Clopidogrel Trial in Patients With Elective Percutaneous Coronary Intervention for Stable Angina and Old Myocardial Infarction (CLEAN)

Safety and Efficacy of Clopidogrel Compared to Ticlopidine in Japanese Patients

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SUMMARY

Clopidogrel in combination with aspirin has been widely used in patients who have undergone coronary stent implantation. However, the benefit to Japanese patients with stable angina (SA) or old myocardial infarction (OMI) undergoing percutaneous coronary intervention (PCI) still remains unclear.

The aim of this multicenter, randomized, double-blind, clinical study was to evaluate the safety of a clopidogrel 300 mg loading dose followed by a 75 mg maintenance dose compared to ticlopidine 100 mg twice daily in patients with SA or OMI undergoing PCI who were on aspirin (81 to 100 mg once daily). The primary endpoint was the composite of safety events comprising clinically significant bleeding, blood disorders, elevated liver function values, and study drug discontinuation up to week 12. The key secondary endpoints were major adverse cardiac events (MACE), major adverse cardiac and cerebrovascular events (MACCE), and bleeding events.

A total of 1003 patients were randomly allocated to receive either clopidogrel or ticlopidine and 931 patients underwent PCI. The cumulative incidence of the composite safety endpoint in the clopidogrel group was statistically lower than that of ticlopidine ($P < 0.0001$, hazard ratio; 0.259; 95%CI; 0.187 to 0.359). There were no statistically significant differences between treatments with respect to MACE at week 12 ($P = 0.7899$) nor to the bleeding events ($P = 0.5292$, stratified log-rank test).

Clopidogrel was found to have a better benefit/risk profile than ticlopidine in Japanese patients with SA or OMI undergoing PCI. (Int Heart J 2012; 53: 91-101)

Key words: Coronary artery disease, Major adverse cardiac events, Major adverse cardiac and cerebrovascular events, Dual antiplatelet therapy, Safety of clopidogrel, Stents

When a stent is implanted in a coronary artery, direct contact between the stent and blood may result in the formation of a thrombus due to the stent being recognized as a foreign object, with the final result being thrombotic occlusion (especially stent thrombosis) and serious myocardial ischemia. Therefore, a powerful antiplatelet drug is required to prevent platelet aggregation after percutaneous coronary intervention (PCI).

In Japan, prior to clopidogrel being approved for coronary indications in 2007, ticlopidine had a long history of being administered with aspirin to patients undergoing PCI.¹⁾ It is a well-known fact that ticlopidine occasionally causes serious adverse drug reactions such as agranulocytosis, thrombotic thrombocytopenic purpura, or hepatopathy.^{2,3)} In particular, it

has been demonstrated that hepatic disorders caused by ticlopidine are observed more frequently in Japanese than in other ethnicities.⁴⁾ Thus, in dual antiplatelet therapy (DAPT) following stent implantation, low dose ticlopidine (200 mg/day) in combination with aspirin (81-200 mg/day) has become a standard regimen in Japan for patients undergoing PCI to avoid ticlopidine-induced complications. Nevertheless 500 mg/day of ticlopidine has been administered to patients undergoing PCI in the United States and Europe.

However, the coronary indication approved to date is limited to acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction) for which PCI is being planned: elective PCI was excluded because neither patients with stable angina (SA) nor old myocardial infarction (OMI)

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This study was supported by Sanofi-Aventis KK, an affiliate of the Sanofi group.

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Received for publication November 25, 2011.

Revised and accepted February 16, 2012.

were included in the pivotal study. To demonstrate the benefit of clopidogrel over ticlopidine in Japanese patients with SA or OMI undergoing PCI, a multicenter, randomized, double-blind, double-dummy, parallel-group study has been conducted.

METHODS

Study population: The study was conducted from December 8, 2008 (first patient randomized) to August 21, 2010 (last patient last visit) at 95 active centers in Japan. Study participants were 20 years of age or older and presented with ischemia on stress test. An additional requirement was coronary angiographic assessment (either $\geq 75\%$ stenosis documented by coronary angiography or severe stenosis confirmed by multi-slice computerized tomography angiography within 2 months before randomization) with an intention to perform elective PCI. Major exclusion criteria were existing 3-vessel coronary artery disease (CAD) with significant lesions, indication for coronary artery bypass surgery, necessity to perform emergency/urgent PCI or staged PCI, and chronic total occlusion or saphenous vein graft as target lesion.

This trial was conducted in accordance with the principles that have their origin in the Declaration of Helsinki (Helsinki, 1964) and all applicable amendments passed by the

World Medical Assemblies, and the International Conference on Harmonization (ICH) and Japanese guidelines for Good Clinical Practice (GCP). Prior to a patient's participation in the trial, the written informed consent form had to be signed and personally dated by the patient, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form was provided to the patient.

Procedure: On day 1, eligible patients were randomized in a double-blind fashion via an independent registration center in a 1:1 ratio to either a clopidogrel group or a ticlopidine group (Figure 1). Previous treatment with aspirin was used as a stratification variable. Immediately after randomization, all patients received the assigned study drug together with the contrast dummy placebo. Specifically, the clopidogrel group received no clopidogrel preparation on day 1 and day 2, a loading dose of clopidogrel (300 mg) on day 3 followed by a maintenance dose (75 mg once daily) from day 4 through week 12 (1st period), whereas the ticlopidine group received ticlopidine 100 mg twice daily (the standard dose for patients with CAD undergoing PCI in Japan) from day 1 through week 12 (Table I). During the 1st period, all patients received aspirin (81-100 mg once daily) as background therapy and the contrast dummy placebo was to be taken in the same manner as the study drugs. The first 300 patients who completed 12 weeks of treatment in the 1st period and who met all of the following transition criteria to

Figure 1. Flow diagram of trial procedure.

