

The FINESSE Trial



(Facilitated Intervention with
Enhanced Reperfusion Speed to
Stop Events)

Stephen Ellis, MD
For the FINESSE Investigators

ESC Vienne 2007



Rational for FINESSE

Time is muscle: early reperfusion

			<u>Mortality</u>
1988	ISIS-2	SK	25% ↓
1993	GUSTO-1	TPA	14% ↓

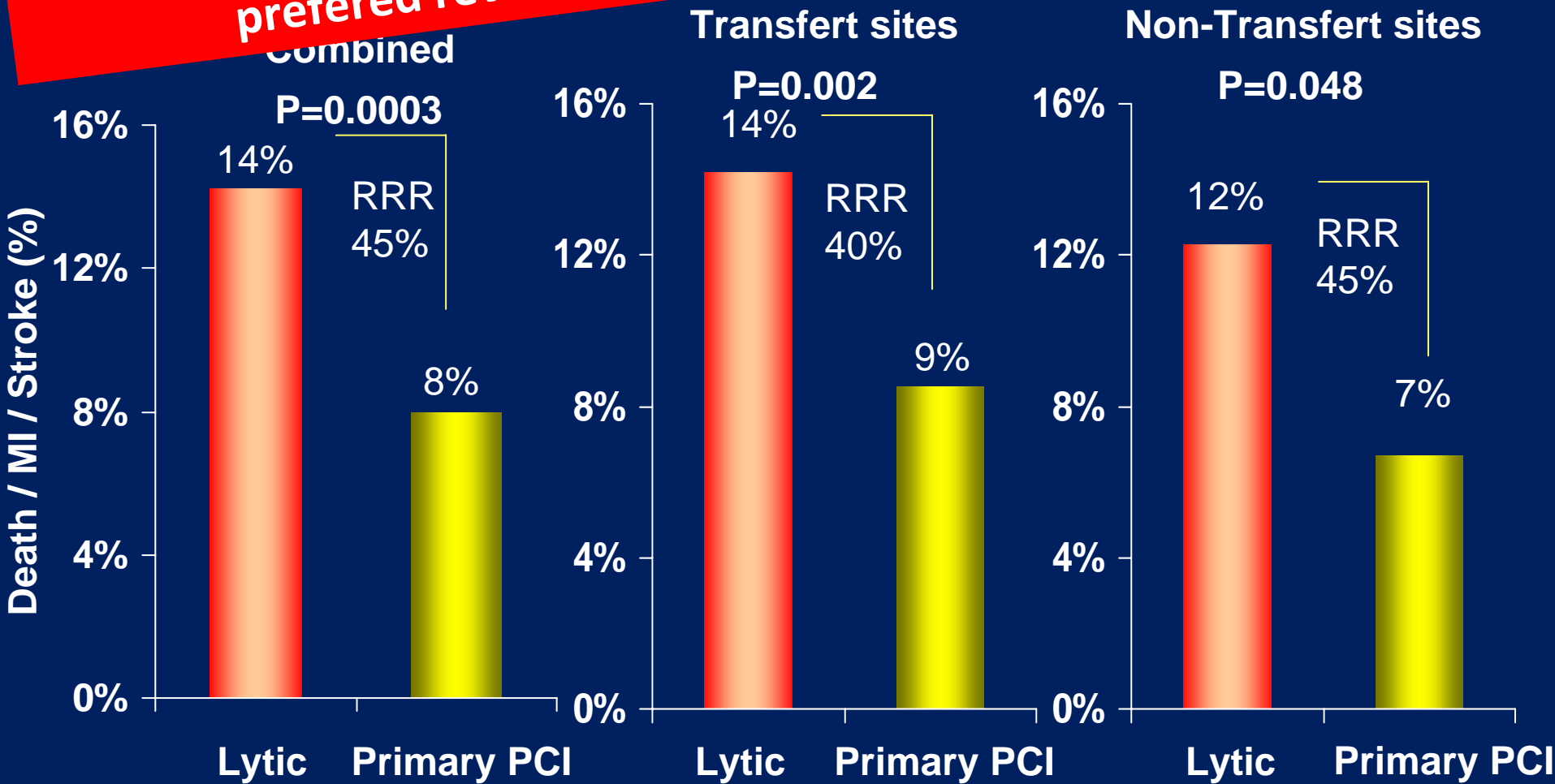
Clinical Impact of Reocclusion after Thrombolysis:

Data from the TAMI trials:

- 810 patients, cath 90 min & 7 days later:
- 12.4% reocclusion
- 58% symptomatic
- In-hospital mortality 11.0% vs 4.5% ($P=0.01$).

Rational for FINESSE

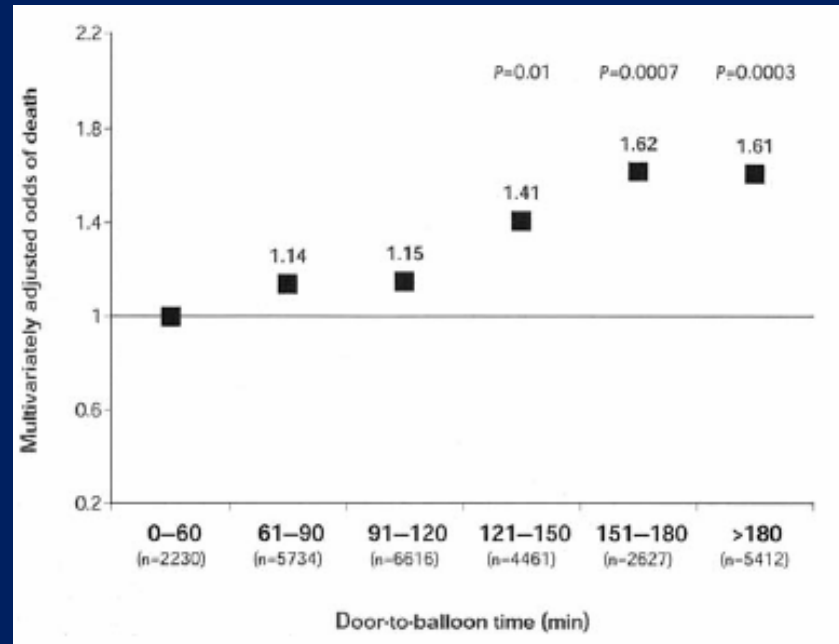
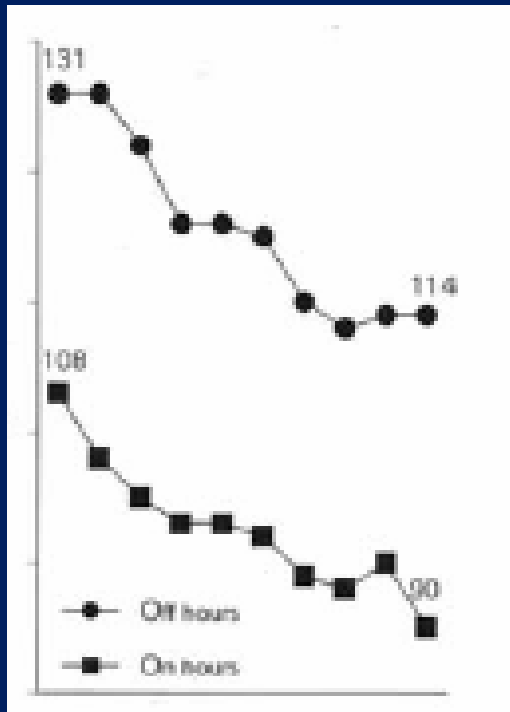
Primary PCI within 60 minutes of medical contact is the preferred revascularization strategy for STEMI



DANAMI-2

Rational for FINESSE

- Delays with primary PCI are common, particularly when patient transfer is required (NRMI: **139 minutes door to balloon time**)
- Door to Balloon time and total ischemic time have been directly related to mortality



Registre RIKS-HIA : mortalité à 30 jours et à 1 an, selon le délai

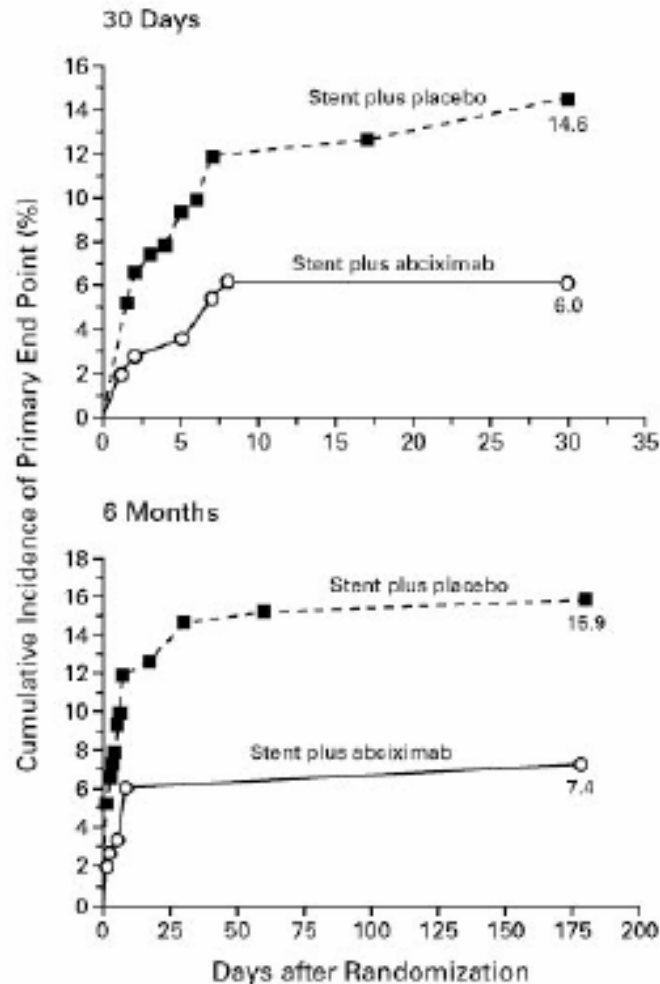
	Thrombolyse intra-hospitalière	Thrombolyse pré-hospitalière	Angioplastie primaire
Mortalité J30, délai < 2 h	8,6	5,6	3,8
Mortalité J30, délai > 2 h	11,4	8,9	4,5
Mortalité 1 an, délai < 2 h	11,9	8,0	6,7
Mortalité 1 an, délai > 2 h	16,3	11,8	7,3

Stenestrand U et coll. JAMA. 2006;296:1749-56.

Selon un registre sur 26 000 infarctus, l'angioplastie primaire est supérieure à la thrombolyse pré-hospitalière même précoce [heartwire > Actualités; 25 oct. 2006]

PLATELET GLYCOPROTEIN IIb/IIIa INHIBITION WITH CORONARY STENTING FOR ACUTE MYOCARDIAL INFARCTION

GILLES MONTALESCOT, M.D., PH.D., PAUL BARRAGAN, M.D., OLIVIER WITTENBERG, M.D., PATRICK ECOLLAN, M.D., SIMON ELHADAD, M.D., PHILIPPE VILLAIN, M.D., JEAN-MARC BOULENC, M.D., MARIE-CLAUDE MORICE, M.D., LUC MAILLARD, M.D., MICHEL PANSIÉRI, M.D., RÉMI CHOUSSAT, M.D., AND PHILIPPE PINTON, M.D., FOR THE ADMIRAL INVESTIGATORS*



59 % reduction in the risk of the primary endpoint in the Abxc group (p=0.01)

53 % reduction in the risk of the primary endpoint in the Abxc group (p=0.02)

ADMIRAL

Major Objectives

Primary: To test if Reteplase/Abciximab Facilitated PCI is superior to Primary PCI with in Lab Abciximab

Cath lab availability uncertain or
Anticipated delay of 1 to 4 hours



Primary PCI with in lab
Abciximab

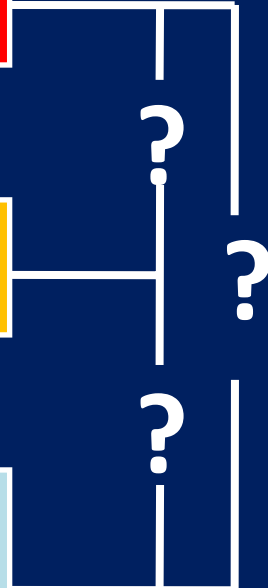
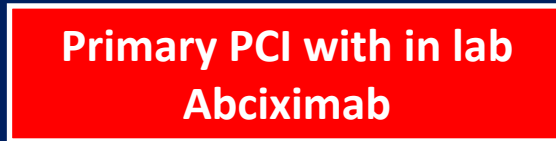
Reteplase/Abciximab
Facilitated
Primary PCI

?

