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ANTICOAGULATION CLINICS: THE ITALIAN EXPERIENCE

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ABSTRACT

Background and Objective. The clinical quality of oral anticoagulant therapy (OAT) depends on how successful physicians and patients are in achieving and maintaining levels of anticoagulation capable of preventing thromboembolic events without increasing the risk of hemorrhagic complications. Concerning the patient, education and compliance are the major problems. As for the physician, on the other hand, the management of patients receiving OAT is a complex task that requires frequent laboratory testing, dosage regulation, prompt diagnosis and treatment of thromboembolic and hemorrhagic events. It requires educated and skilled personnel and a well-organized framework of services. Anticoagulation clinics, which provide patient education, close monitoring of prothrombin time and continuous clinical surveillance, may help in improving the overall quality of OAT.

Information sources. The authors have been working in this field contributing, original papers. In addition, the material examined in this article includes articles published in the journals covered by the Science Citation Index® and Medline®.

State of art and Perspectives. The concept of a coordinated network of medical services specifically devoted to the control of OAT was developed in the Netherlands following the model created by the late Professor Jordan, who in 1949 founded the first thrombosis center at the University of Utrecht. Many other anticoagulant clinics were organized on a voluntary basis in the following decades in the Netherlands. The *Dutch Federation of Thrombosis Centers* was founded in 1971 and each affiliated Center is formally recognized and supported by the central Government. Today, there is a nation-wide system of regionally centralized anticoagulant control for outpatients and home patients that counts approximately 70 anticoagulant clinics (thrombosis centers), covering more than 90% of the country. Similar global approaches to the management of patients receiving OAT were proposed in other countries. In the 1950's, a group of internists and surgeons at the University of Michigan, USA, developed a unit specifically devoted to the diagnosis and treatment of thromboembolic disease, and proposed common strategies, teaching and research programs. In 1959, Sevitt and Gallagher were the first to propose a formal recognition of an anticoagulant unit in Great Britain. Finally, the *Italian Federation of Centers for the Surveillance of Anticoagulant* (FCSA) therapies was founded in 1989. Nowadays, Italian anticoagulation clinics operating in the framework of the FCSA are still voluntary organizations which provide a specific medical service by continuously reorganizing the personnel, structures and resources available to meet increasing demands. Since OAT has a profound social impact, its control should not be left to the good will of dedicated people, but should instead represent a specific task of the public health system. The achievement of a formal recognition of federated centers is essential for their growth, but the unavoidable increase of the expenses needed to support anticoagulation clinics is difficult to bear in a public care system which is currently facing a substantial reduction of financial resources. In a fixed health care budget, a redistribution of existing resources is the only possible solution, but to achieve this goal, public authorities have to be convinced that the management of OAT in specific anticoagulation clinics is cost-effective. A more accurate estimate of costs is needed and should be performed by the FCSA. Finally, the FCSA should strengthen its contacts with patient organizations and other scientific associations in order to develop common action strategies for improving the quality of OAT.

Key words: coagulation, thrombosis, anticoagulant, anticoagulation clinic, bleeding

Since their discovery more than 60 years ago, oral anticoagulants have endured as remarkable drugs and are now the 14th-largest selling medication in the United States.[1] Previously accepted as the standard of care for patients with artificial valves and rheumatic heart disease with atrial fibrillation, its use is increasingly advocated in other conditions where emboli are known to occur.

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Studies that indicate the benefit of long-term oral anticoagulant therapy (OAT) have been presented in some papers discussed during the *First International Winter Meeting on Basic, Laboratory and Clinical Aspects of Thromboembolic Diseases, held in Cortina d'Ampezzo, Italy, on March 9-12, 1994*.[2-11] At the same time, strong evidence has been accumulated from randomized clinical trials indicating that long-term OAT is very effective in preventing stroke in the common condition of non-rheumatic atrial fibrillation.[12]

Although there are few doubts about the efficacy of OAT in the primary and secondary prevention of thromboembolic diseases, safety of the treatment is still a concern since anticoagulant-related bleeding is common and often serious. Bleeding complications may diminish the net benefit of therapy and lead physicians to avoid OAT in many patients. The risk of bleeding is related to several factors (the intensity of OAT, the presence of concomitant diseases, interaction with other therapies, age, etc.) and must be carefully evaluated in individual patients before making the clinical decision to start OAT: does the benefit of OAT outweigh the risk of bleeding?

As a consequence, the clinical quality of OAT depends on how successful physicians and patients are in achieving and maintaining levels of anticoagulation capable of preventing thromboembolic events without increasing the risk of hemorrhagic complications. Concerning the patient, education and compliance are the major problems. As for the physician, on the other hand, management of patients receiving OAT is a complex task that requires frequent laboratory testing, dosage regulation, prompt diagnosis and treatment of thromboembolic and hemorrhagic events. It requires educated and skilled personnel and a well-organized framework of services. Anticoagulation clinics, which provide patient education, close monitoring of prothrombin time and continuous clinical surveillance, may help in improving the overall quality of OAT.

