EARLY MORTALITY AT 30 DAYS OF POST-AMI HEART FAILURE

HOW TO INTERPRET IT AND HOW TO IMPROVE ITS PROGNOSIS

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INTRODUCTION

After creating the Coronary Care Unit and implementing efficient antiarrhythmic therapeutic measures, heart failure (HF) constitutes the most frequent complication of AMI associated to a high in-hospital mortality rate.

It is defined as the inability of the heart to maintain an appropriate blood flow to satisfy the metabolic requirements of tissues as a consequence of loss of functioning myocardium.

POST-AMI HEART FAILURE

Killip & Kimball Index.

Class	Mortality
A: No heart failure	2 - 5 %
B: Mild heart failure	10 – 20 %
C: Acute pulmonary edema	30%
D: Cardiogenic shock	50 – 60 %

INCIDENCE OF POST-AMI HF

Difficulties of epidemiological analysis

- The data come from different types of studies (registries, clinical trials, epidemiological studies).
- Different definitions of HF and infarction are used.
- Patients with cardiogenic shock or with HF prior to the analysis are included or not.
- There are biases in the selection of patients.
- Different populations are evaluated (coronary units, all admittances in a hospital, different age groups).

INCIDENCE OF POST-AMI HF

Difficulties of epidemiological analysis

The comparison of clinical trials with registries shows that patients in clinical studies are younger, with less proportion of women and HF at admittance, and with greater chances of receiving reperfusion procedures, aspirin, and beta blockers, so the incidence in them is considerably lower.

INCIDENCE OF POST-AMI HF

STUDY	TERM OF THE STUDY	HF (%)
Epidemiological studies		
WHAS (USA)	2001	39.9
WHAS (USA)	2005	31.5
Registries		
NRMI 2/3 (USA)	1994-2000	29
GRACE (SCA)	1996-2001	13
Clinical studies		
Meta-analysis	1990-1998	29.4
(GUSTO I; GUSTO IIB; GUSTO III; ASSENT III		
In-TIME II	1997-1998	23
VALIANT (Registry)	1991-2001	23.1
Incidence of post-AMI HF		**25-30**

INCIDENCE OF POST-AMI HF

Early systolic dysfunction of the left ventricle

- Although they are related findings, HF and left ventricular systolic dysfunction (LVSD) are not synonyms.

- A 30-50% of patients with post-AMI HF does not have LVSD and HF is due to mitral dysfunction, arrhythmias, or left ventricular diastolic dysfunction.

- There might be LVSD without clinical signs of HF.

- Specifying the incidence of post-AMI LVSD is even more complex, since it is not evaluated as a routine in several institutions, there are different methods to measure it and the cut point for ejection fraction may vary.

- However, according to literature, a 25-60% of AMI patients will have LVSD, and more than 50% with early LVSD will also present HF.

INCIDENCE OF POST-AMI HF

Early left ventricular systolic dysfunction

STUDY	TERM	EF VALUE	LVSD (%)
Registries			
French CCU	1995	≤ 0.50	52
French USIC 2000	2000	≤ 0.50	46
Clinical studies			
BEAT	1998-1999	< 0.40	31.1
VALIANT registry	1999-2001	≤ 0.40	27.2
MAGIC	1999-2002	< 0.50	60
EMIAT	1990-1995	≤ 0.50	43
DIAMOND-MI	1998	≤ 0.35	29
ARGAMI-2	1996	≤ 0.40	28
TRACE	1990-1992	≤ 0.35	39

Robin A.P.Weier y col Am J Cardiol 2006;97 suppl 13F-25F

POST-AMI HEART FAILURE

HF prognostic factors at admittance

	HF n= 1778	NO HF n= 11929	p
Age	72.5 (63.7-79.5)	64.0 (54.1-72.9)	< 0.0001
Men	60.1	69.6	< 0.0001
Background			
Diabetes	29.9	20.9	< 0.0001
AMI	32	26.7	< 0.0001
TIA/stroke	53.8	59.9	< 0.0001
HTN	59.5	55.7	0.0026
Renal failure	10	6.4	< 0.0001

GRACE Registry 2004; 109: 494-499

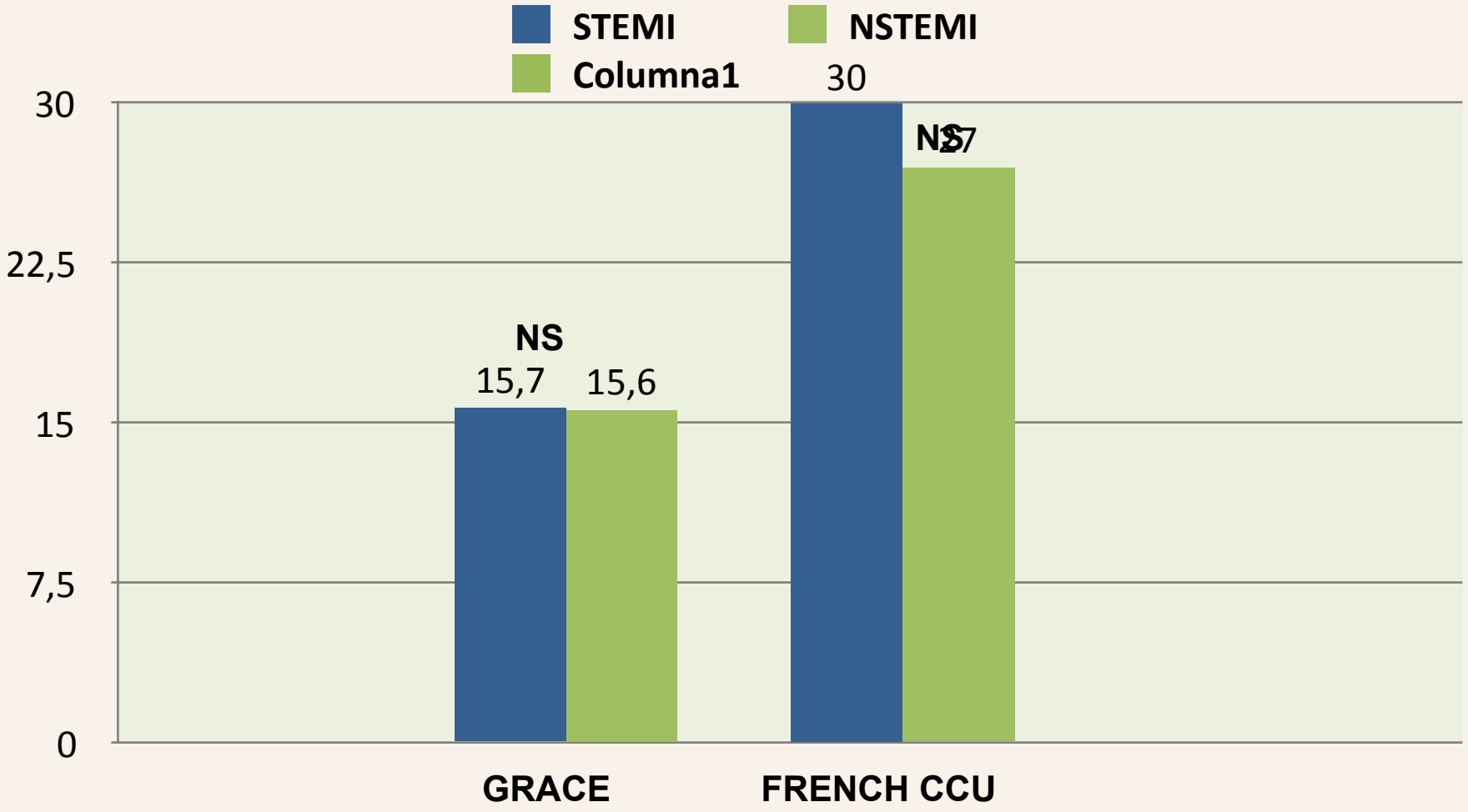
POST-AMI HEART FAILURE

HF prognostic factors at admittance

	OR	95% CI
Advanced age	1.5	1.45 -1.60
High HR	1.23	1.22 -1.28
STEMI	2.1	1.84 - 2.47
NSTEMI	1.6	1.41 - 1.91
Prior use of diuretics	1.5	1.31 – 1.75
LBBB	1.6	1.30 – 2.10

