Prevenzione secondaria: quali farmaci e quali risultati

Dott. Maurizio Nizzoli

U.O. Endocrinologia e Malattie Metaboliche

U.O. Medicina Interna

O.C. G.B. Morgagni - Forlì

Diabete

- Iperglicemia
- Insulinoresistenza
- Condizioni metaboliche associate
- Altre anormalità cellulari

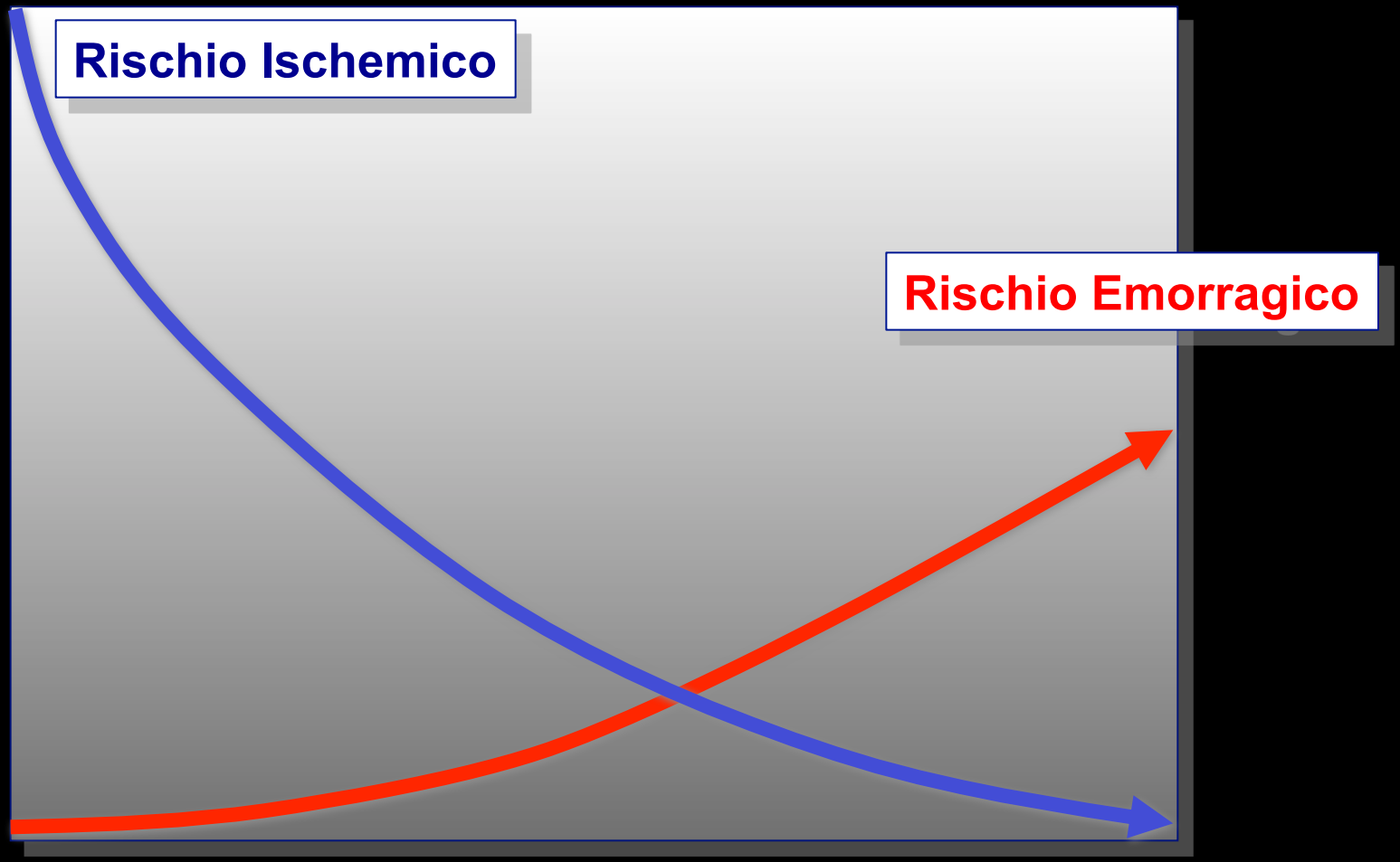
- ↑ Reattività piastrinica
- Disfunzione endoteliale
- Ridotta fibrinolisi
- ↑ Fattori della coagulazione

IPEREATTIVITA' PIASTRINICA

- Adesione
- Attivazione
- Aggregazione
- Ridotta vita
- Ridotta produzione di NO
- Ridotta produzione di prostacicline

Stato Protrombotico

Rischio ischemico vs emorragico



Aggressività della terapia antitrombotica

Recommendations: Antiplatelet Agents (3)

- Use aspirin therapy (75–162 mg/day)
  - **Secondary prevention strategy in those with diabetes with a history of CVD (A)**
- For patients with CVD and documented aspirin allergy
  - Clopidogrel (75 mg/day) should be used (B)
- Combination therapy with ASA (75–162 mg/day) and clopidogrel (75 mg/day)
  - Reasonable for up to a year after an acute coronary syndrome (B)

ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2012;35(suppl 1):S32.

Prevenzione primaria o secondaria ?
Diabete equivalente di rischio coronarico ?

Roma,
9-11 novembre 2012

Macroangiopatia non coronarica avanzata o molto avanzata

Sintomatica
- Precedenti eventi aterotrombotici
- Interventi di rivascolarizzazione

Non sintomatica
- Arteriopatia periferica con ABI < 0.9%
- Stenosi carotidea asintomatica > 50%
- Aneurisma aortico

Score di rischio coronarico (UKPDS) > 30% a 10 aa

Score di rischio coronarico (UKPDS) > 20% a 10 aa + almeno uno dei seguenti :
- Placche ateromasiche determinati stenosi ≥ 20% in qualsiasi distretto
- GFR < 30 ml/min
- Neuropatia autonomica cardiaca
- Disfunzione erettile
- Familiarità di 1° grado positiva per cardiopatia ischemica in giovane età (< 55 aa ♂; < 65 aa ♀)

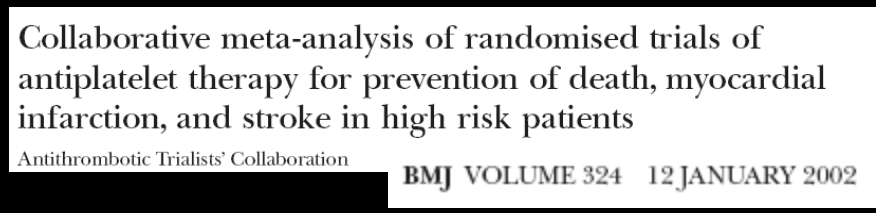
Score di rischio coronarico (UKPDS) > 20% a 10 aa + almeno due dei seguenti:
- GFR < 60 ml/min
- Micro o macroalbuminuria
- Retinopatia laser-trattata/proliferante

Il paziente che soddisfi i criteri riassunti in almeno uno dei riquadri presenta elevata probabilità di coronaropatia silente

Consensus: screening e terapia della cardiopatia ischemica nel paziente diabetico (2010)

Strong Evidence Base: Antithrombotic Trialists' Collaboration[1]

- Objective:
  - to determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events
- Data reviewed:
  - 287 studies involving:
    - 135,000 patients in comparisons of antiplatelet therapy vs control
    - 77,000 patients in comparisons of different antiplatelet regimens
- Main outcome measure:
  - 'serious vascular event': non-fatal myocardial infarction, non-fatal stroke, or vascular death

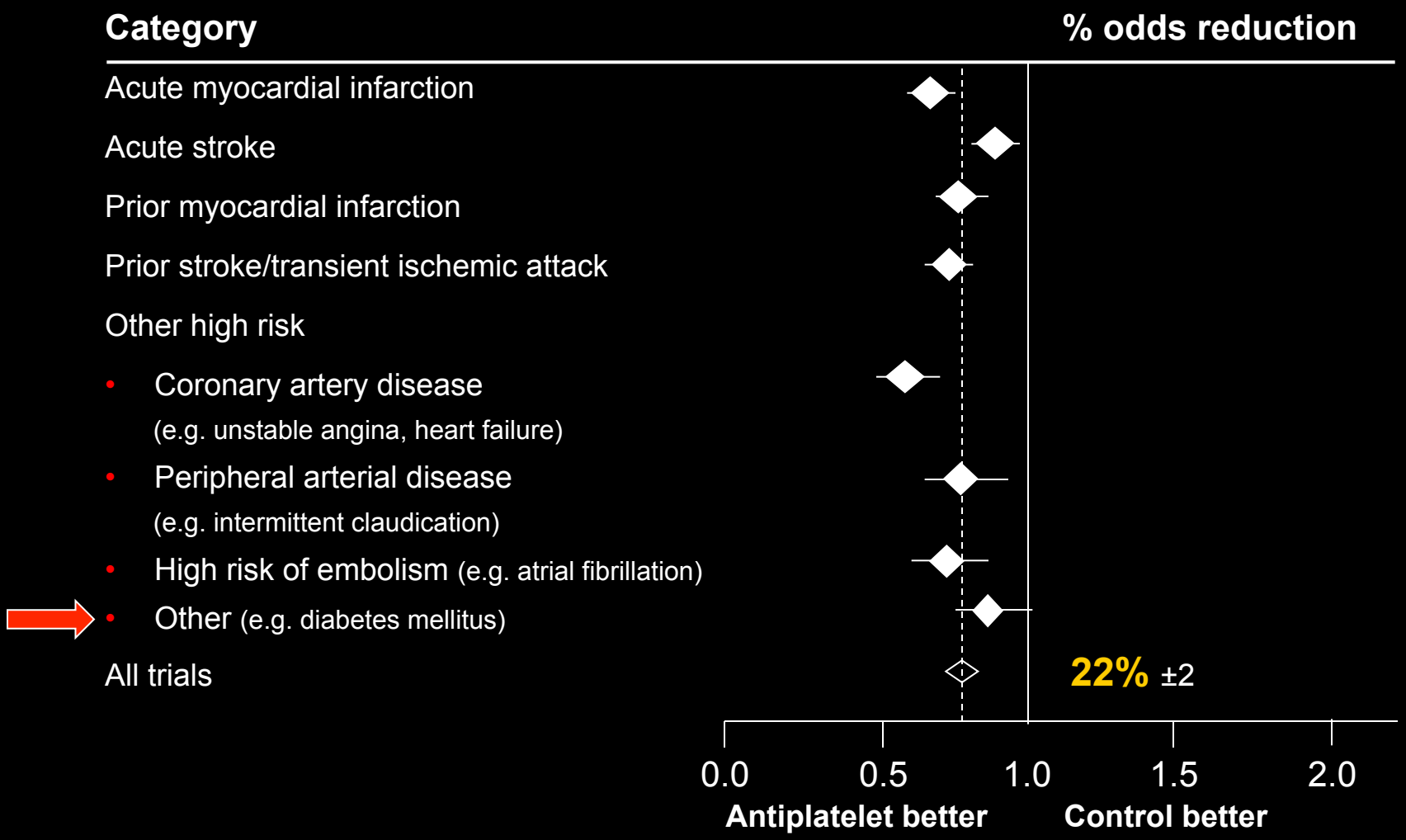

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration

BMJ VOLUME 324 12 JANUARY 2002

1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

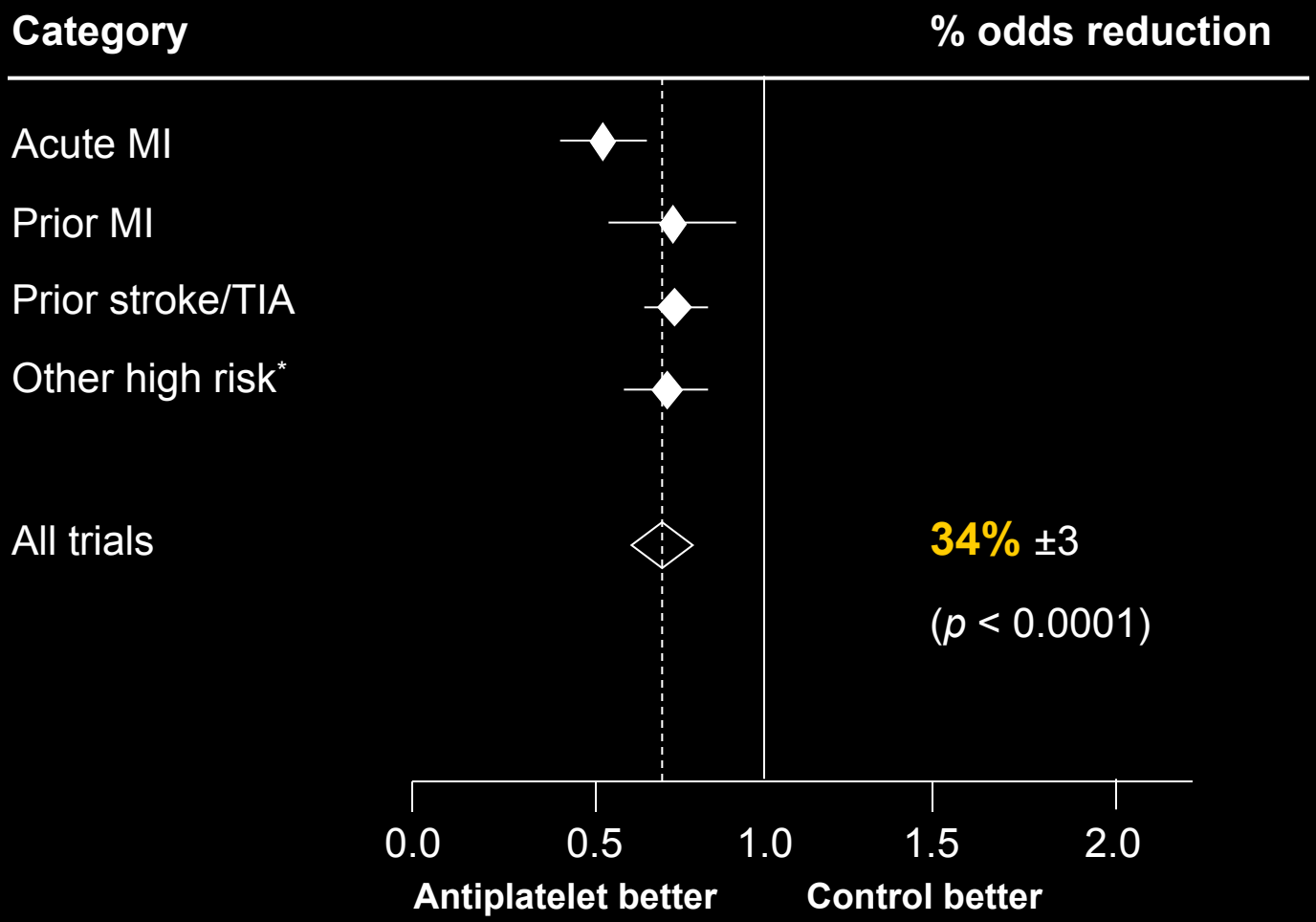
Antithrombotic Trialists' Collaboration:
Efficacy of Antiplatelet Therapy on Vascular Events*[1]



