Antithrombotic strategies in patients with an indication for long-term anticoagulation undergoing coronary artery stenting: safety and efficacy data from a single center

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Key words:
Antiaggregating agents; Anticoagulants; Percutaneous coronary intervention; Stenting.

Background. **Dual antiplatelet therapy is the antithrombotic treatment generally recommended after percutaneous coronary intervention with stent implantation (PCI-S). However, the optimal antithrombotic treatment after PCI-S in case of a concomitant indication for anticoagulation (AC) is unknown. The aim of our study was to determine the strategies adopted at our Institution (where the management of these patients is at the physician's discretion), and to evaluate their relative efficacy and safety.**

Methods. **A retrospective analysis of all PCI-S performed between January 2002-April 2004, was carried out. All patients on AC at the time of PCI-S were identified and the hemorrhagic and thromboembolic complications recorded.**

Results. **Twenty-seven patients (21 males, 6 females, mean age 66.9 ± 10.6 years) on AC because of atrial fibrillation, post-myocardial infarction cardiomyopathy, left ventricular or arterial thrombus, previous cerebrovascular event, and mechanical aortic or mitral valve, were identified. The adopted antithrombotic treatment included: dual antiplatelet therapy in 6 patients (22%), a combination of a single antiplatelet with either aspirin or a thienopyridine and oral AC in 5 (19%), and triple therapy with dual antiplatelet and either oral AC or low-molecular-weight heparin administration in 16 (59%). The overall complication rate at 32.3 ± 5.4 days was 18%, accounted for by two in-hospital major hemorrhages requiring blood transfusion (7%), two minor hemorrhages treated conservatively (7%), and one subacute stent thrombosis requiring emergency percutaneous reintervention (4%).**

Conclusions. **At our Institution, variable antithrombotic strategies are adopted after PCI-S in patients with an indication for AC. Since the overall complication rate was relevant, further properly sized and designed studies are warranted in order to identify the optimal antithrombotic treatment in this patient subset.**

(Ital Heart J 2004; 5 (12): 919-925)

Received August 23, 2004; revision received November 2, 2004; accepted November 3, 2004.

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Introduction

Dual antiplatelet therapy with aspirin and a thienopyridine (either ticlopidine or clopidogrel) has been proven superior to aspirin and oral anticoagulation (AC) on the medium-term occurrence of both adverse cardiac events and hemorrhagic/vascular complications after percutaneous coronary intervention with stent implantation (PCI-S)[1-6]. Therefore, the optimal antithrombotic treatment after PCI-S should include dual antiplatelet administration, even in patients in whom long-term AC is warranted because of atrial fibrillation, mechanical prosthetic heart valve, previous systemic or venous thromboembolism, left ventricular thrombus, or other conditions.

In current practice however, the antithrombotic strategies adopted after PCI-S in this patient subset appear highly variable[7], due to the absence of practice guidelines and the perceived high risk of bleeding associated with the combined administration of dual antiplatelet therapy and long-term AC.

The aim of our study was to evaluate the antithrombotic treatment adopted following PCI-S in patients with an indication for AC at our Institution, where the management of this subgroup is left at the discretion of the attending physician, and to evaluate the relative incidence of hemorrhagic/vascular and thromboembolic complications within 30 days of the procedure.

Methods

A retrospective analysis of our computerized database including all patients who were discharged from hospital after a PCI-S

between January 2002 and April 2004 was performed. All patients with an indication for AC who underwent PCI-S were identified and their medical records reviewed in order to determine the indication for both AC and PCI-S (which were both collected prospectively), and to characterize any clinical events during the study period. The occurrence of complications was evaluated at 30 days for patients who were still hospitalized, and at the time of the visit at the outpatient clinic, which is routinely programmed at about 4 weeks after discharge, for all other patients. The INR values during the 6 weeks following PCI-S were retrieved from the computerized database of our Anticoagulation Clinic to evaluate the early course of oral AC, and its relationship with adverse events. For each patient, the time spent within the INR therapeutic range was estimated using the linear interpolation method, which assumes that the INR value between two consecutive measurements varies linearly, as long as the interval does not exceed 4 weeks[8].

