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Clinical Research

Outcomes Among Clopidogrel, Prasugrel, and Ticagrelor in ST-Elevation Myocardial Infarction Patients Who Underwent Primary Percutaneous Coronary Intervention From the TOTAL Trial

Robert C. Welsh, MD,[a,b] Robinder S. Sidhu, MD,[a,b] John A. Cairns, MD,[c] Shahar Lavi, MD,[d] Sasko Kedev, MD,[e] Raul Moreno, MD,[f] Warren J. Cantor, MD,[g] Goran Stankovic, MD,[h] Brandi Meeks, MEng,[i] Fei Yuan, MMath,[i] Vladimír Džavík, MD,[j] and Sanjit S. Jolly, MD[i]

[a] *Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada*

[b] *University of Alberta, Edmonton, Alberta, Canada*

[c] *University of British Columbia, Vancouver, British Columbia, Canada*

[d] *London Health Sciences Centre, London, Ontario, Canada*

[e] *University Clinic of Cardiology, Sts Curil and Methodius University, Skopje, Macedonia*

[f] *University Hospital La Paz, Madrid, Spain*

[g] *Southlake Regional Health Centre, Newmarket, Ontario, Canada*

[h] *University of Belgrade, Belgrade, Serbia*

[i] *McMaster University and the Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada*

[j] *Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada*

See editorial by Marquis-Gravel et al., pages 1283–1285 of this issue.

ABSTRACT

Background: Robust comparisons between oral P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in ST-elevation myocardial infarction (STEMI) patients who undergo primary percutaneous coronary intervention are lacking. We sought to evaluate outcomes on the basis of P2Y12 inhibitor therapy in patients from the **T**hrombectomy With PCI Versus PCI **A**lone in Patients With STEMI Undergoing Primary PCI (TOTAL) trial.

Methods: We grouped 9932 patients according to P2Y12 inhibitor at hospital discharge: clopidogrel (n = 6500; 65.5%), prasugrel (n = 1244; 12.5%), or ticagrelor (n = 2188; 22.0%). The primary composite end point of cardiovascular death, recurrent myocardial infarction,

RÉSUMÉ

Contexte : Il n'existe pas d'analyse robuste comparant les inhibiteurs P2Y12 à prise orale (clopidogrel, prasugrel et ticagrélor) chez les patients ayant subi un infarctus du myocarde avec élévation du segment ST (STEMI) traités par une intervention coronaire percutanée (ICP) primaire. Nous avons entrepris d'évaluer les résultats chez les patients ayant reçu un traitement par un inhibiteur P2Y12 dans le cadre de l'essai TOTAL (***T**hrombectomy With PCI Versus PCI **A**lone in Patients With STEMI Undergoing Primary PCI*).

Méthodologie : Nous avons réparti 9 932 patients en trois groupes en fonction de l'inhibiteur P2Y12 qui leur a été prescrit à leur sortie de l'hôpital : clopidogrel (n = 6 500; 65,5 %), prasugrel (n = 1 244; 12,5 %)

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy for ST-elevation myocardial infarction (STEMI). Adjunctive medical treatment, including oral dual antiplatelet therapy (aspirin with a P2Y12 adenosine diphosphate receptor inhibitor), is typically initiated as early as possible and continued for 1 year post event.[1,2]

The second-generation thienopyridine, clopidogrel (C) was the only widely used P2Y12 inhibitor for several years. Justification for the C 300 mg loading dose and 75 mg daily for 1 year in the STEMI population who received PPCI was largely extrapolated from trials in non-STEMI[3] and STEMI patients who underwent secondary percutaneous coronary intervention (PCI).[4] Application of a larger loading dose in STEMI-PPCI patients was subsequently shown in 1 small trial[5] and the STEMI subgroup from the **C**lopidogrel and

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Corresponding author: Dr Robert C. Welsh, 2C2 Cardiology, WMC, 8440 112 St NW, Edmonton, Alberta T6G 2B7, Canada. Tel.: +1-780-407-3613; fax: +1-780-407-6452.

E-mail: Robert.Welsh@albertahealthservices.ca

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cardiogenic shock, or New York Heart Association class IV heart failure was examined at 1 year. Secondary efficacy and safety end points were also assessed. Cox proportional hazard ratios were determined and adjusted for confounders via propensity scoring.

Results: Baseline characteristics differing between the 3 groups were mainly age 75 years or older, diabetes, and previous stroke. After adjustment, ticagrelor use was associated with a lower rate of the primary composite outcome compared with clopidogrel (adjusted hazard ratio [aHR], 0.72; 95% confidence interval [CI], 0.57-0.91; $P < 0.02$) and prasugrel (aHR, 0.65; 95% CI, 0.48-0.89; $P = 0.02$). Prasugrel use was not associated with a lower rate of the primary outcome compared with clopidogrel (aHR, 1.09; 95% CI, 0.86-1.39; $P > 0.99$). Neither prasugrel nor ticagrelor were associated with increased risk of stroke compared with clopidogrel. Compared with clopidogrel, ticagrelor was associated with significantly lower rates of major bleeding.

