Clinical Practice

Pharmaco-invasive Therapy for STEMI;
The Most Suitable STEMI Reperfusion Therapy for Transferred Patients in Thailand

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Acute Coronary Syndrome (ACS) is the consequence of atherosclerotic plaque disruption with thrombus formation and significantly increasing different degrees of coronary artery occlusion. Using clinical features, electrocardiogram and cardiac biomarker (troponin), ACS can be divided into

1. Unstable angina
2. Non ST Elevation Myocardial Infarction (NSTMI)
3. STEMI. Diagnosis of STEMI needs ST elevation on ECG.

Figure 1 summarizes ACS pathophysiology, and clinical features. Note that STEMI is the only condition that the infarcted artery is usually completely occluded (acutely)
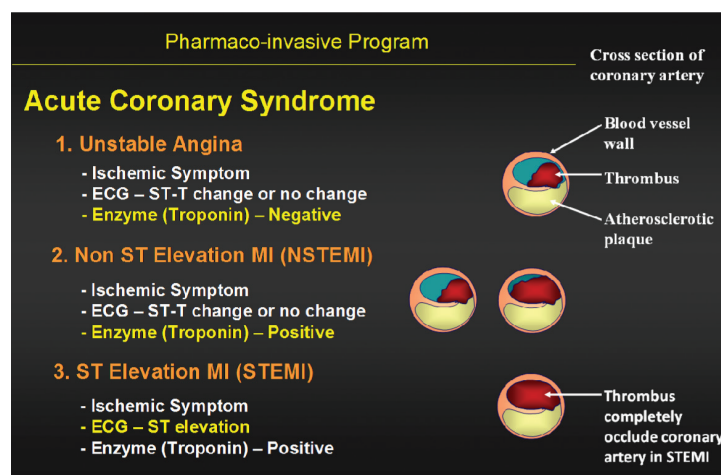

Figure 1: ACS, Pathophysiology, Clinical Features

The management goal of STEMI is to reperfuse the infarct occluded coronary artery **as soon as possible**, to reduce myocardial cell death as much as possible.

There are two reperfusion strategies for STEMI.

1. Thrombolysis with thrombolytic agents.

The advantage of thrombolysis is its ready availability in most hospitals that have full emergency services and that it can be administered in a short period of time. The disadvantages of thrombolysis are lower initial successful rate and higher re-occlusion rate, when compared with PCI.

Table 1: Lists the various PCI terminologies and their definition, timing and effectiveness.

Reperfusion Strategies for STEMI

Reperfusion Strategy	Definition of the Strategy	Timing	Availability/ Effectiveness
Pharmacological Reperfusion (Thrombolytic Therapy) **1986**	(Fibrin specific agents is about twice as effective as Streptokinase (when evaluate TIMI III flow at 90 minutes)	"Door to needle" time should be <30 minutes	**Available in every hospital but effectiveness is less than PCI**
Primary PCI (Hospitals that can perform PCI are limited in every country) **1990s**	Coronary angioplasty / stenting without prior administration of thrombolytic agents or GP IIb/IIIa antagonists.	"Door to Balloon" time 1. <90 minutes (for direct arrival/admission to PCI hospital) 2. <120 minutes (for transferred admission from non PCI hospital)	**Primary PCI is superior to Thrombolytic therapy when performed at appropriate (recommended) time frame**
Various Type of Pharmaco-invasive Therapy			
Facilitated PCI	A pharmacologic reperfusion treatment is given prior to planned (immediate/ early) PCI. The decision to perform PCI is already made before pharmacological reperfusion treatment is initiated	The pharmacological reperfusion treatment is given due to the expected time delay for PCI from various reasons such as transferred admission patient from non PCI hospital	**Several studies failed to show major benefit and currently this strategy is not recommended**
Rescued PCI	PCI in case of failed Thrombolytic / fibrinolytic therapy	Suspecting failed PCI are patients who continue to have chest pain; who has hemodynamic and electrical instability; whose ST elevation resolution less than 50%	**If PCI is offered to most of STEMI either by Primary PCI or Pharmaco-invasive therapy then the term Rescued PCI is not useful (ACC/AHA Guidelines 2009)**
Transferred Primary PCI **2003**	Primary PCI in patient transfer from non PCI hospital to PCI hospital	"Door" of non PCI hospital to "Balloon" of PCI hospital should be <120 minutes	**Difficult to achieve the recommended time.**
Pharmaco-invasive Strategy (that this paper refers to) **2009-2010**	Thrombolytic therapy (with fibrin specific fibrinolytic agents) followed by PCI with in recommended time frame	ESC STEMI Management Guideline, 2009 recommending time from Fibrinolytic to PCI is 3-24 hours (when use fibrin specific fibrinolytic agents)	**Appears most appropriate strategy for transferred patient from non PCI hospitals**

