Managing clinical challenges in patients with NVAF

- Pleiotropic Effect of NOACs vs. VKA, especially on Vascular Protection

Hallym University Sacred Heart Hospital
Hong Euy Lim, M.D.
Comorbid of AF in stable CAD patients

- AF presented in 5-10% of patients with stable coronary artery disease (CAD) (varying according to comorbidities)

AF, atrial fibrillation; CAD, coronary artery disease.
Comorbid of CAD in AF patients

- High CAD prevalence of **18%~46.5%** in AF Patients

CAD, coronary artery disease; PCI, percutaneous coronary intervention.

PLoS ONE 6(9): e24964
Incidence of CAD in > 70 years of AF was even 41%
Platelets: Role in Thrombosis

High Flow

- Fibrin
- RBCs
- Platelets

Slow Flow

- Fibrin
- RBCs
- Platelets

White Thrombus

Coagulation Thrombus

RBCs, red blood cells.
What is the optimal treatment for AF and CAD?

OAC alone vs. OAC + Antiplatelet strategy

<table>
<thead>
<tr>
<th>Major complications in AF</th>
<th>Major clinical events associated with CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and SEE</td>
<td>MI and CV death</td>
</tr>
</tbody>
</table>

More effective for moderate-to-high risk AF to prevent stroke and SEE.

The standard management for CAD to reduce the risk of coronary events.

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CAD, coronary artery disease; AF, atrial fibrillation; SEE, systemic embolic events; MI, myocardial infarction; CV, cardiovascular; OAC, oral anticoagulation. PLoS ONE 6(9): e24964; http://www.acc.org/latest-in-cardiology/articles/2014/07/18/15/34/antithrombotic-therapy-for-patients-with-both-stable-cad-and-afib
AF Trials
Warfarin (Vitamin K OAC) vs. Anti-platelets

Category
Warfarin vs Placebo
Warfarin vs Warfarin low dose
Warfarin vs Aspirin
Warfarin vs Aspirin + Clopidogrel

Meta-analysis of ischemic stroke
or systemic embolism

Favors warfarin
Favors other treatment

JAMA 2001;286:2870
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)

- Patients with an indication for oral anticoagulation undergoing PCI:

  - Concerns about ischemic risk prevailing:
    - 1 mo. Triple Therapy
    - 1 mo. Triple Therapy
    - Dual Therapy up to 6 mo.
    - Dual Therapy up to 12 mo.

  - Concerns about bleeding risk prevailing:
    - Dual Therapy up to 12 mo.
    - OAC alone

- Time from treatment initiation:
  - 1 mo.
  - 3 mo.
  - 6 mo.
  - 12 mo.
  - Beyond 12 mo.

- A = Aspirin
- C = Clopidogrel
- O = Oral anticoagulation

2017 ESC Guideline

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
<table>
<thead>
<tr>
<th>Recent ACS/CS</th>
<th>ESC guideline [36]</th>
<th>ACC/AHA guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding risk low:</strong></td>
<td>TT for up to 6 months [IIaB], followed by OAC + platelet inhibitor (aspirin or clopidogrel) for up to 6 months [IIaA]</td>
<td>NSTE-ACS [42]: The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding [IbC]. STEMI [43]: The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding [IbC]. DES [25]: In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), discontinuation of P2Y12 inhibitor therapy after 6 months may be reasonable [IIbC].</td>
</tr>
<tr>
<td><strong>Bleeding risk high:</strong></td>
<td>TT for 1 month [IIaB], followed by OAC + platelet inhibitor (aspirin or clopidogrel) for up to 11 months [IIaA]</td>
<td>DES [25]: In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable. [IIbC]</td>
</tr>
<tr>
<td><strong>Elective CS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding risk low:</strong></td>
<td>TT for 1 month [IIaB], followed by OAC + platelet inhibitor (aspirin or clopidogrel) for up to 11 months [IIaA].</td>
<td>OAC monotherapy [IIb]</td>
</tr>
<tr>
<td><strong>Bleeding risk high:</strong></td>
<td>TT for 1 month [IIaB], followed by OAC + platelet inhibitor for up to 11 months (aspirin or clopidogrel) [IIaA]. Dual therapy with OAC + clopidogrel for up to 12 months [IIaA] is an alternative if the bleeding risk outweighs the ischemic risk</td>
<td>Warfarin should be administered [IA] (Note: Patients receiving low-dose aspirin for atherosclerosis should continue to receive it) [44,45].</td>
</tr>
</tbody>
</table>

Stable CAD (one year after CS/ACS)

Squared brackets indicate class of recommendation and level of evidence as defined by the guidelines.

