Position paper

Treatment of the antiphospholipid syndrome with direct oral anticoagulants

Position statement of German societies★

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Summary: The antiphospholipid-syndrome (APS) is one of the most severe forms of thrombophilia, which may not only lead to recurrent venous but also to arterial thromboembolic events (TE), and to severe pregnancy complications, respectively. APS is defined by clinical symptoms and specific laboratory findings: 1. Lupus anticoagulant (LA), 2. anticardiolipin-antibodies (ACA), and 3. β2-Glycoprotein I-antibodies (β2GPI-Ab). All test results have to be confirmed after at least 12 weeks. The thrombotic risk is highest, if all 3 test groups are positive. It must be pointed out that the presence of UFH, VKA or DOACs may lead to false positive LA-test results; the addition of a specific absorber after blood sampling may provide reliable results in the presence of DOACs. A prospective randomized controlled trial comparing warfarin and rivaroxaban (TRAPS-trial) including only high-risk patients with triple positive APS was terminated early because of an increased rate of TE in patients treated with rivaroxaban [19 %, mostly arterial, compared to 3 % with warfarin (HR 7.4;1.7–32.9)]. Subsequently, a warning letter was issued by the pharmaceutical manufacturers of DOACs, including a warning of DOAC use in APS-patients, particularly in triple-positive high-risk patients. Conclusions: 1. Clinical suspicion of APS requires careful diagnostic testing. Because of inadequate diagnostic workup, many patients may not even have an APS, and these patients could be adequately treated with a DOAC. 2. Patients with single or double positive antiphospholipid antibodies but without positive LA may have a comparably low thrombotic risk and may also be treated with a DOAC in venous TE – sufficient evidence for that conclusion is not yet available but is suggested by the results of meta-analyses. 3. Triple positive patients or those with APS who suffered from arterial thromboembolism have a very high recurrence risk of thrombosis; the TRAPS-Study shows that these patients should be treated with VKA instead of a DOAC.

Keywords: Antiphospholipid-syndrome, anticoagulation, vitamin K antagonists, direct oral anticoagulants, lupus anticoagulant, anti-phospholipid-antibodies

The antiphospholipid syndrome

Amongst the different types of thrombophilia, the antiphospholipid syndrome (APS) represents the most difficult therapeutic challenge, as it is associated with a very high thrombotic risk. The main clinical manifestations – particularly in young patients – include arterial and venous thrombotic events as well as pregnancy complications [1]. Commonly, there are underlying autoimmune disorders such as systemic lupus erythematosus (i.e. secondary

★ GTH: Society of Thrombosis and Haemostasis Research, DGA: German Society of Vascular Medicine, DGP: German Society of Phlebology, DGK: German Cardiac Society, BDDH: Berufsverband der Deutschen Hämostaseologen, GLVD: German League of Vascular Diseases

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antiphospholipid syndrome). However, patients often present with unprovoked thromboembolism or pregnancy complications without an identifiable underlying cause (primary antiphospholipid syndrome).

Diagnosis

APS is defined on the basis of the abovementioned clinical presentations and certain laboratory findings: positive lupus anticoagulants (LA), anticardiolipin antibodies (ACA, IgG or IgM) and/or β2-glycoprotein I-antibodies (β2GPI-Ab, IgG or IgM). Elevated antibody titers are considered relevant only after they have been retested and confirmed not earlier than 12 weeks after the initial testing. In addition, certain thresholds of ACA and β2GPI-Ab levels are required for the definitive diagnosis of APS. Current criteria for APS classification were developed during the Sapporo Consensus Conference including the Sydney-Revision [2]. The ISTH *SSC Subcommittee* issued laboratory criteria for APS [3]: With triple-positive laboratory findings, all three measurements (LA, ACA and β2GPI-Ab) are positive, which is associated with the highest thrombotic risk. Double-positive APS (mostly LA negative) generally has a lower risk of thrombosis, while single-positive patients (ACA or β2GPI-AK and negative LA) have the lowest risk. Of importance, the DRVVT-test system for LA can provide false positive results in patients treated with direct oral anticoagulants (DOACs), as well as in those treated with vitamin-K antagonists (VKAs), which could lead to an errorneous diagnosis of LA [4, 5]. Therefore, in patients with oral anticoagulation, a treatment pause of at least five half-life times is necessary to avoid false-positive results for LA. During that pause, bridging with low molecular weight heparin may be required in patients at a very high thrombotic risk. With the addition of special absorbers into the blood vial, pausing of DOACs may not be necessary for correct testing for lupus anticoagulants [6].

Treatment

Anticoagulation is the most important treatment for prevention of thrombotic events in APS patients. VKA are considered the current standard of anticoagulant treatment. Low-dose aspirin may be used for primary prevention in patients with triple positive antiphospholipid-antibodies without thromboembolic complications, in APS patients, either as monotherapy or in combination with oral anticoagulation, in particular in patients who had arterial events and present with a concomitant vascular risk profile [7]. DOACs including apixaban, dabigatran, edoxaban or rivaroxaban are increasingly being used in APS patients because of their predictable effect without the need of monitoring and a favorable risk / benefit ratio. In particular, in APS patients with a strong lupus anticoagulant, in whom reliable INR monitoring of VKA treatment is challenging, DOACs may provide advantages with respect to reliable anticoagulation without the need of monitoring. Data based evidence for the use of DOACs, however was missing until recently.

