Thrombosis with Thrombocytopenia - A Vascular Paradox

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ABSTRACT

BACKGROUND
Thrombosis associated with thrombocytopenia is a vascular paradox which we seldom encounter in our clinical practice. We hereby describe four real world clinical situations and their therapeutic management. Since there are no guidelines regarding this subset, most of the treatment is based on few anecdotal reports and consensus data. Hence, we have reviewed the literature to throw light on some pertinent clinically relevant questions. Our objective is to describe and discuss the probable reasons of vascular paradox and its management.

METHODS
It is a descriptive study of four cases collected over one-year period including patients of thrombosis with thrombocytopenia.

RESULTS
In the first case, the patient had pulmonary embolism as a presenting manifestation of leukaemia. Only 5% cases of AML-M3 sub type acute promyelocytic leukaemia present with normal peripheral blood smear. Patient had thrombocytopenia with deep vein thrombosis and pulmonary embolism. In the second case, secondary antiphospholipid antibody syndrome (APLS) presented with illo-femoral deep vein thrombosis associated with thrombocytopenia and bleeding tendency. In the third case, antiphospholipid antibody syndrome with thrombocytopenia was associated with severe pulmonary hypertension and deep vein thrombosis. In the fourth case, patient presented with non-ST elevation myocardial infarction (NSTEMI) with thrombocytopenia. He was diagnosed with idiopathic thrombocytopenic purpura. He had angiographic evidence of critical triple vessel disease. He was treated with coronary bypass surgery after initiating treatment with oral eltrombopag and steroids.

CONCLUSIONS
We have highlighted four clinical situations ranging from frank malignancy to pure vascular pathology, where we have encountered and tackled the vascular paradox of ‘thrombosis and thrombocytopenia’ and reviewed the literature pertaining to these case scenarios.

KEYWORDS
Thrombosis with Thrombocytopenia, APLS, AML-M3, Pulmonary Hypertension, ITP
BACKGROUND

Thrombosis associated with thrombocytopenia is a vascular paradox which we encounter rarely in our clinical practice. It is a therapeutic dilemma as conventional treatment for thrombosis can worsen the bleeding complications of thrombocytopenia. At the same time, thrombocytopenia does not protect against venous or arterial thrombosis. Hence caring for these patients can be challenging. We hereby present four such clinical real-world situations. Since there are no guidelines regarding this subset, most of the treatment is based on few anecdotal reports and consensus data. Hence, we have reviewed the literature to throw light on some pertinent clinically relevant questions like indications for anticoagulation, dosing of anticoagulants, treatment approach to increase platelet count and alternative therapy to anticoagulation in selected patients.

METHODS

It is a descriptive study of four cases collected over one-year period including patients of thrombosis with thrombocytopenia. We included patients who presented with thrombosis with thrombocytopenia from January 2019 to December 2019 after taking proper informed consent. Institutional Ethical Committee clearance was taken before beginning of the study.

RESULTS

Case 1

A 53-year-old gentleman presented with exertional dyspnoea (NYHA-New York Heart Association, class III) of recent onset (12 days). He had type 2 diabetes and hypertension since 5 years and was on treatment for the same. He had no other comorbidities. He was not a smoker.

He was referred to us by the pulmonologist with documented CT (Computed Tomography) pulmonary angiogram evidence of pulmonary embolism. He had tachycardia and tachypnoea and low blood pressure with resting room air saturation of 90%. He had clinical evidence of right sided deep vein thrombosis (DVT) which was proven on duplex ultrasonography. Echo revealed dilated right atrium, right ventricle with mild tricuspid regurgitation and pulmonary artery systolic pressure (PASP) of 75 mm of Hg. (Fig. 1) CT pulmonary angiogram revealed bilateral sub-segmental acute pulmonary embolism. He was thrombolysed with reteplase 10 units two doses thirty minutes apart in view of hypotension. Haemogram revealed neutropenia with thrombocytopenia (platelet count: 40,000 cells / cumm). Adequate neutropenic precautions were undertaken. Echocardiogram on day three showed improved right ventricular function with drop in PASP to 30 mm of Hg with preserved ejection fraction. His dyspnoea had improved. He had no bleeding tendencies. Complete haemogram was monitored on a daily basis. Post thrombolysis, he was treated with inj. Fondaparinux 5 mg dose, subcutaneous once daily.