GRACE Registry 2004; 109: 494-499

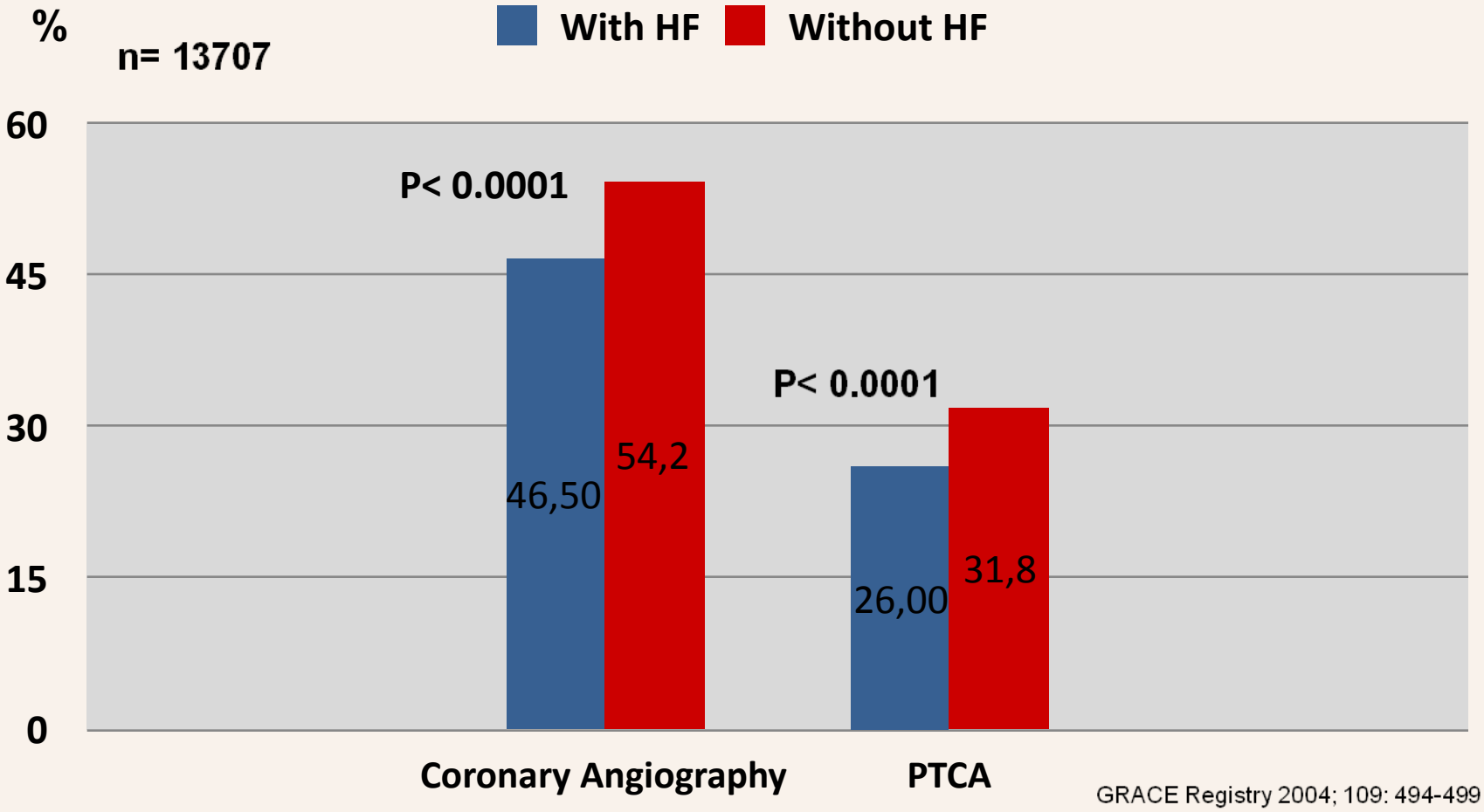
POST-AMI HEART FAILURE



Robin A.P.Weir y col. Am J Cariol 2006; 97 suppl: 13 F-25F

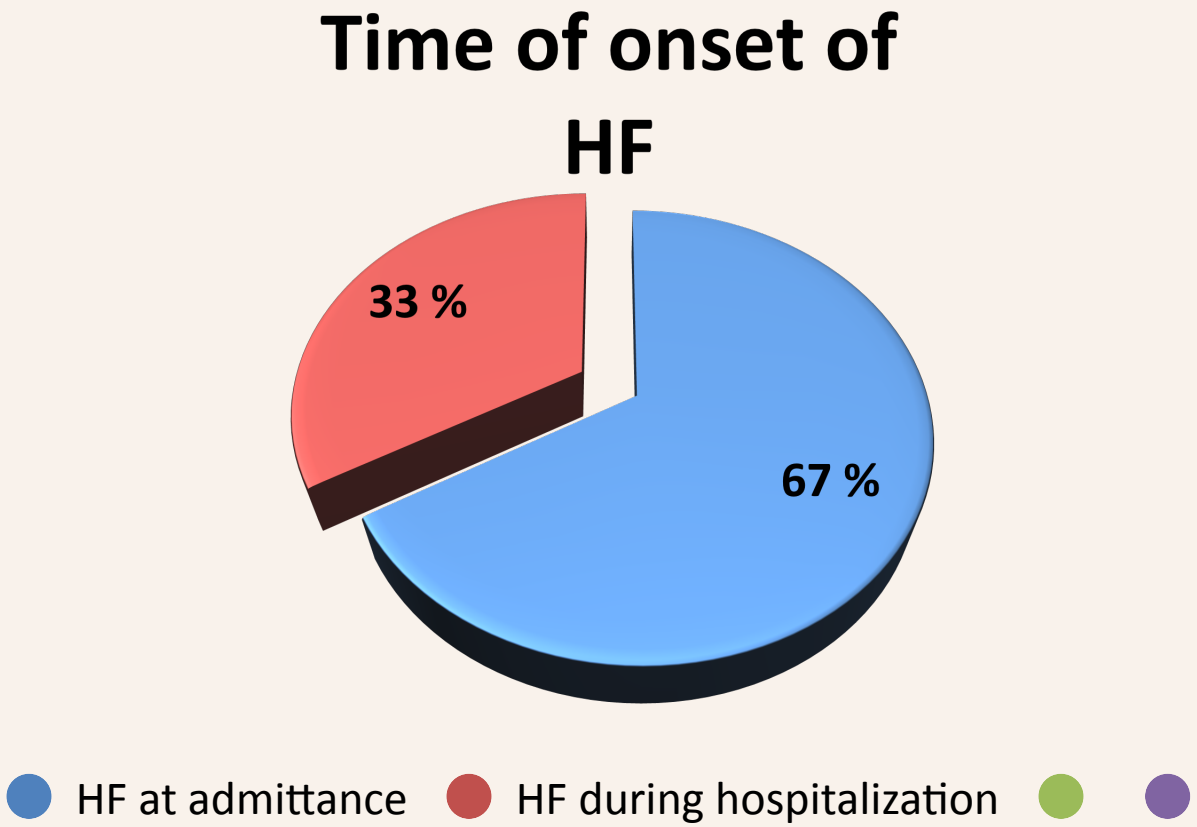
POST-AMI HEART FAILURE

HF prognostic factors at admittance



GRACE Registry 2004; 109: 494-499

POST-AMI HEART FAILURE



GRACE Registry 2004; 109: 494-499

POST-AMI HEART FAILURE

- The analysis of data provided by the NRMI 2 and NRMI 3 reports that those patients wtih smaller infarctions tended to be older with pre-existing morbidity and a high incidence of prior AMI. These patients developed HF at admittance more frequently.

