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Antiphospholipid Antibodies in Vascular Surgery Patients

A Cross-Sectional Study

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Background

Autoantibodies to phospholipid (aPL) have been associated with vascular thromboses in cerebral, coronary, and peripheral venous and arterial sites. To date, no large cross-sectional study has examined the incidence of occurrence of aPL in patients with peripheral arterial disease.

Methods

A cross-sectional study was performed with patients admitted for vascular surgery procedures to treat peripheral arterial disease for 23 months between January 1, 1990 and November 1, 1991. Consecutive patients were evaluated for the presence of aPL. Medical records for each patient were reviewed in detail, and historic, operative, and postoperative parameters were tabulated for relationship to the presence of aPL.

Results

Two hundred thirty-four patients underwent complete testing for aPL. All patients were receiving chronic aspirin therapy. This represented 86% of admissions. Antiphospholipid antibodies were detected in 60 patients (26%). No differences in age, sex, operation performed, or postoperative outcome were found between patients with and without aPL. However, patients with aPL were 1.8 times more likely to have undergone previous lower extremity (LE) vascular surgery than patients without aPL (95% confidence interval = 1.0 – 3.6, $p = 0.047$). Patients with aPL and previous LE vascular surgery were 5.6 times more likely to have had occlusion of that procedure than patients without aPL (95% confidence interval = 1.9 – 16.8, $p = 0.03$). The occluded previous LE procedures had a shorter duration of patency before occlusion in patients with aPL than in those without (mean duration of patency 17 months *vs.* 50 months, $p < 0.003$). Patients with occluded previous LE procedures and aPL were 4 times more likely to be female (95% C. I. = 1.4 – 11.3, $p = 0.018$).

Conclusions

The incidence of aPL in vascular surgery patients is substantial. Vascular surgery patients with aPL are more likely to have failure of previous LE bypass procedures and to be female and the bypass failure occurs significantly more rapidly than in patients without aPL. Based on these data, testing of vascular surgery patients for aPL and investigation of alternative antithrombotic treatment regimens in patients with aPL appears warranted.

An association between the presence of autoantibodies to phospholipid (aPL) and vascular thrombotic events in patients with systemic lupus erythematosus was described in the 1960s.[1] Sensitive tests for the detection of aPL, including the lupus anticoagulant (LA) and anticardiolipin antibodies (aCL), have been developed during the last decade because of increasing interest in their association with various thrombotic disorders, an association also noted in patients without evidence of systemic lupus erythematosus. Relationships have been reported between the presence of aPL and recurrent fetal loss,[2,3] venous thrombosis,[4,5] late graft failure after coronary artery bypass,[6] major cardiovascular events after myocardial infarction,[7] ischemic stroke,[8–10] transient ischemic attack,[11] and peripheral arterial occlusive disease.[12–16]

To date, the association between aPL and peripheral arterial occlusive disease has been suggested by reports describing cohorts of affected cases[12,13,15,16] or by studies that screened only for the presence of LA, i.e., relatively insensitive tests.[14] Determination of the importance of aPL with regard to the population affected by peripheral arterial occlusive disease requires knowledge of the prevalence of aPL in this population, knowledge that can be obtained with a cross-sectional study. Since January 1990, patients admitted to the Vascular Surgery Service at Oregon Health Sciences University for operative treatment of peripheral arterial occlusive disease have been screened routinely for the presence of hypercoagulable disorders. Results of this screening, with respect to the incidence of aPL, form the basis for this report.

METHODS

From January 1, 1990 until Nov 1, 1991, patients admitted to the Vascular Surgery Service at Oregon Health Sciences University Hospital for elective general vascular surgery procedures to treat chronic peripheral arterial disease underwent testing for the presence of thrombotic disorders. Patients undergoing unscheduled admission for emergent or urgent surgery to treat acute thromboembolic events were not included in this study. The tests obtained included complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, protein C activity, free protein S antigen, and antithrombin III, by standard methods, as well as tests for aPL (LA and aCL). Patients discovered to have deficiencies of protein C, protein S, or antithrombin III (n = 5) were excluded from this study. Anticardiolipin antibodies were measured by enzyme-linked immunosorbent assay[17] with several modifications. A single antibody technique was employed using peroxidase conjugated to goat antihuman immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) followed by the addition of substrate [(2,2′ azinobis) 3-ethylbenzthiazoline-6-sulfonic acid (ABTS)] in McIlvain's buffer and hydrogen peroxide. Calf serum (10%) was used as a blocking agent, and patient sera (diluted 1/100) was incubated for 2 hours in cardiolipin-coated microtiter wells. Results were expressed as standard deviations (SD) above the mean optical density from sera obtained from 30 healthy subjects. The normal range was set at 0 to 3 SD. Sera giving optical density of >3 SD were considered positive [aCL(+)]. Lupus anticoagulants were assessed by the APTT and Russell viper venom time method,[18] with confirmation by mixing studies and platelet neutralization tests.[19] Results were reported as positive, negative, or equivocal. Only positive results (LA[+]) were considered significant. For the purpose of this study, patients were considered to be aPL(+) if they were aCL(+) or LA(+).