Hemorrhagic complications were defined according to the classification of Koertke et al.[9] as mild (not requiring medical treatment), moderate (leading to outpatient medical care, not requiring surgical or endoscopic intervention), and severe (requiring transfusion, surgical or endoscopic intervention, inpatient care or causing long-term impairment). Vascular complications were defined as pseudoaneurysms or arterio-venous fistulas occurring at the access site and requiring surgery or prolonged, ultrasound-guided compression. Thromboembolic complications were defined as any clinical manifestation of acute cerebral or peripheral ischemia that was ascertained by objective diagnostic testing. Stent thrombosis was considered to have occurred when an intraluminal filling defect resulting in an occluded or suboccluded coronary artery was detected at angiography, or when death was sudden and unexplained, or when a myocardial infarction occurred in the territory of the treated vessel and stent thrombosis could not be definitively excluded.

All patients with an indication for long-term AC who had undergone successful PCI-S at our Institution, were included in the analysis.

Statistical analysis. Continuous variables are presented as means ± SD, whereas discrete variables are presented as frequencies and percentages.

Results

Twenty-seven patients with an indication for AC who underwent PCI-S at our Institution between January 2002 and April 2004, were identified. The baseline characteristics of the patients, as well as the indications for AC and PCI-S and the procedural characteristics are reported in table I. Permanent atrial fibrillation (44% of cases) represented the most frequent indication for AC, whereas acute myocardial infarction (37%) and stable effort angina (34%) were the most frequent indications for PCI-S. A single-vessel procedure was performed in 23 patients (85%), a saphenous vein graft being the treated vessel in 5. Bare metal stents were used in all but one patient with permanent atrial fibrillation, in whom a sirolimus-eluting stent was implanted.

Table I. Baseline characteristics of the study population.

No. patients	27
Male	21 (78%)
Age (years)	66.9 ± 10.6 (range 42-82)
Indications for anticoagulation	
Permanent atrial fibrillation	12 (44%)
Post-infarction DCM	4 (15%)
Left ventricular thrombus	4 (15%)
Persistent atrial fibrillation	2 (7%)
Previous cerebrovascular accident	2 (7%)
Mechanical mitral valve	1 (4%)
Mechanical aortic valve	1 (4%)
Peripheral artery thrombus	1 (4%)
Indications for PCI-S	
Acute myocardial infarction	10 (37%)
Stable angina	9 (34%)
Unstable angina	3 (11%)
Recent non-Q wave MI	3 (11%)
Recent Q wave MI	2 (7%)
Associated diseases	
Chronic gastritis	2 (7%)
Peptic ulcer	1 (4%)
Diabetes	1 (4%)
Procedural characteristics	
Vessels treated	1.15 ± 0.36
Stents implanted	1.33 ± 0.68
1 stent	20 (74%) (1 drug-eluting)
2 stents	6 (22%)
> 2 stents	1 (4%)
Femoral approach	27 (100%)
Sheath diameter	
6F	24 (89%)
7F	3 (11%)
Use of access-site hemostatic devices	27 (100%)
Use of GP IIb/IIIa inhibitors	8 (30%)

DCM = dilated cardiomyopathy; GP = glycoprotein; MI = myocardial infarction; PCI-S = percutaneous coronary intervention with stent implantation.

Overall, the antithrombotic strategies adopted in these patients were: dual antiplatelet therapy with aspirin and either ticlopidine or clopidogrel in 6 patients (22%), a combination of single antiplatelet therapy with aspirin and oral AC in 5 (19%), and triple therapy with dual antiplatelet regimen and either oral AC or subcutaneous low-molecular-weight heparin (LMWH) in 16 (59%) (Fig. 1).

In patients with permanent atrial fibrillation, antithrombotic treatment included: triple therapy with dual antiplatelet administration and oral AC in 5 cases (42%), dual antiplatelet therapy in 4 (33%) and a com-

