Antithrombotic treatment after coronary artery stenting in patients on chronic oral anticoagulation: an international survey of current clinical practice

Andrea Rubboli, Mauro Colletta, Pietro Sangiorgio, Giuseppe Di Pasquale

Division of Cardiology, Maggiore Hospital, Bologna, Italy

Key words:
Antiaggregating agents; Anticoagulants; Coronary angioplasty; Stenting.

Background. **In the absence of evidence-based data, the optimal antithrombotic treatment after coronary artery stenting in patients on chronic oral anticoagulation (OAC) remains unknown. In order to investigate current practice in this setting, an international survey was carried out.**

Methods. **A questionnaire was e-mailed to 40 internationally renowned, foreign Interventional Centers worldwide.**

Results. **Out of the 24 Centers (60%) replying, only in 13 (54%) is antithrombotic treatment carried out in accordance with a standardized protocol. OAC is stopped in favor of aspirin plus ticlopidine/clopidogrel in selected (low thromboembolic risk) conditions in 13 (54%) Centers. When OAC is continued, the association with a single antiplatelet is employed in a few Centers only, as opposed to triple antithrombotic treatment (OAC and aspirin plus ticlopidine/clopidogrel) which is adopted, selectively or systematically, in the majority (83%) of Centers. In 8 (33%) Centers adopting triple antithrombotic treatment, the dose of OAC is decreased in all patients, whereas in 9 (38%) it is left unchanged. Upon completion of 1 to 3-6 months of antithrombotic treatment with OAC and single/dual antiplatelets, in 9 (38%) Centers this regimen is continued indefinitely, whereas in 10 (41%) antiplatelets are systematically withdrawn. Out of the 13 Centers, selectively exchanging OAC for aspirin plus ticlopidine/clopidogrel, low- or full-dose low-molecular-weight heparin is added in selected (high thromboembolic risk) cases in 3 (23%) and 5 (38%) Centers, respectively. Following 1 to 3-6 months of aspirin plus ticlopidine/clopidogrel antithrombotic treatment, OAC is resumed in all cases in 9 (69%) Centers and in no cases in 1 (8%).**

Conclusions. **Our survey shows a high variability in the current antithrombotic treatment of patients on chronic OAC undergoing coronary artery stenting. Although various regimens may be adopted, the optimal antithrombotic treatment for this patient subset still needs to be identified.**

(Ital Heart J 2004; 5 (11): 851-856)

Received May 26, 2004; revision received September 28, 2004; accepted September 29, 2004.

Address:

Dr. Andrea Rubboli

Unità Complessa di Cardiologia Ospedale Maggiore Largo Nigrisoli, 2 40133 Bologna E-mail: andrearubboli@libero.it

Introduction

Dual antiplatelet therapy with aspirin and a thienopyridine (either ticlopidine or clopidogrel) has been proven superior to oral anticoagulation (OAC) (plus aspirin), after percutaneous coronary intervention (PCI) with stent implantation[1-6]. The 30-day occurrence of major adverse cardiac events such as death, non-fatal myocardial infarction and the need for repeat revascularization, as well as that of hemorrhagic and vascular access-site complications, is in fact lower with the dual antiplatelet regimen as compared to OAC[1-5]. Therefore, the antithrombotic treatment currently recommended after PCI with stent implantation, is a combination of aspirin plus a thienopyridine for 1 to 3-6 months (depending on whether a bare metal or a drug-eluting stent has been implanted), followed by aspirin indefinitely.

However, a number of patients currently undergoing coronary artery stenting appears to have indications for both the dual antiplatelet regimen and OAC, because of atrial fibrillation, a mechanical prosthetic heart valve, previous venous or systemic thromboembolism, left ventricular thrombosis or other conditions. The issue of the optimal antithrombotic treatment in this patient subset has never been addressed, so that no evidence-based data nor practice guidelines are available to assist cardiologists in the management of these patients.

The aim of our study was to carry out a survey of the current antithrombotic management of patients on chronic OAC undergoing coronary artery stenting, in order to investigate and compare the experience of different Institutions.