Patients underwent surgical treatment of their arterial disorders according to principles published from our service for abdominal, extremity, and cerebral vascular disease.[20–25] Results of aPL testing were not available at the time of surgery and thus, did not influence perioperative decision making with regard to the procedures performed or use of antithrombotic agents. All patients received heparin during periods of surgical arterial occlusion. All patients received preoperative and postoperative aspirin (325 mg/day).

For this cross-sectional study, one of the authors (RWC), blinded to the results of aPL testing, reviewed the medical record of each patient. The author performing the record review and assessment of clinical parameters was not involved in the clinical care of any of the patients. Demographic information, information from the recorded medical history, perioperative data, and postoperative events were recorded, including the following parameters: age, sex, tobacco use, diabetes, hypertension, hypercholesterolemia, renal failure, renal transplant, coronary disease, cerebral vascular disease, previous vascular surgery, failure of previous vascular surgery, type of failure of previous vascular surgery (occlusion, infection, etc), antithrombotic therapy, current vascular procedure performed, initial success of the procedure, tissue loss associated with procedure, perioperative mortality, and postoperative graft patency. Each of these factors then was examined with reference to association with the presence or absence of aPL using chi square analysis for conditional variables and one way analysis of variance for continuous variables. Multivariate logistic regression analysis was used to test indepen-

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dence of associations found by univariate analysis. Life-table analysis was used to evaluate the duration of patency of vascular surgery procedures that had been performed before the time of the study. Life tables were compared using the log rank test.

RESULTS

During the study period, 276 patients were admitted for general vascular surgery. Two hundred sixty patients were admitted for arterial reconstructions, and 13 patients were admitted for amputations without arterial reconstructions. Five patients had deficiencies of protein S (three patients), protein C (one patient), or antithrombin III (one patient) and were excluded from this study, leaving 271 patients available for the current cross-sectional study. The arterial reconstructions performed included infrainguinal bypasses (101, 39%), carotid endarterectomies (52, 20%), repairs of abdominal aortic aneurysms (26, 10%), repairs of aortic occlusive disease (29, 11%), extra-anatomic LE bypasses (axillary/femoral or femoral/femoral) (24, 9%), upper extremity revascularizations (15, 6%), visceral or renal revascularizations (6, 2%), and peripheral aneurysm repairs (5, 2%).

Complete testing for the aforementioned hypercoagulable disorders was accomplished for 234 of the 271 patients (86 %). The reasons that testing was not accomplished in the remaining 37 patients (14%) included omission of test order, presence of anticoagulants, or inadequate laboratory specimens. There were no significant differences between the group of 234 patients with complete testing and the group of 37 patients with incomplete testing with regard to age, sex, or medical histories, as shown in Table 1. The testing was therefore, presumed to be sufficient for a satisfactory cross-sectional study. The percentages that follow are all determined based on the total number of patients tested (234) rather than on the total number of patients (271).

Sixty patients (25.6 % of tested patients) were aPL(+). No patients who were aPL(+) also had positive tests for other hypercoagulable disorders. Fifty-three patients (88.3 %) had aCL only, five patients (8.3 %) had LA only, and two patients (3.3 %) had both aCL and LA. Further stratification of patients with aCL(+) by antibody type revealed 25 patients had IgG aCL alone, 7 had IgM alone, 10 had IgA alone, 5 had both IgG and IgM, 3 had both IgG and IgA, 3 had both IgM and IgA, and 2 had all three antibody types.

