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One-year Outcomes of Prasugrel Versus Ticagrelor In Acute Myocardial Infarction Treated With Primary Angioplasty: The PRAGUE-18 Study

Short title: Comparison between prasugrel and ticagrelor in AMI

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ABSTRACT
Background. Early outcomes of patients in the PRAGUE-18 study did not find any significant differences between two potent $P2Y_{12}$ inhibitors.
Objective. The one-year follow-up of the PRAGUE-18 study focused on (1) a comparison of efficacy and safety between prasugrel and ticagrelor, and (2) on 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 PCI were randomized to prasugrel or ticagrelor with an intended treatment duration of 12 months. The combined endpoint was cardiovascular death, MI, or stroke at one year. Since 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; HR, 1.167; 95% CI, 0.742–1.835; 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 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 switched to clopidogrel had (compared to patients who continued the study medications) a lower risk of major cardiovascular events, however they also had lower ischemic risk.
Conclusion. 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.

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CONDENSED ABSTRACT: Prasugrel and ticagrelor are similarly effective and safe during the first year after myocardial infarction treated with primary PCI strategy. Economically motivated early post-discharge switches to clopidogrel were not associated with an increased risk of ischemic events. The findings contribute to arguments in favor of the trend toward personalization of treatment of patients with AMI; an individualized approach assesses and responds to the risk level of ischemia and bleeding in individual patients.

Keywords: myocardial infarction, primary percutaneous coronary intervention, outcome, prasugrel, ticagrelor, switch

Abbreviations
AMI – acute myocardial infarction
pPCI – primary percutaneous coronary intervention
STEMI – myocardial infarction with ST-segment elevation
NSTEMI – myocardial infarction without persistent ST-segment elevation
HR – Hazard ratio
CI – Confidence Interval

TIMI – Thrombolysis in Myocardial Infarction
BARC – Bleeding Academic Research Consortium
TRITON–TIMI - Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
PLATO – Platelet Inhibition and Patient Outcomes

Introduction

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 anti-platelet drugs on the prognosis of patients with MI (3-8). The benefit of dual anti-platelet 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 to 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 one of the new drugs instead of clopidogrel in combination with aspirin for invasively managed AMI (13).

The multicenter PRAGUE-18 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 one of the potent anti-platelet 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 non-adherence (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 one-year follow-up of the PRAGUE-18 study focused on (1) a comparison of efficacy and safety between prasugrel and ticagrelor, and (2) on 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 supplementary 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 primary PCI strategy were enrolled in the study. A diagnosis of AMI was based on clinical presentation and the presence of ST elevation (≥ 1mm) in two related leads at a minimum, or ST depression (≥ 2mm) in three leads at a minimum, or a new bundle branch block. The term 'primary PCI strategy' (an immediate, i.e., within 2 hours 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 (NSTEMI 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 Clinicaltrials.gov NCT02808767.

For a complete list of study committees and the members that supervised study conduct and endpoint adjudication see the Supplementary Appendix, available with the full text of the primary paper at circ.ahajournals.org. 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 less than 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 upon arrival at the hospital (as a rule, directly in the cathlab). The intended treatment duration using study medications was twelve 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 twelve 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, non-fatal 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 and BARC criteria were also followed. Definitions of all study endpoints are provided in the supplementary appendix of the article that presented the short-term results. 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 (www.uzis.cz), specifically the (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) two national cardiology databases, (3a) the National Cardiosurgery Register and (3b) 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- or multi-vessel 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 to clopidogrel (a drug which 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 of the manuscript 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 of this paper (JJ). 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.[15] The power analysis was computed for a primary endpoint difference of 2.5%, a two-sided overall alpha level of 0.05, and a statistical power of 80%. Power and Precision™ software release 4.0 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 5–95 or 25–75 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's exact test; the Mann-Whitney test was used for continuous variables; Bonferroni's 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 one-dimensional and multi-dimensional 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, their 95% confidence intervals, and statistical significance. All analyses were performed using SPSS 24.0.0.1 (IBM Corporation, 2016) and R version 3.3.2 with the ggplot2 2.2.1 package.

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.

The incidence of the key composite efficacy endpoint (cardiovascular death, non-fatal MI, or stroke) was 6.6% in the prasugrel group compared with 5.7% in the ticagrelor group with HR (prasugrel versus ticagrelor), 1.167; 95% CI, 0.742–1.835; P=0.503 (**Table 1, Figure 2**). Risks of additional efficacy endpoints are shown in **Table 1**. There were no significant differences in rates of CV death (3.3% versus 3.0%, P=0.769), non-fatal MI (3.0% versus 2.5%,

P=0.611), stroke (1.1% versus 0.7%, P=0.423), all-cause death (4.7% versus 4.2%, P=0.654), and definite stent thrombosis (1.1% versus 1.5%, P=0.535). Kaplan Meier curves that separately compare time to cardiovascular death, all-cause death, non-fatal MI, and stroke are depicted in **Figure 3A-D**. No significant interaction terms were found in subgroup analyses (Online Table 1).

