Η συμμόρφωση στην Αντιαιμοπεταλιακή Αγωγή ως παράγοντας βελτίωσης της καρδιαγγειακής προστασίας για τους ασθενείς

Διπλή Αντιαιμοπεταλιακή Αγωγή με Κλοπιδογρέλη & ΑΣΟ σε σταθερό συνδυασμό

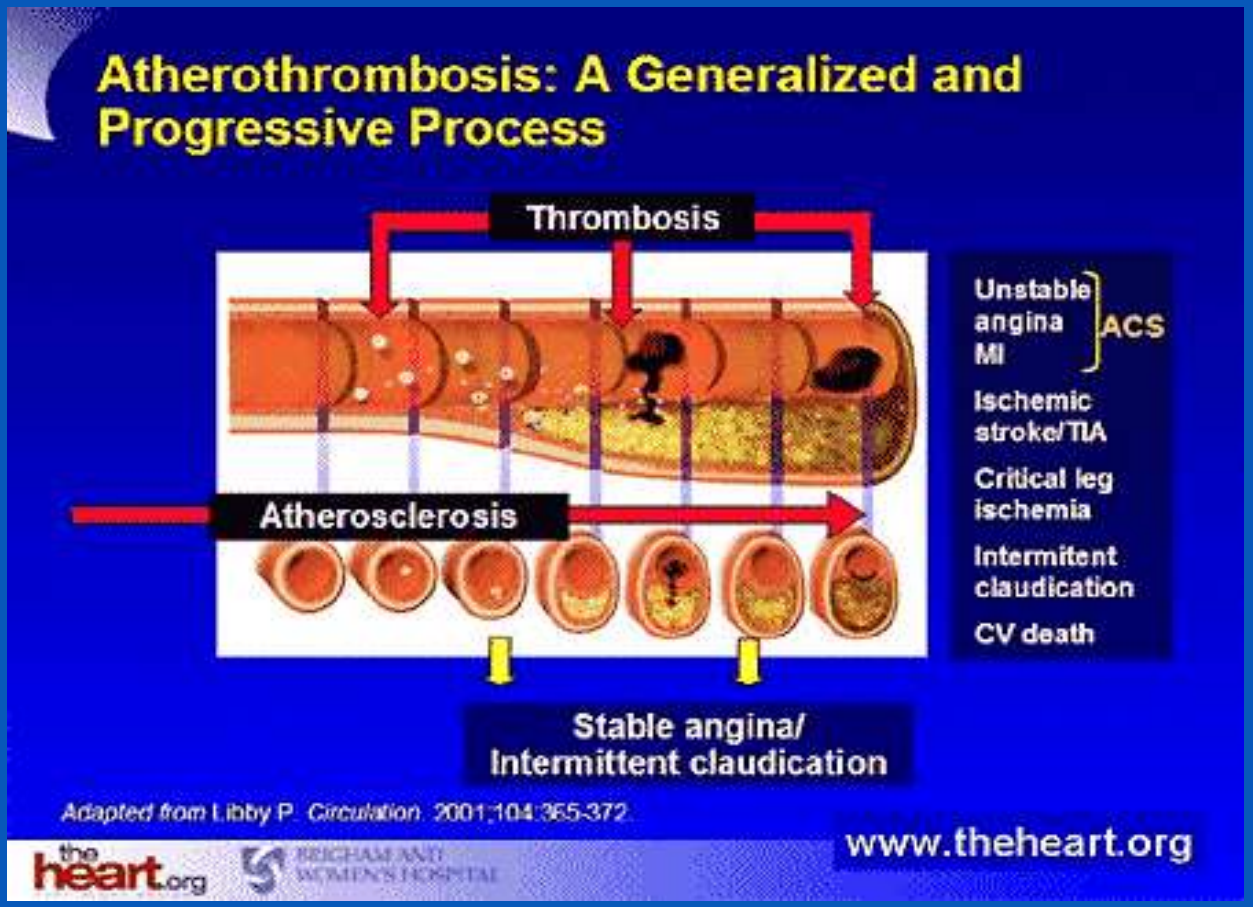
Σ. ΠΑΡΑΣΚΕΥΑΪΔΗΣ

ΔΙΕΥΘΥΝΤΗΣ ΕΣΥ

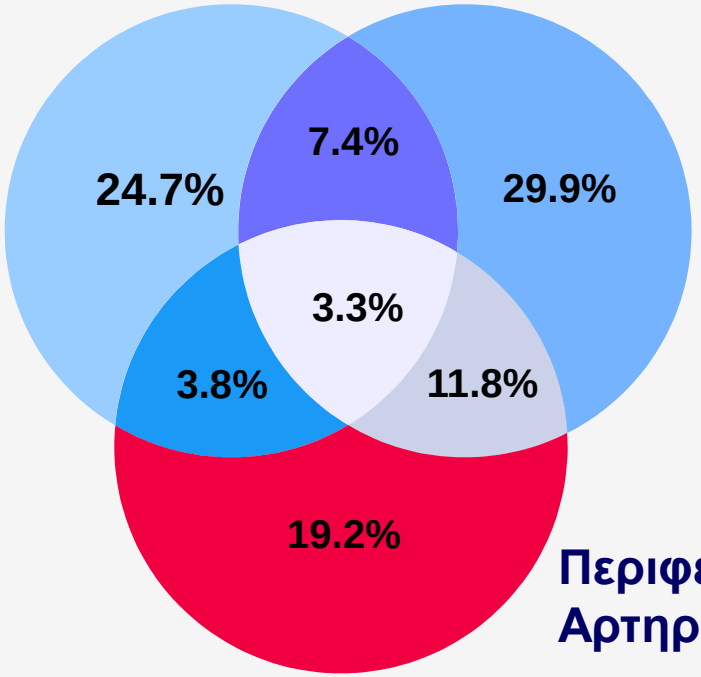
Α ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΑΠΘ

ΝΟΣΟΚΟΜΕΙΟ ΑΧΕΠΑ

ΑΘΗΡΟΘΡΟΜΒΩΣΗ

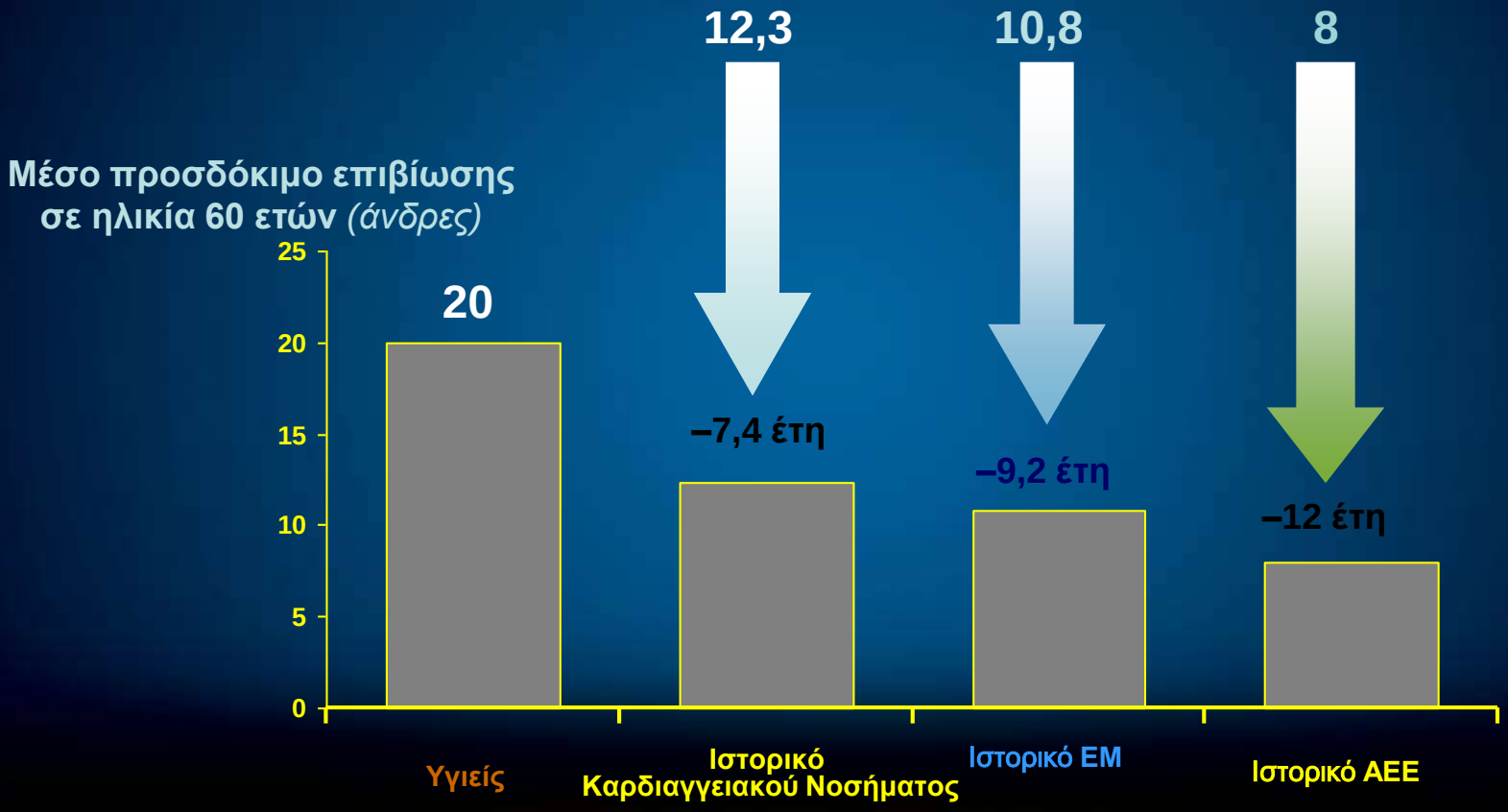


ΑΘΗΡΟΘΡΟΜΒΩΣΗ



*Data from CAPRIE study (n=19.185) [Coccheri S. *Eur Heart J*, 1998; 19 (suppl): p.1268]