Methods

A questionnaire was e-mailed to the Directors of 40 world renowned, high-volume foreign Interventional Centers worldwide. An accompanying letter presenting the investigators, explained the purpose of the study and asked for permission to use the data obtained for publication purposes. The questionnaire included the following 7 questions:

1) *In my Institution, the antithrombotic treatment in patients on chronic OAC (due to either atrial fibrillation, the presence of mechanical prosthetic heart valves, previous venous thromboembolism, etc.) undergoing coronary angioplasty with stent implantation:*
- is standardized according to a protocol;
- is left at the discretion of the attending physician.

2) *In these patients, treatment is changed to a dual antiplatelet regimen (i.e. aspirin plus ticlopidine/clopidogrel) in:*
- all cases;
- selected cases (specify);
- no cases.

3) *When OAC is continued:*

a) aspirin (75-160 mg/day) only is added in:
- all cases;
- selected cases (specify);
- no cases;

b) ticlopidine/clopidogrel (500/75 mg/day) only is added in:
- all cases;
- selected cases (specify);
- no cases;

c) a dual antiplatelet regimen is added in:
- all cases;
- selected cases (specify);
- no cases.

4) *When OAC is continued with either aspirin (75-160 mg/day) or ticlopidine/clopidogrel (500/75 mg/day) or their association added, the dose of anticoagulants (i.e. lower target INR) is decreased in:*
- all cases;
- selected cases (specify);
- no cases.

5) *When OAC is continued with either aspirin (75-160 mg/day) or ticlopidine/clopidogrel (500/75 mg/day) or their association added, antiplatelets are withdrawn 1 to 3-6 months later (depending on whether or not a drug-eluting stent has been implanted) in:*
- all cases;
- selected cases (specify);
- no cases.

6) *When switching to a dual antiplatelet regimen:*

a) low-dose low-molecular-weight heparin (i.e. enoxaparin 4000 IU subcutaneously once daily) is added in:
- all cases;
- selected cases (specify);
- no cases;

b) full-dose low-molecular-weight heparin (i.e. enoxaparin 100 IU/kg subcutaneously twice daily) is added in:
- all cases;
- selected cases (specify);
- no cases.

7) *Having switched to a dual antiplatelet regimen, 1 to 3-6 months later (depending on whether or not a drug-eluting stent has been implanted) OAC is resumed in:*
- all cases;
- selected cases (specify);
- no cases.

The questionnaires were evaluated by each investigator and discrepancies in the interpretation of the answers were resolved either by consensus or by asking the corresponding author.

Results

Out of the 40 Interventional Centers interviewed, 24 (60%) replied. The geographical distribution of the participating Centers included North America in 25% of cases, South America in 8%, and Europe in 67% (Fig. 1).

In 13 (54%) Centers, the antithrombotic strategy for patients on chronic OAC undergoing coronary artery stenting, is reported to be carried out according to a standardized protocol, whereas in the remaining 11 (46%) it is left at the physician's discretion. None of the Centers adopts the systematic OAC suspension and exchange for antiplatelets in all patients, whereas in 54% this strategy is used in selected cases (Table I). In the remaining 46% of Centers, OAC suspension and exchange for antiplatelets is never adopted (Table I). The selected clinical condition generally reported to be treated with dual antiplatelet administration instead of OAC, is represented by atrial fibrillation at low thromboembolic risk. In fact, although even patients with mechanical aortic heart valves are treated with dual antiplatelets in a few Centers, in most of them the pres-

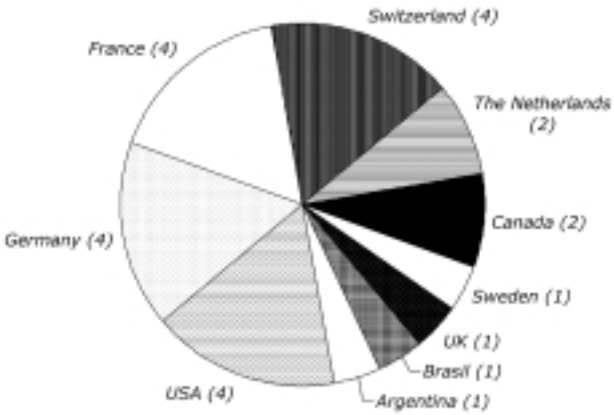

Figure 1. *Geographic distribution and number of Centers participating in the survey.*

Table I. Answers to the questionnaire on the antithrombotic strategies adopted for patients on chronic oral anticoagulation (OAC) and undergoing coronary artery stenting.

