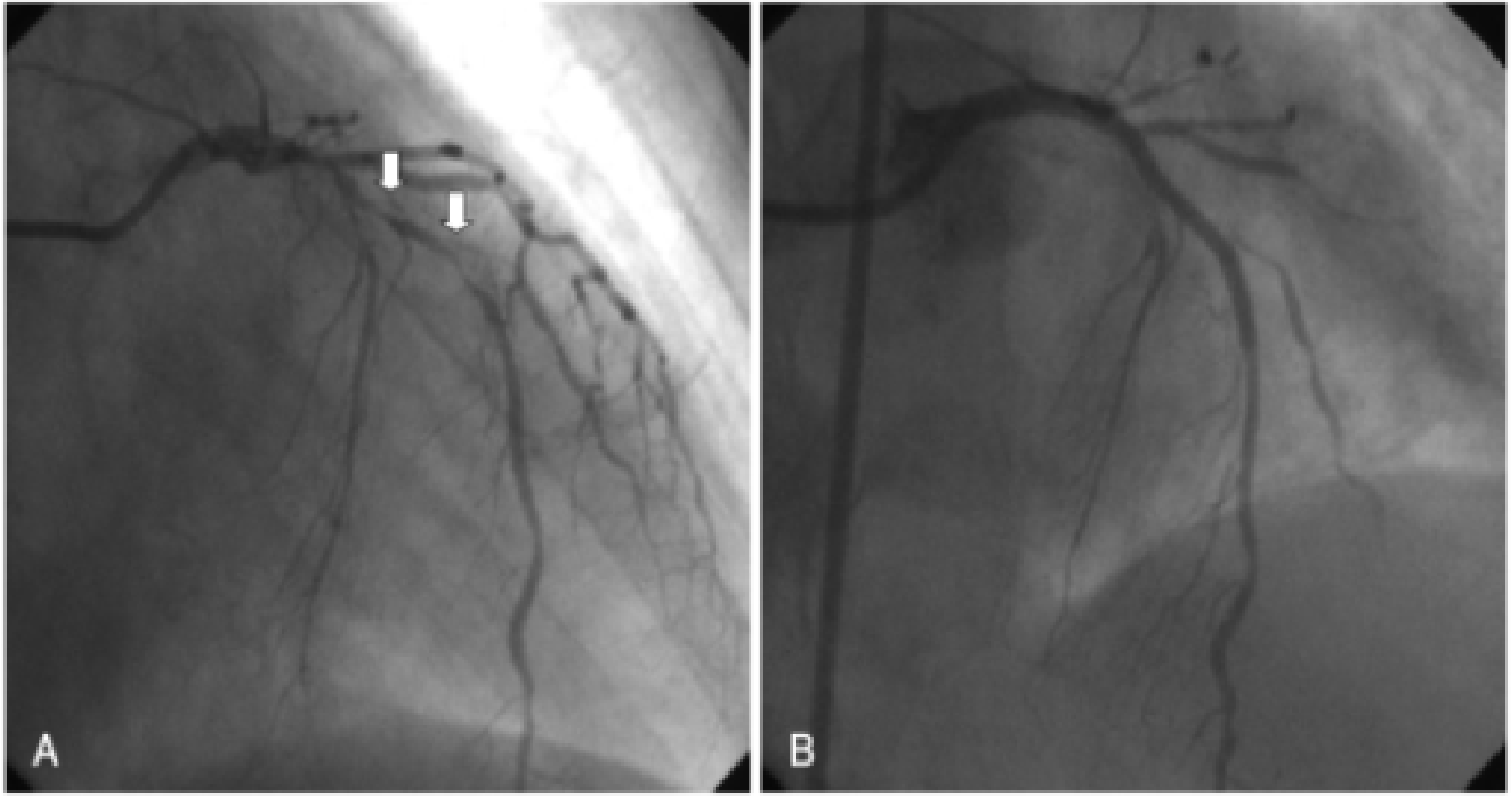
Getting smart about dyspnea and life saving drug therapy in ACS patients

Kobi George
Kaplan Medical Center
Rehovot

Case description

- 78 year old female
- Presented with resting chest pain and dyspnea
- Co-morbidities: hypercholesterolemia, chronic renal failure (creatinine 1.3 mg/dL), Afib and TIA (2008), peptic ulcer disease
- Chronic medications: Perindopril 10mg/day, simvastatin 40 mg/day, Rivaroxaban 15mg/day
- Symptoms persisted over 5 hrs despite medical Tx
- ECG: ST-depression V1-V5, II, III, aVF
- Killip III, BP 100/70, HR120, SaO2 89%
- Blood tests: TnI 3.2 ng/mL – 4,6 ng/L (6 hrs); mild normocytic anemia (Hb 10,9 g/dL), creatinine 1,4 mg/dL
- **Patient is referred for coronary angiography**

Coronary angiography: DES to Mid LAD



What would be the management of therapy after DES implantation?

- Plavix 12 months, Xarelto and Aspirin.
- Plavix 12 months, Xarelto
- Effient 12 months, Xarelto, Aspirin.
- Effient 12 months, Xarelto.
- Brilinita 12 months, Xarelto, Aspirin.
- Brilinta 12 months, Xarelto (with without Aspirin).
- Brilinta, Coumadin (with without Aspirin)