Conclusions: In this observational analysis of STEMI patients who underwent primary percutaneous coronary intervention, ticagrelor was associated with improved outcomes compared with clopidogrel and prasugrel. An appropriately powered randomized trial is needed to confirm these findings.

ou ticagrélor (n = 2 188; 22,0 %). Le critère d'évaluation principal, composé du décès d'origine cardiovasculaire, d'un nouvel infarctus du myocarde, d'un choc cardiogénique ou d'une insuffisance cardiaque de classe IV selon la New York Heart Association, a été évalué après 1 an. Des critères d'efficacité et d'innocuité secondaires ont aussi été évalués. Les rapports des risques proportionnels selon le modèle de Cox ont été calculés et corrigés au moyen d'une analyse des scores de propension pour tenir compte des facteurs de confusion.

Résultats : Les sujets des trois groupes se distinguaient par certaines caractéristiques initiales, soit l'âge (75 ans ou plus), la présence de diabète et les antécédents d'accident vasculaire cérébral (AVC). Après correction, l'emploi du ticagrélor a été associé à un taux inférieur de survenue de l'un ou l'autre des événements du critère d'évaluation principal comparativement au clopidogrel (rapport des risques instantanés corrigé [RRIc] de 0,72; intervalle de confiance [IC] à 95 %, de 0,57 à 0,91; $p < 0,02$) et au prasugrel (RRIc de 0,65; IC à 95 %, de 0,48 à 0,89; $p = 0,02$). L'emploi du prasugrel n'a pas été associé à un taux inférieur de survenue de l'un des événements du critère principal comparativement au clopidogrel (RRIc de 1,09; IC à 95 %, de 0,86 à 1,39; $p > 0,99$). Ni le prasugrel ni le ticagrélor n'ont été associés à un risque accru d'AVC comparativement au clopidogrel. Enfin, le ticagrélor a été associé à des taux d'hémorragie majeure significativement inférieurs comparativement au clopidogrel.

Conclusions : Dans le cadre de notre analyse observationnelle des patients ayant subi un STEMI et traités par intervention coronaire percutanée primaire, les résultats obtenus avec le ticagrélor se sont révélés supérieurs à ceux obtenus avec le clopidogrel ou avec le prasugrel. La réalisation d'une étude avec répartition aléatoire d'une puissance suffisante s'impose pour confirmer ces observations.

Aspirin Optimal Dose **U**sage to **R**educe **R**ecurrent **Ev**ents-**O**rganization to **A**ssess **S**trategies in **I**schemic **S**yndromes (CURRENT-OASIS) trial.[6] C has acknowledged pharmacological properties, including its requirement for metabolism in 2 steps after absorption, which might result in a clinically significant delay to achieve adequate platelet inhibition at the time of PPCI.[7] Furthermore, common genetic polymorphisms mean some patients lack the enzymatic activity necessary to activate the drug,[8] increasing their risk of poor long-term outcomes.[9]

The subsequent development of 2 novel P2Y12 inhibitors, prasugrel (P) and ticagrelor (T), promised more rapid and reliable platelet inhibition. Each drug is backed by a large randomized trial in acute coronary syndrome patients, which established advantage compared with C.[10,11] Neither trial had a large population of STEMI patients who received expedited PPCI. However, the American College of Cardiology and American Heart Association STEMI guidelines currently recommend either T or P over C in patients who undergo PPCI (class IIa, level of evidence: B).[12] The European Society of Cardiology makes an even stronger recommendation for the use of either newer agent over C in this patient group (class I, level of evidence: A), which is consistent with the Canadian Cardiovascular and Canadian Association of Interventional Cardiology antiplatelet guideline recommendations.[1,13] There is currently a relative paucity of clear evidence to guide the optimal P2Y12 inhibitor selection in STEMI patients who receive PPCI. Adequate comparisons between C, T, and P are limited by the available data. Although the agents have important differences, including the mechanisms of P2Y12 receptor inhibition,[7] it is unclear whether this translates into different clinical outcomes. Data from the **T**hr**o**mbec**t**omy With PCI Versus PCI **Al**one in Patients With STEMI Undergoing Primary PCI (TOTAL) trial provides an opportunity to analyze one of the largest contemporary cohorts of STEMI-PPCI patients.[14] Accordingly, this observational analysis was undertaken to evaluate the effect of P2Y12 inhibitor choice on 1-year efficacy and safety outcomes from these trial data.

