this policy, as severe toxic effects of the drug such as bone marrow aplasia and microangiopathic thrombocytopenia, albeit less frequent than ticlopidine, have been described, which might be dose-dependent. The above limitations of ticlopidine and clopidogrel have fostered the search for new $P2Y_{12}$ antagonists. Prasugrel is a new thienopyridine compound with a much faster onset of action than clopidogrel. In a cross-over study, it has been demonstrated that a 60 mg loading dose prasugrel provided rapid and high-grade, irreversible inhibition of ADP-induced platelet aggregation even in those subjects who responded poorly to a standard loading dose of clopidogrel. In addition, prasugrel, at a maintenance dose of 10 mg q.d. prove more effective than clopidogrel both at the approved maintenenace dose (75 mg q.d.) and at the dose of 150 mg q.d. The higher potency of prasugrel compared to clopidogrel reflects more efficient conversion of the pro-drug to the active metabolite. Prasugrel has proven safe in a Phase II trial. In addition, it was more effective than clopidogrel in reducing MACEs in ACS patients undergoing PCI, although its use was also associetd with increased incidence of bleeding. Cangrelor is a fast-acting and rapidlyreversible direct $P2Y_{12}$ antagonist, which was proven safe in Phase II trials and is currently under evaluation in Phase III trials. The effects of the oral administration to patients with atherosclerosis of AZD640, the first oral reversible P2Y12 antagonist, have recently been reported. The DISPERSE study randomized in a double-blind fashion 200 stable atherosclerotic outpatients, who were on treatment with aspirin 75-100 mg once daily, to AZD6140 (50 mg BID, 100 mg BID, 200 mg BID, or 400 mg once daily) or clopidogrel 75 mg once daily for 28 days. The study showed that AZD6140 at doses above 50 mg BID more effectively inhibited platelet aggregation and with less variability than clopidogrel. In addition, the inhibition of platelet aggregation by AZD6140 was very rapid (2 hours post-dose, 96±6.1% for 400 mg once daily) compared to that of clopidogrel. The incidence of bleeding events tended to be higher in patients treated with the 3 higher doses of AZD6140, compared to that observed in patients treated with 50 mg BID or clopidogrel. Perhaps of more concern than the higher incidence of bleeding complications, which can be predicted for treatments that very effectively inhibit platelet function, was the unexpected, relatively high frequency of dyspnoea, which appeared to increase with increasing doses of AZD6140 (10% with 50 mg BID or 100 mg BID, 16% with 200 mg BID, and 20% with 400 mg QD). Another phase II study, DISPERSE-2, showed that the incidence of bleeding complications associated with AZD 6140 was similar to that associated with clopiodgrel. Again AZD6140 was associated with increased incidence of dyspnoea. AZD6140 is currently undergoing Phase III evaluation (PLATO trial), which will address the issues of its efficacy and safety. In conclusion, the pharmacopeia of drugs inhibiting the platelet $P2Y_{12}$ receptor for ADP is rapidly expanding. In the near future, physicians will have a panel of different $P2Y_{12}$ inhibitors to choose from, which will enable them to tailor the most appropriate antithrombotic therapy to the individual patient and risk situation.

PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLISM I

THROMBOPHILIA AND PREGNANCY COMPLICATIONS

B. Brenner

Rambam, Health Care Campus Haifa, Israel

Thrombophilic risk factors are common and can be found in 5% to 25% of Caucasian populations. Because pregnancy is an acquired hypercoagulable state, women having thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or at the postpartum period.[1] *Thrombophilia and fetal loss*. The risk for fetal loss is greater in homozygotes than in heterozygotes with FVL and in female siblings of thrombophilic women who have FVL. A recent meta-analysis demonstrated that FVL is associated with early (OR 2.01, 95% CI, 1.13, 3.58) and late (OR 7.83, 95% CI, 2.83, 21.67) recurrent fetal loss.[2] Fetal loss has also been associated with prothrombin mutation (PTM) but not with the methylenetetrahydrofolate reductase (MTHFR) TT polymorphism. Combined thrombophilic defects were documented in 31 (21%) of 145 women who experienced pregnancy loss, compared with 8 (5.5%) of 145 in control subjects.[3] Differences in type of pregnancy loss (ie, primary or secondary, isolated or recurrent, consecutive or nonconsecutive) and timing (ie, first, second, or third trimester) may also influence the magnitude of these Recently, Lissalde-Lavigne and colleagues[4] reported findings from the NOHA First study. The multivariate analysis clearly demonstrate an overall association between unexplained first pregnancy loss and the two thrombophilic risks factors and PTM Factor V Leiden. As unexplained first pregnancy loss occurred in approximately 10% of gestations, the findings of this study may have significant clinical impact. A recent study by Gris and colleagues[5] demonstrated that in women who had thrombophilia and previous one pregnancy loss after 10 weeks' gestation, enoxaparin at a dose of 40 mg daily resulted in a significantly better live birth rate compared with low-dose aspirin (86% *vs.* 29%, respectively). The differences were found in women who had FVL and factor II G20210A and in women who had protein S deficiency. LIVE-ENOX multicenter, prospective, randomized study recently conducted in Israel[6] comparing two doses of enoxaparin, 40 mg/d and 40 mg/every 12 hours, starting at 5 to 10 weeks of gestation, throughout pregnancy, and for 6 weeks postpartum to women who had thrombophilia and pregnancy loss. Of the 180 women enrolled, live birth rate before the study was only 28%, but during the study, live birth rates were 84% for the 40 mg/d group and 78% for the 80 mg/d group. Late gestational complications decreased after enoxaparin treatment. LMWH prophylaxis during pregnancy enables modulation of systemic hemostatic parameters by way of inhibition of factor Xa and increases in plasmatic total and free TFPI levels and may also modulate TFPI levels at the placental level.[7] *Future perspectives.* The role of aspirin, if any, in the setting of thrombophilia and vascular gestational

