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Antiphospholipid Syndrome and Lupus Anticoagulant: Where do we stand today ?

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ABSTRACT

Lupus Anticoagulant (LAC) is a group of auto antiantibodies that interfere with phospholipid dependent tests like Activated Partial Thromboplastin time (APTT) and dilute Russell Viper venom time (dRVVT) on in vitro basis. LA, anti cardiolipin antibodies (aCL) IgG/IgM, and anti-β2 glycoprotein I antibodies [aβ2GPI]IgG/IgM are three diagnostic criteria for laboratory diagnosis of anti-phospholipid antibodies (aPL). The circulating aPLs in the clinical setting of hypercoagulability state or adverse pregnancy outcomes is termed as anti-phospholipid syndrome (APS).

The laboratory diagnosis of APS is complicated, it includes constellation of tests like solid phase immunoassays for measurement of aCL and a β 2GPI by and coagulation based assays for detection of LAC. LAC diagnosis is especially challenging in the setting of anti-coagulation therapy, numerous modifications to circumvent this interference have rendered success.

The Thrombin generation assays [TGA] for LAC detection and estimation of LAC pathogenicity are available but are yet to be accepted as routine laboratory tests. The medley of assays like Enzyme-linked immunosorbent and chemiluminescent assays are available for detection of aCL and aβ2GPI but due to the non-availability of universal calibrators and standards there is lack of harmonization between various solid phase assays.

In this article we intend to highlight new recommendations of laboratory diagnosis of LAC with special emphasis on diagnosis in the setting of pregnancy and anti-coagulation. For risk assessment in APS other non-criteria aPL like as anti-domain β2 glycoprotein I and anti-phosphatidyl serine/prothrombin antibodies are under evaluation.

There is an ongoing quest towards harmonization of detection of LAC, thus there has been succession of guidelines to meet the challenges and incorporate newly found knowledge every time, namely International Society for Thrombosis and Hematology- Scientific Standardization Committee (ISTH-SSC) guidelines, followed by British Committee for Standards in Hematology (BCSH), Clinical and Laboratory Standards Institute (CLSI) guidelines 2014 and finally guidelines/updates issued by ISTH- SSC in 2018.

KEYWORDS: LAC, Autoantibodies, Immunity, Immunoglobulins, Antibodies

INTRODUCTION

LAC is a heterogeneous group of auto antibodies directed towards various negatively charged phospholipids [PL]–protein complexes, proteins include namely Prothrombin, β2GPI etc. LAC paradoxically causes prolongation of PL dependent tests like APTT, DRVVT etc. on in-vitro basis but clinically it can present with thrombotic sequealae like arterial, and venous thrombosis and pregnancy related morbidity. [1, 2] According to International Society for ISTH-SSC guidelines, APS is defined by the presence of clinical evidence of thrombosis, LAC positivity or the presence of medium to high titres of either aCL or a β 2GPI. [2, 3] The patients with triple positivity i.e. concomitant presence of LAC, aCL and a β 2GPI carry high risk of thrombotic events. [3] The APS patients with persistence of antibodies are offered long term anticoagulation to prevent recurrent

thromboembolic sequealae. [3]

THE HISTORICAL & PRESENT PERSPECTIVES OF PL: DEPENDENT TESTS FOR THE DIAGNOSIS OF LAC:-

Historically, LAC presented as innocuous and unexplained prolongation of APTT without associated clotting factor deficiency in otherwise apparently healthy individuals during routine pre surgical investigations. [3] This led to the pursuit for PL reagents insensitive to LAC. Later, the association between prolonged APTT and thrombotic events or pregnancy related morbidities was established and LAC was established as an antibody that inhibited coagulation. [3] In 1983, Dahlback B et al demonstrated that LAC inhibited several steps in the coagulation cascade. [4] A multi-centre study conducted by Sciascia et al in 2019, observed that the lack of harmonization between LAC testing across the laboratories has underscored the importance of testing antibodies against phosphatidyl serine–prothrombin complexes [PS–PT] in lieu of LAC testing for APS. [5]