The development of anticoagulation clinics

The concept of a coordinated network of medical services specifically devoted to the control of OAT was developed in the Netherlands following the model created by the late Professor Jordan, who in 1949 founded the first thrombosis center at the University of Utrecht. The basic philosophy was that only adequately maintained therapy is of value to a patient, and this requires considerable effort and dedication which cannot be offered if the staff is continually changing. Many other anticoagulant clinics were organized on a voluntary basis in the following decades in the Netherlands. The *Dutch Federation of Thrombosis Centers* was founded in 1971 and each affiliated center is formally recognized and supported by the central government. Today, there is a nation-wide system of regionally centralized anticoagulant control for outpatients and home patients that numbers approximately 70 anticoagulant clinics (thrombosis centers), covering more than 90% of the country.[13] The pivotal element in the activity of the center is the nurse who visits the patients; this nurse is in contact with the patient's referring physician and provides all relevant data for the regulation of the anticoagulant dosage by the center's physician.

Similar global approaches to the management of patients receiving OAT were proposed in other countries. In the 1950's, a group of internists and surgeons at the University of Michigan, USA, developed a unit specifically devoted to the diagnosis and treatment of thromboembolic disease, and proposed common strategies, teaching and research programs. In 1959, Sevitt and Gallagher were the first to propose a formal recognition of an anticoagulant unit in Great Britain. Finally, the *Italian Federation of Centers for the Surveillance of Anticoagulant* (FCSA) therapies was founded in 1989. The background and the main activities of the FCSA in the last seven years will be briefly summarized below.

The Italian experience

After the foundation of the *Italian Society of Hemostasis and Thrombosis* in 1970, researchers and physicians in some health institutions (hospitals, university clinics) started to organize specific services for the clinical diagnosis and treatment of thromboembolism. In these services, control of OAT soon became one of the main activities due to the large number of patients referred by general practictioners and various specialists. During the 1980's, specific issues and problems relating to standardization of laboratory tests and clinical surveillance became very popular in medical literature; at the same time, it was clear that control of OAT in Italy was being left to single physicians that held interest in internal medicine, cardiology or laboratory medicine, with no specific involvement of any national or regional institutions in the approach for an important public health issue. Many operators felt the need for a more homogeneous control of OAT on the national territory. As a result, the representatives of 9 major centers met in Parma on April 19, 1989, and founded the FCSA. By signing the statute of the Federation, the founders agreed upon a common strategy in order to achieve some important objectives:

a. favoring the development of centers specifically devoted to the surveillance of patients on OAT, which includes not just the laboratory test and the prescription of drugs, but also the rigorous selection of patients and meticulous monitoring

and follow-up;
b. standardizing the approaches for the conduction of OAT in the different centers;
c. recommending organizational and technical standards;
d. stimulating participation in quality control programs;
e. implementing continuous education programs for medical and paramedical personnel, and for the patients themselves;
f. planning and organizing multicenter studies;
g. making health administrators and politicians aware of the social impact of OAT and of the need for a formal recognition of the centers by the central goverment and local authorities.

In the first year after the institution of the FCSA, an informative campaign was carried out. Letters of presentation were sent to more than 1,500 health institutions including laboratories, clinics and university hospitals in our country. By the end of 1989, the FCSA had received the participation of about 70 centers, most of them located in northern Italy. To have an idea of the status of OAT control in the different centers, a questionnaire was submitted to all of the affiliated centers. As expected, the results of this survey showed a wide heterogeneity in the conduction of OAT in Italy. For example, only one half of the centers were able to meet the statutory requirement for the contextual execution of the laboratory test and regulation of the dosage, while the other half of the centers could provide only one of the two services. In the prescription of drugs, specific therapeutic ranges for each thromboembolic disease were adopted by a minority of centers; the INR system for the expression of laboratory tests was used by only 40% of the centers, and in 30% of these centers there was no record keeping of clinical events. It was clear that the FCSA's first goal was the definition of the operative standards to be met by affiliated centers in order to qualify as a member of the Federation.

From the initial survey it was also established that the participating centers were taking care of approximately 15,000 patients all over the country, while deductive estimates of the total number of treated patients in Italy on the basis of drug consumption gave figures more than ten times higher (approximately 180,000). A pharmacoepidemiologic study on oral anticoagulant use conducted in the area of Padua in 1992,[14] showed that self-medication is largely (50%) diffused among anticoagulated patients. Since half of these patients are not correctly anticoagulated, the potential danger of self-medication was suggested by the results of the study. General practitioners and cardiologists, who in the same study were found to be in charge of about 20% of patients, could provide a possible alternative to anticoagulation clinics, but there is evidence that few of them are willing to take on this extra task.[15] In addition, before the management of OAT is entrusted to primary care, a substantial program of education and guidance for general practitioners would be required.

The question of whether an anticoagulation clinic offers a real advantage to patients on long-term OAT in terms of clinical quality (i.e. prevention of thromboembolism and low rate of hemorrhagic complications) was addressed by another group of investigators at the Hematology Division in Bergamo.[16] The incidence of clinical events was assessed in a series of 271 patients on OAT for mechanical heart valve prosthesis before and after their enrollment in an anticoagulation clinic. Hemorrhagic complications decreased from 4.9 % to 1.0%/pt-yr (–80%), while thromboembolic events decreased from 6.6% to 0.6%/pt-yr (–91%), clearly demonstrating the utility of a service that is specifically dedicated to the surveillance of OAT.

