Antiplatelet drugs used in endovascular therapy

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Points to be covered by this talk

- Normal platelet function
- Mechanisms of antiplatelet agents
- Bleeding and antiplatelet agents
- Measurement of the effects of antiplatelet agents

Why is it worth knowing about?

- 6 to 8% of entire UK population are taking an antiplatelet agent, rising to 25% in older age groups
- Critical role in preventing cardiovascular disease
- Bleeding is a key side effect

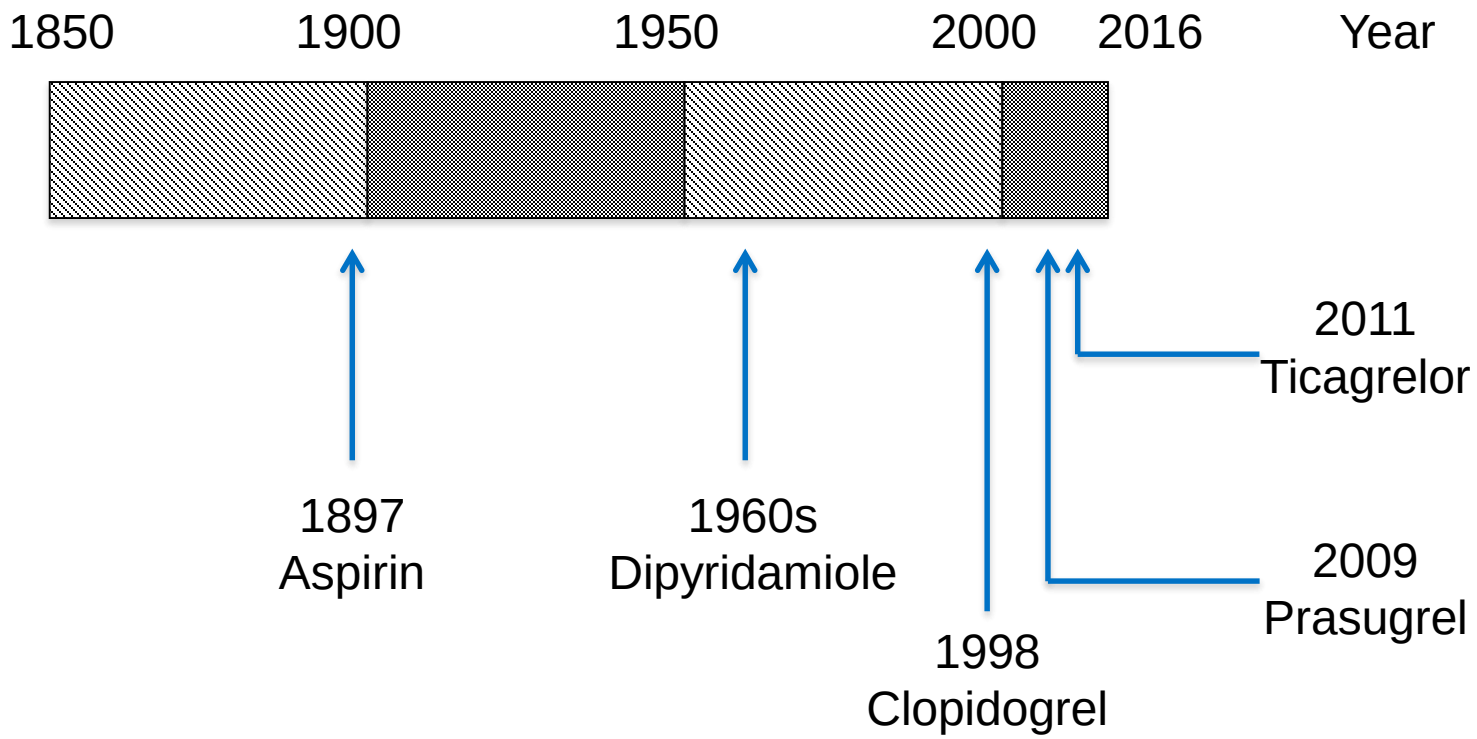
Bhatnagar et al. Heart 2015;101:1182-9

Stroke trials

- First randomised trial for secondary prevention following ischaemic stroke published in 1978
- Patients randomised to aspirin or placebo
- 31% reduction in risk of further stroke or death

The Canadian Cooperative Study Group. N Engl J Med 1978;299:53-9

Antiplatelet agent discovery timeline



New antiplatelet agents in the pipeline include:
Vorapaxar and atopaxar
Daltroban, sulotroban, and terutroban

