Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

Multicenter Randomized PRAGUE-18 Study

Editorial, see p 1613

BACKGROUND: No randomized head-to-head comparison of the efficacy and safety of ticagrelor and prasugrel has been published in the 7 years since the higher efficacy of these newer $P2Y_{12}$ inhibitors were first demonstrated relative to clopidogrel.

METHODS: This academic study was designed to compare the efficacy and safety of prasugrel and ticagrelor in acute myocardial infarction treated with primary or immediate percutaneous coronary intervention. A total of 1230 patients were randomly assigned across 14 sites to either prasugrel or ticagrelor, which was initiated before percutaneous coronary intervention. Nearly 4% were in cardiogenic shock, and 5.2% were on mechanical ventilation. The primary end point was defined as death, reinfarction, urgent target vessel revascularization, stroke, or serious bleeding requiring transfusion or prolonging hospitalization at 7 days (to reflect primarily the in-hospital phase). This analysis presents data from the first 30 days (key secondary end point). The total follow-up will be 1 year for all patients and will be completed in 2017.

RESULTS: The study was prematurely terminated for futility. The occurrence of the primary end point did not differ between groups receiving prasugrel and ticagrelor (4.0% and 4.1%, respectively; odds ratio, 0.98; 95% confidence interval, 0.55–1.73; *P*=0.939). No significant difference was found in any of the components of the primary end point. The occurrence of key secondary end point within 30 days, composed of cardiovascular death, nonfatal myocardial infarction, or stroke, did not show any significant difference between prasugrel and ticagrelor (2.7% and 2.5%, respectively; odds ratio, 1.06; 95% confidence interval, 0.53–2.15; *P*=0.864).

CONCLUSIONS: This head-to-head comparison of prasugrel and ticagrelor does not support the hypothesis that one is more effective or safer than the other in preventing ischemic and bleeding events in the acute phase of myocardial infarction treated with a primary percutaneous coronary intervention strategy. The observed rates of major outcomes were similar but with broad confidence intervals around the estimates. These interesting observations need to be confirmed in a larger trial.

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Clinical Perspective

What Is New?

- The multicenter randomized PRAGUE-18 study is the first head-to-head comparison of prasugrel and ticagrelor in acute myocardial infarction treated with primary or immediate percutaneous coronary intervention.
- The study was designed as a superiority trial and was stopped prematurely because of futility after enrollment of 1230 patients.
- The primary end point was defined as death, reinfarction, urgent target vessel revascularization, stroke, or serious bleeding requiring transfusion or prolonging hospitalization within 7 days after enrollment. The key secondary end point within 30 days was composed of cardiovascular death, nonfatal myocardial infarction, or stroke.

What Are the Clinical Implications?

- The study does not support the hypothesis that one of the newer $P2Y_{12}$ inhibitors is more effective or safer than the other in preventing ischemic and bleeding events in the acute phase of myocardial infarction treated with primary or immediate percutaneous coronary intervention. The observed percentages of major outcomes were similar and with clinically irrelevant differences between the compared groups but with broad confidence intervals around the estimates.
- A randomized study of a sufficient sample size and with an optimal design for an evaluation of equivalence remains a challenge for the comparison of prasugrel and ticagrelor.

Flow restoration through an infarct-related artery via implantation of intracoronary stents during primary percutaneous coronary intervention (PCI) is, if possible, the preferred reperfusion therapy in patients with acute myocardial infarction (AMI) with ST-segment elevation (STEMI).[1] The highest thrombotic risk associated with this condition requires intensive antithrombotic treatment.[2] In addition to aspirin, guidelines recommend the use of ticagrelor or prasugrel over clopidogrel.[1,3] Except for patients after an ischemic stroke, in whom prasugrel is contraindicated, class and level of guideline recommendations are identical for both agents. Physicians are increasingly being confronted with the need to select a $P2Y_{12}$ antagonist as part of the daily care of patients with AMI. For all practical purposes, there has been only 1 randomized trial that supports each of the newer $P2Y_{12}$ inhibitors (ie, prasugrel and ticagrelor) in the treatment of acute coronary syndromes instead of clopidogrel.[4,5] However, the reported use of prasugrel and ticagrelor in routine clinical practice suggests that physicians do not view these agents as interchangeable and tend to favor one over the other for their patients.[6–9]

Economic constraints associated with treatments with newer medications are an important factor in the selection of a $P2Y_{12}$ inhibitor. In addition, the availability of low-cost generic clopidogrel must be taken into account. This factor frequently results in substituting the less costly clopidogrel for newer $P2Y_{12}$ inhibitors over the course of the recommended 12-month treatment interval in many healthcare systems.

The need for a head-to-head comparison of newer $P2Y_{12}$ inhibitors motivated us to perform the PRAGUE-18 study, which was a randomized, multicenter study designed to compare the efficacy and safety of prasugrel and ticagrelor in patients with AMI treated with primary or immediate PCI and to assess the percentages, reasons, and consequences of switching from new $P2Y_{12}$ inhibitors to clopidogrel after the acute phase. This article deals with 7- and 30-day outcomes and thus represents a direct comparison of prasugrel and ticagrelor during these time periods. A 1-year follow-up is ongoing and will be completed in May 2017.

METHODS

The multicenter, randomized PRAGUE-18 study, an open-label, phase IV, controlled, clinical trial, is an academic project with participation of 14 tertiary cardiology centers in the Czech Republic with 24/7 capability to perform primary PCI. The study was conducted with approval of the trial design and protocol by the Ethics Committee for Multicenter Clinical Trials, University Hospital Kralovske Vinohrady, Prague, Czech Republic, and the local ethics committees at each participating site. The study protocol has been registered under PRAGUE-18 (http://www.ClinicalTrials.gov; NCT02808767).

The study was designed by the principal investigators (Z.M. and P.W.) and commented on by steering committee members during the initial investigator meeting. Coordination was managed by the Cardiocenter of the Third Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady in Prague, Czech Republic.[10] The study was an independent project and was conducted without any support from the industry. Study investigators joined and participated on a voluntary basis, out of scientific enthusiasm, without any compensation. A team from the Institute of Biostatistics and Analyses of Masaryk University, Brno, Czech Republic, led by one of the coauthors, was involved in preparing the study (power calculation), in creating and administering the electronic database, and in the statistical analysis of results. Data from the study were recorded through electron case report forms and stored in a database system originally based on a modified version of the TrialDB system. The system was designed as a robust base for the collection of large amounts of data in clinical trials or clinical registries and was fully customized to the structure of the project.

Simple randomization with GraphPad scientific software was adopted for the study. The sealed envelope method was used for distribution of randomization codes. Anonymous patient data, using the patient's serial number in the database and a randomization number, were added to an electronic

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database. Only the investigators had access to the data of participants enrolled at their respective sites during the course of the study.

Proper conduct of the study at the participating sites was supervised by the associated executive and steering committees and by the data monitoring committee of the coordinating site. The data monitoring committee of the coordinating site monitored study progress at individual sites.

The incidence of outcome measures was verified by an independent committee, the members of which were not involved as study investigators and were not aware of the treatment assignments (see the Appendix in the online-only Data Supplement for committee members and study investigators).

The first author (Z.M.) had access to all study data (ie, the protocol, study approval by the ethics committees of the participating sites, informed consent forms of the randomized patients, and, after the database was locked, all entered data and patient source documentation with end points).

Study Patients

Patients with AMI treated with a primary (more general term used for both STEMI and very-high-risk non-STEMI) PCI strategy were enrolled in the study. The study inclusion criteria were the following: AMI indicated for emergent (within 120 minutes of admission to a cardiac center) coronary angiography with or without PCI and a signed informed consent. Hemodynamic instability was not an exclusion criterion for study participation. A diagnosis of AMI was determined from the clinical presentation and an ECG finding of ST-segment elevation on 2 related leads at a minimum by >1 mm, ST-segment depression on 3 leads at a minimum by >2 mm, or a new bundle-branch block. Exclusion criteria for the study were history of stroke, serious bleeding within the past 6 months, indication for long-term oral anticoagulation therapy, administration of clopidogrel ≥300 mg or any other antiplatelet medication (except aspirin and a lower dose of clopidogrel) before randomization, aged >75 years with a body weight <60 kg (ie, the presence of both parameters was an exclusion criterion), moderate or severe hepatic function disorder, concomitant treatment with a strong CYP3A4 inhibitor, and known hypersensitivity to prasugrel or ticagrelor.

Study Design and Treatment

The patients were randomized, after signing the informed consent, to prasugrel or ticagrelor therapy immediately on hospital arrival (which, as a rule, was directly to the catheterization laboratory or, in exceptional cases, to the coronary care unit). The dosing scheme for patients randomized to prasugrel was a 60-mg loading dose and 10 mg once daily as a maintenance dose. In patients aged >75 years of age or in those with a weight <60 kg, the maintenance dose of prasugrel was reduced to 5 mg once daily. Patients assigned to the study arm with ticagrelor received a loading dose of 180 mg and 90 mg twice daily as a maintenance dose.

Administration of the loading dose was recommended immediately after the patients signed the informed consent. In individual cases in which the physician could not exclude the need for urgent surgical revascularization on the basis of previous assessments or in cases involving hemodynamic instability, antiplatelet therapy was delayed until after coronary angiography and immediately before or shortly after PCI. In cases in which primary PCI was not performed, prasugrel therapy was discontinued and replaced by clopidogrel. The decision to perform the procedure and to administer any adjunctive medication to support PCI was left to the discretion of the treating physician.

