Physician Compliance with Outpatient Oral Anticoagulant Guidelines in Auvergne, France

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OBJECTIVE: Oral anticoagulants (OA) are commonly used, but they can lead to severe bleeding. We studied the indications and monitoring of OA in patients treated by general practitioners.

DESIGN: Retrospective cross-sectional study.

SETTING: Primary care.

PATIENTS: Four hundred thirty-eight randomly selected patients of a population of 2,452 patients treated with OA were studied.

INTERVENTIONS: We compared the indications for OA as reported by general practitioners with indications as defined according to recent guidelines.

MAIN RESULTS: Twenty-five percent of patients should not have been treated with OA. Inappropriate indications (13% of patients) were atrial fibrillation without risk factor (3.9%), prior uncomplicated myocardial infarction (2.7%), peripheral arterial disease (2.7%), superficial thrombophlebitis (2.3%), and atherothrombotic ischemic stroke (1.6%). For 12% of patients, the duration of OA was too long (venous thromboembolism without permanent risk factor in 10%). Frequency of International Normalized Ratio (INR) measurement was insufficient for 14% of patients and target INR was not achieved in 31%.

CONCLUSIONS: Our study demonstrated that clinicians' adherence to recommendations regarding indications for OA and management of this treatment should be improved. Implementation of anticoagulation clinics is probably needed.

KEY WORDS: anticoagulants; drug monitoring; indication; warfarin.

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Oral anticoagulants (OA) are effective in the prevention and treatment of thromboembolic complications of vascular disease. However, they have a narrow therapeutic index and bleeding is the most important complication. The average annual rate of major hemorrhages is from 1% to 5%, depending mainly on the intensity of anticoagulation and age.¹ After the age of 65, the prevalence of atrial fibrillation (AF), one of the most important indications of OA, is 5.9%.² Venous thromboembolism is also a major health problem, with an annual incidence that exceeds 1 per 1,000.³ Thus, the number of patients treated with OA is very large and the burden of bleeding complications should be taken

into consideration. Randomized trials have found that specialized, multidisciplinary clinics achieve better management than does usual care.⁴ However, anticoagulation clinics require time, money, and effort. Prior to the wide implementation of these services, reliable data about the real use and monitoring of OA in the general population are needed. The aim of this study was to evaluate the indications and monitoring for OA therapy in a large population treated by general practitioners.

PATIENTS AND METHODS

We studied outpatients treated with oral anticoagulants (OA) in Auvergne, France. According to the last census (1999), the Auvergne area has a total of 1,308,878 inhabitants (51.4% women). All patients included in our study were affiliated members of the Mutualité Sociale Agricole (MSA), one of the public health insurance companies in France. Everyone who works in the French agricultural sector and their families are under a strict obligation to be affiliated to this public insurance company (4.2 million people in France). At the time of our study (February 2000), 157,900 people (mean age 51.6 years, 49.8% women) were affiliated members of the MSA in Auvergne. All patients who made at least 1 request for OA repayment during 1 year were considered as having been treated with OA (2,452 patients or 1.5% of the total population). We selected 506 of these patients (21%) corresponding to 4 randomly selected days of request for OA repayment, using a random-number generator.

Data were obtained from the general practitioner of each patient using a written standard questionnaire. An English version of this original survey instrument is provided in Appendix A. The physicians were able to indicate several reasons to prescribe OA therapy (paragraph 4 of the survey instrument). If necessary, the general practitioner was contacted by telephone in order to specify other comorbid conditions that may have influenced the decision to use or to continue OA therapy. In the case of incomplete questionnaires, the physicians were also interviewed by phone. We then searched the hospital discharge reports for additional clinical information.