Selecting anti-platelet agent

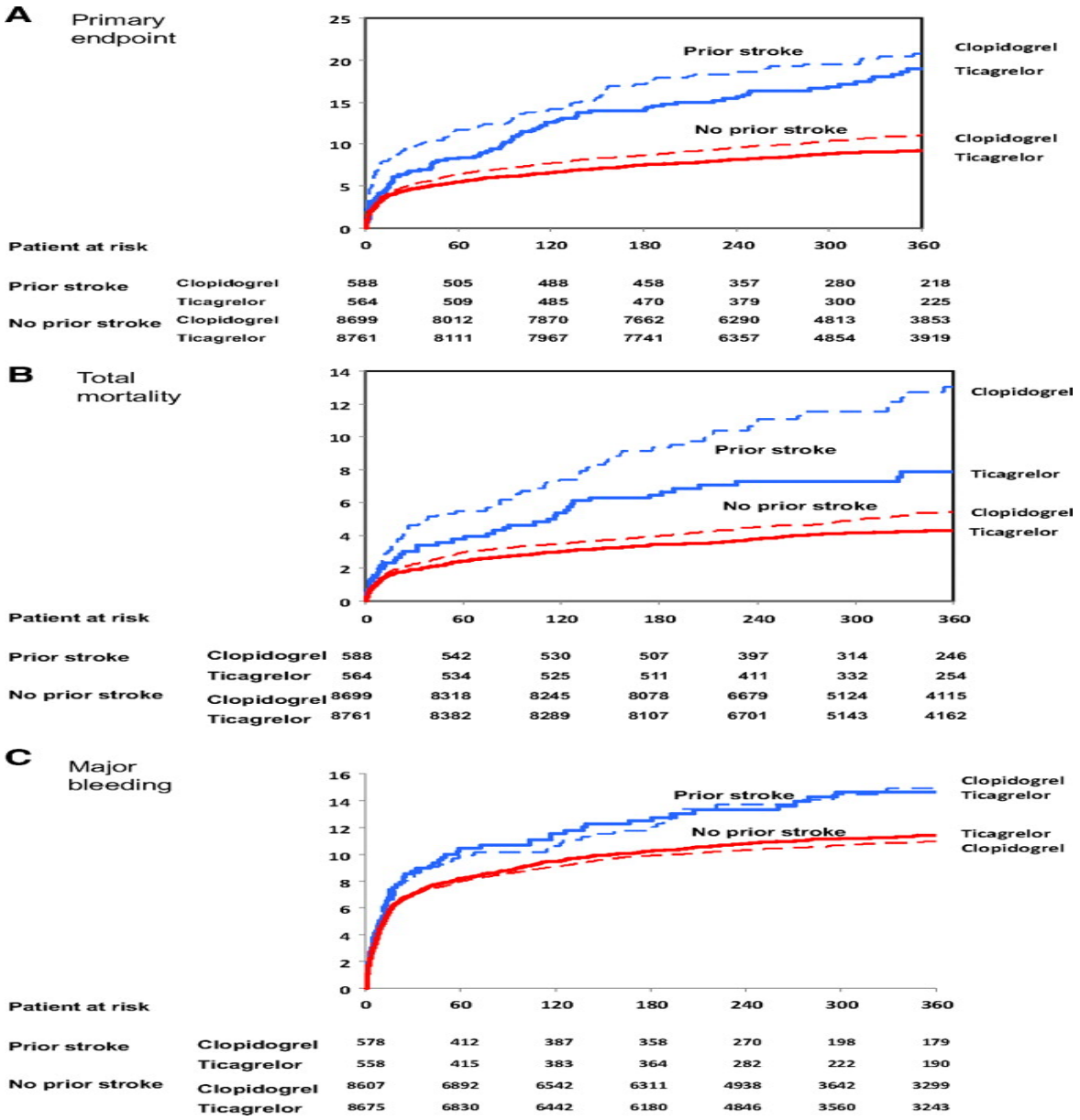
- CLINICAL CONSIDERATIONS:
  - PLANNED PCI VS ACS
  - AGE: 75 YRS OR MORE
  - WEIGHT: 60 KGS OR LESS
  - TIA, STROKE
  - DIABETES
  - POLYMORPHISM
  - ALLERGY
  - THROMBUS BURDEN
  - DAPT VS TAPT

Current ESC guidelines DAPT

Recommendations for oral antiplatelet agents

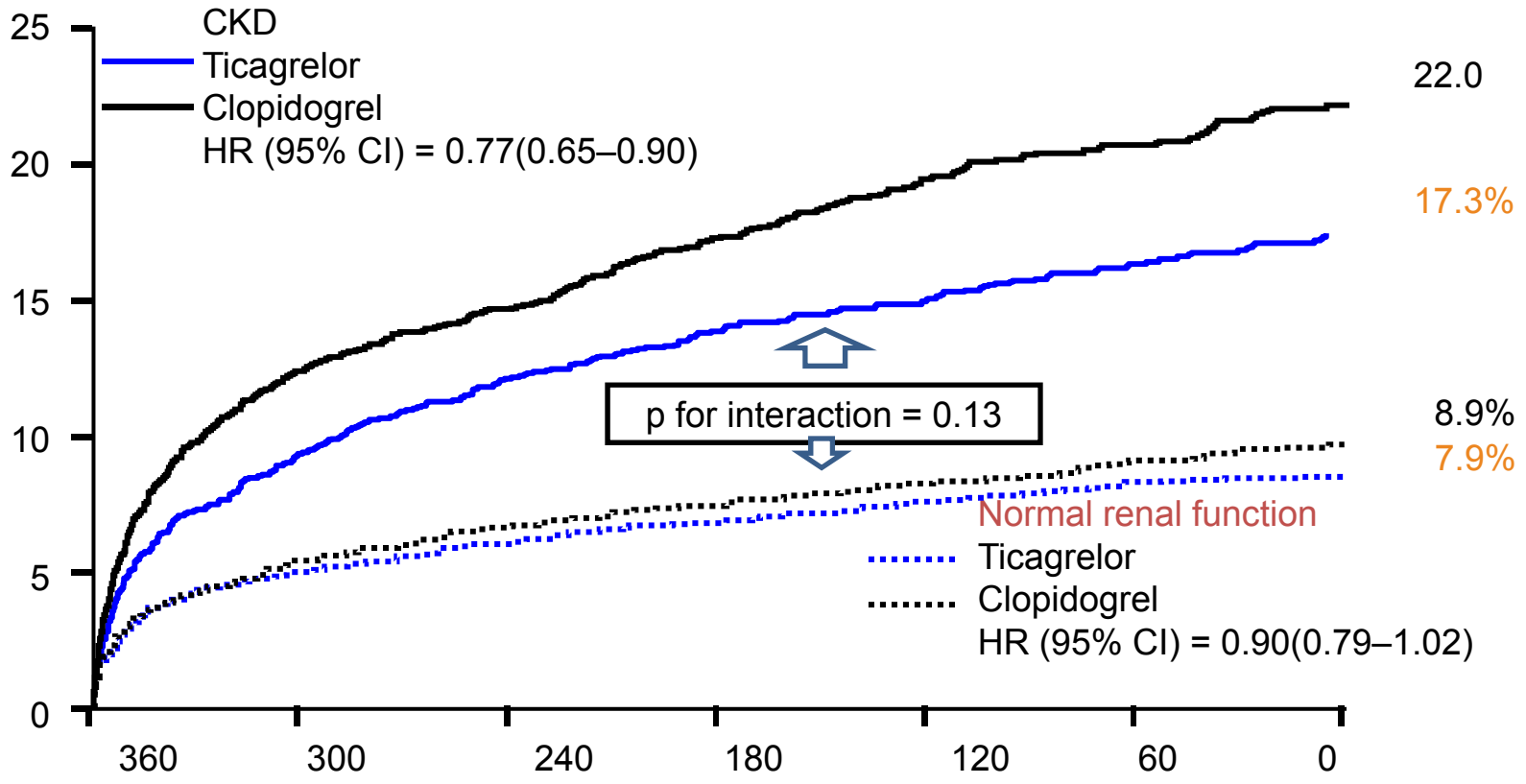
Recommendations	Class [a]	Level [b]	Ref [c]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	107, 108
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A	110, 130, 132
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A	125–127
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C	-
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B	132
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B	130
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A	110, 146, 147
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B	108, 114, 115