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, 2.571–8.491; P<0.001), right bundle branch block on the initial ECG (HR, 4.103; 95% CI, 1.656–10.166; P=0.002), left bundle branch block on the initial ECG (HR, 3.994; 95% CI, 1.459–10.932; P=0.007), bundle branch block on the initial ECG (HR, 3.761; 95% CI, 1.807–7.826; P<0.001), Killip class at admission (HR (Killip II versus Killip I), 2.579; 95% CI, 1.213–5.486; P=0.014 and HR (Killip III+IV versus Killip I), 13.092; 95% CI, 7.982–21.476; P<0.001), any bleeding (HR, 1.850; 95% CI, 1.036–3.304; P=0.038), and multi-vessel disease (HR, 1.808; 95% CI, 1.130–2.893; P=0.013) (Online Table 2).

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, 0.703–1.381; P=0.930 (**Table 1, Figure 4**). There was no significant difference in the rate of major bleeding as defined by the TIMI (0.9% vs. 0.7%, P=0.754) and BARC (2.4% vs. 1.5%, P=0.308) criteria.

The reasons for premature study treatment termination are shown in Online Table 3 (Supplementary Appendix). The difference in the proportion of patients discontinuing treatment with prasugrel and ticagrelor due to adverse effects was non-significant. The percentage of patients who switched during the twelve-months 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 (25–75 percentile) time on the study medication before switching was 8 (5–37) days for prasugrel, and 8 (5–34) 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 4. 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% versus 4.4%, P=0.005), a significantly lower rate of Killip class ≥ 2 at admission (7.9% versus 14.3%, P<0.001), a significantly lower presence of the left main disease (1.0% versus 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 to patients who continued the study medications) a lower risk of major cardiovascular ischemic events (cardiovascular death, non-fatal MI, or stroke) 2.5% versus 8.5%, HR, 0.433; 95% CI, 0.210–0.894; 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, 1.823–6.415; P<0.001 (**Table 2**). Switching to clopidogrel for economic reasons resulted in a significant decrease of the bleeding risk compared to continued treatment with the study drugs, 7.3% versus 13.4%, HR, 0.416; 95% CI 0.246–0.701; 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 5; no significant differences were found.

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 primary PCI strategy. One-year outcomes, in agreement with short-term results, did not confirm the hypothesis that one 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, 0.55–1.73; P=0.939). The difference in the composite efficacy endpoint (cardiovascular death, non-fatal MI, or stroke) at the end of the twelve-month study period was also non-significant; 6.6% in the prasugrel group compared to 5.7% in the ticagrelor group (HR, 1.167; 95% CI, 0.742–1.835 P=0.503) (**Table 1, Figure 2**). 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) non-fatal MI, or stroke at twelve months was 8.7% in patients taking prasugrel and 8.4% in

patients taking ticagrelor (HR, 1.038; 95% CI, 0.703–1.534; P=0.849, Number needed to treat = 333) (Online Figure 2, Supplementary Appendix). Number needed to treat with prasugrel to prevent an identically defined combined ischemic endpoint in the TRITON study (prasugrel versus 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 study (ticagrelor versus clopidogrel) was 53.

During the whole study follow up, no difference in bleeding occurrences were observed between the two compared groups (**Table 1, Figure 4**). The comparison of both drugs from a large all-comer register showed an insignificant difference in their efficacy in terms of one-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 one-year mortality between prasugrel and ticagrelor was reported among ≥65-year-old patients discharged from the hospital after PCI for acute coronary syndromes (5.4% ticagrelor vs. 3.7% prasugrel; HR, 1.3; 95% CI: 0.8–2.2; 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 to 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, Supplementary appendix), and (2) the lower ischemic risk of patients who switched to clopidogrel for economic reasons (Online Table 4). The risk of occurrence of the combined ischemic endpoint was also significantly lower in those patients who switched to clopidogrel compared to 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 2).

With a vision of maximizing the benefit and minimizing the risk of antiplatelet therapy for AMI, the TROPICAL ACS study (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 non-inferior to standard treatment with prasugrel at one 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 one 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 to (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.

Limitations related to the sample size and premature termination of enrollment, because of futility, were discussed in detail in the first paper, which reported on the short-term study

results. The needed sample size based on power calculations was estimated to be 1250 patients in each study arm (estimated occurrences of primary endpoint were 4% versus 6.5%). An interim analysis after the first 1130 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 manuscript 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, i.e., 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 one 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 Medical Knowledge: The multicentre PRAGUE-18 study is 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 pPCI strategy.

