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Anti-phospholipid Syndrome and Testing for Lupus Anticoagulants: Routine Approach Using Siemens APTT Reagents

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Answers for life.

Anti-phospholipid syndrome

Anti-phospholipid syndrome (APS) is an autoimmune disease associated with thrombotic conditions. The diagnosis of APS is based on the combined presence of typical clinical manifestations, either in the form of a vascular thrombotic event or certain repeated complications during pregnancy, typically resulting in recurrent spontaneous miscarriages as well as the presence of antibodies directed against phospholipid-binding proteins. For diagnosis of APS, the presence of at least one clinical and one laboratory criteria as listed in Table 1 is required.

Table 1: Diagnostic criteria for APS[1]

Clinical criteria	
Vascular thrombosis	One or more clinical episodes of objectively verified vascular thrombosis
Pregnancy morbidity	One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
	One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of (i) eclampsia or severe preeclampsia, or (ii) severe placental insufficiency
	Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and chromosomal causes excluded
Laboratory criteria	
Lupus anticoagulants	Lupus anticoagulants (LA) present in plasma on at least two occasions at least 12 weeks apart, according to ISTH guidelines (prolongation of at least one phospholipids-dependent coagulation assay)
ACA	Anticardiolipin IgG/IgM (ACA) antibodies in plasma/serum, present in medium/high titer (>40 GPL/MPL or 99th percentile) on at least two occasions at least 12 weeks apart, measured by a standardized ELISA
Anti-ß2 GPI	Anti-ß2 glycoprotein I IgG/IgM (anti-ß2 GPI) antibodies in plasma/serum, present (>99th percentile) on at least two occasions at least 12 weeks apart, measured by a standardized ELISA (added in 2006)

Anti-phospholipid antibodies (APA)

APA are a heterogeneous group of antibodies, without one common, clearly defined antigenic target. Consequently, no single assay allows detection of all APA; a panel of several tests is required for diagnosis with sufficient sensitivity.

The international guideline for diagnosis of APS[1] includes three different types of assays that complement each other in detection of APA (Figure 1):

• Lupus anticoagulants (LA)

• Anti-cardiolipin antibodies (ACA)

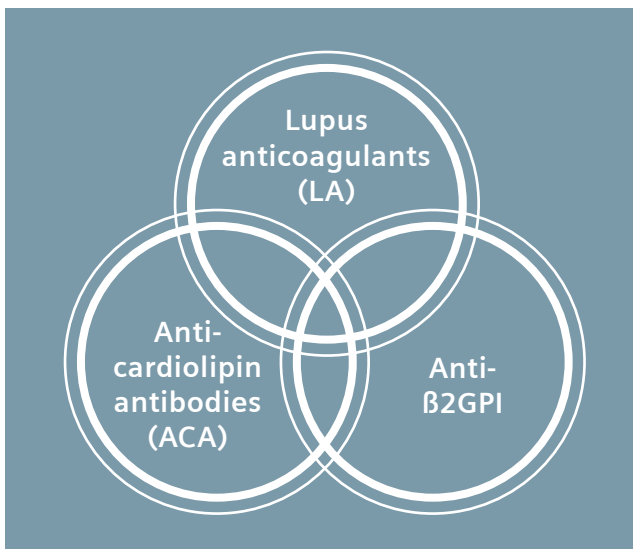• Anti-ß2 glycoprotein I antibodies (anti-ß2 GPI)

Figure 1: Anti-phospholipid antibody subtypes

In cases in which one assay type is positive, further positive reactions in one or both of the other test systems are associated with a markedly increased risk, the highest risk being linked to "triple-positivity."[2]

In the general population, the prevalence of APA is about 5%, and with increasing age, APA are observed even more frequently.

Consequently, a general screening of medical or obstetrical patients is not useful as long as typical clinical symptoms are not present because of the rather low specificity of APA assays.[3]

Among the different types of APA, the lupus anticoagulant (LA) antibodies, characterized by their interference with clotting assays with low phospholipid content, show the strongest association with both thromboembolic and obstetric complications.

