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Dual Antiplatelet Therapy After Percutaneous Coronary Intervention With Stent Implantation in Patients Taking Chronic Oral Anticoagulation

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Objectives The purpose of this study was to evaluate the safety of dual antiplatelet therapy in patients in whom long-term anticoagulation (AC) with warfarin is recommended.

Background The optimal antithrombotic strategy after percutaneous coronary intervention (PCI) for patients receiving AC is unclear.

Methods Consecutive patients who underwent stent implantation and were discharged on triple therapy (defined as the combination of aspirin and thienopyridines and AC) were analyzed.

Results Of the 127 patients with 224 lesions, 86.6% were men, with a mean age of 69.9 ± 8.8 years. Drug-eluting stents (DES) were positioned in 71 (55.9%), and bare-metal stents (BMS) were positioned in 56 (44.1%) patients. Atrial fibrillation (AF) was the main indication (59.1%) for AC treatment. The mean triple therapy duration was 5.6 ± 4.6 months, and clinical follow-up was 21.0 ± 19.8 months. During the triple therapy period, 6 patients (4.7%) developed major bleeding complications; 67% occurred within the first month. No significant differences between DES and BMS were observed in the incidence of major (5.6% vs. 3.6%, respectively, $p = 1.0$) and minor (1.4% vs. 3.6%, respectively, $p = 0.57$) bleeding and mortality (5.6% vs. 1.8%, respectively, $p = 0.39$). A significant difference was observed in favor of DES in target vessel revascularization (14.1% vs. 26.8%, $p = 0.041$).

Conclusions While receiving triple therapy, major bleeding occurred in 4.7% of patients; one-half of the events were lethal, and most occurred within the first month. (J Am Coll Cardiol Intv 2008;1: 56–61) © 2008 by the American College of Cardiology Foundation

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The optimal antiplatelet therapy after percutaneous coronary intervention (PCI) with stent implantation consists of a combination of aspirin and ticlopidine or clopidogrel for the prevention of stent thrombosis (1–4). At the present time, it is still unclear which antithrombotic strategy is optimal for patients in whom long-term anticoagulation (AC) with warfarin is recommended. The risk of bleeding in patients already

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on AC is increased with the addition of dual antiplatelet therapy, although at the same time withholding antiplatelet therapy augments the risk of stent thrombosis. Furthermore, a temporary discontinuation of AC is associated with a higher risk of thromboembolism (5), and current liberal use of drug-eluting stents (DES) might increase the overall risk of stent thrombosis. Therefore, the aim of this study was to evaluate the safety at short- and mid-term clinical follow-up of dual antiplatelet therapy in patients in whom long-term AC with warfarin is recommended.

Methods

All consecutive patients who underwent PCI in our institutions (San Raffaele Hospital and Emo Centro Cuore Columbus, Milan, Italy) from February 1999 to December 2006 and were successively discharged on a triple therapy with aspirin and thienopyridines (ticlopidine or clopidogrel) and oral anticoagulant (warfarin) were analyzed.

All the patients were pretreated with thienopyridines and aspirin before the PCI procedure as follows: 100 mg aspirin and 250 mg ticlopidine twice daily, 75 mg of clopidogrel for at least 5 days, or a loading dose of 300 mg of clopidogrel before the procedure (if the pretreatment regimen was not followed or in the case of emergency PCI). Regarding the oral AC therapy, all the patients who underwent PCI had discontinued warfarin therapy for at least 3 days before hospital admission and were treated with weight-adjusted doses of low molecular weight heparin until 12 h before the index procedure (6). The maximum international normalized ratio (INR) allowed to start the procedure, according to our institution practice, was 1.5. If an emergency PCI was to be done or INR remained >1.5, a radial access was preferable.

Coronary angioplasty and DES implantation were performed according to our practice of fully covering the diseased segment (7–9). At the start of the procedure, a bolus of unfractionated heparin was administered at 100 IU/kg to achieve an activated clotting time >250 s. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator.