*Vascular events = myocardial infarction, stroke or vascular death

1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

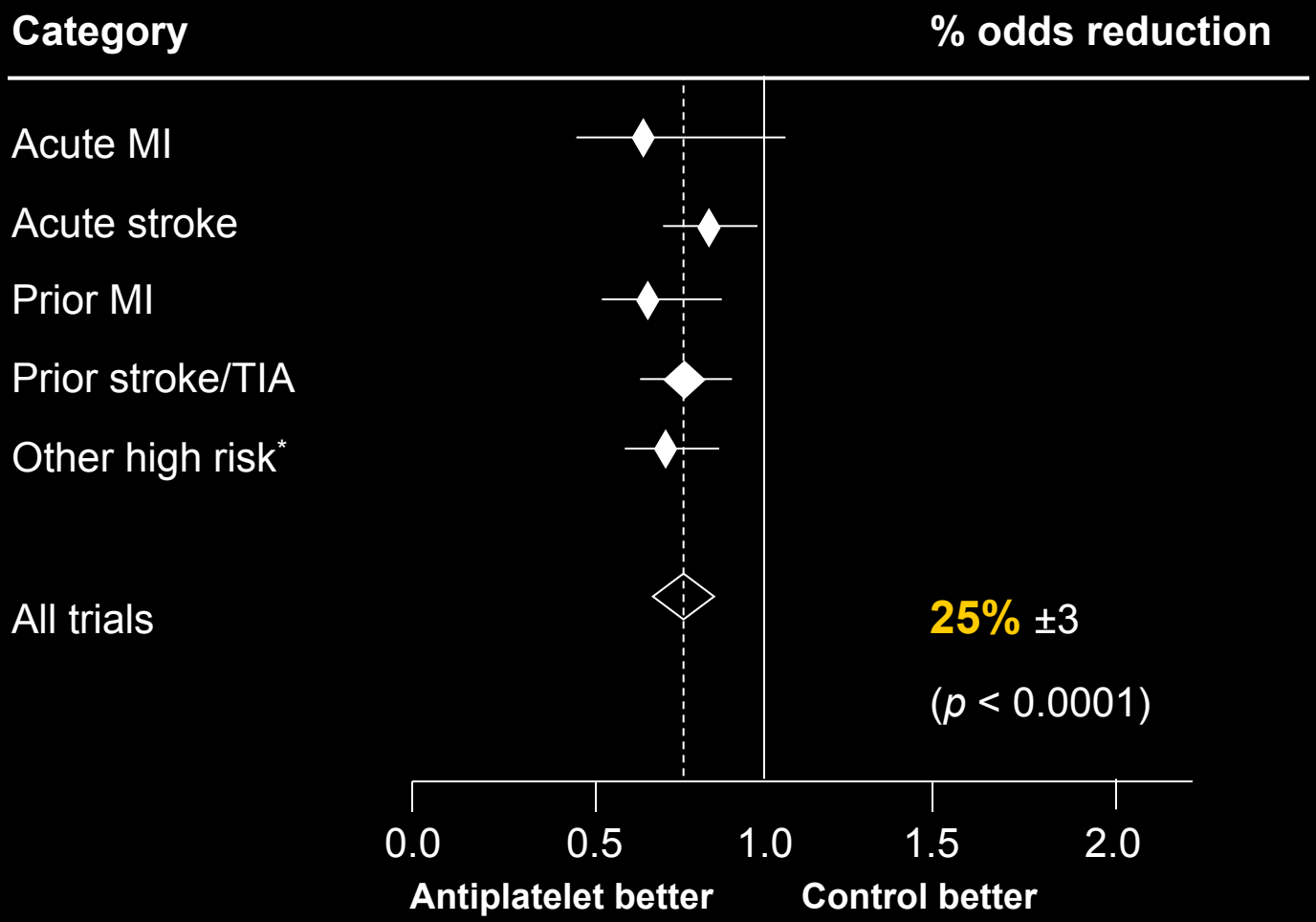
Antithrombotic Trialists' Collaboration:
Reduction in Risk of Non-Fatal Myocardial Infarction[1]



*Coronary artery disease, peripheral arterial disease, high risk of embolism and other high risk conditions (including hemodialysis, diabetes mellitus, carotid disease)

1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

Antithrombotic Trialists' Collaboration:
Reduction in Risk of Non-Fatal Stroke[1]



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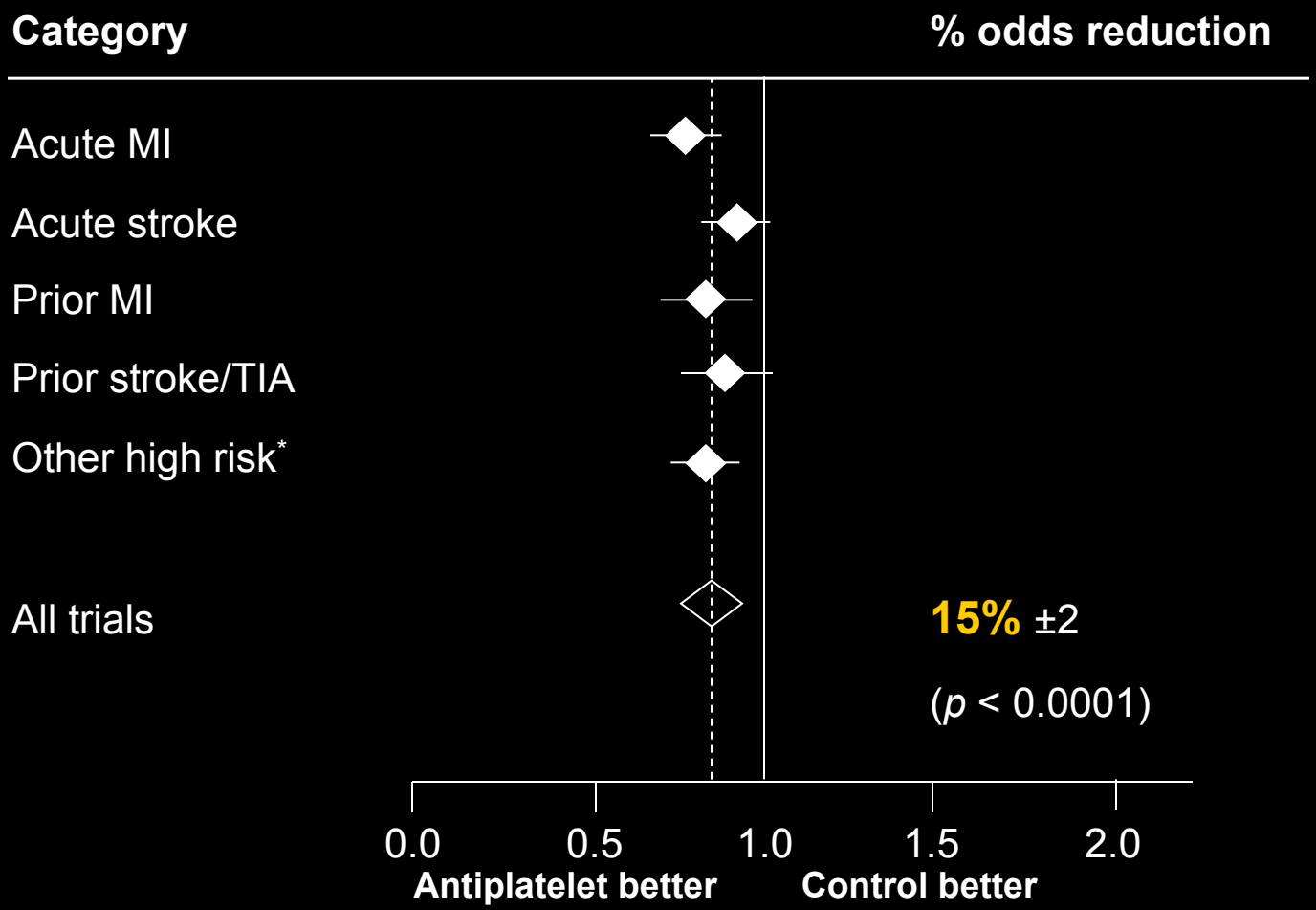
1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

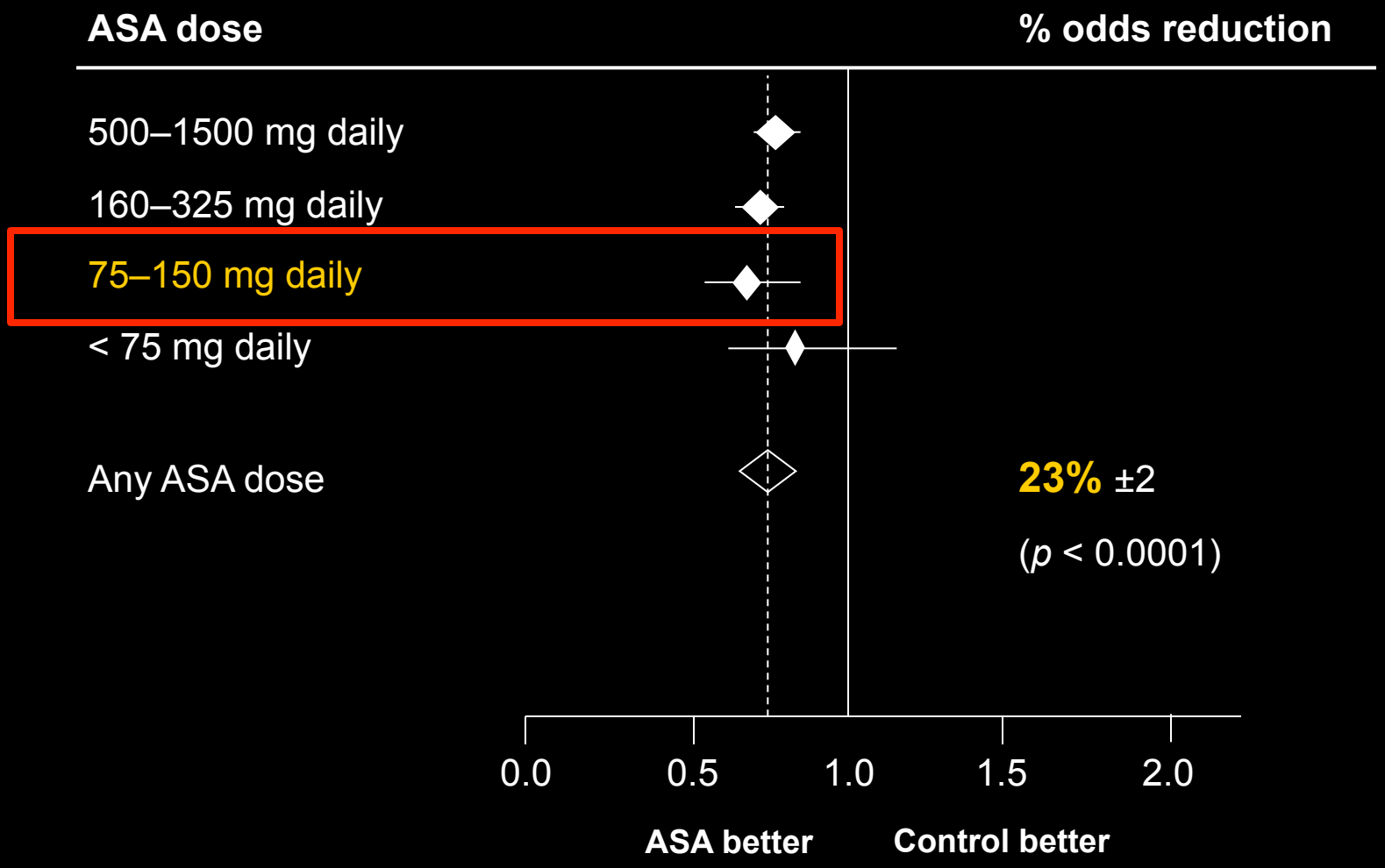
Antithrombotic Trialists' Collaboration:
Reduction in Risk of Vascular Deaths[1]



*Coronary artery disease, peripheral arterial disease, high risk of embolism and other high risk conditions (including hemodialysis, diabetes mellitus, carotid disease)

1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

Antithrombotic Trialists' Collaboration:
Evidence Supports Low Dose ASA (75–150mg)[1]



1. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration

BMJ VOLUME 324 12 JANUARY 2002

- 4500 pz diabetici
  - ASA 23.5% vs control 19.3% (P<0.01)
  - 42 eventi vascolari ogni 1000 pz trattati
- Pz non diabetici
  - ASA 17.2% vs control 13.7% (P<0.00001)
  - 35 eventi vascolari ogni 1000 pz trattati

Il beneficio della terapia antiaggregante è evidente in entrambe le popolazioni

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

Lancet 2009; 373: 1849–60

*Antithrombotic Trialists' (ATT) Collaboration**

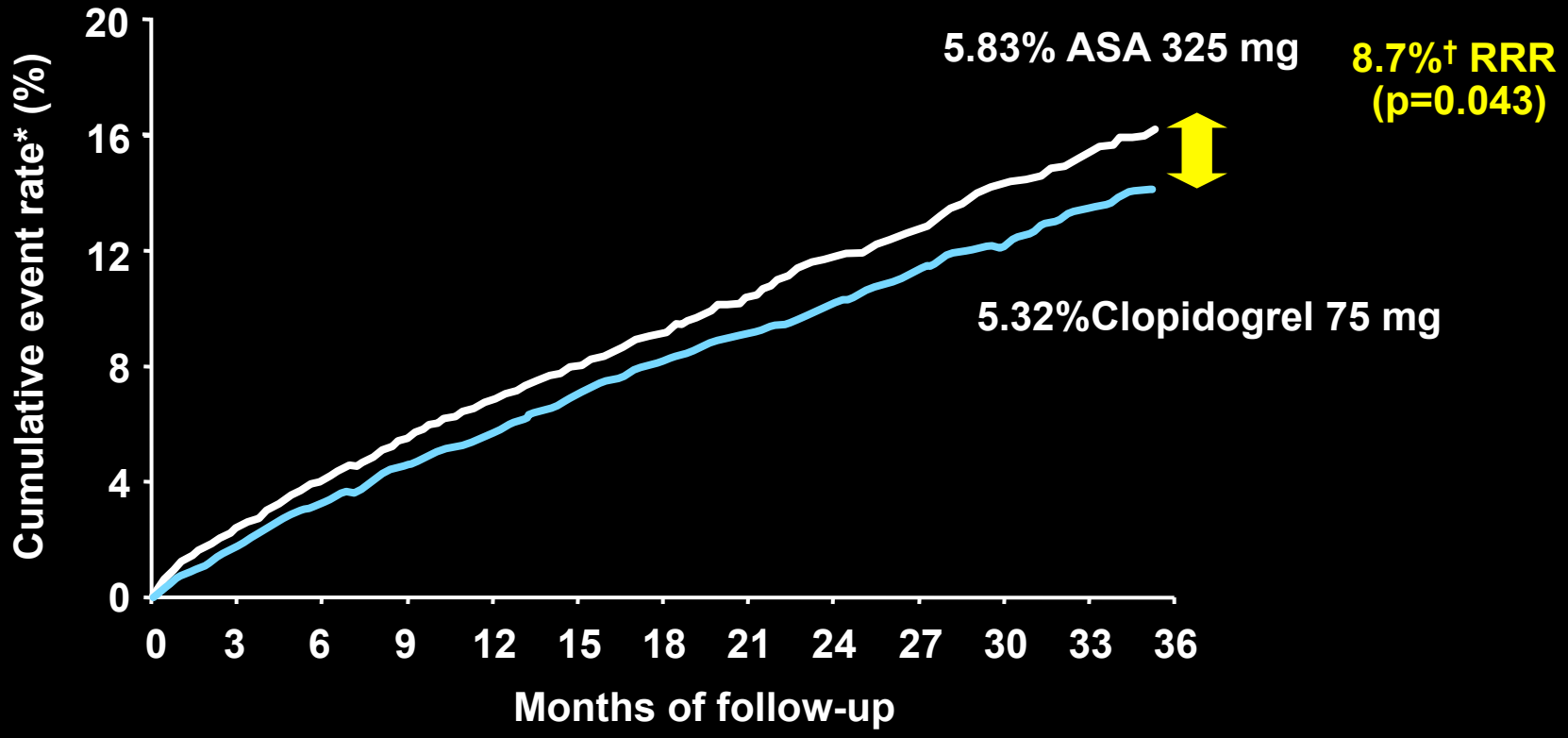
	Number of events (aspirin vs control)		Rate ratio (95% CI) (aspirin vs control)			Yearly absolute difference (% per year)	
	Primary prevention (660 000 person-years)	Secondary prevention (43 000 person-years)	Primary prevention	Secondary prevention	p value for heterogeneity	Primary prevention	Secondary prevention
Major coronary event	934 vs 1115	995 vs 1214	0·82 (0·75–0·90)	0·80 (0·73–0·88)	0·7	−0·06	−1·00*
Non-fatal MI	596 vs 756	357 vs 505	0·77 (0·69–0·86)	0·69 (0·60–0·80)	0·5	−0·05	−0·66
CHD mortality	372 vs 393	614 vs 696	0·95 (0·82–1·10)	0·87 (0·78–0·98)	0·4	−0·01	−0·34
Stroke	655 vs 682	480 vs 580	0·95 (0·85–1·06)	0·81 (0·71–0·92)	0·1	−0·01	−0·46*
Haemorrhagic	116 vs 89	36 vs 19	1·32 (1·00–1·75)	1·67 (0·97–2·90)	0·4	0·01	..†
Ischaemic	317 vs 367	140 vs 176	0·86 (0·74–1·00)	0·78 (0·61–0·99)	0·5	−0·02	..†
Unknown cause	222 vs 226	304 vs 385	0·97 (0·80–1·18)	0·77 (0·66–0·91)	0·1	−0·001	..†
Vascular death	619 vs 637	825 vs 896	0·97 (0·87–1·09)	0·91 (0·82–1·00)	0·4	−0·01	−0·29
Any serious vascular event	1671 vs 1883 (0·51% vs 0·57% per year)	1505 vs 1801 (6·69% vs 8·19% per year)	0·88 (0·82–0·94)	0·81 (0·75–0·87)	0·1	−0·07	−1·49*
Major extracranial bleed	335 vs 219	23 vs 6	1·54 (1·30–1·82)	2·69 (1·25–5·76)	0·2	0·03	..†

MI=myocardial infarction. CHD=coronary heart disease. Non-fatal MI definitions vary; see methods. *Major coronary event rates (percent per year, aspirin vs control) 6·0 vs 7·4 in post-MI trials and 2·4 vs 3·0 in post-cerebral vascular disease trials; corresponding rates of stroke (mainly of unknown cause) 0·6 vs 0·8 in post-MI trials and 3·9 vs 4·7 in post-cerebral vascular disease trials (webappendix pp 14–18). †Stroke causes, and extracranial bleeds, very incompletely reported.