Η Αθηροθρόμβωση μειώνει το προσδόκιμο επιβίωσης κατά περίπου 8-12 έτη σε ασθενείς ηλικίας > 60 ετών



Peeters A, et al. *Eur Heart J*, 2002; 23: 458-466

*** Ανάλυση δεδομένων από τη μελέτη Framingham Heart Study**

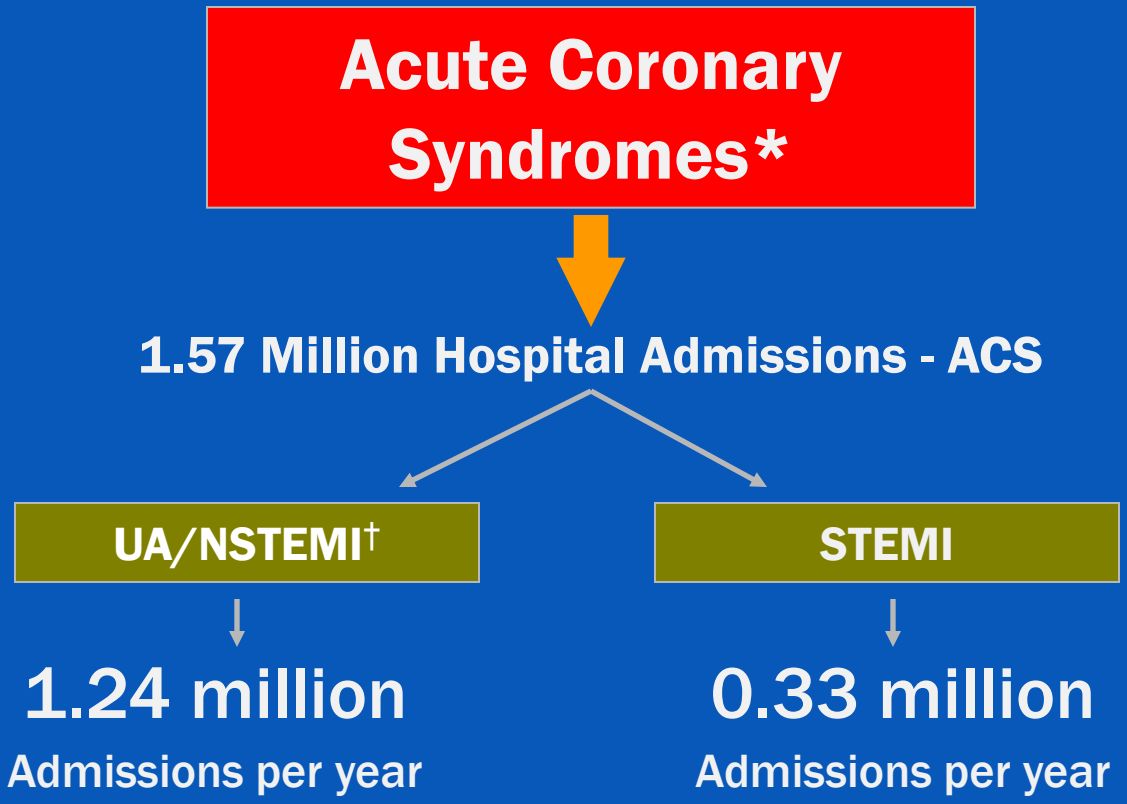
ΘΕΡΑΠΕΙΑ ΑΘΗΡΟΘΡΟΜΒΩΣΗΣ

ΑΘΗΡΩΜΑΤΩΣΗ	ΘΡΟΜΒΩΣΗ
Στατίνες	Ασπιρίνη
Α-ΜΕΑ	Κλοπιδογρέλη
Β-blocker	

ΕΝΔΕΙΞΕΙΣ ΔΙΠΛΗΣ ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΗΣ ΑΓΩΓΗΣ (Dual antiplatelet therapy-DAPT)

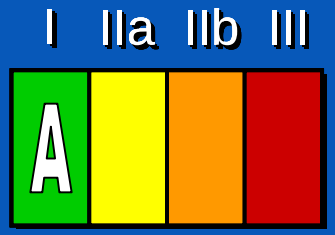
- ΘΕΡΑΠΕΙΑ ΟΞΕΩΝ ΣΤΕΦΑΝΙΑΙΩΝ ΣΥΝΔΡΟΜΩΝ (ΟΣΣ)
- ΜΕΤΑ ΑΠΟ ΤΟΠΟΘΕΤΗΣΗ STENT
- ΠΡΟΛΗΨΗ ΑΕΕ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ (που δεν είναι σε θέση να λάβουν αντιπηκτικά)

ΗΠΑ-ΝΟΣΗΛΕΙΕΣ ΓΙΑ ΟΣΣ



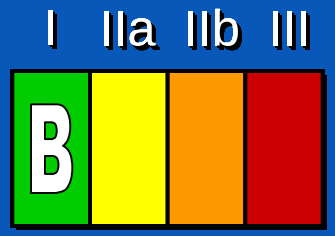
*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA. Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69–171.

UA-NSTEMI GUIDELINES 2011 ACC-AHA
Antiplatelet Therapy



Modified 2011

Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.

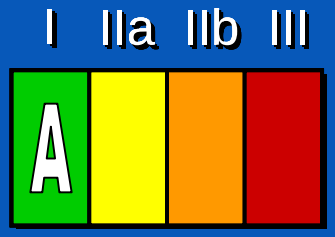


Modified 2011

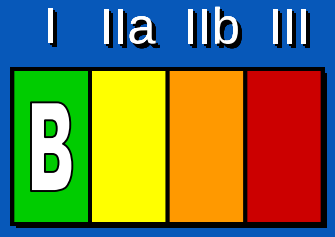
Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.

*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of **300** mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

Initial Invasive Strategy: Antiplatelet Therapy



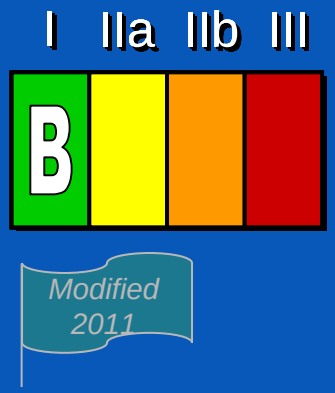
For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)* or an IV GP IIb/IIIa inhibitor.



Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor.†

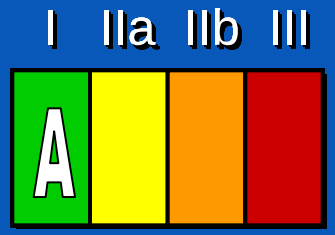
*†Factors favoring administration of both clopidogrel and a GP IIb/IIIa inhibitor include: **delay to angiography, high-risk features, and early ischemic discomfort.**

Initial Conservative Strategy: Antiplatelet Therapy

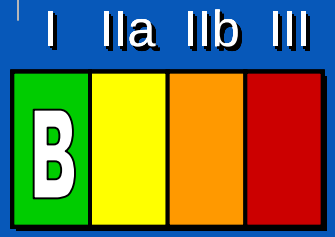


For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected clopidogrel (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for at least 1 month and ideally up to 1 year.

Initial Conservative Strategy: Antiplatelet Therapy



New 2011



New 2011

A loading dose of thienopyridine is recommended for UA/NSTEMI patients for whom PCI is planned. Regimens should be 1 of the following:

a. Clopidogrel 300 to 600 mg should be given as early as possible before or at the time of PCI or

b. Prasugrel 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI.