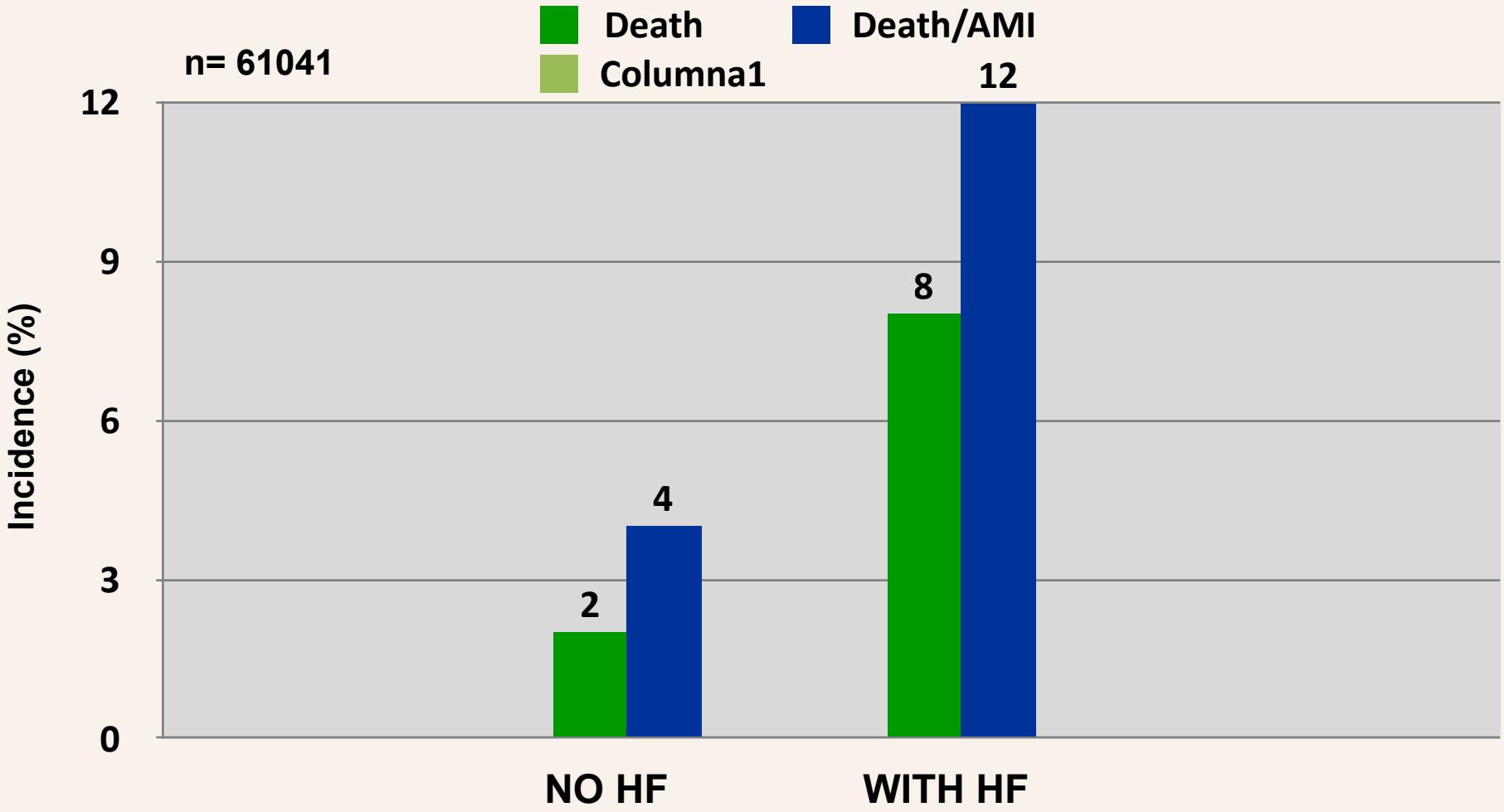
- On the contrary, the group with larger infarctions turned out to be younger, with a lower morbidity and a lower frequency of prior infarction. These patients showed HF more often after admittance.

- Thus, the extent of infarction is an important determinant for the incidence and time of appearance of post-AMI HF.

- Those with morbidity and pre-existing myocardial damage do not tolerate even small infarctions and develop HF early.