Table 2: Comparison of proportional and absolute effects of aspirin in primary and secondary prevention trials

CAPRIE: Superior Efficacy of Clopidogrel 75 mg versus ASA 325 mg

19.185 Patients with recent ischemic stroke, recent MI or symptomatic PAD

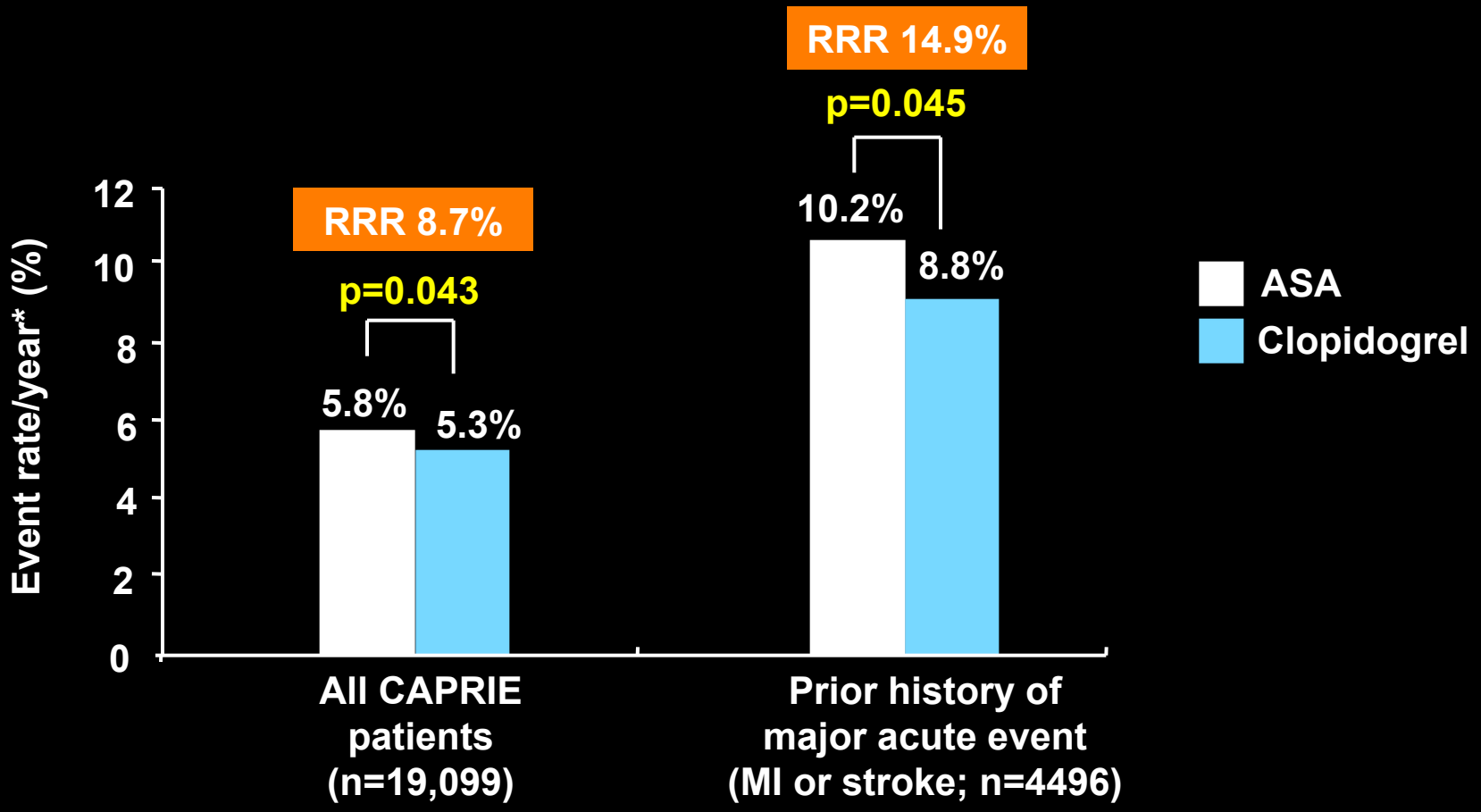


*The combined risk of MI, ischemic stroke or vascular death

†Intent-to-treat analysis (n=19,185)

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

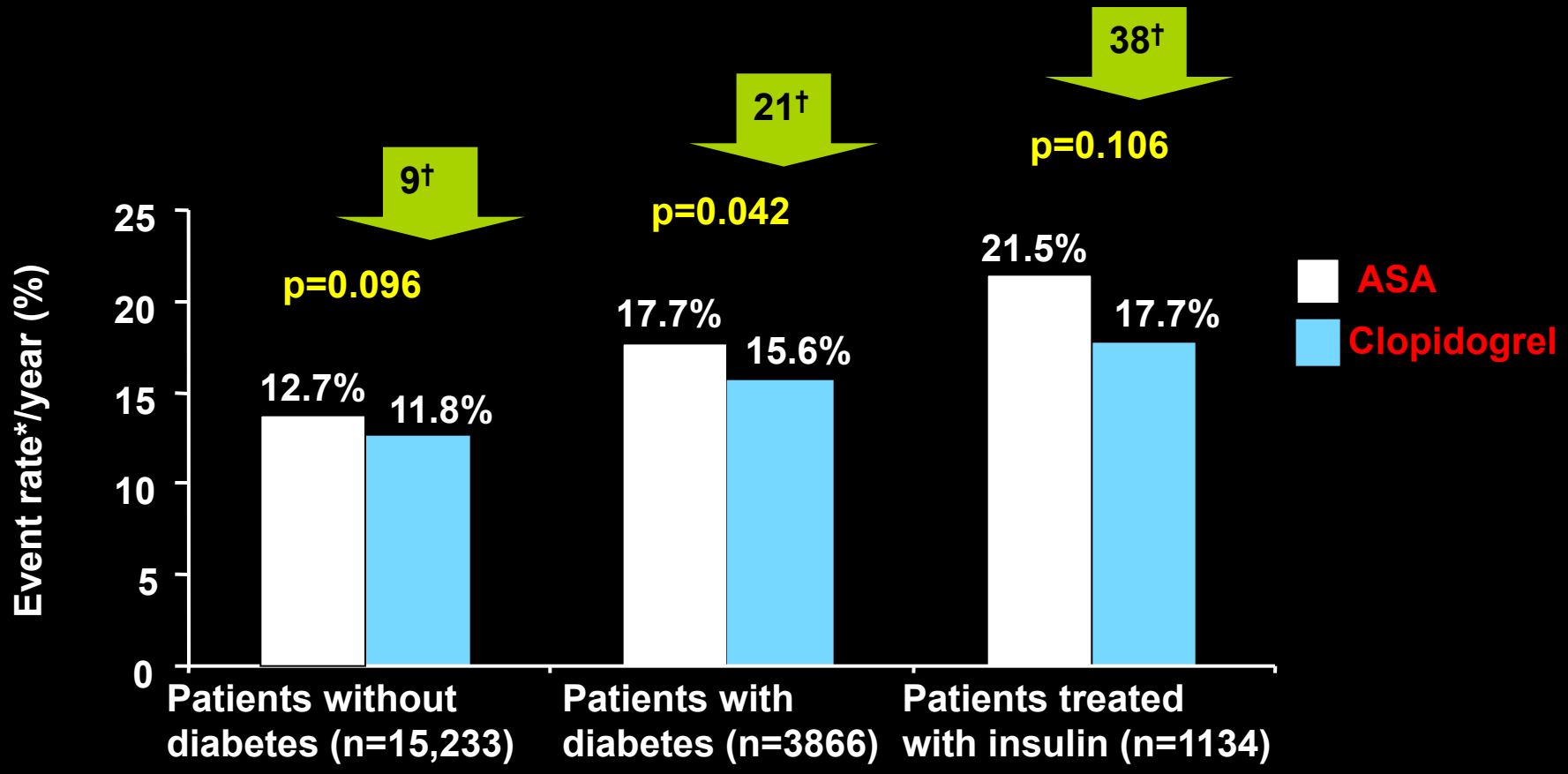
CAPRIE: Clopidogrel Provides Amplified Benefit in Patients with High Vascular Risk



*The combined risk of MI, ischemic stroke or vascular death;
mean duration of treatment was 1.6 years

Ringleb PA, Bhatt DL, Hirsch AT, et al. *Stroke* 2004; 35: 528–532.

CAPRIE: Clopidogrel Provided Amplified Benefit in Patients with Diabetes[1]



*The combined risk of MI, stroke, vascular death or rehospitalization for ischemic events/bleeding

1. Bhatt DL et al. *Am J Cardiol* 2002; 90: 625-628.

CAPRIE: Post hoc sub analysis

CAPRIE (diabetic subpopulation N=3866)	ASA	Clopidogrel	Size effect
Primary endpoint: stroke, MI, vascular death or rehospitalisation for ischaemia or bleeding	**17.5%**	**15.5%**	**RRR 12.4%** **ARR 2.1% p=0.042** **NNT 48**
Incidence of rehospitalisation for any bleeding event	**2.8%**	**1.8%**	**RRR 37%** **(95% CI 3.8 -58.7)** **p=0.0031**
Subset of patients treated with insulin at baseline (N=1.134) Primary endpoint: stroke, MI, vascular death or rehospitalisation for ischaemia or bleeding	**21.5%**	**17.7%**	**RRR 16.7%** **ARR 3.8% p=0.106** **NNT 26.3**

CHARISMA STUDY

ORIGINAL ARTICLE
N Engl J Med 2006;354:1706-17.
The NEW ENGLAND JOURNAL of MEDICINE

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

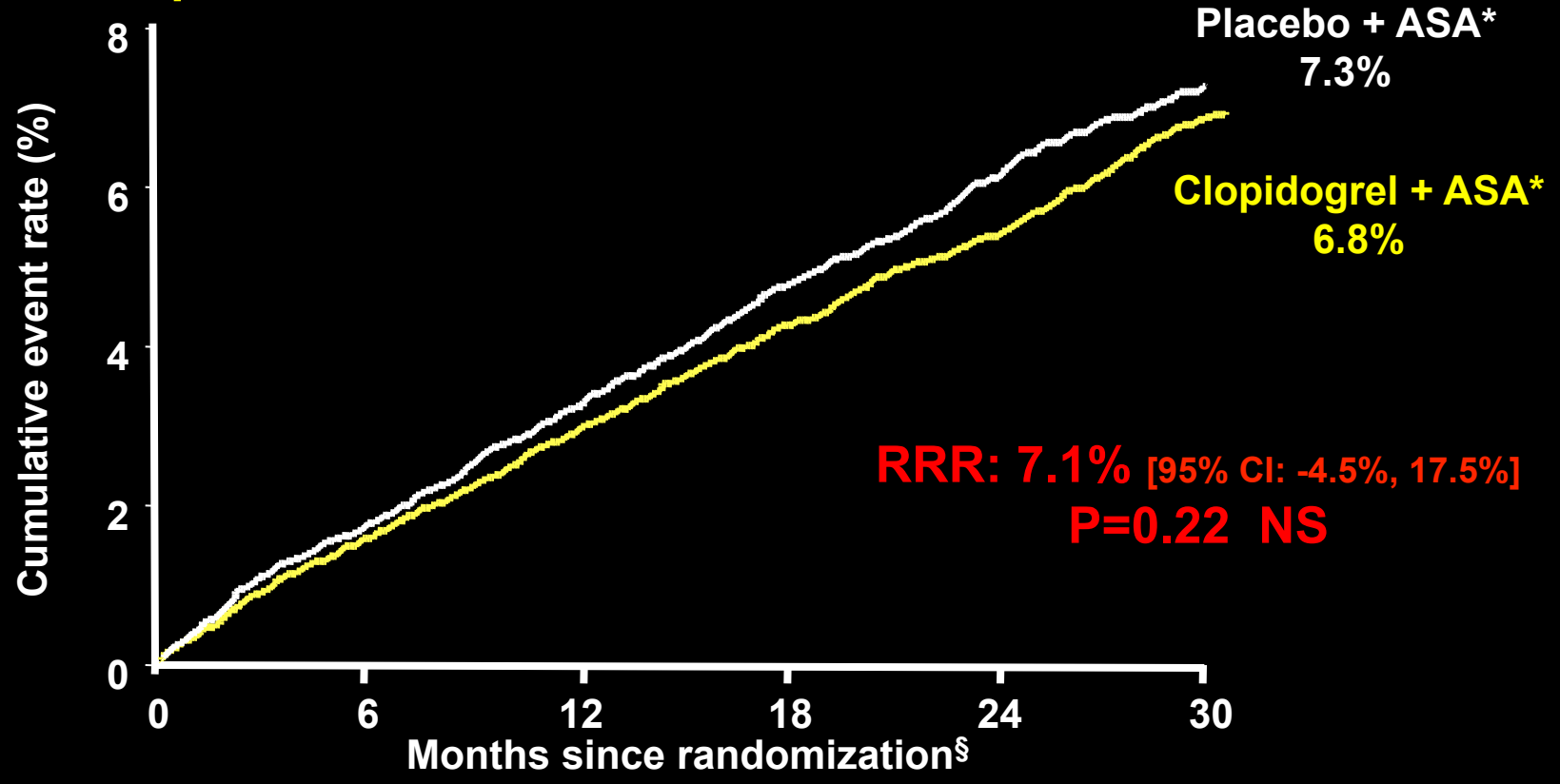
15.603 pz

- 12.153 pz con evidente CVD
- 3.284 pz con fattori di rischio multipli

Clopidogrel 75 mg + ASA (75 -162 mg) VS Placebo + ASA (75 -162 mg)

Primary endpoint: reducing the MI, Stroke, or death from CV causes

Primary Efficacy Outcome (MI, Stroke, or CV Death)†; 12.153 pz with evident cardiovascular disease e 3.284 pz with multiple cardiovascular risk factors



† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death
*All patients received ASA 75-162 mg/day

Bhatt DL, Fox KA, Hacke W, et al. N Engl J Med 2006

CHARISMA study

CHARISMA	ASA + clopidogrel	ASA + placebo	Size effect
Primary endpoint MI, Stroke, or CV death	**NS**		
Secondary endpoint MI, stroke, CV death or hospitalisation for unstable angina, TIA or revascularisation	**16.7%**	**17.9%**	**RR 0.92** 95% CI 0.86 to 0.995 p=0.04
Severe bleeding	**NS**		
Moderate bleeding	**2.1%**	**1.3%**	**RR 1.62** 95% CI 1.27 to 2.08 p=0.001

