

# Primary Angioplasty versus Fibrinolysis in the Very Elderly

## TRIANA

*TR*atamiento 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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# 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

**DSMB:** José Azpitarte (chair)

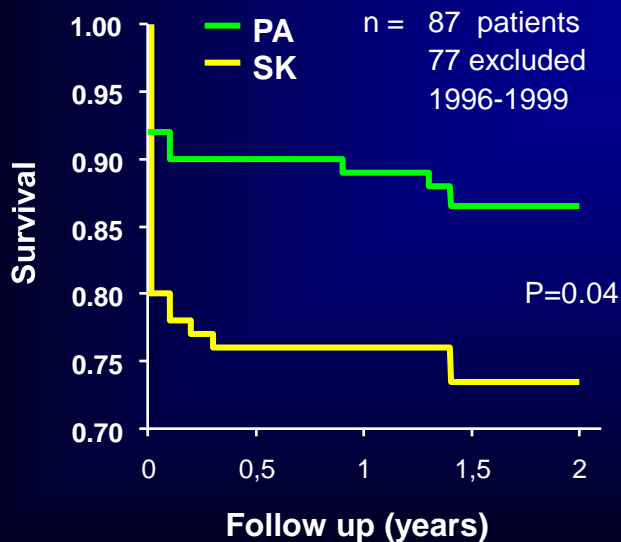
**Adjudication Committee:** Ginés Sanz (chair), Angel Chamorro, Ramón López-Palop, Alex Sionis, Fernando Arós

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- and unrestricted grants from:
- Sanofi-Aventis
  - Boston Scientific
  - Guidant
  - Johnson & Johnson
  - Medtronic

