Real-World Use of Novel P₂Y₁₂ Inhibitors in Patients with Acute Myocardial Infarction: A Treatment Paradox

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Key Words

Acute coronary syndrome · Antiplatelet therapy · Percutaneous coronary intervention · P₂Y₁₂ Inhibitors

Abstract

Objective: To assess the real-world use, clinical outcomes, and adherence to novel P₂Y₁₂ inhibitors. **Methods:** We evaluated 1,093 consecutive acute myocardial infarction patients undergoing a percutaneous intervention. Patients were derived from a prospective, multicenter, nationwide registry and were followed for 30 days; 381 patients (35%) received clopidogrel, 468 (43%) received prasugrel, and 244 (22%) received ticagrelor. Patients treated with clopidogrel were older and more likely to suffer from chronic renal failure and stroke and/or present with non-ST-elevation myocardial infarction (NSTEMI) ($p < 0.01$ for all). Independent predictors of

undertreatment with novel P₂Y₁₂ inhibitors included: older age (OR 0.17; 95% CI 0.1–0.27, $p < 0.0001$), a prior stroke (OR 0.41; 95% CI 0.2–0.68, $p = 0.008$), and NSTEMI (OR 0.37; 95% CI 0.26–0.54, $p < 0.0001$). **Results:** Novel P₂Y₁₂ inhibitors were associated with a lower incidence of cardiovascular events, major bleeding, and/or death (7.6 vs. 11%, HR 0.67; 95% CI 0.43–1, $p = 0.05$). However, after a multivariate analysis this trend was not statistically significant. Patients discharged with ticagrelor versus thienopyridines demonstrated a higher rate of crossover to other P₂Y₁₂ inhibitors (11 vs. 5%, $p = 0.03$). **Conclusions:** In a real-world cohort, there was an underutilization of novel P₂Y₁₂ inhibitors which was more pronounced in higher-risk subsets that might benefit from novel P₂Y₁₂ inhibitors at least as much as other patients.

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Introduction

Since the publication of the CURE [1] study in 2001, dual antiplatelet therapy, including aspirin and P₂Y₁₂ inhibitors, has become the mainstay of antithrombotic therapy for acute coronary syndrome (ACS) patients. Dual antiplatelet therapy has been shown to confer a proven benefit for the prevention of recurrent ischemic events, and it is considered a class I indication for therapy in ACS patients, especially those undergoing percutaneous interventions [2–6]. In recent years a new generation of P₂Y₁₂ inhibitors has evolved, rendering a more potent antiplatelet effect associated with improved clinical outcomes [7, 8] and even reduced mortality [7]. However, these benefits have been at the cost of increased bleeding events [7, 8], as well as specific adverse effects associated with the use of ticagrelor, which could hamper patient compliance as well as the physician preference for this therapy.

Currently there are limited data regarding routine real-world experiences with novel P₂Y₁₂ inhibitors. A limited number of studies [9–15] evaluating the use of novel P₂Y₁₂ inhibitors in various settings have suggested a delayed uptake; however, these studies included mostly patients treated with prasugrel, and thus they effected a somewhat ‘biased’ approach by excluding patients aged >75 years or those with a prior stroke or a body weight <60 kg. Furthermore, those studies addressed only the issue of in-hospital and short-term follow-up. The implementation of trial data and guidelines in daily clinical practice is an important step in the evaluation of drug therapy and its modifications. Consequently, the aim of the present study was to assess the real-world use, implementation, clinical outcomes, and adherence to P₂Y₁₂ inhibitor therapy in the era of novel, oral antiplatelet agents. This assessment was carried out via evaluation of a national, multicenter survey of consecutive patients presenting with acute myocardial infarction (AMI) who underwent a percutaneous coronary intervention (PCI).

Methods

Study Population

We evaluated consecutive patients enrolled into the national, prospective, multicenter Acute Coronary Syndrome Israeli Survey (ACSIS) conducted between March and April 2013, consisting of all 25 intensive cardiac care units and cardiology wards in Israel. The survey was approved by the local ethics committee of each participating hospital. AMI was defined according to the universal definition of myocardial infarction [16]. Medical treatment and invasive procedures were carried out at the discretion of each par-

ticipating center. The ACSIS has no exclusion criteria. Demographic, historical, and clinical data, as well as admission and discharge electrocardiograms, medical therapies, angiographic characteristics, complications, and follow-up data, were all recorded on electronic case report forms by dedicated physicians. Events were prospectively and centrally defined.

