Relationship of admission hematological indexes with myocardial reperfusion abnormalities in acute ST segment elevation myocardial infarction patients treated with primary percutaneous coronary interventions

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BACKGROUND: Elevated values of mean platelet volume (MPV) and elevated white blood cell (WBC) count are predictors of an unfavourable outcome among survivors of ST segment elevation myocardial infarction (STEMI). However, their relationship with reperfusion abnormalities is less clear.

OBJECTIVE: To evaluate the value of admission MPV and WBC count in predicting impaired reperfusion in patients with acute STEMI who are treated with primary percutaneous coronary intervention (PCI).

METHODS: Blood samples were obtained on admission from 368 STEMI patients who underwent successful PCI. According to the 60th minute ST segment resolution ratio, patients were divided into impaired reperfusion and reperfusion groups.

RESULTS: Impaired reperfusion was detected in 40% of study patients. Patients in the impaired reperfusion group had a higher admission MPV (9.8 ± 1.3 fL versus 8.6 ± 1.0 fL; $P < 0.001$) and a higher WBC count ($14.4 \pm 5.5 \times 10^9/L$ versus $12.1 \pm 3.8 \times 10^9/L$; $P < 0.001$) compared with the patients in the reperfusion group. In regression analysis, MPV (OR 2.21, 95% CI 1.69 to 2.91; $P < 0.001$) and WBC count (OR 1.08, 95% CI 1.02 to 1.15; $P = 0.01$) were found to be independently associated with impaired reperfusion. The best cut-off value of MPV for predicting impaired reperfusion was determined to be 9.05 fL, with a sensitivity of 74% and a specificity of 73%.

CONCLUSIONS: The results indicate that leukocytes and platelets have a role in the mediation of reperfusion injury. In patients with STEMI who are undergoing PCI, admission MPV may be valuable in discriminating a higher-risk patient subgroup and thus, may help in deciding the need for adjunctive therapy to improve the outcome.

Key Words: Leukocytes; Platelets; Primary percutaneous coronary intervention; Reperfusion

Lien entre les indices hématologiques à l'admission et les anomalies de reperfusion myocardique dans l'infarctus aigu du myocarde avec susdécalage du segment ST traité par reperfusion coronarienne percutanée primaire

HISTORIQUE : Un volume plaquettaire moyen (VPM) et une formule leucocytaire élevés sont des prédicteurs d'une issue défavorable chez les survivants d'un infarctus aigu du myocarde avec susdécalage du segment ST (ou STEMI, pour ST segment elevation myocardial infarction). Toutefois, leur lien avec les anomalies de reperfusion n'est pas entièrement élucidé.

OBJECTIF : Évaluer l'utilité de mesurer le VPM et la formule leucocytaire à l'arrivée des patients victimes d'un STEMI aigu traités au moyen d'une intervention coronarienne percutanée primaire (ICP) comme facteurs de prédiction des anomalies de reperfusion.

MÉTHODES : On a prélevé des échantillons sanguins à l'admission de 368 patients victimes d'un STEMI qui ont subi une ICP avec succès. À partir du ratio de résolution du segment ST à la 60e minute, les patients ont été classés en deux groupes selon qu'il y avait anomalie de reperfusion ou reperfusion.

RÉSULTATS : Quarante pour cent des patients de l'étude ont présenté une anomalie de reperfusion. Les patients de ce groupe présentaient à l'admission un VPM plus élevé ($9,8 \pm 1,3$ fL vs $8,6 \pm 1,0$ fL; $p < 0,001$) et une numération des globules blancs plus haute ($14,4 \pm 5,5 \times 10^9/L$ vs $12,1 \pm 3,8 \times 10^9/L$; $p < 0,001$), comparativement aux patients du groupe ayant obtenu une reperfusion. À l'analyse de régression, le VPM (RC 2,21, IC à 95 %, 1,69 à 2,91, $p < 0,001$) et la formule leucocytaire (RC 1,08, IC à 95 %, 1,02 à 1,15, $p = 0,01$) se sont révélés associés de façon indépendante à l'anomalie de reperfusion. La valeur seuil du VPM la plus prédictive d'une anomalie de reperfusion a été de 9,05 fL, avec une sensibilité de 74 % et une spécificité de 73 %.

