Exploring the Gray Areas of Anticoagulation

Alyssa Rinaldi, PharmD, BCACP
Outpatient Anticoagulation Clinic Co-Lead
Richard M. Ross Heart Hospital
The Ohio State University Wexner Medical Center

Objectives

• Re-assess historical “gray areas” for Direct Oral Anticoagulant (DOAC) use including in obesity, mechanical heart vales, antiphospholipid syndrome (APS) mechanical heart valves, and treatment of left ventricular (LV) thrombus
• Explore the anticoagulation pipeline including Factor XI inhibitors
### DOAC FDA labeled indications

<table>
<thead>
<tr>
<th>Approved Indication</th>
<th>Apixaban (Eliquis)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Edoxaban (Lixiana)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke prevention in non-valvular afib</td>
<td>Stroke prevention in non-valvular afib</td>
<td>Stroke prevention in non-valvular afib</td>
<td>Stroke prevention in non-valvular afib</td>
<td>Stroke prevention in non-valvular afib</td>
</tr>
<tr>
<td>Treatment of DVT/PE</td>
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<td>Treatment of DVT/PE</td>
</tr>
<tr>
<td>Reduction of recurrence of DVT/PE following initial treatment</td>
<td>Reduction of recurrence of DVT/PE following initial treatment</td>
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<td>Reduction of recurrence of DVT/PE following initial treatment</td>
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</tr>
<tr>
<td>Post-operative VTE prophylaxis</td>
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<td>Post-operative VTE prophylaxis</td>
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</tr>
</tbody>
</table>

**Lexi-Drugs. UpToDate Lexidrug**

### DOAC Dosing

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (Eliquis)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Edoxaban (Lixiana)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Afib</strong></td>
<td>5mg BID</td>
<td>20mg daily</td>
<td>150mg BID</td>
<td>60mg once daily</td>
</tr>
<tr>
<td><strong>VTE Treatment</strong></td>
<td>10mg BID x7 days following by 5mg BID</td>
<td>15mg BID x21days followed by 20mg daily</td>
<td>150mg BID after*</td>
<td>60mg daily after*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;5 days of parenteral therapy</td>
<td>5-10 days of parenteral therapy</td>
</tr>
<tr>
<td><strong>Reduction of recurrence</strong></td>
<td>2.5mg BID</td>
<td>10mg daily</td>
<td>150mg BID</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical prophylaxis</strong></td>
<td>2.5mg BID</td>
<td>10mg daily</td>
<td>110 mg once then 220 mg daily (Post-op)</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Reduction in risk of CV events: 2.5mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lexi-Drugs. UpToDate Lexidrug**
## Warfarin vs DOAC

<table>
<thead>
<tr>
<th>Indication</th>
<th>Warfarin</th>
<th>DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-valvular atrial fibrillation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Valvular atrial fibrillation</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Venous thromboembolism (VTE)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antiphospholipid Syndrome (APS)</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Left Ventricular (LV) thrombus</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*✓ denotes preferred agent*


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## Anticoagulation Special Populations: Obesity
DOAC use in Obesity: VTE

Per International Society on Thrombosis and Hemostasis (ISTH) guidance 2021:
- For treatment of VTE and primary prevention of VTE:
  - May use standard doses of rivaroxaban or apixaban regardless of high BMI and weight
  - AVOID Dabigatran, edoxaban in patients with a BMI >40 kg/m² or weight >120 kg in VTE

<table>
<thead>
<tr>
<th></th>
<th>Phase 3 Studies Comparing DOACs with Vitamin K Antagonist (VKA) in VTE</th>
<th>Phase 4 Studies Comparing DOAC with Vitamin K Antagonist (VKA) in VTE (Including retrospective, prospective &amp; meta-analyses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &gt;35 or BW &gt;120kg</td>
<td>BMI &gt;40</td>
</tr>
<tr>
<td>Apixaban</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Similar outcomes</td>
<td>X</td>
</tr>
<tr>
<td>Pooled DOAC</td>
<td>Similar outcomes</td>
<td>X</td>
</tr>
</tbody>
</table>