Our study cohort consisted of consecutive patients presenting with AMI who underwent PCI, were eligible for novel P₂Y₁₂ inhibitor therapy, and were discharged with any P₂Y₁₂ inhibitor. Adjunctive medical therapies were administered and types of stents were decided upon at the discretion of each participating center and operating physician. It should be noted that, since 2012, prasugrel and ticagrelor, in addition to clopidogrel, have been available in Israel at no additional cost to all patients presenting with AMI who undergo a PCI. Each individual medical center’s institutional review board approved the documentation of patient characteristics and the in-hospital course. Patients were required to give written informed consent for postdischarge follow-up data documentation.

Follow-Up

Follow-up at 30 days was obtained for patients who gave informed consent (n = 751); the follow-up rate was high, available for 689 of them (92%). For those patients whose follow-up was not available, mortality data was assessed via the records of the Ministry of the Interior, which were available for the entire study population. Organization, data acquisition, management, and follow-up were performed at the Israeli Society for the Prevention of Heart Attacks National Coordinating Center. Data checks for completeness and consistency were based on computerized data queries issued at the Coordinating Center and completed from the medical reports attached to each patient form.

Endpoints

The primary aim of the present study was to assess the implementation of therapy with novel P₂Y₁₂ inhibitors and identify independent factors associated with underutilization of novel P₂Y₁₂ inhibitors (prasugrel or ticagrelor). Additional endpoints included compliance to therapy at 30 days with each P₂Y₁₂ inhibitor. Factors associated with the 30-day net adverse clinical outcome (NACE) were also assessed and defined as: death, recurrent ACS, stroke, urgent revascularization, stent thrombosis, and major bleeding, as well as 1-year mortality.

Stent thrombosis, either definite or probable, was defined according to Academic Research Consortium criteria. Major bleeding was defined as a drop in hemoglobin levels ≥ 5 mg/dl, a drop in hematocrit levels >15%, the need to receive >2 units of blood, retroperitoneal bleeding, and/or intracranial bleeding.

Statistical Analysis

Univariate analysis was used to compare the treatment groups. We used Student’s t test and the Mann-Whitney test for normally and abnormally distributed continuous variables, respectively. Categorical variables were compared using the χ^2 test. A multivariate logistic regression analysis was conducted to determine predictors of treatment with clopidogrel versus novel P₂Y₁₂ inhibitors, as well as to identify factors associated with the 30-day NACE in each group. Multivariate Cox proportional hazards regression modeling was used to identify factors associated with 1-year mortality. Covariates in the multivariate models included age, gender,

Fig. 1. Distribution of therapy with the different P₂Y₁₂ inhibitors throughout the study cohort. **a** Distribution of therapy with the different P₂Y₁₂ inhibitors. **b** Distribution of the different P₂Y₁₂ inhibitors according to allocation to STEMI or NSTEMI.

prior stroke, diabetes, and renal failure to control for potential confounding and other covariates. Results are displayed as HR and survival plots. All statistical tests were interpreted at a 2-sided significance level of 0.05, and all confidence intervals had a 2-sided level of 95%, using SAS statistical software, version 9.3, (SAS Institute, Cary, N.C., USA).

Results

This study comprised 1,093 consecutive AMI patients who underwent PCI and received any type of P₂Y₁₂ inhibitor at discharge. Prior to the index event, 43% of the patients had been receiving aspirin and 11% a P₂Y₁₂ inhibitor; the majority (91%) of these patients had received clopidogrel. Figure 1 demonstrates the study cohort distribution based on the P₂Y₁₂ inhibitor therapy received at

discharge after the index event. A total of 381 patients (35%) received clopidogrel, 468 (43%) received prasugrel, and 244 (22%) received ticagrelor.

The patient baseline characteristics as well as a subgroup comparison according to the P₂Y₁₂ inhibitor administered are presented in table 1. Patients treated with clopidogrel compared to those treated with a novel antiplatelet agent were older (mean age 69 ± 13 vs. 59 ± 13 years, respectively, $p < 0.001$) and had a significantly higher risk profile. Clopidogrel-treated patients were more likely to be hypertensive (73 vs. 53%, $p < 0.001$) and to suffer from chronic renal failure (18 vs. 6%, $p < 0.001$) compared to their novel-P₂Y₁₂-inhibitor counterparts. Furthermore, clopidogrel was administered less frequently than novel P₂Y₁₂ inhibitors among ST-elevation myocardial infarction (STEMI) patients. As the eligibilities for treatment with prasugrel and ticagrelor differ