Thrombophilia work-up revealed marginal elevation of homocysteine. Bone marrow aspiration revealed promyelocytic leukaemia, morphologically favouring acute promyelocytic leukaemia (AML-M3). Bone marrow biopsy showed hypercellular marrow with infiltration by acute myeloid leukemic cells. Immunophenotyping revealed promyelocytes expressing CD13, CD 33, CD 45, CD 64, and CD117. CD 55 and 59 were present which ruled out paroxysmal nocturnal haemoglobinuria. Chemotherapy was instituted with retinoic acid (ATRA) by the oncologist. His blood counts started improving. Repeat bone marrow aspiration a month later showed no leukemic blasts or promyelocytes. He, however, did not tolerate chemotherapy with cytarabine and daunorubicin. In view of severe leucopenia (Total leucocyte count: 100 cells / cumm, Hb: 9g % and Platelet: 32,000 cells / cumm) the chemotherapy was withheld. He was continued on retinoic acid. Patient developed neutropenic septicaeinic shock and was treated for the same with prolonged duration of antibiotics and supportive measures. He continues to be in remission and is on follow up.

Case 2

A 29-year-old obese lady presented to us with progressive swelling and tenderness of left lower limb. Her duplex ultrasound showed ilio-femoral proximal deep vein thrombosis with complete occlusion of iliac veins. She had been diagnosed previously with anti- phospholipid antibody syndrome, anti-β2-glycoprotein I positive in view of history of recurrent abortions. She was on oral anticoagulation for six months. Her PT-INR (Prothrombin Time – International Normalized Ratio) was in sub-therapeutic range despite multiple dose modifications. Catheter directed thrombolysis was deferred as her haemogram revealed thrombocytopenia (platelet count of 50,000 cells / cumm) and she was having menorrhagia. In view of inability to give complete anticoagulation, a retrievable inferior venacaval filter was inserted. She was treated conservatively with low molecular weight heparin. Oral anticoagulation was reinstituted after improvement in her platelet counts. She clinically improved.

Case 3

A 28-year-old young adult presented with proximal left sided ilio-femoral deep vein thrombosis which was proven on venous Doppler. His echocardiogram revealed dilated right atrium, right ventricle with severe pulmonary arterial hypertension. CT pulmonary angiogram was normal. He tested positive for anti-β2-glycoprotein I antiphospholipid antibodies, on two occasions twelve weeks apart. Vasculitis profile was normal. Rheumatoid factor was normal. He was diagnosed with primary antiphospholipid antibody syndrome and pulmonary hypertension as no other cause could be found. He had thrombocytopenia with platelet count of 34,000 cells / cumm. Peripheral blood smear was unremarkable. He was treated with subcutaneous Inj Fondaparinux with daily monitoring of platelet count.
Platelet count became normal after a week. He was subsequently started on oral anticoagulants and oral pulmonary vasodilators.

**Case 4**
A middle-aged gentleman presented with recent onset worsening angina; He was diagnosed with non-ST elevation myocardial infarction. Coronary angiogram revealed critical triple vessel disease. He had low platelet count (55,000 / cumm) on haemogram. Bone marrow study confirmed idiopathic thrombocytopenic purpura (ITP). He was treated with oral Eltrombopag 50 mg / day and small dose oral steroids for three weeks with serial platelet count monitoring. Dose of eltrombopag was gradually escalated from 25 mg per day to 50 mg per day. Eltrombopag was started as initial treatment with parenteral dexamethasone did not show improvement in platelet counts. Intravenous immunoglobulins were not considered in view of the cost and the risk of possible transfusion reactions perioperatively. He was on a single antiplatelet agent till his coronary artery bypass surgery (CABG). His platelet count improved to 1.2 lakhs / cumm. He then underwent CABG. Perioperative course was uneventful. He is doing well on follow up.

**DISCUSSION**

We encounter such clinical scenarios where thrombosis exists with thrombocytopenia and puts us in a dilemma whether to treat with thrombolytics / anticoagulants or not. The risk of thrombosis and its consequences as to be weighed against the risk of bleeding. There are no clear-cut guidelines stating the lowest platelet level at which thrombolytics or anticoagulation can be safely given. Bleeding risk is different in different patients according to underlying cause of thrombocytopenia. Compared to primary ITP, antiplatelet drugs, liver disease associated thrombocytopenia are at lower bleeding risk.1

