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Research Article

RELEVANCE OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN THE EVALUATION OF IDIOPATHIC THROMBOSIS

Shajit Sadanand^{1*}, Binoy J Paul², Emil J Thachil³ and Rejadheesh Meletath⁴

¹Medicine Govt. Medical College, Calicut 673008

²Medicine & Rheumatology KMCT Medical College, Calicut

³Consultant Rheumatologist, Lourdes Hospital, Kochi

⁴Department of Medical Microbiology School of Health Sciences, University of Calicut

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ABSTRACT

Introduction: Antiphospholipid antibody syndrome (APS) is an important cause for idiopathic thrombotic events especially in young patients. Failure to recognize APS and initiate prompt treatment leads to considerable morbidity and mortality. There are only very few studies in Asian population on the significance of APS in the evaluation of idiopathic thrombosis. Here we describe the association of different APS tests with thrombotic events in Indian population.

Method: The study was conducted at a Government Medical College in North Kerala, India. All patients who presented to the medicine department with arterial or venous thrombosis as the manifestation of APS during a two-year period were studied. Anticardiolipin (aCL) and anti β 2 glycoprotein (anti β 2G) both IgG and IgM tests were done on patients at presentation and 12 weeks later. Higher of the two values were taken for analysis in relation to clinical manifestations. Patient was considered to be positive for aCL test if the titer was more than 40 GPL or MPL for IgG and IgM aCL tests respectively. Anti β 2G is considered to be positive if the titer is more than 40U/ml for IgG or IgM anti β 2G tests. Lupus anticoagulant test was done by dRVVT (dilute Russel Viper Venom Time) test.

Results: The study population included 77 patients, with majority (58%) between 20 and 40 years. There is statistically significant association between aCL IgG and occurrence of total arterial events ($p=0.0059, r=0.622$) and also for stroke ($p=0.03$) and myocardial infarction (MI) ($p=0.01$).

There is also significant association between aCL IgM positivity and occurrence of total arterial events ($p=0.0004$) and MI ($p=0.05$), but not for stroke. There is also strong association between both anti β 2G isotypes and MI. LA test also showed significant relation with total arterial events ($p=0.0024$), stroke ($p=0.049$) and MI ($p=0.05$).

Conclusions: This study highlights the importance of testing for APS in young patients with idiopathic thrombosis. The concept of triple positivity in APS has also been emphasized by our study.

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INTRODUCTION

Antiphospholipid antibody syndrome (APS) is the commonest acquired thrombophilic disorder resulting in a clinical syndrome characterized by various manifestations ranging from arterial thrombotic events like stroke, myocardial infarction (MI) to venous thrombosis and recurrent pregnancy loss. In fact, APS is now recognized as an important etiological factor for young stroke and MI, especially in those patients with no other significant risk factors for thrombosis. Patients with arterial thrombosis most commonly present with transient

ischemic attack or stroke (50%) or MI (23%) (Saigal R *et al* 2010).

APS is diagnosed in patients with persistently positive antiphospholipid antibodies (aPL) who satisfy the clinical criteria for APS (Saigal R *et al* 2010). These aPL antibodies are a heterogeneous group of autoantibodies, but the tests are commonly done to detect anticardiolipin antibody (aCL) IgG and IgM, anti β 2-glycoprotein I antibody (a β 2G) IgG and IgM; and lupus anticoagulant test (LA) (Saigal R *et al* 2010).

*Corresponding author: Shajit Sadanand

Medicine Govt. Medical College, Calicut 673008

APS is largely an unrecognized problem in many patients especially in the Indian subcontinent. Many APS cases are not diagnosed as patients are not evaluated due to lack of awareness of the entity as an important cause for idiopathic thrombosis and also due to economic constraints. Many patients with young stroke, recurrent stroke, young MI, venous thromboembolic diseases and recurrent pregnancy losses may thus have unrecognized APS as the etiological factor. Failure to recognize APS and to initiate prompt treatment to prevent recurrent thrombotic events in these patients can lead to considerable morbidity and mortality.

