Disclosures

• No relevant financial interests/ affiliations to disclose.
Abbreviations

ACC: American College of Cardiology
AHA: American Heart Association
AF: atrial fibrillation
AUC: area under the curve
BID: twice daily
Cmax: maximum serum concentration
CrCl: creatinine clearance
CKD: chronic kidney disease
CV: cardiovascular
DOAC: direct acting oral anticoagulant
DOPPS: Dialysis Outcomes and Practice Patterns Study
ESC: European Cardiovascular Society
ESRD: end stage renal disease
GFR: glomerular filtration rate
GI: gastrointestinal
HD: hemodialysis
HR: hazard ratio

ICH: intracranial hemorrhage
INR: international normalized ratio
KDIGO: Kidney Disease: Improving Global Outcomes
MI: myocardial infarction
NSAID: non-steroidal anti-inflammatory drug
PK: pharmacokinetics
PO: by mouth
RCT: randomized controlled trial
RR: risk ratio
SCr: serum creatinine
TIW: three times weekly
TTR: time-in-therapeutic range
VTE: venous thromboembolism
Objectives

1. Explain the pathophysiology of atrial fibrillation (AF)-associated stroke, definition of nonvalvular atrial fibrillation (NVAF), and risk stratification scoring systems for thromboembolism/stroke and bleeding.
2. Describe the inherent risks for both thromboembolism/stroke and bleeding in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).
4. Evaluate the available evidence for direct-acting oral anticoagulants (DOACs) in patients with CKD/ESRD.
1. Which of the following does NOT describe one of the inherent risks in patients with end-stage renal disease?

A. Hyperphosphatemia increasing risk of stroke
B. Activation of the renin-angiotensin-aldosterone system, which increases risk of atrial fibrillation
C. Uremic platelet impairment increasing risk of bleeding
D. Frequent heparin exposure increasing risk of bleeding
E. Vitamin K deficiency due to dialysis, which increases risk of bleeding
Pre-Test

2. Which of the following is INCORRECT regarding calciphylaxis/calcification and the matrix G1a protein?

A. Patients with end-stage renal disease have a baseline risk for calcification
B. Matrix G1a protein is an endogenous activator of calcification
C. Warfarin inhibits matrix G1a protein
D. Patients with normal renal function can develop calciphylaxis on warfarin
E. Calciphylaxis presents as severe pain and ischemic events
3. Which of the following anticoagulants should NOT be used in patients with nonvalvular atrial fibrillation and end-stage renal disease, due to higher risk for hemorrhagic death?

A. Apixaban
B. Enoxaparin
C. Rivaroxaban
D. Dabigatran
E. Betrixaban
4. Apixaban 5 mg po BID will be started for stroke prevention in a 74-year-old patient with end-stage renal disease (ESRD) on hemodialysis (HD) and atrial fibrillation. Weight 74 kg, height 174 cm. Which of the following is INCORRECT regarding apixaban?

A. Apixaban undergoes 85% renal excretion as active compounds

B. Apixaban should be reduced to 2.5 mg po BID

C. Apixaban undergoes primarily biliary/intestinal excretion

D. Apixaban can be given regardless of the timing of hemodialysis session

E. Apixaban 5 mg po BID may reduce mortality compared to warfarin in patients with ESRD on HD
Atrial Fibrillation (AF)

• Supraventricular tachyarrhythmia; most common sustained arrhythmia

• Stroke is a complication of AF
  • Left atrial blood stasis is associated with increased risk for left atrial appendage thrombus
  • 5-7-fold higher rate vs the general population

• Causes
  • Hypertension, myocardial infarction, thyroid disorder, stimulant use, etc.

Valvular vs Non-Valvular Atrial Fibrillation

• Valvular AF
  • Moderate-to-severe mitral stenosis (potentially requiring surgical intervention) OR presence of an artificial (mechanical) heart valve
  • Considered an indication for long-term anticoagulation with warfarin

Valvular vs Non-Valvular Atrial Fibrillation

• **Non-Valvular AF**
  
  • AF in the *absence* of moderate-to-severe mitral stenosis or a mechanical heart valve
  
  • **Does not** imply the absence of valvular heart disease

**TABLE 7**

**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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td><strong>Adjusted Stroke Rate (% per y)</strong></td>
</tr>
<tr>
<td>CHADS²</td>
<td><strong>CHADS²</strong></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
<tr>
<td>CHA²DS²-VASc†</td>
<td></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e., female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

- Favor anticoagulation if score ≥ 2 men, ≥ 3 women
### Table 2: The HAS-BLED Score for Risk of Bleeding

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal/liver function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age over 65)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs/alcohol concomitantly</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>Maximum Score</strong></td>
<td>9</td>
</tr>
</tbody>
</table>

The name of the score is derived from the first letter of each risk factor.