In contrast, antibody types such as anti-prothrombin antibodies, which frequently can be detected in APS patients, do not contribute additional independent information to the assay panel of LA, ACA, and anti-ß2 GPI.

The determination of ACA and anti-ß2 GPI is typically based on ELISA assays, which allow detection of IgG and IgM. While IgG antibodies against ACA and/or anti-ß2 GPI are well-established markers of APS, the data connecting IgM antibodies with APS are much weaker and are not consistently positive throughout the different studies.[1]

The determination of LA is much more complex, requiring a 3-step procedure of screening, mixing, and confirmation assays in either dRVVT (diluted Russell Viper venom time) or APTT. In 2009, the ISTH/SSC issued the latest guideline on how to perform and interpret LA testing.[3]

Table 2: APA prevalence in different populations[4]

Population	APA
General population	2–7%
Elderly individuals	12%
Unselected venous thromboembolism	3–17%
Acute cardiovascular events (stroke, AMI)	5–18%
Pregnancies complicated by spontaneous fetal loss	7–42%

SSC recommendations on lupus anticoagulant testing[3]

Patient selection
Two indications exist for LA testing:

- Suspicion of APS, based on the presence of typical clinical symptoms of APS, such as thromboembolism or repeated fetal loss

- Exploration of an unexplained prolonged APTT screening result

Performance of a generalized screen in asymptomatic individuals or patient categories other than those mentioned above is strongly discouraged. As LA can also be detected accidentally in individuals not affected by APS, a confirmation of any positive results is required by retesting after 12 weeks or later to ensure that the antibodies detected were not merely transient in nature.

For reliable interpretation of LA test results, samples should not be taken from patients under anticoagulant therapy; preferably a sample should be taken before initiation of any anticoagulation if testing of thrombophilia markers is indicated. Traditional anticoagulation with vitamin K antagonists, well as the new direct thrombin and FXa inhibitors, severely affects the assays used for determination of LA with frequent false-positive results. Therapy with unfractionated heparin strongly interferes with APTT assays; however, most dRVVT reagents contain an inhibitor for unfractionated heparin.

Preanalytics
The recommended anticoagulant is sodium citrate 0.109 M (3.2%). For preparation of platelet-poor plasma, a double centrifugation, once for 15 min at 2000 g and a second time for 10 min at 2500 g, is most appropriate. A low platelet count is crucial, as platelets will present an additional phospholipid source in the assay and may decrease the sensitivity of the test system.

If not used immediately, the plasma can be frozen at −70°C. The frozen plasma must be thawed at 37°C and mixed thoroughly before testing. In samples to be frozen, the platelet count is even more critical, as platelets may become activated by thawing, which can contribute to a shortening of clotting times.

Choice of screening tests
As LA antibodies are heterogeneous, no single assay shows a perfect sensitivity. By combining different assays, sensitivity can be increased, but in parallel, specificity decreases. To balance for sensitivity and specificity, the guidelines require two (and no more than two) different assay systems based on different principles for exclusion of LA. The sample is considered to be positive if at least one assay system is positive. No more than two different assays are to be used for screening, because, with increasing numbers of assays, the risk for false-positive results becomes too high.

In samples submitted because of a clinical suspicion of APS, dRVVT is the first choice, since this assay format is the most sensitive and specific for detection of LA. If the dRVVT test result is negative, a lupus-sensitive APTT determination is indicated as a second test. Typically such APTT reagents have low phospholipid content.

The guidelines recommend silica-based reagents as the preferred activator and advise against the use of ellagic acid, because low lupus sensitivity has been shown for such reagents in some publications.[5,6]

The papers cited by Pengo[3] as arguments against the use of ellagic acid[5,6] compared different commercially available APTT reagents. However, the reagents compared in these studies differ in many more components than simply the activator used. In contrast, studies that did not support low lupus sensitivity as a general feature of ellagic acid-based APTT reagents were not considered in the guidelines.[7,8]

Dilute PT, KCT, ecarin, and textarin clotting time assays are not recommended as screening tests.

