Can NOACs replace VKA actually in VTE?
• Venous thromboembolism, includes deep venous thrombosis and pulmonary embolism.
WHY?

• common with an annual incidence of approximately one case per 1000 people.

the third most common cause of vascular related death after myocardial infarction and stroke.

considerable morbidity and premature mortality.

WHY?

• The high death rate from PE (exceeding acute MI!) and the high frequency of undiagnosed PE causing “sudden cardiac death” emphasize the need for improved preventive efforts.
• most DVT is occult and resolves spontaneously without complication.

• 50 % of pt. with image-documented venous thrombosis lack specific symptoms.

• As many as 46 % of pt. with classic symptoms have negative Venograms
**Symptoms**

- Edema - Most specific symptom
- Leg pain & Tenderness -
- Warmth or erythema of the skin over the area of thrombosis
- Clinical symptoms of pulmonary embolism (PE) as the primary manifestation

**Signs**

- Calf pain on dorsiflexion of the foot (Homans sign)
- A palpable, indurated, cordlike, tender subcutaneous venous segment
- Variable discoloration of the lower extremity
- Blanched appearance of the leg (because of edema)
• Wirchow triad?

RISK FACTORS

**Common**
- Active cancer
- Prolonged immobility (long journeys, lower limb fracture)
- Recent major surgery
- Pregnancy or recent childbirth

**Uncommon or rare**
- Factor V Leiden
- Anti-thrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Antiphospholipid syndrome
- Active inflammatory bowel disease
- Myeloproliferative disorders
- Oestrogen-containing oral contraceptive (especially when combined with Factor V Leiden)
- Nephrotic syndrome
- Homocystinuria
- Paroxysmal nocturnal haemoglobinuria
- Hyperviscosity syndrome
- Behcet's disease
**WELLS SCORE**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
</tr>
<tr>
<td>Active cancer (treatment ongoing, or within previous 6 months; or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis or recent plaster immobilization of the leg</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for more than 3 days, or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td><strong>Examination</strong></td>
<td></td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling by &gt; 3 cm when compared with asymptomatic leg (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema (greater in the symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Alternative diagnosis?</strong></td>
<td></td>
</tr>
<tr>
<td>An alternative diagnosis (Table 56.3) is as likely or more likely than DVT</td>
<td>−2</td>
</tr>
</tbody>
</table>

**Clinical probability of DVT**

- Score 3 or more: high probability
- Score 1 or 2: intermediate probability
- Score 0 or less: low probability


---

**COMPLICATION**

- **40% of patients have silent PE when symptomatic DVT is diagnosed**

Paradoxic emboli (rare)

Recurrent DVT

Postthrombotic syndrome (PTS)
  (chronic pain, swelling, pigmentation, varicose, ulcer, dryness, eczema, hardening)
What is the role of venous ultrasonography?

- **Proximal ultrasonography**
  - Examines only the common and popliteal veins

- **Whole-leg ultrasonography**
  - Examines entire deep vein system, including calf veins
  - Avoids repeated testing
  - But may identify more patients with isolated, calf vein DVT

- Both methods associated with acceptable 3-month incidence of VTE after negative results
MANAGEMENT

- Anticoagulation - mainstay of therapy:
  Heparins, warfarin, factor Xa inhibitors, and various emerging anticoagulants
- Pharmacologic thrombolysis
- Endovascular and surgical interventions
- Physical measures (eg, elastic compression stockings and ambulation)

Anticoagulant therapy remains the mainstay of therapy for (DVT) because:
- 1- noninvasive,
- 2- treats most patients (approximately 90%) with no immediate demonstrable sequelae of DVT,
- 3- has a low risk of complications,
- 4- its outcome data → an improvement in morbidity and mortality.

Long-term anticoagulation is necessary to prevent the high frequency of recurrence.

Anticoagulation does have problems:
- although it inhibits propagation, it does not remove the thrombus, a variable risk of clinically significant bleeding is observed.
Timeline of Oral Anticoagulant Development

- FDA approval of warfarin: 1954
- Dabigatran approved for NVAF: 2010
- Rivaroxaban approved for NVAF: 2011
- Apixaban approved for NVAF & rivaroxaban approved for DVT/PE: 2012
- Dabigatran and rivaroxaban approved for DVT/PE: 2014
- Edoxaban approved for NVAF, DVT/PE: 2015

THE NAME GAME

- NOAC
  - NOVEL ORAL ANTICOAGULANT
  - NON-VITAMIN K ORAL ANTICOAGULANT
- TSOAC
  - TARGET SPECIFIC ORAL ANTICOAGULANT
- DOAC
  - DIRECT ORAL ANTICOAGULANT

Silva, R. NOACs in NVAF: Cardiovascular and Hematological Agents in Medicinal Chemistry. 2014
HOW DO THEY WORK?

