Long-Term Outcomes in Patients Undergoing Coronary Stenting on Dual Oral Antiplatelet Treatment Requiring Oral Anticoagulant Therapy

ARTICLE *in* THE AMERICAN JOURNAL OF CARDIOLOGY · JANUARY 2009

Impact Factor: 3.28 · DOI: 10.1016/j.amjcard.2008.08.021 · Source: PubMed

Long-Term Outcomes in Patients Undergoing Coronary Stenting on Dual Oral Antiplatelet Treatment Requiring Oral Anticoagulant Therapy

Roberta Rossini, MD, PhD[a,*], Giuseppe Musumeci, MD[a], Corrado Lettieri, MD[b], Maria Molfese, MD[c], Laurian Mihalcsik, MD[a], Paola Mantovani, MD[b], Vasile Sirbu, MD[a], Theodore A. Bass, MD[d], Francesco Della Rovere, MD[c], Antonello Gavazzi, MD[a], and Dominick J. Angiolillo, MD, PhD[d]

In patients undergoing coronary stenting, long-term dual antiplatelet therapy with aspirin and clopidogrel reduces atherothrombotic events but also increases the risk of bleeding. The potential for developing bleeding complications is further enhanced in patients also requiring oral anticoagulant treatment ("triple therapy"). The aim of the study is to assess long-term outcomes associated with the use of triple-therapy in patients undergoing coronary stenting and evaluate how these may be affected by targeting international normalized ratio (INR) values to the lower therapeutic range. We prospectively studied 102 consecutive patients undergoing coronary stenting treated with dual antiplatelet therapy also requiring oral anticoagulation. INR was targeted to the lower therapeutic range (2.0 to 2.5). Patients requiring oral anticoagulant therapy because of mechanical valve prosthesis were excluded. Patients were followed for 18 months, and bleeding, defined according to Thrombolysis in Myocardial Infarction criteria, and major adverse cardiac events were recorded. Outcomes were compared with a control group (n = 102) treated only with dual antiplatelet therapy. The mean duration of triple therapy was 157 ± 134 days. At 18 months, a nonsignificant increase in bleeding was observed in the triple versus dual therapy group (10.8% vs 4.9%, p = 0.1). INR values were higher in patients with bleeding (2.8 ± 1.1 vs 2.3 ± 0.2, p = 0.0001). In patients who had INR values within the recommended target (79.4%), the risk of bleeding was significantly lower compared with patients who did not (4.9 vs 33%, p = 0.00019) and with that observed in the control group (4.9%). An INR >2.6 was the only independent predictor of bleeding. There were no significant differences in major adverse cardiac events between groups (5.8% vs 4.9%, p = 0.7). In conclusion, in patients undergoing coronary stenting on triple therapy, targeting lower therapeutic INR values reduces the risk of bleeding complications. **(Am J Cardiol 2008;102:1618–1623)**

Current guidelines on percutaneous coronary interventions (PCI) and acute coronary syndrome (ACS) recommend ≤12 months of combined aspirin and clopidogrel therapy.[1,2] However, such dual oral antiplatelet treatment regimen is associated with an increased risk of bleeding.[3] The potential for developing bleeding complications is further enhanced in patients also requiring oral anticoagulant treatment ("triple therapy").[4–10] To date most reports on triple therapy are limited to short-term outcomes, and there is a paucity of data regarding the impact of international normalized ratio (INR) values on bleeding complications in these patients. In addition, there are no studies evaluating how targeting INR to the lower range of therapeutic values impacts the risk of developing bleeding complications. The aim of the present study was to assess the long-term outcomes associated with the use of triple therapy in patients undergoing coronary stenting and to evaluate how these may be affected by targeting INR values to the lower therapeutic range.

Methods

All consecutive patients undergoing coronary stent implantation treated with aspirin (100 mg/day) and clopidogrel (75 mg/day) and who also required oral anticoagulant therapy were prospectively evaluated at 3 institutions. Between October 2005 and August 2006, a total of 1,678 consecutive patients underwent stent implantation. Of these, 118 (7%) required concomitant oral anticoagulant therapy. Patients with mechanical valve prosthesis (n = 16) were excluded. In patients meeting study eligibility criteria (n = 102), careful monitoring of INR values was recommended and targeted to be between 2.0 and 2.5. Control of INR was

[a]Divisione di Cardiologia, Dipartimento Cardiovascolare, Ospedali Riuniti di Bergamo, Bergamo, Italy; [b]Divione di Cardiologia, Ospedale Carlo Poma, Mantova, Italy; [c]Divisione di Cardiologia, Ente Ospedaliero Ospedali Galliera, Genova, Italy; and [d]University of Florida College of Medicine-Jacksonville, Jacksonville, Florida, United States. Manuscript received June 4, 2008; revised manuscript received and accepted August 5, 2008.