Major Objectives

Primary: To test if Reteplase/Abciximab Facilitated PCI is superior to Primary PCI with in Lab Abciximab

Cath lab availability uncertain or
Anticipated delay of 1 to 4 hours



Secondary:

To test if Reteplase/Abciximab is superior to facilitation with Abciximab alone

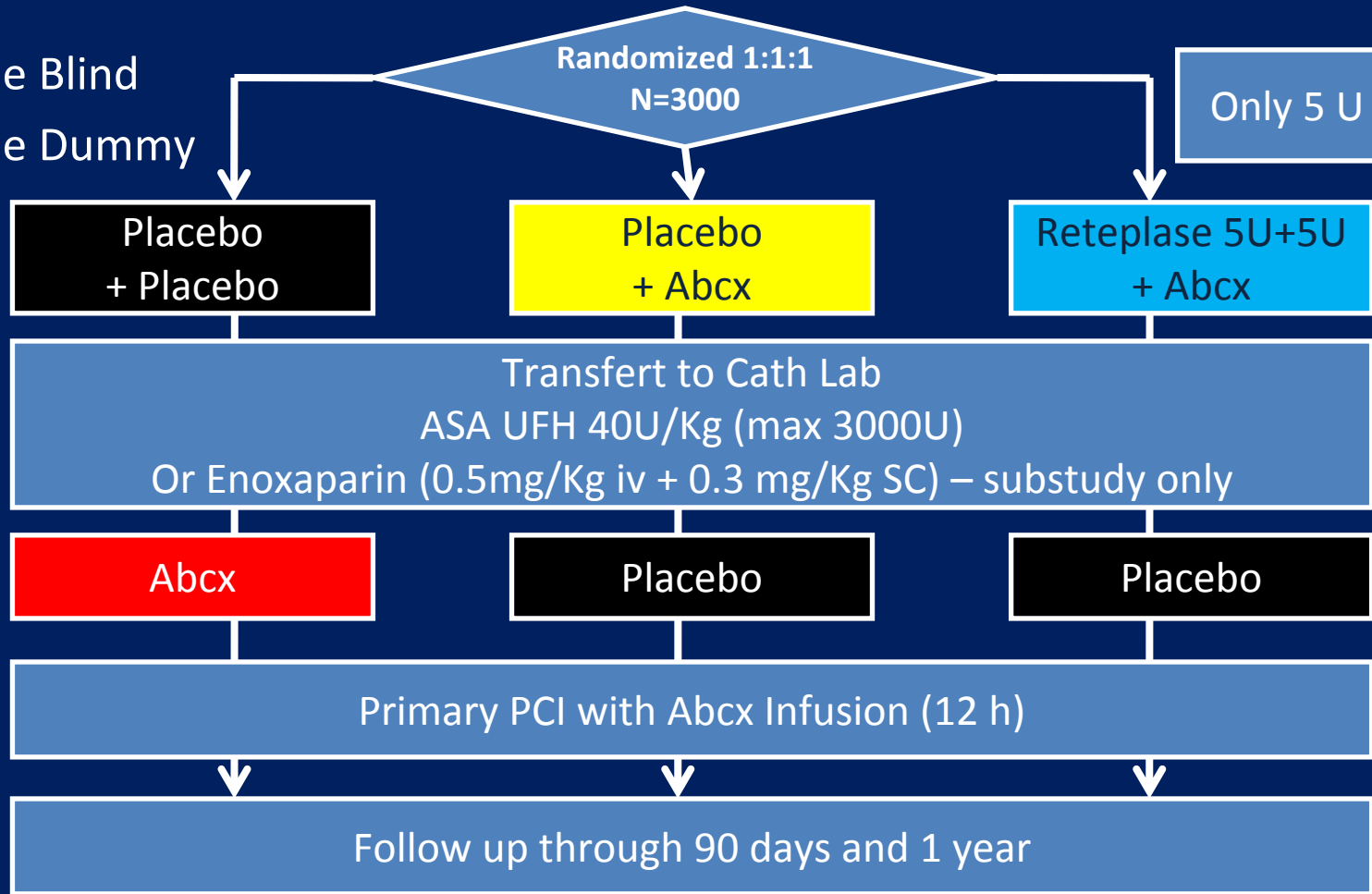
To test if Abciximab Facilitation is superior to Primary PCI with in lab Abciximab

FINESSE: Study Design

Acute STEMI (or new LBBB) within 6 h pain onset

Presenting with estimate time to Cath between 1 and 4 h

Double Blind
Double Dummy



Primary Endpoint

Composite endpoint @ 90 days

- Death
- Rehospitalization for CHF
- Resuscitated ventricular fibrillation occurring > 48h after randomization
- Cardiogenic shock

Major Secondary Endpoints

- **Complications of MI through 90 days**
 - **Rehospitalization or emergency department treatment for CHF**
 - **Resuscitated ventricular fibrillation occurring > 48h after randomization**
 - **Cardiogenic shock**
- **All Cause Mortality through 90 days**
- **% of subjects with ST-segment resolution >70% from pretreatment baseline when assessed 60-90 minutes after randomization**

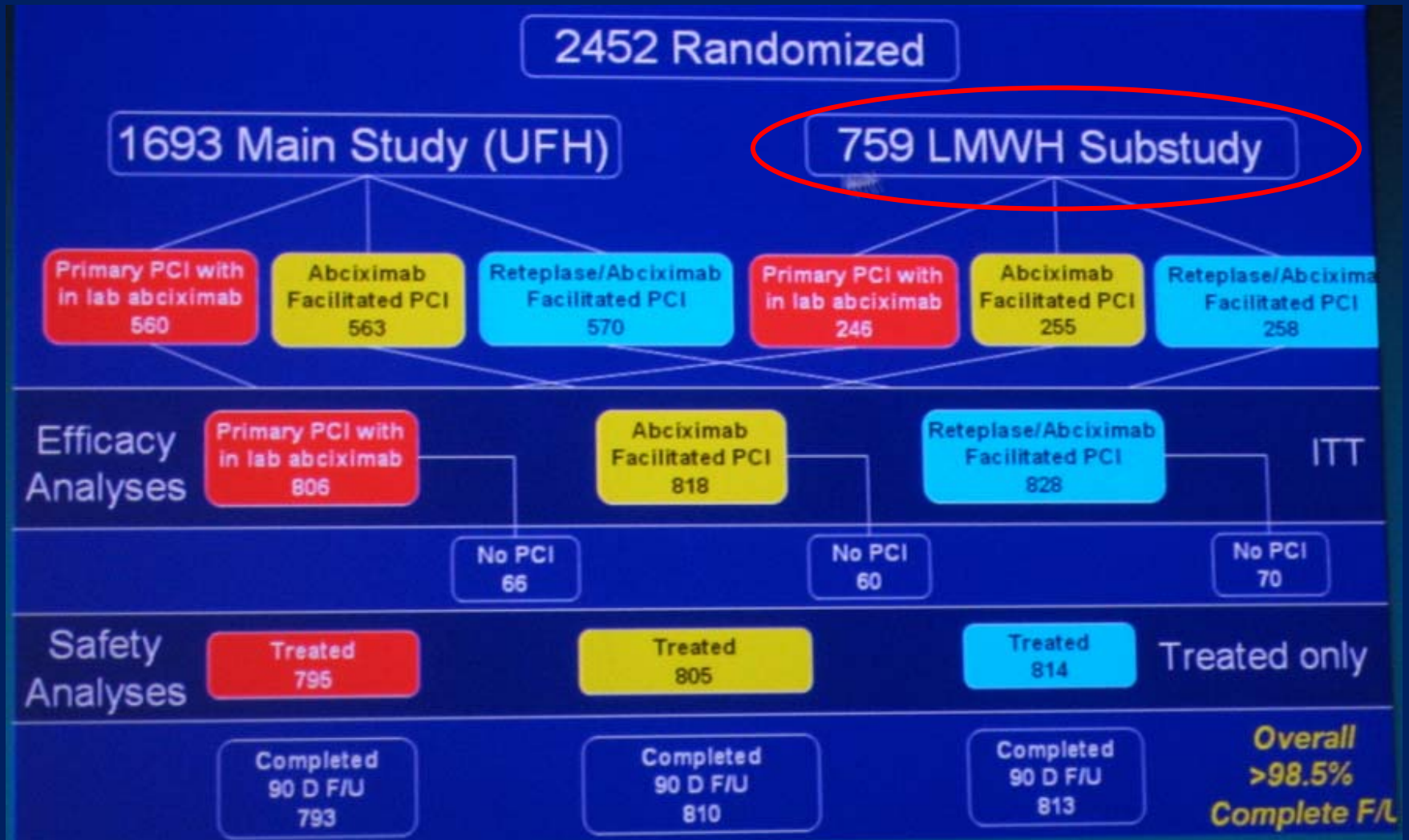
Safety Endpoints

- **Major Safety Endpoints**
 - Nonintracranial TIMI major or minor bleeding through discharge/Day 7
 - ICH including hemorrhagic transformation through discharge/Day 7
- **Other**
 - Disabling stroke or ICH through discharge/day 7
 - Non-disabling stroke through discharge/day 7
 - TIMI major or minor bleeding through discharge/day 7
 - Transfusions
 - Thrombocytopenia
 - AEs and SAEs through discharge/day 7

Key Inclusion / Exclusion criteria

- **Inclusion Criteria**
 - **≥ 21 years of age**
 - **Symptom duration >20 min to 6 hr**
 - **STEMI or new LBBB**
- **Exclusion Criteria**
 - **Local inferior infarction in age <60**
 - **Angiography expected < 60 min or > 4 hr after qualifying ECG**
 - **Prohibited medications (eg bivalirudin, GPIIb/IIIa, fibrinolytic, oral anticoagulant, or LMWH)**
 - **Contraindications for abciximab (eg: active bleeding, recent major surgery; history of stroke or TIA within the previous 2 years or any stroke with a residual neurological deficit)**
 - **UFH within 6 hours prior to randomization unless aPTT ≤70 sec**

