Double#Dose Versus Standard#Dose Clopidogrel According to Smoking Status Among Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

ORIGINAL RESEARCH

Double-Dose Versus Standard-Dose Clopidogrel According to Smoking Status Among Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

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***Background*—**Prior Studies have suggested better outcomes in smokers compared with nonsmokers receiving clopidogrel ("smoker's paradox"). The impact of a more intensive clopidogrel regimen on ischemic and bleeding risks in smokers with acute coronary syndromes requiring percutaneous coronary interventions remains unclear.

***Methods and Results*—**We analyzed 17 263 acute coronary syndrome patients undergoing percutaneous coronary intervention from the CURRENT-OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Symptoms) trial, which compared double-dose (600 mg day 1;150 mg days 2–7; then 75 mg daily) versus standard-dose (300 mg day 1; then 75 mg daily) clopidogrel in acute coronary syndrome patients. The primary outcome was cardiovascular death, myocardial infarction, or stroke at 30 days. Interactions between treatment allocation and smoking status (current smokers versus nonsmokers) were evaluated. Overall, 6394 patients (37.0%) were current smokers. For the comparison of double- versus standard-dose clopidogrel, there were significant interactions in smokers and nonsmokers for the primary outcome (P=0.031) and major bleeding (P=0.002). Double- versus standard-dose clopidogrel reduced the primary outcome among smokers by 34% (hazard ratio [HR] 0.66, 95% confidence interval [CI], 0.50–0.87, P=0.003), whereas in nonsmokers, there was no apparent benefit (HR 0.96, 95% CI, 0.80–1.14, P=0.61). For major bleeding, there was no difference between the groups in smokers (HR 0.77, 95% CI, 0.48–1.24, P=0.28), whereas in nonsmokers, the double-dose clopidogrel regimen increased bleeding (HR 1.89, 95% CI, 1.37–2.60, P<0.0001). Double-dose clopidogrel reduced the incidence of definite stent thrombosis in smokers (HR 0.41, 95% CI, 0.24–0.71) and nonsmokers (HR 0.63, 95% CI, 0.42–0.93; P for interaction=0.19).

***Conclusions*—**In smokers, a double-dose clopidogrel regimen reduced major cardiovascular events and stent thrombosis after percutaneous coronary intervention, with no increase in major bleeding. This suggests that clopidogrel dosing in patients with acute coronary syndromes should be personalized, taking into consideration both ischemic and bleeding risk.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT00335452. **(*J Am Heart Assoc*. 2017;6: e006577. DOI: 10.1161/JAHA.117.006577.)**

Key Words: acute coronary syndrome • antiplatelet • antiplatelet therapy • percutaneous coronary intervention • smoking • stent

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/11/e006577/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- We evaluated the efficacy of a standard-dose (75 mg/d) compared with a 7-day double-dose (150 mg/d) regimen of clopidogrel in current smokers and nonsmokers with acute coronary syndromes (ACS) requiring percutaneous coronary interventions.
- Compared with the standard dose, the 7-day double-dose regimen of clopidogrel reduced the rate of major cardiovascular events in the ACS setting significantly, more among current smokers than in nonsmokers.
- The higher dosing strategy appeared to have less of an effect on increased risk for major bleeding in current smokers than in nonsmokers.
- The double-dose clopidogrel strategy appeared to be particularly effective in heavy smokers (consuming ≥20 cigarettes/d).

What Are the Clinical Implications?

- Smoking is one of the most important preventable risk factors for atherosclerotic diseases and ischemic heart disease, and smoking has a detrimental influence on short- and long-term outcomes in ACS patients.
- It was uncertain whether a higher clopidogrel dose mitigates the elevated risk for early adverse events encountered in current smokers with ACS requiring percutaneous coronary interventions.
- According to our data, a more intensive antiplatelet inhibition may be especially beneficial in smokers presenting with ACS who are referred for early percutaneous coronary intervention.
- Our data also suggest that a personalized clopidogrel-dosing strategy considering risk factors for early adverse outcomes after percutaneous coronary interventions in ACS patients should be applied.

Smoking is one of the most important preventable risk factors for ischemic heart disease and cardiovascular mortality in the general population.[1] Among patients presenting with acute coronary syndromes (ACS), smokers are usually younger and have fewer concomitant health issues, and represent a distinct, but also vulnerable cohort with respect to long-term prognosis. Earlier studies have suggested better short-term outcomes among smokers with myocardial infarction (MI), a phenomenon known as the "smoker's paradox."[2–6] This may be because of the lower age and baseline risk profile in smokers compared with nonsmokers. However, recent studies have highlighted the detrimental influence of smoking on short- and long-term outcome in ACS patients, with a substantially higher risk for re-infarction, stent thrombosis, and death in smokers, irrespective of age.[7–13]

ADP receptor blockers, including clopidogrel, reduce the risk for repeat MI, stroke, and cardiovascular death in patients with an ACS.[14–16] They also reduce the risk for stent thrombosis after percutaneous coronary interventions (PCI) and stenting.[14–16] Despite the advent of new ADP–receptor blockers, such as prasugrel and ticagrelor, clopidogrel remains the most commonly administered thienopyridine after stent placement in most countries. Furthermore, the CURRENT-OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Symptoms) trial has shown that a 7-day double-dose, compared with a standard-dose, regimen of clopidogrel effectively reduced ischemic events and stent thrombosis among patients undergoing PCI for ACS.[16]

Nevertheless, several studies, including data from the clopidogrel landmark trials, suggested differing outcomes among current smokers versus nonsmokers receiving clopidogrel treatment for various cardiovascular conditions (ie, unstable angina or atherosclerotic vascular disease), whereas smoking patients apparently derived greater benefit from clopidogrel.[17,18] These results led to some controversies about the "smoker's paradox" in the context of clopidogrel treatment and its efficacy in current smokers versus nonsmokers.[17,18]

So far, it is uncertain whether a higher clopidogrel dose mitigates the elevated risk for early adverse events including stent thrombosis encountered in current smokers with an ACS undergoing PCI. Therefore, our aim was to assess the influence of a double-dose clopidogrel regimen on clinical outcomes among current smokers versus nonsmokers with ACS undergoing PCI from the CURRENT-OASIS-7 trial.

Methods

Study Design and Patients

This analysis represents a prespecified subgroup analysis of the CURRENT-OASIS 7 trial comparing high-dose versus standard-dose of aspirin and clopidogrel in ACS. This 2×2 factorial trial was conducted between June 2006, and July 2009 at 597 centers in 39 countries. The detailed methodology and the trial's main result have been published earlier.[14–16] In brief, we included patients who had an ACS (with or without ST-segment elevation) confirmed by elevated cardiac enzymes and electrocardiographic evidence of ischemia. Patients were eligible if they were scheduled for early coronary angiography with an intention for PCI, no later than 72 hours after randomization. Our main exclusion criteria were an increased risk of bleeding or active bleeding.[14]

For the present analysis, we included 17 263 patients who underwent a PCI procedure for their index MI with a known smoking status, which represents a subset of the 25 086 patients in the trial, of whom 7823 did not undergo early PCI, and 7 of those undergoing PCI did not have smoking status data available. We defined the smoking status as follows: current smokers were considered as patients smoking at least 1 cigarette (or cigar, or pipe) per day within 30 days and up to the time of admission for their ACS; and nonsmoking patients were defined as former smokers and individuals who never smoked. We also grouped current smokers according to their tobacco/cigarettes consumption, as follows: <10, 10 to 19, and ≥20 cigarettes/d.

