ASHP 2010 SUMMER MEETING & EXHIBITION
June 6–9, 2010
Tampa Convention Center
Tampa, Florida

Controversies in Thrombosis Prevention: Update on Antiplatelet and Anticoagulant Therapies

Tuesday, June 8, 2010
8:00 a.m. – 10:00 a.m.

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Overview of New Antiplatelet and Anticoagulant Drugs

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June 8, 2010

Disclosures

The presenters for this continuing pharmacy education activity report no relevant financial relationships except:

- Robert Lee Page II - Member of speaker's bureau for Astra Zeneca

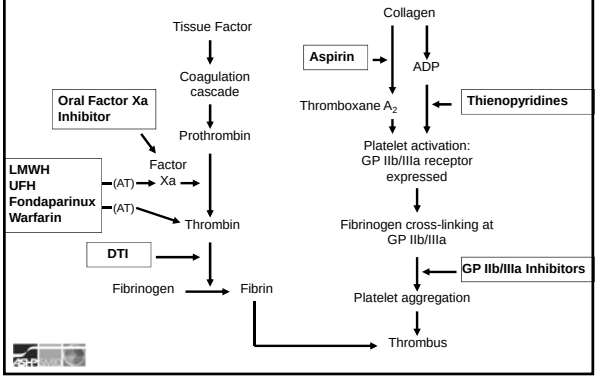
Learning Objectives

- Define the latest issues in antiplatelet and anticoagulation therapy.
- Recommend appropriate therapy using aspirin for the primary prevention of myocardial infarction (MI) in specified cases.
- Identify and correct complications involving clopidogrel interactions in specified cases.
- Identify potential roles in therapy for newer antiplatelet and anticoagulant therapies.

Antiplatelet Therapies

- Oral Antiplatelet Therapy
  - Aspirin
  - Thienopyridines (ADP receptor/P2Y12 inhibitors)
    - ticlopidine
    - clopidogrel
    - prasugrel
    - ticagrelor
- Intravenous Glycoprotein IIb/IIIa Inhibitors
  - abciximab
  - eptifibatide
  - tirofiban

Antithrombotic Therapies



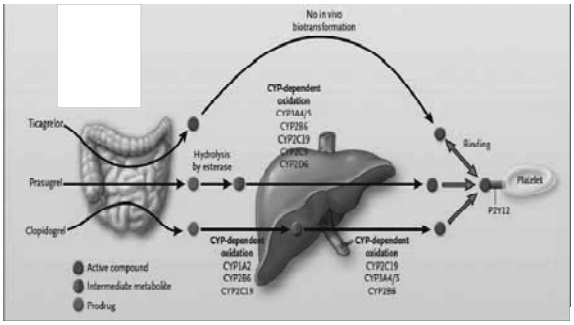
ADP Receptor Antagonists

Drug	Ticlopidine	Clopidogrel	Prasugrel	Ticagrelor
Bioavailability (%)	80-90	➢50	80-100	NA
Protein Binding (%)	98	94-98	NA	NA
Half-life (hours)	12.6	7-8	3.7	12
Metabolism	90% hepatic; no active metabolites	Hepatic active metabolites	Hepatic active metabolites; 70% renal	Orally active
Onset of antiaggregation	< 4 days	2 hours	0.5 hours	2 hours
Steady state of antiaggregation	8-11 days	3-7 days	3 days	2-3 days
FDA approval	Yes	Yes	Yes	Phase III
Reversibility	---	---	---	+

NA = not available

Thromb Haemost 2010;103:496-506.

Thienopyridine Biotransformation

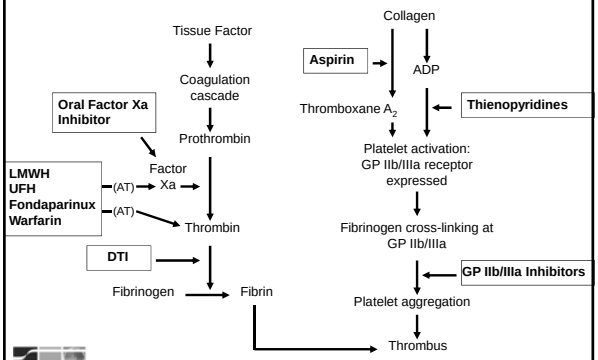


N Engl J Med 2009;361:1108-11.

Anticoagulant Therapies

- Oral Direct Thrombin Inhibitors
  - dabigatran
- Oral Direct Factor Xa Inhibtors
  - apixaban
  - rivaroxaban
- Vitamin K Antagonist
  - warfarin
- Heparin
  - UFH
  - LMWH
    - dalteparin
    - enoxaparin
- IV Direct Thrombin Inhibitors
  - hirudin
  - bilvalirudin
  - argatroban
- Pentasaccharides
  - fondaparinux

Antithrombotic Therapies



New Oral Anticoagulants

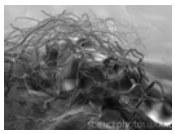
Drug	Rivaroxaban	Apixaban	Dabigatran
Target	Factor Xa	Factor Xa	Thrombin
Bioavailability (%)	90	66	7.2
Half-life (hours)	3.2-9.1	8-15	7.1-17
Metabolism	66% fecal; 33% renal	75% fecal; 25% renal	20% fecal; 80% renal
Elimination pathway	50% unchanged; 50% inactive metabolites	70% unchanged; 30% inactive metabolites	100% unchanged; active metabolites
Substrate of CYP enzymes	Yes (3A4, 2J2)	Yes (3A4)	No
FDA approval	No	No	No

CYP = cytochrome P450

Thromb Haemost 2010;103:572-85. Current Opinion in Hematology 2009;16:347-56.

Controversies in Thrombosis Prevention: Update on Antiplatelet and Anticoagulant Therapies

ACUTE MANAGEMENT



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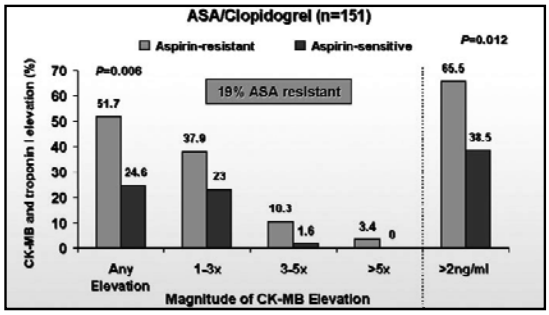
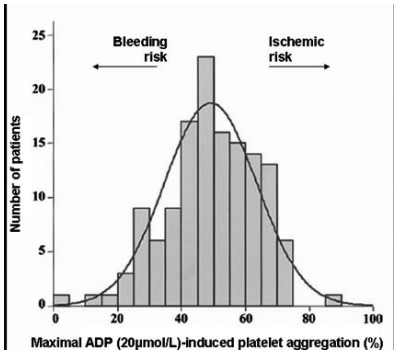
University of Colorado Denver, Schools of Pharmacy & Medicine

Aspirin Response



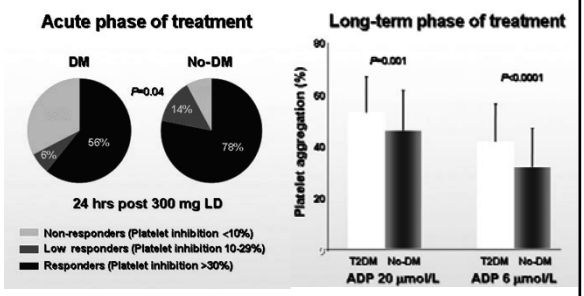
JACC 2004; 43(6): 1122-6.

