Acute Coronary Syndrome:
A Practical Approach

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Disclosures: Dr. E Marc Jolicoeur

- Marc Jolicoeur perceives the following potential financial and intellectual conflicts of interest with this presentation and discloses the following (past 2 years):
- **Research grant:** Astra Zeneca, Boston Scientific (significant)
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- N.B. All funds from these sources have been deposited into university-based research accounts.

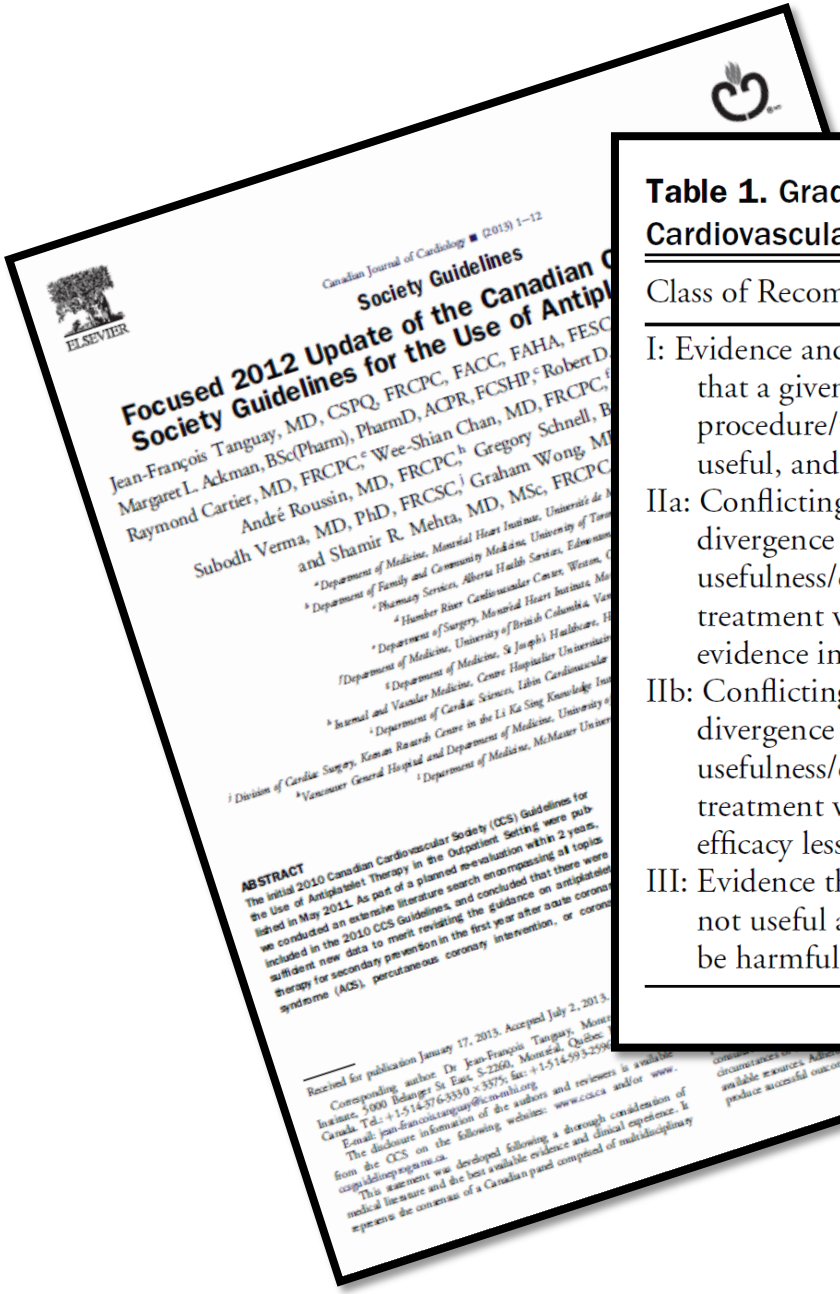
Learning Objectives

After attending this session, participants will be better able to:

- Discuss the medical evidence supporting the recent Canadian practice guidelines on the use of antiplatelet therapy in the outpatients setting;
- Integrate the use of antiplatelet therapy in broader perspective of acute coronary syndrome management;
- Recognize special situations and populations where antiplatelet therapy needs being adjusted

Clinical Guide Sources

- Antithrombotic Management in STEMI
- Antithrombotic Management in NST-ACS
- Related Guides:
  - ASA
  - Clopidogrel
  - Ticagrelor
  - Prasugrel
  - Dabigatran
  - Rivaroxaban
  - Apixaban


Canadian Journal of Cardiology ■ (2013) 1–12

Society Guidelines

Focused 2012 Update of the Canadian C
Society Guidelines for the Use of Antipl

Jean-François Tanguay, MD, CSPQ, FRCPC, FACC, FAHA, FESC
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ABSTRACT

The initial 2010 Canadian Cardiovascular Society (CCS) Guidelines for the Use of Antiplatelet Therapy in the Outpatient Setting were published in May 2011. As part of a planned re-evaluation within 2 years, we conducted an extensive literature search encompassing all topics included in the 2010 CCS Guidelines, and concluded that there were sufficient new data to merit revisiting the guidance on antiplatelet therapy for secondary prevention in the first year after acute coronary syndrome (ACS), percutaneous coronary intervention, or coronary

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Table 1. Grading system used in the preparation of the Canadian Cardiovascular Society antiplatelet consensus statement

Class of Recommendation	Level of Evidence
I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective	A: Data derived from multiple randomized clinical trials or meta-analyses
IIa: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the weight of evidence in favour	B: Data derived from a single randomized clinical trial or large nonrandomized studies
IIb: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the usefulness/efficacy less well established	C: Consensus of opinion by experts and/or small studies, retrospective studies, and registries
III: Evidence that the treatment is not useful and in some cases may be harmful	

Tanguay J-F, *et al.* *Can J Cardiol.* 2013.

Anti-platelet therapy

ST Elevation - ACS

PCI 1º

Lytics

No-reperfusion

-or -

ASA 81mg indefinitely
(or clopidogrel 75 mg if intolerant to ASA)

Clopidogrel 75 mg daily for 12 months if not eligible to ticagrelor or prasugrel

Clopidogrel 75 mg DIE ≥ 1 month, months

Note: a maintenance dose of 150 mg daily should be considered for the first 6 days in patients treated with PCI

for 12 months

Or

Prasugrel 10 mg daily for 12

should to be avoided if prior stroke or TIA.

Note 2: In patients older than 75 years of age or with a body weight < 60 Kg, a dose of 5 mg dai can be considered

Continuation of ticagrelor, prasugrel or clopidogrel for more than 12 months can be considered in patients with high thrombosis risk and low bleeding risk

Anticoagulants

The triple association of rivaroxaban, clopidogrel and ASA should not be considered over the use of dual antiplatelet therapy for the secondary prevention of acute coronary syndrome

The association of an oral anticoagulation (including vitamin K antagonist) with a dual antiplatelet therapy can be appropriate in selected patients, such as those with atrial fibrillation or anterior wall infarction

Dabigatran and apixaban should not be used in combination with antiplatelet therapy for the secondary prevention of ACS

NSTE-ACS

PCI | CABG | MEDICAL

Anti-platelet therapy

ASA 81mg indefinitely
(or clopidogrel 75 mg if intolerant to ASA)

Ticagrelor 90 mg bid x 12 months

-or -

Prasugrel 10 mg die after coronary anatomy has been defined and PCI planned x 12 months

-or -

Clopidogrel 75 mg daily for 12 months if not eligible to ticagrelor or prasugrel

Note 1: should be avoided if prior stroke or TIA., or in patients not treated by PCI

Note 2: avoid pre-loading before PCI

Note 3: In patients older than 75 years of age or with a body weight < 60 Kg, a dose of 5 mg daily can be considered

Note: a maintenance dose of 150 mg daily should be considered for the first 6 days in patients treated with PCI

Anticoagulants

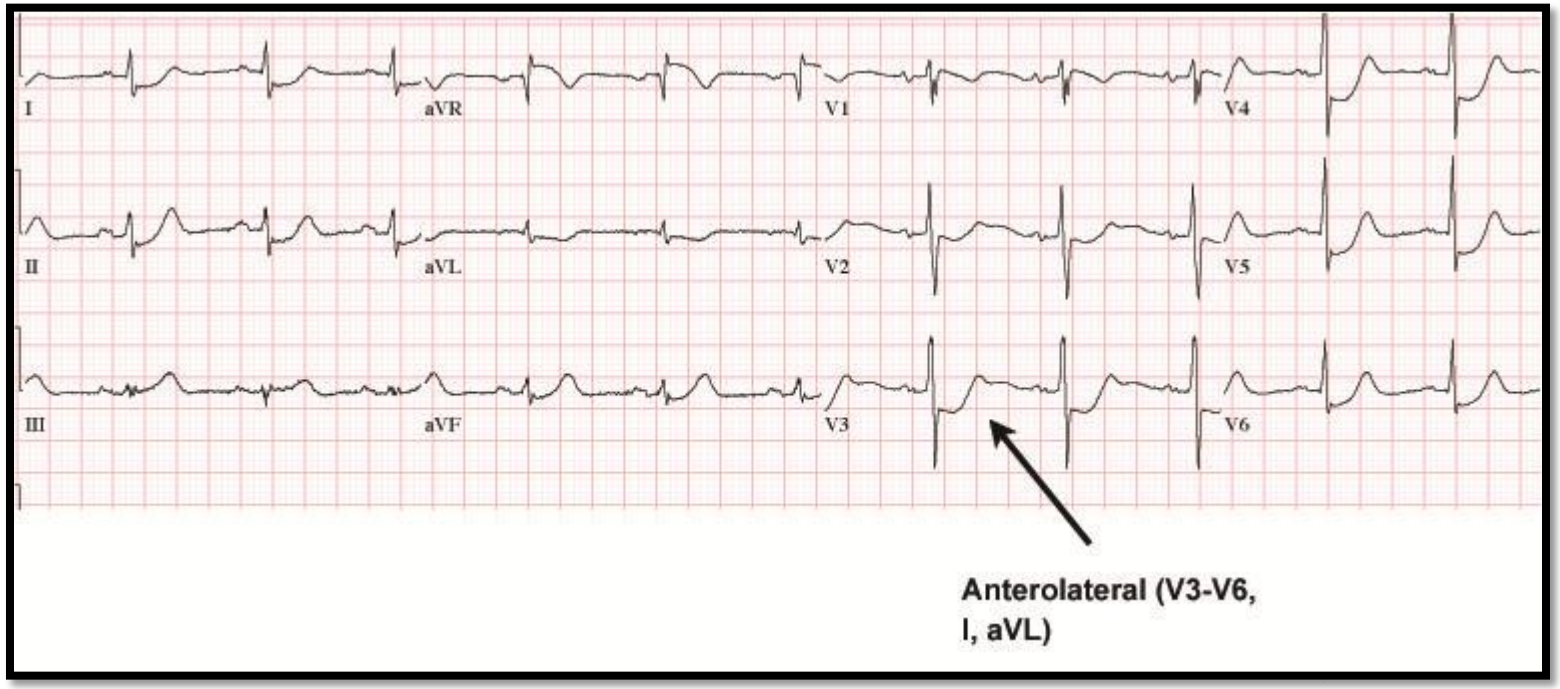
The triple association of rivaroxaban, clopidogrel and ASA should not be considered over the use of ASA with ticagrelor or prasugrel for the secondary prevention of ACS

The association of an oral anticoagulation (including vitamin K antagonist) with a dual antiplatelet therapy can be appropriate in selected patients, such as those with atrial fibrillation and mechanical

Dabigatran and apixaban should not be used in combination with antiplatelet therapy for the secondary prevention of ACS

Case #1:
Late presentation ACS

A 71 year old female shows on a Friday for recurrent chest pain. The ECG displays a normal sinus rhythm with an obvious ST-segment depression and T wave inversion in the anterolateral distribution.

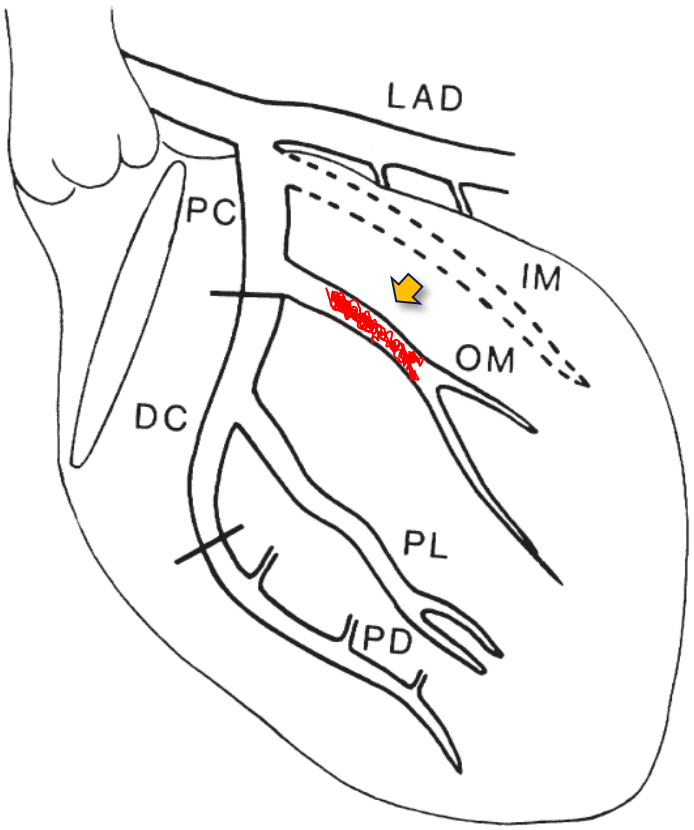


Case #1:
Late presentation ACS

When you send her in the cath lab (Monday afternoon), her biomarkers are still elevated, but she has had no recurrent chest pain for more than 72h and remains hemodynamically stable.

The angiogram shows an occluded large marginal branch.

She weigh 80 kg and was never diagnosed with TIA or stroke.