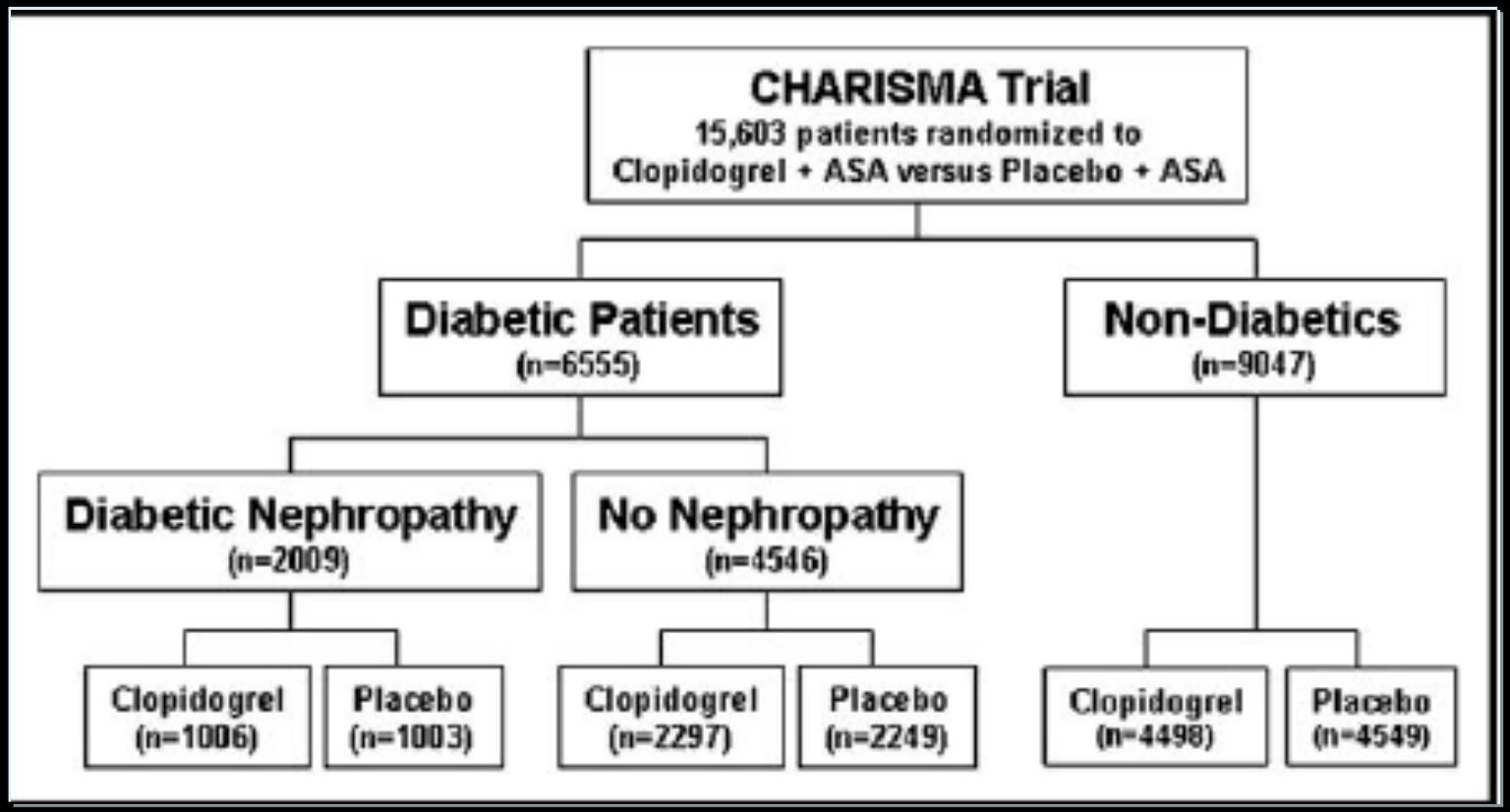
CHARISMA study: subgroup analysis

Roma, 9-11 novembre 2012

CHARISMA: subgroup analysis		ASA + clopidogrel	ASA + placebo	Size effect
Pz with clinically evident CV disease 12.153	Primary endpoint MI, Stroke, or CV death	**6.9%**	**7.9%**	RR 0.88 95% CI 0.77 – 0.998 p=0.046
	Severe bleeding	**NS**		
	Moderate bleeding	**2.1%**	**1.3%**	p<0.001
Pz with risk factors for CVD (asyntomatic) 3.284	Primary endpoint MI, Stroke, or CV death	**6.6%**	**5.5%**	p=0.20
	Death from all causes	**5.4%**	**3.8%**	p=0.04
	Death from CV causes	**3.9%**	**2.2%**	p=0.01
	Severe bleeding	**NS**		
	Moderate bleeding	**NS**		

Clinical Outcomes of Patients With Diabetic Nephropathy Randomized to Clopidogrel Plus Aspirin Versus Aspirin Alone (A post hoc Analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA] Trial)

(Am J Cardiol 2009;103:1359–1363)

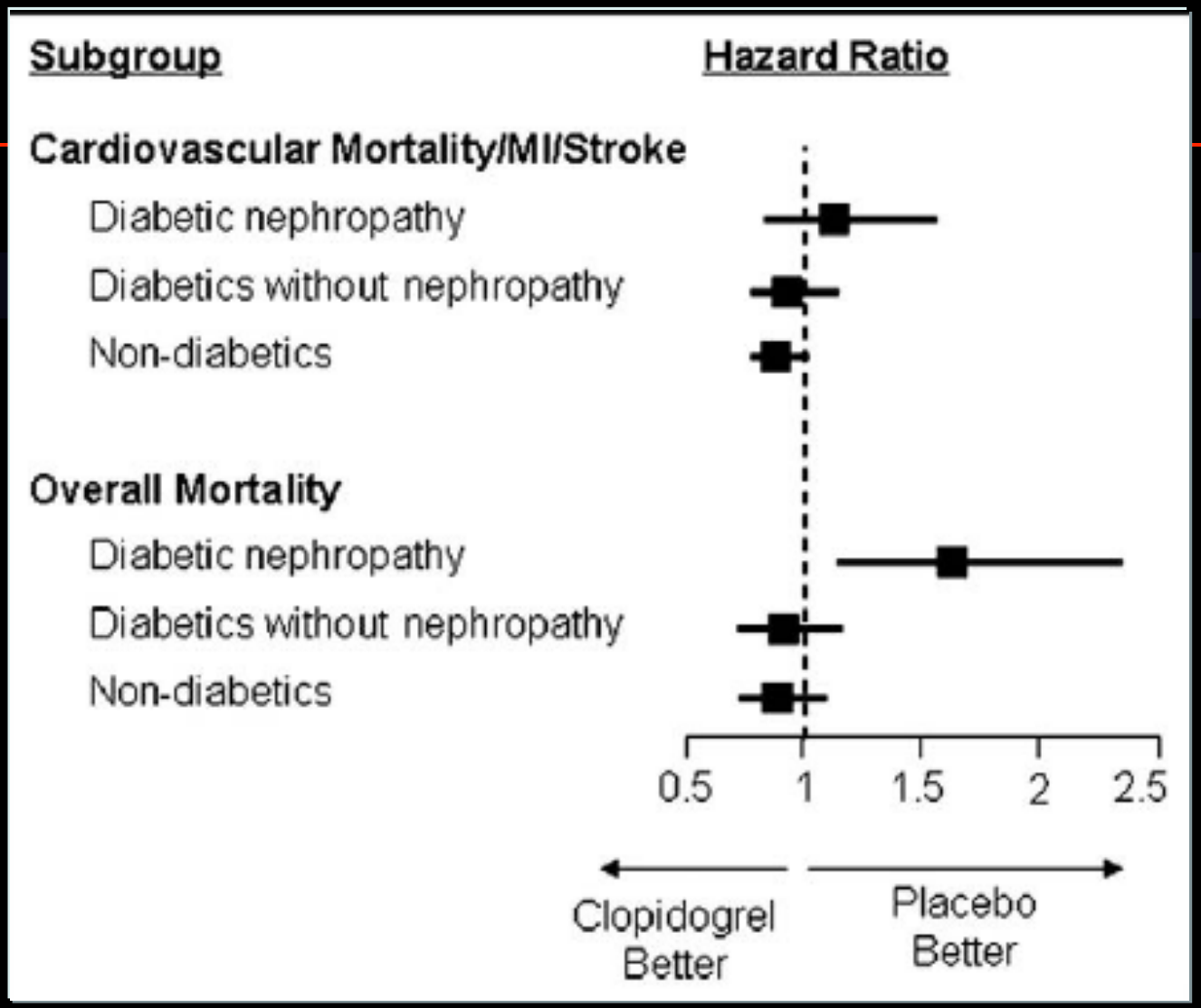


Efficacy end points in the CHARISMA study

Outcome	Nondiabetic 9.047 pz	Diabetic without nefropaty 4.546 pz	Diabetic nefropaty 2.009 pz	p value
Overall CV death/MI/stroke	**6.3%**	**8.3%** 1.4 (1.2 – 1.5)	**8%** 1.3 (1.1 – 1.6)	**< 0.001**
CV death	**2.5%**	**3.6%** 1.5 (1.2 – 1-8)	**4.1%** 1.7 (1.3 – 2.2)	**< 0.001**
Non fatal IMA	**1.9%**	**2.7%** 1.4 (1.1 – 1.8)	**2.5%** 1.4 (1.0 – 1.9)	**0.004**
Non fatal stroke	**2.4%**	**2.9%** 1.2 (1 – 1.5)	**2.1%** 0.9 (0.6 – 1.2)	**0.110**
Overal death	**4.2%**	**5.5%** 1.3 (1.1 – 1.6)	**5.9%** 1.5 (1.2 – 1.8)	**< 0.001**
Overal MI	**2.1%**	**2.9%** 1.4 (1.1 -1.8)	**3%** 1.4 (1.1 – 1.9)	**0.002**
Fatal MI	**0.2%**	**0.4%** 1.7 (0.9 – 3.2)	**0.6%** 2.5 (1.2 – 5.1)	**0.021**

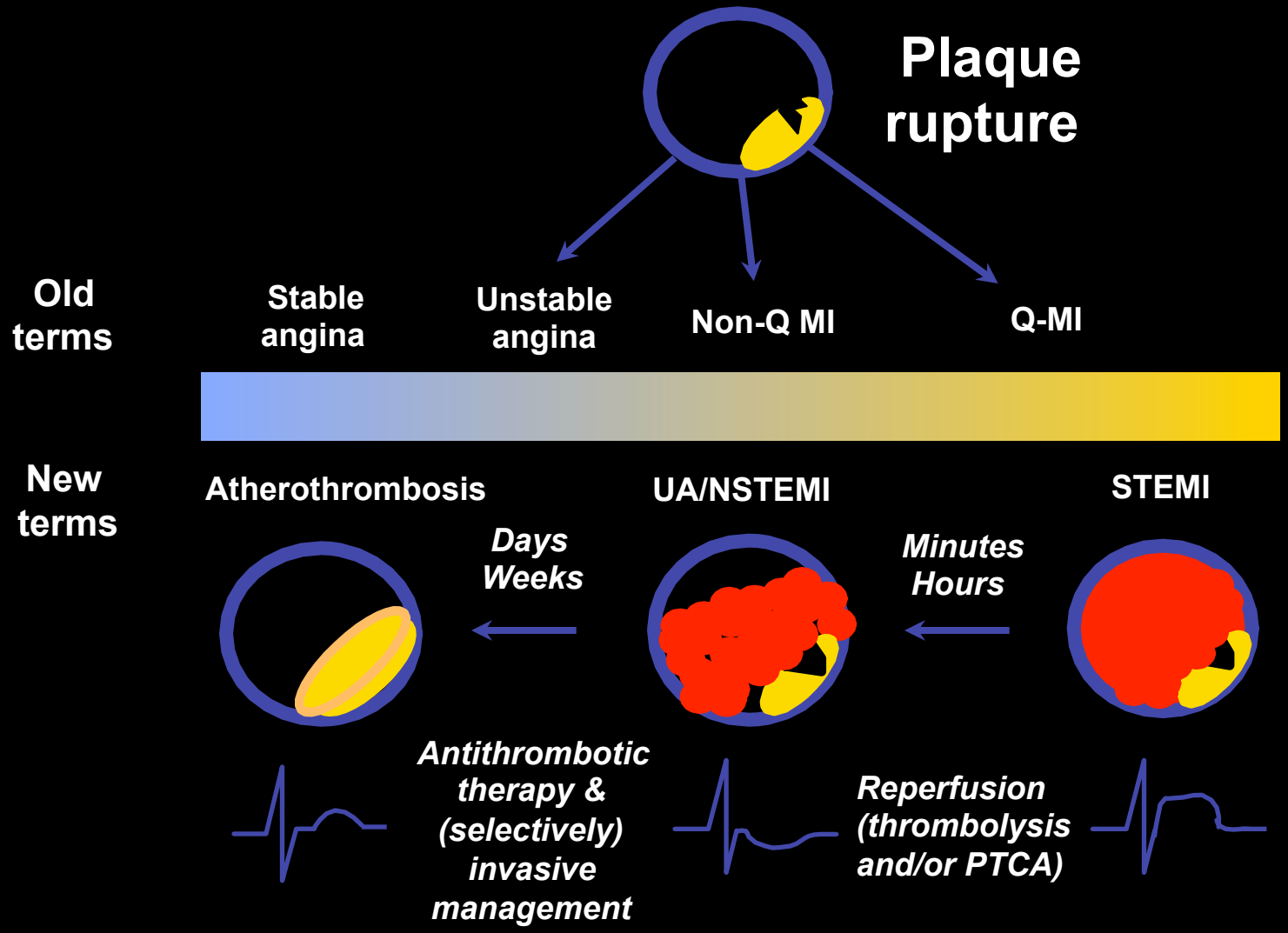
Efficacy and safety endpoints in patients with diabetic nephropaty based on drug assignment

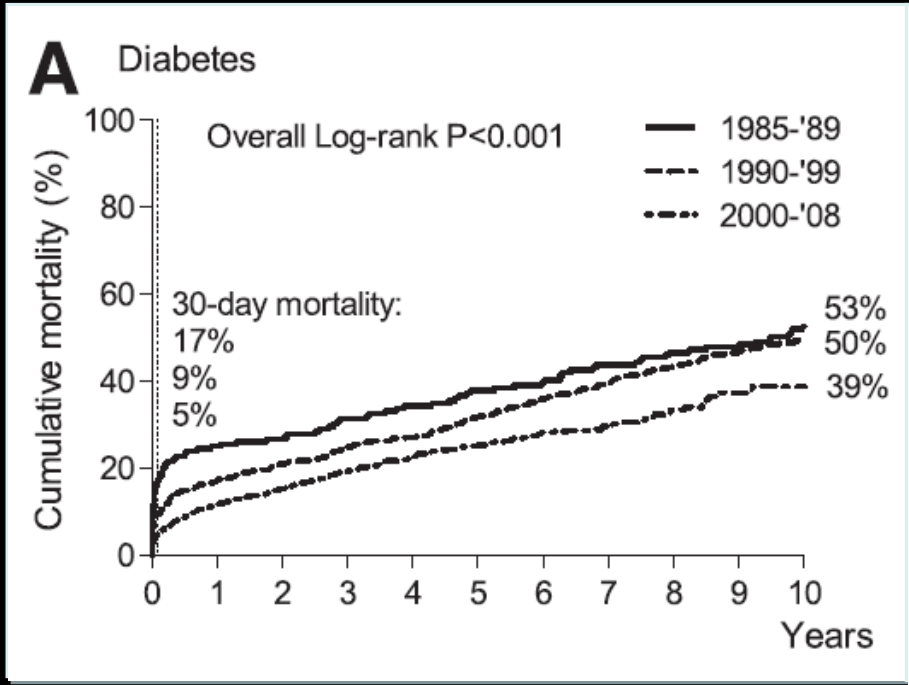
	ASA + Clopidogrel	ASA + Placebo	HR	p value
Overall death	7.3%	4.5%	1.6	0.008
CV death	5.1%	3.1%	1.7	0.023
Overall CV death/MI/ stroke	8.4%	7.5%	1.1	0.405
Non fatal MI	2.2%	2.9%	0.8	0.347
Non fatal stroke	2.0%	2.2%	0.9	0.766
Overall CV/MI/stroke/ hospitalization	16.5%	16.1%	1.0	0.784
Hospitalization	9.6%	10.4%	0-9	0.634
GUSTO severe bleeding	2.6%	1.5%	1.8	0.075
GUSTO moderate bleeding	2.8%	2.4%	1.2	0.543