Patients were advised to use the study medication for 12 months. Use of aspirin was also required with a recommendation of 100 mg daily.

Before discharge from the hospital, patients discussed with their physician the costs associated with the long-term therapy and the benefits of continued treatment with prasugrel and ticagrelor compared with clopidogrel. The study allowed patients who were unable to bear the costs associated with long-term treatment with the study medications to switch to clopidogrel because the latter is fully reimbursed by the state insurance company and poses no financial burden on patients.

Initial contact with the patient took place at the time of randomization, followed by visits on day 7 of hospitalization or at discharge if before day 7, on day 30 (telephone visit), and at 1 year from the index event.

Study End Points

The primary composite end point consisted of all-cause death, reinfarction, stroke, serious bleeding requiring transfusion or prolonging hospitalization, or urgent target vessel revascularization within 7 days after randomization or at discharge if before the seventh day. Henceforth, the full definition is referred to as simply the primary end point. The key secondary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction, or stroke during the follow-up period. Definitions of all study endpoints are presented in the Appendix in the online-only Data Supplement.

Additional secondary end points included definite stent thrombosis within 30 days from enrollment in the study. Academic Research Consortium criteria were used to define stent thrombosis. Bleeding occurrences defined according to the TIMI (Thrombolysis in Myocardial Infarction) and BARC (Bleeding Academic Research Consortium) criteria during the follow-up was a secondary safety end point. Another prespecified outcome measure was the occurrence of the primary end point in patients with Killip class III to IV and in those with diabetes mellitus.

Statistical Analysis

The power analysis was computed using Power and Precision software release 4.0 for a primary end-point difference of 2.5%, a 2-sided overall α level of 0.05, and statistical power of 80% (see the Appendix in the online-only Data Supplement for more details). The needed sample size was estimated at 1250 patients in each study arm. The interim analysis after the first 1130 patients led to a decision to terminate the study early because of futility. The differences in primary end point between study groups were plotted according to rank of recruitment; the difference between study groups was much below the expected clinically significant difference of 2.5%, which was used in the power analysis. Moreover, when real differences were compared with the borderline of minimal difference detected as statistically significant (ie, detectable alternative) for a given number of patients, they never cross.

We considered these results to be sufficient reason to end the study prematurely (see the Appendix in the online-only Data Supplement for more details).

Standard descriptive statistics were applied in the analysis: absolute and relative frequencies for categorical variables and medians supplemented with 5th and 95th percentiles for continuous variables. Statistical significance of differences among groups of patients was tested with the Fisher exact or χ^2 test for categorical variables and the Mann-Whitney test for continuous variables. Odds ratios (ORs), determined on the basis of logistic regression, were used to measure the effect of prasugrel versus ticagrelor with respect to the end points. The analysis was performed with SPSS 23.0.0.0 (IBM Corp).

RESULTS

Study Population

In the period from April 2013 to May 2016, 1230 patients were enrolled in the study at 14 sites in the Czech Republic. The baseline characteristics of the patient set were balanced between the study groups, that is, nonstudy cardiovascular medication, time from the onset of symptoms to hospital admission, door-to-needle time, study drug–to–needle time, characteristics related to primary or immediate PCI, and periprocedural nonstudy antithrombotic therapy (Table 1 and Table I in the online-only Data Supplement). Primary PCI was performed for STEMI or new bundle-branch blocks in both study arms in 94.6% of patients. Almost all patients (99.2%) enrolled in the study underwent primary PCI strategy; radial access was used in two thirds of the patients. At least 1 intracoronary stent was implanted in 96%, with drug-eluting stents used in 68.1% of all patients. An optimal postprocedural result with TIMI grade 3 flow in the infarct-related artery, assessed on-site by the experienced interventional cardiologist, was achieved in almost 95% of the patients.

Hemodynamic instability was not an exclusion criterion for study participation. Nearly 4% of patients in each group were in cardiogenic shock at baseline, and 5.2% were on mechanical ventilation.

Five patients failed to participate in the 30-day follow-up visit. However, information on vital status during the 30-day follow-up period was available for all study participants.

Study End Points

The occurrence of the primary end point did not differ significantly between the groups receiving prasugrel and ticagrelor (4.0% and 4.1%, respectively; OR, 0.98; 95% confidence interval [CI], 0.55–1.73; *P*=0.939; Table 2 and Figure). Furthermore, no significant difference was found in any of the components of the primary end point, that is, death, reinfarction, urgent target vessel revascularization, stroke, serious bleeding requiring transfusion, or prolonged hospitalization.

Table 1. Baseline Characteristics of Study Patients (n=1230)

	Prasugrel (n=634)	Ticagrelor (n=596)	*P* Value
Characteristic			
Men, n (%)	489 (77.1)	439 (73.7)	0.157
Age, y	61.8 (42.7–78.7)	61.8 (44.6–79.8)	0.755
Admission, n (%)			
ECG			
STEMI	568 (89.6)	533 (89.4)	0.899
BBB	33 (5.2)	29 (4.9)	
NSTEMI	33 (5.2)	34 (5.7)	
Killip classification			0.892
I	556 (87.7)	530 (88.9)	
II	44 (6.9)	38 (6.4)	
III	10 (1.6)	7 (1.2)	
IV	24 (3.8)	21 (3.5)	
History			
Hyperlipidemia	212 (33.4)	211 (35.4)	0.469
Hypertension	326 (51.4)	305 (51.2)	0.932
Current smoker	406 (64.0)	392 (65.8)	0.524
BMI ≥30 kg/m^2	206 (33.2)	167 (28.5)	0.082
Diabetes mellitus	127 (20.0)	124 (20.8)	0.736
Previous MI	47 (7.4)	55 (9.2)	0.249
Previous PCI	42 (6.6)	45 (7.6)	0.527
Previous CABG	12 (1.9)	9 (1.5)	0.605
Chronic heart failure	6 (0.9)	6 (1.0)	0.914
Chronic kidney disease	8 (1.3)	8 (1.3)	0.901
Peripheral artery disease	12 (1.9)	18 (3.0)	0.200
Bleeding	5 (0.8)	1 (0.2)	0.219
Procedure, n (%)			
Antithrombotic			
Clopidogrel (<300 mg)	8 (1.3)	7 (1.2)	0.889
Unfractionated heparin	607 (95.7)	568 (95.3)	0.709
Enoxaparin	59 (9.3)	61 (10.2)	0.583
Fondaparinux	10 (1.6)	12 (2.0)	0.564
Glycoprotein IIb/IIIa bailout therapy	123 (19.4)	122 (20.5)	0.639
Radial access	423 (66.7)	394 (66.1)	0.820
Manual aspiration thrombectomy	199 (31.8)	190 (32.2)	0.877

(*Continued*)

Table 1. Continued

	Prasugrel (n=634)	Ticagrelor (n=596)	*P* Value
Primary PCI			
No	5 (0.8)	5 (0.8)	0.999
Yes	629 (99.2)	591 (99.2)	
Type of PCI			
Only PTCA	22 (3.5)	20 (3.4)	0.913
Stent	607 (95.7)	571 (95.8)	
Type of stent (multiple stent types possible)			
Bare metal stent	168 (26.5)	179 (30.0)	0.167
Drug-eluting stent	418 (65.9)	384 (64.4)	0.553
Bioabsorbable vascular scaffold	46 (7.3)	26 (4.4)	0.038
Stent graft	0 (0.0)	1 (0.2)	0.485
Postprocedural TIMI flow grade (n=1220)*			0.524
0	6 (1.0)	6 (1.0)	
1	5 (0.8)	1 (0.2)	
2	25 (4.0)	24 (4.1)	
3	593 (94.3)	560 (94.8)	
Other treatment			
CABG	1 (0.2)	3 (0.5)	0.524
Conservatively	4 (0.6)	2 (0.3)	
Discharge, n (%)			
Aspirin	618 (97.5)	579 (97.%)	0.721
β-Blockers	522 (82.3)	486 (81.5)	0.719
ACE inhibitors/ ARBs	534 (84.2)	496 (83.2)	0.633
Statins	595 (93.8)	558 (93.6)	0.871
Proton pump inhibitors	390 (61.5)	360 (60.4)	0.690

Values are absolute and relative frequencies for categorical variables and medians (5th–95th percentiles) for continuous variables. ACE indicates angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; BBB, bundle-branch block; BMI, body mass index; CABG, coronary artery bypass grafting; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*Not available for patients without PCI.