- WARFARIN
  - INHIBITS VITAMIN K EPOXIDE REDUCTASE
  - FACTORS VII, IX, X, II
- DABIGATRAN
  - DIRECTLY INHIBITS FACTOR II A
- RIVAROXABAN, APIXABAN, EDOXABAN
  - DIRECTLY INHIBITS FACTOR XA

Warfarin has been the primary oral anticoagulant used for treatment of venous thromboembolism but has inherent limitations that detract from its therapeutic utility, with a narrow therapeutic index variability in patients’ responses dependent on a range of factors including diet and concomitant drugs.
WARFARIN

• **Warfarin** therapy is overlapped with heparin for 4-5 days until the INR is therapeutically elevated 2-3 times.

• Heparin must be overlapped with oral warfarin because of initial transient hypercoagulable state induced by warfarin paradoxical thrombosis.

Vitamin K Antagonists – Limitations

• Unpredictable pharmacokinetics and pharmacodynamics, which are affected by:
  • Genetic factors (CYP 2C9 mutation)
  • Drug–drug interactions
  • Consumption of alcohol and foods containing vitamin K

• Monitoring and frequent dose adjustment required to maintain INR within therapeutic window
  • Monitoring is costly, and a burden on patients and society

• Slow onset and offset of action (e.g. if patient requires surgery),
  • requiring bridging with heparin or LMWH
Drug Interactions with VKAs

<table>
<thead>
<tr>
<th>Increased Effect</th>
<th>Decreased Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>Immunosuppressants</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Alubrivar</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Leflunomide</td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>Lokalenästhetika</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Mefenaminsäure</td>
</tr>
<tr>
<td>Anabolika</td>
<td>Methylene-dioxyamphetamine</td>
</tr>
<tr>
<td>Androsteron</td>
<td>Methylprednisolon</td>
</tr>
<tr>
<td>Anthranilic acid derivatives</td>
<td>Metronidazol</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>Monaminooxidasenhemmer</td>
</tr>
<tr>
<td>Benziodarone</td>
<td>Muskelrelaxantialkaloide</td>
</tr>
<tr>
<td>Broad spectrum antibiotics</td>
<td>Nalidixinsäure</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Nifluminsäure</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Nicotinsäurederivate</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Nortryptiline</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Oxyphenbutazon</td>
</tr>
<tr>
<td>Clopenthiazide</td>
<td>Paraaminophenol</td>
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<tr>
<td>Clopidogrel</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Piroxicam</td>
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<tr>
<td>Esomeprazole</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Flutamide</td>
<td>Piroxicam</td>
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<tr>
<td>Glucagon</td>
<td>Piroxicam</td>
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<tr>
<td>Glutethimide</td>
<td>Piroxicam</td>
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<td>Griseofulvin</td>
<td>Piroxicam</td>
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<td>Haloperidol</td>
<td>Piroxicam</td>
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<td>Laxazin</td>
<td>Piroxicam</td>
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<td>Mercaptopurine</td>
<td>Piroxicam</td>
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<td>Neuroleptika</td>
<td>Piroxicam</td>
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<td>Ovulatostimulatoren</td>
<td>Piroxicam</td>
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<td>Phenytoin</td>
<td>Piroxicam</td>
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<td>Purinoderivate</td>
<td>Piroxicam</td>
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<tr>
<td>Pyridoxine</td>
<td>Piroxicam</td>
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<tr>
<td>Rifampicin</td>
<td>Piroxicam</td>
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<tr>
<td>Strophantin</td>
<td>Piroxicam</td>
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<tr>
<td>Thioracil</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Thyrostatika</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Vitamin K Preparations</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Vitamin supplements</td>
<td>Piroxicam</td>
</tr>
</tbody>
</table>

Close INR monitoring is required with EVERY change in medication!

- In contrast, direct oral anticoagulants (DOACs) have relatively stable pharmacokinetics that remove the need for regular monitoring and dose adjustment.
Challenges of Warfarin Use

- Variable dose response
- Narrow therapeutic window
- Need for frequent monitoring
- Long half-life

New Oral Anticoagulants: Advantages

1. No coagulation lab monitoring
2. No dose adjustment
3. No drug-food interactions
4. Rare drug-drug interactions
5. No “bridging” needed prior to invasive procedures or surgery
• Recent non-inferiority trials assessing the efficacy and safety of DOACs compared with warfarin in treatment of acute venous thromboembolism and prevention of recurrent venous thromboembolism have shown comparable efficacy without significantly increased risk of major bleeding.

Rivaroxaban

• Rivaroxaban (Xarelto) is an oral factor Xa inhibitor approved by the FDA in November 2012 for treatment of DVT or pulmonary embolism (PE) and for reduction of the risk of recurrent DVT and PE after initial treatment.

