

Prevention of Venous Thromboembolism in Medical Patients with Thrombocytopenia or with Platelet Dysfunction: A Review of the Literature

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ABSTRACT

Current guidelines for venous thromboembolism (VTE) primary prophylaxis are based on randomized clinical trials that exclude subjects at a potentially high bleeding risk. Thus no specific recommendation/algorithm for pharmacological prophylaxis in patients with thrombocytopenia and/or platelet dysfunction is available. Because at least 25% of subjects admitted to medical departments exhibit these conditions, information on this subject is provided here to optimize their VTE prophylaxis. Low platelet number/function and clotting abnormalities are common in patients with liver cirrhosis. However, these patients have a high incidence of portal and idiopathic venous thromboses, implying that cirrhotic coagulopathy does not protect against thrombosis. At variance with severe thrombocytopenia (< 50,000/ μ L), mild/moderate thrombocytopenia (> 50,000/ μ L) should not interfere with VTE prevention decisions. In severe thrombocytopenia, prophylaxis should be considered on an individual basis, however. In patients with antiphospholipid antibodies and thrombocytopenia, a thrombotic tendency is usually associated rather than a bleeding risk. VTE prophylaxis in high-risk conditions is thus suggested in these patients. Except in cases with contraindications to anticoagulation, antithrombotic prophylaxis should be always considered in hospitalized cancer patients with thrombocytopenia, especially in those with hematologic malignancies and multiple VTE risk factors. Aspirin treatment is not as effective as heparins in lowering the risk of VTE. Studies in stroke suggest that thromboprophylaxis with heparins is safe in patients with ischemic stroke undergoing aspirin treatment. The need for VTE prophylaxis in patients on chronic treatment with aspirin and/or clopidogrel should be evaluated after assessing the individual risk-benefit ratio.

KEYWORDS: Venous thromboembolism, primary prophylaxis, medical patients, thrombocytopenia, antiplatelet agents

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Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), has an important impact on morbidity and mortality among hospitalized patients.¹ Inasmuch as VTE is a well-known complication of surgery, the risk in medical patients is generally underestimated. However, 50 to 70% of VTE and 70 to 80% of PE occur in nonsurgical patients.¹ Massive PE has been reported in 4 to 8% of medical patients who died during hospitalization, two thirds of in-hospital deaths for PE occurring in medical patients.² Multiple risk factors for VTE have been identified in the medical setting (Table 1).³

Pharmacological methods (unfractionated heparin [UFH], low molecular weight heparins [LMWH], fondaparinux, and the newer anticoagulants recently approved in major orthopedic surgery, rivaroxaban and dabigatran etexilate) are safe and effective for preventing VTE.⁴⁻⁷ Although most medical inpatients have multiple risk factors for VTE,^{3,7} large prospective studies

Table 1 Risk Factors for Venous Thromboembolism: Medical Conditions*

• **Strong**

- History of DVT, PE, SVT
- Stroke/other neurological disorders associated with paralysis
- Recent immobilization (> 3 days)
- Increasing age
- Puerperium (< 8 weeks from delivery)
- Cancer (active or occult)
- Cancer therapy (chemo/radiotherapy, hormonal, angiogenesis inhibitors)
- Acute MI and heart failure

• **Moderate/weak**

- Family history of VTE
- Hormone replacement therapy, oral contraception, ongoing pregnancy
- CVC insertion
- Obesity
- COPD, acute respiratory illness
- Sepsis
- Inflammatory bowel disease
- History of miscarriages
- Nephrotic syndrome
- Myeloproliferative syndromes
- Paroxysmal nocturnal hemoglobinuria
- SLE and other connective tissue diseases
- Recent long-distance travel (> 6 hours)
- Antipsychotic drugs
- Cigarette smoking
- Diabetes mellitus
- Varicose veins

*See Di Minno et al³ for further details.

DVT, deep vein thrombosis; PE, pulmonary embolism; SVT, superficial vein thrombosis; MI, myocardial infarction; VTE, venous thromboembolism; CVC, central venous catheter; COPD, chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus.

Table 2 Major Conditions of Acquired Thrombocytopenia*

- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Antiphospholipid antibody syndrome
- Heparin-induced thrombocytopenia
- Disseminated intravascular coagulation
- Drug induced (antiplatelet drugs)
- Liver/renal/bone marrow failure; cancer patients[†]

*Rare congenital or hereditary disorders of platelet function are excluded here.

