS that is not associated with other autoimmune diseases (particularly SLE).[2 3] If APS manifests in association with another autoimmune disease, the currently proposed descriptor would be '[disease name]-associated APS' (eg, 'SLE-associated APS', or 'SLE-APS' for short).[2]

1.4 Epidemiology of APS

APS is generally a rare disease. *Incidence* estimates (per 10^5 persons) range from 2.1 to 2.6 in America to 1.1 in Europe to 0.75 in Asia.[2-4 13] *Prevalence* rates in European and American countries are between 40 and 50 cases per 10^5 persons.[13] Adult APS occurs more frequently in the fourth decade of life in *women* and in the sixth decade of life in *men*.[13] The women to men prevalence ratio for *PAPS* and *SLE-APS* is 3:1 and 7:1, respectively.[2 14]

1.5 Clinical and laboratory findings in APS

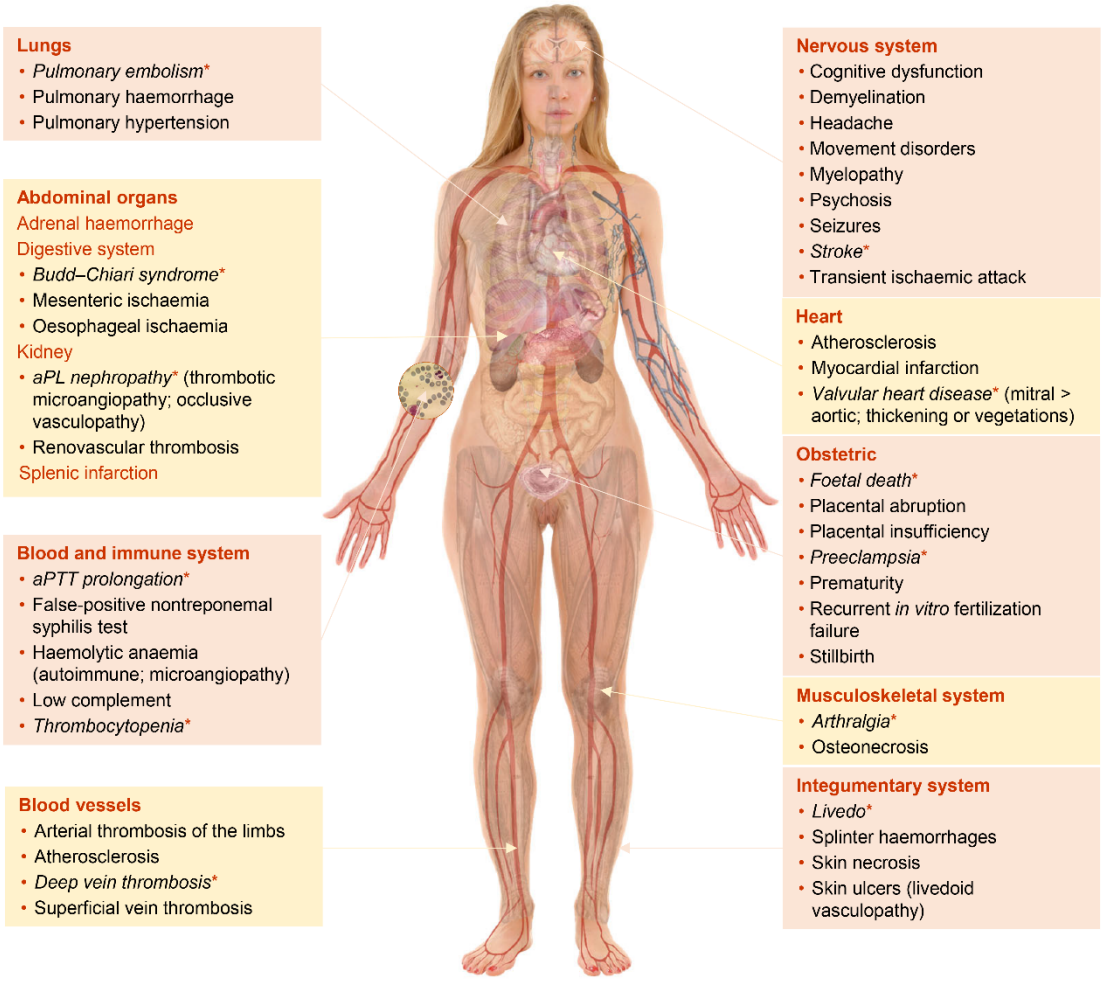


FIGURE 1 **Clinical and laboratory features of APS**. Most common manifestations per organ system are shown in *italics* and marked with an asterisk (*). Own work; background woman figure from *commons.wikimedia.org* [Mikael Häggström], public domain.

APS can manifest itself with a variety of *clinical manifestations* in the circulatory system and pregnancy complications affecting both the mother and the foetus.[2-4 9 14] The most common vascular thrombotic event is deep vein thrombosis, followed by stroke.[2 5 14 15] Obstetric morbidity includes early foetal loss and recurrent miscarriage.[2 16] These clinical findings are due to the propensity of aPL to interfere with normal haemostasis and impair trophoblast functions.[2-4 6 9] However, emerging evidence suggests that aPL may also have other cellular targets, such as components of brain tissues (eg, glia).[2 3] This latter feature may underlie the heterogeneity of neurological findings associated with the syndrome, some of which may not be due to vascular damage.[2 3]

Laboratory features of APS include those specific to the syndrome (ie, aPL_{pos}) as well as more general findings of abnormal haemostasis and other haematological abnormalities. The most commonly found aPL are IgG and/or IgM aCL and/or anti-β2GPI and a positive LA.[2-4 9] Non-APS-specific haematological findings include thrombocytopenia and prolonged activated partial thromboplastin time; the latter is an indirect marker of LA positivity.[2-4]

Clinical and laboratory features of APS per anatomical system involvement are shown in Figure 1 on p. 18.

1.6 Classification criteria and 'non-criteria' manifestations of APS

Classification criteria are a cluster of features standardised to identify individuals with a specific disease in order to facilitate enrolment in population studies.[17] A group of experts meeting in Sapporo, Japan, in 1999 developed preliminary criteria for APS.[2 3] These set of criteria were updated into the 'revised Sapporo classification criteria' (Table 1, p. 20) at a 2006 meeting in Sydney, Australia.[18] The 'Sydney classification criteria' were available until 2023, when the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) jointly published a new set of criteria that deemed significant revisions to both clinical and laboratory features necessary to classify APS for research purposes (Table 2, p. 21).[19]

'Non-criteria' (or 'extra-criteria') manifestations refer to clinical and laboratory features that are epidemiologically associated with APS but were not included in the Sydney classification criteria.[2-4 20] Some of these manifestations were reported in the original description of the syndrome.[2 3] According to the grade of evidence assigned by the working groups of the International Congresses on Antiphospholipid Antibodies held to date,[2 3 20-22] *livedo*, *valvular heart disease*, *aPL-associated nephropathy* and *thrombocytopenia* are among the most important 'non-criteria' features associated with APS. The evidence is less robust for superficial vein thrombosis, movement disorders, and incomplete laboratory APS (eg, lack of persistent aPL_{pos}).[2 21 22] Many other 'non-criteria' manifestations have been identified, such as accelerated atherosclerosis, autoimmune haemolytic anaemia, non-criteria aPL (eg, anti-vimentin/cardiolipin), skin ulcers, migraine-like chronic headache, pulmonary hypertension, and a

history of three non-consecutive miscarriages.[2 3 20] A number of previously 'non-criteria' clinical features are now included in the ACR/EULAR classification criteria for APS (Table 2, p. 21).[19]

TABLE 1 **Summary of the Sydney classification criteria for APS**

Clinical criteria for TAPS	Laboratory criteria
1. Venous thrombosis	1. Positive LA test
2. Arterial thrombosis	2. Medium-high titre IgG and/or IgM aCL
3. Microvascular thrombosis	3. Positive (>99th percentile) IgG and/or IgM anti-β2GPI
Clinical criteria for OAPS	**Classification requirements**
1. First trimester (<10th week of gestation) recurrent foetal loss (three or more)	1. At least one clinical criterion plus one laboratory criterion
2. First trimester (≥10th week of gestation) foetal loss (one or more)	2. Clinical criterion should not be separated from the laboratory criterion for <12 weeks or >5 years
3. Third trimester (<34th week of gestation) preeclampsia or placental insufficiency leading to premature birth (one or more)	

Thrombosis requires objective evidence by imaging and/or histopathology. For obstetric events before the 10th week of gestation, chromosomal abnormalities and/or maternal anatomical and/or hormonal causes of foetal death must be excluded. Obstetric events after 10 weeks of gestation require the presence of a morphologically normal foetus. Laboratory criteria require that an initial positive aPL test be confirmed by a second positive test performed at least 12 weeks after the initial test. Adapted from Miyakis *et al*.[18]

TABLE 2 **Summary of the ACR/EULAR classification criteria for APS**

Clinical criteria for TAPS
Macrovascular thrombosis: • Venous thrombotic event (VTE) with [1 pt] or without [3 pts] a high-risk vascular profile • Arterial thrombotic event (ATE) with [2 pts] or without [4 pts] a high-risk vascular profile Microvascular thrombosis (≥1 of the following): • Suspected [2 pts] livedo racemosa,* livedoid vasculopathy,* aPL-nephropathy,* or pulmonary haemorrhage* • Established [5 pts] livedoid vasculopathy, aPL-nephropathy, pulmonary haemorrhage, myocardial disease,*† or adrenal haemorrhage*
Clinical criteria for OAPS
≥3 consecutive (pre)embryonic (<10th week of gestation) or early foetal deaths (10th–15th week of gestation) [1 pt]
Foetal death (16th–33rd week of gestation) in the absence of severe preeclampsia or placental insufficiency [1 pt]
Severe preeclampsia *or* placental insufficiency (<34th week of gestation), with or without foetal death [3 pts]
Severe preeclampsia *and* placental insufficiency (<34th week of gestation), with or without foetal death [3 pts]
Clinical criteria for other manifestations
Valvular heart disease* with thickening [2 pts] or vegetation [4 pts]
Thrombocytopenia* (20.000–130.000/μL) [2 pts]
Laboratory criteria
Positive LA test – single [1 pt] or persistent [5 pts]
Moderate or high-titre IgM aCL and/or IgM anti-β2GPI [1 pt]
Moderate-titre IgG aCL and/or IgG anti-β2GPI [4 pts]
High-titre IgG aCL *or* IgG anti-β2GPI [5 pts]
High-titre IgG aCL *and* IgG anti-β2GPI [7 pts]
Classification requirements
Entry criteria: at least one clinical criterion *plus* one laboratory criterion
Classification threshold: ≥3 pts from clinical criteria *plus* ≥3 pts from laboratory criteria

*Previously considered 'non-criteria' manifestations. †Does not include acute myocardial infarction with evidenced coronary artery thrombosis. Suspected microvascular thrombosis is based on clinical, laboratory and/or imaging findings. Established microvascular thrombosis requires objective evidence by histopathology (all features), cytology (pulmonary haemorrhage) or imaging (myocardial disease, adrenal haemorrhage). pt(s), point(s). Adapted from Barbhaiya *et al*.[19]

1.7 Diagnosis and clinical heterogeneity of APS

Most clinical features of APS, both thrombotic and obstetric, can be attributed to multiple causes.[4 9] Since no diagnostic criteria are available for APS, the diagnosis requires clinical assessment along with careful interpretation of the laboratory aPL profile.[4] In TAPS, younger patients with a thrombotic event have a higher probability of APS, especially if predisposing factors for a first or recurrent venous and/or arterial thrombosis are not present.[3 4 9] aPL testing is also necessary if OAPS is suspected after excluding other causes of obstetric events similar to those in APS.[4 9] The co-occurrence of 'non-criteria' clinical features may increase clinical suspicion of APS in both TAPS and OAPS.[9] aPL testing should be performed according to International Society on Thrombosis and Haemostasis guidelines.[12] The initial testing should be carried out close to the clinical events and then repeated at least 12 weeks later.[4 6 9] When performing and interpreting the LA test, several preanalytical and analytical variables must be taken into account.[6 9 23] Importantly, classification criteria should not be used alone for diagnostic purposes.[17]

Patients with *SLE* may have aPL_{pos} in 25% to 40% of cases. However, the development of APS is observed in about half of these cases.[2-4] LA is the most commonly detected aPL in SLE-APS.[4] Patients with PAPS are at low risk for subsequent onset of SLE, particularly if they are elderly, men, and do not have valvular heart disease, livedo, or clinical and laboratory findings suggestive of SLE (eg, myalgias, leukopenia).[2]

