



What's New in ACS?

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Disclosures



- Advisory Boards/Speaker Honoraria
 - Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Sanofi Aventis
- Research Support
 - Astra Zeneca, Boehringer Ingelheim

What are the current recommendations?

Medication	In Hospital	Long-Term
Aspirin	160mg to chew, followed by ECASA 81mg daily	ECASA 81mg daily indefinitely
Clopidogrel	300mg or 600mg X 1, followed by 75mg daily	75mg daily \geq 1 year Minimum: 4 weeks (BMS) 3-6 months (DES)

Key Issues with Current Therapy

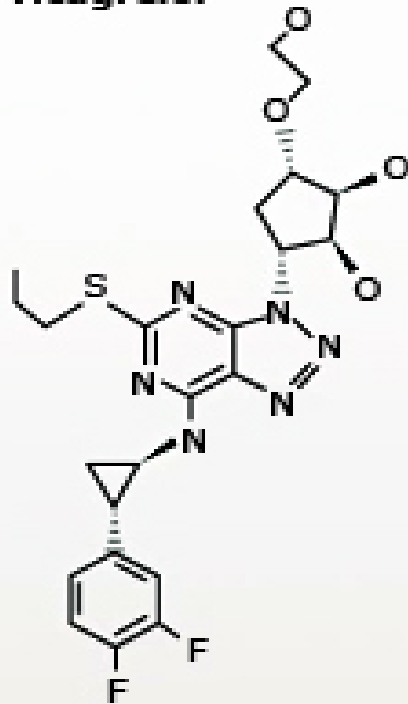


- Slow onset and offset
- Variability in antiplatelet response
- Modest level of platelet inhibition

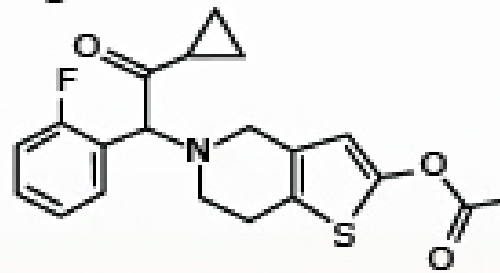
Comparison of Antiplatelet Agents in ACS

	Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta®)
Mechanism	Irreversible	Irreversible	Reversible
Inhibitory effect	+	++	++
Peak response	2-5 h	1-1.5 h	1-3 h
Metabolism	Prodrug (CYP 2C19, 3A, 2B6, 1A2)	Prodrug (3A4, 2B6, 2C9, 2C19)	Not a prodrug
Duration	5-7 days	5-7 days	48-72 h

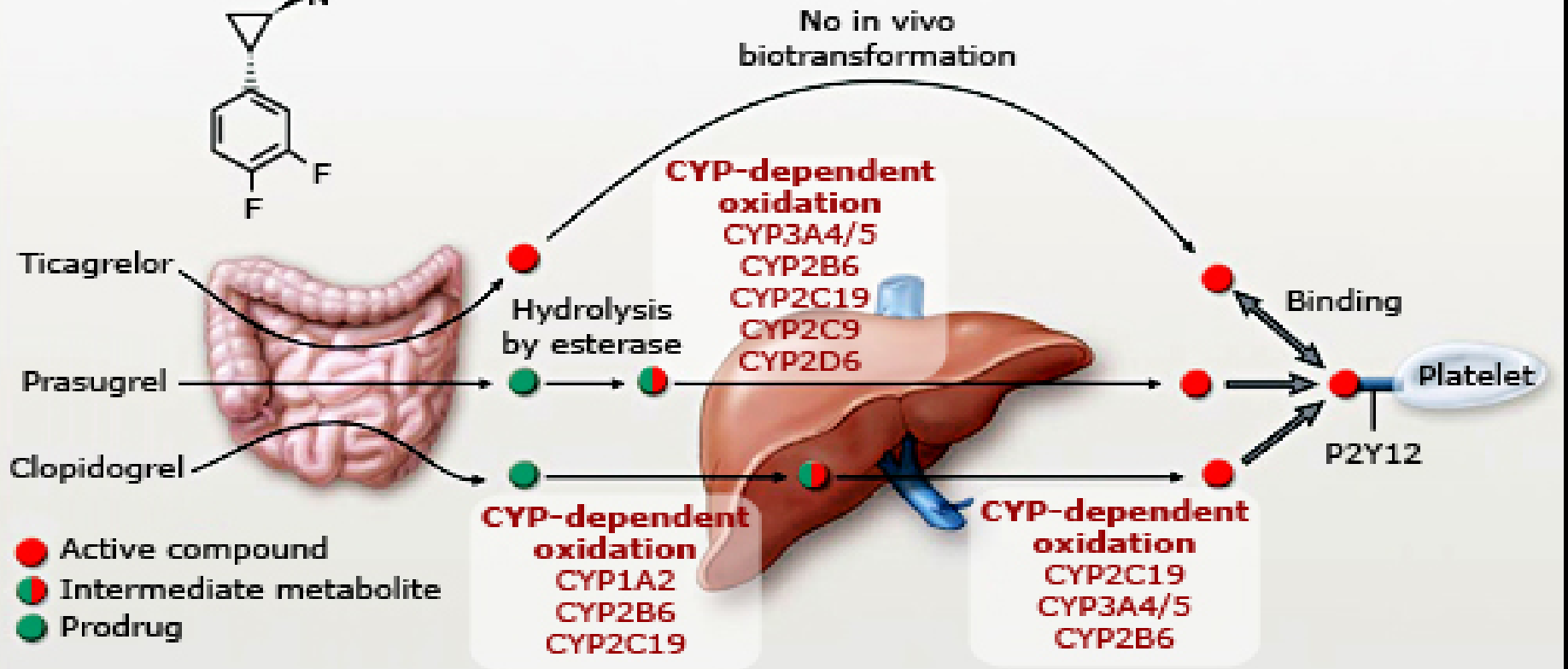
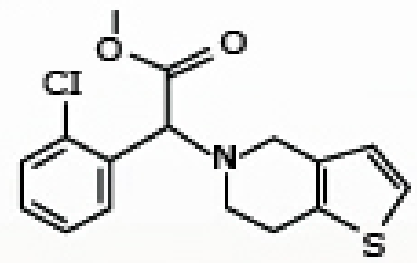
Ticagrelor



