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"Antiplatelet therapy post coronary stenting: What drugs and for how long?"

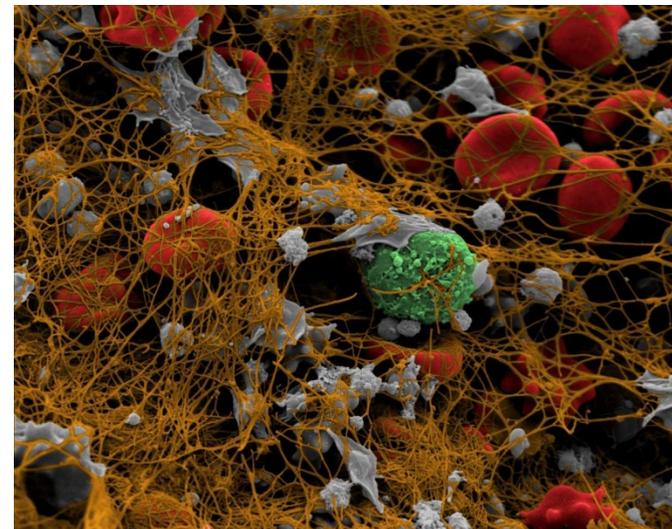
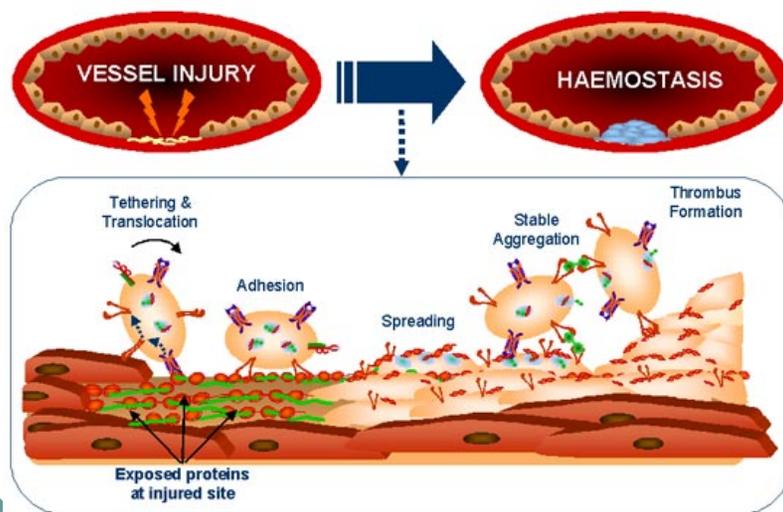
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Disclosures

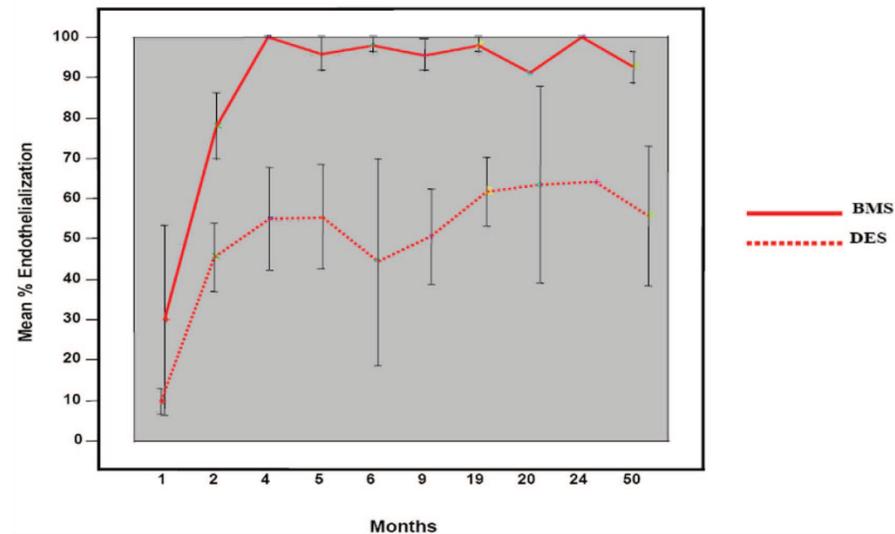
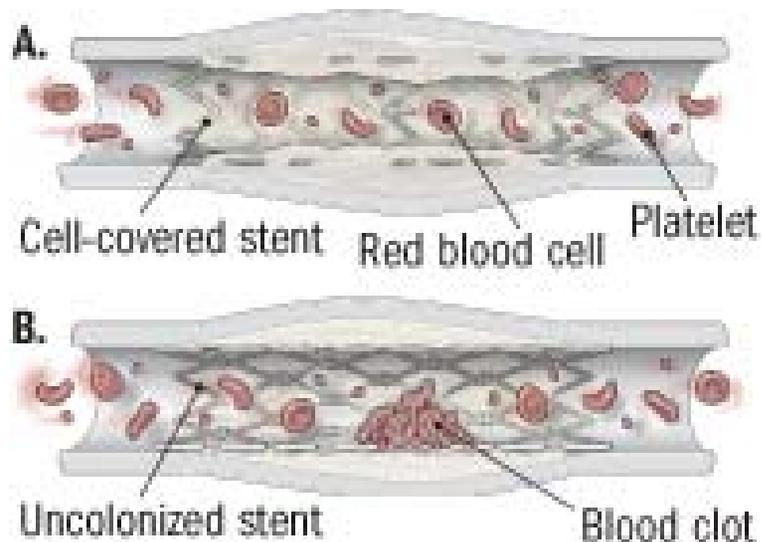
- None

