Dual Anti-Platelet Therapy
DAPT

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Why DAPT?

Cornerstone of treatment - ACS and PCI

➢ To prevent local thrombotic complications related to stent implantation and

➢ To reduce systemic athero thrombotic events
What is DAPT?

DAPT - combination of Aspirin and a P2Y12 receptor inhibitor
P2Y12 inhibitors

- Three generations of thienopyridines, a family of non-direct, orally administered antiplatelet agents that irreversibly block the platelet ADP P2Y$_{12}$ receptor, are approved currently for clinical use.
- Non-thienopyridines—direct, reversible inhibitors namely ticagrelor, cangrelor and elinogrel
- 3 different oral P2Y12 receptor inhibitors are available
  - 2 have obtained the indication for ACS (clopidogrel and ticagrelor)
  - 1 for ACS with planned percutaneous coronary intervention (PCI) (prasugrel).
- In addition, an intravenous direct acting P2Y12 inhibitor, cangrelor, has been recently approved by US and European regulatory agencies for patients undergoing PCI.
History of DAPT

- **Ticlopidine** was the first to receive regular FDA approval in **1991** to reduce ischemic events in CAD patients
  - Ticlopidine for 2-4 weeks after BMS implantation (ISAR and STARS study)

- **Clopidogrel** was approved by the U.S. FDA in **1997** to reduce ischemic event following CAPRIE study

- **Prasugrel** was cleared by FDA in **2009** only for use in the context of PCI following the TRITON-TIMI 38 trial

- **Ticagrelor** received regulatory approval in Europe and US for use to reduce thrombotic events in patients of ACS in **2011** after PLATO trial

- **Cangrelor** was approved by the US FDA for reducing thrombotic events in patients undergoing PCI in **2015** based on the CHAMPION-PHOENIX study
Pharmacological properties of P2Y12 inhibitors

Table 1 | Pharmacological properties of P2Y₁₂-receptor inhibitors

<table>
<thead>
<tr>
<th>Property</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor blockade</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>~6 h</td>
<td>~7 h</td>
<td>8–12 h</td>
<td>3–5 min</td>
</tr>
<tr>
<td>Type of binding</td>
<td>Competitive</td>
<td>Competitive</td>
<td>Noncompetitive</td>
<td>Undetermined*</td>
</tr>
<tr>
<td>Administration route</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Frequency</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Bolus plus infusion</td>
</tr>
<tr>
<td>Onset of action</td>
<td>2–8 h</td>
<td>30 min to 4 h</td>
<td>30 min to 4 h</td>
<td>~2 min</td>
</tr>
<tr>
<td>Offset of action</td>
<td>5–7 days</td>
<td>7–10 days</td>
<td>3–5 days</td>
<td>30–60 min</td>
</tr>
<tr>
<td>Drug interaction with CYP enzymes</td>
<td>CYP2C19</td>
<td>No</td>
<td>CYP3A</td>
<td>No</td>
</tr>
<tr>
<td>Approved settings</td>
<td>ACS (invasively or noninvasively managed) and PCI in patients with ACS</td>
<td>PCI in patients with ACS</td>
<td>ACS (invasively or noninvasively managed)</td>
<td>PCI in patients with or without ACS</td>
</tr>
</tbody>
</table>

*The binding site of cangrelor at the P2Y₁₂-receptor level is not clearly defined; nevertheless, cangrelor is associated with high levels of receptor occupancy preventing ADP signalling. Abbreviations: ACS, acute coronary syndromes; CAD, coronary artery disease; CYP, cytochrome P450; PCI, percutaneous coronary intervention.
A 56 year old male, HTN, smoker had typical chest pain of 6 hours duration. Vitals stable. ECG was taken and tele-transmitted to me from the ambulance for further advice.

Case scenario-1

ECG showed acute anterior STEMI

Advised shift for primary PCI
Aspirin 162 to 325 mg should be given before primary PCI.

After PCI, aspirin should be continued indefinitely.

It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI.
Antiplatelet Therapy to Support Primary PCI for STEMI

A loading dose of a P2Y$_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:
- Clopidogrel 600 mg; or Prasugrel 60 mg; or Ticagrelor 180 mg

P2Y$_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:
- Clopidogrel 75 mg daily; or Prasugrel 10 mg daily; or Ticagrelor 90 mg twice a day*

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

Continuation of a P2Y$_{12}$ inhibitor beyond 1 year may be considered in patients undergoing DES placement.

Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.
Clopidogrel

- Clopidogrel -2nd generation thienopyridine.
- Prodrug
- Must be metabolized by CYP450 enzymes to produce the active metabolite.
- The active metabolite selectively inhibits the binding of ADP to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.
- This action is irreversible. Platelets affected for the remainder of their lifespan (about 7 to 10 days).
- Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.
Clopidogrel trials – ACS/CAD

- Acute STEMI
- UA/NSTEMI
- PCI
- Long-term 2° (1°) prevention

- COMMIT (CCS-2)
- CLARITY TIMI 28
- CURE
- CAPRIE (Lancet 1996)
- CHARISMA

STEMI
UA/ NSTEMI
PCI
MI / stroke
PAD

30 days + Benefit
1 year + Benefit
1 year + Benefit
1-3 years + Benefit

Vasc dis/risk
Up to 3.5 years
CLARITY-TIMI 28 TRIAL

Study design

- Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 years with STEMI < 12 hours
- Randomize
  - Fibrinolytic, ASA, heparin
  - Clopidogrel 300 mg + 75 mg qd
  - Placebo
- Coronary angiogram (2-8 days)
- Primary endpoint: Occluded artery (TIMI flow grade 0/1) or D/MI by time of angiogram
- 30-day clinical follow-up

CV death, MI, RI → urgent revascularization

- Placebo
- Clopidogrel

Odds ratio 0.80
(95% CI 0.65-0.97)
p = 0.026
COMMIT/CCS-2 TRIAL

COMMIT/CCS-2: Clopidogrel and Metoprolol in Myocardial Infarction Trial

Purpose:
To determine whether adding clopidogrel can produce a further reduction in mortality and the risk of vascular events in hospitalized patients admitted with acute STEMI.


COMMIT/CCS-2: Conclusions

- Adding 75 mg daily clopidogrel to aspirin in acute MI prevents ~10 major vascular events per 1000 treated.
- No excess of cerebral, fatal, or transfused bleeds (even with fibrinolytic therapy and in older people).
- Each million MI patients treated for ~2 weeks would avoid 5000 deaths and 5000 non-fatal events.

Chen ZM. Presented ACC 2005
Clopidogrel-DAPT CURE trial

CURE trial and demonstrated a clinical benefit, in an ACS population
Death, MI, or stroke was reduced by 20% in patients (95% CI, 10% to 28%; $P<0.001$).
In the **PCI-CURE** trial, a predefined post randomization subgroup of patients undergoing PCI, the relative risk reduction associated with clopidogrel was 31% (95% CI, 13% to 46%; *P*=0.002).
Pre-hospital antiplatelet therapy
Clopidogrel

Conclusions:
Addition of clopidogrel to medical reperfusion of STEMI with fibrinolysis, heparin, and aspirin before reaching the hospital is feasible in medically equipped ambulances without an apparent increase in bleeding. Furthermore, prehospital clopidogrel tended to show better early coronary patency compared to placebo, a result consistent with that observed in patients randomized in-hospital in the CLARITY-TIMI 28 trial.

