Updated AHA/ACC/HRS Guidelines For the Management of Atrial Fibrillation
2017

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Chairman Cardiology Section
Sparrow TCI
Disclosures

Speakers Bureau – Actelion Pharmaceuticals, Bristol-Myers Squibb, Pfizer

Clinical Research Support – Sanofi Aventis
Case Study

65 year old female with a history of dyslipidemia presents to your office with complaints of palpitations that started last evening. No other past medical history. She admits to similar episodes on and off for the last few months

- Patient was found to be in atrial fibrillation with a rate of 114 bpm. You start her on oral Cardizem for rate control until you determine course of action (rate control vs rhythm control).

- What anticoagulation regimen (if any) should this patient be discharged home on?
65 year old female with a history of dyslipidemia presents to your office with complaints of palpitations that started last evening. No other past medical history. She admits to similar episodes on and off for the last few months

- Patient was found to be in atrial fibrillation with a rate of 114 bpm. You start her on oral Cardizem for rate control until you determine course of action (rate control vs rhythm control).

- What anticoagulation regimen (if any) should this patient be discharged home on? **Oral Anticoagulation (Warfarin/DOAC)**
Summary

• Background of Atrial Fibrillation
• Rate Control vs. Rhythm Control
• Anticoagulation
• Risks of Bleeding
• Interruption or Discontinuation of Oral Anticoagulation for Surgery/Procedures
• Device Based Solutions
• Management of Bleeding
Background

- Atrial fibrillation is the most common sustained arrhythmia
- Affects 2 million Americans -- AF is 0.4% to 1% in the general population
- Expensive - 16 billion
- 6% over the age of 65 experience it
- Responsible for 15% strokes
- Unfortunately, warfarin is received by only 30-60% of appropriate patients
- In the FHS, the lifetime risk of atrial fibrillation (AFib) for adults is 26% for men and 23% for women.
- The 2014 ACC/AHA/HRS Atrial Fibrillation guideline defines Non Valvular Atrial Fibrillation as **AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic valve or mitral valve repair** (January CT et al. Journal of the American College of Cardiology 2014 doi 10/1016 JACC 2014 0.3.022)
## Classification of AFib Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>Spontaneous termination usually &lt; 7 days and most often &lt; 48 hours</td>
</tr>
<tr>
<td>Persistent</td>
<td>Does not interrupt spontaneously and needs therapeutic intervention for termination (either pharmacological or electrical cardioversion)</td>
</tr>
<tr>
<td>Permanent</td>
<td>AFib in which cardioversion is attempted but unsuccessful, or successful but immediately relapses, or a form of AFib for which a decision was taken not to attempt cardioversion</td>
</tr>
</tbody>
</table>
AFib is Responsible for 15-20% of all Strokes

- AFib is responsible for a 5-fold increase in the risk of ischaemic stroke.


AFib Management and the Role of Catheter Ablation- AFIB Alliance Presentation
Atrial Fibrillation: Prevalence Estimates

Turpie A. New oral anticoagulants in atrial fibrillation. EHJ 2007; 29:155-65
Detection of AF at 3 years

Rate of detection in ICM arm was 30.0% vs 3.0% in control arm

CRYptogenic STroke and underlying Atrial Fibrillation (CRYSTAL AF), Richard Bernstein, MD, Ph.D., et al. NEJM June 26, 2014
Despite Increasing DOAC Adoption, Overall Rate of Anticoagulation in High Risk NVAF Patients has Not Improved

Anticoagulant Use in Patients with NVAF and CHADS$_2$ ≥ 2

Results from the NCDR PINNACLE Registry$^1$

Atrial Fibrillation

- Rate Control vs. Rhythm Control
- Anticoagulation
- Bleeding Risk
Atrial Fibrillation

- Rate Control vs. Rhythm Control
Theoretical Benefit of Rhythm Control

• Improved hemodynamics
• Relief of symptoms
• Improved exercise tolerance
• Reduced risk of stroke
• Avoidance of anticoagulants
A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

ABSTRACT

Background There are two approaches to the treatment of atrial fibrillation: one is cardioversion and treatment with antiarrhythmic drugs to maintain sinus rhythm, and the other is the use of rate-controlling drugs, allowing atrial fibrillation to persist. In both approaches, the use of anticoagulant drugs is recommended.

Atrial fibrillation is the most common sustained cardiac arrhythmia, yet the optimal strategy for its management remains uncertain.1-4 During atrial fibrillation, most symptoms (but perhaps not all) are caused by a poorly controlled or irregular ventricular rate, and the associated risk of death is doubled in patients who have
## AFFIRM: 5 Year Outcomes

<table>
<thead>
<tr>
<th>Survival</th>
<th>Rhythm Control</th>
<th>Rate Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>3 year</td>
<td>87%</td>
<td>89%</td>
</tr>
<tr>
<td>5 year</td>
<td>76%</td>
<td>79%</td>
</tr>
</tbody>
</table>

\[ p = 0.058 \]

NO Difference: death, disabling stroke, major bleed, or cardiac arrest

Sinus rhythm maintained in only 63% of rhythm control group

NEJM 2002;347:1825
Affirm Trial

• No survival advantage to rhythm control.
• Rhythm control patients were more likely to be hospitalized with adverse drug effects.
• Both groups had similar stroke risk (1% per yr)
  – Majority of strokes when warfarin stopped or INR subtherapeutic
  – Warfarin required long term even if sinus rhythm restored
• Torsades, bradycardiac arrest more common with rhythm control.
Why haven’t trials comparing restoration of sinus rhythm (rhythm control) with rate control shown a mortality benefit with rhythm control?