- 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



Senior PAMI – Subgroup Age ≥80 years



- 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

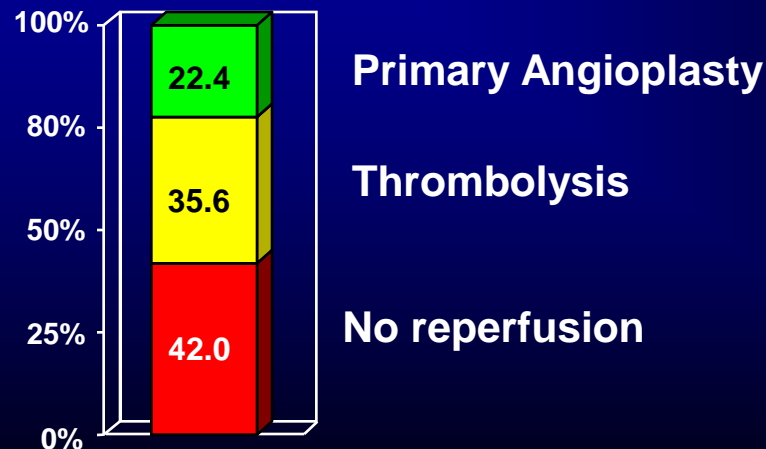
### TRIANA Pilot Study

Spanish Survey

26 Hospitals with active PA program

March – July 2002

410 consecutive patients ≥75 years



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

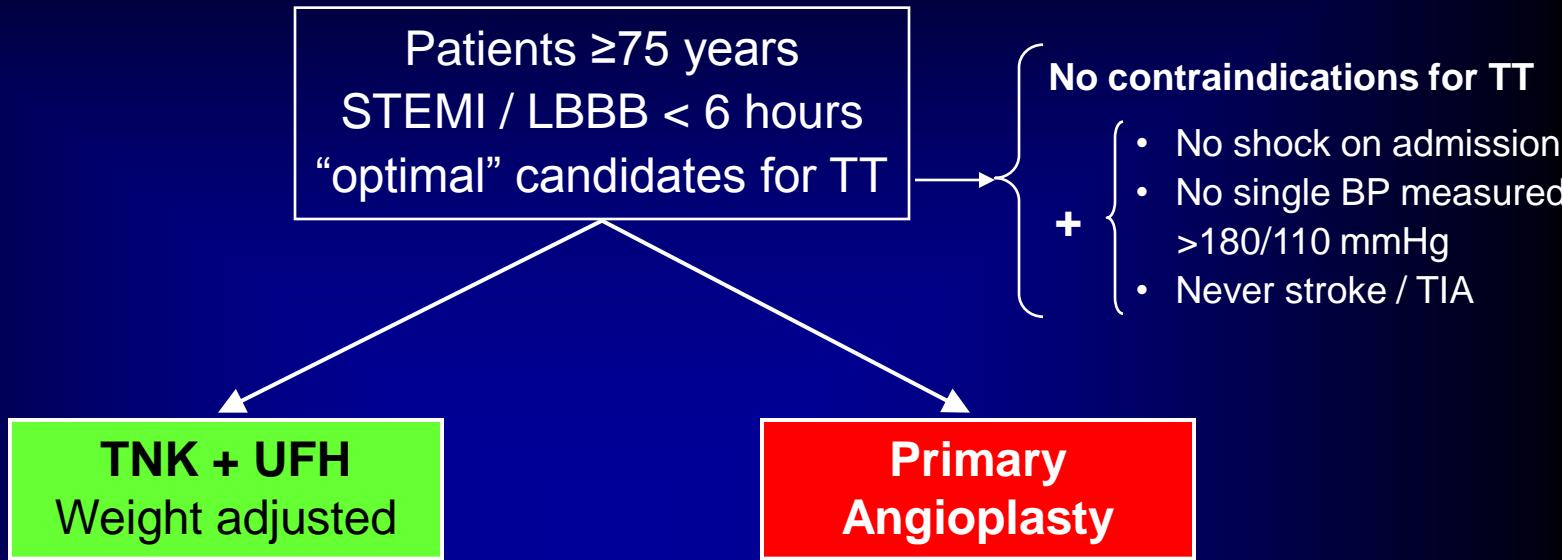
Thiemann DR. *J Am Coll Cardiol* 2002;39:1729-32.