Clopidogrel Response



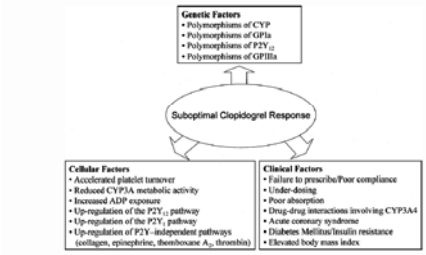
Modified from JACC 2007; 49(14): 1505-16.

Clopidogrel Response



JACC 2006; 48(2): 298-304.
Diabetes 2005; 54(8): 2430-35.

Clopidogrel Variability



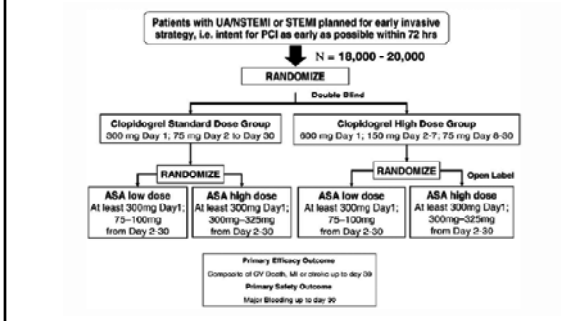
Modified from JACC 2007; 49(14): 1505-16.

Clinical Case

75 yo woman presents to ER with NSTEMI.
PHM: hypertension, dyslipidemia, diabetes, GI bleed
Meds: lisinopril 10 mg daily, atrovastatin 40 mg daily, glipizide 10 mg daily, aspirin 81 mg daily

Cardiology team tells you to load the patient with clopidogrel prior to PCI. What doses do you use?

CURRENT-OASIS 7 Trial



Am Heart J 2008; 156: 1080-1088

CURRENT-OASIS 7 Trial

Results of the aspirin dose comparison: Efficacy and bleeding

Measure	Aspirin 75-100 mg	Aspirin 300-325 mg	Hazard ratio (95% CI)
Cardiovascular death, MI, and stroke (n=25 087)	4.4	4.2	0.96 (0.85-1.08)
PCI cohort (n=17 232)	4.2	4.1	0.98 (0.84-1.13)
No PCI cohort (n=7855)	4.7	4.4	0.92 (0.75-1.14)
Stent thrombosis	2.1	1.9	0.91 (0.73-1.12)
TIMI major bleed	1.03	0.97	0.94 (0.73-1.21)
CURRENT major bleed	2.3	2.3	0.99 (0.84-1.17)
CURRENT severe bleed	1.7	1.7	1.00 (0.83-1.21)

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CURRENT-OASIS 7 Trial

Double vs standard dose of clopidogrel: Primary outcome and components

Measure	Standard clopidogrel therapy	Double clopidogrel therapy	Hazard ratio (95% CI)
Cardiovascular death, MI, and stroke, overall cohort (n=25 087)	4.4	4.2	0.95 (0.84-1.07)
PCI cohort (n=17 232)	4.5	3.9	0.85 (0.74-0.99)
No PCI cohort (n=7855)	4.2	4.9	1.17 (0.95-1.44)
MI, overall cohort	2.2	1.9	0.86 (0.73-1.03)
PCI cohort	2.6	2.0	0.78 (0.64-0.95)
No PCI cohort	1.4	1.7	1.25 (0.87-1.79)
Cardiovascular death, overall cohort	2.2	2.1	0.96 (0.81-1.14)
PCI cohort	1.9	1.9	0.96 (0.77-1.19)
No PCI cohort	2.8	2.7	0.96 (0.74-1.26)
Stroke, overall cohort	0.5	0.5	0.99 (0.70-1.39)
PCI cohort	0.4	0.4	0.88 (0.55-1.41)
No PCI cohort	0.8	0.9	1.11 (0.68-1.82)

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CURRENT-OASIS 7 Trial

Bleeding outcome and stent thrombosis in PCI population

Outcome	Standard clopidogrel therapy (n=8684)	Double clopidogrel therapy (n=8548)	Hazard ratio (95% CI)
Definite stent thrombosis	1.2	0.7	0.58 (0.42-0.79)
TIMI major bleeding	0.5	0.5	1.06 (0.70-1.61)
CURRENT major bleeding	1.1	1.6	1.44 (1.11-1.86)
CURRENT severe bleeding	0.8	1.1	1.39 (1.02-1.90)
Fatal bleeding	0.15	0.07	0.47 (0.18-1.23)
ICH	0.035	0.046	1.35 (0.30-6.04)
Red blood cell transfusion >2U	0.91	1.35	1.49 (1.11-1.98)
CABG-related major bleeding	0.1	0.1	1.69 (0.61-4.7)

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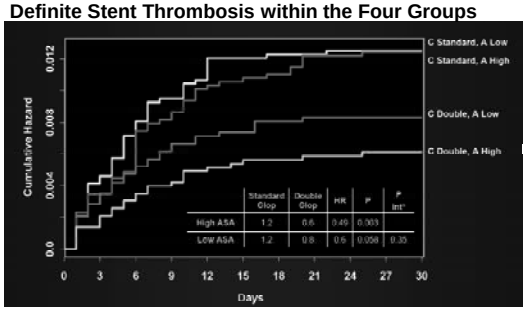
CURRENT-OASIS 7 Trial

Definite Stent Thrombosis within the Four Groups



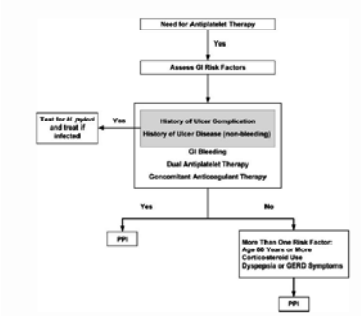
European Society of Cardiology 2009 Congress

Clinical Case

Our 75 year old woman has now undergone PCI with 2 drug-eluting stents. She is being discharged on the following:
metoprolol 25 mg po BID, aspirin 325 mg po daily, clopidogrel 75 mg daily, lisinopril 40 mg daily, glipizide 10mg BID, atorvastatin 80 mg daily.