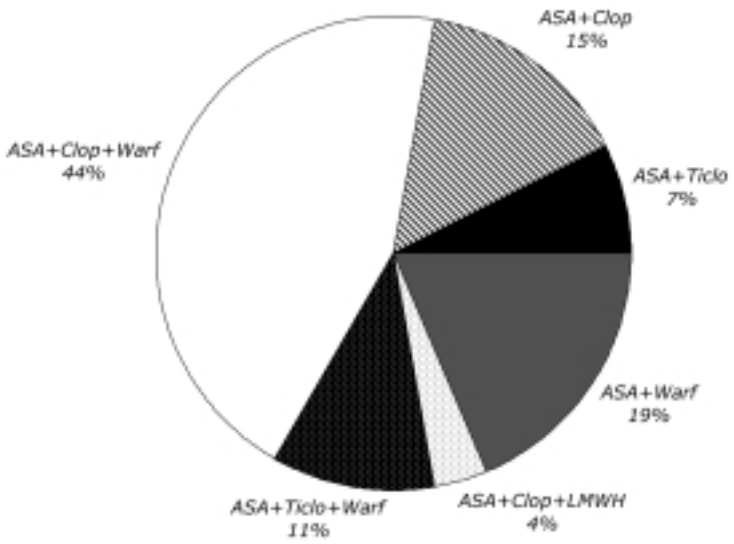

Figure 1. *Antithrombotic regimens adopted in our population after percutaneous coronary intervention with stent implantation. ASA = aspirin; Clop = clopidogrel; LMWH = low-molecular-weight heparin; Ticlo = ticlopidine; Warf = warfarin.*

bination of aspirin and oral AC in 3 (25%) (Fig. 2). The patients with persistent atrial fibrillation were treated with triple therapy in one case (50%) and with dual antiplatelet administration in another case (50%) (Fig. 2). With regard to the patients with post-myocardial infarction dilated cardiomyopathy, triple therapy was given in 2 cases (50%) and dual antiplatelet administration (25%) and a combination of aspirin and oral AC (25%) in 1 case each, whereas the presence of a left ventricular thrombus warranted triple therapy in all 4 cases (100%) (Fig. 2). The single patients with a mechanical mitral valve, mechanical aortic valve and peripheral artery thrombus were respectively treated with a combination of aspirin and oral AC, triple therapy with dual antiplatelets and oral AC and triple therapy with dual antiplatelets and subcutaneous LMWH, whereas both patients with a previous cerebrovascular accident received triple therapy with dual antiplatelet administration and oral AC (Fig. 2).

Overall, within 32.3 ± 5.4 days of the PCI-S hemorrhagic/vascular and thromboembolic complications were observed in 5 cases (18%) (Fig. 3). Two patients (7%) on triple therapy presented, during hospitalization, with severe bleeding requiring blood transfusion:

