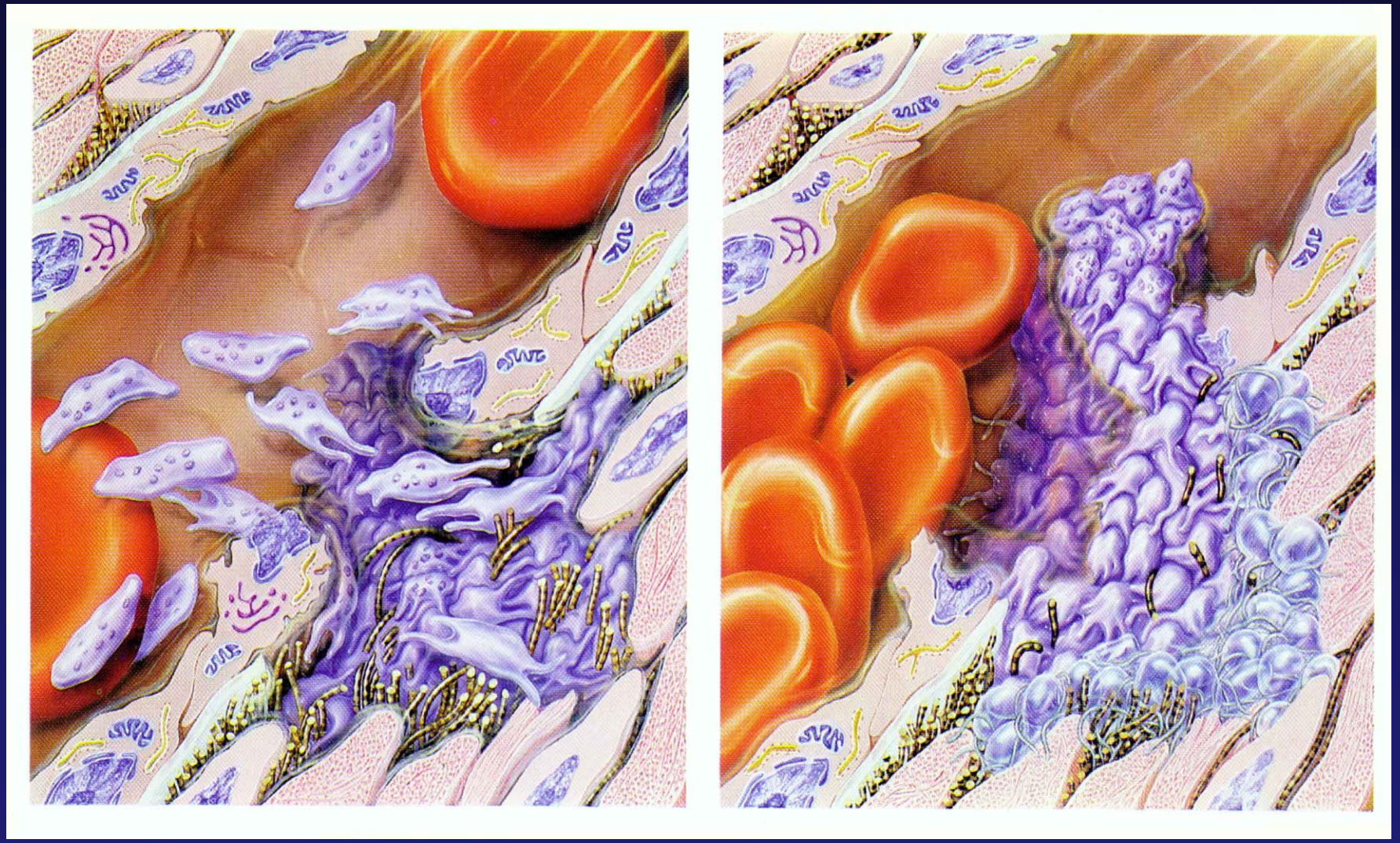
Platelet-Inhibiting Drugs: A Hematologist's Perspective

A. Koneti Rao, M.D.,
Sol Sherry Professor of Medicine
Chief, Hematology Section
Co-Director, Sol Sherry Thrombosis Research Center

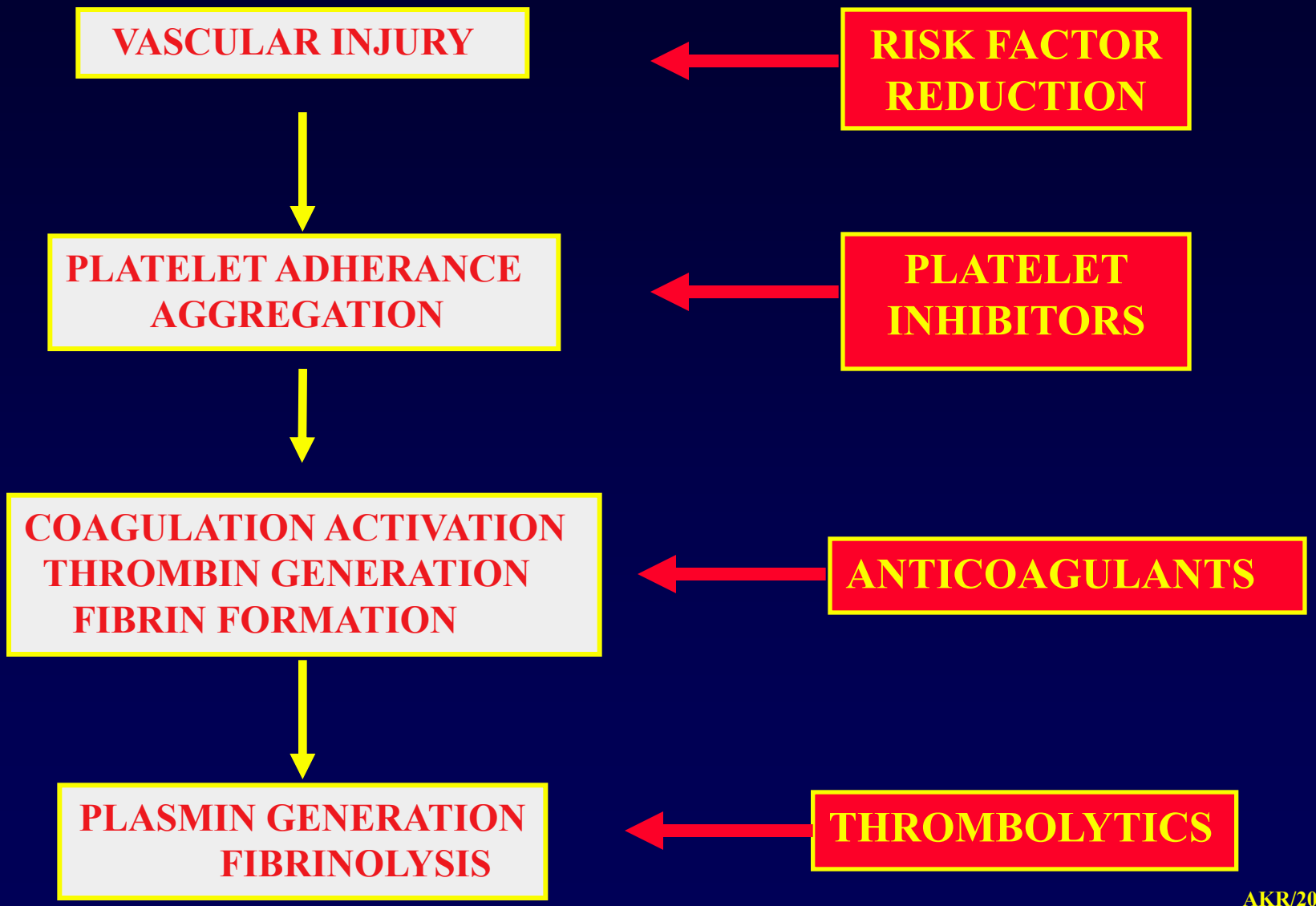
Temple University School of Medicine

2012
Chile



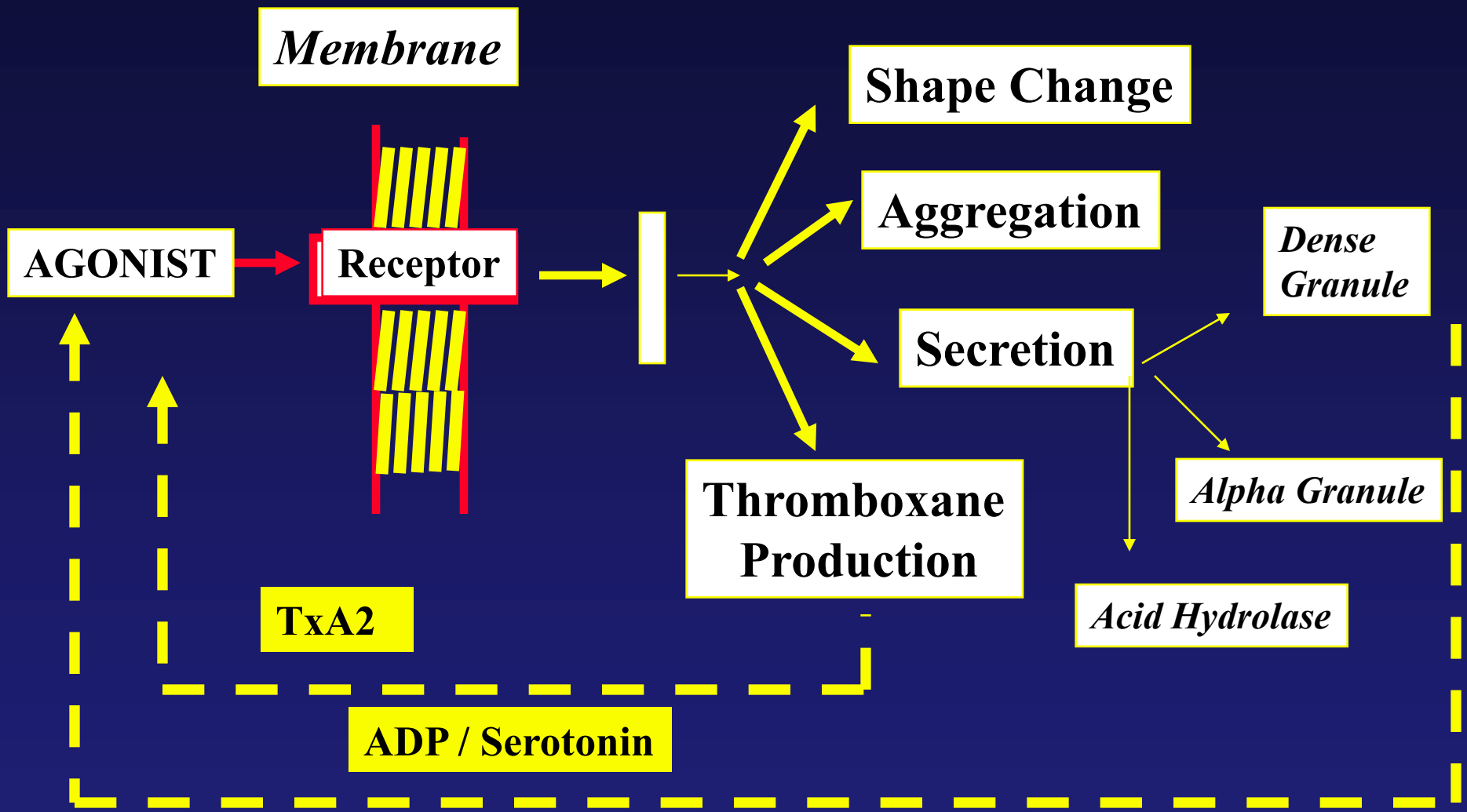
Akkerman JW, Bouma BN, Sixma JJ. Atlas of Hemostasis, 1979.

