Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Atrial Fibrillation

Individual Patient Data from the Pivotal Randomized Trials

Anthony P Carnicelli, MD
On behalf of the COMBINE AF Investigators

(COllaboration between Multiple institutions to Better Investigate Non-vitamin K antagonist oral anticoagulant use in Atrial Fibrillation)
Declaration of Interest

• Grant funding from National Institutes of Health T32 Training Grant

• RE-LY was funded by Boehringer Ingelheim

• ROCKET AF was funded by Johnson & Johnson and Bayer

• ARISTOTLE and AVERROES were funded by Bristol-Myers Squibb and Pfizer

• ENGAGE AF-TIMI 48 was funded by Daiichi Sankyo
Background

RE-LY
- Completed 2009
- N=18,113
- Dabigatran 150mg
- Dabigatran 110mg
- Warfarin

ROCKET AF
- Completed 2010
- N=14,264
- Rivaroxaban (20/15mg)
- Warfarin

AVERROES
- Completed 2010
- N=5,599
- Apixaban (5/2.5mg)
- Aspirin alone

ARISTOTLE
- Completed 2011
- N=18,201
- Apixaban (5/2.5mg)
- Warfarin

ENGAGE AF-TIMI 48
- Completed 2013
- N=21,105
- Edoxaban 60/30mg
- Edoxaban 30/15mg
- Warfarin

FDA-labeled NOAC dose
- N=32,170

Non-FDA-labeled NOAC dose
- N=13,049

Dose adjusted warfarin
- N=29,272

Aspirin alone
- N=2,791

ESC Congress 2020
The Digital Experience


Connolly SJ et al. NEJM 2011; 364:806-17.
Giugliano RP et al. NEJM 2013; 369:2093-104.
Background

2014 study-level meta-analysis

NOAC use → Lower risk of stroke/systemic embolism, intracranial hemorrhage, all-cause death

Advantages of patient level data
- Proper handling of continuous covariates
- Evaluate treatment effect across sub-groups
- Analyze rare events and small subgroups
- Large numbers of events for risk models
- Conduct robust multivariable analyses

Objectives
- Compare pooled, FDA-labeled NOACs versus warfarin for relative efficacy, safety, and composite endpoints
- Test for treatment effect modification by continuous baseline covariates age, body weight, and creatinine clearance
Methods

COMBINE AF database
N=77,282

Exclude: AVERROES patients (N=5,599)

Patients enrolled in RE-LY, ROCKET AF, ARISTOTLE, or ENGAGE AF-TIMI 48
N=71,683 (92.8%)

Exclude: patients randomized to non-FDA-labeled NOAC regimen (i.e. dabigatran 110mg in RE-LY or edoxaban 30/15mg in ENGAGE AF-TIMI 48 (N=13,049)

Final study population
N=58,634 (75.9%)

Pooled NOACs
N=29,362 (38.0%)

Pooled warfarin
N=29,272 (37.9%)

Median follow up duration:
25.8 (18.5-32.2) months
58,541 patient-years
Statistical Analysis

• Outcomes
  • Stroke or systemic embolism
  • All-cause death
  • Net clinical outcome
    • Composite stroke, systemic embolism, major bleeding, all-cause death
  • Major bleeding (ISTH)
  • Intracranial bleeding
  • Gastrointestinal bleeding

• Treatment effect modification by continuous baseline covariates
  • Stratified Cox proportional hazards models with random effects including a covariate-by-treatment interaction
  • Interaction reported as change in hazard ratio per unit increase in baseline covariate
Kaplan-Meier Curves

Stroke/Systemic Embolism

- Hazard Ratio 0.80 (95% CI 0.71-0.90); p<0.001

All-Cause Death

- Hazard Ratio 0.89 (95% CI 0.84-0.94); p<0.001

Number at Risk (number of events)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
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<tbody>
<tr>
<td>Months</td>
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<td></td>
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<tr>
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<td>29229 (0)</td>
<td>29312 (0)</td>
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<td>28027 (336)</td>
<td>28256 (231)</td>
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<td>21907 (602)</td>
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<td>24</td>
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<td>30</td>
<td>8870 (1031)</td>
<td>9027 (837)</td>
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</table>

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<tbody>
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<td>Months</td>
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<td>24</td>
<td>15735 (1987)</td>
<td>15951 (1794)</td>
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<tr>
<td>30</td>
<td>9139 (2289)</td>
<td>9271 (2080)</td>
</tr>
</tbody>
</table>
Kaplan-Meier Curves

