ΣΤΕΦΑΝΙΑΙΑ ΝΟΣΟΣ

ΔΗΜΗΤΡΙΟΣ ΤΟΥΣΟΥΛΗΣ
ΚΑΘΗΓΗΤΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ
ΠΑΝ/ΜΙΟΥ ΑΘΗΝΩΝ

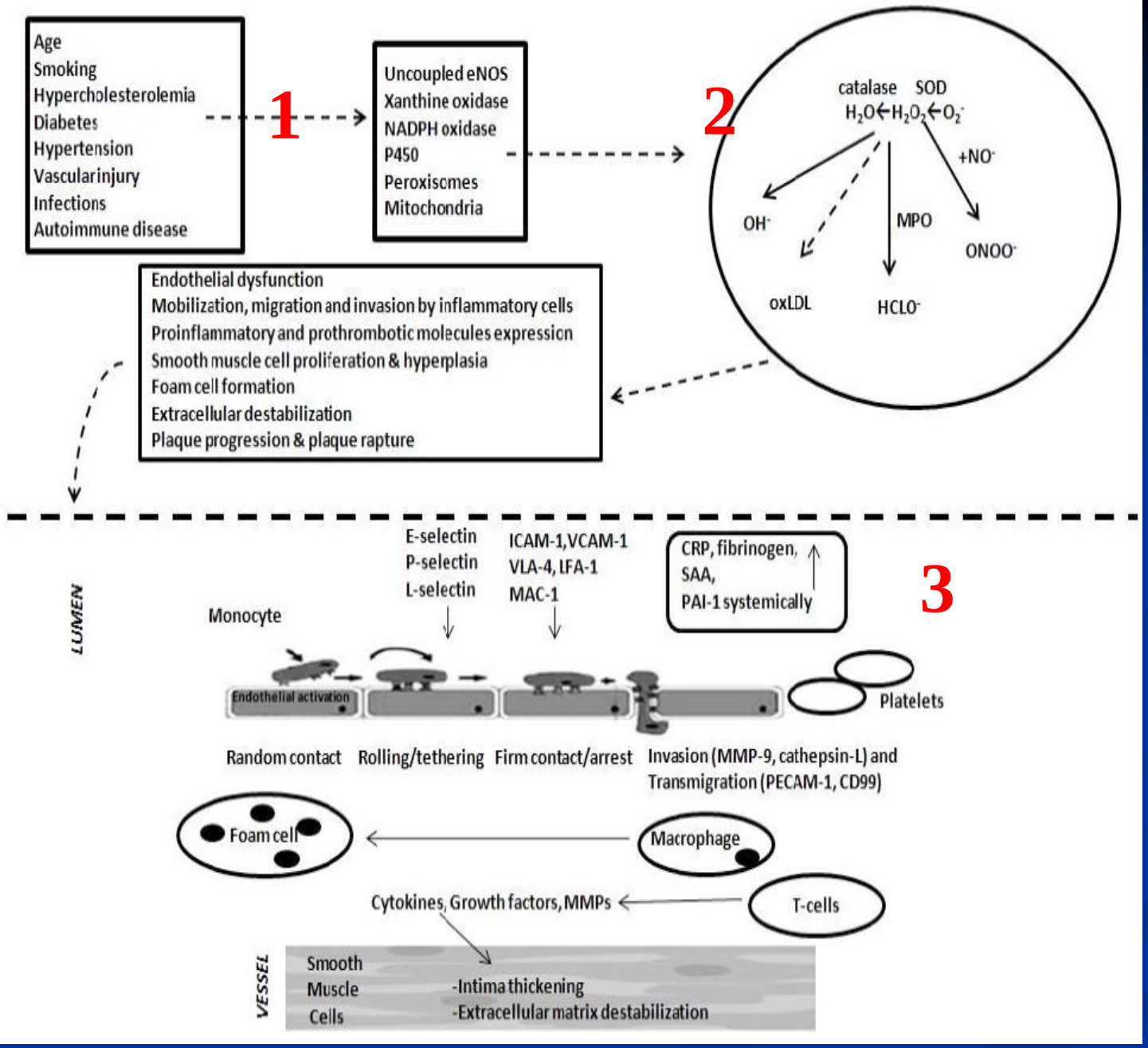
ΣΤΕΦΑΝΙΑΙΑ ΝΟΣΟΣ ΑΘΗΡΩΜΑΤΩΣΗ

Στεφανιαία νόσος

- Στηθάγχη – Herbeden, 1772, Αγγλία.
- Εμφραγμα – Herrick, 1912, Καναδάς.
- Αθηρωματική πλάκα - Virchow – Γερμανία, 1850, Rokitansky - Αυστρία, 1850.

Στεφανιαία νόσος-Παθοφυσιολογία

- Ενδοθήλιον
- Παράγοντες κινδύνου
- Φλεγμονη
- Αθηρωματική πλάκα
- Θρόμβωση



Βασικά στάδια αθηρογένεσης:

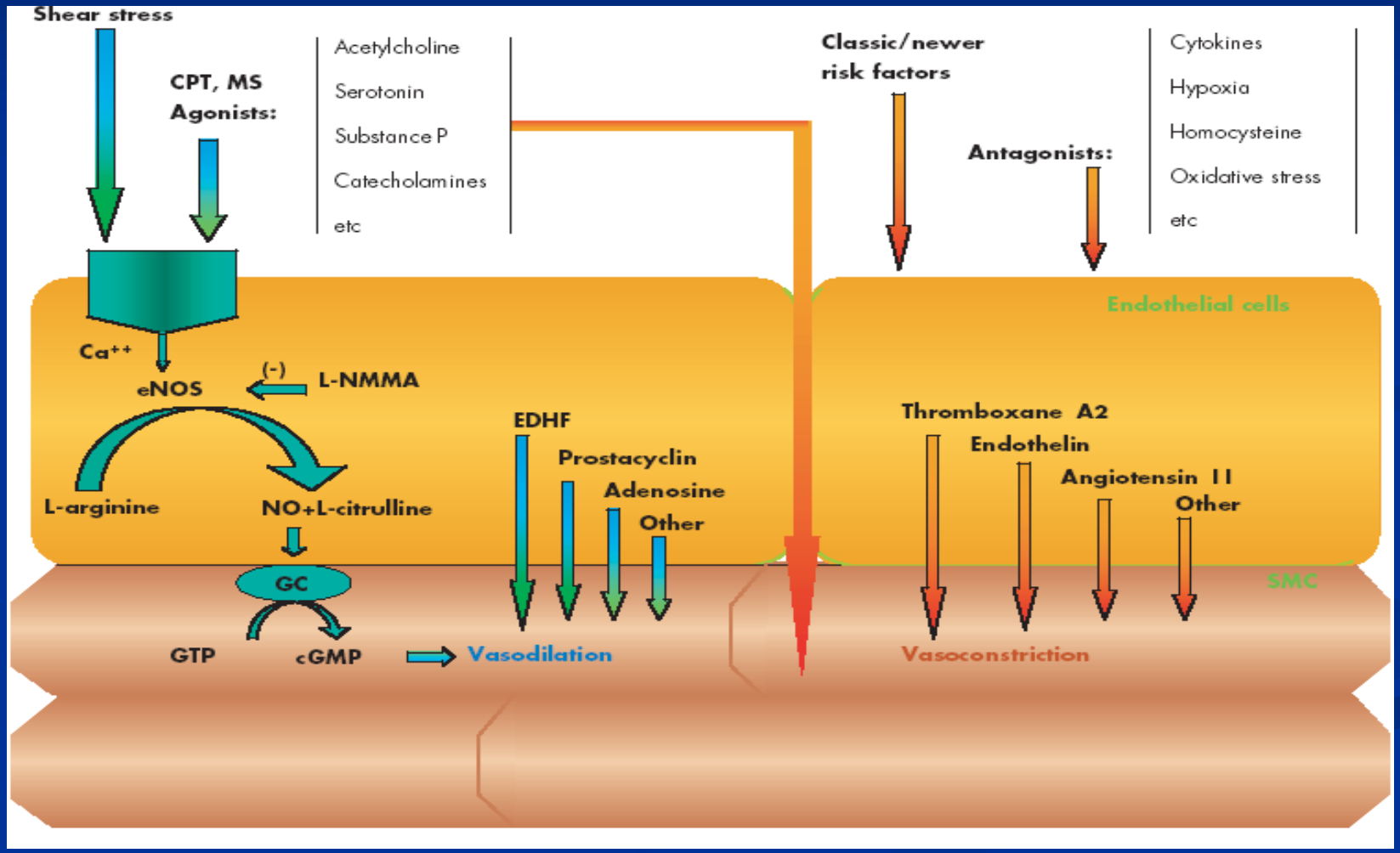
1. **Οι παράγοντες κινδύνου προκαλούν ενδοθηλιακή δυσλειτουργία**
2. **Ταυτόχρονη παραγωγή ελευθέρων ριζών οξυγόνου**
3. **Πυροδότηση τοπικής φλεγμονώδους διεργασίας με παραγωγή κυτοκινών και αυξητικών παραγόντων**

ΑΘΗΡΟΣΚΛΗΠΥΝΣΗ

Stefanadi E, Tousoulis D…Stefanadis C . Curr Med Chem 2010

Βασικές λειτουργίες του ενδοθηλίου

- Διατήρηση του αγγειακού τόνου: αγγειοδιαστολή-αγγειοσύσπαση

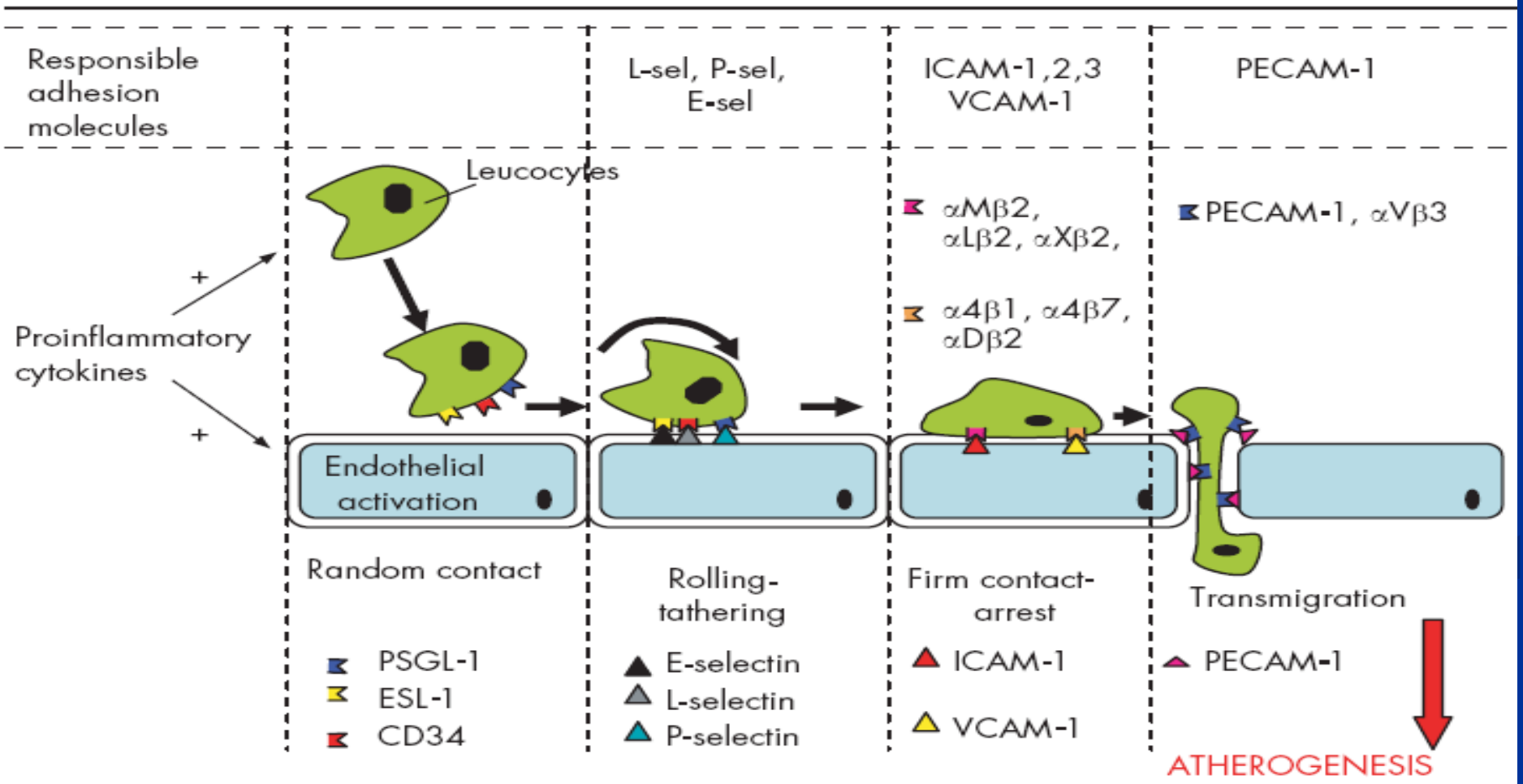


Tousoulis, et al., Heart 2005; 91: 353-358.

ASSESSING INFLAMMATORY STATUS IN CARDIOVASCULAR DISEASE

Dimitris Tousoulis, Charalambos Antoniades, Christodoulos Stefanadis

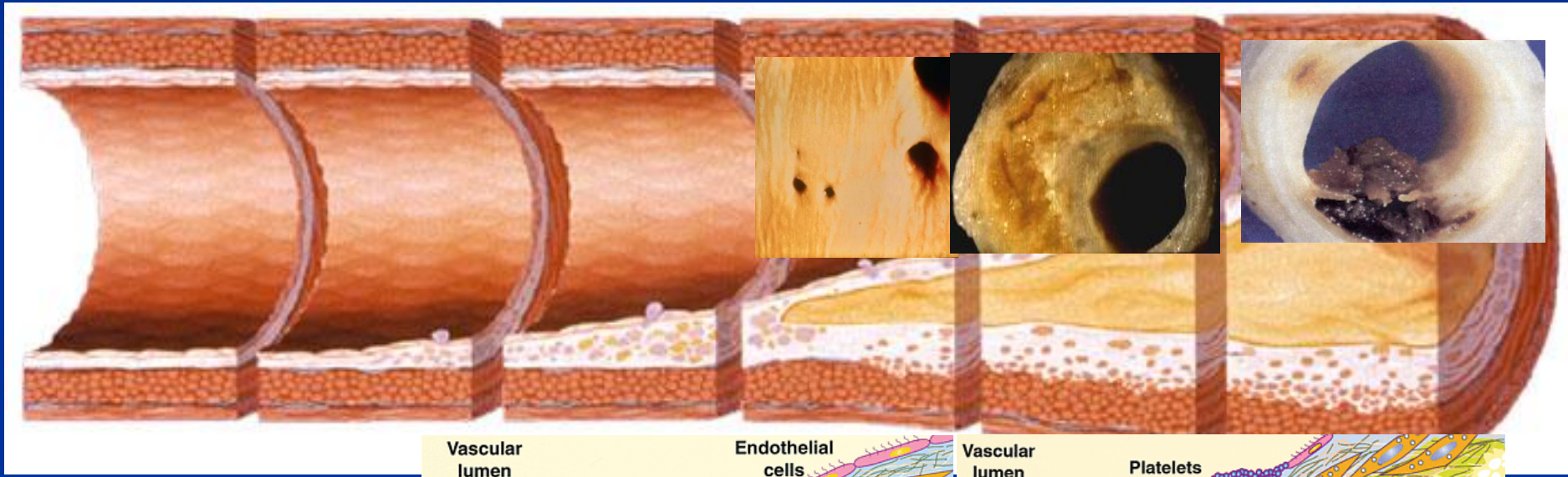
Heart 2007;**000**:000–000. doi: 10.1136/hrt.2006.088211

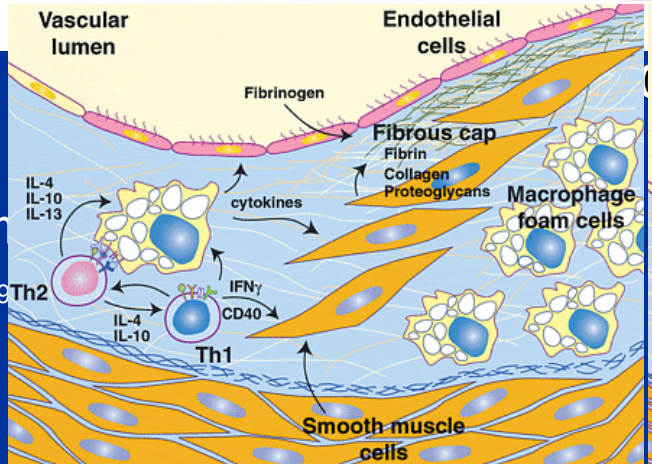


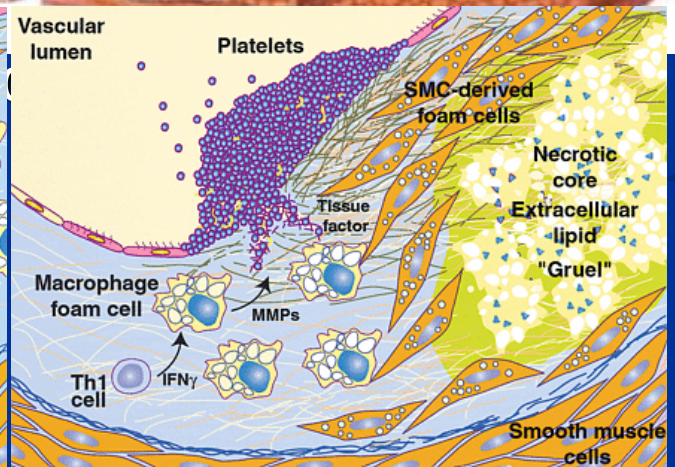
ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ ΣΤΕΦΑΝΙΑΙΑΣ ΝΟΣΟΥ

Atherosclerosis Timeline

Foam Cells | Fatty Streak | Intermediate Lesion | Atheroma | Fibrous Plaque | Complicated Lesion/Rupture



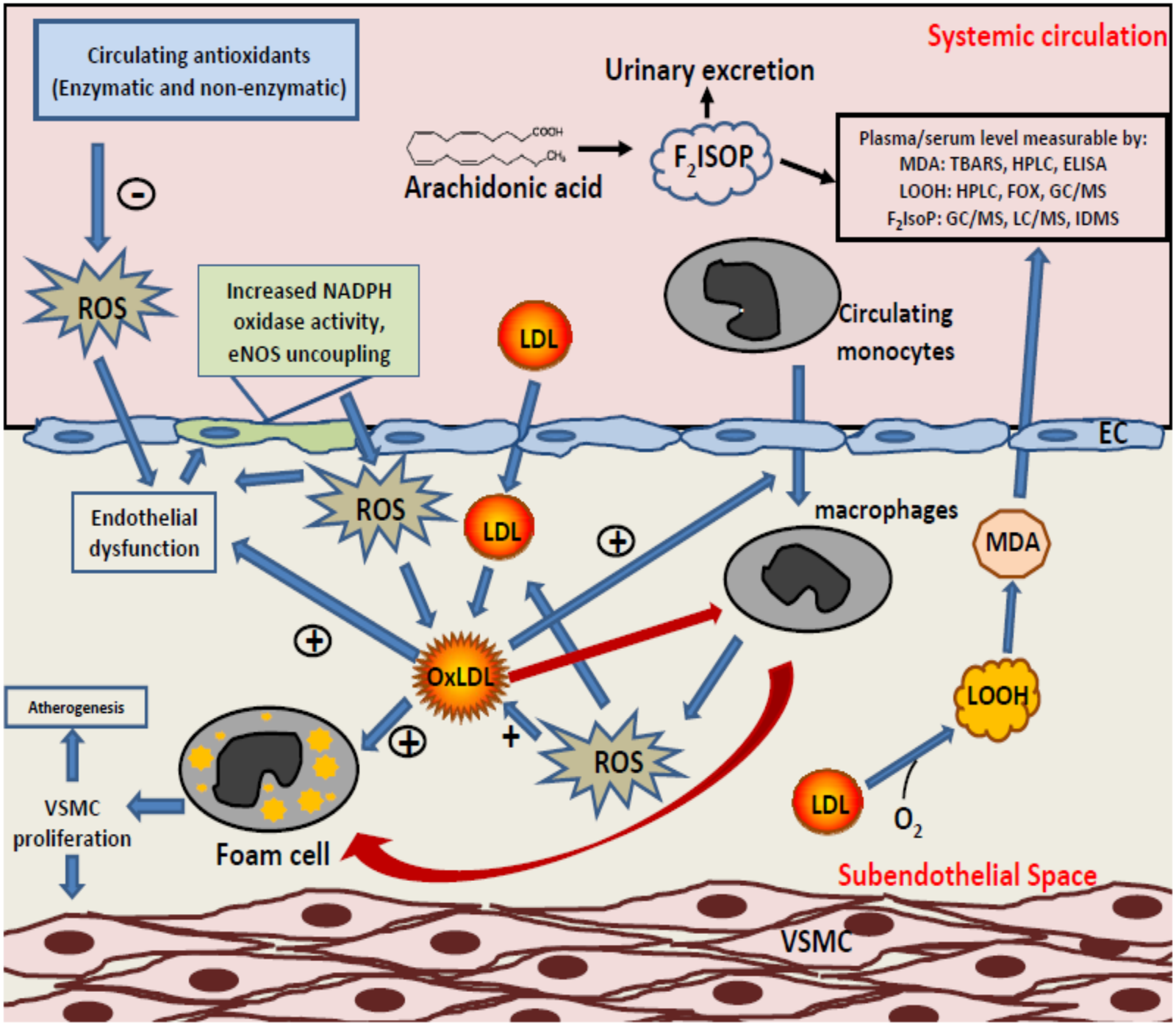




From first decade

Growth mainly by inflam

(Adapted from Stary et al. Circulation. 19


Systemic circulation
Circulating antioxidants
(Enzymatic and non-enzymatic)
Urinary excretion
COOH
CH3
Arachidonic acid
F2ISOP
Plasma/serum level measurable by:
MDA: TBARS, HPLC, ELISA
LOOH: HPLC, FOX, GC/MS
F2IsoP: GC/MS, LC/MS, IDMS
ROS
Increased NADPH
oxidase activity,
eNOS uncoupling
LDL
Circulating
monocytes
EC
Endothelial
dysfunction
ROS
LDL
macrophages
MDA
OxLDL
LOOH
Atherogenesis
ROS
LDL
O2
VSMC
proliferation
Foam cell
Subendothelial Space
VSMC

ΚΛΑΣΣΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ Σ.Ν.

Τρόπος ζωής και άλλα χαρακτηριστικά τα οποία σχετίζονται με αυξημένο κίνδυνο για ΣΝ-Ι

- Δίαιτα πλούσια σε κορεσμένα λιπαρά, χοληστερόλη και θερμίδες
- Αυξημένη αρτηριακή πίεση
- Κάπνισμα
- Αυξημένα επίπεδα ολικής χοληστερόλης
- Μεγάλη κατανάλωση αλκοόλ
- Καθιστική ζωή
- Χαμηλή HDL-χοληστερόλη
- Παράγοντες θρομβογένεσης
- Αυξημένα τριγλυκερίδια
- Υπεργλυκαιμία /διαβήτης
- Παχυσαρκία

Κάπνισμα-Παχυσαρκία

-Αρτηριακή Υπέρταση (ΑΠ ≥ 140/ 90 mmHg ή υπο αγωγή)

-Χαμηλή HDL(<40 mg/dl)

-Διαβήτης-Κάπνισμα

-Οικογενειακό Ιστορικό πρωίμου ΣΝ

(Σε πρώτου Βαθμού συγγενείς: Άνδρες <55, Γυναίκες <65 ετών)

- Ηλικία (Άνδρες ≥45, Γυναίκες ≥55 ετών)

ΓΕΝΕΤΙΚΗ ΣΤΗΝ ΑΘΗΡΩΘΡΟΜΒΩΣΗ

ΕΙΔΙΚΕΣ ΓΟΝΙΔΙΑΚΕΣ ΜΕΛΕΤΕΣ

Table 2 continued

Chromosomal locus	Gene name	Gene symbol	References
17q11.2-q12	Chemokine, CC motif, ligand 2	*CCL2*	McDermott et al. (2005)
17q21.1-q21.2	Chemokine, CC motif, ligand 11	*CCL11*	Zee et al. (2004)
17q21.32	Integrin, beta-3	*ITGB3*	Weiss et al. (1996)
17q23	Angiotensin I-converting enzyme		Cambien et al. (1992)
17q23	Platelet-endothelial cell adhesion molecule 1		Elrayess et al. (2004)
19p13	Purinergic receptor P2Y, G protein-coupled, 11	*P2RY11*	Amisten et al. (2007)
19p13.3-p13.2	Intercellular adhesion molecule 1	*ICAM1*	Podgoreanu et al. (2006)
19p13.2	Zinc finger protein 627	*ZNF627*	Shiffman et al. (2005) and
19q13.1	Transforming growth factor, beta 1	*TGFB1*	Yamada et al. (2008)
19q13.2	Apolipoprotein E	*APOE*	Yokota et al. (2000)
19q13.2	Heterogeneous nuclear ribonucleoprotein U-like 1	*HNRPUL1*	Wilson et al. (1994)
19q13.4	Glycoprotein VI, platelet	*GP6*	Shiffman et al. (2006)
19q13.4	Fc fragment of IgA, receptor for	*FCAR*	Croft et al. (2001)
20p11.2	Thrombomodulin	*THBD*	Iakoubova et al. (2006)
20q11.2-q13.1	Matrix metalloproteinase 9	*MMP9*	Wu et al. (2001)
20q13.11-q13.13	Prostaglandin I2 synthase	*PTGIS*	Zhang et al. (1999)
21q21.2	ADAM metallopeptidase with thrombospondin type 1 motif, 1	*ADAMTS1*	Nakayama et al. (2002)
22q11.2	Catechol-O-methyltransferase	*COMT*	Sabatine et al. (2008)
22q12	Heme oxygenase 1	*HMOX1*	Erikson et al. (2004)
22q12-q13	Lectin, galactoside-binding, soluble, 2	*LGALS2*	Ono et al. (2004)
13q14.11		*VKORC1*	Ozaki et al. (2004)
13q34		*MMP2*	
13q34		*CETP*	
14q13	Collagen, type	*CYBA*	Kuivenhoven et al.
15q15	Proteasome subunit, alpha	*GP1BA*	Inoue et al. (1998)
15q21-q23	Thrombospondin I	*CXCL16*	Murata et al. (1997)
16p13.3	Lipase, hepatic	*SLC6A4*	Lundberg et al. (2005)
16p13	Deoxyribonuclease I		Fumeron et al.
16p11.2	Major histocompatibility complex, class II, transactivator		
16q13	Vitamin K epoxide reductase complex, subunit 1		
16q21	Matrix metalloproteinase 2		
16q24	Cholesteryl ester transfer protein, plasma		
17pter-p12	Cytochrome b(-245), alpha subunit		
17p13	Glycoprotein Ib, platelet, alpha polypeptide		
17q11.1-q12	Chemokine, CXC motif, ligand 16		
	Solute carrier family 6, member 4		

ACE

Yamada et al; Genomic Med. 2008 2:7–22

Στεφανιαία νόσος – Θεραπεία

- Νιτρώδη – Brunten, 1876.
- Στρεπτοκινάση - θρομβόλυση – Ρωσία, 1975.
- Ασπιρίνη, Γερμανία 1980,κλοπιδογρέλη , ΗΠΑ 1990.
- Στατίνη, Ιαπωνία 1994.
- Bypass – Kolesov, Ρωσία ,1964.
- PTCA, Gruentzig, Ελβετία, 1977.
- Stent – Sigwart, Ελβετία,1986.

