Complementary prognostic values of ST segment deviation and Thrombolysis In Myocardial Infarction (TIMI) risk score in non-ST elevation acute coronary syndromes: Insights from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study

Thao Huynh MD MSC¹, James Nasmith MD², The Minh Luong MSC³, Martin Bernier MD¹,
Chantal Pharand PharmD⁴, Zhao Xue-Qiao MD⁵, Robert P Giugliano MD SM⁶, Pierre Theroux MD³

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BACKGROUND: Although the Thrombolysis In Myocardial Infarction (TIMI) score incorporates ST deviation, it does not account for characteristics of the ST deviations. In the present study, it was hypothesized that the magnitude and characteristics of ST deviation may add to the prognostic values of the TIMI risk score in acute coronary syndrome (ACS) patients, particularly in lower-risk patients with a TIMI risk score of less than 5.

OBJECTIVE: To evaluate the prognostic value of combining the TIMI risk score and characteristics of ST deviation in patients with non-ST elevation ACS and a TIMI risk score of less than 5.

METHODS: The death/myocardial infarction (MI) rates of 1296 patients enrolled in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) angiographic substudy were examined.

RESULTS: Patients without a TIMI risk score of 5 or greater, and without an ST deviation of 1 mm or greater had the lowest six-month rate of death/MI (5%). In patients with a TIMI risk score of less than 5, the six-month death/MI rate was increased in those with ST depression of 2 mm or greater compared with patients with a similar TIMI risk score and without ST deviation of 1 mm or greater (24% versus 5%, $P < 0.001$). The presence of ST deviation of 2 mm or greater identified an additional 15% of patients with an increased six-month death/MI rate in patients with a TIMI risk score of less than 5.

CONCLUSION: ST segment deviation of 2 mm or greater confers additional prognostic information in non-ST elevation ACS patients with a TIMI risk score of less than 5. Patients with a TIMI risk score of less than 5 and ST deviation of 2 mm or less had the lowest risk of six-month death/MI.

Key Words: Acute coronary syndromes; Electrocardiogram; Non-ST elevation myocardial infarction; Unstable angina

Les valeurs pronostiques complémentaires de la déviation du segment ST et de l'indice de risque TIMI de thrombolyse en cas d'infarctus du myocarde en présence de syndromes coronariens aigus sans élévation du segment ST : Un aperçu de l'étude PRISM-PLUS sur l'inhibition des récepteurs plaquettaires dans la prise en charge du syndrome ischémique chez les patients limités par des signes et symptômes instables

HISTORIQUE : Même si l'indice TIMI de thrombolyse en cas d'infarctus du myocarde inclut la déviation du segment ST, il ne tient pas compte des caractéristiques de cette déviation. Dans la présente étude, on a postulé que la magnitude et les caractéristiques de la déviation du segment ST pourraient améliorer les valeurs pronostiques de l'indice de risque TIMI chez les patients ayant un syndrome coronarien aigu (SCA), notamment chez les patients à faible risque dont l'indice de risque TIMI est inférieur à 5.

OBJECTIF : Évaluer la valeur pronostique de l'association de l'indice de risque TIMI aux caractéristiques de déviation du segment ST chez des patients atteints d'un SCA sans élévation du segment ST dont l'indice de risque TIMI était inférieur à 5.

MÉTHODOLOGIE : Les auteurs ont examiné les taux de décès et d'infarctus du myocarde (IM) de 1 296 patients inscrits dans l'étude PRISM-PLUS sur l'inhibition des récepteurs plaquettaires dans la prise en charge du syndrome ischémique chez les patients limités par des signes et symptômes instables.

RÉSULTATS : Les patients sans indice de risque TIMI de 5 ou plus et sans déviation du segment ST de 1 mm ou plus présentaient le taux de décès ou d'IM le plus faible au bout de six mois (5 %). Chez les patients dont l'indice de risque TIMI était inférieur à 5, le taux de décès ou d'IM au bout de six mois était plus élevé si la dépression de leur segment ST était de 2 mm ou plus que si leur indice de risque TIMI était similaire mais qu'ils n'avaient pas de déviation du segment ST de 1 mm ou plus (24 % par rapport à 5 %, $P < 0,001$). La présence d'une déviation du segment ST de 2 mm ou plus s'associait à 15 % de plus de patients au taux accru de décès ou d'IM lorsque leur indice de risque TIMI était inférieur à 5.