[†]Because of treatments and/or bone marrow invasion.

consistently show that VTE prophylaxis is significantly underused, with only 30 to 50% eligible patients receiving such prophylaxis. The IMPROVE study,⁸ the RIETE Registry,⁹ and the ENDORSE study¹⁰ extend this concept to show that, in addition to comorbidities (liver disease, renal failure), chronic polypharmacy and advancing age, which are often present in medical patients, enhance the tendency to bleed when heparins or fondaparinux are used. Nonpharmacological methods of thromboprophylaxis (graduated compression stockings, intermittent pneumatic compression devices, and venous foot pumps) reduce VTE without increasing the risk of bleeding.¹¹ However, efforts are still needed to optimize their use, alone or in combination with pharmacological prophylaxis.⁷ Several risk assessment models are available to facilitate VTE primary prophylaxis in medical patients, with prospective validation still ongoing for some of them.^{12,13}

Subjects at a potentially high bleeding risk are commonly excluded in trials on VTE prophylaxis. These exclusions include patients with liver cirrhosis, thrombocytopenia and/or clotting abnormalities, thrombocytopenia in patients with malignancy, and patients with concomitant antiplatelet therapy (aspirin and/or clopidogrel). Thrombocytopenia and/or platelet dysfunction occur in many different settings (Table 2), and at least 25% of subjects admitted to medical departments exhibit thrombocytopenia and/or platelet dysfunction for a variety of causes. In the absence of definitive indications and guidelines to define VTE prophylactic strategies in our medical school, a search of the literature was performed, and we discuss and comment on these results here.

METHODS

We have approached the issue of primary prophylaxis of VTE in medical patients with a particular emphasis on three relevant issues:

1. VTE prophylaxis in patients with liver cirrhosis
2. VTE prophylaxis in patients with thrombocytopenia
3. VTE prophylaxis in patients on chronic antiplatelet treatment

The analysis of these issues was based on experimental and intervention studies and using the series of key terms listed in the following section.

SEARCH STRATEGY AND EVIDENCE ACQUISITION

Using the key terms *VTE prophylaxis AND thrombocytopenia*, *VTE AND prophylaxis*; *VTE AND liver cirrhosis*, *VTE prophylaxis AND liver disease*, *VTE prophylaxis AND cancer*, *VTE prophylaxis AND hematological malignancy*, *VTE prophylaxis AND antiplatelet therapy*, *VTE prophylaxis AND aspirin*, *VTE prophylaxis AND clopidogrel*, *aspirin withdrawal AND cardiovascular risk*, *perioperative time AND antiplatelet drugs*, we searched the Medline database as well as the trial register of the Cochrane group to identify studies (retrospective studies; prospective studies; intervention trials; reviews) published in the area. For an in-depth scrutiny of the information provided by the individual papers, their references were also critically reviewed. In each case and for each report, in addition to clinical relevance, the inherent potential limitations of the individual analyses were also assessed.

THROMBOCYTOPENIA IN LIVER DISEASE

Clotting abnormalities (caused by lowered synthesis of vitamin K-dependent clotting factors and lowered platelet counts) sustain the common perception of patients with liver cirrhosis as having a high risk of bleeding. Accordingly, as a result of the perceived risk of bleeding complications, current guidelines on VTE prophylaxis do not specifically comment on these subjects. However, in patients with liver cirrhosis and with $> 50,000$ platelets/ μL , decreased synthesis of anticoagulant factors and normal generation of thrombin, resulting in a near-normal hemostatic balance, has been reported.¹⁴⁻¹⁶ In keeping with this, portal vein thrombosis and occlusion of small intrahepatic vein branches are common findings in these patients.¹⁷ Autopsy and explantation studies have shown portal vein thrombosis in as many as 54% of cirrhotic patients.^{18,19} The onset of portal vein thrombosis strongly affects the prognosis of liver patients.²⁰ In addition to an increased risk of thrombosis in the splanchnic area, idiopathic VTE is more frequent in the patients with liver disease than in the general population.¹⁴ Northup et al compared 113 cirrhotic inpatients with evidence of VTE with 113 cirrhotic patients without such evidence.¹⁷ The authors found that 0.5% of cirrhotic inpatients had a nonsplanchnic VTE. Consistent with the finding that clotting abnormalities do not protect from thrombosis, neither the international normalized ratio nor the platelet count predicted the thrombotic risk. The fact that low albumin concentrations in these patients independently predicted

the risk of VTE (odds ratio [OR]: 0.24; 95% confidence interval [CI], 0.10 to 0.55; $p < 0.01$), suggested an indirect relation between its circulating levels and natural anticoagulant protein deficiency in liver disease.¹⁷