Prasugrel



Clopidogrel



Update: Antiplatelet Agents in ACS and PCI

	Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta®)
Evidence	CURE PCI-CURE	TRITON-TIMI 38	PLATO
Dose	300-600mg X 1 75 mg od	60mg X 1, 10mg od	180mg X 1 90mg bid
Approved Indications*	<ul style="list-style-type: none"> MI, stroke, PAD (secondary prev'n) ACS +/- PCI 	NSTEMI/STEMI with PCI	—
Availability*	Yes	June 2010	—
Cost	\$2.58/day	\$2.66/day	—

*as of May 2011

Which antiplatelet therapy?

- Should you give a higher dose of clopidogrel?
- Should you use prasugrel?
- Should you use ticagrelor (when it becomes available)?

CURRENT-OASIS-7

UA/NSTEMI
or STEMI

R

STANDARD DOSE

Clopidogrel

Day 1: 300 mg LD + placebo
Day 2-7: 75 mg daily + placebo
Day 8-30: 75 mg daily

HIGH DOSE

Clopidogrel

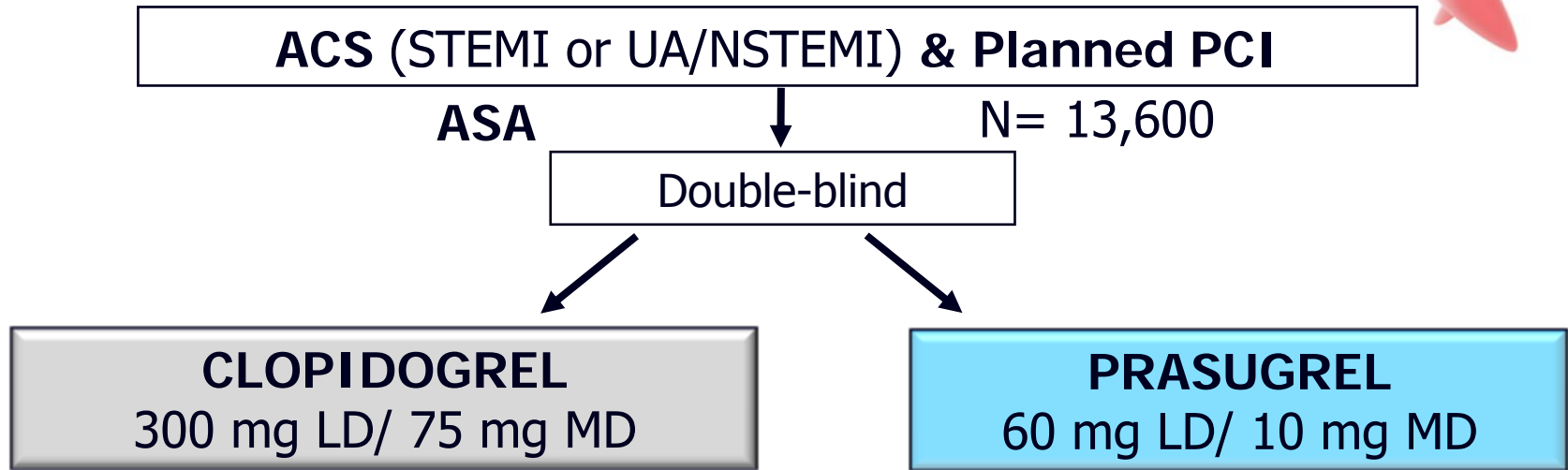
Day 1: 600 mg LD
Day 2-7: 150 mg daily
Day 8-30: 75 mg

All patients:
ASA low dose (75-100mg)
OR high dose (300-325mg)
Up to 30 days

CURRENT-OASIS-7

	High Dose	Standard Dose	p value
CV Death/MI/Stroke	4.2 %	4.4 %	0.30
Major Bleeding	2.5 %	2.0 %	0.01
PCI subgroup	3.9 %	4.5 %	0.039