*Corresponding author: Tel: 00-39-0-3526-6455; fax: 00-39-0-3540-0491.

E-mail address: roberta_rossini@yahoo.it (R. Rossini).

0002-9149/08/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjcard.2008.08.021

performed weekly for the first month after initiation of oral anticoagulant therapy and recommended every 2 weeks afterwards. Oral anticoagulant dose adjustments were made by the referring primary care physicians.

PCI were performed according to current standard techniques, with the final strategy left entirely to the operator's discretion. All patients received a 300 mg loading dose of clopidogrel at the time of coronary intervention. Dual antiplatelet therapy was prescribed according to guideline recommendations[1,2]: (a) 12 months in patients presenting with an ACS irrespective of stent type; (b) 12 months in patients treated with a drug-eluting stent; (c) 1 month in patients not presenting with an ACS with bare metal stent implantation. After drug-eluting stent implantation, longer duration (≤24 months) of dual antiplatelet therapy was used in higher risk patients (e.g., with left main coronary artery stenting, last remaining vessel). An age- (± 5 years) and gender-matched control group (n = 102) with similar clinical presentation (unstable or stable symptoms) was collected from a total population with PCI treated during the same study period at the Ospedali Riuniti di Bergamo. Patients in the control group followed the same treatment recommendations as in the study group.

All patients were followed for 18 months from the beginning of the index antithrombotic therapy to determine the length of the triple therapy and incidence of bleeding events. Clinical visits were performed at 30 days and 18 months. INR values were collected at follow-up visits and at the time of a bleeding event if this occurred. The primary safety endpoint consisted of major and minor bleeding complications at 18 months. The secondary endpoint was defined as the occurrence of major adverse cardiac events (MACE) at 18 months. Bleeding complications were classified as major or minor according to Thrombolysis in Myocardial Infarction criteria.[11] Major bleeding included any intracranial bleeding or any bleeding associated with clinically overt signs associated with a drop in hemoglobin of >5 g/dl. Minor bleeding was defined as any clinically overt sign of bleeding (including observation by imaging techniques) that is associated with a decrease in hemoglobin of ≥3 g/dl and ≤5 g/dl. Hemorrhagic stroke included bleeding within the brain (intracerebral hemorrhage) and bleeding between the inner and outer layers of the tissue covering the brain (subarachnoid hemorrhage).

MACE were defined as death of any cause, nonfatal stroke, and nonfatal acute myocardial infarction. The occurrence of target vessel revascularization and stent thrombosis were also assessed. Stroke was defined as an ischemic cerebral infarction caused by an embolic or thrombotic occlusion of a major intracranial artery. Myocardial infarction was diagnosed if any troponin elevation with symptoms suggestive for ACS was detected. The presence of new pathological Q-waves on electrocardiogram was also diagnosed as myocardial infarction. Target vessel revascularization was defined as a reintervention driven by any lesion located in the stented vessel. Indication for repeat revascularization was based on anginal symptoms and/or proven myocardial ischemia in the target vessel territory and a significant luminal stenosis (>50% diameter stenosis). Stent thrombosis was diagnosed in the presence of ACS with angiographic evidence of either thrombotic vessel occlusion or thrombus within the stent or in autopsy. Thromboembolic complications other than embolic strokes (embolic occlusion of a limb artery, pulmonary embolism) were also recorded.