Patients with and without aPL were compared with regards to age, sex, medical history, vascular surgery history, operation performed, limb loss, and the aforementioned perioperative factors using univariate and multivariate analysis. There were no significant differences in age, sex, medical history, operation performed, limb loss, perioperative mortality, tissue loss, initial operative success, or early graft patency. A statistically significantly increased number of patients with aPL(+) had undergone previous peripheral arterial surgery ($p < 0.04$ by chi square). By multivariate analysis this difference was a result of the significantly higher proportion of patients with aPL who had previous LE revascularization. Forty-eight percent of patients with aPL (29 of 60) had previous LE procedures compared with 34% of patients without aPL (59 of 174). By multivariate logistic regression analysis, patients with aPL were 1.8 times more likely to have had a previous LE procedure than patients without aPL (95 % confidence interval, 1.0 − 3.3, $p = 0.047$).

Occlusive failure of previous LE procedures had occurred before admission in 50 patients. In patients with aPL and previous LE procedures, there was an increased likelihood that the previous LE procedure had failed because of occlusion. Seventy-nine percent of the patients with aPL and previous LE vascular procedures (23 of 29) had occlusive failure of that procedure compared with 46% of patients without aPL (27 of 59). By multivariate logistic regression analysis, patients with aPL and previous LE vascular procedures were 5.6 times more likely to have had an occlusive failure of that procedure than patients without aPL (95% confidence interval = 1.9 − 16.8, $p = 0.003$). In the subset of patients with previous LE procedures, 21 of the 48 (44%) women were aPL(+), whereas only 8 of the 40 (20%) men were aPL(+). Patients with aPL and histories of LE vascular surgery were 4.0 times more likely to be women than men (95% confidence interval = 1.4 − 11.3, $p = 0.018$). The significant differences confirmed by multivariate analysis between patients with aPL(+) and those without aPL are shown in Table 2.

The duration of patency of the 50 previous LE vascular procedures that occluded before the time of the study was evaluated to ensure that the difference in occlusion rates between patients with and without aPL was not simply a result of a difference in the length of time that the grafts had been observed for follow-up before failure. The mean duration of graft patency for the occluded grafts in patients with aPL was 17 months compared with 50 months for patients without aPL ($p < 0.03$ by log rank comparison of life tables). The more rapid loss of graft patency in failed graft patients with aPL is shown in Figure 1.

The mean maximum aCL (IgG, IgM, or IgA, in standard deviation units) present in patients with previous LE bypass procedures ($n = 88$) was 5.16 ± 0.53 SEM; for patients without previous LE bypass procedures ($n = 146$), it was 2.84 ± 1.01 SEM ($p = 0.05$, Wilcoxon rank sum test). The mean maximum aCL of any isotype present in patients with occlusion of previous LE procedures ($n = 50$) was 6.60 ± 1.62 SEM; for patients with previous

Table 1. CHARACTERISTICS PRESENT IN STUDY PATIENT POPULATION

Parameter	Overall (%) (N = 271)	aPL Tested (%) (N = 234)	aPL Not Tested (%) (N = 37)	p Value (Chi Square)
Mean age	64.6 yrs.	65.1 yrs.	61.3	NS*
Men	55.7	54.7	62.2	NS
Women	44.3	45.3	37.8	NS
Diabetes	28.8	28.2	32.4	NS
Smoking	80.4	80.3	81.1	NS
Hypertension	60.5	61.5	54.1	NS
Hypercholesterolemia	28.0	28.6	24.3	NS
Renal failure	5.2	5.1	5.4	NS
Renal transplant	2.6	2.1	5.4	NS
Coronary artery disease	45.0	44.9	45.9	NS
Angina only	12.9	12.8	13.5	NS
MI	22.5	22.6	21.6	NS
CABG	14.8	15.0	13.5	NS
PTCA	4.4	5.1	0.0	NS
Cerebrovascular disease	47.2	46.6	51.4	NS
Asymptomatic > 50% CAS	14.4	14.1	16.2	NS
CVA	16.2	15.4	21.6	NS
TIA	11.1	10.3	16.2	NS
Previous CEA	14.4	15.8	5.4	NS

* One-way analysis of variance.
aPL = antiphospholipid antibody; CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CAS = carotid artery stenosis; CVA = stroke; TIA = transient ischemic attack; CEA = carotid endarterectomy.

LE procedures that did not occlude, it was 3.2 ± 0.93 (p = 0.07). These differences are shown in Table 3. Also shown in Table 3 are the differences in mean aCL level for each isotype (IgG, IgM, and IgA, respectively). Only the difference in mean levels of IgG was significant for the parameters of previous LE bypass and occlusive failure of previous bypass. The numbers of patients with significantly elevated levels of IgM alone and IgA alone were small (IgM, n = 7; IgA, n = 10).