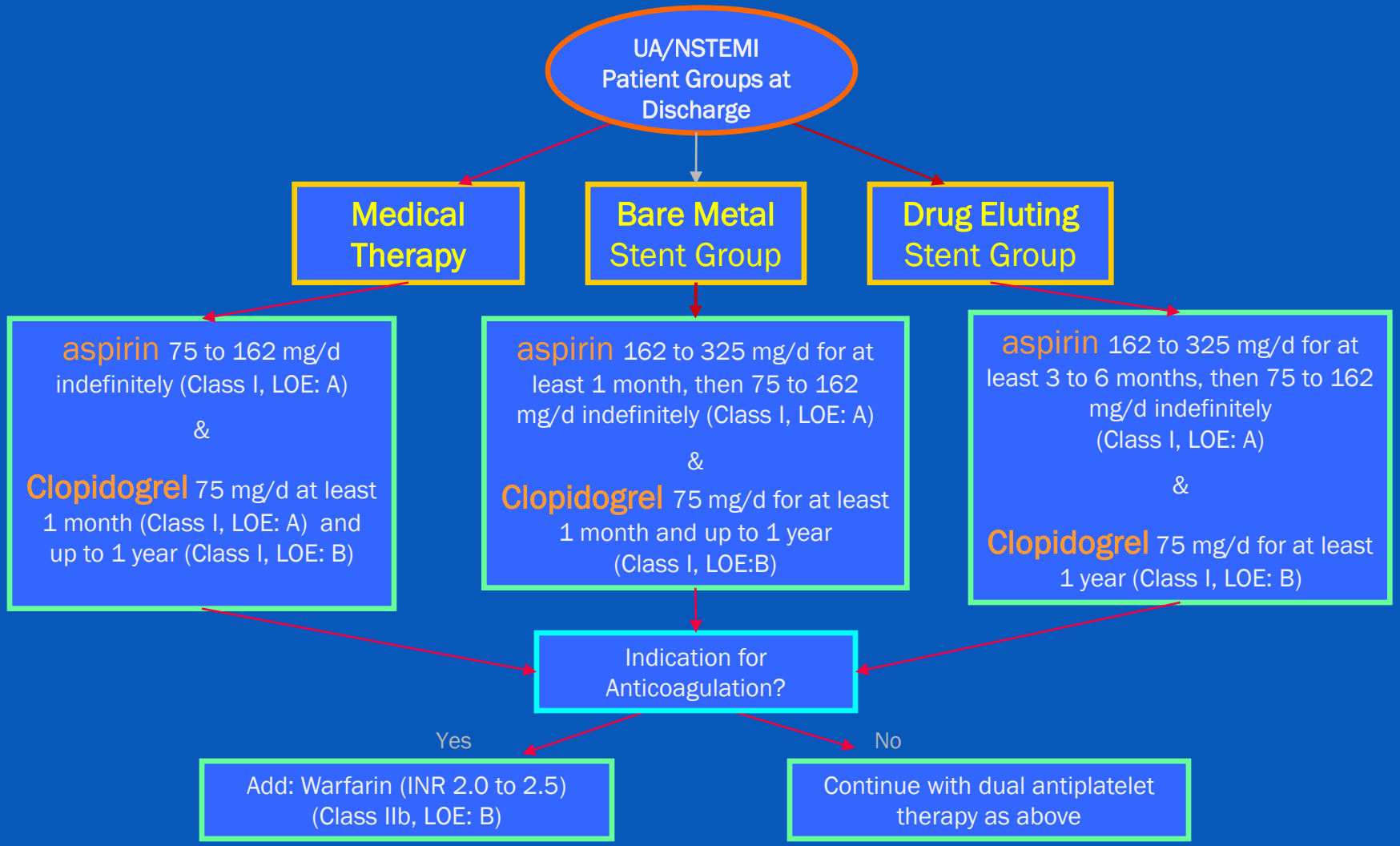
Initial Conservative Strategy: Antiplatelet Therapy

The duration and maintenance dose of thienopyridine therapy should be as follows:

a. In UA/NSTEMI patients undergoing PCI, clopidogrel 75 mg daily or prasugrel 10 mg daily should be given for at least 12 months.

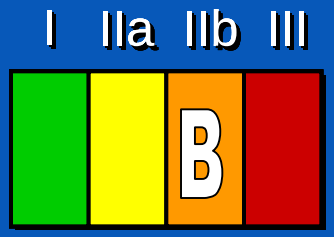
b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered.

Long-Term Antithrombotic Therapy at Hospital Discharge after UA/NSTEMI



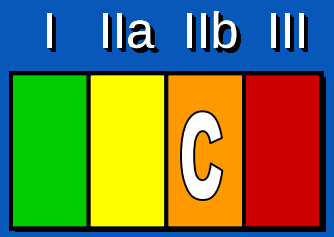
Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 11. INR = international normalized ratio; LOE = level of evidence.

Initial Conservative Strategy: Antiplatelet Therapy



New 2011

Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management.



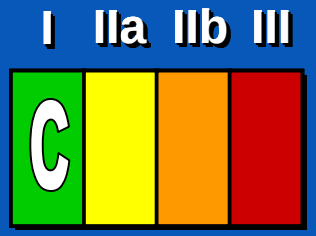
New 2011

Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management.

STEMI-GUIDELINES 2009 AHA/ACC for the use of Thienopyridines

MODIFIED Recommendation

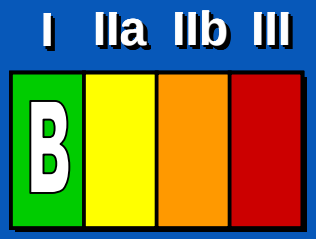
A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:



Clopidogrel at least 300 mg to 600mg should be given as early as possible before or at the time of primary or non-primary PCI.

STEMI-Recommendations for the use of Thienopyridines

MODIFIED Recommendation



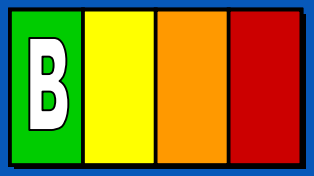
Prasugrel 60 mg should be given as soon as possible for primary PCI.

Thienopyridines

MODIFIED Recommendation

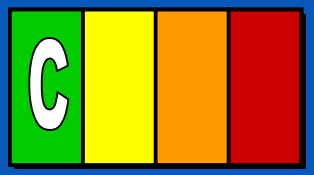
The duration of thienopyridine therapy should be as follows:

I IIa IIb III



a. In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily or prasugrel 10 mg daily should be given for at least 12 months;

I IIa IIb III

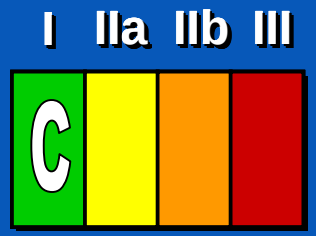


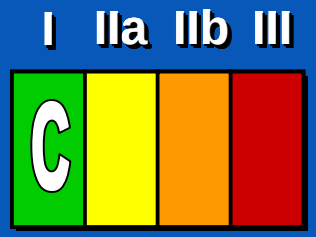
b. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered.

Thienopyridines

MODIFIED

Recommendation (prasugrel added)





In patients taking a thienopyridine in whom coronary artery bypass surgery (CABG) is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect.

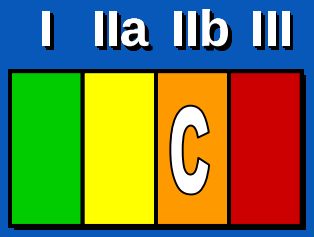
The period of withdrawal should be at least 5 days in patients receiving clopidogrel

and at least 7 days in patients receiving prasugrel,

… unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding.

Thienopyridines

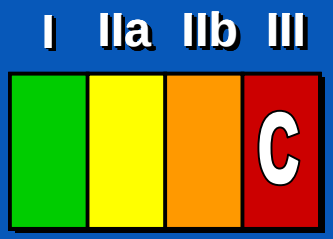
MODIFIED Recommendation



Continuation of clopidogrel or prasugrel > 15 months may be considered in patients undergoing DES stent placement

Thienopyridines

NEW Recommendation



In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual antiplatelet therapy regimen

Κατευθυντήριες Οδηγίες για τη χορήγηση Κλοπιδογρέλης σε ασθενείς με ΟΣΣ

ΕΜΦΡΑΓΜΑ ΜΕ ΑΝΑΣΠΑΣΗ ST (STEMI)

- **Ανεξάρτητα από την αντιμετώπιση των ασθενών (*με θρομβόλυση ή χωρίς θεραπεία επαναιμάτωσης*) :**
  - **δόση φόρτισης Κλοπιδογρέλης 300mg [IIa / C]**
  - **Κλοπιδογρέλη 75mg ημερησίως από του στόματος [1A]**
  - **Μακροχρόνια αγωγή (για ένα έτος) με Κλοπιδογρέλη 75mg [IIa/C]**

Circulation, 2008; 117: 296-329 [published online Dec. 10th, 2007]

Κλοπιδογρέλη σε ΟΣΣ (PCI)
ΔΕΥΤΕΡΟΓΕΝΗΣ ΠΡΟΛΗΨΗ

Πριν την τοποθέτηση Εμποτισμένου με Φάρμακο Stent (DES),
ο καρδιολόγος θα πρέπει να συζητήσει με τον ασθενή

- **την αναγκαιότητα της διπλής αντιαιμοπεταλιακής αγωγής**
- **τη διάρκειά της,**
- καθώς και **να επιβεβαιώσει τη δυνατότητα του ασθενούς να συμμορφώνεται με την επιβεβλημένη για τα DES φαρμακευτική αγωγή (I/B)**

ACC/AHA/SCAI Revascularisation Guidelines 2010

Guidelines ACS- ESC 2011

Recommendations	Class [a]	Level [b]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B

Guidelines ESC 2011

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B

ESC Guidelines 2010 on the management of Atrial Fibrillation

European Heart Journal 2010

European Heart Rhythm Association (EHRA);
Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

www.escardio.org/guidelines

European Heart Journal (2010) 31, 2369-2429

ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.	IIa
Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly.	IIa
The HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly] should be considered as a calculation to assess bleeding risk, whereby a score of ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin.	IIa

Risk factor-based point-based scoring system - CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 ans	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category [i.e. femal sex]	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

Approach to thromboprophylaxis in AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC **vitamin K antagonist, dabigatran**
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

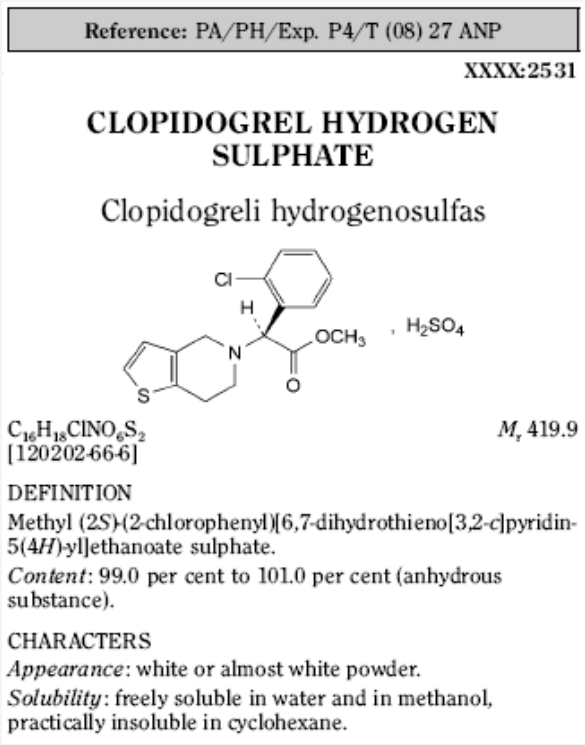
AF = atrial fibrillation; CHA_2DS_2-VASc = cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