Clinically, APS is a highly heterogeneous disease. *Cluster analysis* in some patient cohorts has revealed predominant clinical and laboratory associations, including women with PAPS, venous thrombosis and triple aPL_{pos} or SLE-APS, venous thrombosis, aPL-associated nephropathy, thrombocytopenia and LA positivity, as well as the association between middle age, arterial thrombosis, livedo, neurological manifestations and established atherosclerotic cardiovascular disease (CVD) risk factors.[2 3] Although a number of patients may have clinical findings highly suggestive of APS, the laboratory profile for all three major aPL may be persistently negative. This clinical phenotype has been termed *'sero-negative APS'* and is currently considered a controversial descriptor of the syndrome.[2 20]

CAPS is a very rare, life-threatening form of APS that is associated with the development of microvascular and/or macrovascular manifestations in multiple organs over the course of days to weeks.[2 4 6] Cardiovascular events, renal and pulmonary involvement, and microangiopathic haemolytic anaemia are common.[3 4 9] This form of the disease is associated with a high mortality rate despite aggressive treatment.[4]

1.8 General management of APS

Lifelong antithrombotic therapy as secondary prevention is currently the recommended therapy for patients with APS.[4 6 8 9] *Vitamin K antagonists* (VKAs) are the frontline of treatment, but their use is not permitted during pregnancy.[4 8 9] Anticoagulation monitoring with VKAs requires special considerations, particularly when clotting times are falsely prolonged due to the LA phenomenon.[6 9] The target INR is 2 to 3.[4 8] *Low molecular weight heparin* in therapeutic doses can be used instead of VKAs in pregnant women and patients with recurrent thrombotic events.[4 6 8]

Aspirin has been used in the treatment of asymptomatic carriers of a high-risk aPL profile (eg, LA positivity or triple aPL_{pos}) and is also used in pregnant women and in combination with a VKA in patients with arterial thrombotic events.[4 8 9] *Direct oral anticoagulants* (DOACs) do not appear to be effective in the thromboprophylaxis of patients with APS.[4 6]

Screening for and appropriate control of additional risk factors associated with the occurrence of APS events is recommended for all patients.[4 8]

2. Thrombotic APS

2.1 Thrombogenic effects of aPL

Acquisition of immunogenic properties by β2GPI is the first step in the production of pathogenic aPL.[2-4 6 11] The immunogenicity of this target protein depends on its conformational change upon binding to membrane phospholipids, thereby exposing its DV domain.[2 4 6] This process is thought to be accelerated by co-occurring factors such as an oxidative environment and inflammation (including infections).[2 3] aPL, likely produced by long-lived plasma cells under T lymphocyte signalling and aberrant innate immune cell activity upon exposure to the DV domain,[3 4] then bind specifically but weakly to the DI domain of β2GPI.[2 6]

aPL are able to activate the vascular endothelium, monocytes, neutrophils and platelets and appear to modulate the activity of the complement system.[3 4 6 11] They also exert effects on the coagulation cascade, including abnormal activation of coagulation factors (PT and thrombin are considered important targets of aPL), impairment of fibrinolysis, and inhibition of protein C.[2 4 11] The net effect of these processes is a procoagulant/proinflammatory state at the interface between blood vessel wall, haemostasis and immune system.

It is possible that different types of aPL play different roles in the various cellular and molecular interactions that underlie the prothrombotic environment in APS.[6 11] aPL displaying the LA phenomenon may be associated with abnormalities in platelet physiology, while anti-β2GPI to specific epitopes have been found to impair specific coagulation pathways through increased expression of tissue factor by various cells and tissues.[6]

2.2 Pathogenesis of TAPS

Experimental data suggest that the presence of aPL alone may be a necessary but not sufficient condition for the occurrence of thrombotic events in APS.[4 6 9] According to the '*two-hit hypothesis*', dysregulation of vascular function leading to thrombosis is triggered by the prothrombotic effects of aPL (ie, *first hit*),

followed by the impact of additional precipitating conditions (ie, *second hit*), including inflammation (eg, SLE, infections) and established vascular risk factors for venous and/or arterial thrombosis (eg, obesity, cancer, oestrogen therapy, hypertension).[3 4 6 9] This hypothesis is corroborated by clinical evidence on predictors of a first thrombotic event in human asymptomatic aPL carriers.[24 25] Many of these additional risk factors are also associated with recurrence of thrombotic events in APS.[26-28]

The physiological mechanism of *immunothrombosis* is also involved in the development of thrombotic events in APS.[6 29] This process requires the coordinated activity of neutrophils, monocytes, platelets and the complement system.[29] Neutrophil extracellular traps (NETs) play an important role in triggering *in situ* thrombosis as a defence against the spread of tissue damage by inflammatory stimuli.[4 6 27 29] Excess NETs have been observed in APS, possibly due to aPL-induced increased production (even in the absence of acute thrombotic events) and decreased clearance rate.[6]

2.3 Macrovascular and microvascular manifestations in TAPS

TAPS can affect any size of vein or artery.[2 4 6 15] Venous thrombotic events (VTEs) are more common than arterial thrombotic events (ATEs).[3 13-15] The most common VTE and ATE in APS are deep venous thrombosis of the lower extremities (with or without concurrent pulmonary embolism) and stroke, respectively.[4 14 15] Nevertheless, *macrovascular* thrombotic events can occur in virtually any vascular bed, including splanchnic blood vessels (eg, Budd-Chiari syndrome) or ATEs in the upper extremities,[14 15 20] which represent unusual anatomical sites of thrombosis in other types of prothrombotic conditions. Recurrence of macrovascular manifestations in the same vascular territory is quite common in APS, although the reasons for this pattern of clinical relapse are not fully understood.[2 6]

Microvascular thrombosis is not uncommon in APS and can manifest in clinical syndromes affecting any organ system.[4 6 15] The skin (eg, livedoid lesions) and kidneys (eg, thrombotic microangiopathy) are frequently reported sites of microvascular manifestations.[4 15] Other clinical features suggestive of small vessel thrombosis in APS include osteonecrosis, pulmonary haemor-

rhage, and haemolytic anaemia.[4 6 15 19 20] Diagnosis of microvascular APS requires biopsy-proven lesions.[15 19] Diffuse microvascular disease is a key feature of CAPS.[2-4 9]

2.4 Risk stratification for macrovascular thrombotic events in APS

The 'Sydney classification criteria' highlighted the need to consider *vascular risk factors associated with venous thromboembolism and cardiovascular events* in macrovascular thrombosis in APS. In particular, it has been suggested that established predictors of venous thrombosis or stroke and/or myocardial infarction (MI) should be considered as contributing factors for thrombotic events (Table 3, p. 27).[18] Although this approach is pathophysiologically plausible, it can be a challenging aspect in the study and clinical management of APS, as the syndrome is one of the causes of *unprovoked* venous and/or arterial thrombosis.[30 31] Age appears to be a crucial factor in this context,[18] as older patients are more likely to have a non-aPL cause of a thrombotic event (eg, cancer in VTEs, atherosclerosis in ATEs) despite the presence of aPL_{pos}.

The ACR/EULAR classification criteria expanded and refined the concept of additive vascular risk in macrovascular thrombosis in APS originally proposed in the 'Sydney classification criteria'. The newly proposed *vascular risk profiles*, developed separately for VTEs and ATEs, enable graded stratification of additional risk factors representing mechanisms involved in thrombotic events in the general population (Table 3, p. 27).[19] According to this semi-quantitative risk classification approach, the more severe the risk factors a patient has, the fewer points are assigned to the corresponding vascular risk profile, suggesting that a lower vascular risk score indicates an unprovoked cause of the thrombotic event under study, such as the case of APS. Importantly, the ACR/EULAR vascular risk profiles do not consider age as a determinant of vascular disease.

The Global APS Score (GAPSS) is a risk assessment model (RAM) originally developed for SLE-aPL_{pos} patients to predict the occurrence of thrombotic events in APS.[32] Later, it was also studied in people with PAPS.[33] According to its derivation study, hypertension, hyperlipidaemia, and aPL profile (aCL, anti-β2GPI, LA, anti-PS/PT) are the best predictors of VTEs and/or

ATEs.[32] This RAM was subsequently modified into the adjusted GAPSS (aGAPSS) by excluding anti-PS/PT from the equation and tested in the international APS ACTION cohort using recurrent events as the outcome.[34] Notably, both GAPPS and aGAPSS equations classify cases with triple aPL_{pos} as high risk, regardless of the weights calculated for the traditional vascular risk predictors. Similar to the ACR/EULAR classification criteria, this RAM does not consider age as a risk factor. Various studies have examined the clinical utility of GAPSS/aGAPSS in predicting thrombosis in APS.[33 35] However, none of the currently available recommendations for APS have officially endorsed this tool for use in the classification and/or clinical management of patients.[8 19 36]

TABLE 3 **Vascular risk factors in the classification of APS**

According to the Sydney classification criteria (Adapted from Miyakis *et al*.[18])
Age (men >55 years old; women >65 years old)
Venous thromboembolism: immobilisation; inherited thrombophilias; malignancy; nephrotic syndrome; oral contraceptives; surgery
CVD: chronic kidney disease (stage 3 and above); diabetes mellitus; dyslipidaemia; family history of premature CVD; hypertension; microalbuminuria; obesity; smoking
According to the ACR/EULAR classification criteria (Adapted from Barbhaya *et al*.[19])
Venous thromboembolism (*high-risk profile*: ≥1 major or ≥2 minor risk factors) • Major risk factors – active malignancy; immobilisation during hospitalisation for ≥3 days in the past 3 months; major trauma (fractures; spinal cord injury) in the past 1 month; surgery with anaesthesia for >30 min in the past 3 months • Minor risk factors – active systemic autoimmune disease or inflammatory bowel disease; acute severe infection; central venous catheterisation; obesity; oestrogen-containing hormonal therapy; pregnancy or postpartum period (<6 weeks); immobilisation out of hospital for ≥3 days; surgery with anaesthesia for <30 min in the past 3 months; travel ≥8 hours
CVD (*high-risk profile*: ≥1 major or ≥3 moderate risk factors) • Major risk factors – chronic kidney disease (stage 3 and above); high-risk diabetes mellitus (target-organ damage; prolonged disease duration); severe (grade 3) hypertension; severe hyperlipidaemia (total cholesterol ≥310 mg/dL or low-density lipoprotein cholesterol ≥190 mg/dL) • Moderate risk factors – moderate hyperlipidaemia (treated or untreated; total cholesterol <310 mg/dL or low-density cholesterol <190 mg/dL); moderate-risk diabetes mellitus (without target-organ damage; short disease duration); obesity; persistent hypertension (treated or untreated; grade 1 or 2); smoking

3. Arterial thrombosis in APS

3.1 Epidemiology and disease burden of ATEs in APS

Overall, ATEs account for approximately 44.9% of clinical manifestations at disease onset in APS.[2 14 37] The most common arterial thromboses, in descending order of frequency, are cerebrovascular accidents (stroke and transient ischaemic attack), MI, and arterial thrombosis of the limbs (ie, lower extremity arterial disease).[14 37] In patients with ATE as a presenting feature, virtually all subsequent ATEs occur at the same anatomical site.[4 6] Recurrence rates for stroke and MI are higher than for VTEs.[4 14] These two major ATEs (MATEs) are a significant cause of morbidity and mortality in APS.[14 38] aPL-associated cerebrovascular and coronary artery events account for an estimated 17% and 11% of cases, respectively, in patients younger than 50 years.[5] Furthermore, MI and stroke rank second and third, respectively, in ten-year all-cause mortality in APS.[14]

3.2 Mechanisms of MATEs in APS

Disease-related variables associated with ATEs in APS include the aPL profile and certain disease features. A high-risk aPL profile including LA or triple positivity is considered a strong predictor of ATEs.[8 37 38] Although robust evidence on the association of specific aPL subpopulations with MATEs is currently lacking,[38] data from observational studies suggest that both LA and anti-β2GPI are slightly more prevalent in ATEs than VTEs, while aCL positivity is present in up to one-fifth of cases.[39] Livedo and valvular heart disease cluster with ATEs in APS,[2 3] but the reason for this association remains to be fully elucidated, particularly for features suggestive of microvascular disease.