Mixing and confirmation
If the screening test for LA is positive (i.e., if the clotting time of dRVVT or APTT is prolonged), the next step is a procedure in which patient and normal plasma is mixed to differentiate between a factor deficiency (in which case mixing with normal plasma will correct the clotting time) or the presence of an inhibitor (i.e., an antibody)—either LA or a factor-specific inhibitor. A prolonged clotting time indicates the presence of an inhibitor.

According to the guidelines, a 1:1 proportion of patient plasma to pooled normal plasma (PNP) without pre-incubation is to be used for the mixing study. The PNP is ideally prepared in-house by double centrifugation (<10[7]/mL platelets, to be stored frozen at −70° C) from samples obtained from healthy donors. However, as fresh sample material from healthy donors often is not available in clinical laboratories, commercial lyophilized plasmas can be used as an alternative if the content of all clotting factors is approximately 100%.

The next step after demonstration of the presence of an inhibitor by a prolonged clotting time in the mixing procedure is to prove the phospholipid dependency of the inhibitor in confirmatory tests performed by increasing the concentration of phospholipids in the test system used for screening.

Integrated assays

The revised guideline[4] also includes "integrated assays," which are assay systems composed of two test versions with low and high phospholipid content but otherwise identical composition. An increased ratio of the low (i.e., lupus-sensitive) versus the high (i.e., lupus-insensitive) phospholipid test indicates the presence of LA. This type of test may be especially useful for weak LA samples because the 1:1 dilution in the mixing test may mask weak LA.

Reporting and decision limits

Results of the screening, mixing, and confirmation tests may be expressed as the ratio of patient plasma to PNP. The PNP must be run in parallel with the test plasmas.

For determination of the local cut-off values, the guideline requires at least 40 healthy individuals less than 50 years old, along with calculation of the 99th percentile from this data set. However, for a reliable estimation (confidence level of 95%) of a 99th percentile cut-off, a much higher sample number is required (N ≥ 299). For determination of the 97.5th percentile with a confidence level of 95%, at least 119 samples are required.

The quantitative results should always be accompanied by an interpretation of assay results (presence/absence of LA). In case of dubious/borderline results, a repeated sampling 1 week or more later is recommended.

Regarding interpretation, an LA assay result should always be considered in the context of both the clinical signs and the full laboratory APA profile comprising anti-cardiolipin and anti-ß2 glycoprotein I antibodies.

LA1/2 testing algorithm and interpretation

The Siemens LA1 Screening Reagent (LA1) and LA2 Confirmation Reagent (LA2) represent an "integrated" test system consisting of two dRVVT assays, a screening assay with low phospholipid content, and a confirmation assay with high phospholipid content.

For patients suspected of having LA, testing by LA1 and LA2 is the first choice. Strong LA typically prolong LA1, but rare cases of weak LA may show LA1 results within the reference range. Such weak LA can be identified by an abnormal LA1/LA2 ratio.[9]

The combination of a prolonged LA1 but normal LA2 indicates the presence of a lupus anticoagulant. A prolongation of LA2 suggests a factor deficiency and/or oral anticoagulant therapy (OAT) with vitamin K antagonists being present. In this case, a standard PT is a simple and safe test to exclude presence of OAT or any other FX, FV, or FII deficiency.

If OAT is known to be present, an abnormal result for LA1, LA2, and an LA1 mixing study (but a normal result for the mix in LA2) points to the additional presence of a lupus anticoagulant, whereas abnormality of all four tests suggests a non-lipid-dependent inhibitor (see Table 3 for interpretation).