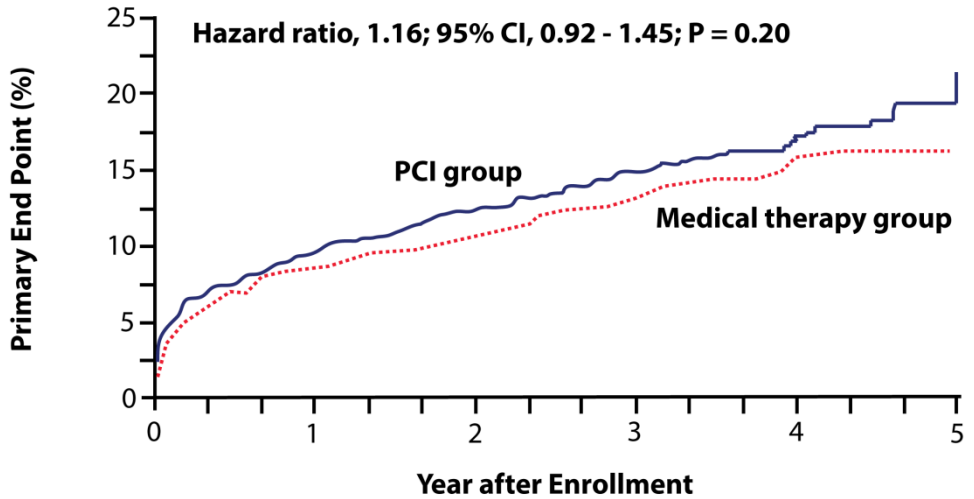
Dunn, RF, *et al*. *Circulation*. 1984;69:477-84.

Audience Poll

Management Options

1) Prasugrel loading + PCI/stent.
2) Ticagrelor loading + PCI/stent
3) Clopidogrel loading + no PCI.
4) Prasugrel loading + no PCI
5) Ticagrelor loading + no PCI.

Medically treated ACS: Evidence



No. at Risk						
PCI group	1082	895	719	482	265	85
Medical therapy group	1084	909	714	474	268	78

As per OAT trial, PCI does not reduce MACE in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction

Hochman, JS, *et al. N Engl J Med.* 2006; 355(23):2395-2407.

Medically treated ACS

- **<u>CCS 2012 Recommendation</u>:**
  - We recommend ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in patients with moderate to high risk NSTEACS managed with medical therapy alone.

    (Strong Recommendation, High-Quality Evidence).

  - We recommend clopidogrel 75 mg daily for at ≥ 1 month in addition to ASA 81 mg daily in patients with STEMI who were managed with either fibrinolytic therapy or no reperfusion therapy.

    (Strong Recommendation, High-Quality Evidence).

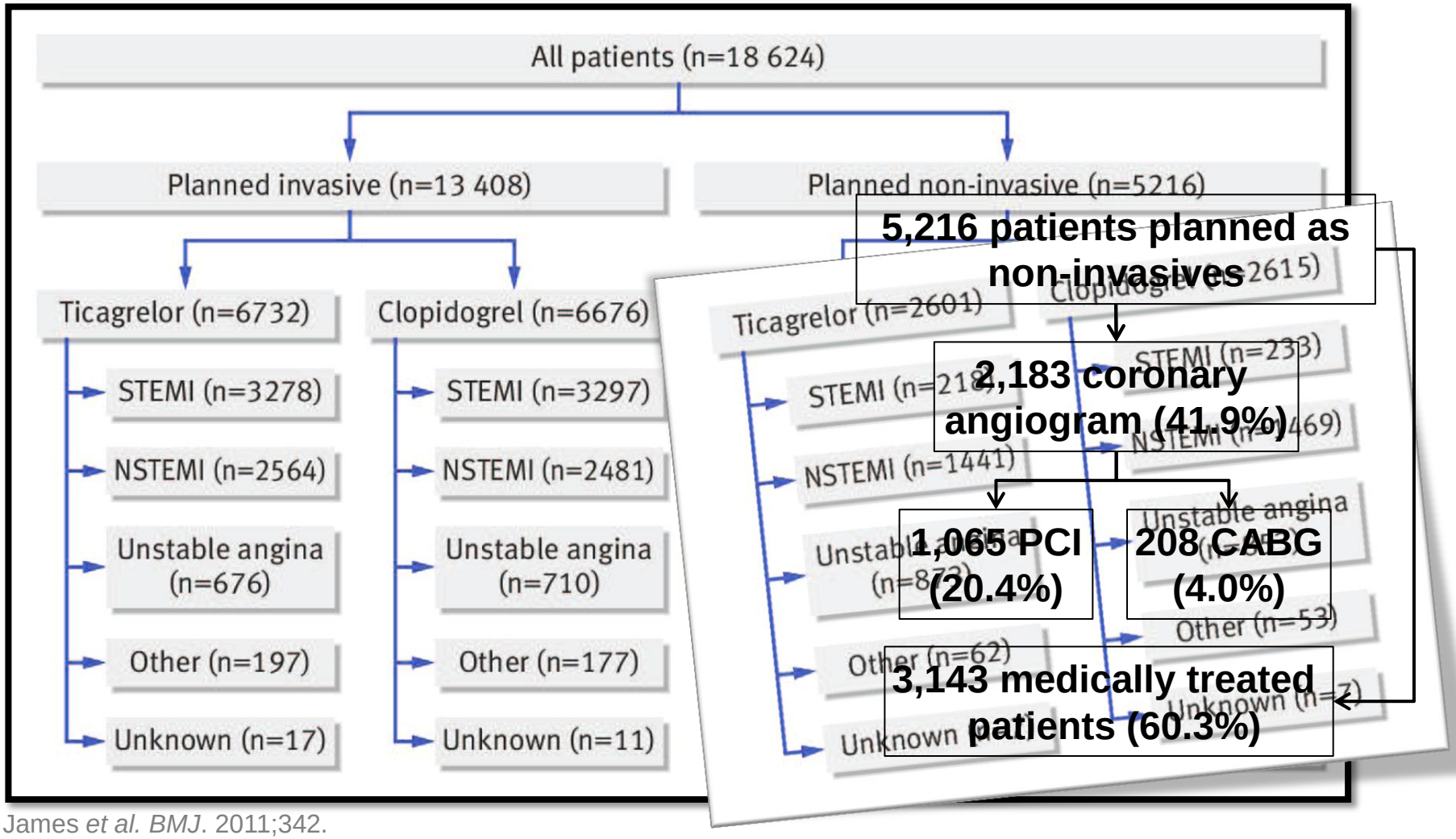
    We suggest that clopidogrel can be continued for 12 months

    (Conditional Recommendation, Low-Quality Evidence).

Tanguay J-F, et al. Can J Cardiol. 2013.

PLATO - distribution

Ticagrelor: 180mg PO Loading dose, then 90 mg twice daily > 6 months



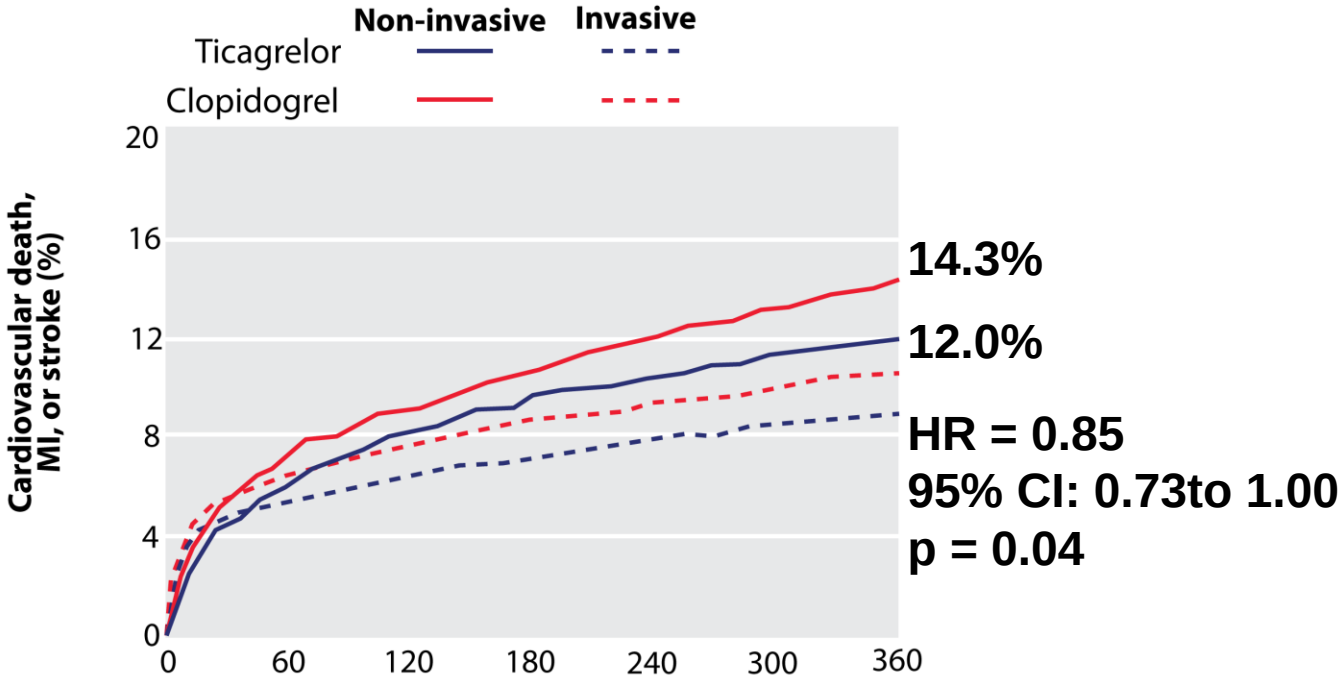
James *et al. BMJ*. 2011;342.

PLATO - distribution

Characteristics	Non-invasive (n=5,216)	Invasive (n=13,408)
Age, median (IQR), y	65 (57-73)	61 (53-69)
Woman, (%)	37%	25%
Weight, median (IQR), kg	78 (69-88)	80 (70-90)
Diabetes, (%)	30%	23%
Past MI history (%)	30%	17%
TIMI score	89	69
STEMI, (%)	9%	49%
NSTEMI, (%)	56%	38%
Unstable angina (%)	35%	13%
Heparin	37%	66%
LMWH	64%	47%
Fundaparinux	5%	2%

James *et al. BMJ*. 2011;342.

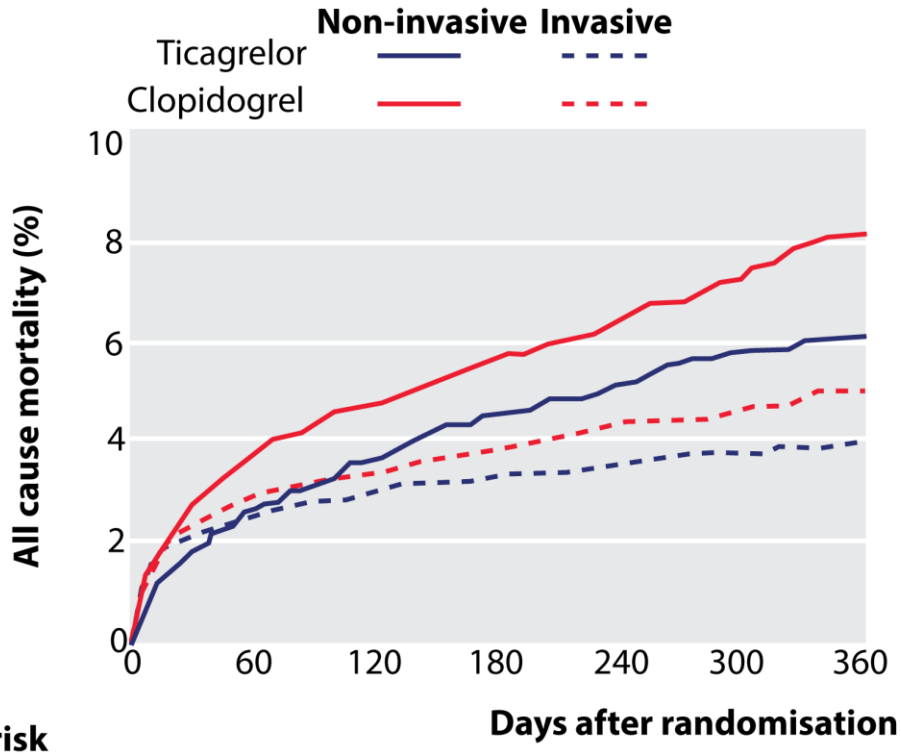
Death/MI/strokes: ticagrelor vs clopidogrel
Non-invasive strategy initially planned



Among medically treated participants (n = 3,948), ticagrelor improved the primary endpoint from 15.2% to 12.2%
(HR = 0.81 95 CI = 0.68 – 0.97)

James *et al. BMJ*. 2011;342.

Death rates: ticagrelor vs clopidogrel
Non-invasive strategy initially planned



8.2%

6.1%

HR = 0.75
95% CI: 0.61 à 0.93
p = 0.01
P interaction = 0.89

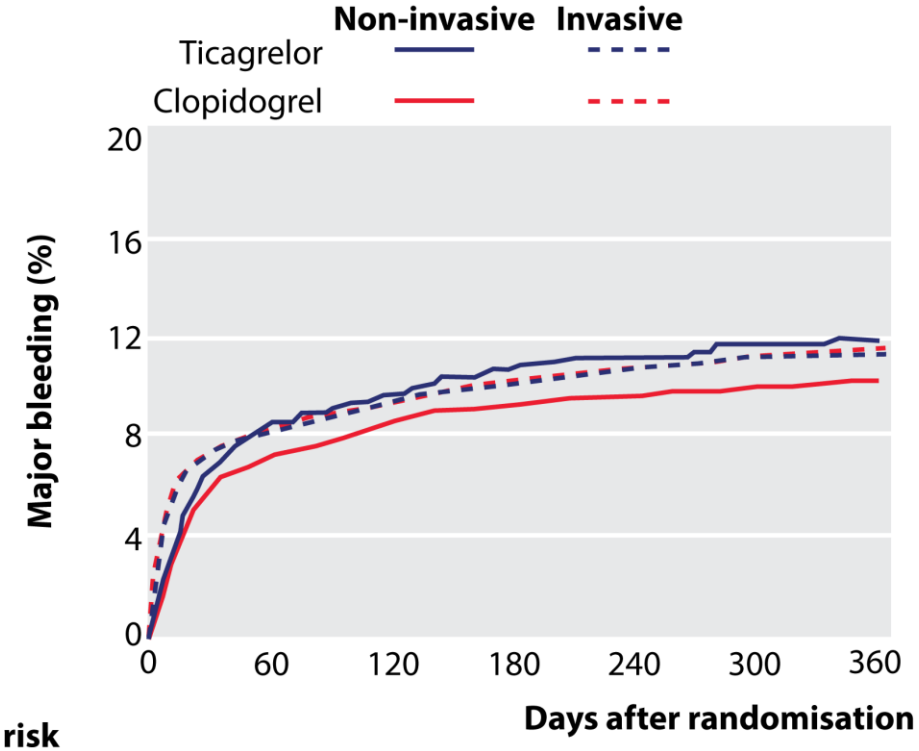
No. at risk

Invasive							
Ticagrelor	6732	6439	6375	6241	5141	3951	3233
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
Ticagrelor	2601	2485	2447	2385	1978	1531	1186
Clopidogrel	2615	2488	2448	2380	1965	1524	1200

James *et al. BMJ*. 2011;342.