The patients had to provide written informed consent to participate. This trial complied with the Declaration of Helsinki. All national regulatory authorities and the ethics committees at the participating centers approved it. This trial was registered with ClinicalTrials.gov, number NCT00335452.

The trial was coordinated by the Population Health Research Institute (McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada), which independently managed the database and performed the primary data analyses. An operations committee, with assistance from an international steering committee and with participation of the sponsor, was responsible for the design, conduct, and reporting of the study. All authors had full access to all the data in the study and had responsibility for the decision to submit the report for publication.

Randomization, Procedures, and Outcomes

The patients were randomized by a 24-hour central automated voice response system. We used permuted block randomization stratified by center.[14–16] A statistician set up a computer-generated random allocation sequence for the data safety and monitoring board. For the clopidogrel dose allocation, patients, those doing the interventions, those evaluating events, and those analyzing the data were masked to group assignment. The aspirin dose allocation was open label, with blinded adjudication of outcomes.

After randomization and before the cardiac catheterization, the patients, who were randomly allocated to double-dose clopidogrel, received a 600-mg loading dose on day 1 followed by 150 mg once daily on days 2 to 7. Those assigned to standard-dose clopidogrel received a 300-mg loading dose on day 1 followed by 75 mg once daily on days 2 to 7. Subsequently, on days 8 to 30, both groups received 75 mg once daily.[14–16]

All participants received a loading dose of aspirin (≥300 mg) on day 1. On days 2 to 30, patients randomly allocated low-dose aspirin received 75 to 100 mg daily, whereas those allocated high-dose aspirin received 300 to 325 mg daily. We strongly discouraged the administration of vitamin K antagonists concurrently with the study drugs during the first 7 days. The other therapies, including anticoagulants, glycoprotein IIb/IIIa antagonists, and the applied stents, were left to the discretion of the treating physician.

Our primary outcome was the composite of cardiovascular death, MI, or stroke from randomization to day 30.[14–16] Secondary outcomes included the primary outcome plus recurrent ischemia, individual components of the composite outcomes, and stent thrombosis as defined by the academic research consortium.[14–16] The applied definitions of outcome events have been described elsewhere.[14] A central committee, blinded for the treatment allocation, adjudicated all efficacy outcomes, including recurrent ischemia, stent thrombosis, and bleeding events.

Statistical Analysis

The analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). For comparison of the baseline demographics according to smoking status (nonsmokers versus current smokers), differences in continuous variables were analyzed by *t* tests, Mann–Whitney *U* test, and differences in categorical variables by χ^2 tests.

All our analyses were based on the intention-to-treat principle. Efficacy and safety analyses were performed with Cox proportional hazards models including terms for treatment group and stratified for admission diagnosis (unstable angina/non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction [STEMI]), aspirin dose, and tertiles of a propensity score for current smoking status in patients undergoing PCI. In order to account for the difference in baseline characteristics between current smokers and nonsmokers, we used a dedicated propensity scoring system for adjustment of the Cox proportional hazards models.

The applied propensity score was derived by using a logistic regression model predicting the probability of current smoking in patients undergoing PCI (n=17 256). We considered the following patient-based baseline variables: age, sex, blood pressure, heart rate, time from symptom onset to randomization, treatment allocation, admission diagnosis ([STEMI] versus unstable angina/non-ST-segment elevation myocardial infarction), pre-randomization anticoagulant use (unfractionated heparin, low-molecular-weight heparin, fondaparinux, glycoprotein IIb/IIIa antagonists), pre-randomization use of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, calcium channel blockers, region (North America/Australia/New Zealand, South America, Western Europe/South Africa, Central and Eastern Europe, Asia), baseline ECG (ST-segment elevation, new left bundle

branch block, ST-segment depression, T-wave inversion, transient ST-segment elevation, none), baseline location of ECG changes (anterior, inferior, other), pre-randomization use of clopidogrel (none, <300 mg, ≥300 mg), pre-randomization use of aspirin, elevated cardiac biomarker, baseline hemoglobin, baseline heart failure (no or yes; if yes, Killip class), prior history of hypertension, dyslipidemia, diabetes mellitus, MI, PCI, or coronary artery bypass graft.

We tested for collinearity among the included variables. The maximum variance inflation factor was 3; therefore, multicollinearity does not appear to be a concern. Additionally, interaction tests were performed to assess the efficacy of the clopidogrel regimens in ACS patients with differing smoking patterns and intensity (nonsmokers, current smokers consuming <10, 10–19, and ≥20 cigarettes/d). Additionally, interaction tests were performed to assess the efficacy of the clopidogrel regimens in ACS patients with differing smoking patterns and intensity (nonsmokers, current smokers consuming <10, 10 to 19, and ≥20 cigarettes/d). Finally, survival curves for the primary outcome and major bleeding events were charted by Kaplan–Meier analyses and the outcomes were compared using log-rank tests. A $P<0.05$ was considered statistically significant.

Results

The baseline characteristics of the 17 263 analyzed patients presenting with ACS and treated with PCI are displayed in Table 1. The mean age was 61.2±11.7 years, 2188 patients (12.7%) were older than 75 years, and 13 029 patients (75.5%) were male. Unstable angina/non-ST-segment elevation myocardial infarction and STEMI presentation were found in 10 899 and 6364 patients, respectively. Overall, 16 323 (94.6%) underwent stent implantation, whereas 9457 (57.9%) received bare-metal stents and 6866 (42.1%) had implanted at least 1 drug-eluting stent. Baseline demographics were basically balanced between the randomly allocated treatment groups (standard versus double-dose clopidogrel regimen); only the number of patients treated with β-blockers and angiotensin-2 receptor blockers differed ($P=0.009$ and $P=0.043$, also highlighted in the Tables S1 and S2).

Current smokers (n=6394) were significantly younger, more frequently males, and more often had a STEMI presentation. They also had fewer comorbidities, including diabetes mellitus, hypertension, dyslipidemia, and established coronary artery disease (Table 1). Current smokers also received more frequently glycoprotein IIb/IIIa inhibitors. The primary outcome, including cardiovascular death, MI, or stroke, did not significantly differ between current smokers compared with nonsmokers (204 [3.2%] versus 514 [4.7%]; adjusted hazard ratio [HR] 0.91, 95% confidence interval [CI], 0.76–1.09, $P=0.30$, respectively, Table 2). There was no significant difference in rates of stent thrombosis between current smokers and nonsmokers (112 [1.8%] versus 221 [2.0%]; HR 1.03, 95% CI, 0.80–1.33, $P=0.80$). Overall, nonsmokers, in comparison to current smokers, showed a trend for a higher rate of major bleedings (166 [1.5%] versus 71 [1.1%]; HR 1.32, 95% CI, 0.97–1.79, $P=0.077$), as displayed in Table 2.

