
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. Since their efficacy was proved in several clinical studies, 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. In 1983 Kirkwood proposed the international normalized ratio (INR) system, approved by the World Health Organisation. Despite a few limitations, the INR, recently reviewed by Poller, 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) 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 500 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%), transfusion services (15%), in 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 and thrombotic complications, atrial fibrillation, different degrees of anticoagulation, 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. In 1983 Kirkwood proposed the international normalized ratio (INR) system, approved by the World Health Organisation. Despite a few limitations, the INR, recently reviewed by Poller, 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.

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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 ximelagatan, pentasaccharides with a long half-life (idaraparinux), 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.

Ximelagatan, a direct thrombin inhibitor, is a prodrug that is rapidly absorbed by the gastrointestinal tract and transformed into melagatan, 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 melagatan is about 4-7 hours, therefore the oral dose of 24 mg is given twice daily. Ximelagatan has been studied successfully in primary and secondary prophylaxis of deep vein thrombosis. Moreover, in patients with non-valvular atrial fibrillation, it showed non-inferiority compared to warfarin. 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, 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 cardioembolic stroke in atrial fibrillation (AMADEUS). Moreover, idraparinux has been evaluated in a phase II trial in the secondary prevention of venous thromboembolism.

Oral direct Xa inhibitors, recently evaluated in coronary heart disease and percutaneous angioplasty, 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).

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), and we often find patients with an incorrect indication for oral anticoagulants. The ISCOAT study 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 shown that when general practitioners prescribed oral anticoagulants, the indications were inappropriate in 25% of the patients. 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. 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 the 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. In particular, it may require good practice to manage critical patients and handle expensive hemostatic drugs.

**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, while 10 to 26% of patients on oral anticoagulants are non-compliant, leading to therapy instability. 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. Though the new drugs have not shown any interaction with food or other drugs, as coumarins have done, 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. 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. 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 ximelagatan and idraparinux and could lead to overdose and bleeding.

**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 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 anticoag-
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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