Methods

Study design

TOTAL was a multicentre, international prospective trial that randomized STEMI patients to manual thrombus aspiration with PPCI vs PPCI alone. The study complied with the Declaration of Helsinki and necessary ethics approval and informed consent of study patients were obtained. The study protocol and results have been reported previously.[14,15] Briefly, patients were eligible if they presented with diagnostic ST-segment elevation (using standard definitions) and underwent PCI within 12 hours of symptom onset. Randomization was done before angiography and patients received aspirin with a P2Y12 inhibitor chosen at the discretion of the local investigator. For this analysis, we compared 3 groups of TOTAL participants who received C, P, and T regarding their efficacy and safety outcomes.

Patient population

Trial recruitment took place between August 2010 to July 2014 involving 87 hospitals in 20 countries, and patients were

followed for 12 months after randomization. For this post hoc analysis, we categorized patients into 3 different groups on the basis of the P2Y12 inhibitor prescribed at the time of hospital discharge after the index event. By study design, patients who died before hospital discharge were excluded from this analysis.

Study outcomes

Consistent with the main trial, the primary efficacy outcome in this analysis was a composite of cardiovascular death, recurrent myocardial infarction (MI), cardiogenic shock, or new/worsening New York Heart Association class IV heart failure. Secondary efficacy outcomes included all-cause mortality, stent thrombosis, PCI (not for index STEMI), target vessel revascularization, rehospitalizations, and recurrent ischemia/unstable angina. All outcomes were reported after 365 days of follow-up post randomization.[16]

Safety outcomes included all major or minor bleeds, and stroke or transient ischemic attack. Major bleeding included severe (fatal, leading to a decrease in hemoglobin of $\geq$ 5 g/dL, significant hypotension, requiring surgery, symptomatic intracranial hemorrhage, or requiring transfusion of 4 or more units of red blood cells), and other nonsevere major (significantly disabling, intraocular bleeding leading to vision loss, or requiring transfusion of 2-3 units of red blood cells). Minor bleeding was defined as any other bleeding not meeting criteria for major bleed or requiring 1 unit of blood transfused. These definitions have been described previously.[15]

Statistical analysis

Analysis was conducted using a modified intention to treat approach on the basis of patients who had undergone PPCI. Baseline categorical variables are reported as percentages. Continuous variables are reported as mean and SD. If data were too skewed, they were summarized using median and interquartile range. Differences between groups were tested with Fisher exact test for categorical variables. *P* values were adjusted using Bonferroni correction to account for pairwise comparison among groups that received either C, P, or T. For continuous variables, analysis of variance and Tukey test were used to compare the means among the 3 groups. If data were skewed, the Kruskal-Wallis test and Bonferroni-corrected Wilcoxon rank sum test were used instead.

The relationship between P2Y12 inhibitor prescribed at hospital discharge and outcomes after 1 year of follow-up was examined using Cox proportional hazard modelling to determine hazard ratios and 95% confidence intervals. To adjust for potential confounders, propensity scores were calculated on the basis of the following variables: age, sex, body mass index, Killip class, creatinine, anterior MI on electrocardiogram, previous MI, previous PCI, previous coronary artery bypass grafting surgery, previous stroke, peripheral arterial disease, hypertension, diabetes, smoking, transported by ambulance, heart rate at baseline, diastolic blood pressure at baseline, systolic blood pressure at baseline, and the use of an intra-aortic balloon pump. These variables were chosen on the basis of literature review and expert opinion. Adjusted analyses on the basis of propensity scoring yielded adjusted hazard ratio (aHR) and 95% confidence interval (CI) for all outcomes. Bonferroni corrected *P* values are provided, after considering the pairwise comparison of 3 groups. With the post hoc nature of the analyses, no further adjustment was made to address multiple testings.

All statistical tests used a 2-sided significance level of 0.05. Statistical analysis was performed using the software SAS version 9.4 (SAS Institute, Cary, NC) and TIBCO Spotfire S+ version 8.2 for Windows (Tibco Software Inc, New York, NY).

Results

Baseline characteristics

Of a total 10,732 STEMI patients randomized there were 10,064 patients who underwent PPCI to form the intention to treat analysis. The analyses of outcomes according to the prescribed P2Y12 inhibitor were on the basis of the 9932 patients with complete data available.

Tables 1 and 2 present the baseline characteristics, conjunctive parenteral antithrombotic medical therapies, and procedural characteristics of the full cohort (left panel) and of the 3 P2Y12 inhibitor groups. Most patients were male (77.5%) and a small proportion were elderly (age older than 75 = 12.7%). Comorbidities were common, especially hypertension (50.0%), current smoking (45.8%), and diabetes (18.2%). Presentation with heart failure (4.2%) or cardiogenic shock (1.0%) was rare, but a large proportion had an anterior infarct on the basis of electrocardiogram (39.8%). Patients were generally revascularized in a timely fashion (hospital to device median time: 53.00 minutes; quartile (Q)1-3, 23.0-90.0 minutes). Thrombectomy was attempted in 52.0% of patients. Additional baseline measures are presented in Supplemental Tables S1 and S2.