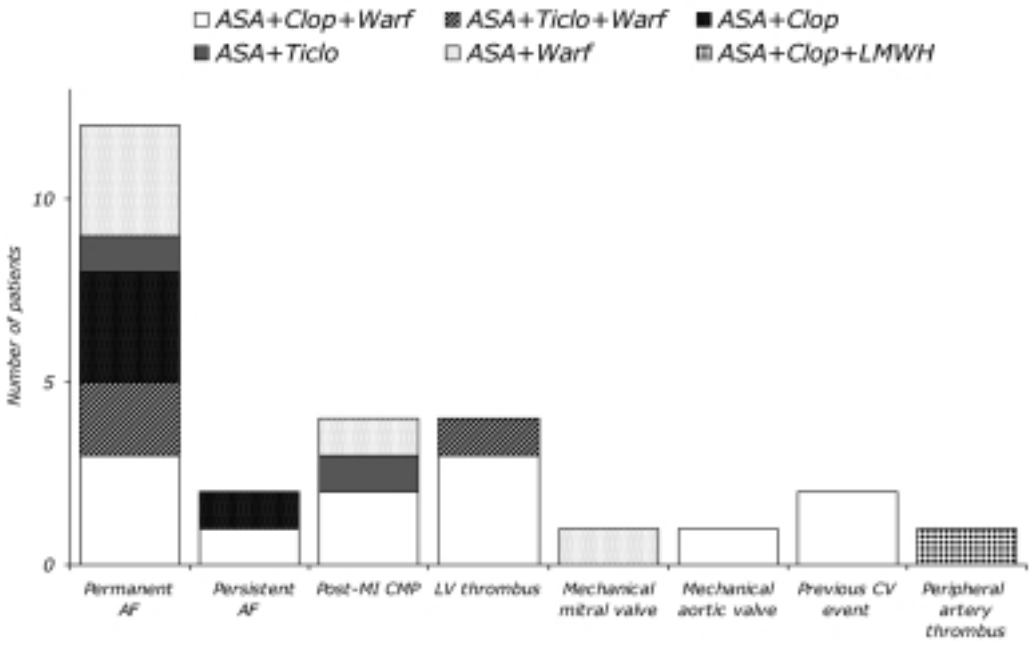

Figure 2. *Antithrombotic regimens adopted in the various subgroups with different indications for long-term anticoagulation. AF = atrial fibrillation; ASA = aspirin; Clop = clopidogrel; CMP = cardiomyopathy; CV = cerebrovascular; LMWH = low-molecular-weight heparin; LV = left ventricular; MI = myocardial infarction; Ticlo = ticlopidine; Warf = warfarin.*

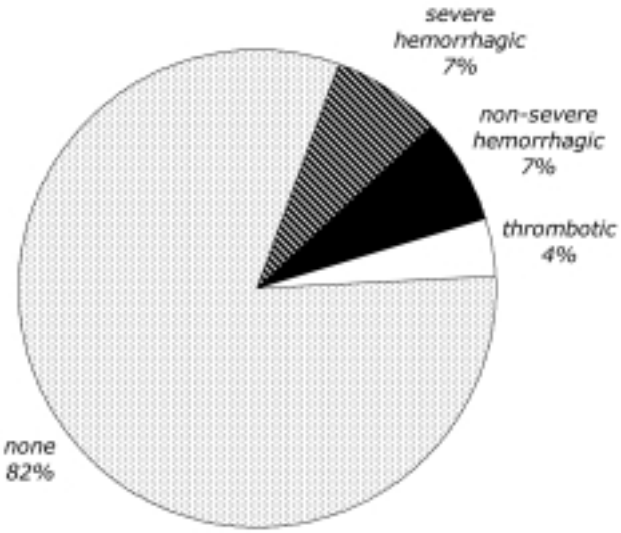

Figure 3. *Thromboembolic and hemorrhagic complication rates at 32.3 ± 5.4 days of follow-up.*

a 77-year-old male with post-myocardial infarction dilated cardiomyopathy and progressively decreasing hemoglobin levels with no overt source of bleeding while on treatment with aspirin, clopidogrel and oral AC, and a 64-year-old female with a recent-onset femoral artery thrombus presenting with gross hematuria and a subsequent fall in hemoglobin levels following the removal of an indwelling urethral catheter while receiving a combination of aspirin, clopidogrel and subcutaneous LMWH. In another 2 cases (7%), early non-severe hemorrhagic complications at the puncture site occurred (Fig. 3), accounted for by one ecchymosis in a patient on triple therapy with aspirin, clopidogrel and oral AC, requiring no treatment, and one hematoma in another patient on dual antiplatelet treatment with aspirin and ticlopidine, managed conservatively on an outpatient basis. A thrombotic complication occurred in a 69-year-old male patient (4%) (Fig. 3) on a combination of aspirin and oral AC because of permanent atrial fibrillation and a previous cerebrovascular accident, who presented with in-hospital subacute stent thrombosis and was successfully treated with emergency reintervention. No deaths or arterial embolism or vascular complications at the puncture site occurred during follow-up.

In all patients, oral AC treatment was halted a few days before PCI-S and on the morning of the procedure the INR values were < 2. During PCI-S, intravenous unfractionated heparin was administered as an initial bolus of 70 IU/kg, followed by additional boluses as necessary to maintain an activated clotting time of 250-300 s. Re-institution of oral AC, when resorted to, was performed in all cases on the same day of PCI-S by administering either 5 or 10 mg of warfarin. Out of the 20 patients receiving oral AC, in combination with either a single or dual antiplatelet regimen, after the PCI-S, 12 (60%) were followed at our Anticoagulation Clinic. The mean INR value during the 6 weeks after PCI-S was 2.32 ± 0.68, whereas the time spent in the INR ranges of 2-3, < 2, and > 3 were 53, 40 and 7%, respectively (Fig. 4). The INR value at the time of the hemorrhagic complication occurring in the patient on triple therapy with a dual antiplatelet regimen and oral AC was 3, whereas it was 1.6 in the patient treated with a combination of aspirin and oral AC and presenting with subacute stent occlusion (Fig. 4).

