STREAM

STRATEGIC REPERFUSION EARLY AFTER MYOCARDIAL INFARCTION

F. Van de Werf, ACC 2013

Frans Van de Werf: Disclosures

- Study grant from Boehringer Ingelheim to perform the STREAM trial , paid to the University of Leuven ,Belgium
- Honoraria from Boehringer Ingelheim for membership of advisory board related to studies with dabigatran in patients with mechanical heart valves

BACKGROUND

- Large registries have demonstrated delays to primary PCI in STEMI patients first presenting to an EMS or a non-cath capable community hospital, requiring subsequent transfer for primary PCI.
- These delays may exceed guideline recommended times and result in a commensurate increase in mobidity and mortality worse.

AIM OF THE STUDY

To compare a strategy of early fibrinolysis followed by coronary angiography within 6-24 hours or rescue PCI if needed
with routine primary PCI
in
STEMI patients presenting within 3 hours after onset of symptoms with at least 2 mm ST-elevation in 2 contiguous leads and who can not undergo primary PCI within 1 hour of first medical contact.

STUDY PROTOCOL

Stream
Strategic Reperfusion Early After Myocardial Infarction

STEMI <3 hrs from onset symptoms, PPCI <60 min not possible, 2 mm ST-elevation in 2 leads

RANDOMIZATION 1:1 by IVRS, OPEN LABEL

Ambulance/ER

Strategy A: bolus tenecteplase

- **<75y:full dose**
  - Aspirin
  - Clopidogrel:
    LD 300 mg + 75 mg QD
  - Enoxaparin:
    30 mg IV + 1 mg/kg SC Q12h
- **≥75y: ½ dose TNK**
  - Aspirin
  - Clopidogrel:
    75 mg QD
  - Enoxaparin:
    0.75 mg/kg SC Q12h

Strategy B: primary PCI

- **no lytic**
- **Antiplatelet and antithrombin treatment according to local standards**

PCI Hospital

ECG at 90 min: ST resolution ≥ 50%

- **YES** → **cor angio >6 to 24 hrs PCI/CABG if indicated**
- **NO** → **immediate cor angio + rescue PCI if indicated**