Competency in Patient Care: Prasugrel and ticagrelor are similarly effective during the first year after myocardial infarction.

Translational Outlook 1: The study is a model for a safe, controlled switch to clopidogrel during the maintenance phase of AMI treatment, which also takes into account patient related risks.

Translational Outlook 2: 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

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Figure legends

Figure 1. 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 (www.uzis.cz).
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.

Figure 2. Key efficacy endpoint. One-year occurrence of cardiovascular death, non-fatal MI or stroke in patients with AMI treated with pPCI strategy and randomized to prasugrel or ticagrelor. Visualisation 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 MI (HR, 1.167; 95% CI, 0.742–1.835; P=0.503).

Figure 3. Efficacy endpoints. One-year occurrence of all-cause death (A), cardiovascular death (B), non-fatal (spontaneous) MI (C), and stroke (D) in patients with AMI treated with pPCI strategy and randomized to prasugrel or ticagrelor. Visualisation 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% versus 4.2%, P=0.654) (A), CV death (3.3% versus 3.0%, P=0.769) (B), non-fatal MI (3.0% versus 2.5%, P=0.611) (C), or stroke (1.1% versus 0.7%, P=0.423) (D).

Figure 4. Bleeding. One-year occurrence of bleeding events in patients with AMI treated with pPCI strategy and randomized to prasugrel or ticagrelor. Visualisation 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 MI (HR, 0.985; 95% CI, 0.703–1.381; P=0.930).

Table 1. End points

	Prasugrel	Ticagrelor	Hazard ratio (95% CI)	P-value
Day 365				
Combined ischemic endpoint				
Death from cardiovascular causes, non-fatal myocardial infarction or stroke	42 (6.6%)	34 (5.7%)	1.167 (0.742–1.835)	0.503
Death from cardiovascular causes	21 (3.3%)	18 (3.0%)	1.099 (0.585–2.062)	0.769
Non-fatal myocardial infarction	19 (3.0%)	15 (2.5%)	1.192 (0.606–2.347)	0.611
Stroke	7 (1.1%)	4 (0.7%)	1.653 (0.484–5.650)	0.423
Definite stent thrombosis	7 (1.1%)	9 (1.5%)	0.732 (0.270–1.965)	0.535
Death from any cause	30 (4.7%)	25 (4.2%)	1.129 (0.664–1.919)	0.654
Bleeding	69 (10.9%)	66 (11.1%)	0.985 (0.703–1.381)	0.930

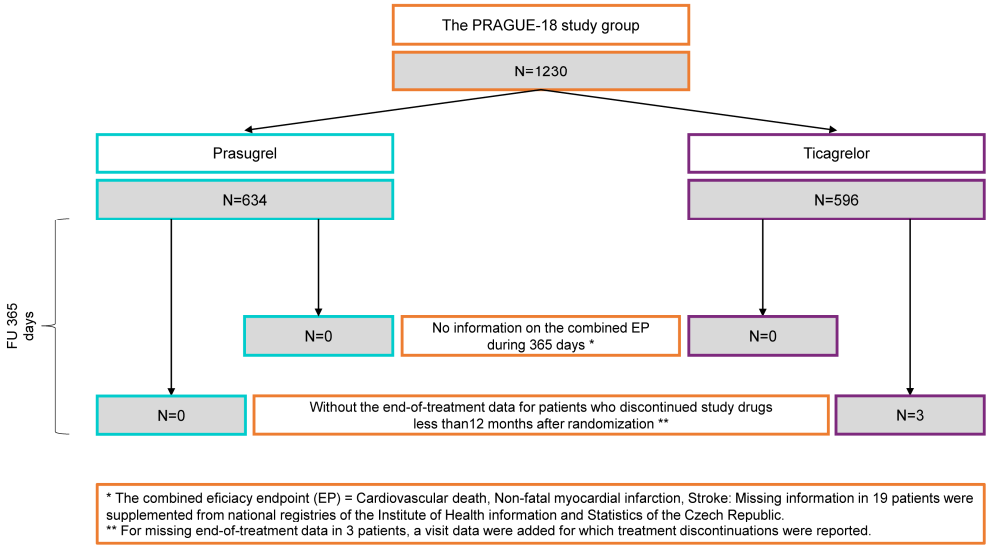
Absolute and relative frequencies were used for categorical variables. The hazard ratio was based on the Cox proportional hazard model (ticagrelor was reference category).