abnormalities remains to be confirmed. As complete thrombophilia work-up is currently elaborate and costly, screening tests are highly warranted. One such potential assay is the protein C global test, which in a preliminary study was found to be abnormal in most women who had recurrent fetal loss and could also identify women who have recurrent fetal loss who do not have any other thrombophilic defect.[8] A recent study in mice demonstrates that a fetomaternal cross-talk in the placental vascular bed may result in control of coagulation by trophoblast cells[9] and preliminary studies in human presented at the recent ISTH Geneva meeting by the NOHA study group, suggest that maternal and paternal EPCR polymorphisms may contribute to risk of fetal loss. Several prospective multicenter controlled studies are currently underway in women with thrombophilia and pregnancy loss.

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THROMBOSIS IN HEMATOLOGICAL MALIGNANCIES

A. Falanga

Hemostasis and Thrombosis Center, Hematology Oncology Dept., Ospedali Riuniti, Bergamo, Italy

The rate of venous thromboembolism (VTE) in patients with acute leukemia or lymphomas is comparable to that of other *high risk* cancer types. Chemotherapy and anti-angiogenic drugs increase the thrombotic risk in patients with lymphomas, acute leukemias and multiple myeloma (MM). Patients with hematologic malignancies often present with a hypercoagulable state or chronic disseminated intravascular coagulation (DIC), in the absence of active thrombosis and/or bleeding. Malignant cell procoagulant properties, cytotoxic therapies, and concomitant infections are major determinants for clotting activation in hematologic malignancies. In acute leukemia, clinical manifestations range from localized venous or arterial thrombosis to a diffuse, life-threatening thrombohemorrhagic syndrome (THS). All *trans* retinoic acid (ATRA) has greatly improved the management of acute promyelocytic leukemia (APL), but has not significantly changed the rate of early hemorrhagic deaths and may actually promote thrombosis. Randomized, controlled trials (RCTs) of different prophylactic regimens to prevent VTE or THS in hematologic malignancies are urgently needed, particularly in patients with lymphoma or MM during chemotherapy, and in patients with APL. Anticoagulant therapy is a particular challenge in patients with hematologic malignancies, since these patients are at very high risk for hemorrhage. No guidelines are available for the prophylaxis or treatment of VTE; extrapolations can be made from existing guidelines for management of patients with other malignancies – prolonged periods of treatment-induced thrombocytopenia in patients with hematologic malignancies, however, require a more judicious application of standard anticoagulant approaches. Use of the newer anticoagulants will require careful assessment of hemorrhagic risk in this group of high risk patients but may be justified under special circumstances.

INDIRECT FACTOR Xa INHIBITORS IN ACUTE CORONARY SYNDROMES

M. Lettino

Cardiology Department, CCU IRCCS S.Matteo Hospital, Pavia, Italy

Acute Coronary Syndromes (ACS) share a common pathophysiology: atherosclerotic plaque rupture or erosion followed by a superimposed thrombosis. Both platelets and the coagulation cascade are involved in the process; in particular activated factor X (fXa) binds to factor Va on the activated platelet surface to form tha prothrombinase complex, which in turn promotes thrombin generation. Factor Xa inhibitors include agents that block factor Xa directly or indirectly. Fondaparinux is the first of a new class of synthetic antithrombotic agents inhibiting fXa. It is a fully synthetically produced pentasaccharide, which specifically binds to antithrombin (AT) with high affinity and by this mechanism specifically inhibits fXa. Fondaparinux has been widely tested in the large spectrum of ACS. The two phase III trials MICHELANGELO OASIS 5 and OASIS 6 have demonstrated that fondaparinux is both equally effective as enoxaparin in reducing risk of major cardiovascular adverse events in patients with NSTE-ACS and superior to unfractionated heparin or placebo in reducing risk of death and myocardial infarction in STEMI patients. The drug is associated with substantially less bleeding, mainly when compared with enoxaparin, with a highly significant better net clinical benefit. Otamixaban and Rivaroxaban are direct fXa inhibitors now under investigation in ACS patients. Otamixaban is an intravenous agent being currently tested in a phase II trial enrolling moderate-to-high risk Non ST-Elevation ACS patients with a planned early invasive strategy. Rivaroxaban is an oral agent with a predictable dose-dependent anticoagulant effect, which has the potential for the prevention of major cardiac adverse event in coronary artery disease and is also being assessed in patients with acute coronary syndromes.