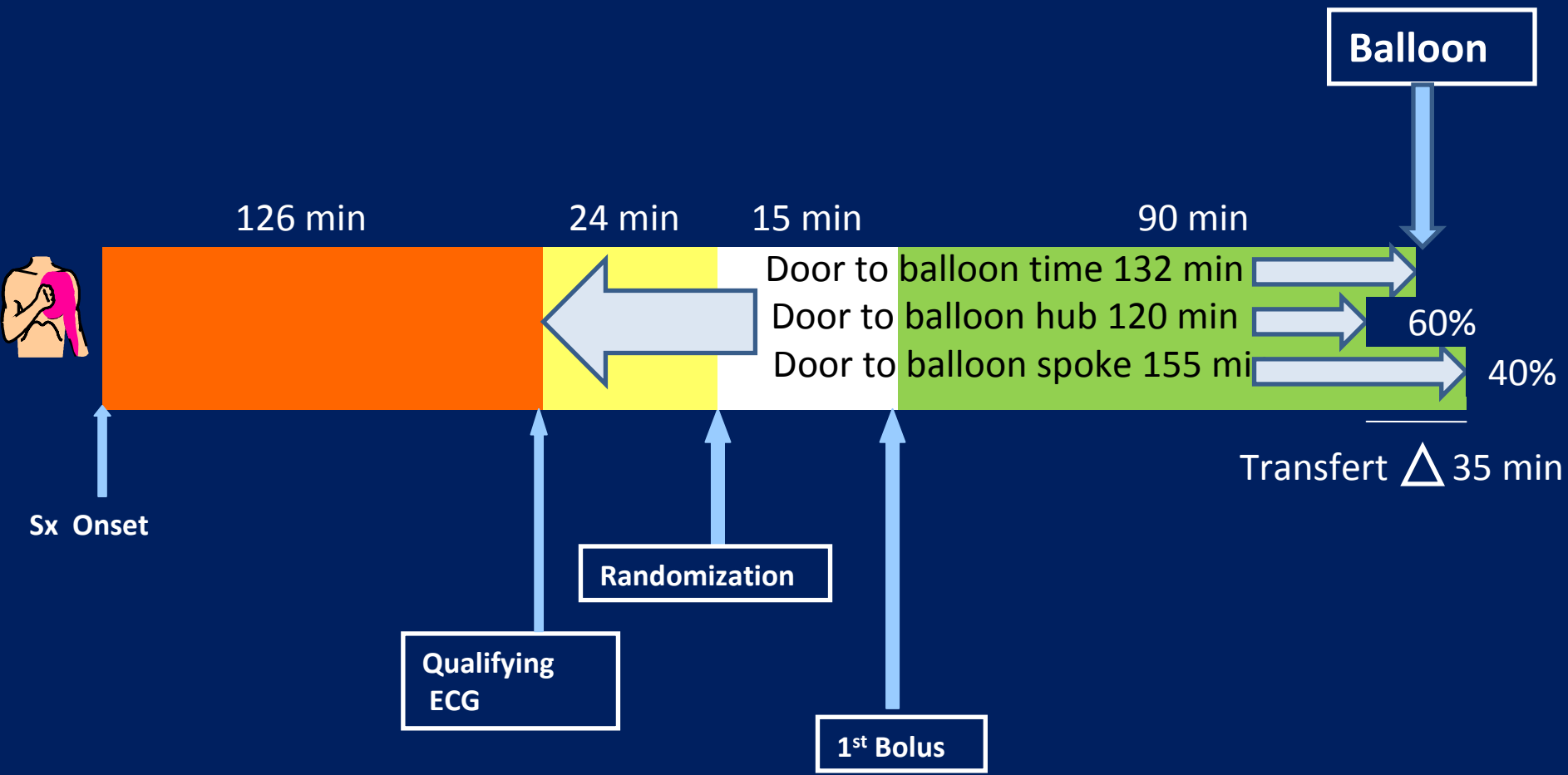
Patient flow



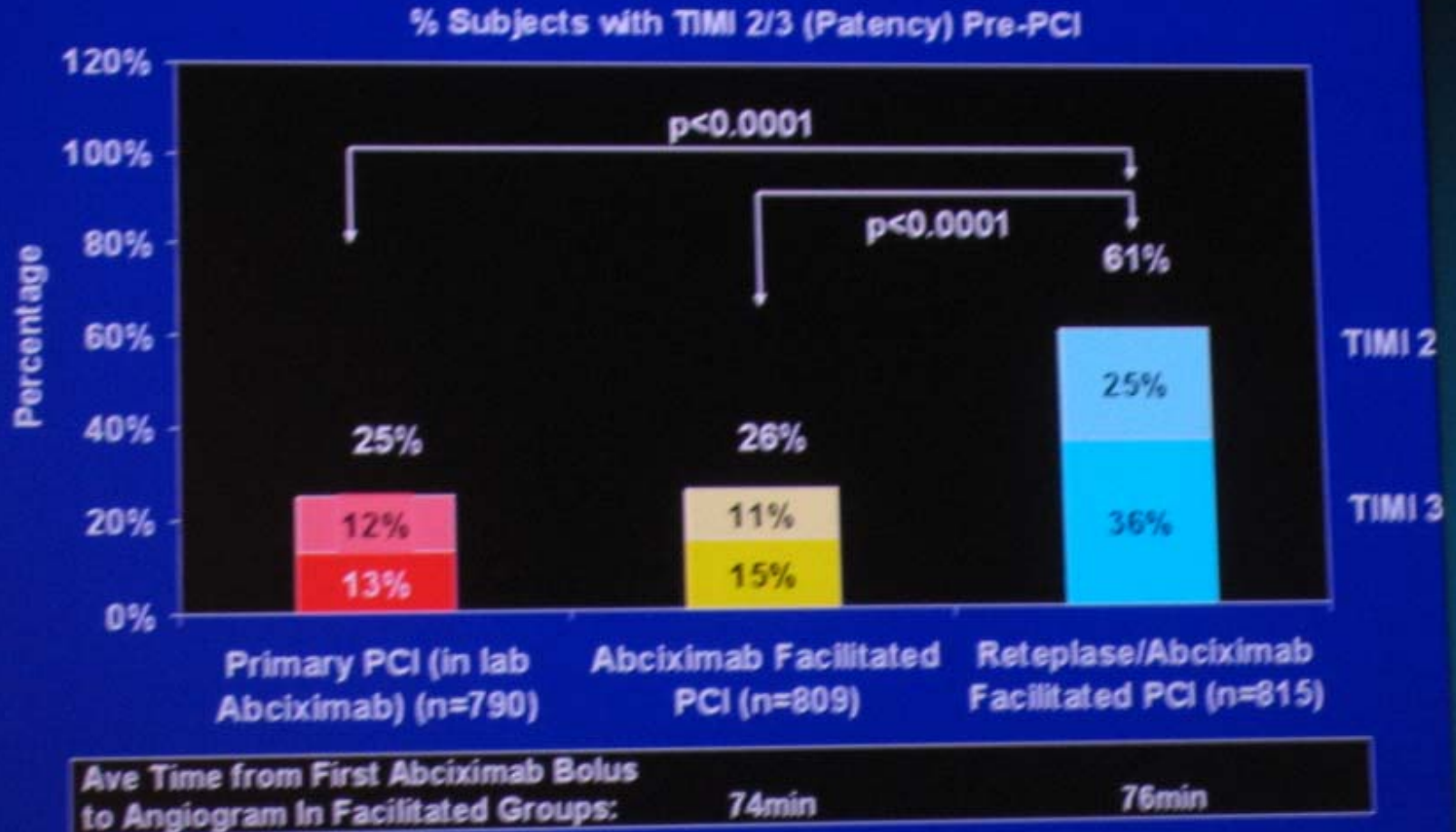
Baseline Demographics / Med Hx

<u>Variable</u>	<u>Primary PCI with in Lab Abx (n = 806)</u>	<u>Abx Facilitated PCI (n = 818)</u>	<u>Retepase/Abx Facilitated PCI (n = 828)</u>
Age (years, mean)	62.5	61.9	62.6
Gender (% Female)	26%	26%	26%
Race (% Caucasian)	98%	98%	98%
Smoker (past or current)	65%	67%	65%
HTN or Rx'ed HTN	46%	50%	48%
Anterior MI (%)	46%	49%	48%
Diabetes	17%	15%	16%
Prior MI	10%	10%	13%
Killip Class >1	10%	11%	9%
Prior PCI	4%	5%	7%
Prior Stroke	2%	2%	2%
High Risk (Anterior MI, Age >70, Killip >1 or HR >100)	65%	68%	67%

Treatments Intervals (median)



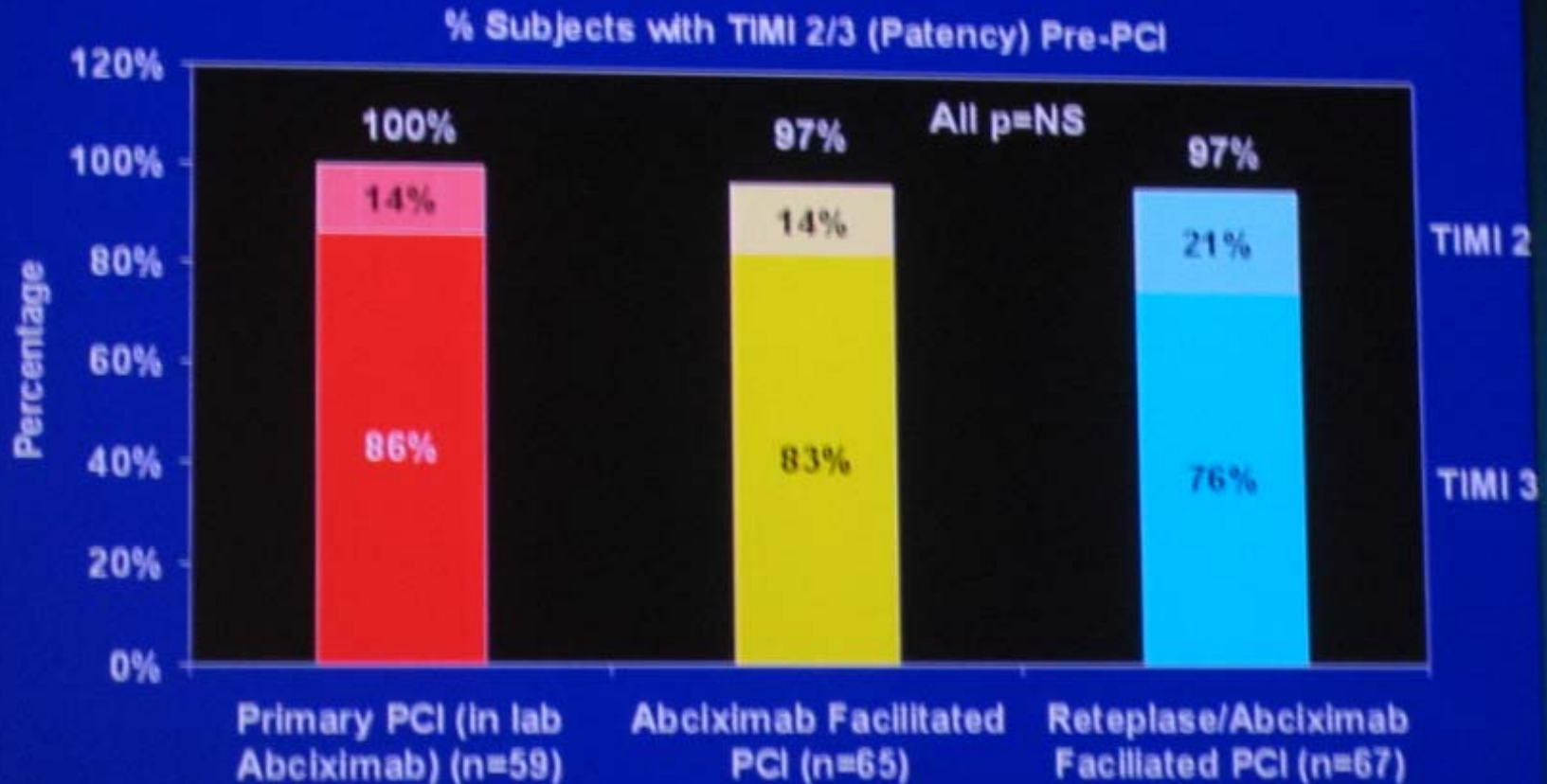
TIMI flow in IRA pre-PCI



Modified ITT Population with Index PCI: ITT, PCI and any dose of study drug (active or placebo); Investigator assessment

TIMI flow in IRA post-PCI

Core Lab analysis (n=191)