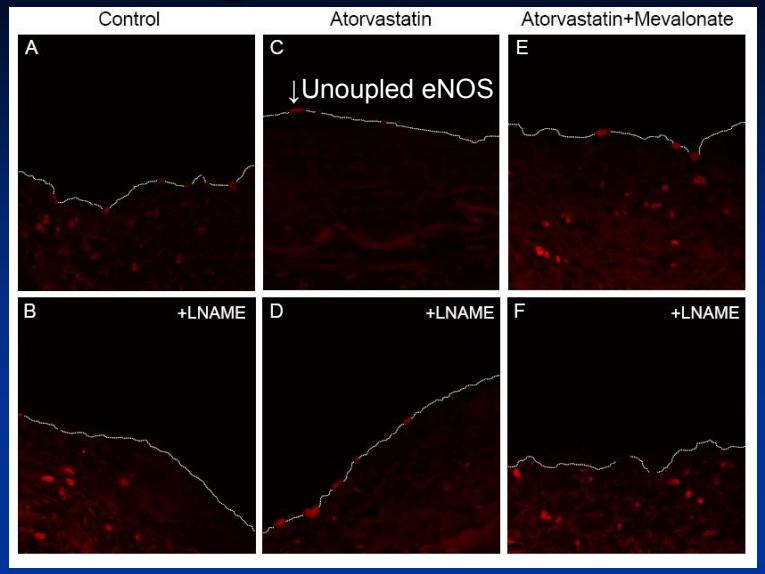
Φαρμακογενετική αγωγής με στατίνες

Table 1 Recent pharmacogenomic studies of statin efficacy and adverse drug responses (ADRs)

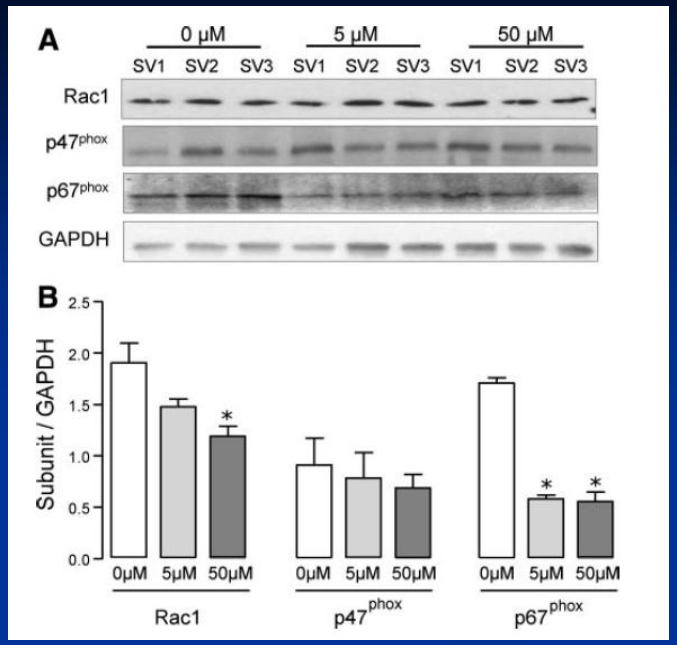
Gene[a]	Variant	Statin[b]	Patients[b]	*n*	Outcome[b]	Observation[b]
Genes involved in statin pharmacodynamics						
APOE	ε_2, ε_3, ε_4	PV	DL	33	PD	ε_4, reduced LDL-cholesterol response
APOE	ε_2, ε_3, ε_4	AV	DL	272	PD	No effect
APOE	ε_2, ε_3, ε_4	PV	REGRESS	815	PD	ε_2, increased HDL, LDL/HDL, lower angiographic response
APOE	ε_2, ε_3, ε_4	M	DL	100	PD	ε_2, increased HDL response
APOE	ε_2, ε_3, ε_4	SV, LV	DM CP	96	PD	ε_4, greater LDL-cholesterol response than ε_2
LPL	Haplotypes	LV	CABG	829	PD	Haplotypes related to elevated and reduced HDL response; elevated TG response; graft progression protection
CETP	TaqIB	PV	CAD	1002	PD, E	No genotypic effect
ACE	In/del	PV	GenHAT	4741	E	No genotypic effect
LOX1	3UTR	AV, SV	DL	751	E	Increased events
CYP7A1	A-204C	PV	DL	33	PD	No genotypic effect
Genes involved in pleiotropic statin response						
eNOS	T-786C	AV	Healthy	30	PL	Altered plasma nitrate, thiobarbituric acid-RS response
IL6	G-174C	AV	CAD	24	PD, PL	No genotypic effect on lipid or IL-6 response
IL6	G-174C	SV	DL	N/A	PL	No genotypic effect on plasma IL-6 response
PAI-1	4G/5G, 5G/5G	PV	HUVECs	N/A	PL	4G/5G, reduced secreted PAI-1 response
Genes involved in statin pharmacokinetics						
SLCO1B1	T521C	SV	Healthy	32	PK-S	Elevated SV in plasma
SLCO1B1	T521C	PV	Healthy	16	PK-M, PD	Higher AUC following multiple doses; no PD response
SLCO1B1	G-11187A, T521C	PV	Pediatric DL/CT	20/12	PK-S, PD	G-11187A-reduced Cmax, AUC, and $t_{1/2}$; greater HDL-cholesterol T521C-reduced TC and LDL-cholesterol response; greater HDL-cholesterol
SLCO1B1	*1a, *1b, *15	PV	Healthy	23	PK-S	*1b-reduced AUC
SLCO1B1	T521C	FLV, PV	Healthy	32	PK-S	Increased AUC for PV but not FLV; men not women
SLCO1B1	*15	PV	DL	33	PD	*15-reduced response at 8 weeks; no change at 1 year
ABCB1	G2677T/A, C3435T	PV	Pediatric DL/CT	20/12	PK-S, PD	No observed response
ABCC2	C1446G	PV	Healthy	41	PK-S	Lower AUC; higher mRNA expression in liver samples
BCRP	C421A	RV	Healthy	14	PK-S	CC-reduced AUC, Cmax
CYP2D6	*1, *4	M	DL	100	PD	*1/*4 and *4/*4, higher efficacy
CYP3A5	*1, *3	SV	Healthy	22	PK-S	*3, elevated plasma AUC; reduced plasma clearance
Genes involved in statin-induced ADRs						
CPT2	Various[c]	M	ADR cases versus controls: HV, non-ADR DL, NSM	136	ADR	Variants that were identified in nonstatin induced myopathy were over-represented in statin ADR cases versus HV and non-ADR controls
PYGM				100		
AMPD1				116/106		
CYP3A5	*3	M	ADR cases, non-ADR controls	50/50	ADR	No genetic effect on rate of ADR
CYP2C9	*2, *3					
CYP2D6	*3, *4, *5, *6					

Mangravite et al; Curr Opin Lipidol 2009;18:409–414

Pharmacogenomics in AMI: Pleiotropic effects of statins

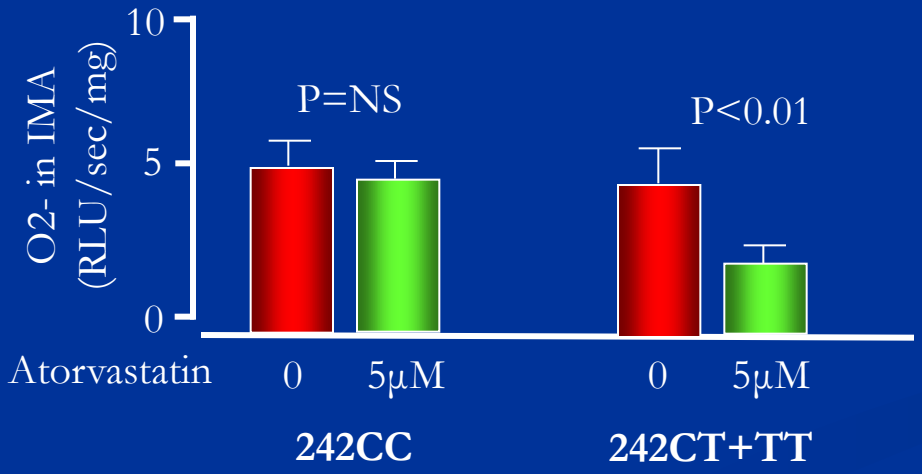


Antoniades C et al; Circulation 2011;24(3):335-45



Antoniades C, Tousoulis D, Stefanadis et al; Circulation 2010;122:66 –73

C242T SNP in p22phox →72 His/Tyr subst



ΑΝΤΙΣΤΑΣΗ ΣΤΗΝ ΚΛΟΠΙΔΟΓΡΕΛΗ

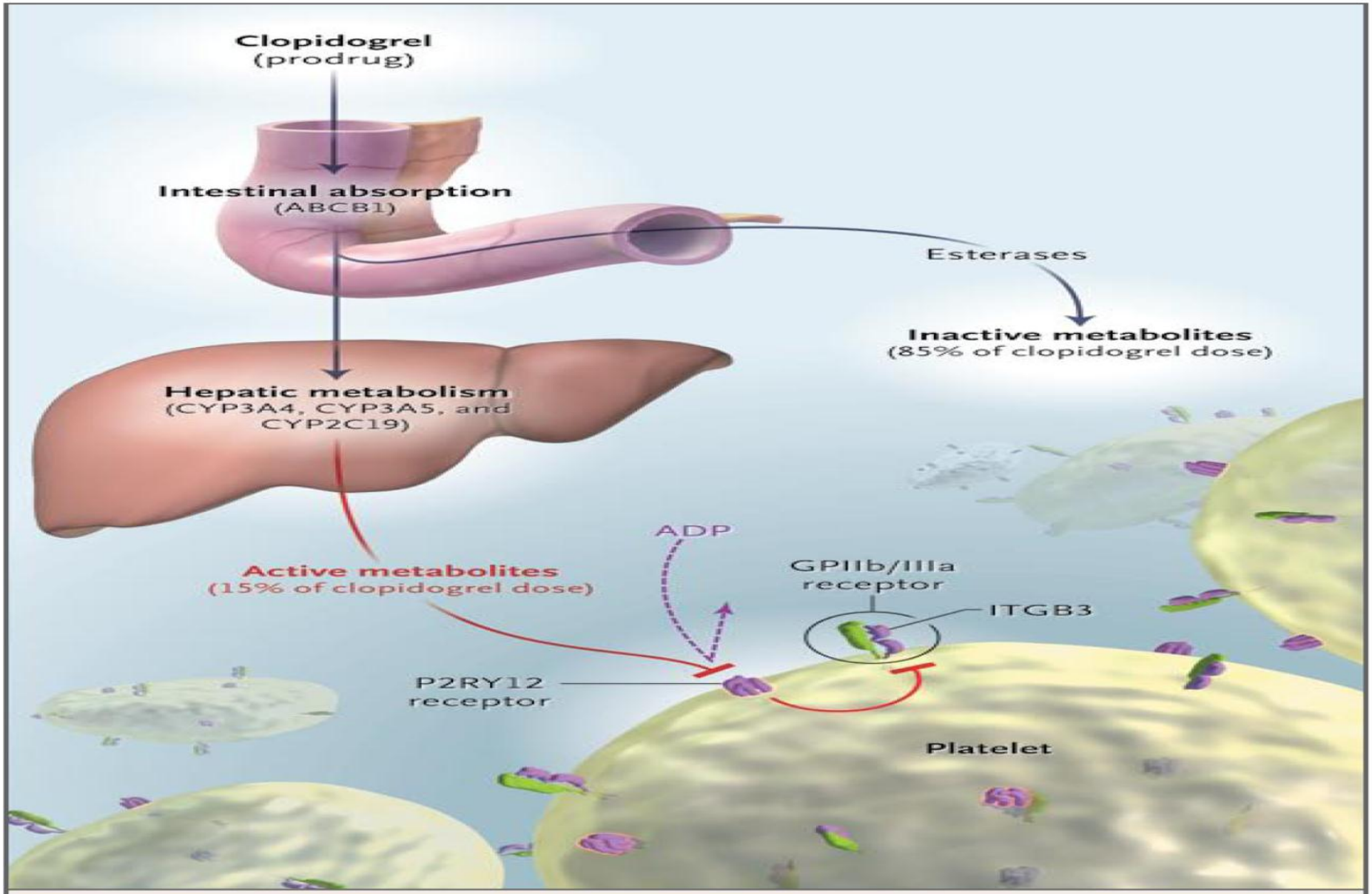


Figure 1. Roles in Clopidogrel Activity of Proteins with Known Genetic Polymorphisms.

Intestinal absorption of the prodrug clopidogrel is limited by an intestinal efflux pump P-glycoprotein coded by the *ABCB1* gene. The majority of the prodrug is metabolized into inactive metabolites by ubiquitous esterases. The minority is bioactivated by various cytochrome P450 (CYP) isoforms into active metabolites. These metabolites irreversibly antagonize the adenosine diphosphate (ADP) receptor (coded by the *P2RY12* gene), which in

Μπορεί να οριστεί ως «η αδυναμία της κλοπιδογρέλης να αναστείλει την συγκόλληση των αιμοπεταλίων που επάγεται από την ADP»

(ανιχνεύονται στοιχεία υπολειπόμενης δραστηριότητας του P2Y12 υποδοχέα μετά από την αγωγή)

De Miguel et al. Thromb Haemost 2008; 100: 196–203

ΚΡΙΤΗΡΙΟ

Εμπειρικά... «ελάττωση <10% της συγκόλλησης των αιμοπεταλίων σε απόκριση στα 5 μmol/L ADP»

Wiviott et al Circulation. 2004;109:3064-3067

Μελέτες αναφερόμενες στην επίπτωση της αντίστασης στην κλοπιδογρέλη

Table 1 Clopidogrel resistance studies

Investigators	*n*	Patients	Clopidogrel dose (mg, load/qd)	Definition of clopidogrel resistance	Time	Incidence
Gurbel et al [9]	92	PCI	300/75	5 and 20 uM ADP-induced aggregation <10% absolute change	24 h	31 35%
Jaremo et al [27]	18	PCI	300/75	ADP-induced fibrinogen binding <40% of baseline	24 h	28%
Muller et al [28]	119	PCI	600/75	5 and 50 uM ADP-induced aggregation <10% relative change	4 h	5 11%
Mobely et al [29]	50	PCI	300/75	1 uM ADP-induced aggregation, TEG and Ichor PW; <10% absolute inhibition	Pre and post	30%
Lepantalo et al [30]	50	PCI	300/75	2 or 5 uM AD-induced aggregation and PFA-100 10% inhibition and 170s	2.5 h	40%
Angiolillo et al [31]	48	PCI	300/75	6 uM ADP-induced aggregation <40% inhibition	10 min, 4 and 24 h	44%
Matetzky et al [32]	60	STEMI	300/75	5 uM ADP-induced aggregation and CPA <10% inhibition	Daily for 5 days	25%
Dziewierz A et al [33]	31	CAD	300	20 uM ADP-induced aggregation <10% absolute change	24 h	23%
Lev El et al [34]	150	PCI	300	5 uM ADP-induced aggregation <10% absolute change	20 24 h	24%
Angiolillo et al [35]	52	Diabetics and non-diabetics	300	<10% relative inhibition	24 h	38% diabetics 3% non-diabetics
Gurbel et al [25]	190	PCI	300 or 600/75	5 and 20 uM ADP-induced aggregation <10% absolute inhibition	24 h	28 32% with 300 mg 8% with 600 mg

Abbreviations— PCI = percutaneous coronary interventions; ADP = adenosine diphosphate; CAD = Coronary artery disease; TEG = thrombelastography; PW = Plateletworks; PFA-100 = Platelet function analyzer-100; CPA = Cone and platelet analyzer.

Gurbel et al. Thrombosis Research 2007;120:311–321

ΜΗΧΑΝΙΣΜΟΙ

- Ιδιοσυγκρασιακά χαρακτηριστικά
- Μειωμένη βιοδιαθεσιμότητα
- Μεταβλητή κάθαρση του ενεργού μεταβολίτη της κλοπιδογρέλης
- Εναλλακτικές οδοί ενεργοποίησης των αιμοπεταλίων
- Γενετικοί πολυμορφισμοί
- Αυξημένη απελευθέρωση ADP
- Αλλαγές στο μεταβολισμό της κλοπιδογρέλης μέσω του κυτοχρώματος CYP3A4
- Αύξηση της αντιδραστικότητας του P2Y12 υποδοχέα από την ομεπραζόλη

Schroeder et al. J Thromb Thrombolysis 2006;22:139–150
De Miguel et al. Thromb Haemost 2008; 100: 196–203

JACC Vol. 53, No. 10, 2009
March 10, 2009:898–903

Multiple Mechanisms Affect the Clopidogrel Response

We read with interest the paper by Ang et al. (1) in a previous issue of the *Journal*. The purpose of the study was to identify factors associated with lower platelet inhibition (PI) with clopidogrel in patients with cardiovascular disease. Their results showed that elevated plasma fibrinogen ≥375 mg/dl is a unique factor associated with lower PI in diabetic patients, whereas increased body mass index remains independently associated with lower PI after clopidogrel therapy. They also identify the presence of diabetes mellitus as a factor associated with lower PI. However, this finding was only significant in the presence of an elevated serum fibrinogen level. No other statistical association with PI was found in the multiple variable model.

Although these findings are interesting, other factors involving clopidogrel response have not been completely evaluated. For example, the impact of genetic polymorphisms or other genetic factors on clopidogrel response has not been evaluated in the study. It is well known that $P2Y_{12}$ receptor inhibition is implemented by an active metabolite of clopidogrel. Therefore, genetic variants of enzymes within the metabolic pathways (P450 enzymes) or downstream targets of the active metabolite (P2Y, platelet glycoproteins IIb/IIIa and Ia) might affect clopidogrel response. Moreover, the metabolic activity of the P450 enzymes varies considerably among individuals. Genetic polymorphisms of the cytochrome P450 isoenzymes such as CYP3A4*1B (rs2740574), CYP3A5*3 (rs776746), and CYP2C19*2 (rs4244285) have been implicated to modulated individual response to clopidogrel (2). However, only CYP2C19*2 (SNP rs4244285, AA genotype) polymorphism association with variable clopidogrel response has been validated in both healthy and acute coronary syndrome individuals (3). The association of platelet glycoproteins IIIa and $P2Y_{12}$ receptor polymorphisms with clopidogrel variable response has not been confirmed in previous studies (4), and it should also be examined in the study by Ang et al. (1).

Finally, other mechanisms, such as cellular factors (accelerated platelet turnover, reduced CYP3A metabolic activity, increased ADP exposure, up-regulation of P2Y pathways), or clinical factors (noncompliance, underdosing, poor absorption) may cause suboptimal clopidogrel response.

This interesting study by Ang et al. (1) sheds some light on mechanisms underlying reduced response of platelets to the antiaggregatory effect of clopidogrel. Although the limited number of patients with lower inhibition of platelet reactivity by clopidogrel makes the findings exploratory, further studies with a larger cohort of patients are needed to elucidate the multiple mechanisms involving clopidogrel response.

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***Dimitris Tousoulis, MD, PhD, FACC**
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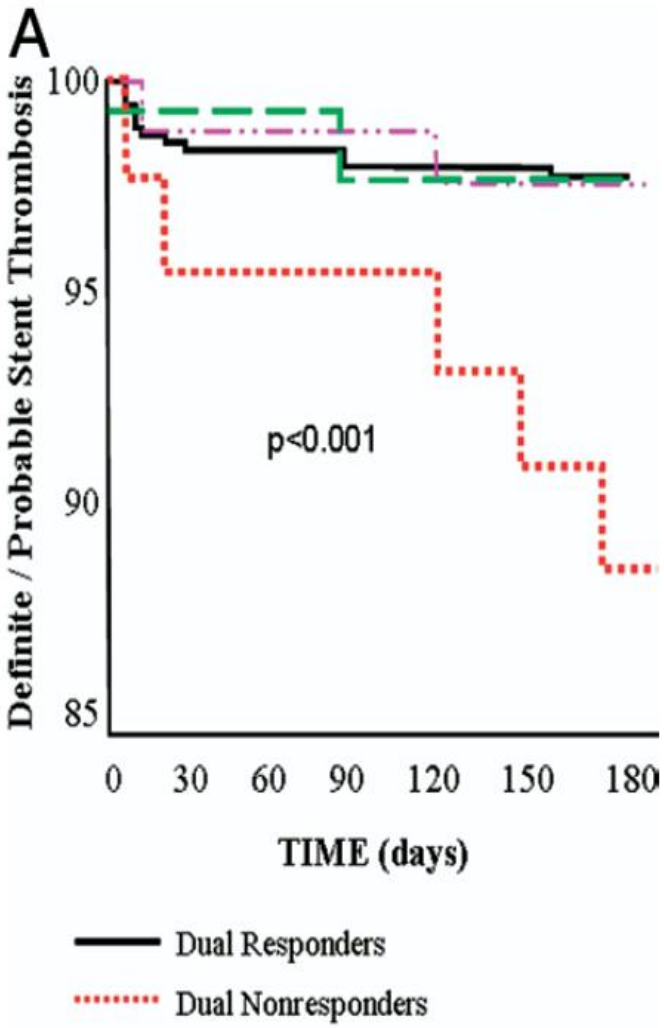
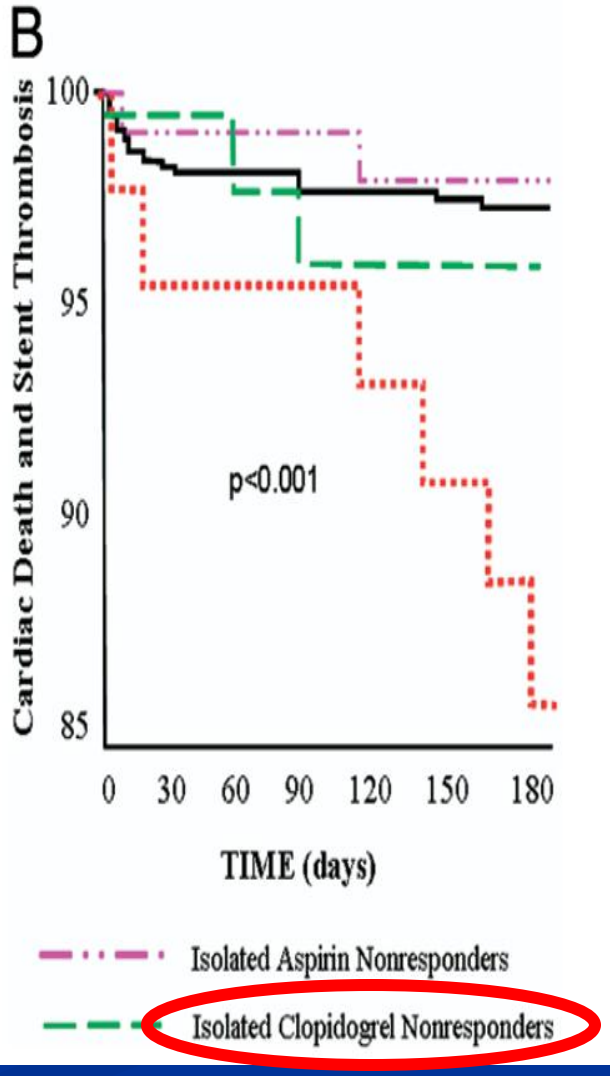
doi:10.1016/j.jacc.2008.09.062

Καμπύλες επιβίωσης Kaplan-Meier αναφορικά στη σχέση θρόμβωσης stent, θανάτου και απόκρισης στην αγωγή με κλοπιδογρέλη και ασπιρίνη

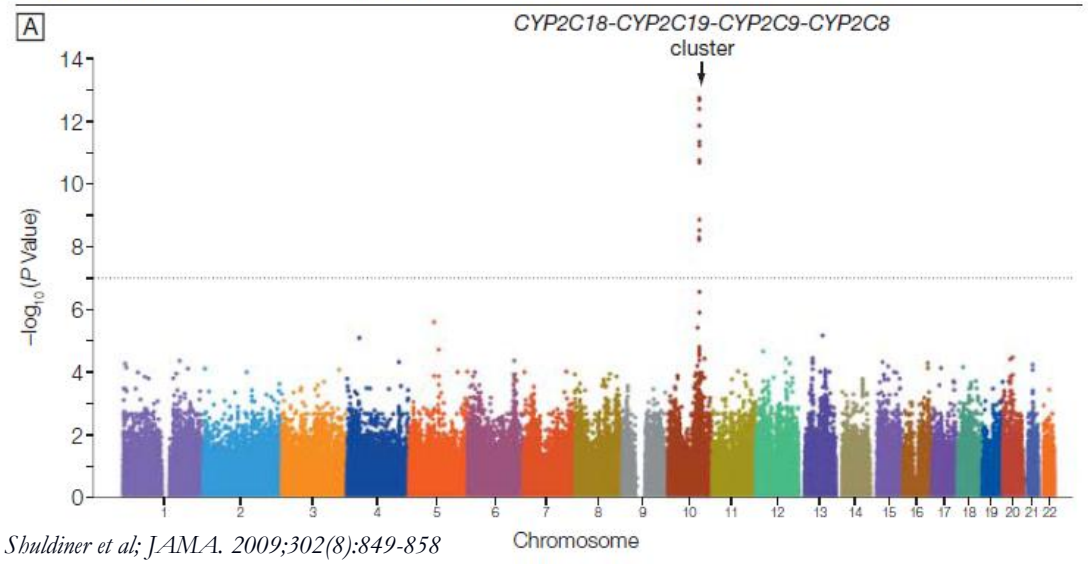




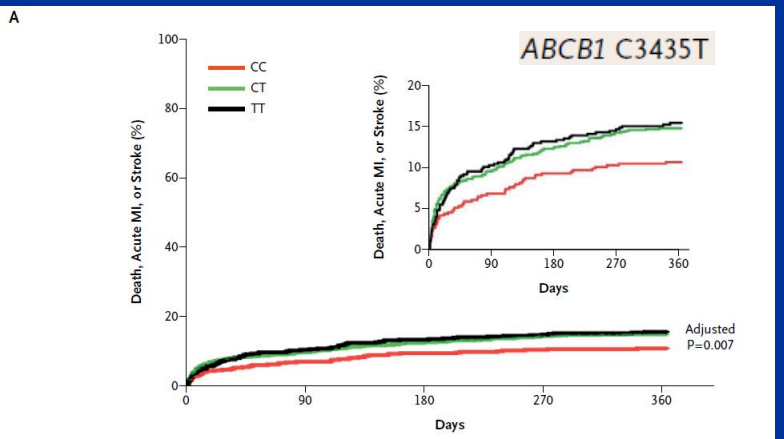
Gori et al. J Am Coll Cardiol 2008;52:734–9

Pharmacognomics in AMI: Clopidogrel

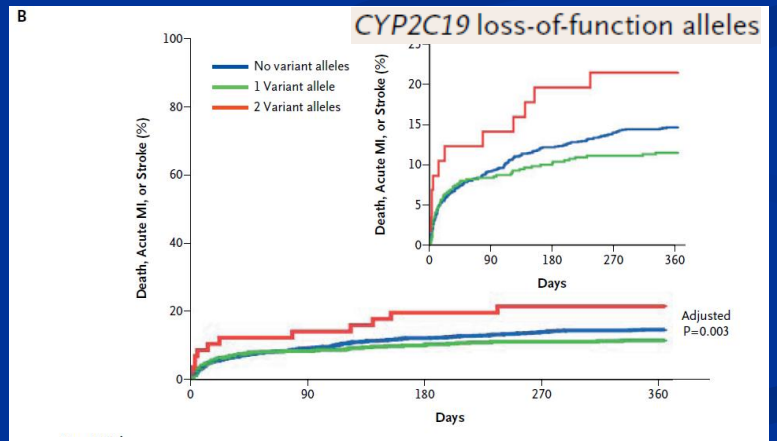
Figure 2. Genome-Wide Association Study of Adenosine Diphosphate–Stimulated Platelet Aggregation in Response to Clopidogrel



Shuldiner et al; JAMA. 2009;302(8):849-858

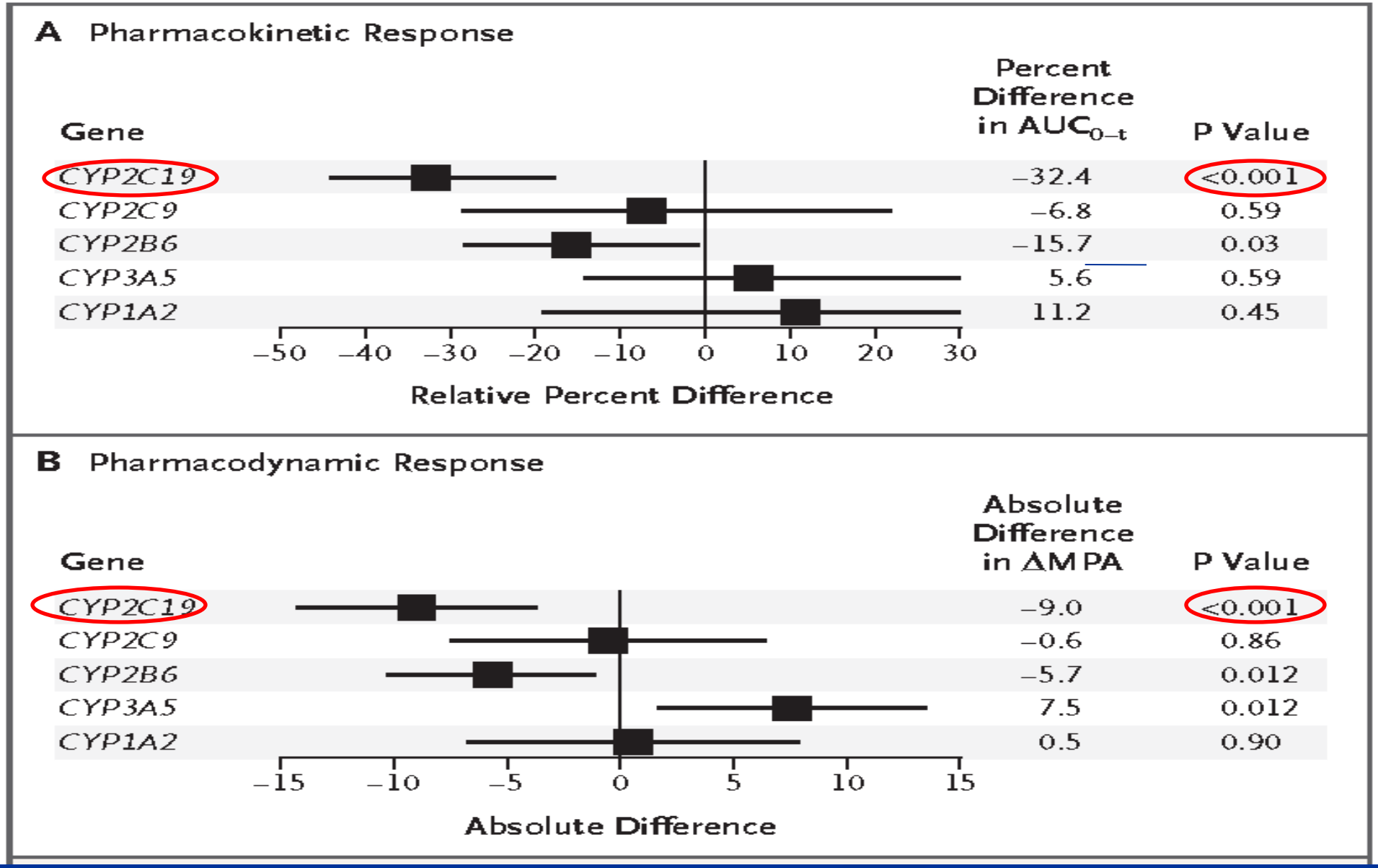


Simon et al; N Engl J Med 2009;360:363-75



Simon et al; N Engl J Med 2009;360:363-75

Ο ρόλος των γενετικών πολυμορφισμών (κυτοχρώματος P-450) στην φαρμακοκινητική και φαρμακοδυναμική απόκριση στην κλοπιδογρέλη



Mega et al. N Engl J Med 2009;360:354-62.

ORIGINAL ARTICLE

Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

Tabassome Simon, M.D., Ph.D., Céline Verstuyft, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrières, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators

ABSTRACT

BACKGROUND

Pharmacogenetic determinants of the response of patients to clopidogrel contribute to variability in the biologic antiplatelet activity of the drug. The effect of these determinants on clinical outcomes after an acute myocardial infarction is unknown.

METHODS

We consecutively enrolled 2208 patients presenting with an acute myocardial infarction in a nationwide French registry and receiving clopidogrel therapy. We then assessed the relation of allelic variants of genes modulating clopidogrel absorption (*ABCB1*), metabolic activation (*CYP3A5* and *CYP2C19*), and biologic activity (*P2RY12* and *ITGB3*) to the risk of death from any cause, nonfatal stroke, or myocardial infarction during 1 year of follow-up.

RESULTS

Death occurred in 225 patients, and nonfatal myocardial infarction or stroke in 94 patients, during the follow-up period. None of the selected single-nucleotide polymorphisms (SNPs) in *CYP3A5*, *P2RY12*, or *ITGB3* were associated with a risk of an adverse outcome. Patients with two variant alleles of *ABCB1* (TT at nucleotide 3435) had a higher rate of cardiovascular events at 1 year than those with the *ABCB1* wild-type genotype (CC at nucleotide 3435) (15.5% vs. 10.7%; adjusted hazard ratio, 1.72; 95% confidence interval [CI], 1.20 to 2.47). Patients carrying any two *CYP2C19* loss-of-function alleles (*2, *3, *4, or *5), had a higher event rate than patients with none (21.5% vs. 13.3%; adjusted hazard ratio, 1.98; 95% CI, 1.10 to 3.58). Among the 1535 patients who underwent percutaneous coronary intervention during hospitalization, the rate of cardiovascular events among patients with two *CYP2C19* loss-of-function alleles was 3.58 times the rate among those with none (95% CI, 1.71 to 7.51).

CONCLUSIONS

Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying *CYP2C19* loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention. (ClinicalTrials.gov number, NCT00673036.)

From Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital Saint-Antoine, and Université Pierre et Marie Curie (UPMC) Paris 06 (T.S., L.Q., E.D.); AP-HP, Hôpital Bicètre, Université Paris Sud 11 (C.V., L.B.); INSERM, Unite 720 (M.M.-K.); AP-HP, Hôpital Bichat; INSERM, Unite 698; and Université Paris 07 (P.G.S.); and AP-HP, Hôpital Européen Georges Pompidou, Université Rene Descartes Paris 05 (N.D.) — all in Paris; Centre Hospitalier Universitaire Besançon, Besançon (N.M.); and INSERM, Unite 558, Toulouse (J.F.) — all in France. Address reprint requests to Dr. Simon at the Department of Pharmacology, UPMC, 27 Rue Chaligny, 75012 Paris, France, or at tabassome.simon@sat.aphp.fr.

Drs. Danchin and Becquemont contributed equally to this article.

This article (10.1056/NEJMoa0808227) was published at NEJM.org on December 22, 2008.