PCI and Arterial Injury

- Endothelial damage and plaque rupture
- Thrombin generation and platelet activation
- Platelets serve as the center of clot formation
- Mimics or propagate the thrombotic milieu of ACS



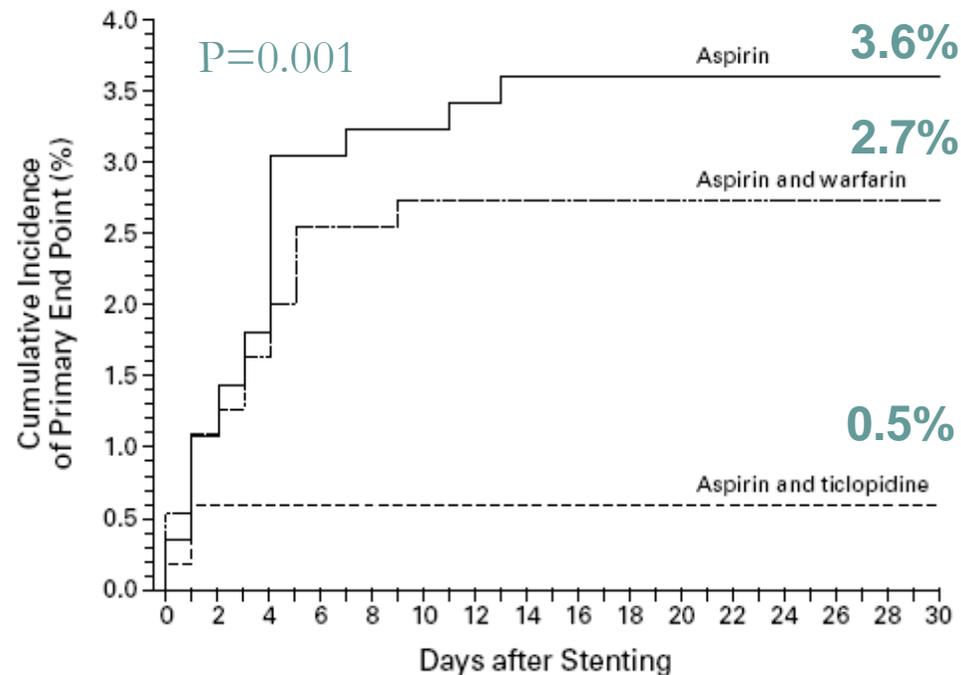
Stents and Arterial Healing



Continued risk of thrombus formation until endothelialization is complete

DAT and Stent Thrombosis

The STARS Trial



Bleeding requiring transfusion 1.8% ASA, 6.2% ASA+warfarin, 5.5% ASA+ticlopidine (P<0.001 for the comparison of all three groups)