Table 1. Baseline characteristics of the study cohort defined by clopidogrel and P₂Y₁₂ inhibitor therapy

Baseline characteristics	Study cohort (n = 1,093)	Clopidogrel (n = 381)	Novel P ₂ Y ₁₂ antiplatelets (n = 712)	p value ^a	Prasugrel (n = 468)	p value ^a	Ticagrelor (n = 244)	p value ^a
Age, years	63±13	69±13	59±11	<0.001	57±8	<0.001	64±12	<0.001
Male sex	80	74	84	<0.001	85	<0.001	80	0.069
BMI	31±30	29±17	32±34	0.83	32±30	<0.001	32±35	<0.001
Smoking	43	31	50	<0.001	57	<0.001	35	0.335
Dyslipidemia	72	77	70	0.01	70	0.024	69	0.019
Hypertension	60	73	53	<0.001	50	<0.001	59	<0.001
Diabetes	35	39	33	0.033	32	0.021	35	0.287
Prior MI	26	31	23	0.008	22	0.003	26	0.228
Prior PCI	30	36	26	0.001	24	<0.001	32	0.256
Prior CABG	7	10	5	<0.001	4	<0.001	7	0.162
Chronic renal failure	10	18	6	<0.001	3	<0.001	11	0.014
CVA/TIA	7	14	4	<0.001	1	<0.001	10	0.206
Prior aspirin therapy	43	52	38	<0.001	36	<0.001	43	0.033
Prior P ₂ Y ₁₂ therapy	11	17	7	<0.001	6	<0.001	12	0.026
STEMI	57	39	66	<0.001	79	<0.001	41	0.640

Values are presented as means ± SD or percents unless otherwise stated. CABG = Coronary artery bypass graft; CVA = cerebrovascular attack; TIA = transient ischemic attack. ^a For comparison between clopidogrel and the specified group.

Table 2. Logistic regression analysis for independent predictors of undertreatment with novel P₂Y₁₂ inhibitors compared to clopidogrel

Independent predictors	OR	95% CI	p value
Age <65 vs. ≥75 years	0.17	0.10–0.27	<0.0001
NSTEMI	0.37	0.26–0.54	<0.0001
Prior CVA/TIA	0.41	0.2–0.68	0.008
No history of hypertension	0.61	0.41–0.87	0.014
No prior clopidogrel therapy	0.52	0.29–0.93	0.048

Logistic regression analysis adjusted for the variables listed and for gender, prior coronary artery disease, peripheral vascular disease, weight, diabetes, smoking, and prior aspirin therapy (all p > 0.05). CVA = Cerebrovascular attack; TIA = transient ischemic attack.

(age, prior stroke, weight), there was a difference between the characteristics of patients treated with prasugrel and ticagrelor such that patients treated with prasugrel, compared to ticagrelor, were younger, without a history of prior stroke and therefore with less history of prior percutaneous interventions and renal failure.

Notably, of the 621 STEMI patients, 472 (76%) received a novel P₂Y₁₂ inhibitor [either prasugrel (60%) or

ticagrelor (16%)], while only 149 (24%) received clopidogrel. In contrast, among those patients presenting with non-STEMI (NSTEMI), novel P₂Y₁₂ therapy was administered in only 50% of cases, with the remaining patients receiving clopidogrel.

Factors Associated with an Increased Likelihood of Treatment with Newer P₂Y₁₂ Inhibitors for MI Patients

The independent predictors of a lower likelihood of treatment with novel P₂Y₁₂ inhibitors, as assessed by multivariate logistic regression, are shown in table 2. These patients were of an older age (87% lower likelihood for patients aged ≤66 years vs. patients aged ≥75 years, p < 0.001), had a history of prior stroke (59% lower likelihood, p = 0.008), and had a diagnosis of NSTEMI (63% lower likelihood, p < 0.001). The presence of hypertension and therapy with clopidogrel prior to the index event was associated with a higher likelihood of receiving novel P₂Y₁₂ therapy (OR 1.64; 95% CI 1.15–2.41, p = 0.014, and OR 1.91; 95% CI 1.07–3.41, p = 0.048, respectively).