C was the most commonly used P2Y12 inhibitor (C, 65.5%; P, 12.5%, T, 22.0%). Although the baseline characteristics between groups were overall similar, several important differences were noted. These included: age 75 years or older (C, 14.5%; P 5.5%; T 11.6%), previous stroke (C, 3.7%; P, 0.7%; T, 2.2%), and the presence of diabetes (C, 18.8%; P, 20.3%; T, 15.2%). Baseline angiographic and procedural characteristics were similar between groups with the exception of increased use of unfractionated heparin and bare metal stents in those treated with C.

Primary efficacy outcomes

The primary composite outcome occurred in 8.5% of patients in the C group, 7.1% in the P group, and 4.6% in the T group (Table 3). The adjusted Kaplan-Meier curve for risk of the primary outcome is shown in Figure 1. After adjusted analysis, the use of T, compared with C, was associated with a reduced risk of the primary composite outcome (aHR, 0.72; 95% CI, 0.57-0.91; $P = 0.02$). Furthermore, T was associated with lower rates of the individual components of New York Heart Association class IV heart failure (T, 0.8%; C, 2.5%; aHR, 0.49; 95% CI, 0.29-0.83; $P = 0.02$). The use of P, however, had no association with the risk of the primary composite outcome over C (aHR, 1.09; 95% CI, 0.86-1.39; $P > 0.99$) or its components.

Compared with P, T was associated with a significant reduction of the primary composite end point (aHR, 0.65; 95% CI, 0.48-0.89; $P = 0.02$).

Table 1. Baseline characteristics of the overall cohort and antiplatelet subgroups

Characteristic	Overall		Clopidogrel		Prasugrel		Ticagrelor		*P*		
	n	Value	n	Value	n	Value	n	Value	Ticagrelor vs clopidogrel	Prasugrel vs clopidogrel	Ticagrelor vs prasugrel
Randomized patients who underwent PPCI (mITT)	10,064		6500	65.5	1244	12.5	2188	22.0			
Patients included (data complete)	9932	100	6500	100	1244	100	2188	100			
Male sex	7698	77.5	4940	76.0	1054	84.7	1704	77.9	0.23	< 0.001	< 0.001
Age older than 75 years	1265	12.7	943	14.5	69	5.5	253	11.6	0.001	< 0.001	< 0.001
Killip heart failure ≥ 2 at entry	419	4.2	298	4.6	60	4.8	61	2.8	< 0.001	> 0.99	0.008
Anterior MI on ECG	3952	39.8	2614	40.2	521	41.9	817	37.3	0.05247	0.85144	0.029
Previous MI	884	8.9	559	8.6	127	10.2	198	9.0	> 0.99	0.21656	0.826
Previous PCI	822	8.3	486	7.5	148	11.9	188	8.6	0.2887	< 0.001	0.007
Previous stroke	296	3.0	239	3.7	9	0.7	48	2.2	0.002	< 0.001	0.002
Peripheral arterial disease	220	2.2	132	2.0	37	3.0	51	2.3	> 0.99	0.13089	0.787
Hypertension	4965	50.0	3443	53.0	560	45.0	962	44.0	0	< 0.001	> 0.99
Diabetes	1809	18.2	1224	18.8	253	20.3	332	15.2	< 0.001	0.666	< 0.001
Smoking - current	4549	45.8	3001	46.2	603	48.5	945	43.2	0.048	0.409	0.009
Transported by ambulance	6548	65.9	4177	64.3	858	69.0	1513	69.1	< 0.001	0.004	> 0.99
UFH	8210	82.7	5779	88.9	862	69.3	1569	71.7	< 0.001	< 0.001	0.413
Fondaparinux	52	0.5	38	0.6	5	0.4	9	0.4	> 0.99	> 0.99	> 0.99
Enoxaparin	851	8.6	547	8.4	123	9.9	181	8.3	> 0.99	0.295	0.355
Bivalirudin	1840	18.5	625	9.6	469	37.7	746	34.1	< 0.001	< 0.001	0.103
GPIIb/IIIa	3920	39.5	2639	40.6	414	33.3	867	39.6	> 0.99	< 0.001	< 0.001
Bare metal stent	5218	52.5	4137	63.6	475	38.2	606	27.7	< 0.001	< 0.001	< 0.001
Drug-eluting stent	4471	45.0	2214	34.1	738	59.3	1519	69.4	< 0.001	< 0.001	< 0.001
Thrombectomy attempted	5162	52.0	3373	51.9	654	52.6	1135	51.9	> 0.99	> 0.99	> 0.99
Hemoglobin, g/dL	9847	14.5 ± 4.8	6438	14.5 ± 4.9	1231	14.7 ± 1.6	2178	14.4 ± 5.5	0.89	0.39	0.31

Data are presented as n (%) for categorical variables and mean ± SD for continuous variables. For categorical variables, *P* values are from Fisher exact test with Bonferroni correction. For a continuous variable, *P* value is from Tukey test. $P \leq 0.05$ is considered significant.