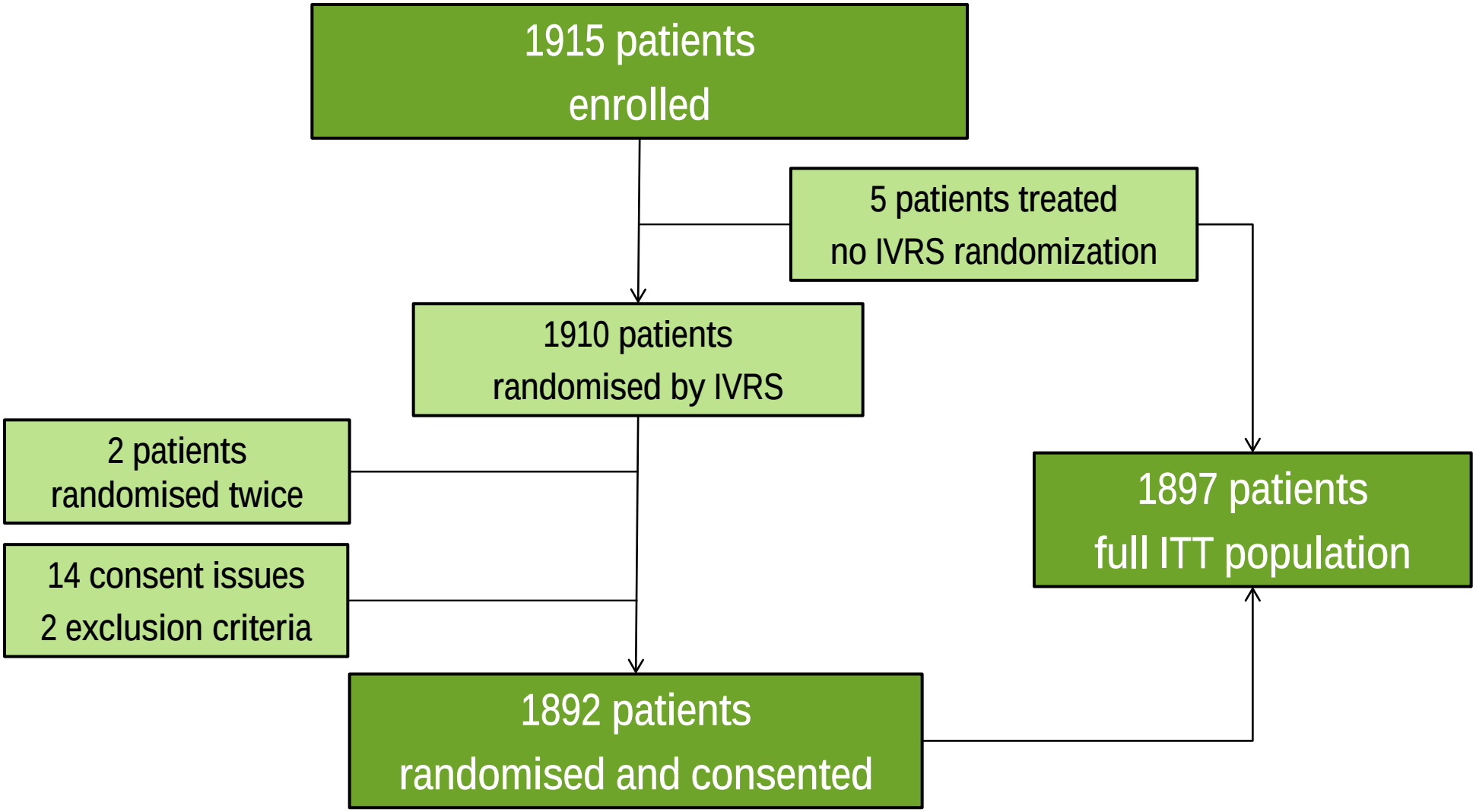
Standard primary PCI

Primary endpoint: composite of all cause death or shock or CHF or reinfarction up to day 30

SAMPLE SIZE AND STATISTICAL ANALYSES

- Around 1000 patients per group was planned
- The rate of the primary endpoint in the primary PCI group was projected to be 15.0%
- There was no formal primary hypothesis
- All analyses are therefore explorative