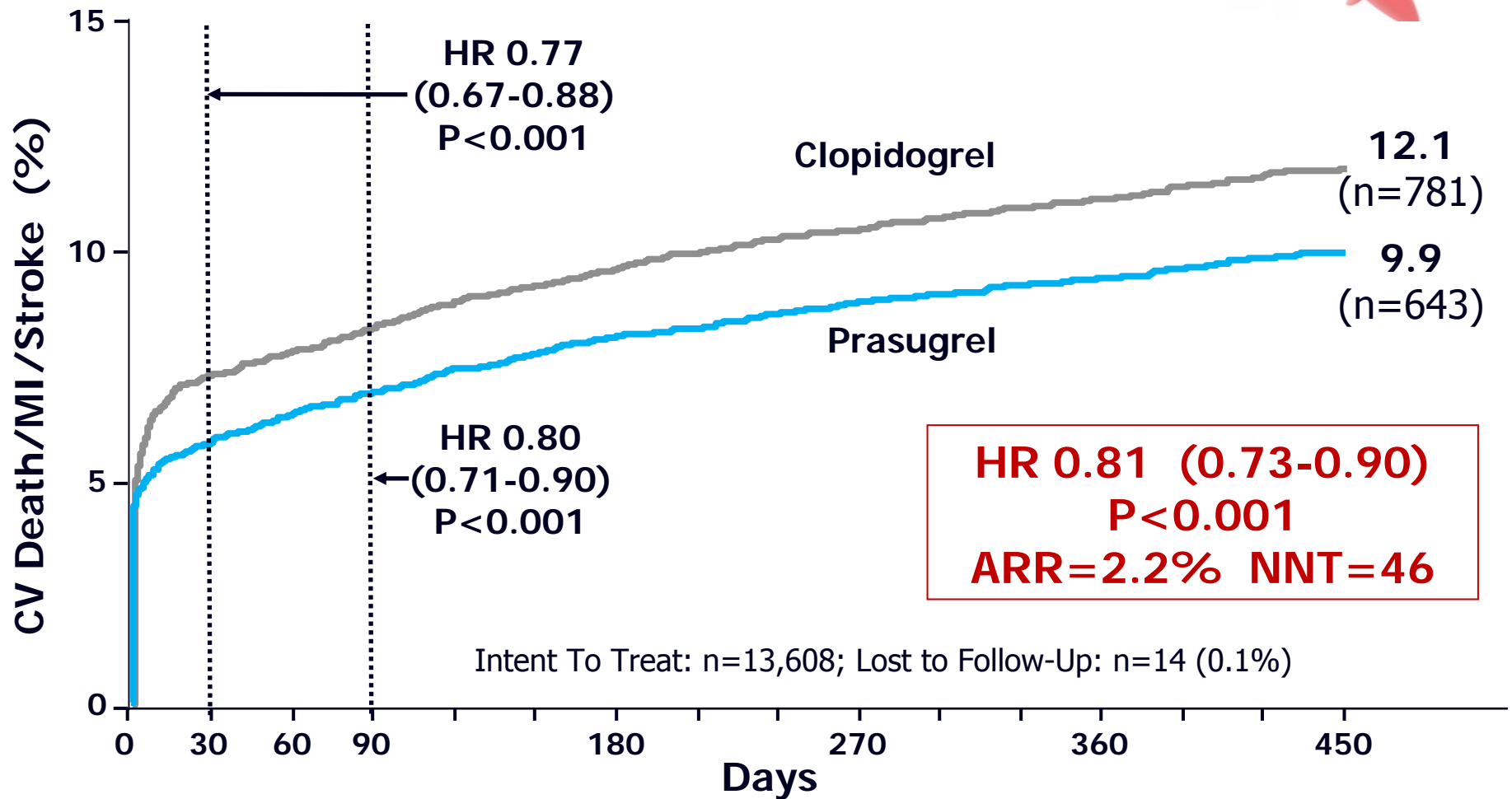
TRITON-TIMI 38



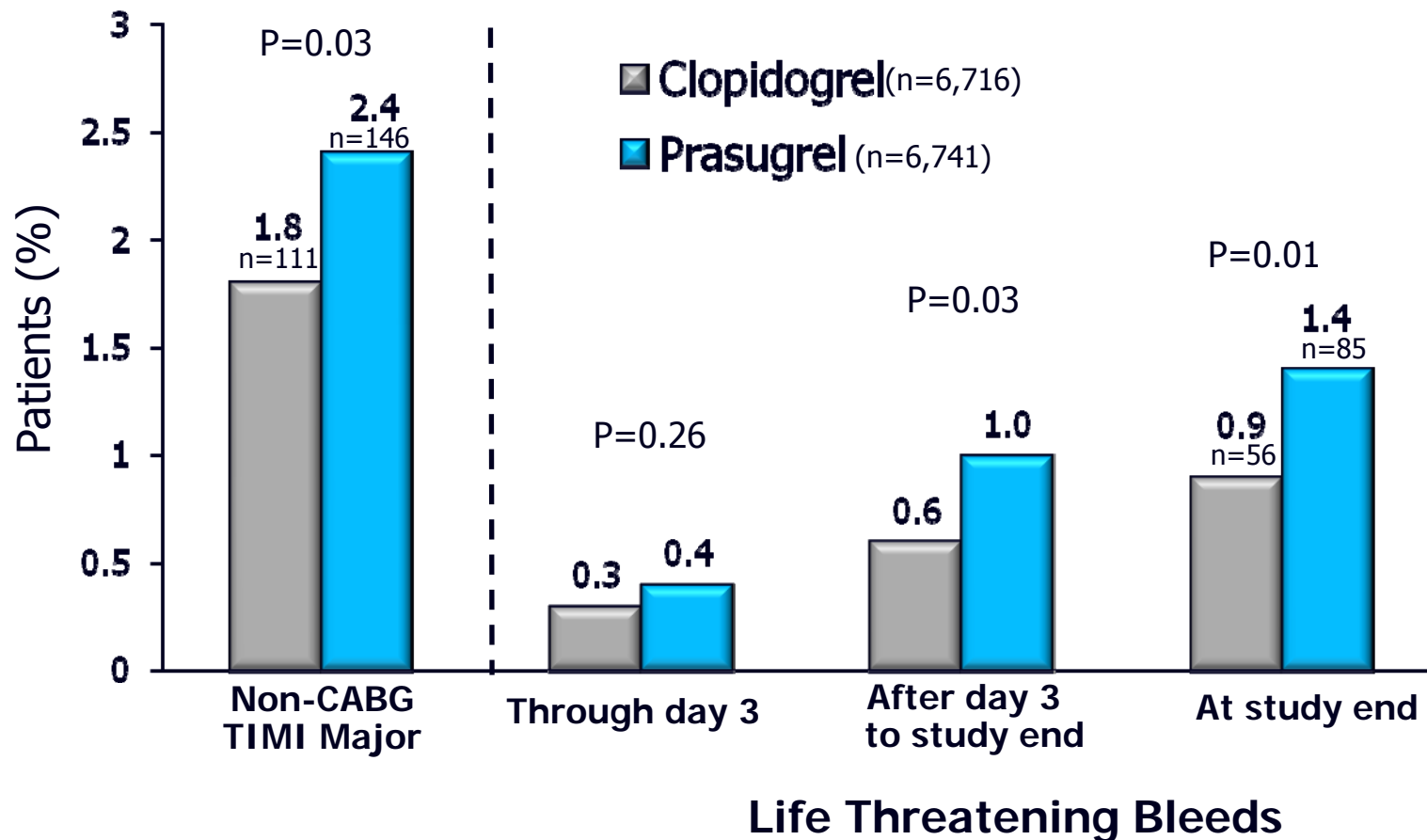
Median duration of therapy - 12 months

1° endpoint:	CV death, MI, Stroke
2° endpoints:	CV death, MI, Stroke, Rehosp-Recurrent Ischemia CV death, MI, UTVR Stent Thrombosis (ARC definite/probable)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key substudies:	Pharmacokinetic, Genomic

TRITON-TIMI 38: CV Death, MI, Stroke



TRITON-TIMI 38: Non-CABG TIMI Major Bleeds



What do the STEMI guidelines say?

Clopidogrel 300-600mg as early as possible before or at the time of PCI (1,C)
Prasugrel 60mg should be given as soon as possible for primary PCI (1,B)

Ticagrelor versus Clopidogrel in ACS (PLATO)

UA/NSTEMI (moderate-to-high risk) STEMI (if primary PCI)
All receiving ASA; clopidogrel-treated or naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel

If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

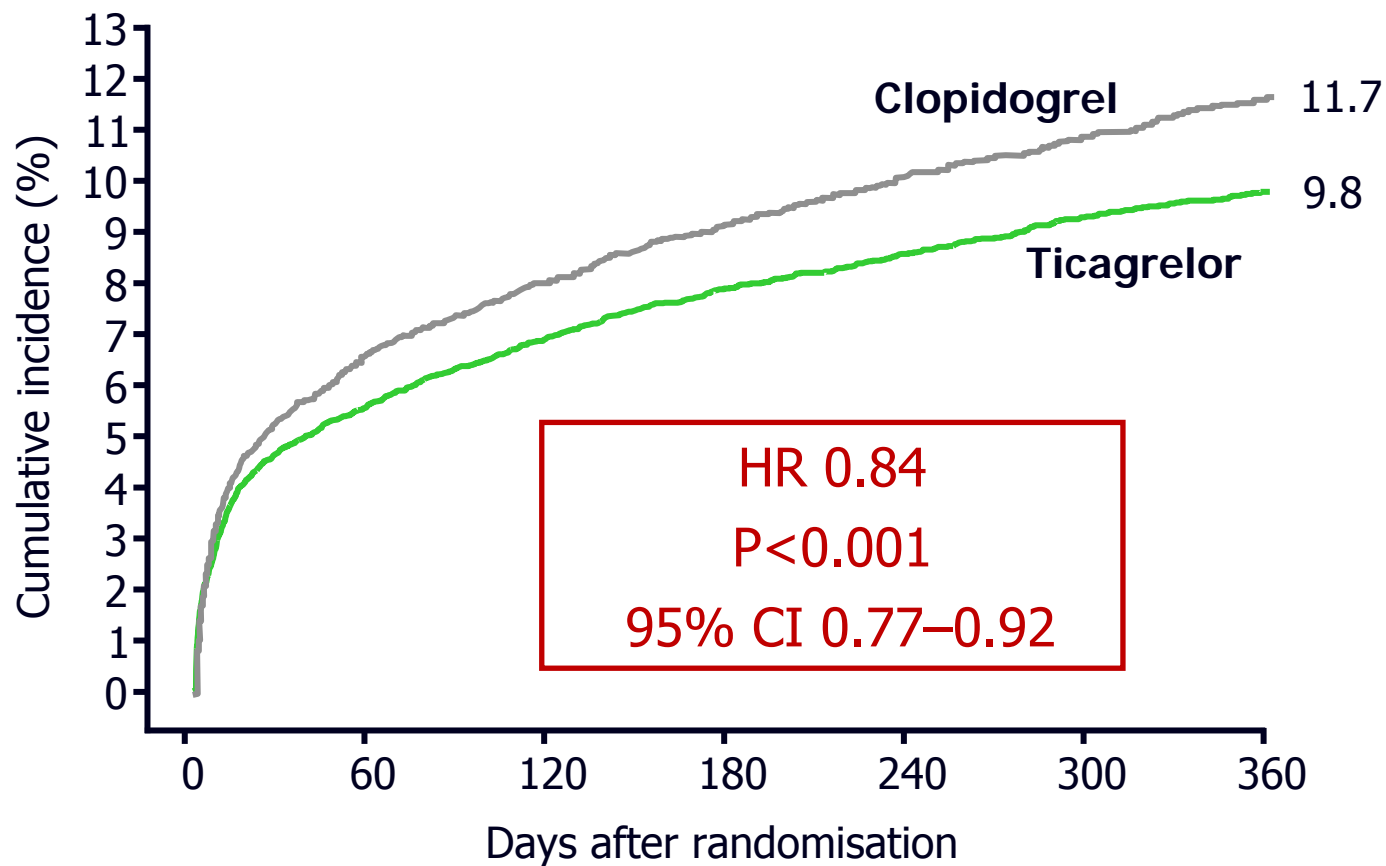
Ticagrelor

180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12 month exposure

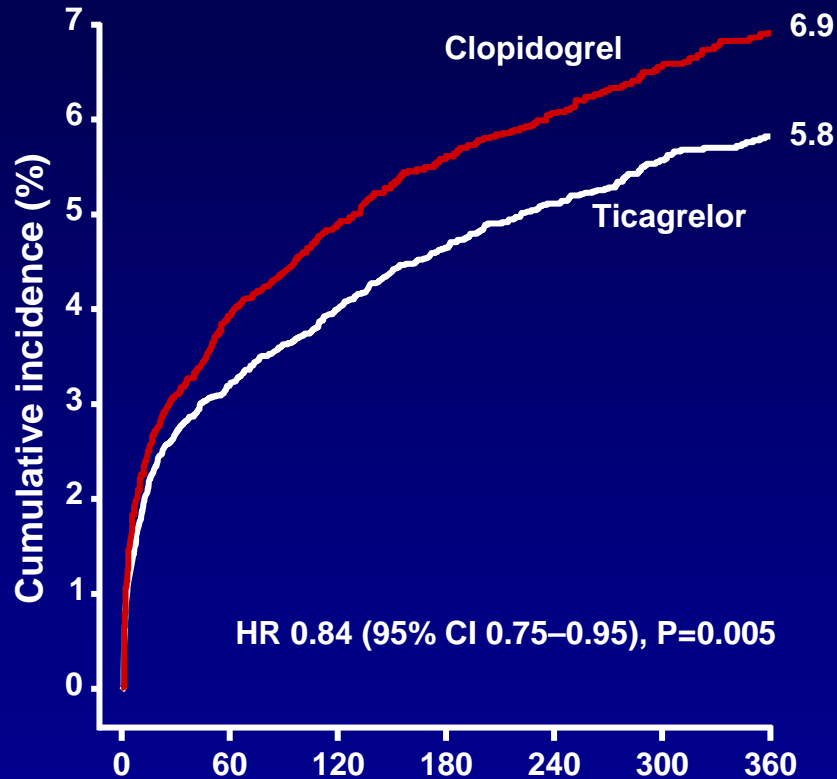
Primary endpoint: CV death + MI + Stroke
Key secondary: CV death + MI + Stroke in patients intended for invasive management
Total mortality + MI + Stroke
CV death + MI + Stroke + recurrent ischaemia + TIA + arterial thrombotic events