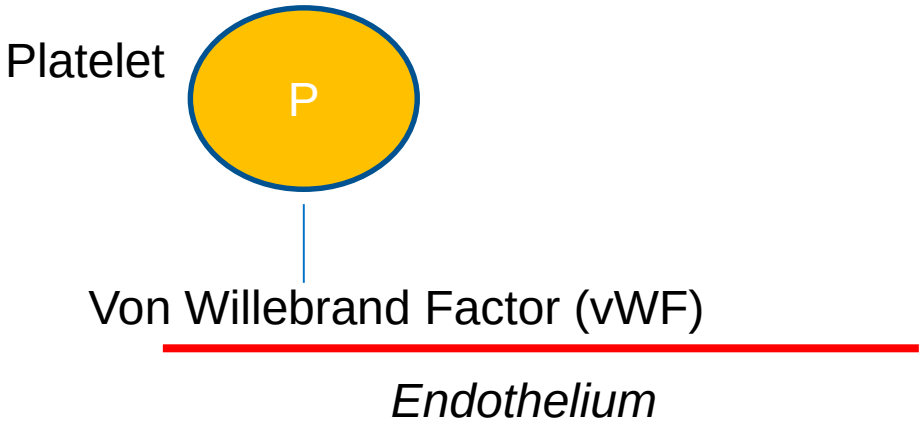
Primary haemostasis

- Three stages (AAA)

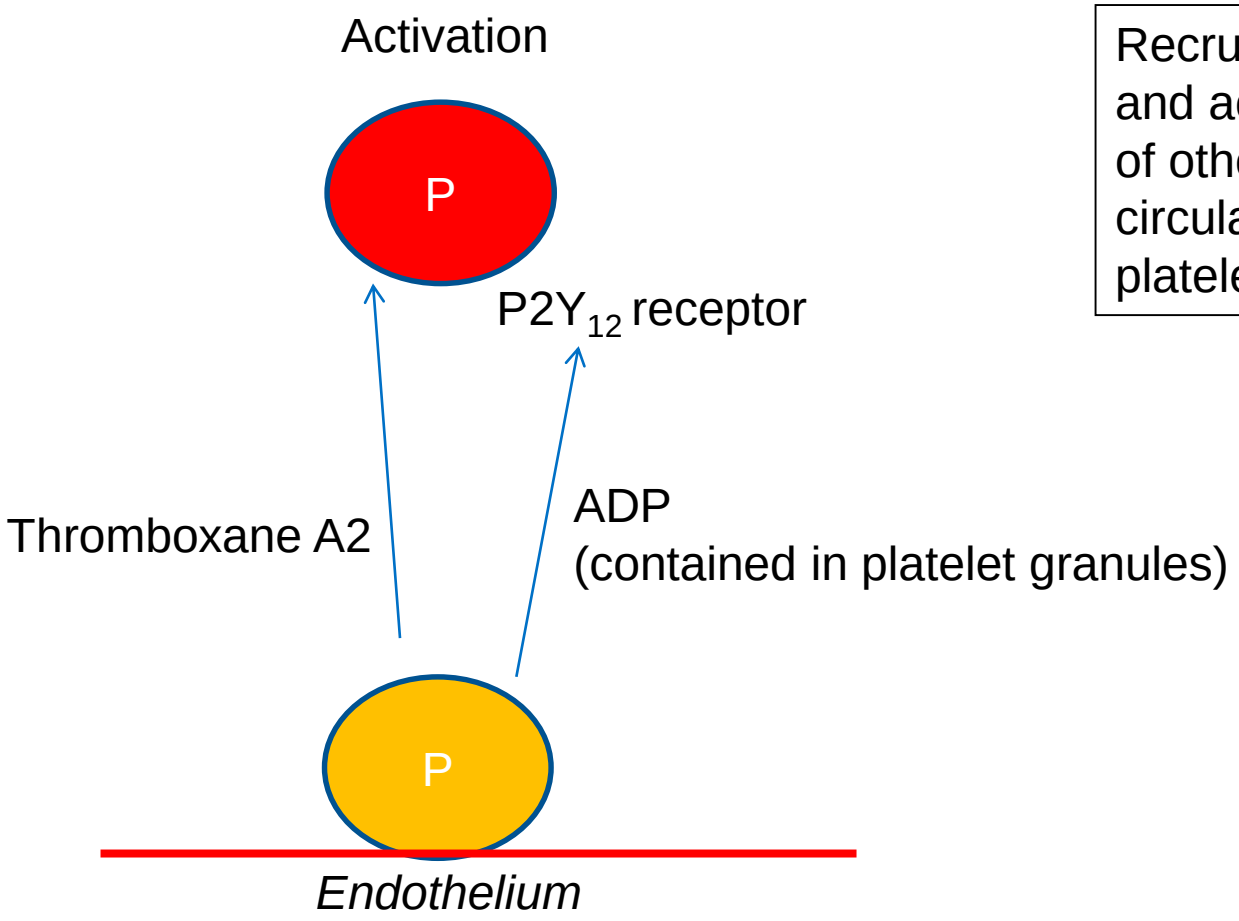
- Adhesion
- Activation
- Aggregation

Image from: http://fineartamerica.com/featured/8-blood-clot-sem-steve-gschmeissner.html