Focusing on the efficacy of double- versus standard-dose clopidogrel, the primary outcome occurred in 330 (3.9%) patients treated with the double-dose regimen and in 392 (4.5%) patients receiving the standard dose (HR 0.86, 95% CI, 0.74–1.00, $P=0.051$; Figure 1). However, there was a significant treatment interaction in active smokers and nonsmokers for the primary outcome (P for interaction=0.031). Double- versus standard-dose clopidogrel resulted in a 34% reduction of the primary outcome among current smokers (HR 0.66, 95% CI, 0.50–0.87, $P=0.003$), whereas in nonsmokers, there was no apparent benefit (HR 0.96, 95% CI, 0.80–1.14, $P=0.61$), as shown in Figure 1. This treatment effect was furthermore highlighted among our survival analyses for the primary outcome. (Figure 2A).

With regard to safety, the double- compared with the standard-dose clopidogrel regimen increased the risk for severe and major bleeding (96 [1.1%] versus 72 [0.8%]; HR 1.38, 95% CI, 1.02–1.88, $P=0.038$; and 139 [1.6%] versus 99 [1.1%]; HR 1.45, 95% CI, 1.12–1.88), $P=0.005$, respectively), as displayed in Figure 1. For major bleeding, there was a significant treatment interaction between current smokers and nonsmokers receiving either the double or standard clopidogrel dose (P for interaction=0.002). There was no apparent difference between the clopidogrel dosing groups in current smokers (31 [1.0%] versus 40 [1.3%]; HR 0.77, 95% CI, 0.49–1.24, $P=0.28$), whereas in nonsmokers, the double- compared with standard-dose clopidogrel regimen significantly increased major bleeding (107 [2.0%] versus 59 [1.1%]; HR 1.89, 95% CI, 1.37–2.60, $P<0.0001$, Figure 1). A similar trend was found for severe bleeding (P for interaction=0.058). The different impact of the 2 clopidogrel-dosing strategies on major bleedings in current smokers and nonsmokers is also highlighted in Figure 2B.

Overall, administration of a double- compared with a standard-dose clopidogrel regimen resulted in a reduction of new MI or stent thrombosis (251 [2.9%] versus 322 [3.7%]; HR 0.80, 95% CI, 0.68–0.95, $P=0.009$). The double- versus standard-dose of clopidogrel led to a 30% reduction in stent thrombosis (135 [1.6%] versus 200 [2.3%]; HR 0.70, 95% CI, 0.56–0.87, $P=0.001$), as displayed in Figure 1. In fact, the double- versus standard-dose regimen reduced the incidence of definite stent thrombosis in current smokers (18 [0.6%] versus 44 [1.4%]; HR 0.41, 95% CI, 0.24–0.71, $P=0.001$) and nonsmokers (40 [0.8%] versus 66 [1.2%]; HR 0.63, 95% CI, 0.42–0.93, $P=0.021$; P for interaction=0.19).

Table 1. Baseline Characteristics Grouped by Smoking Status and Clopidogrel Regimens (Standard Vs Double-Dose)

		Current Smokers			Nonsmokers*		
	Overall	Standard-Dose Clopidogrel Regimen	Double-Dose Clopidogrel Regimen		Standard-Dose Clopidogrel Regimen	Double-Dose Clopidogrel Regimen	
	(n=17 263)	(n=3189)	(n=3205)	*P* Value†	(n=5513)	(n=5349)	*P* Value†
Age, y	61.2±11.7	55.3±9.8	55.3±10.1	0.94	64.6±11.1	64.6±11.2	0.94
Age >75 y, %	2188 (12.7)	92 (2.9)	94 (2.9)	0.91	999 (18.1)	1000 (18.7)	0.44
Males, %	13 029 (75.5)	2668 (83.7)	2701 (84.3)	0.51	3851 (69.9)	3804 (71.1)	0.15
Presentation, %							
STEMI	6364 (36.9)	1432 (44.9)	1457 (45.5)	0.65	1750 (31.7)	1719 (32.1)	0.66
UA/NSTEMI	10 899 (63.1)	1757 (55.1)	1748 (54.5)	0.65	3763 (68.3)	3630 (67.9)	0.66
Comorbidities, %							
Diabetes mellitus, %	3844 (22.3)	476 (14.9)	498 (15.5)	0.49	1457 (26.4)	1411 (26.4)	0.95
Hypertension, %	10 197 (59.1)	1495 (46.9)	1536 (47.9)	0.39	3622 (65.7)	3540 (66.2)	0.59
Dyslipidemia, %	6953 (40.3)	1115 (35)	1175 (36.7)	0.15	2391 (43.4)	2270 (42.5)	0.33
Previous MI, %	2933 (17.0)	363 (11.4)	412 (12.9)	0.071	1096 (19.9)	1061 (19.8)	0.95
Previous PCI, %	2515 (14.6)	308 (9.7)	305 (9.5)	0.85	956 (17.3)	945 (17.7)	0.65
Peripheral arterial disease, %	753 (4.4)	135 (4.2)	134 (4.2)	0.92	246 (4.5)	236 (4.4)	0.90
Antithrombotics before randomization, %							
Aspirin	6444 (37.3)	787 (24.7)	793 (24.7)	0.95	2450 (44.4)	2412 (45.1)	0.49
Clopidogrel	3494 (20.2)	464 (14.6)	509 (15.9)	0.14	1291 (23.4)	1228 (23.0)	0.57
Unfractionated heparin	6685 (38.7)	1205 (37.8)	1238 (38.6)	0.49	2165 (39.3)	2071 (38.7)	0.54
LMWH	6619 (38.4)	1315 (41.2)	1256 (39.2)	0.095	2008 (36.4)	2039 (38.1)	0.071
Fondaparinux	599 (3.1)	115 (3.6)	102 (3.2)	0.35	193 (3.5)	189 (3.5)	0.93
GP IIbIIIa inhibitors	4383 (25.4)	893 (28.0)	887 (27.7)	0.77	1299 (23.6)	1301 (24.3)	0.36
Fibrinolytics‡	534 (8.4)	126 (8.8)	131 (9.0)	0.86	144 (8.2)	133 (7.8)	0.59
Antithrombotics administered during PCI and hospital admission, %							
Unfractionated heparin	15 151 (87.8)	2789 (87.5)	2853 (89)	0.053	4834 (87.7)	4669 (87.3)	0.53
LMWH	8628 (50.0)	1707 (53.5)	1674 (52.2)	0.30	2598 (47.1)	2646 (49.5)	0.015
Fondaparinux	779 (4.5)	141 (4.4)	133 (4.1)	0.59	259 (4.7)	246 (4.6)	0.81
Bivalirudin	960 (5.6)	148 (4.6)	154 (4.8)	0.76	331 (6.0)	327 (6.1)	0.82
GP IIbIIIa inhibitors	7010 (40.6)	1387 (43.5)	1397 (43.6)	0.94	2120 (38.5)	2103 (39.3)	0.36
Postrandomization therapy, %							
β-Blockers	14 555 (84.3)	2685 (84.2)	2735 (85.3)	0.21	4590 (83.3)	4542 (84.9)	0.019
ACE-inhibitors	11 989 (69.5)	2269 (71.2)	2281 (71.2)	0.99	3759 (68.2)	3678 (68.8)	0.53
AT-2-antagonists	1588 (9.2)	224 (7)	201 (6.3)	0.23	615 (11.2)	547 (10.2)	0.12
Ca-channel blockers	2352 (13.6)	333 (10.4)	320 (10)	0.55	864 (15.7)	835 (15.6)	0.93
Statins	15 575 (90.2)	2927 (91.8)	2932 (91.5)	0.66	4932 (89.5)	4780 (89.4)	0.85
Proton-pump inhibitors	5295 (39.9)	1044 (40.4)	1043 (39.8)	0.65	1607 (39.1)	1599 (40.5)	0.22
Lesions treated, %	17 670 (100)	3174 (100)	3248 (100)	–	5727 (100)	5521 (100)	–
Left main	278 (1.6)	49 (1.5)	38 (1.2)		91 (1.6)	100 (1.8)	
Left anterior descending	6131 (34.7)	1000 (31.5)	1055 (32.5)		2053 (35.8)	2023 (36.6)	
Left circumflex	4657 (26.4)	878 (27.7)	880 (27.1)		1498 (26.2)	1401 (25.4)	
Right coronary artery	6159 (34.8)	1217 (38.3)	1235 (38.0)		1906 (33.3)	1801 (32.6)	