N Engl J Med 2009;360:363-75.
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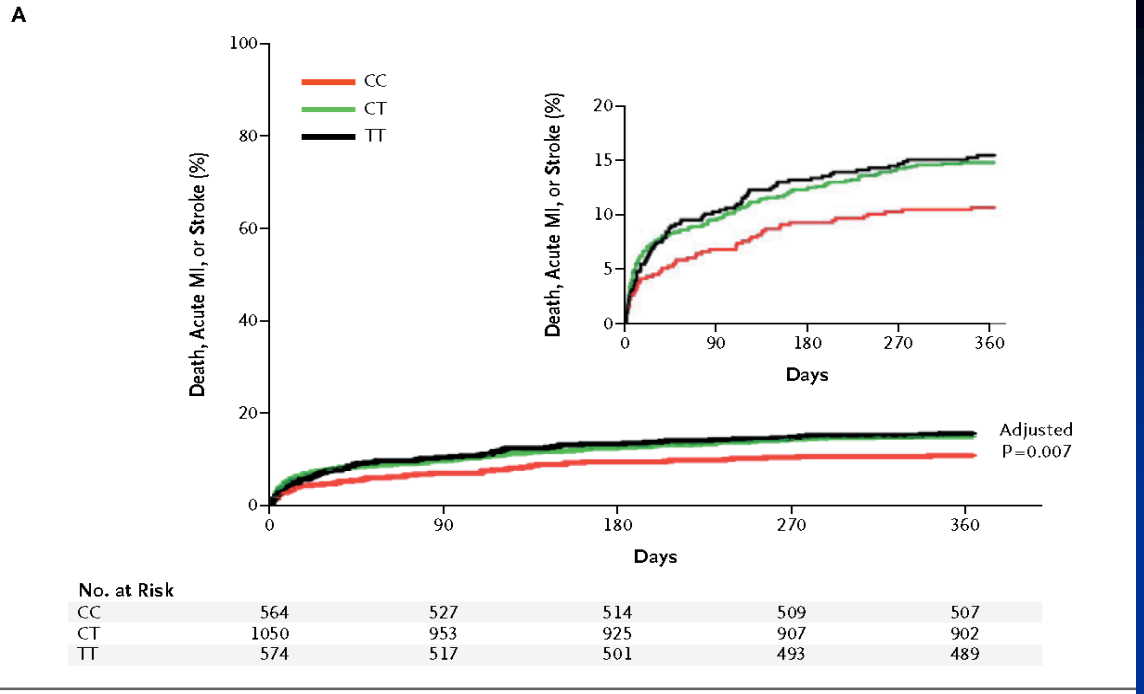
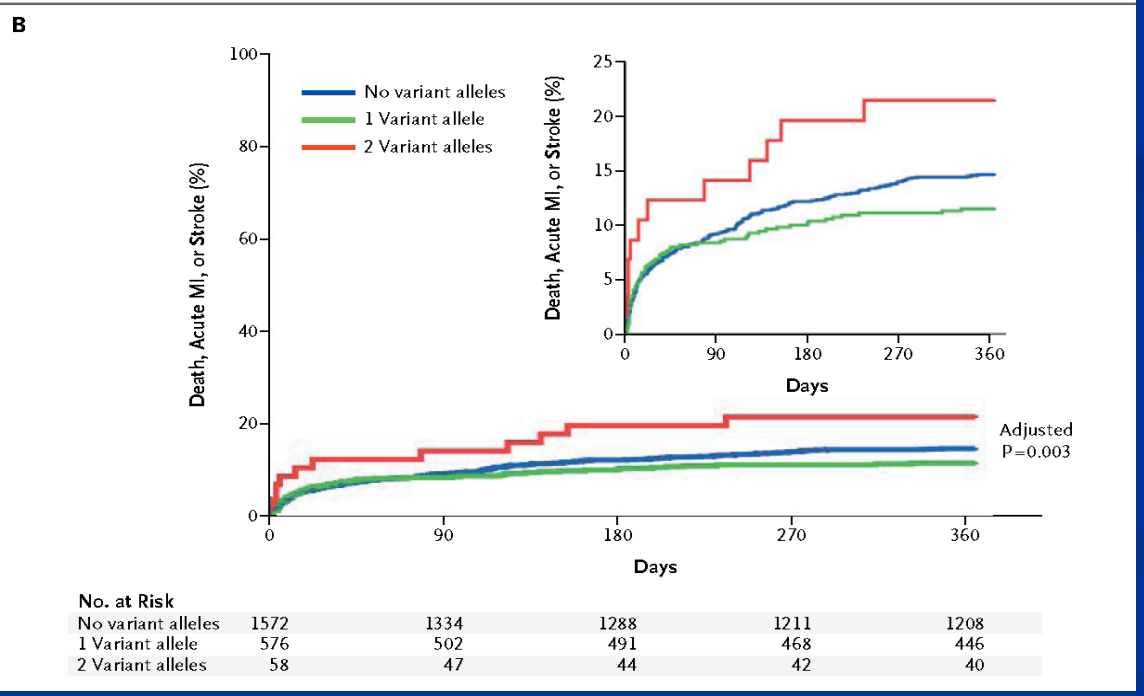
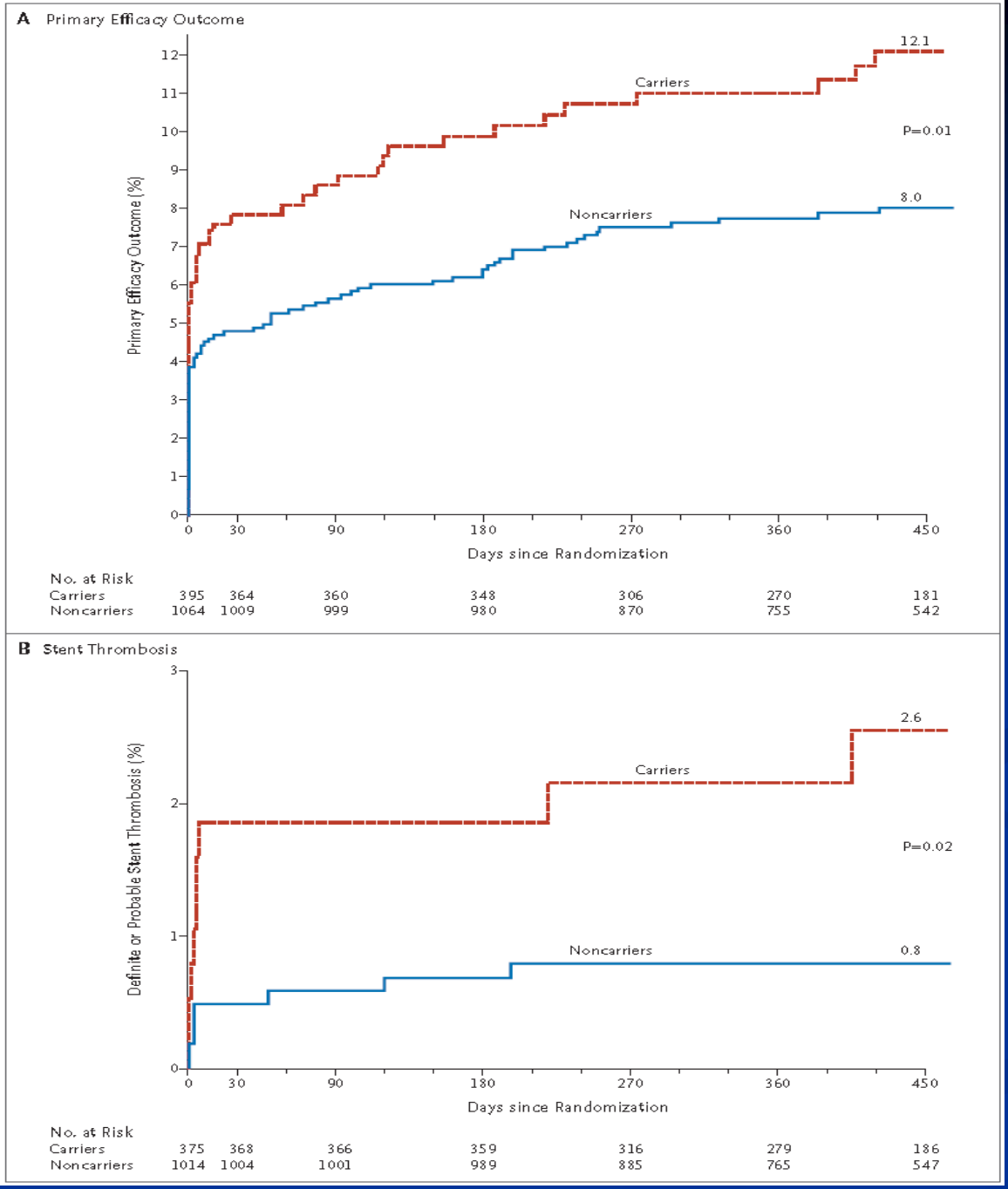
Καρδιαγγειακά συμβάματα βάσει του τύπου των ABCB1 C3435T αλληλίων που είναι παρόντα



Καρδιαγγειακά συμβάματα βάσει του αριθμού των μη λειτουργικών CYP2C19 αλληλίων.



Tabassome et al. N Engl J Med 2009;360:363-75.



Ο ρόλος των γενετικών πολυμορφισμών (κυτοχρώματος P-450) στα καρδιαγγειακά συμβάματα.

Το CYP2C19 αλλήλιο επιδρά αρνητικά αναφορικά στα καρδιαγγειακά συμβάματα συγκριτικά με αυτούς που δε φέρουν το συγκεκριμένο αλλήλιο (ασθενείς με κολπική μαρμαρυγή)

Mega et al. N Engl J Med 2009;360:354-62.

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CLINICAL RESEARCH **Interventional Cardiology**

Cytochrome P450 2C19 681G>A Polymorphism and High On-Clopidogrel Platelet Reactivity Associated With Adverse 1-Year Clinical Outcome of Elective Percutaneous Coronary Intervention With Drug-Eluting or Bare-Metal Stents

Dietmar Trenk, PHD,* Willibald Hochholzer, MD,* Martin F. Fromm, MD,† Ligia-Emilia Chialda, MD,† Andreas Pahl, PHD,† Christian M. Valina, MD,* Christian Stratz, MD,* Peter Schmiebusch, MD,* Hans-Peter Bestehorn, MD,* Heinz Joachim Büttner, MD,* Franz-Josef Neumann, MD*

Bad Krozingen and Erlangen, Germany

Objectives We investigated whether the loss of function *CYP2C19* 681G>A *2 polymorphism is associated with high (>14%) residual platelet aggregation (RPA) on clopidogrel and whether high on-clopidogrel RPA impacts clinical outcome after elective coronary stent placement.

Background The cytochrome P450 (CYP)–dependent conversion of clopidogrel to its active metabolite may contribute to the variability in antiplatelet effect of clopidogrel.

Methods The study included 797 consecutive patients undergoing percutaneous coronary intervention, who were followed-up for 1 year. Adenosine-diphosphate–induced (5 μmol/l) RPA was assessed after a 600-mg loading dose and after the first 75-mg maintenance dose of clopidogrel before discharge. *CYP2C19* genotype was analyzed by real-time polymerase chain reaction.

Results Of the patients included, 552 (69.3%) were *CYP2C19* wild-type homozygotes (*1/*1) and 245 (30.7%) carried at least one *2 allele. Residual platelet aggregation at baseline did not differ significantly between genotypes. On clopidogrel, RPA was significantly ($p < 0.001$) higher in *2 carriers than in wild-type homozygotes (23.0% [interquartile range (IQR) 8.0% to 38.0%] vs. 11.0% [IQR 3.0% to 28.0%] after loading; 11.0% [IQR 5.0% to 22.0%] vs. 7.0% [IQR 3.0% to 14.0%] at pre-discharge). Between *2 carriers and wild-type homozygotes, we found significant ($p < 0.001$) differences in the proportion of patients with RPA >14%, both after loading (62.4% vs. 43.4%) and at pre-discharge (41.3% vs. 22.5%). Residual platelet aggregation >14% at pre-discharge incurred a 3.0-fold increase (95% confidence interval 1.4 to 6.8; $p = 0.004$) in the 1-year incidence of death and myocardial infarction.

Conclusions Patients carrying at least one *CYP2C19*2* allele are more prone to high-on clopidogrel platelet reactivity, which is associated with poor clinical outcome after coronary stent placement (Effect of Clopidogrel Loading and Risk of PCI [EXCELSIOR]; NCT00457236). (J Am Coll Cardiol 2008;51:1925–34) © 2008 by the American College of Cardiology Foundation

JAMA®
The Journal of the American Medical Association

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

A Systematic Review and Meta-analysis

Results We retrieved 32 studies of 42 016 patients reporting 3545 CVD events, 579 stent thromboses, and 1413 bleeding events. Six studies were randomized trials ("effect-modification" design) and the remaining 26 reported individuals exposed to clopidogrel ("treatment-only" design). In treatment-only analysis, individuals with 1 or more *CYP2C19* alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding (relative risk [RR], 0.84; 95% CI, 0.75–0.94; absolute risk reduction of 5–8 events per 1000 individuals), and higher risk of CVD events (RR, 1.18; 95% CI, 1.09–1.28; absolute risk increase of 8–12 events per 1000 individuals). However, there was evidence of small-study bias (Harbord test $P = .001$). When analyses were restricted to studies with 200 or more events, the point estimate was attenuated (RR, 0.97; 95% CI, 0.86–1.09). In effect-modification studies, *CYP2C19* genotype was not associated with modification of the effect of clopidogrel on CVD end points or bleeding ($P > .05$ for interaction for both). Other limitations included selective outcome reporting and potential for genotype misclassification due to problems with the * allele nomenclature for cytochrome enzymes.

Conclusion Although there was an association between the *CYP2C19* genotype and clopidogrel responsiveness, overall there was no significant association of genotype with cardiovascular events.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

CYP2C19 Genotype and Outcomes of Clopidogrel Treatment

TO THE EDITOR: Paré et al. found that among patients with acute coronary syndromes, the effect of clopidogrel as compared with placebo was consistent, irrespective of *CYP2C19* loss-of-function carrier status (*2, *3, and *17 alleles). There are several possible explanations for the discrepancy between these results and those of previous studies. Genetic variants of enzymes within the metabolic pathways (P-450 enzymes) or downstream targets of the active metabolite ($P2Y_{12}$ and platelet glycoproteins IIb/IIIa and Ia) might affect clopidogrel treatment.[1,2] Moreover, other mechanisms such as cellular factors (accelerated platelet turnover, reduced CYP3A metabolic activity, increased exposure to adenosine diphosphate, and up-regulation of P2Y12 pathways) or clinical factors (noncompliance, underdosing, poor absorption, drug-to-drug interactions, diabetes mellitus, and increased body-mass index) may influence platelet response to clopidogrel.[3,4] Further studies must evaluate the contribution of the genomic profile in the individual antiplatelet response, including not only the three studied polymorphisms, but also all the polymorphic genes involved in the pharmacokinetic and pharmacodynamic response to clopidogrel. The total appraisal must also assess the effect of nongenetic factors and mechanisms, mentioned above, on clopidogrel treatment.

Gerasimos Siasos, M.D., Ph.D.
Dimitris Tousoulis, M.D., Ph.D.
Christodoulos Stefanadis, M.D., Ph.D.
University of Athens Medical School
Athens, Greece

NEJM 2011

ΑΝΤΙΜΕΤΩΠΙΣΗ

Με νεότερους ανταγωνιστές του P2Y12 υποδοχέα

- Πρασουγρέλη
- AZD 6140
- Cangrelor

Πρασουγρέλη VS Κλοπιδογρέλη: ο ρόλος της γενετικής

Journal of Thrombosis and Haemostasis, **5**: 2429–2436

ORIGINAL ARTICLE

Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel

J. T. BRANDT,* S. L. CLOSE,* S. J. ITURRIA,* C. D. PAYNE,† N. A. FARID,* C. S. ERNEST II,* D. R. LACHNO,† D. SALAZAR‡ and K. J. WINTERS*

*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA; †Lilly Research Center, Eli Lilly and Company Limited, Windlesham, UK; and ‡Daiichi Sankyo Inc., Parsippany, NJ, USA

Using Pharmacogenetics in Real Time to Guide Warfarin Initiation

A Clinician Update

John F. Carlquist, PhD; Jeffrey L. Anderson, MD

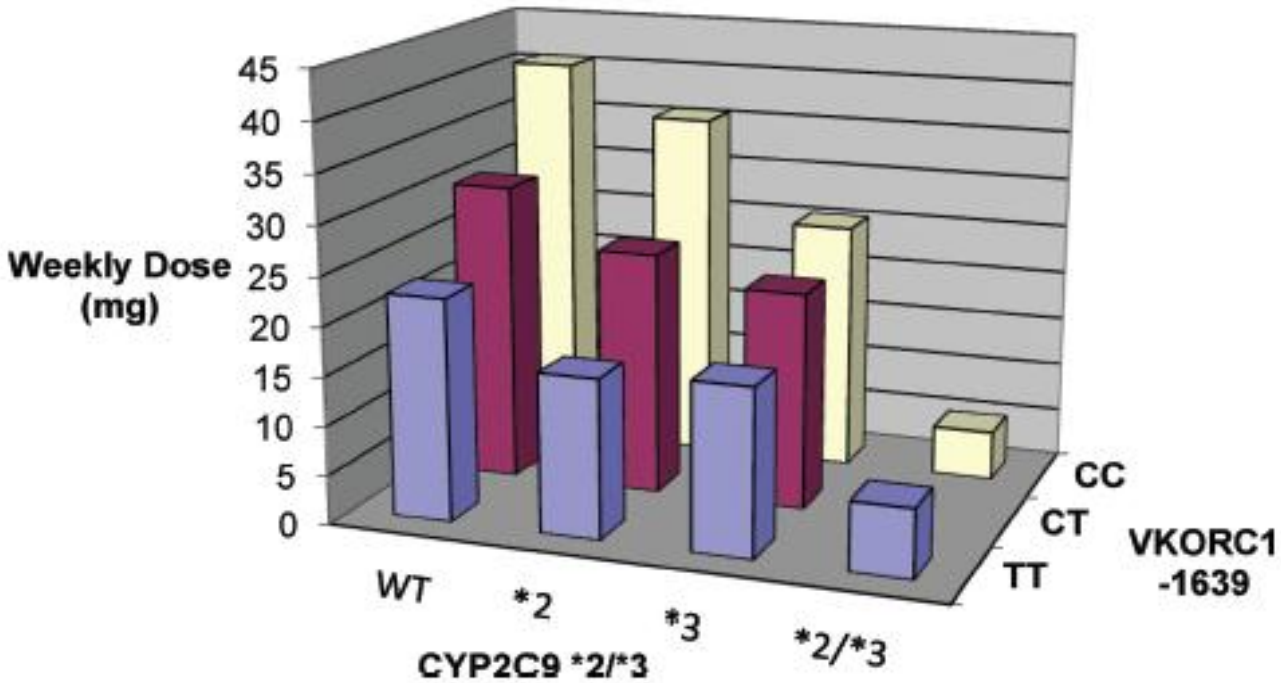


Figure 1. Weekly stable dose for 216 subjects is presented by combined *CYP2C9* and *VKORC1* genotype.[10] WT indicates wild-type (common variant).

doi:10.1111/j.1447-0756.2011.01700.x J. Obstet. Gynaecol. Res. Vol. 38, No. 1: 239–246, January 2012

Haplotypes of heparin-binding epidermal-growth-factor-like growth factor gene are associated with pre-eclampsia

Galhenagey Gayani Harendra, Rohan W. Jayasekara and Vajira H. W. Dissanayake

Table 3 Linkage disequilibrium analysis among polymorphic loci

SNP	rs1862176		rs4150196		rs2074611		rs2237076		rs2074613	
	D′	R^2	D′	R^2	D^2	R^2	D′	R^2	D′	R^2
rs4150196	0.97	0.20								
rs2074611	0.49	0.16	0.69	0.07						
rs2237076	0.73	0.51	0.95	0.20	0.58	0.21				
rs2074613	0.26	0.01	0.58	0.30	0.17	0.005	0.35	0.03		
rs13385	0.07	0.003	0.66	0.15	0.32	0.01	0.23	0.01	0.92	0.33

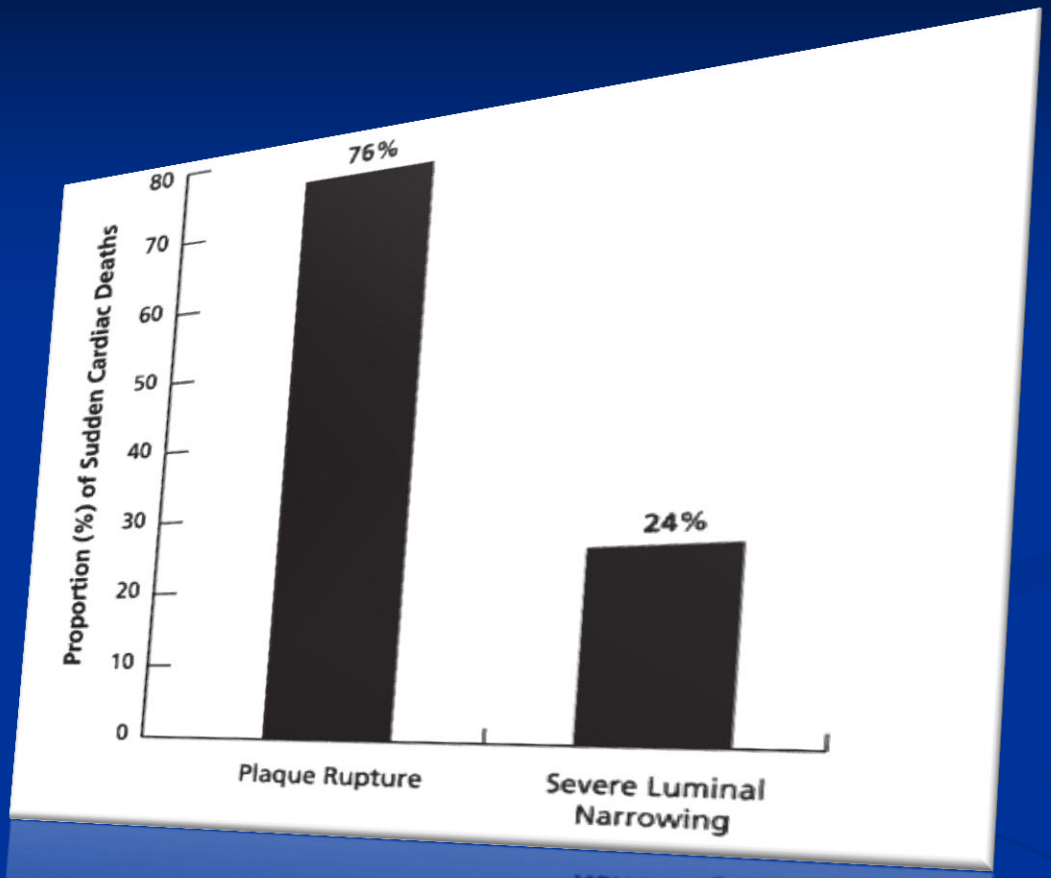
D′, Lewontin disequilibrium coefficient; R^2, correlation coefficient; SNP, single nucleotide polymorphisms.

ΑΝΑΚΕΦΑΛΑΙΩΣΗ

- Η στεφανιαία νόσος κυρίαρχη νόσος
- Η φαρμακευτική αγωγή είναι εξατομικευμένη
- Οι πολυμορφισμοί στους υποδοχείς καθορίζουν την δραστικότητα των φαρμάκων
- Η φαρμακογενετική κυρίως αντιαιμοπεταλιακών και αντιθρομβωτικών καθορίζει την πρόγνωση
- Νέα αντιδραστήρια κρίνονται επιβεβλημμενα

ΟΞΥ ΕΜΦΡΑΓΜΑ ΤΟΥ ΜΥΟΚΑΡΔΙΟΥ

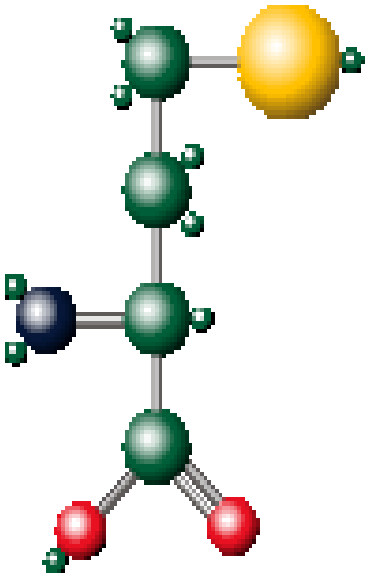
Plaque rupture impact

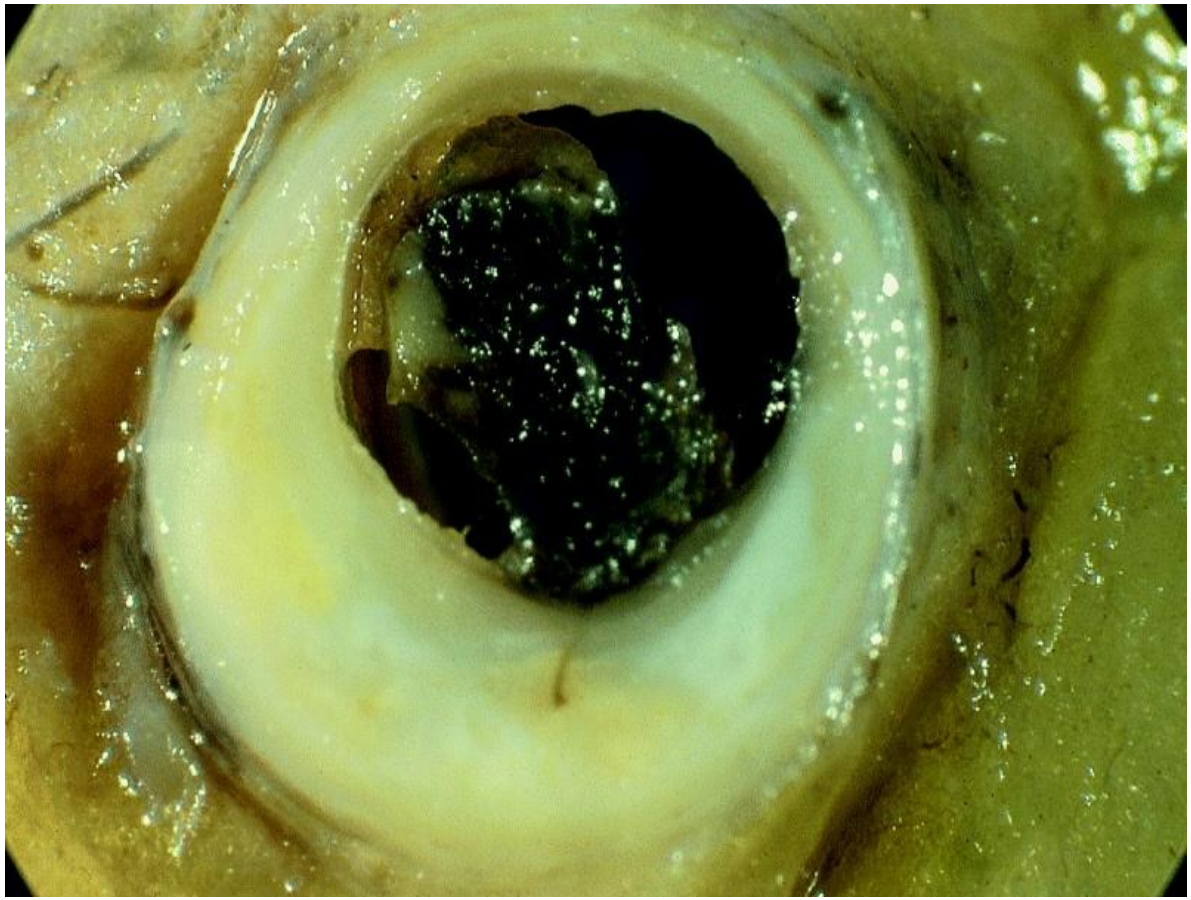


76% of sudden deaths were attributable to plaque rupture, and only 24% of MIs were associated with severe luminal narrowing.