PLATO-Patients with /without history of stroke or TIA



James S K et al. Circulation 2012;125:2914-2921

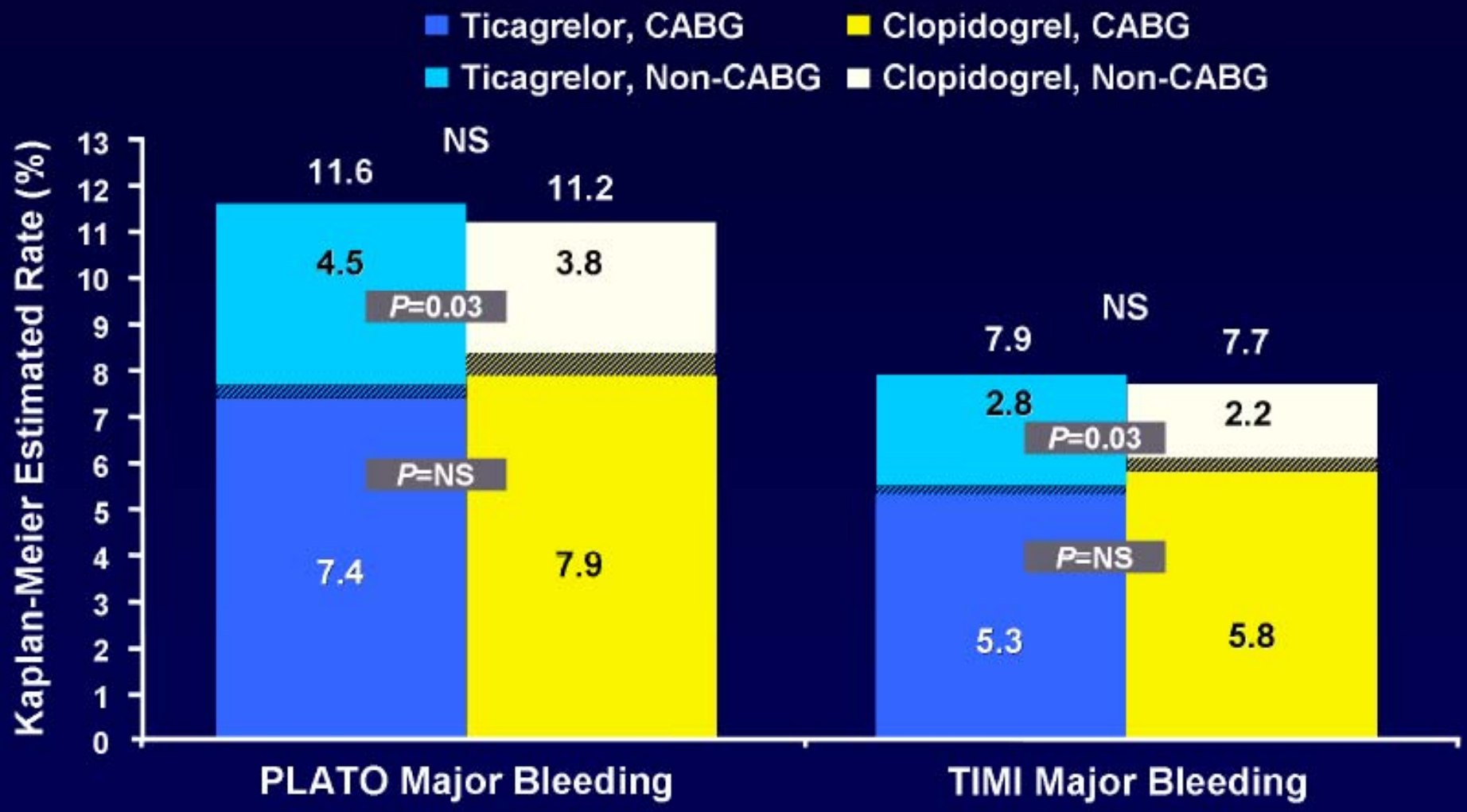
Renal function and outcomes in PLATO: Primary composite endpoint



Primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results

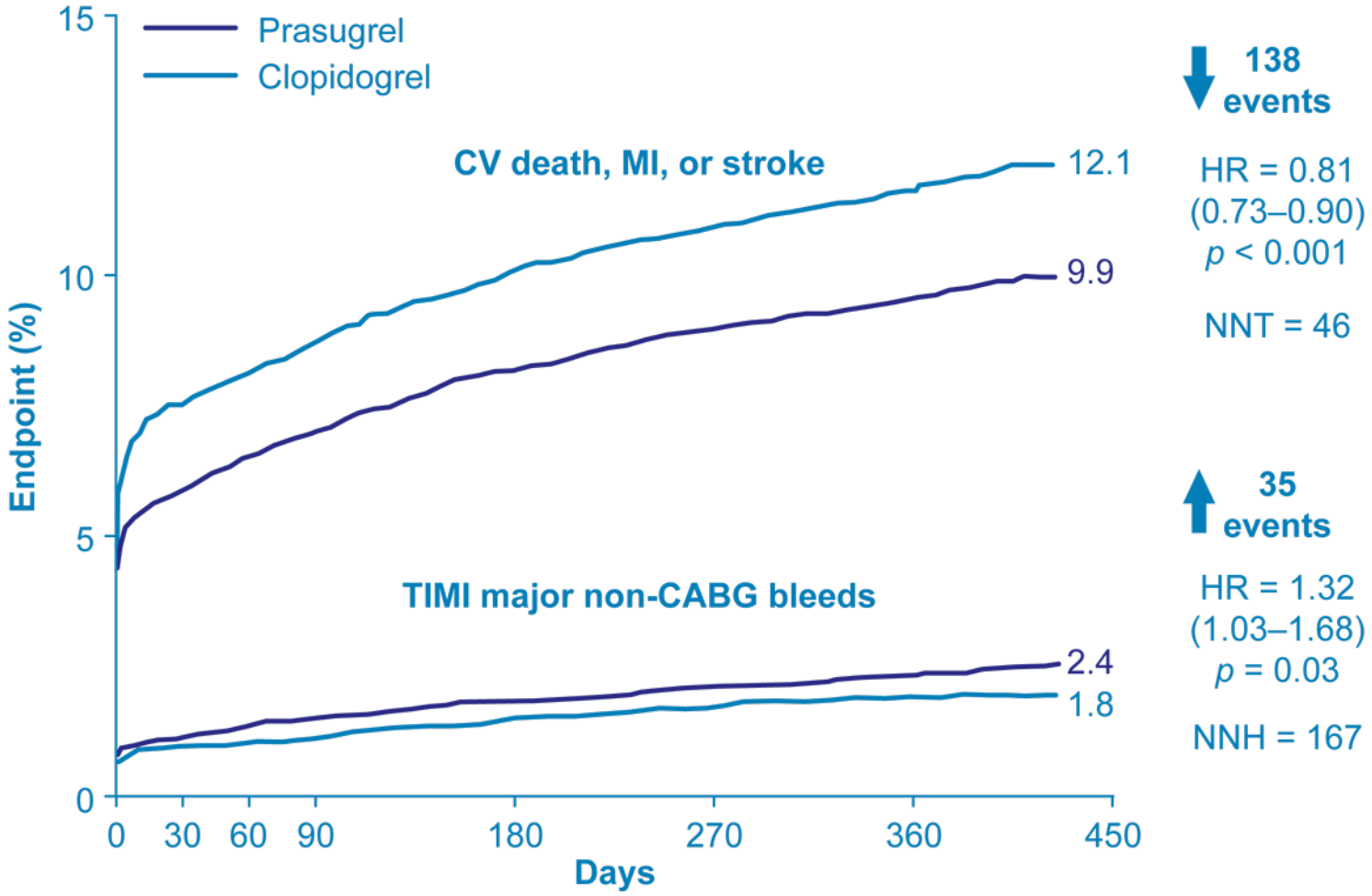
James S, et al. Circulation 2010;122:1056–1067

PLATO: CABG vs. Non-CABG Major Bleeding



Wallentin L, et al. N Engl J Med. 2009;361:1045.

