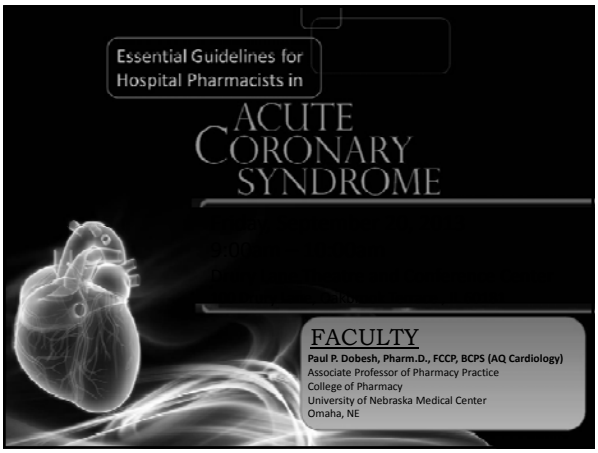
Pre Survey / Evaluation Form

Pre Survey

- Please take a moment to complete the Pre Survey prior to the start of the program
- The Pre Survey is clipped to the front of the workbook

Evaluation Form

- Please take a moment, at the conclusion of the program, to complete the evaluation form in the back of the workbook
- MLI staff will collect both forms at the conclusion of the program



Agenda

5 minutes	Welcome & Introduction
10 minutes	Trends in ACS management with a focus on the current and updated guidelines
15 minutes	Key factors that influence treatment decisions including evidence-based guidelines
20 minutes	Case presentations: An interactive presentation with two challenging case scenarios to determine the appropriate treatment options, technology and/or tools based on current and evolving trends
10 minutes	Summary and Q&A

Learning Objectives

- Discuss current updates on treatment guidelines for ACS
- Review recent advances in treatment, technology/ techniques to improve and relieve symptoms
- Describe the value and need for adherence to treatment guidelines and provide evidence-based solutions to treatment with current therapies
- Examine through different case scenarios the current treatment options/techniques utilized to address ACS

Registered Pharmacy Designation

The Medical Learning Institute Inc is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Completion of this knowledge-based activity provides for 1.0 contact hour (0.10 CEU) of continuing pharmacy education credit.

The Universal Activity Number for this activity is 0468-0000-13-002-L01-P.

CPE Information

Target Audience

- This activity was developed to bring hospital pharmacists up-to-date with the current guidelines and evidence-based approaches for the treatment of acute coronary syndrome

Commercial Support Acknowledgment

- This activity is supported by educational grants from AstraZeneca, Daiichi Sankyo, Inc. and Lilly USA, LLC.

Sponsor

- This activity is sponsored by Medical Learning Institute Inc.

Disclaimer

The information provided at this CE activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.

Recommendations for the use of particular therapeutic agents are based on the best available scientific evidence and current clinical guidelines. No bias towards or promotion for any agent discussed in this program should be inferred.

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Nancy Nesser, JD, Pharm.D	Medical Learning Institute Inc	Has nothing to disclose.

Faculty Disclosure

Paul P Dobesh, Pharm.D., FCCP, BCPS (AQ Cardiology), is a Consultant for Janssen Pharmaceuticals, Pfizer and AstraZeneca. He has also done Research Funding for Daiichi Sankyo, Inc and AstraZeneca. He does not intend to discuss any non-FDA-approved or investigational use of any products/devices.

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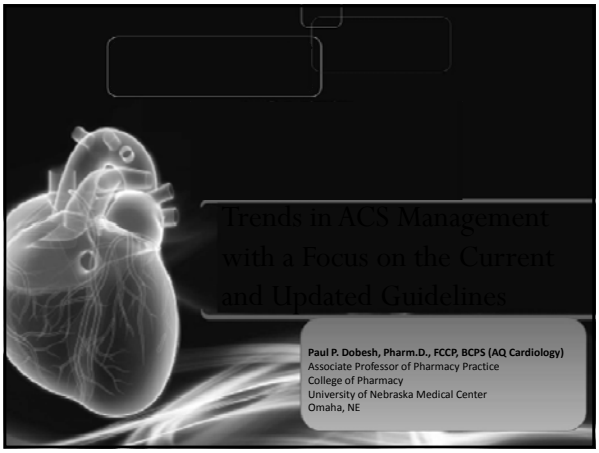
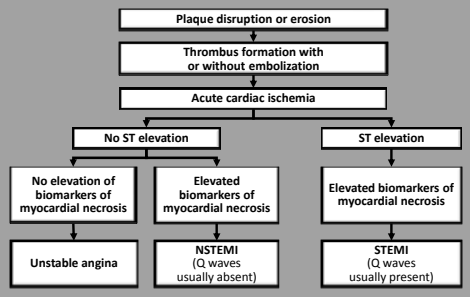


