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Incidence and Clinical Features of Early Stent Thrombosis in the Era of New P2y12 Inhibitors (PLATIS-2)

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Abstract

Early stent thrombosis (EST) (≤ 30 days after stent implantation) is a relatively rare but deleterious complication of percutaneous coronary intervention (PCI). Administration of newer P2Y12 inhibitors (prasugrel and ticagrelor) combined with aspirin has been shown to reduce the incidence of sub-acute and late stent thrombosis, compared with clopidogrel. We investigated the "real life" incidence of EST in patients from a large acute coronary syndrome (ACS) national registry, where newer P2Y12 inhibitors are widely used. Patients were derived from the ACS Israeli Survey (ACSIS), conducted during 2006, 2008, 2010 and 2013. Major adverse cardiac events (MACE) at 30days were defined as all-cause death, recurrent ACS, EST and stroke.Of the 4717 ACS patients who underwent PCI and stenting, 83% received clopidogrel and 17% newer P2Y12 inhibitors. The rate of EST was similar in both groups (1.7% in the newer P2Y12 inhibitor group vs. 1.4% in the clopidogrel-treated patients, p = 0.42). Results were consistent after multivariate analysis (adjusted HR = 1.06 [p = 0.89]). MACE occurred in 6.4% in the newer P2Y12 inhibitor group compared with 9.2% in the clopidogrel group (P<0.01). However, multivariate logistic regression modeling showed that treatment with newer P2Y12 inhibitors was not significantly associated with the secondary endpoint of MACE when compared with clopidogrel therapy [OR = 1.26 95%CI (0.93–1.73), P = 0.136]. The incidence of "real life" EST at 1month is relatively low, and appears to be similar in patients who receive newer P2Y12 inhibitors as well as in those who receive clopidogrel.

Introduction

Early stent thrombosis (EST) (≤ 30 days after stent implantation) is a rare but severe complication which could present as ST-elevation myocardial infarction (STEMI) or sudden cardiac death within the first 30 days after stent implantation [1, 2]. EST is more common following

stent implantation in the context of acute coronary syndrome (ACS) than in stable coronary disease, particularly in patients with multi-vessel disease and in those presenting with a Killip class of ≥2 [1–4]. This observation can be explained by platelet activation and a heightening of the coagulation process as part of the pathogenesis of ACS [5, 6]. Previous studies have shown that several patient-related variables are associated with EST during ACS, such as suboptimal antiplatelet administration, insulin-requiring diabetes, hypertension and baseline renal insufficiency [3–6], in addition to several other independent predictors, such as final stent minimal luminal diameter, non-administration of thienopyridine prior to percutaneous coronary intervention (PCI) and high baseline hemoglobin levels [5–7]. Newer antiplatelet medications, including ticagrelor [8] and prasugrel [9], are associated with a significant reduction in the incidence of late stent thrombosis (>30 days following stent implantation) and sub-acute stent thrombosis (> 24 hours but <30 days after stent implantation). However, neither drug showed reduction in acute stent thrombosis during the first 24 hours after stent implantation, when compared with clopidogrel [8–11], even when ticagrelor was administrated as part of a pre-hospital ACS regimen [12]. Nevertheless, data regarding the rate of EST in the new era of antiplatelet drugs are scarce. Hence, we decided to investigate the trend and incidence of EST in a large national ACS registry in a "real life" setting, where the administration of antiplatelet drugs prior to PCI is standard care, incorporating third generation drug-eluting stents and newer P2Y12 inhibitors (specifically, prasugrel and ticagrelor).

Materials and Methods

Study population

Patients were derived from the ACS Israeli Survey (ACSIS), a nationwide survey conducted during March and April of the years 2006, 2008, 2010 and 2013 in all 25 cardiac units and cardiology wards operating in Israel. Local ethics committee approval was received from each hospital and the study was approved by the Sheba Medical Center Institutional Review Board as well. Participants provided their written informed consent in order to participate in the study. The study population comprised all patients admitted with ACS. Patients who did not undergo PCI with stenting and who did not receive dual antiplatelet therapy were excluded from the study (Fig 1). The diagnosis of ACS was based on the presence of symptoms consistent with angina in addition to electrocardiographic changes compatible with myocardial ischemia and/or cardiac biomarker elevation. Demographic, historical, clinical and angiographic data, as well as prior medical therapy, including medications discontinued throughout the month prior to the index coronary event, were recorded on a pre-specified form for all patients. Patients were managed at the discretion of each center. All patients were either seen or contacted by telephone at 30 days post discharge. Data were collected regarding vital status, repeated procedures, including coronary angiography and/or coronary intervention, and re-hospitalization.