Table 1
Baseline demographics and procedural characteristics

Variable	Triple Therapy (n = 102)	Dual Therapy (n = 102)	p Value
Age (yrs)	67.9 ± 9.3	68.2 ± 8.1	0.2
Men	82 (80.4%)	81 (79.4%)	0.8
Diabetes	23 (22.5%)	24 (23.5%)	0.7
Hypertension*	52 (50.9%)	56 (54.9%)	0.1
Hypercholesterolemia†	58 (56.8%)	54 (52.9%)	0.1
Current smoking	20 (19.6%)	21 (20.6%)	0.2
Previous myocardial infarction	28 (27.4%)	26 (25.5%)	0.1
Previous stroke	15 (14.7%)	16 (15.7%)	0.6
Previous PCI	37 (36.3%)	39 (38.2%)	0.2
Previous coronary by-pass	12 (11.7%)	9 (8.8%)	0.1
Previous ulcer	6 (5.9%)	6 (5.9%)	0.9
Clinical presentation			
Stable angina	22 (21.6%)	21 (20.6%)	0.7
Unstable angina/ non–ST-elevation myocardial infarction	45 (44.1%)	46 (45%)	0.6
ST-elevation myocardial infarction	35 (34.3%)	35 (34.3%)	0.9
Multivessel coronary disease	58 (56.9%)	54 (52.9%)	0.1
Glycoprotein IIb/IIIa inhibitor	48 (47%)	49 (48%)	0.8
Radial approach	33 (32.3%)	35 (34.3%)	0.1
Drug-eluting stent usage	48 (47%)	49 (48%)	0.4
Number of stents/patient	1.5 ± 0.7	1.5 ± 0.9	0.8
Multivessel coronary stenting	48 (47%)	46 (45%)	0.1
Total stent length (mm)	27.5 ± 14	26.4 ± 11	0.4
Left ventricular ejection fraction (%)	47.6 ± 8.7	48.1 ± 9.2	0.2
Medication at discharge			
Nitrates	18 (17.6%)	20 (19.6%)	0.2
Angiotensin-converting enzyme inhibitors	80 (78.4%)	83 (78.4%)	0.8
Angiotensin II receptor blockers	9 (8.8%)	6 (5.9%)	0.1
Calcium antagonist	23 (22.5%)	21 (20.6%)	0.2
β Blocker	78 (76.5%)	79 (77.4%)	0.6
Statin	64 (62.7%)	66 (64.7%)	0.2
Diuretic	53 (52%)	51 (50%)	0.6
Proton pump inhibitor	92 (90.2%)	91 (89.2%)	0.6
Indication for oral anticoagulation			
Atrial fibrillation	68 (66.6%)	—	—
Left ventricular mural thrombus	18 (17.6%)		
Left ventricular aneurysm	5 (4.9%)		
Pulmonary embolism	5 (4.9%)		
Other indication	6 (5.8%)		

* Defined as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on ≥2 separate occasions or use of antihypertensive agents.

† Defined as history or recent cholesterol level ≥ninetieth percentile for age and gender.

Categorical data are presented as absolute values and percentages; continuous data are summarized as mean value ± SD. Chi-square and Fisher's exact tests were used for comparison of categorical variables as appropriate. Comparison

Table 2
Summary of outcome of cumulative events during follow-up

Variable	Triple Therapy (n = 102)	Dual Therapy (n = 102)	p Value
30-days outcome			
Any bleeding	4 (3.9%)	2 (2%)	0.4
Minor bleeding	3 (2.9%)	1 (1%)	0.3
Major bleeding	1 (1%)	1 (1%)	1
MACE	2 (2%)	2 (2%)	1
18-month outcome			
Any bleeding	11 (10.8%)	5 (4.9%)	0.1
Minor bleeding	8 (7.8%)	3 (2.9%)	0.1
Major bleeding	3 (2.9%)	2 (2%)	0.6
MACE	6 (5.8%)	5 (4.9%)	0.7

Table 3
Major and minor bleedings in the triple and dual therapy groups

Variable	Triple Therapy (n = 102)	Dual Therapy (n = 102)
Major bleedings	3 (2.9%)	2 (2)
Intracranial bleeding	0	0
Gastrointestinal bleeding	1 (1%)	1 (1%)
Groin hematoma	1 (1%)	1 (1%)
Urinary bleeding	1 (1%)	0
Minor bleedings	8 (7.8%)	3 (2.9)
Gastrointestinal bleeding	1 (1%)	0
Groin hematoma	1 (1%)	1 (1%)
Epistaxis	1 (1%)	1 (1%)
Decrease in the blood hemoglobin	2 (2%)	1 (1%)
Urinary bleeding	3 (2.9%)	0

of continuous variables was performed by means of Student's *t* test or Wilcoxon rank-sum test as appropriate. All variables with p <0.10 at univariate analysis were included in a stepwise logistic regression analysis. Hazards ratio and 95% confidence intervals (CI) were calculated. p Values <0.05 were considered statistically significant. Event-free survival curves for all bleeding events were constructed by use of the Kaplan-Meier method, and statistical differences between curves were assessed by log-rank test. Receiver-operating characteristic (ROC) analysis was performed to define sensitivity and specificity of INR values obtained at 1-month follow-up. In addition, ROC analysis was used for an exploratory evaluation of the best cutoff point of INR to predict bleeding in our study population; positive and negative predictive values also were derived using this cut-off value.