CONCLUSION : Une déviation du segment ST de 2 mm ou plus conférait de l'information pronostique supplémentaire chez les patients atteints d'un SCA sans élévation du segment ST dont l'indice de risque TIMI était inférieur à 5. Les patients dont l'indice de risque TIMI était inférieur à 5 et dont la déviation du segment ST était de 2 mm ou moins présentaient le risque le plus faible de décès ou d'IM au bout de six mois.

¹McGill Health University Centre, McGill University, Montreal, Quebec; ²Toronto Western Hospital, University of Toronto, Toronto, Ontario;

³Montreal Heart Institute; ⁴Hopital Sacre-Coeur, University of Montreal, Montreal, Quebec; ⁵University of Washington School of Medicine, Seattle, Washington; ⁶Brigham and Women's Hospital, Harvard University, Boston, Massachusetts, USA

Correspondence and reprints: Dr Thao Huynh, 1650 Avenue Cedar, room E-5200, Montreal, Quebec H3G 1A4. Telephone 514-934-1934 ext 43241, fax 514-934-8318, e-mail thao.huynhthanh@mail.mcgill.ca

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Patients with non-ST segment elevation acute coronary syndromes (ACS) have a wide range of risks for death and myocardial infarction (MI). Accurate risk stratification of these patients is essential so that high-risk patients may benefit from appropriate interventions. Numerous scores have been proposed for risk stratification of these patients. Of these, the Thrombolysis In Myocardial Infarction (TIMI) risk score has been extensively validated in clinical trials and observational registries (1-5); its prognostic value has been confirmed for both short-term (1-3) and long-term (4,5) outcomes in non-ST elevation ACS.

Electrocardiography (ECG) is a rapid, simple and noninvasive tool. ST deviations are important prognostic markers in patients with ACS (6-8). Although the TIMI risk score incorporates ST deviations of 0.5 mm or greater, it does not take into account the type (ST depression or ST elevation) or magnitude of the ST deviations beyond 0.5 mm. Patients with low TIMI risk scores (less than 5) have a diverse range of risk for long-term adverse outcomes. In these patients, accurate risk stratification is particularly important for guiding management. The prognostic value of combining TIMI risk score and characteristics of the ST deviations has not yet been ascertained.

We aimed to evaluate the prognostic value of combining the TIMI risk score with ST deviation among patients with non-ST elevation ACS, particularly in lower-risk patients with a TIMI risk score of less than 5.

METHODS

The population, design and main results of the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study were described in the original publication (9). The initial study design involved double-blind random assignment to one of three treatment groups: tirofiban alone, tirofiban plus heparin or heparin alone. The Data and Safety Monitoring Board discontinued enrollment in the tirofiban alone treatment group secondary to an excessive seven-day mortality. For the purpose of the present study, only patients enrolled in the PRISM-PLUS angiographic substudy were included. Patients enrolled in the tirofiban alone arm (n=345) were excluded from the substudy.

Study end points

The primary end point was the six-month rate of death or new MI. MI was defined as a new episode of chest pain, at least 20 min in duration with new Q waves (more than 0.03 s in duration in two or more leads), or a rise in the serum creatine kinase (CK) level to two or more times the upper limit of normal (three or more times for percutaneous coronary angioplasty-related MI) with elevated CK myocardial bands (CK-MBs).

Electrocardiographic analysis

To be enrolled in the PRISM-PLUS study, patients were required to have an ST deviation of 1 mm or greater in at least two limb leads or three precordial leads, or new T wave inversion of 3 mm or greater in at least three leads, or elevated CK-MB. ST elevation had to be transient (less than 20 min). All prerandomization 12-lead ECGs were analyzed by a certified cardiologist (JN) blinded to the patients' outcomes. ST deviation was measured with calipers. A standard calibration of 25 mm/s and 10 mm/mV was used for all ECGs. All patients with pacemaker activity, left ventricular hypertrophy or a QRS width of 0.120 s or greater were excluded. Patients with atrial fibrillation were also excluded due to the possibility of digitalis ingestion. Patients with sinus tachycardia (heart rate 120 beats/min or greater) were excluded because these patients may have had rate-related ST depression.

All leads except AVR were examined for ST deviation. Maximal ST deviation was measured at 0.08 s after the J point. Concave ST elevations judged to be of early repolarization were qualified as normal (ie, no ST elevation). Patients with both ST depression and ST elevation were classified in the predominant ST deviation category

(present in the most number of leads). Only ST deviations of 1 mm or greater were considered (ie, patients with ST deviations of less than 1 mm were considered to have no ST deviation).