The risk of bleeding increases when the platelet count drops below 50,000 cells / cumm. There is 10 % chance for spontaneous bleeding when platelet count is below 20,000 cells / cumm and below 10,000 cells / cumm, the risk of bleeding is 20 %. Intracranial haemorrhages can be catastrophic. In a retrospective study, in patients with haematological malignancies with severe thrombocytopenia and venous thromboembolism, they have found that treatment with oral anticoagulation subgroup have 27 % risk of bleeding especially within the first 31 days in comparison to 3 % risk of bleeding in who are not treated with oral anticoagulants. However, the risk of recurrence in not treated subgroup is 15 % in comparison to 2 % in the treated subgroup.2

With exceptions of active bleeding and contraindications to anticoagulation, In National institute of neurological disorders and stroke (NINDS), data of patients presenting with stroke and thrombocytopenia, thrombolysis with Alteplase has been successfully done with no undue adverse events compared to controls up till platelet count of 1 lakh / cumm. This threshold in NINDS trial was based on expert consensus. It is not recommended to wait for platelet count report before thrombolysis in stroke, myocardial infarction or pulmonary embolism.3

Non-heparin anticoagulants include direct thrombin inhibitors (Parenteral: Argatroban, Bivalirudin, Fondaparinux; Oral: Apixaban, Edoxaban, Rivaroxaban, Dabigatran) are preferred in patients with heparin-induced thrombocytopenia.4

How to tackle malignancies especially haematological associated with the spectrum of thrombosis with thrombocytopenia? Venous thromboembolism is four-fold greater in patients with cancer, more so in solid cancers. Venous thromboembolism is six-fold greater in patients receiving cancer chemotherapy; ninety-fold greater in first 6 weeks after cancer surgery and the risk persists up to thirty-fold till one year.5 Negative D-dimer has the same diagnostic value in pulmonary embolism in patients with or without cancer. Cancer is an adverse prognostic factor. Role of thromboprophylaxis in haematological malignancies is less established though the risk of venous thromboembolism is equal to that of solid cancers.5 Etio/Pathogenesis postulated is direct expression of tissue factors and procoagulants (annexin II receptor expression).

In RIETE cancer registry, (registro informatizado de enfermedad tromboembólica)5 low body weight (< 60 Kg), serum creatinine > 1.2, immobility, overt pulmonary embolism, metastases were associated with higher risk of bleeding (6.2 % vs. 1 % in no risk factors). But this analysis did not include patients with venous thromboembolism (VTE) with baseline thrombocytopenia.

Thirty-day mortality in patients with cancer is 26.4 % and those without cancer are 4.1 %.6 Approximately, 10 % develop cancer (occult cancer) in next 5 - 10 years after an unprovoked pulmonary embolism, highest incidence being in the first year. 5 - 20 % of acute promyelocytic leukaemia is M3 variety characterized by t (15, 17) translocation. Haemorrhagic complications are more common than thrombosis in AML-M3; Coagulopathy is under reported. Coagulopathy is greater with use of Retinoic acid (ATRA), especially during induction. In our first case, the patient had presented to us with pulmonary embolism as a manifestation of leukaemia which was atypical in presentation accounting for only 5 % of AML-M3 subtype where peripheral blood smear was normal. He tolerated thrombolysis and anti-Xa Fondaparinux despite low platelet counts. His platelet counts improved after initiation of chemotherapy. Those with preceding cytopenias and haematological disease are known to have worse prognosis than otherwise, in spite of the treatment.

American society of clinical oncology advocates anticoagulation prophylaxis in cancer patients if the platelet count is > 50,000 cells / cumm.7 Platelet count less than 20,000 cells / cumm is an absolute contraindication for therapeutic anticoagulation.8

The international society on thrombosis and haemostasis [ISTH] consensus guidelines9 recommended the use of full therapeutic doses of anticoagulation without platelet transfusion in patients with cancer associated VTE and a platelet count of more than 50,000 cells / cumm.
Therapeutic doses of anticoagulation with platelet transfusion are recommended until the platelet count reaches the empirical cut-off of 50,000 cells / cumm, if platelet count is below this level. If platelet transfusion is contraindicated, the ISTH suggests (with weak evidence) the insertion of a retrievable inferior vena cava filter and its removal when the platelet count recovers after which anticoagulation has to be resumed.