ECG, electrocardiogram; GPIIb/IIIA, glycoprotein IIb/IIIA inhibitor; MI, myocardial infarction; mITT, modified intention to treat based on completion of primary PCI; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; UFH, unfractionated heparin.

Table 2. Baseline temporal characteristics of the overall cohort and platelet subgroups

Characteristic	Overall		Clopidogrel		Prasugrel		Ticagrelor		*P*		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	Ticagrelor vs clopidogrel	Prasugrel vs clopidogrel	Ticagrelor vs prasugrel
Overall symptom onset to hosp, min	9925	125 (73-220)	6497	135 (78-239)	1242	120 (71-204)	2186	106 (65-180)	0	< 0.01	< 0.01
Ambulance: onset to hosp, min	6544	129 (80-220)	4175	141 (87-240)	857	120 (77-200)	1512	104 (70-173)	0	0	< 0.01
Self-presentation: onset to hosp, min	3379	120 (60-225)	2322	120 (60-234)	385	110 (60-207)	672	117 (57-206)	0.14	0.39	> 0.99
Symptom onset to rand, min	9931	181 (120-290)	6500	197 (131-307)	1244	157 (106-247)	2187	152 (105-242)	0	0	0.9
Hospital to rand, min	9924	43 (15-80)	6497	52 (17-86)	1242	28 (11-56)	2185	30 (13-71)	0	0	< 0.01

Data are presented as n, median, and IQR. *P* values from Wilcoxon rank sum test with Bonferroni correction.
hosp, hospitalization; IQR, interquartile range; rand, randomization.

Secondary efficacy outcomes

T usage was associated with increased repeat PCI compared with C (T, 15.8%; C, 12.8%; aHR, 1.28; 95% CI, 1.11-1.48; $P < 0.01$). Secondary efficacy outcomes are displayed in Table 4. When further compared with P, T was associated with lower rates of repeat PCI.

P was associated with increased rates of recurrent ischemia or unstable angina, repeat PCI, compared with C.

Stent thrombosis (C, 2.0%; P, 2.4%; T, 1.4%) after adjustment was not significantly different between the 3 groups. As well, there were no differences in the incidence of target vessel revascularization between groups (C, 5.3%; P, 4.9%; T, 4.5%).

Safety outcomes

Major bleeding rates according to P2Y12 inhibitor use were: C, 1.8%; P, 1.5%; and T, 1.1%. Safety outcomes are displayed in Table 5. Compared with C, T was associated with less major bleeding (aHR, 0.47; 95% CI, 0.29-0.76; $P \leq 0.01$) and significantly increased minor bleed (T, 10.0%; C, 6.1%; aHR, 1.60; 95% CI, 1.33-1.94; $P < 0.001$).

The overall rates of stroke were low and neither P nor T significantly influenced rates of stroke compared with C or to each other. As well, the combined outcome of stroke or transient ischemic attack did not differ between groups.

Discussion

The main results of this observational analysis of STEMI patients who received primary PCI to assess the association of P2Y12 inhibitors prescribed at discharge on 1-year clinical outcomes were: (1) T is associated with improved outcomes compared with either C or P, with no increase in major bleeds; and (2) P is not associated with any advantage over C in this STEMI-PPCI population. Our study addressed a key knowledge gap in the STEMI literature by directly comparing the 3 available oral P2Y12 inhibitors. Although these striking results should be interpreted carefully because of the study design, we interestingly found consistent benefit associated with T across multiple efficacy end points including components of the primary composite and secondary efficacy events. In contrast, P failed to show any signal of advantage over C.

Previous attempts to answer the question as to the optimal P2Y12 inhibitor in STEMI-PPCI have yielded conflicting results. Multiple meta-analyses have been published on this topic. Although 1 study suggested that T and P improve outcomes in STEMI patients who undergo PCI over C,[17] another showed no differences between any P2Y12 inhibitor,[18] and yet another showed that P was superior to T in STEMI-PPCI patients.[19] Interpreting these meta-analyses is challenging because there is significant heterogeneity of the included studies, and evolving baseline therapies over time. Our study challenges the current guideline recommendations that either novel oral P2Y12 inhibitor is preferred over C in STEMI-PPCI patients.[1,12] Although we conducted a post hoc observational analysis, the implications of our findings should be considered because of the paucity of evidence on this topic.