TRITON: significant reduction in CV death, MI or stroke offset by significant increase in non-CABG TIMI major bleeding[1]



1. Wiviott SD et al. *N Engl J Med* 2007;357:2001–2015.

What do guidelines say on Triple therapy??..

Table 6. Recommendations for Warfarin Therapy

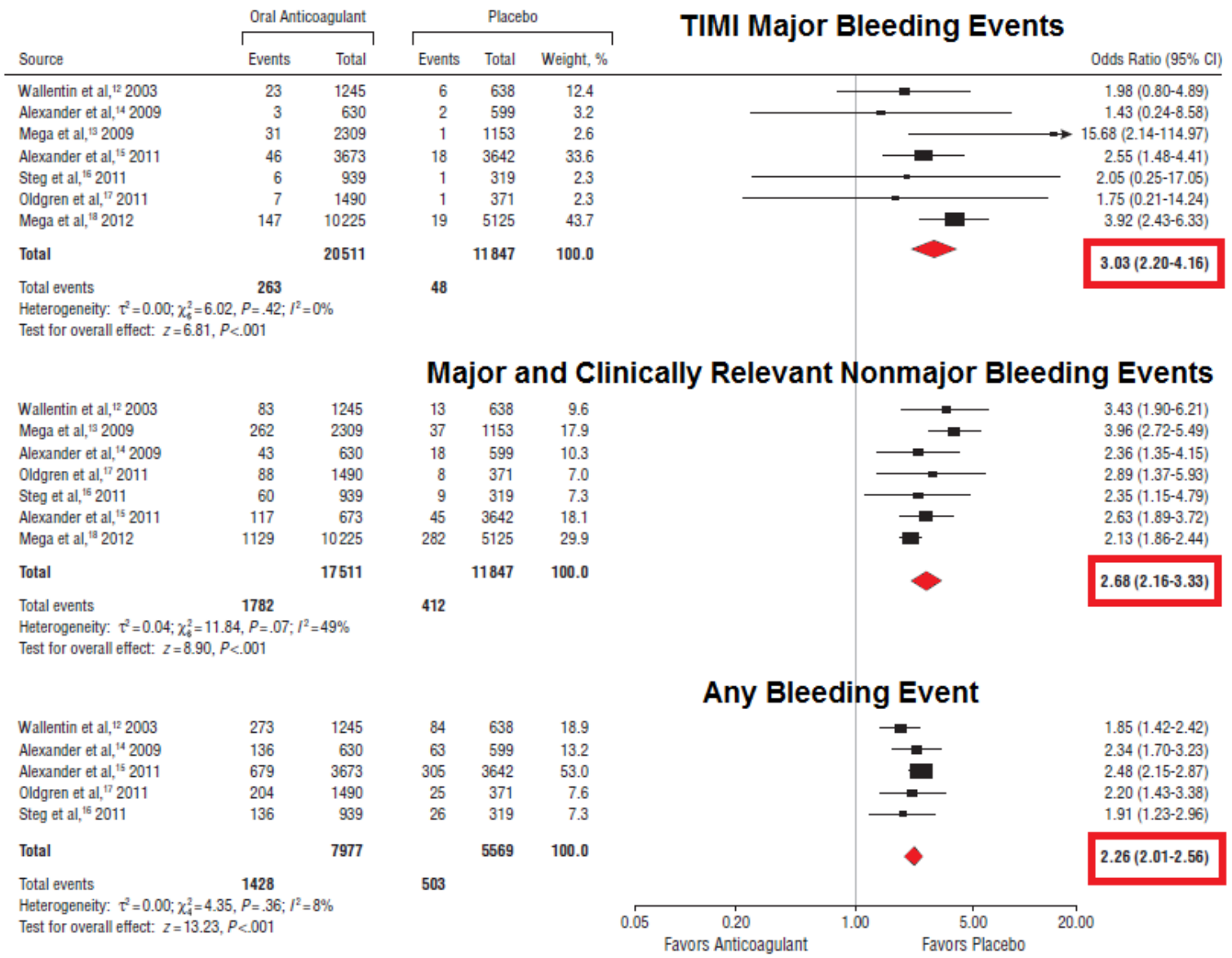
2012 Focused Update Recommendations	2012 Comments
Class I	
1. Use of warfarin in conjunction with aspirin and/or $P2Y_{12}$ receptor inhibitor therapy is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially GI, and seek medical evaluation for evidence of bleeding (7,9,13,14,141–144). *(Level of Evidence: A)*	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
Class IIb	
1. Warfarin either without (INR 2.5 to 3.5) or with low-dose aspirin (81 mg per day; INR 2.0 to 2.5) may be reasonable for patients at high coronary artery disease risk and low bleeding risk who do not require or are intolerant of $P2Y_{12}$ receptor inhibitor therapy (145,146). *(Level of Evidence: B)*	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
2. Targeting oral anticoagulant therapy to a lower INR (e.g., 2.0 to 2.5) might be reasonable in patients with UA/NSTEMI managed with aspirin and a $P2Y_{12}$ inhibitor. *(Level of Evidence: C)*	New recommendation

GI indicates gastrointestinal; INR, international normalized ratio; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Trials of anti-Xa in ACS pts
Triple therapy in ACS patients (Arch Int Med meta analysis)