STRATEGIES FOR ANTITHROMBOTIC THERAPY

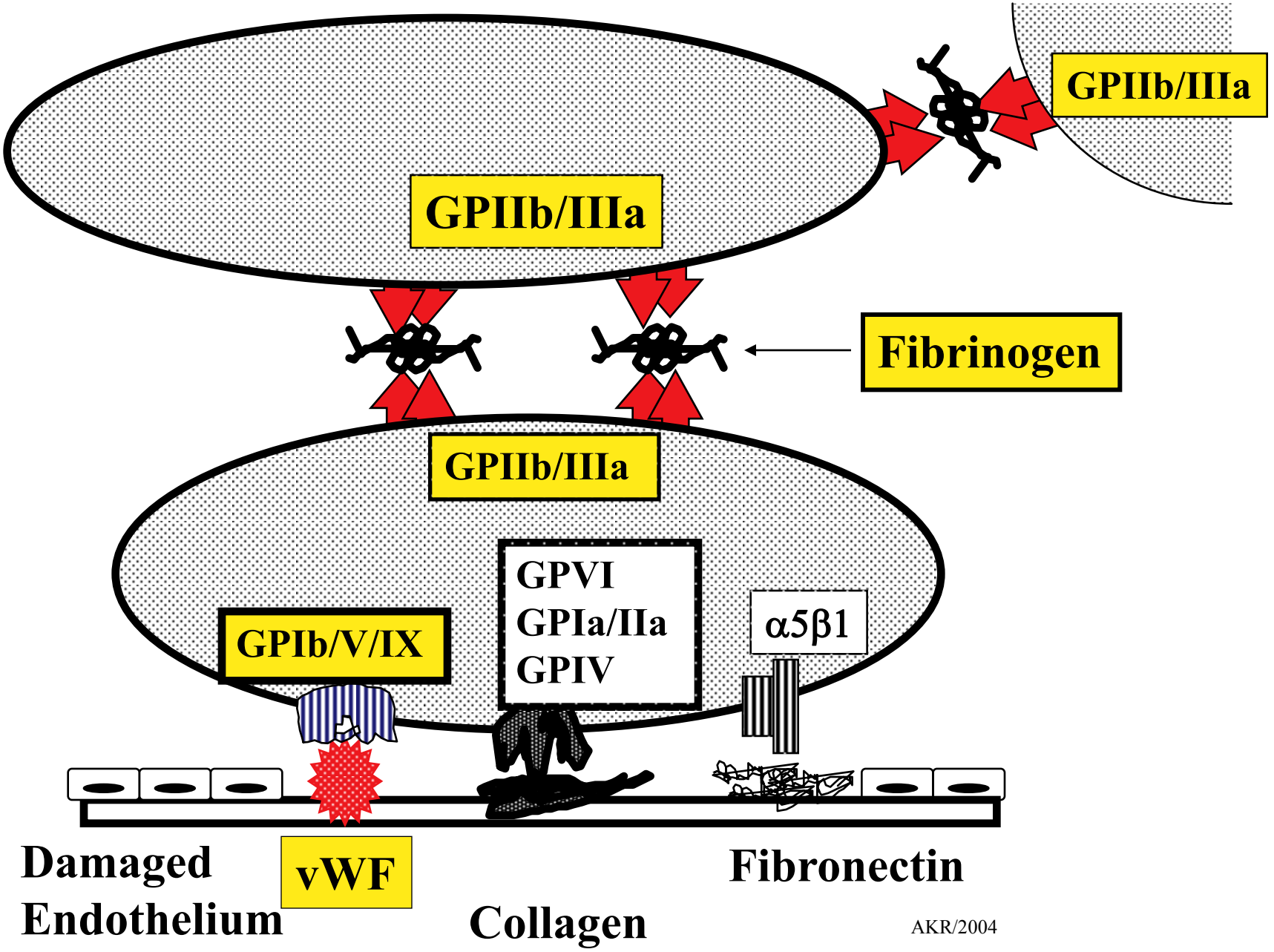


AKR/2003

Platelet Responses to Activation



Rao/2010


GPIIb/IIIa
GPIIb/IIIa
Fibrinogen
GPIIb/IIIa
GPVI
GPIa/IIa
GPIV
GPIb/V/IX
α5β1
Damaged
Endothelium
vWF
Collagen
Fibronectin

AKR/2004


Platelet-Inhibiting Drugs

Platelet Inhibiting Drugs

- Aspirin
- Sulfinpyrazone
- Dipyridamole
- P2Y12 Antagonists
  - Thienopyridines
    - Ticlopidine, Clopidogrel, Prasugrel (*Effient*)
  - Non-Thienopyridine
    - Ticagrelor (*Brilinta*)
- GPIIb/IIIa Inhibitors

  Abciximab (c7E3 Fab, *ReoPro*)