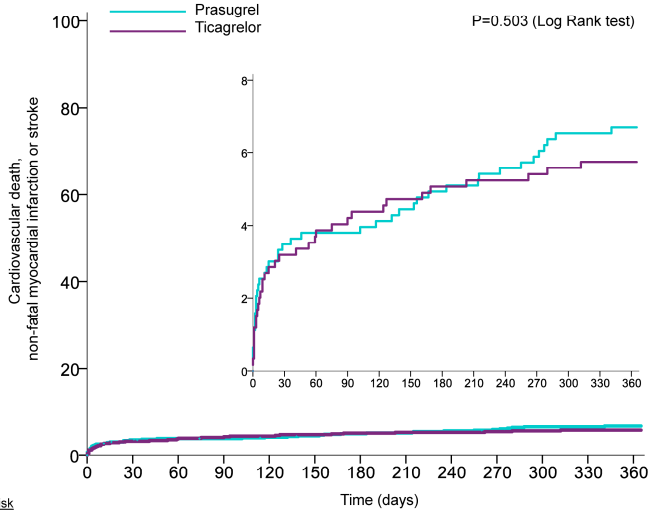
Table 2. Switch to clopidogrel and resulting ischemic and bleeding risks

		HR (95% CI)	P-value
Risk of ischemic endpoint *	Economically motivated switch (N=481)	0.433 (0.210–0.894)	**0.024**
	Switch from other reasons (N=178)	3.420 (1.823–6.415)	**<0.001**
Risk of bleeding	Economically motivated switch (N=481)	0.416 (0.246–0.701)	**0.001**

***** Cardiovascular death, non-fatal myocardial infarction or stroke.

The hazard ratio was based on the Cox proportional hazard model with time dependent covariates.

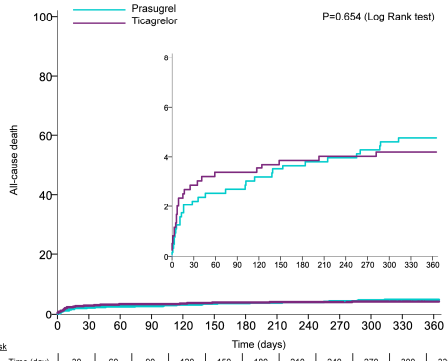




No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	608	603	602	599	596	593	592	589	586	580	576	550
Ticagrelor	575	568	565	562	559	557	556	556	555	554	552	530

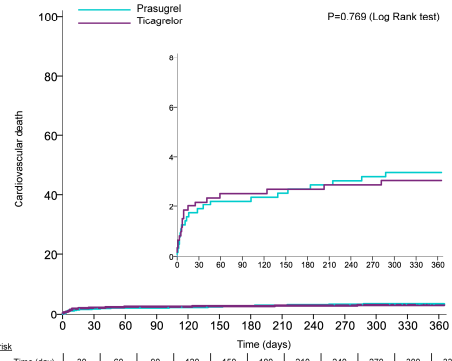
3A



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	618	613	612	609	607	606	605	604	602	599	595	568
Ticagrelor	580	574	574	573	571	571	570	570	570	569	568	544

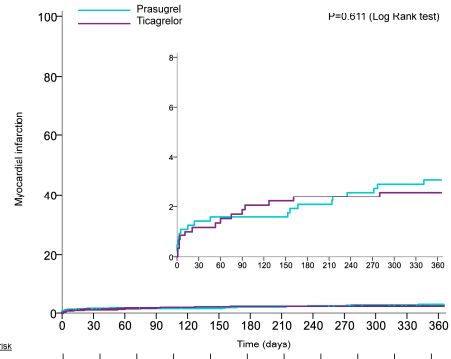
3B



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	618	613	612	609	607	606	605	604	602	599	595	568
Ticagrelor	580	574	574	573	571	571	570	570	570	569	568	544