INR = international normalized ratio.
2. For patients with nonvalvular AF and moderate-to-severe CKD with CHA₂DS₂-VASc scores of 2 or greater, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established. *(Level of Evidence: C)*

2. For patients with nonvalvular AF with a CHA₂DS₂-VASc score of 2 or greater and who have end-stage chronic kidney disease (CKD) (creatinine clearance <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation *(Level of Evidence: B)*.
14. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dl [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl ≤50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA₂DS₂-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban).¹⁴.¹⁻¹¹

13. For patients with AF who have a CHA₂DS₂-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.¹⁴.¹⁻²⁵,¹⁴.¹⁻²⁹,¹⁴.¹⁻³⁰

MODIFIED: New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline)
Stroke prevention in CKD/ESRD

- Most RCTs on DOACs in AF excluded patients on HD and CrCl <25–30mL/min
- Standard of care for this population has historically been **warfarin**
  - Warfarin undergoes extensive hepatic metabolism to **inactive** compounds → renal excretion

*What is the evidence?*
Inherent Risks for CKD/ESRD vs Non-CKD/ESRD

- **1.4-2.5x higher rate of AF**
  - Hypertension, RAAS activation, electrolyte imbalance

- **2x higher rate of stroke**
  - Hypertension, inflammation, abnormal blood coagulation, hyperphosphatemia/calcification

- **10x higher rate of major bleeding on warfarin**
  - Uremic platelet impairment
  - Vascular access, heparin exposure
AF Prevalence

Reinecke et al., JASN 2009;20:705-711
**Stroke Risk**

![Relative Risk of Stroke in Different Subgroups of CKD](image)

- eGFR > 70 ml/min
- eGFR 40–70 ml/min
- eGFR < 40 ml/min
- No CKD
- CKD
- Hemodialysis
- Patients on hemodialysis with atrial fibrillation compared to those without

Nakayama et al. 2006
USRDS 2006
USRDS 2005
Vasquez et al. 2005

Reinecke et al., JASN 2009;20:705-711
Bleeding Risk

• Annual risk of intracerebral hemorrhage
  • General population with atrial fibrillation:
    • 0.1% in patients not on warfarin and 0.3% in patients on warfarin
  • Patients with atrial fibrillation on dialysis
    • 1.1% in patients not on warfarin and 2.6% in those on warfarin

Warfarin quality measure - “Time in Therapeutic Range”

• Duration of time in which the INR values were within a desired range
• Measure of long-term INR control; objective is to maximize TTR
• TTR ranges greatly from 29%-64% in clinical trials; TTR <60% is considered inefficient
• TTR is a widely accepted quality measure to evaluate the safety and efficacy of warfarin therapy
• Clinical trials > clinical practice

Pokorney et al., AHA 2015;170:141-148.e1
Pokorney et al., AHA 2015;170:141-148.e1
2020 Meta-Analysis - Warfarin in ESRD Patients with AF

- 15 studies (n=47,480) – patients with ESRD and AF with/without warfarin
  - Mostly retrospective observational studies
  - Majority were propensity-matched
- Warfarin users (22%) vs non-warfarin users; TTR not always reported; 12/15 on concomitant antiplatelet
- Mean follow up 2.6 (1.4) years
- 4 outcomes:
  - Ischemic stroke, hemorrhagic stroke, bleeding, mortality

Randhawa et al. JAMA Cardiology 2020;3:e202175.
2020 Meta-Analysis - Warfarin in ESRD Patients with AF (con’t)

Randhawa et al., *JAMA Cardiology*; 2020; 3:e202175.
2020 Meta-Analysis - Warfarin in ESRD Patients with AF (con’t)

Randhawa et al., JAMA Cardiology;2020;3:e202175.
2020 Meta-Analysis - Warfarin in ESRD Patients with AF (con’t)

- Warfarin vs no warfarin
  - No difference in major bleeding or mortality rate

- Only 2 studies mentioned outcomes with antiplatelets – no difference in stroke reduction

