Venous Thromboembolism

UPDATES AND GUIDELINES

Steve Zanders, DO FCCP
Intensivist
UNECOM ’99
None

Still Short

Proud to be a UNECOM graduate (1999 !!!)
Impact Factor... why this is important for PCCs
Changes/Updates in Guidelines..Well, ... some
Case Discussion
Pharmacopoeia
Peri-Procedural
Unanswered and Rhetorical Questions
Impact Factor

Why is this so important?

- Occurs often in OP setting
- Follow up with PCP
- New anticoagulants
- The all too familiar "Family" consult

Yes, my wife knits. Why do you ask?
Venous Thromboembolism in the Outpatient Setting

Frederick A. Spencer, MD; Darleen Lessard, MS; Cathy Emery, RN; George Reed, PhD; Robert J. Goldberg, PhD

**Background:** There has been great interest in optimizing prophylaxis against venous thromboembolism (VTE) in the hospital setting. However, data from earlier studies suggest that most VTEs occur in the outpatient setting. The purposes of this observational study were to describe the frequency of VTEs occurring in the outpatient setting, characterize the prevalence of previously identified risk factors for VTE, and identify previous use of VTE prophylaxis.

**Methods:** The medical records of residents from the Worcester metropolitan area diagnosed as having *International Classification of Diseases, Ninth Revision* codes consistent with possible VTE during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors.

**Results:** A total of 1897 subjects had a confirmed episode of VTE. In all, 73.7% of patients developed VTE in the outpatient setting; a substantial proportion of these patients had undergone surgery (23.1%) or hospitalization (36.8%) in the preceding 3 months. Among these patients, 67.0% experienced VTE within 1 month of the preceding hospital encounter. Other major risk factors for VTE in the outpatient setting included active malignant neoplasm (29.0%) or previous VTE (19.9%). Among 516 patients with a recent hospitalization who subsequently developed VTE, less than half (42.8%) had received anticoagulant prophylaxis for VTE during that visit.

**Conclusions:** More VTEs were diagnosed in the 3 months following hospitalization than during hospitalization. Efforts to improve in-hospital use of VTE prophylaxis may help decrease the incidence of outpatient VTE. However, given the shortening of hospital stays, studies of extended VTE prophylaxis following hospital discharge are warranted.

*Arch Intern Med.* 2007;167(14):1471-1475
Any man who can drive safely while kissing a pretty girl is simply not giving the kiss the attention it deserves.

- ALBERT EINSTEIN
Case

42 YO Female

with HER2+ Breast CA

Lupus Anticoagulant +

Renal Failure (CKD 4--Crt 2.4)

Mechanical AVR 10 yrs. ago
42 YO WF with HER2+ Breast CA, Mechanical AVR 10 yrs ago

- 10 day ICU course after influenza pneumonia, VAP
- Picc Line placed for long-term Abx
- Recently discharged from hospital
- Here for follow-up with PCP

• RUE Swollen and "Uncomfortable"
• 8 Weeks pregnant!!
Executive Summary

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Akl, MD, PhD, MPH; Mark Crouther, MD; J. Schünemann, MD, PhD, FACC, for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel*

The eighth iteration of the American College of Chest Physicians Antithrombotic Guidelines presented in a paper version, a narrative evidence summary and rationale for the recommendations, a small number of evidence profiles summarizing bodies of evidence, and some articles with quite extensive summary tables of primary studies. In total, this represented 600 recommendations summarized in 968 pages of text. Many readers responded that the result was too voluminous for their liking or practical use.

Cognizant of this feedback, we worked hard to minimize the length of the text for the ninth iteration of the guidelines Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) without sacrificing key content. A number of topic editors found our shortening edits draconian, but we were determined to produce the leanest product possible.