Continued

Table 1. Continued

		Current Smokers			Nonsmokers*		
	Overall	Standard-Dose Clopidogrel Regimen	Double-Dose Clopidogrel Regimen		Standard-Dose Clopidogrel Regimen	Double-Dose Clopidogrel Regimen	
	(n=17 263)	(n=3189)	(n=3205)	*P* Value†	(n=5513)	(n=5349)	*P* Value†
Saphenous vein/arterial graft	445 (2.5)	30 (0.9)	40 (1.2)		179 (3.1)	196 (3.6)	
Visible angiographic thrombus before PCI	5465 (32.8)	1152 (37.3)	1200 (38.7)	0.27	1595 (30)	1516 (29.3)	0.41
Stents, %							
Bare metal stents (only)	9457 (57.9)	1819 (59.7)	1851 (60.5)	0.55	2950 (57.0)	2832 (56.3)	0.45
Drug-eluting stents	6866 (42.1)	1228 (40.3)	1211 (39.5)	0.55	2224 (43.0)	2201 (43.7)	0.45
Laboratory parameters							
Hemoglobin, g/dL	14.12±1.72	14.59±1.59	14.59±1.63	0.96	13.85±1.72	13.84±1.71	0.88
Glomerular filtration rate, mL/min per 1.73 m^{2}§	81±26	89±28	88±26	0.52	77±24	78±26	0.37

Data are mean (SD) or number (percentage), as appropriate. ACE indicates angiotensin-converting enzyme; GP IIbIIa inhibitors, glycoprotein IIb/IIIa inhibitors; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

*Nonsmokers were classified as current nonsmokers and former smokers.

†*P* values were based on Student *t* tests, Mann–Whitney *U* tests or χ^2 tests, as appropriate.

‡As initial reperfusion strategy.

§Estimated by applying Modification of Diet in Renal Disease Study (MDRD) equation.

Evaluating the efficacy of double- versus standard-dose clopidogrel in ACS patients with differing smoking patterns (nonsmokers, current smokers consuming <10, 10–19, and ≥20 cigarettes/d), we found significant treatment interactions with regard to the primary outcome, risks for repeat MI, stent thrombosis, and major bleedings (*P* for interactions 0.016, 0.026, 0.017, and 0.018, respectively) among those groups, as shown in Table 3. In comparison to non-, light-, and moderate smokers, heavy smokers (consuming ≥20 cigarettes/d) showed a highly significant reduction of the primary end point, the rates of MI and stent thrombosis (*P* for all <0.0001), without relevant increase in bleeding risk, if treated with a double- compared with a standard-dose clopidogrel regimen (Table 3).

Discussion

In this large cohort of patients with ST- and non-ST-segment elevation ACS undergoing early PCI in the CURRENT-OASIS 7 trial, we found that a 7-day double-dose regimen of clopidogrel, in comparison with the standard dose, had significantly greater benefit in reducing the primary outcome in current

Table 2. Clinical Outcomes in Smokers Vs Nonsmokers

	Smoking Status			
Events	Current Smokers (n=6394)	Nonsmokers (n=10 862)	Adjusted HR (95% CI)	*P* Value
Cardiovascular death, MI, or stroke	204 (3.2)	514 (4.7)	0.91 (0.76–1.09)	0.30
Cardiovascular death	83 (1.3)	242 (2.2)	0.87 (0.66–1.14)	0.31
MI	117 (1.8)	280 (2.6)	0.88 (0.69–1.12)	0.29
Stroke	18 (0.3)	48 (0.4)	1.09 (0.60–1.97)	0.79
Stent thrombosis	112 (1.8)	221 (2.0)	1.03 (0.80–1.33)	0.80
Major bleed	71 (1.1)	166 (1.5)	1.32 (0.97–1.79)	0.07
Severe bleed	59 (0.9)	108 (1.0)	1.48 (1.04–2.11)	0.03

Data are numbers (%), unless otherwise indicated. HR (95% CI) indicates hazard ratio (95% confidence interval); MI, myocardial infarction.

	2N	Standard Event(%)	Double Event(%)	HR(95%CI)	P	P for interaction
CV death/MI/Stroke						
Overall	17263	392 (4.5)	330 (3.9)	0.86 (0.74 - 1.00)	0.051	
Non-smokers	10862	269 (4.9)	245 (4.6)	0.96 (0.80 - 1.14)	0.608	
Smokers	6394	122 (3.8)	82 (2.6)	0.66 (0.50 - 0.87)	0.003	0.031
CV death						
Overall	17263	169 (1.9)	160 (1.9)	0.97 (0.78 - 1.21)	0.812	
Non-smokers	10862	120 (2.2)	122 (2.3)	1.08 (0.83 - 1.39)	0.573	
Smokers	6394	48 (1.5)	35 (1.1)	0.70 (0.45 - 1.09)	0.118	0.124
MI						
Overall	17263	226 (2.6)	172 (2.0)	0.78 (0.64 - 0.96)	0.017	
Non-smokers	10862	152 (2.8)	128 (2.4)	0.89 (0.70 - 1.12)	0.312	
Smokers	6394	73 (2.3)	44 (1.4)	0.60 (0.41 - 0.87)	0.007	0.084
Stroke						
Overall	17263	36 (0.4)	30 (0.4)	0.87 (0.54 - 1.42)	0.582	
Non-smokers	10862	26 (0.5)	22 (0.4)	0.91 (0.51 - 1.62)	0.756	
Smokers	6394	10 (0.3)	8 (0.3)	0.76 (0.30 - 1.93)	0.568	0.753
Stent thrombosis						
Overall	17263	200 (2.3)	135 (1.6)	0.70 (0.56 - 0.87)	0.001	
Non-smokers	10862	127 (2.3)	94 (1.8)	0.79 (0.60 - 1.03)	0.081	
Smokers	6394	72 (2.3)	40 (1.3)	0.54 (0.37 - 0.80)	0.002	0.127
Major bleed						
Overall	17263	99 (1.1)	139 (1.6)	1.45 (1.12 - 1.88)	0.005	
Non-smokers	10862	59 (1.1)	107 (2.0)	1.89 (1.37 - 2.60)	0.000	
Smokers	6394	40 (1.3)	31 (1.0)	0.77 (0.49 - 1.24)	0.283	0.002
Severe bleed						
Overall	17263	72 (0.8)	96 (1.1)	1.38 (1.02 - 1.88)	0.038	
Non-smokers	10862	41 (0.7)	67 (1.3)	1.71 (1.16 - 2.52)	0.007	
Smokers	6394	31 (1.0)	28 (0.9)	0.91 (0.54 - 1.52)	0.708	0.058