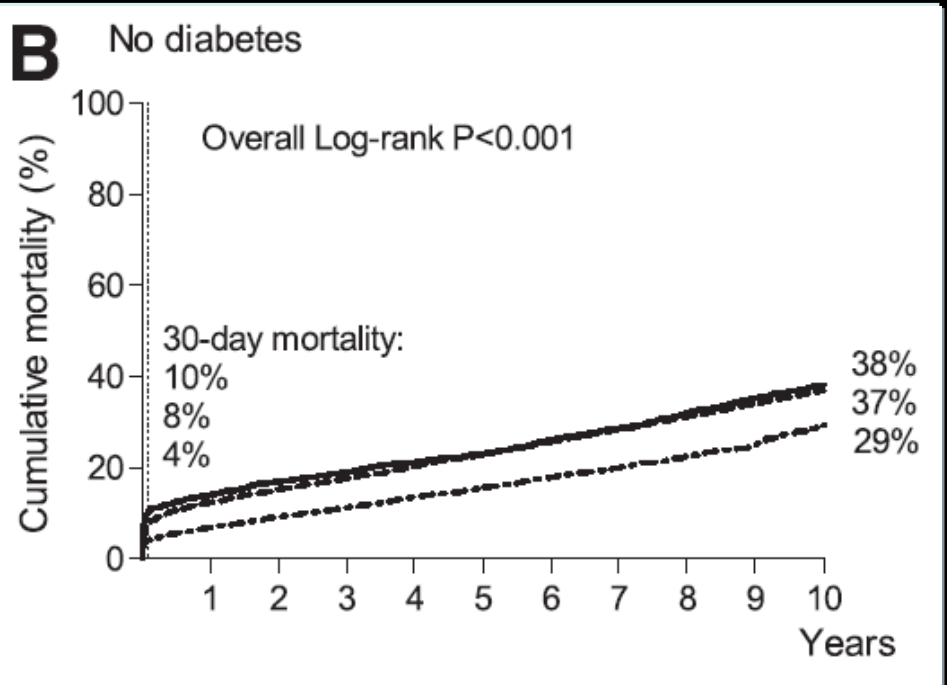


Effect of drug assignment and diabetic nephropaty status on the primary endpoint and overall mortality

ACUTE CORONARY SYNDROMES



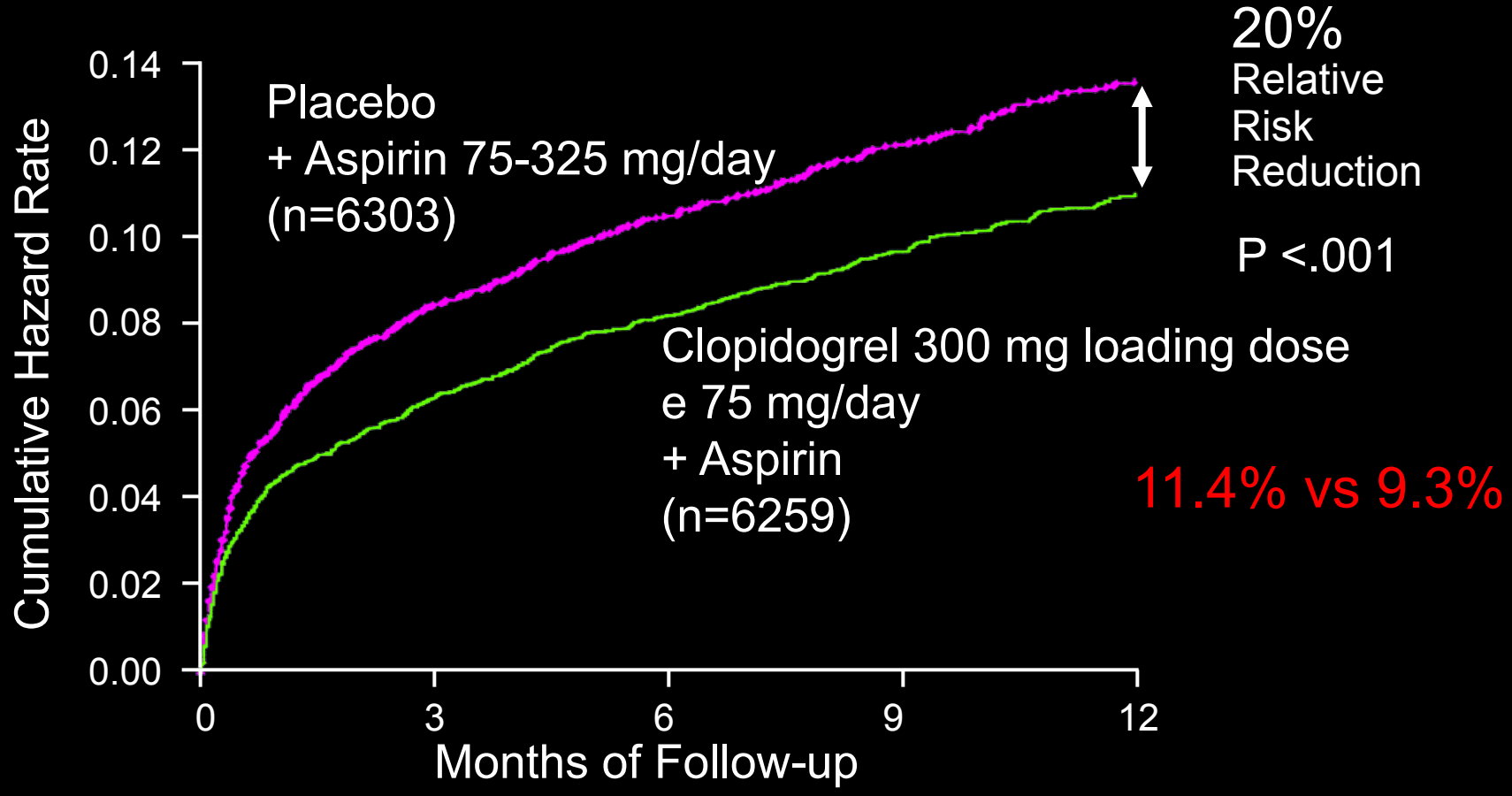




Short- and Long-Term Mortality After Myocardial Infarction in Patients With and Without Diabetes

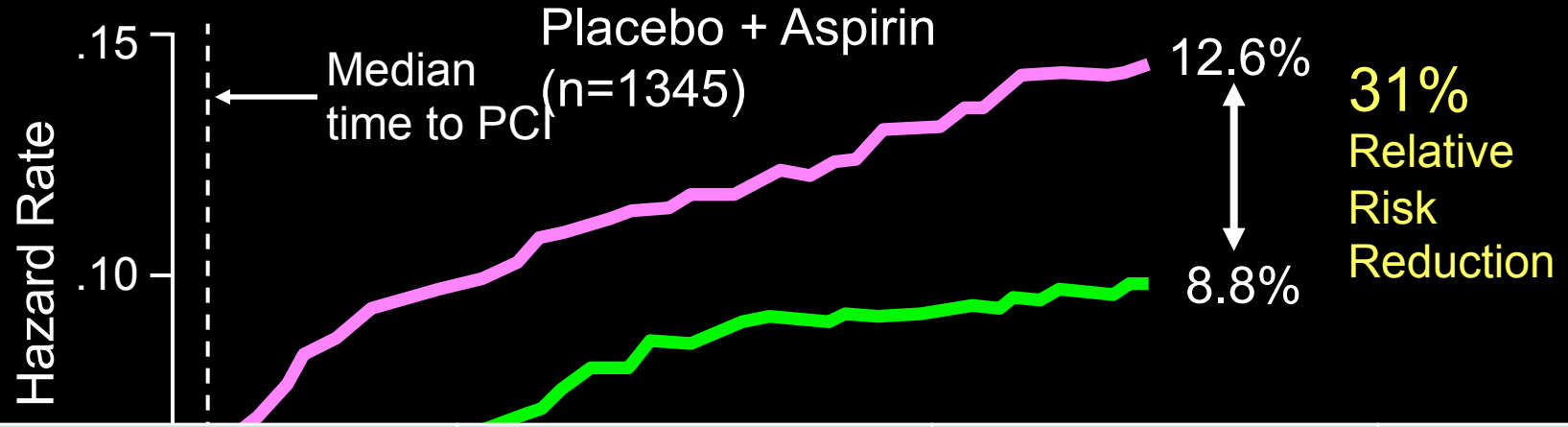
DIABETES CARE, VOLUME 35, OCTOBER 2012

CURE Study: 12562 pz con UA/NSTEMI
Primary End Point: MI/Stroke/CV Death



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

PCI-CURE Study: CV Death or MI From Randomization



	ASA + Clopidogrel	ASA + Placebo	
Primary endpoint: composite vascular death, MI or Stroke	9.3 %	11.4 %	p<0.001
Major bleeding	3.7 %	2.7 %	p=0.001
Life-threatenig bleeding	2.2 %	1.8 %	p=0.13 NS

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

Large-scale randomised clinical trials evalueting efficacy of dual antiplatelet therapy

Roma,
9-11 novembre 2012

Study	Drugs	Setting	N.pz	Results	N. Pz Diabetes	Results
CURE	ASA + clopidogrel vs ASA	USA or NSTEMI	12.562	9.3% vs 11.4% RR=0.80	2.840	14.2% vs 16.7% RR=0.84
PCI - CURE	ASA + clopidogrel vs ASA	NSTEMI	2.658	4.5% vs 6.4% RR=0.70	540	12.9% vs 16.5% RR=77
CREDO	ASA + Clopidogrel vs ASA	Elective PCI	2.116	8.5% vs 11.5% RRR=26.9%	560	NA RRR=11.2%
CLARITY	ASA + clopidogrel vs ASA	STEMI with fibrinolis	3.491	15% vs 21.7% OR=0.64	575	NA
PCI - CLARITY	ASA + clopidogrel vs ASA	STEMI	1.863	3.6% vs 6,2% OR=0.54	282	6% vs 10.1% OR=0.61

Parlare di terapia antiaggregante nelle sindromi coronariche acute e nello stroke è la stessa cosa ?

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

Lancet 2004; 364: 331–37

Match study (7599 pz)	Clopidogrel + ASA 75 mg	Clopidogrel + placebo	Size effect
Primary endpoint (ischaemic stroke, MI, vascular death or rehospitalisation for acute ischaemia	**15.7%**	**16.7%**	**RR 6.4%** 95% CI (-4.6 – 16.3) **AR 1%** p=0.244
Life-threatening bleeding	**2.6%**	**1.3%**	**RR 1.36** 95% CI (0.64-1.88) p<0.0001
Major bleeding	**2%**	**1%**	**RR 1.36** 95% CI (0.86-1.86) p<0.0001
Minor bleeding	**3%**	**1%**	p<0.0001

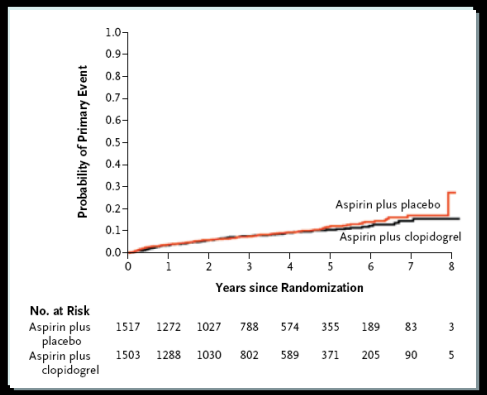
- Non vi è alcuna differenza di mortalità tra i due gruppi
- Una analisi post hoc nella popolazione diabetica 5197 pz (circa 70%) non ha evidenziato alcuna differenza 15.1% vs 16.8 %

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*

N Engl J Med 2012;367:817-25.

	ASA 325 mg + Placebo	ASA 325 mg + clopidogrel 75 mg	HR
Primary endpoint	2.7%	2.5%	0.92 (0.72 – 1.16) p=0.48
Maior bleedind	1.1%	2.1%	1.97 (1.41 – 2.71) p< 0.001
All death	1.4%	2.1%	1.52 (1.14 – 2.04) p<0.004
Diabetici	3.8%	3.6%	0.93
No Diabete	2.1%	1.9%	0.93



- 3020 pz con recente ictus lacunare con follow up di 3.4 anni
- Primary endpoint: recidiva di ictus

Effect of Addition of Clopidogrel to Aspirin on Mortality
Systematic Review of Randomized Trials

Santiago Palacio, MD; Robert G. Hart, MD; Lesly A. Pearce, MS; Oscar R. Benavente, MD

(*Stroke*. 2012;43:2157-2162.)

Risultati relativi a oltre 90.000 pz in follow up per almeno un anno
ASA + Clopidogrel vs ASA

Risultati	OR
Mortalità a breve termine 14 g – 3 mesi	**0.93** (CI 0.87 – 0.99)
Mortalità a lungo termine > 3 mesi	**0.97** (CI 0.91 – 1.04)
IMA	**0.82** (CI 0.74 – 0.91)
Emorragie fatali	**1.35** (CI 0.97 - 1.90)

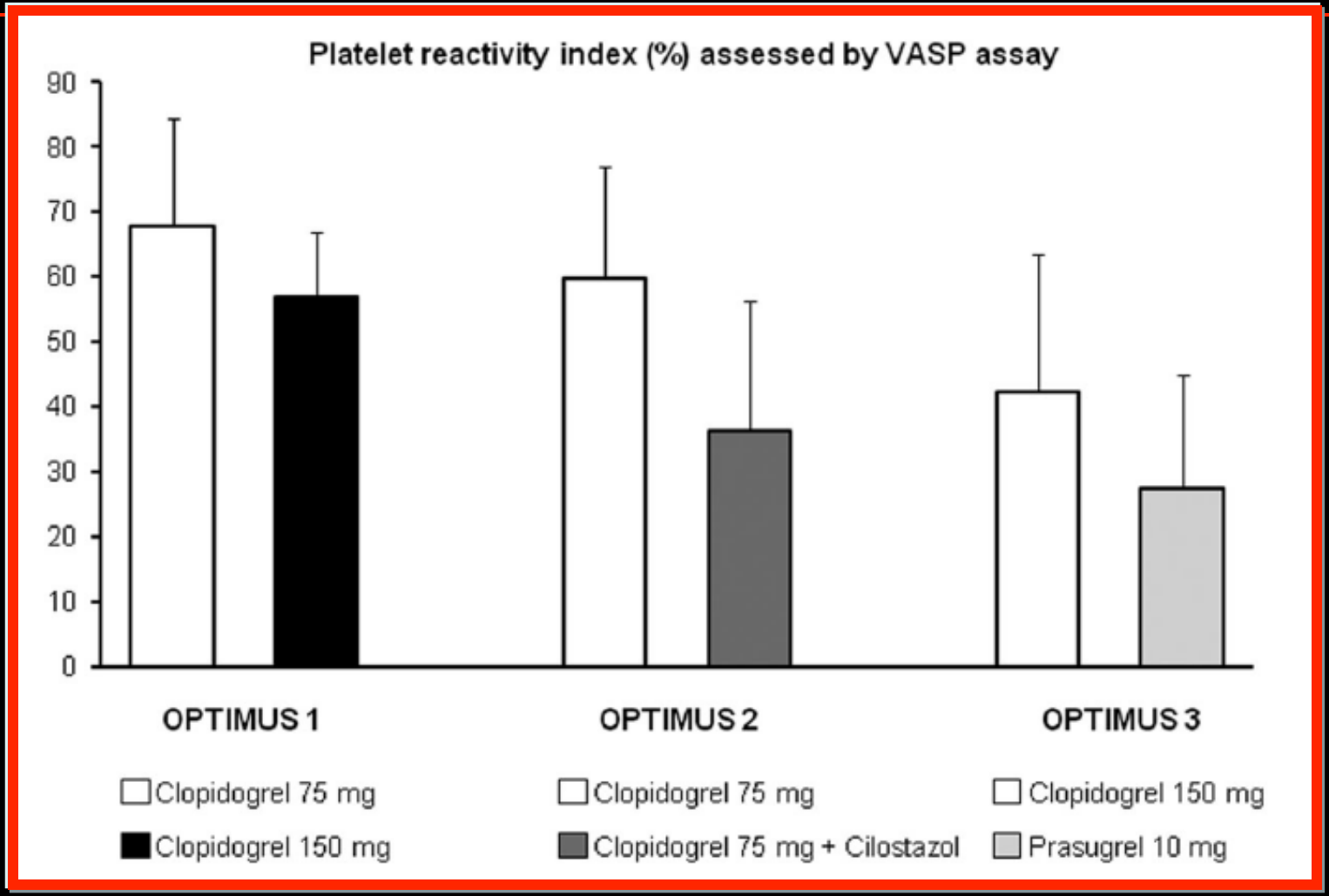
E LA RESISTENZA ALLA TERAPIA ANTIAGGREGANTE ?

RECIDIVA ?

Resistenza a ASA e CLOPIDOGREL

ASA	Inadeguato blocco COX-1 specie nei pz diabetici; ibuprofene; migliorare il compenso metabolico ? Aumentare la dose ?
CLOPIDOGREL	Fattori genetici, fattori cellulari, fattori clinici (in particolare diabetici insulinotrattati)

FARMACI PIU EFFICACI o DOSE INSUFFICIENTE o ASSOCIAZIONE DI PIU' FARMACI ?



