Do We Facilitate Facilitated Percutaneous Coronary Intervention and Pre-Intervention Thrombolysis?

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Several well designed clinical randomized control trials showed that compared with thrombolysis, percutaneous coronary intervention (PCI) was the superior reperfusion strategy for reducing death, reinfarction, and stroke in patients with ST-segment elevation myocardial infarction (STEMI).^{1,2} Thus, PCI has been widely used as a reperfusion therapy at hospitals that have the capability of PCI in clinical practice settings. However, these trials were conducted at high volume hospitals with skilled physicians.^{1,2} In addition, the number of capable hospitals to perform PCI is not necessarily high, especially in rural areas in Japan, as well as in other foreign countries. Therefore, the focus for the reperfusion strategy in acute phase has been shifted toward how we treat the patients transferred to hospitals that do not have PCI facilities or that have PCI facilities but longer door-to-balloon time required (more than 90 min).

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Recently, facilitated PCI, which is defined as planned PCI immediately after administration of thrombolytic agents, glycoprotein IIb/IIIa inhibitors, or both, has been proposed in these conditions. The facilitated PCI is considered to be a therapy, bridging the time delay between admission and initial balloon inflation time. Several clinical randomized control trials examining efficacy of that strategy on outcomes as compared with primary PCI have been conducted under various conditions.^{3,4} Theoretically, the potential benefits of this strategy are thought to be reduced time to reperfusion, smaller infarct size, improved patient stability, less artery thrombus burden in the culprit lesion, greater procedural success rate with less number of devices during procedure, preserved left ventricular function and subsequent improved survival. As expected, the patency rate defined as Thrombolysis In Myocardial Infarction grade flow at initial angiography was significantly better in the facilitated PCI group as compared with the primary PCI group.⁵ However, unexpectedly facilitated PCI was significantly associated with higher mortality rate derived from a meta-analysis comparing the efficacy between facilitated and primary PCI.⁵

However, in Japan, there is little evidence regarding the efficacy and safety of pre-intervention thrombolysis in STEMI patients.^{6,7} In this issue of the Journal, Itoh et al reported results of the IMPORTANT study, which is a prospective

multicenter clinical randomized trial comparing efficacy of pre-intervention thrombolysis and primary PCI in patients with STEMI in rural areas in Japan.⁸ Primary endpoints of this study were patency rate at initial angiography and left ventricular ejection fraction (LVEF) at 6 months after the onset of STEMI. Patients with risks for bleeding were carefully excluded by study design. Secondary endpoint included major adverse cardiac events (MACE) for 5 years, which were defined as a composite of sudden death, cardiac death, non-fatal myocardial infarction, cerebrovascular accident, admission for heart failure, and any coronary revascularization (PCI or aorto-coronary bypass surgery). The patency rate of infarct related artery at initial angiography was significantly higher in pre-intervention thrombolysis group as compared with the primary PCI group (69% vs 17%, $P<0.001$). The LVEF at 6 months was also significantly greater in the pre-intervention thrombolysis group as compared with the primary PCI group (61.6% vs 55.0%, $P=0.01$). Although this study was not designed to detect differences in the secondary endpoints such as MACE for 5 years, the pre-intervention thrombolysis group had a lower MACE-free rate than the primary PCI group. After dividing the patients assigned to pre-intervention thrombolysis group into 2 categories according to performance of PCI followed by thrombolysis (facilitated PCI) or thrombolysis alone, the subsequent MACE-free rate was significantly lower in thrombolysis alone than the primary PCI group (thrombolysis alone: 48.1% vs primary PCI: 80.9%, $P=0.01$), the event-free rate did not differ between the facilitated PCI and the primary PCI group (facilitated PCI: 73.7% vs primary PCI: 80.9%, $P=0.39$). In this context, we might need to interpret these observations with caution, because patients were not randomized to either facilitated PCI or thrombolysis alone. The facilitated PCI appeared to be done in cases with significant residual stenosis in the infarct related artery after thrombolysis, which might lead to a bias. Furthermore, bleeding complications, which might also be considered to be the strength of the study, was similar between the pre-intervention thrombolysis and the primary PCI groups.

Although previous trials showed that initial patency rate for coronary angiography and LVEF as surrogate endpoints were significantly better in pre-intervention thrombolysis than in primary PCI, which are consistent with the results in the current study, superiority of pre-intervention throm-

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bolysis for mortality over primary PCI has not been proved consistently. In a review article by Zimarino et al, several explanations for this discrepancy were suggested.⁴ First, sub-optimal antithrombotic adjunctive treatment has been indicated. Patients who had bolus administration of GP IIb/IIIa did not receive continuous heparin infusion. This might lead to an increased risk of early thrombotic complications, resulting in diminishing the benefits of earlier reperfusion by thrombolysis. Second, unlike the current trial by Itoh et al, thrombolytic therapy might induce bleeding complications including stroke, hemorrhagic infarction, and free wall rupture, which might cause increased mortality. Third, short time interval between thrombolysis and following PCI might mitigate the benefit of a thrombolytic agent. Although, facilitated PCI is recommended as Class IIb indication as reperfusion therapy for the American College of the Cardiology/American Heart Association guidelines,⁹ we need to learn what patients would have beneficial effect on outcomes with facilitated PCI. Gersh et al suggested that in patients presenting 2 to 3 h after onset of symptoms, facilitated PCI might move patients from the plateau to the descending limb of the curve with a substantial improvement in myocardial salvage and mortality.¹⁰ In this regard, under adequate time interval between thrombolysis and followed by PCI, patients with higher risk of cardiovascular events and a low bleeding risk (characterized as younger patients) within 2 to 3 h after symptom onset might have beneficial effects of facilitated PCI on cardiovascular events without bleeding complications.

Furthermore, the NORDISTEMI trial, a randomized controlled trial examining efficacy and safety of immediate transfer for angioplasty vs ischemia-guide management after thrombolysis for STEMI in areas with very long transfer distances, reported that the primary endpoint defined as a composite of death, reinfarction, stroke, or new ischemia at 12 months did not reach statistically significant difference between the groups (21% vs 27%, $P=0.19$).¹¹ However, when new ischemia was excluded from the primary endpoint, the incidence of the composite of death, reinfarction, or stroke at 12 months was significantly lower in patients assigned to angioplasty than those assigned to conservative treatment (6% vs 16%, $P=0.01$), in accordance with the current study showing that the MACE-free rate were higher in the facilitated PCI group than in the thrombolysis alone group (73.7% vs 48.1%). Combined previous trials with the current trial, we might interpret that facilitated PCI/pre-interventional thrombolysis is superior to thrombolysis and has a non-inferior effect on outcomes compared to primary PCI. In rural areas, there might be few physicians who are familiar with management for mechanical reperfusion, less available for

capability of cardiac catheterization, or longer transfer distance to PCI facilities than in urban areas. Therefore, we further need to explore and establish optimal targets and/or optimal treatment strategy, which are equal efficacy on outcomes to primary PCI in areas and hospitals that do not have PCI facilities.

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