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

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

To compare the efficacy and safety of primary angioplasty and fibrinolytic treatment in patients  $\geq 75$  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' + clinical data

→ Urgent PCI (GPI discouraged)

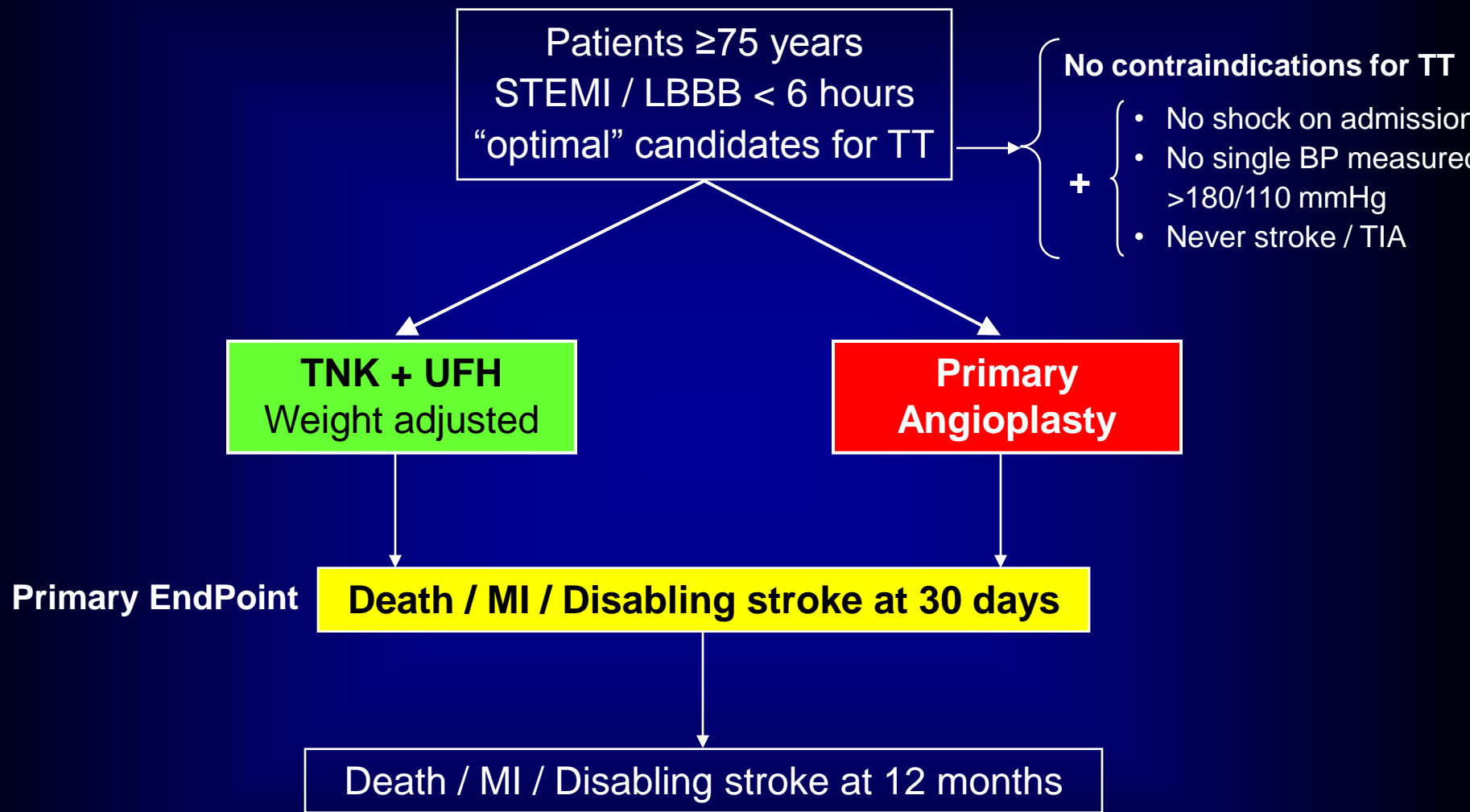
**Coronary revascularisation** only if evidence of recurrent myocardial ischemia (spontaneous/provoked)