To date, the only randomized trial to compare P with T in STEMI-PPCI patients was conducted in a single country and stopped early because of statistical futility.[20] However, the

Table 3. One year primary efficacy outcome on the basis of P2Y12 inhibitor prescribed at discharge

	C, n (%)	P, n (%)	T, n (%)	Comparison	Adjusted HR	95% CI	Observed P^*	Corrected $P^\dagger$
Primary composite outcome	536 (8.5)	85 (7.1)	93 (4.6)	T vs C	0.72	0.57-0.91	0.005	0.02
				P vs C	1.09	0.86-1.39	0.475	> 0.99
				T vs P	0.65	0.48-0.89	0.006	0.02
CV death	249 (3.9)	28 (2.3)	38 (1.9)	T vs C	0.70	0.49-1.00	0.054	0.16
				P vs C	0.94	0.63-1.41	0.768	> 0.99
				T vs P	0.79	0.47-1.30	0.350	> 0.99
Recurrent MI	160 (2.5)	28 (2.3)	34 (1.7)	T vs C	0.89	0.60-1.32	0.552	> 0.99
				P vs C	1.40	0.95-2.07	0.093	0.28
				T vs P	0.61	0.37-0.99	0.045	0.14
Cardiogenic shock	138 (2.2)	20 (1.7)	22 (1.1)	T vs C	0.65	0.40-1.04	0.072	0.22
				P vs C	0.92	0.56-1.52	0.742	> 0.99
				T vs P	0.65	0.35-1.21	0.173	0.52
NYHA classification IV heart failure	156 (2.5)	22 (1.8)	17 (0.8)	T vs C	0.49	0.29-0.83	0.008	0.02
				P vs C	1.11	0.69-1.77	0.672	> 0.99
				T vs P	0.51	0.26-0.98	0.044	0.13

C, clopidogrel; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association; P, prasugrel; T, ticagrelor.

* Observed *P* values from Cox proportional hazard models.

† Bonferroni-corrected version of observed *P* values.

primary end point of the study was reported after only 7 days post STEMI, whereas our current study evaluated outcomes after 1 year of follow-up according to the antiplatelet agent used at the time of hospital discharge. A longer duration of observation might be needed to elucidate differences between P2Y12 inhibitors. This has been suggested by trials in acute coronary syndrome patients who did not undergo PPCI. **T**a**r**geted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**g**y to Medicall**y** Manage **A**cute **C**oronary **S**yndromes (TRILOGY ACS) failed to show any benefit with long-term P over C after a median of 17 months of follow-up, in keeping with our current findings.[21]

Potential explanations for our disparate findings between T and P might arise from their differing pharmacological profiles. P is a thienopyridine that requires metabolic activation to become functional[22]; whereas T is active on ingestion and binds to a distinct site on the P2Y12 receptor.[23] However, both attain similar therapeutic effects in STEMI patients immediately after a loading dose[24] and neither showed any superiority in lab testing of platelet inhibition in STEMI patients who underwent PPCI after 24 hours.[25] Although this possibly accounts for the equivocal short-term findings of Prasugrel versus Ticagrelor in Patients with Acute Myocardial Infarction treated with Primary Percutaneous Coronary Intervention (PRAGUE-18) our study is suggestive of alternate mechanisms leading to T's therapeutic advantage.

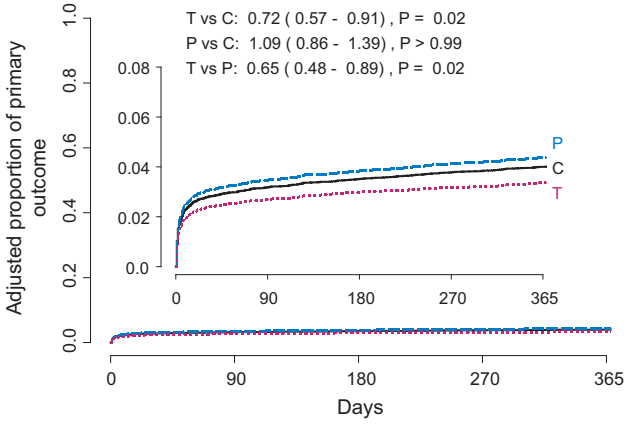

Figure 1. Kaplan-Meier curves of adjusted risk of primary outcome (cardiovascular death, recurrent myocardial infarction, cardiogenic shock, New York Heart Association classification IV heart failure) on the basis of P2Y12 inhibitor prescribed at discharge. CI, confidence interval; Clop, clopidogrel; Prasug, prasugrel; Ticag, ticagrelor.