Major Bleeding

- **Warfarin**: Hazard Ratio 0.86 (95% CI 0.74-1.01); p=0.065
- **NOAC**: Hazard Ratio 0.86 (95% CI 0.74-1.01); p=0.065

Intracranial Bleeding

- **Warfarin**: Hazard Ratio 0.45 (95% CI 0.36-0.58); p<0.001
- **NOAC**: Hazard Ratio 0.45 (95% CI 0.36-0.58); p<0.001

**Number at Risk (number of events)**

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>NOAC</th>
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<tbody>
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<td>18382 (1311)</td>
<td>18258 (1117)</td>
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<tr>
<td>12618 (1555)</td>
<td>12577 (1321)</td>
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<td>7009 (1886)</td>
<td>7050 (1434)</td>
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**Number at Risk (number of events)**

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>NOAC</th>
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<tbody>
<tr>
<td>29187 (0)</td>
<td>29270 (0)</td>
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<td>25900 (132)</td>
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<td>23995 (219)</td>
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<td>18854 (306)</td>
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<td>13037 (369)</td>
<td>12986 (159)</td>
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<td>7299 (398)</td>
<td>7317 (179)</td>
</tr>
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</table>
Kaplan-Meier Curves

**Gastrointestinal Bleeding**

- **Warfarin**
  - Number at Risk (number of events):
    - 29187 (0)
    - 25792 (160)
    - 23804 (269)
    - 18677 (330)
    - 12906 (377)
    - 7226 (395)
- **NOAC**
  - Number at Risk (number of events):
    - 29270 (0)
    - 25393 (335)
    - 23577 (436)
    - 18413 (508)
    - 12791 (564)
    - 7206 (588)

**Hazard Ratio**
- 1.58 (95% CI 1.39-1.79); p<0.001

**Net Clinical Outcome**

- **Warfarin**
  - Number at Risk (number of events):
    - 29187 (0)
    - 25567 (999)
    - 23446 (1744)
    - 18260 (2327)
    - 12504 (2758)
    - 6946 (3012)
- **NOAC**
  - Number at Risk (number of events):
    - 29270 (0)
    - 25323 (890)
    - 23378 (1555)
    - 18178 (2040)
    - 12502 (2445)
    - 6996 (2666)

**Hazard Ratio**
- 0.89 (95% CI 0.83-0.94); p<0.001

**Net clinical outcome** = composite stroke, systemic embolism, major bleeding, all-cause death
Interaction Testing

Stroke or Systemic Embolism

- **Age**: HR > 1 favors warfarin, HR < 1 favors NOACs
  - Hazard Ratio decreases 5.0% (1.6% - 8.4%) per 10 mL/min decrease in CrCl
- **Body Weight**: HR > 1 favors warfarin, HR < 1 favors NOACs
- **Creatinine Clearance**: HR > 1 favors warfarin, HR < 1 favors NOACs
  - Hazard Ratio decreases 5.0% (1.6% - 8.4%) per 10 mL/min decrease in CrCl

**Graphs**

- Age (years) at baseline
- Body weight (kg) at baseline
- Creatinine clearance (mL/min) at baseline

**Statistical Significance**

- p-int = 0.130
- p-int = 0.110
- p-int = 0.005
Hazard Ratio decreases 8.8% (0.8% - 16.1%) per 10 year decrease in age

Hazard Ratio decreases 5.2% (1.7% - 8.5%) per 10 kg decrease in weight
Interaction Testing

**All-Cause Death**

**Age**
- Hazard Ratio decreases 3.1% (0.01% - 6.0%) per 10 kg decrease in weight

**Body Weight**
- Hazard Ratio decreases 3.1% (0.8% - 5.3%) per 10 mL/min decrease in CrCl
Summary

• Sharing of de-identified data across multiple international coordinating centers provides a unique model for academic collaboration
  • COMBINE AF will serve as an important resource for many future collaborative analyses

• NOAC use results in consistently lower rates of stroke, death, and intracranial hemorrhage compared with warfarin across most subgroups

• For continuous baseline covariates age, body weight, creatinine clearance there was evidence of statistical interaction regarding treatment effect for various outcomes
  • For example, the benefit of NOAC over warfarin with respect to stroke was more pronounced in patients with lower creatinine clearance

• These data further support the value of NOACs over warfarin for a broad population of patients with atrial fibrillation
THANK YOU!

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