In 2020, Bowles L et al studied the coagulation profile in SARS Cov-2 patient's sample. Amongst 216 samples, 44 samples [20%] samples were found to have prolonged APTT values. Out of 44 samples with prolonged APTT, 34 samples were further tested for LAC screening by lupus-sensitive APTT and DRVVT followed by mixing studies, out of which 31[91%] tested positive for LAC. In the retrospective control cohort of 540 samples received for LAC testing, 43 [8%] had prolonged APTT of 30 seconds or more and only 11 out of 43 [26%] tested positive for LAC. The percentage positivity of LAC was significantly higher in the test cohort with SARS-Cov-2 infection as compared with the control cohort. [P<0.001] In this study group of SARS Cov-2 positive patients positive, 91% of the patients with prolonged APTT tested positive for LAC and often had concomitant factor XII deficiency. It was observed in this study that the SARS Cov-2 infection was not associated with bleeding tendency, as factor XII is not vital for haemostasis but persistence of LAC predisposed SARS Cov-2 patients to thrombotic events. [6]

APS, LAC AND PREGNANCY:-

Gebhart et. al studied the mortality rates and factors which influence mortality in Lupus positive patients, a prospective observational study with a sample size of 151(82% females) patients was carried out for 8.2 years (median time period), 30 patients (20%) developed 32 thromboembolic events (TEEs) out of 15are arterial events and 17 are venous events and 20 patients (13%) had a fatal outcome. On univariate analysis, it was analysed that de novo thrombosis was associated with adverse survival outcomes. {Ratio [HR] 5 8.76; 95% confidence interval [CI], 3.46-22. 16] }. The variables like age, hypertension, sex, and positive history of thrombosis anticoagulation at inclusion, concomitant autoimmune disease, and positivity for antibodies against cardiolipin [aCL] and β2GPI are not risk factors for thrombosis and poor survival. [HR 5 5.95; 95% CI, 2.43-14.95], In survival analysis, the cohort of patients with persistent LAC positivity had poorer survival outcomes when matched with age and sex with a matched Austrian reference population. Hence, it was concluded that the TE events contributed to adverse survival outcomes in patients with persistent LAC positivity. Thus treatments directed towards the prevention of TEEs in LAC-positive patients can improve survival outcomes in this group of patients. [7]

Gebhart. et. al conducted a prospective study on 82 women of reproductive age group in high-risk category with persistent LAC positivity to identify risk factors for adverse pregnancy outcomes and hence decide on therapeutic interventions to mitigate the risks. In the prospective study group of 82 women, 23 had 40 pregnancies within the Vienna Lupus Anticoagulant and Thrombosis Study. Out of 40 pregnancies, 28 pregnancies had complications (70%), 22[55%] had spontaneous abortions and 6 had preterm deliveries <34th week of gestation, {15% 3 due to severe preeclampsia/HELLP [haemolysis, elevated hepatic enzymes, and thrombocytopenia] syndrome}, 3 due to placental dysfunction. Single abortion was followed by catastrophic APS. It was concluded that a history of pregnancy complications, thrombosis and elevated pre-pregnancy aPL levels were not associated with pregnancy-related morbidity or mortality. The risk of pregnancy-related adverse outcomes is nearly 70% /pregnancy in the high-risk group with persistent LAC positivity in women. The higher index of circulating Abs, % i.e., Rosner Index is a marker of aggressive LAC phenotype was a risk factor for adverse gestational outcomes in the cohort of LAC positive women. [8]

DIAGNOSTIC ALGORITHM FOR LAC [1–3] :-

Criteria for patient selection:

The selection of patients is of paramount importance as inadvertent selection will lead to an increase in false positive rates and unnecessary treatment in extreme conditions. The history of unprovoked arterial/venous thrombosis in young patients, setting of autoimmune disorders like Systemic Lupus erythematous (SLE) or malignancies. [1, 9] Another set of patients requiring LAC testing are women with recurrent abortions, stillbirths and preterm deliveries. The incidental finding of prolonged APTT during pre-operative screening, without evidence of factor deficiencies, merits LAC testing. [3, 10]

LAC testing is recommended with testing for aCL, and aβ2GPI, to assess the risk in patients suspected to have APS: [10]

- Younger patients (<50 years) with unprovoked venous thromboembolism (VTE)
- VTE at unusual sites.
- Younger patients (<50 years) with ischemic stroke, transient ischemic attack or other evidence of brain ischemia.

