Αντιαιμοπεταλιακή αγωγή στο σακχαρώδη διαβήτη.

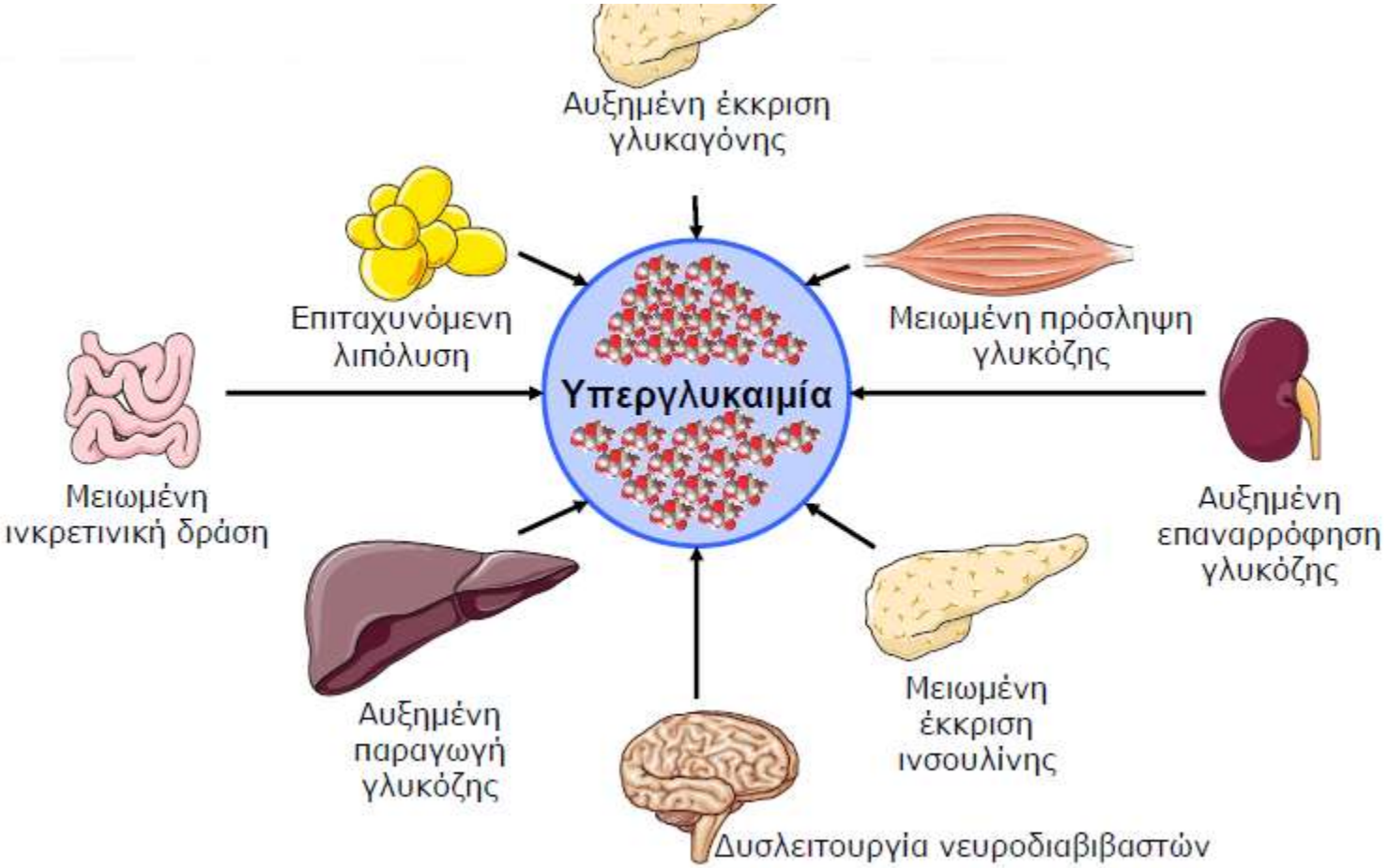
Πρωτοπαθής, δευτεροπαθής πρόληψη των καρδιαγγειακών συμβαμάτων

Δημήτριος Σκούτας

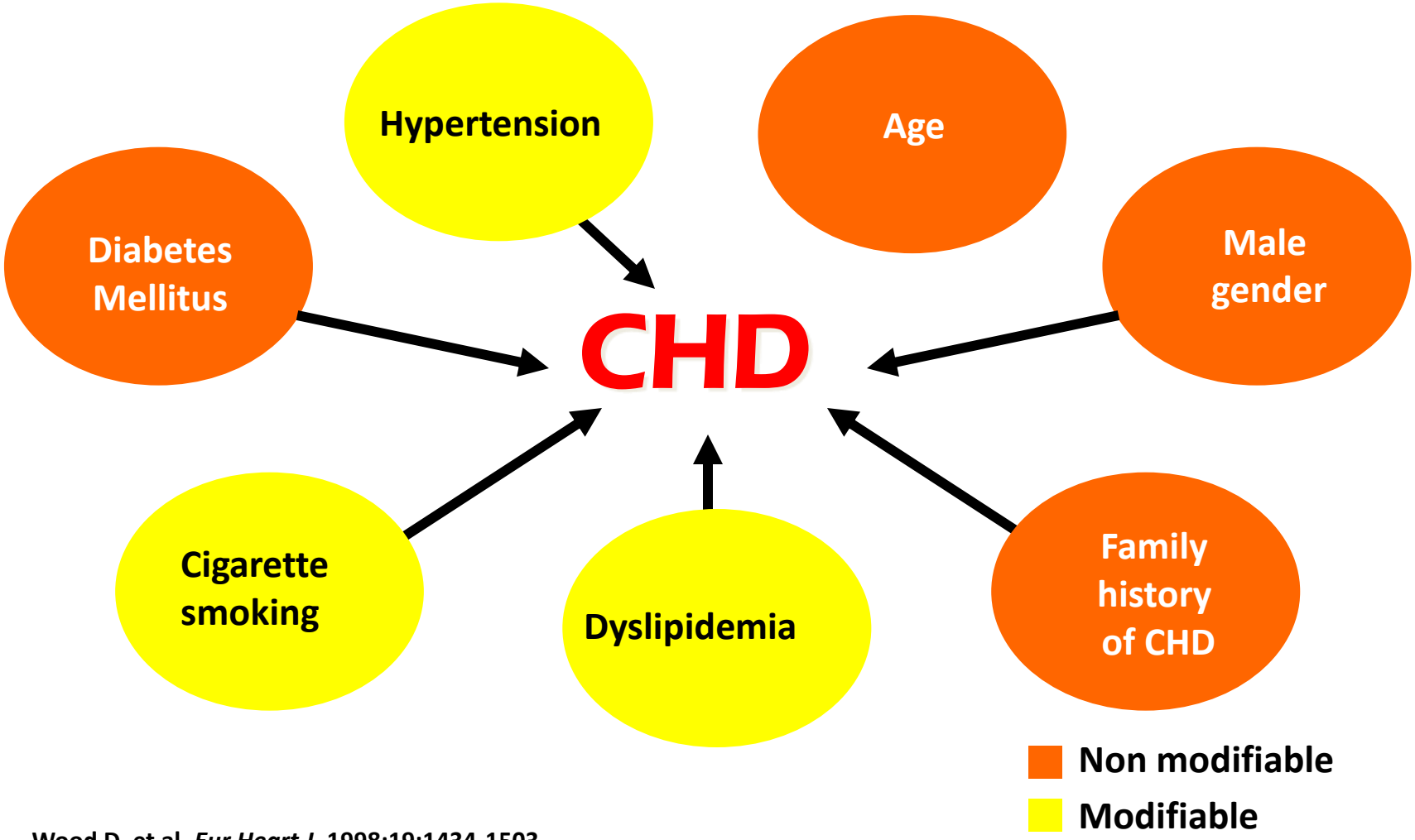
Ειδικός Παθολόγος-Διαβητολόγος

Διδάκτωρ Ιατρικής Σχολής ΔΠΘ

Η παθοφυσιολογία του ΣΔ το 2017



Παράγοντες κινδύνου για ΚΑΝ

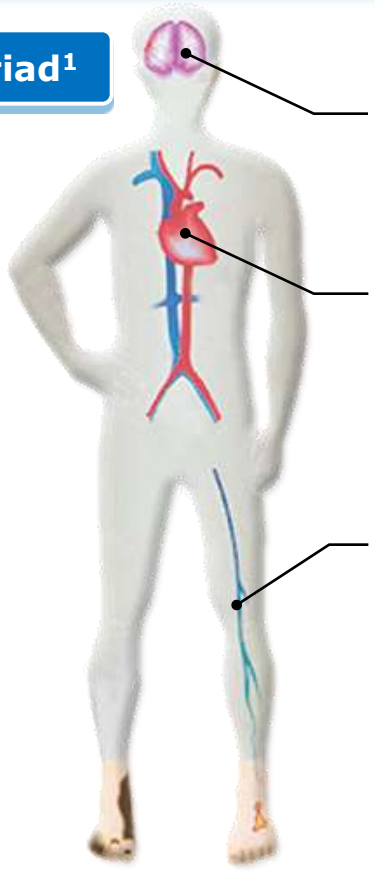


Wood D, et al. *Eur Heart J.* 1998;19:1434-1503.

Ο ΣΔ2 αυξάνει σημαντικά τον κίνδυνο για καρδιαγγειακή νόσο

- Overall, people with diabetes are **2-4 times** more likely to develop **cardiovascular disease** than those without diabetes[1]

The cardiovascular triad[1]



Cerebrovascular disease

- **2–4** times increased risk of **stroke**[2,3]
- **2-6**-times greater risk of **TIA**[1]

Coronary heart disease

- **2-**times increased risk of **CHD**[3,4]
- **2**-times increased risk of **non-fatal MI**[3]
- **2-3**-times increased risk of **heart failure**[1]

Peripheral vascular disease

Alongside microvascular disease and neuropathy, contributes to:[1]

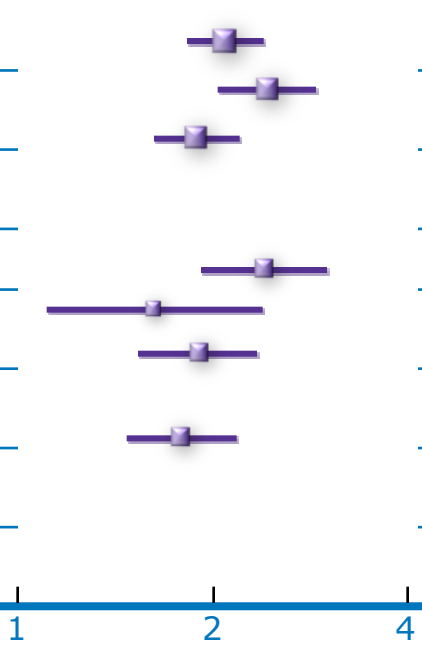
- **15-40**-times higher risk of **lower-limb amputation**
- **3-9**-times higher risk of **intermittent claudication**

1. International Diabetes Federation. Time to Act. 2001. Available at: http://www.idf.org/webdata/docs/Diabetes%20and%20CVD.pdf. Accessed: September 5, 2010. 2. Folsom AR, et al. Diabetes Care. 1999;22:1077-83. 3. Emerging Risk Factors Collaboration. Lancet. 2010;375:2215-22. 4. Huxley R, et al. BMJ. 2006;332:73-8.

Ο ΣΔ2 αυξάνει σημαντικά τον κίνδυνο για καρδιαγγειακό σύμβαμα: μετα-ανάλυση 102 προοπτικών μελετών

Hazard ratios* for vascular outcomes in people with vs without diabetes at baseline

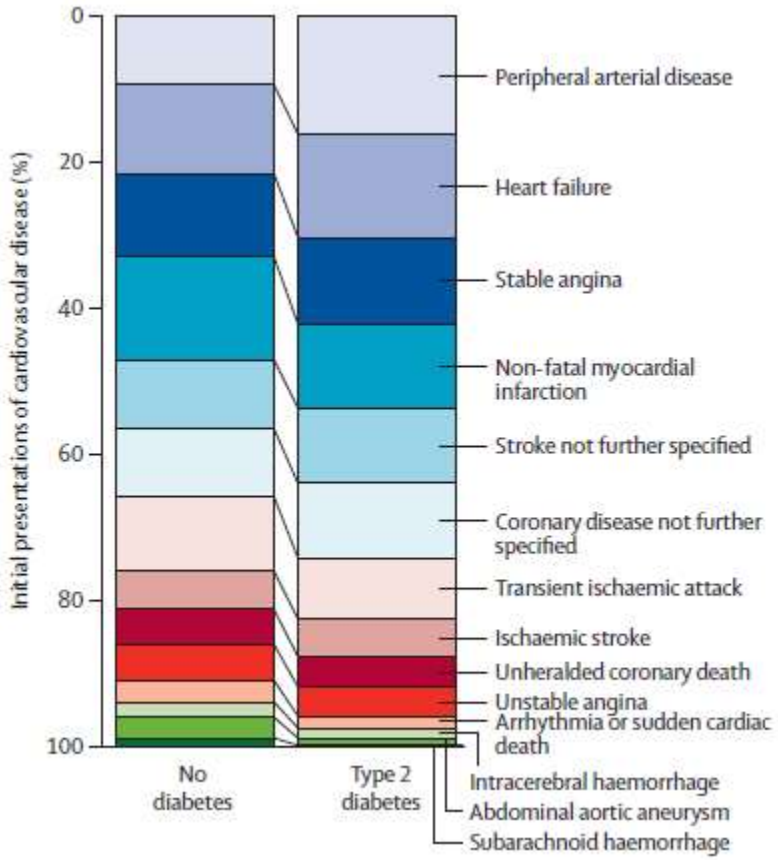
	Number of cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease*	26,505	2.00 (1.83-2.19)	64 (54-71)
Coronary death	11,556	2.31 (2.05-2.60)	41 (24-54)
Non-fatal myocardial infarction	14,741	1.82 (1.64-2.03)	37 (19-51)
Stroke subtypes†			
Ischaemic stroke	3799	2.27 (1.95-2.65)	1 (0-20)
Haemorrhagic stroke	1183	1.56 (1.19-2.05)	0 (0-26)
Unclassified stroke	4973	1.84 (1.59-2.13)	33 (12-48)
Other vascular deaths	3826	1.73 (1.51-1.98)	0 (0-26)



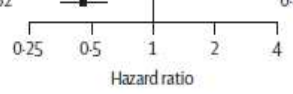
*Adjusted for age, smoking status, body mass index, systolic blood pressure, and where appropriate stratified by sex and trial arm
†Includes both fatal and non-fatal events

Emerging Risk Factors Collaboration. Lancet. 2010;375:2215-22.

Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people

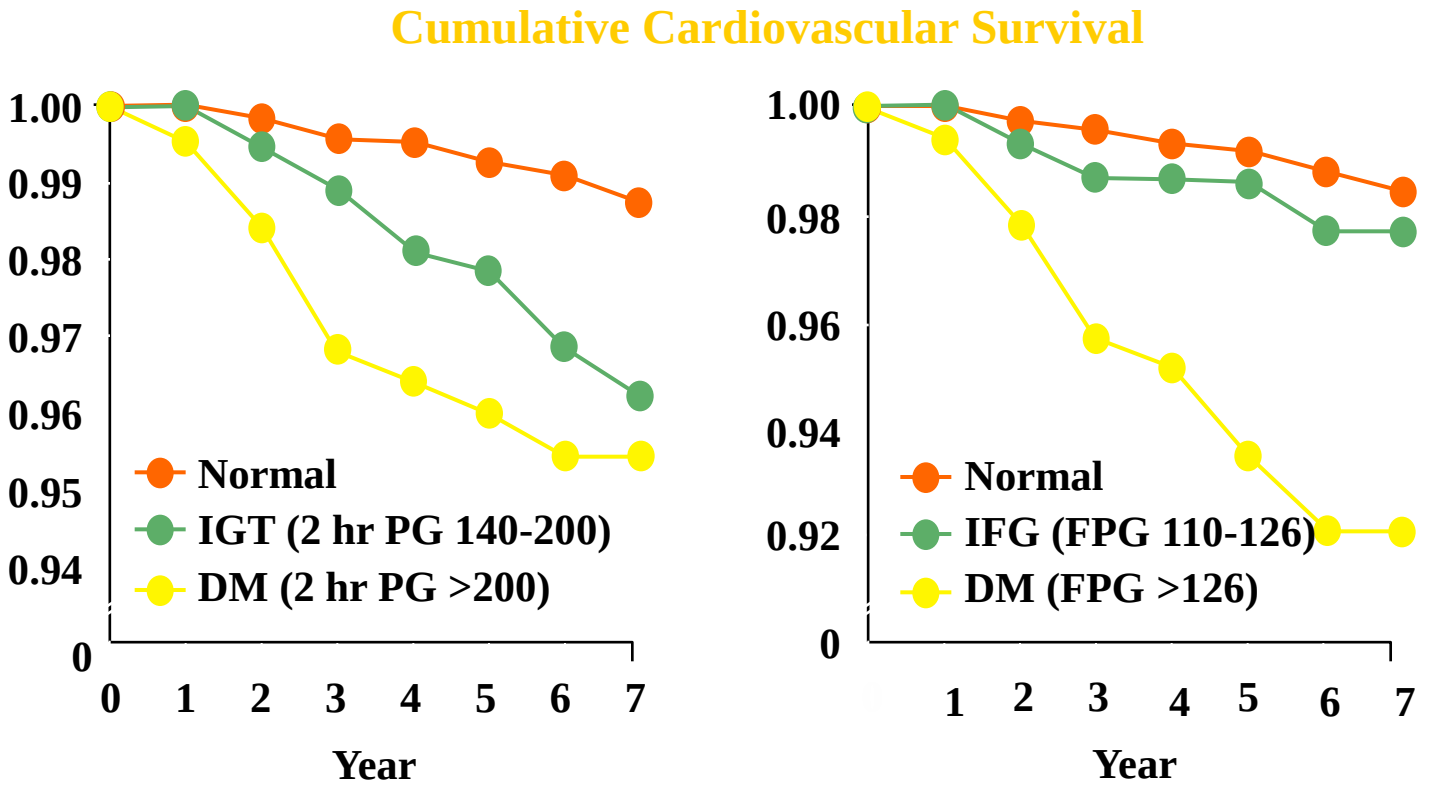


Initial presentation of cardiovascular disease	Number of events: No diabetes	Number of events: Type 2 diabetes	Hazard ratio (95% CI)	p value
Stable angina	12 232	728	1·62 (1·49–1·77)	<0·0001
Unstable angina	5286	245	1·53 (1·32–1·76)	<0·0001
Non-fatal myocardial infarction	15 191	706	1·54 (1·42–1·67)	<0·0001
Unheralded coronary death	5101	255	1·43 (1·23–1·65)	<0·0001
Heart failure	13 072	866	1·56 (1·45–1·69)	<0·0001
Arrhythmia or sudden cardiac death	3218	100	0·95 (0·76–1·19)	0·65
Transient ischaemic attack	10 990	513	1·45 (1·31–1·60)	<0·0001
Ischaemic stroke	5643	316	1·72 (1·52–1·95)	<0·0001
Subarachnoid haemorrhage	1260	11	0·48 (0·26–0·89)	0·020
Intracerebral haemorrhage	2265	84	1·28 (1·02–1·62)	0·035
Peripheral arterial disease	10 074	992	2·98 (2·76–3·22)	<0·0001
Abdominal aortic aneurysm	3051	62	0·46 (0·35–0·59)	<0·0001



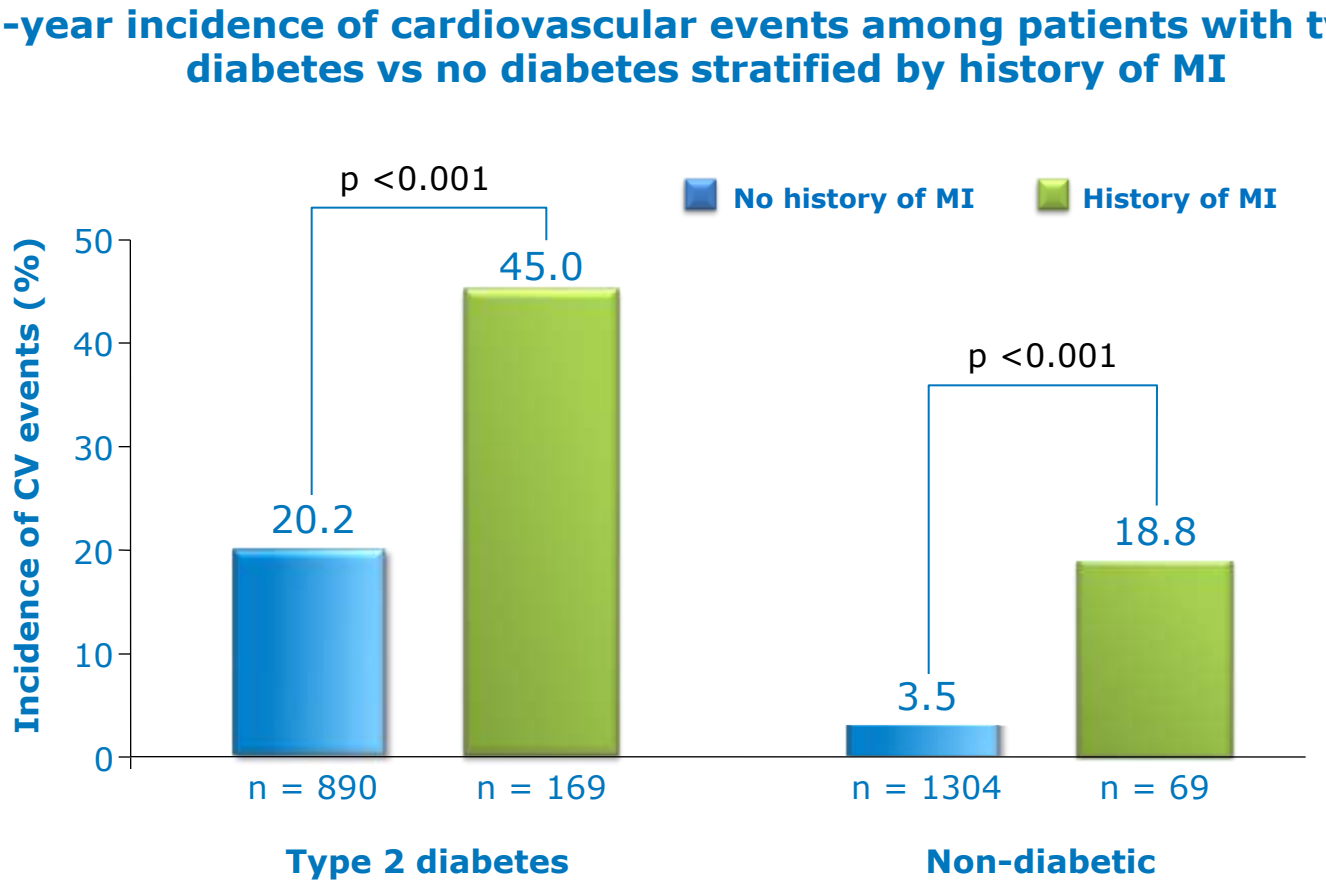
Lancet Diabetes Endocrinol 2015; 3: 105–13

Η διαταραχή ανοχής γλυκόζης είναι παράγων καρδιαγγειακού κινδύνου



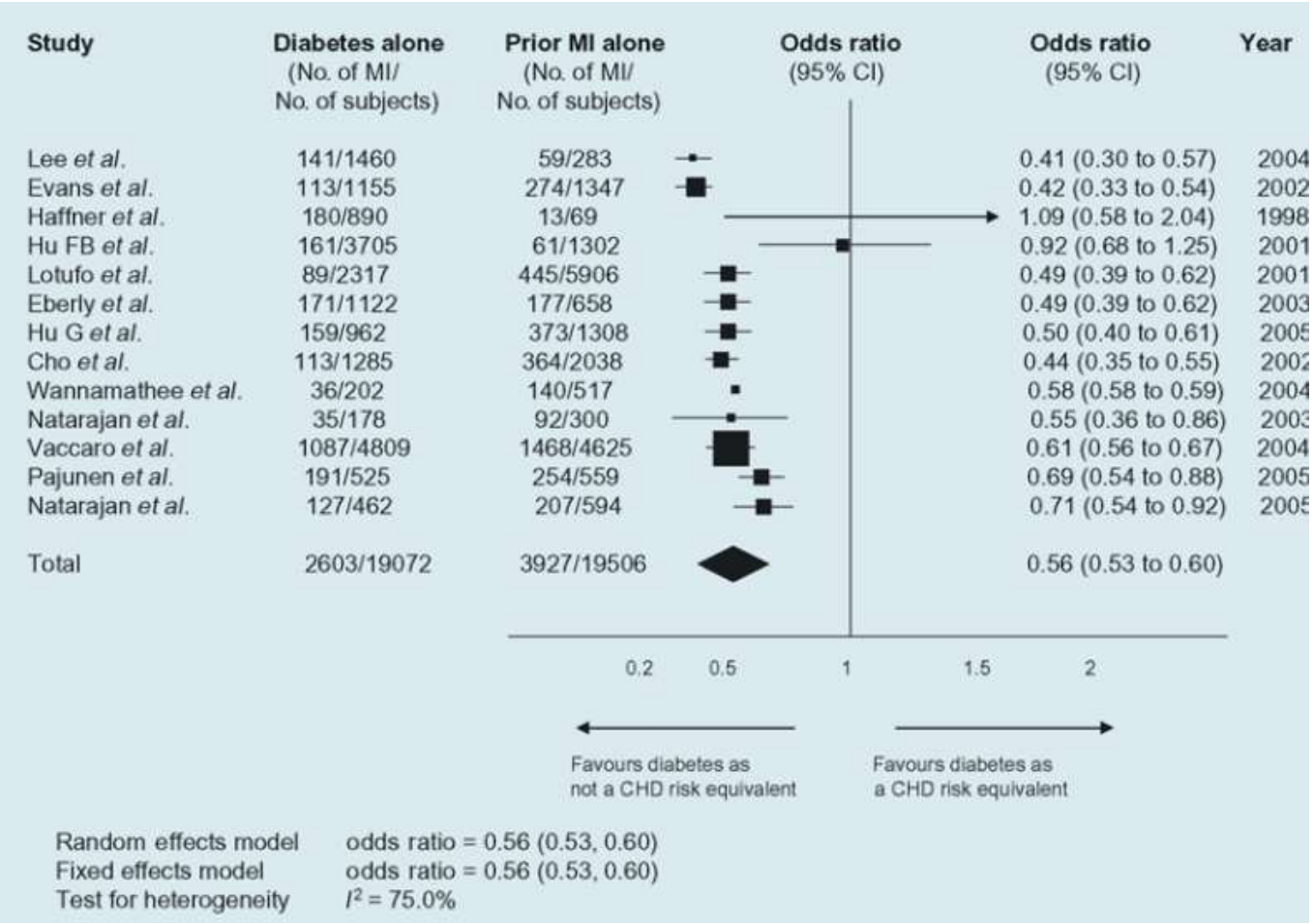
Tominaga M, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose.FUNAGATA DIABETES STUDY *Diabetes Care* 1999;22:920-4.

Ο ΣΔ 2 αυξάνει τον καρδιαγγειακό κίνδυνο ως ιστορικό προηγηθέντος ΕΜ



Haffner SM, et al. N Engl J Med. 1998;339:229-34.

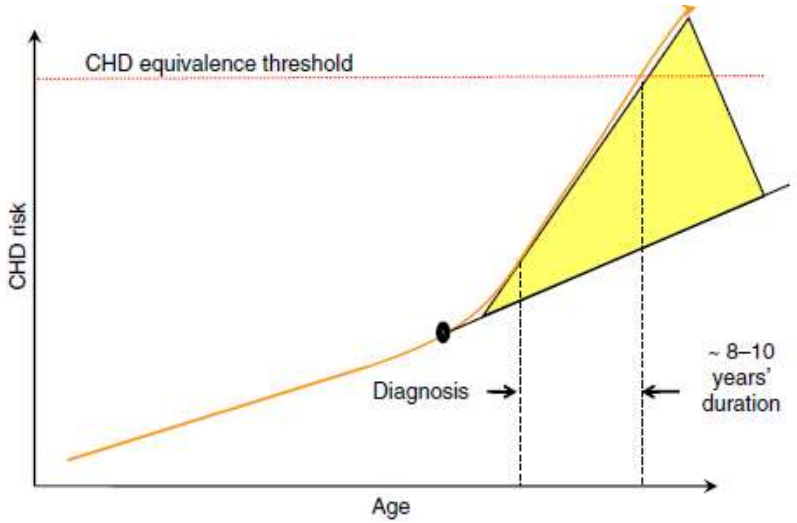
Is diabetes a coronary risk equivalent? Systematic review and meta-analysis



Effects of diabetes alone compared with prior myocardial infarction alone on odds of developing fatal or non-fatal myocardial infarction.

Diabet. Med. 26, 142–148 (2009)

Diabetes as a CHD ‘risk equivalent’?

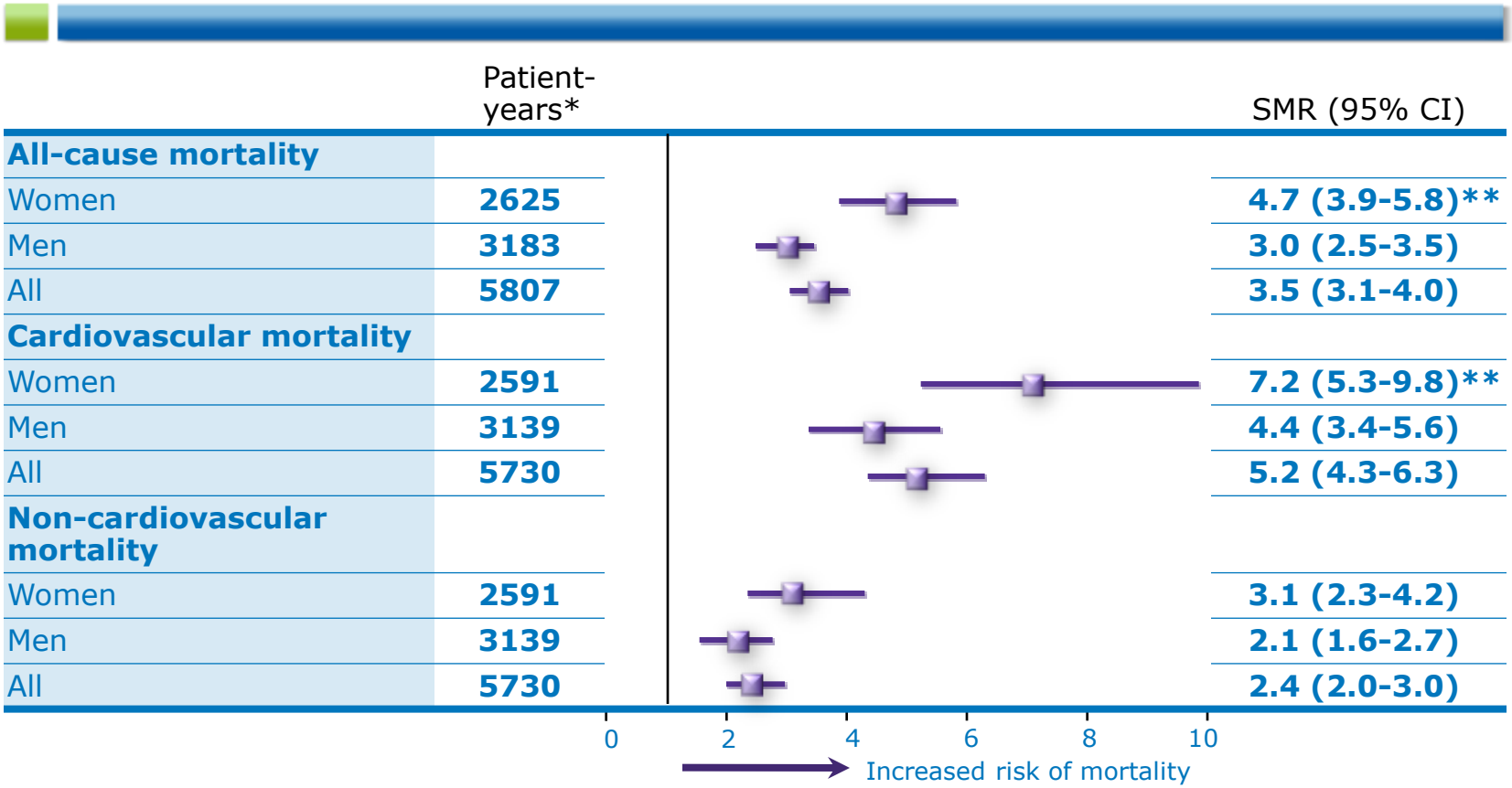


- Diabetes is not a CHD risk equivalent state at diagnosis or in those with short duration of disease (less than about a decade)
- **Risk levels approach CHD risk equivalence after a diabetes duration of about a decade or in those with proteinuria or low eGFR**
- Diabetic patients with existing CHD have a vascular risk well in excess of those with CHD but without diabetes

Diabetologia (2013) 56:686–695

Καρδιαγγειακή και μη θνητότητα στα άτομα με ΣΔ2

Standardised mortality rates (SMR) for men and women with type 2 diabetes

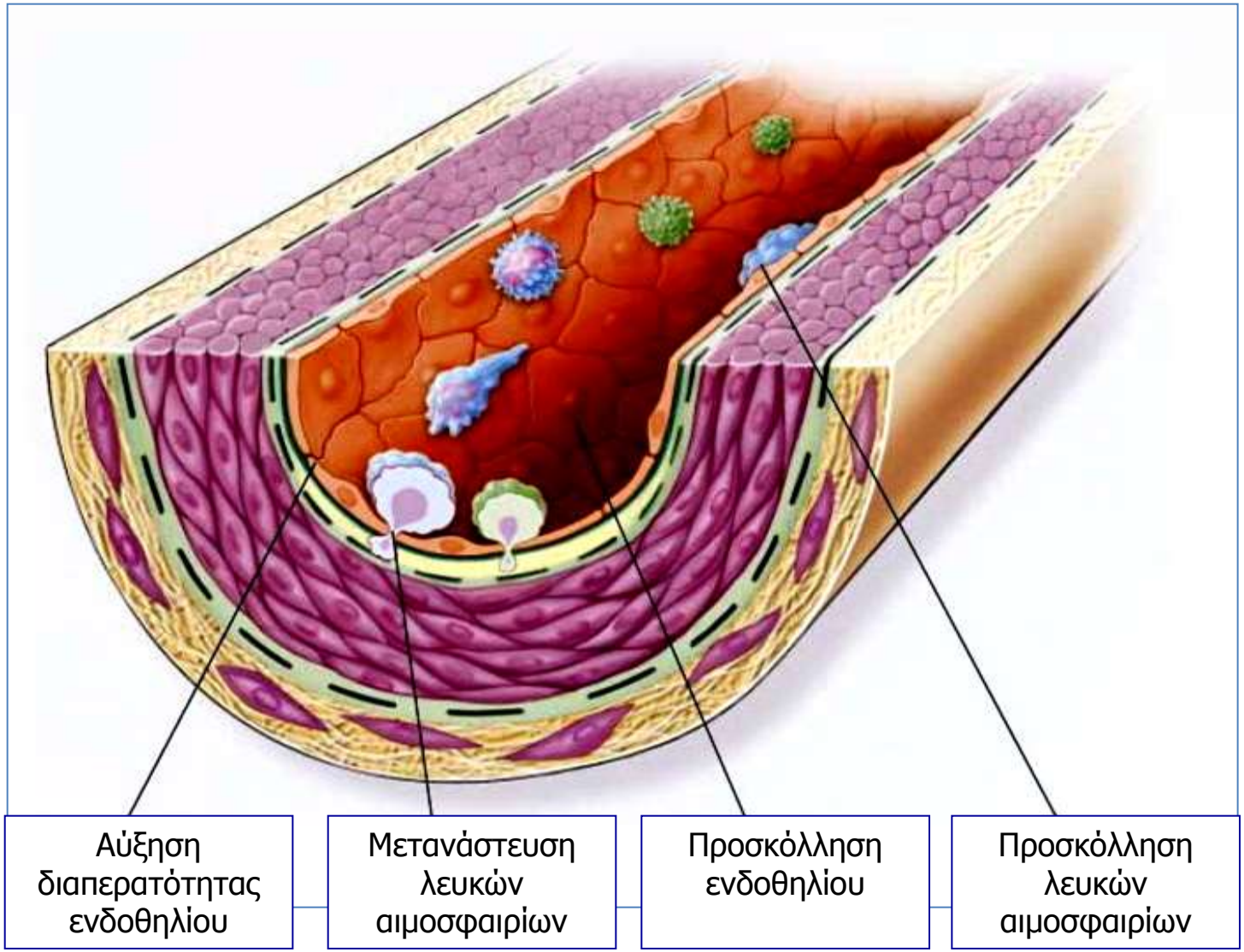


*Follow-up from 1974-2005 for all-cause mortality and 1974-2004 for cardiovascular and non-cardiovascular mortality
**p<0.01 for difference between men and women

Allemann S, et al. Swiss Med Wkly. 2009;139(39-40):576-83.