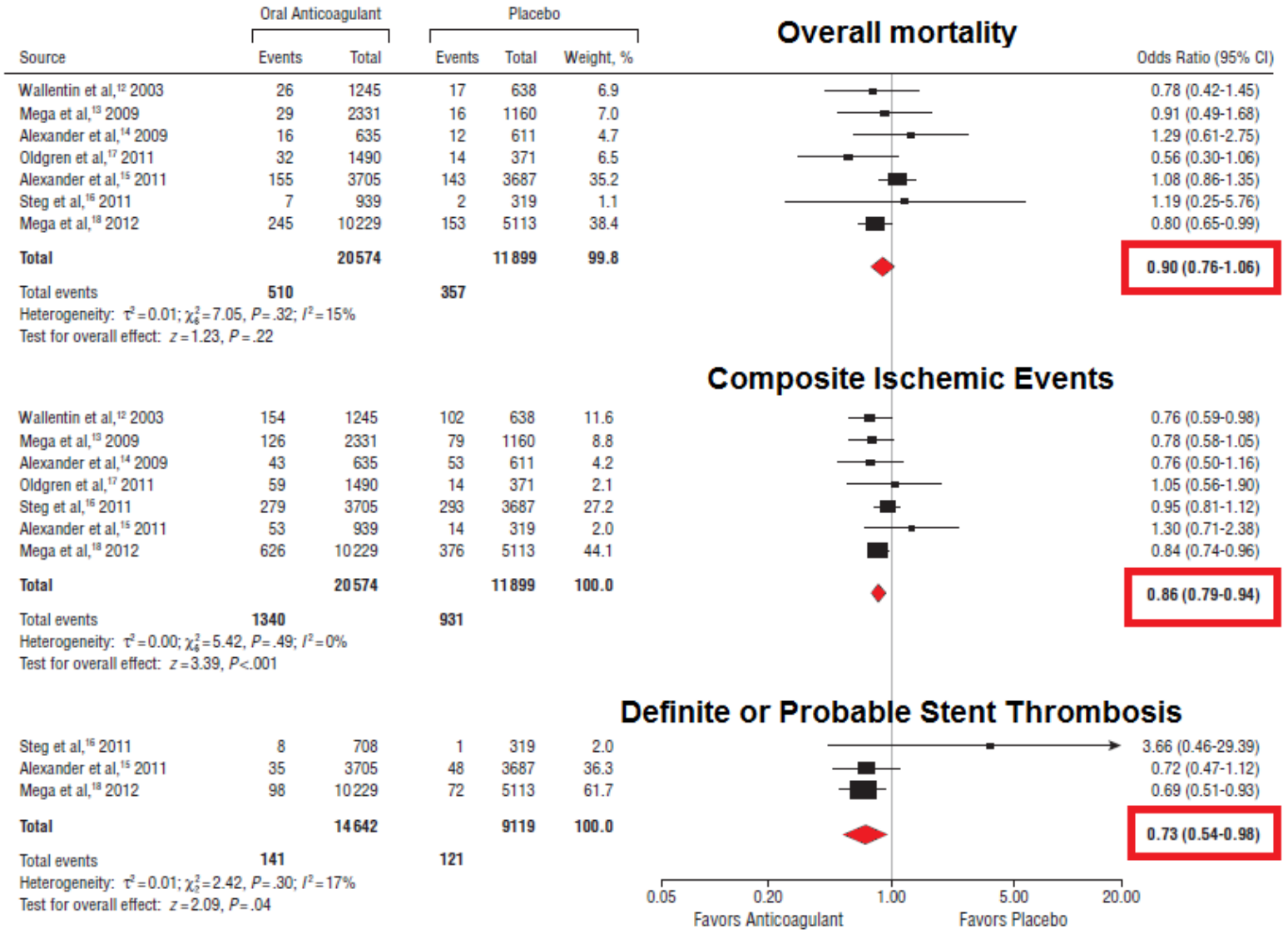
Source	Time Between ACS Event and Randomization, d	New-Generation Oral Anticoagulant Agent Administered (Total Daily Doses, mg)	Phase of the Trial	Design of the Trial	Exclusion Criteria	Composite Ischemic Events End Point Definition
Wallentin et al,[12] 2003	<14	Ximelagatran (48, 72, 96, 120)	II	Dose-finding superiority study	PCI in the past 4 mo or planned within 60 d, OAC, HR for bleeding, recent stroke	MI, severe recurrent ischemia, overall mortality
Mega et al,[13] 2009	<7	Rivaroxaban (5, 10, 20)	II	Dose-finding study	History of any intracranial hemorrhage, OAC, planned PCI within 30 d of randomization	MI, stroke, severe recurrent ischemia, overall mortality
Alexander et al,[14] 2009	<6	Apixaban (5, 10, 20[a])	II	Dose-finding study	Planned catheterization, HR for bleeding, stroke in the past 3 mo, long-term use of NSAID or high-dose aspirin, OAC	MI, severe recurrent ischemia, ischemic stroke, cardiovascular mortality
Alexander et al,[15] 2011[a]	<7	Apixaban (10)	III	Superiority study	HR for bleeding, ischemic stroke in the past 7 d, OAC, use of high-dose aspirin	MI, ischemic stroke, cardiovascular mortality
Steg et al,[16] 2011	<7	Darexaban (10, 30, 60)	II	Dose-finding study	OAC, HR for bleeding, recent stroke or TIA in the past 12 mo before the index event	MI, stroke, severe recurrent ischemia, overall mortality
Oldgren et al,[17] 2011	<14	Dabigatran (100, 150, 220, 300)	II	Dose-finding study	OAC, severe stroke in the past 6 mo or any stroke in the past 14 d, HR for bleeding	MI, nonhemorrhagic stroke, overall mortality
Mega et al,[18] 2012	<7	Rivaroxaban (5, 10)	III	Superiority study	HR for bleeding, previous intracranial hemorrhage, previous ischemic stroke or TIA in patients receiving DAPT during the trial	MI, stroke, cardiovascular mortality

Bleeding with triple therapy



Source	Oral Anticoagulant Events	Oral Anticoagulant Total	Placebo Events	Placebo Total	Weight, %	Odds Ratio (95% CI)
TIMI Major Bleeding Events						
Wallentin et al,[12] 2003	23	1245	6	638	12.4	1.98 (0.80-4.89)
Alexander et al,[14] 2009	3	630	2	599	3.2	1.43 (0.24-8.58)
Mega et al,[13] 2009	31	2309	1	1153	2.6	15.68 (2.14-114.97)
Alexander et al,[15] 2011	46	3673	18	3642	33.6	2.55 (1.48-4.41)
Steg et al,[16] 2011	6	939	1	319	2.3	2.05 (0.25-17.05)
Oldgren et al,[17] 2011	7	1490	1	371	2.3	1.75 (0.21-14.24)
Mega et al,[18] 2012	147	10225	19	5125	43.7	3.92 (2.43-6.33)
Total		**20511**		**11847**	**100.0**	**3.03 (2.20-4.16)**
Total events	**263**		**48**			
Heterogeneity: $\tau^2=0.00$; $\chi^2_6=6.02$, $P=.42$; $I^2=0\%$						
Test for overall effect: $z=6.81$, $P<.001$						
Major and Clinically Relevant Nonmajor Bleeding Events						
Wallentin et al,[12] 2003	83	1245	13	638	9.6	3.43 (1.90-6.21)
Mega et al,[13] 2009	262	2309	37	1153	17.9	3.96 (2.72-5.49)
Alexander et al,[14] 2009	43	630	18	599	10.3	2.36 (1.35-4.15)
Oldgren et al,[17] 2011	88	1490	8	371	7.0	2.89 (1.37-5.93)
Steg et al,[16] 2011	60	939	9	319	7.3	2.35 (1.15-4.79)
Alexander et al,[15] 2011	117	673	45	3642	18.1	2.63 (1.89-3.72)
Mega et al,[18] 2012	1129	10225	282	5125	29.9	2.13 (1.86-2.44)
Total		**17511**		**11847**	**100.0**	**2.68 (2.16-3.33)**
Total events	**1782**		**412**			
Heterogeneity: $\tau^2=0.04$; $\chi^2_6=11.84$, $P=.07$; $I^2=49\%$						
Test for overall effect: $z=8.90$, $P<.001$						
Any Bleeding Event						
Wallentin et al,[12] 2003	273	1245	84	638	18.9	1.85 (1.42-2.42)
Alexander et al,[14] 2009	136	630	63	599	13.2	2.34 (1.70-3.23)
Alexander et al,[15] 2011	679	3673	305	3642	53.0	2.48 (2.15-2.87)
Oldgren et al,[17] 2011	204	1490	25	371	7.6	2.20 (1.43-3.38)
Steg et al,[16] 2011	136	939	26	319	7.3	1.91 (1.23-2.96)
Total		**7977**		**5569**	**100.0**	**2.26 (2.01-2.56)**
Total events	**1428**		**503**			
Heterogeneity: $\tau^2=0.00$; $\chi^2_4=4.35$, $P=.36$; $I^2=8\%$						
Test for overall effect: $z=13.23$, $P<.001$						

