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A GUIDE TO ORAL ANTICOAGULANT TREATMENT

RECOMMENDATIONS OF THE ITALIAN FEDERATION OF ANTICOAGULATION CLINICS (FCSA)

THIRD GENERAL AGREEMENT

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FEDERATION OF ANTICOAGULATION CLINICS (FCSA) Web site: www.fcsa.it

Objectives and Characteristics

Oral anticoagulant therapy (OAT) is of significant and growing importance in the treatment and prevention of thromboembolic conditions and of vascular pathology in general. Numerous patients are undergoing this therapy in Italy and in the rest of the world, and their number is constantly growing. It is a well known fact that periodic clinical and laboratory checks are strictly necessary to optimize the therapeutic effectiveness of OAT and to minimize its risks. The management of patients in OAT includes a number of activities (laboratory tests, posology prescriptions, patients' training, scientific updating, monitoring and treatment of the complications, etc) that are carried out in an interdisciplinary context.

In 1989 a group of Italian Anticoagulant Clinics organized the Federation of Anticoagulation Clinics (FCSA), as a result of their awareness of the difficulties and of the number of practical problems that need to be addressed and solved in order to organize a valid OAT patients' management program and to co-ordinate the Clinics' work. The FCSA offers its services to Clinics that already manage this therapy, to Clinics that intend to start doing so and to individual physicians who have an interest in this subject.

The FCSA's goals are to:

- co-ordinate and support those engaged in this activity;
- help physicians and administrators understand the medical and social relevance of an efficient and effective OAT patients' management program, and to encourage regional and national institutions that are responsible for health policies to be more attentive;
- enhance the development of adequate Anticoagulation Clinics;
- produce practical *guides* to support proper therapy management;
- enhance the standardization of laboratory methods and the comparability of results among Anticoagulation Clinics;
- implement specific quality controls;
- contribute to the professional training and updating of the medical and paramedical personnel involved in these activities;
- offer member clinics practical support (by sending specifically prepared documentation, etc.) in carrying out their various activities, especially the literature required to inform general practitioners and patients;
- promote specific Conventions and to carry out multicenter studies on the clinical results and side effects of OAT.

How to join FCSA or to receive information about it

Clinics that intend to become Ordinary Members of the FCSA must:

- express prothrombin time results as an International Normalized Ratio;
- prescribe the daily dosage of the anticoagulant drug at the time of the prothrombin time determination;
- guarantee the clinical monitoring of the anticoagulated patients;
- participate in specific external quality controls promoted and managed by the FCSA;
- ensure that at least one physician of the Clinic takes one of the training courses periodically organized by the FCSA (this is necessary for the Clinic's membership to be fully valid)

Individual physicians who are interested in oral anticoagulation therapy and who intend joining the FCSA have no specific obligations.

Registration forms, information sheets and the Federation's Statutes can be requested from the FCSA office (c/o Dr. Vittorio Pengo, Clinica Cardiologica, Centro Trombosi, Ospedale "Ex-Busonera", via Gattamelata, 64 – 35128 Padua, Italy, phone/fax +39.049.8215658) or they can be downloaded from the Federation's web site at www.fcsa.it.

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Founded on April 19th, 1989.

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Bergamo	(Div. Di Ematologia, Ospedali Riuniti)
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RECOMMENDATIONS OF THE ITALIAN FEDERATION OF ANTICOAGULATION CLINICS (FCSA)

Guest Editor
Sabino Iliceto, Padua, Italy

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A GUIDE TO ORAL ANTICOAGULANT TREATMENT

RECOMMENDATIONS OF THE ITALIAN FEDERATION OF ANTICOAGULATION CLINICS (FCSA)

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1. ORAL ANTICOAGULATION THERAPY (OAT)

1.1. General principles of OAT

In recent years oral anticoagulation therapy (OAT) has been widely recommended for the treatment and/or prevention of numerous thromboembolic conditions. It has been applied in many fields of vascular pathology (venous or arterial), attracting the interest of physicians, surgeons, and medical specialists.

The aim of this therapy is to lower blood coagulability in a controlled and reversible way in order to obtain maximum protection against thromboembolic events with the lowest risk of bleeding. This level of anticoagulation, which varies according to the different diseases, is defined as the *therapeutic target* or *therapeutic range*. The first definition refers to an optimal value of the laboratory test, the second one to an interval between two values.

In order to optimize the effectiveness and safety of oral anticoagulants (OAs), patients must be checked periodically on the basis of clinical and laboratory (biological effect of the drug) testing. The management of patients during OAT therefore presupposes the convergence of a number of medical activities and expertise. Moreover, OAT entails following guidelines and performing checks, the results of which will only improve as medical and paramedical staffs become more experienced and specialized in these fields. All these skills are available in specialized centers (*Anticoagulation Clinics*).

1.2. The mechanism of action of oral anticoagulants (OA)

OAs are low molecular weight coumarin (dicoumarol)-derived compounds, which are rapidly and easily absorbed when administered orally. In blood, about 97-99% of the molecules bind to proteins (albumin) and hence only a small portion of the total amount (namely the free part which is in dynamic equilibrium with the bound portion) is pharmacologically active. The plasma half-life and thus the duration of action vary according to the type of drug and the dose administered.

Metabolism of OAS takes place almost entirely in the liver, whereas the metabolites (in part still pharmacologically active) are eliminated in the urine and feces.

These drugs carry out their action in hepatocytes by blocking the reduction of vitamin K-epoxide into vitamin K via competitive inhibition of the epoxide-reductase enzyme. In this way, the gamma-carboxylation (which is essential for their biological activity) of factors II, VII, IX, and X already synthesized by liver cells, is inhibited. It is thanks to residues of gamma-carboxyglutammic acid that the factors are bound by calcium ions to the negatively-charged phospholipid surface of cells, the site where clotting reactions occur. This effect is proportional to the dose of drug taken, provided many other biological and clinical conditions are the same.

2. ORAL ANTICOAGULANTS CURRENTLY AVAILABLE IN ITALY: FEATURES AND CHOICES

The following coumarin derivatives with anticoagulant properties are currently available on the Italian market:

a) Warfarin sodium [3-(α-acetonylbenzyl)-4-hydroxycoumarin] (COUMADIN®, Bristol-Myers Squibb, Rome, 5 mg tablets);
b) Acenocoumarol [3-(α-acetonyl-p-nitrobenzyl)-4-hydroxycoumarin] (SINTROM®, Novartis Farma S.p.A, Origgio, VA. 4 mg and 1 mg tablets).

Both products are rapidly absorbed by the gastrointestinal tract and reach peak plasma concentrations in 90 minutes, by binding to albumin. These substances concentrate in the liver, where they are metabolized through different routes, and are then excreted through the bile or the urine (*Hirsh 1991*). These two drugs (apart from their different pharmacological preparations: 5 mg, 4 mg, and 1 mg) differ essentially for their biological half-life.

Warfarin is produced as a racemic mixture of two optical isomers (L and R). Both forms are rapidly absorbed, but have quite different plasma half-lives, namely 46 hours for the R isomer and 32 hours for the L isomer, which is pharmacologically more active (*Suttie 1994*).

Acenocoumarol, on the other hand, has a half-life of approximately 12 hours, which is definitely shorter than the two forms of warfarin. It has been shown that this feature causes a fluctuation in the plasma levels of factor VII when acenocoumarol is administered every 24 hours (*Thijsen 1988*).

Based on these pharmacological and commercial features, it is theoretically possible to establish a criterion for directing the choice of the OA.

Warfarin, because of its longer half-life, has a more stable effect on inhibiting the synthesis of vitamin K-dependent factors and is theoretically the drug of choice in long-term treatment.

Acenocoumarol, on the one hand, offers the advan-

tage that its anticoagulant effect is supposedly much faster to reverse, which is useful in case of bleeding due to overdosage; moreover, it is available in Italy in two commercial preparations.

One milligram preparations could help to improve compliance for those patients (the elderly, the blind, the disabled, etc.) who have difficulty in cutting tablets of 5 mg warfarin if they need low doses of OAs.

In reality, recent studies have demonstrated that, in most patients, there are no clinically significant differences in OAT clinical management with one drug or the other (*Palareti 1996, Barcellona 1998*).

A third drug, phenprocoumon [3-(phenyl-propyl-4-hydroycoumarin] (Marcumar®, Roche, Basel, Switzerland) should be mentioned, because of its wide use in Europe, although it is not available in Italy. Phenprocoumon has a half-life of about 60 hours, and therefore therapeutic dosage variations of this drug would, theoretically, take longer to have an effect than those of acenocoumarol and warfarin.

3. INDICATIONS FOR OAT, THERAPEUTIC RANGES AND DURATION OF THERAPY

Some indications for OAT have been consolidated for decades, but new indications have emerged in more recent years. In fact, although well defined in general terms, this subject is continually undergoing minor adjustments due to the large number of trials (recently concluded or still underway) aimed at defining the best therapeutic regimens.

In particular, the following points are currently being studied:

1) the use of lower INR targets;
2) the validity of alternative therapeutic approaches using antiplatelet drugs, which are easier to manage; and
3) possible advantages of combining OAs with antiplatelet therapy.

The FCSA working group, which has examined this topic, thinks it is more correct to indicate the INR target for each indication rather than the therapeutic range, as in the past. This decision comes from the common experience that physicians tend to maintain their patients near the lower value of the therapeutic range, for fear of bleeding complications, and this often leads to an inadequate treatment. The use of a therapeutic target (instead of a range) has also been recently introduced into the Guidelines for OAT of the British Committee for Standards in Hematology (*BCSH, 1998*).

3.1. Heart valve prostheses

Chronic treatment with OAs significantly reduces the risk of thromboembolism in patients with prosthetic heart valves.

3.1.1. Mechanical prostheses

The typical INR range recommended for patients with mechanical heart valve prostheses has, for a long time, been 3-4.5 for a long time. However, American Scientific Societies have presented recommendations suggesting both the use of lower INR target values (*Bonow 1998, Stein 2001a*) to reduce bleeding risk, and a better characterization of patients in order to identify subgroups at lower embolic risk. A retrospective analysis (*Cannegieter 1995*) indicated the range of 3-4 as the one in which a lower number of total adverse events (thromboembolic+hemorrhagic) could be observed. Patients at higher embolic risk were those with a mitral prosthesis, with respect to those with an aortic prosthesis; in general, young patients (<50 years) had a very low thromboembolic risk. This study also highlighted that a target INR lower than 3.5 was associated with an excessive number of inadequately anticoagulated patients (i.e. with an INR < 2.5). Two studies published in the last decade have provided important new data. The results of the French AREVA study (*Acar 1996*) show that an INR between 2 and 3 may be suitable in patients with single and bileaflet tilting-disk prostheses (St. Jude type) in the aortic position and low embolic risk (sinus rhythm, normal ejection fraction, no previous thromboembolism and normal left atrium volume). Furthermore, an Italian study (*Pengo 1997*) demonstrated that a target INR of 3 is equally effective and is accompanied by fewer bleeding events with respect to a target INR of 4 in patients with mitral and aortic mechanical prostheses who had been operated at least 6 months earlier. In the light of this new evidence, for several patients it is possible to suggest an INR target lower than that previously recommended.

The association of OAT with antiplatelet drugs is sometimes indicated in patients at high risk and in those with concomitant ischemic heart disease, on a case-by-case basis. In these cases the more common association is with aspirin 100 mg/day, but in the first month after the positioning of a coronary stent, antiplatelet treatment with ticlopidine (or clopidogrel) and aspirin is needed while continuing OAT.

In this brief period, clinical surveillance and a careful monitoring of INR changes are of particular importance.

Finally, another point to be stressed is that in cases of recurrent embolism even with correct therapy, replacement surgery with the implantation of a biological prosthesis should be considered (*Israel 1994*). A new operation is also indicated in some patients with chronic anemia due to mechanical hemolysis, provided occult bleeding and other causes of anemia have been excluded.

3.1.2. Biological prostheses

Patients with biological prostheses have a relevant thromboembolic risk especially in the first three months after the operation. This is true especially for those with mitral prostheses who are commonly anticoagulated, while in some Clinics patients with aortic prostheses are treated only with aspirin, in the light of recent data from the literature (*Moinuddeen 1998*). Since the only available clinical trial on OAT in patients with biological prostheses included both aortic and mitral cases (*Turpie 1988*) and demonstrated the effectiveness of INR values included between 2 and 2.3, the FCSA, in agreement with the American College of Chest Physicians ACCP (*Stein 2001a*), recommends OAT (target INR 2.5) for three months after the operation in all patients with biological heart valve prostheses. After three months the treatment is stopped and possibly replaced by antiplatelet therapy (*Stein 2001a*). On the other hand, OAT must be continued in patients with chronic atrial fibrillation (long-term), the presence of intra-atrial thrombi at the time of surgery (until thrombi are no longer detectable), or embolism during treatment; in the last case it is recommended that OAT be continued for up to 12 months (target INR 2.5) (*Stein 2001a*).

Recommendations

A) Mechanical prostheses

Long-term OAT is indicated in all patients with mechanical heart valve prostheses. In patients with single and bileaflet tilting-disk prostheses in the aortic position (St. Jude, Medtronic Hall or Carbomedics type) and low embolic risk (sinus rhythm, normal ejection fraction, no previous thromboembolism, left atrium of normal volume), long-term OAT is recommended with a target INR of 2.5. Long-term OAT is recommended to patients with old caged-ball mechanical prostheses and in those with double prostheses, with a target INR of 3.5. In all the other patients with mechanical heart valve prostheses, long term OAT is recommended with a target INR of 3. In case of embolism during well conducted OAT or in patients at high risk, a target INR of 3.5 or the addition of aspirin 100 mg/day (or, in patients with intolerance to aspirin, dipyridamole 400 mg/day) can be considered on a case-by-case basis. The addition of aspirin should also be taken into consideration in patients with concomitant ischemic heart disease and it is mandatory (possibly in association with ticlopidine or clopidogrel in the early stage) when positioning coronary stents. OAT should be monitored with a particular care during the period of concomitant treatment with aspirin and ticlopidine or clopidogrel. In the case of recurring embolism in spite of appropriate treatment, a new operation must be taken into consideration, with implantation of a biological prosthesis. A new operation should also be considered in the case of chronic anemia from mechanical hemolysis.

B) Biological prostheses

OAT is recommended with a target INR of 2.5 for three months after the operation in patients with biological heart valve prostheses. After three months the treatment is interrupted and possibly replaced with antiplatelet therapy. In contrast, OAT should be continued in patients with chronic atrial fibrillation (long-term), in the presence of intra-atrial thrombi at the time of surgery (until thrombi are no longer detectable) or embolism during treatment (up to 12 months) (target INR of 2.5).

3.2. Heart valve diseases

Mitral valve prolapse, calcification of the mitral annulus and aortic and tricuspid valvulopathy in the absence of atrial fibrillation and a history of embolism are not indications for OAT. The same applies to asymptomatic patients with patent *foramen ovalis* and aneurysm of the atrial septum. In patients with pure mitral regurgitation, OAT is indicated only in particular cases with heart failure and cardiomegaly, on a case-by-case basis. In rheumatic mitral valvulopathy with sinus rhythm, OAT (target INR of 2.5) should be evaluated on the basis of the risk/benefit ratio for each patient, considering in particular the dilation of the left atrium (left atrial diameter > 55 mm), the severity of stenosis with its hemodynamic changes and the age of the patient. In contrast, OAT to achieve a target INR of 2.5 is always indicated in the presence of atrial fibrillation or previous embolism (Hirsh and Fuster 1994a) as also stated in both the ACCP (Salem 2001) and BCSH (BCSH 1998) recommendations.

Recommendations

In patients with rheumatic mitral valvulopathy and atrial fibrillation and/ or a history of embolism, long term OAT, with a target INR of 2.5, is recommended.

In patients with rheumatic mitral valvulopathy with sinus rhythm and without previous embolism, OAT can be indicated (long-term target INR of 2.5) on a case-by-case basis, according to the patient's clinical characteristics and echocardiography data (left atrial diameter > 55 mm).

No prophylaxis is necessary in the syndrome of mitral prolapse, calcification of the mitral annulus and aortic and tricuspid valve disease in the absence of atrial fibrillation and a history of embolism.

3.3. Intracardiac thrombosis

Regardless of the associated pathology, OAT (target INR of 2.5) is indicated in the case of thrombosis of the cardiac chambers, for as long as the thrombosis is detectable. As a result of recent technical progress in echocardiography (particularly transesophageal), which offers an increased sensitivity and precision in identifying and defining endocavitary thrombi, it is felt that OAT can be dis-

continued when the thrombus characteristics indicate a low embolic risk (stratified, without a pedunculus, not mobile). With regards to the atrial thrombi, even in the absence of specific studies, it seems reasonable to continue OAT independently of the ultrasound characteristics of the thrombi.

This recommendation, which should be carefully evaluated for each patient, is not based on the results of controlled clinical trials but is widely accepted (BCSH 1998).

Recommendations

In patients with thrombosis of the cardiac chambers, OAT is recommended (target INR of 2.5) until the thrombosis is no longer detectable.

OAT can also be interrupted when the thrombosis in the left ventricle has ultrasound characteristics associated with low embolic risk.

3.4. Atrial fibrillation (AF)

A) AF and associated mitral valve disease

OAT is mandatory in cases of AF associated with mitral valve disease. A target INR of 2.5 is generally recommended (*Hirsh and Fuster 1994a*); however, should embolic complications arise despite correct treatment, the FCSA recommends a target INR of 3.5 or combination with aspirin 100 mg daily. In these cases it is, however, appropriate to verify the compliance to treatment and to recommend investigations to identify the pathogenesis of thromboembolism.

B) Non-valvular-atrial fibrillation (NVAF)

Since the early 1990's, numerous studies have shown the effectiveness of OAT in the primary prevention of embolism, particularly cerebral, in patients with NVAF. Such studies include: AFASAK (*Petersen 1989*), BAATAF (*The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990*), SPAF I (*Stroke Prevention in Atrial Fibrillation Study 1991*), CAFA (*Connoly 1991*), and SPINAF (*Ezekowitz 1992*). In these patients, the FCSA, in agreement with ACCP (Albers 2001), recommends a target INR of 2.5, despite significant results being achieved in two studies (SPINAF and BAATAF) even with lower anticoagulation levels (INR 1.4–2.8 and 1.5–2.7, respectively). Lower INR values might be appropriate in particular subgroups of patients. A problem that has not been completely clarified yet is the risk/benefit ratio of the treatment in patients aged 75 or more. In such patients, OAT is more effective than aspirin (325 mg/day), as shown in SPAF II (*Stroke Prevention in Atrial Fibrillation Investigators 1994*), but it is associated with a greater risk of hemorrhagic complications. Elderly subjects and other high risk categories were randomized in a new study (SPAF III, 1996) to receive either enough warfarin to maintain an INR between 2.0 and 3.0 or warfarin to obtain a maximum INR of 1.5, together with ASA 325 mg/day. This study demonstrated that in NVAF patients with a high risk of stroke, the higher intensity OAT significantly reduced thromboembolic complications, compared to the treatment with ASA and low intensity OAT, with no differences in hemorrhagic complications.

These data have been further confirmed in a retrospective study that highlighted how OA dosages that maintain INR below 2.0 increase the risk of thromboembolism, and that this risk reaches its maximum value in the absence of treatment (INR=1) (*Hylek, 1996*). The results of these two studies led other researchers to prematurely close their studies on the effectiveness of very low dosages of warfarin in preventing thromboembolism. As a matter of fact, the AFASAK 2 (*Gullov 1998*) and the MIWAF (*Pengo 1998*) studies were interrupted because the data collected confirmed the results of SPAF III: that is, low intensity OAT cannot prevent the formation and embolization of left atrial thrombi. In conclusion, stroke prevention is not achieved with very low intensity anticoagulation and it can only be partially obtained with ASA in low risk patients.

The first 5 studies on the use of OA in NVAF were evaluated in a meta-analysis (*Atrial Fibrillation Investigators 1994*). The patients in the placebo group had an annual incidence of thromboembolism of 4.5%; OA reduced this incidence to 1.4% per year (risk reduction = 68%). Warfarin was capable of reducing stroke risk in all age groups, except for patients younger than 65 years without other risk factors. The annual stroke incidence in this group was 1% both with or without OA prophylaxis. The meta-analysis also highlighted that the independent risk factors for strokes were age, previous thromboembolism, hypertension and diabetes.

The same analysis of risk factors in the low dosage warfarin plus aspirin group of the SPAF III study (*SPAF III 1998*) confirmed that previous thromboembolism, hypertension (systolic BP >160 mm Hg) and advanced age in women are risk factors. Moreover, heart failure in the previous three months (or an ejection fraction < 25% at echocardiography) was also considered a risk factor, while diabetes was not comprised among risk factors in this study. Elderly patients with at least one risk factor were considered, in both analyses, at high risk of stroke (about 8% per year). In a more recent analysis of all participants in the ASA or ASA plus very low warfarin dosage arm of the SPAF studies, all the risk factors for stroke mentioned above were confirmed, but it also emerged that female patients and estrogen therapy are further independent risk factors, while a regular alcohol intake seems to be a protective factor (*Hart 1999*).

The FCSA's recommendations are substantially the same as those of the ACCP's sixth consensus conference (*Albers 2001*), at which it was decided

to consider the major risk factors of thromboembolism as the risk factors that appear in both the meta-analyses, while diabetes and coronary artery disease were considered as minor risk factors. However, some reservations have been made about the indiscriminate treatment with OAs of all patients with NVAF over 75 years of age. This is a very relevant issue in clinical practice, since most patients with AF are, in fact, over 75 years of age.

It should be stressed here that the BCSH (*BCSH 1998*) highlights that the decision to use OAT in elderly patients with NVAF and other associated pathologies should be taken on a case-by-case basis. It is known that the bleeding risk in patients treated with OA increases with age (*Palareti 1996, Fihn 1996*). Other bleeding risk factors have been reported in the literature, but require confirmation from other studies. Previous gastrointestinal bleeding seems to be a significant risk factor (*Landefeld 1989a*), while other factors such as previous stroke and the presence of some associated conditions (recent myocardial infarction, serum creatinine > 1.5 mg/dL, hematocrit < 0.30, diabetes) do not seem to be as significant (*Beyth 1998*). Recently, data analysis of patients with NVAF from the ISCOAT study (*Pengo 2001a*) led to the conclusion that the risk of a major hemorrhage in these patients is significantly higher in those over 75 years of age. As a matter of fact, the frequency of major bleeding in these patients is 5.1% per year, while that of thromboembolism is only 3.5% per year when there are no other associated risk factors (*Atrial Fibrillation Investigators 1994*). As a result, OAT does not seem to be justified in all patients >75 years. International guidelines on antithrombotic prophylaxis in patients with AF include only OAs or aspirin.

The absence of indobufen in the North American market is the principal reason why it is not included in the ACCP's recommendations. It is worth mentioning that the *Italian Study of Atrial Fibrillation* (SIFA) (*Morocutti,1997*) randomized 916 AF patients with recent TIA or stroke (without residual disability) to receive either indobufen or warfarin. Results did not show a significant difference in the incidence of primary endpoints (ischemic or hemorrhagic non-fatal stroke, systemic embolism, non-fatal myocardial infarction, pulmonary embolism and vascular death) between the two groups (10.6% indobufen, 9% warfarin). Total bleeding complications were 0.6% in the indobufen group and 5.1% in the warfarin group. This study, although it has some limitations, gives a basis for a valid alternative to warfarin in the secondary prevention of strokes in elderly patients with AF. Further confirmation is expected from the *Studio Italiano Fibrillazione Atriale II* (SIFA II), in which indobufen is compared with ASA in patients with contraindications to OAT. According to the *Family of trials* scheme, this study will enrol 2,200 patients, 1,300 of whom in a primary prevention study and 900 in a secondary prevention study. The follow-up will last 42 months.

Recommendations

A) AF associated with mitral valve disease

Long-term OAT with a target INR of 2.5 is recommended in patients with AF associated with mitral valve disease.

In case of embolism during OAT in patients with mitral valve disease and AF, a higher INR target (3.5) or the addition of antiplatelet treatment such as aspirin (100–325 mg) are recommended.