The British Committee for Standard in Haematology [BCSH] recommends the use of a full therapeutic dose of low molecular weight heparin to treat established VTE in cancer patients with a platelet count above 50,000 cells / cumm. It recommends half dose of low molecular weight heparin when the platelet count is between 25000 - 50,000 cells / cumm. It is recommended that anticoagulation therapy be withheld when the platelet count is less than 25,000 cells / cumm.10

What is APLS? Antiphospholipid antibody syndrome (APLS) is an autoimmune disorder characterized by vascular thrombosis and / or pregnancy related morbidity in the presence of antiphospholipid antibodies. These include cardiolipin or β2-glycoprotein I (β2-GPI) antibodies or lupus anticoagulant (LA), which are phospholipid-binding proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets. At least one clinical and one laboratory criteria are required to classify a patient with APLS.11

No underlying systemic autoimmune disease is detected in approximately half the patients with APLS. The prevalence of clinical APLS is 10 % in systemic lupus erythematosus (SLE) and an estimated cumulative prevalence on follow up is around 30 %.12-15

What is the rate of recurrence in patients with APLS? How long should we treat with oral anticoagulation? In a retrospective study by Derksen et al. 12 of 19 patients with APLS and venous thrombosis had recurrent thromboembolic events (63 %), all of which occurred in patients in whom anticoagulation had been stopped in a median follow up of 8 years.16 Recurrence occurred more frequently in patients in whom anticoagulation had been stopped after stopping therapy. Khamashita et al. calculated the recurrence rate in this period to be 1.30 events per year.16 This recurrence rate is higher than in patients with a first idiopathic deep vein thrombosis after 3 months of treatment (0.27 events per year).16,17

Meta-analysis confirmed that long term anticoagulation in patients with venous thromboembolism reduces the risk of recurrence.18

Kearon et al. quantified a 95 % risk reduction with 3 months of warfarin therapy.19 The risk of recurrent thromboembolic events reaching stabilization at 9 months after the first event independently of the duration of anticoagulation. Independent predictors of thrombotic events are persistent high titers of antiphospholipid antibodies (IgG > 40 GPL U) and prior thrombosis.20-23

Is thrombocytopenia an epiphenomenon? Is it an associated reactive idiopathic thrombocytopenic purpura? Or Is thrombocytopenia because of consumption coagulopathy? Thrombocytopenia is commonly associated with APLS. Its reported prevalence is 20 to 40 %.24,25 However, it is not necessary to establish the diagnosis of definitive APLS according to the revised reported classification criteria. Antiphospholipid antibodies are present in 40 % of chronic ITP patients with elevated risk of future APLS.26 Decreased platelet counts had not become apparent before the onset of vascular symptoms in our cases. Therefore, it is reasonable to speculate that thrombocytopenia was an epiphenomenon accompanying APLS.

Antiphospholipid antibodies are prevalent in idiopathic thrombocytopenic purpura, but their phospholipid protein profile differs from APLS. The difference in antiphospholipid antibodies may result in opposite clinical manifestations in two disorders. In our second case, secondary APLS was seen in association with SLE presenting with proximal deep vein thrombosis (DVT) and thrombocytopenia. In our third case, pulmonary hypertension was found associated with antiphospholipid antibody positivity. This association is rare and is found as isolated reports in the literature.27

Treatment of thrombocytopenia associated with APLS is the same way as we treat ITP associated thrombocytopenia. Bleeding is uncommon and is usually seen with catastrophic APLS. Intravenous methylprednisolone has consistently demonstrated to increase the platelet counts. Intravenous immunoglobulins may show a more rapid increase in platelet counts and should be considered in emergencies.28,29 Unless accompanied by ITP immunosuppressive therapy is not routinely recommended in patients with APLS.

What is Eptrombopag? Eptrombopag is a thrombopoietin-receptor agonist used as an effective treatment for ITP30,31 as well as hepatitis C-associated thrombocytopenia. It is a non-peptide ligand, binding the thrombopoietin receptor on megakaryocytes and platelets thereby enhancing the megakaryocyte production and platelet maturation. However, adverse effects of the agent include thrombotic episodes due to the release of platelet materials into the circulation. It is used as a second line agent in treatment of chronic ITP in steroid non-responders or partial responders.

Can novel oral anticoagulants (NOACs) be used in place of Vitamin K antagonists (VKAs) in anticoagulation failures in patients with APLS? Because INR values may be significantly influenced by a strong lupus anticoagulant dependent on the reagent used for measuring prothrombin time the use of VKA can pose practical difficulties in some patients with APLS. NOACs do not require routine monitoring of their anticoagulant effects in clinical practice. Case reports on patients with APLS experiencing recurrent thromboembolic events while on NOACs have questioned their usefulness in this highly prothrombotic disorder. Further studies are needed to define the role of NOACs in patients with definitive APLS. Until then VKAs should be used for APLS. Long term anticoagulation is warranted in patients with venous thrombosis and persistently positive antiphospholipid antibodies.