1. Adhesion



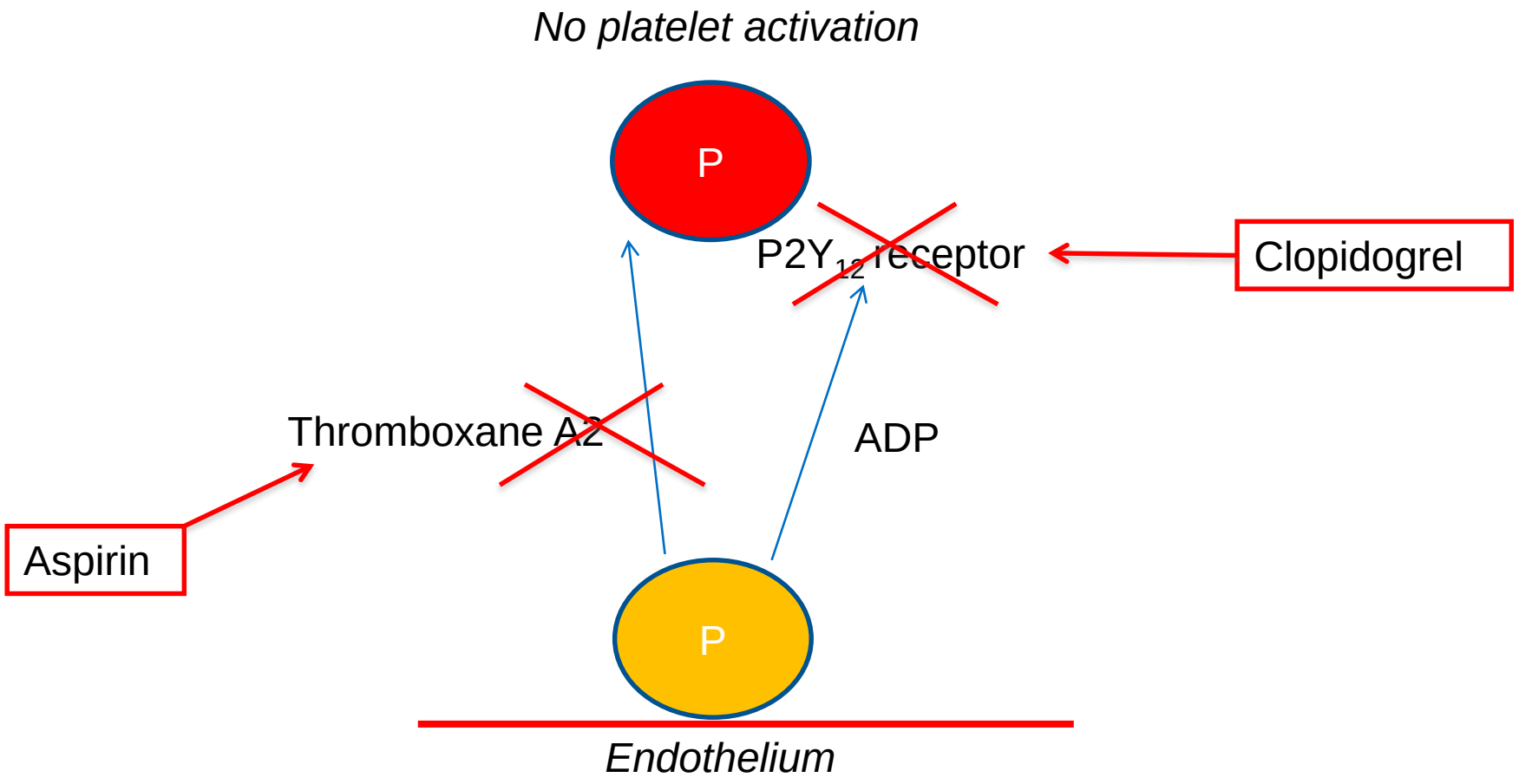
2. Activation



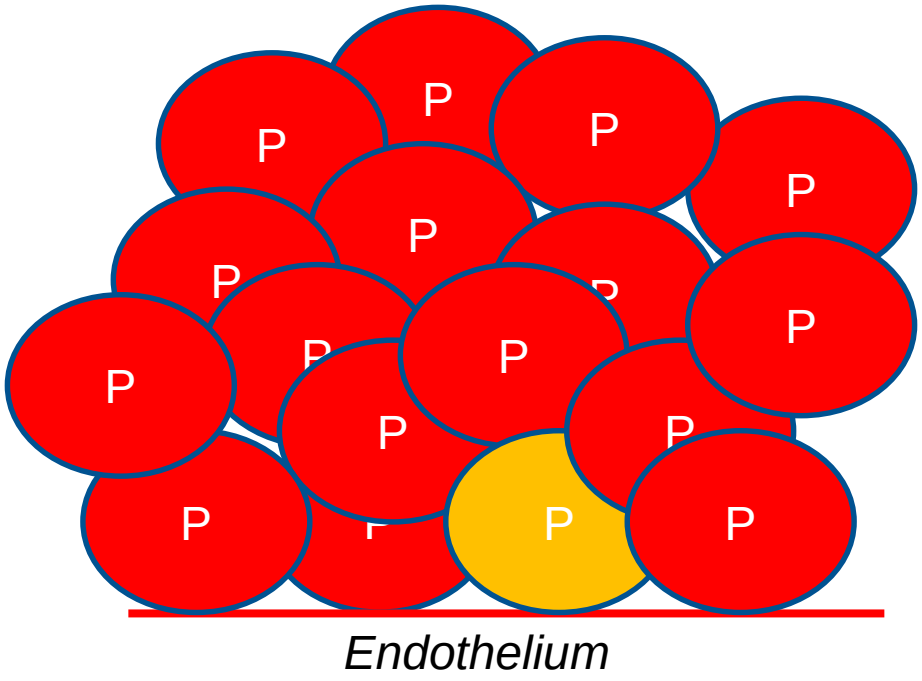
Recruitment and activation of other circulating platelets

ADP: adenosine diphosphate

Platelet activation inhibition by antiplatelet agents

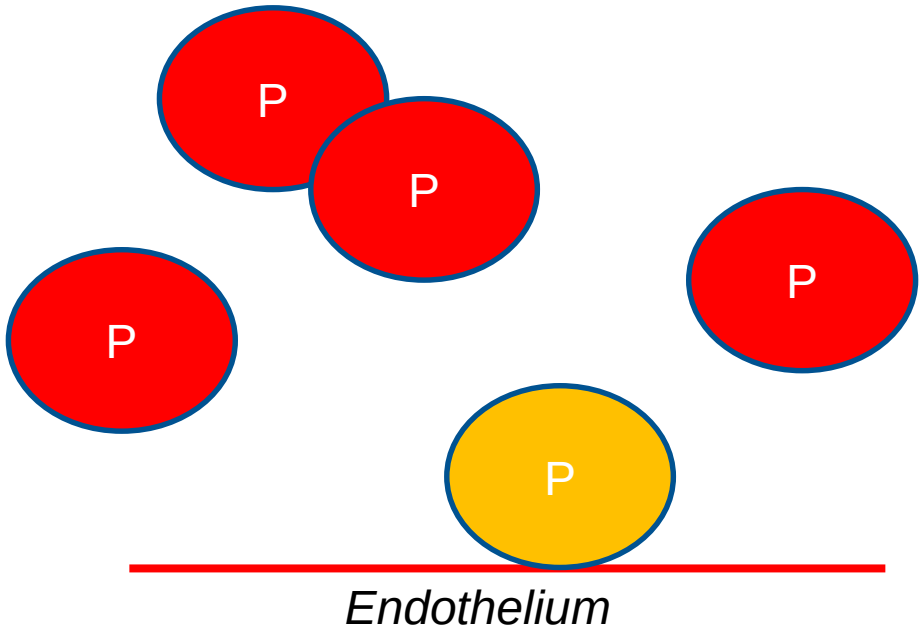


3. Aggregation



Platelets aggregate together through their fibrinogen receptors (glycoprotein IIb/IIIa)

Abciximab/tirofiban



Abciximab

Inhibition of glycoprotein IIb/IIIa prevents aggregation

Types of antiplatelet agent

Antiplatelet agent	Class	Mechanism
Aspirin	Cyclooxygenase-1 inhibitor	Prevent platelet activation
Dipyridamole	Phosphodiesterase inhibitor	
Clopidogrel	$P2Y_{12}$ receptor antagonists	
Prasugrel		
Ticagrelor		
Abciximab	Glycoprotein IIb/IIIa inhibitors	Prevent platelet aggregation
Tirofiban		

Duration of effect

Antiplatelet agent	Time to onset of action	Duration of effect
Aspirin	<1 hour *(4 hours if enteric coated)*	5 to 7 days
Dipyridamole	1.25 hours	5 to 7 days
Clopidogrel	4 to 8 hours	5 to 7 days
Prasugrel	2 to 4 hours	5 to 7 days
Ticagrelor	1.5 hours	3 to 5 days

Estcourt et al. Br J Haematol 2016; doi: 10.1111/bjh.14423
Makris et al. Br J Haematol 2013;160:35-46

Clinical case

- 77 year old man taking aspirin 75 mg daily of ischaemic heart disease
- Undergoing elective coil embolisation of a cerebral aneurysm
- Complications of procedure result in an intracerebral bleed
- Would you try anything to reverse the aspirin?