VENOUS THROMBOSIS IN THE ELDERLY

C. Berteanu,[1] M. Berteanu,[2] L. Azamfirei,[3] D. Ionescu[4]

[1]Department of Anaesthesia & Intensive Care-University Hospital Bagdasar-Arseni; [2]Bucharest Medical University; [3]Tg. Mures Medical University; [4]Cluj Medical University, Bucharest, Romania

The elderly are at increased risk for developing venous thromboembolic disease (VTED), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). VTED is an entity distinct from arterial thromboembolic disease, which may occur in conditions such as atrial fibrillation or with the use of prosthetic cardiac valves. DVT usually occurs in the veins of the lower extremities (due to dependency causing stasis and slowed venous return to the heart) but can also occur in the upper extremities, cerebral sinus, liver, and retinal veins. PE in the setting of DVT results from a fragment of clot being dislodged and transported through the bloodstream to the lungs, which may cause potentially fatal respiratory compromise. Additionally, DVT can lead to a postthrombotic syndrome characterized by pain, swelling, and ulceration in the affected limb. Etiology, diagnosis and therapy may all be different in the elderly compared with young or middle-aged adults. For several diseases, risk factors have been shown to have reverse effects in old age, e.g. high serum cholesterol and hypertension no longer mortality among the very old, and may even have an opposite effect, which has been named *reverse epidemiology*.[1-4] Not only may risk factors act differently at various age, but the results of their effects may also differ because of the exponential rise in incidence of venous thrombosis with age. Risk factors may have a different prevalence in the old than in the young (e.g. immobilization, cancer, and drug use). It is remarkable that while it can easily be shown that the majority of cases of thrombosis occur in the old, and a substantial number among the very old, studies into etiology and management are almost completely restricted to younger age groups. While the overall incidence of venous thrombosis is 1-2 per 1000 year, it is close to 1% per year in the very old. The case-fatality rate of thrombosis is high in the elderly, particularly among those with cancer. The risk of major hemorrhage during anticoagulant treatment is also strongly age-dependent contributing to the vulnerability of the old patient with thrombosis. There has been no notable change in the overall incidence of VTED over the past few decades.[5,6] The increased risk of VTED was first noted in patients undergoing major ortopedic and general surgery procedures. Although there are increasing numbers of these procedures performed in geriatric patients, the benefit of prophylactic anticoagulation has been clearly demonstrated, and its use has become the standard of care in most circumstances. Unfortunately, the risk of VTED is often underestimated in geriatric medical patients (those immobilized, hospitalized, or residing in a nursing home with medical or neurological disease such as stroke, cancer, chronic obstructive pulmonary disease, or cardiac disease), in part because many patients with VTED, including those who die from PE, have no clinical manifestations, so that this condition remains underrecgnized. As this population of patients grows, an examination of the risks and benefits of prophylactic anticoagulation for the prevention of VTED in geriatric medical patients is timely. Several methods of prophylaxis have been studied. Nonpharmacological strategies include elastic compression stockings, intermittent pneumatic compression, leg elevation, and early mobilization, but these approaches are generally regarded as adjunctive to anticoagulants unless anticoagulants are contraindicated. Anticoagulants that have been studied and are in use for thromboprophylaxis in elderly medical patients include low-dose unfractionated heparin (UFH), low-molecular weight heparins (LMWHs), heparinoid, and adjusted-dose warfarin, although LMWHs are most commonly employed at the present time. The use of aspirin to inhibit platelet aggregation is nof little benefit in preventing VTED. New modalities for primary prevention of VTED, including the synthetic pentasaccharide fondaparinux and the direct thrombin inhibitor ximelagatran, have not undergone sufficient clinical testing in geriatric medical patients at this time. In conclusion venous thrombosis in the elderly should be a focus of future studies. Environmental risk factors, particularly immobilization, play an important in the etiology of thrombosis in the elderly, and cause a substantial proportion of the total number of cses because risk factor associated with disease are more prevalent in old than in young individuals. Abnormalities in the clotting system, either genetic or acquired, appear to be equally and possibly more important in the elderly than in young and middle-aged individuals. Despite the higher risk of morbidity and mortality from VTED in geriatric medical patients, prophylactic anticoagulation is underused. Awareness of the factors that contribute to the risk of VTED in elderly patients is essential to the identification of candidates for prophylaxis. The advantages of LMWHs over low-dose UFH for thromboprophylaxis include predictable dose-related effects with no need for routine laboratory monitoring, equal or better efficacy and safety, and the potential for use in the ambulatory and long-term care setting.

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