Table 3: LA1/2 assay interpretation

Patient plasma		Mix patient plasma + normal plasma		Interpretation*
LA1	LA2	LA1	LA2	
N	N/A	N/A	N/A	LA not detected; second screening assay required to exclude LA*
ABN	N	N/A	N/A	LA present
ABN	ABN	N	N	LA not detected;** possibly factor deficiency, e.g., oral anticoagulant therapy
ABN	ABN	ABN	N	Probably strong LA present; or concomitant factor deficiency, e.g., oral anticoagulant therapy. Perform PT.
ABN	ABN	ABN	ABN	No lipid-dependent inhibitor detected; possibly other inhibitor***

ABN: Abnormal
N: Normal
N/A: Not applicable
*Few weak LA may show a normal LA1 result but an abnormal LA1/2 ratio.
**For exclusion of LA, a second assay is always required.
***In case of a very strong LA, phospholipid content of LA2 may not be sufficient to normalize the LA2 clotting time, even after mixing.
   The degree of correction by LA2 compared to LA1 in the mix should be calculated.

However, in the rare presence of very strong LA, the phospholipid content of LA2 may not be sufficient to neutralize all antibodies present, resulting in a still-prolonged LA2 clotting time. In this case, performance of LA1 and LA2 on a 1:1 diluted sample in PNP or the classic 3-step algorithm of screening, mixing, and confirmation should be used.[10]

APTT testing algorithm for lupus anticoagulants and performance of Pathromtin SL, Dade Actin FSL, and Dade Actin FS Reagents: Results of a Siemens APTT study

Aim of the study
Several studies investigating lupus sensitivity of APTT reagents produced conflicting results with regard to the sensitivity of ellagic acid-based reagents.

Therefore, our intention was to perform a side-by-side comparison of the silica-based reagent Pathromtin® SL and the ellagic acid-based reagents Dade® Actin® FSL and Dade Actin FS. Based on the phospholipid content of the Dade Actin reagents, we expected a high LA sensitivity for Dade Actin FSL reagent, but a low LA sensitivity for Dade Actin FS reagent.

Further, the use of an APTT method with low LA sensitivity as a confirmatory assay after an initial screen with an APTT method with high LA sensitivity was investigated, as well as the performance of APTT mixing tests.

Description of samples
In an internal study performed at Siemens Healthcare Diagnostics in Marburg, Germany, the 99th percentile cut-off and, alternatively, the 97.5th percentile cut-off were determined for the different APTT methods on the BCS® XP System in 154 frozen plasma samples from healthy donors who were considered negative for LA (the reference panel).

To test lupus sensitivity, 100 commercially available frozen plasma samples characterized by a positive dRVVT test were included in the study. To exclude the presence of anticoagulant therapy, all samples were tested by PT (Thromborel® S reagent) and thrombin time (BC Thrombin). There were no samples with prolonged PT, but three samples with prolonged thrombin time were excluded from further evaluation. There was no clinical information available for the dRVVT-positive plasmas, which were considered status positive for the presence of LA in the further evaluation. Thus, the lupus panel included 97 samples.

Table 4a: LA1/LA2 cut-offs*

| | Reference Panel | | |
	Median*	97.5th percentile	99th percentile
LA1 (sec)	33.5	40.9	44.5
LA1 mixing (sec)	35.0	39.5	41.2
LA2 (sec)	32.2	36.4	39.8
LA1/LA2 ratio	1.04	1.18	1.30

Table 4b: APTT cut-offs*

| | Reference Panel | | |
	Median*	97.5th percentile	99th percentile
PSL (sec)	32.2	41.8	43.7
PSL mixing (sec)	32.2	35.7	36.3
PSL/AFS ratio	1.11	1.26	1.27
AFSL (sec)	28.4	35.7	37.3
AFSL mixing (sec)	28.6	31.0	32.1
AFS (sec)	28.8	35.4	39.8
AFSL/AFS ratio	0.99	1.07	1.10

*All samples were frozen before testing. Therefore, clotting times may be longer than the expected values provided in the IFU or Application Sheet, which are based on testing of fresh samples from healthy donors.