• EINSTEIN-DVT and EINSTEIN-PE trials suggested that rivaroxaban is as effective in preventing VTE recurrence as enoxaparin followed by a VKA and may be associated with less bleeding

• in addition, the data suggested rivaroxaban use in high-risk groups (eg, fragile patients, cancer patients, and patients with a large clot).
Apixaban

- In March 2014, the FDA approved apixaban (Eliquis) for the additional indication of prophylaxis of DVT and PE in adults who have undergone hip- or knee-replacement surgery (ADVANCE 1, 2, and 3 clinical trials).

In August 2014, apixaban was approved for treatment of DVT and PE (AMPLIFY and AMPLIFY-EXT (extended treatment) studies).

Data from the AMPLIFY-EXT trial showed that extended anticoagulation (12 months) with apixaban shortened hospital stays, reduced symptomatic recurrent venous thromboembolism or all-cause death without an associated increase in major episodes of hemorrhage when compared with placebo.

Dabigatran

- Dabigatran (Pradaxa) inhibits free and clot-bound thrombin and thrombin-induced platelet aggregation.

- This agent was FDA approved in April 2014, for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days.

- The RE-COVER and RE-COVER II trials included patients with DVT and PE who were treated with parenteral anticoagulant therapy for 5-10 days.

- The RE-SONATE trial and RE-MEDY trials included patients (n=2856) with acute DVT and PE who had completed at least 3 months of anticoagulant therapy. Results from this trial showed dabigatran was noninferior to warfarin in the extended treatment of VTE and carried a lower risk of major or clinically relevant bleeding than warfarin.
Edoxaban

• Edoxaban (Savaysa) was approved by the FDA in January 2015 for the treatment of DVT and PE in patients who have been initially treated with a parenteral anticoagulant for 5-10 days.
• Hokusai-VTE study that included 4,921 patients with DVT and 3,319 patients with PE.
• The investigators concluded that edoxaban was not only noninferior to high-quality standard warfarin therapy but also caused significantly less bleeding in a broad spectrum of patients with VTE, including those with severe PE.

Betrixaban

• Betrixaban (Bevyxxa), a FXa inhibitor, was approved by the FDA in June 2017 for the prophylaxis of VTE in adults hospitalized for acute medical illness who are at risk for thromboembolic complications owing to moderate or severe restricted mobility and other risk factors that may cause VTE.
• APEX studies
• Those who received betrixaban showed significant decreases in VTE events (4.4%) compared with patients in the enoxaparin group.
### Metabolism and Elimination of DOACs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Bioavailability</th>
<th>P-gp</th>
<th>CYP3A4 Substrate</th>
<th>Renal Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>~5%</td>
<td>✓</td>
<td>No</td>
<td>80%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>66%*</td>
<td>✓</td>
<td>Yes (~33%)</td>
<td>33%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>50%</td>
<td>✓</td>
<td>Yes (~25%)</td>
<td>25%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>62%</td>
<td>✓</td>
<td>No</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Note: In (SCOA) anticoagulants oral direct medication practical the for guidance al. et AE, Burnett 2016, Thrombolysis Thromb/treatment. VTE 2011, Europace NAF. in NOACs of Use Practical on Guide

- Apixaban least impacted by renal impairment and approved for patients receiving intermittent hemodialysis
### ANTICOAGULANT COMPARISON: DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Antiplatelets</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>No adjustment</td>
<td>Precaution</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Precaution</td>
<td>Precaution</td>
<td>Precaution</td>
<td>Avoid</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Avoid</td>
<td>Precaution</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Safe</td>
</tr>
<tr>
<td>NSAID/ASA</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
</tr>
<tr>
<td>Clopidogrel-antiplatelets</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Unknown</td>
<td>Caution</td>
<td>Caution</td>
<td>Unknown</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Avoid</td>
<td>Caution</td>
<td>Caution</td>
<td>Avoid</td>
</tr>
<tr>
<td>Heparin/ticagrelor</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

**Not for Use in Some Populations (Yet)**

- **Pregnancy**
  - Not advised in pregnancy: cross the placenta
- **Breast feeding**:
  - Not advised for women who are breast-feeding
- **Chronic kidney disease**: apixaban an option
- **Patients on interacting medication**
  - Some HIV meds, seizure meds, some anti-arrhythmia
**VTE Therapy Overview**

**Approved DOAC Dosing for VTE Treatment**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Dose Adjustment for Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran*</td>
<td>150 mg twice daily AFTER 5 days of parenteral anticoagulation</td>
<td>Avoid use if CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Rivaroxaban**</td>
<td>15 mg twice daily x 21 days followed by 20 mg daily</td>
<td>Avoid use if CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Apixaban**</td>
<td>10 mg twice daily x 7 days followed</td>
<td>No dosage adjustment required</td>
</tr>
<tr>
<td>Edoxaban*</td>
<td>60 mg daily AFTER 5 days of parenteral anticoagulation</td>
<td>15-50 -ml/min :30 mg once daily</td>
</tr>
</tbody>
</table>

*Dosing may be different with concomitant p-glycoprotein inhibitors or inducers.**

**Dosing may be different with concomitant p-glycoprotein and strong CYP3A4 inhibitors or inhibitors**
Duration of Anticoagulation

- For the first episode of deep venous thrombosis (DVT), patients should be treated for 3-6 months.
- Recurrent episodes should be treated for at least 1 year
- Indefinite therapy is recommended for patients with recurrent episodes of venous thrombosis regardless of the cause

The American College of Chest Physicians (ACCP) recommends cessation of anticoagulant therapy after 3 months of treatment in those with:

1. surgery-associated acute proximal DVT,
2. an acute proximal DVT or PE provoked by a nonsurgical transient risk factor,
3. a first unprovoked VTE and a high risk of bleeding. (In those with a low or moderate bleeding risk, extend anticoagulation without a scheduled stop date.)

- Patients with cancer have a particularly higher rate of DVT recurrence than noncancer patients.
- Long-term therapy for DVT is strongly recommended.
- Studies have shown a lower rate of venous thromboembolism (VTE) recurrence without increasing the risk of bleeding with low-molecular-weight heparin (LMWH) therapy.
Complications of Anticoagulant Therapy

- Hemorrhagic complications are the most common adverse effects.
  - Major bleeding: 3-10%.
  - High-risk populations: 5-23% (>65 y, history of stroke, GI bleed, renal insufficiency, diabetes)
- Patients who require indefinite anticoagulation double the risk.
- Significant bleeding (i.e., hematemesis) should be thoroughly investigated because anticoagulant therapy may unmask a preexisting disease (cancer, peptic ulcer disease, A-V malformation)

- Systemic embolism
- Chronic venous insufficiency
- Postthrombotic syndrome (i.e., pain and edema in the affected limb without new clot formation)
- Soft tissue ischemia associated with massive clot and very high venous pressures - phlegmasia cerulea dolens
Reversal of Anticoagulation

(1) Discontinuation of the drugs  Due to the short half-life of FXa inhibitors, is sufficient when there is time to await spontaneous clearance.

- (2) Remove drug
  - Hemodialysis or hemofiltration for dabigatran

- (3) Neutralize drug
  - Specific reversal agents
    - (a) Prothrombin complex concentrates (PCCs)
      These contain 3 or 4 of the vitamin K–dependent coagulation factors, as well as proteins C and S.
      PCCs can be used to address severe bleeding in patients taking NOACs in high enough dosages.
      an initial dose of 25 to 50 U/kg of PCCs in life-threatening emergencies, to be repeated if necessary.
    - (b) Idarucizumab (Pradbind)
      Idarucizumab is a humanized antibody fragment directed against dabigatran.
      completely reverse the anticoagulant effect of dabigatran within minutes;
      on October 16, 2015, it was approved by the FDA as an antidote for dabigatran.

- (4) Andexanet alfa
  a recombinant, modified FXa molecule that acts as a decoy protein that is catalytically inactive but has a high affinity for FXa inhibitors. an antidote for apixaban, edoxaban, and rivaroxaban, reverse the anticoagulant effects of apixaban and rivroxban in human volunteers.

- (5) Aripazine (ciraparantag)
  a synthetic small molecule, has broad activity against both old (heparin, low molecular weight heparin) and new oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban). A 2014 study of human volunteers demonstrated that administration of aripazine reversed the prolonged clotting time caused by edoxaban.
Guidelines Support Using DOACs

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Chest Physicians Guideline and Expert Panel Report:</td>
<td>In patients with DVT of the leg or PE and no cancer, as</td>
</tr>
<tr>
<td>Antithrombotic Therapy for VTE Disease</td>
<td></td>
</tr>
<tr>
<td>2016 European Society of</td>
<td>When oral anticoagulation is initiated in a patient with</td>
</tr>
<tr>
<td>Guideline Recommendations</td>
<td></td>
</tr>
</tbody>
</table>
LAST MESSAGE

• NOACs are equally effective as VKA in treating and preventing recurrent VTE & VTE-related mortality
• NOACs cause less major bleeding than VKA
• convenient & reliable to use
  No need for regular monitoring
• NOACs are more expensive

Don’t forget to Do a D-O-A-C Double-Check

• Drug-drug interactions (pharmacokinetic and pharmacodynamics interactions
• Organ function (liver/renal)
• Adjustments (of any of the above as well as age and weight)
• Counsel!
Thank You