- Sensitivity analyses using **leave-one-out method**
  - Variables remained consistent except HR for hemorrhagic stroke

- Other meta-analyses showed similar findings; intrinsic limitations of such meta-analyses

Medicare claims database of ESRD patients with AF (n=8410), 2007-2013

- 36% of subjects with CHA2DS2-VASc ≥2 were anticoagulated
  - 98% of anticoagulated patients on warfarin, remaining on DOAC; TTR not reported
- Patients on anticoagulation:
  - Younger, had less comorbidities, and less likely to have been previously hospitalized for bleeding → propensity matched 1:2

2020 Medicare Claims Data Study (con’t)

- Limitations of a claims database study – unable to assess adherence, TTR, drug interactions, etc.

Increased Risk of Stroke and Death for Warfarin Users with ESRD and AF

- A retrospective cohort study compared ESRD patients with AF in warfarin (44.7%) vs non-warfarin users, 2003-2004 (n=1671)
  - Mean follow up 1.6 years; TTR not reported; 14% on concomitant antiplatelet but outcomes not reported
  - Analyses also done with covariate and propensity score adjustment model

- Warfarin users had **2x increase in risk for new stroke** (P=0.001), remained significant after adjustment
  - **Both** ischemic (HR 1.81, 95% CI 1.12-2.92) & hemorrhagic (HR 2.22, 95% 1.01-4.91)

- Warfarin users had **4x increase in death** from stroke (P=0.009), remained significant after adjustment

Warfarin and Calciphylaxis

- ESRD patients have vascular calcification at baseline
- Matrix G1a protein prevents calcium deposition in arteries
  - Vitamin K–dependent protein
- Inhibition by warfarin → calciphylaxis of the arterial vessel wall
- Characterized as severe pain, ischemic events, mortality
- Reported in patients taking warfarin, even with normal renal function
- Possible risk factor for ischemic stroke in warfarin users?

Stroke prevention in CKD/ESRD

• Standard of care for this population has historically been warfarin → is this appropriate?
  • Unfavorable risk/benefit ratio
  • Guidelines do not have a consensus (ACC/AHA, ECS, KDIGO)

• DOACs are being increasingly used for AF and CKD/ESRD
## Available drug options for AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard dose</th>
<th>Adjusted dose for renal impairment/failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td></td>
<td>Titrate per INR goal</td>
</tr>
<tr>
<td><strong>Direct-acting oral anticoagulants (DOAC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg BID</td>
<td>2.5 mg BID if meet 2 of 3 criteria (≥80 years, ≤60 kg, Scr ≥1.5 mg/dl)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg daily with evening meal</td>
<td>15 mg daily (CrCl ≤50 ml/min)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg daily</td>
<td>30 mg daily (CrCl 15-50 ml/min; not if CrCl &gt;95 ml/min) <strong>Not recommended in CrCl &lt;15 ml/min</strong></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg BID</td>
<td>75 mg BID (CrCl 15-30 ml/min) <strong>Not recommended in CrCl &lt;15 ml/min or dialysis</strong></td>
</tr>
</tbody>
</table>
**Dabigatran in ESRD/HD**

- Dabigatran (n=281) vs warfarin (n=8064)
  - Prospective prevalence study of an ESRD/HD database, 2010-2014
  - 84.7% of dabigatran users on 75 mg BID; **TTR 13.7%**
    - Dabigatran users were younger, and had **higher rates of previous bleed** vs warfarin users
  - Follow-up for 2 years; average time on dabigatran and warfarin were 168 and 175 days, respectively
  - **Higher risk of hemorrhagic death for dabigatran** (RR, 1.78, P=0.006)
  - **Ischemic stroke**/arterial embolism – warfarin vs dabigatran, 6.2% vs 10.6%

*Chan et al., Circulation 2015; 131: 972–979*
Dabigatran in ESRD/HD (con’t)

• Sensitivity analyses:
  • After adjustment for baseline differences
    • Risk of major bleeding was still higher with dabigatran (RR 1.64, P=0.03)
  • After exclusion of TTR <60%
    • Dabigatran was still associated with an increased risk for major bleeding (RR 1.46, P=0.0001)
  • Dabigatran – 85% renal excretion as active metabolites, up to 60% dialyzable and efficacy correlated with trough levels