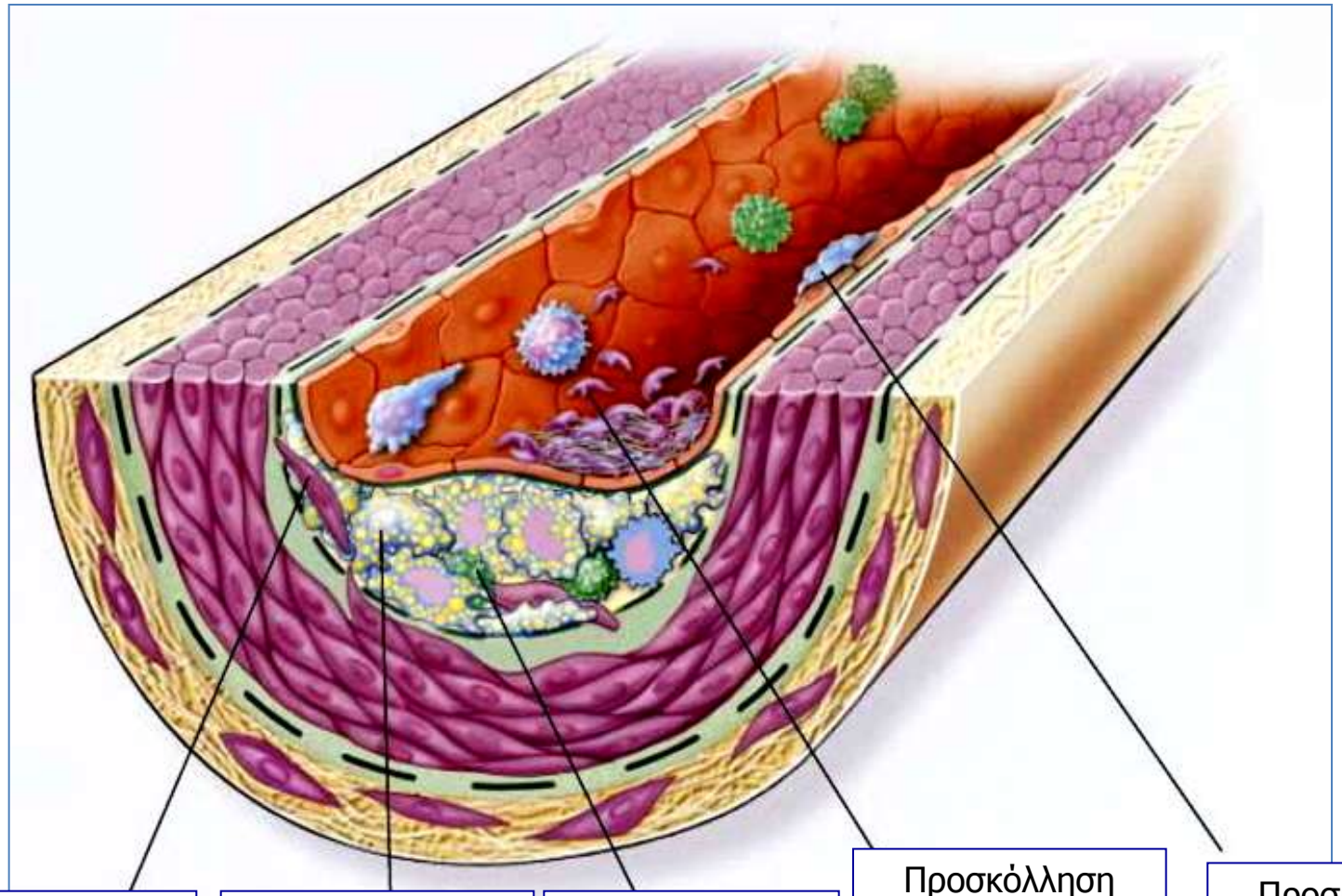
Παθοφυσιολογία αθηροσκλήρωσης

Δυσλειτουργία ενδοθηλίου στην Αθηροσκλήρωση



Παθοφυσιολογία αθηροσκλήρωσης

Σχηματισμός λιπώδους πλάκας στην Αθηροσκλήρωση



Μετανάστευση λείων μυϊκών κυττάρων

Σχηματισμός αφρωδών κυττάρων

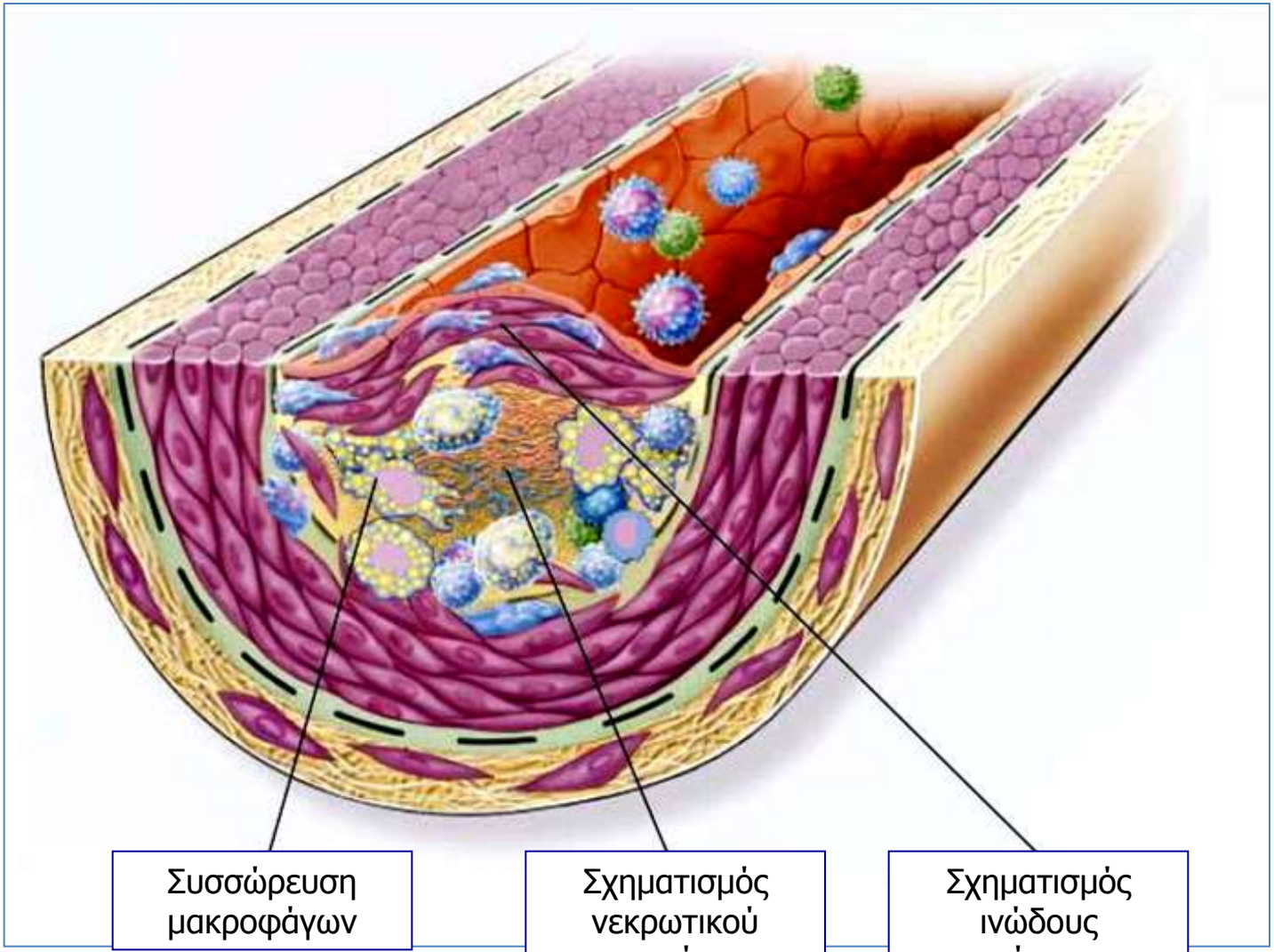
Ενεργοποίηση Τ-λεμφοκυττάρων

Προσκόλληση και συσσώρευση αιμοπεταλίων

Προσκόλληση και είσοδος λευκών αιμοσφαιρίων

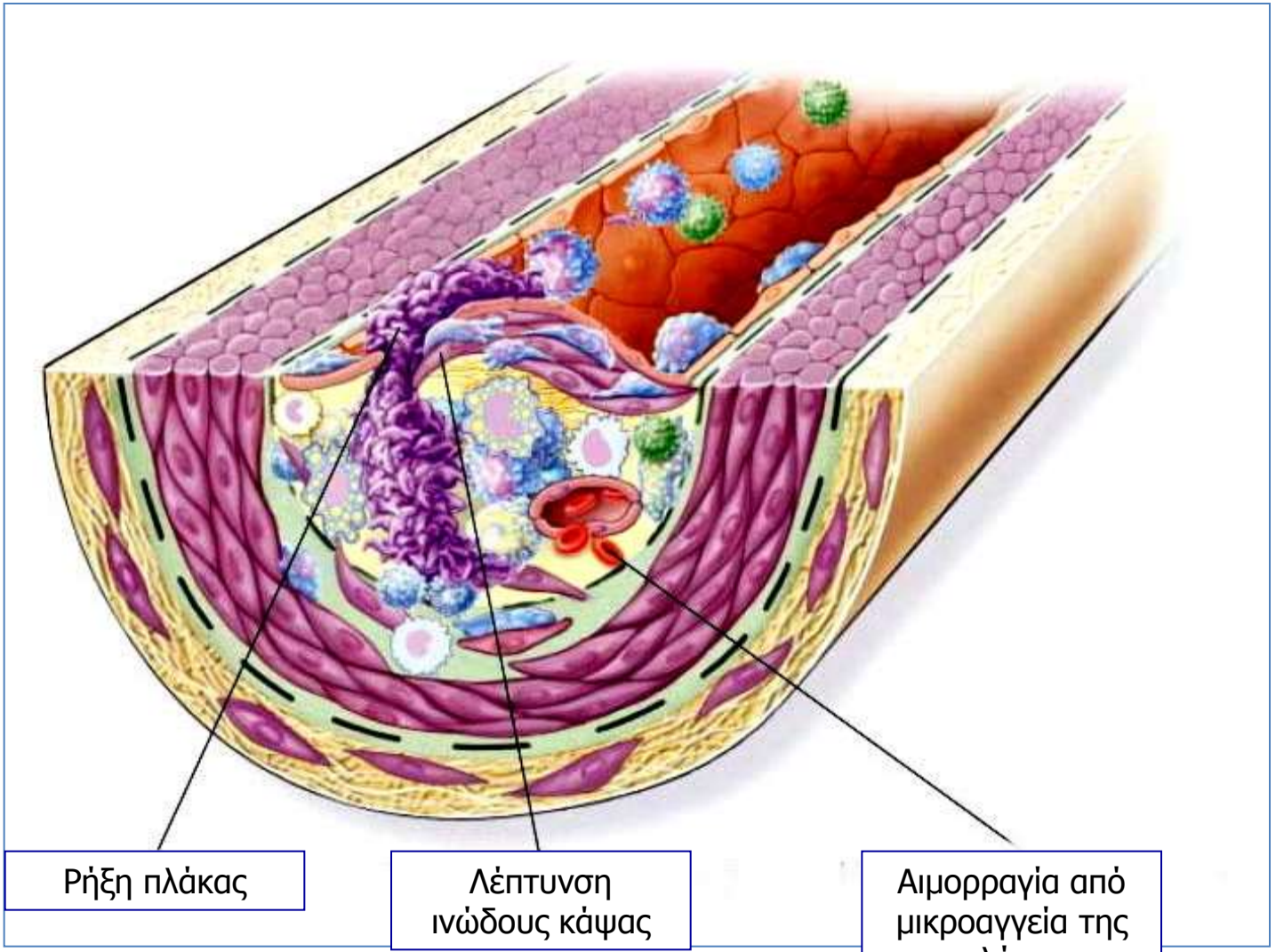
Παθοφυσιολογία αθηροσκλήρωσης

Προχωρημένη βλάβη στην Αθηροσκλήρωση

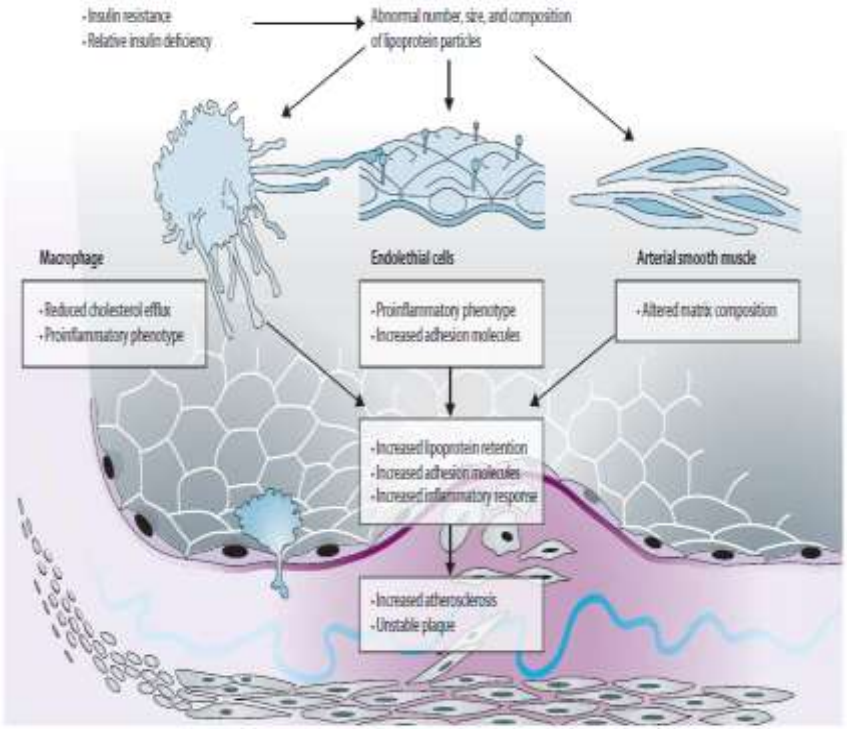


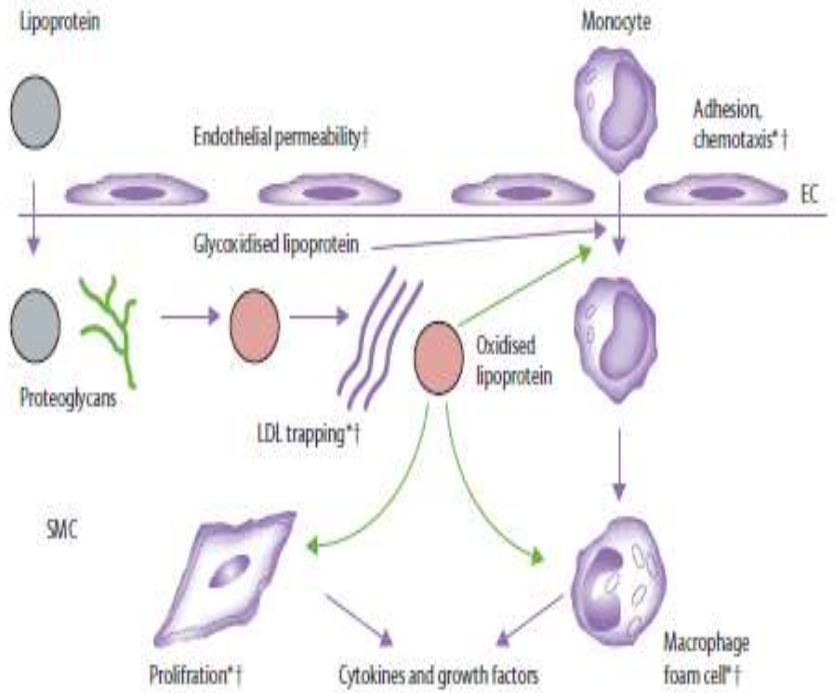
Παθοφυσιολογία αθηροσκλήρωσης

Ασταθείς ινώδεις πλάκες στην Αθηροσκλήρωση

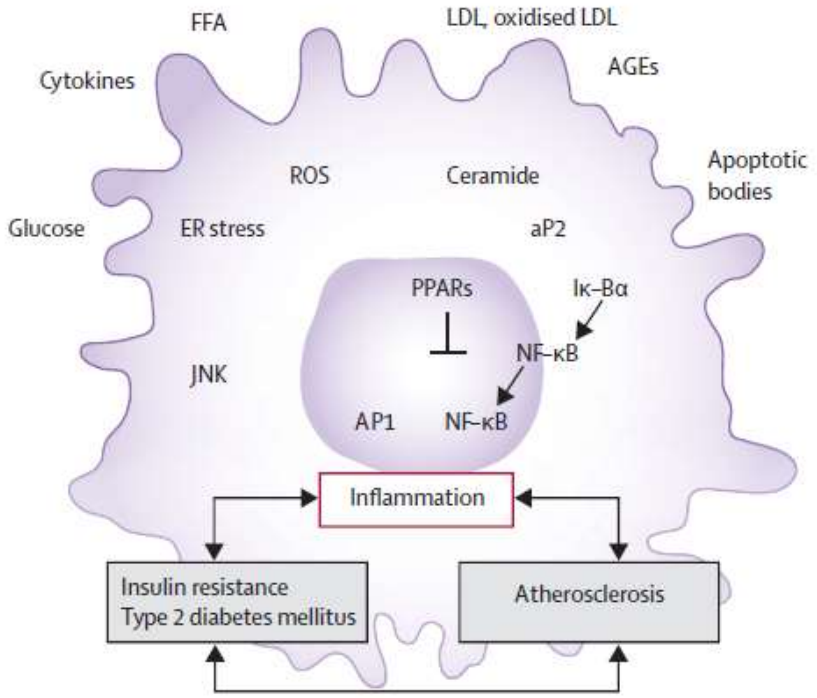


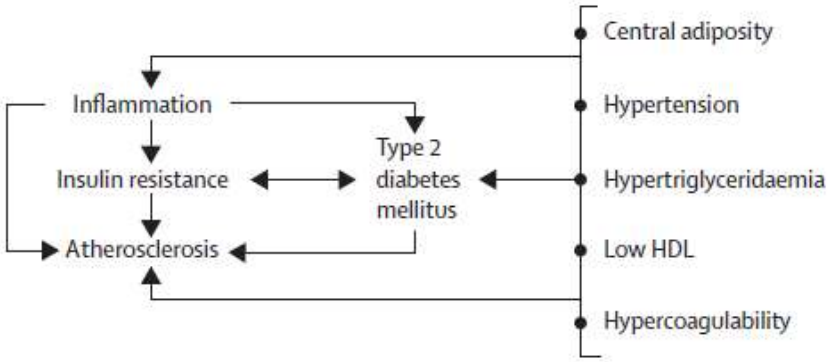
Διαβητική δυσλιπιδαιμία και αγγειακό τοίχωμα



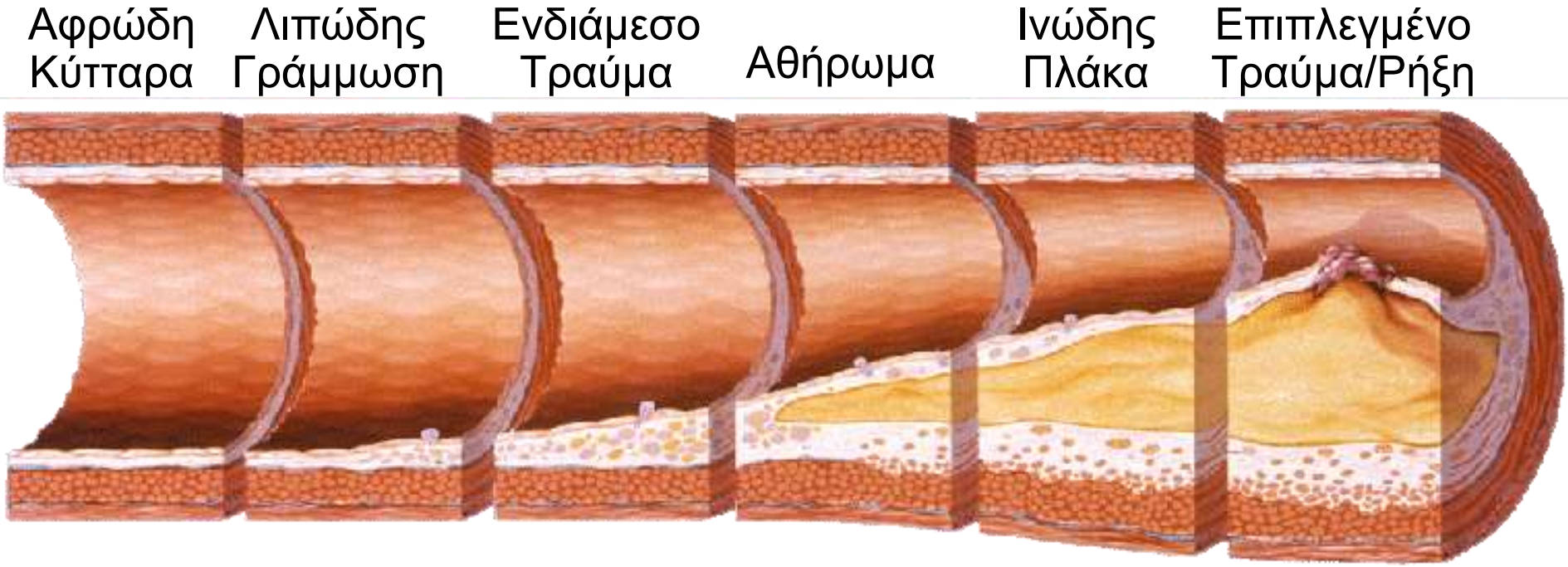


Φλεγμονή –ΣΔ-Αθηροσκλήρωση





Φυσική ιστορία της αθηρωματικής πλάκας

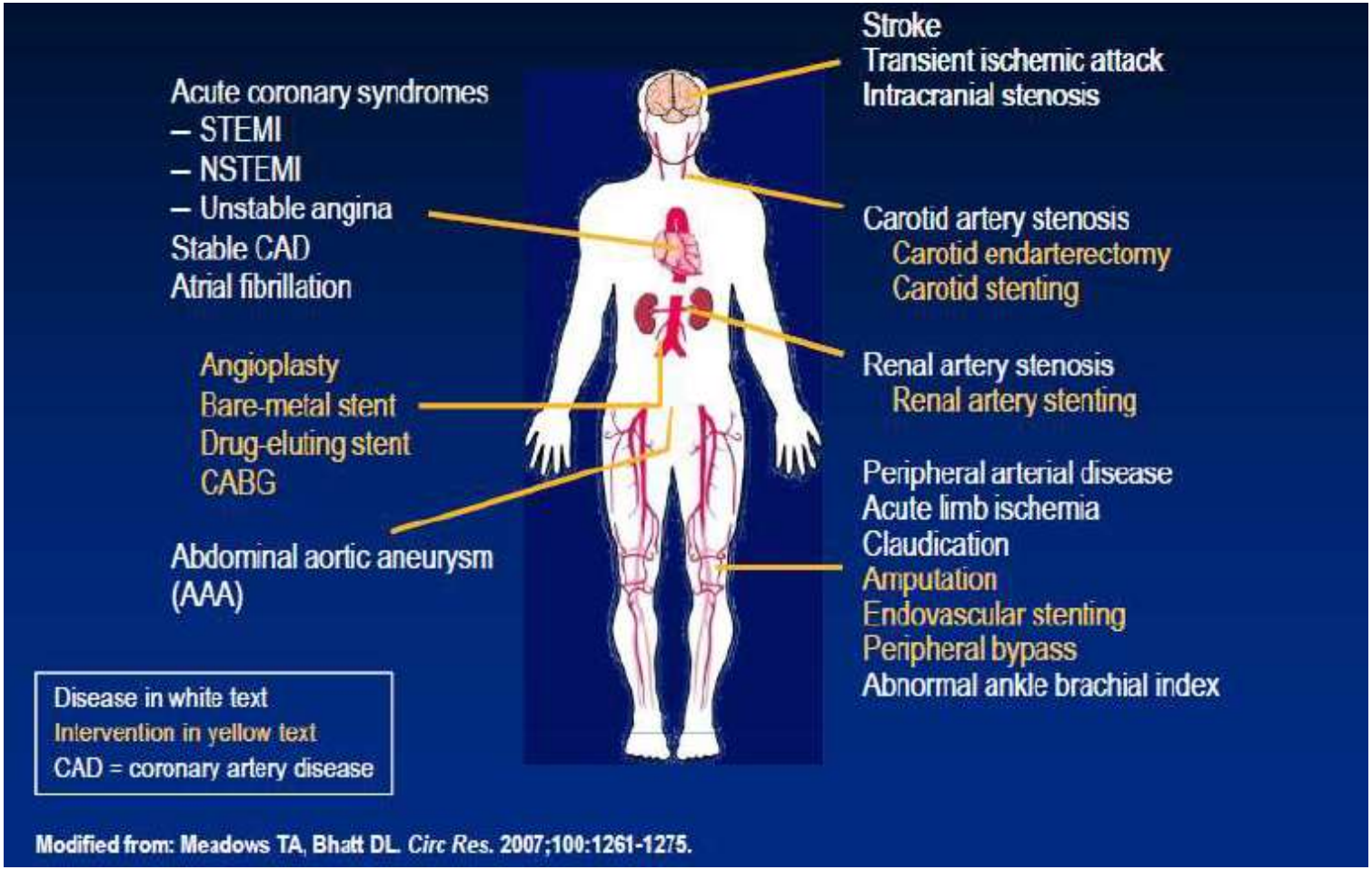


Ενδοθηλιακή δυσλειτουργία

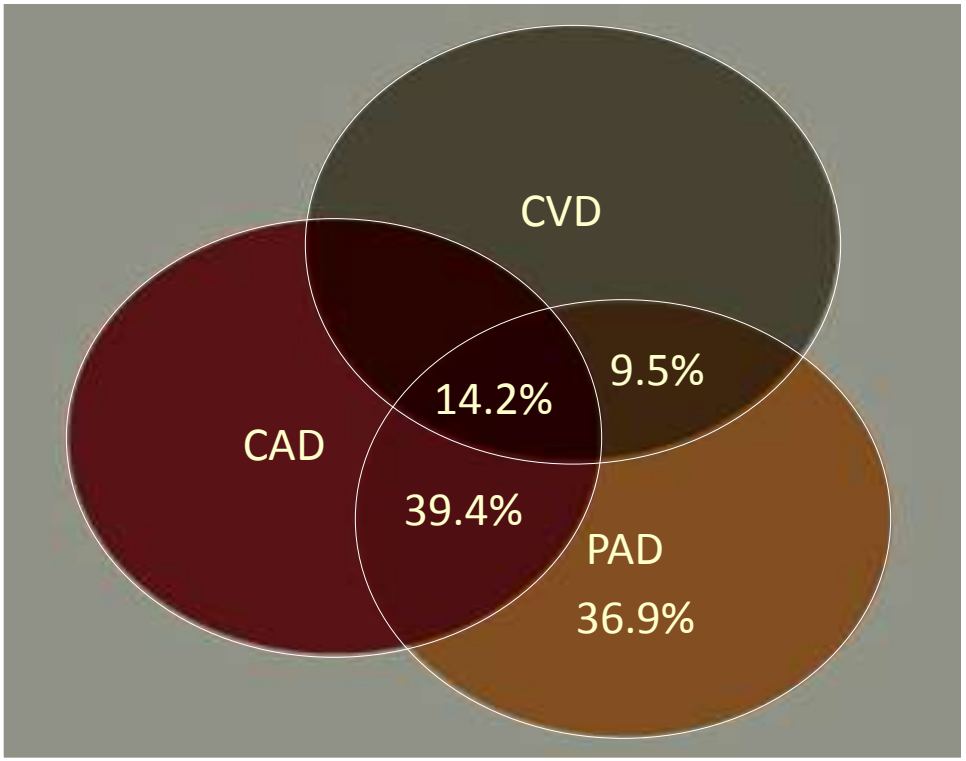
Από την 1η δεκαετία	Από την 3η δεκαετία	Από την 4η δεκαετία
Αύξηση κυρίως από συσσώρευση λιπιδίων	Λεία μυϊκά κύτταρα και κολλαγόνο	Θρόμβωση, αιμάτωμα

Stary HC et al. *Circulation* 1995;92:1355-1374.

