Primary Angioplasty versus Fibrinolysis in the Very Elderly

TRIANA

TRatamiento del Infarto Agudo de miocardio eN Ancianos

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on behalf of the

Working Group on Ischemic Heart Disease and CCUs

Working Group on Interventional Cardiology

Spanish Society of Cardiology

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TRIANA Study Organization

Sponsor: Spanish Society of Cardiology
WG on Ischemic Heart Disease & CCUs
WG on interventional Cardiology

Steering Committee: Héctor Bueno (chair), Rosana Hernández-Antolín (co-chair), Joaquín J. Alonso, Amadeo Betriu, Angel Cequier, Eulogio J. Garcia, Magda Heras, Jose L. Lopez-Sendon, Carlos Macaya

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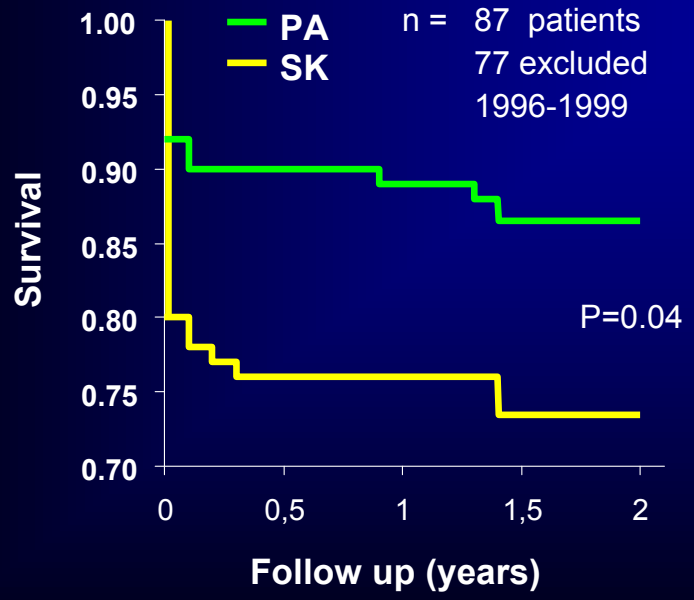
- Sanofi-Aventis
- Boston Scientific
- Guidant
- Johnson & Johnson
- Medtronic

Background

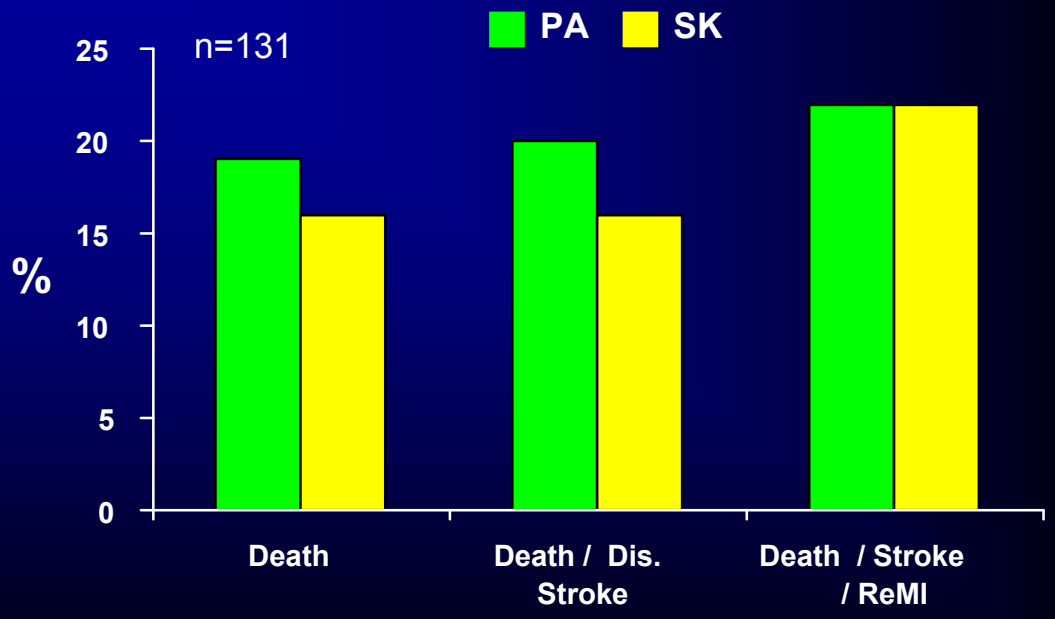
- Increasing population aging
- Very old patients with STEMI more frequently admitted to CCUs
- Primary PCI preferred therapy for STEMI patients in general
- Scarce direct evidence for both reperfusion strategies in patients >75 years old

Zwolle RCT in patients ≥75 years old



De Boer MJ. *J Am Coll Cardiol* 2002;39:1723-28.

