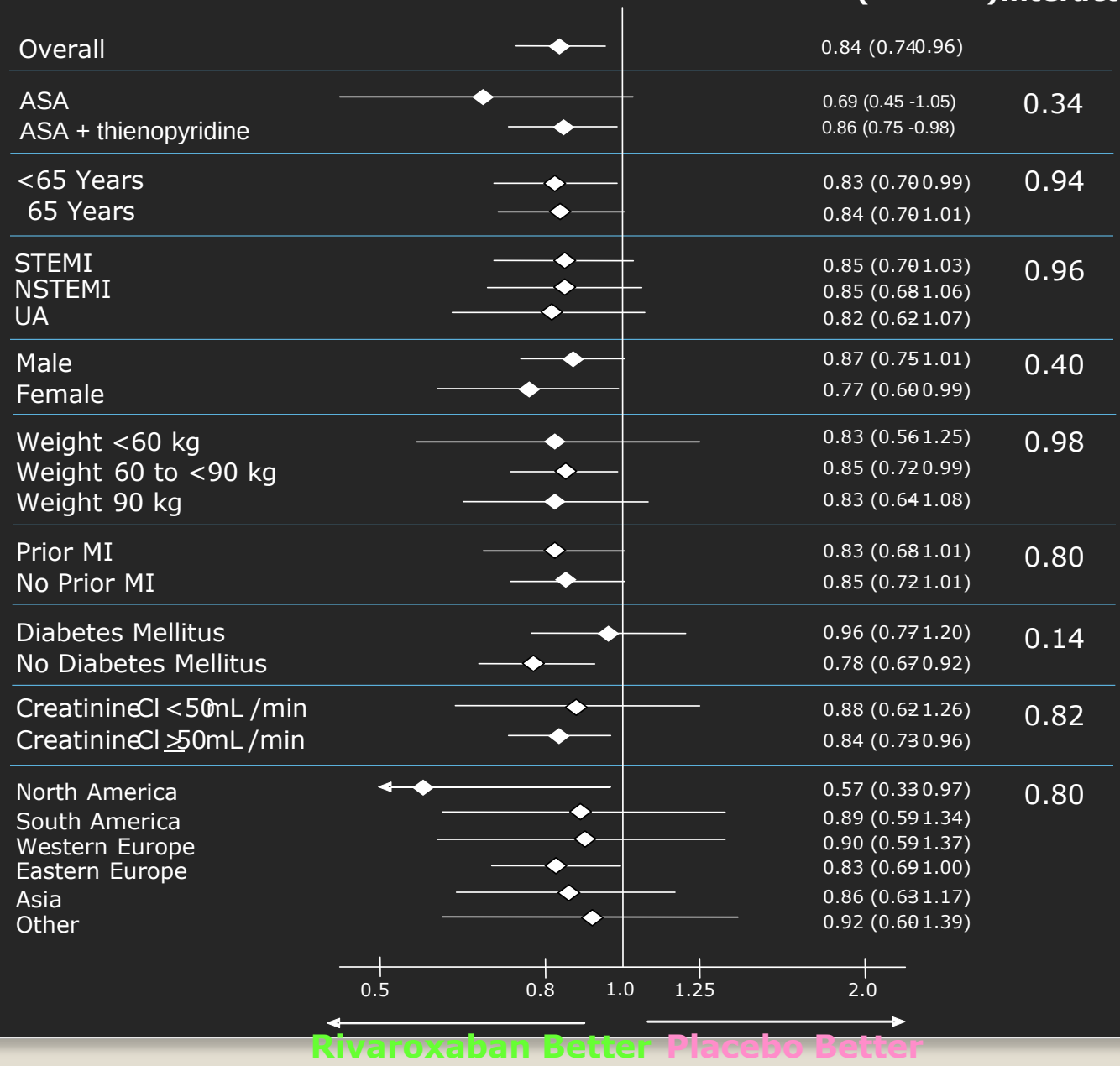
Randomized Clinical Trials: the Holy Grail

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY SUBGROUP RESULTS (mITT)



Study

CURE (3)
CURRENT OASIS 7(1)
TRITON TIMI (3)*
PLATO (7)
CAPRIE(3)
CHARISMA(3)

RE-LY (6)
ROCKET AF(1)
ARISTOTLE

RCTs and subgroup analysis

The answer to a RCT that does not confirm one's beliefs is not the conduct of several subanalyses until one can see what one believes. Rather the answer is to re-examine one's beliefs carefully.

Subgroup analyses are particularly prone to over interpretation, and one is tempted to suggest "don't do it (or at least don't believe it) for many trials, but this suggestion is probably contrary to human nature. Subgroup analysis is a machine for generating false negatives

…What it has been said about subgroup analysis

“. . . some investigators selectively report only the more interesting subgroup analyses, thereby leaving the reader (and us) unaware of how many less exciting subgroup analyses were looked at and not mentioned”. Disappointingly, most trials reporting subgroup analyses noted a subgroup difference that was highlighted in the conclusions—so much for cautious interpretation! Lancet 2000;355:1064

Subgroup analysis

Do we need them?

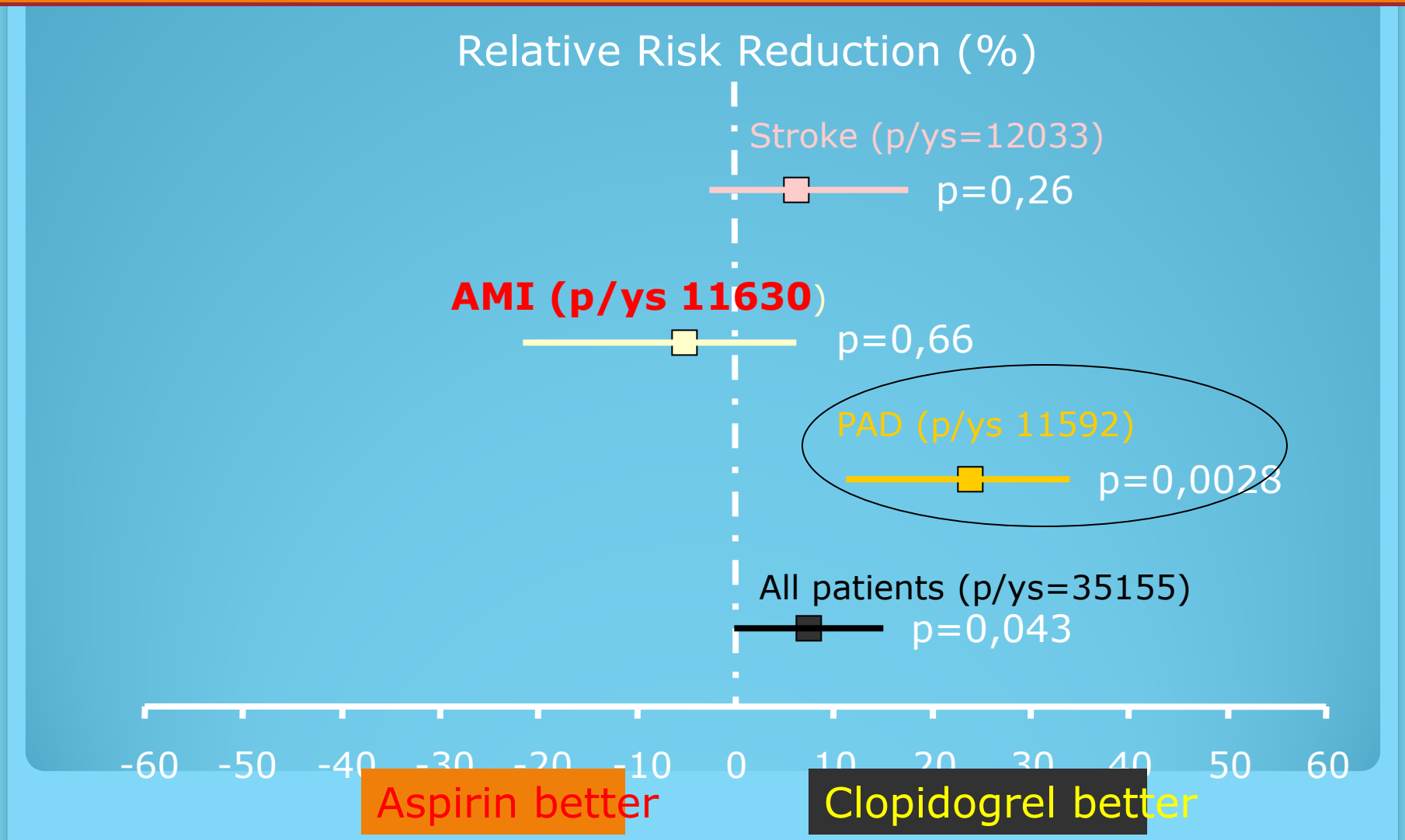
Usually small groups or excluded as Elderly, Women , PVD, Stroke CABG, CKD, Bleeding

When to believe a subgroup analysis

- **Large RCT**
- **How many subgroup analyses were performed?**
  - The larger the number, the larger the possibility of a spurious finding.
- **Is the Magnitude of the Subgroup Difference Large?**
  - The larger the difference between the observed effects in particular subgroups, the more plausible that the difference is real.
- **Is the Subgroup Difference Consistent Across Studies?**
  - Consult meta-analyses and systematic reviews
- **Is it a *post hoc* or an *ad hoc* analysis?**
  - The credibility of any apparent subgroup difference that arises out of post hoc rather than a priori hypotheses is questionable.
  - Hypothesis-generating vs. hypothesis testing

Subgroup analysis after a borderline or negative RCTrial

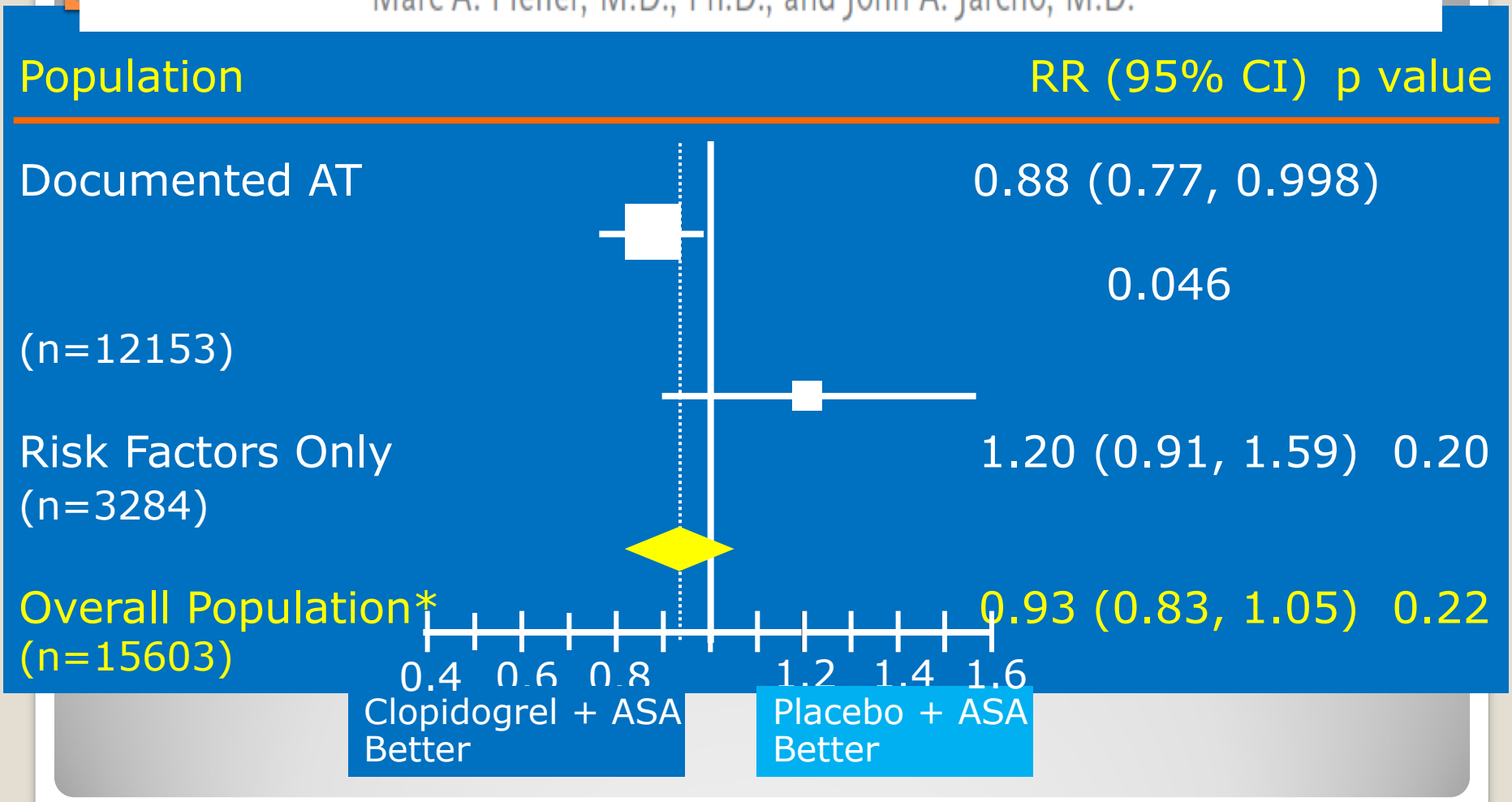
CAPRIE: primary efficacy end-point. Subgroup-analysis



CAPRIE Lancet 1996;348:1329–

The Charisma of Subgroups and the Subgroups of CHARISMA

Marc A. Pfeffer, M.D., Ph.D., and John A. Jarcho, M.D.