- Attempts at restoration of sinus rhythm not always successful
  - AFFIRM Trial: only 63% of “rhythm control” group were in sinus rhythm
  - Antiarrhythmics used to maintain sinus rhythm associated with a 25-50% annual failure rate.
- Long term anticoagulation not mandated in the “rhythm control” group
  - Those in afib at risk for stroke
- Medications used to maintain sinus rhythm risk of proarrhythmia and other toxicity
Our Approach (Evidence + Practice)

• Rhythm control as preferred therapy
  – First episode afib
  – Reversible cause (alcohol)
  – Symptomatic patient despite rate control
  – Patient unable to take anticoagulant (falls, bleeding, noncompliance)
  – CHF precipitated or worsened by afib
  – Young afib patient (to avoid chronic electrical and anatomic remodeling that occurs with afib)
Our Approach (Evidence + Practice)

• Rate control as preferred therapy
  – Age $\geq$ 65, less symptomatic, hypertension
  – Recurrent afib
  – Previous antiarrhythmic drug failure
  – Unlikely to maintain sinus rhythm (enlarged LA)
Approach to Selecting Drug Therapy for Ventricular Rate Control for Atrial Fibrillation

- **No Other CV Disease**
  - Beta blocker
  - Diltiazem
  - Verapamil

- **Hypertension or HFpEF**
  - Beta blocker
  - Diltiazem
  - Verapamil

- **LV Dysfunction or HF**
  - Beta blocker
  - Digoxin

- **COPD**
  - Beta blocker
  - Diltiazem
  - Verapamil

- **Amiodarone**

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. © American College of Cardiology Foundation and American Heart Association
Rate Control Options

• **Beta blocker**
  – Avoid carvedilol (Coreg) - less effective in AV node blockade

• **Calcium channel blocker**
  • Diltiazem, Verapamil

• **Digoxin**
  • Not as the sole agent - May be harmful

**Conclusion**
• This meta-analysis on the effects of digoxin on all-cause mortality indicates that digoxin is associated with increased mortality risk in patients with AF or congestive HF. The effect was strongest in AF patients. These observations call for randomised trials evaluating dose-adjusted digoxin therapy. Until these have been completed, digoxin should be used with great caution, especially when used for rate control in AF.
Lenient versus Strict Rate Control in Patients with Atrial Fibrillation


ABSTRACT

BACKGROUND
Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

METHODS
We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate < 110 beats per minute) or a strict rate-control strategy (resting heart rate < 80 beats per minute and heart rate during moderate exercise < 110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years.

From the Department of Cardiology (I.C.V.G., H.F.G., H.L.H., D.J.V.V., M.P.V.B.) and the Trial Coordination Center, Department of Epidemiology (H.L.H., J.A.B.-K.), University Medical Center Groningen, University of Groningen, Groningen; the Interuniversity Cardiology Institute of the Netherlands, Utrecht (I.C.V.G.); Maastricht University Medical Center, Maastricht (H.J.G.M.C.); Deventer Hospital, Deventer (Y.S.T.); Academic Medical Center, University of Amsterdam (J.G.P.T.), and VU University Medical Center (O.K.) — both in Amsterdam; Amphia Hospital, Breda (A.M.A.); Medical Center, Alkmaar (J.H.C.); Kennemer Hospital, Haarlem (R.T.); and Rijnstate Hospital, Arnhem (H.A.B.) — all in the Netherlands. Address correspondence to Dr. Van Gelder.
Primary Outcomes

Cardiac death
CHF
Stroke
Systemic embolism
Major bleed
Syncope
Sust VT
Cardiac arrest
Life threat compl of antiarrhythm
Pacemaker

Secondary Outcomes

Symptoms

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.

The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.
Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Isabelle C. Van Gelder, M.D., Hessel F. Groenveld, M.D.,
Harry J.G.M. Crijns, M.D., Ype S. Tuininga, M.D., Jan G.P. Tijssen, Ph.D.,
A. Marco Alings, M.D., Hans L. Hillege, M.D., Johanna A. Bergsma-Kadijk, M.Sc.,
Jan H. Cornel, M.D., Otto Kamp, M.D., Raymond Tukkie, M.D.,
Hans A. Bosker, M.D., Dirk J. Van Veldhuisen, M.D.,
and Maarten P. Van den Berg, M.D., for the RACE II Investigators*

BACKGROUND

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Most patients in Lenient HR < 100
Anticoagulation Strategies
How do we determine stroke risk?

- **CHADS2**
  - Congestive heart failure - 1pt
  - Hypertension - 1pt
  - Age > 75 - 1 pt
  - Diabetes - 1pt
  - Stroke or TIA - 2 pts

- 0 points – **low risk** (1.2-3.0 strokes per 100 patient years)
- 1-2 points – **moderate risk** (2.8-4.0 strokes per 100 patient years)
- ≥ 3 points – **high risk** (5.9-18.2 strokes per 100 patient years)
How do we determine stroke risk?

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

Gregory Y. H. Lip, MD; Robby Nieuwlaat, PhD; Ron Pisters, MD; Deirdre A. Lane, PhD; and Harry J. G. M. Crijns, MD

Stroke Risk Stratification in AF

**CHADS₂**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
</tbody>
</table>

**CHA₂DS₂-VASc**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Vasc dz (MI, PAD, aortic ath)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Annual Risk of Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**Relationship between CHA₂DS₂-VASc score and annual risk of stroke**

Validation of a Modified CHA₂DS₂-VASc Score for Stroke Risk Stratification in Asian Patients With Atrial Fibrillation
A Nationwide Cohort Study

Tze-Fan Chao, MD*; Gregory Y.H. Lip, MD*; Chia-Jen Liu, MD; Ta-Chuan Tuan, MD; Su-Jung Chen, MD; Kang-Ling Wang, MD; Yenn-Jiang Lin, MD; Shih-Lin Chang, MD; Li-Wei Lo, MD; Yu-Feng Hu, MD; Tzeng-Ji Chen, MD; Chern-En Chiang, MD, PhD; Shih-Ann Chen, MD

Background and Purpose—The age threshold for an increased stroke risk for patients with atrial fibrillation may be different for Asians and non-Asians. We hypothesized that a modified CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female) scheme, mCHA₂DS₂-VASc, which assigned one point for patients aged 50 to 74 years, may perform better than CHA₂DS₂-VASc score for stroke risk stratification in Asians.

Methods—This study used the Taiwan National Health Insurance Research Database, which included 224,866 newly diagnosed atrial fibrillation patients. The predictive accuracies of ischemic stroke of CHA₂DS₂-VASc and mCHA₂DS₂-VASc scores were compared among 124,271 patients without antithrombotic therapies. From the whole cohort, 15,948 patients had a CHA₂DS₂-VASc score 0 (males) or 1 (females), and 8654 patients had an mCHA₂DS₂-VASc score 1 (males) or 2 (females). The latter were categorized into 3 groups, that is, no treatment, antiplatelet therapy, and warfarin, and the risks of ischemic stroke and intracranial hemorrhage (ICH) were compared.