BUT….you remember something about a controversy regarding PPIs-Clopidogrel…what do you do?

ACC-AHA-ACG Joint Statement
October 2008



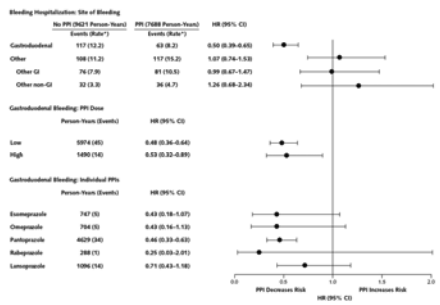
Modified from http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191087v1

ACC-AHA-ACG Joint Statement
October 2008

- Recommendation: PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury.
- Traditional doses of H2-receptor antagonists (H2RAs) do not prevent most NSAID-related gastric ulcers (although high doses may be better).

http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191087v1

Hospital Data: Bleeding

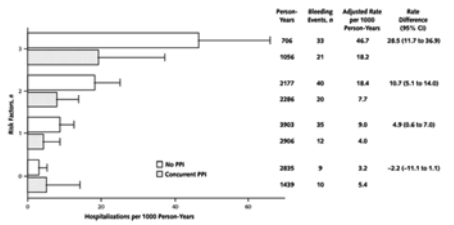


GI = gastrointestinal; HR = hazard ratio; PPI = proton-pump inhibitor.
* Rate is per 1000 person-years. Analysis by PPI dose and individual drug excludes person-time with concurrent use of multiple PPIs.

Modified from Ann Intern Med. 2010;152:337-345.

Hospital Data: Bleeding

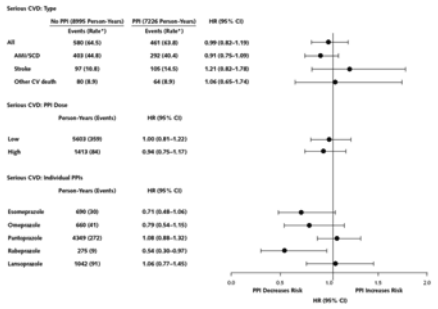
Risk for hospitalizations for gastroduodenal bleeding in current users of clopidogrel, according to concurrent use of PPIs."Rate Difference" is for nonusers of PPIs versus current users and is adjusted for potential confounders.



The individual risk factors are age 65 years or older, history of hospitalization for upper gastrointestinal disease or bleeding, recent use of anticoagulants, current use of other medications that increase bleeding risk (systemic corticosteroids, nonsteroidal anti-inflammatory drugs, or cyclooxygenase-2 inhibitors), and any hospital discharge in the past year. PPI = proton-pump inhibitor

Modified from Ann Intern Med. 2010;152:337-345.

Hospital data: CV Events



AMI = acute myocardial infarction; CV = cardiovascular; CVD = cardiovascular disease; HR = hazard ratio; PPI = proton-pump inhibitor; SCD = sudden cardiac death.
* Rate is per 1000 person-years. Analysis by PPI dose and individual drug excludes person-time with concurrent use of multiple PPIs.

Ann Intern Med. 2010;152:337-345.

BUT WAIT.....AGAIN

Clinical events in PCI patients as to whether they were discharged on a PPI or not

End point	PPI (%)	No PPI (%)
MACE	6.4	6.4
Death	2.8	2.5
MI	3.3	3.0
Death/MI	5.6	5.1
TVR	2.2	3.0
Stent thrombosis	1.8	1.5

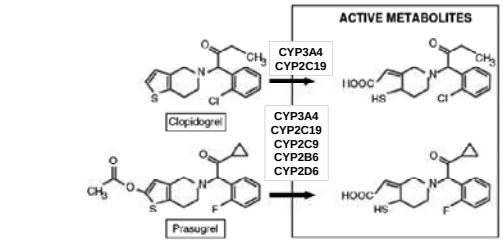
MACE=Major adverse cardiovascular events (death, MI, TVR, or stent thrombosis)
TVR=Target vessel revascularization

ACC 2010 Scientific Meeting. Atlanta, GA

Bottom Line

1. **Patients on PPIs should only receive a PPI for a solid indication. Consider antacids and H-2 blockers when appropriate.**
2. **Prasugrel…but be careful of patient characteristics.**
3. **Coming down the pipeline… ticagrelor**

Prasugrel



CYP 3A4 inhibitors
macrolides, diltiazem/verampamil, azoles, cyclosporine/tacrolimus grape fruit juice

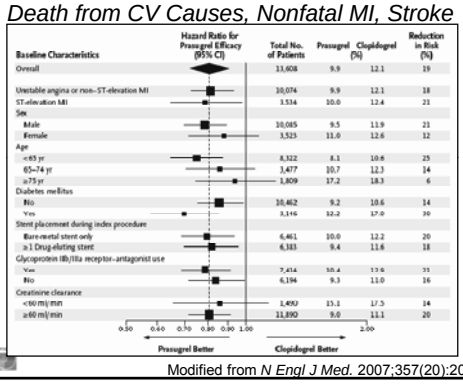
CYP 2C19 inhibitors
omeprazole, fluvoxamine, cimetidine

CYP 3A4 Inducers
rifampin, rifapentine, carbamazepine, barbiturates, St. John's Wort

Prasugrel

TRITON TIMI-38

Death from CV Causes, Nonfatal MI, Stroke



Modified from *N Engl J Med.* 2007;357(20):2001-2015.

Prasugrel

TRITON TIMI-38

Efficacy and Safety in Subgroups

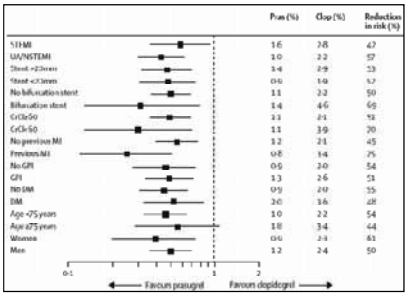
End Point	Prasugrel	Clopidogrel	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients/total no. (%)			
Age ≥75 yr, body weight <60 kg, or history of stroke or TIA				
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	198/1320 (16.1)	199/1347 (16.0)	1.02 (0.84–1.24)	0.83
Non–CABG-related TIMI major bleeding	52/1305 (4.3)	38/1328 (3.3)	1.42 (0.93–2.15)	0.10
Death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding	249/1320 (20.2)	239/1347 (19.0)	1.07 (0.90–1.28)	0.43

Modified from *N Engl J Med.* 2007;357(20):2001-2015.