Senior PAMI – Subgroup Age ≥80 years

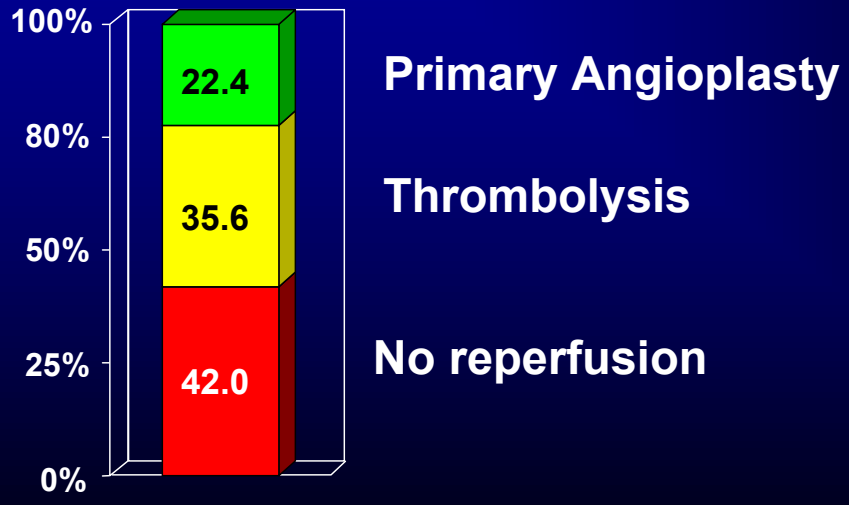


Grines C. Personal Communication. *TCT,* Washington, 2005

Background

- Increasing population aging
- Very old patients with STEMI more frequently admitted to CCUs
- Primary PCI preferred therapy for STEMI patients in general
- Scarce direct evidence for both reperfusion strategies in patients >75 years old
- Thrombolysis still the most frequently reperfusion therapy used over the world, including older patients

TRIANA Pilot Study
Spanish Survey
26 Hospitals with active PA program
March – July 2002
410 consecutive patients ≥75 years



Bardají A. *Rev Esp Cardiol* 2005;58:351-8.

Study Rationale

Therefore, the current state of reperfusion strategies for AMI patients older than 75 years satisfies a primary rationale for randomized trials: clinical uncertainty about the best course of action. This problem can no longer be neglected.

Ideally, new randomized trials of reperfusion therapies would focus on patients older than 75 years who present with AMI and overcome prior obstacles to such research.

Ayanian JZ, Braunwald E. *Circulation* 2000;101:2224-6.

there is a desperate need for definitive, community-based, multicenter trials comparing intravenous thrombolytic treatment with primary percutaneous transluminal coronary angioplasty in elderly patients, both within tertiary hospitals and after emergent transfer

Thiemann DR. *J Am Coll Cardiol* 2002;39:1729–32.

Results from ongoing randomized trials such as Senior PAMI will be essential in guiding future therapies for the growing elderly populatior

Keeley EC, de Lemos JA. *Eur Heart J* 2005;26:1693–4.

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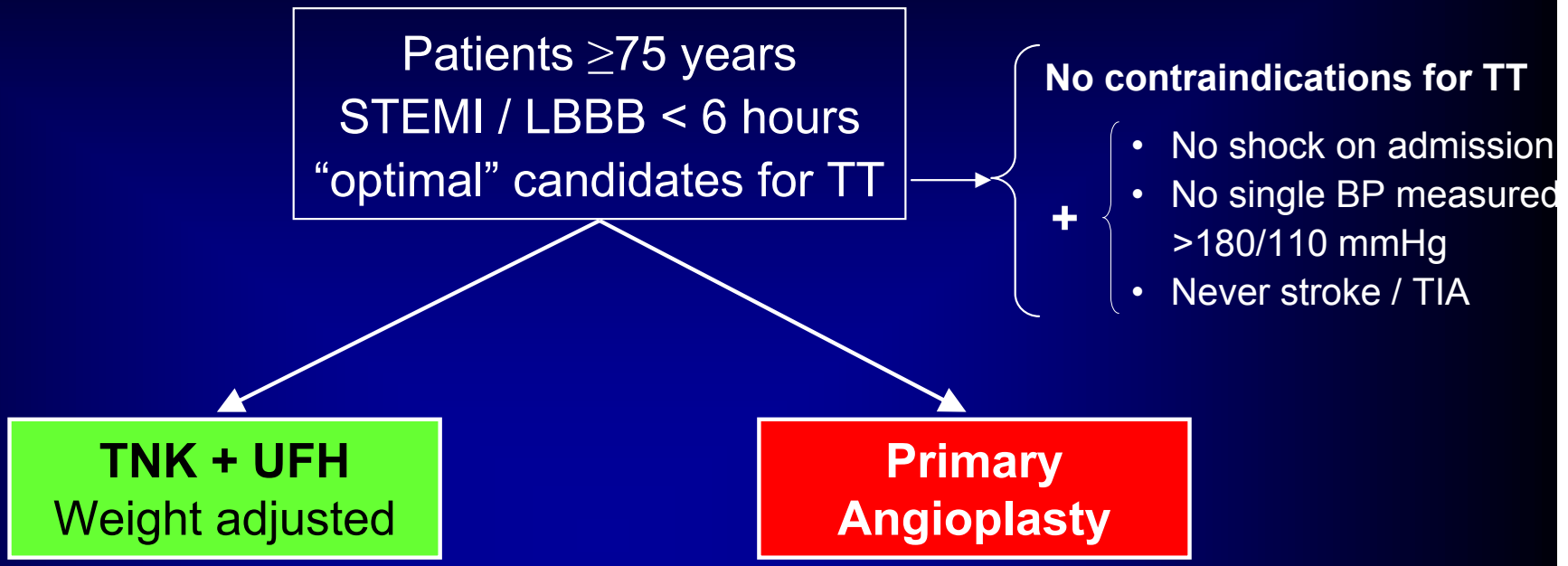
Study Objective

To compare the efficacy and safety of primary angioplasty and fibrinolytic treatment in patients ≥75 years-old with STEMI who are eligible for thrombolytic therapy in Spanish medical centres with an active program of primary angioplasty

Study Design



Tenecteplase (TNK): Single weight-adjusted bolus

Anticoagulation with **UFH:**
Bolus 60 U/kg (maximum 4000 U)
Infusion for aPTT x 1,5-2 (maximum 1000 U/h)