Results—During a follow-up of 538,653 person-years, 21,008 patients experienced ischemic stroke. The mCHA₂DS₂-VASc performed better than CHA₂DS₂-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For 8654 patients having an mCHA₂DS₂-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH compared with nontreatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models.

Conclusions—In this Asian atrial fibrillation cohort, the mCHA₂DS₂-VASc score performed better than the CHA₂DS₂-VASc and would further identify atrial fibrillation patients who may derive a positive net clinical benefit from oral anticoagulation. (Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.116.013880.)
# Risk-Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute risks and RRs of stroke and bleeding and the patient’s values and preferences.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with nonvalvular AF, the CHA₂DS₂-VASc* score is recommended for assessment of stroke risk.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>For patients with AF who have mechanical heart valves, warfarin is recommended, and the target INR intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the type and location of the prosthesis.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*CHA₂DS₂-VASc indicates Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category.

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. © American College of Cardiology Foundation and American Heart Association
# Summary- Non Valvular AF

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>CHADs-2-VASC Score</th>
<th>Recommended Therapy</th>
</tr>
</thead>
</table>
| Two or more Risk Factors    | 2                  | ACC- Oral Anticoagulation  
ESC- Oral Anticoagulation        |
| One Risk Factor             | 1                  | ACC- Aspirin 81 mg or Oral Anticoagulation (Exception Female Gender only)  
ESC- Oral Anticoagulation    |
| No Risk Factors             | 0                  | ACC- Aspirin 81 mg daily  
ESC- No Therapy               |
Stroke Risk Stratification in AF

Journal of the American College of Cardiology
Volume 65, Issue 3, January 2015
DOI: 10.1016/j.jacc.2014.10.052

Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA₂DS₂-VASc Score of 1
Leif Friberg, Mika Skeppholm, Andreas Terént

Abstract

Background Patients with atrial fibrillation (AF) and ≥1 point on the stroke risk scheme CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) are considered at increased risk for future stroke, but the risk associated with a score of 1 differs markedly between studies.

Objectives The goal of this study was to assess AF-related stroke risk among patients with a score of 1 on the CHA₂DS₂-VASc.

Methods We conducted this retrospective study of 140,420 patients with AF in Swedish nationwide health registries on the basis of varying definitions of "stroke events."

Results Using a wide "stroke" diagnosis (including hospital discharge diagnoses of ischemic stroke as well as unspecified stroke, transient ischemic attack, and pulmonary embolism) yielded a 44% higher annual risk than if only ischemic strokes were counted. Including stroke events in conjunction with the index hospitalization for AF doubled the long-term risk beyond the first 4 weeks. For women, annual stroke rates varied between 0.1% and 0.2% depending on which event definition was used; for men, the corresponding rates were 0.5% and 0.7%.

Conclusions The risk of ischemic stroke in patients with AF and a CHA₂DS₂-VASc score of 1 seems to be lower than previously reported.
Atrial Fibrillation

• Anticoagulation Strategies
  – Aspirin
  – Warfarin
  – Dabigatran (Direct Thrombin Inhibitor)
  – Rivaroxaban (Factor Xa Inhibitor)
  – Apixaban (Factor Xa Inhibitor)
  – Endoxiban (Factor Xa Inhibitor)
Atrial Fibrillation

• Anticoagulation Strategies
Efficacy of Warfarin
Compared with Control in Five Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Events</th>
<th>Patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>27</td>
<td>811</td>
</tr>
<tr>
<td>BAATAF</td>
<td>15</td>
<td>922</td>
</tr>
<tr>
<td>CAFA</td>
<td>14</td>
<td>478</td>
</tr>
<tr>
<td>SPAF</td>
<td>23</td>
<td>508</td>
</tr>
<tr>
<td>SPINAF</td>
<td>29</td>
<td>972</td>
</tr>
<tr>
<td>Combined*</td>
<td>108</td>
<td>3691</td>
</tr>
</tbody>
</table>

Risk Reduction, %

*Total risk reduction for all 5 studies combined is 68%
Warfarin

THE GOOD
• Effective
• Reversible
• Inexpensive

THE BAD
• Slow onset of action
• Regular monitoring
• Food interaction
• Medication interaction
• Difficult titration-regular dose adjustments
• Variable response
• Bleeding risks
• “bridging”
Patients Assigned to Warfarin in AF Trials

Intensity of Anticoagulation When Stroke Occurred

**INR Ratio**

- **AFASAK**
- **CAFA**
- **SPAF I**
- **BAATAF**
- **SPINAF**

**PT Ratio (ISI 2.4)**

- **ACCP recommendation**: INR: 2.0–3.0
- **Target range for individual study**
Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation

# Time in Therapeutic Range (TTR)

## INR Data

<table>
<thead>
<tr>
<th>INR range</th>
<th>Warfarin Median (25th, 75th)</th>
</tr>
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<tbody>
<tr>
<td>&lt;1.5</td>
<td>2.7 (0.0 – 9.0)</td>
</tr>
<tr>
<td>1.5 to &lt;1.8</td>
<td>7.9 (3.5 – 14.0)</td>
</tr>
<tr>
<td>1.8 to &lt;2.0</td>
<td>9.1 (5.3 – 13.6)</td>
</tr>
<tr>
<td><strong>2.0 to 3.0</strong></td>
<td><strong>57.8 (43.0 – 70.5)</strong></td>
</tr>
<tr>
<td>&gt;3.0 to 3.2</td>
<td>4.0 (1.9 – 6.5)</td>
</tr>
<tr>
<td>&gt;3.2 to 5.0</td>
<td>7.9 (3.3 – 13.8)</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>0.0 (0.0 – 0.5)</td>
</tr>
</tbody>
</table>

Based on Rosendaal method with all INR values included

Based on Safety Population

Emerging Therapies

Modified from the Am J Health-Syst Pharm;65:1520
The Ideal Anticoagulant

- Oral
- Once daily dosing
- Quick onset
- Limited monitoring
- Limited or no drug interactions
- Available and effective antidote
- Wide therapeutic index
- **Low cost**
### Table 1: Study characteristics.

