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Comparison Between Ticlopidine and Clopidogrel in Patients Undergoing Primary Stenting in Acute Myocardial Infarction: Results From the CADILLAC Trial

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Objective: The aim of this article is to examine whether clopidogrel and ticlopidine treatments produce similar clinical outcomes for patients receiving primary stenting for acute myocardial infarction (AMI). Background: Prior studies have yielded conflicting results on the relative safety and efficacy of clopidogrel and ticlopidine after stent implantation, warranting an evaluation in primary stenting for AMI. Methods: In the multicenter, prospective CADILLAC trial, patients undergoing primary infarct stenting were treated at operator discretion with either ticlopidine (931 patients) or clopidogrel (163 patients) and then followed for 1 year. Baseline clinical and angiographic characteristics were comparable except for baseline TIMI 0/1 flow (72.5% clopidogrel vs. 63.9% ticlopidine, $P = 0.04$). Results: Patients receiving clopidogrel had more recurrent ischemia in hospital (6.1 vs. 2.8%, $P = 0.02$) and at 30 days (10.5 vs. 5.8%, $P = 0.02$), more moderate and severe bleeding at 30 days (7.4 vs. 2.7%, $P = 0.002$), and similar rates of stent thrombosis out to 1 year ($P = 0.11$). By multivariable analysis, clopidogrel use was an independent predictor for recurrent ischemia in hospital ($P = 0.0002$), and at 30 days ($P = 0.012$); and of moderate and severe bleeding in hospital ($P = 0.002$), and at 30 days ($P = 0.001$). Conclusions: Despite thienopyridines similarities, their efficacy may be different within the first 30 days of primary stenting for AMI. A prospective, randomized trial is required to confirm these findings. © 2008 Wiley-Liss, Inc.

Key words: ticlopidine; clopidogrel; acute myocardial infarction; CADILLAC trial

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INTRODUCTION

The addition of ticlopidine to aspirin in patients undergoing elective stenting significantly reduced stent thrombosis rates to <1.0% [1,2] and 0.5% in the Stent Anticoagulation Restenosis Study (STARS) [3]. In spite of this success, ticlopidine is associated with significant hematologic toxicity (neutropenia and thrombotic thrombocytopenic purpura) in <1.0% of cases [4–7]. Clopidogrel has a lower side effect profile, a more rapid onset of action with its convenient once-a-day dosing regimen, and similar subacute stent thrombosis (SAT) rates compared with ticlopidine. Thus, clopidogrel has become the preferred thienopyridine in combination with aspirin.

Recent studies, however, found substantial variability in the platelet inhibitory response from clopidogrel in patients undergoing elective coronary stenting [8]. Matetzky et al. reported clopidogrel resistance occurring in a significant percentage of STEMI patients and associated it with a higher risk of recurrent cardiovascular events [9]. Clopidogrel did not confer significant inhibition of platelet activation by the thrombin-related activating peptide (TRAP) [10], suggesting that the new thienopyridine might be less effective in clinical situations such as ACS characterized by high thrombin generation. This new insight prompted our investigation comparing the antiplatelet effects of clopidogrel and ticlopidine in patients with AMI.

METHODS

Study Population

The CADILLAC trial has been described in detail elsewhere [11]. Briefly, 2,082 patients with AMI were prospectively randomized at 76 sites in nine countries to receive one of four reperfusion strategies in a 2 × 2 factorial design: (i) balloon percutaneous transluminal coronary angioplasty (PTCA); (ii) PTCA with abciximab (ReoPro, Centocor and Eli Lilly); (iii) MultiLink or MultiLink Duet stent implantation (Guidant, San Jose, CA); or (iv) MultiLink or MultiLink Duet stent implantation with abciximab. All patients who met the angiographic enrollment criteria underwent randomization. Enrollment criteria included clinical symptoms of AMI for <12 hr and either ≥1 mm of ST-segment elevation in two contiguous leads or a high-grade angiographic stenosis with an associated regional wall-motion abnormality. The angiographic inclusion criterion was the finding of a native coronary artery vessel with a lesion that was no longer than 64 mm and had a reference diameter of 2.5–4.0 mm. Major exclusion criteria included cardiogenic shock or a saphenous vein graft infarct lesion. Patients were further omitted if the angiographic findings indicated that noninterventional (medical or surgical) management was the proper approach, if multivessel angioplasty was required during the index procedure, or if prespecified anatomical conditions were present that would reduce the likelihood of successful stenting.