Με απρόβλεπτες συνέπειες



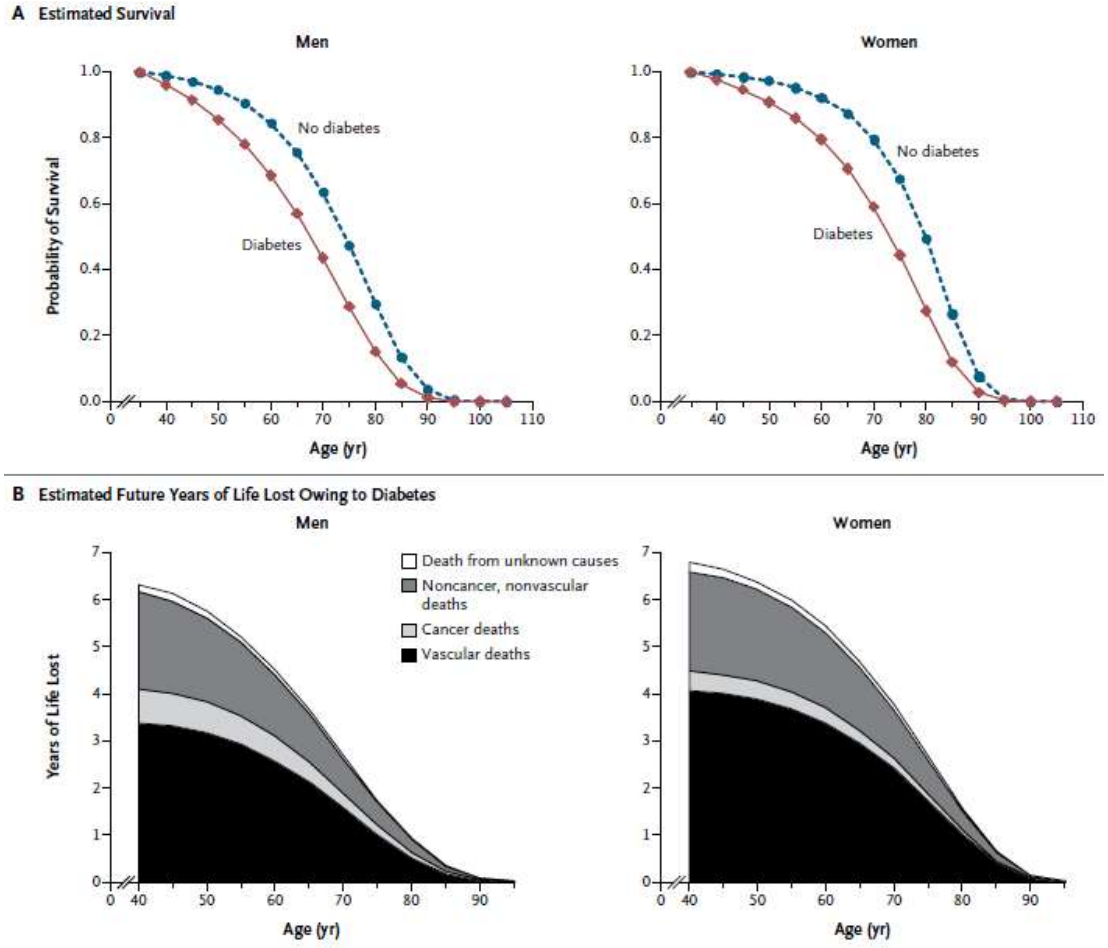
Όταν υπάρχει μακροαγγειοπάθεια…



Patients with one manifestation
often have coexistent disease in other vascular beds.

Bhatt DL, et al. REACH Investigation. Presented at: American College of Cardiology Annual Scientific Session; March 8, 2005; Orlando, FL. Abstract 1127-96.

Επιβίωση και ΣΔ



Βιολογικοί δείκτες και κίνδυνος αθηροσκλήρωσης

Λιπίδια

Lp(a) -apoA/apoB

Μέγεθος/πυκνότητα σωματιδίων

Οξείδωση

- Ox-LDL
- MPO

Φλεγμονή

- CRP
- IL-6
- TNF
- Lp-PLA2
- CD40L
- CSF
- SAA
- IL-18
- Μόρια προσκόλλησης

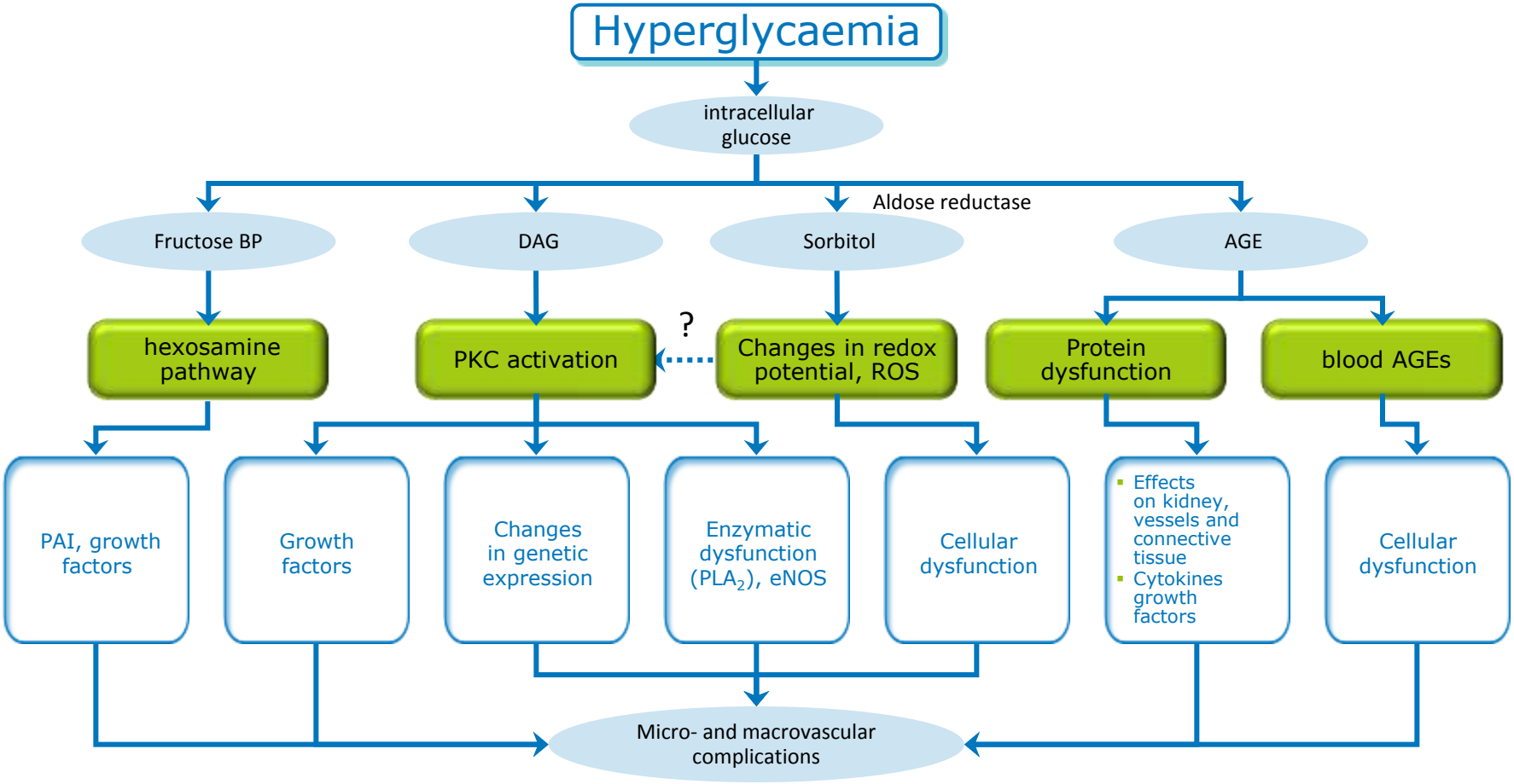
Γενετικοί

- Asp299Gly πολυμορφισμός στο γονίδιο TLR4
- MCP-1 2578G αλλήλιο
- CX3CR1 υποδοχέας χημοκινών πολυμορφισμός V249I
- 16Gly παραλλαγή του β2-αδρενεργικού υποδοχέα
- 260T/T CD14 αλλήλιο
- 117 Thr/Thr παραλλαγή του CSF
- LIGHT

Αιμόσταση - Θρόμβωση

- Ομοκυστεΐνη
- TAFI
- D-διμερή
- tPA/PAI-1
- Ινωδογόνο

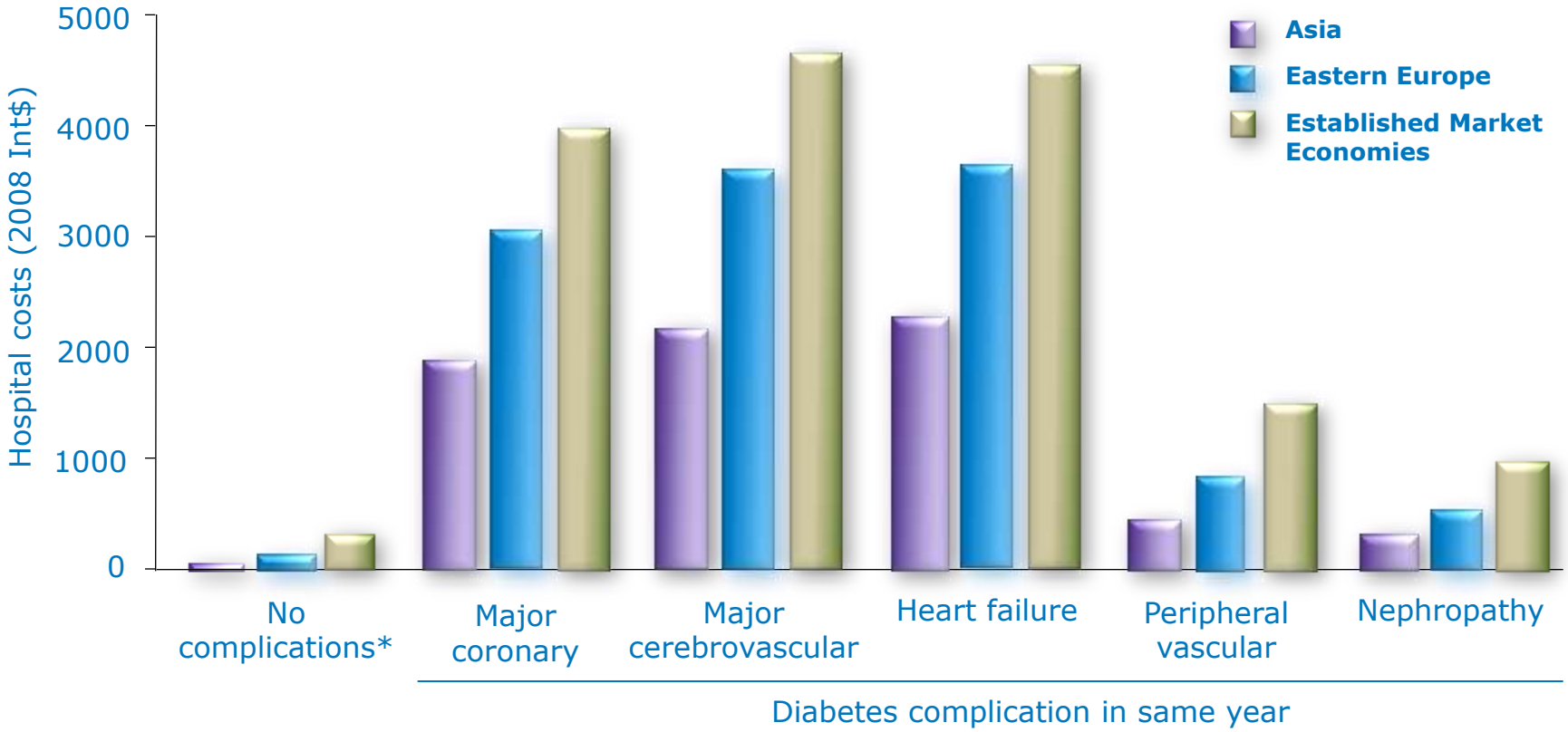
Παθοφυσιολογική σχέση υπεργλυκαιμίας και επιπλοκών



PAI: plasminogen activator inhibitor; DAG: diacylglycerol; PKC: protein kinase C; PLA2: phospholipase A2; eNOS: endothelial nitric oxide synthase; AGE: advanced glycation end-products

Blazquez-Medela AM, et al. Curr Diabetes Rev. 2010;6(2):68-87.

Νοσοκομειακό κόστος για ασθενείς με ή χωρίς διαβητικές επιπλοκές

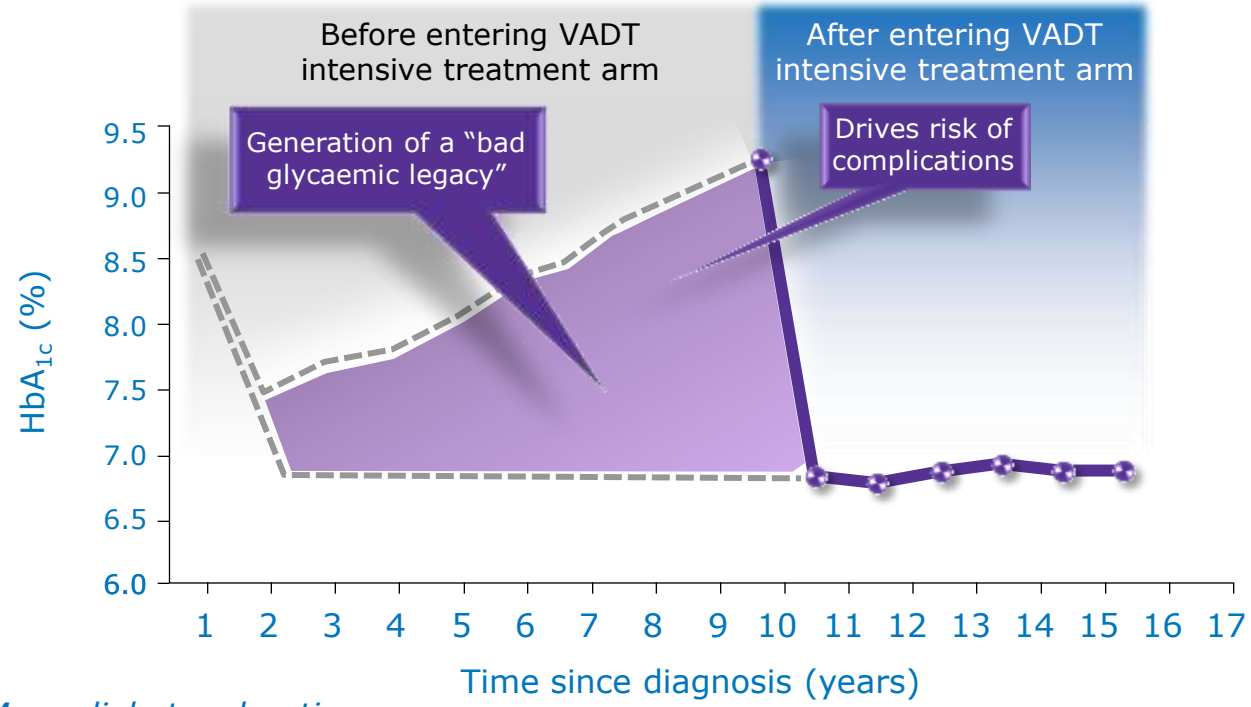


* "No complications" signifies none of the 5 complications listed

Clarke PM, et al. PLoS Med. 2010 23;7(2):e1000236.

Η κακή μεταβολική μνήμη είναι κάτι το οποίο πρέπει να έχουμε υπόψη μας

Hypothetical representation of the natural history of diabetes patients recruited in VADT



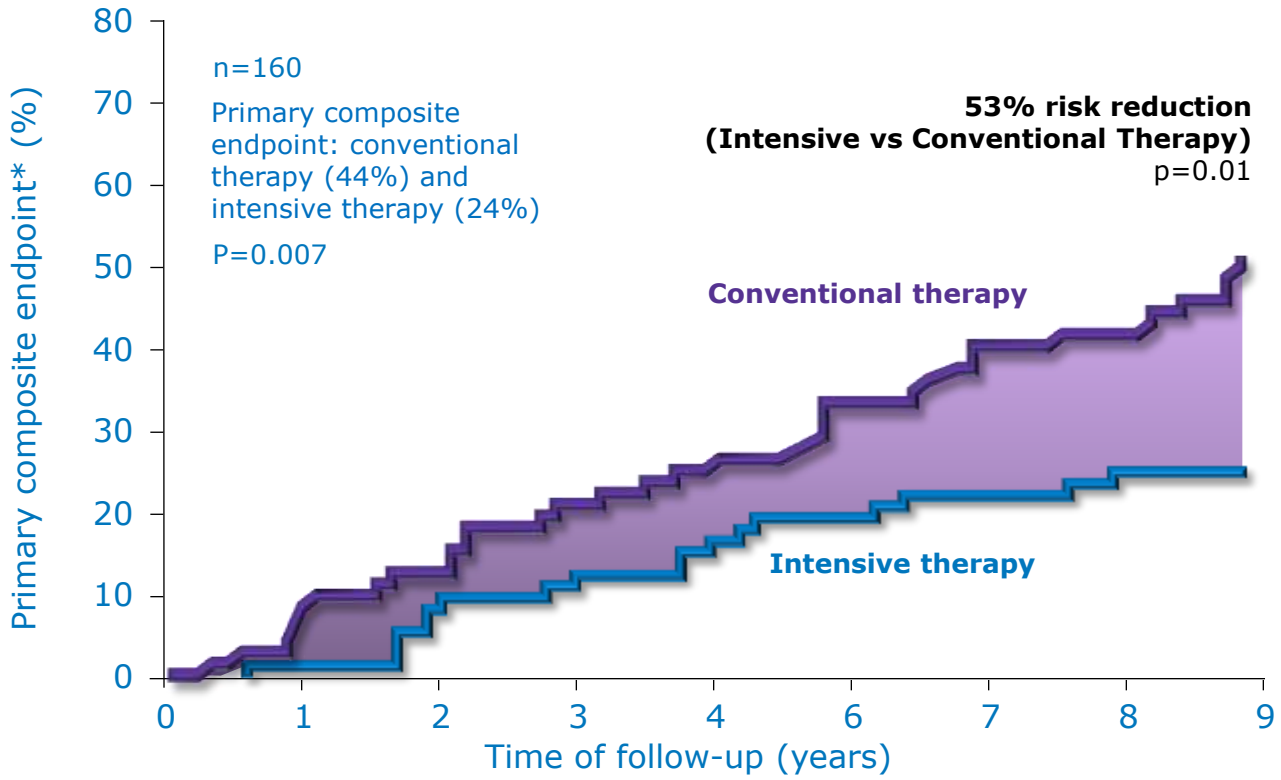
Upper dotted line represents the time course of HbA_{1c} estimated on the basis of the average glucose profile described by the UKPDS

Lower dotted line represents the ideal time course of glycaemic control. The solid line represents the time course of HbA_{1c} in the VADT

Mean diabetes duration at baseline = 11.5 years

Del Prato S. Diabetologia. 2009;52:1219-26.

STENO-2: Η πολυπαραγοντική αντιμετώπιση μειώνει τα καρδιαγγειακά συμβάματα



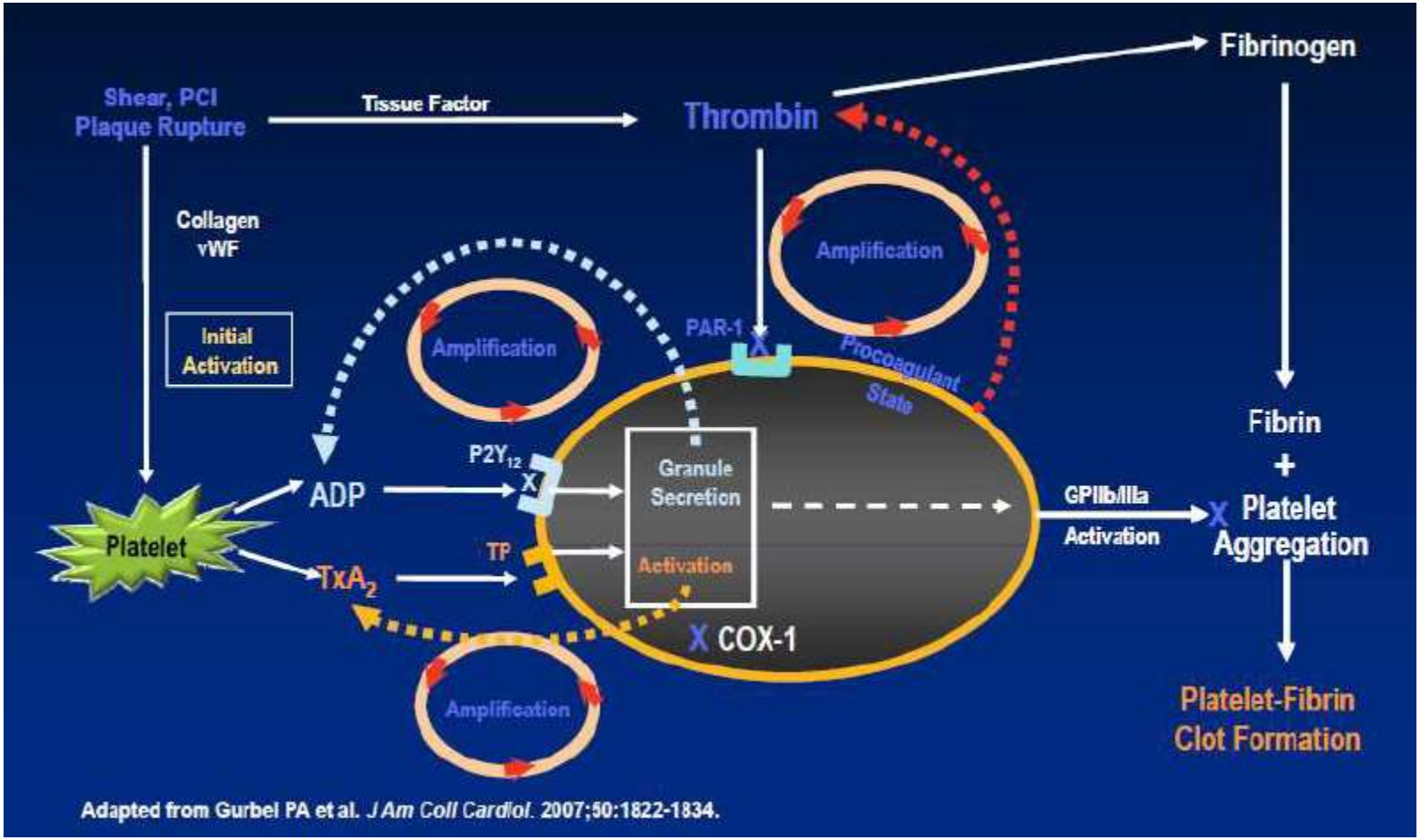
- In addition to ~50% relative risk reduction in the primary composite endpoint, a sustained benefit on CV events was also observed in the intensive management group over an additional 5.5 years[2]

*Death from CV causes, non-fatal MI, CABG, PCI, non-fatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease

1. Gaede P, et al. N Engl J Med. 2003;348:383-93. 2. Gaede P, et al. N Engl J Med. 2008;358(6):580-91.

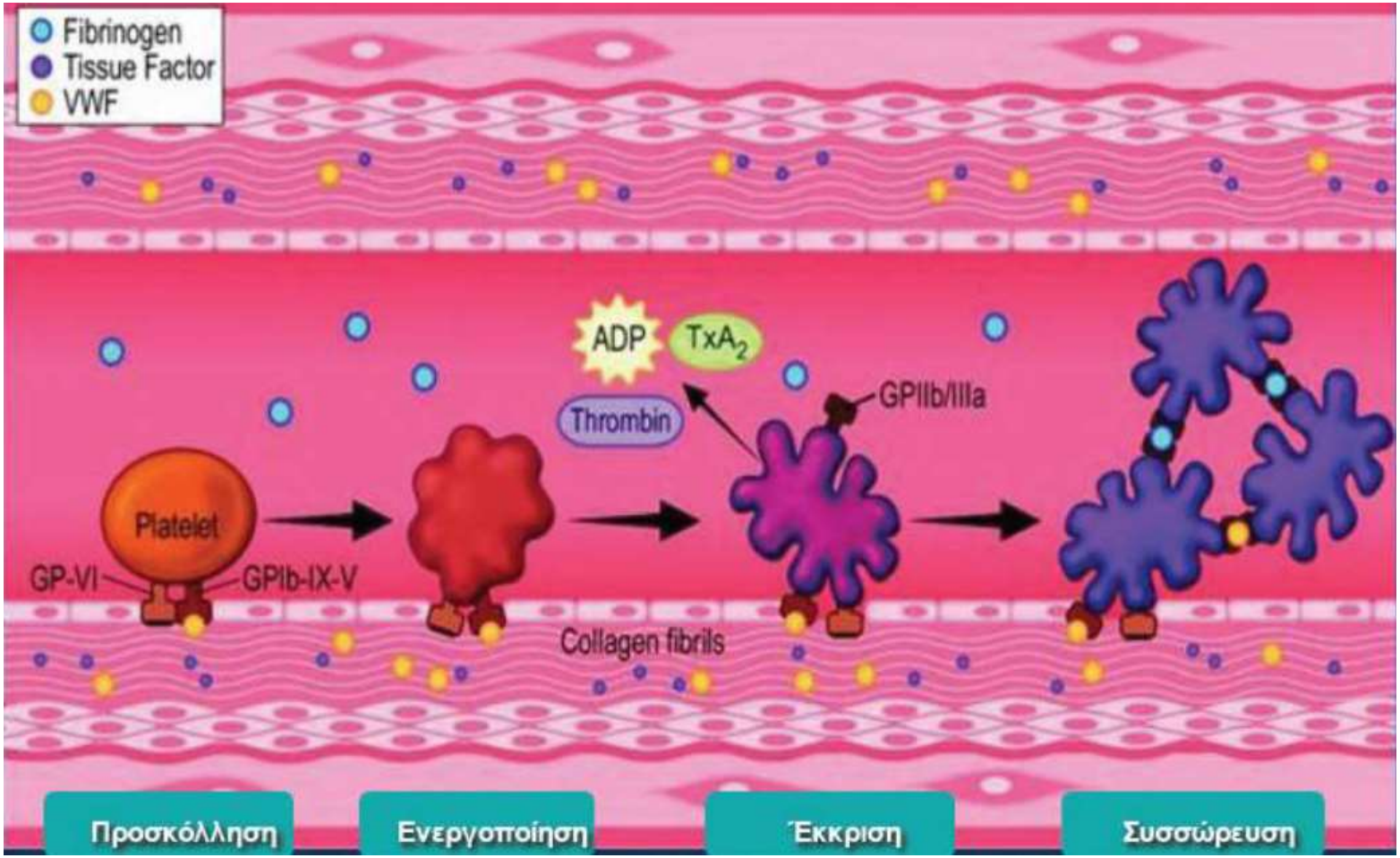
Η θεραπεία της αθηροσκλήρωσης στο ΣΔ2

Ο ρόλος των αιμοπεταλίων στην αθηροθρόμβωση

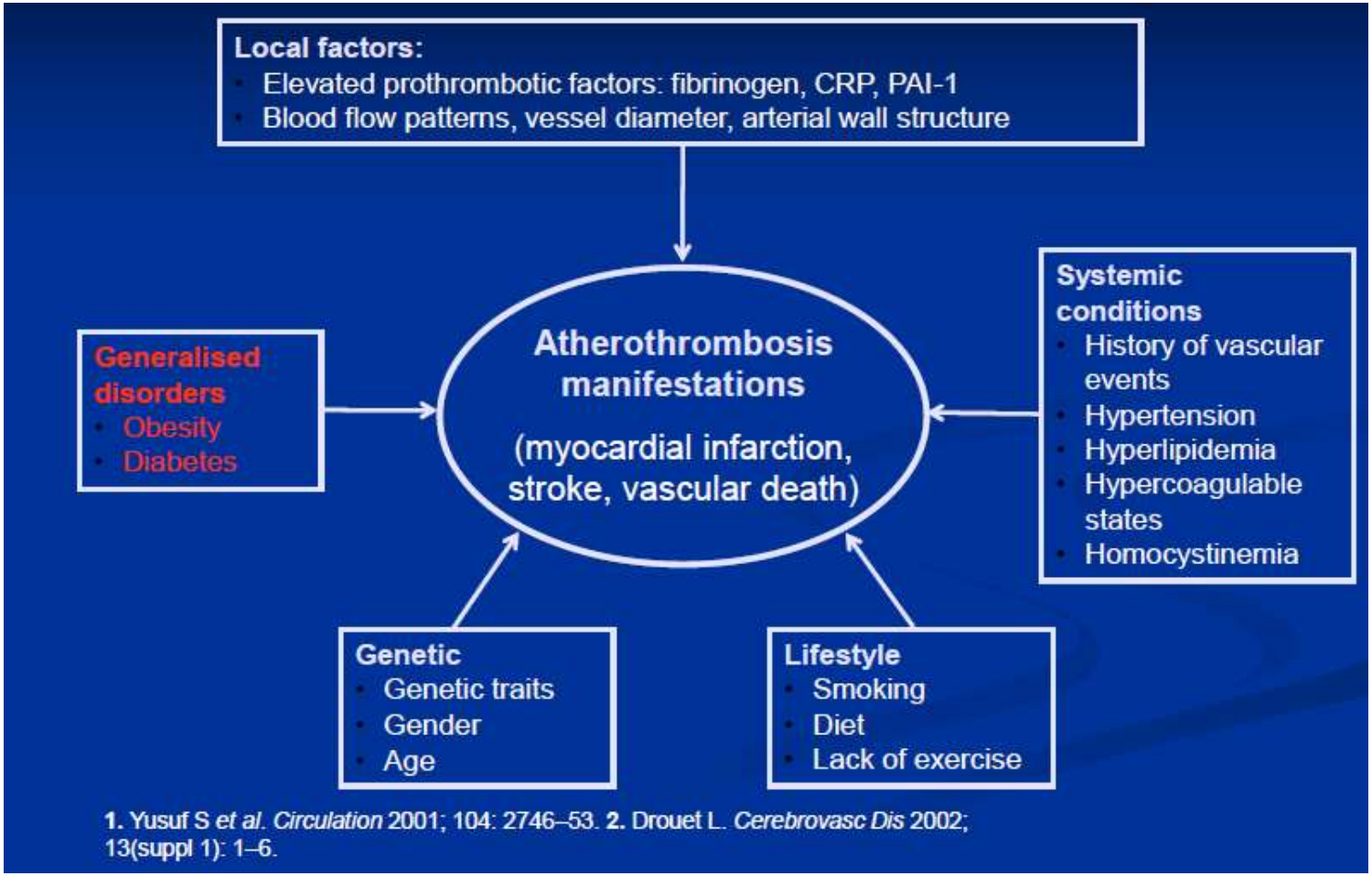


Adapted from Gurbel PA et al. *J Am Coll Cardiol.* 2007;50:1822-1834.