**UFH** 60 U/Kg (maximum 4000 IU)

**Abciximab** Dependent on operator's decision

**Clopidogrel** LD dose 300 mg + MD 75 mg/day

## Study Design



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

## Primary

Incidence of the composite all-cause death, re-infarction 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

1. **Subjects  $\geq 75$  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  $\geq 2$  mm in 2 or more precordial leads
  - ST-elevation  $\geq 1$  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/ $\mu$ L
  - 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

- 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

	Thrombolysis n=134	Primary PCI n=132	
Times (min)			
Door to treatment	52 (32 - 72)	99 (73 - 131)	*
Randomisation-treatment	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

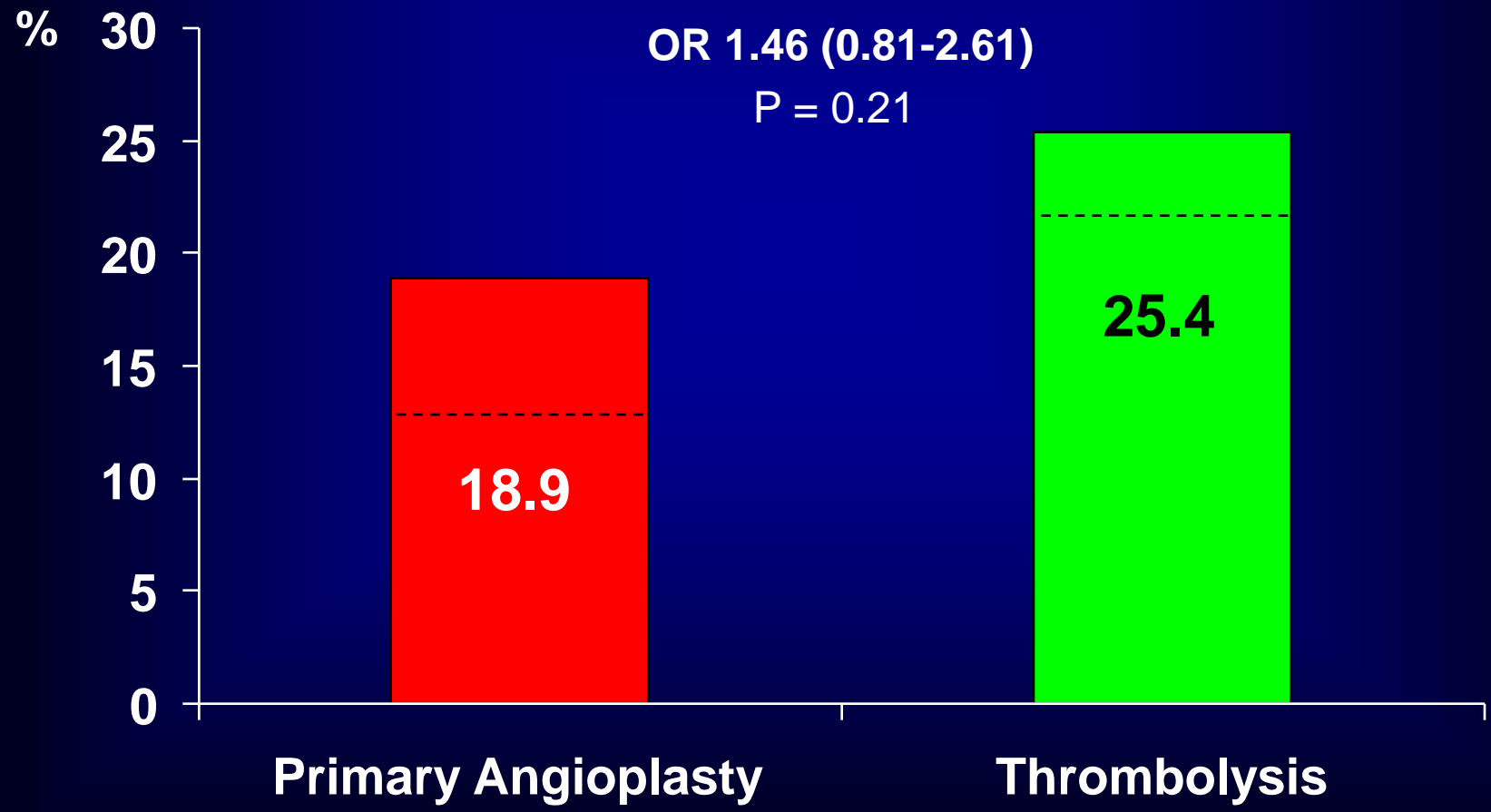
	Thrombolysis n=134	Primary PCI n=132
IRA: LM/LAD/CX/RCA (%)	-	1 / 42 / 14 / 37
Pre-PCI lesion stenosis (%)	-	96.4 ± 11.6
TIMI flow pre-PCI 0/1/2/3 (%)	-	67 / 13 / 11 / 9
Stent (%)	-	84
Dose UFH (U)	-	5069 ± 1793
GP Ib/IIIA inhibitors (%)	-	44
IABP (%)	-	4.5
Post PCI stenosis (%)	-	10.6 ± 25
TIMI flow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