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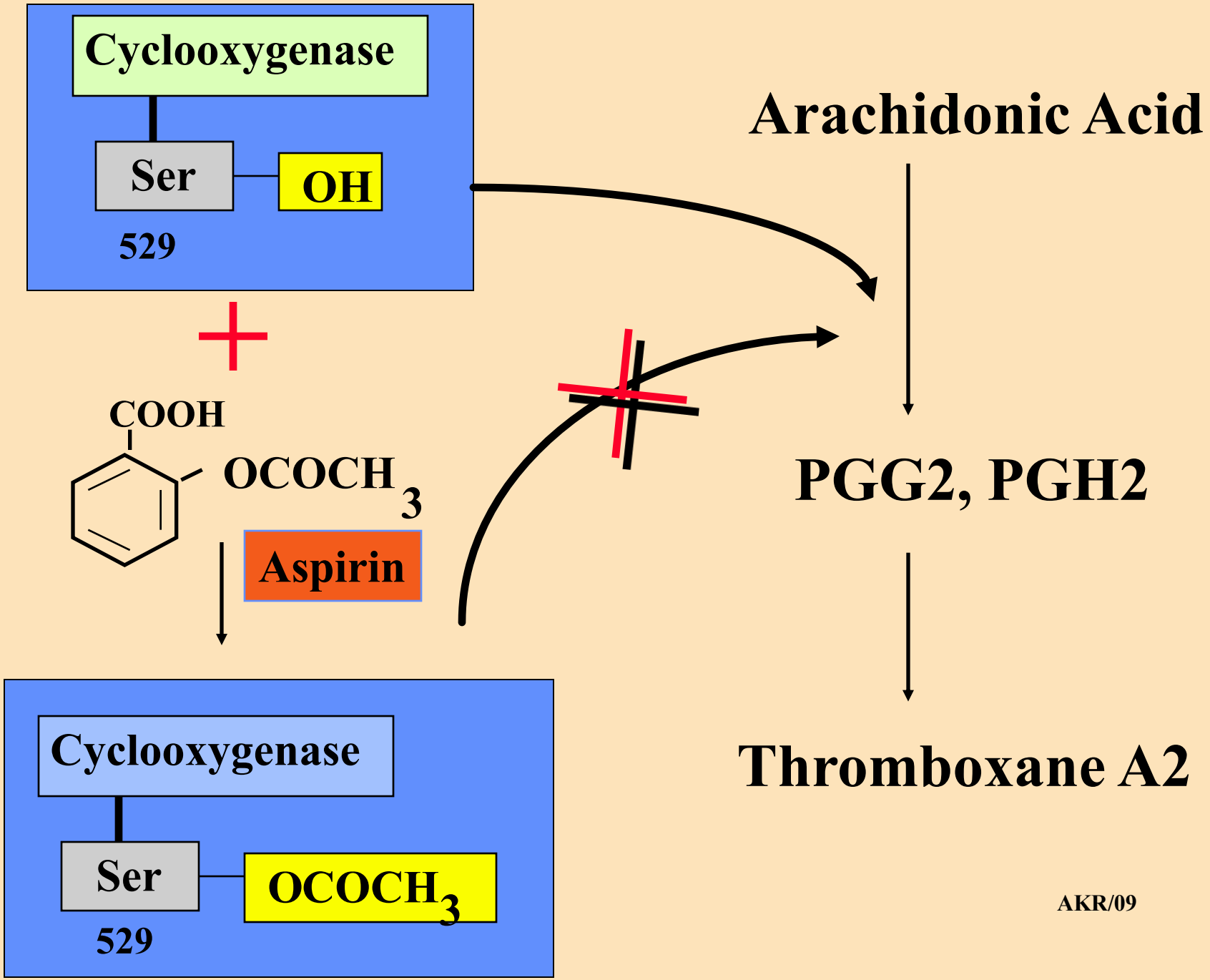
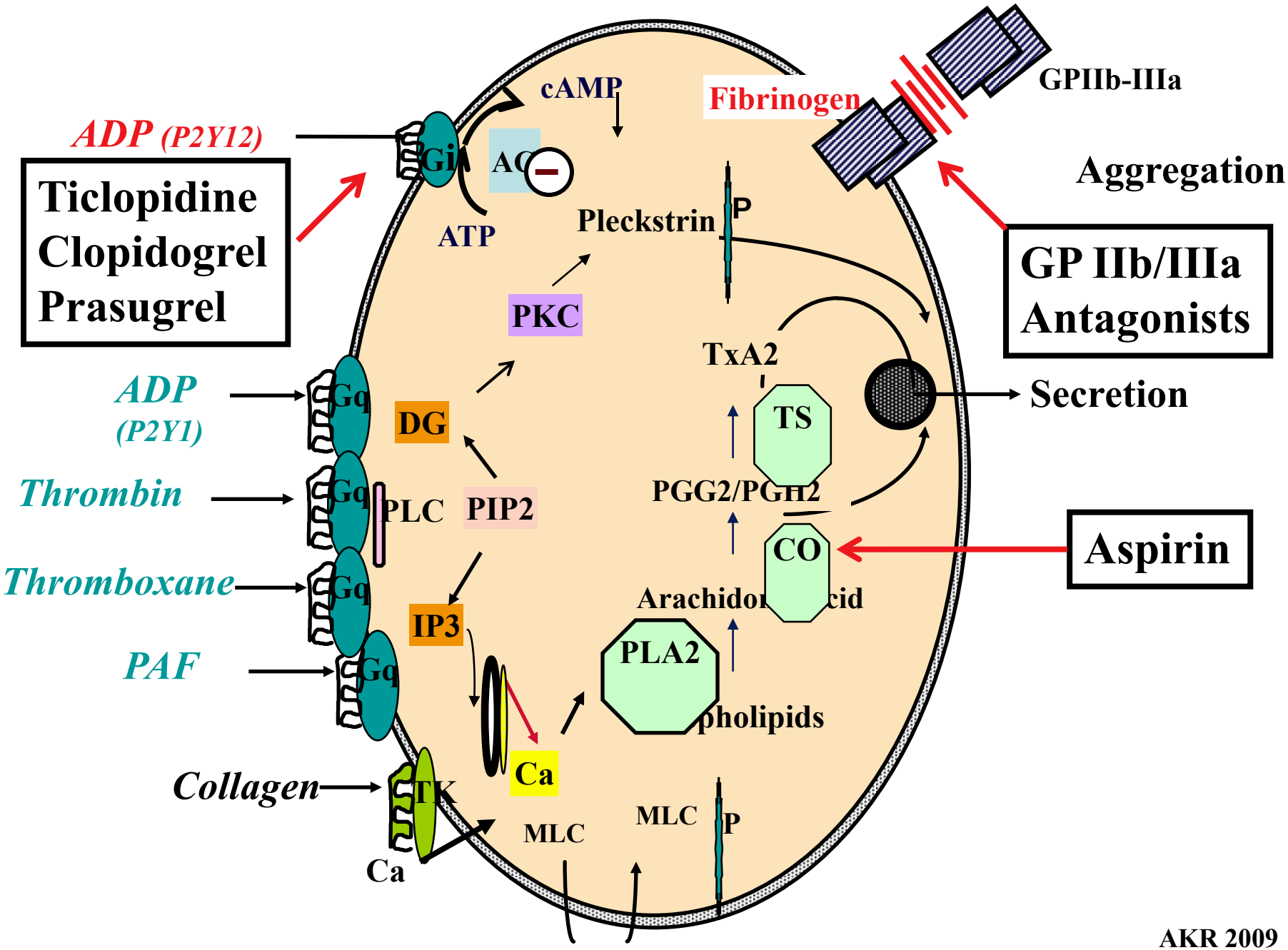

Cyclooxygenase
Ser
OH
529
Arachidonic Acid
COOH
OCOCH3
Aspirin
PGG2, PGH2
Cyclooxygenase
Ser
OCOCH3
529
Thromboxane A2

AKR/09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Antagonists
Pleckstrin
P
PKC
ADP
(P2Y1)
Gq
DG
TxA2
TS
Secretion
Thrombin
PLC
PIP2
PGG2/PGH2
CO
Aspirin
Thromboxane
Arachidonic acid
IP3
PLA2
PAF
phospholipids
Ca
Collagen
TK
MLC
MLC P
Ca
AKR 2009

Aspirin Pharmacokinetics

- Rapidly absorbed in stomach and small intestine
- Peak levels at 30-40 min after ingestion
- Plasma concentration decays: half-life of 15-20 min
- Inhibition of platelet function evident at 1 hour
- Irreversibly inactivates COX in platelets
- Acetylates the enzyme in megakaryocytes as well

AKR/2010

Aspirin as Antithrombotic Agent

- Effective in a wide range of arterial disorders
- Reduces vascular deaths by 15% and vascular events by 30% in high risk patients
- Effective when used long-term in doses 50-100 mg/day
- No convincing evidence that higher doses are more effective
- Lower doses (300 mg) produce fewer GI side effects than higher doses (1200 mg)
- Bleeding risks increased with increasing aspirin dose (75-325 mg/d) with or without clopidogrel (CURE Trial)

Potential Cumulative Impact of Four Secondary-Prevention Treatments

	Relative Risk	2 Year Event Rate
None	..	8%
Aspirin	25%	6%
β-blockers	25%	4.5%
Lipid lowering (by 1-5 mmol)	30%	3.5%
ACE inhibitors	25%	2-3%

Cumulative relative risk reduction if all 4 drugs used ~ 75%

Events = cardiovascular death, myocardial infarction, or strokes

Yusuf, S. Lancet 360:3, 2002

SECOND INTERNATIONAL STUDY OF INFARCT SURVIVAL (ISIS-2)

- 17,187 patients with chest pain (up to 24 hrs) and suspected AMI
- Randomized: SK (1.5U, 60 min); ASA 160 mg/day; both; neither
- Vascular mortality at 5 wk was reduced

Placebo			(Deaths 13.2%)
SK	25%	p<0.00001	(Deaths 10.4%)
ASA	23%	p<0.00001	(Deaths 10.7%)
SK + ASA	42%	p<0.00001	(Deaths 8.0%)

- The ASA reduced nonfatal reinfarction and nonfatal stroke
- No increase in cerebral hemorrhage with ASA but some with SK
- Beneficial effects of ASA and SK highly significant at 15 mo

Lancet 1988;2:349

Indirect Comparison of Aspirin Dosages in Reducing Vascular Events in High-Risk Patients

Aspirin Dose (mg/day)	No of Trials	No of Patients	Odds Reduction %
500-1500	34	22,451	19±3
160-325	19	26,513	26±3
75-150	12	6,776	32±6
<75	3	3.655	13±8

Patrono et al, Chest 133; 2008:199S

Aspirin and Primary Prevention of Vascular Events: Meta-analysis

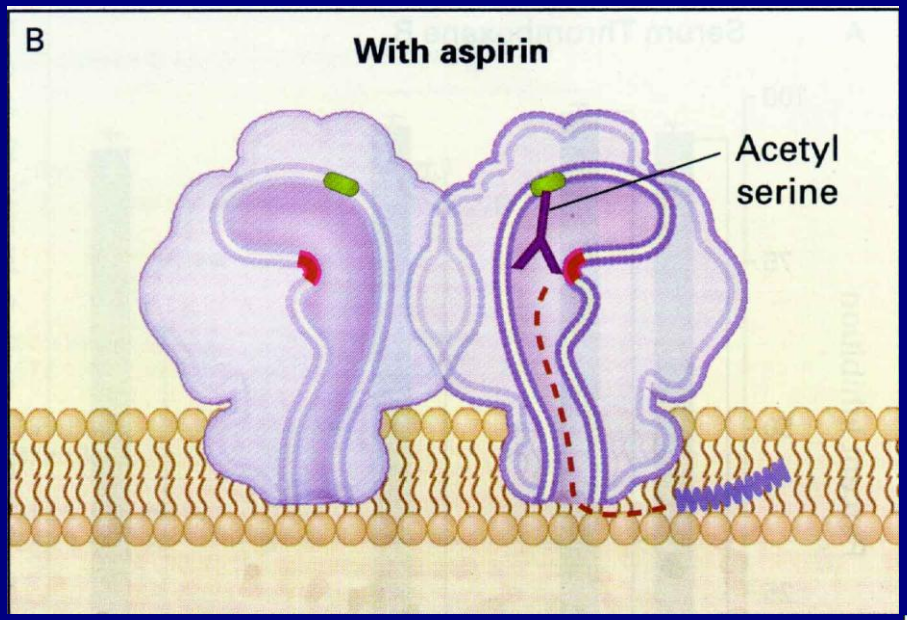
- Six Primary Prevention trials (92,873 participants)
- Mean Follow-up 6 years
- 15% reduction in odds of CV events
- 23% in total coronary heart disease
- 24% in nonfatal MI
- No overall effect on stroke
- No significant effect on vascular death or on overall mortality

Bertolucci, Amer J Card 2006, 98:746

Interaction of NSAIDs with Antiplatelet Effect of Aspirin

- Concomitant administration of Ibuprofen (but not diclofenac, tylenol or rofecoxib) antagonizes irreversible platelet inhibition by aspirin
- Aspirin is a irreversible inhibitor of Cox-1
- Cox-1 inhibition by ibuprofen is short lived
- Ibuprofen competitively inhibits aspirin access to acetylation site in Cox-1
- May limit cardioprotective effect of aspirin