* Analysis of treatment response for the pre-specified subgroups of symptomatic and asymptomatic patients

Adapted from Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006 – In press

CURRENT-STEMI PCI

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
- ✓Planned Early (<72 h) Invasive Management with **intended PCI**
- ✓Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 6d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)

Angio 24,769

PCI 17,232

STEMI 6,346

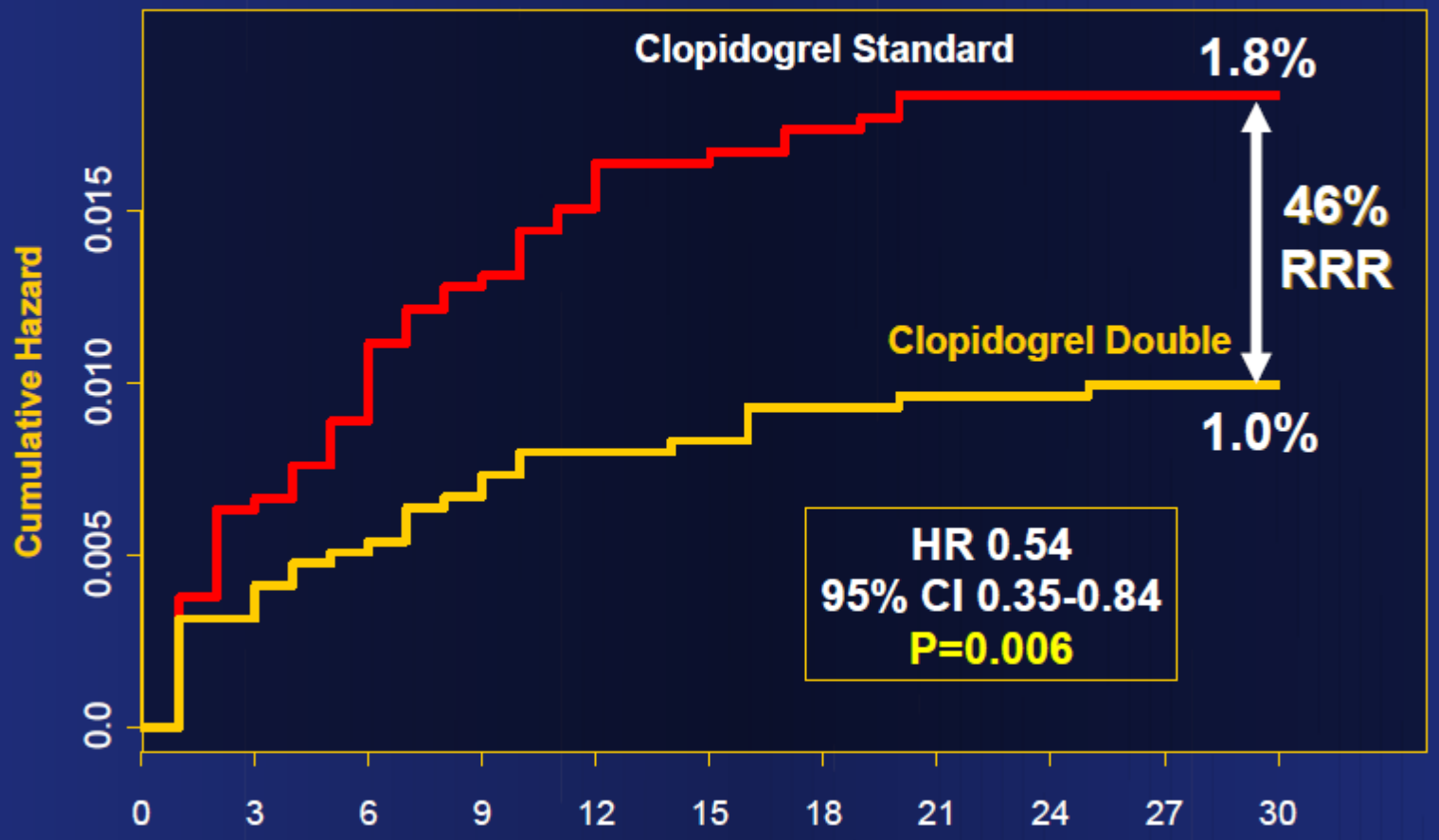
UA/NSTEMI 10,886

Primary PCI 5,362

Other PCI 984

Mehta SR. TCT2009

CURRENT STEMI-PCI: Definite Stent Thrombosis



Mehta SR. TCT2009

Oral Antiplatelet Therapy

A loading dose of a P_2Y_{12} receptor inhibitor should be given to patients undergoing PCI with stenting. Options include:

a. Clopidogrel 600 mg (ACS and non-ACS)
b. Prasugrel 60 mg (ACS)
c. Ticagrelor 180 mg (ACS)

Levine GN, et al. *J Am Coll Cardiol*. 2011 Oct. 31 [Epub ahead of print]

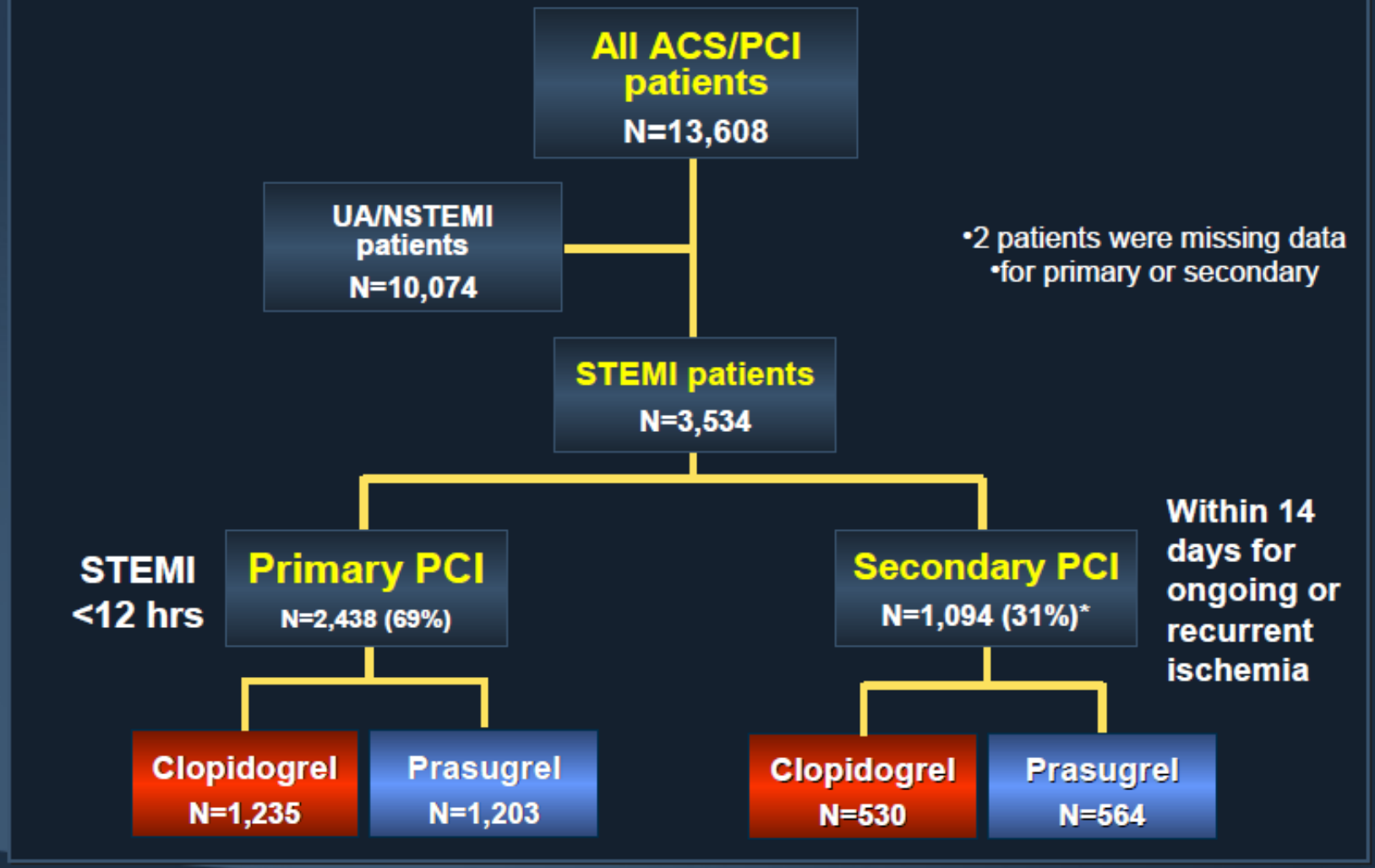
Most subgroup findings tend to exaggerate reality.

Be especially suspicious of investigators highlighting a subgroup treatment effect in a trial with no overall treatment effect.

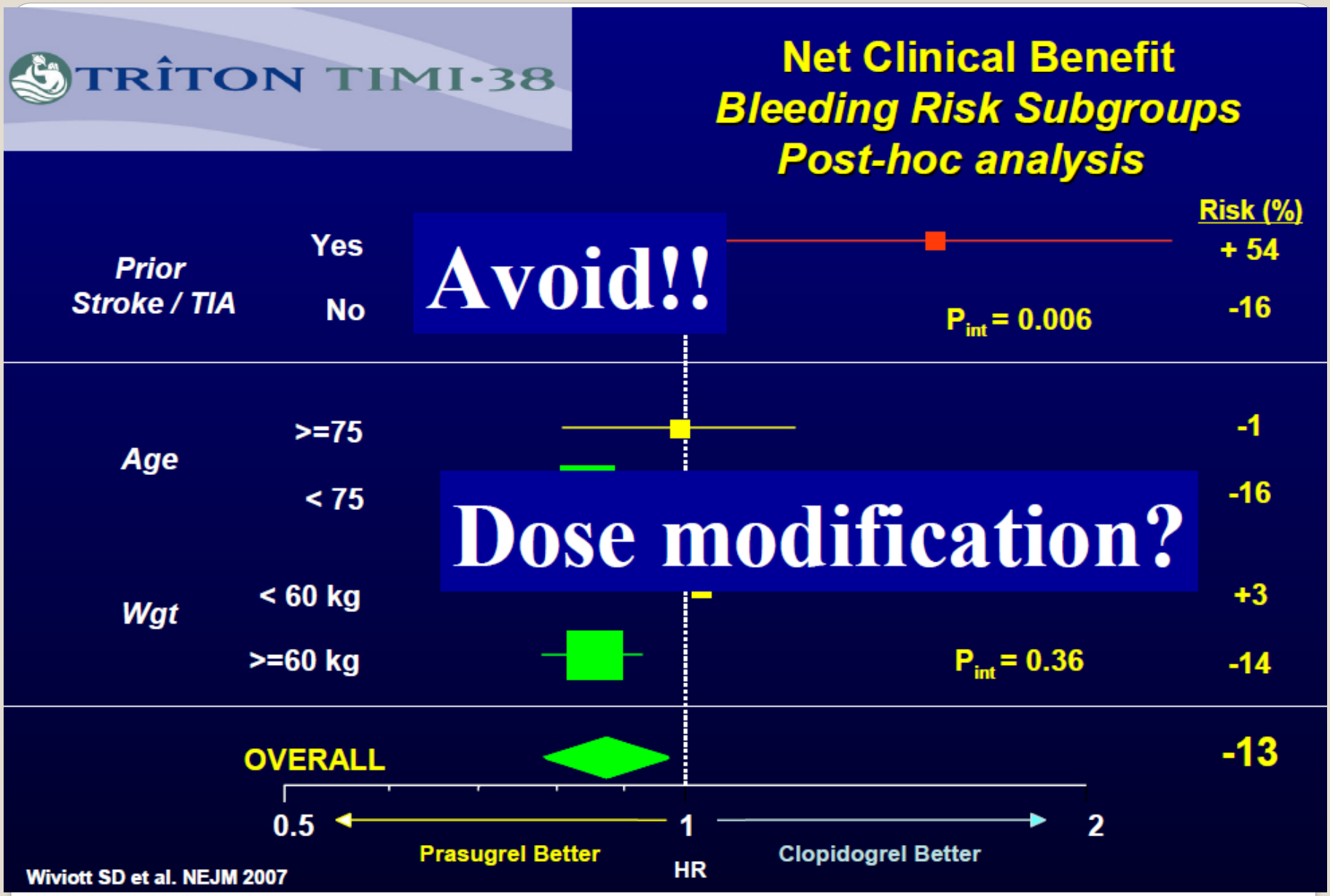
They are usually superfluous subgroup salvages of otherwise indeterminate (negative) trials