MI alone / CV death alone / Stroke alone / Total mortality
Primary safety: Total major bleeding

PLATO: CV Death, MI or Stroke

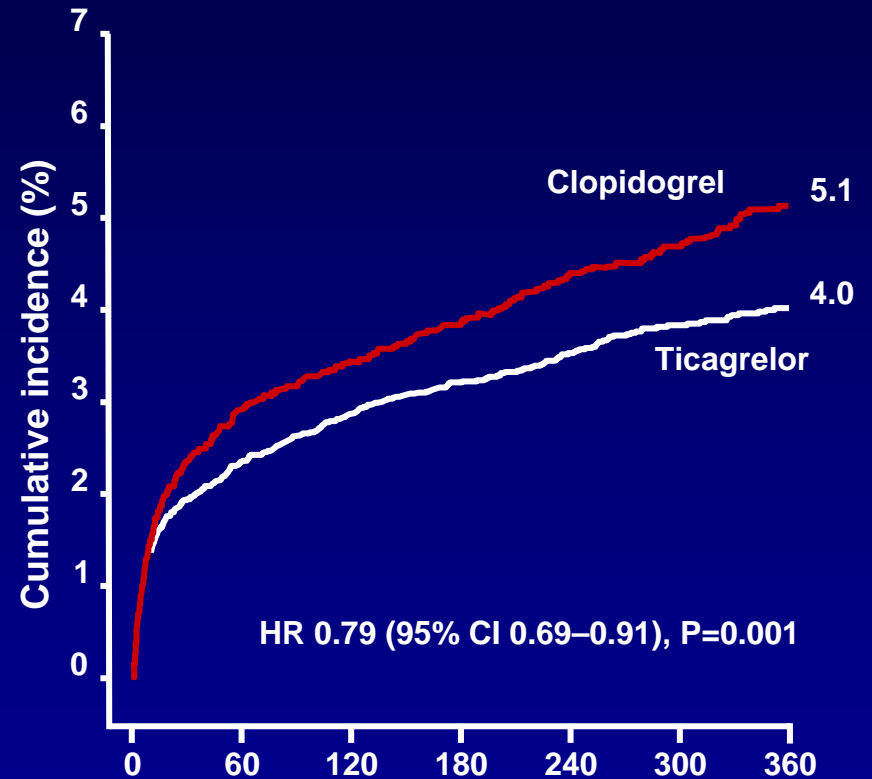


K-M Estimates of Time to Secondary Efficacy Endpoints

Myocardial infarction



Cardiovascular death



No. at risk	Days after randomisation						
	0	60	120	180	240	300	360
Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