Various studies and meta-analyses suggested that pre-treatment with clopidogrel in patients with STEMI could reduce the rate of ischemic events without excess bleeding, but its effectiveness may be limited by its slow onset of action and the variable response.
Drawbacks with clopidogrel

The percentage of “low responders” or “resistant” patients ranges from 5% to 40% across studies
Clinical effects of LD >300 mg

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>N0.</th>
<th>Population</th>
<th>LD-CLOPI</th>
<th>Clinical End Point</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMYDA</td>
<td>2005</td>
<td>255</td>
<td>Elective PCI and NSTE-ACS</td>
<td>300 mg vs.. 600 mg</td>
<td>Death, MI, or TVR at 30 days</td>
<td>52% R.R reduction</td>
</tr>
<tr>
<td>Cuisset et.al</td>
<td>2006</td>
<td>292</td>
<td>NSTE-ACS</td>
<td>300 mg vs. 600 mg</td>
<td>Death, stent thrombosis, recurrent ACS, and stroke at 30 days</td>
<td>decreased the rate of MACE (5% versus 12%; P0.02)</td>
</tr>
<tr>
<td>Bonello et al</td>
<td>2009</td>
<td>429</td>
<td>Elective PCI and NSTE-ACS</td>
<td>600 mg vs. repeated bolus of 600 mg</td>
<td>Stent thrombosis at 30 days</td>
<td>improve prognosis stent thrombosis (0.5% versus 4.2%; P0.01), bleeding (4% versus 5%).</td>
</tr>
<tr>
<td>ARMYDA-RELOAD</td>
<td>2010</td>
<td>503</td>
<td>Elective PCI and NSTE-ACS</td>
<td>Placebo vs. 600 mg in patients under chronic clopidogrel therapy</td>
<td>Death, MI, or TVR at 30 days</td>
<td>MACE no different , no increased bleeding, ACS subgroup did benefit (6.4 versus 16.3%; P0.033),</td>
</tr>
<tr>
<td>CURRENT-OASIS 7</td>
<td>2010</td>
<td>25 086</td>
<td>NSTE-ACS</td>
<td>300 mg vs. 600 mg</td>
<td>Death, MI, and stroke at 30 days</td>
<td>patients with ACS who underwent PCI, the double-dose regimen led to a nominal 25% decrease in CV events (3.9% versus 4.5%).</td>
</tr>
</tbody>
</table>

600 mg loading dose is associated with reduced resistance and increased responsiveness to clopidogrel, as well as a greater magnitude of platelet inhibition and faster onset-of-action.
Inhibition of platelet aggregation (%) obtained 4 hours after loading when measured with 20 μmol /L ADP with light transmittance aggregometry in patients with ACS [IPA=(RPA at baseline−RPA at H4)−RPA at baseline].

Doses greater than 900 i.e.1200 mg were tested tin PRINC and PREPAIR trials and showed to have the maximum platelet inhibition.
In the subgroup of patients undergoing PCI, the high dose strategy was associated with a decrease in the rates of ischemic outcomes (3.9% versus 4.5%; hazards ratio [HR], 0.85; \( P=0.036 \)), and reduced the risk of stent thrombosis by 30%, at the expense, of a significant increase in major bleedings.
Clopidogrel 600 mg vs 300 mg loading dose

Meta-analysis; N = 1567; Primary endpoint: Cardiac death or MI at 1 month

<table>
<thead>
<tr>
<th></th>
<th>Favors high loading</th>
<th>Favors low loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALBION</td>
<td></td>
<td>1.03 (0.09-11.5)</td>
</tr>
<tr>
<td>ARMYDA-2</td>
<td></td>
<td>0.35 (0.14-0.87)</td>
</tr>
<tr>
<td>CLEAR PLATELETS</td>
<td></td>
<td>0.36 (0.05-2.61)</td>
</tr>
<tr>
<td>Cuisset et al</td>
<td></td>
<td>0.46 (0.19-1.09)</td>
</tr>
<tr>
<td>Gurbel et al*</td>
<td></td>
<td></td>
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<tr>
<td>ISAR-CHOICE*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muller et al*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>0.42 (0.23-0.75)</td>
</tr>
<tr>
<td>Non-randomized studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiolillo et al*</td>
<td></td>
<td>1.28 (0.44-3.74)</td>
</tr>
<tr>
<td>Seyfarth et al*</td>
<td></td>
<td>1.28 (0.44-3.74)</td>
</tr>
<tr>
<td>Wolfram et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.28 (0.44-3.74)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.54 (0.32-0.90)</td>
</tr>
</tbody>
</table>

*No events in either group
†Peto fixed-effect method

Current recommendations for Clopidogrel in STEMI

ESC guidelines and ACC/AHA 2013 Guidelines for STEMI:

- loading dose of 300-600 mg followed by a maintenance dose of 75 mg/day, in patients with ACS, including those undergoing PCI

  a. Adjunct to fibrinolytic therapy:
     - 300mg LD in patients ≤ 75 mg; and 75 mg in patients ≥ 75 yrs (class IA)
     - 75 mg MD for at least 14 days and up to 1 yr (class IA;C)

  b. Adjunct to PCI:
     - 600mg LD 4-8 hours prior to PCI (class IA)
     - MD of 75 mg for 1 year (class IB)

  c. Adjunct to PCI after fibrinolytic therapy:
Ticagrelor- First choice

- Direct acting reversible blocker of P2Y12 platelet receptor
- Half life of approx 12 hours.
- Inhibit P2Y12 mediated platelet aggregation completely
The PLATO Trial (Ticagrelor vs Clopidogrel)

1998

2011

Ticagrelor – out with the old, in with the new?

PLATO study design

NSTEMI ACS (moderate-to-high risk) STEMI (if primary PCI) (N=18,624)
Clopidogrel-treated or -naive; randomized<24 hours of index event

At randomization, 13,408 (72%) of patients were specified by the Investigator: intent for invasive strategy

Clopidogrel (n=6,676)
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre-PCI)

Ticagrelor (n=6,732)
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6-12 months treatment

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

PCI = percutaneous coronary intervention; CV = cardiovascular; PI = principal investigator
PLATO RESULTS

Positive results
• Primary end point fell significantly by 16%
• 16% reduction in MI
• 21% reduction in CV death
• 22% relative reduction in mortality
• Rate of stent thrombosis reduced significantly from 1.9% to 1.3%
• Greater clinical efficacy in non-invase, STEMI, previous clopidogrel patients

Negative results
• No benefit in sub group in whom aspirin dose was high
• 0.7% absolute (19% relative) higher incidence of non-CABG major bleed
• Moderate to minor dyspnoea was more common
• Ventricular pauses exceeding 5 sec occurred more frequently
Ticagrelor, the reversible, more intense P2Y\textsubscript{12} antagonist, is a more effective alternative to clopidogrel for one year in ACS patients managed with an invasive strategy, for the continuous prevention of ischemic events, stent thrombosis and death without an increase in major bleeding.