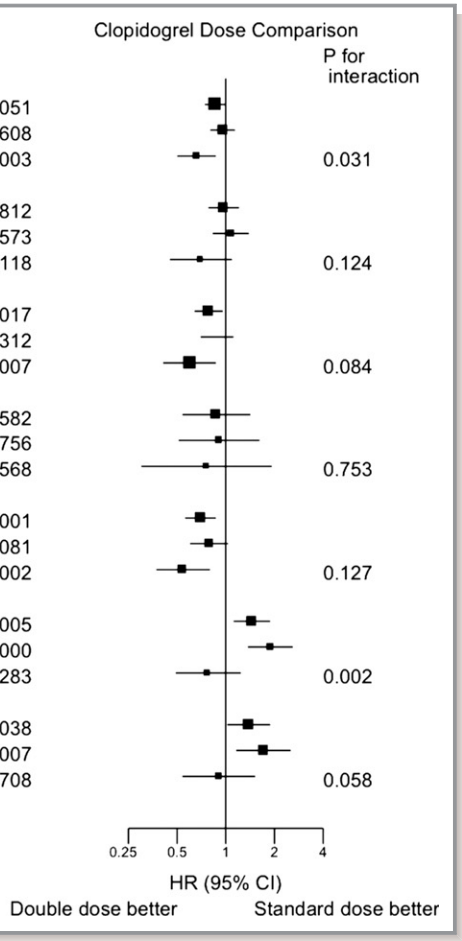

Figure 1. Outcomes for the clopidogrel dose comparison according to smoking status (current smokers vs nonsmokers). Data are number (%), unless otherwise indicated. CV indicates cardiovascular; HR (95% CI), hazard ratio (95% confidence interval); MI, myocardial infarction.

smokers than in nonsmokers. In active smokers, the primary outcome of cardiovascular death, MI, and stroke, was reduced by 34% (95% CI, 0.50–0.87), without an apparent increase in major bleeding. By contrast, this benefit was not observed in nonsmokers, but there was an increase in major bleeding in those patients. Stent thrombosis was significantly reduced in both current smokers and nonsmokers. Overall, the double-dose clopidogrel regimen might be more effective in heavy smokers (consuming ≥20 cigarettes/d). Compared with nonsmokers, current smokers with an ACS were approximately 1 decade younger, had fewer concomitant diseases, and presented more frequently with a STEMI, and had lower absolute rates of the primary outcome. However, despite the younger age, the rates of stent thrombosis were similar in current smokers and nonsmokers.

The clinical efficacy of clopidogrel in smokers and nonsmokers with ACS and the "smoker's paradox" remain controversial topics. Several studies have shown significant interactions in outcomes among current smokers versus nonsmokers treated with clopidogrel.[8,19–21] An analysis of the CLARITY-TIMI (Clopidogrel and Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction) 28 trial revealed significantly lower risk for repeat ischemic events in smokers, who smoked at least 10 cigarettes/d and were additionally treated with clopidogrel to aspirin, compared with nonsmokers.[19] In an analysis from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, clopidogrel therapy among current smokers was related to a 32% reduction in all-cause mortality compared with current smokers treated with placebo (4.9% versus 7.2%, respectively, *P* for interaction=0.018). Additionally, a post hoc analysis of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial was in line with those studies by indicating that patients in the clopidogrel-treated smoker group had a significantly lower rate of the primary outcome (consisting of ischemic stroke, MI, or vascular death) compared with the nonsmoker group (*P* for interaction=0.01).[21] Those results were lately questioned by a pooled analysis including 1314 patients undergoing PCI, which found no significant differences in platelet reactivity in current and nonsmokers treated with clopidogrel after adjusting for hemoglobin levels.[22] This

