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1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated With Prasugrel Versus Ticagrelor

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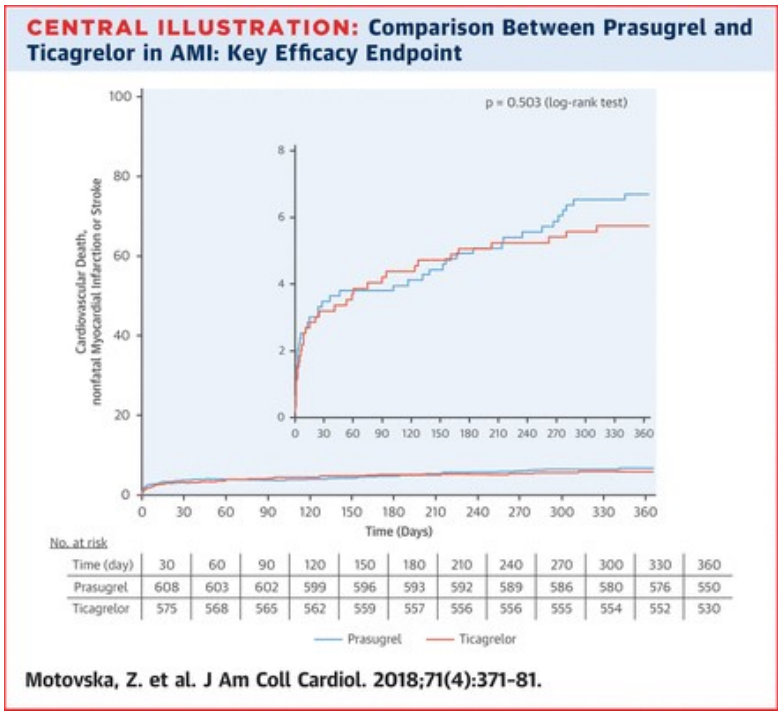
Central Illustration



Abstract

Background Early outcomes of patients in the PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) study did not find any significant differences between 2 potent $P2Y_{12}$ inhibitors.

Objectives The 1-year follow-up of the PRAGUE-18 study focused on: 1) a comparison of efficacy and safety between prasugrel and ticagrelor; and 2) the risk of major ischemic events related to an economically motivated post-discharge switch to clopidogrel.

Methods A total of 1,230 patients with acute myocardial infarction (MI) treated with primary percutaneous coronary intervention were randomized to prasugrel or ticagrelor with an intended treatment duration of 12 months. The combined endpoint was cardiovascular death, MI, or stroke at 1 year. Because patients had to cover the costs of study medication after hospital discharge, some patients decided to switch to clopidogrel.

Results The endpoint occurred in 6.6% of prasugrel patients and in 5.7% of ticagrelor patients (hazard ratio: 1.167; 95% confidence interval: 0.742 to 1.835; p = 0.503). No significant differences were found in: cardiovascular death (3.3% vs. 3.0%; p = 0.769), MI (3.0% vs. 2.5%; p = 0.611), stroke (1.1% vs. 0.7%; p = 0.423), all-cause death (4.7% vs. 4.2%; p = 0.654), definite stent thrombosis (1.1% vs. 1.5%; p = 0.535), all bleeding (10.9% vs. 11.1%; p = 0.999), and TIMI (Thrombolysis In Myocardial Infarction) major bleeding (0.9% vs. 0.7%; p = 0.754). The percentage of patients who switched to clopidogrel for economic reasons was 34.1% (n = 216) for prasugrel and 44.4% (n = 265) for ticagrelor (p = 0.003). Patients who were economically motivated to switch to clopidogrel had (compared with patients who continued the study medications) a lower risk of major cardiovascular events; however, they also had lower ischemic risk.

Conclusions Prasugrel and ticagrelor are similarly effective during the first year after MI. Economically motivated early post-discharge switches to clopidogrel were not associated with an increased risk of ischemic events. (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction [PRAGUE-18]; NCT02808767)

Key Words

myocardial infarction **outcome** **prasugrel** **primary percutaneous coronary intervention** **switch** **ticagrelor**

Acute myocardial infarction (AMI) caused by atherothrombosis is a manifestation of systemic involvement of the arterial vascular bed and the presence of vulnerable atherosclerotic plaques in coronary arteries **(1,2)**. Platelets are crucial for the formation of an occlusive thrombus attached to the rupture and fissure of an unstable plaque in an infarct-related artery. The role of platelet activation and subsequent aggregation has been verified by the substantial impact of antiplatelet drugs on the prognosis of patients with MI **(3–8)**. The benefit of dual antiplatelet therapy on clinical outcomes is most prominent in the acute phase of MI. It is also significant during the initial months after the event and continues to be important in the long term **(9,10)**.