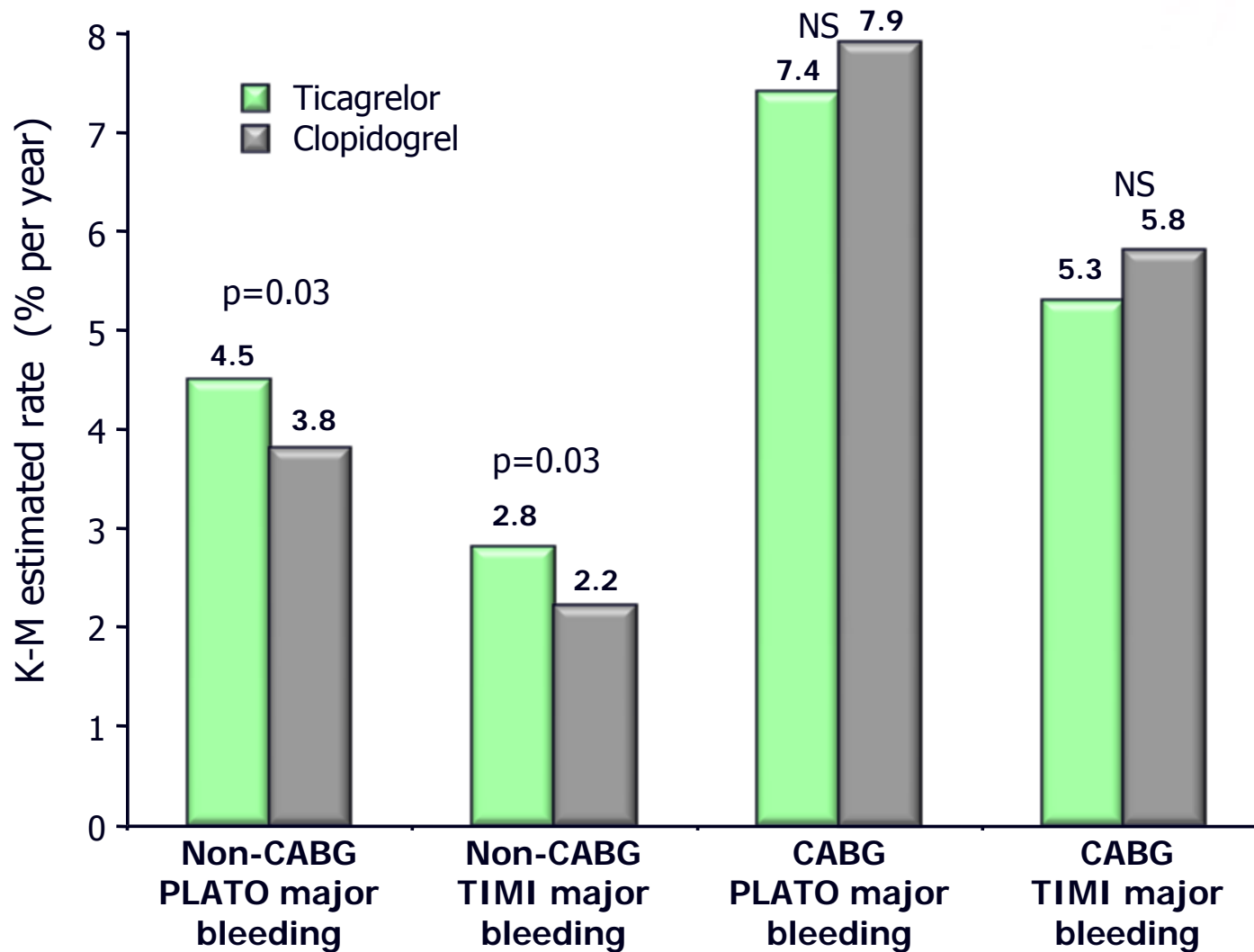
No. at risk	Days after randomisation						
	0	60	120	180	240	300	360
Clopidogrel	9,333	8,294	8,822	8,626	7119	5,482	4,419
Ticagrelor	9,291	8,865	8,780	8,589	7079	5,441	4,364