Procedure

Before undergoing catheterization, patients received 324 mg of chewable aspirin (or 250 mg intravenously at European centers), a 5000-U bolus of heparin, and either 500 mg of ticlopidine or 300 mg of clopidogrel orally. Abciximab (ReoPro, Centocor, Malvern, PA) was administered as a bolus of 0.25 mg per kilogram of body weight, followed by a 12-hr infusion at a rate of 0.125 μg per kilogram per minute (maximum 10 μg per minute). The dose of heparin was calculated with the use of a nomogram to achieve an activated clotting time of at least 350 sec (200–300 sec among the patients assigned to receive abciximab). In the two PTCA groups, crossover to stenting was allowed if there was residual stenosis after the procedure of more than 50% despite prolonged balloon inflations or a dissection of at least type C. Similarly, patients randomly excluded from the abciximab treatment were allowed to receive provisional or bail out doses for no-reflow or persistent thrombus. Procedure success was defined as a final residual stenosis of <50%, final TIMI 3 flow, and freedom from Major Adverse Cardiac Events (MACE) within 7 days of the procedure. After the intervention, patients received 325 mg of aspirin indefinitely and those who received stents were given 250 mg of ticlopidine orally twice daily or 75 mg of clopidogrel orally per day for 4 weeks. Follow-up visits were scheduled at 1, 6, and 12 months.

Endpoints and Definitions

The primary endpoint was the occurrence of MACE. We classified stent thrombosis as angiographic renarrowing or closure of the infarct vessel with a visible thrombus within 30 days of the index PCI. Death within 30 days possibly related to early thrombosis and reinfarction in the infarct territory without angiographic confirmation was also considered surrogates for early thrombosis. Recurrent ischemia was defined by the presence of recurrent ischemic symptoms or new electrocardiographic changes.

Statistical Analysis

Categorical data were compared using Fisher's exact test. Continuous variables are summarized as medians with interquartile ranges and compared using the Wilcoxon rank sum test and Mann-Whitney rank sum test. The influence of baseline demographic, angiographic,

TABLE I. Baseline Clinical Characteristics

Clinical features	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P Value
Age (years)	59.00 (55.00, 68.00)	59.00 (50.00, 70.00)	0.52
Male sex (%)	72.3	76.1	0.34
Weight (kg)	81.65 (72.00, 91.82)	81.65 (72.58, 93.00)	0.43
Renal insufficiency (CrCl < 60) (%)	17.3	17.0	1.0
Diabetes (%)	17.1	15.3	0.65
Current smoker (%)	45.0	44.8	1.0
Hypercholesterolemia (%)	38.9	34.4	0.29
Hypertension (%)	48.4	46.6	0.67
History of previous myocardial infarction (%)	13.3	14.7	0.62
Previous percutaneous coronary intervention (%)	10.3	12.3	0.49
Previous coronary bypass surgery (%)	1.7	1.2	1.00
ST-segment elevation or left bundle branch block (%)	87.5	91.6	0.18
Non-ST-segment elevation (%)	12.5	8.4	0.18
Number of diseased vessels: 1 (%)	51.1	47.9	0.45
Number of diseased vessels: 2 (%)	33.5	41.1	0.06
Number of diseased vessels: 3 (%)	15.4	11.0	0.19
Killip class: 2 or 3	10.9	9.8	0.78
Symptom onset to hospital arrival (hr)	1.92 (1.00, 3.49)	1.55 (1.00, 3.77)	0.41
Symptom onset to first balloon inflation (hr)	4.05 (2.87, 6.10)	4.13 (2.75, 6.64)	0.98

and procedural variables on the composite of recurrent ischemia, ischemic TVR, and moderate or severe bleeding were evaluated with logistic regression using the χ^2 test and the results expressed as odds ratios with 95% confidence intervals (CI). The Kaplan-Meier method was then used to estimate the event-free survival curves for recurrent ischemia and moderate or severe bleeding.

RESULTS

Patients treated with stents were divided into two groups according to the postprocedure thienopyridine received. Fifty-four stented patients who took both ticlopidine and clopidogrel and 34 stented patients who received neither were excluded from this analysis. In addition, 150 PTCA patients who crossed over, receiving a stent and a thienopyridine, were included in this analysis. Therefore, the study population comprised 931 patients treated with stents and ticlopidine, and 163 patients treated with stents and clopidogrel. Baseline clinical, angiographic, and procedural characteristics were similar between the two groups (Table I), except for preprocedure TIMI 0/1 flow ($P = 0.04$) and the use of three or more stents ($P = 0.03$), which was more common in the clopidogrel group. The incidence of final TIMI-3 flow was not statistically different between the two groups. Abciximab use and procedural ACT levels were similar as well (Table II). The thienopyrindine administered postprocedure was given at discharge in 95.1% of clopidogrel patients and 94.3% of ticlopidine patients and there was no thienopyridine crossover after discharge. The rates of use for β-blockers, statins, anticoagulants, and angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARBs) were significantly higher in clopidogrel-treated patients postprocedure and at discharge (Table III).