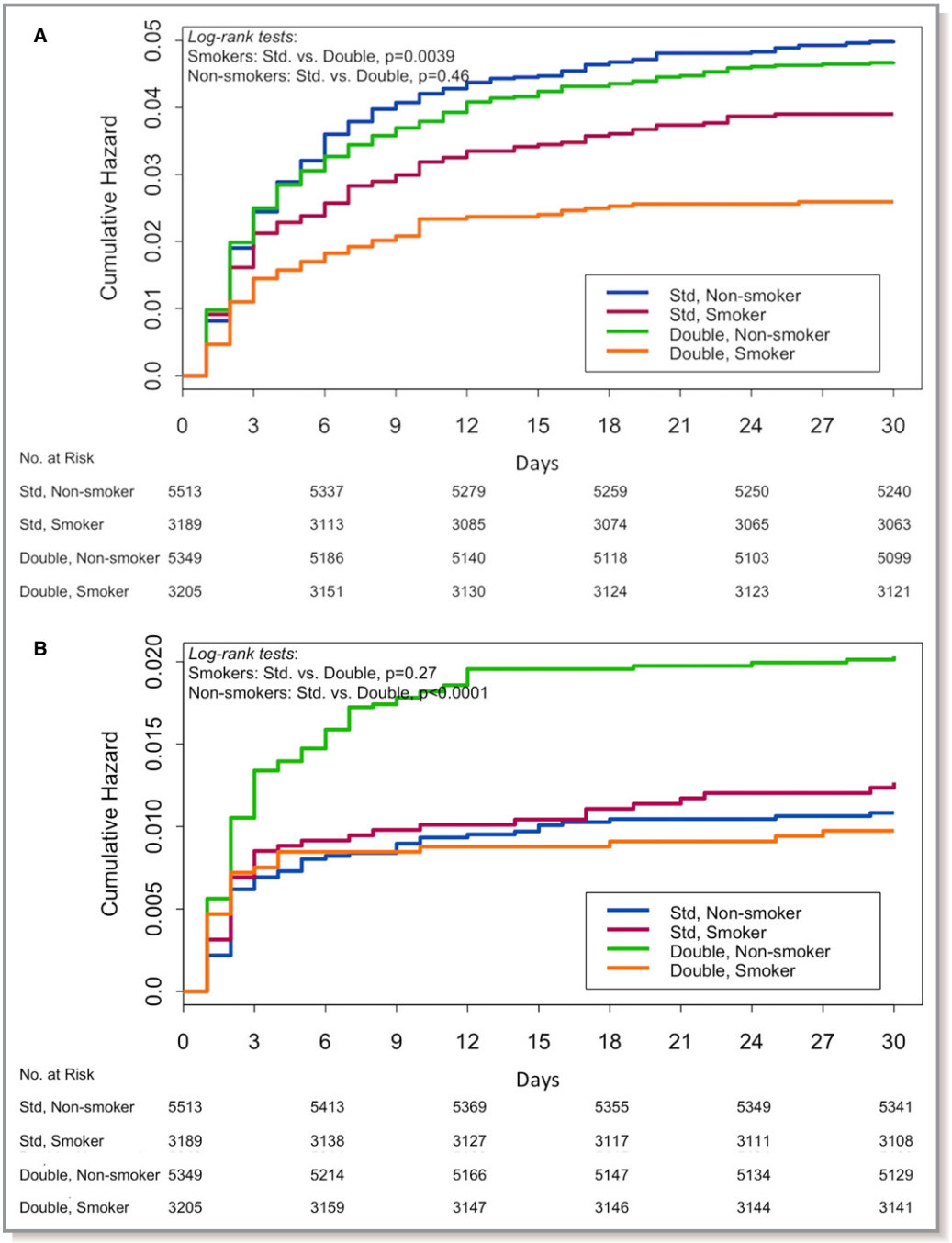

Figure 2. Kaplan–Meier curves for the primary outcome of cardiovascular death, myocardial infarction, or stroke (A) and major bleeding (B) in current smokers and nonsmokers receiving either a standard (Std.) or double-dose clopidogrel regimen. No. indicates number.

association and its clinical implications remain partially unclear and require further investigation. In this context, our analysis may render important additional insights about clopidogrel's activity and efficacy among smokers and nonsmokers.

Smoking negatively influences the coagulation system at multiple levels: first, it triggers platelet aggregation; second, it promotes a procoagulatory state with increased levels of factor VII and fibrinogen, but also decreased fibrinolytic activity; third, smoking causes endothelial dysfunction, which also impairs healing of the endothelium after stenting and in turn increases the risk for stent thrombosis and in-stent restenosis.[23,24]

The pharmacokinetics and pharmacodynamics of clopidogrel may be influenced by multiple factors, including smoking status, genetic polymorphisms, and other medications metabolized through the cytochrome P450 system.[19,21,25–29]

Table 3. Efficacy and Safety Outcomes for the Clopidogrel Dose Comparison According to Smoking Patterns and Intensity

		Clopidogrel Dose		Standard Vs Double-Dose Clopidogrel		
Events	Smoking Status*	Standard (n=8702)	Double (n=8554)	Adjusted HR (95% CI)	*P* Value	*P* for Interaction
Cardiovascular death, MI, or stroke	Nonsmokers	269 (4.9)	245 (4.6)	0.96 (0.80–1.14)	0.608	0.016
	Current smokers, <10 cigarettes/d	17 (4.3)	22 (5.2)	1.21 (0.64–2.28)	0.567	
	Current smokers, 10 to 19 cigarettes/d	27 (3.6)	22 (2.9)	0.78 (0.45–1.37)	0.393	
	Current smokers, ≥20 cigarettes/d	78 (3.8)	38 (1.9)	0.48 (0.33–0.71)	<0.0001	
Cardiovascular death	Nonsmokers	120 (2.2)	122 (2.3)	1.08 (0.83–1.39)	0.573	0.314
	Current smokers, <10 cigarettes/d	8 (2)	10 (2.3)	1.11 (0.43–2.87)	0.823	
	Current smokers, 10 to 19 cigarettes/d	10 (1.3)	6 (0.8)	0.58 (0.21–1.60)	0.292	
	Current smokers, ≥20 cigarettes/d	30 (1.5)	19 (0.9)	0.62 (0.35–1.11)	0.106	
MI	Nonsmokers	152 (2.8)	128 (2.4)	0.89 (0.70–1.12)	0.312	0.026
	Current smokers, <10 cigarettes/d	9 (2.3)	12 (2.9)	1.31 (0.55–3.11)	0.545	
	Current smokers, 10 to 19 cigarettes/d	17 (2.3)	15 (2)	0.85 (0.42–1.70)	0.645	
	Current smokers, ≥20 cigarettes/d	47 (2.3)	17 (0.8)	0.37 (0.21–0.64)	<0.0001	
Stroke	Nonsmokers	26 (0.5)	22 (0.4)	0.91 (0.51–1.62)	0.756	0.999
	Current smokers, <10 cigarettes/d	1 (0.3)	0 (0)	0 (0–0)	0.997	
	Current smokers, 10 to 19 cigarettes/d	2 (0.3)	2 (0.3)	0.87 (0.12–6.20)	0.890	
	Current smokers, ≥20 cigarettes/d	7 (0.3)	6 (0.3)	0.85 (0.28–2.52)	0.765	
Stent thrombosis	Nonsmokers	127 (2.3)	94 (1.8)	0.79 (0.60–1.03)	0.081	0.017
	Current smokers, <10 cigarettes/d	4 (1)	9 (2.1)	2.27 (0.69–7.45)	0.175	
	Current smokers, 10 to 19 cigarettes/d	14 (1.9)	11 (1.4)	0.77 (0.35–1.71)	0.527	
	Current smokers, ≥20 cigarettes/d	54 (2.6)	20 (1)	0.36 (0.22–0.61)	<0.0001	
Major bleed	Nonsmokers	59 (1.1)	107 (2)	1.89 (1.37–2.60)	<0.0001	0.018
	Current smokers, <10 cigarettes/d	6 (1.5)	4 (0.9)	0.66 (0.19–2.36)	0.525	
	Current smokers, 10 to 19 cigarettes/d	17 (2.3)	12 (1.6)	0.66 (0.32–1.38)	0.272	
	Current smokers, ≥20 cigarettes/d	17 (0.8)	15 (0.7)	0.91 (0.45–1.85)	0.804	
Severe bleed	Nonsmokers	41 (0.7)	67 (1.3)	1.71 (1.16–2.52)	0.007	0.222
	Current smokers, <10 cigarettes/d	4 (1)	2 (0.5)	0.48 (0.09–2.64)	0.400	
	Current smokers, 10 to 19 cigarettes/d	13 (1.8)	12 (1.6)	0.87 (0.40–1.90)	0.722	
	Current smokers, ≥20 cigarettes/d	14 (0.7)	14 (0.7)	1.05 (0.49–2.25)	0.890	

Data are numbers (%), unless otherwise indicated. HR (95% CI) indicates hazard ratio (95% confidence interval); MI, myocardial infarction.
*Patients (n): Nonsmokers, 6747; light smokers (<10 cigarettes/d), 1368; moderate smokers (10–19 cigarettes/d), 1368; and heavy smokers (≥20 cigarettes/d), 6594.