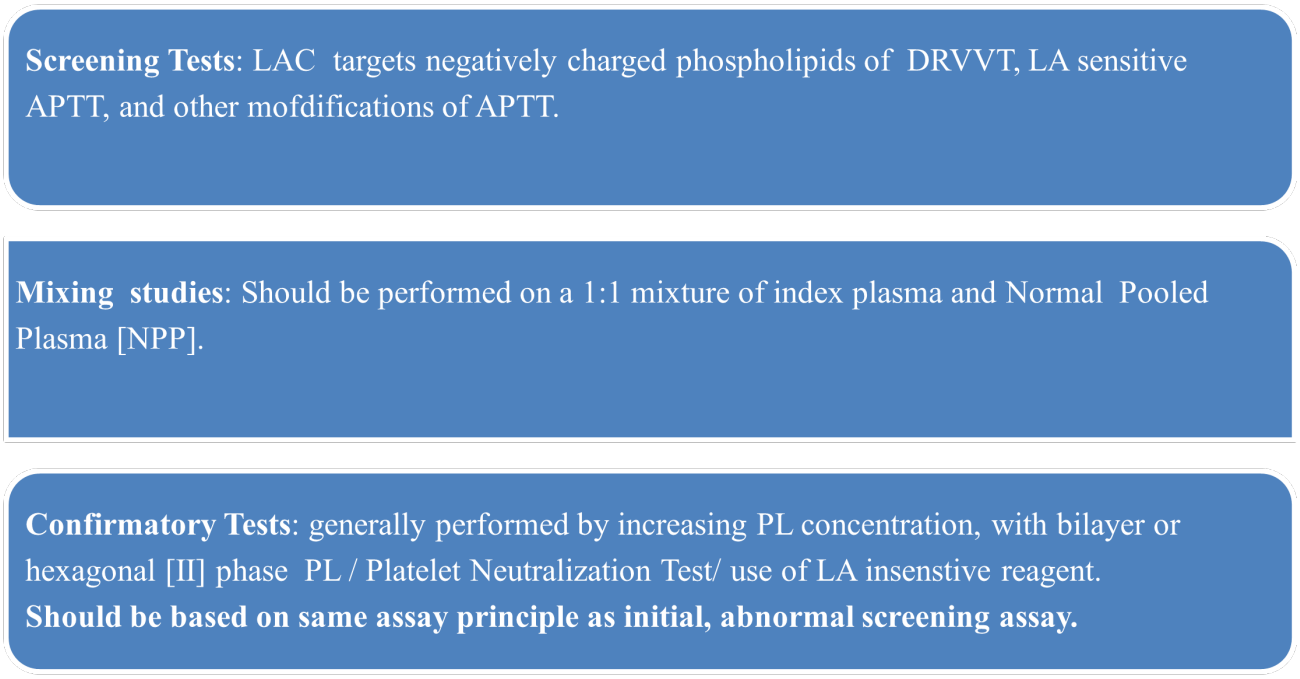

Figure 1: Three step diagnostic algorithm for LAC detection: Screen: Mix: Confirm

- Arterial thrombosis in other sites in younger patients (<50 years).
- Recurrent VTE unexplained by suboptimal anticoagulation, patient non-compliance or malignancy.
- Micro vascular thrombosis.
- Complications related to pregnancy: fetal loss after 10 WOG, recurrent first trimester miscarriages, prematurity (<34 WOG).
- Associated with severe pre eclampsia, HELLP syndrome, placental insufficiency (fetal growth retardation), stillbirth.
- Systemic lupus erythematous: testing for LAC is part of the diagnostic criteria and contributes to risk assessment.

LA testing could be considered in the following situation: [3, 10]

- younger patients [<50 years] with non-criteria clinical manifestations, i.e. those not included in the Sydney criteria, e.g. cognitive dysfunction, valvular heart disease with the presence of co-existing systemic autoimmune diseases.
- Patients with incidental and unexplained prolongation of APTT test.
- Immune thrombocytopenia, particularly with presence of arthralgias or arthritis, photo sensitivity, oral ulcers, hair loss, rash, TEEs.
- Livedo reticularis, with associated other systemic autoimmune diseases or mild thrombocytopenia.
- Patients of younger age [<50 years] following provoked VTE when the provoking environmental factor is comparatively milder.