Clinical Outcomes: Clopidogrel versus Novel P₂Y₁₂ Antiplatelet Therapy

NACE and its components at 30 days of follow-up are shown in table 3. The primary unadjusted outcome of

Table 3. Net adverse clinical events at 30 days and mortality at 1 year

	Entire study cohort	Clopidogrel	Novel P ₂ Y ₁₂ antiplatelets	p value ^a	Prasugrel (n = 468)	p ^a value	Ticagrelor (n = 244)	p value ^a
At 30 days								
NACE	8.8	11	7.6	0.05	6.4	0.016	9.8	0.637
Mortality	1.1	1.6	0.8	0.26	0.6	0.186	1.2	0.723
ACS	5.4	5.8	5.2	0.68	4.0	0.246	7.4	0.424
Stroke	0.3	0.8	–	0.01	–	0.054	–	0.164
Stent thrombosis	1.6	1.3	1.7	0.63	1.3	0.969	2.5	0.287
Urgent revascularization	1.2	1.1	1.3	0.75	0.4	0.281	2.9	0.091
Major bleeding	0.8	1.3	0.6	0.19	0.4	0.156	0.8	0.568
Mortality at 1 year	4.8	8.4	3.0	<0.0001	2.7	<0.001	3.4	0.014

Values are presented as percents unless otherwise stated. ^a For comparison between clopidogrel and the specified group.

NACE was significantly lower with novel P₂Y₁₂ inhibitors compared to clopidogrel therapy (7.6 vs. 11%, respectively; unadjusted HR 0.67; 95% CI 0.43–1, p = 0.05).

After adjusting for confounding variables (age, gender, prior stroke, diabetes, and renal failure), the trend for NACE reduction with novel P₂Y₁₂ inhibitors was not statistically significant (HR 0.68; 95% CI 0.38–1.22, p = 0.19) in the total population and in risk subsets.

The 1-year mortality was lower in the novel-P₂Y₁₂ group (8.4 vs. 4.8%, p < 0.0001); however, after adjusting for confounding variables, this was not statistically significant (HR 0.78; 95% CI 0.44–1.4, p = 0.4).

Compliance with P₂Y₁₂ Antiplatelet Therapy

The adherence to thienopyridine therapy at 30 days of follow-up, as shown in figure 2, was high at 91% for both clopidogrel and prasugrel, but it was 86% for ticagrelor (p = 0.07 for thienopyridines vs. ticagrelor). The discontinuation rate was 4% with clopidogrel and 3% with prasugrel and ticagrelor. A switch to a different P₂Y₁₂ inhibitor occurred in only 5 and 6% of patients treated with clopidogrel and prasugrel, respectively, and in 11% of patients treated with ticagrelor (p = 0.03 for the difference between thienopyridines and ticagrelor).

Discussion

The current study provides evidence of and insight into the incorporation of novel P₂Y₁₂ inhibitors, both prasugrel and ticagrelor, into daily clinical practice and its association with patient outcomes. In a real-world cohort of patients eligible for all available P₂Y₁₂ inhibitors

Fig. 2. Adherence to therapy and crossover rate between different P₂Y₁₂ inhibitors at 30 days. Each dark grey column represents the percent of consistency for each P₂Y₁₂ medication at discharge. The light grey areas at the top of each column represent a switch to another P₂Y₁₂ medication, while the black areas represent discontinuation of P₂Y₁₂ at 30 days of follow-up. Tx = Therapy. * p = 0.07.

according to the Israeli Ministry of Health policy, we have shown that: (1) there is still an underutilization of novel P₂Y₁₂ inhibitors and (2) the underutilization of novel P₂Y₁₂ inhibitors is more pronounced in higher-risk subsets.

Our findings are consistent with recent studies evaluating the trends of contemporary use of antiplatelet strategies, mainly prasugrel. In a retrospective US registry, Bae et al. [9] demonstrated that out of 83,567 ACS patients undergoing PCI only 9,404 (11%) received prasugrel. The EPICOR international study [10] demonstrated an underuse of prasugrel, with only about 10% of ACS patients receiving prasugrel and almost 90% receiving clopidogrel. The SCAAR registry [11] also demonstrated that patients with ACS were less likely to receive prasugrel than clopidogrel; again, prasugrel-treated patients were found to be younger, with fewer comorbidities. All of these studies evaluated only patients receiving prasugrel and did not evaluate the use of ticagrelor. In addition, these studies did not assess adherence to treatment or 1-year mortality, factors which are provided in the current analysis. Two additional registries have reviewed the use of ticagrelor, but these reports are limited to the evaluation of either the appropriateness of use [13] or the contemporary use of P₂Y₁₂ inhibitors [15], without evaluating in-hospital and postdischarge patient outcomes, as well as adherence to therapy. Again, as in the current analysis, it was demonstrated that clopidogrel is the most commonly used P₂Y₁₂ inhibitor.