Catella-Lawson et al. NEJM 2001;345:1809-17



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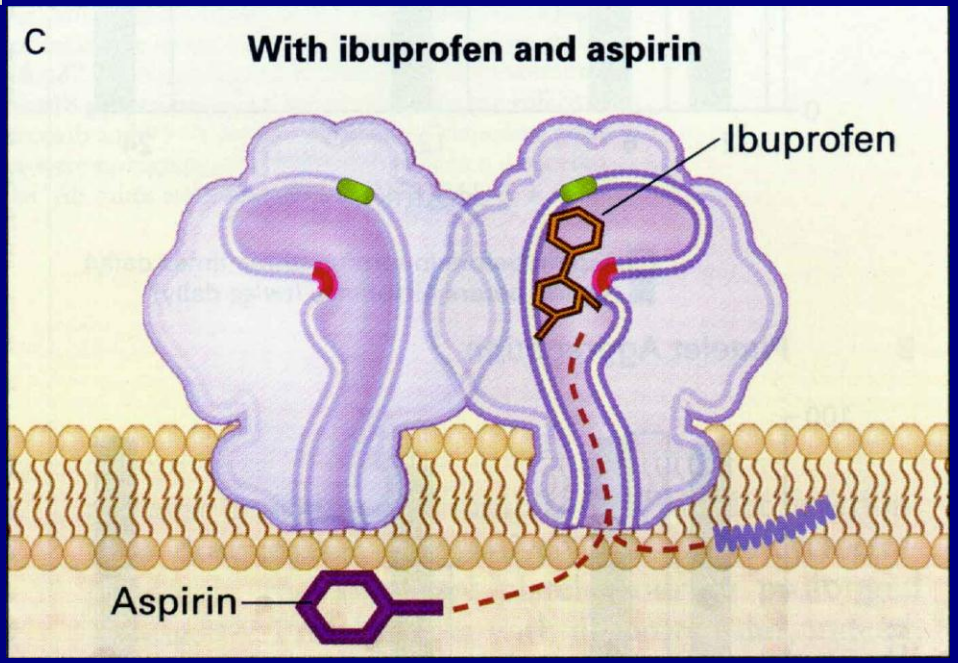

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Dipyridamole/Aspirin Combination (Aggrenox)

- Dipyrimidole is a pyrimido pyrimidine derivative
- Increases platelet cAMP
- Inhibits cyclic nucleotide phosphodiesterase and blockade of adenosine uptake
- Formulation: Aspirin (25 mg); Extended release
  Dipyridamole (200 mg); twice daily
- European Stroke Prevention Study 2: 6602 patients; randomized to placebo, aspirin, Aggrenox
- In patients with prior stroke or TIA: 2 years stroke rates:
  Placebo 15.2%
  Aspirin 12.5% (Reduction 19%; p = 0.0009)
  Aggrenox 9.5% (Reduction 37%; p < 0.001)

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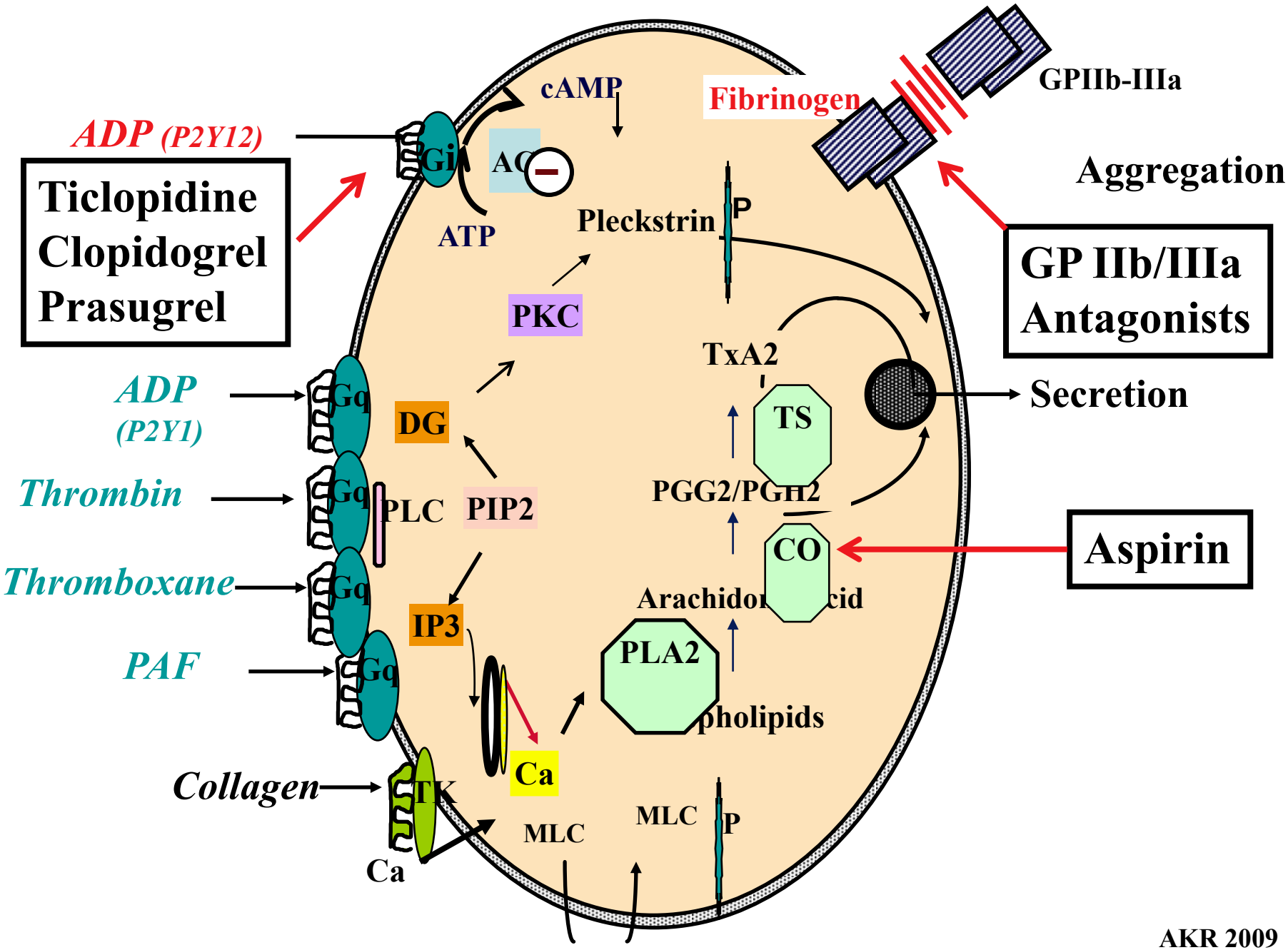
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Ca
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TK
MLC
MLC P
Ca
AKR 2009

P2Y12 Antagonists: Thienopyridines Ticlopidine, Clopidogrel, Prasugrel

- Thienopyridine derivatives
- Prodrugs: Converted to active metabolites by liver cytochrome P450 isozymes
- Irreversible Inhibitors

Direct Inhibitors: *Ticagrelor, Cangrelor, Elinogrel (Not FDA Approved)*

Ticlopidine

- **Indication: To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke**
- **Dosage: 250 mg b.i.d**

Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events

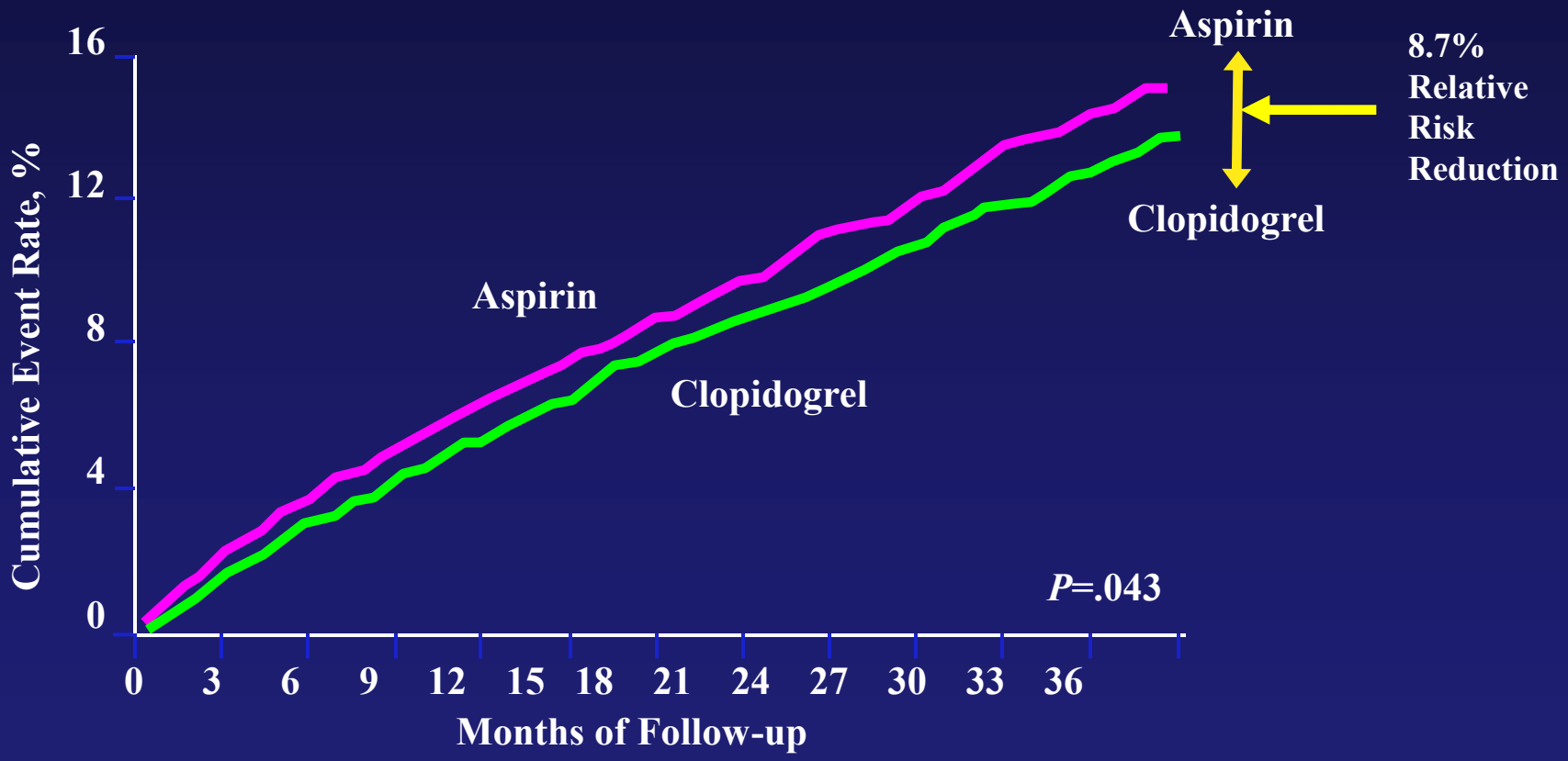
CAPRIE Study: Design

Study Design	**Prospective, randomized, blinded**
Number of Patients	**19,185 patients with atherosclerotic vascular disease**
Inclusion Criteria	**Recent ischemic stroke (≤6 mo)** **Recent MI (≤35 d)** **Established peripheral arterial disease**
Study Drugs	**Clopidogrel: 75 mg qd** **Aspirin: 325 mg qd**
Treatment Duration	**Up to 3 y (mean, 1.6 y)**
Investigational Centers	**304 in 16 countries, including the US**

CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.