Prasugrel and ticagrelor, compared with clopidogrel, have shown higher efficacy in terms of reducing major cardiovascular events, relative to the increased risk of major bleeding **(7,8)**. The net clinical benefit (occurrence of major cardiovascular events and major bleeding events unrelated to coronary artery bypass graft surgery) **(11,12)** was the line of reasoning for preferring 1 of the new drugs instead of clopidogrel in combination with aspirin for invasively managed AMI **(13)**.

The multicenter PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) study was the first randomized head-to-head comparison of prasugrel and ticagrelor, with regard to efficacy and safety, in patients with AMI undergoing primary percutaneous coronary intervention (pPCI) strategy. The early outcomes related to the hospitalization phase did not support the hypothesis that 1 of the potent antiplatelet drugs was more effective or safer than the other in preventing ischemic and bleeding events **(14)**.

Globally, patient-reported financial hardship associated with medication expenses was linked to a greater likelihood of medication nonadherence **(15)**. Participating sites did not have any opportunity for study medication reimbursement after discharge. Therefore, the design of the present study anticipated that cost sharing of the study drugs might result in patients switching to clopidogrel.

The 1-year follow-up of the PRAGUE-18 study focused on: 1) a comparison of efficacy and safety between prasugrel and ticagrelor; and 2) the risk of major ischemic events related to an economically motivated post-discharge switch to clopidogrel.

Methods

The randomized PRAGUE-18 study was an open-label, phase IV, controlled clinical trial. Tertiary cardiology centers in the Czech Republic with 24/7 capability to perform pPCI were involved in the study. A complete list of collaborating sites and all investigators is provided in the Online Appendix. The multicenter ethics committee at the University Hospital Kralovske Vinohrady in Prague, Czech Republic (the coordinating site **[16]**), and the ethics committee of each of the participating sites, approved the study. The study was an independent academic project without any support from pharmaceutical companies. Details of the study design and methods were published previously **(14)**. In summary, patients with AMI treated with a pPCI strategy were enrolled in the study. A diagnosis of AMI was based on clinical presentation and the presence of ST-segment elevation (≥1 mm) in 2 related leads at a minimum, or ST-segment depression (≥2 mm) in 3 leads at a minimum, or a new bundle branch block. The term “pPCI strategy” (an immediate, i.e., within 2 h of hospital admission, coronary angiography ± PCI) was used for both ST-segment elevation MI (STEMI) and very high-risk MI without persistent ST-segment elevation (non-STEMI with ongoing ischemia). Patients were enrolled in the study after they signed an informed consent form. Criteria that excluded study participation were as follows: history of stroke, serious bleeding within the previous 6 months, indication for chronic oral anticoagulation therapy, administration of clopidogrel ≥300 mg or of any other antiplatelet medication before randomization (with the exception of aspirin and a lower dose of clopidogrel), patients older than 75 years whose body weight was also <60 kg (i.e., the presence of both parameters simultaneously was an exclusion criterion), moderate or severe hepatic dysfunction, concomitant treatment with a strong CYP3A4 inhibitor, or known hypersensitivity to prasugrel or ticagrelor. The study protocol was registered under PRAGUE-18 (NCT02808767).

For a complete list of study committees and the members that supervised study conduct and endpoint adjudication, see the supplementary appendix of the primary paper **(14)**. The data monitoring committee of the coordinating site monitored the study at all sites at regular intervals and supervised the completeness of the data gathered and entered.