Definition and endpoints

Stent thrombosis was diagnosed based on the Academic Research Consortium specifications for probable or definite stent thrombosis [8]. Stent thrombosis was defined as early (0–30 days), Late (>30 days) and very late (>12 months). Early stent thrombosis was further divided into acute (<24 hours) and sub-acute (1–30 days).

Mortality at 30 days was determined for all participants from hospital charts and by matching the identification numbers of the patients with the Israeli National Population Registry. The primary endpoint was defined as a definite early stent thrombosis, with secondary combined end points being pre-specified as all-cause mortality, recurrent ACS, stent thrombosis and/or stroke at 30 days. A new or recurrent myocardial infarction (MI) was defined as

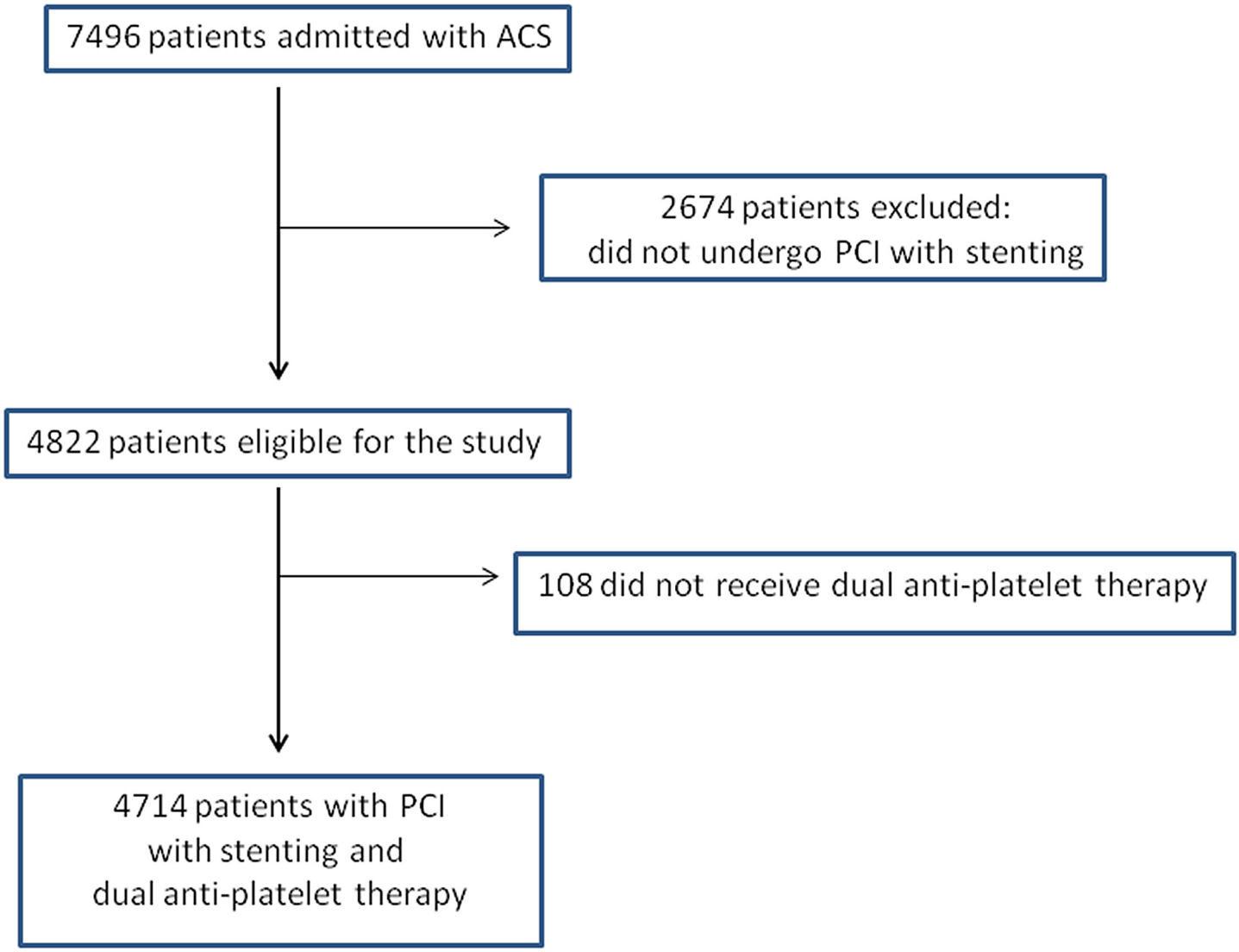

Fig 1. Patients' enrollment flow chart.