	No. Centers
A dual antiplatelet regimen is switched to in:	
All cases	0
Selected cases	13 (54%)
No cases	11 (46%)
When OAC is continued,	
a) aspirin only is added in:	
All cases	1 (4%)
Selected cases	5 (21%)
No cases	18 (75%)*
b) a thienopyridine only is added in:	
All cases	2 (8%)
Selected cases	1 (4%)
No cases	21 (88%)*
c) a dual antiplatelet regimen is added in:	
All cases	15 (62%)
Selected cases	5 (21%)*
No cases	4 (17%)
When OAC is continued with either aspirin or a thienopyridine or their association added, the dose of OAC is decreased in:	
All cases	8 (33%)*
Selected cases	7 (29%)
No cases	9 (38%)
When OAC is continued with either aspirin or a thienopyridine or their association added, antiplatelets are withdrawn 1 to 3-6 months later in:	
All cases	10 (41%)
Selected cases	5 (21%)
No cases	9 (38%)
When switching to a dual antiplatelet regimen,	
a) low-dose low-molecular-weight heparin is added in:	
All cases	0
Selected cases	3 (23%)
No cases	10 (67%)
b) full-dose low-molecular-weight heparin is added in:	
All cases	0
Selected cases	5 (38%)
No cases	8 (62%)
Having switched to a dual antiplatelet regimen, 1 to 3-6 months later OAC is resumed in:	
All cases	9 (69%)
Selected cases	3 (23%)
No cases	1 (8%)

* in one Center anticoagulation is achieved by administering full-dose low-molecular-weight heparin instead of OAC.

ence of prosthetic heart valves constitutes an exclusion criterion for such a regimen.

In the Centers continuing anticoagulation in addition to (either single or dual) antiplatelet treatment, OAC with warfarin (or acenocumarol) is maintained in all but one case, where a full dose of the subcutaneous low-molecular-weight heparin dalteparin is administered instead for 2 to 3 weeks, before OAC is recommenced. The addition of aspirin only to OAC is performed in all patients by 4% of Centers and in no cases by 75% (Table I). In the remaining 21%, this strategy is reported to be adopted in selected patients (Table I), such as those with a perceived high hemorrhagic risk for whom a less aggressive treatment with one antiplatelet agent only is preferred. Similarly, the addition to OAC of either ticlopidine or clopidogrel only is reported to be carried out by 8% of Centers in all patients and by 88% in none (Table I). In the 4% of Centers selectively using the association of OAC and a thienopyridine (Table I), this antithrombotic regimen is essentially adopted in patients with a previous history of gastrointestinal bleeding. Finally, triple therapy with OAC and aspirin plus a thienopyridine, is adopted by 62% of Centers in all cases and by 21% in selected cases, whereas the remaining 17% reports that it never resorts to this regimen (Table I). The clinical conditions selectively treated with triple therapy include atrial fibrillation at high thromboembolic risk, the presence of mechanical heart valves, previous venous or systemic thromboembolism and the implantation of multiple or long stents, especially if located at the proximal site of functionally important vessels.

The dose of OAC in the Centers adding, either systematically or selectively, antiplatelet treatment, is reported to be decreased in no cases in 38%, in selected cases in 29%, and in all cases in 33% (Table I). A history of a previous major hemorrhagic event or, more in general, a perceived high hemorrhagic risk, represents the main indication to decrease the target INR during triple treatment in the Centers selectively adopting this policy.

After 1 to 3-6 months of combined treatment with OAC and antiplatelets, the latter are withdrawn in 41% of Centers in all patients, and in 21% in selected clinical conditions, such as previous venous thromboembolism, mechanical heart valves and atrial fibrillation, especially in case of a history of peptic ulcer or previous gastrointestinal bleeding. In the remaining Centers, dual therapy with OAC and a single antiplatelet agent (either aspirin or a thienopyridine) is continued indefinitely (Table I).

In none of the 13 Centers reporting selective exchange of OAC for a dual antiplatelet regimen is low-molecular-weight heparin systematically added in all cases, whereas in 38 and 23% of Centers, full-dose and low-dose low-molecular-weight heparin respectively, are associated with antiplatelets in selected cases (Table I). Valvular heart disease, atrial fibrillation with an enlarged left atrium and previous venous thromboembolism constitute the main conditions reported to prompt, in some Centers, the addition of low-dose low-molecular-weight heparin, whereas full-dose low-molecular-weight heparin is added in the presence of mechanical prosthetic valves and previous systemic thromboembolism.

