RECURRENT VENOUS THROMBOSIS DESPITE ‘OPTIMAL ANTIcoAGULATION THERAPY’ FOR ANTIPHOSPHOLipID SYNDROME – COULD NEW ORAL ANTIcoAGULANTS SOLVE THE PROBLEM?

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SUMMARY – The aim was to determine the validity of the international normalized ratio (INR) and prothrombin time (PT) as a monitor for warfarin therapy in patients with lupus anticoagulants and recurrent thrombosis, and to investigate alternative approaches to monitoring warfarin therapy and new treatment options in these patients. A case is described of a 63-year-old female with antiphospholipid syndrome and recurrent venous thrombosis despite optimal adjusted warfarin therapy. In patients with lupus anticoagulants, the INRs obtained while receiving warfarin vary and often overestimate the extent of anticoagulation, while PT without receiving warfarin is often prolonged. In conclusion, lupus anticoagulants can influence PT and lead to INR that does not accurately reflect the true level of anticoagulation. Optimizing of (warfarin) oral anticoagulation therapy could be achieved by individual monitoring of anticoagulation effect with a test that is insensitive to lupus anticoagulants (chromogenic factor X assay). Emerging oral anticoagulants, direct thrombin inhibitors and direct factor Xa inhibitors, such as dabigatran and rivaroxaban, with a predictable anticoagulant response and little potential for food or drug interactions, have been designed to be administered in fixed doses without coagulation monitoring and could be the treatment choice for these patients.

Key words: Antiphospholipid syndrome – complications; Antiphospholipid syndrome – drug therapy; Thrombosis – etiology; Thrombosis – prevention and control; Warfarin – therapeutic use; Case report

Introduction

The term antiphospholipid syndrome (APS) or Hughes syndrome is used to link a variety of thromboembolic events to antibodies against specific pro-
antibody binding to β2-glycoprotein on the resting endothelial cells, nucleus activation, and up-regulation of adhesion molecules, secretion of cytokines, expression of tissue factor, and metabolism of prostacyclins; 2) oxidant-mediated injury of vascular endothelium; antiphospholipid antibodies may promote atherogenesis by acting against oxidized low-density lipoprotein (LDL). In this potential mechanism, the antibodies bind to β2-glycoprotein I, which is also known as apolipoprotein H and is present in oxidized LDL. Uptake of oxidized LDL by macrophages leads to macrophage activation, damage to endothelial cells, and subsequent promotion of thrombosis; 3) interference with phospholipid-binding proteins involved in the regulation of coagulation; β2-glycoprotein I plays a regulatory role within the coagulation pathways and may act as a natural anticoagulant. The binding of antiphospholipid antibodies to β2-glycoprotein I may inhibit its anticoagulant activity. Other phospholipid-binding proteins, such as tissue factor-factor VIIa complex and prekallikrein, which are components of the extrinsic and intrinsic coagulation pathways, respectively, may be targets of antiphospholipid antibodies; 4) by the effect on platelets, antiphospholipid antibodies may promote their activation, facilitating adherence to the endothelium. One model suggests that the binding of antibodies to β2-glycoprotein I increases platelet adhesion to collagen, as well as platelet aggregation; 5) by impairing the FV and FVIII degradation induced by protein C (PC); 'second hit' hypothesis, where antiphospholipid antibodies could inhibit enzymatic function of PC and PS complex. The exact mechanism of hypercoagulability in these patients remains unclear. However, in patients with pre-existing antibody disease, acute conditions that exacerbate the inflammatory response induce hypercoagulability and risk of thrombosis. Prolonged anticoagulation is the treatment of choice for patients with thrombosis and antiphospholipid syndrome. Warfarin has numerous limitations, including slow onset and offset of action, a narrow therapeutic range, and a metabolism that is affected by diet, drugs, and genetic polymorphisms. Because of its unpredictable dose response, warfarin requires careful coagulation monitoring to ensure that the therapeutic anticoagulant effect is achieved. However, there is still debate about the optimal intensity of anticoagulation. The other aspect relates to the monitoring of oral anticoagulation, which is still an unsolved issue in patients with antiphospholipid antibodies. Laboratory control of oral anticoagulant therapy by use of prothrombin time and international normalized ratio (PT-INR) might be inappropriate in lupus anticoagulant-positive patients because the INR may not reflect the true level of anticoagulation.