Reversal of antiplatelet agents

- Very little evidence but consider:
  - Tranexamic acid 1 gram iv
  - Platelet transfusion

Keeling et al. Br J Haematol 2016;175:602-13
Sprigg et al. Lancet 2018;391:2107-15

PATCH trial

- Randomised trial of platelet transfusion for patient with intracerebral haemorrhage taking antiplatelet agents
- No improvement in bleeding with platelet transfusions
- Platelet transfusion resulted in a significant increase in mortality and disability

Baharoglu et al. Lancet 2016;387:2605
Image: neuroradiologycases.com

Controversy for testing platelet function in interventional neuroradiology

- Some patients have ischaemic events despite antiplatelet therapy
- Impaired response to antiplatelet agents on platelet function tests may be associated with high risk of ischaemic events
- Who should we test? What with? What should we do if the results are abnormal?

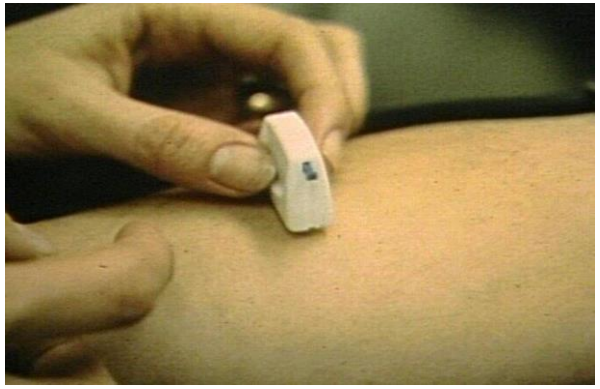
Measuring the effects of antiplatelet agents

- Template bleeding time
- Platelet function analyser 100
- Light transmission aggregometry
- VerifyNow®
- TEG platelet mapping

Template bleeding time

- No longer used in UK

- Poor sensitivity and specificity



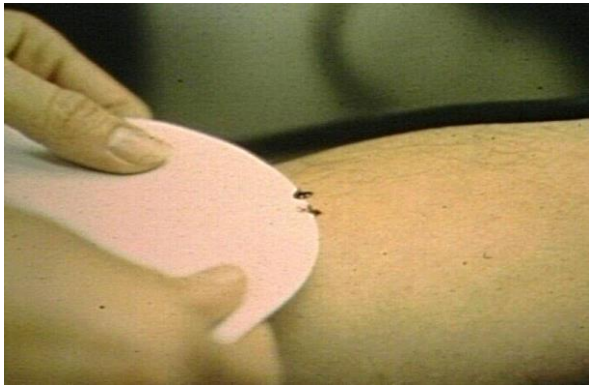
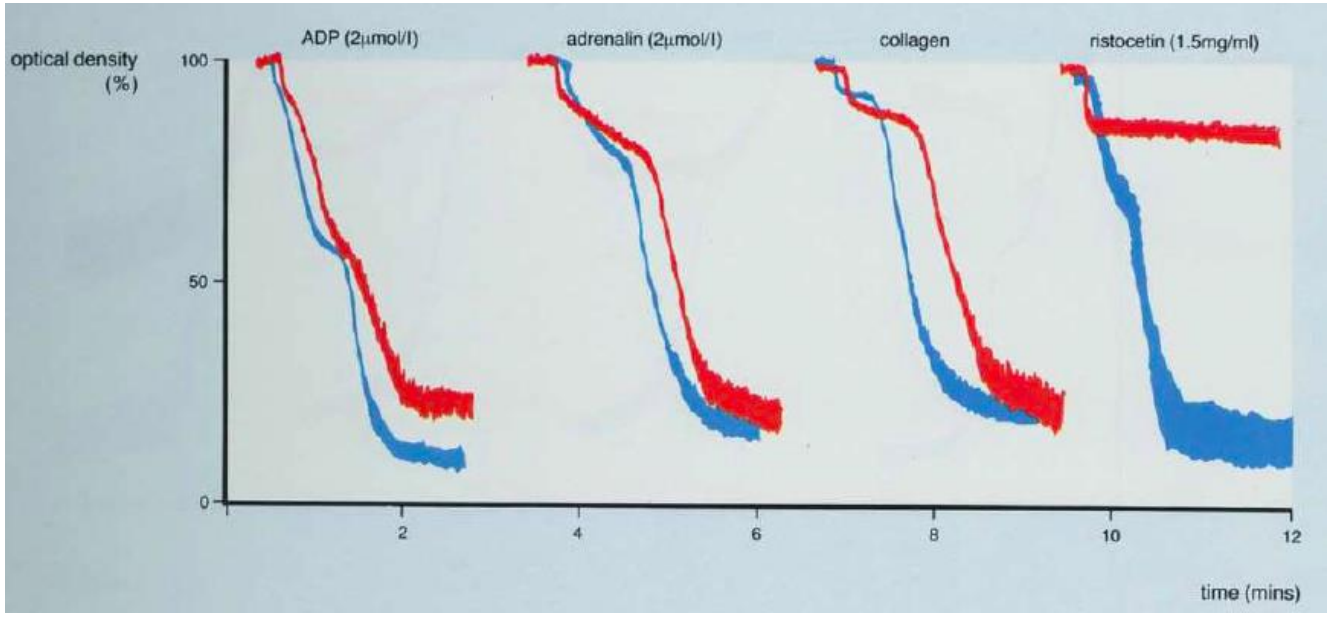