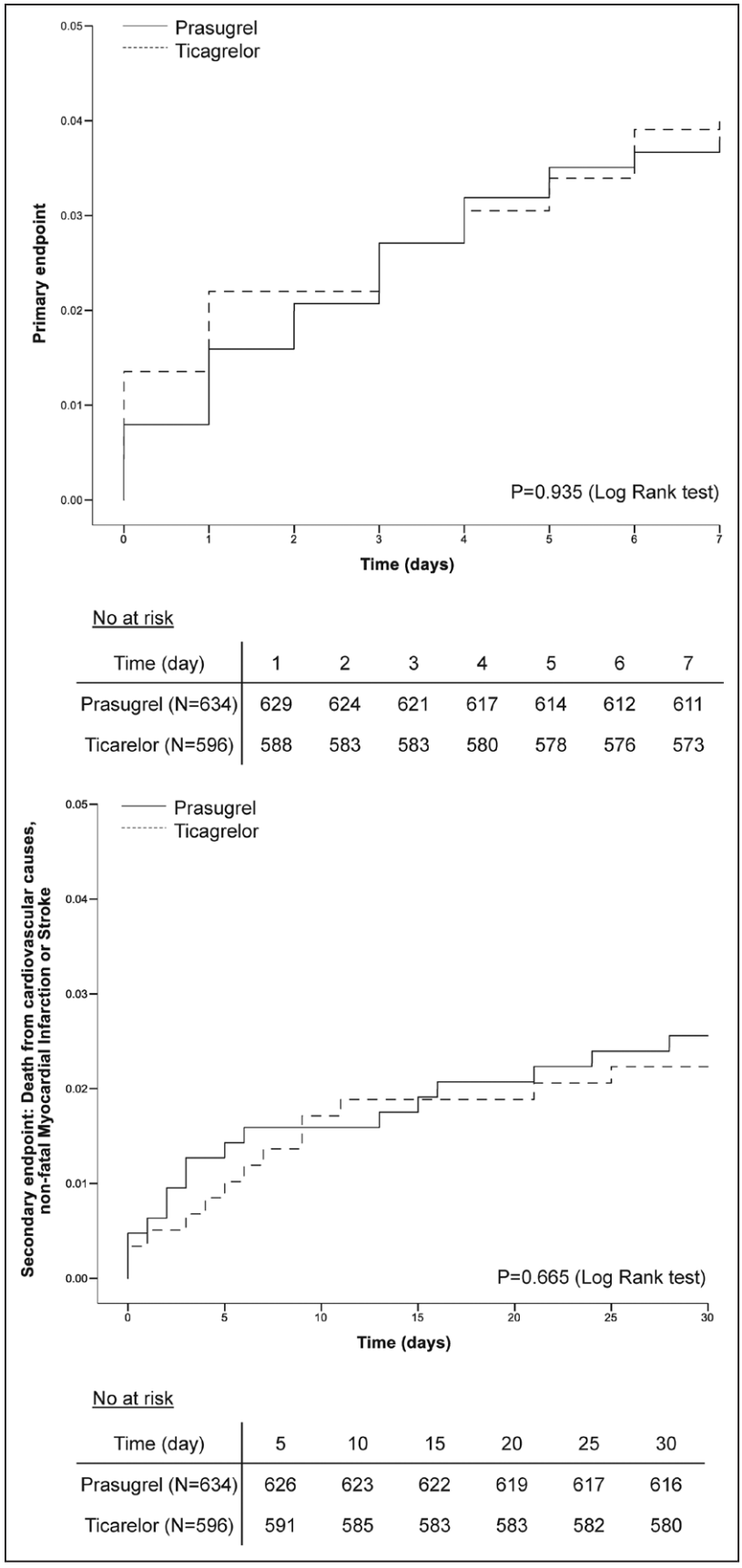
The occurrence of key secondary end points within 30 days after randomization, composed of cardiovascular death, nonfatal myocardial infarction, or stroke, also did not show any significant difference between prasugrel and ticagrelor (2.7% and 2.5%, respectively; OR, 1.06; 95% CI, 0.53–2.15; *P*=0.864; Table 2 and Figure). The results were also consistent for both the primary and key secondary end points across the analyzed subgroups of the whole study population (Table II in the online-only Data Supplement). There was no significant difference in the risk of the primary net clinical end point between prasugrel and ticagrelor in relation to age (aged ≥75 years; n=121; OR, 0.69; 95% CI, 0.19–2.48), presence of diabetes mellitus (n=251; OR, 0.86; 95% CI, 0.30–2.45), pre-PCI cardiogenic shock (n=45; OR, 0.79; 95% CI, 0.19–3.24), and pre-PCI Killip class higher than II (n=62; OR, 1.18; 95% CI, 0.33–4.26). No interactions were statistically significant.

Serious bleeding requiring transfusion or prolonging the hospital stay was a component of the net primary end point. Any bleeding unrelated to bypass surgery was recorded throughout the follow-up period. No significant difference was found between patients on prasugrel and ticagrelor according to TIMI and BARC bleeding events (Table 3 and Figure I in the online-only Data Supplement).

DISCUSSION

Evidence from randomized studies comparing the benefits of prasugrel and ticagrelor in patients with STEMI treated with primary PCI is still lacking. Subgroup analyses of studies comparing the newer $P2Y_{12}$ inhibitors with clopidogrel provide only limited information on the population of patients who are treated with emergent primary PCI for STEMI.[11–13] Published landmark analyses of the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) and PLATO (Platelet Inhibition and Patient Outcomes) studies discussed the maximum effectiveness of ticagrelor and especially prasugrel in the acute phase of myocardial infarction, during the first 7 days in which the thrombotic risk is highest.[14,15] According to the published data, the cumulative incidence of ischemic events differed between patients treated with ticagrelor and those treated with prasugrel during this phase of AMI. Documented differences were the basis for superiority design of the presented study in which a homogeneous (with respect to the highest thrombotic risk) patient population with STEMI was enrolled. The selected net primary end point reflects both important aspects of antiplatelet treatment: efficacy and safety.[16,17]

The observed occurrences of major efficacy and safety outcomes in the multicenter randomized PRAGUE-18 study comparing prasugrel and ticagrelor were similar but with broad confidence intervals around the estimates because of the small number of subjects. Compared with clopidogrel, the clinical benefit of these drugs is the re-



No at risk

Time (day)	1	2	3	4	5	6	7
Prasugrel (N=634)	629	624	621	617	614	612	611
Ticarelor (N=596)	588	583	583	580	578	576	573

No at risk

Time (day)	5	10	15	20	25	30
Prasugrel (N=634)	626	623	622	619	617	616
Ticarelor (N=596)	591	585	583	583	582	580

Figure. Cumulative Kaplan-Meier estimates of the percentages of the primary and key secondary end points.

Table 2. End Points

End Point	Prasugrel, n (%)	Ticagrelor, n (%)	OR (95% CI)	*P* Value
Day 7				
Primary end point: death resulting from any cause, reinfarction, urgent revascularization, stroke, or serious bleeding requiring transfusion or prolonging hospital stay	25 (4.0)	24 (4.1)	0.98 (0.55–1.73)	0.939
Death resulting from any cause	8 (1.3)	12 (2.0)	0.62 (0.25–1.53)	0.302
Reinfarction	6 (1.0)	4 (0.7)	1.41 (0.40–5.03)	0.594
Urgent revascularization	9 (1.4)	7 (1.2)	1.21 (0.45–3.26)	0.714
Stroke	1 (0.2)	1 (0.2)	0.94 (0.06–15.00)	0.963
Serious bleeding requiring transfusion or prolonging hospital stay	8 (1.3)	7 (1.2)	1.07 (0.39–2.96)	0.900
Day 30				
Key secondary end point: death resulting from cardiovascular causes, nonfatal myocardial infarction, or stroke	17 (2.7)	15 (2.5)	1.06 (0.53–2.15)	0.864
Death resulting from cardiovascular causes	8 (1.3)	8 (1.3)	0.94 (0.35–2.52)	0.901
Nonfatal myocardial infarction	8 (1.3)	7 (1.2)	1.07 (0.39–2.97)	0.895
Stroke	2 (0.3)	1 (0.2)	1.88 (0.17–20.74)	0.608
Definite stent thrombosis	3 (0.5)	5 (0.9)	0.56 (0.13–2.35)	0.428
Death resulting from any cause	14 (2.2)	16 (2.7)	0.82 (0.40–1.69)	0.589

CI indicates confidence interval; and OR, odds ratio. Values are absolute and relative frequencies for categorical variables. Statistical significance of differences between patient groups was tested with the χ^2 test or Fisher exact test (categories with low frequencies). The OR estimate was based on logistic regression.

sult of their greater antiplatelet efficacy and its faster onset.[18,19] Although the drugs differ in their mode of action on $P2Y_{12}$ receptors, the level of inhibition of platelet aggregation is quite similar.[7] Randomized study in patients with STEMI undergoing primary PCI have confirmed that neither of the new $P2Y_{12}$ inhibitors was superior to the other in laboratory antiplatelet efficacy.[20]

Percentages of cardiovascular death, ischemic events, definite stent thrombosis, and bleeding events in subgroup analyses of patients with STEMI included in the TRITON-TIMI 38 study, which was designed to verify the benefit of prasugrel over clopidogrel, and PLATO study, which compared the benefit and risks of ticagrelor and clopidogrel, were essentially similar.[11,12] However, comparisons of subgroup analyses of randomized trials whose designs and study populations differ are often prone to bias. A retrospective analysis of a large register comparing efficacy and safety of prasugrel and ticagrelor in patients undergoing PCI for acute coronary syndrome was limited by significant differences in the baseline characteristics of patients on prasugrel and those on ticagrelor.[6] After propensity matching, major adverse cardiovascular events, mortality, and major bleeding events associated with prasugrel were not inferior to the occurrence of events associated with ticagrelor.