Clopidogrel (since Dec 06) → 75 mg/day x 28 days

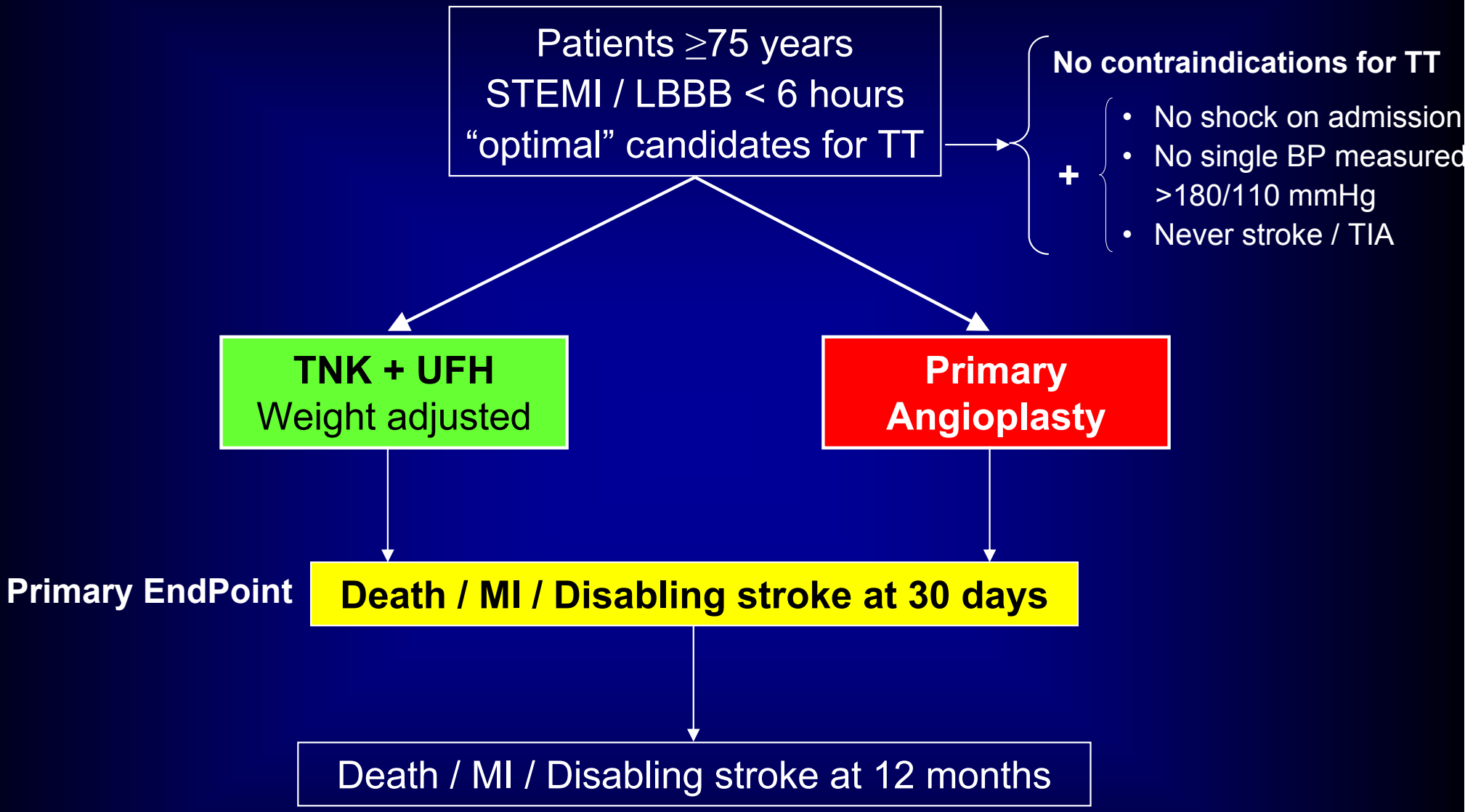
Rescue PCI if no reperfusion criteria
↓>50% ST segment at 90´ + clínical data
→ Urgent PCI (GPI discouraged)

Coronary revascularisation only if evidence of recurrent myocardial ischemia (spontaneous/provoked)

UFH	60 U/Kg (maximum 4000 IU)
Abciximab	Dependent on operator´s decission
Clopidogrel	LD dose 300 mg + MD 75 mg/day

www.clinicaltrials.gov

Study Design



www.clinicaltrials.gov

Analysis

Sample size: 570 patients needed to detect with 80% power a 40% RRR (8.9% absolute risk difference)

Randomisation: 24 hour central randomisation

Analysis: Intention to treat

Follow-up: Local - 100%

End Point Adjudication: Blinded, by independent committee

Endpoints

Primary

Incidence of the composite all-cause death, re-infartion or disabling stroke at 30 days

Secondary

- Recurrent ischemia requiring emergency cath at 30 days
- All-cause mortality at 30 days
- Cause of death at 30 days (pump failure/mechanical comp/other)
- Death, disabling stroke or new HF at 30 days
- Major bleeding during hospital admission

- All-cause mortality at 12 months
- Time to death, reinfarction or disabling stroke during FU
- Time to death, reinfarction, disabling stroke or non-elective hospital readmission for cardiac causes during FU

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Inclusion Criteria

1. Subjects **≥ 75 years of age or older**
2. **Diagnosis of STEMI**: chest pain or any symptom of myocardial ischemia of, at least, 20 minutes of duration, not responding to nitrate therapy, within first 6 hours from symptom onset and, at least, one of the following:
    - ST-elevation ≥ 2 mm in 2 or more precordial leads
    - ST-elevation ≥ 1 mm in 2 or more anterior leads
    - De *novo* (or probably *de novo*) LBBB
3. **Informed consent**

