Cardiovascular Pharmacology: What You Need to Know Now

Robert Barcelona, PharmD, BCPS
Clinical Pharmacy Specialist, Cardiology
University Hospitals Case Medical Center

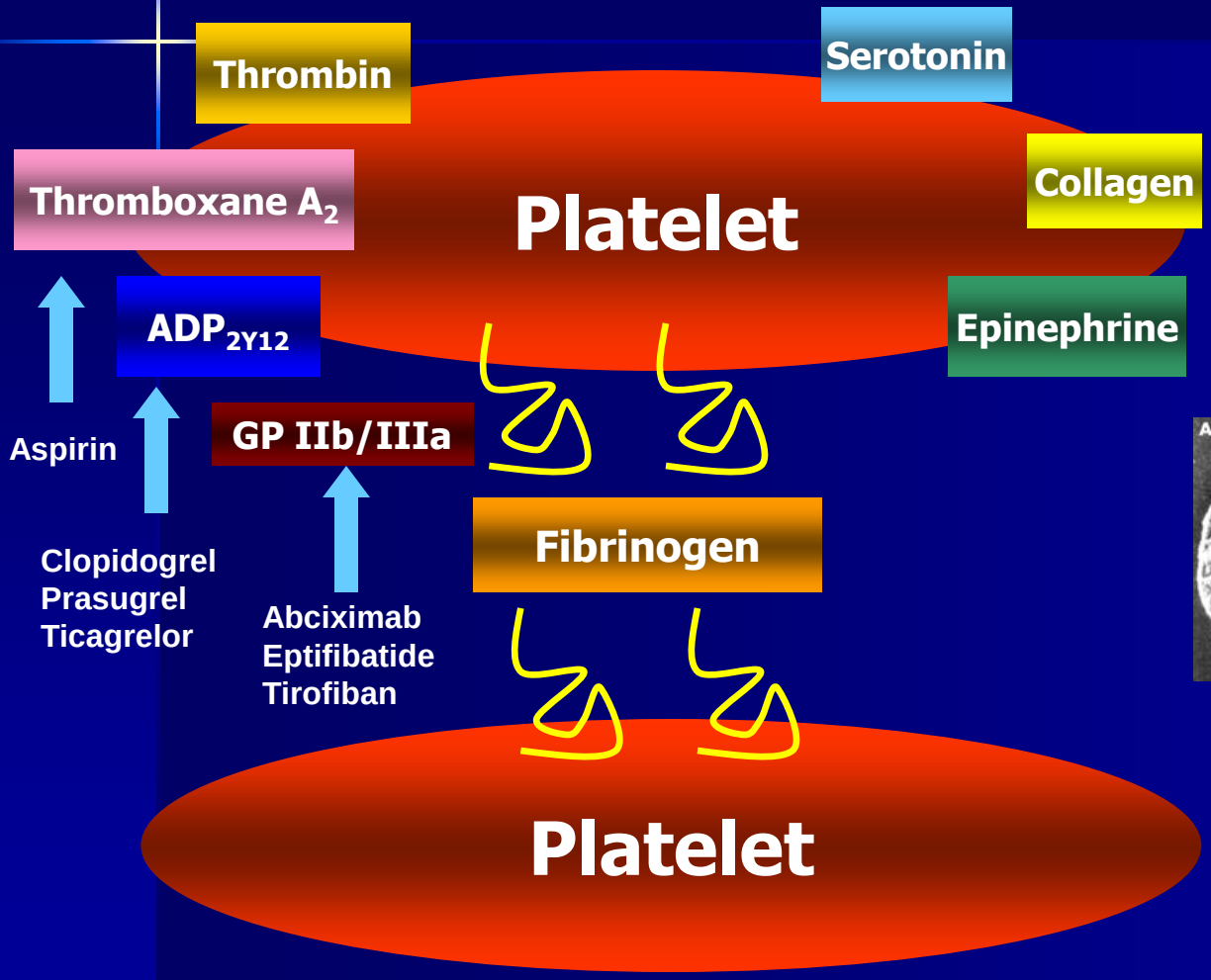
Disclosure

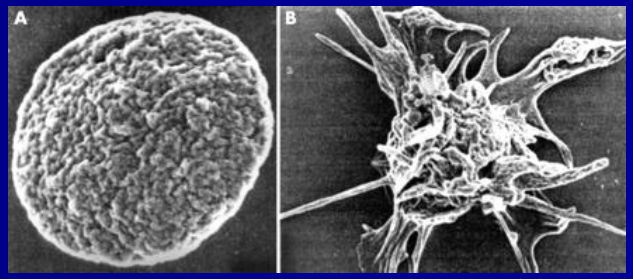
-

Objectives

- Discuss the pharmacology of current and recently approved antiplatelet agents used in acute coronary syndromes (ACS)
- Discuss the pharmacology of warfarin and recently approved oral anticoagulants
- Review the updates made to HMG-CoA reductase inhibitors labels

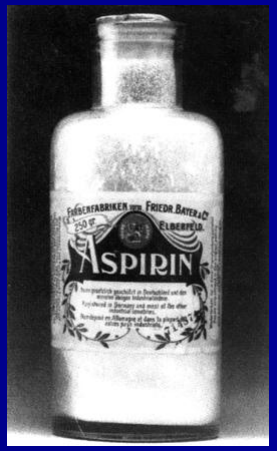
Antiplatelet Pharmacology





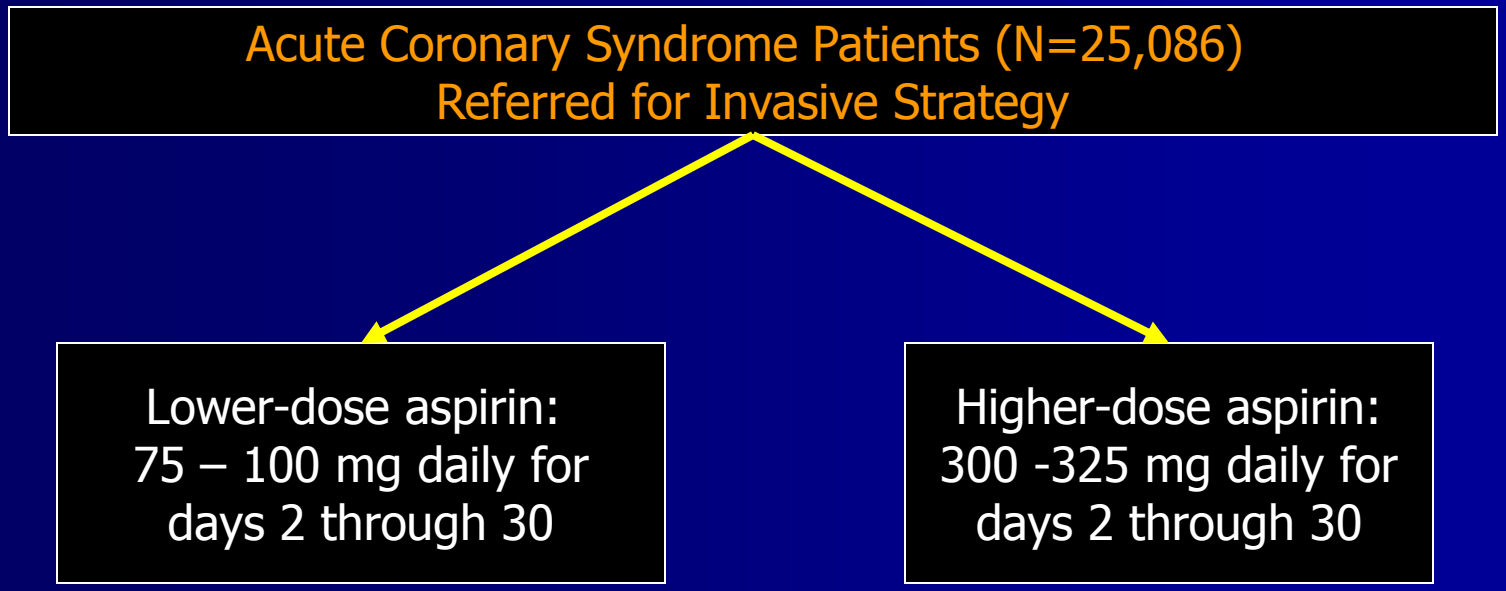
Aspirin

- Prevention and treatment of MI and stroke; adjunctive therapy in revascularization procedures
- Inhibits formation of thromboxane A_2, **irreversibly** binding to platelet
- Dose
  - 162 – 325 mg administered upon presentation (Class I)
- Adverse effects
  - GI upset
  - Bleeding
- Guideline recommendations:
  - After PCI use of aspirin should be continued indefinitely
  - After PCI reasonable to use aspirin 81 mg/day in preference to higher maintenance doses (Class IIa)



Kushner FG. Circulation 2009;120:271-306.
Anderson JL. Circulation 2007;116:e 148-304
Knight CJ. Heart 2003;89:1273-8