CAPRIE Study

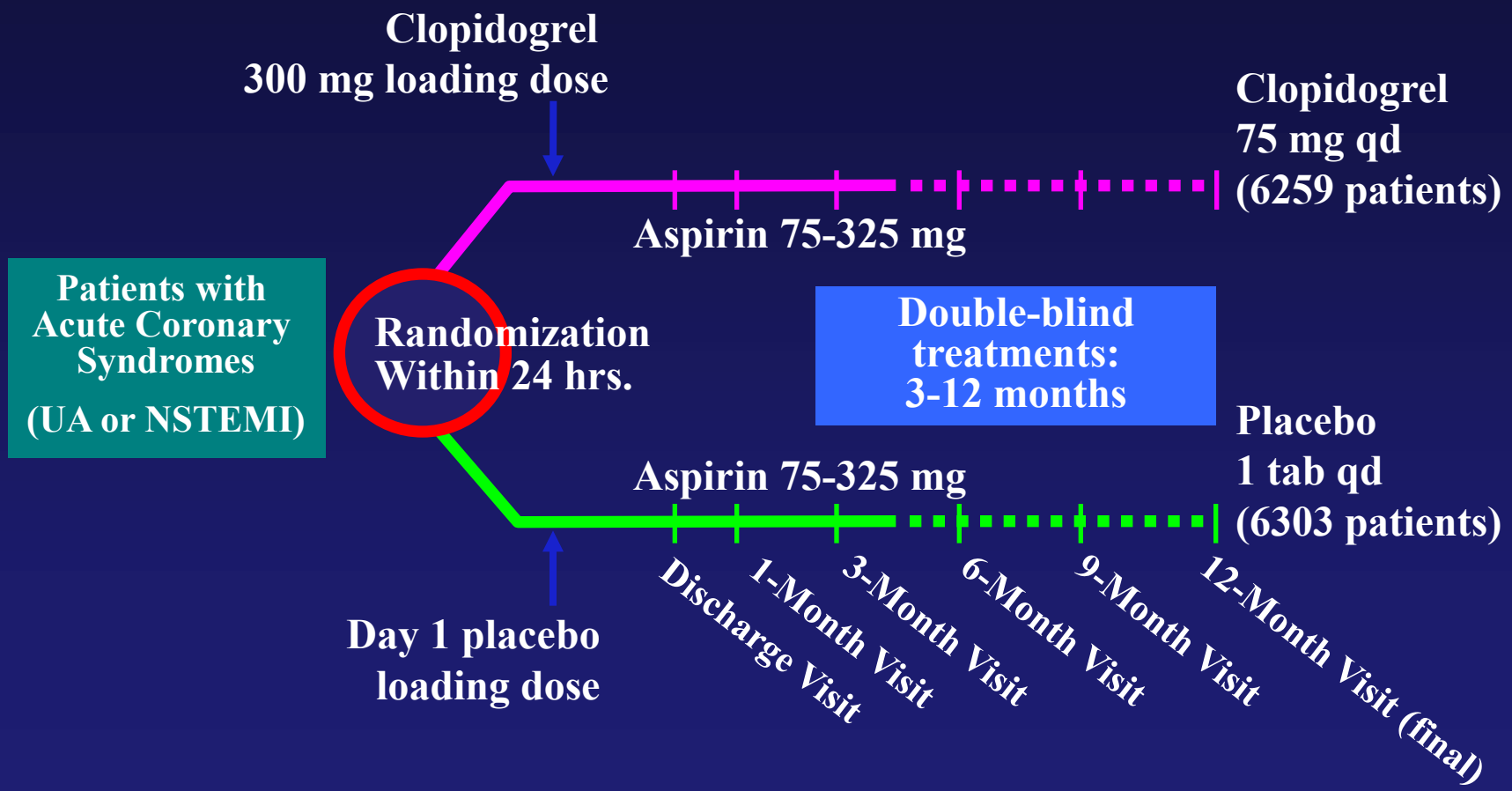
Efficacy of Clopidogrel in Primary Analysis of MI, Ischemic Stroke, or Vascular Death



ITT analysis.

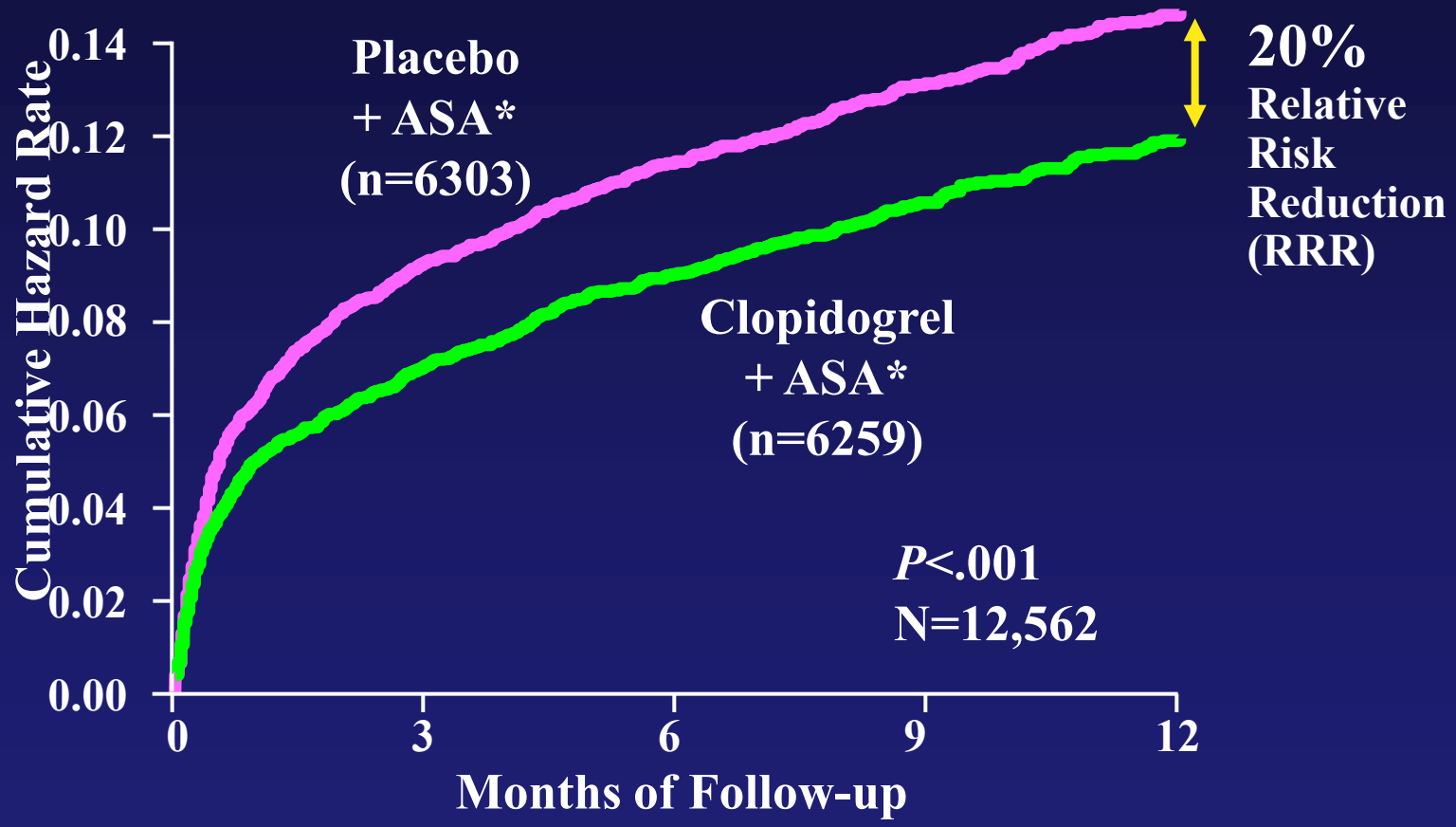
CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.

CURE Study: Patient Randomization



Modified from CURE Study Investigators. *Eur Heart J*. 2000;21:2033-2041.

CURE Study: Primary End Point —MI/Stroke/CV Death



*In addition to other standard therapies.

Yusuf S, et al. *N Engl J Med.* 2001;345:494-502.

CURE TRIAL: CLOPIDOGREL IN ADDITION TO ASPIRIN IN ACUTE CORONARY SYNDROMES

	Clopidogrel	Placebo	Relative Risk
Major Bleeds	3.7%	2.7%	1.38 ($p < 0.001$)
> 2 units Transfusion	2.8%	2.2%	1.30 ($p = 0.02$)
Life-Threatening Bleeds	2.2%	1.8%	1.21 ($p = 0.03$)

Yusuf S et al NEJM 345:494, 2001

Clopidogrel

Clinical benefit of adding clopidogrel to aspirin therapy:

- **ACS, Unstable angina, NSTEMI: *CURE***
- **PCI: *PCI-CURE*, *CREDO***
- **STEMI: *CLARITY-TIMI 28*, *COMMIT***

But….