Talking Points

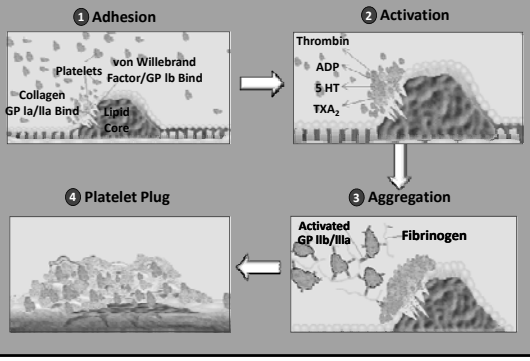
- Review the pathophysiology of acute coronary syndromes
- Identify the critical role of antiplatelet therapy in ACS patients
- Present the relevant clinical practice guidelines for ACS patients
- Review the recent clinical trials of antiplatelet agents in ACS patients
- Given a patient case, discuss the key decision points in selection of antiplatelet agents

Acute Coronary Syndrome



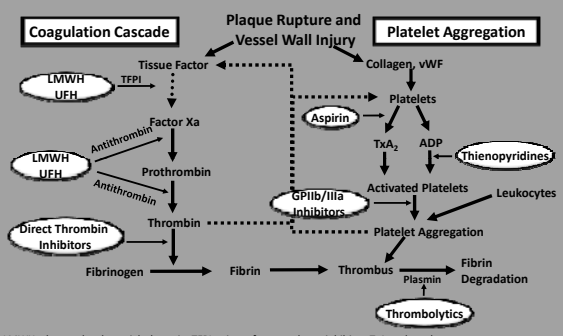
ACS = Acute Coronary Syndrome; NSTEMI = Non-ST segment-Elevation Myocardial Infarction; STEMI = ST segment-Elevation Myocardial Infarction.
Grech ED, Ramsdale DR. *BMJ*. 2003;326:1259-1261.

Platelet Cascade in ACS



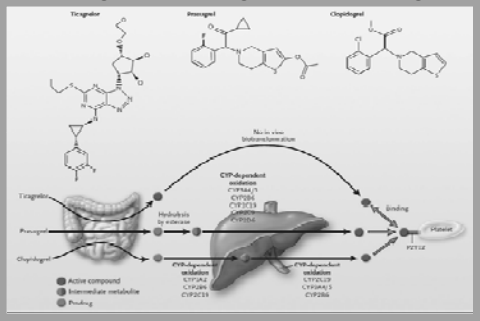
Antithrombotic Therapies

Sites of Action



LMWH = low-molecular weight heparin. TFPI = tissue factor pathway inhibitor. TxA_2 = thromboxane A_2. UFH = unfractionated heparin. vWF = von Willebrand factor.
Selwyn AP. *Am J Cardiol*. 2003;91:3H-11H.

Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor

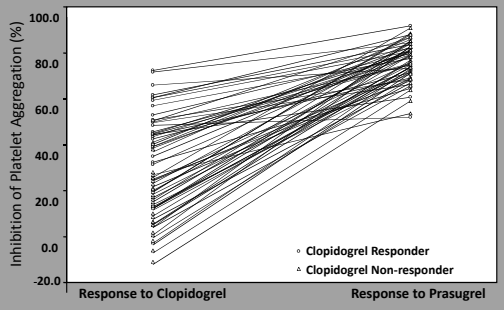


Schömig A. *N Engl J Med*. 2009;361:1108-1111.

Clinical Issues with Clopidogrel

- Variability of platelet inhibition
  - Drug – Drug interactions (PPIs)
  - Up to 40% of patients are "nonresponsive"
  - Role of platelet function testing?
  - What to do with the results?
- Genetic polymorphisms in metabolism
  - Prodrug that must undergo two CYP450 enzymes conversion steps
  - CYP 2C19 loss-of-function alleles
    - Heterozygous vs. homozygous
    - Connection of clinical outcomes debated

Inhibition of Platelet Aggregation (IPA) at 24 Hours



*Responder = ≥ 25% IPA at 4 and 24 h

Brandt J et al. *Am Heart J* 2007;153:66.e9-66.e16.

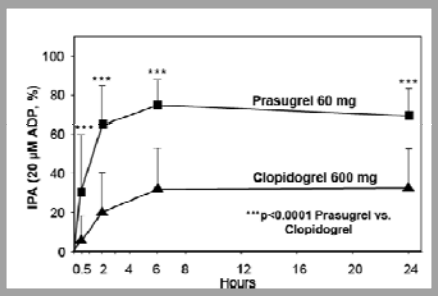
Ticagrelor Pharmacokinetics

- Cyclopentyl triazolopyrimidine P2Y12 inhibitor
- Rapid oral absorption
- Oral bioavailability 30% to 42%
- Metabolized by CYP3A4/5
  - Tmax 1.5 hr (range 1-4 hrs)
- $t_{1/2}$ 6.9 hr
- Active metabolite AR-C124910XX (~30%-40% of activity)
  - Tmax 2.5 hr
- Vd_{ss} 88L
- Highly protein bound (> 99%)
- Elimination 58% feces, 26% urine
- AUC of parent increased 21% and active metabolite decreased 22% with food
  - May be taken with or without food
- No dosage adjustments for age, sex, body weight, ethnicity, renal impairment, mild hepatic impairment
- Contraindicated in moderate and severe hepatic impairment (not studied)

