Fact Checking the Lore of Hypercoagulable Work Up

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Interests: Disorders of thrombosis and hemostasis, anticoagulation therapy, hemostatic therapy

Purpose and Overview: To help the audience understand the utility of hypercoagulable work up in various clinical situations.

Educational Objectives: At the conclusion of this lecture, the listener should be able to

1. **Name the inherited and acquired hypercoagulable states**
2. **Differentiate between the hypercoagulable states associated with arterial versus venous thromboses**
3. **Identify the main determinants of duration of anticoagulation for venous thromboembolism**
4. **Know the appropriate time to test for hypercoagulable states if desired**
5. **Know the appropriate reasons for hypercoagulable tests**

What are hypercoagulable states?

Hypercoagulable states are disorders or conditions that result in an increased risk for thrombosis, or thrombophilia. Hypercoagulable states can be inherited or acquired. In most cases, having a hypercoagulable state alone does not necessarily result in thrombosis. For example, factor V Leiden is the most common inherited thrombophilic defect that results in a resistance to activated protein C, such that the mutated factor V is not inactivated by activated protein C. Factor V Leiden happens to be very common in the Caucasian population, to the tune of about 5% of Caucasians carry the mutation(1). Fortunately, not everyone with the mutation will develop a clot; observational studies demonstrate that by age 50 carriers of factor V Leiden have about a 20% chance of developing first life time thrombosis(2). Thus, many carriers of factor V Leiden do not even know that they have it as many live through their entire lives without experiencing a thrombotic event. In most patients with thrombosis, the clot results from the patient having an underlying risk factor (factor V Leiden or estrogen use) with a timely trigger such as immobilization, surgery or trauma.

Hypercoagulable states can be categorized as persistent and transient; persistent risk factors can be fixed or variable over time(3).

Persistent Fixed	Age Inherited thrombophilias	
Persistent Variable	Cancer Myeloproliferative neoplasms Inflammatory bowel disease	Obesity Antiphospholipid antibodies/lupus anticoagulant
Transient	Surgery Trauma OCP use or pregnancy	Prolonged travel (>8 hrs) Infection

Hypercoagulable states carry vastly different risks for first lifetime venous thromboembolism (VTE) (4)

Risk Factor	**Odds Ratio**	**Risk Factor**	**Odds Ratio**
Surgery	21.7	Central line or pacemaker	5.6
Trauma	12.7	Neurologic disease	3.0
Inpatient stay	8.0	Superficial vein thrombosis	4.3
Cancer with chemo	6.5	Varicose vein (age 45)	4.2
Cancer without chemo	4.0		

Attributable risks of venous thromboembolism (5)

Risk Factor	**Attributable Risk**	**Risk Factor**	**Attributable Risk**
Hospitalization or nursing home	61.2	Trauma	12.5
Hospitalization with surgery	24.2	Congestive heart failure	11.8
Hospitalization without surgery	22.5	Prior central line or pacemaker	10.5
Nursing home	14.4	Neuro disease with paresis	8.2
Active cancer	19.8	Prior superficial vein thrombosis	4.3
Cancer with chemotherapy	6.8	Varicose vein/vein stripping	6.0
Cancer without chemotherapy	13.0		

Inherited hypercoagulable states are frequently sought after(1)

Common	G1691A mutation in factor V (factor V Leiden)
	G20210A mutation in factor II (prothrombin gene mutation)
	C677T mutation in MTHFR
Rare	Antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
Very rare	Dysfibrinogenemia
	Homozygous homocysteinuria
Probably inherited	Increased factor VIII, IX, XI, or fibrinogen
	*factor VIII and fibrinogen are acute phase reactants

Frequency of inherited thrombophilias among healthy subjects and patients with venous thromboembolism(1)

Inherited thrombophilia	**Healthy subjects**		**Unselected patients**		**Selected patients**	
	Total	**Affected**	**Total**	**Affected**	**Total**	**Affected**
Factor V Leiden	16,150*	4.8	1142	18.8	162	40
	2192**	0.05				
Prothrombin gene	11932*	2.7	2884	7.1	551	16
	1811**	0.06				
Protein C deficiency	15070	0.2-0.4	2008	3.7	767	4.8
Protein S deficiency			2008	2.3	649	4.3
Antithrombin deficiency	9669	0.02	2008	1.9	649	4.3

* all subjects were white ** all subjects were African or Asians

What hypercoagulable states should we consider?