Clinical outcomes are shown in Table IV. Rates of MACE for patients receiving clopidogrel and ticlopidine were similar at all time points. Stent thrombosis in hospital was observed in 0.3% (3 of 931 patients) of the ticlopidine group versus 1.2% (2 of 163 patients) of the clopidogrel group ($P = 0.16$). From discharge though 1 year, there was no additional documented stent thrombosis in either group. Clopidogrel-treated patients had significantly more recurrent ischemia in hospital and at 30 days ($P = 0.02$) but not at 6 months or 1 year (Fig. 1). There was no significant difference in ischemia-driven TVR between the groups.

The incidence of moderate or severe bleeding complications was significantly higher in the clopidogrel group compared with the ticlopidine group up to 1 year (7.4% with clopidogrel vs. 3.0% with ticlopidine, $P = 0.006$; Fig. 2). Most of these bleeding complications occurred within the first 30 days. Furthermore, a trend for more disabling stroke was observed up to 6 months in clopidogrel-treated patients.

By multivariable analysis, clopidogrel use was an independent predictor of recurrent ischemia in hospital and at 30 days (Table V) and moderate or severe bleeding in hospital and at 30 days (Table VI).

DISCUSSION

The rare but potentially lethal hematologic side effects of ticlopidine have prompted the search for safer, yet equally effective pharmacologic agents [12]. Clopidogrel (Plavix™), a thienopyridine derivative

TABLE II. Angiographic and Procedural Characteristics

	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P Value
Angiographic features (core lab)			
Infarct vessel location: right coronary artery (%)	45.9	48.5	0.55
Infarct vessel location: left anterior descending artery (%)	35.9	36.8	0.86
Infarct vessel location: left circumflex artery (%)	18.0	14.7	0.37
Left ventrticular ejection fraction (%)	55.91 (47.18, 63.97)	57.32 (49.82, 63.38)	0.52
Prebifurcation (%)	33.8	39.0	0.24
Lesion location in ostium (%)	9.5	8.1	0.66
Calcification moderate-heavy (%)	18.3	16.9	0.74
Aneurysmal lesion (%)	1.3	2.5	0.28
Prethrombus (%)	54.4	53.8	0.93
Preprocedure reference diameter (mm)	2.97 (2.63, 3.35)	2.96 (2.63, 3.38)	0.91
Preprocedure diameter stenosis (%)	100.00 (73.26, 100.00)	100.00 (80.64, 100.00)	0.20
Preprocedure TIMI 0/1 (%)	63.9	72.5	0.04
Preprocedure TIMI 2 (%)	11.4	8.8	0.41
Preprocedure TIMI 3 (%)	24.7	18.8	0.11
Final-TIMI 3 (%)	97.2	94.4	0.08
Final-no dissection (%)	97.0	95.0	0.23
Final-thrombus (%)	2.4	1.9	1.00
Procedure features			
ACT during procedure (sec)	322 (255.00, 384.00)	323(264.00,363.00)	0.90
Number of stents implanted: 1 (%)	75.0	69.9	0.18
Number of stents implanted: 2 (%)	20.8	21.5	0.84
Number of stents implanted: 3 or more (%)	4.2	8.6	0.03
Maximum balloon diameter (mm)	3.50 (3.00, 3.50)	3.50 (3.00, 3.50)	0.90
Maximum balloon pressure (atm)	14.00 (12.00, 16.00)	14.00 (12.00, 16.00)	0.10
Abciximab used (%)	53.4	54.6	0.80

TABLE III. Medications at Admission, Postprocedure, and Discharge

	Admission			Post PCI			Discharge		
	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value
Aspirin	25.7	30.7	0.18	99.6	100.0	1.0	97.6	98.1	1.0
Ticlopidine	3.0	0.6	0.11	100.0	0.0	<0.0001	94.3	0.0	<0.0001
Clopidogrel	0.2	0.6	0.38	0.0	100.0	<0.0001	0.0	95.1	<0.0001
Anticoagulant	1.0	1.2	0.67	9.9	19.0	0.002	5.4	11.1	0.01
β-blocker	15.0	13.5	0.72	86.8	94.5	0.004	77.7	86.4	0.01
ACE inhibitor/ARBs	9.2	9.2	1.0	44.3	55.8	0.007	32.8	46.9	0.0007
Statin	11.5	15.3	0.19	29.1	39.3	0.01	28.3	38.9	0.009

Results are expressed as number (%).