Falk E, …,Fuster V. Coronary plaque disruption. Circulation 1995;92:657– 671

Ασταθής πλάκα





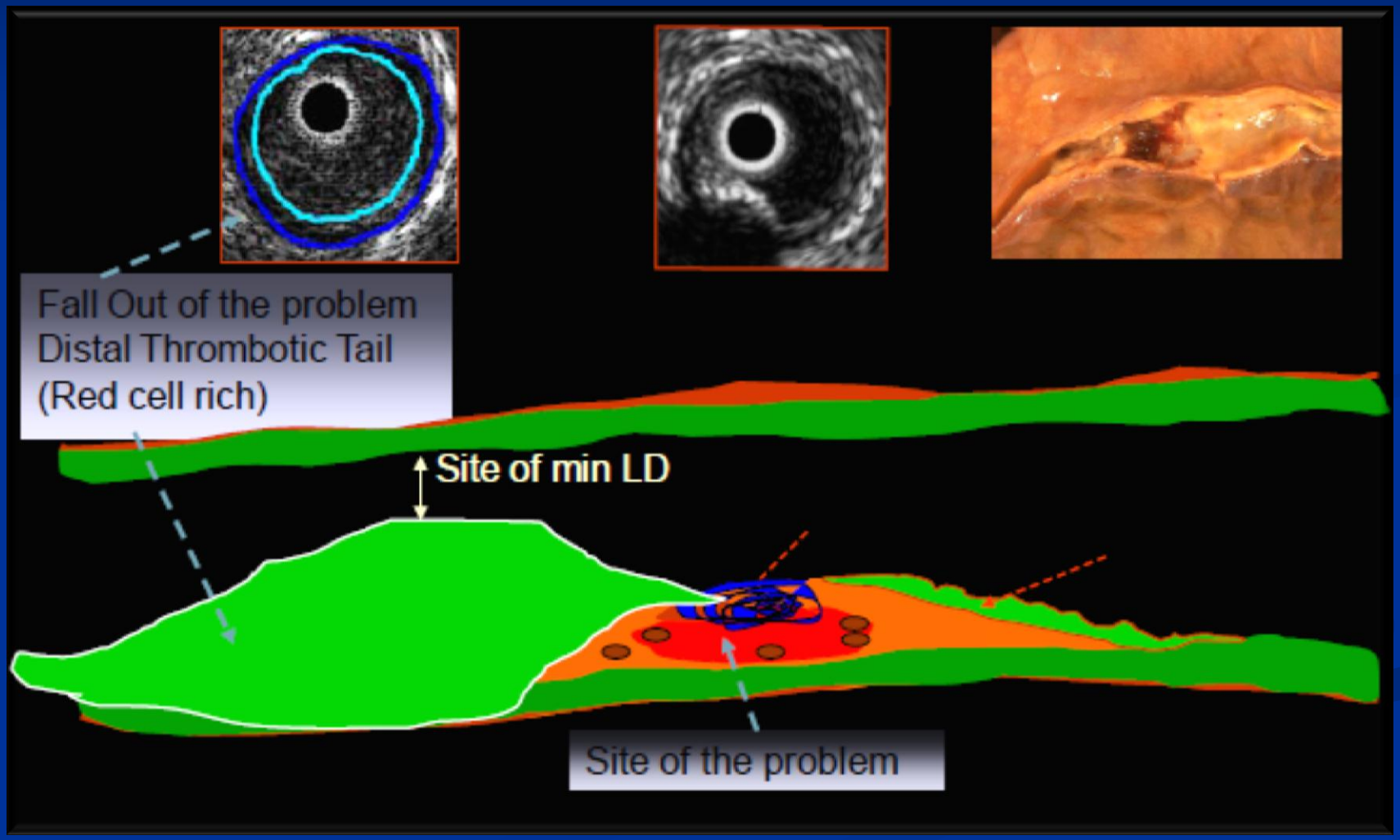
ΑΣΤΑΘΗΣ ΠΛΑΚΑ

- Ρηξη
- Διαβρωση (erosion)
- Αιμορραγια

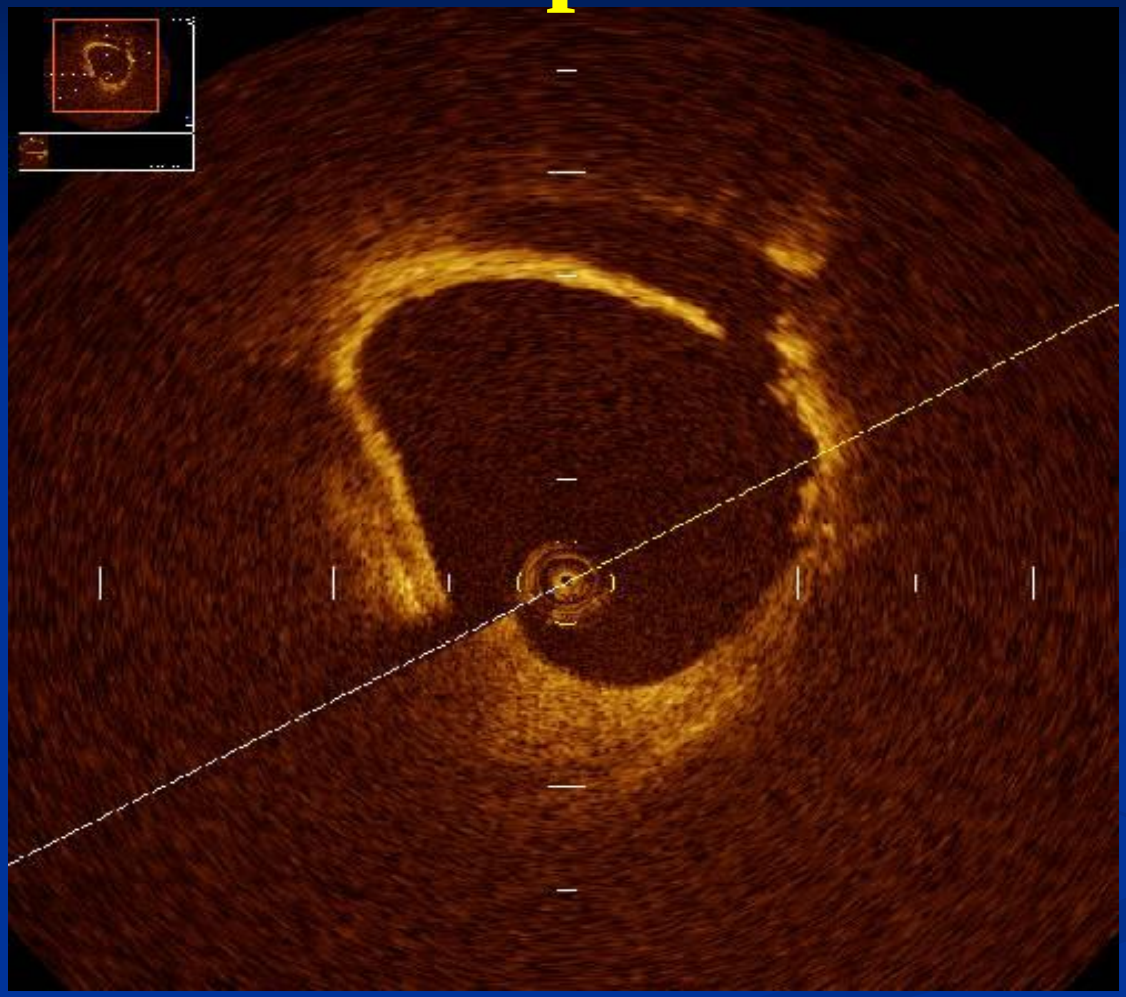
Χαρακτηριστικά ασταθούς πλάκας

- λεπτη καψα
- μεγαλος λιπωδης πυρηνας
- μικρες στενωσεις
- εστερικη χοληστερολη

Plaque rupture and minimal stenosis



In vivo demonstration of cap rupture



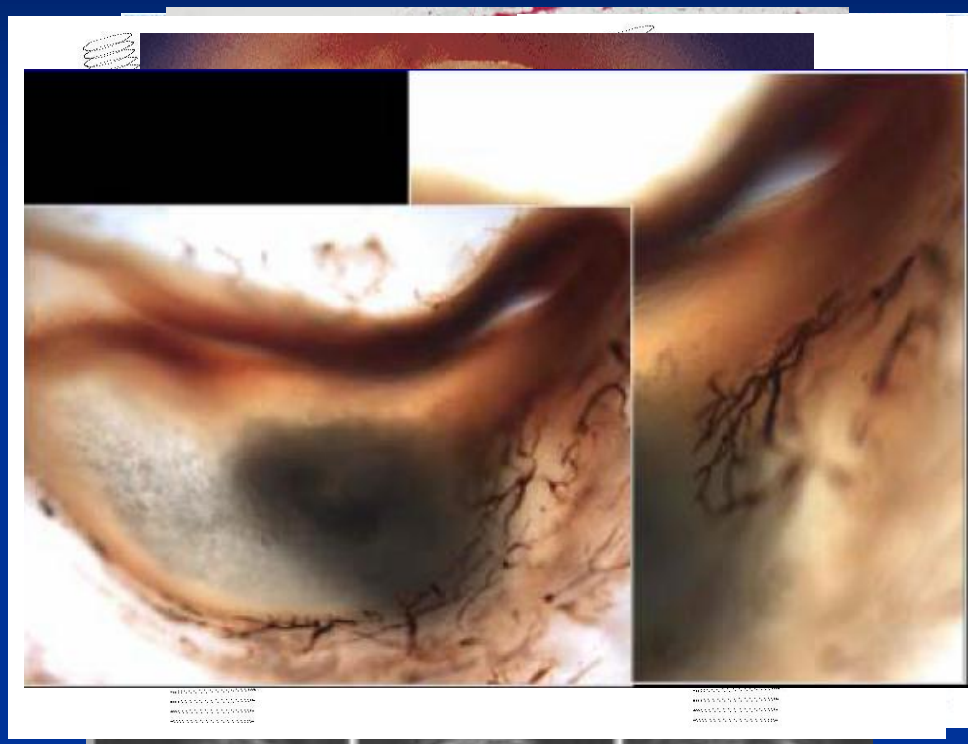
Vulnerable Plaque Components

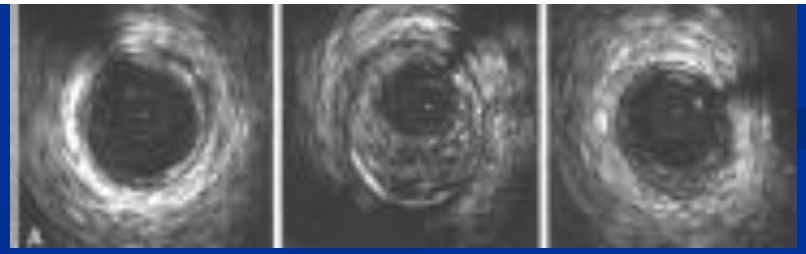
- Fibrous Cap Thickness< 65 μm
- Large Necrotic Core
- Inflammation
- Positive Remodeling

VP Meeting, Eur Heart J 2004.
Schaar, Stefanadis et al

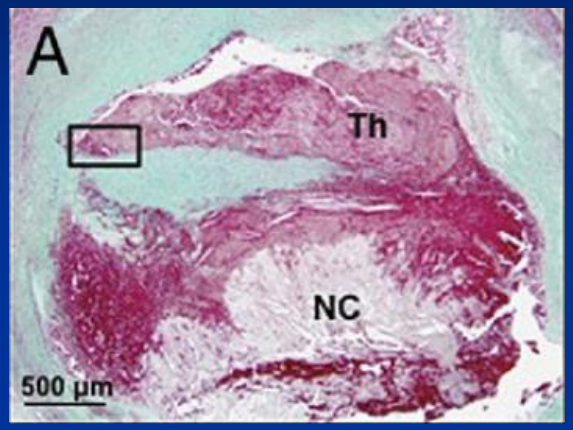
- Reduced shear stress
- Intravascular Hemorrhage
- Neovascularization

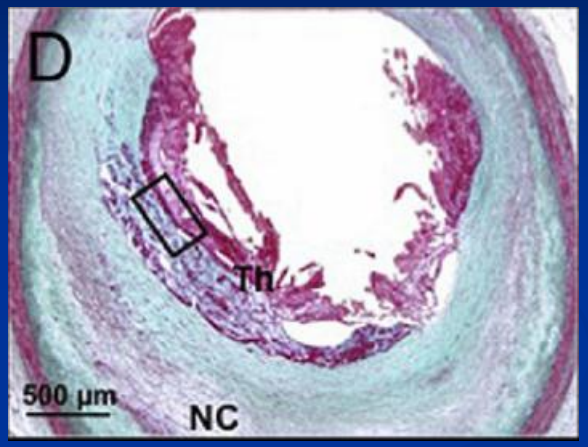
VP Meeting, P. Serruys, A. Colombo, C. Stefanadis, S. Casscells, J. Schaar, 2007





Plaque rupture vs. Plaque erosion

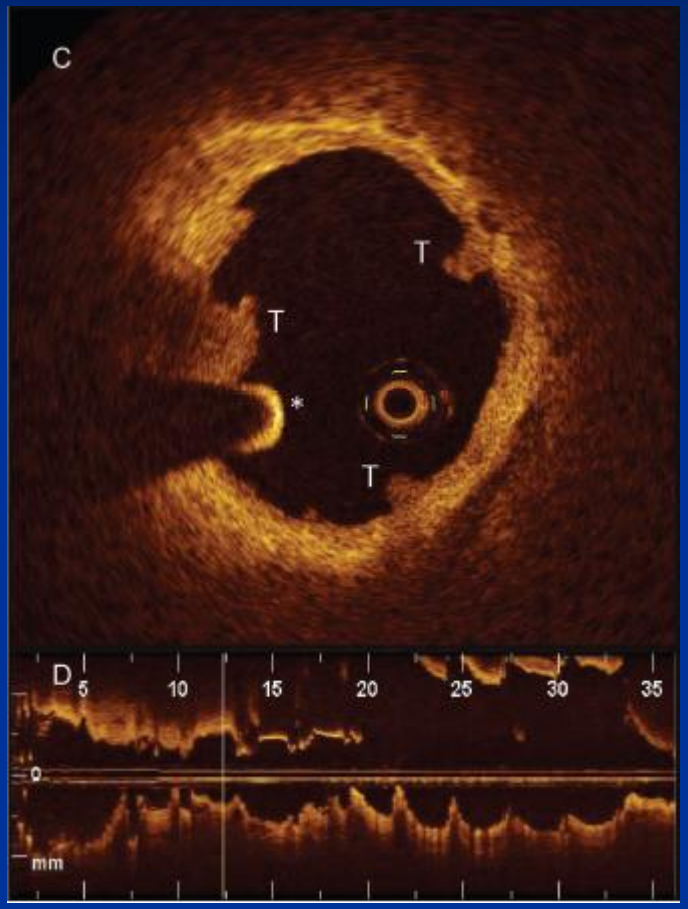


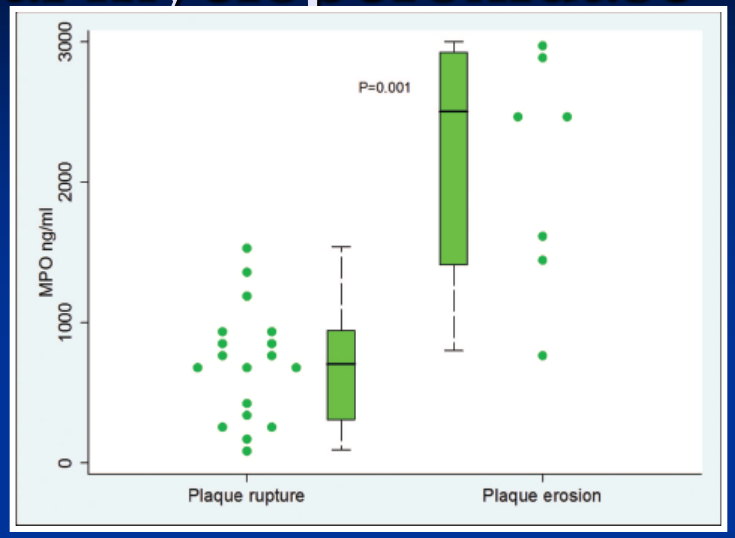


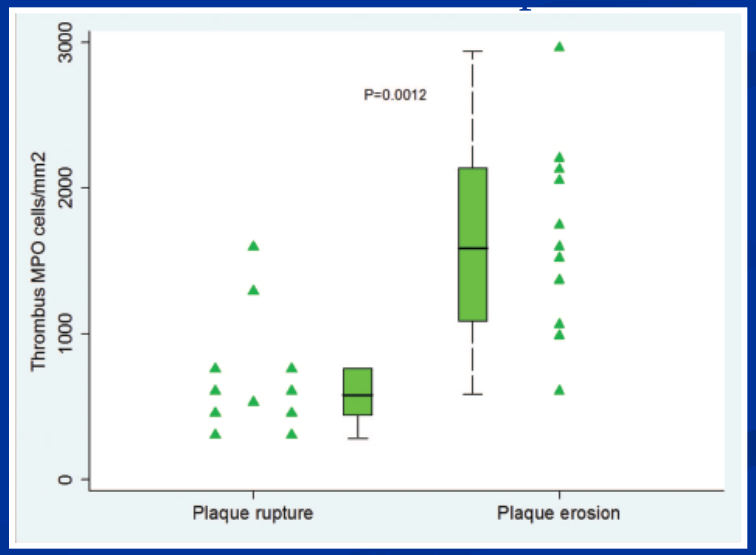
	Plaque rupture (n=65)	Plaque erosion (n=50)	p-value
Stenosis (%)	77.1±13.8	71.3±14.9	0.02
Necrotic core area (%)	38.3 ± 23.4	18.3 24.4	< 0.0001
Plaque burden	231 ± 67	190 ± 72	0.008
Intimal Macrophages (%)	3.44 ± 2.77	2.53 ± 2.65	0.03
Male Gender (%)	89	74	0.008

Virmani R, et al., JACC Oct 2009

Plaque erosion: Association with systemic and local myeloperoxidase

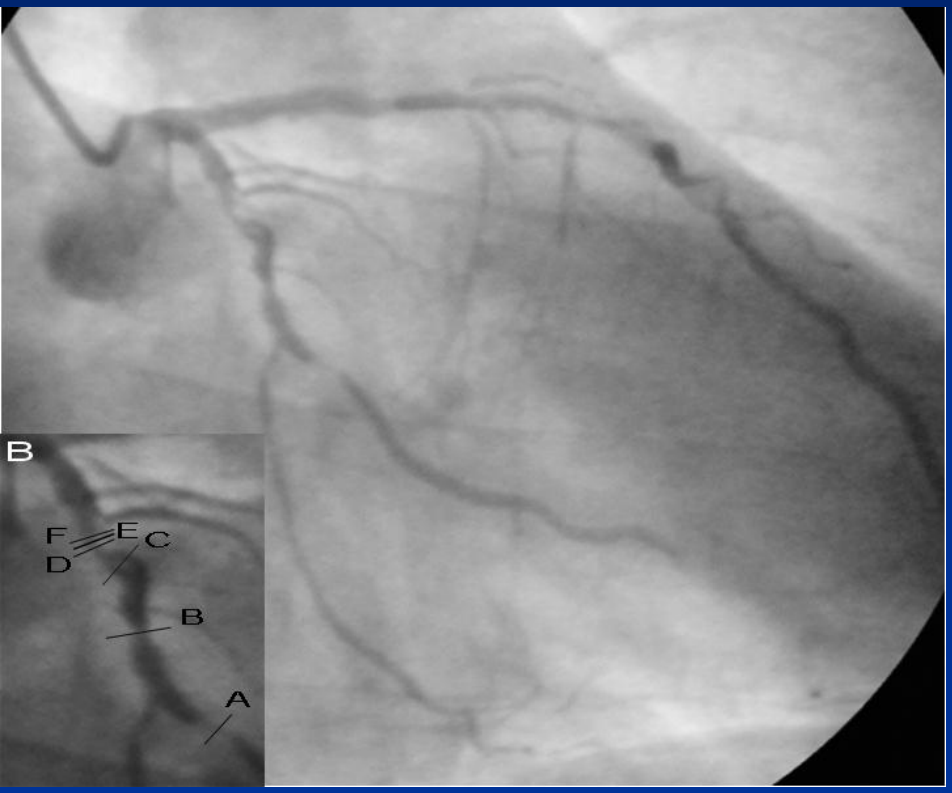


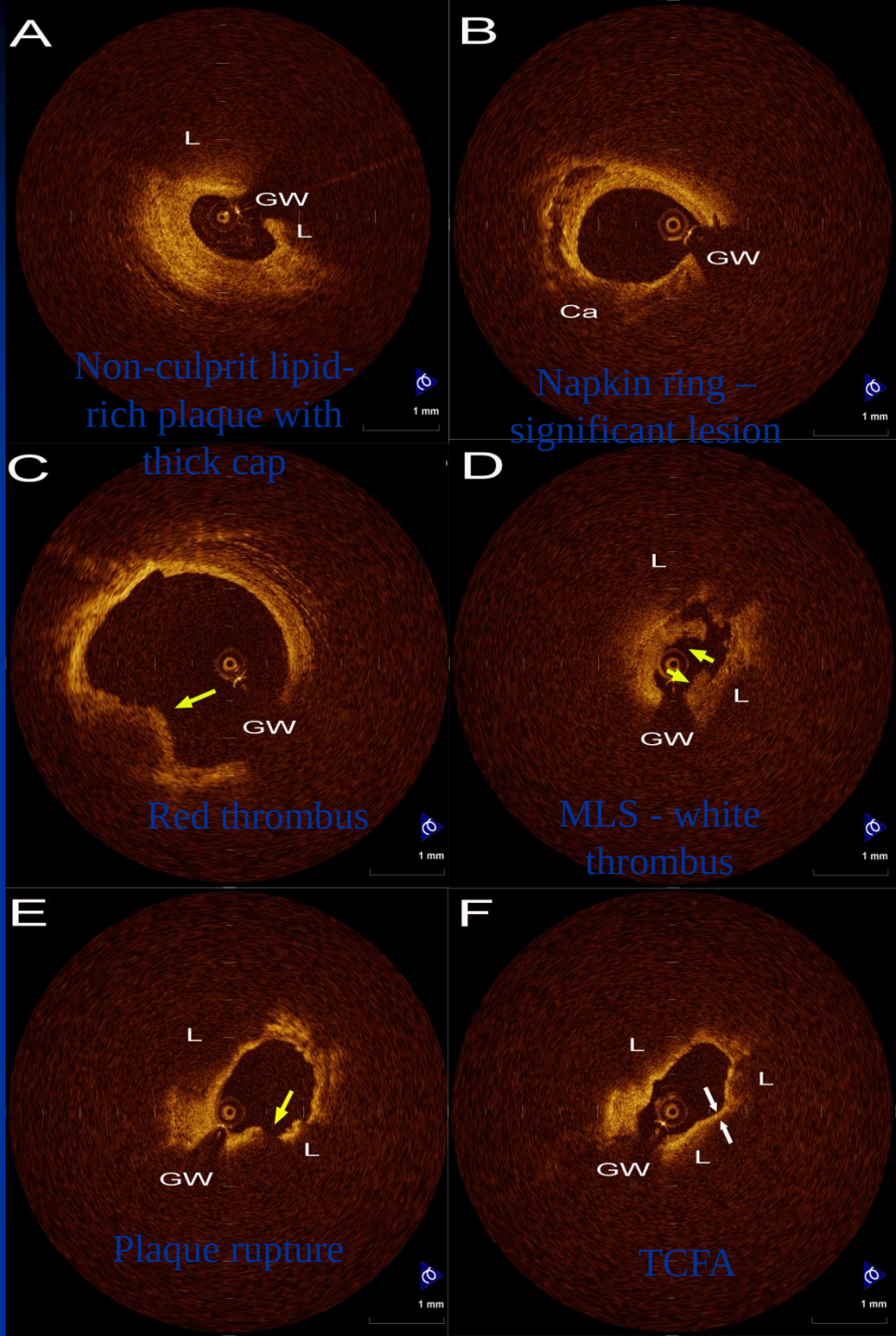




Ferrante G et al., Circulation. 2010;122:2505-2513

OCT imaging in ACS

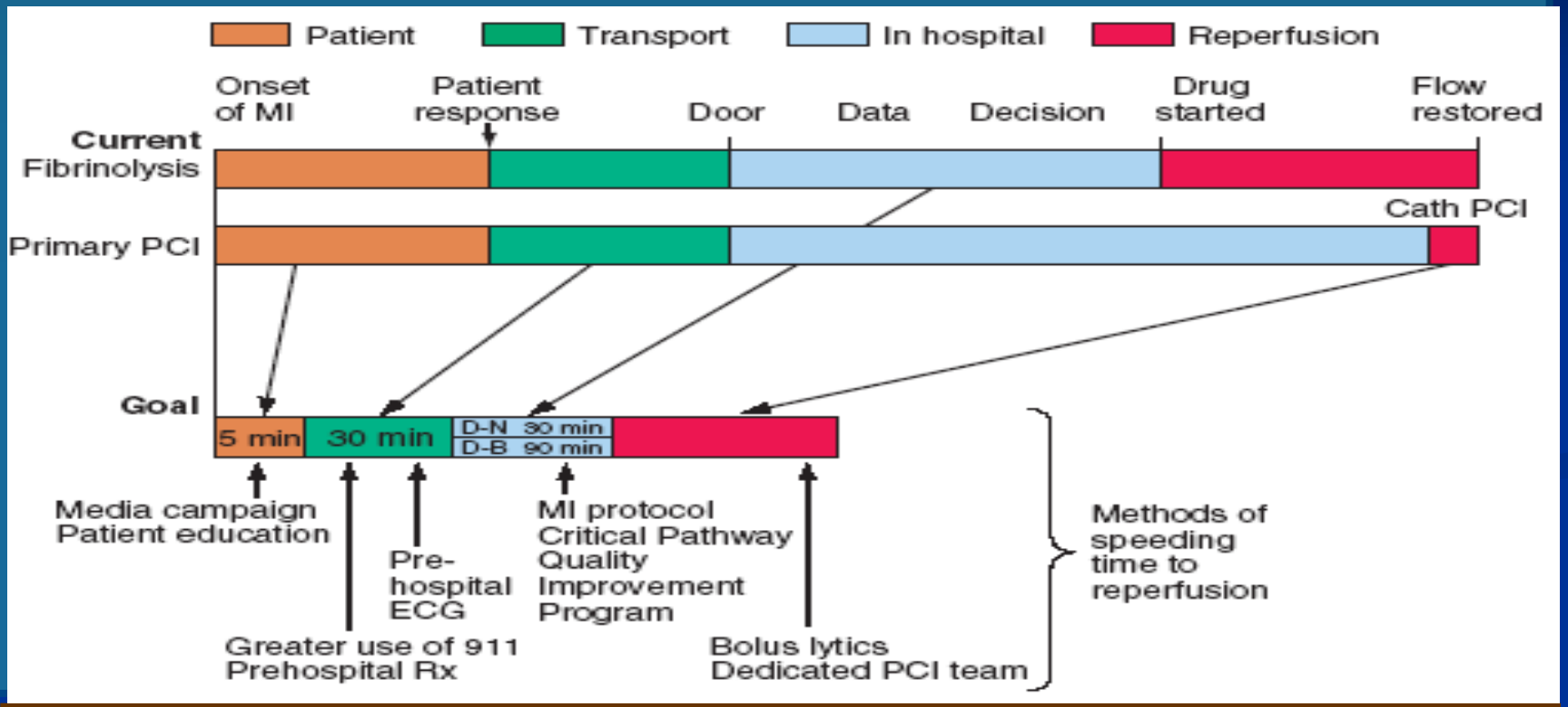




Toutouzas, Synetos..Stefanadis . Heart July 2010

ΘΕΡΑΠΕΙΑ ΣΤΟ ΟΞΥ ΕΜΦΡΑΓΜΑ ΤΟΥ ΜΥΟΚΑΡΔΙΟΥ

Ποιος είναι ο στόχος μας;



«Σε ασθενείς με επίμονη ↑ST και έναρξη πόνου <12 ώρες…
… μηχανική ή φαρμακευτική επαναιμάτωση»

Braunwald's HD,9th ed. 55;1112

Υπάρχουσα κατάσταση

- Η Ελλάδα είναι χώρα με ιδιαίτερα γεωμορφολογικά χαρακτηριστικά

- Η αεροδιακομιδή μέσω ελικοπτέρου σε κεντρικό νοσοκομείο της Αθήνας ή της Θεσσαλονίκης χρειάζεται τουλάχιστον 3 ώρες

- Το έτος 2009 πραγματοποιήθηκαν συνολικά 1.196 αποστολές- πτήσεις, 2.905 ώρες πτήσης και μεταφορά συνολικά 1.646 ασθενών

- Το κόστος ανά ώρα πτήσης είναι 5.602,6 € για ένα Super Puma και 9.693,8 € για ένα C-130

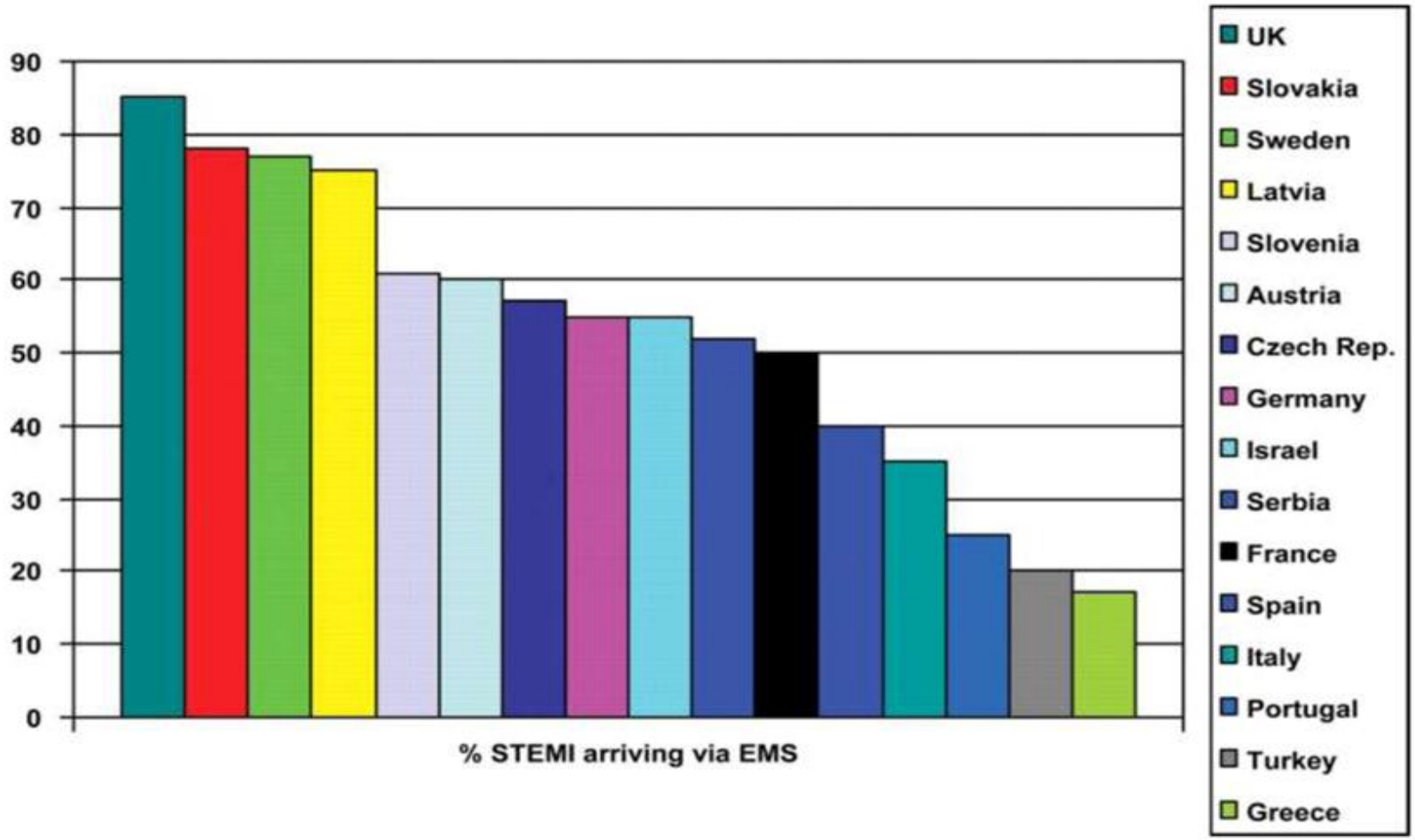
Επίπτωση STEMI

- 9000-10000 STEMI στην Ελλάδα
- ~3000-4000 STEMI στο Λεκανοπέδιο Αττικής (1 STEMI ανά 1000 κατοίκους)
- Μόλις στο 9% των stemi <200pPCI million/year
- Λιγότεροι από 30% εντός 3 ωρών

Προβλήματα Σχετιζόμενα με το Σύστημα Υγείας

- Καλή και συνεχή ενημέρωση του κοινού
- Σωστή διάγνωση- Ανάπτυξη τηλεϊατρικής
- Πιθανή αναδιάρθρωση του χάρτη
- Διαθεσιμότητα σε 24ωρη βάση κινητών μονάδων για μεταφορά των ασθενών- κόστος
- Δημιουργία ειδικής ομάδας άμεσης υποδοχής και διακίνησης του εμφραγματία εντός της νοσοκομειακής μονάδος
- Δημιουργία κινητών μονάδων παροχής προνοσοκομειακής θρομβόλυσης

Percentage of STEMI patients arriving to the first hospital via EMS services.