Not all hypercoagulable states are created equal. Deficiencies of natural anticoagulants carry a high risk for thrombosis, while factor V Leiden, prothrombin gene mutation, and elevated factor VIII confer much lower risk.

Risk of first venous thrombosis in 2479 relatives of 877 probands associated with thrombophilia(6)				
Defect	**Observation yrs**	**Relatives with event**	**Annual incidence**	**Adjusted RR**
Antithrombin (60)	1416	25	1.77 (1.14-2.60)	28.2 (13.5-58.6)
Protein C (91)	2301	35	1.52 (1.06-2.11)	24.1 (13.7-42.4)
Protein S (94)	1846	35	1.90 (1.32-2.64)	30.6 (26.9-55.3)
High FVIII (776)	26315	130	0.49 (0.41-0.51)	7.1 (4.3-11.8)
Factor V Leiden (652)	18237	89	0.49 (0.39-0.60)	7.5 (4.4-12.6)
Prothrombin (288)	8324	28	0.34 (0.22-0.49)	5.2 (2.8-9.7)

More importantly, venous thrombosis and arterial thrombosis are associated with different sets of hypercoagulable states. The inherited hypercoagulable states are risk factors for VTE, while their association with arterial thromboses is modest at best(2, 7), particularly in the younger patients(8). Arterial thromboses are mainly caused by atherosclerotic disease and atrial fibrillation. When arterial thromboses occur in young patients without evidence of atherosclerosis or atrial fibrillation, one needs to consider the possibility of estrogen, cocaine, anabolic steroids, Buerger's disease, vasospastic disorder (Raynaud's), vascular anatomic abnormalities, and vasculitides. Hypercoagulable states associated with arterial thrombotic events include antiphospholipid syndrome, heparin-induced thrombocytopenia, elevated levels of procoagulants (factor VIII, IX, XI, fibrinogen, von Willebrand factor), high risk inherited defects (natural anticoagulant deficiencies, homozygous or double heterozygous mutations) myeloproliferative neoplasms, and paroxysmal nocturnal hemoglobinuria. MTHFR polymorphisms are no longer considered risk factors for arterial thromboses in the US due to folate supplementation in the food supply(8).

When should we test for hypercoagulable states?

Due to potential interference from acute phase reaction, large clot burden, and use of anticoagulants, clotting-based assays should not be performed at the time of the initial presentation. It is well established that acute phase reaction leads to increases in procoagulants, and protein S activity can decrease due to increased C4b binding protein. Heparin and low molecular weight heparins interfere with antithrombin testing(9). Along with the heparin molecules, the direct oral anticoagulants often cause false-positive results of lupus anticoagulant(10). Vitamin K antagonists will lower protein C and protein S activities as both of these are vitamin K-dependent. Even ELISA-based assays for antiphospholipid antibodies can be altered by thrombotic events(11). In addition, test results would not alter treatment strategy at the time of the acute event for VTE. For arterial thrombosis, it is unknown whether presence of hypercoagulable states would alter the treatment (antiplatelet therapy versus anticoagulant therapy). To avoid the issues with testing, it is best to hold off on testing when the patient is admitted to the hospital for thrombosis(9). In addition, proper counseling with experienced hematologist is highly recommended(12). If testing is desired, it is best performed with proper counseling, off of anticoagulants, away from the time of acute thrombosis. A reasonable time to consider testing is at the end of the planned anticoagulation therapy, when the results potentially may have an impact on the decision regarding anticoagulation. Reduction in false positive (and false negative) results and significant cost savings can be achieved by simply restricting hypercoagulable testing in the inpatient setting(13, 14).

Why do we test for hypercoagulable states?

Whenever a test is performed, the results should have an impact on the clinical management of the patient. It is certainly reasonable to perform tests for the sake of knowledge or information, but the patients and clinician should understand the implications of the test results. In clinical practice, there is significant enthusiasm in testing for hypercoagulable states, with the idea that presence of hypercoagulable states makes a difference in how patients are treated. A significant proportion of referrals to hematology are requests to perform hypercoagulable work up or to interpret results of tests already done. The question remains, does presence of hypercoagulable state makes a difference in how patients are treated?

