The Anticoagulation Conundrum in AF

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Atrial fibrillation (AF) is a common arrhythmia, especially among the elderly.
Risk Factors for developing Atrial Fibrillation

- Increasing Age
- Hypertension
- Diabetes Mellitus
- Myocardial Infarction
- Heart Failure
- Obesity
- Sleep Apnea
- Cardiothoracic Surgery
- Smoking
- Exercise
- Alcohol Use
- Hyperthyroidism
- Family history
- European ancestry
- Genetic variants
- Left ventricular hypertrophy
- LA enlargement
- Elevated CRP or BNP
ATRIAL FIBRILLATION

at least 10% of elderly people (≥75 years) have AF

Rhythm

- AF
- NSR
Comorbid conditions in Medicare Beneficiaries with Atrial Fibrillation
Age >65, N=2,426,865

- Hypertension 83%
- Ischemic heart disease 63.8%
- Hyperlipidemia 63.8%
- Heart failure 51.4%
- Anemia 42.3%
- Arthritis 39.8%
- Diabetes Mellitus 36.5%
- Chronic kidney disease 32.3%
- COPD 23.2%
- Cataracts 22.5%

J Am Coll Cardiol. 2014:64(21):e1-e76.doi:10.1016/j.jacc.2014.03.022
Mean number of conditions they had is 5.8

Median number is 6
Comorbid conditions in Medicare Beneficiaries with Atrial Fibrillation
Age <65, N=105,867

- Hypertension 81.1%
- Ischemic heart disease 64.5%
- Hyperlipidemia 60.0%
- Heart failure 59.3%
- Diabetes Mellitus 53.1%
- Anemia 45.6%
- Chronic kidney disease 40.3%
- Arthritis 33.0%
- Depression 33.0%
- COPD 31.4%

J Am Coll Cardiol. 2014:64(21):e1-e76. doi:10.1016/j.jacc.2014.03.022
Mean number of conditions they had is 5.8

Median number is 6
ATRIAL FIBRILLATION

The number of adults with AF is projected to increase to more than 5.6 million by the year 2050 in the U.S., with more than half of individuals aged 80 years or older.¹

Risk of Stroke in Atrial Fibrillation

Annualized Rates of AF and Stroke Diagnoses for Select Risk Factor Combinations

- Diabetes
- Renal
- HTN
- CAD
- Age 65-74
- HF
- Age 75+
- Diabetes + Age 75+
- HTN + Age 75+
- CAD + Age 75+
- Renal + Age 75+
- HF + Age 75+

AF Rates: Blue
Stroke Rates: Red
Bleeding Vs. Stroke

Although oral anticoagulant therapy with a vitamin K antagonist (VKA) reduces the risk of stroke by 64%,\(^2\) the risk of major bleeding in patients treated with vitamin K antagonists is estimated to increase by 46% for every 10-year increase in age in comparison with age <40.\(^3\)


DAMNED IF YOU DO
AND DAMNED IF
YOU DON’T
We choose our joys and sorrows long before we experience them.

Khalil Gibran
2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation:

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society
CHADS2-Vasc Score

- Heart failure
- Hypertension
- Age
  - >75 - 2 points
  - >65 - 1 point
- Diabetes
- Stroke or TIA
  - Stroke - 2 points
  - TIA - 1 point
- Vascular disease
  - Myocardial Infarction
  - Peripheral vascular disease
  - Previous bypass surgery

Total Score: 9
## KNOW YOUR STROKE RISK

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk</th>
<th>Score</th>
<th>CHA2DS2-VASc Score</th>
<th>Adjusted stroke rate (% / year)</th>
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<tbody>
<tr>
<td>CHF or LVEF &lt;40%</td>
<td>1</td>
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</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Age &gt; 75</td>
<td>2</td>
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<tr>
<td>Diabetes</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Stroke / TIA / Thromboembolism</td>
<td>2</td>
<td>5</td>
<td>6.7</td>
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<tr>
<td>Vascular Disease</td>
<td>1</td>
<td>6</td>
<td>9.8</td>
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<tr>
<td>Age 65-74</td>
<td>1</td>
<td>7</td>
<td>9.6</td>
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<tr>
<td>Female</td>
<td>1</td>
<td>8</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>15.2</td>
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</table>