<table>
<thead>
<tr>
<th>Studies</th>
<th>RE-LY (1)</th>
<th>ROCKET AF (2)</th>
<th>ARISTOTLE (3)</th>
<th>ENGAGE AF-TIMI 48 (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial size (n)</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.5</td>
<td>73</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63.5%</td>
<td>59.3%</td>
<td>64.5%</td>
<td>61.9%</td>
</tr>
<tr>
<td>Mean CHADS$_2$</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Intervention vs Comparator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Two intervention arms: 1. Dabigatran 150 mg bid 2. Dabigatran 150 mg bid</td>
<td>Rivaroxaban 20 mg daily</td>
<td>Apixaban 5 mg bid</td>
<td>Two intervention arms: 1. Edoxaban 30 mg daily 2. Edoxaban 60 mg daily</td>
</tr>
<tr>
<td>Dose modification</td>
<td>No</td>
<td>Yes, at randomisation</td>
<td>Yes, at randomisation</td>
<td>Yes, at randomisation and during study</td>
</tr>
</tbody>
</table>
| Criteria for modified dose | N/A | 15 mg daily in patients with CrCl 30–49 ml/min | 2.5 mg bid in patients who met 2 of the 3 following criteria:  
  - age >80 years,  
  - weight <60 kg,  
  - creatinine >133 µmol/l | Half dose in patients with any of the following criteria:  
  - CrCl 30–50 ml/min,  
  - weight <60 kg,  
  - concomitant use of potent p-glycoprotein inhibitors such as verapamil, quinidine, dronedarone. Standard dose resumed once these medications ceased. |
| Comparators | Open label warfarin | Blinded warfarin | Blinded warfarin | Blinded warfarin |
| Outcomes | | | | |
| Primary efficacy | Stroke or systemic embolism | Stroke or systemic embolism | Stroke or systemic embolism | Stroke or systemic embolism |
| Primary safety | Major bleeding | Major bleeding + clinically relevant non major bleeding | Major bleeding | Major bleeding |

Bid = twice-daily dose; CrCl = creatinine clearance as per Cockcroft Gault formulas; kg = kilogram; mg = milligram.
Clinical Trials

- Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
  - **RE-LY Trial**
    - Dabigatran 110mg PO BID or 150mg PO BID (blinded) to open-label warfarin 1, 3, or 5mg (goal INR 2-3) in patients with non-valvular Afib and one or more of the following risk factors:
      - Previous stroke, TIA, or systemic embolism
      - LVEF<40%
      - Symptomatic heart failure, NYHA class ≥2
      - Age ≥75 years
      - Age ≥65 years with DM, CAD, or HTN
  - 18,113 patients randomized and followed for a median of 2 years
  - TTR for warfarin: 64% (mean)
• Dabigatran 150 mg twice daily
  – More effective than warfarin in stroke prevention
    • Dabigatran (150mg) 1.11%/yr
  – Equivalent bleeding to warfarin but Less hemorrhagic stroke than warfarin
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

ABSTRACT

BACKGROUND
Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS
In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS
From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John’s National Academy of Health Sciences, Bangalore, India (D.X.); FuWai Hospital, Beijing (J.Z.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); Lady
### Table 2: Recommendation for emerging antithrombotic agents

<table>
<thead>
<tr>
<th>2011 Focused update recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>New recommendation</td>
</tr>
<tr>
<td>1. Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance &lt;15 mL/min) or advanced liver disease (impaired baseline clotting function).[^3] (Level of Evidence: B)</td>
<td></td>
</tr>
</tbody>
</table>
Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

Ken Uchino, MD; Adrian V. Hernandez, MD, PhD

**Background:** The original RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin in patients with atrial fibrillation. We systematically evaluated the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran.

**Methods:** We searched PubMed, Scopus, and the Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as secondary outcomes. The fixed-effects Mantel-Haenszel (M-H) test was used to evaluate the effect of dabigatran on MI or ACS. We expressed the associations as odds ratios (ORs) and their 95% CIs.

**Results:** Seven trials were selected (N=30,514), including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis. Control arms included warfarin, enoxaparin, or placebo administration. Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20,000 [1.19%] vs control, 83 of 10,514 [0.79%]; OR\(_{M-H}\), 1.33; 95% CI, 1.03-1.71; \(P=.03\)). The risk of MI or ACS was similar when using revised RE-LY trial results (OR\(_{M-H}\), 1.27; 95% CI, 1.00-1.61; \(P=.05\)) or after exclusion of short-term trials (OR\(_{M-H}\), 1.33; 95% CI, 1.03-1.72; \(P=.03\)). Risks were not heterogeneous for all analyses (\(I^2=0\%\); \(P≥.30\)) and were consistent using different methods and measures of association.

**Conclusions:** Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Rivaroxaban (Xarelto®)

- Once daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- No routine lab testing
- No reversal
  - Half life 5-9 hours
- Coagulation testing: aPTT
- Discontinuation: increased stroke
## Key Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Death,</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke,</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Embolism</strong></td>
<td>3.11</td>
<td>3.63</td>
<td>0.86 (0.74, 0.99)</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Stroke Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhagic</strong></td>
<td>0.26</td>
<td>0.44</td>
<td>0.59 (0.37, 0.93)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Ischemic</strong></td>
<td>1.34</td>
<td>1.42</td>
<td>0.94 (0.75, 1.17)</td>
<td>0.581</td>
</tr>
<tr>
<td><strong>Unknown Type</strong></td>
<td>0.06</td>
<td>0.10</td>
<td>0.65 (0.25, 1.67)</td>
<td>0.366</td>
</tr>
<tr>
<td><strong>Non-CNS Embolism</strong></td>
<td>0.04</td>
<td>0.19</td>
<td>0.23 (0.09, 0.61)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>0.91</td>
<td>1.12</td>
<td>0.81 (0.63, 1.06)</td>
<td>0.121</td>
</tr>
<tr>
<td><strong>All Cause Mortality</strong></td>
<td>1.87</td>
<td>2.21</td>
<td>0.85 (0.70, 1.02)</td>
<td>0.073</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td>1.53</td>
<td>1.71</td>
<td>0.89 (0.73, 1.10)</td>
<td>0.289</td>
</tr>
<tr>
<td><strong>Non-vascular</strong></td>
<td>0.19</td>
<td>0.30</td>
<td>0.63 (0.36, 1.08)</td>
<td>0.094</td>
</tr>
<tr>
<td><strong>Unknown Cause</strong></td>
<td>0.15</td>
<td>0.20</td>
<td>0.75 (0.40, 1.41)</td>
<td>0.370</td>
</tr>
</tbody>
</table>