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### Table 1—Current Approach to Grades of Recommendations*

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Clarity of Risk/Benefit</th>
<th>Methodologic Strength of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Clear</td>
<td>Randomized trials without important limitations</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1B</td>
<td>Clear</td>
<td>Randomized trials with important limitations (inconsistent results, methodologic flaws†)</td>
<td>Strong recommendations, likely to apply to most patients</td>
</tr>
<tr>
<td>1C+</td>
<td>Clear</td>
<td>No RCTs, but RCT results can be unequivocally extrapolated, or overwhelming evidence from observation studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1C</td>
<td>Clear</td>
<td>Observation studies</td>
<td>Intermediate-strength recommendation; may change when stronger evidence available</td>
</tr>
<tr>
<td>2A</td>
<td>Unclear</td>
<td>Randomized trials without important limitations</td>
<td>Intermediate-strength recommendation; best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2B</td>
<td>Unclear</td>
<td>Randomized trials with important limitations (inconsistent results, methodologic flaws)</td>
<td>Weak recommendation; alternative approaches likely to be better for some patients under some circumstances</td>
</tr>
<tr>
<td>2C</td>
<td>Unclear</td>
<td>Observation studies</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

*Since studies in categories B and C are flawed, it is likely that most recommendations in these classes will be level 2. The following considerations will bear on whether the recommendation is grade 1 or grade 2: the magnitude and precision of the treatment effect, patients’ risk of the target event being prevented, the nature of the benefit, the magnitude of the risk associated with treatment, variability in patient preferences, variability in regional resource availability and health-care delivery practices, and cost considerations. Inevitably, weighing these considerations involves subjective judgment.
9th Edition

- Increased Range of Interventions Covered
- Summary of findings tables offering decidedly succinct but informative
- Less Staunch...Exclusion of “strong opinions”
- “Front-Line” Physicians on Panel (not involved with research)
- ASA As DVTP--OMG
- Plane Rides and Such?
Guidelines . . .
Health State Utility
... aka “patient preference”
Health State Utility
aka “patient preference”
HSU typically assessed on a scale of 0 to 1.
0=equivalent or worse health; 1=optimal health.
Subjective: A patient or participant’s utility value reflects
his or her opinions or attitudes toward a given health
state or outcome
Analog scales; Standard Gamble; Time Trade Off; Prob.
Trade-off; Decision Aids; Scenario; Interviews/Surveys
Disutility refers to the burden or negative outcomes
associated with a particular health state

Table 2—[Section 3.0] Atrial Fibrillation Studies

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Study Population</th>
<th>Study Design</th>
<th>Methods for Eliciting Preferences</th>
<th>Therapy</th>
<th>Outcomes Considered</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso-Coello et al/2006</td>
<td>Random sample of 96 patients at risk for AF</td>
<td>Cross-sectional interview</td>
<td>PTOT feeling thermometer</td>
<td>W/A</td>
<td>Major stroke</td>
<td>Given an absolute risk reduction in stroke of 3% over 2 y, the mean number of bleeds that patients were willing to accept on warfarin was 10 (range, 0-100) before switching to aspirin (on average, 1 stroke = 3 bleeds). Participants clustered at the extremes, with ~40% willing to accept &lt; 10 bleeds, and 19 (~20%) willing to accept &gt; 35 bleeds. See Table 1 for HSUs.</td>
</tr>
<tr>
<td>Devereaux et al/2001</td>
<td>61 at risk for AF (unspecified number may have had previous experience with warfarin)</td>
<td>Cross-sectional interview</td>
<td>PTOT</td>
<td>W/A/NT</td>
<td>Minor bleed</td>
<td>Fifty-seven percent of participants were willing to accept 22 extra bleeds in 100 patients over a 2-y period on warfarin given a stroke reduction of eight. The remaining 43% of patients would accept between one and 21 bleeds. Participants may have been willing to accept more bleeds but were not given the option to choose more than 22. Thus, for almost 60% of patients, the relative disutility of stroke vs bleed was ~3:1 or greater.</td>
</tr>
<tr>
<td>Fuller et al/2004</td>
<td>81 patients from general physician clinic (8 were taking warfarin)</td>
<td>Cross-sectional</td>
<td>Presentation of hypothetical scenarios where participants were asked to choose between drug A and drug B</td>
<td>W/P</td>
<td>Stroke burden (regular blood tests)</td>
<td></td>
</tr>
<tr>
<td>Gage et al/1996</td>
<td>70 patients with AF (31 were taking warfarin, 23 were taking aspirin, 5 were taking both)</td>
<td>Cross sectional interview with decision analysis</td>
<td>TTO and SG</td>
<td>W/A</td>
<td>Mild stroke, Moderate stroke, Severe stroke</td>
<td>Mean utility of life on warfarin was 0.987 and life on aspirin, 0.989. Participants varied significantly in their health state valuations, especially when valuing moderate stroke. See Table 1 for more complete HSUs.</td>
</tr>
<tr>
<td>Gage et al/1995</td>
<td>57 patients with AF (one-half of whom were taking warfarin)</td>
<td>Cross sectional interview with decision analysis</td>
<td>TTO</td>
<td>W/A/NT</td>
<td>Well with W, Well with A, Mild stroke, Moderate to severe stroke, Recurrent stroke</td>
<td>The utility associated with daily life on warfarin (0.99) and aspirin (0.98) were high, whereas life with stroke was associated with a low utility (0.58 for moderate to severe stroke). See Table 1 for additional HSUs.</td>
</tr>
</tbody>
</table>
### Patient Values and Preference

