Antiplatelet Therapy: Current Recommendations for Choice of Agent and Concurrent Therapy with Warfarin and Novel Oral Anticoagulants

S. Hinan Ahmed, MD
Anti-platelet Therapy: Simple Answer

- Bare metal stent ~ 30 days
- Drug eluting stent ~ 12 months
Many Questions?

• What agent (thienopyridine) to use?
• How long to continue dual anti-platelet therapy?
• What dosage to use?
• When to interrupt therapy?
• What about triple therapy?
Case 1 DT

- 55 y/o male with HTN, MV repair, dyslipidemia with chest discomfort and ischemia on MPI.

4.0 x 15 BMS

- A) 30 Days
- B) 1 year
- C) Indefinitely
Background

• BALLOON ANGIOPLASTY
  – Tear plaque & vessel wall
  – Redistribute plaque longitudinally
  – Elastic recoil, 30-35% residual diameter stenosis
  – Dissection, abrupt closure, 5-8%
Background

• Inhibition of platelet function post coronary intervention is an important adjunctive treatment that reduces ischemic complications

• Adding a short course (2-4 weeks) of an adenosine diphosphate (ADP) P2Y$_{12}$ receptor antagonist to ASA offers greater protection following coronary intervention

Schomig et al, NEJM 1996;334:1084
Bertrand et al, Circ 1998;98:1597
Leon et al, NEJM;339:1665
Urban et al, Circ 1998;98:2126
Background

1980s
ASA

1991-1993
Escalation of anticoagulant regimens, with up to seven agents (aspirin, dextran, heparin, dipyridamole, sulfinpyrazone, urokinase and warfarin)

1994
Dextran, heparin, ASA, dipyridamole and warfarin

1996
ASA and ticlopidine

Barnathan et al, Circ 1987
Schwartz et al, NEJM 1988
Popma et al, Chest 2001
Era of the Stents
Case 2 AF

- 58 y/o with HTN, dyslipidemia presented with inferior STEMI.

4.0 x 18 BMS

- A) 30 Days
- B) 1 year
- C) Indefinitely
Stent Thrombosis

- Acute: Within 24 hours
- Sub acute: Within 30 days
- Late: Within 1 year
- Very Late: > 1 year
Stent Thrombosis

- **Definite** — ACS plus angiographic or autopsy confirmation.
- **Probable** – Unexplained death occurring within 30 days after the index procedure or a MI occurring at any time after the index procedure that was documented by ECG or imaging to occur in an area supplied by the stented vessel in the absence of angiographic confirmation of ST or other culprit lesions.
- **Possible** - Unexplained death occurring more than 30 days after the index procedure.
Stent Thrombosis: Risk Factors

Procedural characteristics

- Emergent Procedure
- Incomplete stent expansion
- Greater stent length, small vessel caliber
- Residual plaque burden and small stent area on intracoronary ultrasound
- Bifurcation stenting
- Residual thrombus or persistent dissection after stent placement
- Inflow or outflow obstruction
- Sub therapeutic periprocedural anticoagulation
Stent Thrombosis: Risk Factors

Patient characteristics

- Absence of dual anti-platelet therapy (or non-responsiveness) at the time of the event.
- Left ventricular dysfunction
- Active malignancy
- Renal insufficiency
- Diabetes
- Race
- Cocaine use
- Prior brachytherapy
- Age > 65
Stent Thrombosis: Why we Care?

Mortality Following Stent Thrombosis*

- **Stent thrombosis**
  - N = 210
  - 25.9%
  - HR 13.1
  - (95% CI 9.8 - 17.5)
  - P < 0.0001

- **No stent thrombosis**
  - N = 12,634
  - 2.6%

*ARC Definite + Probable

Wiviott SD et al SCAI-ACC/2 2008
Platelet: Friend or Foe
Platelet Mediated Thrombosis

- Platelet Collagen Receptor (GPIa)
- ADP (P2Y12) Receptor
- TXA2 Receptor
- Prasugrel
- Clopidogrel
- Ticlopidine
- Ticagrelor
- Abciximab
- Eptifibatide
- Tirofiban
- GP IIb/IIIa Receptor
- Fibrinogen
- Aspirin

Intact Endothelium
Collagen
vWF
Endothelial Damage

No currently approved antiplatelet agents specifically target Adhesion

Most approved antiplatelet agents affect different aspects of Platelet Activation

GP = glycoprotein; vWF = von Willebrand factor; ADP = adenosine diphosphate; TX = thromboxane.