Event Rates are per 100 patient-years
Based on Safety on Treatment Population
## Primary Safety Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate or N (Rate)</td>
<td>Event Rate or N (Rate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>3.60</td>
<td>3.45</td>
<td>1.04 (0.90, 1.20)</td>
<td>0.576</td>
</tr>
<tr>
<td>&gt;2 g/dL Hgb drop</td>
<td>2.77</td>
<td>2.26</td>
<td>1.22 (1.03, 1.44)</td>
<td>0.019</td>
</tr>
<tr>
<td>Transfusion (&gt; 2 units)</td>
<td>1.65</td>
<td>1.32</td>
<td>1.25 (1.01, 1.55)</td>
<td>0.044</td>
</tr>
<tr>
<td>Critical organ bleeding</td>
<td>0.82</td>
<td>1.18</td>
<td>0.69 (0.53, 0.91)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bleeding causing death</td>
<td>0.24</td>
<td>0.48</td>
<td>0.50 (0.31, 0.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>55 (0.49)</td>
<td>84 (0.74)</td>
<td>0.67 (0.47, 0.94)</td>
<td>0.019</td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>37 (0.33)</td>
<td>56 (0.49)</td>
<td>0.67 (0.44, 1.02)</td>
<td>0.060</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>2 (0.02)</td>
<td>4 (0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdural</td>
<td>14 (0.13)</td>
<td>27 (0.27)</td>
<td>0.53 (0.28, 1.00)</td>
<td>0.051</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>4 (0.04)</td>
<td>1 (0.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Event Rates are per 100 patient-years
Based on Safety on Treatment Population
Apixaban (Eliquis®)

- Twice daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- Lower overall mortality
- No routine lab testing
- No reversal
  - Half life 8-15 hours
- Coagulation testing: PT, aPTT
Apixaban (Eliquis®)

- **Class:** Factor Xa inhibitor

- **MOA:** Direct-acting, reversible factor Xa inhibitor. Inhibits the conversion of prothrombin to thrombin.

- **FDA approved indication:** Still in the late-stage of clinical development for the prevention and treatment of thromboembolic events.

- **Dose:**
  - 5 and 2.5 mg twice daily
  - Note: Doses being studied in clinical trials.
  - 2.5mg PO BID for Scr ≥ 1.5mg/dL, age ≥ 80, body weight ≤ 60 kg
ARISTOTLE Trial: Apixaban¹,²

AF or atrial flutter
18,206 randomized

Double-blind

Warfarin INR, 2.0-3.0

Apixaban
(5 mg twice daily; 2.5 mg twice daily in selected patientsᵃ)

• Is apixaban noninferior to standard therapy (warfarin) in preventing stroke and systemic embolism in moderate- to high-risk (stroke; at least 1 risk factor) AF patients?
• ¹ efficacy end point: confirmed ischemic or hemorrhagic stroke, or systemic embolism
• ² efficacy end points: composite of confirmed ischemic or hemorrhagic stroke, systemic embolism, and all-cause death
• ¹ safety end point: time to first occurrence of confirmed major bleeding
• Treatment period: up to 4 years (until 448 primary outcome events have been observed — >90% power to demonstrate noninferiority);
  – Stratified by warfarin-naïve status

¹ At least 2 of: age ≥80 y, weight ≤60 kg, or serum Cr ≥1.5 mg/dL

2. ClinicalTrials.gov identifier: NCT00412984
3. AF 2011: Therapeutic Update Presentation. Gerald V. Naccarelli M.D
## Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=9120) Event Rate (%/yr)</th>
<th>Warfarin (N=9081) Event Rate (%/yr)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism*</td>
<td>1.27</td>
<td>1.60</td>
<td>0.79 (0.66, 0.95)</td>
<td>0.011</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.19</td>
<td>1.51</td>
<td>0.79 (0.65, 0.95)</td>
<td>0.012</td>
</tr>
<tr>
<td>Ischemic or uncertain</td>
<td>0.97</td>
<td>1.05</td>
<td>0.92 (0.74, 1.13)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.24</td>
<td>0.47</td>
<td>0.51 (0.35, 0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic embolism (SE)</td>
<td>0.09</td>
<td>0.10</td>
<td>0.87 (0.44, 1.75)</td>
<td>0.70</td>
</tr>
<tr>
<td>All-cause death*</td>
<td>3.52</td>
<td>3.94</td>
<td>0.89 (0.80, 0.998)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke, SE, or all-cause death</td>
<td>4.49</td>
<td>5.04</td>
<td>0.89 (0.81, 0.98)</td>
<td>0.019</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.53</td>
<td>0.61</td>
<td>0.88 (0.66, 1.17)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Part of sequential testing sequence preserving the overall type I error
Is apixaban more effective than ASA in preventing stroke and systemic embolism in moderate to high-risk (stroke; at least 1 risk factor) AF patients?

1^o efficacy end point: confirmed ischemic or hemorrhagic stroke or systemic embolism

2^o study end points: as above, including MI or vascular death

1^o safety end point: major bleeding

Study period: until 226 primary outcome events have been observed

In June 2010, BMS-Pfizer announced that the study had been stopped early because a predefined interim analysis revealed clear evidence of a clinically important reduction in stroke and systemic embolism. Results presented at ESC 2010, Stockholm, Sweden.
AVERROES: Stroke or Systemic Embolic Event

Cumulative Risk

RR = 0.45
95% CI, 0.32-0.62
P < 0.001

Table:

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk ASA</th>
<th>No. at Risk Apixaban*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2791</td>
<td>2809</td>
</tr>
<tr>
<td>3</td>
<td>2720</td>
<td>2761</td>
</tr>
<tr>
<td>6</td>
<td>2541</td>
<td>2567</td>
</tr>
<tr>
<td>9</td>
<td>2124</td>
<td>2127</td>
</tr>
<tr>
<td>12</td>
<td>1541</td>
<td>1523</td>
</tr>
<tr>
<td>18</td>
<td>626</td>
<td>617</td>
</tr>
<tr>
<td>21</td>
<td>329</td>
<td>353</td>
</tr>
</tbody>
</table>


1. AF 2011: Therapeutic Update Presentation. Gerald V. Naccarelli M.D
**AVERROES: Results (efficacy)**

- Apixaban significantly reduced risk of stroke or systemic embolic events by 54%
- The trial was stopped early when the data and safety monitoring board performed a prespecified interim analysis showing significant benefit with apixaban