Chan et al., Circulation 2015; 131: 972–979
Rivaroxaban in ESRD/HD

- Retrospective claims analysis of St. IV-V CKD/HD patients with AF and anticoagulated, U.S. Truven MarketScan data, 2012-2017
  - Rivaroxaban (n=1896) vs warfarin (n=4848)
  - 88% on HD; mean follow-up 1.4 (0.6-2.7) years; time on anticoagulant mean 112 (38-260) days
  - 38.7% of rivaroxaban users on <20 mg/day; TTR not assessed/reported
  - Differences in baseline variables adjusted (including CHA2DS2-VASc and HAS-BLED components)

Rivaroxaban in ESRD/HD (con’t)

- Rivaroxaban had non-significant reduction in stroke/systemic embolism
- Rivaroxaban significantly reduced major bleeding vs warfarin (HR 0.68, 95% CI, 0.47-0.99)
  - Driven by reductions in both intracranial and GI bleeding but individual outcomes not significant
- 66% undergoes renal excretion (33% are active compounds)

Apixaban PK study in ESRD

• Open-label, parallel-group, single-dose study
  • 8 subjects with ESRD on HD vs 8 subjects with normal renal function
    • Apixaban 5 mg x1 given to healthy subjects
    • Apixaban 5 mg x2 to ESRD subjects, separated by ≥7 days (2h pre-HD and after 4h-HD session)
  • All HD heparin-free
  • ESRD subjects had modest increase (36%) in AUC and no difference in Cmax or anti-Xa activity vs subjects with normal renal function
  • No significant difference in concentrations pre- or post-HD

Inpatient Apixaban Use in Severe Renal Impairment or ESRD/HD

- Retrospective single-center study of renally impaired patients on apixaban or warfarin, 2014-2015
  - 72% for AF, rest for VTE; 63% severe renal impairment, rest were ESRD/HD
- Apixaban patients matched 1:1 to warfarin patients with baseline therapeutic INR (n=73 in each arm)
  - 62% of apixaban users received 2.5 mg BID; TTR 67.5%
- Bleeding/stroke outcomes assessed while inpatient and 5 months post-discharge
Inpatient Apixaban Use in Severe Renal Impairment or ESRD/HD (con’t)

- Apixaban vs warfarin - average days on therapy, 4.3 and 3.8 days, respectively
  - Non-significant reduction in major bleeding (9.6% vs 17.8%, p=0.149) and composite bleeding (21.9% vs 27.4%, p=0.442)
  - Similar rates of stroke (7.5% in each group), no recurrent VTE in either group
- No differentiation between type of stroke
- After excluding stroke cases due to subtherapeutic INR and inappropriate apixaban doses, stroke rate in apixaban vs warfarin - 2.7% vs 4.1%
- Still higher than historical rates

Apixaban vs Warfarin in Dialysis Patients

- Single-center, retrospective study of dialysis patients, 2011-2015
  - Patients enrolled 1:3 for apixaban (n=40) and warfarin (n=120) groups; **not matched but no significant differences**
  - Apixaban group was slightly older, higher rate of previous bleeding; same CHA2DS2-VASc score; 70% of indication was for AF, 30% for VTE
  - 57.5% of apixaban users took 2.5 mg BID; **TTR not assessed/reported**
  - No significant differences in bleeding
    - **Numerically higher rate of major bleeding** for warfarin group
    - Major interacting medications - **47.5% (warfarin)** vs 0% (apixaban)

Apixaban in ESRD/HD

- Retrospective cohort study of Medicare beneficiaries, ESRD on dialysis, apixaban vs warfarin (n=25,523), 2010-2015
  - 91% on warfarin; 44% of apixaban users on 5 mg BID; TTR not assessed; no data on body weight or Scr
  - Main analysis in prognosis-matched cohorts for each outcome (1:3 for apixaban to warfarin)
    - Average time on apixaban and warfarin was 105 and 157 days respectively, before death/drug discontinuation

Siontis et al., Circulation 2018;138:1519-1529.
Apixaban in ESRD/HD (con’t)

• No difference in ischemic stroke/systemic embolism between apixaban and warfarin (HR 0.88, P=0.29)

• Significantly lower risk of major bleeding for apixaban vs warfarin (HR 0.72, P<0.001)

• Non-significant reduction in mortality for apixaban (HR 0.85, P=0.06)
Apixaban in ESRD/HD (con’t)