Smoking, in particular, directly promotes the activity of cytochrome P450 (CYP) 1A2 and 2B6, which are important isoenzymes for the metabolic activation of clopidogrel.[19,21,26,29] Consequently, a higher clopidogrel dose in current smokers may result in a higher level of its active metabolite, resulting in a greater antiplatelet effect.

Regarding the newer antiplatelet agents and their interaction with smoking, the recently published PARADOX (Prospective, Randomized Trial of Clopidogrel and Prasugrel in Smokers and Non-Smokers) study indicated that prasugrel had a greater active metabolite level and pharmacodynamic efficacy compared with clopidogrel irrespective of the smoking status.[29] The same applies for ticagrelor, which is more effective than clopidogrel, regardless in both smokers and nonsmokers.[9] In terms of clinical outcomes, no interactions were found between non- and current smokers with an ACS in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial.[30] However, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial, which enrolled ACS patients age <75 years not

undergoing revascularization, revealed a significant interaction between smokers and nonsmokers treated with prasugrel compared with clopidogrel with regard to the composite primary end point of death from cardiovascular causes, nonfatal MI, or stroke. In fact, this outcome was reduced by 46% among smokers receiving prasugrel instead of clopidogrel (HR 0.54 [95% CI, 0.39–0.74]), whereas in nonsmokers this effect was not seen (HR 1.06 [95% CI, 0.90–1.24]; *P* for interaction<0.0001).[31]

If a double- compared with a standard-dose clopidogrel regimen reduces the risk of cardiovascular death, MI, or stroke in all current versus nonsmokers with ACS, also including patients receiving only medical management has been tested in the CURRENT-OASIS 7 patient population, as published earlier.[15] There, we found a nonsignificant reduction of the primary outcome with the double- versus standard dosing regimen (2.9% versus 3.6%; HR 0.80 [95% CI, 0.63–1.02, *P*=0.07]) among current smokers (n=8373), but no significant difference among nonsmokers (n=16 701, 4.8% versus 4.8%; HR 0.99 [95% CI, 0.86–1.14], *P*=0.89; *P* for interaction=0.14).[15] Although there seems to be a trend suggesting a possible advantage of the higher clopidogrel regimen in all current smokers with ACS presentation, irrespective of their PCI status, more data are required to confirm this hypothesis.

Finally, one needs to take into account that the double-dose clopidogrel regimen also increased the rates of hemorrhagic events. However, the bleeding rates were lower among current smokers compared with nonsmokers. This might be partially explained by the differences in the baseline characteristics between current and nonsmokers, including among others, higher prevalence of females, higher age, worse renal function, and lower hemoglobin levels among the nonsmoking patients, which are known predictors for bleeding events in ACS patients.[32,33] Since bleeding complications are associated with worse outcomes and high mortality rates in ACS patients treated with PCI, physicians should aim for a personalized antithrombotic strategy, which carefully weighs the treatment risks and benefits.[32,33] As indicated by our study, this seems also to apply for the clopidogrel dosing in ACS patients.

Our results should be interpreted in the context of some limitations. First, this is a subgroup analysis and should therefore be interpreted as hypothesis-generating. However, it is noteworthy that the sample size is very large, the treatment groups are randomized, and the interaction *P* value for treatment effect in current smokers and nonsmokers was significant. Second, we are also not able to provide pharmacokinetic, dynamic, and genetic data, which may have rendered additional insights about clopidogrel's interaction with smoking. Third, follow-up was only 30 days, which is relatively short. However, the highest risk of thrombotic events after ACS occurs within the first 30 days. Finally, information about post-PCI smoking habits has not been collected, which might have also added important insights in this study's context.

Conclusions

Compared with the standard dose, a 7-day double-dose regimen of clopidogrel reduced the rate of major cardiovascular events in the ACS setting significantly more among current smokers than in nonsmokers. It also had less of an effect on increased risk for major bleeding in current smokers than in nonsmokers. The double-dose clopidogrel strategy appeared to be particularly effective in heavy smokers (consuming ≥20 cigarettes/d). Therefore, a more intensive antiplatelet inhibition may be especially beneficial in smokers presenting with ACS who are referred for early PCI. These data also suggest that a personalized clopidogrel-dosing strategy considering risk factors for early adverse outcomes after PCI in ACS patients should be applied.

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SUPPLEMENTARY MATERIAL

Table S1 Baseline characteristics grouped by smoking status

	Overall *(n=17,263)*	***Non-smoker***[†] *(n=10,862)*	***Current smoker*** *(n=6,394)*	***P-value***[*]
Age (years)	61.2±11.7	64.6±11.2	55.3±9.9	<0.0001
Age >75years (%)	2,188 (12.7)	1,999 (18.4)	186 (2.9%)	<0.0001
Males (%)	13,029 (75.5)	7,655 (70.5)	5,369 (84.0)	<0.0001
Presentation (%):				
STEMI	6,364 (36.9)	3,469 (31.9)	2,889 (45.2)	<0.0001
UA/ NSTEMI	10,899 (63.1)	7,393 (68.1)	3,505 (54.8)	<0.0001
Diabetes mellitus (%)	3,844 (22.3)	2,868 (26.4)	974 (15.2)	<0.0001
Hypertension (%)	10,197 (59.1)	7,162 (65.9)	3,031 (47.4%)	<0.0001
Dyslipidemia (%)	6,953 (40.3)	4,661 (42.9)	2,290 (35.8)	<0.0001
Previous MI (%)	2,933 (17.0)	2,157 (19.9)	775 (12.1)	<0.0001
Previous PCI (%)	2,515 (14.6)	1,901 (17.5)	613 (9.6)	<0.0001
Peripheral arterial disease (%)	753 (4.4)	482 (4.4)	269 (4.2)	0.47
Antithrombotics prior to randomization (%):				
Aspirin	6,444 (37.3)	4,862 (44.8)	1,580 (24.7)	<0.0001
Clopidogrel	3,494 (20.2)	2,519 (23.2)	973 (15.2)	<0.0001
Unfractionated heparin	6,685(38.7)	4,236(39)	2,443(38.2)	0.31
LMWH	6,619(38.4)	4,047(37.3)	2,571(40.2)	<0.0001
Fondaparinux	599(3.5)	382(3.5)	217(3.4)	0.67
GP IIbIIIa inhibitors	4,383(25.4)	2,600(23.9)	17,80(27.8)	<0.0001
Fibrinolytics[‡]	534 (8.4)	277 (8.0)	257 (8.9)	0.19
Antithrombotics administered during PCI and hospital admission (%):				
Unfractionated heparin	15,151 (87.8)	9,503 (87.5)	5,642 (88.2)	0.15
LMWH	8’628 (50.0)	5’244 (48.3)	3’381 (52.9)	<0.0001
Fondaparinux	779 (4.5)	505 (4.6)	274 (4.3)	0.27
Bivalirudin	960 (5.6)	658 (6.1)	302 (4.7)	<0.0001
GP IIbIIIa inhibitors	7’010 (40.6)	4’223 (38.9)	2’784 (43.5)	<0.0001
Post-randomization therapy (%):				
β-blockers	14,555 (84.3)	9,132 (84.1)	5,420 (84.8)	0.23
ACE-inhibitors	11,989 (69.5)	7,437 (68.5)	4,550 (71.2)	<0.0001
AT-2-antagonists	1,588 (9.2)	1,162 (10.7)	425 (6.6)	<0.0001
Ca-channel blockers	2,352 (13.6)	1,699 (15.6)	653 (10.2)	<0.0001
Statins	15,575 (90.2)	9,712 (89.4)	5,859 (91.6)	<0.0001
Proton-pump inhibitors	5,295 (39.9)	3,206 (39.8)	2,087 (40.1)	0.74
Lesions treated (%):	17,671	11,248 -	6,418	-