Όξινη Θειϊκή Κλοπιδογρέλη
Σκεύασμα Αναφοράς

- Η Όξινη Θειϊκή Κλοπιδογρέλη επιλέχθηκε ανάμεσα σε **20.000 διαφορετικά υπό εξέλιξη μόρια**, ώστε να διαθέτει ιδανική ισορροπία αποτελεσματικότητας και ασφάλειας

- Όπως ρητά αναφέρεται στην **πατέντα *Sanofi SA: US4529596 (1985) &US4847265 (1989)*** που είναι σε ισχύ στην Ελλάδα **έως τα μέσα 2013**, «το Plavix® αποτελεί όξινο θειϊκό άλας του d-εναντιομερούς της ουσίας PCR 4099, όπως ονομαζόταν σε μελέτες από τη Sanofi»[1]

- Το d-εναντιομερές της Κλοπιδογρέλης (SR 25989) χρειάζεται να μεταβολισθεί in vivo για να εκδηλώσει την αντιαιμοπεταλική δράση[2-3]



Reference: PA/PH/Exp. P4/T (08) 27 ANP

XXXX:2531

CLOPIDOGREL HYDROGEN SULPHATE

Clopidogreli hydrogenosulfas

$C_{16}H_{18}ClNO_6S_2$ M_r 419.9
[120202-66-6]

DEFINITION

Methyl (2*S*)-(2-chlorophenyl)[6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]ethanoate sulphate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: freely soluble in water and in methanol, practically insoluble in cyclohexane.

Απόσπασμα από PHARMEUROPA Vol. 21, No. 3, July 2009

1. KS Bhukhanwala et al. *Expert Opinion Ther. Patents*, 2006; 16 (12): 1609-1611
2. Herbert JM et al. *Cardiovascular Drug Res*, 1993; 11: 180-198
3. Savi P et al. *Clin Appl Thrombosis Haemostasis*, 1996; 2: 35-42

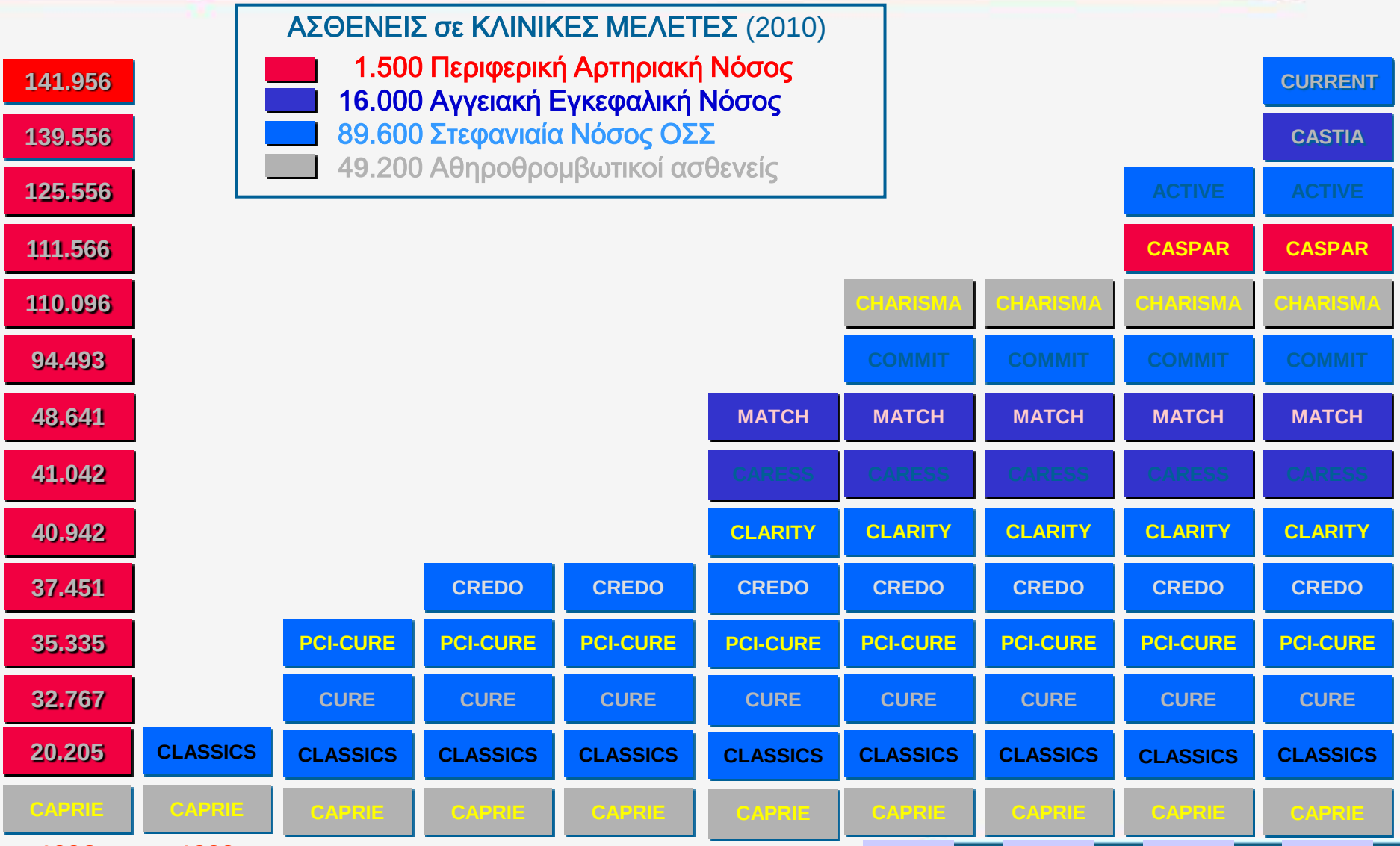
Όξινη Θειϊκή Κλοπιδογρέλη
Βιβλιογραφική και Κλινική Τεκμηρίωση

- Περισσότεροι από **150.000 ασθενείς** σε Κλινικές Μελέτες
- Έχει συνταγογραφηθεί σε περισσότερους από **100.000.000 ασθενείς** παγκοσμίως

- **www.clinicaltrials.gov**
  - Μέχρι σήμερα έχουν συνολικά καταγραφεί και αναρτηθεί στην ιστοσελίδα www.clinicaltrials.gov **220 μελέτες της Όξινης Θειϊκής Κλοπιδογρέλης,** που βρίσκονται σε διάφορες φάσεις ανάπτυξης[1]
- **Εταιρικό δίκτυο Sanofi-Aventis**
  - **186 μελέτες της Όξινης Θειϊκής Κλοπιδογρέλης** στις οποίες είναι χορηγός η Sanofi-Aventis[2]

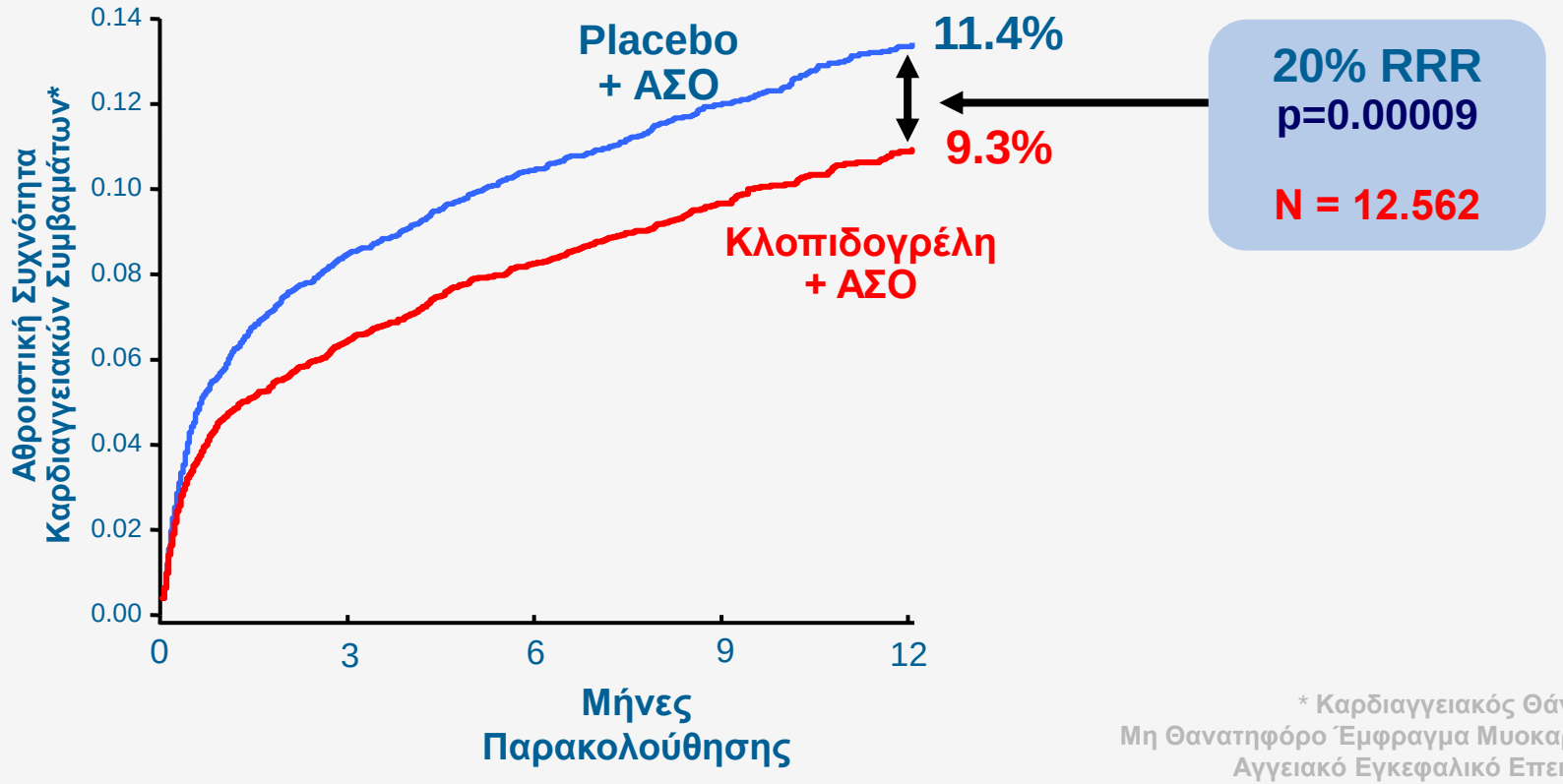
1. Available at www.clinicaltrials.gov *[τελευταία ενημέρωση 23 Δεκεμβρίου 2010]*
2. Sanofi-Aventis data [*τελευταία ενημέρωση 20 Δεκεμβρίου 2010]*

