15. Aguilar-Martinez P, Esculie-Coste C, Bismuth M, Giansily-Blaizot M, Larrey D, Schved JF. Transferrin receptor-2 gene and non-C282Y homozygous patients with hemochromatosis. Blood Cells Mol Dis 2001;27:290-3.
16. Barton EH, West PA, Rivers CA, Barton JC, Acton RT. Transferrin receptor-2 (TFR2) mutation Y250X in Alabama Caucasian and African American subjects with and without primary iron overload. Blood Cells Mol Dis 2001;27:279-84.
17. Lee PL, Halloran C, West C, Beutler E. Mutation analysis in the transferring receptor 2 gene in patients with iron overload. Blood Cell Mol Dis 2001;27:285-9.
18. Roetto A, Totaro A, Piperno A, Piga A, Longo F, Garozzo G, et al. New mutations inactivating transferrin receptor 2 in hemochromatosis type 3. Blood 2001;97:2555-60.
19. Girelli D, Bozzini C, Roetto A, Alberti F, Daraio F, Colombari R, et al. Clinical and pathologic findings in hemochromatosis type 3 due to a novel mutation in transferrin receptor 2 gene. Gastroenterology 2002;122: 1295-302.
20. Piperno A, Roetto A, Mariani R, Pelucchi S, Corengia C, Daraio F, et al. Homozygosity for transferrin receptor-2 Y250X mutation induces early iron overload. Haematologica 2004; 89:359-60.
21. Biasiotto G, Belloli S, Ruggeri G, Zanella I, Gerardi G, Corrado M, et al. Identification of new mutations of the HFE, hepcidin, and transferrin receptor 2 genes by denaturing HPLC analysis of individuals with biochemical indications of iron overload. Clin Chem 2003;49:1981-8.
22. Mattman A, Huntsman D, Lockitch G, Langlois S, Buskard N, Ralston D, et al.Transferrin receptor 2 (TfR2) and HFE mutational analysis in non-C282Y iron overload: identification of a novel TfR2 mutation. Blood 2002;100:1075-7.
23. Le Gac G, Mons F, Jacolot S, Scotet V, Ferec C, Frebourg T. Early onset hereditary hemochromatosis resulting from a novel TFR2 gene nonsense mutation (R105X) in two siblings of north French descent. Br J Haematol 2004;125:674-8.
24. Hattori A, Wakusawa S, Hayashi H, Harashima A, Sanae F, Kawanaka M, et al. AVAQ 594-597 deletion of the TfR2 gene in a Japanese family with hemochromatosis. Hepatol Res 2003;26:154-6.
25. Harris ZL, Takahashi Y, Miyajima H, Serizawa M, MacGillivray RT, Gitlin JD. Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. Proc Natl Acad Sci USA 1995;92:2539-43.
26. Sohda T, Okubo R, Kamimura S, Ohkawara T. Hemochromatosis with HFE gene mutation in a Japanese patient. Am J Gastroenterol 2001;96:2487-8.
27. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood 2003;102:783-8.
28. Roetto A, Papanikolaou G, Politou M, Alberti F, Girelli D, Christakis J, et al. Mutant antimicrobial peptide hepcidin is associated with severe juvenile hemochromatosis. Nat Genet 2003;33:21-2.
29. Papanikolaou G, Samuels ME, Ludwig EH, MacDonald ML, Franchini PL, Dube MP, et al. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. Nat Genet 2004;36:77-82.
30. Bridle KR, Frazer DM, Wilkins SJ, Dixon JL, Purdie DM, Crawford DH, et al. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homoeostasis. Lancet 2003; 361:669-73.
31. Gehrke SG, Kulaksiz H, Herrmann T, Riedel HD, Bents K, Veltkamp C, et al. Expression of hepcidin in hereditary hemochromatosis: evidence for a regulation in response to the serum transferrin saturation and to non-transferrin-bound iron. Blood 2003;102:371-6.
32. Kawabata H, Fleming RE, Gui D, Moon SY, Saitoh T, O'kelly J, et al. Expression of hepcidin is down-regulated in TfR2 mutant mice manifesting a phenotype of hereditary hemochromatosis. Blood 2005;105:376-81.
33. Nemeth E, Roetto A, Garozzo G, Ganz T, Camaschella C. Hepcidin is decreased in TFR2-Hemochromatosis. Blood 2005; 105:1803-6.
34. Johnson MB, Enns CA. Regulation of transferrin receptor 2 by transferrin: diferric transferrin regulates transferrin receptor 2 protein stability. Blood 2004;104:4287-93.
35. Robb A, Wessling-Resnick M.Regulation of transferrin receptor 2 protein levels by transferrin. Blood 2004;104:4294-9.
36. Vogt TM, Blackwell AD, Giannetti AM, Bjorkman PJ, Enns CA. Heterotypic interactions between transferrin receptor and transferrin receptor 2. Blood 2003;101:2008–14.
37. Pietrangelo A, Caleffi A, Henrion J, Ferrara F, Corradini E, Kulaksiz H, et al. Juvenile haemochromatosis associated with pathogenic mutations of adult hemochromatosis genes. Gastroenterology 2005;128:470-9.