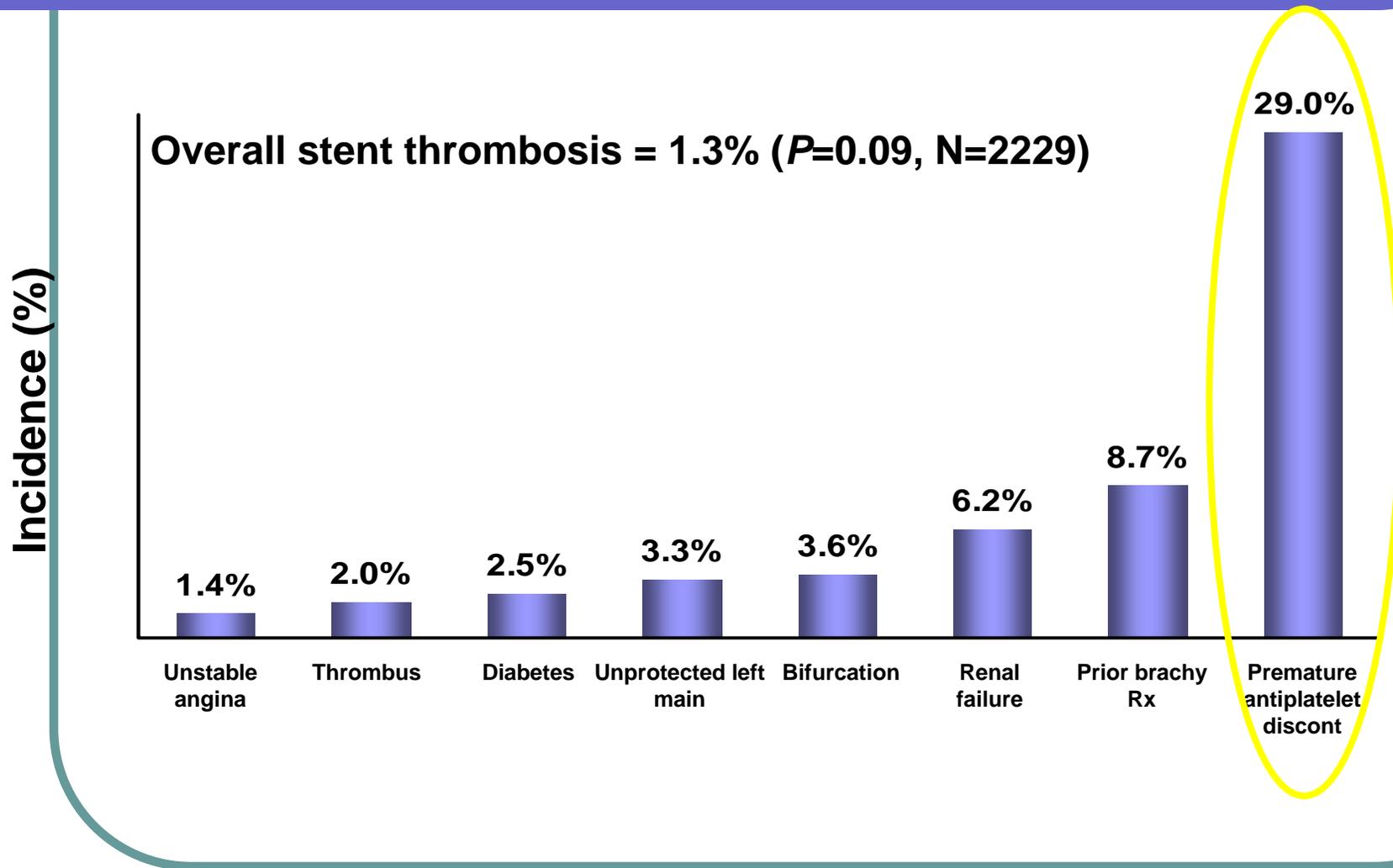
Drivers for Type and Duration of DAT

- Risk of recurrent ischemic events/stent thrombosis vs. bleeding risk
- Clinical indication for stenting
 - ACS
 - Stable CAD
- Type of stent
 - Bare metal (BMS)
 - Drug Eluting (DES)