Table I. Study Drug Administration

Group	Clopidogrel group		Ticlopidine group	
Timing	After breakfast	After dinner	After breakfast	After dinner
Day 1 and 2	□	□	■	■
Day 3	●●●●□	□	○○○○■	■
Day 4 to Week 12	●□	□	○■	■

● : Clopidogrel 75 mg tablet, ○ : Clopidogrel placebo, ■ : Ticlopidine 100 mg tablet, □ : Ticlopidine placebo. When the first administration was in the afternoon on day 1, only one tablet was to be taken after dinner.

Table II. Definition of Safety Events of Interest

Component class	Definition
Clinically significant bleeding	<ul style="list-style-type: none"> •Pseudoaneurysms caused by a catheterization. •Bleeding from puncture sites requiring surgical repair (excluding cases for which a causal relationship with study drugs can be ruled out). •Bleeding requiring transfusion of at least 4 units (1 unit: 200 mL) of erythrocytes, or equivalent whole blood. •Symptomatic intracranial bleeding. •Symptomatic retroperitoneal bleeding. •Bleeding associated with decreases in hemoglobin of 5 g/dL or more compared with baseline.
Blood disorders in which a causal relationship with the study drugs cannot be ruled out	<ul style="list-style-type: none"> •WBC of less than 3,000/mm³ •Neutrophils of less than 1,500/mm³ •Platelets of less than 100,000/mm³
Elevated liver function values	•ALT, γ -GTP, ALP or total bilirubin elevated by 50% or more compared with baseline and causal relationship with the study drugs cannot be ruled out (changes within normal range in the institution are excluded).
Study drug discontinuation due to adverse drug reaction	•Skin disorders, gastrointestinal disorders, bleeding, hepatic disorders, or significant decrease of leukocytes, neutrophils or platelets, in which causal relationship with the study drugs cannot be ruled out.

the 2nd period were enrolled in an open-label long-term treatment study: patients with drug compliance over 75% and who underwent the posttreatment laboratory tests at week 12; a patient whose condition warranted 52 weeks of thienopyridine treatment as judged by the investigator; patients who are expected to comply with long-term treatment and come to follow-up visits up to week 52; and patients who have given written informed consent to the 2nd period. The patients in the extended treatment sub-set received clopidogrel 75 mg once daily together with aspirin (81-100 mg once daily) until week 52 regardless of the treatment group to which they were assigned in the 1st period.

Percutaneous coronary intervention: Index PCI planned before randomization was performed between day 4 and day 8 to avoid any imbalance in the antiplatelet effect between groups at the time of the index PCI. Levels of creatine kinase and the creatine kinase MB fraction or levels of troponin were measured at pretreatment, and 6-12 hours, 12-24 hours, and 24-48 hours after PCI.

Outcomes: The primary endpoint was the elapsed time in days from the randomization to the first occurrence of the composite safety event during the 1st period. The safety events of interest comprised clinically significant bleeding, blood disorders, elevated liver function values, and study drug discontinuation due to an adverse drug reaction (Table II). The secondary endpoints were a major adverse cardiovascular event (MACE), which is a composite of all-cause mortality, acute myocardial infarction, revascularization or stent thrombosis, a major adverse cardiac and cerebrovascular event (MACCE), which is a composite of all-cause mortality, acute myocardial infarction, revascularization, stent thrombosis, or ischemic stroke. Bleeding was also assessed according to the CURE definition,⁵⁾ the Thrombolysis in Myocardial Infarction (TIMI) criteria, and the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria. For an evaluation of long-term safety and efficacy, cumulative incidences of these parameters until week 52 were also estimated. An event adjudication committee that was masked to treatment allocation adjudicated the safety events of interests, MACE, and MACCE.

Sample size: The sample size was calculated based on the results of the previous studies for acute coronary syndrome (ACS) and stroke using Japanese patients.⁶⁾ In the ACS study, the hazard ratio (HR) of the safety events of interest between clopidogrel and ticlopidine was 0.72 at day 28 for patients who had undergone PCI appropriately, and cumulative incidence curves suggested that the difference between clopidogrel and ticlopidine would increase even after day 28. Another study in patients with stroke also showed that the difference in the incidence of the safety events of interest continuously increased until week 12. Therefore, it was expected that relative risk reduction in the clopidogrel group for the safety events of interest at 3 months would be at least 28%. In the long-term study of the above-mentioned ACS study, the cumulative incidence of the safety events of interest in the clopidogrel group was 26% at 3 months. From these results, assuming that 26% of the patients reached the primary endpoint in the clopidogrel group at 3 months and that the HR of clopidogrel versus ticlopidine was 0.72, 493 patients per group were required in order to show a significant difference between treatments, using a log-rank test with 80% power and a 5% two-sided significance

level. Thus, sample size of the 1st period in this study was set at 1000 patients.

Taking into account the duration of DAPT recommended in overseas guidelines, in this study we established a second period for the evaluation of the long-term safety of clopidogrel. This is because clopidogrel is commonly used for 12 months in patients with SA/OMI when they have undergone coronary stent implantation.⁷⁾ In order to detect adverse events with a 3% or greater frequency level as a true cumulative one year incidence, 100 patients exposed for a minimum of one year are required. However, long-term ticlopidine treatment is not ethically acceptable due to the risk of serious adverse drug reactions. Therefore, we integrated the 2nd period with a subset of 300 patients who received open-label clopidogrel for 40 weeks after the 12-week double-blind period regardless of the treatment group assigned in the 1st period. This allowed long-term safety to be investigated in a minimum of 100 patients treated with clopidogrel from the beginning of the 1st period.