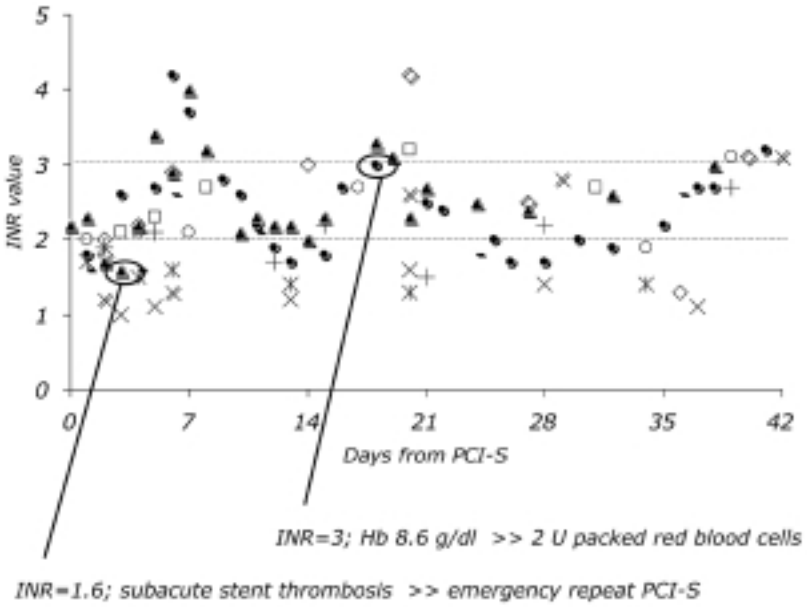

Figure 4. *Course of the INR values during the first 6 weeks after percutaneous coronary intervention with stent implantation (PCI-S) in the 12 patients discharged on oral anticoagulation (in combination with either single or dual antiplatelet therapy), followed at our Anticoagulation Clinic. Hb = hemoglobin.*

Discussion

To date, the issue of the optimal antithrombotic treatment to be used in patients with an indication for AC undergoing PCI-S has not been addressed. In fact, no evidence-based data or practice guidelines are available to assist cardiologists in the management of these patients. Indeed, a high variability in the antithrombotic strategies adopted in 24 international world-renown interventional centers emerged from a recent survey carried out by our group[7]: triple therapy with dual antiplatelet administration and oral AC is reported to be used in all cases by 62% of centers, whereas a combination of a single (either aspirin or ticlopidine/clopidogrel) antiplatelet drug and oral AC is systematically adopted by 12%. Besides, 54% of centers report exchanging oral AC for dual antiplatelet therapy in selected clinical conditions[7].

Also in our Institution, where the management of these patients is left at the discretion of the attending physician (as is the case in about half of the centers participating in our survey)[7], the antithrombotic strategies for patients with an indication for AC undergoing PCI-S proved to be highly variable (Fig. 1). Such variability was observed for all indications for AC, being the highest, however, for permanent atrial fibrillation (Fig. 2), where a process of risk stratification is commonly adopted in clinical practice when instituting antithrombotic therapy[10]. The small size of both the overall population and the individual subgroups of patients however, greatly hampers adequate appreciation of the role played by risk stratification in the choice of the various regimens. Evidence-based knowledge of the use of a combination of aspirin and oral AC before dual antiplatelet therapy was introduced in clinical practice[1-5], as well as the concern of major hemorrhagic risks when dual antiplatelet treatment is to be associated with oral AC, might better account for the strategies adopted. In fact, although proven significantly less effective than dual antiplatelet therapy[1-5], the combination of aspirin and oral AC was found to carry an absolute risk of death, non-fatal myocardial infarction and of the need for repeat revascularization at 30 days as low as 0.65, 3.8 and 4.2% respectively[5]. These data confirm that this strategy is an acceptable option for patients in whom it is necessary to not suspend AC after PCI-S. On the other hand, the exchange of oral AC for dual antiplatelet therapy, as has occurred in 22% of our patients, appears acceptable for patients with non-high thromboembolic risk, as suggested by the results of the Clopidogrel-Aspirin Atrial Fibrillation (CLAAF) pilot study[11] and the Warfarin/Aspirin Study in Heart Failure (WASH)[12]. In patients with non-high risk permanent or persistent atrial fibrillation, the administration of either aspirin plus clopidogrel or oral AC was comparably safe and effective both in terms of the short-term detection of thrombi or spontaneous echocontrast at transesophageal echocardiography and in terms of the occurrence of thromboembolic or hemorrhagic events[11]. On the other hand, aspirin and oral AC, as well as no antithrombotic treatment, were also comparable in terms of the long-term occurrence of death, non-fatal myocardial infarction or non-fatal stroke in patients with heart failure[12].