An expert committee of 7 physicians from the regional university hospital defined accurate indications and monitoring of OA in January 2000. The prescribing physicians did not know these predefined criteria. Briefly, the following indications for OA were considered as appropriate: 1) Venous thromboembolism: 6 months' duration or less after a first episode, long-term duration after recurrence, or permanent risk factors such as cancer or antiphospholipid antibodies;⁵⁻⁸ 2) AF with mitral stenosis, or nonvalvular AF

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for patients over 65 or with 1 of the following risk factors: systemic hypertension, diabetes, prior transient ischemic attack, or stroke;⁹ 3) Mechanical heart valves (for biological prostheses, use of OA for 3 months or less after surgery was considered as appropriate);¹⁰ 4) Congestive heart failure and/or after acute myocardial infarction with large hypokinetic area or aneurysm of left ventricle;¹¹ 5) Peripheral vascular surgery: in particular situations less than 1 year after surgery;¹² and 6) Prevention of venous thromboembolism after orthopedic surgery for 6 weeks or less.¹³

Appropriate monitoring of OA treatment was defined by the expert committee as follows: 1) Monitoring based on International Normalized Ratio (INR) and not only on prothrombin time; 2) INR target range 2.0 to 3.0 except for mechanical heart valves (target 3.0 to 4.0), and 3) One month maximum interval between 2 tests (1 week after a modification of dosage).

When the indication reported by the physician did not match any appropriate indication as defined by the expert committee, the authors (MR, CB, AA) reviewed the questionnaire to classify the indications as appropriate or inappropriate.

RESULTS

A total of 426 general practitioners participated in this study and completed the questionnaire. Four hundred and thirty-eight questionnaires (85.6% of the 506 selected patients) were returned to the investigators; all were completely filled out after telephone calling. Of these 438 patients, 59% were male (mean age 71.4 years), and 41% were female (mean age 74.7 years). Only 14.4% of these patients treated with OA were less than 65 years old and 13.5% were over 80. Fluindione and acenocoumarol were the most frequently prescribed OA, respectively, in 52% and 46% of cases. Warfarin was rarely used (1%). The initial prescription of OA was written by a cardiologist in 61.4% of cases, by a general practitioner in 19.6%, by a surgeon in 8.2%, by a chest physician in 3%, and by another specialist in 7.8%. Prescription of OA was then renewed by general practitioners in 97.3% and by a cardiologist in 1.8% of cases. At the time of the study, the duration of OA treatment was 6 months or less for 16.5% of patients, from 6 to 24 months for 26.5%, and 24 months or more for 56%.

The most commonly reported indications for OA (Table 1) were atrial fibrillation (45%), venous thromboembolism (35%), mechanical heart valves (10.5%), prior myocardial infarction (9%), and peripheral occlusive arterial disease (8%). Other indications are listed in Table 1. For 30% of the 438 patients, OA were prescribed for more than 1 indication.

According to the defined items of the expert committee, a total of 110 patients (25%) should not have been treated with OA. For 13% of patients, the indications were considered as inappropriate. These inappropriate indications were AF without risk factors (3.9% of the 438 patients), prior

Table 1. Indications for Oral Anticoagulants as Reported by General Practitioners in the 438 Patients

Reported Indications	n (%)
Atrial fibrillation	197 (45)
Without valve dysfunction	106 (24.2)
Without risk factor for stroke*	17 (3.9)
Venous thromboembolism (VTE)	153 (34.9)
Venous thrombosis with pulmonary embolism	68 (15.5)
Venous thrombosis without pulmonary embolism	72 (16.4)
Pulmonary embolism alone	13 (3)
Recurrent VTE	75 (17.1)
Heart valve prostheses	46 (10.5)
Mechanical	42 (9.6)
Biological	4 (0.9)
Without other indication for OA [†]	1 (0.2)
Prior myocardial infarction	40 (9.1)
Uncomplicated	12 (2.7)
Peripheral occlusive arterial disease	37 (8.4)
Without other indication for OA [†]	12 (2.7)
Atherothrombotic ischemic stroke	26 (5.9)
Without other indication for OA [†]	7 (1.6)
Superficial thrombophlebitis	23 (5.3)
Without other indication for OA [†]	10 (2.3)
Cardiac insufficiency	6 (1.4)
Prevention after orthopedic surgery	2 (0.5)
Other	3 (0.7)

OA, oral anticoagulants.

* Patients over 65 years or with systemic hypertension, diabetes, prior transient ischemic attack, or stroke.