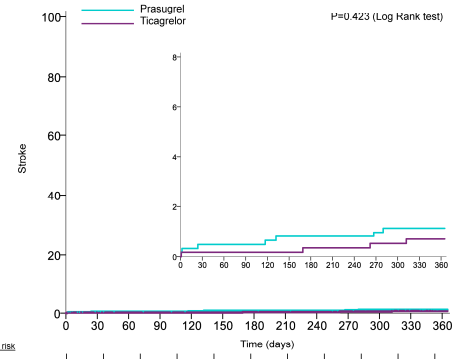
3C



No at risk

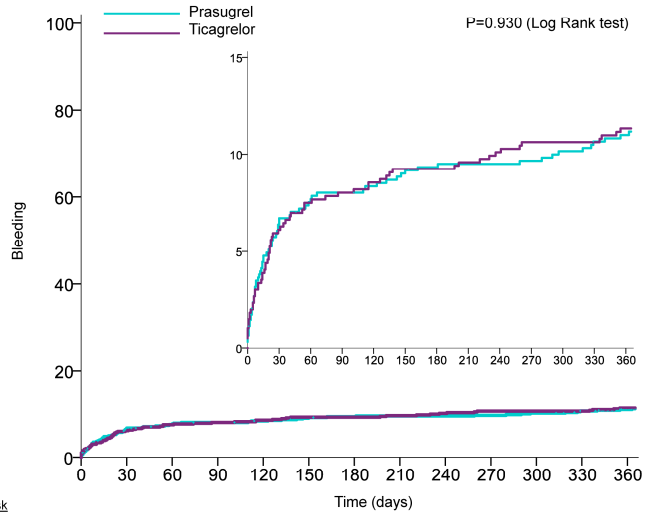
Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	610	605	604	603	602	599	598	595	593	589	585	559
Ticagrelor	576	569	566	563	560	559	558	558	558	556	555	533

3D



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	616	611	610	607	605	604	603	602	599	596	592	565
Ticagrelor	580	574	573	572	570	569	568	568	267	567	565	541



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	579	567	563	559	554	551	550	550	547	542	535	513
Ticagrelor	547	534	531	527	522	522	519	516	513	512	511	485

One-year outcomes of prasugrel versus ticagrelor in acute myocardial infarction treated with primary angioplasty

SUPPLEMENTAL MATERIAL

Online Table 1a Subgroup analysis for ischemic outcome

	Patients	Ischemic endpoint		HR (95% CI)	P-value for
		Prasugrel	Ticagrelor	Prasugrel : Ticagrelor	interaction
Total					
	N=1230	42 (6.6%)	34 (5.7%)	1.167 (0.742–1.835)	-
Age					
<75	N=1108	37 (6.4%)	27 (5.1%)	1.260 (0.767–2.069)	0.565
≥75	N=122	5 (9.3%)	7 (10.3%)	0.873 (0.277–2.751)	
Killip classification					
I–III	N=1184	32 (5.3%)	25 (4.3%)	1.214 (0.720–2.049)	0.564
IV	N=46	10 (40.0%)	9 (42.9%)	0.886 (0.360–2.182)	
I+II	N=1167	28 (4.7%)	23 (4.0%)	1.158 (0.667–2.010)	0.772
III+IV	N=63	14 (40.0%)	11 (39.3%)	1.000 (0.454–2.204)	
Chronic kidney disease					
No	N=1214	41 (6.6%)	34 (5.8%)	1.138 (0.722–1.793)	–
Yes	N=16	1 (12.5%)	0 (0.0%)	–	
Diabetes					
No	N=980	31 (6.1%)	23 (4.9%)	1.257 (0.733–2.156)	0.642
Yes	N=250	11 (8.7%)	11 (8.9%)	0.998 (0.433–2.302)	
Weight					
< 60	N=27	1 (7.7%)	1 (7.1%)	1.038 (0.065–16.599)	0.926
≥ 60	N=1203	41 (6.6%)	33 (5.7%)	1.173 (0.742–1.855)	
STEMI					
No	N=72	2 (5.6%)	4 (11.1%)	0.468 (0.086–2.558)	0.274
Yes	N=1158	40 (6.7%)	30 (5.3%)	1.259 (0.784–2.021)	

Combined Ischemic Endpoint = Cardiovascular death, nonfatal myocardial infarction, or stroke.

Absolute and relative frequencies were used for categorical variables.

The hazard ratio estimate was based on the Cox proportional hazard model.

Online Table 1b Subgroup analysis for bleeding outcome

	Patients	Bleeding		HR (95% CI)	P-value for
		Prasugrel	Ticagrelor	Prasugrel : Ticagrelor	interaction
Total					
	N=1230	69 (10.9%)	66 (11.1%)	0.985 (0.703–1.381)	-
Age					
<75	N=1108	60 (10.4%)	57 (10.8%)	0.966 (0.672–1.388)	0.639
≥75	N=122	9 (16.7%)	9 (13.2%)	1.227 (0.487–3.092)	
Killip classification					
I–III	N=1184	64 (10.5%)	63 (10.9%)	0.958 (0.677–1.357)	0.538
IV	N=46	5 (20.0%)	3 (14.3%)	1.444 (0.344–6.066)	
I+II	N=1167	62 (10.4%)	60 (10.5%)	0.978 (0.686–1.395)	0.989
III+IV	N=63	7 (20.0%)	6 (21.4%)	0.966 (0.324–2.879)	
Chronic kidney disease					
No	N=1214	67 (10.7%)	63 (10.7%)	1.002 (0.710–1.414)	0.608
Yes	N=16	2 (25.0%)	3 (37.5%)	0.594 (0.099–3.561)	
Diabetes					
No	N=980	55 (10.8%)	56 (11.8%)	0.914 (0.630–1.326)	0.363
Yes	N=250	14 (11.1%)	10 (8.1%)	1.368 (0.608–3.081)	
Weight					
< 60	N=27	2 (15.4%)	1 (7.1%)	1.997 (0.181–22.051)	0.553
≥ 60	N=1203	67 (10.8%)	65 (11.1%)	0.971 (0.691–1.366)	
STEMI					
No	N=72	4 (11.1%)	1 (2.8%)	3.843 (0.429–34.392)	0.205
Yes	N=1158	65 (10.9%)	65 (11.6%)	0.940 (0.666–1.325)	