*CHF = congestive heart failure; TIA - transient ischemic attack; LVEF = left ventricular ejection fraction.*
### Table Title:
Comparison of the CHADS2 and CHA2DS2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

<table>
<thead>
<tr>
<th>Definition and Scores for CHADS2 and CHA2DS2-VASc</th>
<th>Stroke Risk Stratification With the CHADS2 and CHA2DS2-VASc Scores</th>
<th>Adjusted Stroke Rate (% per y)</th>
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<tbody>
<tr>
<td>CHADS2: Congestive HF 1</td>
<td>CHADS2: 0</td>
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<tr>
<td>Hypertension 1</td>
<td>1</td>
<td>2.8</td>
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<tr>
<td>Age ≥75 y 1</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Diabetes mellitus 1</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>Stroke/TIA/TE 2</td>
<td>4</td>
<td>8.5</td>
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<tr>
<td>Maximum score 6</td>
<td>5</td>
<td>12.5</td>
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<td>CHA2DS2-VASc: Congestive HF 1</td>
<td>CHA2DS2-VASc: 0</td>
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<tr>
<td>Hypertension 1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Age ≥75 y 2</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Diabetes mellitus 1</td>
<td>3</td>
<td>3.2</td>
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<tr>
<td>Stroke/TIA/TE 2</td>
<td>4</td>
<td>4.0</td>
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<tr>
<td>Vascular disease (prior MI, PAD, or aortic 1 plaque) 5</td>
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<td>6.7</td>
</tr>
<tr>
<td>Age 65-74 y 1</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Sex category (i.e., female sex) 1</td>
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<td>9.6</td>
</tr>
<tr>
<td>Maximum score 9</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>15.20</td>
</tr>
</tbody>
</table>
Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA$_2$DS$_2$-VASc Score of 1


Figure Legend:

Annual Event Rates

In the Swedish National Patient Register, annual event rates varied depending on whether only ischemic strokes were counted (yellow bars) or additional factors were included. For patients with a CHA2DS2-VASc (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65–74 years, sex category) score of 1, the low annual event rates, varying between 0.5% and 0.9%, call into question the need for or use of oral anticoagulation therapy in these low-risk patients. The entries in parentheses are the International Classification of Diseases-10th Revision Code or Swedish Procedure Code.
HAS-BLED Score

- Hypertension
- Abnormal renal or hepatic function
  - One point each
- Stroke
- Previous major bleeding
- Labile INR on warfarin
- Elderly >65
- Drugs or alcohol
  - One point each
Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular AF (Meta-Analysis)

ACTIVE-W indicates Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-W; AF, atrial fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; ATAFS, Antithrombotic Therapy in Atrial Fibrillation Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation Study; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; JAST, Japan AF Stroke Prevention Study; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibrillation; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; PATAF, Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation; SAFT, Swedish Atrial Fibrillation Trial; SIFA, Studio Italiano Fibrillazione Atriale; SPAF, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; and UK-TIA, United Kingdom–Transient Ischemic Attack.
NOVEL ORAL ANTICOAGULANTS

Where do they fit?
Figure Legend:

Coagulation Cascade
AT indicates antithrombin and VKAs, vitamin K antagonists.
Novel Oral Anticoagulants

NOACS

- Dabigatran – direct thrombin inhibitor
- Rivaroxaban – factor Xa
- Apixaban – factor Xa
- Edoxaban – factor Xa
Ischemic Stroke Prevention

The graph illustrates the scale of 10 strokes on placebo/control for different treatments. The treatments are listed as follows:

- Placebo/Control
- Antiplatelet
- Aspirin
- Clop + Aspirin
- Clop + Warfarin
- Warfarin
- Dabigatran 150mg
- Rivaroxaban
- Apixaban

The percentages shown indicate the reduction in stroke risk compared to placebo/control.
# Atrial Fibrillation Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY</th>
<th>ARISTOTLE</th>
<th>ROCKET-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized Open Label N=18,113</td>
<td>Randomized Double blind N=18,209</td>
<td>Randomized double blind &amp; dummy N=14,000</td>
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<tr>
<td>Treatment</td>
<td>Dabigatran 150 mg, BID 110 mg, BID</td>
<td>Apixaban 5 mg, BID</td>
<td>Rivaroxaban 20 mg, Qday</td>
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<tr>
<td>Comparator</td>
<td>Warfarin 2-3 (67% TTR)</td>
<td>Warfarin 2-3 (66% TTR)</td>
<td>Warfarin 2-3 (57.8% TTR)</td>
</tr>
<tr>
<td>Mean CHADS$_2$</td>
<td>2.1</td>
<td>2.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Time Therapeutic Range = TTR

RE-LY: Dabigatran 150 mg BID significantly reduced time to first stroke and systemic embolism relative to warfarin.
ARISTOTLE: Primary Outcome Stroke (ischemic or hemorrhagic) or Systemic Embolism

- **p (non-inferiority) < 0.001**
- **HR 0.79 (95% CI, 0.66–0.95);**
- **p (superiority) = 0.011**

**Apixaban**
- 212 patients, 1.27% per year

**Warfarin**
- 265 patients, 1.60% per year

**No. at risk**
- Apixaban: 9120, 8726, 8440, 6051, 3464, 1754
- Warfarin: 9081, 8620, 8301, 5972, 3405, 1768

ROCKET AF: Rivaroxaban vs Warfarin: Risk of Stroke and Non-CNS Systemic Embolism by ITT analysis*

<table>
<thead>
<tr>
<th>Days from randomization (Days)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>90</td>
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<tr>
<td>180</td>
<td></td>
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<tr>
<td>270</td>
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<tr>
<td>360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>450</td>
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<tr>
<td>810</td>
<td></td>
<td></td>
</tr>
<tr>
<td>900</td>
<td></td>
<td></td>
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</tbody>
</table>

Cumulative event rate (%)

HR (95% CI): 0.88 (0.74, 1.03)†

No. at risk

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>7081</td>
<td>6927</td>
<td>6774</td>
</tr>
<tr>
<td>6620</td>
<td>6470</td>
<td>5580</td>
</tr>
<tr>
<td>4779</td>
<td>3820</td>
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<td>2058</td>
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<td>7090</td>
<td>6910</td>
<td>6755</td>
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<td>6590</td>
<td>6440</td>
<td>5561</td>
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<td>4756</td>
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<td>2944</td>
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<td>2069</td>
<td>1319</td>
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</table>

Abbreviations: HR = hazard ratio, PTY = patient year.
*Included all randomized subjects followed for events both on and off study drug until end-of-study site notification (N=14,171).
†Noninferiority to warfarin for the primary composite endpoint of time to first occurrence of stroke or non-CNS systemic embolism was demonstrated, but superiority to warfarin was not demonstrated.

### Primary Endpoints

**Atrial Fibrillation Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC</th>
<th>VKA</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran</td>
<td>Warfarin</td>
<td>RR 0.66, 95% CI 0.53-0.82, P &lt; 0.001 superiority</td>
</tr>
<tr>
<td></td>
<td>1.1%</td>
<td>1.7%</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban</td>
<td>Warfarin</td>
<td>HR 0.79, 95% CI 0.66-0.95, P &lt; 0.001 Non-I, P = 0.01 Superiority</td>
</tr>
<tr>
<td></td>
<td>1.3%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>HR 0.79, 95% CI 0.66-0.96, P = &lt;0.001 Non-Inferiority</td>
</tr>
<tr>
<td></td>
<td>1.7%</td>
<td>2.2%</td>
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</table>
## Major Bleeding
### Atrial Fibrillation Trials