Exclusion Criteria

1. Documented contraindication to the use of thrombolytics
    - Internal active bleeding or known history of hemorrhagic diathesis
    - History of previous stroke of any kind or at any time
    - Intracranial tumor, arteriovenous malformation, aneurysm or cerebral aneurysm repair
    - Major surgery, parenchymal biopsy, ocular surgery or severe trauma within 6 weeks prior to randomisation
    - Unexplained puncture in a non-compressible vascular location in the last 24 hours prior to randomisation
    - Confirmed arterial hypertension during the acute phase, previous to randomisation, with one reliable measurement of systolic BP >180 mmHg or diastolic BP >110 mmHg
    - Known thrombocytopenia < 100.000 platelets/μL
    - Prolonged (>20 minutes) or traumatic cardiopulmonar resuscitation in the 2 weeks prior to randomisation
    - Symptoms or signs suggesting aortic dissection

Exclusion Criteria

2. Cardiogenic shock
3. Estimated door-to-balloon time >120 minutes
4. Administration of thrombolysis within 14 days prior to randomisation
5. Administration of any GP IIa/IIIb inhibitor within 24 hours prior to randomisation
6. Administration of any LMWH within 8 hours prior to randomization
7. Current oral anticoagulant treatment
8. Suspected AMI secondary to occlusion of a coronary lesion treated previously with PCI (within previous 30 days for conventional stents and within previous 12 months for DES)
9. Dementia or acute confusional state at the time of randomisation
10. Incapacity/unwillingness to give informed consent
11. Known renal failure (basal creatinine> 2,5 mg/dl)
12. Reduced expected life expectancy (<12 months)
13. Participation in another RCT trial within previous 30 days

Results: Recruitment

- Study initiated in March 2005
- 23 hospitals participated
- 266 patients were recruited
- Study interrupted in December 2007 for slow recruitment

Results: Baseline Characteristics

	Thrombolysis n=134	Primary PCI n=132
Age (years)	81.2 ± 4.6	81.0 ± 4.3
Gender (% males)	56.1	56.7
Risk Factors (%)		
HTN	59.1	67.9
Dyslipidemia	27.3	41.8 *
Diabetes	34.1	26.1
Current smoker	15.2	11.2
Previous CVD (%)		
MI	7.6	9
Stable angina	13.6	10.4
PCI	3.8	5.2
CHF	0.8	1.5
PAD	9.1	10.4

*p=0.013

Results: Baseline Characteristics

	Thrombolysis n=134	**Primary PCI** n=132
Time to randomisation (min)	180 (135 - 255)	180 (135 - 262)
Admission SBP (mmHg)	132 ± 23	136 ± 25
Admission DBP (mmHg)	74 ± 13	75 ± 16
Admission HR (bpm)	73 ± 18	76 ± 18
Killip class (% I / II / III)	82 / 15 / 3	84 / 11 / 3
Anterior location (%)	49	42
Baseline Creatinine (mg/dl)	1.13 ± 0.34	1.09 ± 0.36
Baseline Glucose (mg/dl)	176 ± 75	167 ± 81
Baseline Hemoglobin (g/dl)	13.7 ± 1.9	13.8 ± 1.6

Results: Management

	Thrombolysis n=134	Primary PCI n=132	
Times (min)			
Door to treatment	52 (32 - 72)	99 (73 - 131)	*
Randomisation-treatmet	10 (5 - 15)	59 (35 - 75)	*
Symptom onset-treatment	195 (150 - 270)	245 (191 - 310)	*
Dose TNK (mg)	37 ± 6.1	-	
UFH(%)	78	-	
Dose UFH bolus (U)	3851 ± 729	-	
Effective reperfusion (%)	74	-	
Urgent cath (%)	16	-	
Rescue PCI (%)	15	-	