Patients with AMI treated with pPCI were randomly assigned to prasugrel (60 mg initial dose and a maintenance dose of 10 mg daily, or 5 mg daily for those older than 75 years of age or those who weighed <60 kg), or to ticagrelor (180 mg initial dose and a maintenance dose of 90 mg twice daily). The study enrollment phase was terminated

prematurely for futility. The initial drug dose was administered immediately after patient randomization, which took place on arrival at the hospital (as a rule, directly in the catheterization laboratory). The intended treatment duration using study medications was 12 months. A dose of 100 mg daily was recommended for concomitant treatment with aspirin. The indication for PCI after coronary angiography and the decision to administer any adjunctive medication in support of PCI were left to the discretion of the threating physicians.

Patients in the study were followed for 12 months after enrollment. Short-term study results were published, which involved a comparison between prasugrel and ticagrelor efficacy and safety in the hospitalization phase of AMI and the first month after the event. The key combined endpoint for a mutual comparison of the study drugs for the entire study period was the occurrence of cardiovascular death, nonfatal MI, or stroke. Furthermore, the occurrence of individual components of the key combined endpoint, all-cause death, definite stent thrombosis (according to the Academic Research Consortium criteria), and bleeding defined according to TIMI (Thrombolysis In Myocardial Infarction) and Bleeding Academic Research Consortium criteria were also followed. Definitions of all study endpoints are provided in the supplementary appendix of the article that presented the short-term results **(14)**. The occurrence of events during the study follow-up was recorded at the time of scheduled visits. After the study, the occurrence of monitored events was further verified by connecting the study's electronic database with the data of national databases of the Institute of Health Information and Statistics of the Czech Republic, specifically the following: 1) Database of Deaths, which, at the population level, collects all information about deaths; 2) the National Register of Hospitalized Patients, which contains data about all hospitalizations at the national level; and 3) 2 national cardiology databases—the National Cardiosurgery Register and the National Register of Cardiovascular Interventions.

Study drugs were fully reimbursed during hospitalization. After discharge, the state insurance company paid the cost of prasugrel in patients with STEMI and left main disease, proximal left anterior descending-vessel disease, or multivessel disease; however, treatment with ticagrelor for these conditions was not covered. Based on the protocol, prior to the end of their hospitalization, every patient was informed about the out-of-pocket costs for study drug treatment. Patients were also informed, by their treating physician, about the clinical benefits of long-term treatment with prasugrel/ticagrelor compared with clopidogrel (a drug that was fully reimbursed by state insurance). The study protocol allowed patients, who were not willing to accept the costs associated with a study medication, to switch to clopidogrel. Information regarding termination of study medications was recorded. In cases of ambiguity, the date and the reason for the drug switch were verified by the prescribing doctors and in individual cases by the health insurance company.

The authors had access to all study data after the database was closed. Independent analyses were performed in cooperation with the database administrator, the Institute of Biostatistics and Analyses of Masaryk University (Brno, Czech Republic), under the leadership of one of the co-authors (J.J.). The authors drafted the manuscript and take full responsibility for this report, attest to the fidelity of this report to the study protocol, and made the decision to submit the manuscript for publication.

Statistical analysis

The calculation method for the sample size, with respect to the defined primary endpoint was described in detail in the supplementary material accompanying the first paper **(14)**. The power analysis was computed for a primary endpoint difference of 2.5%, a 2-sided overall alpha level of 0.05, and a statistical power of 80%. Power and Precision software, release 4.0 (Biostat, Englewood, New Jersey) was adopted for the power analysis.

The presented analysis uses standard descriptive statistics to describe the data, absolute and relative frequencies for categorical variables, and the median with a 5th to 95th or 25th to 75th percentile for continuous data. Number needed to treat was used for the description of practical significance of differences in endpoint occurrence. Statistical significance of differences in categorical variables between patient groups was tested using Fisher exact test; the Mann-Whitney *U* test was used for continuous variables; Bonferroni correction was used to take into account the problem of multiple testing of separated tests for each treatment switch reason. The occurrence of events over time was described and visualized using the Kaplan-Meier methodology; the statistical significance of differences between groups was tested using log-rank test. The maximum follow-up length was set as 365 days. The significance of predictors for the occurrence of events was evaluated using the 1-dimensional and multidimensional Cox proportional hazards model (the Cox proportional hazards model with time-dependent covariates was adopted for switches to clopidogrel) and was described using hazard ratios (HRs), their 95% confidence intervals (CIs), and statistical significance. All analyses were performed using SPSS version 24.0.0.1 (IBM Corporation, Armonk, New York) and R version 3.3.2 with the ggplot2 2.2.1 package (R Project, Vienna, Austria).