Activated Platelet

IV Gp IIb/IIIa Inhibitors

Adhesive proteins
thrombospondin
fibrinogen
p-selectin
vWF

Coagulation factors
factor V
factor XI
PAI-1

Inflammatory factors
platelet factor 4
CD 154 (CD 40 ligand)
PDGF

Clopidogrel
Prasugrel
Ticagrelor
Cangrelor

Aspirin

Heparin
Bivalrudin

TXA, thromboxane; PDGF, platelet-derived growth factor.
Platelet Function
Platelet Reactivity Varies Widely Among Patients on Clopidogrel

Maximal aggregation 5 µmol/L ADP (%) following 600 mg loading dose
Change in ADP-Induced Platelet Aggregation 75 mg chronic dosing

N=1001

Hochholzer et al. *Circulation* 2005
Drug Metabolism
Case 3 JA

- 60 y/o male with HTN, DM, presented with anterior STEMI, cardiogenic shock.

Left main bifurcation DES

- A) 30 Days
- B) 1 year
- C) Indefinitely
(Clinical Studies)
Clopidogrel: PCI-CURE

N = 2,658 patients undergoing PCI

Pretreatment

Open-label thienopyridine

N = 1345

30 days post PCI

End of follow-up
Up to 12 months after randomization

* In combination with standard therapy

Clopidogrel: PCI-CURE (1 year)

![Graph showing cumulative hazard rate for death or MI over days of follow-up between Placebo + ASA* and Clopidogrel + ASA*.]

- Placebo + ASA*: 12.6%
- Clopidogrel + ASA*: 8.8%
- 31% RRR
- $P = 0.002$
- $N = 2658$

* In combination with standard therapy

Clopidogrel: CREDO

- **Pre-treatment 3-24 h before PCI**
  - Clopidogrel 300 mg + ASA† (325 mg)
  - Placebo + ASA† (325 mg)

- **PCI**
  - Clopidogrel 75 mg QD + ASA† 325 mg QD

- **28 Days**
  - Clopidogrel 75 mg QD + ASA† (81-325 mg) QD

- **12 Months**
  - Clopidogrel 75 mg QD + ASA† (81-325 mg) QD
  - Placebo QD + ASA† (81-325 mg) QD

† Plus other standard therapies
* Both groups received clopidogrel 75 mg + ASA 325 mg at time of procedure

Clopidogrel: CREDO (1 year)

* Plus ASA and other standard therapies

**Prasugrel: Triton-TIMI 38 (Study Design)**

- **ACS (STEMI or UA/NSTEMI) & Planned PCI**
- **Double-blind**
- **N= 13,600**

**Medication Comparison**
- **ASA**
- **PRASUGREL**
  - 60 mg LD/ 10 mg MD
- **CLOPIDOGREL**
  - 300 mg LD/ 75 mg MD

**Endpoints**
1. **1st endpoint:** CV death, MI, Stroke
2. **2nd endpoints:**
   - CV death, MI, Stroke, Rehosp-Rec Isch
   - CV death, MI, UTVR
   - Stent Thrombosis (ARC definite/prob.)

**Safety endpoints:** TIMI major bleeds, Life-threatening bleeds

**Key Sub-studies:** Pharmacokinetic, Genomic

**Median duration of therapy - 12 months**

*Wiviott SD et al AHJ 152: 627, 2006*
Prasugrel: Triton-TIMI 38

Wiviott SD et al. NEJM 2007; 357: 2001-2015
Ticagrelor: PLATO

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

### 6–12-month exposure

#### NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
- Clopidogrel-treated or -naive;
- randomised within 24 hours of index event (N=18,624)

**Clopidogrel**
- 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**
- 180 mg loading dose, then 90 mg bid maintenance;
  (additional 90 mg pre-PCI)

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PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack
Ticagrelor: PLATO (Primary End Point)

<table>
<thead>
<tr>
<th>Days after randomisation</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>11.7</td>
<td>9.8</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
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<tr>
<td>180</td>
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<tr>
<td>240</td>
<td></td>
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<tr>
<td>300</td>
<td></td>
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<tr>
<td>360</td>
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HR 0.84 (95% CI 0.77–0.92), p=0.0003

No. at risk

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
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</thead>
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<tr>
<td>Ticagrelor</td>
<td>9,333</td>
<td>8,628</td>
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<tr>
<td>Clopidogrel</td>
<td>9,291</td>
<td>8,521</td>
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</table>

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval
# Ticagrelor: PLATO (Secondary End Points)

<table>
<thead>
<tr>
<th>Myocardial Infarction</th>
<th>Cardiovascular Death</th>
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<tr>
<td><strong>Clopidogrel</strong></td>
<td><strong>Ticagrelor</strong></td>
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<tr>
<td>No. at risk</td>
<td>No. at risk</td>
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<tr>
<td>9,333</td>
<td>9,333</td>
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<tr>
<td>8,678</td>
<td>8,799</td>
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<td>6,796</td>
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<td>8,822</td>
<td>4,191</td>
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<td>8,865</td>
<td>4,109</td>
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</table>