As mentioned before, the data of the initial survey performed by the FCSA regarding the activity of affiliated centers indicated that education had to become the first and main priority of the federation. Since 1990, the Directive Board of the FCSA has organized annual meetings of representatives from all federated centers in order to discuss in detail the various aspects of OAT from both a practical and scientific point of view; at the end of each meeting, a consensus must be reached and formal guidelines have to be determined. The first booklet containing the FCSA recommendations for the management and surveillance of OAT was published in 1991, and is updated regularly. Specific guidelines for oral surgery in patients on OAT were published in 1994, and in the same year, the guidelines for heparin therapy were also completed. One publication was entirely devoted to the patient's education and contained all the fundamental rules to be followed during OAT. This booklet, called the "*vademecum* for patients on OAT", was distributed to all patients attending federated clinics and to the regional patient associations. A second booklet, called the "*passport* of patients on OAT", contained all the information on the location and activities of federated centers and was intended to facilitate OAT control during the vacation period and for patients who travel.

The promotion of the standardization of laboratory testing has been the second most important activity of the FCSA during the last seven years. The use of the INR system for expressing the results was strongly encouraged and is now considered mandatory for all federated centers. An external quality control program was implemented in 1992 to allow laboratories to evaluate their performance, and is repeated regularly twice a year. The interlaboratory variation of INR has decreased from an initial level of 15% to about 6% in the last evaluation.

Table 1. Minimum laboratory standards proposed by the FCSA for the management of oral anticoagulant therapy.

Adequate personnel: technicians, nurses, and physicians should be specifically educated on the management of OAT.
Organization : blood sampling, transport, storage and centrifugation should be carried out following appropriate methods for hemostatic assays.
Instruments : adequate centrifuges, coagulometers, and computers should be available.
Reagents: low, instrument-specific ISI thromboplastins should be used; the geometric means of 20 normal subjects should be used to obtain the ratio value.
Expression of the results: the INR system should be used.
Recording : both written and computer recording of data should be assured.
Quality control: internal and external programs should be regularly executed

Table 2. Minimum clinical standards proposed by the FCSA for the surveillance of oral anticoagulant therapy.

Drug prescription: the center takes the responsibility for the indication and counter-indications of OAT, for therapeutic ranges, for the duration of treatment, for the pharmacologic associations and for the therapeutic quality control (i.e., the assessment of the proportion of time spent by anticoagulated patients within the assigned therapeutic range).
Permanent education of patients
Recording of data and follow-up : systematic recording of laboratory data, dosage regulation, and all clinical events (thromboembolism and hemorrhagic complications) ; decision to stop the treatment; search of patients lost during follow-up.
Global clinical assistance: preparation of patients for surgery, availability of consultants (cardiologists, angiologists, dentists, etc.) and all services needed for the diagnosis of thromboembolism and bleeding (CT scan, endoscopy, etc).
Provision of consultants for other departments
Participation in educational meetings and research studies

During the last national meeting of the FCSA held in Bologna at the end of February 1996, the minimum operative standards in both the laboratory and clinical activities of affiliated centers were established (Tables 1 and 2).

Lastly, the FCSA has considered research as an essential part of its own development and as a tool for promoting knowledge about OAT. The first perspective study on the bleeding complications of OAT (ISCOAT) has been recently completed and the results of this important study were presented in this meeting by Dr. Palareti, President of the FCSA.

Future perspectives

Italian anticoagulation clinics operating in the framework of the FCSA are still voluntary organizations which provide a specific medical service by continuously re-organizing the personnel, structures and resources available to meet increasing demands. Since OAT has a profound social impact, its control should not be left to the good will of dedicated people, but should instead represent a specific task of the public health system. The achievement of a formal recognition of the federated centers is essential for their growth, but the unavoidable increase of the expenses needed to support anticoagulation clinics is difficult to bear in a public care system which is currently facing a substantial reduction of financial resources. In a fixed health care budget, a redistribution of existing resources is the only possible solution, but to achieve this goal, public authorities have to be convinced that the management of OAT in specific anticoagulation clinics is cost-effective. A more accurate estimate of costs is needed and should be performed by the FCSA.

In the last seven years, the number of new participants in the FCSA has increased steadily, so that today there are 135 active centers spread throughout the national territory. The FCSA should promote the institution of new centers in the weaker areas: to achieve this goal, the organization of periodic educational programs is essential to recruit new physicians, nurses and technicians. Further efforts are necessary to assess the quantity of services required, their organization and their location. Effective planning at an early stage will hopefully prevent the inappropriate treatment of patients and the poor monitoring and follow-up that occur if services are overwhelmed or not well-organized. Without the appropriate changes in service availability and organization, the wide use of OAT for the new, common indication of non-rheumatic atrial fibrillation is expected to produce more harm than benefit.[15]

In conclusion, FCSA should improve its contacts with patient organizations and with other scientific associations in order to develop common action strategies for improving the quality of OAT.

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