Recommendations for the timing of LAC testing:

The appropriate timing of testing is of paramount importance for correct diagnosis and interpretation. [3] The recent guidelines defer LAC testing during acute TEEs as coagulation factors namely factor VIII (pro-coagulant) and acute phase reactants can be falsely increased during acute TEEs leading to erroneous interpretation of results. C - reactive protein, which is also an acute phase reactant, affects the APTT results. [3, 9] There is a physiological increase in LAC and other coagulation factors during pregnancy rendering the interpretation more difficult. [3, 10] LAC Positivity may show inconsistent positivity in SLE and pregnant patients. [10–13] Positive/negative results for aCL and aβ2GPI during pregnancy do not exclude/ establish the diagnosis of APS. Hence, repeat testing for LAC, aCL and a β2GPI is recommended post-partum to establish the correct diagnosis of APS. [10–13] Yelnik. CM et al. suggested that first-trimester LAC testing results are reliable, the coagulation factors return to baseline levels by 6 weeks post-partum and hence repeat testing is recommended at 3 months post-delivery. [12, 14]

In the event of arterial thrombosis, we cannot defer LAC testing to rule out the presence of LAC in view of the requirement for early institution of appropriate anticoagulant treatment to prevent further TEEs. [3] The patients presenting with acute TEEs are already on anticoagulation therapy namely heparins, Vitamin K antagonists (VKAs) Or DOACs hence rendering the interpretation more difficult. [3, 11]

It is recommended that repeat testing is mandatory after an initial positive result on a second occasion after a difference of at least 12 weeks to confirm persistent positivity which is deemed to be clinically significant. This is a consensus decision across all the guidelines. [1, 10]

PRE-ANALYTICAL VARIABLES : [1–3, 10]

CHOICE OF TESTS :-

The choice of first-line test is a perennial question being tried to be answered across ISTH-SSC guidelines 2009, BCSH guidelines, CLSI 2014 guidelines and the most recent update by ISTH-SSC. [1, 2, 10] CLSI guidelines 2014 recommended tests based on two different assay principles and affecting a different part of the coagulation cascade. The ISTH-SSC update recommends two assays based on different principles, one of them should be DRVVT and another LA sensitive aPTT, i.e. Low PL concentration and silica as activator. [2] DRVVT is preferred for its specificity, whereas APTT is useful for its sensitivity which is dependent on PL concentration in the reagent, hence both tests complement each other. [2] The update recommends against other PL-dependent assays due to a lack of uniformity in the reagent composition, poor precision and limited commercial access. [2, 10] The dilute Prothrombin time [dPT] is a sensitive test for LAC detection and was included in first-line screening assays in BCSH guidelines and second-line testing in CLSI guidelines 2014, but its use is discouraged due to variation in the reagent composition. [1, 2, 10, 15] The Kaolin CT[KCT] assay activates the intrinsic pathway of the coagulation pathway using Kaolin as an activator without extraneous PL source. However, it is sparingly used because of lack of standardization, unavailability of confirmatory assay and incompatibility with optical clot detection analysers. [2, 10, 16] Moore GW et al evaluated combination of Taipan snake venom time [TSVT] and ecarin time [ET] as an assay for LAC detection in a multicentre setting and the results were promising, showing better sensitivity for LAC evaluation and lesser interference due to DOACs on comparison with the combination of aPTT and dRVVT [2, 17, 18] Oscutarin C used in TSVT assay activates PL and calcium-dependent, Factor V independent conversion of Prothrombin to thrombin. [18] Whereas, ecarin in ET activates the step of conversion of Prothrombin to thrombin independent of the PL-based co-factors. [2] ET is PL independent hence TSVT/ET assay combination can be used as both duos of screening and confirmatory assays but more extensive multi-centric studies are required before this combination can be recommended for routine practice. [2, 18] TSVT/ET assay combination can be an ideal assay for use in anti-coagulated samples as this assay is least affected by VKAs and DOACs [anti-Factor Xa]. [2, 19]