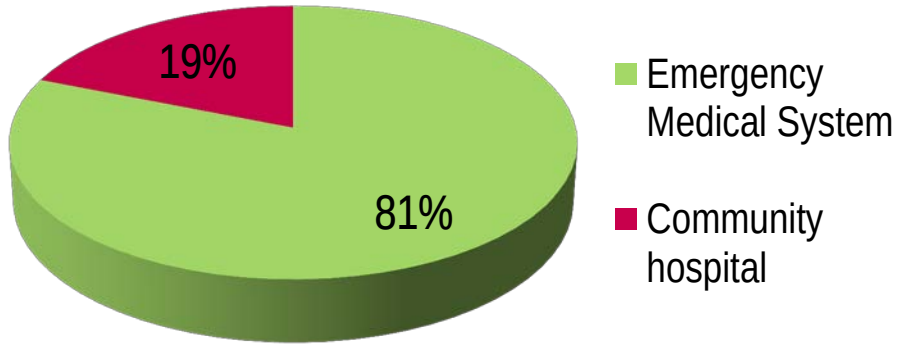
STREAM PATIENTS



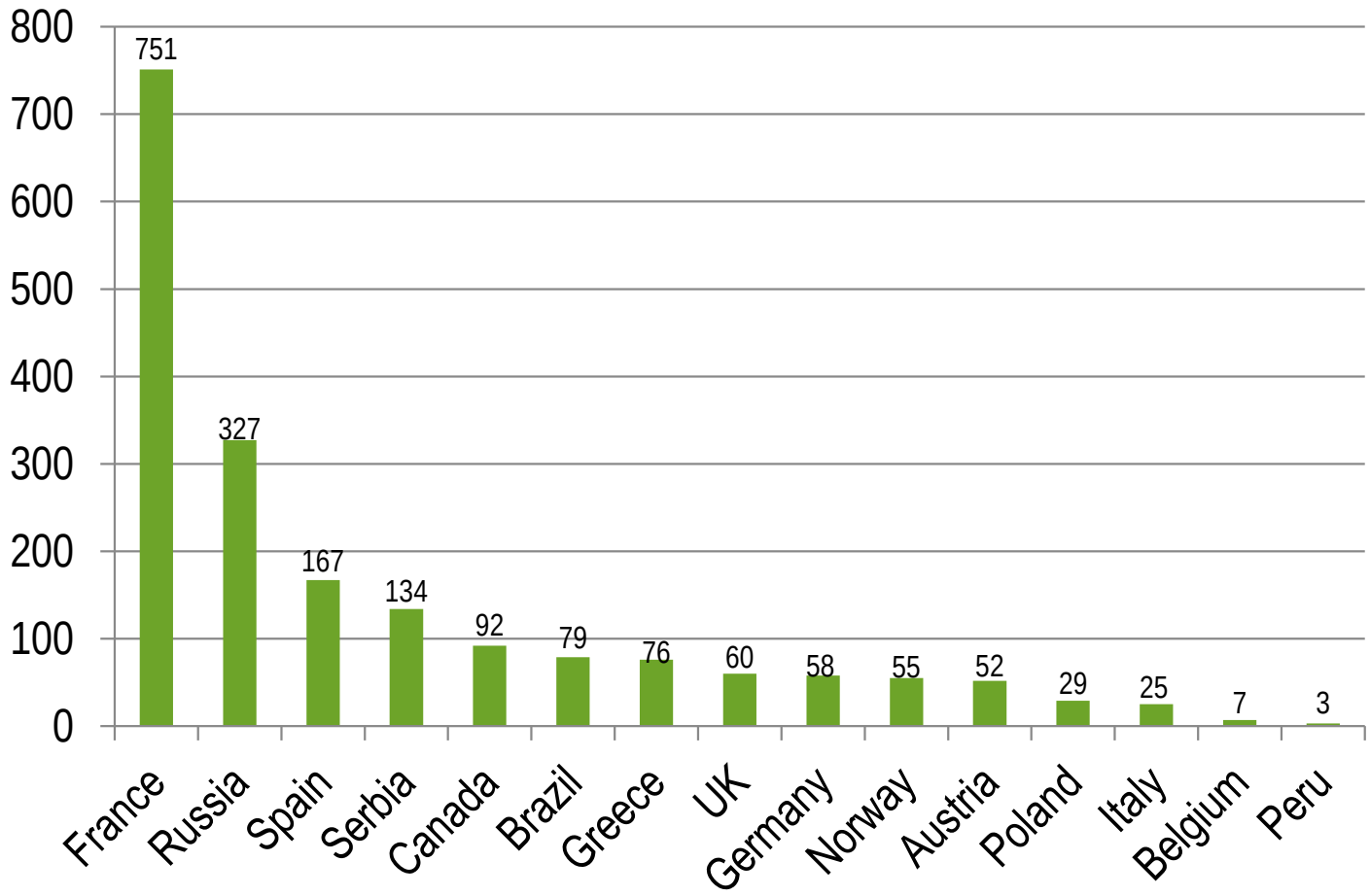
ENROLLMENT AND KEY DATES

- 1892 patients randomized by 99 sites in 15 countries
- First patient in: March 19, 2008
- Last patient in: July 26, 2012
- Last patient out: Sep 7, 2012

Enrolment setting



PATIENTS PER COUNTRY



BASELINE CHARACTERISTICS (1)

		Pharmaco-invasive (N=944)	PPCI (N=948)
Age (yrs)		59.7 (12.4)	59.6 (12.5)
Age >75 y (%)		134/944 (14%)	121/948 (13%)
Women (%)		194/944 (21%)	208/948 (22%)
Weight (kg)		80.5 (14.8)	80.0 (14.9)
Killip class (%)	I II/III IV	842/895 (94%) 52/895 (6%) 1/895 (<1%)	844/894 (94%) 47/894 (5%) 3/894 (<1%)
Heart rate (bpm)		74.9 (18.4)	75.5 (18.1)
Systolic BP (mmHg)		135.0 (22.7)	135.9 (23.3)
Infarct location	Anterior Inferior Other	453/942 (48%) 468/942 (50%) 21/942 (2%)	431/946 (46%) 497/946 (53%) 18/946 (2%)