B) NVAF

Long-term antithrombotic prophylaxis is recommended in patients with NVAF, according to the following scheme:

Risk factors	*Recommended treatment*
One major risk factor§ or > 1 minor risk factor***	*Warfarin (target INR of 2.5)*
1 minor risk factor	*ASA 325 mg/day or warfarin (target INR of 2.5)*
No risk factor	*ASA 325 mg/day*

**Major risk factors: Previous TIA, systemic embolism or stroke, hypertension, impaired left ventricular function, age >75 years. **Minor risk factors: Age included between 65 and 75 years, diabetes, coronary artery disease. §In subjects older than 75 years of age: a) the anticoagulant treatment is strongly recommended in the presence of other thromboembolic risk factors; b) each case must be evaluated separately in the presence of other thromboembolic risk factors, but with a positive hemorrhagic profile (e.g. family history positive for major hemorrhages or personal history positive for: previous brain hemorrhage, cerebral angiomatosis, recent major bleeding, recent diagnosis of pathologies of the gastrointestinal tract with bleeding risk – in particular, diagnosis of peptic ulcer in the last 5 weeks – or genito-urinary tract disorders with bleeding risk); c) in the absence of other thromboembolic risk factors (besides age) it could be more prudent to treat the patient with ASA, or not to treat the patient at all, if at the same time there is a positive hemorrhagic profile.*

Once the treatment has been decided, this should be started with dosages close to the maintenance dosage (i.e. 2.5–5 mg/day of warfarin) and monitoring must be particularly careful in the first three months of treatment. A possible alternative to OAT in the secondary prevention of systemic embolism in elderly patients with NVAF is indobufen at a dose of 100–200 mg twice a day (dose decided on the basis of renal function).

3.5. Recent atrial fibrillation to be treated with electrical or pharmacological cardioversion

The current classification of atrial fibrilaltion (AF) distinguishes a paroxysmal AF, in which there is spontaneous arrhythmia interruption within 24-48

hours, *persistent* AF, in which the arrhythmia does not cease spontaneously but only with therapeutic intervention, and the *permanent or chronic* form, in which it is not deemed appropriate to restore sinus rhythm or in which sinus rhythm cannot be restored. It should be remembered that patients with paroxysmal (intermittent) AF can be classified as patients at thromboembolic risk, using the same criteria that are used for the chronic type (*Hart 2000*).

Systemic embolism is the most serious complication of cardioversion of AF. Anticoagulation is indicated if the arrhythmia has been present for more than 48 hours.

Heparin, at anticoagulant doses, followed by OAT, is the strategy used in emergency situations. OAT is administered to stable patients (target INR of 2.5) for 3 weeks before cardioversion (*Albers 2001*). Treatment should be continued for at least 4 weeks after the cardioversion, because the recovery of atrial contractility may sometimes need up to two weeks from the recovery of the sinus rhythm. It is worth stressing that the above period (at least three weeks before, at least four weeks after) should be understood as starting once the therapeutic range has been reached. In other hyperkinetic arrhythmias, OAT is indicated only in cases with periods of AF.

According to some authors (*Hart 2001*), it could be prudent to continue OAT for three months after the cardioversion, since a significant percentage of patients revert to AF during this period. Again, it is important to highlight that the duration of OAT, particularly before cardioversion, should be calculated from when the INR value falls within the therapeutic range.

A recent study compared the conventional strategy (oral anticoagulant 3 weeks before and 4 weeks after effective cardioversion) and cardioversion driven by transesophageal echocardiography preceded by anticoagulation with heparin to prolong the aPTT from 1.5 to 2.5 times the normal, 24 hours before (hospitalized patients) or warfarin 5 days before the procedure (outpatients) (*Klein 2001*). No difference was found in the rate of embolic events; a higher number of bleeding events was found in the conventional group.

Recommendations

In patients with a recent onset of AF (>48 hours) to be treated with cardioversion, OAT is recommended (target INR of 2.5) for three weeks before and 4 weeks after the cardioversion. The initial 3 weeks period starts from the moment in which the INR reaches the therapeutic value. When possible, the strategy of guided cardioversion in a patient with a negative transesophageal echocardiography (absence of atrial thrombi) preceded by a brief period of anticoagulation (therapeutic doses of heparin for at least 24 hours or warfarin for 5 days) also seems to be effective and safe.

3.6. Dilated cardiomyopathy

To date, there is no general agreement about the use of OAT in these patients. As a matter of fact, OAT was recommended by the ACCP's Second Consensus Conference (*Second ACCP Consensus Conference 1989*), but more recent recommendations have not further considered this as an indication for OAT, probably because of a lack of prospective controlled clinical trials aimed at clarifying the risk/benefit ratio of such treatment. Nevertheless, the last edition of the BCSH recommendations (*BCSH 1998*), still considers this as an indication for OAT with a target INR of 2.5, due to the embolic risk of this condition (*Fuster 1981, Schecter 1996*).

The use of OAT should presumably be limited to patients with a high risk of embolism (i.e. presence of AF, previous embolic events, and echocardiographic evidence of intracardiac thrombosis) (*Cheng and Spingler 1994*). A group of patients at particular risk seems to be women with ejection fraction < 25% (*Dries 1997*). In the absence of such conditions, the FCSA suggests that dilated cardiomyopathy is a relative indication which should be assessed in each individual patient, taking into account the risk of bleeding (target INR of 2.5, long term).

Recommendations

Long-term OAT, with a target INR of 2.5, is recommended in patients with dilated cardiomyopathy at high embolic risk (presence of AF, previous embolic episodes, ultrasound evidence of cardiac chamber thrombosis). Otherwise, OAT represents a relative indication, which must be assessed in each individual patient in relation to the bleeding risk.

3.7. Acute myocardial infarction

In clinical practice, aspirin has replaced OAT for the secondary prevention of thrombotic events in most patients with acute myocardial infarction. A recent meta-analysis (*Anand and Yusuf, 1999*), which examined 31 clinical studies published between 1960 and 1999, did however confirm that high intensity OAT (INR > 2.8) significantly reduces mortality, re-infarction and stroke in patients with acute myocardial infarction. In a smaller number of studies OAT was used at moderate intensity (INR 2-3) and the meta-analysis of these clinical trials demonstrated a significant reduction of re-infarctions and strokes, but not of mortality. While in the high intensity studies the advantage clearly overcomes the risk of bleeding complications induced by the treatment, this is not the case for the moderate intensity studies, in which the treatment of 1,000 patients prevented 24 events but provoked 35 major hemorrhages. The same meta-analysis provided potentially interesting data about the advantages of the association of OAT at moderate/high intensity with aspirin, in comparison with aspirin alone, with prevention of 54 events/1,000 patients treated with

only 16 additional hemorrhages. The recently published CHAMP study (Fiore 2002) compared the effectiveness of warfarin (target INR of 1.5-2.5) plus aspirin (81 mg) with the effectiveness of aspirin monotherapy (162 mg) in reducing total mortality after myocardial infarction. No difference was found between the two treatments. However, the mean INR actually achieved in patients on combined therapy was 1.8, so that it is possible that INR levels above 2 are needed to obtain an effect, as suggested by the results of WARIS-2 and ASPECT-2 (see 3.14.3). In reality, over recent years, the clinical treatment of ischemic heart disease has changed radically and, indeed even the patients themselves are very different from those enrolled in previous trials. It is clear that OAT cannot nowadays be recommended to all patients after a myocardial infarction.

Patients suffering from acute myocardial infarction at lower risk of thromboembolism are often treated with low-dose subcutaneous heparin therapy (15,000 IU/day) during hospitalization, while aspirin (100-325 mg/day) should be started as soon as possible and continued for a long time. In low risk patients with contraindications to or intolerance of aspirin, some options can be considered: low-dose heparin (*Neri Serneri 1987*), ticlopidine or clopidogrel (*Cairns 2001*) or OAT (see below for the recommended INR).

Patients with myocardial infarction who have a higher thromboembolic risk (Q-wave anterior infarction, severe heart failure, mural thrombosis, history of systemic or pulmonary embolism and AF) should receive anticoagulant therapy with heparin followed by OAT for at least 3 months, continuing long-term in the case of chronic AF. The target INR recommended by the ACCP (*Cairns 2001*) in all these cases is 2.5. However, as mentioned above, while there is a significant reduction in the risk of strokes and pulmonary embolism at such an anticoagulation level (Hirsh, 1991), the main available studies which demonstrated a reduction of recurrent infarctions – Sixty Plus (*Sixty Plus Reinfarction Group, 1980*), WARIS (*Smith 1980*) and, in a more doubtful way ASPECT (*Anticoagulants in Secondary Prevention of Events in Coronary Thrombosis Reasearch Group, 1994*) – and of mortality (Sixty Plus and WARIS) employed much higher target INRs (2.8-4.8). Furthermore, a re-examination of the ASPECT study data (*Azar 1996*) revealed that the optimal anticoagulation intensity needed to prevent cumulated thromboembolic and bleeding events produced INR values between 3 and 4. For this reason, the British guidelines (BCSH, 1998) recommend a target INR of 3.5 in patients for whom OAT is the antithrombotic treatment chosen after myocardial infarction. Thus, while the indication for OAT is unanimous for higher risk patients (*Cairns 2001*), even if different opinions exist about the recommended target INR, OAT is less employed for low risk patients (*Cairns 1994 and 2001*), essentially because there are other available drugs which are safer and just as effective, such as aspirin (*Antithrombotic Trialists' Collaboration 2002*) and low-dose heparin (*Neri Serneri 1987*). As mentioned above, clinical trials currently underway are comparing the effects of low-dose warfarin plus aspirin with aspirin alone; their results will help to clarify some uncertainties in this field.

Recommendations

Long-term therapy with aspirin 100-325 mg/day is recommended in patients with myocardial infarction and low thromboembolic risk. In patients with acute myocardial infarction and high thromboembolic risk, OAT to reach a target INR of 2.5 is recommended in the first three months following infarction; this should be followed by long-term treatment with aspirin (100-325 mg/day).

A target INR of 3.5 and a therapy duration of at least 3 years are recommended in patients with previous myocardial infarction in whom OAT is used as the only treatment for the prevention of re-infarction.

3.8. Other cardiological indications

OAT is not indicated for the management of patients who have had surgical coronary re -vascularization or PTCA (*van den Meer 1993, Stein 2001b*). On the contrary, this is now an established indication for the use of antiplatelet drugs, in particular for the prevention of early re-stenosis after PTCA and to maintain the patency of venous grafts. At least three major studies have demonstrated the superiority of the ticlopidine–aspirin association versus OAT plus aspirin in patients treated with coronary stents (*Schomig 1996, Leon 1998, Bertrand 1998*). Nevertheless, OAT (INR 2-3) is sometimes still used during the first three months after an operation in patients with coronary stents, principally in the place of anti-platelet drugs (ticlopidine or clopidogrel plus aspirin) in those patients with intolerance of and/or contraindications to such drugs or if there are other indications for the use of OAT.

The ACCP recommends OAT (target INR of 2.5) for several months in patients with unstable angina who, after an initial treatment with heparin, cannot continue their antiplatelet treatment because of contraindications to the use of aspirin, ticlopidine and clopidogrel (*Cairns 2001*). Several trials currently in progress are comparing the usefulness of OAT and antiplatelet therapy, sometimes even in combination. These studies may identify new indications and new therapeutic regimens.

3.9. Cerebral arterial disease

Antiplatelet treatment with aspirin 160-300 mg/day should be started within 48 hours in patients with acute ischemic stroke (*SPREAD 1999*).

Patients with cardioembolic stroke from heart disease with high embolic risk and a small to moderate lesion (< 30% of a hemisphere), in whom a CT scan carried out at least 48 hours after the onset of the symptoms excludes a hemorrhagic transformation, should be treated with heparin followed by OAT (target INR of 2.5). It is commonly agreed that such an indication exists also for patients with acute stroke and subocclusive stenosis of an arterial branch who are waiting for surgical treatment (*SPREAD 2001*), while the use of OAT is controversial in patients with dissection of the large arterial trunks, even if OAT is often prescribed by neurologists for three months after the event in these patients.

In patients with indications for anticoagulant treatment who are hypertensive (with inappropriate blood pressure control) or who have a large area of ischemia (>30% of a hemisphere), anticoagulant treatment should be delayed for at least two weeks.

In patients in whom non-valvular AF is the presumable cause of the stroke, OAT should be started immediately after the CT scan carried out at 48 hours post-event, to lower the risk of early embolic recurrence.

OAT is not presently recommended in non-embolic cerebrovascular diseases (except in the above mentioned cases) given the negative results of the SPIRIT study (*SPIRIT 1997*) which evaluated the effects of OAT (INR 3-4.5) in patients with atherothrombotic stroke and which was interrupted because of an excess of bleeding complications, perhaps due, at least in part, to the high INR range chosen. The ESPRIT study, which is evaluating the effectiveness of OAT at moderate intensity (INR 2-3) in patients with non-cardioembolic ischemic stroke, is currently in progress. At the moment antiplatelet therapy is, therefore, indicated for these patients (aspirin 100-325 mg/day) for long-term secondary prevention. An exception is the antiphospholipid antibody syndrome (see paragraph 3.13)

Recommendations

Treatment with heparin, followed by long-term OAT (target INR of 2.5), is recommended in patients with cardioembolic stroke due to cardiac disease with high embolic risk, with a small or moderate lesion (< 30% of a hemisphere), in whom a CT scan carried out at least 48 hours after the onset of the symptoms excludes hemorrhagic transformation). Anticoagulant treatment should be delayed for at least two weeks in patients with an indication for anticoagulant treatment who are hypertensive (with inappropriate blood pressure control) or who have a large area of ischemia (>30% of a hemisphere). In patients in whom non-valvular AF is the presumable cause of the stroke, OAT should be started directly after the CT scan carried out 48 hours post-event. In all other patients with non-cardioembolic stroke, antiplatelet treatment is recommended.

3.10. Peripheral arterial disease

For a long time OAT has been widely, although empirically, used in vascular reconstruction surgery. A rather old study with several methodological problems showed a 50% reduction in mortality from myocardial infarction and vascular death (*Kretschmer 1988*) with very long-term OAT at a therapeutic range included between INR 2.5 and 4.5, calculated a posteriori, in patients undergoing a femoropopliteal bypass. More recently, the effect of the combination of warfarin (INR 2-3) and aspirin (325 mg/day) as compared to aspirin alone was evaluated in 56 patients at high risk of thrombosis (poor quality veins, poor arterial flow or previous unsuccessful bypass) undergoing vascular reconstruction surgery with the application of a venous infrainguinal bypass (*Sarac 1998*). In a three-year follow-up, the patency of the bypass and the number of saved limbs were significantly higher in the group treated with warfarin. The BOA study (*Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group, 2000*) recently compared treatment with aspirin (80 mg/day) with that of OAT (INR 3-4.5) in patients who underwent an infrainguinal bypass with a mean follow-up period of 21 months. The two treatments were, substantially, found to be equivalent, although OAT was superior in preventing occlusion of the venous bypass and of ischemic events, while aspirin was more effective in patients with non-venous bypass and was accompanied by a lower number of hemorrhages.

The FCSA working group does not recommend the use of OAT in peripheral arterial disease, given the the lack of adequate clinical studies. In this disease, antiplatelet drugs are the treatment of choice, also in consideration of the fact that these patients often have a diffuse vascular disease with increased risk of myocardial infarction and atherothrombotic stroke. It should also be remembered that the Italian ISCOAT study demonstrated that, compared to other OAT patients, patients on OAT because of peripheral or cerebral arterial disease are at increased hemorrhagic risk (*Palareti 1996*).

OAT may be indicated for selected patients with infra-inguinal venous bypass who have a high thromboembolic risk (long and thin grafts with scarce flow) (*Jackson 2001*). In these cases the association with aspirin can further reduce the risk of a thrombotic occlusion, although it increases the risk of hemorrhage.

Recommendations

Antithrombotic prophylaxis with antiplatelet drugs is recommended in patients with peripheral arterial disease. OAT (target INR of 2.5), associated with aspirin (80-325 mg/day), can be indicated on a case-by-case basis in selected patients with infra-inguinal venous bypasses at high thrombotic risk.

3.11. Prevention of post-operative deep vein thrombosis

The effectiveness of OAs in the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) has been demonstrated in several controlled clinical studies in which the therapeutic range was set at INR values included between 1.5 and 4.0 (*Taberner 1978; Francis 1983; Poller 1987a; Powers 1989*). Treatment was found to be equally effective when it was started before surgery or on the first day after surgery, with an overall duration of 5-7 days. Although the risk of clinically significant post-surgical bleedings during a moderate intensity anticoagulation regimen is low, prophylaxis with OAs is nonetheless more complex than the use of fixed low-dose heparin or low molecular weight heparin. For this reason, prophylaxis with OAs is generally reserved to very high-risk patients (namely those with previous PE/DVT, or those undergoing major orthopedic surgery) (*Hirsh 1991*) and/or those with previous heparin-induced thrombocytopenia or intolerance to heparins. In Italy, a contraindication to the use of heparin is nowadays almost the only indication for OAT in this clinical setting. For this indication, the FCSA recommends *a target INR of 2* for a period of time to be determined on a case-by-case basis. In principle, however, treatment should be continued at least until full mobilization. In cases of very high bleeding risk, it is better not to exceed an INR value of 2. In the light of several recent studies, OAT is presently considered the second choice in these patients in orthopedic surgery, low molecular weight heparin being the treatment of choice. The use of OAT should, however, be considered in patients with a history of heparin-induced thrombocytopenia.

Recommendations

OAT (target INR of 2) is recommended on a case-by-case basis in patients with contraindications to heparin prophylaxis who undergo high risk surgery; OAT should be continued until complete mobilization.

3.12. Treatment of deep vein thrombosis, pulmonary embolism and prophylaxis of recurrences

The usefulness of long-term OAT after heparin in cases of DVT and PE has been positively proven in several controlled clinical trials (*Hull 1979, Hull 1982*). These studies demonstrated how OAT is effective in the secondary prevention of venous thromboembolism, reducing the risk of thromboembolic recurrences. Recent observations have also suggested that well-controlled OAT helps to reduce venous thrombosis (*Caprini 1999*). The therapeutic INR range included between 2.0 and 3.0 was found to be equally effective as the range between 2.5 and 4.5, but given the lower bleeding risk, the former treatment should be considered as the standard treatment. The only exception could be in patients with antiphospholipid antibodies (see paragraph 3.13).

On the other hand, the optimal duration of OAT is still unclear, particularly after a single episode of venous thromboembolism. The risk of recurrence is estimated to be about 10 cases per hundred patient-years in the first year after the interruption of OAT. Later on, this risk tends to diminish progressively; although it does not disappear. The cost/benefit ratio of using OAT in the secondary prophylaxis of venous thromboembolism is therefore more complex than for other indications, because the risk of thromboembolic recurrences is not constant over time. Some hereditary defects of hemostasis, especially if combined with each other (e.g. FV Leiden and prothrombin variant G20210A), increase the risk of recurrence (*DeStefano 1999*). Acquired pathologies (e.g. cancer) also expose the patient to a higher risk of recurrences. Particular attention must also be paid to episodes of *idiopathic* thromboembolism, which arise without specific circumstantial factors, (e.g. trauma, immobilization, surgery, pregnancy and or puerperium). In patients with single episodes of venous thromboembolism, the duration of OAT should be personalized according to some directives. When the onset of thromboembolism is related to transitory circumstantial risk factors (e.g. surgery), the treatment period can be limited to three months. In patients with idiopathic thromboembolism or with known thrombophilic defects, the suggested anticoagulation period is at least six months (*Kearon 1999*). At this stage no controlled studies clarify up to when the risk of recurrence remains greater than the risk of hemorrhagic complications. Based on risk/benefit models, the maximum duration of OAT in patients with idiopathic thrombosis (possibly associated with thrombophilic anomalies, such as the FV Leiden) could be of about 18-24 months (*Prins 1999*). Such extended periods of anticoagulation for a single episode of venous thromboembolism appear justified only for young patients (in whom the cost of a possible recurrence would be particularly high), who have a good compliance and in which OAT is monitored effectively. The results of one randomized study (*Schulman 1997*) suggest that, after two episodes of idiopathic venous thromboembolism, OAT should be continued indefinitely.

The duration of therapy does, however, remain somewhat unclear. Cases of relapsing thromboembolism would certainly be reduced if OAT was continued for a long time in all patients, but many of them would be needlessly exposed to the risk of bleeding and to the costs of OAT monitoring. At present, a treatment period of 3-6 months for patients without a persistent risk of thromboembolism, and more prolonged (or indefinite) treatment in cases

of continuous risk (deficiency of physiological coagulation inhibitors, recurrent DVT, etc.) are recommended. Although a recent randomized study (*Levine 1995*) suggested a *short* treatment period (one month) for non-complicated DVT without persistent risk factors, the FCSA study group advises the above-mentioned *traditional* prescriptions (i.e. 3-6 months). A special case is the antiphospholipid antibody syndrome. Retrospective studies (*Kamashta 1995*) have indicated the need to maintain the highest therapeutic range (3-4.5) in patients with this syndrome if spontaneous venous or arterial thrombosis occurs. This approach is not, however, accepted unanimously.

According to a recent trial (*Shulman, 1997*), prolonged OAT may be useful for recurrence. However, the duration of OAT should be decided on a case-by-case basis, taking into account the risk of bleeding.

In patients with pulmonary hypertension, OAT has a primary role in the treatment of conditions secondary to recurrent pulmonary embolism. However, even in the case of primary pulmonary hypertension, post-mortem and biopsy studies documented the presence of thrombi occluding pulmonary venules and arterioles. The use of OAT in these patients can improve prognosis and thus is recommended by several experts, although there is no broad consensus either on its indication or on the target INR (*Fuster 1984*).

According to the FCSA study group, pulmonary hypertension, both primary and secondary to chronic thromboembolism, is a relative indication that should be clinically evaluated on a case-by-case basis. A long term INR target of 2.5 is recommended in these cases.

In recent years, the use of caval filters has generated a particular problem in the management of venous thromboembolism. The only accepted indications for positioning a caval filter in a patient with DVT/PE are an absolute contraindication to anticoagulant treatment and failure of anticoagulant therapy with thromboembolic recurrences during a well-conducted treatment (*Streiff 2000*). Although the positioning of a permanent filter is associated with an increased incidence of the recurrence of DVT at two years (*Decousus 1998*), no study has shown the usefulness of long-term OAT in these patients. For this reason there is currently no consensus on this issue and the decision should be taken on a case-by-case basis.

Recommendations

Treatment with heparin, followed by OAT (INR target of 2.5) for at least three months, is recommended in patients with DVT and/or PE.

OAT for a period of at least six months is recommended in patients with a first episode of idiopathic DVT and/or PE or persistent risk factors (among which, a thrombophilic risk factor). Treatment for at least one year is recommended in the case of multiple thrombophilic defects or hereditary homozygous thrombophilia.

OAT for an indefinite period is recommended for patients with recurring idiopathic DVT and/or PE or with persisting risk factors.

In patients with primitive pulmonary hypertension and chronic throembolic hypertension, long-term OAT (INR target of 2.5) is recommended, with a clinical evaluation of the patient on a case-by-case basis.

3.13. Antiphospholipid antibody syndrome

The antiphospholipid antibody syndrome (APS) can be defined as the association of: a) arterial and/or venous thrombosis and/or recurrent abortion with b) a persistent positivity of laboratory tests for lupus anticoagulant or anticardiolipin antibodies (*Greaves 1999*). The therapeutic target and the optimal duration of OAT in patients with APS and thrombosis are still under investigation. Two retrospective analyses (*Rosove and Brewer 1992, Khamashta 1995*) previously demonstrated that a high INR (>3.0) was associated with a significantly reduced incidence of re-thrombosis, but also with a non-negligible risk of severe hemorrhages. Subsequent studies on cohorts of consecutive non-randomized patients (*Ginsberg 1995, Prandoni 1996, Rance 1997, Schulman 1988, Gonzales-Trujillo 2000*) suggested that a more moderate therapeutic target (target INR of 2.5) can be just as effective and less risky, especially in patients with venous thrombosis. Randomized, prospective clinical trials are currently in progress and the results are awaited within 2003. In the meantime, based on the currently available data, the *British Society of Haematology* (BSH) published the following guidelines for the secondary prophylaxis of thrombosis in patients with APS (*Greaves 2000*):

a) first venous thrombosis: INR 2.5, duration up to 6 months;
b) first arterial thrombosis: INR 2.5, indefinite duration,
c) recurrent thromboses: INR 3.5 (if the recurrence occurred during OAT at a lower target value), indefinite duration;
d) in all cases: careful prevention and treatment of reversible risk factors (e.g. avoidance of oral contraceptives).