Warfarin therapy was restarted at the maintenance dose within 24 h after the procedure, and the patients remained on low molecular weight heparin treatment until an optimal INR for each pathology was achieved. The control of INR values was left to the referral cardiologist. To our best knowledge, the cardiologists advise periodic control of INR in order to dose warfarin appropriately. During the follow-up period, the patients were asked whether they followed their cardiologists' advice and whether their INR was maintained optimally. We do not have any evidence that there were any patients with INR out of the desired range.

Dual antiplatelet therapy (aspirin 100 mg daily and clopidogrel 75 mg or ticlopidine 250 mg twice daily) was administrated in all patients for at least 1 month after bare-metal stent (BMS) and 6 to 12 months after DES implantation. All patients were advised to maintain aspirin (100 mg daily) lifelong.

Clinical follow-up was scheduled for all patients at 1, 6, and 12 months by office visit or direct telephone call. Detailed questions on general health status, major adverse cardiac and cerebrovascular events (MACCE), bleeding complications, recurrent hospital admissions, and actual pharmacological treatment (including the length of the triple therapy and the reason for and date of discontinuation of any of the 3 drugs) were asked to all the monitored patients.

Definitions. The events analyzed during hospital stay and at clinical follow-up were MACCE and bleeding complications.

The MACCE were defined as the occurrence, during hospital stay and at clinical follow-up, of any of the following: all-cause death, myocardial infarction (MI), target lesion revascularization, target vessel revascularization (TVR), cerebrovascular events, and stent thrombosis.

Deaths were classified as cardiac, cerebral, or not from cardio-cerebral causes. Death of unknown cause was adjudicated as cardiac.

An MI was defined as a 2 times increase of the upper limit of normal serum creatine kinase in conjunction with positive creatine kinase-myocardial band isoenzyme (10).

Any revascularization performed on the treated segment was defined as target lesion revascularization, whereas any reintervention performed on the treated vessel was defined as TVR.

The stent thrombosis definition used in this study is consistent with the newest consensus of the Academic Research Consortium based on the trilevel certainty classification (definite, probable, and possible) and timing (acute, subacute, late, and very late) (11).

Cerebrovascular events included stroke (ischemic or hemorrhagic), cerebral hemorrhage, transient ischemic attacks, and reversible ischemic neurological deficits adjudicated by a neurologist and confirmed by computed tomography scanning (12).

Abbreviations and Acronyms

AC = anticoagulation
AF = atrial fibrillation
BMS = bare-metal stent(s)
INR = international normalized ratio
MACCE = major adverse cardiac and cerebrovascular events
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

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Bleeding complications were divided into minor and major (5). Major bleeding was defined as the cumulative occurrence of intracranial or intraocular bleeding, hemorrhage at the vascular access site requiring intervention, a reduction in hemoglobin levels of at least 5 g/dl, reoperation for bleeding or transfusion of a blood product (at least 2 U), or bleeding causing substantial hypotension requiring the use of inotropic agents. All other bleeding events were considered minor (e.g., epistaxis, blood traces in the stool).

Statistical analysis. Statistical analysis was performed with SPSS software version 10.1 (SPSS Inc., Chicago, Illinois). Continuous variables are reported as the mean value ± SD and are compared with the Student *t* test. Categorical variables are presented as percentages and are compared with the chi-square test.

Results

Baseline clinical characteristics are summarized in Table 1.

One hundred twenty-seven patients (with 224 lesions) were included in the analysis: 30 (24.0%) were diabetic, 94 (74.0%) had multivessel disease, mean age was 69.9 ± 8.8 years, and left ventricular ejection fraction was 44.9 ± 13.2%. There were no significant differences in the baseline clinical characteristics between the DES and BMS group (Table 1), except for unstable presentation of the patients in the BMS group (32.1% vs. 15.5% in DES, p = 0.04).