HR=hazard ratio; CI=confidence intervals; K-M=Kaplan-Meier

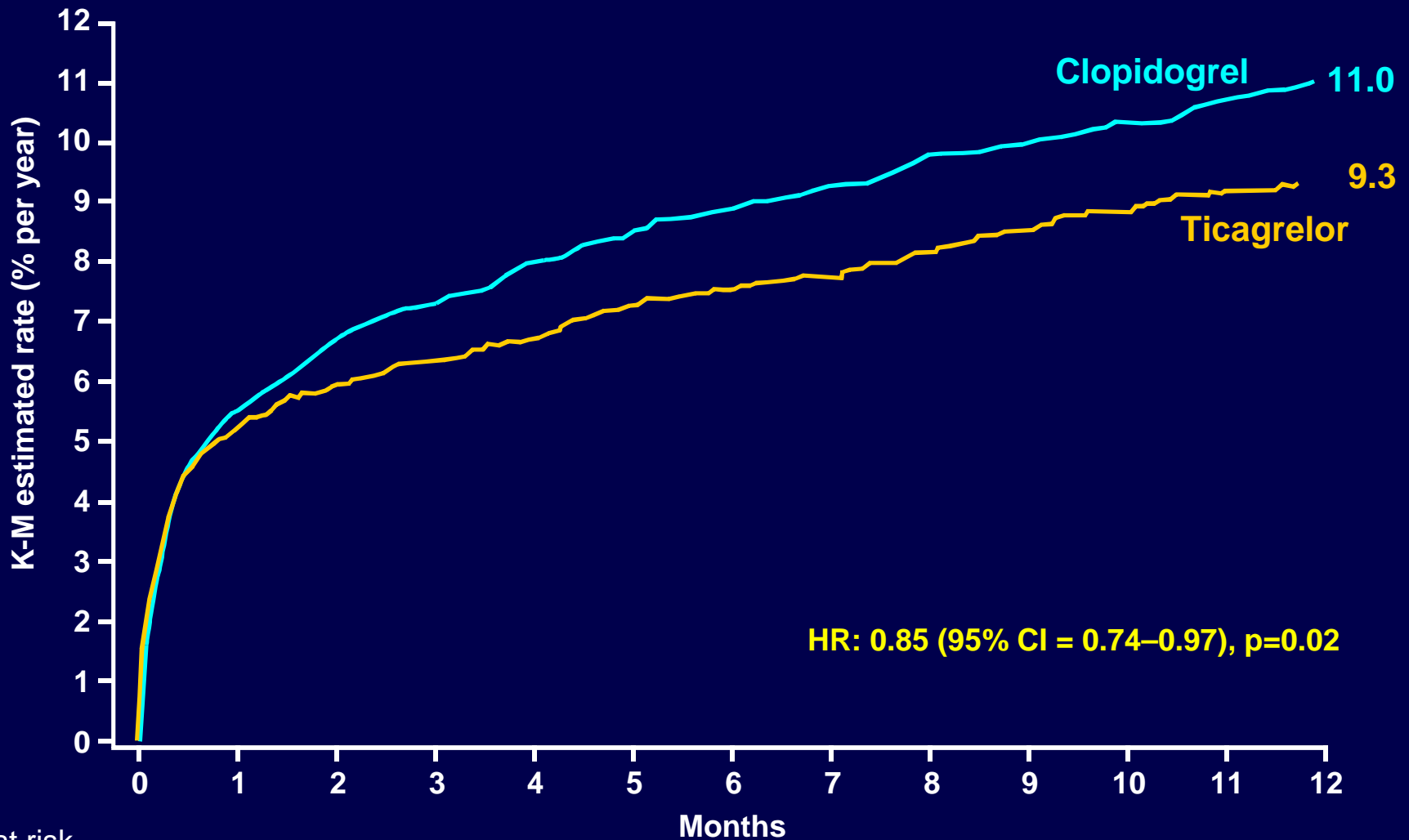
Wallentin L, et al. *New Engl J Med.* 2009;361.

^aThese slides have been provided, on request, by the AstraZeneca Medical Affairs

PLATO Non-CABG and CABG-related Major Bleeding



Primary endpoint: CV death, MI or stroke



No. at risk	Months						
Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868

Stent Thrombosis

	Treatment	Clopidogrel	OR	P value
TRITON				
Definite or probable	1.1 %	2.4 %	0.48	<0.001
PLATO				
Definite or probable	2.2%	2.9 %	0.75	0.02

Key Issues

- Adherence is important
- Significant risk associated with stopping therapy
- Do not stop antiplatelet therapy before a procedure without specific instructions from a cardiologist
- Hospital to community transition is key

Your Health, Your Heart: ACS Management Education Kit



- Patient information booklet
- Medication Schedule
- Wallet Card

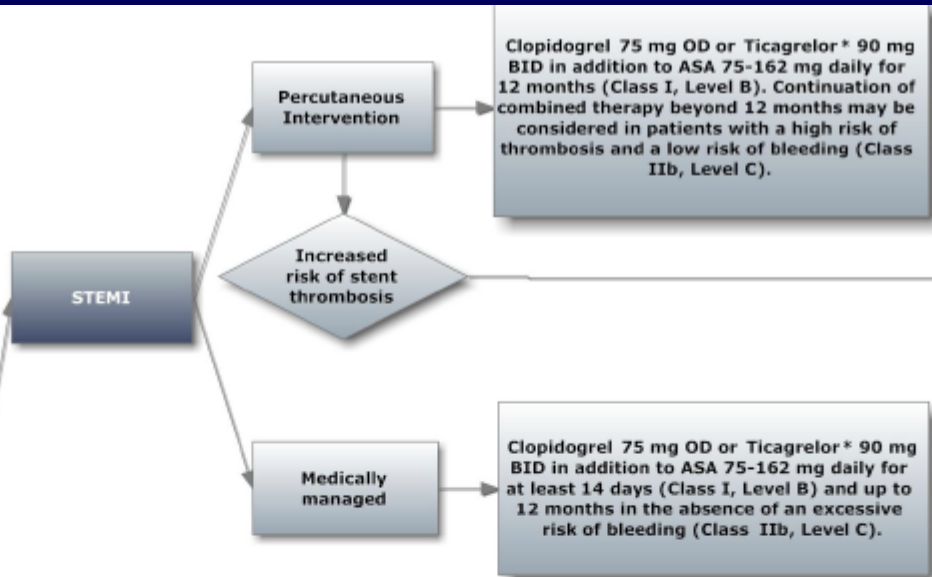
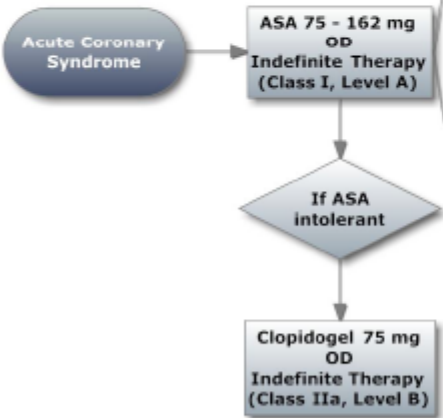