ACC/AHA guidelines 2013/ESC GUIDELINES
- 180 mg LD as early as possible or at the time of PCI (class IB)
- 90 mg twice a day as MD
Pre-hospital Ticagrelor

Prehospital administration of ticagrelor in patients with acute STEMI appeared to be safe but did not improve pre-PCI coronary reperfusion.
The new oral P2Y$_{12}$-receptor antagonists inhibit platelet function in less than 1 hour, which is compatible with transfer times for primary PCI.

The Take Home
Pre-hospital ticagrelor “may not pay off immediately” but giving it earlier rather than later should be encouraged, a study author says.
Switch over:
Clopidogrel to Ticagrelor
HOW?
P2Y12 switching regimens

Only evidence-PLATO TRIAL

- 46% of ticagrelor subjects had received clopidogrel mainly as loading dose, subsequently ticagrelor loading dose of 180 mg within 24 hours
- Suggestion: Acute phase (within 24 hours of onset of chest pain) administer loading dose of 180 mg unless active bleeding) regardless of the timing of clopidogrel dose
SHIFT-OVER study: Switch From Ongoing Clopidogrel Treatment to Ticagrelor in Patients With Acute Coronary Syndrome

- Randomized, single-blinded, single center study
- Aspirin-treated patients with ACS (n = 50) receiving clopidogrel were randomly assigned to either ticagrelor 90 mg (no LD) plus 90 mg twice daily or 180-mg LD plus 90 mg Bd
- At 2 hours after the first dose, residual platelet aggregation was significantly reduced in both arms, with no difference between groups;

- This suggests that switching from clopidogrel to ticagrelor without a reloading dose is feasible, and it does not delay platelet inhibition in patients with ACS
- **Recommended:** clopidogrel to ticagrelor- 90 mg bd. Refrain from loading doses
Clopidogrel to novel inhibitors

• Incidence is 5-50%

• RESPOND TRIAL
  – Stable CAD patients based on HPR as responders and non-responders.
  – PR decreased significantly in those on ticagrelor

• Clopidogrel to ticagrelor
  – In acute phase: LD 180 mg irrespective of timing to be given followed by 90 mg bd
  – In chronic phase, 90 mg bd can be initiated without loading dose
WHY NOT PRASUGREL?

- A third generation thienopyridine
- Orally administered prodrug that needs hepatic biotransformation into its active metabolite to irreversibly block the P2Y$_{12}$ receptor.
- Pharmacological advantages over clopidogrel:
  - It is more effectively converted into its active metabolite (oxidized in 1 step)
  - displays a faster onset of action (within 30 min)
  - greater degree of platelet inhibition (10 times potency)
  - less variability in response, even when compared with high dose clopidogrel.
RESULTS

- **The primary efficacy end point**, over a follow-up period of 15 months, occurred in 9.9% of patients treated with prasugrel and in 12.1% of patients treated with clopidogrel, thus resulting in a significant **19% relative reduction with prasugrel** (HR, 0.81 [0.73–0.90]; *P*<0.001).

- This benefit was hampered by an increased risk of TIMI major non-coronary artery bypass graft (CABG) related bleeding (2.4% versus 1.8%; *P*=0.03), including fatal bleeding (0.4% versus 0.1%; HR, 4.19 [1.58–11.11]; *P*=0.002), which occurred mostly in the maintenance phase of prasugrel treatment.
A pre-specified net clinical benefit was performed and a significant net clinical benefit was associated with prasugrel therapy despite the excess in bleeding:

- marked reduction in nonfatal MI, approximately 40%
- 52% reduction of the rates of definite or probable stent thrombosis
- Such benefit was both early (<30 days) and late (up to 15 months)
- both BMS and DES
- The benefit was striking (30%) in diabetics
CONCLUSION

- Prasugrel proved superior over clopidogrel but at the cost of excess bleeding
Prasugrel 10 mg was compared with clopidogrel 75 mg in 7243 patients younger than 75 years being managed medically following NSTEMI. No difference occurred in the primary composite endpoints of cardiovascular death, MI, or stroke nor in severe bleeding.
Recommendations-prasugrel

- **ACC/AHA guidelines**
  - LD of 60 mg as early as possible or at time of PCI (class IB)
  - MD of 10 mg daily for 12 months (class IB)
  - CI in patients with previous TIA/CVA
  - Not recommended for patients >75 yrs (class IB)
  - Considered lower doses of patients <60 kg (class IB)

- **ESC guidelines**
Pre-treatment with prasugrel

ACCOAST: Results

- Pretreating NSTE-ACS patients with prasugrel at the time of diagnosis, rather than after angioplasty, does not improve ischemic events but does drive up major bleeding complications.

- The trial's data and safety monitoring committee stopped enrollment at 4033 patients in November 2012 after noticing an increase in major and life-threatening bleeding and no reduction in CV events.

- The primary efficacy end point was not significantly different between the two treatment groups at seven or 30 days. TIMI major bleeding (either related to CABG or not) was significantly higher in the pretreatment group at both time points, as were rates of non-CABG TIMI major bleeding and life-threatening bleeding.

<table>
<thead>
<tr>
<th>End point</th>
<th>Pretreatment n (%)</th>
<th>No pretreatment n (%)</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, 7 d</td>
<td>203 (10.0)</td>
<td>105 (0.8)</td>
<td>1.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary end point, 30 d</td>
<td>219 (10.6)</td>
<td>216 (10.8)</td>
<td>0.997</td>
<td>0.96</td>
</tr>
<tr>
<td>All CABG or non-CABG TIMI major bleeding, 7 d</td>
<td>52 (2.6)</td>
<td>27 (1.4)</td>
<td>1.90</td>
<td>0.006</td>
</tr>
<tr>
<td>All CABG or non-CABG TIMI major bleeding, 30 d</td>
<td>56 (2.8)</td>
<td>29 (1.5)</td>
<td>1.97</td>
<td>0.002</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>22 (1.1)</td>
<td>4 (0.2)</td>
<td>5.40</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACCOAST: no difference in efficacy endpoint between pretreatment with prasugrel or no pretreatment.
SWITCH OVER IN ACS

- Clopidogrel To Prasugrel

TRIPLET STUDY

- No statistically significant difference in platelet inhibition was observed at any time point across the 3 groups.