*TT can be extended for up to 6 months if the ischemic risk is increased (e.g. due to anatomical/procedural features).

Effect of long-term treatment of VKA (Warfarin) on vascular structure
Differential pathology and clinical impact of valvular vs. vascular calcification.

Cardiovascular calcification is an active and degenerative bone-like process affecting the cardiovascular tissues. Both vessels and valves show an athero-inflammatory background and, despite the commonalities and overlap of several risk factors (such as aging, hyperlipidaemia or kidney disease), both atherosclerosis and calcific VHD are two independent pathologic entities. The biological progression of the disease, tissue characteristics and clinical impact stand those differences. The result is the independent plaque rupture primary outcome found in the progression of VHD. An increased stiffness or sclerosis induces an increased aortic pulse wave, triggering hypertension, and a reduction in coronary perfusion. Besides, the pressure overload caused by a sclerotic pre-stadium and observed in the progression of the VHD leads to LV structural and hemodynamic changes. Symptomatology onset and calcification burden are poor prognosis predictors associated with multiple adverse cardiovascular complications, such as left ventricular hypertrophy (LVH), aortic valve stenosis, congestive heart failure (HF), ascending aorta aneurysm, myocardial infarction (MI), and peripheral vascular disease (PVD).
Medial and Intimal Vascular Calcification

Calcification Promoters
- Dexamethasone
- PTH 7-34
- TNF-α
- Oncostatin
- Klotho-/-

Calcification Inhibitors
- Fetuin
- BMP7
- Osteoprotegerin
- Collagen IV
- PTHrP
- Osteopontin
- MGP
- Pyrophosphate

Key Players
- BMP2
- CBfa1
- Osteocalcin
- Ox. Str.
- P
- Collagen I
- Fibronectin
- ALP
- Leptin
- Wnt
- LDLox
- Vit D3
- Ca
**MGP prevents Medial and Intimal Calcification**

**MGP** (Matrix G1 Protein non-carboxylated) prevents Medial and Intimal Calcification.

MGP is the main inhibitor of vascular calcification, and vitamin K is required for full activity of MGP.

Pleiotropic effect of NOACs on vascular structure
Figure 4: Overview of pathophysiology of atherothrombosis and the role of factor Xa and thrombin. Dysregulation of endothelial cells forms the basis for the initial development of atherosclerosis and plaques develop through the accumulation of lipid deposits and foam cells. Increased expression of adhesion molecules and release of pro-inflammatory cytokines by activated endothelial cells promotes recruitment of blood cells. The sustained inflammation reduces plaque stability and promotes plaque rupture. Both factor Xa and thrombin contribute to the development of atherothrombosis. F, factor; PAR, proteinase-activated receptor; SMC, smooth muscle cell.
In pre-clinical study, it was found that factor Xa inhibitors may have anti-inflammatory effects by inhibiting PAR2-mediated pro-inflammatory signaling pathway. However, further studies are needed to confirm the mechanisms responsible for these renal outcomes of NOAC.

Randomized trial of Rivaroxaban vs. warfarin in the evaluation of progression of coronary atherosclerosis

Am Heart J 2018;127–130
Study Design

- Enrolled total 120 NVAF* patients from April 2015 to May 2016
- Randomized to Warfarin or Rivaroxaban group followed for 52 weeks at Harbor UCLA Medical Center
- 97 patients completed the 1-year protocol with baseline and follow-up CCTA* images
- Excluded: Segments with stents, Patients with coronary artery bypass graft from the analysis