The FCSA considerations are as follows:

a) the above reported BSH guidelines can be considered as a first reference, because they are recent and methodologically accurate;
b) while awaiting more sound scientific data, the intensity and the duration of OAT should be decided on a case-by-case basis, taking into account the severity of the thrombotic event and the risk of hemorrhage in each patient.

Thus, deviations from the above cited guidelines are justified, if required by the clinical characteristics of the patient. In particular, the FCSA study group suggests caution in stopping OAT six months after the first episode of venous thrombosis , especially in the case of a spontaneous event or in the presence of elevated titers of antiphospholipid antibodies. In this setting, particular significance should be given to lupus anticoagulant positivity, which is the major risk factor for recurrent thromboembolism.

Recommendations

In patients with antiphospholipid antibody syndrome and thrombosis, the following antithrombotic prophylaxis is recommended:

- **in patients with a first episode of DVT/PE: target INR of 2.5 lasting at least 6 months; long-term, in case of a spontaneous event and of persistently high antibody titers;**
- **in patients with a first arterial thrombosis: target INR of 2.5, long-term;**
- **in patients with recurrent thromboses: target INR of 3.5 (if the recurrence occurred during OAT at a lower INR value), long-term.**

The intensity and duration of OAT should be decided on a case-by-case basis, bearing in mind the severity of the thrombotic event and the hemorrhagic risk of each patient.

3.14. Association between OAT and antiplatelets

In general, OAs are indicated for the prevention of the thrombosis that occurs in association with, or as a consequence of, stasis of the blood (e.g. AF, DVT), while antiplatelet drugs are used to prevent thrombosis that occurs due to fast-flowing c blood conditions (e.g. arteriopathy). Although the association of OAs and antiplatelets is not generally recommended, the combined use of these two categories of drugs could be useful for some categories of patients.

3.14.1. Mechanical cardiac valvular prostheses

Carriers of cardiac valvular prostheses, have always been considered at high risk of embolism, although the recent use of more bio-compatible prostheses with a better hemodynamic profile seems to have reduced this risk. However, since there are clinical and physiopathological bases for the combined use of OAs and antiplatelets, several studies in the past tested the effectiveness of warfarin plus dipyridamole or warfarin plus aspirin, without convincing results and with a notable increase of the hemorrhagic risk in patients treated with warfarin associated with elevated doses of aspirin (500-1,000 mg/day).

More recently, a study by Turpie (*Turpie 1993*) tested the association of warfarin (INR 3.0-4.5) plus aspirin 100 mg/day, demonstrating a significant reduction of thromboembolism and death compared to the use of warfarin only, without a significant increase of the hemorrhagic events. The reduction in mortality was determined largely by the reduction of myocardial infarction and of sudden death.

In conclusion, based on the current low incidence of thromboembolism in mechanical cardiac valvular prosthesis carriers who are properly treated with OAT, the association of warfarin in therapeutic doses with aspirin 100 mg/day can be considered only on a case-by-case basis in some patients:

- patients with previous myocardial infarction or ascertained ischemic heart disease or who were operated for aorta coronary by-pass in the absence of consistent hemorrhagic risk;
- patients who had an embolic episode (e.g. TIA) notwithstanding the correct functioning of the prosthesis and a proper anticoagulant treatment:
- patients with non-recent double prostheses, or valvulated aortic tube in the absence of significant hemorrhagic risk (*Pengo 1997*).

3.14.2. Atrial fibrillation

The association of aspirin (325 mg/day) and warfarin in low doses (INR included between 1.2 and 1.5) was tested in patients at high embolic risk in the SPAF III study (*SPAF III, 1996*). The clinical hypothesis was to reduce the hemorrhagic events connected with therapy with standard OAs, especially in elderly patients. In this study, the aspirin-warfarin association did not reduce the hemorrhagic events connected with standard anticoagulant therapy and was non-effective in preventing thromboembolism in this group of patients. The AFASAK 2 study (*Gullov 1998*) obtained the same results; in this study a group of patients was treated with warfarin at a low fixed dosage (1.25 mg/day) plus aspirin 300 mg/day. In conclusion, clinical studies did not show that in the association of warfarin in low doses and aspirin had advantages in the prevention of thromboembolism in patients with NVAF.

3.14.3. Primary and secondary prevention of myocardial infarction

A coronary thrombosis is formed in a high flow area (platelet activation) and it extends and consolidates after the occlusion of the blood vessel (fibrin deposition). Both aspirin and OAs proved to be effective in preventing acute coronary events and vascular death. The Thrombosis Prevention Trial (*MRC 1998*) was a primary prevention study of ischemic heart disease; in one of the arms of the study, patients at risk of acute coronary syndromes (with elevated levels of factor VII) received aspirin

75 mg/day associated with warfarin (target INR of 1.5). The use of aspirin plus warfarin was more effective than that of single agents in reducing coronary events, but at the expense of a higher number of hemorrhagic events (aorta rupture and dissecting aneurysms increased significantly).

In secondary prevention, the CARS study (*Coumadin Aspirin Reinfarction Study Investigators 1997*) demonstrated that the association of fixed doses of warfarin (1 or 3 mg/day) and aspirin in doses of 80 mg/day in patients with a previous myocardial infarction is not superior to monotherapy with 160 mg/day of aspirin. Aspirin associated with warfarin 3 mg/day also caused an increase in the number of spontaneous hemorrhagic events compared to the number associated with monotherapy with 160 mg/day of aspirin. The WARIS II study (Warfarin-Aspirin Re-infarction Study) has been recenty published (Hurlen 2002). This study compared three different treatments in 3,630 patients younger than 75 years of age with a recent myocardial infarction: aspirin 160 mg/day; warfarin with a target INR of 2.8-4.2; aspirin 75 mg/day plus warfarin with a target INR of 2-2.5. The primary endpoint of the study was the combination of death, non fatal re-infarction and thromboembolic stroke. The average follow-up was 4 years. One of the three primary endpoints was reached in 241 (20%), 203 (16.7) and 181 (15%) patients of the three treatment groups, respectively, with a significant difference between the combined therapy and the aspirin therapy. Major hemorrhagic events were observed in 8, 33 and 28 patients of the three groups, respectively, with statistically significant differences but low absolute numbers.

These results are similar to those obtained in ASPECT-2 study (*van Es 2002*) in which low-dose aspirin, high intensity OAT and combined low-dose aspirin and moderate intensity OAT were investigated in 999 patients with acute coronary syndrome (45% with ST elevation myocardial infarction).

In conclusion, the combined use of aspirin and warfarin increases hemorrhagic risk and should be chosen for selected cases with acute coronary syndromes at high risk; at this stage there is not a consensus on a clear-cut indication for the combined use of aspirin and warfarin in primary or secondary prevention of acute coronary syndromes.

At present, aspirin alone should be used in secondary prevention, in doses of 150-325 mg/day.

The association of aspirin and warfarin can only be considered on a case-by-case basis in those situations in which monotherapy proved to be non effective.

3.15. Indications and therapeutic targets in elderly patients

Advanced age can increase the risk of hemorrhagic complications during OAT in relation to numerous factors, such as:

a) reduced metabolic clearance, with consequent increased sensitivity to the effect of OAs;
b) assumption of numerous drugs interfering with OAs; this is common in elderly patients;
c) frequent co-morbid conditions;
d) vascular fragility with a possible increase in the risk of intracranial hemorrhage.

The possibility of reduced compliance due to a decline in cognitive functions should be considered together with the above factors. Advanced age also coincides with the period in which cardiovascular diseases (such as NVAF) start to appear, with a consequently higher risk of thromboembolism. As a result of this increased risk, elderly patients may be the ones who receive most benefit from OAT. The number of elderly patients with indications for OAT is increasing markedly due to the large number of patients with NVAF and to the longer life expectancy. One third of the patients enrolled in the ISCOAT study were older than 70 years of age at the beginning of the treatment and 8% of the patients were over 80 years. In this study (*Palareti, 2000*) more thrombotic and bleeding events were observed in patients over 75 years than in younger patients, although this difference was not significant. However, intracranial bleeding and fatal thrombotic events were significantly more frequent in elderly patients.

The risk of both bleeding and thrombotic events in elderly patients was lower for INR values included between 2.0 and 2.9, while INR values < 2.0 were associated with a higher thromboembolic risk, without completely eliminating the hemorrhagic risk. These data indicate that age is not, per se, a contraindication to OAT. A target INR of 2.5 proved to be the most effective and safe, and should be chosen in elderly patients; higher targets should be set for selected cases only. It is, however, advisable to be particularly careful and accurate when managing OAT in old and very old patients, in order to minimize important fluctuations of INR levels. Indeed, changes in daily doses in elderly patients should be very prudently managed, since the required daily amount of OAs is significantly lower than it is in younger subjects.

3.16. Non-indications for OAT

It is common for Anticoagulation Clinics to receive patients who are already on OAT for conditions for which the clinical effectiveness of OAT has not been proven. The registration of these patients at the Anticoagulation Clinic can be discussed with the physician who gave the indication for the treatment (often an ophtalmologist in the case of thrombosis of the central retinal vein; the vascular surgeon in patients with lower limb obstructive arterial disease; the neurologist in the

case of non-cardiogenic cerebral ischemia) (*BCSH 1998*). The discussion should be focused on the lack of clinical studies on the effectiveness of OAT in these clinical conditions and on the possibility of an increased hemorrhagic risk in patients with atherosclerotic vascular disease (*ISCOAT, Palareti 1996*). However, in some cases the patient (e.g. a patient with repeated TIA notwithstanding antiplatelet treatment) should be accepted for the OA drug use and definition of correct posology, but should be sent back to the referring doctor for regulatory issues (signature of informed consent). It should, however, be highlighted that the indication for OAT can be valid in the presence of the antiphospholipid antibody syndrome also in patients with the above mentioned conditions, and in particular in those with a stroke at a young age or retinal vein thrombosis (*BCSH 1998*).

4. Contraindications to OAT and conditions leading to an increased risk of complications

It is important to remember that when OAT is started, proper therapeutic management depends on three factors (the so called *triangle of good therapeutic practice*):

1) a reliable laboratory;
2) an experienced physician; *and*
3) a co-operative patient.

If one of the three elements is not working properly, the risks of OAT increase.

The essential guidelines on proper laboratory checks (PT expressed in INR, therapeutic range and so on) are illustrated in chapters 15 and 16.

The physician must be aware not only of the indications for treatment, but also of the absolute contraindications to OAT and of other conditions leading to the risk of complications (*Poller 1987; Samama 1992*). In reality, in some conditions that are commonly considered as contraindications to OAT, OAs may be prescribed in most patients, provided that proper medical or health care support is available. At this stage, what really is relevant is the careful assessment of the risk/benefit ratio of OAT on a case-by-case basis. For these reasons, OAT candidates must first be carefully examined. During the medical examination, the following data should be recorded: age, gender, clinical condition for which OAT is indicated, concomitant diseases, pharmacological treatments, diet, psychosocial conditions, including information about the patient's family, the name and address of the general practitioner and how far the Anticoagulation Clinic is from the patient's house.

Lastly, the patient's co-operation is required. For this reason, the patient must be given proper training, by carefully illustrating the purpose of the therapy and its possible risks. Most importantly, the patient must understand that proper management of the therapy is crucially important to the achievement of the best results with the lowest risk.

4.1. Absolute contraindications (Table 1)

OAT should never be prescribed in the following conditions.

4.1.1. Pregnancy

OAs should never be administered during the first trimester of pregnancy, because of the fetal malformations that they could cause; nor should they be administered during the last 4 to 6 weeks of pregnancy, because of the risk of bleeding in the new-born, given that the anticoagulant passes through the placenta (see chapter 5).

4.1.2. Recent major hemorrhage, particularly if life-threatening

In the case of a major life-threatening hemorrhage (see classification listed in chapter 21), it is recommended not to administer OAs for an appropriate period of time (at least 1 month).

4.2. Conditions with a particularly high risk of complications (Table 1)

OAT must be considered as a high-risk treatment in several other conditions, both in general and in the presence of specific pathologies. OAT should be taken into consideration after a comparative analysis of all other possible treatments (if available) and after properly assessing the risk/benefit ratio.

4.2.1. General conditions

The importance of the patient's co-operation for achieving a good therapeutic management has already been stressed. A serious risk factor is the presence of severe psychiatric disorders, dementia or other conditions entailing a lack of or irregular cooperation of the patient (*Palareti 1997a*). On the other hand, these conditions should not be considered as contraindications if the patient can be supported by social assistants or by his/her family. Partially similar to this condition is the case of chronic alcoholism; even if support is available, it should be borne in mind that this condition is often associated with liver damage, thrombocytopenia and/or thrombocytopathy, as well as an increased risk of cerebral bleeding, which could be further worsened by OAT.

4.2.2. Cardiovascular diseases

Severe hypertension is a significant hemorrhagic risk factor for OAT patients. Nevertheless, it is believed that hypertensive patients, particularly if affected by mild to moderate hypertension, can be

Table 1. Absolute contrraindications of OAT.

A) ABSOLUTE CONTRAINDICATIONS	
Pregnancy	First trimester and last weeks of pregnancy (see chapter 5)
Major hemorrhage	within 1 month after the life-threatening event
B) CONDITIONS AT RISK OF COMPLICATIONS	
General psychiatric disorders	Noncompliant patient, alcoholism
Cardiovascular diseases	Severe hypertension, bacterial endocarditis, pericarditis, severe cardiac failure
Kidney diseases	Severe renal insufficiency, recent kidney biopsy
Neurological disorders	Recent cerebral accident not related to embolism, recent surgery or trauma of the CNS or of the eyes, cerebral aneurysm
Gastrointestinal diseases	Ulcerative colitis, active peptic ulcer, esophageal varicosity, hiatal hernia, colon diverticulosis
Liver diseases	Severe liver failure, biliary diseases, recent liver biopsy
Blood disorders	Pre-existing bleeding disorders, thrombocytopenia, thrombocytopathy
Miscellaneous	Retinopathy, lumbar puncture, arterial injections

placed on OAT when indicated, provided there is a proper pharmacological control of the blood pressure values.

Other typical risk factors include: bacterial endocarditis (risk of disseminating septic emboli), pericarditis (risk of hemopericardium), and severe cardiac failure (risk of excessive bleeding due to the altered metabolism of OAs).

4.2.3. Kidney diseases

Severe renal insufficiency is a condition with a high hemorrhagic risk, due to the altered clearance of OAs. Moreover, in the case of renal biopsy, one must avoid starting OAT within the two weeks following biopsy, due to the risk of hemoperitoneum.

4.2.4. Neurological disorders

All neurological conditions listed in Table 1 have a high risk of complications. It should also be added that older patients have a high risk of cerebral hemorrhage due to alterations in drug metabolism and most probably degenerative alterations of cerebral vessels. Careful clinical surveillance should, therefore, be provided, but being elderly *per se* is not a contraindication.

4.2.5. Gastro-intestinal diseases

Ulcero-hemorrhagic rectocolitis, active gastroduodenal ulcers (detected via endoscopy or X-ray), gastroesophageal varices, hiatal hernia and colonic diverticulitis are possible causes of gastrointestinal bleeding during OAT.

According to some French authors, esophageal varices, hiatal hernia and colonic diverticulitis were found to be the most frequent causes of gastroenteric hemorrhage after gastroduodenal ulcer. However, only active bleeding is a contraindication to OAT. In the absence of bleeding, the indication should be decided on a case-by-case basis, evaluating the risk/benefit ratio.

4.2.6. Liver diseases

Severe liver failure and cholestatic jaundice increase the hemorrhagic risk, due to the altered metabolism of the anticoagulant.

OAT can, however, be prescribed to patients with thrombosis of the portal vein and suprahepatic vessels. In patients who have had liver biopsy, it is necessary to wait two weeks before starting OAT, because of a high risk of hemoperitoneum.

4.2.7. Blood disorders

Various blood disorders are an obvious contraindication to OAT. In particular, patients suffering from severe thrombocytopenia (< 50,000/μL) or thrombocytopathy have a high hemorrhagic risk. A particular thrombocytopathy is that induced by antiplatelet drugs. It should be stressed that the combination of antiplatelet drugs and OAT should be avoided, unless otherwise specified in the therapeutic protocol.

4.2.8. Miscellaneous

Some invasive procedures such as lumbar puncture (risk of intramedullary hemorrhage) and arterial puncture (for example, to perform cardiac catheterization) can be extremely dangerous, also because of the depth of the puncture. If such procedures must be performed in patients on OAT, it is advisable to reduce OAT and to utilize superficial arteries for access (namely radial rather than femoral arteries) in order to facilitate external manual compression for hemostatic purposes.

Intramuscular injections should also be avoided.

As for vaccinations (e.g. against influenza or hepatitis), it is advisable to perform subcutaneous injections or injections into a muscle mass that can be pressed on and easily controlled visually, for example the deltoid muscle.

4.3. Other conditions at risk of complications

As mentioned above, advanced age entails a significantly higher risk of bleeding, though age often coincides with the onset of an increased thromboembolic risk, due to cardiovascular diseases (e.g. NVAF).

In cases in which OAT is indicated, a careful evaluation of its risk/benefit ratio must be performed.

Controlled clinical trials using lower doses of OA with the aim of reducing the risk of bleeding while maintaining therapeutic efficacy are currently in progress. However, the results of the SPAF III trial provide evidence against a general reduction of the target INR (SPAF III, 1996).

Some clinical conditions that are relative contraindications to OAT can be removed by local surgery (hemorrhoidectomy in patients suffering from severe hemorrhoids; hysterectomy in patients with otherwise uncontrollable menometrorrhagia that causes anemia), evaluating the risk/benefit ratio on a case-by-case basis.

Certain cases of malnutrition, biliary disease and steatorrhea (characterized by deficient intake and malabsorption of vitamin K) as well as hypocaloric diets can alter the equilibrium between the metabolism of vitamin K and of the OAs (antivitamin K). Thyrotoxicosis and myxedema can also change the metabolism of OAs.

Patients who have recently undergone surgery and who have moderate liver, kidney and cardiac dysfunction require a careful evaluation of the risk/benefit ratio.

Retinopathies and inflammatory bowel disease without bleeding are considered relative contraindications. However, in such cases OAT requires strict clinical surveillance and should be reserved to conditions presenting a high risk of thromboembolism. Obviously, in patients recently operated on or with cardiac, renal or moderate hepatic dysfunction, a careful evaluation of the risks vs. benefits should be made.

Finally, one last remark about breast-feeding is necessary. Until a few years ago, women taking OAs were advised not to breast-feed because it was assured that the mother's milk contained OAs. However, warfarin in mother's milk is either present in negligible amounts (25 ng/ml) (*Orme 1977*) or it is not present at all, according to a recent re-examination of the subject (*Clark 2000*). Breast feeding during OAT is, therefore, to be considered safe.

To date, it has not been scientifically proven that these drugs are present in breast milk. According to some British authors, women can easily breast-feed as long as the newborn infants are provided with oral supplements of vitamin K. Nonetheless, there is not unanimous consensus on treating infants with vitamin K.

5. OAT DURING PREGNANCY

OAT during pregnancy requires special care due to the risks it might entail for the mother and the fetus, as well as the relative lack of information available in the literature.

OA drugs can cross the placental barrier and can seriously affect the development of the fetus, causing a number of lesions that depend on the week of gestation in which the exposure to the drug takes place:

- teratogenic effects: chondrodysplasia punctata (saddle nose, nasal hypoplasia, frontal bossing, short height), optical atrophy, congenital cataracts and mental retardation. The entire first trimester appears to be at risk for teratogenis, particularly during the 6th to 9th week of pregnancy. The incidence of chondrodysplasia after exposure to OAs is estimated to be between 14.6-46.3% between the 6th and 12th week of pregnancy (*Ginsberg 1989*);
- fetal bleeding: this may cause neurological alterations (intracerebral hemorrhage). The risk appears to be greater during the last few weeks of pregnancy;
- bone alterations: most probably due to a reduction in osteocalcins, the vitamin-K dependent factors of calcium metabolism (see Chapter 12).

Table 2. Clinical conditions for which proper anticoagulant therapy is indicated during pregnancy (OAT or heparin).

Deep vein thrombosis and pulmonary embolism during pregnancy
Mechanical heart valves
Myeloproliferative diseases with previous thromboembolism
Previous idiopathic venous thromboembolism, with/without thrombophilic defects (after the first trimester)

Because of the severity of fetal alterations induced by OAs, these drugs should be used with extreme caution and reserved only for very few clinical conditions during pregnancy (see Table 2). In general, women of child-bearing age treated with OAs should receive special consideration.

OAT patients must be properly informed about the risks of starting a pregnancy during the therapy and a pregnancy test should always be performed before starting OAT. Moreover, Anticoagulation Clinics must periodically remind female OAT patients that they should always notify their intention of getting pregnant or report any menstruation delay.

A pregnancy test should always be performed in women reporting delayed menstruation during OAT; if negative, the test should be repeated after 3 days. Detailed information and careful clinical surveillance are recommended for female OAT patients who want to get pregnant; a pregnancy test must be carried out immediately in case of a delay in menstruation.

In women with a positive pregnancy test, OAT will have to be interrupted and replaced by suitable prophylaxis with heparin, which is then used throughout pregnancy. Heparin doses should maintain the PTT ratio (ratio of PTT of patient's plasma

to PTT of normal plasma) between 1.5-2.0 (2.0-2.5 in cases of patients with mechanical heart valves). Full doses of heparin are needed for this purpose (e.g. 7,500–10,000 U s.c. 2-3 times a day). Lower doses (e.g. 5,000 U s.c. 2-3 times a day) are not sufficiently protective (*Ginsberg 1999*). The use of low molecular weight heparin is a safe alternative (*Sanson 1999*) in pregnant women for the secondary prophylaxis of venous thromboembolism (e.g. enoxaparin 40 mg/day, *Ellison 2000*). However, there are no controlled trials about the safety and effectiveness of the use of low molecular weight heparin for the prophylaxis of thromboembolism in pregnant women with mechanical prosthetic valves. As an alternative to the therapy with heparin for the entire duration of the pregnancy, low intensity OAT (target INR of 2.2-2.3) can be prescribed, but only after the first trimester and until the 36th week. Since OAs are commonly considered to be contraindicated during pregnancy, their possible benefits and risks should be discussed with the patient before prescribing them. After the 36th week of pregnancy, anticoagulation with heparin should however be started again, following the directions described above. Heparin therapy should be suspended close to the time of labor, until delivery is completed. OAT should then be started again.

If the child is born via Cesarean section, 4-5 days should be allowed for surgical wounds to heal before starting OAT, during which time antithrombotic prophylaxis with low-dose heparin should be maintained. Only traces of OAs are found in mother's milk. Breast-feeding, therefore, may be allowed during OAT.

Heparin treatment may have some side effects. Besides the risk of bleeding, there is a definite risk of osteoporosis, which nonetheless does not appear to increase the risk of spontaneous bone fractures (*Ginsberg 1989*). The most serious side-effect is heparin-induced thrombocytopenia, mediated by anti-heparin-platelet factor 4 antibodies which can be further complicated by thrombotic (sometimes catastrophic) events. Thus, physicians must be aware of the risk of this complication, taking certain precautions (properly instructing the patient, controlling platelet counts, correctly searching for anti-heparin-platelet factor 4 antibodies), which are deemed mandatory, particularly between the 5th-6th day and the end of the first month of therapy (Rodeghiero 1995).

The FCSA has opened a registry on pregnancy in patients with mechanical prosthetic valves (see the FCSA web site).

6. OAT in children

The main indications for OAT in pediatric patients are the treatment of deep vein thrombosis (often associated with the use of venous catheters in intensive care patients) and antithrombotic prophylaxis in children with mechanical heart valves or a familial thrombophilic diathesis. All these conditions have a high risk of thromboembolism also during childhood and thus warrant the use of OAT.

The most affected age groups are during the first year of life, generally because of thrombophlebitis due to the use of venous catheters, and adolescence.

Both these age groups present therapy management problems. In breastfed infants, OAT monitoring is difficult because of the method of food intake and because of the different physiology of the hemostatic system. In adolescent patients, the focus shifts to the psychological impact of the constant monitoring of this chronic therapy on the development of patient's self-identity. However, the relative rarity of pediatric patients who require anticoagulation and the consequent lack of clinical studies make it difficult to provide specific guidelines for OA management in children. Many recommendations are extrapolated from experience gained treating adult patients, which serve as a reference. This chapter highlights some fields in which therapy management has particular characteristics.