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed December 2011

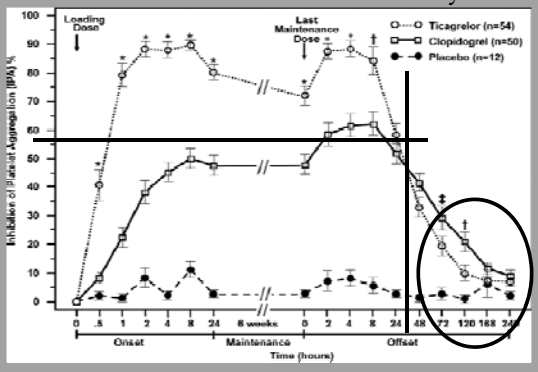
Onset and Peak Effect

Prasugrel vs. Clopidogrel



Wiviott SD, et al. *Circulation*. 2007;116:2923-2932. Image available at http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-03-Lilly.pdf.

The ONSET/OFFSET Study



Grubel PA, et al. *Circulation* 2009;120:2577-2585.

Clinical Practice Guidelines

Applying Classification of Recommendations and Level of Evidence

Class I	Class IIa	Class IIb	Class III
Benefit >>> Risk Procedure/ Treatment **SHOULD** be performed/ administered	*Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	*Benefit ≥ Risk* *Additional studies with broad objectives needed; Additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	*Risk ≥ Benefit* *No additional studies needed* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**

Level A:	Recommendation based on evidence from multiple randomized trials or meta-analyses Multiple (3-5) population risk strata evaluated; General consistency of direction and magnitude of effect
Level B:	Recommendation based on evidence from a single randomized trial or non-randomized studies Limited (2-3) population risk strata evaluated
Level C:	Recommendation based on expert opinion, case studies, or standard-of-care Very limited (1-2) population risk strata evaluated

Aspirin in PCI

Time Relative to PCI	Recommendation	COR	LOE
Pre-PCI	Aspirin 81-325 mg before PCI if already on aspirin therapy	I	B
	Nonenteric-coated aspirin 325 mg before PCI if not on aspirin therapy	I	B
PCI	Aspirin administered at time of PCI	I	B
Post-PCI	After PCI, aspirin continued indefinitely.	I	A
	After PCI, use of 81 mg/d of aspirin in preference to higher maintenance doses.	IIa	B

Levine GN, et al. Circulation. 2011; J Am Coll Cardiol. 2011;58:e44-122.

2012 ACCF/AHA Select Recommendations for Antiplatelet Rx in UA/NSTEMI

Recommendation	COR	LOE
Early Invasive Strategy, Medium to High Risk Patients:		
Before PCI: clopidogrel (LOE=B), ticagrelor (LOE=B) or GPI (LOE=B)	I	B
At the time of PCI: clopidogrel (LOE=A), prasugrel (LOE=B), ticagrelor (LOE=B) or GPI (LOE=A)	I	A or B
Initial Conservative (noninvasive) Strategy:		
Clopidogrel or ticagrelor added to aspirin and continued for up to 12 months	I	B
Class III Recommendations:		
Prasugrel potentially harmful as part of DAPT in patients with a prior Hx of CVA and/or TIA	III – Harm	B

DAPT=Dual Antiplatelet Therapy
Jneid H, et al. *J Am Coll Cardiol*. 2012 (http://circ.ahajournals.org/content/126/7/875).

$P2Y_{12}$ Inhibitor Therapy Post-Stent

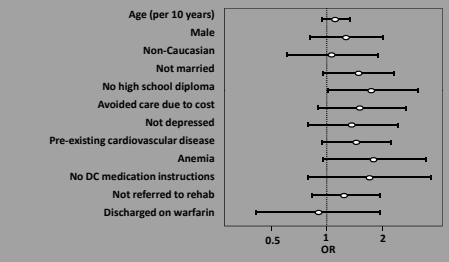
Recommendation	COR	LOE
Post-Stent Implantation (BMS or DES) for ACS, $P2Y_{12}$ inhibitor Rx at least 12 months	I	B
Post-DES for non-ACS, clopidogrel for at least 12 mo if patients are not at high risk of bleeding.	I	B
Post-BMS for non-ACS, clopidogrel for a minimum of 1 mo and ideally up to 12 mo	I	B
Counseling patients on the importance of compliance with DAPT and to not discontinue Rx before discussion with the relevant cardiologist	I	C
Earlier discontinuation (eg, < 12 mo) of $P2Y_{12}$ inhibitor if the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation	IIa	C
Continuation of $P2Y_{12}$ Rx beyond 12 mo in patients undergoing DES placement.	IIb	C

$P2Y_{12}$ Inhibitor = clopidogrel, prasugrel or ticagrelor
Levine GN, et al. Circulation. 2011; J Am Coll Cardiol. 2011;58:e44-122.

PREMIER Registry

Factors Associated with Discontinuing Thienopyridine Therapy

Nearly 1 in 7 patients (13.6%) reported discontinuing therapy 1 month post-discharge



Fully adjusted, multivariable, logistic-regression model for discontinuing thienopyridine therapy within 30 days of discharge for an MI treated with a DES. Point estimates are represented by points, and the 95% CIs are shown as bars.
DC = discharge.
Spertus JA, et al. *Circulation*. 2006;113:2803-2809.