Results

A total of 102 study patients were available for the present analysis; 64 patients were discharged on triple therapy, and 34 of these were already on oral anticoagulation for >1 month at the time of hospitalization. Oral anticoagulation was suspended in patients already on oral anticoagulation, except for those presenting with ST-elevation myocardial infarction (n = 11), and PCI was performed when an INR value <1.5 was reached. In the remaining 38 patients, the need for oral anticoagulant therapy occurred 42 ± 33 days after hospital discharge. The main indications for anticoagulant therapy are listed in Table 1. The mean duration of triple therapy was 157 ± 134 days (range 30 to 540). All patients were successfully followed for 18 months from the beginning of the index anticoagulant therapy. Baseline demographics of the study and control groups are listed in Table 1.

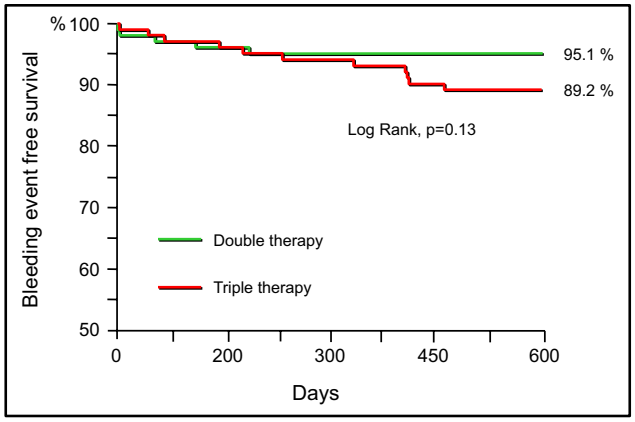

Figure 1. Cumulative event-free survival from overall bleeding in patients on triple and dual therapy.

Bleeding complications occurring in both patients and controls are listed in Tables 2 and 3. No difference in 30-day bleeding complications was found between the 2 groups. In both groups, there was a patient with a large groin hematoma requiring transfusion. The patient in the triple therapy group was already on warfarin at the time of PCI, and a glycoprotein IIb/IIIa inhibitor was used during the revascularization procedure. At 18-month follow-up, a nonsignificant increase in bleeding was observed in the triple versus dual therapy group. The incidence of major bleeding was similar between the 2 groups, and none of these bleeding events were fatal. In the triple therapy group, 1 patient had hematuria, which required transfusion, and another had gastrointestinal bleeding. In the control group, 1 patient had gastrointestinal bleeding. There was a higher incidence, albeit not statistically significant, of minor bleeding in patients on triple therapy than in controls both at 30 days (p = 0.3) and at 18 months (p = 0.1). The mean INR value at the time of bleeding was significantly higher in patients with any bleeding (2.8 ± 1.1 vs 2.3 ± 0.2, p = 0.0001), major bleeding (3.3 ± 0.6 vs 2.3 ± 0.2, p = 0.0003), and minor bleeding (2.6 ± 0.3 vs 2.3 ± 0.2, p = 0.006). Cumulative distribution curves showed a trend towards higher bleeding rates in patients on triple therapy (log-rank p = 0.13; Figure 1).

In the overall study population, the INR value at 30 days was 2.4 ± 0.5. All patients had an INR greater than the minimum therapeutic value of 2.0. INR values were within the recommended target (2.0 to 2.5) in 81 patients (79.4%) and were significantly lower compared with that in the remaining 21 patients (20.6%; 3.1 ± 0.8 vs 2.2 ± 0.2, p <0.0001). Bleeding complications were lower in patients who were within targeted INR values versus those who were not at 30 days (0% vs 4.8%, p = 0.05) and 18 months (4.9% vs 33%, p = 0.00019). The incidence of major (0% vs 14.3%, p = 0.001) and minor (4.9% vs 19%, p = 0.03)