Results

A total of 1,230 patients with AMI were enrolled in the study. They were treated using the pPCI strategy at 14 participating sites. Baseline patient- and procedure-related characteristics were well matched as reported in the first article **(14)**. Patient randomization was completed in May 2016 and the follow-up period was completed in May 2017. No patients were lost to follow-up. The parameters used, and the occurrences of ischemic and bleeding events were available for all patients enrolled in the study (**Figure 1**). Information about the precise date of switching from the study medication was not specified in 3 patients; in these patients, the date of the visit during which the termination of therapy was recorded was used as the treatment discontinuation date.

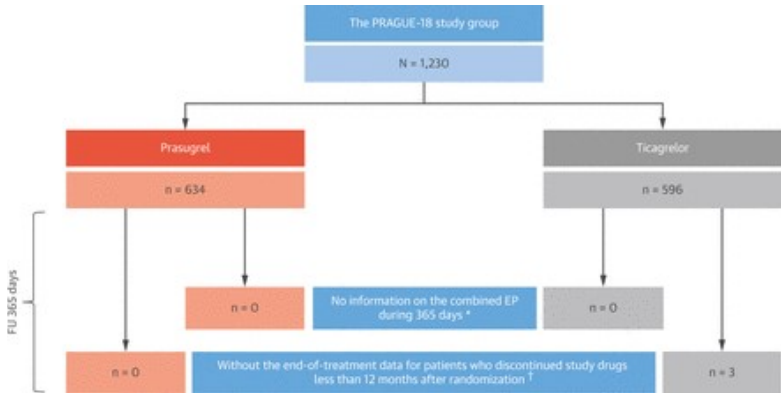


Figure 1 **Download figure | Open in new tab | Download powerpoint**
Study Flow Chart

Occurrences of events during the study follow-up were recorded at the time of scheduled visits. After the study, the occurrence of monitored events was further verified by connecting the study's electronic database with data from the national databases of the Institute of Health Information and Statistics of the Czech Republic. No patients were lost to follow-up. Information about the precise date of switching from the study medication was not specified in 3 patients; in these patients, the date of the visit during which the termination of therapy was recorded was used as the treatment discontinuation date. *The combined efficacy endpoint was cardiovascular death, nonfatal myocardial infarction, or stroke. Missing information in 19 patients was supplemented from national registries of the Institute of Health Information and Statistics of the Czech Republic. †For missing end-of-treatment data in 3 patients, a visit date was added corresponding to the date that treatment discontinuation was reported. EP = efficacy endpoint; FU = follow-up; PRAGUE-18 = Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction.

The incidence of the key composite efficacy endpoint (cardiovascular death, nonfatal MI, or stroke) was 6.6% in the prasugrel group compared with 5.7% in the ticagrelor group (HR [prasugrel vs. ticagrelor]: 1.167; 95% CI: 0.742 to 1.835; p = 0.503) (**Table 1**, **Central Illustration**). Risks of additional efficacy endpoints are shown in **Table 1**. There were no significant differences in rates of cardiovascular death (3.3% vs. 3.0%; p = 0.769), nonfatal MI (3.0% vs. 2.5%; p = 0.611), stroke (1.1% vs. 0.7%; p = 0.423), all-cause death (4.7% vs. 4.2%; p = 0.654), and definite stent thrombosis (1.1% vs. 1.5%; p = 0.535). Kaplan-Meier curves that separately compare time to cardiovascular death, all-cause death, nonfatal MI, and stroke are depicted in **Figures 2A to 2D**. No significant interaction terms were found in subgroup analyses (Online Tables 1 and 2).

Central Illustration **Download figure | Open in new tab | Download powerpoint**

Comparison Between Prasugrel and Ticagrelor in AMI: Key Efficacy Endpoint

One-year occurrence of cardiovascular death, nonfatal myocardial infarction, or stroke in patients with acute myocardial infarction (AMI) treated with primary percutaneous coronary intervention strategy and randomized to prasugrel or ticagrelor. Visualization of time-to-event analysis was done using the Kaplan-Meier estimate of survival function. Differences between prasugrel and ticagrelor were tested using log-rank test. Prasugrel and ticagrelor are similarly effective during the first year after myocardial infarction (hazard ratio: 1.167; 95% confidence interval: 0.742 to 1.835; p = 0.503).

