Oral anticoagulant therapy today: efficacy, safety, open problems

Gualtiero Palareti

Cardiovascular Department, Angiology and Blood Coagulation, University of Bologna, Bologna, Italy

(Ital Heart J 2000; 1 (Suppl 3): S126-S128)

Address:

Dr. Gualtiero Palareti

Divisione di Angiologia e Coagulazione Policlinico S. Orsola-Malpighi Via Massarenti, 9 40138 Bologna

Safety and efficacy

Oral anticoagulant therapy (OAT) is effective in the prevention and treatment of thromboembolic complications in patients with cardiovascular disease. The number of patients on chronic OAT has increased dramatically in recent decades. However this effective treatment is still underutilized in clinical practice. Both the fear of complications, especially bleeding, and the practical difficulties associated with the therapy, which is undoubtedly demanding, are frequently stated as concerns by physicians, preventing a wider use of the treatment for patients who would benefit from it.

The incidence of bleeding varies widely in published studies[1,2]. OAT safety was investigated in a recent collaborative study[3] that recorded all bleeding events occurring in an inception cohort of more than 2700 patients prospectively monitored in Italian anticoagulation clinics for a total period of more than 2000 patient/years. In that study the rates of bleeding complications were 0.25, 1.1 and 6.2% patient/year of treatment for fatal, major and minor events, respectively, figures that were substantially lower than those reported in previous observational studies. Though bleeding events occurred also at a very low anticoagulation intensity (7.7% patient/year at < 2.0 international normalized ratio-INR), the rate was the lowest in the 2.0-2.9 INR category (4.8% patient/year), increasing sharply in association with higher INR levels (relative risk for INR levels > 4.5 = 7.91, $p < 0.0001$).

The efficacy of OAT was also examined in the same cohort of patients, and the thrombotic complications or treatment failures recorded during treatment were analyzed in a subsequent paper[4]. The rates of fatal and major thrombotic events were 1% patient/year and 1.9% patient/year, respectively, lower than that reported in the few available studies on the same topic. The frequency of thrombotic events was, however, much higher (17.5%) when INR levels were < 1.5, decreasing to 2.3% for INRs within the 2-2.99 category (relative risk of INRs < 2.0 vs 2 = 1.88, $p < 0.05$). These results prove that a moderate intensity regimen (2.0-3.0 INR), associated with the careful monitoring of patients in specifically trained anticoagulation clinics, is not only safe but also effective against thrombosis.

Duration of oral anticoagulant therapy for the treatment of venous thromboembolism

A first course of heparin followed by a period of OAT is the treatment of choice in patients with an acute episode of venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and/or pulmonary embolism. This treatment is intended to reduce the rate of recurrences, which is particularly high in the first months after the acute event, and of post-thrombotic syndrome.

The optimal duration of OAT after a first VTE episode is however still debated. The usual duration of treatment after a first episode of idiopathic DVT is 3 to 6 months. Recent studies, however, examined the effect of longer periods of treatment and showed lower recurrence rates in comparison with shorter treatment periods[5,6]. The advantage of the longer treatment duration was mainly observed in patients with permanent risk factors for thrombosis[5]. In a second trial[7] patients with a recurrent DVT episode were treated either for 6 months or indefinitely, and evaluated after a 4-year follow-up. The

cumulative recurrence rate was 20.7% in the definite period group, and only 3% in the indefinite; the relative risk was 8-fold higher in the shorter period group.

The present answer to the issue of optimal duration is therefore to carefully evaluate persistent and/or transient prothrombotic factors in each patient. It has been proposed to classify DVT patients into low, intermediate, and high recurrence risk groups, respectively candidates for a short, intermediate or indefinite term anticoagulant therapy. After an episode of postoperative or post-traumatic DVT, and in the absence of permanent risk factors, < 6 months of OAT may be indicated. From the presently available data, it can be affirmed that the duration of treatment should not depend on the results of the echographic follow-up. More clinical trials are needed in specific categories of well characterized patients, as those with inherited or acquired thrombophilia.

Oral anticoagulant therapy for venous thromboembolism in cancer patients

It has long been known that VTE complications are frequent in patients with malignant diseases, sometimes even preceding the diagnosis of malignancy[8]. The treatment of acute VTE in cancer patients varies greatly from one clinician to another, mainly due to the concern that OAT may be less safe or less effective in cancer patients. Some reports[9-11], though not all[12], have outlined a higher bleeding risk, as well as more frequent VTE recurrence during OAT in these patients.

In a recent evaluation of patients with cancer treated with OAT for VTE (n = 95), who were included in the ISCOAT study, we found that these patients, when compared with patients without malignancy treated for the same reason, had statistically significant higher rates of major (5.4 vs 0.9%) and minor (16.2 vs 3.6%) bleeding[13]. These patients also showed a trend towards a higher rate of thrombotic complications (6.8 vs. 2.5%; p = 0.058; relative risk 2.5, confidence interval 0.96-6.5). The rate of thrombotic events was significantly higher in both cohorts when the INR was < 2.0.