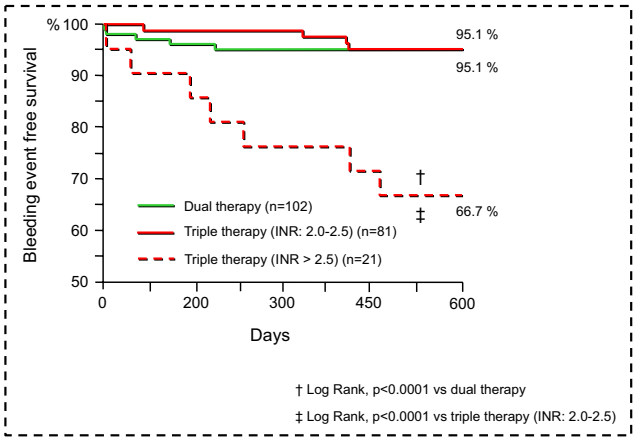

Figure 2. Cumulative event-free survival from overall bleeding in patients who were on dual therapy, on triple therapy within targeted INR values (2.0 to 2.5), and those who were not (>2.5).

bleeding was lower in patients within recommended INR values. The overall incidence of bleeding was similar in patients on triple therapy with targeted INR values and controls on dual antiplatelet therapy (4.9% vs 4.9%, p = ns). Cumulative distribution curves of the overall incidence of any bleeding in patients on dual therapy and on triple therapy within targeted INR values and those who were not are shown in Figure 2. The optimal ROC-defined INR value cut point between sensitivity and specificity for all bleeding was 2.6. This cut-off value had a specificity of 89%, a sensitivity of 66%, a negative predicted value of 95%, and a positive predictive value of 44%. In the triple therapy group, use of glycoprotein receptor blocker (odds ratio 2.7, 95% CI 1.1 to 6.2, p = 0.03), value of INR >2.6 (odds ratio 9.8, 95% CI 2.6 to 27.1, p = 0.0007), women (odds ratio 2.0, 95% CI 0.6 to 4.7, p = 0.04), and smoking (odds ratio 2.9, 95% CI 1.1 to 7.1, p = 0.02), were significant predictors of any bleeding at 18 months in univariate analyses. Multivariable analysis showed that only an INR >2.6 predicted overall bleeding (hazards ratio 19.2, 95% CI 4.3 to 44.6, p = 0.0003).

The overall MACE rate was similar in the 2 groups (Table 2). There were 3 deaths (1 cardiac), 1 ischemic stroke, and 2 nonfatal myocardial infarction in the triple therapy group, and 1 cardiac death, 2 ischemic strokes, and 2 nonfatal myocardial infarction in controls. The noncardiac deaths in the triple therapy group were secondary to intestinal occlusion and a car accident. The incidence of target vessel revascularization (1% vs 2.9%, p = 0.3) and stent thrombosis (1% vs 2%, p = 0.5) was also similar in the 2 groups. All 3 episodes of stent thrombosis led a nonfatal myocardial infarction. In the triple therapy group, the single episode of stent thrombosis occurred in a bare metal stent at 60 days post-PCI in a patient who suspended aspirin therapy. In the dual antiplatelet therapy group, 1 episode of stent thrombosis occurred 2 days after bare metal stent implantation in a patient compliant to therapy and the other 16 months post-PCI after clopidogrel withdrawal. No thromboembolic complications other than embolic strokes occurred.

Discussion

The optimal antithrombotic therapy in patients undergoing coronary stenting in whom dual antiplatelet therapy is required but who also have an indication for oral anticoagulation represents a common clinical problem that clinicians frequently face. The fine balance between safety and efficacy in this cohort needs careful consideration. In fact, discontinuation of antiplatelet therapy increases the risk of stent thrombosis, and even temporary withholding of anticoagulant increases the risk of thromboembolic events.[12–14] Conversely, addition of oral anticoagulation to the drug regimen of patients requiring dual antiplatelet therapy potentially enhances the risk of bleeding.[4–10,15] To date there are no large scale studies or randomized trials that have addressed the optimal antithrombotic regimen in patients with PCI also requiring long-term anticoagulation in addition to standard dual oral antiplatelet therapy ("triple therapy"). The main finding of this study is that in patients on triple therapy with an INR within the lower therapeutic range (2.0 to 2.5), which represented the recommended target, had a bleeding risk comparable with that of patients only on dual therapy. Conversely, patients with INR values above the recommended target had a higher long-term risk of bleeding. Ultimately, an INR value >2.6, which was determined on ROC analysis, was the only independent predictor of bleeding. Overall, our findings support the recent PCI guideline update in which an INR of 2.0 to 2.5 is recommended (class I, level of evidence C) for patients requiring warfarin, clopidogrel, and aspirin therapy after PCI (2).