INTEGRATED TESTING AND THREE-STEP PROCEDURE:-

The step-wise approach of Screen Mix Confirmatory Test helps reduce costs; if screening assays are not prolonged mixing and confirmatory assays are deferred. However, in routine practice paired testing with screening and confirmatory assay is done simultaneously followed up by mixing assay as stated in CLSI 2014. The CLSI guidelines & ISTH –SSC update recommend that all positive screen results should be followed up by confirmatory assay, irrespective of the results of the mixing assay. To compensate for the daily variation, analysing a Normal Pooled Plasma [NPP] in each test run is recommended by CLSI guidelines. [2]The result of the confirmatory assay is expressed as LAC ratio: [[Screen patient/ Screen NPP]]/ [[confirm patient]/ [confirm NPP]], or as normalized percentage correction [[screen patient]/ [screen PNP] / [confirm patient]/ [confirm PNP]]/ [[screen patient]/[screen PNP]] * 100 reduces inter-laboratory and inter run variation. [2, 10]

Screening Assay :

LAC targets negatively charged PLs of DRVVT, LA-sensitive APTT, other modifications of APTT, dilute Prothrombin Time (PT) and VLVT, which employs the FX activator from bluntnosed viper venom. The endpoint of the screening test is the prolongation of clotting time (CT). [1, 2]

Mixing assay :

In this step, the screening assay is performed on the mixture of 1:1 index plasma [patient plasma]: NPP. The CT is prolonged in the presence of LAC. It is recommended to interpret with an index of circulating anticoagulant or mixing test-specific cut-off. The ISTH-SSC update recommends NPP with pooling plasma from at least 40 normal donors. [2] Mixing assay results are expressed as a normalized ratio: screen mix/screen NPP. [1, 2]

Confirmatory assay:

The confirmatory tests are generally performed by either increasing PL concentration with bilayer or hexagonal [II] phase PL or Platelet Neutralization Test or use of LA insensitive reagent. The CT is shortened in the presence of excess PL, as excess PL quenches LAC. The confirmatory assay should be based on same assay principle as initial, abnormal screening assay. [1–3]

Newer Assays under consideration for LAC detection:

The coagulation tests for LAC detection are labour intensive, fraught with interferences and the interpretation is complicated too. There is a paradigm shift with interest in the thrombin generation assay [TGA]/ Thrombin generation test, which is a global assay that gives holistic information about the major part of the coagulation cascade and has high sensitivity for LAC detection, unlike clot-based assays which give limited information. Therefore, maybe in future on further validation, TGA might replace multiple available assays and steps. [2]

Pre-analytical Variables	ISTH-SSC guidelines	BCSH guidelines	CLSI guidelines	ISTH-SSC Update
Centrifugation speed and time for preparation of Platelet Poor Plasma (PPP)	Double Centrifugation is recommended.	Double Centrifugation is recommended.	Double Centrifugation/ Single centrifugation if target is achieved	Double centrifugation: 2000g X15 min. at room temperature [RT]
Target final platelet count in PPP	Target final platelet count of <10 X 10^9/L is advocated.	Target final platelet count of <10 X 10^9/L is advocated.	Target final platelet count of <10 X 10^9/L is advocated.	Target final platelet count of <10 X 10^9/L is advocated.
Usage of Plasma filtration	Defer usage of plasma filtration through 0.22-lm	Ultracentrifugation is discouraged, Because of possible micro particle formation. Rejects use of plasma filtration through 0.22-lm	Ultracentrifugation is discouraged. Rejects use of plasma filtration through 0.22-lm	–

Table 1: Guidelines Recommendations

TGA assay measures both pro-coagulant and anti-coagulant forces simultaneously in real time, and the thrombogram shows multiple derived parameters. [2, 20–22]

The principle of TGA is the measurement of thrombin after the interaction of tissue factor and PL and can be used to assess the coagulability state, whether it is hypo or hyper. Originally TGA was very labour-intensive and could not be easily standardized, hence could not be introduced in routine practice. [2]