Key Clinical Trials

CURRENT Trial - Study Design

ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
✓ Planned Early (<24 h) Invasive Management with intended PCI
✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

n=25,087

- **Clopidogrel 600 mg load, 150 mg/d x 7d, then 75 mg/d**
  - **Aspirin 300-325 mg/d**
  - **Aspirin 75-100 mg/d**
- **Clopidogrel 300 mg load, then 75 mg/d**
  - **Aspirin 300-325 mg/d**
  - **Aspirin 75-100 mg/d**

PCI 17,232 (70%) No PCI 7,855 (30%)

Efficacy Outcomes:	**CV Death, MI or stroke at day 30**
	Stent Thrombosis at day 30
Safety Outcomes:	**Bleeding**
Key Subgroup:	**PCI v No PCI**

N Engl J Med 2010;363:930-42.

CURRENT Trial ASA Dose Comparison

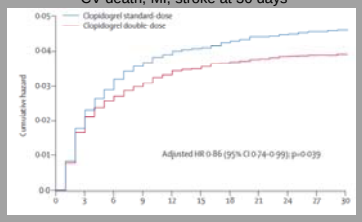
	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

GI Bleeds: 30 (0.2%) v 47 (0.4%), P=0.04

CURRENT-OASIS 7

Benefit in PCI Subgroup with 600-mg vs. 300-mg Clopidogrel Loading Dose

CV death, MI, stroke at 30 days



Prespecified subgroup analysis, n=17,263

Double-dose clopidogrel regimen can be considered in ACS with planned stenting

Mehta SR, et al. *Lancet* 2010.

CURRENT Trial Results

Clopidogrel Double vs. Standard Dose

	Clopidogrel				
	Standard N=12579	Double N=12508	Hazard Ratio	95% CI	P
TIMI Major	0.95	1.04	1.09	0.85-1.40	0.50
CURRENT Major	2.0	2.5	1.25	1.05-1.47	0.01
CURRENT Severe	1.5	1.9	1.23	1.02-1.49	0.03
Fatal	0.11	0.13	1.15	0.56-2.35	0.71
ICH	0.05	0.03	0.67	0.19-2.37	0.53
RBC transfusion ≥ 2U	1.76	2.21	1.26	1.06-1.51	0.01
CABG-related Major	0.9	1.0	1.10	0.85-1.42	0.48

N Engl J Med 2010;363:930-42.

TRITON-TIMI 38

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA required

N = 13,608

Double-blind

Median duration of therapy: 12 months

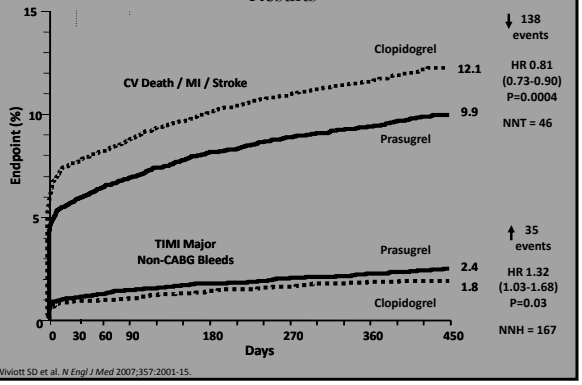
Clopidogrel	Prasugrel
300-mg LD	60-mg LD
75-mg MD	10-mg MD

1° end point:	CV death, MI, stroke
2° end points:	Stent thrombosis
	CV death, MI, stroke, rehosp-rec Isch
	30, 90 day: CV death, MI, stroke
	30, 90 day: CV death, MI, UTVR
Safety end points:	TIMI major bleeds, life-threatening bleeds
Key substudies:	Pharmacokinetic, genomic

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

TRITON TIMI-38 Trial

Results



Wiviott SD et al. *N Engl J Med* 2007;357:2001-15.

TRITON-TIMI 38 Trial

Net Clinical Benefit by Subgroup

Prasugrel vs. Clopidogrel by Subgroup		
Prior Stoke or TIA	HR 1.54 (1.02 – 2.32); p=0.04	3.8%
≥ 75 Years of Age	HR 0.99 (0.81 – 1.21); p=0.92	16%
Weight ≤ 60 kg	HR 1.03 (0.69 – 1.53); p=0.89	

80% of patients in TRITON-TIMI 38 demonstrated a significant reduction in CV death, MI, or stroke without an increase in bleeding

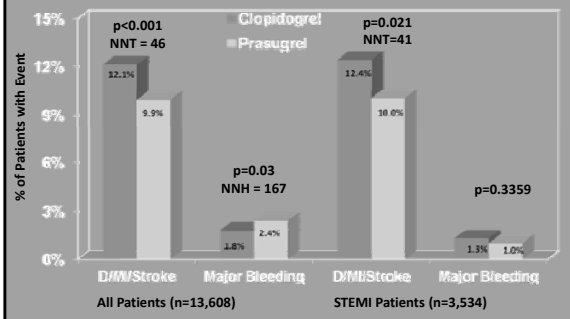
CV Death/MI/Stroke 11.0% clopidogrel vs. 8.3% prasugrel; p<0.0001
Major Bleeding 1.5% clopidogrel vs. 1.9% prasugrel; p=0.17

Wiviott SD, et al. *N Engl J Med* 2007;357:2001-15.
Wiviott SD, et al. *Am J Cardiol* 2011;108:905-911.