Case Report

A 63-year-old female patient with a 15-year history of recurrent venous thromboembolism was admitted to the hospital because of clinical and ultrasound verified acute deep ileofemoral thrombosis of the right leg. She had no recent immobilization, trauma or surgery. During the last seven years, she was taking warfarin with INR values of 2.2-3.5 in last three months. The INR range was 2.5-5.0. After warfarin withdrawal and administration of fractionated heparin (dalteparin) and methylprednisolone (1 mg/kg i.v.), prothrombin activity remained continuously low, about 25%. Other findings: positive lupus anticoagulant test 3.30 (normal range <1.3), high anticardiolipin antibody titer, IgG type >120 U/mL units and IgM 17.8 U/mL units, low fibrinogen levels, increased fibrinogen degradation products and D-dimers. Mild thrombocytopenia (56x10⁹/L) and anemia (Hb 108 g/L) with positive direct antiglobulin test (DAT) were recorded in peripheral blood, and platelet polymorphism with normal myelopoiesis and erythropoiesis in bone marrow aspirate. Electrocardiogram, chest radiography and serum testing for cancer markers (CEA, CA 19-9, CA 125, Ca 15-3) were normal.

After 8-day heparin therapy and reduction of local edema and pain, warfarin was reinstituted in a dose of 3 mg/day and INR 2.5 was recorded. In two weeks of discharge, the patient developed cellulitis of the right calf with thrombophlebitis of superficial veins. Synchronous therapy with a beta-lactam antibiotic, warfarin and low-dose fractionated heparin resolved the inflammation and thrombophlebitis.

In her past history, 15 years before, venous thrombosis was diagnosed and continuous oral anticoagulation prescribed. Her family history was contributory for venous thrombosis. Ten years before, she had relapsing deep vein thrombosis on the contralateral calf.
complicated with pulmonary embolism, and seven years before she had venous rethrombosis despite continuous warfarin therapy. Until 7 years before, she had a high titer of anticardiolipin antibodies of IgG type (98 U/mL units, normal <10 U/mL units) and IgM (30 U/mL units, normal <7 U/mL units). The diagnosis of antiphospholipid syndrome was established. The complement C3 and C4 activity was normal and platelet count decreased (72x10^9/L). Molecular assessments of the genes for FV Leiden and prothrombin G20210A mutation were normal. At the same time, signs of renal failure (creatinine 155 mmol/L, potassium 5.6 mEq/L, creatinine clearance 48 mL/min) and atherosclerosis of leg arteries were noticed. Abdominal ultrasonography revealed glomerulosclerosis of the right kidney and a function of the left one, with occlusion of the left renal artery. IgG monoclonal gammopathy with normal results of bone marrow aspiration and normal skeletal radiography fulfilled the criteria of monoclonal gammopathy of undetermined significance.

Discussion

The case presented illustrates recurrent venous thrombosis in warfarin treated antiphospholipid syndrome. Three retrospective studies report that recurrent thrombosis occurred in 52%, 69%, and 51.8% of patients with antiphospholipid syndrome during the follow up period (5, 6 and 6.4 years, respectively), regardless of antithrombotic strategy. prospectively, Schulman et al. demonstrated that in patients with an initial venous thromboembolic event who completed 6 months of oral anticoagulant therapy the risk of recurrent thrombosis was 29% in patients with anticardiolipin antibodies as compared to 14% in those without these antibodies (P=0.0013). The high concentration of IgG and IgM anticardiolipin antibodies in our patient could aggravate hypercoagulation state and cause recurrent venous thromboses, as well accelerate atherosclerosis of leg arteries. Despite continuous oral anticoagulation of medium to high intensity and ‘optimal warfarin dosage’, she developed five episodes of recurrent venous thromboembolism in a 15-year period.