T, ticlopidine; C, clopidogrel; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PCI, percutaneous coronary intervention.

with a similar mechanism of action as ticlopidine, has been shown to be an effective antiplatelet agent in patients after coronary stent implantation with a more favorable tolerability and safety profile [13–15]. Ischemic and major bleeding events did not differ significantly between clopidogrel- and ticlopidine-treated patients in these series. Three randomized trials (Muller et al. [16] CLASSICS, [7] and TOPPS, [17]) comparing ticlopidine and clopidogrel revealed no significant difference between the agents in preventing stent thrombosis or MACE following elective PCI and stenting. In contrast, a large retrospective analysis [18] and a smaller randomized trial [19] found a higher rate of stent thrombosis and cardiac death, respectively, in patients treated with clopidogrel versus ticlopidine. Yet, all studies confirmed the improved tolerability of clopidogrel over ticlopidine, as assessed by the incidence of discontinuation of therapy because of allergic reactions or hematological abnormalities. Thus, the use of clopidogrel in combination with aspirin has become the preferred regimen after intracoronary stent implantation for elective PCI patients. A comparison of the two thienopyridines in patients undergoing primary stenting for AMI, however, has not been performed previously.

TABLE IV. Clinical Outcomes and Bleeding Complications Up to 1 Year

	In hospital			30 Days			6 Months			1 Year		
Adverse Events	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value	Ticlopidine $N = 931$	Clopidogrel $N = 163$	P value
MACE[a]	2.4	3.7	0.29	3.6	4.3	0.64	9.8	9.9	0.94	13.3	13.1	0.98
Any death	1.2	0.6	1.0	1.7	1.2	0.64	2.6	3.1	0.73	3.2	5.6	0.13
Any MI	0.3	0.0	1.0	0.8	0.0	0.27	2.0	0.6	0.23	2.3	0.6	0.17
Any disabling stroke	0.0	0.6	0.15	0.1	0.6	0.17	0.2	1.3	0.05	0.6	1.3	0.31
Ischemic TVR (%)	1.2	2.5	0.26	1.6	2.5	0.45	6.8	5.0	0.44	9.5	7.0	0.34
Recurrent ischemia (%)	2.4	6.1	0.02	5.8	10.5	0.02	14.6	15.6	0.62	18.2	19.4	0.61
Stent thrombosis (%)	0.3	1.2	0.16	0.3	1.2	0.11	0.3	1.2	0.11	0.3	1.2	0.11
Moderate/severe bleeding (%)	1.9	6.1	0.005	2.7	7.4	0.002	2.9	7.4	0.004	3.0	7.4	0.006
Thrombocytopenia[b]	N/A	N/A	N/A	0.5	1.2	0.28	0.5	1.2	0.28	0.5	1.2	0.28

T group, ticlopidine; C group, clopidogrel.
[a]MACE; composite of death, reinfarction, disabling stroke, or ischemic TVR (target vessel revascularization).
[b]Thrombocytopenia <50,000 platelets (cells/mm^3).

Fig. 1. Event-free survival curves for recurrent ischemia up to 1-year comparing Ticlopidine to Clopidogrel.

Fig. 2. Event-free survival curves for moderate/severe bleeding up to 1-year comparing Ticlopidine to Clopidogrel.

Our study raises several important concerns regarding the use of clopidogrel in the context of the CADILLAC patient population. Patients treated with clopidogrel following primary stent implantation for AMI had more recurrent ischemia out to 30 days and more moderate or severe bleeding complications. In fact, by multivariable analysis, clopidogrel use was an independent predictor for recurrent ischemia and moderate or severe bleeding in hospital and at 30 days.