Figure 2 **Download figure | Open in new tab | Download powerpoint**

Efficacy Endpoints

One-year occurrence of all-cause death (A), cardiovascular death (B), nonfatal (spontaneous) myocardial infarction (C), and stroke (D) in patients with acute myocardial infarction treated with primary percutaneous coronary intervention strategy and randomized to prasugrel or ticagrelor. Visualization of time-to-event analysis was done using Kaplan-Meier estimate of survival function. Differences between prasugrel and ticagrelor were tested using log-rank test. No significant differences between prasugrel and ticagrelor were observed in the occurrence of all-cause death (4.7% vs. 4.2%; p = 0.654) (A), cardiovascular death (3.3% vs. 3.0%; p = 0.769) (B), nonfatal myocardial infarction (3.0% vs. 2.5%; p = 0.611) (C), or stroke (1.1% vs. 0.7%; p = 0.423) (D).

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Table 1
Endpoints

The following were identified in the study population as significant risk predictors of the combined ischemic endpoint: suboptimal result or unsuccessful PCI (HR: 4.672; 95% CI: 2.571 to 8.491; p < 0.001), right bundle branch block on the initial electrocardiogram (ECG) (HR: 4.103; 95% CI: 1.656 to 10.166; p = 0.002), left bundle branch block on the initial ECG (HR: 3.994; 95% CI: 1.459 to 10.932; p = 0.007), bundle branch block on the initial ECG (HR: 3.761; 95% CI: 1.807 to 7.826; p < 0.001), Killip class at admission (HR [Killip II vs. Killip I]: 2.579; 95% CI: 1.213 to 5.486; p = 0.014; and HR [Killip III + IV vs. Killip I]: 13.092; 95% CI: 7.982 to 21.476; p < 0.001), any bleeding (HR: 1.850; 95% CI: 1.036 to 3.304; p = 0.038), and multivessel disease (HR: 1.808; 95% CI: 1.130 to 2.893; p = 0.013) (Online Table 3).

Bleeding events occurred in 10.9% of patients in the prasugrel group and in 11.1% in the ticagrelor group (HR: 0.985; 95% CI: 0.703 to 1.381; p = 0.930) (**Table 1**, **Figure 3**). There was no significant difference in the rate of major bleeding as defined by TIMI (0.9% vs. 0.7%; p = 0.754) and Bleeding Academic Research Consortium (2.4% vs. 1.5%; p = 0.308) criteria.

Figure 3
Bleeding

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One-year occurrence of bleeding events in patients with acute myocardial infarction treated with primary percutaneous coronary intervention strategy and randomized to prasugrel or ticagrelor. Visualization of time-to-event analysis was done using the Kaplan-Meier estimate of survival function. Differences between prasugrel and ticagrelor were tested using log-rank test. Prasugrel and ticagrelor were similarly safe during the first year after myocardial infarction (hazard ratio: 0.985; 95% confidence interval: 0.703 to 1.381; p = 0.930).

The reasons for premature study treatment termination are shown in Online Table 4. The difference in the proportion of patients discontinuing treatment with prasugrel and ticagrelor due to adverse effects was nonsignificant. The percentage of patients who switched during the 12-month study course to clopidogrel for economic reasons was 34.1% (n = 216) for prasugrel, and 44.4% (n = 265) for ticagrelor (p = 0.003 with Bonferroni correction for number of "switch reasons" categories). The median time on the study medication before switching was 8 (interquartile range [IQR]: 5 to 37) days for prasugrel, and 8 (IRQ: 5 to 34) for ticagrelor (p = 0.789). Patient cost sharing for study drugs was the most common reason for switching to clopidogrel after hospital discharge, for both treatment arms (69.7% of switches from prasugrel and 75.9% from ticagrelor; p = 0.316 with Bonferroni correction). The time distribution for switching drug treatment for economic reasons is presented in Online Figure 1.