CONCLUSIONS : Ces résultats indiquent que les leucocytes et les plaquettes jouent un rôle dans la modulation des lésions de reperfusion. Chez les patients victimes d'un STEMI qui subissent une ICP, le VPM à l'admission permettrait de distinguer un sous-groupe de patients plus à risque et pourrait influencer sur la décision de recourir à un traitement d'appoint pour améliorer le pronostic.

Because it offers prompt and complete recanalization of an occluded infarct-related artery (IRA), primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for ST segment elevation myocardial infarction (STEMI) at PCI-capable hospitals. However, in a significant proportion of patients, microvascular and myocardial reperfusion cannot be regained in spite of successfully restored (Thrombolysis In Myocardial Infarction [TIMI] grade 3) epicardial blood flow (1,2). This occurrence, better known as the

'no-reflow phenomenon', is associated with progressive left ventricular dysfunction and increased risk of congestive heart failure, myocardial infarction (MI) and mortality (2).

Platelets play an important role in the pathogenesis of acute coronary syndromes (3). It has been shown that platelet size, measured as mean platelet volume (MPV), correlates with their reactivity (4). Accordingly, large platelets are more dense, metabolically and enzymatically more active and have higher thrombotic potential than

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small ones (5,6). Moreover, an elevated MPV has been recognized as an independent risk factor for adverse clinical outcomes among survivors of myocardial infarction (7). However, the association of elevated MPV with reperfusion abnormalities is less clear (8,9).

Inflammation is known to be an important risk factor for the development of cardiovascular events (10). The leukocyte response, observed during STEMI, is supposed to be a pivotal component of the systemic inflammatory response to injury (11). The white blood cell (WBC) count on admission was shown to be a strong and independent predictor of increased morbidity and mortality in patients with acute myocardial infarction (12). Moreover, Barron et al (12) reported that elevated WBC count was associated with reduced epicardial and myocardial blood flow in patients with acute STEMI who were treated with fibrinolytic therapy.

The aim of the present study was to assess a possible relationship between WBC count and MPV levels on admission and impaired myocardial reperfusion in patients with acute STEMI who were successfully recanalized with primary PCI. To assess myocardial reperfusion, ST segment elevation resolution (STR) criteria were used on a 12-lead electrocardiogram (ECG).

METHODS

From January 2005, to January 2007, 368 patients admitted to the Ankara Yuksek Ihtisas Hospital Cardiology Clinic (Ankara, Turkey) with a diagnosis of STEMI – within 12 h of symptom onset (within 24 h if cardiogenic shock was present) – who were successfully treated with primary PCI, were primarily enrolled in the study. STEMI was defined as typical chest pain lasting longer than 30 min, accompanied by ST segment elevation of at least 1 mm in two or more contiguous ECG leads.

Patients who were treated with fibrinolytic therapy in the previous 24 h, were on oral anticoagulation therapy, had a history of bleeding diathesis, renal insufficiency (creatinine greater than 176.8 $\mu\text{mol/L}$), malignancy, chronic inflammatory disease and active infection, and patients with intraventricular conduction abnormalities were excluded from the study. Thus, two patients with a malignancy, 11 patients with renal impairment, two patients who were on oral anticoagulation therapy and 10 patients with bundle branch blocks were excluded. The remaining 343 patients (78% men), with a mean ($\pm$ SD) age of 58 ± 11 years, formed the final study population. Permission to perform the study was obtained from the local ethics committee.

In all cases, on presentation and before any treatment was given, venous peripheral blood samples for the leukocyte count and MPV measurement were drawn. Blood samples were collected into standardized tubes containing dipotassium EDTA and all measurements were performed on a Beckman Coulter LH 750 Analyzer (Beckman Coulter Inc, USA).

All patients were administered 300 mg of oral acetylsalicylic acid on presentation. From all patients, before cardiac catheterization, written informed consent was obtained by a physician. Subsequently, for each patient, coronary angiography via a femoral artery approach was performed in multiple projections. At the discretion of the operator, the glycoprotein IIb/IIIa inhibitor (tirofiban) was administered to the patients in the catheterization laboratory as a 20 $\mu\text{g/kg}$ bolus followed by a 0.15 $\mu\text{g/kg/min}$ infusion for 24 h. Following 600 mg of oral clopidogrel loading, primary PCI was performed using standard techniques. All patients were administered intravenous unfractionated heparin on a routine basis. Stent implantation to the IRA was strongly encouraged, except in cases involving IRA with heavy calcification or a reference lumen diameter of less than 2.5 mm, or after coronary angioplasty with a stent-like result on the treatment site.