The future of anticoagulation clinics: a journey to thrombosis centers?

Coumarins were discovered in the late 1930s as a result of decades of research spent identifying the cause of a hemorrhagic disease in cattle. At first they were used as rat poison, but from the mid 1950s they began to have some clinical impact.[1] Since their efficacy was proved in several clinical studies,[2] the use of coumarins, in particular warfarin, has increased progressively in many countries. Concomitantly with their clinical use, there was a need for more precise laboratory control, since bleeding can at times be fatal. Over the years the prothrombin time, as a monitoring test to tailor the dosage of oral anticoagulants in the single patient, underwent a process of standardization, which was started in 1962 by Leon Poller.[3] In 1983 Kirkwood[4] proposed the international normalized ratio (INR) system, approved by the World Health Organisation. Despite a few limitations, the INR, recently reviewed by Poller,[5] is currently the standard way to express the result of a prothrombin time test, and has served to validate the efficacy of oral anticoagulants in a number of clinical studies.

The organization of anticoagulation clinics in Italy

The need for periodic monitoring and the complexity of the therapy have given rise to a whole culture on this topic and led to the creation of Centers for the surveillance of anticoagulation drugs in Europe and the US: the so-called anticoagulation clinics.

In Italy the Federation for the Surveillance of Anticoagulated Patients (FCSA)[6] was founded in 1989 with the aim of improving standardization in oral anticoagulation therapy in the country. From the initial 8 founding institutions, the Federation has grown into a network of more than 300 anticoagulation clinics spread over the country. From a survey performed by the FCSA in 2003 it emerged that these clinics were located in general laboratories (39%), trasfusion services (15%), or departments of internal medicine (10%), hematology (9%), cardiology (8%), and angiology (4%). A minority (15%) have declared that they are thrombosis services. A more detailed survey will be necessary to know exactly how Anticoagulation Clinics actually work in terms of activities other than the surveillance of oral anticoagulation. Each year national congresses, courses, and workshops are held for physicians, technicians, and nurses. Many studies have been conducted and published by FCSA Centers in the past few years. These have dealt with several aspects of oral anticoagulant therapy, such as hemorrhagic[7] and thrombotic complications,[8] atrial fibrillation,[9] different degrees of anticoagulation in prosthetic heart valves,[10] malignancy,[11] the elderly,[12] computerized therapy management,[13] and the patient's own point of view.[14]

A guide to oral anticoagulant therapy has recently been published.[15] Moreover, studies on portable coagulometers and on the management of therapy using these devices[16] have led to the publication of a consensus document by the FCSA on this topic.[17]

Nevertheless, for some time now a new concept has been taking shape: new anti-thrombotic drugs will replace Anticoagulation Clinics and perhaps cause their downfall, since it has been shown in clinical trials that these new drugs will probably render laboratory monitoring unnecessary in clinical practice. If we consider that

the main indications for these new drugs will be non-valvular atrial fibrillation and deep vein thrombosis, it is immediately obvious that coumarins could be replaced almost entirely.

Anticoagulation clinics and the new drugs

But what are these drugs? They are ximelagatran, pentasaccharides with a long half-life (idraparinux), oral direct Xa inhibitors, and a combination of antiplatelet drugs (aspirin and clopidogrel). When they are introduced on the market in the near future, patients will be able to take two tablets a day or self-administer an injection once a week, without ever having to go to an Anticoagulation Clinic for monitoring.