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elevation of myocardial biomarkers with either repeated symptoms suggestive of ischemic and/or new ECG changes. To determine repeat MIs during the qualifying hospitalization, myocardial biomarkers were re-elevated to at least twice that of the last one measured. Recurrent ACS was defined as a recurrent MI or a recurrent ischemic event necessitating re-hospitalization or unscheduled revascularization.

Statistical Analysis

Continuous variables are presented as mean ± SD or median and inter-quartile range, and categorical variables are expressed as percentages. Continuous variables were compared with the Student *t*-test if data followed a normal distribution and with Wilcoxon Rank sum test if data were skewed. Categorical variables were compared using chi-square test or Fisher's exact test when indicated. All tests were two-sided, and values of $p<0.05$ were considered statistically significant.

We used a logistic regression model in order to account for confounding baseline differences between the clopidogrel-treated patients and those receiving the newer P2Y12 inhibitors. This model included the following pre-specified variables: age (continuous), gender, hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease (CAD), current smoking, prior stroke, chronic congestive heart failure, prior MI, prior PCI or coronary artery bypass grafting, chronic renal failure, diagnosis [STEMI vs. non-STEMI (NSTEMI)] on arrival, and P2Y12 inhibitor treatment. Statistical analysis was performed using SAS software (version 8.2, SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

Of the 4714 consecutive patients with ACS who underwent PCI with stenting and received dual antiplatelet therapy in the ACSIS surveys, 3916 (83%) were treated with clopidogrel during hospitalization and 798 (17%) with the newer P2Y12 inhibitors [501 (11%) with prasugrel, and 297 (6%) with ticagrelor] (Fig 2). Baseline characteristics and prior medical therapy of the study patients are presented in Table 1. Patients who received newer P2Y12 inhibitors displayed important differences compared with those treated with clopidogrel, which included: a younger age, a higher frequency of males, STEMI at presentation, and a lower frequency of renal failure. In addition, patients receiving newer P2Y12 inhibitors tended towards a lower frequency of prior stroke and hypertension.

Early stent thrombosis

The rate of EST was similar among patients treated with newer P2Y12 inhibitors compared with clopidogrel (1.7% vs. 1.4%, respectively, p = 0.42; Fig 3). Acute and sub-acute stent thrombosis occurred in 46% vs. 56% and 54% vs. 44% with newer P2Y12 inhibitors compared with clopidogrel, respectively, p = 0.55). STEMI patients experienced a higher overall EST rate compared with other ACS patients, EST occurred at similar rates for both the newer P2Y12 inhibitors and clopidogrel (Fig 3). Moreover, the EST rate did not differ significantly throughout the years 2006, 2008, 2010 and 2013 (1%, 2.5%, 1.1%, 1.5%, respectively, P = 0.3) (Fig 4). Consistent with these univariate findings, multivariate logistic regression modeling showed that male gender and presentation with STEMI on admission were the only independent risk factors for

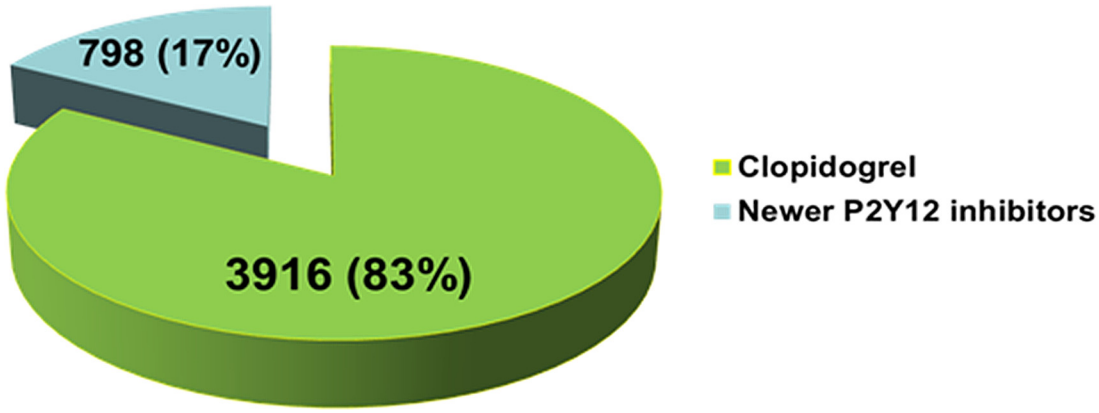

Fig 2. Antiplatelet drug distribution.