Established CVD risk (CVR) factors also appear to be predictive of MATEs in APS. Evidence from large cohort studies suggests that hypertension, lipid disorders, and smoking are common in patients with TAPS,[2 14] while the aGAPSS derivation study identified abnormal blood pressure (BP) and hyperlipidaemia as independent predictors of thrombosis.[34] According to a pilot study

examining a revised version of aGAPSS for CVD (aGAPSS$_{CVD}$),[40] the presence of diabetes mellitus (DM) is also associated with ATEs, in addition to the above-mentioned CVR factors. These results are consistent with the 'two-hit' hypothesis proposed for the pathogenesis of TAPS.[6 9]

Pathophysiologically, MATEs in APS can occur due to *in situ* thrombosis or thromboembolism. Regarding the latter mechanism, valvular heart disease is of particular interest in CVD in APS.[27 38] Stroke is probably the most heterogeneous manifestation in terms of the underlying mechanism, since both arterial thromboembolism and atherosclerotic carotid artery stenosis may be present in stroke patients with APS.[38] As would be expected with any thrombophilia,[41] MI with non-obstructive coronary arteries is a relatively common finding in TAPS,[2 38 42 43] but concomitant significant atherosclerosis of the coronary arteries has also been described in approximately 25% of cases.[43] Patients with APS are at risk of premature and accelerated atherosclerosis,[44 45] but the relative contribution of this mechanism in incident and recurrent MATEs has not been established. Microvascular disease and embolism may also be responsible for MI in APS.[38]

3.3 Current issues in the management of MATEs in APS

Recurrence of MATEs is an important clinical issue in the care of APS patients.[4 38] In fact, recurrent MATEs are more common than recurrent VTEs in fully anticoagulated patients.[27] However, discontinuation of antithrombotic treatment does not affect the incidence of ATEs compared to VTEs,[46] suggesting that optimal measures for secondary thromboprophylaxis for stroke and/or MI in APS remain to be determined. DOACs should be avoided in patients with a history of ATE,[4 6 38] and switching to VKAs has been suggested for patients with a history of VTE and a first ATE. The use of aspirin as adjunctive therapy has been introduced in various guidelines for the treatment of ATEs, including the EULAR recommendations,[8] but the effectiveness of this intervention is not clearly established. In addition, pharmacological agents with pleiotropic effects such as statins or hydroxychloroquine have been proposed to reduce the incidence of recurrent ATEs in APS.[4 8 38] However, evidence is limited due to surrogate outcomes from *in vitro* studies or insufficiently powered studies.

PART **B**

LITERATURE REVIEW

4. Aim and significance of the study

4.1 Study objective

The main objective of the present thesis was to investigate the clinical and laboratory determinants of a first and/or recurrent MATE in patients with APS. Considering that MATEs in this syndrome are nosological entities that share clinical features and outcomes with the major cardiovascular events described in the general population,[2 3 47] the investigation focused on established CVR factors as introduced in the currently available risk stratification tools, some of which are also included in the classification criteria of APS.[19] Both predictors of a first cardiovascular event as introduced in the two commonly used risk prediction models Systematic Coronary Risk Evaluation (SCORE; developed for the European population)[47] and Pooled Cohorts Risk Equation (PCRE; developed for the North American population)[48] and predictors of a recurrent cardiovascular event included in the Second Manifestations of Arterial Disease (SMART)[49] tool were examined. Most of the CVR variables weighted in these models are also included in the aGAPSS[34] and aGAPSS$_{CVD}$[40] equations developed specifically for the APS population and in the vascular risk factor assessment section of the classification criteria of APS.[19]

The use of generic CVR prediction models has been proposed by EULAR for CVR assessment in APS.[36] The same recommendations also suggest the use of disease-related CVR factors, such as the aPL profile, while increasing evidence highlights a number of APS-specific features as predictors of MATEs in the syndrome (reviewed in **Topic 3.2**, p. 28). Therefore, this thesis also investigated the impact of disease features as determinants of the occurrence or recurrence of major cardiovascular events in APS patients. The clinical and laboratory features examined are summarised in Table 4 on p. 32.

As a secondary objective, the present investigation explored the relative weight of each of the identified independent predictors of MATEs compared to the weight suggested by the classification criteria of APS.

TABLE 4 **Summary of CVR factors included in generic and disease-related RAMs and the classification criteria of APS**

General CVR factors	SCORE2	PCRE	SMART	aGAPSS, $aGAPSS_{CVD}$	ACR/EULAR*
Gender	Yes	Yes	Yes	No	No
Age	Yes	Yes	Yes	No	No
Smoking	Yes	Yes	Yes	Yes†	Yes
Blood pressure	Yes	Yes	Yes	Yes	Yes
Blood lipids	Yes	Yes	Yes	Yes	Yes
Specific CVR factors					
Anatomical site of thrombosis	No	No	Yes	No	No
History of thrombosis	No	No	Yes	No	No
Kidney disease	Yes‡	Yes	Yes	No	Yes
Obesity	No	No	No	Yes†	Yes
Diabetes mellitus	Yes‡	Yes	Yes	Yes†	Yes
Antithrombotic treatment	No	No	Yes	No	No
aPL profile	No	No	No	Yes	No

* CVR factors assessed as cumulative load.

† Only included in the $aGAPSS_{CVD}$ equation.

‡ Not included in the original SCORE2 equation. Considered separately as a CVR modifier.

4.2 Significance of the study

The literature review underlying the present thesis acted as an exploratory study aimed at better characterising the major predictors of MATEs in APS and addressing potential issues with the assessment of CVR factors and disease-related features as significant determinants of major cardiovascular events in patients with APS.

5. Methods

5.1 PICO question

The present literature review aimed at the following scientific inquiry, formulated according to the PICO (*P*opulation *I*ntervention *C*omparator *O*utcome) process in clinical research: “In patients with APS, which clinical and laboratory variables related to established CVR factors and/or disease-specific features independently predict the occurrence and/or recurrence of MATEs such as stroke and myocardial infarction?”

Based on the results of the above question, an exploratory analysis aimed at the similarities and differences of the identified predictors of MATEs with CVR factors in SCORE2, PCRE, SMART, aGAPSS, aGAPSS$_{CVD}$ and the classification criteria of APS was conducted.

5.2 Search strategy

The PubMed/MEDLINE library was searched for articles related to the PICO question from its inception to May 2024. The major terms introduced in the search strategy are outlined in Table 5 on p. 34.

5.3 Inclusion and exclusion criteria

Studies included in the literature review included those pertaining to full-text English language articles examining cardiovascular outcomes such as arterial thrombosis, stroke or MI in adult patients with APS. Study selection was based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol. Because CVR factors specific to the nosology of APS were first introduced in the Sydney classification criteria, articles published before 2005 were excluded from the review.

TABLE 5 **Search strings in the PubMed/MEDLINE database**

Query	Search terms	Results
#19*	#18 NOT ("Case Reports" [Publication Type] OR "Editorial" [Publication Type] OR "Letter" [Publication Type] OR "Congress" [Publication Type])	213
#18	#17 NOT (("Adolescent"[MeSH Terms] OR "Child"[MeSH Terms] OR "Infant"[MeSH Terms] OR adolescen*[Title/Abstract] OR child*[Title/Abstract] OR infant*[Title/Abstract] OR teenager*[Title/Abstract] OR youth*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) NOT ("Adult"[Mesh] OR adult*[Title/Abstract] OR man[Title/Abstract] OR men[Title/Abstract] OR woman[Title/Abstract] OR women[Title/Abstract]))	374
#17	#16 NOT (animals[mh] NOT humans[mh])	382
#16	#7 AND English[la]	386
#15†	#14 NOT ("Case Reports" [Publication Type] OR "Editorial" [Publication Type] OR "Letter" [Publication Type] OR "Congress" [Publication Type])	581
#14	#13 NOT (("Adolescent"[MeSH Terms] OR "Child"[MeSH Terms] OR "Infant"[MeSH Terms] OR adolescen*[Title/Abstract] OR child*[Title/Abstract] OR infant*[Title/Abstract] OR teenager*[Title/Abstract] OR youth*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) NOT ("Adult"[Mesh] OR adult*[Title/Abstract] OR man[Title/Abstract] OR men[Title/Abstract] OR woman[Title/Abstract] OR women[Title/Abstract]))	918
#13	#12 NOT (animals[mh] NOT humans[mh])	987
#12	#6 AND English[la]	989
#11‡	#10 NOT ("Case Reports" [Publication Type] OR "Editorial" [Publication Type] OR "Letter" [Publication Type] OR "Congress" [Publication Type])	550
#10	#9 NOT (("Adolescent"[MeSH Terms] OR "Child"[MeSH Terms] OR "Infant"[MeSH Terms] OR adolescen*[Title/Abstract] OR child*[Title/Abstract] OR infant*[Title/Abstract] OR teenager*[Title/Abstract] OR youth*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) NOT ("Adult"[Mesh] OR adult*[Title/Abstract] OR man[Title/Abstract] OR men[Title/Abstract] OR woman[Title/Abstract] OR women[Title/Abstract]))	717
#9	#8 NOT (animals[mh] NOT humans[mh])	755
#8	#5 AND English[la]	758

TABLE 5 (*continues from page 34*)

Query	Search terms	Results
#7	#1 AND #4	451
#6	#1 AND #3	1187
#5	#1 AND #2	884
#4	"myocardial infarction"[Title/Abstract] OR "heart attack"[Title/Abstract] OR "acute coronary syndrome"[Title/Abstract] OR "acute coronary syndrome"[MeSH Terms] OR "cardiovascular event*"[Title/Abstract] OR "cardio-vascular event*"[Title/Abstract] OR "coronary artery event*"[Title/Abstract] OR "cardio-vascular"[Title/Abstract]	286998
#3	(((((acute stroke[MeSH Terms]) OR (cerebral stroke[MeSH Terms])) OR (acute cerebrovascular accident[MeSH Terms])) OR (cerebrovascular accident[MeSH Terms])) OR (stroke[Title/Abstract])) OR (cerebrovascular[Title/Abstract])	422086
#2	"arterial thrombosis"[Title/Abstract] OR "arterial thromb*"[Title/Abstract]	12032
#1	"antiphospholipid syndrome"[MeSH Terms] OR "antiphospholipid syndrome"[Title/Abstract] OR "anti-phospholipid syndrome"[Title/Abstract] OR "antiphospholipid antibody syndrome"[Title/Abstract] OR "anti-phospholipid antibody syndrome"[Title/Abstract] OR "Hughes"[Title/Abstract]	15317

* Final search string for “antiphospholipid syndrome” and “myocardial infarction”.

† Final search string for “antiphospholipid syndrome” and “stroke”.

‡ Final search string for “antiphospholipid syndrome” and “arterial thrombosis”.

6. Results

6.1 Study selection

After introducing the main search terms of 'APS', 'arterial thrombosis', 'stroke' and 'myocardial infarction' and applying exclusion search terms related to the English language, animal studies, adult population, and article types with low level of evidence (case reports, letters to the Editor, conference abstracts, etc), a total of 1344 records (arterial thrombosis: 550; stroke: 581; MI: 213) were identified in the PubMed/MEDLINE database (Figure 2, 3 and 4, pp. 39–41). Of these, 326 records published before 2005 were excluded. After screening titles and abstracts, 172 articles regarding all three search strings were sought for retrieval. One hundred and forty-two retrieved records, as well as a number of hand-searched articles (four for arterial thrombosis, one for stroke, two for MI), underwent full-text reading. After adjusting for duplicates and cross-referenced records among the three search results, 71 unique articles were reviewed (**Appendix**, p. 60).

6.2 Association of CVR factors with arterial thrombosis in APS

Male gender and *older age* were identified as predictors of ATEs in five[28 50-53] and seven[51 52 54-58] studies, respectively. Nine,[25 28 40 51 52 56 59-61] fourteen[25 27 28 51 52 55 56 59 60 62-66] and nine[27 28 51 52 54-56 60 63 64] studies, respectively, found *smoking*, *BP* and *lipid profile* to be associated with ATEs. *Renal disease* and *obesity* were predictors of recurrent ATEs in one study each.[40 54] *DM* was found to impact ATEs in two studies.[25 40] Another two studies reported data on *atherosclerosis*.[56 67]

In 20 studies, *aPL positivity* was associated with a first or recurrent event.[59 68 27 40 51 53 55 56 58 60 61 63 69-76] The *anatomical site of thrombosis* and *history of ATEs* were identified as determinants of events in three[51 77 78] and 11[27 51-55 72 77-80] studies, respectively. Fifteen studies[72 77-90] found that the use of antithrombotic medications may influence cardiovascular outcomes, particularly in the event of recurrent ATEs with the use of DOACs (11/15 studies).