In spite of the concern that the bleeding risks associated with the administration of triple therapy with aspirin, a thienopyridine and AC may be prohibitively high, this strategy has been adopted for the majority of our patients (59%) (Fig. 1). Orford et al.[13] recently reported on the efficacy and safety at 30 days of aspirin, clopidogrel and warfarin in the setting of PCI-S performed in patients with an indication for AC: out of 66 patients retrospectively identified over a 32-month period, 6 (9.2%) experienced a bleeding event, requiring blood transfusion in 2 cases, whereas no thromboembolic complications or stent thrombosis occurred. Although higher than reported in this study[13], and in others where aspirin and a thienopyridine (1.8%) or aspirin and oral AC (6.5%)[1-5] were administered after PCI-S, the 14% bleeding rate observed in our population (Fig. 3) should be viewed in the light of some considerations. First, appropriate comparisons of the bleeding rates in the different studies are difficult due to the highly variable definitions of hemorrhagic complications[1-4] or even the lack of any definition[13]. In our opinion, the classification of bleeding events by Koertke et al.[9], which we adopted, provides a good estimation of both the clinical relevance and of the impact on the caregivers' management of the hemorrhagic event. Second, the two major hemorrhagic complications (7%) we observed consisted of one late blood transfusion in the absence of an overt source of bleeding, therefore shedding doubt on its relationship with the ongoing triple therapy with aspirin, clopidogrel and oral AC (also considering that the INR value was in the therapeutic range at the time of the event) (Fig. 4), and of one gross urethral bleeding during triple therapy with aspirin, clopidogrel and LMWH, which occurred upon accomplishing a somewhat traumatic maneuver, such as the removal of an indwelling catheter. It is unknown whether the use of oral AC rather than subcutaneous LMWH, which was probably used because of the anticipated short duration of the AC treatment, may have influenced the occurrence, and the severity, of the hemorrhagic complication in this latter patient. Finally, the overall 7% rate of minor bleeding events, all occurring at the arterial access site, favorably compares with the data of previous reports[3,14-16], although the use of different definitions of bleeding events must once again be acknowledged. An optimal arterial puncture technique, along with the intraprocedural use of low-dose, weight-adjusted unfractionated heparin, probably accounts for the low bleeding rate and the absence of vascular complications at the access site in our population. In this regard, the adopted antithrombotic regimen appears to be of lesser importance, since a minor

bleeding event was observed even with dual antiplatelet therapy, whereas the application of access-site hemostatic devices, which were used in all our patients, has been shown to possibly even increase hematoma formation as compared to standard manual compression[17].

As opposed to a good safety profile, the overall efficacy of the antithrombotic strategies adopted at our Institution appears highly unsatisfactory. The 4% rate of short-term thrombotic complications (Fig. 3) is, in fact, substantially higher than the 0.3-0.4% rates previously reported after PCI-S with either dual antiplatelet therapy or aspirin plus oral AC[1,2]. Of note, at the time of the event, the INR value in our patient was below the therapeutic range (Fig. 4), although oral AC had been restarted a few days earlier. Indeed, the pro-thrombotic state known to occur early after oral AC initiation as a consequence of protein C and S suppression before factors II, VII, IX and X are inhibited, may well account for the adverse event. Therefore, adequate ongoing AC should be assured whenever a coronary stent is being inserted.