Tests performed

In all samples, the following tests were performed:

- LA1 Screening reagent, LA2 Confirmation reagent, integrated LA assay, LA1 mixing

- Pathromtin SL (PSL) reagent: silica-based reagent; conforms with SSC recommendation

- Dade Actin FSL (AFSL) reagent: ellagic acid-based reagent with low phospholipid content; not recommended by SSC

- Dade Actin FS (AFS) reagent: ellagic acid-based reagent with high phospholipid content; not recommended by SSC

Further, mixing studies with a 1:1 mix of sample and pooled normal plasma were performed for Pathromtin SL and Dade Actin FSL reagents.

While Pathromtin SL and Dade Actin FSL reagents were used as screening tests, Dade Actin FS reagent, with its established low lupus sensitivity, was used as a confirmation test; screen to confirm ratios were calculated for Pathromtin SL (PSL/AFS) and Dade Actin FSL (AFSL/AFS).

All tests were performed on the BCS XP system.

Results

Before calculation of the upper reference-range limits for cut-off definition, results were tested for potential outliers according CLSI guideline C28-A3c, but no outliers were observed.

In Tables 4a and 4b, the median, 97.5th percentile, and 99th percentile determined for the reference panel of 154 healthy donor samples are shown for LA1/2 and APTT methods.

In Table 5, the results obtained for the lupus panel are summarized.

Table 5: Lupus sensitivity

	Lupus Panel				
	Median	**n < 97.5th percentile**	**n < 99th percentile**	**Sensitivity (%) 97.5th percentile cut-off******	**Sensitivity (%) 99th percentile cut-off******
LA1 (sec)	57.1	0	1	100	99.0
LA1 mixing (sec)	46.1	6	18	93.8	81.4
LA2 (sec)	37.5	37	80	N/A	N/A
LA1/LA2 ratio	1.5	0	2	100.0	97.9
PSL (sec)	46.9	27	39	72.2	59.8
PSL mixing (sec)	38.9	23	28	76.3	71.1
PSL/AFS ratio	1.3	53	54	45.4	44.3
DAFSL (sec)	42.9	4	17	95.9	82.5
DAFSL mixing (sec)	35.4	2	4	97.9	95.9
DAFS (sec)	37.1	58	77	40.2	20.6
DAFSL/DAFS ratio	1.2	20	30	79.4	69.1

**Sensitivity calculation is based on the assay-specific cut-offs listed in Tables 3 and 4.

In the LA1/2 test system applying the 99th percentile cut-off, lupus sensitivity was 99% for the LA1 screening step, 98% for the LA1/2 ratio with confirmation, and 81% in the LA1 mixing. If the lower, 97.5th percentile cut-off is used, sensitivities of 100% for LA1/2 and 94% for LA1 mixing were observed. Thus, the LA-positive status was, in general, confirmed for the samples of the lupus panel.

For the APTT tests, the highest sensitivity was seen for Dade Actin FSL reagent, with 82% applying the 99th percentile cut-off (96% with 97.5th percentile cut-off), whereas for Pathromtin SL, the reagent compliant with the SSC recommendation, sensitivity was only 60% (72%), which is significantly lower than the ellagic acid reagent Dade Actin FSL. The APTT by Dade Actin FSL reagent is highly correlated to the LA1/2 ratio (r^2= 0.74, Figure 2). The lupus samples not detected by Dade Actin FSL reagent are all in the low-positive range, with LA1/2 ratios below 1.4. In contrast, the correlation is lower for Pathromtin SL reagent (Figure 3), with a much lower slope, and normal APTT results for samples with LA1/2 ratios up to 2.2. For Dade Actin FS reagent, the known low lupus sensitivity was again confirmed (21%/40%), with nearly no relationship between APTT and LA 1/2 ratio (Figure 4).

In the APTT mixing studies (run on all samples irrespective of the initial APTT result), sensitivities in general were even higher than in the APTT test (Table 5), as the more narrow distribution of the reference samples and consequently low cut-off resulted in slightly abnormal results for several samples just below cut-off in the initial APTT. In the mixing study, Dade Actin FSL reagent again showed higher sensitivity than Pathromtin SL reagent, with a close correlation between Dade Actin FSL reagent mixing and LA1/2 ratio (r^2= 0.86, Figure 5).