Venous Thromboembolism: This is the most common reason to perform hypercoagulable work up in our clinical practice. Yet it should be noted that the major evidence based guidelines do not take the results of hypercoagulable studies into consideration(15, 16). The misconception prevalent amongst clinicians is that presence of hypercoagulable state increases the risk of recurrent thrombosis and therefore patients with hypercoagulable states should be treated with long term anticoagulation therapy. However, this is NOT supported by available data. One must be careful to differentiate between risk of first life time venous thrombosis, and risk of *recurrent* thrombosis. Hypercoagulable states do in fact increase the risk of first life time venous thrombosis as shown above, but they do not increase the risk of recurrent thrombosis(17-22).

	Recurrent Venous Thromboembolism(20)	
Hypercoagulable state	**% per patient-year (95% CI)**	**Hazard ratio (95% CI)**
Factor V Leiden	0.8 (0.2-2.2)	0.7 (0.2-2.6)
Prothrombin gene mutation	0.0 (0.0-2.9)	0 (no calculable)
Antiphospholipid antibodies	2.3 (0.4-6.7)	2.9 (0.8-10.5)
Antithrombin deficiency	0.0 (0.0-7.0)	0 (not calculable)
Factor VIII elevation	0.7 (0.0-4.0)	0.7 (0.1-5.4)
Factor XI elevation	0.6 (0.0-3.5)	0.7 (0.1-5.0)
Homocysteine elevation	0.7 (0.0-3.9)	0.7 (0.1-5.3)
Number of abnormalities		
0	1.1 (0.5-2.3)	1.0 (reference)
1	0.8 (0.3-1.9)	0.7 (0.2-2.3)
2	1.0 (0.1-3.5)	0.8 (0.2-4.1)
1 or more	0.8 (0.3-1.7)	0.7 (0.3-2.0)
2 or more	0.8 (0.1-2.9)	0.7 (0.2-3.4)
All patients	0.9 (0.6-1.5)	

This is referred to the “thrombophilia paradox,” a consequence of limited dichotomous testing made worse by test inaccuracy and imprecision(23). One potential approach to circumvent the problems of individual hypercoagulable tests is to assess the risk of thrombosis in relation to the composite effect of hypercoagulable states, known or unknown. The D-dimer and thrombin generation potential have been validated in clinical studies, and are found to be independent predictors of recurrent thrombosis(24-28). Thus, it is not surprising that clinical prediction scores use negative d-dimer to identify patients at low enough risk for recurrent thrombosis to consider stopping anticoagulation therapy(29-31).

Antiphospholipid antibody syndrome is an acquired hypercoagulable state due to presence of autoantibodies against β_2-glycoprotein I with lupus anticoagulant activity(32-34). It is the common belief amongst practicing hematologist that patients with thrombotic antiphospholipid syndrome should be anticoagulated long term for secondary prophylaxis. However, there is a paucity of data from randomized control trials addressing the duration of anticoagulation for this particular patient population. The DURAC (Duration of Anticoagulation Study Group) found that presence of anti-cardiolipin antibodies predict for early recurrent venous thromboembolism and death following 6 months of anticoagulation therapy(35). However, there is not a trial to establish the benefit of long term anticoagulation in antiphospholipid patients with VTE. In a trial comparing 3 months versus prolonged anticoagulation therapy in patients with unprovoked VTE, a subgroup analysis showed that testing positive for lupus anticoagulant at the time of randomization was associated with increased risk of recurrent VTE upon cessation of anticoagulation at 3 months(36). In a trial comparing 1 months versus 3

months of anticoagulation therapy with *provoked* VTE, a subgroup analysis showed that testing positive for antiphospholipid antibodies or lupus anticoagulant at the time of randomization was *not* associated with an increased risk of VTE recurrence(37). If the evidence based guidelines (ACCP, NICE) are followed, the antiphospholipid patients will be properly treated accordingly.

In summary, presence individual hypercoagulable states do not predict for recurrent thrombosis, and thus testing for the hypercoagulable states do not alter the duration of anticoagulation therapy. It should also be noted that there are no clinical trials specifically addressing the duration of anticoagulation therapy in patients with defined hypercoagulable states, demonstrating a benefit of long term anticoagulation therapy for the hypercoagulable patients.