- 71% male, mean age 61.3 years
- Warfarin N=51
- Rivaroxaban N=46

NVAF: non valvular atrial fibrillation; CCTA: coronary computed tomography angiography
Am Heart J 2018;127 - 130.
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n = 51)</th>
<th>Rivaroxaban (n = 46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.2 ± 11.7</td>
<td>62.5 ± 10.5</td>
<td>0.294</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>39 (76.5%)</td>
<td>30 (65.2%)</td>
<td>0.222</td>
</tr>
<tr>
<td>BMI*, kg/m²</td>
<td>32.3 ± 7.6</td>
<td>33.6 ± 7.2</td>
<td>0.401</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>49 (96.1%)</td>
<td>40 (87.0%)</td>
<td>0.145</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>22 (43.1%)</td>
<td>14 (30.4%)</td>
<td>0.196</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>37 (72.5%)</td>
<td>31 (67.4%)</td>
<td>0.580</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>4 (7.8%)</td>
<td>6 (13%)</td>
<td>0.510</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>31 (60.8%)</td>
<td>30 (65.2%)</td>
<td>0.652</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>21 (41.2%)</td>
<td>23 (50.0%)</td>
<td>0.383</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3 ± 1.3</td>
<td>1.1 ± 0.8</td>
<td>0.289</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>145.9 ± 40.7</td>
<td>154.3 ± 42.5</td>
<td>0.385</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>41.2 ± 11.6</td>
<td>41.8 ± 10.7</td>
<td>0.786</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>78.8 ± 42.8</td>
<td>71.6 ± 45.8</td>
<td>0.426</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>136.9 ± 87.4</td>
<td>171.7 ± 102.6</td>
<td>0.075</td>
</tr>
<tr>
<td>INR*</td>
<td>2.52 ± 0.98</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

BMI: body mass index INR: international normalized ratio; Am Heart J 2018;127–130.
## Results

Difference in plaque volumes between baseline and follow-up between Warfarin and Rivaroxaban groups

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n = 51)</th>
<th>Rivaroxaban (n = 46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Absolute PV</em> change (mm³)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total *</td>
<td>40.5 (9.6-97.3)</td>
<td>26.3 (4.5-61.5)</td>
<td>.123</td>
</tr>
<tr>
<td>Noncalcified *</td>
<td>30.1 (2.3-72.3)</td>
<td>20.1 (0.3-45.5)</td>
<td>.259</td>
</tr>
<tr>
<td>**Fibrous ***</td>
<td>13.9 (0-48.4)</td>
<td>0.2 (−13.4 to 29.3)</td>
<td><strong>.035</strong></td>
</tr>
<tr>
<td>Fibrous fatty *</td>
<td>2.9 (0-23.6)</td>
<td>9.8 (0-26.8)</td>
<td>.582</td>
</tr>
<tr>
<td>Low attenuation *</td>
<td>0.2 (0-4.2)</td>
<td>1.2 (−0.2 to 10.6)</td>
<td>.475</td>
</tr>
<tr>
<td>Calcified *</td>
<td>3.9 (0-29.2)</td>
<td>0.8 (0-9.8)</td>
<td>.220</td>
</tr>
<tr>
<td><strong>Normalized PV change (mm³)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total *</td>
<td>51.1 (12.1-94.7)</td>
<td>26.9 (5.4-62.8)</td>
<td>.120</td>
</tr>
<tr>
<td>Noncalcified *</td>
<td>30.1 (2.2-74.6)</td>
<td>19.0 (0.2-57.5)</td>
<td>.236</td>
</tr>
<tr>
<td>**Fibrous ***</td>
<td>14.6 (0-55.0)</td>
<td>0.2 (−14.5 to 26.3)</td>
<td><strong>.035</strong></td>
</tr>
<tr>
<td>Fibrous fatty *</td>
<td>3.6 (0-19.3)</td>
<td>8.0 (0-27.3)</td>
<td>.633</td>
</tr>
<tr>
<td>Low attenuation *</td>
<td>0.2 (0-4.4)</td>
<td>1.1 (−0.2 to 10.2)</td>
<td>.460</td>
</tr>
<tr>
<td>Calcified *</td>
<td>3.6 (0-29.0)</td>
<td>0.8 (0-12.0)</td>
<td>.203</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range)

PV: plaque volume;
Am Heart J 2018;127–130.
Risk of Myocardial Infarction in Anticoagulated Patients With Atrial Fibrillation