**Cumulative incidence (%)**

- Ticagrelor: PLATO (Secondary End Points)

**Graphs**

**Myocardial infarction**
- Clopidogrel: 6.9%
- Ticagrelor: 5.8%
- HR 0.84 (95% CI 0.75–0.95), p=0.005

**Cardiovascular death**
- Clopidogrel: 5.1%
- Ticagrelor: 4.0%
- HR 0.79 (95% CI 0.69–0.91), p=0.001
Ticagrelor: PLATO

Primary Efficacy Endpoint:
CV death + MI + Stroke

- Ticagrelor (864 / 9333)
- Clopidogrel (1014 / 9291)

Kaplan-Meier Estimated Rate (%)

- Tic vs. Clop: HR 0.84 (0.77, 0.92) p-value <0.001

Primary Safety Endpoint:
Total major bleeding

- Ticagrelor (961 / 9235)
- Clopidogrel (929 / 9186)

Kaplan-Meier Estimated Rate (%)

- Tic vs. Clop: HR 1.04 (0.95, 1.13) p-value 0.434
Ticagrelor: PLATO (Summary)

• Reversible, more intense $\text{P2Y}_{12}$ receptor inhibition for one year with ticagrelor in comparison with clopidogrel in a broad population with ST- and non-ST-elevation ACS provides
  – Reduction in myocardial infarction and stent thrombosis
  – Reduction in cardiovascular and total mortality
  – No change in the overall risk of major bleeding

Ticagrelor is a more effective alternative than clopidogrel for the continuous prevention of ischemic events, stent thrombosis and death in the acute and long-term treatment of patients with ACS.
Case 4 JW

- 65 y/o female with HTN, DM, dyslipidemia with chest discomfort and ischemia on MPI.

3.0 x 28 DES

- A) 30 Days
- B) 1 year
- C) Indefinitely
Is bigger always better?
What dose to use?
**Clopidogrel: GRAVITAS**

- **Elective or Urgent PCI with DES***
- **VerifyNow P2Y12 Test 12-24 hours post-PCI**
  - **PRU ≥ 230**
    - **High-Dose Clopidogrel†** clopidogrel 600-mg, then clopidogrel 150-mg daily X 6 months
    - **Standard-Dose Clopidogrel†** clopidogrel 75-mg daily X 6 months

**Primary Efficacy Endpoint:** CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo  
**Key Safety Endpoint:** GUSTO Moderate or Severe Bleeding at 6 mo  
**Pharmacodynamics:** Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled  
All patients received aspirin (81-162mg daily)
Clopidogrel: GRAVITAS (Primary Endpoint)

Cumulative Incidence of CV death, non-fatal MI, or ST (%)

2.3% vs. 2.3%
HR 1.01 (95% CI 0.58 - 1.76)
p=0.98

No. at Risk
High Dose Clopidogrel 1109
Standard Dose Clopidogrel 1105

Days
0 30 60 90 120 150 180 210
0 1 2 3 4

High-Dose Clopidogrel
Standard-Dose Clopidogrel
What do the guidelines say?
A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:

Clopidogrel at least 300 mg to 600mg† should be given as early as possible before or at the time of primary or non-primary PCI.

Prasugrel or Ticagrelor should be given as soon as possible for primary PCI.
Guidelines: STEMI/NSTEMI

The duration of thienopyridine therapy should be as follows:

a. In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily† or prasugrel 10 mg§ daily should be given for at least 12 months;

b. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered.
A loading dose of a P2Y$_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting. Options include:

a. Clopidogrel 600 mg (ACS and non-ACS patients).

b. Prasugrel 60 mg (ACS patients).

c. Ticagrelor 180 mg (ACS patients).
a) In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y$_{12}$ inhibitor therapy should be given for at least 12 months. Options include: clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily.

b) In patients receiving a DES for a non–ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding.

c) In patients receiving a BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).
Guidelines: PCI

For patients who require PCI and who are scheduled for elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty, or BMS implantation followed by 4 to 6 weeks of DAPT, is reasonable.

For patients with a DES who must undergo urgent surgical procedures that mandate the discontinuation of DAPT, it is reasonable to continue aspirin if possible and restart the P2Y$_{12}$ inhibitor as soon as possible in the immediate postoperative period.
Guidelines: PCI

Continuation of clopidogrel, prasugrel or ticagrelor **beyond 12 months** may be considered in patients undergoing DES placement.