Relatively few data are available on those patients that sustain a recurrent thromboembolic event in the setting of therapeutic oral anticoagulation. Optimal therapy for patients with lupus anticoagulants who have sustained a thromboembolic event is controversial. A variety of treatment strategies have been used, including addition of antiplatelet agents to higher-intensity oral anticoagulation, conversion from oral anticoagulants to therapeutic dose low-molecular weight heparin, and addition of immunomodulatory strategies. Immunomodulatory therapies that have been anecdotally used in patients with antiphospholipid syndrome include steroids, cyclophosphamide, and rituximab, but these are generally used in combination with an aggressive antithrombotic strategy. Rosove and Brewer recommend that the INR in these patients should be maintained at 2.6 or greater because a higher recurrence rate was seen in patients whose INR was less than 2.6. For the same reason, Khamashita et al. recommend high-intensity anticoagulation with INR of 3.0 or greater for patients with antiphospholipid antibodies and thrombotic events. In contrast, Ginsberg et al. suggest that an INR of 2.0 to 3.0 is sufficient because they saw no recurrent thrombosis during conventional-intensity warfarin therapy. However, none of these studies considered the observation that patients with lupus anticoagulants may have a spontaneous, non-medication induced PT prolongation. Our patient had positive lupus anticoagulants with in vitro prolongation of activated partial thromboplastin time (APTT) and PT. Lupus anticoagulants are antiphospholipid antibodies that interfere with phospholipid-dependent coagulation reactions in vitro. They are frequently associated with prolonged APTT or dilute Russell viper venom time. Antiphospholipid antibodies have been shown to interfere in vitro with the activation of factor X by the intrinsic factor-F X complex and of prothrombin by the prothrombinase complex, being the mechanism of therapy resistant hypercoagulation state in our patient. Although it has been stated that prolonged PT is ‘uncommon’ in patients with lupus anticoagulants, Horellou et al. describe 57 patients with lupus anticoagulants, 31 of them having prolonged PT (53%). Because some patients with lupus anticoagulants have a prolonged PT as the result of antibody-mediated decrease in F II activity, Horellou et al. measured these levels and found them to be normal in 30 of these patients. Fleck et al. report that PT was prolonged by
more than 2 seconds in 12 of 42 (28.6%) patients with lupus anticoagulants and normal factor II activity.

In some patients, particularly those with prolonged baseline PT, the INR will not be reliable and such situation was in our patient in the last 15 years. Optimal therapeutic management for these patients would be established by the prothrombin-proconvertin time or chromogenic factor X assay. We could not obtain diagnostic kit for these assays despite intensive efforts invested in search for it. In other patients, the INR obtained by using thromboplastin that is relatively insensitive to lupus anticoagulants may be sufficient. However, a normal baseline PT does not guarantee that the INR will be accurate in this patient. As neither chromogenic factor X nor prothrombin-proconvertin time assay is widely available to many clinicians, alternative approaches to anticoagulant therapy in these patients should be identified.

Other authors claim that warfarin therapy often fails in patients with antiphospholipid antibodies and venous thromboembolic disease and that these patients “are best managed by use of long-term heparin therapy.” Although low-molecular-weight heparins may increase the risk of osteoporosis and eliminate the need for monitoring, the cost of these medications currently precludes their long-term use in most patients. Fondaparinux is a new subcutaneous anticoagulant that indirectly inhibits factor Xa. It has been shown to be safe and effective in the acute treatment of deep vein thrombosis and pulmonary emboli, and also in venous thrombosis prevention in patients undergoing hip and knee surgery. As with the new antiplatelet agents, no controlled studies exist on the long-term use of heparin for secondary thrombosis prevention in antiphospholipid syndrome, although heparin has been used empirically in warfarin-resistant antiphospholipid syndrome patients.

A host of potential new oral anticoagulant agents (Fig. 1), which could become much-needed replacements for warfarin and could also be used as an alternative to heparins or other antithrombin agents, are making good progress in development, with at least two agents now in phase III trials. However, experts are cautious following the fall from glory of the first such agent to be developed, ximelagatran, which actually reached the market in Europe but was swiftly withdrawn because of liver toxicity. Nevertheless, as there are so many new compounds in development, researchers are optimistic that this time at least one or two will succeed and provide millions of patients who are or should be taking warfarin with a much more user-friendly treatment.