Subgroup analysis after a positive trial

TRITON-TIMI 38 STEMI



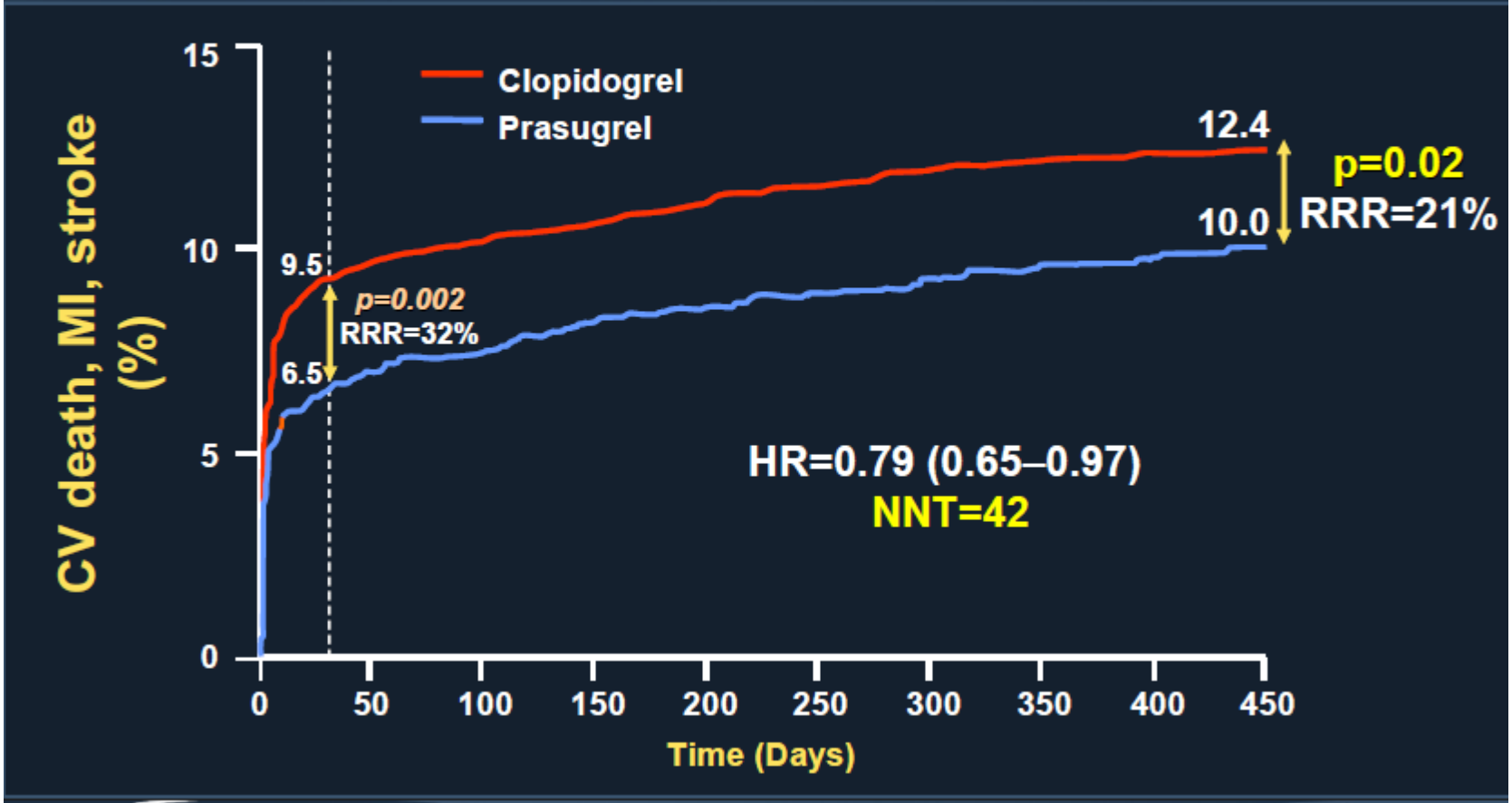
Montalescot G et al. *Lancet* 2009;373:723–31


TRÎTON TIMI-38
Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis
Risk (%)
Prior Stroke / TIA
Yes
+ 54
Avoid!!
No
-16
P_int = 0.006
Age
>=75
-1
< 75
-16
Dose modification?
Wgt
< 60 kg
+3
>=60 kg
-14
P_int = 0.36
OVERALL
-13
0.5
1
2
Prasugrel Better
HR
Clopidogrel Better
Wiviott SD et al. NEJM 2007

TRÎTON TIMI·38

TRITON-TIMI 38 STEMI

CV Death, MI or Stroke at 15 Months



CARDIOVASCULAR RESEARCH FOUNDATION

Montalescot G et al. *Lancet* 2009;373:723–31

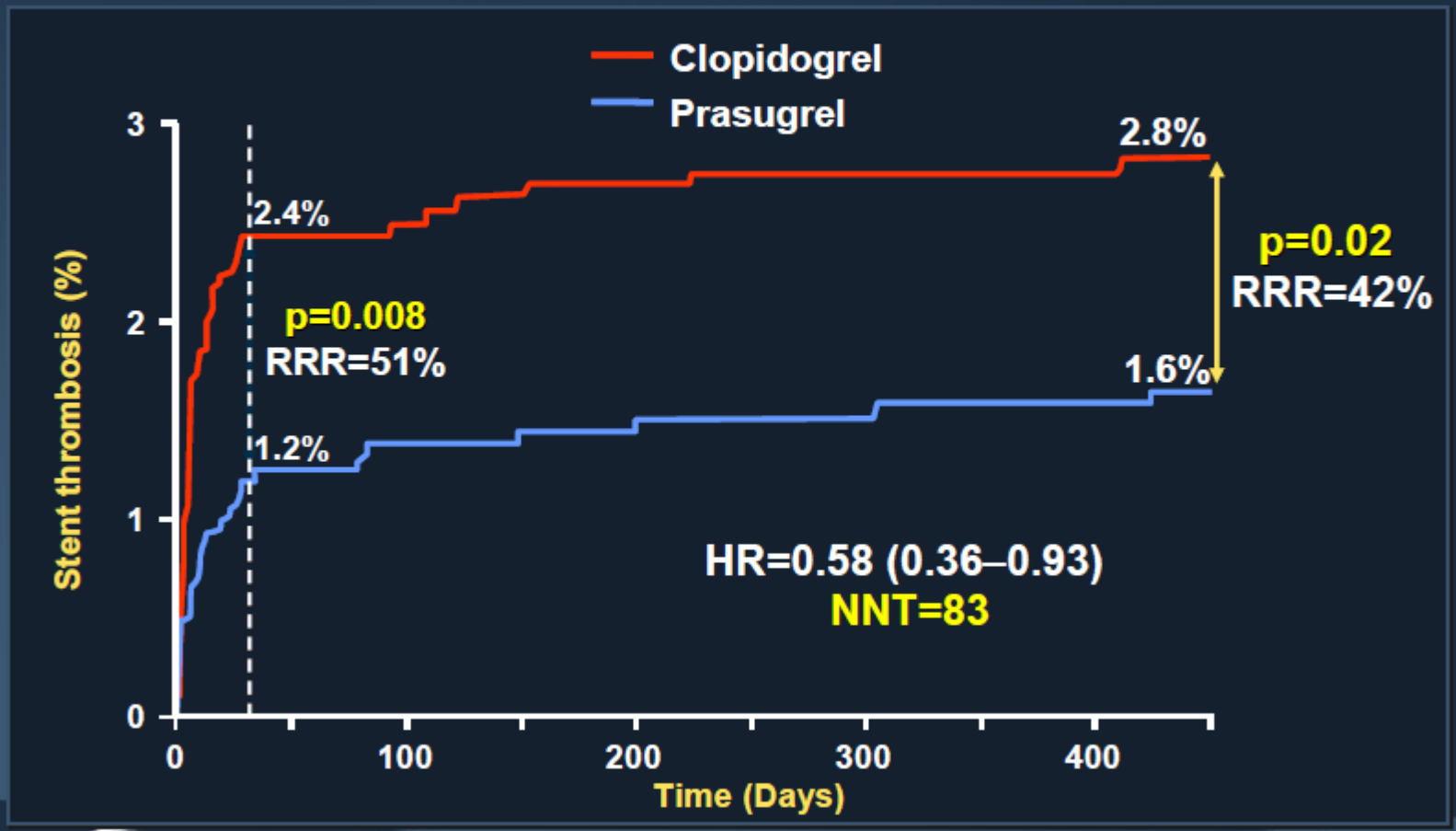
Columbia University Medical Center

New York-Presbyterian

TRÎTON TIMI-38

TRITON-TIMI 38 STEMI

Stent Thrombosis: ARC Definite/Probable



Montalescot G et al. *Lancet* 2009;373:723–31

CARDIOVASCULAR RESEARCH FOUNDATION

Columbia University Medical Center

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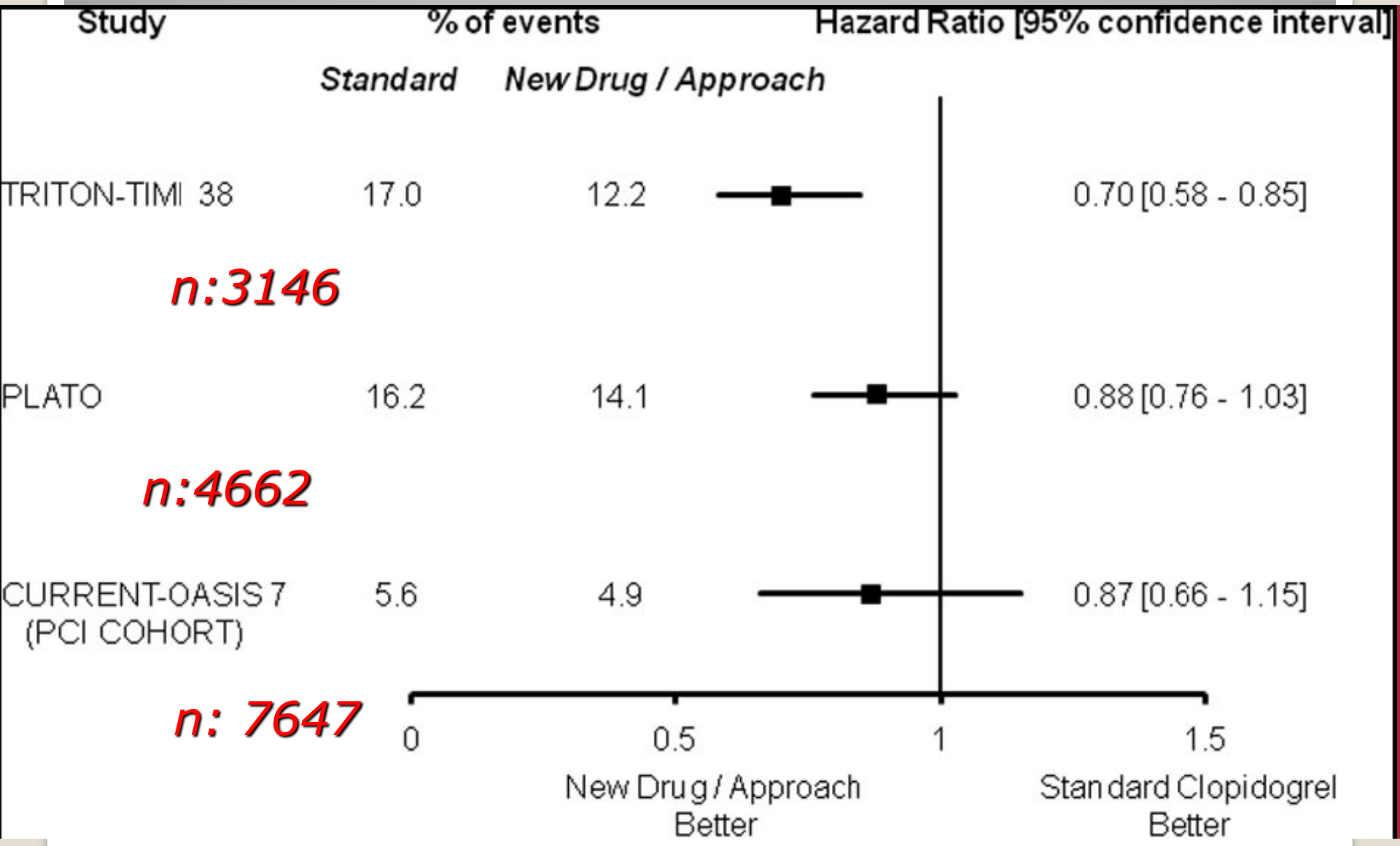
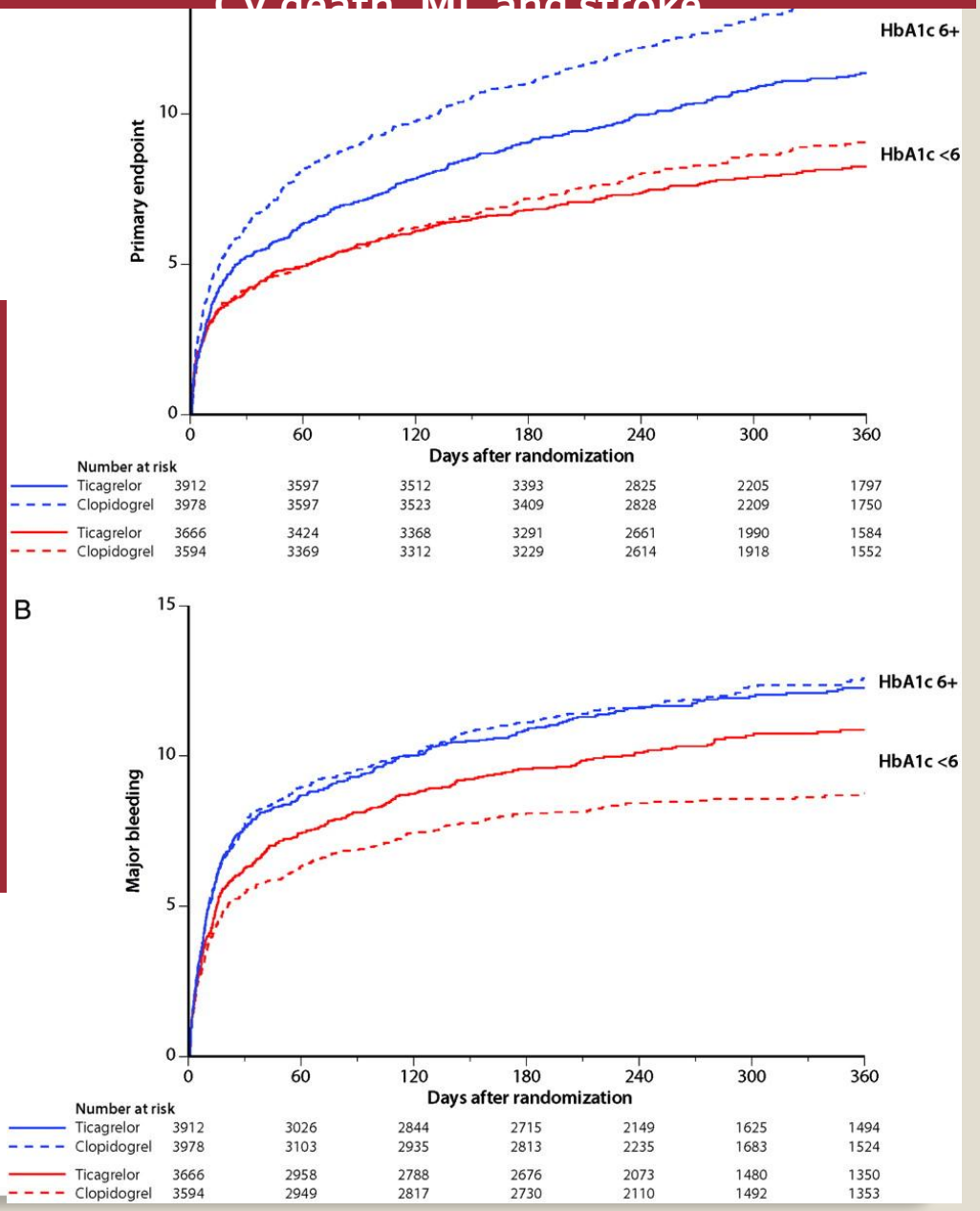
Diabetes Mellitus

