Antiplatelet Therapy

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Epidemiology: Coronary Heart Disease

- 15.4 million Americans have CHD (6.4% of Americans age ≥ 20 years)
  - Prevalence is estimated to be ≈ 18% by 2030
- Estimated direct and indirect cost of CHD in 2010 was $204.4 billion
- CHD is the leading cause of death in the US (~ 1 in every 6 deaths)

Go AS, et al. *Circulation* 2013 **DOI: 10.1161/01.cir.0000441139.02102.80**;128.

AHA/ACCF Guideline

AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update

A Guideline From the American Heart Association and American College of Cardiology Foundation

Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association

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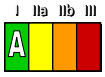
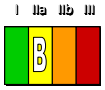
Smith S et al. *Circulation.* 2011;124:2458-2473

AHA/ACCF Aspirin Recommendations
(Secondary Prevention)



Start and continue indefinitely aspirin 75 to 162 mg/d in all patients unless contraindicated

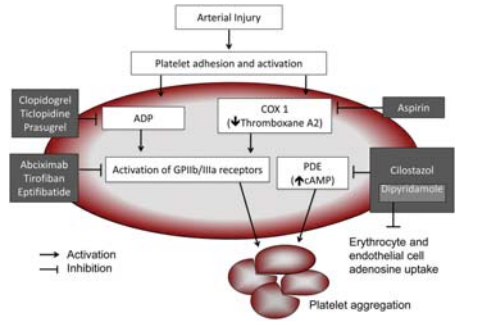
For patients undergoing CABG, aspirin (100 to 325 mg/d) should be started within 6 hours after surgery to reduce saphenous vein graft closure



In post-PCI-stented patients, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses.

Smith SC Jr., et al. *Circulation* 2011;124:2458-2473.

Platelet aggregation and antiplatelet medication interactions
Aspirin inhibits cyclooxygenase (COX) leading to a decrease in thromboxane A2.



Lazzaro M A , and Zaidat O O Neurology 2012;78:501-506

AMERICAN ACADEMY OF NEUROLOGY

$P2Y_{12}$ Inhibitors

- Effectively inhibit ADP-induced platelet aggregation by selectively and irreversibly blocking the $P2Y_{12}$ receptor.
- $P2Y_{12}$ inhibitors and aspirin inhibit platelet aggregation through different pathways; therefore, combined antiplatelet therapy provides complementary and additive benefits compared to either agent alone.

$P2Y_{12}$ Receptor Inhibitor Recommendations

I IIa IIb III

B

Clopidogrel 75 mg/d for patients allergic or intolerant to aspirin.

I IIa IIb III

A

A $P2Y_{12}$ inhibitor (plus aspirin) for patients post ACS or post PCI with stent placement.

I IIa IIb III

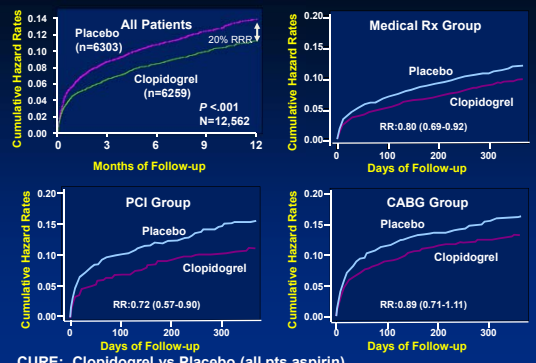
A

For patients receiving a stent during PCI for ACS, a $P2Y_{12}$ inhibitor should be given for at least 12 months:

- Clopidogrel 75 mg daily or
- Prasugrel 10 mg daily or
- Ticagrelor 90 mg twice daily

Smith SC Jr., et al. *Circulation* 2011;124:2458-2473.