# Results: In-hospital treatments

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

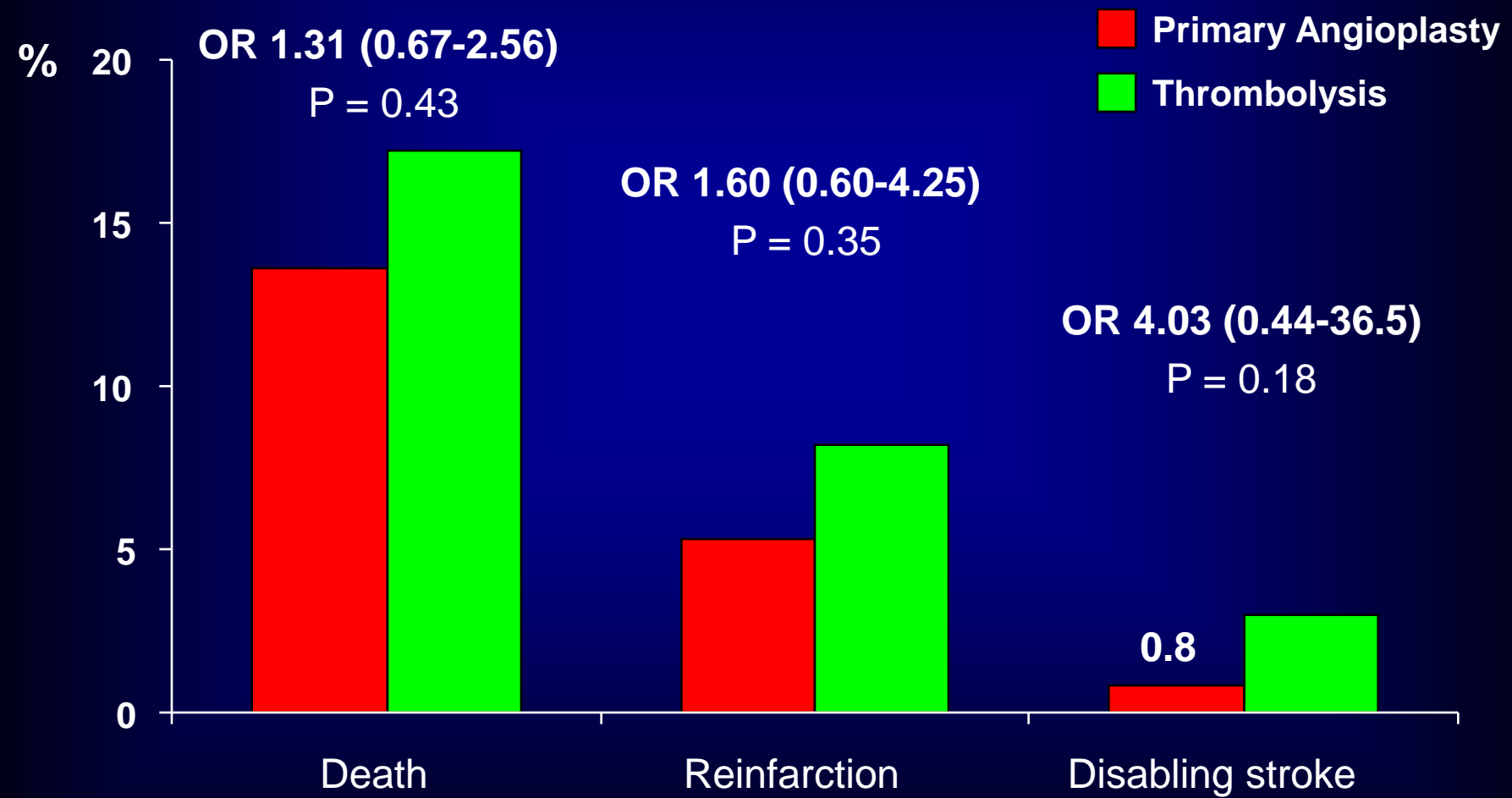