Image from: http://www.pathguy.com/sol/14132.jpg

Light transmission aggregometry

- Gold standard test

- Requires specialist skills to perform



Red: patient
Blue: control

Platelet function analyser 100

- Point of care test & easy to use. Has a pipetting step.
- Low sensitivity and specificity

usa.healthcare.siemens.com/hemostasis/systems/pfa-100

VerifyNow®

- Point of care test
- Designed to assess antiplatelet drug activity
- Easy to use (no need for pipetting)

Thromboelastography (TEG) platelet mapping

- Point of care test
- Designed to assess antiplatelet drug activity
- Easy to use (no need for pipetting)

One example protocol

	Aspirin	Clopidogrel
Starting dose	75mg daily	75mg daily
Check platelet function		
If poor response	⇧ Dose or switch to alternate drug	⇧ Dose or switch to alternate drug
If too much response	⇩ frequency	⇩ frequency

Delgado Almandoz et al. J Neurointerv Surg 2013;5:iii3-10

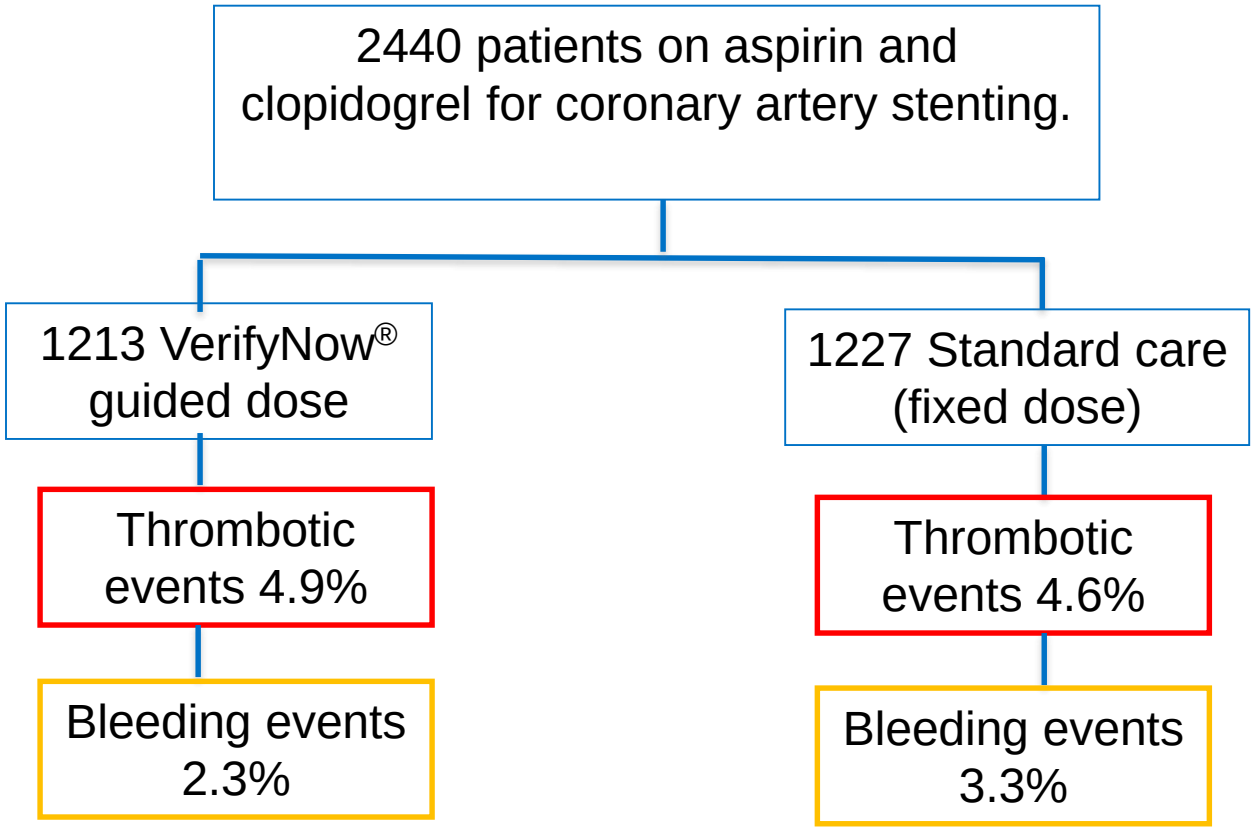
American College of Cardiology Guidelines 2011

- Platelet function testing may be considered in patients at high risk for poor clinical outcomes

