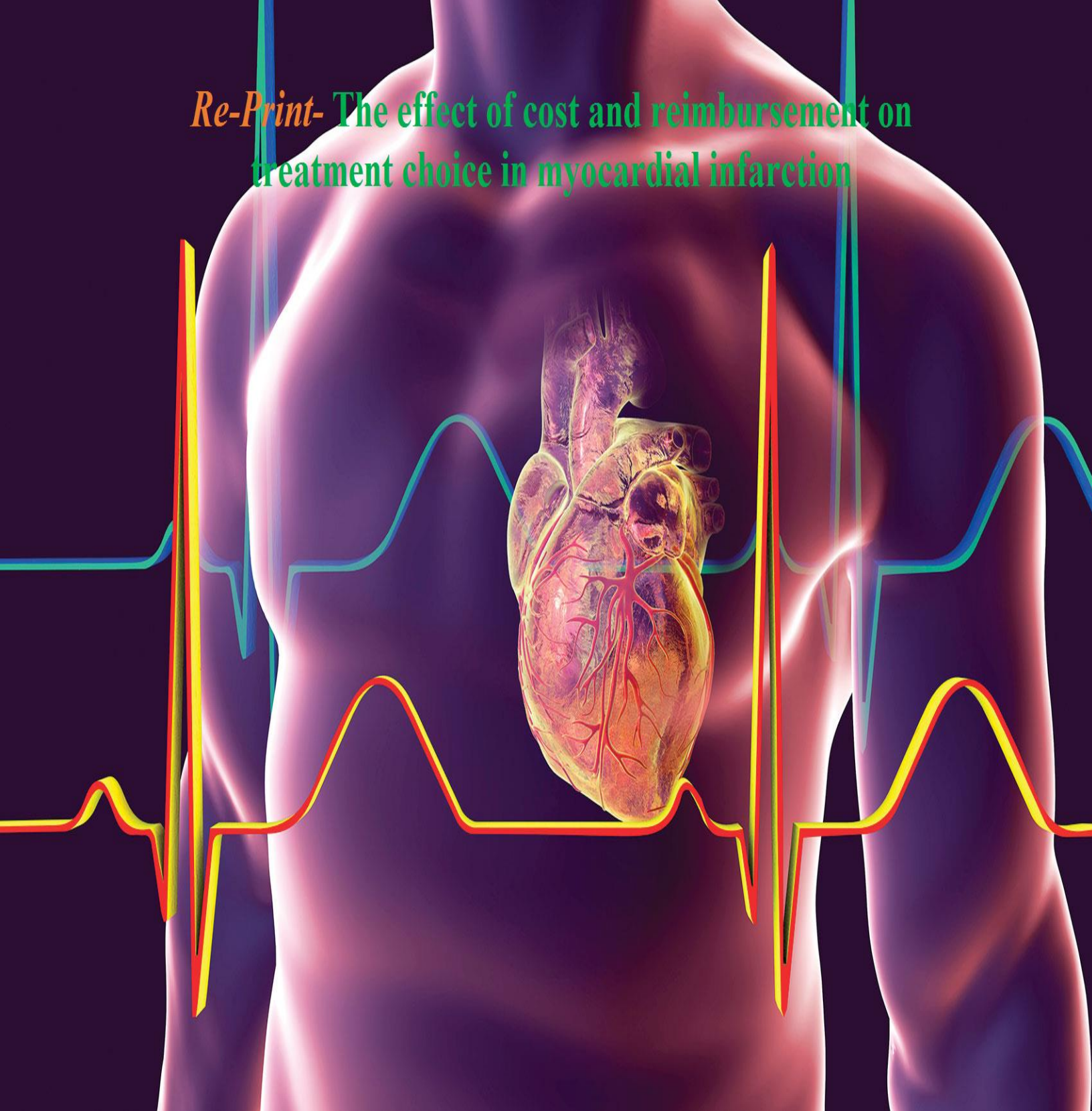


*Re-Print-* The effect of cost and reimbursement on  
treatment choice in myocardial infarction