Upon completion of the 1 to 3-6 month course of the dual antiplatelet regimen, 69% of the 13 Centers adopting such a policy, reports resumption of OAC in all cases, whereas in 23% this is accomplished in selected cases, which generally include atrial fibrillation at high thromboembolic risk or associated with mitral valve disease or a poor left ventricular function, recent venous thromboembolism and previous embolic stroke (Table I). In the remaining 8%, OAC is never resumed (Table I).

Discussion

The results of our survey show a very high variability in the antithrombotic management of patients on chronic OAC undergoing PCI with stent implantation who, in an era of standardization, and optimization, of medical care (as pursued by the endorsement of practice guidelines), are treated according to a standardized protocol only in about one half of cases. Also, most of the strategies appear to be based on common sense rather than on sound evidence, since this patient subset has never been investigated. The only available evidence on the issue of OAC and antiplatelets after coronary artery stenting comes from the four historical clinical trials in which OAC (plus aspirin) was compared to a dual antiplatelet regimen with aspirin and ticlopidine[1-4]. The occurrence of adverse cardiac events, represented by a composite of cardiac death, non-fatal myocardial infarction and need for repeat revascularization, at 4 to 6 weeks after the procedure, was significantly reduced by dual antiplatelet treatment in all studies: 1.6 vs 6.2% in ISAR[1], 0.5 vs 2.7% in STARS[2], 5.6 vs 11% in MATTIS[3], and 2.4 vs 9.9% in FANTASTIC[4]. Similarly, in all studies the occurrence of hemorrhagic/vascular complications in the dual antiplatelet group was lower: 0.8 vs 12.7% in ISAR[1], 7.5 vs 8.2% in STARS[2], 1.7 vs 6.9% in MATTIS[3], and 13.5 vs 21% in FANTASTIC[4]. Overall, the relative risk of adverse cardiac events and hemorrhagic/vascular complications at 4 to 6 weeks after the procedure was significantly decreased with the dual antiplatelet regimen by about 30 to 80% and 10 to 90%, respectively[1-4]. In absolute terms, however, the risk of adverse cardiac events with OAC plus aspirin was on average as low as 7% (range 2.7 to 11%), whereas that of hemorrhagic/vascular complications was about 12% (range 6.9 to 21%)[1-4]. In no trial, however, was the mortality significantly modified by the treatment regimen[1-4].

In the light of the above-mentioned data, the addition of aspirin to OAC, adopted either selectively or systematically by 25% of the participating Centers following coronary stenting in patients (at low thromboembolic risk) on chronic OAC (Table I), appears an acceptable antithrombotic strategy. On the other hand, the addition of a thienopyridine (either ticlopidine or clopidogrel) to OAC reported by 12% of Centers (Table I) appears less justifiable. The clinical efficacy superior to that of aspirin[7] is likely to be at the basis of such a policy which probably represents an attempt to maximize the antithrombotic protection shown in the historical trials comparing OAC and aspirin to a dual antiplatelet regimen[1-3], by exchanging aspirin for a more potent antiplatelet agent. However, when aiming at the optimal prevention of both stent thrombosis and thromboembolic complications of associated diseases, a dual antiplatelet regimen with both aspirin and a thienopyridine should be added to OAC. Major concerns about the safety of such an aggressive regimen, as well as the absence of clinical evidence supporting its use, might anticipate a restricted use of triple therapy. On the contrary, such a regimen is unexpectedly adopted by most Centers, even representing the standard for all patients in 62% of them (Table I). It appears therefore, that the safety of triple therapy is not perceived as an issue, especially taking into account that the dose of OAC, when associated with antiplatelet administration (either single or dual), is systematically reduced in all patients in a minority of Centers only (Table I). Yet, the adjunct of antiplatelet agents to OAC has been shown to significantly increase the risk of (major) bleeding (odds ratio 1.66, 95% confidence interval 1.18-2.34, p = 0.003)[8],

which in turn, overall is reported to occur in about 1 to 7% per year in patients on chronic OAC for various clinical conditions[9-12]. In a recent paper by Orford et al.[13] retrospectively examining the population undergoing PCI at the Mayo Clinic (Rochester, MN, USA) over a 2.5-year period, bleeding complications occurred within 30 days in 6 out of 66 (9.2%) patients discharged on triple therapy with OAC, aspirin and clopidogrel. Whereas hemorrhagic events were minor and not strictly related to OAC in 50% of cases, in the remaining 3 patients major bleeding (requiring blood transfusions in 2 of them) occurred. Indeed, the prothrombin time was very prolonged in all patients presenting with major hemorrhage, as shown by INR values even higher than 12[13].