Absolute and relative frequencies were used for categorical variables.

The hazard ratio estimate was based on the Cox proportional hazard model.

Online Table 2 Predictors of ischemic endpoint occurrence over a period of 365 days

	HR (95% CI)	P-value
CHARACTERISTIC		
Men	0.728 (0.446 – 1.187)	0.203
Age > 75 years	1.754 (0.947 – 3.249)	0.074
BMI > 30	0.643 (0.379 – 1.091)	0.102
ADMISSION		
Time from the onset of symptoms > 3 hours	1.232 (0.769 – 1.976)	0.385
Time from the onset of symptoms > 6 hours	1.435 (0.859 – 2.396)	0.168
ECG		
Left bundle brunch block	3.994 (1.459 – 10.932)	**0.007**
Right bundle brunch block	4.103 (1.656 – 10.166)	**0.002**
Bundle brunch block	3.761 (1.807 – 7.826)	**<0.001**
Killip classification		
I	reference	
II	2.579 (1.213; 5.486)	**0.014**
III+IV	13.092 (7.982; 21.476)	**<0.001**
History		
Hyperlipidemia	0.724 (0.438 – 1.197)	0.208
Hypertension	1.479 (0.934 – 2.343)	0.095
Current or stop smoker	0.587 (0.374 – 0.922)	**0.021**
Current smoker	0.517 (0.323 – 0.826)	**0.006**
Diabetes mellitus	1.621 (0.987 – 2.661)	0.056
Previous myocardial infarction	1.705 (0.877 – 3.316)	0.116
Previous PCI	0.934 (0.377 – 2.312)	0.882
Previous CABG	2.400 (0.757 – 7.616)	0.137
Chronic heart failure	1.336 (0.186 – 9.611)	0.773

Chronic kidney disease	0.982 (0.137 – 7.062)	0.986
Peripheral artery disease	1.929 (0.705 – 5.280)	0.201
Bleeding	1.850 (1.036 – 3.304)	**0.038**
PROCEDURE		
Postprocedural TIMI flow grade < 3	2.164 (0.994 – 4.708)	0.052
Number of diseased vessels > 1	1.808 (1.130 – 2.893)	**0.013**
Left main disease	1.213 (0.382 – 3.848)	0.743
PCI postprocedural result – suboptimal or failure	4.672 (2.571 – 8.491)	**<0.001**
*TREATMENT**		
Economically motivated switch to clopidogrel	0.433 (0.210–0.894)	**0.024**
Switch to clopidogrel from other reasons	3.420 (1.823–6.415)	**<0.001**

Combined Ischemic Endpoint = Cardiovascular death, nonfatal myocardial infarction, or stroke.

The hazard ratio estimate was based on Cox proportional hazard model.

* The hazard ratio estimate was based on Cox proportional hazard model with time dependent covariates.

Online Table 3 Reasons for switching to clopidogrel

	Prasugrel	Ticagrelor	P-value
Economic reasons (Patient cost sharing)	216 (34.1%)	265 (44.4%)	**0.003**
Chronic anticoagulation therapy	19 (3.0%)	21 (3.5%)	0.999
Adverse effects	31 (4.9%)	24 (4.0%)	0.999
Other	44 (7.0%)	39 (6.5%)	0.999

Absolute and relative frequencies were used for categorical variables; statistical significance of differences between patient groups were tested using the Fisher exact test (Bonferroni correction was used).