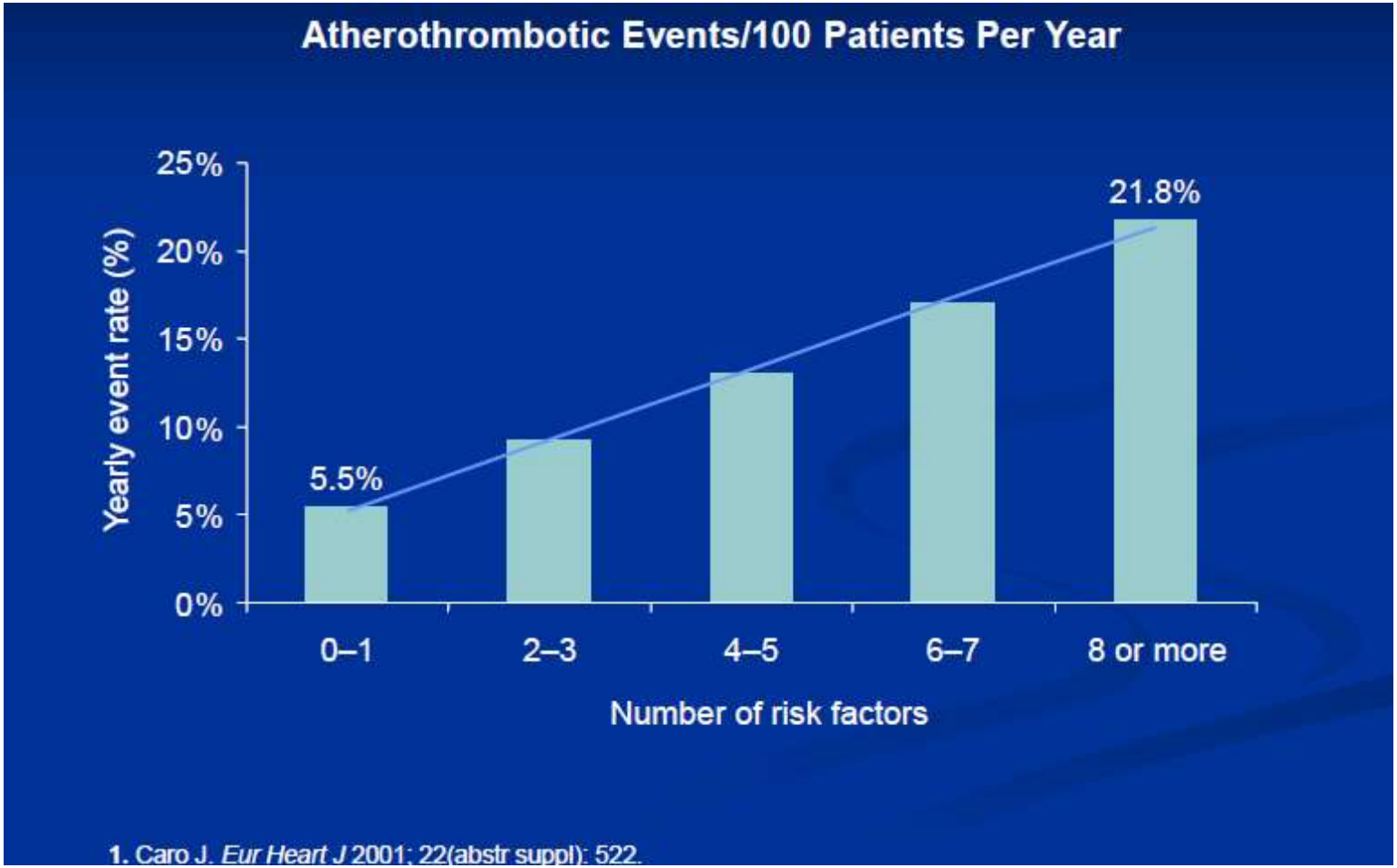
Αιμοστατικός ρόλος των αιμοπεταλίων



Ποιοι είναι αυτοί που κινδυνεύουν;



Και πόσο;



1. Caro J. *Eur Heart J* 2001; 22(abstr suppl): 522.

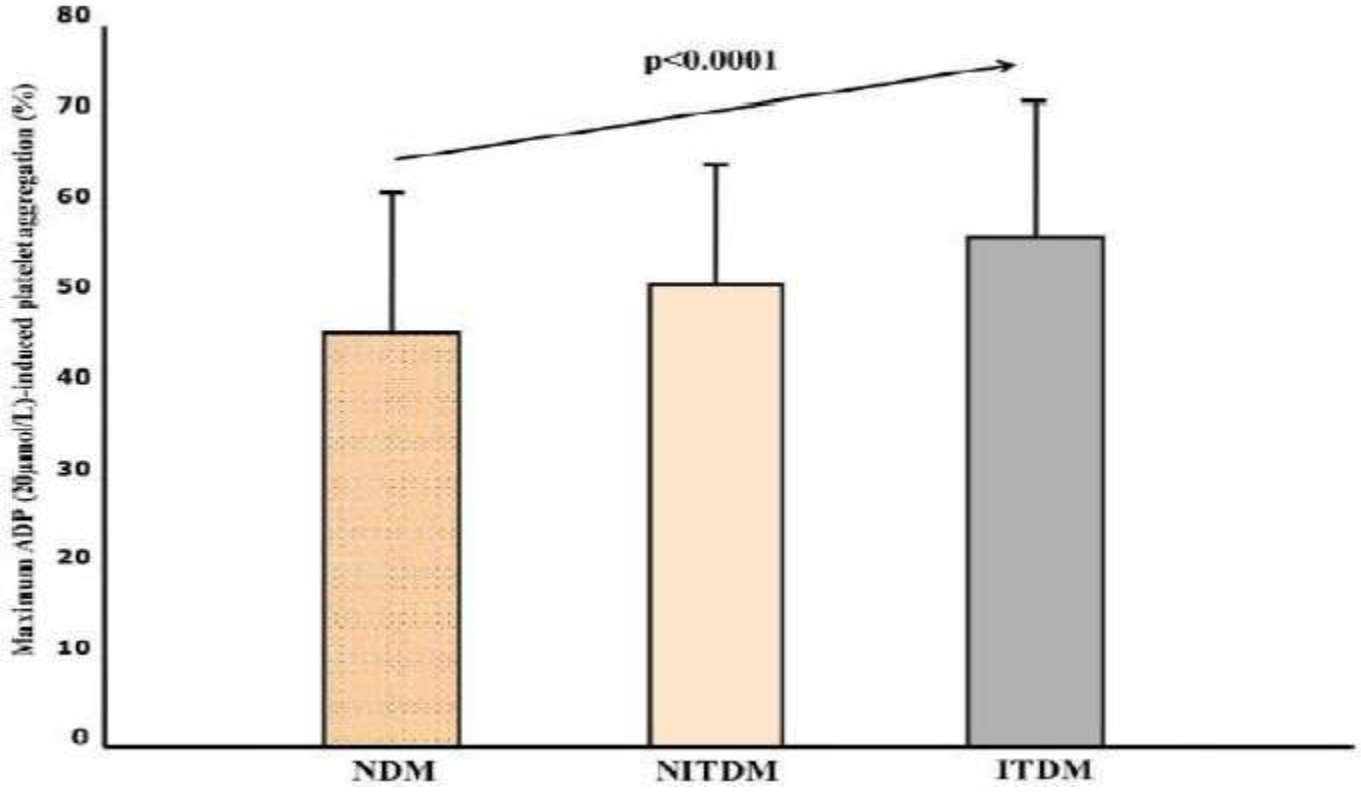
Μηχανισμοί θρόμβωσης στον ΣΔ

Impaired fibrinolysis	**Impaired platelet function**
Increased PAI-1 and a-2 antiplasmin	Increased adhesion, aggregation, and activation (GP IIb/IIIa, Psel, CD40L)
Decreased t-PA	
Impaired coagulation	**Endothelial dysfunction**
Increased fibrinogen	Increased adhesion molecules (VCAM, etc)
Increased vWF	Increased Leukocyte-endothelial interaction
Increased thrombin	Increased oxidative cell stress (induction NFκB)
Increased FVII, FVIII	Impaired vasodilation (increased ET-1, decreased NO)
Decreased AT-III	Impaired endothelial regeneration
Decreased sulfated heparins	

Reasons for Increased Platelet Aggregation and Adhesion in Patients With Diabetes

- Patients with diabetes reduced membrane fluidity
- Altered calcium and magnesium homeostasis
- Increased arachidonic acid metabolism
- Increased thromboxane A2 synthesis
- Decreased prostacyclin production
- Decreased nitric oxide production
- Decreased antioxidants levels
- Increased expression of activation – dependent adhesion molecules.(e.g.,Gp IIb/IIIa,P- selectin)

Συσσώρευση αιμοπεταλίων και ΣΔ



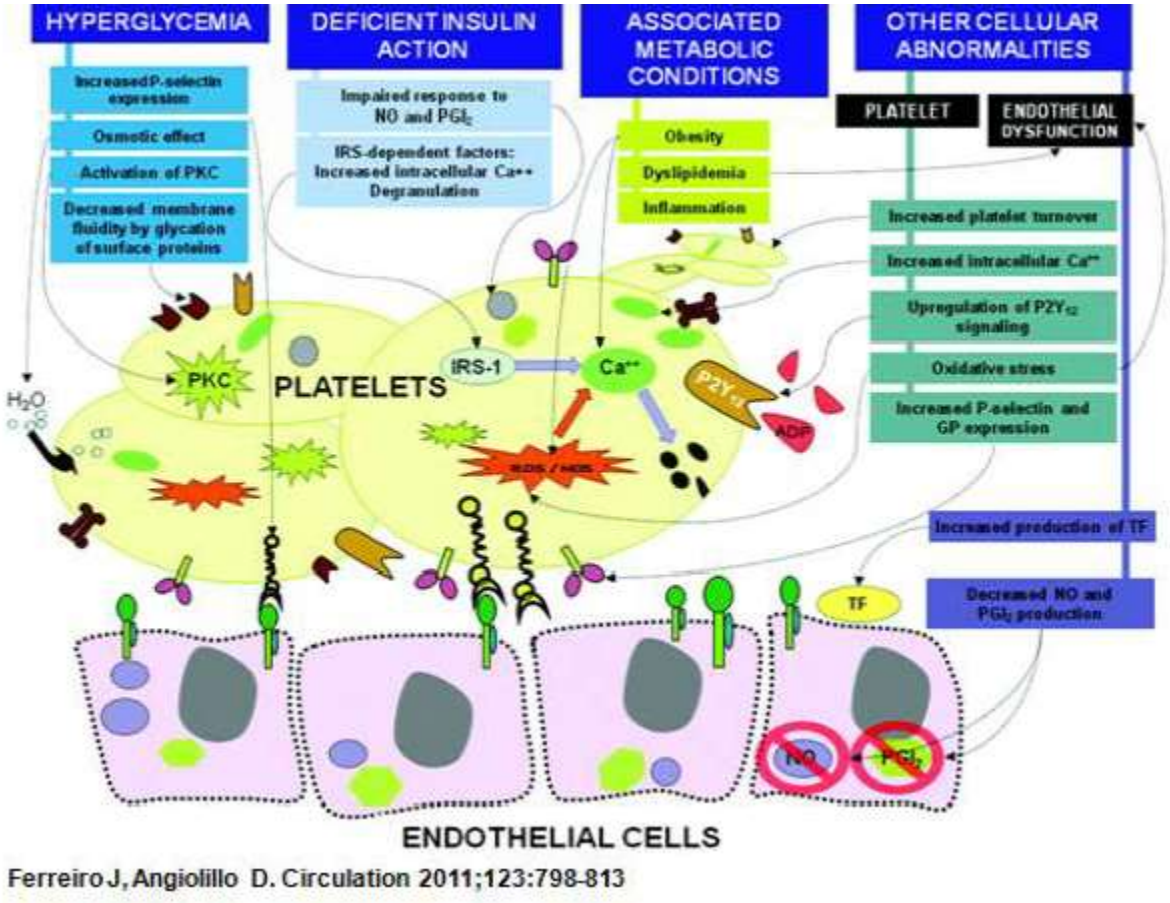
Αιμοπετάλια & Σακχαρώδης Διαβήτης

Οι ΣΔ ασθενείς έχουν υψηλό κίνδυνο για καρδιαγγειακά νοσήματα και αθηροθρομβωτικές επιπλοκές

- Γενικότερα βρίσκονται σε Προθρομβωτική κατάσταση λόγω:
  - Μειωμένης ινωδόλυσης
  - ενδοθηλιακής δυσλειτουργίας &
  - αυξημένης ενεργοποίησης των Plts

J Cardiovasc. Trans. Res (2013) 6: 329-345

Παράγοντες που ευθύνονται για την δυσλειτουργία των αιμοπεταλίων στον ΣΔ



Ferreiro J, Angiolillo D. Circulation 2011;123:798-813

Παράγοντες που επηρεάζουν την λειτουργία των Plts στον Σακχαρώδη Διαβήτη

Α) ΥΠΕΡΓΛΥΚΑΙΜΙΑ - αυξημένη ενεργοποίηση ή υπεραντιδραστικότητα των Plts λόγω:

- **γλυκοζυλίωσης των πρωτεϊνών** της επιφάνειας των Plts με αποτέλεσμα μείωση της διαπερατότητας της μεμβράνης και αύξηση της προσκόλλησης
- **ενεργοποίησης της πρωτεϊνικής κινάσης C** (μεσολαβητής της ενεργοποίησης των Plts)
- **αυξημένης ενδοκυττάριας συγκέντρωσης ασβεστίου** λόγω γλυκοζυλίωσης των κυκλοφορούντων χαμηλής πυκνότητας λιποπρωτεϊνών
- **παραγωγής δραστικών ριζών οξυγόνου**
- **μειωμένης παραγωγής του ενδοθηλιακού NO**
- **ενεργοποίησης της έκφρασης** των GPIIb/IIIa γλυκοπρω-τεϊνών και της P-σελεκτίνης λόγω της ωσμωτικής δράσης της γλυκόζης

Lemkes B.A. et al J Thrombosis & Haemostasis, 2010: 8, 1663-1669

Παράγοντες που επηρεάζουν την λειτουργία των Plts στον Σακχαρώδη Διαβήτη

Α) ΥΠΕΡΓΛΥΚΑΙΜΙΑ

- ✓ **αναστέλλει την ινωδόλυση** αυξάνοντας την συγκέντρωση του αναστολέα του ενεργοποιητή του πλασμιγόνου (PAI-1)

- ✓ **επάγει την πήξη** αυξάνοντας τις συγκεντρώσεις προπηκτικών παραγόντων (TF, vWF)

Παρατηρείται μείωση των δεικτών ενεργοποίησης των Plts, ύστερα από σωστή ρύθμιση της γλυκόζης

Μελέτες: DIGAMI, DIGAMI-2, ACCORD, CHIPS, NICE-SUGAR

Lemkes B.A. et al Journal Thrombosis & Haemostasis, 2010: 8, 1663-1669

Παράγοντες που επηρεάζουν την λειτουργία των Plts στον Σακχαρώδη Διαβήτη

Β) ΑΝΕΠΑΡΚΕΙΑ – ΑΝΤΙΣΤΑΣΗ στην ΙΝΣΟΥΛΙΝΗ:

- ✓ τα Plts διαθέτουν **υποδοχείς για την ινσουλίνη (IR)** και **υποδοχείς τύπου ινσουλίνης** για τον αυξητικό παράγοντα 1 (IGF-1)

- ✓ η σύνδεση της ινσουλίνης στους υποδοχείς **αυξάνει** στην επιφάνεια των Plts **την έκφραση του υποδοχέα της** με την αδενυλική κυκλάση συνδεμένης προστακυκλίνης

- ✓ η παρουσία του IGF-1 στα κοκκία των Plts και η έκφραση του υποδοχέα του στην επιφάνειά τους συμβάλλει στην **ενεργοποίηση των PLts και την παθογένεση της καρδιαγγειακής νόσου** στους ΣΔ ασθενείς

Lemkes B.A. et al Journal of Thrombosis & Haemostasis, 2010: 8, 1663-1669

Παράγοντες που επηρεάζουν την λειτουργία των Plts στον Σακχαρώδη Διαβήτη

Β) ΑΝΕΠΑΡΚΕΙΑ – ΑΝΤΙΣΤΑΣΗ στην ΙΝΣΟΥΛΙΝΗ:

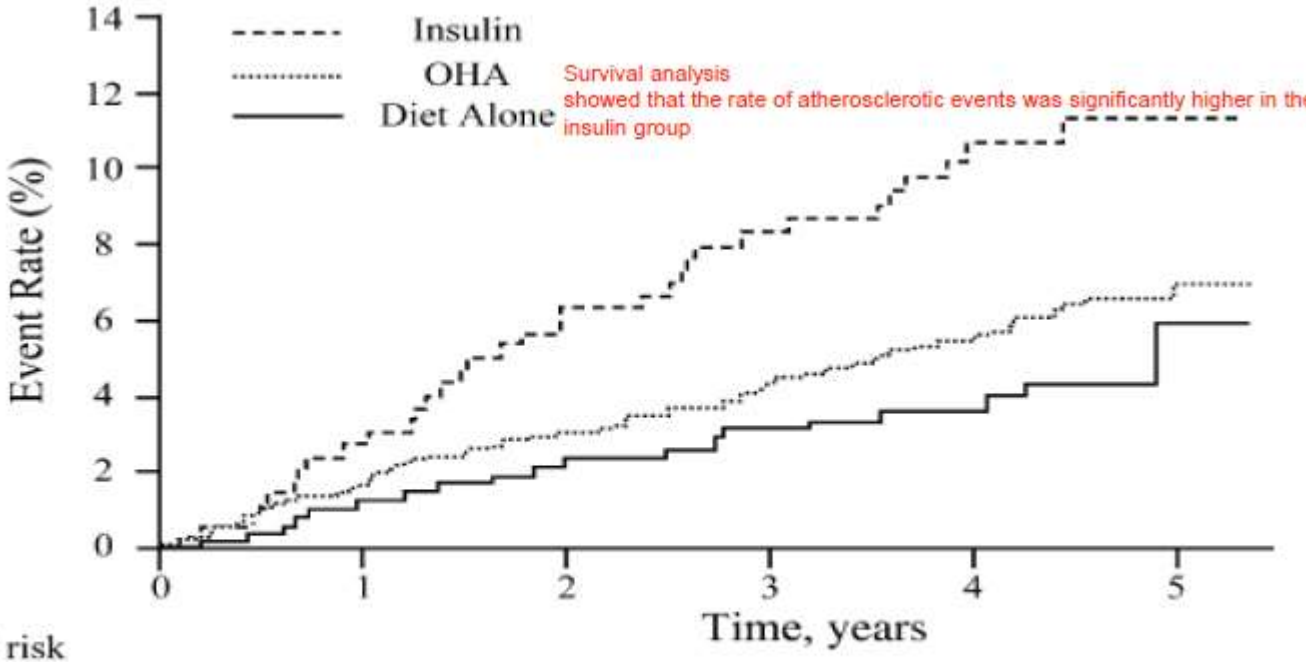
- ✓ **Γενετικές παραλλαγές του IRS-1** σχετίζονται με διαφορετικό προφίλ λειτουργίας των Plts που παρατηρούνται σε ΣΔ ασθενείς (**Αυτοί οι ασθενείς είναι σε αυξημένο καρδιαγ-γειακό κίνδυνο**)

- ✓ δράση των θειαζολιδινεδιονών που επηρεάζουν τις δράσεις της ινσουλίνης στην λειτουργία των Plts

(Μελέτες PERISCOPE, SIMPHONY, SIMPHONY-2, APPROACH)

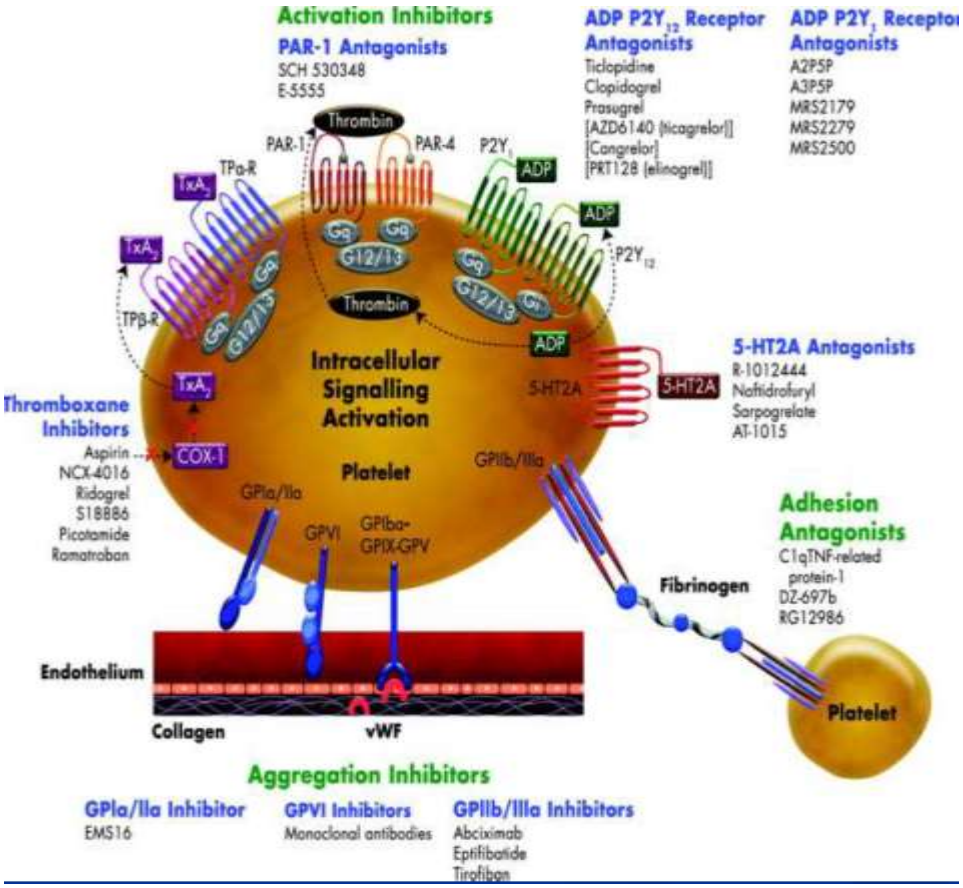
J Cardiovasc. Trans. Res (2013) 6: 329-345

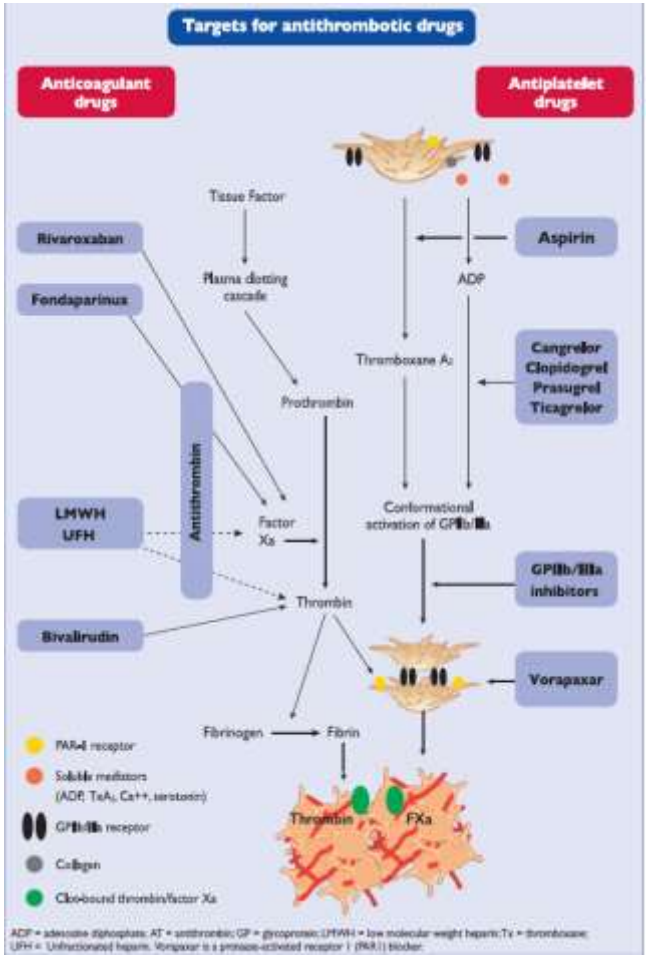
Η θεραπεία επηρεάζει;



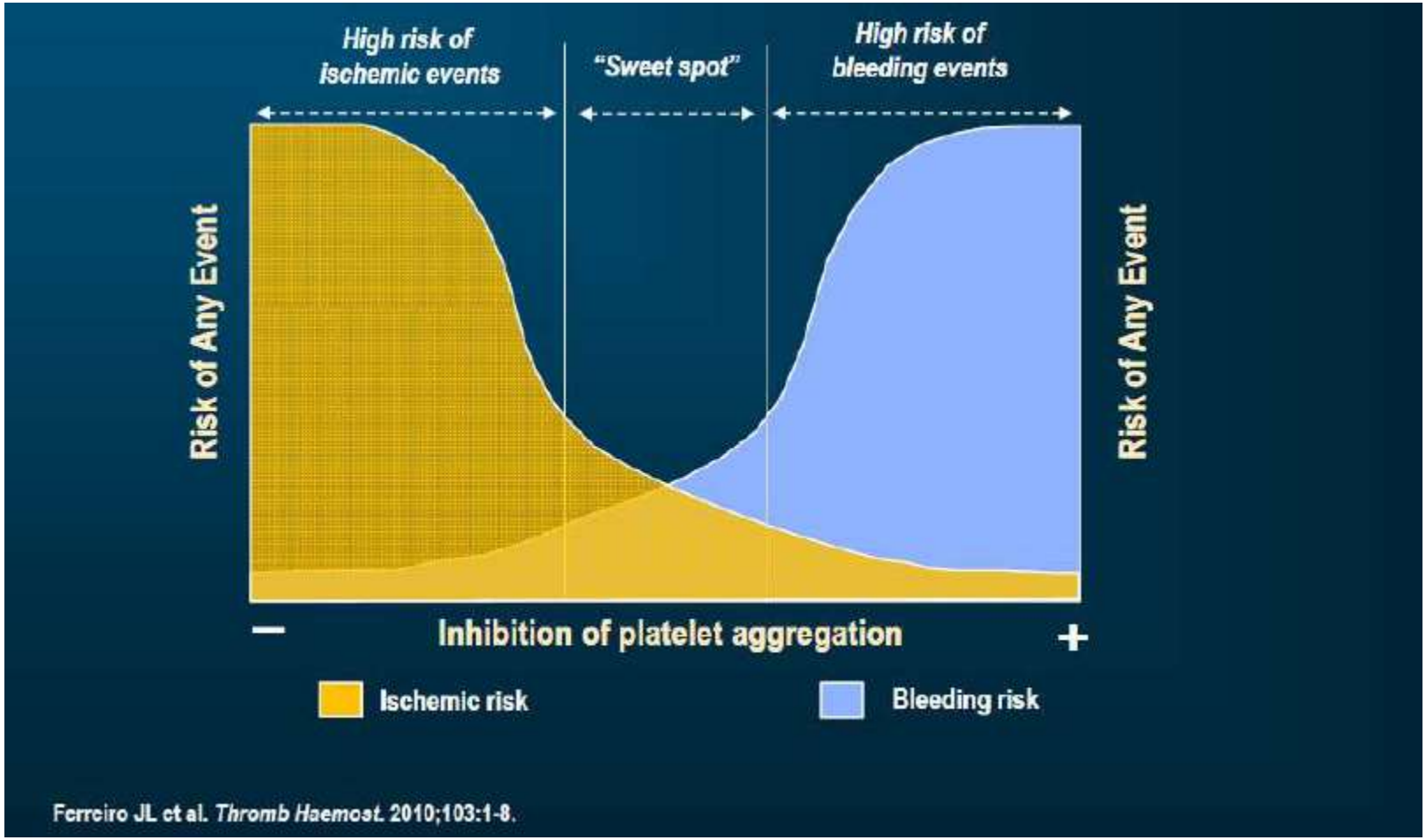
No. at risk						
Insulin	326	306	288	271	199	11
OHA	1750	1680	1613	1536	1131	223
Diet Alone	463	445	424	405	288	41

Αντιθρομβωτικοί παράγοντες





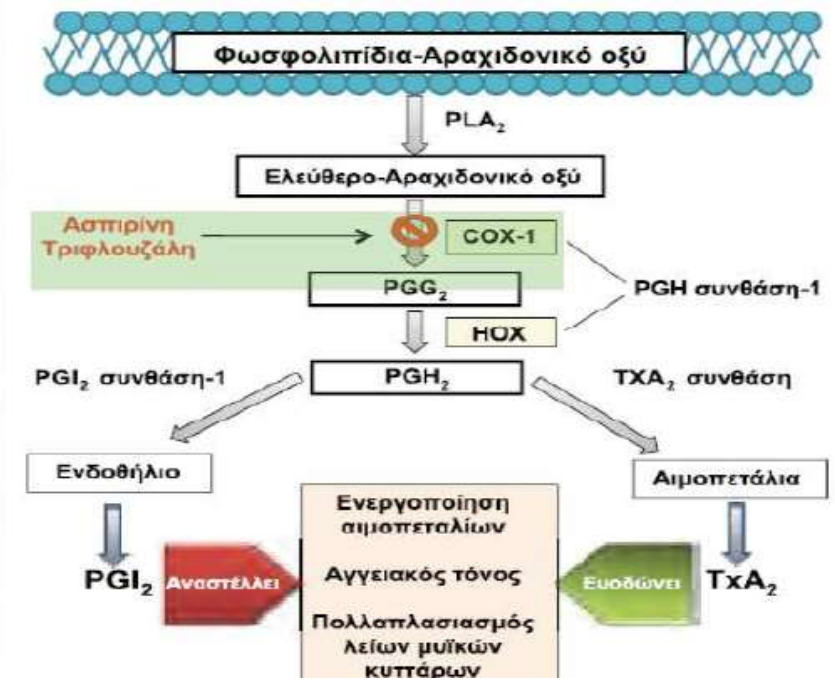
Αναστολή συσσώρευσης αιμοπεταλίων και αγγειακά συμβάματα



Ασπιρίνη

ΙΠΠΟΚΡΑΤΗΣ: φλοιός ιτιάς
παυσίπονο-αντιπυρετικό
1853 Charles Frederic Gerhardt…σαλικυλικό οξύ
1897 Bayer
1899 κυκλοφορία ασπιρίνης
1948 αντιαιμοπεταλιακή δράση ασπιρίνης

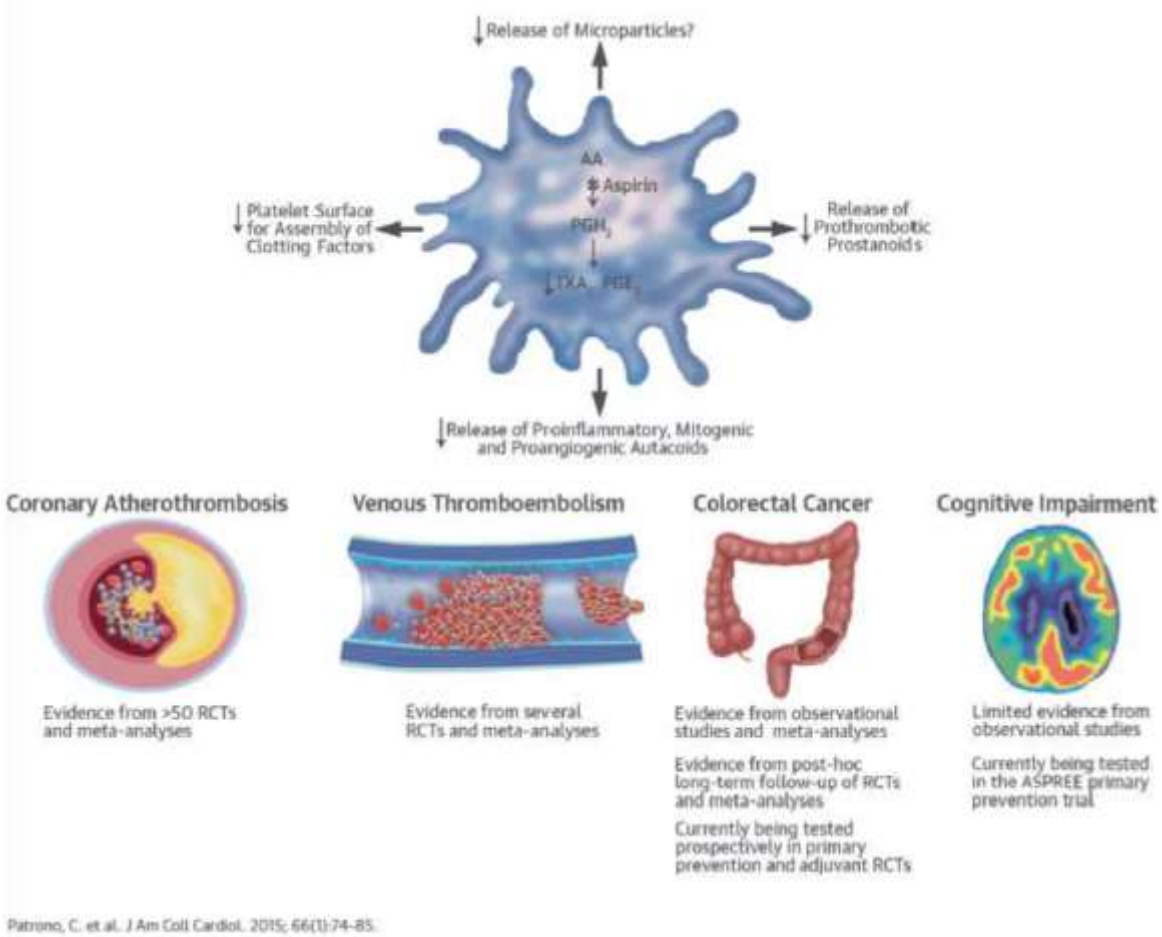
Ακετυλοσαλικυλικό οξύ



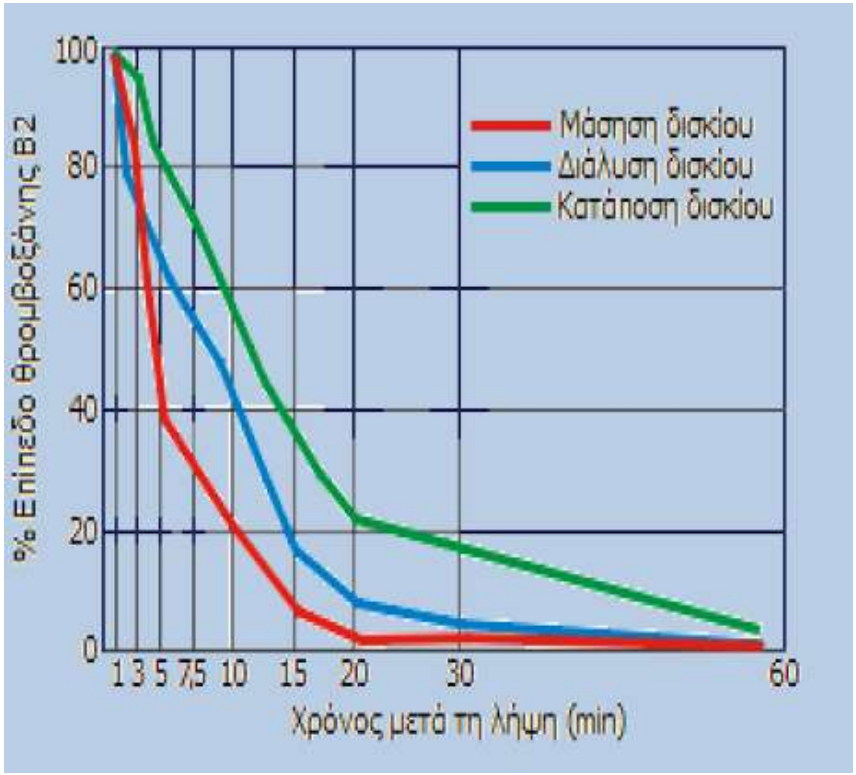
Ασπιρίνη και αιμοπετάλια

- Τα αιμοπετάλια είναι ιδιαίτερα ευαίσθητα στη δράση της ασπιρίνης.
- Αυτό οφείλεται στο ότι, σε αντίθεση με άλλα κύτταρα, **τα αιμοπετάλια δεν έχουν την ικανότητα να επαναπαράγουν κυκλοοξυγονάσες.**
- Στην πράξη αυτό σημαίνει, ότι μία δόση μόλις 40 mg ασπιρίνης θα αναστείλει την κυκλοοξυγονάση των αιμοπεταλίων **για 5 έως 10 ημέρες, που** είναι ο μέσος χρόνος ζωής τους

Αναστολή PLT με μικρές δόσεις ασπιρίνης

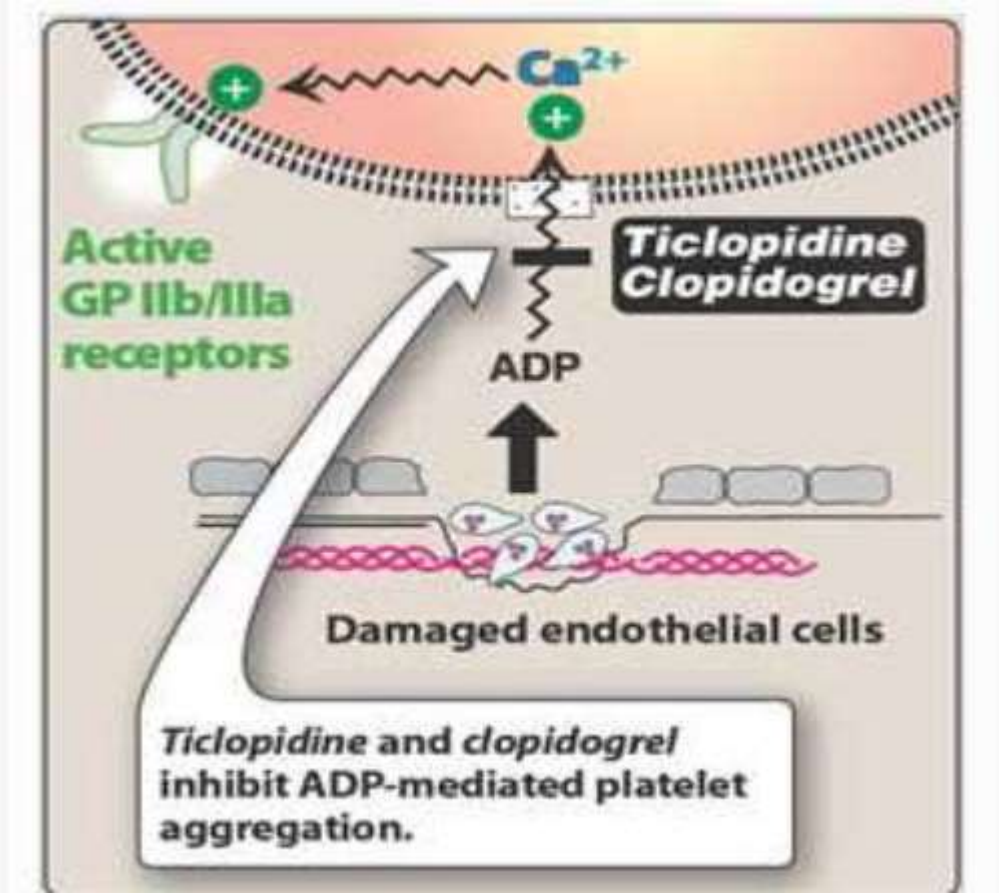


Patrono, C. et al. J Am Coll Cardiol. 2015; 66(1):74-85.