Variability of the platelet inhibitory response has been reported with clopidogrel [8] and clopidogrel resistance has also been documented in a significant percentage of ST-elevated myocardial infarction (STEMI) patients. Together, these issues are thought to be asso-

TABLE V. Multivariate Predictors of Recurrent Ischemia

	Estimate	*P* Value	Odds Ratio (95% CI)
In-hospital multivariate predictors			
Post-PCI clopidogrel	1.510	0.0002	4.53 (2.05, 10.02)
Randomized to abciximab	−0.991	0.03	0.37 (0.15, 0.90)
LAD location	0.832	0.04	2.30 (1.03, 5.13)
Killip Class: 2/3	1.084	0.02	2.96 (1.16, 7.51)
30-Day multivariate predictors			
Post-PCI clopidogrel	0.711	0.012	2.04 (1.17, 3.54)
Age	−0.025	0.018	0.98 (0.96, 1.00)
Killip class: 2/3	0.986	0.002	2.68 (1.45, 4.96)

Multivariate predictors are using stepwise variable selection. Candidate predictors are abciximab randomization, diabetes, female, age, hyperlipidemia, hypertension, current smoker, LAD, renal insufficiency, previous MI, previous CABG, Killip class 2/3, triple vessel disease, history of CVA, MI to angio time, moderate/severe calcification, baseline TIMI 0/1, baseline RVD, baseline MLD, post-cath statin, post-cath ticlopidine, post-cath clopidogrel, total stent length.

TABLE VI. Multivariate Predictors of Moderate/Severe Bleeding

In-hospital multivariate predictors	Estimate	*P* value	Odds ratio (95% CI)
Post-PCI clopidogrel	1.248	0.002	3.48 (1.61, 7.56)
Age	0.041	0.02	1.04 (1.01, 1.08)
Previous CABG	1.781	0.015	5.94 (1.42, 24.83)
30-Day multivariate predictors	**Estimate**	***P* Value**	**Hazard ratio (95% CI)**
Post-PCI clopidogrel	1.115	0.001	3.05 (1.57, 5.92)
Female	1.001	0.004	2.72 (1.38, 5.36)
Previous CABG	1.337	0.034	3.81 (1.10, 13.14)
History of CVA	1.232	0.028	3.43 (1.14, 10.32)

Multivariate predictors are using stepwise variable selection. Candidate predictors are abciximab randomization, diabetes, female, age, cholesterolemia, hypertension, current smoker, LAD, renal insufficiency, previous MI, previous CABG, Killip class 2/3, triple vessel disease, history of CVA, MI to angio time, moderate/severe calcification, baseline TIMI 0/1, baseline RVD, baseline MLD, discharge statin, post-cath ticlopidine, post-cath clopidogrel, post-cath anticoagulant.

ciated with a higher risk of recurrent cardiovascular events in patients undergoing coronary stenting after acute myocardial infarction (AMI) [9]. Furthermore, there is some evidence to suggest that clopidogrel does not confer significant inhibition of platelets when activated by the TRAP [10]. This suggests that clopidogrel might be less effective in clinical situations characterized by high thrombin generation such as acute coronary syndrome and, specifically, acute MI. Thus, these pharmacologic features might explain the higher frequency of recurrent ischemia seen with clopidogrel in the CADILLAC trial.

The incidence of moderate or severe bleeding was significantly higher in the clopidogrel group at 1 year, mostly from bleeding complications occurring within the first 30 days. Although the frequency of anticoagulant therapy (warfarin) was significantly higher in this group, use of clopidogrel remained an independent predictor of moderate to severe bleeding. When comparing clopidogrel with placebo, some large STEMI studies (CLARITY [20], COMMIT [21]) have not identified an association with bleeding. In contrast, the CURE [22] and CREDO [23] trials, performed in lower risk patients, have presented evidence confirming clopidogrel's link with such complications. Despite the discrepancies between different studies, it is important to note that in patients with moderate and severe bleeding, antiplatelet therapy discontinuation is more common, a factor well known to be associated with more ischemic events following intracoronary stenting [24]. Furthermore, recent analyses from large trials of patients with acute coronary syndromes demonstrated the critical influence of early bleeding on later ischemic events [25]. Altogether, the evidence presented in this analysis and that from others might suggest that clopidogrel has a higher antiplatelet effect, which leads to more bleeding and subsequent ischemic events related to therapy discontinuation. Indeed, the difference in ischemic events occurs early and does not exist more beyond the first few months. Although this putative sequence of events linking more antiplatelet effect to bleeding and subsequent ischemic events may be operative, a recent analysis from the TRITON-TIMI 38 trial in 12,844 patients undergoing stent implantation and randomized to clopidogrel or prasugrel (a more rapidly active and potent thienopyridine-like drug) did not support this scenario [26]. Including 25% of patients with STEMI, and the rest with NSTEMI, TRITON showed that prasugrel therapy is associated with statistically significant absolute reduction of 15 events (death, MI, or stroke) for every 1,000 patients treated (20% relative risk reduction) and 12 events of stent thrombosis (52% relative risk reduction). This important benefit was countered by a significant excess of five episodes of major bleeding for 1,000 patients treated, resulting in a 14% reduction in the net clinical outcome combining ischemic and bleeding events (12 vs. 13.7%, $P = 0.002$). In other words, in this analysis from CADILLAC both ischemic and hemorrhagic events were reduced with ticlopidine versus clopidogrel, while the other studies including that using a novel and more powerful platelet inhibitor showed a tradeoff between reduction in one and excess in the other. Yet again, a randomized trial specifically addressing clopidogrel in this light is necessary for a greater understanding.