Stable cardiovascular disease or asymptomatic patients with multiple CV risk factors – *CHARISMA*

Combination of Clopidogrel + ASA not more effective than aspirin alone (MI, stroke or death from CV causes)

Michelson AD, Nature Reviews, Drug Discovery 2010,9:154-169

Clopidogrel: Indications

- For reduction of atherosclerotic events (MI, stroke and vascular death) in patients with atherosclerosis documented by recent stroke, recent MI, or established peripheral arterial disease
- Acute coronary syndromes
- Dose: 75 mg once daily; ACS - loading dose 300 mg

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Clopidogrel: Adverse Effects

- Bleeding events
- Thrombotic thrombocytopenia purpura

Ticlopidine and TTP

- 60 cases of ticlopidine associated TTP
- >60 years age, 50% male
- 72% received ticlopidine for stroke prevention
- 66% had normal platelet counts within 2 weeks of TTP
- Prescribed for: <1 month ~80% patients
  <2 weeks ~15% patients
- Overall survival 67%
- Plasmapheresis most important predictor of mortality (mortality: 50% - no plasmapheresis
  24% - with plasmapheresis

Bennett CL et al: Ann Int Med 128:541, 1998

Thrombotic Thrombocytopenic Purpura Associated with Clopidogrel

- Duration 3/1998 through 3/2000
- 11 patients - TTP developed during or soon after treatment
- 10 patients received drug for ≤14 days
- 10 responded to plasma exchange; one died
- 2 required ≥20 exchanges before clinical improvement
- 2 had relapses up to 7 months from onset, while not on drug

Bennett C et al NEJM 342: 1773-1777, 2000

Clopidogrel – Response Variability

- Reveals interpatient response variability
- Hyporesponsiveness associated with major adverse clinical events (post-PCI)

Mechanisms: Clinical, Genetic, Cellular Factors

- Noncompliance
- Drugs metabolized by cytochrome P450 in liver may reduce effectiveness (eg. Proton pump inhibitor (Omeprezole))
- Cigarette smoking increasing clopidogrel's effectiveness (induction of P450, CYP1A2)
- Common reduced-function isoform of CYP2C19 (30% European ancestry, 40% African ancestry, >50% Asian)
- Pre-clopidogrel response to ADP predicts post-clopidogrel response to ADP

Michelson AD, Nature Reviews, Drug Discovery 2010,9:154-169

Prasugrel (Effient)

- Metabolized by liver cytochrome P450
- Inhibits platelet P2Y12 receptor
- More efficiently metabolized to active metabolite than clopidogrel
- Metabolized by esterases, less dependent on P450
- Prasugrel loading (60 mg) more rapid, potent and consistent inhibition of platelet function than 300 mg and 600 mg clopidogrel
- 10 mg Prasugrel: more potent and consistent inhibition than clopidogrel (75 mg or 150 mg daily)

Michelson AD, Nature Reviews, Drug Discovery 2010;9:154-169

Prasugrel

TRITON-TIMI 38

- Phase III, 13,608 patients with ACS and scheduled PCI
- Prasugrel (60 mg loading, 10 mg maintenance) versus clopidogrel (300 mg; 75 mg maintenance)
- Prasugrel significantly reduced ischemic events, including stent thrombosis (primary efficacy end point: 9.9% vs 12.1%)
- Increased risk of major bleeding (2.4% vs 1.8%) including fatal bleeding
- Less clinical efficacy and greater bleeding: age >75 years; body weight <60 kg, history of stroke or TIA
- Greater benefit: Undergoing PCI; Diabetes

Michelson AD, Nature Reviews, Drug Discovery 2010;9:154-169
Wiviott SD, New Eng J Med 2007;357:2001-2015
Wiviott SD, Circulation 2008;118:1626-1636

Novel P2Y12 Antagonists
Direct Acting and Reversible

- **Ticagrelor (*PLATO*)**
- **More potent and acts rapidly than clopidogrel**
- **Dyspnea and Ventricular pauses**
- **Oral, twice daily**
- **Superior to clopidogrel in ACS (PLATO)**

- **Cangrelor (*CHAMPION* – PCI, *CHAMPION-PLATFORM*)**
- **Intravenously**
- **Trials stopped**
- **"Bridge" for patients on clopidogrel**

- **Elinogrel**
- **Oral or IV**

Michelson AD, Nature Reviews, Drug Discovery 2010;9:154-169

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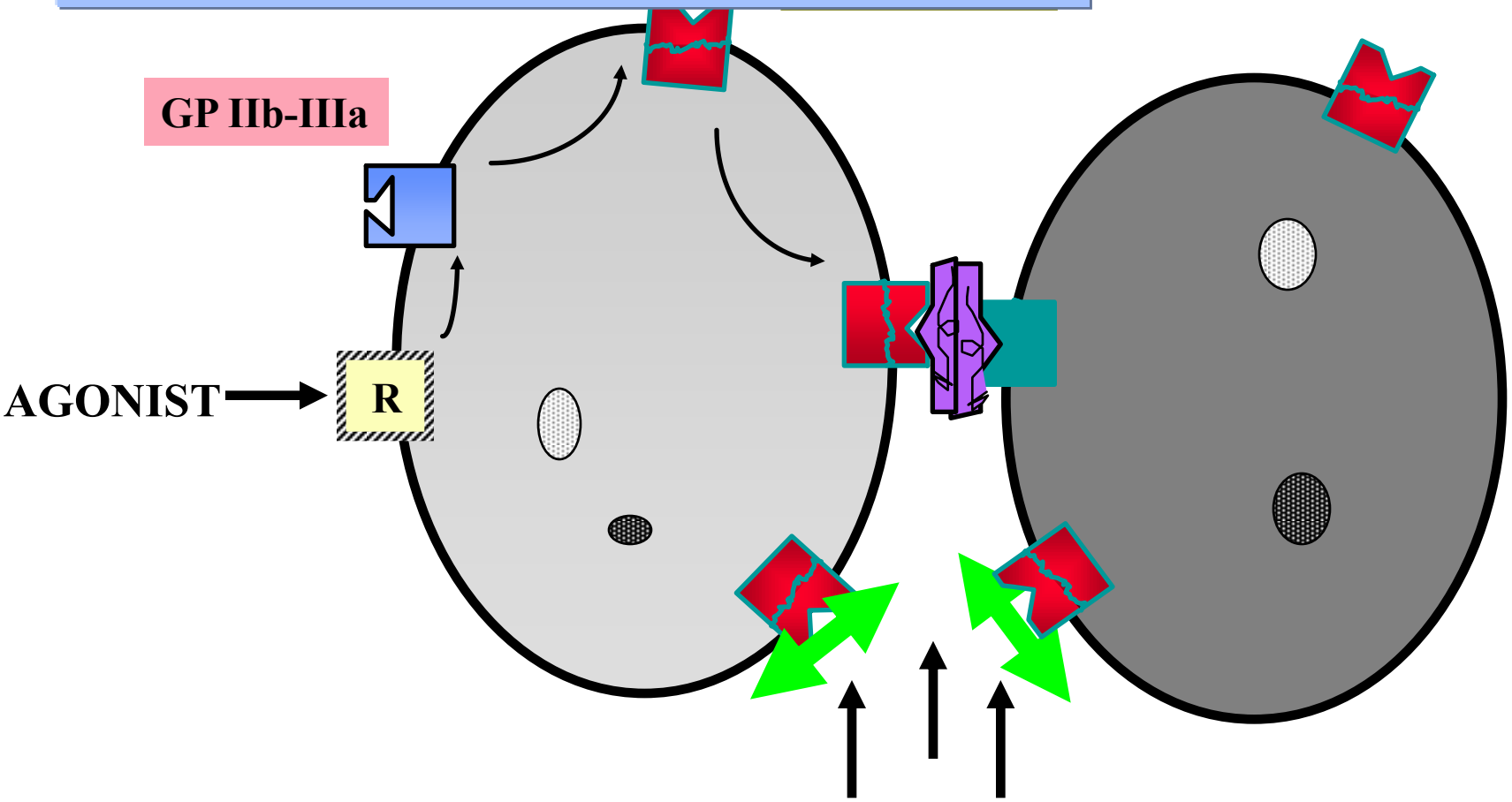
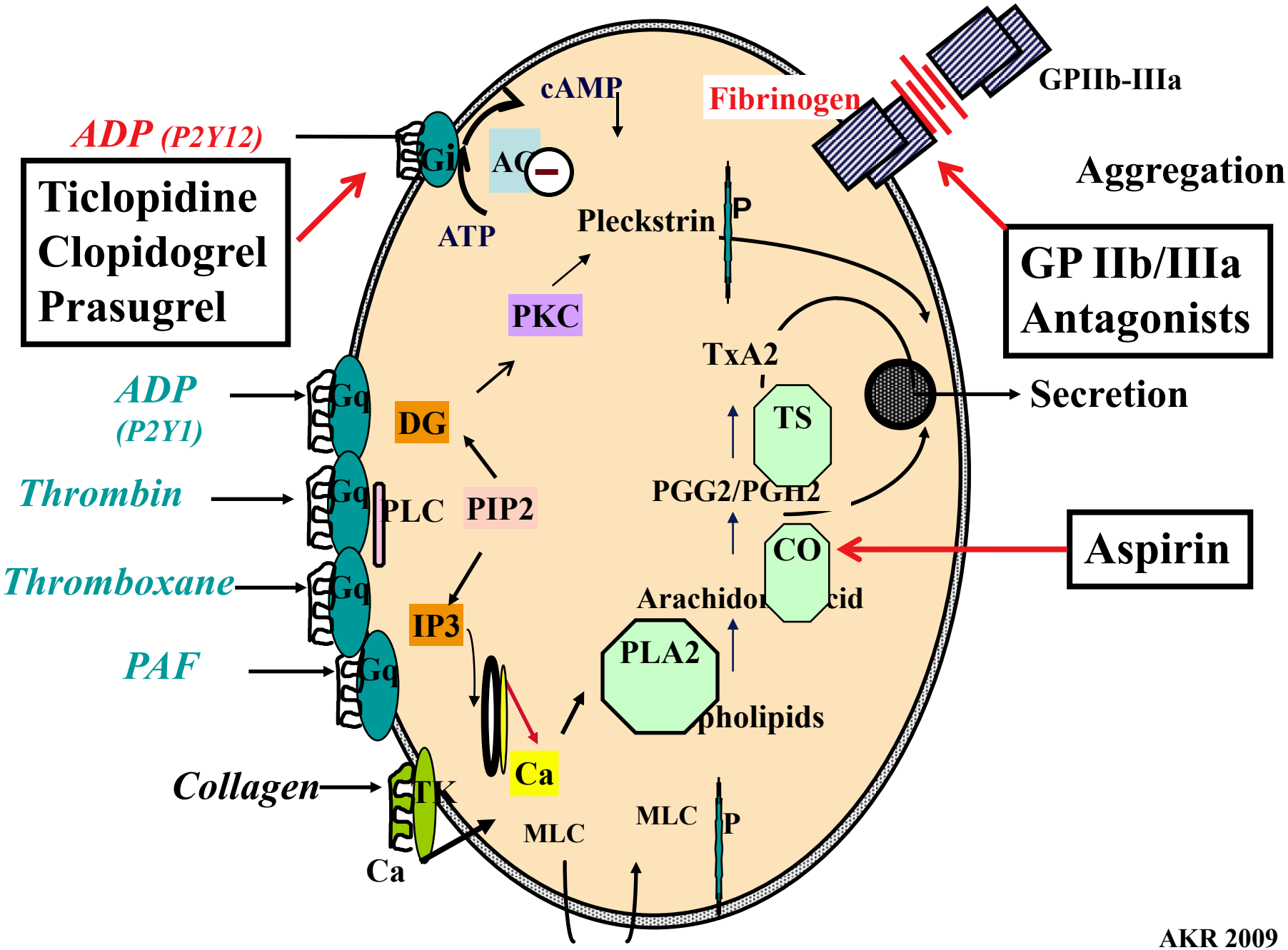
GPIIb-IIIa Antagonists (Fibans)