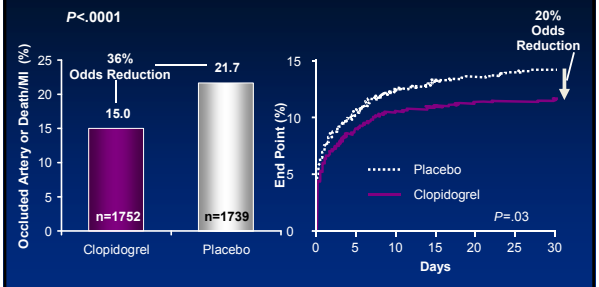
CURE: Clopidogrel in UA/NSTEMI
1º Outcome (CV death/MI/stroke) by Management Strategy



CURE: Clopidogrel vs Placebo (all pts aspirin)

Yusuf S, et al. *N Engl J Med*. 2001;345:494-502. Fox KAA, et al. *Circulation*. 2004;110:1202-1208.

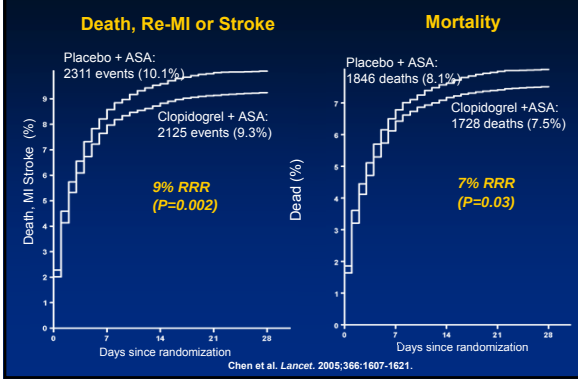
CLARITY-TIMI 28: Clopidogrel with Thrombolysis for STEMI
1º Endpoint: Occluded Artery (or D/MI)



All patients received aspirin.

Sabatine et al. *N Engl J Med*. 2005;352:1179-1189.

COMMIT: CLOPIDOGREL in 46,000 AMI Pts



Chen et al. *Lancet*. 2005;366:1607-1621.

CURE: Major Bleeding by Aspirin Dose Through Follow-up

Aspirin Dose	Placebo + Aspirin#	Clopidogrel + Aspirin#
75–100 mg	1.9%*	3.0%**
101–199 mg	2.8%*	3.4%**
200–325 mg	3.7%*	4.9%**

#, Other standard therapies were used as appropriate.

* P = 0.0001 for comparison of increasing ASA doses in Placebo Group;

** P = 0.0009 for comparison of increasing ASA doses in Clopidogrel group

Peters RJ et al. Circulation. 2003;108:1682-87.

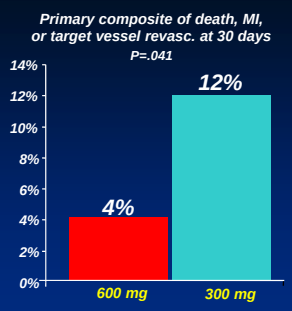
What dose of Clopidogrel? ARMYDA-2 Trial

255 patients with stable CAD or NSTEMI prior to PCI
13% received GP IIb/IIIa inhibitors
20% received drug-eluting stents

Randomized 4-8 Hours Pre-PCI

High Loading Dose of Clopidogrel 600 mg Pre-PCI

Standard Loading Dose of Clopidogrel 300 mg Pre-PCI



ARMYDA-2 = Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty.
Patti G, et al. Circulation. 2005;111:2099-2106.

CURRENT-OASIS 7: Clopidogrel Results

Patients with UA/NSTEMI or STEMI planned for early invasive strategy
(ie, intended for PCI as early as possible within 72 hours)

Randomize

Clopidogrel Standard-dose Group
Clopidogrel 300 mg (+ placebo) day 1 followed by 75 mg (+ placebo) from days 2 to 7; 75 mg from days 8 to 30

Clopidogrel High-dose Group
Clopidogrel 600 mg LD day 1 followed by 150 mg from days 2 to 7; 75 mg from days 8 to 30

	Standard	Double	HR (95% CI)	*P*-value
CV death/MI/Stroke				
Overall (N=25,086)	4.4	4.2	0.94 (0.83-1.06)	0.30
PCI (n=17,263)	4.5	3.9	0.86 (0.74-0.99)	0.039
No PCI (n=7823)	4.3	4.9	1.14 (0.92-1.40)	0.23

LD = loading dose.
CURRENT-OASIS 7 Investigators, et al. *N Engl J Med*. 2010;363:930-942.
Mehta SR, et al. *Lancet*. 2010;376:1233-1243.