*p<0.001

Results: Angiographic results and management

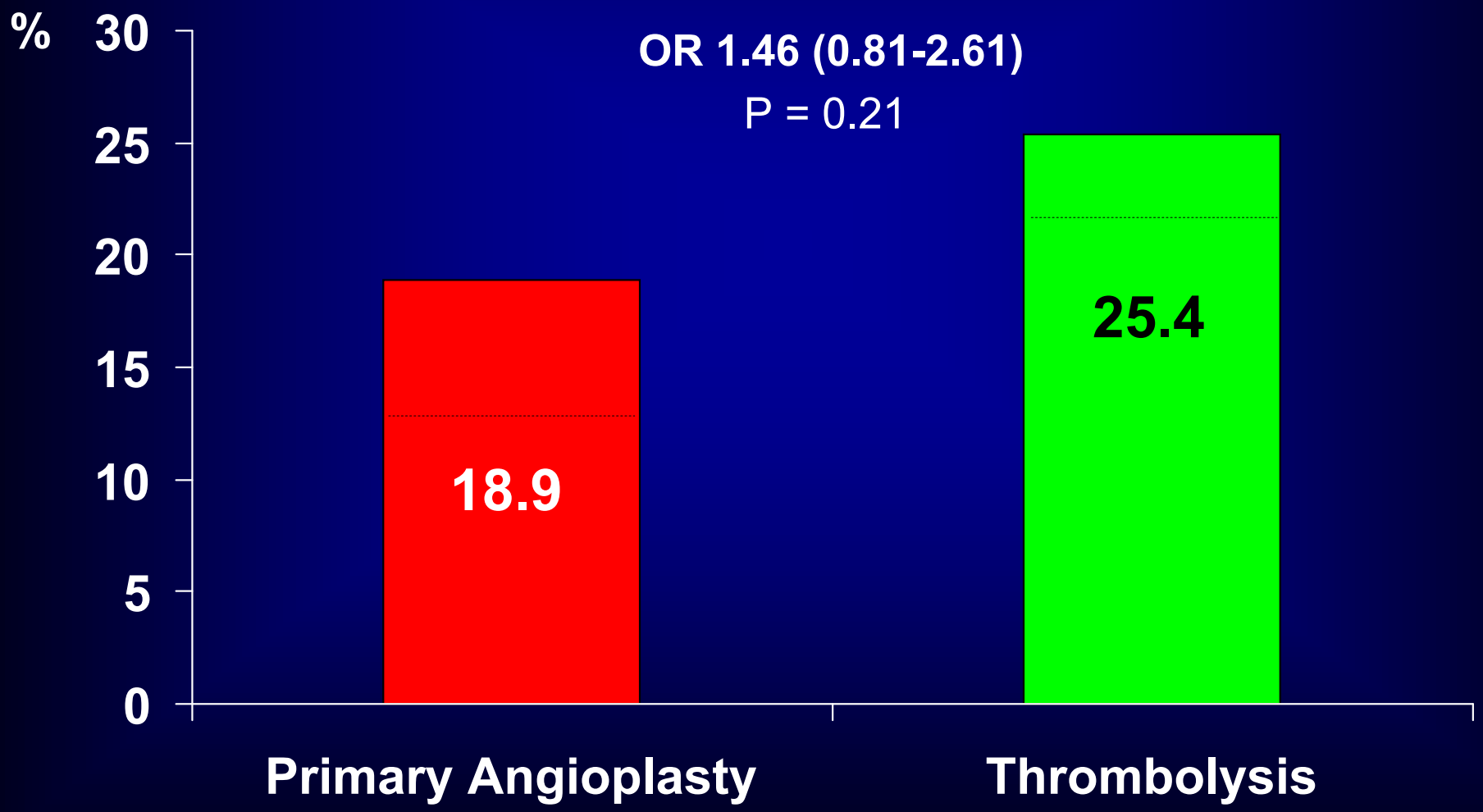
	Thrombolysis n=134	Primary PCI n=132
IRA: LM/LAD/CX/RCA (%)	-	1 / 42 / 14 / 37
Pre-PCI lesion stenosis (%)	-	96.4 ± 11.6
TIMI flow pre-PCI 0/1/2/3 (%)	-	67 / 13 / 11 / 9
Stent (%)	-	84
Dose UFH (U)	-	5069 ± 1793
GP Ib/IIIA inhibitors (%)	-	44
IABP (%)	-	4.5
Post PCI stenosis (%)	-	10.6 ± 25
TIMI flow post-PCI (% 0/1/2/3)	-	6 / 2 / 10 / 82

Results: In-hospital treatments

	Thrombolysis n=134	Primary PCI n=132	
Aspirin	97	96	
Clopidogrel	**63**	**92**	<0.001
UFH	98	96	
LMWH	**37**	**54**	0.006
GP IIb/III inhibitors	**8**	**44**	0.003
iv GTN	**68**	**50**	0.004
Beta-blockers	76	77	
ACEI	86	82	
Statins	87	89	
Diuretics	45	50	
Nitrates	41	37	
Inotropic agents	16	20	