Το πλέον εκτεταμένο Πρόγραμμα Κλινικών Μελετών με **συμμετοχή περισσότερων από 150.000 ασθενών**



The CURE study

CURE = Clopidogrel in Unstable angina to prevent Recurrent Events



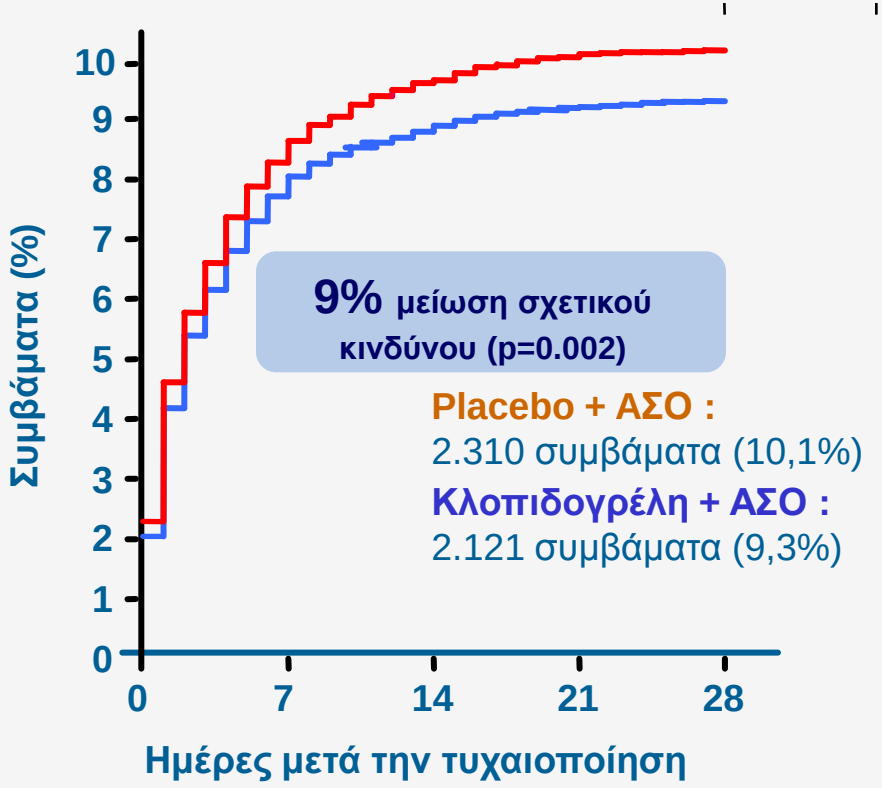
* Καρδιαγγειακός Θάνατος, Μη Θανατηφόρο Έμφραγμα Μυοκαρδίου, Αγγειακό Εγκεφαλικό Επεισόδιο

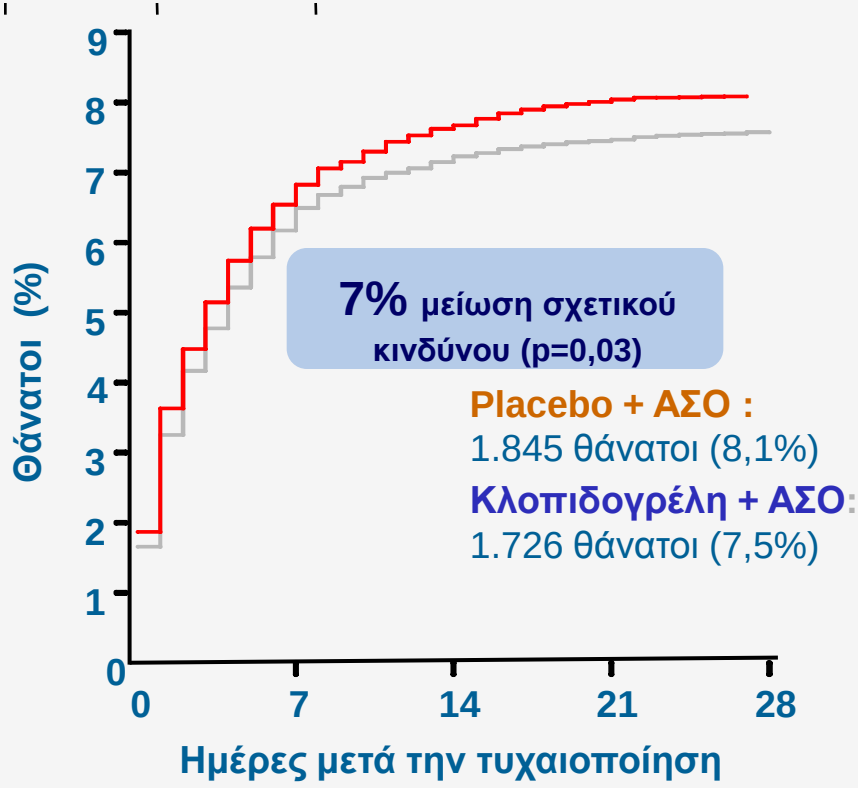
Yusuf S, et al. N Engl J Med 2001;345(7):494-502

Η Κλοπιδογρέλη + ΑΣΟ μειώνει τον κίνδυνο θανάτου, υποτροπής ΟΕΜ και ΑΕΕ σε ασθενείς με STEMI

The COMMIT study

COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial

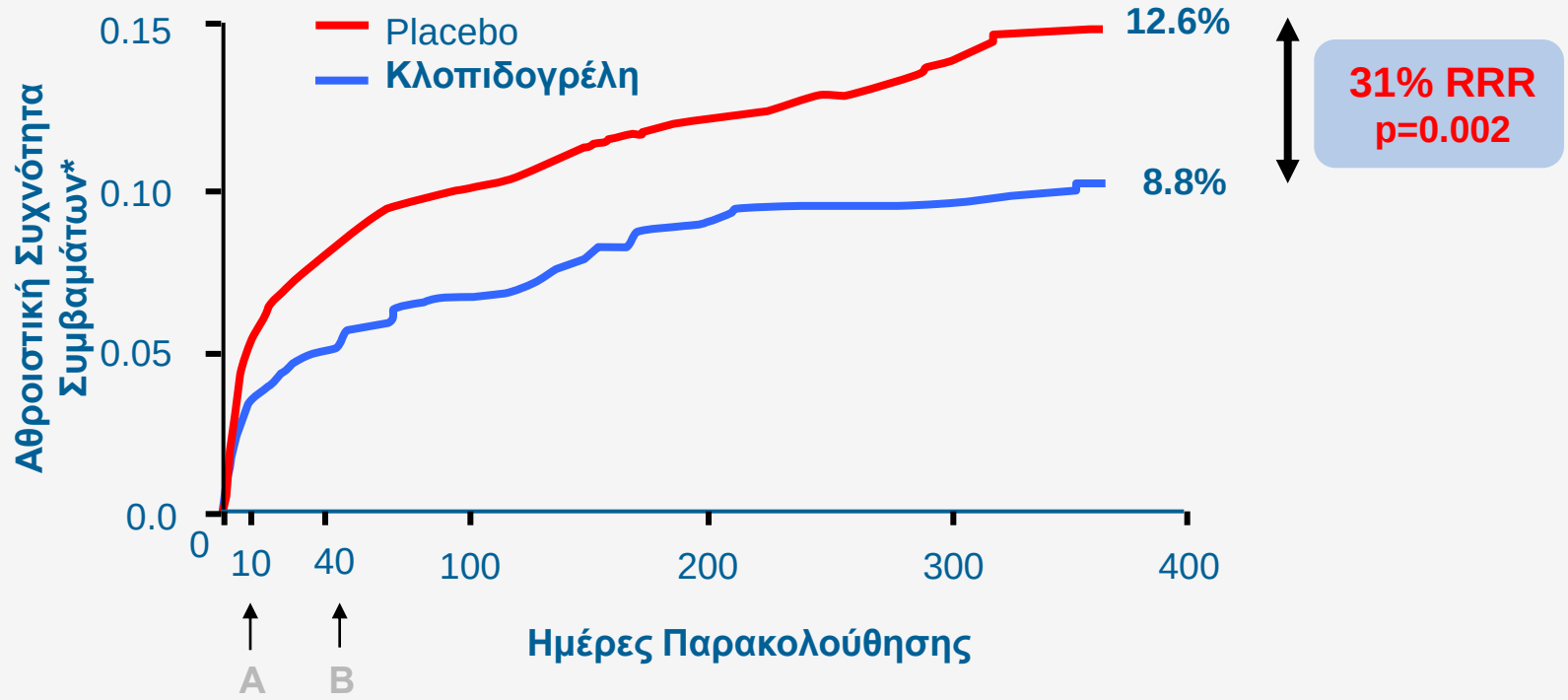




Chen ZM, et al. Lancet 2005;366(9497):1607-21

The PCI-CURE study

Η Κλοπιδογρέλη +ΑΣΟ μειώνει τον κίνδυνο Καρδιαγγειακών Συμβαμάτων σε επεμβατικά αντιμετωπιζόμενους (με PCI) ασθενείς με ασταθή στηθάγχη ή έμφραγμα Non-STEMI