Online Table 4 Patient characteristics and economically motivated switch to clopidogrel

	SWITCH TO CLOPIDOGREL		P-value
	No	Yes	
CHARACTERISTIC			
Men	579 (77.3%)	352 (73.2%)	0.103
Age	61.4 (43.0–78.5)	62.3 (44.1–79.3)	0.236
BMI > 30	223 (29.8%)	172 (35.8%)	**0.029**
ADMISSION			
Time from the onset of symptoms (hours)	2.7 (0.8–36.0)	2.8 (0.8–24.0)	0.368
ECG			
STEMI	689 (92.0%)	446 (92.7%)	0.663
NSTEMI	35 (4.7%)	31 (6.4%)	0.195
Left bundle brunch block	17 (2.3%)	1 (0.2%)	**0.002**
Right bundle brunch block	17 (2.3%)	6 (1.2%)	0.281
Bundle brunch block	33 (4.4%)	7 (1.5%)	**0.005**
Killip classification			
I	642 (85.7%)	443 (92.1%)	
II	59 (7.9%)	23 (4.8%)	**0.004**
III	11 (1.5%)	6 (1.2%)	
IV	37 (4.9%)	9 (1.9%)	
I	642 (85.7%)	443 (92.1%)	**<0.001**
≥ II	107 (14.3%)	38 (7.9%)	
History			
Hyperlipidemia	251 (33.5%)	171 (35.6%)	0.461
Hypertension	359 (47.9%)	271 (56.3%)	**0.004**
Smoker	467 (62.3%)	331 (68.8%)	**0.023**

Diabetes mellitus	148 (19.8%)	102 (21.2%)	0.562
Previous MI	58 (7.7%)	45 (9.4%)	0.343
Previous PCI	52 (6.9%)	35 (7.3%)	0.821
Previous CABG	11 (1.5%)	10 (2.1%)	0.500
Chronic heart failure	8 (1.1%)	4 (0.8%)	0.774
Chronic kidney disease	12 (1.6%)	4 (0.8%)	0.308
Bleeding	3 (0.4%)	3 (0.6%)	0.684
Peripheral artery disease	21 (2.8%)	15 (3.1%)	0.733
PROCEDURE			
Postprocedural TIMI flow grade < 3	41 (5.5%)	16 (3.3%)	0.095
Number of diseased vessels > 1	384 (51.3%)	240 (50.0%)	0.682
Left main disease	36 (4.8%)	5 (1.0%)	**<0.001**
Postprocedural result – suboptimal + failure	44 (5.9%)	15 (3.1%)	**0.028**
LABORATORY			
HGB	144.0 (120.0–169.0)	143.0 (118.0–165.0)	0.103
Tr	227.0 (141.0–352.0)	224.0 (138.0–345.0)	0.915
Urea	5.3 (3.1–9.8)	5.2 (3.2–8.7)	0.248
Creatinine	82.0 (54.0–133.0)	82.0 (52.0–117.0)	0.523

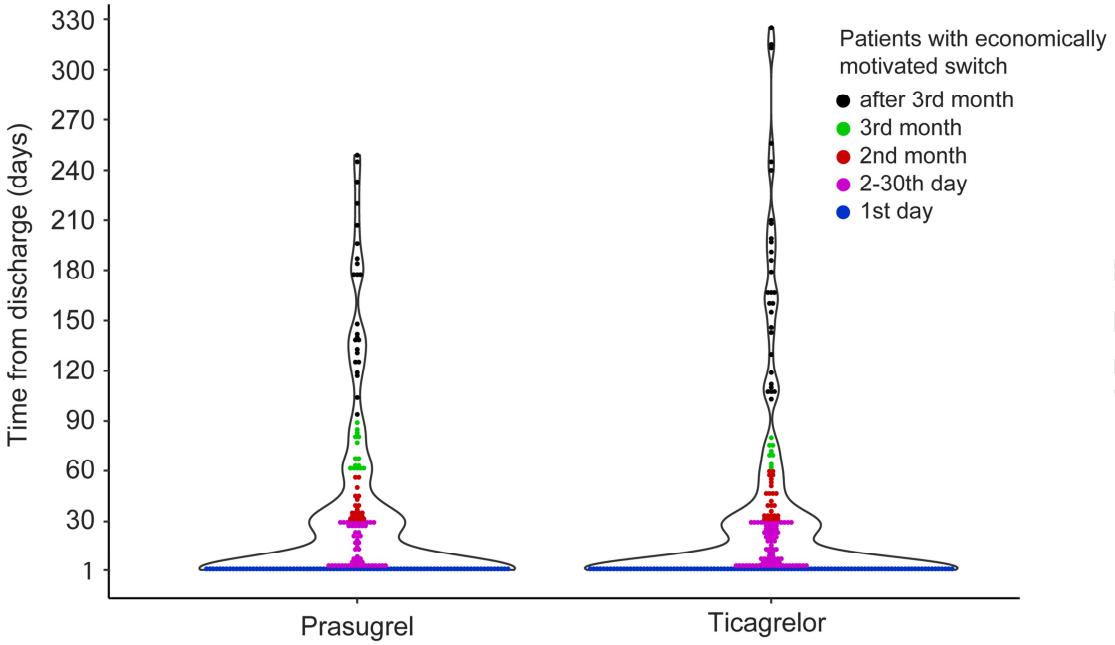
Absolute and relative frequencies were used for categorical variables. Statistical significance of differences between patient groups were tested using the Fisher exact test. Continuous parameters were described by median (5^{th}; 95^{th} percentile) and statistical significance of differences between patient groups were tested using the Mann-Whitney test.