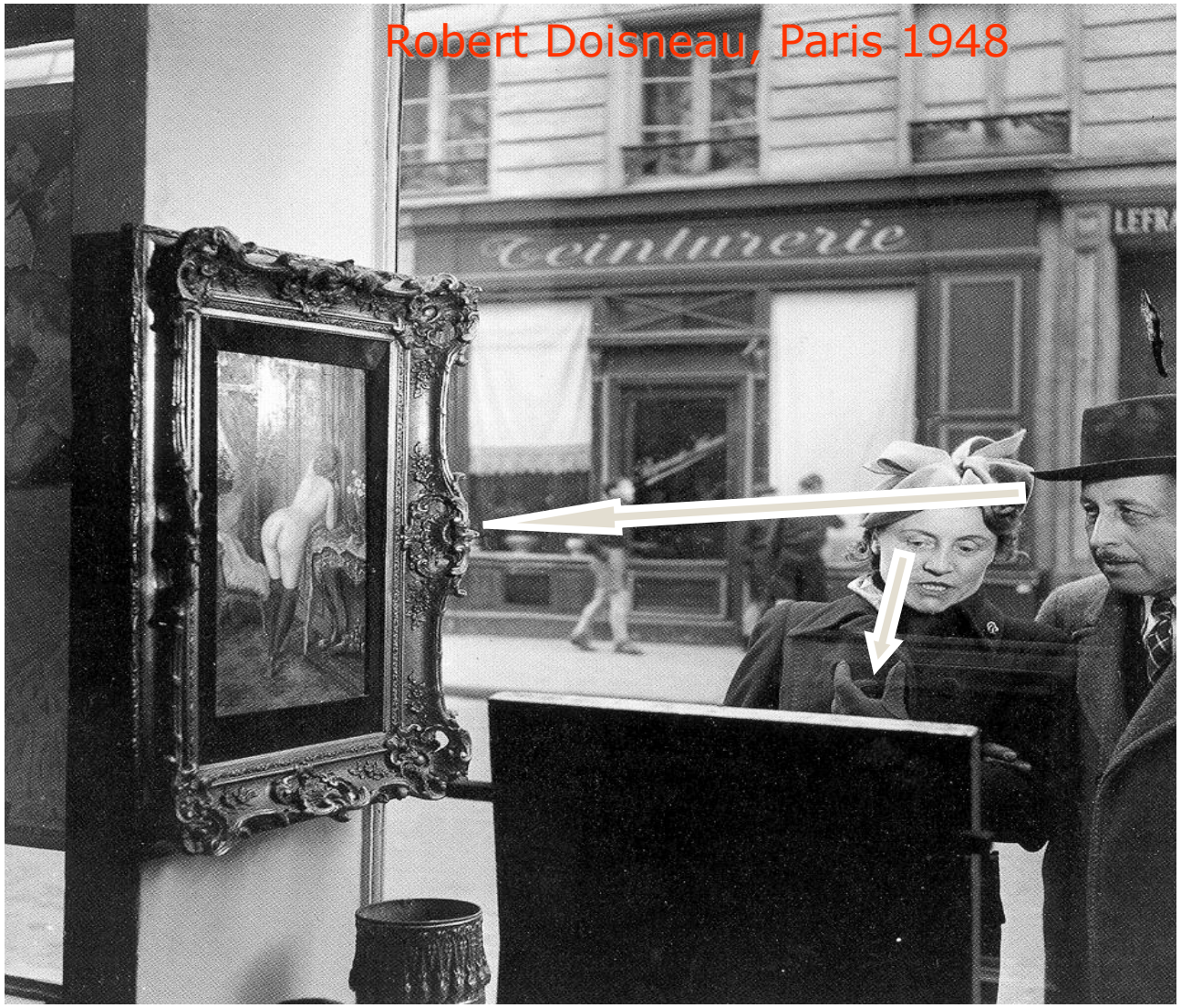


PLATO diabetes. . .

Ticagrelor (solid lines) and clopidogrel (dotted lines) groups in patients with levels of HbA1c at baseline above median of 6% (blue lines) and below median of 6% (red lines).



Not all trials provide perfect consistency



Subgroup analyses are an important part of the analysis of a RCT. However, they are commonly overinterpreted and can lead to further research that is misguided or, worse, to suboptimal patient care.

Consider a RCT designed to determine whether a new treatment is more effective than an established treatment and assessed with a test, based on all randomized patients, of the null hypothesis that the treatments have equal efficacy, as measured in terms of the primary end point.

Then, subgroup analyses are conducted to assess whether different types of patients respond differently to the new treatment. This sounds simple enough, but there are several important sources of confusion and uncertainty regarding such subgroup analyses.

Ευρήματα από ανάλυση υπο-ομάδων

- Βασική αρχή: Εάν υπάρχει μια (μέτρια) διαφορά ανάμεσα σε δύο θεραπείες όσον αφορά κάποιο σύμβαμα, τότε η διαφορά αυτή μπορεί να είναι μεγαλύτερη ή μικρότερη σε διακριτές υπο-ομάδες ασθενών αλλά είναι απίθανο να είναι αντίθετη

Προτεινόμενες συστάσεις σχετικά με την ανάλυση υπο-ομάδων

- Περιορισμός αναλύσεων σε ΠΡΟ-καθορισμένες υπο-ομάδες με γνώμονα κάποια λογική παθοφυσιολογική βάση προηγούμενης έρευνας
- Ανάλυση μόνο εφόσον υπάρχει στατιστική σημαντικότητα στο συνολικό αποτέλεσμα
- Διόρθωση τιμής p για πολλαπλές συγκρίσεις (0.05/n, πχ εάν γίνουν 20 συγκρίσεις να απαιτείται $p<0.05/20=0.0025$)
- Να θεωρείται ότι τα ευρήματα απαιτούν περαιτέρω έρευνα και ότι δεν είναι αποδεικτικά
- Να μην δίνεται υπερβολική σημασία

Medical research and patients are best served when subgroup analyses are well planed and appropriately analyzed and when conclusion and recommendations about clinical practice are guided by the strength of the evidence.

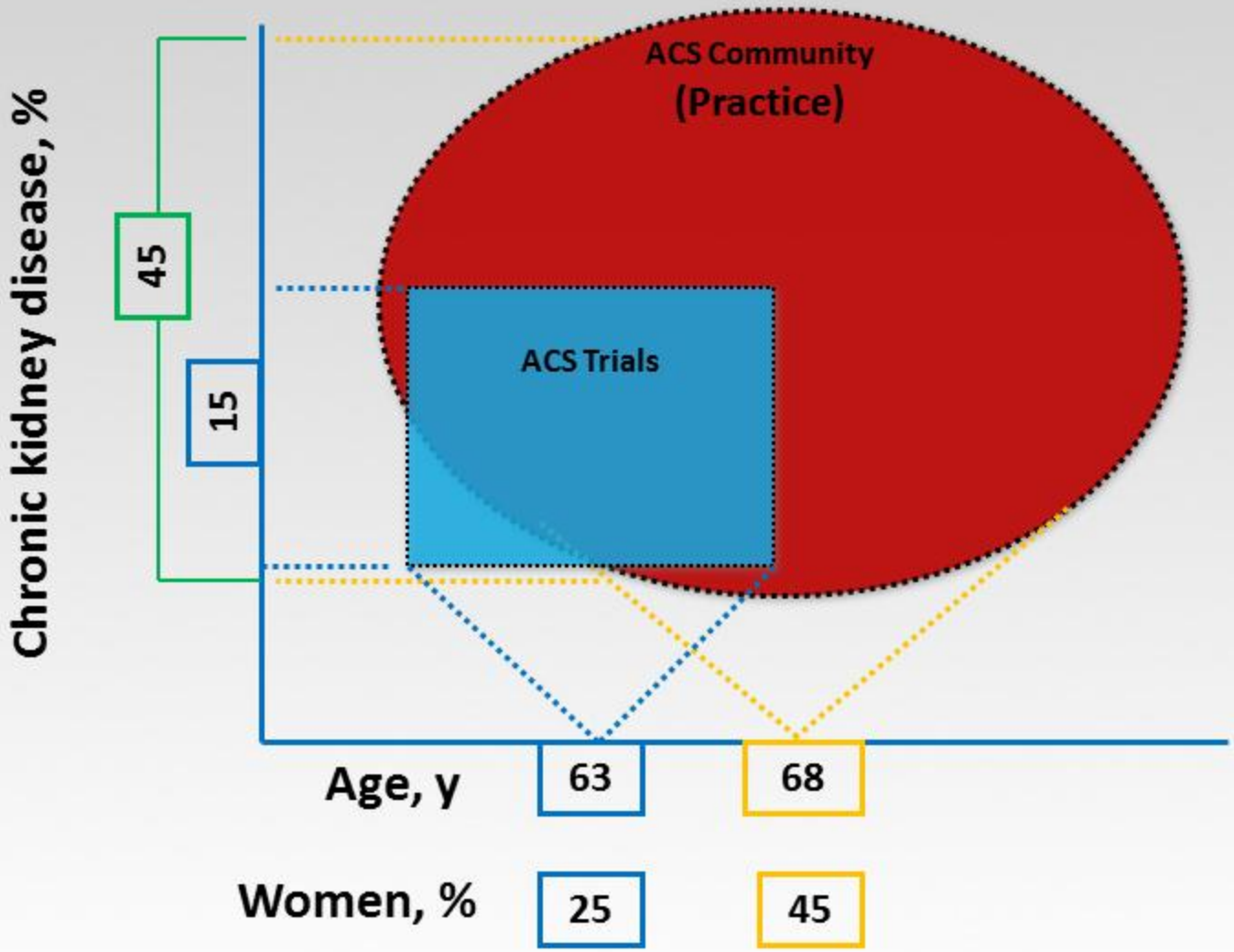
PLATO diabetes…

- TRITON: Numerical reduction in CV death and significant reduction in MI [5% (40% relative)] with prasugrel in DM pts
- Relatively lower reduction in MI with ticagrelor in PLATO may be explained by
  - Higher average loading dose of clopidogrel in the clopidogrel arm
  - Pre-treatment with clopidogrel in 50% pts in the ticagrelor arm
  - TRITON results depend on *early periprocedural MI*, detection facilitated by *delay of subject enrolment until after CANG*. PLATO enrolled pts soon after the index event, making early MI detection more difficult. Thus, any apparent *difference in MI results* between trials likely results from study design rather than actual outcome.