A nationwide Danish population-based case-control study²¹ evaluated the relative risk (RR) of VTE in 99,444 patients affected by liver disease with or without cirrhosis, compared with 496,872 healthy controls. Patients with liver disease had a significantly higher RR of VTE, ranging from 1.74 (95% CI, 1.54 to 1.95) for cirrhotic patients to 1.87 (95% CI 95%, 1.73 to 2.03) for noncirrhotic liver disease. When the analysis was restricted to 67,519 cases with idiopathic VTE and 308,614 population controls, slightly higher RR were found: 2.06 (95% CI, 1.79 to 2.38) for cirrhotic patients and 2.10 (95% CI, 1.91 to 2.31) for noncirrhotic liver disease.²¹ In addition to clotting abnormalities,²² chronic liver disease is characterized by platelet dysfunction and by a variable extent of thrombocytopenia (platelet count $< 140,000/\mu\text{L}$), the latter due to platelet sequestration by the spleen and to bone marrow suppression by chronic hepatitis C infection and/or by interferon therapy. The association between chronic hepatitis C infection and thrombocytopenia is still unclear, but hepatic fibrosis may play a role. The liver is the main site for the production of thrombopoietin, the cytokine that controls megakaryocyte development and platelet production.²³ Thrombopoietin levels and platelet counts are related to liver function impairment and to the severity of fibrosis in chronic hepatitis C infection.²³⁻²⁶ The skin bleeding time is prolonged in up to 40% of cirrhotic patients.¹⁶ However, prolongation of this in vivo hemostatic test does not predict the risk of bleeding in these patients.¹⁶ Platelet adhesion studies show that, under flow conditions, high levels of von Willebrand factor (VWF), a major laboratory feature in patients with cirrhosis, may compensate the defect of platelet number and function.²⁷

Thrombocytopenia is present in $\sim 75\%$ of cirrhotic patients.²⁸ Mild (75,000 to 150,000/ μL) or moderate thrombocytopenia (50,000 to 75,000/ μL , present in $\sim 13\%$ of cirrhotic patients) does not interfere with prophylaxis and treatment decisions. However, a negligible spontaneous bleeding risk has been documented for invasive procedures (endoscopic procedures, biopsy, dental extractions) in patients with chronic liver disease and platelet counts $\geq 50,000/\mu\text{L}$.²⁸ Conversely, a not negligible spontaneous hemorrhagic risk is present in severe thrombocytopenia ($< 50,000/\mu\text{L}$).²⁸

VTE prophylaxis in cirrhotic patients should be considered in conditions of a high thromboembolic risk and in subjects with platelet counts $\geq 50,000/\mu\text{L}$ (Table 3). When major risk factors for bleeding are present, graduated compression stockings or intermittent pneumatic compression should be considered.^{7,11,14} Patients with lower platelet counts should be considered

Table 3 Venous Thromboembolism Prophylaxis in Patients with Liver Cirrhosis and/or Thrombocytopenia: Strategies of Prevention

Spontaneous Hemorrhagic Risk	Recommendation
Low risk: Platelet count > 90,000	Pharmacological prophylaxis*
Intermediate risk: Platelet count 50,000–90,000	Pharmacological prophylaxis*
High risk: Platelet count < 50,000	Prophylaxis in selected cases* Nonpharmacological methods†

*VTE prophylaxis should be performed as long as the additional risk factor for thrombosis is present.

†Graduated compression stockings, intermittent pneumatic compression, devices, and venous foot pumps.

for prophylaxis on an individual basis.²⁸ In this respect, heparins are safe and effective in the treatment of portal vein thrombosis in patients with liver cirrhosis.²⁹

OTHER CAUSES OF THROMBOCYTOPENIA

With the exception of subjects with active bleeding or with contraindications to anticoagulation, the Guidelines of the American Society of Clinical Oncology suggest that antithrombotic prophylaxis should be considered in hospitalized cancer patients when platelet counts are > 50,000/ μ L.³⁰ Nevertheless, thromboprophylaxis is performed only in limited cases of patients with malignancy. The Italian Society for Studies on Haemostasis and Thrombosis has promoted guidelines for the management of patients with platelet disorders or thrombocytopenia, underlining that the risk of spontaneous bleeding increases dramatically for very low platelet counts (< 10,000 to 20,000/ μ L) and that the bleeding risk is different among different patients according to the underlying cause of thrombocytopenia.³¹ Compared with primary immune thrombocytopenia, platelet dysfunction induced by antiplatelet drugs or associated with liver disease is at a lower risk of bleeding.³¹ In the following paragraphs, we review the data concerning the risk of venous thrombosis and the need for thromboprophylaxis in several conditions of thrombocytopenia.