- The treatment-emergent adverse events, including those hemorrhagic, were low and evenly distributed across treatment groups.
SWAP study

- The was a multicenter, randomized, double blind trial to assess the pharmacodynamic response after switching to prasugrel from clopidogrel MD therapy
  - Switching from clopidogrel to prasugrel 10-mg MD, with or without LD, resulted in significantly higher platelet inhibition at 7 days as assessed by multiple platelet function testing.
  - When switching was initiated with prasugrel 60-mg LD, a significant reduction in platelet aggregation was observed at 2 hours and continued for 24 hours after the first dose.
  - No TIMI major bleeding event occurred. Observed bleeding complications were all considered minimal according to the TIMI criteria and were similar between groups.
Clopidogrel to Prasugrel

• In the acute phase: 60 mg LD irrespective of timing of clopidogrel dosing followed by MD of 10 mg daily

• Chronic phase: 10 mg to be give 24 hours after last dose of clopidogrel
Switching P2Y<sub>12</sub>-receptor inhibitors in patients with coronary artery disease
Fabiana Rollini, Francesco Franchi & Dominick J. Angiolillo
Nature Reviews Cardiology 13, 11–27 (2016) doi:10.1038/nrcardio.2015.113
• This patient was taken up for Primary angioplasty under coverage of Ticagrelor And Aspirin. Successful PTCA To Proximal LAD was done and Promus stent was implanted.
  – Would u continue ticagrelor. For how long?
  – If he does not tolerate or cannot afford ticagrelor, how can we shift to other antiplatelets?
  – Any role for platelet inhibition studies?
What is the optimal duration of DAPT?
• Initially prescribed for 4 weeks after BMS implantation,
• increased to 3 months after SES in 2003,
• 6 months after PES in 2004.
• Soon, duration of clopidogrel therapy to 12 months, on the basis of findings in PCI-CURE, CREDO and observational studies
  — all stents were BMS

• In PLATO and TRITON-TIMI 38, DES were used in 19% and 40% of cases, respectively, but all these stents were first-generation sirolimus-eluting stents and PES.
Stent type has emerged as an important risk factor for stent thrombosis

Newer-generation DES, are associated with a risk of stent thrombosis approximately one half that of the first generation DES
ACC/AHA Task Force on Clinical Practice Guidelines: writing committee

• **Q1.** When compared with 12 months, is 3 to 6 months of DAPT as effective in 1) preventing stent thrombosis, 2) preventing major adverse cardiac events (MACE), and/or 3) reducing bleeding complications?

• **Q2.** When compared to 12 months, does >12 (18 to 48) months of DAPT result in 1) differences in mortality rate, 2) decreased MACE, 3) decreased stent thrombosis, and/or 4) increased bleeding?

• **Q3.** In post-MI patients who are clinically stable and >12 months past their event, does continued DAPT, compared with aspirin monotherapy, result in differences in 1) mortality rate, 2) decreased nonfatal MI, 3) decreased MACE, and/or 4) increased bleeding?
Duration of DAPT After Implantation of Newer-Generation DES

- 11 RCT- 33,051 patients who underwent implantation of predominantly newer generation DES.
- All 11 RCTs were judged to be of moderate to high quality, with at least moderate relevance, fidelity, and freedom from bias.

Trials of DAPT Duration after Stenting (Months after PCI)
- DES Late (n=5045) – 12 to 36 months
- DAPT DES (n=9961) – 12 to 30 m
- DAPT BMS (n=1687) – 12 to 30 m
- ITALIC (n=1850) – 6 to 24 m
- PRODIGY (n=2014) – 6 to 24 m
- ARCTIC-Interruption (n=1259) – 6 to 24 m
- ISAR-SAFE (n=4000) – 6 to 12 m
- EXCELLENT (n=1443) – 6 to 12 m
- OPTIMIZE (n=3119) – 3 to 12 m
- RESET (n=2117) – 3 to 12 m
## Prolonged DAPT trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Trial Completion</th>
<th>Primary Study endpoint</th>
<th>Trial design and outcome</th>
<th>Expected event rate in control group (%)</th>
<th>Observed event rate in control group (%)</th>
<th>% of newer generation stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES LATE (12 vs. 36 mo)</td>
<td>2010</td>
<td>Extension of ZEST-LATE and REALLATE</td>
<td>Cardiac death, MI, or stroke &lt;24h</td>
<td>Superiority not shown</td>
<td>2.7</td>
<td>2.6</td>
<td>30</td>
</tr>
<tr>
<td>ARCTIC (12 vs. 18 mo)</td>
<td>2014</td>
<td>Extension of ARCTIC</td>
<td>Death, MI, ST. Stroke or urgent TVR</td>
<td>Superiority not shown</td>
<td>6.0</td>
<td>4.0</td>
<td>63</td>
</tr>
<tr>
<td>SECURITY (6 vs. 12 mo)</td>
<td>2014</td>
<td>Stopped after 1,399 enrolled of 2,740</td>
<td>Cardiac death, MI, ST, or stroke</td>
<td>Non-inferiority confirmed</td>
<td>4.5</td>
<td>4.5</td>
<td>100</td>
</tr>
<tr>
<td>ITALIC (6 vs. 24 mo)</td>
<td>2015</td>
<td>Stopped after 2,031 enrolled of 2,475 planned</td>
<td>Death, MI, urgent TVR, stroke, or major bleeding</td>
<td>Non-inferiority confirmed</td>
<td>3.0</td>
<td>1.5</td>
<td>100</td>
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<tr>
<td>DAPT (12 vs. 30 mo)</td>
<td>2015</td>
<td>Enrollment completed</td>
<td>Co primary: ST and MACCE</td>
<td>Superiority shown</td>
<td>0.5/2.9</td>
<td>0.5/2.4</td>
<td>59</td>
</tr>
<tr>
<td>OPTIDUAL (12 vs. 48 mon)</td>
<td>2015</td>
<td>(Stopped after 1,385 enrolled of 1,966 Planned)</td>
<td>Death, MI, stroke, or major bleed</td>
<td>Superiority not shown</td>
<td>7.0</td>
<td>7.5</td>
<td>59</td>
</tr>
</tbody>
</table>
18 to 48 Months of DAPT Versus 6 to 12 Months of DAPT

• 6 RCTs- 20,973 patients
  – Prolonged DAPT, reduced the risk of MI (OR: 0.67; 95% CI: 0.47 to 0.95) and stent thrombosis (OR: 0.42; 95% CI: 0.24 to 0.74) and produced a borderline reduction in the prospectively defined primary endpoints (OR: 0.85; 95% CI: 0.72 to 1.00).
  – Prolonged DAPT was associated with no difference in all-cause death (OR: 1.14; 95% CI: 0.92 to 1.42) but increased major hemorrhage (OR: 1.58; 95% CI: 1.20 to 2.09).
• The annual rate of major haemorrhage was
  – 1.26% (prolonged DAPT) vs. 0.80% (shorter course)
  – 13 of 1,000 patients had major bleeding during each year of extended therapy, as compared with 8 receiving shorter courses of DAPT.