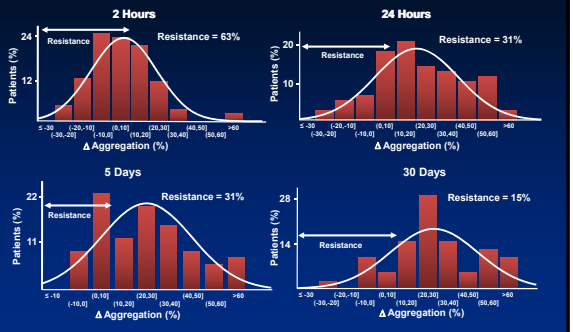
FDA Boxed Warning on Clopidogrel

3/12/2010 - The Boxed Warning in the drug label includes information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel. Poor metabolizers do not effectively convert clopidogrel to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers.

Accessed March 29, 2011 at:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm

The First Clopidogrel Resistance Study (300 mg): A Fingerprint of Clopidogrel Response Variability



Gurbel PA, et al. *Circulation*. 2003;107:2908-2913.

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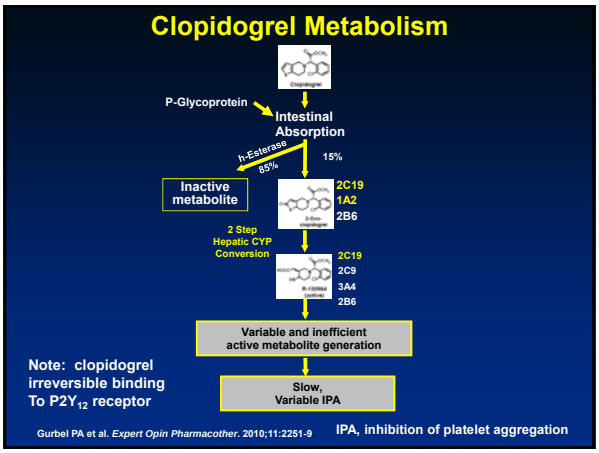
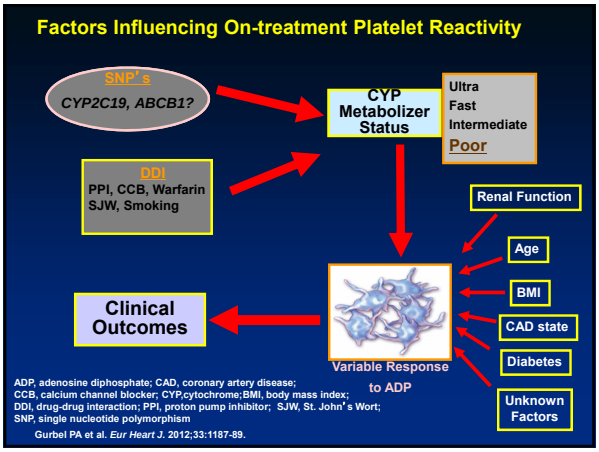




Genotype Testing/Platelet Function Testing

- Genetic test kits are available to identify the presence of ≥ 1 of the loss-of-function CYP2C19 alleles
  - Expensive
  - Not routinely covered by insurance
- No prospective studies showing the routine use of these tests coupled with modification of antiplatelet therapy improves clinical outcomes or reduces subsequent CV events
- Consider on a case-by-case basis, especially in patients who have recurrent ACS events despite ongoing therapy with clopidogrel

Jneid H et al, *Circulation* 2012;126:875-910.