PLATO diabetes…

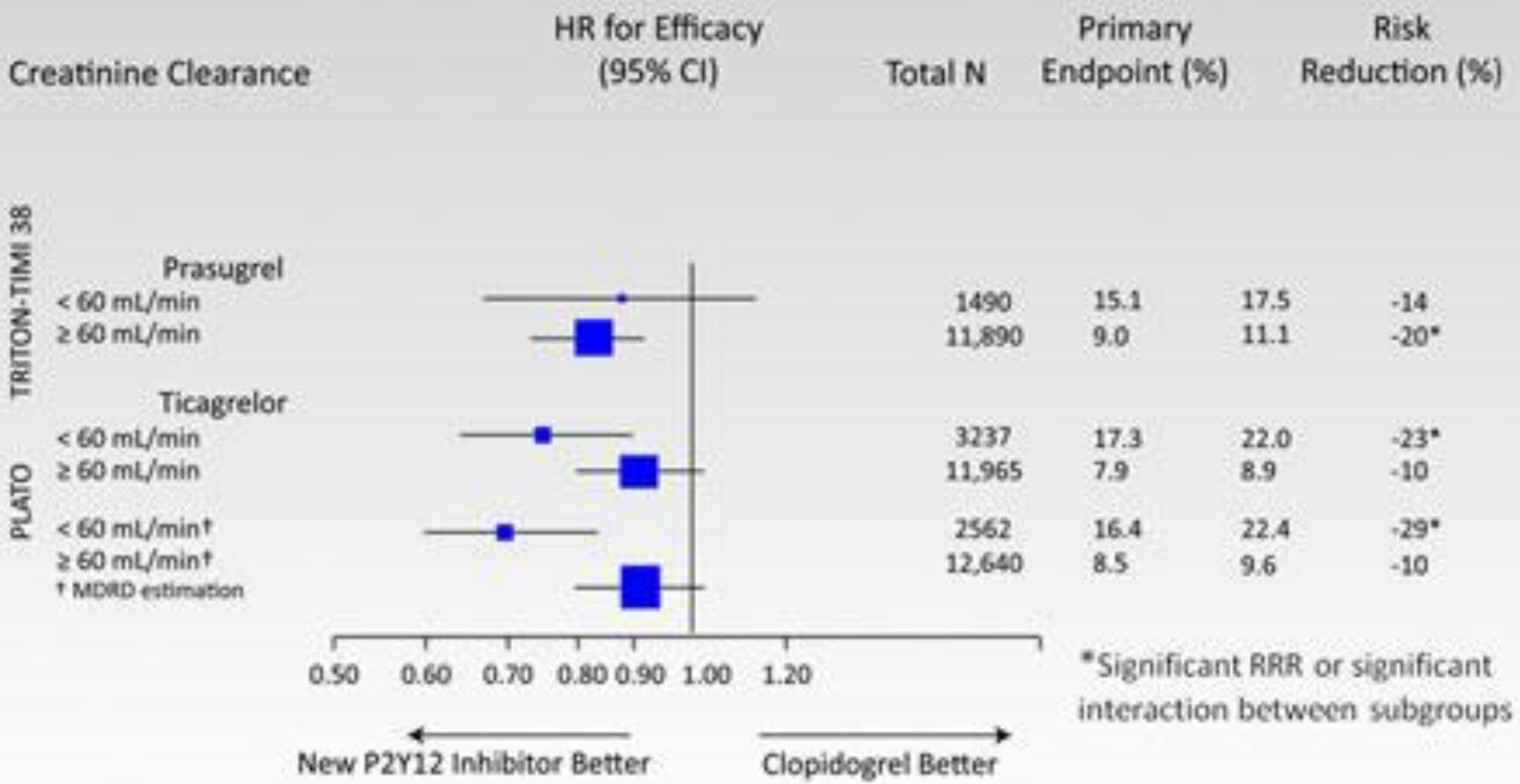
- High platelet reactivity in DM
  - Higher dose of ticagrelor could have resulted in greater clinical benefit???
    - Predicted steady-state plasma exposure of ticagrelor and its active metabolite not different in patients with or without DM (AZ internal data)
- Very high levels of platelet inhibition may not be sufficient for adequate protection against ischaemic events in patients with DM.
  - *The prothrombotic condition that DM constitutes may require anti-thrombin or other long-term anti-coagulation therapy for a more general prevention of CV events...*

ACS Trials vs Community Practice



Lee PY, et al. *JAMA*. 2001;286:708-713.
Coga SG, et al. *JAMA*. 2005;296:1377-1384.

Prasugrel and Ticagrelor Not Affected



From Montalescot G, et al. *Circulation*. 2010;122:1049-1052.
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ROCKET- AF trial-
Rivaroxaban in AF Pts with Moderate Renal Impairment

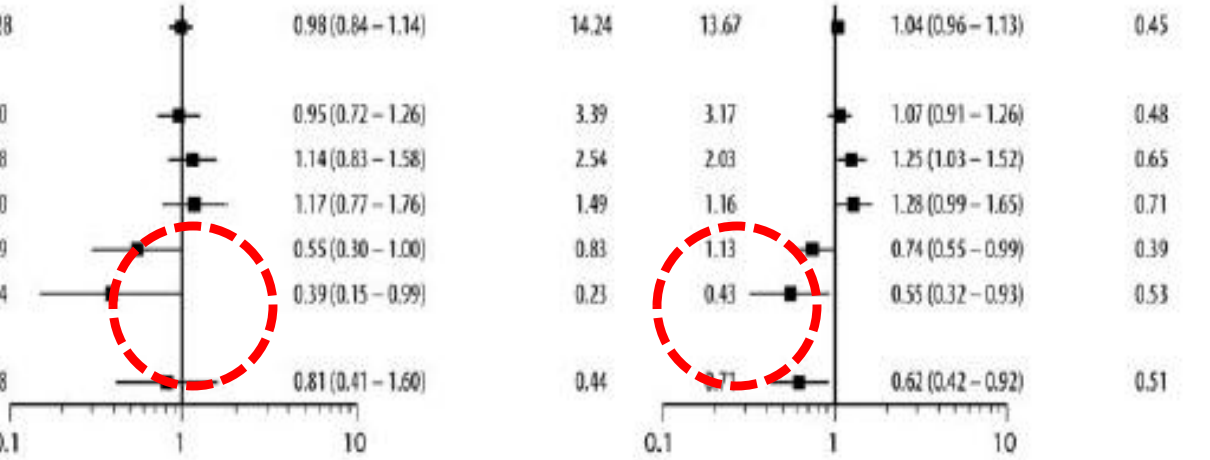
- **14264 ασθενείς με ΚΜ με $CHADS_2$ score ≥ 2 και μέτρια νεφρική δυσλειτουργία: rivaroxaban 20 mg/day or 15 mg/day if CrCl 30–49 mL/min or dose-adjusted warfarin (INR: 2.0– 3.0)**

  - Μεγαλύτερη συχνότητα μειζόνων και κλινικά σημαντικών αιμορραγιών σε ασθενείς με ΝΑ, ανεξάρτητα από το είδος της θεραπείας

  - Παρόμοια συχνότητα αιμορραγιών με μειωμένη δοσολογία rivaroxaban και θεραπείας με warfarin

  - Λιγότερες θανατηφόρες αιμορραγίες με rivaroxaban (0.28 vs. 0.74% per 100 p-y; P = 0.047)

Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Rivaroxaban 15 mg (N=1474)†	Warfarin N=1476	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban 20 mg (N=5637)†	Warfarin N=5640	HR (95% CI) Rivaroxaban vs Warfarin	Interaction
Primary Safety Endpoint	17.82	18.28	0.98 (0.84 – 1.14)	14.24	13.67	1.04 (0.96 – 1.13)	0.45
Major Bleeding	4.49	4.70	0.95 (0.72 – 1.26)	3.39	3.17	1.07 (0.91 – 1.26)	0.48
Hematocrit or Hemoglobin Drop	3.76	3.28	1.14 (0.83 – 1.58)	2.54	2.03	1.25 (1.03 – 1.52)	0.65
Transfusion	2.34	2.00	1.17 (0.77 – 1.76)	1.49	1.16	1.28 (0.99 – 1.65)	0.71
Clinical Organ	0.76	1.39	0.55 (0.30 – 1.00)	0.83	1.13	0.74 (0.55 – 0.99)	0.39
Fatal Bleeding	0.28	0.74	0.39 (0.15 – 0.99)	0.23	0.43	0.55 (0.32 – 0.93)	0.53
Intracranial Hemorrhage	0.71	0.88	0.81 (0.41 – 1.60)	0.44	0.71	0.62 (0.42 – 0.92)	0.51



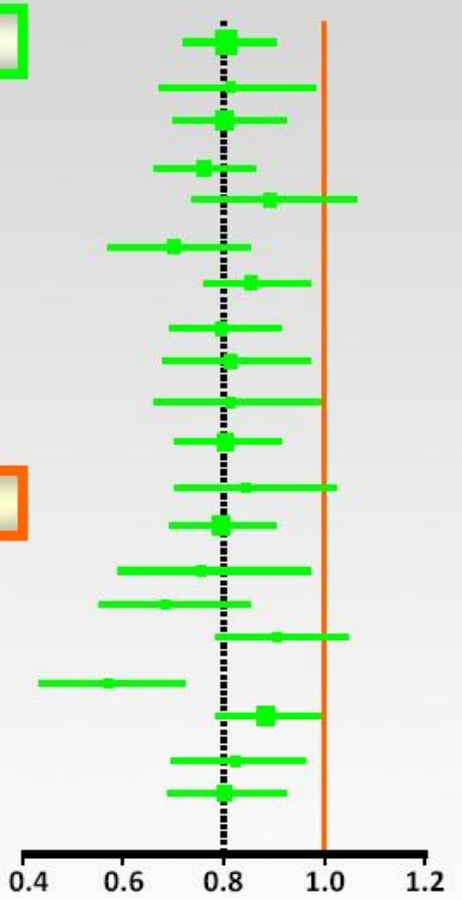
* These data are from the safety population on treatment, which included patients who received at least 1 dose of study drug and were followed regardless of adherence to protocol for events while on study drug or within 2 days of last dose.

† Event rates per 100 pt/yrs of follow-up

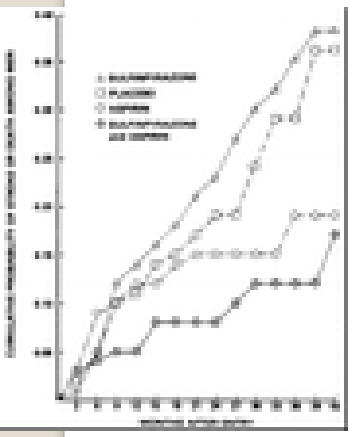
Fox K, et al: Eur Heart J 2011; 32: 2387– 2394

CURE: Outcomes With Clopidogrel in Various Subgroups

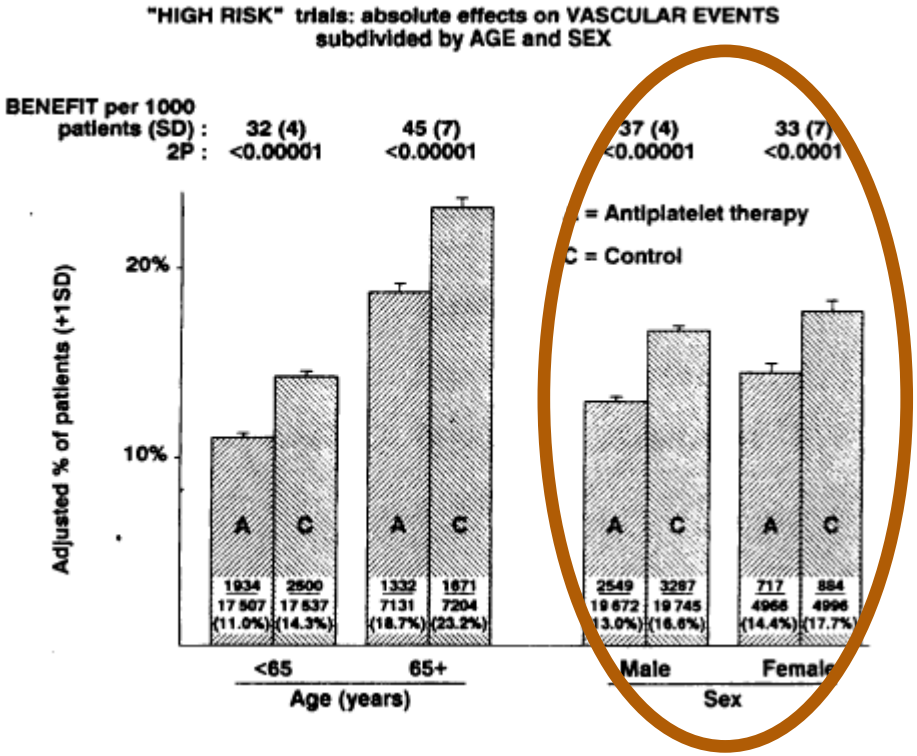
Characteristic	No. of Patients	Percentage of Patients With Event: Clopidogrel + ASA	Percentage of Patients With Event: Placebo + ASA
Overall	12562	11.4	9.3
Associated MI	3283	11.3	13.7
No associated MI	9279	8.6	10.6
Male sex	7726	9.1	11.9
Female sex	4836	9.5	10.7
< 65 yr old	6354	5.4	7.6
> 65 yr old	6208	13.3	15.3
ST-segment deviation	6275	11.5	14.3
No ST-segment deviation	6287	7.0	8.6
Enzymes elevated at entry	3176	10.7	13.0
Enzymes not elevated at entry	9386	8.8	10.9
Diabetes	2840	14.2	16.7
No Diabetes	9722	7.9	9.9
Low risk	4187	5.1	6.7
Intermediate risk	4185	6.5	9.4
High risk	4184	16.3	18.0
History of revascularization	2246	8.4	14.4
No history of revascularization	10,316	9.5	10.7
Revascularization after randomization	4577	11.5	13.9
No revascularization after randomization	7985	8.1	10.0



