NAME OF PROJECT

Registry on Augmented antithrombotic treatment regimens for patients with arterial thrombotic APS

Subcommittee

Lupus Anticoagulant/Antiphospholipid Antibodies of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

Person responsible (Chair subcommittee/ Principal Investigator): Katrien Devreese/ Sam Schulman

Background

Although venous thromboembolism is the most common clinical manifestation of antiphospholipid syndrome (APS), the proportion of serious arterial events such as stroke (35%) and peripheral arterial thrombosis (8%) is alarming. (1, 2) The presence of antiphospholipid antibodies and/or lupus anticoagulant increases the risk of recurrent thrombotic events. (3) This risk is particularly high after initially arterial compared to venous thrombotic events, (14-20% versus 5-10%), see Table:

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Recurrence – initial arterial event</th>
<th>Recurrence – initial venous event</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAPS(4)</td>
<td>5 of 25 = 20%</td>
<td>4 of 77 = 5%</td>
</tr>
<tr>
<td>Ordi-Ros(5)</td>
<td>10 of 71 = 14%</td>
<td>9 of 139 = 6%</td>
</tr>
<tr>
<td>Crowther(6)</td>
<td>4 of 27 = 15%</td>
<td>4 of 87 = 5%</td>
</tr>
<tr>
<td>Malec(7)</td>
<td>7 of 42 = 17%</td>
<td>15 of 157 =10%</td>
</tr>
</tbody>
</table>

A recent systematic review and meta-analysis of 17 studies found that the 2-year proportion of recurrent thrombosis was, for patients with initial arterial event and taking anticoagulants, 0.22 (95% confidence interval [CI], 0.15-0.31), or taking antiplatelet therapy, 0.22 (95% CI, 0.18-0.26), and for those with initial venous event it was, for those taking anticoagulant therapy, 0.054 (95% CI, 0.037-0.079), or not taking anticoagulants, 0.18 (95% CI, 0.15-0.21).(8)

The non-vitamin K antagonist oral anticoagulants (NOACs) are less effective than warfarin in APS, particularly for reduction of stroke, as summarized in a Cochrane review. (9)

For patients with arterial events it is appealing to use antiplatelet therapy, and a systematic review and meta-analysis presented at the SSC of ISTH 2020 concluded that antiplatelet therapy was more effective...
than NOACs or moderate intensity warfarin to reduce the risk for recurrent arterial thrombosis.(10) The antiplatelet group may have consisted of studies with single antiplatelet as well as dual antiplatelet regimens.

In a second meta-analysis presented at the same meeting, antithrombotic regimens were analyzed separately for vitamin K antagonist (VKA) of high intensity, VKA of moderate intensity, VKA plus an antiplatelet agent, single antiplatelet therapy, or dual antiplatelet therapy.(11) It concluded that combinations, either VKA plus single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT) seemed more effective to reduce the risk for recurrent arterial and/or recurrent any thrombosis in patients with an initial arterial event.

In patients with arterial disease but without APS there is increasing evidence for the benefit of dual pathway inhibition, using low-dose aspirin with low-dose rivaroxaban (2.5 mg BID).(12, 13) For patients with arterial thrombosis in combination with APS there is thus also a rationale for dual pathway inhibition, but in view of the hypercoagulable state, the anticoagulation should be with therapeutic dose and with a VKA rather than a NOAC. Unfortunately, VKAs are difficult to manage in some patients and DAPT might also be effective and definitely easier to manage.

**Guideline recommendations**

The European League against Rheumatism (EULAR) published in 2019 the following recommendations (14), based on a systematic review of the literature.(15)

<table>
<thead>
<tr>
<th>In patients with definite APS and first arterial thrombosis</th>
<th>Level of evidence</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with VKA is recommended over treatment with LDA only</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual’s risk of bleeding and recurrent thrombosis</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Treatment with VKA with INR 2–3 plus LDA may also be considered</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Rivaroxaban should not be used in patients with triple aPL positivity and arterial events</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis</td>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>
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Level of evidence: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (and low-quality RCT); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case series and poor-quality cohort and case–control studies; 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’

Grade of recommendation (GoR): A: consistent level 1 studies; B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Similar recommendations have been issued in a guidance document from ISTH,(16) and in the 16th International Congress on Antiphospholipid Antibodies Task Force Report.(17) The latter document also includes the possibility of using high intensity VKE, i.e. INR range 3.0-4.0, currently re-evaluated in the RISAPS randomized controlled trial (ClinicalTrials.gov Identifier: NCT03684564).

Why is this registry needed?