Prasugrel

TRITON TIMI-38

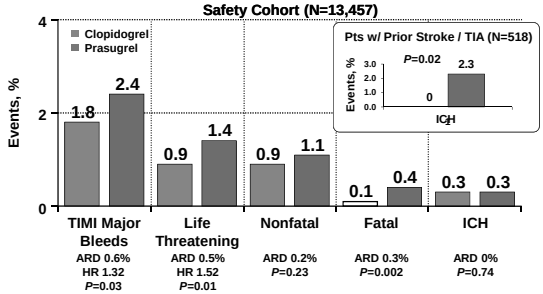
Subgroup Analysis on ARC Stent Thrombosis



Modified form The Lancet 2008; 371:1353-1363.

Prasugrel

TRITON TIMI-38



ARD = absolute risk difference; HR = hazard ratio; ICH = intracranial haemorrhage; NNH = number needed to harm; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction.
Adapted from Wiviott SD, et al. Presented at: American Heart Association Scientific Sessions 2007; 4-7 November, 2007; Orlando, FL.
Wiviott SD, et al. *N Engl J Med.* 2007;357:2001-2015.

Ticagrelor

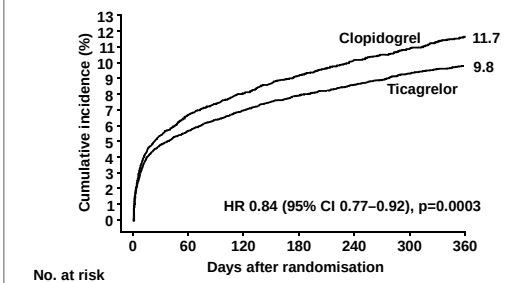
Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **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

Ticagrelor: PLATO

PLATO

Composite of CV death, MI or stroke

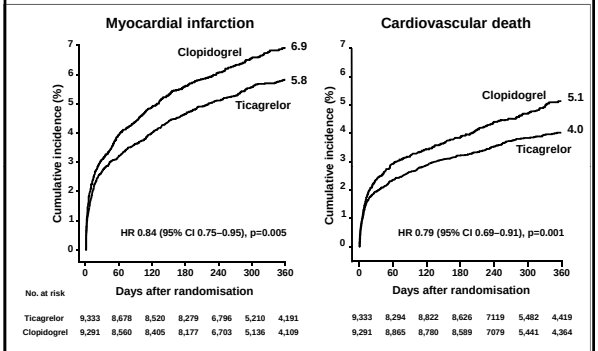


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

Ticagrelor: PLATO

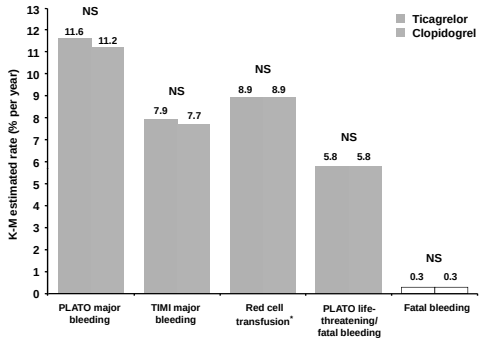
PLATO



No. at risk							
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
Ticagrelor	9,333	8,294	8,822	8,626	7119	5,482	4,419
Clopidogrel	9,291	8,865	8,780	8,589	7079	5,441	4,364

Ticagrelor: PLATO

PLATO



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15; *Proportion of patients (%); NS = not significant

Ticagrelor: PLATO

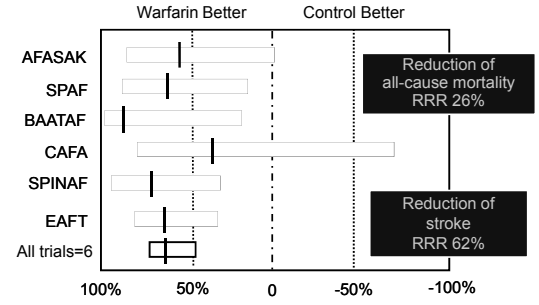
- **Based on 1,000 patients admitted to hospital for ACS, using ticagrelor instead of clopidogrel for 12 months resulted in**
  - **14 fewer deaths**
  - **11 fewer myocardial infarctions**
  - **6–8 fewer cases with stent thrombosis**
  - **No increase in bleedings requiring transfusion**
  - **9 patients may switch to thienopyridine treatment because of reversible symptoms of dyspnoea**
- **Treating 54 patients with ticagrelor instead of with clopidogrel for one year will prevent one event of CV death, MI or stroke**

Clinical Case

Our 70 year old woman has now undergone PCI with 2 drug-eluting stents. She is being discharged on the following:
metoprolol 25 mg po BID, aspirin 325 mg po daily, clopidogrel 75 mg daily, lisinopril 40 mg daily, esomeprazole 20 mg daily, glipizide 10mg BID, atorvastatin 80 mg daily.

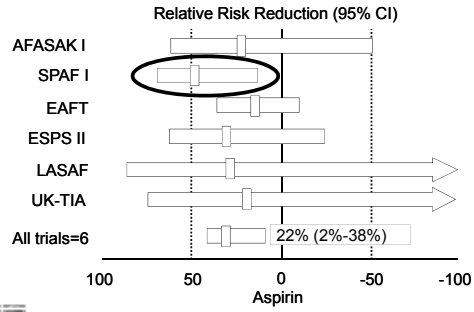
Now our patient has developed atrial fibrillation. It is decided that to rate control this patient but what about anticoagulation…our patient doesn't want to take "rat poison."

Anticoagulation in AF
Stroke Risk Reductions



Ann Intern Med. 1999;131:492-501.

Aspirin vs Placebo
Reduction of Risk of Thromboembolism in AF



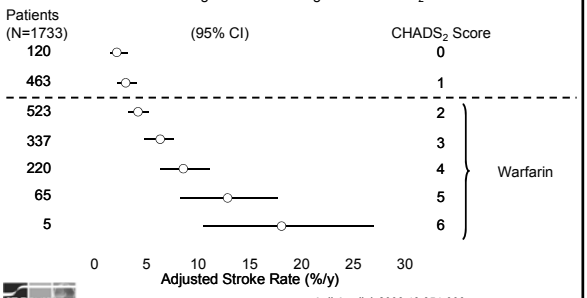
Ann Intern Med. 1999;131:492-501.

$CHADS_2$ Risk Stratification Scheme

Risk Factors	Score
C Recent congestive heart failure	1
H Hypertension	1
A Age ≥75 years	1
D Diabetes mellitus	1
S_2 History of stroke or transient ischemic attack (TIA)	2

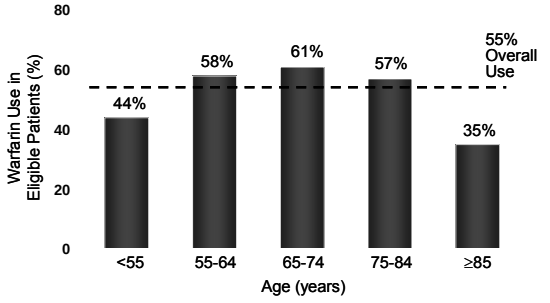
J Am Coll Cardiol. 2004;43:929-935.