Yusuf S, et al. NEJM 2001; 345: 494-502



The *Canadian Cooperative Study* Group. NEJM *1978;299:53-59.*

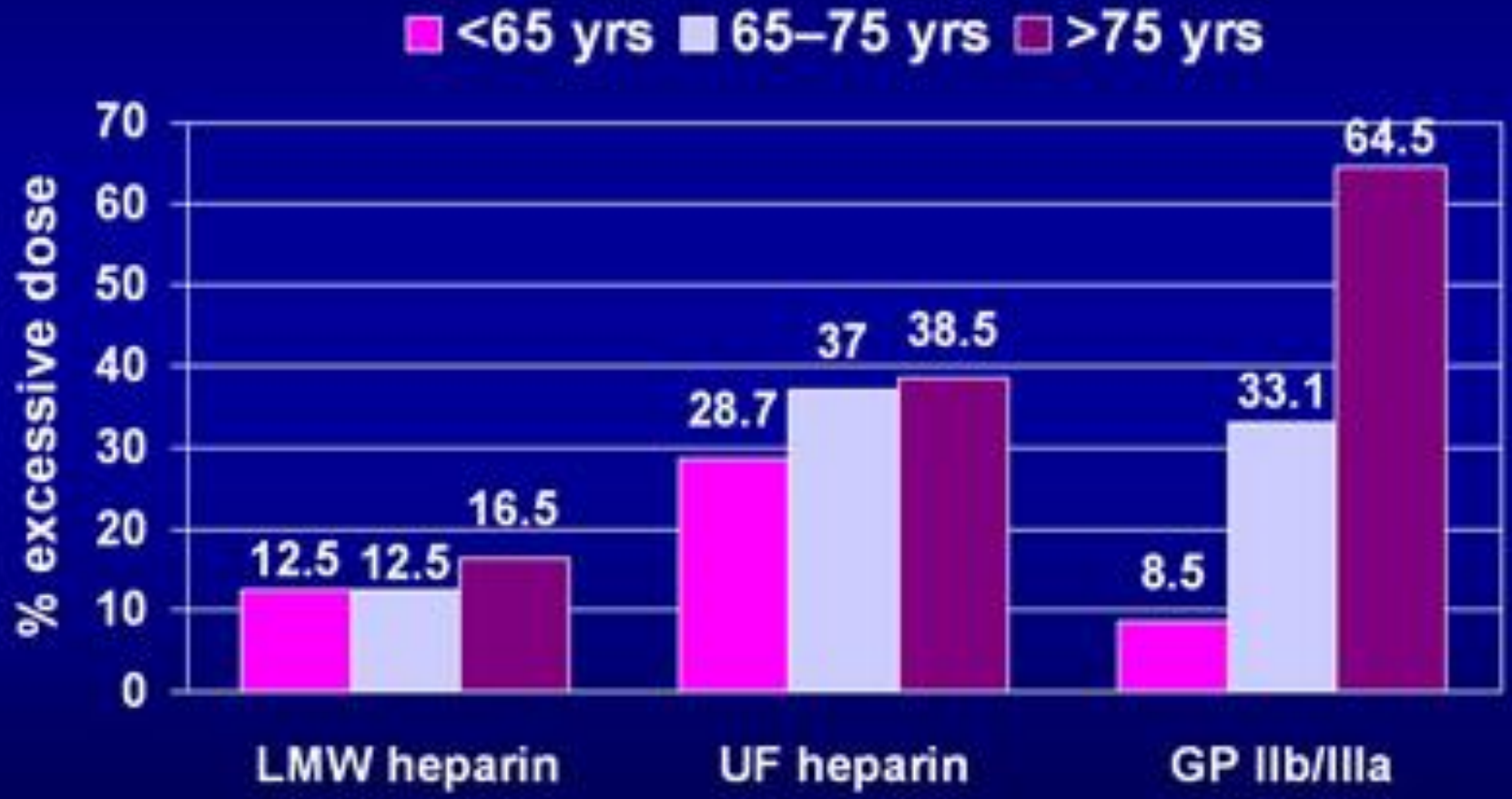


Antiplatelet Trialists' Collaboration. *BMJ. 1994;*308:81-106.

Aspirin effect on stroke in women

- Is There External Evidence That Supports the Hypothesized Subgroup Difference?
  - Does the subgroup effect make sense?
    - Different populations (including animal studies)
    - Similar interventions (drug-class effect)
    - Similar outcomes (surrogate outcomes)

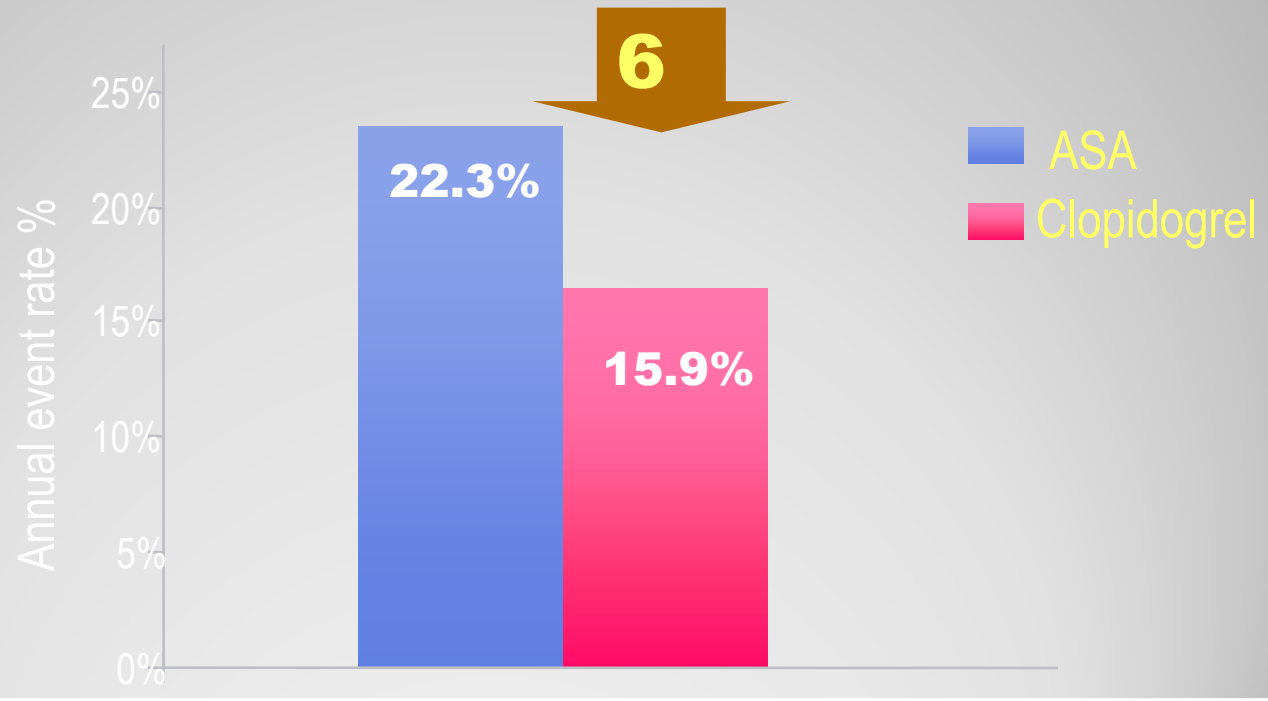
CRUSADE: Excessive dosing of anticoagulants by age



Alexander et al *JAMA* 2005;294:3108–3116

Stroke, MI, VD, hospitalization for ischemic events/bleeding

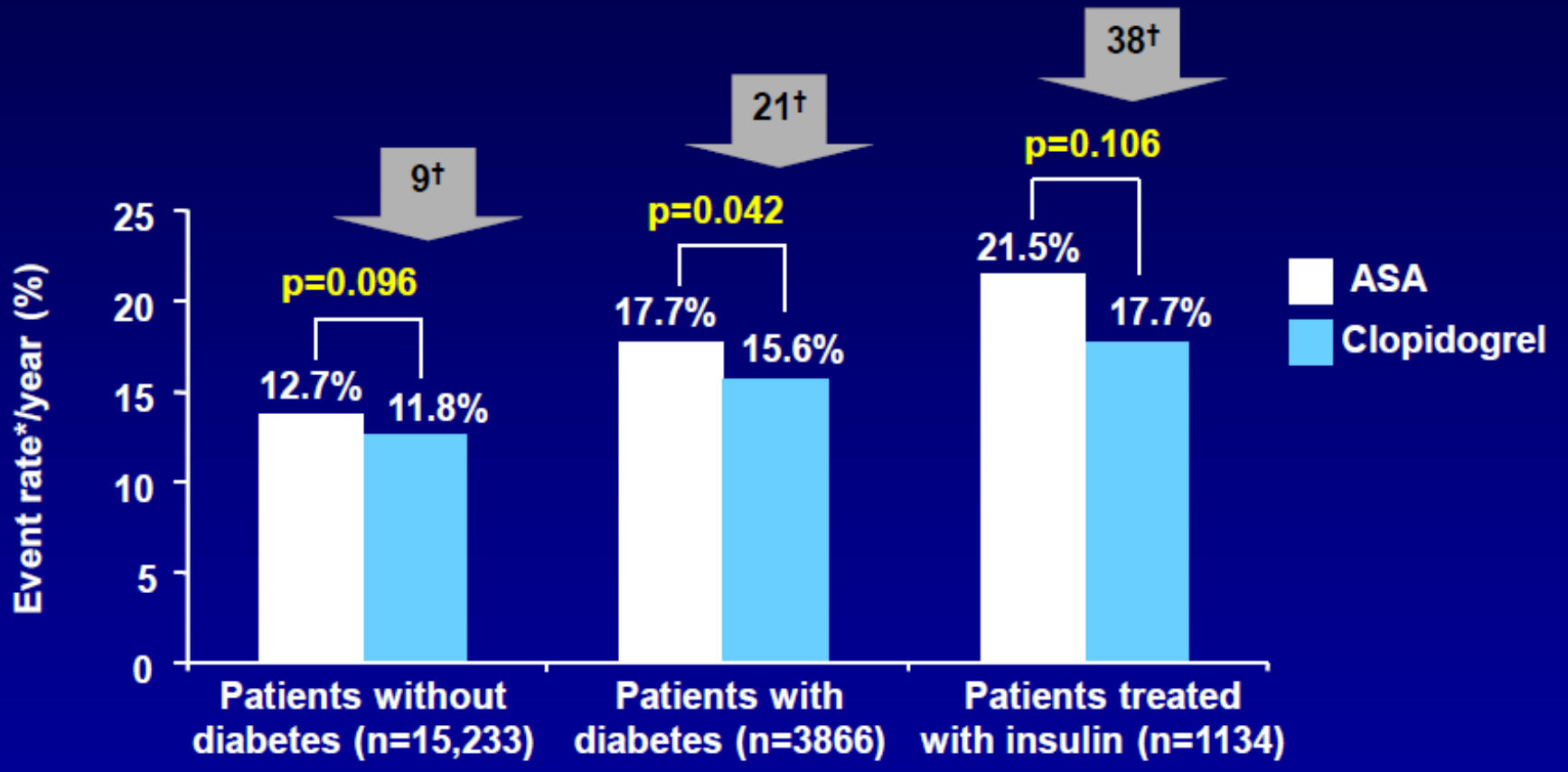
Events prevented / 1000 patients per year over ASA



Overall benefit: p = 0.001; multivariate analysis

Bhatt et al. J Am Coll Cardiol 2000;35(Suppl A):383 Bhatt, unpublished data

CAPRIE: Clopidogrel Provided Amplified Benefit in Patients with Diabetes

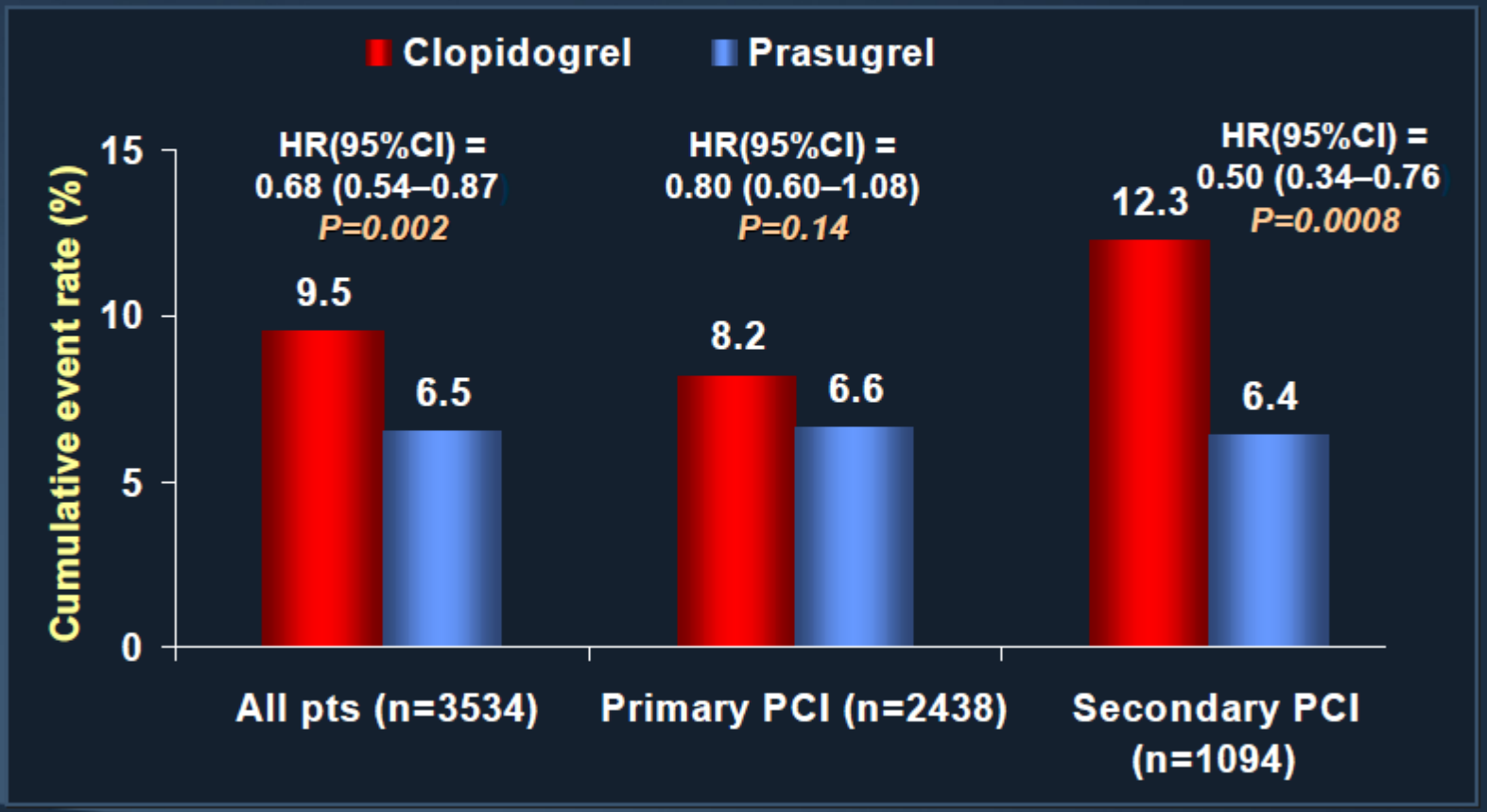


*MI, stroke, vascular death or rehospitalization for ischemic events/bleeding
†Number of events prevented per 1000 patients per year compared with ASA