Prasugrel Warnings and Contraindications

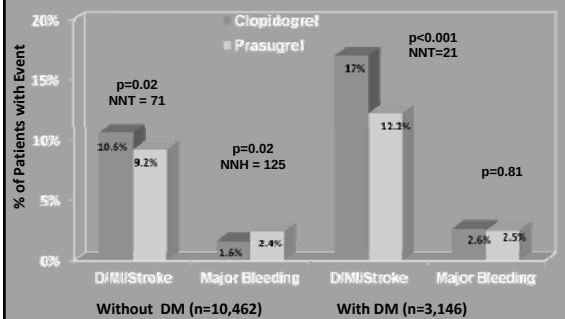
- History of stroke or TIA
  - Prasugrel is contraindicated
- Patients age ≥ 75 years
  - Prasugrel generally not recommended ***EXCEPT:***
    - STEMI or
    - Diabetes mellitus

TRITON TIMI-38
Patients with STEMI



Wiviott SD, et al. *N Engl J Med* 2007;357:2001-2015.
Montalescot G, et al. *Lancet* 2009;373:723-731.

TRITON TIMI-38
Patient with Diabetes Mellitus

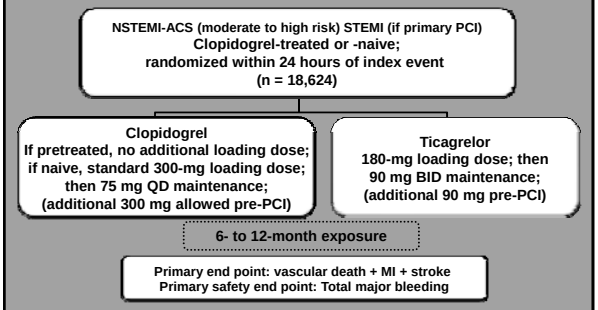


Wiviott SD, et al. *N Engl J Med* 2007;357:2001-2015.
Wiviott SD, et al. *Circulation* 2008;118:1626-1636.

Prasugrel Warnings and Contraindications

- History of stroke or TIA
  - Prasugrel is contraindicated
- Patients age ≥ 75 years
  - Prasugrel generally not recommended ***EXCEPT:***
    - STEMI or
    - Diabetes mellitus
- Patients with weight ≤ 60 kg
  - Caution due to increased risk of bleeding
  - Consider a 5 mg maintenance dose

PLATO Study Design

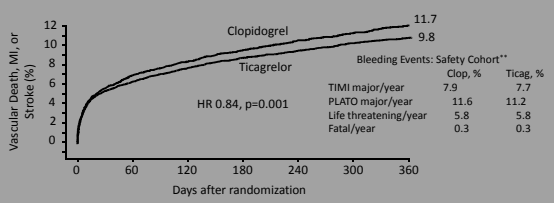


Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

TICAGRELOR* KEY EVIDENCE:
SECONDARY PREVENTION

Platelet Inhibition and Patient Outcomes (PLATO) Study

18,624 patients with moderate to high risk ACS randomized to clopidogrel (300- to 600-mg LD and 75-mg MD) or ticagrelor (180-mg LD and 90 mg 2 times/day MD) for 12 months



Bleeding Events: Safety Cohort**

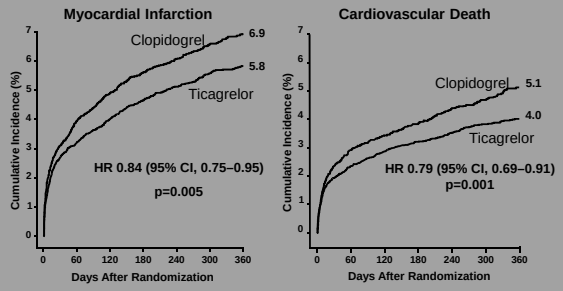
	Clop, %	Ticag, %
TIMI major/year	7.9	7.7
PLATO major/year	11.6	11.2
Life threatening/year	5.8	5.8
Fatal/year	0.3	0.3

Ticagrelor reduces ischemic events with no higher rate of PLATO-defined bleeding

****No statistically significant differences were observed in bleeding rates overall.**

Data from Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

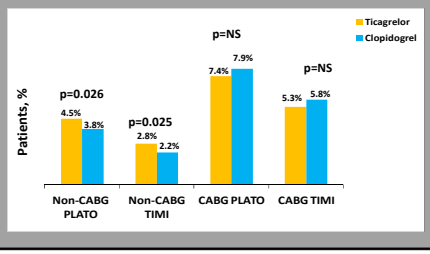
PLATO
Secondary Efficacy Endpoints



Data from Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

PLATO

Major Bleeding Non-CABG and CABG Related



Total PLATO major bleeding: 11.6% ticagrelor vs. 11.2% clopidogrel; *P* = 0.43
Total TIMI major bleeding: 7.9% ticagrelor vs. 7.7% clopidogrel; *P* = 0.57

Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

PLATO

Holter Monitoring & Bradycardia-Related Events

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
Holter monitoring at 30 days	**(n = 985)**	**(n = 1006)**	
Ventricular pauses ≥ 3 seconds, %	2.1	1.7	0.52
Ventricular pauses ≥ 5 seconds, %	0.8	0.6	0.60
Bradycardia-related event, %	**(n = 9235)**	**(n = 9186)**	
Pacemaker insertion	0.9	0.9	0.87
Syncope	1.1	0.8	0.08
Bradycardia	4.4	4.0	0.21
Heart block	0.7	0.7	1.00

Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

PLATO

Other Adverse Events

	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
% increase in creatinine from baseline			
At 1 month	10 ± 22	8 ± 21	< 0.001
At 12 months	11 ± 22	9 ± 22	< 0.001
Follow-up visit	10 ± 22	10 ± 22	0.59
% increase in uric acid from baseline			
At 1 month	14 ± 46	7 ± 44	< 0.001
At 12 months	15 ± 52	7 ± 31	< 0.001
Follow-up visit	7 ± 43	8 ± 48	0.56

Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

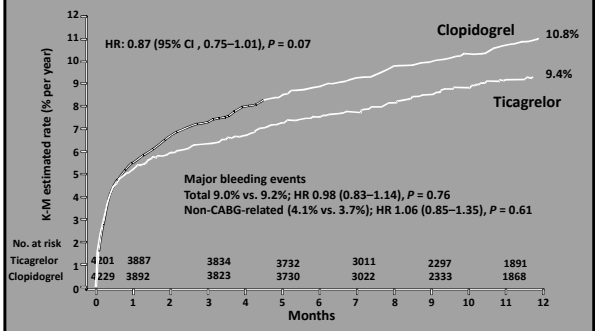
PLATO

Key Efficacy Subgroups

- STEMI primary PCI
- Planned invasive strategy
- Planned noninvasive strategy
- Diabetes mellitus

PLATO STEMI Primary Endpoint

Vascular Death, MI, or Stroke



Data from Steg PG, et al. *Circulation*. 2010;122:2131-2141.

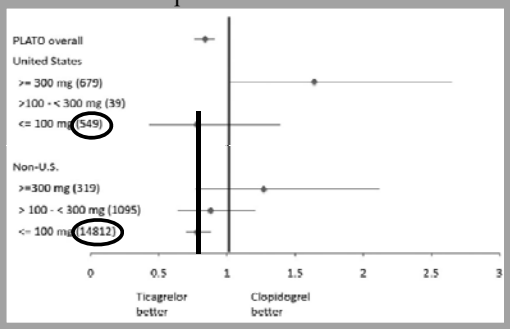
PLATO Invasive

End Point*	Ticagrelor (n = 6732)	Clopidogrel (n = 6676)	HR for Ticagrelor (95% CI)	*P*-value†
Primary objective, %				
CV death + MI + stroke	9.0	10.7	0.84 (0.75–0.94)	0.0025
Secondary objectives, %				
Total death + MI + stroke	9.4	11.2	0.84 (0.75–0.94)	0.001
CV death + MI + stroke + ischemia + TIA + arterial thrombotic events	13.2	15.3	0.85 (0.77–0.93)	0.0005
MI	5.3	6.6	0.80 (0.69–0.92)	0.002
CV death	3.4	4.3	0.82 (0.68–0.98)	0.025
Stroke	1.2	1.1	1.08 (0.78–1.50)	0.646
Total (all-cause) death	3.9	5.1	0.81 (0.68–0.95)	0.010

*The percentages are K-M estimates of the rate of the end point at 12 months. Patients could have had more than one type of end point.. †By univariate Cox model.

Data from Cannon CP, et al. *Lancet*. 2010;375:283-293.

Ticagrelor PLATO Trial
Aspirin Interaction?

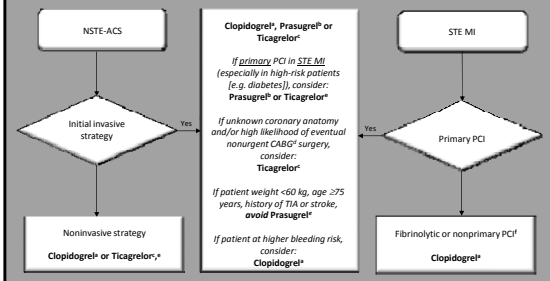


Gaglia MA and Waksman R. *Circulation* 2011;123:451-456.

Clinical Evidence Summary

- Clopidogrel is currently the only agent with evidence in:
  - STEMI patients receiving fibrinolysis
- Prasugrel more effective than clopidogrel in ACS patients undergoing PCI
  - Bleeding – Stroke/TIA, age ≥ 75 yrs, ≤ 60 kg
  - Efficacy – especially STEMI and patients with DM
- Ticagrelor more effective than clopidogrel in ACS patients undergoing PCI
  - Not in US patients – same at best
  - Twice daily dosing
  - Unique adverse effects

Proposed Use of $P2Y_{12}$ Inhibitors in ACS



ACS = acute coronary syndrome; CABG=coronary artery bypass surgery; NSTE=non-ST-segment elevation; TIA = transient ischemic attack
Adapted from Crouch MA, et al. *Ann Pharmacother*. 2011;45:1151-1156, with permission.