New evidence for the anticoagulation in APS

Recently, a first direct comparison of VKA and DOACs in the treatment of APS was published. The TRAPS trial (*Trial on Rivaroxaban in AntiPhospholipid Syndrome*), a randomized, open, multicenter non-inferiority study with blinded end point adjudication compared the efficacy and safety of rivaroxaban, 20 mg once daily (15 mg once daily in impaired renal function) with warfarin (target INR 2.0 to 3.0) in high-risk patients with thrombotic APS [8]. This trial exclusively enrolled high-risk patients with triple positivity. The study was terminated early after the inclusion of 120 patients (59 with rivaroxaban and 61 with warfarin, respectively) because of an increased rate of thrombotic events in the rivaroxaban arm. After a mean follow-up of 569 days, there were 19 % thrombotic events with rivaroxaban (mainly arterial), compared to 3 % in the warfarin group (HR 7.4; 95 % CI 1.7–32.9). Major bleeding occurred in six patients: 4 (7 %) with rivaroxaban and 2 (3 %) with Warfarin (HR 2.3; 95 % CI 0.4–12.5). No deaths were documented [8].

A recent international meta-analysis of individual patient data [9] analyzed 447 patients, who were treated with Rivaroxaban (n = 290), Dabigatran (n = 144) or Apixaban (n = 13), respectively. A high thrombotic recurrence of 16 % was observed after a mean follow-up of 12.5 months. In the triple positive patients, a significantly elevated risk for recurrence was confirmed [4-fold increase (56 % vs. 23 %; OR = 4.3; 2.3–7.7; $p < 0.0001$)] and was observed in patients with a prior arterial event or *small vessel disease*. The study also showed that DOACs are not effective in all APS patients [9]. However, there is also evidence that DOACs are an effective and safe alternative to VKA in low risk APS patients with prior venous thromboembolism [10].

PRAC recommendations of the EMA

Following the results of the TRAPS-trial the *Pharmacovigilance Risk Assessment Committee (PRAC)* of the *European Medicines Agency (EMA)* published a new product information wording for the DOACs apixaban, dabigatran etexilate, edoxaban, rivaroxaban [11] with special warnings and precautions for patients with antiphospholipid syndrome on May 9 2019 (https://www.ema.europa.eu/en/documents/other/new-product-information-wording-extracts-prac-recommendations-signals-adopted-8-11-april-2019-prac_en.pdf):

Table I. Antithrombotic treatment options in patients with the antiphospholipid syndrome depending on the clinical presentation and the laboratory test results.

Severity of the antiphospholipid syndrome	DOAC treatment (use only therapeutic doses)	VKA treatment	Addition of aspirin
APS with arterial events	No use of DOACs	VKA is gold standard	Consider additional aspirin with vascular risk factors
Severe APS with triple positivity and venous thromboembolism (LA and ACA-Ab and β2-GPI-Ab)	No use of DOACs	VKA is gold standard	Not required
Moderate APS with double antibody positivity, negative LA and venous thromboembolism (ACA-Ab and β2-GPI-Ab)*	DOACs possible	VKA alternatively	Not required
Mild APS with single antibody positivity, negative LA and venous thromboembolism (ACA-Ab or β2-GPI-Ab)*	DOACs possible	VKA alternatively	Not required
No APS (e.g. falsely positive LA)	DOACs	VKA alternatively	Not required

*Regular follow up (clinically and antibody testing) e.g. annually is recommended, as underlying diseases, such as systemic lupus erythematosus may develop, or antiphospholipid antibodies may diminish over time (especially low titer antibodies). DOAC: direct oral anticoagulant; VKA: vitamin K antagonist.

DOACs, including rivaroxaban/apixaban/edoxaban/dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

In addition, on May 23, 2019 the German Federal Institute for Drugs and Medical Devices recommended for patients with APS, who are currently treated with a DOAC for prevention of thromboembolic events, to assess whether the continuation of this treatment is adequate and to consider switching to VKA, particularly in high risk patients:

(https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2019/rhb-doaks.html)

Conclusions

1. There are several practical conclusions which can be drawn from the currently available evidence: Initiating a diagnostic workup for APS requires a clear clinical indication. In clinically suspected APS, a careful diagnostic workup in a specialized laboratory is indispensable for the risk stratification of the APS patients. Many patients – perhaps even the majority of those being classified as APS – may not even have the disease, as the laboratory diagnosis may not have been adequate (see above). These patients, who do not have APS, represent a low risk group for recurrent VTE, and their venous thromboembolism is adequately treated with a DOAC [12].
2. Patients with single or double positive antiphospholipid antibodies without detection of LA (ACA- and/or β2GPI-Ab positivity) have a comparably low risk for thrombosis and may also be sufficiently treated with a DOAC, if they had had prior ***venous*** events. However, it must be emphasized that at present there is no specific evidence for the treatment with DOACs in this patient group. Nevertheless, the meta-analysis from 2019 may indicate that this approach is reasonable [10].
3. Patients with a high-risk APS and positivity in all three APS tests, and APS patients with prior arterial events, however, have a very high risk for thrombotic complications. The TRAPS-Study [8] showed that these patients should not be treated with DOACs and should rather be treated with VKA (in the study warfarin) with a target INR of 2.0 to 3.0. It is unclear whether patients with prior arterial thrombotic events should be treated with aspirin in addition, which is suggested by the TRAPS-Study. The TRAPS-Study thus confirms the use of VKAs as standard treatment in high risk APS with triple positivity [1] instead of DOACs.

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