Data are mean (SD) or number (%)

BASELINE CHARACTERISTICS (2)

%	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
Previous MI	81/940 (9%)	98/947 (10%)	0.20
Previous PCI	60/942 (6.37%)	83/944 (8.79%)	0.06
Previous CABG	2/944 (<1%)	3/946 (<1%)	>0.999
Previous congestive heart failure	3/939 (<1%)	16/945 (2%)	0.004
Hypertension	434/930 (47%)	414/932 (44%)	0.33
Diabetes	113/934 (12%)	123/939 (13%)	0.51

TIME DELAYS

Time difference (min)	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
Onset to first medical contact	62 (40,100)	61 (35,100)	0.36
Onset to randomisation	91 (68,132)	92 (65,132)	0.89
Onset to hospital admission	150 (110,202)	140 (100,185)	<0.001
Onset to start of reperfusion treatment (Tenecteplase or sheath insertion)	100 (75,143)	178 (135,230)	<0.001
Randomisation to arrival at cath lab	483 (135,1140)	67 (45,98)	<0.001
Randomisation to sheath insertion	492 (148,1157)	77 (57,112)	<0.001
Onset to arrival at cath lab	600 (245,1235)	170 (125,220)	<0.001

Time intervals are median (Q1, Q3)

TIME DELAYS

Time difference (hours)	Pharmaco-invasive (N=944)
Randomisation to sheath insertion	
36% required rescue/urgent PCI	2.2 hours (1.8, 2.7)
64% non urgent angiography	17 hours (11, 22)

Time intervals are median (Q1, Q3)