Although providing some clues on the underinvestigated issue of the optimal antithrombotic treatment in patients with an indication for long-term AC undergoing PCI-S, our study appears greatly limited by the small size and the observational and retrospective design. Furthermore, adequate estimation of the hemorrhagic/vascular and thromboembolic complication rates in the population of patients regularly receiving dual antiplatelet therapy after PCI-S, could not be obtained for comparison: whereas, in fact, accurate data collection and follow-up are performed at our Institution for peculiar patient subsets (such as those with an indication for long-term AC), even when they are referred from other centers, for the majority of these latter patients (accounting for about 20-25% of our laboratory caseload), subsequent care and follow-up is carried out at the referring center, where they are transferred back within a few to 24 hours of the elective PCI-S. Therefore, both clinical trials and large-scale registries are required to determine the optimal antithrombotic strategy in such a setting and to assess current processes of care and compliance to "best practice". In the meanwhile, either dual antiplatelet therapy with aspirin and a thienopyridine (for conditions at low thromboembolic risk, such as non-valvular, atrial fibrillation or dilated cardiomyopathy) or triple therapy with aspirin, a thienopyridine and oral AC (for high thromboembolic risk conditions, such as mechanical heart valve, previous systemic embolism, recent venous thromboembolic disease, etc.) should be considered. Since the likelihood of bleeding events is influenced by the intensity of AC rather than the simultaneous use of antiplatelet agents[18], a combination of oral AC with a single antiplatelet agent is probably no longer indicated. However, careful and frequent monitoring of the INR values, is warranted whenever the antithrombotic treatment includes oral AC. Besides the fact that the bleeding risk may indeed be higher with the administration of multiple antithrombotic agents, frequent INR determination has been shown to increase the time spent within the target range (which was about 50% only in our population), leading in turn, to fewer adverse events[19]. Finally, the development of periprocedural regimens including bridging of AC with LMWH during the suspension of oral AC appears highly advisable. The facility of use of LMWH, which may be administered subcutaneously, in a fixed weight-based dose, and with no need for laboratory monitoring[20] renders, in fact, this option very attractive, as suggested by a very recent study including 650 consecutive patients with an indication for long-term oral AC undergoing an invasive surgical or non-surgical procedure (coronary angiography with or without PCI-S in 34% of cases), in whom the adoption of a standardized periprocedural AC regimen with subcutaneous LMWH was associated with 2-week thromboembolic and major bleeding complication rates of only < 1 and 1-2% respectively[21].

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. N Engl J Med 1998; 339: 1665-71.
3. 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 1996; 98: 1597-603.
4. 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.
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. Rubboli A, Colletta M, Sangiorgio P, Di Pasquale G. Antithrombotic treatment after coronary artery stenting in patients on chronic oral anticoagulation: an international survey of current clinical practice. Ital Heart J 2004; 5: 851-6.
8. Ten Berg JM, Hutten BA, Kelder JC, Verheugt FW, Plokker T. Oral anticoagulant therapy during and after coronary angioplasty. The intensity and duration of anticoagulation are essential to reduce thrombotic complications. Circulation 2001; 103: 2042-7.
9. Koertke H, Minami K, Boethig D, et al. INR self-management permits lower anticoagulation levels after mechanical heart valve replacement. Circulation 2003; 108 (Suppl 1): II75-II78.

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. Lorenzoni R, Lazzerini G, Cocci F, De Caterina R. Short-term prevention of thromboembolic complications in patients with atrial fibrillation with aspirin plus clopidogrel: the Clopidogrel-Aspirin Atrial Fibrillation (CLAAF) pilot study. Am Heart J 2004; 148: e6.
12. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart Failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004; 148: 157-64.
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. Nasser T, Mohleri EI, Wilensky R, Hathaway D. Peripheral vascular complications following coronary interventional procedures. Clin Cardiol 1995; 18: 609-14.
15. Waksman R, King SB 3rd, Douglas JS, et al. Predictors of groin complications after balloon and new-device coronary intervention. Am J Cardiol 1995; 75: 886-9.
16. Applegate R, Grabarczyk M, Little W, et al. Vascular closure devices in patients treated with anticoagulation and IIb/IIIa receptor inhibitors during percutaneous revascularization. J Am Coll Cardiol 2002; 40: 78-83.
17. Koreny M, Riedmueller E, Siostrzonek P, Muellner M. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization. Systematic review and meta-analysis. JAMA 2004; 291: 350-7.
18. Hirsh J, Dalen J, Anderson D, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119 (Suppl): 8S-21S.
19. Spencer FA, Becker RC. When guidelines collide ... Am Heart J 2004; 147: 395-7.
20. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanism of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119 (Suppl): 64S-94S.
21. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin. Assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med 2004; 164: 1319-26.