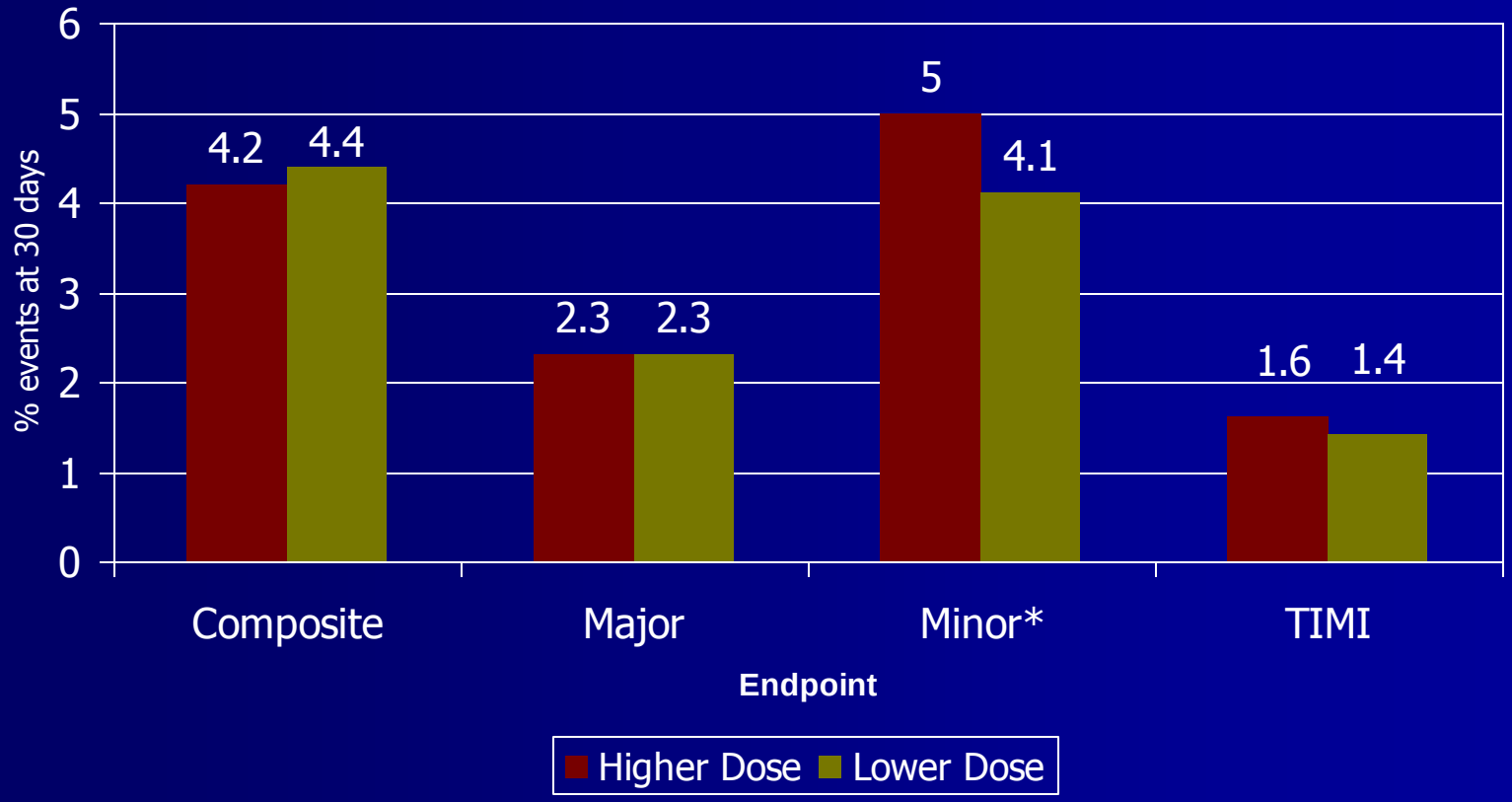
CURRENT-OASIS 7: Aspirin Dosing



- Primary Outcome: Time to CV death, MI, or stroke, up to day 30
- Safety Outcome: major bleeding

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

CURRENT-OASIS 7: Aspirin Dosing



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

Clopidogrel (Plavix®)

- Reduces rate of atherothrombotic events in patients with ACS managed medically (Class I) **OR** with PCI (Class I)
- Thienopyridine that blocks the $P2Y_{12}$ ADP receptor **irreversibly** binding to the platelet
- Loading dose 300 – 600 mg given as early as possible at time of primary or nonprimary PCI (Class I)
- Maintenance dose 75 - 150 mg daily
- Pro-drug that requires hepatic metabolism to active metabolite
  - Genetic variability may effect platelet inhibition of clopidogrel
- Side effects
  - Bleeding
  - Thrombotic thrombocytopenia purpura

Kushner FG. Circulation 2009;120:271-306.
Anderson JL. Circulation 2007;116:e 148-304

CURE

ACS patients (N=12,562) w/o ST-elevation with ECG changes or (+) cardiac biomarkers; only 21% underwent PCI

Clopidogrel 300 mg then 75 mg daily; Aspirin 75 – 325 mg daily

Placebo; Aspirin 75 – 325 mg daily

Endpoint	Clopidogrel (%)	Placebo (%)
1st Primary Outcome: CV death, MI, Stroke*	9.3	11.4
2nd Primary Outcome: CV death, MI, Stroke, refractory ischemia	16.5	18.8
Major Bleeding**	3.7	2.7
Minor bleeding***	1.4	0.9

*P<0.001
**P=0.03
***P=0.01
Yusuf S. N Engl J Med 2001;345:494-502

CURRENT-OASIS 7: Clopidogrel Dosing (PCI Subset)

ACS patients (N=17,263) undergoing early invasive strategy

Double-Dose Clopidogrel:
600 mg loading dose
then 150 mg daily x 6 days,
then 75 mg daily

Standard-Dose Clopidogrel:
300 mg loading dose
then 75 mg daily

Events	Double (%)	Standard (%)
CV death/MI/Stroke at 30 days*	3.9 (4.2)	4.5 (4.4)
CV death	1.9 (2.1)	1.9 (2.2)
MI**	2 (1.9)	2.6 (2.2)
Stroke	0.4 (0.5)	0.4 (0.5)
Stent thrombosis***	0.7 (1.6)	1.3 (2.3)

(): data from entire CURRENT-OASIS 7

*P=0.039
**P=0.018
***P=0.0001
Mehta SR. Lancet 2010;376:1233-43.

Prasugrel (Effient™)

- Pro-drug thienopyridine that irreversibly binds to platelets
- Single CYP-450-depedent path to active metabolite
- ~6 times more potent than clopidogrel
- Onset: 30 minutes
- Dosing: 60 mg load then 10 mg daily
- Contraindicated in:
  - Active bleeding
  - Previous TIA or stroke
- Use cautiously in:
  - Weight <60 kg
  - Age ≥ 75 years
- No interaction with PPIs
- More bleeding compared to clopidogrel

TRITON-TIMI 38

Moderate- to high-risk ACS patients (N=13,608) undergoing PCI

Prasugrel 60 mg loading dose
then 10 mg daily

Clopidogrel 300 mg loading dose
then 75 mg daily

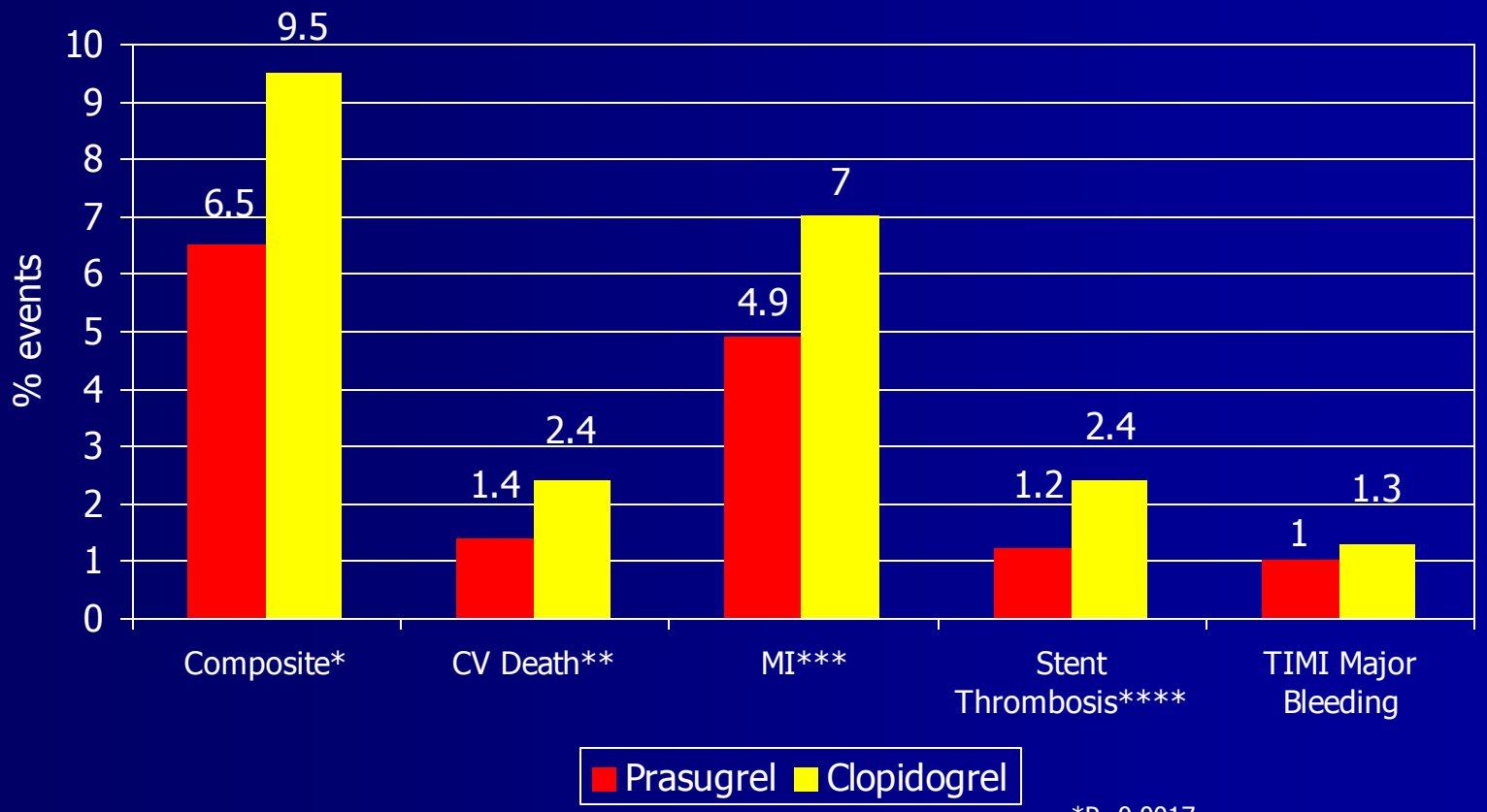
3 groups with no benefit or developed net harm with prasugrel (primary endpoint):

- Previous stroke or TIA: **19.1% prasugrel vs. 14.4% clopidogrel**
- ≥ 75 years of age: **no benefit**
- Weight < 60 kg: **no benefit**

Events	Prasugrel (%)	Clopidogrel (%)	RR (%)
CV death/MI/Stroke*	9.9	12.1	-18
MI*	7.3	9.5	-23
Stent Thrombosis*	1.1	2.4	-54
Major Bleeding**	2.4	1.8	33

*P<0.001
**P=0.03
Wiviott SD. N Engl J Med 2007;357:2001-15.

TRITON-TIMI 38: STEMI Cohort (N=3,534)



*P=0.0017
**P=0459
***P=0106
****P=0.0084
Montalescot G. Lancet 2009;373:723-31

Ticagrelor (Brilinta™)

- Non-thienopyridine (cyclopentyl-triazolo-pyrimidine) that binds to $P2Y_{12}$ portion of ADP receptor
- Indication:
  - With aspirin for secondary prevention of thrombotic cardiac events in patients with ACS managed medically or with PCI and/or CABG
- After initial loading dose of 325 mg aspirin, maintenance dose should be 75-100 mg
- Does not require metabolic conversion to active form
- Onset of activity: 30 minutes (similar to 600 mg clopidogrel at 8 hours); peaks at 2 hours
- Half-life: 7 – 12 hours
- Dosing: 180 mg load then 90 mg twice daily (w/ or w/o food)
- Adverse effects: bleeding, dyspnea (often resolved)
- July 2010: FDA Cardiovascular and Renal Drugs Advisory Committee voted to recommend approval; approved July 2011

PLATO

ACS patients presenting within 24 hours (N=18,264)
~60% underwent PCI, ~4% cardiac surgery

- Ticagrelor 180 mg loading dose then 90 mg twice daily
- Clopidogrel 300 – 600 mg loading dose then 75 mg daily

3 patient groups with attenuated benefit with ticagrelor:

- Weighing less than median weight for their sex
- Not taking lipid-lowering drugs at randomization
- Enrollment in North America

Events	Ticagrelor (%)	Clopidogrel (%)
CV death/MI/Stroke*	9.8	11.7
Death from vasc causes**	4	5.1
Stent Thrombosis***	1.3	1.9
Major Bleeding	11.6	11.2
Dyspnea*	13.8	7.8

*P<0.001
**P=0.001
***P=0.009

Wallentin L. N Engl J Med 2009;361:1045-57.