$CHADS_2$ Risk Criteria for Stroke in Nonvalvular AF
Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the $CHADS_2$ Index



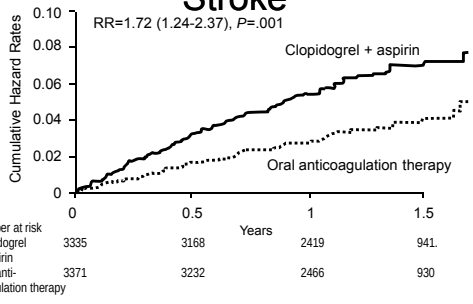
J Am Coll Cardiol. 2006;48:854-906.

Warfarin for Atrial Fibrillation
Limitations Lead to Under-treatment



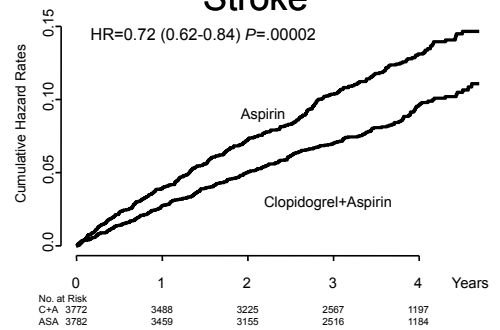
. *Ann Intern Med* 1999;131:927.

ACTIVE-W: Cumulative Risk of Stroke



*ACTIVE=Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events.
Primary outcome: stroke, systemic embolus, MI, vascular death.
Clopidogrel + aspirin=5.6% risk/year vs warfarin=3.93% risk/year.
Lancet. 2006;367:1903-1912.

ACTIVE-A: Cumulative Risk of Stroke



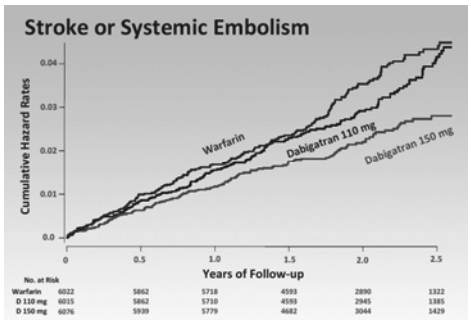
New England J Med. 2009;360:2066-2078.

Clinical Case

Our 70 year old woman has now undergone PCI with 2 drug-eluting stents. She is being discharged on the following:
metoprolol 25 mg po BID, aspirin 325 mg po daily, clopidogrel 75 mg daily, lisinopril 40 mg daily, glipizide 10mg BID, atorvastatin 80 mg daily.

The medical team wants to know what are the newest agents to replace warfarin.

RELY: Dabigatran



Modified from *NEJM* 2009;361:1139-51.

ARISTOTLE: Apixaban

Atrial fibrillation with at least 1 additional risk factor for stroke

Randomize
Double blind
(N = 15 000)

- Age ≥75 years
- Prior stroke, TIA, or SE
- CHF or LVEF ≤40%
- Diabetes mellitus
- Hypertension

Apixaban 5 mg oral, b.i.d.
+
Warfarin placebo

Apixaban placebo, b.i.d.
+
Warfarin (target INR 2-3)

Warfarin/warfarin placebo adjusted INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke and systemic embolism

Other outcomes: death, MI, bleeding
Stratified by warfarin-naïve status

448 events over anticipated 2 year median followup;
>90% power to show non-inferiority
(apixaban vs warfarin upper bound of 95% CI <1.38)

http://clinicaltrials.gov/ct2/show/NCT00412984 *Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation

ROCKETAF: Rivaroxaban

AF

Risk Factors (≥2)
- Age ≥75 years
- CHF
- Diabetes mellitus
- Hypertension OR
- Prior stroke, TIA, or SE

Randomized
Double blind/Double dummy
(N ~ 14000)

rivaroxaban
20 mg daily

warfarin
(target INR: 2.5;
2-3 inclusive)

Monthly monitoring and adherence to standard of care guidelines

Primary outcome: stroke and non-CNS systemic embolism
Statistics: non-inferiority, >95% power, 2.3% warfarin event rate

*Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

http://clinicaltrials.gov/ct2/show/NCT00403767?term=Rivaroxaban+Once+daily+oral&rank=1

Controversies in Thrombosis Prevention: Update on Antiplatelet and Anticoagulant Therapies

Tuesday, June 8, 2010
8:00 a.m. – 10:00 a.m.

Chronic Anticoagulation and Antiplatelet Pharmacotherapy

Joel C. Marrs, PharmD, BCPS, CLS
Assistant Professor
University of Colorado
June 8, 2010

Learning Objectives

- Define the latest issues in antiplatelet and anticoagulation therapy.
- Recommend appropriate therapy using aspirin for the primary prevention of myocardial infarction (MI) in specified cases.
- Identify and correct complications involving clopidogrel interactions in specified cases.
- Identify potential roles in therapy for newer antiplatelet and anticoagulant therapies.

Chronic Anticoagulation (Atrial Fibrillation)

- Why do we need an alternative to warfarin?
- What do the guidelines tell us?
- Do we have any data on new oral anticoagulants in atrial fibrillation yet?
- What is the data on pharmacist run anticoagulation clinics?

Vignette

HPI: TF is a 70 yof who is presenting to clinic for a follow-up visit to get her INR checked. She is frustrated by needing to come into clinic every 2-3 weeks since last being hospitalized 3 months ago to have her INR checked. She wants to go off of the warfarin because of the monitoring.

PMH: STEMI (2 stents placed 3 month ago)
Atrial Fibrillation (chronic)
Hypertension
Dyslipidemia

Social Hx: (-) tobacco; (-) ETOH

Vignette

Current medications include: **All: NKDA**
metoprolol tartrate 50 mg po bid
warfarin 5mg MWF, 7.5 mg all other days
simvastatin 40mg po qhs
lisinopril 20 mg po daily
aspirin 81 mg po daily
clopidogrel 75 mg po daily

Vitals/Labs today at clinic are as follows:
BP 130/85, HR 70, RR 25, Ht 5'7", Wt 150 lbs
INR = 2.2

Questions

Do the CHEST guidelines indicate this patient for chronic warfarin therapy?

What is the patients' CHADS2 Score?