Pre- and post-PCI epicardial blood flow in the IRA was graded according to the TIMI classification by two experienced cardiologists who were unaware of the clinical history and laboratory measurements of the patients. After angioplasty, a successful procedure was defined as achievement of TIMI grade 3 flow in the IRA without significant (greater than 20%) residual stenosis.

Standard 12-lead ECGs with a paper speed of 25 mm/s and amplification of 10 mm/mV were recorded on admission and 60 min after angioplasty by using a Cardiofax 9132 K (Nihon Kohden, Japan) ECG machine. The sum of ST segment elevations was measured to the nearest 0.025 mV, 20 ms after the end of the QRS complex from leads I, aVL and V1 to V6 for anterior myocardial infarction and leads II, III, aVF, V5 and V6 for inferior infarction for both the admission and postangioplasty ECGs, as described previously (13). STR was defined as the ratio of the sum of ST segment elevations on the presentation ECG to that on the ECG performed 60 min after PCI. The rate of improvement in ST elevation was defined as either complete resolution (70% or greater) or nonresolution (less than 70%) (13). STR was measured by an investigator who was blinded to clinical, laboratory and angiographic findings of the patients.

After PCI, patients were divided into two groups according to STR – the reperfusion (complete STR) group and the impaired reperfusion (nonresolution) group.

Statistical analysis

Continuous data were presented as mean $\pm$ SD. Differences in continuous variables between the groups were determined by Student's *t* test or the Mann-Whitney U test for variables with or without normal distribution, respectively. One sample Kolmogorov-Smirnov test was used to test for normal distribution of continuous variables. Categorical variables were presented as percentages and compared with the χ^2 test or Fisher's exact test. Associations between two continuous variables were measured with the Spearman correlation coefficient. For the factors found to be related to impaired reperfusion in univariate analysis, regression analyses were performed, using the backward elimination technique to determine their impact independently. To determine the best cut-off value of MPV for predicting impaired reperfusion, a receiver operating characteristic (ROC) analysis was performed. The area under the ROC curve was calculated. From the ROC curves, the best cut-off value was determined and, at that point, sensitivity and specificity were determined. $P < 0.05$ was considered to be statistically significant and CIs were 95%. All analyses were performed using SPSS 11.5 (SPSS Inc, USA).

RESULTS

Based on an STR ratio of 70% as the threshold value for reperfusion, 137 (40%) study group patients were found to have impaired reperfusion. A comparison of patients' baseline clinical and angiographic characteristics between reperfusion and impaired reperfusion groups is presented in Table 1. The two groups were similar in terms of sex, smoking habits, history of hypertension and diabetes mellitus, and previous revascularization ($P > 0.05$). Conversely, compared with patients in the reperfusion group, patients in the impaired reperfusion group were older (60 ± 12 years versus 57 ± 11 years; $P = 0.021$) and had a longer pain-to-balloon interval (6.3 ± 3.6 h versus 3.9 ± 2.5 h; $P < 0.001$) and a higher incidence of anterior MI (65% versus 48%; $P = 0.002$). Although the two groups did not differ in terms of admission heart rate and systolic blood pressure, a significant difference between the groups was detected when Killip class was considered ($P < 0.001$).

On admission angiography, the IRA was found to be patent (TIMI grade 3 flow) in 58 (17%) patients. A comparison of angiographic findings of the groups revealed that, while patients in the impaired reperfusion group were more likely to have the left anterior descending artery as the IRA (65% versus 48%; $P = 0.010$) and were more likely to have three-vessel disease (31% versus 22%; $P = 0.047$), they were less likely to have a patent IRA on admission (7% versus 24%; $P < 0.001$). The two groups did not differ in terms of stent use during the PCI (93% versus 94%, respectively; $P = 0.924$).