*Καρδιαγγειακός Θάνατος ή Έμφραγμα Μυοκαρδίου από την Τυχαιοποίηση

A = μέσος χρόνος από την τυχαιοποίηση έως την PCI (10 ημέρες)

B = 30 ημέρες μετά το μέσο χρόνο διενέργειας της PCI

Mehta SR, et al. Lancet 2001; 358(9281): 527-533

Αντιαιμοπεταλιακή Αγωγή σε ασθενείς με ΟΣΣ

- Η πλειοψηφία των ασθενών με ΟΣΣ λαμβάνουν **Κλοπιδογρέλη + ΑΣΟ κατά την έξοδο από Νοσοκομείο**[1] : στην Ευρωπαϊκή Ένωση 63 – 76%, στις Η.Π.Α. 56%
- Οι πλέον πρόσφατες Διεθνείς Κατευθυντήριες Οδηγίες[2-6] συνιστούν διπλή αντιαιμοπεταλιακή αγωγή με Κλοπιδογρέλη + ΑΣΟ για **διάστημα 12 μηνών μετά από Οξέα Στεφανιαία Σύνδρομα**

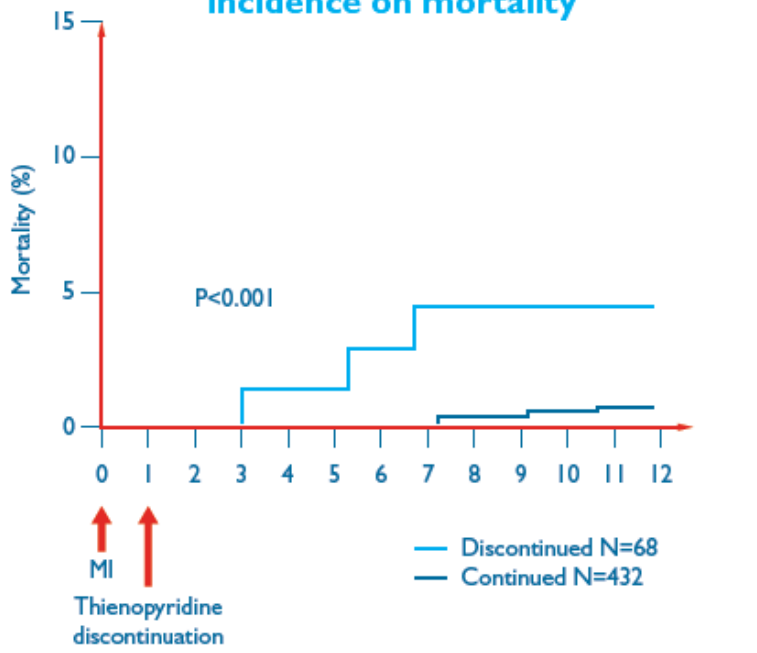
- Σαφής σύσταση στις Κατευθυντήριες Οδηγίες[3] για τον **κίνδυνο υποτροπής καρδιαγγειακών συμβαμάτων σε διακοπή της Διπλής ΑΑΑ** (προσωρινά ή μόνιμα)

1. European ACV Analyser, 2008
2. ACC/AHA Guidelines (Circulation, 2009; 120: 2271-2306)
3. ACC/AHA Guidelines (Circulation, 2007; 116: 803-877)
4. ESC Guidelines (European Heart Journal, 2008; 29 (23): 2909-2945)
5. ESC Guidelines (European Heart Journal, 2007; 28 (13): 1598-1660)
6. ACCP Guidelines (Chest, 2008; 133: 71S-109S)

Η Συμμόρφωση ασθενών με ΟΣΣ μειώνεται σταδιακά με το χρόνο και μπορεί να οδηγήσει σε αύξηση καρδιαγγειακών συμβαμάτων ή θρομβώσεων στα stents

Premature discontinuation of dual antiplatelet therapy increase mortality in DES patients

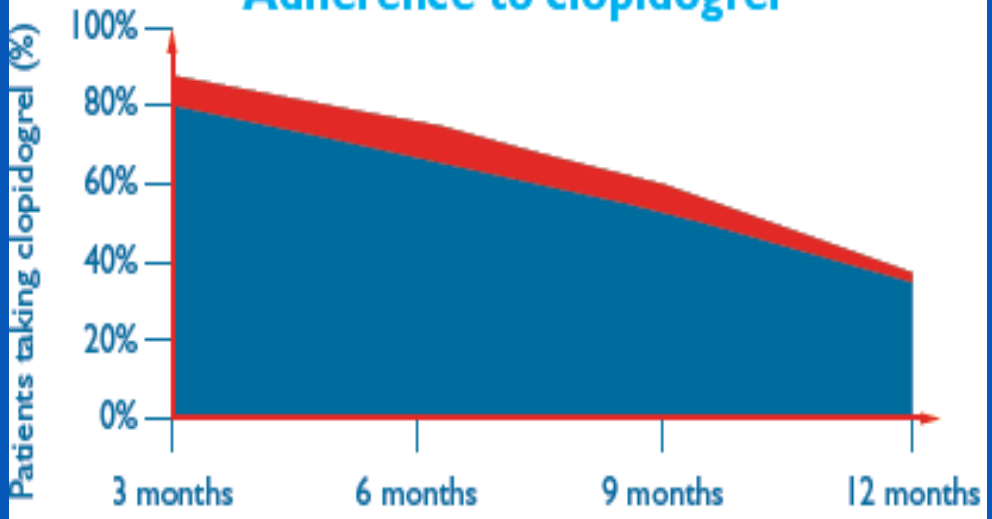
Thienopyridine discontinuation at 1 month incidence on mortality



Adapted from Spertus J.A. *et al. Circulation* 2006; 113(24): 2803-9.[20]

Adherence to clopidogrel decrease over time in both PCI and medically treated patients

Adherence to clopidogrel



Adapted from Ho P.M. *et al. JAMA* 2008; 299(5): 532-9.[19]

Treatment compliance needs to be improved

JAMA®

Online article and related content current as of October 20, 2010.

Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents

Ioannis Iakovou; Thomas Schmidt; Erminio Bonizzoni; et al.

JAMA. 2005;293(17):2126-2130 (doi:10.1001/jama.293.17.2126)

Conclusions The cumulative incidence of stent thrombosis 9 months after successful drug-eluting stent implantation in consecutive "real-world" patients was substantially higher than the rate reported in clinical trials. Premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of thrombotic events.

Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

A Science Advisory From the AHA, ACC, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians

Grines C et al, Circulation 2007

The leading adverse event associated with early antiplatelet discontinuation is stent thrombosis, and the majority of these events lead to acute MI or death.

Grines CL, et al. Circulation. 2007

DES are now being used in high-risk lesions, and reports have suggested that they may be associated with delayed (or absent) endothelialization, localized hypersensitivity reactions, and late stent thrombosis

Grines CL, et al. Circulation. 2007

- Stent thrombosis most commonly occurs in the first month after stent implantation and referred to as "**subacute stent thrombosis**"

- Many cases of "**late-stent thrombosis**", occurring months or years after stent implantation, have been reported – especially in patients treated with DES

Grines CL, et al. Circulation. 2007

The incidence of death or MI associated with angiographically documented stent thrombosis was 64.4% in a pooled analysis of 6 trials and registries from the 1990s.

Mortality rates due to presumed or documented stent thrombosis range from 20% to 45%.

Grines CL, et al. Circulation 2007

- The average reported occurrence of subacute stent thrombosis is 1% and the timing of thrombosis seems to be delayed in DES.

- Late stent thrombosis was not readily apparent in BMS but was reported to occur in 0.19% of patients in a large DES registry.