### Primary and secondary end points

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Apixaban (n=2809), %</th>
<th>Aspirin (n=2791), %</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>1.6</td>
<td>3.6</td>
<td>0.46 (0.33–0.64)</td>
</tr>
<tr>
<td>Stroke, embolic event, MI, or vascular death</td>
<td>4.1</td>
<td>6.2</td>
<td>0.66 (0.53–0.83)</td>
</tr>
<tr>
<td>- MI</td>
<td>0.7</td>
<td>0.8</td>
<td>0.85 (0.48–1.50)</td>
</tr>
<tr>
<td>- Vascular death</td>
<td>2.5</td>
<td>2.9</td>
<td>0.86 (0.64–1.16)</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>11.8</td>
<td>14.9</td>
<td>0.79 (0.68–0.91)</td>
</tr>
<tr>
<td>Total death</td>
<td>3.4</td>
<td>4.4</td>
<td>0.79 (0.62–1.02)</td>
</tr>
</tbody>
</table>
AVERROES: Major Bleeding

RR=1.13  
95% CI, 0.74-1.75  
P=.57


1. AF 2011: Therapeutic Update Presentation. Gerald V. Naccarelli M.D
The risk of major bleeding increased by a statistically nonsignificant 14%.
There was no increased risk of fatal or intracranial hemorrhage, two particular concerns with AF patients who receive anticoagulation therapy.

### Bleeding events

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Apixaban (n=2809), %</th>
<th>Aspirin (n=2791), %</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>1.4</td>
<td>1.2</td>
<td>1.14 (0.74–1.75)</td>
</tr>
<tr>
<td>Clinical relevant nonmajor bleed</td>
<td>3.0</td>
<td>2.6</td>
<td>1.18 (0.88–1.58)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5.2</td>
<td>4.1</td>
<td>1.27 (1.01–1.61)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.1</td>
<td>0.1</td>
<td>0.84 (0.26–2.75)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.4</td>
<td>0.3</td>
<td>1.09 (0.50–2.39)</td>
</tr>
</tbody>
</table>
ENGAGE AF–TIMI 48: Edoxaban

- Is edoxaban noninferior to standard therapy (warfarin) in preventing stroke and systemic embolism in moderate- to high-risk (CHADS₂ score ≥2) AF patients?
- 1° efficacy end point: composite primary end point of stroke and systemic embolic events
- 2° efficacy end points: composite clinical outcome of stroke, systemic embolic events, and all-cause mortality; also major bleeding events
- Treatment period: up to 2 years

ClinicalTrials.gov identifier NCT00781391. AF 2011: Therapeutic Update Presentation. Gerald V. Naccarelli M.D
ENGAGE AF–TIMI 48: Edoxaban

A Stroke or Systemic Embolic Event

Hazard ratio and 97.5% confidence intervals
High-dose edoxaban vs. warfarin, 0.87 (0.73–1.04); P=0.08
Low-dose edoxaban vs. warfarin, 1.13 (0.96–1.34); P=0.10

No. at Risk
Warfarin  7036  6798  6615  6406  6225  4593  2333  536
High-dose edoxaban  7035  6816  6650  6480  6283  4659  2401  551
Low-dose edoxaban  7034  6815  6631  6461  6277  4608  2358  534

B Major Bleeding

Hazard ratio and 95% confidence intervals
High-dose edoxaban vs. warfarin, 0.80 (0.71–0.91); P<0.001
Low-dose edoxaban vs. warfarin, 0.47 (0.41–0.55); P<0.001

No. at Risk
Warfarin  7012  6116  5630  5278  4941  3446  1687  370
High-dose edoxaban  7012  6039  5594  5232  4910  3471  1706  345
Low-dose edoxaban  7002  6218  5791  5437  5110  3635  1793  386
DOAC Events Summary

A. Primary Efficacy Outcome

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>212</td>
<td>9120</td>
<td>265</td>
<td>9081</td>
<td>0.80 [0.67, 0.95]</td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>182</td>
<td>6015</td>
<td>199</td>
<td>6022</td>
<td>0.92 [0.75, 1.12]</td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>134</td>
<td>6076</td>
<td>199</td>
<td>6022</td>
<td>0.67 [0.54, 0.83]</td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>383</td>
<td>7034</td>
<td>337</td>
<td>7036</td>
<td>1.14 [0.99, 1.31]</td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>296</td>
<td>7035</td>
<td>337</td>
<td>7036</td>
<td>0.88 [0.75, 1.02]</td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>269</td>
<td>7081</td>
<td>306</td>
<td>7090</td>
<td>0.88 [0.75, 1.03]</td>
</tr>
</tbody>
</table>

B. Haemorrhagic stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>40</td>
<td>9120</td>
<td>78</td>
<td>9081</td>
<td>0.51 [0.35, 0.75]</td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>14</td>
<td>6015</td>
<td>45</td>
<td>6022</td>
<td>0.31 [0.17, 0.57]</td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>12</td>
<td>6076</td>
<td>45</td>
<td>6022</td>
<td>0.26 [0.14, 0.50]</td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>30</td>
<td>7034</td>
<td>90</td>
<td>7036</td>
<td>0.33 [0.22, 0.50]</td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>49</td>
<td>7035</td>
<td>90</td>
<td>7036</td>
<td>0.54 [0.39, 0.77]</td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>29</td>
<td>7061</td>
<td>50</td>
<td>7082</td>
<td>0.58 [0.37, 0.92]</td>
</tr>
</tbody>
</table>
### C. Non-haemorrhagic stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Risk Ratio 95% CI</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>162</td>
<td>9120</td>
<td>175</td>
<td>9081</td>
<td>0.92 [0.75, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>159</td>
<td>6015</td>
<td>142</td>
<td>6022</td>
<td>1.12 [0.90, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>111</td>
<td>6076</td>
<td>142</td>
<td>6022</td>
<td>0.77 [0.61, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>333</td>
<td>7034</td>
<td>235</td>
<td>7036</td>
<td>1.42 [1.20, 1.67]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>236</td>
<td>7035</td>
<td>235</td>
<td>7036</td>
<td>1.00 [0.84, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>156</td>
<td>7061</td>
<td>172</td>
<td>7082</td>
<td>0.91 [0.73, 1.13]</td>
<td></td>
</tr>
</tbody>
</table>