Optimal Duration of DAT Post-stenting

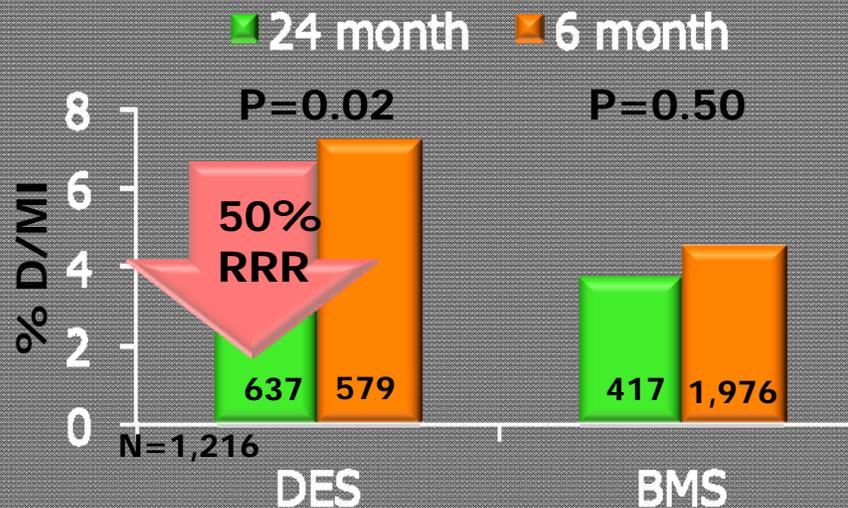
- Short answer
 - 12 months DAT for all PCI patients independent of stent type or procedural indication
 - Lifelong continuation of single antiplatelet agent
- Caveats
 - Patients (all or selected) may benefit from a more prolonged course of DAT
 - Risk of bleeding outweighs the anticipated benefit of thienopyridine therapy, earlier discontinuation should be considered (BMS 1 month, SES 3 months, PES/EES/ZES 6 months)
 - Risk of early discontinuation lower in BMS patients
 - Unclear if 12 months is superior to shorter duration DAT