6.1. Indications for OAT

A recent study performed on 319 children (*Streif 1999*) shows that in about 60% of the patients, the indications for OAT are the primary prevention of arterial thromboembolism in patients with congenital cardiopathy (36%), Fontan's operation (atrio-pulmonary connection) (16%) and prosthetic heart valves (12%). In the remaining cases, the indication was secondary prophylaxis of lower or upper limb vein thrombosis (in the latter, often in association with venous catheters), pulmonary embolism or cerebral veins thrombosis.

6.2. Anticoagulation levels

OAT is not recommended in patients under 30 days of age, because of the still low prothrombin levels in neonates and the consequently increased hemorrhagic risk (*Schmidt 1992*). It is generally advised to use low molecular weight heparins in these very young patients. Thrombin generation in children on OAT is actually lower than that in adults treated with the same levels of anticoagulation (*Massicotte 1998*), suggesting that anticoagulation levels lower than the ones used for adults could be sufficient for children. On the other hand, INR targets lower than in the past years have been recently proposed also for adults, so that at present recommendations for adults and children are not significantly different.

6.3. Starting OAT

OAT should always be started together with heparin therapy, especially in patients under one

year of age. The suggested warfarin starting dose is 0.2 mg/kg on the first day, followed by the doses shown in Table 3 (Chapter 8) for further INR adjustment. However, it should be remembered that the average warfarin dose able to maintain the INR within the therapeutic range in children is, on average, higher than the one required for adolescents and adults (0.3 vs. 0.09 and 0.08 mg/kg, respectively) (*Andrew 1994a*). As in the adult patients, it is necessary to check that PT, PTT, fibrinogen and a complete blood count are within normal ranges before starting OAT. Liver function should also be evaluated and, in case of hepatic dysfunction or a PT ratio higher than 1.2, the starting dose should be reduced to 0.1 mg/kg/day.

6.4. OAT monitoring in children

OAT management is less satisfactory than in adult patients, often because of a more irregular food intake and more frequent episodes of infections. Therefore, the INR needs to be tested more frequently in children (*Andrew 1994b*).

The percentage of patients with an INR within the therapeutic range varies from 37% for children under 1 year of age to 53% in adolescents. Children being breastfed (hence with a poor intake of vitamin K) can experience episodes of overdosage, while on the other hand children receiving total parenteral nutrition can develop a resistance to warfarin, because of the vitamin K present in parenteral fluids. The percentage of children with an INR within the therapeutic range could probably be improved by using portable PT monitors, for additional home testing, but few data are available on the use of these devices in children. Particular attention must be paid to dietary vitamin K intake.

6.5. Duration of OAT in children

The same recommendations outlined for adults can substantially be applied to pediatric patients. As for adults, there are no precise recommendations about the optimal duration of OAT after an episode of venous thromboembolism, particularly after idiopathic thromboses with or without thrombophilia.

7. PRELIMINARY EVALUATION OF THE PATIENTS TO BE PLACED ON OAT

Before starting OAT, whether in hospital or at an outpatient clinic, it is best to follow a standard procedure in order to:

a) identify the main indication for the anticoagulant therapy (and possibly other secondary indications);
b) exclude the presence of serious contraindications and assess minor ones;

Table 3. Example of a protocol for starting OAT (protocols are especially valid for hospitalized patients in whom daily INR checks are possible).

	ADULTS		*CHILDREN*	
Day	*INR*	*Warfarin (mg)*	*INR*	*Warfarin (mg)*
1	<1.5	10	<1.3	0.2/kg
2	<1.8	10	1.1-1.4	0.2 /kg
	1.8-2.0	5	1.5-1.9	0.1/kg
	2.1-3.0	2.5	2.0-3.0	0.1/kg
	>3.0	0	3.1-4.0	0.5/kg
			>4.0	0
3	<2	10	1.1-1.4	0.2/kg
	2.0-2.5	5	1.5-1.9	0.1/kg
	2.6-3.5	2.5	2.0-3.0	0.1/kg
	>3.5	0	3.1-4.0	0.5/kg
			>4.0	0
4	<1.5	10	1.1-1.4	0.2/kg
	1.5-2.0	7.5	1.5-1.9	0.1/kg
	2.1-3.0	5	2.0-3.0	0.1/kg
	3.1-3.5	2.5	3.1-4.0	0.5/kg
			>4.0	0

c) define the desired therapeutic range, which should be suitable for both the main reason for the therapy and for the patient's condition;
d) determine the expected duration of the therapy;
e) clarify how and by whom the patient will be monitored during OAT.

Anticoagulation Clinics often do not agree with the indications for OAT for which the patients are sent to the Clinic; the same is true for the proposed period of treatment. When patients register at the Clinic, it is therefore necessary to re-evaluate their indications and their target INR (see chapter 3). Likewise, the patient should be re-assessed when the therapy is suspended.

In order to comply with the above points, the standard procedure must include a general medical examination and some laboratory tests (the results of which are often already available if the patient has been recently hospitalized.

7.1. History and clinical examination

The patient's general clinical conditions must be assessed, together with the main (and possible secondary) indications for OAT and the resulting risk of thromboembolism. As for the definition of the indications for OAT, in order to have a uniform classification and to be able to compare data from different Anticoagulation Clinics, it is recommended the use of FCSA's classification, which is available on request, is used. This classification has already been distributed to all the companies producing

software programs for OAT management.

It is necessary to evaluate the degree to which patients can co-operate and the possible presence of conditions that may reduce their reliability or make them completely unreliable (mental deficiency, severe psychosis, alcoholism, drug addiction, etc). The successful outcome of treatment depends on the full co-operation of the patient or, alternatively, of his/her relatives or acquaintances who are willing to assist the patient, or an efficient home-care social service. The absence of these conditions is an absolute contraindication to the treatment.

Clinical examination (and the patient's history) must exclude the presence of absolute contraindications (this is a rare event; see chapter 4) and must assess the extent of possible relative contraindications (*Poller 1987b*). A bleeding tendency is to be considered as an absolute or relative contraindication depending on its severity. When contraindications are not absolute, it is necessary to evaluate the risk/benefit ratio.

According to some authors, advanced age should be considered a contraindication (somewhat relative) to therapy; however, there is no agreement on this matter (*see Beyth and Landefeld 1995 for an overview of this subject*). The majority of the available studies, including a recent trial conducted by the FCSA (*ISCOAT, Palareti 1996*), confirmed that elderly patients have a higher incidence of both major and minor hemorrhagic complications. Before starting treatment in older patients (>75 years), it is therefore necessary to carefully check all possible personal risk factors that can cause bleeding, namely: previous hemorrhages, peptic ulcer, previous cerebrovascular events, non-controlled arterial hypertension conditions reducing the patient's alertness and/or conditions that may reduce his/her compliance (when nobody can assist the patient properly), chronic alcoholism, frequent falls, use of NSAIDs, and impossibility of being properly followed-up.

There are probably many reasons why very old patients have a higher risk of bleeding during OAT, including a greater tendency to have adverse reactions to drugs; a more marked effect of the anticoagulant, which generally entails using lower doses (about half); high incidence of co-morbidity, with frequent combinations of drugs often interacting with OAT; reduced compliance; higher vascular fragility.

The possible presence of lesions causing anemia (hemorrhoids, hiatus hernia, peptic ulcer, abnormalities of the uterus, and esophageal varices) should be checked during the medical examination. Likewise, it is also necessary to check the presence of pathologies entailing the need for a therapy which could potentially interfere with OAT (arthritis, gout, dyslipidemia, diabetes, etc.) or which can increase the incidence of hemorrhages, as has been demonstrated for the intake of NSAIDs and OAs in elderly patients (*Shorr 1993*).

7.2. Preliminary laboratory tests

Before starting OAT, the following tests should be performed or, if they are already available, evaluated:

- basic coagulation tests (PT, APTT, fibrinogen)
- complete blood count with platelets and serum iron, transferrin and ferritin (to assess possible sideropenic microcytic anemia and to have, in any case, a reference value for possible suspected cases of unrecognized bleeding during treatment)
- serum transaminase, gamma glutamyl transpeptidase, bilirubin, cholinesterase, total proteins and protein electrophoresis (to assess liver function)
- pregnancy test in all women of child-bearing age.

7.3. Conversation with the patient at the beginning of OAT

A medical specialist must always have a conversation with the patient before starting OAT, in order to provide important information and clarify the most significant aspects of OAT. In particular, it is necessary to illustrate to the patient the general aims of OAT, the mechanism of drug action and the associated risks, distinguishing between the possible onset of minor bleeding (nosebleeds, menorrhagia, hematuria, bleeding of the gums, etc.) and the onset of major bleeding, which requires immediate medical intervention. It is also necessary to explain that drug dosage (a single intake per day, at the same time in the afternoon or at night before going to sleep, no matter if before or after dinner) may often change and that the reason for the periodic PT checks is to adjust the dosage according to the obtained effects.

The patient must be given a clear explanation of the details of the report they receive, with the results of the PT tests (expressed in INR) and the daily therapeutic prescription, specifying which INR therapeutic targets are recommended to the patient. Patients must be warned not to take acetylsalicylic acid or other antiplatelet drugs, unless they receive specific indications from the physicians at the Anticoagulation Clinic. Patients must also always report all changes in their overall drug treatment to the Clinic's staff members. No particular restrictions apply to diet, although it is important to maintain constant eating habits, avoiding overeating and, particularly, the intake of excessive amounts of alcoholic drinks. Such drinks are allowed, but with moderation. Finally, patients should avoid the irregular intake of large amount of foodstuffs rich in vitamin K, such as lettuce,

broccoli, and spinach (see chapter 12).

Female patients of child-bearing age must be informed about the potential teratogenic risks of OAT, particularly during the first stage of pregnancy. These women should be informed that they must immediately notify the Anticoagulation Clinic of their intention to get pregnant or in any case immediately report a pregnancy or a delay in their menstrual cycle (a detailed description of complications during pregnancy is given in chapter 5). The information pamphlet *Booklet for Patients on Oral Anticoagulant Treatment* [prepared and distributed by the Association of Anticoagulated Patients (AIPA) and the FCSA] should be given to the patient during the first visit. The patient should be encouraged to read this booklet at home and to ask for explanations and clarifications during his/her next check-up. This booklet can be requested from the AIPA or the FCSA.

8. STARTING OAT: INDUCTION DOSAGE, SCHEDULE AND INTAKE PROCEDURE

OAT induction must be carried out taking into account that no reasonably certain parameters are currently available to estimate the daily average dosage for each patient. It is only possible to expect that dosage will, on average, be lower for elderly patients and for patients with liver disease than for other patients. It, therefore, appears to be appropriate to start OAT with a 5 mg warfarin maintenance dose, and to expect to reach therapeutic INR levels in 4 to 7 days. As a matter of fact, recently published data indicate that 5 mg of warfarin offer greater guarantees than a double dose, in terms of a lower risk of overdosage, and a higher probability of reaching the therapeutic target within a few days (*Harrison et al 1997; Tait et al 1998*). If treatment begins using acenocoumarol, it should be remembered that the warfarin/acenocoumarol ratio is 2 to 1 in about 85% of patients (a 5 mg warfarin tablet has the same anticoagulant results as 2.5 mg of acenocoumarol) (*Barcellona et al 1998*). An alternative protocol uses a moderate initial dose (e.g. 10 mg of warfarin), which is approximately twice the average maintenance dosage (*Hirsh and Fuster, 1994a*); this strategy does, however, increase the overdosage risk and must be used only when INR checks can be carried out frequently (e.g. in hospitalized patients). Using high initial doses (e.g. 20-40 mg of warfarin) does not offer particular advantages, can make dosage stabilization more difficult, and is potentially dangerous. As a matter of fact, a rapid drop in protein C (vitamin-K dependent physiological anticoagulant, with a short half-life), which is still not compensated for by the concomitant reduction of vitamin K-dependent coagulation factors with a longer half-life (factors II, IX, X), can induce thrombosis in the microcirculation, with the onset of skin necrosis, particularly in patients with congenital protein C and S deficiency (*Broekmans 1983*). OAT induction, particularly in non-hospitalized patients and in those in whom the start of OAT is not urgent (e.g. patients with stable chronic atrial fibrillation) should therefore be carried out with a 5 mg/day warfarin dosage; as already indicated, this dosage allows stable anticoagulation to be reached in 4-7 days. An algorithm which is useful for determining the maintenance dosage using the 5th day INR after 4 days of treatment with 5 mg of warfarin per day has been recently published (*Pengo 2001b*). If the antithrombotic effect is more urgent (e.g. in patients with cardiac diseases carrying a high risk of embolism), then warfarin can be started at a dosage of 10 mg/day for the first two days then 5 mg for the two next days, with a PT check after 4 days and then every 4-7 days until a therapeutic level is achieved and maintained. This procedure should, however, be avoided in elderly patients. When immediate anticoagulation is required (e.g. thrombosis in progress), therapy must be started with heparin, introducing warfarin early, as illustrated in chapter 9 (*Hirsh and Fuster 1994a*).

In children, therapy is generally started at loading doses of 0.2 mg/kg/day for the first two days. Subsequent doses depend on the INR values measured daily during the first week of therapy (*Andrew 1994a*).

Induction protocols that enhance dosage adjustment during the first days of treatment have been developed for both adults (*Fennerty 1984*) and children (*Andrew 1994a*). With these protocols, which aim to reach and maintain INR values between 2 and 3, a dosage that corresponds to the maintenance dosage is normally reached on the 4th day. As already indicated, OA drugs should be taken in a single dose, always at the same time of day, in the afternoon or in the evening and in any case always after PT results.

More sophisticated induction algorithms have been developed. These are often capable of approximating the following maintenance dose rather well, based on the anticoagulant response to the dosage load in the first days. These algorithms were determined on very wide statistical bases and have been implemented in several dedicated software programs (see chapter 18).

9. TRANSITION FROM HEPARIN THERAPY TO OAT

The current recommendation is to administer warfarin (5-10 mg/day) early, from the 2nd or 3rd day of heparin therapy, discontinuing the heparin when the INR reaches values > 2 for two consecutive days (*Gallus 1986*). In this way, the time of heparin treat-

ment is reduced with the advantage of shortening the time the patient spends in hospital and lowering the risk of heparin-induced thrombocytopenia (Hirsh and Fuster 1994b).

Two randomized studies in patients with proximal venous thrombosis have shown that short-term heparin therapy (4-5 days) is as effective and well tolerated as longer-term therapy (9-10 days) (*Gallus 1986; Hull 1990*). However, this conclusion does not necessarily hold for patients with massive iliofemoral thrombosis or severe pulmonary embolism since these cases were either excluded or rare in the two trials (*Hirsh and Fuster 1994b*).

In these situations, current guidelines still recommend a longer heparin treatment. Although no studies are available on this subject, a duration of about 10 days seems to be reasonable (*Hyers 2001*). Also in this case there are no valid reasons for delaying the beginning of OAT.

PT and APTT should be checked every day until discontinuation of heparin. When carrying out PT tests, it is preferable to use methods that are not too sensitive to the presence of heparin, such as those based on pre-dilutions of the sample or containing polybrene.

Both daily APTT checks and the use of reagents scarcely sensitive to heparin for the PT are superfluous when using low molecular weight heparins.

As already indicated (chapter 8), the antithrombotic effectiveness of OAs cannot be considered to be adequate for the first 4-5 days of the therapy because of the long half-life of some K-dependent coagulation factors, in particular factor II, and the consequent slow decrease of these factors after the beginning of OAT.

It is, therefore, necessary to remember that possible high INR values in the first 2-3 days of treatment do not represent a reliable indication of effective antithrombosis, since they are due to the early reduction of coagulation factor VII that has a very short half-life. When it is necessary to obtain an adequate level of anticoagulation quickly – e.g. in a patient with thrombosis in progress - it is generally best to use full anticoagulant doses of heparin therapy (unfractionated or low molecular weight heparin), and then to overlap OAT for a few days.

A further confounding factor can be present in patients treated concomitantly with heparin and OAT. As a matter of fact, unfractionated heparin (i.v. sodium heparin, or s.c. calcium heparin), especially in high doses, can cause a prolongation of the PT and therefore an increase of INR. Such an effect could be misleading, leading one to presume that the desired INR has been reached with OAT, whereas the INR increase is at least partially due to the simultaneous administration of heparin. In this case early interruption of the heparin therapy could be dangerous. This problem does not occur with low molecular weight heparins, which cause only minor variations of PT and APTT, even at therapeutic dosages. OAT should, however, be overlapped for a few days to ensure adequate protection of the patient, regardless of the type of heparin used. The most frequent clinical situation connected with such a need is the treatment of venous thromboembolism. It is currently recommended to start OAT as early as possible during heparin therapy (with either unfractionated heparin or low molecular weight heparin).

In the absence of evident contraindications to OAT (e.g. when there is no imminent necessity of invasive operations that would require to withdraw therapy), the first dose of warfarin (or acenocoumarol) can be given within the first 24 hours from beginning the heparin therapy. This procedure allows the desired OAT antithrombotic effect to be reached more quickly; this, in turns, allows heparin treatment to be suspended earlier, reducing the risk of thrombocytopenia correlated to it, the duration of hospitalization and costs (*Hirsh and Fuster 1994b*).

As shown in chapter 8, the problem of determining the initial dose of OAT, cannot be considered to be totally solved from a scientific point of view. The most commonly used initial doses in the clinical practice are 5-10 mg of warfarin (1-2 tablets of Coumadin) or 4 mg of acenocoumarol (one 4 mg tablet of Sintrom).

10. DISCONTINUING OAT

As far back as 1953, Cosgriff described that the frequency of thromboembolic recurrences was higher after the interruption of OAs, than during the period of treatment. While commenting this observation, the author suggested that «*....during prolonged treatment of patients with anticoagulants, a state of hypercoagulability can generate after terminating dicoumarol.*»

Cosgriff was the first to use the expression *rebound effect* to indicate this condition of hypercoagulability. Since then, the rebound effect has become the object of much discussion, and several observational, non-controlled clinical studies produced contradictory results. Many authors suggested that recurrent thromboembolism after termination of OAs is mainly due to the effect of a renewed thrombotic tendency, no longer inhibited by the anticoagulant drugs, in the patient (*Wright 1960*).

Scientific interest in this subject was rekindled when new laboratory methods were developed, which were sensitive enough to detect possible blood hypercoagulability. Changes in certain clotting tests after sudden withdrawal of OAs were first described in 1964 by Poller and Thomson, who later observed that these changes were less significant when OAT was discontinued gradually (*Poller and Thomson 1965*). Much more recently, other

changes in clotting tests indicating the existence of a hypercoagulable state after discontinuing OAT have been reported, such as: a progressive increase in fibrinopeptide A (a marker of increased thrombin activity) in plasma from patients with myocardial infarction (*Harenberg 1983*); an excessive increase in the procoagulant zymogens VII and IX, not compensated for by an adequate and timely increase in plasma levels of protein C and S, two physiological anticoagulant factors which also are vitamin K dependent (*Schofield 1987; Grip 1991*); and a significant rise of the activated form of factor VII (*Raskob 1995*). Finally, studies (*Palareti 1994; Palareti 1995*) have shown that interruption of OAT induces a moderate activation of the clotting system, which is not detectable during treatment. This phenomenon occurs sooner and more intensively when OAs are stopped suddenly rather than gradually. It has also been found to be transient and of little clinical relevance in the majority of cases. In some cases, however, such changes have turned out to be more pronounced and more prolonged. It may be surmised that these patients have a higher risk of recurrent thromboembolism after termination of OAs, although this has not yet been proven. Similar results were later reported after the suspension of both warfarin (*Genewein 1996; Ascani 1999*) and of acenocumarol (*Tardy 1997*).

Despite these data confirming the onset of biological changes after OAT withdrawal, there are currently no prospective studies demonstrating the clinical usefulness of gradual discontinuination of OAT. Therefore a gradual reduction of the daily dose before complete OAT interruption is commonly felt to be unnecessary.

Before discontinuing OAT it is nonetheless advisable to carry out a medical examination of the patient and to perform the appropriate tests and evaluations. This is necessary to exclude the existence of new clinical conditions that require the continuation of the therapy and that are different from the clinical conditions forming the original indication.

11. RESISTANCE TO OAs

As already known, the response to treatment with OAs is extremely variable and depends on a number of patient-related and/or environmental factors, many of which are poorly understood or predictable. Some of these factors have been recently described, including genetic polymorphisms of cytochrome P 450, the principal enzymatic system that catalyzes the conversion of warfarin into inactive metabolites (*Aithal 1999*). On the other hand, the possible fluctuations of the OAs' effect, even with stable drug doses, justify the need for adequate and constant laboratory checks; the time interval between two consecutive checks should be no more than a few weeks.

Some possible causes of different anticoagulant effects can be taken into account to predict the patient's response better.

Some points to be considered are:

a) the intensity of the response to OAs is, at least in part, inversely correlated to the patient's age, particularly in patients older than 50 years of age (*Gurwitz 1991*); this means that, on average, younger patients need proportionally higher doses;
b) in children, especially under one year of age, the per-kg doses of OAs required to maintain a desired therapeutic range are considerably higher (more than four times) than in adults (*Andrew 1994a*);
c) on average, absolute doses of OAs required to maintain a desired therapeutic range are directly correlated to body weight (*Dobrzansky 1993*);
d) different ethnic groups can have different sensitivities to OAs (*Poller and Taberner 1982*).

11.1. Patients with poor anticoagulation

It is not uncommon to find patients who need high doses of OAs to maintain the INR within the desired therapeutic range. There are many reasons that explain this phenomenon. The following list is an attempt to classify them in order of frequency, from the most common one to the rarest:

a) lack of patient's co-operation (intake errors, poor compliance);
b) interaction with other drugs;
c) a diet containing high levels of vitamin K;
d) metabolic alterations (hypothyroidism, hypercholesterolemia);
e) malabsorption of the drug;
f) genetic factors.

The most frequent problems can be solved by properly informing and training patients to remember to take the prescribed drug at the same time of the day, without forgetting it. Patients must also be asked to report any other drugs they are taking, along with their eating habits, particularly the intake of vegetables that are rich in vitamin K (*Kalra 1988*).

The drugs most notably interfering with therapy are anticonvulsants, particularly barbiturates, which, because of their enzyme-inducing mechanism, make the liver metabolism of OAs much faster, thus considerably reducing their half-life.

It is sometimes difficult to achieve the desired therapeutic range with *average* doses of OAs. This phenomenon occurs in patients with metabolic alterations such as hypothyroidism and hypercholesterolemia (*Robinson 1990*).

Cases of specific OA malabsorption are considerably rare. Malabsorption syndromes generally

cause the opposite problem, namely a hypersensitivity to the action of OAs, because they tend to reduce vitamin K absorption.

Finally, cases of true resistance to OAs are extremely rare. This phenomenon is linked to hereditary factors, as confirmed by the description of several families showing a genetically-determined resistance to warfarin (*O'Reilly 1960; O'Reilly 1970; Alving 1985*).

11.2. Therapy with OAs in "resistant" patients

After it has been ascertained that the problem does not stem from specific and modifiable eating habits, an increase in the daily dose of OAs is generally sufficient to reach the desired INR. Daily doses of 15-20 mg of warfarin (12-16 mg of acenocoumarol) are not uncommon in patients treated with anticonvulsants. There is no conclusive evidence about toxicity linked to such doses and the only precaution worth to be suggested to these patients is to be careful if the drug influencing the anticoagulation is suddenly discontinued or reduced. In some rare cases, fractionated administration of OAs (i.e. divided into 2 daily doses, to be taken between meals) can make it easier to reach and maintain the desired INR levels.

There are no studies to date on the treatment of patients with genetically-determined resistance to OAs. Should it be impossible to reach therapeutic INR values utilizing very high doses of OAs, then the only solution to propose the use of heparin. It could be useful to replace warfarin with acenocoumarol (or *vice versa*) or possibly to replace both with phenprocoumon (whose commercial name is Marcumar®; this drug is not available in Italy, but can be easily purchased in Switzerland), since the resistance to OAs can be determined by a mutation of the epoxide-reductase enzyme, which induces a reduced affinity to OAs.

12. FACTORS INFLUENCING THE ANTICOAGULANT EFFECT OF OAT:DIET, LIVING HABITS, SEASONAL VARIATIONS

12.1. Vitamin K and diet

There are many molecular forms of vitamin K, including phylloquinone, which is found in vegetables, and menaquinone, which is synthesized by gut bacteria. Since the liver deposits of vitamin K are rather limited, the minimum daily requirement is 1 mg/kg/day. Most of the vitamin K in our body comes from the vegetables in our diet; Table 4 lists the vitamin K content of the most common vegetables. A normal diet includes between 300 and 500 mg/day of vitamin K, which is well above the minimum requirements.