• A risk-benefit analysis found that extending DAPT to 18 to 48 months, as compared with stopping DAPT after 6 to 12 months, resulted in
  – 3 fewer stent thromboses (95% CI: 2 to 5)
  – 6 fewer MIs (95% CI: 2 to 11) but
  – 5 more major bleeds (95% CI: 3 to 9) and
  – a statistically non significant 2 more deaths (95% CI: -1 to 4) per 1,000 patients per year
NIPPON

- NIPPON trial is a multi-center randomized study to test the non-inferiority of 6 months DAPT compared with 18 months DAPT following NOBORI stent
- NOBORI is a DES with bio absorbable polymer and abluminal coating
- 6 months of DAPT was statistically non-inferior to 18 months of DAPT in terms of net adverse clinical and cerebrovascular events, including all cause death, Q-wave or non-Q wave MI, cerebrovascular events, and major bleeding. However, the results need to be interpreted with caution given premature termination of enrollment, an open-label design with frequent crossover and a wide non-inferiority margin.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Trial Completion</th>
<th>Primary Study endpoint</th>
<th>Trial design and outcome</th>
<th>Expected event rate in control group (%)</th>
<th>Observed event rate in control group (%)</th>
<th>% of newer generation stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRODIGY (6 vs. 24 mo)</td>
<td>2012</td>
<td>Enrolment completed</td>
<td>Death, MI or stroke</td>
<td>Superiority not shown</td>
<td>8.0</td>
<td>10.1</td>
<td>67</td>
</tr>
<tr>
<td>EXCELLENT (6 vs. 12 mo)</td>
<td>2012</td>
<td>Enrolment completed</td>
<td>Cardiac death, MI or ischemia driven TVR</td>
<td>Non-inferiority confirmed</td>
<td>10</td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>RESET (3 vs. 12 mo)</td>
<td>2012</td>
<td>Enrolment completed</td>
<td>Cardiac death, MI, ST revas or bleeding</td>
<td>Non-inferiority confirmed</td>
<td>10.5</td>
<td>4.7</td>
<td>85</td>
</tr>
<tr>
<td>OPTIMIZE (3 vs. 12 mo)</td>
<td>2013</td>
<td>Enrolment completed</td>
<td>NACCE-death, MI, stroke or bleed</td>
<td>Non-inferiority confirmed</td>
<td>9.0</td>
<td>6.0</td>
<td>100</td>
</tr>
<tr>
<td>ISAR-SAFE (6 vs. 12 mo)</td>
<td>2015</td>
<td>Stopped after 4,005 enrolled of 6,000 Planned</td>
<td>Death, MI, ST, stroke, or TIMI major bleed</td>
<td>Non-inferiority confirmed</td>
<td>10.0</td>
<td>1.5</td>
<td>72</td>
</tr>
</tbody>
</table>
Kaplan-Meier curves for the primary end point of target vessel failure. – EXCELLENT trail

A

- 6-month DAPT
- 12-month DAPT

P=0.60

Target vessel failure (%)

Days since randomization

B

- 6-month DAPT
- 12-month DAPT

P=0.85

Target vessel failure (%)

Days since randomization

12 Months of DAPT Versus 3 to 6 Months of DAPT

• 5 RCTs-12,078 patients
• DAPT of 12 months’ duration was associated with No differences in:
  – Death (odds ratio [OR]: 1.17; 95% CI: 0.85 to 1.63),
  – Major hemorrhage (OR: 1.65; 95% CI: 0.97 to 2.82)
  – MI (OR: 0.87; 95% CI: 0.65 to 1.18),
  – Stent thrombosis (OR: 0.87; 95% CI: 0.49 to 1.55), and
  – Primary endpoint for each study (OR: 0.96; 95% CI: 0.80 to 1.16).
Duration of DAPT determinant

Ischemic events (MI, CPK raise, Stent thrombosis)

Bleeding
Bleeding risk

- CKD
- ACS presentation
- Liver disease
- PAD
- Cardiogenic shock
- Female gender
- Increased risk of mortality
- Procedural factors
  - Use of GPI
  - Femoral access
- Chronic oral anticoagulation
- Older age
- Haematological factors
Overlap Between Bleeding and Ischemic Risk Clinical Factors

- Low PRU
- Chronic NSAIDS
- Previous bleeding
- Liver disease
- Hemorrhagic diathesis
- PUD
- Older age
- Low BMI

- Females
- Gender
- CKD
- Anemia
- ACS
- PVD
- Cardiogenic shock
- CHF

- Lesion complexity, High PRU
- Thrombus burden
- Multivessel CAD
- Incomplete apposition
- Thrombotic diathesis
- DAPT disruption
- DM
- Stent length/diameter
- Type of stent
Optimal duration of DAPT

• Safer, newer-generation DES may be treated with a minimum DAPT duration of 3 to 6 months to prevent early and largely stent-related thrombotic events.
  – EXCELLENT trial surmised that “DAPT may not be necessary beyond the initial 6 months, at least in low-risk patients
  – RESET trial: “With newer-generation DES, 6 months DAPT might be sufficient, and 3 months not completely off the wall in low-risk groups
  – SECURITY trial concluded, “Shorter DAPT duration seems very reasonable to consider and is increasingly used in the art of taking care of these patients
DAPT AFTER BVS

• BVS – PCI
• 2012 - 2014 BVS implantation strategy resulted in high acute and subacute scaffold thrombosis rate
• Low late ST rate while on continuous DAPT
• Minor effect of DAPT termination after 12 months on ST rate
• ST at planned DAPT termination might be result of suboptimal implantation
• Effect of DAPT termination for BVS similar to DES
Platelet inhibition studies

- RESPOND trial
- TRANSLATE-ACS TRIAL
- GRAVITAS study
- ARCTIC TRIAL
- Morphine increases platelet reactivity. Hence higher dose of antiplatelets required
- Gender differences
- Ongoing studies

Guidelines recommendation:
- Class III recommendation - routine use of platelet function testing is not advised
- Class IIb in patients at high risk for poor clinical outcome
The efficacy of high dose clopidogrel (600 mg initial dose and 150 mg daily thereafter for 6 months) versus standard dose clopidogrel (no additional loading dose and 75 mg daily) was compared in 2214 patients with high on-treatment reactivity, on the basis of Verify Now P2Y12 assay measurement, 12 to 24 hours after PCI with drug-eluting stents.

- No differences in the rates of ischemic (2.3% versus 2.3%; HR, 1.01 [0.58–1.76]; P=0.97) or bleeding outcomes (1.4% versus 2.3%; HR, 0.59 [0.31–1.11]; P=0.10) were found.
- Thus, a benefit of a tailored strategy with clopidogrel therapy was not observed in this trial.