Left main	279(1.6)	191 (1.7)	87 (1.4)	
Left anterior descending	6,130 (34.7)	4,076 (36.2)	2,054 (32.0)	
Left circumflex	4,656 (26.3)	2,900) (25.8)	1,756 (27.4)	
Right coronary artery	6,161 (34.9)	3,706 (32.9)	2,451 (38.2)	
Saphenous vein / arterial graft	445 (2.5)	375 (3.3)	70 (1.1)	
Visible angiographic thrombus before PCI	5,466/16675 (32.8)	3,111/10484 (29.7)	2,353/6186 (38.0)	<0.0001
Stents (%)*:*				
Bare metal stents (only)	9,457 (57.9)	5,782 (56.6)	3,670 (60.1)	<0.0001
Drug eluting stents	6,866 (42.1)	4,425 (43.4)	2,439 (39.9)	<0.0001
Laboratory parameters:				
Hemoglobin (g/dL)	14.1±1.7	13.8±1.7	14.6±1.6	<0.0001
Glomerular filtration rate (mL/min/1.73m^2) [§]	81±26	77±25	88±27	<0.0001

Data are mean (standard deviation) or number (percentage), as appropriate. GP IIbIIa inhibitors = Glycoprotein IIb/IIIa inhibitors; LMWH = Low molecular weight heparin; MI = Myocardial infarction; NSTEMI = Non-ST-segment elevation myocardial infarction; PCI = Percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = Unstable angina.

[*] P values were based on student's t-tests, Mann-Whitney U- tests or Chi-square tests, as appropriate.

[†] *Non*-smokers were classified as current non-smokers and former smokers.

[‡] As initial reperfusion strategy.

[§] Estimated by applying Modification of Diet in Renal Disease Study (MDRD) equation.

Table S2 Baseline characteristics grouped by clopidogrel regimen (standard versus double-dose)

	Standard-dose clopidogrel regimen *(n=8,702)*	***Double-dose clopidogrel regimen*** *(n=8,554)*	***P-value****
Age (years)	61.2±11.6	61.2±11.7	0.69
Age >75years (%)	1,092 (12.5)	1,096 (12.8)	0.61
Males (%)	6,520 (74,9)	6,509 (76.0)	0.086
Presentation (%):			
STEMI	3,183 (36.6)	3,181 (37.2)	0.42
UA/ NSTEMI	5,520 (63.4)	5,379 (62.8)	0.42
Smoking status (%):			
Current smoker	3189 (36.6)	3205 (37.5)	0.26
Never smoked	3441 (39.5)	3306 (38.6)	0.23
Former smoker	2072 (23.8)	2043 (23.9)	0.91
Diabetes mellitus (%)	1,934 (22.2)	1,910 (22.3)	0.89
Hypertension (%)	5,117 (58.8)	5,080 (59.4)	0.45
Dyslipidemia (%)	3,506 (40.3)	3,447 (40.3)	0.99
Previous MI (%)	1,459 (16.8)	1,474 (17.2)	0.43
Previous PCI (%)	1,264 (14.5)	1,251 (14.6)	0.87
Peripheral arterial disease (%)	381 (4.4)	372 (4.3)	0.92
Antithrombotics prior to randomization (%):			
Aspirin	3,237 (37.2)	3,207 (37.5)	0.71
Clopidogrel	1,755 (20.2)	1,739 (20.3)	0.81
Unfractionated heparin	3,371(38.7)	3,314(38.7)	0.97
LMWH	3,323(38.2)	3,296(38.5)	0.68
Fondaparinux	308(3.5)	291(3.4)	0.61
GP IIbIIIa inhibitors	2,192(25.2)	2,191(25.6)	0.55
Fibrinolytics‡	270 (8.5)	264 (8.3)	0.79
Antithrombotics administered during PCI and hospital admission (%):			
Unfractionated heparin	7'624 (87.6)	7'527 (87.9)	0.51
LMWH	4'305 (49.5)	4'323 (50.5)	0.17
Fondaparinux	400 (4.6)	379 (4.4)	0.59
Bivalirudin	479 (5.5)	481 (5.6)	0.74
GP IIbIIIa inhibitors	3'507 (40.3)	3'503 (40.9)	0.41
Post-randomization therapy (%):			
β-blockers	7,275 (83.6)	7,280 (85.0)	0.009
ACE-inhibitors	6,028 (693)	5,961 (69.6)	0.60

AT-2-antagonists	839 (9.6)	749 (8.8)	0.04
Ca-channel blockers	1,197 (13.8)	1,155 (13.5)	0.61
Statins	7,860 (90.3)	7,715 (90.1)	0.66
Proton-pump inhibitors	2,651 (39.6)	2,644 (40.2)	0.49
Lesions treated (%):	8900	8771	
Left main	140 (1.6)	139 (1.6)	-
Left anterior descending	3,053 (34,3)	3,077 (35.1)	
Left circumflex	2,374 (26.7)	2,282 (26)	
Right coronary artery	3,124 (35.1)	3,037 (34.6)	
Saphenous vein / arterial graft	209 (2.3)	236 (2.7)	
Visible angiographic thrombus before PCI	2,747/8399 (32.7)	2,719/8276 (32.9)	0.84
Stents (%)*:*			
Bare metal stents (only)	4,769 (58.0)	4,688 (57.9)	0.86
Drug eluting stents	3,453 (42.0)	3,413 (42.1)	0.86
Laboratory parameters:			
Hemoglobin (g/dL)	14.1±1.7	14.1±1.7	0.96
Glomerular filtration rate (mL/min/1.73m^2) [§]	81± 26	82±27	0.62

Data are mean (standard deviation) or number (percentage), as appropriate. GP IIbIIa inhibitors = Glycoprotein IIb/IIIa inhibitors; LMWH = Low molecular weight heparin; MI = Myocardial infarction; NSTEMI = Non-ST-segment elevation myocardial infarction; PCI = Percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = Unstable angina.

[*] P values were based on student's t-tests, Mann-Whitney U- tests or Chi-square tests, as appropriate.

[†] *Non*-smokers were classified as current non-smokers and former smokers.

[‡] As initial reperfusion strategy.

[§] Estimated by applying Modification of Diet in Renal Disease Study (MDRD) equation.