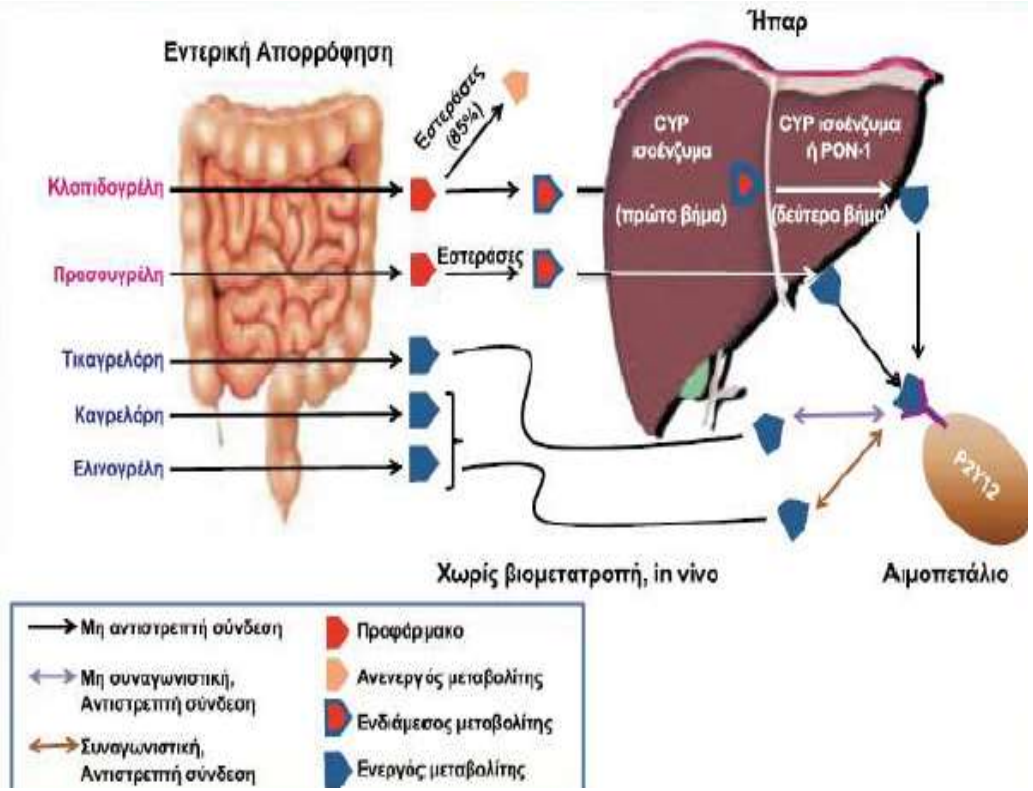
- ✓ Χαμηλές δόσεις ασπιρίνης για μεγάλο χρονικό διάστημα διακόπτουν τον σχηματισμό θρομβοξάνης Α2 (ΤΧΑ2) στα PLT, αναστέλλοντας τη συσσώρευση των PLT
- ✓ **Καθημερινές δόσεις μόλις 40 mg ασπιρίνης** παρεμποδίζουν σε μεγάλο ποσοστό την απελευθέρωση ΤΧΑ2, **ενώ η βιοσύνθεση της χρήσιμης προσταγλανδίνης Ι2 (προστακυκλίνη: δραστικός** αντιθρομβωτικός και αγγειοδιασταλτικός παράγοντας) **επηρεάζεται ελάχιστα**
- ✓ Ωστόσο, **σοβαρή αρνητική επίπτωση της** μακροχρόνιας λήψης ασπιρίνης είναι η μείωση της πηκτικής ικανότητας του αίματος **και η αύξηση της πιθανότητας αιμορραγικών επεισοδίων ανάλογα με** τις λαμβανόμενες δόσεις

Ανταγωνιστές υποδοχέων ADP



Ανταγωνιστές υποδοχέων ADP

- ✓ **Τικλοπιδίνη**
- ✓ **Κλοπιδογρέλη**
- ✓ **Πρασουγρέλη**
- ✓ **Τικαγρελόρη**
- ✓ Καγρελόρη
- ✓ Ελινογρέλη



Τι ισχύει στην πρωτογενή πρόληψη;

Design and eligibility criteria of primary prevention trials

	Dates of recruitment	Participating countries	Year of main publication	Number of participants	Mean duration of follow-up (years)	Target population	Eligible age range (years) at entry	Aspirin regimen	Randomised factorial comparison	Placebo control
British Doctors' Study[33]	Nov 1978–Nov 1979	UK	1988	5139	5·6	Male doctors	19–90	500 mg daily	None	No
US Physicians' Health Study[42]	Aug 1981–Apr 1984	USA	1988	22071	5·0	Male doctors	45–73	325 mg alternate days	β carotene vs placebo	Yes
Thrombosis Prevention Trial[8]	Feb 1989–May 1994	UK	1998	5085	6·7	Men with risk factors for CHD	45–69	75 mg daily	Warfarin vs placebo	Yes
Hypertension Optimal Treatment Trial[12]	Oct 1992–May 1994	Europe, North and South America, Asia	1998	18790	3·8	Men and women with DBP 100–115 mm Hg	50–80	75 mg daily	Three blood pressure regimens	Yes
Primary Prevention Project[13]	June 1993–Apr 1998	Italy	2001	4495	3·7	Men and women with one or more risk factors for CHD	45–94	100 mg daily	Vitamin E vs open control	No
Women's Health Study[14]	Sep 1992–May 1995	USA	2005	39876	10·0	Female health professionals	≥45	100 mg alternate days	Vitamin E vs placebo	Yes

CHD=coronary heart disease. DBP=diastolic blood pressure.

Antithrombotic Trialists' (ATT) Collaboration **Lancet 2009; 373: 1849–60**

Diabetes in “primary prevention” Antiplatelet agents

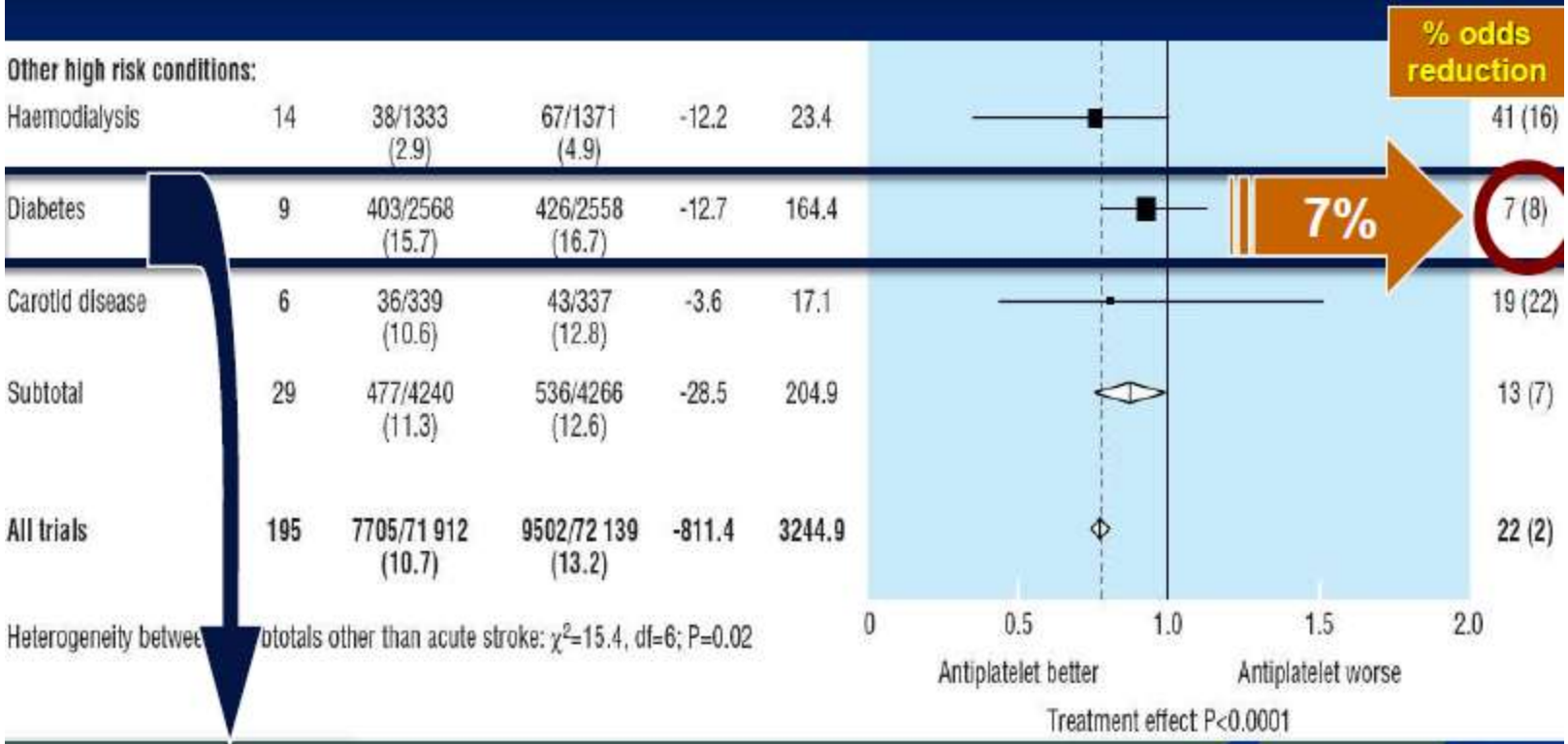
The proportion of diabetic patients in primary prevention studies is SMALL.

- PPP: 17%
- HOT: 8%
- PHS: 2%
- BMD: 2%
- TPT: 2%

< 20 %

Hayden M et al. U.S. Preventive Services Task Force. Ann Intern Med. 2002;136:161-172

Diabetes in"primary prevention": Antiplatelet agents "Antithrombotic Trialists Collaboration" 2002



Much of the new information comes from the early treatment diabetic retinopathy study, in which 3711 people with diabetes (and, generally, no history of myocardial infarction or stroke) were allocated to receive 650 mg aspirin dailyor placebo.

BMJ 2002, vol 24: 71-86

Ασπιρίνη και πρωτογενής πρόληψη στο ΣΔ …JPAD

JAMA®

Online article and related content current as of November 9, 2008.

Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial

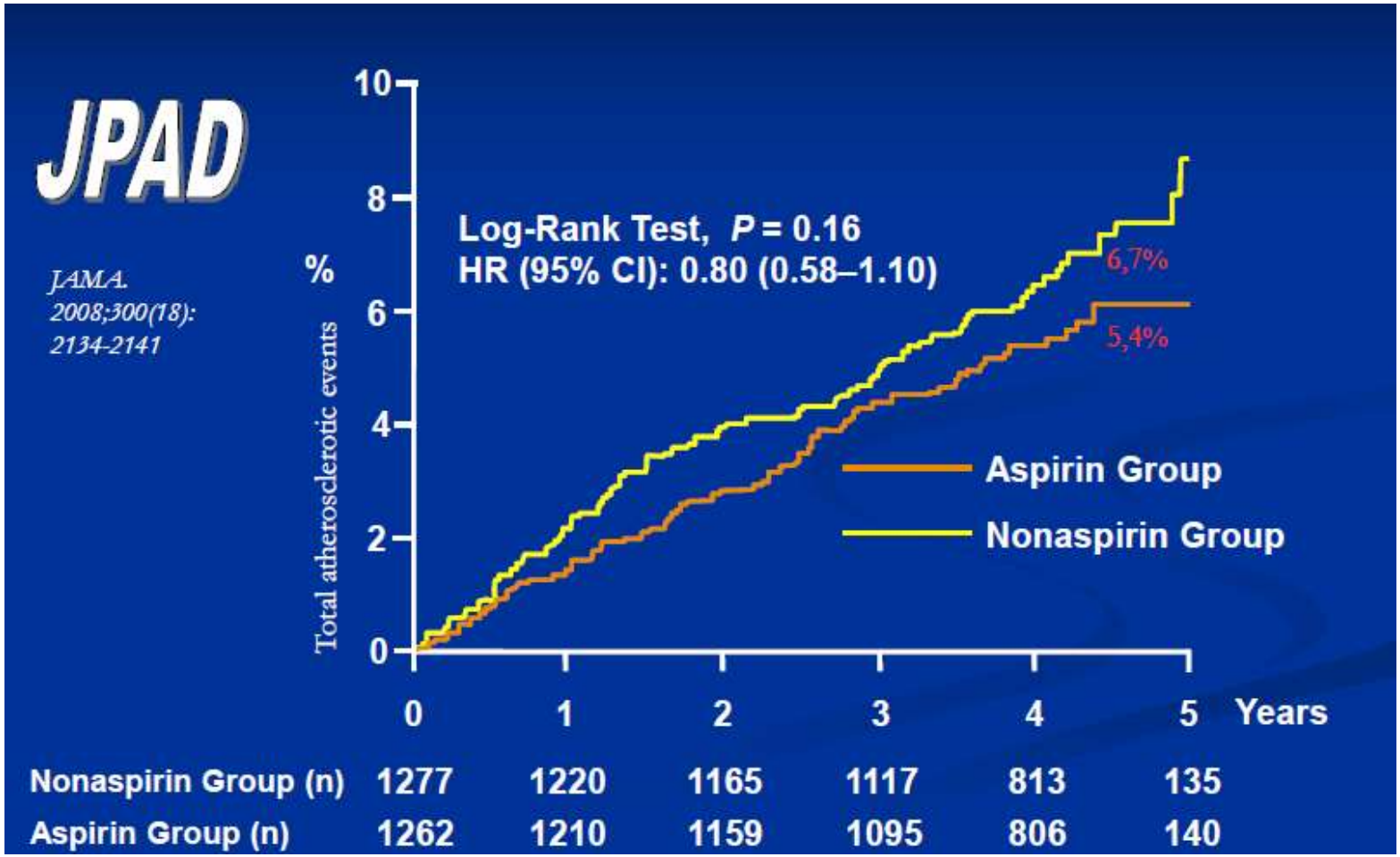
Hisao Ogawa; Masafumi Nakayama; Takeshi Morimoto; et al.

JAMA. published online Nov 9, 2008; (doi:10.1001/jama.2008.623)

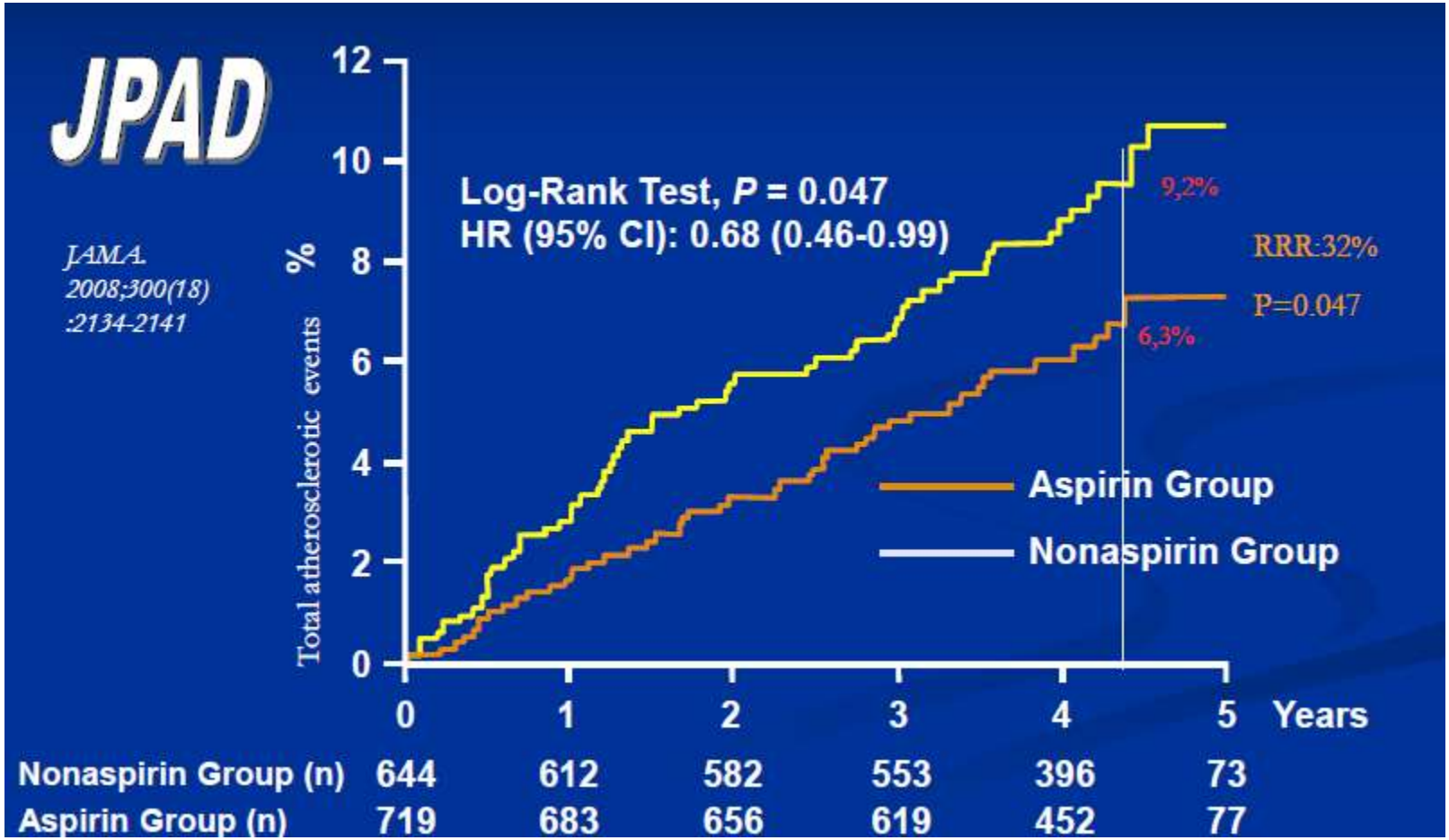
Clinical outcomes	HR (95% CI)	p
Primary end point*	0.80 (0.58–1.10)	0.16
Fatal coronary or cerebrovascular events	0.10 (0.01–0.79)	0.0037
All-cause mortality	0.90 (0.57–1.14)	0.67
Atherosclerotic events* (among age >65 y)	0.68 (0.46–0.99)	0.047

*Composite of sudden death; death from coronary, cerebrovascular, or aortic causes; nonfatal MI, unstable angina, new exertional angina; nonfatal ischemic or hemorrhagic stroke; transient ischemic attack; or nonfatal aortic or peripheral vascular disease

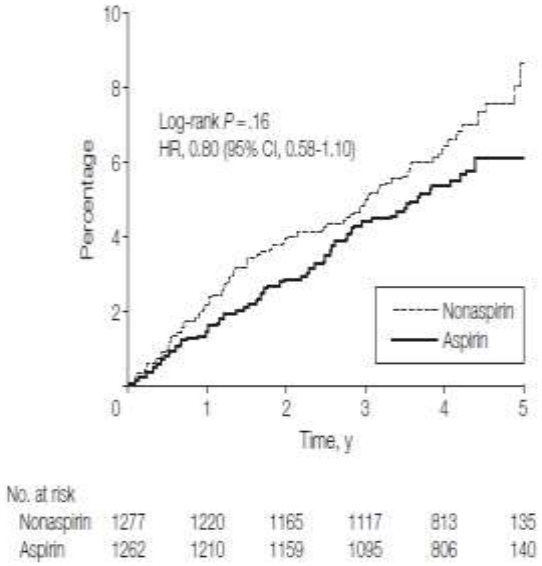
Primary End Point: Total Atherosclerotic Events According to the Treatment Groups

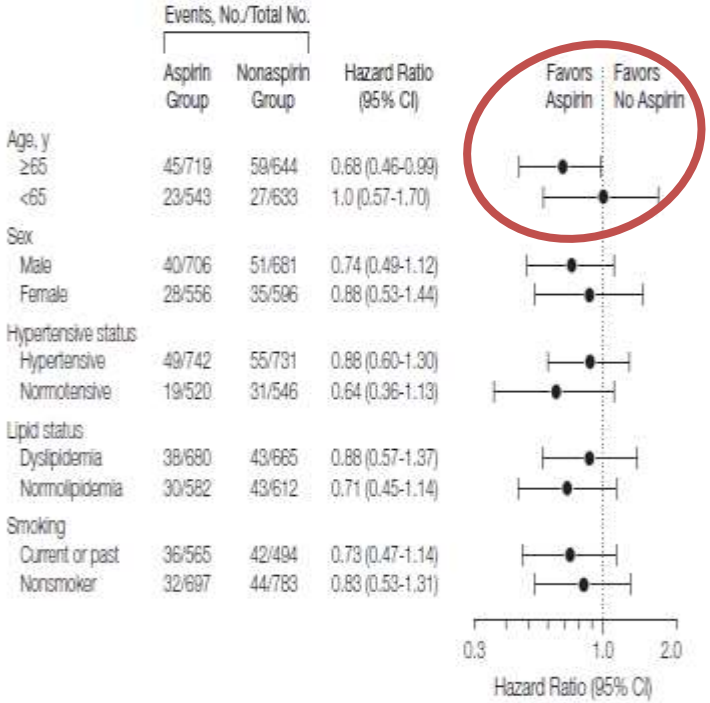


Total Atherosclerotic Events According to the Treatment Groups: Subgroup Aged 65 Years or Older



Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes





Conclusion In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

JAMA. 2008;300(18):2134-2141

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

10-Year Follow-Up of a Randomized Controlled Trial

Yoshihiko Saito, MD, PhD
Sadanori Okada, MD, PhD
Hisao Ogawa, MD, PhD
Hirofumi Soejima, MD, PhD
Mio Sakuma, MD, PhD
Masafumi Nakayama, MD, PhD
Naofumi Doi, MD, PhD
Hideaki Jinnouchi, MD, PhD
Masako Waki, MD, PhD
Izuru Masuda, MD, PhD
Takeshi Morimoto, MD, PhD
For the JPAD Trial Investigators

BACKGROUND: The long-term efficacy and safety of low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus are still inconclusive.

METHODS: The JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) was a randomized, open-label, standard care–controlled trial examining whether low-dose aspirin affected cardiovascular events in 2539 Japanese patients with type 2 diabetes mellitus and without preexisting cardiovascular disease. Patients were randomly allocated to receive aspirin (81 or 100 mg daily; aspirin group) or no aspirin (no-aspirin group) in the JPAD trial. After that trial ended in 2008, we followed up with the patients until 2015, with no attempt to change the previously assigned therapy. Primary end points were cardiovascular events, including sudden death, fatal or nonfatal coronary artery disease, fatal or nonfatal stroke, and peripheral vascular disease. For the safety analysis, hemorrhagic events, consisting of gastrointestinal bleeding, hemorrhagic stroke, and bleeding from any other sites, were also analyzed. The primary analysis was conducted for cardiovascular events among patients who retained their original allocation (a per-protocol cohort). Analyses on an intention-to-treat cohort were conducted for hemorrhagic events and statistical sensitivity.

RESULTS: The median follow-up period was 10.3 years; 1621 patients (64%) were followed up throughout the study; and 2160 patients (85%) retained their original allocation. Low-dose aspirin did not reduce cardiovascular events in the per-protocol cohort (hazard ratio, 1.14; 95% confidence interval, 0.91–1.42). Multivariable Cox proportional hazard model adjusted for age, sex, glycemic control, kidney function, smoking status, hypertension, and dyslipidemia showed similar results (hazard ratio, 1.04; 95% confidence interval, 0.83–1.30), with no heterogeneity of efficacy in subgroup analyses stratified by each of these factors (all interaction $P>0.05$). Sensitivity analyses on the intention-to-treat cohort yielded consistent results (hazard ratio, 1.01; 95% confidence interval, 0.82–1.25). Gastrointestinal bleeding occurred in 25 patients (2%) in the aspirin group and 12 (0.9%) in the no-aspirin group ($P=0.03$), and the incidence of hemorrhagic stroke was not different between groups.

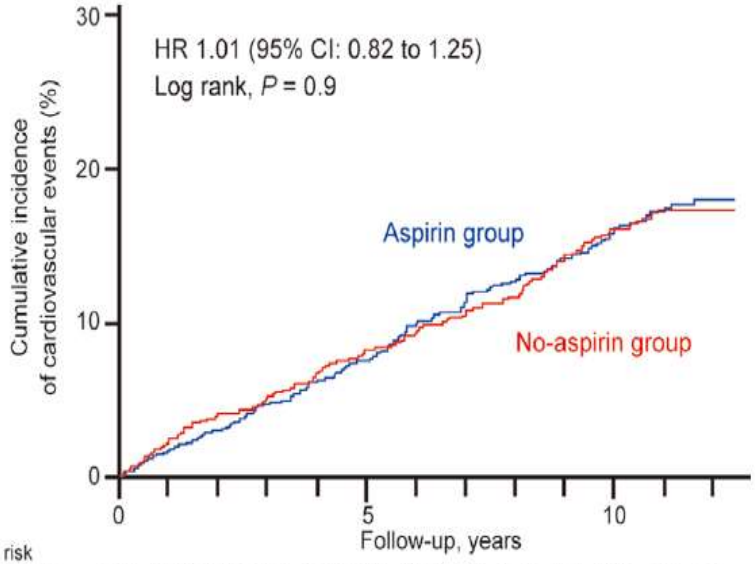
CONCLUSIONS: Low-dose aspirin did not affect the risk for cardiovascular events but increased risk for gastrointestinal bleeding in patients with type 2 diabetes mellitus in a primary prevention setting.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00110448.

Correspondence to: Yoshihiko Saito, MD, PhD, First Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara, Japan 634-8522. E-mail yssaito@naramed-u.ac.jp

Sources of Funding, see page 667

Key Words: aspirin ■ diabetes mellitus ■ hemorrhage ■ primary prevention



CONCLUSIONS

The posttrial follow-up of the JPAD trial, comprising a mean observation during and after the trial of >1 decade, indicated that long-term therapy with low-dose aspirin is not associated with lower cardiovascular events in Japanese patients with type 2 diabetes mellitus in a primary prevention setting. On the other hand, low-dose aspirin therapy was associated with and significantly increased the incidence of gastrointestinal bleeding.

