Pharmacology of Antiplatelet and Anticoagulants Agents
# Antiplatelet Therapy: Common Oral Agents

<table>
<thead>
<tr>
<th></th>
<th>Acetylsalicylic acid (ASA)</th>
<th>Clopidogrel bisulfate*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Aspirin</td>
<td>Plavix®</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Salicylate</td>
<td>Thienopyridine</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Active Drug</td>
<td>Pro-Drug</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>81-325 mg daily</td>
<td>75 mg daily</td>
</tr>
<tr>
<td><strong>Major Bleeding Risk (%)</strong></td>
<td>2-3%¹</td>
<td>1-4% alone²,³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-5% w/ ASA⁴</td>
</tr>
</tbody>
</table>

²Diener HC et al. *Lancet* 2004;364;331-7  
³Plavix® package insert. www.sanofi-synthelabo.us  
⁵Hass WK. *NEJM* 1989;321:501-7  
⁶Urban P. *Circulation* 1998;98:2126-32  
⁷Ticlid® package insert. www.rocheusa.com

*Clopidogrel is generally given preference over Ticlopidine because of a superior safety profile*
Antiplatelet Therapy: Targets

- ADP=Adenosine diphosphate
- COX=Cyclooxygenase
- TXA\(_2\)=Thromboxane A\(_2\)
- Gp IIb/IIla (Fibrinogen Receptor)
- Gp 2b/3a Inhibitors
- Clopidogrel bisulfate
- Ticlopidine hydrochloride
- Aspirin
- Dipyridamole
- Collagen Thrombin

ADP=Adenosine diphosphate, COX=Cyclooxygenase, TXA\(_2\)=Thromboxane A\(_2\)

Aspirin: Mechanism of Action

Membrane Phospholipids → Arachidonic Acid → COX-1 → Prostaglandin H₂ → Thromboxane A₂ (↑ Platelet Aggregation, Vasoconstriction) and Prostacyclin (↓ Platelet Aggregation, Vasodilation)
Thienopyridine: Mechanism of Action

Clopidogrel or Ticlopidine

- ADP / ATP
- P2Y1
- Gi coupled
- Calcium mobilization
- Cation influx
- P2X1
- Gq coupled
- No effect on fibrinogen receptor
- Platelet shape change
- Transient aggregation
- Calcium mobilization
- Gi2 coupled
- Sustained Aggregation Response
- Fibrinogen receptor activation
- Thromboxane A2 generation

Aspirin Evidence: Secondary Prevention

Effect of antiplatelet treatment* on vascular events**

<table>
<thead>
<tr>
<th>Category</th>
<th>% Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>1.0</td>
</tr>
<tr>
<td>Acute CVA</td>
<td>0.5</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.0</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>1.5</td>
</tr>
<tr>
<td>Other high risk</td>
<td>2.0</td>
</tr>
<tr>
<td>CVD (e.g. unstable angina, heart failure)</td>
<td></td>
</tr>
<tr>
<td>PAD (e.g. intermittent claudication)</td>
<td></td>
</tr>
<tr>
<td>High risk of embolism (e.g. Afib)</td>
<td></td>
</tr>
<tr>
<td>Other (e.g. DM)</td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td></td>
</tr>
</tbody>
</table>

*Aspirin was the predominant antiplatelet agent studied

**Include MI, stroke, or death

Aspirin Evidence: Primary Prevention

RR of MI in Men

- BDT, 1988
- PHS, 1989
- TPT, 1998
- HOT, 1998
- PPP, 2001

Combined

RR = 0.68 (0.54-0.86)  
P=0.001

RR of MI in Women

- HOT, 1998
- PPP, 2001
- WHS, 2005

Combined

RR = 0.99 (0.83-1.19)  
P=0.95

RR of CVA in Men

- HOT, 1998
- PPP, 2001

Combined

RR = 1.13 (0.96-1.33)  
P=0.15

RR of CVA in Women

- WHS, 2005

Combined

RR = 0.81 (0.69-0.96)  
P=0.01

CVA=Cerebrovascular accident, MI=Myocardial infarction, RR=Relative risk

HEPARIN

• Source biological
• Unfractionated (UFH)
• Low molecular weight (LMWH)
• Target: activated factors
Molecular weight distributions of LMWHs and heparin

Hirsh, J. et al. Chest 2004;126:188S-203S
• Unfractionated heparin (UFH)
DRUG TARGETS

- LOW MOLECULAR WEIGHT HEPARIN (LMWH)
- Enoxaparin
CI: DVT/PE and prevention of VTE

ADRs:
- Bleeding
- Thrombocytopenia-HIT
- Osteoporosis

Monitor aPTT & platelet count
Warfarin: Mechanism of Action

## Warfarin Evidence: Secondary Prevention

### Warfarin and Antiplatelet Therapy in Heart Failure (WATCH) Trial

1,587 patients with HF and LVSD (EF <0.35) randomized to aspirin (162 mg), clopidogrel (75 mg), or warfarin (mean INR=2.6) for 23 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin (n=523)</th>
<th>Warfarin (n=540)</th>
<th>Clopidogrel (n=524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, or stroke (%)</td>
<td>20.5</td>
<td>19.8</td>
<td>21.8</td>
</tr>
<tr>
<td>HF hospitalizations (%)</td>
<td>22.2</td>
<td>16.1</td>
<td>18.3</td>
</tr>
<tr>
<td>Major bleeding (number of episodes)</td>
<td>19</td>
<td>30</td>
<td>13*</td>
</tr>
</tbody>
</table>

*p=0.012 vs warfarin

**There is no significant benefit to clopidogrel or warfarin over aspirin in LVSD for reduction of hard end points**

EF=Ejection fraction, HF=Heart failure, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction

Massie BM. American College of Cardiology 2004 Scientific Sessions; Mar 7-10, 2004; New Orleans, LA
Dabigatran

- Direct, specific, competitive thrombin inhibitor
- Half-life 12-17 hours
- Uses P-gp transporter with bowel absorption
- Clearance:
  - 80% renal excretion
  - Not a substrate of CYP 450 enzymes
- Oral, twice daily dosing without need for coagulation monitoring

Adapted from Weitz et al, 2005; 2008
Rivaroxaban

- Direct, specific, competitive factor Xa inhibitor
- Half-life 5-13 hours
- Clearance:
  - 1/3 direct renal excretion
  - 2/3 metabolism via CYP 450 enzymes
- Oral, once daily dosing with largest meal without need for coagulation monitoring

Adapted from Weitz et al, 2005; 2008
Apixaban

- Direct, specific, competitive factor Xa inhibitor
- Half-life 12 hours
- Clearance:
  - 27% direct renal excretion
  - Biliary and direct intestinal excretion
  - P-gp transport
- Oral, twice daily dosing without need for coagulation monitoring: 5mg bid. 2.5mg bid with at least 2 of: 80 or older, weight ≤60kg, creatinine ≥1.5
<table>
<thead>
<tr>
<th>Pradaxa</th>
<th>Xarelto</th>
<th>Eliquis</th>
</tr>
</thead>
</table>
| 150mg bid Cr.Cl >30  
75mg bid Cr.Cl 15-30  
Avoid Cr.Cl <15 | 20mg Cr.Cl >50  
15mg Cr.Cl 15-50  
Avoid Cr.Cl <15 | 5mg bid  
2.5mg bid if 2 or more:  
>80, ≤60kg, >creat 1.5 |
| With or without food | Largest meal | With or without food |
| Avoid with rifampin, quinidine  
If Cr.Cl 30-50, reduce dose to 75mg bid with Multaq and ketoconazole. If Cr.Cl <30, avoid Multaq and ketoconazole. Verapamil may increase levels | Avoid rifampin, carbamazepine, phenytoin, St. John’s wart. Avoid ketoconazole,itraconazole, lopinavir/ritonavir, itonavir, indinavir/ritonavir, conivaptan. Avoid amiodarone, diltiazem, verapamil, Multaq, erythromycin, Ranexa, azithromycin, cimetidine if Cr.Cl 15-50 | Avoid rifampin, carbamazepine, phenytoin, St. John’s wart. Reduce to 2.5mg bid with ketoconazole,itraconazole, Biaxan. If on 2.5mg bid, stop Eliquis. |
<table>
<thead>
<tr>
<th>PRADAXA</th>
<th>XARELTO</th>
<th>ELIQUIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Converting from warfarin: start when INR&lt;2</td>
<td>Converting from warfarin: start when INR&lt;3</td>
<td>Converting from warfarin: start when INR&lt;2</td>
</tr>
<tr>
<td>Rapid onset</td>
<td>Rapid onset</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>No monitoring (PTT)</td>
<td>No monitoring (INR, PTT, anti-factor Xa activity)</td>
<td>No monitoring (INR, PTT, anti-factor Xa activity)</td>
</tr>
<tr>
<td>1-2 day hold if Cr.Cl ≥50</td>
<td>At least 24 hours</td>
<td>At least 24 hours low risk</td>
</tr>
<tr>
<td>3-5 if Cr.Cl &lt;50</td>
<td></td>
<td>At least 48 hours high risk</td>
</tr>
<tr>
<td>Baseline Cr.Cl, at least 6 monthly</td>
<td>Baseline Cr.Cl, at least 6 monthly</td>
<td>Baseline Cr.Cl, at least 6 monthly</td>
</tr>
<tr>
<td>Extreme caution with epidural catheters</td>
<td>Extreme caution with epidural catheters</td>
<td>Extreme caution with epidural catheters</td>
</tr>
<tr>
<td>Cannot crush</td>
<td>Can crush (apple sauce)</td>
<td>Cannot crush</td>
</tr>
<tr>
<td>PRADAXA</td>
<td>XARELTO</td>
<td>ELIQUIS</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>DVT, PE, extended</td>
<td>DVT, PE, extended</td>
<td>DVT, PE, extended</td>
</tr>
<tr>
<td></td>
<td>Hip and knee prophylaxis</td>
<td>Hip and knee prophylaxis</td>
</tr>
</tbody>
</table>
## Warfarin Evidence: Primary Prevention

### Thrombosis Prevention Trial (TPT)

5,499 men at high risk for CHD randomized to aspirin (75 mg), warfarin (mean INR=1.5), warfarin and aspirin, or placebo for 6.4 years

<table>
<thead>
<tr>
<th></th>
<th>WA* N=1277</th>
<th>W* N=1268</th>
<th>A* N=1268</th>
<th>P* N=1272</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI and coronary death (primary end point)</td>
<td>71 (0.87%)</td>
<td>83 (1.03%)</td>
<td>83 (1.02%)</td>
<td>107 (1.33%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>29 (0.36%)</td>
<td>22 (0.27%)</td>
<td>18 (0.22%)</td>
<td>26 (0.32%)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>103 (1.24%)</td>
<td>95 (1.14%)</td>
<td>113 (1.36%)</td>
<td>110 (13.1%)</td>
</tr>
<tr>
<td>RRR of primary end point compared to placebo</td>
<td>34% (p=0.006)</td>
<td>21% (p=0.02)</td>
<td>20% (p=0.04)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Warfarin has similar efficacy to aspirin**

*WA=Warfarin and aspirin, W=Warfarin, A=Aspirin, P=Placebo