Table 1. Baseline Characteristics of the Study Population

	Total (n = 127)	DES (n = 71)	BMS (n = 56)	p Value
Age, yrs	69.9 ± 8.8	68.8 ± 8.6	70.2 ± 7.6	0.61
Male gender, n (%)	110 (86.6)	61 (85.9)	49 (87.5)	1.0
Hypertension, n (%)	85 (66.9)	50 (70.4)	35 (62.5)	0.45
Diabetes, n (%)	30 (24.0)	16 (22.5)	14 (25)	0.83
Noninsulin-dependent diabetes, n (%)	26 (86.7)	12 (75.0)	14 (100.0)	
Insulin-dependent diabetes, n (%)	4 (13.3)	4 (25.0)	0 (0.0)	
Hyperlipidemia, n (%)	59 (46.4)	38 (53.5)	21 (37.5)	0.05
Current smoker, n (%)	8 (6.3)	6 (8.5)	2 (3.6)	0.46
Family history of CAD, n (%)	45 (35.4)	23 (32.4)	22 (39.3)	0.46
Previous MI, n (%)	68 (53.5)	38 (53.5)	30 (53.6)	1.0
Previous PCI, n (%)	48 (37.8)	28 (39.4)	20 (35.7)	0.71
Previous CABG, n (%)	39 (30.7)	23 (32.4)	16 (28.6)	0.70
LVEF, %	44.9 ± 13.2	44.6 ± 12.7	47.4 ± 15.5	0.24
Stable angina, n (%)	60 (47.2)	34 (47.9)	26 (46.4)	0.04
Unstable angina, n (%)	29 (22.8)	11 (15.5)	18 (32.1)	0.04
STEMI, n (%)	4 (3.1)	1 (1.4)	3 (5.4)	0.32
CHADS2 risk score for AF patients	1.79 ± 1.23	1.96 ± 1.21	1.59 ± 1.21	0.32

AF = atrial fibrillation; BMS = bare-metal stents; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHADS2 = Congestive heart failure, Hypertension, Age >75 years, Diabetes, prior transient ischemic attack, or Stroke-2; DES = drug-eluting stents; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Procedural Characteristics

	Total	DES	BMS	p Value
Number of patients treated	127	71 (55.9)	56 (44.1)	
Total stent length, mm	25.5 ± 11.8	27.7 ± 11.9	21.9 ± 10.4	<0.001
Number of stents/lesion	1.1 ± 0.3	1.2 ± 0.4	0.9 ± 0.6	<0.001
Maximum balloon diameter, mm	3.11 ± 0.58	3.00 ± 0.45	3.24 ± 0.71	<0.001
Maximum pressure inflation, atm	16 ± 4	17 ± 4	14 ± 4	0.30

atm = atmosphere; other abbreviations as in Table 1.

Twenty-nine (22.8%) patients presented with unstable angina; 4 (3.1%) had ST-segment elevation MI requiring a primary PCI (1 in the DES group vs. 3 in the BMS group, p = 0.32). In the DES group, the number of stents implanted and total stent length were larger and vessel diameter smaller (Table 2). In most (55.9%) of the patients, DES were implanted with a greater prevalence of sirolimus-eluting stents (SES) over paclitaxel-eluting stents (PES) (59.2% vs. 35.2%).

The most frequent indication for long-term AC therapy with warfarin was atrial fibrillation (AF) (75 patients, 59.1%). The other indications (Table 3) included left ventricular mural thrombus, prosthetic valves, history of pulmonary embolism or deep vein thrombosis, evidence of coronary or peripheral aneurysm, or complicated peripheral bypass grafting (defined as "Other" in Table 3). The average risk of thromboembolic events in the subgroup with AF was 1.79 ± 1.23 according to the Congestive heart failure, Hypertension, Age >75 years, Diabetes, prior transient ischemic attack, or Stroke-2 points (CHADS2) score (5).