Table 2. POSITIVE ASSOCIATIONS WITH PRESENCE OF ANTIPHOSPHOLIPID ANTIBODIES CONFIRMED BY LOGISTIC REGRESSION ANALYSIS

Factor	Odds Ratio	95% Confidence Interval	p Value
Previous lower extremity vascular procedure	1.8	1.0–3.3	0.047
Occlusive failure of previous lower extremity procedure	5.6	1.9–16.8	0.003
Female sex and previous lower extremity procedure	4.0	1.4–11.3	0.018

Chi square testing for trends showed no significant linear trend for an association between increasing levels of aCL, increasing frequency of previous LE bypass, occlusion of previous LE bypass or female sex (data not shown). The cumulative distribution of maximum aCL

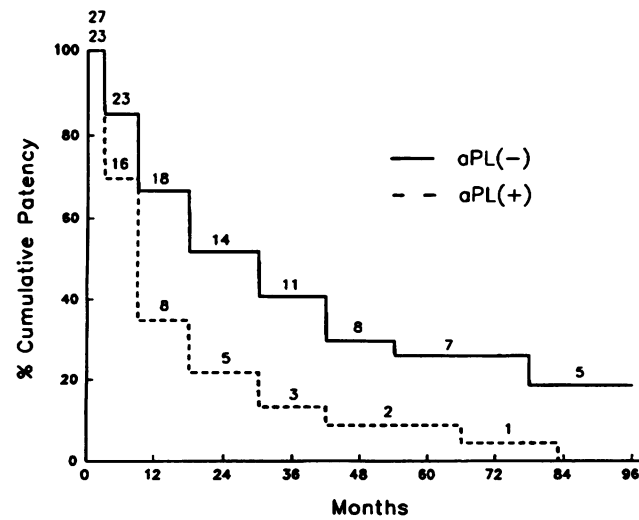

Figure 1. Life table comparing duration of patency of occluded bypass grafts performed before the study in patients with aPL(+) (dotted line) and in patients with aPL(−) (solid line).

Table 3. LEVELS OF ANTICARDIOLIPIN ANTIBODIES

Category	n	Max aCL	IgG	IgM	IgA
Previous lower extremity bypass	88	5.16 ± 0.53	9.73 ± 1.04	1.02 ± 0.32	0.63 ± 0.10
		>p = 0.05	>p = 0.005	>NS	>NS
No previous lower extremity bypass	146	2.84 ± 1.01	4.40 ± 0.36	0.96 ± 0.27	1.23 ± 0.34
Failure of previous lower extremity bypass	50	6.61 ± 1.62	5.75 ± 1.66	1.36 ± 0.54	0.60 ± 0.15
		>p = 0.05	>p = 0.005	>NS	>NS
No failure of lower extremity bypass	38	3.26 ± 0.93	2.63 ± 0.96	0.58 ± 0.18	0.66 ± 0.12

Mean standard deviations above control mean ± SEM.
p value determined by Wilcoxon rank sum test.
Max aCL = highest level of any isotype (IgG, IgM, or IgA).

levels in patients with previous LE bypass (n = 88) is compared with the distribution of maximum aCL levels in patients without previous LE bypass (n = 146) in Figure 2. The two curves diverge at approximately 3.0 standard deviation units and maintain uniform separation for the remainder of the range of maximum aCL values.

DISCUSSION

In western countries, atherosclerosis is sufficiently common in aged individuals to blur the distinction between disease state and normal aging. Despite the widespread prevalence of atherosclerotic changes, many individuals remain free of symptoms of atherosclerosis during their entire lives and die of unrelated causes. One feature that distinguishes symptomatic atherosclerotic disease from atherosclerosis as a normal asymptomatic aging process is the occurrence of thrombosis. Important symptomatic events, including myocardial infarction, stroke, and LE arterial occlusions, have been demonstrated to result from thromboses associated with atherosclerotic plaques in the affected arterial beds. Thus, there currently is widespread interest in identifying laboratory markers associated with thrombosis in humans.