<table>
<thead>
<tr>
<th>Condition (#48)</th>
<th>Outcome Considered</th>
<th>Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial Fibrillation (16)</strong></td>
<td>Mixed, VKA/ASA Stroke vs. Bleed (GI,other)</td>
<td><strong>Bleed better than Stroke</strong></td>
</tr>
<tr>
<td><strong>VTE/DVT Prophylaxis (5)</strong></td>
<td>DVT/VTE, PTS/PPS vs Bleed (any)</td>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td><strong>Stroke and MI Prophylaxis (4)</strong></td>
<td>ASA: M,m CVA vs. Bleed</td>
<td><strong>Variable: ASA &gt; CV events</strong></td>
</tr>
<tr>
<td><strong>Stroke/MI Thrombolytic (6)</strong></td>
<td>TX vs. None vs. Bleed</td>
<td><strong>Bleed better than Stroke</strong></td>
</tr>
<tr>
<td><strong>Tx Burden (17)</strong></td>
<td>Prophylaxis: all types vs Burden of Prophylaxis</td>
<td>IPC worse than SQ Injection Mixed VKA</td>
</tr>
</tbody>
</table>
Conclusions...

- Pts. would rather have GI bleed vs. Stroke (2:1-3:1)
- Pts. might probably would rather an MI than GI bleed (1:1-2:1)
- Pts. equivocal for bleed vs. DVT
- Pts. would rather have PTS/PPS than death from bleed
- VKA minimally invasive to QOL, but still concerned
- Aversion to VKA’s wanes...
- SubQ injections better than compressive wear
Conclusions...

- Small number of studies, Small “n”, methodological limitations
- Large variability findings, appreciable heterogeneity
- Values and preferences vary significantly
- Previously treated vs. Never treated
- Cognitive dissonance
Lines, travel and bearers

✨ Out-pt., Cancer, Central Line (Picc): No prophylaxis

✨ But...if VTE + CVC {Heparinoids(2B); VKA(2C)}--Keep catheter in if needed.

✨ Chronic Illness, immobile at home/NH: No Prophylaxis (2C)

✨ Long-Distance Travel, risk of VTE: Exercise, aisle seating, below knee GCS 15-30 mmHg. No ASA, anticoagulants even if + for thrombophilia

✨ “We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.”
Pharmacopeia
## Anticoagulants

### Antithrombotics (thrombolytics, anticoagulants and antiplatelet drugs) (B01)

<table>
<thead>
<tr>
<th><strong>Antithrombotics</strong></th>
<th><strong>Anticoagulants</strong></th>
<th><strong>Antiplatelet drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>Heparin group/ glycosaminoglycans/ (bind antithrombin)</td>
<td>Glycoprotein IIb/IIIa inhibitors</td>
</tr>
<tr>
<td>ADP receptor/P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitors</td>
<td>Factor Xa inhibitors (with some II inhibition)</td>
<td>ADP receptor/P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitors</td>
</tr>
<tr>
<td>Prostaglandin analogue (PGI&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>Heparin group/ glycosaminoglycans/ (bind antithrombin)</td>
<td>Prostaglandin analogue (PGI&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>COX inhibitors</td>
<td>Factor Xa inhibitors (with some II inhibition)</td>
<td>COX inhibitors</td>
</tr>
<tr>
<td>Thromboxane inhibitors</td>
<td>Direct Xa Inhibitors</td>
<td>Thromboxane inhibitors</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>Direct thrombin (II) inhibitors</td>
<td>Phosphodiesterase inhibitors</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

### Vitamin K antagonists (inhibit II, VII, IX, X)
- coumarins: Acenocoumarol, Coumatetralyl, Dicoumarol, Ethyl biscoumacetate
- Phenprocoumon
- Warfarin<sup>†</sup>
- 1,3-Indandiones: Clorindione, Diphenadione, Phenindione
- other: Ticlopirod

### Other
- Antithrombin III
- Defibrotide
- Protein C (Drotrecogin alfa)
- Ramatroban
- REG 1

### Plasminogen activators: r-tPA (Alteplase, Retepase, Tenecteplase)
- UPA (Saruplase, Urokinase)
- Anistreplase
- Montepase
- Streptokinase<sup>†</sup>

### Other serine endopeptidases: Ancrod, Brinase, Fibrinolysin

### Other
- Citrate
- EDTA
- Oxalate
The New Antithrombotic Drugs

New AntiCoagulants

- Direct Thrombin Inhibitors:
  - Univalent: Only Bind at Active Site Thrombin: Argatroban (IV); Dabigatran (Pradaxa, PO)
  - Bivalent: Bind Actively and at Exosite I Complex: Hirudin/oids (Bival., Lepir., Desirudin)

Indirect Thrombin Targeting

Xabans
The New...”Blood Thinners”...

What’s Wrong With What We Have. . . ?

- Negative Side-Effect Profiles
- Drug Trials and Results vs Actual Patient Outcomes
- Decreased Responsiveness Over Time
- Variability in Patients, Genotypes, Other Medication Use, Co-Morbid Conditions
  - Especially in ASA and Thienopyridines
- Costs, Labs, Patient Dissatisfaction/compliance (VKA)
  - RE-LY trial: INR >2 >67%--Stroke 5-6%; <2, >50%--Stroke 12%
- Reversal Agents, PLEASE...
The New Oral Anticoagulants (NOACs)

- VTE 3rd leading cause of death (vascular)
- >15,000 patients in new OAC trials
- Multiple countries Involved
- Warfarin still needed
Ok, So why should I use them ?

<table>
<thead>
<tr>
<th>Good</th>
<th>VS</th>
<th>... BAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>Unfamiliarity</td>
<td></td>
</tr>
<tr>
<td>Shorter t1/2</td>
<td>Uncertainty</td>
<td></td>
</tr>
<tr>
<td>Less Interactions</td>
<td>Unreversible</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Newbie</td>
<td></td>
</tr>
<tr>
<td>No Dose Adjustments</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HUS Evaluations Equivocal</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin K antagonists (VKA) inhibit the synthesis of the coagulation Factors II, VII, IX, X.

Legend:
- = inactive factor
- = active factor
= transformation
= catalysis

Direct Factor Xa inhibition:
- Rivaroxaban
- Apixaban
- Edoxaban

Indirect via antithrombin:
- Fondaparinux

Indirect via antithrombin:
- Low molecular weight heparin
- Unfractionated heparin

Direct thrombin inhibition:
- Hirudin
- Argatroban
- Bivalirudin
- Dabigatran

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www.thrombosisadviser.com
<table>
<thead>
<tr>
<th>Drug/®</th>
<th>Indications (FDA)</th>
<th>Status</th>
</tr>
</thead>
</table>
| Rivaroxaban/Xarelto | Tx: DVT/PE(11/12); NV-Afib (11/11)  
Proph: DVT (knee, hip) (7/11)  
Reduce Recurrence DVT/PE: (11/12) | FDA Approved for Indications  
FDA Rejected use for stents (8/13) |
| Apixaban/Eliquis | NV-Afib                                                                         | Approved 12/2012                                               |
| Edoxaban/Lixiana | Proph: DVT, Lower Limb  
Tx: VTE, includ. PE                                                               | DVT Proph.: Japan 2011  
NEJM: Sept 1, 2013                                                           |
| Betrixaban       | Proph: VTE, In-Hosp/OP                                                           | ???????????  
Phase III Trials: Portola  
Merck withdrew interest 3/2011                                               |
| Otamixaban       | CAD                                                                             | Withdrawn, Sanofi 2013                                         |
| Darexaban        | Afib  
CAD  
DVT/PE Proph                                                                      | Astella Withdrew 9/2011                                         |
| Andexanet Alpha/PRT4445 | Bleeding  
Antidote for Direct Xa Inhibitors                                             | Phase III Trials                                               |
Hey, about that Dabigatran or Pradaxa drug??

(Dabigatran)

Direct Thrombin Inhibitor

FDA Approved for Non-Valvular AFib

Recent Request for VTE Submitted to FDA

Post-Marketing Bleed??

**Diagram**

Direct Factor Xa inhibition:
- Rivaroxaban
- Apixaban
- Edoxaban

Indirect via antithrombin:
- Fondaparinux

Indirect via antithrombin:
- Low molecular weight heparin
- Unfractionated heparin

Direct thrombin inhibition:
- Hirudin
- Argatroban
- Bivalirudin

- **Dabigatran**
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*

ABSTRACT

BACKGROUND
Dabigatran (Pradaxa ®), Xabans

Cons

- Overall, NOT better than Warfarin if INR stable
- Doubled risk of major GI Bleed, especially Lower
- Cannot use in renal failure (CrCl < 30 mL/mn)
- Mechanical Heart Valves: Not studied/approved
- Tartaric Acid base= GI upset
- No sure laboratory test
- Pt. Compliance: BiD dosing, Non-monitored
- Cost
Testing Hemostatic Function

- **Dabigatran**

  - Thrombin Clotting Time (TCT): Linear except at low doses (prolongs)
    - If “nl” : Probably safe
  - aPTT/ACT: Curvilinear Dose Response, Subject to Lab issues, ?Screening?
    - 2 X’s = Peak drug level (chronic)
    - 1.5 X’s = 12 hours
  - PT/INR Insensitive
  - Ecarin Clotting Time (ECT): Specific for Thrombin Generation: In Development
  - Hemoclot Thrombin Inhibitor (HTI): In Development
Testing Hemostatic Function

Factor Xa Inhibitors: ....Xabans

- PT/INR/aPTT: Not sensitive, may be good screening tool
- Anti-Factor Xa assay predicts [C] but not effect
  - Need specific drug for calibration
- In Development
  - Therapeutic Drug Levels ?=? Bleeding
  - Antidote
**Dabigatran (Pradaxa ®), Xabans**

**PROS**

- Good for Unexplained Warfarin Control
- Less Strokes with 150 mg dose
- Less CNS Bleeds

**Drug Interactions**

---

**Table 2. Drug interactions with at least 50% change in the exposure to dabigatran or rivaroxaban**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Interacting drug</th>
<th>Δ exposure, %</th>
<th>Interacting drug</th>
<th>Δ exposure, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp inhibition</td>
<td>Ketoconazole*</td>
<td>150</td>
<td>Ketoconazole*</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>~ 50†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-gp induction</td>
<td>Rifampicin</td>
<td>−67</td>
<td>Rifampicin</td>
<td>−50</td>
</tr>
<tr>
<td></td>
<td>St John’s wort</td>
<td>ND</td>
<td>St John’s wort</td>
<td>ND</td>
</tr>
<tr>
<td>CYP3A4 inhibition</td>
<td>Ketoconazole*</td>
<td>160</td>
<td>Clarithromycin</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>50</td>
<td>Ritonavir</td>
<td>50</td>
</tr>
<tr>
<td>CYP3A4 induction</td>
<td>Rifampicin</td>
<td>−50</td>
<td>St John’s wort</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND indicates not determined.

*Contraindicated.

†Variable depending on the formulation of verapamil.
### Issues Related to All New OAC

#### Conversion...

**Table 3. Suggested strategy for conversion from dabigatran or rivaroxaban to warfarin**

<table>
<thead>
<tr>
<th>Calculated creatinine clearance, mL/min</th>
<th>Dabigatran: start day with warfarin*</th>
<th>Rivaroxaban: start day with warfarin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Day −3</td>
<td>Day −4</td>
</tr>
<tr>
<td>31-50</td>
<td>Day −2</td>
<td>Day −3</td>
</tr>
<tr>
<td>15-30</td>
<td>Day −1</td>
<td>Day −2</td>
</tr>
</tbody>
</table>

*Dabigatran/rivaroxaban is stopped on day 0. The longer overlap with rivaroxaban is justified by its half-life being shorter than that of dabigatran and by the concern about thromboembolic events shortly after transitioning from rivaroxaban to warfarin.*

[^6]: [footnote reference]
How do I Put this thing in Reverse ??!!
**Updated Guidelines**

Hey, What About Good Ol' Aspirin?

Most widely researched >100 randomized trials (high-risk patients)

Reduced vascular death by 15%, nonfatal vascular events by 30%. (Overall net benefit = 20-25% reduction)

Dosing: Well done studies have shown:

- Effective (long term) range between 50 and 100 mg/d, ?? 30 mg/d?
- Dose requirements equal any clinical setting
- Afib: Warfarin/OAC > ASA (inc. clopidogrel)
- DVT:
  - Orthopedics: Yes, but Heparin/oids Preferred
  - Surgery: Similar to Orthopedics
- Non-Surgical: Appears Non-inferior -- need larger studies

---

**Table 1—Vascular Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Dose**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lowest Effective Daily Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attack and ischemic stroke&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
</tr>
<tr>
<td>Men at high cardiovascular risk</td>
<td>75</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75</td>
</tr>
<tr>
<td>Stable angina</td>
<td>75</td>
</tr>
<tr>
<td>Unstable angina&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75</td>
</tr>
<tr>
<td>Severe carotid artery stenosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>100</td>
</tr>
<tr>
<td>Acute myocardial infarction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>160</td>
</tr>
<tr>
<td>Acute ischemic stroke&lt;sup&gt;a&lt;/sup&gt;</td>
<td>160</td>
</tr>
</tbody>
</table>

<sup>a</sup>Higher doses have been tested in other trials and not found to confer any greater risk reduction.
Peri-Procedural
Peri-Procedure

- Approximately 6 million people on anticoagulant therapy
- Significant number on dual therapy (VKA/ASA, ASA/Thienopyridine)
- Bleeding risks with/out procedures
- Yearly, 10% undergo procedures which require adjudication of therapy
- Data governing consensus is limited, usually single-centered
- What do we do with anti-coagulation during procedures?
Global Thrombotic Risks...

- **Recent VTE, No Anticoagulation: Early risk 50%**
  - **Highest risk of recurrence: first 30 days**
  - **Treatment reduces risk approximately 10% in first 30 days**
  - **Risk further decreases to 4-5% after 90 days**

- **Arterial Embolic Disease**
  - **0.5-1%/day in first month after initial event**
  - **Fatal or significant neurologic event occurs ~60%**
  - **Afib, no valve disease = embolic event 4-5%/yr (no anticoagulation)**
  - **Risk reduced by greater than 60% on anticoagulation**
## Peri-Procedure

**Easy Answers**

- 🟢 High Risk Pt/Low Bleed Risk → Continue Anti-Coagulant
- 🟢 Low Risk Pt/High Bleed Risk → Hold Anti-Coagulant

**Difficult Answers**

- 🔴 High Risk Pt/High Risk Bleed
- 🔴 Moderates?
- 🔴 Elective, Urgent, Emergent?
- 🔴 Recent Trials: To Bridge or Not to Bridge?!
<table>
<thead>
<tr>
<th>Agent</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
<th>Recommended Interval between Last Dose and Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulant agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (Coumadin, Bristol-Myers Squibb)</td>
<td>Oral</td>
<td>Inhibition of vitamin K-dependent factors II, VII, IX, and X for γ-carboxylation; and proteins C and S</td>
<td>1–8 days, depending on INR and patient characteristics; INR decreases to ≤ 1.3 in approximately 93% of patients within 5 days⁶⁶</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Intravenous or subcutaneous</td>
<td>Antithrombin activation (inhibition of factors IIa, IXa, Xa, XIIa, and Xla)</td>
<td>Intravenous, 2–6 hr, depending on dose; subcutaneous, 12–24 hr, depending on dose</td>
</tr>
<tr>
<td>Low-molecular-weight heparins (enoxaparin [Lovenox, Sanofi Aventis] and dalteparin [Fragmin, Eli Lilly])</td>
<td>Subcutaneous</td>
<td>Antithrombin activation (inhibition of factor Xa and, to a lesser extent, factor IIa)</td>
<td>24 hr</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra, GlaxoSmithKline)</td>
<td>Subcutaneous</td>
<td>Antithrombin activation (factor Xa inhibitor)</td>
<td>36–48 hr</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa, Boehringer Ingelheim)</td>
<td>Oral</td>
<td>Direct thrombin inhibitor</td>
<td>1 or 2 days with creatinine clearance rate of ≥50 ml/min; 3–5 days with creatinine clearance rate of &lt;50 ml/min</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto, Bayer Healthcare)</td>
<td>Oral</td>
<td>Direct factor Xa inhibitor</td>
<td>21 days when renal function is normal; 2 days with creatinine clearance rate of 60–90 ml/min; 3 days with creatinine clearance rate of 36–59 ml/min; and 4 days with creatinine clearance rate of 15–29 ml/min⁶⁶</td>
</tr>
<tr>
<td>Apixaban (Eliquis, Bristol-Myers Squibb)</td>
<td>Oral</td>
<td>Direct factor Xa inhibitor</td>
<td>1 or 2 days with creatinine clearance rate of &gt;50 ml/min; 3 days with creatinine clearance rate of 30–59 ml/min and 5 days with creatinine clearance rate of &lt;30–49 ml/min</td>
</tr>
<tr>
<td>Desirudin (Ieparvask, Canyon Pharmaceuticals)</td>
<td>Subcutaneous</td>
<td>Direct thrombin inhibitor</td>
<td>2 hr</td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Oral</td>
<td>Cyclooxygenase inhibitor (irreversible effect)</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Aspirin and dipyrdamole (Aggrenox, Boehringer Ingelheim)</td>
<td>Oral</td>
<td>Phosphodiesterase inhibitor</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Clopidogrel (Plerixa, Otsuka Pharmaceutical)</td>
<td>Oral</td>
<td>Phosphodiesterase inhibitor</td>
<td>2 days</td>
</tr>
<tr>
<td>Thienopyridine agents (clopidogrel [Plavix, Sanofi Aventis], ticlodidine [Ticlid, Rodre], prasugrel [Effient, Eli Lilly], and ticagrelor [Brilinta, AstraZeneca])</td>
<td>Oral</td>
<td>ADP receptor antagonist</td>
<td>5 days (clopidogrel and ticagrelor), 7 days (prasugrel), or 10–14 days (ticlodidine)</td>
</tr>
</tbody>
</table>

⁶ ADP denotes adenosine diphosphate, aPTT activated partial thromboplastin time, FDA Food and Drug Administration, INR international normalized ratio, and PCC prothrombin complex concentrate.

†PCCs are either 3-factor or 4-factor concentrates. Nonactivated 4-factor PCCs contain factors II, VII, IX, and X and proteins C and S, and nonactivated 3-factor PCCs contain factors II, IX, and X and only small amounts of factor VII. For details, see the Supplementary Appendix.

‡Factor VII inhibitor bypass activity provides both factor II (prothrombin) and factor Xa for rapid and sustained thrombin generation. For details, see the Supplementary Appendix.
Table 2—Clinical Characteristics Composing the

Table 2—[Section 1.4.3] CHADS\textsubscript{2} Score\textsuperscript{30} for Assessment of Stroke Risk in Patients With Nonrheumatic AF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Congestive heart failure exacerbation</td>
<td>1</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq 75$ y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior history of Stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

CHADS\textsubscript{2} = congestive heart failure, hypertension, age $\geq 75$ years, diabetes mellitus, prior stroke or transient ischemic attack. See Table 1 legend for expansion of other abbreviation.
VKA’s

- Stop 5 days before procedure (1C); Restart 12-24 hrs later (2C)
- MHValve, A-fib, VTE (Embolic) @ High Risk: Bridge (2C) CHADS2
  - Bridge with UFH or LMWH
- MHValve, A-fib, VTE Low Risk: No Bridge (2C)
- “In-Betweeners”: Assess risk, procedure, patient preference
- Minor Dental: Continue, Pro-Hemostatic agent OR Stop 2-3 days before
Aspirin

- Minor Dental/Derm/Cataract: Continue ASA (2C)
- Moderate-High Risk for CV events: Non-Cardiac---Continue (2C)
- Low Risk: Stop 7-10 days prior to procedure (2C)
- CABG?: Continue ASA (2C)
- other Anti-Platelets: Stop 5 Days before (2C)
- Dual Anti-Platelet: Delay procedure 6 wks BMS, 6 mos: DES (1C)
- Dual Therapy and Urgent/Emergent Procedure: Continue (2C)
Pre-Procedure--NOAC’s

Table 4. Timing of interruption of dabigatran or rivaroxaban before surgery or invasive procedures

<table>
<thead>
<tr>
<th>Calculated creatinine clearance, mL/min</th>
<th>Half-life, hours</th>
<th>Timing of last dose before surgery</th>
<th>Standard risk of bleeding*</th>
<th>High risk of bleeding†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 80</td>
<td>13 (11-22)</td>
<td>24 h</td>
<td>2 d</td>
<td></td>
</tr>
<tr>
<td>&gt; 50- ≤ 80</td>
<td>15 (12-34)</td>
<td>24 h</td>
<td>2 d</td>
<td></td>
</tr>
<tr>
<td>&gt; 30- ≤ 50</td>
<td>18 (13-23)</td>
<td>2 d</td>
<td>4 d</td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>27 (22-35)</td>
<td>4 d</td>
<td>6 d</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12 (11-13)</td>
<td>24 h</td>
<td>2 d</td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>Unknown</td>
<td>2 d</td>
<td>4 d</td>
<td></td>
</tr>
</tbody>
</table>

*Examples are cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy.

†Examples are major cardiac surgery, insertion of pacemakers or defibrillators (resulting from the risk for pocket hematoma), neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery.
**Assuring Safety...**

**Anti-coagulation and Procedures**

- Communication **ALL** providers
- Advanced planning
- Assess risk of VTE
- Assess risk of bleeding
- Involve patients in decisions
- Prevent premature cessation of meds (AntiPlt & Stents)
- Conservative discontinuation and reinitiation
References, Studies


**Diagnosis**--Lower Extremity DVT (LEDVT)

- Test based on Pre-test Probability, No Uniform Test (2B)

- Well’s Criteria: Not validated in outpatient setting

- Clinical exam not predictive

- What about Distal DVT’s: Recheck if probability high, treat based on HUS

- No D-Dimer if probability high and Venogram no longer required

- Recurrence? Evaluate based on clinical scenario

- Pregnant? Pretest, D-Dimers and Compression
**Diagnosis--Upper Extremity DVT (UEDVT)**

- Secondary more common than de novo (5-10% of all VTE’s)
- Still has risks (5-10%)
- Well’s Criteria: No validated in outpatient setting nor for UEDVT
- Clinical exam not predictive--based on catheters, swelling, pain
- Diagnosis not gold-standard (even for venograms)
- Few studies and most answers extrapolated from LEDVT
- Tx: To Remove or Not Remove Catheter, Then Tx