A comparison of patient characteristics for those who switched their study treatment to clopidogrel for economic reasons versus patients, who did not change treatment, is presented in Online Table 5. Patients who switched to clopidogrel due to the costs associated with prasugrel and ticagrelor therapy had a significantly lower appearance of bundle branch block on the baseline ECG (1.5% vs. 4.4%; p = 0.005), a significantly lower rate of Killip class ≥2 at admission (7.9% vs. 14.3%; p < 0.001), a significantly lower presence of the left main disease (1.0% vs. 4.8%; p < 0.001), the portion of those with a suboptimal post-procedural result or technically unsuccessful PCI was 3.1% versus 5.9% (p = 0.028).

Patients who were economically motivated to switch to clopidogrel, had (when compared with patients who continued the study medications) a lower risk of major cardiovascular ischemic events (cardiovascular death, nonfatal MI, or stroke) (2.5% vs. 8.5%; HR: 0.433; 95% CI: 0.210 to 0.894; p = 0.024). Premature termination of study medications for other than economic reasons resulted in a significant increase of the occurrence of the ischemic endpoint (HR: 3.420; 95% CI: 1.823 to 6.415; p < 0.001) (**Table 2**). Switching to clopidogrel for economic reasons resulted in a significant decrease of the bleeding risk compared with continued treatment with the study drugs (7.3% vs. 13.4%; HR: 0.416; 95% CI: 0.246 to 0.701; p = 0.001) (**Table 2**). A comparison of the occurrence of ischemic and bleeding events, after switching to clopidogrel, between patients who were initially randomized to prasugrel and those initially randomized to ticagrelor are detailed in Online Table 6; no significant differences were found.

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Table 2

Switch to Clopidogrel and Resulting Ischemic and Bleeding Risks

Discussion

The multicenter PRAGUE-18 study was the first and, for now, the only completed randomized study aimed at performing a direct comparison of prasugrel and ticagrelor in patients with AMI treated using the pPCI strategy. One-year outcomes, in agreement with short-term results, did not confirm the hypothesis that 1 of the potent $P2Y_{12}$ inhibitors was more efficient and/or safer than the other. Previously reported primary net-clinical endpoint (death resulting from any cause, re-MI, urgent revascularization, stroke, serious bleeding requiring transfusion, or serious bleeding prolonging the hospital stay) at day 7 (or at discharge if before the seventh day) was 4.0% in prasugrel and 4.1% in ticagrelor (odds ratio: 0.98; 95% CI: 0.55 to 1.73; p = 0.939). The difference in the composite efficacy endpoint (cardiovascular death, nonfatal MI, or stroke) at the end of the 12-month study period was also nonsignificant; 6.6% in the prasugrel group compared with 5.7% in the ticagrelor group (HR: 1.167; 95% CI: 0.742 to 1.835; p = 0.503) (**Table 1**, **Central Illustration**). No significant interactions were found between the subgroups and the occurrence of the combined endpoint.

Periprocedural MI was not a component of efficacy outcomes because unlike spontaneous MI, which is a powerful predictor of subsequent mortality among AMI patients undergoing PCI, the diagnosis and impact of periprocedural MI on the patient prognosis are not clear **(17)**. Notwithstanding, when a periprocedural MI was included in the efficacy outcome, which is the case for many randomized studies comparing the efficacy and safety of antithrombotics in pPCI, the occurrence of cardiovascular death, spontaneous or periprocedural nonfatal MI, or stroke at 12 months was 8.7% in patients taking prasugrel and 8.4% in patients taking ticagrelor (HR: 1.038; 95% CI: 0.703 to 1.534; p = 0.849; number needed to treat: 333) (Online Figure 2). Number needed to treat with prasugrel to prevent an identically defined combined ischemic endpoint in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) study (prasugrel vs. clopidogrel) was 46. In a similar way, the number needed to treat with ticagrelor for the prevention of an identically defined ischemic endpoint in the PLATO (A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome) study (ticagrelor vs. clopidogrel) was 53.

During the whole study follow-up, no difference in bleeding occurrences were observed between the 2 compared groups (**Table 1**, **Figure 3**). The comparison of both drugs from a large all-comer registry showed an insignificant difference in their efficacy in terms of 1-year STEMI mortality. Considering the differences in the risk characteristics of patients treated with prasugrel and those treated with ticagrelor, the relevance of this comparison is limited **(18)**. After matching for risk profile, no significant difference in 1-year mortality between prasugrel and ticagrelor was reported among patients ≥65 years of age who were discharged from the hospital after PCI for acute coronary syndromes (5.4% ticagrelor vs. 3.7% prasugrel; HR: 1.3; 95% CI: 0.8 to 2.2; p = 0.31) **(19)**.