In conclusion, patients with malignancy treated with OAT have a higher bleeding rate and possibly an increased risk of recurrent thrombosis compared with patients without malignancy. We believe that a safer and more effective anticoagulant treatment is needed for this challenging group of patients.

Oral anticoagulant therapy in the elderly

Some of the indications for OAT (e.g. VTE and atrial fibrillation) are particularly frequent in elderly people, the fastest growing population of our society. More than one third of all patients included in a recent collaborative prospective Italian study were aged > 70 years when they started OAT, and 8% were > 8 0 years[3]. It has long been debated whether the risk of bleeding during OAT is higher in older patients[14]. Many reasons can be at the basis of a higher risk for bleeding complications during OAT in elderly subjects: they require lower coumarin doses, are more likely to be taking interacting drugs and to have more comorbid conditions, they have been reported to have increased vascular fragility, a factor which may increase the risk of intracranial bleeding[15]. Non-compliance with OAT has been reported to be similar in elderly and younger patients[16]. Nevertheless, non-compliance could also contribute due to the complexity of the drug regimen, a lack of a clear understanding of the purpose of the treatment by the elderly who are prone to mental impairment[17].

In a recent study[18], bleeding and thrombotic events occurring during OAT in 461 patients, aged 75 years when they started OAT, and in 461 patients aged < 70 years, matched for sex, OAT indication and treating center, were analyzed. Bleeding rate was 9.9 and 6.6% patient/year in elderly patients and controls, respectively (p = NS), and 2.1 and 1.1% for major bleeding (p = NS). However, 6 and 1 events respectively were fatal (all intracranial, relative risk 6.4, p = 0.047). Thrombosis rate was 4.2 and 2.5% patient/year in elderly patients and controls, respectively (p = NS); however 13 and 5 events were fatal (relative risk 2.8, p = 0.041). Thrombosis rate was lower (1.5%) for INR between 2.0 and 2.9; it was higher during the first 90 treatment days (p < 0.001) and 6/7 venous events occurred at INR < 2.0.

In line with these results, we consider that a non-significant trend towards a higher rate of both bleeding and thrombotic complications can be expected in elderly patients treated with OAT. However, the risk of intracranial bleeding and fatal thrombotic events is significantly higher in these subjects.

References

1. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding - clinical epidemiology, prediction, and prevention. Am J Med 1993; 95: 315-28.
2. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. Chest 1995; 108 (Suppl): S276-S290.
3. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study. Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT). Lancet 1996; 348: 423-8.
4. Palareti G, Manotti C, Dangelo A, et al. Thrombotic events during oral anticoagulant treatment: results of the inception-cohort, prospective, collaborative ISCOAT study. Thromb Haemost 1997; 78: 1438-43.
5. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. N Engl J Med 1995; 332: 1661-5.
6. Kearon C, Gent M, Hirsh J, et al. A comparison of three

months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340: 901-7.
7. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med 1997; 336: 393-8.
8. Prandoni P, Lensing AWA, Buller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 1992; 327: 1128-33.
9. Moore F, Osteen R, Karp D, Steele G, Wilson R. Anticoagulants, venous thromboembolism and the cancer patient. Arch Surg 1981; 116: 405-7.
10. Clarke-Pearson DL, Synan IS, Creasman WT. Anticoagulation therapy for venous thromboembolism in patients with gynecologic malignancy. Am J Obstet Gynecol 1983; 147: 369-75.
11. Chan A, Woodruff RK. Complications and failure of anticoagulation therapy in the treatment of venous thromboembolism in patients with disseminated malignancy. Aust N Z J Med 1992; 22: 119-22.
12. Bona RD, Sivjee KY, Hickey AD, Wallace DM, Wajcs SB. The efficacy and safety of oral anticoagulation in patients with cancer. Thromb Haemost 1995; 74: 1055-8.
13. Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost, in press.
14. Beyth RJ, Landefeld CS. Anticoagulants in older patients: a safety perspective. Drugs Aging 1995; 6: 45-54.
15. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994; 120: 897-902.
16. Arnsten JH, Gelfand JM, Singer DE. Determinants of compliance with anticoagulation: a case-control study. Am J Med 1997; 103: 11-7.
17. Palareti G, Poggi M, Guazzaloca G, Savino A, Coccheri S. Assessment of mental ability in elderly anticoagulated patients: its reduction is associated with a less satisfactory quality of treatment. Blood Coagul Fibrinolysis 1997; 8: 411-7.
18. Palareti G, Hirsh J, Legnani C, et al. Oral anticoagulation treatment in the elderly - a nested, prospective, case-control study. Arch Intern Med 2000; 160: 470-8.