Ximelagatran, a direct thrombin inhibitor, is a prodrug that is rapidly adsorbed by the gastrointestinal tract and transformed into melagatran, whose clearance is well correlated with that of creatinine. It is a dipeptide analog of the Aα chain of fibrinogen that competitively inhibits thrombin. The half-life of melagatran is about 4-7 hours; therefore the oral dose of 24 mg is given twice daily.[18] Ximelagatran has been studied successfully in primary[19] and secondary prophylaxis[20] of deep vein thrombosis. Moreover, in patients with non-valvular atrial fibrillation, it showed non-inferiority compared to warfarin.[21,22] However an increase in serum alanine aminotransferase has been found in 6% of the treated patients.

Idraparinux, a pentasaccharide modified to obtain a higher affinity to antithrombin and a half-life of about 130 h,[23] is currently being studied in a large trial, which began recently. The design of this study is to randomize about 5,700 patients to once-weekly idraparinux or warfarin for the prevention of cardio-embolic stroke in atrial fibrillation (AMADEUS).[24] Moreover, idraparinux has been evaluated in a phase II trial in the secondary prevention of venous thromboembolism.[25]

Oral direct Xa inhibitors, recently evaluated in coronary heart disease[26] and percutaneous angioplasty,[27] will challenge coumarins further in the primary and secondary prophylaxis of thromboembolism. Finally aspirin and clopidogrel are being investigated in a large trial involving 6,700 patients with atrial fibrillation (ACTIVE).[28]

One question immediately arises: if anticoagulation clinics are destined to disappear in the near future, because their primary purpose, the surveillance of coumarin treatment, will no longer be necessary, what should we do with them? Should they be dismantled? We believe it would be a terrible mistake if they were, for several reasons which we shall try to outline here.

Counselling on antithrombotic drugs

In the first place anticoagulation clinics could become counselling centers for the anti-thrombotic drugs that will be used in the near future. Today one of the main tasks of the Centers is whether or not to confirm the indication for oral anticoagulants, heparins, or antiplatelet drugs. In other words anticoagulation clinics should improve this ability further by proposing the most appropriate antithrombotic treatment in each patient. Today there still is a gray area in which a correct indication for oral anticoagulants is difficult to identify (e.g. dilated cardiomyopathy, patent foramen ovale, aortic plaque),[29] and we often find patients with an incorrect indication for oral anticoagulants. The ISCOAT study[7] showed that patients with peripheral arteriopathy or non-cardioembolic ischemic stroke, who do not have an indication for oral anticoagulants, had the highest risk of bleeding. It was also been shown that when general practitioners prescribed oral anticoagulants, the indications were inappropriate in 25%of the patients.[30] On the other hand physicians are often reluctant to prescribe oral anticoagulants to patients over 75 years of age with atrial fibrillation, despite clear evidence that this is an appropriate indication.[31] If this incorrect behavior is of concern today, it could become even worse in the near future when more therapeutic choices are available, especially if left in not very expert hands. Anticoagulation Clinics therefore should be considered reference points for antithrombotic drug counselling.

The treatment of drug complications will be another role for the Anticoagulation Clinics, since the reversal of the new anticoagulant drugs has not yet been studied extensively and may therefore prove difficult.[32] In particular, it may require good practice to manage critical patients and handle expensive hemostatic drugs.[33]

Surveillance of antithrombotic drugs

Another crucial aspect when dealing with new anticoagulants or new antithrombotic drugs is adherence to therapy. It is known that patients requiring long-term therapy omit about 40% of their daily medication,[34] while 10 to 26% of patients on oral anticoagulants are non-compliant, leading to therapy instability.[35] Educating patients has been shown to be crucial to the quality of oral anticoagulant management, since the time spent in the therapeutic range may drop in patients who are not aware of why they are taking coumarins or who forget the daily dose.[36] Though the new drugs have not shown any interaction with food or other drugs, as coumarins have done,[37,38] it still seems unwise for us to administer drugs and leave patients unattended during therapy. In our experience a questionnaire on a few basic aspects of oral anticoagulant therapy significantly improved the time spent in the therapeutic range.[36] Periodic visits, for example every four months, could also be important, as the patient's education may improve over time, as has been suggested with coumarins.[39] A questionnaire could be administered to remind patients of the danger of omitting the antithrombotic drug and information could be given about general health issues, regular drug assumption, and hemorrhagic or thrombotic episodes. A laboratory control of serum alanine aminotransferase and creatinine could also be helpful, especially in the elderly. Deterioration of renal function could cause an accumulation of ximelagatran and idraparinux and could lead to overdose and bleeding.[18,41]