Clopidogrel: in ACS

Who:	**UA/NSTEMI (Invasive and Conservative)** **STEMI (PCI, Fibrinolysis, Med Rx)**
Who not:	**Planned CABG,** **?2C19 known homozygous** **Active / very high risk for bleeding**
Where:	**Emergency Department**
When:	**Early and late – 1 year ?longer**
How:	**300 mg load (or 600 mg load pre-PCI).** **Platelet and genetic testing unproven.** **Use with PPI if GI bleed risk factors.**

Length of Maintenance Therapy

- At least 4 weeks of treatment with dual antiplatelet therapy after bare metal stent
- At least 12 months of treatment with dual antiplatelet therapy after drug eluting stent
- ↑ risk of recurrent CV events with premature discontinuation of $P2Y_{12}$ inhibitors
- Need to weigh bleeding risk in patients undergoing procedures/surgery

Clopidogrel Precaution

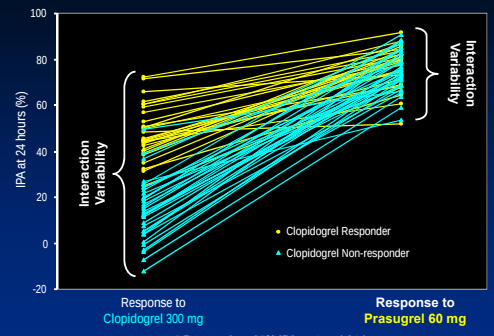
- CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole
  - Retrospective reports of adverse CV outcomes with combination
  - Conflicting data exists
  - The PPI omeprazole has been reported to significantly decrease platelet inhibition by clopidogrel
  - Patient education required with OTC products available

Prasugrel **Ticagrelor**

- More rapid onset and greater antiplatelet effect
  Lesser/no resistance
- No influence of gene polymorphism and major drug-drug interactions

Irreversible **Reversible binding**

Prasugrel Is Effective for Clopidogrel Nonresponders



* Responder ≥25% IPA at 4 and 24 hours

Brandt JT. *Am Heart J.* 2007;153:66e9.

IPA, inhibition of platelet aggregation

TRITON-TIMI 38 Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ n=13,600

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

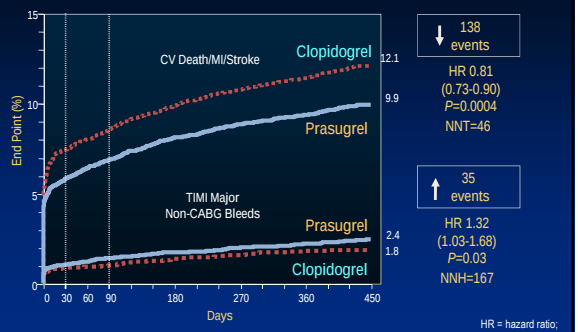
Median duration of therapy - 12 months

1º endpoint: CV death, MI, stroke
2º endpoints: CV death, MI, stroke, rehosp-rec isch
CV death, MI, UTVR

UTVR = urgent target vessel revascularization; NSTEMI = non-ST segment elevation MI

Wiviott SD et al. *Am Heart J.* 2006;152:627-635.

