Combining antiplatelet and anticoagulant therapy in patients with ischemic heart disease

Kedar Sankholkar, MD, FACC
67 year old man with hypertension and atrial fibrillation on DOAC c/o typical chest pain. Stress test positive for ischemia and angiogram reveals severe stenosis of mid LAD, treated with a drug-eluting stent placed without issue.

- What antithrombotic therapy should be given?
- Does the regimen change over time? If so, after how long?
- What if he had come in with an acute coronary syndrome?
Lifelong anticoagulation is recommended to reduce stroke risk in atrial fibrillation (Afib).

Dual antiplatelet therapy (DAPT) is recommended to reduce stent thrombosis and secondary atherosclerotic cardiovascular disease in patients with coronary artery disease status post percutaneous coronary intervention (CAD s/p PCI).

If the patient has both afib and CAD, the optimal antithrombotic therapy has not been well studied and bleeding risk has shown to be 2-5 fold higher with triple therapy (aspirin, oral anticoagulant, P2Y₁₂ inhibitor) than DAPT. Holmes DR et al. J Am Coll Cardiol. 2009;54(2):95.

Bleeding after PCI is an independent predictor of 1 year mortality Ndrepepa G. J Am Coll Cardiol. 2008;51(7):690.
PICO

- Patient Population studied
- Intervention arm
- Control arm
- Outcomes measured
WOEST
(What is the Optimal antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting)

- **P**: indication for OAC (e.g. AF (69%) or mechanical valve) undergoing PCI (prospective, randomized)

- **I**: OAC + 75mg clopidogrel (Double Therapy)

- **C**: OAC + 75mg Clopidogrel + 80mg Aspirin (Triple Therapy)
  - Atleast 1 month for BMS and 1 year for DES

- **O**: 1° = all bleeding events (TIMI criteria),
  2° = combination of stroke, death, MI, stent thrombosis and target vessel revascularization
WOEST Results

- Double therapy group had significantly lower rate of bleeding complications at one year
- Trial was small (573 patients), but no evidence of an increased risk of thrombotic events by withholding of aspirin

PIONEER AF-PCI

P: international, multicenter, randomized, open-label trial of 2,124 patients with Nonvalvular AFib and recent coronary stent placement

I: 1:1:1 ratio: 15mg qd rivaroxaban + P2Y12 inhibitor x 12 mo’s (group 1) or 2.5 mg BID rivaroxaban + DAPT 1,6 or 12mo’s (group 2).

C: ”standard therapy” with Vit K antagonist + DAPT for 1, 6, or 12 months (group 3)

O: 1°= TIMI criteria bleeding or bleeding requiring medical attention.

2°= major adverse cardiovascular event (a composite of death from cardiovascular causes, myocardial infarction, or stroke) or stent thrombosis
PIONEER AF-PCI

Results:

- Lower bleeding (1°) in rivaroxaban arms with similar rates of death from MI or stroke (2°)

PIONEER-AF Study
Limitations

- Not powered to establish superiority or noninferiority for 2nd efficacy endpoints (broad confidence intervals)
- DAPT duration was not randomized
- Used rivaroxaban dosages that are not approved for stroke prophylaxis in AF
RE-DUAL PCI
(Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation)

- **P**: international, multicenter, randomized open-label trial of 2,725 patients with nonvalvular AF who had undergone PCI with stenting who underwent PCI

- **I**: *Dual therapy* w/ dabigatran (110mg or 150mg BID) + P2Y₁₂ inhibitor (clopidogrel or ticagrelor)

- **C**: *Triple therapy* w/ warfarin + P2Y₁₂ inhibitor + *aspirin* (1-3 mo’s)

- **O**: 1° = major or clinically relevant non major bleeding event
  2° = noninferiority for composite efficacy endpoint of thromboembolic events (MI, CVA, or systemic embolism), death, or unplanned revascularization.
Results:

1°: 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group (hazard ratio, 0.72; 95% CI, 0.58 to 0.88; P < 0.001 for noninferiority).

2°: 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (hazard ratio, 1.04; 95% CI, 0.84 to 1.29; P = 0.005 for noninferiority).

For afib patients who had PCI, dual therapy (dabigatran + P2Y₁₂ inhibitor) resulted in a risk of bleeding events that was significantly lower than with triple therapy (warfarin + P2Y₁₂ inhibitor + aspirin).

Dual therapy with dabigatran was noninferior to triple therapy with warfarin with respect to the rate of thromboembolic events.
- Validates WOEST findings with higher statistical power

Limitations:
- Not powered to allow for comparisons of individual components of 2° endpoint
- Difficult to assess how each medicine (warfarin, dabigatran, aspirin) contributed to 1° and 2° endpoints.
### Summary and Synthesis of Guideline, Expert Consensus Documents, and Comprehensive Review Article Recommendations on the Management of Patients Treated With Triple Therapy (14, 88, 91-93)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA_2DS_2-VASC, HAS-BLED)</td>
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<tr>
<td>Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients</td>
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<tr>
<td>Consider a target INR of 2.0-2.5 when warfarin is used</td>
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<tr>
<td>Clopidogrel is the P2Y12 inhibitor of choice</td>
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<tr>
<td>Use low-dose (≤100 mg daily) aspirin</td>
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<tr>
<td>PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding</td>
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</table>

CHAD DS-VASC indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; INR, international normalized ratio; and PPIs, proton pump inhibitors.
Combination of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.
### Recommendations for combination therapy with oral anticoagulants and antiplatelets