Dual Antiplatelet Therapy

- Loading dose of thienopyridine recommended for patients for whom PCI planned (Class I)
- After PCI reasonable to use 81 mg/d aspirin in preference to higher maintenance doses (Class IIa)
- **Should be administered for minimum of 12 months** (Class I)
  - Recommended minimum duration of dual antiplatelet therapy for following stents:
    - BMS: 1 month (ideally 12 months)
    - Drug eluting stents: 12 months
- Continuation of DAPT beyond 12 months considered in patients undergoing DES implantation (Class IIb)
- Risk of stent thrombosis, MI and/or death increases when discontinued
- Decision to discontinue dual antiplatelet therapy in patients with DES or BMS should only be made by cardiologists

Levine GN. Circulation 2011;124:e574-e651.

ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines

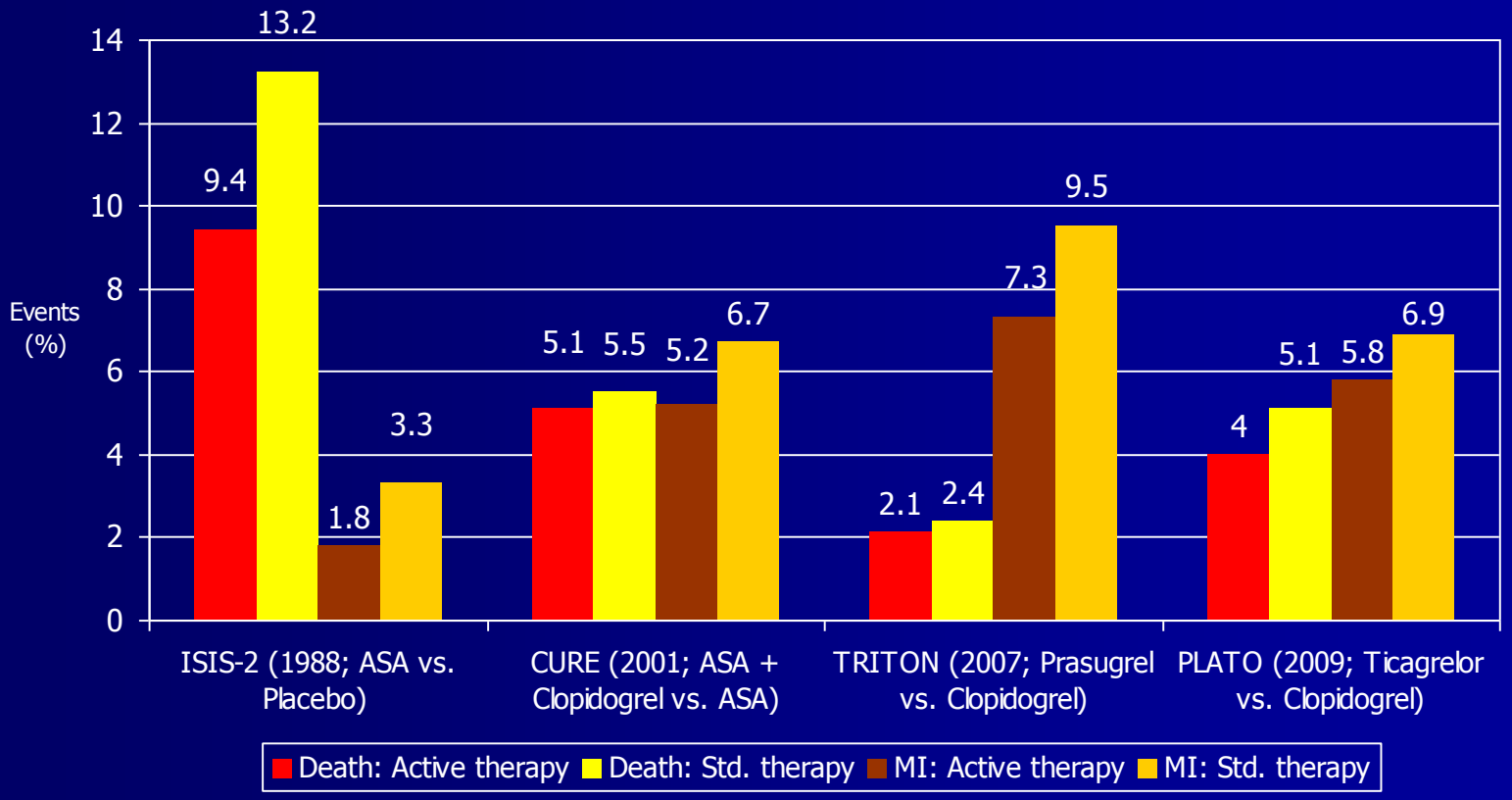
- A significant association between PPI use and increased CV events has been inconsistently demonstrated in observational studies
- Prior GI bleeding is strongest and most consistent risk factor for GI bleeding on antiplatelet therapy
- Advanced age; concomitant use of warfarin, steroids or NSAIDS; or *H. pylori* infection all raise risk of GI bleeding with antiplatelet therapy
- Risk reduction with PPIs is substantial in patients with risk factors for GI bleeding and may outweigh any potential reduction in CV efficacy of antiplatelet treatment because of a drug-drug interaction

Hlatky MA. Circulation 2010;122:2619-33

Comparison of $P2Y_{12}$ Inhibitors

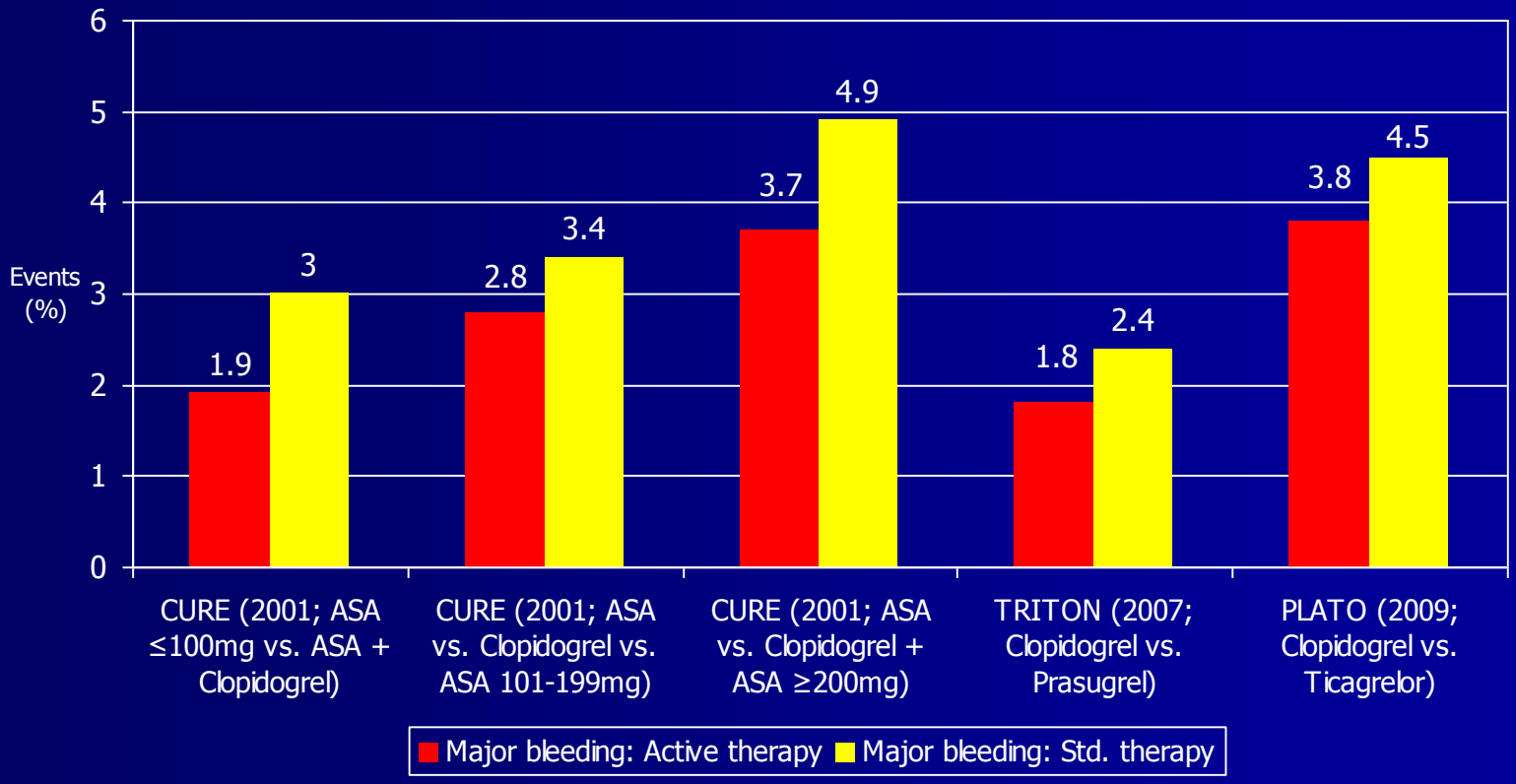
	Clopidogrel	Prasugrel	Ticagrelor
Prodrug	Yes	Yes	No
Frequency	Once daily	Once daily	Twice daily
Onset of action	Delayed	Rapid	Rapid
Offset of action	Delayed	Delayed	Rapid
Individual variability	Large	Small	Small
CYP-450 activation	Yes (twice)	Yes (once)	No
Irreversible inhibition	Yes	Yes	No
Maintenance ASA (mg)	81 – 325	81 - 162	≤ 100
Relative potency	Low	High	High
Onset	Within 2 hours	<30 minutes	30 minutes
Time to peak (h)	≥2 (with 600 mg)	2	2
Half-life	Life of platelet	Life of platelet	7 – 12 hours
Days to hold before CABG	> 5	> 7	> 3

Review of Clinical Trials: Clinical Complications



ISIS-2. Lancet 1988;8607:349-60
Yusuf S. N Engl J Med 2001;345:494-502
Wiviott SD. N Engl J Med 2007;357:2001-15
Wallentin L. N Engl J Med 2009;361:1045-57