Limitations to Vitamin K Antagonists

- Slow onset and offset of action
- Narrow therapeutic index
- Variable and unpredictable anticoagulation effects due to
  - Genetic polymorphisms of CYP P450 2C9 and VKORC1* genes
  - Multiple drug and food interactions
  - Concurrent disease states
- Need for monitoring of anticoagulant effects and dose adjustments

* Vitamin K epoxide reductase complex subunit 1 (VKORC1)

Seminars in Thrombosis and Hemostasis 2009;35:515-24.

ACCP 2008 Recommendations for Stroke Prevention (CHEST)

Risk Factors	Therapy
Any high risk factor or ≥2 moderate risk factors	Warfarin (INR 2-3 or 2.5-3.5 if mechanical valve) (1A)
One moderate risk factor	Warfarin (INR 2-3) (1A) *or* ASA 75 to 325mg QD (1B)
No Risk factors and age ≤75	ASA 75 to 325 mg QD (1B)

Risk Factors per CHADS2 Score

Chest 2008;133;546-592 *J Am Coll Cardiol.* 2004;43:929-935.

Trial Data (New Anticoagulants)

- Dabigatran
  - RE-LY (completed)
- Apixaban
  - ARISTOTLE (ongoing)
  - AVERROES (ongoing)
- Rivaroxaban
  - ROCKETAF (ongoing)
  - Pending FDA approval for prophylaxis of DVT/PE in patients undergoing hip- or knee-replacement surgery (declined approval in May 2009 pending further evaluation)

Am Heart J 2010;159:340-347. Am Heart J 2010;159:331-9.
Am Heart J 2010;159:348-353. N Engl J Med 2009;361:1139-51.

Oral Anticoagulants

Drug	Warfarin	Rivaroxaban	Apixaban	Dabigatran
Target	Vitamin K epoxide reductase	Factor Xa	Factor Xa	Thrombin
Half-life (hours)	40	3.2-9.1	8-15	7.1-17
Monitoring	INR-adjusted	Not needed	Not needed	Not needed
Administration	Once daily	Once daily	Once-twice daily	Once-twice daily
Metabolism	CYP450	66% fecal; 33% renal	75% fecal; 25% renal	20% fecal; 80% renal
Antidote or treatment of bleeding	Vit K + FFP, APCC, or recombinant FVIIa	Recombinant Factor Xa derivative, APCC, recombinant FVIIa	Recombinant Factor Xa derivative	No antidote
Assay	PT/INR	Antifactor Xa, PiCT, HepTest	Antifactor Xa	Ecarin Clotting time
Drug Interactions	CYP 2C9, 1A2, 3A4	CYP 3A4 Inhibitor	CYP 3A4 Inhibitor	PPI decrease absorption

Current Opinion in Hematology 2009;16:347-56.

Pharmacist Run Anticoagulation Clinical Data

Measures of Anticoagulation Control

Measure	Usual Care Model	Nurse Model	Pharmacist Model
INR time in range (%)*	57.4	71.8	83.6
INR values in range (%)*	49.4	67.3	74.9
INR > 5.0 (%)*	2.9	2.0	1.2
Hospitalizations			
Rate (#/100)*	13.9	12.3	5.4
Relative Risk (95% CI)†	2.59 (1.29-5.18)	2.29 (1.23-4.25)	----
ED visits			
Rate (#/100)*	5.6	5.6	1.2
Relative Risk (95% CI)†	4.40 (1.24-15.59)	4.45 (1.42-13.98)	----

* $p < 0.05$ for all comparisons vs pharmacist † $p < 0.01$ for all comparisons vs. pharmacists

Pharmacotherapy 2010;30:327-338.

Pharmacist Run Anticoagulation Comparison of Previous Trials

Measures of Anticoagulation Control		
Trial	Usual Care Model	Pharmacist Model
Hospitalization Rate*		
Chamberlain MA, et al	19.7	4.7
Chiquette E, et al.	19.0	5.0
Rudd KM, et al.	13.9	5.4
ED visits Rate*		
Chamberlain MA, et al	NR	NR
Chiquette E, et al.	22.0	6.0
Rudd KM, et al.	5.6	1.2

* number/100 NR = not reported

Arch Intern Med 1998;158:1641-7.
Pharmacotherapy 2010;30:327-338. J Am Board Fam Pract 2001;14:16-21.

Aspirin for Primary Prevention

- What does the trial data tell us?
- Is there a difference in men versus women?
- What are the consensus guideline recommendations?

Vignette

HPI: TF is a 60 yof who is in clinic today for a yearly check up. She reports taking her medications as prescribed and tries to exercise most days of the week which is usually walking 30-45 minutes.

PMH: Hypertension
Dyslipidemia
Social Hx: (+) tobacco (1ppd x 35 years); (-) ETOH
Current medications include: **All:** NKDA
HCTZ 25 mg po daily
atorvastatin 10mg po qhs
lisinopril 5 mg po daily
Vitals/Labs today at ED are as follows:
BP 135/90, HR 80, RR 25, Ht 5'5", Wt 140 lbs
TC 170, LDL-C 120, HDL-C 45, TG 130

Questions

What do you think this patients Framingham CHD Risk Score is?

What is this patients Framingham Stroke Risk Score?

Should this patient be taking aspirin daily?

Primary Prevention Trials

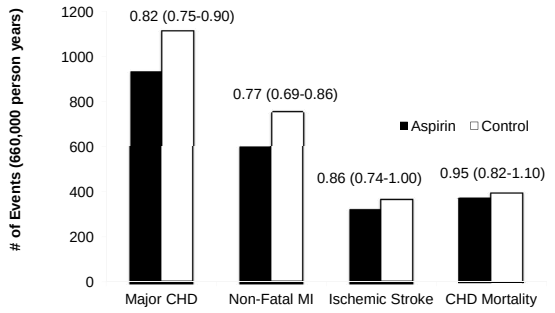
	BMD	PHS	TPT	HOT	PPP	WHI
Year	1988	1989	1998	1998	2001	2005
Duration (yrs)	5.8	5	6.8	3.8	3.6	10.1
Patients	5,139	22,071	2,540	18,798	4,495	39,876
Dosage	500 mg daily	325 mg QOD	75 mg daily	75 mg daily	100 mg daily	100 mg QOD
Control	none	Placebo	Placebo	Placebo	none	Placebo
Patients	Male physicians	Male physicians	Men with high CV risk	Men & women with hypertension	Men & women with ≥ 2 major CV risk factors	Apparently healthy women; health care professionals
Age (yrs)	<60 yrs, 46.9%; 60–69 yrs, 39.3%; 70–79 yrs, 13.9%	Mean 53 (40–84)	Mean 57.5 (45–69)	Mean 61.5 (50–80)	<60 yrs, 29%; 60–69 yrs, 45%; 70–79 yrs, 24%	Mean 54.6 45-54 yrs, 60%; 55–64 yrs, 30%; ≥65 yrs, 10%
Quality	Fair	Good	Good	Good	Fair	Good

Lancet 2009;373:1849-60.