Among the various tests for APS, the most important test which has significant relation with arterial thrombotic events is the anti cardiolipin antibody test (aCL) (Cojocaru M *et al* 2003; Finazzi G *et al* 1996 and Urbanus RT *et al* 2009). Majority of previous studies have demonstrated a relation between either IgG aCL alone or a combination of aCL and β 2 Gisotypes and arterial thrombotic events (Meroni PL *et al* 2007; Stanley Tuhim *et al* 1999). Previous studies have varied with respect to population studied, method of antibody determination, and definition of positive titer and have shown varying degrees of association with arterial events as a whole or to individual arterial events like stroke or MI (Urbanus RT *et al* 2009; Meroni PL *et al* 2007; Stanley Tuhim *et al* 1999). There have been very few studies in Asian population on the significance of APS testing in the evaluation of idiopathic thrombosis, especially arterial thrombosis (Lien LM *et al* 2006). Here we describe the relationship between the individual APS tests and various thrombotic events in patients with APS who presented with arterial or venous thrombosis to a tertiary care hospital of North Kerala, India.

MATERIALS AND METHODS

The study was conducted at Government Medical College, Calicut which is the largest tertiary level referral hospital and teaching institution in North Kerala, India. All patients who presented to the medicine department of Government Medical College, Calicut with thrombotic events in the form of stroke, MI or deep vein thrombosis (DVT) as the clinical manifestation of APS during the two year period from September 2010 to August 2012 were included in the study. Patients with preexisting connective tissue disease like SLE were excluded from the study as it could not be determined whether the thrombotic manifestation was due to connective tissue disease or due to primary APS. Patients in whom the APS tests could be performed only once and patients above 55 years were also excluded from the study. The study was approved by the Institutional Ethics Committee, and signed informed consent was taken from all the patients who participated in the study. In this study, the aCL and β 2G of both isotypes- IgG and IgM were done on patients 12 weeks apart and the higher of the two values of each parameter was taken for analysis to determine the relation to clinical manifestations. The tests were performed using quantitative enzyme-linked immunosorbent assay kits (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany). Patient was considered to be positive for aCL test if the titer was more than 40 GPL (G Phospholipid units) or MPL (MPhospholipid units) for IgG and IgM aCL tests respectively (Finazzi G *et al* 1996; Steven R *et al* 2004). Anti β 2G test was considered positive if the titer is more than 40U/ml for IgG or IgM anti β 2G tests (Audrain Ma *et al* 2002;

Wong RCW *et al* 2008). Lupus anticoagulant test (LA) was done by dRVVT (dilute Russel Viper Venom Time) based Lupus Anticoagulant detection system (Tulip Diagnostics (P) Ltd; Goa, India). The relation between the various clinical manifestations of APS and individual tests for APS were determined statistically using SPSS 16 (Statistical Package for Social Science) windows version 16 (SPSS for Windows, Version 16.0. Chicago, SPSS Inc.).

RESULTS

A total of 77 patients were studied and majority (58%) were males. Majority (58%) belonged to the 20-40 year group and the mean age was 38 years with standard deviation of 3.566. 59 patients (76.6%) had arterial thrombotic events alone, of whom 53 patients had one arterial event and six patients had two arterial events and two patients had both arterial and venous events (Table 1). The arterial event in patients who had both arterial and venous thrombosis was stroke. Venous thrombotic events in the form of deep vein thrombosis (DVT) was seen in 20 patients of which two patients had both arterial and venous thrombosis and remaining 18 out of total 77 patients (23.4%) had DVT alone as the clinical manifestation of APS. Commonest thrombotic event was stroke seen in 42 (54.5%) patients, of which 52% were males. The second major arterial event was MI seen in 23 (29.9%) patients of whom 19 (82.6%) were males (Table 2). aCL IgG was positive in 30 (39%) patients while aCL IgM was positive in 19 (24.7%) patients (Table 3). Anti β 2G IgG and IgM tests were positive in 16 (20.8%) and 15 (19.5%) patients respectively (Table 3). LA tests could not be performed on all patients due to technical issues as many of them were on oral anticoagulants, but was positive in 11 out of 17 patients (64.7%) in whom the test was done

Table 1 Distribution of APS cases according to arterial or venous events

Sex distribution (N=Total number of patients)	Distribution of Thrombotic Events				
	Single arterial event	Two Arterial event	Venous alone (No Arterial event)	Both arterial & venous events	All venous events
MALE (N=36+3+6=45)	36	3	6	2	8
FEMALE (N=17+3+12=32)	17	3	12	0	12
TOTAL (N=53+6+18=77)	53	6	18	2	20

Table 2 Distribution of APS cases according to type of events

Thrombotic Event	Male	Female	Total
Stroke	22	20	42
MI	19	4	23
DVT	8	12	20

Total arterial events = 42+23 =65; 6 patients had 2 arterial events- Stroke and MI.