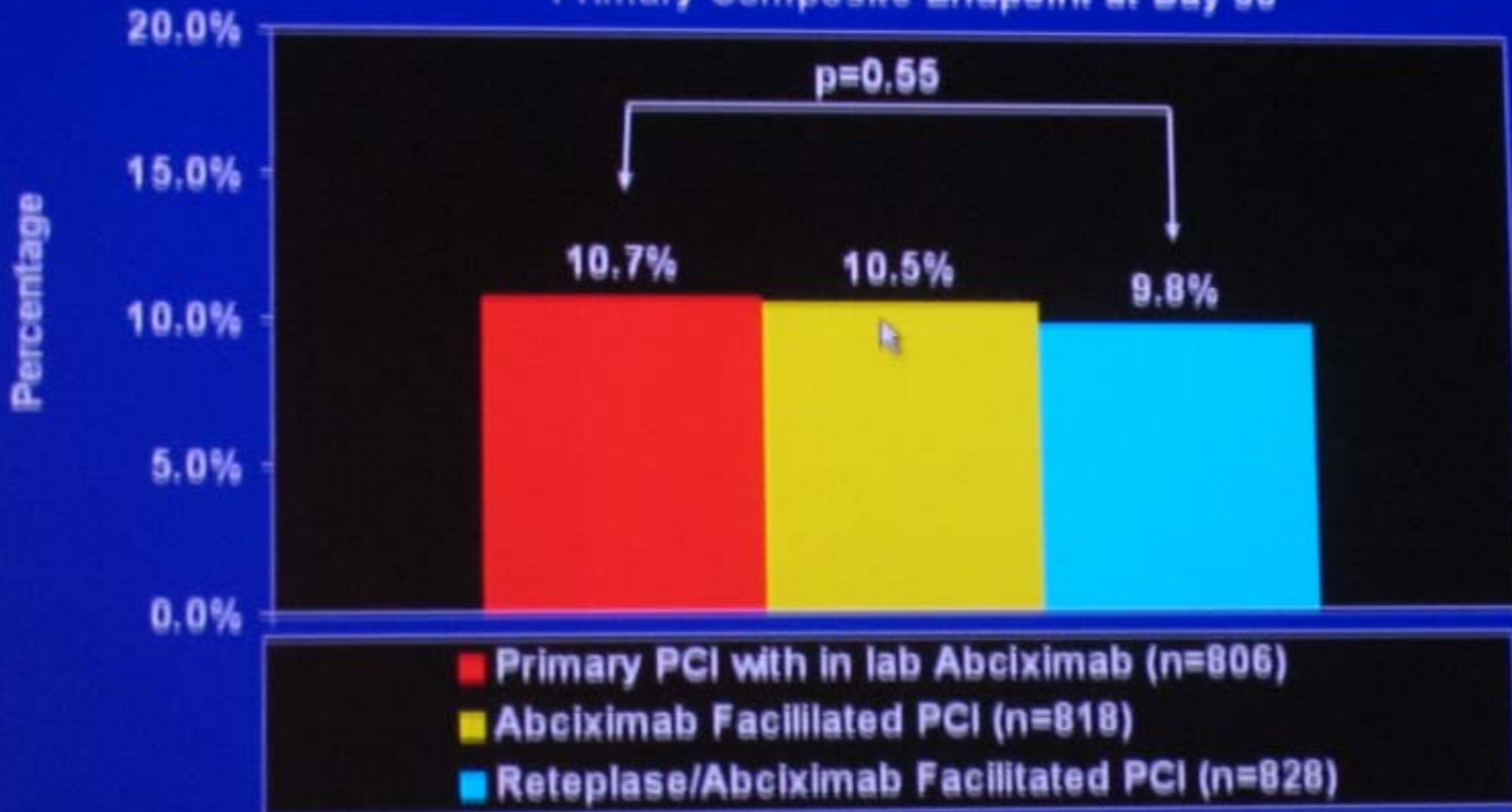
* TIMI 3 $p < 0.001$

FINESSEANGIO SUBSTUDY: Italy, Netherlands, Poland, UK

Preliminary

Primary Endpoint: Death, CHF, Resuscitated VF, Cardiogenic shock

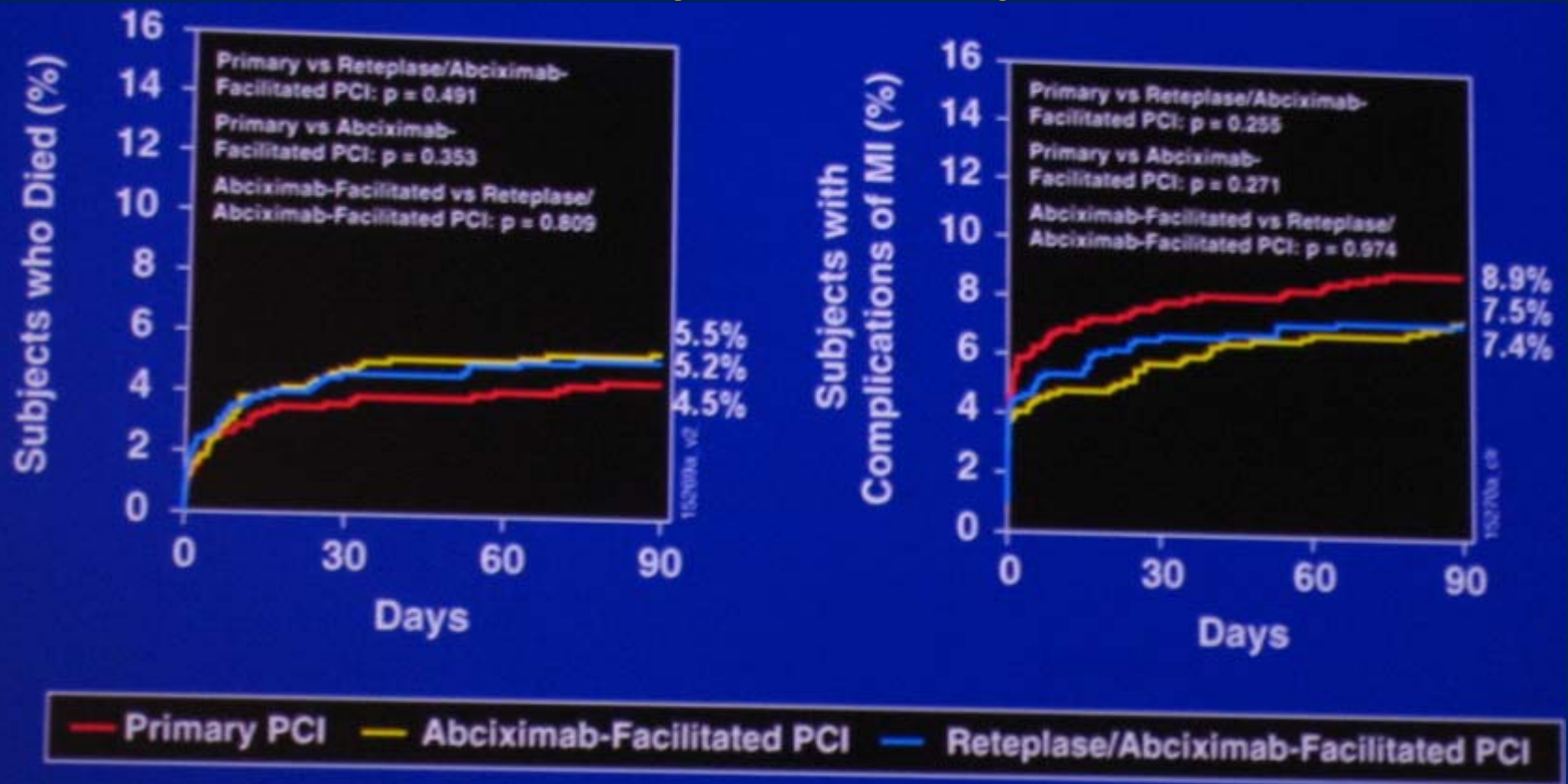
Primary Composite Endpoint at Day 90



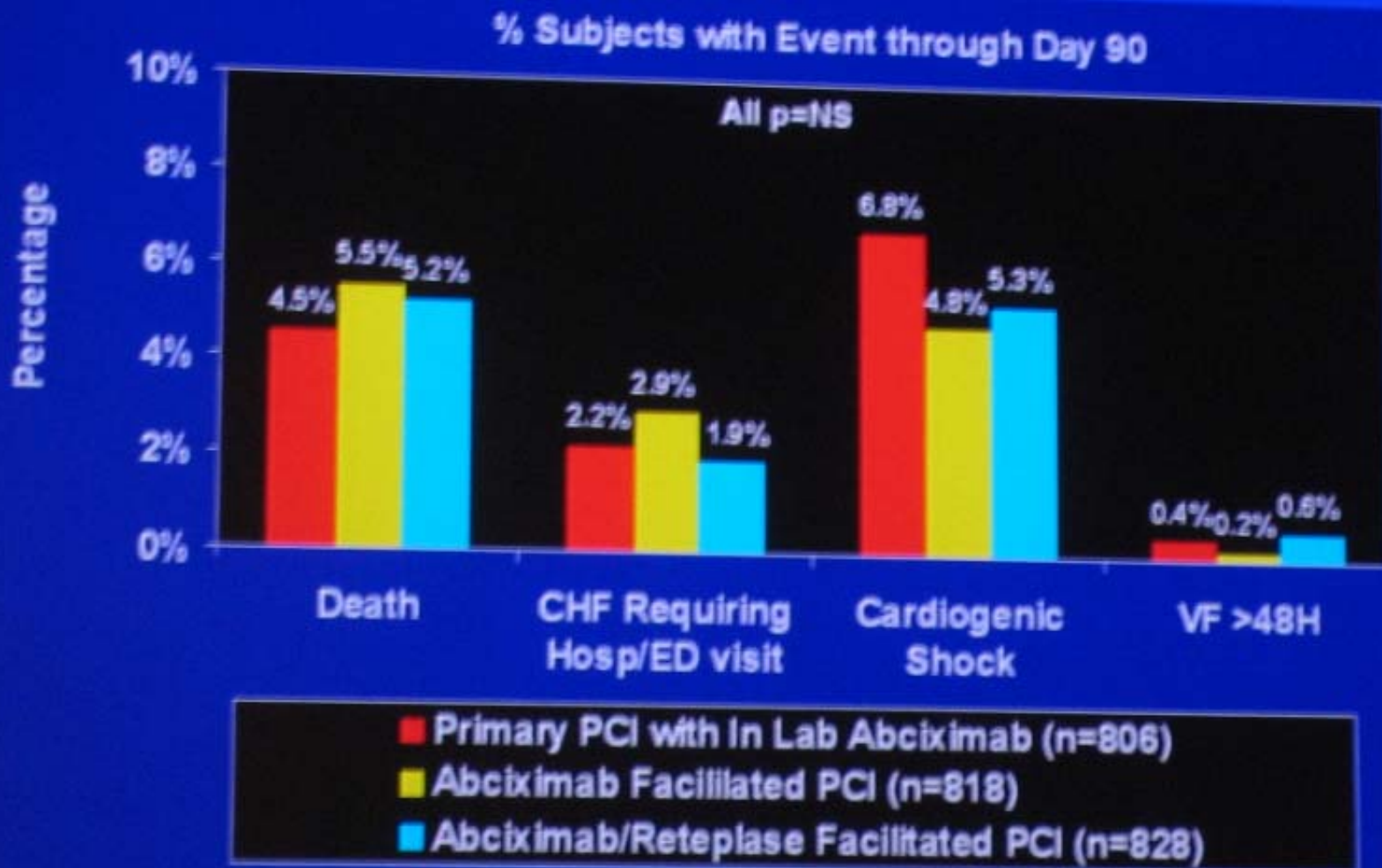
Major Secondary Endpoints

All Cause Mortality

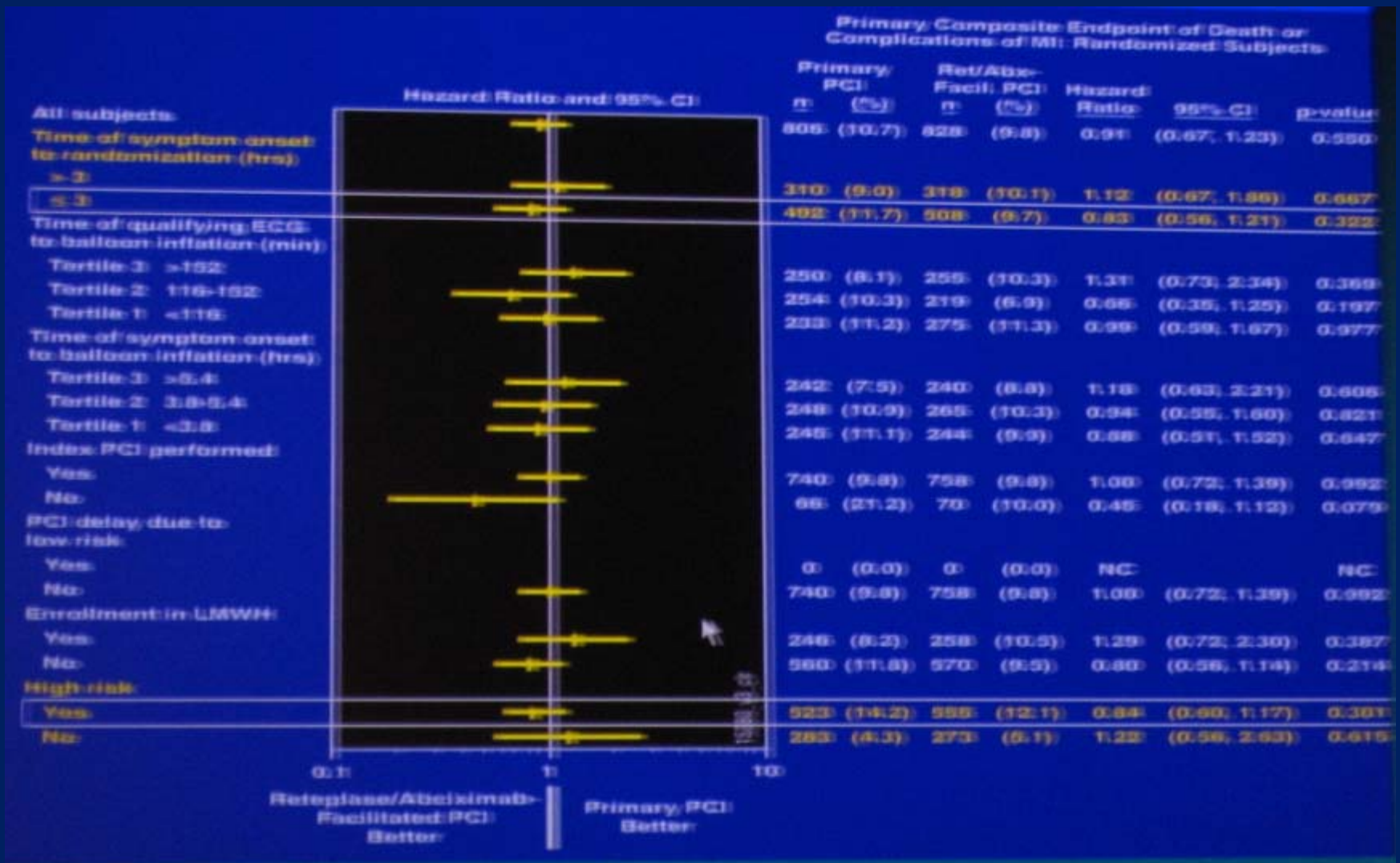
Complications of MI



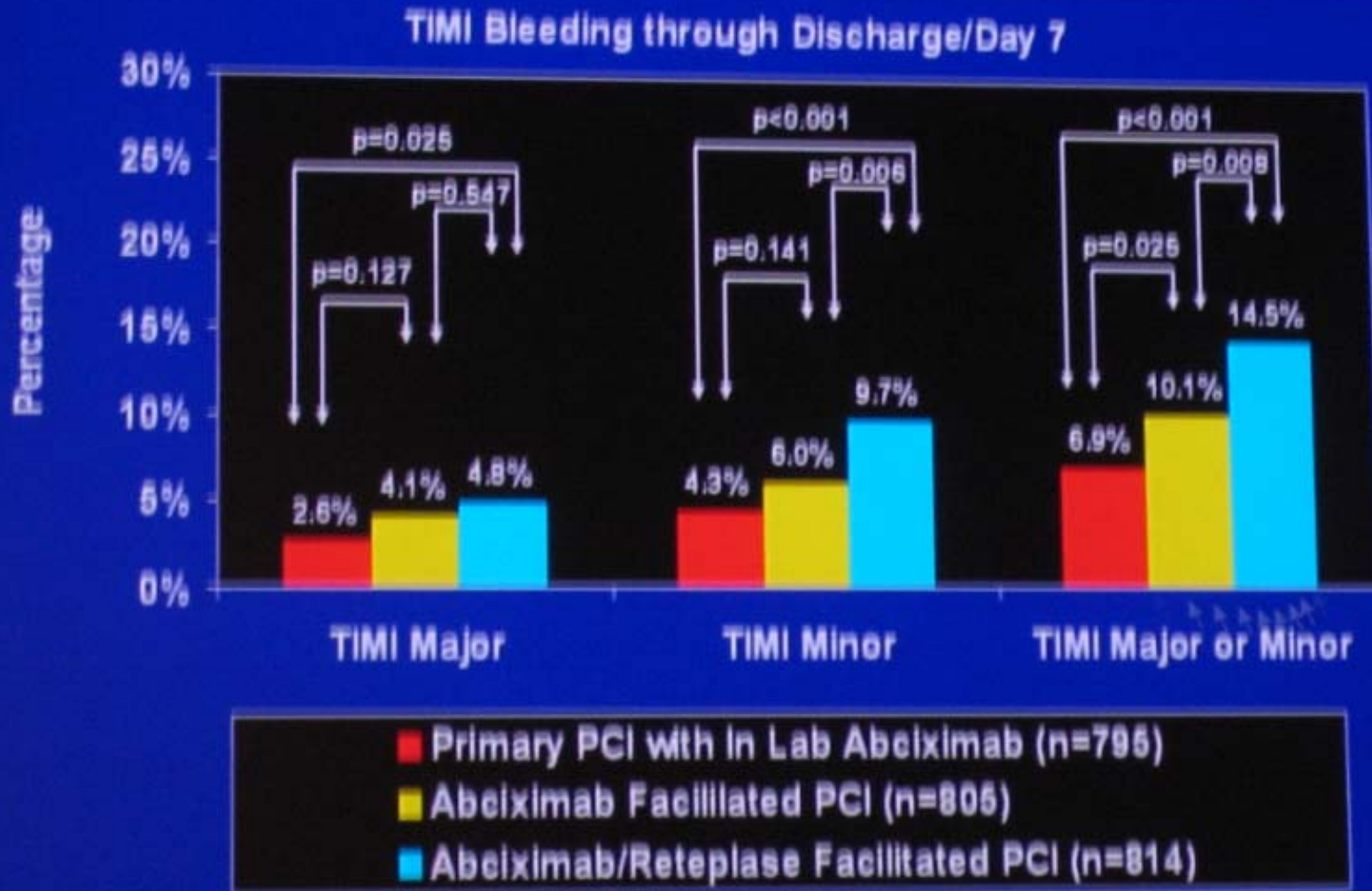
Primary Endpoint by Components



Pre-specified Subgroup Analysis: Reteplase/Abcx vs Primary PCI



TMI Major or Minor Bleeding non ICH through discharge/Day 7



Summary (1)

- **No significant improvement in the primary endpoint** or components was observed with either Reteplase/Abcx or Abcx facilitated PCI compared to Primary PCI with in lab administration of Abcx
- Significant **increases** were observed in non ICH **TIMI Major plus Minor bleeding in Reteplase/Abcx** compared to all other groups
- There were **no increase in total stroke** observed in the Reteplase/Abcx compared to all other groups
- Reteplase/Abcx administered early was associated with an increased in Pre-PCI TIMI 3 flow and >70% ST-segment resolution @ 60-90 min
- Post-PCI TIMI 3 flow and ST-segment resolution @ 180-240 min was similar in all 3 strategies

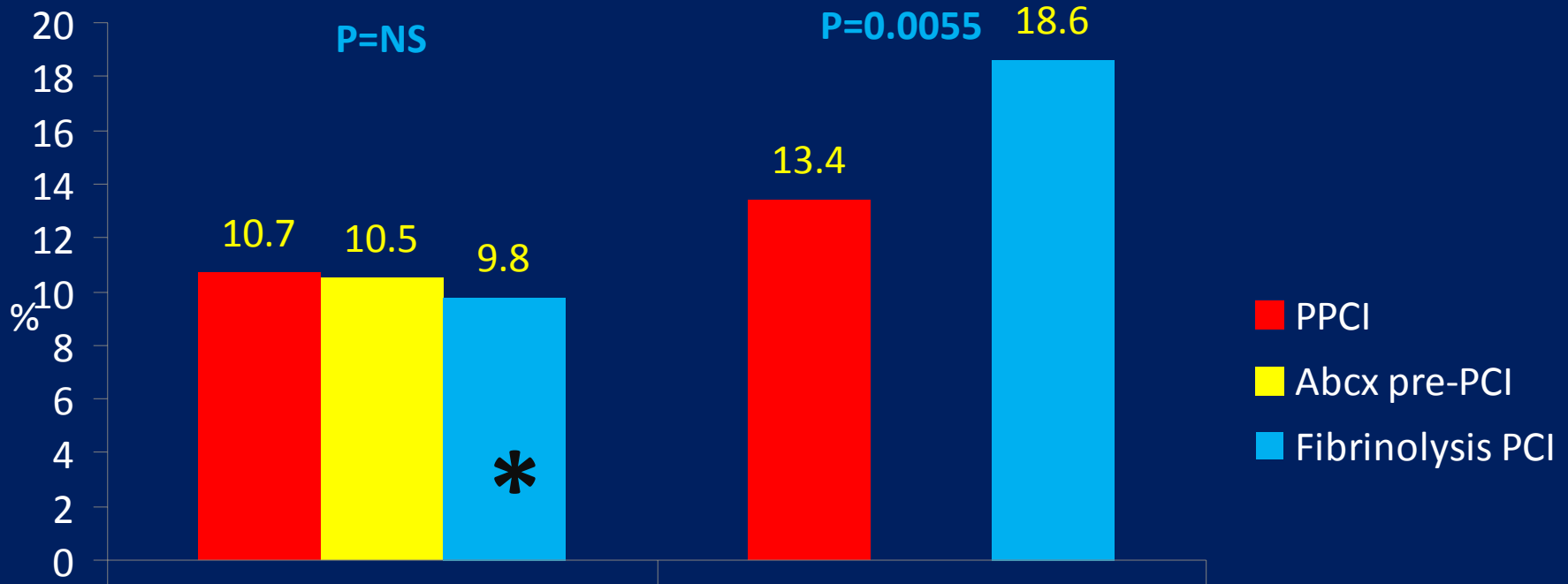
Summary (2)

- In general, there was a **consistent lack of benefit** for either facilitated strategy in the primary endpoint across the pre-specified subgroups