Bleeding rates: ticagrelor vs clopidogrel

Non-invasive strategy initially planned



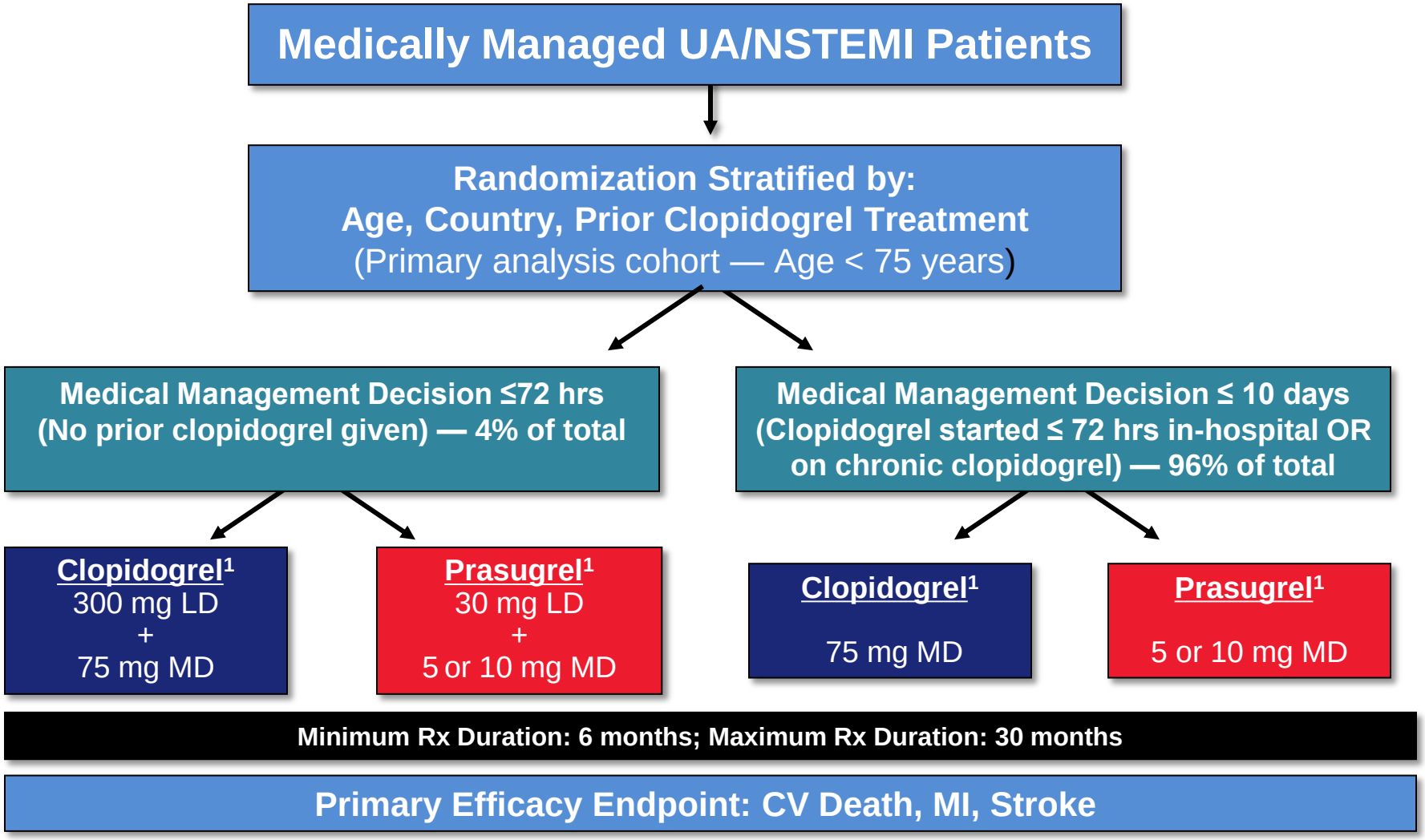
11.9%
10.3%

HR = 1.17
95% CI: 0.98 à 1.39
p = 0.08

No. at risk

Invasive							
Ticagrelor	6651	5238	4948	4766	3730	2748	2721
Clopidogrel	6585	5220	4985	4798	3756	2760	2507
Non-invasive							
Ticagrelor	2584	2008	1878	1779	1399	1035	912
Clopidogrel	2601	2085	1945	1872	1453	1081	972

James *et al. BMJ*. 2011;342.

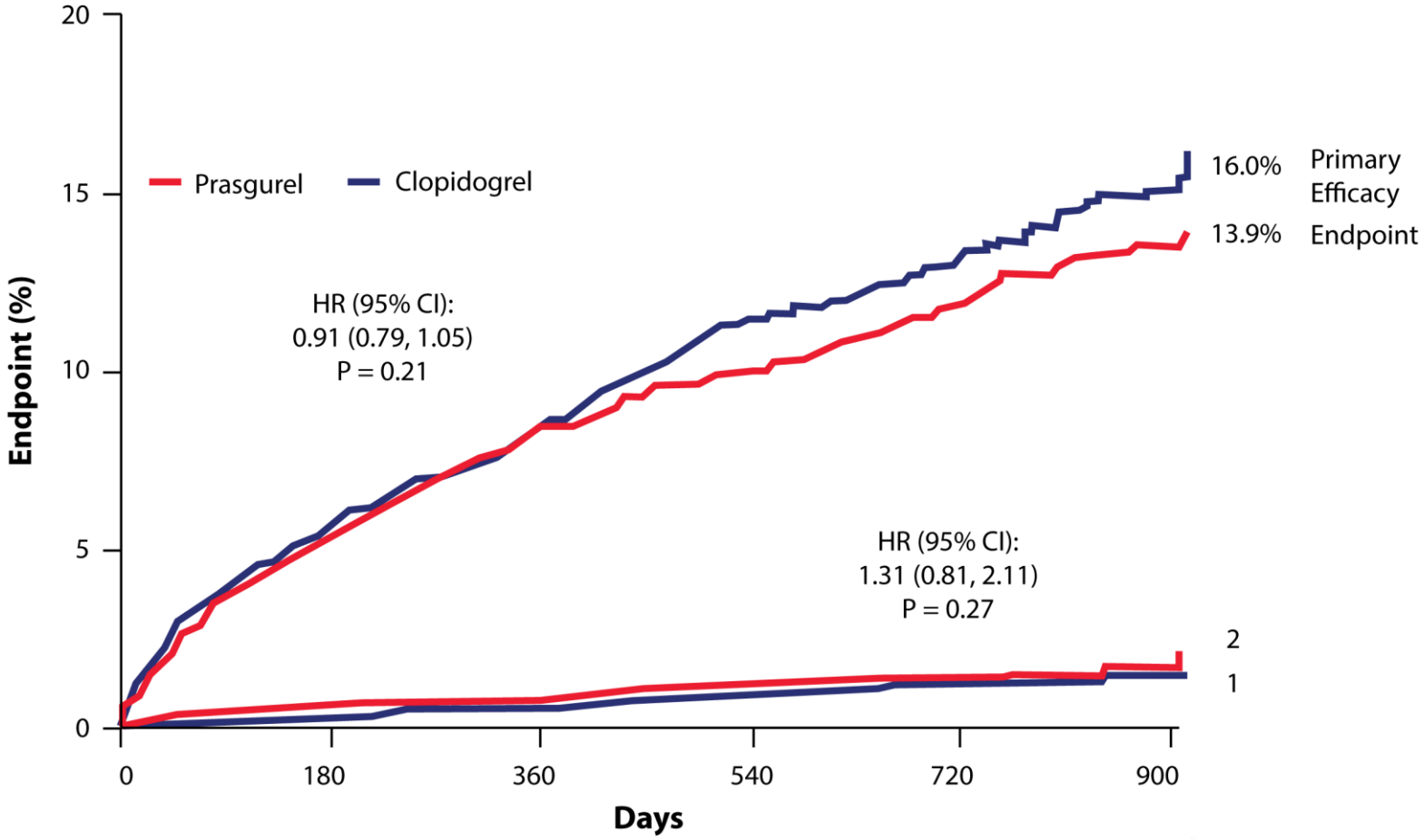


1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given..

Adapted from Chin CT et al. *Am Heart J* 2010;160:16

Primary Efficacy Endpoint and TIMI Major *Bleeding Through 30 Months*

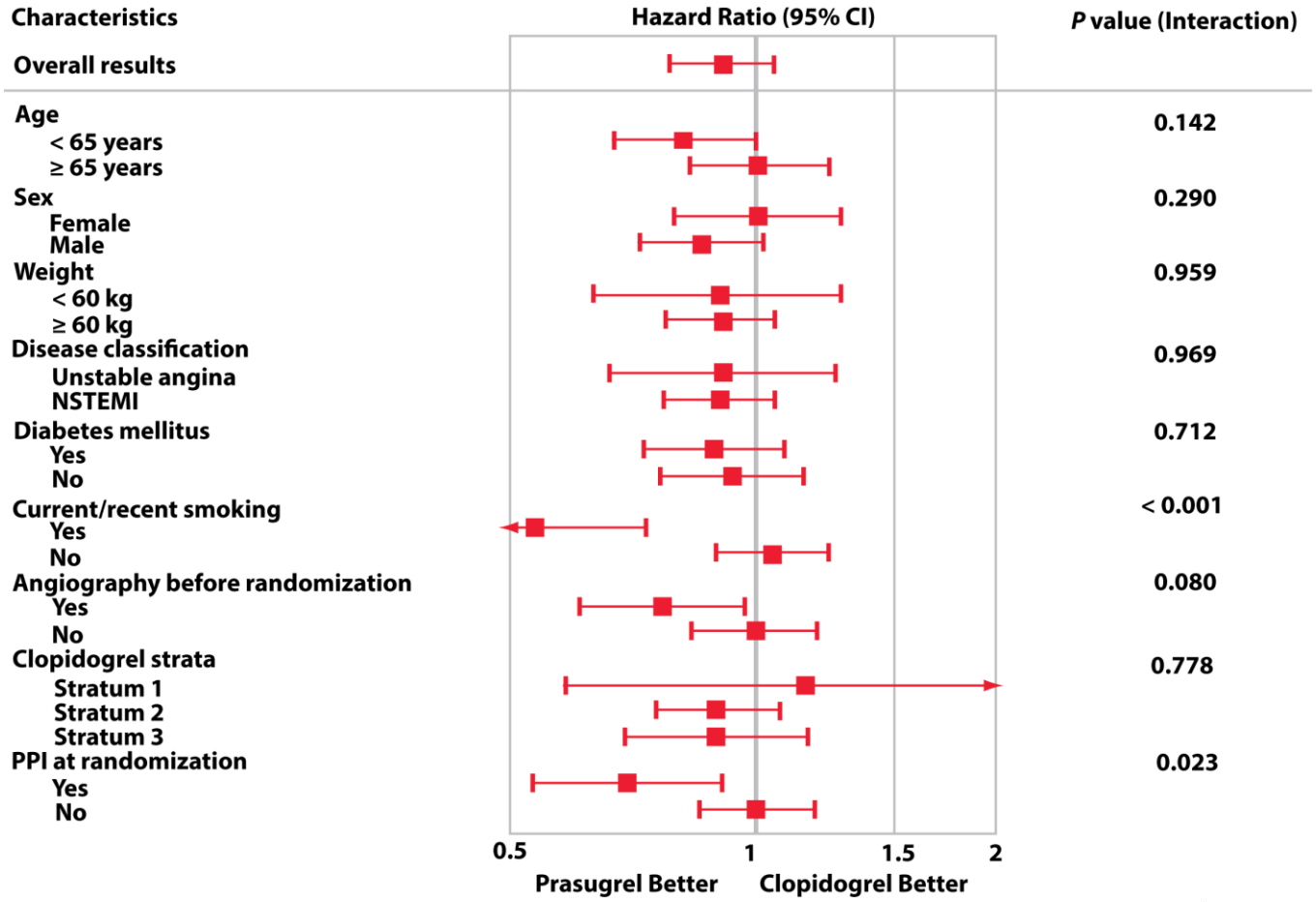
(Age < 75 years, N = 7243)



Roe, MT, *et al. N Engl J Med*. 2012; 367:1297.

Primary Endpoint
Pre-Specified

Sub-Groups (Age < 75 years)



TRILOGY vs PLATO for medically treated ACS

Clinical characteristics of the TRILOGY population as compared to conservatively treated patients in PLATO

	TRILOGY	PLATO
Age ≥ 75 years	22	21
Prior MI (%)	43	30
Prior CABG (%)	16	7
Diabetes (%)	38	30
Prior CHF (%)s	16	7
Killip class ≥ 2	12	09 - 14[a]

MI + myocardial infarction, CABG = coronary artery bypass graft, CHF = congestive heart failure.

[a] 0.9% in ticagrelor treated STEMI patients, 1.4% in clopidogrel-treated STEMI patients.

De Servi, S., *et al. Int J Cardiol*. 2013;167(4):1638-1639.

Case #2:
Trifecta or triple threat?

- A 61 year old man has had two distinct NSTEMI episodes in the last 6 months, one requiring a DES in the RCA and the other requiring a DES in the mid-LAD
- He has been taking ASA 81mg + clopidogrel 75mg daily for 6 months and compliance is not an issue
- You resident ask you whether it would be a good idea to initiate anticoagulation before hospital discharge given the patient's recurrent ACS episodes.

Audience Poll

What will you answer your resident?