In-hospital and long-term MACCE and bleeding complications. During hospital stay, no patient died and 7 (5.5%) had periprocedural MI (4.2% in the DES group vs. 7.1% in the BMS group, p = 0.70). No groin hematomas or other periprocedural bleeding complications were observed. The mean clinical follow-up was 21.0 ± 19.8 months (25.5 ± 24.0 in the BMS group vs. 16.9 ± 14.0 in the DES group, respectively; p = 0.021). Patients were on concomitant dual antiplatelet and AC therapy for 5.6 ± 4.6 months. This time period was significantly prolonged in the DES group as compared with the BMS group (7.7 ± 3.6 months vs. 3.1 ± 3.6 months; p < 0.001).

Table 3. Indications for Long-Term Anticoagulation Therapy

Atrial fibrillation, n (%)	75 (59.1)
Left ventricular mural thrombus, n (%)	12 (9.4)
Prosthetic valve, n (%)	15 (11.8)
Pulmonary embolism, n (%)	7 (5.5)
Deep venous thrombosis, n (%)	3 (2.4)
Coronary aneurysm, n (%)	4 (3.1)
Other, n (%)	3 (2.4)

Table 4. MACCE at Follow-Up

	Total (n = 127)	DES (n = 71)	BMS (n = 56)	p Value
Follow-up length, months	21.0 ± 19.8	16.9 ± 14.0	25.5 ± 24.0	0.021
Triple therapy length, months	5.6 ± 4.6	7.7 ± 3.6	3.1 ± 3.6	<0.001
Major bleeding, n (%)	6 (4.7)	4 (5.6)	2 (3.6)	1.0
Minor bleeding, n (%)	3 (2.4)	1 (1.4)	2 (3.6)	0.57
MACCE, n (%)	30 (23.6)	14 (19.7)	16 (28.6)	0.20
Death, n (%)	5 (3.9)	4 (5.6)	1 (1.8)	0.39
MI, n (%)	2 (1.6)	1 (1.4)	1 (1.8)	1.0
CABG, n (%)	3 (2.4)	0 (0)	3 (5.4)	0.075
TVR, n (%)	25 (19.7)	10 (14.1)	15 (26.8)	0.041
TLR, n (%)	21 (16.5)	9 (12.7)	12 (21.4)	0.099
Definite stent thrombosis, n (%)	1 (0.8)	1 (1.4)	0 (0)	1.00

AF = atrial fibrillation; MACCE = major adverse cardiac and cerebrovascular events; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

The MACCE and bleeding complications that occurred during clinical follow-up are summarized in Table 4.

Five patients (3.9%) died (5.6% in the DES group vs. 1.8% in the BMS group; p = 0.39) during follow up. Four of them died in the DES group; 3 died of major bleeding while on triple therapy (2 in the DES group, 1 in the BMS group). The detailed characteristics of the patients and causes of death are described in Table 5.

Overall, only 1 patient had a definite stent thrombosis. The event occurred 1 month after the index procedure after acetylsalicylic acid and warfarin discontinuation, owing to severe gastrointestinal hemorrhage requiring blood transfusion.

While on triple therapy, 6 (4.7%) patients developed major bleeding: 3 (50%) of them died, and the remaining 4 experienced severe comorbidities (Table 6). Most of the major bleeding occurred within the first month from the index procedure. Minor bleeding occurred in only 3 patients, and in 2 of them within the first month (Table 7). No significant differences between DES and BMS were observed in the incidence of major bleeding (5.6% vs. 3.6%, p = 1.0), minor bleeding (1.4% vs. 3.6%, p = 0.57), and MACCE (19.7% vs. 28.6%, p = 0.20).

A significant difference in favor of DES was observed in the occurrence of TVR (14.1% vs. 26.8%, respectively, p = 0.041).

Discussion

The main findings of this study are: 1) major bleeding occurred in 4.7% of the patients on concomitant treatment with dual antiplatelet therapy and long-term AC with warfarin; 2) most of the major bleeding complications occurred within the first month from the index procedure; 3) no significant difference was observed between BMS and DES in the occurrence of bleeding complications (either major or minor), mortality, and MACCE; and 4) a significant difference in favor of DES was observed in the occurrence of TVR.