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Table 1. Patients' baseline characteristics prior to medical therapy following the index ACS.

	Clopidogrel N = 3916 (83%)	Newer P2Y12 inhibitors N = 798 (17%)	P-value
Age, mean (SD), y	62 (±12)	59 (±11)	<0.01
Male, %	3144 (80%)	667 (83.5%)	0.03
STEMI	2018 (51.5%)	520 (65%)	<0.001
Dyslipidemia	2768 (71%)	558 (69.9%)	0.6
Hypertension	2288 (58.6%)	437(54.7%)	0.06
Diabetes mellitus	1273 (32%)	258 (32.3%)	0.9
Chronic renal failure	328 (8.4%)	48(6%)	<0.001
Prior MI	1006 (25.7%)	185(23.1%)	0.14
Prior PCI	1119 (28.6%)	207(25.93%)	0.14
Prior CVA/TIA	268 (6.9%)	41(5.1%)	0.08
Aspirin	1798 (46%)	310 (38.8%)	<0.003
Clopidogrel	382 (9.8%)	51(6.4%)	<0.002
Beta Blockers	1335 (34.4%)	195 (24.4%)	<0.001
ACE-I/ARBs	1424 (36.5%)	247 (31%)	<0.001
Statins	1794 (46.2%)	317 (39.7%)	<0.001

ACS. Acute coronary syndrome; SD, Standard deviation; STEMI, ST-elevation myocardial infarction; MI, Myocardial infarction, PCI, Percutaneous coronary intervention; CVA, Cerebrovascular accident; TIA, Transient ischemic attack; ACE-I, Angiotensin converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers

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EST, whereas treatment with newer P2Y12 inhibitors was not significantly associated with EST compared with clopidogrel therapy (adjusted HR = 1.06 [p = 0.89]) (Table 2).

Major Adverse Cardiac Events

The secondary endpoint of major adverse cardiac events (MACE) occurred in only 6.4% in the newer P2Y12 inhibitor group compared with 9.2% in the clopidogrel group (P<0.01). The difference was driven mainly by all-cause mortality (1.1% vs. 2.7%, respectively, p = 0.01) and recurrent ACS (3.1% vs. 4.8%, respectively, p = 0.04) that were both lower in the newer P2Y12 inhibitor group (Fig 5). However, multivariate logistic regression modeling showed that, after adjustment for confounders, treatment with newer P2Y12 inhibitors was not significantly associated with the secondary endpoint of MACE compared with clopidogrel therapy [OR = 1.26 95%CI (0.93–1.73), P = 0.136].

$$\text{ACS} = \text{Acute coronary syndrome}$$

$$\text{Adjusted OR for overall MACE}* = [1.26 95\%\text{CI } (0.93 - 1.73),\ \text{P} = 0.136]$$

* Age (continuous), gender, hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease, current smoking, prior stroke, chronic congestive heart failure, prior myocardial infarction, prior percutaneous coronary intervention or coronary artery bypass grafting, chronic renal failure, diagnosis (ST-elevation myocardial infarction vs. non ST-elevation myocardial infarction) on arrival and P2Y12 inhibitor treatment.

Discussion

The findings of the current study suggest that: 1) the rate of EST at 1month post-discharge in a contemporary "real life" setting is relatively low (in the range of 1.0%-1.5%); 2) over the past