The new agents furthest on the development are the factor IIa inhibitor dabigatran and the factor Xa inhibitor rivaroxaban. These agents are initially being developed for the prevention of thrombosis in orthopedic surgery patients, but both dabigatran and rivaroxaban are also now starting late-stage trials for the prevention of stroke in atrial fibrillation patients (as a replacement for warfarin) and in the treatment of acute coronary syndromes.

Rivaroxaban is an anticoagulant in a novel class that exerts its effect by directly binding to the active site of factor Xa. Activated factor X serves as the link between the extrinsic and intrinsic pathways of the coagulation cascade, and serves as the rate limiting step in the production of thrombin. Its action results in a dose-dependent increase in both PT and APTT. Rivaroxaban appears to be well absorbed following oral administration, with a bioavailability.

Fig. 1. Targets of new anticoagulant drugs.

Oral factor Xa inhibitors (rivaroxaban, apixaban) bind directly to factor Xa and prevent thrombin generation. Dabigatran etexilate, an orally active direct thrombin inhibitor, undergoes metabolic activation to dabigatran, which binds to the active site of thrombin (factor IIa) and blocks its capacity to convert fibrinogen to fibrin, to activate platelets, and to amplify its own generation by activating factors V, VIII, and XI. By blocking the active site of thrombin, dabigatran also blocks the activation of protein C and thrombinactivatable fibrinolysis inhibitor by the thrombin/thrombomodulin complex.
of 60% to 80%, achieving maximal factor Xa inhibition within 3 hours. Half-life is approximately 6 to 7 hours, but may be extended, requiring dosage adjustment, in elderly patients and those with renal insufficiency. Increases in dosage were associated with increased effect on coagulation studies and with increased bleeding, but not necessarily increased efficacy. Based on these, phase III studies specific to venous thromboembolism prophylaxis used fixed oral doses of rivaroxaban 10 mg given once daily and did not use monitoring of coagulation studies. Thus far, studies comparing rivaroxaban to enoxaparin in the setting of venous thromboembolism prophylaxis have shown improved efficacy with similar safety after major orthopedic surgery (RECORD study group). This agent is also under investigation for treatment and secondary prevention of venous thromboembolism (EINSTEIN), prevention of stroke in patients with atrial fibrillation (ROCKET-AF) and medical management of acute coronary syndromes (ATLAS ACS TIMI 51). After 2008, rivaroxaban is currently approved in the UK, Canada and Europe for prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. In the USA, rivaroxaban approval is pending due to the Food and Drug Administration (FDA) concerns about the risks of bleeding (RECORD study: “any major bleeding” event occurring in 0.39% of the rivaroxaban group and 0.21% of the enoxaparin group) and substantial risk of liver injury/hepatotoxicity.

Of the new oral anticoagulants, dabigatran etexilate is a drug in the most advanced stage of development. Dabigatran etexilate is an oral prodrug with rapid onset of action, resulting in anticoagulant effects within 2 hours of administration. The pharmokinetic and pharmacodynamic profiles are predictable with dose-proportional increase in the concentration curves, with steady state achieved in 3 days. Dabigatran is predominately eliminated via the kidney (up to 80%), and does not undergo hepatic metabolism, nor were clinically significant drug-drug interactions observed when tested with atorvastatin, diclofenac, or digoxin. Small differences in drug clearance were observed in women and the elderly, and thought to be related to change in renal function. The Prevention of Venous Thromboembolism after Total Hip Replacement (RE-NOVATE) trial compared dabigatran 150 mg or 220 mg daily to enoxaparin 40 mg subcutaneous daily in 3494 patients for prevention of venous thromboembolism or all-cause mortality. This trial was the first to use dabigatran for an extended period of time, with treatment continuing to a median of 33 days postoperatively. Dabigatran again showed benefit compared to enoxaparin (absolute risk reduction by 1.9% and 0.7%); however, it did not demonstrate an increase in bleeding. Two fatal bleeds occurred during this trial, both in patients receiving dabigatran. Study authors conclude that dabigatran was not inferior to enoxaparin in the prevention of venous thromboembolism. The Thromboembolism Prevention After Knee Surgery (RE-MODEL) trial and Dabigatran versus Enoxaparin in Preventing Venous Thromboembolism Following Total Knee Arthroplasty (RE-MOBILIZE) trial were similar in design to RE-NOVATE, with the exception of the patient population evaluated. The RE-MODEL trial used lower dose enoxaparin (40 mg daily s.c.), whereas the RE-MOBILIZE trial used enoxaparin 30 mg bid s.c. bid as active control. RE-MODEL was able to demonstrate noninferiority of dabigatran at both doses (150 mg and 220 mg daily), with the composite of venous thromboembolism and all-cause mortality occurring in 40.5%, 36.4%, and 37.7%, with each regimen of dabigatran and enoxaparin respectively. Bleeding rates were low across all groups during the treatment period of 6 to 10 days and throughout 3-month follow up. All arms had higher than expected rates of venous thromboembolism. However, when compared to enoxaparin 30 mg s.c. twice daily, dabigatran did not reach the pre-specified noninferiority outcome for the composite of deep vein thrombosis, PE, and all-cause mortality. The primary endpoint occurred in 33.7% with dabigatran 150 mg daily, 31.1% with dabigatran 220 mg daily, and 25.3% with enoxaparin 30 mg twice daily during the 12- to 15-day treatment. These trials indicate the need for a larger trial to support the use of dabigatran over a regimen of twice daily enoxaparin following total knee replacement.