Table 4. Vitamin K content of some foodstuffs.

Food stuff	*Vitamin K (µg per 100 g)*	*Food stuff*	*Vitamin K (µg per 100 g)*
Whole milk	1	Rabbit	4.5
Lamb	5.7	Chicken with bones	4.5
Chicken breast	6.7	Horse meat	6.7
Ham	7.3	Bresaola	7.1
Sarago fish	3.3	Mullet	3.7
Red mullet	4	Sole	3.8
Fresh tuna fish	10	Tuna fish in olive oil	11
Bel Paese cheese	5	Swiss cheese	5
Fontina cheese	5	Parmigiano cheese	5
Fresh pecorino cheese	5	Sweet Provolone cheese	5
Certosino cheese	5	Mozzarella cheese	5
Fresh ricotta cheese	5	Potatoes	4
Semolina	3.8	Pasta	3.8
Rise	3.8	Corn meal	3.8
Bread	3	Olive oil, corn oil	50
Butter	50	Carrots	10
Mushrooms	6.4	Asparagus	11
Spinach	108	Tomatoes	18
Lettuce	160	Beets	4
Broccoli	33	Cabbage	34
Cauliflower	33	Cucumber	4
Peas	7	Beans	14
Apples	4.6	Strawberries	12
Oranges	4	Eggs (n. = 1)	25

12.2. Vitamin K and osteoporosis

It is now known that, in addition to vitamin K-dependent coagulation factors, other vitamin K-dependent proteins exist in the plasma, in the bones, and in other organs such as the kidneys, pancreas, spleen, lungs, and placenta. Among these, the best known protein is osteocalcin, which is found in the extracellular matrix of the bone. Although the function of osteocalcin is not yet completely clear, its level in serum is considered an important indicator of osteoblastic activity. As in the coagulation proteins, glutamic acid residues (Gla residues) facilitate the binding of Ca ions to hydroxyapatite; in other words, proper bone calcification requires the presence of osteocalcin that is functionally activated via Gla residues (*Shearer 1995*).

An vitamin K intake of at least 1 µg/kg/day is probably essential for the proteins involved in coagulation to work optimally. However, there are still some doubts as to the dietary supply of vitamin K in the elderly. In 1985, a study was published on the serum levels of vitamin K in two groups of patients: one included older patients (63-88 years old) with fracture of the femur; the other included patients (60-85 years old) who had suffered from fractured vertebrae 8 months to 5 years before the study. In both groups, vitamin K values were sig-

nificantly lower (98±20 and 79±10 pg/mL) than those observed in a group of healthy people (355±51 pg/mL), similar for gender and age (51-81 years) (*Hart 1985*). These findings suggest that there is a link between osteoporosis and low levels of vitamin K. This is probably true, considering the result of a subsequent study by Knapen *et al.* (1989), who compared osteocalcin levels, calciuria, and the ability of osteocalcin to bind hydroxyapatite in a group of women of child-bearing age (25-40 years) and in a group of post-menopausal women (nuns/55-75 years) before and after a 14-day treatment with 1 mg/day of oral vitamin K. The results of this study pointed out that the group of nuns showed a significant rise in osteocalcin levels, a reduction in calciuria, and an improved ability of osteocalcin to bind hydroxyapatite after 14 days of treatment. Although the data are not conclusive, it is possible that supplementing the diet of elderly people with relatively low doses of vitamin K could reduce the incidence of fractures linked with osteoporosis.

12.3. OAs and osteoporosis

At this point, we might question whether coumarin drugs can induce a decrease in bone density, since they compete with vitamin K for the epoxide-reductase enzyme, thereby inducing a marked reduction of Gla residues in vitamin K-dependent proteins. The answer is still not definitive, because only two studies in the literature studied this topic, and they yielded conflicting results (*Fiore, 1990; Rosen, 1993*). Nevertheless, it should be remembered that a recent study showed that prolonged treatment with OA can increase the risk of vertebral and rib fractures (*Caraballo, 1999*).

12.4. Diet of known vitamin K content and OAs

It is well-known that 20-25% of the patients treated with OAs have poor anticoagulation for the following reasons (*Kumar 1989*):

a) poor compliance
b) drug interaction
c) intercurrent diseases.

Moreover, not enough attention has been paid to diet. The literature only contains anecdotal reports about the variability of oral anticoagulation after ingestion of large quantities of vegetables (*Kempin 1983; Kalra 1988*). These reports take into consideration only a few foodstuffs, while the authors conclude that patients on OAT should avoid eating vegetables rich in vitamin K (broccoli, lettuce, spinach, cabbage, etc). It would appear more rational to administer a diet of known vitamin K content, especially to manage patients with poor OAT control not caused by the three above mentioned reasons. For this reason, a diet of known vitamin K content (40 μg/day) was followed for two months by a group of patients with poor OAT control (*Marongiu 1992*). The results of this study pointed that the percentage of INR values within the therapeutic range (84%) during the diet with known vitamin K content was significantly higher (p= 0.002) than in the two previous months in which the patients were on a free diet (53%).

The average INR values were found to be significantly higher (p=0.03) during the diet under examination (2.9) than during the free diet (2.6). These findings suggest that a diet of known vitamin K content can be successfully prescribed for patients with poorly controlled anticoagulation. A detailed history of the patient's dietary habits should be collected before starting such a dietary treatment. OAT patients may not need to be treated with a low vitamin K diet, provided that the vitamin K intake is kept constant (even if it as high as about 300-400 μg/day). To facilitate implementation of this dietary treatment, a complete list of foodstuffs and their uses was published a few years ago (*Sorano, 1993*).

More recently, a longer list of foods was published. This extended the range of foods with a known vitamin K content which may be included in the diet (*Boot 1997*). The general recommendation is to let the patients eat what they wish, and introduce a constant amount of vegetables in their diet. Patients should be informed about the risk of eating large quantities of cabbage, broccoli or lettuce irregularly, as these foods may alter their level of anticoagulation. In fact, careful questioning often reveals a large intake of these foods the night before blood tests that resulted in an unexpectedly low INR value. A diet of known vitamin K content should only be prescribed to patients with a poor control of OAT and very irregular dietary habits, and should be used only very rarely in everyday practice.

12.5. Habits and life-style

Seasonal variations in the prothrombin time induced by OAs were studied by Manotti *et al.* (1994); their study highlighted significantly lower INR values during the spring (2.92) and summer (2.93) than during the autumn (3.09) and winter (3.11) (p=0.018). These findings were correlated to the fact that a larger amount of fresh vegetables rich in vitamin K are sold in the spring and summer around Parma, where the study was conducted. It is worth noting that these differences were not clinically significant, but once again they indicate that diet may play a role in the management of OAT patients.

The quality of life of patients on OAT was evaluated via a questionnaire in a relatively small group of patients (179) participating in the Boston Area

Anticoagulation Trial (*Lancaster 1991*). The results of this study, published in 1991, indicate that treatment did not significantly modify the lifestyle of the patients; in other words, in most cases warfarin did not limit the physical activity of the patients (72%), who were also not concerned about possible bleeding (79%). About 40% of the patients interviewed felt themselves more protected by OAT.

A research questionnaire on quality of life was recently distributed to two groups of patients in the FCSA Clinics of Cagliari and Padua (*Barcellona 2000*). The results showed that OAT was a restriction to the patients' daily lives in 11% of the cases, because the patients were afraid of the possibility of bleeding or having a recurrent thrombotic episode and were worried about forgetting to take OA pills. Twenty-three percent of the patients considered it difficult to maintain the PT at a therapeutic value because of seasonal changes, the introduction of new drugs, or because of difficulties in maintaining a constant vegetable intake. Among the results obtained, it is significant to notice that patients with a low degree of education believed that the explanations given to them by the physicians at the Anticoagulation Clinic were too complex, and that they felt that the physicians did not dedicate enough time to the patients. This suggests that more attention should be paid to the education of the patients, in order to obtain the best possible adherence to OAT.

13. DRUG INTERACTIONS IN OAT

The association of other drugs with OA can deeply influence the management of OAT. This phenomenon is relevant from a clinical and epidemiological point of view, because most of the patients for whom OAT is prescribed usually require complex pharmacological therapies; this is true especially for elderly patients with multiple pathologies. OAs have particularly unfavorable pharmacological characteristics that make them easily to interact with other drugs. Some of these characteristics are:

a) the binding (>95%) with plasmatic proteins, from which OAs can be displaced by several drugs;
b) the hepatic metabolism dependent on the enzymatic system of P450 cytochrome, which is itself influenced by the activity of many drugs;
c) the rather narrow "therapeutic window", outside of which hemorrhagic and thrombotic complications occur.

A large number of pharmacological interferences with OAs , and in particular with warfarin, have been reported in the literature. However, it is often difficult to identify such phenomena in the clinical practice, because the variations of anticoagulation levels can depend on other frequent factors of variability, such as discrepancy in the performances of laboratory methods, patients' compliance to the therapy or diet. Moreover, it is necessary to establish the real clinical value of the different drug interactions on a case-by-case basis. In most cases, these interactions are of moderate entity and do not translate into an actual increase of hemorrhagic or thrombotic complications.

13.1. Definition of pharmacological interference

A drug is said to interfere with OAs when its intake or withdrawal causes changes in anticoagulation levels (INR) that induce significant adjustments of OA dosage (> 25%) in patients who show good compliance, were within therapeutic range during the previous three controls, and in the absence of other possible causes of variations (*Wells et al. 1994*).

By using strict evaluation criteria, Wells *et al.* (1994) analyzed almost 800 reports of possible pharmacological interactions that were published between 1966 and 1993. The available data supported a high probability (level of evidence 1) judgement about interaction with OAs for only 43 drugs (16 drugs increasing OA effects, 10 inhibiting them and 17 without any effect). By applying this definition to 1,000 mostly cardiological patients treated at the Anticoagulation Clinic of Padua during 5 years, 51 cases of drug interference were identified. As many as 19 of these cases involved the reaction to a potent antiarrhythmic agent (amiodarone).

FCSA has recently created a register for drug surveillance (the web site of FCSA).

13.2. Mechanisms

A drug can interfere with the biological activity of OAs via different mechanisms (Freedman 1994):

– Some drugs act by modifying absorption, protein binding or OA liver metabolism, ultimately determining a variation in OA plasma concentrations (pharmacokinetic type interaction). In this case, it is possible to offset the effect of these drugs by correctly varying the anticoagulant dosage. In the case of chronic coadministration of interfering drugs, it is therefore relatively simple to reach and maintain stable INR values. The problem becomes much more difficult to manage when sudden changes in combined therapy are necessary, due to the addition or discontinuation of interacting drugs. In this case, treatments that may be indispensable to the patient should never be stopped, and it could be more practical to plan for earlier and more frequent laboratory checks, in order to better regulate the OA dosage.
– Other drugs interact with different components of the hemostatic system (e.g. the concentra-

tion of the clotting factors or platelet function), without modifying OAs concentration (pharmacodynamic type interaction). In this case, interfering drugs, such as aspirin or ticlopidine, should only be used with extreme caution in combination with OAs and only in situations where their real effectiveness has been shown to produce a negligible increase in the risk of bleeding.
- Lastly, some drugs interfere with multiple mechanisms, both pharmacodynamic and pharmacokinetic (e.g. some anti-inflammatory drugs).

It should then be remembered that some drugs can determine interactions that vary over time, such as sulfinpirazone, that initially provokes a potentiating effect on warfarin through its mobilization from protein binding, and then an inhibition by induction of its hepatic metabolism (*Nenci et al, 1982.*)

13.3. Relevant clinical interactions

Previous editions of this guide included extensive lists of drugs which interfere with OAT, grouped according to their class and on whether they yielded a reinforcing or inhibiting effect. A shorter list is published in this edition of the guide (Table 5); this list, that can more easily be remembered, includes only those drugs that are considered to have a highly probable interaction with OAs (evidence level 1), according to the above mentioned study (*Wells et al. 1994*). A complete list of all potentially interfering drugs, reported in alphabetical order and by commercial name, is included in a booklet published by the Rome FCSA Anticoagulation Clinic (*Dept of Hematology, La Sapienza University, Rome*), that can be consulted on the FCSA's web site (*www.fcsa.it*).

Table 6 lists the most commonly used and relatively safe drugs to be used in OAT patients; this list provides a quick guide in the more common situations of clinical practice. As already mentioned, OAT patients often need concomitant therapy with interfering drugs; in this case the physician can predict the approximate OA dosage variations. For example, starting treatment with amiodarone will require an average 35% decrease (range 23-46%) of the average warfarin dose; withdrawing this treatment will induce a greater variability, but on average warfarin dosage has to be increased by 60%.

Likewise, when treatment is begun with antiepileptic drugs, warfarin dosage should be increased ranging from 25% for barbiturates to 100% for carbamazepine (*Croop and Bussey, 1997*). Barbiturates or carbamazepine therapy could, on the other hand, be influenced by OAT, since cases of minor epileptic crises have been reported after patients started OAT.

As for analgesic–anti-inflammatory drugs, which are very frequently associated to OAT in the clinical practice, it should be remembered that many interfering drugs can also cause gastric lesions and can induce easily bleeding injuries in OAT patients.

Pure painkillers, such as paracetamol, should be used for the treatment of pain, especially if it is not associated to inflammation; otherwise, anti-inflammatory drugs that are less damaging on the stomach, such as ibuprofene, should be used. A new class of anti-inflammatory drugs, i.e. cicloxygenase 2 (cox-2) inhibitors, has been recently introduced in the clinical practice; these drugs should be less damaging on the stomach than traditional NSAIDs and should not significantly inter-

Table 5. Pharmacological interactions of significant clinical relevance.

Antibiotics	*Cardiovascular drugs*	*Anti-Inflammatory drugs*	*Central nervous system drugs*	*Gastrointestinal drugs*	*Miscellaneous*
Reinforcing OAT					
Cotrimoxazole	Amiodarone	Acetylsalicylic acid		Cimetidine	Tamoxifen
Ciprofloxacin	Quinidine	Phenylbutazone		Omeprazole	Danazol
Erythromycin	Propafenone	Piroxicam			
Tetracycline	Propranolol				
Isoniazide	Sulfinoyrazone				
Metronidazole	Fibrates				
Fluconazole	Sinvastatin				
Miconazole	Acetylsalicylic acid				
	Ticlopidine				
Inhibiting OAT					
Rifampicin	Cholestyramine		Carbamazepine	Sucralfate	Vitamin K
Nafcillin			Phenobarbital		
			Phenytoin		

Table 6. A rapid guide to the choice of drugs to be used in association with oral anticoagulants.

Antibiotics
Penicillins
Aminoglycosides
Enoxacin
Paramomycin
Cardiovascular drugs
Atenolol
Disopiramide
Flecainide
Lidocaine
Calcium-blockers
Furosemide
ACE – inhibitors
Pravastatin
Digoxin
Antinflammatory drugs and painkillers
Paracetamol
Ibuprofen
Naproxen
Corticosteroids
Central nervous system drugs
Benzodiazepines
Tricyclic antidepressants
SSRI*
Sodium valproate
Ethosuximide
Miscellaneous
Ranitidine
Pantoprazole
Metformin
Anti-influenza vaccination

*Serotonin-selective reuptake inhibitors

fere with OAs. However, the association of these drugs with OAT still requires caution, because only a limited number of studies on healthy volunteers are available. Nowadays, no relevant pharmacological interferences have been found by the FCSA Clinics; however, a definite clarification of this issue will require a specific study on patients in stable OAT.

13.4. Practical aspects

The risk of hemorrhagic or thrombotic complications due to pharmacological interference can be minimized with appropriate measures. First of all, an adequate patient education is fundamental; patients must learn to consult the Clinic or a physician before beginning or suspending an associated treatment. This applies not only to traditional drugs, but also to all herbal preparations and homeopathic treatments (*Argento 2000*). Patients should also be instructed to record and report the use of any drugs or preparations, including over the counter drugs and drugs for topic use (creams, ointments, etc.), and to inform any caregivers that they are on OAT. The physician in charge of OAT monitoring should give to the patients a list of non-interfering drugs for the treatment of common health problems, such as fever or pain.

If a chronic treatment with interfering drugs is started or suspended, frequency of laboratory checks must be increased and OA dosage adjusted until a new stable level is achieved.

14. EDUCATION OF ANTICOAGULATED PATIENTS

14.1. Importance of informing/educating the patient

A number of findings indicate that anticoagulated patients are not sufficiently informed about the potential complications and risks of OAT (*Lancaster 1991*) and this also has, obviously, a negative consequence on their compliance.

In a recent study, a questionnaire was used to evaluate patients' knowledge about OAT (*Taylor 1994*). The results of this study showed that the physicians of Anticoagulation Clinics provided better advice and more complete information than hospital ward doctors. Nevertheless, there was a considerable gap between the information given to the patients and what the patients had actually learned about OAT. Physicians were not providing patients with enough information and recommendations, and patients were in turn unable to understand and utilize their advice.

Physicians in charge of anticoagulated patients therefore need to provide a whole set of information and should cultivate the patient's education, with the support of a team of well-trained nurses. Naturally, once this practice has been implemented, the information that a patient has retained should be reassessed from time to time.

Thorough knowledge of the risks and benefits of OAT can positively influence a patient's quality of life. A study considering the influence of low-dose warfarin on the perceived quality of life in patients affected by atrial fibrillation and treated with OA found that there is no difference between patients treated with warfarin and a comparable group treated with a placebo, except for those who suffered from one episode of bleeding (*Lancaster 1991*), in whom a negative effect on the perceived quality of life was recorded. Of course, such negative effects can be offset by the confidence of knowing the protective effectiveness of OAT. These findings show the importance of correct, continuous education for anticoagulated patients, both in terms of perceived quality of life and of compliance during the anticoagulant therapy.

14.2. "Therapeutic" health education of patients

This is an ongoing process of garnering information and learning about the many aspects of good therapeutic practice, of the risks linked to OAT, and of the importance of contacting the Anticoagulation Clinic when necessary.

Within the framework of the patient's education, the following items should be considered:

A) Explanation of:
- purposes and risks of OAT;
- duration of treatment: short-term (3-6 months) or long-term (lifelong);
- need to conduct periodic checks (both clinical and laboratory tests);
- need to be meticulous about taking the anticoagulant drug;
- helpful tips to remind patients about taking their drugs (for example, written notes in their daily agenda, etc.), informing them that if they forget to take their OA drug one day, they should not take a double dose the next day.

B) Information about:
- the risk of pharmacological interference (causing increased drug effect, with an increased risk of bleeding, or reduction in drug effect, and a consequent rise in thrombotic risk), providing a list of (relatively) safe drugs to take for common problems such as fever and pain.
- the danger of spontaneous variations in dosage: a higher dose can increase the risk of bleeding; a lower dose can increase the risk of thromboembolism;
- the need to contact the Anticoagulation Clinic immediately in the case of bleeding, whether minor or major, so that INR and complete blood count can be checked at once and so that the possibility of discontinuing OAT and/or administering vitamin K or coagulation factor concentrates can be assessed;
- the need to inform the Anticoagulation Clinic in advance of any scheduled surgery, whether major or minor (e.g. as dental extractions), in order to utilize appropriate protocols for the reduction or suspension of OAT, possibly replacing OA with heparin, according to the patient's needs;
- the relationship between routine OAT practice and the patient's health, which may interfere with the level of anticoagulation. In particular, more attention should be focused on febrile conditions due to common intercurrent illnesses (flu, bronchitis, urinary tract infection, etc.), evaluating the possibility of modifying anticoagulant dosage and/or the date of the next check-up (which will be scheduled sooner, owing to the possible association of other drugs, such as antibiotics, anti-inflammatory agents, analgesics, that could interfere with OA).

Moreover, attention will have to be paid to a possible deterioration of the basic disease, which could be associated with changes in food assumption / digestion, and in co-medication, and the consequent need to modify anticoagulant dosage.

In conclusion, a considerable amount of intellectual resources and time should be spent in enhancing the patients' knowledge and improving the relationship between them and the physicians at the Anticoagulation Clinic. The goal is clearly to optimize results: lower risks and increase treatment effectiveness.

The importance of *therapeutic* education for patients affected by chronic diseases has been recently restated in a report by a working group of the World Health Organization (*WHO 1998*), in the area of continuing educational programs for health personnel in the field of prevention of chronic diseases. This program is particularly appropriate for the *chronic* condition of patients, undergoing long-term OAT.

Educating the patient consists in helping the patient to acquire or maintain the competence they need, to adapt their lives in the best possible way to a chronic condition, and to the consequent chronic therapy, and is a continuous and integral part of the patient's care.

According to this report, education must be structured, organized and offered systematically to every patient in a variety of ways (interactive seminaries, news sheets, videos, etc). The program multidisciplinary, because it entails group work and must include an evaluation of the learning process and of its effects. It is a continuous process, integrated into the patient's treatment and centered on the patient's needs, and should be given by specifically trained personnel. It comprises an education program, which begins with an analysis of the patient's problems and the identification of the objectives, and continues with determining the contents of the course, the teaching material to be used and lastly, an evaluation of the obtained results.

The teaching material consists of conferences, which can also be personalized, written guidelines, audio/video registrations and so on. The contents should be based on the following themes: *Generalities of coagulation*, *Purposes and risks of OAT*, *Target INR*, *Checks Frequency of checks*, *Drug interactions*, *Diet and vitamin K*, *Intercurrent diseases*, *Hemorrhagic symptoms*, *Thrombotic symptoms*, *Major and minor surgery* and *Pregnancy*.

Booklets with the above mentioned educational information for anticoagulated patients are currently available at the FCSA Clinics. Specific brochures are being prepared for every pathology

in which anticoagulant treatment is indicated, together with an educational video, which is being produced in collaboration with the Italian Association for Anticoagulant Patients (AIPA).

As for the patients' level of learning, this can be verified either directly with pre- and post – education tests (questionnaires), or, in a more result-oriented way, by tests of treatment quality, for example, the time spent by patients within the therapeutic range, or the clinical performance over time, such as the frequency of hemorrhagic and/or thrombotic episodes.

Naturally, many obstacles can be encountered while implementing a *therapeutic* educational program for patients. These obstacles include lack of human resources (expert teachers), insufficient group work, insufficient motivation within Health Institutions, and the lack of educational and financial resources (both short and long term). However, each Center must at least offer a structured program of monthly or three-monthly meetings with patients, because these meetings are without any doubt the ideal way to obtain effective and safe anticoagulant treatment.

It is clear that in order to guarantee the success of such education, teachers must be trained and the opinion of the patients should always be held in proper consideration, remembering that therapeutic education remains a continuous process, centered on the patient.

15. LABORATORY MONITORING OF OAT: PROTHROMBIN TIME

OAT laboratory checks should be carried out periodically during OAT by monitoring the prothrombin time (PT). The PT is defined as the coagulation time (in seconds) of a mixture of citrated platelet-poor plasma, tissue thromboplastin and calcium ions. The test is sensitive to the deficiency induced by oral anticoagulants (factors II, VII and X, whose syntheses depend on vitamin K). Moreover, PT is sensitive to the deficiency of factor V and fibrinogen (*Quick 1935*). A variation of the test described above uses *combined* reagents that, in addition to tissue thromboplastin, contain optimal amounts of factor V and fibrinogen, with the purpose of making the test more specific for monitoring OAT (*Owren 1959*). Such modified tests, which were very popular in the past, especially in the Netherlands and in Scandinavia, have the disadvantage of much longer coagulation times than those obtained using plain thromboplastins. Since some of these tests use bovine thromboplastin, they are also highly sensitive to the activation of factor VII.

15.1. Sources of variability and PT standardization

There are many pre-analytical and analytical variables influencing PT that make it very difficult to compare results obtained in different laboratories, as well as those obtained in the same laboratory on different days. The importance of standardizing pre-analytical and analytical procedures is obvious, given that the anticoagulant drug dosage is based solely on test results.