DOAC use in Obesity: Atrial fibrillation

Patel et al (2024):
- Analyzed data from COMBINE AF (pooled patient data from 4 pivotal randomized trials of NOAC vs warfarin in atrial fibrillation)
- Effect of DOAC on outcomes of stroke/systemic embolism generally consistent across spectrum of BMI and body weight relative to warfarin
- Reduction in intracranial hemorrhage by DOAC appears preserved across spectrum of BMI and body weight relative to warfarin
DOAC use in Obesity

- The use of apixaban and rivaroxaban at standard doses is appropriate
- Avoid use of dabigatran and edoxaban

- For both treatment of VTE and stroke prophylaxis in atrial fibrillation in obesity ≥40kg/m² consider DOAC therapy
- Risk vs benefit discussion in these populations
- Potentially more data for rivaroxaban > apixaban

Data remains limited in patient with BMI ≥ 50kg/m² and weight ≥ 150kg as these populations remain underrepresented in trials

- Potentially more data for rivaroxaban > apixaban

Recommend against routine monitoring of DOAC levels

Anticoagulation Special Populations: Mechanical Heart Valve
DOAC use in Mechanical Heart Valves

RE-ALIGN (2013)

- Dabigatran vs. warfarin in patients undergoing bileaflet mechanical aortic and/or mitral valve replacement OR prior valve replacement >3 months prior
- Interim analysis showed excess thromboembolism and bleeding compared to warfarin
- Trial stopped early as a result

PROACT Xa (2023)

- Apixaban vs. warfarin in patients with On-X aortic mechanical aortic valve implanted at least 3 months prior to enrollment
- Interim analysis showed excess thromboembolism compared to warfarin
- Trial also stopped early as a result

NEJM Evid 2023; 7: doi: 10.1056/EVIDoa2300067

DOAC use in Mechanical Heart Valves

Given the results of the previous two trials, DOAC use in Mechanical Heart Valves is contraindicated and should be avoided due to excess thromboembolic risk
Anticoagulation Special Populations: Antiphospholipid Syndrome (APS)

### DOAC use in APS

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Description</th>
<th>Results</th>
</tr>
</thead>
</table>
| **TRAPS (2018)** | Randomized controlled trial; non-inferiority | - Rivaroxaban vs VKA in patients with triple-positive APS (n=120)  
- Trial was **terminated early** after primary outcome of thromboembolic events, major bleeding, or death  
19% in rivaroxaban arm vs 3% VKA; HR 6.7; 95% CI 1.5-30.5; P=0.01 |
| **Ordi-Ros et al (2019)** | Randomized controlled trial; non-inferiority at RR 1.40 | - Rivaroxaban vs VKA in patients with thrombotic APS (n=190)  
- Primary efficacy outcome of proportion of patients with new thrombotic events  
- Recurrent thrombosis occurred in 11 patients (11.6%) in rivaroxaban, 6 (6.3%) VKA; RR **1.83** [95% CI, 0.71 to 4.76]  
- Stroke occurred 9 times in rivaroxaban arm, 0 in VKA RR, 19.00 [CI, 1.12 to 321.9] |
| **Khairani et al (2022)** | Meta-analysis of 4 Randomized controlled trials | - DOACs compared to VKA associated with **increase of subsequent arterial thrombotic events**; OR: 5.43; 95% CI: 1.87-15.75; P < 0.001  
- DOACS compared to VKA associated with **increase of composite arterial thrombotic events or VTE** OR: 4.46; 95% CI: 1.12-17.84; P = 0.03 |
DOAC use in APS

• 2019 EULAR Recommendations for the management of antiphospholipid syndrome in adults
  • DOACs should be avoided in patients with triple aPL positivity and history of arterial events
  • DOACS may be considered in patients with difficulty achieving target INR or contraindications to VKA

• However, given information published after the guidelines it appears DOACS are associated with increased risk of arterial thrombosis and stroke regardless of history of arterial thrombosis and positivity status (triple vs. double vs. single)