• Sensitivity analyses (prognosis-matched):
  • Apixaban 5 mg BID vs 2.5 mg BID
    • Significantly lower risks of ischemic stroke/systemic embolism (HR 0.61, P=0.04)
    • Significantly lower death rate (HR 0.64, P=0.01)
  • Apixaban 5 mg BID vs warfarin
    • Significantly lower risks of ischemic stroke/systemic embolism (HR 0.64, P=0.04)
    • Significantly lower death rate (HR, 0.63, P=0.003)
    • Significantly lower rates of major bleeding (HR 0.71, P=0.02)

Siontis et al., Circulation 2018;138:1519-1529.
Apixaban in ESRD/HD (con’t)

• Sensitivity analyses (prognosis-matched) (con’t):
  • Apixaban 2.5 mg BID vs warfarin
    • Significantly less major bleeding with apixaban (HR 0.71, P=0.007) but not stroke/SE or death

• Both apixaban doses and warfarin had similar rates of ICH rates & GI bleeding
  • Annual ICH rate 3.1% >> 0.33% (ARISTOTLE)

• Mostly biliary/direct intestinal excretion; only 27% undergo renal excretion as active compounds

Siontis et al., Circulation 2018;138:1519-1529.
Apixaban vs No Anticoagulation?

- Meta-analysis of 16 nonrandomized, observational studies of HD patients with AF
  - All except 2 compared warfarin vs no anticoagulation; high heterogeneity in the studies
    - 1 involved rivaroxaban/dabigatran vs warfarin
    - 1 involved apixaban vs warfarin (Siontis et al., 2018)
  - Mean follow-up period 18-52.8 months

Kuno et al., JACC 2020; 75:273–85
### FIGURE 3: Effect of Anticoagulant on the Primary Efficacy Outcome (Stroke/SE)

#### Table: Comparison of Other vs. Apixaban 5 mg (Random Effects Model)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 2.5 mg</td>
<td>1.69</td>
<td>[0.88-3.23]</td>
</tr>
<tr>
<td>No-Anticoagulant</td>
<td>1.69</td>
<td>[0.86-3.33]</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.54</td>
<td>[0.82-2.91]</td>
</tr>
</tbody>
</table>
FIGURE 4  Effect of Anticoagulant on the Secondary Efficacy Outcome (Death)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison: Other vs Apixaban 5 mg</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 2.5 mg</td>
<td>1.62</td>
<td>[1.11-2.35]</td>
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</tr>
<tr>
<td>No-Anticoagulant</td>
<td>1.64</td>
<td>[1.11-2.42]</td>
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</tr>
<tr>
<td>Warfarin</td>
<td>1.54</td>
<td>[1.07-2.22]</td>
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</tbody>
</table>
### Figure 5: Effect of Anticoagulant on the Primary Safety Outcome (Major Bleeding)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison: Other vs. Apixaban 5 mg</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td>Apixaban 2.5 mg</td>
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<td>1.01</td>
<td>[0.75-1.37]</td>
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<tr>
<td>Dabigatran</td>
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<td>2.09</td>
<td>[1.42-3.09]</td>
</tr>
<tr>
<td><strong>No-Anticoagulant</strong></td>
<td></td>
<td>1.08</td>
<td>[0.79-1.47]</td>
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<tr>
<td>Rivaroxaban</td>
<td></td>
<td>1.94</td>
<td>[1.25-3.02]</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>1.41</td>
<td>[1.07-1.88]</td>
</tr>
</tbody>
</table>

(All HRs are from a Random Effects Model)
Since then...

- RENAL-AF trial
  - 1st RCT to **randomize apixaban** (n=82) vs **warfarin** (n=72) to ESRD-HD patients with AF and CHA2DS2-VASc ≥ 2
    - 71% of apixaban users were on 5 mg BID (n=82); TTR 44.3%
    - Median CHA2DS2-VASc score 4, 21% with previous bleed, 19% previous stroke, 40% on concomitant aspirin
  - Apixaban vs warfarin outcomes
    - **Similar** rates of bleeding and stroke at 1 year
  - Trial **stopped early** due to loss of funding (target n was 760)

More forthcoming...

• AXADIA-AFNET 8 study (ongoing)
  - Randomize ESRD-HD patients with AF to **apixaban to warfarin**; aiming for n of 222 and follow-up of 24 months
  - Primary outcome is a composite of major or clinically relevant, nonmajor bleeding episodes or death
  - Secondary outcome is rate of thromboembolic events

• AVKDIAL study (ongoing)
  - Randomize ESRD-HD patients with AF to **warfarin to no anticoagulation**; aiming for n of 855
  - Primary outcome is a composite of bleeding and thrombotic events

AXADIA (ClinicalTrials.gov: NCT02933697)
Alternative to Pharmacologic Stroke Prevention?