Abciximab (Reopro): ***Chimeric Fab Fragment***
Eptifibatide (Integrilin)
Tirofiban (Aggrastat)

RAO 8/07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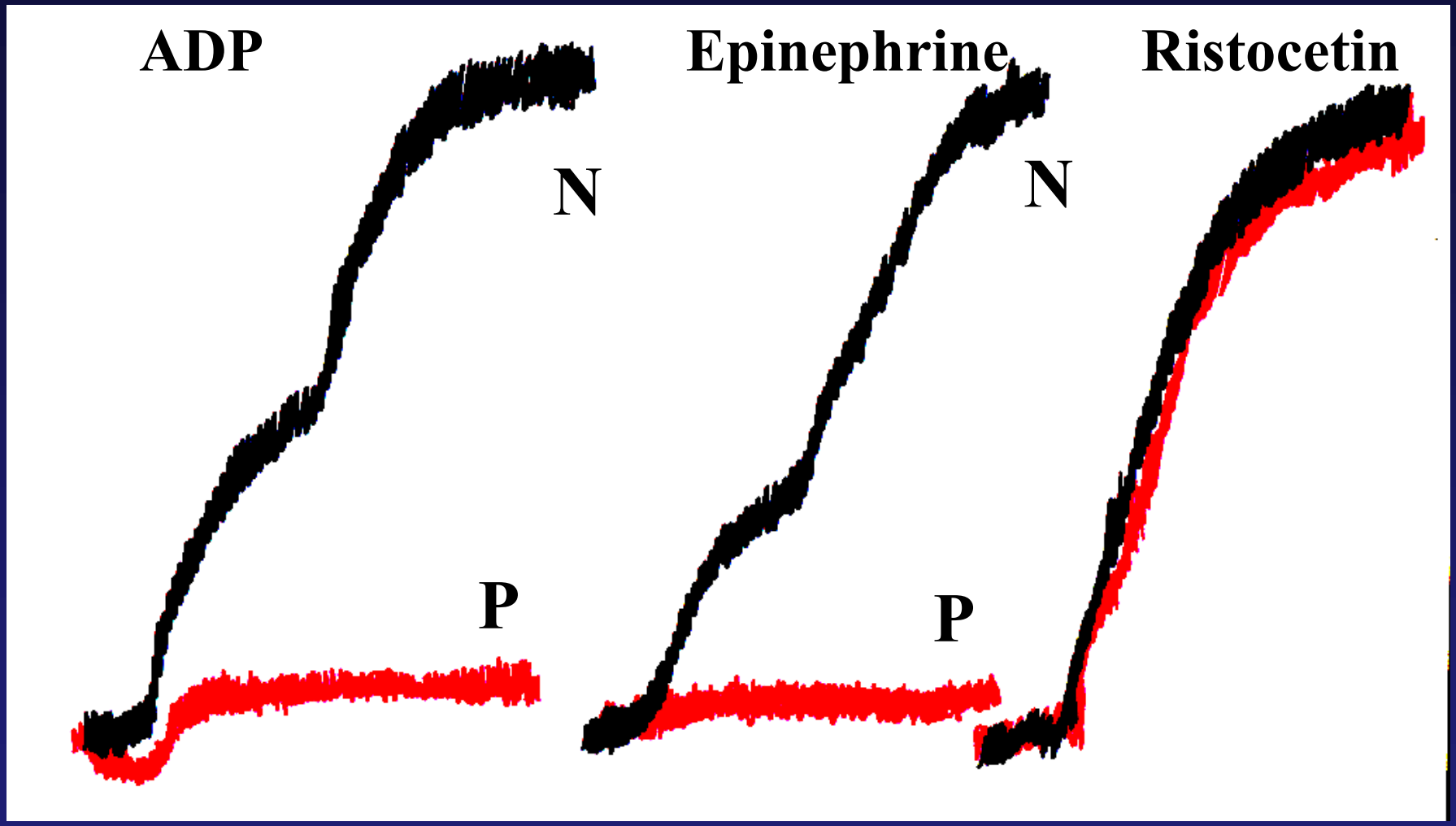
AKR 2009

GPIIb-IIIa Deficiency or Blockade



GPIIb-IIIa Antagonists

- **Indications: Acute coronary syndromes, and in conjunction with percutaneous coronary interventions**

- **Major side effects:**
  - **Hemorrhage**
  - **Thrombocytopenia**

GPIIb-IIIa Antagonists and Thrombocytopenia

- Occurs with all GPIIb-IIIa Antagonists
- May occur in patients not previously exposed
- Incidence:
  - Abciximab (Reopro): 0.5 - 1.0%,
    (>10% with repeat exposure)
  - Tirofiban, Eptifibatide: 0.2 - 0.5%
- May be acute (within hours) or delayed
- Acute profound thrombocytopenia < 20,000/ul
  0.3% in some trials

AKR 8/07

Thrombocytopenia with Tirofiban and Eptifibatide: Mechanisms

- Antibody mediated and drug-dependent
- Drug binds to GPIIb-IIIa and induces neoepitope recognized by Ab
- "Naturally occurring" antibodies: present in persons not previously exposed

Rao 8/2007

Thrombocytopenia with Abciximab: Mechanisms

- Abciximab is a chimeric human-mouse Fab specific for GPIIIa
- Antibodies causing thrombocytopenia recognize murine component of chimeric Abciximab
- "Naturally occurring" antibodies
- In some patients thrombocytopenia onset delayed over several days

Rao 8/2007

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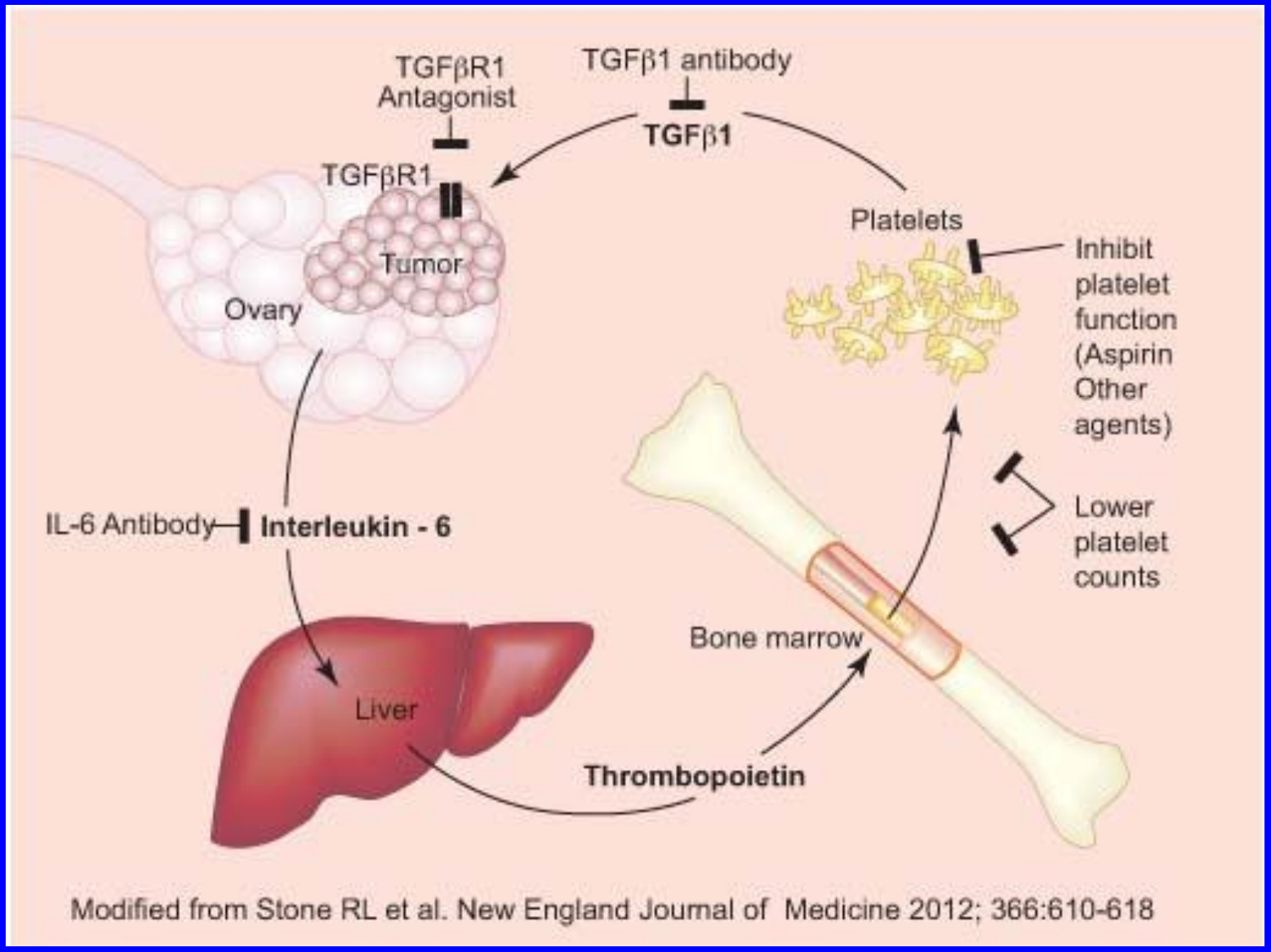
Cilostazol (Pletal)