- Overall **outcomes in the FINESSE were better than expected** in patients with longer delays resulting in lower power than originally planned, despite a high risk population
- Despite stopping prematurely due to difficulty in enrollment (**82% of planned size**), it is unlikely that the overall results of the study would have differed if full enrollment had been achieved

Primary Endpoint @ 90 Days

Death, Shock, readmission
for CHF, VF > 48h

Death, Shock, any CHF



FINESSSE

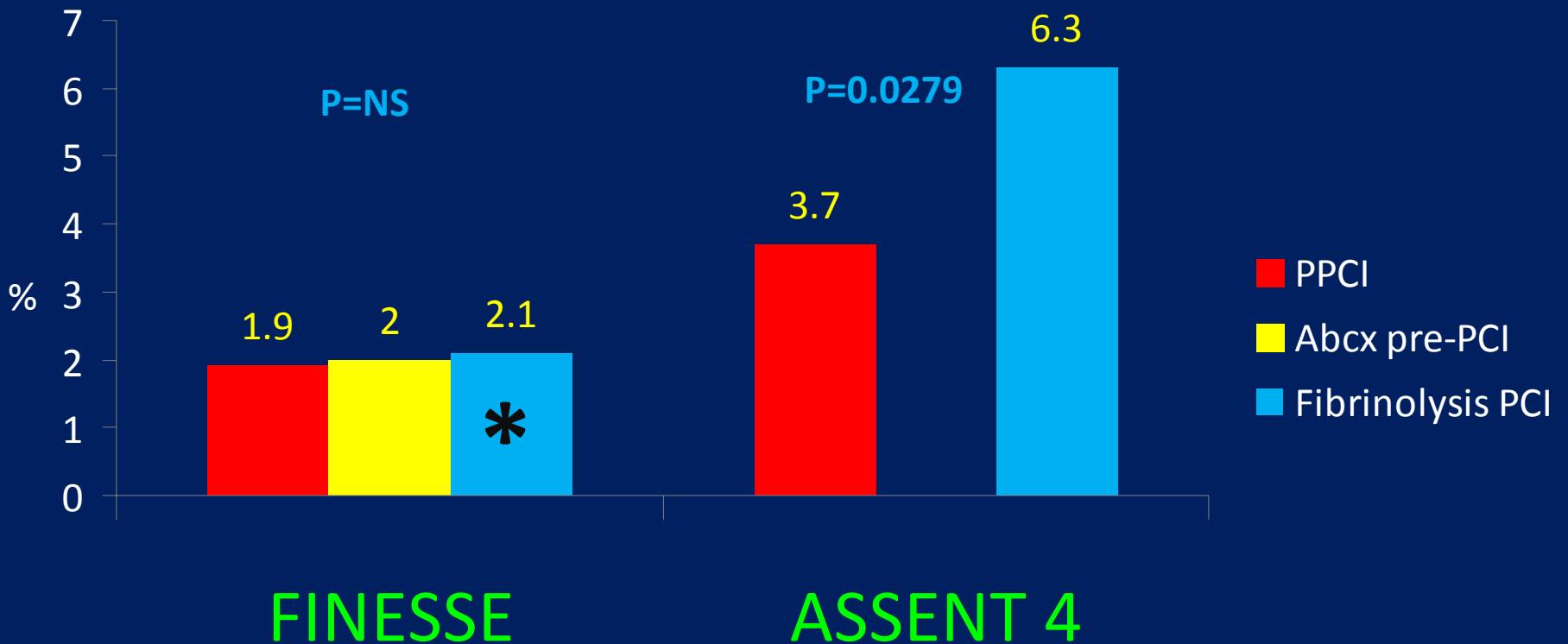
ASSENT 4

* ½ dose Reteplase + Abcx

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Lancet 2006;367:569-78

Reinfarction @ 90 Days



* ½ dose Reteplase + Abcx

ESC 2007

Lancet 2006;367:569-78

Conclusions

- **Neither facilitated PCI strategy provided clinical benefit** compared with primary PCI with in lab Abcx
- Reteplase/Abcx facilitation, and to a lesser extend Abcx facilitation, **increased bleeding** compared to the in lab administration of Abcx
- **Primary PCI with in lab Abcx provides a better benefit: risk profile** than the 2 facilitated strategies in patients with STEMI who can undergo PCI within 4 hours of first medical contact

Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials

*Ellen C Keeley, Judith A Boura, Cindy L Grines
Lancet 2006; 367: 579–88*

Interpretation Facilitated PCI offers no benefit over primary PCI in STEMI treatment and should not be used outside the context of randomised controlled trials. Furthermore, facilitated interventions with thrombolytic-based regimens should be avoided.