The APTT ratio with Dade Actin FSL and Dade Actin FS reagents show more moderate sensitivity at 69% (79%) than the APTT mixing with Dade Actin FSL reagent. For Pathromtin SL reagent, the corresponding sensitivities are even lower, at about 45%. In the method comparison between the Dade Actin FSL/Dade Actin FS reagents ratio, only a weak correlation is observed (Figure 6).

Discussion

The comparison of APTT reagents using different activators revealed a significantly higher sensitivity for the ellagic acid-based Dade Actin FSL reagent versus the silica-based reagent Pathromtin SL reagent, an APTT reagent recommended by the SSC guidelines. Similar results have already been described by others, which demonstrates that the lupus sensitivity of APTT reagents is not determined by the activator used, but by the phospholipid source and content, as well as other ingredients. This fact is further demonstrated by the difference in lupus sensitivity seen for Dade Actin FSL and Dade Actin FS reagents, which both use the same activator but employ phospholipids of different source and concentration.

Regarding the final influence of the activator, no assessment can be made, as to the best of our knowledge there has never been a study published comparing APTT reagents with identical phospholipid and buffer composition but different activators. This topic has also been discussed in the Lupus Anticoagulant session at the 58th SSC Meeting 2012 in Liverpool. The majority of contributors to the discussion agreed that the APTT activator is not relevant for LA sensitivity.

Among the APTT reagents tested in this study, Dade Actin FSL reagent clearly showed the highest sensitivity, and only slightly lower sensitivity than dRVVT. With regard to confirmation testing, the 1:1 mix of patient sample and pooled normal plasma was highly sensitive in this study. Clearly positive samples with LA1/2 ratio above 2 were also consistently positive in an APTT ratio of the lupus-sensitive Dade Actin FSL reagent versus the Dade Actin FS reagent, which only slightly reacts to strong lupus anticoagulants.

Based on our results, we generated a proposed APTT testing and interpretation scheme for lupus anticoagulants, as illustrated in Table 6.

In addition to the choice of the most appropriate testing system, the cut-off definition has a high impact on test sensitivity. Generally, with a lower cut-off, sensitivity increases at the cost of specificity. However, specificity in LA testing can be maintained by choosing a 99th percentile cut-off in the mixing and confirmation steps. On the other hand, choosing a 97.5th percentile cut-off in the screening step (initial APTT) contributes to a final increase in sensitivity.
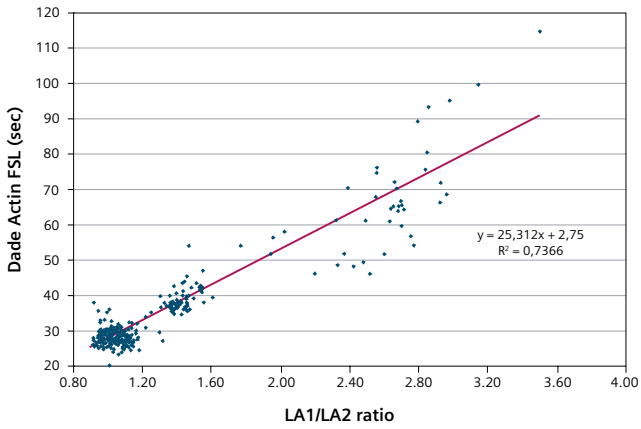
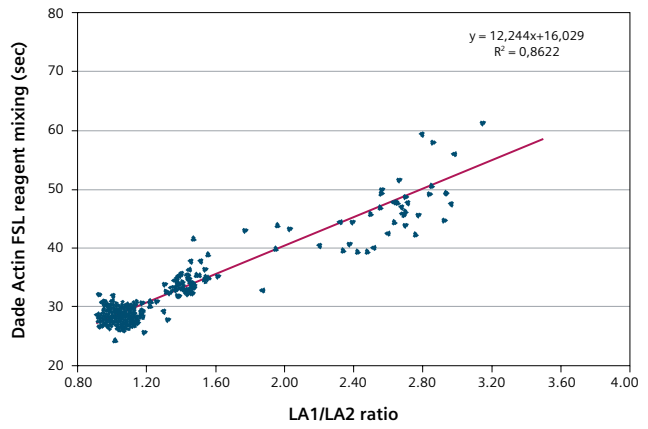**Figure 2: Method comparison—Dade Actin FSL reagent versus LA1/2 ratio**