Thrombosis that complicates malignancy³² is a frequent cause of death in cancer patients,^{33,34} and up to 20% of patients with VTE are affected by overt or occult tumors.³⁵ In addition to the inherent thrombogenic potential of some forms of cancer, the thromboembolic risk in malignancy is further increased by prolonged immobilization, surgery, radiotherapy, chemotherapy, hormonal therapy, and by central venous catheter (CVC) insertion.^{36–39} The rate of VTE in patients with hematologic malignancies, who often have severe thrombocytopenia, is as high as in patients with solid tumors.⁴⁰ The role of thromboprophylaxis in patients with solid tumors is well established.³⁰ In contrast, only limited data are available in patients with hematologic malignancies.

Intensive chemotherapy regimens in patients with cancer are often complicated by severe thrombocytopenia. The potentially higher than expected bleeding risk

of these individuals hampers anticoagulant prophylaxis, even when needed. Herishanu et al⁴¹ reported the effect of VTE treatment (for CVC-related venous thrombosis) or prophylaxis with the LMWH enoxaparin in 10 patients (6 men, 4 women) with hematologic malignancies and severe thrombocytopenia (< 20,000/ μ L) due to high-dose chemotherapy for bone marrow transplantation. In these patients, no major bleeding was observed. During the periods of severe thrombocytopenia, the LMWH dosage was adjusted according to the estimated individual risk of bleeding. In the group treated with prophylactic doses of LMWH, the daily dosage ranged from 0.25 mg/kg to 1 mg/kg; in the group treated for CVC-related venous thrombosis, the daily dosage ranged from 0.5 mg/kg to 2 mg/kg. The authors concluded that this individualized strategy is safe and efficient in these patients to balance bleeding and thrombotic risks.⁴¹

A prospective, observational, and multicenter study assessed the incidence of, and the risk factors for, symptomatic VTE after CVC positioning in patients with hematologic malignancies.⁴² A total of 458 consecutive CVC insertions were registered in 416 patients (81.2% of whom had thrombocytopenia [$< 50,000/\mu$ L] and 53.2% with severe thrombocytopenia [$< 10,000/\mu$ L]). The incidence of events over the observation period (3 months or up to catheter removal) was 1.5% for CVC-related DVT; 0.4% for lower limb DVT; 1.3% and 0.6% for total and fatal PE, respectively; 3.9% for superficial thrombophlebitis; 6.1% for CVC malfunction/occlusion of thrombotic origin, and 1.1% for atherothrombotic events.⁴² Severe bleeding and CVC-related infections were observed in 3.5% and 4.6% of patients, respectively. None of the variables evaluated helped predict venous thrombosis; only thrombocytopenia was associated with a trend for a lower risk (OR: 0.52; 95% CI, 0.26 to 1.07). No severe bleeding was observed in those patients who had received antithrombotic prophylaxis (daily dosages > 5000 UI of UFH, or LMWH).⁴²

Thrombocytopenia in patients with the antiphospholipid syndrome is usually not associated with bleeding complications. By interacting with platelets, antiphospholipids (aPL) increase platelet activation and, in turn, thrombosis. Regardless of thrombocytopenia

nia, in patients with aPL, primary VTE prophylaxis in high-risk conditions (immobilization, acute respiratory diseases) should be considered.^{43,44}

Disseminated intravascular coagulation (DIC) is a condition carrying both a high hemorrhagic and thrombotic risk. Because of the raised thrombotic risk, immobilized patients with DIC in intensive care units should be considered for heparins/fondaparinux prophylaxis.⁴⁵