Switching between $P2Y_{12}$ inhibitors occurs commonly in clinical practice. However, the clinical effect of most switching strategies is not fully determined **(20)**. The PRAGUE-18 study reflected a real clinical scenario; the cost burden associated with prasugrel/ticagrelor therapy (compared with clopidogrel), after hospital discharge, is a reality in most countries where the drugs are available. Costs are an important consideration and studies have shown that as out-of-pocket costs increase, medication adherence declines **(21)**. Reduced costs associated with a generic formulation of clopidogrel and concerns about increased risk of bleeding with prasugrel and ticagrelor remain the most important reasons for de-escalation **(22)**. The proportion of study patients ending prasugrel/ticagrelor treatment prematurely for economic reasons reflects the financial burden associated with the cost of treatment in the Czech Republic. The out-of-pocket costs were comparable for both drugs. The higher discontinuation rate for ticagrelor was a consequence of selective discrimination in favor of prasugrel, which was fully reimbursed by state insurance in patients with risky findings on coronary angiography (specified under Methods).

In accordance with the methodology of the study, patients who wanted to switch to clopidogrel for economic reasons were able to do so after consultation and agreement with their doctor(s), who were active in trying to convince patients to continue the study drugs (see Methods). This fact is supported by: 1) the time distribution of switches for economic reasons after discharge (most of those who switched to clopidogrel from the study drugs did so immediately after discharge from the hospital and after consultation with their study physician) (Online Figure 1, Online Appendix); and 2) the lower ischemic risk of patients who switched to clopidogrel for economic reasons (Online Table 5). The risk of occurrence of the combined ischemic endpoint was also significantly lower in those patients who switched to clopidogrel compared with those who continued with the study drugs (**Table 2**).

The substitution of a potent $P2Y_{12}$ inhibitor with clopidogrel (for economic reasons) resulted in a significant reduction in bleeding risk. In agreement with published papers **(23,24)**, the PRAGUE-18 study documented that bleeding in AMI patients treated with stent implantation significantly increased the risk of major cardiovascular events (Online Table 3).

With a vision of maximizing the benefit and minimizing the risk of antiplatelet therapy for AMI, the TROPICAL ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes Trial) **(25)** verified the hypothesis that a stage-adapted treatment that uses potent platelet inhibition in the acute phase, followed by de-escalation to clopidogrel in the maintenance phase could be an alternative approach to the recently recommended antiplatelet management of AMI treated with PCI. In the study, the switch to clopidogrel was guided by testing platelet function. As shown by the study, the guided switch to clopidogrel in the maintenance phase was noninferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit; it resulted in a significant reduction of bleeding and did not increase the risk of ischemic complications. Identical conclusions were derived from a study that evaluated the net-clinical benefit of switching to clopidogrel from the recommended treatment with potent $P2Y_{12}$ inhibitors in patients without ischemic complications 1 month after index AMI **(26)**.

The importance of the concept of “the need to switch therapy” was recently emphasized by the fact that an international consensus document was developed to address this issue **(22)**. The PRAGUE-18 study presents an algorithm of a safe, controlled switch to clopidogrel during the maintenance phase of AMI treatment. The study also contributes to arguments in favor of the trend toward personalization of treatment of patients with AMI **(27)**; an individualized approach assesses and responds to the risk level of ischemia and bleeding in individual patients. Despite the published data from registries that cast doubt on the benefit of newer drugs compared with (less effective **(28)**) clopidogrel during the maintenance phase of AMI treated with PCI, such a change is only safe in a selected population of low-risk patients, as shown in our study. In agreement with the conclusions of other randomized clinical studies **(7,8)**, switching to clopidogrel from one of the newer drugs (for reasons other than economic) was associated with a significant risk of major ischemic events.