Anticoagulation clinics and the laboratory

One of the requirements of Anticoagulation Clinics in Italy is that they should be able to perform the monitoring test (PT) in the same Center or use a laboratory within the same hospital. Moreover they must also be able to perform periodic laboratory controls. Though the number of daily PT may drop dramatically in the future, laboratories could be a very good background for other activities. Anticoagulation Clinics should deal with the quality control of diagnostics for inherited thrombophilia, lupus anticoagulant, and homocystinemia. As a matter of fact in the first case, early data have shown that standardization has not been reached yet in the detection of mutations in factor V (FV: R506Q) and prothrombin (G20210A), the two most frequent DNA polymorphisms[42] associated with an increased risk of venous thromboembolism. An effort must be made therefore in this direction by planning standardization programs to improve the performance of clinical laboratories. The same should be said about screening for lupus anticoagu-

lant, which is now performed by a large number of Italian laboratories. Results published recently show that the sensitivity of lupus anticoagulant detection is satisfactory, but the specificity needs to be improved.[43]

Another aspect of thrombophilia was seen when a collaborative study was conducted on the comparison of methods used to measure blood concentrations of homocysteine,[44] a sulphured amino acid involved in the pathophysiology of venous and arterial thrombosis.[45,46] The results indicate that an international plasma standard would be useful to improve comparability in the measurement of homocysteinemia between laboratories. It may, therefore, be possible to organize periodic quality checks that should also involve the diagnostics of other thrombophilic defects, such as protein C and S deficiency. In particular, protein S detection, as pointed out a few years ago,[47] suffers from several analytical and interpretative pitfalls and there is a lack of guidelines on whether to perform the assay on free or total protein S and on how it should be performed. A collaborative study could oblige Centers to show data relating to the local population of healthy subjects and selected patients. The goals could be two: to clarify the role of protein S as a risk factor for venous thromboembolism and to implement a reliable measurement of protein S in daily laboratory practice.

Anticoagulation clinics will probably be involved in assaying D-dimer in the near future, concomitantly with the detection of residual vein thrombosis, since this information could be used as an aid to decide whether or not to continue anticoagulant therapy, though not necessarily with coumarin derivatives, considering the promising data published recently on the subject.[48,49]

Finally, anticoagulation clinics should counsel carriers of thrombophilic abnormalities.

Anticoagulation clinics and imaging diagnosis

Anticoagulation centers are generally integrated in hospitals equipped with radiological facilities, where a reliable diagnosis of thromboembolic events can be made. Diagnostics have advanced thanks to the imaging produced by multislice computed tomography (CT),[50] which has been shown to be more accurate than planar ventilation-perfusion pulmonary scintigraphy in the diagnosis of pulmonary embolism.[51] Moreover, it provides a direct visualization of emboli and/or other findings.[52] New diagnostic systems, such as CT lung perfusion,[53] magnetic resonance imaging,[54] and the possibility of examining pulmonary vessels together with the entire venous axis are now available.[55] It is expected that in the near future more sophisticated techniques, such as molecular imaging, will be available for the diagnosis of vascular obstruction. Molecular imaging in magnetic resonance with targeted paramagnetic microparticles is an emerging science aimed at the detection of the biochemical markers of diseases.[56] Doctors in Anticoagulation Clinics today could also acquire skills in this aspect of radiological diagnostics.

Conclusions

In conclusion, we can envisage numerous activities for Anticoagulation Clinics in the future. Some of these are new and others could be significantly improved. If they develop, they will lead to great results over the entire whole country by delivering an important service to the local population. In the near future, though coumarins will probably coexist with the new drugs for several years, the Centers could be transformed into Thrombosis Centers, possibly acknowledged by the Ministry of Health and consequently by local administrations.

This paper is about the future of Anticoagulation Clinics, but the future has already arrived for a number of them. The most advanced Anticoagulation Clinics should guide other less expert Centers by involving them in clinical studies and laboratory standardization.