POST-AMI HEART FAILURE

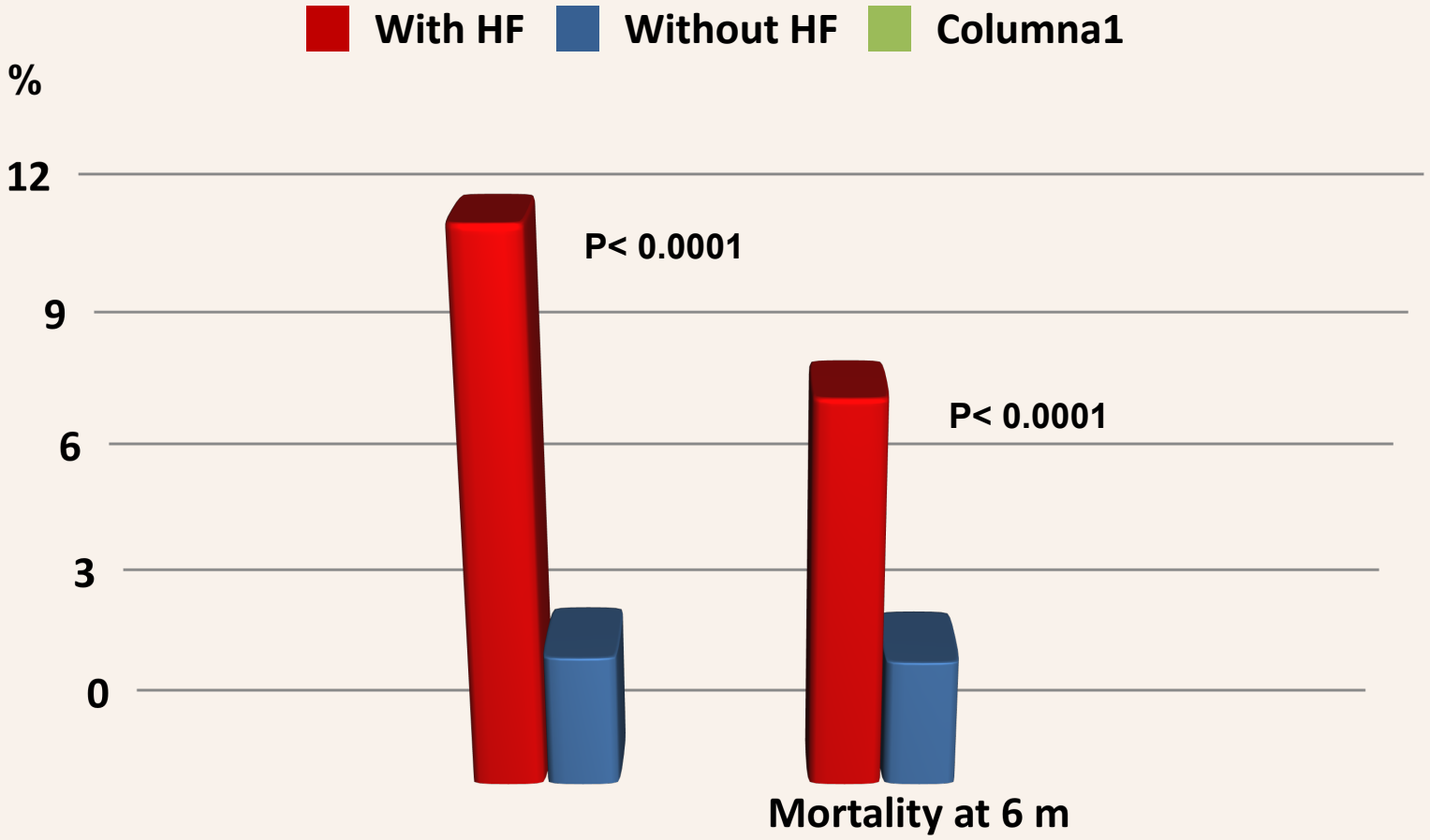
Mortality at 30 days



Hasdai y col. Am Heart J. 2003; 145: 73-79

POST-AMI HEART FAILURE

In-hospital mortality and at 6 months



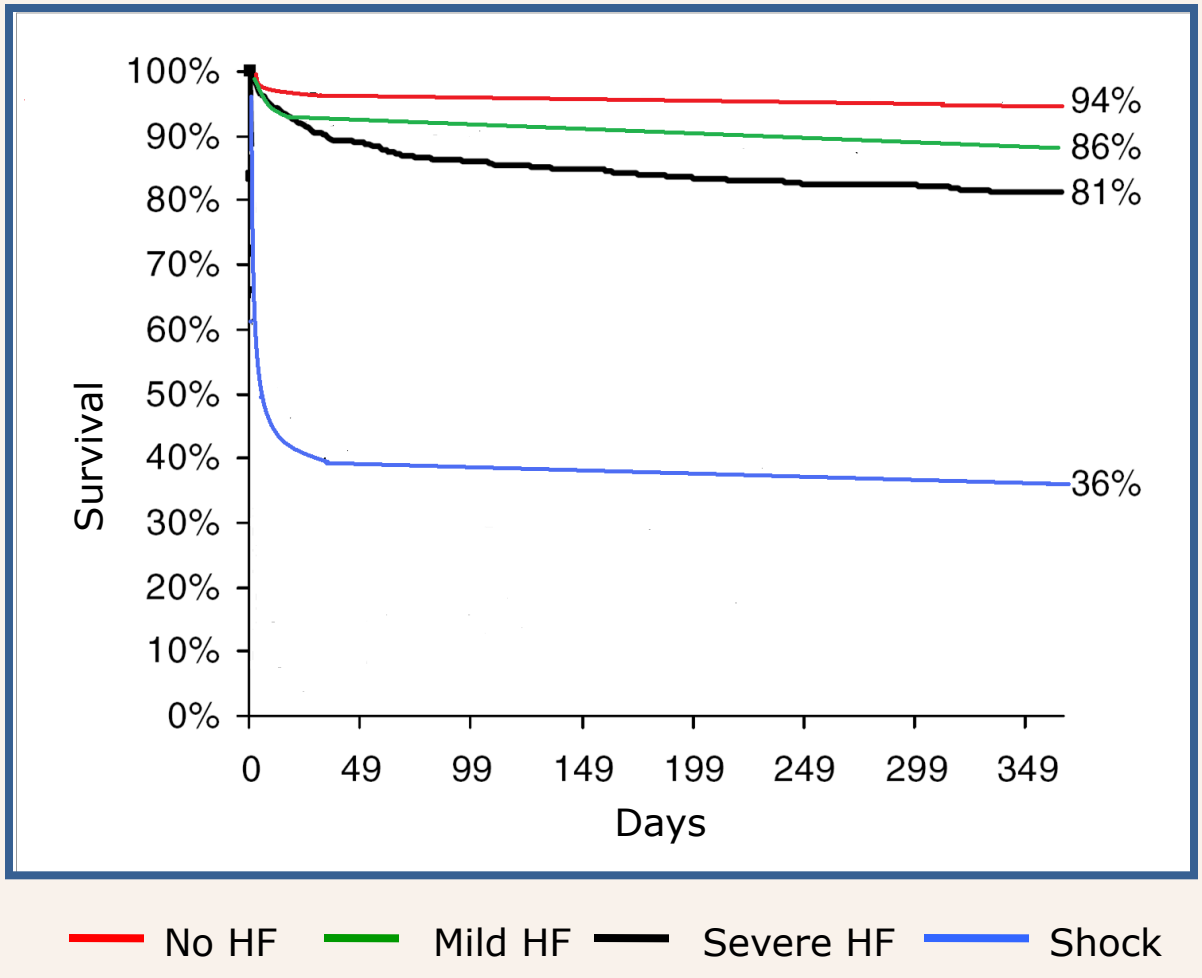
GRACE Registry 2004; 109: 494-499

POST-AMI HEART FAILURE

Mortality

n= 15078

P < 0.0001



Kashani y col Eur. Heart J 2004: 25: 1702- 1710

POST-AMI HEART FAILURE

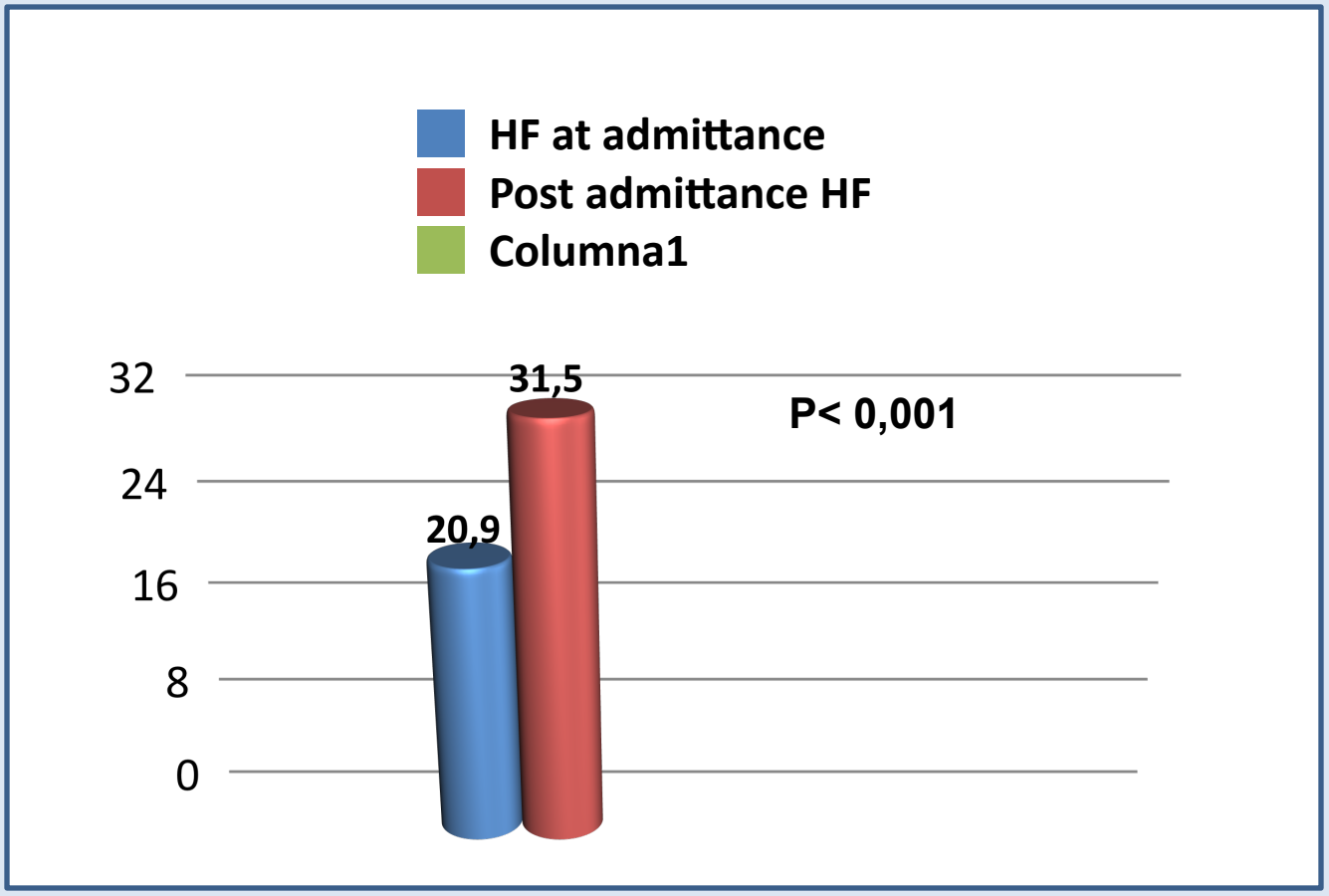
Mortality

	OR	95% CI
HF at admittance	1.68	1.62 – 1.75
Age	1.58	1.55 – 1.61
Stroke	1.36	1.29 – 1.44
Diabetes	1.21	1.17 – 1.26
Prior HF	0.92	0.88 – 0.97

Am. J. Cardiol 1996; 78: 1124 - 1128

POST-AMI HEART FAILURE

In-hospital mortality



Circulation. 2002;105:2605-2610.)

POST-AMI HEART FAILURE

Mortality

- Both patients with HF at admittance that failed to solve it clinically during hospitalization and those who developed HF only after admittance, show a worse evolution than those with HF at admittance and solved during hospitalization.

- Post-AMI HF does not only affect mortality but also morbidity of patients that present it:

	with HF	without HF	p
Re-AMI	3.0 %	2.7 %	= 0.002
Stroke	2.2 %	1.4 %	< 0.001
VT/VF	11.2 %	9.0 %	< 0.001

Circulation. 2002;105:2605-2610.

POST-AMI HEART FAILURE

Pathophysiology

In a setting of AMI, the determinants of heart failure are:

1.- Size of infarcted area

2.- Ventricular distensibility

3.- Functional state of remaining myocardium

4.- Mechanical complications

5.- Rhythm disorders

SIZE OF INFARCTED AREA

- The extent of ventricular function alteration caused by AMI is directly proportional to the extent of the necrotic area and circulatory conditions that surround it.

- With the loss of an amount enough of myocardial mass, the pump function is decreased. The minute-volume, systolic volume, blood pressure, and dp/dt max decrease and the end systolic volume increases. Paradoxical systolic expansion of the infarcted area decreases the systolic volume even more.

- The left ventricle (LV) dilates during the first hours and days after AMI, so that regional and global pressure increase according to Laplace's Law.

SIZE OF INFARCTED AREA

- The degree of dilation depends on the size of the AMI, permeability of the infarct related artery (IRA)) and activation of the renin-angiotensin-aldosterone system (RAAS).
- The probability to develop HF symptoms correlates to ventricular function parameters.
- The first alteration is a **reduction of diastolic relaxation** that is observed in infarctions that compromise **8%** of ventricular mass.
- With **≥15% losses, ejection fraction reduces** and volume and end systolic pressure increase.
- The **signs of HF** appear with **≥25%** losses of ventricular mass.
- **Cardiogenic shock** accompanies a **≥40%** contraction alteration

FUNCTIONAL STATE OF REMAINING MYOCARDIUM

- Extensive coronary artery disease may compromise irrigation, as well as prior infarctions and fibrosis that could alter its performance.

- The myocardial territory in risk constituted by ischemic cells, but that could be recovered, is extremely important. Viability depends on the existence or not of an appropriate residual flow after IRA recanalization or the presence of collateral circulation developed before AMI.

- On the contrary, the loss of collateral arteries secondary to occlusion of the responsible vessel, a condition that will generate remote ischemia, is another factor that contributes to ventricular function impairment.