Statistical analysis: The analyses of key endpoints during the 1st period were performed in the modified intended-to-treat (mITT) population, which was a randomized population who had their index PCI analyzed according to the allocated treatment unless otherwise specified. Although PCI involves a risk of iatrogenic thrombotic occlusion, stable angina or old myocardial infarction without invasive treatment has no risk of thrombotic occlusion. Thus the investigator had to discontinue the study drug treatment when patients had not undergone index PCI up to day 8. Since the rate of study drug discontinuation due to no index PCI was estimated to be more than 5%, this special population with an insufficient exposure to the study drug was deleted from primary analysis for the safety evaluation. Nevertheless, the analyses of key endpoints were performed also in the entire randomized population regardless of whether study drug administration was initiated or not, as sensitivity analyses. All patients were followed up until week 12 or the day in which study withdrawal for any reason was decided by the investigator. Time to the first occurrence of the events from randomization to week 12 was compared between the clopidogrel and ticlopidine groups using a log-rank test with a two-sided 5% significance level. In addition, cumulative incidences and their 95% confidence intervals (CIs) were estimated with the Kaplan-Meier method and Greenwood's formula. HRs with 95% CIs were estimated using the Cox model with the treatment groups as factors. Patients in whom no events occurred during the 1st period were considered as a right censor at the last observed date in the 1st period or day 91 whichever came first. When a complete onset date was not known, missing dates were inputted from the midpoint of the possible term. The composition of the first event in each endpoint was summarized using count and percentage by treatment group.

The analyses of key endpoints during 52 weeks of treatment were performed in the long-term evaluation (LTE) population, which was the population that completed the 1st period of the study and enrolled in the 2nd period, by treatment group assigned at randomization. Cumulative incidences of events up to week 52 and their 95% CIs were estimated with the Kaplan-Meier method and Greenwood's formula. Patients in whom no events occurred were considered as a right censor at the last observed date or day 371, whichever came first. When a complete onset date was not known, missing dates were inputted

Figure 2. Trial profile.

from the midpoint of the possible term. The composition of the first event in each endpoint was summarized using count and percentage by treatment group. This trial has been registered with ClinicalTrials.gov, number NCT00821834.

RESULTS

Study patients: A total of 1003 patients were randomly allocated to receive either clopidogrel or ticlopidine (ie, all randomized population), of which 931 patients underwent an index PCI and were included in the mITT population (Figure 2). The remaining 72 randomized patients had not received index PCI primarily because no significant stenosis was present at the time when diagnostic coronary angiography was performed after randomization. The first 301 eligible patients out of the

Table III. Demographics and Patient Characteristics at Baseline

Variable	mITT population		LTE population	
	Clopidogrel (n = 466)	Ticlopidine (n = 465)	CLOP-CLOP (n = 158)	TIC-CLOP (n = 143)
Age (years)	68.2 (9.0)	68.2 (8.8)	68.2 (7.8)	69.1 (8.2)
≥ 75 years	120 (25.8%)	122 (26.2%)	30 (19.0%)	38 (26.6%)
Female sex	136 (29.2%)	131 (28.2%)	42 (26.6%)	40 (28.0%)
Weight (kg)	63.11 (11.07)	62.62 (10.55)	63.07 (10.04)	62.98 (9.33)
< 50 kg	53 (11.4%)	48 (10.3%)	16 (10.1%)	8 (5.6%)
<u>Admission diagnosis</u>				
SA	397 (85.2%)	405 (87.1%)	130 (82.3%)	121 (84.6%)
Old MI	32 (6.9%)	22 (4.7%)	14 (8.9%)	5 (3.5%)
SA and old MI	37 (7.9%)	38 (8.2%)	14 (8.9%)	17 (11.9%)
Aspirin pretreatment	383 (82.2%)	377 (81.1%)	124 (78.5%)	115 (80.4%)
<u>Smoking [n (%)]</u>				
Never	180 (38.6%)	161 (34.6%)	53 (33.5%)	45 (31.5%)
Current	71 (15.2%)	59 (12.7%)	26 (16.5%)	16 (11.2%)
Former	215 (46.1%)	245 (52.7%)	79 (50.0%)	82 (57.3%)
<u>Medical history</u>				
PCI/CABG	69 (14.8%)	69 (14.8%)	23 (14.6%)	27 (18.9%)
Angina pectoris/MI	31 (6.7%)	30 (6.5%)	11 (7.0%)	9 (6.3%)
Cerebrovascular disease	60 (12.9%)	65 (14.0%)	22 (13.9%)	24 (16.8%)
Peripheral arterial disease	19 (4.1%)	24 (5.2%)	5 (3.2%)	7 (4.9%)
Heart failure	13 (2.8%)	27 (5.8%)	5 (3.2%)	12 (8.4%)
Diabetes mellitus	191 (41.0%)	191 (41.1%)	67 (42.4%)	73 (51.0%)
Hypertension	369 (79.2%)	360 (77.4%)	130 (82.3%)	105 (73.4%)
Hyperlipidemia	357 (76.6%)	357 (76.8%)	125 (79.1%)	104 (72.7%)
Liver dysfunction	52 (11.2%)	61 (13.1%)	24 (15.2%)	16 (11.2%)
Renal dysfunction	43 (9.2%)	51 (11.0%)	15 (9.5%)	16 (11.2%)
<u>Lesion location</u>				
RCA	151 (32.4%)	139 (29.9%)	48 (30.4%)	46 (32.2%)
LCX	89 (19.1%)	98 (21.1%)	34 (21.5%)	27 (18.9%)
LAD	263 (56.4%)	265 (57.0%)	88 (55.7%)	85 (59.4%)
LMCA	3 (0.6%)	4 (0.9%)	0	3 (2.1%)
Other	4 (0.9%)	7 (1.5%)	0	1 (0.7%)
<u>ACC/AHA classification</u>				
Type A	107 (23.0%)	99 (21.3%)	33 (20.9%)	27 (18.9%)
Type B1	148 (31.8%)	150 (32.3%)	57 (36.1%)	52 (36.4%)
Type B2	139 (29.8%)	141 (30.3%)	42 (26.6%)	44 (30.8%)
Type C	72 (15.5%)	75 (16.1%)	26 (16.5%)	20 (14.0%)
<u>Stent implanted at index PCI</u>				
BMS	83 (17.8%)	73 (15.7%)	24 (15.2%)	13 (9.1%)
DES (w/wo BMS)	377 (80.9%)	382 (82.2%)	132 (83.5%)	128 (89.5%)
Any PCI without stent	6 (1.3%)	10 (2.2%)	2 (1.3%)	2 (1.4%)

Data are mean (SD) or number (%). SA indicates stable angina; MI, myocardial infarction; BMS, bare metal stent; DES, drug eluting stent; mITT, modified intended-to-treat; and LTE, long-term evaluation.

patients who completed the 1st period were transferred to the 2nd period with clopidogrel (ie, LTE population).