Online Table 5 Risk of ischemic and bleeding events after an economically motivated post-discharge switch to clopidogrel*

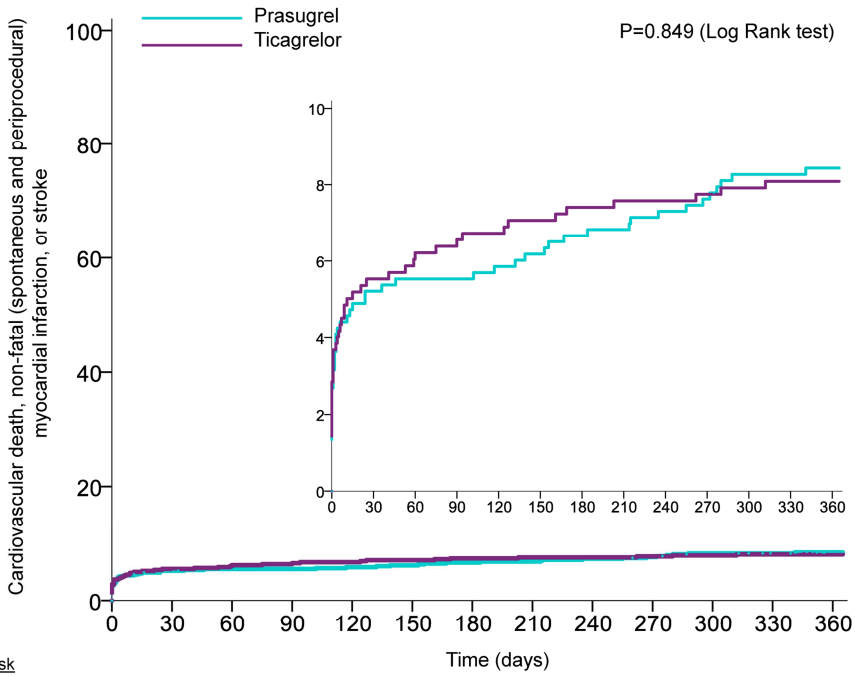
	Prasugrel	Ticagrelor	HR (95% CI)	P-value
All switches (N=481)				
Ischemic endpoint	7 (3.2%)	5 (1.9%)	1.712 (0.543–5.394)	0.359
Bleeding	15 (6.9%)	20 (7.5%)	0.921 (0.472–1.799)	0.810
Switch during 30 days (N=320)				
Ischemic endpoint	5 (3.6%)	3 (1.6%)	2.218 (0.530–9.281)	0.275
Bleeding	8 (5.8%)	12 (6.6%)	0.884 (0.361–2.163)	0.787
Switch during 60 days (N=401)				
Ischemic endpoint	7 (4.0%)	3 (1.3%)	2.966 (0.767–11.471)	0.115
Bleeding	12 (6.8%)	16 (7.1%)	0.948 (0.448–2.004)	0.889
Switch after 60 days (N=80)				
Ischemic endpoint	0 (0.0%)	2 (4.9%)	–	–
Bleeding	3 (7.7%)	4 (9.8%)	0.799 (0.179–3.571)	0.769

Absolute and relative frequencies were used for categorical variables. The hazard ratio was based on the Cox proportional hazard model (ticagrelor was the reference category).

* Switching to clopidogrel due to out-of-pocket costs was not a result of randomization. Additionally, study drugs reimbursement after hospital discharge was conditioned by specific regulations that affected prasugrel and ticagrelor differently (described in the Methods section).



Online Figure 1. Time distribution of economically motivated switches to clopidogrel after discharge



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	597	592	591	588	585	582	581	578	575	569	565	539
Ticagrelor	561	554	551	548	545	543	542	542	541	540	538	517

Online Figure 2. Cumulative Kaplan-Meier estimate of the percentages of cardiovascular death, non-fatal (spontaneous and periprocedural) myocardial infarction, or stroke. The difference between Prasugrel and Ticagrelor was tested using the Log Rank test. The occurrence of the composite efficacy endpoint during the twelve months study period was 8.7% in patients taking prasugrel and 8.4% in patients taking ticagrelor (HR, 1.038; 95% CI, 0.703–1.534; P=0.849).

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