Which Agent and When?

ACS Situation	Preferred $P2Y_{12}$ Inhibitor
NSTE ACS medical management	**Ticagrelor > Clopidogrel > Prasugrel**
NSTE ACS PCI	Ticagrelor or Prasugrel > Clopidogrel
Patients < 60 kg	**Ticagrelor > Clopidogrel**
Patients ≥ 75 years	Ticagrelor > Clopidogrel
Patients with history of TIA or stroke	Ticagrelor > Clopidogrel
Diabetes Mellitus	Prasugrel > Ticagrelor > Clopidogrel
NSTE ACS CABG surgery	Clopidogrel?
STEMI PCI	Prasugrel > Ticagrelor > Clopidogrel
STEMI with fibrinolytics	00000Clopidogrel

Adapted from Dobesh PP. *Pharmacotherapy* 2009;29:1393-1396.

Antiplatelet Drug Therapy: Additional Considerations

Clopidogrel Drug Interactions
FDA Advisory November 17, 2009

- Clopidogrel is converted to its active metabolite in part by CYP2C19
- Omeprazole is a CYP2C19 inhibitor
- Omeprazole decreases active metabolite concentrations by 45%
- Omeprazole reduces antiplatelet effect (ex vivo platelet aggregation; e.g., VerifyNow) by up to 47%
- Limited pharmacokinetic data on other PPIs
- No data from well-designed clinical trials to determine the clinical significance of this interaction

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm. Accessed April 2011.

Prasugrel Drug Interactions

- Prasugrel: No clinically significant drug-drug pharmacokinetic interactions have been identified to date

Ticagrelor Drug-Drug Interactions

- Metabolized by CYP3A4/5
  - Avoid use with strong CYP3A4 inhibitors
    - Ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, atazanavir, indinavir, saquinavir, nelfinavir, telithromycin, voriconazole
    - Ketoconazole AUC increased 7.3-fold and Cmax by 7.3-fold (decreased AUC/Cmax of active metabolite)
  - Avoid use with strong CYP3A inducers
    - Rifampin, dexamethasone, phenytoin, carbamazepine, phenobarbital
    - Rifampin decreased AUC by 86% and Cmax by 73% (and decreased AUC of active metabolite)

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm Accessed December 2011

Ticagrelor Drug-Drug Interactions

- Inhibitor of CYP2C9 (moderate) *in vitro*
  - No drug interactions identified to date
    - Not studied with warfarin
- P-glycoprotein substrate and weak inhibitor
  - Increased digoxin AUC by 28% and Cmax by 75%
  - Monitor digoxin serum concentrations when adding ticagrelor or changing digoxin dose
- Can increase CYP3A4 statin concentrations
  - Avoid use with simvastatin over 40 mg
  - Avoid use with lovastatin over 40 mg

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm Accessed December 2011

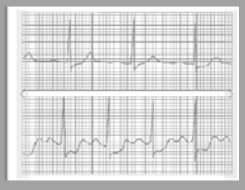
Case Study

- 56 year-old male with a medical history of HTN and DM presenting to the hospital ED with a 6 hour history of chest squeezing and tightness
- PE:
  - BP 148/92, HR 88; Ht 72 in, Wt 90 kg, afebrile
  - 3 cm JVD, lungs rales; regular S1, S2, -S3, -S4, no murmur
  - Abdomen obese, soft, with mild epigastric tenderness; -FOBT
  - Extremities without edema, pulses 1-2+ throughout

Case Study

(Continued)

- ECG: 2 mm ST depression, Leads V4-V6 with symmetrical T wave inversion
- CXR: heart failure
- Labs:
  - Hct 45, WBC 8.7, Plts 238K
  - Na 138, K 4.2
  - BUN 41, SCr 1.82 mg/dL
  - Gluc 142
  - Est CrCl 58 mL/min (CG)
  - CK-MB 6 (ULN <6)
  - TnT 3.80 (ULN <0.10)
  - LDL 130 mg/dL, HDL 32 mg/dL, TGs 149 mg/dL



Case Study

(Continued)

- Medications taken prior to admission:
  - Aspirin 81 mg daily
  - Metformin 1 g BID
  - Ramipril 10 mg daily
  - HCTZ 12.5 mg daily
  - Amlodipine 10 mg daily
- ASA 325 mg administered in ED

Questions for Discussion

- Evaluate the patient's medications taken prior to admission for primary prevention of a CHD event
- Is this unstable angina, NSTEMI ACS, or STEMI ACS?
- Is an interventional approach or medical management approach indicated at this time?