Baseline characteristics in the mITT population were well balanced among the randomization group (Table III). A total of 86.1% of patients in the mITT population were diagnosed as having stable angina (SA) and 81.6% of patients had been treated with aspirin before randomization. Overall, 915 (98.3%) received stents; 156 (16.8%) received bare-metal stents and 759 (81.5%) had at least one drug-eluting stent. The

cumulative exposures to active drug in the clopidogrel group and in the ticlopidine group in the 1st period were 102.6 and 97.7 patient/year, respectively. The mean (SD) duration of exposure was 80.4 (15.2) days for clopidogrel and 76.7 (21.3) days for ticlopidine, and thus the duration in the clopidogrel group was longer than that in the ticlopidine group. This might have resulted from the fact that many patients discontinued study drug treatment in the ticlopidine group even though the theoretical treatment duration for ticlopidine was 2 days longer

Table IV. Major Outcomes Observed as the First Event in the 1st Period - mITT Population

	Clopidogrel (n = 466)	Ticlopidine (n = 465)	Hazard ratio ^a (95% CI ^b)	P ^c
Safety event of interest	47 (10.1%)	159 (34.2%)	0.259 (0.187, 0.359)	< 0.0001
Clinically significant bleeding	4 (0.9%)	3 (0.6%)		
Blood disorder	7 (1.5%)	15 (3.2%)		
Elevated liver function value	27 (5.8%)	136 (29.2%)		
Study drug discontinuation due to ADR	16 (3.4%)	56 (12.0%)		
Clinically significant bleeding	4 (0.9%)	3 (0.6%)	1.328 (0.297, 5.936)	0.7092
Blood disorder	8 (1.7%)	16 (3.4%)	0.495 (0.212, 1.158)	0.0977
Elevated liver function value	28 (6.0%)	141 (30.3%)	0.172 (0.115, 0.258)	< 0.0001
Study drug discontinuation due to ADR	18 (3.9%)	61 (13.1%)	0.281 (0.166, 0.476)	< 0.0001
MACE	43 (9.2%)	45 (9.7%)	0.945 (0.622, 1.436)	0.7899
All-cause mortality	0	0		
Acute myocardial infarction	36 (7.7%)	43 (9.2%)		
Revascularization	7 (1.5%)	2 (0.4%)		
Stent thrombosis	0	0		
MACCE	43 (9.2%)	48 (10.3%)	0.886 (0.587, 1.337)	0.5611
All-cause mortality	0	0		
Acute myocardial infarction	36 (7.7%)	43 (9.2%)		
Revascularization	6 (1.3%)	2 (0.4%)		
Stent thrombosis	0	0		
Ischemic stroke	1 (0.2%)	3 (0.6%)		
Bleeding event [CURE definition]	6 (1.3%)	4 (0.9%)	1.497 (0.422, 5.306)	0.5292
Life-threatening bleeding	3 (0.6%)	1 (0.2%)		
Major bleeding	0	2 (0.4%)		
Minor bleeding	3 (0.6%)	1 (0.2%)		
Bleeding event [TIMI criteria]	6 (1.3%)	6 (1.3%)	1.004 (0.324, 3.115)	0.9938
Major bleeding	2 (0.4%)	1 (0.2%)		
Minor bleeding	4 (0.9%)	5 (1.1%)		
Bleeding event [GUSTO criteria]	3 (0.6%)	2 (0.4%)	1.522 (0.254, 9.109)	0.6433
Severe/Life-threatening bleeding	3 (0.6%)	0		
Moderate bleeding	0	2 (0.4%)		
Any bleeding ^d	89 (19.1%)	91 (19.6%)	0.969 (0.724, 1.298)	0.8328

a: Estimated using Cox proportional hazard model with treatment group as the factor and aspirin pretreatment as stratification variable; b: Estimated using Kaplan-Meier technique with Greenwood's formula; c: P are calculated using log-rank test for treatment group with aspirin pretreatment as stratification variable; d: Any bleeding was all bleeding includes TIMI minimal bleeding or GUSTO mild bleeding. A patient can be counted in several categories when multiple events occurred on the same day as the first event. Outcomes whose hazard ratio and cumulative incidence have been estimated with the Kaplan-Meier method and Greenwood's formula are shaded in blue. CI indicates confidence intervals; ADR, adverse drug reaction; MACE (major adverse cardiac event), all-cause mortality, acute myocardial infarction (development of new abnormal Q waves not present at baseline, creatine kinase (CK) and creatine kinase MB (CK-MB) or troponin elevations), revascularization (PCI, CABG, and coronary thrombolytic therapy, which were performed after the start of study drug administration (excludes index PCI and planned PCI based on diagnostic CAG)) or stent thrombosis (definite or probable based on the ARC classification); and MACCE (major adverse cardiac and cerebrovascular event), all-cause mortality, acute myocardial infarction, revascularization, stent thrombosis or ischemic stroke (defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours, without evidence of primary intracranial hemorrhage).

Figure 3. Kaplan-Meier curves in the 1st period - mITT population. **A:** The cumulative incidence of the safety events of interest in the clopidogrel group was significantly lower than that of the ticlopidine group (8.9% [95%CI, 6.3% to 11.5%] versus 30.9% [95%CI, 26.7% to 35.1%] at week 12; adjusted HR, 0.259; 95% CI, 0.187 to 0.359; $P < 0.0001$). **B:** No significant difference was observed in the cumulative incidence of MACE between the two groups (9.0% [95%CI, 6.4% to 11.6%] versus 9.7% [95%CI, 7.0% to 12.4%] at week 12; adjusted HR, 0.945; 95%CI, 0.622 to 1.436; $P = 0.7899$).

than that of clopidogrel.