The combination of aspirin and thienopyridines is the optimal antiplatelet therapy after PCI for the prevention of stent thrombosis (1–4). The recommended duration of dual antiplatelet therapy is at least 1 month in patients receiving BMS. Current product labeling recommends dual antiplatelet therapy for 3 months after SES and 6 months after PES implantation. Recently it has been recommended that after DES implantation, dual antiplatelet therapy should be continued for at least 12 months and aspirin be continued lifelong (13). However, nearly 10% of patients referred for PCI also have clear evidence-based indications for long-term AC (14). Recently the ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) study had to be stopped early because of the clear superiority of oral AC over dual antiplatelet therapy in stroke prevention in patients with AF. Furthermore, it has been largely reported that a temporary discontinuation of AC is associated with a higher risk of thromboembolism (5,15–17). At the present time, there are no

Table 5. Characteristics of the Patients Who Died During Follow-Up

	Patient #				
	1	2	3	4	5
Age, yrs	83	73	72	66	74
CAD	3-vessel	2-vessel	2-vessel	2-vessel	2-vessel
EF, %	35	60	30	38	50
Indication for triple therapy	AF	AF	Aortic biological prosthesis	Coronary aneurysms	AF
CHADS2 risk score	6	1	NA	NA	1
Stent type	SES	BMS	SES	PES	SES
Description of the event	Cardiocirculatory arrest after hemodialysis	Subarachnoid hemorrhage and death	Cardiac arrest 10 days after redo aortic valve prosthesis	Cerebral hemorrhage and death	Cerebral hemorrhage and death
Time from the procedure, months	2	1	24	2	0.5

EF = ejection fraction; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; other abbreviations as in Table 1.

Table 6. Characteristics of the Patients With Major Bleeding Complications

Patient #	Age (yrs)	Reason for Warfarin	Type of Stent Implanted	Thromboembolic Risk (CHADS2 Score)	Time to Event/Triple Therapy Duration (Months)	Event Description
1	66	Coronary aneurysms	PES	NA	2	Cerebral hemorrhage and death
2	74	AF	SES	1	0.5	Cerebral hemorrhage and death
3	57	AF	PES	5	3	Subarachnoid hemorrhage with subsequent disabling neurological deficits
4	73	AF	BMS	0	1	Subarachnoid hematoma and death
5	75	Pulmonary embolism	SES	NA	1	Colon (diverticular) hemorrhage, requiring hemotransfusion (Hb 6.4 g/dl)
6	66	AF	PES	4	1	Severe gastrointestinal hemorrhage (Hb 6.0 g/dl), requiring hemotransfusion. ASA and warfarin interrupted complicated by STEMI with angiographic evidence of stent thrombosis, treated with primary PCI

AF = atrial fibrillation; ASA = acetylsalicylic acid; DVT = deep vein thrombosis; Hb = hemoglobin level; other abbreviations as in Tables 1 and 5.

evidence-based guidelines on the management of patients on concomitant treatment with long-term AC and dual antiplatelet therapy, and thus various antithrombotic combinations are used in everyday practice.

In the series from Orford et al. (18) and Karjalainen et al. (14), the overall bleeding rates were 9.2% and 11.4%, respectively. The incidence of major bleeding while on triple therapy was 3.1% (18) and 6.6% (14,19). Porter et al. (20) described 2 major bleeding events in the population of 180 patients on triple therapy. Buresly et al. (21) reported the incidence of bleeding events with 5 different antiplatelet and AC regimens in 21,443 elderly (age >65 years) patients after acute MI. In this study, the group treated with dual antiplatelet therapy combined with AC was very small (12 patients), and no significant statistical analysis could be obtained. However, the authors pointed out independent predictors of bleeding: age, cerebrovascular disease, diabetes, chronic renal failure, peptic ulcer disease, and bleeding during index hospital stay. The largest study published recently (22) reported a 5.9% incidence of in-hospital major bleeding on triple therapy in patients (n = 580) presenting with acute coronary syndrome.