FDA Rulings on Aspirin

- December 8, 2003
  - The FDA's Cardiovascular and Renal Drug Advisory Committee votes not to approve aspirin for the primary prevention of myocardial infarction (MI).
- The committee voted overwhelmingly against the petition sought by Bayer Corp
  - Petition: To approve ASA for the reduction of risk of a first MI in moderate risk patients, those with a 10 year CHD risk of < 20%
  - Voting
    - 11 against, 3 for approval
- Despite the existing data (5 major trials at the time), the committee felt the evidence supporting the extended label for ASA was inconsistent at best or lacking at worst.

Antithrombotic Trialists' Collaboration



Lancet 2009;373:1849-60.

Meta-Analysis Aspirin for Primary Prevention (Men vs. Women)

Outcome		Percentage of Patients [Odds Ratio [95% CI)]	
		Men	Women
Benefits	CV Events	4.47% vs. 4.82% 0.86 (0.78-0.94)	2.35% vs. 2.65% 0.88 (0.79-0.99)
	Myocardial Infarction	1.86% vs. 2.76% 0.68 (0.54-0.86)	0.92% vs. 0.91% 1.01 (0.84-1.21)
	Ischemic Stroke	1.84% vs. 1.61% 1.00 (0.72-1.41)	0.84% vs. 1.08% 0.76 (0.63-0.93)
	CV Mortality	1.85% vs. 1.66% 0.99 (0.86-1.14)	0.69% vs. 0.73% 0.90 (0.64-1.28)
	All-cause Mortality	4.00% vs. 3.94% 0.93 (0.85-1.03)	2.89% vs. 3.02% 0.94 (0.74-1.19)
Risks	Major Bleeding	0.81% vs. 0.48% 1.72 (1.35-2.20)	0.71% vs. 0.46% 1.68 (1.13-2.52)

JAMA 2006;295:306-13.

Consensus Guidelines

Organization	Population	Dose (mg/day)
AHA (primary)	10-yr CHD Risk ≥ 10%	75-160
AHA (secondary)	All patients w/o contraindications	75-162
ADA (DM only)	10-yr CHD Risk ≥ 10% or Men > 50 or women > 60 with 1 major CV Risk Factor* All patients with history of CVD	75-162
USPSTF	see table on next page	75-162.5
ACCP	10-yr CHD Risk ≥ 10%	75-100
ASHP	Possibly for 10-yr CHD Risk ≥ 6%; Yes for 10-yr CHD Risk ≥ 10%	75-162

*Major CV Risk Factors include: family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria

USPSTF Recommendations

Risk Level at Which CVD Events Prevented Exceeds GI Harms			
Men		Women	
Age	10 year CHD Risk	Age	10 year Stroke Risk
45-59	≥ 4%	45-59	≥ 3%
60-69	≥ 9%	60-69	≥ 8%
70-79	≥ 12%	70-79	≥ 11%

Ann Intern Med. 2009;150:396-404.

Recent Trials

- Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial
  - Low dose ASA as primary prevention did not reduce the risk of cardiovascular events in T2DM
- Prevention and Progression of Arterial Disease and Diabetes (POPADAD)
  - Low dose ASA no CV event benefit as primary prevention in patients with asymptomatic PAD and Diabetes
- Aspirin for Asymptomatic Atherosclerosis (AAA) trial
  - Low dose ASA no reduction in vascular events in asymptomatic subjects with a low ankle/brachial index (ABI)

JAMA. 2008;300(18):2134-2141 BMJ 2008;337:a1840 JAMA. 2010;303:841-848.

Primary Prevention Meta-analysis

	RR, serious vascular events (95% CI)	RR, extracranial bleeding (95% CI)
ATTC (6 trials)*	0.88 (0.82-0.94)	1.54 (1.30-1.83)
ATTC + JPAD, POPADAD, AAA	0.90 (0.85-0.96)	1.47 (1.26-1.71)

***The 2009 ATTC meta-analysis combined patient-level data from the British Doctors Study, the US Physicians Health Study, the Thrombosis Prevention Trial, Hypertension Optimal Trial (HOT), the Primary Prevention Project, and the Women's Health Study**

Das J. American College of Cardiology 2010 Scientific Sessions; March 14-16, 2010; Atlanta, GA.

Clopidogrel/PPI Interaction

- Does a drug interaction exist?
- What about pharmacogenomic issues?
- What has the data shown us?
- How do we manage in the outpatient setting?

Vignette

HPI: TF is a 70 yof who is presenting to clinic for a follow-up visit to get her INR checked. She is frustrated by needing to come into clinic every 2-3 weeks since last being hospitalized 3 months ago to have her INR checked. She wants to go off of the warfarin because of the monitoring.

PMH: STEMI (2 stents placed 3 month ago)
Atrial Fibrillation (chronic)
Hypertension
Dyslipidemia

Social Hx: (-) tobacco; (-) ETOH

Vignette

Current medications include: **All: NKDA**

metoprolol tartrate 50 mg po bid
warfarin 5mg MWF, 7.5 mg all other days
simvastatin 40mg po qhs
lisinopril 20 mg po daily
aspirin 81 mg po daily
clopidogrel 75 mg po daily

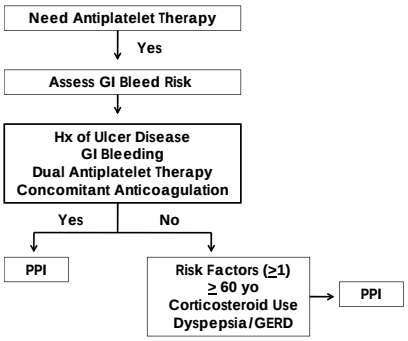
Vitals/Labs today at clinic are as follows:
BP 130/85, HR 70, RR 25, Ht 5'7", Wt 150 lbs
INR = 2.2

Questions

Should this patient be on a proton pump inhibitor? Are specific PPIs preferred?

Is an H2 Blocker an option for this patient?

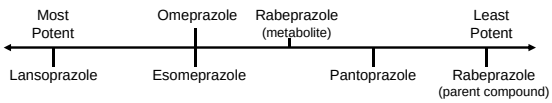
Algorithm Assessing the Need for PPI



J Am Coll Cardiol 2008;52:1502-17.

Drug Interaction

- Clopidogrel is a prodrug and must be metabolized by the cytochrome P450 isoenzymes CYP3A5 and CYP2C19 to active metabolites
- PPIs can competitively inhibit CYP2C19



- Reduction of active metabolites can decrease the antiplatelet effect of clopidogrel
- The antiplatelet effect of clopidogrel can be affected by polymorphisms in CYP2C19

N Engl J Med. 2009;360:363-75. Am Heart J. 2009;157:148e1-e5.
CMAJ. 2009;180:713-8. Drug Metab Dispos 2004;32:821-7.