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References

1. Mannucci PM, Poller L. Venous thrombosis and anticoagulant therapy. Historical review. Br J Haematol 2001;114:258-70.
2. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest 2004;126:204S-33S.
3. Poller L. The standardisation of oral anticoagulant treatment. The Manchester Regional Thromboplastin Scheme. Br Med J 1964;2:565-6.
4. Kirkwood TBL. Calibration of reference thromboplastin and standardisation of the prothrombin time ratio. Thromb Haemost 1983;36:230-6.
5. Poller L. International Normalized Ratio (INR): the first 20 years. J Thromb Haemost 2004;2:849-60.
6. Berrettini M. Anticoagulation clinics: the Italian experience. Haematologica 1997;82:713-7.
7. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996;348:423-8.
8. Palareti G, Manotti C, DAngelo A, Pengo V, Erba N, Moia M, et al. Thrombotic events during oral anticoagulant treatment: results of the inception-cohort, prospective, collaborative ISCOAT study: ISCOAT study group (Italian Study on Complications of Oral Anticoagulant Therapy). Thromb Haemost 1997;78:1438-43.
9. Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A multicenter inception cohort study. Thromb Haemost 2001;85:418-22.
10. Pengo V, Barbero F, Banzato A, Garelli E, Noventa F, Biasiolo A, et al. A comparison of a moderate with moderate-high intensity oral anticoagulant treatment in patients with mechanical heart valve prostheses. Thromb Haemost 1997; 77:839-44.
11. Palareti G, Legnani C, Lee A, Manotti C, Hirsh J, D'Angelo A et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost 2000;84:805-10.
12. Palareti G, Hirsh J, Legnani C, Manotti C, D'Angelo A, Pengo V, et al. Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. Arch Intern Med 2000; 28: 470-8.
13. Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). Haematologica 2001;86:1060-70.
14. Barcellona D, Contu P, Sorano GG, Pengo V, Marongiu F. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost 2000;83:49-53.
15. A guide to oral anticoagulant treatment. Haematologica 2003; 88 Suppl 2:1-47.
16. Tripodi A, Chantarangkul V, Mannucci PM. Near-patient testing devices to monitor oral anticoagulant therapy. Br J Haematol 2001;113:847-52.
17. Self-testing and self management of oral anticoagulant thera-