Grines CL, et al. Circulation 2007

Predictors of DES Thrombosis: Considerations for Prolonged Dual Antiplatelet Therapy

Clinical	Angiographic
Advanced Age	Long Stents
ACS	Multiple Lesions
Diabetes	Overlapping stents
Low Ejection Fraction	Ostial or bifurcation lesions
Prior brachytherapy	Small vessels
Renal failure	Suboptimal stent results

Grines CL, et al. Circulation 2007

- **The leading independent predictor for stent thrombosis in multivariate analyses is premature discontinuation of thienopyridine therapy**

- **In a large observational cohort study of patients treated with DES, stent thrombosis occurred in 29% of patients in whom antiplatelet therapy was discontinued prematurely**

Grines CL, et al. Circulation 2007

Premature discontinuation of antiplatelet therapy may occur for many reasons

- Cost of clopidogrel may discourage prescription renewal
- Older age
- Not referred for cardiac rehabilitation
- Did not finish high school
- Not seeking health care due to cost
- Not receiving discharge instructions for medication use
- Greater likelihood of having preexistent CV disease or anemia
- Not being married

Grines CL, et al. Circulation 2007

Πρόσφατες σημαντικές μελέτες σχετικά με την πρόωρη διακοπή χορήγησης Κλοπιδογρέλης + ΑΣΟ

Incidence of Death and Acute Myocardial Infarction Associated With Stopping Clopidogrel After Acute Coronary Syndrome

Ho MP, Peterson ED et al. ***JAMA****, 2008; 299: 532-539*

ΣΚΕΠΤΙΚΟ και ΣΧΕΔΙΑΣΜΟΣ της Μελέτης

- n=8095 ασθενείς, 2003-2005

  διάγνωση εξόδου : **ΟΕΜ ή Ασταθή Στηθάγχη** και αγωγή με Κλοπιδογρέλη

- Αποκλείστηκαν ασθενείς με θρομβωτικά επεισόδια υπό αγωγή με Κλοπιδογρέλη

- **συντηρητικά** ► **42,3%** έλαβαν στην έξοδο Κλοπιδογρέλη

  ► **72,3%** εκτελούσαν τις συνταγές στα Φαρμακεία των Νοσοκομείων

  ► **45%** διέκοψαν την Κλοπιδογρέλη χωρίς θρομβωτικά συμβάματα πριν τη διακοπή (διάρκεια θεραπείας : 302 μέρες)

- **PCI** ► **93,9%** έλαβαν κατά την έξοδο Κλοπιδογρέλη (BM Stent: 65%)

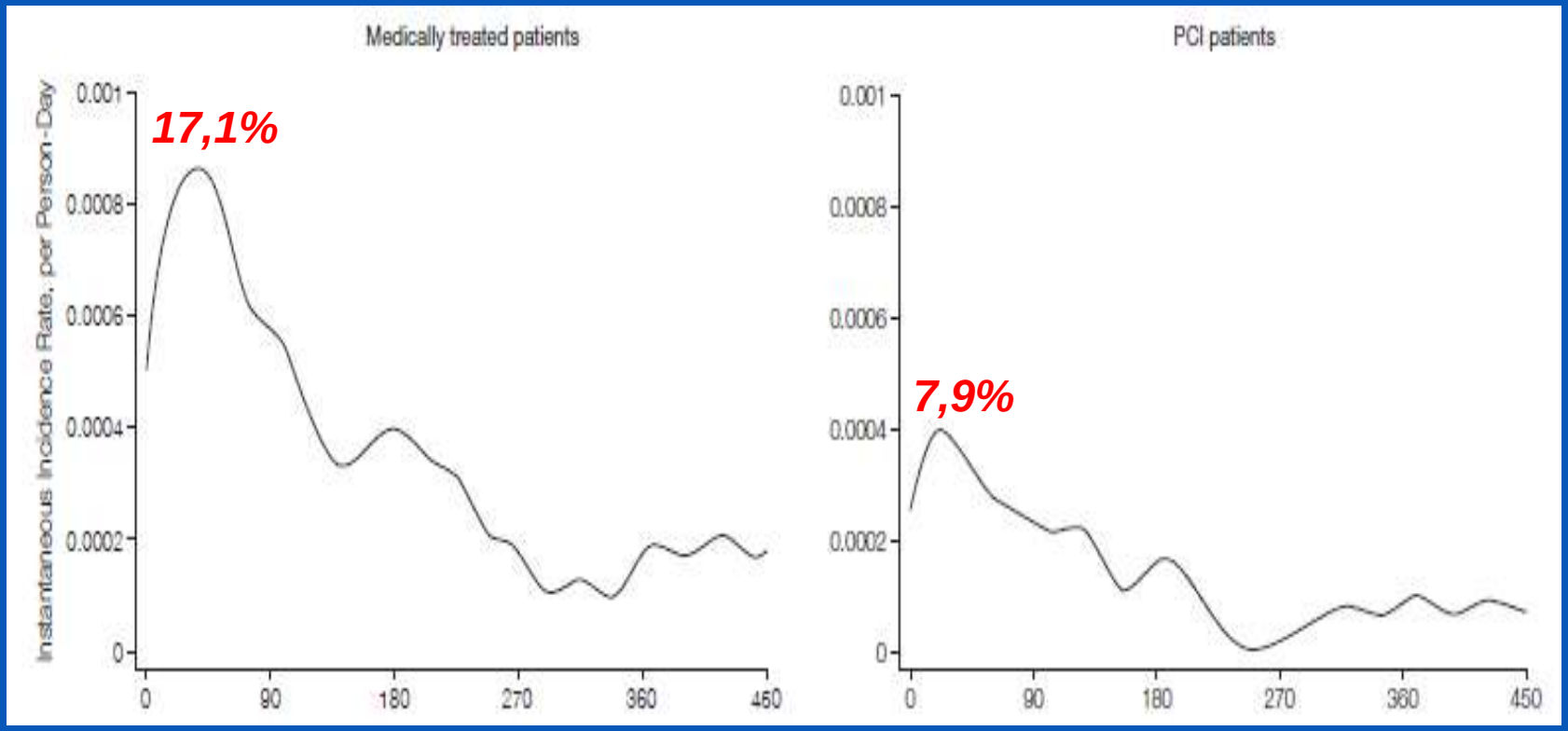
  ► **87,4%** εκτελούσαν τις συνταγές στα Φαρμακεία των Νοσοκομείων

  ► **60%** διέκοψαν την Κλοπιδογρέλη χωρίς θρομβωτικά συμβάματα πριν τη διακοπή (διάρκεια θεραπείας :278 μέρες)

Ho MP, Peterson ED et al. JAMA, 2008; 299: 532-539

ΘΑΝΑΤΟΣ Ή ΟΕΜ

συντηρητικά PCI



ημέρες μετά τη διακοπή της κλοπιδογρέλης

Ho MP, Peterson ED et al. JAMA, 2008; 299: 532-539

ΣΥΜΠΕΡΑΣΜΑ

Ο κίνδυνος θανάτου ή ΟΕΜ ήταν στατιστικώς σημαντικά υψηλότερος κατά την **αρχική περίοδο 90 ημερών μετά τη διακοπή της αγωγής με κλοπιδογρέλη** σε όλες τις υποομάδες ασθενών (συντηρητικά ή επεμβατικά, διαβητικοί ή μη κλπ) λόγω θρομβωτικών επεισοδίων πιθανώς από **rebound** φαινόμενο στη **κλοπιδογρέλη**

Ho MP, Peterson ED et al. JAMA, 2008; 299: 532-539

Prevalence, Predictors, and Long-Term Prognosis of Premature Discontinuation of Oral Antiplatelet Therapy After Drug Eluting Stent Implantation

Rossini R et al. Am J Card 2011, 107: 186-194

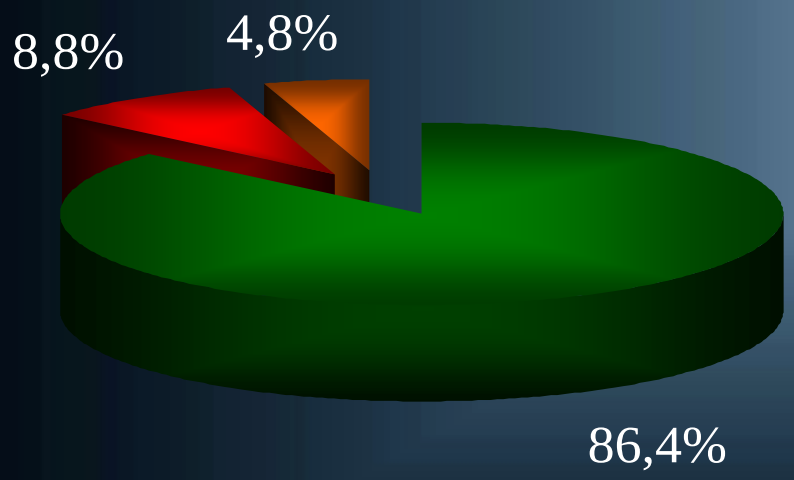
Methods

- We studied 1358 consecutive pts treated with DES and discharged on dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day)
- Clopidogrel was maintained for 12 months
- **Pts were followed-up for 32.4±11.3 months**
- Prevalence and predictors of aspirin and/or clopidogrel discontinuation were assessed
- Major adverse cardiac events (MACE), defined as **death, acute coronary syndrome leading to hospitalization, and stroke**, were recorded. **Probable/possible/definite stent thrombosis** were also recorded

Rossini R et al. Am J Card 2011, 107: 186-194

Results

8.8% *of patients* ***discontinued one or both antiplatelet agents within the first 12 months*** *(early discontinuation) and* ***4.8%*** *withdrew aspirin after 1 year (****late discontinuation****)*