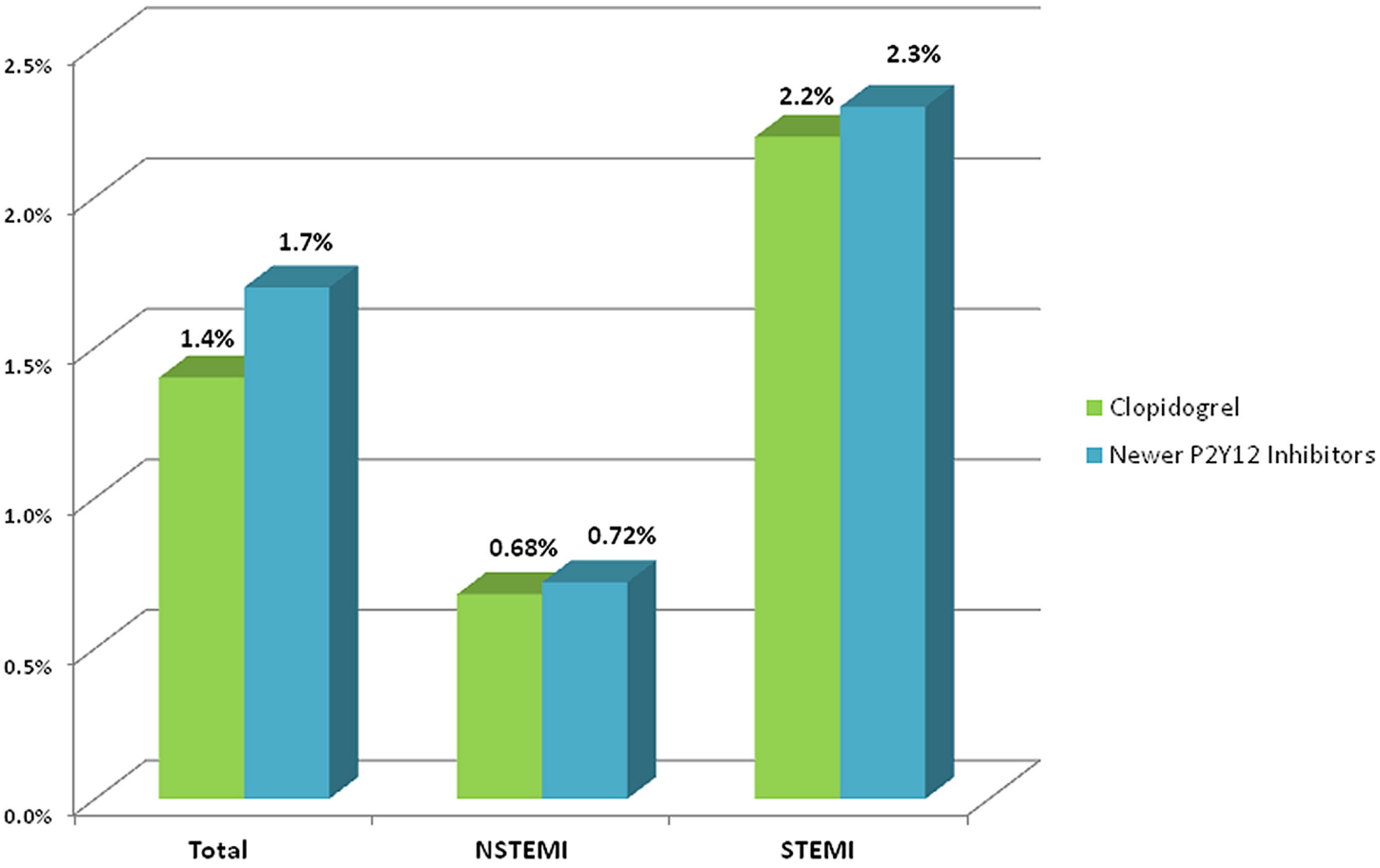

Fig 3. Early stent thrombosis rate.

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decade EST rates within the first month after stent implantation have remained constant despite changes in medical and interventional strategies; and 3) despite data from major randomized clinical trials favoring therapy with newer P2Y12 inhibitors over clopidogrel, our findings suggest that in a "real life" setting both 1-month EST and MACE rates might be similar in patients treated either with newer P2Y12 inhibitors or with clopidogrel. Of note, due to the relatively low rate of EST in our population (4717 patients), a larger sample may be required to show statistically significant differences between the two groups.