Wide fluctuations in the INR values, especially during the initial titration phase, are a well-known event during OAC. About 60% of the time only are INR readings within the target range[14,15], with about 25 and 15% of the remaining time spent above and below it respectively[16]. Both an insufficient quality and the degree of OAC have been shown to influence the (bleeding and thromboembolic) complication rate[16,17], with subtherapeutic INR levels (i.e. < 2) not providing adequate protection against ischemic stroke, even in low-risk patients such as those with nonvalvular atrial fibrillation[18]. However, it is unknown whether the association of a dual antiplatelet regimen with subtherapeutic levels of OAC, which is possibly adopted by some of the Centers reporting they either systematically or selectively decrease the dose of OAC when antiplatelets are added, might be of any efficacy in the prevention of thromboembolic complications.

The limitation of the hemorrhagic and thromboembolic risks of triple therapy might be probably accomplished by exchanging OAC for anticoagulants with a more stable and predictable dose-response relationship, such as low-molecular-weight heparins. Although this strategy was adopted systematically by a single Center reporting not to interrupt anticoagulation, and selectively by 38% of Centers exchanging OAC for a dual antiplatelet regimen, no sound evidence is available about the safety or efficacy of low-molecular-weight heparins given for this condition as well as for others in which OAC is commonly used. Indeed, the addition of enoxaparin to the combination of aspirin and clopidogrel in patients at high risk for stent thrombosis was associated with a trend toward more major hemorrhages (3.3% for enoxaparin vs 1.6% for placebo, $p = 0.08$) and a significant increase in minor bleedings (25 vs 5.1%, $p < 0.001$)[19]. Whereas the adjunct of low-dose low-molecular-weight heparin to the combination of aspirin and clopidogrel performed by 23% of Centers exchanging OAC for dual antiplatelet therapy might be interpreted as an attempt to minimize the hemorrhagic risk while providing some anticoagulation effect, again no evidence supporting this strategy is available. In fact, low-dose subcutaneous low-molecular-weight heparin has been proven to be effective for the prophylaxis of venous thromboembolism only[20]. Nevertheless, whether a therapeutic effect might be achieved by adding a dual antiplatelet regimen to low-dose low-molecular-weight heparin, is at present unknown.

Subsequent antithrombotic treatment following completion of either a dual antiplatelet or a combined OAC and antiplatelet course, again appears widely variable. While the demonstrated clinical efficacy superior to (single) antiplatelet treatment might have anticipated the reintroduction of OAC performed by most Centers having switched to dual antiplatelet therapy, it is of note that the two strategies of withdrawing antiplatelets and maintaining at least one agent in the Centers having adopted a combination therapy, are almost equally represented (Table I). The combination of aspirin and moderate- (INR 2-3) to high- (INR > 2.8) dose OAC has been shown superior to aspirin alone for secondary prevention in patients with ischemic heart disease and stroke, while no clear differences with respect to moderate-high-dose OAC alone were observed[21,22]. Therefore, either one of these regimens appears advisable for the long-term treatment of patients with an indication for OAC who have undergone PCI with stent implantation, although a significant bleeding risk should be acknowledged[21,22]. Careful and frequent monitoring of the INR is warranted in these patients, irrespective of whether OAC and aspirin or OAC alone are given, since bleeding events are related to the dose of OAC rather than to the simultaneous use of antiplatelets[21,22].