Other terminologies include: Urgent PCI; Adjunctive or Early Elective PCI; Late PCI

2. Percutaneous Coronary Intervention (PCI).

PCI is only available in a small number of all hospitals in any country (about 25% in US). It has high successful reperfusion rate but this technique requires a longer period of time to deliver, particularly if the patient has to be transferred from non PCI capable hospital.

Early on, thrombolysis and primary PCI strategies were considered separately and appeared to compete with each other. They both have advantages and disadvantages points as aforementioned. In the past 25 years, there has been extensive research to find out which single or combination of strategies works the best and for what situation.

Table 2. Thrombolytic Agents. Note that streptokinase is only half as effective as those fibrin specific products when look at TIMI 3 flow (normal coronary artery blood flow) by coronary angiogram at 90 minutes following thrombolytic administration.

	Thrombolytic Agents			
	Streptokinase	Alteplase (r-tPA)	Reteplase	Tenecplase (TNKase)
Fibrin selective	-	+++	++	++++
Half Life	30 min	5 min	15 min	18 min
Dose (Bolus / Drip)	D	B & D	Bx2	Bx1
Adjunctive Heparin	No	Yes	Yes	Yes
Possible Allergy	Yes	No	No	No
TIMI 2/3 Flow in 90 min.	60%	80%	80%	80%
TIMI 3 Flow in 90 min.	32%	50-60%	60%	60%
Cost	+	+++	+++	+++

Evolution of reperfusion therapy for STEMI

Evolution of reperfusion therapy for STEMI can be summarized into 4 periods. Any one of these strategies are still being utilized depending on the situations. It is expected that the practice guidelines will change further for this dynamic condition. Pre hospital thrombolysis is not included in this article.

1. Thrombolytic therapy (1986).

Streptokinase was the thrombolytic agent most used in reperfusion therapy for STEMI early on. It has since been replaced by fibrin specific products which are more effective (Table 2). The current popular agent is Tenectaplase (TNK), a fibrin specific thrombolytic agent which is easy to administer. Because of its lower cost, despite lower efficacy, streptokinase is still being used in countries with less financial resources, including Thailand.

Thrombotytic therapy is more effective if it can be given within 3 hours after the onset of symptoms such as chest pain. We have not yet been able to shorten up the time from chest pain onset to the time of first medical contact (FMC). We should be able to control the time from FMC to the time of delivering the thrombolytic agent which was recommended to be <30 minutes. The so call **"Door to Needle" time is <30 minutes.**

2. Primary PCI (1990s).

Primary Percutaneous Coronary Intervention therapy has been performed since early-mid 1990s. Primary PCI is the therapy to open the infarct occluded coronary artery with angioplasty and stent placement without preceding thrombolytic therapy (See Table 1. for various PCI terminologies and their definition, timing and effectiveness)

Recommended median time for Primary PCI is < 90 minutes from FMC to infarct coronary artery open. The so-called "Door to Balloon" time is < 90 minutes. Primary PCI has better results than thrombolysis when both approaches are performed with in the recommended time frame. Early data has been collected exclusively from **direct arrival/admission** patients.