Circulation. 2017;135:659–670. DOI: 10.1161/CIRCULATIONAHA.116.025760

Ασπιρίνη και ΣΔ και ΠΑΝ (POPADAD trial)

BMJ

RESEARCH

The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease

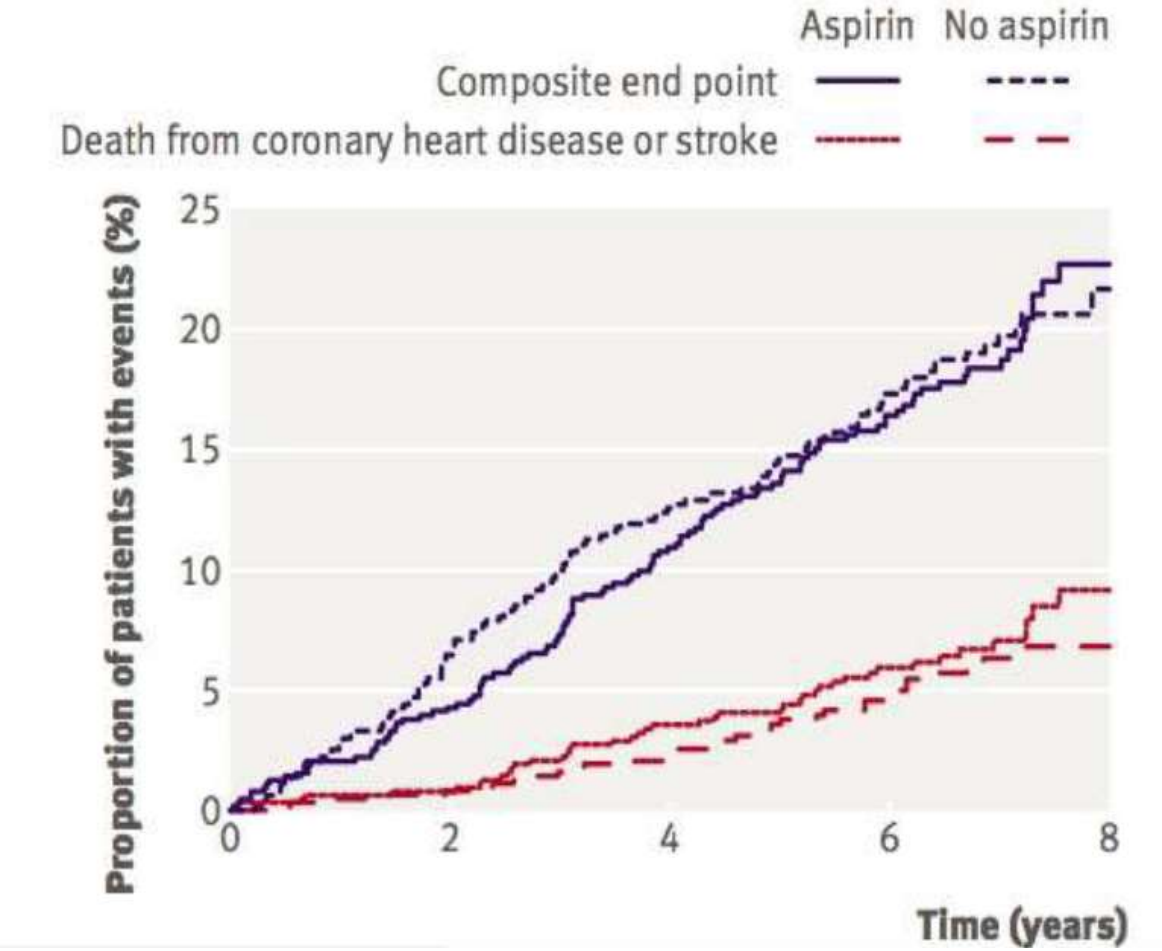
Belch J et al. BMJ 2008

Ασπιρίνη και ΣΔ και ΠΑΝ (POPADAD trial)

Table 1 | Baseline characteristics. Values are medians (interquartile ranges) unless stated otherwise

Characteristics	Aspirin plus antioxidant (n=320)	Aspirin plus placebo (n=318)	Placebo plus antioxidant (n=320)	Placebo plus placebo (n=318)
Mean (SD) age (years)	61.0 (10.0)	60.0 (10.1)	60.0 (10.3)	60.1 (9.7)
No (%) women	169 (53)	183 (58)	181 (57)	180 (57)
Time since diagnosis of diabetes (years)	6.7 (2.9-12.9)	6.0 (2.7-13.0)	5.7 (2.4-11.7)	6.4 (2.6-11.6)
No (%) treated with insulin	107 (33)	112 (35)	96 (30)	91 (29)
Ankle brachial pressure index	0.90 (0.82-0.95)	0.91 (0.84-0.95)	0.89 (0.81-0.94)	0.90 (0.83-0.96)
Mean (SD) HbA_{1c} level (%)	8.0 (1.8)	8.0 (1.7)	7.9 (1.8)	7.9 (1.7)

Asymptomatic “PAD” and diabetes
ASA ineffective (but ABI 0.9…)



Belch J et al. BMJ 2008

BMJ

RESEARCH

Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials

Giorgia De Berardis, research officer,[1] Michele Sacco, research officer,[1] Giovanni F M Strippoli, editor and regional coordinator of the Cochrane Renal Group,[1,2] Fabio Pellegrini, senior biostatistician,[1] Giusi Graziano, biostatistician,[1] Gianni Tognoni, institute director,[3] Antonio Nicolucci, department head[1]

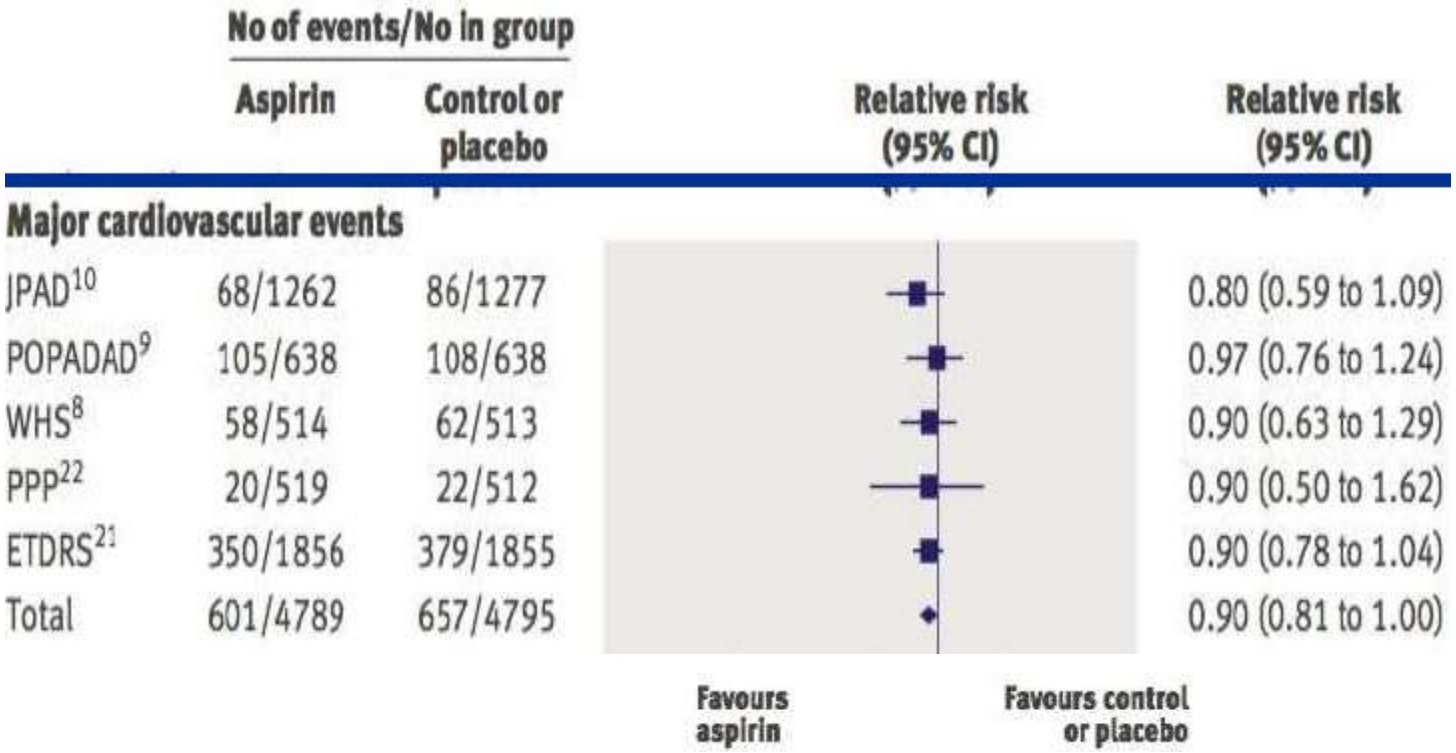
De Berardis G et al. BMJ 2009; 399

Meta-analysis in primary prevention 2009
ASA and diabetes: Studies, dose and Tx duration

Table 1 | Design of trials of aspirin therapy included in meta-analysis

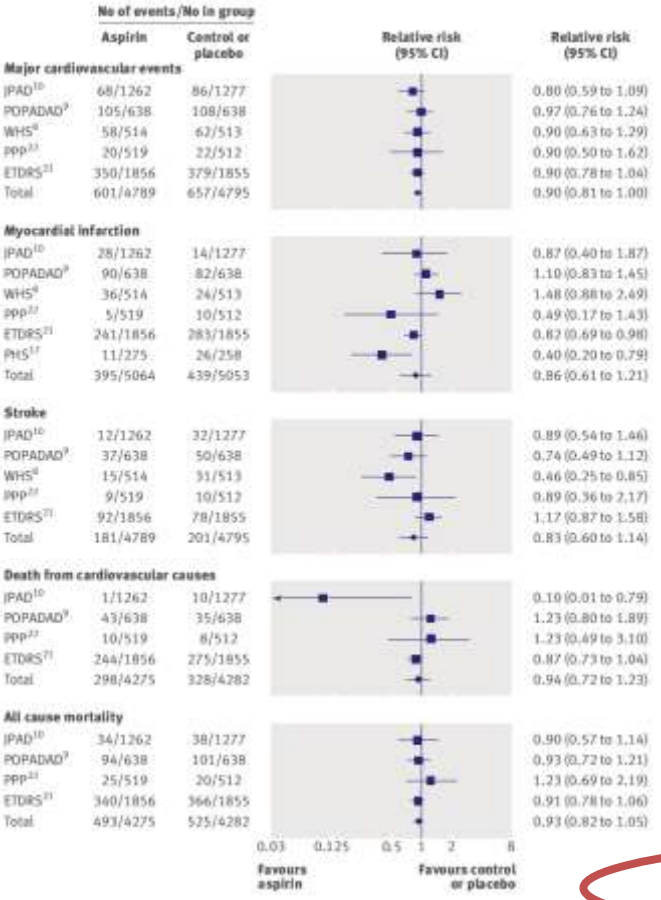
Features	PHS 1989[17]	ETDRS 1992[21]	PPP 2003[22]	WHS 2005[8]	POPADAD 2008[9]	JPAD 2008[10]
Country	USA	USA	Italy	USA	Scotland	Japan
Type of trial	Primary	Mixed	Primary	Primary	Primary	Primary
Study design	Randomised double blind, placebo controlled trial	Randomised double blind, placebo controlled trial	Randomised open trial with 2×2 factorial design	Randomised double blind, 2×2 factorial, placebo controlled trial	Randomised double blind, 2×2 factorial, placebo controlled trial	Randomised open labe controlled trial with blinded end point assessment
Patient population	Healthy men	Men and women with type 1 and type 2 diabetes	Men and women aged >50 with ≥1 risk factors for cardiovascular disease	Healthy women	Patients aged ≥40 years with type 1 or type 2 diabetes and an ankle brachial pressure index ≤0.99 but no symptomatic cardiovascular disease	Patients with type 2 diabetes without histo of atherosclerotic disea
Aspirin dose	325 mg every other day	650 mg/day	100 mg/day	100 mg every other day	100 mg/day	81 or 100 mg per day
No of people with diabetes (% of sample where appropriate)	533 (2.4)	3711	1031	1027 (2.6)	1276	2539
Duration of therapy (years)	5	5	3.6	10.1	6.7	4.37

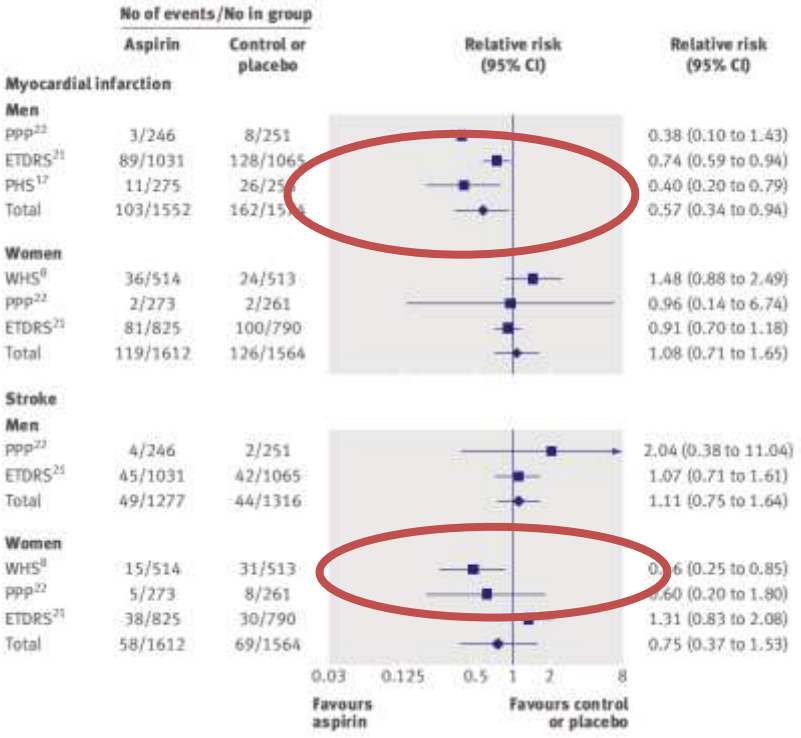
Meta-analysis in primary prevention 2009 ASA and diabetes: Major CV events



De Berardis G et al. BMJ 2009; 399

Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials





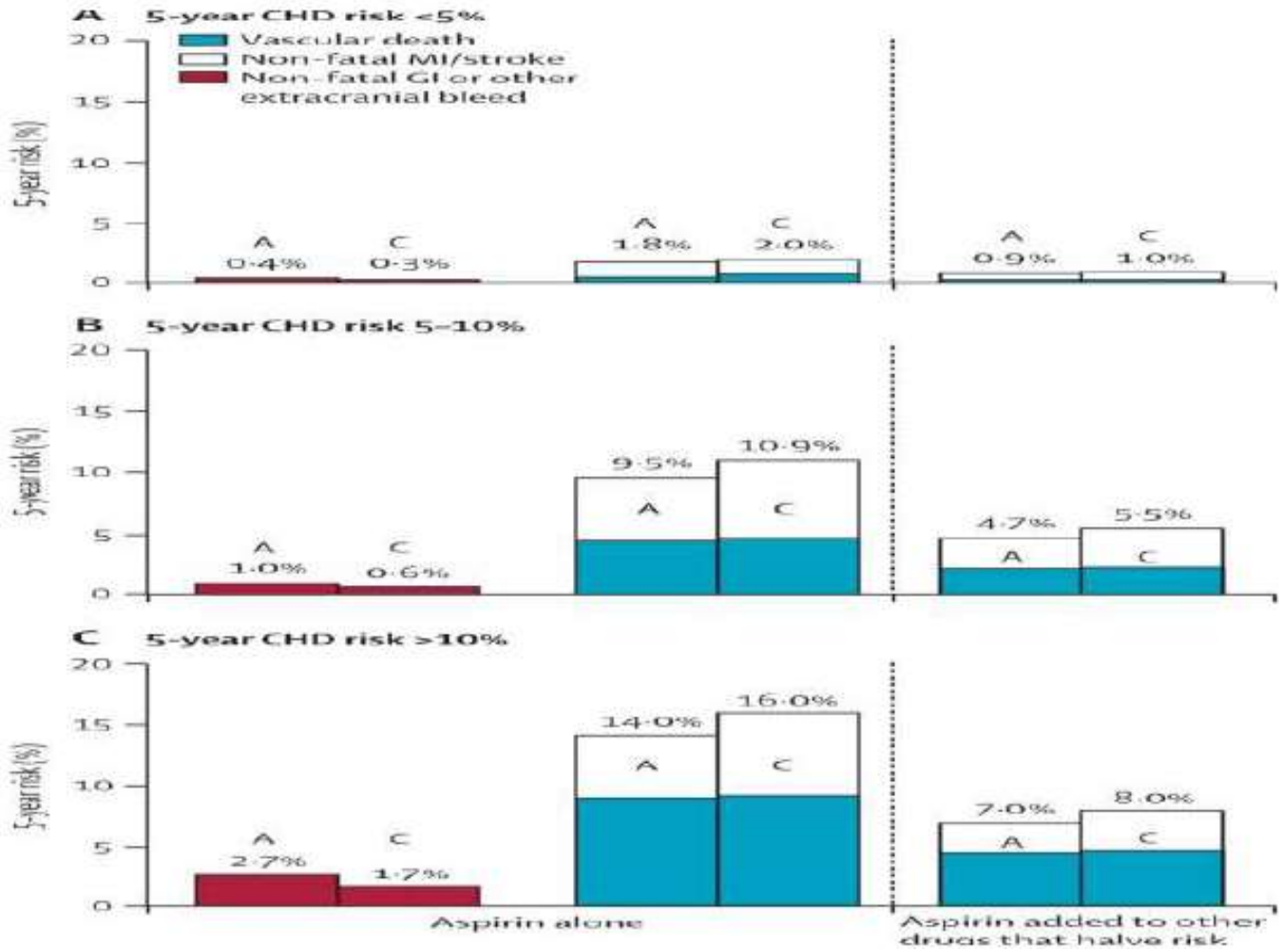
This meta-analysis suggests that the benefit of aspirin in the primary prevention of major cardiovascular events or death in people with diabetes may be lower than in other high risk populations

Aspirin significantly reduced the risk of myocardial infarction in men by 43%, whereas no benefit was found in women

The expected benefits of aspirin in people with diabetes might not exceed the risk of major bleedings, particularly among those at low cardiovascular risk (<20% over 10 years), or among older patients (>70 years) at high risk of bleeding

BMJ 2009;339:b4531

ASA in primary prevention trials



Antithrombotic Trialist Collaboration Lancet 2009;373:1849-60

Κατευθυντήριες οδηγίες ADA 2017 (Πρωτογενής πρόληψη)

Ασπιρίνη (75 – 162 mg) σε άτομα με ΣΔ τύπου 1 και 2 και αυξημένο καρδιαγγειακό κίνδυνο (10ετή κίνδυνο>10%)

-Άνδρες >50 χρόνων

-Γυναίκες > 60 χρόνων

-με τουλάχιστον ακόμη ένα παράγοντα κινδύνου (κληρονομικό ΣΝ, υπέρταση, δυσλιπιδαιμία, κάπνισμα, αλβουμινουρία) (C)

Diabetes Care Volume 40, Supplement 1, January 2017 S82

Κατευθυντήριες οδηγίες ADA 2017 (Πρωτογενής πρόληψη)

Ασπιρίνη δεν συνιστάται σε ενήλικες με ΣΔ για πρόληψη ΣΝ με μικρό ΚΑ κίνδυνο

(10ετής ΚΑ κίνδυνος < 5 %)

-Άνδρες < 50 χρόνων

-Γυναίκες < 60 χρόνων

-χωρίς άλλο σοβαρό παράγοντα ΚΑ κινδύνου

-Ο κίνδυνος από αιμορραγία είναι μεγαλύτερος του οφέλους (C)

Diabetes Care Volume 40, Supplement 1, January 2017 S82

Κατευθυντήριες οδηγίες ADA 2017 (Πρωτογενής πρόληψη)

Σε ασθενείς που ανήκουν σε αυτές τις ηλικιακές ομάδες και έχουν άλλους παράγοντες κινδύνου (10ετής ΚΑ κίνδυνος 5-10 %) συνιστάται κλινική εκτίμηση (Ε)

Diabetes Care Volume 40, Supplement 1, January 2017 S82

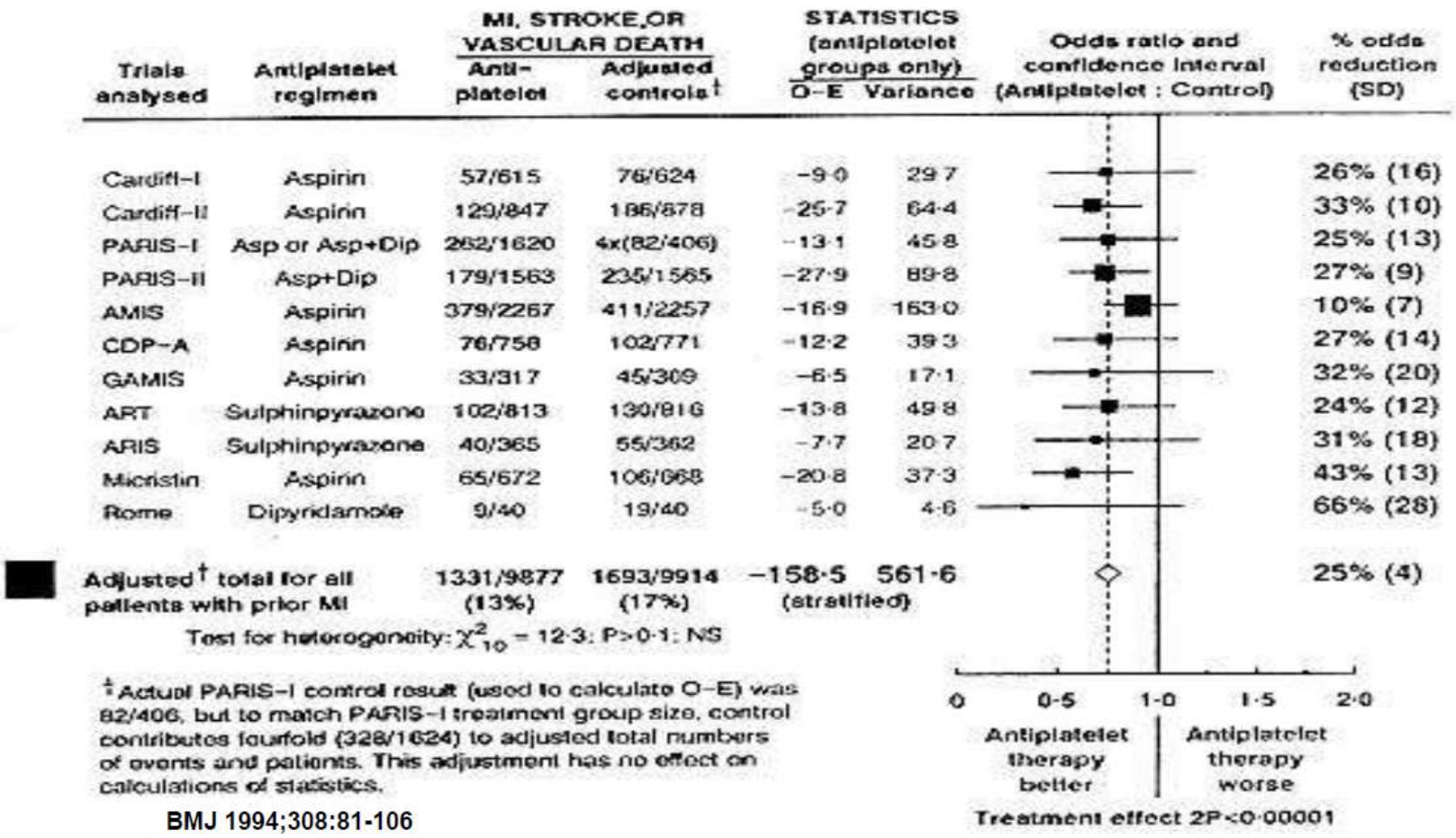
Δευτερογενής πρόληψη

Antithrombotic Trialists Collaboration(ATT)

Καθιέρωσε την χορήγηση αντιαιμοπεταλιακής αγωγής μετά ΟΕΜ, ΑΕΕ ή ΤΙΑ.

287 μελέτες, 212.000 ασθενείς υψηλού κινδύνου(οξεία ή προϋπάρχουσα αγγειακή νόσο ή άλλες υπάρχουσες καταστάσεις που υποδηλώνουν υψηλό κίνδυνο για αποφρακτική αγγειακή νόσο)

Proportional effects on vascular events (myocardial infarction, stroke, or vascular death) in 11 randomised trials of prolonged antiplatelet therapy (for one month or more) versus control in patients with prior myocardial infarction.



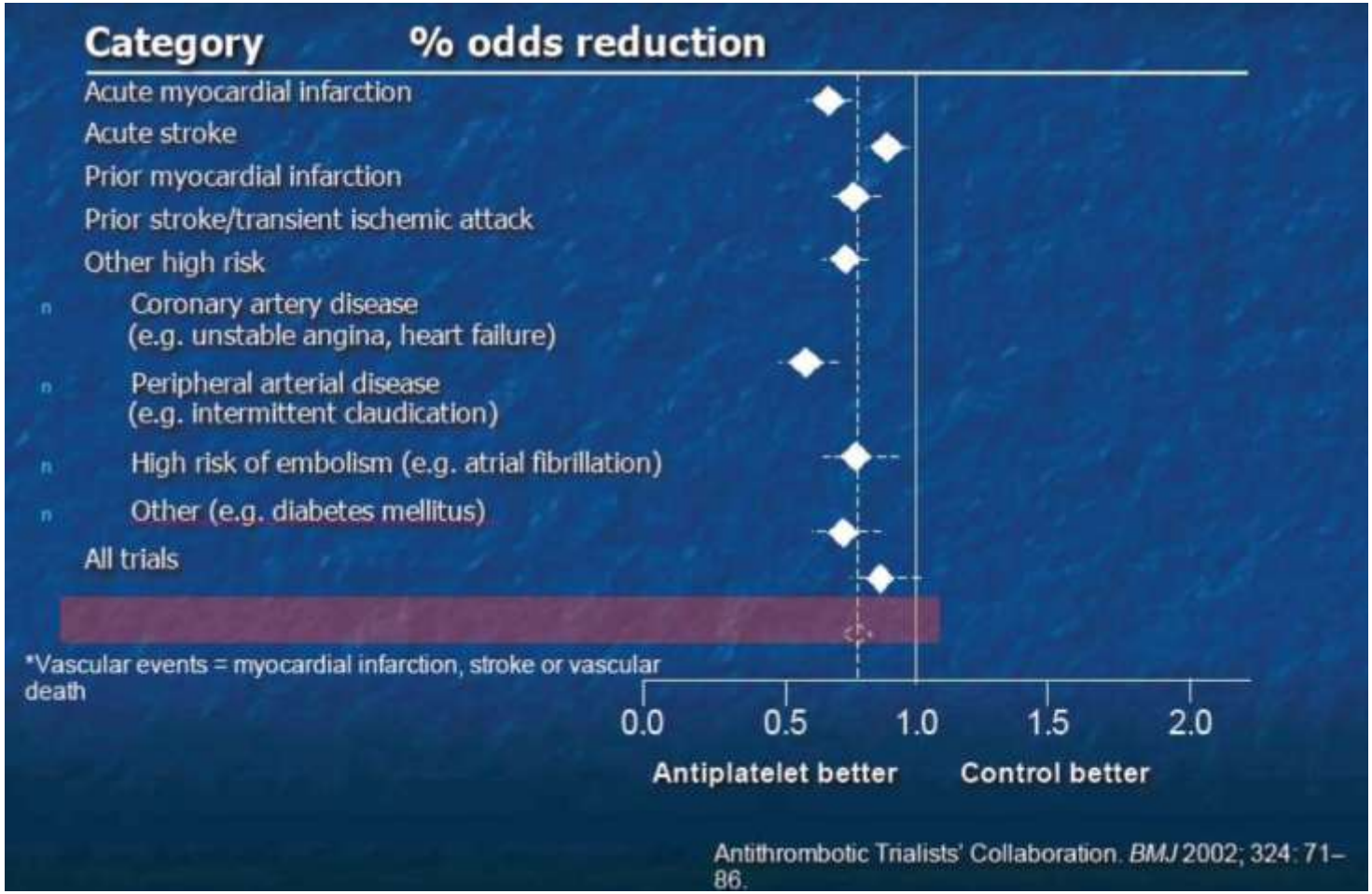
Trials analysed	Antiplatelet regimen	MI, STROKE, OR VASCULAR DEATH: Anti-platelet	MI, STROKE, OR VASCULAR DEATH: Adjusted controls†	STATISTICS (antiplatelet groups only): O-E	STATISTICS (antiplatelet groups only): Variance	Odds ratio and confidence interval (Antiplatelet : Control)	% odds reduction (SD)
Cardiff-I	Aspirin	57/615	76/624	−9·0	29·7		26% (16)
Cardiff-II	Aspirin	129/847	186/878	−25·7	64·4		33% (10)
PARIS-I	Asp or Asp+Dip	262/1620	4x(82/406)	−13·1	45·8		25% (13)
PARIS-II	Asp+Dip	179/1563	235/1565	−27·9	89·8		27% (9)
AMIS	Aspirin	379/2267	411/2257	−16·9	163·0		10% (7)
CDP-A	Aspirin	76/758	102/771	−12·2	39·3		27% (14)
GAMIS	Aspirin	33/317	45/309	−6·5	17·1		32% (20)
ART	Sulphinpyrazone	102/813	130/816	−13·8	49·8		24% (12)
ARIS	Sulphinpyrazone	40/365	55/362	−7·7	20·7		31% (18)
Micristin	Aspirin	65/672	106/668	−20·8	37·3		43% (13)
Rome	Dipyridamole	9/40	19/40	−5·0	4·6		66% (28)
	Adjusted† total for all patients with prior MI	1331/9877 (13%)	1693/9914 (17%)	−158·5 (stratified)	561·6		25% (4)

Test for heterogeneity: $\chi^2_{10} = 12{\cdot}3$; P>0·1; NS

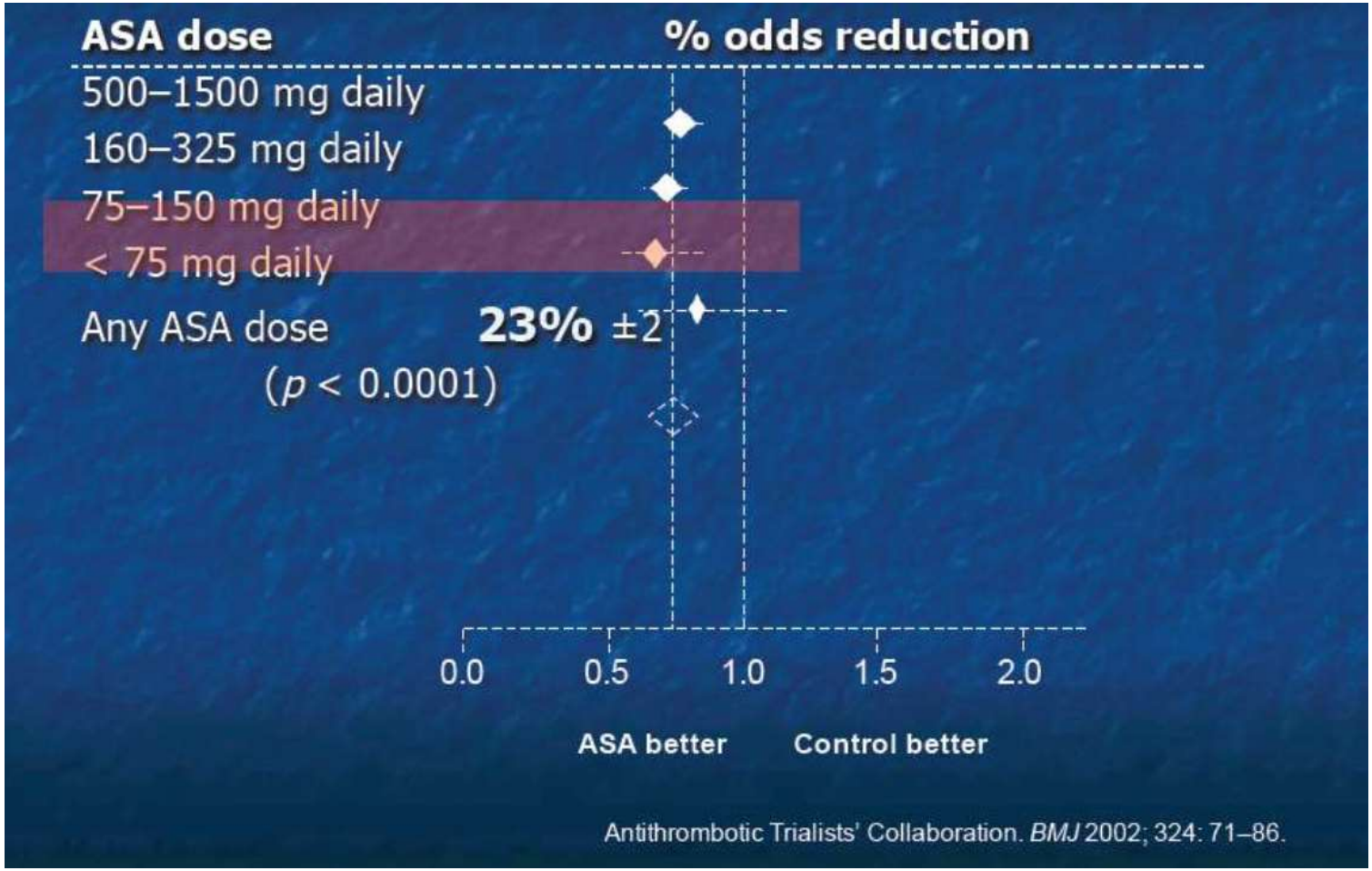
†Actual PARIS-I control result (used to calculate O-E) was 82/406, but to match PARIS-I treatment group size, control contributes fourfold (328/1624) to adjusted total numbers of events and patients. This adjustment has no effect on calculations of statistics.