1) Add warfarin to the DAPT, (WARIS II trial)
2) Add Rivaroxaban 2.5 mg daily to the DAPT, (ATLAS TIMI 51 trial)
3) Add apixaban 5mg bid to the DAPT (APPRAISE-II trial)
4) Stop clopidogrel and switch to either ticagrelor or prasugrel
5) Continue clopidogrel + ASA as it is and consider extending it beyond 1Y

Triple THERAPY FOR 2ND PREVENTION

Drug-eluting stent

Bare metal stent

PTCA

Unstable angina

NSTEMI

STEMI

Stable CAD

Bleeding risk

Compliance

Atrial fibrillation

Mechanical heart valve

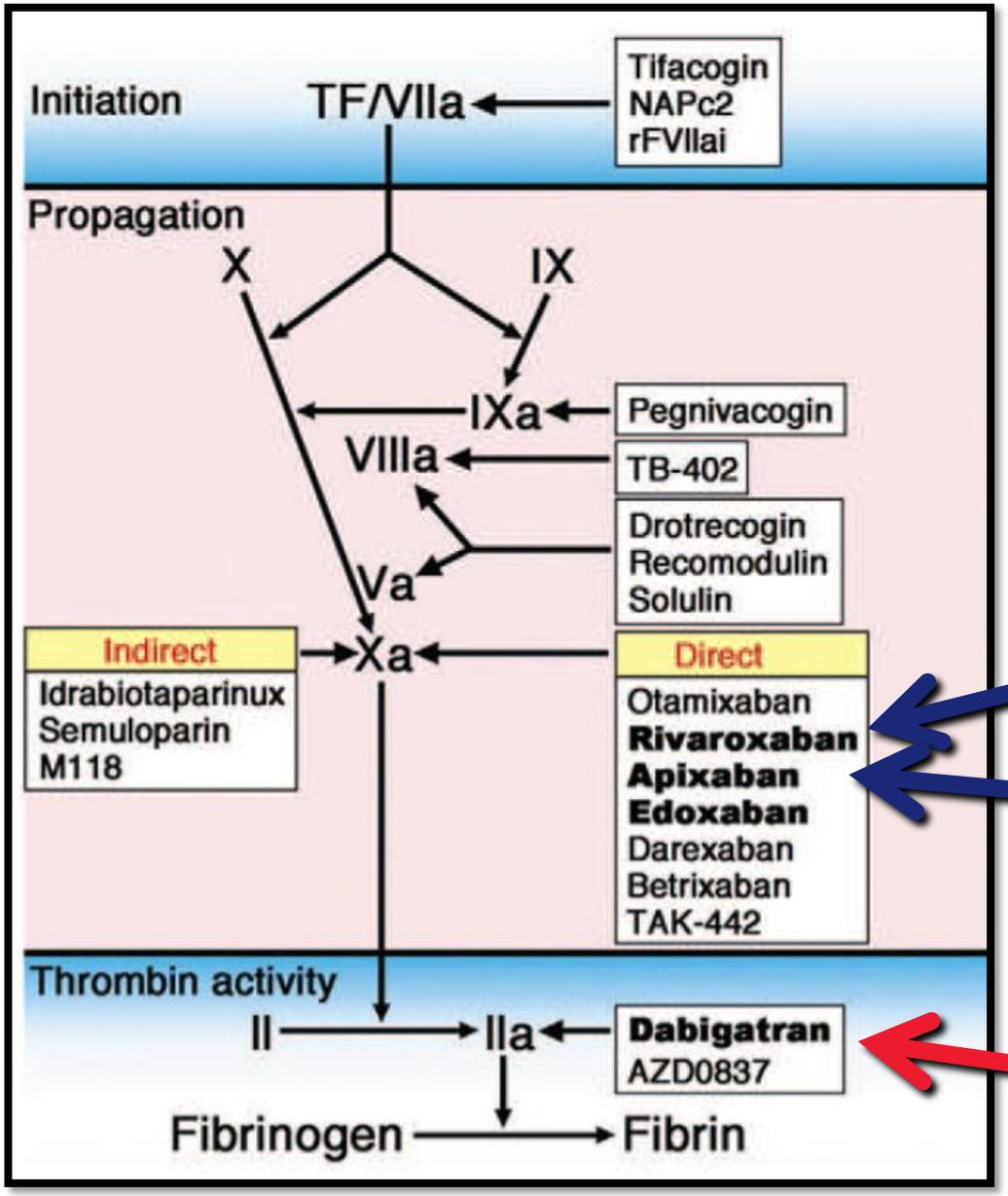
Anterior scar

NOACs for Secondary prevention after ACS

- **<u>CCS 2012 Recommendation:</u>**
  - We suggest against the use of triple therapy with rivaroxaban, clopidogrel, and ASA over the use of DAPT with ticagrelor or prasugrel plus ASA for secondary prevention of ACS

    (Conditional Recommendation, Very Low-Quality Evidence)

  - We recommend against the use of dabigatran and apixaban at any dose in combination with antiplatelet therapy for secondary prevention of ACS (Strong Recommendation, High-Quality Evidence).



ATLAS-ACS II

APPRAISE II

REDEEM

De Caterina, R, et al. J Am Coll Cardiol. 2012;59(16):1413-1425.

ORIGINAL ARTICLE

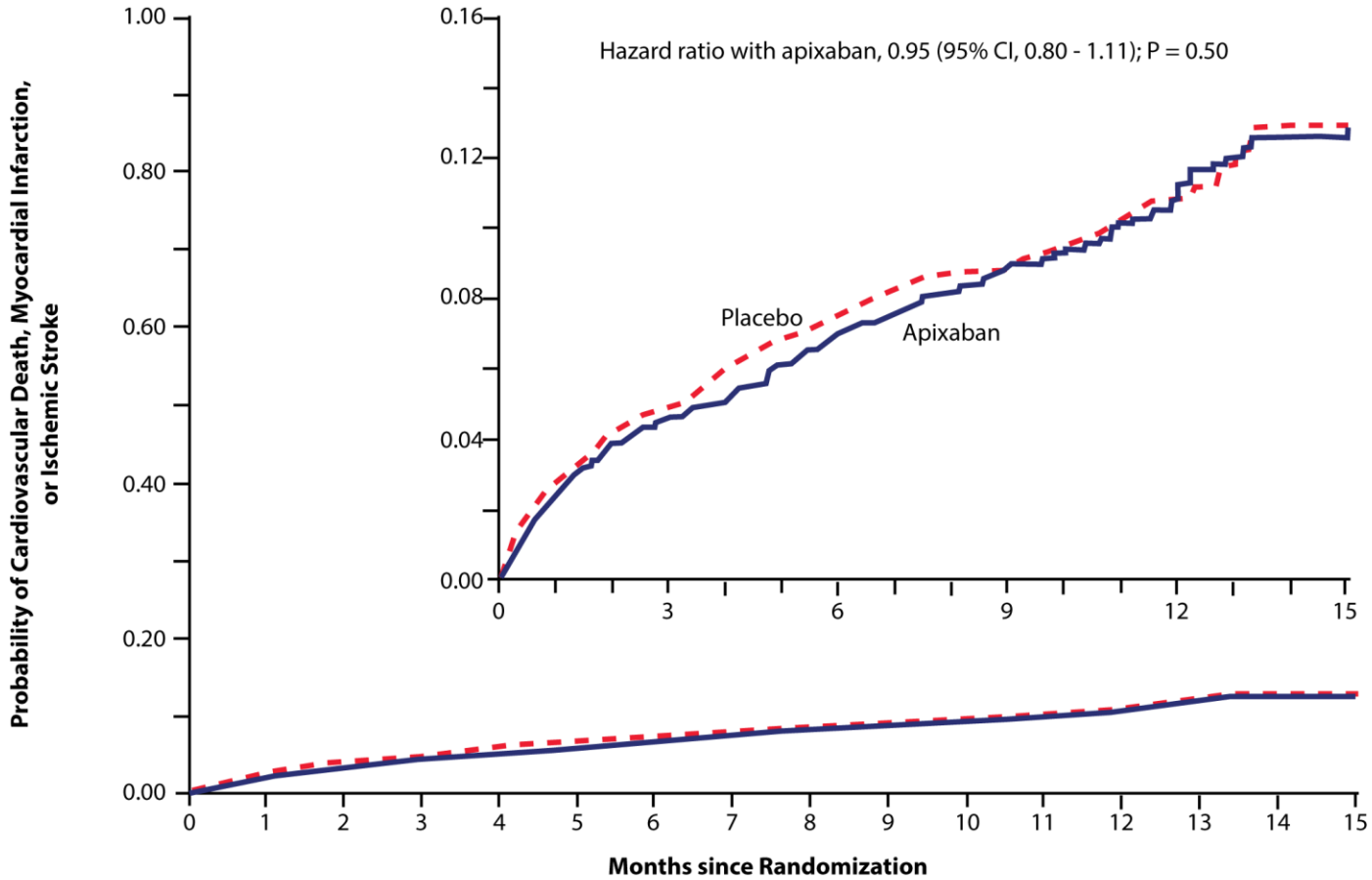
Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

APPRAISE-II

CONCLUSIONS

The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events. (Fund
Myers Squibb and Pfizer; APPRAISE-2 ClinicalTrials.gov number, NCT

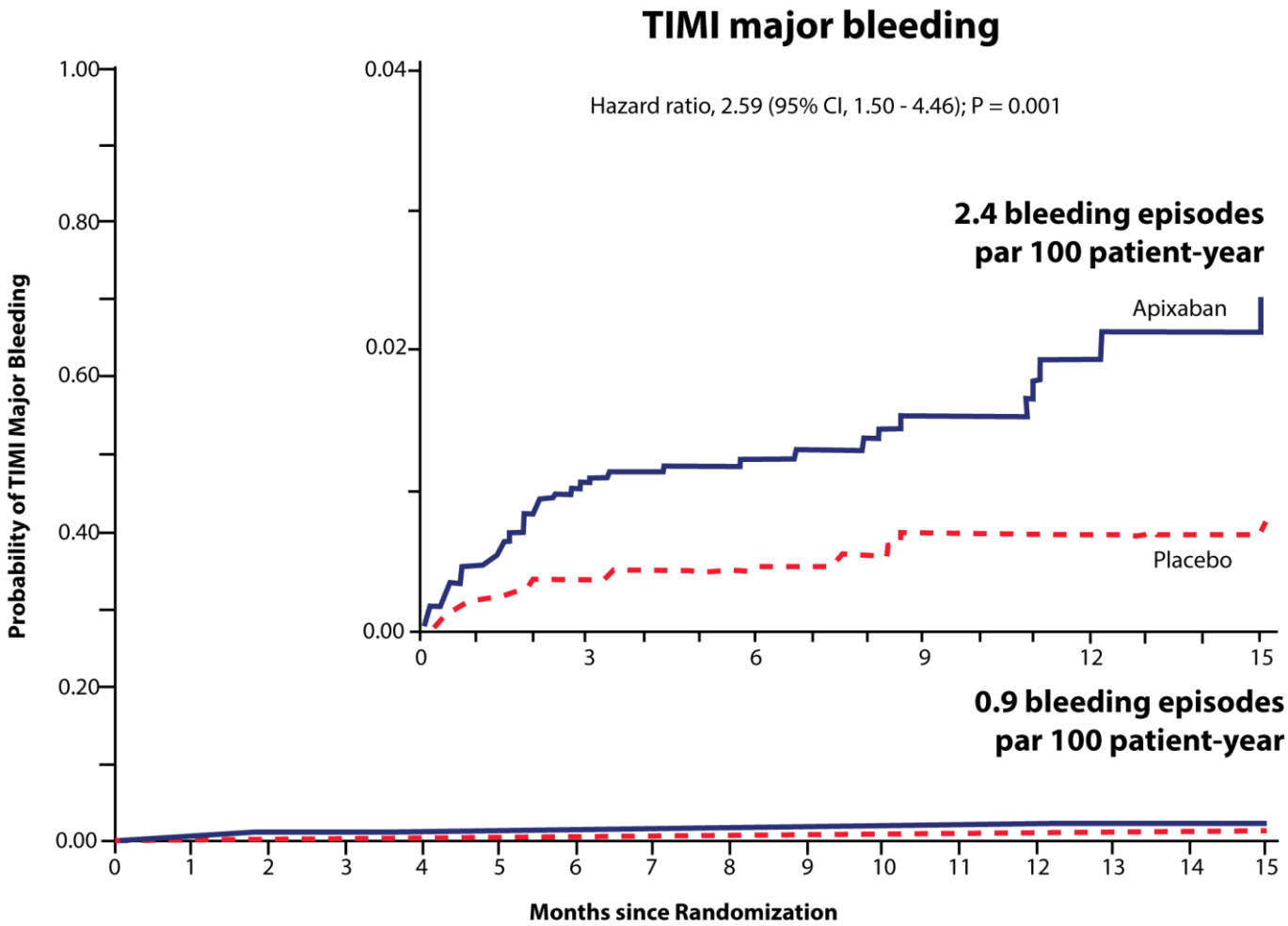
Mega JL, et al. N Engl J Med. 2012;366(1):9-19.



No. at Risk

Apixaban	3705	3356	3048	2799	2552	2312	2025	1739	1525	1277	1021	797	561	390	254	154
Placebo	3687	3316	3014	2751	2537	2272	2030	1728	1495	1248	987	803	571	412	267	164

Kaplan-Meier Curves for Primary Efficacy Outcome.
The primary efficacy outcome was the composite of cardiovascualr death, myocardial infarction, or ischemic stroke. An intention-to-treat analysis was used to compare patients assigned to apixaban with those assigned to placebo. The inset shows the same data on an enlarged y axis.



No. at Risk

Apixaban	3672	3187	2815	2558	2264	2063	1794	1517	1326	1104	884	698	506	344	225	143
Placebo	3643	3178	2881	2600	2339	2133	1884	1573	1369	1137	905	734	532	380	240	151

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

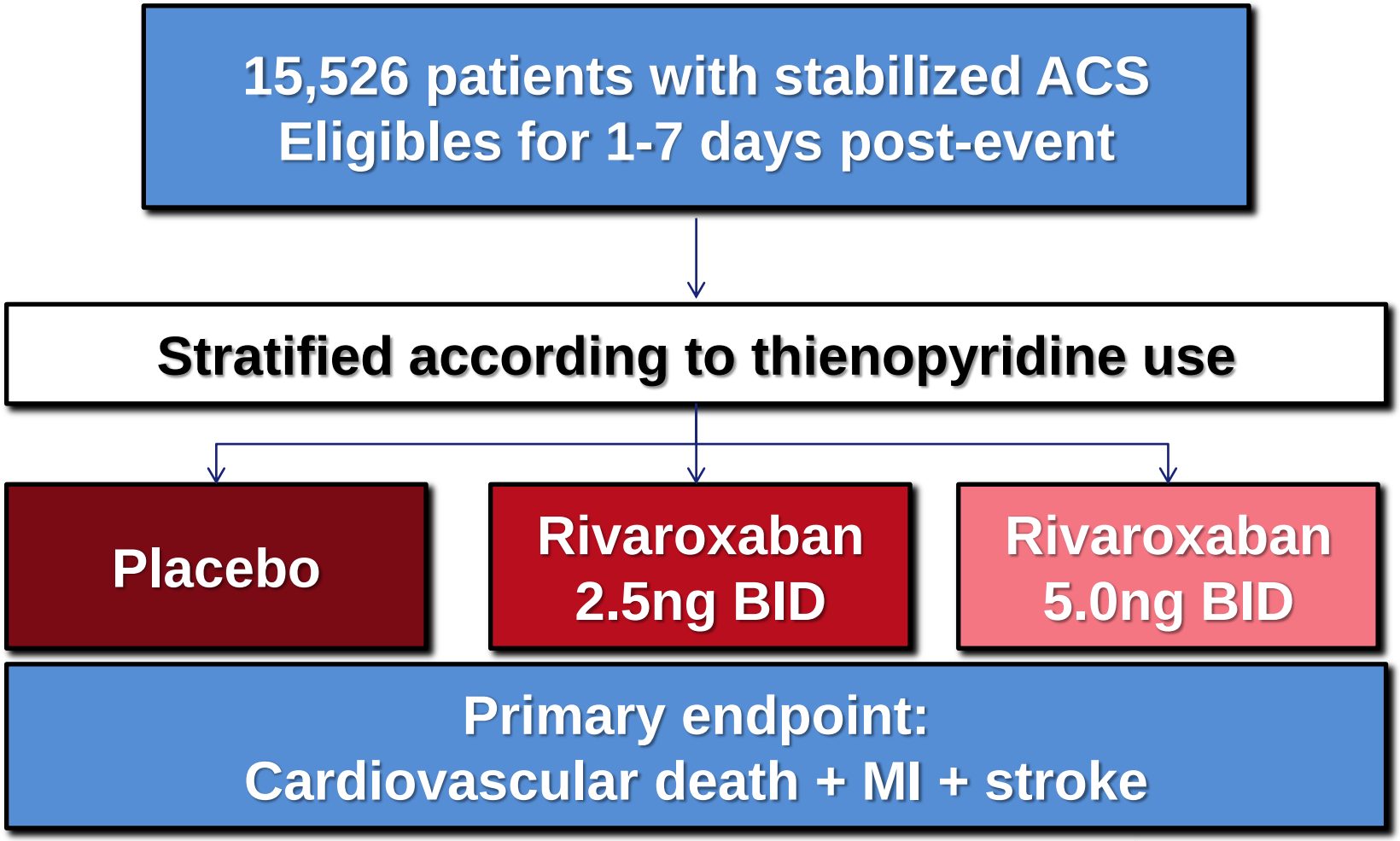
ATLAS-ACS II TIMI 51

CONCLUSIONS

In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer Healthcare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)