Anticoagulation Special Populations: LV Thrombus
Treatment of LV Thrombus

LV thrombus in non-ischemic cardiomyopathy

- Typically anticoagulation for 3-6 months. May consider discontinuation if LVEF improves to >35% in addition to resolution of thrombus
- May consider indefinite anticoagulation without improvement in LVEF despite optimal GDMT, persistent apical akinesis/dyskinesis or patients with proinflammatory/hypercoagulable states

LV thrombus after Acute Myocardial Infarction

- Optimal duration of anticoagulation is unknown, consider 3-6 months
- Risk vs. benefit of anticoagulation in addition to antiplatelet therapy

Mural (laminated) thrombus

- If persistent (particularly if organized/calcified) risk of embolization likely low and shared-decision making regarding continuation of oAC

DOAC use in LV Thrombus

Per Management of Patients at Risk for and With Left Ventricular Thrombus: A Scientific Statement From the American Heart Association (2022):

“DOACs are considered by this writing group to be a reasonable alternative to VKA in patients with LV thrombus”
DOAC use in LV Thrombus

- Per currently available data, DOACs (apixaban and rivaroxaban) are non-inferior to warfarin in treatment of LV thrombus

- DOACs may be preferable in several patient populations:
  - Patients at higher bleed risk
  - Need for concomitant anti-platelet therapy (DAPT)
  - Patients with barriers to regular INR monitoring or a time in therapeutic range (TTR) < 50%

- Limited data exists regarding appropriate DOAC dosing strategies (dosing for use in atrial fibrillation vs. treatment of acute VTE)
Anticoagulation Pipeline: Anti-Xi inhibitors

Anti-Xla

• Anti-Xa inhibitors (apixaban, rivaroxaban) have become first line anticoagulant in many indications as previously discussed

• Gaps in anticoagulation therapy remain
  • Warfarin still preferred in certain patient populations (mechanical valve, antiphospholipid syndrome)
  • Optimal anticoagulation in populations at higher risk of bleeding (elderly, ESRD)
Anti-Xla

Stroke prevention in atrial fibrillation
Thromboprophylaxis in orthopedic surgery
Secondary prevention following Acute Coronary Syndrome (ACS)

Secondary prevention after non-cardioembolic stroke
Thromboprophylaxis after foreign material implantation
### Anti-Xla

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Admin/dosing</th>
<th>Trial</th>
</tr>
</thead>
</table>
| Abelacimab    | Monoclonal antibody FXI/FXla  | Subcutaneous (SQ), monthly | Phase III (treatment of cancer-associated VTE)  
Phase III (atrial fibrillation)  
Phase II (atrial fibrillation)* |
| Asundexian    | Small molecule                | Oral, daily           | Phase III (atrial fibrillation)*  
Phase II (post-ACS)  
Phase II (post-stroke) |
| Fesomersen    | Antisense oligonucleotide of FXI | SQ, weekly           | Phase II (thrombosis in ESRD)* |
| Milvexian     | Small molecule                | Oral, daily           | Phase III (atrial fibrillation)  
Phase III (post-ACS)  
Phase III (post-stroke)  
Phase II (VTE prophylaxis)*  
Phase II (post-stroke)* |
| Osocimab      | Monoclonal antibody FXIa      | Intravenous (IV)/SQ, monthly | Phase II (ESRD)* |
| Xisomab 3G3   | Monoclonal antibody FXI       | Intravenous           | Phase II (prevention of catheter-associated thrombosis in cancer) |

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**Anti-Xia: asundexian**

- **Stroke prevention in atrial fibrillation**
  - Phase II: PACIFIC-AF (safety)
    - Asundexian 20/50mg daily vs apixaban BID: 0.42 (0.25-0.67) *significantly lower rate* of all *bleeding* events
  - Phase III: OCEANIC-AF (safety/efficacy)
    - Asundexian 50mg daily vs apixaban BID: Stopped early due to *inferior efficacy* in preventing *stroke/systemic embolism*, data not yet released