Eighteen studies included data on the *strength of association* of CVR factors with ATEs.[25 28 40 52-54 56 59 60 62-64 66 67 70-72 79] In descending order of frequency (number of studies in parentheses), these were aPL (seven; criteria aPL in three; non-criteria aPL in three; both in one), BP (three), lipids (two), male gender (one), smoking (one), DM (one), atherosclerosis (one), antithrombotics (one), and atrial fibrillation (one). Among variables amenable to risk-stratified management, BP and lipids were reported as the strongest determinants in four[52 59 62 66] and three[54 56 64] studies, respectively.

6.3 Association of CVR factors with stroke in APS

An association between stroke and *male gender*, *older age*, *smoking*, *BP* and *lipids* was observed in four,[28 91-93] five,[57 92-95] six,[28 40 60 61 91 93] four[60 92 95 96] and six[60 92 96-98] studies, respectively. BP (two studies)[92 95] and smoking (four studies)[28 60 91 93] showed a greater *strength of association* with cerebrovascular events. One study found an association with *obesity*[40] and three studies with DM.[40 92 94] Two studies found no association between *renal disease* and stroke.[69 92] Objectively documented *atherosclerosis* was reported in four studies.[40 96 99 100]

Four studies[60 79 81 91] found no association between the *anatomical site of thrombosis* and cerebrovascular events. Another four studies[79 91 92 96] reported an association between a *history of thrombosis* and stroke. Thirteen studies have linked *aPL* to stroke.[40 60 61 69 93 95 96 99-104] The use of *antithrombotics* resulted in a higher risk of cerebrovascular events in seven studies;[77 79 81 85 90 100 102] five studies involved DOACs and two studies pertained to antiplatelets.

6.4 Association of CVR factors with MI in APS

Coronary artery events were associated with *male gender* and *BP* in two studies each.[28 50 63 105] Three studies found *older age* to be associated with MI.[93 98 106] *Smoking* and *lipid disorders* predicted events in four studies each.[28 40 50 61 63 105 107] One study reported an association with *DM*[40] and two studies found no association with *renal disease*.[67 105] *Atherosclerosis* of the coronary arteries

was observed in three studies.[40 67 108] Dyslipidaemia was the *strongest* modifiable independent variable in two MI studies.[28 107]

One study found no association between the *anatomical site of thrombosis* and recurrent MI.[79] In two studies,[79 107] a *history of thrombosis* was associated with the occurrence of a coronary artery event. Eight studies reported that criteria *aPL* were associated with events.[40 50 61 63 93 102 105 109] Antithrombotics were a risk factor for MI in three studies (two reported the use of antiplatelet agents and one reported DOACs).[79 102 105]

6.5 Sensitivity analysis of reviewed studies

The number of positive or null associations between CVR factors and vascular outcomes are summarised in Table 6 on p. 42. In descending order of frequency, among risk factors, renal disease, obesity, anatomic site of thrombosis, and history of ATEs were reported least frequently. Eight of 20, six of 13 and two of eight studies examining the association between aPL positivity and ATEs, stroke and MI, respectively, did not address the effects of other CVR factors.

All five major CVR factors (ie, male gender, older age, smoking, BP, and lipids) were examined as follows: ATEs: 11 studies;[28 51-56 64 67 79 110] stroke: seven studies;[28 79 91-93 95 96] MI: four studies.[28 79 105 107] Focusing on recurrent events, a cumulative load of vascular damage attributable to CVR factors (ie, the simultaneous presence of at least two established CVR factors) was observed in eight studies on ATEs,[27 28 40 51 54 55 79 111] four studies on stroke[28 40 91 92] and two studies on MI.[28 40]

A number of studies have reported definitions of atherosclerotic CVR factors that conform to either the European Society of Cardiology or American College of Cardiology/American Heart Association guidelines. Specifically, the frequency of reporting on established descriptors was as follows: *smoking*: 9/17 studies on ATEs, 4/6 studies on stroke, and 4/4 studies on MI; *BP*: 9/19 studies on ATEs, 2/4 studies on stroke, and 4/8 studies on MI; *lipid disorders*: 1/18 studies on ATEs, 0/4 studies on stroke, and 1/7 studies on MI; *obesity*: 2/9 studies on ATEs, 2/3 studies on stroke, and 2/4 studies on MI; *DM*: 3/17 studies on ATEs, 2/4 studies on stroke, and 1/7 studies on MI.

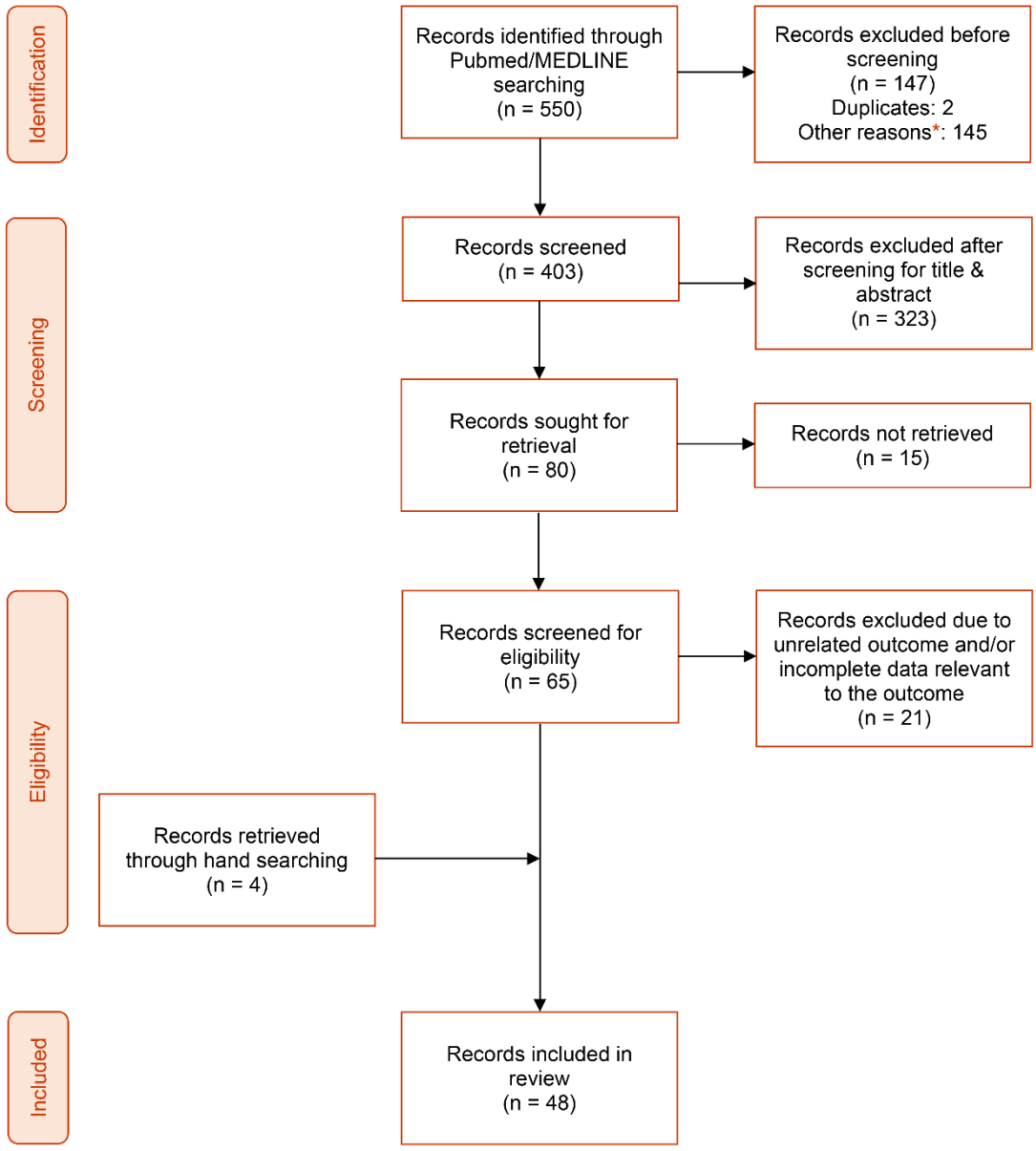


FIGURE 2 **Flowchart of study selection for arterial thrombosis in APS**. *Studies published before 2005. [Own work]

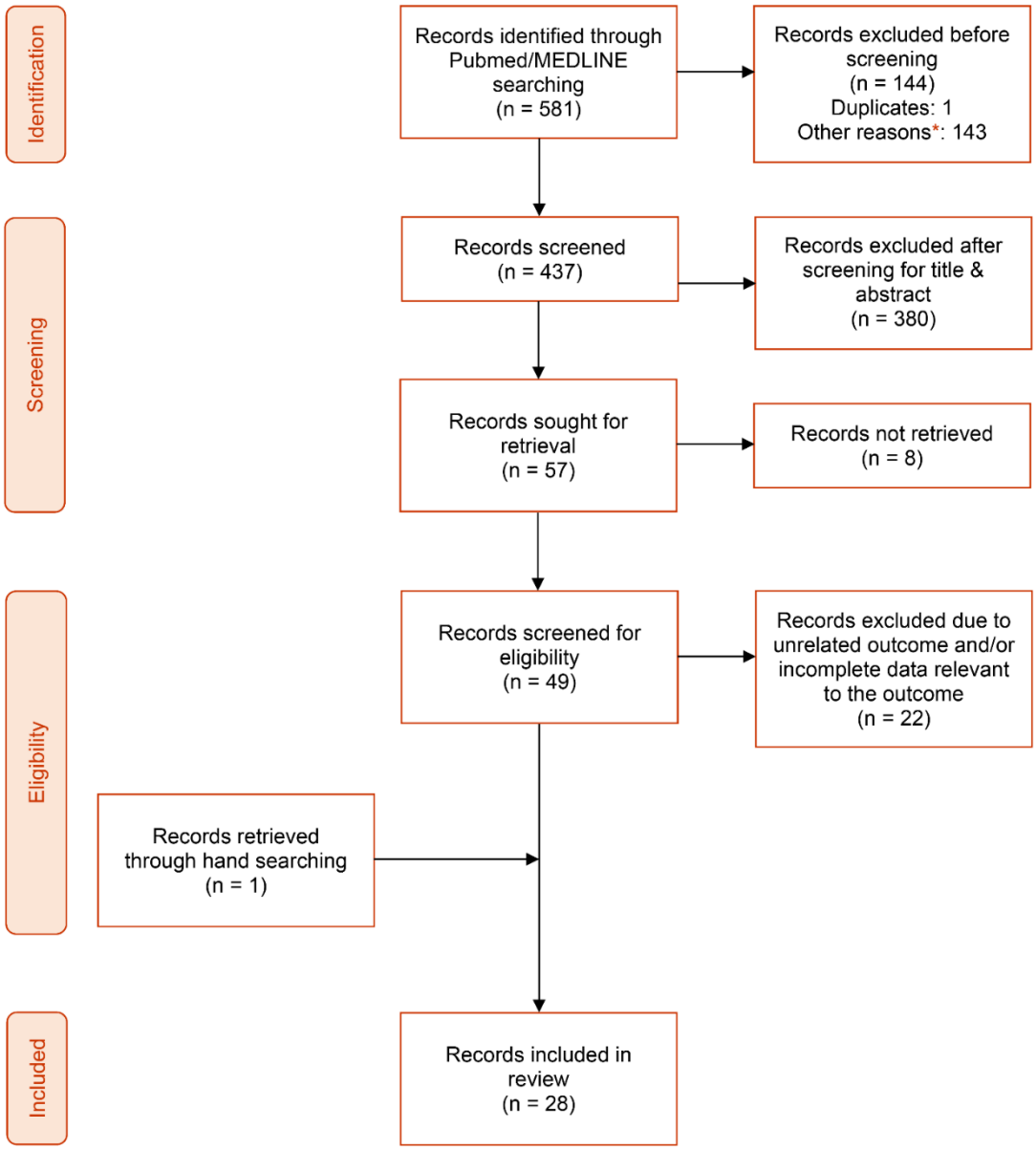


FIGURE 3 **Flowchart of study selection for stroke in APS**. *Studies published before 2005. [Own work]

