An Overview of the use of DOACs in Advanced Age and End Stage Renal Disease
Presenter

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• No financial conflicts of interest
Objectives

- Discuss the use of anticoagulants in the frail or very old
- Discuss age-based thresholds of benefit with anticoagulation in AFib
- Review the use of DOACs in end-stage kidney disease
DOACs are commonly prescribed

- Now exceed warfarin as the most commonly prescribed oral anticoagulants
- May have more favorable efficacy and safety profiles than VKAs
Nursing Home Patients with AFib, 2011 - 2016

- Warfarin use declining
- DOAC use increasing
  - Half received standard doses, half lowered doses
  - Apixaban the most common DOAC (54%), followed by rivaroxaban (36%)

Alculsky M et al., JHA, 2019
Anticoagulation in Older Adults

- Guidelines currently recommend anticoagulation for AFib for all patients ≥ 75 years old

Among people with AFib ≥ 65 years, 82% had at least 1 geriatric syndrome
Is Anticoagulation Always Appropriate?

• 15,217 nursing home residents with atrial fibrillation and advanced dementia: 33% were on anticoagulants during their last 6 months of life

• All patients had advanced dementia and were dependent in their ADLs
  • Age 80-89 → 51% on anticoagulants
  • Age ≥ 90 → 34% on anticoagulants

• 26% of people on hospice were prescribed anticoagulants

Ouellet GM et al., JAMA Intern Med, 2021
Anticoagulation Continued at the End of Life

- A case series of 214 patients with metastatic cancer and cancer-associated venous thrombosis
- Anticoagulation commonly continued
  - 50% continued LMWH until death; 11% until within 7 days of death
- Bleeding occurred in 7% of people who continued anticoagulants

Noble S et al., BMJ Support Palliat Care 2019
How Old is Too Old for Anticoagulation?

- Study of 14,946 patients with AFib, 75+ years
- Markov model of net gain in Quality Adjusted Life Years with different anticoagulant treatment strategies
- Accounted for life expectancy
- QALY of ≤ 0.1 considered minimal benefit
  - Equivalent to changing from regular to high dose statin in a patient with stable coronary artery disease

Shah SJ et al., Circ: CV Qual Outcomes 2019
Quality-Adjusted Life Years Gained with Anticoagulation

Warfarin

Apixaban

Shah SJ et al., Circ: CV Qual Outcomes 2019
Take Home Points

• With advancing age, there are diminishing returns from anticoagulants
  • Competing risk of death from other causes
• Anticoagulants may have minimal benefits after certain ages:
  • After age 87 years for warfarin, age 92 for apixaban
• Important to engage patients in shared decision-making
The Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) Trial

- Randomized, double-blind, placebo controlled trial
  - 184 hospitals in Japan

- Participants:
  - Older adults (age 80+ years) with AFib and high stroke risk ($\text{CHADS}_2 \geq 2$) who were considered “inappropriate candidates for standard anticoagulation”
  - CrCl 15-30 ml/min, history of bleeding, low body weight

- Randomized to lower-dose (15mg) edoxaban vs. placebo

Okumura et al., NEJM 2020
ELDERCARE-AF Trial

- 492 patients randomized to edoxaban, 492 to placebo
  - Mean age = 86.6 years
  - Mean CrCl = 36.3 ml/min
  - 40.6% categorized as frail
  - 43% had received anticoagulants in the past

- Median duration = 466 days

- 30% did not complete the full study
  - 156 (16%) withdrew before trial completion
  - 135 (14%) died prior to completion

Okumura et al., NEJM 2020
**Stroke/Systemic Embolism**

Hazard ratio, 0.34 (95% CI, 0.19–0.61)  
P<0.001

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<th></th>
<th>Edoxaban</th>
<th>Placebo</th>
<th>HR</th>
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<tbody>
<tr>
<td>Stroke</td>
<td>2.3%</td>
<td>6.7%</td>
<td>0.34 [0.19-0.6]</td>
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<tr>
<td>Death</td>
<td>9.9%</td>
<td>10.2%</td>
<td>0.97 [0.7-1.4]</td>
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No. at Risk

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<tr>
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<th>Edoxaban, 15 mg</th>
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<tr>
<td>Months since Randomization</td>
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<td>36</td>
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Okumura et al., NEJM 2020
Major Bleeding