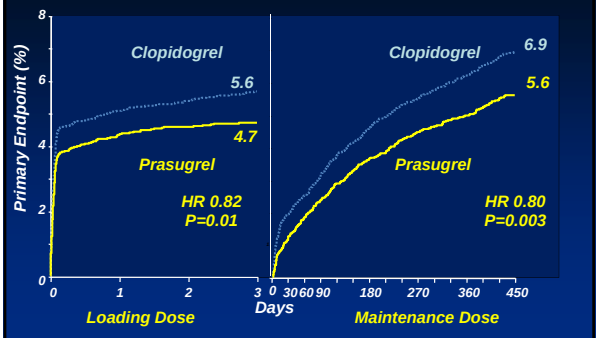
TRITON TIMI-38: Efficacy and Safety



HR = hazard ratio;
NNT = number needed to treat; NNH = number needed to harm

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

TRITON TIMI-38: Timing of Benefit *(Landmark Analysis)*



Wiviott SD et al. *NEJM* 2007;357:2001-15

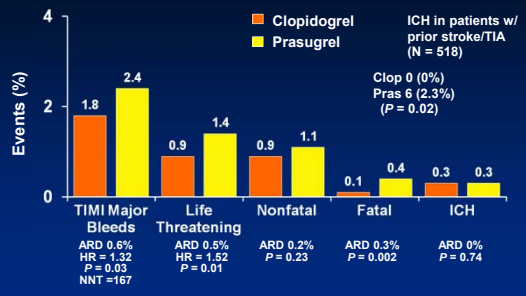
Triton TIMI-38: Major efficacy end points in overall cohort at 15 mo.

End Point	Pras (N=6813) no. of patients (%)	Clop (N=6795) no. of patients (%)	HR for Prasugrel (95% CI)	p value
CV Death, non-fatal MI or non-fatal stroke (1º end pt)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
CV Death	133 (2.1)	150 (2.4)	0.89 (0.70-1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67-0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71-1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78-1.16)	0.64
CV Death, nonfatal MI, or urgent TVR	652 (10.0)	798 (12.3)	0.81 (0.73-0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75-0.92)	<0.001
Urgent TVR	156 (2.5)	233 (3.7)	0.66 (0.54-0.81)	<0.001
CV Death, nonfatal MI, nonfatal stroke or rehosp for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76-0.92)	<0.001
Stent thrombosis ‡	68 (1.1)	142 (2.4)	0.48 (0.36-0.64)	<0.001

‡ Definite or Probable

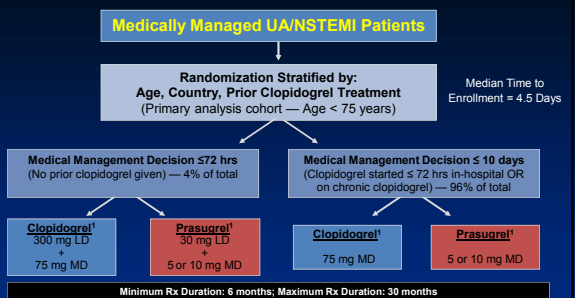
Wiviott et al. *New Engl J Med* 2007

TRITON TIMI-38: Bleeding Events



ICH = intracranial hemorrhage; ARD = absolute risk difference; TIA = transient ischemic attack.
Wiviott SD et al. *N Engl J Med.* 2007:357:2001-2015.

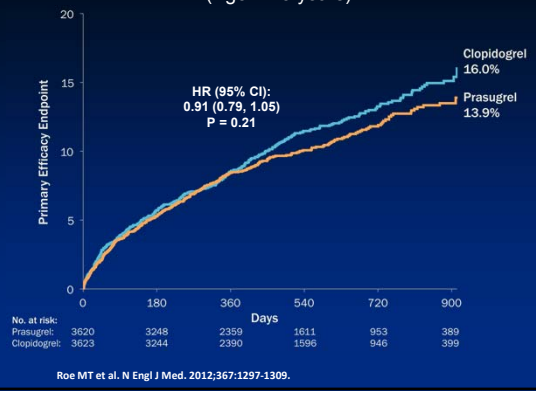
TRILOGY ACS Study Design



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;160:16-22.e1.

LD, loading dose; MD, maintenance dose

TRILOGY ACS: Primary Efficacy Endpoint to 30 Months
(Age < 75 years)



Roe MT et al. N Engl J Med. 2012;367:1297-1309.

Prasugrel Labeling

Prasugrel was approved for reducing thrombotic cardiovascular events, including stent thrombosis, in the following patients with acute coronary syndrome who will be managed with percutaneous coronary intervention (PCI): those with unstable angina or non-ST elevation myocardial infarction (NSTEMI) and those with ST-elevation MI (STEMI), when managed with either primary or delayed PCI.