py: consensus of the italian federation of anticoagulation clinics. Haematologica 2003 Suppl 3;88:1-10.
18. Gustafsson D. Oral direct thrombin inhibitors in clinical development. J Intern Med 2003;254:322-34.
19. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost 2003; 1:2490-6.
20. Schulman S, Wahlander K, Lundstrom T Clason SB, Eriksson H. THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003;349:1713-21.
21. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. Lancet 2003;362:1691-98.
22. Verheugt FW. Can we pull the plug on warfarin in atrial fibrillation? Lancet 2003;362:1686-7.
23. Herbert JM, Herault JP, Bernat A, van Asterdam RG, Lormean JC, Petitou M. Biochemical and pharmacological properties of SANORG 34006, a potent and long-acting synthetic pentasaccharide. Blood 1998;91:4197-205.
24. Donnan GA, Dewey HM, Chambers BR. Warfarin for atrial fibrillation: the end of an era ? Lancet Neurol 2004;3:305-8.
25. Persist Investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg 3006) to replace warfarin for the secondary prevention of deep vein thrombosis: a phase II evaluation. J Thromb Haemost 2004;2:47-53.
26. Dyke CK, Becker RC, Kleiman NS, Hochman JS, Bovill EG, Lincoff AM, et al. First experience with direct factor Xa inhibition in patients with stable coronary disease: a pharmacokinetic and pharmacodynamic evaluation.Circulation 2002;105: 2385-91.
27. Alexander JH, Dyke CK, Yang H, Becker RC, Hasselblad V, Zillman LA, et al. Initial experience with factor-Xa inhibition in percutaneous coronary intervention: the XaNADU-PCI Pilot. J Thromb Haemost 2004;2:234-41.
28. Hankey GJ. Ongoing and planned trials of antiplatelet therapy in the acute and long-term management of patients with ischaemic brain syndromes: setting a new standard of care. Cerebrovasc Dis 2004;17 Suppl 3:11-6.
29. Cauli C, Barcellona D, Marongiu F. Oral anticoagulant therapy in the primary and secondary prophylaxis of stroke. Ital Heart J 2003;4:755-67.
30. Ruivard M, Berger C, Achaibi A Campagne C, Philippe P. Physician compliance with outpatient oral anticoagulant guidelines in Auvergne, France. J Gen Intern Med 2003;18: 903-7.
31. McCrory DC, Matchar DB, Samsa G, Sanders LL, Pritchett EL. Physician attitudes about anticoagulation for nonvalvular atrial fibrillation in the elderly. Arch Intern Med 1995;155:277-81.
32. Warkentin TE, Crowther MA. Reversing anticoagulants both old and new. Can J Anaesth 2002;49:S11-25.
33. Levi M, Bijsterveld NR, Keller TT. Recombinant factor VIIa as an antidote for anticoagulant treatment. Semin Hematol 2004; 41 Suppl 1:65-9.
34. Pearson RM. Who is taking their tablets? Br Med J 1982;285: 757-8.
35. van der Meer FJ, Briet E, Vandenbroucke JP, Sramek DI, Versluijs MR, Rosendaal FR. The role of compliance as a cause of instability in oral anticoagulant therapy. Br J Haematol 1997;98:893-900.
36. Barcellona D, Contu P, Marongiu F. Patient education and oral anticoagulant therapy. Haematologica 2002;87:1081-6.
37. Marongiu F, Sorano GG, Conti M, Mameli G, Biondi G, Licheri D, et al. Known vitamin K intake and management of poorly controlled oral anticoagulant therapy. Lancet 1992;340: 545-6.
38. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. Ann Intern Med 1994;121:676-83.
39. Barcellona D, Fenu L, Marongiu F. Oral anticoagulant therapy: should doctors change the way they give explanations to patients? Thromb Haemost 2003;90:159-60.
41. Koopman MMW, Buller HR. Short- and long-acting synthetic pentasaccharides. J Intern Med 2003;254:335-42.
42. Tripodi A, Peyvandi F, Chantarangkul V, Menegatti M, Mannucci PM. Relatively poor performance of clinical laboratories for DNA analyses in the detection of two thrombophilic mutations. A cause of concern. Thromb Haemost 2002;88: 690-1.
43. Tripodi A, Biasiolo A, Chantarangkul V, Pengo V. Lupus anticoagulant (LA) testing: performance of clinical laboratories assessed by a national survey using lyophilized affinity-purified immunoglobulin with LA activity. Clin Chem 2003;49: 1608-14.
44. Tripodi A, Chantarangkul V, Lombardi R, Lecchi A, Mannucci Pm, Cattaneo M. Multicenter study of homocysteine measurement: performance characteristics of different methods, influence of standards on interlaboratory agreement of results.Thromb Haemost 2001;85:291-5.
45. D'Angelo A, Mazzola G, Crippa L, Fermo I, Viganò D'Angelo S. Hyperhomocysteinemia and venous thromboembolic disease. Haematologica 1997;82:211-9.
46 Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis.Thromb Haemost 1999;81:165-76.
47. Faioni EM. Reliable estimates of plasma protein S levels: are we getting closer ? Thromb Haemost 2001;86:1139-40.
48. D'Angelo A and Piovella F. Optimal duration of oral anticoagulation therapy after a first episode of venous thromboembolism: where to go ? Haematologica 2002;87:1009-13.
49. Palareti G, Legnani C, Cosmi B, Valdre L, Lunghi B, Bernardi F, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation 2003;108:313-8.
50. Remy-Jardin M, Mastora I, Remy J. Pulmonary embolus imaging with multislice CT. J Radiol Clin North Am 2003;41:507-19.
51. Coche E, Verschuren F, Keyeux A, Goffette P, Goncette L, Hainaut P, et al. Diagnosis of acute pulmonary embolism in outpatients: comparison of thin-collimation multi-detector row spiral CT and planar ventilation-perfusion scintigraphy. Radiology 2003;229:757-65.
52. Ghaye B, Remy J, Remy-Jardin M. Non-traumatic thoracic emergencies: CT diagnosis of acute pulmonary embolism: the first 10 years. Eur Radiol 2002;12:1886-905.
53. Schoepf UJ, Bruening R, Konschitzky H, Becker Cr, Knez A, Weber J, et al. Pulmonary embolism: comprehensive diagnosis by using electron-beam CT for detection of emboli and assessment of pulmonary blood flow. Radiology 2000;21:693-700.
54. van Beek EJ, Wild JM, Fink C, Moody AR, Kauczor HU, Oudkerk M. MRI for the diagnosis of pulmonary embolism. J Magn Reson Imaging 2003;18:627-40.
55. Moll S. Use of combined CT venography and CT pulmonary arteriography. J Thromb Haemost 2003;1:637.
56. Moffat BA, Reddy GR, McConville P, Hall De, Chenevert TL, Kopelman RR, et al. A novel polyacrylamide magnetic nanoparticle contrast agent for molecular imaging using MRI. Mol Imaging 2003;2:324-32.