# Results: Primary Endpoint

Death, reinfarction or disabling stroke incidence at 30 days

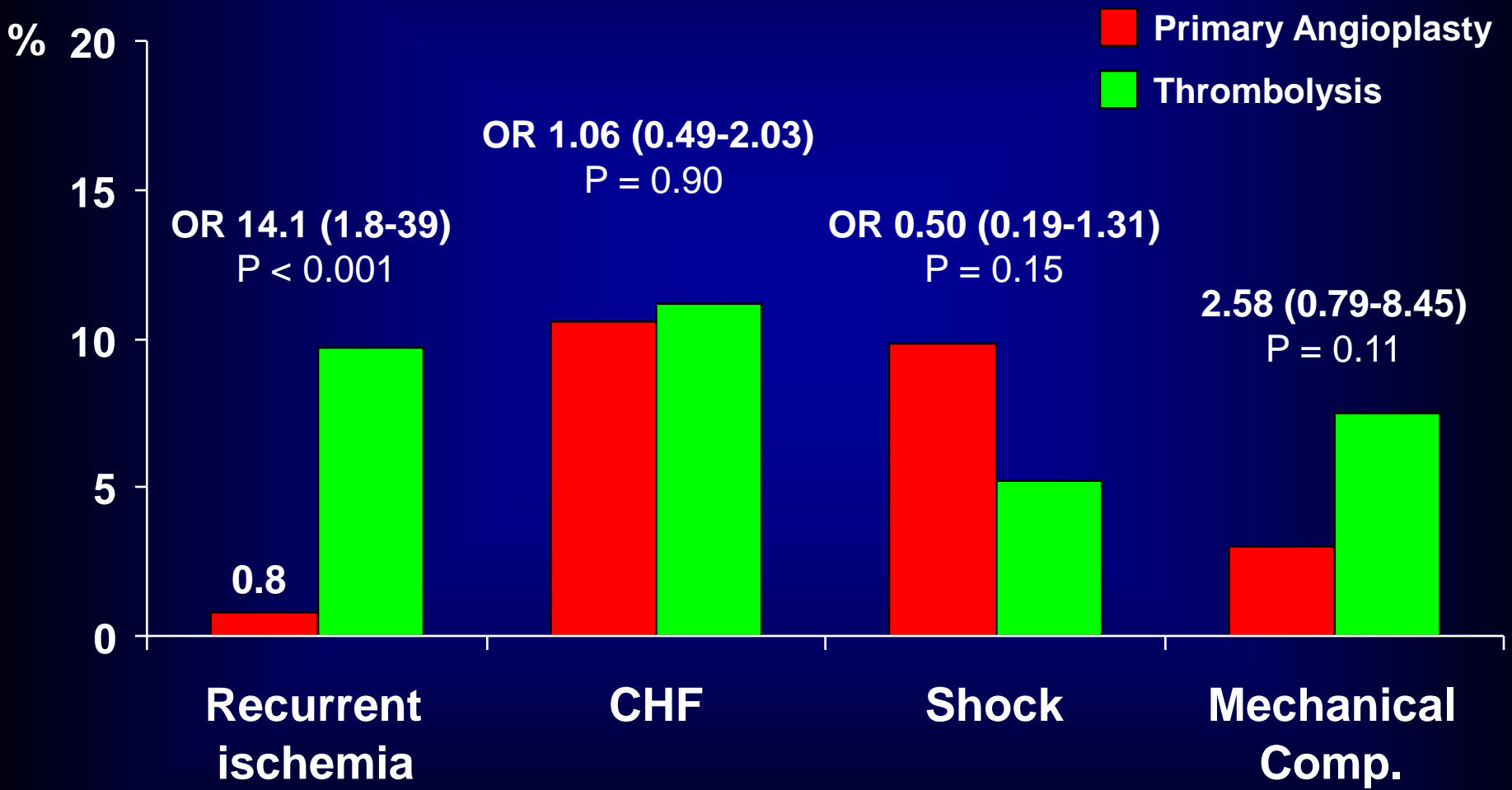