Review of Clinical Trials: Bleeding Complications



Peters RJ. Circulation 2003;108:1682-87.
Wiviott SD. N Engl J Med 2007;357:2001-15
Wallentin L. N Engl J Med 2009;361:1045-57

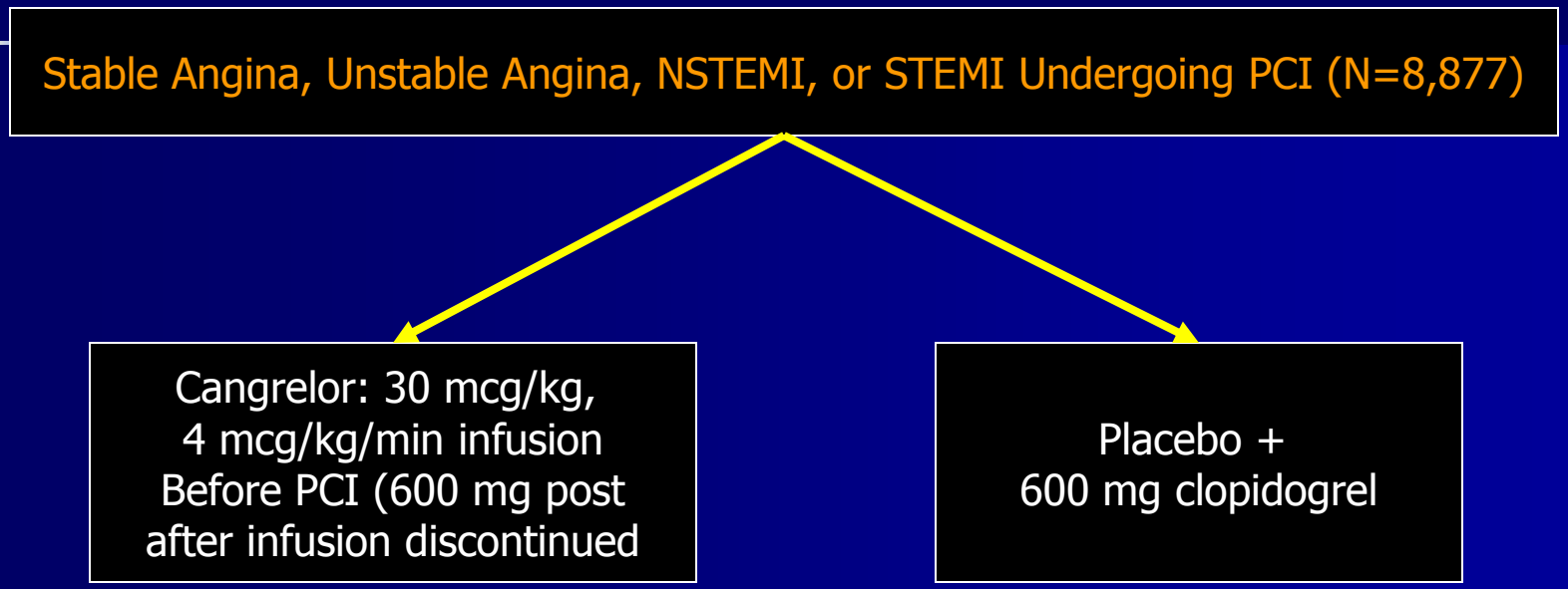
Limitations of Current Antiplatelet Agents

- Homeostasis
  - Current pathways needed for routine hemostasis and pathologic thrombosis
- Bleeding Risk
  - Dose-dependent increase bleeding risk with aspirin
  - Newer agents associated with greater risk of bleeding
- Continued events due to other platelet activation pathways
  - Thrombin-mediated platelet activation occurs via protease-activated receptor-1 (PAR-1) binding
  - Thrombin produced locally by tissue factor
  - PAR-1 required for pathological thrombus but may required for protective thrombosis

Cangrelor

- Analogue of adenosine triphosphate (ATP)
- Intravenous, reversibly-binding $P2Y_{12}$ inhibitor
- Not a pro-drug
- Rapidly inactivated by dephosphorylation
- Half-life: < 10 minutes
- Platelet function normalizes within 30-60 minutes after discontinuation
- Transition to clopidogrel complicated

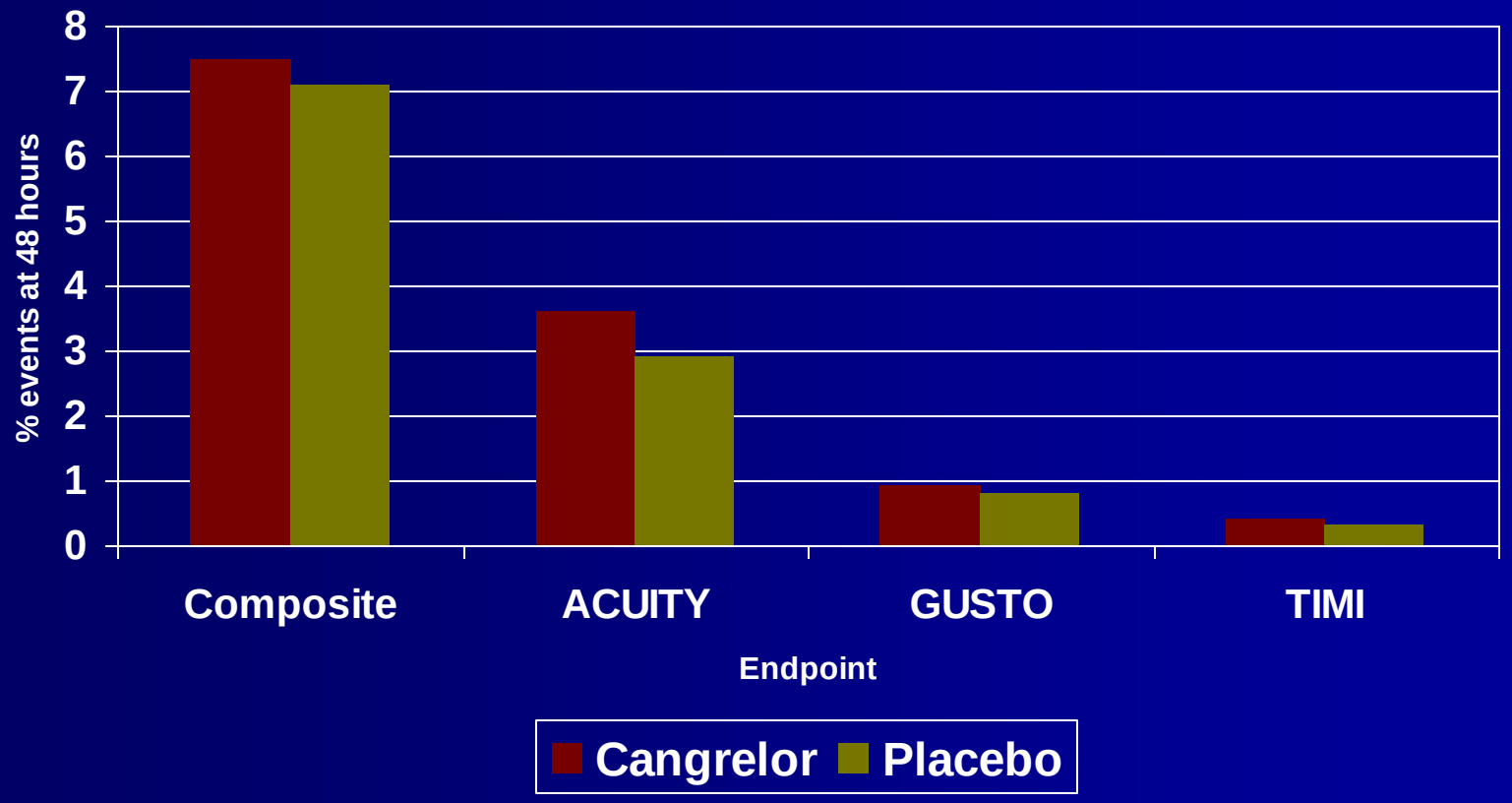
CHAMPION-PCI



- Primary Efficacy Endpoint: Composite of death from any cause, MI, or ischemia-driven revasc at 48 hours after PCI
- Bleeding: analyzed based on ACUITY, GUSTO, and TIMI criteria

Harrington RA. N Engl J Med 2009;361:2318-29

CHAMPION-PCI: Results at 48 hours



Harrington RA. N Engl J Med 2009;361:2318-29

CHAMPION-PLATFORM

Stable CAD or non-STEMI ACS Patients (N=5,362)

Cangrelor: 30 mcg/kg,
4 mcg/kg/min infusion
Before PCI (600 mg post
after infusion discontinued

Placebo +
600 mg clopidogrel

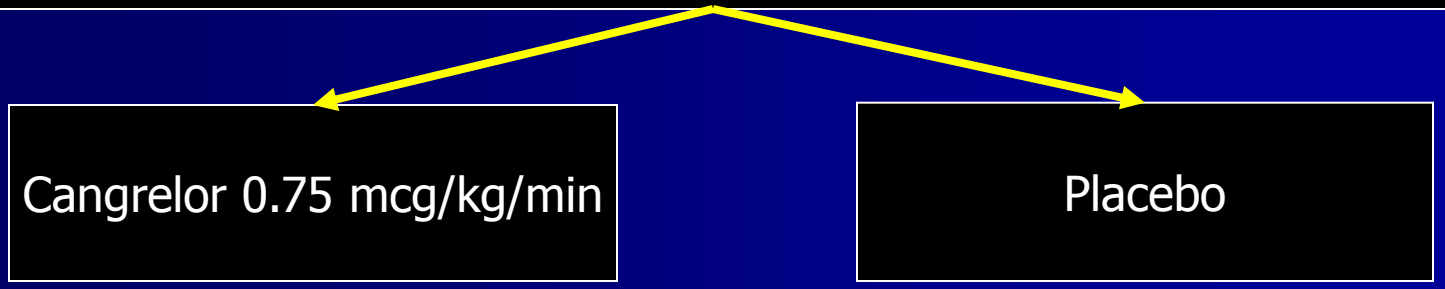
Trial terminated early since unlikely to show superiority of cangrelor

Events	Cangrelor (%)	Clopidogrel (%)
CV death/MI/Ischemia driven revasc	7	8
Death*	0.2	0.7
Stent Thrombosis*	0.2	0.6
TIMI Major Bleeding**	0.3	0.3

Bhatt DL. N Engl J Med 2009;361:2330-40

BRIDGE

Two Part Study:
1. Open-label, dose-finding phase
2. ACS patients or treated with, receiving thienopyridine, and awaiting CABG (N=210)