Study limitations

Limitations related to the sample size and premature termination of enrollment, because of futility, were discussed in detail in the first paper **(14)**, which reported on the short-term study results. The needed sample size based on power calculations was estimated to be 1,250 patients in each study arm (estimated occurrences of primary endpoint were 4% vs. 6.5%). An interim analysis after the first 1,130 patients led to a decision to terminate the study early due to futility. The difference in primary endpoint between treatment groups was consistently low and with a growing number of patients it became stabilized around 0.1% (occurrence of the primary endpoint was around 4% in both compared groups). Real differences between study arms did not reach the minimal level of statistical significance during any part of the enrollment period. We considered these arguments to have been sufficient reasons for ending the study prematurely. The present paper focuses on the secondary endpoint for which the power of the study was not computed. Additionally, the post hoc power analysis for the difference in the combined ischemic endpoint between the study arms was computed to be 10%. We used the number-needed-to-treat calculation for an illustration of clinical relevance of the observed difference between prasugrel and ticagrelor relative to the occurrence of the ischemic endpoint **(29)**. Intention-to-treat analysis was used to compare the efficacy and safety of the study drugs. The intention-to-treat principle should be applied for comparisons of treatment arms, in randomized trials with a superiority design, and with heterogeneous treatment duration **(30,31)**. This approach was part of the study design; in other words, a switch from the study drugs was anticipated and allowed.

The observed consequences of switching or not switching to clopidogrel were not the results of a randomized comparison. Benefit and harm of a transition from recommended potent $P2Y_{12}$ inhibitors to clopidogrel in AMI shortly after discharge, based on patient-related risk and procedural results, must be validated in a proof-of-concept randomized trial.

Conclusions

One-year results from this head-to-head comparison between prasugrel and ticagrelor, in agreement with the results observed in the early phase, did not confirm the hypothesis that 1 of the potent $P2Y_{12}$ inhibitors is more effective or safer than the other in acute myocardial infarction treated with primary angioplasty. Economically motivated, early post-discharge switch to clopidogrel, when approved by treating physicians, was not associated with increased risk of ischemic events.

Perspectives
COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients with MI undergoing primary PCI, antiplatelet therapy with prasugrel or ticagrelor is associated with similar outcomes during the first year.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to confirm the risks and benefits of selective post-discharge transition from a potent $P2Y_{12}$ inhibitor to clopidogrel based on patient and procedural characteristics following primary PCI in patients with acute MI.

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Appendix

Online Data [S0735109717415245_mmc1.docx]

Footnotes

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Abbreviations and Acronyms

AMI	acute myocardial infarction
CI	confidence interval
ECG	electrocardiogram
HR	hazard ratio
IQR	interquartile range
pPCI	primary percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

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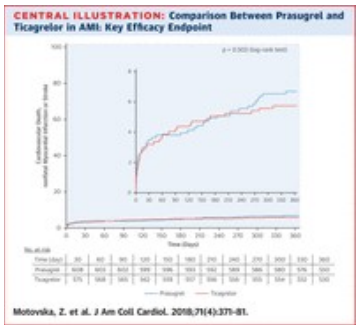

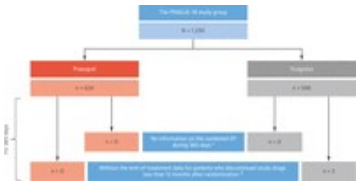

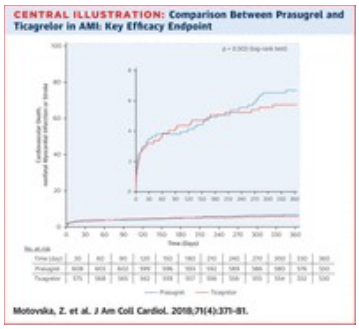

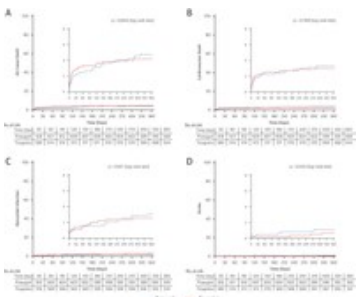

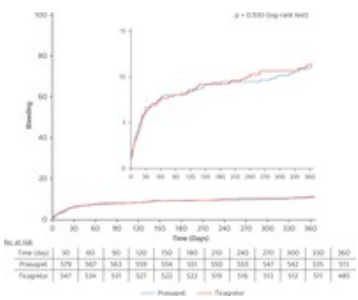

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