Hazard of Premature Discontinuation of Antiplatelet Therapy in DES Patients

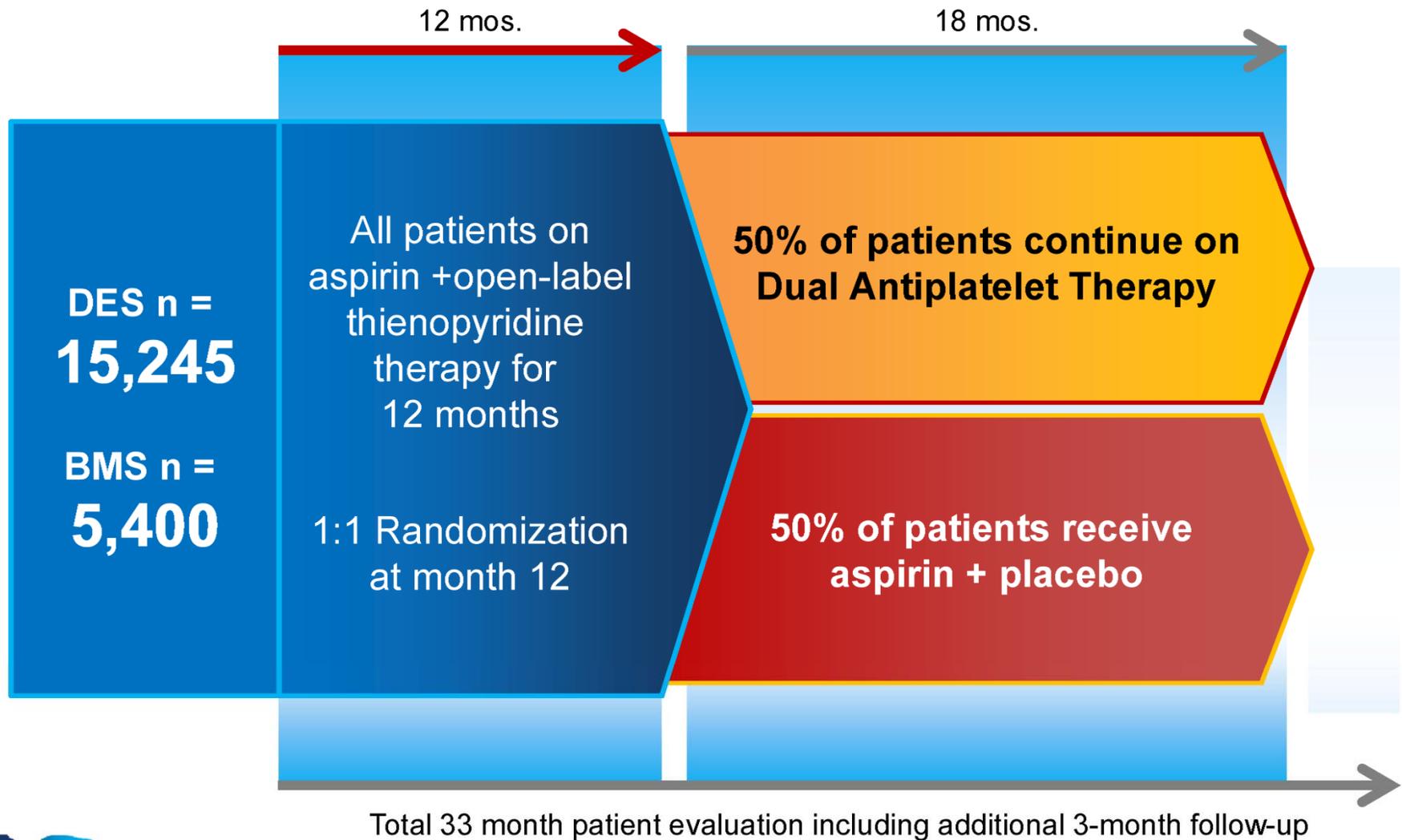


Registry Data: Prolonged Duration of DAPT Beneficial in DES?

24 Month Events in Patients who
Discontinued or did not Discontinue Clopidogrel
at 6 Months Stratified by Stent



Dual Antiplatelet Therapy (DAPT) Study



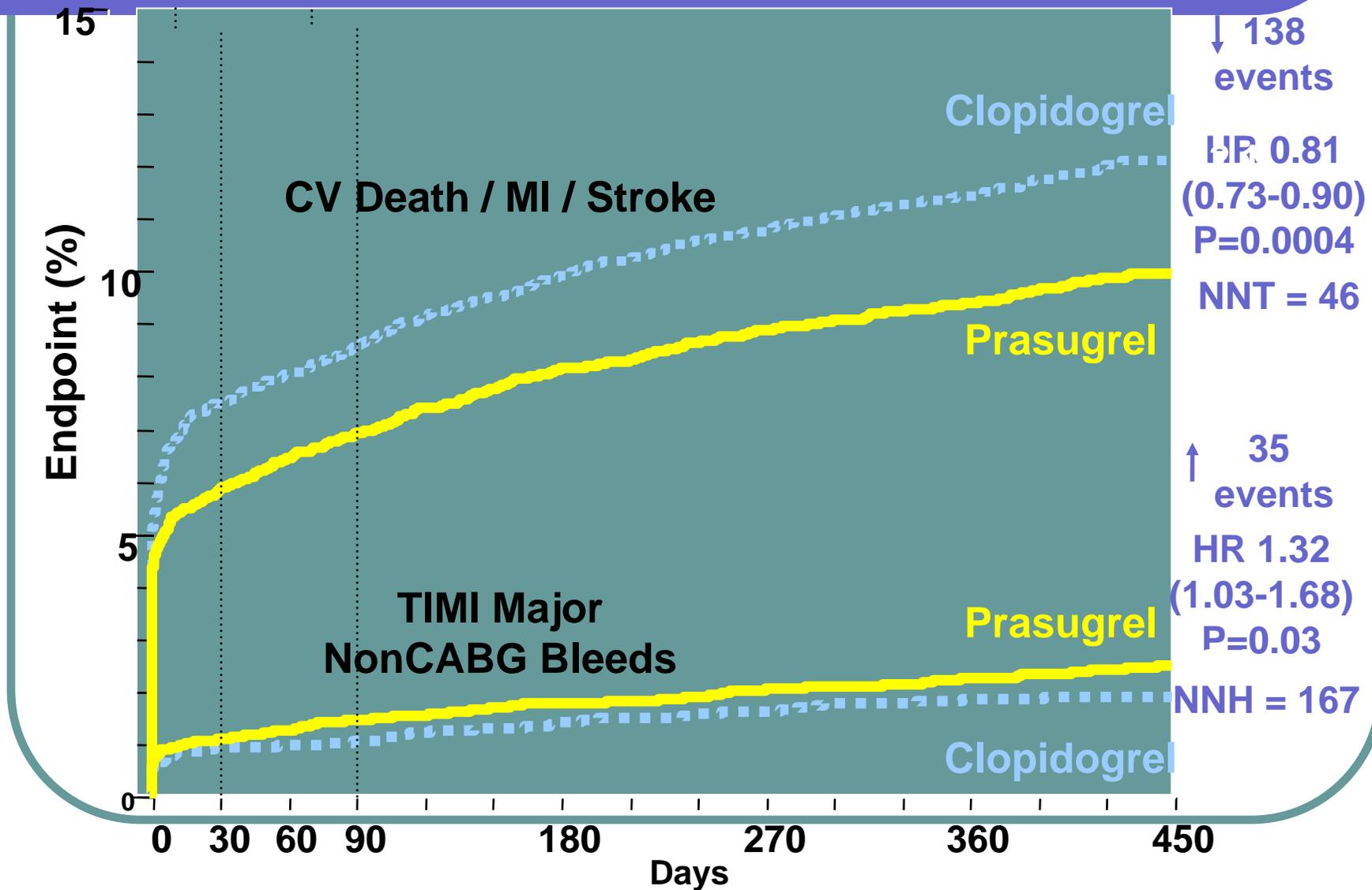
Which antiplatelet agents post-stenting?