The TIMI risk score

The TIMI risk score is composed of seven independent clinical risk indicators evaluated at the time of random assignment (age of 65 years or older, the presence of three or more risk factors for coronary artery disease, known significant coronary stenosis, ST deviation of 0.5 mm or greater, elevated cardiac biomarker serum levels, severe angina in the previous 24 h, and use of acetylsalicylic acid in the previous seven days) (1). For each patient, the score was calculated as the sum of the number of risk indicators present (score range 0 to 7). Because PRISM-PLUS patients were required to have severe angina within the previous 24 h to be eligible for enrollment in the study, all patients had a minimum score of 1. Because data concerning previous coronary artery disease were not collected, this risk score was modified to incorporate previous MI or coronary revascularization (10). Elevated cardiac biomarkers included elevation of serum CK at two or more times the institutional upper limit of normal and/or elevated CK-MB. Due to protocol-specified inclusion criteria, only patients with an ST deviation of 1 mm or greater were enrolled in the study. Therefore, only patients with ST deviation of 1 mm or greater were given one point for the risk indicator of ST deviation.

Coronary angiography

Coronary angiography was performed at a mean of 65 h after random assignment (11). Standard coronary views with six- to seven-inch image fields were obtained. Sublingual or intracoronary nitroglycerin was used in all patients before the coronary injections. The culprit lesion was identified with help from the baseline ECG. Quantitative coronary angiographic assessments of per cent stenosis, thrombus grade and TIMI flow were performed at the core angiographic laboratory at the University of Washington in Seattle, Washington, USA (blinded to patients' outcomes, ECG findings and TIMI risk scores).

Statistical analysis

Patients were classified into five mutually exclusive groups – no ST deviation; ST depression of 1 mm or greater, and less than 2 mm; ST depression of 2 mm or greater; ST elevation of 1 mm or greater, and less than 2 mm; and ST elevation of 2 mm or greater – according to the characteristics of their maximal ST deviation. Categorical variables were presented as proportions and continuous variables as means. Categorical variables were compared using χ^2 two-tailed testing, and continuous variables were compared by Student's two-tailed testing. $P < 0.05$ was considered to be significant. All analyses were performed with SPSS 15.0 (SPSS Inc, USA).

RESULTS

A total of 1491 patients were enrolled in the PRISM-PLUS angiographic substudy. Of these patients, 192 patients had missing ECGs or the presence of confounders (ventricular pacemaker activity, left ventricular hypertrophy, atrial fibrillation, sinus tachycardia with a heart rate of 120 beats/min or greater, or a QRS width of 0.12 s or greater). TIMI risk scores were missing for three patients. Thus, there were 1296 patients with ECGs, TIMI scores and angiographic results available for analysis.

Baseline clinical characteristics of the patients are presented in Table 1. Patients without ST deviation were younger with lower proportions of diabetes mellitus, hypertension, previous MI and coronary artery bypass graft surgery ($P < 0.001$). Patients with ST deviation had similar baseline characteristics, except that patients with an ST elevation of 2 mm or greater were younger and less likely to be women or to have diabetes ($P < 0.001$).

The angiographic results are shown in Table 2. Patients without ST deviation had the highest proportion of nonsignificant coronary artery disease at 14% and the lowest mean per cent stenosis of the culprit coronary artery at 69% ($P < 0.001$). Significant coronary artery

TABLE 1
Baseline clinical characteristics stratified by ST deviation

Clinical characteristic	No ST deviation (n=268)	ST depression (n=803)		ST elevation (n=225)	
		<2 mm (n=675)	≥2 mm (n=128)	<2 mm (n=137)	≥2 mm (n=88)
Age, years, mean ± SD	58.5±11.5	63.5±10.8	66.5±10.8	62.2±10.8	59.4±12.0
Women, %	32.7	32.9	26.6	37.2	23.9
Diabetes mellitus, %	16.8	16.8	24.4	21.2	17.0
Hypertension, %	47.8	57.6	54.7	50.4	48.9
Previous myocardial infarction, %	39.6	41.6	40.6	41.6	45.5
Previous percutaneous coronary intervention, %	12.3	10.7	7.8	13.1	10.2
Previous coronary artery bypass graft surgery, %	10.1	16.3	18.0	13.1	11.4
Increased creatine kinase-myocardial band, %	50.0	39.3	51.6	51.1	46.6
Combination of tirofiban and heparin, %	50.0	39.1	46.1	42.3	46.6