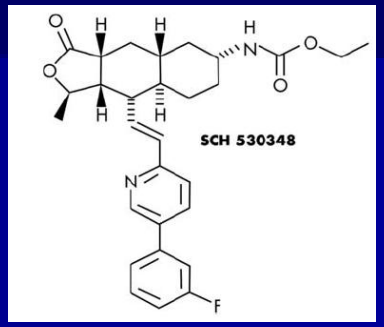
Dose of 0.75 mcg/kg/min determined to provide platelet inhibition of ≥ 60% by VerifyNow

Events	Cangrelor (%)	Clopidogrel (%)
Platelet inhibition (PRU < 240)*	98.8	19
CABG Related bleeding	11.8	10.4

*P<0.001

Angiolillo DJ. JAMA 2012;307:265-74

Vorapaxar (SCH 530348)



- Orally active reversible PAR-1 inhibitor
- Does not affect prothrombin time
- In animal studies no increased bleeding when used with aspirin and clopidogrel
- 40-mg dose inhibits ~30% thrombin mediated platelet activation at 30 minutes; ≥ 80% at 1 hour
- Half-life: 126 – 269 hours
- Hepatically metabolized

TRA-CER

Non-STEMI ACS patients (N=12,944) receiving standard medical therapy

Vorapaxar 40 mg loading Dose then 2.5 mg daily

Placebo

- Primary efficacy endpoint: Composite of CV death, MI, stroke, urgent revasc
- Primary safety endpoints: Composite of moderate-severe bleeding according to GUSTO classification and clinically significant bleeding according to TIMI classification
- Stopped early because of safety concerns (↑ ICH if history of stroke)

Events	Vorapaxar (%)	Placebo (%)
Primary endpoint	15.9	17
Myocardial infarction	9.6	10.8
Moderate or severe bleeding	6.1	4.5
Severe bleeding	2.2	1.4
Hemorrhagic stroke	0.3	0.1

Tricoci P. N Engl J Med 2012;366:20-33

TRA 2^{O}P TIMI-50

- Secondary prevention study (n=26,449)
- Randomized to vorapaxar 2.5 mg daily or placebo
- Primary endpoint: composite of CV death, MI, stroke, urgent revasc
- Results: vorapaxar ↓ primary endpoint but significant ↑ in bleeding, including ICH

Potential Uses of Future Agents

- Prevent future ischemic outcomes
- If patients temporarily unable to take oral $P2Y_{12}$ inhibitors
- Need to continued $P2Y_{12}$ inhibitor but need invasive/surgical procedure and interruption of therapy harmful

Platelet Function Studies

- High on-treatment platelet reactivity (HPR) to ADP major risk factor for post-PCI ischemic events (up to 30%)
- Some patients may not respond to clopidogrel due to CYP2C19 polymorphisms
- Other causes of HPR include: diabetes, obesity, smoking, renal dysfunction
- Consensus definition lacking
- Is there need to develop personalized approach similar to other cardiovascular medicines? (e.g., statins, beta-blockers, diuretics)

Tello-Montoliu A. Future Cardiol 2011;7:381-402.
Sibbing D. Thromb Haemost 2011;106:191-202

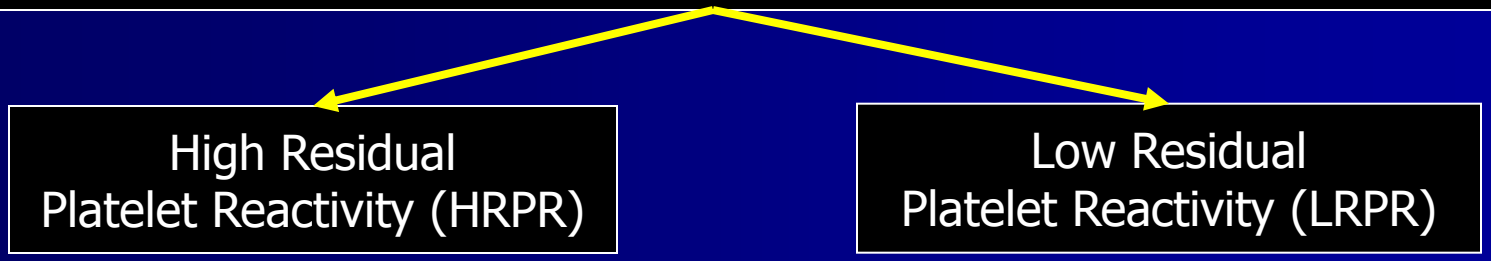
Comparisons of Platelet Function Assays

Test	Basis	Able to monitor	Advantages	Disadvantages
Light transmission aggregometry (LTA)	Platelet aggregation	Aspirin, $P2Y_{12}$ inhibitors	Historical gold standard, instrument adjustment possible, good predictivity, long experience	Large sample volume, time consuming, complex sample preparation, no standardization
VASP phosphorylation state (flow cytometry)	$P2Y_{12}$ activation-dependent signaling	$P2Y_{12}$ inhibitors	Whole-blood assay, very small sample volume, longer sample storage possible, P2Y12 receptor specific	Time consuming, complex sample preparation, need flow cytometer, weak sensitivity and predictivity
VerifyNow	Platelet aggregation	Aspirin, $P2Y_{12}$ inhibitors	Whole-blood assay, simple and rapid, standardized procedures	No assay adjustment possible, expensive cartridges
Platelet works	Platelet aggregation	Aspirin, $P2Y_{12}$ inhibitors	Whole-blood assay, simple and rapid	Not widely used, limited study results

Tello-Montoliu A. Future Cardiol 2011;7:381-402.
Sibbing D. Thromb Haemost 2011;106:191-202

RECLOSE 2-ACS

Prospective, observational cohort of 1,789 consecutive ACS patients undergoing PCI; all received 325 mg aspirin and loading dose of 600 mg followed by aspirin 325 mg daily + clopidogrel 75 mg daily ≥ 6 months



- Primary endpoint: composite of cardiac death, MI, any urgent coronary revasc, and stroke at 2-uear follow-up

Event	HRPR (%)	LRPR (%)
Primary endpoint	14.6	8.7
Stent thrombosis	6.1	2.9

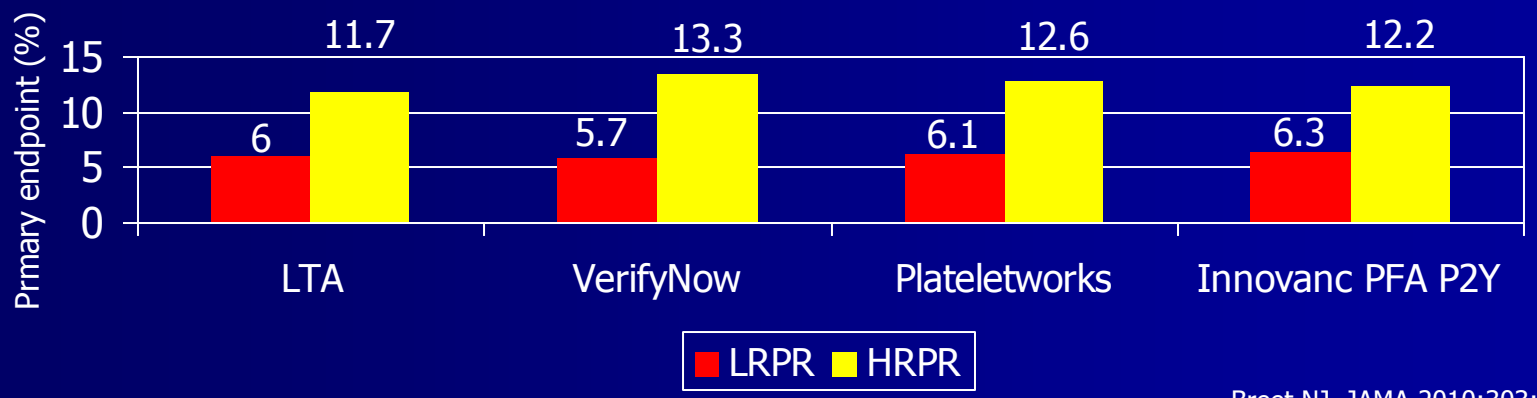
Parodi G. JAMA 2011;306:1215-23.

POPULAR

Consecutive patients (n=1,069) with established CAD scheduled for elective PCI with stent implantation and received clopidogrel

Platelet tests used:
- Light transmittance aggregometry
- VerifyNow P2Y12 assay
- Plateletworks assay
- Innovance PFA P2Y assay
- IMPACT-R
- Dade PFA-100

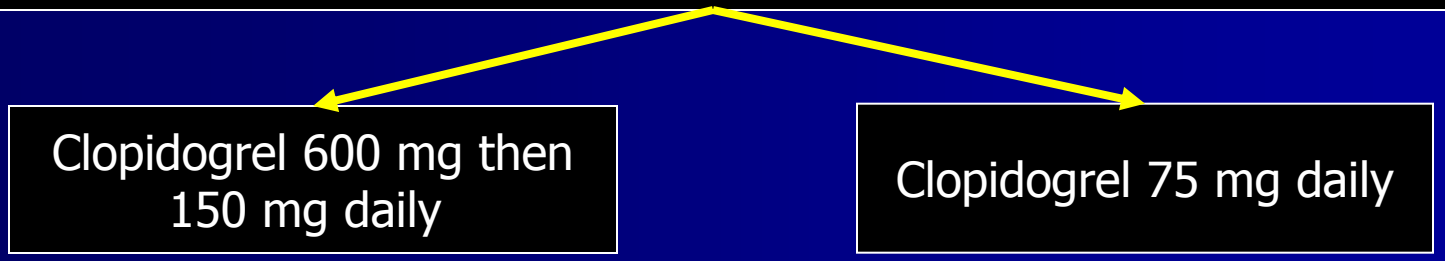
- Primary endpoint: composite of all-cause death, nonfatal MI, stent thrombosis, and ischemic stroke



Breet NJ. JAMA 2010;303:754-62.

GRAVITAS

Stable angina or ischemia or NSTEMI (N=5,429);
Platelet function assay measure 12 – 24 hours after PCI
If PRU ≥ 230



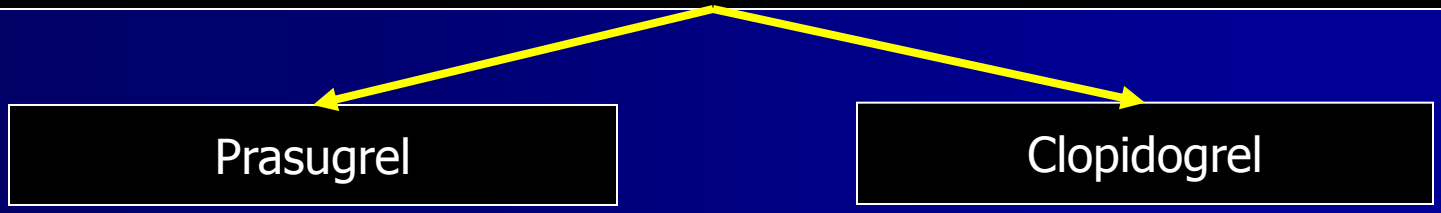
- Primary endpoint: First occurrence of CV death, non-fatal MI, or definite/probable stent thrombosis in non-responders 6 months after randomization
- 80% had stable coronary disease
- 41% of patients screened had PRU ≥ 230

Event	High clopidogrel (%)	Standard Clopidogrel (%)
Primary endpoint	2.3	2.3
GUSTO severe bleeding	1.4	2.3

Price MJ. JAMA 2011;305:1097-1105.