- >90% of thrombus accumulation occurs in the LAA
- Left Atrial Appendage (LAA) occlusion – e.g. Watchman Device
  - PROTECT-AF study in nonvalvular AF (n=707)
    - 2/3s had CHADS2 score of 1-2; 2.3 year follow up
    - Noninferior to warfarin for primary composite (stroke, systemic embolism, and all-cause mortality) (RR 0.62, 95% CI 0.35-1.25)
    - No difference in ischemic stroke (RR 1.30, 95% CI 0.66–3.60)
    - Rates of hemorrhagic stroke were lower (RR 0.09, 95% CI 0-0.45)
  - For CKD - observational data suggest that LAA occlusion device may be an option, but need prospective RCTs
Conclusion

• CKD/ESRD patients have both a high bleeding risk and stroke/thromboembolic risk, but excluded from RCTs

• **Limited** high-quality data
  
  • **Inconsistent** definitions of bleeding, stroke, etc.
  
  • High heterogeneity among study populations; **different** patient risks for thromboembolism/stroke and bleeding

  • **Not typically assessed/reported:** TTR, medication adherence, body weight and Scr, drug interactions, use of antiplatelets/ outcomes

• Must carry out **individualized risk assessment** for each patient; reevaluate risks vs benefits periodically
Conclusion (con’t)

• Based on available evidence, if the decision is to anticoagulate...
  
  • Likely not appropriate to use “warfarin” due to increased bleeding, stroke, and death
  
  • Dabigatran shouldn’t be used in ESRD due to increased risk of hemorrhagic death; no data for edoxaban in ESRD; may use rivaroxaban in ESRD cautiously
  
  • Apixaban has the most data on efficacy and safety in CKD/ESRD
    
    • Reduction in stroke, bleeding, and mortality compared to warfarin
    
    • Use 5 mg vs 2.5 mg if patients qualify due to possible reduction in stroke and mortality
    
    • Mortality benefits may be seen even compared to no anticoagulation
  
  • Need large RCTs to characterize the net clinical benefit of anticoagulation in this high-risk patient group
Post-Test

1. Which of the following does NOT describe one of the inherent risks in patients with end-stage renal disease?

   A. Hyperphosphatemia increasing risk of stroke
   B. Activation of the renin-angiotensin-aldosterone system, which increases risk of atrial fibrillation
   C. Uremic platelet impairment increasing risk of bleeding
   D. Frequent heparin exposure increasing risk of bleeding
   E. Vitamin K deficiency due to dialysis, which increases risk of bleeding
1. Which of the following does NOT describe one of the inherent risks in patients with end-stage renal disease?

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Post-Test

2. Which of the following is INCORRECT regarding calciphylaxis/calcification and the matrix G1a protein?

A. Patients with end-stage renal disease have a baseline risk for calcification

B. Matrix G1a protein is an endogenous activator of calcification

C. Warfarin inhibits matrix G1a protein

D. Patients with normal renal function can develop calciphylaxis on warfarin

E. Calciphylaxis presents as severe pain and ischemic events
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E. Calciphylaxis presents as severe pain and ischemic events
3. Which of the following anticoagulants should NOT be used in patients with nonvalvular atrial fibrillation and end-stage renal disease, due to higher risk for hemorrhagic death?

A. Apixaban
B. Enoxaparin
C. Rivaroxaban
D. Dabigatran
E. Betrixaban
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A. Apixaban
B. Enoxaparin
C. Rivaroxaban
D. Dabigatran
E. Betrixaban
Post-Test

4. Apixaban 5 mg po BID will be started for stroke prevention in a 74-year-old patient with end-stage renal disease (ESRD) on hemodialysis (HD) and atrial fibrillation. Weight 74 kg, height 174 cm. Which of the following is INCORRECT regarding apixaban?

A. Apixaban undergoes 85% renal excretion as active compounds
B. Apixaban should be reduced to 2.5 mg po BID
C. Apixaban undergoes primarily biliary/intestinal excretion
D. Apixaban can be given regardless of the timing of hemodialysis session
E. Apixaban 5 mg po BID may reduce mortality compared to warfarin in patients with ESRD on HD
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Thank you!

Any questions?

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References


References