Recently, Ninivaggi M et al. released recommendations on various pre-analytical variables like blood collection, handling of samples, processing, and sample storage; analytical variables like reagent concentration; dilution of samples and temperature conditions; calibration and replicate testing and post-analytical considerations like calculation, interpretation of results; reference values etc. to reduce inter-laboratory variations and bring harmonization in the TGA results. [2, 23] There has been an attempt to automate TGA to reduce the hands-on time of technical persons and decrease inter-individual variation. TGAs have evolved from early benchtop methods to robot-assisted analytical systems with assay-specific quality controls which are amenable to standardization. [2, 24] There is an ongoing search for specific biomarkers which can be measured by solid phase assays too. [2]

RECOMMENDATIONS FOR LAC TESTING IN THE SETTING OF ANTICOAGULATION:

In the present era, there is a changing trend with the replacement of oral VKAs e.g. Warfarin etc. with DOACs [oral anticoagulants against Factor Xa/ thrombin] due to limitations and adverse effects of VKAs. LAC testing is an integral requirement for thrombophilic patients already on anticoagulant therapy. Earlier guidelines like ISTH-SSC, and BCSH guidelines did not extensively discuss LAC detection in DOACs, CLSI guidelines 2014 recommended against LAC testing in patients on DOACs. [25]

The testing for LAC in anti-coagulated patients has been discussed in a separate guidance document of ISTH-SSC LA/aPL. [10] The clinical information about the anti-coagulation status of the patient is essential before LAC testing for proper interpretation and a decrease in interference. [2] It is recommended to perform PT, aPTT and thrombin time [TT] before initiating LAC testing to gather more information about the coagulation status of the patient. However normal aPTT & PT do not rule out the presence of DOACs or LMWH in the sample and TT identifies the presence of heparin. [2, 10] Also it is recommended to measure anti-FXa activity in samples subjected to LAC testing in patients anti-coagulated with LMWH or unfractionated heparins. In cases where relevant clinical details like anticoagulation are not available, the test results of LAC testing should be reported with warnings on the feasible false positivity due to lack of treatment-related information. [2, 10]

Analytical Variables/ considerations	ISTH-SSC guidelines	BCSH guidelines	CLSI guidelines	ISTH-SSC Update
Number of specific assays	dRVVT and LAC sensitive APTT only indicated	No limit on the number of assays	No limit on the number of assays	Two tests based on different principles recommended as first line assays.
Activator	Silica	Silica, Ellagic acid, Kaolin	Silica, Ellagic acid, Kaolin	Silica is most preferred. Ellagic acid is sparingly used.
Algorithm of testing	Screen-mix-confirm. Confirm only when mixing study is positive.	States that in the absence of other causes of prolonged CT, samples with negative mixing tests but clear positive screen and Confirm tests on undiluted plasma can be considered LA positive.	Screen-confirm- mix. Considers the mixing step as the last one and unnecessary in specific Circumstances.	Screen-mix-confirm. Confirmatory tests should be performed if the screening test suggests presence of LAC, even if mixing test results are not suggestive of presence of LAC.
Confirmatory Tests	Confirmatory test is performed if the both screening test and the mixing test with screening reagent suggest LA presence. In confirmatory tests increased PL concentration is used. With bilayer or hexagonal [II] phase PL.	Recommends usage of high PL concentration, platelet neutralization procedure [PNP] or LA-insensitive reagent.	Recommends usage of same assay principle as initial, abnormal screening assay. 2. Solid phase immune assays for antibodies against phospholipid (e.g. ACL, B2GP1)are not regarded as Confirmatory tests for LA detection.	Recommends usage of increasing the concentration of PL used in the screening test. ● PL from synthetic source / Bilayer or hexagonal [II] phase PL. should be used.
Cut-off value for a positive LAC assay	99th percentile	97.5th percentile (if Gaussian)	97.5th percentile (if Gaussian)	99th percentile on 40 normal donors for screening and mixing test

Table 2: Analytical considerations [1–3, 10]

The options available for LAC testing in patients on DOACs/ Heparin/ VKA are as stated below: [2, 10, 25–32]