The second management question regarding anticoagulation therapy is the intensity of such treatment. This is less relevant today in the era of direct oral anticoagulants, as none of the new drugs have long term data with different doses. With warfarin therapy, there is no clinical study to demonstrate that patients with defined hypercoagulable states benefit from more intense warfarin therapy with higher INR goals(38). Antiphospholipid syndrome patients were thought to require a higher INR of 2.5 to 3.5 based on retrospective data(39), but two randomized control studies demonstrated lack of benefit of the higher INR range(40, 41). Thus, presence of defined hypercoagulable states also does not demand more intensive anticoagulation therapy.

Young stroke: In the vast majority of ischemic cerebrovascular accidents, the cause is atherosclerotic disease or cardioembolic from atrial fibrillation. The major exception is the younger population (<50 years old) with stroke, where alternative causes need to be considered, including hypercoagulable states. A plausible reason to test for hypercoagulable states in young stroke patients is that anticoagulation therapy may be needed in place of or in addition to antiplatelet therapy. Available data including prospective studies have demonstrated that factor V Leiden and prothrombin gene mutation are not risk factors for first ischemic strokes in the elderly(42-44), and at best a weak association in the young(45-47). A meta-analysis of 19 case-control studies involving 3028 cases showed a small but statistically significant association between prothrombin gene mutation and stroke (odds ratio 1.44 95% CI 1.11-1.86)(48). The rare natural anticoagulant deficiencies have been shown to be associated with stroke in case control studies(49). When considering risk of recurrent ischemic stroke, an Italian study of 1867 young adults with first ischemic strokes had 163 events, but no association was found between factor V Leiden or the prothrombin gene mutation and recurrent vascular or ischemic events(50). Presence of antiphospholipid antibodies is associated with first ischemic strokes as well as recurrent strokes in the young patients and in lupus patients(51).

Since a causal relation with ischemic stroke has not been definitively established for most hypercoagulable states, there is no valid indication for testing in all patients with ischemic strokes for hypercoagulable states(52). The most recent AHA/ASA recommendations on secondary prevention of ischemic stroke in 2014 state that the usefulness of hypercoagulable screening is unknown, and depending on the individual patient circumstances, anticoagulation therapy might be considered in those with abnormal findings(53). There are no randomized control study comparing the relative benefit of antiplatelet therapy and anticoagulation therapy. Again, a special case is made for antiphospholipid syndrome. The WARSS/APASS study compared warfarin versus aspirin in stroke patients with a one-time measurement of antiphospholipid antibodies showed no difference in recurrent thrombo-occlusive events(54). Other trials in antiphospholipid syndrome patients addressed treatment of VTE rather than ischemic stroke(40, 41). The AHA/ASA guidelines recommend antiplatelet therapy for those with positive antiphospholipid antibody testing but not meeting criteria for syndrome. In those with stroke and antiphospholipid syndrome, there is no consensus amongst international experts(55).

Anticoagulation therapy can be considered for those with lupus or other manifestations of antiphospholipid syndrome(51).

In a retrospective review of 145 consecutive patients with hypercoagulable work up done while admitted with ischemic stroke or transient ischemic attack (TIA) at Zale Lipshy between January 2011 and Sept 2014, 50 patients were found to have at least one positive test, and only 2 out of 50 patients had a change in clinical management because of the test results (unpublished data). The most common abnormalities were elevated factor VIII (17/95) and reduced protein S activity (14/96); both of these are part of acute phase reaction. One patient was found to have markedly elevated antiphospholipid antibodies and multiple strokes, and was placed on warfarin for secondary prevention; the other patient was started on anticoagulation therapy for patent foramen ovale after being found to be heterozygous for factor V Leiden. Thus, in our own experience hypercoagulable work up for stroke and TIA patients rarely changed the clinical management

In summary, inherited hypercoagulable states are not risk factors for stroke except possibly in the younger patients. Antiphospholipid antibodies are risk factors for ischemic stroke and TIA in the young patients and in patients with lupus. However, there are no randomized data demonstrating the relative benefit of antiplatelet therapy versus anticoagulation therapy in patients with ischemic stroke, including in antiphospholipid syndrome. Despite the lack of clinical utility of hypercoagulable work up in stroke patients, the practice is prevalent, including certified advanced comprehensive stroke centers.