Our series represents a large group of patients (n = 127) on concomitant treatment with dual antiplatelet therapy and AC. In all patients the triple therapy was prescribed and continued for 5.6 ± 4.6 months. In some patients dual antiplatelet therapy was prolonged (more than 1 month) after BMS implantation. This fact depended on the decision of the patients' cardiologists, who preferred to continue this therapeutic regimen, especially in the cases of multivessel coronary artery disease in diabetic patients or in patients treated during unstable onset of angina with percutaneous stent implantation. Despite the clinical characteristics of the patients (almost 23% had unstable angina, mean left ventricular ejection fraction was 44.9 ± 13.2%, and mean age 69.9 ± 8.8 years), no patient died during hospital stay and 7 (5.5%) had periprocedural MI. Moreover, none of these patients had in-hospital bleeding complications. At 21.0 ± 19.8 months' clinical follow-up, the overall bleeding rate was 7.1% with a 4.7% incidence of major bleeding. In all patients the bleeding complication occurred while on concomitant treatment with dual antiplatelet therapy and AC. Interestingly, 50% of the patients having major bleeding died of this complication. Major bleeding events occurred early after the procedure.

To reduce the occurrence of bleeding events, the patients at lower thromboembolism risk (e.g., CHADS2 <2) might be considered for temporary interruption of warfarin therapy and a limited period of time on double antiplatelet therapy only. However, the exact duration of dual antiplatelet therapy in patients necessitating warfarin, even if at low risk of thromboembolism, cannot be clearly established on the basis of this study.

Comparison between DES and BMS. In most of the patients (55.9%), DES were implanted with a greater prevalence of SES over PES (59.2% vs. 35.2%, respectively). The length of triple therapy was significantly prolonged in the DES as compared the with BMS group (7.7 ± 3.6 months vs. 3.1 ±

Table 7. Characteristics of the Patients With Minor Bleeding Complications

Patient #	Age (yrs)	Indication for Warfarin	Type of Stent Implanted	Thromboembolic Risk (CHADS2 Score)	Time to Event/Triple Therapy Duration (Months)	Event Description
1	87	AF	BMS	1	1	Bleeding gastric ulcer not requiring hemotransfusion or surgery
2	68	Pulmonary embolism	BMS	NA	1	Hematuria and hemoptysis
3	70	AF	SES	2	6	Epistaxis

Abbreviations as in Tables 1, 5, and 6.

3.6 months; $p < 0.001$). Despite this, no significant differences in the incidence of major bleeding (5.6% vs. 3.6%), minor bleeding (1.4% vs. 3.6%,), and MACCE (19.7% vs. 28.6%) were observed between DES and BMS at follow-up. Conversely, a significant difference in favor of DES was observed in the occurrence of TVR (14.1% vs. 26.8%, $p = 0.041$). Although 4 of a total of 5 deaths occurred in the DES group, no significant difference was observed in mortality (5.6% vs. 1.8%). In addition, among these 4 deaths, 1 patient died after redo aortic surgery and another patient died owing to cerebral hemorrhage at day 15 after stenting, when dual antiplatelet therapy would have been required even with implantation of a BMS.

Study limitations. This is a retrospective analysis, and thus no "a priori" sample size has been calculated. Moreover, the number of patients analyzed is relatively small, mostly because of the limited indication for the concomitant treatment with dual antiplatelet and AC therapy after PCI. No data are available on the exact INR values when bleeding events occurred, although we do not have any anamnesis-based evidence of inadequate INR control. Moreover, the comparison between DES and BMS is probably underpowered because of the retrospective nature of the study and small sample size, and no conclusions could be drawn regarding differences in mortality as well as safety between the study groups.

Conclusions

Our study shows that the long-term prognosis of patients on long-term AC and dual antiplatelet therapy after PCI is associated with an overall bleeding rate of 7.1%, with a 4.7% incidence of major bleeding. One-half of the major bleeding complications were fatal. The optimal strategy for treating patients undergoing PCI with stent implantation and requiring long-term AC is still unclear and will depend on individual patient risk factors for thromboembolism and bleeding.

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