### D. Systemic Embolism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Risk Ratio 95% CI</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>15</td>
<td>9120</td>
<td>17</td>
<td>9081</td>
<td>0.88 [0.44, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>15</td>
<td>6015</td>
<td>21</td>
<td>6022</td>
<td>0.72 [0.37, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>13</td>
<td>6076</td>
<td>21</td>
<td>6022</td>
<td>0.61 [0.31, 1.22]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>29</td>
<td>7034</td>
<td>23</td>
<td>7036</td>
<td>1.26 [0.73, 2.18]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>15</td>
<td>7035</td>
<td>23</td>
<td>7036</td>
<td>0.65 [0.34, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>5</td>
<td>7061</td>
<td>22</td>
<td>7082</td>
<td>0.23 [0.09, 0.60]</td>
<td></td>
</tr>
</tbody>
</table>
## DOAC Bleeding Summary

### A. Major bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio 95% CI</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>327</td>
<td>9088</td>
<td>462</td>
<td>9052</td>
<td>0.70 [0.61, 0.81]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>322</td>
<td>6015</td>
<td>397</td>
<td>6022</td>
<td>0.81 [0.70, 0.94]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>375</td>
<td>6076</td>
<td>397</td>
<td>6022</td>
<td>0.94 [0.82, 1.07]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>254</td>
<td>7002</td>
<td>524</td>
<td>7012</td>
<td>0.49 [0.42, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>418</td>
<td>7012</td>
<td>524</td>
<td>7012</td>
<td>0.80 [0.70, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>395</td>
<td>7111</td>
<td>386</td>
<td>7125</td>
<td>1.03 [0.89, 1.18]</td>
<td></td>
</tr>
</tbody>
</table>

### B. Major gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Risk Ratio 95% CI</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>105</td>
<td>9088</td>
<td>119</td>
<td>9052</td>
<td>0.88 [0.68, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>133</td>
<td>6015</td>
<td>120</td>
<td>6022</td>
<td>1.11 [0.87, 1.42]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>182</td>
<td>6076</td>
<td>120</td>
<td>6022</td>
<td>1.50 [1.20, 1.89]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>129</td>
<td>7002</td>
<td>190</td>
<td>7012</td>
<td>0.68 [0.55, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>232</td>
<td>7012</td>
<td>190</td>
<td>7012</td>
<td>1.22 [1.01, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>224</td>
<td>7111</td>
<td>154</td>
<td>7125</td>
<td>1.46 [1.19, 1.78]</td>
<td></td>
</tr>
</tbody>
</table>
## C. Intracranial bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5mg bid</td>
<td>52</td>
<td>9088</td>
<td>122</td>
<td>9052</td>
<td>0.42</td>
<td>[0.31, 0.59]</td>
</tr>
<tr>
<td>Dabigatran 110mg bid</td>
<td>27</td>
<td>6015</td>
<td>87</td>
<td>6022</td>
<td>0.31</td>
<td>[0.20, 0.48]</td>
</tr>
<tr>
<td>Dabigatran 150mg bid</td>
<td>36</td>
<td>6076</td>
<td>87</td>
<td>6022</td>
<td>0.41</td>
<td>[0.28, 0.60]</td>
</tr>
<tr>
<td>Edoxaban 30mg daily</td>
<td>41</td>
<td>7002</td>
<td>132</td>
<td>7012</td>
<td>0.31</td>
<td>[0.22, 0.44]</td>
</tr>
<tr>
<td>Edoxaban 60mg daily</td>
<td>61</td>
<td>7012</td>
<td>132</td>
<td>7012</td>
<td>0.46</td>
<td>[0.34, 0.62]</td>
</tr>
<tr>
<td>Rivaroxaban 20mg daily</td>
<td>55</td>
<td>7111</td>
<td>84</td>
<td>7125</td>
<td>0.66</td>
<td>[0.47, 0.92]</td>
</tr>
</tbody>
</table>

---

# Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD
(Based on Prescribing Information for the United States)*

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Warfarin</th>
<th>Dabigatran†</th>
<th>Rivaroxaban†</th>
<th>Apixaban†</th>
<th>Edoxiban†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/mild impairment</td>
<td>Dose adjusted for INR 2.0–3.0</td>
<td>150 mg BID (CrCl &gt;30 mL/min)</td>
<td>20 mg QD with the evening meal (CrCl &gt;50 mL/min)</td>
<td>5.0 or 2.5 mg BID‡</td>
<td>CrCl &gt;95 DO NOT USE CrCl 51-94 60 mg QD</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>Dose adjusted for INR 2.0–3.0</td>
<td>150 mg BID (CrCl &gt;30 mL/min)</td>
<td>15 mg QD with the evening meal (CrCl 30–50 mL/min)</td>
<td>5.0 or 2.5 mg BID‡</td>
<td>30 mg QD CrCl 15–50 mL/min</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>Dose adjusted for INR 2.0–3.0 §</td>
<td>75 mg BID (CrCl 15–30 mL/min)</td>
<td>15 mg QD with the evening meal (CrCl 15–30 mL/min)</td>
<td>No recommendation ¶</td>
<td>Not recommended (CrCl &lt;15 mL/min)</td>
</tr>
<tr>
<td>End-stage CKD not on dialysis</td>
<td>Dose adjusted for INR 2.0–3.0 §</td>
<td>Not recommended¶ (CrCl &lt;15 mL/min)</td>
<td>Not recommended¶ (CrCl &lt;15 mL/min)</td>
<td>No recommendation ¶</td>
<td>Not recommended (CrCl &lt;15 mL/min)</td>
</tr>
<tr>
<td>End-stage CKD on dialysis</td>
<td>Dose adjusted for INR 2.0–3.0 §</td>
<td>Not recommended¶ (CrCl &lt;15 mL/min)</td>
<td>Not recommended¶ (CrCl &lt;15 mL/min)</td>
<td>Not recommended (CrCl &lt;15 mL/min)</td>
<td>Not recommended (CrCl &lt;15 mL/min)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: In a population-based study of patients receiving DOAC agents, we found apixaban had the most favorable GI safety profile and rivaroxaban the least favorable profile. GI bleeding events among patient aged 75 years or older taking DOACs increased with age; the risk was greatest among persons 75 years. Apixaban had the most favorable GI safety profile among all age groups.
Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; Lindsey R. Sangaralingham, MPH; M. Fernanda Bellolio, MD, MS; Robert D. McBane, MD; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

**Background**—The introduction of non–vitamin K antagonist oral anticoagulants has been a major advance for stroke prevention in atrial fibrillation; however, outcomes achieved in clinical trials may not translate to routine practice. We aimed to evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin.