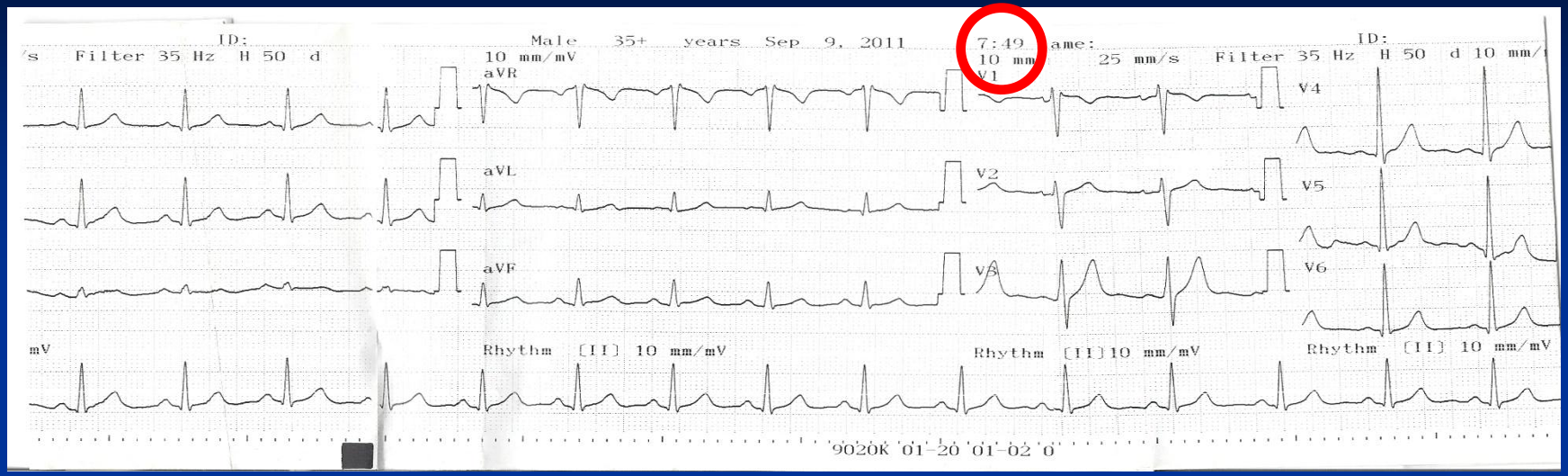


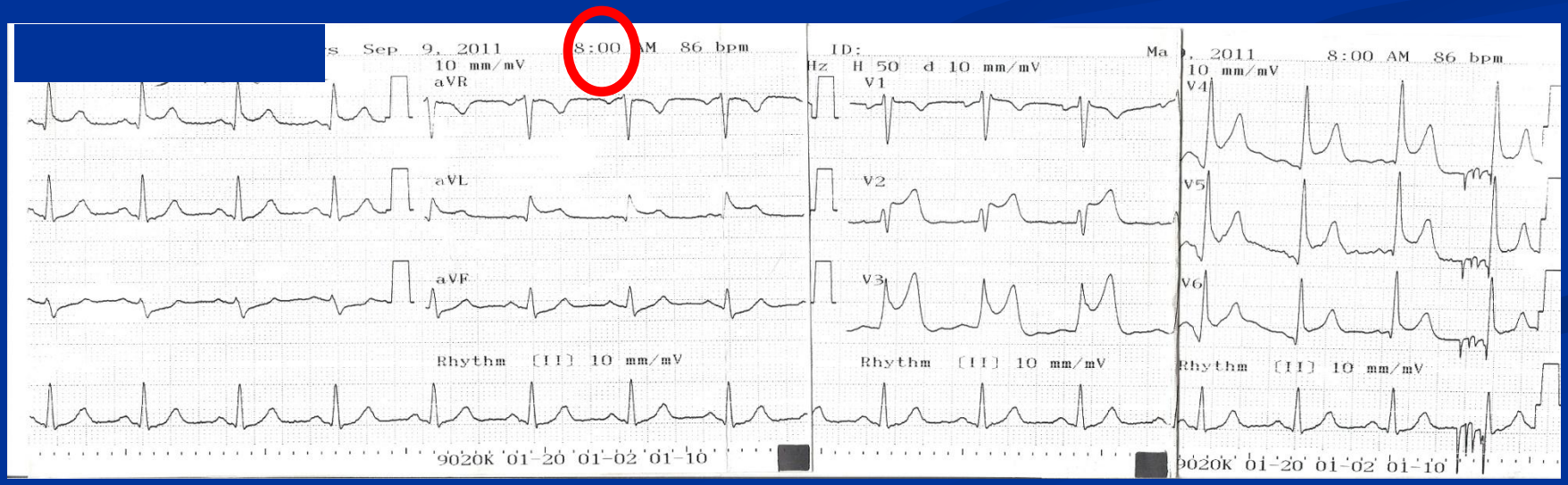
Widimsky P et al. Eur Heart J 2010;31:943-957

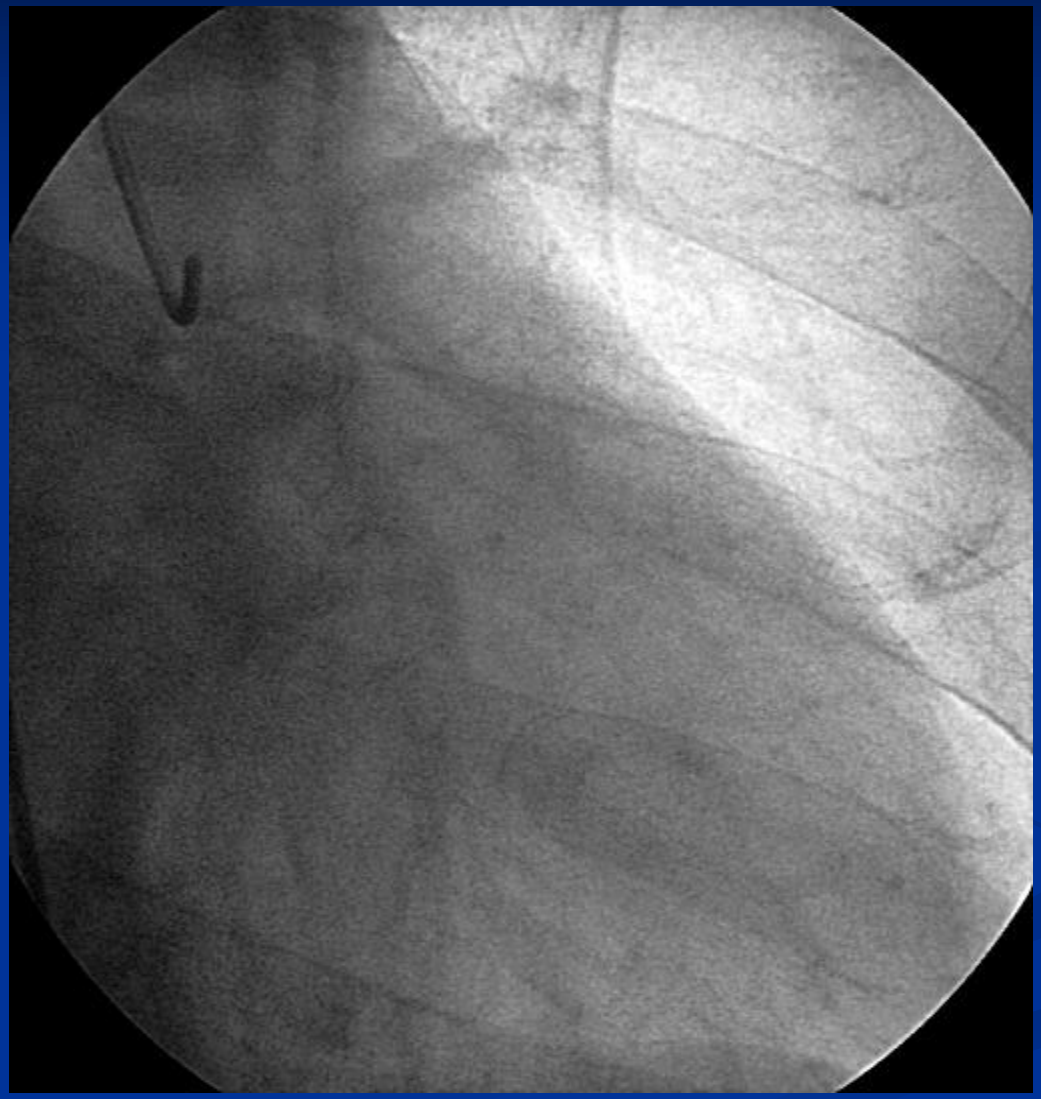
Προβλήματα Σχετιζόμενα με την Ίδια τη Νόσο

- Καρδιογενή καταπληξία
- Στεφανιαία νόσο 3 αγγείων
- Στεφανιαία νόσο στελέχους
- Μεγάλο φορτίο θρόμβου στην ένοχη αρτηρία
- Ανεπιτυχή προσπάθεια pPCI
- Φαινόμενο μη επαναρροής (No Reflow)
- Δυσκολία χορήγησης αντιαιμοπεταλιακών

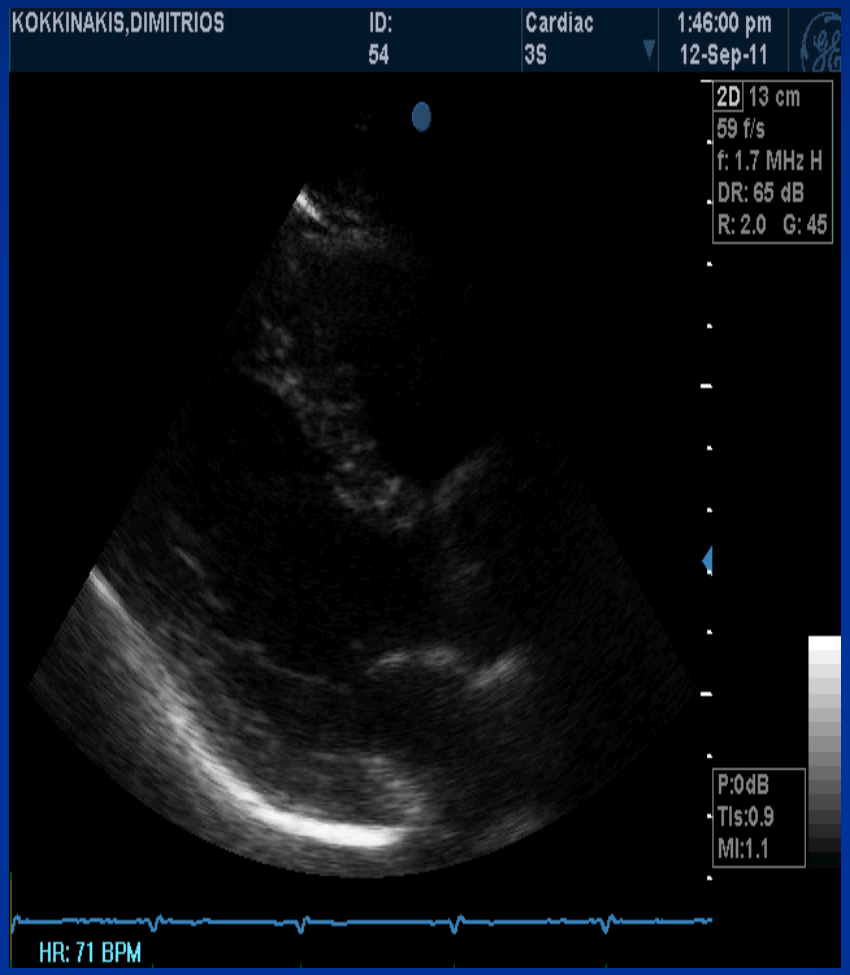
Ασθενής 54 ετών, καπνιστής με θετικό οικογενειακό ιστορικό, προσέρχεται στο ΤΕΠ λόγω διάχυτου προκάρδιου άλγους με υφέσεις και εξάρσεις από 15 min

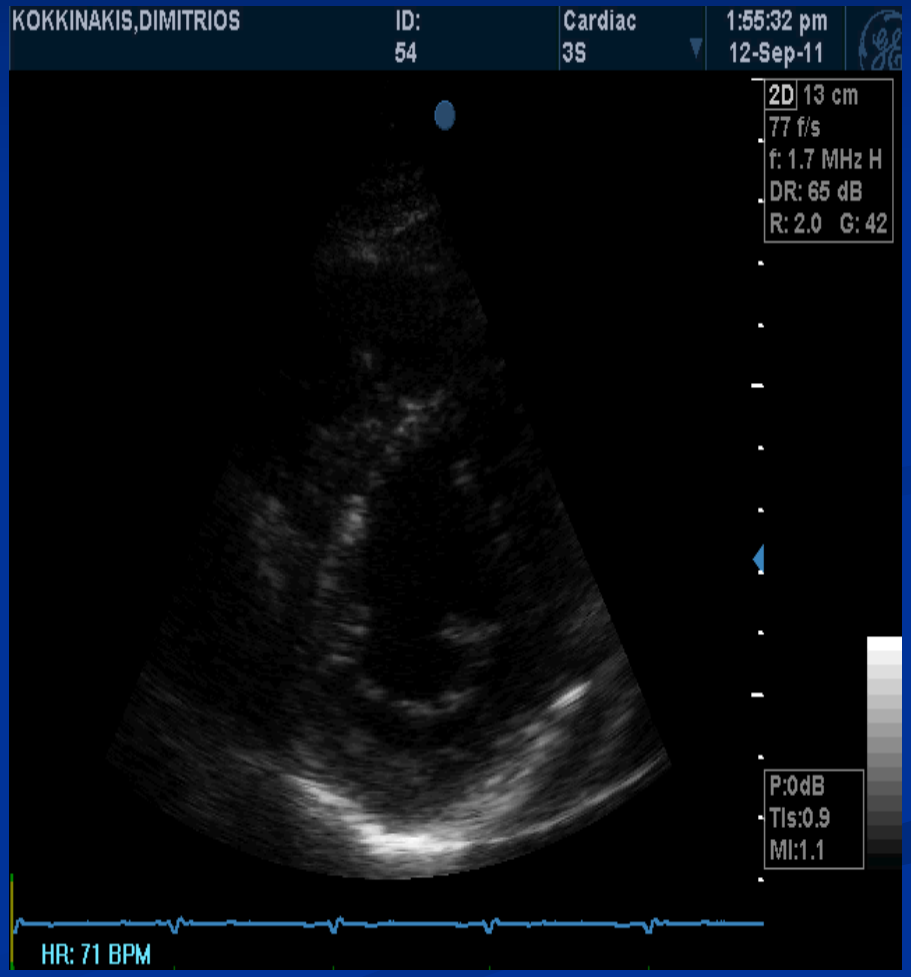




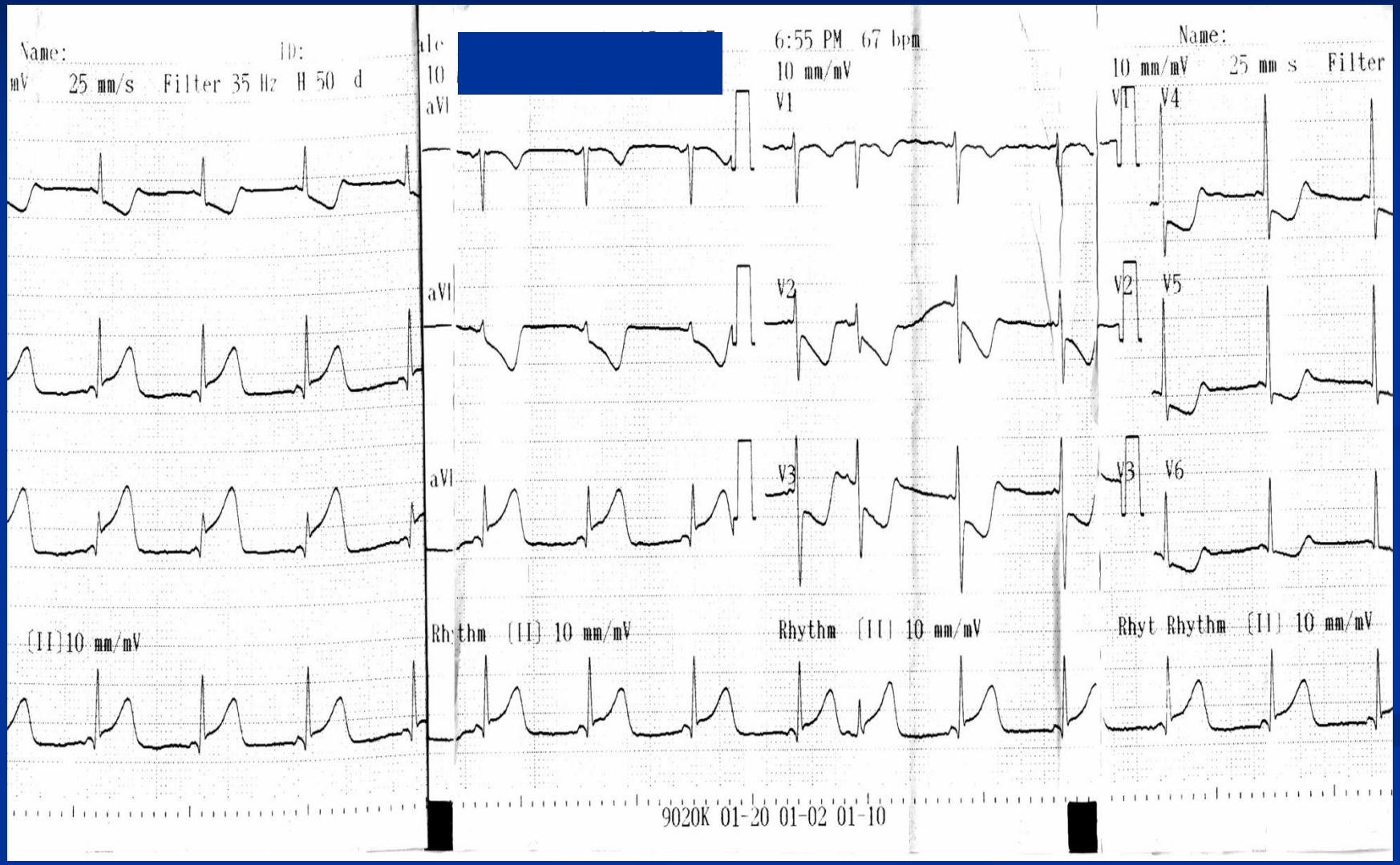


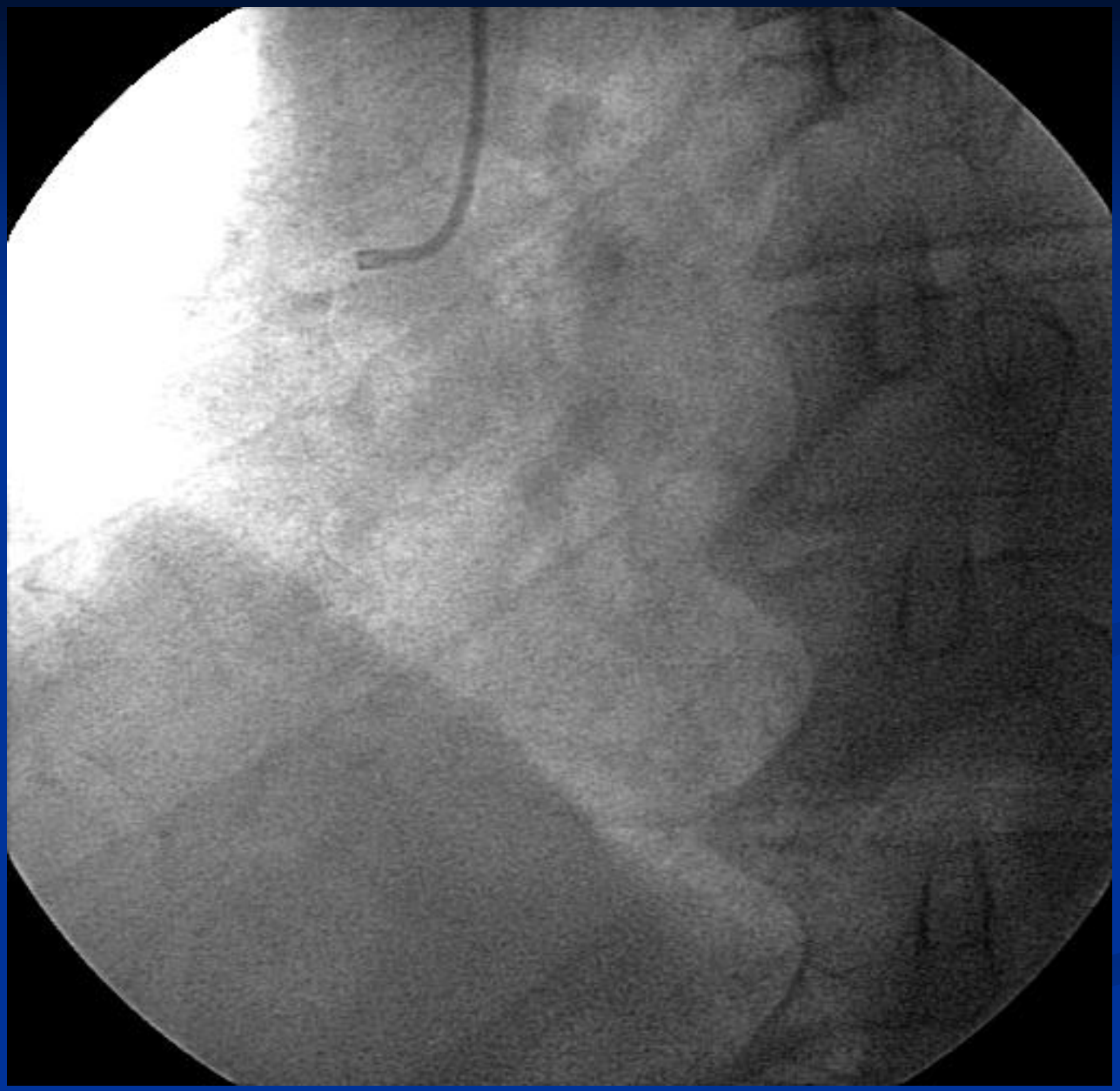
Υπερηχογράφημα εξόδου…

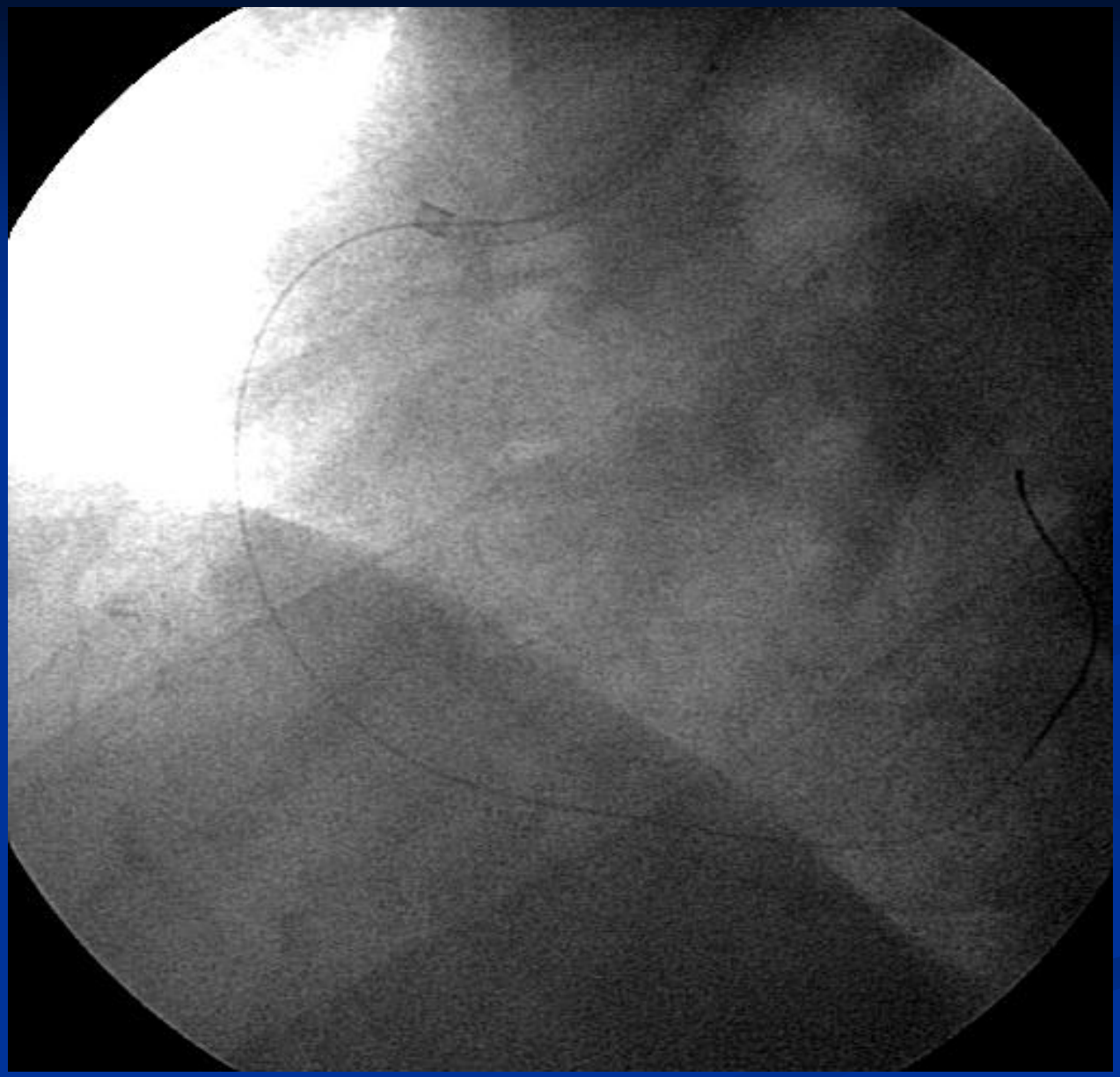




Ασθενής 48 ετών, καπνιστής, υπερλιπιδαιμικός προσέρχεται στο Τ.Ε.Π. λόγω οπισθοστερνικού άλγους με αντανάκλαση στο επιγάστριο από 4 ώρες…

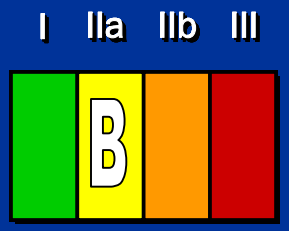




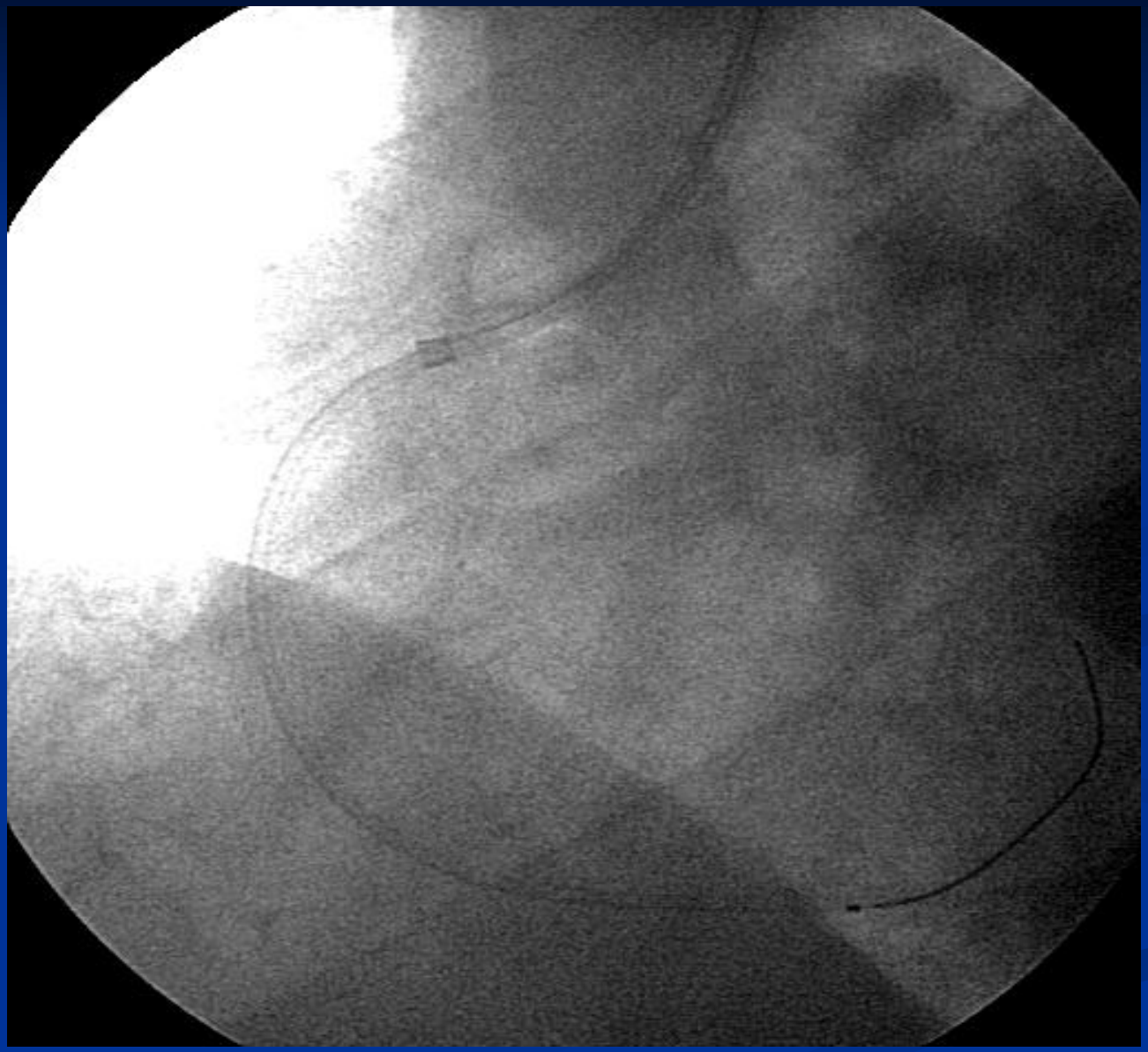


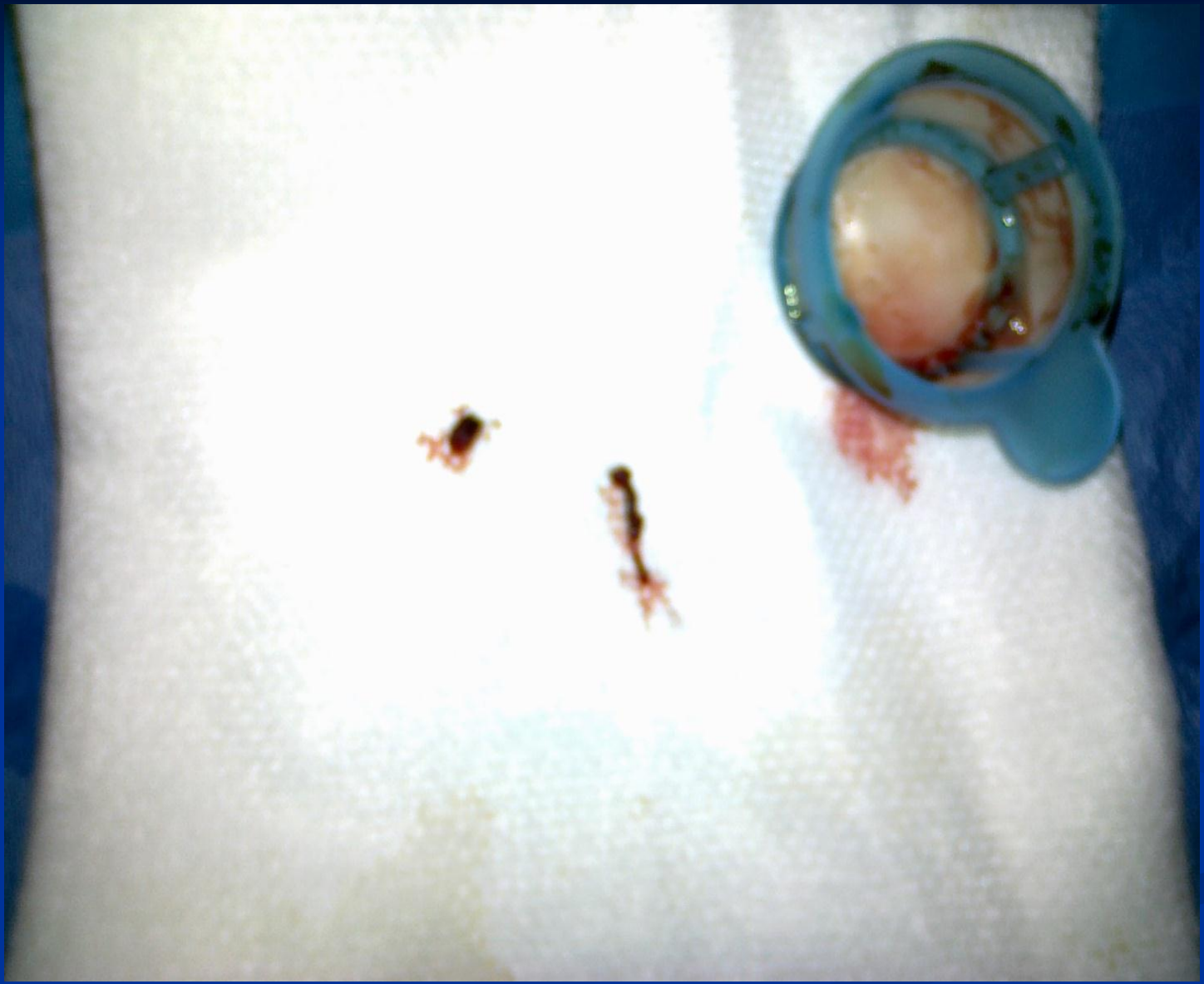
Thrombus Aspiration During PCI for STEMI