Clinical outcome with triple therapy

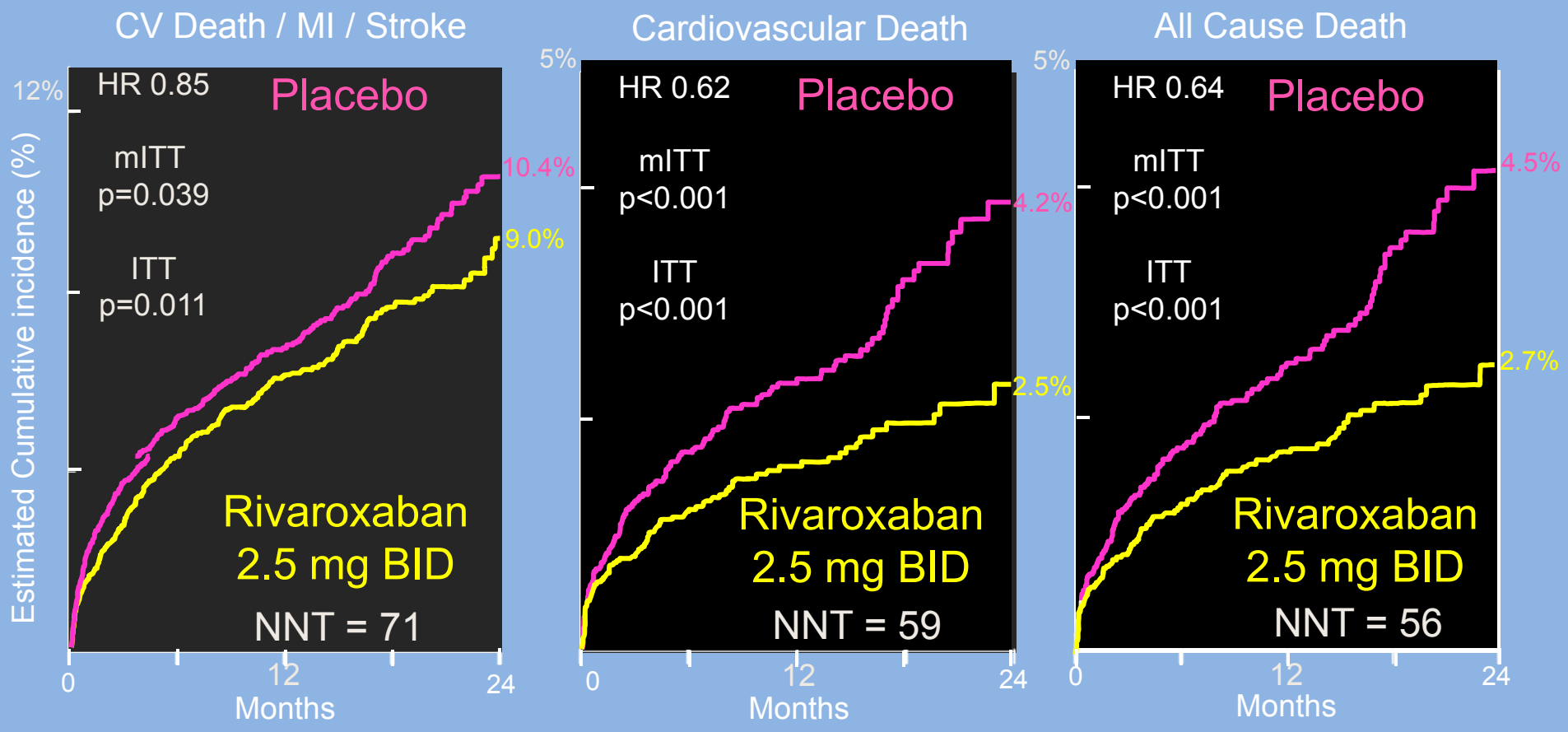


Conclusions

- **Based on the pooled results:**
  - The use of new-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an ACS was associated with a dramatic increase in major bleeding events
  - Significant but moderate reductions in the risk for stent thrombosis or composite ischemic events were observed, without a significant effect on overall mortality
  - Regarding the net clinical benefit, treatment with new generation oral anticoagulant agents provided no advantage over placebo

ATLAS ACS 2 TIMI 51

EFFICACY ENDPOINTS:
Very Low Dose 2.5 mg BID
Patients Treated with ASA + Thienopyridine



Gibson CM, NEJM 2012

The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

WOEST

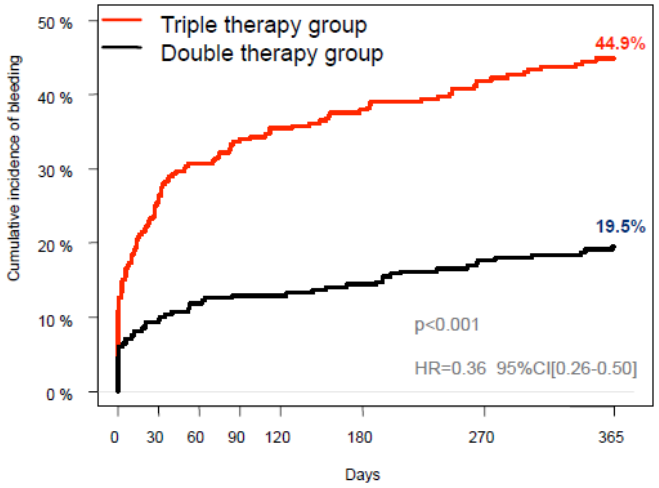
Aim of the study

To test the hypothesis that in patients on OAC undergoing PCI, *clopidogrel alone* is superior to the combination *aspirin and clopidogrel* with respect to bleeding but is not increasing thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)

DeWilde. Lancet 2013

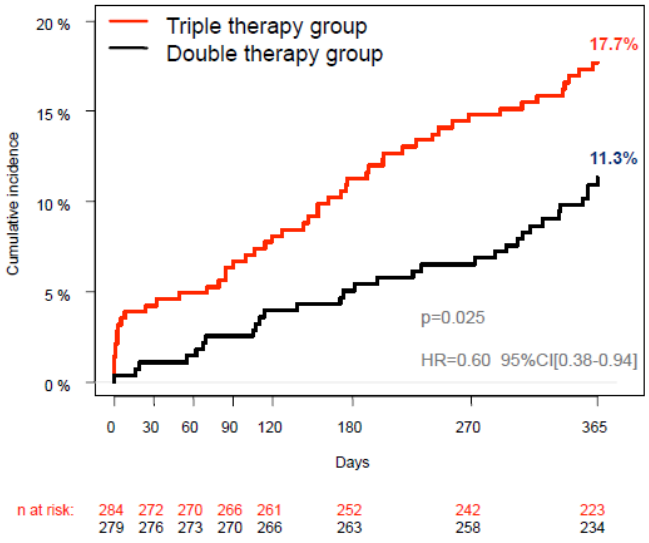
WOEST

Primary Endpoint: Total number of bleeding events (TIMI criteria)



WOEST

Secondary Endpoint (Death, MI,TVR, Stroke, ST)



WOEST

Conclusions

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting
2. In this study which was specifically designed to detect bleeding events, the bleeding rate was higher than expected
3. Primary endpoint was met: OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way
4. Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death
5. Less all-cause mortality with double therapy

DeWilde. Lancet 2013

One week post discharge in E.R

- Patient again complains of dispnea

• The symptom appeared at the day of discharge and is not associated with either physical strain or position. Not accompanied by chest pain.