- The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing percutaneous coronary intervention is not recommended

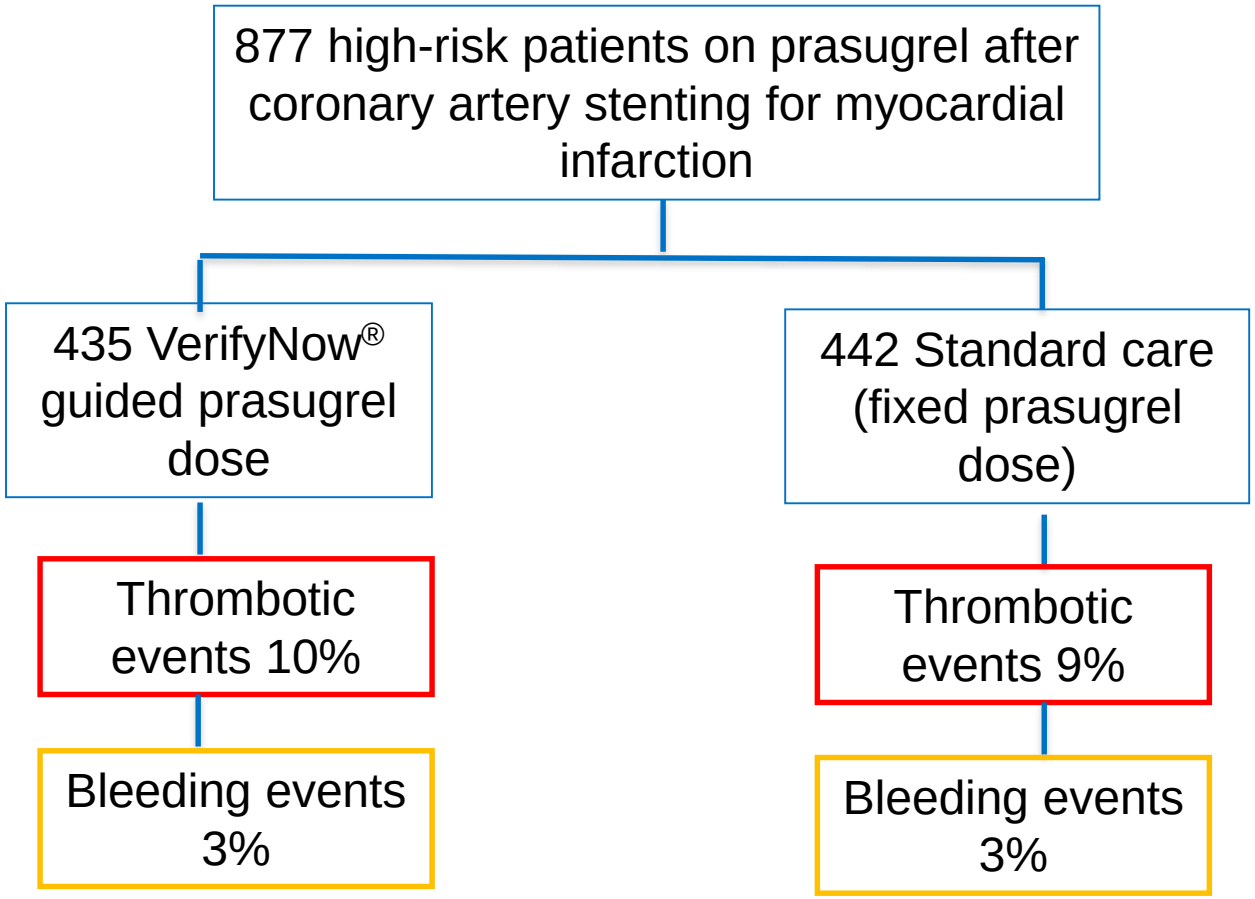
Levine et al. Circulation 2011;124:e574-651

VerifyNow® in interventional cardiology



Collet et al. NEJM 2012;367:2100-9

VerifyNow® in interventional cardiology



Cayla et al. Lancet 2016;388:2015-22

Can we pick out patients with high or low platelet reactivity and adjust the dose?

TRIGGER-PCI trial: 423 patients on prasugrel or clopidogrel

Trial stopped early due to futility

GRAVITAS trial: 2214 patients randomised to high or low dose clopidogrel following PCI