Christina Ji-Young Lee, MD,\textsuperscript{a,b} Thomas Alexander Gerds, PhD,\textsuperscript{c,d} Nicholas Carlson, MD, PhD,\textsuperscript{c,d} Anders Nissen Bonde, MD,\textsuperscript{1} Gunnar Hilmar Gislason, MD, PhD,\textsuperscript{b,d} Morten Lamberts, MD, PhD,\textsuperscript{1} Jonas Bjerre-Olesen, MD, PhD,\textsuperscript{b} Jannik Langtved Pallisgaard, MD, PhD,\textsuperscript{1} Morten Lock Hansen, MD, PhD,\textsuperscript{b} Christian Torp-Pedersen, MD, DMS\textsuperscript{a}

\textbf{ABSTRACT}

\textbf{BACKGROUND} Evidence is conflicting as to the efficacy of direct oral anticoagulation (DOAC) and vitamin K antagonist (VKA) for prevention of myocardial infarction (MI).

\textbf{OBJECTIVES} This study aimed to investigate the risk of MI associated with the use of apixaban, dabigatran, rivaroxaban, and VKA in patients with atrial fibrillation.

\textbf{METHODS} Patients with atrial fibrillation were identified using Danish health care registers and stratified by initial oral anticoagulant treatment. Standardized absolute 1-year risks were estimated based on Cox regression for hazard rates of MI hospitalizations and mortality. Reported were absolute risks separately for the oral anticoagulation treatments and standardized to the characteristics of the study population.

\textbf{RESULTS} Of the 31,739 patients included (median age, 74 years; 47\% females), the standardized 1-year risk of MI for VKA was 1.6\% (95\% confidence interval [CI]: 1.3 to 1.8), apixaban was 1.2\% (95\% CI: 0.9 to 1.4), dabigatran was 1.2\% (95\% CI: 1.0 to 1.5), and rivaroxaban was 1.1\% (95\% CI: 0.8 to 1.3). No significant risk differences were observed in the standardized 1-year risks of MI among the DOACs: dabigatran versus apixaban (0.04\%; 95\% CI: −0.3 to 0.4), rivaroxaban versus apixaban (0.1\%; 95\% CI: −0.4 to 0.3), and rivaroxaban versus dabigatran (−0.1\%; 95\% CI: −0.5 to 0.2). The risk differences for DOACs versus VKA were all significant: −0.4\% (95\% CI: −0.7 to −0.1) for apixaban, −0.4\% (95\% CI: −0.7 to −0.03) for dabigatran, and −0.5\% (95\% CI: −0.8 to −0.2) for rivaroxaban.

\textbf{CONCLUSIONS} No significant risk differences of MI were found in the direct comparisons of DOACs, and DOACs were all associated with a significant risk reduction of MI compared with VKA. (J Am Coll Cardiol 2018;72:17-26) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.
FIGURE 1 Selection of Study Cohort

Oral anticoagulant-naïve patients with atrial fibrillation
January 1, 2013 — June 30, 2016
n = 34,755

Valvular atrial fibrillation
(n = 805)
Age <30 or >100 years
(n = 70)
Total hip or knee arthroplastic <5 weeks
(n = 340)
Chronic kidney disease
(n = 1,801)

Total excluded, n = 3,016

Study population, n = 31,739

VKA
n = 8,913
(28%)

Apixaban
n = 8,611
(27%)

Dabigatran
n = 7,377
(23%)

Rivaroxaban
n = 6,838
(22%)
In patients with nonvalvular atrial fibrillation:

What is the risk of MI when treated with the following oral anticoagulants?

- Apixaban
- Dabigatran
- Rivaroxaban
- Vitamin K Antagonist

NOACs can prevent progressive renal dysfunction

Adapted from Böhm M et al, J Am Coll Cardiol 2015;65:2481–2493
The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: A nationwide cohort study in Taiwan

Chan YH et al. *Int J Cardiol.* 2018 Aug 15;265:83-89
Result

• Three NOACs were all associated with a significantly lower risk of AKI compared with warfarin for both CKD-free and CKD cohort

hazard ratio, [95% confidential interval]
• 0.65, [0.60–0.72] for apixaban
• 0.68, [0.64–0.74] for dabigatran
• 0.73, [0.68–0.79] for rivaroxaban

and CKD cohorts
• 0.50, [0.45–0.56] for apixaban
• 0.54, [0.49–0.59] for dabigatran
• 0.53, [0.49–0.58] for rivaroxaban

AKI, acute kidney injury; CKD, chronic kidney disease; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation
Class Effect of NOACs?
Rivaroxaban was associated with significantly less reduction in CrCl vs. warfarin.