TABLE 2
Angiographic characteristics stratified by ST deviation

Angiographic characteristic	No ST deviation (n=268)	ST depression (n=803)		ST elevation (n=225)	
		<2 mm (n=675)	≥2 mm (n=128)	<2 mm (n=137)	≥2 mm (n=88)
Nonsignificant coronary disease*, %	14.2	4.6	2.4	4.5	7.2
Single-vessel disease, %	31.0	22.9	8.0	36.8	32.5
Double-vessel disease, %	25.7	28.2	24.0	21.8	24.1
Triple-vessel disease, %	23.9	44.3	65.6	36.8	36.1
Mean stenosis of the culprit coronary artery, %, mean ± SD	69.2±22.4	76.5±16.0	77.6±15.5	76.7±18.1	74.0±13.9
TIMI coronary flow grade 3, %	78.8	78.2	76.9	75.6	89.2
Corrected TIMI frame count, mean ± SD	21.2±18.0	21.3±16.3	21.3±21.3	22.7±16.9	21.4±16.8

*Nonsignificant coronary disease was defined as <50% stenosis of any major coronary artery or branch. TIMI Thrombolysis In Myocardial Infarction

TABLE 3
Six-month death/myocardial infarction rates stratified by Thrombolysis In Myocardial Infarction (TIMI) risk scores and ST deviations

TIMI risk score	Six-month death/myocardial infarction rate, %					
	No ST deviation ≥1 mm (n=268)	ST deviation ≥2 mm (n=216)	ST depression (n=803)		ST elevation (n=225)	
			<2 mm (n=675)	≥2 mm (n=128)	<2 mm (n=137)	≥2 mm (n=88)
1–4 (n=913)	5.2 (n=232)	13.3* (n=141)	11.5* (n=452)	24.3** (n=74)	13.6* (n=88)	14.1* (n=67)
≥5 (n=383)	13.9 (n=36)	12.2 (n=75)	20.2** (n=223)	14.8 (n=54)	12.2 (n=49)	19.2** (n=21)

*P<0.05 compared with patients without ST deviations ≥1 mm; **P<0.001 compared with patients without ST deviations ≥1 mm

TABLE 4
Six-month death/myocardial infarction rates stratified by ST deviation and assigned treatment

Treatment	Six-month death/myocardial infarction rate, %				
	No ST deviation (n=265)	ST depression		ST elevation	
		<2 mm (n=675)	≥2 mm (n=128)	<2 mm (n=137)	≥2 mm (n=88)
Combination of heparin and tirofiban	5.4	12.5	20.3	6.9	14.6
Heparin alone	9.0	13.4	20.0	16.9	20.0

disease and triple-vessel coronary disease were documented in 95% and 44%, respectively, of patients with ST depressions of greater than 1 mm. There was no difference in the mean TIMI frame counts among the five groups of patients.

The six-month death/MI rates, stratified by ST deviation and TIMI risk scores, are shown in Table 3. In patients with a TIMI risk score of less than 5, patients without ST deviation of 1 mm or greater had the lowest six-month death/MI rate at 5%. An ST deviation of 2 mm or greater identified an additional 15% of patients (141 of 913 patients) with a twofold increased six-month death/MI rate (13% versus 5%, P<0.05). In patients with a low TIMI risk score, patients with an ST depression of 2 mm or greater had a markedly increased six-month death/MI rate compared with patients without ST

deviation of 1 mm or greater (24% versus 5%, P<0.001). Patients with a TIMI risk score of 5 or greater had increased six-month rates of death/MI that ranged from 12% to 20%. Sensitivity analyses with the inclusion of 129 patients with sinus tachycardia (heart rate of more than 120 beats/min) showed similar results.

The effect of treatment on the six-month rate of death/MI per assigned treatment and per category of ECG, is shown in Table 4. Although the six-month rate of death/MI was lower in patients with ST elevation who received the combination of heparin and tirofiban compared with patients who received only heparin, this did not reach statistical significance. There was also no significant benefit of the combination of heparin and tirofiban across all other categories of ST deviations.

DISCUSSION

The TIMI risk score has been shown to be predictive of short- and long-term adverse outcomes in several randomized clinical trials and observational registries (1-6). Lower-risk patients with a TIMI risk score of less than 5 have a diverse range of risks for major adverse cardiac outcomes. More accurate stratification of these patients is necessary to identify patients who may benefit more from aggressive coronary intervention. ST segment deviation predicts increased risks of major adverse cardiovascular events in ACS patients (12-14). Previous investigators have extensively validated the prognostic value of ECG abnormalities and/or troponin values (12-21). However, no previous study has assessed the predictive value of combining the TIMI risk score and ECG deviation in non-ST elevation ACS, especially for more optimal risk stratification of patients with a low TIMI risk score of less than 5.