Although the EULAR recommendation is to use VKA alone as the first choice for arterial APS, two recent meta-analyses indicate that at least the regular intensity VKA (INR 2.0-3.0) might not be the most effective regimen. (10) (11) The consequences of arterial thrombosis are very serious, in view of the events including stroke, myocardial infarction or peripheral arterial thrombosis with risk for loss of limb. Antiplatelet agents have demonstrated effectiveness for the reduction of (recurrent) stroke,(18) myocardial infarction,(19) and for peripheral arterial disease(20) in the general population. Dual pathway inhibition has demonstrated superiority over single antiplatelet or single anticoagulant therapy in patients with stable coronary artery disease or stable peripheral arterial disease to reduce stroke, limb loss and death,(12) as well as in the more acute setting of peripheral arterial disease after revascularization.(13) It was, however, observed in both studies that the risk of major bleeding increased with the anticoagulant plus antiplatelet regimen versus single agent treatment.

It is critical to evaluate whether any combination regimen is safe and effective in patients with APS. Here, the hypercoagulability is more pronounced than in the non-APS population and this might balance out the increased risk of bleeding seen with dual pathway inhibition.

Whereas dual pathway inhibition with an anticoagulant (rivaroxaban) plus an antiplatelet agent (aspirin) proved effective in the two large trials mentioned above, rivaroxaban is not recommended for patients with arterial APS.(14, 16, 17) Warfarin plus aspirin is among the recommended regimens by EULAR, and the ICAPA Task Force.(14, 17) Warfarin is, however, often difficult to manage and if DAPT has similar effect, it is a much more convenient regimen.

This begs the question whether DAPT is having any effect on the risk for venous thromboembolism in patients with arterial APS. In 8 studies that compared different antithrombotic regimens and that reported separately results for patients with index event arterial thrombosis, the recurrent events were during the follow-up in a total of 445 patients 75 arterial and 12 venous thrombotic events, thus a 6-fold difference. Even if venous events are less of a problem, this should not be neglected. There is, however, evidence that aspirin is effective to prevent venous thromboembolism after hip- or knee

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replacement, and partially effective to prevent recurrent venous thromboembolism. The proposed registry will allow retrospective inclusion of patients up to 12 months back and thus a patient with dual antithrombotic therapy after a stroke or myocardial infarction, and who at some point during the year afterward is diagnosed with APS, can be evaluated for the period on DAPT, even if the treating physician decides at that point to change the regimen to include a VKA. There may be other patients for whom DAPT is a suitable choice, e.g. treatment with DAPT has already been used since several months without any recurrence, contraindications to VKA, choice of the physician and the patient due to difficulties with blood sampling, monitoring, drug-interactions etc.

A registry is easier to recruit patients for, compared to a randomized clinical trial. The latter provides a huge challenge in rare diseases. Only a small minority of patients with arterial thrombotic disease have APS, and among patients with APS venous thromboembolism is more common than arterial thrombosis. In order to obtain results within a realistic timeframe, an international registry is most feasible. Furthermore, it can be managed at a low cost, whereas a randomized clinical trial will be very expensive, and the prospects of obtaining funding for a trial comparing generic agents such as warfarin, aspirin and clopidogrel are slim.

**Aim of the registry**

The primary aim is to compare a VKA, i.e. warfarin, acenocoumarol, phenprocoumon etc, with therapeutic range, INR 2.0-3.0 plus low-dose aspirin (75-100 mg) with DAPT. The latter will typically be low-dose aspirin plus clopidogrel (75 mg daily) but other combinations will be acceptable. The comparison will address efficacy and safety. The registry will also include patients treated with VKA alone at standard- or high-intensity, since this is recommended by EULAR and will serve as reference groups in comparison with VKA + low-dose aspirin and versus DAPT.

A secondary objective is to analyze how the cardiovascular risk factors (hypertension, hyperlipidemia, obesity, smoking, diabetes, and heart failure), venous thrombotic risk factors (previous venous thromboembolism, cancer, immobility, chronic inflammatory disease) and anti-phospholipid profile contribute to recurrent arterial thrombosis.

**Primary efficacy outcome**

Composite of arterial thrombosis (stroke, myocardial infarction, peripheral arterial thrombosis or embolism), venous thromboembolism (thrombosis in any deep vein or pulmonary embolism that is larger than subsegmental), and vascular death. The diagnosis must be verified with objective imaging techniques, autopsy or death certificate.

**Principal safety outcome**

Major bleeding according to the ISTH definition.

**Secondary efficacy outcomes**
Each component of the composite outcome; all-cause mortality

Inclusion criteria

1. Patients of at least 18 years of age with confirmed APS according to Sydney criteria and with first or recurrent arterial thrombotic manifestation, including those with asymptomatic brain infarcts on diagnostic imaging.
2. Treatment with either A) a VKA with therapeutic range, INR 2.0-3.0 plus low-dose aspirin (75-100 mg daily), B) a VKA alone with therapeutic range, INR 2.0-3.0 or C) VKA with therapeutic range, INR 3.0-4.0, or D) with a dual antiplatelet regimen, if considered appropriate by the treating physician.
3. Signed informed consent obtained.