TRIGGER-PCI

Patients (N=423 out of planned 2,150)
with PRU > 208 while on clopidogrel



- Primary endpoint: CV death or MI at 6 months
- Terminated early since there would not be enough endpoints for meaningful analysis: only 1 clinical endpoint throughout follow-up

Evaluation time	Prasugrel (%)	Clopidogrel (%)
Day 90 (PRU > 208)	5.9	70.4
Day 176 (PRU > 208)	5.8	70.8

ARMYDA-BLEEDS

Consecutive clopidogrel-treated patients (N=310) with:

1. Indication for PCI for inducible ischemia or non-STEMI ACS and
2. Clopidogrel therapy before PCI as 600 mg load or long-term therapy for ≥ 5 days
   - Platelet reactivity evaluated before PCI and at 8 and 24 hours post-PCI

using VerifyNow P2Y12 assay

- Primary endpoint: 30-day incidence of major bleeding or entry-site complications according to quartile distribution of P2Y12 reaction units (PRU)
- Age > 70 years and use of GPIIb/IIIa inhibitors also increased risk of primary endpoint

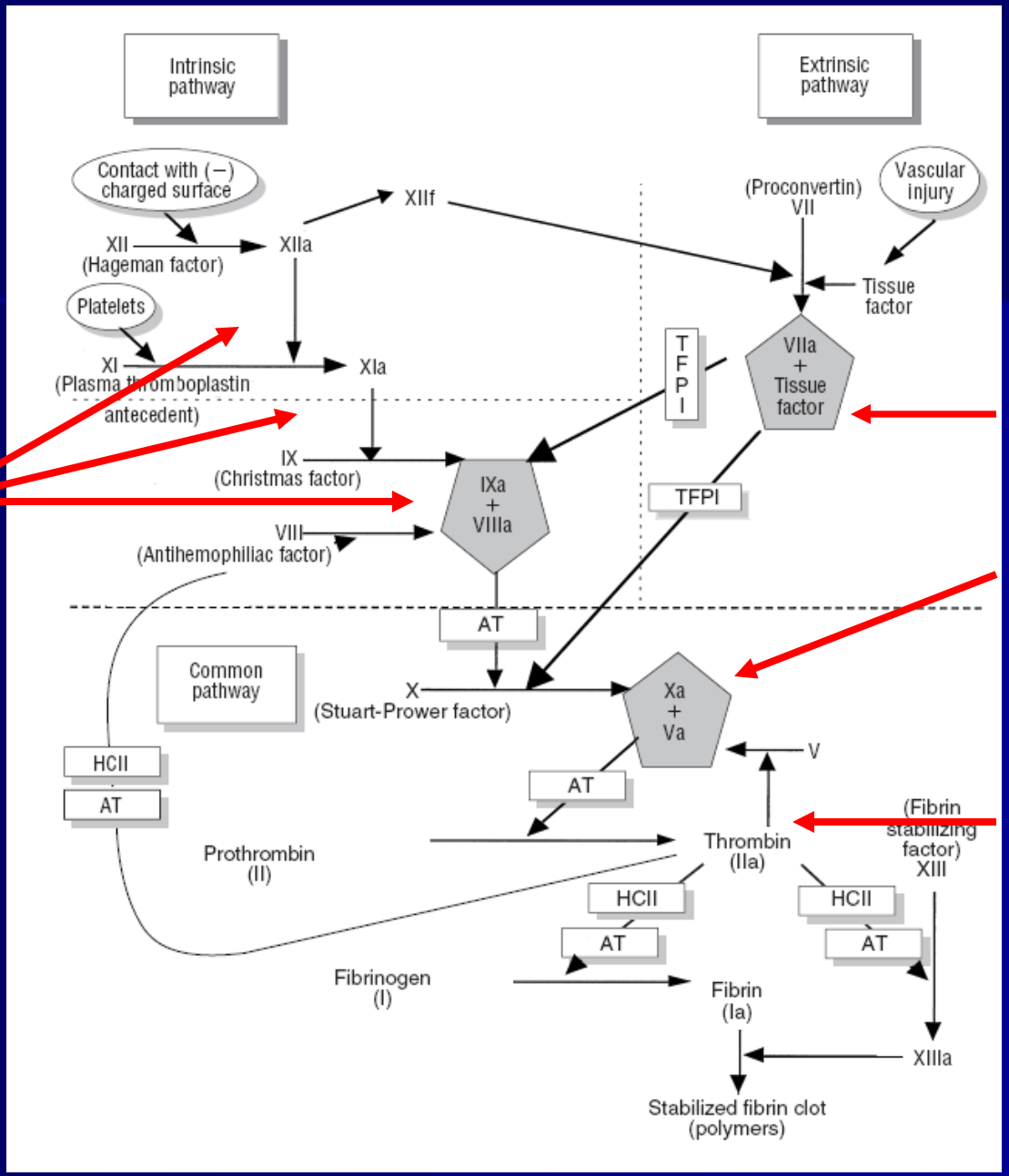
Event	1st Quartile (%)	2nd Quartile (%)	3rd Quartile (%)	4th Quartile (%)
Primary endpoint	10.1	6.3	1.4	1.3

Patti G. Am J Cardiol 2011;107:995-1000.

ACCF/AHA Guidelines on Platelet Function Testing

- Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management (Class IIb)
- Platelet function testing may be considered in patients at high risk for poor clinical outcomes (Class IIb)
- In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered (Class IIb)
- Routine use of platelet function testing to screen patients with clopidogrel who are undergoing PCI not recommended (Class III)

Levine GN. Circulation 2011;124:e574-e651.



Heparin
Warfarin (IXa)

Warfarin

Heparin
Enoxaparin
Fondaparinux
Warfarin

Heparin
Enoxaparin
Warfarin
Argatroban
Bivalirudin

Haines ST *Pharmacotherapy*: 6th ed. 377, 2005

Indirect Anticoagulants

- Unfractionated heparin (UFH)
- Low molecular weight heparin
  - Enoxaparin (Lovenox®)
- Fondaparinux (Arixtra®)
- Warfarin (Coumadin®)

Limitations of Current Anticoagulants

- Need for cofactor
- Unpredictability
- Monitoring
- Elimination route
- Bleeding
- Drug Interactions

Warfarin (Coumadin®)

- Inhibits vitamin K dependent clotting factors and initially inhibits natural anticoagulant factors
- Racemic mixture of R and S enantiomers
- S enantiomer 2-5 times greater activity (strong warfarin)

Factors	Half-life (hours)
VII	5-6
IX	24
X	30-50
II	96
Protein C	8-10
Protein S	42-60

Ansell J Chest 126; 205S, 2004

Warfarin Adult Dosing and Monitoring

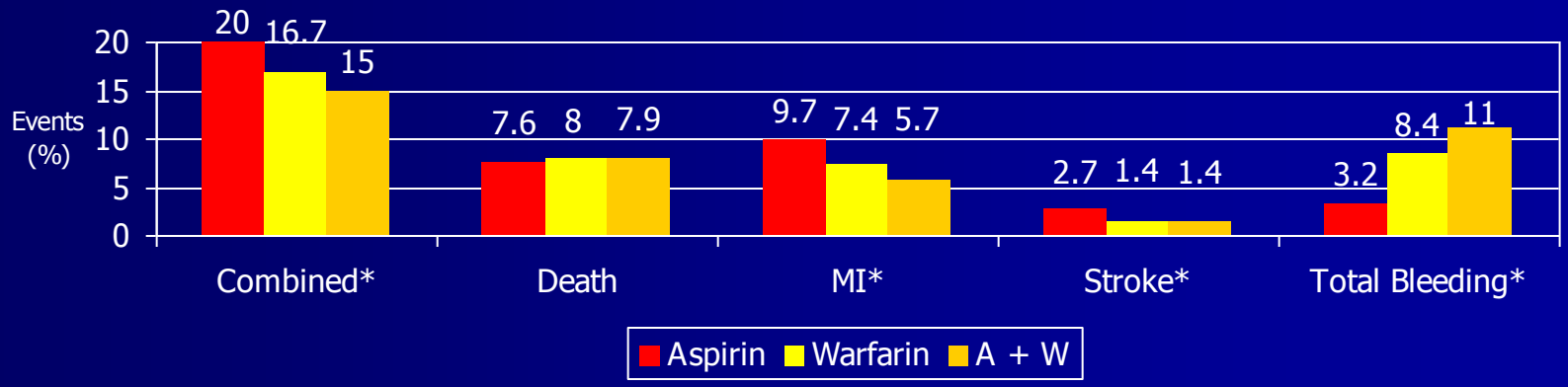
- Typical starting dose 5 mg daily
  - Consider lower initial doses in following patients:
    - Elderly / low body weight
    - Heart failure
    - Liver dysfunction
- Onset of action 24 – 72 hours
- Peak effect takes 5 – 7 days
- Mean half-life of 40 hours
- Almost entirely metabolized by hepatic enzyme CYP450 2C9
- Narrow therapeutic range: most patients target INR 2-3
- Patients should maintain consistent amounts of vitamin K in diet
- Drug that may decrease warfarin requirements:
  - Amiodarone
  - Bactrim™
  - Metronidazole
- Adverse reactions: bleeding, warfarin skin necrosis

Ansell J Chest 126; 205S, 2004

Warfarin: WARIS II

Patients (N=3,630) hospitalized for acute myocardial infarction

- Aspirin 160 mg
- Warfarin (INR goal: 2.8 – 4.2)
- Warfarin (INR goal: 2 – 2.5)