Our study was the first to evaluate the value of ST deviation in combination with the TIMI risk score for more optimal stratification of ACS patients, particularly in lower-risk patients (TIMI risk score of less than 5). A maximal ST deviation of 2 mm or greater in any lead except for AVR, and a TIMI risk score of 5 or greater indicate the highest risk of six-month death/MI (20%). Even in low-risk patients, as suggested by a TIMI risk score of less than 5, an ST deviation of 2 mm or greater indicates an increased six-month death/MI rate. The absence of ST deviation of 2 mm or greater is suggestive of a low six-month death/MI rate.

We propose a simple algorithm to identify ACS patients with increased six-month death/MI rates. Patients with ACS should have their TIMI risk score calculated and ECG examined for ST deviation. Aggressive coronary and medical interventions are generally recommended in patients with a TIMI risk score of 5 or greater (1,3,10). For patients with a TIMI risk score of less than 5, consideration should be given for invasive intervention in patients with ST deviation of 2 mm or greater, because these patients had a higher six-month death/MI rate than patients with a similar risk score and absence of ST deviation of 2 mm or greater. On the other hand, conservative medical management may be more appropriate in patients with low TIMI risk score and absence of ST deviation of 2 mm or greater, because these patients had low six-month death/MI rates.

The present study also provided a correlation between coronary angiography and ECG in a relatively large sample of patients with ACS. Significant coronary artery disease was observed in almost all patients with ST depression, with triple-vessel disease present in one-half of these patients. This finding was in agreement with the Framingham and Fast Revascularization During Instability in Coronary Artery Disease (FRISC) II study (22), which reported a prevalence of 35% and 10% of triple-vessel and left main coronary diseases, respectively.

In the present study, ST deviation alone was not predictive of combined tirofiban and heparin treatment reducing the six-month rate of death/MI. However, there was a nonsignificant lower six-month rate of death/MI among patients with transient ST elevation who received the combination of tirofiban and heparin compared with those who only

received heparin. It was possible that we failed to show a significant benefit of tirofiban in patients with transient ST elevation due to reduced power secondary to the small number of patients in this category.

Limitations

The present study has several limitations. First, the present ECG analysis was limited to patients enrolled in the PRISM-PLUS angiographic substudy. Because patients who underwent coronary angiograms were more likely to have more severe angina, our results may not extrapolate to patients with less severe symptoms. Second, the PRISM-PLUS study was completed before troponin testing became clinically available. Only CK-MB values were available in our patients. Because troponin elevation is more sensitive than CK-MB for mild myocardial ischemia (15), this may have further increased the selection bias of higher-risk patients. Thus, our results may not be applicable to lower-risk ACS patients. Third, we did not assess the outcomes in patients with isolated T wave inversion without ST deviation. These patients constituted a very small group of 25 patients and were classified as patients without ST deviation. Except for the Thrombin Inhibition in Myocardial Infarction (TRIM) and FRISC II studies (6,22), almost all other previous studies (7-14) did not show an increased risk of adverse outcomes in patients with isolated T wave inversion. Fourth, because data concerning documented previous coronary artery disease were not collected in the PRISM-PLUS study, we modified the TIMI risk score to incorporate previous MI or coronary revascularization. Fifth, we did not consider ST deviation of less than 1 mm. Patients with ST deviation of 0.5 mm or greater are at increased risk of six-month death/MI (14). Finally, the additional prognostic value of ST deviation to the TIMI score may not be applicable to other more comprehensive ACS risk scores such as the Global Registry of Acute Coronary Events (GRACE) or Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) scores.

CONCLUSION

We demonstrated the complementarities of TIMI scores and ST deviations in patients with ACS. Patients with ACS should have their TIMI risk score calculated and ECG examined for ST deviation. The presence of maximal ST deviation of 2 mm or greater in any lead except for AVR, and a TIMI risk score of 5 or greater indicated a high rate of six-month death/MI (20%). The absence of both features indicated the lowest risk of six-month death/MI (5%). In lower-risk patients with a TIMI risk score of less than 5, ST deviation of 2 mm or greater identified an additional 15% of patients with an increased six-month death/MI rate. We conclude that ST deviation of 2 mm or greater can be particularly useful in risk stratifying lower-risk ACS patients with a TIMI risk score of less than 5.

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