The GRAVITAS trial, the first large-scale clinical trial, designed to examine whether adjustment of clopidogrel therapy, on the basis of platelet function testing using a point-of-care assay, safely improves outcome after PCI with drug-eluting stents in clopidogrel resistant patients, did not show any superiority of 150 mg vs. 75 mg of clopidogrel.
- It was a flat trial. For the primary composite end point, there was no difference;
- 34% of events in the group of patients that was monitored,
- 31% in the control group, no difference statistically speaking.
- It was the same for the main secondary end point,
- urgent revascularization and/or stent thrombosis
## Gender difference in PI - NIMS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No</td>
<td>112(78.9%)</td>
<td>30(21.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>57.1 ± 9.6</td>
<td>56.2 ± 10.4</td>
<td>0.7</td>
</tr>
<tr>
<td>HTN</td>
<td>67 (59.8%)</td>
<td>22(73.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>DM</td>
<td>43(38.4%)</td>
<td>19(63.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>SM</td>
<td>45(39.3%)</td>
<td>1(3.3%)</td>
<td>0.000</td>
</tr>
<tr>
<td>PVD</td>
<td>2(1.8%)</td>
<td>0(0%)</td>
<td>0.15</td>
</tr>
<tr>
<td>CVA</td>
<td>2(1.8%)</td>
<td>0(0%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Female</th>
<th>Male</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>12.3 ± 1.4</td>
<td>13.5 ± 2.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Chad Vas Score</td>
<td>2.7 ± 0.95</td>
<td>1.4 ± 1.3</td>
<td>0.000</td>
</tr>
<tr>
<td>ACS</td>
<td>60(53.6%)</td>
<td>16(53.3%)</td>
<td>0.98</td>
</tr>
<tr>
<td>LVD</td>
<td>49(43.8%)</td>
<td>8(26.7%)</td>
<td>0.067</td>
</tr>
<tr>
<td>GPI</td>
<td>9(8.04%)</td>
<td>4(13.3%)</td>
<td>0.43</td>
</tr>
</tbody>
</table>
Gender difference in PI

- There are 9 (30%) females with high on-treatment platelet reactivity in whom there are nil events in them.
- There are 24 (21.43%) males with high on-treatment platelet reactivity in whom there are 3 non cardiac events (AV fistula, CSA+CIN, CCF) in them.
- Even total event rate (MACCE) is higher in females (10%) than in males (8.04%), which is not statistically significant (Chi square test person = 1.238, p=0.266, and fisher exact test p= 0.545, OR = 0.00, 95% CI 0.00 to 6.649, RR = 0.00, 95% CI 0.00 TO 5.389).

Conclusion:

- Though there is a tendency of high on-treatment platelet reactivity in females, this is not translated into the clinical events at one year.
ONGOING STUDIES

• TROPICAL-ACS study:
  – To assess the use of novel P2Y12 inhibitors therapies on the basis of pharmacodynamic studies.
  – Prasugrel to clopidogrel if PR is below threshold

• HEIGHTEN study:
  – Effect of switching patients with HPR from prasugrel to ticagrelor
• This patient presented 5 months later with acute abdomen-intestinal obstruction requiring emergency surgery.

• What advice would you give-DISCONTINUE ANTIPLATELETS?
DURATION DEPENDING ON TYPE OF STENT

- Zotarolimus-3 months
- RESET trail
- 2,117 patients with coronary artery stenosis into 2 groups according to DAPT duration and stent type: 3-month DAPT following Endeavor zotarolimus-eluting stent (E-ZES) implantation (E-ZES+3-month DAPT, n=1,059) versus 12-month DAPT following the other DES implantation (standard therapy, n=1,058).
- E-ZES+3-month DAPT was non-inferior to the standard therapy with respect to the occurrence of the primary endpoint.

- OPTIMIZE trail
- Results of the OPTIMIZE trial showed the non-inferiority of 3-month DAPT to standard 12-month therapy after implantation of a zotarolimus-eluting stent (ZES; Endeavor, Medtronic). Importantly, abbreviated DAPT did not increase the risk of stent thrombosis.
• Antiplatelet Therapy and Outcomes in Patients Undergoing Surgery After Stenting
• SAS registry tracks the feasibility and outcomes of patients treated according to 2014 Italian consensus recommendations
• Aspirin should be continued perioperatively in most surgeries, as should DAPT in surgeries with low-surgical risk
• 85% of the 1,082 patients
• In-hospital rate of net adverse clinical events (death, MI, ST, and bleeding) was 12.7%, while 30-day MACE and ST rates were 3.5% and 0.2%, respectively
• Implications: Adherence to Italian consensus recommendations is feasible, with event rates within the “acceptable range,” say researchers.
• LEADERS trail
• The aim of this pre specified sub study was to evaluate the safety and efficacy of the Bio Freedom™ BA9 DCS followed by 1 month DAPT in patients presenting with an ACS
• In ACS patients with high bleeding risk a polymer-free BA9-DCS combined with 1-month DAPT displays significantly better efficacy and safety than a BMS, the latter driven by significantly lower cardiac mortality and MI.
• Current guidelines should be reconsidered for high bleeding risk patients presenting with ACS: → BMS can no longer be recommended → Data on DES with shortened DAPT are scarce → Bio Freedom™ BA9-DCS has strongest evidence in these patients.
Continuation of DAPT after 1 year

- The CHARISMA sub study and the PEGASUS trial evaluated initiation of DAPT beyond 1 year among patients with prior MI, regardless of whether PCI had been undertaken at the time of the MI.

- In the setting of PCI, the DAPT trial alone evaluated the impact of extended-duration DAPT in the subgroup of patients presenting with MI as the clinical indication for PCI and showed that
  - Continued DAPT beyond 1 year reduced the rate of MACCE by a larger amount in patients presenting with MI (3.9% versus 6.8%, p<0.001) than in patients without MI at presentation (4.4% versus 5.3%; p for interaction=0.03)

- These findings highlighted the potential benefit of DAPT among patients with high athero-thrombotic risk.
• Treatment with DAPT beyond 1 year after DES implantation reduces MI and stent thromboses, it is associated with increased mortality because of an increased risk of noncardiovascular mortality not offset by a reduction in cardiac mortality
  – 21% increase in mortality rate with prolonged DAPT was seen in RCTs and supported by several other published reports
The DAPT trial met its primary endpoints and thus stood apart from the remaining 10 RCTs, which either refuted a superiority hypothesis or met a non-inferiority hypothesis.

- The DAPT trial reported that prolonged therapy was associated with a borderline increase in mortality rate. Although the mortality outcome in the trial has been attributed to non-cardiovascular causes.
- The DAPT investigators (68) reported that the 4,703 patients who underwent EES implantation had higher mortality rates after 30 months of DAPT than after 12 months of therapy (2.1% versus 1.1%, p=0.02).
- In a subgroup analysis of the DAPT trial, investigators (44) found that the reduction in MACCE seen with prolonged DAPT was greater for patients with MI at presentation (3.9% versus 6.8%; HR: 0.56; p<0.001) than for those without MI at presentation for PCI (4.4% versus 5.3%; HR: 0.83; p=0.08; interaction p=0.03).
DAPT SCORE

- Factors Used to Calculate a “DAPT Score”
- Variable Points
- Age ≥75 y: -2
- Age 65 to <75 y: -1
- Age <65 y: 0
- Current cigarette smoker: 1
- Diabetes mellitus: 1
- MI at presentation: 1
- Prior PCI or prior MI: 1
- Stent diameter <3 mm: 1
- Paclitaxel-eluting stent: 1
- CHF or LVEF <30%: 2

Saphenous vein graft PCI 2 A score of ≥2 is associated with a favourable benefit/risk ratio for prolonged DAPT while a score of <2 is associated with an unfavourable benefit/risk ratio. CHF indicates congestive heart failure; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and PCI, percutaneous coronary intervention. Adapted with permission from Yeh et al.
Ticagrelor for secondary prevention
PEGASUS-TIMI 54

- Patients with myocardial infarction 1 to 3 years previously were assigned to ticagrelor, 90 or 60 mg twice daily, or to placebo, in addition to low-dose aspirin.