Alexander, JH, et al. N Engl J Med. 2012;366:9

ATLAS-ACS II TIMI 51



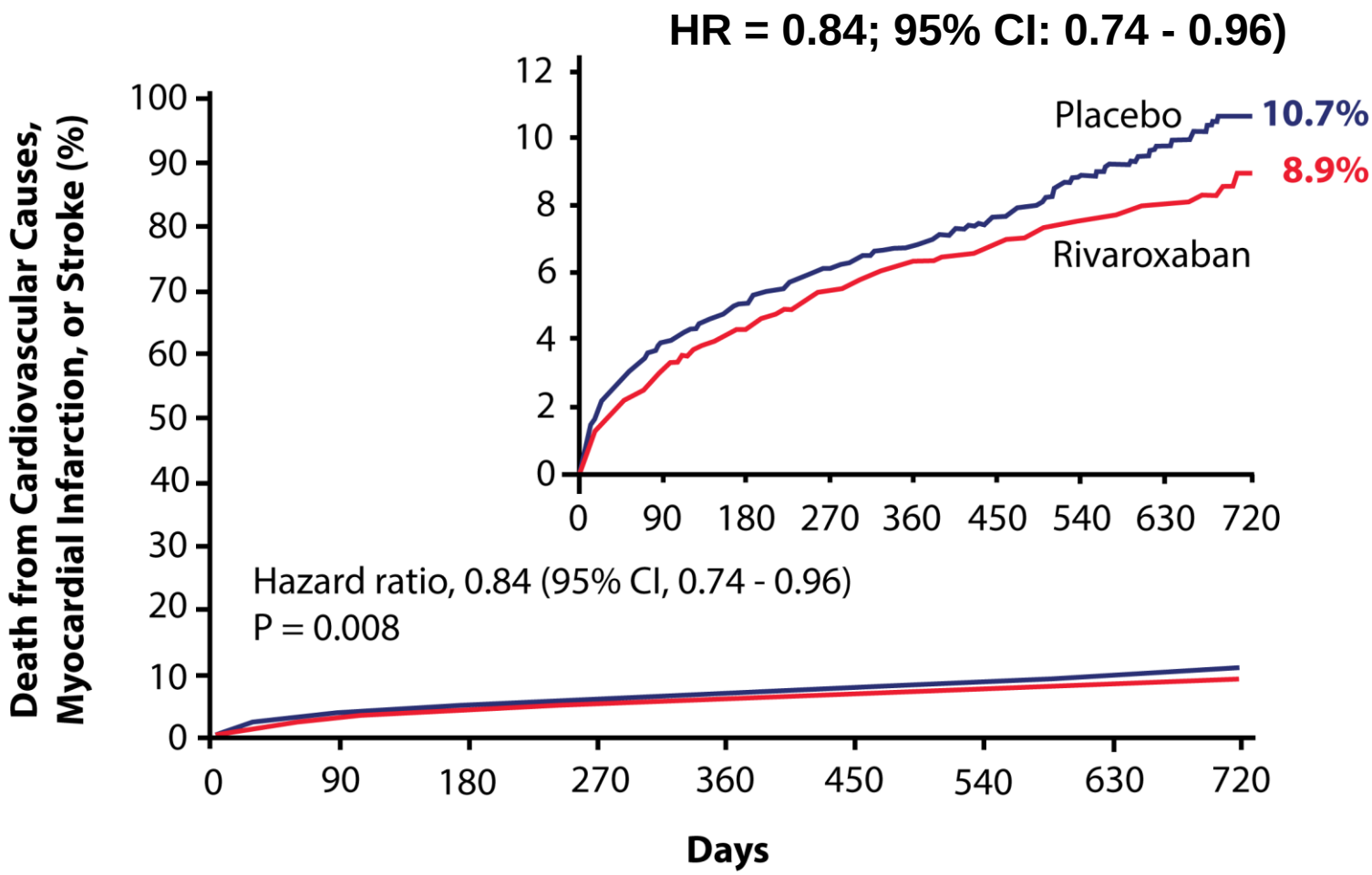
Average length of treatment = 13 months

Alexander, JH, et al. N Engl J Med. 2012;366:9

ATLAS - distribution

Characteristics	Rivaroxaban 2.5m Bid (n=5,174)	Rivaroxaban 5mg Bid (n=5,176)	Placebo (n=5,176)
Age (median), y	62	62	62
Male, %	75%	74%	75%
Weight, median, kg	78	78	78
Initial diagnosis			
STEMI, (%)	50%	50%	51%
NSTEMI, (%)	26%	26%	25%
Unstable angina	24%	24%	24%
CABG + PCI	60%	60%	60%
ASA	99%	99%	99%
P2Y12 inhibitors (mostly clopidogrel)	93%	93%	93%

Alexander, JH, et al. N Engl J Med. 2012;366:9



No. at Risk

Rivaroxaban	10,229	8817	7797	6324	5137	3967	2830	1747	831
Placebo	5113	4437	3974	3253	2664	2059	1460	878	421

Alexander, JH, et al. N Engl J Med. 2012;366:9

ATLAS – Results

	Rivaroxaban 2.5 mg B.I.D. (n = 5,114)	Rivaroxaban 5 mg B.I.D. (n = 5,115)	Placebo (n = 5,113)	2.5 mg B.I.D. vs. Placebo	Rivaroxaban Combined vs. Placebo
Efficacy outcomes					
CV death	94 (2.7)‡	132 (4.0)	143 (4.1)	0.66 (0.51–0.86)	0.80 (0.65–0.99)
Myocardial infarction	205 (6.1)	179 (4.9)	229 (6.6)	0.90 (0.75–1.09)	0.85 (0.72–1.00)
Ischemic stroke	30 (1.0)	35 (0.9)	34 (1.0)	0.89 (0.55–1.45)	0.97 (0.66–1.47)
Stent thrombosis	47 (2.2)	51 (2.3)#	72 (2.9)	0.65 (0.45–0.94)	0.69 (0.51–0.93)
Safety outcomes					
ICH	14 (0.4)††	18 (0.7)‡‡	5 (0.2)	2.83 (1.02–7.86)	3.28 (1.28–8.42)
Fatal bleeding	6 (0.1)	15 (0.4)	9 (0.2)	0.67 (0.24–1.89)	1.19 (0.54–2.59)

De Caterina, R, et al. J Am Coll Cardiol. 2012;59(16):1413-1425.

ATLAS-II vs. APPRAISE-II

Table 4 APPRAISE-2 Versus ATLAS-2: Baseline Characteristics/Concomitant Medications/Follow-up

	APPRAISE-2 (N = 7,392)	ATLAS-2 (N = 15,526)
Age, yrs	67 (median)	62 (mean)
Diabetes mellitus, %	47.8	32.0
Heart failure or LVEF <40% associated with index ACS event, %	40.2	—
Previous cerebrovascular disease, %	10.0	Excluded
Renal function	28.9% with impaired renal function	Median CrCl 85 ml/min (interquartile range: 68–105)
Index ACS event type		
STEMI, %	39.6	50.3
NSTEMI, %	41.6	25.6
Unstable angina, %	18.2	24.0
Aspirin, %	97	99
Thienopyridine, %	81 (dual)	93
Follow-up	8.0 months (median)	13.1 months (mean duration of treatment with a study drug)

De Caterina, R, et al. J Am Coll Cardiol. 2012;59(16):1413-1425.

NOACs for Secondary prevention after ACS

- **<u>CCS 2012 Recommendation:</u>**
  - We suggest against the use of triple therapy with rivaroxaban, clopidogrel, and ASA over the use of DAPT with ticagrelor or prasugrel plus ASA for secondary prevention of ACS
    (Conditional Recommendation, Very Low-Quality Evidence)
  - This recommendation recognizes the benefit of rivaroxaban but put it into perspective with the similar finding observed with ticagrelor and prasugrel with an apparent lesser bleeding risk – this is subject to interpretation
  - Plus there is the compliance – two is better than three

What will you answer your resident?

1) Add warfarin to the DAPT STOP
(WARIS II trial)
2) Add Rivaroxaban 2.5 mg daily to the DAP STOP
(ATLAS TIMI 51 trial)
3) Add apixaban 5mg bid to the DAPT STOP
(APPRAISE-II trial)
4) Stop clopidogrel and switch to either ticagrelor or prasugrel
5) Continue clopidogrel + ASA as it is and consider extending it beyond 1Y

Continuing and Switching P2Y12 inhibitors

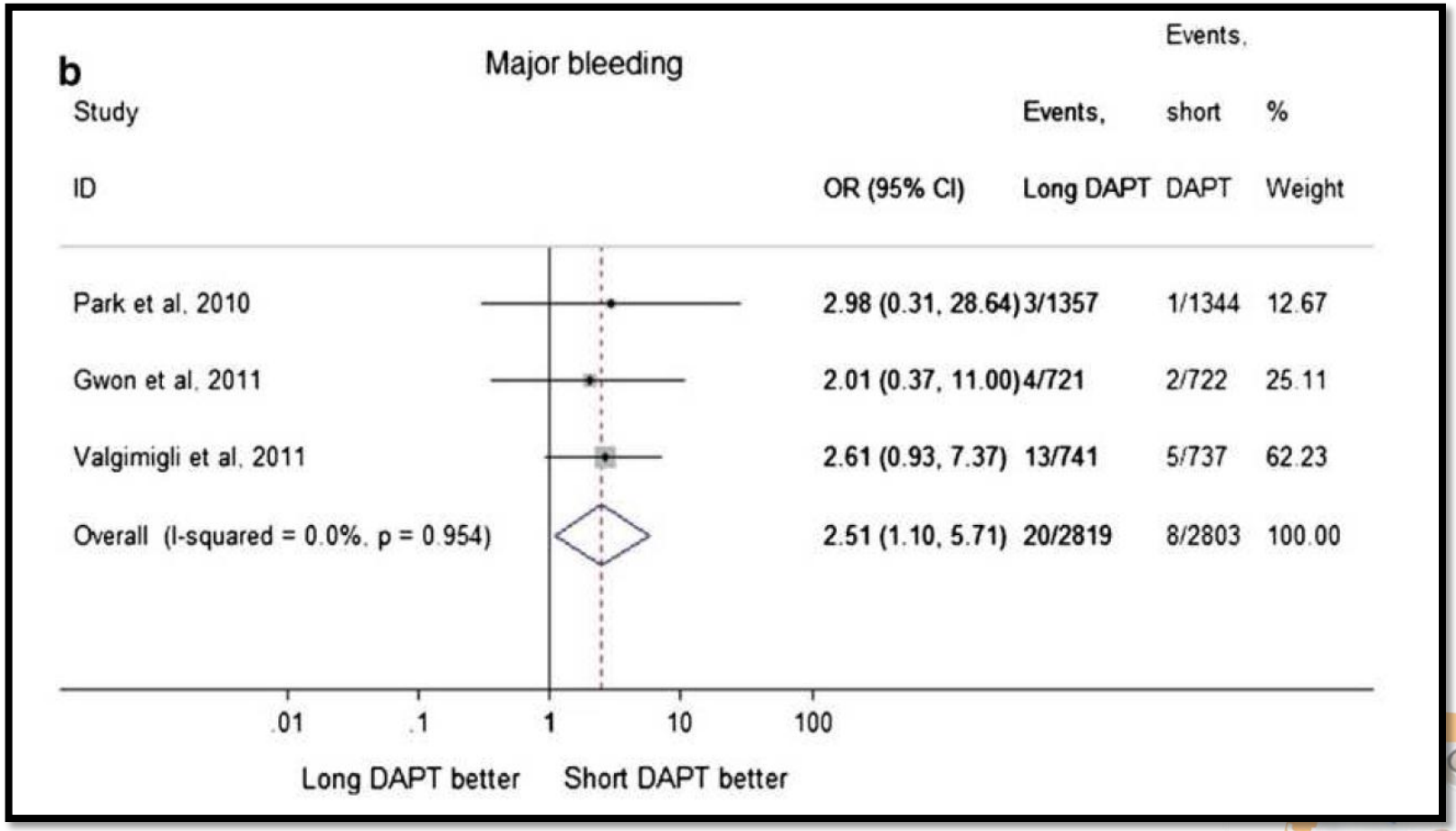
- **<u>CCS 2012 Recommendation:</u>**
  - We suggest against switching the P2Y12 inhibitor initially selected at discharge unless there is a compelling clinical reason (eg, stent thrombosis, bleeding, or cardiovascular event)

    (Conditional Recommendation, Very Low-Quality Evidence)

  - We suggest continuation of a P2Y12 inhibitor with ASA beyond 12 months be considered in patients with a high thrombosis risk and a low bleeding risk

    (Conditional Recommendation, Low-Quality Evidence).

The optimal duration of P2Y12 inhibitor remains unknown



DAPT > 12 months **DAPT ≤ 12 months**

Valgimigli, M, *et al. Int J Cardiol.* 2013.

Case #3:
We Have a Bleeder!