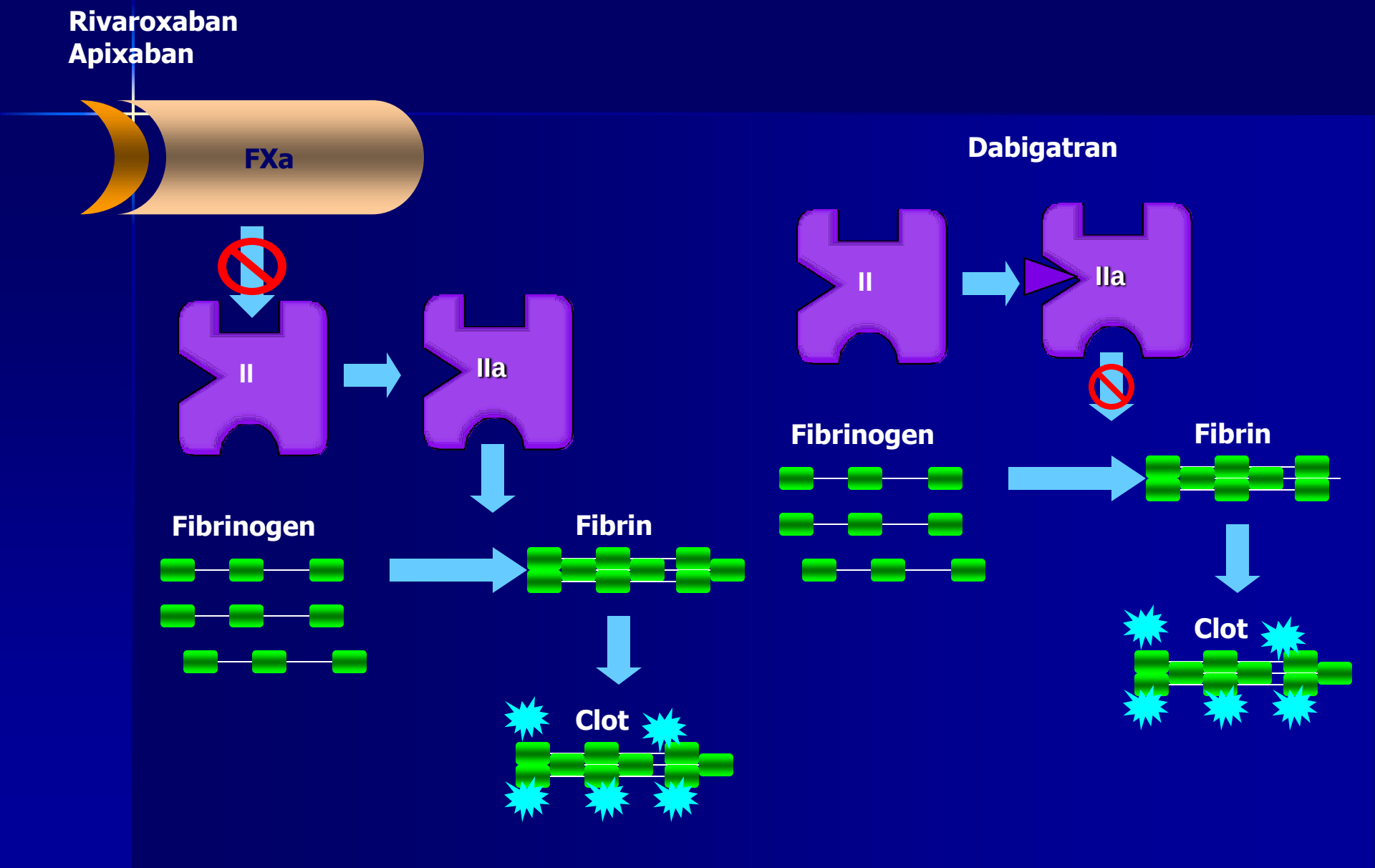
Hurlen M. N Engl J Med 2002;347:969-74

Dual Antiplatelet Therapy and Warfarin (Triple therapy)

- Some patients may require aspirin, clopidogrel, and warfarin
- 3 – 5 x increase risk of major bleeding complications with triple therapy vs. dual antiplatelet therapy
- If triple therapy required:
  - Low dose aspirin (<100 mg/day)
  - Conventional clopidogrel dosing (75 mg)
  - Lower INR target (2 – 2.5)
  - Consideration of prophylactic PPI

Holmes DR. JACC 2009;54:95-109

Pharmacology of Newer Anticoagulants



Dabigatran (Pradaxa®)

- Indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF)
- Specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule
- Capsules should not be broken, opened, or chewed as it will result in increase exposure to the drug
- Bottles containing 60 capsules only have 60-day expiration
- Dyspepsia common adverse effect
- Cost: ~$180/month

Dabigatran Pharmacokinetics

- Peak plasma concentrations and anticoagulant effects occur 0.5 – 2 hours after oral administration
- At recommended doses, dabigatran etexilate prolongs:
  - Activated partial thromboplastin time (aPTT)
  - Ecarin clotting time (ECT)
  - Thrombin time (TT)
- Eliminated primarily in the urine (90%)
- Cytochrome P450 enzymes are not involved in metabolism

RE-LY

Afib (n=18113)AND at least one of the following: previous stroke or TIA, EF <40%, NYHA class II or higher, age at least 75 or age 65 – 74 plus DM, HT< or CAD

Dabigatran 110 or 150 mg twice daily

Warfarin adjusted to INR 2 – 3

- Mean $CHADS_2$ score 2.1; 30% with score ≥ 3
- Warfarin group INR 64% time in therapeutic range

Events	Dabigatran 110 mg (%/year)	Dabigatran 150 mg (%/year)	Warfarin (%/year)
Stroke or systemic embolism*	1.53	1.11	1.69
Major bleeding**	2.71	3.11	3.36
Hemorrhagic stroke*	0.12	0.10	0.38
GI bleeding***	1.12	1.51	1.02

*P<0.001; non-inferiority both dabi- doses
**P=0.003; dabi- 110 mg vs. warfarin
***P<0.001 dabi- 150 mg vs. warfarin
Connolly SJ. N Engl J Med 2009;361:1139-51.

Rivaroxaban (Xarelto®)

- Rapid, reversible, oral factor Xa inhibitor, competitively inhibiting free and clot-bound factor Xa
- Reaches peak activity within 2 hours
- Terminal half-life: 5 – 9 hours
- ~30% excreted renally
- Dosing:
  - Nonvalvular AF: if CrCL >50 mL/min 20 mg once daily with evening meal; if CrCL 15 – 50 mL/min 15 mg once daily
  - Prophylactic anticoagulation: 10 mg once daily
- **Boxed warning**: if must be discontinued for reason besides bleeding, consider administering another anticoagulant

ROCKET-AF

Nonvalvular atrial fibrillation (N=14,264); 87% had $CHADS_2 \geq 3$

Rivaroxaban 20 mg once daily (15 mg if CrCL 30-49 mL/min)

Warfarin titrated to INR of 2.5

- Warfarin group INR 55% time in therapeutic range
- Primary efficacy: Composite of stroke and non-CNS systemic embolism
- Primary safety: Major and non-major clinically relevant bleeding events

Events	Rivaroxaban (%/year)	Warfarin (%/year)
Primary efficacy (as-treated)*	1.7	2.2
Primary safety	14.9	14.5
Major bleeding	3.6	3.4
Intracranial hemorrhage**	0.5	0.7

- At end of study took 13 days in rivaroxaban group to reach therapeutic range vs. 3 days in warfarin group
- More primary events in rivaroxaban group vs. warfarin during 1st moth after study end (22 vs. 7; *P*=0.008)

*P<0.001
**P=0.02

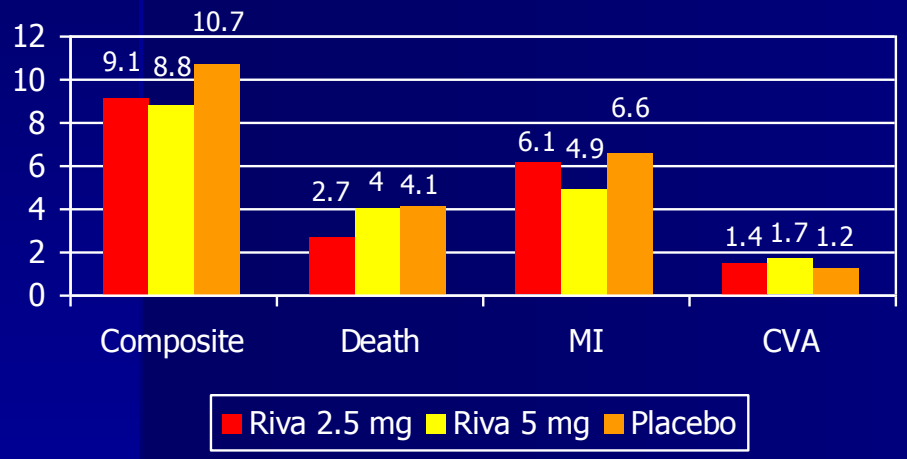
Patel MR. N Engl J Med 2011;365:883-91.

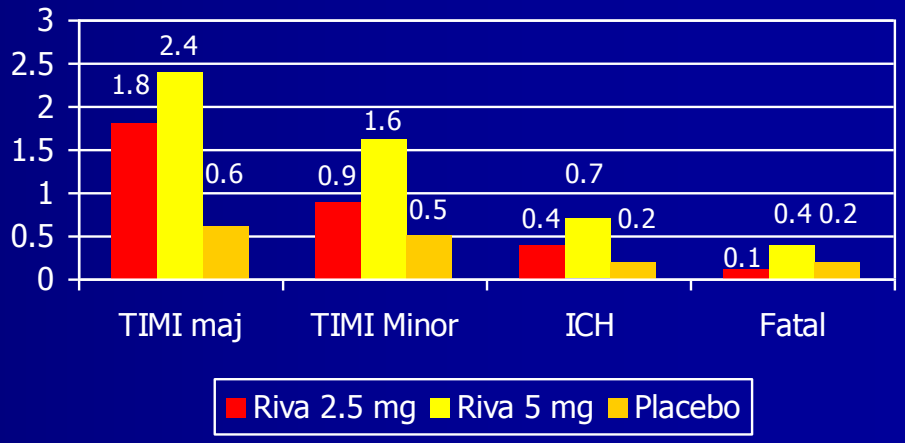
ATLAS ACS-2 TIMI 51

ACS patients (N=15,526) receiving standard medical therapy
(incl. low-dose aspirin and thienopyridine; ~60% underwent PCI or CABG

Rivaroxaban 2.5 or 5 mg twice daily

Placebo





*Bleeds requiring medical attention:

- Rivaroxaban 2.5 mg: 12.9%
- Rivaroxaban 5 mg: 16.2%
- Placebo: 7.5%

Mega JL. N Engl J Med 2012;366:9-19

Apixaban (Eliquis™)

- Direct, orally active, selective, reversible, and noncompetitive inhibitor of free and clot-bound factor Xa
- Dosing: 2.5 – 5 mg twice daily investigated
- Peak effect within 1 – 3 hours
- Half-life: 8 – 15 hours
- Renal elimination: 30%

ARISTOTLE

Afib or flutter (N=18,201) at enrollment or ≥ 2 episodes at least 2 weeks apart in 12 months before enrollment; ≥ 1 of CHADS2 risk factors for stroke

Apixaban 5 mg twice daily;
2.5 mg twice daily if ≥ 2 or more of following criteria: age ≥ 80, <60 kg, SCr.> 1.5 mg/dL

Warfarin adjusted to INR 2 – 3 with algorithm to adjust dose

- $CHADS_2$ score ~ 2 in both groups; 30% with score ≥ 3
- Warfarin group INR 66% time in therapeutic range

Events	Apixaban (%/year)	Warfarin (%/year)
Stroke or systemic embolism*	1.27	1.6
Death from any cause**	3.52	3.94
Major Bleeding*	2.13	3.09

*P<0.001
**P=0.047
Granger CB. N Engl J Med 2011;365:981-92.