Kaul et al.32 followed up 54 APLS patients on secondary thrombosis prevention with aspirin, clopidogrel and low molecular weight heparin. The recurrence rates were 5.4, 9.1 and 3.1 per 100 patients respectively over a period of two years. Hence it is not recommended to use P2Y12 inhibitors.

J Evid Based Med Healthc, pISSN - 2349-2562, eISSN - 2349-2570 / Vol. 7 / Issue 51 / Dec. 21, 2020 Page 3113
In a small randomised trial by Cohen H et al. involving 116 patients, in patients with APLS, concluded that rivaroxaban could only be an alternative to warfarin.3 In EINSTEIN CHOICE trial, among patients with venous thromboembolism who required continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban than aspirin. Both therapeutic (20 mg) and prophylactic dose (10 mg) of rivaroxaban reduced the risk in comparison to aspirin, without a significant increase in bleeding rates.34

The risk of major bleeding is 2 to 3 % per year both in patients with and without APLS on warfarin. Thus, the optimal duration of treatment is somewhere between the risk of thrombosis and the risk of bleeding. The American College of Chest Physicians (ACCP) recommends for patients with APLS and a venous thromboembolic event, warfarin therapy with a target INR of 2.5 (INR 2 - 3) (Grade 1A) for 12 months (Grade 1C). It suggests indefinite anticoagulant therapy should be considered (Grade 1C) for recurrent events. Higher therapeutic INR 3 to 4 is advised for arterial recurrent events or events occurring at therapeutic INR.35 Lastly, when do we use Inferior venacaval filters? In symptomatic cases with acute proximal venous thromboembolism and contraindication to the use of anticoagulation or anticoagulation failure and hemodynamically unstable cases, retrievable inferior venacaval filters can be used.36,37 It is pertinent to select appropriate cases and also use retrievable filters with longer retrieval interval spans. Retrieval of IVC filters is important as there is high risk of inferior vena caval obstruction. The published retrieval rates in the United States are often as low as 30 %.38

CONCLUSIONS

We have highlighted four clinical situations ranging from frank malignancy to pure vascular pathology, where we have encountered and tackled the vascular paradox of ‘thrombosis and thrombocytopenia’ and reviewed the literature pertaining to these case scenarios. Only few case reports pertaining to massive pulmonary embolism with thrombocytopenia, APLS with VTE with severe thrombocytopenia and haematological malignancies with thromboembolism have been reported in literature. Since these situations in clinical practice are random, data regarding available therapeutic strategies are sparse.

Abbreviations

AML - Acute Myelocytic Leukaemia
PASP - Pulmonary Artery Systolic Pressure
CTPA - CT Pulmonary Angiogram
DVT - Deep Vein Thrombosis
VTE - Venous Thromboembolism
APLS - Antiphospholipid Antibody Syndrome
CABG - Coronary Arteries Bypass Surgery
ITP - Idiopathic Thrombocytopenic Purpura
NINDS - National Institute of Neurological Disorders and Stroke
ATRA - Retinoic Acid
BCSH - British Committee for Standard in Hematologic ISTH - International Society on Thrombosis and Haemostasis
ASCO - American Society of Clinical Oncology
SLE - Systemic Lupus Erythematosus
VKA - Vitamin K Antagonists
ACCP - American College of Chest Physicians