Primary endpoint: evaluation of safety events of interest: In the mITT population, a total of 47 patients (10.1%) in the clopidogrel group experienced a primary endpoint, as compared with 159 patients (34.2%) in the ticlopidine group (Table IV). The cumulative incidence of the safety events of interest in the clopidogrel group was significantly lower than that for the ticlopidine group (adjusted HR, 0.259; 95% CI, 0.187 to 0.359; $P < 0.0001$; Figure 3A). Among 72 patients who were not included in the mITT population, 3 patients in the clopidogrel group and 2 patients in the ticlopidine group experienced safety events of interest before study drug discontinuation, though the incidence curves in the all randomized population were consistent with those in the mITT population (10.0% versus 32.1%; adjusted HR, 0.275; 95% CI, 0.200 to 0.378; $P < 0.0001$).

This benefit can be attributed primarily to a lower rate of elevated liver function values (6.0% versus 30.3%; adjusted HR, 0.172; 95% CI, 0.115 to 0.258; $P < 0.0001$) and to study drug discontinuation due to adverse drug reactions (3.9% versus 13.1%; adjusted HR, 0.281; 95% CI, 0.166 to 0.476; $P < 0.0001$) in the clopidogrel group; the rate of clinically significant bleeding in the two groups was similar (0.9% versus 0.6%; adjusted HR, 1.328; 95% CI, 0.297 to 5.936; $P = 0.7092$).

Although the prespecified explorative subgroup analyses for identifying the prognostic factors on primary endpoint showed a potential interaction between treatment and a "History of PCI and CABG" ($P = 0.0147$), no other significant interactions were observed (Table V). The clinical relevance of such an interaction is difficult to assess due to the small size of this subgroup of patients, and other factors related to patient history might influence the occurrence of safety events of interest. However, the hazard ratio of clopidogrel against ticlopidine in both the presence and absence subgroups in terms of the "History of PCI and CABG" showed a homogeneous effect on the safety events of interest (hazard ratio: 0.219 [95%CI: 0.152 to 0.316] in absence subgroup, 0.623 [95%CI:

0.289 to 1.344] in presence subgroup).

Secondary endpoints: safety and efficacy during the 1st period:

For the efficacy endpoint during the 1st period, no significant difference was observed in the cumulative incidence of MACE in the two groups (9.2% versus 9.7%; adjusted HR, 0.945; 95%CI, 0.622 to 1.436; $P = 0.7899$; Figure 3B). The distributions of component classes in the two groups were similar, as shown in Table IV. The most frequently observed first MACE was acute myocardial infarction; 36 patients in the clopidogrel group and 43 patients in the ticlopidine group: of these, Q-wave myocardial infarction was observed in only one patient in each group.

For MACCE also, there was no significant difference in the cumulative incidence between groups (9.2% versus 10.3%; adjusted HR, 0.886; 95%CI, 0.587 to 1.337; $P = 0.5611$). With regard to the component classes of MACCE, ischemic stroke was observed in one patient (0.2%) in the clopidogrel group and in 3 patients (0.6%) in the ticlopidine group.

Regarding bleeding events (CURE definition), no statistically significant difference was observed (adjusted HR, 1.497; 95%CI, 0.422 to 5.306; $P = 0.5292$). The rate of the event for the clopidogrel and ticlopidine groups was 1.3% and 0.9%, respectively. Looking at the details of the first bleeding events (CURE definition), life-threatening bleedings during the 1st period were observed in 0.6% (3/466) of the clopidogrel group and 0.2% (1/465) of the ticlopidine group. Among them, a causal relationship with the study drug in 2 cases, reported as catheter site haemorrhage and coronary artery dissection in the clopidogrel group, was ruled out by the study investigators since these events were thought to be procedural complications. Thus, life-threatening bleeding possibly related to the study drug was confined to one patient in each group.

There was consistency in the bleeding events according to the TIMI criteria (Major and Minor), GUSTO criteria (Severe and Moderate) and any bleeding (including TIMI Minimal or GUSTO mild). Clopidogrel did not significantly increase bleeding risk compared to ticlopidine (TIMI bleeding; 1.3% versus 1.3%; adjusted HR, 1.004; 95%CI, 0.324 to 3.115;

