



Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction

The TRANSFER-AMI trial

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on behalf of the TRANSFER-AMI Investigators



Trial Sponsors

- **Canadian Institutes of Health Research (CIHR)**
- **Hoffman La Roche, Canada**
- **Stents provided by Abbott Vascular Canada**

Disclosures

- **Consulting Fees & Speakers Honoraria received by Hoffman La Roche**



Background

- **Treatment delays can reduce or eliminate the benefits of primary PCI**
- **STEMI pts presenting to non-PCI centres often cannot undergo primary PCI in timely manner, and therefore receive fibrinolysis**
- **The role and optimal timing of routine early PCI after fibrinolysis has not been established**
- **Early studies in the pre-stent era failed to show a benefit of early PCI after fibrinolysis, possible harm**
- **More recent studies in stent-era more positive but include only modest number of patients**



Objective

- **Determine the efficacy and safety of routine early PCI within 6 hours of fibrinolysis (pharmacoinvasive strategy) using contemporary PCI techniques and pharmacotherapy**
- **Higher Risk STEMI Patients**
- **Non-PCI centres where timely primary PCI not an option, and fibrinolysis is the optimal initial reperfusion therapy**



High Risk ST Elevation MI within 12 hours of symptom onset

TNK + ASA + Heparin or Enoxaparin + Clopidogrel

Randomization*

Pharmacoinvasive Strategy
Urgent Transfer to PCI Centre

Standard Treatment

Assess chest pain, ST \uparrow resolution
at 60-90 minutes after randomization



Failed Reperfusion**

Successful Reperfusion

Cath / PCI within 6 hrs
regardless of
reperfusion status

Cath and Rescue
PCI \pm GP IIb/IIIa
Inhibitor

Elective Cath
 \pm PCI
> 24 hrs later

Repatriation of stable patients within 24 hrs of PCI

Community
Hospital
Emergency
Department

PCI Centre
Cath Lab

** ST segment resolution < 50% & persistent chest pain, or hemodynamic instability



Inclusion Criteria

- Within 12 hrs of symptom onset
- ≥ 2 mm ST-segment elevation in 2 anterior leads

OR

- ≥ 1 mm ST-segment elevation in 2 inferior leads and at least one of the following high-risk criteria:
 - SBP < 100
 - HR > 100
 - Killip Class II-III
 - ≥ 2 mm ST-segment depression in anterior leads
 - ≥ 1 mm ST-segment elevation in V_4R



Selected Exclusion Criteria

- **Cardiogenic Shock prior to randomization**
- **Primary PCI available within 60 minutes**
- **Consent not obtained within 30 minutes of TNK**

- **PCI within 1 month**
- **Previous CABG**
- **Use of Enoxaparin in last 12 hours in patient > 75 years of age**



Medical Therapy for All Patients

- **TNK**
- **Heparin**
 - 60 U/kg bolus (max 4000 U)
 - 12 U/Kg/hr infusion (max 1000 U/hr)
- **Enoxaparin in pts \leq 75 yrs of age**
 - 30 mg IV bolus
 - 1 mg/kg sc injection (max 100 mg) 15 minutes later
- **ASA 160-325 mg**
- **Clopidogrel 300mg bolus (75 mg if $>$ 75 years of age)**
- **All other meds as per ACC/AHA STEMI guidelines**



PCI for Pharmacoinvasive Group

- **PCI of culprit lesion at time of cath if $\geq 70\%$ stenosis or 50-70% stenosis with high-risk features (thrombus, ulceration, spontaneous dissection) regardless of coronary flow**
- **Stents used whenever technically possible, use of Abbott vascular stents (ML Vision, Mini Vision) encouraged**
- **GP IIb/IIIa inhibitors left to operator's discretion**



Endpoints

- **1° Efficacy Endpoint: 30-day composite of Death, Reinfarction, Recurrent Ischemia, CHF, shock ***
- **2° Efficacy Endpoints: Death / Reinfarction at 6 months and 1 Year**
- **Safety Endpoints: Bleeding (GUSTO Severe, TIMI Major)**
- **Endpoints adjudicated by a clinical events committee blinded to treatment group**