<table>
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<tr>
<th>Study</th>
<th>NOAC</th>
<th>VKA</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 3.3%</td>
<td>Warfarin 3.6%</td>
<td>RR 0.93, 95% CI 0.81-1.07, P = 0.31</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban 2.1%</td>
<td>Warfarin 3.1%</td>
<td>HR 0.69, 95% CI 0.60-0.8, P = &lt; 0.001</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 5.6%</td>
<td>Warfarin 5.4%</td>
<td>HR 1.04, 95% CI 0.90-1.20, P = 0.58</td>
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</tbody>
</table>
Intracranial Hemorrhage
Atrial Fibrillation Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC</th>
<th>VKA</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 0.3%</td>
<td>Warfarin 0.7%</td>
<td>RR 0.40 95% CI 0.27-0.60, P= &lt;0.001</td>
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<td>ARISTOTLE</td>
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<td>Warfarin 0.8%</td>
<td>HR 0.42 95% CI 0.30-0.58, P = &lt;0.001</td>
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<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 0.5%</td>
<td>Warfarin 0.7%</td>
<td>HR 0.67 95% CI 0.47-0.93, P = 0.02</td>
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<tr>
<td>Analysis</td>
<td>No. of Studies</td>
<td>Events NOACs (n/N)</td>
<td>Events VKAs (n/N)</td>
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<tr>
<td>--------------------------------</td>
<td>----------------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>All studies</td>
<td>12</td>
<td>1456/30959</td>
<td>1304/23548</td>
</tr>
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<td>Published studies</td>
<td>9</td>
<td>1457/30370</td>
<td>1303/23433</td>
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<tr>
<td>High quality studies</td>
<td>6</td>
<td>1455/29822</td>
<td>1302/23163</td>
</tr>
<tr>
<td>Short-term outcome</td>
<td>8</td>
<td>9/1670</td>
<td>5/710</td>
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<td>Long-term outcome</td>
<td>4</td>
<td>1489/28929</td>
<td>1259/22638</td>
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<tr>
<td>Only Phase III dose-regimens</td>
<td>11</td>
<td>1485/30303</td>
<td>1304/23522</td>
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<tr>
<td>Excluding low dose dabigatan</td>
<td>12</td>
<td>1158/24538</td>
<td>1304/23548</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of Studies</th>
<th>Events NOACs (n/N)</th>
<th>Events VKAs (n/N)</th>
<th>Risk Ratio (95% CI)</th>
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<tr>
<td>All studies</td>
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<td>180/30599</td>
<td>307/23548</td>
<td>0.46 (0.39-0.56)</td>
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<tr>
<td>Published studies</td>
<td>9</td>
<td>180/30370</td>
<td>307/23433</td>
<td>0.46 (0.39-0.56)</td>
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<td>306/23163</td>
<td>0.46 (0.39-0.56)</td>
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<td>Short-term outcome</td>
<td>8</td>
<td>4/1670</td>
<td>1/710</td>
<td>0.94 (0.31-2.97)</td>
</tr>
<tr>
<td>Long-term outcome</td>
<td>4</td>
<td>176/26929</td>
<td>306/22638</td>
<td>0.46 (0.38-0.55)</td>
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<td>Only Phase III dose-regimens</td>
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<td>178/30305</td>
<td>307/23522</td>
<td>0.48 (0.38-0.55)</td>
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<td>Excluding low dose dabigatan</td>
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<td>153/24538</td>
<td>307/23548</td>
<td>0.48 (0.40-0.58)</td>
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</table>
# Dosing Schedules

## Atrial Fibrillation

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<thead>
<tr>
<th>Agent</th>
<th>Dosing Recommendations</th>
</tr>
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<tbody>
<tr>
<td><strong>Dabigatran</strong>&lt;br&gt;75mg, 150mg</td>
<td>CrCl &gt; 30 cc/min: 150 mg, BID&lt;br&gt;CrCl 15 to 30 cc/min: 75 mg, BID&lt;br&gt;Avoid &lt; 15 cc/min</td>
</tr>
<tr>
<td><strong>Apixaban</strong>&lt;br&gt;2.5mg, 5mg</td>
<td>CrCl &gt; 15 cc/min: 5 mg, BID&lt;br&gt;Any 2 ( &gt; 80 yrs, &lt; 60 kg, SCr &gt; 1.5mg/dL: 2.5 mg, BID)&lt;br&gt;Avoid &lt; 15 cc/min</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong>&lt;br&gt;10mg, 15mg, 20mg</td>
<td>CrCl &gt; 50 cc/min: 20 mg, Qday&lt;br&gt;CrCl 15-50 cc/min: 15 mg, Qday&lt;br&gt;Avoid CrCl &lt; 15 cc/min</td>
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</table>
# Pharmacologic Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
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</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>7%</td>
<td>60%-80%</td>
<td>80%</td>
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<tr>
<td><strong>Half-Life</strong></td>
<td>12-17 hrs</td>
<td>7-11 hrs</td>
<td>12 hrs</td>
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<tr>
<td><strong>Clearance</strong></td>
<td>80% renal</td>
<td>60% renal</td>
<td>25% renal</td>
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<tr>
<td></td>
<td>33% biliary</td>
<td>33% biliary</td>
<td>75% biliary</td>
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<td><strong>Metabolism</strong></td>
<td>Conjugation to</td>
<td>CYP3A4</td>
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<tr>
<td></td>
<td>active glucuronides</td>
<td>CYP2J2</td>
<td></td>
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<tr>
<td><strong>P-GP interaction</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes minimal</td>
</tr>
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</table>

Galanis T et al Thromb Thrombolysis 2011;31:310-320
# Laboratory Testing New Oral Agents

<table>
<thead>
<tr>
<th>Lab Tests</th>
<th>Useful Lab Test</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>ECT</td>
<td>Chromogenic Anti-Xa</td>
<td>Chromogenic Anti -Xa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>aPTT, PT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>aPTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak</td>
<td>PT / INR</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Palladino M et al A J Hem 2012;87 Suppl:S127-S132
## Novel Anticoagulant Comparison

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dialyzable</strong></td>
<td>Yes</td>
<td>Probably Not</td>
<td>Probably Not</td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>628 Daltons</td>
<td>436 Daltons</td>
<td>460 Daltons</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>35%</td>
<td>&gt;90%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Catalytic Binding Site</strong></td>
<td>Reversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>Reversing Agent</strong></td>
<td>No</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

American College of Cardiology
Online Risk Calculator

- www.sparctool.com
- ACC Anticoagulation Evaluator
COFACT (Prothrombin Complex Concentrate)
1. Non-activated PCC
2. Factor II, VII, IX, X
3. Protein C, S, ATIII
4. 50 IU PCC/kg dosing
Dabigatran 150mg BID

PCC or Placebo

Dabigatran 150mg BID

PCC or Placebo

## Four Factor vs Three Factor PCC

### Rivaroxaban Reversal

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reduction PT (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beriplex (50 IU/kg)</td>
<td>2.5 sec – 3.5 sec</td>
</tr>
<tr>
<td>Profilnine (50 IU/kg)</td>
<td>0.6 – 1.0 sec</td>
</tr>
</tbody>
</table>

Rivaroxaban 20mg, BID x 4 days
30 minute following infusion effect noted

GI Bleed
Rivaroxaban

PTT
PT/INR
Abnormal

Normal Hemodynamic Status
Impaired Hemodynamic Status

Transfuse

Recheck: CBC, PT/INR & PTT

Re-Evaluate

PCC
50 IU/kg over 5-10 minutes

Transfuse

PCC
PRBC

Recheck: CBC, PT/INR & PTT

Re-Evaluate
CNS Bleed
Dabigatran

PTT
Creatinine

Abnormal

Presence of any of following:
- Neuro Deterioration
- Renal Dysfunction (CrCl < 50 ml/min)
- Recent Dabigatran Dose (< 6 hrs prior)

Neuro Intact

Monitor
Neuro Status

Dialysis
Recheck PTT
Q6hrs x 24 hrs

Reassess Need for Anticoagulation

Neuro Intact

Neuro Deterioration

Dialysis as indicated by PTT/TT

Neuro Stable

CNS Bleed
Dabigatran

Dialysis removes 60%
Package Insert
Recommendations

- Dabigatran
  - FFP, Prothrombin Complex Concentrate
  - Activated Factor VII
  - Dialysis
- Rivaroxaban & Apixaban
  - Prothrombin Complex Concentrate
  - Four Factor Concentrate (KCentra)
  - FFP
Drug Interactions
<table>
<thead>
<tr>
<th>Action</th>
<th>Agents</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Inhibitors CYP3A4 &amp; P-gp</td>
<td>Ketoconazole, Itraconazole, Ritonavir, Clarithromycin</td>
<td>Reduce Dose to 2.5 mg, BID On 2.5 mg, BID, D/C</td>
</tr>
<tr>
<td>Other Inhibitors CYP3A4 &amp; P-gp</td>
<td>Diltiazem, Naproxen</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Strong Inducers CYP3A4 &amp; P-gp</td>
<td>Rifampin</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Action</td>
<td>Agents</td>
<td>Recommendations</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Strong P-gp Inducers and CYP3A4 Inducers</td>
<td>Rifampin, Carbamazepine, Phenytoin, St. John’s Wort</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Strong CYP3A4 Inhibitor and P-gp inhibitors</td>
<td>Ketoconazole, Itraconazole, Ritonavir, Lopinavir, Indinavir, Conivaptan</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Other Inhibitors CYP3A4 &amp; P-gp</td>
<td>Clarithromycin, Erythromycin, Fluconazole</td>
<td>May increase riva effect</td>
</tr>
</tbody>
</table>
# Dabigatran

<table>
<thead>
<tr>
<th>Action</th>
<th>Agents</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Inhibitors</td>
<td>Ketoconazole, Dronedarone</td>
<td>CrCl 30 – 50 cc/min reduce dose 75mg, BID</td>
</tr>
<tr>
<td>P-gp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Inhibitors</td>
<td>Verapamil, Amiodarone, Quinidine, clarithromycin</td>
<td>No dose adjustment unless CrCl is 15 to 30 cc/min to 75 mg, BID</td>
</tr>
<tr>
<td>P-gp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong Inducers</td>
<td>Rifampin</td>
<td>Avoid use</td>
</tr>
<tr>
<td>CYP3A4 &amp; P-gp</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis [see Boxed Warning].

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.
The role of aspirin in Stroke Prevention for Atrial Fibrillation
Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA2DS2-VASc Score of 1


Figure Legend:

Annual Event Rates

In the Swedish National Patient Register, annual event rates varied depending on whether only ischemic strokes were counted (yellow bars) or additional factors were included. For patients with a CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65–74 years, sex category) score of 1, the low annual event rates, varying between 0.5% and 0.9%, call into question the need for or use of oral anticoagulation therapy in these low-risk patients. The entries in parentheses are the International Classification of Diseases-10th Revision Code or Swedish Procedure Code.
WOEST  ESC, Hotline III, Munchen, August 28th, 2012

The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Carlos Van Mieghem, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet and Jurriën ten Berg

The WOEST Trial= What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (clinicaltrials.gov NCT00769938)
Background

1/ Long term oral anticoagulant therapy (OAC) is obligatory (class I) in:
   - most patients with atrial fibrillation
   - patients with mechanical heart valves

2/ Over 30% of these patients have concomitant ischemic heart disease. When these patients need to undergo percutaneous coronary stenting, there is also an indication for aspirin and clopidogrel.

3/ Triple therapy (OAC, aspirin and clopidogrel) is recommended according to the guidelines but is also known to increase the risk of major bleeding. Major bleeding increases mortality.

4/ No prospective data available.
Aim of the study

To test the hypothesis that in patients on OAC undergoing PCI, clopidogrel alone is superior to the combination aspirin and clopidogrel with respect to bleeding but is not increasing thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)
573 patients underwent 1:1 randomization

284 were assigned to Double therapy group

No PCI (n=3)
Withdrawn informed consent (n=2)*
Lost to follow up (n=1)
Did not meet inclusion criteria (n=1)

279 patients were included in Intention to treat analysis

289 were assigned to Triple therapy group

No PCI (n=1)
Withdrawn informed consent (n=2)*
Lost to follow up (n=1)
Did not meet inclusion criteria (n=2)

284 patients were included in Intention to treat analysis

* withdrawn informed consent: in double group 2 patients and triple group 1 patient were included in intention to treat analysis until the day of withdrawal
Primary Endpoint: Total number of TIMI bleeding events

WOEST

- **Triple therapy group**: 44.9%
- **Double therapy group**: 19.5%

**p<0.001**

**HR=0.36  95%CI[0.26-0.50]**

**n at risk:**
- Days 0: 284, 279
- Days 30: 210, 253
- Days 60: 194, 244
- Days 90: 186, 241
- Days 120: 181, 241
- Days 180: 173, 236
- Days 270: 159, 226
- Days 365: 140, 208
<table>
<thead>
<tr>
<th>Factor</th>
<th>Group</th>
<th>Triple</th>
<th>Double</th>
<th>P-value for interaction</th>
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<tbody>
<tr>
<td>age</td>
<td>&lt;75 years</td>
<td>79</td>
<td>82</td>
<td>0.9157</td>
</tr>
<tr>
<td></td>
<td>&gt;75 years</td>
<td>200</td>
<td>194</td>
<td></td>
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<tr>
<td>gender</td>
<td>female</td>
<td>50</td>
<td>65</td>
<td>0.8217</td>
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<td></td>
<td>male</td>
<td>234</td>
<td>214</td>
<td></td>
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<tr>
<td>ACS</td>
<td>no</td>
<td>195</td>
<td>207</td>
<td>0.7210</td>
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<tr>
<td></td>
<td>yes</td>
<td>86</td>
<td>69</td>
<td></td>
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<tr>
<td>OAC</td>
<td>AF/AFlut</td>
<td>162</td>
<td>164</td>
<td>0.1116</td>
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<tr>
<td></td>
<td>Mechanical valve</td>
<td>25</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>47</td>
<td>48</td>
<td>0.7761</td>
</tr>
<tr>
<td>Stent type</td>
<td>BMS</td>
<td>90</td>
<td>94</td>
<td>0.7894</td>
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<tr>
<td></td>
<td>DES</td>
<td>194</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>284</td>
<td>279</td>
<td></td>
</tr>
</tbody>
</table>

Forest plot of primary endpoint Hazard Ratios

double therapy better <= triple therapy better
Secondary Endpoint (Death, MI, TVR, Stroke, ST)

WOEST

Cumulative Incidence

Days

n at risk: 284 272 270 266 261 252 242 223
279 276 273 270 266 263 258 234

p = 0.025
HR = 0.60  95%CI[0.38-0.94]
MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis
All-Cause Mortality

**WOEST**

**Triple therapy group**

**Double therapy group**

HR = 0.39, 95% CI [0.16-0.93]

p = 0.027

n at risk: 284 281 280 280 279 277 270 252

Days

Cumulative incidence of death

0 % 2.5 % 5 % 7.5 %
Conclusions

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting

2. In this study which was specifically designed to detect bleeding events, the bleeding rate was higher than expected

3. Primary endpoint was met: OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way

4. Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death

5. Less all-cause mortality with double therapy
THE WOEST TRIAL

- A diminishing role of aspirin is seen
- Aspirin and antiplatelet in stenting had the same outcome as antiplatelet alone with less bleeding
- Drug-eluting stents are also recommended over bare metal stents in patients with AF
- New generation drug-eluting stents are less thrombogenic and may not require prolonged dual antiplatelet drugs
- Prolonged triple therapy can substantially increase the risk of bleeding.
Novel Anticoagulants for AF: What have we learned?