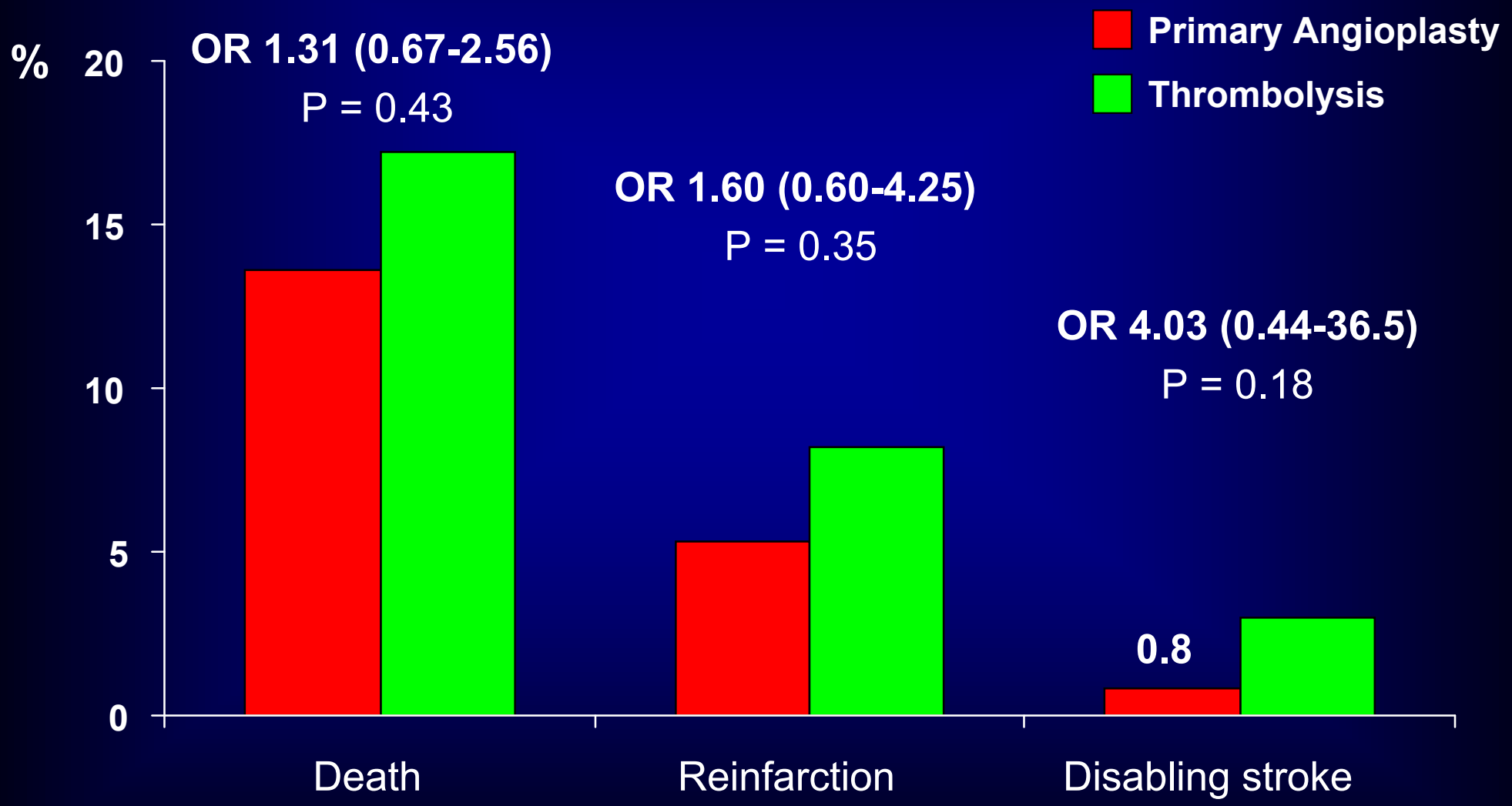
Results: Primary Endpoint

Death, reinfarction or disabling stroke incidence at 30 days

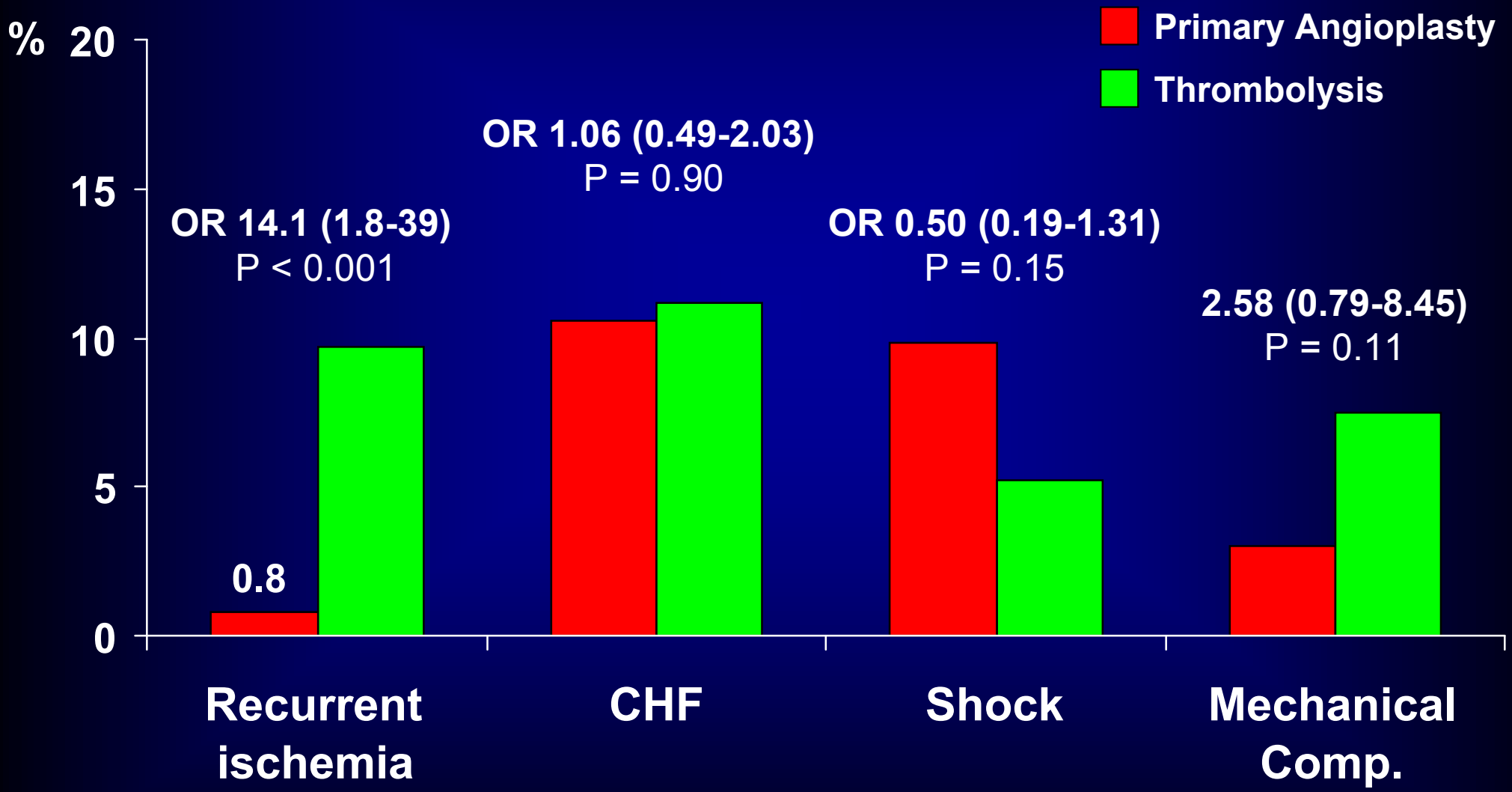