* Endpoint definitions – Cantor WJ, Am Heart J 2008; 155: 19-25



Sample Size Estimation

- **Estimated primary endpoint event rate of 21% with Standard Treatment based on analysis of STEMI trial database at DCRI**
- **Anticipated 5% loss to follow-up**
- **Required 1,158 patients to demonstrate 30% reduction in event rate with Pharmacoinvasive Strategy with 80% Power***
- **Nov 13/07- Based on enrollment challenges, lack of additional funding and lower loss to follow-up, Steering Committee decided to complete enrollment Dec 31/07 → 1059 patients**

* Cantor WJ, Am Heart J 2008; 155: 19-25



PRELIMINARY

**Jul 2004 – Dec 2007: 1059 Patients Enrolled
in 3 Provinces
(42 Enrolling Centres, 11 PCI Centres)**



**March 25, 2008: 1030 Patients with
query-free baseline characteristics**



**1010 Patients with complete and
fully adjudicated data and 30-day
status known**



Baseline Characteristics

PRELIMINARY

	Standard Treatment (n=508)	Pharmacoinvasive Strategy (n=522)
Age (years)	56 (49, 66)	57 (51, 66)
Age > 75 (%)	10	9
Sex (% female)	20	21
Medical History (%)		
Prior Angina	11	12
Prior MI	10	11
Prior PCI	4	6
Prior Stroke/TIA *	1	3
Hypertension	34	33
Hyperlipidemia	29	27
Current smoker	42	44
Diabetes	15	15

* p < 0.05



PRELIMINARY

Presenting Characteristics

	Standard Treatment (n=508)	Pharmacoinvasive Strategy (n=522)
Weight (kg)	80 (70, 91)	80 (70, 91)
Heart rate (beats/min)	77 (66, 90)	74 (63, 88)
Systolic BP (mm Hg)	145 (130, 160)	146 (130, 165)
Diastolic BP (mm Hg)	84 (74, 95)	84 (73, 95)
Killip Class		
I	91	92
II	7	7
III	1	1
Anterior ST-elevation	52	56
Inferior ST-elevation	47	44
Symptom Onset to TNK (hrs)	2 (1, 3)	2 (1, 3)



Procedures

PRELIMINARY

	Standard Treatment (n=508)	Pharmacoinvasive Strategy (n=522)
Cardiac Cath performed (%)	82	97
Time- TNK to Cath (hrs)	27 (4, 69)	3 (2, 4)
PCI performed (%)	62	84
Stent used (% of PCI cases)	98	98
Time- TNK to PCI (hrs)	18 (4, 73)	4 (3, 5)
PCI within 6 hrs of TNK (% PCI)	38	89
PCI within 12 hrs of TNK (% PCI)	47	97
GP IIb/IIIa inhibitor use (%)	53	73
CABG performed (%)	8	6