The only two large clinical trials to demonstrate an advantage of ticagrelor and prasugrel over clopidogrel in patients with ACS were the TRITON and PLATO trials, which enrolled more than 10,000 patients each [7, 9]. The rate of EST in our trial was in accord with the rate of EST in both these trials while in smaller clinical trials the rate of stent thrombosis was even lower [13–15]. Much like the use of newer antiplatelet therapy, others trials also sought to show a benefit of prolonged dual antiplatelet therapy in preventing stent thrombosis, but failed due to the relatively small number of patients [13–20]. The only trial that succeeded was the DAPT trial which also enrolled nearly 10,000 patients [21]. Hence, it might be that the newer antiplatelet agents have only a modest impact on the rate of stent thrombosis, and therefore a possible difference is seen only after treating thousands of patients. Even in the PLATO and TRITON trials, not only were stent thrombosis rates very low but overall event reduction rates were also low, with the number needed to treat being particularly high. Furthermore, the

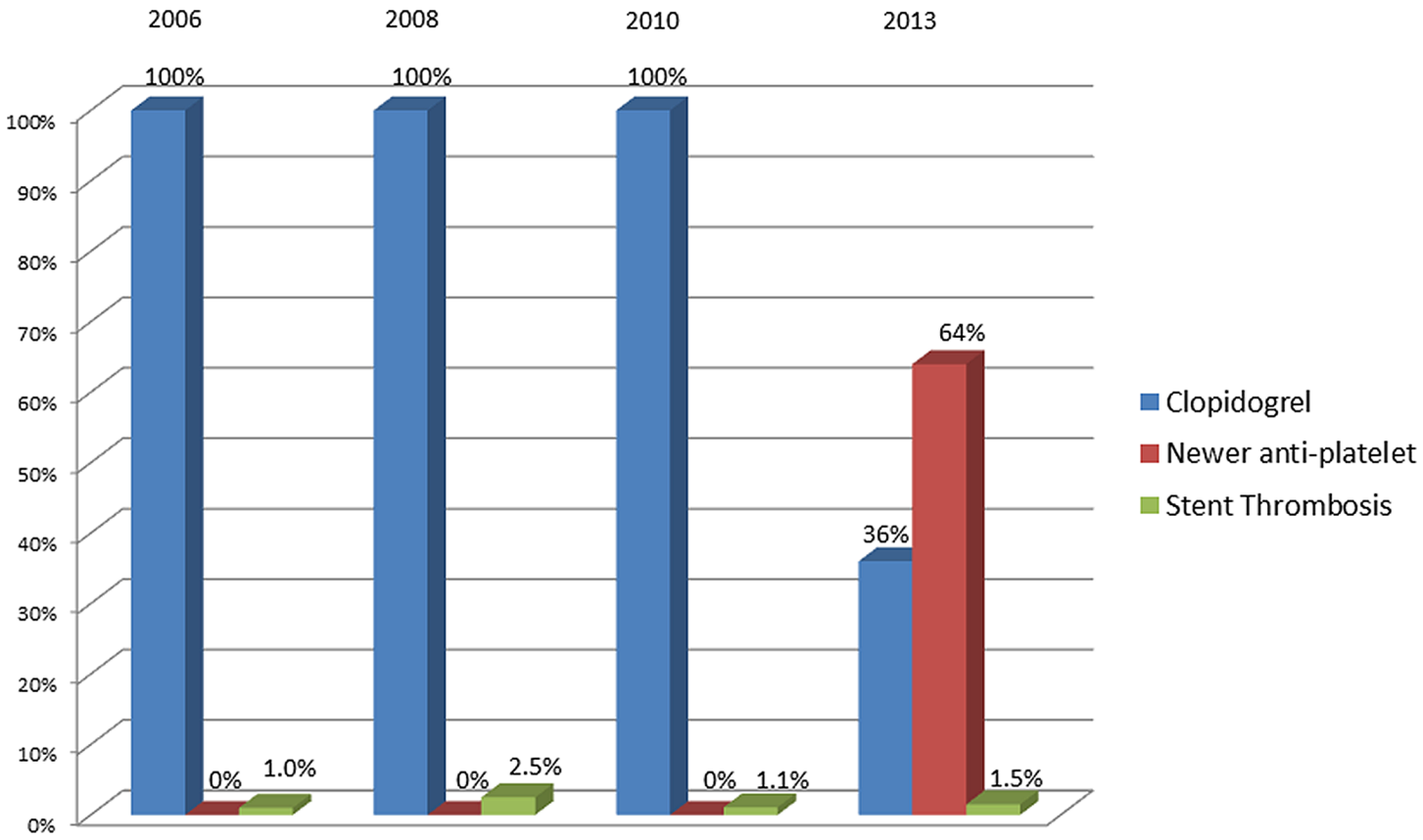

Fig 4. Antiplatelet distribution and stent thrombosis rate per year.