Both prasugrel and ticagrelor have been shown in randomized controlled trials to lower ischemic complications in bleeding events [7, 8]. Thus, it was our intention to evaluate the use of a more contemporary approach of treatment with a novel P₂Y₁₂ inhibitor. While prasugrel and ticagrelor are not interchangeable, they provide the clinician with the tools for the novel P₂Y₁₂ contemporary approach as opposed to therapy with clopidogrel. In the current study, patients treated with clopidogrel compared to those treated with novel P₂Y₁₂ inhibitors were older and had significantly more comorbidities, including renal failure and hypertension, and they were more likely to have a history of prior stroke or peripheral vascular disease. Our real-world findings demonstrate a treatment paradox. Younger and less complex patients were more likely to receive the novel therapy, while older patients with more comorbidities including renal failure, a prior stroke, or heart failure, deemed to be at a higher risk for thrombotic events and more likely to benefit from more efficient P₂Y₁₂ inhibition, were receiving clopidogrel.

Several recent subgroup analyses comparing clopidogrel to novel P₂Y₁₂ inhibitors in predefined subgroups of patients have demonstrated improved outcomes with the latter therapy. A subanalysis from the PLATO trial by James et al. [17] showed an inverse relationship between

renal function and the benefit of ticagrelor over clopidogrel. ACS patients with a glomerular filtration rate <60 cm³/min derived a significantly greater benefit from ticagrelor compared to clopidogrel than patients with a better renal function [17]. Likewise, the efficacy and safety of ticagrelor seemed to be greater in patients with a history of prior stroke [18]. Additionally, a study by Husted et al. [19] showed that the clinical benefit of ticagrelor and its overall safety compared to clopidogrel are not age dependent. A prespecified subgroup analysis of the TRITON study suggested that prasugrel might confer a greater benefit over clopidogrel in diabetic compared to nondiabetic patients [8].

The results of the above mentioned studies [17–19] suggest an equal or even greater benefit from the novel antiplatelet agents over clopidogrel in older and higher-risk patients. These studies also demonstrated the same difference in patient characteristics when comparing clopidogrel and novel antiplatelet therapies (especially prasugrel). They all found that clopidogrel treatment was administered more frequently in complex patients, and that STEMI patients rather than NSTEMI patients were more likely to receive a novel P₂Y₁₂ inhibitor [9–12, 14, 15].

We have demonstrated that patients receiving novel P₂Y₁₂ inhibitors have a relatively low incidence of NACE, comparable to that reported in other randomized trials [7, 8]. Furthermore, Bae et al. [9] also demonstrated that, while by univariate analysis NACE was found to be significantly lower in the novel P₂Y₁₂-treated group, this was no longer significant after adjustment for confounding variables. Similar results were found for mortality at 1 year.

When assessing adherence to therapy, as shown in figure 2, patients discharged with ticagrelor demonstrated a trend towards a lower adherence to therapy, with a significantly higher rate of crossover (11%) to other medications when compared to thienopyridines. For patients treated with thienopyridines, the crossover rate was significantly lower at 5 and 6% for clopidogrel and prasugrel, respectively. This phenomenon might be explained by the fact that the side effect profile of ticagrelor is inferior to that of prasugrel and clopidogrel due to a reported higher incidence of dyspnea [7], ventricular pauses [20], and anxiety [21]. Conversely, the lower discontinuation rate of therapy with clopidogrel and prasugrel was comparable and did not differ.

Limitations

The current study is derived from a prospective registry, and therefore treatment was not chosen at random.

This raises the possibility of unmeasured confounders which might have influenced medication preference. Nonetheless, this design could strengthen our findings by providing a real-world snapshot of contemporary clinical practice. As this was a national registry, our results might not be applicable in different regions of the globe. This moderately sized registry may still be underpowered to detect an overall statistically significant treatment effect between the two study groups after multivariate adjustment, as well as to detect statistically significant subgroup differences. As such, an analysis between each of the two novel P₂Y₁₂ inhibitors was not made; rather, the approach of treatment with a novel P₂Y₁₂ inhibitor (for which all patients were eligible) versus clopidogrel was analyzed. However, to the best of our knowledge, this is the largest registry to date to report such outcomes, which include

adherence to both prasugrel and ticagrelor. Furthermore, our results, taken from an actual nationwide survey, include all operating centers throughout the country and not simply selective academic centers.