BMJ 1994;308:81-106

Αποτελεσματικότητα της αντιαιμοπεταλιακής θεραπείας



Αγγειακά συμβάματα και δόση ασπιρίνης



Αδιαμφισβήτητο το όφελος από την αντιαιμοπεταλιακή αγωγή στην δευτερογενή πρόληψη των καρδιαγγειακών συμβαμάτων

Κατευθυντήριες οδηγίες ADA 2017 (Δευτερογενής πρόληψη)

- Χορήγηση ασπιρίνης για δευτερογενή πρόληψη (75–162 mg/day) σε διαβητικούς με ιστορικό καρδιοαγγειακής νόσου. (A)

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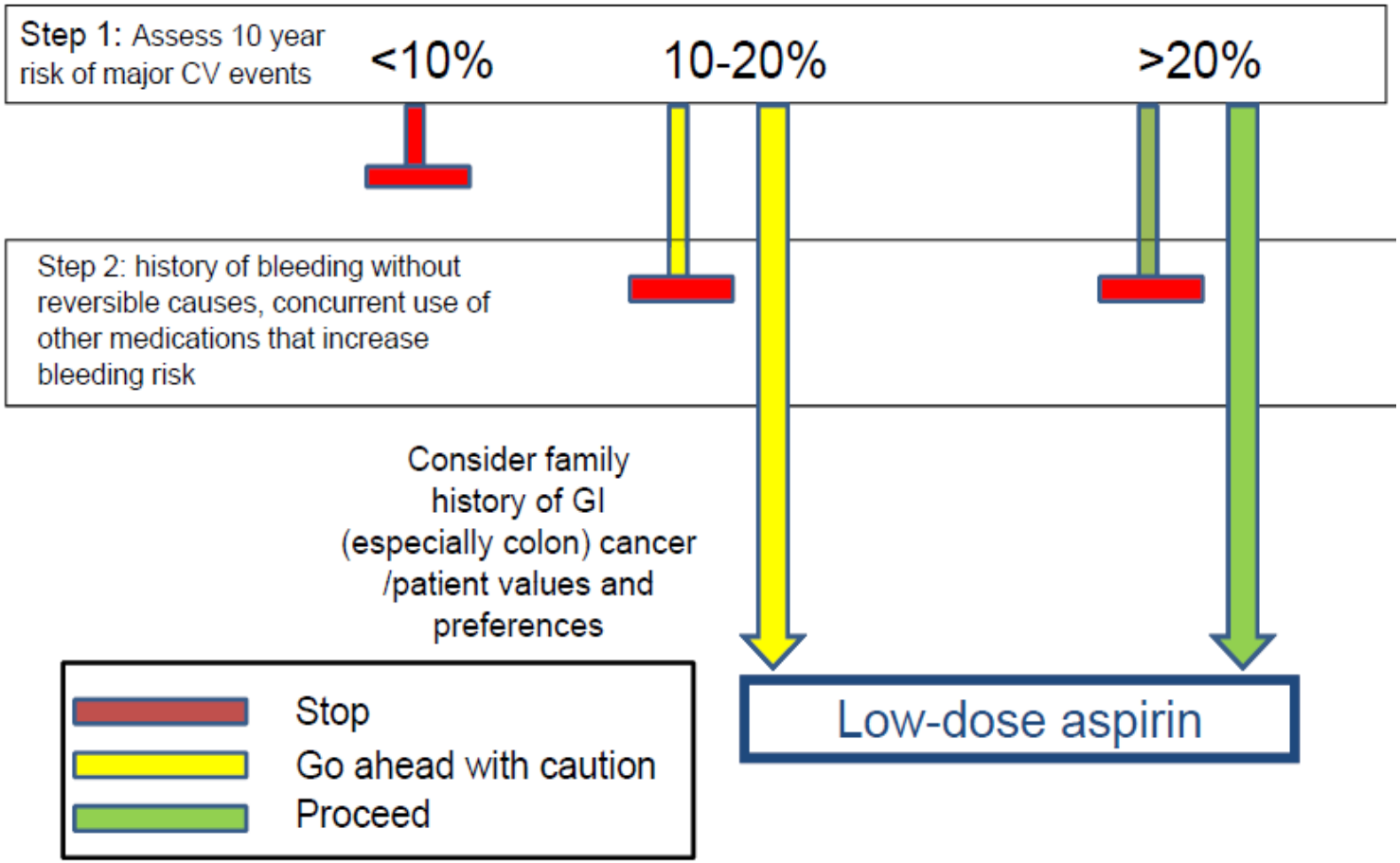
Προτεινόμενες Νέες Κατευθυντήριες οδηγίες από την Ευρωπαϊκή Καρδιολογική Εταιρία (WG on Thrombosis)



Halvorsen et al. JACC 2014

Κατευθυντήριες οδηγίες ADA 2017 (Δευτερογενής πρόληψη)

Για ασθενείς με αθηροσκληρωτική καρδιαγγειακή νόσο και τεκμηριωμένη αλλεργία στην ασπιρίνη, η κλοπιδογρέλη (75 mg / ημέρα)είναι φάρμακο εκλογής. Β

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CAPRIE Trial (Clopidogrel vs Aspirin to Prevent Recurrent Ischemic Events)

Σκοπός :να συγκρίνει την αποτελεσματικότητα και την ασφάλεια της κλοπιδογρέλης 75 mg vs ΑΣΟ 325 mg

Διπλή- τυφλή τυχαιοποιημένη προοπτική πολυκεντρική μελέτη (384 κέντρα σε 16 χώρες)

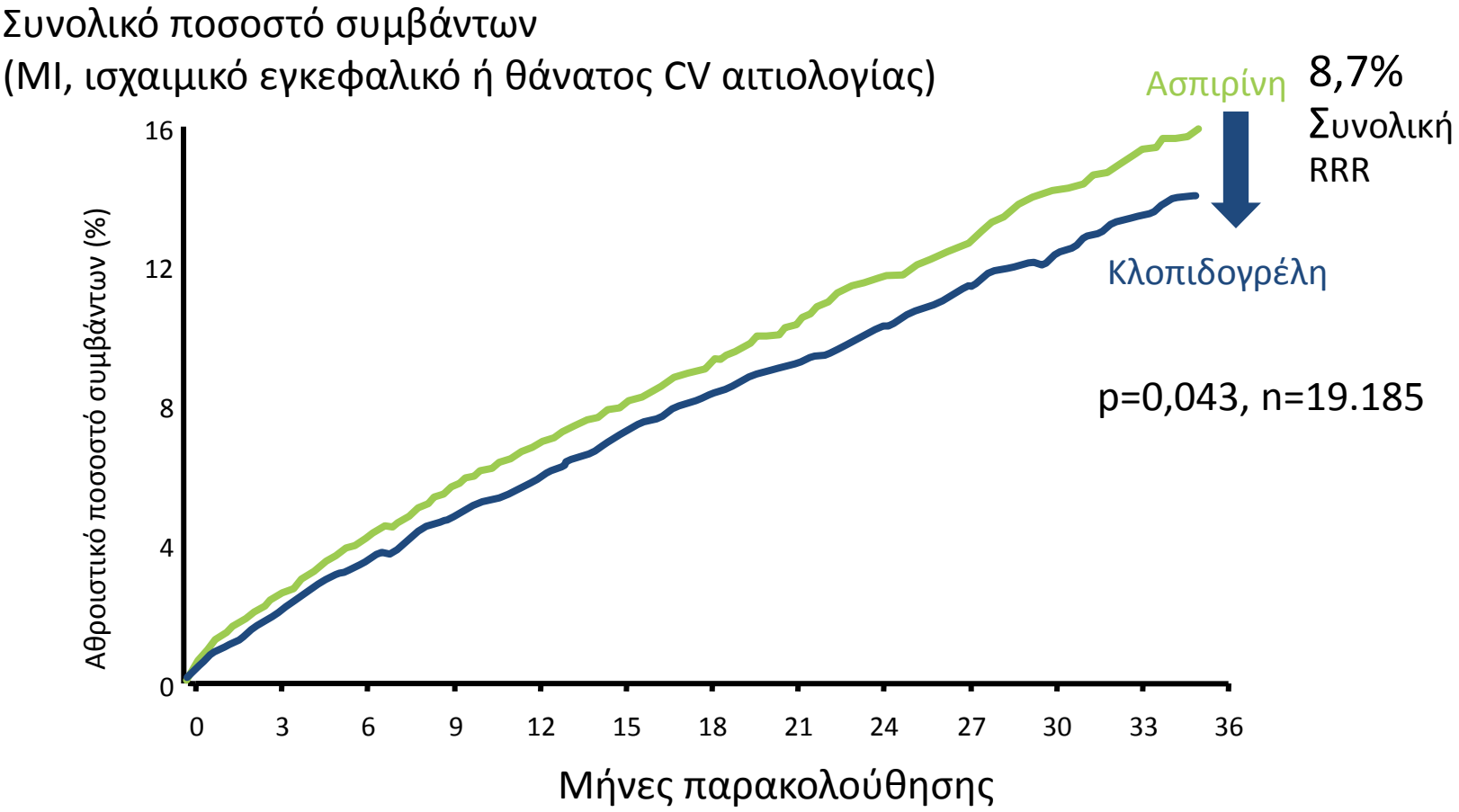
Παρακολούθηση των 19.185 ασθενών 1-3 χρόνια με: *Ισχαιμικό εγκεφαλικό επεισόδιο*

Έμφραγμα του μυοκαρδίου

Περιφερική αρτηριακή νόσο

CAPRIE Steering Comitee Lancet 1996;348:1329-39

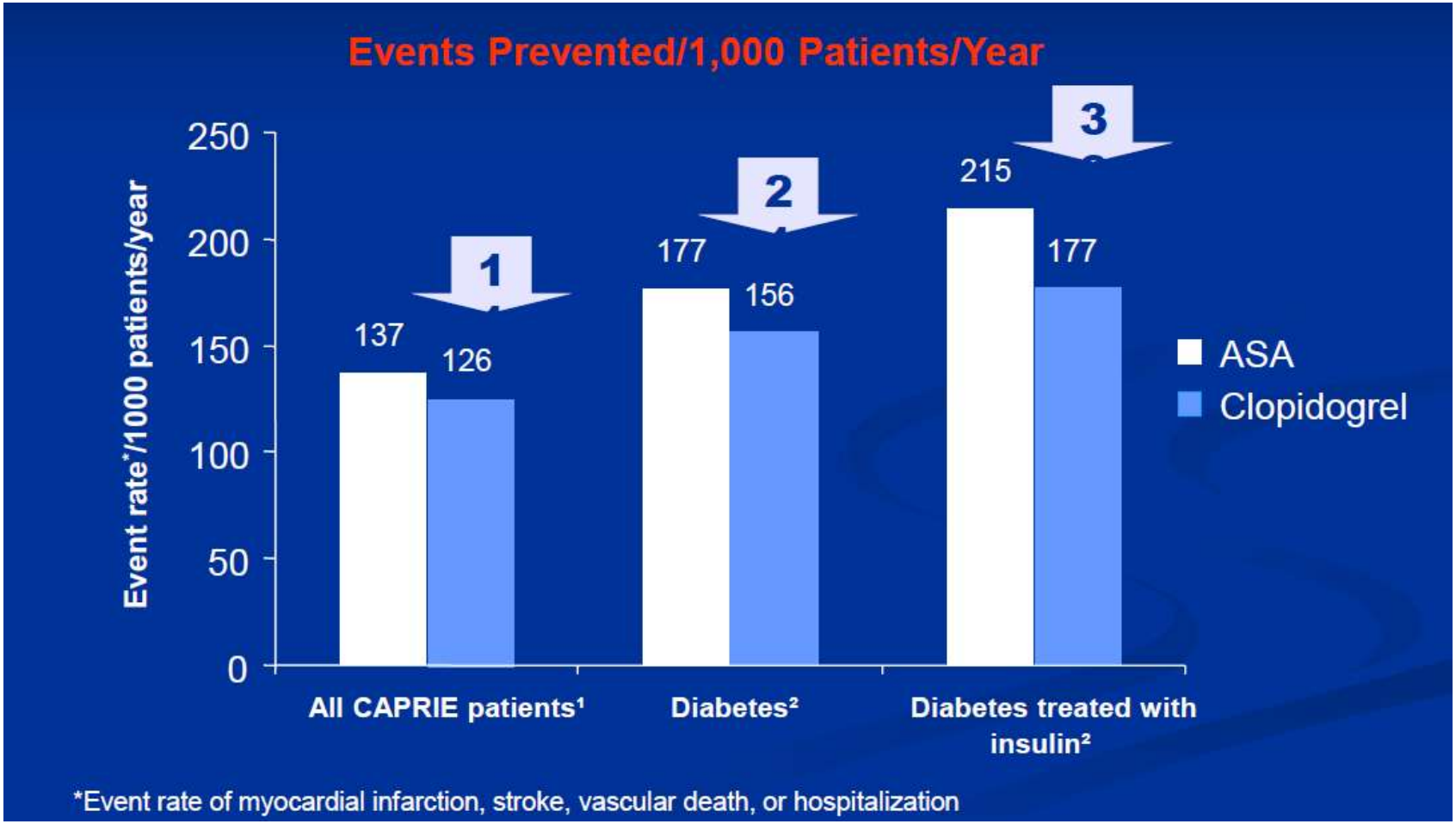
CAPRIE: 8,7% μείωση του σχετικού κινδύνου στο συνολικό πληθυσμό με την κλοπιδογρέλη



CAPRIE: Κλοπιδογρέλη έναντι ασπιρίνης σε ασθενείς με κίνδυνο ισχαιμικών επεισοδίων
Ασθενείς με MI, AEE ή PAD

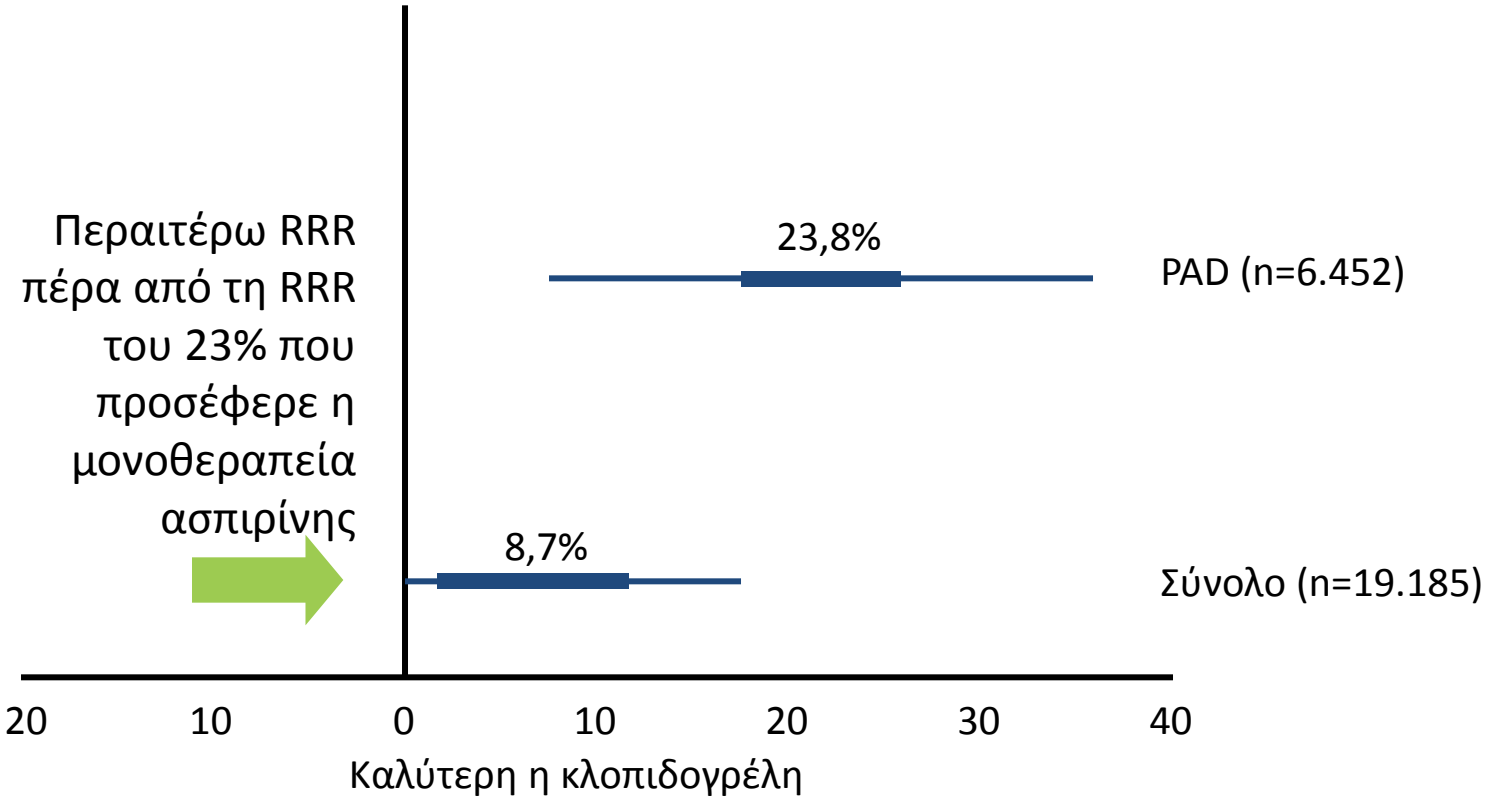
CAPRIE Steering Committee. Lancet 1996;348:1329–1339.

CAPRIE: Amplified Benefit of Clopidogrel in Patients with Diabetes



1. Bhatt DL *et al. Am Heart J 2000; 140: 67–73. 2. Jarvis B, Simpson K. Drugs 2000; 60: 347–77.*

CAPRIE: Μείωση σχετικού κινδύνου* συνολικά και σε ασθενείς με PAD†



*Συνδυασμός ισχαιμικού εγκεφαλικού επεισοδίου (IS), MI ή θανάτου αγγειακής αιτιολογίας

†Καθώς η μελέτη CAPRIE δεν είχε ισχύ για να αξιολογήσει την αποτελεσματικότητα μεμονωμένων υποομάδων, δεν είναι σαφές εάν οι διαφορές της RRR μεταξύ των νόσων βάσει των οποίων εντάχθηκαν οι ασθενείς στη μελέτη είναι πραγματικές ή τυχαίες.

CAPRIE Steering Committee. Lancet 1996;348: 1329–1339.

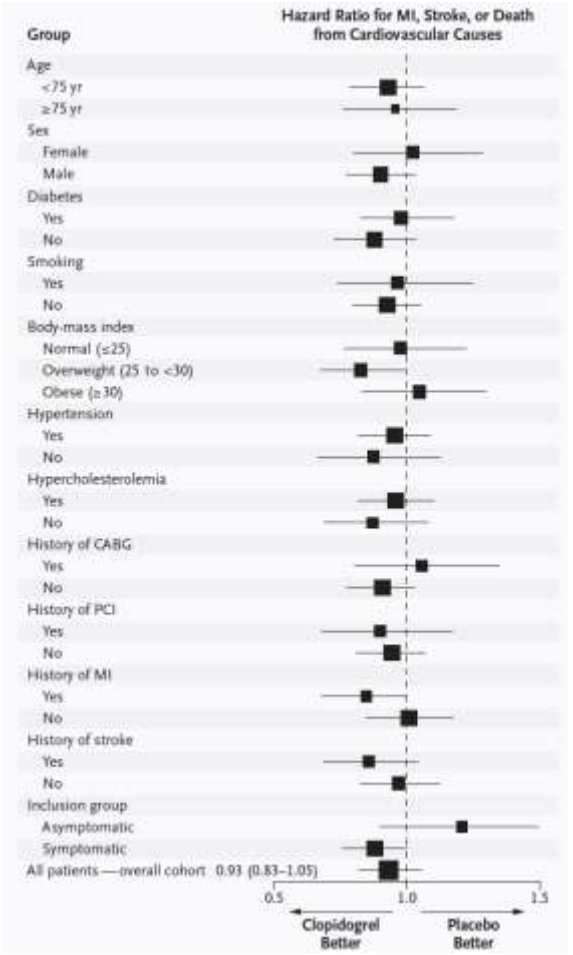
Μήπως οι συνδυασμοί αντιαιμοπεταλιακών φαρμάκων είναι περισσότερο αποτελεσματικοί;

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization,Management and Avoidance (CHARISMA)

Ασθενείς υψηλού κινδύνου όχι όμως με ACS (πολλαπλούς παράγοντες κινδύνου ή κλινικά επιβεβαιωμένη καρδιοαγγειακή νόσο).

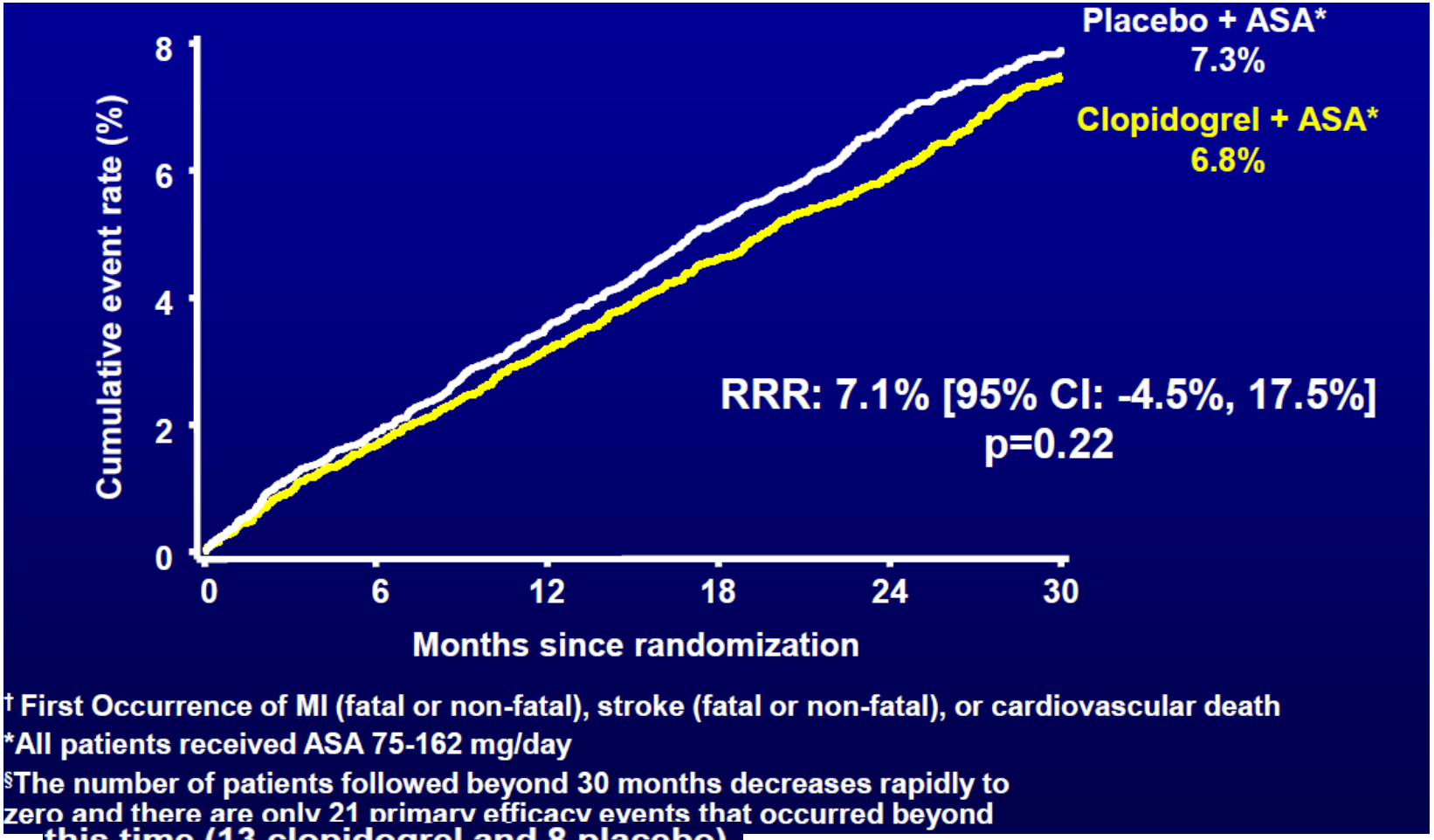
N=15.603

Ασπιρίνη + κλοπιδογρέλη vs ασπιρίνη



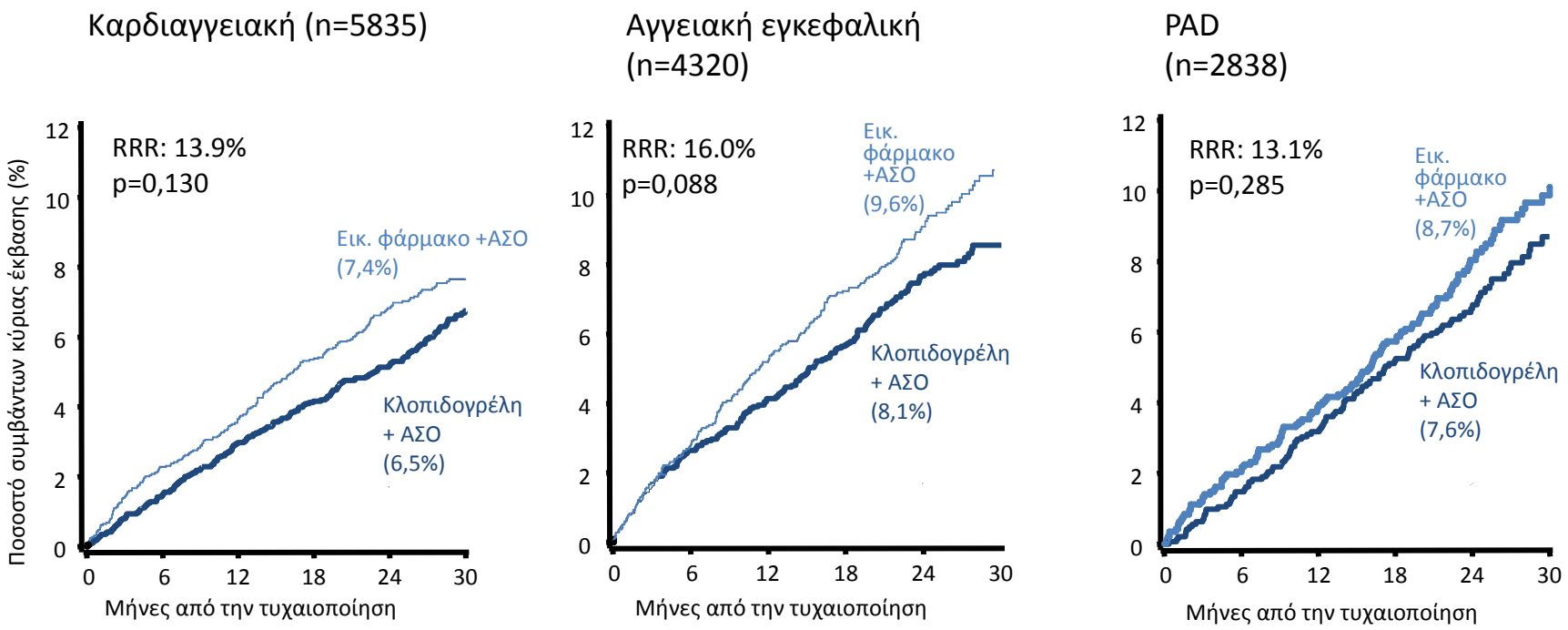
N Engl J Med 2006;354:1706-17

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†



Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006.

CHARISMA: Ασθενείς με τεκμηριωμένη καρδιαγγειακή νόσο: Κύρια έκβαση (MI/Εγκεφαλικό/Θάνατος CV αιτίας)† ανά κριτήρια εισαγωγής*



†MI (θανατηφόρο ή μη θανατηφόρο), εγκεφαλικό επεισόδιο (θανατηφόρο ή μη θανατηφόρο) ή θάνατος καρδιαγγειακής αιτιολογίας

*Οι ασθενείς μπορεί να ικανοποιούσαν περισσότερα από ένα κριτήρια εισαγωγής

Όλοι οι ασθενείς έλαβαν ΑΣΟ 75-162 mg/ημέρα

Bhatt DL. Παρουσιάστηκε στη ACC 2006.

CHARISMA –Συμπεράσματα

- Όχι στατιστικά σημαντικά πιο αποτελεσματική η διπλή αντιαιμοπεταλιακή θεραπεία σε σχέση με την μονοθεραπεία (6.8%vs 7.3%, p=0.22) στην μείωση καρδιαγγειακού θανάτου,ΕΜ,ΑΕΕ
- Με ΣΔ το 42% του συνολικού πληθυσμού n=6555
- Χωρίς όφελος ο συνδυασμός των αντιαιμοπεταλιακών και στον ΣΔ

Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006.

Οξύ στεφανιαίο σύνδρομο (ΟΣΣ)

CURE: Design

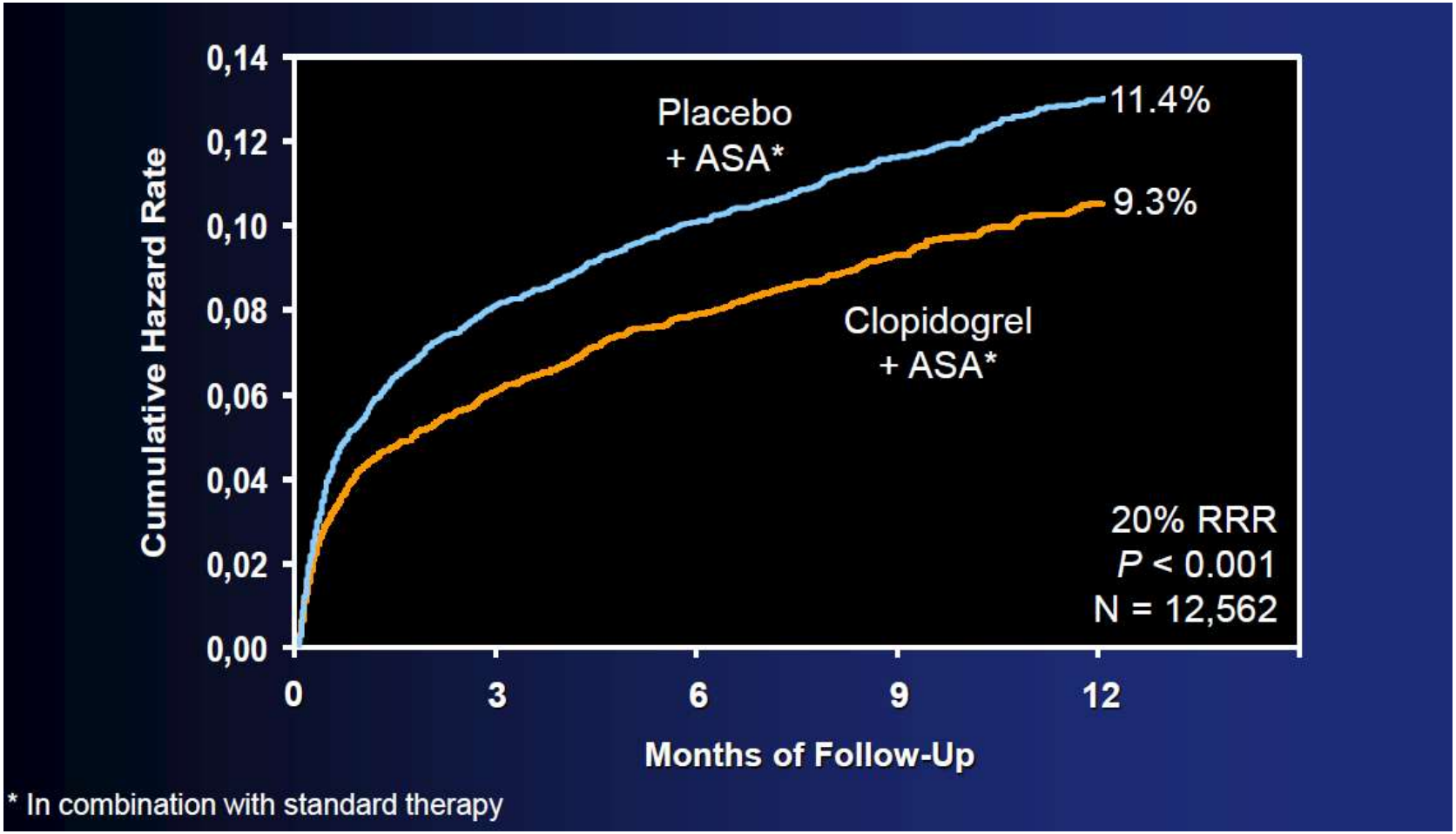
- Objective: to evaluate the early and long-term efficacy and safety of clopidogrel (300/75 mg) on top of standard therapy (including ASA)
- Double-blind, randomized, prospective trial Multicenter (482 centers in 28 countries)
- Follow-up of 12,562 patients from 3 months to 1 year with acute coronary syndromes (without ST segment elevation)

Primary endpoint: first occurrence of any component of the cluster of:

- cardiovascular death
- myocardial infarction
- stroke (ischemic, hemorrhagic, or of uncertain type)

The CURE Trial Investigators. *N Engl J Med 2001; 345: 494–502.*

Primary End Point - MI/Stroke/CV Death



The CURE Trial Investigators. *N Engl J Med 2001; 345: 494–502*

Bleeding complications

Variable	Clopidogrel Group (N=6259)	Placebo Group (N=6303)	Relative Risk (95% CI)	P Value
	no. (%)			
Major bleeding	231 (3.7)	169 (2.7)	1.38 (1.13–1.67)	0.001
Necessitating transfusion of ≥2 units of blood	177 (2.8)	137 (2.2)	1.30 (1.04–1.62)	0.02
Life-threatening	135 (2.2)	112 (1.8)	1.21 (0.95–1.56)	0.13
Fatal	11 (0.2)	15 (0.2)		
Causing 5 g/dl drop in hemoglobin level	58 (0.9)	57 (0.9)		
Requiring surgical intervention	45 (0.7)	43 (0.7)		
Causing hemorrhagic stroke	7 (0.1)	5 (0.1)		
Requiring inotropic agents	34 (0.5)	34 (0.5)		
Necessitating transfusion of ≥4 units of blood	74 (1.2)	60 (1.0)		
Non–life-threatening	96 (1.5)	57 (0.9)	1.70 (1.22–2.35)	0.002
Site of major bleeding				
Gastrointestinal	83 (1.3)	47 (0.7)		
Retroperitoneal	8 (0.1)	5 (0.1)		
Urinary (hematuria)	4 (0.1)	5 (0.1)		
Arterial puncture site	36 (0.6)	22 (0.3)		
Surgical site	56 (0.9)	53 (0.8)		
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75–2.56)	<0.001
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48–1.94)	<0.001

Οξύ στεφανιαίο σύνδρομο

Recommendations	Class[a]	Level[b]
Oral antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose[d] of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy.	I	A

Antiplatelet treatment			
3	A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
	• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[c] for all patients at moderate to high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
	• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if there are no contraindications.[c]	I	B
	• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B
4	It is not recommended to administer prasugrel in patients in whom the coronary anatomy is not known.	III	B

STEMI TREATMENT (2)
PRIMARY PCI - FIRST 24 HOURS AND DAYS 2-7

Prehospital

Aspirin	150-300 mg
Heparin	70 IU/kg

Ticagrelor	180 mg
or Prasugrel	60 mg
or Clopidogrel	600 mg

PCI

Bivalirudin
or GPI: Eptifibatide
Tirofiban
Abciximab
Follow local in-lab instruction/dosing

CCU/ICCU

Metoprolol	25 mg BID
or Carvedilol	3,25 mg BID
or Bisoprolol	2,5 mg QD

High dose potent statins, i.e.
Atorvastatin 80 mg QD

Medication Titration Day 2-7

Aspirin	75–100 mg QD
Ticagrelor	90 mg BID
or Prasugrel	10/5 mg QD
or Clopidogrel	75 mg QD

(if ticagrelor/prasugrel unavailable)

Metoprolol	200 mg QD
or carvedilol	25 mg BID
or bisoprolol	5 mg BID

or Ca-antagonist (see NSTEACS chapter)

Start ACEI or ARB in LVSD, CHF or DM or to control BP

Aldosterone RB in LVSD, CHF or DM

Start or continue anti-hyperglycemic medication

Reference: Steg G et al. Eur Heart J. (2012);33:2569-619 [7]

Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI.