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

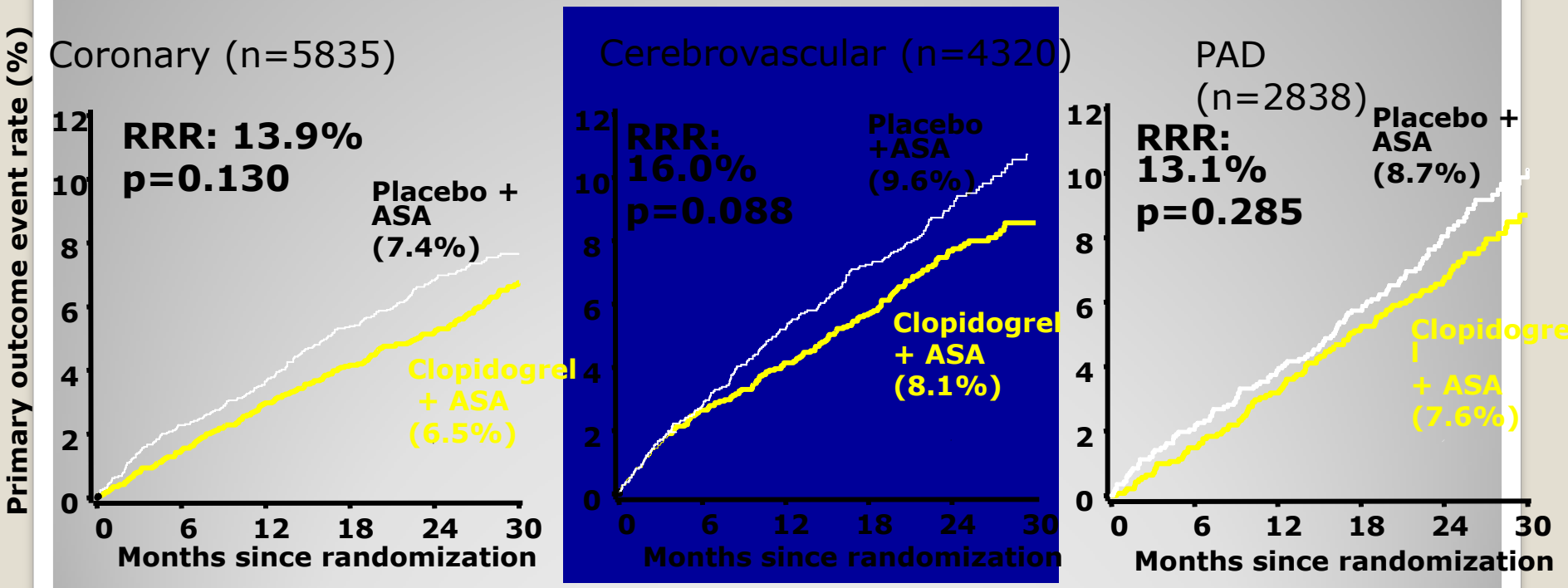
TRITON-TIMI-38

1° Endpoint: CV Death, MI or Stroke at 15 Months



Montalescot G et al. *Lancet* 2009;373:723–31

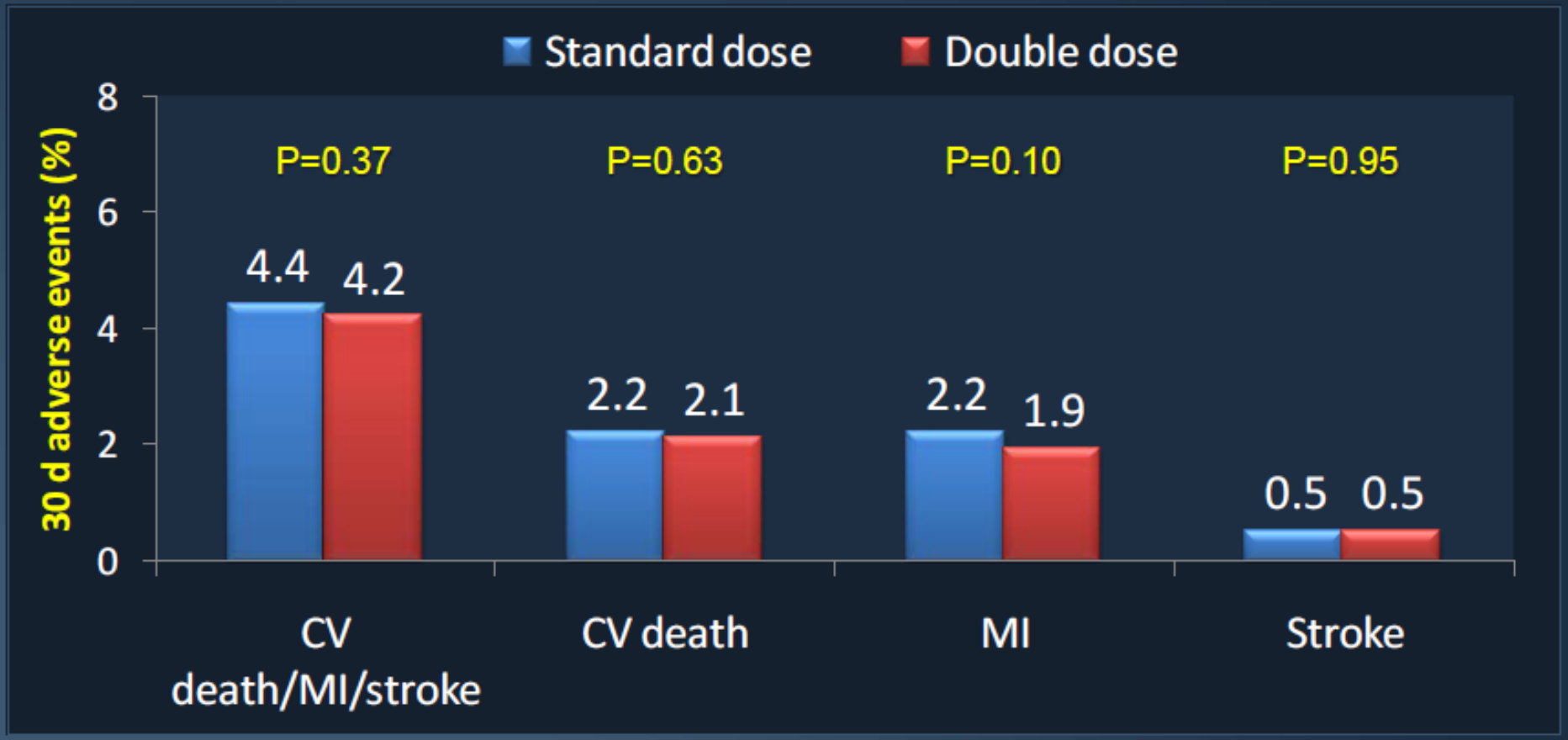
Symptomatic Cohort: Primary Outcome (MI/Stroke/CV Death)† by Entry Criteria*



†MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death
*Patients may have met more than one inclusion criteria
All patients received ASA 75-162 mg/day

CURRENT

25,087 pts with ACS (UA/NSTEMI 70.8%, STEMI 29.2%) undergoing early invasive management randomized to clopidogrel double-dose (600 mg then150 mg/d x 7d then 75 mg/d) vs standard dose (300 mg then 75 mg/d) for 30 days

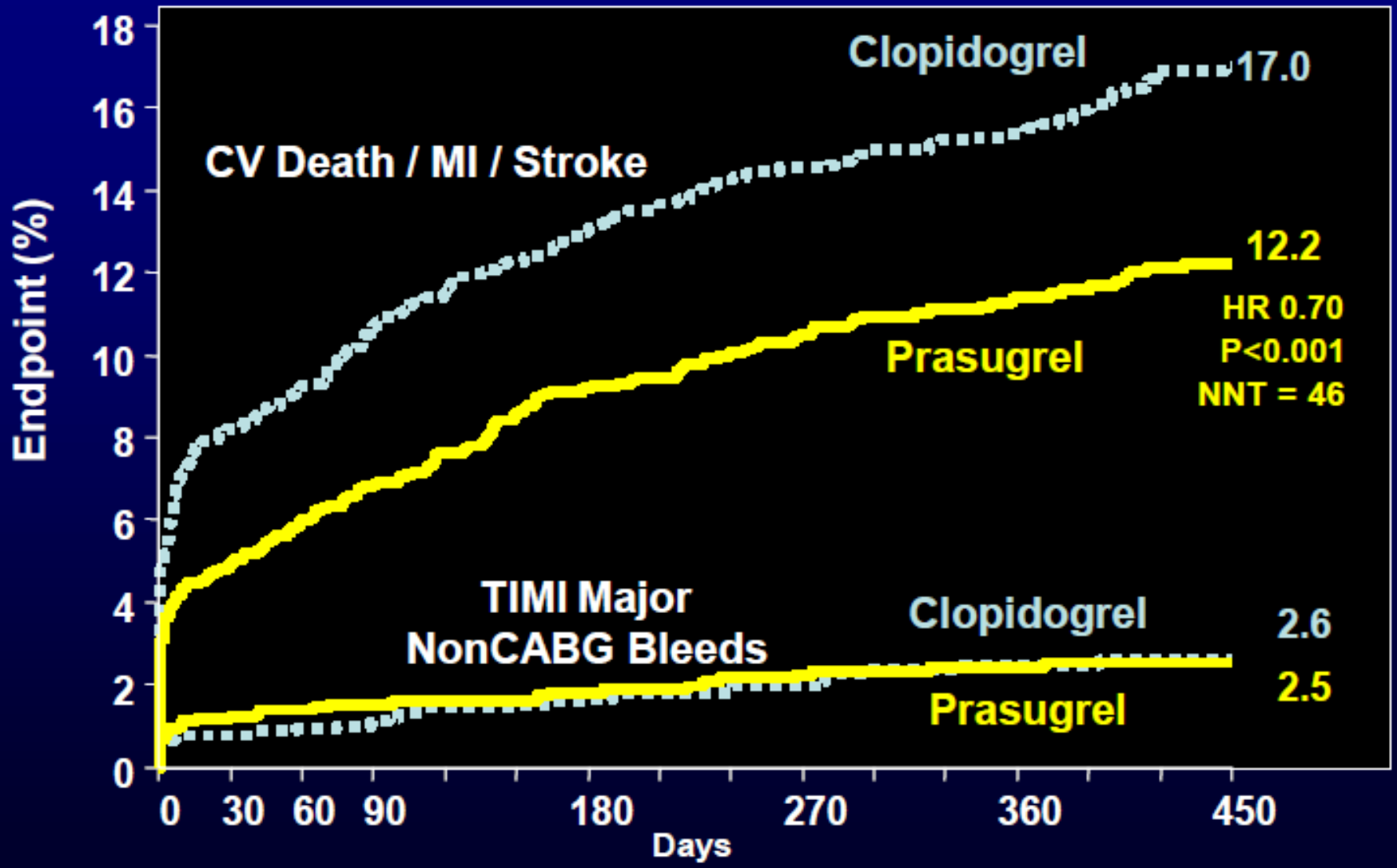


Mehta S. ESC 2009 and TCT 2009

TRITON TIMI-38

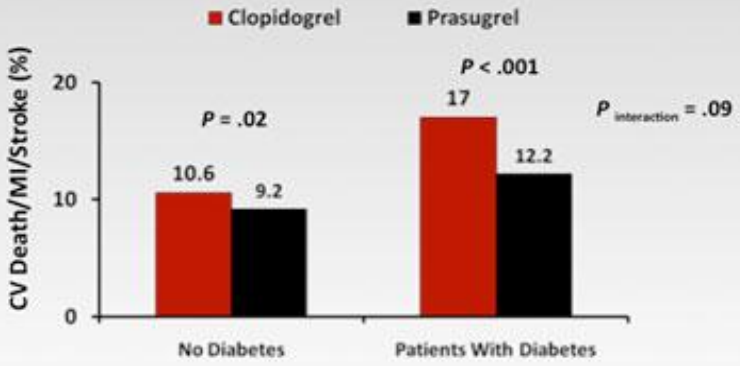
Diabetic Subgroup

N=3146



Wiviott SD, Circulation 2008

TRITON-TIMI 38 Diabetes Subgroup: Efficacy



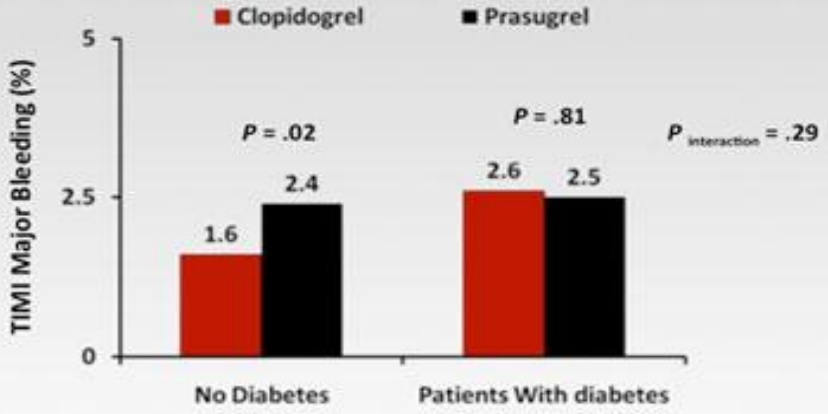
n = 10,462
HR, 0.86
(0.76-0.98)

n = 3146
HR, 0.70
(0.58-0.85)

Acute Coronary Syndromes

Wiviott SD, et al. *Circulation*. 2008;118:1626-1636.