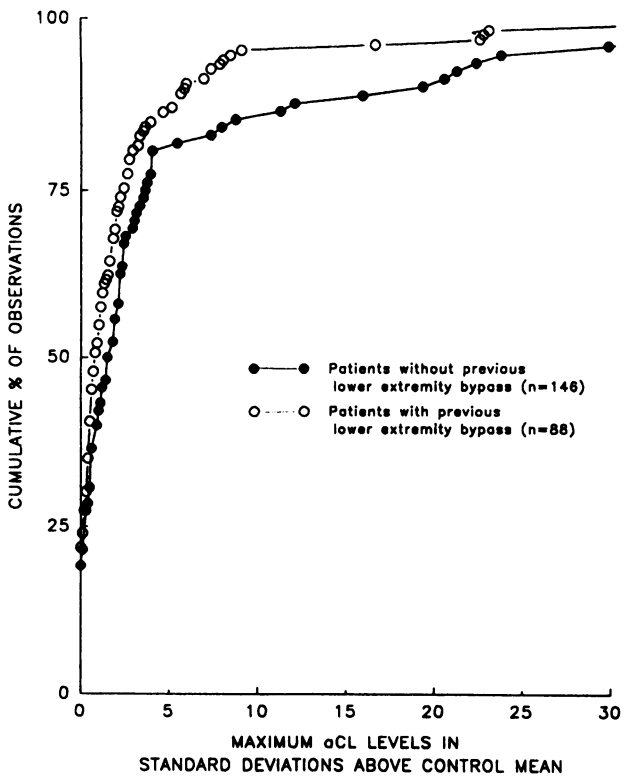

Figure 2. Cumulative distribution graph comparing maximum aCL (of any isotype, IgG, IgM, or IgA) levels in patients with previous lower extremity bypass operations (n = 88) to the aPL levels in patients with no previous lower extremity bypass operations (n = 146).

Autoantibodies to phospholipid were initially identified in patients with systemic lupus erythematosus, and were associated with thrombotic events in systemic lupus erythematosus patients.[1,26,27] Further development of test procedures has allowed identification of other aPL besides the classic lupus anticoagulant, and these also have been demonstrated to be associated with thrombotic events including venous thrombosis,[4,5] coronary disease,[6,7] stroke,[8,9,11] and transient cerebral ischemia.[10] An association between aPL and thrombotic events in the peripheral arteries has been documented by the case reports of Shortell et al.,[12] Eldrup-Jorgensen et al.,[13,15] and Ahn and co-workers.[16] To date, only a single study, by Donaldson et al.[14] has performed cross-sectional screening for the presence of aPL in the peripheral arterial disease population; the test method used by these investigators, screening for LA, was limited by failure to screen for aCL. The prevalence of LA found (3%) is not different from that in the present report. Thus, to our knowledge, the incidence of aPL in a large group of general vascular surgery patients as measured by testing for LA and aCL has not been documented previously.

We describe a remarkable prevalence of aPL(+) (25.6%) in consecutive patients undergoing vascular surgery for peripheral arterial disease. These data may not be representative of the peripheral arterial disease popu-

lation at large because of selection bias. In this study, 86% of the consecutive patients were screened. There were no significant differences in demographic or disease characteristics between those patients tested and those not tested as seen in Table 1. The present study is, therefore, an adequate and representative cross-section of the study population. However, this population is selected highly for patients with severe disease. The Vascular Surgery Service at our University Hospital is a tertiary referral service, serving a large geographic and population area. Patients admitted for surgery are notable for advanced age and a high incidence of failure of previous vascular procedures, especially LE procedures. This study should, therefore, be regarded as cross-sectional for patients with severe peripheral arterial disease. The prevalence of aPL in populations with less severe peripheral vascular disease is unknown.

The presence of aPL in this study was associated significantly with occlusive failure of previous LE arterial surgery (odds ratio 5.6, $p = 0.003$), and this association was even stronger in women than in men (odds ratio 4.0, $p = 0.018$). Patients with previous LE procedures were more likely to have experienced failure, and it occurred much earlier (17 months *vs.* 50 months, $p < 0.03$) in the presence of aPL. Each of these associations emphasizes the relationship between aPL and the occurrence of thrombotic events in peripheral vascular disease, a relationship suggested previously in the coronary and cerebral circulations.

In this study, there was no detectable association between presence of aPL and perioperative mortality, tissue loss associated with surgery, or early failure of procedures performed. Postoperative follow-up for these patients is quite short, and differences in intermediate and long-term success of the surgical procedures performed at the time of the study, if they exist, are not yet detectable.

Although all three antibody types for aCL (IgG, IgM, and IgA) appeared in this study, there was a significant association with the study variables only for IgG when considered alone (Table 3). The number of patients with IgM and IgA positive in this study are too small to permit conclusions regarding the significance of these as isolated findings.