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	776,794
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	–
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B	828
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B	823
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact.	I	B	777,846–848
GP IIb/IIIa inhibitors should be considered for bail-out or evidence of no-reflow or a thrombotic complication.	IIa	C	–
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B	271,834, 835,849
Anticoagulants			
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A	–
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C	
Unfractionated heparin: 70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50–70 U/kg i.v. bolus with GPIIb/IIIa inhibitor.	I	C	
Bivalirudin 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 hours after the procedure.	IIa	A	243,840,841
Enoxaparin i.v. 0.5 mg/kg with or without GP IIb/IIIa inhibitor.	IIa	B	788,842,843, 844,850

[a]Class of recommendation. [b]Level of evidence. [c]References. ASA: acetylsalicylic acid; GP: glycoprotein; i.v.: intravenous; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

Recommendations for antithrombotic treatment in patients with NSTE-ACS undergoing PCI.

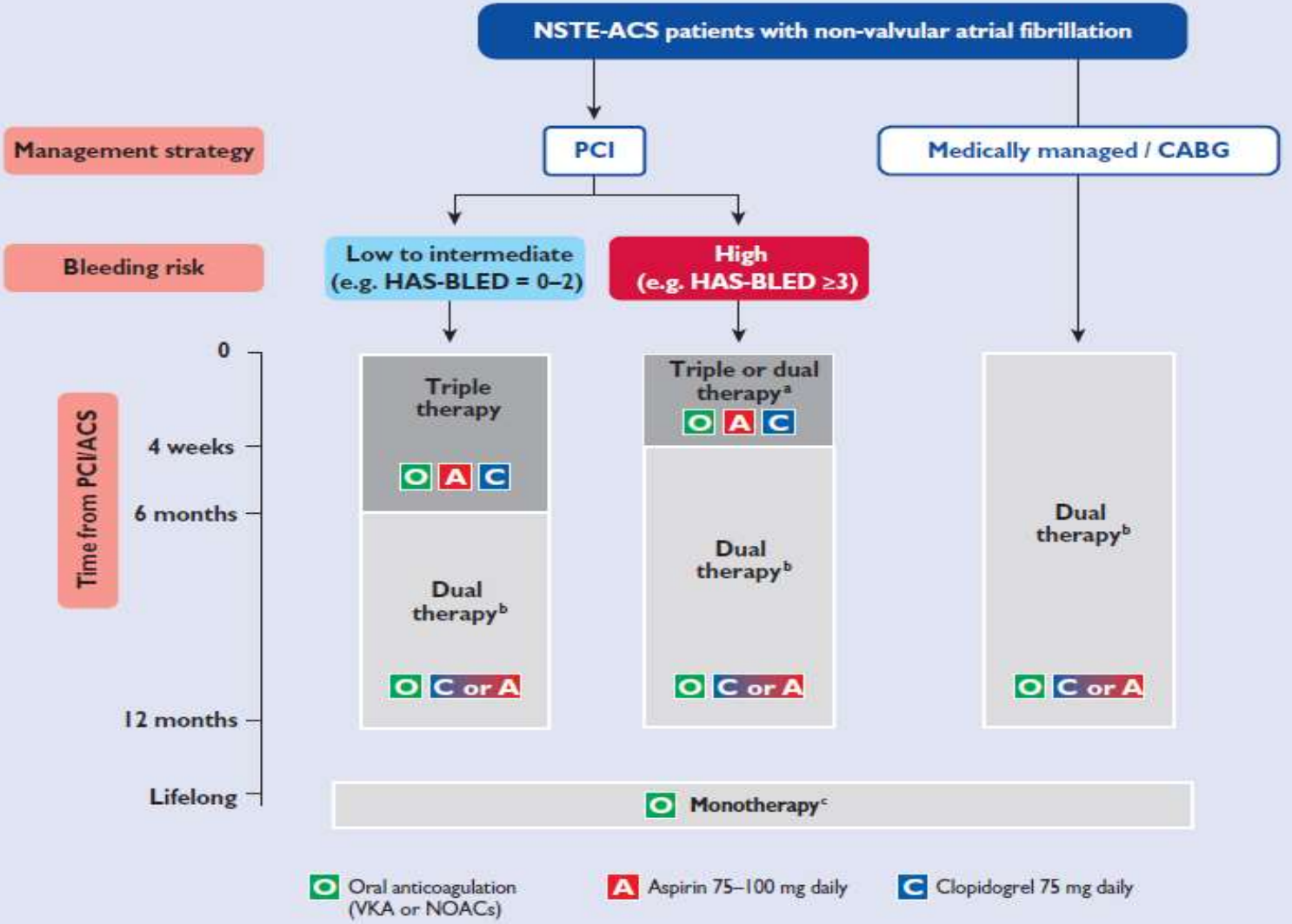
Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	774,776,794
A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	337,341,825
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication.	I	B	337
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B	341
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812,825
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C	
Pre-treatment with prasugrel in patients in whom coronary anatomy not known, is not recommended.	III	B	826
Pre-treatment with GP IIb/IIIa antagonists in patients in not known, is not recommended.	III	A	357,815
Anticoagulant therapy			
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A	180
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C	
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GP IIb/IIIa receptor inhibitor during PCI.	I	A	815–817
UFH is recommended as anticoagulant for PCI if patients cannot receive bivalirudin.	I	C	
In patients on fondaparinux (2.5 mg daily s.c.), a single bolus UFH (85 IU/kg, or 60 IU/kg in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated during PCI.	I	B	827
Enoxaparin should be considered as anticoagulant for PCI in patients pre-treated with subcutaneous enoxaparin.	IIa	B	788
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated.	IIa	C	
Crossover of UFH and LMWH is not recommended.	III	B	820

[a]Class of recommendation. [b]Level of evidence. [c]References. ASA: acetylsalicylic acid; GP: glycoprotein; i.v.: intravenous; LMWH: low-molecular-weight heparin; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; UFH: unfractionated heparin

Recommendations for antithrombotic treatment in SCAD patients undergoing PCI.

Recommendations for PCI	Class[a]	Level[b]	Ref[c]
Pretreatment with antiplatelet therapy			
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once anatomy is known and decision to proceed with PCI preferably 2 hours or more before the procedure.	I	A	789–792
Pretreatment with clopidogrel may be considered in patients with high probability for significant CAD.	IIb	C	
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg or more may be considered once the indication for PCI is confirmed.	IIb	C	
Antiplatelet therapy during PCI			
ASA is indicated before elective stenting.	I	B	776,793,794
ASA oral loading dose of 150–300 mg (or 80-150 mg i.v.) is recommended if not pre-treated.	I	C	
Clopidogrel (600 mg loading dose or more, 75 mg daily maintenance dose) is recommended for elective stenting.	I	A	795–798
GP IIb/IIIa antagonists should be considered only for bail-out.	IIa	C	
Antiplatelet therapy after stenting			
DAPT is indicated for at least 1 month after BMS implantation.	I	A	791,799–801
DAPT is indicated for 6 months after DES implantation.	I	B	799,802,803
Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk.	IIb	A	804,805
Life-long single antiplatelet therapy, usually ASA, is recommended.	I	A	776,794
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C	-
DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk.	IIb	C	-
Anticoagulant therapy			
Unfractionated heparin 70–100 U/kg.	I	B	806
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) in case of heparin-induced thrombocytopenia.	I	C	-
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour during the procedure) in patients at high bleeding risk.	IIa	A	783–785
Enoxaparin i.v. 0.5 mg/kg.	IIa	B	786,788,807

[a]Class of recommendation. [b]Level of evidence. [c]References. ASA: acetylsalicylic acid; BMS: bare-metal stent; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; GP: glycoprotein; i.v.: intravenous; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease



ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [2 points], Diabetes, Stroke [2 points] – Vascular disease, Age 65–74, Sex category; DAPT = dual antiplatelet therapy; NOACs = non-vitamin K antagonist oral anticoagulants; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; VKAs = vitamin K antagonists. Adapted from Lip et al.[234]

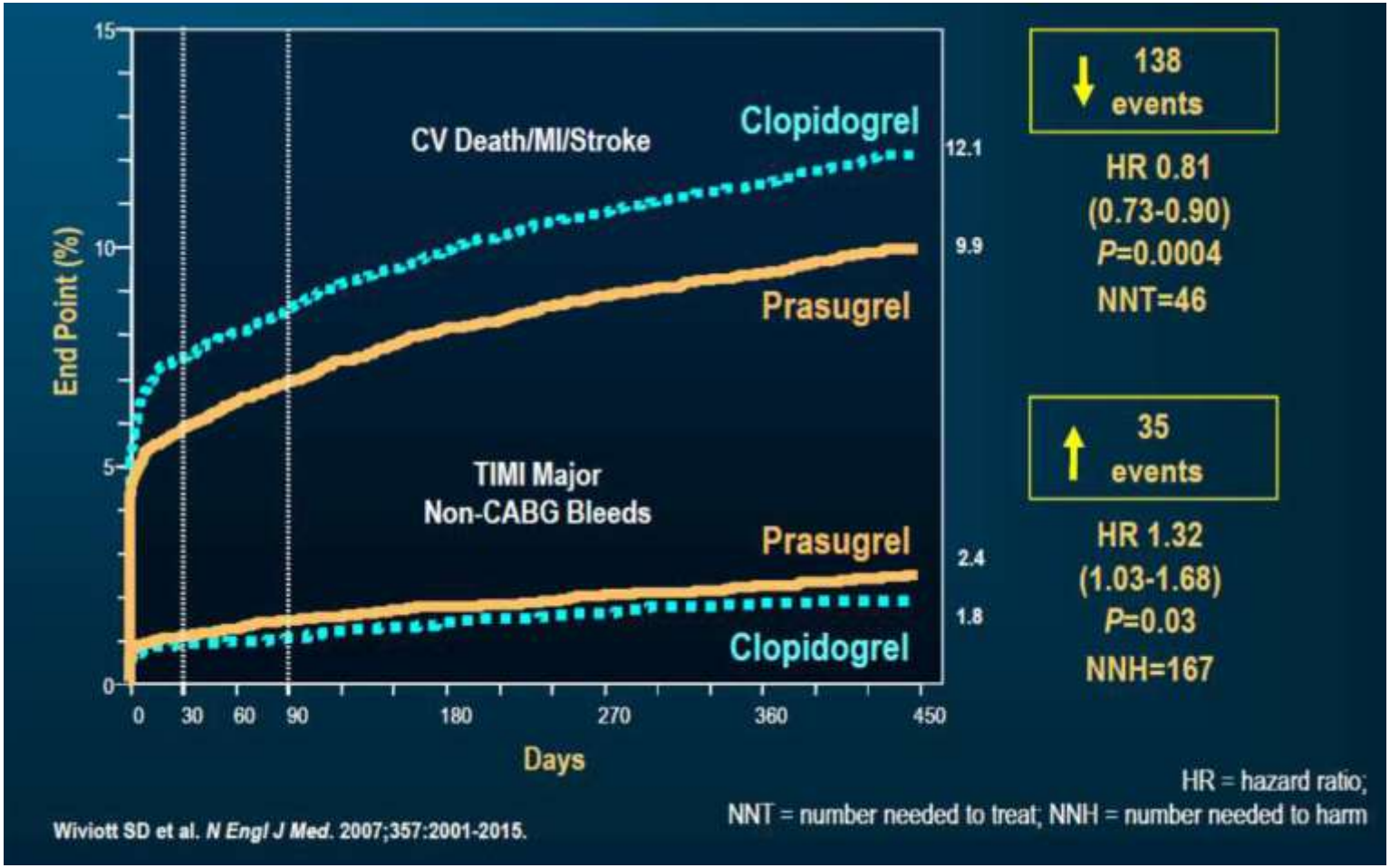
[a]Dual therapy with oral anticoagulation and clopidogrel may be considered in selected patients (low ischaemic risk).

[b]Aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (i.e., oral anticoagulation plus single antiplatelet); triple therapy may be considered up to 12 months in patients at very high risk for ischaemic events.

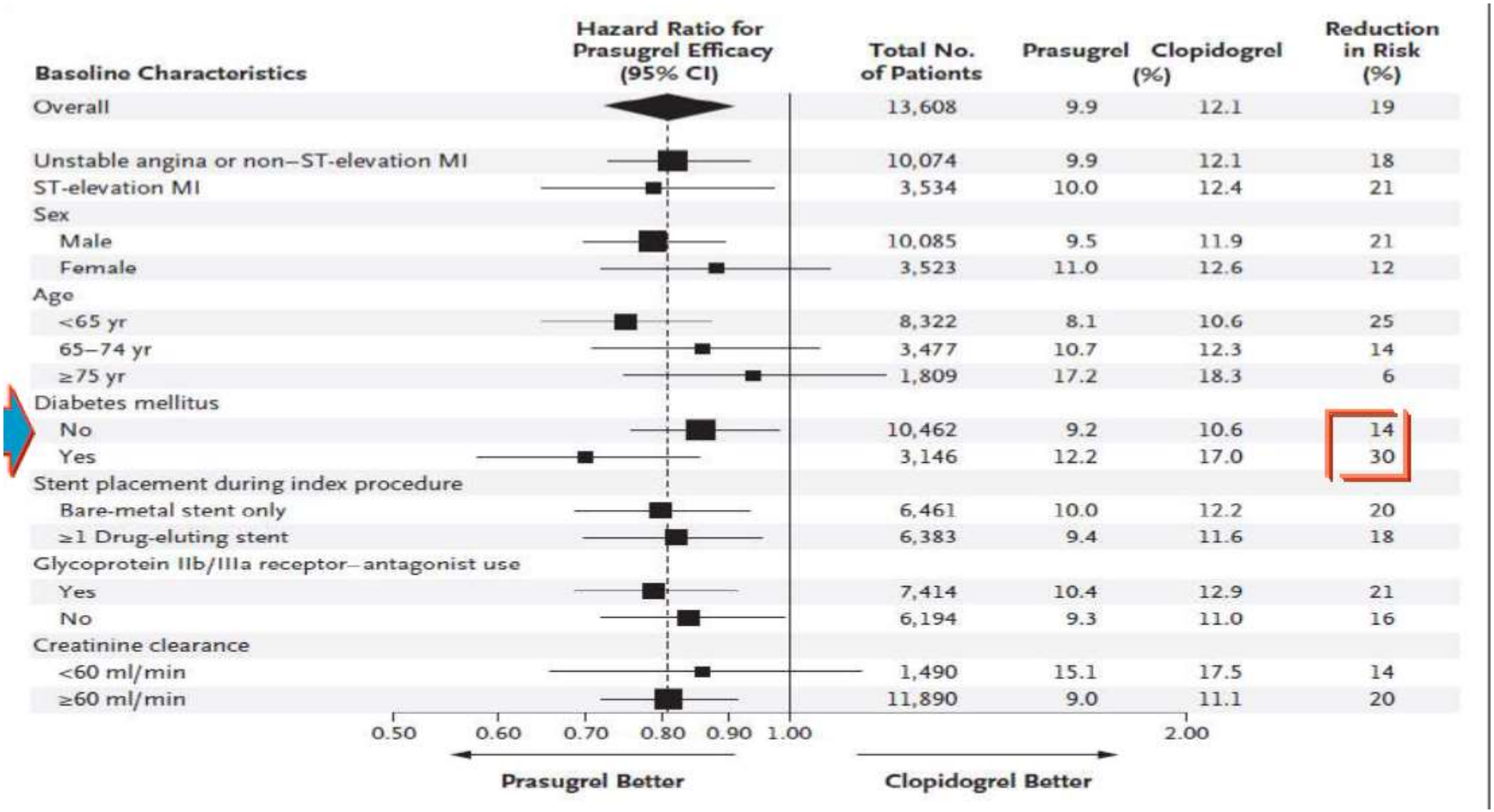
[c]Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) beyond one year may be considered in patients at very high risk of coronary events. In patients undergoing coronary stenting, dual antiplatelet therapy may be an alternative to triple or a combination of anticoagulants and single antiplatelet therapy if the CHA_2DS_2-VASc score is 1 (males) or 2 (females).

Σύγκριση θειενοπυριδινών

TRITON-TIMI 38



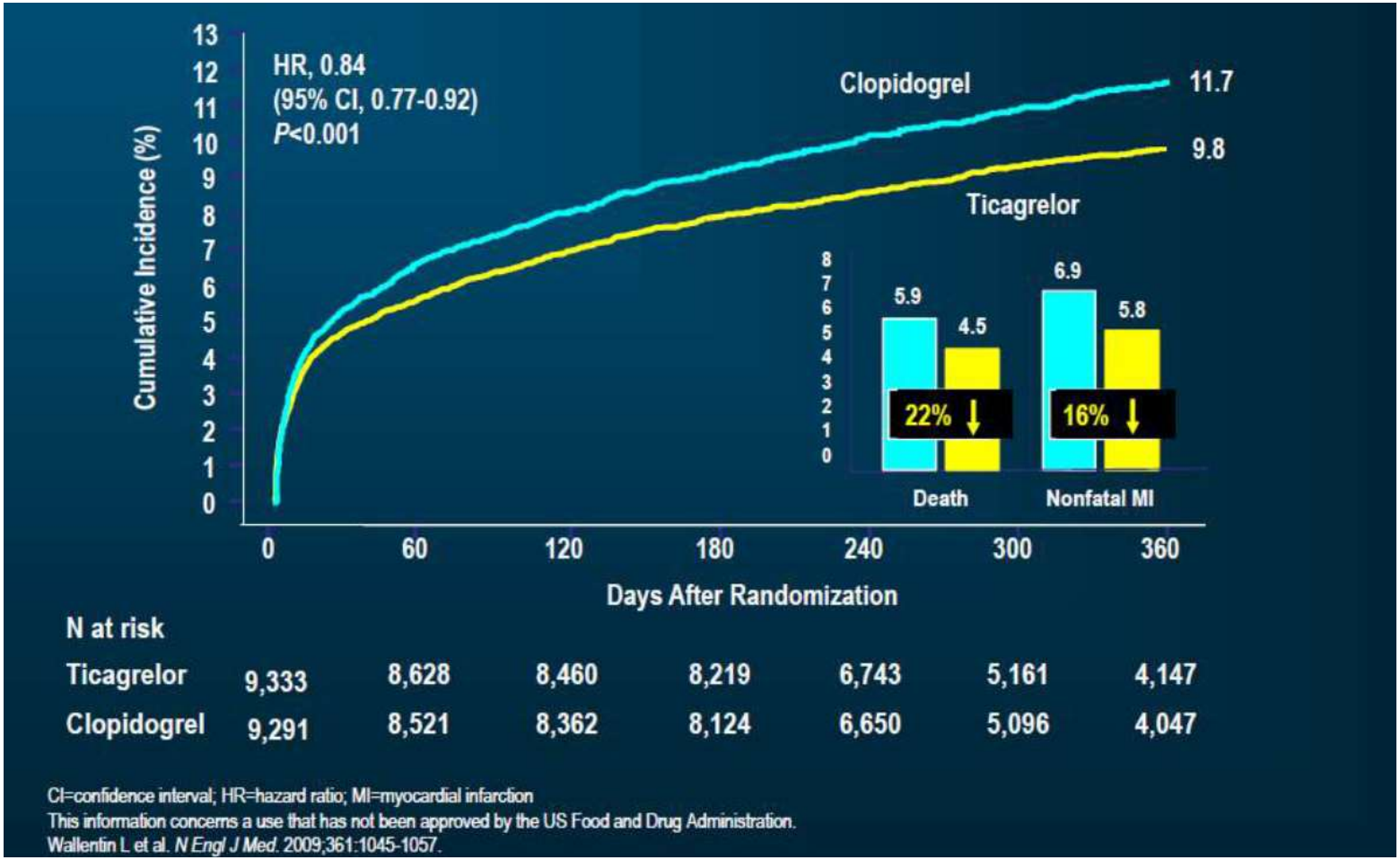
TIMI 38



Baseline Characteristics	Total No. of Patients	Prasugrel (%)	Clopidogrel (%)	Reduction in Risk (%)
Overall	13,608	9.9	12.1	19
Unstable angina or non–ST-elevation MI	10,074	9.9	12.1	18
ST-elevation MI	3,534	10.0	12.4	21
Sex				
Male	10,085	9.5	11.9	21
Female	3,523	11.0	12.6	12
Age				
<65 yr	8,322	8.1	10.6	25
65–74 yr	3,477	10.7	12.3	14
≥75 yr	1,809	17.2	18.3	6
Diabetes mellitus				
No	10,462	9.2	10.6	14
Yes	3,146	12.2	17.0	30
Stent placement during index procedure				
Bare-metal stent only	6,461	10.0	12.2	20
≥1 Drug-eluting stent	6,383	9.4	11.6	18
Glycoprotein IIb/IIIa receptor–antagonist use				
Yes	7,414	10.4	12.9	21
No	6,194	9.3	11.0	16
Creatinine clearance				
<60 ml/min	1,490	15.1	17.5	14
≥60 ml/min	11,890	9.0	11.1	20

Wiviott SD N. Engl. J. Med 2007:357:2001-2015

PLATO Primary Efficacy analysis Cardiovascular Death, MI or Stroke



CI=confidence interval; HR=hazard ratio; MI=myocardial infarction
This information concerns a use that has not been approved by the US Food and Drug Administration.
Wallentin L et al. *N Engl J Med*. 2009;361:1045-1057.

Efficacy of Antiplatelet Therapies in ACS Results in the Diabetes Mellitus Subgroups

Study	# pts	Regimen	Primary end-point	Results overall	# pts DM	Results in DM
Cure	12 562	ASA+CL VS ASA	CV death, non fatal MI, stroke at 1 yr	9.3 vs 11.4% RR= 0.80	2 840	14.2 vs 16.7% RR=0.84 ns
PCI-CURE	2 658	ASA+CL VS ASA	Cv death, MI or urgent TVR at 30 days	4.5 vs 6.4% RR= 0.70	504	12.9 vs 16.5% RR=0.77 ns
CREDO	2 116	ASA+CL VS ASA	Death, MI or stroke at 1 yr	8.5 vs 11.5% RRR=26.9%	560	% NA RRR=11.2% ns
COMMIT	45 852	ASA+CL VS ASA	Death, reinfarct or stroke at discharge or 28 days	9.2 vs 10.1% OR=0.91	NA	NA
CLARITY	3 491	ASA+CL VS ASA	Occluded infarct-related artery on angiography or death or recurrent MI before angiography	15 vs 21.7% OR=0.64	575	NA
PCI-CLARITY	1 863	ASA+CL VS ASA	CV death, recurrent MI or stroke at 30 days	3.6 vs 6.2% OR=0.54	282	6 vs 10.1% OR=0.61 ns
TRITON-TIMI 38	13 608	ASA+PRA VS ASA+CL	CV death, non-fatal MI or non-fatal stroke at 15 mo.	9.9 vs 12.1% HR=0.81	3 146	12.2 vs 17% HR=0.70
PLATO	18 624	ASA+TICA VS ASA+CL	Death from vascular causes, MI or stroke at 12 mo.	9.8 vs 11.7% HR=0.84	4 662	14.1 vs 16.2% HR=0.88 ns

(Adapted from Ferreiro JL et al. *Circulation 2011; 123: 798-813)*

Κατευθυντήριες οδηγίες ADA 2017

Η διπλή αντιαιμοπεταλιακή θεραπεία είναι χρήσιμη για ένα χρόνο μετά από ένα οξύ στεφανιαίο σύνδρομο και μπορεί να έχει οφέλη πέρα και από αυτή την περίοδο. Β

Diabetes Care Volume 40, Supplement 1, January 2017 S82

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Antiplatelet therapy in patients with diabetes

Recommendations	Class [a]	Level [b]
Antiplatelet therapy with aspirin in DM-patients at low CVD risk is not recommended.	III	A
Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb	C
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in DM.	I	A
A $P2Y_{12}$ receptor blocker is recommended in patients with DM and ACS for 1 year and in those subjected to PCI (duration depending on stent type). In patients with PCI for ACS preferably prasugrel or ticagrelor should be given.	I	A
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B

Management of patients with stable and unstable coronary artery disease and diabetes

Recommendations	Class [a]	Level [b]
It is recommended that patients with CVD are investigated for disorders of glucose metabolism.	I	A
Beta-blockers should be considered to reduce mortality and morbidity in patients with DM and ACS.	IIa	B
ACE-I or ARBs are indicated in patients with DM and CAD to reduce the risk for cardiovascular events.	I	A
Statin therapy is indicated in patients with DM and CAD to reduce the risk for cardiovascular events.	I	A
Aspirin is indicated in patients with DM and CAD to reduce the risk for cardiovascular events.	I	A
Platelet $P2Y_{12}$ receptor inhibition is recommended in patients with DM and ACS in addition to aspirin.	I	A
Insulin-based glycaemic control should be considered in ACS patients with significant hyperglycaemia (>10 mmol/L or >180 mg/dL) with the target adapted to possible co-morbidities.	IIa	C
Glycaemic control, that may be accomplished by different glucose-lowering agents, should be considered in patients with DM and ACS.	IIa	B

European Heart Journal (2013) **34**, 3035–3087

- Άνδρας 54 ετών
- ΣΔ, δυσλιπιδαιμία

✓LDL=160 mg/dl

✓HDL=38 mg/dl

✓TG=152 mg/dl

- ΑΠ: 140/90 mmHg

➢10ετής καρδιαγγειακός κίνδυνος (ACC/AHA) = 16%

Πρέπει να λάβει ασπιρίνη για πρωτογενή πρόληψη;

1. Ναι
2. Όχι

Annals of Internal Medicine

CLINICAL GUIDELINE

Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

Kirsten Bibbins-Domingo, PhD, MD, MAS, on behalf of the U.S. Preventive Services Task Force*

Adults aged 50 to 59 y with a ≥10% 10-y CVD risk	Adults aged 60 to 69 y with a ≥10% 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

Ann Intern Med 2016 Apr 12

- Άνδρας 72 ετών
- ΣΔ, ΑΥ, δυσλιπιδαιμία
- Ισχαιμικό ΑΕΕ προ 4 ετών
- Έκτοτε, υπό ασπιρίνη 100 mg qd
- Προσφάτως, διεγνώσθη καρκίνος εγκαρσίου κόλου
- Πρόκειται να υποβληθεί σε χειρουργική εκτομή του όγκου

Η ασπιρίνη πρέπει:

1. να συνεχισθεί
2. να διακοπεί 7-10 ημέρες πριν
3. να διακοπεί & να αντικατασταθεί από ΗΧΜΒ

Η ασπιρίνη πρέπει:

1. **να συνεχισθεί**
2. να διακοπεί 7-10 ημέρες πριν
3. να διακοπεί & να αντικατασταθεί από ΗΧΜΒ

Η ασπιρίνη κατά την περιεγχειρητική περίοδο

- Γενικώς, πρέπει να συνεχίζεται

- Εξαιρέσεις:

✓ *Ασθενείς με χαμηλό καρδιαγγειακό κίνδυνο, που υποβάλλονται σε μείζον χειρουργείο (οπότε διακόπτεται 7-10 ημέρες πριν)*

✓ *Ενδοκράνιες εγχειρήσεις*

Anaesthesia 2015; 70 (1)(Suppl):58–67
Chest 2012; 141(2)(Suppl):7S–47S

CLINICAL GUIDELINE

Annals of Internal Medicine

Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

Kirsten Bibbins-Domingo, PhD, MD, MAS, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2009 USPSTF recommendation on aspirin use to prevent cardiovascular disease (CVD) events and the 2007 recommendation on aspirin and nonsteroidal anti-inflammatory drug use to prevent colorectal cancer (CRC).

Methods: The USPSTF reviewed 5 additional studies of aspirin for the primary prevention of CVD and several additional analyses of CRC follow-up data. The USPSTF also relied on commissioned systematic reviews of all-cause mortality and total cancer incidence and mortality and a comprehensive review of harms. The USPSTF then used a microsimulation model to systematically estimate the balance of benefits and harms.

Population: This recommendation applies to adults aged 40 years or older without known CVD and without increased bleeding risk.

Recommendations: The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation)

The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C recommendation)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (I statement)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (I statement)

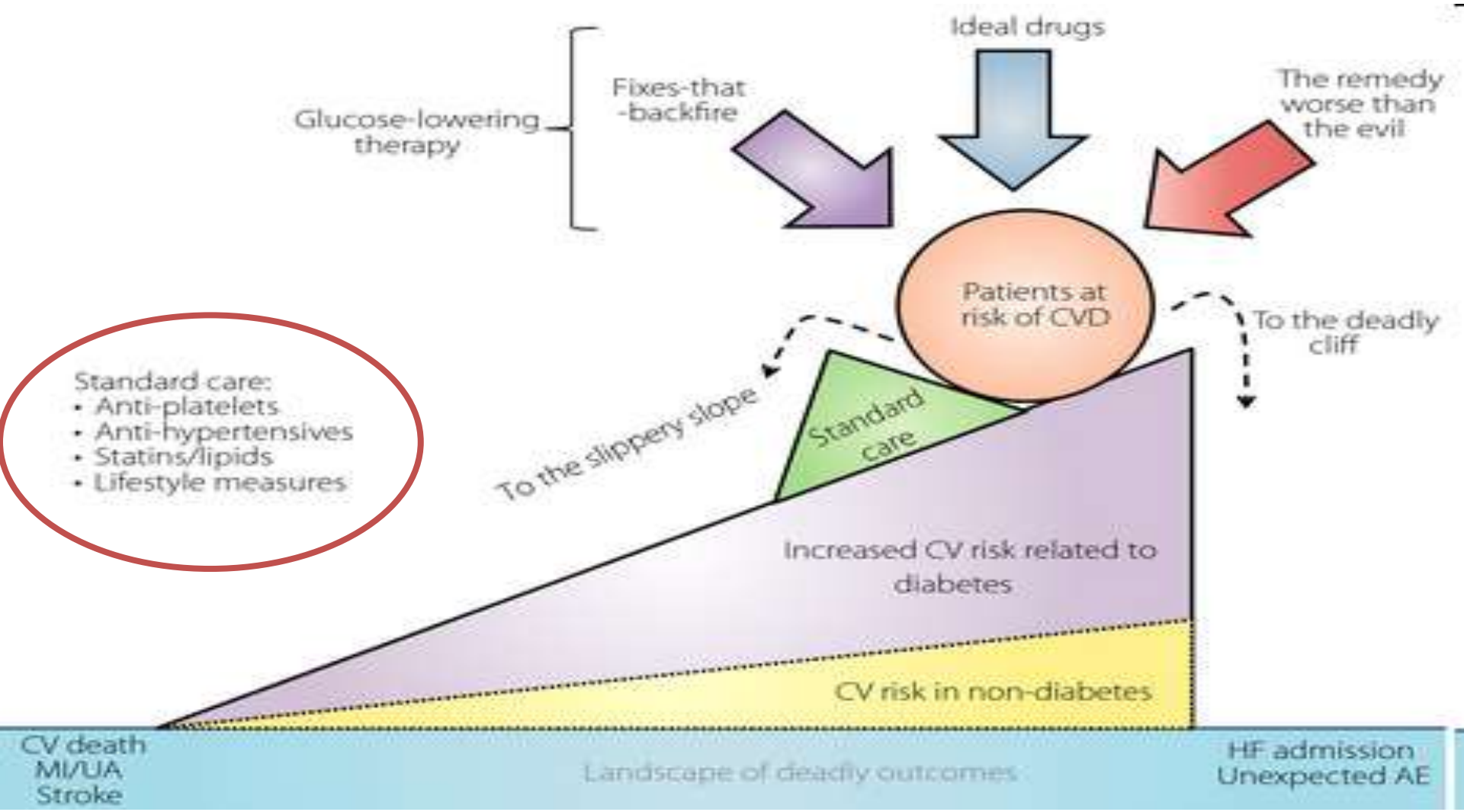
Ann Intern Med. 2016;164:836-845. doi:10.7326/M16-0577 **www.annals.org**

For author affiliation, see end of text.

This article was published at www.annals.org on 12 April 2016.

* For a list of members of the USPSTF, see the **Appendix** (available at www.annals.org).

The good, the bad, or the ugly?



Journal of Diabetes Investigation 2015; 6: 597-599


Thank you