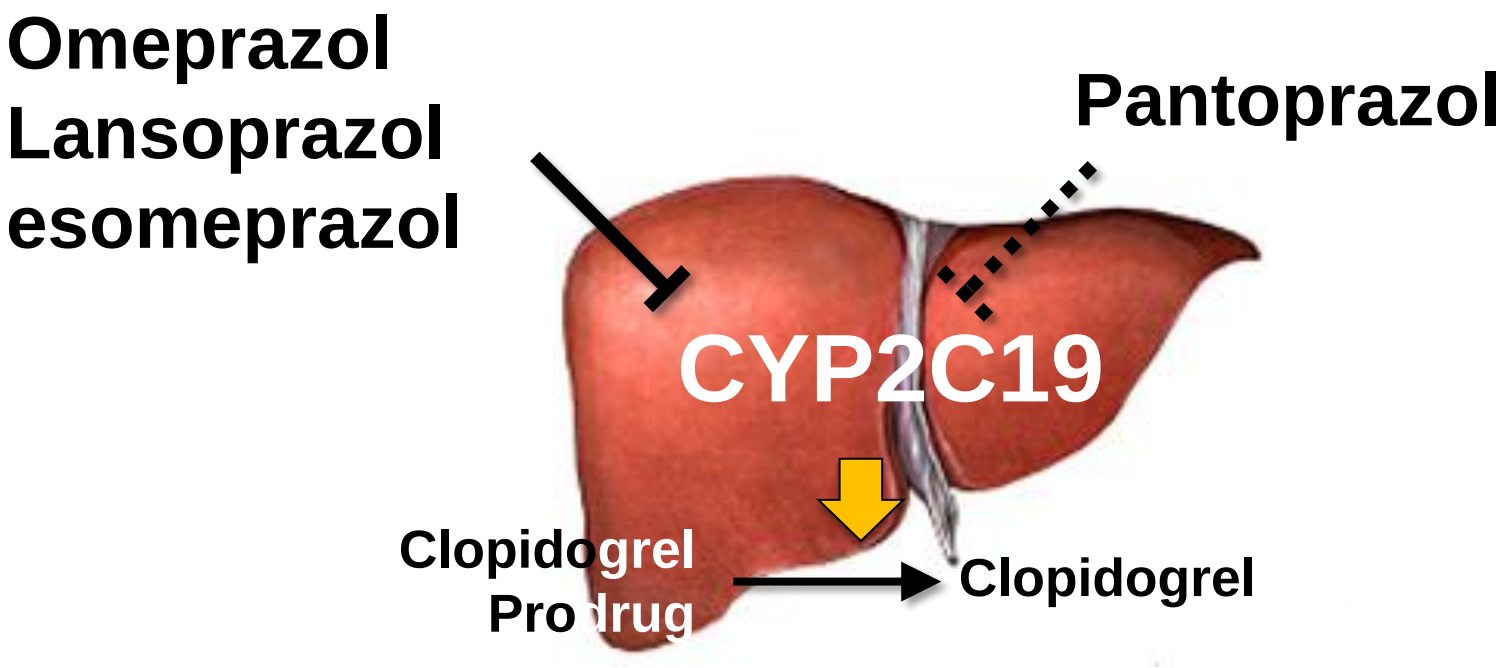
- A 65 year old man shows up at your office for mild microcytic anemia (HB = 110)
- Your initial investigation does not show anything in particular other than the fact that he is taking ASA 81 with clopidogrel 75mg daily for a stent he received 9 months ago
- You suspect a gastritis and you want to initiate a proton-pump inhibitor, while awaiting for the GI scope
- Should this patient have been given a PPI 9 months ago?

Should PPI be given to all patients with DAPT?

- **<u>CCS 2012 Recommendation:</u>**
  - We recommend selective use of PPIs in patients receiving DAPT at high risk of upper gastrointestinal bleeding (Strong Recommendation, Moderate-Quality Evidence).

- Several dimensions to this recommendation:
  1) "There is no doubt that PPI reduces the risk of GI bleeding on patients treated with DAPT"
  2) PPIs use might mitigate the beneficial effects of clopidogrel
  3) PPIs with newer P2Y12 inhibitors: a channeling bias?

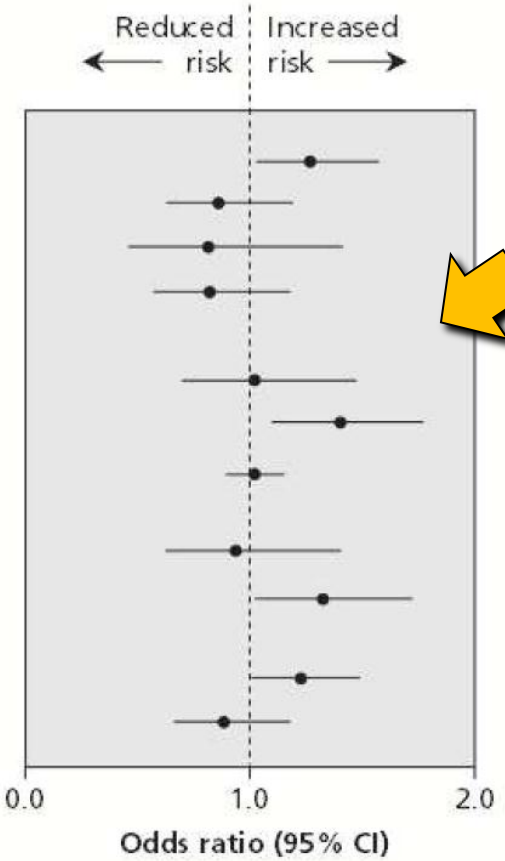
The specific case of Clopidogrel?



Pantoprazol vs other PPIs with clopidogrel

Population-based study on 13 636 Canadian prescribed clopidogrel

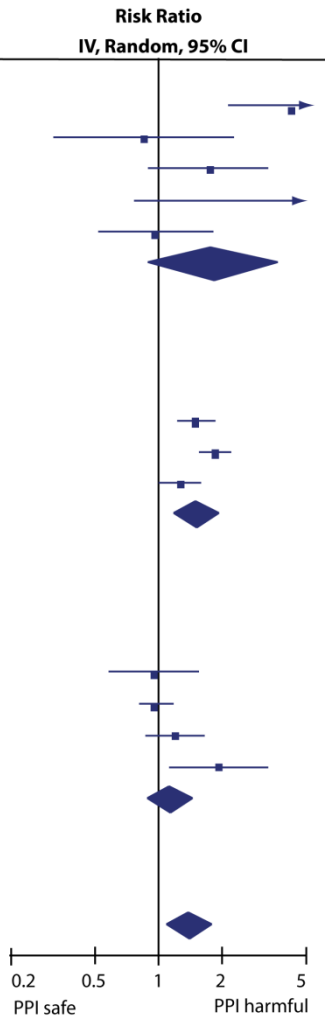
Analysis*	Cases n/N	Controls n/N	Odds ratio (95% CI)
Recurrent MI < 90 days			
Current	194/734	424/2 057	1.27 (1.03–1.57)
Previous	63/734	195/2 057	0.86 (0.63–1.19)
Remote	17/734	68/2 057	0.81 (0.46–1.41)
Death < 90 days	71/323	188/916	0.82 (0.57–1.18)
Proton pump inhibitor			
Pantoprazole	46/734	125/2 057	1.02 (0.70–1.47)
Other	148/734	299/2 057	1.40 (1.10–1.77)
Patients not receiving clopidogrel	438/6 277	1 300/17 291	1.02 (0.90–1.15)
Histamine-H_2 antagonists	37/734	106/2 057	0.94 (0.63–1.40)
Patients with no history of heart failure	134/525	319/1 638	1.33 (1.02–1.72)
Recurrent MI < 1 year	240/982	497/2 626	1.23 (1.01–1.49)
Death < 1 year	116/531	269/1 407	0.89 (0.67–1.18)



Juurlink, DN., *et al. CMAJ*. 2009;180(7): 713-718.

PPI on patients taking clopidogrel for ACS

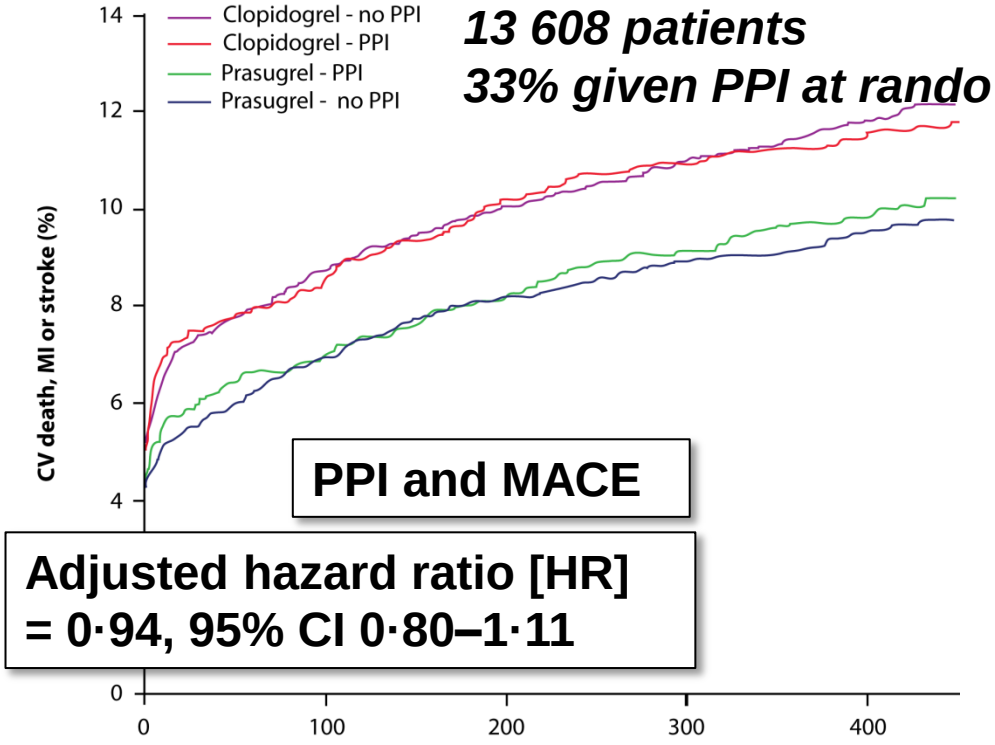
Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
Unadjusted Observational Data		
Pezella 2008	6.1%	4.29 [2.24, 8.23]
Ramirez 2009	3.6%	0.85 [0.32, 2.25]
Sarafoff 2009	6.1%	1.76 [0.92, 3.38]
Yasuda 2009	0.9%	7.35 [0.78, 69.35]
Zairis 2008	6.5%	0.97 [0.52, 1.80]
Subtotal (95% CI)	23.1%	1.82 [0.90, 3.70]
Heterogeneity: Tau² = 0.43; Chi² = 14.16, df = 4 (*P* = 0.006); *I*² = 72%		
Test for overall effect: Z = 1.66 (*P* = 0.10)		
Observational Data Adjusted for Confounders		
Hall 2009	12.5%	1.50 [1.22, 1.84]
Ho 2009	12.9%	1.86 [1.57, 2.20]
Juurlink 2009	12.3%	1.27 [1.03, 1.57]
Subtotal (95% CI)	37.7%	1.54 [1.23, 1.92]
Heterogeneity: Tau² = 0.03; Chi² = 7.95, df = 2 (*P* = 0.02); *I*² = 75%		
Test for overall effect: Z = 3.76 (*P* = 0.0002)		
Data from propensity-matched or trial participants		
Bhatt 2009	8.2%	0.96 [0.59, 1.56]
O'Donoghue 2009	12.8%	0.98 [0.82, 1.17]
Rassen 2009	10.7%	1.22 [0.89, 1.68]
Stockl 2009	7.5%	1.92 [1.12, 3.28]
Subtotal (95% CI)	39.1%	1.15 [0.89, 1.48]
Heterogeneity: Tau² = 0.03; Chi² = 6.36, df = 3 (*P* = 0.10); *I*² = 53%		
Test for overall effect: Z = 1.08 (*P* = 0.28)		
Total (95% CI)	100.0%	1.43 [1.15, 1.77]
Heterogeneity: Tau² = 0.08; Chi² = 48.39, df = 11 (*P* < 0.00001); *I*² = 77%		
Test for overall effect: Z = 3.27 (*P* = 0.001)		



23 trials including 93,278 patients

Kwok *et al*, *Aliment Pharmacol Ther* 2010;31(8):810-823.

TRITON PPI sub-study



No. at risk					
Clopidogrel - no PPI	4538	4014	3619	3158	2690
Clopidogrel - PPI	2257	1994	1757	1533	1269
Prasugrel - PPI	2272	2050	1827	1559	1296
Prasugrel - no PPI	4541	4101	3666	3236	2715

Unadjusted cumulative incidence of CV death, MI, or stroke through long-term follow-up
Patients were or were not on a PPI in combination with clopidogrel or prasugrel in the TRITON-TIMI 38 trial.
CV = cardiovascular. MI = myocardial infarction. PPI = proton-pump inhibitor.

O'Donoghue, ML., *et al. Lancet*. 2009; 374: 989–97.

Case #4:
The infamous surgery

- A 66 year old woman needs a surgery for a fractured hip
- She underwent a DES implantation (2nd generation) 4 months ago in her distal RCA during a STEMI
- The surgeon wants to stop her daily dose of prasugrel 10 mg before the surgery

P2Y12 inhibitors duration for non-ACS indications

- **<u>CCS 2012Recommendation:</u>**
  - We recommend that in patients receiving a BMS who are unable to tolerate clopidogrel for 12 months (eg, increased risk of bleeding or scheduled noncardiac surgery), the minimum duration of therapy should be 1 month

    (Strong Recommendation, High-Quality Evidence).