One potential mechanism relates to T's actions beyond platelet inhibition. Adenosine is an endogenous nucleoside that is known to increase coronary blood flow[26] and improves outcomes if given during PCI.[27] T has been shown to inhibit cellular reuptake of adenosine,[28] leading to increased coronary blood flow in humans.[29] Another beneficial effect of T might result from direct effects on endothelial function. A small trial showed that improvements in vascular reactivity were more pronounced with T use compared with C.[30]

Safety

Our study showed that although minor bleeds were significantly increased with T and P over C, major bleeds were not. In fact, the adjusted rates of major bleeding were 50% lower with T compared with C. Rates of bleeding in our study were lower than previously reported with T use in STEMI-PPCI,[31] but similar to P in the entire cohort of STEMI patients.[32] The relatively lower rate of bleeding events in the current analysis might reflect more cautious prescribing practices with the novel P2Y12 inhibitors or alternatively be related to the assessment of outcomes on the basis of the agent used at hospital discharge. Our finding of no increased major bleed or stroke risk corroborates recent meta-analyses of the P2Y12 inhibitors in STEMI-PPCI.[17-19]

Strengths

The key strength of this study was the novel and consistent findings from a contemporary cohort of STEMI patients who underwent PPCI. Although TOTAL used a different composite end point than either **Plat**elet Inhibition and Patient **O**utcomes (PLATO)[10] or **Tr**ial to Assess **I**mprovement in **T**herapeutic **O**utcomes by Optimizing Platelet Inhibitio**n**

Table 4. One year secondary efficacy outcomes on the basis of P2Y12 inhibitor prescribed at discharge

	C, n (%)	P, n (%)	T, n (%)	Comparison	Adjusted HR	95% CI	Observed P^*	Corrected $P^\dagger$
Secondary composite (CV death, MI, or stroke)	425 (6.7)	69 (5.8)	80 (4.0)	T vs C	0.77	0.60-0.99	0.043	0.13
				P vs C	1.10	0.84-1.44	0.490	> 0.99
				T vs P	0.68	0.49-0.95	0.0239	0.07
All-cause mortality	298 (4.7)	33 (2.8)	45 (2.2)	T vs C	0.70	0.50-0.97	0.031	0.09
				P vs C	0.95	0.65-1.38	0.786	> 0.99
				T vs P	0.80	0.50-1.28	0.351	> 0.99
Recurrent ischemia/ unstable angina rehospitalization	17 (0.3)	14 (1.2)	7 (0.3)	T vs C	1.43	0.55-3.76	0.464	> 0.99
				P vs C	3.23	1.45-7.21	0.004	0.01
				T vs P	0.33	0.13-0.83	0.019	0.06
All rehospitalizations	1053 (16.7)	237 (19.8)	381 (18.9)	T vs C	1.08	0.95-1.23	0.237	0.71
				P vs C	1.20	1.03-1.40	0.021	0.06
				T vs P	0.87	0.74-1.03	0.099	0.30
Stent thrombosis (definite or probable)	128 (2.0)	29 (2.4)	29 (1.4)	T vs C	1.04	0.68-1.60	0.846	> 0.99
				P vs C	1.38	0.89-2.13	0.152	0.46
				T vs P	0.63	0.37-1.08	0.096	0.29
PCI (not for index STEMI)	807 (12.8)	241 (20.2)	319 (15.8)	T vs C	1.28	1.11-1.48	< 0.001	< 0.01
				P vs C	1.59	1.35-1.86	< 0.001	< 0.001
				T vs P	0.73	0.61-0.87	< 0.001	< 0.001
Target vessel revascularization	336 (5.3)	58 (4.9)	91 (4.5)	T vs C	0.88	0.69-1.13	0.325	0.97
				P vs C	0.90	0.67-1.22	0.489	> 0.99
				T vs P	0.91	0.65-1.28	0.580	> 0.99

C, clopidogrel; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; P, prasugrel; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; T, ticagrelor.

* Observed *P* values from Cox proportional hazard models.

† Bonferroni-corrected version of observed *P* values.

With Prasugrel **T**hrombolysis **i**n **M**yocardial **I**nfarction 38 (TRITON-TIMI 38),[11] our conclusions remained unchanged when we examined secondary efficacy and safety outcomes. Moreover, to control the type I error rate and avoid spurious significant findings, a conservative approach such as Bonferroni correction was adopted. The conclusions still hold regardless this correction. Additionally, all patients in our analysis underwent timely PPCI within 12 hours of symptom onset. This contrasts with the STEMI subgroups of PLATO[31] and TRITON-TIMI 38,[32] which included a number of patients who underwent secondary PCI (2706 patients, 72.1%; and 1203 patients, 68.0%, respectively underwent PPCI).