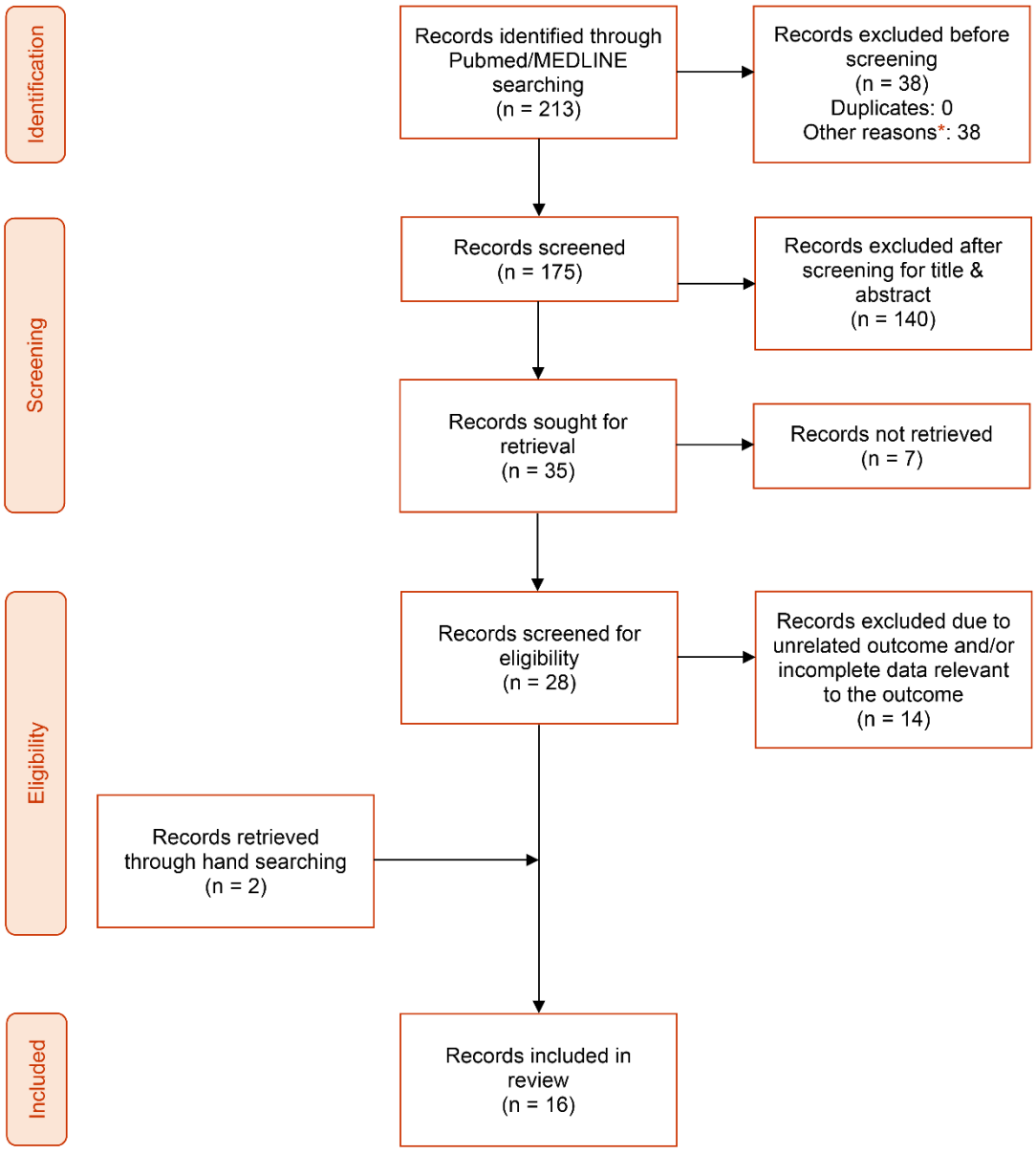


FIGURE 4 **Flowchart of study selection for MI in APS**. *Studies published before 2005.

[Own work]

TABLE 6 **Studies reporting the association of general and specific CVR factors with vascular outcomes in APS**

	Arterial thrombosis			Stroke			Myocardial infarction		
	Positive association	Null association	NR/NE	Positive association	Null association	NR/NE	Positive association	Null association	NR/NE
Gender (male)	5	9	34	4	7	17	2	5	9
Age (older)	7	12	29	5	6	17	3	6	7
Smoking	9	12	27	6	6	16	4	6	6
BP	14	7	27	4	6	18	2	6	8
Lipids	10	11	27	6	6	14	4	3	9
Renal disease	1	2	45	0	2	26	0	2	14
Obesity	1	0	47	1	4	23	1	3	12
DM	2	17	29	3	6	19	1	6	9
Anatomical site of thrombosis	3	7	38	0	4	24	0	1	15
History of thrombosis	11	3	34	4	2	22	2	2	12
Antithrombotic treatment	15	1	32	7	3	18	3	1	12
aPL profile	20	7	21	13	3	12	8	1	7

NR/NE, not reported/not examined.

7. Discussion

TAPS is a high vascular risk disease characterised by recurrent events and challenges in appropriate risk stratification and clinical management, particularly in the case of MATEs such as stroke or MI. Identifying those variables that best predict the risk of developing ATEs would help optimise care by intervening at the population and individual patient levels. In the case of APS, it has been suggested to adopt the recommendations available for the general population,[19 36 38] although this approach is not without limitations. Based on the results of the present review, a number of CVR factors introduced into general[47 48] and disease-specific RAMs[34 40] and risk profiles[18 19] may actually influence the cardiovascular prognosis of APS patients. However, the mixed evidence observed in the reviewed studies requires particular attention to a number of issues, including the weighting of each CVR factor, the clustering of risk factors, and the potentially differential impact of the various established and disease-related predictors on each type of CVD.

Age is a well-established non-modifiable vascular risk factor that has been incorporated in most general RAMs available to date.[47-49] A positive association with MATEs in APS was found in approximately half of the studies on stroke and/or MI. However, up to two-thirds of studies did not specifically address age as a CVR factor. Gender is also an important non-modifiable CVR factor that was not examined as often in the studies reviewed. Remarkably, both these risk factors are not included in the aGAPSS equations[34 40] and were not introduced in the ACR/EULAR vascular risk profiles.[19] Considering that both large observational studies[28] and cluster analyses[2 3] have delineated these two variables as predictors of ATEs in APS, the impact of age and gender on cardiovascular outcomes in this syndrome would need to be re-evaluated with a view to their inclusion in disease-specific RAMs and risk profiles of classification criteria.

Smoking is a predisposing factor for cardiovascular events[47-49] and has also been described as a trigger for the occurrence and recurrence of ATEs in APS.[3 38 40] In the latter case, most of the studies examined in the present review established an association between tobacco use and MI, although a significant

number of studies also found that smoking associates with arterial thrombosis in general. aPL-positive women who smoke are also at high risk of acute thrombosis including stroke and MI.[112] Tobacco use has been identified as an additional factor increasing the risk of thrombosis in APS[3 20] and is included in both the RAMs specifically developed for the syndrome[40] and its classification criteria.[19]

Elevated BP levels can have profound effects on vascular function and anatomy.[47 113] It is also a major risk factor for all types of stroke,[113] which represents the most common first and recurrent MATE in APS.[2 3] In the studies reviewed, hypertension was highlighted as a triggering factor for arterial thrombosis in APS, with potentially greater impact on stroke than in MI. BP is also one of the most important modifiable CVR factors, and risk-stratified management has been proposed to reduce cardiovascular damage in the general population.[113] The vascular risk profiles introduced by the ACR/EULAR classification criteria for APS also include BP grading relevant to patients' risk of thrombosis.[19] However, none of the reviewed studies found that the BP profiles reported in these classification criteria confer a higher or lower risk of occurrence or recurrence of ATEs in APS.

Abnormal lipid metabolism is a hallmark of vascular damage in symptomatic atherosclerosis and, in this context, lipid-lowering medications are routinely prescribed for primary and secondary prevention of CVD.[114] aPL_{pos} is associated with accelerated atherosclerosis,[44 45] but the relative contribution of aPL and lipid disorders to its pathophysiology remains unclear. Nevertheless, dyslipidaemia was found to be associated with ATEs in a large number of studies examined in this review. Specific patterns of lipid perturbations have been suggested by the ACR/EULAR classification criteria to influence the vascular risk profile in APS;[19] however, comparisons with the dyslipidaemia descriptors used in the reviewed studies were not possible.

Obesity is considered a risk factor for CVD when it is associated with a metabolically unhealthy profile that influences other CVR factors such as BP, lipids, and chronic inflammation.[47] Renal impairment, particularly chronic kidney disease, is also a comorbidity that increases CVR.[47 113] Both risk factors were identified as independent predictors of ATEs in APS in one study each, although in the case of kidney disease, the reported estimated glomerular filt-

ration rate did not correspond to the threshold used to define chronic kidney disease.[54] Interestingly, obesity and renal disease are also risk factors for VTEs included in the ACR/EULAR classification criteria.[19] An association be-tween DM and arterial thrombosis was observed particularly in stroke in APS. DM has also been suggested to contribute to cardiovascular harm in TAPS.[3 40]

One of the most intriguing aspects of APS is the propensity for thromboses to recur as events of the same nature and possibly at the same location, particularly in the case of ATEs.[3 14] Therefore, these features could be employed as additional risk classifiers for CVR management in APS. Regrettably, few studies examined history and anatomical site of thrombosis as predictors of ATEs. Nevertheless, these potential risk indicators were present more frequently in stroke than in MI. Neither the site of thrombosis nor a history of an event of the same type were included in the disease-specific RAMs developed in APS[34 40] or the ACR/EULAR classification criteria.[19] SMART, a clinical risk algorithm for the general population includes both risk classifiers,[49] but there is very limited and indirect evidence for its usefulness for CVR prevention in APS.[115]

Given the importance of the aPL profile in defining TAPS,[2 3 18 19] it is one of the most extensively studied thrombotic risk factors in this disease. The majority of studies identified in this review also suggest that all three criteria aPL are predictors of MATEs. A number of studies have also found that 'non-criteria' aPL may have an impact on cardiovascular outcomes. This was particularly evident in the case of anti-PS/PT.[56 60 75] Given that this type of antibodies appears to be involved in the LA phenomenon,[2 6] it is not clear whether their measurement and assessment may have implications for ATEs beyond the consideration of LA, which is already included in the aGAPSS equations.

The type, dosage and duration of antithrombotic treatment are of exceptional clinical importance in TAPS.[3 8 38] To date, most studies have focused on the use of anticoagulants, particularly comparing VKAs with DOACs. Systematic appraisal of the evidence published in recent years suggests that the use of DOACs should be avoided in APS patients with ATEs as it increases the risk of recurrent events,[77 81 87 89] especially stroke. The use of aspirin to prevent recurrence of events has been less investigated. Results from studies included in the present review suggest that antiplatelet agents may play a role in the management of stroke and/or MI in APS.[79 80 100 105] The use of antithrombotics

has been incorporated in the SMART tool for the general population.[49] Nevertheless, the ability of antithrombotic use as a potential CVR classifier in APS has yet to be formally addressed.

Evidence from the general population suggests that the constellation of different CVR factors may increase the risk of events,[47-49] and this attribute underscores the development of RAMs. In APS, the derivation studies of aGAPSS and aGAPSS$_{CVD}$, both of which examined predictors of thrombotic events in multivariate models,[34 40] corroborate this fact in APS as well. Another multi-centric observational study has also identified more than one CVR factor as an independent predictor of events in this syndrome.[28] The Sydney and ACR /EULAR classification criteria also highlighted that clustering of risk factors may impact cardiovascular health in APS.[19] However, cumulative risk profiles as introduced in the later set of criteria were not examined in any of the identified studies in this review.

Objectively documented atherosclerosis is considered a validated CVR classifier due to its association with established determinants of cardiovascular events and their occurrence.[47 114] Considering that aPL have an proatherogenic effect,[2] the use of atherosclerosis markers in CVR assessment in APS could be confounded by their association with the patients' immunological profile. However, meta-analyses of observational studies have found that the association between atherosclerosis and APS is not confounded by CVR factors.[44 45] Therefore, the finding of atherosclerotic damage associated with ATEs in a number of studies could also help refine the actual risk of arterial events in APS independently of aPL$_{pos}$. Despite these considerations, neither the EULAR recommendations for CVR management in APS[36] nor the ACR/EULAR classification criteria[19] have endorsed this modality as a risk predictor.