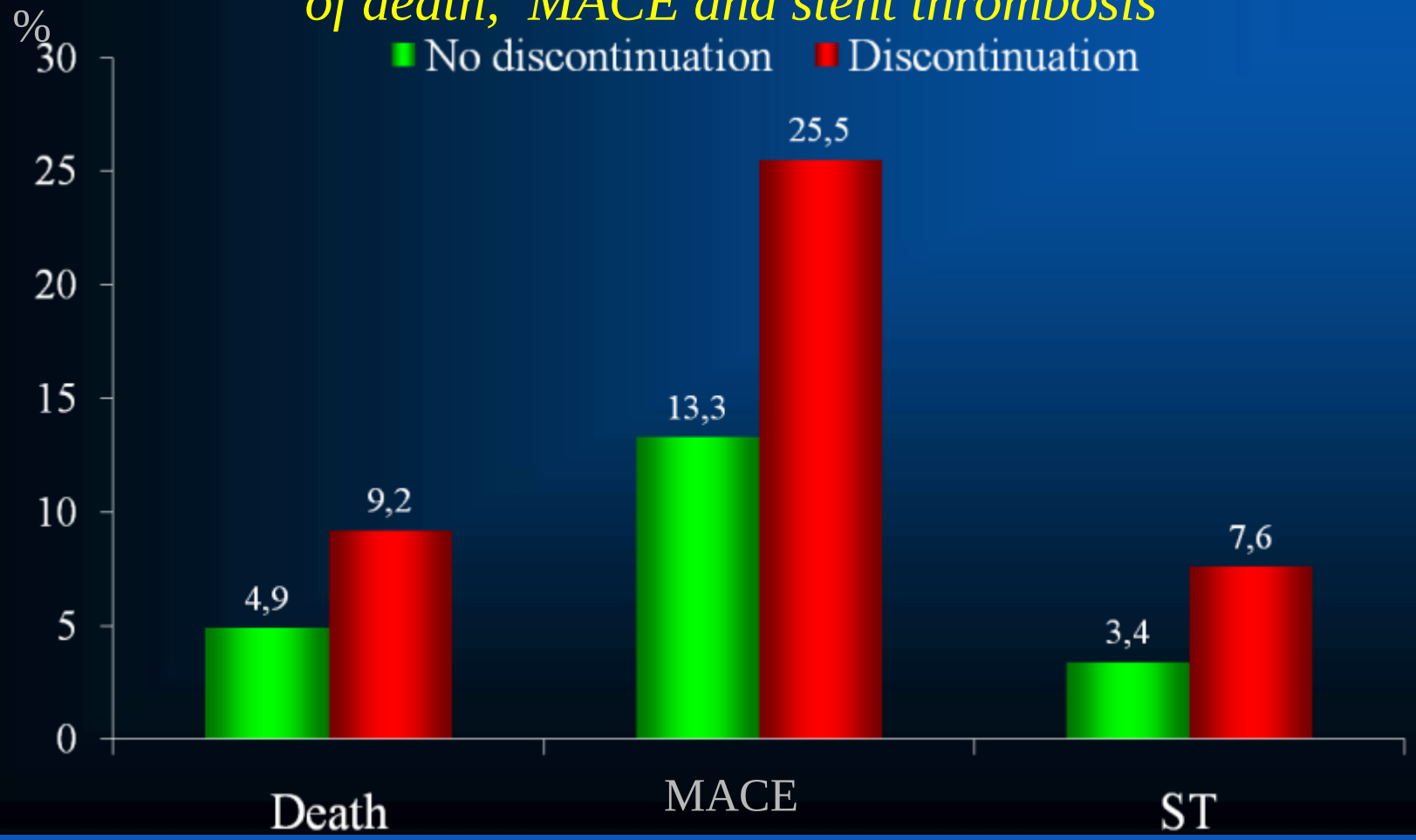
Discontinuation Causes

- Surgery 34.5%
- Bleeding 21%
- Medical decision 17.6%
- Dental interventions 7.6%
- Economic/burocratic reasons 5.9%
- Anticoagulant therapy 5.0%

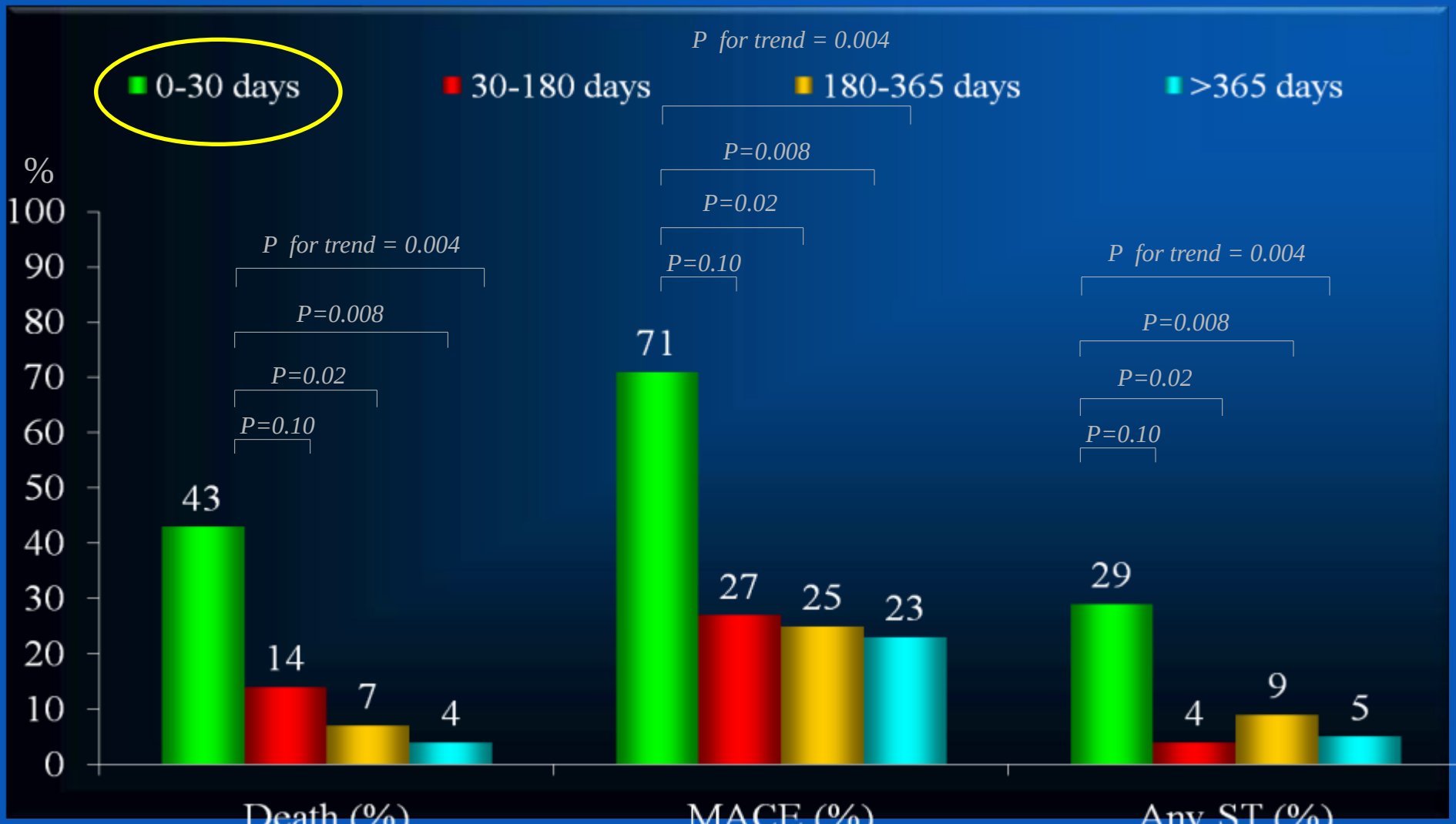
Rossini R et al. Am J Card 2011, 107: 186-194

Discontinuation and Prognosis

Patients who discontinued antiplatelet therapy had a higher incidence of death, MACE and stent thrombosis



Death, MACE or stent thrombosis and time of discontinuation



Rossini R et al. Am J Card 2011, 107: 186-194

ΣΥΜΠΕΡΑΣΜΑ ΜΕΛΕΤΗΣ

- Η πρώιμη διακοπή της αντιαιμοπεταλιακής αγωγής είναι συχνή το 1ο έτος μετά τη τοποθέτηση stent και συνδέεται με μείζονα καρδιαγγειακά συμβάματα όπως θρόμβωση του stent και θάνατο

- Χρειάζονται καλύτερες στρατηγικές για τη συμμόρφωση των ασθενών που είναι επιρρεπείς στη διακοπή της αντιαιμοπεταλιακής αγωγής

ΣΥΝΔΥΑΣΜΟΣ ΚΛΟΠΙΔΟΓΡΕΛΗΣ (75 mg) ΚΑΙ ΑΣΠΙΡΙΝΗΣ (100 mg) ΣΕ ΕΝΑ ΧΑΠΙ

Duoplavin

ΣΥΜΠΕΡΑΣΜΑ

- Ενδειξη διπλής αντιαιμοπεταλιακής αγωγής :
 1) οξέα στεφανιαία σύνδρομα (ΟΣΣ) ανεξαρτήτως συντηρητικής ή επεμβατικής (PCI) αντιμετώπισης
 2) κολπική μαρμαρυγή με αντένδειξη στα αντιπηκτικά

- Η πρόωρη διακοπή της κλοπιδογρέλης στα ΟΣΣ (PCI) συνοδεύεται με αυξημένα καρδιαγγειακά συμβάματα λόγω θρόμβωσης

- Η ύπαρξη συνδυασμού κλοπιδογρέλης (75 mg) και ασπιρίνης (100 mg) σε ένα χάπι συμβάλει σημαντικά στη συμμόρφωση των ασθενών με προφανή ωφέλη

ΣΑΣ ΕΥΧΑΡΙΣΤΩ ΓΙΑ
ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