The baseline characteristics of the PRAGUE-18 study population were well balanced between the compared groups and comparable to those in contemporary studies of patients with AMI who underwent primary PCI.[21–23] Patient mortality was low and is in accordance with rates reported in contemporary, published, randomized studies.

Table 3. Bleeding Within 30 Days of Study Enrollment

	Prasugrel, n (%)	Ticagrelor, n (%)	OR (95% CI), Prasugrel: Ticagrelor	*P* Value
TIMI minimal	4 (0.8)	8 (1.7)	0.47 (0.14–1.56)	0.212
TIMI minor	1 (0.2)	1 (0.2)	1.00 (0.62–16.03)	0.999
TIMI major	3 (0.6)	3 (0.7)	0.86 (0.17–4.27)	0.851
BARC 1	14 (3.1)	12 (3.3)	0.94 (0.43–2.05)	0.872
BARC 2	10 (2.2)	10 (2.7)	0.81 (0.33–1.97)	0.640
BARC 3	4 (0.8)	2 (0.5)	1.60 (0.29–8.81)	0.586
BARC 5	…	…	…	…

Values are absolute and relative frequencies for categorical variables. BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; OR, odds ratio; and TIMI, Thrombolysis in Myocardial Infarction.

Results of the presented study are consistent with the actual and reportedly changing trend in the prognosis of patients with STEMI treated with primary PCI, with the predominance of radial access (66.4%) and the use of drug-eluting stents supported by the most efficient available dual or triple (bailout therapy with a glycoprotein IIb/IIIa inhibitor) antiplatelet therapy. A 30-day mortality of <3% in patients with radial access has also been demonstrated in a study in which patients with STEMI were treated with PCI and a 600-mg loading dose of clopidogrel.[22] There was a 30-day on-treatment cardiovascular mortality of 2.3% in a study in which newer $P2Y_{12}$ inhibitors were used for dual antiplatelet therapy in <30% of the study population of patients with STEMI treated with primary PCI and thrombectomy.[23]

Patients with cardiogenic shock were excluded from the TRITON-TIMI 38 study.[5] In the PLATO study, <1% of the patients with STEMI enrolled were higher than Killip class II at baseline.[4] The Killip classification at admission was not an exclusion criterion for the PRAGUE-18 study. The incidence of the primary end point was 7 times higher for patients with cardiogenic shock compared with patients with Killip class I to III. The Killip classification did not influence the difference in the occurrence of primary end points between prasugrel- and ticagrelor-treated patients. Our previous study documented strong and comparable antiplatelet efficacy for prasugrel and ticagrelor in the vast majority of patients with AMI after out-of-hospital cardiac arrest who were treated with mild therapeutic hypothermia.[24] Patients with cardiogenic shock are generally not included in randomized, clinical studies, and reported results on the efficacy and safety of the medications are very rare in this group of patients. Unfortunately, the results of the PRAGUE-18 study, given the small number of patients enrolled, cannot offer relevant arguments on the differences between benefits and risks of newer drugs for subgroups of patients.

Concerns about a higher risk of bleeding associated with prasugrel compared with ticagrelor are still being discussed.[6–9,25] Large, contemporary registry data show that prasugrel used according to recommendations is safe in patients undergoing PCI for STEMI.[26] The prasugrel dose was reduced during the maintenance phase of the PRAGUE-18 study in patients >75 years of age and in patients weighing <60 kg. The incidence of bleeding complications associated with the study medications was low in both treatment arms, and the differences in the percentages of serious bleeding events did not reach statistical significance. Real-world evidence from 12 European registries shows that there are no major differences between prasugrel and ticagrelor with regard to the incidence of bleeding in patients with STEMI.[9]

On the basis of the results of the TRITON-TIMI 38 study, the use of prasugrel is generally not recommended for older patients or those with low body weight because prasugrel was not associated with a net clinical benefit in these subsets.[7] A subgroup analysis of PRAGUE-18 study showed that patients >75 years had a higher risk of primary net clinical end point compared with younger patients. Age >75 years, however, did not influence the difference between the incidence of primary end point between those treated with prasugrel and those treated with ticagrelor. Nevertheless, this finding should be viewed in the context of the previously discussed limitations of subgroup analyses.

This study has several limitations. It was an open-label study. However, all primary end-point events were adjudicated by an independent event adjudication committee that was unaware of treatment allocation. The study was underpowered to draw the final conclusion of a direct comparison of efficacy and safety of prasugrel and ticagrelor. The study was terminated prematurely because of futility. The difference between study groups was much below the expected clinically significant difference (2.5% absolute reduction; relative risk reduction, 39%), which was used in the power analysis, and the CIs for the estimation of the incidence of events were quite wide. However, identified differences in the occurrence of a primary end point between the compared groups were very low in absolute numbers and clinically irrelevant (0.1%; number needed to treat=1000). Depending on the order in which patients were included in the study, the difference of occurrence of the primary end point between treatment arms was consistently low, and with a growing number of patients, it became stabilized around this value (Figures II and III in the online-only Data Supplement).

The results of PRAGUE-18 study point to the suitability of the noninferiority study design comparing efficacy and safety of both drugs on a sufficiently large patient sample size. The execution of a randomized study with a population including many thousands of patients is extremely expensive. Therefore, we cannot expect the industry to fund a head-to-head trial as part of a postlicensing evaluation.[27] This is also supported by the fact that our purely academic study was the first study to compare both drugs since the publication of the results from the TRITON and PLATO studies 7 years ago. We therefore hope that, despite the limitations of the presented study, the results of the PRAGUE-18 study will contribute to clinical practice.

CONCLUSIONS

This head-to-head comparison of prasugrel and ticagrelor, based on a small number of patients and events, does not support the hypothesis that one is more effective or safer than the other in preventing ischemic and bleeding events in the acute phase of myocardial infarction treated with primary or immediate PCI. The observed percentages of major outcomes were similar, with clinically irrelevant differences between the compared groups but broad CIs around the estimates. A randomized study of a sufficient sample size and with an optimal design for

an evaluation of equivalence remains a challenge for the comparison of prasugrel and ticagrelor.

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DISCLOSURES

Dr Motovska reports receiving speaking and advisory board fees from AstraZeneca and Eli Lilly. Dr Varvarovsky reports receiving honoraria form AstraZeneca and Eli Lilly. Dr Rokyta reports receiving lecture fees from AstraZeneca. Dr Widimsky reports receiving honoraria from AstraZeneca, Eli Lilly, and Daiichi Sankyo. The other authors report no conflicts.

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FOOTNOTES

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Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study

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INCLUSION CRITERIA

Acute myocardial infarction (ST elevation on two related leads at a minimum, by more than 1 mm, or ST depression on three leads at a minimum, by more than 2 mm, or a new bundle branch block) indicated for emergency (within 120 minutes of admission to the cardiocenter) coronary angiography ± PCI, and a signed informed consent.

EXCLUSION CRITERIA

History of stroke,

Serious bleeding within the last 6 months,

Indication for chronic oral anticoagulation therapy (e.g. atrial fibrillation, prosthetic heart valve, pulmonary embolism),

Administration of clopidogrel ≥ 300 mg or any of other antiplatelet medication (with the exception of aspirin and a lower dose of clopidogrel) before randomization,

Patients older than 75 years whose body weight was also < 60 kg (i.e., the presence of both parameters was an exclusion criterion),

Moderate or severe hepatic function disorder,

Concomitant treatment with a strong CYP3A4 inhibitor (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir),

Known hypersensitivity to prasugrel or ticagrelor.

END POINT DEFINITIONS

Death was defined as a summary of death from any cause. Re-infarction was defined according to the Third Universal Definition of Myocardial Infarction. Stroke was defined as a rapid onset of a new neurological deficit caused by an ischemic or hemorrhagic central nervous system event with symptoms lasting at least 24 hours from their onset or leading to death. Urgent target vessel revascularization was defined as a new emergent/urgent revascularization of the vessel dilated at the initial procedure driven by recurrent signs of ischemia occurring after completion of the initial PCI. The key secondary efficacy endpoint was a composite of cardiovascular death, non-fatal myocardial infarction or stroke during the follow-up period.

Cardiovascular death was defined as any death for a demonstrable cardiovascular cause, or any death that was not clearly attributable to a non-cardiovascular cause. Non-fatal myocardial infarction was required to be distinct from the index event and was defined according to the Third Universal Definition of Myocardial Infarction.