Considerable heterogeneity in the definition of risk exposures was observed across the studies reviewed. Furthermore, a large number of studies did not provide definitions of risk predictors. These results are inconsistent with the granularity with which the vascular risk profiles of the ACR/EULAR classification criteria were compiled and may represent a further challenge in the characterisation and further assessment of cardiovascular events in APS. Indeed, the ACR/EULAR classification criteria lacked a clear explanation for how the moderate and high CVR features were derived from the European Society of

Cardiology CVR prevention guidelines.[116] Due to the fact that fewer points are assigned to a more severe CVR profile compared to a moderate risk profile, it is plausible to assume that this type of assessment would be used to better differentiate atherothrombotic from non-atherothrombotic events in APS. Despite this hypothesis, it is noteworthy that the vast majority of studies included in this review did not separately report event rates for thrombosis due to atherosclerosis compared with those due to unprovoked stroke and/or MI. This observation, together with the inability to pool results due to the variable, incomplete, or even lack of formal description of CVR factors, should raise awareness to the methodological issues in cardiovascular research in APS.

8. Conclusion

The present exploratory analysis sought to examine the frequency, strength of association and overall impact of established, emerging and disease-related CVR factors on MATEs such as stroke and MI to highlight similarities and differences with risk predictors in validated RAMs and the vascular risk profiles available in the APS classification criteria. Based on the results of the reviewed studies, a number of well-characterised risk factors such as smoking, BP, dyslipidaemia, aPL_{pos}, and type of antithrombotic treatment, which have been incorporated in general and disease-specific RAMs, are valuable in the CVR assessment of patients. However, the observed heterogeneity in exposures and outcomes, particularly in the definition of CVR factors, argues for better standardisation of risk exposures by type (stroke versus MI) and origin (atherothrombotic versus non-atherothrombotic) of vascular outcome to validate the usefulness of all available RAMs as well as the vascular risk profiles provided by the classification criteria of APS.

References

1. World Health Organization. ICD-11 revision. [Available from: https://icd.who.int/browse11/l-m/en] [
2. Cervera R, Espinosa G, Khamashta M (eds). *Antiphospholipid Syndrome in Systemic Autoimmune Diseases*. Second edition Elservier; 2017.
3. Erkan D, Lockshin MD (eds). *Antiphospholipid Syndrome – Current Research Highlights and Clinical Insights*: Springer International Publishing; 2017.
4. Appel GB, Erkan E, Lockshin MD, Lockwood CJ, Ortel TL, Schur PH, Zuily S. *Antiphospholipid Antibody Syndrome*. Crowther M, Glassock RJ, Pisetsky DS, Schur PH (eds). UpToDate: UpToDate, Waltham, MA; 2023.
5. Arachchillage DRJ, Pericleous C. Evolution of antiphospholipid syndrome. *Semin Thromb Hemost* 2023;49:295-304.
6. Knight JS, Branch DW, Ortel TL. Antiphospholipid syndrome: advances in diagnosis, pathogenesis, and management. *BMJ* 2023;380:e069717.
7. Tincani A, Fontana G, Mackworth-Young C. The history of antiphospholipid syndrome. *Reumatismo* 2023;74.
8. Tektonidou MG, Andreoli L, Limper M*, et al.* EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 2019;78:1296-304.
9. Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. *N Engl J Med* 2018;378:2010-21.
10. Horstman LL, Jy W, Bidot CJ*, et al.* Antiphospholipid antibodies: paradigm in transition. *J Neuroinflammation* 2009;6:3.
11. Green D. Pathophysiology of antiphospholipid syndrome. *Thromb Haemost* 2022;122:1085-95.
12. Vandevelde A, Chayoua W, de Laat B*, et al.* Semiquantitative interpretation of anticardiolipin and antibeta2glycoprotein I antibodies measured with various analytical platforms: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. *J Thromb Haemost* 2022;20:508-24.

13. Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S*, et al.* Epidemiology of antiphospholipid syndrome in the general population. *Curr Rheumatol Rep* 2022;23:85.
14. Cervera R, Serrano R, Pons-Estel GJ*, et al.* Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015;74:1011-8.
15. Gaspar P, Sciascia S, Tektonidou MG. Epidemiology of antiphospholipid syndrome: macro- and microvascular manifestations. *Rheumatology (Oxford)* 2024;63:SI24-SI36.
16. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R*, et al.* The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 1000 consecutive cases. *Autoimmun Rev* 2019;18:406-14.
17. Aggarwal R, Ringold S, Khanna D*, et al.* Distinctions between diagnostic and classification criteria? *Arthritis Care Res (Hoboken)* 2015;67:891-7.
18. Miyakis S, Lockshin MD, Atsumi T*, et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295-306.
19. Barbhaiya M, Zuily S, Naden R*, et al.* The 2023 ACR/EULAR antiphospholipid syndrome classification criteria. *Arthritis Rheumatol* 2023;75:1687-702.
20. Sciascia S, Amigo MC, Roccatello D*, et al.* Diagnosing antiphospholipid syndrome: 'extra-criteria' manifestations and technical advances. *Nat Rev Rheumatol* 2017;13:548-60.
21. Abreu MM, Danowski A, Wahl DG*, et al.* The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. *Autoimmun Rev* 2015;14:401-14.
22. Sciascia S, Radin M, Cecchi I*, et al.* 16th International congress on antiphospholipid antibodies task force report on clinical manifestations of antiphospholipid syndrome. *Lupus* 2021;30:1314-26.
23. Devreese KMJ, de Groot PG, de Laat B*, et al.* Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis:

Update of the guidelines for lupus anticoagulant detection and interpretation. *J Thromb Haemost* 2020;18:2828-39.

24. Pablo RD, Cacho PM, Lopez-Hoyos M*, et al.* Risk factors for the development of the disease in antiphospholipid antibodies carriers: a long-term follow-up study. *Clin Rev Allergy Immunol* 2022;62:354-62.
25. Li C, Zuo Y, Zhang S*, et al.* Additional risk factors associated with thrombosis and pregnancy morbidity in a unique cohort of antiphospholipid antibody-positive patients. *Chin Med J (Engl)* 2022;135:658-64.
26. Saraiva Sda S, Custodio IF, Mazetto Bde M*, et al.* Recurrent thrombosis in antiphospholipid syndrome may be associated with cardiovascular risk factors and inflammatory response. *Thromb Res* 2015;136:1174-8.
27. Niznik S, Rapoport MJ, Avnery O*, et al.* Patterns of recurrent thrombosis in primary antiphospholipid syndrome-multicenter, real-life long-term follow-up. *Front Immunol* 2022;13:843718.
28. Moreno-Torres V, Royuela A, Tarin C*, et al.* Impact of cardiovascular risk factors in antiphospholipid syndrome: an observational study from the Spanish national registry. *Clin Exp Rheumatol* 2022;40:2161-66.
29. Marcos-Jubilar M, Lecumberri R, Paramo JA. Immunothrombosis: molecular aspects and new therapeutic perspectives. *J Clin Med* 2023;12.
30. May JE, Moll S. Unexplained arterial thrombosis: approach to diagnosis and treatment. *Hematology Am Soc Hematol Educ Program* 2021;2021:76-84.
31. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107:I9-16.
32. Sciascia S, Sanna G, Murru V*, et al.* GAPSS: the Global Anti-Phospholipid Syndrome Score. *Rheumatology (Oxford)* 2013;52:1397-403.
33. Sciascia S, Radin M, Sanna G*, et al.* Clinical utility of the global anti-phospholipid syndrome score for risk stratification: a pooled analysis. *Rheumatology (Oxford)* 2018;57:661-65.
34. Radin M, Sciascia S, Erkan D*, et al.* The adjusted global antiphospholipid syndrome score (aGAPSS) and the risk of recurrent thrombosis: Results from the APS ACTION cohort. *Semin Arthritis Rheum* 2019;49:464-68.

35. Zhao Y, Huang C, Qi W*, et al.* Validation of three prediction models for thrombosis recurrence in antiphospholipid syndrome patients based on a prospective cohort. *RMD Open* 2023;9.
36. Drosos GC, Vedder D, Houben E*, et al.* EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. *Ann Rheum Dis* 2022;81:768-79.
37. Cervera R, Piette JC, Font J*, et al.* Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis and rheumatism* 2002;46:1019-27.
38. Cheng C, Cheng GY, Denas G*, et al.* Arterial thrombosis in antiphospholipid syndrome (APS): Clinical approach and treatment. A systematic review. *Blood Rev* 2021;48:100788.
39. Schreiber K, Sciascia S, de Groot PG*, et al.* Antiphospholipid syndrome. *Nat Rev Dis Primers* 2018;4:17103.
40. Di Minno MND, Scalera A, Tufano A*, et al.* The association of adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) with cardiovascular disease in subjects with antiphospholipid antibodies. *Atherosclerosis* 2018;278:60-65.
41. Niccoli G, Camici PG. Myocardial infarction with non-obstructive coronary arteries: what is the prognosis? *Eur Heart J Suppl* 2020;22:E40-E45.
42. Nevras V, Milaras N, Katsioulis C*, et al.* Acute coronary syndromes in antiphospholipid syndrome-above suspicion: a systematic review. *Curr Probl Cardiol* 2023;48:101503.
43. Munguia-Realpozo P, Mendoza-Pinto C, Etchegaray-Morales I*, et al.* Non-invasive imaging in antiphospholipid syndrome to assess subclinical coronary artery disease. *Autoimmun Rev* 2023;23:103505.
44. Ambrosino P, Lupoli R, Di Minno A*, et al.* Markers of cardiovascular risk in patients with antiphospholipid syndrome: a meta-analysis of literature studies. *Ann Med* 2014;46:693-702.
45. Karakasis P, Lefkou E, Pamporis K*, et al.* Risk of subclinical atherosclerosis in patients with antiphospholipid syndrome and subjects with antiphospholipid antibody positivity: a systematic review and meta-analysis. *Curr Probl Cardiol* 2023;48:101672.

46. Ortel TL, Meleth S, Catellier D*, et al.* Recurrent thrombosis in patients with antiphospholipid antibodies and an initial venous or arterial thromboembolic event: a systematic review and meta-analysis. *J Thromb Haemost* 2020;18:2274-86.
47. Visseren FLJ, Mach F, Smulders YM*, et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227-337.
48. Arnett DK, Blumenthal RS, Albert MA*, et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;140:e596-e646.
49. Dorresteijn JA, Visseren FL, Wassink AM*, et al.* Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart* 2013;99:866-72.
50. Truglia S, Capozzi A, Mancuso S*, et al.* Relationship between gender differences and clinical outcome in patients with the antiphospholipid syndrome. *Front Immunol* 2022;13:932181.
51. Qi W, Zhao J, Huang C*, et al.* Clinical characteristics and prognosis of patients with antiphospholipid antibodies based on cluster analysis: an 8-year cohort study. *Arthritis Res Ther* 2022;24:140.
52. Zuily S, Clerc-Urmes I, Bauman C*, et al.* Cluster analysis for the identification of clinical phenotypes among antiphospholipid antibody-positive patients from the APS ACTION Registry. *Lupus* 2020;29:1353-63.
53. Forastiero R, Martinuzzo M, Pombo G*, et al.* A prospective study of antibodies to beta2-glycoprotein I and prothrombin, and risk of thrombosis. *J Thromb Haemost* 2005;3:1231-8.
54. Pengo V, Sarti L, Antonucci E*, et al.* Patients with antiphospholipid syndrome and a first venous or arterial thrombotic event: clinical characteristics, antibody profiles and estimate of the risk of recurrence. *Clin Chem Lab Med* 2024.
55. Ogata Y, Fujieda Y, Sugawara M*, et al.* Morbidity and mortality in antiphospholipid syndrome based on cluster analysis: a 10-year longitudinal cohort study. *Rheumatology (Oxford)* 2021;60:1331-37.