The hematological indexes analyzed showed that while the reperfusion and impaired reperfusion groups were similar in terms of platelet count and fibrinogen levels, there were significant differences in WBC count and MPV (Table 2). Compared with the patients in the reperfusion group, the patients in the impaired reperfusion group were found

TABLE 1
Comparison of patients' baseline clinical and angiographic characteristics between reperfusion and impaired reperfusion groups

	Reperfusion (n=206)	Impaired reperfusion (n=137)	P
Age, years*	57±11	60±12	0.021
Male sex, n (%)	165 (80)	103 (75)	0.281
Systemic hypertension, n (%)	76 (37)	55 (40)	0.322
Diabetes mellitus, n (%)	45 (22)	37 (27)	0.272
Active smokers, n (%)	96 (47)	58 (42)	0.437
Pain-to-balloon time, h*	3.9±2.5	6.3±3.6	<0.001
Heart rate, beats/min*	77±11	79±13	0.122
Systolic BP, mmHg*	114±15	112±18	0.855
Killip class on presentation, n (%)			<0.001
I to II	180 (87)	98 (72)	
III to IV	26 (13)	39 (28)	
MI history, n (%)	19 (9)	19 (14)	0.179
CABG history, n (%)	4 (2)	8 (6)	0.072
MI subgroup, n (%)			0.002
Anterior wall	98 (48)	89 (65)	
Non-anterior wall	108 (52)	48 (35)	
Infarct-related artery, n (%)			0.010
LAD	98 (48)	89 (65)	
RCA	86 (42)	35 (26)	
LCx	19 (9)	10 (7)	
Saphenous graft	3 (1)	3 (2)	
Baseline TIMI flow, n (%)			<0.001
TIMI 0 to 2	157 (76)	128 (93)	
TIMI 3	49 (24)	9 (7)	
3-vessel disease, n (%)	45 (22)	43 (31)	0.047
Stent utilization, n (%)	193 (94)	128 (93)	0.924
Tirofiban administration, n (%)	122 (59)	52 (38)	<0.001
Peak CK-MB, U/L*	327±191	521±223	<0.001

*Data presented as mean ± SD. BP Blood pressure; CABG Coronary artery bypass graft; CK-MB Creatinine kinase MB fraction; LAD Left anterior descending artery; LCx Left circumflex artery; MI Myocardial infarction; RCA Right coronary artery; TIMI Thrombolysis In Myocardial Infarction

to have a higher MPV (9.8±1.3 fL versus 8.6±1.0 fL; $P<0.001$) and a higher WBC count (14.4±5.5×10⁹/L versus 12.1±3.8×10⁹/L; $P<0.001$) on admission.

Correlates of WBC count and MPV

MPV on admission had a positive correlation with age ($r=0.126$, $P=0.019$) and admission WBC count ($r=0.187$, $P=0.001$), and was negatively correlated with the platelet count ($r=-0.137$, $P=0.011$). The WBC count showed a weak positive correlation with pain-to-balloon interval ($r=0.127$, $P=0.019$).

Tirofiban therapy

Tirofiban was administered in 174 (51%) patients at the discretion of the operator. When tirofiban usage was considered, the proportion of patients who took the drug was significantly higher in the reperfusion group than the impaired reperfusion group (59% versus 38%; $P<0.001$). The patients who were prescribed tirofiban were older (59 years versus 57 years; $P=0.04$) than the patients who did not take the drug. However, there were no significant differences in terms of sex, MI location or classical risk factors for the atherosclerosis and hematological parameters studied.

To understand the independent impact of individual variables that were found to be related to impaired reperfusion in univariate analysis, a regression analysis with a backward elimination technique was performed. Variables used included age, pain-to-balloon interval, anterior

TABLE 2
Comparison of admission hematological parameters between the reperfusion and impaired reperfusion groups

	Reperfusion (n=206)	Impaired reperfusion (n=137)	P
WBC count, ×10 ⁹ /L	12.1±3.8	14.4±5.5	<0.001
Platelet count, ×10 ⁹ /L	278±74	271±96	0.472
MPV, fL	8.6±1.0	9.8±1.3	<0.001
Fibrinogen, µmol/L	9.26±3.35	9.64±3.29	0.270