Circulation **February 22, 2011**

Diabetes and Antiplatelet Therapy in Acute Coronary Syndrome

José Luis Ferreiro, MD; Dominick J. Angiolillo, MD, PhD

Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes

The CURRENT–OASIS 7 Investigators*

(N Engl J Med 2010;363:930-42.

25.086 pz con sindrome coronarica acuta, di cui 23% diabetici
Clopidogrel carico 600 mg, 150 mg x 6 giorni, 75 mg/die
Clopidogrel carico 300 mg, 75 mg/die
ASA 300-325 mg/die
ASA 75-100 mg/die

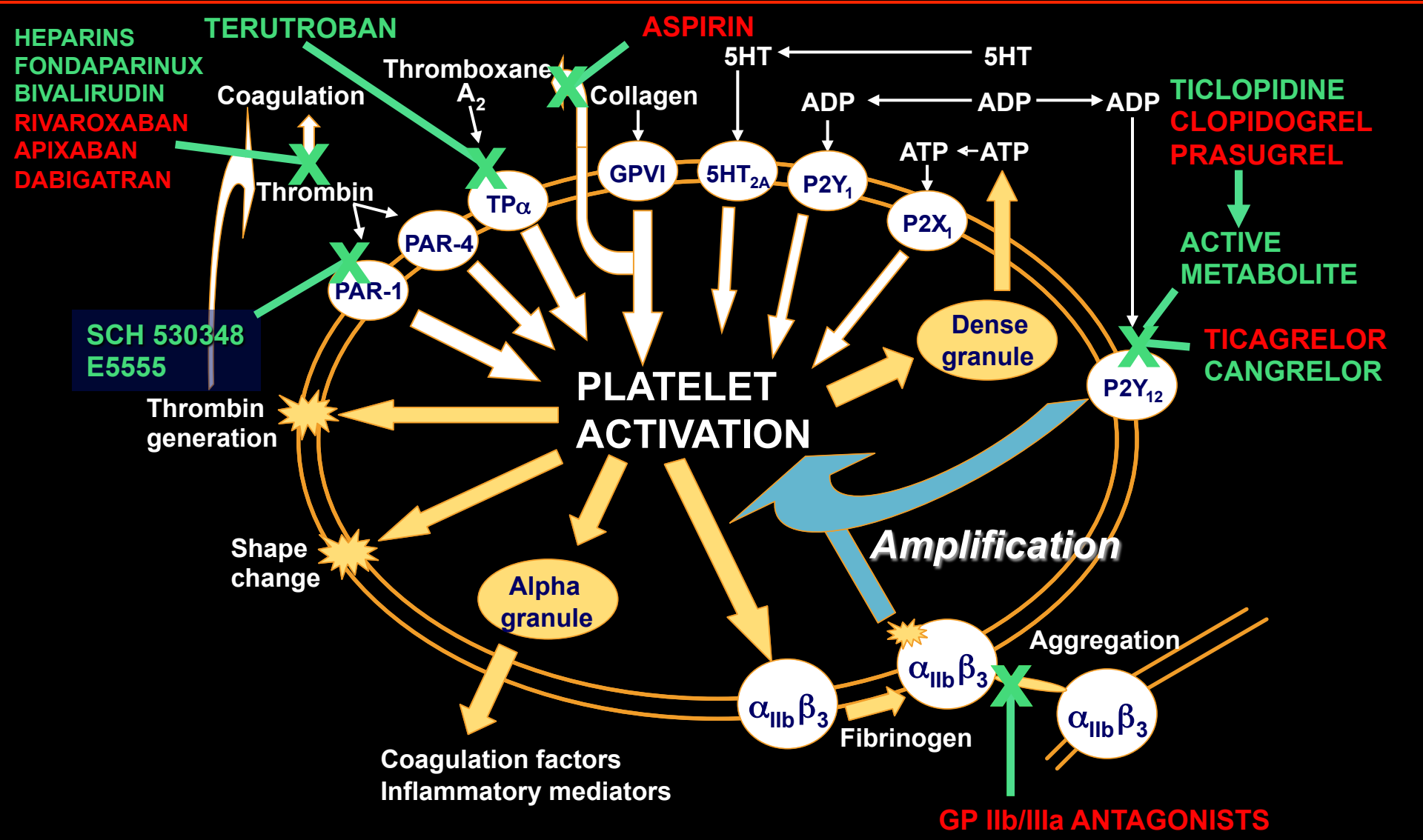
End point Primario: morte cardiovascolare, IMA or Stroke a 30 giorni

CLOPIDOGREL	Double dose	Standard dose	
Primary endpoint	4.2%	4.4%	p=0.30
Stent Thrombosis	1.6%	2.3%	p=0.001
Major bleeding	2.5%	2%	p=0.01

ASA	Higher dose	Lower dose	
Primary endpoint	4.2%	4.4%	p=0.61
Major bleeding	2.3%	2.3%	p=0.90

Targets for Platelet Inhibition

Roma,
9-11 novembre 2012



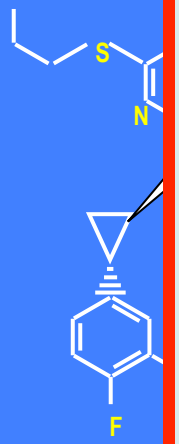
GP = glycoprotein; PAR = protease-activated receptor; TP = thromboxane A_2 / prostaglandin H_2.

Storey RF. *Curr Pharm Des*. 2006;12:1255-1259.

Antiplatelets Drug metabolism

Roma,
9-11 novembre 2012

Ticagre



Ticagrelo

Prasugre

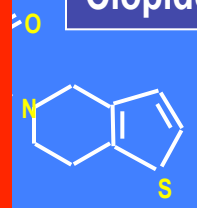
Clopidog

Table 8 $P2Y_{12}$ inhibitors

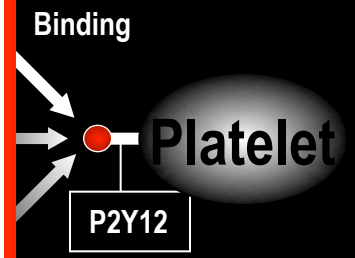
	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect[a]	2–4 h	30 min	30 min
Duration of effect	3–10 days	5–10 days	3–4 days
Withdrawal before major surgery	5 days	7 days	5 days

[a]50% inhibition of platelet aggregation.

Clopidogrel



Active compoud
Intermediate metabolite
Prodrug



Trial Design Comparison & Background Philosophy

N Engl J Med 2007;357:2001-15.

TRITON TIMI-38

- 13.608 pz
- Scheduled PCI
- Within 72 h from symptom onset
- Clopidogrel «naive»
- 15 month Follow-up

Selected patient cohort with known coronary anatomy and planned revascularization

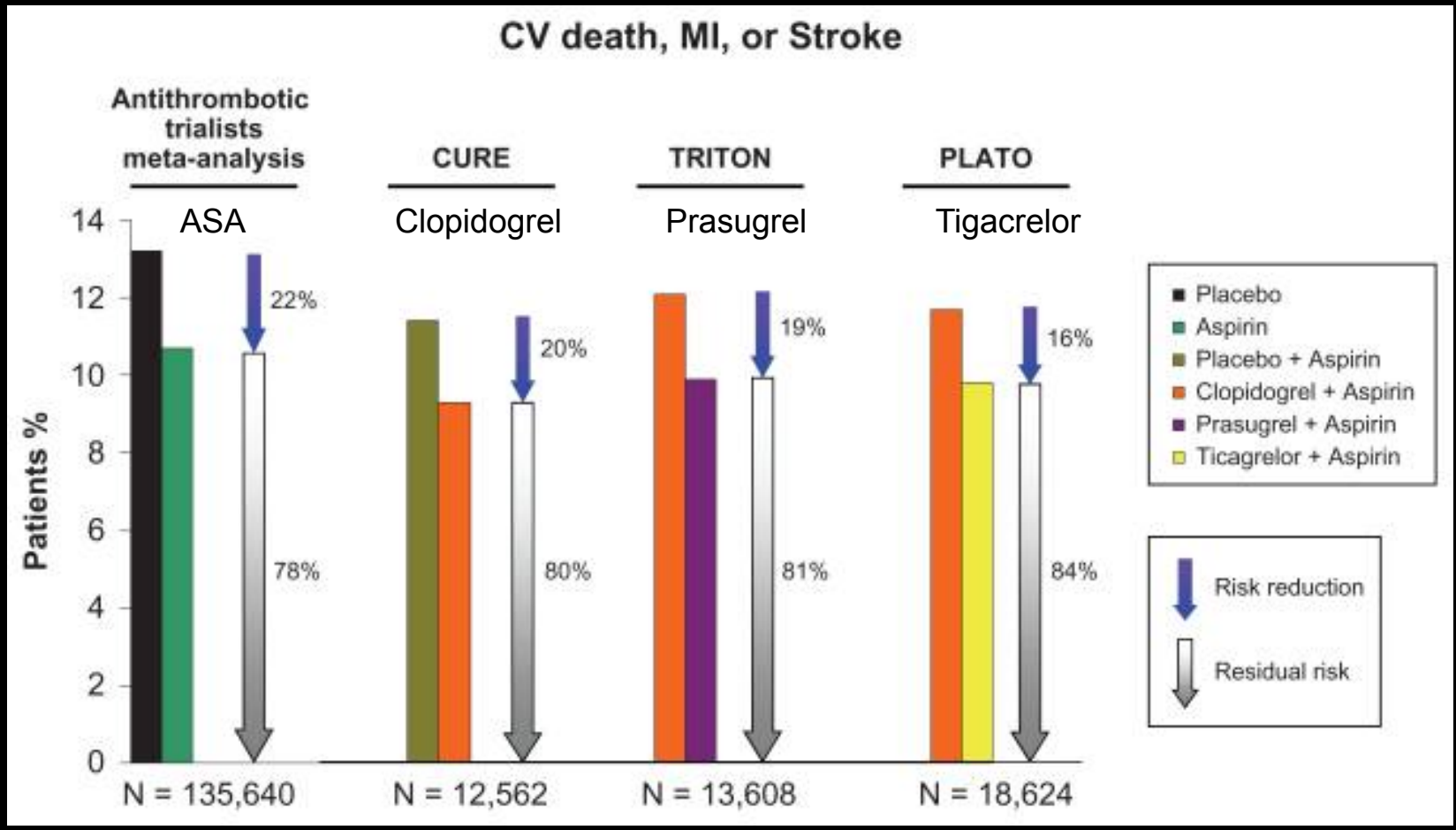
N Engl J Med 2009;361:1045-57.

PLATO

- 18.604 pz
- All ACS comers
- Within 24 h from symptom onset
- Clopidogrel allowed (47% of pts with LD)
- 12 month Follow-up

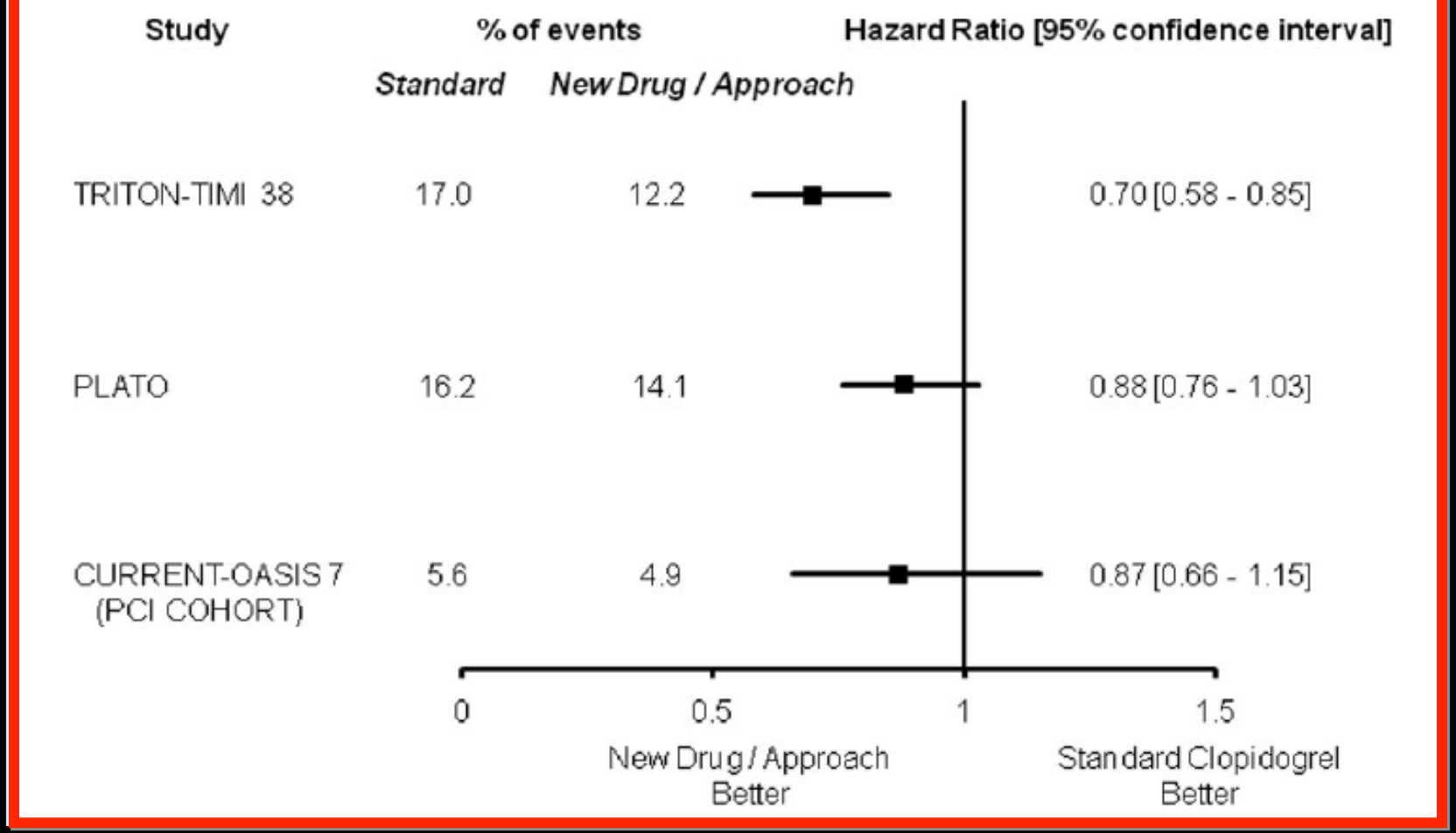
More «Real World» strategy with roughly 30% primarily conservative treated patients, 10% CABG and 60% PCI-treated patients

Risk reduction and residual risk for cardiovascular (CV) death, myocardial infarction (MI), or stroke *in patients receiving antiplatelet therapy*



CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events;
PLATO, Platelet Inhibition and Clinical Outcomes;
TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel.