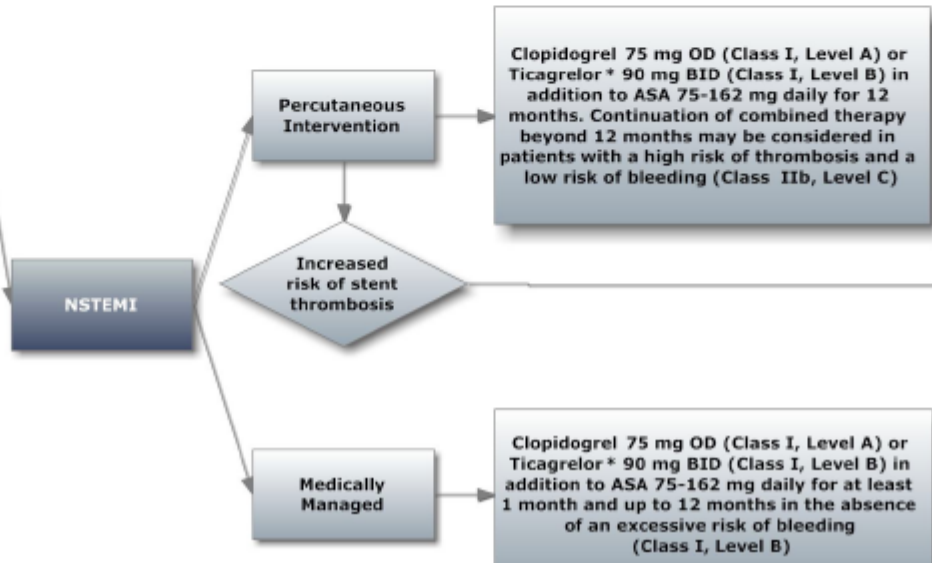
Antiplatelet Therapy for Secondary Prevention in the First Year Following an Acute Coronary Syndrome

RECOMMENDATIONS

Working Group: Jean-François Tanguay, MD, CSPQ, FRCP(C), FACC, FAHA, FESC;
Michael P. Love, MB, ChB, MD, MRCP; and Robert C. Welsh, MD, FRCP, FACC



- Prasugrel 10 mg daily may be considered in the absence of:
- increased bleeding risk
 - likely to undergo CABG within 7 days
 - history of stroke or transient ischemic attack (TIA)
 - age > 75 years
 - weight < 60 kg
- (Class IIa, Level B)



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*Currently under review by Health Canada. All recommendations concerning Ticagrelor are conditional on approval by Health Canada.

Ticagrelor

	Ticagrelor n=9333	Clopidogrel n=9291
Dyspnea	13.8%	7.8%
Dyspnea requiring discontinuation	0.9%	0.1%

PLATO NEJM 2009;361:1045-57

	Ticagrelor n=57	Clopidogrel n=54
Dyspnea	38.6%	9.3%
Judged related to drug	24.6%	3.7%
Dyspnea requiring discontinuation	5.2%	
Started < 24 h	8/22	
Started < 1 week	17/22	

ONSET/OFFSET JACC 2010;56:185-93

Ticagrelor



- Dyspnea is usually mild, transient, sometimes leads to discontinuation
 - Some brief episodes lasting minutes, others sustained or intermittent episodes occurring over several weeks.
- When it happens, most commonly in the first week
- Reversible upon drug discontinuation
- No pulmonary parameters affected
- Mechanism unknown

Triple Therapy: Benefit vs Risk

- Prevalence of major bleeding with triple therapy
 - 2.6 – 4.6% at 30 days
 - 7.4 – 10.3% at 12 months
- Triple therapy seems to have an acceptable risk–benefit ratio provided it is kept short (e.g. 4 weeks) and the bleeding risk is low

Table 11 Antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	Elective	Bare-metal	<u>1 month</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin \leq 100 mg/day + clopidogrel 75 mg/day <u>Lifelong</u> : VKA (INR 2.0–3.0) alone
	Elective	Drug-eluting	<u>3 (-olimus^a group) to 6 (paclitaxel) months</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin \leq 100 mg/day + clopidogrel 75 mg/day <u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) <u>Lifelong</u> : VKA (INR 2.0–3.0) alone
	ACS	Bare-metal/ drug-eluting	<u>6 months</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin \leq 100 mg/day + clopidogrel 75 mg/day <u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) <u>Lifelong</u> : VKA (INR 2.0–3.0) alone
High (e.g. HAS-BLED score \geq 3)	Elective	Bare-metal ^c	<u>2–4 weeks</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin \leq 100 mg/day + clopidogrel 75 mg/day <u>Lifelong</u> : VKA (INR 2.0–3.0) alone
	ACS	Bare-metal ^c	<u>4 weeks</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin \leq 100 mg/day + clopidogrel 75 mg/day <u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) <u>Lifelong</u> : VKA (INR 2.0–3.0) alone

ACS = acute coronary syndrome; AF = atrial fibrillation; INR = international normalized ratio; VKA = vitamin K antagonist.

Gastric protection with a proton pump inhibitor (PPI) should be considered where necessary.

^aSirolimus, everolimus, and tacrolimus.

^bCombination of VKA (INR 2.0–3.0)+aspirin \leq 100 mg/day (with PPI, if indicated) may be considered as an alternative.

^cDrug-eluting stents should be avoided as far as possible, but, if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary.

Adapted from Lip et al.⁶¹

Triple Therapy: Strategies

- Avoid DES where possible
- 6 months triple Rx for ACS with low bleeding risk
- 4 weeks triple Rx for ACS with high bleeding risk
- Up to 12 months double Rx (VKA + clopidogrel) post ACS or with DES

Questions and Comments