Table S1. Baseline characteristics of study patients (N=1 230)

Characteristics	Prasugrel (N=634)	Ticagrelor (N=596)	P-value
Median Time from symptom onset to hospital arrival	2.8 (0.9; 39.0)	2.5 (0.8; 24.0)	0.148
Median Door-to-Needle Time	19.0 (5.0; 100.0)	18.0 (5.0; 112.0)	0.945
Chronic therapy			
Aspirin	101 (15.9%)	91 (15.3%)	0.749
Beta Blocker	114 (18.0%)	113 (19.0%)	0.658
Angiotensin-converting–enzyme inhibitor	150 (23.7%)	133 (22.3%)	0.576
Angiotensin-receptor blocker	68 (10.7%)	64 (10.7%)	0.994
Statin	104 (16.4%)	114 (19.1%)	0.211
Proton Pump inhibitor	34 (5.4%)	42 (7.0%)	0.220
Procedure			
Initial TIMI Flow grade (N=1220)			
0	340 (54.1%)	303 (51.3%)	
1	71 (11.3%)	55 (9.3%)	0.309
2	106 (16.9%)	117 (19.8%)	
3	112 (17.8%)	116 (19.6%)	
1-vessel disease	314 (49.5%)	292 (49.0%)	
2- vessel disease	188 (29.7%)	180 (30.2%)	0.976
3-vessel disease	132 (20.8%)	124 (20.8%)	
Left main - disease	22 (3.5%)	19 (3.2%)	0.783
Culprit			
LMCA	5 (0.8%)	7 (1.2%)	0.491
LAD	253 (39.9%)	222 (37.2%)	0.339
LAD (DB)	35 (5.5%)	34 (5.7%)	0.888
Cx	74 (11.7%)	60 (10.1%)	0.367
Cx (MB)	52 (8.2%)	35 (5.9%)	0.111
RCA	250 (39.4%)	263 (44.1%)	0.095
Initial laboratory evaluation			
Hemoglobin; Median, g/L	145.0 (119.0; 170.0)	142.0 (119.0; 166.0)	0.030
Platelet count; Median, ($x10^9$/L)	225.0 (141.0; 346.0)	225.5 (138.0; 357.0)	0.768
Creatinin; Median, µmol/l	81.0 (54.0; 127.0)	83.0 (53.0; 123.0)	0.522

Absolute and relative frequencies for categorical variables; median supplemented by 5^{th}-95^{th} percentile for continuous variables

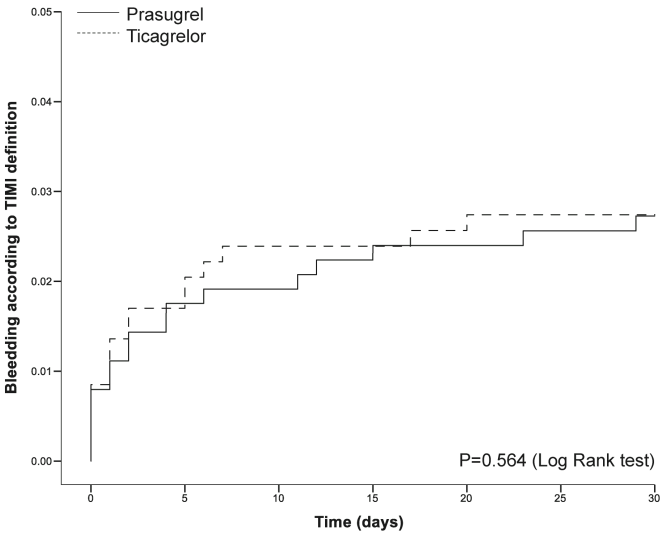
TIMI denotes thrombolysis in myocardial infarction, LAD - left anterior descending artery; DB-diagonal branches, LMCA - left main coronary artery; RCA- right coronary artery, Cx - circumflex artery, MB- marginal branch

Table S2. SUBGROUP ANALYSIS

Characteristics	Patients (N=1230)	Primary end point Prasugrel (N=634)	Primary end point Ticagrelor (N=596)	OR (95% CI)[1] Prasugrel : Ticagrelor	P-value of interaction
Age					
<75	1109	21 (3.7%)	17 (3.2%)	1.13 (0.59; 2.17)	0.496
≥75	121	4 (7.4%)	7 (10.4%)	0.69 (0.19; 2.48)	
Killip classification					
I-III	1185	20 (3.3%)	19 (3.3%)	0.99 (0.52; 1.88)	0.772
IV	45	5 (20.8%)	5 (25.0%)	0.79 (0.19; 3.24)	
I+II	1168	18 (3.0%)	19 (3.4%)	0.89 (0.46; 1.72)	0.700
III+IV	62	7 (21.2%)	5 (18.5%)	1.18 (0.33; 4.26)	
Chronic kidney disease					
No	1214	25 (4.0%)	22 (3.8%)	1.07 (0.60; 1.92)	-
Yes	16	0 (0.0%)	2 (25.0%)	-	
Diabetes					
No	979	18 (3.6%)	16 (3.4%)	1.04 (0.53; 2.07)	0.761
Yes	251	7 (5.6%)	8 (6.5%)	0.86 (0.30; 2.45)	
Weight					
<60	27	0 (0.0%)	1 (7.1%)	-	-
≥60	1203	25 (4.1%)	23 (4.0%)	1.02 (0.57; 1.82)	
Site					
† FNKV Praha	328	11 (6.7%)	11 (6.9%)	0.97 (0.41; 2.31)	0.153
FNUSA Brno	252	4 (3.3%)	4 (3.1%)	1.04 (0.26; 4.26)	
FN Brno	164	2 (2.5%)	2 (2.4%)	1.08 (0.15; 7.84)	
FN Plzeň	146	1 (1.3%)	1 (1.4%)	0.92 (0.06; 14.99)	
AGEL a.s.	94	0 (0.0%)	2 (4.2%)	-	
FNHK	61	0 (0.0%)	1 (3.6%)	-	
České Budějovice	48	0 (0.0%)	0 (0.0%)	-	
Karlovy Vary	39	1 (4.2%)	2 (13.3%)	0.28 (0.02; 3.43)	
VFN Praha	34	3 (12.5%)	0 (0.0%)	-	
Třinec – Podlesí	30	2 (12.5%)	0 (0.0%)	-	
FN Ostrava	19	0 (0.0%)	1 (14.3%)	-	
Ústí nad Labem	6	1 (20.0%)	0 (0.0%)	-	
FN Olomouc	5	0 (0.0%)	0 (0.0%)	-	
Na Homolce	4	0 (0.0%)	0 (0.0%)	-	

[1] based on logistic regression

†Patients with Killip IV at baseline in the site FNKV N=38 (11.6%) from all randomized patients (N=328)
Patients with Killip IV at baseline in all other sites N= 7 (0.8%) from all randomized patients (N = 902)



No at risk

Time (day)	5	10	15	20	25	30
Prasugrel (N=634)	623	622	618	617	615	614
Ticarelor (N=596)	586	582	581	580	579	578

Figure S1. BLEEDING

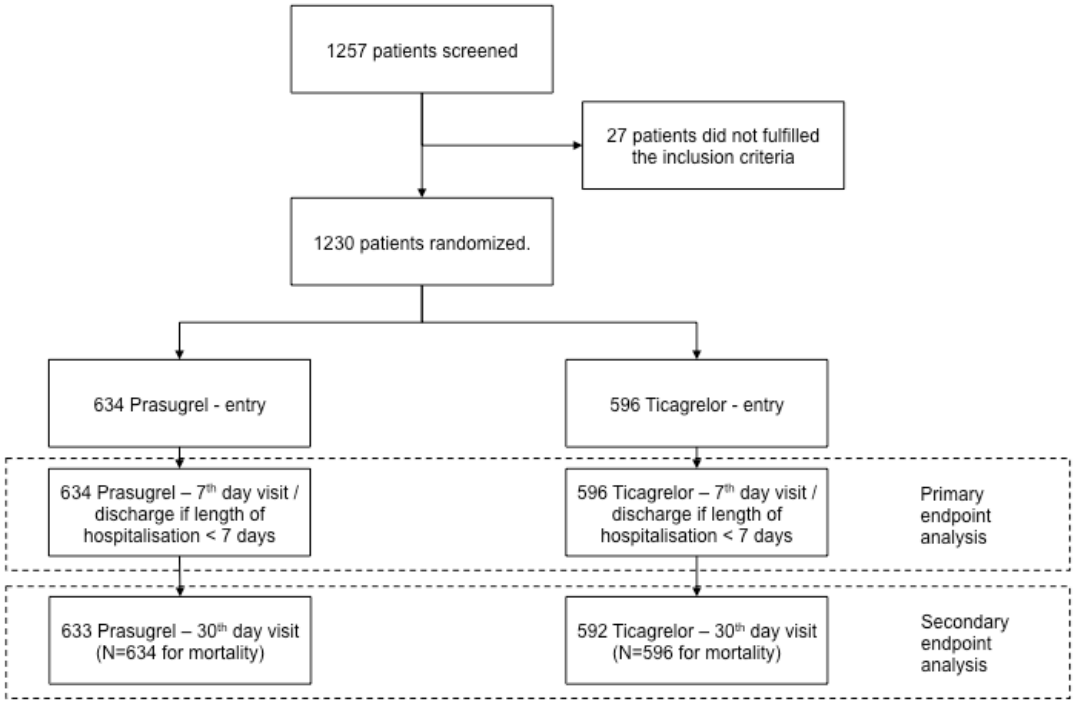


Figure S2. STUDY FLOW CHART

Prague 18: power analysis and sample size estimate

Power calculation for design based
over superiority hypothesis

Definition of study design

The power analysis and sample size estimate is based on the following assumptions:

- **Well defined target group.** The study is aimed on STEMI patients with primary PCI treated with prasugrel or ticagrelor.
- **Superiority hypothesis.** The study aims to show superiority of ticagrelor over prasugrel with respect to composite endpoint (defined in detail in the next slide).
- **Balanced design.** The study will be randomized in 1:1 ratio, i.e. prasugrel and ticagrelor study group will have the same sample size.
- **Time-related design.** The study will focus on the occurrence of pre-specified major cardiovascular events in time, i.e. time-to-event analysis will be employed.