Results: Primary Endpoint components

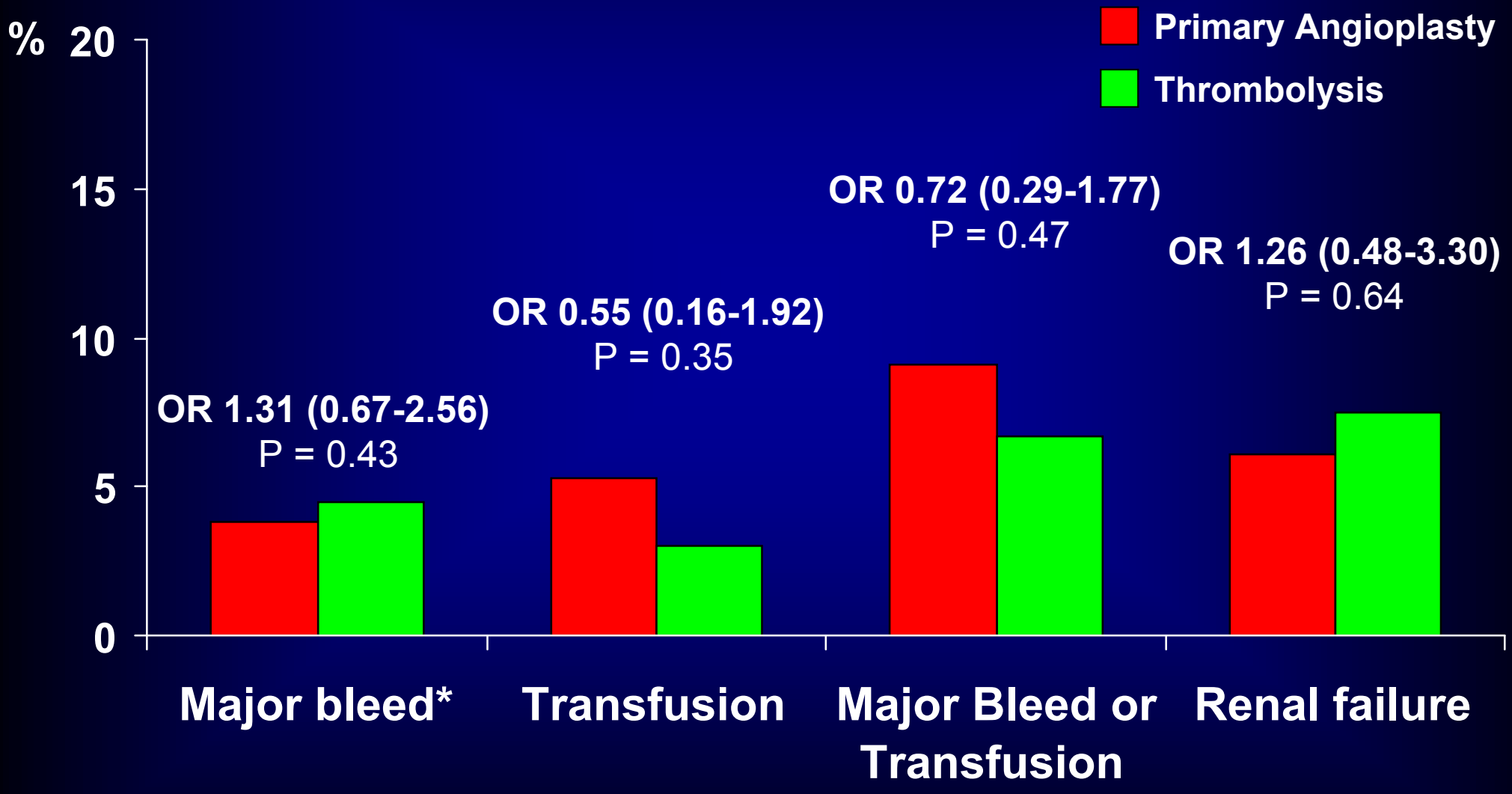
Death, reinfarction or disabling stroke incidence at 30 days