# Results: Primary Endpoint components

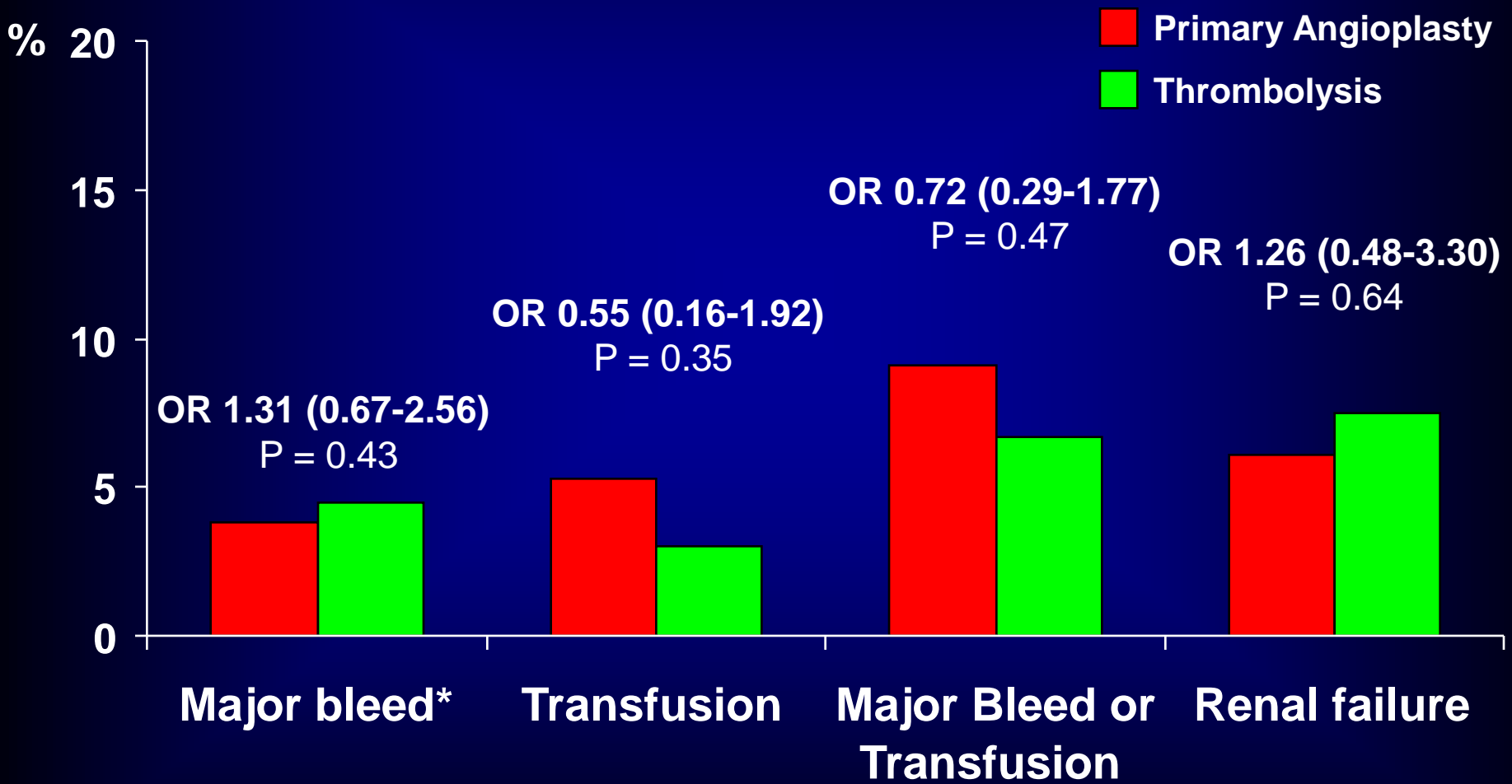
Death, reinfarction or disabling stroke incidence at 30 days