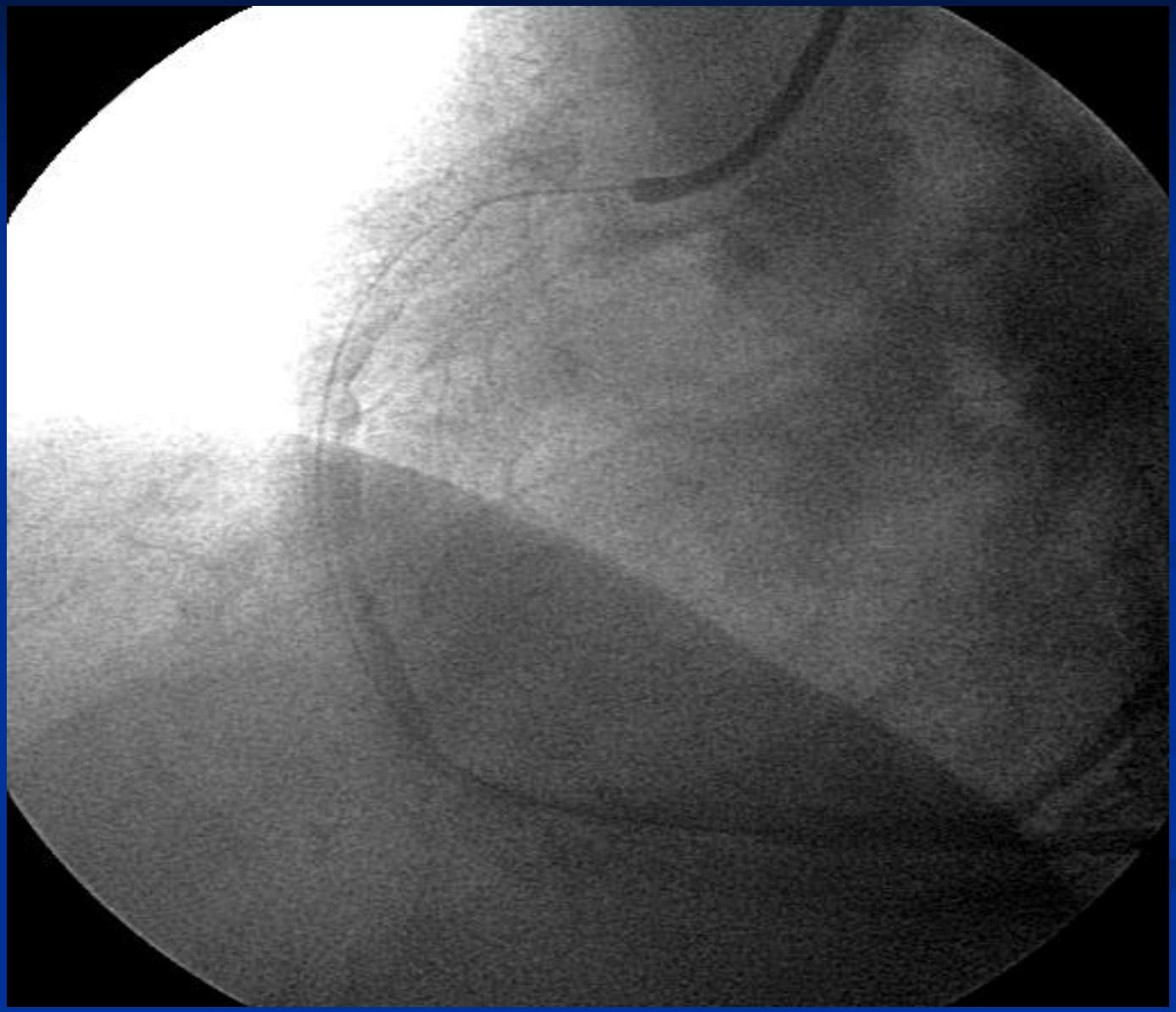
NEW Recommendation



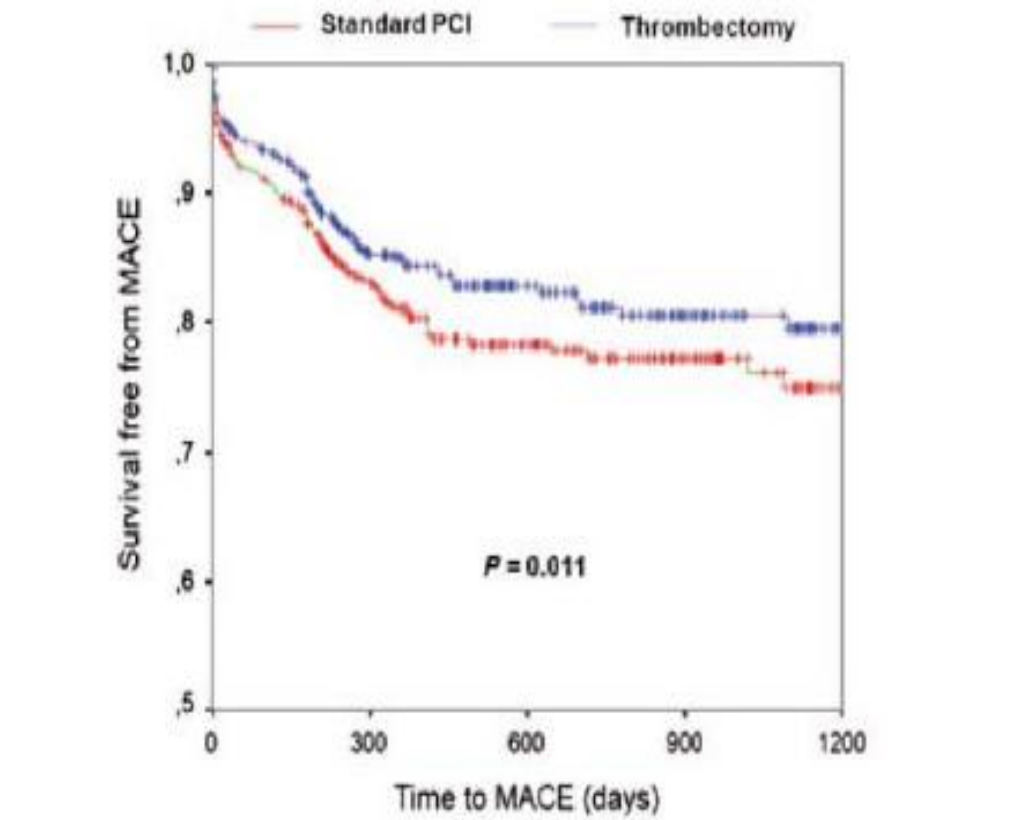
Aspiration thrombectomy is reasonable for patients undergoing primary PCI







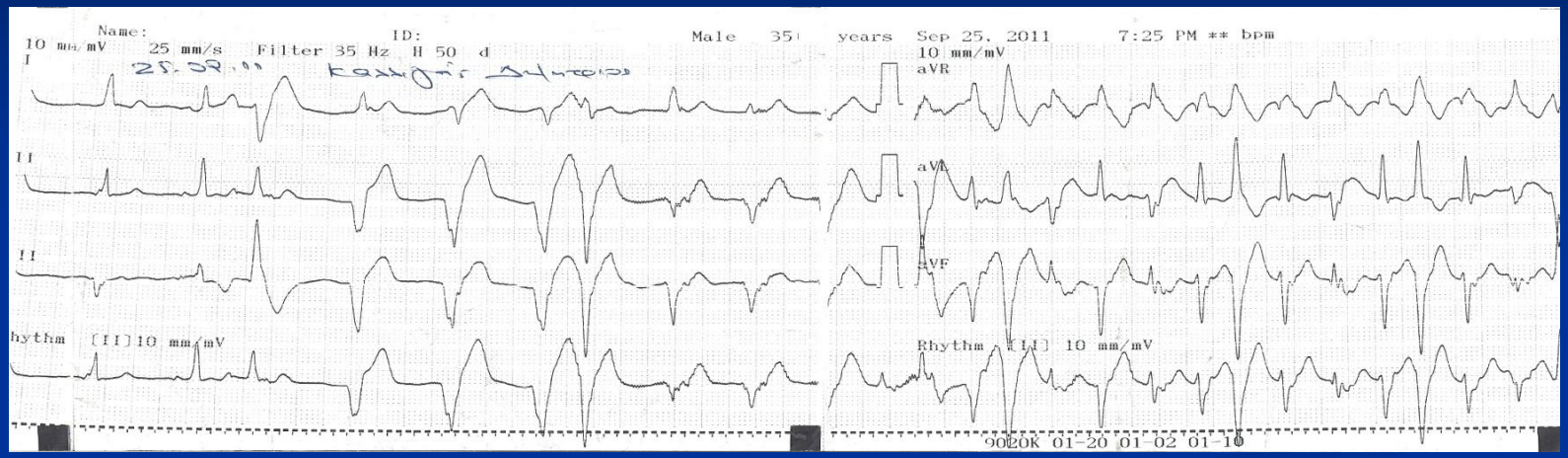
Thrombus Aspiration During Stemi

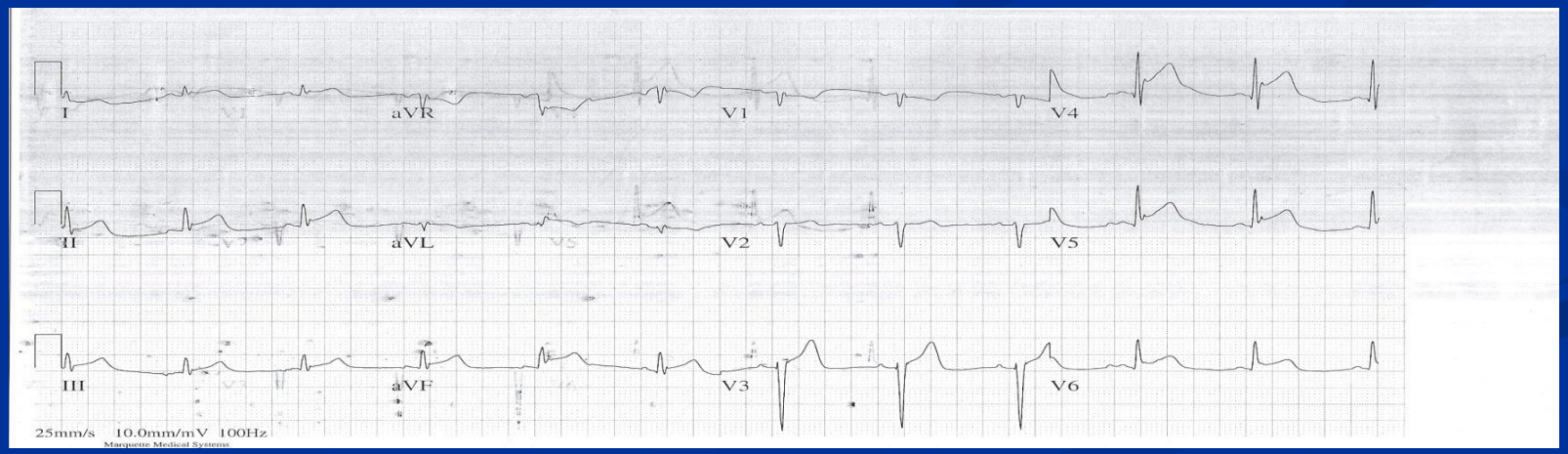


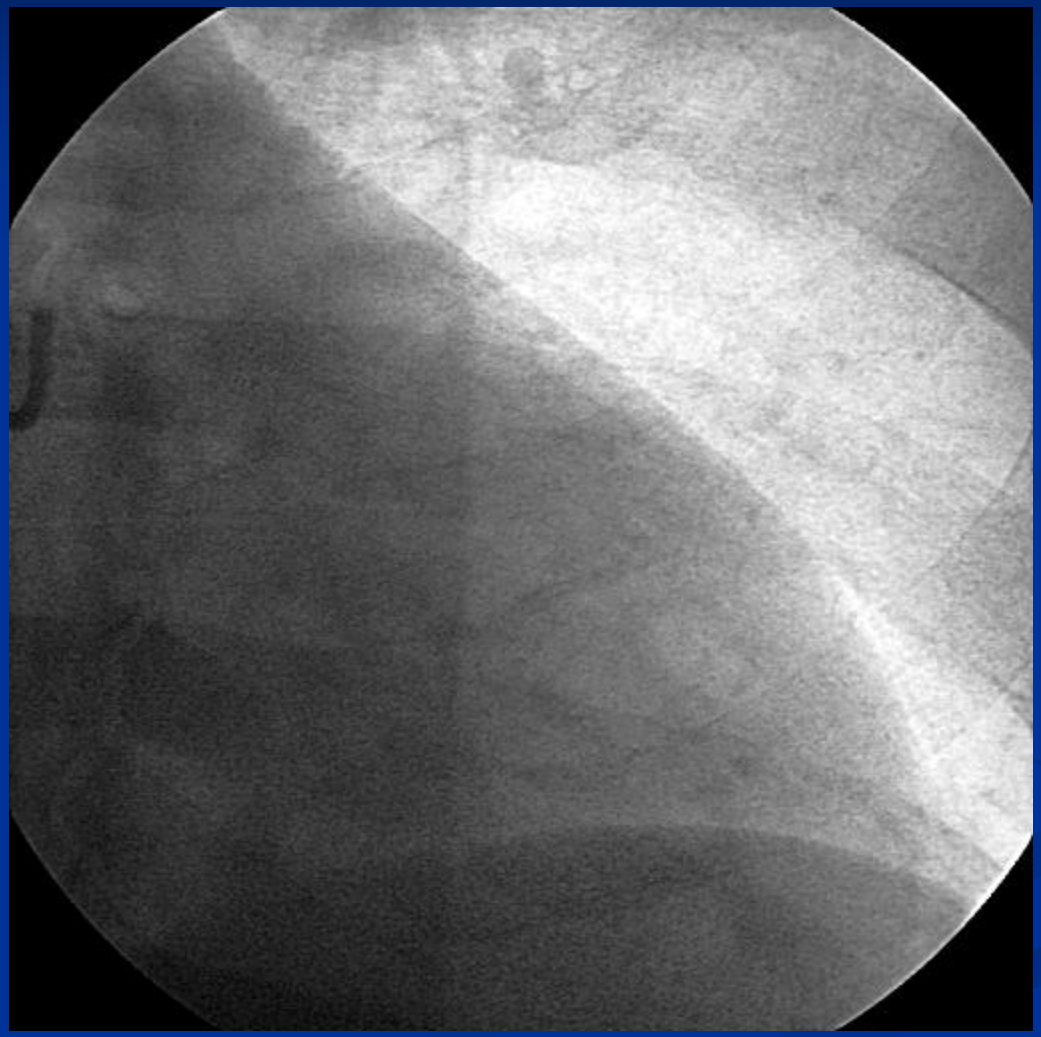
Patients at risk					
Standard PCI	1333	768	164	96	37
PCI with thrombectomy	1339	777	159	99	48

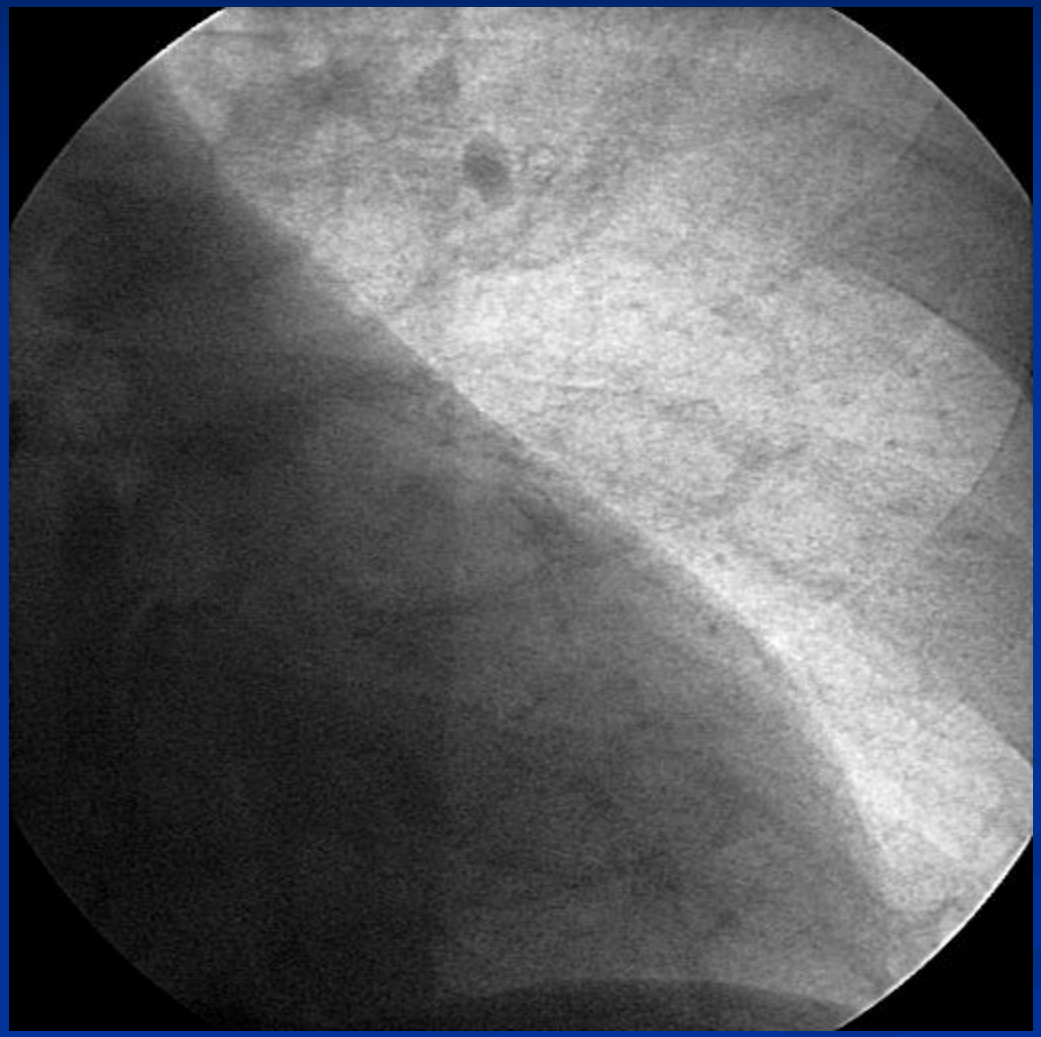
Burzotta F.Euroheart,2009

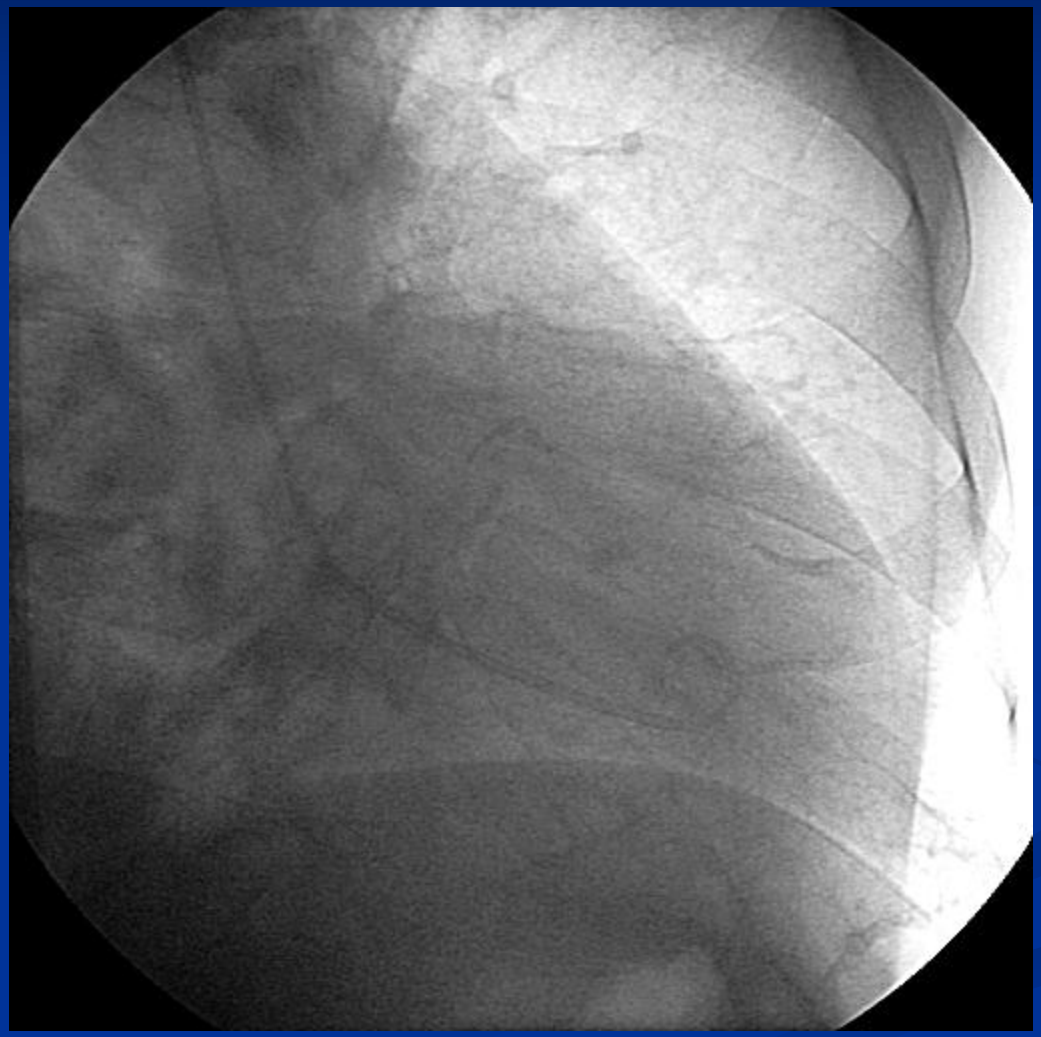
Ασθενής 38 ετών βαρύτατος καπνιστής, σακχαροδιαβητικός, διακομίζεται από Π.Ι. ακριτικού νησιού λόγω προσθίου εμφράγματος από 8 ώρου…κατά την διάρκεια της αεροδιακομιδής διασωληνώνεται. Στα ΤΕΠ:

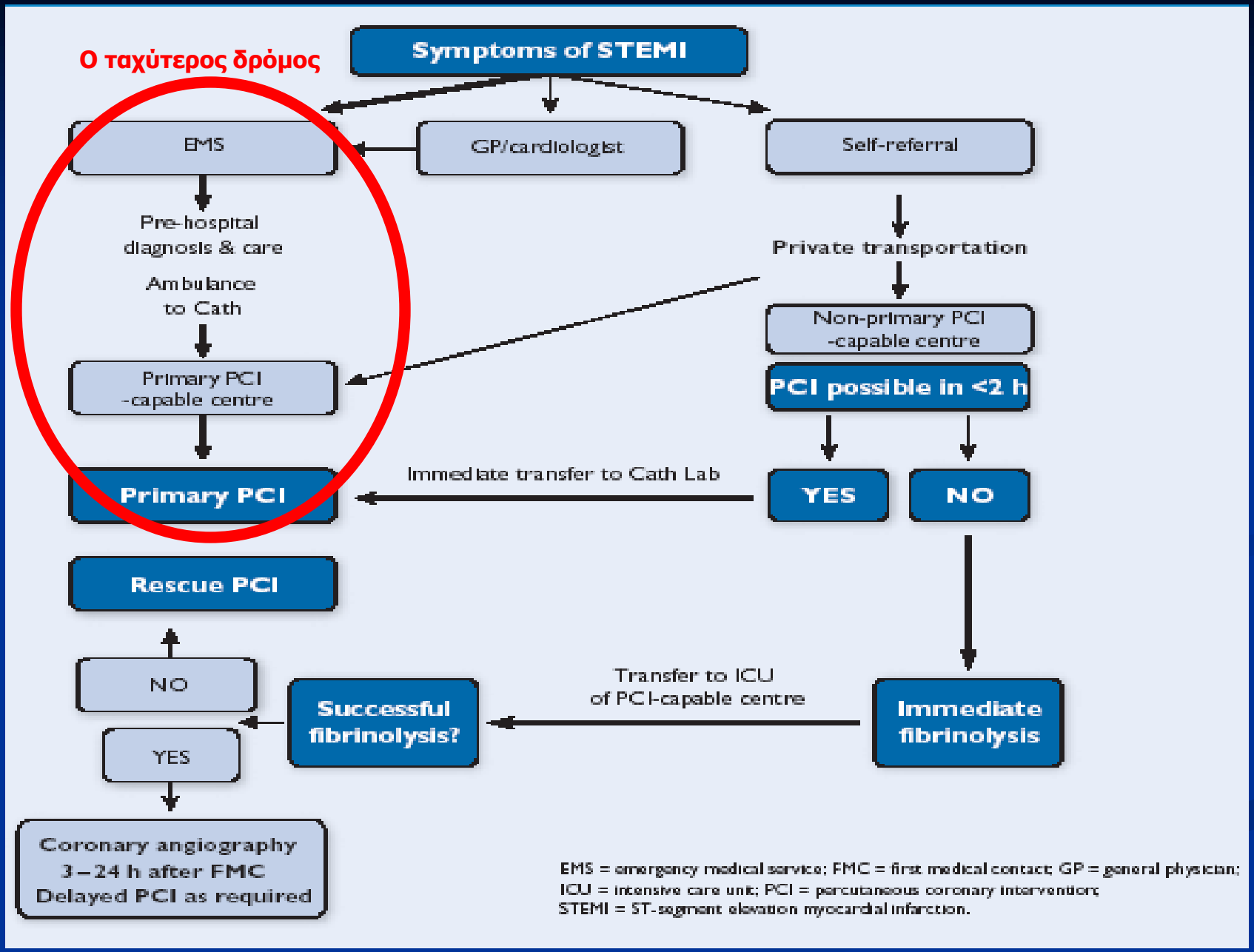










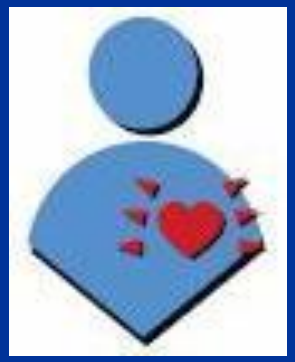


ESC guidelines 2010

Χρονικά διαστήματα με σημασία στον αλγόριθμο αντιμετώπισης του STEMI

Συνολικός ισχαιμικός χρόνος

(total ischemic time)

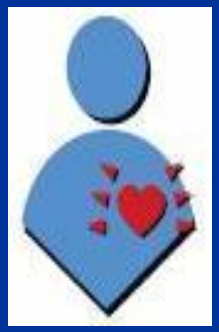


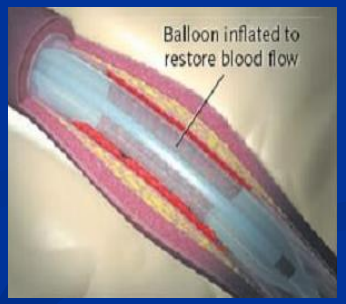
- Έναρξη άλγους έως επαναιμάτωση
- Ιδανικά <120 min
- Εξαρτάται από ασθενή και Σύστημα Υγείας
- Είναι στ' αλήθεια εφικτό;

ESC guidelines 2010

FMC-to-Balloon

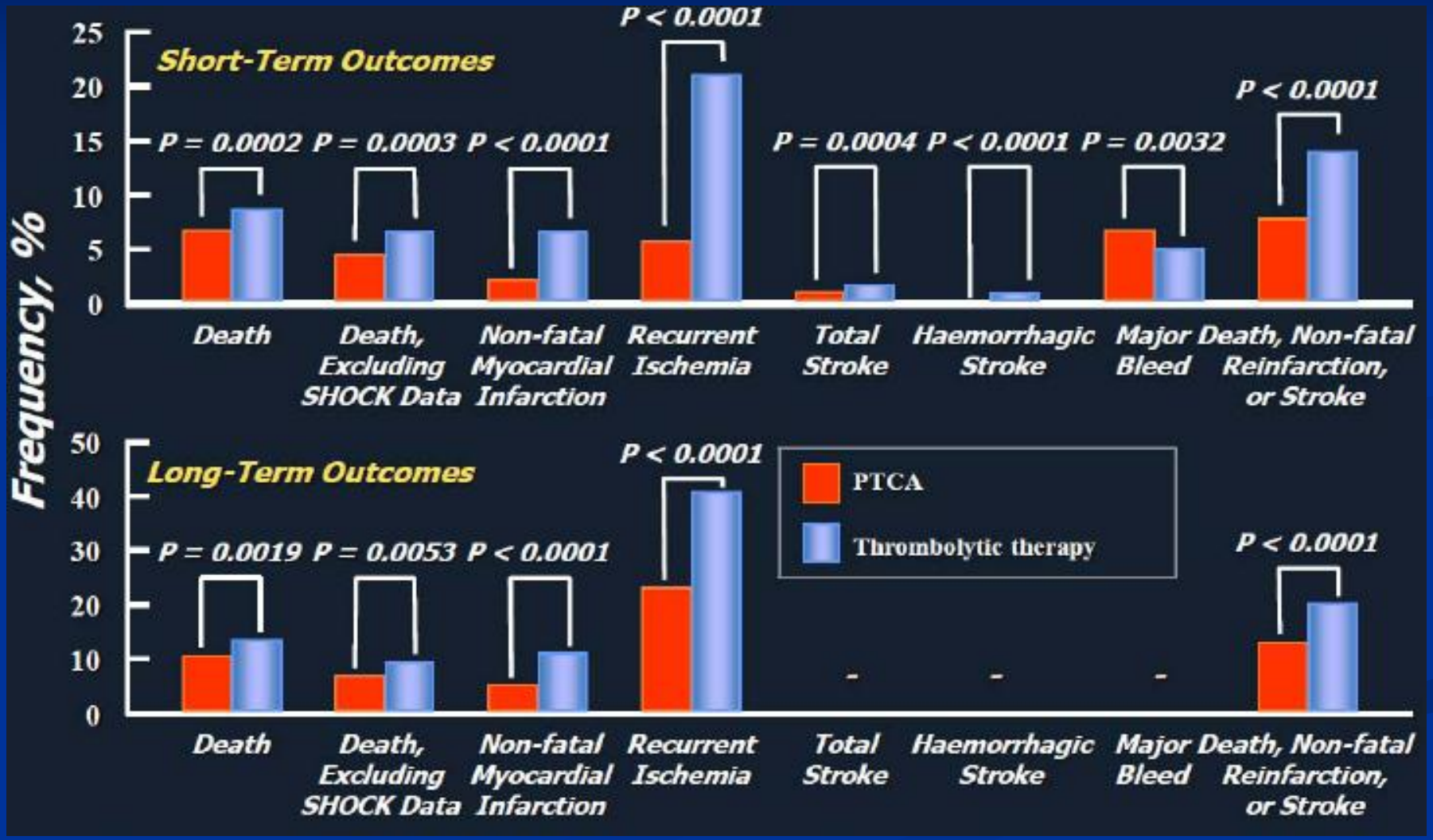
(FMC: First Medical Contact)





- Πρώτη ιατρική επαφή (σπίτι ή νοσοκομείο) έως έκπτυξη μπαλονιού
- Ιδανικά <120 min (ή <90 min σε ειδικές περιπτώσεις)
- Εξαρτάται από Σύστημα Υγείας
- Πόσο συχνά το πετυχαίνουμε;

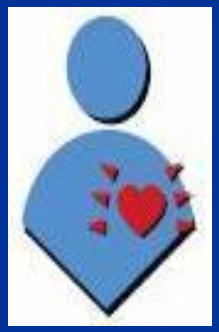
Σύγκριση πρωτογενούς αγγειοπλαστικής με ενδονοσοκομειακή θρομβόλυση



Keely et al. Lancet 2003

FMC-to-Needle

(FMC: First Medical Contact)



- Πρώτη ιατρική επαφή (σπίτι ή νοσοκομείο) έως χορήγηση θρομβόλυσης
- Ιδανικά <30 min
- Εξαρτάται από Σύστημα Υγείας
- Κατά κανόνα εφικτό

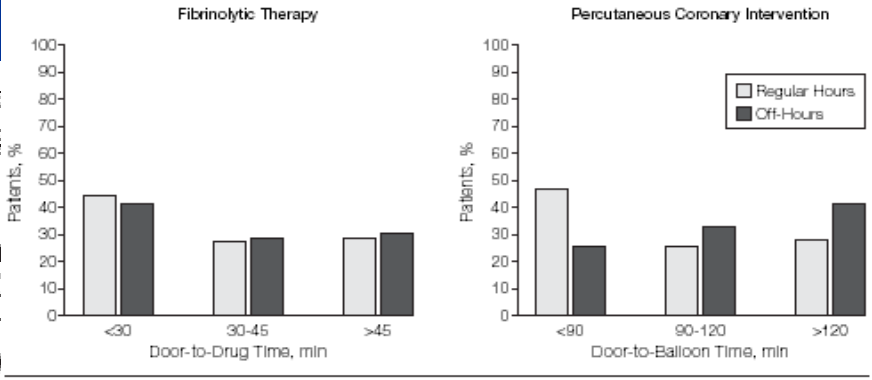
Η θρομβόλυση δεν καθυστερεί ενώ η PPCI εξαρτάται από την ώρα και την ημέρα

Relationship Between Time of Day, Day of Week, Timeliness of Reperfusion, and In-Hospital Mortality for Patients With Acute ST-Segment Elevation Mvocardial Infarction

David J. Magid, MD, MPH
Yongfei Wang, MS
Jeph Herrin, PhD
Robert L. McNamara, MD, MHS
Elizabeth H. Bradley, PhD
Jeptha P. Curtis, MD
Charles V. Pollack, Jr, MD
William J. French, MD
Martha E. Blaney, PharmD
Harlan M. Krumholz, MD, SM

JAMA. 2005;294:803-812

Figure 1. Guideline Adherence for Fibrinolytic Therapy and Percutaneous Coronary Intervention by Patient Arrival Period



Regular hours include weekdays, 7 AM to 5 PM. Off-hours include weekdays 5 PM to 7 AM and all times on the weekend days. American College of Cardiology and the American Heart Association guidelines recommend that door-to-drug times be 30 minutes or less; and door-to-balloon times be 90 minutes or less.[15]

Results Most fibrinolytic thera during off-hours. Door-to-drug minutes) than regular hours (33 interval [CI], 0.7-1.4; $P<.001$). longer during off-hours (116.1 n 21.3 minutes; 95% CI, 20.5-2 guideline recommended times regular hours (47%; $P<.001$) occurred much more commor (27.7%; $P<.001$). Longer off-h longer interval between obtaining the electrocardiogram and patient arrival at the catheterization laboratory (off-hours, 69.8 minutes vs regular hours, 49.1 minutes; $P<.001$). This pattern was consistent across all hospital subgroups examined. Furthermore, patients presenting during off-hours had significantly higher adjusted in-hospital mortality than patients presenting during regular hours (odds ratio, 1.07; 95% CI, 1.01-1.14; $P=.02$).