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MACE rate was also similar in both our study groups, which again raises the question as to whether the newer antiplatelet agents provide only a modest effect on MACE. These findings are in line with the retrospective cohort analysis of the PROMETHEOUS trial [22] which examined 19,914 ACS patients, of whom 80% were treated with clopidogrel and the rest with prasugrel. The prasugrel-treated patients were younger and had less co-morbidity than those receiving clopidogrel. As in our study, after adjustment for baseline variables, MACE was similar in both groups, although in the PROMETHEOUS trial the reduction in the risk of all-cause mortality remained significant. Nevertheless, paradoxically, as in our study, bleeding rates were reduced with prasugrel in the unadjusted analysis. Another interesting point that might

Table 2. Multivariate logistic regression model for early stent thrombosis*.

	Odds Ratio	95% Confidence Interval	P-value
Gender (Male)	2.416	1.236–4.725	0.0099
Prior PCI	2.420	0.995–5.886	0.0514
STEMI vs. NSTEMI on presentation	5.290	2.375–11.783	<0.001

PCI, Percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; NSTEMI, Non ST-elevation myocardial infarction

* The findings were further adjusted for the following co-varieties: Age (continuous), hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease, current smoking, prior stroke, chronic congestive heart failure, prior myocardial infarction, prior coronary artery bypass grafting, chronic renal failure, and P2Y12 inhibitors treatment.

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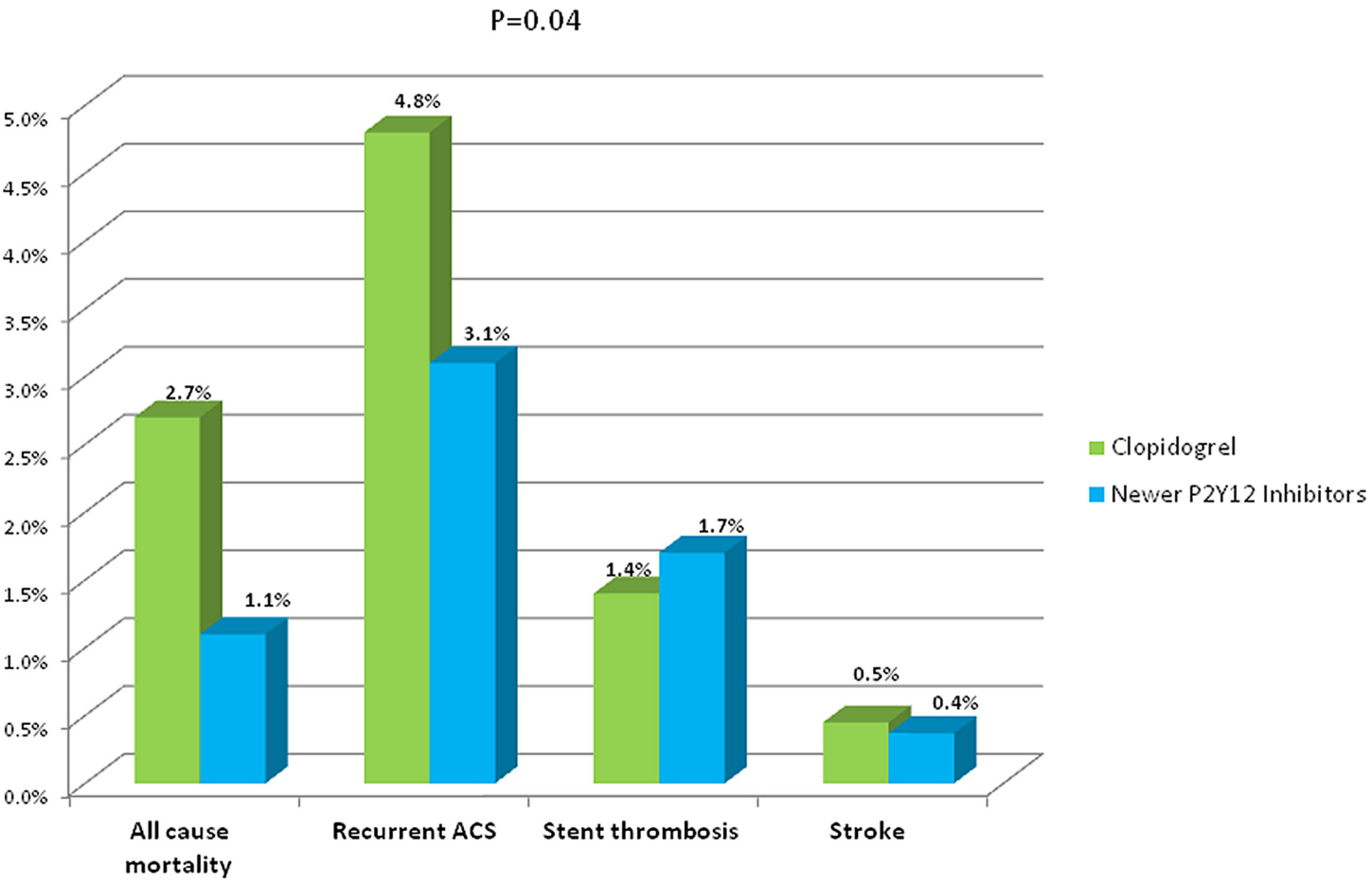