Post-Operative VTE: Another clinical scenario where hypercoagulable testing is perceived to make a difference is risk of thrombosis after invasive procedures. A Mayo Clinic study examined whether presence of hypercoagulable state was a predictor of short-term thromboembolism or major bleeding after an invasive procedure in chronically anticoagulated patients. Periprocedural event rates were low, and neither inherited or acquired hypercoagulable states was a predictor of thromboembolism, major bleeding, or mortality after temporary interruption of chronic anticoagulation for an invasive procedure(56).

Thromboembolism, Major Bleeding, and Death by Thrombophilia Category(56)			
Variable N, 95% CI	Severe thrombophilia (76)	Nonsevere thrombophilia (89)	Negative/Normal (197)
Thromboembolism	0 (0-5)	0 (0-4)	0 (0-2)
Major bleeding	1 (0-7)	1 (0-6)	2 (0-4)
Death	0 (0-5)	2 (0-8)	2 (0-4)
Severe: natural anticoagulant deficiencies, homozygous factor V Leiden or prothrombin gene mutation, compound heterozygous, or antiphospholipid syndrome.			
Non-severe: heterozygous factor V Leiden or prothrombin gene mutation			

As mentioned, presence of hypercoagulable state does increase the risk for first lifetime VTE, including in patients who are undergoing surgery. However, the increase in risk from the hypercoagulable states is low for the common hypercoagulable states(57), and insignificant compared to the risk of thrombosis imposed from the surgery itself(58). In addition, absence of a defined hypercoagulable state is not synonymous with low risk of post-operative thrombosis. In patients with known history of VTE, only a minority test positive for a currently defined hypercoagulable state(59-62). Presence of hypercoagulable state does not increase the risk of recurrent thrombosis in patients with VTE provoked by major transient risk factors including surgery(37). Both the ACCP and NICE guidelines recommend short-term anticoagulation for those with post-operative VTE, without regards to whether there is a

hypercoagulable state defined or not(15, 16). One of the first recommendations from the American Society of Hematology Choosing Wisely Campaign was to recommend against testing for hypercoagulable states in patients with VTE provoked by a major transient risk factor(63).

Microvascular Thrombosis in Plastic Surgery: Flap failure due to microvascular thrombosis is a major concern, and hematologists are often called upon to look for hypercoagulable states in patients with flap failure. It should be noted that the surgeons' experience is the major determinant of flap failure. Various groups have published that increasing experience at high volume centers have very low failure rates(64-70). Randomized control trials were conducted to examine whether provision of anticoagulation therapy can reduce microvascular thrombosis rate; there was no benefit with low molecular weight dextran, aspirin, tissue factor pathway inhibitor, or heparin(71, 72). In fact, there is no consensus amongst plastic surgeons as to what to do with anticoagulation therapy after microvascular surgery(73). There are many case reports of free flap losses associated with presence of hypercoagulable states(74-78). One retrospective cohort study with 2032 consecutive free flaps showed that presence of hypercoagulable state had an adverse impact on the microsurgery outcome. However, no flap failure or thrombosis occurred in the 7 patients with hereditary thrombophilia without a personal history of thrombosis, while 12 flap thrombosis and 8 failures were seen in 51 patients with history of macrovascular venous or arterial thrombosis or another acquired hypercoagulable disorder(79). Thus, acquired risk factors including prior thrombosis appear to be more predictive of flap outcome.

Renal Transplantation: In renal transplantation, the major determinant of a successful outcome is the rate of rejection. Renovascular complications are the major cause of early allograft loss due to non-immunologic causes, and presence of hypercoagulable state is one of several factors that determine vascular rejection rate(80-84). Factor V Leiden is associated with acute vascular rejection and early graft loss(85), decreased one-year graft survival(86), and primary renal allograft thrombosis(87). Prothrombin gene mutation is associated with poor allograft outcomes, early allograft loss and decreased allograft survival(88-90). A prospective study with 165 kidney transplant patients showed that those with factor V Leiden, prothrombin gene mutation and MTHFR C677T had significantly higher vascular rejection rates(85).