PCI with coronary stenting (BMS or DES) **should not be performed** if the patient is not likely to be able to tolerate and comply with DAPT for the appropriate duration of treatment based on the type of stent implanted.
Triple Therapy
TT: Indications

- Atrial fibrillation (AF),
- Deep venous
- Thromboembolism, pulmonary embolism,
- Mechanical valve surgery
THREE MONTHS AGO A 62 YEAR PATIENT UNDERGOES PERCUTANEOUS INTERVENTION WITH PLACEMENT OF BARE METAL STENT TO THE LAD AFTER SUFFERING A MYOCARDIAL INFARCT

You recommend?

- ASA 325 mg daily + Plavix 75 mg daily for 1 year.
- ASA 325 mg + Plavix 75 mg for one dose, followed by ASA 81 mg daily + Plavix 75 mg daily for at least 1 year
- ASA 325 mg + Plavix 75 mg daily 1 month followed by ASA 81 mg daily + warfarin 5 mg daily for 11 months
- ASA 81 mg daily

Guidelines

Post MI

- Dual antiplatelet (DAP) therapy for one year regardless of stent type
- DAP for 12 months
  - ASA 81 + P2Y12 receptor blocker
  - Plavix 75 mg
  - Prasugrel 10 mg
  - Ticagrelor 90
  Prasugrel is not recommended in pt with active pathologic bleeding, Hx. Of TIA/stroke or >75 yrs old; reduce dose if weight <60 kg
  ASA 81 mg indefinitely

Stable CAD

BMS: DAP for 1 month then ASA 81 mg
DES: DAP for 1 year then ASA 81 mg

Medical Management:

ASA 81 mg daily
WOEST
Triple therapy vs. Clopidogrel + VKA

- Treat with triple therapy of ASA + P2Y12 receptor inhibitor + OAC?
- Or OAC + P2Y12

Has-BLED-Predicting bleeding risk in AF

<table>
<thead>
<tr>
<th>Hypertension</th>
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</thead>
<tbody>
<tr>
<td>Abn Renal/liver</td>
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<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Bleeding history</td>
</tr>
<tr>
<td>Labile INR</td>
</tr>
<tr>
<td>Elderly</td>
</tr>
<tr>
<td>Drug/ETOH</td>
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</table>

![Graph showing bleeding events per year](image)

NOAC

Factor Xa-Inhibitors
Rivaroxaban
Apixaban

Direct Thrombin Inhibitor
Dabigatran
## Pharmacology of Warfarin and New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban*</th>
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<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Vitamin K-dependent factors</td>
<td>Factor II</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Time to peak effect</strong></td>
<td>3-4 d</td>
<td>1 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Variable</td>
<td>150 mg BID</td>
<td>20 mg OD</td>
<td>5 mg BID</td>
<td>30 mg OD and 60 mg OD</td>
</tr>
<tr>
<td></td>
<td>75 mg BID</td>
<td>(15 mg OD for renal impairment)</td>
<td></td>
<td>(2.5 mg BID for high risk)</td>
<td></td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>12-17 h</td>
<td>7-11 h</td>
<td>12 h</td>
<td>9-11 h</td>
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<tr>
<td><strong>Renal clearance, %</strong></td>
<td>minor</td>
<td>80</td>
<td>35</td>
<td>25</td>
<td>50</td>
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<tr>
<td><strong>Anticoagulation monitoring</strong></td>
<td>Required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>eGFR exclusion criteria (mL/min)</strong></td>
<td>n.a.</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
<td>&lt; 25</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

*Not currently approved in the US
Cases
Case 1 DT

- 55 y/o male with HTN, MV repair, dyslipidemia with chest discomfort and ischemia on MPI.

4.0 x 15 BMS

- A) 30 Days
- B) 1 year
- C) Indefinitely
Case 2 AF

- 58 y/o with HTN, dyslipidemia presented with inferior STEMI.

4.0 x 18 BMS

A) 30 Days
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Case 3 JA

- 60 y/o male with HTN, DM, presented with anterior STEMI.
- Left main bifurcation DES
  - A) 30 Days
  - B) 1 year
  - C) Indefinitely
Case 4 JW

- 65 y/o female with HTN, DM, dyslipidemia with chest discomfort and ischemia on MPI.

3.0 x 28 DES

- A) 30 Days
- B) 1 year
- C) Indefinitely
Case 5 SP

- 50 y/o male with HTN, tobacco use, dyslipidemia with chest discomfort and ischemia on MPI.
- 3.0 x 23 and 2.75 x 18 DES (Cullotte bifurcation)

- A) 30 Days
- B) 1 year
- C) Indefinitely
Case 6 AW

- 75 y/o male with CAD, previous BMS, AAA, new colon Ca presented with VF (stent thrombosis).

3.0 x 18 BMS

- A) 30 Days
- B) 1 year
- C) Indefinitely
Case 7 RT

- 55 y/o male with inf STEMI.

3.5 x 15 BMS

- A) 30 Days
- B) 1 year
- C) Indefinitely
Acknowledgements

Thank You