15.1.1. Pre-analytical variables (see Tripodi 1989).

Blood should be taken via clean venepuncture with minimum stasis, in order to prevent contamination with tissue factor, which would activate early and non-controlled coagulation. The collection and storage of blood must be carried out with no-contact material (i.e. syringes and test tubes made of plastic or siliconized glass). The use of vacuum systems to collect blood samples is acceptable and should be encouraged, because it allows this important pre-analytical step to be standardized. The anticoagulant of choice is trisodium citrate (bihydrated) 0.109 M, corresponding to 3.2% concentration. Unfortunately, no consensus has yet been reached on the citrate concentration to be used to anticoagulate the blood. In some countries (the U.K and the Netherlands), lower concentrations corresponding to 0.105 M (3.1%) are more popular. In other countries a concentration corresponding to 0.129 M (3.8%) is more widely used. Recent observations in the literature show that the concentration of citrate can considerably influence the INR value (*Chantarangkul, 1999*). As a result, the adoption of the recommended concentration cannot be deferred any longer. When collecting tubes with 0.109 M citrate are not available, it is possible to use tubes with a 0.105 M concentration. As a matter of fact, there is no significant difference in the concentration range 0.105-0.109 M (*van den Besselaar 2000*). Anticoagulant and blood must be quickly mixed at a constant ratio of 1 to 9. Since the anticoagulant remains confined to plasma, its concentration will depend on the patient's hematocrit (the higher the hematocrit, the greater the concentration of citrate in plasma and *vice versa*). Hypercitrated plasmas lead to coagulation times that are proportionately longer and *vice versa*. In theory, it would be important to adjust the blood/anticoagulant ratio in all those cases in which hematocrit differs from normal values. In practical terms, it is enough to adjust the amount of anticoagulant (tables and formulae are available for this purpose) for extreme hematocrit values (i.e., lower than 30% or higher than 60%).

Larger and more dangerous deviations from the correct ratio are often obtained when vacuum sys-

tems are used improperly, such as when blood samples are drawn too quickly, or when defective test tubes without a sufficient vacuum are used. Blood must be centrifuged immediately after sampling (2,000 g, which correspond to roughly 3,500-4,000 rpm using standard table top centrifuges), and the plasma thus obtained must be stored capped (to avoid loss of carbon dioxide) at room temperature for a maximum of 3-4 hours. Plasma must not be stored at lower temperatures, because this would probably activate factor VII leading to a decrease of the clotting time. When the storage time is long, plasma must be kept in a sealed test tube, to prevent major losses of CO2 and pH variations.

15.1.2. Analytical variables

Besides having accurate dispensers (i.e. pipettes or delivery pumps) and thermostated systems (i.e. instrumentation or water baths), which should always be kept under control, the most important variable for test standardization is the different sensitivities of commercially available thromboplastins to the deficiency induced by OAT. Thromboplastins of different origin, but also those of the same species, may yield extremely different clotting times when the test is carried out on the same plasma. Over the years, the need to remedy this situation led to a series of proposals. These started by expressing results initially as percentage activity, extrapolated from a calibration curve prepared by using diluted normal plasma and then as a ratio with normal plasma (ratio).

Neither of these two attempts, however, was able to harmonize the results obtained by different laboratories, so that in the early 1970s a new system was tried. This consisted of calibrating commercial reagents via standard reference thromboplastins, with the aim of deriving an index that could link all reagents, thus allowing the conversion of results into a universal scale (*Kirkwood 1983*). In the early 1980s, a calibration system was devised and the first international standard thromboplastin was introduced. In 1983, with the official approval of the World Health Organization (WHO), the INR (International Normalized Ratio) was introduced for the expression of the PT results to monitor OAT.

15.2. Calibration of thromboplastins and the INR system

According to the WHO recommendations (*WHO Expert Committee on Biological Standardization 1999*), in order to calibrate a thromboplastin reagent against the International Standard, the PT should be measured with both reagents for plasmas from at least 20 healthy subjects and 60 patients on stabilized OAT. A calibration plot is then built by reporting on a double log scale the PTs obtained with the standard thromboplastin (vertical axis) versus the PTs obtained with the thromboplastin to be calibrated (horizontal axis). The relationship that exists between the data points is approximately linear. The line slope, called the ISI (International Sensitivity Index), expresses the sensitivity of the thromboplastin to be calibrated relative to the International Standard. If the thromboplastin to be calibrated has the same sensitivity as the Standard, the coagulation time obtained with the two reagents will be very similar; the line then has a slope of 45°, the tangent is equal to 1 and the ISI is 1.0. (equal sensitivity). An ISI greater than 1 means lower sensitivity compared to the Standard and *vice versa*. Once the ISI value of the working thromboplastin is known, it is possible to transform the PT obtained on plasmas of OAT patients into an INR. The conversion is obtained by dividing the patient's PT by that of the mean normal PT obtained under the same experimental conditions and raising this ratio to a power equal to the ISI of the thromboplastin used for testing. The INR value thus obtained represents the value that would have been obtained if the International Standard had been used for the measurement of the PT instead of the working reagent. The reliability of both parameters of calibration (ISI and mean normal PT) are the crucial factors of the ISI/INR system.

15.2.1. ISI

The ISI influences the INR in an exponential fashion, magnifying even minor differences in coagulation time, especially with high ISI reactants. In Italy, there is still no legislation regulating the certification of the ISI values of thromboplastin reagents. These values are usually provided by the producer of the reagent. Due to the variability among batches, even of the same thromboplastin, the values printed on the package cannot be extrapolated and used for other batches of the same material. Furthermore, since it has been shown that ISI values may vary even using different instrumentation (*Chantarangkul 1992*), it is essential that producers of reagents indicate for which instrumentation the ISI value is intended. Since it would be far too costly to calibrate each reagent on the market with the vast array of instrumentation available today, International Standardization Authorities are currently evaluating the possibility of appropriately modifying the calibration procedure.

It is very likely that in the near future, local calibrations will be made directly on the system employed by individual users, by using a limited number of freeze-dried plasmas previously calibrated against the International Standard (Poller 1995). The validity of this system is still the object of several studies and will not therefore be addressed in this booklet.

The first advocates the use of a set of freeze-dried calibrant plasmas with assigned PT in terms of an appropriate international standard. These

plasmas can be used locally to determine the PT with the system under calibration. A calibration plot is then built by reporting certified PT values versus local PT values on a double log scale, thus deriving the local ISI (*Poller 1995*). The second system advocates the use of lyophilized plasmas with assigned INR in terms of an appropriate international standard (*Houbouyan & Goguel 1997*). These plasmas should then be used to determine the local PT and to construct a calibration curve (certified INR versus local PT), from which it would be ultimately possible to derive the patients' INR. Both systems seem to be promising (*Houbouyan & Goguel 1997; Chantarangkul 1999*), but remaining problems should be solved before they can be safely used in the standardization of the PT. Until then, caution should be exerted and these systems should be employed only after having provided evidence that their results are comparable to those obtained with the conventional calibration system.

15.2.2. Mean normal PT for calculating INR

There are three possible options, reported here in order of priority.

(i) The geometric mean of PT based on 20 or more healthy subjects, calculated under the same experimental conditions (same batch of reagent and instrumentation) used for determining the patients' PT. This value must necessarily be recalculated for each new batch of reagents. The use of this system implies a careful evaluation of the intralaboratory daily quality check.

(ii) The PT value obtained daily with a pool of frozen normal plasma, which will be analyzed during the same testing series as the patients.

(iii) The PT value obtained daily with a pool of freeze-dried normal plasma. In these last two cases, it is essential to make sure that the value is not significantly different from the one obtained using a geometric mean of 20 or more healthy subjects.

The choice will have to be made on the basis of local conditions (availability of healthy subjects, proper equipment for freezing and storing, etc.).

15.3. Validity of the INR

The INR system allows the differences between systems to be minimized and the results obtained in different laboratories to be compared, with good approximation. It is important, however, to remember that this is a system based on the evaluation of averages. As a result, INR differences obtained with different systems on plasmas of individual patients may be occasionally recorded. In particular, the INR system is reasonably accurate in the following situations (*WHO Expert Committee on Biological Standardization 1999*):

1. Patients on oral anticoagulant therapy.

The ISI is determined by using plasma from patients on oral anticoagulant therapy. It should not therefore be expected that the ISI is valid in every clinical condition, besides oral anticoagulant therapy.

2. For an anticoagulation range included between 1.5–4.5 INR.

The ISI is determined by using plasmas from anticoagulated patients, in the range included between 1.5 and 4.5 INR. As a result there may be no correspondence among INR values obtained with different systems outside this range. For the same reasons, the INR value may not be exactly proportional to the anticoagulation level for values greater than 4.5.

3. In a stable phase of the therapy.

The ISI is determined by using plasmas from patients stabilized within their therapeutic range. During the induction phase, factor VII, which has a relatively short half-life, is the first vitamin K dependent factor to decrease; as a result, different systems could measure different values of INR because of their different responsiveness to this factor.

15.4. Effect of heparin on the INR

PT too can be influenced by heparin, although significantly less so than APTT; this has to be taken into account when heparin therapy is overlapped with OAT.

Information on the responsiveness of different thromboplastins to heparin is very scarce and anecdotal (*Lutomski 1987; Schultz 1991*); however, it can be surmised that it may vary considerably according to the system used. It is, therefore, dangerous to generalize. Some commercial reagents include the addition of optimal amounts of substances that neutralize heparin, such as, prolybrene or heparinase. Such reagents should be insensitive to heparin when present in quantities up to 1.0 U/mL. For a correct interpretation of the results, the laboratory should be aware of the responsiveness of its reagent to heparin (*Leech 1998*), and also of the presence of substances that neutralize heparin and of their consequences (*Tripodi 1999*).

Whenever possible it is preferable to use insensitive reagents.

15.5. Effect of lupus anticoagulant on the INR

Although PT is not particularly sensitive to lupus anticoagulant (LA), its presence in plasma could result in an artificial increase of the INR.

There are at least five independent studies investigating the effect of LA on the INR, but they reached opposing conclusions. Two studies con-

cluded that INR is not reliable in the presence of LA, because it does not appear to represent the true level of anticoagulation and it would actually depend upon the reagent used (*Della Valle 1996, Moll 1997*). Three more recent studies minimized the relevance of this effect, confirming it for only one of the studied reagents and for a limited number of patients (*Lawrie 1997, Robert 1998, Tripodi 2001b*). It would, therefore, appear that the effect of LA on PT-INR is marginal for most reagents.

However, considering the heterogeneity of LA, one cannot exclude the possibility that there are patients for whom the PT-INR is inadequate. A typical example are those patients in whom basal PT is already prolonged before starting OAT. In these cases the available alternatives to INR are scarce.

Combined thromboplastins (to which with optimal amounts of factor V and fibrinogen have been added) could minimize the effect of LA, since a higher plasma dilution is used with such reagents. However, these are only anecdotal observations that need to be confirmed. Furthermore, there are only a limited number of commercially available *combined* reagents and for most of them it would be difficult to obtain the ISI value for the instrumentation used in the laboratory.

Another feasible alternative would be to measure factor X with chromogenic substrates after activation with Russell viper venom. This type of measurement does not need the contribution of phospholipids and should therefore be insensitive to LA. However, the clinical experience on the appropriate therapeutic range with factor X is lacking, making this approach difficult in practice.

15.6. Determination of the INR with portable coagulometers

Portable coagulometers (also called monitors) are becoming increasingly popular for determining the INR. They have the advantage of allowing quick determination of the INR outside the laboratory (suburban hospital districts, communities, general practitioners, the patients themselves).

The monitor consists of a small measuring unit and of a reactive strip the size of a credit card, or smaller, which contains lyophilized thromboplastin and calcium ions. The sample consists of a drop of unmeasured capillary or venous non-citrated blood, which is placed by the operator on the reactive area of the strip. The blood, absorbed into the strip by capillarity, rehydrates thromboplastin, thus starting the coagulation reactions.

The end point of the reaction (measured as a conventional clotting time) is determined in some models by the formation of the first fibrin filaments, which interrupt the flow in the capillaries, and in other models by the generation of thrombin. Clotting time is then converted automatically into INR by means of the calibration parameters (ISI and mean normal PT), recorded by the manufacturer into the code of the reactive strip.

Recent experience has shown that monitors can be properly calibrated by employing the same calibration principles used for conventional systems (*Tripodi 1993, Tripodi 1997, Tripodi 2001a, Poller 2002*). As a result, the main requirement for their reliability is calibration accuracy (ISI and mean normal PT). It is in the user's best interest to expect from the monitor manufacturer the same calibration accuracy quality that laboratories commonly require for the conventional systems. Even in the absence of official guidelines, the manufacturers should calibrate their monitors according to state-of-the-art recommendations (*Tripodi 2001a*), using thromboplastin international standards and calibration protocols used for the conventional systems (*WHO Expert Committee on Biological Standardization 1999*). The users should verify the monitors' reliability by comparing their results with those obtained by a reference system.

The reference system can be the international standard, or, alternatively, a system calibrated on the international standard (*Tripodi 2001a*). Compared to the conventional systems, monitors certainly have the advantage of more simple drawing of the blood required for the test. In terms of standardization, however, this is a double-edged blade. On the one hand, it reduces the pre-analytical variability due to the effects of the anticoagulants, test tubes, centrifugation and storage of the sample until the analysis is carried out. On the other hand, there is the risk of accentuating the relevance of the intrinsic variability of a drop of blood obtained by a finger stick.

It is therefore indispensable to draw the blood very carefully and to train the user properly, whoever this may be, before using a monitor in daily therapy monitoring.

16. EVALUATING THE QUALITY OF PROTHROMBIN TIME

The results of prothrombin time (PT) must be checked on a regular basis by a reliable quality assurance program. This should include both within- and inter-laboratory schemes (*Tripodi 1993*).

16.1. Within-laboratory quality control

These can be carried out in-house by testing aliquots of control plasmas in parallel to patients' plasmas. To implement these programs, aliquots of two or more plasma samples (normal and variably anticoagulated) are needed. They should be of the same batch and in sufficient amounts for a relatively long working period (5-6 months). It is pos-

sible to use commercial plasmas or frozen pools from healthy subjects or patients on oral anticoagulants, e.g. mixing the residues of daily collections and then freezing them in small aliquots. Freezing must be a quick process, to be carried out with a mix of dry ice and methanol, into which the sealed test tubes must be put. Liquid nitrogen works just as well, and it is easier to use.

After freezing, test-tubes must be stored at a temperature of -70° C. This ensure stability for at least six months. The program consists of a preliminary period lasting approximately 20 days, in which the control plasma(s) are tested in parallel to patients' plasma under the same conditions. At the end of this preliminary period, the average and standard deviation (SD) are calculated. On the basis of these results, a control chart is built (one for each control plasma), plotting the average value and the intervals comprising one, two and three SDs above and below the mean value on the vertical axis. The working sessions are identified on the horizontal axis. This chart is then used for the following checks, by plotting results obtained with the same plasma during each of the following analytical working sessions. After a few work days, this chart will begin to take on its characteristic appearance, with individual points clustered randomly around the average value. According to the laws of statistics, if the individual results are distributed only on the basis of random error, it can be expected that 95% of these data will be within the interval comprised between ±2SD from the average. The daily control mentioned above should be implemented also for the portable monitors (*Tripodi 2001*). However, this may be a challenge since the control material cannot be fresh non-citrated blood. Surrogate materials mimicking blood are usually provided by the manufacturers of the monitors. If the check is carried out by a laboratory, statistical data analysis should be performed by the laboratory technician; if the check is carried out by the patient or by a general practitioner, the analysis should be carried out by a third party, for example the check could be carried out by the laboratory which the patient or his/her general practitioner uses.

16.2. Inter-laboratory quality control

Usually these are more complicated programs, which are meant to tackle the problem of comparability of the results obtained in different laboratories operating under conditions that are similar in terms of methods, reagents and instrumentation. The participating laboratory can thus compare its results with those of others using the same system and possibly obtain information about the differences between the performance of its own reagent and others.

In coagulation, these programs primarily work by comparing the participant's own results with a mean consensus value obtained from the results of all the participants in the scheme, after elimination of any outliers. For the analysis to be meaningful, the number of participants must be relatively high. Homogeneous groups of less than 10-15 laboratories are of scarce practical use.

Given the peculiarity of OAT laboratory checks, specific programs should be developed. One of the FCSA's statutory objectives is to organize programs for Associate Clinics. In these schemes, freeze-dried plasmas obtained from patients on oral anticoagulants are provided to the participants. These exercises are carried out every three months. Results are collected centrally in Milan and are analyzed independently of the used reagent. In this way, it is possible to obtain an estimate of the global variability of the INR measured on the same plasmas. The coefficient of variation (CV) obtained in these exercises over the past few years ranges between 12 and 15%. Such values are comparable to those obtained in external quality assessment schemes performed in other countries of the European Union.

The objective for the near future is to implement standardization programs capable of reducing the CV to less than 10%.

It is to be hoped that a more precise calibration of reagent-instrumentation systems (see previous chapter) will lead to improved comparability of the results obtained in different laboratories across the country. It is not, however, reasonable to expect major results.

An intrinsic PT variability, which does not depend on the INR system and which will difficult to reduce further in spite of the continuous improvements in reagents and instrumentation, will always exists; this is easily proven by analyzing the data for each group of reagents. It is, therefore, reasonable to set the objective for inter-laboratory CV for INR at around 5-8%; these are the results obtained for many analytes in clinical chemistry (except for enzymes), where the intrinsic method variability is certainly lower than that of the PT test.

The problems related to inter-laboratory quality control schemes for portable monitors have not as yet been satisfactorily addressed and currently there is no widespread experience. One of the major problems is that in this case, monitors require native non-citrated blood. Thus, as mentioned above, it would be impossible to provide the same sample to all of the users to measure the INR (*Tripodi 2001*). A feasible alternative (at least for some brands of monitors) is to provide freeze-dried plasmas, which should however be recalcified before application to the monitor (*Tripodi 2001*). This clearly complicates the operations and the check validity.

17. OAT QUALITY CONTROL

In 1948, Wright *et al*., who were among the first to use OAT in the prevention of thromboembolism stated: «*It is not enough to say that a patient is being administered anticoagulant drugs. The questions that have to be answered are: in what amounts?, for how long?, what levels of effectiveness were attained?, and how long have such levels been maintained for? This information is necessary in order to establish if a possible failure was caused by the treatment itself or if the responsibility lies in those administering this therapy*».

Even back then it was deemed necessary to measure the effectiveness of OAT. This evaluation can be carried out by recording the incidence of hemorrhagic or thrombotic complications (clinical quality of treatment), or by analyzing the time that each patient spends within the preset therapeutic range (therapeutic level quality). The former obviously requires large numbers of patients and long observation times to reach sufficient statistical power, since clinical complications are fortunately quite rare. An approximate evaluation can, however, be made through an indirect marker, i.e., by measuring the time spent by each patient within pre-fixed (*therapeutic*) limits of anticoagulation (laboratory quality).

The standardization of the method of measuring anticoagulation levels and the introduction of the ISI/INR system allowed analysis of the therapeutic level quality to be carried out properly, so that the results of the various Anticoagulation Clinics were comparable. Among other advantages, this system has allowed physicians to identify specific therapeutic levels for several pathologies; this made it possible to evaluate the degree of anticoagulation objectively and compared the achieved level with the pre-set objectives (for more details refer to chapter 15).

Three studies that were carried out to evaluate the effectiveness of OAT in the prevention of thromboembolism in patients who survived myocardial infarction (*The Sixty Plus Reinfarction Study Group 1980; Smith 1990; Azar 1994*) showed that positive results were determined by the adequacy of OAT (the effectiveness level was estimated at 65-70% of the checks within the therapeutic range).

Analysis of the therapeutic level quality should be part of the daily practice of each Clinic, since only proper statistical analyses of the anticoagulation values obtained in patients allow systematic dysfunctions of the treatment to be identified and perhaps corrected.

With this kind of knowledge, therefore, we will be able to improve the effectiveness of OAT and ultimately the patients' quality of life.

Broekmans and Loeliger (1982) found that treatment quality, in a group of patients with mechanical heart valves followed by the Thrombosis Center at Leiden University, was low, because of an inadequate level of anticoagulation. By making proper corrections (i.e. increasing the prescribed drug doses), the following year a marked improvement was found in the number of controls falling within the therapeutic range.

The improvement of therapeutic level quality is not merely of statistical value, but it can also have important clinical implications. Dettori and Manotti (1990) highlighted that as a result of an improvement in the laboratory quality of OAT, clinical quality also improved remarkably, with a significant reduction in thromboembolic complications, in a group of patients with mechanical heart valves followed for a period of four years. It is therefore essential for each Anticoagulation Clinic to make periodic checks on the laboratory quality of OAT treatment, in order to guarantee their patients the best therapeutic effectiveness.

The analysis of the therapeutic level quality also allows evaluation of other practical aspects of OAT. It has, in fact, been possible to prove objectively that the first few months of treatment are a critical period worthy of the utmost attention, since patients were most frequently found to be inadequately treated during this period (*van den Besselaar 1988, Palareti, 1996, 1997*). Another useful aspect of checking treatment quality is that it is possible to assess the effects of the different properties of various anticoagulant drugs. For example, drugs with a longer half-life provide a better treatment effectiveness than do those with a shorter half-life (*Fekkes 1971; Rosendaal 1993*), at least for long- term treatment (*Pattacini 1994*). Moreover, it was shown that treatment provided by specially equipped clinical units for the management of anticoagulated patients, such as Anticoagulation Clinics, was markedly better than that provided by general practitioners (*Cortelazzo 1993, Chiquette 1998*). It was also possible to compare the difference in treatment quality when OAT was prescribed in the traditional way versus computer-aided systems (*Poller 1998*), as well as the performance of different computerized systems (*Azar 1994*).

The use of statistical analysis dedicated to the quality control of the therapeutic level is also fundamental for evaluating the effectiveness of some types of new surveillance procedures that have been proposed in these last few years: direct involvement of General Practitioners (Fitzmaurice 2000) and patients' *self testing* and *self-management* (*Cromheecke 2000*).

Finally, as explained in a following paragraph, it is also possible to use some statistical analyses, based on the calculation of the time spent by each individual patient within his/her pre-set therapeutic range, to evaluate the incidence of complications in relationship to the achieved anticoagula-

tion levels (*Azar 1994*); this could allow the most appropriate therapeutic levels for each given pathology to be determined.

17.1. Methods for the statistical evaluation of therapeutic level quality

17.1.1. Analysis of INR values (calculation of the percentage of checks that fall within the therapeutic limits)

a) Cumulative calculation of the percentage of results (INRs) that fall within the therapeutic limits, in comparison with the total number of results (*McInnes 1981, Duxbury1982*). This is certainly the simplest approach, but it does not objectively reflect the effectiveness or the ineffectiveness of OAT, since it can be offset by the increased statistical weight of less stable patients, who are likely to have a greater number of checks during a given period, as compared to stable patients, who are likely to have a lower number of tests.

b) Calculation of the percentage of INR results that fall within the therapeutic limits, using only one result per patient in the given period of time (*cross-section of files*). This method, which is also easy to perform, is quite objective in assessing treatment adequacy; however, this method only uses a limited number of checks for each patient (*van den Besselaar 1988*).

c) Calculation of the number of results within the therapeutic limits for each patient, in relation to the total number of checks performed during a given period of time, and subsequently grouping the patients into different classes of treatment quality according to the percentage of results within, below or above the intended therapeutic ranges (*Dettori and Manotti 1990*). This analysis is simple and objective, but does not take into account possible INR fluctuations during the interval between one test and the next.

17.1.2. Analysis of the time (weeks) spent by each individual patient within his/her therapeutic limits

a) The number of weeks a patient spends within the therapeutic limits is calculated by assigning the entire time elapsed between two checks at the measured INR level to a single check. In the case that an INR falls outside the fixed limits, it is assumed that the weeks between the two checks are assigned entirely to the second check. This calculating methodology is not objective, because it assumes too drastic a change in the level of anticoagulation between one test and the next, and therefore presumably does not reproduce what actually occurs (*Duxbury 1982*).

b) The number of weeks spent within therapeutic limits is calculated by equally dividing them between one check and the next. This method is better than the previous one, because it can reflect closely what can really happen in each patient, although it does so in a rather gross way, by considering the level of anticoagulation in relation to the time elapsed between one test and the next.

17.1.3. Analysis of the time (days) spent by each patient within the therapeutic limits (linear interpolation method)

This method calculates the number of days that each patient spent within defined INR categories (progressing by 0.1 INR fractions) between one test and the next. This method, which is derived from the method described in paragraph 17.1.2a, is currently the most reliable system for correctly evaluating the effectiveness of OAT.