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## Re-Print- The effect of cost and reimbursement on treatment choice in myocardial infarction

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### Summary

Treatment of acute myocardial infarction (AMI) has been with tissue plasminogen activator (tPA) alone since 1987, at an original cost of \$2,000 which has risen to \$5,000. Over the past decade tPA has been replaced by percutaneous coronary intervention (PCI), an invasive, more time-consuming hospital procedure. The mortality results of the two treatments were similar, but the PCI cost and reimbursement are at least 5-fold higher. At the time, another fibrinolytic regimen was developed which is more effective, but it was ignored, and PCI continued to be the treatment choice and major source of revenue.

### Reperfusion treatment of AMI

The triggering cause of AMI is a thrombus which blocks perfusion of a portion of the myocardium. If reperfusion is restored within 1-2 hours, mortality, is significantly reduced [1]. The fastest reperfusion method is fibrinolysis, which is a simple, low cost, outpatient treatment. Unfortunately, the experience with tissue plasminogen activator (tPA) was so disappointing that it caused fibrinolysis to lose creditability. Consequently, it was replaced by percutaneous coronary intervention (PCI), which is a higher cost, time-consuming hospital procedure.

The 6- and 12-month AMI mortality after PCI or tPA is similar [2]. However, the cost of the two treatments is quite different. The median reimbursement for PCI in the US in 2009 was \$19,349 [3]. It is higher now, so that this procedure has become a significant source of revenue for hospitals and departments of cardiology; a financial benefit that is difficult to ignore when evaluating alternative, lower cost treatments like fibrinolysis.

In 1995, a clinical trial (PATENT trial) was conducted in 101 AMI patients who were treated with a sequential combination of tPA and urokinase plasminogen activator (uPA). Treatment was initiated by a small 5 mg bolus of tPA (by comparison, the tPA dose in standard fibrinolytic therapy is 100 mg), this was followed by a 90-minute infusion of prouPA, the zymogenic form of uPA. This treatment almost doubled the infarct artery patency of GUSTO, the best of the tPA trials (82% vs 45% at 24h) and brought mortality down from 6% to 1%. The only patient who died received treatment too late when he was already in shock [4].

The rationale for this treatment was based on in vitro findings that showed tPA and prouPA had complementary modes of action that made their combination synergistic [5] especially when administered sequentially [6]. Unfortunately, a second PATENT trial could never be done since the

company that sponsored the trial, Farmitalia, was sold to Pharmacia, which decided to discontinue their cardiovascular product line. However, the exceptional results of this trial were published in a leading cardiology journal, but the findings were ignored, and no follow-up was ever done by anybody. It was as if the simplicity and low-cost of this treatment were liabilities rather than assets.

The 1% mortality seen in this trial was additionally noteworthy. Although it could be attributed simply to chance, it is more likely that the more effective fibrinolysis due to the synergistic effect of the combination improved reperfusion in the micro circulation of myocardium better than previous treatments. The microcirculation is where the essential exchange of oxygen and nutrients takes place, not in the epicardial arteries. With tPA or with PCI, the microcirculation is reperfused only 25-35% of the time [7, 8], which testifies to the inadequacy of current AMI treatment.

Reperfusion of the micro circulation is rarely cited as an objective, rather it is coronary patency which is how therapeutic success has been judged. This criterion also favors more costly procedures like PCI which can provide handsome angiographic images. The fact that this coronary patency is not associated with reperfusion of an essential portion of the circulation two-thirds of the time tends to be ignored.

By contrast, significantly more effective fibrinolysis can be induced when both activators are administered sequentially due their synergistic effect [5, 6]. As a result, significantly better reperfusion of the micro circulation in excess of 35% is the likely result and explains why in the PATENT trial AMI mortality was reduced to 1%. The fact that a simple low-cost treatment by fibrinolysis was used probably explains why the PATENT study has been ignored for the past 25 years.

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