Selected Medications Used

PRELIMINARY

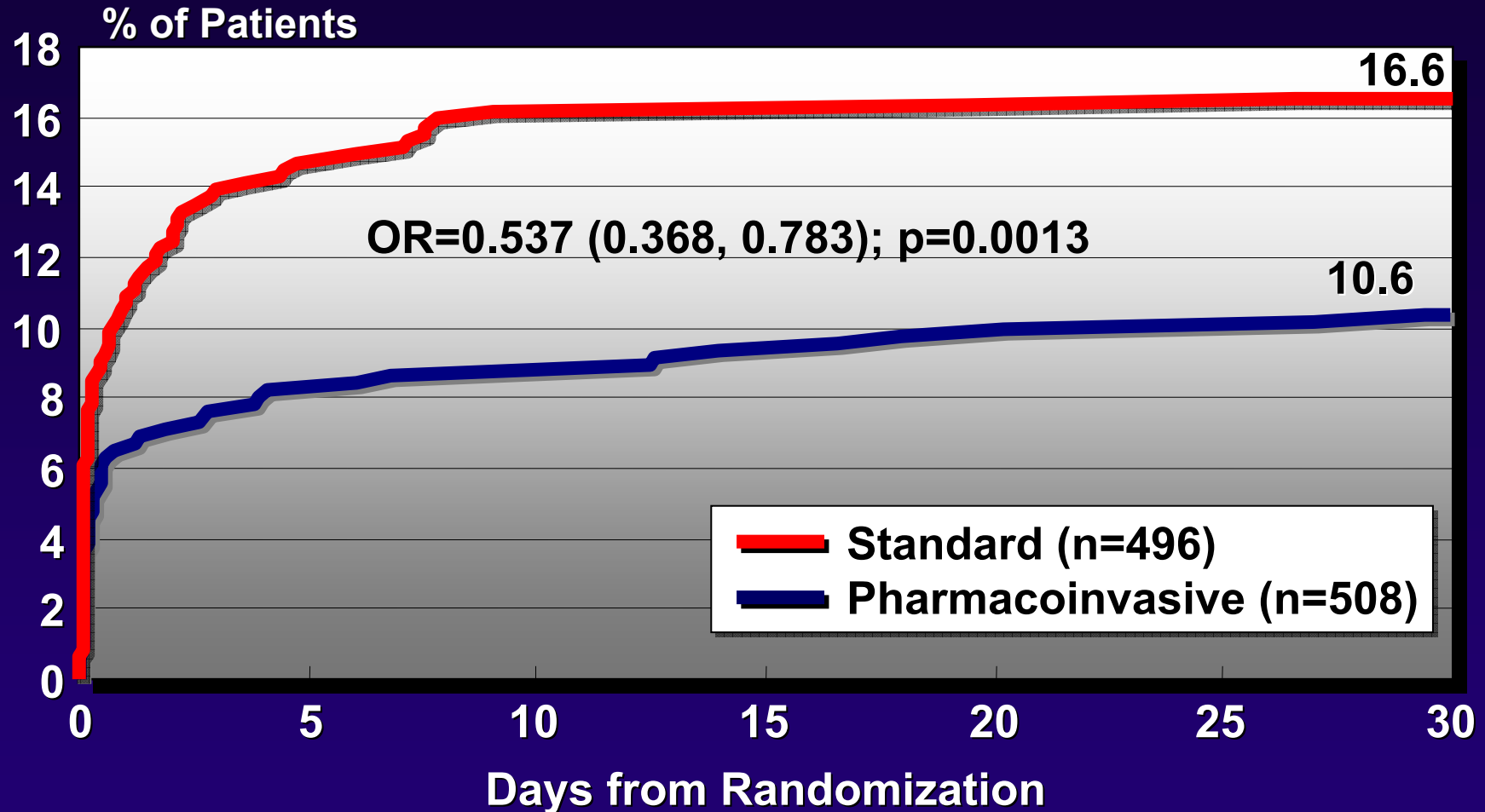
	Standard Treatment (n=508)	Pharmacoinvasive Strategy (n=522)
ASA 1 st 6 hrs	97	98
Clopidogrel 1 st 6 hrs *	69	87
Heparin	57	57
Enoxaparin	55	51
Beta Blocker 1 st 6 hrs	61	55
ASA at discharge	85	85
Clopidogrel at discharge	73	79
Warfarin at discharge	8	10
Beta Blocker at discharge	79	81
ACE Inhibitor or ARB at discharge	75	74
Lipid Lowering at discharge	84	84

* p < 0.05



Primary Endpoint: 30-Day Death, re-MI, CHF, Severe Recurrent Ischemia, Shock

PRELIMINARY



n=496	422	415	415	414	414	412
n=508	468	466	463	461	460	457



Components of Primary Endpoint

PRELIMINARY

	Standard Treatment (n=498)	Pharmacoinvasive Strategy (n=512)	P-Value
Death	3.6	3.7	0.94
Reinfarction	6.0	3.3	0.044
Recurrent Ischemia	2.2	0.2	0.019
New or worsening CHF	5.2	2.9	0.069
Cardiogenic Shock	2.6	4.5	0.11
Death/MI/Ischemia	11.7	6.5	0.004