Figure 5: Method comparison—Dade Actin FSL reagent mixing versus LA1/2 ratio
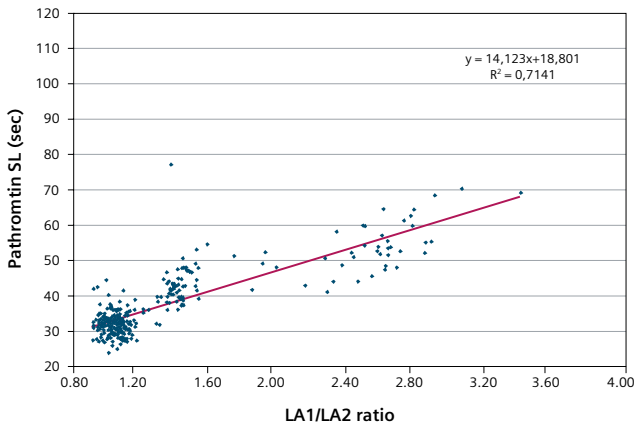

Figure 3: Method comparison—Pathromtin SL reagent versus LA1/2 ratio
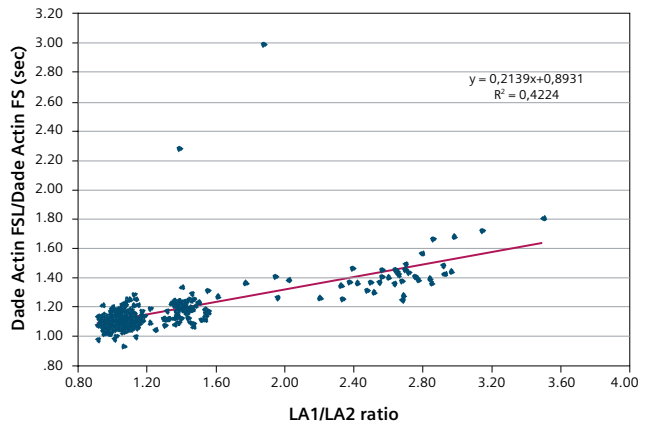

Figure 6: Method comparison—APTT ratio Dade Actin FSL reagent/ Dade Actin FS reagent to LA1/2 ratio
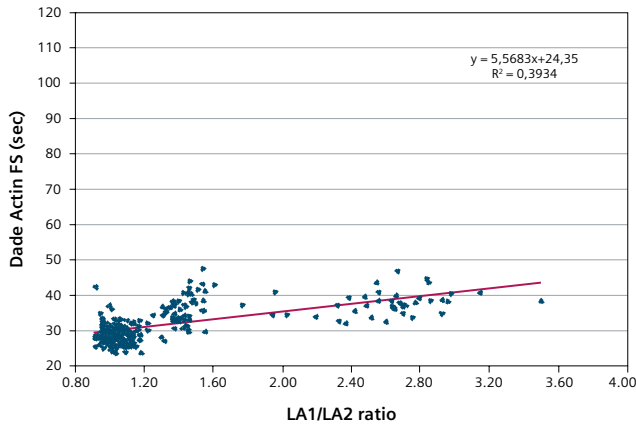

Figure 4: Method comparison—Dade Actin FS reagent versus LA1/2 ratio

Proposed APTT testing scheme

In the APTT, Dade Actin FSL reagent showed superior LA sensitivity compared to Pathromtin SL reagent and therefore is the recommended Siemens APTT screening reagent for lupus anticoagulants. To allow detection of weak LA, we recommend using the 97.5th percentile of healthy donors as the cut-off, as otherwise weak-positive LA may be missed.