• ECG: no signs of ischemia

• Physical exam: ND

• Echocardiography, Chest X ray, BNP testing ordered

At this stage what would you do:

- Recath
- Pulmonary function testing
- Switch Brilinta to Clopidogrel.
- Reduce Brilinta dose
- Start diuretics and admit to hospital
- Reassure after obtaining test results

Dyspnea in PLATO

- Dyspnea was reported more frequently by patients on ticagrelor than clopidogrel (13.8% vs 7.8%; *P*<0.001)
  - Most episodes lasted less than a week
  - Ticagrelor-associated dyspnea was mostly mild to moderate and did not affect efficacy
- 0.9% patients on ticagrelor and 0.1% patients on clopidogrel discontinued study drug because of dyspnea (*P*<0.001)
- The higher frequency of dyspnea with ticagrelor was not associated with any detectable detrimental effect on pulmonary function compared with clopidogrel

Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057; Storey R, et al. *JACC.* 2010;55(Suppl 1):A108.E1007.

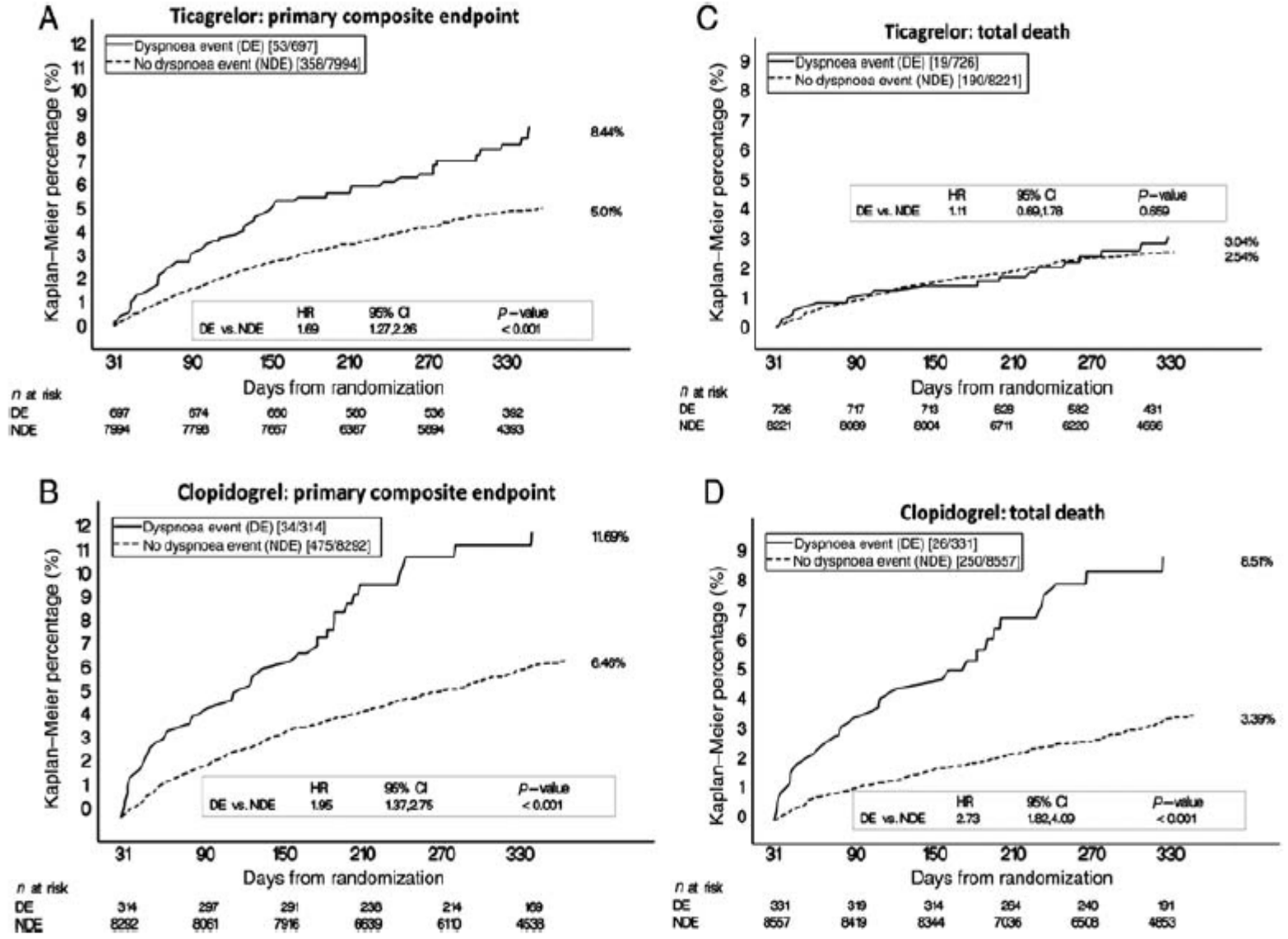


Figure 2 K–M curves for events between 31 and 360 days in (*A* and *C*) ticagrelor-treated patients or (*B* and *D*) clopidogrel-treated patients with or without onset of dyspnoea up to 30 days post randomization showing (A, B) primary composite endpoint; and (C, D) total death.

Clinical outcomes of patients reporting dyspnea post randomization according to treatment group

Table 4 Clinical outcomes of patients reporting dyspnoea post randomization compared with those not reporting dyspnoea, according to treatment group