Table V. Subgroup Analyses of Safety Events of Interest-mITT Population

	Clopidogrel (n = 466)	Ticlopidine (n = 465)	Hazard ratio ^a (95% CI) ^a	P for interaction ^b
<u>Aspirin pretreatment</u>				0.3145
Absence	7/83 (8.4%)	35/88 (39.8%)	0.179 (0.079, 0.403)	
Presence	40/383 (10.4%)	124/377 (32.9%)	0.281 (0.197, 0.402)	
<u>Age</u>				0.6923
< 65	15/140 (10.7%)	55/140 (39.3%)	0.225 (0.127, 0.399)	
[65-75]	20/206 (9.7%)	69/203 (34.0%)	0.253 (0.153, 0.416)	
≥ 75	12/120 (10.0%)	35/122 (28.7%)	0.330 (0.171, 0.636)	
<u>Weight</u>				0.4862
< 50	6/53 (11.3%)	25/48 (52.1%)	0.174 (0.071, 0.424)	
[50-70]	27/293 (9.2%)	98/304 (32.2%)	0.253 (0.165, 0.387)	
≥ 70	14/120 (11.7%)	36/113 (31.9%)	0.323 (0.174, 0.600)	
<u>Sex</u>				0.0794
Male	32/330 (9.7%)	94/334 (28.1%)	0.315 (0.211, 0.471)	
Female	15/136 (11.0%)	65/131 (49.6%)	0.174 (0.099, 0.306)	
<u>Smoking</u>				0.1856
Never	16/180 (8.9%)	67/161 (41.6%)	0.174 (0.101, 0.301)	
Current	9/71 (12.7%)	22/59 (37.3%)	0.293 (0.135, 0.637)	
Former	22/215 (10.2%)	70/245 (28.6%)	0.336 (0.208, 0.542)	
<u>Type of stent at index PCI</u>				0.3569
No stent	0/6	2/10 (20.0%)	0.000 (0.000, NC)	
Bare metal stent (BMS)	7/83 (8.4%)	32/73 (43.8%)	0.149 (0.066, 0.338)	
Drug eluting stent (DES)	38/370 (10.3%)	123/377 (32.6%)	0.285 (0.198, 0.410)	
Both (BMS and DES)	2/7 (28.6%)	2/5 (40.0%)	0.550 (0.077, 3.943)	
<u>Primary disease</u>				0.5316
Stable angina (SA)	38/397 (9.6%)	141/405 (34.8%)	0.242 (0.169, 0.346)	
Myocardial infarction (MI)	5/32 (15.6%)	7/22 (31.8%)	0.483 (0.153, 1.527)	
Both (SA and MI)	4/37 (10.8%)	11/38 (28.9%)	0.321 (0.102, 1.010)	
<u>History of PCI and CABG</u>				0.0147
Absence	36/397 (9.1%)	143/396 (36.1%)	0.219 (0.152, 0.316)	
Presence	11/69 (15.9%)	16/69 (23.2%)	0.623 (0.289, 1.344)	
<u>History of cerebrovascular disease</u>				0.2752
Absence	39/406 (9.6%)	139/400 (34.8%)	0.242 (0.170, 0.345)	
Presence	8/60 (13.3%)	20/65 (30.8%)	0.387 (0.170, 0.880)	
<u>History of peripheral arterial disease</u>				0.2975
Absence	44/447 (9.8%)	152/441 (34.5%)	0.249 (0.178, 0.349)	
Presence	3/19 (15.8%)	7/24 (29.2%)	0.552 (0.143, 2.135)	
<u>History of heart failure</u>				0.4048
Absence	46/453 (10.2%)	146/438 (33.3%)	0.269 (0.193, 0.375)	
Presence	1/13 (7.7%)	13/27 (48.1%)	0.121 (0.016, 0.924)	
<u>History of diabetes mellitus</u>				0.2455
Absence	32/275 (11.6%)	93/274 (33.9%)	0.299 (0.200, 0.447)	
Presence	15/191 (7.9%)	66/191 (34.6%)	0.202 (0.115, 0.354)	
<u>History of hypertension</u>				0.9886
Absence	9/97 (9.3%)	33/105 (31.4%)	0.264 (0.126, 0.553)	
Presence	38/369 (10.3%)	126/360 (35.0%)	0.257 (0.179, 0.370)	
<u>History of hyperlipidemia</u>				0.6851
Absence	11/109 (10.1%)	35/108 (32.4%)	0.293 (0.149, 0.578)	
Presence	36/357 (10.1%)	124/357 (34.7%)	0.251 (0.173, 0.363)	
<u>History of liver dysfunction</u>				0.3613
Absence	42/414 (10.1%)	131/404 (32.4%)	0.278 (0.197, 0.394)	
Presence	5/52 (9.6%)	28/61 (45.9%)	0.169 (0.065, 0.439)	
<u>History of renal dysfunction</u>				0.7106
Absence	42/423 (9.9%)	142/414 (34.3%)	0.255 (0.181, 0.360)	
Presence	5/43 (11.6%)	17/51 (33.3%)	0.305 (0.112, 0.827)	

a: Estimated using Cox proportional hazard model with treatment group as the factor in the subgroup, b: P for treatment by covariate interaction was calculated comparing model chi-squares of likelihood ratio test between models with interaction and without interaction. Abbreviations as in Table III.

$P = 0.9938$, GUSTO bleeding; 0.6% versus 0.4%; adjusted HR, 1.522; 95%CI, 0.254 to 9.109; $P = 0.6433$, Any bleeding; 19.1% versus 19.6%; adjusted HR, 0.969; 95%CI, 0.724 to 1.298; $P = 0.8328$).

Secondary endpoints: safety and efficacy in 52-week treatment:

The cumulative incidence of MACE at week 52 in the LTE population was 16.7% (95% CI, 10.8% to 22.6%) in the CLOP-CLOP group, which was treated with clopidogrel for

Figure 4. Kaplan-Meier curves in long-term treatment - LTE population. **A:** The cumulative incidences of the safety events of interest in the CLOP-CLOP group and TIC-CLOP group (11.5% [95%CI, 6.5% to 16.5%] and 37.9% [95%CI, 29.9% to 45.8%] at week 52). **B:** The cumulative incidence curves by 12 weeks landmark analysis of both treatment groups were found to be comparable (7.1% [95%CI, 3.0% to 11.1%] and 5.8% [95%CI, 1.9% to 9.6%] at week 52). **C:** The incidence of MACE in the CLOP-CLOP group and TIC-CLOP group (16.7% [95% CI, 10.8% to 22.6%] and 23.5% [95% CI, 16.5% to 30.5%] at week 52). **D:** 12 weeks landmark analysis shows a similar incidence curve for MACE (12.3% [95%CI, 7.1% to 17.5%] and 16.0% [95%CI, 9.8% to 22.1%] at week 52).

the entire 52 weeks, and 23.5% (95% CI, 16.5% to 30.5%) in the TIC-CLOP group, which was treated with ticlopidine for the first 12 weeks followed by clopidogrel for 40 weeks (Figure 4C). According to the landmark analysis, which is defined as the assessment during the 2nd period, the cumulative incidence of MACE was 12.3% (95% CI, 7.1% to 17.5%) in the CLOP-CLOP group and 16.0% (95% CI, 9.8% to 22.1%) in the TIC-CLOP group. Both treatment groups had similar incidence curves throughout the landmark analysis period by the Kaplan-Meier method (Figure 4D).

The cumulative incidence of MACCE at week 52 in the LTE population was 17.4% (95% CI, 11.4% to 23.3%) in the CLOP-CLOP group and 24.2% (95% CI, 17.1 to 31.3%) in the TIC-CLOP group. Of these, the cumulative incidence based on landmark analysis was 12.9% (95% CI, 7.6% to 18.2%) in the CLOP-CLOP group and 16.0% (95% CI, 9.8% to 22.1%) in the TIC-CLOP group.