Answers

- Evaluate the patient's medications taken prior to admission for primary prevention of a CHD event
  - ASA for primary prevention indicated for all patients age greater than 50 yrs by 2012 ACCP Chest Guidelines or in patients with a >10% risk of a CHD event within 10 years (optional 5% to 10%) by the ADA/AHA DM ASA for primary prevention guidelines)
  - Statin would be indicated to LDL at least <100 mg/dL
  - HTN goal <140/90 mmHg with ACE-I as drug of choice

Answers

- Is this unstable angina, NSTEMI or STEMI ACS?
  - NSTEMI
    - Positive elevated troponin
- Is an interventional approach or medical management approach indicated at this time?
  - For NSTE ACS, perform risk stratification
    - High risk features are ST-segment depression, DM, positive troponin

? Which Antiplatelet Agents Would you Select for this Patient?

1. ASA plus a GPIIb/IIIa inhibitor
2. ASA plus clopidogrel
3. ASA plus prasugrel
4. ASA plus ticagrelor
5. ASA plus a $P2Y_{12}$ inhibitor plus a GP IIb/IIIa inhibitor

Answers

- "Pick 2" antiplatelet agents (ASA 325 mg plus a second agent)
  - If UFH, can initiate a GP IIb/IIIa inhibitor
    - $P2Y_{12}$ inhibitor at presentation or at time/or just following PCI
  - If bival, initiate $P2Y_{12}$ inhibitor in ED

Anderson JL, et al. *Circulation*. 2012.

Answers

- Patient considerations for selecting between $P2Y_{12}$ inhibitors and a GP IIb/IIIa inhibitor
  - DM
  - CKD
    - Eptifibatide dosing reduction if CrCl <50 mL/min
    - Eptifibatide contraindicated if dialysis
  - Other risk factors for bleeding
    - E.g., if patient had hx of any ischemic stroke cannot give prasugrel; any ischemic stroke within 30 days cannot give eptifibatide

Anderson JL, et al. *Circulation*. 2012.

Selection Considerations for $P2Y_{12}$ Inhibitors

- Trial data/study design: Efficacy and Safety
  - Timing of administration in trial
    - Initial invasive versus conservative approach
    - Pre- or Post-angiography
  - Patient subgroups
    - DM
- Variability in response
- Platelet function testing being used?
- Genotyping available?
- Transitioning to surgery

Selection Considerations for $P2Y_{12}$ Inhibitors

- Patient risk factors for bleeding
  - Prior stroke/TIA, low body weight <60 kg, age ≥75 yrs
- Adherence
  - Insurance
- Drug interactions with clopidogrel and ticagrelor

Answer

$P2Y_{12}$ Inhibitors for Initial Invasive Approach

- Clopidogrel 600 mg, Prasugrel 60 mg or Ticagrelor 180 mg (2, 90 mg capsules)
- Before PCI:
  - Clopidogrel (Class IB recommendation)
  - Ticagrelor (Class IB recommendation)
- At the time of PCI (after angiography)
  - Clopidogrel (Class IA recommendation)
  - Prasugrel (Class IB recommendation)
  - Ticagrelor (Class IB recommendation)

Anderson JL, et al. *Circulation*. 2012.

Case Study

- Following PCI with placement of a drug-eluting stent in the LAD coronary artery, an echocardiogram is performed on hospital day two indicating an EF of 45%

QUESTION

– What medications are indicated for secondary prevention?

Secondary Prevention*

Recommendations		COR	LOE
Lipid management with lifestyle modification and lipid-lowering pharmacotherapy	Lifestyle modification	I	B
	Statin therapy	I	A
	Statin therapy which lowers LDL to <100 mg/dL and achieves at least a 30% lowering of LDL	I	C
	Statin therapy which lowers LDL to <70 mg/dL in very high-risk patients	IIa	B
Blood pressure control (with a blood pressure goal of <140/90 mm Hg)	Lifestyle modification	I	B
	Pharmacotherapy	I	A
Diabetes management (e.g., lifestyle modification and pharmacotherapy) coordinated with the patient's primary care physician and/or endocrinologist		I	C
Complete smoking cessation		I	A

*Comprehensive secondary prevention recommendations in the ACCF/AHA Secondary Prevention and Risk Reduction 2011 Update

Summary

- Three $P2Y_{12}$ inhibitors
  - Benefits of DAP therapy
    - Decreased recurrent infarction
    - Stent thrombosis
    - Ticagrelor with mortality benefit
  - Safety
    - Increased non-CABG bleeding
    - Core cohort analysis with prasugrel
  - Selection of antiplatelet agents likely based upon key efficacy and safety subgroups as well as drug interactions

Summary
(Continued)

- No clear role for pharmacokinetic or platelet aggregation testing in P2Y12 inhibitor selection
- Be aware of important drug-drug interactions with clopidogrel and ticagrelor
- Consider options for PPIs with clopidogrel
  - New guidelines
  - Preferred over H2 blockers
  - PPIs not for routine use
  - No specific PPI recommended (or not recommended)
  - FDA and product labeling clear

Post-Program Survey and Credit Certificates

- Your participation in this activity will only be recorded if you provide us with your NABP e-profile number and date of birth (MMDD)
- To assess the educational impact of this activity, you will receive an e-mail requesting your participation in a follow-up survey in accordance with our accrediting body.

PLEASE HELP US BY FILLING OUT THE FOLLOW-UP SURVEY IN 90 DAYS.