Number of patients with arterial events =59 (65-6 =59).

Total Venous events = 20; 2 patients had both arterial and venous events and the arterial event was stroke.

Number of patients with venous events alone=18 (20-2).

Total number of patients=77 [59 (arterial) +18(venous)]

Table 3 APS test positivity among cases according to type of events

Thrombotic Event	aCL IgG positive	aCL IgM positive	aβ2G IgG positive	aβ2G IgM positive
Stroke (N=42)	21	9	10	8
MI (N=23)	14	9	6	5
DVT(N=20)	3	7	3	5
Total Number of Events	38	25	19	18
Total Number of Patients Positive	30*	19**	16#	15##

N= Number of events

*6 patients who were positive for aCL IgG had 2 arterial events and 2 patients had both arterial and venous events. Number of patients positive for aCL IgG = 30= 38-(6+2)

**6 patients who were positive for aCL IgM had 2 arterial events. Number of patients =19(25-6)

3 patients who were positive for aβ2G IgG had 2 arterial events. Number of patients = 16(19-3)

3 patients who were positive for aβ2G IgM had 2 arterial events. Number of patients =15(18-3)

Relationship between the aCL IgG levels and arterial thrombosis

It was noted that 29 out of 30 patients (96.6%) with positive aCL IgG had at least one arterial thrombotic event. Also all patients with two arterial events were aCL IgG positive. Thus relation between the aCL IgG titers and number of arterial events was highly significant with a p value of 0.00059. There was significant correlation between aCL IgG levels and arterial events on measuring Pearson’s correlation coefficient, with an r value of 0.622 (Fig. 1).

Regarding individual arterial events like stroke, as 21 out of 30 patients (70%) with positive aCL IgG had suffered from stroke (Table 3), the results are statistically significant with p value of 0.03. Also there was some positive correlation between aCL IgG levels and occurrence of stroke with an r value of 0.439 (Fig.2). Similarly statistically significant association between aCL IgG and cardiac events were obtained with p value of 0.01 as 38 out of 47 patients (80.9%) who were negative for aCL IgG did not develop cardiac event.

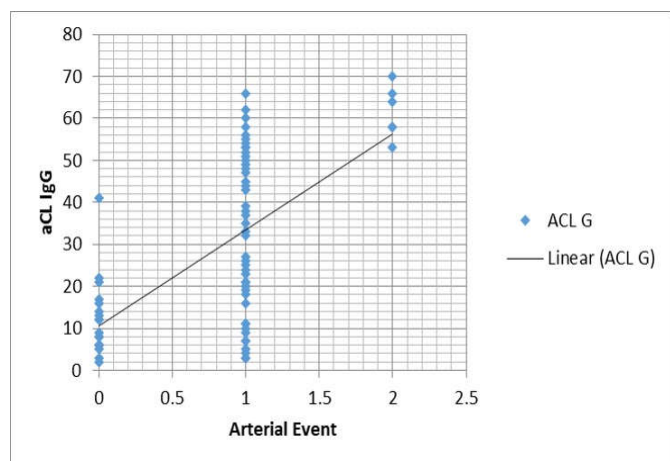


Fig 1 Correlation between the aCL IgG levels and arterial events

aCL IgG anti cardiolipin antibody IgG
 GPL G Phospholipid units - Y axis
 r Pearson's Correlation coefficient= 0.622