Black Box Warning with Prasugrel

Prasugrel can cause significant, sometimes fatal, bleeding

Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke

In patients age 75 and older, prasugrel is generally not recommended because of the increased risk of intracranial and fatal bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI). In these situations, the drug's effect appears to be greater, and its use may be considered.

Additional risk factors for bleeding include:

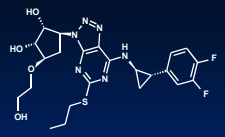
- **body weight < 60 kg**
- **propensity to bleed**
- **concomitant use of medications that increase the risk of bleeding**

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022307s003lbl.pdf

Summary: Prasugrel

- Prasugrel superior to clopidogrel in ACS undergoing PCI
- Prasugrel not superior to clopidogrel in medical management of ACS
- Prasugrel is administered initially with a single 60 mg oral loading dose (at time of ACS). Thereafter, treatment is continued with 10 mg orally once daily.
  - Consider lowering maintenance dose to 5 mg in patients < 60 kg.
- Contraindicated in prior TIA or stroke and active bleeding
- Generally not recommended in patients ≥ 75 years old
- Duration of dual oral antiplatelet therapy (DAPT) 1 year or more

Ticagrelor: an oral reversible $P2Y_{12}$ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP); not a thienopyridine

- Direct acting
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
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

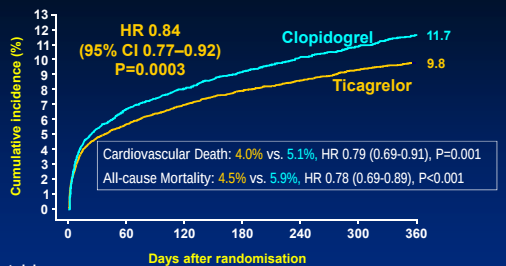
Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid; CV = cardiovascular

Wallentin L et al. *NEJM* . 2009;361:1045-57.

PLATO Primary efficacy endpoint: CV death, MI or stroke

18,624 Patients w/in 24 hrs of onset of ACS



Cardiovascular Death: 4.0% vs. 5.1%, HR 0.79 (0.69-0.91), P=0.001
All-cause Mortality: 4.5% vs. 5.9%, HR 0.78 (0.69-0.89), P<0.001

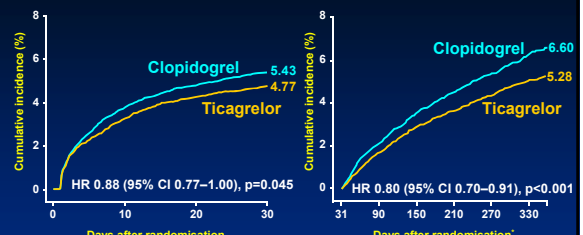
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

HR = hazard ratio; CI = confidence interval

Wallentin L, et al. *NEJM* 2009;361:1045-57; Wallentin 2009 ESC Presentation

Treating 54 pts with ticagrelor instead of with clopidogrel for 1 year will prevent one event of CV death, MI or stroke.

PLATO Primary efficacy endpoint over time (composite of CV death, MI or stroke)



No. at risk

Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

*Excludes patients with any primary event during the first 30 days

Wallentin L et al. *NEJM* 2009;361:1045-57.

PLATO: major efficacy endpoints

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Stent thrombosis (Definite or probable)	118 (2.2)	158 (2.9)	0.75 (0.59 – 0.95)	0.02
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

The percentages are K-M estimates of the rate of the endpoint at 12 months.