TRITON-TIMI 38 Diabetes Subgroup: Safety



n = 10,462
HR, 1.43
(1.07-1.91)

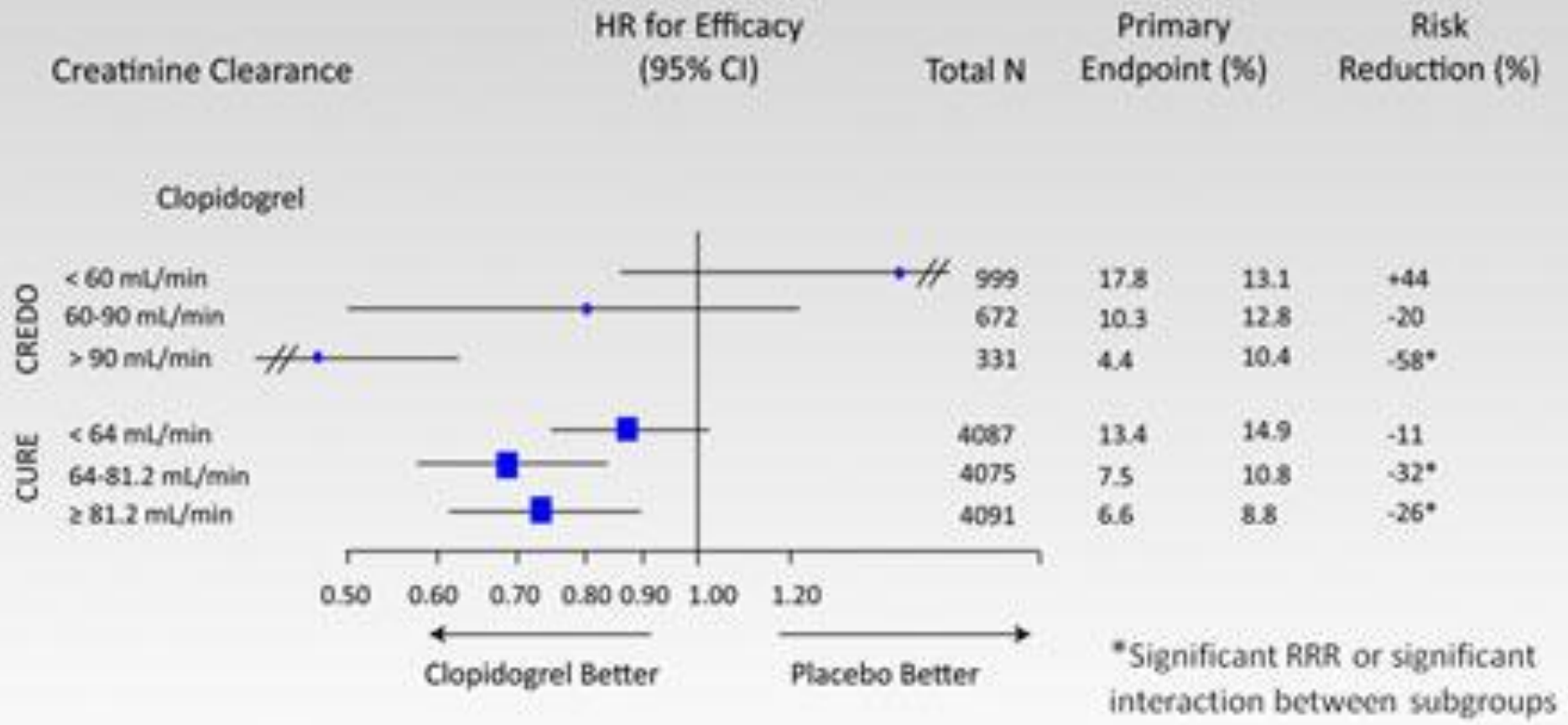
n = 3146
HR, 1.06
(0.66-1.69)

Acute Coronary Syndromes

Wiviott SD, et al. *Circulation*. 2008;118:1626-1636.

theheart.org | Medscape

Clopidogrel Less Effective in Renal Dysfunction



From Montalescot G, et al. *Circulation*. 2010;122:1049-1052.
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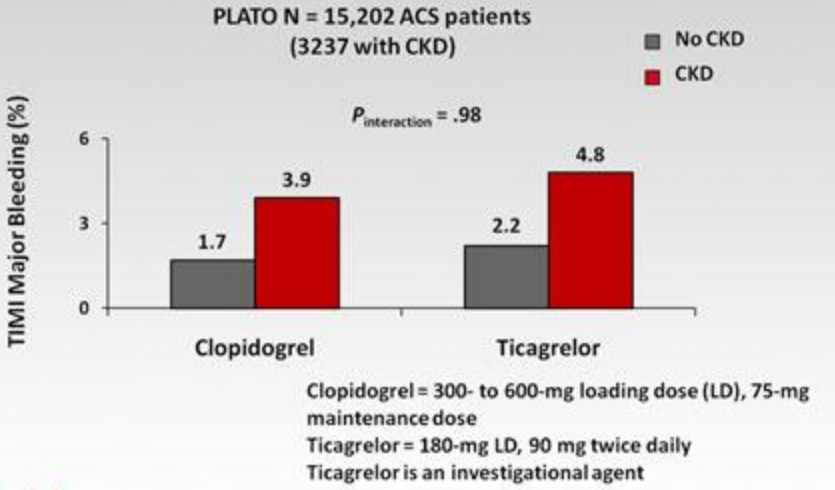
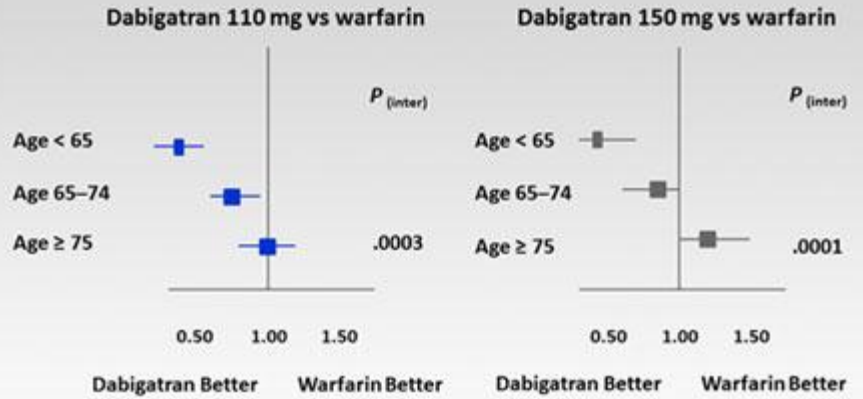
PLATO: Non-CABG TIMI Major Bleeding by CKD Status



Clopidogrel = 300- to 600-mg loading dose (LD), 75-mg maintenance dose
Ticagrelor = 180-mg LD, 90 mg twice daily
Ticagrelor is an investigational agent

James S, et al. *Circulation*. 2010;122:1056-1067.

Risk of Major Bleeding in RE-LY Trial: Age



http://spaf.pradaxa.com/content/dam/internet/chc/pradaxa/com_COPY/documents/SmPC%20English%20version%20anx_104049_en_04Aug2011.pdf

Eikelboom JW, et al. *Circulation*. 2011;123:2363–2372

Arrhythmia & EP

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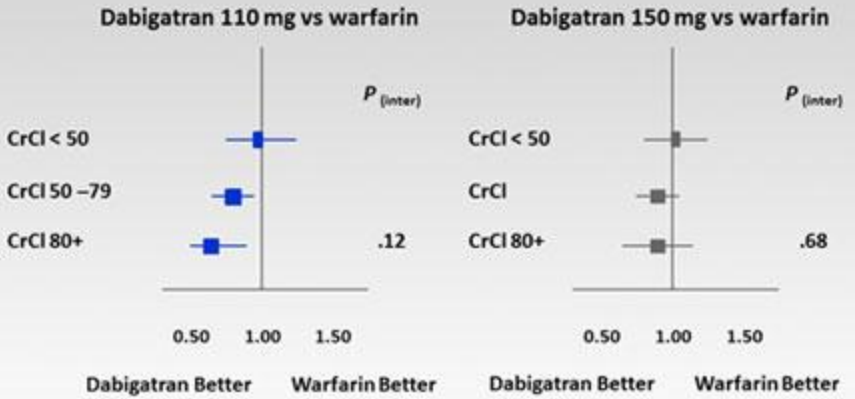
Risk of Major Bleeding in RE-LY Trial: Creatinine Clearance



http://spaf.pradaxa.com/content/dam/internet/chc/pradaxa/com_COPY/documents/SmPC%20English%20version%20anx_104049_en_04Aug2011.pdf

Eikelboom JW, et al. *Circulation*. 2011;123:2363–2372

Arrhythmia & EP

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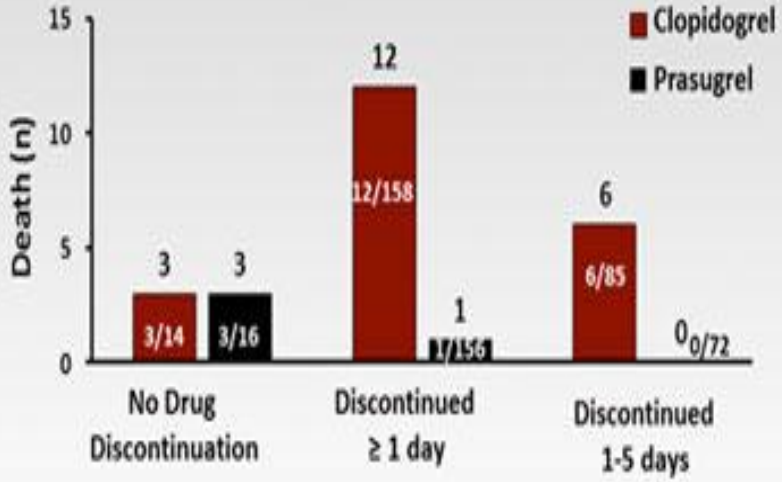
TRITON-TIMI 38: Post-hoc Analysis in Patients Who Underwent CABG

N = 346 patients who underwent CABG at some stage during 15-month follow-up
85% elective, nearly all resumed drug ≤ 7 days post-op



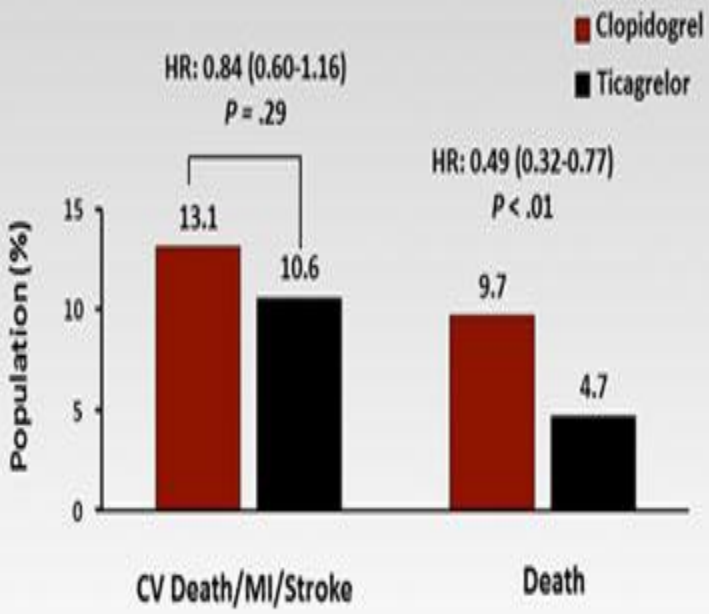
Clopidogrel = 300-mg load, 75 mg daily
Prasugrel = 60-mg load, 10 mg daily

Acute Coronary SYNDROMES

Smith PK, et al. American Heart Association 2010. Abstract 10881.

PLATO: Outcomes in CABG Patients

(N = 1261; Drug discontinued ≤ 7 days)



Clopidogrel = 300- to 600-mg load, 75 mg daily
Ticagrelor = 180-mg load, 90 mg twice daily

Acute Coronary SYNDROMES

Held C, et al. *J Am Coll Cardiol.* 2010;57:672-684.

CABG and P2Y12 Inhibitors seccation

CABG Bleeding and Clopidogrel Cessation

N = 3779 CABG/valve patients; 26.4% received preoperative clopidogrel

Cessation Interval	Adjusted OR	95% CI	*P* Value
Intraoperative/Postoperative Blood Transfusion			
≤ 24 hours (n = 324)	2.4	1.8-3.3	.0001
2 days (n = 120)	1.7	1.1-2.6	.027
3 days (n = 90)	1.1	0.6-1.8	.836
4 days (n = 98)	2.0	1.2-3.3	.006
5 days (n = 110)	1.0	0.6-1.6	.929
> 5 days (n = 257)	0.9	0.7-1.3	.622
Hemorrhagic Complication			
≤ 24 hours	2.1	1.3-3.6	.004
2 days	0.7	0.2-2.2	.520
3 days	1.2	0.4-3.3	.776
4 days	0.9	0.3-3.1	.926
5 days	0.8	0.3-2.7	.764
> 5 days	1.1	0.5-2.1	.880

Herman CR, et al. *Ann Thorac Surg*. 2010;89:397-402.

Elderly - Women

Diabetes mellitus

Stroke (history or not)

PVD

CABG

CKD (patients with CKD were excluded from75% of published CAD trials) Kidney Intern 2006

Common group for subanalysis

There is understandable desire on the part of both practitioners and investigators for refinement of the overall findings of any randomized trial. For practitioners, there is the desire to know more about risks and benefits for their specific patients. For investigators, the massive effort of a major international clinical trial seems to warrant more than one hypothesis-testing P value. Unfortunately, this exploration of the data, generally termed subgroup analysis, is notoriously fraught with multiple hazards, especially the play of chance and uncontrollable confounders.[11-13] Indeed, there are numerous examples from randomized trials in which an apparently important differential response to therapy suggested by a subgroup analysis generated a hypothesis that was subsequently refuted in a trial designed to test that hypothesis.[13]