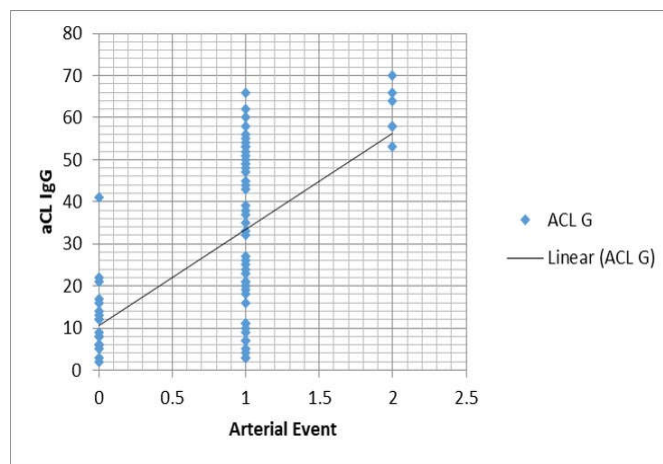


Fig 2 Correlation between the aCL IgG levels and stroke

aCL IgG anti cardiolipin antibody IgG
 GPL G Phospholipid units - Y axis
 CVA Stroke (Cerebrovascular accident)
 r Pearson's Correlation coefficient = 0.439

Relationship between the aCL IgM levels and arterial thrombosis

As 12 out of 19 patients (63.2%) positive for aCL IgM had at least one arterial event and all patients with two arterial events were positive for aCL IgM test, the relationship between aCL IgM values and arterial events was significant (p=0.0004). On the other hand, with regards to individual arterial event like stroke, it was noted that 33 out of 58 patients (56.9%) with low aCL IgM levels had a stroke and that results are not statistically significant (p value=0.469). The findings were further strengthened by obtaining an r value of - 0.17 on measuring the correlation coefficient. However with respect to the relation between aCL IgM test and MI, statistically significant results were obtained with p value of 0.05 as it was observed that 44 out of 58 patients (75.9%) with low aCL IgM levels had no MI.

Relationship between the Antiβ2G IgG test and arterial thrombosis

As 46 out of 61 patients (75.4%) who were negative for anti β2G IgG test had at least one arterial event, the results were not statistically significant (p value 0.181). With regards to relation between anti β2G IgG test and individual arterial event like stroke, similar results were obtained with p value of 0.473. However, statistically significant association between antiβ2G IgG test and MI was noted with p value 0.04 as it was observed that 10 out of 16 patients (62.5%) with positive anti β2G IgG test had cardiac event like MI while 44 out of 61 patients with negative anti β2G IgG test did not have any MI.

Relationship between the Antiβ2G IgM test and arterial thrombosis

As 47 out of 62 patients (75.8%) who were negative for anti β2G IgM test had at least one arterial event, the results were not statistically significant (p value 0.176).With regards to relation between anti β2G IgM test and individual arterial event like stroke, as patients who were positive for anti β2G IgM test were almost equally divided among stroke and non- stroke group, results were not statistically significant (p value = 0.91). However, statistically significant association between anti β2G IgM test and MI was noted with p value 0.03 as it was noted

that 44 out of 62 patients (71%) with negative anti β 2G IgM test did not develop any cardiac event like MI.

Relationship between the LA test and arterial thrombosis

As 9 out of 11 patients (81.8%) with positive LA test had at least one arterial event and all patients with two arterial events had positive LA test, the results were statistically significant with p value 0.0024. This was further corroborated by calculating Pearson's correlation coefficient between LA test positivity and arterial events which gave an r value of 0.482 (Fig. 3). Similar relation was observed between LA test and stroke (p value 0.049) as 9 out of 11 patients who were LA test positive had stroke. Also the relation between LA test and cardiac events like MI was statistically significant with p value of 0.05.