LIMITATIONS

This analysis was not prespecified in the CADILLAC trial design, is retrospective, and can only be considered hypothesis generating. Because the CADILLAC trial coincided with the gradual introduction of clopidogrel as adjunctive antiplatelet therapy during PCI, a disproportionate number of patients were on ticlopidine in the study. The trial protocol recommended that patients receive a loading dose of 500 mg ticlopidine or 300 mg of clopidogrel before undergoing catheterization, however, the timing, prescription details, and temporal discontinuation of antiplatelets were not recorded in this trial. Moreover, the overall medical regimen of the patients was left to the discretion of the investigator. Finally, because of the very low incidence of stent thrombosis, the sample size of this study does not provide adequate power to detect a difference in stent thrombosis rates between the two thienopyridines.

CONCLUSIONS

These data corroborate the relative safety and efficacy of the combination of aspirin and thienopyridines in patients undergoing primary stenting with bare metal stents for AMI. However, the efficacy of clopidogrel and ticlopidine in patients undergoing primary stenting for AMI may not be the same. The use of ticlopidine, not clopidogrel, in combination with aspirin may, in fact, be the most effective regimen after primary stenting for AMI patients during the first 30 days. A prospective randomized trial would be required to further elucidate the relative efficacy of the two thienopyridines.

REFERENCES

1. Schomig 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;334:1084–1089.
2. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–1971.
3. 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;339:1665–1671.
4. Bennett CL, Kiss JE, Weinberg PD, et al. Thrombotic thrombocytopenic purpura after stenting and ticlopidine. Lancet 1998;352:1036–1037.
5. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989;1:1215–1220.
6. Steinhubl SR, Tan WA, Foody JM, Topol EJ.Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. EPISTENT Investigators. Evaluation of platelet IIb/IIIa inhibitor for stenting. JAMA 1999;281:806–810.
7. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: The clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102:624–629.
8. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–2913.
9. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171–3175.
10. Muller I, Seyfarth M, Rudiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001;85:92–93.
11. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–966.
12. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, Yarnold PR, Kwaan HC, Green D. Thrombotic thrombocytopenic purpura associated with ticlopidine. A review of 60 cases. Ann Intern Med 1998;128:541–544.
13. Berger PB, Bell MR, Rihal CS, et al. Clopidogrel versus ticlopidine after intracoronary stent placement. J Am Coll Cardiol 1999;34:1891–1894.
14. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99:2364–2366.
15. Mishkel GJ, Aguirre FV, Ligon RW, Rocha-Singh KJ, Lucore CL. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. J Am Coll Cardiol 1999;34:1884–1890.
16. Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000;101:590–593.
17. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. Circulation 2001;104:539–543.
18. Wolak A, Amit G, Cafri C, Gilutz H, Ilia R, Zahger D. Increased long term rates of stent thrombosis and mortality in patients given clopidogrel as compared to ticlopidine following coronary stent implantation. Int J Cardiol 2005;103:293–297.
19. Mueller C, Roskamm H, Neumann FJ, Hunziker P, Marsch S, Perruchoud A, Buettner HJ. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary artery stents. J Am Coll Cardiol 2003;41:969–973.
20. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179–1189.
21. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet 2005;366:1607–1621.
22. 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.

23. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. JAMA 2002;288: 2411–2420.
24. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implementation of drug-eluting stents. JAMA 2005;293:2126–2130.
25. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB III, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: An analysis from the ACUITY Trial. J Am Coll Cardiol 2007;49:1362–1368.
26. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman JP, Van de Werf F, Downey WE, Scirica BM, Murphy SA, Antman EM;TRITON-TIMI 38 Investigators. Intensive oral antiplatelet therapy for reduction of ischemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: A subanalysis of a randomized trial. Lancet 2008;371:1353–1363.