Exclusion criteria

1. Inability to follow the patient due to geographical or other reasons.
2. Patients with documented poor compliance.
3. Aspirin allergy.
4. Bleeding risk that in the opinion of the treating physician makes combination antithrombotic therapy unsafe.
5. Pregnancy or planned pregnancy.

Patients can be included within 12 months from the arterial thromboembolic event, as long as there have not been subsequent venous thromboembolic events. Prior venous thromboembolic events are allowed, i.e. before the most recent arterial event.

The registry is not prescriptive, i.e. does not instruct the treating physician to use one or another of the regimens studied.

Recruitment and follow-up

The registry is not an interventional study. Thus, the decision on the treatment regimen should have been made by the treating physician on clinical grounds and judgement, prior to recruitment to the registry, i.e. prior to informing the patients about the registry. The information should include that VKA is the recommended standard, either alone or in combination and, in case DAPT is chosen, an explanation to the patient for what reasons it should be used or continued.

Patients that have been started on either of the two regimens after the most recent arterial thromboembolic event and within the past 12 months can be approached and informed about the study. If the patient meets the inclusion criteria and does not have any of the exclusion criteria, the investigator or designated representative obtains consent for collection of data.

The investigator will collect data from medical records and from the patient at inclusion, and the intention is to follow the patient for 24 months. Every 6 months (i.e. at 6, 12, 18 and 24 months after
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inclusion) the investigator team obtains information from the patient regarding any thrombotic events, bleeding and interruptions of or change in antithrombotic treatment. This can be done by face-to-face visit or by phone or video. If that is not possible, the reason should be documented and medical records should be reviewed for any interim events. If no information is obtained on this review and the patient is unavailable for two consecutive 6-monthly time points, the patient is considered lost to follow-up.

Data entry

Data is entered in RedCap using the ISTH REDCap data collection system – retrospectively for the baseline data and prospectively for the follow-up data. REDCap is available without interruption over the Internet via the e-CRF. Secure access will be granted to study site after required information has been received – ability to recruit, continuity of study staff, proof of Ethics approval for jurisdictions where it is required.

Investigators

Any physician interested in the topic may join as a local investigator. Hematologists, Rheumatologists, Neurologists, Cardiologists etc. are welcome to contribute patients.

Sample size

Studies on arterial APS or that included arterial APS together with venous APS, and used Sydney criteria had generally a sample size of less than 100 patients, with the one by Jackson et al being the largest with 139 cases with arterial APS.(23) We will aim for 150 patients recruited during 3 years and thus the last follow-up at 5 years.

In our meta-analysis, 4 studies using VKA plus single platelet agent had 14 venous or arterial thrombotic events reported in 108 patients (13%), corresponding to 2.7% per year of follow-up.(23-26) In 2 studies using DAPT there were 3 events among 35 patients (9%), corresponding to 1.6% per year of follow-up.(24, 26) We will not be able to analyze for non-inferiority for DAPT versus VKA + SAPT, unless we have a sample size of 312 cases with equal distribution of samples in each group. This is very unlikely, and it would take too many years to complete. Rather, we will obtain a signal of too high risk of thromboembolic events if the event rate during 2 years of treatment exceeds 20%, as was the case for VKA alone or for SAPT.

It is clear that registry data will have selection bias and we will, by collecting data an APS phenotype and cardiovascular risk factors, make adjustments for observed differences between the treatment groups.

Expected timeline: Project stage/set up

After revisions and approval by the SSC Lupus anticoagulant/antiphospholipid antibodies Chair and Co-chairs, it will take 1-2 months to set up the registry in REDCap. The registry will be advertised, when ready, via the ISTH website and emails and it will be announced at the SSC Meeting in Philadelphia and
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progress reported with renewed calls for recruitment at annual congresses. Key opinion leaders will be contacted directly to encourage participation.

First patient in: Q2, 2021

Last patient in: Q2, 2024

Last patient – last follow-up: Q2, 2026.

Manuscript preparation Q3, 2026.

The registry will be managed by the Clinical Thromboembolism Research Program at McMaster University, which in the past coordinated the International Registry of Recurrent Venous Thromboembolism on Anticoagulation in Patients with Cancer for the ISTH SSC.(27)

If recruitment falls behind the expected rate, we will introduce a minor monetary recruitment incentive, and support for that will be explored.

Event adjudication

Arterial and venous thrombotic events, death, and major bleeds will be assessed and classified by an independent Event Adjudication Committee, consisting of at least 3 members. Each event will be assessed independently by 2 members and in case of disagreement, the third member will decide. In case all three have diverging assessments a consensus meeting will be arranged.

Publication

The SSC Chairs and Co-chairs that have been involved in the registry will be invited to co-author the manuscript. In addition, other investigators with top recruitment will be invited. Other investigators and Adjudication Committee members will be included in the appendix as part of the study group.

Registration

The registry will be registered on Clinicaltrials.gov.

References

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