In case of a prolonged Dade Actin FSL reagent APTT screen, the next step is to perform Dade Actin FS reagent as a lupus-insensitive APTT confirmation test, and/or to test Dade Actin FSL reagent on a 1:1 mix of the patient sample in pooled normal plasma (PNP). An abnormally high ratio of Dade Actin FSL/FS reagents clearly supports the presence of lupus anticoagulants. However, some weak LA may show a normal result in this ratio.

Sensitivity of the APTT mix strongly depends on the cut-off used. If the cut-off of the APTT screen (i.e., normal APTT) is applied for the APTT mix as well, weak LA will be missed, as the reference range for the APTT mix is much narrower compared to the normal APTT due to reduced variation of the concentration of single factors. If the more-narrow, specific reference range of the APTT mix is applied, this method provides high sensitivity.

Conclusion

Applying the proposed testing scheme, a sensitivity of 78.4% is observed for the combination of abnormal Dade Actin FSL screen, abnormal Dade Actin FSL mix, and abnormal Dade Actin FSL/FS ratio. When combining confirmed and suspected LA, the sensitivity was 95.8%.

Applying this proposed APTT testing scheme to our study panel, the following results were obtained:

Table 6: Study results and interpretation for the proposed APTT testing scheme

Dade Actin FSL (97.5th perc.)	Dade Actin FSL mixing (97.5th perc.*)	Dade Actin FSL/ Dade Actin FS ratio (97.5th perc.)	No. of samples in study (total N=97)	Interpretation
N	N/A	N/A	4**	LA not detected***
ABN	N	N	0	LA not detected***
ABN	ABN	ABN	76	LA present[§]
ABN	N	ABN	0	Weak LA suspected[§] (LA or other inhibitor)
ABN	ABN	N	17[†]	Weak LA suspected[§] (LA or other inhibitor)

ABN: Abnormal
N: Normal
N/A: Not applicable
*Cut-off specific for Dade Actin FSL mix.
**Two samples tested negative in LA1/2 as well; two samples were LA1/2 weak positive (ratio <1.5).
***Second assay required to conclusively exclude LA.
[§]If anticoagulant therapy is excluded, and PT and thrombin time are normal.
[†]The LA1/2 ratio for these 18 samples ranged from 1.31 to 1.61, with 13 samples showing an LA1/2 ratio <1.5.

References

1. 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.

2. Pengo V, Banzato A, Bison E, et al. Antiphospholipid syndrome: critical analysis of the diagnostic path. Lupus. 2010;19:428-31.

3. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/ Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-40.

4. Khamashta MA (Editor). Hughes Syndrome, Second Edition, Springer 2006; page 12.

5. Tripodi A, Biasiolo A, Chantarangkul V, Pengo V. Lupus anticoagulant (LA) testing: performance of clinical laboratories assessed by a national survey using lyophilized affinity-purified immunoglobulin with LA activity. Clin Chem. 2003;49:1608-14.

6. Arnout J, Meijer P, Vermylen J. Lupus anticoagulant testing in Europe: an analysis of results from the first European Concerted Action on Thrombophilia (ECAT) survey using plasmas spiked with monoclonal antibodies against human beta2-glycoprotein I. Thromb Haemost. 1999;81:929-34.

7. Denis-Magdelaine A, Flahault A, Verdy E. Sensitivity of sixteen APTT reagents for the presence of lupus anticoagulants. Haemostasis. 1995;25:98-105.

8. Brandt JT, Triplett DA, Musgrave K, Orr C. The sensitivity of different coagulation reagents to the presence of lupus anticoagulants. Arch Pathol Lab Med. 1987;111:120-4.

9. Moore GW, Henley A, Greenwood CK, Rangarajan S. Further evidence of false negative screening for lupus anticoagulants. Thromb Res. 2008;121:477-84.

10. Favaloro EJ, Bonar R, Marsden K. Internal quality control and external quality assurance in testing for antiphospholipid antibodies: Part II – Lupus anticoagulant. Semin Thromb Hemost. 2012;38:404-11.

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