Death

	Facilitated intervention (n/N; %)	Primary intervention (n/N; %)	Death	p
Platelet glycoprotein IIb/IIIa inhibitor				
van't Hof, et al (On-TIME) ²	9/245 (4%)	2/247 (1%)		0.032
Lee, et al (TIGER-PA) ³	1/50 (2%)	1/50 (2%)		1.00
Mesquita-Gabriel, et al (ERAMI) ⁴	4/36 (11%)	5/38 (13%)		0.79
Amici, et al (REGOMOBILE) ⁵	0/52	1/48 (2%)		0.44
Zoman, et al ⁶	0/56	4/56 (7%)		0.067
Cutlip, et al ⁷	0/28	1/30 (3%)		0.50
Gyongyosi, et al (RecPro-BRIDGING) ⁸	0/28	0/27		0.99
Zeymer, et al (INTAMI) ⁹	2/53 (4%)	2/49 (4%)		0.94
Belandj, et al ¹⁰	1/27 (4%)	1/28 (4%)		0.98
Subtotal	17/575 (3%)	17/573 (3%)		0.94
Thrombolytic therapy				
Van de Werf, et al (ASSENT-4 PCI) ¹¹	50/828 (6%)	32/836 (4%)		0.039
O'Neill, et al (SAM) ¹²	0/58	0/63		0.97
Widimsky, et al (FRAGUE) ¹³	12/100 (12%)	7/101 (7%)		0.22
Vermeert, et al (LIMI) ¹⁴	6/74 (8%)	5/75 (7%)		0.74
Ross, et al (FACT) ¹⁵	11/302 (4%)	10/304 (3%)		0.81
Fernandez-Aviles, et al (GRACIA-2) ¹⁶	3/104 (3%)	5/108 (5%)		0.51
Subtotal	82/1466 (6%)	59/1487 (4%)		0.042
Combination therapy				
ADVANCE-MI ¹⁷	5/69 (7%)	0/77		0.026
Kaschat, et al (BRAVE) ¹⁸	2/125 (2%)	2/128 (2%)		0.98
Subtotal	7/194 (4%)	2/205 (1%)		0.44
Total	106/2235 (5%)	78/2265 (3%)		0.04



Lancet 2006; 367: 579–88

Non-fatal reinfarction

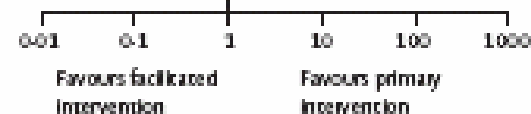
	Facilitated intervention (n/N: %)	Primary intervention (n/N: %)	Non-fatal reinfarction	p
Platelet glycoprotein IIb/IIIa inhibitor				
van't Hof, et al (On-TIME) ²	3/245 (1%)	2/247 (1%)		0.65
Lee, et al (TIGER-PA) ³	0/50 (0%)	1/50 (2%)		0.48
Mesquita-Gabriel, et al (ERAMI) ⁴	n/a	n/a		
Amiz, et al (RECOMBILE) ⁵	2/52 (4%)	0/48		0.27
Zornan, et al ⁶	0/56	0/56		1.00
Cudlip, et al ⁷	0/28	1/30 (3%)		0.50
Gyongyosi, et al (ReoPro-BRIDGING) ⁸	0/28	0/27		0.99
Zeymet, et al (INTAMI) ⁹	3/53 (6%)	0/49		0.15
Bellandi, et al ¹⁰	0/27	0/28		0.99
Subtotal	8/539 (1%)	4/535 (1%)		0.53
Thrombolytic therapy				
Van de Werf, et al (ASSENT-4 PCI) ¹¹	43/819 (5%)	24/832 (3%)		0.016
O'Neill, et al (SAMMI) ¹²	0/58	0/63		0.97
Widimsky, et al (PRAGUE) ¹³	7/100 (7%)	1/101 (1%)		0.03
Vermeer, et al (LIMI) ¹⁴	4/74 (5%)	1/75 (1%)		0.17
Ross, et al (PACT) ¹⁵	9/302 (3%)	8/304 (3%)		0.80
Fernandez-Aviles, et al (GRACIA-2) ¹⁶	1/104 (1%)	1/108 (1%)		0.98
Subtotal	64/1457 (4%)	35/1483 (2%)		0.006
Combination therapy				
ADVANCE-MI ¹⁷	1/69 (1%)	2/77 (3%)		0.63
Kastrati, et al (BRAVE) ¹⁸	1/125 (1%)	0/128		0.47
Subtotal	2/194 (1%)	2/205 (1%)		0.98
Total	74/2190 (3%)	41/2223 (2%)		0.006



Lancet 2006; 367: 579–88

Bleeding

	Facilitated intervention (n/N: %)	Primary intervention (n/N: %)	Major bleeding	P
Platelet glycoprotein IIb/IIIa inhibitor				
van't Hof, et al (On-TIME) ²	11/245 (4%)	8/247 (3%)		0.47
Lee, et al (TIGER-PA) ³	1/50 (2%)	1/50 (2%)		1.00
Mesquita Gabriel, et al (ERAMI) ⁴	4/36 (11%)	2/38 (5%)		0.36
Amez, et al (REOMOBILE) ⁵	1/52 (2%)	1/48 (2%)		0.95
Zorman, et al ⁶	16/56 (29%)	11/56 (20%)		0.27
Curtip, et al ⁷	2/28 (7%)	2/30 (7%)		0.94
Gyongyosi, et al (ReoPro-BRIDGING) ⁸	1/28 (4%)	2/27 (7%)		0.53
Zeymer, et al (INTAMI) ⁹	2/53 (4%)	2/49 (4%)		0.94
Bellandi, et al ¹⁰	1/27 (4%)	2/28 (7%)		0.57
Subtotal	39/575 (7%)	31/573 (5%)		0.30
Thrombolytic therapy				
Van de Werf, et al (ASSENT-4 PCI) ¹¹	46/829 (6%)	37/838 (4%)		0.29
O'Hell, et al (SAM) ¹²	15/58 (26%)	2/63 (3%)		0.0001
Widimsky, et al (FRAGUE) ¹³	8/111 (7%)	0/97		0.010
Vermeer, et al (LIMI) ¹⁴	0/74	0/75		1.00
Ross, et al (FACT) ¹⁵	26/302 (9%)	25/304 (8%)		0.86
Fernandez-Aviles, et al (GRACIA-2) ¹⁶	1/104 (1%)	3/108 (3%)		0.23
Subtotal	96/1478 (7%)	67/1485 (5%)		0.17
Combination therapy				
ADVANCE-MI ¹⁷	17/69 (25%)	8/77 (10%)		0.023
Kastrat, et al (BRAVE) ¹⁸	7/125 (6%)	2/128 (2%)		0.08
Subtotal	24/194 (12%)	10/205 (5%)		0.006
Total	159/2247 (7%)	108/2263 (5%)		0.010



Lancet 2006; 367: 579–88

Pourquoi FINESSE et ASSENT 4 sont-elles négatives?

- **Le traitement anti-thrombotique suboptimal:**
 - **ASSENT-4 PCI:** pas de charge précoce de Clopidogrel, pas d'énoxaparine
 - **FINESSE:** pas de charge précoce de Clopidogrel, enoxaparine étudiée que dans un sous-groupe
- **Angioplastie systématique même si flux TIMI 3**
- **Patients inclus plus de 6h après le début des symptômes**

The CARESS in AMI Trial



**Combined Abciximab RE-teplase Stent Study in
Acute Myocardial Infarction**

Carlo di Mario, MD

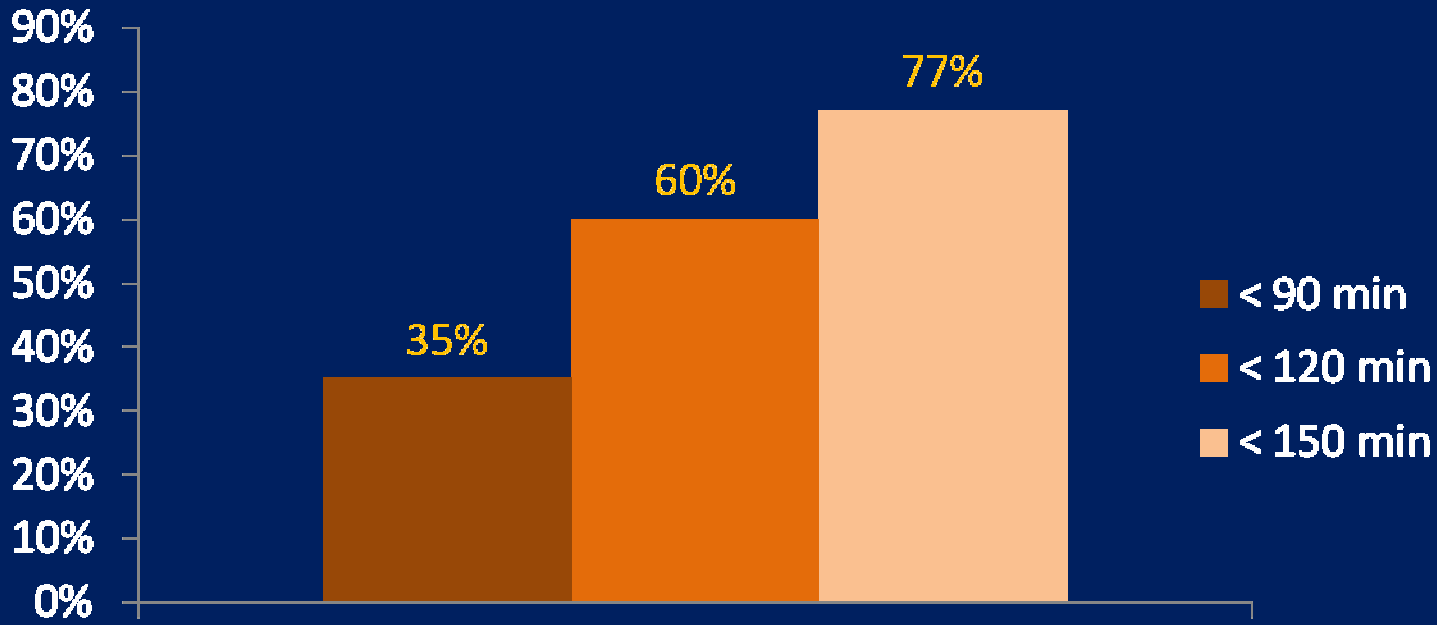
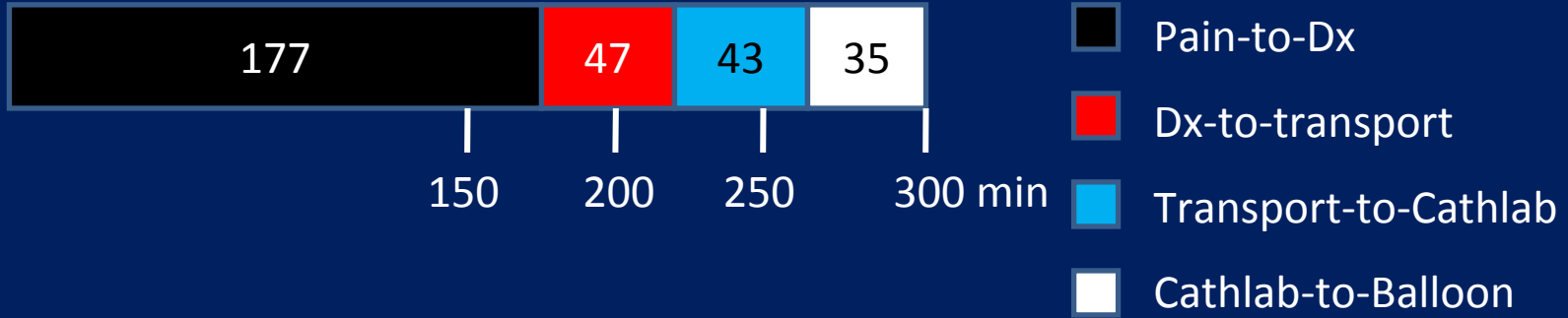
For the CARESS Investigators

ESC Vienne 2007

AIM

Comparison of an early transfert of patients after Thrombolysis to a PCI center versus a strategy of medical treatement continued in the admission hospital and transfert for rescue PCI only if there is evidence of no reperfusion

1650 STEMI pts in the EUROTRANSFERT Registry 2005-2007



Diagnosis to Balloon time



CARESS Study Design

STEMI patients <12 hrs from symptom onset
<75 yr old and with no contraindications to lytics
admitted to centres without PCI facilities and
at least one high risk feature: >15 mm ST Elevation
new onset LBBB, previous MI, Killip Class ≥ 2 , < 35% LVEF

FACILITATED PCI

Urgent transfer after
lysis to nearest PCI centre
for PCI plus stenting

MEDICAL TREATMENT/ RESCUE

Admit to CCU and only
transfer for PCI if persistent
ST elevation at 90 min (>50% basal
ECG) , chest pain or haemodynamic
compromise

Primary outcome: Death, Reinfarction, Refractory Ischemia at 30 Days

CARESS Treatment Summary

ASA 300-500 mg iv
2 X 5U Bolus (30') Reteplase
UFH (40U/Kg (max 3000U) + 7 U/Kg/h)
Abcx 0.25 mg/Kg Bolus +
0.125 µg/Kg/minX12h

Facilitated PCI

Med Tx / Rescue PCI

40U/Kg Heparin Bolus (max 3000U) +
7 U/Kg/h during transfert
PCI ACT adjusted to 200-250'' and
Heparin stopped after procedure

40U/Kg Heparin Bolus (max 3000U) +
7 U/Kg/h for 24 hours
In Case of rescue PCI ACT adjusted to
200-250'' and Heparin stopped after
procedure

**Clopidogrel Started in the Cathlab and maintained for 1-12 months
only after Stenting up to Nov 2005 (514 Pts, 82%)**

Primary Endpoint

Composite Endpoint:

- Death
- Reinfarction
- Refractory Ischemia

CARESS Patient flow Chart

600 Patients Randomized

Facilitated PCI

299 Patients

1 Excluded (consent not valid)
1 patient data not available
(No transfert to PCI Center = 9)

30 Days data not yet available = 3

294 (98%) with 30 Days data

Med Tx / Rescue PCI

301 Patients

1 Withdrew consent (no MI)
(2 pts Retepl/Abcx not started)

30 Days data not yet available = 2

298 (99%) with 30 Days data

Baseline Characteristics

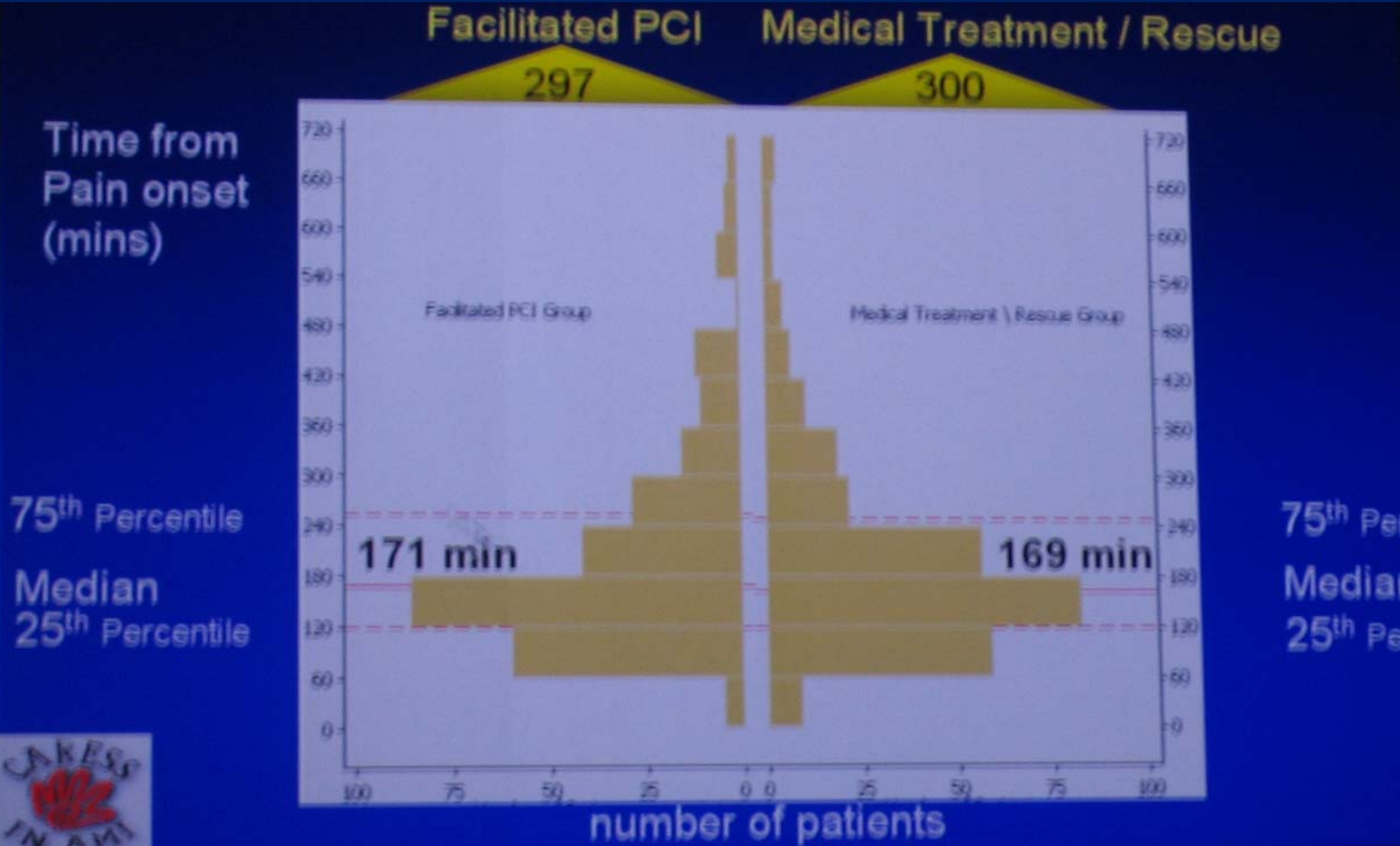
Facilitated PCI
n=297

Med Tx / Rescue PCI
n=300

Age, mean yrs (SD)	59.6 (9.8)	60.1 (10.2)
Male, n (%)	238 (79.3)	232 (77.9)
Diabetes, n (%)	44 (14.8)	44 (15.2)
SBP, mean mmHg (SD)	138 (25)	137 (22)
Previous MI, n (%)	29 (9.7)	35 (11.8)
Anterior MI, n (%)	130 (43.4)	149 (49.7)
Killip class 2-3, n (%)	128 (43.0)	133 (44.3)
LVEF, mean % (SD)	46.8 (9.9)	44.7 (9.4)

(No significant differences between the two groups)

Time Distribution Graph: Pain onset to Reteplase

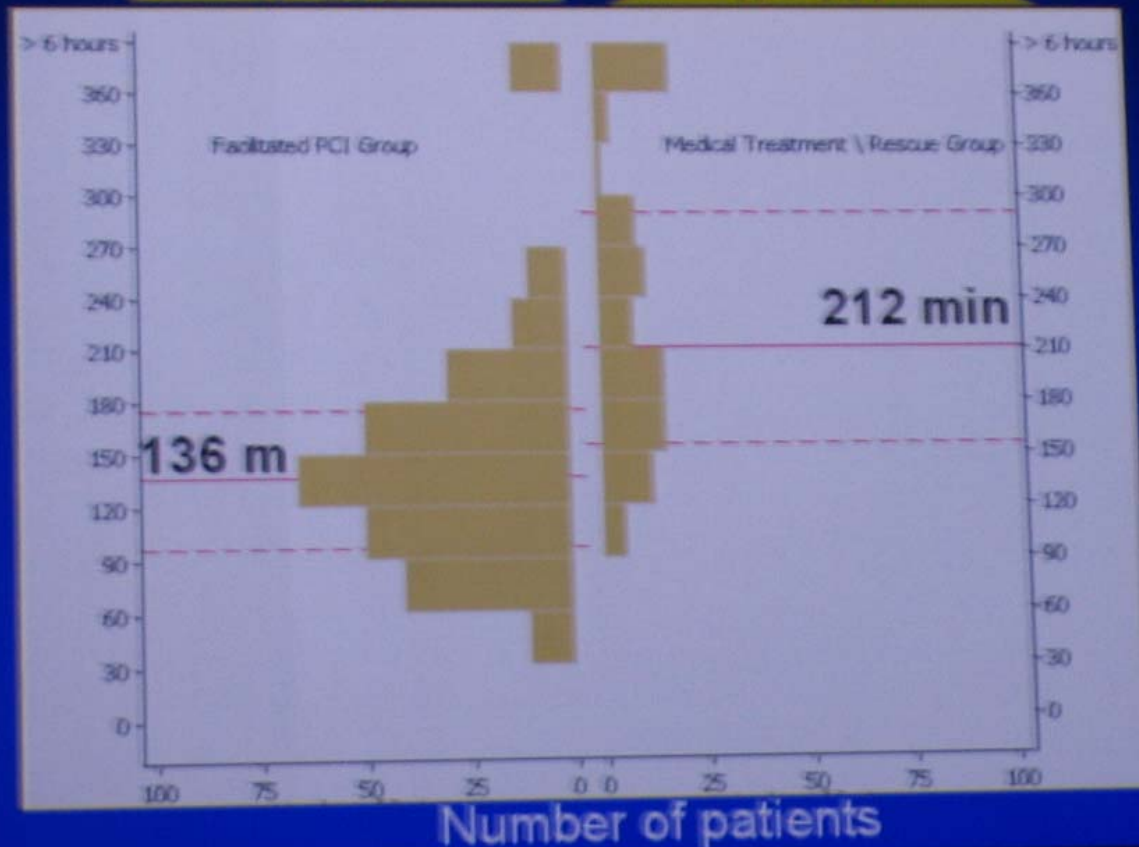


Time Distribution Graph: Reteplase to Angiography

Facilitated PCI Rescue (35.7%)
Transfer time 60 (35, 90) 58 (35, 85)
n=288 n= 107

Time from
Reteplase
Start (min)