It is common practice to combine both antiplatelet and anticoagulant drugs. However, the use of single or dual antiplatelet agent in combination with oral anticoagulation is often arbitrary. Data derived from a retrospective analysis of the Global Registry of Acute Coronary Events (GRACE) registry demonstrated varying practices of single versus dual antiplatelet therapy in patients who required oral anticoagulation following coronary stenting.[10] To date this registry has the largest population of patients on triple therapy in which 580 patients with ACS were discharged on warfarin and dual antiplatelet regimen and 220 patients received warfarin and single antiplatelet therapy. However, limited data on the safety of triple versus dual therapy emerged from this registry. In fact, in this retrospective analysis only in-hospital major bleeding data was provided. Importantly, there was almost a fivefold increase in risk of cerebrovascular events in patients not treated with oral anticoagulation. The importance of using anticoagulant treatment adjunct to antiplatelet therapy was also underscored in a retrospective study conducted in patients with atrial fibrillation undergoing PCI (n = 426) that demonstrated a lower incidence of overall MACE as well as mortality, although the use of oral anticoagulation in addition to antiplatelet therapy was associated with a nonsignificant increase in major bleeding.[16] Karjalainen et al[8] retrospectively analyzed patients with PCI (n = 239) on warfarin therapy in which aspirin and clopidogrel usage was the most common treatment option (48%) in the warfarin group. They found that the prognosis of warfarin-treated patients was unsatisfactory irrespective of the antithrombotic combinations used, and bleeding com-

plications, more common in the triple therapy group, had a crucial role. Similar to our study, warfarin therapy, smoking, glycoprotein IIb/IIIa receptor blocker usage, and female gender were associated with a greater risk of bleeding.[8] The limitations of the study are related to its retrospective nature and that decisions to use specific drug combinations were made by the local physicians according to their perceptions of risks and benefits for particular patients, resulting in potential study bias. Indeed, other studies have addressed bleeding complications in patients with PCI on triple therapy. However, the duration of the triple therapy was often short, and none addressed how targeting lower therapeutic INR values affected outcomes.[4,7] Orford et al[5] were the first to report the incidence of hemorrhagic complications during 4 weeks of triple therapy in 66 patients with PCI in which 6 (9.2%) reported a bleeding event and 2 required a blood transfusion. Porter et al[4] assessed the incidence of bleeding complication in a cohort of patients with PCI (n = 180) on triple therapy for 30 days during which 20 patients developed bleeding complications, 18 of which were minor episodes. Rogacka et al[7] addressed the safety of triple therapy in patients with PCI (n = 127) followed for a mean period of 21 ± 19 months. The incidence of major bleeding was 4.7%, which occurred mostly within the first month and were fatal in half of the cases. Limitations of this study included the lack of INR values and of a control group.

The main complication of oral anticoagulant therapy is bleeding, the risk of which is related to the intensity of anticoagulation.[17] In our study, we prospectively studied patients who were treated with warfarin in addition to dual antiplatelet therapy irrespective of their bleeding risk. This is the first study that addresses outcomes associated with INR values in patients on triple therapy. In our study most bleeding complications occurred in patients with INR values greater than our recommended target (2.0 to 2.5), but the incidence of any bleeding was similar in patients on triple therapy with INR within the targeted range and controls on dual antiplatelet therapy. Recent studies have underscored the importance of reducing bleeding complications. In fact bleeding has important prognostic implications, including mortality.[18,19] Even mild to moderate bleeding events are associated with poorer long-term prognosis compared with those patients without bleeding.[20] Also, the net clinical benefit of large scale clinical trials assessing novel antithrombotic agents are largely driven by the prevalence of bleeding complications.[21,22] Our findings show how targeting INR values to the lower therapeutic range reduces bleeding risk in patients requiring triple therapy, which remains effective in preventing ischemic complications as demonstrated by the low MACE rate at long-term follow-up. In particular, the incidence of ischemic stroke was identical to the dual therapy group, supporting that the maintenance of INR values within the lower therapeutic range, in addition to dual antiplatelet therapy, can guarantee a protective effect in patients with thromboembolic risk.