- Aspirin
 - 81-325 mg daily up to 6 months
 - 81-162 mg after 6 months
- P2Y12 ADP-receptor inhibitor
 - Thienopyridine
 - Ticlopidine (Ticlid) 250mg BID
 - Clopidogrel (Plavix) 75 mg daily
 - Prasugrel (Effient) 10 mg daily (5 mg daily)
 - ACS
 - Cyclopentyltriazolopyrimidine
 - Ticagrelor (Brilique) 90 mg BID
 - ACS

Limitations of Clopidogrel

- Delayed onset of action due to pro-drug metabolism
 - 4 to 5 days after daily administration of 75 mg clopidogrel
 - 2-6 hours after loading dose
- Substantial inter-individual variability in platelet inhibition
 - Extent of metabolism of the pro-drug
 - Drug-drug interactions (PPIs)
 - Genetic Polymorphisms
- Non or hypo-responders have higher risk of ischemic events
- Irreversible
 - Problem for patients who need to undergo CABG

Prasugrel vs Clopidogrel in ACS: TIMI38



Ticagrelor vs Clopidogrel in ACS: PLATO Study

- Randomized double-blind study 18,624 patients
- Composite of CV death, MI, or stroke
 - 9.8 vs 11.7% HR 0.84 (0.77, 0.92) 0.0003
- Lower risk of stent thrombosis
 - 1.3 vs 1.9% HR 0.67 (0.50-0.91) p=0.0091
- Adverse events ticagrelor vs clopidogrel
 - HR for major bleeding: 1.04 (0.95 to 1.13) NS
 - Major or minor bleeding: 1.11 (1.03–1.20) 0.008
 - Dyspnea 1.84 (1.68–2.02) <0.001
 - Drug discontinuation 6.12 (3.41–11.01) <0.001
 - Ventricular pauses ≥ 3 sec 5.8 vs 3.6%, p 0.01
 - trend towards higher rate syncope

Cautions with New Agents

Prasugrel

- Higher bleeding risk
 - Contraindicated in patients with prior stroke
 - Caution age >75, weight <60kg (5 mg daily)
- Irreversible, slow offset of action
 - CABG bleeding risk higher than clopidogrel

Ticagrelor

- Metabolized by CYP3A, avoid or dose adjust drugs with similar metabolism (simva/pravachol)
- Low dose aspirin recommended 100mg or less
- Contraindicated: prior ICH, active bleeding, liver failure
- Side effect to monitor dyspnea 14% and bradycardia/pauses 6%
- Reversible, faster offset of action
 - CABG bleeding risk same as clopidogrel

Conclusions

- DAT should be given for 12 months in patients with low risk of bleeding until further studies are available
- ASA/clopidogrel combination indicated for non-ACS patients
- ACS patients weigh risks and benefits of more potent antiplatelet agents
 - High bleeding risk: ASA/clopidogrel
 - Prior GI bleed, stroke, advanced age, malignancy, anemia/thrombocytopenia, concurrent use of anticoagulants, steroids, or NSAIDS
 - High ischemic risk: ASA/prasugrel or ASA/ticagrelor
 - STEMI, DM, PAD, complex PCI incl. LM, bifurcation
 - Cost

PPIs and Thienopyridines

- Clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding.
- Patients with prior GI bleeding are at highest risk for recurrent bleeding on antiplatelet therapy.
 - Advanced age; concurrent use of anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin; and *Helicobacter pylori* infection.
- Use of a PPI or histamine H2 receptor antagonist (H2RA) reduces the risk of upper GI bleeding compared with no therapy. PPIs are superior to H2RAs.
- PPIs are recommended to reduce GI bleeding among patients with a history of upper GI bleeding. PPIs are appropriate in patients with multiple risk factors for GI bleeding who require antiplatelet therapy.
- Routine use of either a PPI or an H2RA is not recommended for patients at lower risk of upper GI bleeding
- Pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. Controversial whether clinically meaningful differences exist.
- Clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both CV and GI complications