ANGIOGRAPHIC FINDINGS

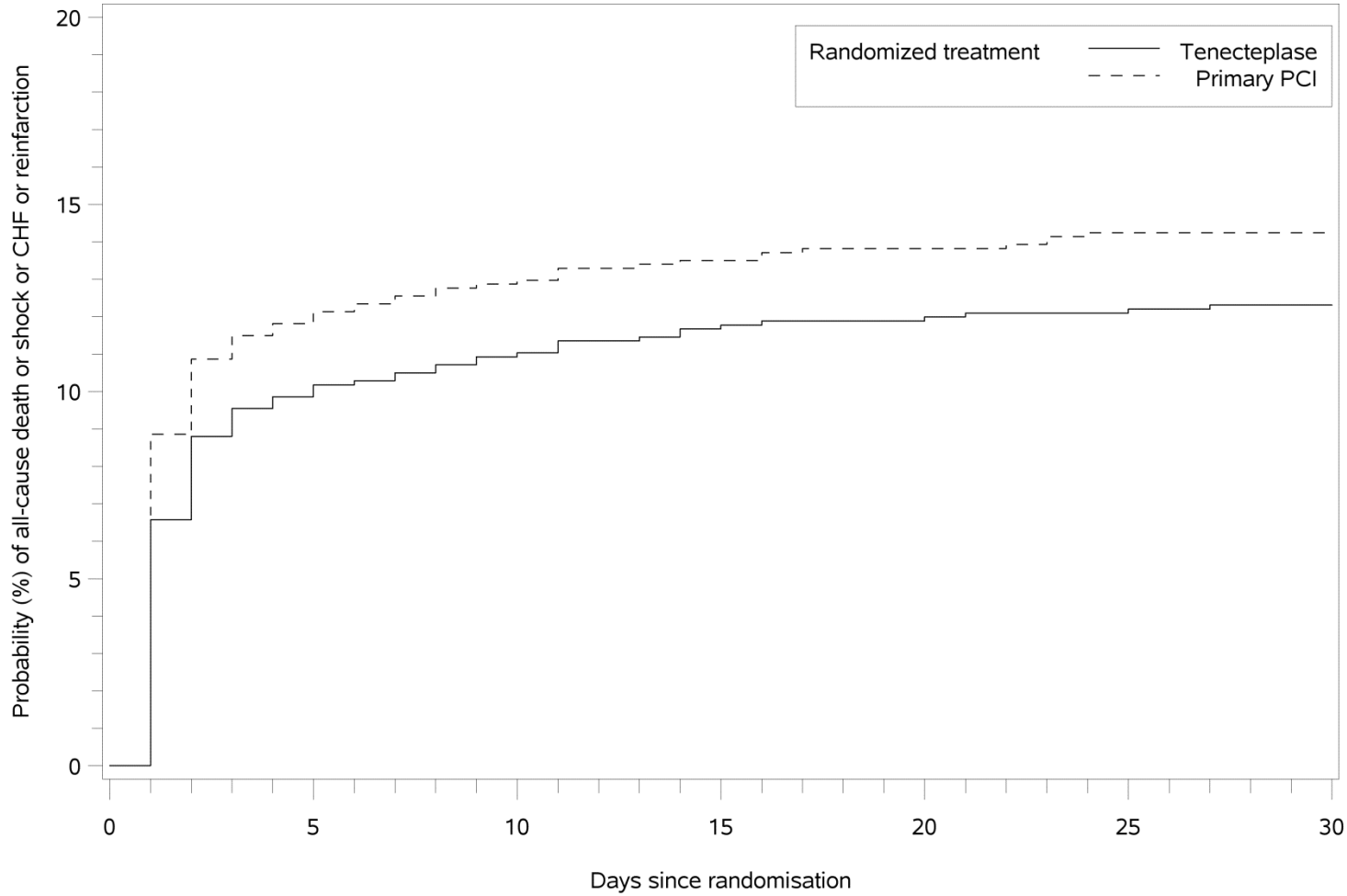
	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
TIMI flow before PCI			<0.001
TIMI 0	141/884 (16%)	534/900 (59%)	
TIMI 1	88/884 (10%)	91/900 (10%)	
TIMI 2	138/884 (16%)	89/9000 (10%)	
TIMI 3	517/884 (58%)	186/900 (21%)	
TIMI flow after PCI			0.41
TIMI 0	18/819 (2%)	24/884 (3%)	
TIMI 1	12/819 (1%)	11/884 (1%)	
TIMI 2	43/819 (5%)	33/884 (4%)	
TIMI 3	746/819 (91%)	816/884 (92%)	
Urgent coronary angiography	331/911 (36.3%)		
PCI performed	736/915 (80%)	838/933 (90%)	<0.001
CABG performed	44/943 (4.7%)	20/947 (2.1%)	0.002
Stents deployed	704/736 (96%)	801/838 (96%)	0.95

PRIMARY ENDPOINT

%	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
All cause death or shock or reMI or CHF	116/939 (12.4%)	135/943 (14.3%)	0.21

The 95 CI of the observed incidence in the pharmaco-invasive arm would exclude a 1.11% absolute or 9% relative excess compared with PPCI

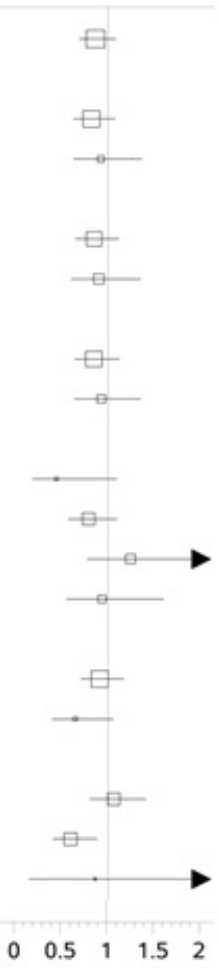
KAPLAN-MEIER CURVES FOR PRIMARY ENDPOINT



Number at risk							
Tenecteplase	943	848	837	829	827	825	823
Primary PCI	948	836	824	818	815	811	811