The efficacy of dabigatran in stroke prevention in 18,113 patients with atrial fibrillation was addressed by the RELY noninferiority trial. In a blinded fashion, the fixed doses of dabigatran 110 mg or 150 mg were administered twice daily and, in an unblinded fashion, adjusted-dose warfarin. The median follow
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up duration was 2.0 years. The primary outcome was stroke or systemic embolism. Resulting rates of primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (P<0.001 for noninferiority), and 1.11% per year in the group that received 150 mg of dabigatran (P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003), but in the group receiving 150 mg of dabigatran the incidence of bleeding was higher, 3.11% (P=0.31). There was also a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150-mg dose than with warfarin. The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P=0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051). Until now, this trial had the longest follow up of dabigatran administration and the only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia. Elevation in serum aspartate aminotransferase or alanine aminotransferase level to more than 3-fold upper limit of the normal range was not more frequent with dabigatran at either dose than with warfarin.

The efficacy and safety of dabigatran in the prevention of venous thrombosis recurrence was tested in the RE-COVER randomized, double-blind noninferiority trial. Oral dabigatran administered at a dose of 150 mg twice daily was compared with warfarin that was dose-adjusted to achieve INR of 2.0 to 3.0 in 1274 patients with acute venous thromboembolism that were initially administered parenteral anticoagulation therapy for a median of 9 days. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Safety endpoints included bleeding events, acute coronary syndromes, other adverse events, and results of liver function tests. Recurrent venous thromboembolism was recorded in 30 (2.4%) of 1274 patients randomly assigned to receive dabigatran as compared with 27 (2.1%) of 1265 patients randomly assigned to warfarin (P<0.001 for noninferiority). Major bleeding episodes occurred in 20 (1.6%) patients assigned to dabigatran and 24 (1.9%) patients assigned to warfarin; and episodes of any bleeding were observed in 205 (16.1%) patients assigned to dabigatran and 277 patients assigned to warfarin. The numbers of deaths, acute coronary syndromes and abnormal liver function tests were similar in the two groups. Adverse events leading to discontinuation of the study drug occurred in 9.0% of patients assigned to dabigatran and 6.8% of patients assigned to warfarin (P=0.05), therefore the safety profile of dabigatran is similar to that of warfarin.

Despite these encouraging new therapeutic approaches, warfarin is the gold standard for the reduction of hypercoagulability status. Much of the success of rivaroxaban and dabigatran will depend on how they can penetrate the existing market and then expand their current scope. However, there are a number of factors that could constrain their uptake. Current therapies are well entrenched in physicians’ minds and benefit from large amounts of clinical data; overcoming the physicians’ familiarity will be difficult. Warfarin has been in use for more than half a century.

All anti-clotting agents carry a risk of unwanted bleeding events, and the new oral anticoagulants are no exception. Although antidotes for these drugs are in preclinical development, they will not be available in short term. Prices could be another significant obstacle, particularly at the time of drastic cost-containment strategies in healthcare systems, as some payers will go for the less expensive option. Another factor in the market is the expected approval of biosimilar versions of enoxaparin, which will lead to greater interest in this field and potentially lower prices. Rivaroxaban and dabigatran also face some serious competition from other competitor drugs now in development.