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The Lancet. 2022; 10333:1383-1390
Anti-Xia: abelacimab

Stroke prevention in atrial fibrillation

- Phase II: AZALEA-TIMI 71 (safety)
- Abelacimab 90mg/150mg monthly vs rivaroxaban 20mg daily: terminated early due to greater than expected benefit in major/non-clinically relevant major bleeding (1.0% vs 0.7% vs 3.7%; p < 0.05)
- Phase III: LILAC-TIMI 76 (safety/efficacy)
- TBD

References

- Apixaban. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://online.lexi.com
- Rivaroxaban. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://online.lexi.com
- Dabigatran. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://online.lexi.com
- Edoxaban. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://online.lexi.com
- Wang TY et al. Apixaban or Warfarin in Patients with an On-X Mechanical Aortic Valve. NEMJ Evid. 2023; 2(7) DOI: 10.1056/EVIDoa2300067
- Ruff, CT on behalf of the AZALEA-TIMI 71 Committee. AZALEA-TIMI 71. AHA Scientific Session Late Breaking Clinic Trial. November 12, 2023. Philadelphia, PA
Objectives

• Describe the role of aspirin and oral P2Y\textsubscript{12} inhibitors for patients with chronic coronary disease (CCD) or acute coronary syndromes (ACS) with or without percutaneous coronary intervention (PCI)

• Evaluate the advantages and disadvantages of the different P2Y\textsubscript{12} inhibitors

• Discuss how antiplatelet recommendations change if oral anticoagulation is indicated
Case #1

62 YO F admitted to the Emergency Department (ED)
- Abdominal pain and nausea. A couple of days before she took a test capsule for GI study.
- Sudden urge to have a bowel movement.
- In bathroom had sudden onset of severe chest pain
  - EKG showed ST-elevation

PMH:
CAD – LAD stent (unknown type) 2016
Hyperlipidemia
Chronic diarrhea

PSH:
Cholecystectomy 1992

Case #1

- Patient instructed to stop both clopidogrel (Plavix) and aspirin 9 days prior to GI workup

- STEMI alert
  - Acute thrombosis of previous Left Anterior Descending (LAD) stent

- Left heart catheterization with successful thrombectomy and balloon angioplasty
Case #2

57 YO M
  – Admitted for an elective urology procedure

PMH
CAD with a history of 3 cardiac stents (unknown type) in 2019
Peyronie’s and Erectile Dysfunction

PSH
Colonoscopy

• Post Procedure
  • Chest Pain and diaphoresis
  • EKG showed ST-elevation
  • Emergent cath - 100% thrombotic occlusion of prox and mid Right Coronary Artery (RCA) at site of previous stents S/P thrombectomy and PCI with bare metal stent placement x 3

• Patient instructed to discontinue aspirin for 10 days prior to procedure
Stent Evolution: 
Restenosis vs Stent Thrombosis

First Generation DES
Restenosis 5 – 15%

Second Generation DES
Restenosis < 5 %

Otsuko F. Circulation 2014;129:211-223
Risk of Mortality
Stent Thrombosis versus Bleeding

Mortality associated with stent thrombosis

<table>
<thead>
<tr>
<th>Drug Eluting Stents</th>
<th>Bare Metal Stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 - 45%</td>
<td>9 - 21%</td>
</tr>
</tbody>
</table>

Mortality associated with bleeding after PCI at 12-24 months

7.3 - 13%

Essentials of Thrombosis

![Thrombosis Diagram]

Thrombosis 2012;2012:956-962
JACC 2015;66:1036-45
Circ Cardiovasc Interv 2016;9:e003519
Circ Cardiovasc Interv 2010;3:140-7
JACC 2015;65:1411-20
JACC Cardiovasc Interv 2016;9:1450-7
Sites of Antithrombotic Action