56. Elbagir S, Grosso G, Mohammed NA*, et al.* Associations with thrombosis are stronger for antiphosphatidylserine/prothrombin antibodies than for the Sydney criteria antiphospholipid antibody tests in SLE. *Lupus* 2021;30:1289-99.
57. Grimaud F, Yelnik C, Pineton de Chambrun M*, et al.* Clinical and immunological features of antiphospholipid syndrome in the elderly: a retrospective national multicentre study. *Rheumatology (Oxford)* 2019;58:1006-10.
58. Stojanovich L, Markovic O, Marisavljevic D*, et al.* Influence of antiphospholipid antibody levels and type on thrombotic manifestations: results from the Serbian National Cohort Study. *Lupus* 2012;21:338-45.
59. Yoneda K, Ueda Y, Tanimura K*, et al.* Association of anti-beta2-glycoprotein I/HLA-DR complex antibody with arterial thrombosis in female patients with systemic rheumatic diseases. *Arthritis Res Ther* 2023;25:195.
60. Naranjo L, Ostos F, Gil-Etayo FJ*, et al.* Presence of extra-criteria antiphospholipid antibodies is an independent risk factor for ischemic stroke. *Front Cardiovasc Med* 2021;8:665741.
61. Urbanus RT, Siegerink B, Roest M*, et al.* Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. *Lancet Neurol* 2009;8:998-1005.
62. Zuo Y, Fan J, Sarode R*, et al.* Identifying additional risk factors for thrombosis and pregnancy morbidities among antiphospholipid antibodies carriers. *Clin Appl Thromb Hemost* 2018;24:980-85.
63. Radin M, Schreiber K, Costanzo P*, et al.* The adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for risk stratification in young APS patients with acute myocardial infarction. *Int J Cardiol* 2017;240:72-77.
64. Matyja-Bednarczyk A, Swadzba J, Iwaniec T*, et al.* Risk factors for arterial thrombosis in antiphospholipid syndrome. *Thromb Res* 2014;133:173-6.
65. Danowski A, de Azevedo MN, de Souza Papi JA*, et al.* Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. *J Rheumatol* 2009;36:1195-9.

66. de Souza AW, Silva NP, de Carvalho JF*, et al.* Impact of hypertension and hyperhomocysteinemia on arterial thrombosis in primary antiphospholipid syndrome. *Lupus* 2007;16:782-7.
67. Gan Y, Zhao Y, Li G*, et al.* Risk factors and outcomes of acute myocardial infarction in a cohort of antiphospholipid syndrome. *Front Cardiovasc Med* 2022;9:871011.
68. Reshetnyak TM, Cheldieva FA, Cherkasova MV*, et al.* Antibodies to domain i beta(2)-glycoprotein 1 in patients with antiphospholipid syndrome and systemic lupus erythematosus. *Dokl Biochem Biophys* 2023;511:219-26.
69. Tonello M, Calligaro A, Favaro M*, et al.* The first thrombotic event in purely obstetric antiphospholipid syndrome patients and in antiphospholipid antibody carriers: comparison of incidence and characteristics. *Arch Gynecol Obstet* 2021;303:455-61.
70. Zhang S, Wu Z, Zhang W*, et al.* Antibodies to phosphatidylserine/prothrombin (aPS/PT) enhanced the diagnostic performance in Chinese patients with antiphospholipid syndrome. *Clin Chem Lab Med* 2018;56:939-46.
71. Zhang S, Wu Z, Zhang W*, et al.* Clinical performance of non-criteria antibodies to phospholipids in Chinese patients with antiphospholipid syndrome. *Clin Chim Acta* 2019;495:205-09.
72. Dufrost V, Risse J, Reshetnyak T*, et al.* Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis. *Autoimmun Rev* 2018;17:1011-21.
73. Ruiz-Garcia R, Serrano M, Martinez-Flores JA*, et al.* Isolated IgA anti-beta2 glycoprotein I antibodies in patients with clinical criteria for antiphospholipid syndrome. *J Immunol Res* 2014;2014:704395.
74. Reynaud Q, Lega JC, Mismetti P*, et al.* Risk of venous and arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: a systematic review and meta-analysis. *Autoimmun Rev* 2014;13:595-608.
75. Hoxha A, Ruffatti A, Tonello M*, et al.* Antiphosphatidylserine/prothrombin antibodies in primary antiphospholipid syndrome. *Lupus* 2012;21:787-9.

76. Pengo V, Bison E, Ruffatti A*, et al.* Antibodies to oxidized LDL/beta2-glycoprotein I in antiphospholipid syndrome patients with venous and arterial thromboembolism. *Thromb Res* 2008;122:556-9.
77. Mohtashim A, Azhar A, Mazhar S*, et al.* Factor Xa inhibitors vs. warfarin in patients with Hughes syndrome: a systematic review and meta-analysis of randomized controlled trials. *Ann Med Surg (Lond)* 2024;86:2992-3000.
78. Shah BB, Shankar A, Kumar V*, et al.* Direct oral anticoagulants vs. vitamin K antagonists in patients with antiphospholipid syndrome: a systematic review and meta-analysis. *Ann Med Surg (Lond)* 2023;85:3574-82.
79. Ohnishi N, Fujieda Y, Hisada R*, et al.* Efficacy of dual antiplatelet therapy for preventing recurrence of arterial thrombosis in patients with antiphospholipid syndrome. *Rheumatology (Oxford)* 2019;58:969-74.
80. Jackson WG, Oromendia C, Unlu O*, et al.* Recurrent thrombosis in patients with antiphospholipid antibodies and arterial thrombosis on antithrombotic therapy. *Blood Adv* 2017;1:2320-24.
81. Khairani CD, Bejjani A, Piazza G*, et al.* Direct oral anticoagulants vs vitamin k antagonists in patients with antiphospholipid syndromes: meta-analysis of randomized trials. *J Am Coll Cardiol* 2023;81:16-30.
82. Attachaipanich T, Aungsusiripong A, Piriyakhuntorn P*, et al.* Antithrombotic therapy in antiphospholipid syndrome with arterial thrombosis: a systematic review and network meta-analysis. *Front Med (Lausanne)* 2023;10:1196800.
83. Adelhelm JBH, Christensen R, Balbi GGM*, et al.* Therapy with direct oral anticoagulants for secondary prevention of thromboembolic events in the antiphospholipid syndrome: a systematic review and meta-analysis of randomised trials. *Lupus Sci Med* 2023;10.
84. Wu X, Cao S, Yu B*, et al.* Comparing the efficacy and safety of direct oral anticoagulants versus vitamin K antagonists in patients with antiphospholipid syndrome: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis* 2022;33:389-401.
85. Woller SC, Stevens SM, Kaplan D*, et al.* Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. *Blood Adv* 2022;6:1661-70.

86. Schulz A, Herrmann E, Ott O*, et al.* Thromboembolic antiphospholipid syndrome (APS): efficacy and safety of different anticoagulants-Results of the APSantiCO registry. *J Clin Med* 2022;11.
87. Lee YH, Song GG. Direct oral anticoagulants versus warfarin in patients with antiphospholipid syndrome: a meta-analysis of randomized controlled trials. *Lupus* 2022;31:1335-43.
88. Gullapalli K, Prasad RM, Al-Abcha A*, et al.* Efficacy and safety of direct oral anticoagulants in patients with antiphospholipid syndrome: a systematic review and meta-analysis. *Cureus* 2022;14:e29449.
89. Dufrost V, Wahl D, Zuily S. Direct oral anticoagulants in antiphospholipid syndrome: meta-analysis of randomized controlled trials. *Autoimmun Rev* 2021;20:102711.
90. Ordi-Ros J, Saez-Comet L, Perez-Conesa M*, et al.* Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. *Ann Intern Med* 2019;171:685-94.
91. Liu M, Li G, Song X*, et al.* Prevalence, risk factors, and prognosis of central nervous system manifestations in antiphospholipid syndrome. *Sci Rep* 2023;13:8915.
92. Fan Y, Xu Y, Zhang S*, et al.* Stroke and Risk Factors in Antiphospholipid Syndrome. *J Pers Med* 2023;14.
93. Djokovic A, Stojanovich L, Stanisavljevic N*, et al.* Relationship between cerebrovascular and valvular manifestations in a Serbian cohort of patients with antiphospholipid syndrome. *Clin Exp Rheumatol* 2018;36:850-55.
94. Song X, Fan Y, Jia Y*, et al.* A novel aGAPSS-based nomogram for the prediction of ischemic stroke in patients with antiphospholipid syndrome. *Front Immunol* 2022;13:930087.
95. Urbanski G, Yelnik CM, Maillard H*, et al.* Antiphospholipid syndrome with isolated isotype m anticardiolipin and/or anti-b2GPI antibody is associated with stroke. *Stroke* 2018;49:2770-72.
96. Gaspersic N, Zaletel M, Kobal J*, et al.* Stroke and antiphospholipid syndrome-antiphospholipid antibodies are a risk factor for an ischemic cerebrovascular event. *Clin Rheumatol* 2019;38:379-84.

97. Becarevic M, Ignjatovic S. Proinflammatory proteins in female and male patients with primary antiphospholipid syndrome: preliminary data. *Clin Rheumatol* 2016;35:2477-83.
98. Becarevic M, Andrejevic S, Miljic P*, et al.* Serum lipids and anti-oxidized LDL antibodies in primary antiphospholipid syndrome. *Clin Exp Rheumatol* 2007;25:361-6.
99. Rodriguez-Sanz A, Martinez-Sanchez P, Prefasi D*, et al.* Antiphospholipid antibodies correlate with stroke severity and outcome in patients with antiphospholipid syndrome. *Autoimmunity* 2015;48:275-81.
100. Okuma H, Kitagawa Y, Takagi S. Investigation of antiphosphatidyl-serine antibody and antiphosphatidyl-inositol antibody in ischemic stroke patients. *Clin Dev Immunol* 2010;2010:439230.
101. Radin M, Schreiber K, Cecchi I*, et al.* The risk of ischaemic stroke in primary antiphospholipid syndrome patients: a prospective study. *Eur J Neurol* 2018;25:320-25.
102. Pengo V, Denas G, Zoppellaro G*, et al.* Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018;132:1365-71.
103. Sciascia S, Sanna G, Khamashta MA*, et al.* The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. *Ann Rheum Dis* 2015;74:2028-33.
104. Ali HY, Abdullah ZA. Anti-beta(2)-glycoprotein I autoantibody expression as a potential biomarker for strokes in patients with anti-phospholipid syndrome. *J Immunotoxicol* 2008;5:173-7.
105. de Carvalho JF, Rodrigues CEM. Primary antiphospholipid syndrome with and without acute myocardial infarction/angina: a cross-sectional study. *Rheumatol Ther* 2022;9:581-88.
106. Stepien K, Nowak K, Wypasek E*, et al.* High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: comparison with cryptogenic stroke. *Int J Cardiol* 2019;290:1-6.
107. Maor E, Fefer P, Varon D*, et al.* Thrombophilic state in young patients with acute myocardial infarction. *J Thromb Thrombolysis* 2015;39:474-80.

108. Nazir S, Tachamo N, Lohani S*, et al.* Acute myocardial infarction and antiphospholipid antibody syndrome: a systematic review. *Coron Artery Dis* 2017;28:332-35.
109. Pastori D, Bucci T, Triggiani M*, et al.* Immunoglobulin G (IgG) anticardiolipin antibodies and recurrent cardiovascular events. A systematic review and Bayesian meta-regression analysis. *Autoimmun Rev* 2019;18:519-25.
110. Grika EP, Ziakas PD, Zintzaras E*, et al.* Morbidity, mortality, and organ damage in patients with antiphospholipid syndrome. *J Rheumatol* 2012;39:516-23.
111. Navarro-Carpentieri D, Del Carmen Castillo-Hernandez M, Majluf-Cruz K*, et al.* Impact ofclassical risk factors for arterial or venous thrombosis in patients with antiphospholipid syndrome. *Clin Appl Thromb Hemost* 2018;24:834-40.
112. Erkan D, Harrison MJ, Levy R*, et al.* Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis and rheumatism* 2007;56:2382-91.
113. Williams B, Mancia G, Spiering W*, et al.* 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104.
114. Mach F, Baigent C, Catapano AL*, et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88.
115. Drosos GC, Konstantonis G, Sfikakis PP*, et al.* Cardiovascular risk assessment in patients with antiphospholipid syndrome: a cross-sectional performance analysis of nine clinical risk prediction tools. *RMD Open* 2023;9.
116. Piepoli MF, Hoes AW, Agewall S*, et al.* 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315-81.