Results: Other outcomes



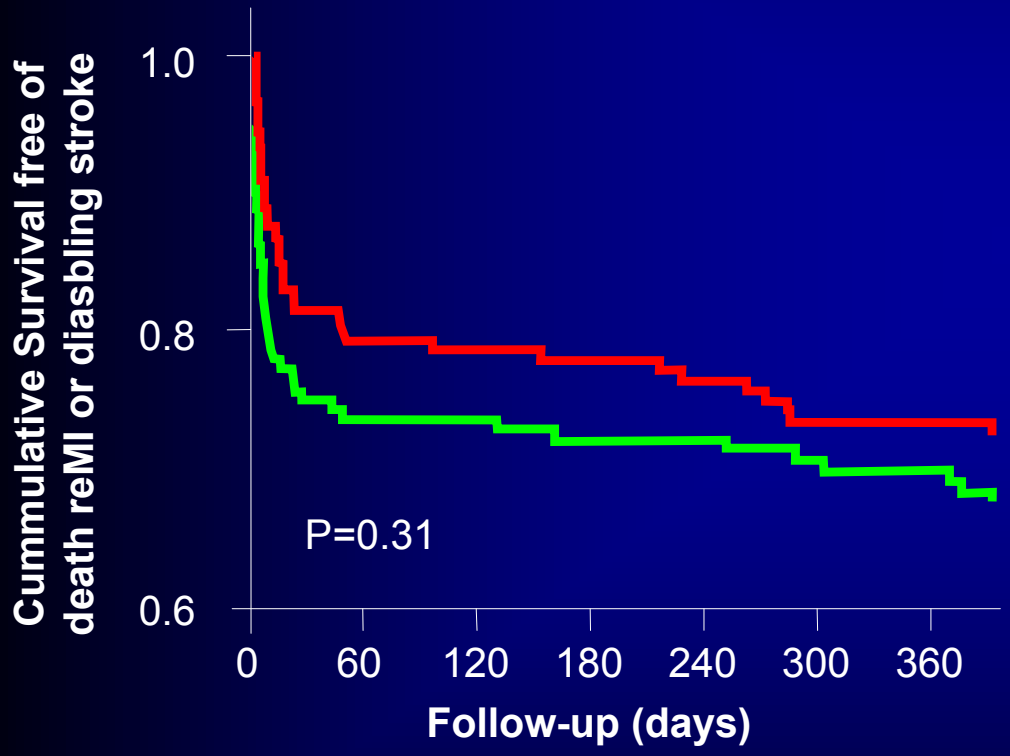
Results: Safety outcomes



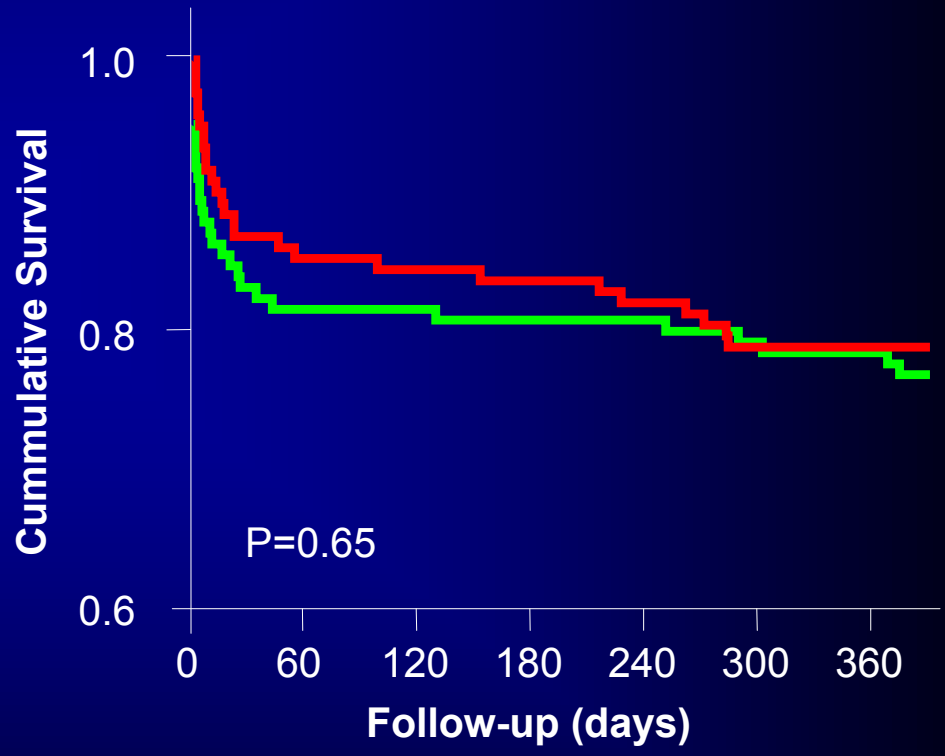
* One ischemic stroke in TT arm at day 7, after elective PCI → hemorrhaghic conversion 24 hours later

Results: 12-month outcomes

Composite endpoint



All-cause mortality



Results: 12-month outcomes

	Thrombolysis n=134	Primary PCI n=132	OR (95%CI)
Death/ReMI/Disabling stroke	32.1	27.3	1.26 (0.74-2.14)
Death	23.1	21.2	1.12 (0.63 - 1.99)
ReMI	10.4	8.3	1.28 (0.56 - 2.9)
Disabling stroke	3.0	0.8	4.03 (0.44 - 36.5)
Urgent rehospitalisation	14.3	13.7	1.05 (0.52 – 2.1)
Recurrent ischemia	11.9	0.8	17.8 (2.3 – 136.0)
New HF	14.9	14.4	1.04 (0.53 – 2.1)
Major bleeding	5.2	6.1	0.85 (0.3 - 2.43)

Conclusions

- TRIANA did not prove (due to lack of power), but is consistent with, a superiority of primary angioplasty in reducing death, reinfarction and disabling stroke compared with thrombolysis in very old patients with STEMI.
- Primary angioplasty is superior to thrombolysis in reducing reintervention due to recurring ischemia.
- Whether the potential early advantage of primary angioplasty is mantained during follow-up needs to be explored
- Thrombolysis can be performed with an acceptable risk of intracerebral bleeding in such patients

Participating Investigators and Centers

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Definitions (1)

Reinfarction

Within first 24 hours: Recurrent symptoms of ischemia at rest accompanied by new or recurrent ST-elevation > 0.1 mV in, at least, 2 or more adjacent leads for at least 30 minutes.

After first 24 hours: Presence of new Q-waves in 2 or more leads or increase of CK, CK-MB or troponine levels higher than the upper limit of normal or greater than anticipated levels.

Disabling stroke: Presence of new permanent focal or generalized neurologic symptoms affecting the normal life of a patient, associated to abnormal findings in CT scan or MRI (ischemic or hemorrhagic lesions)

Heart failure: Presence of new symptoms/signs after the first 24 hours suggesting heart failure (dyspnea, orthopnea, S3, rales on pulmonary auscultation associated to signs of pulmonary congestion in chest X.-ray)

Recurrent ischemia: Cardiac catheterization indicated for angina with ST-segment deviation or T-wave inversion, provided that reinfarction criteria are not fulfilled.

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Definitions (2)

Shock: presence of hypotension (systolic blood pressure < 90 mmHg without body fluids response accompanied with signs of low cardiac output)

Mechanical complication: Clinical evidence of severe mitral regurgitation secondary to total/partial rupture of a papillary muscle, rupture of intraventricular septum or rupture of left ventricular free wall confirmed by any diagnostic technique.

Major bleeding: Cerebral hemorrhage or any bleeding associated with a hemoglobin drop ≥ 5 gr/dL, or an absolute hematocrit drop ≥15%