Patients with high titers of antiphospholipid antibodies might be at risk for early graft loss or worse outcome. A high rate of graft loss in 11 patients with antiphospholipid syndrome (high titer antiphospholipid antibodies or positive lupus anticoagulant with lupus, frequent abortions, frequent thrombosis of arteriovenous shunts, biopsy-proven microrenal angiopathy, or thrombocytopenia) was observed in a multicenter study; all 7 patients who did not receive anticoagulation at the time of renal transplantation lost the allograft within one week as a result of renal thrombosis(91). However, another study with 61 renal allograft recipients with positive titers of IgG or IgM anticardiolipin antibodies (≥15) showed no difference in allograft loss or 25% reduction in estimated glomerular filtration rate one month after transplantation(92). Recent data suggest that the mTORC (mechanistic target of rapamycin complex) pathway is involved the pathophysiology of renal vascular lesions associated with the nephropathy seen in some patients with antiphospholipid syndrome; no renal transplant patients with positive antiphospholipid antibodies receiving sirolimus, an mTOR inhibitor, developed recurrent vascular lesions on biopsy compared to those who did not receive sirolimus(93). Thus, antiphospholipid antibody positive patients receiving kidney transplant may benefit from sirolimus or other mTOR inhibitors to prevent graft loss. However, it remains difficult to predict who is at risk for thrombosis in asymptomatic patients with elevated titers of antiphospholipid antibodies or positive lupus anticoagulant. Patients with a triple positive profile (elevated titers of anti-cardiolipin and anti-β_2-glycoprotein I antibodies and positive lupus anticoagulant) are considered at the highest risk, and lupus

anticoagulant is strongly associated with thrombosis compared to the antiphospholipid antibodies alone(94).

Various groups have examined the role of perioperative and postoperative anticoagulation in renal transplant patients with hypercoagulable states. A prospective study from Hershey Medical Center with 37 patients with one or more hypercoagulable states showed that when treated with prophylactic anticoagulation and triple immunosuppressive therapy, these patients undergoing renal transplant did not have increased rate of graft loss or rejection compared to those with no documented thrombophilia; however significant bleeding was observed (35% versus 5%)(95). Another prospective study from ULB-Erasme Hospital in Brussels showed that when every patient was given aspirin, presence of hypercoagulable risk factors did not result in increased rate of thromboembolic events, acute rejection, graft or patient survival in renal transplant patients(96); the authors concluded that systemic screening for hypercoagulable states was not necessary. Another group from New Jersey pre-emptively anticoagulated renal transplant patients with hypercoagulable states in a prospective cohort study, and showed that prophylactic anticoagulation resulted in a 2.6-fold reduction in the expected incidence of allograft thrombosis; the authors' enthusiasm for pretransplant screening for hypercoagulable states was tempered by the increased rate of significant bleeding in the anticoagulated patients (60% in the first 30 post-transplant days) and nearly 67% needed surgical evacuation of hematoma(97). A retrospective cohort study of renal transplant recipients from Seattle showed that preemptive anticoagulation was associated with a nonsignificant decrease in allograft thrombosis but associated with a significant increase in risk of hemorrhage(98). Another retrospective study of 235 consecutive renal transplant patients from Brown University showed that in 10 patients with hypercoagulable state the rate of acute rejection was 20%, comparable with the rate observed in non-hypercoagulable patients; in 8 patients with hypercoagulable states found on preoperative screening who received perioperative heparin and postoperative oral anticoagulation, 2 developed perinephric hematomas requiring evacuation(99).

Overall, renal transplant patients with a documented hypercoagulable state or prior thrombotic history are considered at increased risk for graft failure, especially due to graft thrombosis. Prophylactic anticoagulation therapy has been utilized, but studies demonstrate increased bleeding. The optimal strategy for thrombophilia screening and peri-transplant management of patients with documented thrombophilia need to be prospectively studied.

Concluding Remarks

Hypercoagulable states are frequently tested in clinical practice with questionable clinical utility. Currently available data demonstrate no need for hypercoagulable testing in patients with VTE to identify patients at high risk for recurrent thrombosis. The low risk inherited hypercoagulable states are not associated with arterial thromboses including stroke except in the younger patients with stroke. However, there is no data to suggest anticoagulation therapy provides benefit over antiplatelet therapy in patients with arterial thromboses. Hypercoagulable states appear to predict for flap failure due to microvascular thrombosis in plastic surgery as well as in patients undergoing renal transplantation; however, the optimal strategy in using anticoagulation therapy to prevent thrombotic complications in these specific patient groups need to be studied in prospective trials. Hypercoagulable tests should be done at the appropriate time in select patients with proper patient counseling regarding the implications of test results.

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