Definition of endpoint

- Study endpoint is defined as a composite endpoint comprising of **cardiovascular death, non-fatal myocardial infarction or non-fatal stroke**.
- The incidence of these events will be evaluated at 30 days and at 12 months.
  - Occurrence of the endpoint in STEMI patients treated with prasugrel/ticagrelor was assumed to be similar as in STEMI primary PCI subsets of studies TRITON-TIMI 38 (Montalescot et al., 2009) and PLATO (Steg et al., 2010)
  - At 30 days the occurrence of endpoint is 6.6% (STEMI primary PCI for prasugrel in Montalescot et al., 2009):
    - **value <u>6.5% at 30 days</u> was taken into account as input (base) in the power analysis**
  - For 12 months the following occurrences of endpoint were considered: 10.2% (STEMI primary PCI patients for prasugrel at 15 months in Montalescot et al., 2009) and 9.4% (STEMI primary PCI patients for ticagrelor at 12 months in Steg et al., 2010)
    - **value <u>9.5% at 12 months</u> was taken into account as input (base) in the power analysis**
- The sample size estimate was calculated for power (1 – β) 80% and 90%.

Methodology

- The estimation was based on power analysis and sample size analysis for survival (time–to–event) endpoints. Sample size calculated for this type of endpoint will also cover the other potential outcomes, like binary measures, etc.

- A two-sided overall alpha level of 0.05 was used for all analyses.

- The results are provided for 80% and 90% power and absolute expected difference in the composite endpoint from 1% to 3%.

- The analysis was computed using software Power And Precision™, release 4.0.

Change in endpoint

- Change in endpoint does not change methodology for calculation of potential outcome -> previous page: ”Sample size calculated for this type of endpoint will also cover the other potential outcomes, like binary measures, etc.”
- Therefore, the tables do not have to be modified and de facto the table for "Composite endpoint : day 30 can be fully used for the day 7 as well (with a simple transcription of the heading, since the calculation is not dependent on the time point).

Sample size estimate

Composite endpoint at 30 days

Reference	Compared events	Absolute difference	Relative difference	HR	N (prasugrel)	N (ticagrelor)
Power = 80%, α=0.05						
6.5	3.5	3.0	46.2%	0.53	829	829
6.5	4.0	2.5	38.5%	0.61	1 250	1 250
6.5	4.5	2.0	30.8%	0.69	2 040	2 040
6.5	5.0	1.5	23.1%	0.76	3 780	3 780
6.5	5.5	1.0	15.4%	0.84	8 851	8 851
6.5	7.5	1.0	15.4%	1.16	10 215	10 215
6.5	8.0	1.5	23.1%	1.24	4 690	4 690
6.5	8.5	2.0	30.8%	1.32	2 722	2 722
6.5	9.0	2.5	38.5%	1.40	1 795	1 795
6.5	9.5	3.0	46.2%	1.49	1 284	1 284
Power = 90%, α=0.05						
6.5	3.5	3.0	46.2%	0.53	1 109	1 109
6.5	4.0	2.5	38.5%	0.61	1 673	1 673
6.5	4.5	2.0	30.8%	0.69	2 730	2 730
6.5	5.0	1.5	23.1%	0.76	5 061	5 061
6.5	5.5	1.0	15.4%	0.84	11 849	11 849
6.5	7.5	1.0	15.4%	1.16	13 675	13 675
6.5	8.0	1.5	23.1%	1.24	6 278	6 278
6.5	8.5	2.0	30.8%	1.32	3 643	3 643
6.5	9.0	2.5	38.5%	1.40	2 403	2 403
6.5	9.5	3.0	46.2%	1.49	1 718	1 718

Composite endpoint at 12 months

Reference	Compared events	Absolute difference	Relative difference	HR	N (prasugrel)	N (ticagrelor)
Power = 80%, α=0.05						
9.5	6.5	3.0	31.6%	0.67	1 283	1 283
9.5	7.0	2.5	26.3%	0.73	1 900	1 900
9.5	7.5	2.0	21.1%	0.78	3 051	3 051
9.5	8.0	1.5	15.8%	0.84	5 567	5 567
9.5	8.5	1.0	10.5%	0.89	12 847	12 847
9.5	10.5	1.0	10.5%	1.11	14 115	14 115
9.5	11.0	1.5	15.8%	1.17	6 412	6 412
9.5	11.5	2.0	21.1%	1.22	3 685	3 685
9.5	12.0	2.5	26.3%	1.28	2 408	2 408
9.5	12.5	3.0	31.6%	1.34	1 706	1 706
Power = 90%, α=0.05						
9.5	6.5	3.0	31.6%	0.67	1 718	1 718
9.5	7.0	2.5	26.3%	0.73	2 544	2 544
9.5	7.5	2.0	21.1%	0.78	4 084	4 084
9.5	8.0	1.5	15.8%	0.84	7 453	7 453
9.5	8.5	1.0	10.5%	0.89	17 199	17 199
9.5	10.5	1.0	10.5%	1.11	18 896	18 896
9.5	11.0	1.5	15.8%	1.17	8 584	8 584
9.5	11.5	2.0	21.1%	1.22	4 933	4 933
9.5	12.0	2.5	26.3%	1.28	3 223	3 223
9.5	12.5	3.0	31.6%	1.34	2 284	2 284

References

- Montalescot, G; Wiviott, SD; Brounwald, E; Murphy, SA; Gibson, CM; McCabe, CH; Antman, EM; Group Author(s): TRITON-TIMI 38 Investigators (2009) Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. LANCET Volume: 373 Issue: 9665 Pages: 723-731.
- Steg, PG; James, S; Harrington, RA; Ardissino, D; Becker, RC; Cannon, CP; Emanuelsson, H; Finkelstein, A; Husted, S; Katus, H; Kilhamn, J; Olofsson, S; Storey, RF; Weaver, D; Wallentin, L; Group Author(s): PLATO Study Grp (2010) Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention A Platelet Inhibition and Patient Outcomes (PLATO) Trial Subgroup Analysis. CIRCULATION Volume: 122 Issue: 21 Pages: 2131-2141.
- Power and Precision version 4.0. The estimation algorithm can be found in: http://www.power-analysis.com/pdfs/power_precision_manual.pdf, Appendix C, page 303.

ENROLLMENT OF PATIENTS AND PREMATURE ENDING OF THE STUDY

Figure F1 shows data about enrollment over time; the enrollment pattern over time is stable.

Figure F1: Enrollment of patients

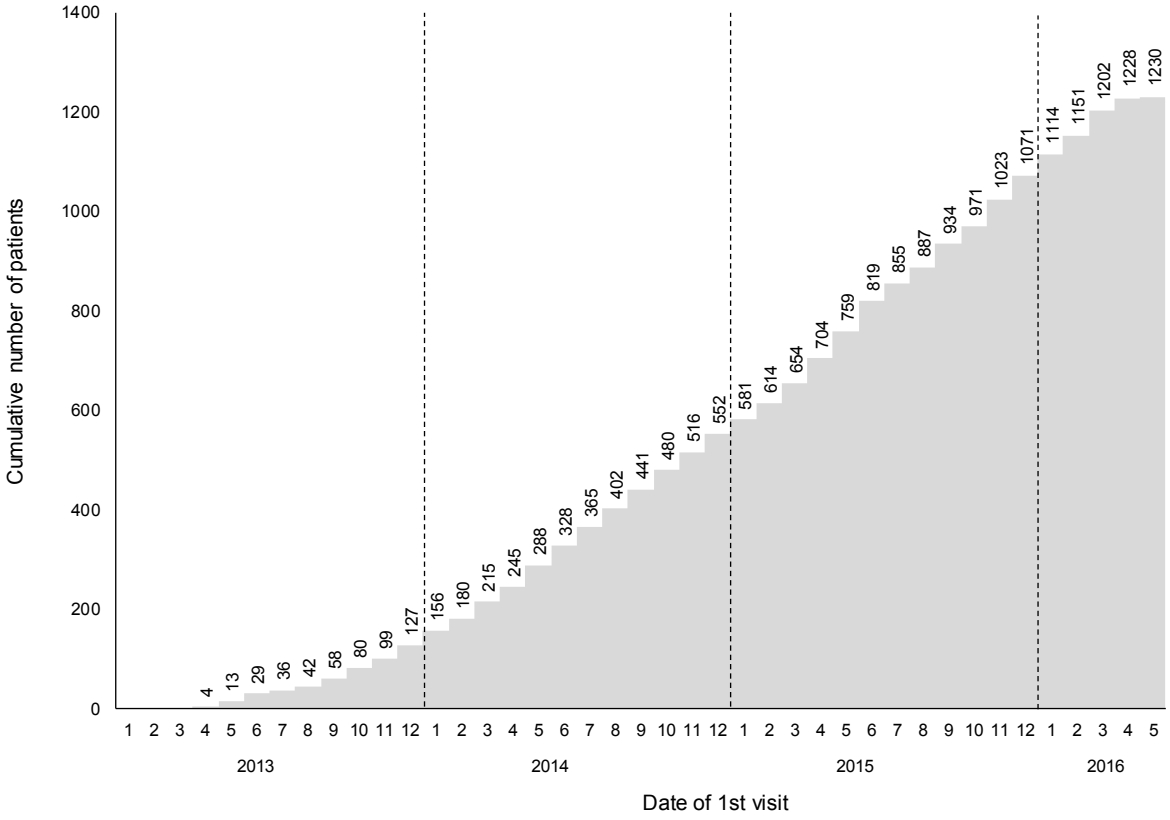
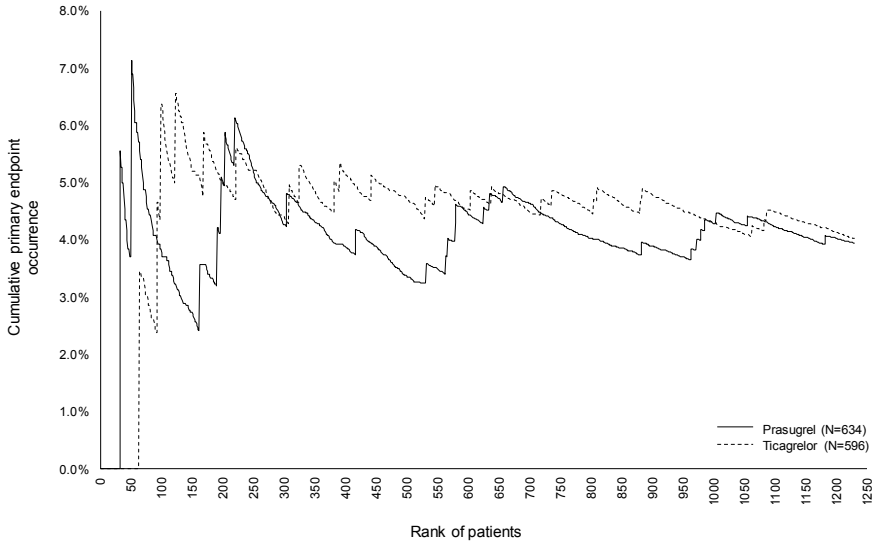