The main assumption of this method of analysis is that INR values between two tests may vary linearly over time by reduced INR fractions. In this way, the number of days spent in the different INR classes can be calculated for each patient; it is therefore possible to establish the amount of real time spent by individual patients or groups of patients within, above or below the intended therapeutic ranges (*Azar 1994*). This method gives an objective evaluation of what occurs in patients being treated with OAT between one check and the next. If a patient's results are below the therapeutic level at a given check and they are above such level at the following check, then this method allows the time that the patient must have spent within the therapeutic range to be calculated (*Rosendaal 1993*).

Recently, other methods have been proposed to calculate the time spent by patients with an INR-below, within or above the therapeutic range (*Hutter 1999, Marco 2000*). These methods are certainly more complex from the statistical point of view and are therefore difficult to apply in practice; in any case, they do not offer a greater advantage over the original linear interpolation method. This type of analysis also makes it possible to evaluate the incidence of clinical events (bleedings and thromboses) as a function of the anticoagulation intensity (*Smith 1990*).

In order to use the more sophisticated statistical analyses to evaluate OAT adequacy, Anticoagulation Clinics must have a computerized data filing system and specialized analytical software. However, Anticoagulation Clinics that do not have the above systems and the software can easily use more simple analytical methods (for example, cross-section of files), that do not require computerized data filing systems.

Each Anticoagulation Clinic must organize its work so that it can evaluate the effectiveness of the treatment that it offers to its patients, because only by consistently and periodically checking treatment quality (highlighting possible pitfalls in the prescription of OAT) can the correct measures be taken to improve the patient's quality of life,

which is the real goal of every Anticoagulation Clinic.

In conclusion, the effectiveness of OAT essentially depends on the quality of laboratory tests assaying the level of anticoagulation, on the ability to adjust drug doses, on the active participation of patients, and on how well the Anticoagulation Clinic is organized. To this end, serial checking of treatment quality provides a parameter of paramount importance (*van den Besselaar 1988*).

18. INFORMATION TECHNOLOGY AND OAT PRACTICE

In recent years, information technology has played an important role in organizing medical office work through the now traditional computer applications of data filing and storage, preparation and printing of medical reports and statistical evaluations.

Furthermore, dedicated computer programs have been developed to integrate these traditional OAT management applications with a number of specific functions that are particularly aimed at increasing the reliability of the inherently difficult monitoring of patients. Some of these computer programs were originally designed to work on minicomputers (*Wiegman and Vossepoel 1977*), while most of them, including all recent ones, can be used on personal computers. The main functions of these programs is to create a file to record all the patient's personal data (general and clinical information), print personalized medical reports for each visit and perform various types of statistical analyses (Table 7).

With just a few slight changes, another traditional application that can be used in monitoring OAT is the transmission of test results from the analysis laboratory directly to the patient's file, via a local network; this sharply reduces possible data transcription errors, which are possible when manual data transmission is used. Magnetic cards or a bar code reader, linked to a dedicated computer at the admission desk, can also be part of this network, further reducing the risk of errors in patient identification and sample manipulation.

Computer programs specifically designed to solve OAT problems have been introduced (*Wilson and James 1984*). Retrospective and prospective preliminary studies also made it possible to evaluate the usefulness of such programs in some cases, demonstrating improved treatment quality in groups of patients treated with computer-assisted systems versus *traditional* patient management (*Wilson and James 1984; Poller 1993*).

In particular, several major Italian Anticoagulation Clinics used a computer program that certainly simplified medical work in this field, without reducing clinical effectiveness. This program, called PARMA (*Programma per Archiviazione, Registrazione e Monitoraggio degli Anticoagulati*), was developed at the Center for Hemostatic Diseases of the Parma General Hospital (Italy) during the 1980s and was tested under various clinical conditions (*Saetti 1986; Mariani 1990*). Later on, a specialized company redesigned and upgraded the computer program in co-operation with the Parma-based Clinic. A further upgrade was recently possible thanks to collaboration with the FCSA. The latest version of this program offers many interesting advanced functions, providing a high degree of automation in the management of patients on OAT, making it one of the most prominent accomplishments in this field.

Table 7. Information technology applications for managing patients during OAT.

Filing and storage of patient information
Optimized reporting
Scheduling of next visits
Quality control and statistical evaluations
Direct connection with the testing laboratory
Integrated network (data bank)
"Automatic" prescription of therapy
Estimate of the maintenance dose

The program consists of a file, in the form of a relational database, which creates a medical file for each patient, consisting of several electronic pages: one containing general background information, one for medical history and clinical data, one for recording possible concomitant diseases, complications or associated interfering treatments, etc.

The page for monitoring the patient's follow-ups is the core of the program. This page is a matrix-like form in which the patient's therapeutic and laboratory results are recorded (one line for each check), providing on-line availability of all essential clinical information (contraindications, complications, associated drugs, etc.) together with the results of recent visits (obtained level of anticoagulation and prescribed dose of anticoagulant). In the same page, general information on the patient, such as diagnosis, target degree of anticoagulation, age, sex, type of drug, are also present on line, and further details can always be easily recalled. This follow-up form has specific features that greatly simplify the daily management of patients under treatment.

As a matter of fact, it is possible to automatically calculate the value of anticoagulation levels, based on the patient's and normal coagulation times, and of the ISI of the thromboplastin being used, which can therefore be expressed in terms of INR. In a relatively high percentage of patients (more than 2/3), the program is also capable of

automatically suggesting a dosage prescription, which is then considered by the physician.

This computer program contains a number of specific algorithms, based on both the patient's test results and clinical data, and on several years of experience of an Anticoagulation Clinic with a very large number of patients. These algorithms are capable of confirming the current dose (in stable patients), as well as proposing a change of dosage for most of the patients whose INR is out of their range.

With this aim, data obtained in the daily checks undergo a series of exclusion tests, integrated by a series of confirmation criteria — mainly concerning the obtained level of anticoagulation (in relation to the pre-set range), its degree of stability over the last few checks, the presence of particular clinical conditions or interfering drugs, etc. — that allow the computer program to choose between the different therapeutic options. The effectiveness and safety of these *automatic prescription* proposal modules have been tried and tested via prospective trials on large series of patients (*Manotti 1994, 1997*).

This computer program is also useful in the initial stage of therapy induction, because a specific algorithm is capable of estimating the maintenance dose for each patient rather well, based on the individual characteristics of the pharmacological effect of the priming OA dose.

More recently, a new module was implemented in the PARMA program making it possible to calculate an approximate, presumed individual maintenence dosage of the anticoagulant from the pharmacological effect of the priming dose. This new utility is still under prospective, comparative study in the field, but the first results seem to hold out promise for shortening the initial very unstable period covering the first weeks of a treatment.

The computer program produces a personalized print-out report that is given to the patient (either on standard paper or on pre-printed forms), with laboratory data and clear and precise therapeutic advice, and possible additional remarks for the patient or for his/her general practitioner.

An issue of paramount importance for proper management of OAT is accurate verification of *treatment quality* from both a clinical standpoint (by recording and calculating the frequency of hemorrhagic complications or thromboembolic events) and from the point of view of laboratory testing point of view (by using statistical analyses of the laboratory tests results). The above mentioned computer program allows this verification to be carried out easily and quickly, using specifically developed functions that can be easily learned. As previously mentioned such clinical controls can only be performed effectively in large groups of patients followed for long periods of time, because of the relative rarity of these events. Laboratory quality control based on statistical analysis of PT results is, therefore, the main practical way of monitoring the quality of treatment. With the aid of specialised software, such as the PARMA program, these controls can be performed both easily and quickly, via specifically designed functions. Indeed, daily, monthly or yearly tests can be carried out almost automatically, thereby checking the performance of the Anticoagulation Clinic and comparing it to the performance of other Clinics that use the same computer program.

18.1. Practical considerations

Cost/benefit analyses clearly indicate that the advantages of using information technology to manage anticoagulated patients in an Anticoagulation Clinic far outweigh all practical problems. Besides the significant advantage of drastically reducing the number of errors during data transferral, it has been calculated that there are economic benefits even for Clinics with just a few dozen patients. The initial cost of using information technology is limited to the purchase of a personal computer and a few essential items such as a printer, and a back-up system. This hardware cost clearly varies according to the complexity of the computer system. Anticoagulation Clinics serving less than 100 patients have an initial investment cost estimated at around €2,500; large Clinics (more than 1,000 patients) using two or more PCs connected to a local network, could spend two or three times as much.

The cost of the software must then added: this can double the expense for small/medium size Clinics. Apart from making this initial, certainly not excessive investment to purchase computer hardware and software, a number of delicate issues remains to be addressed:

- hardware maintenance, which can be secured by stipulating a customer-service contract with a specialized company;
- personnel training: software providers very often organize training courses to help medical staff become more familiar with their new programs;
- software technical assistance: before choosing a software dedicated to OAT, it is necessary to make sure that adequate and timely assistance can be provided by competent professionals, in order to solve all practical problems of daily office management.

The benefits accruing from information technology are always significant, because they allow to manage large numbers of patients to be managed in an organized and reliable way.

As a matter of fact, there are relevant practical advantages: reduction of the time required to do

the job and almost complete elimination of transcription errors, which yields an improvement in the accuracy of therapeutic decisions. Reducing the need for written reports contributes to improving the Clinic's efficiency, e.g. by making it possible to have the admissions schedule constantly updated and by allowing quick and easy identification of drop-outs. Furthermore, all controlled clinical trials tend to show an (often very significantly) improved treatment quality in patients followed with computer-aided systems. The tendency towards increasing homogeneity in the therapeutic decisions by different physicians should not be forgotten. Lastly, thanks to computers, it is becoming ever easier to organize controlled multicenter studies, as several recent studies conducted by the FCSA have shown (*ISCOAT study: Palareti 1996, 1997b*).

18.2 Co-operative project for the "decentralized management" of OAT

The Parma FCSA Clinic recently started a project aimed at de-centralizing OAT surveillance using more sophisticated information technology, in co-operation with local Public Health authorities and a group of general practitioners.

This project aims at providing participating general practitioners with the information technology support (hardware, software and training) required to manage OAT properly, with various possible degrees of involvement. In this framework, general practitioners are able to access the Hospital server from their own office by means of a modem/internet connection. This enables the general practitioners to review their patients' data and possibly to prescribe their therapy and to schedule the date of the next appointment. The laboratory datum (INR value) can be obtained at an approved laboratory which is accessible to the patients, or also (by means of a *next to the patient* dosage method) at the doctor's office or at the patient's home, under the supervision of the general practitioner.

The general practitioner can therefore benefit from the advantages of the dedicated software, including the algorithms which help to define the adequate dose of anticoagulant, and the possibility of quickly consulting on-line the medical specialists of the Clinic about particular problems (drug interferences, complications, preparation for surgical operations, etc.). If necessary (e.g. after an urgent hospital admission), the patient can access his/her entire clinical history, which is stored in the central database. It is clear that it is necessary to implement all precautions required to ensure network safety and to protect the patients' privacy and their confidential relationship with their general practitioner.

This project has already begun. It has been estimated that 18 months will be required to complete and bring up to speed the hardware structure, the organization, the training of participating personnel and all other activities and to work for a sufficiently long period to be able to assess assessing the obtained performance.

If the results are positive, the advantages of such a solution will be evident for all participants; in particular:

- better quality treatment for the patients, thanks to the increase in medical time dedicated to surveillance, with the convenience of a local referral point closer to home, and a reduction of waiting time;
- professional and scientific updating and training for the general practitioners, resulting in a better patient/physician relationship;
- reduction in the quantity of work at the Hospitals, with no losses in the quality of the clinical assistance offered to the patients; the relevant statistical value of the centralized observation of large numbers of patients remains unchanged.
- lastly, an important general advantage could be the easy transferability of this solution to other national or possibly foreign scenarios. This system could be expected to be particularly useful in remote, rural and/or mountain areas, where the distances between patients (often elderly or with a limited mobility) and the Anticoagulation Clinic are great, especially in those regions in which there are few Clinics or these are unevenly distributed.

19. DECENTRALIZATION OF OAT MANAGEMENT BY MEANS OF PORTABLE COAGULOMETERS

19.1. Introduction

A chapter of these guidelines is entirely devoted to this topic, in consideration of the specificity and of the problems related to the management of the therapy. Portable coagulometers have been discussed in chapter 15.4. The reader should therefore refer to that chapter for more information on their technical characteristics, reliability of INR measurement, etc. This chapter only addresses general management issues.

It should be realized that therapy control is actually the simplification of a wider activity, which consists in the laboratory and clinical surveillance of the patient on OAT. As a matter of fact, it has been demonstrated that there is an increase in complications when the patient is not adequately informed about the potential complications of the therapy and when visits do not adequately take into account the clinical situation.

The introduction of monitors for self-testing of the INR (see Chapter 15.4) and OAT self-manage-

ment represents a new management model whose effectiveness in terms of cost/benefit ratio has not been completely defined yet. This management model was introduced in the United States in the 1980's (*Ansell 1989*); however, in recent years, it has been receiving a much wider consensus, especially in Germany (*Taborski 1999*).

Clinical studies recently carried out in Austria (*Watzke 2000*), The Netherlands (*Cromheecke 2000*) and Italy (*Cosmi 2000*), demonstrate that self-management is at least equally effective as traditional management. However, these conclusions are based on surrogate end-points (evaluation of the time spent with an INR within the therapeutic range). As a result, reasonable margins of uncertainty remain and a positive answer can be given only by clinical studies based on more solid end-points (evaluation of adverse events). The experience accumulated with the previously described co-operative studies make the FCSA the most suitable institution to organize studies of such complexity.

19.2. Types of decentralized management

OAT surveillance management can be decentralized in several ways.

19.2.1. Management fully assisted by the Anticoagulation Clinic

The patient refers to a suburban district center, connected to the Anticoagulation Clinic (here called Clinic), where he/she finds a health operator (usually a nurse), who receives the patient, gathers all the information useful for the management of the therapy (adverse events, interfering drugs, etc.), performs laboratory testing (with a monitor or a conventional coagulometer), sends the results (together with all other relevant information) to the Clinic where the prescribing physician prepares the prescription and transmits it to the patient.

19.2.2. Management fully assisted by the general practitioner

This can be considered as a variant of the previous type. In this case the patient refers to the general practitioner (GP), who performs the INR testing with the monitor and prescribes the therapy.

19.2.3. Management partially assisted by the Anticoagulation Clinic

The patient (or a relative) directly performs the INR testing at home (with a monitor) and then sends the result (together with all other relevant information) to the Clinic, where the physician prepares the prescription and transmits it to the patient.

19.2.4. Management partially assisted by the general practitioner

The patient (or a relative) performs the INR testing at home (with a monitor) and then sends the result (together with all other relevant information) to the GP, who prepares the prescription and transmits it to the patient.

19.2.5. Self-management

The patient (or a relative) performs the INR testing at home (with a monitor) and autonomously calculates the proposed therapy on the basis of a specific algorithm.

19.3. How to achieve decentralized management

All options are theoretically possible, but they imply different levels of organization and different problems. This justifies the presence of a number of different recommendations.

19.3.1. Management fully assisted by the Anticoagulation Clinic

The responsibility falls entirely on the Clinic; the reader should therefore refer to the general recommendations presented and discussed in the present guidelines. In particular, it is important that the operator, especially if he/she is not a specialized operator (such as a laboratory technician), is adequately trained to perform INR testing properly. If testing is performed with the monitor, it is important that training be carried out under the direct responsibility of the Clinic. The operator must receive adequate information on the principles of the test (PT-INR), on the expected differences of the results obtained with whole blood versus plasma, capillary blood versus venous blood, etc. The operator must also be trained to draw capillary blood properly. It is essential to verify that the importance of test standardization is understood, in order to minimize the variability of the results. The instrument must be under the direct responsibility of the laboratory associated with the Clinic, which must also be responsible for carrying out internal and external quality controls.

19.3.2. Management fully assisted by the general practitioner

The responsibility rests on the GP, who besides knowing the problems of OAT, must be adequately trained on the use of the monitor and on all its implications. Training must be organized and carried out by the manufacturer of the monitor or, if the GP works in collaboration with the Clinic, by the Clinic itself. The GP will also be responsible for the quality control of the results.

19.3.3. Management partially assisted by the Anticoagulation Clinic

This type of management implies a more complex level of organization, because tests will be performed by non-professional operators, i.e. the patient or one of his/her relatives. In this case operator training must adequately relate to the importance of the operation to be carried out.

It is important to evaluate the objectively measurable capacity of the operator (patient or relative) with simple tests which have been clinically validated (*Palareti 1997a*). Individuals (patients or relatives) who do not have sufficient expertise, or who are not sufficiently motivated must be excluded from this type of management. Furthermore, it is recommended to that these tests are carried out periodically, in order to detect possible changes that may occur during the therapy. In the other cases, some training sessions should be organized on the general characteristics of the therapy and on the use of portable coagulometers. It is totally inadequate and also dangerous for a patient (or a relative) to use the monitor to determine the INR without specific training. Theoretical and practical training courses should be organized, with the objective of allowing patients to take the tests autonomously; this is already done in Northern European countries. Training responsibility rests entirely on the manufacturer and/or the Anticoagulation Clinic, although there are no regulations that specify obligations and responsibilities.

The responsibility of the quality control of the results rests on the operator (whether patient or others), assisted by the manufacturer and/ or the Clinic.

19.3.4. Management partially assisted by the general practitioner

The same recommendations listed above are valid for this type of management too. It is clear that in this case the responsibilities will fall on the GP rather than on the Clinic.

19.3.5. Self-management

The same recommendations on the use of the monitor, as listed in section 19.3.3, apply. In addition, in this type of management adequate development of the issues related to the algorithms for self-prescription is necessary. A uniform algorithm (possibly discussed and approved by the FCSA), to be used across the country, would be preferable. The responsibility for correct application of the algorithm obviously rests on the patients themselves, who must however be put in the best operating conditions by the Clinic or by their GP, through appropriate training courses and continuous assistance.

19.4. Regulatory information

1. The prescription of the monitors to the patients must be given on the basis of a therapeutic plan agreed upon by the Clinic or the GP; the prescription should have a limited time validity and it should not last more than one year. After this period of time the therapeutic plan must be reassessed.
2. The therapeutic plan must include certification that the patient (or a relative or a health operator) has been trained to use a specific monitor and that he/she is capable of correctly performing the tests. The certificate must bear the name of the Clinic or GP responsible for the therapeutic prescription.
3. Should the patient request self-prescription, he/she must be given specific training, which must be reported on the therapeutic plan.
4. The reasons for reimbursement of the cost of the monitor and test cards must be reported in the therapeutic plan (e.g. limited deambulation, patient living in a remote area, impossibility of finding adequate venous access).
5. Finally, the therapeutic plan should include a description of the possible way (e.g. fax, mobile phone, e-mail) of communicating the test results to the Clinic or to the GP who prescribed the therapy. The therapeutic plan should also include a description of the way in which the prescribed therapy is to be sent from the Clinic or GP to the patient.

20. SURGERY AND INVASIVE PROCEDURES DURING OAT

All types of surgery or invasive procedure performed in patients on OAT require careful evaluation by several specialists, including hematologists, internists, cardiologists, anesthesiologists, and surgeons. Therapeutic decisions depend on the correct consideration of:

1) the potential risk of thromboembolic events, should OAT be reduced or discontinued;
2) the specific risk of bleeding for each surgical or invasive procedure, especially in relation to the entity and the site of the trauma and the possibility of adopting optimal local hemostatic measures.

Guidelines on this topic are available in the literature (Kearon 1997 and 1998, Bonow 1998, Hirsh 2001).

Schematically, we can envisage two scenarios:

A) Continuation of OAT

This is possible for situations at a low risk of bleeding, with superficial tissue trauma for which local hemostatic procedures (e.g. compression, antifibrinolytic drugs, fibrin glue) can be used:

- punctures and catheterization of superficial veins and arteries (e.g. the femoral artery for insertion of a Seldinger catheter);
- sternal puncture and bone marrow biopsy. In such procedures, although prolonged compression can prevent the onset of hematoma, it is advisable to obtain an INR value of about 2, in order to reduce the hemorrhagic risk without increasing the thromboembolic one.
- skin biopsies, minor dermatologic surgery, biopsy of mucosa that is easily accessible and explorable (oral cavity, vagina), minor eye surgery;
- endoscopic examinations without surgery;
- simple tooth extraction in the absence of infection or surgical cuts; in these cases, it is advisable to use local hemostatic agents, suture alveolar edges and rinse the mouth with a 5% tranexamic acid solution, 4-5 minutes every 6 hours for five-six days, combined with antibiotic therapy.

If the expected risk of bleeding is higher (e.g. multiple tooth extractions in the presence of infections, biopsy of deep tissues, intra-ocular surgery or cataract with retro-bulbar anesthesia) and the risk of thromboembolism is not high (in most cases, excluding patients with prosthetic heart valves or intracardiac thrombosis), OAT can be temporarily modified reducing INR to values between 1.5 and 2.

Note: patients being treated with OAT should be told to avoid, wherever possible, intramuscular injections (especially for high injection volumes) so as not to run the risk of local hematomas.

B) Transient discontinuation of OAT

This is necessary when trauma is expected to affect deep tissues that are not easily accessible to local hemostatic measures:

a) major elective surgery, general or specialized;

b) explorative cavity punctures (thoracentesis, paracentesis, cerebrospinal fluid taps);

c) biopsies of deep tissues (liver, kidney, bone, even if CT- or US-guided) or mucosa (gastrointestinal, respiratory, genital) not accessible by direct inspection;

d) central neuraxial blocks (subarachnoid and epidural anaesthesia).

In elective procedures, OAT should be discontinued 3-5 days prior to surgery, without giving vitamin K, and the operation done when the INR is < 1.5 (White 1995). During this period of OAT discontinuation and with an INR < 2.0 treatment should be started with:

— unfractionated heparin (UFH), 5000 IU every 8-12 hours sc) or, in patients with high thrombotic risk (e.g. mechanical heart valve prosthesis or recent arterial or venous thromboembolism), at a dose (sc or by IV continuous infusion), to obtain and maintain a PTT ratio of 1.5;
— low molecular weight heparin (LMWH) at the prophylactic doses used in the patients with high venous thromboembolic risk.

Heparin should be discontinued before surgery (generally 12 hours in advance when using sc UFH or LMWH and 6 hours when using UFH by IV infusion) and resumed 12-24 hours after surgery. When the hemorrhagic risk (e.g. neurosurgery, prostatectomy) heparin is resumed only after clinical evaluation and in general after at least 48-72 hours.

OAT should be resumed at the usual doses as soon as feeding allows this and in relation to the time required for tissue recovery. The OAT should be administered in association with heparin until the INR value is within the therapeutic range for two consecutive days.

For emergency surgery, OAT must be neutralized as soon as possible via slow I.V. infusion (for 15-30 minutes) of vitamin K1 (10-20 mg) (Konakion) and surgery performed with an INR value below 1.5 (generally after 6-12 hours). In order to restore normal hemostasis immediately, it concentrates of prothrombin complexes (20-30 U/kg), must be infused.

20.1. Central neuraxial blocks (subarachnoid and epidural anesthesia)

Regional anesthesia, in association with perioperative heparin prophylaxis or therapy, is safe and effective provided the patients and the anesthesiologic technique are selected carefully. There are no controlled studies for evaluating the risk of spinal hematoma during therapy or prophylaxis with heparin. Published anecdotal data suggest that (*Horlocker 1997 and 1998*) the following management:

— I.V. or sc UFH: i) perform the spinal puncture or the catheter placement at least 1 hour before starting I.V. heparin, or more than 4 hours after I.V. heparin discontinuation and after sc heparin administration; ii) maintain a PTT ratio not higher than 1.5; iii) remove the catheter only after PTT normalization.
— LMWH: i) perform the spinal puncture or the catheter placement 10-12 hours after the last dose; ii) remove the catheter at least 10-12 hours after the last dose and give the following dose at least 2 hours after its removal.

The following must in any case be remembered:

1. do not give drugs that interfere with hemostasis,
2. postpone surgery in the case of a difficult, bloody or traumatic procedure (bloody tap);
3. perform careful neurologic monitoring in the

post-operative period for the early detection of motor or sensory blockades (sphincteric alterations, progression of paresthesia and hyposthenia).
4. In case of spinal hematoma, perform rapid surgical decompression (<6 hours after the onset of symptoms).

The FCSA has opened a file in its web site (www.fcsa.it) for the collection of data on complications in OAT patients undergoing surgery.

