NAME OF PROJECT: Explaining the Discrepancies of INR Measurements Between Point-Of-Care and Traditional Testing in Antiphospholipid-Positive Patients.

Subcommittee

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

Person responsible (Chair / Principal Investigators): Pr K Devreese / Pr S Zuily and other investigators from French networks involved in the project (INNOVTE and FAI²R networks)

Description Abstract

Thrombotic Antiphospholipid Syndrome (APS) requires a long-term anticoagulation [EULAR]. Together with warfarin, direct oral anticoagulants (DOACs) have been developed to treat patients with a history of venous thromboembolism or stroke. However, based on a recent randomized controlled trial that was negative, the European Medicines Agency stated in June 2019 that APS patients should not be treated with DOACs, and especially those at high risk, i.e. with triple aPL-positivity (all three laboratory criteria for definite APS). Thus, warfarin remains the cornerstone of thromboprophylaxis in APS patients.

Monitoring warfarin is not an easy task. Indeed, stringent laboratory monitoring is mandatory exposing patients to frequent follow-up, fastidious dosing that can be impacted by numerous drug and food interactions. Thus, APS patients' health-related quality of life may be impaired. To determine the anticoagulant effect of warfarin, the international normalized ratio (INR) can be obtained with either a venous blood sample by the use of traditional laboratory testing or a point-of-care (POC) coagulometer, such as the Coaguchek XS. This POC method has the ability to provide an INR in an ambulatory setting in a few minutes. The advantages of this technique are to allow a secure monitoring by the patient itself, to decrease the cost of serial traditional venous blood tests, and to increase health-related quality of life.

Regarding the reliability of the POC system, Christensen et al. performed a systematic review and demonstrated that the precision of the measure was reliable for clinical use (1). In APS patients, because of possible interactions between antiphospholipid antibodies (aPL) and reagent used in prothrombin time INR assay, two studies were performed. In 2017, Taylor et al. found that the mean INR difference between the CoaguChek XS and laboratory was 0.68 (2). Furthermore, this difference was significantly higher in APS patients than in controls when the target INR was 2 to 3 but not above 3. Of note, the 2-3 target INR range is what is recommended for secondary venous thromboprophylaxis in APS. Finally, authors found that the higher the target INR, the higher the variability between POC and laboratory, however, without reaching statistical significance when results were compared to controls. No explanations of this variability were examined. On the other hand, Isert and al. did not observe a higher disagreement between INR test results from CoaguChek and traditional test (3). However, the frequency of INR variation above 0.5 was high in APS patients, but comparable with controls (55.6% vs. 67.8%, p=0.05). They found that INR variability between POC and traditional testing was not impacted by the lupus anticoagulant (LA) test (55.8% had an INR variation above 0.5). Of note, to measure INR using the CoaguChek system, instead of analyzing capillary blood, venous blood was dropped on a test strip according to Plesch et al. Even if it has been

showed that there is no significant deviation between results from capillary with those from corresponding venous blood samples on the CoaguChek XS system, a bias could emerge from this methodology. Furthermore, no deep analysis was performed to identify the reason for variability.

Despite non-significant variability when INR testing from CoaguChek and laboratory were compared between APS patients and controls, device companies recommended against the use of POC device use in APS: in the CoaguChek Package Insert provided by Roche it is stated that "*The presence of anti-phospholipid antibodies such as Lupus antibodies can potentially lead to prolonged clotting times, i.e., elevated INR values. A comparison to an anti-phospholipid antibodies-insensitive laboratory method is recommended if the presence of anti-phospholipid antibodies is known or suspected.*" Furthermore, in the technical bulletin provided by HemoSense which provided until recently another POC system – the INRatio –, it is stated that "*Anticoagulant or anti-thrombotic drugs such as Heparin and Low Molecular Weight Heparin will cause the INR to be higher because they are affecting the coagulation cascade directly*". Taken together, physicians as well as APS patients cannot use any POC system to monitor long term warfarin therapy (4).

Our research hypothesis is that aPL profile (strength of the LA, aPL titers, and triple aPL-positivity) or other factors may play a role in the INR variability between POC and traditional laboratory testing. So far, no study addressed this issue. Therefore, our objective is to investigate why in some APS patients POC and laboratory INRs are concordant (INR difference <0.5), by comparing characteristics of APS patients with and without a significant variability above 20% between the POC and the traditional laboratory system. This personalized medicine research study will help identify a subset of APS patients who could use securely a POC system to monitor their long-term anticoagulation.

Design and methodology (Data expected to collect, sample size and statistical analysis):

Different patient groups will be investigated:

a. Patients with LA and no anticardiolipin nor antiβ_2-glycoprotein 1 antibodies (single LA)
b. Patients with LA and anticardiolipin and antiβ_2-glycoprotein 1 antibodies (triple aPL-positive)
c. Patients with another aPL profile of criteria aPL (not single LA or triple aPL-positive)
d. Patients with no aPL treated with vitamin K antagonists

Data collected:

Demographic data (age, gender), cardiovascular risk factors, APS-related clinical manifestations, aPL profile, concomitant medications.