Regarding long-term safety, the cumulative incidence of safety events of interest at week 52 in the LTE population was 11.5% (95% CI, 6.5% to 16.5%) in the CLOP-CLOP group and 37.9% (95% CI, 29.9% to 45.8%) in the TIC-CLOP group (Figure 4A). In contrast, the cumulative incidence based on landmark analysis was 7.1% (95% CI, 3.0% to 11.1%) in the CLOP-CLOP group and 5.8% (95% CI, 1.9% to 9.6%) in the TIC-CLOP group. Similarly, comparable incidence curves

were also observed in both treatment groups throughout the landmark analysis period using the Kaplan-Meier method (Figure 4B).

The cumulative incidences of time to the first bleeding events (CURE definition) from randomization to week 52 in the LTE population were 5.2% (95% CI, 1.7% to 8.6%) and 3.6% (95% CI, 0.5% to 6.7%) in the CLOP-CLOP group and TIC-CLOP group, respectively, whereas those from randomization to week 12 in the mITT population were 1.3% (95% CI, 0.3% to 2.3%) and 0.9% (95% CI, 0.0% to 1.7%) in the CLOP-CLOP group and TIC-CLOP group, respectively.

DISCUSSION

The CLEAN study demonstrated that in patients who underwent elective PCI, the subsequent 12 weeks of clopidogrel treatment significantly reduced the relative risk of safety events of interest by 74%, and the absolute risk of such events by 24% in the mITT population, as compared to ticlopidine. Among 72 patients who were not included in the mITT population, 5 patients experienced the safety events of interest. However, the trend for the cumulative incidences observed in all randomized population was consistent with that in the mITT population, a fact which suggests the study results were

Table VI. Major Outcomes Observed as the First Event in LTE Population

	52 weeks		2 nd period (Landmark analysis: beyond Week12)	
	CLOP-CLOP (n = 158)	TIC-CLOP (n = 143)	CLOP-CLOP (n = 158)	TIC-CLOP (n = 143)
<i>Safety event of interest</i>	19 (12.0%)	54 (37.8%)	12 (7.6%)	8 (5.6%)
Clinically significant bleeding	4 (2.5%)	4 (2.8%)	4 (2.5%)	3 (2.1%)
Blood disorder	1 (0.6%)	3 (2.1%)	0	1 (0.7%)
Elevated liver function value	10 (6.3%)	46 (32.2%)	3 (1.9%)	3 (2.1%)
Study drug discontinuation due to ADR	7 (4.4%)	7 (4.9%)	7 (4.4%)	4 (2.8%)
<i>MACE</i>	26 (16.5%)	33 (23.1%)	19 (12.0%)	22 (15.4%)
All-cause mortality	0	0	0	0
Acute myocardial infarction	9 (5.7%)	17 (11.9%)	1 (0.6%)	2 (1.4%)
Revascularization	18 (11.4%)	17 (11.9%)	19 (12.0%)	21 (14.7%)
Stent thrombosis	0	0	0	0
<i>MACCE</i>	27 (17.1%)	34 (23.8%)	20 (12.7%)	22 (15.4%)
All-cause mortality	0	0	0	0
Acute myocardial infarction	9 (5.7%)	17 (11.9%)	1 (0.6%)	2 (1.4%)
Revascularization	18 (11.4%)	17 (11.9%)	19 (12.0%)	21 (14.7%)
Stent thrombosis	0	0	0	0
Ischemic stroke	1 (0.6%)	1 (0.7%)	1 (0.6%)	0
<i>Bleeding event [CURE definition]</i>	8 (5.1%)	5 (3.5%)	7 (4.4%)	4 (2.8%)
Life-threatening bleeding	4 (2.5%)	3 (2.1%)	3 (1.9%)	2 (1.4%)
Major bleeding	1 (0.6%)	1 (0.7%)	1 (0.6%)	1 (0.7%)
Minor bleeding	3 (1.9%)	1 (0.7%)	3 (1.9%)	1 (0.7%)
<i>Bleeding event [TIMI criteria]</i>	3 (1.9%)	5 (4.0%)	3 (1.9%)	4 (2.8%)
Major bleeding	3 (1.9%)	3 (2.1%)	3 (1.9%)	2 (1.4%)
Minor bleeding	0	2 (1.4%)	0	2 (1.4%)
<i>Bleeding event [GUSTO criteria]</i>	4 (2.5%)	1 (0.7%)	3 (1.9%)	1 (0.7%)
Severe/Life-threatening bleeding	1 (0.6%)	0	0	0
Moderate bleeding	3 (1.9%)	1 (0.7%)	3 (1.9%)	1 (0.7%)
<i>Any bleeding</i>	56 (35.4%)	48 (33.6%)	37 (23.4%)	24 (16.8%)

A patient can be counted in several categories when multiple events occurred on the same day as first event.
Abbreviations and explanations as in Table IV.

robust. In other words, the exclusion of patients not included in mITT population did not affect the interpretation of the study results. The benefit of clopidogrel was due to a lower rate of liver dysfunction and a lower rate of study drug discontinuation, and the results were consistent across all subgroups, supporting our hypothesis that DAPT with clopidogrel provides a significant clinical benefit to patients with stable CAD who undergo PCI. Ticlopidine occasionally induces serious or problematic safety events such as agranulocytosis, thrombotic thrombocytopenic purpura or hepatopathy, and at present there is no alternative, approved drug with a powerful antiplatelet effect capable of preventing thrombotic occlusion, despite a definite need for DAPT following stent implantation. Treatment with clopidogrel leads to a significant reduction in the rate of study drug discontinuation, thereby providing clinical benefit to patients who undergo PCI. Moreover, the significantly lower rate of elevated liver function values seen with clopidogrel treatment, compared to ticlopidine, is of substantial benefit, especially as there is a higher rate of ticlopidine-induced liver dysfunction in Japanese as compared with other ethnicities.⁴⁾