Efficacy of new drugs/approaches in reducing adverse outcomes in diabetes mellitus from large-scale trials

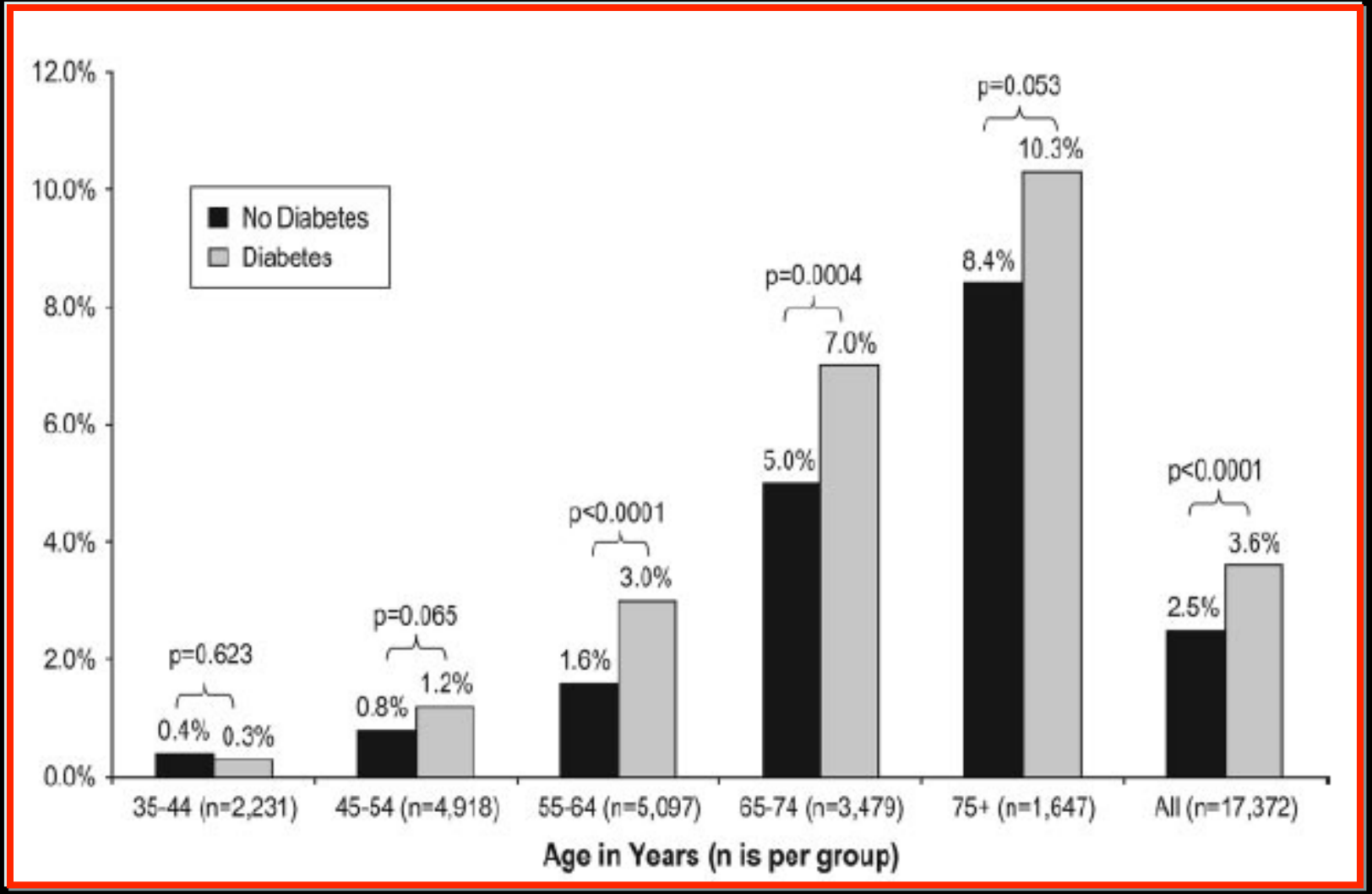


Circulation **February 22, 2011**

Diabetes and Antiplatelet Therapy in Acute Coronary Syndrome

José Luis Ferreiro, MD; Dominick J. Angiolillo, MD, PhD

Diabete e Fibrillazione Atriale



Prevalence of atrial fibrillation by age and diabetes status; Diabetes Care, 2009

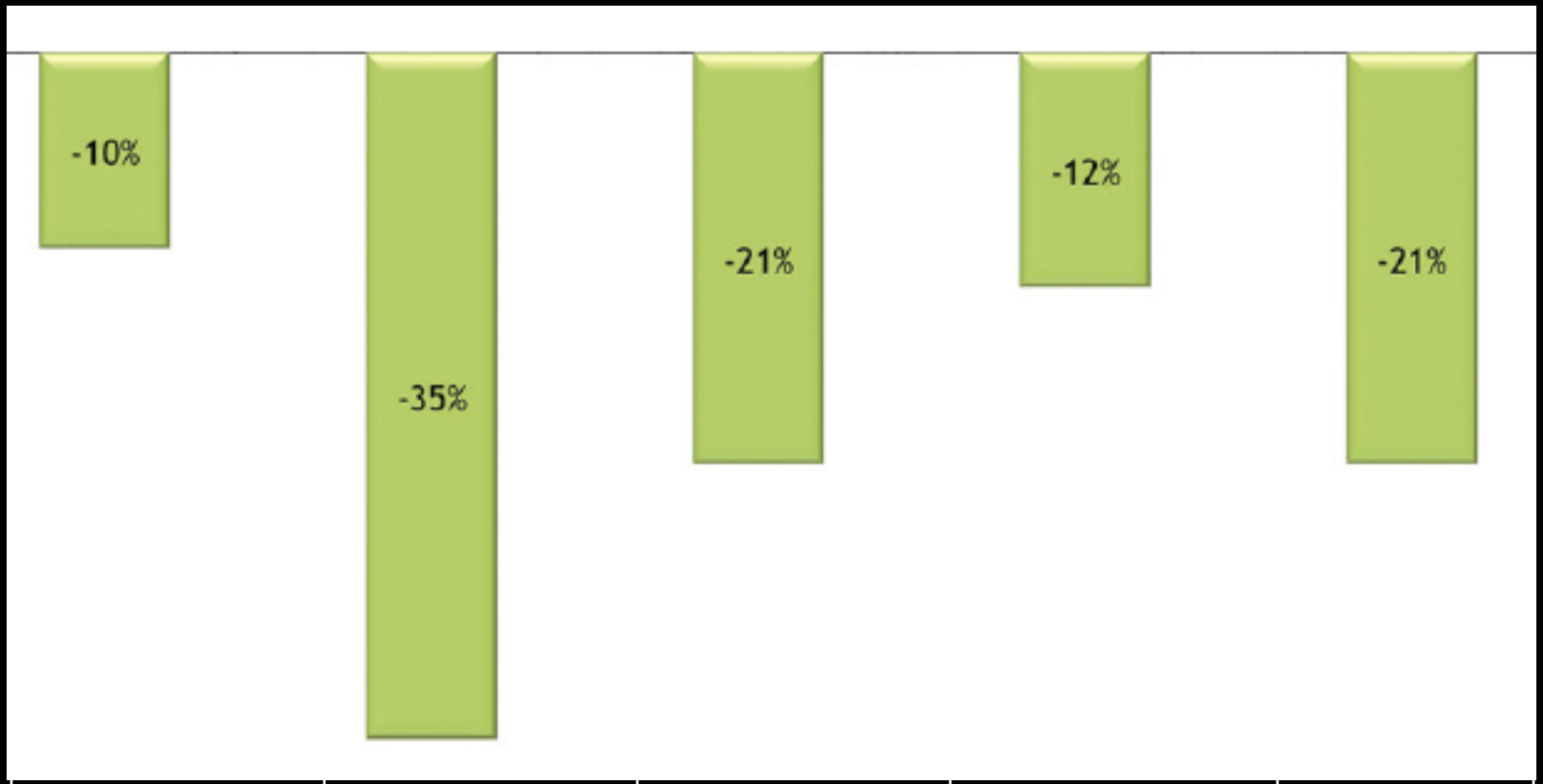
I nuovi anticoagulanti orali

Roma,
9-11 novembre 2012

	RE-LY (dabigatran)	ROCKET-AF (rivaroxaban)	ARISTOTLE (apixaban)
Età (anni)	71,5 ± 8,5 (media)	73 (mediana)	70 (mediana)
Rapporto M/F (%)	64/36	60,3/39,7	64,5/35,5
Follow-up (mesi)	30	28	30
TTR (%, media)	64	55	62,2
$CHADS_2 \geq 2$ (%)	67	100	66
$CHADS_2 \geq 3$ (%)	32,6	87	30,2
Pregresso ictus/TIA (%)	20	54,9 (pregresso ictus/ TIA/embolia sistemica)	19,2
ASA al basale (%)	39,0	36,3	31,3
Pregresso infarto miocardico acuto (%)	16,8	16,6	14,5
Ipertensione arteriosa (%)	78,8	90,3	87,3
Diabete mellito (%)	23,2	40,4	25,0
Scompenso cardiaco (%)	32,0	62,6	35,5
FA parossistica (%)	32,4	17,5	15,1
FA permanente/persistente (%)	67,6	81,1	84,9

Italian Journal of Medicine (2012) 6, 153—169

Riduzione del rischio relativo (RRR) di ictus ischemico ed emorragico e tromboembolismo sistemico dei nuovi anticoagulanti orali rispetto al Warfarin

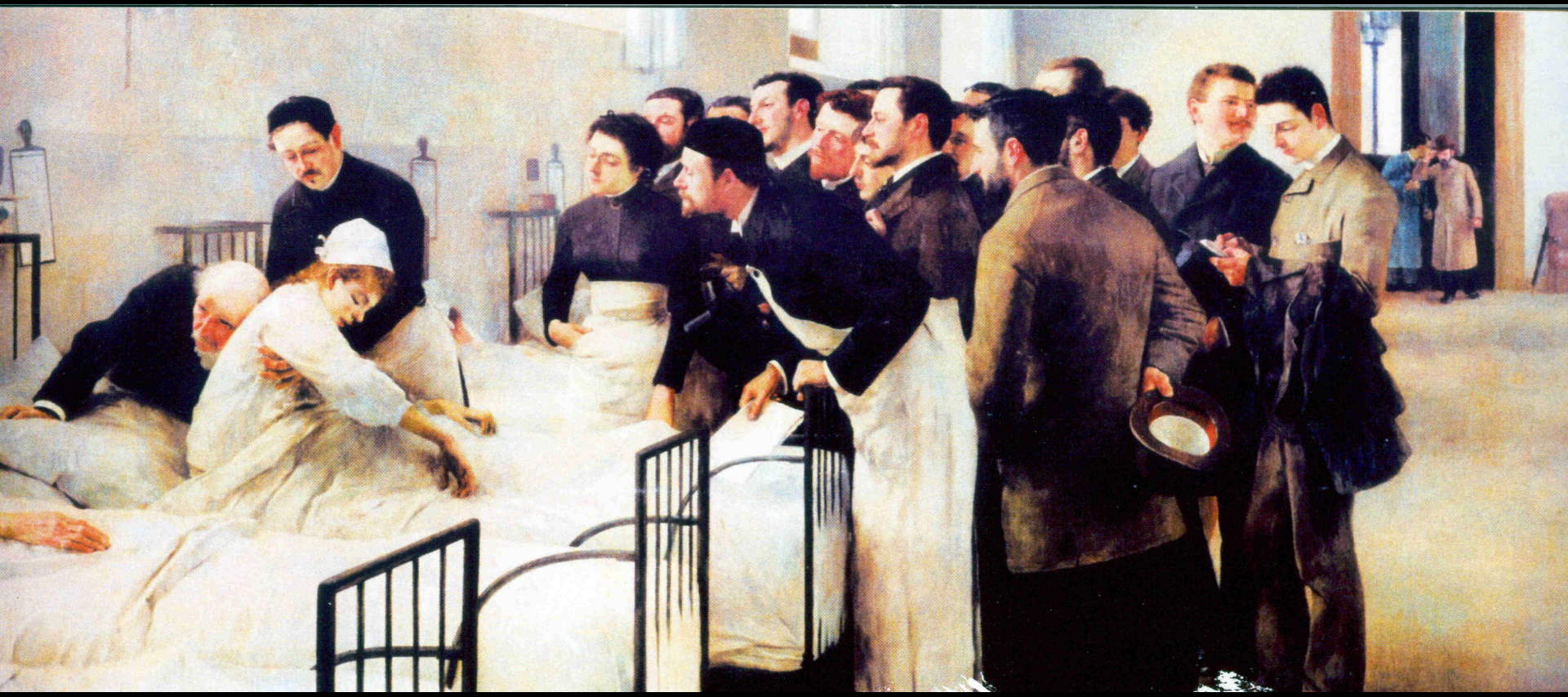


Dabigatran 110 bid	Dabigatran 150 bid	Rivaroxaban per protocollo	Rivaroxaban intention to treat	Apixaban
- 10 %	- 35 %	- 21 %	- 12 %	- 21 %

Italian Journal of Medicine (2012) 6, 153—169

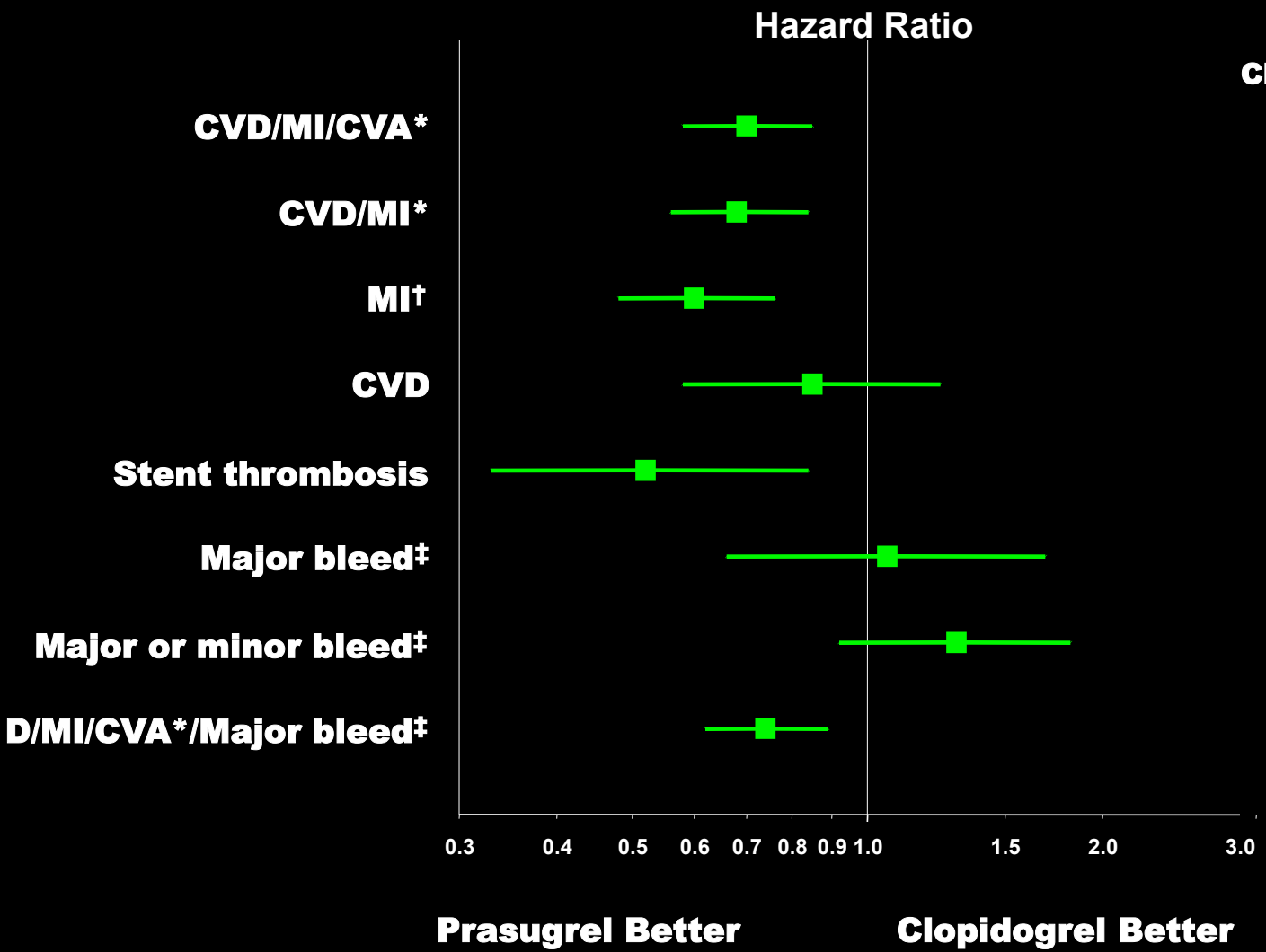
Conclusioni

- Nonostante la terapia il rischio residuo per eventi cardiovascolare è ancora elevato
- Il rischio emorragico è ancora elevato
- Dobbiamo risolvere il problema della variabilità della risposta
- Oggi possiamo personalizzare la terapia
- Sono in arrivo PAR-1 / antagonisti recettoriali della Trombina
  - ATOPAXAR
  - VORAPAXAR