Data presented as mean ± SD. MPV Mean platelet volume; WBC White blood cell

TABLE 3
Independent predictors of impaired reperfusion in regression analysis

	Beta	OR	95% CI	P
Pain-to-balloon time, h	0.22	1.25	1.14–1.37	<0.001
Anterior MI subgroup	0.59	1.80	1.04–3.09	0.034
Tirofiban administration	-0.84	0.43	0.25–0.74	0.002
WBC count, ×10 ⁹ /L	0.08	1.08	1.02–1.15	0.01
MPV, fL	0.79	2.21	1.69–2.91	<0.001

MI Myocardial infarction; MPV Mean platelet volume; WBC White blood cell

MI subgroup, Killip class, TIMI flow lower than grade 3 in initial angiography, three-vessel disease, tirofiban administration, admission WBC count and MPV. As a result, MPV (OR 2.21, 95% CI 1.69 to 2.91; $P<0.001$), WBC count (OR 1.08, 95% CI 1.02 to 1.15; $P=0.01$), pain-to-balloon time (OR 1.25, 95% CI 1.14 to 1.37; $P<0.001$), anterior MI (OR 1.80, 95% CI 1.04 to 3.09; $P=0.034$) and tirofiban administration (OR 0.43, 95% CI 0.25 to 0.74; $P=0.002$) were determined to be independent predictors of impaired reperfusion (Table 3).

To determine the best cut-off value of MPV for predicting impaired reperfusion, ROC analyses were performed. The area under the ROC curve for MPV, which was used to detect impaired reperfusion, was 0.78 (95% CI 0.73 to 0.83; $P<0.001$). An MPV value of 9.05 fL was determined to be the best discriminating value for impaired reperfusion. An MPV value of 9.05 fL had a sensitivity of 74% and a specificity of 73% in predicting impaired reperfusion after successful angioplasty (Figure 1).

DISCUSSION

Summary of findings

In the study group patients, pain-to-balloon time, anterior MI location, glycoprotein IIb/IIIa administration, admission WBC count and admission MPV variables were independently associated with impaired myocardial reperfusion. In addition, the ROC analysis demonstrated that an MPV of 9.05 fL had good diagnostic value in predicting impaired reperfusion with satisfactory sensitivity and specificity.

In our study, microvascular reperfusion was evaluated by STR on 12-lead ECG, which is a physiological index of cellular perfusion following successful epicardial reperfusion (13,14). Detection of 'complete ST resolution' (70% or greater) following reperfusion therapy is supposed to be a reliable indicator of successful reperfusion at both the epicardial and microvascular level, and an indicator of an excellent prognosis (14). Moreover, in previous studies, it was shown that among patients with a patent IRA, those who had complete STR (70% or greater) had a significantly lower mortality rate compared with patients with incomplete STR (14). Furthermore, it was reported that an STR of 70% or greater after reperfusion therapy is best at predicting small infarcts and preserved left ventricular function (14,15).

In the present report, in accordance with the current literature, we have verified that a significant proportion of patients (40%) have impaired reperfusion at tissue level, after apparently successful angioplasty. The exact mechanism of the reperfusion abnormalities despite the presence of a patent epicardial IRA after acute MI is not clearly

known but it is likely multifactorial, including leukocyte- and platelet-mediated injury to the microvasculature (16).

In the present study, we detected a longer pain-to-balloon time, representing longer ischemia duration as an independent predictor of impaired reperfusion. Similarly, the association of late reperfusion with impaired reperfusion, larger infarct size and higher one-year mortality rate, even after optimal primary angioplasty, has been reported (17). It was also proposed that with the delay in reperfusion, the thrombus gets older and more organized, which results in a higher incidence of distal microembolization and poor myocardial perfusion (18).

The underlying mechanism of the lower frequency of reperfusion in anterior MI is not clear. It was proposed that the response of microvasculature to reperfusion and propensity of distal embolization differs between anterior and nonanterior MI (18).

Our finding of the association of impaired reperfusion with higher MPV and WBC count suggested that leukocytes and platelets, either individually or, more likely, in cooperation, take part in the mediation of reperfusion injury. The positive correlation we observed between MPV and WBC count further supports this cooperative action. The interaction among leukocytes, platelets and endothelial cells is important in atherogenesis and the maintenance of blood flow and vascular tone in healthy and disease states.