No difference in thrombotic events or bleeding

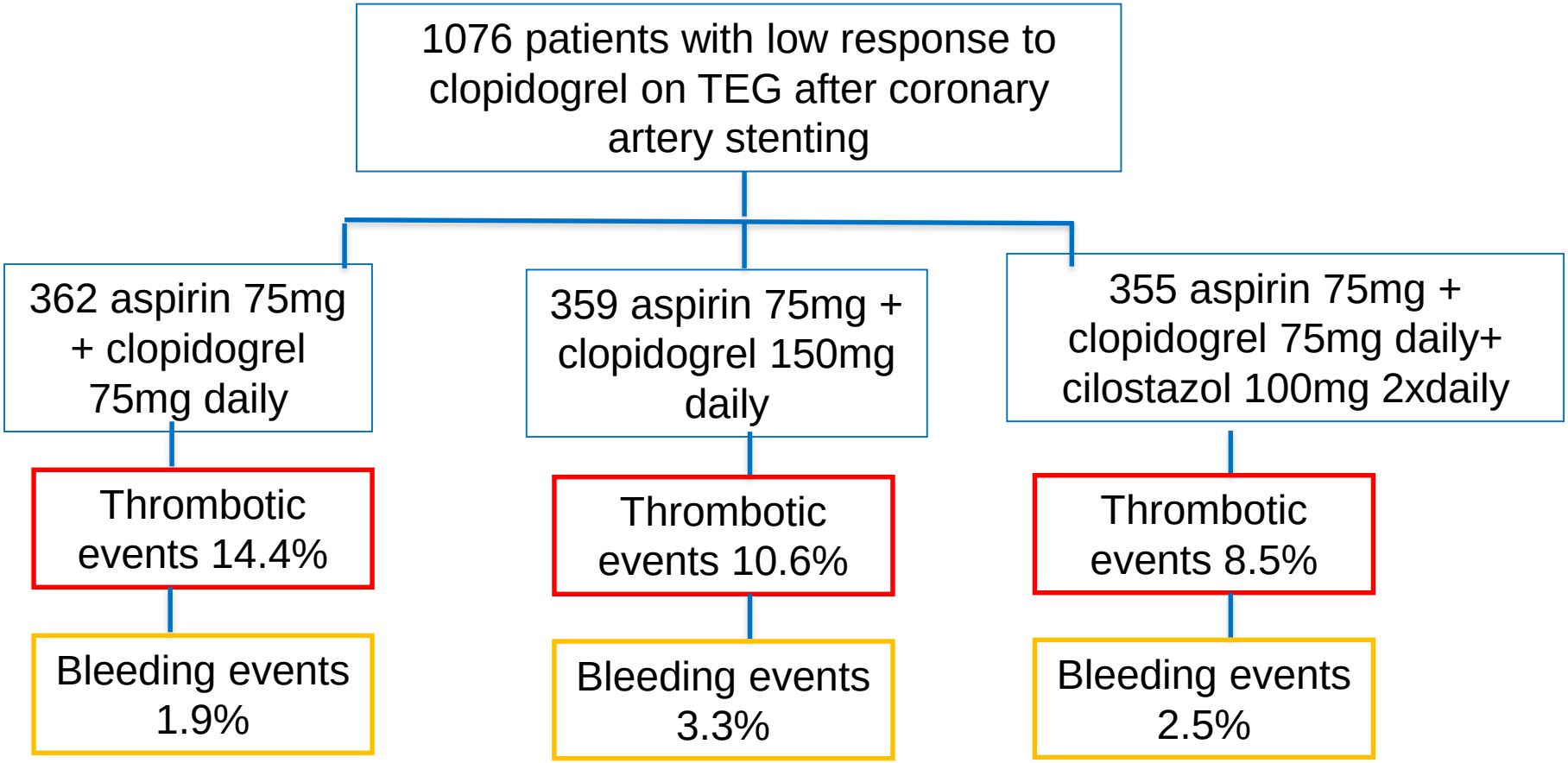
Trenk et al. J Am Coll Cardiol 2012;59:2159-64
Price et al. JAMA 2011;305:1097-105

American College of Cardiology Guideline update 2016

- In interventional cardiology…
- To date, no RCT has demonstrated that routine platelet function testing or genetic testing to guide $P2Y_{12}$ inhibitor therapy improves outcome.
- The routine use of platelet function and genetic testing is not recommended

Levine et al. Circulation 2016;134:e123-55

Thromboelastography (TEG) to guide antiplatelet dose adjustment (CREATIVE trial)



Tang et al. Circulation 2018;137:2231-45

International Society on Thrombosis and Haemostasis (ISTH) 2018

- Consider platelet reactivity in management of patients

- Not recommended for adjusting antiplatelet doses or duration of therapy

Frelinger et al. J Thromb Haemost 2018;16:2341-6

Summary

- Three stages to platelet aggregation
  - 1. Adhesion
  - 2. Activation (most antiplatelet agents work here)
  - 3. Aggregation

- Most commonly used antiplatelet agents are:
  - Cyclooxygenase-1 inhibitors (aspirin)
  - Phosphodiesterase inhibitors (dipyridamole)
  - $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, ticagrelor)

Summary part 2

- Peri-operatively
  - Takes 5 to 7 days for platelet function to normalise when antiplatelet agents are stopped
- Tests
  - Platelet function analyser 100, TEG platelet mapping and VerifyNow® are quick tests
  - Light transmission aggregometry is gold standard