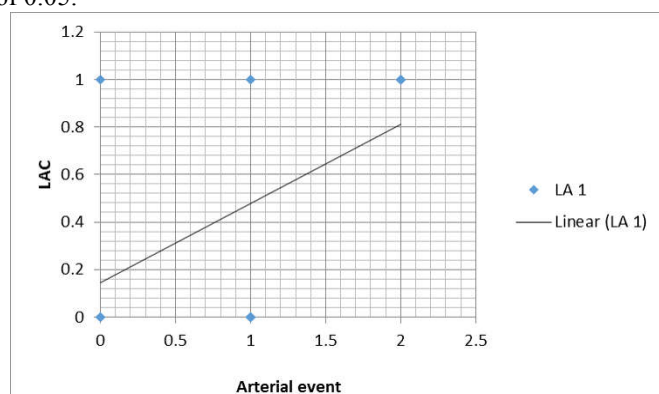


Fig 3 Correlation between the LA test and arterial events

LAC Lupus Anticoagulant Test- Y axis
r Pearson's Correlation coefficient = 0.482

Relationship between venous thrombosis and various APS tests

Venous thrombosis was seen in 20 out of 77 patients (25.9%) with APS studied, out of whom 18 patients had one episode of deep vein thrombosis alone as the clinical manifestation of APS. There is statistically significant association between aCL IgG and venous thrombosis with p value 0.011. However no statistically significant relation between venous thrombosis and other APS tests- viz aCL IgM (p value 0.213), anti β 2G IgG (p value 0.59), anti β 2G IgM (p value 0.469) and LA (p value 0.524) was noted in our study.

Relation between triple positivity and thrombotic events

The concept of triple positivity in APS which implies that risk for clinical complications of APS increases significantly when a patient is positive for all three APS test- aCL, anti β 2G and LA is well described and has been proven in our study also (Andreoli Let al 2013, Pengo V et al 2005). It was noted that all APS patients who had suffered from a recurrence of arterial thrombotic event had triple positivity. Among all APS patients with recurrent thrombotic event either arterial or venous, at least two APS tests were positive in 57.14% patients.

DISCUSSION

The relation between aCL IgG and clinical manifestations of APS

In our study there is statistically significant association between aCL IgG and occurrence of arterial events (p value =0.00059, r value = 0.622), with higher titers in those with two arterial

events, which is similar to a study from Romani a(Cojocaru M et al 2003).

Our study showed positive correlation between aCL IgG levels and occurrence of stroke (p value 0.03) which is similar to the study report from Romania by Cojocaru IM et al in which IgG aCL was positive in 36% cases of ischemic stroke and there was statistically significant association between the two parameters (Cojocaru M et al 2003). Similar association between stroke and aCL IgG levels were reported in a case control study involving 524 stroke patients and 1020 controls which showed a four-fold risk of stroke in patients with elevated aCL IgG (Stanley Tuhim et al 1999).

In our study there was also statistically significant relation between cardiac event like MI and aCL IgG (p value =0.01), which is in tune with an Italian case control study involving young premenopausal females with MI (Finazzi G et al 1996). The Italian study showed that IgG aCL antibodies, but not ANA, were significantly associated with acute myocardial infarction in premenopausal women (Finazzi G et al 1996; Meroni PL et al 2007). Our study also showed significant association between IgG aCL test and venous thrombosis with p value 0.011.

The relation between aCL IgM and clinical manifestations of APS

In our study there is statistically significant relation between aCL IgM values and arterial events (p=0.0004), with higher aCL IgM levels in patients with two arterial events. Our study also demonstrated that there was significant relation between aCL IgM and MI with p value of 0.05. Similar association between aCL IgM and arterial thrombotic events were noted by Finazzi G et al (1996). Interestingly, no statistically significant relation between aCL IgM levels and stroke was noted in our study. Also a study published in Lancet Neurology in 2009 did not find any statistically significant relation between aCL IgM and stroke or myocardial infarction (Urbanus RT et al 2009). We are not sure whether the discordance in association is influenced by any confounding factors or other geographical or racial factors. Detailed studies with larger sample size and covering wider geographical area is warranted to probe this finding.

The relation between anti β 2G tests and clinical manifestations of APS

Our study demonstrated statistically significant association between anti β 2G IgG and IgM tests and cardiac events with p values 0.04 and 0.03 respectively. Our findings were similar to the Italian study showed that anti β 2G antibodies were significantly associated with acute myocardial infarction in premenopausal women (Finazzi G et al 1996; Meroni PL et al 2007). However our findings differed from the RATIO study published in Lancet regarding the relation between arterial thrombotic events and anti β 2G antibodies (Urbanus RT et al 2009). No significant relation was noted between anti β 2G IgG and IgM tests and stroke or total arterial events in our study.