Conclusions

Despite evidence of the superiority of prasugrel and ticagrelor, a significant number of patients, especially those who are older have more comorbidities and those who present with NSTEMI, still receive clopidogrel. It appears that there is still room for improvement regarding the implementation of guidelines and the incorporation of these novel agents into the current clinical practice.

References

- 1 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK: Clopidogrel in unstable angina to prevent recurrent events trial investigators: effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
- 2 Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, et al: 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139–e228.
- 3 O’Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362–e425.
- 4 Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, et al: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999–3054.
- 5 Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Mario CD, Dickstein K, Ducrocq G, Fernandez-Aviles F, et al: ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC). *Eur Heart J* 2012;33:2569–2619.
- 6 Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, et al: 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541–2619.
- 7 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al: PLATO Investigators: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–1057.
- 8 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy SA, et al: TRITON-TIMI 38 Investigators: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–2015.
- 9 Bae JP, Faries DE, Ernst FR, Lipkin C, Zhao Z, Moretz C, Lieu HD, Effron MB: Real-world observations with prasugrel compared to clopidogrel in acute coronary syndrome patients treated with percutaneous coronary intervention in the United States. *Curr Med Res Opin* 2014;30:2207–2216.
- 10 Bueno H, Sinnaeve P, Annemans L, Danchin N, Licour M, Medina J, Pocock S, Sánchez-Covisa J, Storey RF, Jukema JW, et al: EPICOR Investigators: Opportunities for improvement in anti-thrombotic therapy and other strategies for the management of acute coronary syndromes: insights from EPICOR, an international study of current practice patterns. *Eur Heart J Acute Cardiovasc Care* 2016;5:3–12.
- 11 Damman P, Varenhorst C, Koul S, Eriksson P, Erlinge D, Lagerqvist B, James SK: Treatment patterns and outcomes in patients undergoing percutaneous coronary intervention treated with prasugrel or clopidogrel [from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)]. *Am J Cardiol* 2014;113:64–69.
- 12 Sherwood MW, Wiviott SD, Peng SA, Roe MT, Delemos J, Peterson ED, Wang TY: Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the national cardiovascular data registry. *J Am Heart Assoc* 2014;3:e000849.
- 13 Alexopoulos A, Goudevenos JA, Xanthopoulos X, Defferes S, Sitafidis G, Kanakakis I, Hamilos M, Parissis H, Ntalas IV, Angelidis C, et al: Implementation of contemporary oral antiplatelet treatment guidelines in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a report from the Greek Antiplatelet Registry (GRAPE). *Int J Cardiol* 2013;168:5329–5335.
- 14 Sandhu A, Seth M, Dixon S, Share D, Wohns D, Lalonde T, Moscucci M, Riba AL, Grossman M, Gurm HS: Contemporary use of prasugrel in clinical practice: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Circ Cardiovasc Qual Outcomes* 2013;6:293–298.

- 15 Karve AM, Seth M, Sharma M, LaLonde T, Dixon S, Wohns D, Gurm HS: Contemporary use of ticagrelor in interventional practice (from Blue Cross Blue Shield of Michigan Cardiovascular Consortium). *Am J Cardiol* 2015;115:1502–1506.
- 16 Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal definition of myocardial infarction. *Circulation* 2007;116:2634–2653.
- 17 James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, Harrington RA, Horrow J, Katus H, Keltai M, et al: Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2010;122:1056–1067.
- 18 James SK, Storey RF, Khurmi NS, Husted S, Keltai M, Mahaffey KW, Maya J, Morais J, Lopes RD, Nicolau JC, et al; PLATO study group: Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. *Circulation* 2012;125:2914–2921.
- 19 Husted S, James S, Becker RC, Horrow J, Katus H, Storey RF, Cannon CP, Heras M, Lopes RD, Morais J, et al; PLATO study group: Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. *Circ Cardiovasc Qual Outcomes* 2012;5:680–688.
- 20 Stark U, Brodmann M, Lueger A, Stark G: Antiarrhythmic effects of adenosine on ischemia-induced ventricular fibrillation. *J Crit Care* 2001;16:8–16.
- 21 Stutzmann GE, Marek GJ, Aghajanian GK: Adenosine preferentially suppresses serotonin_{2A} receptor-enhanced excitatory postsynaptic currents in layer V neurons of the rat medial prefrontal cortex. *Neuroscience* 2001;105:55–69.