Vi ringrazio per l' attenzione

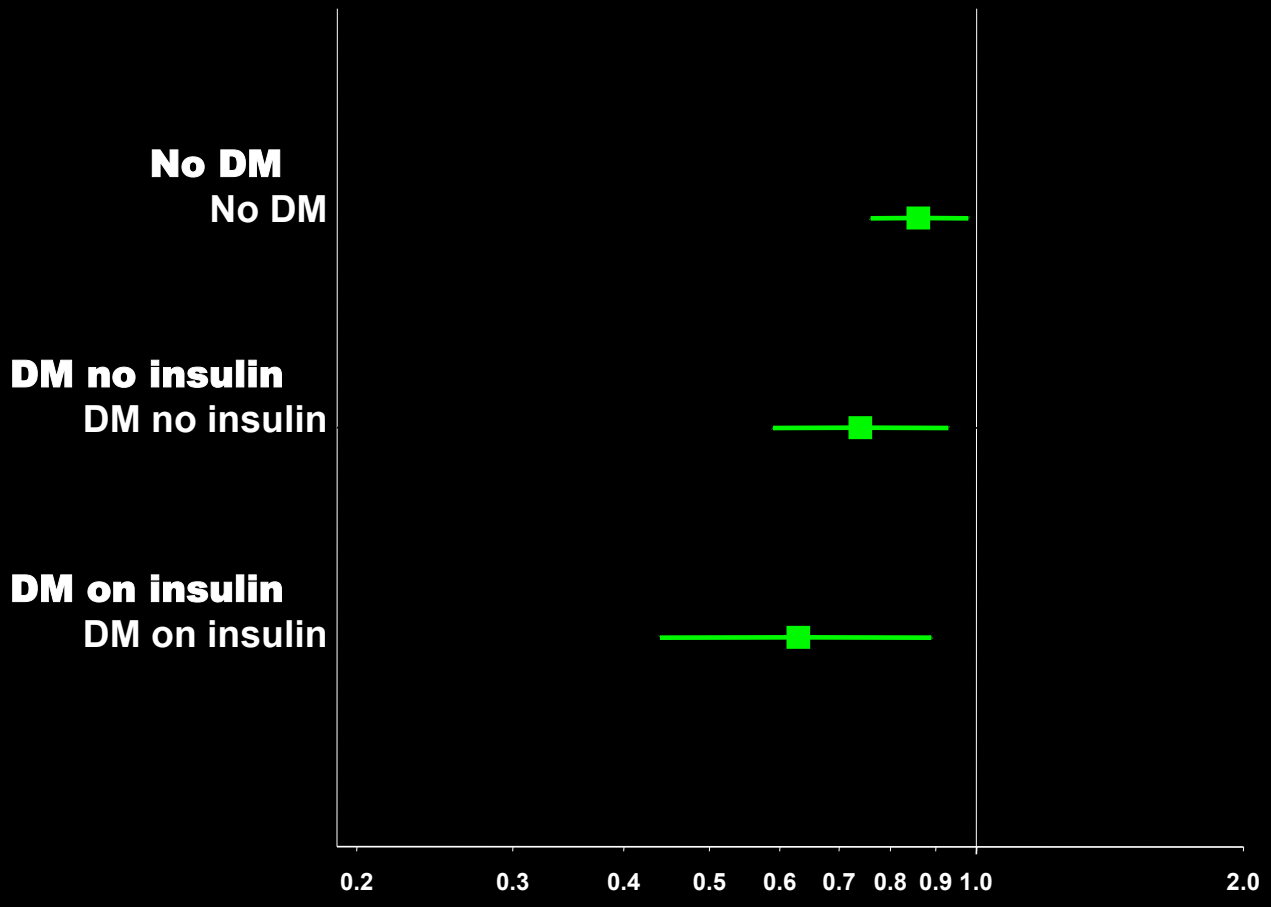
Triton TIMI-38: Clinical Events by DM Status



	Clopidogrel (%)	Prasugrel (%)
CVD/MI/CVA*	17.0	12.2
CVD/MI*	15.4	10.8
MI†	13.2	8.2
CVD	4.2	3.4
Stent thrombosis	3.6	2.0
Major bleed‡	2.6	2.5
Major or minor bleed‡	4.3	5.3
D/MI/CVA*/Major bleed‡	19.2	14.6

Wiviott SD, et al. *Circulation*. 2008;118:1626

Triton TIMI-38: Reduction in Primary End Point by DM Status and Treatment Group



	Clopidogrel (%)	Prasugrel (%)	Reduction In Risk (%)
No DM	10.6	9.2	14
DM no insulin	15.3	11.5	26
DM on insulin	22.2	14.3	37

Wiviott SD, et al. *Circulation*. 2008;118:1626

Comparison of Efficacy & Safety by Diabetes Status

Roma,
9-11 novembre 2012

TRITON TIMI-38 | PLATO

Efficacy	Event rate%	ARR%	NNT	Event Rate%	ARR	NNT
CVDeath/MI/Stroke	12.2 vs 17.0	5,2	21	14.1 vs 16.2	2.1	48
CV death	3.4 vs 4.2	1.2	81	7.0 vs 8.7	1.7	59
Non fatal IMI	13.2 vs 8.2	5.0	20	8.4 vs 9.1	0.7	142
Safety	**Event rate%**	**AR%**	**NNH**	**Event rate%**	**AR**	**NNH**
Non CABG Major bleeding	2.5 vs 2.6	-	-	5.5 vs 4.9	1.4	72
CABG Major bleeding	NA	-	-	9.3 vs 10.4	-	-

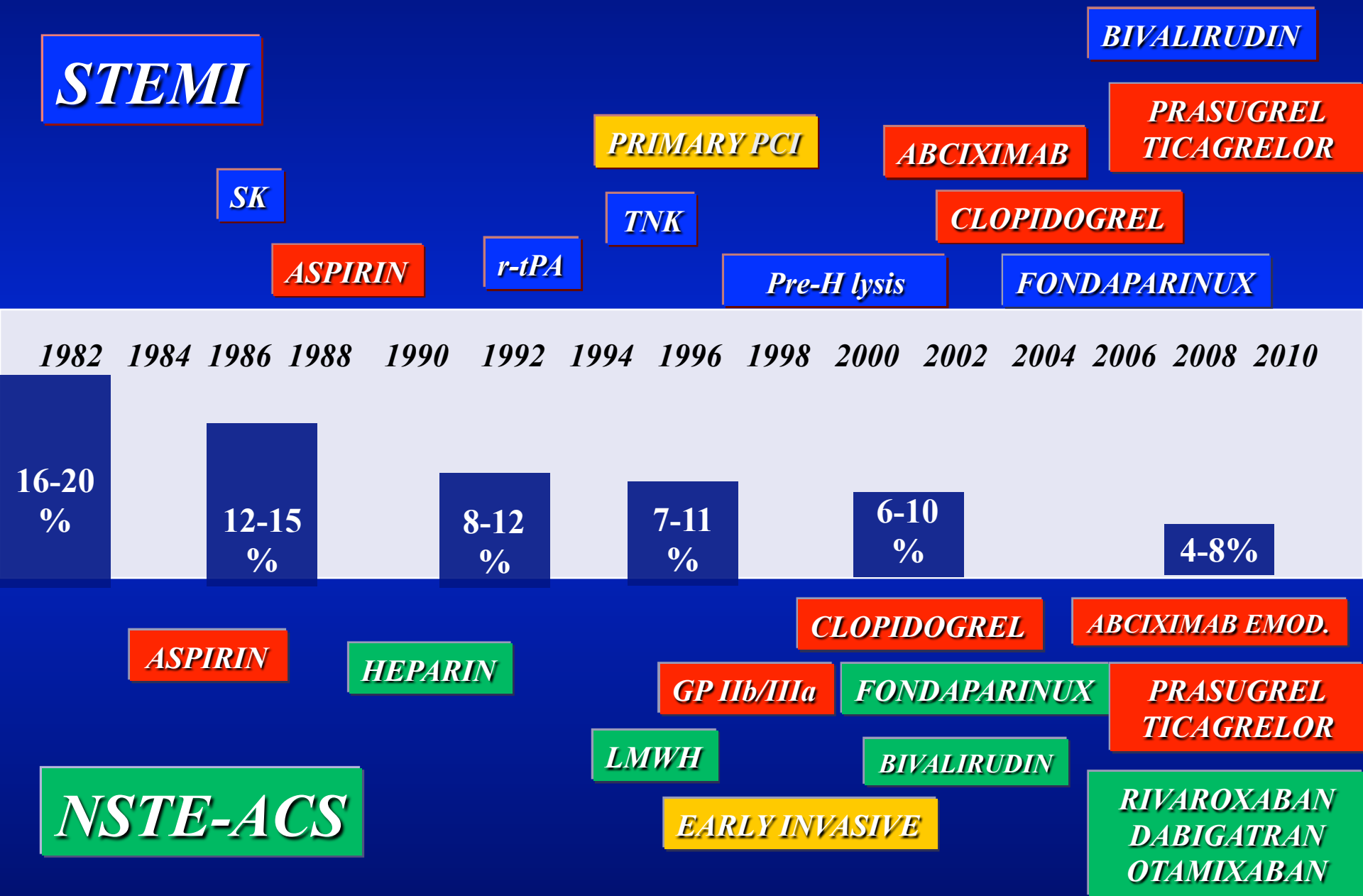
Comparison of Efficacy & Safety by Diabetes Type

Roma,
9-11 novembre 2012

TRITON TIMI-38 | PLATO

Efficacy	Event rate%	ARR%	NNT	Event Rate%	ARR	NNT/NNH
Diabetes on Insulin						
CVDeath/MI/Stroke	14.3 vs 22.2	7.7	13	17.7 vs 16.2	2.1	48
Death	NA	NA	-	10.0 vs 11.7	1.7	59
Major bleeding	1.9 vs 2.3	- 0.4	-	15.1 vs 15.1	0.0	-
Stent Thrombosis	1.8 vs 5.7	3.9	26	NA	NA	-
Diabetes no Insulin						
CVDeath/MI/Stroke	11.5 vs 15.3	3.8	26	13.1 vs 14.2	1.1	91
Death	NA	NA		6.2 vs 7.8	1.6	63
Major bleeding	2.7 vs 2.7	0.0	-	13.8 vs 14.7	0.9	111
Stent Thrombosis	**2.0 vs 3.0**	1.0	100	NA	NA	-

Mortalità dei pazienti con SCA



Mortalità dei pazienti con STROKE

ICTUS ISCHEMICO ACUTO

PREVENZIONE E TRATTAMENTO COMPLICANZE NEUROLOGICHE E INTERNISTICHE

TAO

ASPIRIN A

TICLOPIDINA

CLOPIDOGREL

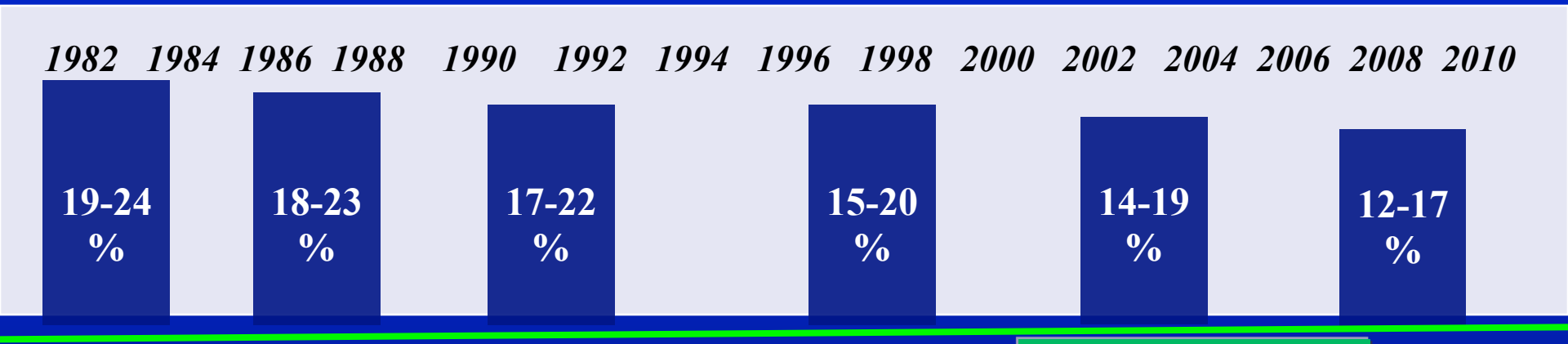
ASA-DIPIRIDAMOLO ER

CEA

R - TPA

STROKE UNIT

PTA



PREVENZIONE E TRATTAMENTO COMPLICANZE NEUROLOGICHE E INTERNISTICHE

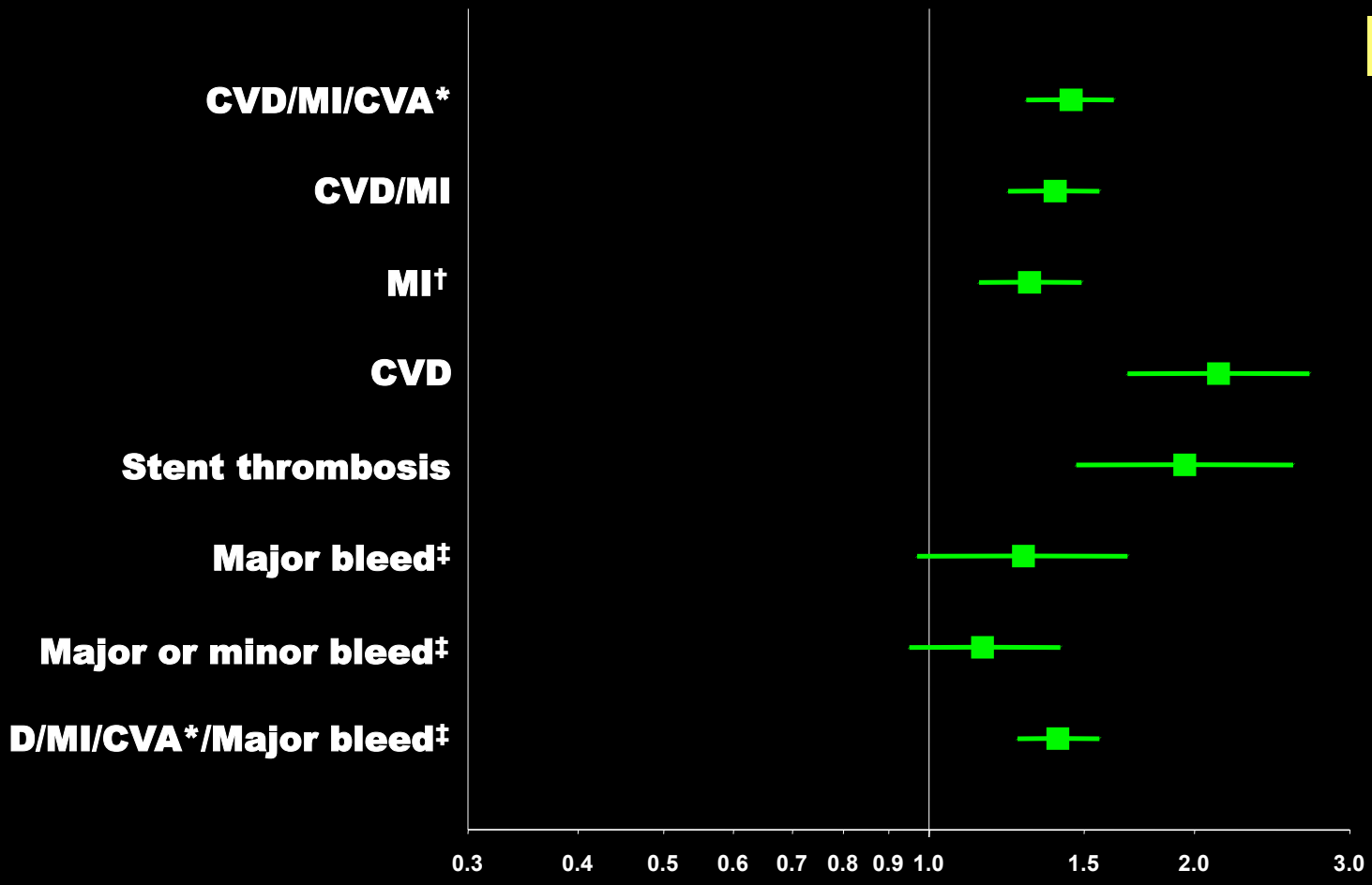
RIABILITAZIONE PRECOCE

STROKE UNIT

ICTUS EMORRAGICO: mortalità 30-40%

Triton TIMI-38: Clinical Events by DM Status

Roma, 9-11 novembre 2012



	DM (%)	No DM (%)
CVD/MI/CVA*	14.6	9.9
CVD/MI	13.1	9.2
MI†	10.7	8.0
CVD	3.8	1.8
Stent thrombosis	2.8	1.4
Major bleed‡	2.6	2.0
Major or minor bleed‡	4.8	4.2
D/MI/CVA*/Major bleed‡	16.9	11.9

CVD,cardiovascular death; MI, myocardial infarction;
CVA, cerebrovascular accident; D, death; DM, diabetes mellitus
*The composite of cardiovascular death, nonfatal MI, or nonfatal stroke
†Any MI (fatal or nonfatal)
‡Not related to CABG

Wiviott SD, et al. *Circulation*. 2008;118:1626