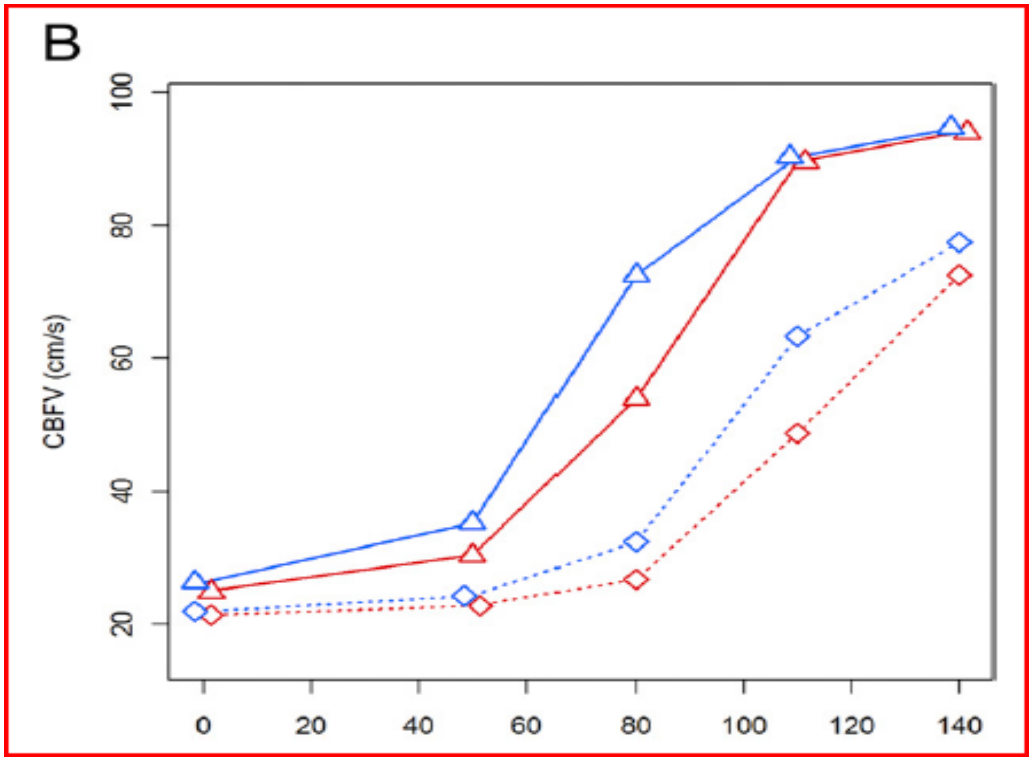
n (K–M%)	Ticagrelor, *n* = 9235			Clopidogrel, *n* = 9186		
	Dyspnoea, *n* = 1339	No dyspnoea, *n* = 7896	*P*-value	Dyspnoea, *n* = 798	No dyspnoea, *n* = 8388	*P*-value
Primary composite endpoint (%)	151 (11.9)	701 (9.4)	<0.001	117 (15.7)	882 (11.2)	0.008
Myocardial infarction (%)	112 (8.7)	393 (5.4)	0.008	83 (11.3)	515 (6.6)	0.173
Stroke (%)	21 (1.7)	102 (1.4)	0.423	9 (1.3)	95 (1.2)	0.278
CV death (%)	39 (3.3)	306 (4.1)	<0.001	37 (4.8)	391 (5.0)	0.036
Total mortality (%)	47 (3.9)	342 (4.6)	<0.001	48 (6.4)	443 (5.7)	0.007
Major bleed (%)	164 (13.7)	797 (11.2)	0.591	96 (13.5)	833 (11.0)	0.436
Major or minor bleed (%)	256 (21.4)	1083 (13.7)	0.117	136 (18.8)	1079 (14.2)	0.032

P-values are from a Cox proportional hazards model with explanatory variables for treatment group, occurrence of first dyspnoea event (as a time-dependent covariate) and treatment-dyspnoea interaction, and adjusted for age, weight, diabetes mellitus, history of congestive heart failure, smoking status, history of chronic renal disease, and prior dyspnoea; all hazard ratios for Dyspnoea vs. No dyspnoea are >1.

K–M, Kaplan–Meier.

Ticagrelor augments adenosine-induced physiological responses in human subjects

- Theophylline infusion significantly reduced the adenosine induced CBFV-AUC in both study groups.

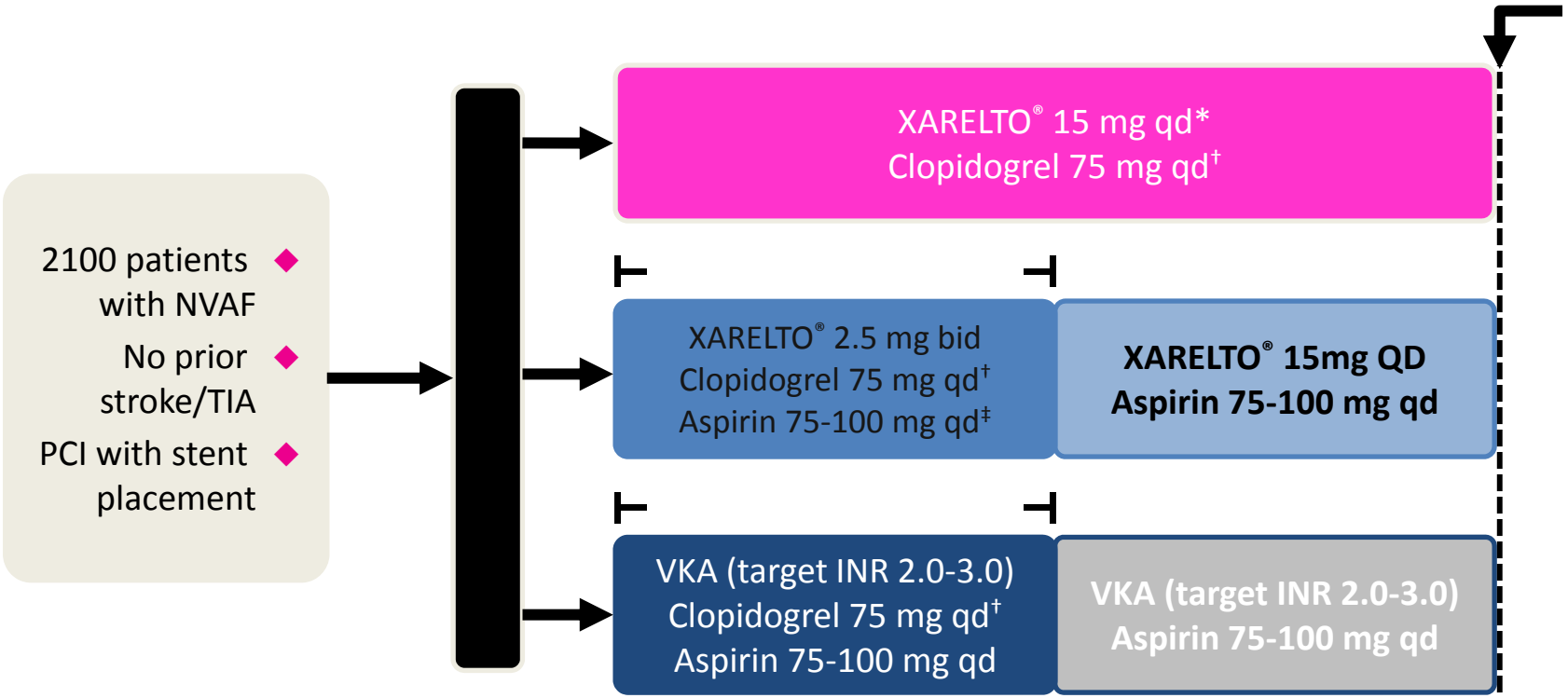


Symbols :
post-placebo red solid line,
post theophylline (placebo) - red dotted line,
Post-ticagrelor blue solid line.
Post theophylline (ticagrelor) - blue dotted line.

Points to consider in this patient

1. **Overall risk of stroke by CHADS2VASC/CHADS2**
2. **Overall risk of recurrent ACS**
3. **Safety of using different P2Y12 inhibitors**
4. **Safety of using NOACS with and without DAPT**
5. **Reversibility of P2Y12 inhibitors**
6. **Reversibility of NOACS.**
7. **Safety of P2Y12 inhibitors after stroke.**
8. **Antidotes**

XARELTO® (rivaroxaban) Use in Patients With AF Undergoing PCI: PIONEER AF-PCI



- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis