To thin or Too thin?
Anticoagulation 2019

Thomas Haffey, D.O. FACOI, FACC, FNLA
Professor of Medicine
ACOI Annual meeting Oct 2019
Attributes of The Ideal anticoagulant?

- Oral administration
- Rapid onset/offset of action
- Wide therapeutic range
- Predictable therapeutic effect with fixed dosing
- Well defined pharmacokinetics in renal/hepatic disease
- No food or drug-drug interactions
- No monitoring required (but available)
- Easily reversible
- Cost effective
Oral Anticoagulants in AF<sup>a,b</sup>
A Brief History

- VKAs (e.g., warfarin, phenprocoumon): introduced in the 1950s
  - Mechanism of action: inhibit hepatic vitamin K-dependent synthesis of multiple coagulation factors
  - Inexpensive and widely used, but have unpredictable anticoagulant effects
  - Require frequent monitoring and dose adjustment; bridging with parenteral anticoagulant
- NOACs (first approved by the FDA in 2010 [dabigatran])
  - Mechanism of action: interrupt coagulation cascade
  - Do not require routine monitoring
  - Antidotes/reversal agents are not yet widely available

Coagulation Cascade and Anticoagulant Action<sup>c</sup>

- Warfarin
- VII
- VIIa
- Tissue factor
- X
- Xa
- Thrombin (IIa)
- Prothrombin (II)
- Fibrinogen (I)
- Fibrin (Ia)

Factor Xa inhibitors
- Rivaroxaban
- Apixaban
- Betrixaban
- Edoxaban

Thrombin inhibitors
- Dabigatran

References:
- Steinberg BA, et al. BMJ. 2014;348:g2116<sup>2</sup>
Indications

- Vitamin K antagonists (VKAs) oral vitamin antagonists
- Prevention of arterial and venous thromboembolic events (VTE)
- Safe and effective if a high time in the therapeutic range is achieved
- Challenge in context of drug and food interaction and liver disease
- Thromboembolism (undertreatment)
- Bleeding (overtreatment)
Warfarin Mode of Action

Prothrombin precursor → Carboxylase → Reduced vitamin K

Vitamin K epoxide reductase

Oxidised vitamin K → Warfarin → Coagulation factors

Onset of action - >5 days; not until INR >2 for 24hrs

Vit K dependent Coagulation factors
FII
FVII
FIX
FX
Terminology

• VKA

• INW

• NOAC

• DOAC International Society on Thrombosis and Haemostasis

Direct Oral Anticoagulants

1. Indications for using DOAC’s
2. Types of DOACS
3. Half –life and mode of elimination
4. DOACs and organ failure
5. Reduced absorption and enterohepatic recirculation
6. Monitoring of DOAC
Conclusion
attractive options for anticoagulation.

Advantages  DOACs > VKAs
rapid onset and offset of anticoagulant effect
fixed dosing
fewer drug and dietary interactions
no monitoring requirement
DOAC Time line

Dabigatran **RE-LY 2009**

Rivaroxaban **Rocket-AF 2010**

Apixaban **Aristotle 2011**

Edoxaban **Engage 2013**

Betrixaban **Apex 2016**
Absorption and Metabolism of NOACs

Dabigatran
- Esterase-mediated hydrolysis
- No CYP450
- Bioavailability 3-7%
- $t_{1/2}$ = 12-17h

Rivaroxaban
- P-gp
- Bioavailability: 66% (without food)
- >80% (with food)
- $t_{1/2}$ = 5-9h (young)
- 11-13h (elderly)

Apixaban
- P-gp
- Bioavailability 50%
- $t_{1/2}$ = 12h

Edoxaban
- P-gp
- Bioavailability 62%
- $t_{1/2}$ = 9-11h

There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolism/excretion. The brackets around (Cyp3A4) with apixaban indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged.

Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors. HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.

Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:8.
<table>
<thead>
<tr>
<th></th>
<th>Vitamin K Antagonists</th>
<th>FXa Inhibitors</th>
<th>Direct Thrombin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>Inhibition of hepatic synthesis of vitamin K-dependent coagulation factors</td>
<td>Direct inhibition of FXa</td>
<td>Direct inhibition of FXa</td>
</tr>
<tr>
<td><strong>Time to peak effect</strong></td>
<td>72–96</td>
<td>0.5–3</td>
<td>3</td>
</tr>
<tr>
<td>(hours)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half-life hours</strong></td>
<td>20–60</td>
<td>5–9 (9–13 in elderly)</td>
<td>8–13</td>
</tr>
<tr>
<td><strong>Bioavailability %</strong></td>
<td>100</td>
<td>80</td>
<td>66</td>
</tr>
<tr>
<td><strong>Recommended therapeutic dose and frequency</strong></td>
<td>Adjusted-dose based on INR; once daily</td>
<td>20 mg; once daily</td>
<td>5 mg; twice daily</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Required using INR</td>
<td>Not required</td>
<td>In case of hemorrhage or renal impairment, FXa-dependent assays may be used¹¹</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>1% excreted unchanged in the urine</td>
<td>66% renal elimination</td>
<td>50% renal elimination</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>CYP2C9, CYP1A2, CYP3A4 inhibitors</td>
<td>Potent CYP3A4 inhibitors and P-glycoprotein inhibitors¹⁵</td>
<td>Potent CYP3A4 inhibitors¹⁵</td>
</tr>
<tr>
<td><strong>Drug reversal</strong></td>
<td>Vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant FVIIa¹²</td>
<td>FVIIa partially reverses rivaroxaban anticoagulant effect¹²</td>
<td>FVIIa partially reverses rivaroxaban anticoagulant effect¹²</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Severe active bleeding, pregnancy, breast feeding, documented hypersensitivity¹³</td>
<td>Severe active bleeding; severe renal impairment¹⁴</td>
<td>Severe active bleeding; severe renal impairment</td>
</tr>
</tbody>
</table>
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
RE-LY

- N = 18,113, Follow-up median 2 years, CHADS2 median 2.1, open-label

- Inclusion: Afib on EKG w/in last 6 months, plus at least one: CVA, TIA, LVEF < 40%, NYHA class II or great HF symptoms w/in 6 months and age of at least ≥75 or 65-74 plus DM, HTN, or CAD

- Exclusion: severe heart-valve disorder, stroke w/in 14 days or severe stroke w/in 6 months, increased risk of bleeding, CrCl < 30, liver dx, prenancy

- Randomized to 110 or 150 mg of dabigitran BID vs unblinded warfarin (ASA <100 mg or other antiplatelet agents allowed)

- Primary outcome: stroke or systemic embolization

- Safety outcome: major hemorrhage (reduction of Hgb by 2 g/dL, 2 units of PRBCs, or symptomatic bleeding in critical area)
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*
ROCKET-AF

- N = 14,264, Follow-up median 1.6 yrs, CHADS2 median 3, double-blind
- Inclusion: Non-valvular Afib by EKG w/ hx of stroke, TIA, or embolism or with at least a CHADS2 ≥ 2
- Randomized to rivaroxaban 20 mg daily or 15 mg daily depending on CrCl vs warfarin
- Primary outcome: stroke and embolism
- Safety end point: major and non-major clinically relevant bleeding
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group*
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*
Action Points

• The direct oral anticoagulant rivaroxaban did not demonstrate noninferiority to dose-adjusted vitamin K antagonists (VKAs) for secondary prophylaxis in patients with thrombotic antiphospholipid antibody syndrome (APS).

• Note that recurrent thrombotic events in the rivaroxaban group were predominantly arterial, with a high rate of stroke (nine events vs none for those receiving VKAs).
Betrixaban

• Bevyxxa
• Once daily Factor Xa inhibitor
• Extended prophylaxis of venous thromboembolism (VTE)
• Bevyxxa (betrixaban) is indicated for the prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
• The recommended dose of Bevyxxa is an initial single dose of 160 mg starting on day 1, followed by 80 mg once daily taken for 35 to 42 days at the same time each day with food.
Betrixaban

• **Warning: Spinal / Epidural Hematoma**

• Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis.
Bevyxxa

• An epidural catheter should not be removed earlier than 72 hours after the last administration of Bevyxxa.

• The next Bevyxxa dose is not to be administered earlier than 5 hours after the removal of the catheter.

• If traumatic puncture occurs, delay the administration of Bevyxxa for 7 hours.

• Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary.
**Bevyxxa** Use in severe renal impairment

- Patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min computed by Cockcroft-Gault) taking Bevyxxa may have an increased risk of bleeding events.

- Reduce dose of Bevyxxa, monitor patients closely, and promptly evaluate any signs or symptoms of blood loss in these patients.
Bevyxxa
Concomitant P-glycoprotein (P-gp) Inhibitors

• Avoid use of Bevyxxa in patients with severe renal impairment receiving concomitant P-gp inhibitors.

• Patients on concomitant P-gp inhibitors with Bevyxxa may have an increased risk of bleeding. Reduce dose of Bevyxxa, monitor patients closely, and promptly evaluate any signs or symptoms of blood loss in these patients.
P-gp inhibitors

- Valspodar
- Quinidine
- Verapamil
- Cyclosporin
- Spironolactone
- Ketoconazole
- Erythromycin

- Amiodarone
- Diltiazem
- Itraconazole

Bevyxxa  Hepatic impairment

• Bevyxxa has not been evaluated in patients with hepatic impairment, because these patients may have intrinsic coagulation abnormalities.

• Bevyxxa is **not recommended** in patients with hepatic impairment.
Bevyxxa

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement.

Discontinue Bevyxxa in patients with active pathological bleeding.

There is **no** established way to reverse the anticoagulant effect of betrixaban, which can be expected to persist for **at least 72 hours after the last dose.**
Factors contributing toward a pro-hemorrhagic state in chronic kidney disease

1. Alterations in platelet synthesis, composition and activation
   - Synthesis of platelet activating factor
   - Hemodilution related platelet activation and thrombocytopenia
   - Oxidative stress leading to platelet inactivation

2. Dysfunctional platelet - vessel wall interactions
   - Activated composition of platelet α-granules
   -_Activated endothelial cells

3. Reduced platelet aggregation
   - Circulating fibrinogen fragments act as competitive inhibitors at the GP Ib/IIa receptor
   - Fibrinogen
   - Fibrinogen fragment
   - Function of GP Ib/IIa receptor complex

4. Anemia
   - Platelet- vessel wall interaction
   - Inhibition of PGI2
   - NO scavenging

Drugs
- Anticoagulants
- Antiplatelets
- NSAIDs
- β-lactam and 3rd generation cephalosporin antibiotics

Invasive procedures
- Hemodialysis
- Administration of heparin
- Platelet activation at dialysis membrane
- Central venous catheter insertion
- Arteriovenous fistula cannulation
- Surgical procedures

Shankar Kumar et al. J Am Coll Cardiol 2019;74:2204-2215
Table 2: Effect of Direct Oral Anticoagulants on Haemostasis Tests and Drug Concentration Quantification\textsuperscript{44–57}

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Quantification</th>
<th>PT</th>
<th>aPTT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Dilute TT (DTI assay), ECT, chromogenic anti-IIa assay</td>
<td>Variable depending on reagent</td>
<td>If normal, excludes supratherapeutic concentration</td>
<td>If normal, excludes clinically-relevant concentration</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-Xa concentration (calibrated for rivaroxaban)</td>
<td>If normal, excludes supratherapeutic concentration; can be used for crude estimation</td>
<td>Less sensitive than PT</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Anti-Xa concentration (calibrated for apixaban)</td>
<td>Insensitive; might have normal PT, despite therapeutic concentration</td>
<td>Insensitive; might have normal aPTT, despite therapeutic concentration</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Anti-Xa concentration (calibrated for edoxaban)</td>
<td>If normal, excludes clinically-relevant concentration</td>
<td>If normal, excludes clinically-relevant concentration</td>
<td>Insensitive</td>
</tr>
</tbody>
</table>

\textsuperscript{aPTT = activated partial thromboplastin time; DTI = direct thrombin inhibitor; ECT = ecarin clotting time; NOAC = new/novel oral anticoagulant; PT = prothrombin time; TT = thrombin time.}
Strategy for managing acute bleeding with DOAC

**History and Physical Examination**
- Determination of the time of ingestion of last non-vitamin K oral anticoagulant (NOAC) dose
- Determination of concomitant ingestion of medications with potential interaction with NOACs
- Assess renal function
- Assess the severity of bleeding and hemodynamic stability
- Determination of the etiology of bleeding

---

**Is the patient hemodynamically stable?**

**Yes**
- Promote diuresis to enable renal drug elimination
- Consider monitoring the anticoagulant effect using diluted thrombin time for dabigatran and the chromogenic anti-Xa assay for factor Xa inhibitors

**No**
- For dabigatran
  - Consideridarucizumab: recent FDA approval with phase III study ongoing
  - If unavailable, consider FEIBA
- For factor Xa inhibitors
  - 4-factor PCC
  - In development: andexanet alfa
- For all NOACs
  - Coagulation products: PCC, FEIBA, rFVIIa
  - In development: aripazine (PER0777)

---

**Clinical stability with supportive care?**

**Yes**
- Continue supportive measures
- Consider monitoring with dilute thrombin time for dabigatran and the chromogenic anti-Xa assay for factor Xa inhibitors

**No**
- Volume resuscitation with blood products when appropriate
- Local hemostasis when possible
- Promote diuresis
- Consider activated charcoal for dabigatran or apixaban
- Ingestion within 2.6 hours
- Consider hemodialysis for dabigatran
Atrial fibrillation + PCI

• An edoxaban-based dual regimen was noninferior to standard triple therapy (P2Y12 inhibition, aspirin, and a vitamin K antagonist) on the composite endpoint of major or clinically relevant non-major bleeding over 12 months in patients with atrial fibrillation (AF) who had percutaneous coronary intervention (PCI).

• Note that use of dual antithrombotic therapy did not imply that aspirin should be omitted in the peri-PCI period
Lessons learned from PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI trials:

• An NOAC should be the anticoagulant of choice and used at the dose shown to be effective in regulatory trials of AF
• A VKA-based triple antithrombotic regimen should generally be avoided
• Pending a full assessment of prasugrel or ticagrelor combined with an NOAC, clopidogrel is the P2Y12 inhibitor of choice because it was the most used in the trials
• Dual antithrombotic therapy seems to be the best option for patients with AF who have had PCI when concerns about bleeding prevail over concerns about stent thrombosis
Cost - antidotes

• Andexant $580.00
  • 800 mg bolus
  • 960 mg infusion
  • 3300 mg /100 ml vial

• Idaucizumab
  • 4200.00 /dose
<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl (ml/min)</th>
<th>Half-life (h)</th>
<th>Risk of bleeding (h)</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>≥80</td>
<td>13</td>
<td>24</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥50 to &lt;80</td>
<td></td>
<td>24–48</td>
<td>48–72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥30 to &lt;50</td>
<td></td>
<td>48–72</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≥30</td>
<td>9</td>
<td>24</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
<td>48</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>≥30</td>
<td>8</td>
<td>24</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
<td>48</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>≥30</td>
<td>10–14</td>
<td>24</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
<td>48</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

*CrCl = creatinine clearance using Cockcroft-Gault method*
ANNEXA-4: Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Ongoing, multicenter, prospective, open-label, single-group study. **Not a placebo-controlled trial.**

Included 67 patients from April 2015 to July 2016 who had acute major bleeding.

Primary outcomes:
- Percent change in the anti-Xa activity
- Rate of excellent or good hemostatic efficacy 12 hours after the infusion.

Primary sites of bleeding: **GI 33/67 (49%), intracranial 28/67 (42%), other bleeding sites in 6/67 (9%)** which included a nose bleed...

All patients received a bolus followed by a 2-h infusion of the drug.
How ANDEXANET Works

Andexanet has a rapid onset with a half-life of approximately 1 hour. The package insert states 5-7 hours. Based on the phase 2 trials demonstrating the change in anti-Factor Xa activity in healthy volunteers, in addition to the safety profile observed in ANNEXA-4, Andexanet received FDA approval on May 3, 2018.

1. Andexxa (andexanet alfa) [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals, Inc; May 2018.
ANNEXA-4: Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Mean (± SD) time from ED presentation to the administration bolus was **4.8 ± 1.8 hours**. (what was everyone doing?). Clinical hemostasis was evaluated 12 hours after the andexanet infusion, adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis.

Anti-Xa activity **re-elevated at 2 hours post-infusion**. When the infusion is discontinued, andexanet starts to dissociate from the Xa inhibitors resulting in the potential to inhibit FXa.

Thrombotic events occurred in 12/67 (18%)

During the 30-day follow-up, 15% of the patients died.

How it Works
How ANDEXANET Works

Andexanet is a recombinant modified Factor Xa molecule that binds and sequesters the FXa inhibitors, rivaroxaban and apixaban. In addition, Andexanet inhibits the activity of Tissue Factor Pathway Inhibitor (TFPI), increasing tissue factor-initiated thrombin generation.[1]

Kcentra Factor IX concentrate

- $2.17/IU cost
- 2500 IU /$5425
- 5000 IU / $10,850 max dose
OAC - Choosing Wisely

Patients with **compliance problems**?
- Warfarin (monitoring)
- Rivaroxaban or Edoxaban (daily dosing)

Patient with **history of GI Bleeding**?
- warfarin, Apixaban or Edoxaban (NOT dabigatran, rivaroxaban)

Patient with **Kidney dysfunction**
- consider Apixaban or warfarin

**Survival**?
- Apixaban demonstrated an overall survival advantage compared to warfarin
Anticoagulants in Atrial fibrillation: Adherence among elders reduces stroke risk by 40%  

**Takeaway**  
Persistent adherence to an oral anticoagulant among Medicare beneficiaries with a new Atrial fibrillation diagnosis is tied to a 40% stroke risk reduction.  

**Why this matters**  
Sticking with the anticoagulant plan is important among these patients, who tend to drop off in the first year, with only a third making it to 12 months.  

Source: *Am J Cardiovasc Drugs*  
Curated by: Emily Willingham, PhD  
September 18, 2019
Anticoagulants in Atrial fibrillation:
Adherence among elders reduces stroke risk by **40%**

Source: *Am J Cardiovasc Drugs* Curated by: Emily Willingham, PhD September 18, 2019

**Key results**
Only 35.0% spent the follow-up remaining adherent.
Adherence was tied to reduced stroke risk vs nonuse: aHR, 0.62 (95% CI, 0.52-0.74).
Partial adherence was also linked to reduced risk, just less so: aHR, 0.74 (95% CI, 0.57-0.95).
Risk decreases did not differ with adherence to an oral anticoagulant vs warfarin: HR, 0.77 (95% CI, 0.56-1.04).

**Study design**
Funding: National Heart, Lung and Blood Institute.

**Limitations**
Limitations of claims data, including no confirmation that filled prescriptions were actually used.
warfarin

• Mechanical heart valves
• Patient preference
• Cost prohibitive
• Poor renal Function
• **questionable patient compliance (longer half life, daily dosing**
• Ability to monitor are advantages) vs (liability and do you feel comfortable utilizing in non-compliant patient?)
Indications

Stroke prevention in atrial fibrillation (non-valvular)
  - dabigatran
  - rivaroxaban
  - apixaban
  - Edoxaban

Treatment of arterial and venous thromboembolic events (VTE)

Thromboprophylaxis following major orthopedic surgery

Prevention atherothrombotic events following acute coronary syndrome (ACS)
  - rivaroxaban
rivaroxaban

• Superior to aspirin for prevention DVT post Hip surgery
Table 1: Drug Interactions with Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased concentration</strong></td>
<td>Strong p-gp inhibitors: ketoconazole, ciclosporin, tacrolimus, ritonavir, dronedarone Caution with: amiodarone, verapamil, clarithromycin, quinidine, ticagrelor</td>
<td>Strong CYP3A4 and p-gp inhibitors: ketoconazole, ritonavir, dronedarone Caution with: ciclosporin, tacrolimus</td>
<td>Strong CYP3A4 and p-gp inhibitors: ketoconazole, ritonavir, dronedarone Caution with: ritonavir</td>
<td>Strong p-gp inhibitors: reduce dose with ketoconazole, ciclosporin, dronedarone Caution with: ritonavir</td>
</tr>
<tr>
<td><strong>Reduced concentration</strong></td>
<td>Strong p-gp inducers: rifampicin, St John’s wort, carbamazepine, phenytoin, barbiturates, dexamethasone</td>
<td>Strong CYP3A4 and p-gp inducers: rifampicin, St John’s wort, carbamazepine, phenytoin, barbiturates</td>
<td>Strong CYP3A4 and p-gp inducers: rifampicin, St John’s wort, carbamazepine, phenytoin, barbiturates</td>
<td>Strong p-gp inducers: rifampicin, St John’s wort, carbamazepine, phenytoin, barbiturates, dexamethasone</td>
</tr>
</tbody>
</table>

p-gp = P-glycoprotein.
CENTRAL ILLUSTRATION: Proposed Approach to Stroke Thromboprophylaxis in a Patient With Concomitant Chronic Kidney Disease and Atrial Fibrillation

- Decision to anticoagulate based on current clinical guidelines and randomized controlled trial (RCT)-derived consensus statements with direct oral anticoagulants (DOACs) favored.*

- Anticoagulate only after careful consideration of benefit and harm.†

- No RCT-based evidence to support oral anticoagulant therapy (OAT). Does individual circumstance, clinician and patient preference favor OAT?

- Consider non-pharmacological treatment method (e.g., left atrial appendage occlusion) or no therapy

- Registry evidence favors DOAC over vitamin K antagonist (VKA) for both efficacy and safety. If vascular calcification, calciphylaxis or glomerular hemorrhage are a concern, avoid VKAs. Use appropriate (usually labelled) dose of OAT.‡


Shankar Kumar et al. J Am Coll Cardiol 2019;74:2204-2215
<table>
<thead>
<tr>
<th>Age</th>
<th>Normal renal function or CKD stages 1-2</th>
<th>CKD stage 3</th>
<th>CKD stage 4</th>
<th>CKD stage 5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75 years</td>
<td>(Extensive RCT data available) Warfarin—adjusted dose</td>
<td>(Reasonable representation in RCTs) Warfarin—adjusted dose</td>
<td>(No RCT data) Dabigatran 75 mg twice daily approved by FDA.</td>
<td>(No RCT data) Warfarin—adjusted dose Apixaban 5 mg or 2.5 mg PO BID*</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150 mg PO BID</td>
<td>Dabigatran 150 mg PO BID</td>
<td>Apixaban 5 mg or 2.5 mg PO BID*</td>
<td>Apixaban 2.5 mg daily*</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 20 mg PO daily</td>
<td>Rivaroxaban 15 mg PO daily</td>
<td>Apixaban 5 mg PO daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban 5 mg PO BID*</td>
<td>Apixaban 5 mg or 2.5 mg PO BID*</td>
<td>Apixaban 30 mg PO daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Edoxaban 60 mg PO daily</td>
<td>Edoxaban 30 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Edoxxaban is not recommended if CrCl &gt; 95 ml/min.)</td>
<td>(Edoxaban is not recommended if CrCl &gt; 95 ml/min.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>Based on meta-analysis of 10 RCTs ** involving 25,031 patients &gt; 75 years, newer anticoagulants (Dabigatran/Rivaroxaban/Apixaban) equivalent to conventional therapy in efficacy and bleeding risk. In ENGAGE AF TIMI 48 for Edoxaban, 40% patients were ≥ 75 yrs and 17% ≥ 80 years of age.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Description:**
Legend: RCT = randomized controlled trial; CrCl = creatinine clearance; BID = twice daily.

*Based on the ARISTOTLE trial, FDA label recommends dose of apixaban to be reduced to 2.5 mg twice daily if any two of the following criteria are met: age ≥ 80 years, creatinine ≥ 1.5 mg/dl or weight ≤ 60 kg.

CENTRAL ILLUSTRATION: Standardized Absolute 2-Year Risk of Osteoporotic Fractures Among Atrial Fibrillation Patients

![Graph showing the standardized absolute risk of initiating osteoporotic medication over time for Vitamin K Antagonist (VKA) and Direct Oral Anticoagulant (DOAC).]

<table>
<thead>
<tr>
<th>Standardized Absolute 2-Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Fracture</td>
</tr>
<tr>
<td>VKA</td>
</tr>
<tr>
<td>DOAC</td>
</tr>
<tr>
<td>Initiation of Osteoporotic Medication</td>
</tr>
<tr>
<td>VKA</td>
</tr>
<tr>
<td>DOAC</td>
</tr>
</tbody>
</table>


Casper Binding et al. J Am Coll Cardiol 2019;74:2150-2158
COST

Savaysa  Edoxaban        $332.00/month

Eliquis  apixaban       $473.25/month  5 mg bid
                       $473.25/ month  2.5 mg bid

Xarelto  rivaroxiban   $477.30  10 mg /d
                       $477.30  20 mg/d

Pradaxa  dabigatran   $266.44
Summary

• Non-inferior for prevention of stroke/embolism in Afib
• Non-inferior for treatment of DVT/PE
• NNT for clinical benefit are large
• Probable reduced hemorrhagic stroke rate
• Reduced rate of fatal bleeding events
• Increased incidence of GI bleeds
• Perhaps increased incidence of MIs with dabigatran
• Cost of drug/year $3000
The End