The relation between LA tests and clinical manifestations of APS

Various studies have shown that LA test is significantly associated with both arterial and venous thrombotic events

(Andreoli L *et al* 2013). Our study showed a statistically significant relation between LA test and arterial events in total (p value 0.0024, r value 0.482), stroke (p value 0.049) and myocardial infarction (p value 0.05), but not for venous thrombosis (p value 0.524).

APS tests in cardiac events like young MI

Our study highlights the consistent association between cardiac events like young MI and all APS tests currently done viz- acLIgG (p value =0.01), acL IgM (p value =0.05), anti β 2G IgG (p value 0.04), anti β 2G IgM (p value 0.03), and LA (p value 0.05). Thus it is important to work up for APS in patients with young MI especially in those cases with no other risk factors.

The concept of triple positivity in APS

Our study also highlights the concept of triple positivity in APS by demonstrating the presence of recurrent thrombosis in patients who are positive for all three commonly done APS tests.

CONCLUSION

Our study has reemphasized the clinical relevance of testing for antiphospholipid antibodies and lupus anticoagulant in the evaluation of idiopathic thrombotic events- both arterial and venous in Indian population. The clinical implication of triple positivity in APS has been highlighted further by our study. Our study reinforces the need for performing more than one type of APS tests in the evaluation of idiopathic thrombosis as multiple test positivity suggests higher risk for recurrent thrombosis and need for aggressive management with high intensity anticoagulation in such cases. Thus we have to do more than one test in APS for better risk stratification as multiple APS test positivity in patients may warrant a more intensive management strategy. This has great implication in the clinical evaluation for APS even in the presence of resource constraints.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

Audrain Ma, El-Kouri D, Hamidou MA, *et al*: Value of autoantibodies to beta (2)-glycoprotein 1 in the diagnosis of antiphospholipid syndrome. *Rheumatology* (Oxford) 2002; 41:550-553

Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D, on behalf of APS Action. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res (Hoboken)* 2013; 65:1869-73

Cojocaru M, Muşuroi C, Botezat M. Study of anti-cardiolipin and anti-beta2-glycoprotein I antibodies in patients with ischemic stroke. *Rom J Intern Med.* 2003; 41(2):189-204.

Finazzi G, Brancaccio V, Moia M, *et al*. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four year prospective study from the Italian Registry. *Am J Med.* 1996; 100:530-536.

Lien LM, Chen WH, Chiu HC, Pan WH, Chen JR, Bai CH. High titer of anticardiolipin antibody is associated with first-ever ischemic stroke in Taiwan. *Cerebrovasc Dis.* 2006; 22(4):225-30

Meroni PL, Peyvandi F, Foco L, Bernardinelli L, Fetiveau R, Mannucci PM, Tincani A. Anti-beta 2 glycoprotein I antibodies and the risk of myocardial infarction in young premenopausal women. *J Thromb Haemost.* 2007; 5 (12): 2421-8.

Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. Antibody profiles for the diagnosis of antiphospholipid syndrome. *ThrombHaemost* 2005; 93: 147-152.

Saigal R, Kansal A, Mittal M, Singh Y, Ram H. Antiphospholipid antibody syndrome. *J Assoc Physicians India.* 2010; 58:176-84.

Stanley Tuhim, MD; Jacob H. Rand, MD; Xiao-Xuan Wu, MD; Jesse Weinberger, MD; Deborah R. Horowitz, MD; Martin E. Goldman, MD; James H. Godbold, PhD. Elevated Anticardiolipin Antibody Titer Is a Stroke Risk Factor in a Multiethnic Population Independent of Isotype or Degree of Positivity *Stroke*, 1999; 30(8):1561-5.

Steven R. Levine, *et al*. The APASS Writing Committee. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA.* 2004; 291:576-584.

Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra. Antiphospholipid antibodies and risk of myocardial infarction and ischemic stroke in young women in the RATIO study: a case-control study. *Lancet Neurol.* 2009; 8(11):998-1005.

Wong RCW, Flavaloro EJ, Adelstein S, *et al*: Consensus guidelines on anti-beta 2 glycoprotein I testing and reporting. *Pathology* 2008 Jan; 40(1):58-63

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