Oral P2Y_{12} Inhibitor Comparison

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading Dose</strong></td>
<td>300-600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>75 mg daily</td>
<td>10 mg daily</td>
<td>90 mg BID</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP 2C19</td>
<td>CYP 3A, 2B6</td>
<td>CYP 3A</td>
</tr>
<tr>
<td><strong>Time to 50% Platelet Inhibition (min)</strong></td>
<td>120-240</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(600 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximal Platelet Inhibition (%)</strong></td>
<td>35</td>
<td>79</td>
<td>88</td>
</tr>
</tbody>
</table>
P2Y$_{12}$ Mechanism of Action
### Benefits of Dual Antiplatelet Therapy (DAPT) in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Duration (months)</th>
<th>Antiplatelet Therapy</th>
<th>Incidence of Primary Composite Endpoint* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin vs Aspirin + Clopidogrel</td>
<td>11.4 vs 9.3</td>
</tr>
<tr>
<td>Triton-TIMI 38</td>
<td>ACS/PCI</td>
<td>15</td>
<td>Aspirin + Clopidogrel vs Aspirin + Prasugrel</td>
<td>12.1 vs 9.9</td>
</tr>
<tr>
<td>PLATO</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin + Clopidogrel vs Aspirin + Ticagrelor</td>
<td>11.7 vs 9.8</td>
</tr>
</tbody>
</table>

*Primary Composite Endpoint – Death from Cardiovascular (CV) Causes, Non-fatal myocardial infarction (MI) or Non-fatal stroke

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### Risks of Dual Antiplatelet Therapy (DAPT) in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Duration</th>
<th>Antiplatelet Therapy</th>
<th>Incidence of Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin vs Aspirin + Clopidogrel</td>
<td>2.7 vs 3.7 (p=0.001)</td>
</tr>
<tr>
<td>Triton-TIMI 38</td>
<td>ACS/PCI</td>
<td>15</td>
<td>Aspirin + Clopidogrel vs Aspirin + Prasugrel</td>
<td>1.8 vs 2.4 (p=0.03)</td>
</tr>
<tr>
<td>PLATO</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin + Clopidogrel vs Aspirin + Ticagrelor</td>
<td>2.2 vs 2.8 (p=0.03)</td>
</tr>
</tbody>
</table>

These rates are under the umbrella of a clinical trial NOT real world Patients who require oral anticoagulation are excluded

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Find the Balance

### Increased Ischemic Risk/Risk of Stent Thrombosis (May Favor Longer-Duration DAPT)
- Advanced age
- Acute coronary syndrome presentation
- Extensive coronary artery disease
- Diabetes mellitus
- Chronic kidney disease
- Prior myocardial infarction
- Prior stent thrombosis
- Heart failure
- Current smoker

### Increased Bleeding Risk (May Favor Shorter-Duration DAPT)
- Advanced age
- Diabetes mellitus
- History of prior bleeding
- Oral anticoagulant therapy
- Female sex
- Low body weight
- Chronic kidney disease
- Liver disease
- Anemia
- Chronic steroid or NSAID therapy

### Multi-vessel disease
- Stent undersizing or underexpansion
- Small stent diameter
- Long stent length (>80 mm)
- Short stent length (<3mm)
- Bifurcation stents
- In-stent restenosis
- Multiple stents (≥ 3 stents)
- First-generation drug-eluting stent

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Tools to Find the Balance

<table>
<thead>
<tr>
<th>PRECISE-DAPT Score</th>
<th>DAPT Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of use</td>
<td>At time of coronary stenting</td>
</tr>
<tr>
<td>DAPT duration strategies assessed</td>
<td>Short DAPT (3-6 months)</td>
</tr>
<tr>
<td></td>
<td>vs Standard/long DAPT (12-24 months)</td>
</tr>
<tr>
<td>Score calculator</td>
<td>0 to 100 points</td>
</tr>
</tbody>
</table>

**Score range:**
- Decision making cut-off:
  - ≥ 25 vs 3-6 months of DAPT
  - <2 vs 12-24 months of DAPT
- Limitations:
  - Clopidogrel 88%
  - Validated in PLATO cohort (Ticagrelor)
  - Excluded patients on long term anticoagulation