COMPENSATING MECHANISMS

- The decrease of systolic volume triggers cardiac and peripheral compensating mechanisms to maintain a proper tissue perfusion. However, each of them may lead, in a paradoxical and direct or indirect way, an even greater impairment and thus generate a vicious circle that will have to be interrupted with a proper therapeutic strategy.

- Due to the implications in the evolution of patients with post-AMI HF, among peripheral mechanisms it is the neurohormonal system activation that stands out (sympathetic nervous system, RAAS) since it determines an increase of systemic vascular resistance that leads to a greater decline of ventricular function, multiorgan dysfunction, and death

COMPENSATING MECHANISMS

- In the particular case of **cardiogenic shock**, this classical paradigm of peripheral compensation may not be observed in certain patients, but on the contrary, reduced vascular resistance is verified by the development of systemic inflammatory response syndrome (SIRS) due to the release of inflammatory mediators (cytokines) that lead to an exaggerated expression of the enzyme inducing nitric oxide (iNOS).

- The excessive production of nitric oxide and its derivatives such as peroxynitrite produce deleterious effects such as inhibition of cardiac contractility, systemic vasodilation induction, suppression of mitochondrial respiration of non-ischemic myocardium and a variable decrease of adrenergic response.

POST-AMI HEART FAILURE

How to improve prognosis

Considering the significance of the size of the infarction as a key determinant to develop post-AMI HF, the concept of the possibility of modifying it has promoted the development of a large number of experimental and clinical trials over the last few decades. The efforts to limit the extent of the infarcted area have been guided by different approaches to:

1. Early reperfusion
2. Reduction of myocardial energy demand
3. Manipulation of myocardial energy production sources.
4. Prevention of reperfusion injury.

POST-AMI HEART FAILURE

Reduction of AMI size

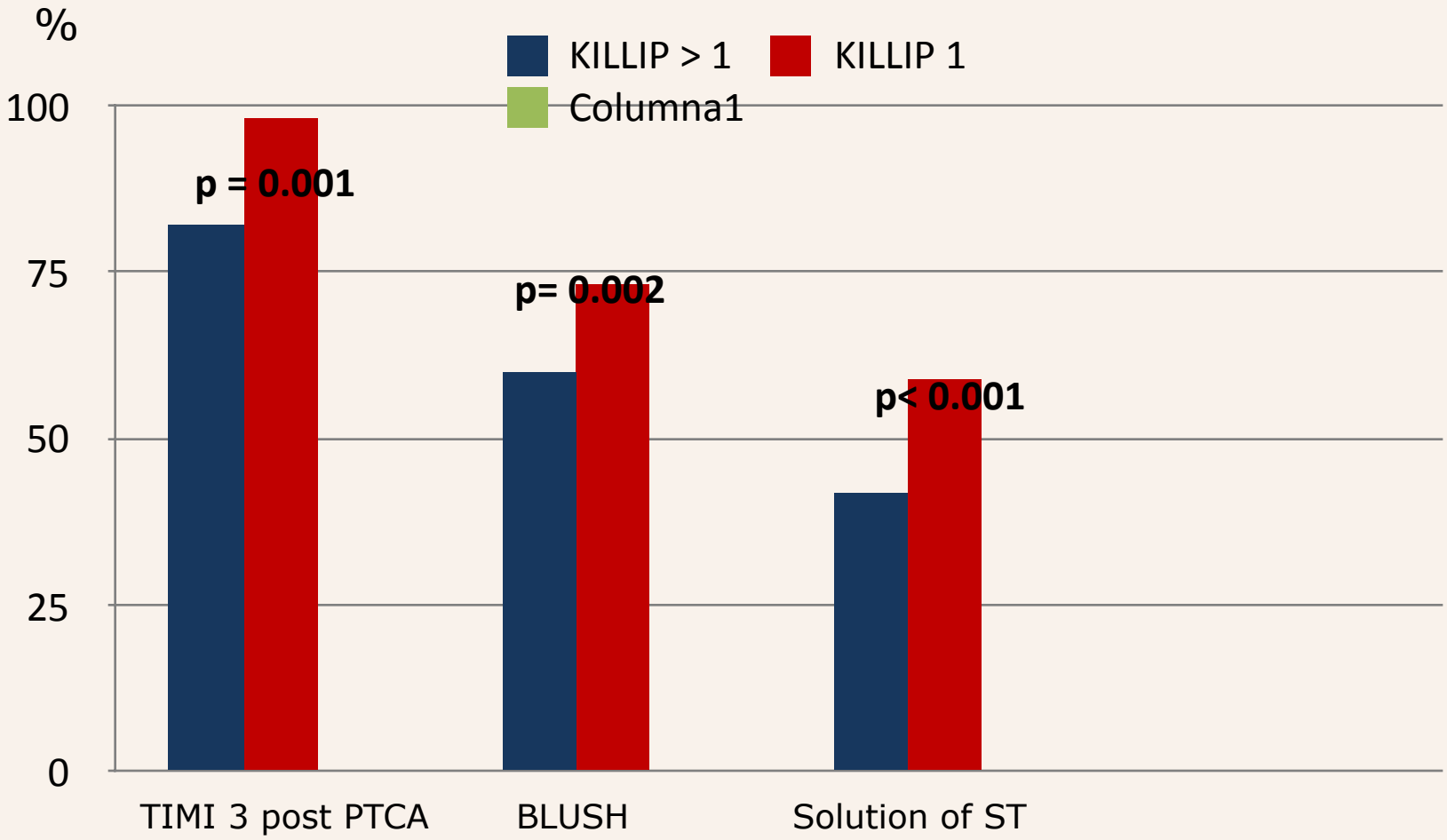
General measures

They tend to optimize a balance between myocardial oxygen input and demand to save the ischemic areas that surround the infarction.

✓Physical and emotional rest of the patient to lower the heart rate.
✓Oxygenation: kinetic support, oxygen mask, bronchodilators, noninvasive ventilation or endotracheal intubation for mechanical respiratory assistance.
✓Maintain a proper systolic pressure.
✓Management of tachyarrhythmia and bradyarrhythmia.
✓Correction of electrolytic disorders and acid-base state.
✓Management of associated conditions: severe anemia, infections accompanied by fever and tachycardia.