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>After elective coronary stenting for stable coronary artery disease in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events.</td>
<td>IIa</td>
<td>B</td>
<td>522, 524</td>
</tr>
<tr>
<td>After an ACS with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events.</td>
<td>IIa</td>
<td>C</td>
<td>520</td>
</tr>
<tr>
<td>After an ACS without stent implantation in AF patients at risk of stroke, dual treatment with an oral anticoagulant and aspirin or clopidogrel should be considered for up to 12 months to prevent recurrent coronary and cerebral ischaemic events.</td>
<td>IIa</td>
<td>C</td>
<td>520</td>
</tr>
<tr>
<td>The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding.</td>
<td>IIa</td>
<td>B</td>
<td>520</td>
</tr>
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<td>Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.</td>
<td>IIb</td>
<td>C</td>
<td>524, 525</td>
</tr>
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2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS
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2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

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<tr>
<td>IIa</td>
<td>4. If triple therapy (oral anticoagulant, aspirin, and P2Y12 inhibitor) is prescribed for patients with AF at increased risk of stroke (based on CHA2DS2-VASc risk score of 2 or greater) who have undergone percutaneous coronary intervention (PCI) with stenting for ACS, it is reasonable to choose clopidogrel in preference to prasugrel (S7.4-4, S7.4-5). <strong>NEW: New published data are available.</strong></td>
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<tr>
<td>IIa</td>
<td>5. In patients with AF at increased risk of stroke (based on CHA2DS2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a P2Y12 inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy (S7.4-3, S7.4-6–S7.4-8). <strong>NEW: New RCT data and data from 2 registries and a retrospective cohort study are available.</strong></td>
</tr>
<tr>
<td>IIa</td>
<td>6. In patients with AF at increased risk of stroke (based on CHA2DS2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with P2Y12 inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy (S7.4-2). <strong>NEW: New published data are available.</strong></td>
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<tr>
<td>IIa</td>
<td>7. In patients with AF at increased risk of stroke (based on CHA2DS2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a P2Y12 inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy (S7.4-1). <strong>NEW: New published data are available.</strong></td>
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</tbody>
</table>

January CT, et al. JACC (2019)
8. If triple therapy (oral anticoagulant, aspirin, and P2Y₁₂ inhibitor) is prescribed for patients with AF who are at increased risk of stroke (based on CHA₂DS₂-VASc risk score of 2 or greater) and who have undergone PCI with stenting (drug eluting or bare metal) for ACS, a transition to double therapy (oral anticoagulant and P2Y₁₂ inhibitor) at 4 to 6 weeks may be considered (S7.4-9, S7.4-10).

NEW: New published data are available.
Step 1: Determine thrombotic risk and bleeding risk

- **High risk of thrombotic event after PCI:**
  - Complicated PCI
  - Multivessel CAD with diabetes
  - Suboptimal PCI results
  - Age > 65
  - Prior stent thrombosis

- **High risk of bleeding event:**
  - H/o gastrointestinal bleed or TIMI major bleed (intracranial bleeding or clinically significant overt signs of hemorrhage associated with >5.0 g/dL decrease in hemoglobin level)

### HAS-BLED

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver or Renal Function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Maximum Score** = 9

Saraoff N, Holmes D. Coronary artery disease patients requiring combined anticoagulant and antiplatelet therapy. Uptodate.com
Step 2

- Which anticoagulant?
  - DOACs have lower rates of intracranial hemorrhage (shown in RE-LY, ROCKET AF, ARISTOTLE.).
  - Dabigatran or rivaroxaban supported by clinical trials, but apixaban (5mg BID) and edoxaban being used in patients with AF and CAD. Consider switching to trial supported DOACs:
    - Dabigatran 150mg BID studied and approved in U.S. (110mg studied and used outside the US)
    - Rivaroxaban lower dose of 15mg (PIONEER-AF, but underpowered for stroke risk reduction) or 20mg (standard dose)
  - Reasonable to stay on warfarin if INR can be easily maintained 2-2.5. Low threshold to switch to NOAC if labile INR, difficulty with blood draws.

- Antiplatelet choice and duration:
  - Clopidogrel is the P2Y_{12} inhibitor of choice; ticagrelor may be a reasonable alternative in high ischemic and low bleeding risk patients ; avoid prasugrel
  - Discontinue antiplatelet after 1 year in most patients, 6 months in low ischemic risk and > 1 year in select high ischemic risk patients.
  - Stable ischemic heart disease, beyond 12 months not well studied. Consider OAC plus aspirin or clopidogrel if high thrombotic risk.

- Sarafoff N, Holmes D. Coronary artery disease patients requiring combined anticoagulant and antiplatelet therapy. Uptodate.com
Key points

- The rate of any bleeding on DAPT + Anticoagulation is 15-40% per year (Gibson CM et al. N Engl J Med. 2016;375(25):2423)

- Prasugrel or ticagrelor as part of triple therapy should be avoided unless there is a clear need for these agents (e.g. stent thrombosis on aspirin plus clopidogrel), given the lack of evidence and the greater risk of major bleeding compared with clopidogrel.

- Most of the patients enrolled in the clinical trials of individuals with AF and coronary artery disease received either dabigatran or rivaroxaban. However, patients in practice who require anticoagulant and antiplatelet therapy have also received apixaban or edoxaban. There is a lack safety and efficacy data for these anticoagulants in this setting and studies are ongoing.
Key points

- A double-therapy regimen (oral anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor) by the time of hospital discharge should be considered for most patients, whereas extending the use of aspirin beyond hospital discharge (i.e., triple therapy) should be considered only for selected patients at high ischemic/thrombotic and low bleeding risks and for a limited period of time. Angiolillo et al. Circulation. 2018;138:527–536.

- In aggregate, the data to date on comparisons of double versus triple therapy demonstrate that double therapy significantly reduces the risk of bleeding without a signal of harm with regard to stent thrombosis in clinical trials that enrolled both patients with stable ischemic disease and patients with ACS. January CT, et al. JACC (2019)