APPENDIX

List of unique articles included in the review

First author	Year	Title	Journal
Adelhelm, J. B. H., et al.	2023	Therapy with direct oral anticoagulants for secondary prevention of thromboembolic events in the antiphospholipid syndrome: a systematic review and meta-analysis of randomised trials	Lupus Sci Med 10(2)
Ali, H. Y.	2008	Anti-beta(2)-glycoprotein I autoantibody expression as a potential biomarker for strokes in patients with anti-phospholipid syndrome	J Immunotoxicol 5(2): 173-177
Attachaipanich, T., et al.	2023	Antithrombotic therapy in antiphospholipid syndrome with arterial thrombosis: a systematic review and network meta-analysis	Front Med (Lausanne) 10: 1196800
Bala, M. M., et al.	2020	Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome	Cochrane Database Syst Rev 10(10): Cd012169
Bećarević, M.	2016	Proinflammatory proteins in female and male patients with primary antiphospholipid syndrome: preliminary data	Clin Rheumatol 35(10): 2477-2483
Bećarević, M., et al.	2007	Serum lipids and anti-oxidized LDL antibodies in primary antiphospholipid syndrome	Clin Exp Rheumatol 25(3): 361-366
Danowski, A., et al.	2009	Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus	J Rheumatol 36(6): 1195-1199
de Carvalho, J. F.	2022	Primary antiphospholipid syndrome with and without acute myocardial infarction/angina: a cross-sectional study	Rheumatol Ther 9(2): 581-588
de Souza, A. W., et al.	2007	Impact of hypertension and hyperhomocysteinemia on arterial thrombosis in primary antiphospholipid syndrome	Lupus 16(10): 782-787
Di Minno, M. N. D., et al.	2018	The association of adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) with cardiovascular disease in subjects with antiphospholipid antibodies	Atherosclerosis 278: 60-65

Djokovic, A., et al.	2014	Association between cardiac manifestations and antiphospholipid antibody type and level in a cohort of Serbian patients with primary and secondary antiphospholipid syndrome	Isr Med Assoc J 16(3): 162-167
Djokovic, A., et al.	2022	Cardiac manifestations in primary antiphospholipid syndrome and their association to antiphospholipid antibodies' types and titers-cross-sectional study of Serbian cohort	Clin Rheumatol 41(5): 1447-1455
Djokovic, A., et al.	2018	Relationship between cerebrovascular and valvular manifestations in a Serbian cohort of patients with antiphospholipid syndrome	Clin Exp Rheumatol 36(5): 850-855
Dufrost, V., et al.	2021	Direct oral anticoagulants in antiphospholipid syndrome: meta-analysis of randomized controlled trials	Autoimmun Rev 20(1): 102711
Dufrost, V., 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	Autoimmun Rev 17(10): 1011-1021
Elbagir, S., et al.	2021	Associations with thrombosis are stronger for antiphosphatidylserine/prothrombin antibodies than for the Sydney criteria antiphospholipid antibody tests in SLE	Lupus 30(8): 1289-1299
Fan, Y., et al.	2023	Stroke and risk factors in antiphospholipid syndrome	J Pers Med 14(1)
Forastiero, R., et al.	2005	A prospective study of antibodies to beta2-glycoprotein I and prothrombin, and risk of thrombosis	J Thromb Haemost 3(6): 1231-1238
Gan, Y., et al.	2022	Risk factors and outcomes of acute myocardial infarction in a cohort of antiphospholipid syndrome	Front Cardiovasc Med 9: 871011
Gašperšič, N., et al.	2019	Stroke and antiphospholipid syndrome-antiphospholipid antibodies are a risk factor for an ischemic cerebrovascular event	Clin Rheumatol 38(2): 379-384
Grika, E. P., et al.	2012	Morbidity, mortality, and organ damage in patients with antiphospholipid syndrome	J Rheumatol 39(3): 516-523

Grimaud, F., et al.	2019	Clinical and immunological features of antiphospholipid syndrome in the elderly: a retrospective national multicentre study	Rheumatology (Oxford) 58(6): 1006-1010
Gullapalli, K., et al.	2022	Efficacy and safety of direct oral anticoagulants in patients with antiphospholipid syndrome: a systematic review and meta-analysis	Cureus 14(9): e29449
Hoxha, A., et al.	2012	Antiphosphatidylserine/prothrombin antibodies in primary antiphospholipid syndrome	Lupus 21(7): 787-789
Jackson, W. G., et al.	2017	Recurrent thrombosis in patients with antiphospholipid antibodies and arterial thrombosis on antithrombotic therapy	Blood Adv 1(25): 2320-2324
Jara, L. J., et al.	2005	The impact of gender on clinical manifestations of primary antiphospholipid syndrome.	Lupus 14(8): 607-612
Khairani, C. D., et al.	2023	Direct oral anticoagulants vs vitamin K antagonists in patients with antiphospholipid syndromes: meta-analysis of randomized trials	J Am Coll Cardiol 81(1): 16-30
Li, C., et al.	2022	Additional risk factors associated with thrombosis and pregnancy morbidity in a unique cohort of antiphospholipid antibody-positive patients	Chin Med J (Engl) 135(6): 658-664
Liu, M., et al.	2023	Prevalence, risk factors, and prognosis of central nervous system manifestations in antiphospholipid syndrome	Sci Rep 13(1): 8915
Maor, E., et al.	2015	Thrombophilic state in young patients with acute myocardial infarction	J Thromb Thrombolysis 39(4): 474-480
Matyja-Bednarczyk, A., et al.	2014	Risk factors for arterial thrombosis in antiphospholipid syndrome	Thromb Res 133(2): 173-176
Mohtashim, A., et al	2024	Factor Xa inhibitors vs. warfarin in patients with Hughes syndrome: a systematic review and meta-analysis of randomized controlled trials	Ann Med Surg (Lond) 86(5): 2992-3000
Moreno-Torres, V. et al.	2022	Impact of cardiovascular risk factors in antiphospholipid syndrome: an observational study from the Spanish national registry	Clin Exp Rheumatol 40(11): 2161-2166

Naranjo, L., et al.	2021	Presence of extra-criteria antiphospholipid antibodies is an independent risk factor for ischemic stroke	Front Cardiovasc Med 8: 665741
Navarro-Carpentieri, D., et al.	2018	Impact of classical risk factors for arterial or venous thrombosis in patients with antiphospholipid syndrome	Clin Appl Thromb Hemost 24(5): 834-840
Nazir, S., et al.	2017	Acute myocardial infarction and antiphospholipid antibody syndrome: a systematic review	Coron Artery Dis 28(4): 332-335
Niznik, S., et al.	2022	Patterns of recurrent thrombosis in primary antiphospholipid syndrome-multicenter, real-life long-term follow-up	Front Immunol 13: 843718
Ogata, Y., et al.	2021	Morbidity and mortality in antiphospholipid syndrome based on cluster analysis: a 10-year longitudinal cohort study	Rheumatology (Oxford) 60(3): 1331-1337
Ohnishi, N., et al.	2019	Efficacy of dual antiplatelet therapy for preventing recurrence of arterial thrombosis in patients with antiphospholipid syndrome	Rheumatology (Oxford) 58(6): 969-974
Okuma, H., et al.	2009	Comparison between single antiplatelet therapy and combination of antiplatelet and anticoagulation therapy for secondary prevention in ischemic stroke patients with antiphospholipid syndrome	Int J Med Sci 7(1): 15-18
Okuma, H., et al.	2010	Investigation of antiphosphatidyl-serine antibody and antiphosphatidyl-inositol antibody in ischemic stroke patients	Clin Dev Immunol 2010: 439230
Ordi-Ros, J., et al.	2019	Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial	Ann Intern Mned 171(10): 685-694
Pastori, D., et al.	2019	Immunoglobulin G (IgG) anticardiolipin antibodies and recurrent cardiovascular events. A systematic review and Bayesian meta-regression analysis.	Autoimmun Rev 18(5): 519-525
Pengo, V., et al.	2008	Antibodies to oxidized LDL/beta2-glycoprotein I in antiphospholipid syndrome patients with venous and arterial thromboembolism	Thromb Res 122(4): 556-559
Pengo, V., et al.	2024	Patients with antiphospholipid syndrome and a first venous or arterial thrombotic event: clinical characteristics, antibody profiles and estimate of the risk of recurrence	Clin Chem Lab Med

Pengo, V., et al.	2018	Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome	Blood 132(13): 1365-1371
Qi, W., et al.	2022	Clinical characteristics and prognosis of patients with antiphospholipid antibodies based on cluster analysis: an 8-year cohort study	Arthritis Res Ther 24(1): 140
Radin, M., et al.	2017	The adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for risk stratification in young APS patients with acute myocardial infarction	Int J Cardiol 240: 72-77
Radin, M., et al.	2018	The risk of ischaemic stroke in primary antiphospholipid syndrome patients: a prospective study	Eur J Neurol 25(2): 320-325
Reshetnyak, T. M., et al.	2023	Antibodies to domain i β(2)-glycoprotein 1 in patients with antiphospholipid syndrome and systemic lupus erythematosus	Biochem Biophys 511(1): 219-226
Reynaud, Q., et al.	2014	Risk of venous and arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: a systematic review and meta-analysis	Autoimmun Rev 13(6): 595-608
Rodríguez-Sanz, A., et al.	2015	Antiphospholipid antibodies correlate with stroke severity and outcome in patients with antiphospholipid syndrome	Autoimmunity 48(5): 275-281
Ruiz-García, R., et al.	2014	Isolated IgA anti- β2 glycoprotein I antibodies in patients with clinical criteria for antiphospholipid syndrome	J Immunol Res 2014: 704395
Schulz, A., et al.	2022	Thromboembolic antiphospholipid syndrome (APS): efficacy and safety of different anticoagulants-results of the APSantiCO registry	J Clin Med 11(16)
Sciascia, S., et al.	2014	Anti-prothrombin (aPT), anti-phosphatidylserine/prothrombin (aPS/PT) antibodies, and the risk of thrombosis in the antiphospholipid syndrome. A systematic review	Thromb Haemost 111(2): 354-364
Sciascia, S., et al.	2015	The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review	Ann Rheum Dis 74(11): 2028-2033

Shah, B. B., et al.	2023	Direct oral anticoagulants vs. vitamin K antagonists in patients with antiphospholipid syndrome: a systematic review and meta-analysis	Ann Med Surg (Lond) 85(7): 3574-3582
Song, X., et al.	2022	A novel aGAPSS-based nomogram for the prediction of ischemic stroke in patients with antiphospholipid syndrome	Front Immunol 13: 930087
Stepien, K., et al.	2019	High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: comparison with cryptogenic stroke	Int J Cardiol 290: 1-6
Stojanovich, L., et al.	2012	Influence of antiphospholipid antibody levels and type on thrombotic manifestations: results from the Serbian National Cohort Study	Lupus 21(3): 338-345
Tonello, M., et al.	2021	The first thrombotic event in purely obstetric antiphospholipid syndrome patients and in antiphospholipid antibody carriers: comparison of incidence and characteristics	Arch Gynecol Obstet 303(2): 455-461
Truglia, S., et al.	2022	Relationship between gender differences and clinical outcome in patients with the antiphospholipid syndrome	Front Immunol 13: 932181
Urbanski, G., et al.	2018	Antiphospholipid syndrome with isolated isotype M anticardiolipin and/or anti-b2GPI antibody is associated with stroke	Stroke 49(11): 2770-2772
Urbanus, R. T., et al.	2009	Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study	Lancet Neurol 8(11): 998-1005
Woller, S. C., et al.	2022	Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial	Blood Adv 6(6): 1661-1670
Wu, X., et al.	2022	Comparing the efficacy and safety of direct oral anticoagulants versus vitamin K antagonists in patients with antiphospholipid syndrome: a systematic review and meta-analysis	Blood Coagul Fibrinolysis 33(7): 389-401
Yoneda, K., et al.	2023	Association of anti-β2-glycoprotein I/HLA-DR complex antibody with arterial thrombosis in female patients with systemic rheumatic diseases	Arthritis Res Ther 25(1): 195

Zhang, S., et al.	2018	Antibodies to phosphatidylserine/prothrombin (aPS/PT) enhanced the diagnostic performance in Chinese patients with antiphospholipid syndrome	Clin Chem Lab Med 56(6): 939-946
Zhang, S., et al.	2019	Clinical performance of non-criteria antibodies to phospholipids in Chinese patients with antiphospholipid syndrome	Clin Chim Acta 495: 205-209
Zuily, S., et al.	2020	Cluster analysis for the identification of clinical phenotypes among antiphospholipid antibody-positive patients from the APS ACTION Registry	Lupus 29(11): 1353-1363
Zuo, Y., et al.	2018	Identifying additional risk factors for thrombosis and pregnancy morbidities among antiphospholipid antibodies carriers	Clin Appl Thromb Hemost 24(6): 980-985