REDUCTION OF SIZE OF AMI

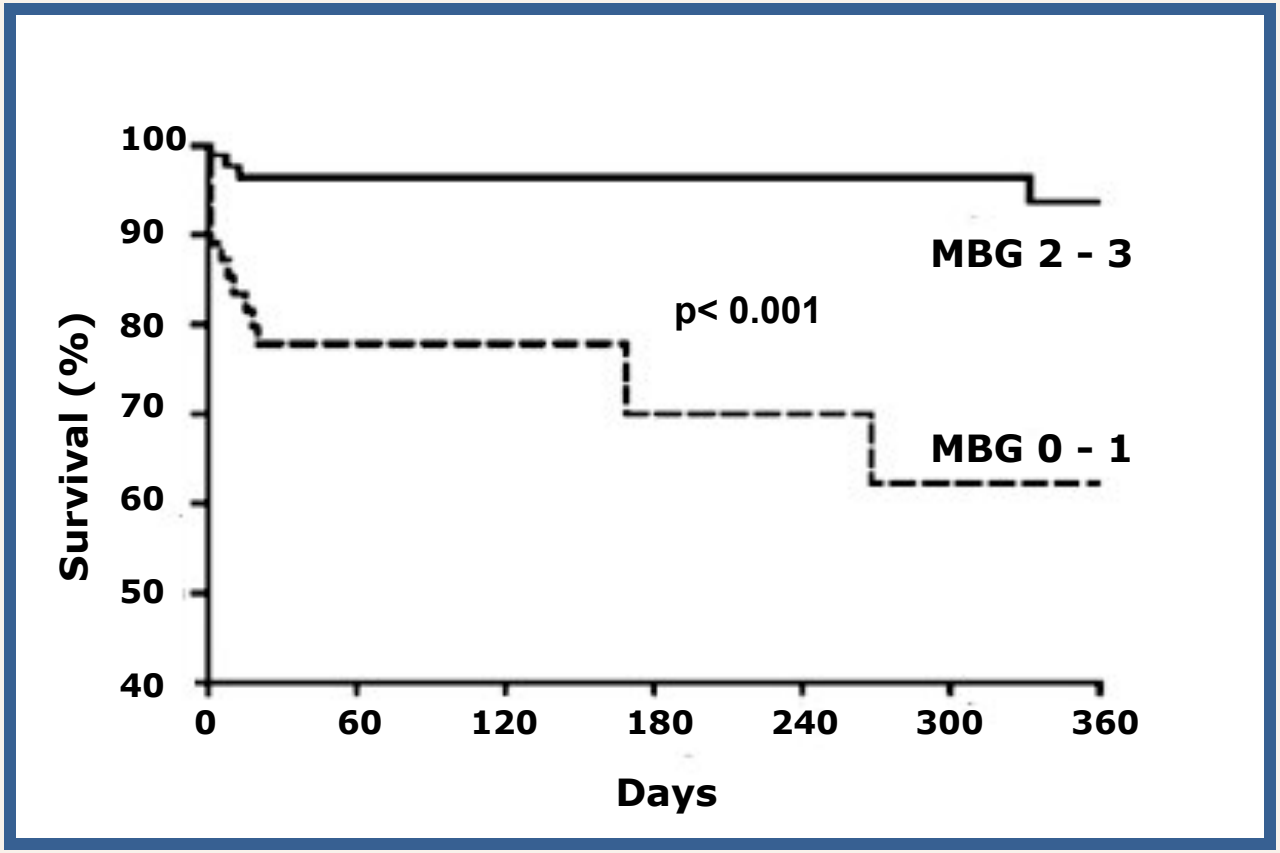
Reperfusion



Giuseppe De Luca y col. Am. Heart J. 2009; 158: 416-21

REPERFUSION

Survival in Killip and Kimball > 1



Giuseppe De Luca y col. Am. Heart J. 2009; 158: 416-21

POST-AMI HEART FAILURE

Reperfusion

- The two strategies of reperfusion developed over the last decades, a pharmacological one with fibrinolytic drugs and primary angioplasty (PTCA), achieve an acceleration of the recanalization process of IRA, maximizing the amount of myocardium saved, taking into account as rule that **time** and not the type of reperfusion is the critically relevant aspect. Thus, a recovery of LV systolic function is achieved, as well as an improvement in survival in the short and long term.

- Primary PTCA produces a superior benefit in survival compared to fibrinolytic agents. This superiority is directly linked to a better patency of IRA (90% vs 65%).

POST-AMI HEART FAILURE

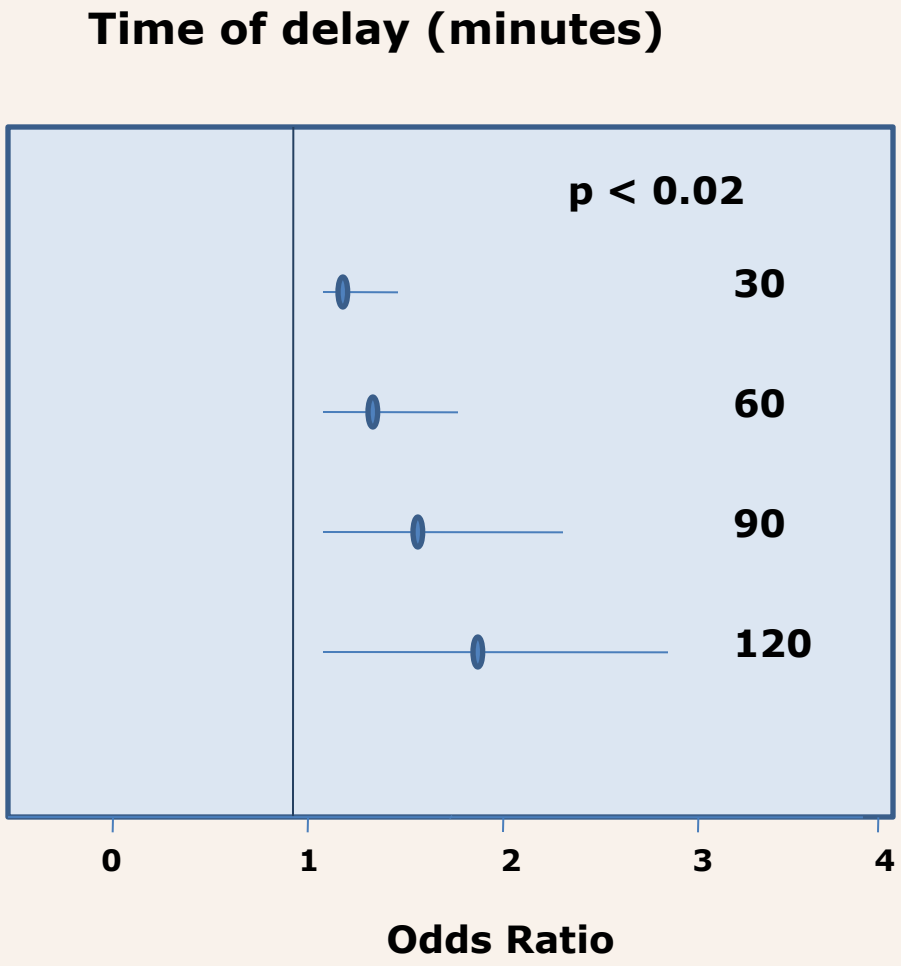
Reperfusion

- Primary PTCA also achieves a higher LVEF at discharge and lower percentages of re-infarction, stroke, and HF.

- However, a delay from the moment at which the patient gets in touch with medical care until performing the angioplasty (PTCA), makes this benefit not be always achieved, and in this case, fibrinolytic drugs are a resource that may be used more quickly.

POST-AMI HEART FAILURE

Reperfusion



Am. Heart J. 2002; 144 (3)

POST-AMI HEART FAILURE

Choice of reperfusion treatment

Fibrinolytic treatment

.- Early presentation (≤ 3 h since the onset of symptoms, delay for an invasive strategy).

.- PTCA is not an option because:

- Laboratory not available
- Difficult vascular access
- Difficulties to obtain access to an experimented hemodynamics lab.

.- Delays for an invasive strategy

- Prolonged transportation
- (door-to-balloon)-(door-to-needle) time > 1 h
- Door-to-balloon time > 90 minutes

ACC/AHA Guidelines 2006

POST-AMI HEART FAILURE

Choice of reperfusion treatment

Invasive strategy

.- Trained hemodynamics laboratory available

- Door-to-balloon time < 90 minutes
- (door-to-balloon)-(door-to-needle) time < 1 hour

.- AMI of high risk: Cardiogénic shock; Killip ≥ 3

.- Contraindications for fibrinolytic drugs (including increased risk of bleeding and stroke).

.- Delayed presentation (> 3 hours).

.- Doubtful diagnosis of AMI

If admittance is < 3 h and there is no delay for an invasive strategy, there are no preferences for any of the 2 modalities.

ACC/AHA Guidelines 2006

POST-AMI HEART FAILURE

Choice of reperfusion management

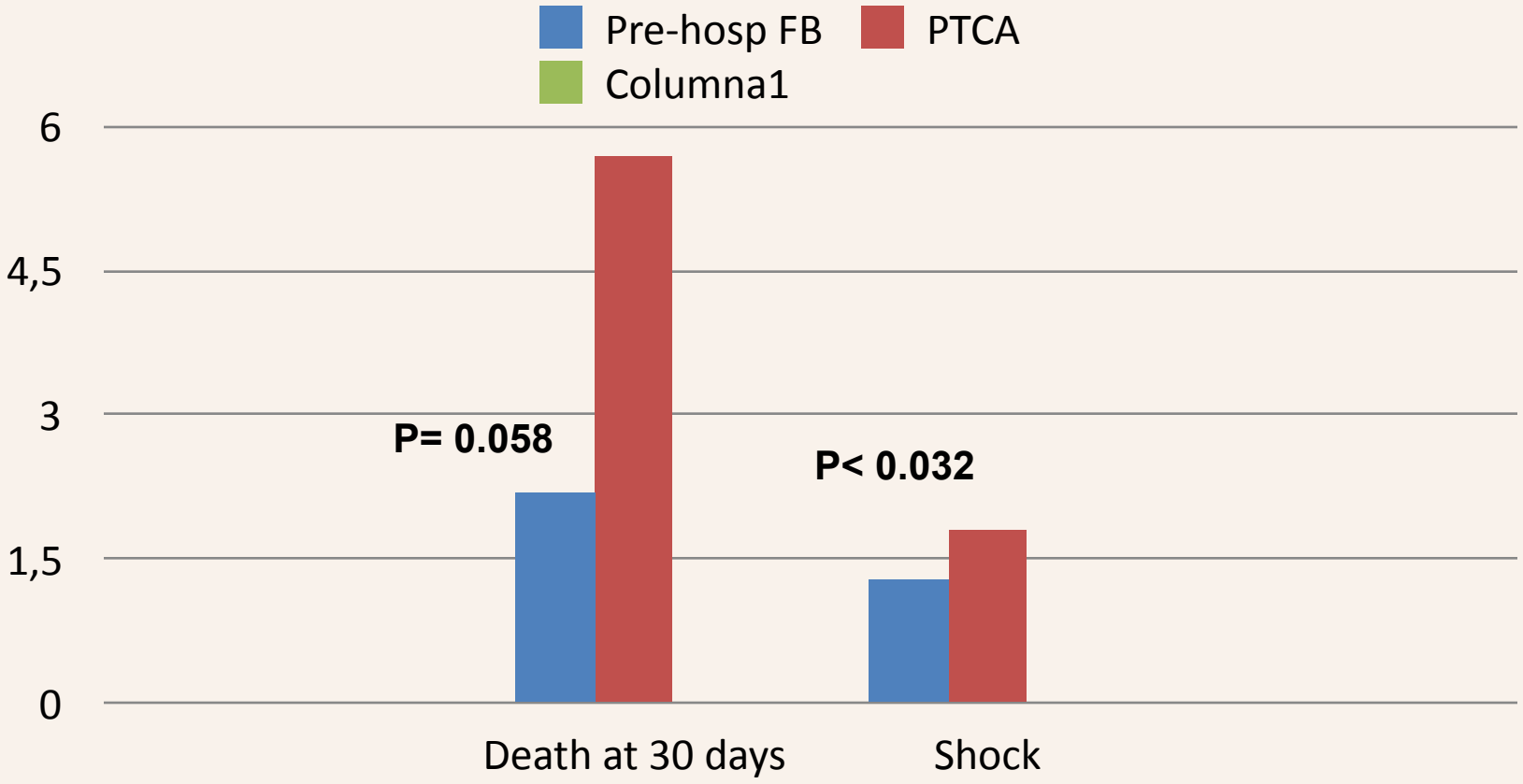
- Taking into account that the benefits granted by fibrinolytic agents occur when they are administered, preferably within the first hour of the onset of symptoms, the modality of **pre-hospital fibrinolysis** was evaluated in several trials.