PATIENTS ON ANTIPLATELET THERAPY

The number of people presently treated with aspirin for primary and secondary prophylaxis (coronary heart disease, myocardial infarction, coronary artery bypass grafting, ischemic stroke, individuals at high cardiovascular risk [e.g., patients with diabetes] or on dual antiplatelet therapy [aspirin plus clopidogrel] for percutaneous coronary intervention and coronary stents) is dramatically increasing. These patients should be considered for VTE prophylaxis (pharmacological or mechanical) in cases of hospitalizations for ischemic stroke, acute medical illnesses, congestive heart failure, acute respiratory disease, or sepsis. The Antiplatelet Trialists' Collaboration meta-analysis showed a 25% risk reduction of PE in vascular patients treated with aspirin.⁴⁶ Thus aspirin is not as efficient as heparins in reducing VTE risk, and the American College of Chest Physicians Guidelines⁷ recommend not routinely administering aspirin for VTE prophylaxis either in surgery or in medical patients. In surgery, the usual tendency in patients on treatment with aspirin and/or

other antiplatelet agents was to withdraw the administration of these drugs for 7 to 10 days, and replace them with UFH or with LMWH.⁴⁷ However, a meta-analysis for the secondary prevention of coronary artery disease (50,279 patients) showed that, after aspirin withdrawal, there is a threefold increase in cardiac complications rate (OR: 3.14; $p < 0.0001$), with the maximal risk (up to 90-fold) observed in patients with coronary stent implantations (OR: 89.78; $p < 0.0001$).⁴⁸ The risk of arterial thrombosis recurrence during temporary antiplatelet therapy withdrawal is even higher in patients on dual antiplatelet therapy.⁴⁹ However, the use of UFH or LMWH for VTE prevention is considered safe in patients on antiplatelet treatment for prevention of ischemic stroke recurrence.⁵⁰ Likewise, the safety of the association of antiplatelet drugs with mechanical leg compression for prevention of VTE is established.

RECOMMENDATIONS

Venous Thromboembolism Prophylaxis in Patients with Liver Disease

In cirrhotic patients, VTE prophylaxis should be considered in subjects at high thromboembolic risk with a platelet count $\geq 50,000/\mu\text{L}$ (Table 3) and should be performed as long as the additional risk factor(s) for venous thrombosis is (are) present. In patients with very low platelet counts and abnormal coagulation tests, prophylaxis should be considered on an individual basis.

Table 4 Management of Medical Patients on Antiplatelet Treatment Who Require Venous Thromboembolism Prophylaxis*

CVD/CHD Risk	Recommendation
Low risk <ul style="list-style-type: none"> • > 6 months after MI, PCI, BMS, CABG, stroke • > 12 months after stroke (if with complications) 	Stop antiplatelet therapy and give prophylactic dose of LMWH [†]
Intermediate CVD/CHD risk <ul style="list-style-type: none"> • 6–24 weeks after MI, PCI with BMS, CABG, stroke (no complication) • > 12 months after DES • Low ejection fraction • Diabetes mellitus • High-risk stents (long, proximal, multiple, overlapping, small vessels, bifurcation) 	Maintain antiplatelet drug + add LMWH (prophylactic dose) [†]
High CVD/CHD risk <ul style="list-style-type: none"> • < 6 weeks after MI, PCI, BMS, CABG • < 6 months after the same if complications occur • < 12 months after high-risk DES • < 2 weeks after stroke 	Maintain antiplatelet drug + add LMWH (prophylactic dose) [†]

*See Kamphuisen and Agnelli⁵⁰ for further details.

[†]Venous thromboembolism prophylaxis should be performed as long as the additional risk factor for thrombosis is present.

CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; BMS, bare metal stent; CABG, coronary artery bypass grafting; LMWH, low molecular weight heparin; DES, drug-eluting stent.

Venous Thromboembolism Prophylaxis in Subjects with Other Thrombocytopenias

The risk of spontaneous bleeding increases dramatically for platelet counts $< 10,000$ to $20,000/\mu\text{L}$. The risk of bleeding is different among different patients, according to the cause of thrombocytopenia. Regardless of thrombocytopenia, thromboprophylaxis is mandatory in patients with aPL and in patients with DIC in intensive care units.

In conditions of a high thrombotic risk, an individualized antithrombotic strategy is safe and efficient. In patients with hematologic malignancies, thrombocytopenia is associated with a trend to a lower risk of symptomatic VTE after CVC positioning. No severe bleeding is observed in patients with hematologic malignancies who receive heparins.

Venous Thromboembolism Prophylaxis in Patients on Chronic Antiplatelet Therapy

In patients with intermediate/high risk of cardiovascular events (previous cardiovascular event or recent stent implantation) hospitalized for a medical condition (ischemic stroke, acute medical illness, congestive heart failure, respiratory acute disease, sepsis), it is sound to maintain antiplatelet therapy and to add UFH, LMWH, or fondaparinux for VTE prophylaxis as long as the additional risk factor for thrombosis is present.