Figure F2 describes differences in primary endpoints between study groups according to rank of recruitment; the difference between study groups is much below the expected clinically significant difference of 2.5%, which was used in the power analysis (after the first 150 enrolled patients). Moreover, comparing real differences with a minimal difference detected as statistically significant (i.e. detectable alternative) for given number of patients (Figure F3), it never crosses. We consider these results to be sufficient reason to end the study prematurely.

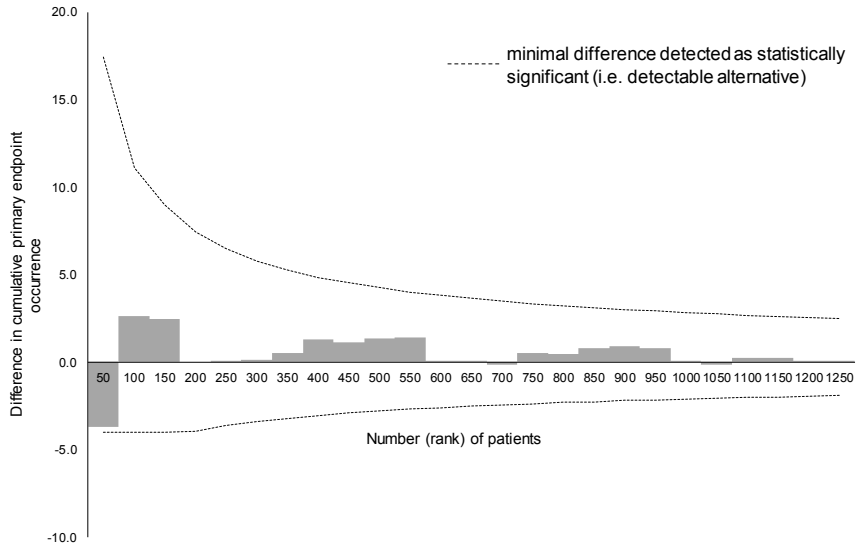
Figure F2: Occurrence of primary endpoint according to enrollment of patients and study group.



Difference in cumulative primary endpoint occurrence (ticagrelor – prasugrel) based on the given rank of patients in registry

50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800	850	900	950	1000	1050	1100	1150	1200	1230
-3.7%	2.6%	2.5%	0.0%	0.0%	0.1%	0.5%	1.3%	1.1%	1.4%	1.4%	0.1%	0.1%	-0.2%	0.5%	0.5%	0.8%	0.9%	0.8%	0.0%	-0.2%	0.3%	0.3%	0.1%	0.1%

Figure F3 Comparison of real differences in primary endpoint occurrence (ticagrelor – prasugrel) and the minimal difference detected as statistically significant (i.e. detectable alternative) based on power analysis



Difference in cumulative primary endpoint occurrence (ticagrelor – prasugrel) based on the given rank of patients in registry

50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800	850	900	950	1000	1050	1100	1150	1200	1230
-3.7%	2.6%	2.5%	0.0%	0.0%	0.1%	0.5%	1.3%	1.1%	1.4%	1.4%	0.1%	0.1%	-0.2%	0.5%	0.5%	0.8%	0.9%	0.8%	0.0%	-0.2%	0.3%	0.3%	0.1%	0.1%

Carolyn: Welcome to circulation on the run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. [Carolyn Nam 00:00:08], associate editor from the national heart center and Duke National University of Singapore ...

In just a moment we will be discussing the exciting new results of the [Prague 00:00:21] 18 study of prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary or cutaneous coronary intervention. But first, here's your summary of this week's issue ...

The first study represents the largest published study on the association between PR interval and cardiac resynchronization therapy with defibrillator versus implantable cardioverter defibrillator and real world outcomes. Dr. Friedman and colleagues from Duke Clinical Research Institute studied 26,451 CRT eligible patients from the National Cardiovascular Data Registry ICD Registry. They found that a PR interval at or above 230 milliseconds was associated with increased rates of heart failure, hospitalizations, or death among CRTD but not ICD patients. The real world comparative effectiveness of CRTD versus ICD was significantly less among patients with a PR interval above 230 milliseconds compared to patients with a shorter PR interval.

The authors discuss that these findings may be due to the association between a prolonged PR interval and factors associated with lower rates of CRT response such as non-left bundle branch block morphology, ischemic heart disease, or atrial arrhythmias. It could also be due to the association between delayed AV conduction, disordered diastolic filling, and contemporary CRT reprogramming strategies. The take home message is: in CRT patients with a prolonged PR interval, recognize that they are at high risk for poor outcomes and merit close follow up and consideration of AV optimization ...

The next study is the first adolescent study of serum lipidomics that identifies a new panel of serum glycerophosphocholines that are associated with cardiovascular risk. First author Dr. [Sine 00:02:29], corresponding author Dr. [Palsova 00:02:31], and colleagues from Hospital for Sick Children in University of Toronto recognize that atherogenic dislipidemia is traditionally assessed with high abundance lipids, such as cholesterol and triacylglycerols, which accumulate at millimolar levels in blood. Current advancements in mass spectrometry now allow the discovery and study of new low abundance lipids, which circulate at micro- or nanomolar blood levels. And one such example are the glycerophosphocholine metabolites.

They studied a population based sample of 990 adolescents with age range 12-18 years using liquid chromatography electrospray ionization mass spectrometry. They identify several novel glycerophosphocholines that were associated with multiple cardiovascular disease risk factors. Mediation analysis revealed that these novel glycerophosphocholines mediated their respective relationships between visceral fat and cardiovascular disease risk factors. Furthermore, a particular glycerophosphocholine shown recently to predict incident coronary heart disease in older adults was already associated with several cardiovascular disease risk factors in

these adolescents.

The clinical implication is that the development of a lipidomics signature that could facilitate early intervention or treatment of those at high risk of cardiovascular disease or monitor response interventions could help triage limited healthcare resources. Furthermore, future research on glycerophosphocholines might improve biological understanding of disease and identify potential drug targets to impede cardiovascular disease development ...

The next study also describes plasma lipidomic profiles but this time in patients with type 2 diabetes. This study is from first author Dr. [Elchuri 00:04:35], corresponding author Dr. [Meekly 00:04:37], and colleagues from the Baker IDI Heart and Diabetes Institute in Melbourne, Australia. These authors performed a targeted lipidomic analysis using liquid chromatography electrospray ionization tandem mass spectrometry in a case cohort of 3,779 patients with type 2 diabetes and one or more additional cardiovascular risk factors from the advance trial.

They found that sphingolipids, phospholipids, cholesterol esters, and glycerol lipids were associated with future cardiovascular events and cardiovascular death. The addition of 7 lipid species to a base model of 14 traditional risk factors and medications improved the prediction of cardiovascular events. The prediction of cardiovascular death was also improved with the incorporation of 4 lipid species to the base model. These results were further validated in a subcohort of type 2 diabetes from the lipid trial. In summary, this important study demonstrates the potential of plasma lipid species as biomarkers for cardiovascular risk stratification in diabetes ...