Fig 5. Secondary end points at 30 days.

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contribute to the modest effect of newer antiplatelet agents on stent thrombosis is their inability to change prognosis and the rate of stent thrombosis in patients non-responsive to clopidogrel. Previous data have demonstrated a strong correlation between clopidogrel non-responsiveness and adverse cardiac events which appeared to influence the incidence of stent thrombosis [10]. Moreover, an increased rate of EST was observed in non-responders compared with responders in patients scheduled for stent implantation after a 600 mg loading dose of clopidogrel [23]. Furthermore, high on-treatment platelet reactivity was found to be a strong independent predictor of stent thrombosis [24], an issue which led to the development of the newer P2Y12 inhibitors in order to overcome this limitation. However, several large clinical trials failed to show any improvement in MACE or stent thrombosis in non-responders even when the clopidogrel dose was doubled [25] or when treatment was replaced by a newer antiplatelet agent [26, 27]. Hence, changing one drug might not suffice in lowering the rate of stent thrombosis to the extent of preventing it altogether, particularly when taking into account that stent thrombosis is a multi-factorial process [28–30]. Predictors of early and late stent thrombosis following PCI with stenting have been studied in registries and post hoc analyses from clinical trials and may be categorized by: 1) the stent; 2) the patient; 3) the procedure; and 4) the type and duration of antiplatelet therapy [31–37]. It is therefore reasonable to assume that

the addition of a more potent antiplatelet agent might achieve only a modest reduction in stent thrombosis rates. Moreover, a more recent study which interrogated an autopsy registry to investigate the histopathologic features of EST in patients presenting with ACS, found that the percent of necrotic core prolapse, medial tear, or incomplete apposition was significantly greater in the EST patients compared with the other patients [38]. These histopathologic features, which are prominently mechanical in nature, will probably, not be influenced by a better P2Y12 inhibitor alone.

To the best of our knowledge, this is the first study to demonstrate that the use of newer P2Y12 inhibitors is not superior to clopidogrel in terms of EST and MACE at 30 days following PCI and stent implantation in ACS patients selected from a large national registry in a "real life" setting.

Study Limitations

Due to its observational non-randomized design, the current study is subject to limitations as described in detail previously [39]. Thus, despite efforts to control for confounding factors by applying multivariate analysis, we cannot exclude unmeasured factors which could have biased the results of the comparison between clopidogrel-treated and newer antiplatelet treated patients such as lesion characteristics and stent type and size. Another potential limitation of the study is the length of the follow-up period. Since the type of ACS (STEMI vs. unstable angina/NSTEMI) has different effects on short- and long-term prognosis, the study results regarding clinical outcomes can be applied only to short-term prognosis. Further studies are needed to examine the long-term MACE of these patients and whether newer P2Y12 inhibitors would be more beneficial in this high-risk patient subset.

Conclusions

In summary, in this national, multicenter, contemporary "real life" setting, we did not observe any clinically meaningful differences in EST rates between clopidogrel-treated and newer antiplatelet-treated patients after PCI and stent implantation. Furthermore, it appears that throughout the past decade EST rates have been relatively low and have not changed significantly despite major changes in medical management and interventional technologies. In contrast, the rate of MACE following ACS (including mainly death and re-infarction) remains relatively high in the range of 6–9%. These findings suggest that more focus on the implementation of secondary prevention strategies is warranted in this population.

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Author Contributions

Conceived and designed the experiments: EA AA IG. Performed the experiments: EA. Analyzed the data: A. Segev A. Sabbag IM. Contributed reagents/materials/analysis tools: IG MS SA. Wrote the paper: EA SM IG. Quality analysis and manuscript proofing: DZ AP RB.

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