- At 3 years, ticagrelor reduced the risk of cardiovascular death, MI, or stroke but increased the risk of major bleeding.

- In patients with a myocardial infarction more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding.
The addition of ticagrelor, at a dose of 90 mg twice daily or 60 mg twice daily, to low-dose aspirin reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased in the risk of TIMI major bleeding among patients who had had a myocardial infarction 1 to 3 years earlier.
Long-Term Use of DAPT After MI

- Activation of platelets, with resultant thrombosis, occurs not only in response to implantation of DES, but also as part of the process of atherosclerosis. Patients with a recent athero thrombotic coronary event are at high risk of recurrent events. Several trials have demonstrated the ability of DAPT to inhibit platelet activation and reduce the risk of recurrent MI in the year after an acute MI.

- Current guidelines recommend that DAPT should be continued for up to 12 months after MI.
# NIMS STUDY- DAPT

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<th>No (%)</th>
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</thead>
<tbody>
<tr>
<td>Total no.</td>
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</tr>
<tr>
<td>Male</td>
<td>100 (78.74%)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (21.26%)</td>
</tr>
<tr>
<td>DM</td>
<td>95 (74.8%)</td>
</tr>
<tr>
<td>HTN</td>
<td>98 (77.17%)</td>
</tr>
<tr>
<td>SM</td>
<td>20 (15.74%)</td>
</tr>
<tr>
<td>Prior MI or PCI</td>
<td>10 (7.87%)</td>
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<tr>
<td>MI as presentation at procedure time</td>
<td>12 (9.44%)</td>
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<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MEAN</th>
<th>SD</th>
<th>Median</th>
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<td>9.2</td>
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<tr>
<td>YEAR SINCE PTCA</td>
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<td>3.0</td>
<td>6</td>
<td>1 - 15</td>
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<tr>
<th>Complication</th>
<th>No of Cases</th>
<th>Mean Age</th>
<th>DAPT Score</th>
<th>Average Years of follow up</th>
<th>Sex</th>
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<tbody>
<tr>
<td>CSA</td>
<td>3</td>
<td>51</td>
<td>1.67</td>
<td>7.33</td>
<td>2 (M), 1 (F)</td>
</tr>
<tr>
<td>CVA</td>
<td>1</td>
<td>66</td>
<td>1</td>
<td>4</td>
<td>1 (F)</td>
</tr>
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</table>
Scatterplot of DAPT SCORE vs year since PTCA

<table>
<thead>
<tr>
<th>DAPT score</th>
<th>No of patients</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
<td>16 (12.6%)</td>
<td>Nil</td>
</tr>
<tr>
<td>One</td>
<td>52 (40.9%)</td>
<td>Two (one CVA, one CSA) (1.6%)</td>
</tr>
<tr>
<td>Two</td>
<td>45 (35.4%)</td>
<td>Two (CSA) (1.6%)</td>
</tr>
<tr>
<td>Three</td>
<td>14 (11%)</td>
<td>Nil</td>
</tr>
<tr>
<td>Four</td>
<td>01 (0.8%)</td>
<td>Nil</td>
</tr>
</tbody>
</table>
DAPT Study cont...

Conclusion

DAPT beyond one year has benefits in terms of low associated complications and low incidence of coronary events
At 2 years there was no difference in death, MI, or stroke (primary endpoint) for women compared with men (adjusted HR 0.91; 95% CI 0.65-1.26)

There was no sex difference for the primary endpoint when DAPT durations were compared.

Men had an increased risk of bleeding compared with women that was driven by BARC 2 events.


Impact Of Gender on 2-Year Clinical Outcomes in Patients Treated With 6- or 24-Month DAPT

Pre specified sex-based analysis from the PRODIGY trial of patients with ACS or stable CAD.

Implications: After PCI, men and women have similar bleeding and ischemic risk, suggesting gender is not an important consideration in selection of DAPT duration.
Case scenario-2

• 64 year old male, diabetic and hypertensive presented with typical chest pain. ECG suggestive of significant ST depression in chest leads. Diagnosed as ACS-NSTEMI. Patient was taken up for angiogram which showed TVD requiring surgery.

• Which antiplatelet agent would you have preferred?
1,899 patients underwent CABG post-randomization. The protocol recommended ticagrelor/placebo to be withheld for 24 to 72 h and clopidogrel/placebo for 5 days preoperatively.

In the subgroup of patients undergoing CABG within 7 days after the last study drug intake, ticagrelor compared with clopidogrel was associated with a substantial reduction in total and CV mortality without excess risk of CABG-related bleeding.
Cangrelor

- Analogue of ATP and the first reversible intravenous P2Y12 inhibitor.
- Does not undergo metabolic transformation
- Binds to P2Y12 receptor in a dose dependent fashion
- Potent, >90% platelet inhibition
- High levels of receptor occupancy, preventing ADP signalling
- Very short half life: 3-6 min
- Recovery of platelet function is very rapid: 30-60 min

- FDA approval for use in PCI who did not receive oral P2Y12 inhibitor
- Adjunct to PCI to prevent peri-procedural MI

Cangrelor

- Intravenous ADP–P2Y₁₂ receptor antagonist
  - Rapid acting: quick onset, quick offset
  - Plasma half-life of 3–6 minutes
  - 60 minutes for return to normal platelet function
Switch over

• **Cangrelor to oral inhibitors**
  – Interaction exists between clopidogrel, prasugrel and Cangrelor
  – Clopidogrel or prasugrel should not be started before cangrelor infusion as their effect is nullified
  – In the acute setting, bolus and infusion of cangrelor should be started before PCI and continued for the duration of procedure (<4 hours)

• **Clopidogrel or prasugrel loading dose should be given immediately after discontinuation of infusion**

• **Ticagrelor can be given before. After or during cangrelor infusion without interaction**

• **Oral inhibitors to cangrelor**
  – Infusion can be started at any time
Recommendations for antiplatelet discontinuation before Surgery.