Based on these observations, we conclude that aPL are present in approximately one quarter of patients with severe symptomatic peripheral arterial disease and are associated strongly with premature occlusive failure of LE arterial repairs, especially in women. Screening for the presence of aPL in such patients seems indicated to identify a subgroup of patients at higher risk for graft failure. Whether the subsequent clinical course of these patients can be altered favorably by anticoagulant or other antithrombotic therapy is an important issue that must be addressed by future controlled clinical trials.

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Discussion

DR. ALEXANDER W. CLOWES (Seattle, Washington): This is really a most interesting report that you have just heard because I think the study that Dr. Taylor and his associates describe is perhaps the first large prospective cross-sectional study to demonstrate a major thrombotic cause for failure of reconstructions. I think that for those of us who toil in this field it sheds some light in a rather murky area. The fact that they found a 26% incidence of these autoantibodies to phospholipid is rather surprising.

The most important observation that they have made is that there is a strong correlation between the presence of the antibodies and evidence of accelerated thrombosis of previous reconstructions. This observation raises questions about the interactions between the blood and the wall.

All of us were brought up with the notions put forth by Virchow more than a hundred years ago that thrombosis is accounted for not only by changes in the blood but also by alterations in blood flow and alterations at the level of the arterial wall. Atherosclerosis develops in locations of altered blood flow where there is turbulence. The atherosclerotic wall exhibits abnormal expression of various pro-coagulant factors which might interact with the blood; in particular, tissue factor and plasminogen activator inhibitor Type 1 are abnormally expressed in the wall and might in combination with the abnormality in the blood lead to what I view as a devastating situation.

I have three questions for Dr. Taylor. I would like him to address the issue of the association between the presence of the antibodies to phospholipid, the high incidence of failure of reconstructions, and the rapid progression of intrinsic primary disease. Is the failure rate in these grafts due to primary thrombosis or is it due to accelerated intimal hyperplasia?

If you look at the results closely, you will note that 70% of the failures occurred within 12 months. This is the interval when wound healing is going on at its greatest rate. Hence, graft failure could be the consequence not only of clot formation, but also acceleration of the wound-healing process in the wall.

The second question has to do with what strategy we should use now to diminish the failure of reconstructions. Do we just simply put all patients on coumadin?

And finally, could Dr. Taylor provide a bit more explanation as to what these antibodies actually are doing to promote this pro-coagulant state?

DR. KEITH D. CALLIGARO (Philadelphia, Pennsylvania): I have two questions.

First, how many of your patients were less than 50 years old? It's been recommended that hyper-coagulable states should be screened in all vascular patients under 50. You mentioned that age did not correlate with the lupus anticoagulant.

Secondly, you mentioned in one of your slides the chicken-or-egg relationship, and the question is, do patients who have had repeated failures somehow induce some type of reaction that causes them to have a positive lupus anticoagulant or is it really the fact that this is present before they have thrombosed their grafts?

DR. LAZAR J. GREENFIELD (Ann Arbor, Michigan): I'd like to add my congratulations to the authors and ask a couple of questions.

You had separated out the group with cardiolipin but it wasn't clear whether there was a correlation with patients with previous MI. This has been thought to be one of the possible mechanisms for the establishment of these antibodies and I wonder if you were able to establish that relationship.

Also, since you had a higher female population with evidence of lupus anti-coagulant, were any of these patients screened for lupus and did they actually have any other clinical evidence of lupus disorders? The other obvious concern is whether they had any hidden venous disease, and I wonder if you screened any of them for deep vein thrombosis.

Finally, one of the mechanisms that is thought to operate with this disorder is through platelet dysfunction, and I wonder if you screened any of them for platelet disorder.

DR. KAJ H. JOHANSEN (Seattle, Washington): Dr. Taylor's study documents an association between antiphospholipid antibodies and the failure of prior lower extremity revascularization procedures. Not only that, the rate of failure of these grafts appears to be accelerated, a phenomenon that seems to be restricted primarily to women.

If, as Dr. Taylor indicates, the success of the current procedure is not affected by these patients' antiphospholipid status, would Dr. Taylor speculate on why prior operation outcomes seem to have been highly related to antiphospholipid status?

This study was completed in late 1991. Has subsequent follow-up of patients' index operations suggested an increased failure of those operations as well?

Finally, do we know the prevalence of the antiphospholipid antibodies in a control age-matched population?