1. Replace aPL testing in patients on DOACs with solid phase assays for aCL & aβ2 GPI. But the assays for aCL & aβ2GPI carry high variability and there is no clear-cut association with the thrombotic risk. Hence the omission of LAC testing is not a very good alternative.
2. LAC testing in patients on DOACs at trough levels, can limit false positive and false negative LAC results, but the false results cannot be entirely excluded. DRVVT test is extremely sensitive to even low concentrations of DOAC levels; hence it is preferable to do LAC testing in DOAC naïve patients.
3. The option of cessation of DOAC therapy for 24-48 hours is available, but it is clinically unacceptable due to the possibility of adverse clinical outcomes.
4. The option of replacing DOAC therapy with LMWH for 24-48 hours before sample collection. But in most of the circumstances, it is not clinically acceptable due to the risk of adverse clinical outcomes.
5. Usage of reagents insensitive to heparin in heparinised samples. The reagents can be rendered insensitive to heparin by the addition of heparin neutraliser in reagents for PT and DRVVT.
6. There are commercially available adsorption products like DOAC-Stop® and DOAC-Remove®] which contain activated carbon and are known to avoid interferences in LAC detection. It has been established that the addition of activated charcoal/carbon to citrated plasma samples removes interferences due to DOACs in coagulation assays like PT, aPTT, dRVVT, and SCT assays by adsorbing small, neutral or positively charged particles like DOACs.
7. The filtration techniques are also available for the removal of interferences due to DOACs from plasma samples. But studies have reported incomplete and inconsistent removal of DOACs from plasma samples by both adsorption and filtration techniques hence resulting in false positive and false negative results.
8. The TSVT/ET assay can also be used to investigate LAC in patients treated with direct anti-FXa inhibitors, but not for direct thrombin inhibitors. [33]

A single-centre trial compared the results of the DOAC adsorption assay and TSVT/ET in overcoming anti-FXa DOAC interference. [34] Because the studies have shown discrepant results more studies analysing [non] superiority studies of DOAC adsorption technique to TSVT/ET in DOAC spiked plasma samples are recommended. [34]

CONCLUSION:

The laboratory diagnosis and risk stratification of LAC persists to be enigmatic for both clinicians and laboratories, due to availability of constellation of tests and guidelines. All the currently available tests for detection of LAC have their limitations, like being labour intensive, interferences due to acute phase proteins, physiological increase in coagulation factors in pregnancy, samples from anti-coagulated patient. Many strategies are under evaluation to mitigate the inferences due to anti-coagulants and acute phase reactants. There is availability of numerous platforms and assays for analysis of aCL IgG/IgM, and aβ2GPI IgG/IgM, which leads to lack of harmonization across the laboratories. LAC, aCL IgG/IgM, and β2GPI IgG/IgM testing should be done in a parallel manner to enable efficient interpretation and risk stratification. Novel assays like TGA /DOAC adsorption procedures/ TSVT-ET combination can change the landscape of LAC testing in the near future. The biomarkers like aPS/PT and aDI can be used in addition to aCL and aβ2 GPI to calculate risk estimates. The interpretation of LAC results and diagnosis of APS requires close interplay between clinical and laboratory professionals.

ABBREVIATIONS:

LA: Lupus Anticoagulant

aCL: anticardiolipin antibodies

aβ2 GPI: anti-β2 glycoprotein I

aPL: antiphospholipid antibodies

APTT: Activated partial thromboplastin time

DRVVT: dilute Russell viper venomtime

APS: anti-phospholipid syndrome

PT: Prothrombin Time.

CT: Clotting Time.

NPP: Normal Pooled Plasma

BCSH: British Committee for Standards in Hematology

ISTH-SSC: International Society for Thrombosis and Hemostasis- Scientific Standardization Committee

LMWH: Low molecular weight heparin.

VTE: Venous thromboembolic event.

DOAC: Direct Oral anticoagulant

SLE: Systemic Lupus erythematous

VKAs: Vitamin K antagonists

dPT: dilute prothrombin time

KCT: Kaolin CT

TSVT: Taipan snake venom time

EC: ecarin time

RT: Room temperature.

PPP: Platelet Poor plasma

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