- In trials, NOACs are clearly as good as moderately controlled warfarin and probably are better.
- The reduction in intracranial hemorrhage is an unexpected but crucially important benefit.
- For patients on well controlled long term warfarin with TTR (time in therapeutic range) of 75%, there may not be much to gain other than the convenience of a NOAC.
The choice of NOAC for AF

All appear worthy and there are no head to head comparisons however

- Dabigatran
  - Particularly effective for ischemic stroke
  - Most sensitive to renal insufficiency
  - Dyspepsia

- Apixaban
  - Impressive bleeding results

- Rivaroxaban
  - Once daily

- Edoxaban
  - Just approved in early January, once daily dosing
What of PCI and AF patients?

- PIONEER AF-PCI
  - Looking at rivaroxaban plus various combinations of DAPT, warfarin and/or aspirin
Conclusions

- Warfarin, aspirin and clopidogrel are recommended for AF concomitant with ACS
- Optimal duration of such therapy is unclear
- Ongoing trials will explore the role of NOACs and P2Y12 inhibitors with or without aspirin
- Decisions related to anticoagulation should be personalized.
Surgery and Anticoagulation

- Probably a topic all on its own
- Very important and a source of litigation
- Best analysis of recent literature suggests doing minor procedures on uninterrupted anticoagulation for high risk groups such as metallic heart valves and persistent AF
  - EP study and ablation
  - Device implantation or change out
  - Cardiac catheterization
Anticoagulation and Surgery

- If interruption is absolutely necessary, forgoing bridging when possible leads to less bleeding complications.
Approach to Selecting Drug Therapy for Ventricular Rate Control

*Drugs are listed alphabetically.
†Beta blockers should be instituted following stabilization of patients with decompensated HF. The choice of beta blocker (e.g., cardioselective) depends on the patient’s clinical condition.
‡Digoxin is not usually first-line therapy. It may be combined with a beta blocker and/or a nondihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with HF.
§In part because of concern over its side-effect profile, use of amiodarone for chronic control of ventricular rate should be reserved for patients who do not respond to or are intolerant of beta blockers or nondihydropyridine calcium antagonists.

COPD indicates chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and LV, left ventricular.

Figure Legend:
Approach to Selecting Drug Therapy for Ventricular Rate Control

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COPD indicates chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and LV, left ventricular.
Strategies for Rhythm Control in Patients With Paroxysmal* and Persistent AF†

*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIA recommendation).
†Drugs are listed alphabetically.
‡Depending on patient preference when performed in experienced centers.
§Not recommended with severe LVH (wall thickness >1.5 cm).
¶Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia.
¶Should be combined with AV nodal blocking agents.

AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.
**Figure Legend:**

Mechanisms of AF

AF indicates atrial fibrillation; Ca++, ionized calcium; and RAAS, renin-angiotensin-aldosterone system.
Atrial Tachycardias

Diagram summarizing types of atrial tachycardias often encountered in patients with a history of AF, including those seen after catheter or surgical ablation procedures. P-wave morphologies are shown for common types of atrial flutter; however, the P-wave morphology is not always a reliable guide to the reentry circuit location or the distinction between common atrial flutter and other macroreentrant atrial tachycardias.

*Exceptions to P-wave morphology and rate are common in scarred atria.

AF indicates atrial fibrillation; bpm, beats per minute; and ECG, electrocardiogram (72,80).
Thank you for your attention.