INR testing:

For each patient, INR will be tested by two POC methods and the traditional laboratory INR:

a) Capillary blood: INR testing using the CoaguChek POC device and a second POC device (to be determined) (Nancy) at time of consult
b) Venous blood: INR testing using a traditional testing (Nancy at time of consult and Ghent on stored sample)

Objectives:

For each patient:

- We will compare POC and traditional INR measurements: To identify any variation ≥ 20%
- We will measure criteria (LA, aCL IgG and IgM, aβ2GPI IgG and IgM) and non-criteria aPL tests (antiphosphatidylserine-prothrombine IgG and IgM, aCL and aβ2GPI IgA) to identify whether any positivity of these aPL could explain the interference between POC and traditional INR results ≥ 20%

Logistics:

For each patient, we will need 1 POC strip for each POC device. If 120 patients will be included, thus corresponding to 2x120 strips.

One CoaguChek device is already available in Nancy (one center). One other type of POC device will be used (to be defined).

Statistical analyses:

We will use paired *t* / Wilcoxon/Fisher test to examine the accuracy CoaguChek XS–based INRs using laboratory-based INRs as reference. The paired *t* test will be stratified by patient population (APS patients and control group), subgroup, and laboratory-based INR values (<2.0, 2.0–3.0, 3.1–4.0, and >4.0), respectively. We will use *t* test to examine if deviation of CoaguChek XS–based from laboratory based INRs is different between APS patients and control group within each INR range. Finally, we will calculate and compare the proportions of INR pairs with difference of greater than 20% between the 2 patient populations using χ^2 test, which indicates clinically significant INR difference. All analyses will be conducted with SAS 9.4 (SAS Institute, Inc, Cary, NC).

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Inclusion criteria:

- Patients with diagnosis of thrombotic APS according to Sydney criteria
- Age > 18 years
- Patients are volunteers, informed and signed the consent form for participation. IRB approval is pending.

Exclusion criteria:

- Pregnant women

One hundred and twenty patients will be required (30 patients in each group; 90 thrombotic APS and 30 controls). We expect to include 5 patients per month in each center. Two centers will be involved in the project (Nancy and Ghent). Thus, at least one year is necessary to achieve our goal.

Patients will be recruited during their usual follow-up by specialists working within expert centers devoted to APS. They will receive standard of care patient management.

The investigator will check for eligibility inclusion criteria and give information about the study (orally and informed consent). After patient agreement, the informed consent will be signed. At the end of the clinical assessment, INR measurements will be performed (1 INR using CoaguChek POC device, 1 INR using alternative POC device and 1 venous blood drawn for conventional INR at Nancy and Ghent).

Expected timeline: Project stage/set up

Project stage/set up: October 2021
Launch of the project: End 2021
Duration: 10 months
Finalization/ analysis: December 2022
Reporting: First, results will be reported at the SSC annual meeting. Furthermore, an abstract reporting all preliminary results will be submitted to the ISTH annual meeting. We aim to report this in an original article.

Expected outcomes

If reasons for INR variation in APS patients using CoaguChek POC device are understood, this will help identify a subgroup of APS patients that could use this device for better quality of care and health-related quality of life.

We could imagine that in the future the CoaguChek POC device will no longer be contraindicated in all APS patients and the current recommendation of caution by the manufacturer will be only restricted to a selected APS population at risk of variability.

Description of project set/up and management, needed infrastructure and resources:

The project will be led by the Lupus anticoagulant/aPL SSC subcommittee.

Regarding resources, for each patient, we will use two POC strips for INR testing in 120 patients. CoaguChek devices will not be necessary for this study since a device is already available in Nancy Academic Hospital. Purchase of the alternative device will be investigated (sponsoring, leasing, …). INR

will be tested also on venous blood. The budget for testing is estimated to 20 451 USD and 2000 USD for shipping the samples to the central lab for aPL and INR testing.

Katrien Devreese will be in charge of the INR testing on venous blood specimens and aPL testing; in total 3.5 mL citrated plasma will be needed. Two or more citrated tubes, depending of volume of the tubes will be needed (1.8 mL plasma for LAC testing, 1.5 mL for other aPL, 0.5 mL for PT). The recruiting centers have to double centrifugate the citrated plasma and store it in two aliquots, frozen by -80°C. Samples will be transported from the participating centers to Ghent on dry ice.

References

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2. Taylor J, Richter C, Lindamood C, Liu X, Zumberg M, Fletcher B. Accuracy of CoaguChek XS in Patients With Antiphospholipid Syndrome. Point of Care: The Journal of Near-Patient Testing & Technology. 2017;16(4):161–3.

3. Isert M, Miesbach W, Schüttfort G, Weil Y, Tirneci V, Kasper A, et al. Monitoring anticoagulant therapy with vitamin K antagonists in patients with antiphospholipid syndrome. Ann Hematol. 2015 Aug;94(8):1291–9.

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