# Results: Other outcomes

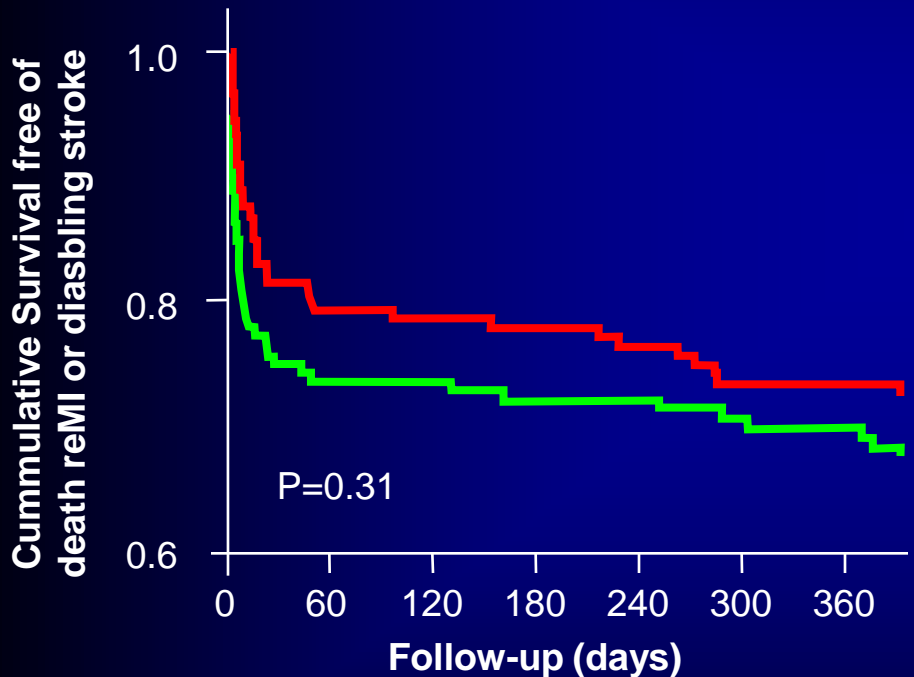


## Results: Safety outcomes

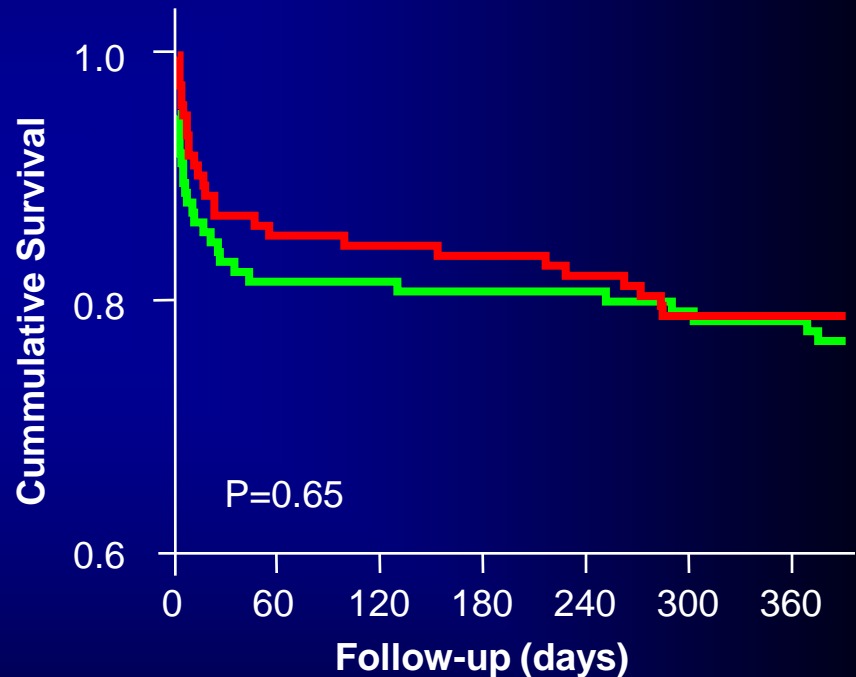


\* One ischemic stroke in TT arm at day 7, after elective PCI → hemorrhagic conversion 24 hours later

### 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)
<b>Recurrent ischemia</b>	<b>11.9</b>	<b>0.8</b>	<b>17.8 (2.3 – 136.0)</b>
New HF	14.9	14.4	1.04 (0.53 – 2.1)
Major bleeding	5.2	6.1	0.85 (0.3 - 2.43)

- 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 maintained during follow-up needs to be explored
- Thrombolysis can be performed with an acceptable risk of intracerebral bleeding in such patients

## Hospital - City

Hospital Gen. Univ. "Gregorio Marañón" - Madrid  
 Hospital 12 de Octubre - Madrid  
 Hospital Virgen de la Salud - Toledo  
 Hospital Clínic - Barcelona  
 Hospital Clínico San Carlos - Madrid  
 Hospital Central de Asturias - Oviedo  
 Hospital Bellvitge - Barcelona  
 Hospital Univ. Virgen de las Nieves - Granada  
 Hospital Univ. de Canarias - Las Palmas  
 Hospital de Navarra - Pamplona  
 Hospital Juan Canalejo - A Coruña  
 Hospital Santa Creu i Sant Pau - Barcelona  
 Hospital Juan Ramón Jiménez - Huelva  
 Complejo Hospitalario - León  
 Hospital Marqués de Valdecilla - Santander  
 Hospital Clínico Universitario - Valladolid  
 Hospital Virgen de la Victoria - Málaga  
 Hospital Univ. Son Dureta - Palma de Mallorca  
 Hospital Cruces - Bilbao  
 Hospital Virgen de la Macarena - Sevilla  
 Hospital Universitario La Paz - Madrid  
 Hospital Txagorritxu - Vitoria  
 Hospital Universitario - Santiago de Compostela

## PI Cath Lab

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 Felipe Hernández  
 José Moreu  
 Amadeu Betriu  
 Rosana Hernández-Antolín  
 César Morís  
 Ángel Cequier  
 Rafael Melgares  
 Francisco Bosa  
 Román Lezaún  
 José Manuel Vázquez  
 Joan García Picart  
 José Díaz Fernández  
 Felipe Fernández Vázquez  
 José Javier Zueco  
 Alberto San Román  
 José M<sup>a</sup> Hernández García  
 Armando Bethencourt  
 Xabier Mancisidor  
 Rafael Ruiz  
 Nicolás Sobrino  
 Alfonso Torres  
 Antonio Amaro

## PI CCU

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 Juan Carlos Tascón  
 José Moreu  
 Magda Heras  
 Antonio Fernández-Ortiz  
 Ignacio Sánchez de Posada  
 Enrique Esplugas  
 Rafael Melgares  
 Martín Jesús García-Glez  
 José Ramón Carmona  
 Alfonso Castro-Beiras  
 José Domínguez de Rozas  
 José Díaz Fernández  
 Norberto Alonso  
 Chema San José  
 Carolina Hernández  
 Ángel García Alcántara  
 Miquel Fiol  
 Xabier Mancisidor  
 Rafael Hidalgo  
 Isidoro González  
 Fernando Arós  
 Michel Jaquet

# 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.

## 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  $\geq 5$  gr/dL, or an absolute hematocrit drop  $\geq 15\%$