In conclusion, the results of our survey show a very high variability in the antithrombotic management of patients on chronic OAC undergoing PCI with stent implantation, so that indications for a common practice are difficult to achieve. In the absence of sound evidence supporting a definite strategy, various regimens, based on accurate thromboembolic risk stratification, may currently be adopted: a temporary exchange of OAC for dual antiplatelet administration in low-risk conditions (i.e. isolated atrial fibrillation or dilated cardiomyopathy without previous thromboembolism), medium-term triple therapy with either low-molecular-weight heparin or OAC plus dual antiplatelet treatment in moderate-to-high-risk conditions (i.e. mitral valve prosthesis, recent deep vein thrombosis, left ventricular thrombus, etc.), and long-term triple therapy with OAC plus aspirin and clopidogrel in the very high-risk setting (i.e. following brachytherapy for in-stent restenosis in the presence of a prosthetic mitral valve)[13,23]. However, since neither efficacy nor safety data are available for any of the suggested strategies, specific clinical trials are needed in order to identify the optimal medium- and long-term antithrombotic treatment for the various subsets (at different thromboembolic risk) of patients on OAC undergoing coronary artery stenting. It is foreseen that this patient subgroup, which at present is likely to represent no more than 10% of the

whole population of subjects undergoing PCI, is likely to increase progressively along with the aging of the population and the continuously increasing number of both PCI procedures and the use of stents (not only in the coronary tree).

Acknowledgments

We would like to express our gratitude to Paul W. Armstrong and Robert C. Welsh, Jean-Pierre Bassand, Eric R. Bates, Jorge Belardi, Martial G. Bourassa and Bruno Farah, Bernard Chevalier, Nicolas Danchin, Carlo Di Mario, Eric Eeckhout, Lars Grip, Eberhard Grube, Neal S. Kleiman, Bernhard Meier, Marie-Claude Morice, Franz-Josef Neumann, Jeffrey J. Popma, Wolfgang Rutsch, Timothy A. Sanborn, Albert Schömig, Patrick W. Serruys, Ulrich Sigwart and Edoardo Camenzind, J. Eduardo M.R. Sousa, Philip Urban and Freek W.A. Verheugt for their participation in this survey.

References

1. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996; 334: 1084-9.
2. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998; 339: 1665-71.
3. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS). Circulation 1998; 98: 2126-32.
4. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study. Circulation 1998; 98: 1597-603.
5. Cosmi B, Rubboli A, Castelvetri C, Milandri M. Ticlopidine versus oral anticoagulation for coronary stenting. Cochrane Database Syst Rev 2001; (4): CD002133.
6. Casella G, Ottani F, Pavesi PC, et al. Safety and efficacy evaluation of clopidogrel compared to ticlopidine after stent implantation: an updated meta-analysis. Ital Heart J 2003; 4: 677-84.
7. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. Ann Intern Med 1998; 129: 394-405.
8. Little SH, Massel DR. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev 2003; (4): CD003464.
9. Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 2001; 119 (Suppl): 220S-227S.
10. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest 2001; 119 (Suppl): 194S-206S.
11. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002; 100: 3484-8.
12. ESPRIT. Oral anticoagulation in patients after cerebral ischemia of arterial origin and risk of intracranial hemorrhage. Stroke 2003; 34: E45-E46.
13. Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. Am Heart J 2004; 147: 463-7.
14. van den Besselaar AM, van der Meer FJ, Gerrits-Drabbe CW. Therapeutic control of oral anticoagulant treatment in the Netherlands. Am J Clin Pathol 1988; 90: 685-90.
15. Gadisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands. Arch Intern Med 2003; 163: 2639-46.
16. Torn M, van der Meer FJ, Rosendaal FR. Lowering the intensity of oral anticoagulant therapy. Effects on the risk of hemorrhage and thromboembolism. Arch Intern Med 2004; 164: 668-73.
17. Edmunds LH. Thrombotic and bleeding complications of prosthetic heart valves. Ann Thorac Surg 1987; 44: 430-45.
18. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003; 349: 1019-26.
19. Batchelor WB, Mahaffey KW, Berger PB, et al. A randomized, placebo-controlled trial of enoxaparin after high-risk coronary stenting: the ATLAST trial. J Am Coll Cardiol 2001; 38: 1608-13.
20. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 337: 688-98.
21. Brouwer MA, Verheugt FW. Oral anticoagulation for acute coronary syndromes. Circulation 2002; 105: 1270-4.
22. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. J Am Coll Cardiol 2003; 41 (Suppl S): 62S-69S.
23. Spencer FA, Becker RC. When guidelines collide ... Am Heart J 2004; 147: 395-7.