- Compared with in-hospital fibrinolysis, it produced, in a meta-analysis of 6434 patients, a significant reduction of mortality. (odds ratio: 0.83; 95% CI 0.70- 0.98 p= 0.03).

- The comparison of pre-hospital fibrinolysis with transfer to a center for PTCA in the CAPTIM study, did not reveal significant differences in terms of mortality or in the composite end point (re-infarction, stroke, death at 30 days).

POST-AMI HEART FAILURE

Pre-hospital fibrinolytic drugs vs transfer for PTCA



CAPTIM Circulation 2003; 108 : 2851- 6

POST-AMI HEART FAILURE

Rescue PTCA

	PTCA (%)	CONTROL (%)	P
Mortality	7.3	10.4	0.09
HF	12.7	17.8	0.05
Re-infarction	6.1	10.7	0.04
Stroke	3.4	0.7	0.04
Bleeding	16.6	3.5	< 0.001

Wijeisundera y col JACC 2007; 49: 422-430

POST-AMI HEART FAILURE

Microvascular damage

- In spite of restoring epicardial flow, many patients display suboptimal myocardial perfusion. This suggests that post-AMI HF may also develop as a consequence of extensive necrosis associated to severe microvascular damage.

- The high mortality rate linked to impaired myocardial perfusion, makes evident the need to try harder to improve circulation in small vessels, beyond restoring epicardial flow.

- Although several factors may contribute to microvascular dysfunction, **microvascular reperfusion injury** has been considered as the main determinant of this phenomenon.

POST-AMI HEART FAILURE

Microvascular damage

TYPES OF REPERFUSION INJURY

Stunning: prolonged contractile dysfunction of myocytes saved by reperfusion because of cell metabolism alterations that reduce energy production.

No-reflow phenomenon: progressive microvascular reperfusion damage.

Arrhythmias by reperfusion

Lethal reperfusion injury : cell death induced by cell reperfusion.

POST-AMI HEART FAILURE

Microvascular damage

Mediators of lethal reperfusion injury and evaluated strategies

1) **Oxidative stress.** Antioxidants
2) **Intracellular calcium overload.** Diltiazem, cariporide
3) **Rapid restoration of cell PH.**
4) **Metabolic modulation.** Glucose therapy, insulin, potassium
5) **Magnesium**
6) **Inflammation.** Pexelizumab; P-selectin antagonist
7) **Adenosine**

POST-AMI HEART FAILURE

Microvascular dysfunction

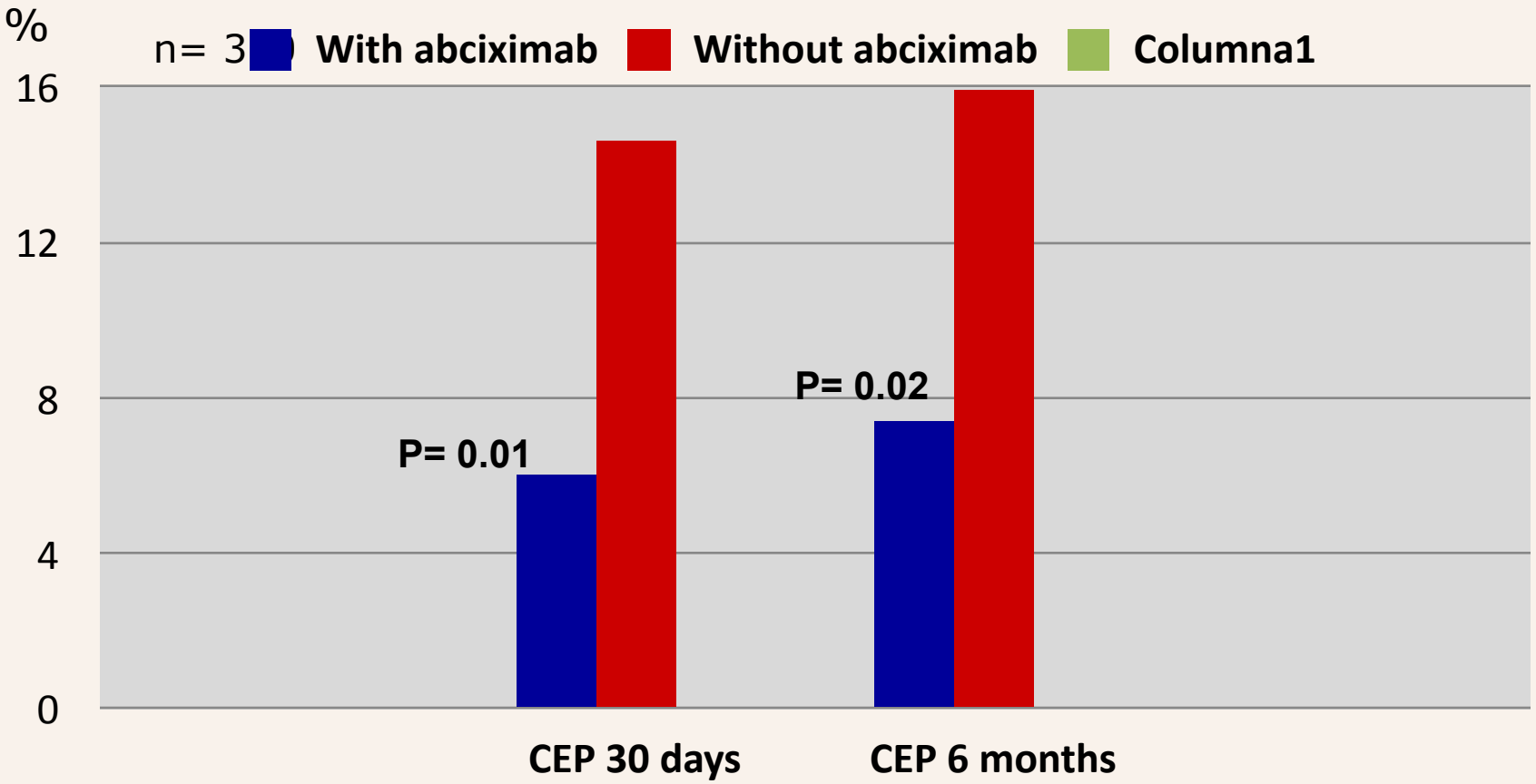
- Added to the injury by reperfusion, another mechanism linked to microvascular dysfuncion is the **distal embolization** observed in a high percentage in the highest Killip and Kimbal indices.

- In this regard, pharmacological therapy (IIb/IIIa inhibitors) and mechanical therapy (manual aspiration of thrombus) have been proposed as strategies to protect the microcirculation of this complication during PTCA, and thus prevent a greater deterioration of ventricular function.

- In the particular setting of shock, some studies suggest that thrombus aspiration may obtain a better solution for ST segment and a significant reduction of in-hospital mortality.

Microvascular dysfunction

IIb/IIIa inhibitors and PTCA in cardiogenic shock



ADMIRAL NEJM 2001 344: 1895-1903

POST-AMI HEART FAILURE

- Although pharmacological or invasive revascularization has caused a significant decrease in the mortality of AMI patients, reperfusion is not always effective to limit myocardial damage and prevent ventricular function impairment.
- This is how a ventricular remodeling process could develop, both in the infarcted and non-infarcted segments, which in turn progressively worsens systolic function, and subsequently the prognosis.