[†] As defined by the expert committee; see text.

uncomplicated myocardial infarction (2.7%), peripheral occlusive arterial disease (2.7%), superficial thrombophlebitis (2.3%), and atherothrombotic nonembolic ischemic stroke (1.6%). For 12% of patients, the indications were appropriate but the duration of OA treatment was longer than the expected duration as defined by the expert committee. This 12% of cases included venous thromboembolism without permanent risk factors (10%), vascular peripheral surgery (1.5%), biological heart valve in 1 case, and prevention after orthopedic surgery in 1 case. Among the 110 patients who were treated with OA for inappropriate indications or over too long a period, we found 19 patients with major risk factors for bleeding such as severe hypertension, renal or hepatic insufficiencies, prior stroke, or progressive gastrointestinal ulcers.

For 7.5% of patients, monitoring of OA treatment was based on prothrombin time alone without regard for the INR. Insufficiency of testing for INR (less than 1 test a month) was noted for 14% of the 438 patients. At the time of the study, 69% of the last INR measurement was in the target range. Eight percent of the patients experienced bleeding complications during OA treatment (7% of the 110 patients who should not have been treated with OA according to the expert committee). Thirty-one percent of these patients needed hospitalization.

DISCUSSION

We found inappropriate use of OA in 25% of patients. Moreover, frequency of INR measurement was insufficient for 14% of patients.

Atrial fibrillation without risk factor was the most common inappropriate indication found in this study. Randomized controlled studies have convincingly shown that OA therapy is effective for prevention of stroke in nonvalvular AF, with an acceptable risk of major hemorrhage.^{14–19} However, the risk of stroke is very low in patients without concomitant risk factors and aspirin would be preferable. The risk factors of a stroke in AF are prior transient ischemic attack or stroke, systemic hypertension, diabetes, or being over 65 years of age.²⁰ These factors were absent in this group and we considered that these patients should receive aspirin as was recommended in recent guidelines.²¹

Prior uncomplicated myocardial infarction was the second cause of inappropriate use of OA in our study. However, the role of OA in coronary artery disease remains controversial. A meta-analysis found that high-intensity and moderate-intensity OA is effective in reducing myocardial infarction and stroke but increases the risk of bleeding.²² Our study was conducted before the results of the recent ASPECT-2 study.²³ This study compared the effect of high-intensity coumadin (target INR 3.0 to 4.0) and aspirin plus moderate-intensity coumadin (target INR 2.0 to 2.5) with aspirin (80 mg per day) alone in patients who had had an acute coronary event. The authors found that treatment with high-intensity OA or moderate-intensity OA plus aspirin was more effective than aspirin alone in reduction of subsequent cardiovascular events and death. Major bleeding was rarely observed in this study with the same frequency in the three treatment groups. Minor bleeding was more frequent only in the combination treatment. At the end of our study, these findings were not known and we considered that OA treatment after an uncomplicated myocardial infarction was not appropriate. Moreover, the ASPECT-2 study is not a double-blind trial and further studies seem to be necessary to evaluate the benefit-risk ratio of OA after an acute coronary event.

Oral anticoagulants were prescribed in 2.7% of patients for uncomplicated peripheral occlusive arterial disease. Aspirin or clopidogrel reduces ischemic complications and should be preferred to OA in this indication.²⁴ It is recommended that long-term oral anticoagulation with OA with or without aspirin should not be used routinely in patients after infrainguinal bypass and other vascular reconstruction. OA prevents infrainguinal vein graft occlusion but the risk of severe hemorrhage is higher than aspirin for a non-life-threatening complication.^{24,25} A recent study²⁶ confirmed these results in lower extremity arterial bypass surgery with an increased risk of morbidity and mortality in the group of patients treated with warfarin plus aspirin compared with the patients treated with aspirin alone. However, OA treatment after vascular reconstruction is subject to wide practice variations among surgeons and use of OA

was considered possibly in peripheral vascular surgery less than 1 year after surgery.

Superficial thrombophlebitis was the fourth cause of inappropriate use for OA in our study (2.3% of patients). Superficial thrombophlebitis is a common clinical condition often observed in patients with large varicose veins. In this case, OA does not prevent extension of the thrombus, nor new deep venous thrombosis.²⁷ Superficial thrombophlebitis can be associated with systemic conditions like cancer, myeloproliferative disorders, thromboangiitis obliterans (Buerger's disease), or Behcet's syndrome. In these conditions, OA treatment could be considered but our patients did not have features of these diseases.