ROCKET AF (n=12,612)¹
CrCl changes over 21 months²
Median CrCl at baseline¹ 68 mL/min

ARISTOTLE (n=14,913)³
eGFR* changes over 12 months
eGFR at baseline NR

RE-LY (n=16,490)⁴
eGFR* changes over 30 months
Mean eGFR at baseline⁴ 66 mL/min

Mean change in CrCl (mL/min)
Rivaroxaban: -3.5 vs. Warfarin: -4.3

Mean change in eGFR (mL/min)
Apixaban: -1.42 vs. Warfarin: -0.92

Dabigatran 110 mg: -2.57 vs. Dabigatran 150 mg: -2.46 vs. Warfarin: -3.68

Favours rivaroxaban
Favours warfarin
Favours dabigatran

Renal Outcomes in Anticoagulated Patients with AF

Yao X et al, J Am Coll Cardiol 2017;70:2621–2632
### Patient Population

- 9,769 adult patients (≥18 years of age) with NVAF who received an OAC between 1 October 2010 and 30 April 2016

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Patients were required to have ≥12 months of continuous enrolment in both medical and pharmacy insurance plans before treatment initiation (defined as the baseline period)</td>
<td>◆ Warfarin-experienced patients</td>
</tr>
<tr>
<td>◆ Patients with linked serum creatinine results at both baseline and follow-up</td>
<td>◆ Patients with valvular AF, kidney failure and other indications for NOAC use</td>
</tr>
<tr>
<td>◆ New users of OACs</td>
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</tbody>
</table>

Follow-up started from the day after treatment initiation until end of treatment, defined as the earliest date of the following: discontinuation or switch of index medication, end of enrolment in health insurance plans or end of the study period.
Renal Outcomes – All NOACs

- At 2 years, the cumulative risk was
  - 24.4% for $\geq 30\%$ decline in eGFR
  - 4.0%, doubling of serum creatinine
  - 14.8% for AKI
  - 1.7% for kidney failure

- Compared with warfarin, the use of NOACs was associated with reduced risks of $\geq 30\%$ decline in eGFR, doubling of serum creatinine and acute kidney disease

<table>
<thead>
<tr>
<th>Renal outcomes</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 30%$ decline in eGFR</td>
<td>0.77 (0.66–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.62 (0.40–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>0.68 (0.58–0.81)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant

Real-world Evidence Confirms that Renal Function is Maintained in Patients Receiving Rivaroxaban

<table>
<thead>
<tr>
<th>Renal outcome</th>
<th>No. of events</th>
<th>HR</th>
<th>HR (95% CI)</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong> (N=1,883)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% decline in eGFR</td>
<td>166</td>
<td>0.88</td>
<td></td>
<td>-12% (p=ns)</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>20</td>
<td>0.80</td>
<td></td>
<td>-20% (p=ns)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>131</td>
<td>0.84</td>
<td></td>
<td>-16% (p=ns)</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>13</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong> (N=1,216)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% decline in eGFR</td>
<td>103</td>
<td>0.72</td>
<td></td>
<td>-28% (p=0.01)</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>12</td>
<td>0.64</td>
<td></td>
<td>-36% (p=ns)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>63</td>
<td>0.55</td>
<td></td>
<td>-45% (p&lt;0.001)</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>4</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong> (N=2,485)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% decline in eGFR</td>
<td>208</td>
<td>0.73</td>
<td></td>
<td>-27% (p&lt;0.001)</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>21</td>
<td>0.46</td>
<td></td>
<td>-54% (p&lt;0.01)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>145</td>
<td>0.69</td>
<td></td>
<td>-31% (p&lt;0.001)</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>14</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are not intended for direct comparison between NOACs, therefore it should be carefully interpreted.
AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRR, relative risk reduction
Comparative Safety and Effectiveness of NOACs vs. Phenprocoumon in Patients with NVAF and Renal Disease – Results from the RELOADED Study