Apixaban, an orally active factor X inhibitor, was tested in the ADVANCE-2 study. Patients undergoing elective unilateral or bilateral total knee replacement were randomized to receive oral apixaban 2.5 mg twice daily (n=1528) or subcutaneous enoxaparin 40 mg once daily (n=1529). Venous thromboembolism was reported in 147 (15%) of 976 apixaban patients and 243 (24%) of 997 enoxaparin patients (relative risk 0.62 [95% CI 0.51-0.74]; P<0.0001; absolute risk reduction 9.3% [5.8-12.7]). Major or clinically relevant
non-major bleeding occurred in 53 (4%) of 1501 patients receiving apixaban and 72 (5%) of 1508 patients treated with enoxaparin (P=0.09)35.

Another novel oral factor Xa inhibitor under development is betrixaban. Not only has betrixaban demonstrated anti-clotting activity in venous thromboembolism prevention trials in total knee replacement surgery patients, and showed promises for stroke prevention in atrial fibrillation, but is the only novel oral anti-clotting agent being tested in patients with renal malfunction.

Corticosteroids and other immunosuppressant therapies, such as azathioprine, cyclophosphamide and methotrexate, and rituximab (monoclonal antibody) have been reported in some studies to decrease the titers of lupus anticoagulant and antcardiolipin antibodies, but do not seem to decrease thrombotic risk. Because of the high antcardiolipin antibody titer in our patient, we administered corticosteroids hoping to reduce the chance for thrombosis recurrence, but corticosteroids may have been the precipitating factor of cutaneous infection and concomitant superficial thrombophlebitis in our patient. The critical areas for future research include identification of patients with antiphospholipid antibodies that are at the highest risk of thrombotic complications, developing new antithrombotic agents that are efficacious and safe, and investigating novel approaches to eliminate the autoantibody and, hopefully, the increased prothrombotic state.

References


Recurrent venous thrombosis despite ‘optimal anticoagulation therapy’ for antiphospholipid syndrome: can new oral anticoagulants solve the problem?


Ciljevi su analizirati uzroke neuspjeha “optimalno doziranog” varfarina kod prevencije recidiva duboke venske tromboze kod bolesnika s antifosfolipidnim sindromom. Opisuje se slučaj 63-godišnje bolesnice s antifosfolipidnim sindromom i recidivima venske tromboze tijekom uzimanja varfarina. Vrijednosti INR bile su u terapijskim granicama. Analizirali su se patofiziološki mehanizmi nastanka tromboze i literaturni podaci. Rezultati su pokazali kako u bolesnika s pozitivnim lupus antikoagulans (LA) testom vrijednost PV-INR ne daje pravu sliku protuzgrušavajućeg učinka varfarina. Aktivnost PV je zbog interferencije često lažno smanjena, iako u času mjerenja bolesnik ne uzima varfarin ili drugi antagonist vitamina K. Zaključak je kako prisutnost LA može interferencijom lažno smanjiti aktivnost u PV testu i rezultirati nalazom INR koji ne odražava pravo stanje protuzgrušavajuće aktivnosti izazvane varfarinom. U tom bi slučaju umjesto PV testa trebalo mjeriti aktivnost faktora Xa kromogenom metodom koja je neosjetljiva na LA. Drugo moguće rješenje bi u bolesnika s antifosfolipidnim sindromom bila zamjena varfarina novim lijekovima, oralnim inhibitorima trombina i faktora X. Ovi lijekovi u fiksnoj dozi s predvidivim te o hrani i lijekovima uglavnom neovisnim protuzgrušavajućim učinkom imaju djelotvornost i nuspojave uglavnom slične varfarinu, ali ne trebaju kontrole INR.

Ključne riječi: Antifosfolipidni sindrom – komplikacije; Antifosfolipidni sindrom – terapija lijekovima; Tromboza – etiologija; Tromboza – prevencija i kontrola; Varfarin – terapijska primjena; Prikaz slučaja