The duration of OA treatment after a first episode of venous thromboembolism is still a controversial question.²⁸ We found that 10% of our patients receive OA for too long a period, i.e., more than 6 months after a first episode without permanent risk factors. Two studies compared 3 months versus extended OA therapy after a first episode of idiopathic venous thromboembolism.^{29,30} Prolonged course of OA therapy is associated with a reduced incidence of recurrence. However, the clinical benefit associated with extending the duration of OA to 1 year is not maintained after the therapy is discontinued.³⁰ Thus, long-course OA with a target INR of 2 to 3 is not actually recommended after a first episode of venous thromboembolism without permanent risk factors.²⁸ Studies with long-course, low-dose OA are underway. Recently, Ridker et al. showed that a long-term, low-intensity warfarin therapy (INR 1.5–2) was an effective method of preventing recurrent venous thromboembolism after an idiopathic episode.³¹

In our study, target INR was not achieved in 31% of patients. In clinical practice, the time that patients spent in the target range of INR is from 30% to 60%.³² Nevertheless, these results cannot be directly comparable with ours because the design of our study is cross-sectional and we do not have follow-up.

Our study has several limitations. First, the data were retrospectively collected. Second, we were often unable to verify the information, particularly when the OA was first prescribed by a nonhospital practitioner. Third, it is possible that our questionnaire played an educational role. For these reasons, we estimate that inappropriate indications or monitoring of OA are probably underestimated. Inversely, other studies showed that many apparently eligible patients with atrial fibrillation at increased risk of stroke were not receiving OA.³³ Moreover, a study shows that anticoagulation for stroke prevention is feasible, safe, and effective in clinical practice, even in elderly people.³⁴

A randomized controlled study showed that a comprehensive program of anticoagulant management can reduce the rate of major bleeding by half or more over 6 months in older patients.³⁵ This program included not only patient education, coaching, and self-monitoring of prothrombin time but also a guideline-based consultation that assessed the patient's indications for therapy. Our study demonstrated that selection of patients for OA therapy and monitoring

of this treatment are often inadequate. Thus, the diffusion and application of methods that improve appropriate use of OA are needed.

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APPENDIX A

*Questionnaire About Oral Anticoagulant Therapy***1. Start of OA (date)****2. Speciality of the physician who began the therapy by OA****3. Expected duration of OA therapy**

less than 3 months

from 6 months to 2 years

3 months

more than 2 years

6 months

unknown

4. Indication for OA therapy

Venous thromboembolism

deep venous thrombosis with pulmonary embolism

isolated deep venous thrombosis

isolated pulmonary embolism

Heart valve prostheses

mechanical (aortic)

mechanical (mitral)

biological

Atrial fibrillation

with abnormality of the valves

without abnormality of the valves

Superficial thrombophlebitis

Prior uncomplicated myocardial infarction

Atherothrombotic non-embolic ischemic stroke

Peripheral occlusive arterial disease

Prevention after orthopedic surgery

Other

5. Explorations of initial pathology

Pulmonary angiography

Helical computed tomography

Arteriography

Holter ECG

Cardiac echography

Arterial echo-Doppler

Venous echo-Doppler

Phlebography

Tomoscintigraphy

Other

6. Previous venous thromboembolism

Yes

No

One

Two or more

Exploration

7. Biological Data

Creatininemia

Yes

No last ($\mu\text{mol l}^{-1}$)

To monitor OA therapy, do you use

Prothrombin time

INR?

less than once/monthly

once/monthly

twice/monthly

more than twice/monthly last INR

intended INR

8. Comorbid conditions

Hypertension

Severe hypertension

Non-embolic stroke

Renal insufficiency

Hepatic insufficiency

Progressive gastrointestinal ulcer

Diabetes

Cardiac insufficiency

Familial thrombophilia

9. Adverse effects of OA therapy

Minor (without hospital admission)

Yes

No

Date

Diagnosis

Major (admission to hospital)

Yes

No

Date

Diagnosis

Hospital

Department

(Send a copy of the hospitalization report)