

## FACILITATED ANGIOPLASTY: FACT OR FICTION? THE ROLE OF THIENOPRIDINES

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Kolaylaştırılmış anjiyoplasti akut miyokard infarktüsü nedeniyle trombolitik tedavi verilen hastalarda, ilk 12 saat içinde rutin perkütan trans-luminal koroner anjiyoplasti yapılmasıdır. Buna rağmen bu politikanın her iki reperfüzyon yönemi açısından avantajları ve diğer yandan düzeltilebilen dezavantajları mevcuttur. Daha önce yapılmış çalışmalar bu yönde cesaret verici sonuçlar ortaya koymuştur. Çok etkili antiagregan tedavi ve gelişmiş anjiyoplasti teknolojilerinden

sonra, son zamanlarda dikkat çekici yaklaşımlar denenmektedir.

Bu derleme, kolaylaştırılmış anjiyoplasti ile ilgili son literatürler gözden geçirilerek yazılmıştır.

Anahtar kelimeler: Kolaylaştırılmış anjiyoplasti, Thienopridin

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### GİRİŞ

While both percutaneous coronary intervention (PCI) and thrombolytic therapies are used for reperfusion, following an ST-segment-elevation myocardial infarction (STEMI), the former generally is considered superior in terms of more complete revascularization and greater reductions in morbidity and mortality<sup>1</sup>. However, because of the logistic issues all patients can not be treated with PCI. For example, at the beginning of the decade, less than 25% of United States acute-care hospitals had PCI programs<sup>2</sup>. Transfer of the patients to PCI centers impacts time to treatment, which guidelines emphasize is a critical element of efficacy of therapy<sup>3</sup>. In order to represent the 'Yealife' experience, a recent analysis of NMRI 3 and 4 data regarding STEMI patients undergoing inter-hospital transfer for primary PCI found that total door-to-balloon time from initial receiving hospital to PCI hospital was a median of 180 minutes; median door-to-door time was 120 minutes, and for patients arriving at a PCI hospital initially, median door-to-balloon time was 53 minutes<sup>4</sup>. Considering these figures, not surprisingly 4.2% of patients had total door-to-balloon times <90 minutes as recommended by ACC/AHA guidelines<sup>3</sup>. On the other hand, in recent trials transfer times of 60 minutes or less could be achieved.

We need a new approach that combines the advantages of both reperfusion modalities. One under consideration is facilitated PCI, in which thrombolytic agents are administered to patients prior to reperfusion via PCI. The rationale for such a strategy is several-fold, including reducing treatment delay; having an already reperfused infarct related artery (IRA) at the time of PCI; achieving rescue PCI more quickly in failed lytic therapy; preventing reocclusion, the 'Aschille's heel' of the lytic therapy, by scaffolding the vessel wall with stents. In other words, facilitation with a thrombolytic agent has been proposed as a strategy to improve outcomes: thrombolysis to establish early patency followed by PCI to assure complete and sustained reperfusion.

Recently 2 prospective and randomised clinical trials were either published or presented on the subject giving conflicting results and leading such a confusion that impacts the every day practice<sup>5,6</sup>. The ASSENT-4 and CAPITAL AMI trials have recently addressed the merits of such a strategy using full-dose thrombolytic therapy.

ASSENT-4 compared tenecteplase (TNK)-facilitated PCI to primary PCI alone. The primary endpoint was a composite of death, congestive heart failure (CHF), or shock at 90 days. The trial planned to enroll 4,000 patients but was stopped unexpectedly after randomizing 1,667 patients because of excessive ischemic events in the TNK-facilitated PCI group. Preliminary results were presented in September 2005 at the ESC

Table 1: CAPITAL AMI and ASSENT-4 trial details

	CAPITAL AMI		ASSENT-4	
	Lytic	fPCI	fPCI	pPCI
Year published	2005		2005	
Design	Lytic vs fPCI		fPCI vs pPCI	
Lytic used	Tenecteplase		Tenecteplase	
Primary end point	Death,reMI,re-USAP stoke at 6 months		Death.CHF, shock at 90 days	
Angina-TNK time (min.)	120		153	
Angina-PCI time (min.)	204		245	
			9.8	
GPIIb/IIIa (%) 53.5	0	14	63	63
Thienopyridine	57	91	no	no
UFH after TNK, routine	yes	yes	43.6	15
TIMI III flow (Before PCI,%)		52	87.6	88.7
TIMI III flow(After PCI,%)		89	4.1	1.9
Re-MI (%)	13.3	4.7	6	3.8
Mortality,30 day (%)	3.6	2.3	10.4	3.0
USAP or reMI	18.1	7.0		

fPCI:facilitated percutaneous coronary intervention;pPCI:primary PCI;TNK: Tenecteplase, reMIrecurrent myocardial infarction;USAP:unstable angina pectoris;CHF:congestive heart failure;UFH:unfractionated heparin

meeting in Stockholm. At 30 days, mortality in the TNK-facilitated PCI arm was higher: 6.0% vs. 3.8% than in the primary PCI alone group (p=0.04). Reinfarction also was higher with facilitated PCI: 4.1% vs. 1.9%(p=0.01).