20.2. Cataract surgery

Cataract surgery is relatively frequently indicated in patients on OAT because of the high average age of this population. Some comments on the hemorrhagic risks related to this type of surgery are therefore appropriate. With present-day techniques that imply limited incision of the cornea (non-vascularized tissue), the risk of surgical bleeding is practically nil. Possible bleeding complications are linked to the type of anesthesia. Cases have been reported of retro- and peri-bulbar hematomas in OAT patients following retro- and peribulbar anesthesia. Despite the lack of data on the incidence of these complications, it should be borne in mind that retro- and peribulbar anesthesia requires normal blood coagulability and hence discontinuation of OAT. Retro- and peribulbar anesthesia should therefore be considered to be contraindicated in patients under OAT in whom the thrombotic risk following the discontinuation of treatment is high. In contrast, cataract surgery can go ahead without anticoagulant discontinuation in all those subjects in whom local anesthesia or general anesthesia can be used. The risk/benefit and cost/benefit ratios of the different options (e.g. surgery without OAT discontinuation vs surgery with retrobulbar anesthesia and OAT discontinuation) should be evaluated in each patient on the basis of a general consideration of that patient's risk factors (thrombotic and hemorrhagic).

21. HEMORRHAGIC COMPLICATIONS AND THERAPEUTIC FAILURE OF OAT

21.1. Hemorrhagic complications

The most frequent complication during OAT is spontaneous bleeding in different sites and with different severity. It is extremely important to have a common measure for evaluating bleeding intensity (fatal, major, minor, insignificant); these are listed in Table 8. The adoption of different classification criteria of the hemorrhagic events, is, in fact, an important factor in the variability of the results of clinical studies in this field and it makes it difficult to compare different studies (*Graafsma 1997*).

As for the severity and sites of bleeding, in order to establish a uniform classification and data comparability among the different Anticoagulation Clinics, the classification designed by the FCSA is recommended. This is available on request, and has already been distributed to companies producing software programs for the management of OAT in Italy.

Table 8. Classification of bleeding events (Palareti 1996).

A) MAJOR BLEEDING
- 1) Fatal: when death occurs because of bleeding (i.e. death would not have occurred if the patient had not on OAT);
- 2) any bleeding occurring in the following sites (regardless of intensity):
  - intracranial (confirmed by CT scan and/or MR)
  - ocular (causing reduced vision)
  - articular (major joints);
  - retroperitoneal
  - (
- 3) any bleeding requiring surgery or invasive procedures;
- 4) any bleeding causing a reduction in hemoglobin >2 g/dL or requiring a transfusion of 2 or more units of blood;

B) MINOR BLEEDING
- Any bleeding that does not fall into the above categories.

Note. Slight bruising (smaller than the size of a coin and up to a total number of five), occasional nosebleeds (without need for plugging), and occasionally bleeding hemorrhoids should not be considered as significant bleeding events.

Complete overviews on the hemorrhagic complications of OAT can be found in the literature (*Landefeld and Beyth 1993, Fihn 1993, van der Meer 1993, Palareti 1996, Levine 2001*).

A retrospective study (*Cortelazzo 1993*) and, more recently, a prospective study (*Chiquette 1998*), have shown that the incidence of bleeding is lower when OAT is monitored by Anticoagulation Clinics which are specifically designed for managing outpatients with a highly trained medical staff. Besides the Italian Anticoagulation Clinics, other Clinics should be mentioned: the Anglo-American Anticoagulation Clinics, the Dutch Thrombosis Centers and the Spanish Hemostatic Services). This is true not only when comparing results with those of General Practitioners, but also, and even more, with those of patients using self-medication (without any medical advice), a practice that unfortunately still occurs due to the lack of an adequate network of Anticoagulation Clinics capable of satisfying the growing needs of the territory.

The FCSA conducted a multicenter prospective study on the hemorrhagic complications of OAT involving 34 Clinics across Italy. This study monitored more than 2,700 consecutive unselected patients from the beginning of OAT, for a total follow-up period of more than 2,000 patient/years (p/y). This study, known as ISCOAT (*Palareti 1996*), showed that patients monitored by the FCSA Anticoagulation Clinics had a rather low overall incidence of hemorrhagic complications (7.5% p/y), of

which 0.25% p/y were fatal (all intracranial), 1.09% p/y were major (6 digestive tract, 5 ocular, 4 cerebral, 3 hemarthrosis, 2 hemoptysis, 1 retroperitoneal, 1 hematuria) and 6.2% p/y were minor with a prevalence of haematuria, proctorrhagia, menometrorrhagia, digestive tract bleeding, hematomas/bruising, and nosebleeds.

The incidence of bleeding reported in this study was considerably lower (approximately one-third) than that found on average in similar investigations (observational studies) and substantially similar to the data reported in experimental studies, which only considered highly selected groups of patients, usually with a low risk of bleeding (see Table 9).

During the ISCOAT study, the following conditions were considered to be independent risk factors for hemorrhagic complications:

a) when INR values temporally correlated with bleeding were > 4.5 (relative risk --RR-- versus values < 4.5 = 5.96; $p<0.0001$);
b) when the indication for OAT was based on peripheral or cerebral arterial vasculopathy (RR versus all other indications = 1.72; $p<0.001$);
c) when the patient's age exceeded 70 years (RR versus <70 = 1.69; $p<0.001$);
d) during the first 90 days of treatment (RR of treatment after 90 days versus first 90 days = 0.4; $p<0.001$).

There was no significant correlation with gender, the intended therapeutic range or the type of OA drug (warfarin or acenocoumarol).

Although the number of hemorrhagic complications increases exponentially for INR values > 4.5, bleeding can also appear at very low INR values.

In the ISCOAT study group, a 7.7% p/y incidence of bleeding was found in correlation with extremely low INR values (<2). This confirms that bleeding does not always correspond to therapeutic hyperdosage, but may sometimes be correlated with the presence of local organic lesions underlying the hemorrhage, and OAT is merely the triggering factor. If bleeding occurs, PT and PTT as well as a platelet count are mandatory. If the PT is within the therapeutic range and other tests are normal, a possible underlying pathological lesion should be searched for. As a matter of fact, in some studies (*Wilcox 1988; Landefeld 1989b*) a lesion was found in 34-50% of the cases of gastrointestinal bleeding and in 33% of the cases of hematuria. It is, therefore, often possible to make an early diagnosis of different kinds of lesions that were previously unrecognized.

Other personal risk factors have been highlighted and associated with the occurrence of bleeding complications (*Landefeld et al. 1989a*): arterial hypertension (especially systolic), the presence of other severe morbid conditions (especially cardiac, hepatic and renal), history of stroke, and gastrointestinal bleeding.

Table 9. Incidence (×100 pt/yrs of treatment) of hemorrhagic complications reported in the ISCOAT study (Palareti, 1996,) as compared to the mean values in available studies - both observational and experimental - taken from Landefeld and Beyth's overview (1993).

Bleeding	*ISCOAT*	*Observational studies*	*Experimental studies*
Fatal	0.25	0.8	0.4
Major	1.1	4.9	2.4
Major+Minor	7.2	15	8.5

A score index was recently proposed and prospectively evaluated with good results, in order to predict the risk of major hemorrhages in anticoagulated ambulatory patients (*Beyth 1998*). The index includes 4 independent risk factors: age > 65 years, previous gastrointestinal hemorrhages, previous stroke and at least one of the following morbid conditions: recent myocardial infarction, renal failure, serious anemia, diabetes.

Another condition which is certainly associated with an increased risk of hemorrhagic complications is cancer in patients who are treated with OAs for venous thromboembolic events (*Palareti 2000a*). A particular feature of this type of patients is that the hemorrhagic tendency is poorly related to the INR level, and all levels of anticoagulation are possible and frequent, presumably in relation to local pathologic alterations caused by the cancer, or to other associated conditions (e.g. with the therapy treatments).

It has been demonstrated that old age is an important risk factor for the onset of hemorrhagic complications.

A recent Italian case-control study (*Palareti 2000b*), derived from the population of the ISCOAT study, demonstrated that in subjects who were over 75 years when they started OAT, there was only a non-significant tendency to a higher incidence of total hemorrhagic events (and also of thrombotic events) in comparison with rates in subjects matched for all other conditions but less than 70-years old. However, intracranial bleeding and fatal thrombotic complications were significantly more frequent in the older patients.

The same study demonstrated that while low levels of anticoagulation (INR < 2.0) in the elderly did not prevent hemorrhagic complications, they were associated with less effective protection from thrombotic events. In conclusion, a moderate level of anticoagulation (INR between 2.0 and 3.0) resulted to be both safe and effective for elderly patients.

The FCSA has opened a file on intracranial hemorrhages which complicate OAT (see www.fcsa.it web site).

21.2. Thrombotic failures

In comparison with the important amount of scientific work dedicated to hemorrhagic complications, relatively little attention has been paid to the frequency of thrombotic failures during OAT (*Fihn 1993, Gitter 1995*). The ISCOAT observational study investigated the thrombotic complications that occurred in the study population (*Palareti 1997b*).

The total incidence of thrombotic complications was 3.5% p/y during treatment (1.0% of fatal events and 1.9% of major events*).

The risk was significantly higher in the following conditions (similar to the ones listed for the bleeding events): during the first three months of treatment, in subjects over 70 years, and when the indication for treatment was arterial disease.

The incidence of thrombotic events was particularly high (17.5% p/y) in relation to INR levels < 1.5, while it was only 2.3% for INR values ranging between 2.0 and 3.0. Thus, the study confirmed the effectiveness of moderate INR levels (2.0-3.0), and highlighted the risk associated with lower anticoagulation levels, old age and inappropriate indications for OAT, which are typical of most cases of arterial diseases.

22. NON-HEMORRHAGIC COMPLICATIONS OF OAT

Non-hemorrhagic complications of OAT are relatively uncommon (*for a complete overview see Levine 1986 and Gallerani 1995*).

Adverse reactions due to hypersensitivity, such as dermatitis, skin rashes and itchiness, are uncommon and can occur weeks or months after starting therapy (*Sheps 1959, Kwong 1978*). Alopecia has also been reported (*Umlas 1998*).

The most serious of all non-hemorrhagic complications is skin necrosis (*see overviews by Cole 1988 and Eby 1993*). This serious complication appears primarily in the induction phase of OAT (but there is a case-report of it occurring some days after OA withdrawal (*Wynn 1997*). This reaction occurs more frequently in patients with protein C or protein S deficiency, and/or in combination with antiphospholipid antibody syndrome (*Moreb 1989; Wattiaux 1994*).

Skin necrosis seems to be due to thrombosis of capillaries and venulas of the dermis, and is located especially in sites rich in adipose tissue. Painful maculo-papular lesions initially appear and then rapidly turn into blood blisters and necrotic areas. The thrombotic process appears to be triggered by a further reduction of physiological vitamin K-dependent anticoagulants (with a short half-life) when the level of clotting factors has not been sufficiently reduced. A case of defibrination due to the exacerbation of intravascular coagulation was also reported in a patient with protein C deficiency at the beginning of treatment with warfarin, immediately after discontinuing heparin (*Francis and Mc Gehel 1985*). In patients who have experienced skin necrosis and need long-term anticoagulant treatment, therapy with coumarins can be resumed following this scheme: anticoagulation is started by administering I.V. unfractionated heparin to obtain a PTT ratio of 1.5-2.5; warfarin is then added in small doses (2.5-5 mg/day) until an INR > 2.0 is reached for at least two consecutive days; heparin is then stopped (*Jillella and Lutcher, 1996*). The practice of a *bridge* heparin administration at the beginning of OAT is also indicated in patients with protein C or protein S deficiency in order to prevent the risk of skin necrosis.

Another rare complication is the so-called *purple toes syndrome* (*Feder and Auerback 1961; Hyman 1987*) characterized by the appearance of a purple coloration of the toes and other general alterations, especially involving kidneys, which can be serious or even fatal (*Rhodes 1996*). This most serious complication has been attributed to cholesterinic microemboli due to the rupture (either spontaneous or after iatrogenic trauma) of the atheromatous plaques, with subsequent release into the circulation of their lipid content. This phenomenon can occur in all subjects with diffuse atherosclerotic alterations; but it is enhanced by OAT and usually appears within the first weeks of treatment, thus requiring immediate withdrawal of OAT.

Lastly, it should be remembered that vitamin K is involved in bone metabolism (see chapter 12) and that, as recently reported (*Caraballo 1999*), prolonged anticoagulation therapy can increase the risk of bone fractures, particularly of ribs and vertebrae.

The FCSA opened a file on non-hemorrhagic complications of OAT (see www.fcsa.it web site).

23. THERAPEUTIC APPROACH IN CASES OF OVERDOSAGE AND HEMORRHAGIC COMPLICATIONS

23.1 Overdosage

We use the term overdosage to mean when INR exceeds the upper limit value of the therapeutic range assigned to the patient. This may be due to excessive OAT caused by a mistake by the patients

**The following were considered to be major thrombotic complications in the ISCOAT study: deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, peripheral arterial embolism, acute worsening of peripheral arteriopathy necessitating vascular surgery.*

Table 10. Time necessary to reach the desired INR values after withdrawal of OAs.

Baseline conditions	*Target INR*	*Necessary time*
INR 2.0 - 3.5	1.0 - 1.5	3 - 4 days
INR 5.0 - 8.0	2.0 - 3.0	3 days
INR > 8.0	2.0 - 3.0	4 - 5 days

or other people or due to the patient's increased sensitivity to OAs for a number of possible reasons: concomitant diseases (diarrhea, fever), interfering drugs, excessive alcohol intake, seasonal and dietary variations, thyrotoxicosis, and liver disease. Generally, it is felt that overdosage may expose the patient to the risk of bleeding when INR exceeds the value of 5. Table 10 shows the approximate time necessary to correct an overdosage condition by only suspending the administration of the daily dose of OAs.

23.2. Therapeutic practice

Continuing daily administration of OAT is subordinate to the patient's INR value and, above all, to the presence/absence of bleeding, to its intensity and site. If the INR value goes beyond 5.0, which is considered a threshold for higher bleeding risk, witholding OAs for a day generally brings INR values down to 5 in about 24-48 hours. As an alternative, the administration of 2 mg of vitamin K per os (two drops) consistently brings INR values well below 5 within 24 hours. This amount of vitamin K does not induce a subsequent period of resistance to OAs. Therefore, in patients without hemorrhagic complications and with INR values slightly in excess of 5 (say between 5 and 6), warfarin therapy may be withheld for one day or the daily dosage reduced by 1.25-2.5 mg, controlling INR after one week. This way of dealing with overdosage appears to be particularly suitable in patients who are being controlled at home and for whom it might be too dangerous to prescribe self-medication with vitamin K. In the case of overdosage with INR values exceeding 6 or with values higher than 5 but with bleeding complications, it is best to use an oral vitamin K administration scheme.

The therapeutic tools available for treating hemorrhagic complications, beyond simply reducing or discontinuing therapy, are administration of vitamin K and blood derivatives, namely concentrates of prothrombin complex and fresh frozen plasma. Vitamin K needs at least 4-6 hours of latency to work, even if administered intravenously. Therefore this treatment is not adequate in the presence of major bleeding; furthermore, if vitamin K is administered in high doses, it may become too difficult to bring the patient's INR back into his/her therapeutic range.

Prothrombin complex concentrates are immediately effective and are safe in terms of transmission of viral diseases. However, they often contain activated factors with the consequent risk of both a excessive *correction* of the coagulability and thrombotic complications. On the other hand, it is more difficult to correct hypocoagulability with fresh frozen plasma, because of the large volumes required. Moreover, there is also a risk, although limited, of transmitting viral diseases. It has recently been demonstrated that the administration of fresh frozen plasma cannot produce a complete normalization of factor IX, which often remains at insufficient levels (*Makris 1997*).

23.3. General criteria

It has been demonstrated (*Pengo 1993*), and recently confirmed (*Crowther 2000*), that low doses of orally administered vitamin K (2 mg= 2 drops of Konakion) can correct high INR values more quickly and without negative side-effects, compared to simply withdrawing OAs.

An INR value of 7.0 or 8.0 can be chosen as the threshold above which it is essential to correct the excessive anticoagulation immediately, by administering at least vitamin K. Lower INR values can also represent an indication for pharmacological reversal of anticoagulation, based on the evaluation of the single patient, taking into account the presence of other hemorrhagic risk factors, such as age > 75 years, recent surgery, stroke, peptic ulcer, or the existence of hemorrhagic complications.

The period of OA suspension/reduction for overdosage must be decided on the basis of the actual INR value and taking into consideration the usual doses of OA taken by the patient.

It should be remembered that acenocoumarol has a shorter half-life than warfarin and a greater anticoagulant activity.

*Recommendations (modified from Hirsh 2001)**

- **If INR is above the therapeutic range, but below 5.0, without hemorrhages or conditions which require a rapid return to therapeutic range: reduce dosage.**
- **If INR is over 5.0, but below 8.0, without hemorrhages: OAT should be suspended and then started again with a reduced dose; otherwise, 2 mg of vitamin K1 can be administered orally; this approach should be preferred when INR is > 7.0, in patients at higher hemorrhagic risk and**

**All these recommendations are not based on evidence from clinical studies, but on experts consensus (grade C2).*

for any situation in which a rapid restoration of the usual levels of anticoagulation is indicated (surgery, invasive procedures etc.). Values of INR within the therapeutic range are usually reached within 24 hours. Otherwise, an additional 2 mg dose of vitamin K1 can be given;

- **For INR values above 8.0, without hemorrhagic complications, the recommendation is to administer 3-5 mg of vitamin K1 per os, withdrawing OA administration for two days and checking the INR after 48 hours, with possible further administration of vitamin K1.**
- **In the presence of minor bleeding, without overdosage, it is appropriate to look for the possible cause of the hemorrhage and to maintain the INR within the therapeutic range or to reduce it, depending on the clinical conditions.**
- **In case of minor bleeding associated with overdosage, it is appropriate to rapidly bring the INR back into the therapeutic target, by means of the above indicated interventions.**
- **In case of major bleeding, it is necessary to obtain rapid and complete coagulation normalization. This is to be done by: interrupting OAT and administering 5 mg of vitamin K1 i.v. (by slow infusion, which can be repeated after 12 hours); administering fresh frozen plasma (possibly using plasma which has been treated to inactivate viruses) in doses of 15 ml/Kg of body weight, or of prothrombin concentrates in doses of 35-50 U/Kg, combined with concentrates of factor VII in doses of 20 U/Kg. The choice between these two approaches should be based on the specific evaluation of the risks related to the active bleeding and to the possible thrombotic complications.**
- **In case of intracranial hemorrhages, or risk of death, it is preferable to use prothrombin concentrates (plus factor VII), instead of fresh frozen plasma, in order to guarantee almost immediate and complete normalization of blood coagulability (Boulis 1999).**

24. LEGAL RESPONSIBILITIES OF CLINICS

OAT control is a medical activity that can cause transient or permanent damage to the patient, sometimes because of improper therapy management.

We must immediately specify that, even in the absence of specific medico-legal regulations on the services offered by Anticoagulation Clinic staff, it is clear that such services are part of those described in Articles 2229 and subsequent ones of the Civil Law.

We are not citing such articles for the sake of conciseness; however, these articles indicate that a physician has a contractual obligation to provide a diligent, prudent and skilled service, while respecting the patient's personality; the patient, on the other hand, has, among other duties, an obligation to follow the therapeutic prescriptions.

According to Gerin: «*Prudence stems from the culture and specific skills of the physician, from his/her experience and his/her being wise. Therefore, a physician is prudent when s/he behaves according to the rules of science, demonstrating of knowing well the immediate consequences of his/her actions. So, a physician is prudent when s/he acts according to science, avoiding all those actions that medical science discourages. On the other hand, a physician is imprudent when s/he operates against all principles of medical science and goes beyond his/her personal capabilities*».

Skill is not only knowledge, but especially the ability of knowing what to do. Knowledge can only derive from the experience of others; the ability of knowing what to do derives particularly from one's own experience. It follows that the physician should not do anything that s/he has not directly learned and experienced, either in University or later. As for the expression *diligence*, this term derives from *diligere*, that means to love with pure love, to hold dear as well as appreciate, respect and honor.

The ethical and technical contents of this expression cannot be missed; it is important to remember that *loving* what you do, having therefore an interest in what you do, means that one's attention is vigilant and prompt, certainly focused on single activities. It is therefore easy to avoid those distractions and deficiencies that can be the basis of fault.

Remembering that, as a general rule, the physician should operate prudently, skillfully and diligently. Referring to the specific job description of an Anticoagulation Clinic physician, we wish to specify that the greater the physician's knowledge of thromboembolic diseases and of OAT, the greater his/her professional responsibilities if the patient suffers damage.

The following can be established:

- the fact that the physicians of an Anticoagulation Clinic offer their professional services on a voluntary basis does not represent an excuse for possible professional errors. Health operators are required to have a cultural background and a professional skill, in the specific subject area, greater than that of the average medical professional.
- Disregarding the concepts of prudence, skill and diligence increases their professional responsibility.
- A physician cannot be considered guilty for possible damage to the patient when the latter did not follow all the therapeutic prescriptions

which, in this case, are of paramount importance.
- On the other hand, the physician must be able to identify those patients who, due to physical or mental impairment, are not capable of following the recommendations given to ensure the safety and effectiveness of OAT. Each Clinic should be capable of demonstrating that OAT control is properly carried out, according to state-of-the-art knowledge based on medical literature and on the recommendations of scientific and health authorities.
- Each patient must have a personal clinical file to record the initial clinical test data, the following clinical and laboratory checks, the therapy prescriptions and the requests for the follow-up visits. The Clinic should keep a complete and orderly archive of the data and the laboratory should regularly carry out internal and external quality controls.
- All health operators who are involved in OAT management can theoretically be held responsible, although it should be remembered that the direct primary responsibility lies with the physician who prescribes the therapy. The other health operators have secondary responsibilities (e.g. the Clinic Director may be questioned on his/her choice of the health operators). In this context, the hoped for formalization of the Clinic would bring about a more precise definition of roles and responsibilities.
- Educating a patient to manage of OAT correctly is part of the Clinic's duties: this activity must be carried out and the Clinic must be able to prove that it was carried out. The patient should be informed of all the practical aspects of OAT management and of the possible risks of the treatment. At the beginning of the treatment it is appropriate for the patient to give his/her informed consent, preferably in a written form and in the presence of witnesses.

25. INTEGRATION BETWEEN CLINICS AND OTHER PHYSICIANS

The main physicians who integrate the activity of an FCSA Clinic are the General Practitioner (GP) and other medical specialists, including both the physicians who sent the patient to the Clinic (cardiologists, heart surgeons, etc.) and those who can be consulted by the Clinic for specific necessities (dentists, general surgeons etc).

1) General practitioners

The GP should be adequately informed even when the patient's management is totally the responsibility of the Clinic. When starting OAT, it is therefore useful to communicate, by phone or in writing, the purpose, duration and target INR of the therapy and to discuss possible important clinical issues. The GP should be informed about the organization of the Clinic for urgent issues, particularly regarding where the patient should be sent to in case of emergency.

During the follow-ups, the Clinic and the GP must keep in touch and discuss any new issue that could be relevant for the patient's health. If some clinical problems require the consultation of other specialists, it is appropriate for the Clinic to inform the GP and to take a decision with him/her. In any case, it is necessary to remember the relevance of drug interference in the management of OAT; this requires a timely exchange of information between the Clinic and the GP about any therapeutic modifications.

Lastly, it should be borne in mind that many patients receiving OAT are managed directly by the GP. The FCSA is interested in effective and safe management of OAT also for these patients and started a collaboration with the Italian Society of General Practitioners (SIMG) for the preparation of informative material and the development of common treatment guidelines (*FCSA-SIMG Task Force, 2000*).

A pilot study of a collaborative model to manage patients on OAT is ongoing in the province of Parma (Northern Italy). An information technology network has been put in place to allow strict collaboration at various levels, between a group of GPs and a specialized hospital Clinic (see chapter 18.2).

2) Other medical specialists

The interactions between FCSA Clinics and other medical specialists are various and complex and cannot be extensively discussed in this paragraph. It is, however, appropriate to emphasize two important points:

a) when a Clinic accepts to follow a patient on OAT, it takes the responsibility to decide the duration and intensity of the therapy. The FCSA recommends that associated Clinics do not manage anticoagulated patients with duration and intensity levels decided by others, unless there is full agreement. In these cases it is recommended that the best therapeutic strategy is established together with the medical specialist who sent the patient for OAT treatment;
b) the FCSA recommends the use of written management protocols, prepared in co-operation with the specialist whenever possible. Examples of such protocols for Surgery are available on the FCSA's web site (www.fcsa.it) and can also be used as models for other requirements of the Clinics.

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