- This process is closely linked to neurohormonal activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), thus having significant therapeutic implications.

POST-AMI HEART FAILURE

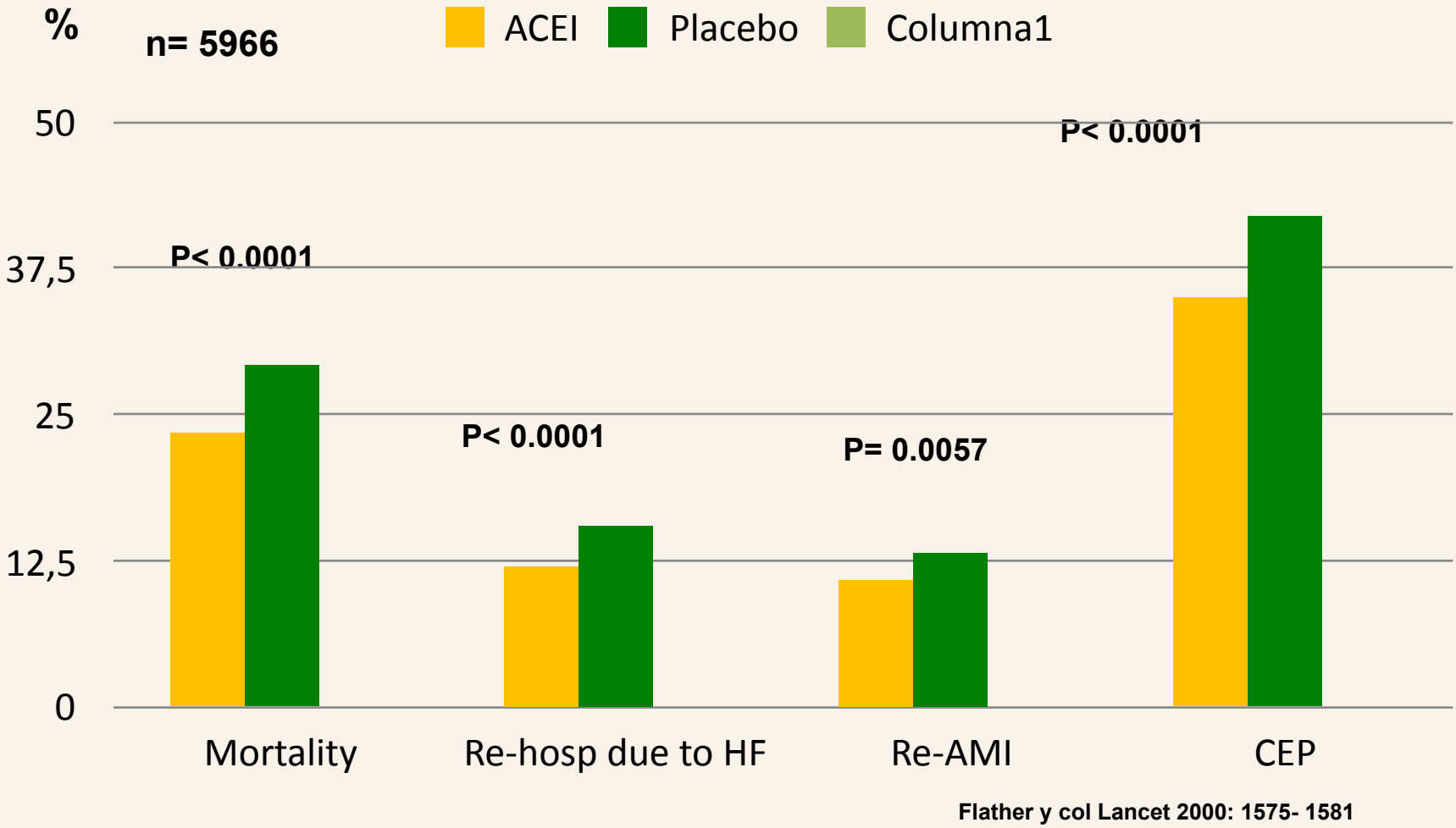
Mortality and ACEI

Study	Drug	Follow-up	Placebo (%)	ACEI (%)	P
SMILE	Zofenopril	42 days	6.5	4.9	NS
		12 mos	14.1	10	0.01
SAVE	Captopril	42 mos	25	20	0.019
AIRE	Ramipril	15 mos	23	17	0.002
TRACE	Trandolapril	26 mos	42	35	0.001

ACEI: angiotensin converter enzyme inhibitors

POST-AMI HEART FAILURE

Mortality and ACEI



Flather y col Lancet 2000: 1575- 1581

POST-AMI HEART FAILURE

- Although ACEI are effective in post-AMI HF, it was observed that aldosterone of RAAS is not completely inhibited by these agents.

- Although the mechanism of this aldosterone “escape” is not clearly defined and taking into account the significant role of it in post-AMI HF, a complete hormone blockade beyond ACEI is essential to achieve a more sustained benefit.

- In this regard, the VALIANT study evaluated the additive effects of valsartan, an antagonist of angiotensin II receptors (ARAII) in patients with post-AMI HF.

POST-AMI HEART FAILURE

- The combination of ACEI and ARA II did not yield an additional clinical advantage in terms of morbidity and mortality. Anyway, this study showed non-inferiority of valsartan, so in those cases in which ACEI is not well tolerated (coughing), they can be replaced by this type of drug.

- A third modality to block RAAS is through aldosterone blockade with beneficial effects as the RALES study showed in chronic HF.

- These observations have promoted the evaluation of such strategy in patients with post-AMI HF.

POST-AMI HEART FAILURE

Eplerenone

	RR (%)	p
Total mortality	15	0.008
CV mortality	17	0.005
CEP	13	0.002
Sudden cardiac death	21	<0.03
Hosp due to HF	15	0.03

POST-AMI HEART FAILURE

Eplerenone

Follow-up at 30 days

	RR (%)	p
Total mortality	31	0.004
CV mortality	32	0.003
Sudden cardiac death	37	0.051

EPHESUS JACC 2005; 46: 425- 431

POST-AMI HEART FAILURE

Beta blockers

- Initially used orally, in the pre-thrombolytic era, as secondary prevention for their benefits on mortality and re-infarction incidence, beta blockers were considered contraindicated in patients with post-AMI HF, with the idea that a blockade of sympathetic activity could be harmful.

- The success of ACEI as first-line therapy to improve the prognosis of AMI and the advent of reperfusion therapies have made of beta blocking benefits something uncertain.

POST-AMI HEART FAILURE

CAPRICORN study

	RR (%)	p
Total mortality	23	0.031
CV mortality	25	0.024
Non-fatal AMI	40	0.014
Atrial fibrillation	59	0.003
Malignant arrhythmias	76	0.0001

Lancet 2001; 357: 1385- 1390

CONCLUSIONS

- Heart failure is a very frequent complication after AMI associated to significant mortality and morbidity.

- The main determinant is the loss of functioning myocardium that starts up a series of compensating mechanisms that paradoxically may induce a greater and progressive deterioration of ventricular function.

CONCLUSIONS (cont'd)

- Thus, a timely reperfusion taking into account time and not the way to implement it (fibrinolytic agents or PTCA), appears as the critical determinant of the evolution of patients that present this complication.

- Both IRA recanalization and the achievement of an appropriate myocardial perfusion are key to recover ventricular function through limiting the size of the AMI.

- In this regard, great advances in reperfusion strategies and technology have allowed to obtain an efficient epicardial reperfusion.

CONCLUSIONS (cont'd)

- However, great results have not been achieved yet at microvascular level, which still constitutes a limitation at the moment of reducing the size of infarction.

- The implementation of therapies that act on the neurohormonal system activation (SNS, RAAS) tending to reduce ventricular remodeling in these patients has been remarkably beneficial with a significant impact on mortality and morbidity in the short and long term.

CONCLUSIONS (cont'd)

- The current trends in post-AMI HF incidence and prognosis evaluated in large registries such as GRACE, report a reduction of this complication over time (9% decrease in STEMI and 6.5% in NSTEMI by the end of 2005).
- Likewise, the WHAS study verified a decrease of in-hospital mortality when comparing terms since 1975 to year 2005.

CONCLUSIONS (cont'd)

- Taking into account that these findings were observed in spite of a progressively older population, as well as with increasing co-morbidities (diabetes, hypertension, prior HF, etc), these better trends probably reflect improvements in reperfusion techniques, more effective adjunct therapies, and increased use of therapeutic resources in the last few decades.

- However, mortality by post-AMI HF is still high and these therapies are still underused in many places, so we should focus our efforts in ensuring that each and every elegible patients is treated appropriately according to the evidence to optimize the evolution of this severe complication of AMI.