Safety Endpoints - Bleeding

PRELIMINARY

	Standard Treatment (n=498)	Pharmacoinvasive Strategy (n=512)	P-Value
Intracranial hemorrhage	1.2	0.2	0.066
TIMI scale			
Major	4.6	4.3	0.88
Major (non-CABG-related)	3.2	2.2	0.33
GUSTO scale			
Severe	1.4	0.6	0.22
Severe (non-CABG-related)	1.2	0.6	0.34
Transfusions	5.5	7.1	0.31



Conclusions

- For high-risk STEMI patients receiving fibrinolysis at non-PCI centres, urgent transfer and PCI within 6 hours is associated with a 6% absolute (and 46% relative) reduction in ischemic complications at 30-days and no excess in major bleeding complications, compared with standard treatment
- Transfers to PCI centres should be initiated immediately after fibrinolysis without waiting to see whether reperfusion is successful
- Regional systems should be developed to ensure timely transfers of STEMI patients to PCI centres



Acknowledgements



- **Coordinating Centre:**
 - Canadian Heart Research Centre (CHRC)
- **Data Safety Monitoring Committee:**
 - Magnus Ohman (Chair), Peter Berger, Chris Buller, Karen Pieper
- **Steering Committee:**
 - Warren Cantor (Principal Investigator), David Fitchett, Anatoly Langer, Bjug Borgundvaag, Michael Heffernan, John Ducas, Eric Cohen, Vladimir Dzavik, Shamir Mehta, Charles Lazzam, Laurie Morrison, Brian Schwartz, Shaun Goodman (Study Chair)

Participating Sites

PCI Sites

St Michael's: S Goodman, B Zile; Trillium: C Lazzam, A Carter; Sunnybrook: E Cohen, L Balleza, E Hsu; Saint Boniface: J Ducas, S Aceves, A Munoz; Toronto General: V Dzavik, A Patel; Southlake: S Miner, K Robbins; Rouge Valley Centenary: S Kassam, B Hart, B Bozak; St. Mary's: HH Kim, I Janzen; Hamilton: S R Mehta, S Brons; London: K Sridhar, T Oke; Hôpital du Sacré- Coeur: E Schampaert, C Mercure.

Referring Sites

Credit Valley: P Pageau, R Durdos; St. Joseph's: R Choi, C Vardy; North York: B Lubelsky, J Coldwell; Ajax: J Burstein, C Harrison, T Eyman; Scarborough General: J Cherry, B Ross; Royal Victoria: B Burke, S Snow; Scarborough Grace: W Ho Ping Kong, D Hutton; William Osler: A Lee, M Coons, J Nigro; Lakeridge Oshawa: R Bhargava, J Easton; Oakville: M Heffernan, R Franks; St. Catherines : S Pallie, S Krekorian; Toronto East General: C Lefkowitz, E Klakowitz; Grace General: J Ducas, A Munoz, SL Aceves; Sarnia: N Ali, L Robichaud; Winnipeg HSC: W Palatnick; Seven Oaks: R de Faria; Victoria General: J Ducas; Ross Memorial Hosp: N Krishnan, C McBride; Norfolk General: D Kennedy, M Robinson; Huntsville: M Mensour, S Tumber; Mt Sinai Hosp: B Borgundvaag, M Loftus; Stratford: M Mann, Y Balmain; Peterborough: N K Greene, N Turney; West Haldimand: S Chiu, K Marshall; Owen Sound: G Kumar, M Peart; Stevenson Memorial: J Hirst, L Johnston; Selkirk General: G Manca; Concordia General: G Torossi, A Munox, S Aceves; Grand River: R Fowlis, I Janzen; South Muskoka: A Shearing, D Lorbetsky; York Central: E Gangbar; Greater Niagara: G Zimakas, D Zaniol; Headwaters: J McKinnon, L Miller; CSSS d'Antoine-Labelle-Mt Laurier: E Belley, J Vincent