3. Transferred Primary PCI (2003)

Refers to Primary PCI therapy in which the patient transfers from first hospital to PCI capable hospital. Recommended median time for transferred primary PCI is < 120 minutes from FMC (of the first hospital) to infarct coronary artery open (of the PCI hospital). This recommended time is hard to achieve even in developed countries (Figure 2 for US) with better transport systems available. However there were more than 30 % of the
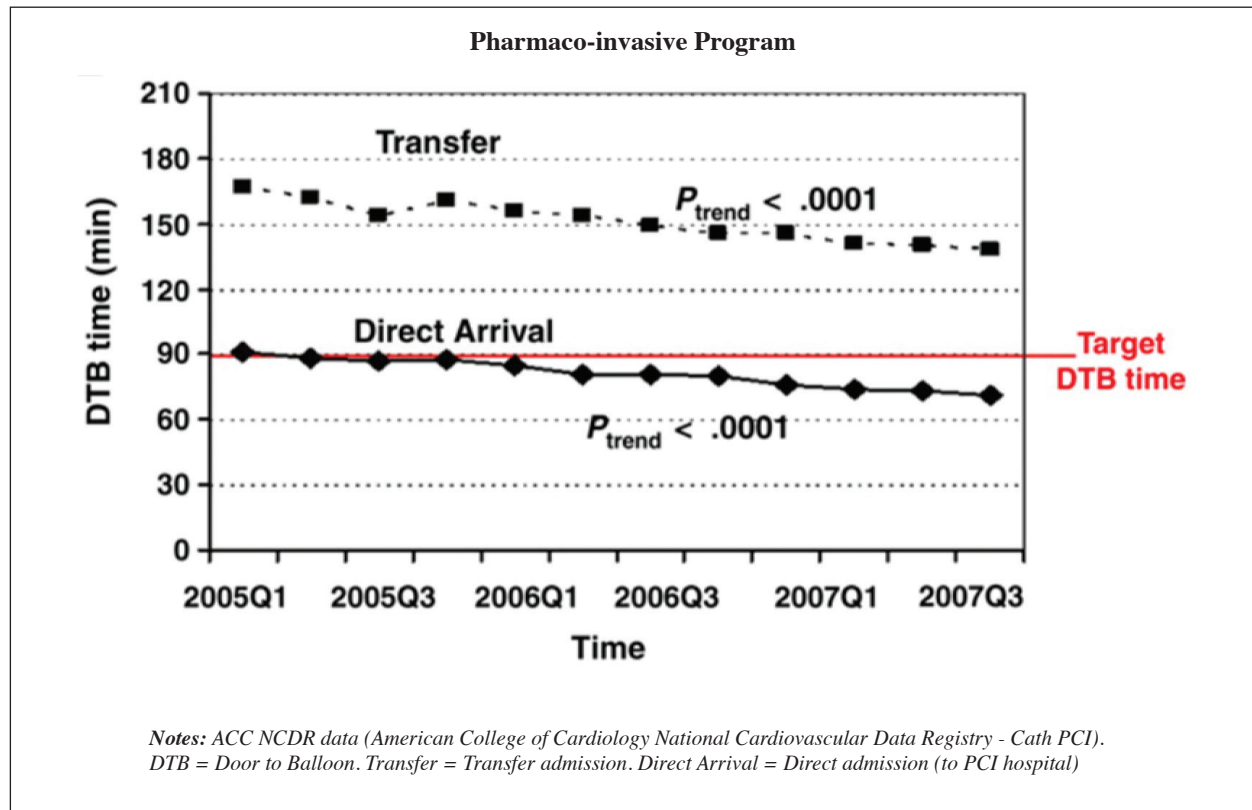
Pharmaco-invasive Program

Notes: ACC NCDR data (American College of Cardiology National Cardiovascular Data Registry - Cath PCI).
DTB = Door to Balloon. Transfer = Transfer admission. Direct Arrival = Direct admission (to PCI hospital)

Figure 2: *Graph shows US median Door to Balloon time is now about 70-80 minutes for "Direct arrival/admission patients".However median time for Door (First medical contact of the first hospital) to Balloon (PCI hospital) for transferred patients is still over 140 minutes.*

patients that could achieve this timeline (NCDR 2005-2006) suggesting that not only is the shorter distance between the two hospitals important but also the development and execution of the proper protocol is necessary to help the achievement of this goal.