NOAC: non-VKA oral anticoagulant; NVAF: Non-Valvular Atrial Fibrillation

## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Phenprocoumon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>N=22,339</td>
<td>N=16,201</td>
<td>N=2,828</td>
<td>N=23,552</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>N=5,121</td>
<td>N=4,750</td>
<td>N=682</td>
<td>N=7,289</td>
</tr>
<tr>
<td>Mean age (SD*)</td>
<td>70.7 (12.0)</td>
<td>73.6 (11.6)</td>
<td>72.1 (11.4)</td>
<td>74.1 (9.9)</td>
</tr>
<tr>
<td></td>
<td>75.9 (9.4)</td>
<td>78.5 (9.1)</td>
<td>77.0 (9.2)</td>
<td>77.2 (8.4)</td>
</tr>
<tr>
<td>Women</td>
<td>41.9%</td>
<td>43.9%</td>
<td>40.0%</td>
<td>41.9%</td>
</tr>
<tr>
<td>Reduced dose</td>
<td>24.5%</td>
<td>33.4%</td>
<td>23.0%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>40.4%</td>
<td>44.1%</td>
<td>38.3%</td>
<td>39.8%</td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc (SD)</td>
<td>3.6 (1.9)</td>
<td>4.1 (1.9)</td>
<td>3.7 (1.8)</td>
<td>4.1 (1.7)</td>
</tr>
<tr>
<td>Mean modified HAS-BLED (SD)</td>
<td>2.5 (1.2)</td>
<td>2.8 (1.2)</td>
<td>2.6 (1.2)</td>
<td>2.8 (1.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31.3%</td>
<td>33.6%</td>
<td>30.6%</td>
<td>48.7%</td>
</tr>
<tr>
<td></td>
<td>48.2%</td>
<td>49.1%</td>
<td>48.7%</td>
<td>50.3%</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>37.0%</td>
<td>39.4%</td>
<td>34.7%</td>
<td>46.5%</td>
</tr>
<tr>
<td></td>
<td>51.3%</td>
<td>51.9%</td>
<td>47.7%</td>
<td>59.2%</td>
</tr>
<tr>
<td>History of IS*/TIA*/SE*</td>
<td>13.4%</td>
<td>21.1%</td>
<td>11.8%</td>
<td>15.6%</td>
</tr>
<tr>
<td></td>
<td>18.5%</td>
<td>27.2%</td>
<td>15.8%</td>
<td>19.7%</td>
</tr>
<tr>
<td>History of major bleeding</td>
<td>3.6%</td>
<td>4.3%</td>
<td>2.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td>6.6%</td>
<td>7.3%</td>
<td>5.3%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Malignant diseases</td>
<td>15.2%</td>
<td>16.6%</td>
<td>15.3%</td>
<td>16.0%</td>
</tr>
<tr>
<td></td>
<td>20.6%</td>
<td>22.0%</td>
<td>21.7%</td>
<td>20.2%</td>
</tr>
</tbody>
</table>

SD: standard deviation; IS: ischemic stroke; TIA: transient ischemic attack; SE: systemic embolism

Results

Cox Proportional-Hazard Regression Analysis-adjusted for more than 100 selected baseline covariates

NOAC vs. Phenprocoumon

ESRD/Dialysis 0.34 (0.23; 0.51) 0.67 (0.49; 0.92)
ESRD/Dialysis renal 0.27 (0.16; 0.43) 0.43 (0.29; 0.63)
AKI 0.78 (0.66; 1.00) 0.9 (0.69; 1.17)
AKI renal 0.77 (0.58; 1.01) 0.99 (0.8; 1.22)

Favors Rivaroxaban
Favors Phenprocoumon
Favors Apixaban
Favors Phenprocoumon

AKI: acute kidney injury; ESRD: end-stage renal disease; ICH: intracranial hemorrhage; SE: systemic embolism
Take Home Messages

Compared with VKA,

◆ **NOACs** have revealed a **significant risk reduction of AMI and AKI** in real world evidences.

◆ **Rivaroxaban** prevented the **progression of calcified plaque burden** in NVAF patients with stable coronary artery disease.

◆ **Rivaroxaban** prevented the **renal function decline over time**, however, Apixaban did not show any difference in real world evidences.

OD, once daily; NVAF, non-valvular atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury
Thank You For Your Attention!