Conclusions Presentation during off-hours was common and was associated with substantially longer times to treatment for PCI but not for fibrinolytic therapy. To achieve the best outcomes, hospitals providing PCI during off-hours should commit to doing so in a timely manner.

Overall, after adjusting for all patient covariates, patients presenting during off-hours had significantly higher in-hospital mortality than patients presenting during regular hours (OR, 1.07; 95% CI, 1.01-1.14; $P=.02$). When we

Όμως, στους 100 ασθενείς με πρόθεση για θρομβόλυση…

Αντένδειξη:	**≈ 20 ασθενείς**	Crit Pathw Cardiol 2002;1:44
Αποτυχία επαναιμάτωσης:	**≈ 20 ασθενείς**	Am J Cardiol 1996;78:1
Νέα ισχαιμία (ενδονοσοκ.):	**≈ 20 ασθενείς**	J Am Coll Cardiol 2003;42:7-16

Σύνολο: 60% αποτυχία επαναιμάτωσης

TIMI 3 POH

Θρομβόλυση

pPCI

In-hospital time to treatment of patients with acute ST elevation myocardial infarction treated with primary angioplasty: determinants and outcome. Results from the registry of percutaneous coronary interventions in acute myocardial infarction of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte

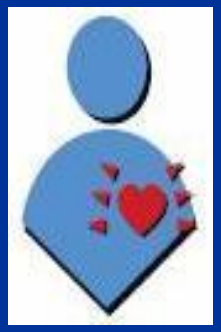
R Zahn[1], A Vogt[2], U Zeymer[1], A K Gitt[1], K Seidl[1], M Gottwik[3], M A Weber[4], W Niederer[5], B Mödl[6], H-J Engel[7], U Tebbe[8], J Senges[1], for the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte

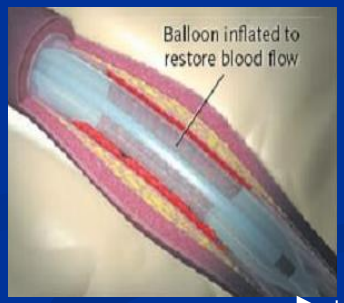
		Time (min)			
	Overall	0–30	31–60	>60	p Value
Number of patients	4815	1487	17[illegible]	1551	
Age (years)	61.4 (12.5)	61.0 (12.2)	60.[illegible] (12.4)	62.3 (12.9)	0.002
Women	25.6%	23.5%	24.1%	29.5%	0.025
Prior PTCA	8.7%	8.5%	9.2%	8.3%	0.261
Prior CABG	2.5%	2.6%	1.9%	3.0%	0.675
Anterior wall MI	42.1%	42.4%	40.9%	43.1%	0.933
Bundle branch block	1.5%	0.94%	1.7%	1.9%	0.497
Cardiogenic shock	14.1%	16.3%	12.9%	13.2%	0.166
TIMI 3 flow after primary angioplasty	87.5%	89.3%	89.0%	84.1%	0.0005

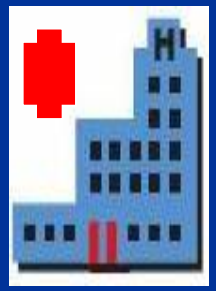
TIMI grade 3 flow was achieved in 87.5% of all patients.

PCI-related delay*

(PCI: Percutaneous Coronary Intervention)

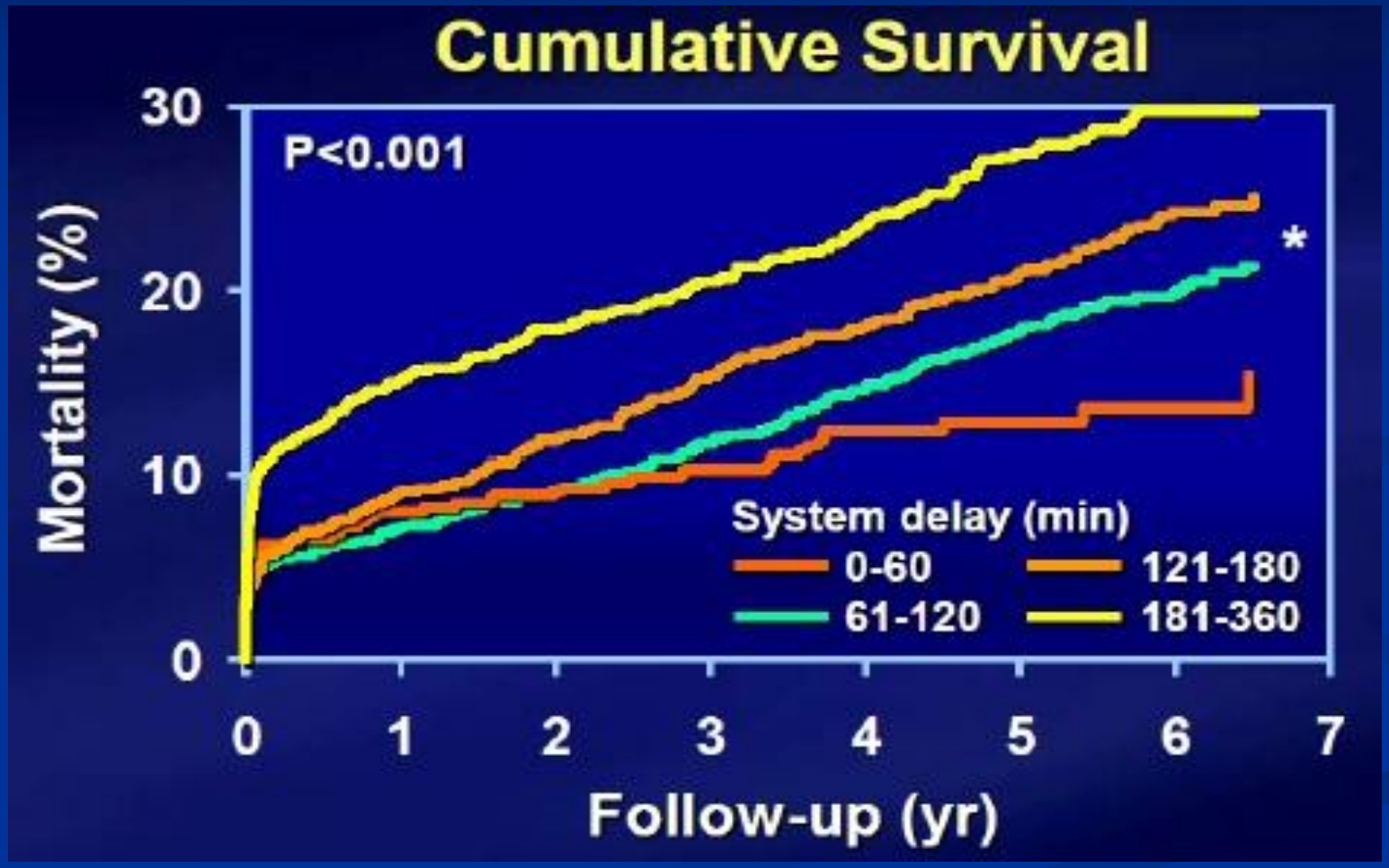




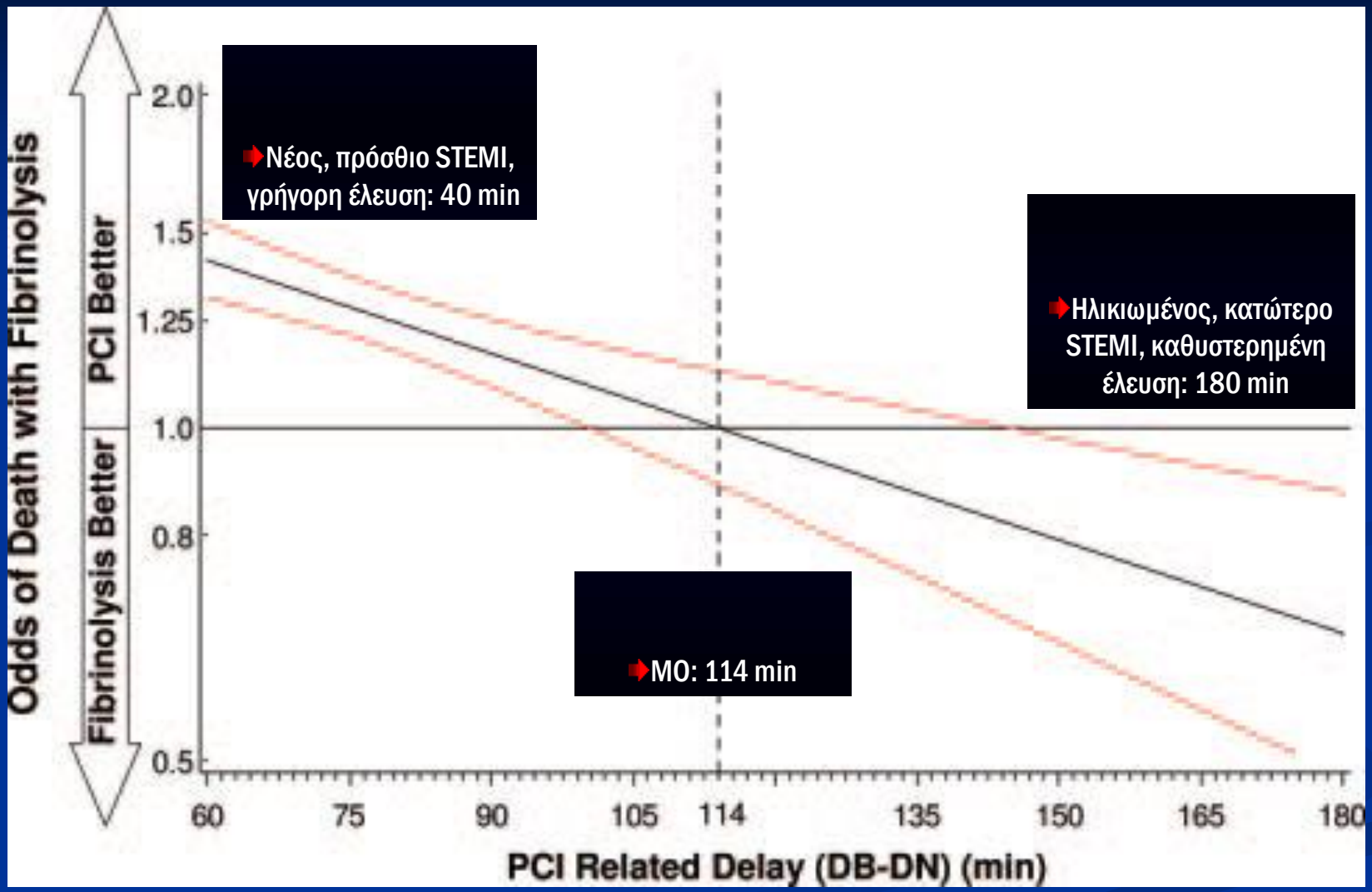


* PCI-related delay

Καθυστέρηση του συστήματος και θνητότητα στους ασθενείς που υποβλήθηκαν επαναιμάτωση με PPCI



Terkelsten CJ,et al.JAMA 2010;304(7):763-771



Pinto et al, Circulation 2006;114

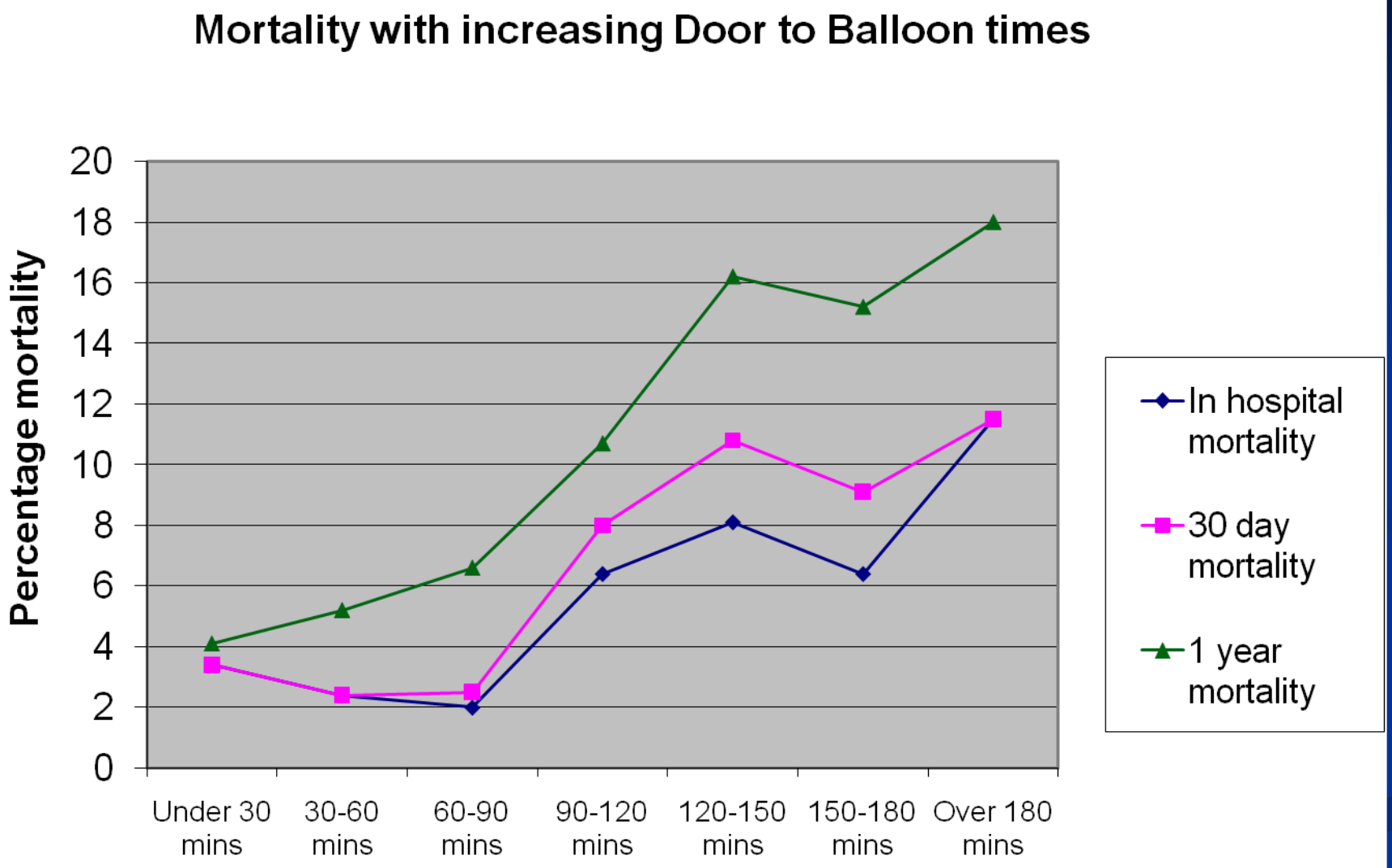
Μεταφορά μετά την πρώτη ιατρική επαφή

- Να έχουν σαφώς οριστεί για κάθε ΤΕΠ Νοσοκομείου: Αιμοδυναμικό Εργαστήριο αναφοράς και εκτιμώμενος χρόνος για μεταφορά και διάνοιξη.

- Άμεση απόφαση αν κατεύθυνση προς PCI-κέντρο ή κοντινό Νοσοκομείο χωρίς PCI.

- Ενεργοποίηση της ομάδας PCI (Αιμοδυναμικό έτοιμο εντός 60 min από την αρχική κλήση, 24 ώρες/7 ημέρες)

Class IA, ESC guidelines 2010


Mortality with increasing Door to Balloon times
Percentage mortality
20
18
16
14
12
10
8
6
4
2
0
Under 30 mins
30-60 mins
60-90 mins
90-120 mins
120-150 mins
150-180 mins
Over 180 mins
In hospital mortality
30 day mortality
1 year mortality

Ενδονοσοκομειακά

- Δεν πρέπει να χάνεται χρόνος στο τμήμα επειγόντων περιστατικών ή στην μονάδα εμφραγμάτων .

- **Ο ασθενής θα πρέπει να μεταφέρεται κατευθείαν στο αιμοδυναμικό εργαστήριο.**

Class III, ESC guidelines 2010

Οι ασθενείς που μεταφέρονται από νοσοκομεία χωρίς αιμοδυναμικό δύσκολα πετυχαίνουν τον στόχο

Door-to-balloon times in NRMI transfer patients

Door-to-balloon time	% of patients
<90 min	4.2
<2 h	16.2
2-4 h	55.4
>4 h	28.4

"These results reveal an important discrepancy between the performance of primary PCI in transfer patients within a real-world setting and the strategy tested in recent randomized clinical trials," the researchers write. "Hospitals without PCI capability that are planning to use a transfer strategy for STEMI patients need to be aware of their own total door-to-balloon times and to incorporate this information into clinical decision making when selecting between reperfusion strategies," they say.

US National Registry of Myocardial Infarction
Circulation 2005; 111:761-767

Non-PCI centers can greatly reduce mortality in ST-elevation-MI patients by getting them on their way within 30 minutes after their arrival to a hospital that performs PCI

"door-in-to-door-out" (DIDO) < 30 min (μόνο το 13%)

in-hospital mortality was significantly higher among patients with DIDO times >30 minutes than among those with DIDO times ≤30 minutes

Journal of the American Medical Association 2011

Pre-hospital triage for primary angioplasty: direct referral to the intervention center versus interhospital transport.

- METHODS: Consecutive pre-hospital patients with STEMI, who were referred to our intervention center for primary angioplasty between 2005 and 2007, were studied. After pre-hospital diagnosis, patients were either directly transported to our center or referred through a nonintervention center. The catheterization laboratory was activated before transport to the intervention center.

- CONCLUSIONS: After ambulance-based diagnosis of STEMI, direct transport to an intervention center with pre-hospital notification of the catheterization laboratory more than triples the proportion of patients treated within the time window of the guidelines.

Με την άμεση μεταφορά του ασθενούς σε αιμοδυναμικό εργαστήριο μετά την διάγνωση του ΟΕΜ, χωρίς την παρεμβολή άλλου νοσοκομείου, τριπλασιάζεται το ποσοστό των ασθενών που αντιμετωπίζονται μέσα στους χρόνους που προβλέπουν οι οδηγίες

- .

JACC Cardiovasc Interv. 2010 Jul;3(7):705-11

Συστάσεις για την πρωτογενή αγγειοπλαστική

I A	Η προτιμότερη θεραπεία αν πραγματοποιηθεί από έμπειρη ομάδα το συντομότερο δυνατό μετά την 1η ιατρική επαφή
I B	FMC-TO-BALLOON <120 min ή <90 min υπό προϋποθέσεις
I B	Σε ασθενείς με καταπληξία ή αντένδειξη για θρομβόλυση ανεξαρτήτως χρονικής καθυστέρησης
IIa C	Σε ασθενείς με >12 ώρες πόνο, αν συνεχίζεται η ισχαιμία (ΗΚΓ ή κλινικά)
IIb B	Σε σταθερούς ασθενείς με >12 ώρες πόνο
III B	Σε σταθερούς ασθενείς με >24 ώρες πόνο, με πλήρως αποφραγμένη την ένοχη αρτηρία

ESC guidelines 2010

Prognostic impact of staged versus "one-time" multivessel percutaneous intervention in acute myocardial infarction: analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial.

OBJECTIVES:
The purpose of this study was to compare a one-time primary percutaneous coronary intervention (PCI) of the culprit and nonculprit lesions with PCI of only the culprit lesion and staged nonculprit PCI at a later date in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease.

BACKGROUND:
In patients with STEMI and multivessel disease, it is unknown whether it is safe or even desirable to also treat the nonculprit vessel during the primary PCI procedure.

METHODS:
In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, 668 of the 3,602 STEMI patients enrolled (18.5%) underwent PCI of culprit and nonculprit lesions for multivessel disease. Patients were categorized into a single PCI strategy (n = 275) versus staged PCI (n = 393). The endpoints analyzed included the 1-year rates of major adverse cardiovascular events and its components, death, reinfarction, target-vessel revascularization for ischemia, and stroke.

RESULTS:
Single versus staged PCI was associated with higher 1-year mortality (9.2% vs. 2.3%; hazard ratio [HR]: 4.1, 95% confidence interval [CI]: 1.93 to 8.86, $p < 0.0001$), cardiac mortality (6.2% vs. 2.0%; HR: 3.14, 95% CI: 1.35 to 7.27, $p = 0.005$), definite/probable stent thrombosis (5.7% vs. 2.3%; HR: 2.49, 95% CI: 1.09 to 5.70, $p = 0.02$), and a trend toward greater major adverse cardiovascular events (18.1% vs. 13.4%; HR: 1.42, 95% CI: 0.96 to 2.1, $p = 0.08$). The mortality advantage favoring staged PCI was maintained in a subgroup of patients undergoing truly elective multivessel PCI. Also, the staged PCI strategy was independently associated with lower all-cause mortality at 30 days and at 1 year.

CONCLUSIONS:
A deferred angioplasty strategy of nonculprit lesions should remain the standard approach in patients with STEMI undergoing primary PCI, as multivessel PCI may be associated with a greater hazard for mortality and stent thrombosis. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction

Αντιμετώπιση μόνο της ένοχης βλάβης…

Kornowski R et all.J Am Coll Cardiol. 2011 Aug 9;58(7):704-11.

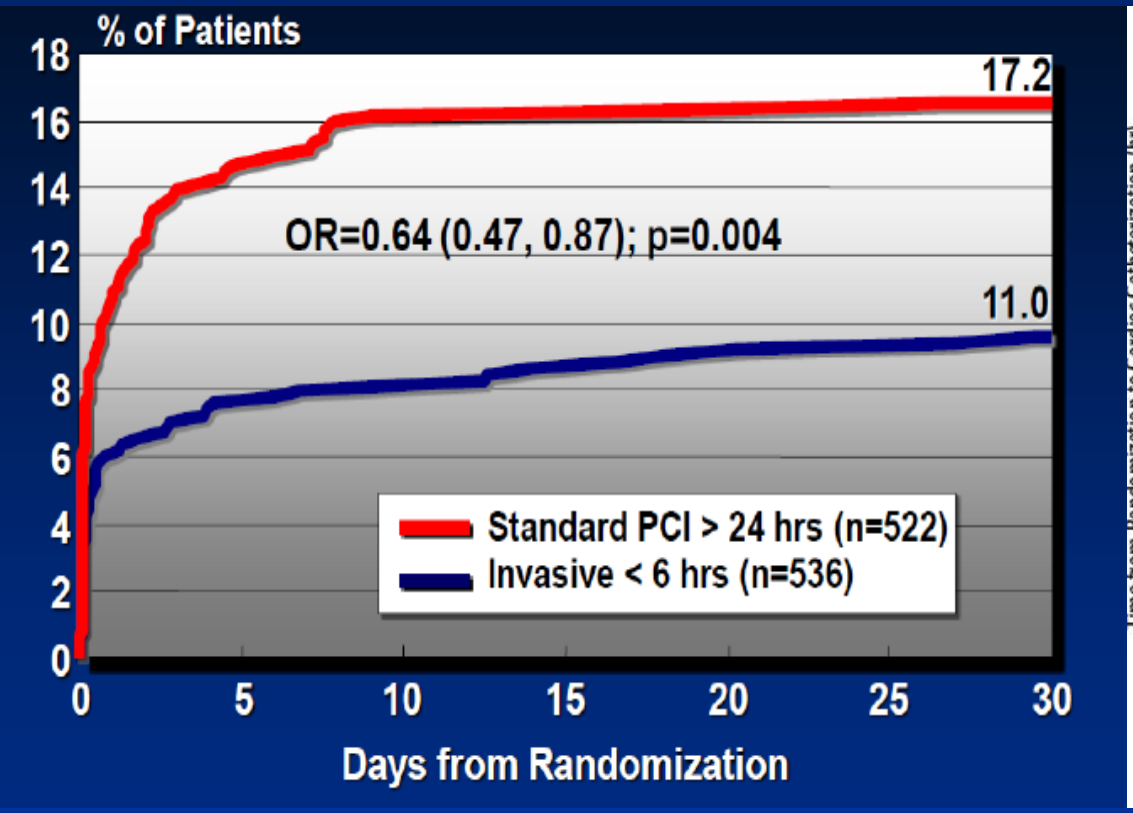
Προϋποθέσεις για PCI - κέντρα

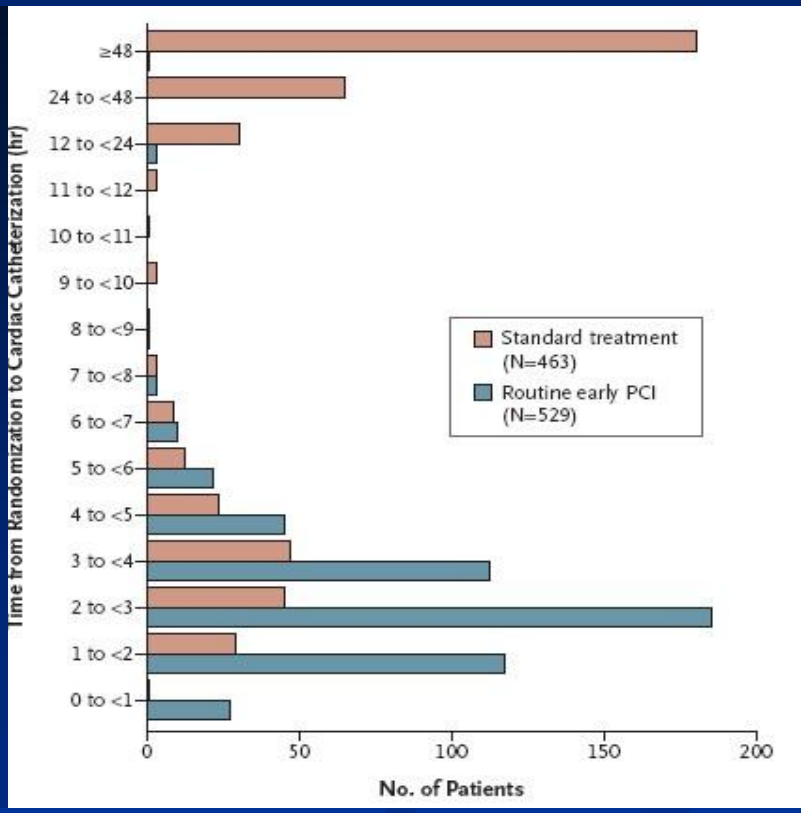
- > 200 παρεμβάσεις / έτος (εκ των οποίων > 36 pPCIs)
- Έμπειρος επεμβατικός καρδιολόγος με 75 PCIs / έτος
- Επαρκής επάνδρωση αιμοδυναμικού για κάλυψη 24ωρης εφημερίας

Antman et al. 2004 ACC/AHA guidelines for the management of pts with STEMI. JACC 2004;44

Μεταφορά σε PCI – κέντρα μετά από επιτυχή θρομβόλυση

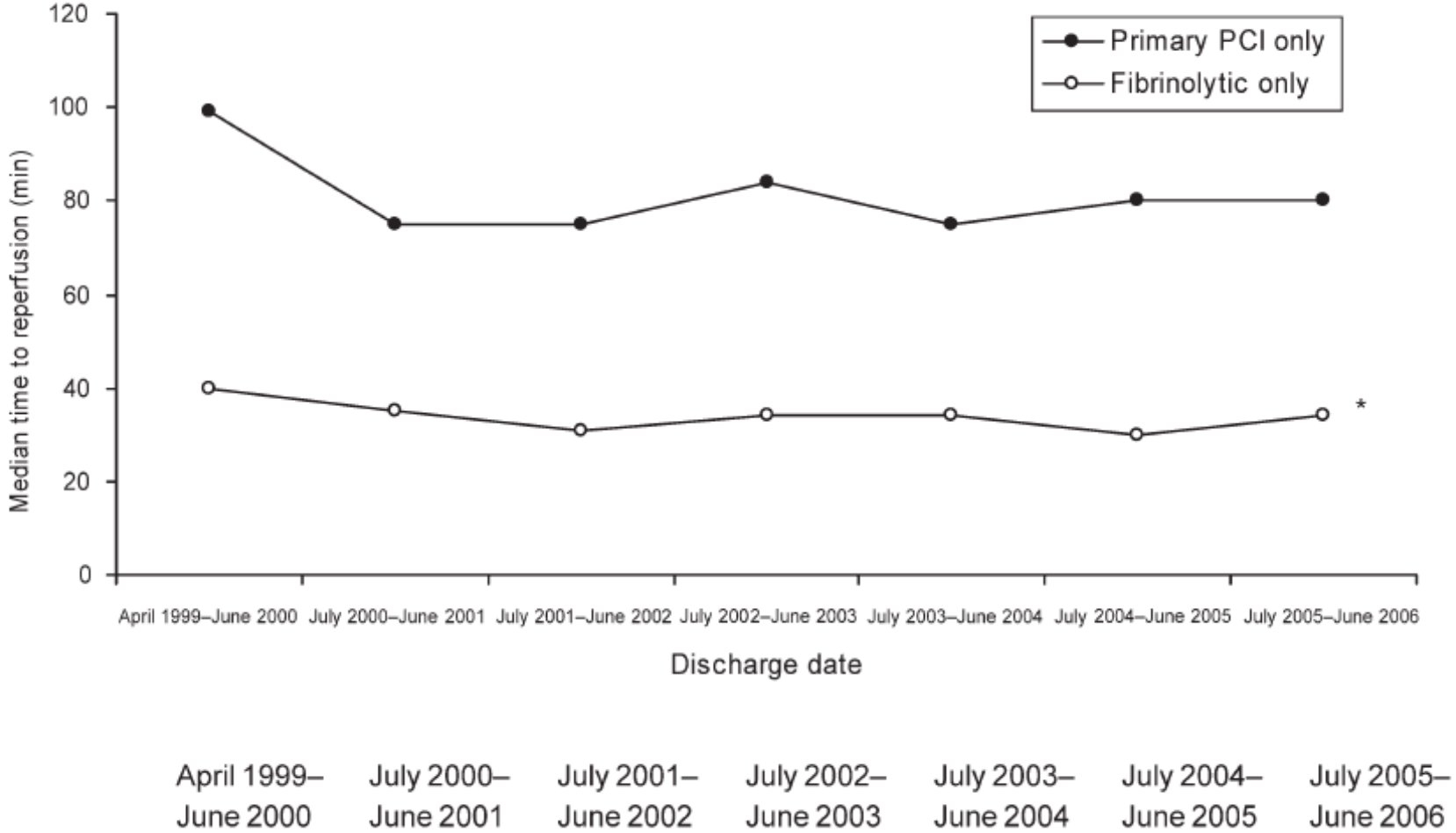
TRANSFER - AMI





- Πρώιμη (εντός 6 ωρών) Σ/Φ ρουτίνας μετά από θρομβόλυση καλύτερη από την καθιερωμένη θεραπεία (χωρίς αύξηση αιμορραγικού κινδύνου).