Transferred Primary PCI is not suitable (or not possible) in the locations or countries with slow transportation time (for whatever any reason).

4. *Pharmaco-invasive approach (2009-2010).*

To off-set the time delays in transferred patients the researcher has combined the quickness and ready availability of thrombolytic (pharmaco) therapy and the delayed but complete reperfusion of PCI (invasive). There have been few approaches with different terminologies, timing between the two strategies, and different clinical set up (Table 1).

Facilitated PCI failed the test likely due to a too short period from thrombolysis to PCI. Immediate PCI after

fibrinolytic therapy causes significant increase in mortality, nonfatal reinfarction, urgent target lesion revascularization and stroke and a trend toward a higher rate of major bleeding.

The pharmaco-invasive therapy in this paper in particular, refers to the technique whereby there is a time elapse of 3-24 hours between thrombolysis (pharmaco) and PCI (invasive) when using fibrin specific thrombolytic agents. This approach has been endorsed by the most recent guidelines of both ESC and ACC/AHA. Whether or not there should be a greater time delay (>3 hours) when using streptokinase is not yet known.

The pharmaco-invasive strategy appears most suitable for Thailand or similar countrie or similar situations. There should be sufficient time for transferring the patient (does not have to be within 3 hours or more) and sufficient time to perform PCI with in 24 hours. Door to needle of the first hospital (PCI non capable) should remain the same (<30 minutes).

Recommendations for Pharmaco-invasive therapy as follows:

1. Extensive education to medical and hospital personel involved in taking care of these patients.
2. Develop patient pathway and flow protocol (Examples are in Appendix)
3. Speed of the process during thrombolysis therapy is important.
4. ECG should be done with in 10 minutes after FMC (First Medical Contact).
5. Thrombolytic agent should be administered with in 30 minutes after FMC.
6. Transfer the patient
7. PCI to be performed in 3-24 hours after thrombo-lytic administered (ESC).
8. Detailed data collection and analysis (performance measurement) for further program improvement is necessary.

Example of some protocols are available in the Appendix

Protocol for Pharmaco-invasive therapy for STEMI Management.

Bangkok Hua Hin Hospital (BHN)

(Transferring Protocol)

Brief
1. Diagnosis (ECG should be done in <10 minutes)
2. Scan and Email ECG to BHT
3. Call BHT CCU2.
   (May call again in few minutes to confirm with BHT CCU2)
4. BHN receives call back from BHT cardiologist (In <10 minutes)
5. Administration of the thrombolytic agent at BHN
   (should be within 30 minutes from "Door" or "FMC" (First Medical Contact)
6. Arrange for transferring
7. Preparing the patient
8. Lab
9. Fill in the "Transfer Information" sheet and send it with the patient (or Fax)
   (There is a more detailed form specific to each hospital)

Bangkok Hua Hin Hospital (BHN)

| Patient name | Date: _____ |

Pharmaco-Invasive Program
Transfer Information

Timing

Onset of Symptoms: _____   Entering ER: _____

ECG: _____   Sending ECG: _____

BHT Call back: _____

Thrombolysis: _____   Agent: _____

Leaving ER: _____   Transported by: _____

Reason of Delay Thrombolytic Therapy: _____

Clinical Data

AGE _____   DOB _____   Gender _____

Vital signs

Temp: _____   BP: _____   Pulse: _____   Rhythm: _____

Patient condition   ☐ Stable /   ☐ Unstable /   ☐ CHF

History   ☐ CAD /   ☐ Previous MI /   ☐ Previous CABG

☐ Previous CPI /   ☐ Cardiomyopathy./   ☐ CHF./   ☐ Prosthetic valve.

☐ Bleeding./   ☐ Renal Failure. /   ☐ CVA. /   ☐ COPD. /   ☐ Dye allergy

Additional Information

_____
_____
_____
_____

Signature ER MD _____   Referral MD

_____   Referral MD

PHONE	BHT CCU2	02 310 3126 / 02 755 1327
FAX	BHT CCU2	02 755 1326

Check list of record sent: (√)						
Transfer Note	ER Note	Doctor Note	All ECG	Lab	Log of Rx/Time	Others
			(May fax)			

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