75th Percentile
Median
25th Percentile



75th Peri

Median

25th Peri



CARESS-in-AMI: Facilitated PCI group only

Pre-PCI

Post-PCI

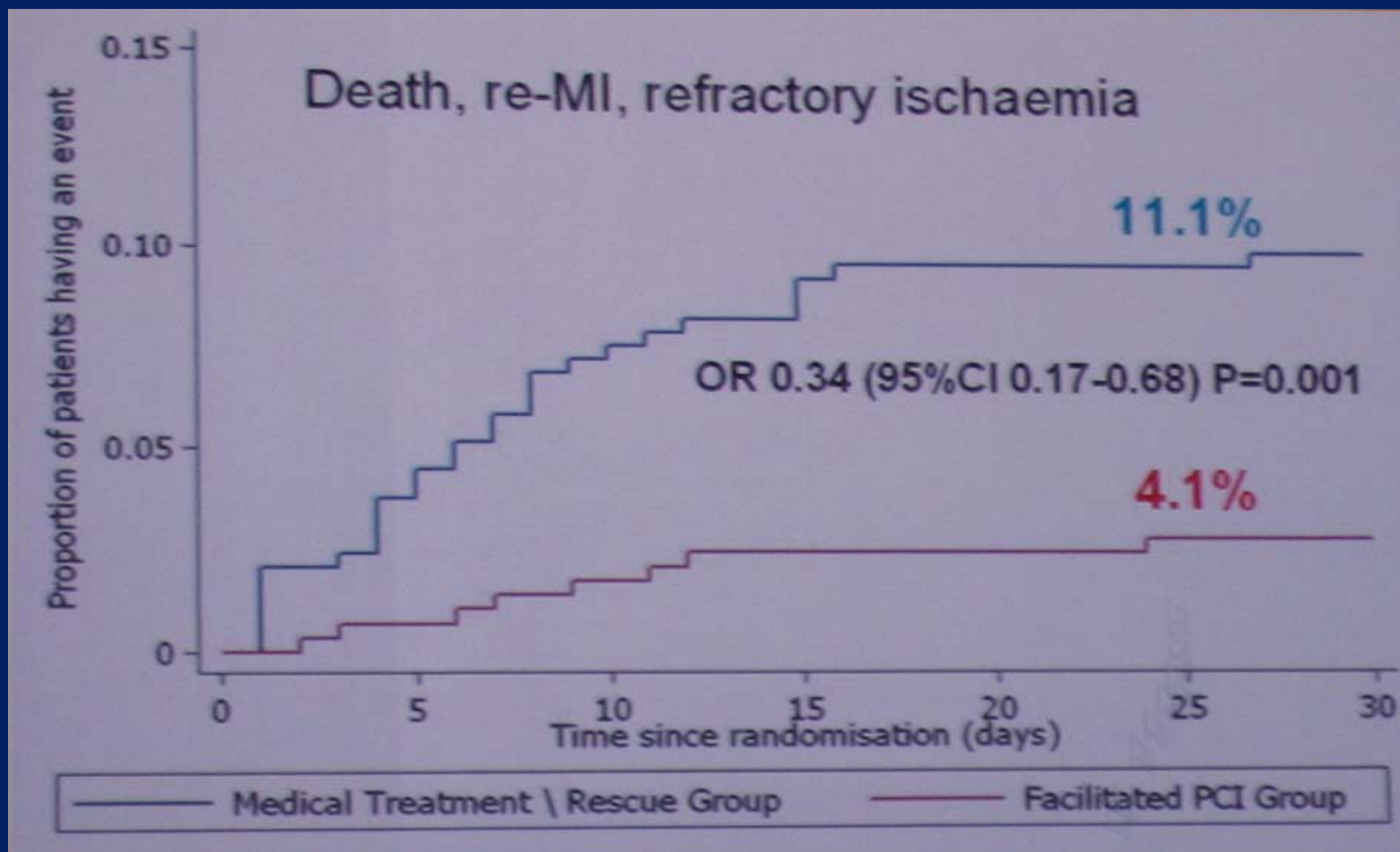


Hospital stay and Pre-discharge Tx

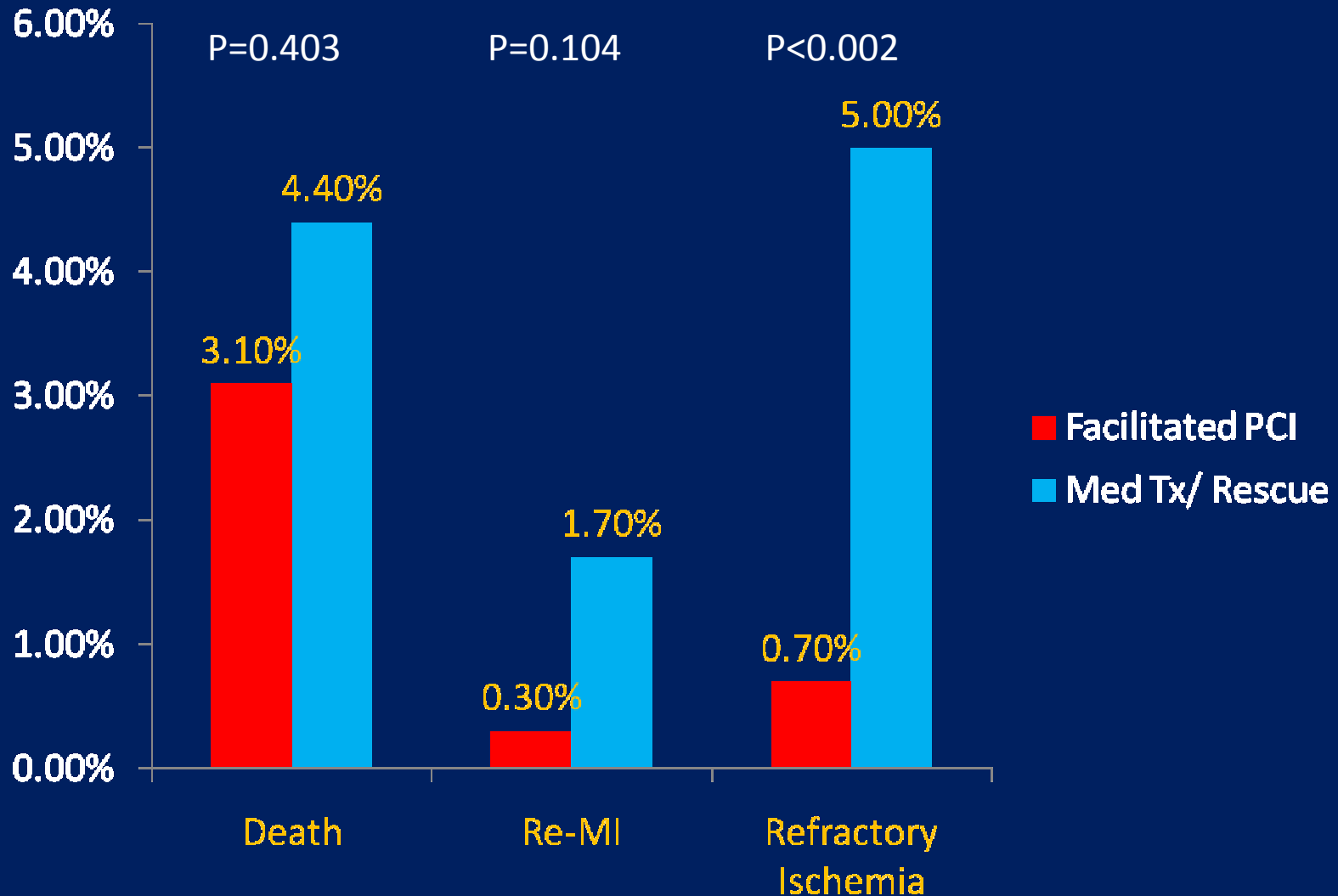
	Facilitated PCI n= 294	Medical /Rescue n= 298	p-value
Length of stay (Median days IQR)	7 (6, 9)	9 (7, 11)	<0.001
Beta blocker*	248 (84.4)	246 (82.5)	0.945
Statin*	262 (89.1)	266 (89.3)	0.304
Clopidogrel/ ticlop*	249 (84.7)	164 (55.0)	<0.001
ACE inhibitor*	259 (88.1)	247 (82.9)	0.230

* Drugs at discharge (%)

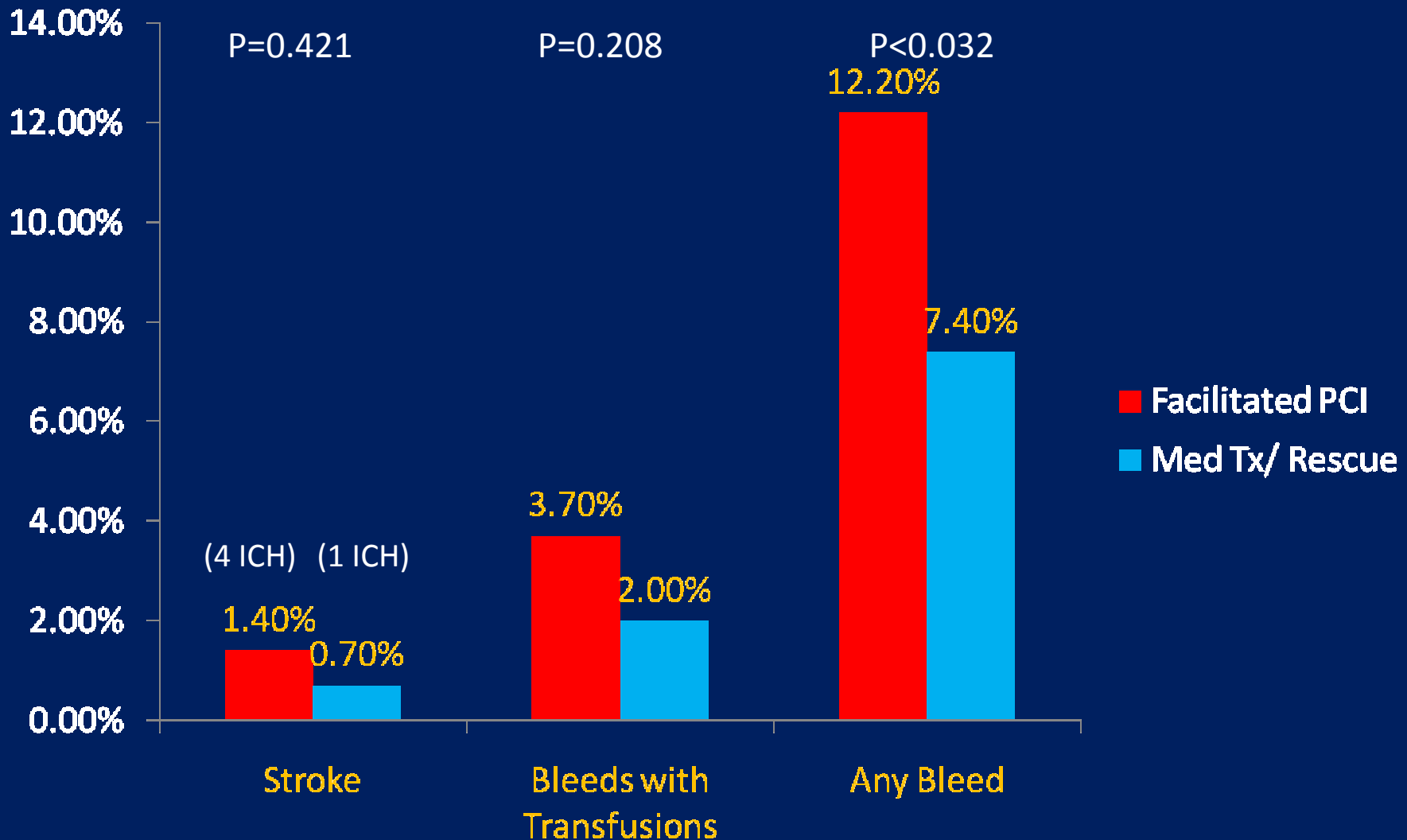
Primary Endpoint @ 30 Days



Individual Endpoints @ 30 Days



Safety Outcome @ 30 Days



Conclusions (1)

- Immediate transfert of high risk STEMI pts treated with half dose Reteplase and Abcx from non-PCI Hospitals to high volume PCI Centers (Facilitated PCI) yields a highly significant **63% proportional reduction of the composite endpoint of Death, re-MI, and refractory Ischemia.**
- The reduction in risk in the facilitated PCI group was **driven largely by refractory Ischemia**, but there were consistent favourable trends for Death and re-MI

Conclusions (2)

- Event reduction was present **despite the use of rescue PCI in more than one third of the control group**
- **Severe Bleeding was rare in both groups** with 0.8% of all patients having an ICH, probably because of the exclusion of older patients and patients at high risk of bleeding

Conclusions (3)

- The **better outcome strikingly contrast with results of other facilitated angioplasty trials**, likely because of the deleterious effect of platelet aggregation of Fibrinolysis was balanced by the simultaneous use of **Abcx**
- This trial **confirms** and expands the indication of the ESC guidelines to **early PCI after lysis**, suggesting that **high risk STEMI** patients should be immediately transferred for PCI after Lysis

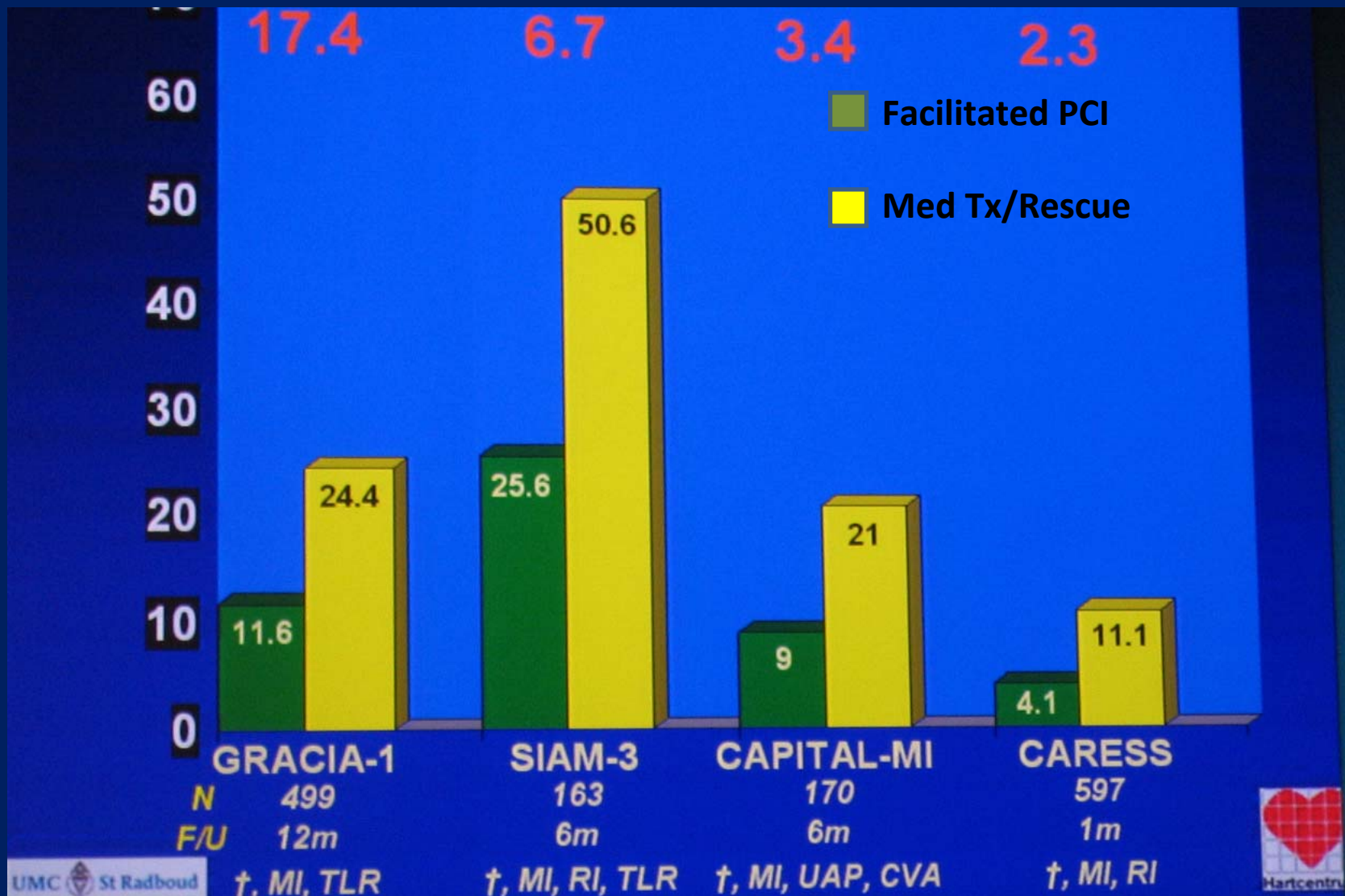
Angioplastie facilitée en 2007

- Sur la base des résultats de FINESSE, ASSENT-4 et de la méta-analyse de Keeley (Lancet 2006), l'angioplastie facilitée n'a pas sa place dans l'infarctus de type STEMI que ce soit par la Fibrinolyse, Fibrinolyse 1/2dose associée aux antiIIbIIIa ou AntiIIbIIIa seuls.

Angioplastie facilitée en 2007

- Si un traitement thrombolytique est administré, dans quelles conditions et quels délais faut-il prévoir une angiographie / PCI au vu des résultats d'ASSENT-4 et FINESSE?

Time Interval Lytic to PCI (Hours)



Angioplastie facilitée en 2007

- Sur la base de la théorie de l'artère ouverte, un traitement pharmacologique fibrinolytique avant l'angioplastie ne peut être bénéfique que pour les patients suivants:

- Présentation précoce <2-3h du début des symptômes
- Menace d'un territoire myocardique important
- Délai prolongé jusqu'à l'angioplastie

Sous pré-traitements antithrombotiques recommandés

Angioplastie différée en cas de flux TIMI 3 après traitement fibrinolytique

Angioplastie facilitée en 2007

**L'angioplastie facilitée cède sa place
à une approche pharmaco-invasive**