  - We suggest in patients at very high risk of bleeding, the minimum duration of treatment may be 2 weeks

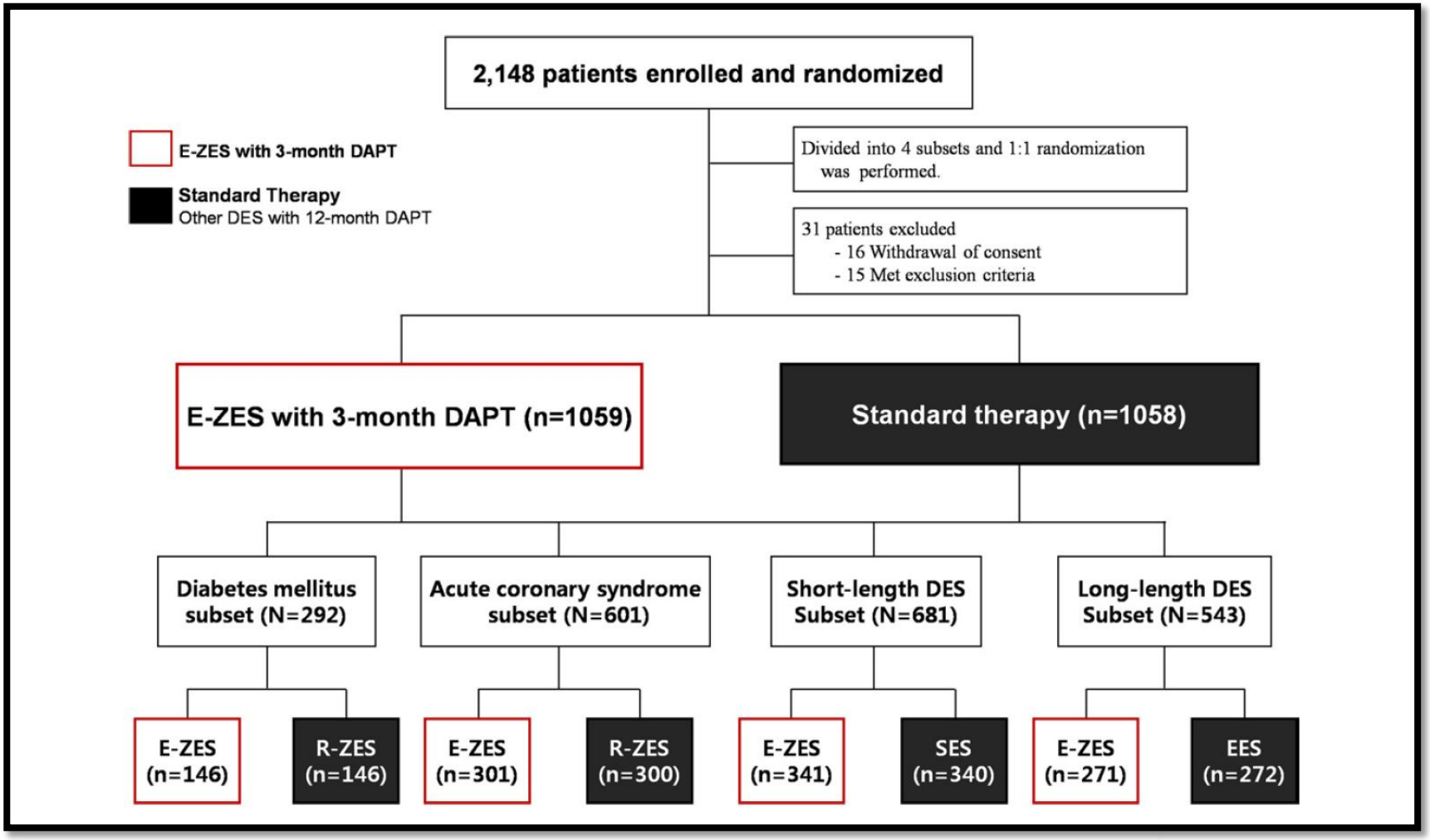
    (Conditional Recommendation, Low-Quality Evidence).

P2Y12 inhibitors duration for non-ACS indications

- **<u>CCS 2012Recommendation:</u>**
  - We suggest that in patients receiving a 2nd generation DES who are unable to tolerate clopidogrel for 12 months (eg, increased risk of bleeding or scheduled noncardiac surgery), the minimum duration of therapy may be 3 months.

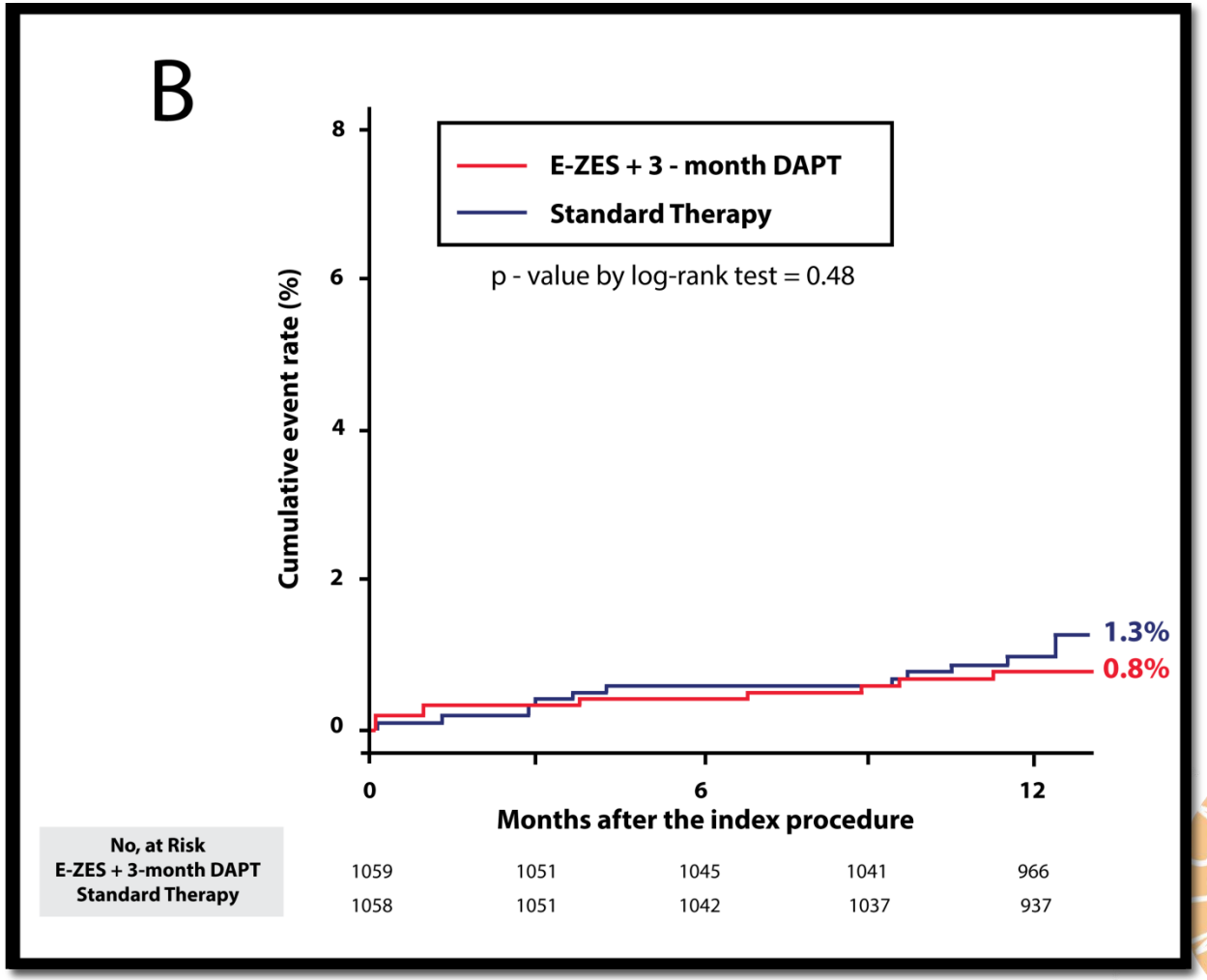
(Conditional Recommendation, Low-Quality Evidence).

The RESET trial



Kim, BK., et al. J Am Coll Cardiol. 2012;60(15):1340-1348.

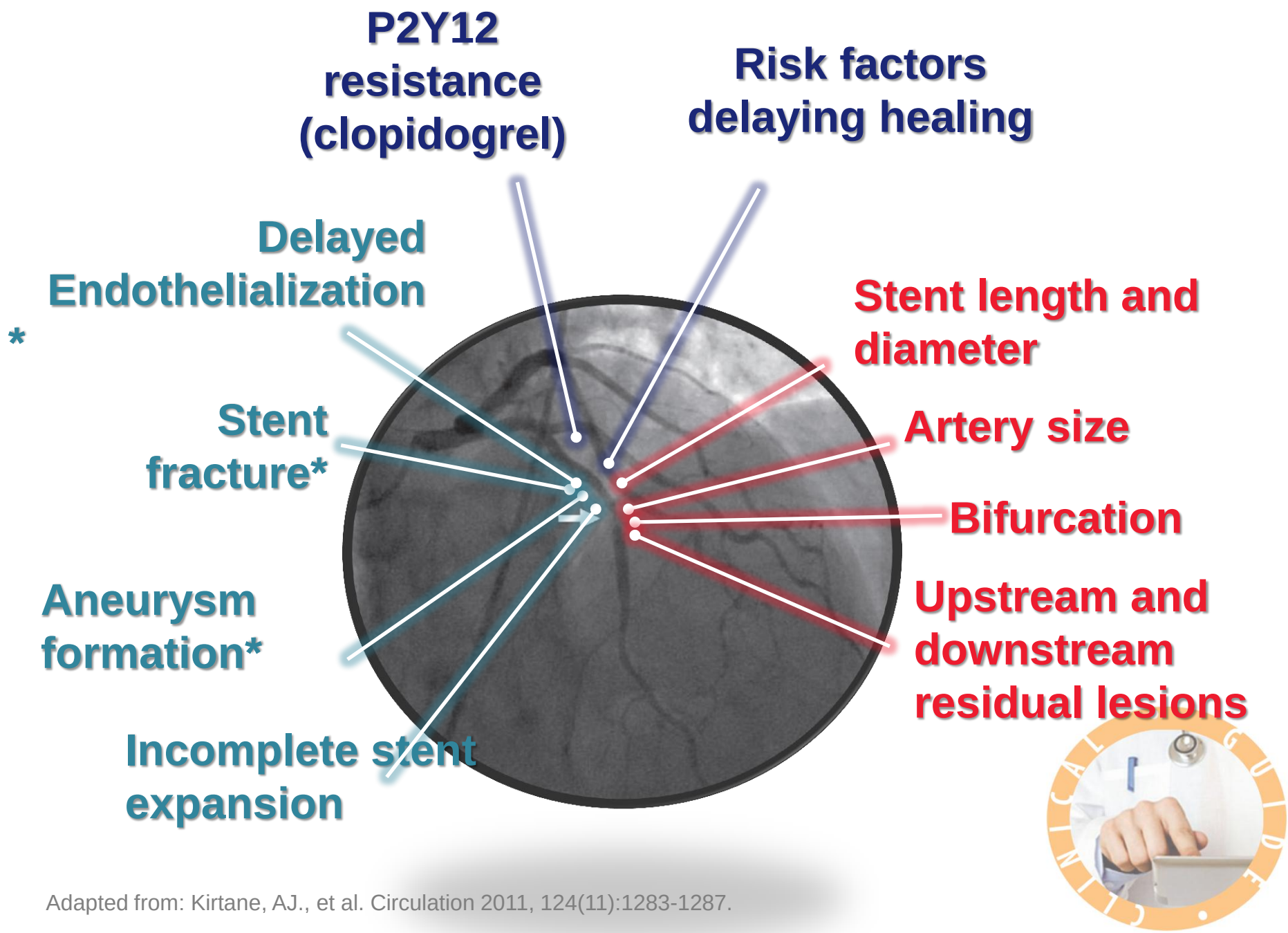
The RESET trial



Kim, BK., et al. J Am Coll Cardiol. 2012;60(15):1340-1348.

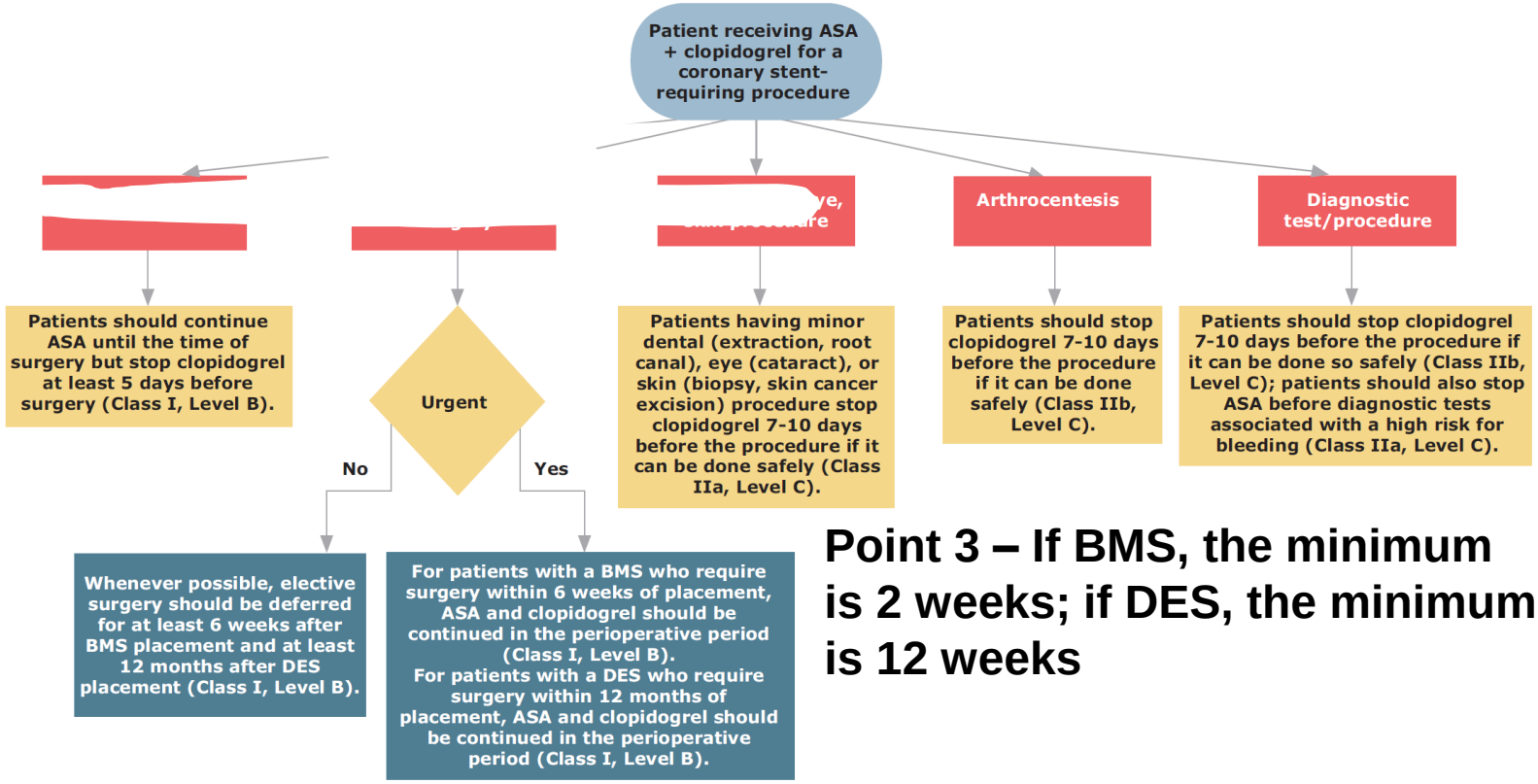
P2Y12 inhibitors cessation

- Before surgery:
  - Stop clopidogrel 5 days ahead
  - Stop ticagrelor 5 days ahead
  - Stop prasugrel 7 days ahead
  - Never stop a P2Y12 inhibitor if you are not aware of the stent position (left main, prox LAD), the context where it was implanted (ACS vs. elective), and the procedural result (good vs. bad apposition)



Adapted from: Kirtane, AJ., et al. Circulation 2011, 124(11):1283-1287.