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Tosetto A, Balduini CL, Cattaneo M, et al. Italian society for haemostasis and thrombosis. Management of bleeding and of invasive procedures in patients with platelet disorders and/or thrombocytopenia: Guidelines of the Italian society for haemostasis and thrombosis (SISET). Thrombosis Research 2009;124(5):e13-e18.
[2] Houghton DE, Key NS, Zakai NA, et al. Analysis of anticoagulation strategies for venous thromboembolism during severe thrombocytopenia in patients with hematologic malignancies: a retrospective cohort. Leukaemia & Lymphoma 2017;58(11):2573-2581.
[3] National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333(24):1581-1587.
[4] Sweetland S, Green J, Liu B, et al. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. BMJ 2009;339:b4583.
[5] Guasconi G, Frasson S, La Regina M, et al. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. Thromb Res 2013;131(1):24-30.
[6] Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346(10):752-763.
[7] Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology Guideline: Recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. Journal of Clinical Oncology 2007;25(34):5490-5505.
[8] Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology
clinical practice guideline update. J Clin Oncol 2013;31(17):2189-2204.
[9] Di Nisio M, Lee AYY, Carrier M, et al. Diagnosis and treatment of the incidental venous thrombosis in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost 2015;13(5):880-883.
[10] Watson HG, Keeling DM, Laffan M, et al. Guideline on aspects of cancer-related venous thrombosis. Br J Haematol 2015;170(5):640-648.
[11] Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4(2):295-306.
[12] Robertson B, Greaves M. Antiphospholipid syndrome: an evolving story. Blood Reviews 2006;20(4):201-212.
[13] Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42(7):1309-1311.
[14] Perez-Vasquez ME, Villa AR, Drenkard C, et al. Influence of disease duration, continued follow up and further antiphospholipid testing on the frequency and classification category of antiphospholipid syndrome in a cohort of patients with SLE. J Rheumatol 1993;20(3):437-442.
[15] Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992;117(4):303-308.
[16] Derksen R, de Groot PG, Kater L, et al. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. Ann Rheum Dis 1993;52(9):689-692.
[17] Khamashtha MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid antibody syndrome. N Engl J Med 1995;332(15):993-997.
[18] Win K, Rodgers GM. New oral anticoagulants may not be effective to prevent venous thromboembolism in patients with antiphospholipid syndrome. Am J Hematol 2014;89(10):1017.
[19] Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Eng J Med 1999;340(12):901-907.
[20] Pinede J, Duhat P, Cucherat M, et al. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials. J Intern Med 2000;247(5):553-562.
[21] Schulman, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. Am J Med 1998;104(4):332-338.
[22] Fonseca AG, D’Cruz DP. Controversies in the antiphospholipid syndrome: can we ever stop warfarin? Journal of Autoimmune Diseases 2008;5:6.
[23] Ost D, Tepper J, Mihara H, et al. Duration of anticoagulation following venous thromboembolism: a meta – analysis. JAMA 2005;294(6):706-715.
[24] Galli M, Finazzi G, Barbui T. Thrombocytopenia in the antiphospholipid syndrome. Br J Haematol 1996;93(1):1-5.
[25] Diz-Kucukkaya R, Hacihanefoglu A, Yenerel M, et al. Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytic purpura: a prospective cohort study. Blood 2001;98(6):1760-1764.
[26] Bidot CJ, Jy W, Horstman LL, et al. Antiphospholipid antibodies (APLA) in immune thrombocytic purpura (ITP) and antiphospholipid syndrome. Am J Hematol 2006;81(6):391-396.
[27] Luchi ME, Asherson RA, Lahita RG. Primary idiopathic pulmonary hypertension complicated by pulmonary arterial thrombosis. Arthritis and Rheumatism 1992;35(6):700-705.
[28] Hakim AJ, Machin SJ, Isenberg DA. Autoimmune thrombocytopenia in primary antiphospholipid syndrome and systemic lupus erythematosus: the response to splenectomy. Semin Arthritis Rheum 1998;28(1):20-25.
[29] Artim-Esen B, Diz-Kucukkaya R, Iananc M. The significance and management of thrombocytopenia in antiphospholipid syndrome. Curr Rheumatol Rep 2015;17(3):14.
[30] Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007;357(22):2237-2247.
[31] Dmytrijuk A, Robie-Suh K, Rieves D, et al. Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytic purpura. Oncology (Williston Park) 2009;23(13):1171-1177.
[32] Kaul M, Erkan D, Artim-Esen B, et al. Warfarin alternatives for secondary thrombosis prophylaxis in antiphospholipid syndrome (APS). Arthritis Rheum 2005;52:5595.
[33] Cohen H, Hunt BJ, Efthymiou M, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Hematol 2016;3(9):e426-e436.
[34] Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med 2017;376(13):1211-1222.
[35] Kearon C, Akp EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th Ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(Suppl 2):e419S-e496S.
[36] Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16):1788-1830.
[37] Kaufman JA, Kinney TB, Streiff MB, et al. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology multidisciplinary consensus conference. J Vasc Interv Radiol 2006;17(3):449-459.

[38] Dixon A, Stavropoulos SW. Improving retrieval rates for retrievable inferior vena cava filters. Expert Rev Med Devices 2013;(10):135-141.