New FDA Boxed Warning

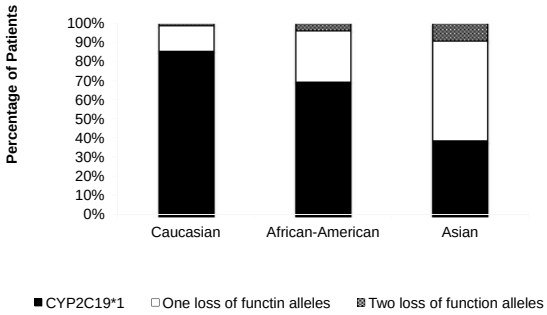
Warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel. Poor metabolizers do not effectively convert clopidogrel to its active form in the body.

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.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforpatientsandProviders/ucm203888.htm

CYP2C19 Genotype Frequencies by Race



Clin Pharmacokinet 2002;41:913–58. Annu Rev Pharmacol Toxicol 2001;41:815–50.

Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated with Aspirin

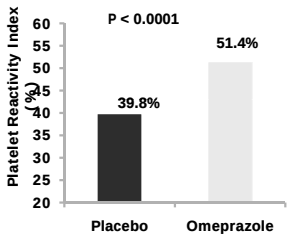
Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, Mansourati J, Mottier D, Abgrall JF, Boschat J, for the OCLA investigators*

Omeprazole Clopidogrel Aspirin (OCLA) Study

J Am Coll Cardiol 2008;51:256-60.

OCLA

- Treatment Arms:
  - Omeprazole 20 mg daily
  - Placebo
- Eligible patients:
  - Elective PCI w/Stent
- Exclusion Criteria
  - Previous Tx clopidogrel
  - Previous Tx PPI
  - Hx of thrombocytopenia
  - Liver disease
  - Hx GI ulcer
- Primary Endpoint (7 days):
  - Platelet Reactivity Index (PRI)



PRI: Platelet Reactivity Index as measured by vasodilator stimulated phosphoprotein (VASP)

J Am Coll Cardiol 2008;51:256-60.

Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome

Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS

JAMA 2009;301:937-44.

Adverse Outcomes Following Hospitalization for ACS

Outcome	Clopidogrel without PPI (N =2961)	Clopidogrel with PPI (N =5244)	OR (95%CI)	Adj OR (95%CI)
Primary		%		
Death or rehospitalization for ACS	20.8	29.8	1.62 (1.45-1.80)	**1.25 (1.11-1.41)**
Secondary				
Rehospitalization for ACS	6.9	14.6	2.29 (1.95-2.69)	1.86 (1.57-2.20)
Revascularization	11.9	15.5	1.36 (1.19-1.55)	1.49 (1.30-1.71)
All-cause Mortality	16.6	19.9	1.24 (1.10-1.40)	0.91 (0.80-1.05)

ACS = Acute Coronary Syndrome; PPI = proton pump inhibitor; OR = odds ratio

JAMA 2009;301:937-44.

A population-based study of the drug interaction between proton pump inhibitors and clopidogrel

Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, Henry DA, Kopp A, Mamdani MM

CMAJ. 2009;180:713-8.

Association between PPI and Adverse Outcomes

Outcome	Cases (n/N)	Controls (n/N)	OR (95%CI)
Recurrent MI < 90 days			
Current	**194/734**	**424/2057**	**1.27 (1.03-1.57)**
Previous	**63/734**	**195/2057**	**0.86 (0.63-1.19)**
Remote	**17/734**	**68/2057**	**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**	**125/2057**	**1.02 (0.70-1.47)**
Other	**148/734**	**299/2057**	**1.40 (1.10-1.77)**
H2 Blocking agent	**37/734**	**106/2057**	**0.94 (0.63-1.40)**
Recurrent MI < 1 yr	**240/982**	**497/2626**	**1.23 (1.01-1.49)**
Death < 1 yr	**116/531**	**269/1407**	**0.89 (0.67-1.49)**

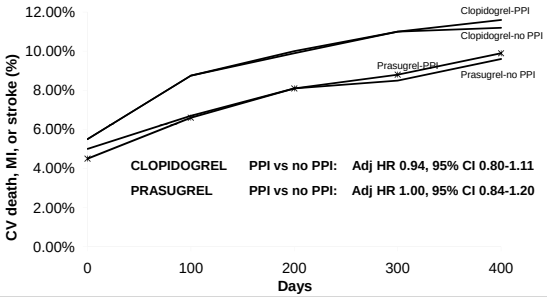
CMAJ. 2009;180:713-8.

Society of Cardiovascular Angiography and Interventions (SCAI) Statement

"SCAI urges health care providers who are treating post-stenting patients on dual-antiplatelet therapy to consider prescribing a histaminergic (H2) blocker or antacids instead of a PPI considering the high risk for adverse events shown in this study. H2 blockers are not metabolized by the CYP enzyme system that is responsible for activating the pro-drug, clopidogrel, into the active metabolite of clopidogrel that has antiplatelet actions. Therefore, there is no inhibition of the antiplatelet effect of clopidogrel by H2 blockers."

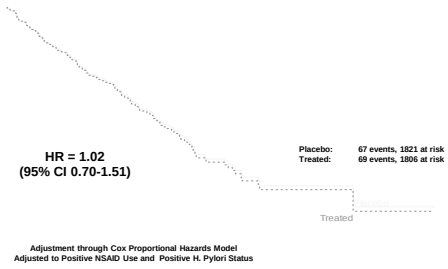
http://www.scai.org/pr.aspx?PAGE_ID=5870 (May 2009)

TRITON-TIMI-38



Lancet. 2009;374:989-97.

COGENT Trial



Bhatt D. TCT 2009; September 24, 2009; San Francisco, CA.

COGENT Event Rates

End point	Placebo (n)	PPI (n)	p
All CV events	**67**	**69**	**NS**
MI	**37**	**36**	**NS**
Revascularization	**67**	**69**	**NS**
GI events	**67**	**38**	**0.007**

Bhatt D. TCT 2009; September 24, 2009; San Francisco, CA.

Take Home Message

- Refer to CHEST guidelines to determine who is indicated for Anticoagulation in patients with Atrial Fibrillation.
- New oral anticoagulation agents are currently being studied in the Atrial Fibrillation population and may be FDA approved in the future.

Take Home Message

- 2009 USPSTF guidelines for primary prevention of cardiovascular disease with ASA indicate therapy based on risk.
- Controversy remains about what CHD or Stroke Risk indicates ASA in a primary prevention population.

Take Home Message

- A drug interaction between PPIs and clopidogrel exists, but the clinical implications are variable based on patient populations.
- Focus should be placed on evaluating whether a patient needs GI protection with a PPI or H2 Blocker while receiving dual antiplatelet therapy.