ASA and Clopidogrel before surgery



Point 3 – If BMS, the minimum is 2 weeks; if DES, the minimum is 12 weeks

Point 1 – Do not stop ASA and Clopidogrel simultaneously
Point 2 – Stop clopidogrel 5-7 days before surgery

Bell, AD., et al, Can J Cardiol 2011;27 Suppl A: S1-59

Case #5:
New Onset AF

- A 80 year old woman presents to your ER for a new onset AF
- She had high blood pressure and her ejection fraction is 40% (with no apparent valvular heart disease).
- CHADS score = 3
- HAS-BLED score = 5 (10% bleeding risk)
- She was stented 3 weeks ago in her circumflex artery for a NST-ACS, unfortunately with a DES. She is treated with ASA 81 mg and clopidogrel 75mg daily.

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing

(clinicaltrials.gov NCT00769938)

Dewilde, WJM., *et al. Lancet* 2013; 381(9872): 1107–15.

Study design
WOEST

Inclusion criteria:

1) W x ≥ 1y
2) PCI
3) Age:18 to 80

Exclusion criteria:

1) Stroke, IC bleed
2) Cardiogenic shock
3) Ulcer < 6 monts
4) Major bleed < 1y

R

Double therapy
W +
75mg Clopidogrel qd

Triple thérapie
W +
75mg Clopidogrel qd +
80mg Aspirin qd

1 month min post BMS
1 y post DES

Open label

Follow up: **1 year**

1º Endpoint : ***All bleeding***

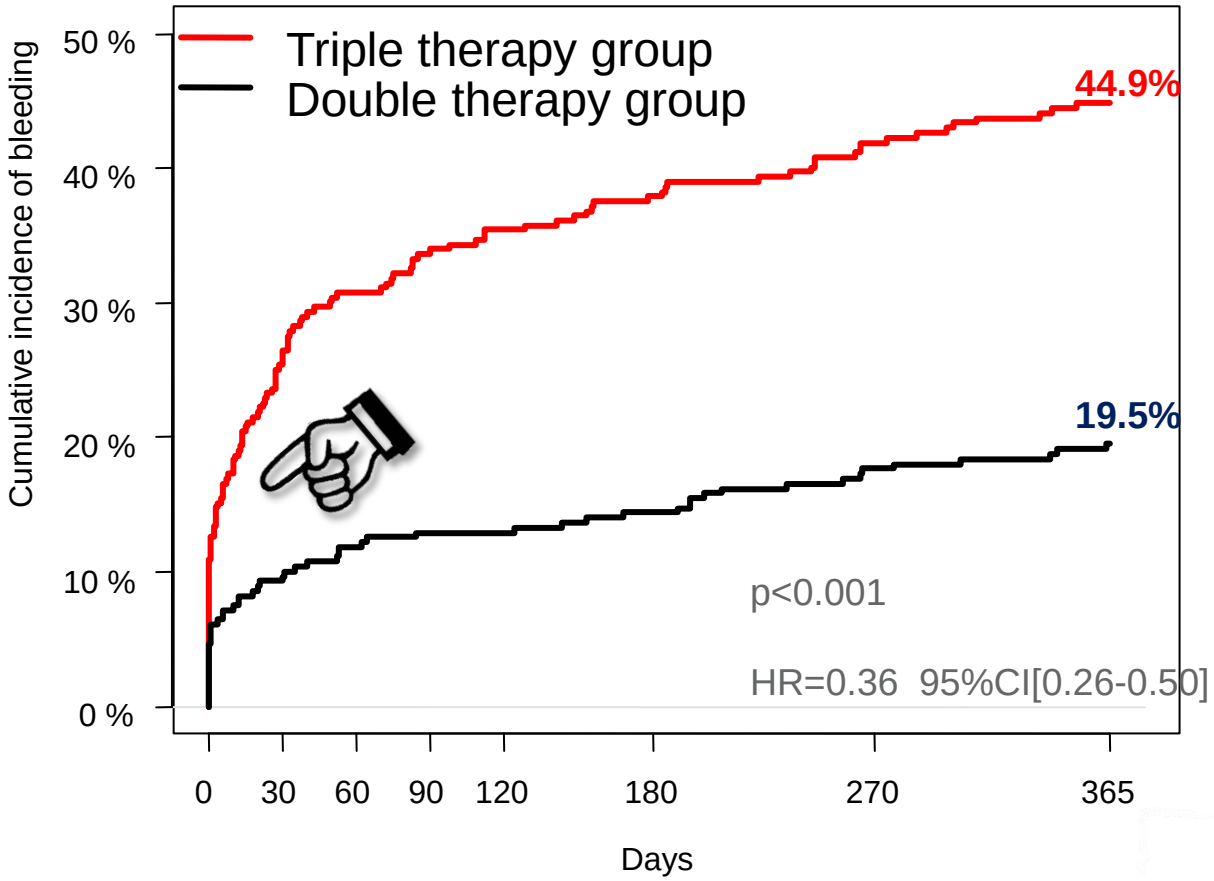
2nd endpoint: ***stroke/death/MI/TVR***

Characteristics

	Double therapy n=279 (%)	Triple therapy n=284 (%)
Age	70.3 (±7.3)	69.5(±8.0)
Male	214 (76.7%)	234 (82.4%)
BMI(kg/m2)	27.5 (±4.3)	27.9 (±4.2)
Diabetes	68 (24.4%)	72 (25.4%)
Hypertension	193 (69.2%)	193 (68.0%)
Infarctus	96 (34.4%)	100 (35.2%)
CHF	71 (25.4%)	70 (24.6%)
Stroke	49 (17.6%)	50 (17.6%)
Indication for W		
FA/Aflutter	164 (69.5%)	162 (69.2%)
Prosthetic valve	24 (10.2%)	25 (10.7%)
Other	48 (20.3%)	47 (20.1%)
ACS a 1st presentation	69 (25.0%)	86 (30.6%)

Primary Endpoint

Total number of TIMI bleeding events

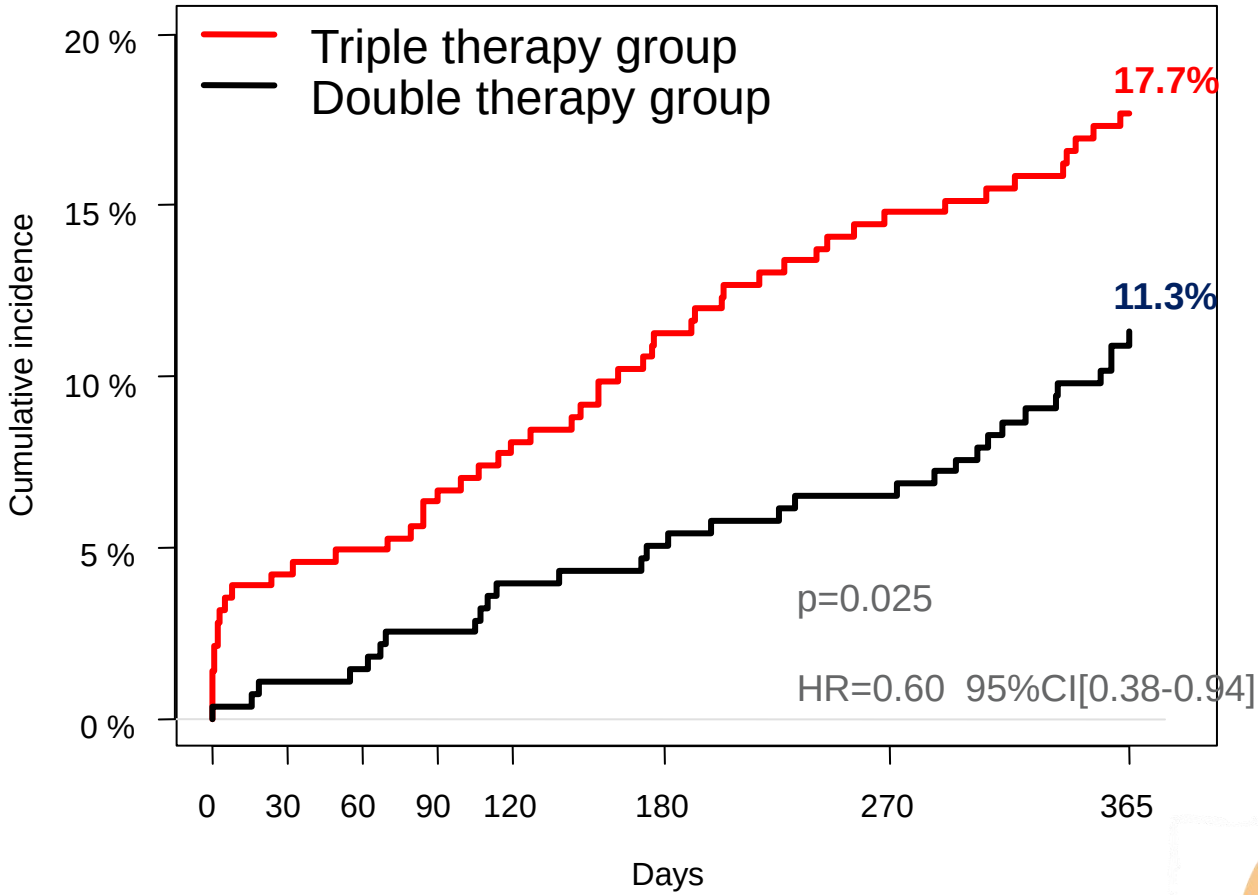


n at risk:	284	210	194	186	181	173	159	140
	279	253	244	241	241	236	226	208

WOEST (n=573)

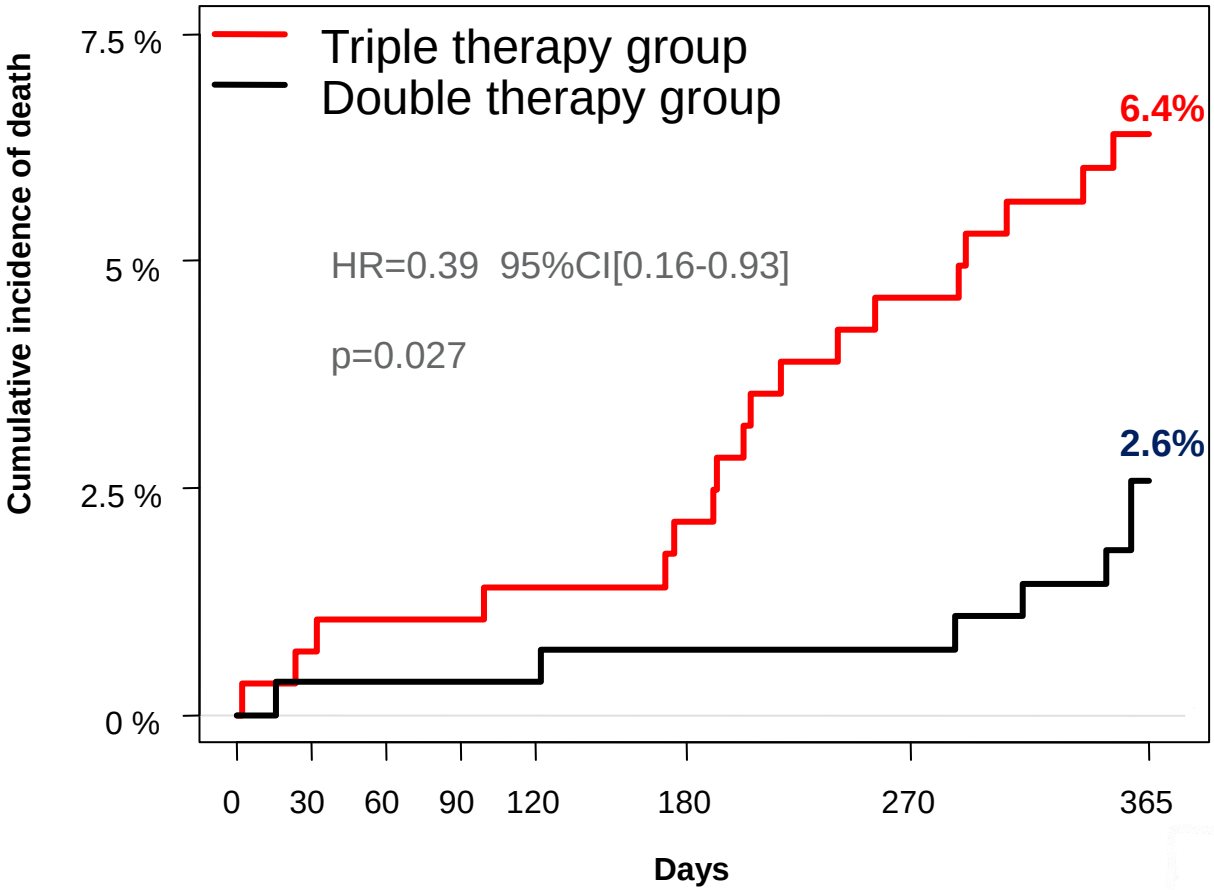
Endpoint	Double therapy	Triple therapy	p
Death	2.6%	6.4%	0.027
MI	3.3%	4.7%	0.382
Target vessel revascularization	7.3%	6.8%	0.876
Stroke	1.1%	2.9%	0.128
Stent thrombosis	1.5%	3.2%	0.165
Bleeding (NNT - 4)	19.5%	44.9%	< 0.001

Secondary Endpoint
Death, MI,TVR, Stroke, ST



n at risk:	284	272	270	266	261	252	242	223
	279	276	273	270	266	263	258	234

All-Cause Mortality



n at risk:	284	281	280	280	279	277	270	252
	279	278	276	276	276	275	274	256

Take-home Messages

- In STE-ACS, Ticagrelor can be used in patients managed with either PCI, CABG, or medical therapy alone, whereas prasugrel should be used only in patients undergoing PCI.
- There might be patients in whom combining an oral anticoagulant with DAPT is warranted, such as patients with atrial fibrillation or a mechanical heart valve who develop ACS. Attention is needed to monitor and minimize the duration of “triple antithrombotic therapy” considering the high risk for bleeding associated with such treatment.

Take-home Messages

- PPIs should not be used routinely in all patients taking DAPT but should be considered in patients at higher risk of gastrointestinal bleeding. If PPI are to be used with clopidogrel, agents with minimal effect on CYP2C19 should be favored.
- Seek advices from an interventional cardiologist if you need to stop a P2Y12 inhibitor early and you are not certain of the stent type (BMS vs. DES, and generation), position and apposition.

Take-home Messages

- If PCI is required in patients taking long-term anticoagulation, Canadian, European and US guidelines recommend the use of triple therapy with aspirin, clopidogrel, and oral anticoagulation. These recommendations are based on expert opinions. In a recent RCT, ASA discontinuation has been associated with a reduction in bleeding risk with no increase in thrombotic risk.