CAPITAL AMI trial randomized 170 pts to TNK-facilitated PCI vs. TNK alone. The combined primary endpoint in this trial was death, reinfarction, recurrent unstable ischemia, or stroke at 6 months. CAPITAL AMI showed that TNK-facilitated PCI significantly reduced ischemic events at both 30 days (9.3% vs. 21.7%; p=0.03) and 6 months (11.6% vs. 24.45; p=0.04) compared to TNK alone. At 30 days, mortality was 2.3% in the TNK-facilitated PCI compared to 3.6% in the TNK-alone group (p=0.68), and reinfarction, 4.7%vs.13.3%,(p=0.06).

Although the two trials differ from each other in design and definition of endpoints, the two trials have a common feature, which is a TNK-facilitated PCI arm and researchers asked the question whether PCI facilitated with full-dose tenecteplase was superior to the use of PCI or thrombolytic therapy alone. These two trials came to very different conclusions, and the reasons might be, as discussed widely, the impact of the treatment modalities themselves, or the unplanned and unnoticed difference in the use of antiaggregan and anticoagulant treatments.

The similarities and differences between both studies are listed in Table-1.

In both studies patients underwent PCI at similar time intervals after thrombolysis: the median TNK-to-

balloon time was 90 minutes in CAPITAL AMI and 104 minutes in ASSENT-4. The two trials used the same vweight-adjusted intravenous TNK bolus and the same vweight-adjusted intravenous unfractionated heparin bolus, 60 units per kg (maximum4000 units). However, in ASSENT-4 a heparin infusion was not initiated after the initial bolus in contrast to CAPITAL AMI where this was routinely done. The ASSENT-4 investigators likely omitted the heparin infusion to limit major bleeding.This omission may partially explain the relatively low success with reperfusion of the IRA on the initial angiogram reported by the ASSENT-4 investigators as compared to that reported in CAPITAL AMI: TIMI 3 flow 43% vs. 52%; patency 62% vs. 84%, respectively (Table -1).

It is possible that once the anticoagulation effect of the initial bolus of heparin wore off, patients in ASSENT-4 were exposed to reocclusion. In patients with STEMI, thrombolysis may dissolve much of the thrombus overlying the ulcerated plaque, but the disrupted endothelium and residual thrombus may reactivate the coagulation cascade leading to reocclusion. Adequate anticoagulation during the first hours of STEMI is needed to prevent this complication. Large randomized trials have not conclusively demonstrated the clinical benefits of heparin as an adjunct to tissue plasminogen activators in patients with STEMI, but several small trials have documented superior coronary patency associated with appropriate use of intravenous heparin<sup>79</sup>. Furthermore, one third of the patients in the TNK-facilitated PCI arm of

ASSENT-4 did not receive additional heparin in the catheterization laboratory. In summary, procedural decreased use of UFH after TNK bolus in ASSENT-4 may have led to increased ischemic events in TNK-facilitated PCI arm .

In CAPITAL AMI, clopidogrel was prescribed to 91% of patients at the time of PCI assigned to TNK-facilitated PCI arm and to 57% of patients assigned to TNK alone arm ( $p < 0.001$ ). Further more, TNK alone patients received the drug 2 days later than the TNK-facilitated PCI arm counterparts. On the other hand there was no difference regarding thienopyridine use in ASSENT-4 trial . Recent trials have suggested that in patients initially treated with thrombolysis, combination antiplatelet therapy with aspirin and clopidogrel improves coronary patency and clinical outcomes; specifically, this was evident in the results of both CLARITY-TIMI 28 and PCI-CLARITY trials<sup>101</sup>. Patients in ASSENT-4 and in CAPITAL AMI were not prescribed a thienopyridine at the time of randomization. The increased ischemic events in the lytic arm of CAPITAL AMI could only be the result of decreased and late use of thienopyridines but not from the PCI performed as proposed by the investigators. The absolute and relative risk reduction of clopidogrel for new ischemic events in CLARITY-TIMI 28 trial at 30 days were 2.5 % and 18 %, respectively. This amount of difference which was held just by adding clopidogrel to lytic treatment is sufficient to explain the main difference of increased recurrent myocardial infarction that arose in CAPITAL AMI. The very same difference might have been caused only by clopidogrel instead of routine PCI.

Also the use of glycoprotein (GP) IIb/IIIa inhibitors was restricted in the TNK-facilitated PCI arms of ASSENT-4 and CAPITAL AMI because of the risk of major bleeding if combined with full-dose thrombolytic therapy. However, GP IIb/IIIa inhibitors were given to 50.5% of the patients in the PCI-alone arm of ASSENT-4. Again the higher antithrombotic drug treatment might have been the real difference in ASSENT-4 instead of TNK facilitation.

Taken together, a relatively inadequate anticoagulation regimen combined with suboptimal antiplatelet therapy may have contributed to the relatively low initial patency of the IRA and the higher rate of early clinical events in patients assigned to the TNK-facilitated PCI arm of ASSENT-4 (10.4 % vs 3 %). On the contrary, again a late and insufficient use of antiplatelet therapy in Lytic alone arm of CAPITAL AMI trial may have led to increased early ischemic complications (18.1 % vs 7 %).

New trials are needed to explore the real effect of 'facilitation' that intend to use the similar amount of anticoagulant and antiaggregant medication per protokol. One is underway named FINESSE trial which investigate the effect of lytic vs GP IIb/IIIa receptor inhibitors vs placebo facilitation in STEMI .

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