The last study sheds new light on the optimal ablation method for atypical atrioventricular nodal reentrant tachycardia or atypical ARNVT. Dr. [Catrisis 00:06:10] and colleagues from Beth Israel Deaconess Medical Center, Harvard Medical School in Boston, Massachusetts study 2,079 patients with AVNRT subjected to slow pathway ablation. In 113 patients, atypical AVNRT or coexistent atypical and typical AVNRT without other concomitant arrhythmias was diagnosed. Ablation data and outcomes were compared to a group of age and sex matched control patients with typical AVNRT. The authors found that in the atypical group slow pathway ablation was accomplished from the right septum in 110 patients and from the left septum in 3 patients. There was no need for additional ablation lesions at other anatomical sites and no cases of AV block were encountered.

In summary AVNRT, regardless of the type, appears to be successfully ablated by targeting the anatomic area of the slow pathway. When a right septal approach is not successful, the anatopic area of the slow pathway can be ablated from the left septum and so it seems the slow pathway participates in both typical and atypical AVNRT. The take home messages are that catheter ablation at the anatomical area of the slow pathway from the right or left septum may be the treatment of choice for atypical AVNRT. The approach is not associated with an increased risk of inadvertent AV block. The recurrence rate following ablation of atypical AVNRT may not be significantly higher than that seen following the ablation of typical AVNRT.

Those were the highlights from this week's issues. And now for our feature paper ...

We're so pleased to have with us today for our podcast interview first and corresponding author of the Prague 18 study, Dr. [Zuzana Motovska 00:08:12] from Charles University in Prague. Welcome Zuzana.

Zuzana: Thank you for having me.

Carolyn: We're also so lucky to have Dr. [Gabriel Stig 00:08:21], associate editor from Paris, and I understand you're even traveling at the moment. Thank you, Gabriel for making the time.

Gabriel: Yes, hello Carolyn, hello Zuzana.

Carolyn: So let me start by congratulating you Zuzana on this first head-to-head comparison study of prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary or cutaneous coronary intervention. And what a lovely study acronym of course, Prague 18. Could you maybe start by describing, in the Czech Republic before your study, how were clinical decisions being made between prasugrel and ticagrelor in these patients?

Zuzana: The current guidelines prefer newer P2Y12 inhibitors over clopidogrel for patients with acute coronary syndromes. Prasugrel and ticagrelor are being increasingly used in patients [with just 00:09:15] primary PCI in Czech Republic. Analysis of our registry documented that doctors did not view these two drugs as interchangeable and prasugrel is a drug associated with a high risk of bleeding. Our data show that safety in terms of bleeding risk was the most important aspect under consideration when choosing one of new agents for an individual patient. The same observation has been reported from other contemporaries from other countries and according to the published subgroup analysis of [stratum 00:09:54] and other studies we have also perceived prasugrel to be a more effective agent for primary PCI. We prefer this drug in patients with a high thrombotic risk.

Carolyn: Could you, maybe now, clearly describe what you did in this study and what were your findings?

Zuzana: The Prague 18 study truly [inaudible 00:10:19] was designed to test the hypothesis on whether one of the newer drugs, prasugrel or ticagrelor, is more effective and safer than the other one in acute myocardial infarctions, which is the primary [treatment 00:10:36] strategy. We randomized the total 1,230 in 14 participating sites. I highlighted hemodynamic instabilities, was not an [excluding 00:10:52] criterion for study participation. The patients were randomized for prasugrel or ticagrelor immediately on hospital arrival and the recommended dosing regiments were used for both drugs. The prasugrel dose was reduced during the maintenance phase in patients over 75 and [reduced vein 00:11:12] was the [sixth 00:11:14] feature around presence of both these parameters was an exclusion criterion.

So, what we find. Fewer [unsourced 00:11:23] primary endpoint composed of all cause of death or reinfarction show serious bleeding or urgent vessel revascularization within 7 days after randomization or discharge if prior to the seventh day. They did not differ between groups, either for in 4 person prasugrel group and in 4.1 person in ticagrelor group. The appearance of key secondary end point composed of cardiovascular death, nonfatal MI, or nonfatal stroke. Within 30 days did not show any significant difference between prasugrel and ticagrelor, furthermore no significant difference was found in any of the components of the primary and secondary endpoints and also no significant difference was observed in the appearance of definite vein thrombosis [inaudible 00:12:17] days after randomization.

So the study did not show any difference between ticagrelor and prasugrel in the early phase of a mild [treatable 00:12:26] primary PCI. Because of small sample size the confidence for the estimation of the [interval 00:12:35] of either were quite high, however we identify differences, which are very low in absolute numbers and [inaudible 00:12:45]

Carolyn: That was very nicely explained Zuzana, thank you. Now could you share a little bit more about, were you powered for this analysis and the decision to stop early.

Zuzana: Oh yes, the power analysis was computed for primary endpoint difference of 2.5 person and the needed sample size was estimated at 2,500 patients. The interim analysis led to a decision to terminate the study prematurely because of futility. No significant difference in primary endpoint was found between the two study drugs in the course of the entire randomization process, moreover the difference in appearance of the primary endpoint between the compare groups was declining with a growing number of randomized patients and analyzed on the different 0.1% and this was the decision why we stopped the trial prematurely.

Carolyn: Right. Gabriel could you comment a little bit as the associate editor managing this paper, how do you think it's going to impact practice?

Gabriel: First of all, let me start by congratulating Zuzana and the team of the Prague 18 trial for this academic trial. I think it's really important that we have a clinically led effort to investigate optimal treatments in modern cardiology in general and specifically in acute coronary syndromes. We've known for several years now, through large randomized trials, that the novel P2Y12 agents, ticagrelor and prasugrel, are clearly superior to clopidogrel but we don't know which of the two agents to choose and we know that comparison across trials are fraught with major methodological problems. So with evidence that prasugrel is superior to clopidogrel for PCI treated ACS patients, there was evidence that ticagrelor was superior to clopidogrel for ACS patients in general but we didn't have any rational data on which to base a rational selection process between the two agents.

Really, I think it's an important issue and often people state that these are delicate differences between agents, and we shouldn't expect that this is going to impact clinical

outcomes. Actually it does impact clinical outcomes because we know that those novel agents have had a roughly 20% reduction in major heart outcomes compared to clopidogrel so this is not a moot point. It's not a minute difference, it's a huge difference and it's an important clinical issue. That's my first point, I think it's an important question and I really want to commend the investigators for launching this trial despite not having the support of industry.

The second point I want to make is I think that the results from the trial are not yet complete because we don't have the one year follow-up and I know that this is planned and the investigators are continuing follow-up of their patient cohort, which I think is going to be important because it's conceivable that differences may emerge over time as was, in fact, the case in some of the previous trials. In [plato 00:15:49] there was a modest difference early on but the curves diverged over time between clopidogrel and ticagrelor so it's conceivable that differences that are absent at 30 days might emerge over time.

In fact, I have a question for Zuzana. One of the interesting features and important issues that needs to be addressed is ... I know that in some sites in the Czech Republic, because of the out of pocket expenses related to the cost of the novel agents, it was allowed for patients to be switched back to clopidogrel after hospital discharge. Do you have any sense of what is the proportion of patients who are scaled back to clopidogrel instead of prasugrel or ticagrelor after initial index submission?

Zuzana: Thank you Gabriel, it's true the study ... a lot of patients who are unable to bear the cost associated with long term treatment with the study medications and switch to clopidogrel. Therefore, a second goal of the study was to assess the rate, the reason, and also the consequences of switching from a study drug to clopidogrel after the acute phase in the course of 12 months follow-up. We are not focusing on the study completion and analysis that are related to the second study. There are, of course, patients who switch from prasugrel or ticagrelor to clopidogrel also in first 30 days and this proportion was about one third of patients.

Gabriel: The other point I want to make really relates to the power issues and Zuzana already pointed out herself this important issue. The paper is actually accompanied by an excellent and very cogent editorial by Steve [Webiok 00:17:31], who discusses explicitly and in great detail the issue of sample size. We know that the relative difference between the novel agents and clopidogrel is in the range of 20% so we might expect that the difference between the two novel agents themselves, when we compare prasugrel and ticagrelor, might be less. Yet the study was powered for actually a greater relative risk reduction than what was seen in the pivotal trials of prasugrel and ticagrelor compared to clopidogrel. So the study is really on the low end of the power spectrum and I think, as you pointed out Zuzana, it's important to keep in mind that the confidence interval for the relative risk between ticagrelor and clopidogrel both act together on prasugrel, both for the primary endpoint, which is a combination of efficacy and safety, as well as for the key secondary endpoint of efficacy.

It's really very wide and we can't rule out a major benefit or a major detrimental effect

of one agent versus the other. I think this is important to keep in mind because many people equate a neutral result of a trial, a non-significant result, particularly in the [secondary 00:18:36] trial, with lack of difference or clinical equivalence or non-inferiority and I think it's important to remember the readers that this is not a non-inferiority trial, it's not a clinical equivalence trial, it's superiority trial that is actually with a neutral result. It's really and important issue.

Yet, because it's the first head-to-head comparison, because it's an academic effort independent, and because it's going to report one year outcomes, I think this is a critical effort and the investigators need to be lauded for that. Even if this study isn't powered, it will be able to be pulled in further meta-analysis with other upcoming studies that are similar that also may be underpowered and provide us with a hint of evidence of what might be the best agent to use, which is an every day clinical question. This is a very, very common condition and any unbiased evidence we can get from randomized trials is very valuable ...

Carolyn: Thank you, everyone, for listening to this episode of circulation on the run. Tune in next week ...