### Score calculator
- Age
- WBC
- Hb
- CrCl
- Prior bleeding

### Score range:
- ≥ 25 → 3-6 months of DAPT
- <2 → Long DAPT
- ≥2 → Long DAPT
- <2 → Standard DAPT

**Limitations:**
- Clopidogrel 65%; prasugrel 35%
- Excluded prior bleeding/thrombotic events
- Excluded patients on long term anticoagulation

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Yeh RW. JAMA. 2016;215:1735-49
Costa F. The Lancet. 2017;389:102-34
## Dual Antiplatelet Therapy (DAPT) Recommendations (without oral anticoagulation)

**Bare Metal Stent for Acute Coronary Syndrome (2016 DAPT Guidelines)**
Aspirin 81 mg daily uninterrupted lifelong plus clopidogrel 75 mg daily or prasugrel 10 mg daily or ticagrelor 90 mg twice daily for a minimum of 1 month (Class 2) ideally at least 12 months (Class 1)

**Drug-eluting Stent for Acute Coronary Syndrome**
Aspirin 81 mg daily plus clopidogrel 75 mg daily or prasugrel 10 mg daily or ticagrelor 90 mg twice daily for ideally at least 12 months (Class 1) up to 3 years (Class 2b) followed by SAPT

**Bare Metal Stent for Chronic Coronary Disease (2016 DAPT Guidelines)**
Aspirin 81 mg daily uninterrupted lifelong plus clopidogrel 75 mg daily for a minimum of 1 month (Class 1) consider up to 12 months (Class 2)

**Drug-eluting Stent for Chronic Coronary Disease**
Aspirin 81 mg daily plus clopidogrel 75 mg daily for 6 months followed by SAPT (Class 1)

*Option for High bleeding risk:*
Aspirin 81 mg daily plus clopidogrel 75 mg daily for 1 – 3 months followed by clopidogrel 75 mg daily for up to 12 months (Class 2a) followed by SAPT (Class 1)

**Medical Management of Acute Coronary Syndrome**
Aspirin 81 mg daily uninterrupted lifelong (Class 1) plus clopidogrel 75 mg daily or Ticagrelor 90 mg twice daily for ideally at least 12 months (Class 1)

SAPT = Single Antiplatelet Therapy

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## DAPT Recommendations Focus on DES (without oral anticoagulation)

**Drug-eluting Stent for Acute Coronary Syndrome**
Aspirin 81 mg daily plus clopidogrel 75 mg daily or prasugrel 10 mg daily or ticagrelor 90 mg twice daily for ideally at least 12 months (Class 1) up to 3 years (Class 2b) followed by SAPT

**Drug-eluting Stent for Chronic Coronary Disease**
Aspirin 81 mg daily plus clopidogrel 75 mg daily for 6 months followed by SAPT (Class 1)

*Option for High bleeding risk:*
Aspirin 81 mg daily plus clopidogrel 75 mg daily for 1 – 3 months followed by clopidogrel 75 mg daily for up to 12 months (Class 2a) followed by SAPT (Class 1)

**Acute Coronary Syndrome without Stent**
Aspirin 81 mg daily uninterrupted lifelong (Class 1) plus clopidogrel 75 mg daily or Ticagrelor 90 mg twice daily for ideally at least 12 months (Class 1)

SAPT = Single Antiplatelet Therapy
DAPT Recommendations Focus on DES (with oral anticoagulation)

<table>
<thead>
<tr>
<th>Drug-eluting Stent for Acute Coronary Syndrome or Chronic Coronary Disease</th>
</tr>
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<tbody>
<tr>
<td>Aspirin 81 mg daily plus clopidogrel 75 mg daily plus DOAC for up to 1 month followed by clopidogrel plus DOAC for up to 6 months (Class 1) followed by DOAC alone (Class 2b)</td>
</tr>
</tbody>
</table>