In patients at low cardiovascular risk or with a high tendency to bleed, the risk-benefit ratio between cardiovascular recurrence and VTE prevention should be carefully evaluated. In these patients, withdrawing aspirin during VTE prophylaxis with UFH, LMWH, or fondaparinux (i.e., during the time of hospitalization or the time of exposure to newer VTE risk conditions) may be considered (Table 4).

Patients with acute coronary syndromes are routinely treated with dual antiplatelet therapy for 2 to 4 weeks after percutaneous dilation, 6 weeks after the implantation of a bare metal stent, and 12 months after a drug-eluting stent implantation. Withdrawing antiplatelet agents during this time frame has to be avoided, and adjunctive VTE prophylaxis with UFH, LMWH, or fondaparinux when needed should be evaluated on an individual basis.

AREAS OF FUTURE RESEARCH AND CONCLUSION

With the exception of cases of severe thrombocytopenia, VTE prevention in thrombocytopenic patients hospitalized for acute medical conditions should be considered. However, the prophylaxis in patients with thrombocytopenia and/or platelet dysfunction is often avoided. To improve information in the area, the following concepts should be pursued.

- Clinical effectiveness and cost effectiveness in preventing VTE provide the rationale for the routine use of short-course UFH, LMWH, or fondaparinux in hospitalized medical patients. However, current knowledge implies that VTE prophylaxis should be performed as long as the additional risk factors for thrombosis are present. New data emerging on cirrhotic coagulopathy argue for their bleeding risk as less severe than expected. Similar considerations may be applied to other patients with abnormal platelet counts or to vascular patients on chronic antiplatelet therapy. Because of their higher than normal bleeding risk, ad hoc information on the optimal prophylaxis and optimal duration of this prophylaxis in medical patients are needed, with emphasis on those with thrombocytopenia and/or platelet dysfunction.
- Studies in ischemic stroke suggest that thromboprophylaxis with low doses of LMWH is safe in patients on aspirin treatment.⁵⁰ However, data from randomized trials on the net benefit of pharmacological VTE prophylaxis in the setting of patients on long-term antiplatelet therapy are lacking. Guidelines on the perioperative handling of patients on antiplatelet therapy have been established^{49,51} that may be useful to define strategies/newer trials in hospitalized medical patients on chronic antiplatelet therapy who might benefit from VTE prophylaxis.
- A relatively unstable coagulation balance is present in cirrhotic patients that may easily be perturbed (hemorrhages and thrombosis are both possible). Laboratory coagulation tests as well as the bleeding time do not predict the risk of bleeding; nor do they provide information as to protection from thrombosis. VTE prevention and treatment in cirrhotic patients, even if thrombocytopenic, is often necessary. In view of the easy and relatively inexpensive measurements of serum albumin, to improve prophylaxis in this setting the correlation between low albumin concentration and the risk of VTE should be evaluated in large numbers of individuals. Moreover, the extent to which low albumin levels reliably predict low levels of anticoagulant protein C (i.e., of a protein with a shorter half-life) should be quantified.
- Analyzing plasmas from 134 cirrhotic patients and from 131 healthy controls, Tripodi et al²² found that the median ratio of thrombin generation, assessed by the endogenous thrombin potential with/without thrombomodulin was higher in patients than in controls (0.80 versus 0.66; $p < 0.001$). This argues for a hypercoagulable state in liver cirrhosis that is maximal in Child-Pugh class C patients. This hypercoagulable state (median ratio of thrombin generation: 0.86) is similar to that observed in patients with congenital protein C deficiency (median ratio of thrombin generation: 0.76). Whether correcting low levels of

protein C in subjects with cirrhosis will affect their tendency to thrombose as well as their thrombocytopenia-related tendency to bleed should be elucidated.

- In cirrhotic patients, protein C levels decrease proportionally to the Child-Pugh classes.²² Raised circulating levels of factor VIII are reported in cirrhotic patients. The increases in this coagulation protein are related to the Child-Pugh class (the highest levels, mean value ~200%, are found in Child-Pugh class C).²² Whether, in addition to low protein C, raised circulating levels of factor VIII and VWF will help define a bleeding/thrombotic score in liver disease that also takes into consideration thrombocytopenia should be properly explored.

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