Hazard ratio, 1.87 (95% CI, 0.90–3.89) P=0.09

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<th>Edoxaban</th>
<th>Placebo</th>
<th>HR</th>
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<tbody>
<tr>
<td>Major bleeding</td>
<td>3.3%</td>
<td>1.8%</td>
<td>1.87 [0.9-3.9]</td>
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<tr>
<td>Clinically relevant non major</td>
<td>14.5%</td>
<td>8.9%</td>
<td>1.6 [1.1-2.3]</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>45%</td>
<td>38%</td>
<td>1.2 [0.96-1.5]</td>
</tr>
<tr>
<td>All Bleeding</td>
<td>63%</td>
<td>45%</td>
<td>1.35 [1.1-1.6]</td>
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Take Home Points

• Lower dose edoxaban reduced the risk of stroke in AFib in patients not considered appropriate for standard dose anticoagulation
• Many patients stop treatment
• Associated with increased bleeding risk, although major bleeding rates were modest
Moving on to End Stage Renal Disease...
Anticoagulation and End Stage Kidney Disease

• Use of anticoagulants for patients on hemodialysis (HD) is controversial
  • Higher risk for thromboembolism AND bleeding
Hemodialysis – Anticoagulate or Not?

- Systematic review and meta-analysis of warfarin for AFib in HD
- 47,280 patients across 15 studies

Randhawa MS, et al., JAMA Netw Open 2020
DOACs and End Stage Kidney Disease

• Patients with ESRD were excluded from pivotal clinical trials of DOACs
• Nevertheless, DOAC use has been increasing over time
  • 25,523 patients with AFib and ESRD on dialysis
  • By 2015, 27% of new anticoagulant prescriptions were for apixaban
• Limited high-quality evidence on DOACs in ESRD

Siontis KC et al., Circulation 2018
Apixaban in ESRD/dialysis

• Pharmacokinetic study of 8 patients on HD and 8 healthy controls (mean age 47)
  • Patients given a single 5 mg dose of apixaban
  • Serial measures of apixaban concentration
  • Apixaban in ESRD had modestly higher AUC (36%)
  • FDA approved apixaban in HD without dose adjustment

Wang et al., J Clin Pharm 2016
Apixaban in ESRD/dialysis

- Pharmacokinetic study of 7 patients on HD
  - Compared steady-state apixaban (2.5mg BID vs 5mg BID for 8 days)
  - Apixaban concentration accumulated over time

- 2.5mg BID $\rightarrow$ ~median therapeutic levels in clinical trials
- 5mg BID $\rightarrow$ supratherapeutic concentrations

Mavrakanas et al., JASN 2017
Hemodialysis - Warfarin vs. DOAC?

• Valkyrie study
  • 132 patients on HD randomized to VKA vs. rivaroxaban 10 mg daily
  • Rivaroxaban had favorable net clinical benefit over VKA

• RENAL-AF study (preliminary)
  • 154 patients on HD randomized to warfarin vs. apixaban (mostly 5 mg BID)
  • No significant difference in outcomes
    • Bleeding: 26% vs. 22% (p>0.05)
    • Stroke: 2.8% vs. 2.4%
Hemodialysis - Warfarin vs. DOAC?

- Observational study of 29,997 patients on HD taking warfarin, rivaroxaban, or dabigatran
  - Rivaroxaban and dabigatran associated with worse outcomes (hospitalization or death from bleeding)

- Observational study of 6744 patients with CKD/HD taking warfarin or rivaroxaban
  - No difference in stroke, but rivaroxaban had lower bleeding risk

Chan KE et al., Circulation 2015
Coleman CI et al., Am J Med 2019
Medicare Patients with AFib on Dialysis

- 2,351 people on apixaban vs. 23,172 on warfarin
- Apixaban at 5mg BID associated with lower risk of stroke
  - VS. apixaban 2.5 BID: HR 0.61 [0.37-0.98]
  - VS. warfarin: HR 0.64 [0.42-0.97]

Apixaban had similar efficacy to warfarin RR=0.88 [0.7-1.1]

...and lower bleeding risk RR=0.72 [0.6-0.9]
Take Home Points

• The net benefits of anticoagulation for people with end stage kidney disease are still unclear

• The preferred anticoagulant or dose to use in HD also unclear
  • Conflicting observational data with rivaroxaban
  • Some evidence for a benefit with apixaban over warfarin
View from Mt. Davidson, Miraloma Park neighborhood
Session Recap

• Anticoagulants are commonly continued in nursing home patients, people with advanced dementia, and those nearing the end of life
• May be reasonable to discontinue anticoagulants after a certain age
• Low-dose edoxaban may be an option for elders with AFib
• The net benefits of anticoagulation for people with end stage kidney disease are still unclear
• The optimal choice and dose of anticoagulant in dialysis not clear
  • Some studies support the use of DOACs in HD
THANK YOU

View of Golden Gate Park from UCSF Medical Center