The NEW ENGLAND JOURNAL of MEDICINE



April 1999–June 2000	July 2000–June 2001	July 2001–June 2002	July 2002–June 2003	July 2003–June 2004	July 2004–June 2005	July 2005–June 2006

- Δεν υπάρχουν άλλα περιθώρια βελτίωσης των χρόνων;

Eagle et al. Eur Heart J.2008;29

The NEW ENGLAND JOURNAL of MEDICINE

VOL. 357 NO. 20

ESTABLISHED IN 1812 NOVEMBER 15, 2007 WWW.NEJM.ORG

2000 THIS WEEK IN THE JOURNAL

PERSPECTIVE

1993 The Ongoing Regulation of Generic Drugs
R.G. Frank

1996 Closing the Affordability Gap for Drugs in Low-Income Countries R. Steinbrook

ORIGINAL ARTICLES

2001 **Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes**
S.D. Wiviott and Others

IMAGES IN CLINICAL MEDICINE

2067 Quinolone-Associated Rupture of the Achilles' Tendon
H Vyas and G. Krishnaswamy

e22 Harlequin's Darker Side
M E. Duddy and M R. Baker

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

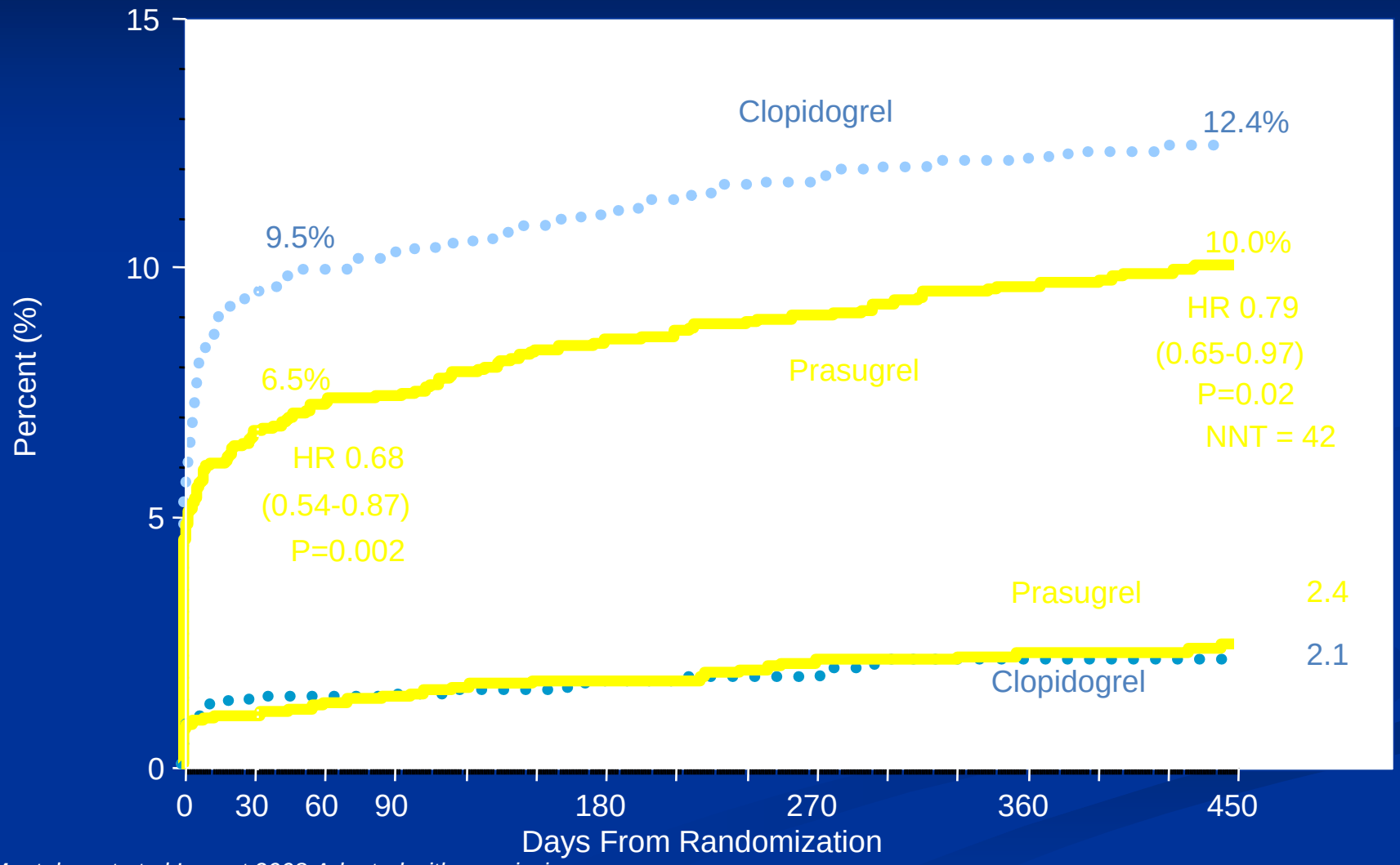
2068 A Man with Inflammatory Bowel Disease and Recent Onset of Fever and Bloody Diarrhea

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M D., Eugene Braunwald, M.D., Carolyn H McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M D., and Elliott M Antman, M.D., for the TRITON–TIMI 38 Investigators*

TRITON TIMI-38

STEMI Cohort N=3534



Montalescot et al Lancet 2008.Adapted with permission from Antman EM.

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel[d]	I	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B
	Upstream GPIIb–IIIa antagonists	III	B

Increasing the maintenance dose of clopidogrel for 1–2 weeks might be effective in STEMI patients

European Heart Journal
doi:10.1093/eurheartj/ehq277

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes

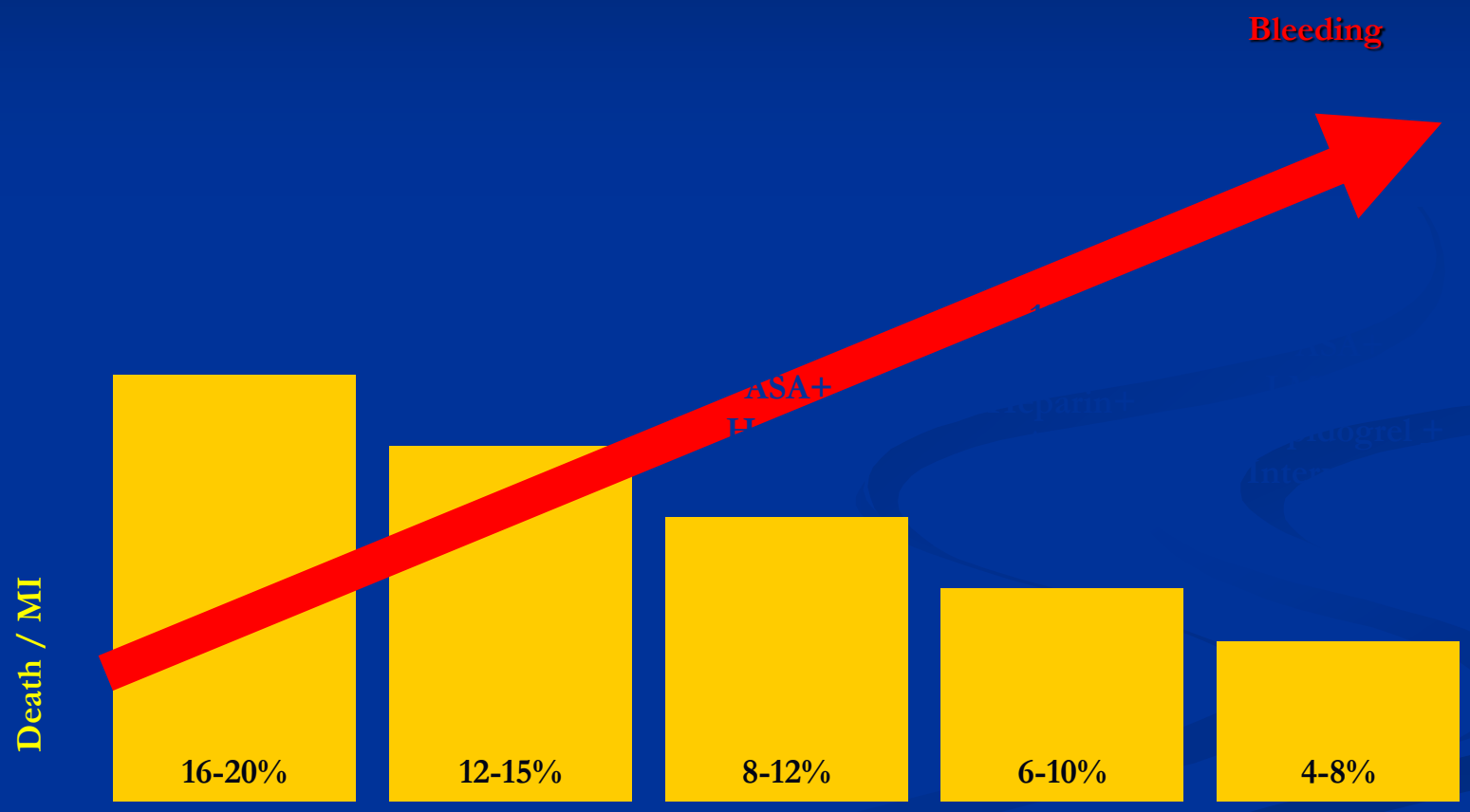
The CURRENT–OASIS 7 Investigators*

CONCLUSIONS

In patients with an acute coronary syndrome who were referred for an invasive strategy, there was no significant difference between a 7-day, double-dose clopidogrel regimen and the standard-dose regimen, or between higher-dose aspirin and lower-dose aspirin, with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke. (Funded by Sanofi-Aventis and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00335452.)

N.Engl. J Med.2010 Sep2;363(10):976-7

Increased Efficacy at the Price of Increased Bleeding

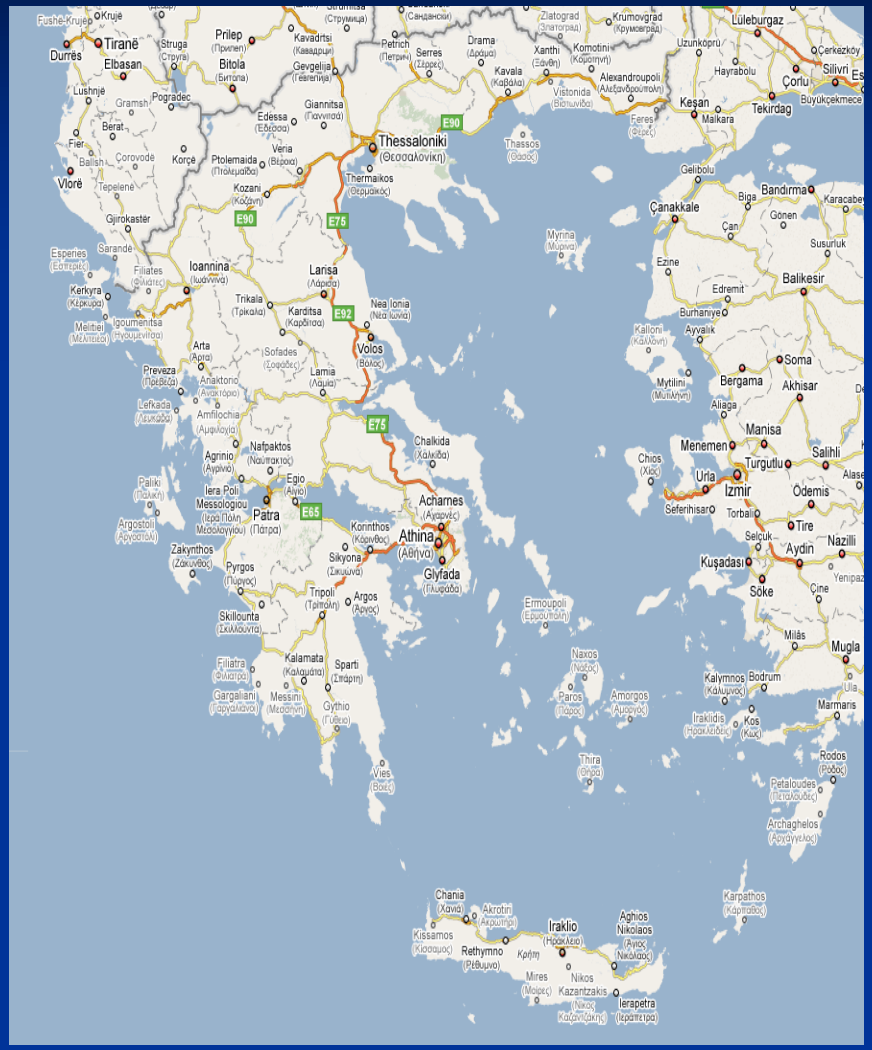


Impact of In-Hospital Major Bleeding on Late Clinical Outcomes After Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial.

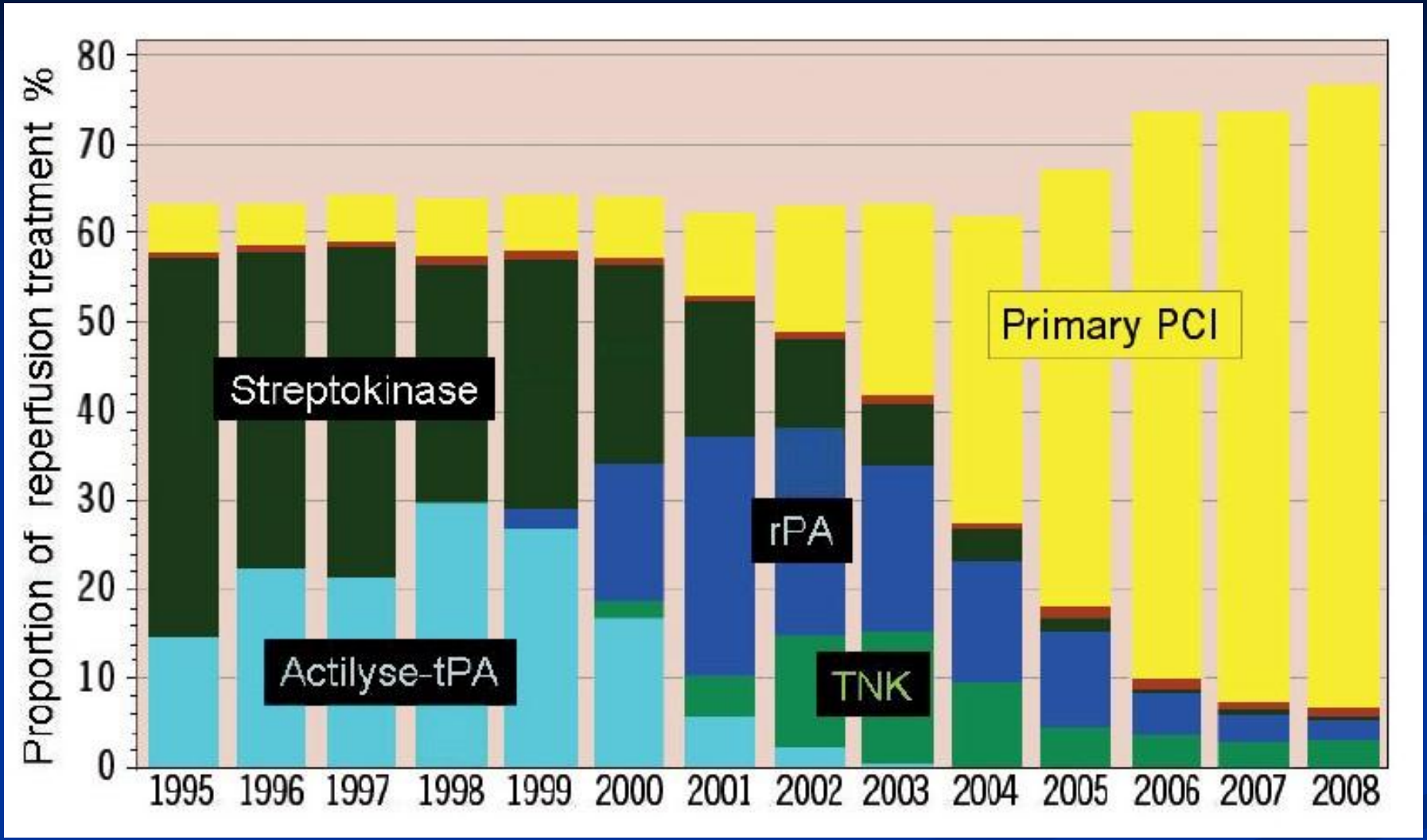
OBJECTIVES:
We aimed to investigate the long-term prognosis of patients with in-hospital major bleeding (IHMB).
BACKGROUND:
The effect of IHMB on the long-term prognosis of patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction is unknown.
METHODS:
Primary PCI was performed in 3,345 (92.9%) of 3,602 patients in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial; in-hospital protocol-defined non-coronary artery bypass graft-related major bleeding developed in 231 (6.9%). We examined medication use at discharge, mortality, and major adverse cardiovascular events (composite of death, reinfarction, stroke, or ischemic target vessel revascularization) at 3-year follow-up in patients with and without IHMB.
RESULTS:
At 3-year follow-up, patients with IHMB had higher mortality (24.6% vs. 5.4%, $p < 0.0001$) and major adverse cardiovascular events (40.3% vs. 20.5%, $p < 0.0001$). The deleterious effect of major bleeding was observed within 1 month, between 1 month and 1 year, and between 1 and 3 years. IHMB was an independent predictor of mortality (hazard ratio: 2.80; 95% confidence interval: 1.89 to 4.16, $p < 0.0001$) at 3-year follow up.
CONCLUSIONS:
Patients with IHMB after primary PCI have significantly increased 3-year rates of morbidity and mortality. Further investigation is warranted to understand the mechanisms underlying this relationship and to further improve outcomes in patients with ST-segment myocardial infarction.

Οι αιμορραγίες που σχετίζονται με την πρωτογενή αγγειοπλαστική αυξάνουν την θνητότητα και νοσηρότητα και μακροπρόθεσμα(3 ετία)

Suh JW, JAmCollCardiol 2011 Oct 18;58(17):1750-6.


Tiranë
Durrës
Elbasan
Thessaloniki
Larisa
Volos
Ioannina
Athina
Patra
Izmir
Bursa
Ankara
Konya
Antalya
Mersin
Adana
Gaziantep
Kayseri
Samsun
Trabzon
Erzurum
Van
Diyarbakır
Malatya
Eskişehir
Kocaeli
Ankara
Iraklio
Rethymno
Chania
Ierapetra

Ανατ. Μακεδονία και Θράκη
1
Δυτική Μακεδονία
7
Βόρειο Αιγαίο
Ήπειρος
2
Θεσσαλία
1
Στερεά Ελλάδα
1
Ιόνιοι νήσοι
2
24
Πελοπόννησος
Νότιο Αιγαίο
Νότιο Αιγαίο
Κρήτη
2
Χάρτης Αιμοδυναμικών Εργαστηρίων



EuroIntervention 2009;5:**299-309**

Ρεαλιστικοί στόχοι για τις υπόλοιπες Ευρωπαϊκές χώρες

EuroIntervention EuroIntervention 2009;5:299-309

How to set up an effective national primary angioplasty network: lessons learned from five European countries

pPCI για >70% των ασθενών με STEMI

pPCI για >600 ασθενείς ανά εκατομμύριο πληθυσμού ανά έτος

Υπάρχοντα PCI κέντρα θα πρέπει να αντιμετωπίζουν όλους τους ασθενείς με pPCI (λειτουργία 24 ώρες)

Ζητούμενα από το Σύστημα Υγείας Ι

Κεντρικό όργανο λήψης αποφάσεων για τη διαχείριση του κάθε ασθενούς

Καρδιολόγος on-call

Έλεγχος των επιμέρους χρονικών παραμέτρων (κυκλοφορικός φόρτος, απόσταση/ ετοιμότητα PCI-κέντρου)

Επικοινωνία με ΕΚΑΒ, PCI-κέντρο, Νοσοκομείο υποδοχής (αν διαφορετικό)

Ζητούμενα από το Σύστημα Υγείας ΙΙ

Να έχουν σαφώς οριστεί για κάθε ΤΕΠ Νοσοκομείου: Αιμοδυναμικό Εργαστήριο αναφοράς και εκτιμώμενος χρόνος για μεταφορά και διάνοιξη

Προνοσοκομειακό ΗΚΓ

- Άμεση απόφαση αν κατεύθυνση προς PCI-κέντρο ή κοντινό Νοσοκομείο χωρίς PCI
- Ενεργοποιείται η ομάδα PCI (Αιμοδυναμικό έτοιμο εντός 30 min)

European Heart Journal (2009) **30**, 1598–1606
doi:10.1093/eurheartj/ehp156

CLINICAL RESEARCH
Coronary heart disease

Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up

Eric Bonnefoy[1]*, Philippe Gabriel Steg[2], Florent Boutitie[3], Pierre-Yves Dubien[4], Frédéric Lapostolle[5], Jérome Roncalli[6], Frederic Dissait[7], Gérald Vanzetto[8], Alain Leizorowicz[9], and Gilbert Kirkorian[10] for the CAPTIM Investigators[†]

[1]UMR 5558, Univeristé Lyon 1 et Centre d'Investigation Clinique, Hôpital Cardio-Vasculaire et Pneumologique, Hospices Civils de Lyon, 69394 Lyon Cedex 03, France; [2]INSERM U-698, Université Paris 7, AP-HP, Hôpital Bichat, Paris, France; [3]Hospices Civils de Lyon, Service de Biostatistique, UMR 5558, CHU de Lyon, Lyon, France; [4]SAMU 69 – Hospices Civils de Lyon, Lyon, France; [5]SAMU 93, Bobigny, France; [6]Pôle Cardiovasculaire – Rangueil, Toulouse, France; [7]SAMU 63, Centre Hospitalier Universitaire, Clermont Ferrand, France; [8]Service de Cardiologie, Centre Hospitalier Universitaire, Grenoble, France; [9]Université Lyon I et service de pharmacologie clinique, Hospices Civils de Lyon, Lyon, France; and [10]UMR 5558, Université Lyon 1 et CIC, Hospices Civils de Lyon, Lyon, France

Received 4 September 2008; revised 18 March 2009; accepted 19 March 2009; online publish-ahead-of-print 8 May 2009

Aims The CAPTIM (Comparison of primary Angioplasty and Pre-hospital fibrinolysis In acute Myocardial infarction) study found no evidence that a strategy of primary angioplasty was superior in terms of 30-day outcomes to a strategy of pre-hospital fibrinolysis with transfer to an interventional facility in patients managed early at the acute phase of an acute myocardial infarction. The present analysis was designed to compare both strategies at 5 years.

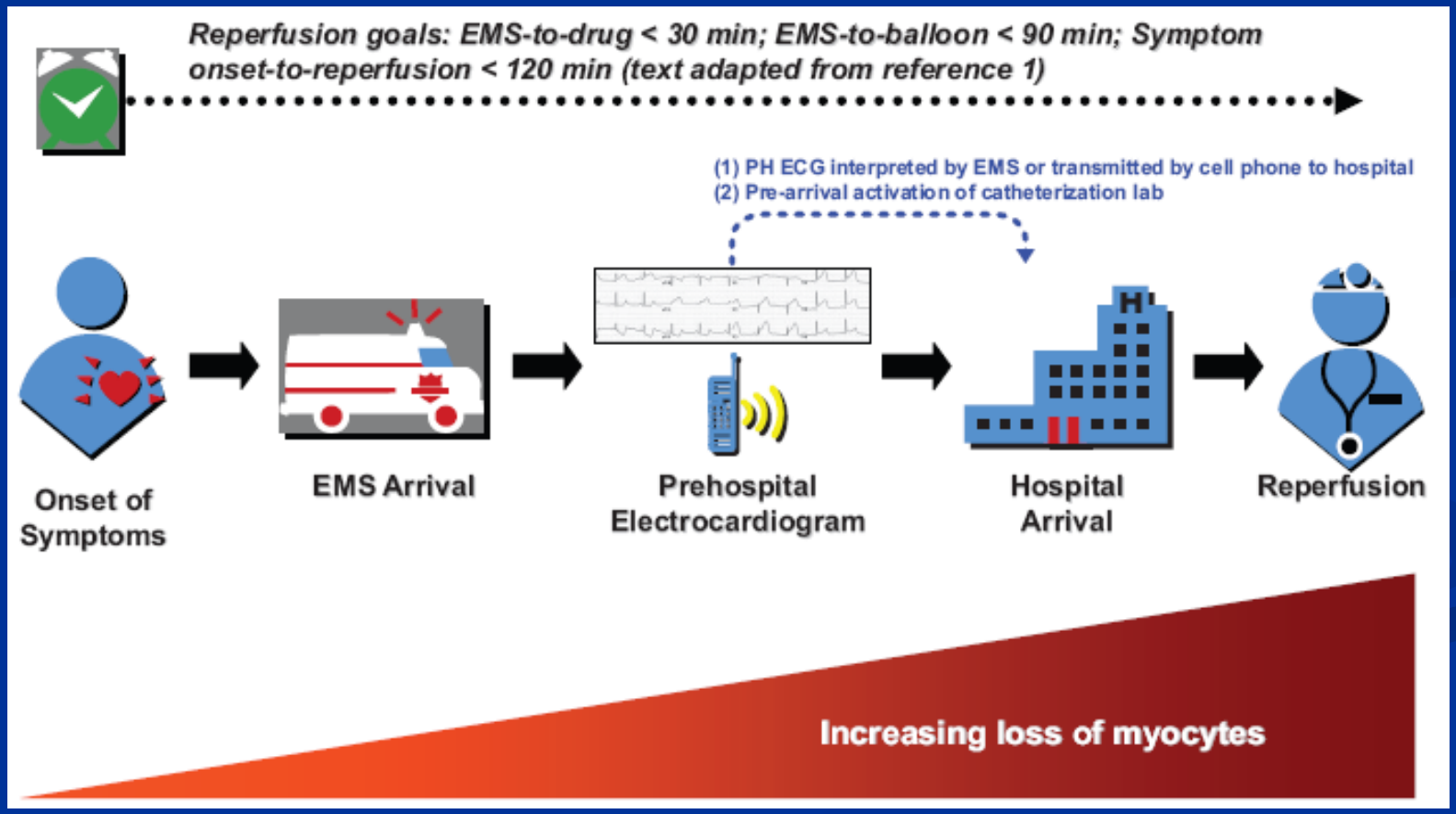
Methods and results The CAPTIM study included 840 patients managed in a pre-hospital setting within 6 h of an acute ST-segment elevation myocardial infarction. Patients were randomized to either a primary angioplasty ($n = 421$) or a pre-hospital fibrinolysis (rt-PA) with immediate transfer to a centre with interventional facilities ($n = 419$). Long-term follow-up was obtained in blinded fashion from 795 patients (94.6%). Using an intent-to-treat analysis, all-cause mortality at 5 years was 9.7% in the pre-hospital fibrinolysis group when compared with 12.6% in the primary angioplasty group [HR 0.75 (95% CI, 0.50–1.14); $P = 0.18$]. For patients included within 2 h, 5 year mortality was 5.8% in the pre-hospital fibrinolysis group when compared with 11.1% in the primary angioplasty group [HR 0.50 (95% CI, 0.25–0.97); $P = 0.04$], whereas it was, respectively, 14.5 and 14.4% in patients included after 2 h [HR 1.02, (95% CI 0.59–1.75), $P = 0.92$].

Conclusion The 5-year follow-up is consistent with the 30-day outcomes of the trial, showing similar mortality for primary percutaneous coronary intervention and a policy of pre-hospital lysis followed by transfer to an interventional center. In addition, for patients treated within 2 h of symptom onset, 5-year mortality was lower with pre-hospital lysis.

Ίδια ποσοστά θνητότητας εντός των 30 ημερών για τους ασθενείς που μεταφέρθηκαν για πρωτογενή αγγειοπλαστική με αυτούς που έλαβαν θρομβόλυση προνοσοκομειακά και στηνσυνέχεια μεταφέρθηκαν για αγγειοπλαστική

Προνοσοκομειακό ΗΚΓ και προνοσοκομειακή θρομβόλυση

- Ηλεκτρονική αποστολή στο Κέντρο Λήψης Αποφάσεων
- Αξιολόγηση από Καρδιολόγο υπηρεσίας



ΣΥΜΠΕΡΑΣΜΑΤΑ

Στεφανιαία νόσος η κυρίαρχη νοσος της εποχής

Οι παράγοντες κινδύνου καθοριστικοι

Η επαναιμάτωση στο ΟΕΜ αμεση και καθοριστική για την επιβίωση