Comparison of New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
FDA Indication	Nonvalvular atrial fibrillation	Nonvalvular atrial fibrillation; postoperative thromboprophylaxis	Pending FDA approval
Target	Factor IIa (thrombin)	Factor Xa	Factor Xa
Binding to catalytic site	Reversible	Reversible	Reversible
Onset (hours)	0.5 – 2	0.5 – 3	0.5 – 2
Half-life (hours)	7 – 17	3 – 10	8 – 15
Route of elimination	Urine: 90% Feces: 10%	Urine: 70% Feces: 30%	Urine: 30% Feces: 70%
Effect on anticoagulation labs	Prolongs PT and aPTT but varies with different reagents	Prolongs PT but not sensitive at low concentrations	Prolongs PT and aPTT but not know with different reagents

Converting Between Anticoagulants

Converting from (**below**) to (**yellow**):	**Enoxaparin**	**IV Heparin**	**Warfarin**	**Dabigatran**	**Rivaroxaban**
Enoxaparin	---	12-24 hours last enoxaparin dose (based on renal function)	Concurrently with enoxaparin (if bridging)	≤ 2 hours prior to next regularly scheduled dose of enoxaparin	≤ 2 hours prior to next regularly scheduled dose of enoxaparin
IV Heparin	~ 1 hour after IV heparin discontinuation	---	Concurrently with IV heparin (if bridging)	At time of IV heparin discontinuation	At time heparin discontinuation
Warfarin	When INR <2	When INR <2	---	When INR <2	When INR < 3
Dabigatran	12 hours (if CrCL ≥ 30) or 24 hours (if CrCL < 30)	12 hours (if CrCL ≥ 30) or 24 hours (if CrCL < 30)	1-3 days based on CrCL	---	≤ 2 hours prior to next regularly scheduled evening dose
Rivaroxaban	24 hours after discontinuation of rivaroxaban	24 hours after discontinuation of rivaroxaban	Initiate warfarin **AND** parenteral anticoagulant 24 hours after discontinuation of rivaroxaban	24 hours after discontinuation of rivaroxaban	---

Which Agent to Choose?

- Items to consider:
  - Comorbidities
  - Compliance
  - Insurance
  - Need for dual antiplatelet therapy
  - Outcomes
  - Patient preference

Select ACCF/AHA Guidelines on Anticoagulant Therapy

- Reasonable to prescribe warfarin post-STEMI patients w/ LV dysfunction and extensive regional wall-motion abnormalities (Class IIa)
- May be considered in patients with severe LV dysfunction, w/ or w/o HF (Class IIb)
- Anticoagulation with vitamin K antagonist recommended for patients with > 1 moderate risk factor
- Dabigatran useful alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal disease (CrCL < 15 mL/min), or advanced liver disease (Class I)

FDA Expands Advice on STATIN RISKS

If you're one of the millions of Americans who take statins to prevent heart disease, the Food and Drug Administration (FDA) has important new safety information on these cholesterol-lowering medications.

FDA is advising consumers and health care professionals that:

- Routine monitoring of liver enzymes in the blood, once considered standard procedure for statin users, is no longer needed. Such monitoring has not been found to be effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use.
- Cognitive (brain-related) impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users.
- People being treated with statins may have an increased risk of raised blood sugar levels and the development of Type 2 diabetes.
- Some medications interact with lovastatin (brand names include Mevacor) and can increase the risk of muscle damage.

This new information should not scare people off statins, says Amy G. Egan, M.D., M.P.H., deputy director for safety in FDA's Division of Metabolism and Endocrinology Products (DMEP). "The value of statins in preventing heart disease has been clearly established," she says. "Their benefit is indisputable, but they need to be taken with care and knowledge of their side effects."

FDA will be changing the drug labels of popular statin products to reflect these new concerns. (These labels are not the sticker attached to a prescription drug bottle, but the package insert with details about a prescription medication, including side effects.)

The statins affected include:

- Altoprev (lovastatin extended-release)
- Crestor (rosuvastatin)
- Lescol (fluvastatin)
- Lipitor (atorvastatin)
- Livalo (pitavastatin)
- Mevacor (lovastatin)
- Pravachol (pravastatin)
- Zocor (simvastatin).

Products containing statins in combination with other drugs include:

- Advicor (lovastatin/niacin extended-release)
- Simcor (simvastatin/niacin extended-release)
- Vytorin (simvastatin/ezetimibe).

"The value of statins in preventing heart disease has been clearly established."

Update to All Statin Labeling

- Liver enzyme tests before initiating and when clinically indicated thereafter
- Memory loss and confusion reported with statin use
- Increases in blood sugar levels reported with statin use

http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm

Updates to Simvastatin Labeling

- Maintain patients on simvastatin 80 mg only if taking that dose for ≥ 12 months
- Do not initiate 80 mg dose
- Place patients who do not meet LDL goal on simvastatin 40 mg on alternative LDL-lowering therapy
- Switch patients who need to be initiated on drug that interacts with simvastatin to an alternative statin with less potential for drug-drug interaction
- Drug interaction updates
  - Avoid with:
    - Cyclosporine
    - Danazol
    - Gemfibrozil
    - Posaconazole
  - Do not exceed 10 mg simvastatin with:
    - Diltiazem
    - Verapamil
  - Do not exceed 20 mg simvastatin with:
    - Amiodarone
    - Amlodipine
    - Ranolazine

http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm

Updates to Lovastatin Labeling

- Lovastatin CYP3A4 substrate
- Strong inhibitors will increase exposure to lovastatin
- Following drugs now contraindicated with lovastatin
  - Boceprevir
  - Cyclosporine
  - Gemfibrozil
  - Posaconazole
  - Telaprevir
- New dose limitations of 20 mg of lovastatin with following drugs:
  - Diltiazem
  - Verapamil

http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm

Updates to Atorvastatin and Rosuvastatin Labeling

- Atorvastatin
  - Avoid with:
    - Ritonavir
    - Tipranavir
  - Use lowest dose as possible with:
    - Lopinavir + ritonavir
  - 20 mg maximum dose with:
    - Darunavir + ritonavir or fosamprenavir ± ritonavir
    - Saquinavir + ritonavir
  - 40 mg maximum dose with:
    - Nelfinavir
- Rosuvastatin
  - 10 mg maximum dose with:
    - Atazanavir ± ritonavir
    - Lopinavir ± ritonavir

http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm

Statins and Cognitive Impairment

- Individual over age of 50 experienced notable, but ill-defined memory loss or impairment
- Reversible upon discontinuation of statin therapy
- Onset highly variable (days to years after exposure)
- No association between specific statin or statin dose, age, or concomitant medication use

Mechanism of Statins and Cognitive Impairment

- Cholesterol important in following
  - Myelin sheath formation
  - Neurotransmitter receptor expression
  - Neuron synapse development
  - Steroid hormones involved in brain signaling
  - Transport of antioxidants

Evans MA. Pharmacotherapy 2009;29:800-11.

Statins and Glucose Levels

- 27% increase in investigator-reported diabetes in JUPITER trial
- Substudy of PROVE-IT TIMI 22 showed worsening glycemic contril with high-dose atorvastatin vs. pravastatin
  - 0.5% increase in HbA1c (44% atorva- vs. 28% pravastatin)
- Increased diabetes with high dose statin?
  - OR: 1.12 (95% CI, 1.01-1.22)
  - CV events: 0.84 (95% CI, 0.75-0.94)
  - Number needed to harm (for new diabetes): 498
  - Number needed to treat (for CV event reduction): 155

Preiss D. JAMA 2011;305:2256-64

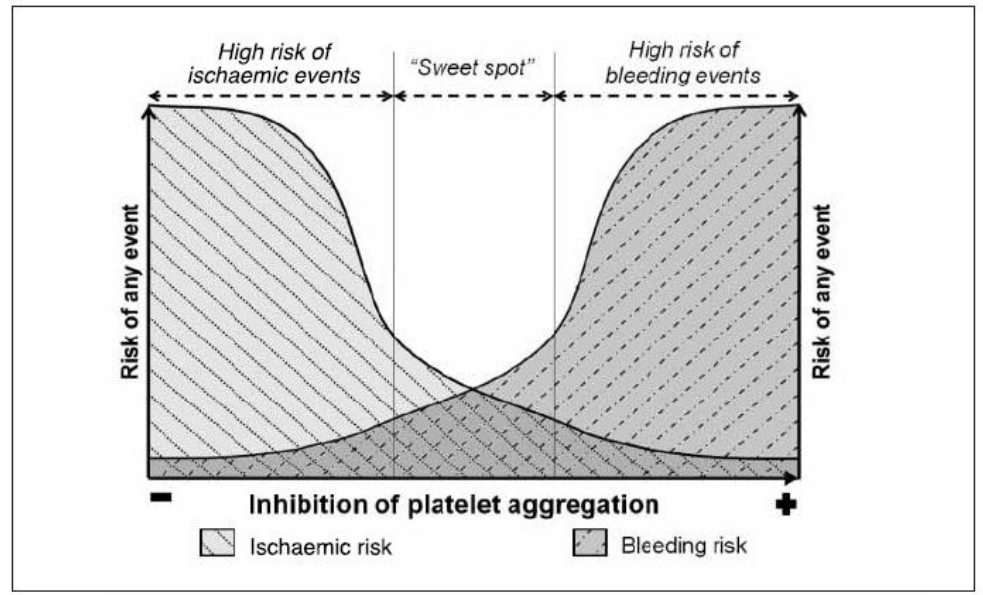
Mechanism of Statins and Increased Glucose Levels

- May interfere with normal glucose metabolism
- Decreased cellular glucose uptake
- Insulin resistance by inhibition of isoprenoid biosynthesis (intermediate in cholesterol production)
- Decreased insulin secretion
- May uncover diabetes in high-risk population

Rajpathak SN. Diabetes Care 2009;32:1924-29.

Conclusion

- Balance of preventing ischemic complications vs. bleeding risk
- Finding "Sweet Spot"



- Platelet function monitoring: Which will benefit from it?
- Dealing with new anticoagulants
- Benefits and risks of statin therapy

Ferreiro JL. Thromb Haemost 2010;103:1128-1135.

Questions