Although at present this is the first study addressing long-term outcomes associated with INR values in patients on triple therapy, larger sample size studies are warranted to confirm the present data. The present study, in fact, served as an exploratory pilot analysis, which needs to be confirmed in adequately powered studies.[23] Moreover, a small percentage of the enrolled patients had a strong indication to oral anticoagulation with a target INR of 2.0 to 3.0 (e.g., pulmonary embolism, left ventricular thrombus), which could have induced an overestimation of the efficacy of triple therapy with a low INR range (2.0 to 2.5) in preventing thromboembolic complications. In addition, our results cannot be extrapolated to patients with mechanical valve prostheses, typically requiring higher INR values, who were excluded from this study. The incidence of bleeding in our study was low compared with that of other studies using triple therapy. In addition to the lower INR values in our study population, reduced bleeding events, especially gastrointestinal, may be attributed to our prophylactic broad usage of proton pump inhibitors, which may also reduce clopidogrel-induced platelet inhibitory effects.[24] Differences in bleeding definitions may also contribute to disparities in studies. It may be argued that INR values vary over time and that the choice of a single time point value at 30 days used for the ROC analysis in our study may not be reflective of oral anticoagulant control during the long-term follow-up period.

1. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, et al, for the American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction. *J Am Coll Cardiol* 2007;50:e1–e157.
2. King SB III, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO, Feldman TE, Kern MJ, O'Neill WW, Schaff HV, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol* 2008;51:172–209.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
4. Porter A, Konstantino Y, Iakobishvili Z, Shachar L, Battler A, Hasdai D. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2006;68:56–61.
5. Orford JL, Fasseas P, Melby S, Burger K, Steinhubl SR, Holmes DR, Berger PB. Safety and efficacy of aspirin, clopidogrel and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J* 2004;147:463–467.
6. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives and warfarin in elderly patients following acute myocardial infarction. *Arch Int Med* 2005;165:784–789.
7. Rogacka R, Chieffo A, Michev I, Airoldi F, Latib A, Cosgrave J, Montorfano M, Carlino M, Sangiorgi GM, Castelli A, et al. Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation. *J Am Coll Cardiol Intv* 2008;1:56–61.
8. Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaittinen MA, Airaksinen TJ, Niemelä M, Vahlberg T, Airaksinen KE. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J* 2007;28:726–732.
9. Khurram Z, Chou E, Minutello R, Bergman G, Parikh M, Naidu S, Wong SC, Hong MK. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol* 2006;18:162–164.
10. Nguyen MC, Lim YL, Walton A, Lefkovits J, Agnelli G, Goodman SG, Budaj A, Gulba DC, Allegrone J, Brieger D; GRACE Investigators. Combining warfarin and antiplatelet therapy after coronary stenting in the

Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? *Eur Heart J* 2007;28:1717–1722.
11. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis In Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;11:1–11.
12. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol* 2005;45:947–953.
13. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519–1521.
14. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–1912.
15. DeEugenio D, Kolman L, DeCaro M, Andrel J, Chervoneva I, Duong P, Lam L, McGowan C, Lee G, DeCaro M, et al. Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. *Pharmacotherapy* 2007;27:691–696.
16. Ruiz-Nodar JM, Marín F, Hurtado JA, Valencia J, Pinar E, Pineda J, Gimeno JR, Sogorb F, Valdés M, Lip GY. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. *J Am Coll Cardiol* 2008;51:818–825.
17. Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz J. Antithrombotic therapy in patients undergoing percutaneous coronary intervention. *Chest* 2004;126:576S–599S.
18. Rao SV, Eikelboom JA, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non–ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28:1193–1204.
19. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006;114:774–782.
20. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, Moliterno DJ, Lincoff AM, Armstrong PW, Van de Werf F, Califf RM, Harrington RA. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol* 2006;47:809–816.
21. Mehta SR, Granger CB, Eikelboom JW, Bassand JP, Wallentin L, Faxon DP, Peters RJ, Budaj A, Afzal R, Chrolavicius S, Fox KA, Yusuf S. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007;50:1742–1751.
22. Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Feit F, Colombo A, McLaurin BT, et al; ACUITY Investigators. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007;369:907–919.
23. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004;10:307–312.
24. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, Mansourati J, Mottier D, Abgrall JF, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;51:256–260.