Subgroup analyses for primary endpoint within 30 days

All cause death or shock or CHF or reinfarction within 30 days	Group A (N=944)	Group B (N=948)	Relative Risk (95% CI)	P-value
Overall event rate	116/ 939 (12.4%)	135/ 943 (14.3%)	0.86 (0.68; 1.09)	0.21
Age [years] (Interaction: p=0.63)				
< 75 (%)	80/ 805 (9.9%)	100/ 823 (12.2%)	0.82 (0.62; 1.08)	0.16
>= 75* (%)	36/ 134 (26.9%)	35/ 120 (29.2%)	0.92 (0.62; 1.37)	0.68
Time to randomisation [hours] (Interaction: p=0.81)				
0-<2 (%)	79/ 642 (12.3%)	93/ 640 (14.5%)	0.85 (0.64; 1.12)	0.24
>=2 (%)	37/ 297 (12.5%)	42/ 303 (13.9%)	0.90 (0.60; 1.36)	0.61
Sex (Interaction: p=0.71)				
Male (%)	77/ 746 (10.3%)	90/ 737 (12.2%)	0.85 (0.63; 1.13)	0.25
Female (%)	39/ 193 (20.2%)	45/ 206 (21.8%)	0.93 (0.63; 1.35)	0.69
Systolic blood pressure [mmHg] (Interaction: p=0.16)				
< 100 (%)	5/ 36 (13.9%)	14/ 44 (31.8%)	0.44 (0.17; 1.10)	0.08
100 to <140 (%)	56/ 465 (12.0%)	68/ 444 (15.3%)	0.79 (0.57; 1.09)	0.15
140 to <160 (%)	34/ 269 (12.6%)	27/ 266 (10.2%)	1.25 (0.77; 2.00)	0.37
>= 160 (%)	21/ 169 (12.4%)	25/ 188 (13.3%)	0.93 (0.54; 1.61)	0.81
Killip class (Interaction: p=0.23)				
I (%)	95/ 838 (11.2%)	104/ 839 (12.4%)	0.91 (0.70; 1.17)	0.46
II - IV (%)	16/ 52 (30.8%)	24/ 50 (48.0%)	0.64 (0.39; 1.06)	0.08
Infarct location (Interaction: p=0.06)				
Anterior (%)	80/ 449 (17.8%)	72/ 429 (16.8%)	1.06 (0.79; 1.42)	0.69
Inferior (%)	34/ 467 (7.3%)	61/ 494 (12.3%)	0.59 (0.40; 0.88)	0.01
Other (%)	2/ 21 (9.5%)	2/ 18 (11.1%)	0.86 (0.13; 5.48)	0.87



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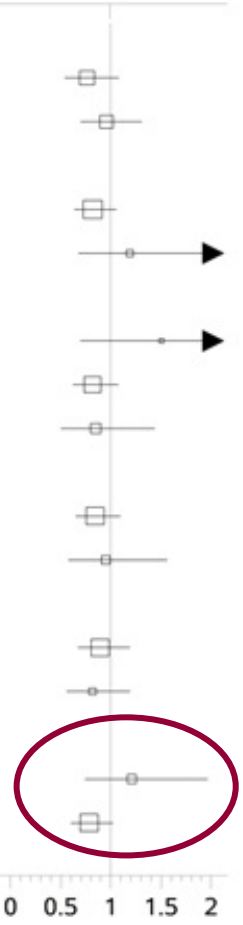
Subgroup analyses for primary endpoint up to 30 days