Limitations

The major limitations of this analysis were those of any observational analysis. Because patients were not randomized to a specific P2Y12 inhibitor, potential confounders could not be eliminated. Instead, the drugs were chosen solely at the discretion of the prescribing investigator and could have been influenced by patterns of practice, health economics, or perceived bleeding risks. Selection bias might have played a role in choosing antiplatelet strategy because of the US Food and Drug Administration's black box warning for bleeding for P and T. Additionally, we did not capture the utilization of

Table 5. One year safety outcomes on the basis of P2Y12 inhibitor prescribed at discharge at 1 year

	C, n (%)	P, n (%)	T, n (%)	Comparison	Adjusted HR	95% CI	Observed P^*	Corrected $P^\dagger$
Stroke	64 (1.0)	8 (0.7)	14 (0.7)	T vs C	0.62	0.33-1.17	0.140	0.42
				P vs C	0.70	0.32-1.53	0.370	> 0.99
				T vs P	0.78	0.32-1.90	0.587	> 0.99
Stroke or TIA	80 (1.3)	11 (0.9)	16 (0.8)	T vs C	0.54	0.31-0.97	0.039	0.12
				P vs C	0.73	0.37-1.44	0.364	> 0.99
				T vs P	0.65	0.30-1.44	0.290	0.87
TIA	17 (0.3)	3 (0.3)	2 (0.1)	T vs C	0.28	0.06-1.31	0.107	0.32
				P vs C	0.84	0.22-3.20	0.804	> 0.99
				T vs P	0.31	0.05-1.94	0.210	0.63
Major bleed (including severe)	114 (1.8)	18 (1.5)	23 (1.1)	T vs C	0.47	0.29-0.76	0.002	< 0.01
				P vs C	0.72	0.42-1.23	0.224	0.67
				T vs P	0.60	0.32-1.13	0.116	0.35
Severe bleed	91 (1.4)	14 (1.2)	20 (1.0)	T vs C	0.50	0.30-0.85	0.010	0.03
				P vs C	0.65	0.36-1.20	0.172	0.52
				T vs P	0.69	0.34-1.38	0.290	0.87
Minor bleed	382 (6.1)	89 (7.4)	201 (10.0)	T vs C	1.60	1.33-1.94	< 0.001	< 0.001
				P vs C	1.27	0.99-1.64	0.059	0.18
				T vs P	1.28	0.99-1.66	0.059	0.18

C, clopidogrel; CI, confidence interval; HR, hazard ratio; P, prasugrel; T, ticagrelor; TIA, transient ischemic attack.

* Observed *P* values from Cox proportional hazard models.

† Bonferroni-corrected version of observed *P* values.

oral anticoagulants, which might affect the antiplatelet strategy and associated outcomes, especially bleeding rates. Moreover, although we incorporated an extensive list of variables known to be associated with adverse clinical outcomes into the propensity model for adjustment, there are still possibly unmeasured confounders that were not adjusted, and that could bias this analysis. Additionally, we grouped patients according to the P2Y12 inhibitor prescribed at discharge. Patients might have received another P2Y12 inhibitor on presentation or during the index hospital stay. Although this might influence events in the short-term, our study assessed outcomes 1 year after randomization. Thus, grouping patients on the basis of drug at discharge represents the longest exposure period to a particular P2Y12 inhibitor.

Finally, our analysis could be underpowered. The TOTAL study was not designed and powered to find differences of risks in outcomes among the drug strategies used. Despite this, our results still hold merit because current guideline recommendations for novel P2Y12 inhibitors[1,12] are similarly on the basis of underpowered subgroup analyses of larger trials.[31,32] Although the currently ongoing randomized trial, **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen: **R**apid **E**arly **A**ction for **C**oronary **T**reatment (ISAR-REACT) 5 trial, will provide much needed insight in comparing P with T, it too might be underpowered. The investigators have designed this trial with the assumption that events will occur at rates much higher than we observed in our current study.[33] Improved therapies in STEMI-PPCI patients have led to an overall reduction in clinical events, resulting in significant limitations for clinical investigators. Mounting trials large enough show superiority in P2Y12 inhibitor use are likely too costly and impractical. Thus, our study, a robust observational analysis in a contemporary STEMI-PPCI population, provides important observations to help answer the question of optimal P2Y12 inhibitor.

Conclusion

In this post hoc analysis of STEMI patients who underwent primary PCI from the TOTAL trial, T was associated with better efficacy compared with C and P. Neither T nor P were associated with and increased risk of major bleeding or stroke compared with C. Although we attempted to adjusted for baseline differences, an appropriately powered randomized trial is needed to confirm these findings.

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Supplementary Material

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