Regarding efficacy, the CLEAN study showed that clopidogrel (a 300 mg loading dose followed by a maintenance dose of 75 mg once daily) had adequate efficacy with regard to

the cumulative incidences of MACE and MACCE, compared to low dose ticlopidine, during 12 weeks of treatment. Low dose ticlopidine (200 mg/day) in combination with aspirin (81-200 mg/day) was standard DAPT in Japanese patients with CAD who underwent PCI. The regimen was empirically introduced, with careful tapering of the ticlopidine dose, taking into consideration the risk-benefit balance in individual patients in whom a coronary stent had been implanted. Therefore, the efficacy of the regimen is believed to not be inferior to that used in Western countries where 500 mg/day of ticlopidine is administered. Indeed, extremely low incidences of stent thrombosis (0.54% at 1 year and 0.77% at 2 years) have been reported in the J-Cypher registry,⁸⁾ in which most of the patients received DAPT comprising aspirin and low dose ticlopidine. These facts suggest that clopidogrel definitely has efficacy in preventing MACE in Japanese patients without increasing the risk of bleeding. In addition, the distribution of classes of MACE in the clopidogrel group was similar to that in the ticlopidine group (Table IV). More specifically, the most frequent type of event for the first MACE was acute myocardial infarction in both groups. Of these, Q-wave myocardial infarction was observed in only one patient in each group; most events were characterized by elevation of periprocedural cardiac en-

zyme values. Stent thrombosis was not reported for either the first MACE or the first MACCE, as defined in the protocol, although one case of stent thrombosis due to plaque rupture proximal to the implanted stent was reported in the clopidogrel group as a second event; acute myocardial infarction (ST segment elevation that was documented on ECG) was observed 4 days before the onset of stent thrombosis. Therefore, acute myocardial infarction was considered to be the first MACE or MACCE, but not stent thrombosis in the context of this protocol. However, as mentioned above, clopidogrel is thought to have adequate efficacy in Japanese patients who undergo PCI.

A limitation of the study was the single-arm design (absence of a control group) in the 2nd period, making objective evaluation during this period more difficult. Ideally, a double-blind, parallel comparison design should be expanded into the 2nd period for evaluation of the long-term efficacy and safety of clopidogrel, but the long-term administration of ticlopidine cannot ethically be allowed taking into account its serious safety concerns. Likewise, long-term DAPT beyond 12 weeks is not always beneficial for patients who undergo PCI; for example, DAPT for patients without stent implantation or patients in which implanted BMS are fully covered by neointimal might be inappropriate. Nevertheless, the cumulative incidence curves of MACE and MACCE showed no specific tendency to increase (Figure 4C, D); almost all the events observed during the 2nd period involved revascularization, probably due to restenosis; no stent thrombosis was observed (Table VI). These rates were similar to those for target lesion revascularization after stent implantation in Japan.⁹⁾ With respect to the safety (cumulative incidence of safety events of interest, bleeding events and other safety endpoints) of long-term administration of clopidogrel (75 mg once daily for 52 weeks in total), neither specific changes in rates nor significant events were observed (Table VI, Figure 4). These findings suggest that clopidogrel has a significant clinical benefit in terms of sustained efficacy, without major safety concerns.

On the other hand, the cumulative incidence curve of the safety events of interest in the TIC-CLOP group showed stabilization following the switch to clopidogrel treatment. The incidence curve in the TIC-CLOP group with respect to landmark analysis and the distribution of events among the categories were similar to those in the CLOP-CLOP group despite the cumulative incidence in the ticlopidine group in the 1st period being statistically higher than that in the clopidogrel group. Concomitant medication was comparable in both groups. In addition, landmark analysis revealed no particular changes in MACE in the 2nd period. Therefore, our data suggest a potential clinical benefit from a later switch to clopidogrel treatment for patients started on ticlopidine treatment, without any apparent increase in the bleeding risk.

Regarding the comparison between the CLOP-CLOP group and TIC-CLOP group in the LTE population, we did not perform any direct comparison because the risk of imbalance between groups on patient selection in the 2nd period by chance could not be ruled out. In fact, Kaplan-Meier curves of MACE in the TIC-CLOP group during the 1st period in the LTE population were higher than that in the CLOP-CLOP group (Figure 4C). The clinical relevance of such a difference is difficult to assess scientifically due to nonrandomized enrollment criteria and no stratification in the 2nd period.

The results of the CLEAN study demonstrated the effica-

cy and safety of clopidogrel in Japanese patients who underwent elective PCI. Although the number of elective PCI procedures performed in Japan is increasing, there have been no studies to date that have provided clinical evidence for the efficacy and safety of antiplatelet drugs in these patient settings. Outside Japan, clopidogrel is widely used as an antiplatelet drug in patients with CAD who have undergone PCI since 3 randomized controlled studies¹⁰⁻¹²⁾ and several registries and meta-analyses¹³⁻¹⁸⁾ suggest that clopidogrel seems to be at least as effective as ticlopidine, and clopidogrel has fewer adverse drug reactions and is better tolerated compared to ticlopidine. In fact, a loading dose of 300 mg of clopidogrel followed by a maintenance dose of 75 mg once daily is used in this setting^{19,20)} and the same regimen will also be applied to Japanese patients for whom PCI is planned, regardless of whether the PCI is elective or urgent.

Conclusion: Clopidogrel was shown to have a benefit-risk profile superior to that of ticlopidine, in the treatment of Japanese patients with stable angina or old myocardial infarction for whom elective PCI is planned. In addition, a change to clopidogrel could provide clinical benefits for patients where treatment with ticlopidine was initiated but hepatic disorders subsequently became apparent.

ACKNOWLEDGMENTS

The authors wish to thank all the investigators, staff, and patients who participated in the study for their valuable contributions.

DISCLOSURE

TI, TK, TU, MN, KI, HY, and YI have received honoraria and/or research funding from Sanofi-Aventis KK and/or served as a consultant to Sanofi-Aventis KK. MK is an employee of Sanofi group.

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