All cause death or shock or CHF or reinfarction within 30 days	Group A (N=944)	Group B (N=948)	Relative Risk (95% CI)	P-value
Hypertension (Interaction: p=0.34)				
No (%)	48/ 494 (9.9%)	67/ 516 (13.0%)	0.76 (0.54; 1.08)	0.12
Yes (%)	65/ 431 (15.2%)	66/ 412 (15.9%)	0.96 (0.70; 1.31)	0.78
Diabetes (Interaction: p=0.24)				
No (%)	93/ 816 (11.6%)	115/ 813 (14.1%)	0.82 (0.63; 1.06)	0.12
Yes (%)	21/ 113 (18.5%)	19/ 122 (15.6%)	1.19 (0.68; 2.09)	0.55
Weight [kg] (Interaction: p=0.35)				
<60 (%)	12/ 47 (25.5%)	9/ 53 (17.0%)	1.50 (0.70; 3.25)	0.30
60 to <90 (%)	81/ 648 (12.5%)	99/ 647 (15.3%)	0.82 (0.62; 1.07)	0.15
>=90 (%)	23/ 244 (9.4%)	27/ 243 (11.1%)	0.85 (0.50; 1.44)	0.54
Place of randomization (Interaction: p=0.68)				
Ambulance (%)	91/ 764 (11.9%)	107/ 757 (14.1%)	0.84 (0.65; 1.09)	0.20
Community hospital (%)	25/ 175 (14.3%)	28/ 186 (15.1%)	0.95 (0.58; 1.56)	0.84
Timi risk score (Interaction: p=0.71)				
< 5 (%)	73/ 749 (10.0%)	82/ 745 (11.2%)	0.89 (0.67; 1.19)	0.43
>= 5 (%)	31/ 114 (28.2%)	41/ 118 (34.6%)	0.82 (0.56; 1.19)	0.29
Time of randomization (Interaction: p=0.13)				
Before Amendment (%)	31/ 192 (16.1%)	25/ 187 (13.4%)	1.21 (0.74; 1.97)	0.45
After Amendment (%)	85/ 747 (11.4%)	110/ 756 (14.6%)	0.78 (0.60; 1.02)	0.07



SINGLE ENDPOINTS UP TO 30 DAYS

%	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
All death	43/939 (4.6%)	42/946 (4.4%)	0.88
Cardiac death	31/939 (3.3%)	32/946 (3.4%)	0.92
CHF	57/939 (6.1%)	72/943 (7.6%)	0.18
Cardiogenic shock	41/939 (4.4%)	56/944 (5.9%)	0.13
Reinfarction	23/938 (2.5%)	21/944 (2.2%)	0.74
Rehosp cardiac reason	45/939 (4.8%)	41/943 (4.3%)	0.64

STROKE RATES UP TO DAY 30

%	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
Total stroke (all types)	15/939 (1.6%)	5/946 (0.5%)	0.03
Intracranial haemorrhage	9/939 (1.0%)	2/946 (0.2%)	0.04
after amendment 2*:	4/747 (0.5%)	2/758 (0.3%)	0.45
Primary ischaemic stroke without haemorrhagic conversion	5/939 (0.5%)	3/946 (0.3%)	0.51

*Amendment 2 (Aug 2009): dose reduction of tenecteplace by 50% in patients 75 years of age or older

STROKE RATES UP TO DAY 30

	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
Total population			
Total stroke	15/939 (1.60%)	5/946 (0.53%)	0.03
Fatal stroke	7/939 (0.75%)	4/946 (0.42%)	0.39
ICH	9/939 (0.96%)	2/946 (0.21%)	0.04
Fatal ICH	6/939 (0.64%)	2/946 (0.21%)	0.18
Post amemdment population(n=1505)			
Total stroke	9/747 (1.20%)	5/758 (0.66%)	0.30
Fatal stroke	3/747 (0.40%)	4/758 (0.53%)	>0.999
ICH	4/747 (0.54%)	2/758 (0.26%)	0.45
Fatal ICH	2/747 (0.27%)	2/758 (0.26%)	>0.999

IN-HOSPITAL BLEEDING COMPLICATIONS

%	Pharmaco-invasive (N=944)	PPCI (N=948)	P-value
Major non-ICH bleed	61/939 (6.5%)	45/944 (4.8%)	0.105
Minor non-ICH bleed	205/939 (21.8%)	191/944 (20.2%)	0.395
Blood transfusions	27/937 (2.9%)	22/943 (2.3%)	0.473

CONCLUSIONS

Fibrinolysis with bolus tenecteplase and contempory antithrombotic therapy given before transport to a PCI-capable hospital coupled with timely coronary angiography

- is as effective as primary PCI in STEMI patients presenting within 3 hours of symptom onset who cannot undergo primary PCI within one hour of first medical contact.
- is associated with a small increased risk of intracranial bleeding.
- provides the opportunity for a measured approach to invasive coronary interventions, circumventing an urgent procedure in about two thirds of fibrinolytic treated STEMI patients.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

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