Leukocyte-platelet interaction in mediating reperfusion injury may be possible in one of the following forms. First, during the reperfusion of ischemic myocardium, leukocyte or platelet aggregates or leukocyte-platelet complexes can plug coronary microvessels, resulting in impairment of coronary flow (19). In addition, leukocytes and platelets are capable of interacting with each other by means of soluble factors, which either activate the other or increase its response to separate stimulating agents. During the reperfusion injury, P-selectin, which is expressed on the platelet surface and can bind neutrophils to platelets and both cell types to the endothelium, was thought to be a key mediator of a platelet-neutrophil interaction (20). Another possibility is that leukocytes and platelets interact and cooperate metabolically to facilitate transcellular biosynthesis of some mediators of inflammation such as leukotrienes (21).

Platelets may create reperfusion abnormalities through secretion of prothrombotic and vasoconstrictor mediators such as thromboxane, serotonin and thrombin (22). Furthermore, platelets may augment an inflammatory response by secreting a variety of inflammatory mediators (eg, thromboxane A₂, P-selectin and platelet factor 4), thus adding further to leukocyte-mediated injury (23).

Conversely, leukocytes also release a variety of mediators, including cytokines, complement products, proteolytic enzymes and oxygen-derived free radicals, which may either interact with platelet-derived mediators or contribute to platelet-mediated injury (11,24).

The presence of increased leukocyte-platelet binding has been shown in patients with acute coronary syndromes (25). Adhesion of platelets to circulating myeloid leukocytes *in vitro* and *in vivo* is related to platelet activation (26). It is known that reperfusion of the ischemic myocardium often leads to rapid accumulation and adhesion of leukocytes to the endothelium, which are supposed to be the initial steps of leukocyte-mediated reperfusion injury (27,28). We might speculate that patients with a higher MPV have a higher potential for platelet-leukocyte interaction and thus, are more prone to platelet-activated, leukocyte-mediated reperfusion injury. Accordingly, in experimental models, interfering with P-selectin function, which is supposed to be the key linking molecule between platelets and leukocytes, has been shown to reduce neutrophil infiltration and subsequent myocardial damage after reperfusion (29).

In our study group, greater ST resolution was detected in patients who took the tirofiban, compared with patients who did not take the drug. Although the patients were not randomized based on tirofiban administration in our study group, this finding points out potential beneficial effects of tirofiban administration on microvascular reperfusion. It is likely that, by inhibiting platelet activation and aggregation,

Figure 1) The receiver operating characteristic (ROC) curve for mean platelet volume to predict impaired reperfusion. The area under the ROC curve is 0.78 (95% CI 0.73 to 0.83; $P < 0.001$)

tirofiban reduces the occurrence of platelet microembolization and subsequent microvascular plugging and dysfunction, thus improving myocardial reperfusion (30).

Previous reports

Huczek et al (8) showed the association of higher MPV values with angiographic no-reflow and long-term adverse clinical events in acute STEMI patients treated with primary PCI. In the present study, as a surrogate for reperfusion, we used STR, a physiological marker of tissue perfusion, instead of an angiographic view. Similar to our findings, Sezer et al (9) showed that higher MPV and neutrophil counts were associated with microvascular injury using intracoronary hemodynamic measurements. Unlike our study, they included only anterior MI patients, and their study size was relatively smaller.

Study limitations

We used STR as a microvascular reperfusion indicator. The use of other modalities for the detection of cellular reperfusion, such as contrast echocardiography, could change the reperfusion and impaired reperfusion group distribution. In addition, our finding related to the beneficial effect of tirofiban treatment on reperfusion should be treated with caution because the patients were not randomized based on drug administration. To better delineate this association, further large-scale randomized trials should be conducted.

CONCLUSION AND CLINICAL IMPLICATIONS

Elevated WBC count and higher MPV values on admission were independently associated with impaired microvascular reperfusion in patients with STEMI who were treated with primary PCI. It is possible that elevated WBC count and high MPV values on presentation are simple surrogate markers of worse microvascular injury. Further studies should be conducted to evaluate whether the pharmacological treatment regimens targeted to platelets and leukocytes are valuable in preventing microvascular injury. Admission MPV may be valuable in identifying a higher-risk patient subgroup for the development of impaired reperfusion. Hence, it may help in planning adjunctive therapy to improve the outcome in patients with STEMI who are undergoing primary PCI.

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