Wallentin L et al. *NEJM* .2009;361:1045-57

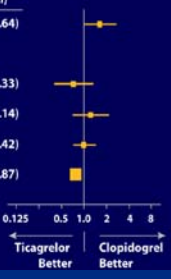
PLATO: Major Bleeding, Holter Monitoring and Other Related Events

Bleeding	Ticagrelor (n=9235)	Clopidogrel (n=9186)	*P*-value
Total Major — PLATO criteria, %	11.6	11.2	0.43
Total Major — TIMI criteria , %	7.9	7.7	0.57
Non-CABG Major — PLATO criteria, %	4.5	3.8	0.026
Non-CABG Major — TIMI criteria , %	2.8	2.2	0.025
Holter Monitoring at First Week	**Ticagrelor (n=1451)**	**Clopidogrel (n=1415)**	***P*-value**
Ventricular pauses ≥3 seconds, %	5.8	3.6	0.01
Ventricular pauses ≥5 seconds, %	2.0	1.2	0.10
All Patients	**Ticagrelor (n=9235)**	**Clopidogrel (n=9186)**	***P*-value***
Dyspnea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
Bradycardia-related Event, %			***P*-value**
Syncope	1.1	0.8	0.08
Bradycardia	4.4	4.0	0.21

**P*-values were calculated using Fischer's exact test.
Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

PLATO: Primary Efficacy Outcome US and Non-US and by ASA Dose

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



Mahaffey K et al. *Circulation.* 2011;124:544-54

Ticagrelor – FDA Label "Boxed Warning"

WARNING: BLEEDING RISK

- **Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start ticagrelor in patients planned to undergo urgent coronary bypass graft surgery (CABG). When possible, discontinue ticagrelor at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of ticagrelor (5.1).**
- **If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events (5.5).**

WARNING: Aspirin Dose and Ticagrelor Effectiveness

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=04020155

Summary: Ticagrelor

- Reduces major cardiovascular events (including cardiovascular mortality and all-cause mortality) in ACS patients managed invasively or medically.
- Ticagrelor is administered initially with 180 mg (two 90 mg tablets) as an oral loading dose (at time of ACS).
  Thereafter, treatment is continued with 90 mg TWICE DAILY
- Should be used with low dose aspirin (75-100 mg/day)
- Contraindicated with history of intracranial hemorrhage, active bleeding, and severe hepatic impairment
- Duration of dual oral antiplatelet therapy (DAPT) 1 year or more

Considerations When Selecting a $P2Y_{12}$ Inhibitor

- Clopidogrel → only generic agent
- Patient adherence → ticagrelor is a bid drug
- Black box warnings
- Possibility of poor metabolizers of clopidogrel (↑ CV events)
- Prasugrel → no history of TIA or stroke
- Ticagrelor → no history of ICH, need for low-dose aspirin

Need for Adherence

- REACH registry → Less than 50% of patients are fully adherent with secondary prevention medications; nonadherence is associated with worse outcomes at 4 years (CV death, MI, stroke).
  - At 1 year, 16% of patients had discontinued antiplatelet agents.
- Large observational cohort study of patients treated with DES → stent thrombosis occurred in 29% of patients in whom antiplatelet therapy was prematurely discontinued.
- PREMIER registry → mortality rate over 11 months of those who stopped thienopyridine therapy was 7.5% vs 0.7% in those who continued therapy (HR 9.0, P <0.001).
- Illness perceptions influence adherence to DAPT in patients with stable CAD

Kumbhani DJ et al, *Am J Med* 2013;126:693-700
Iakovou I et al., *JAMA* 2005;293:2126-2130
Spertus JA et al., *Circulation* 2006;113:2803-2809
Fennessy MM et al., *J Cardiovas Nurs* 2013;28:573-583

Critical Patient Education

- *Need for at least 12 months of dual antiplatelet therapy with DES*
- Thoroughly educate patients prior to discharge about why they need antiplatelet therapy and the risk of prematurely discontinuing therapy.
- Instruct patients to contact their cardiologist before stopping any antiplatelet therapy, even if instructed by another HCP.
- Advise patients to consider deferring elective procedures for which there is a significant risk of bleeding until completing an appropriate course of antiplatelet therapy.