- Cyclic nucleotide Phosphodiesterase 3 inhibitor
- Increases cAMP levels in platelets
- Inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress
- Indicated for the reduction of symptoms of intermittent claudication (PAD)

Cancer and Platelets



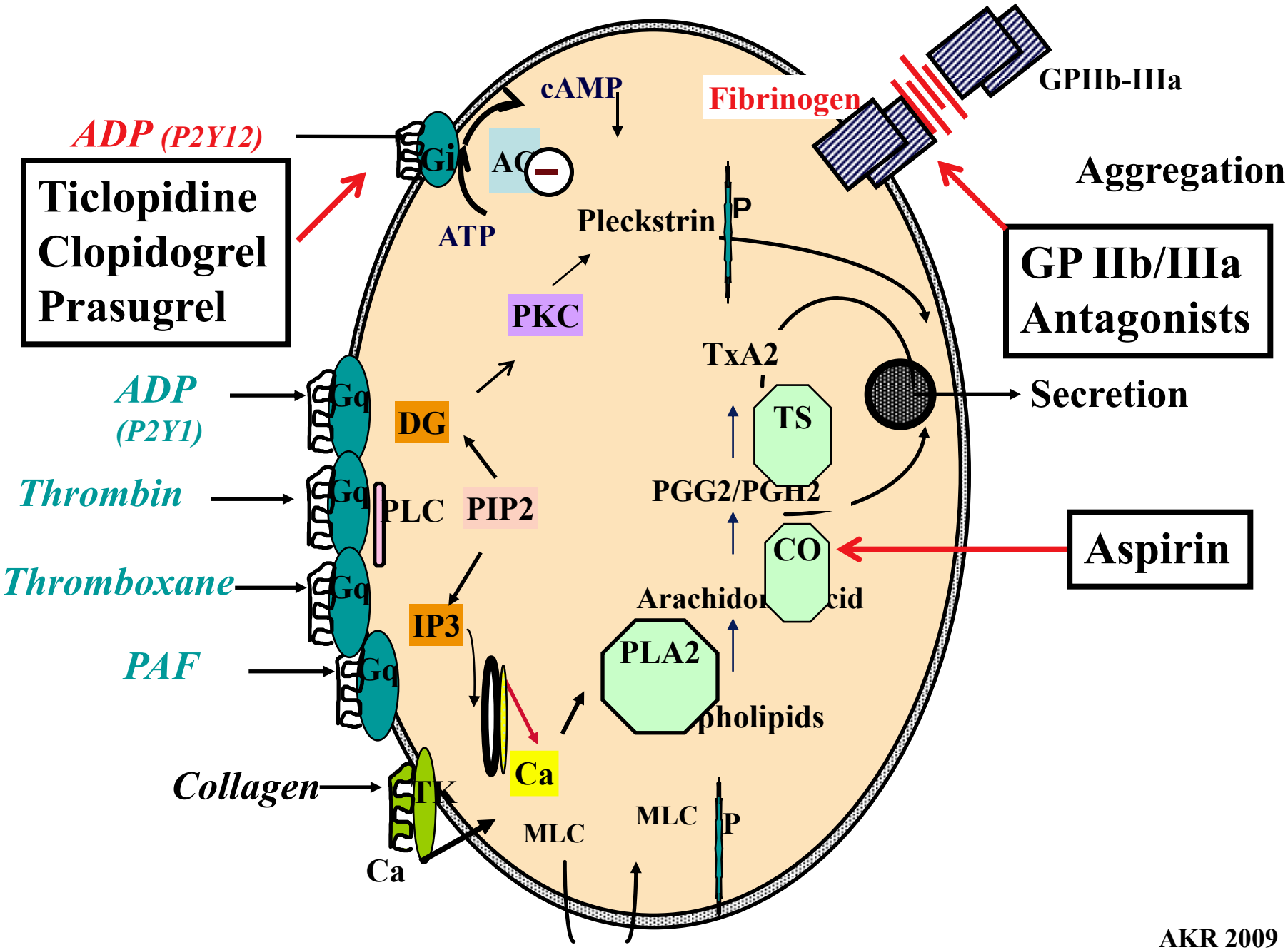
Rao, AK and Rao, D, *Blood, 2012 (In Press)*

Novel Anti-Platelet Drugs

- Combined P2Y1 and P2Y12 Antagonists
- Novel GPIIb-IIIa antagonists
- PAR1 Antagonists (Thrombin Receptor)
- Glycoprotein Ib Antagonists
- Glycoprotein VI Antagonists
- α2β1 Antagonists
- Thromboxane Receptor Antagonists
- Serotonin Receptor (5HT-2A) Antagonists
- Prostaglandin E2 Receptor (EP3) Antagonists

- PI3Kβ Antagonists
- P-selectin-P-selectin Ligand1 Signaling Antagonists
- NO-releasing variant of aspirin

Michelson AD, Nature Reviews, Drug Discovery 2010;9:154-169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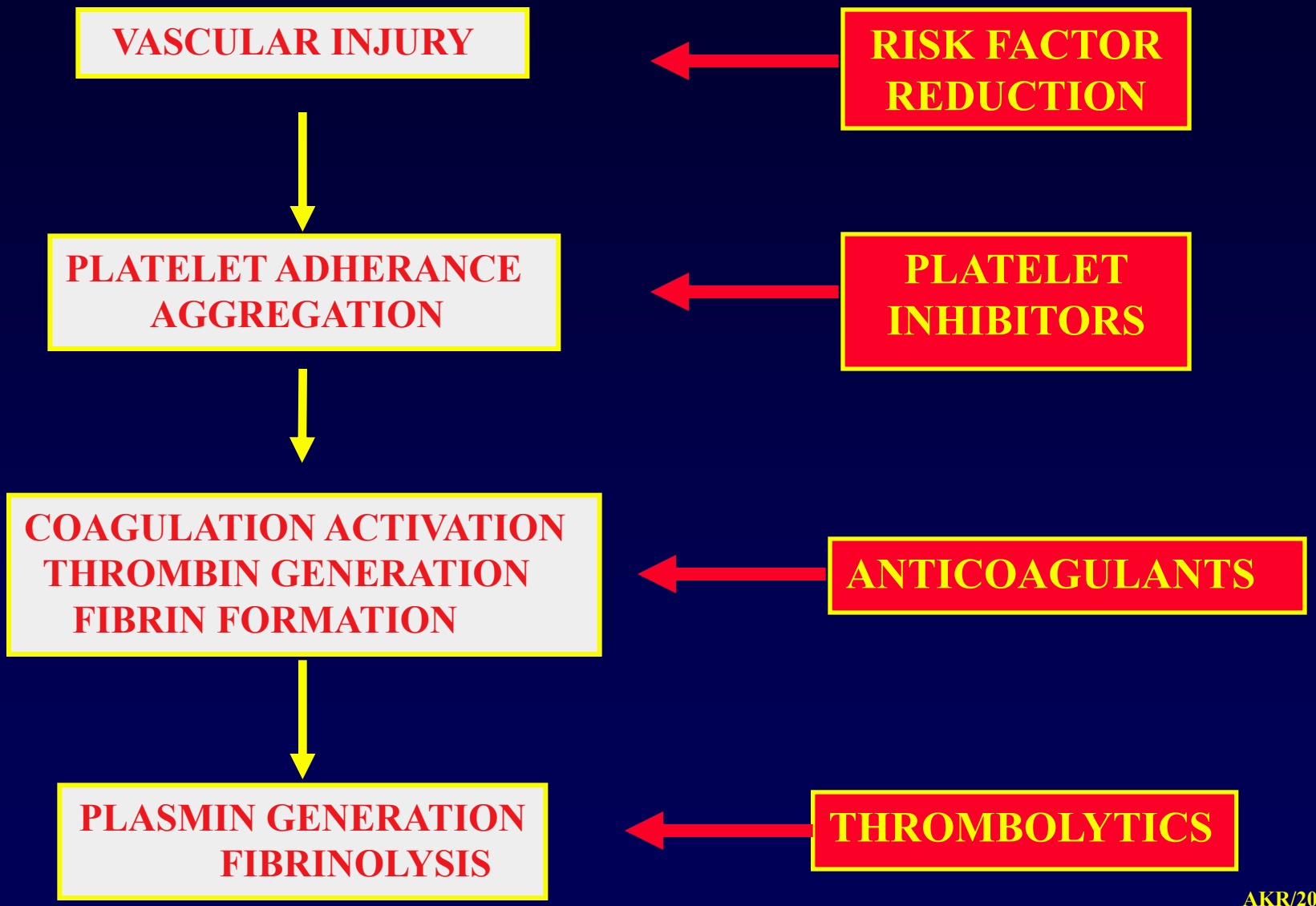

AKR/2003

Lavalette/ AKR