Antiplatelets at time of CABG: 2014 ACC/AHA UA/NSTEMI

- Initiate and continue ASA
- Discontinue clopidogrel/ticagrelor 5 days before, and prasugrel 7 days before ELECTIVE CABG
- Discontinue clopidogrel/ticagrelor Upto 24 hrs before urgent CABG.
- May perform urgent CABG<5 days after discontinuing clopidogrel/ticagrelor, and < 7 days after discontinuing prasugrel
- Discontinue eptifibatide/tirofiban at least 2-4 hrs before, and abciximab ≥ 12 hrs before CABG
Recommendations for DAPT after CABG

- COR LOE Recommendations
  - I C-EO - In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, P2Y12 inhibitor therapy should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed.
  - I C-LD - In patients with ACS (NSTE-ACS or STEMI) being treated with DAPT who undergo CABG, P2Y12 inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS (52-54, 118-120).
  - I B-NR - In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60, 75-78).
  - IIb B-NR - In patients with SIHD, DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency (121125).
Aspirin-optimal dose

- **NSTEMI**
  - The Antithrombotic Trialists’ Collaboration: greatest risk reduction was found with doses from 75 to 150 mg
  - Meta analysis showed doses 100 mg/d were associated with a significantly lower rate of major bleeding events than doses 200 mg/d
  - CURRENT-OASIS 7 Trial: Compared with low-dose aspirin, aspirin doses of 300 to 325 mg did not result in any significant differences in the primary outcome and in major bleeding

- **ACC/AHA 2012 guidelines for UA/NSTEMI:**
  - 162-325 mg LD
  - 75-100 mg/d MD indefinitely

- **PCI guidelines:**
  - 81-325 mg LD for those taking ASA before PCI (class IB)
  - Non-enteric ASA 325 mg LD for those not on chronic ASA (class IB) before PCI
  - ASA to be continued indefinitely (class IA), 81 mg/day is preferred (class IIaB)

- **ESC guidelines:**
STEMI

• ACC/AHA guidelines for STEMI 2013 in PCI:
  – 162-325 mg LD before procedure (class IA)
  – 81-325 mg daily MD indefinitely (class IA)
  – 81 mg is the preferred maintenance dose (class IIaB)

• ACC/AHA guidelines in adjunct to TLT:
  – 162-325 mg LD (class IA)
  – 81-325 mg MD daily indefinitely (class IA)
  – 81 mg is the preferred MD (class IIaB)

• ESC guidelines:
• Trials/evidence
Antiplatelet superior in diabetics

TRITON-TIMI-38

Diabetes in TRITON (n=3,146)

- Ischemia (death/MI/stroke)
  - Clopidogrel: 17.0%
  - Prasugrel: 12.2% (HR 0.70, P<0.001, NNT = 21)

- Bleedings
  - Clopidogrel: 2.6
  - Prasugrel: 2.5
PLATO TRIAL

**Primary Endpoint - MACE**

- **Ticagrelor in Diabetic Patients**
  - HR 0.84 (95% CI 0.72 - 0.99)
  - ARR 1.5%; P=0.03

- **Ticagrelor in Non-Diabetic Patients**
  - HR 0.84 (95% CI 0.74 - 0.96)
  - ARR 1.1%; P=0.01

**Benefit in Diabetic vs. Non-Diabetic Patients:**

Interaction P=0.99

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**CENTRAL ILLUSTRATION:** Ticagrelor in Patients With Diabetes: Consistent Reduction in Ischemic Endpoints

**Efficacy of Ticagrelor in Diabetics With Prior MI**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ticagrelor Placebo</th>
<th>HR</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>CVD/MI/Stroke</td>
<td>10.1</td>
<td>0.85</td>
<td>0.09</td>
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<tr>
<td>Cardiovascular Death</td>
<td>10.0</td>
<td>0.83</td>
<td>0.05</td>
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<tr>
<td>Coronary Heart Disease</td>
<td>10.1</td>
<td>0.84</td>
<td>0.03</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>4.1</td>
<td>0.82</td>
<td>0.19</td>
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<tr>
<td>Coronary Heart Disease</td>
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<td>0.74</td>
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<td>Myocardial Infarction</td>
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<td>Stroke</td>
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<td>0.64</td>
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<tr>
<td>Myocardial Infarction</td>
<td>3.4</td>
<td>0.66</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Based on n = 8,806 Patients

PCI in AF

• 75 year old male diabetic, hypertensive known CAD with severe LV dysfunction, post CABG status presented with unstable angina. ECG showed AF which was not there previously. Angio showed LIMA patent, PCI done to LMCA to LCX.

• What is the antiplatelet regimen to be given for him?
ROCKET AF

• Use of DAPT and Patient Outcomes in Those Undergoing PCI: The ROCKET AF Trial
• Analysis of the 151 patients (~1%) who underwent PCI after being randomized to rivaroxaban or warfarin.
• More than 80% remained on the anticoagulant they were randomized to in ROCKET AF
• Oral antiplatelet therapy given after PCI was highly varied and included clopidogrel plus aspirin, aspirin alone, clopidogrel alone, or no antiplatelet therapy in some cases
• Compared with patients in the trial who did not have PCI, those who did had more thrombotic events and bleeding
• Implications: Optimal treatment strategies remain unclear, leaving knowledge gaps for physicians faced with these vulnerable patients.
Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.
REDUAL – PCI

• Ongoing study
• The main objective of this study is to compare a Dual Antithrombotic Therapy (DAT) regimen of 110mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (110mg DE DAT) and 150mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (150mg DE-DAT) with a Triple Antithrombotic Therapy (TAT) combination of warfarin plus clopidogrel or ticagrelor plus ASA $\leq$ 100mg once daily (warfarin-TAT) in patients with Atrial Fibrillation that undergo a PCI with stenting (elective or due to an Acute Coronary Syndrome).
The proposed algorithm for the decisions concerning the use and duration of dual antiplatelet therapy in acute coronary syndrome patients, irrespective of the use of stents:

**No Q wave, No prior stent, No prior CABG, No CAG, No CT scan, Negative troponin, High bleeding risk**

**SAPT only**

**3 m DAPT**
- Documented obs. CAD, Recent /prior bleeding, Scheduled surgery, oral anticoagulation needed

**6 m DAPT**
- Documented obs. CAD, Bleeding risk factors (age, gender,...)

**> 12 m DAPT**
- Documented CAD, No excess bleeding risk, no bleeding event

Gilles Montalescot, and Marc S. Sabatine
Eur Heart J 2016;37:344-352
Take home message

- DAPT is the crux of treatment in patients with ACS and those undergoing PCI

- Ticagrelor and Prasugrel are far more superior to Clopidogrel, but clopidogrel is more frequently used
Rate of ischemic events (CV death, MI, stroke) at 30 days in patients with ACS in the CURRENT, TRITON, and PLATO trials.
Safer, newer-generation DES may be treated with a minimum DAPT duration of 3 to 6 months

Extension of DAPT beyond 12 months entails a risk-benefit assessment.
- Extension of DAPT beyond 12 months to prevent MI may be optimal in patients at relatively low bleeding risk of <2% over 2 years
- DAPT SCORE

In Patients with prior MI prolonged DAPT is advised at a cost of increased bleeding events.

Switch over of P2Y12 inhibitors is safe though further trials on clinical outcome are warranted