**Option for High bleeding risk:**
Aspirin 81 mg daily plus clopidogrel 75 mg daily plus DOAC for 1 month followed by clopidogrel 75 mg daily plus DOAC for up to 6 months followed by DOAC alone (Class 2a)

<table>
<thead>
<tr>
<th>Acute Coronary Syndrome or Chronic Coronary Disease without Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOAC Alone (Class 2b)</td>
</tr>
</tbody>
</table>

DOAC = Direct Oral Anticoagulant

Virani SS, J Am Coll Cardiol 2023 82:833-955

Factors Preventing Continuation of Ticagrelor

- Side Effects: Dyspnea, Bradycardia
- Drug Interactions: 3A4 Inducers P-glycoprotein
- Indication for Oral Anticoagulation: Triple Therapy (Limited data)
- Patient Adherence: Once vs Twice Daily
- Cost: Insurance
### Drug Interactions with Ticagrelor

- Ticagrelor is metabolized by CYP 3A
- Weak CYP 3A inhibitor

<table>
<thead>
<tr>
<th>Strong CYP 3A inhibitors</th>
<th>CYP 3A inducers</th>
<th>CYP 3A substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretrovirals</td>
<td>Carbamazepine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Rifampin</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Phenytoin</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Dexamethasone</td>
<td>Diltiazem, Verapamil</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Phenobarbital</td>
<td>Ator, simva, lovastatin</td>
</tr>
</tbody>
</table>

- Ticagrelor and active metabolite are P-glycoprotein (PgP) substrates and weak inhibitors PgP
  - Monitor digoxin levels
  - Dabigatran

### Switching Between P2Y₁₂ Inhibitors

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
<th># Converting to alternative P2Y₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>75 mg daily (start the next day)</td>
<td>Ticagrelor 180 mg x 1 then Ticagrelor 90 mg every 12 hours (12 hours after loading dose)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>60 mg x 1 (start the next day)</td>
<td>Ticagrelor 180 mg x 1 then Ticagrelor 90 mg every 12 hours (12 hours after loading dose)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>180 mg x 1 (12 hours after loading dose)</td>
<td>Ticagrelor 90 mg every 12 hours (12 hours after loading dose)</td>
</tr>
</tbody>
</table>

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<tr>
<th># Convert to alternative P2Y₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 75 mg daily (start the next day)</td>
</tr>
<tr>
<td>Ticagrelor 180 mg x 1 then Ticagrelor 90 mg every 12 hours (12 hours after loading dose)</td>
</tr>
<tr>
<td>Prasugrel 60 mg x 1 then Prasugrel 10 mg daily (start the next day)</td>
</tr>
</tbody>
</table>

**When escalating to prasugrel or ticagrelor from clopidogrel, the dose can be given regardless of the timing and dosing of the previous clopidogrel regimen.**

**Contraindications:**
- History of ICH, VTE, Thrombotic/crit use in the past 24 hours
- Relative contraindications:
  - Age >75, weight >90 kg, recent trauma/surgery, oral anticoagulant use

**Relative contraindications:**
- Risk for bradycardia, severe hepatic dysfunction, strong CYP3A4 inhibitors/inducers, severe diapase at baseline, oral anticoagulant use, thrombotic/crit use in the past 24 hours

*If converting from ticagrelor or prasugrel to clopidogrel because patient is high blood risk or has a recent bleed, regardless of time from event, can consider omitting or reducing loading dose after discussion with interventional Cardiology.*

ACS = Acute Coronary Syndrome; CVA = Cerebral Vascular Accident; ICH = intracranial hemorrhage; PCI = Percutaneous Coronary Intervention; TIA = transient ischemic attack
Conclusions

• Understanding the current recommendations for DAPT is clinically important

• Balancing the ischemic and bleeding risk is key
  • Early cessation of DAPT is problematic
  • Patients should remain on at least one antiplatelet medication following stent placement unless on oral anticoagulation

• Patient education is key
  • Pharmacists can be instrumental in providing this education

• Involve the patient’s cardiologist to ensure safe transitions of care