**Methods and Results**—Using a large US insurance database, we identified privately insured and Medicare Advantage patients with nonvalvular atrial fibrillation who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015. We created 3 matched cohorts using 1:1 propensity score matching: apixaban versus warfarin (n=15 390), dabigatran versus warfarin (n=28 614), and rivaroxaban versus warfarin (n=32 350). Using Cox proportional hazards regression, we found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, P=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, P=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, P=0.56). For major bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR 0.45, 95% CI 0.34–0.59, P<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, P<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20, P=0.60). All non–vitamin K antagonist oral anticoagulants were associated with a lower risk of intracranial bleeding.

**Conclusions**—In patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. (*J Am Heart Assoc.* 2016;5:e003725 doi: 10.1161/JAHA.116.003725)
Guidelines for Management of AF

BRIEF REPORT


Craig I. Coleman, Matthias Antz, Kevin Bowrin, Thomas Evers, Edgar P. Simard, Hendrik Bonnemeier and Riccardo Cappato

University of Connecticut School of Pharmacy, Storrs, CT, USA; Hospital Oldenburg, Department of Cardiology, Oldenburg, Germany; Bayer Pharma AG, Berlin, Germany; Bayer Pharma AG, Wuppertal, Germany; Action Inc., New York, NY, USA; University Medical Center of Schleswig-Holstein, Department of Electrophysiology and Rhythmology, Kiel, Germany; Arrhythmia and Electrophysiology Research Center, Humanitas Clinical and Research Center, Rozzano, MI, Italy

ABSTRACT

Background: Little data exists regarding the effectiveness and safety of rivaroxaban or apixaban versus warfarin in nonvalvular atrial fibrillation (NVAF) patients treated outside of clinical trials.

Methods: This was a retrospective study using MarketScan claims from January 2012 to October 2014. We included adults, newly initiated on rivaroxaban, apixaban or warfarin, with a baseline CHA2DS2-VASc score ≥2, ≥2 diagnosis codes for NVAF and ≥180 days of continuous medical and prescription benefits. Patients with a prior stroke, systemic embolism or intracranial hemorrhage (ICH) were excluded. Eligible rivaroxaban or apixaban users were 1:1 propensity-score matched individually to warfarin users. Cox regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for rivaroxaban and apixaban versus warfarin for the combined endpoint of ischemic stroke or ICH and each endpoint individually.

Results: Upon matching 11,411 rivaroxaban to 11,411 warfarin users, rivaroxaban was associated with a significant reduction of the combined endpoint of ischemic stroke or ICH versus warfarin (HR = 0.61, 95% CI = 0.45-0.82). ICH was significantly reduced (HR = 0.53, 95% CI = 0.35-0.79) and ischemic stroke nonsignificantly reduced (HR = 0.71, 95% CI = 0.47-1.07) by rivaroxaban versus warfarin. After matching 4083 apixaban and 4083 warfarin users, apixaban was found to nonsignificantly reduce the combined endpoint of ischemic stroke or ICH versus warfarin (HR = 0.63, 95% CI = 0.35-1.12) and to reduce ICH risk (HR = 0.38, 95% CI = 0.17-0.88). Ischemic stroke risk was nonsignificantly increased with apixaban (HR = 1.13, 95% CI = 0.49-2.63) versus warfarin.

Limitations: Sample size and number of combined events observed were relatively small. Residual confounding could not be ruled out.

Conclusions: Rivaroxaban and apixaban were associated with less ICH than warfarin and both are likely associated with reductions in the combined endpoint. Further investigation to validate the numerically higher rate of ischemic stroke with apixaban versus warfarin is required.
Anticoagulation Strategies

Choose the OAC drug considering the patient profile and/or preferences

- **RECURRENT STROKE/TIA DESPITE WELL CONTROLLED VKA**
  - Consider agent with superior efficacy for preventing both IS and hemorrhagic stroke
  - If CrCl < 15mls/min, VKA
  - D150
  - A R D75 E30

- **PATIENT HAS MODERATE-SEVERE RENAL IMPAIRMENT**
  - *ie. CrCl 15-49 mls/min*
  - A D110

- **HIGH RISK OF GI BLEEDING**
  - A

- **GI SYMPTOMS OR DYSPESIA**
  - Consider also increased risk of bleeding
  - D110
  - A E

- **HIGH RISK OF BLEEDING [HAS-BLED≥3]**
  - Consider agent with lowest bleed incidence
  - D110
  - A E

- **Patient preference for once daily dosing**
  - R VKA E

Trends in DOAC Prescription
Who should remain on warfarin?

- Patient already receiving warfarin and stable whose INR is easy to control
- If dabigatran, rivaroxaban, apixaban or edoxaban not available
- Cost
- If patient not likely to comply with twice daily dosing (Dabigatran, Apixaban or edoxaban)
- Chronic kidney disease/ESRD (GFR < 15 ml/min)
How about Clopidogrel + Aspirin?

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

ABSTRACT

BACKGROUND
Vitamin K antagonists reduce the risk of stroke in patients with atrial fibrillation but are considered unsuitable in many patients, who usually receive aspirin instead. We investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with atrial fibrillation.

METHODS
A total of 7554 patients with atrial fibrillation who had an increased risk of stroke and for whom vitamin K-antagonist therapy was unsuitable were randomly assigned to receive clopidogrel (75 mg) or placebo, once daily, in addition to aspirin. The primary outcome was the composite of stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes.
## Vascular events and major bleeding: ACTIVE-W final results

<table>
<thead>
<tr>
<th>End point</th>
<th>Clopidogrel + ASA</th>
<th>Warfarin</th>
<th>Relative risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular events (%/year)</td>
<td>5.64</td>
<td>3.63</td>
<td>1.45</td>
<td>0.0002</td>
</tr>
<tr>
<td>Major bleeding (%/year)</td>
<td>2.4</td>
<td>2.2</td>
<td>1.06</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Guidelines for Management of AF

Barriers to Treatment-

• Patients are often reluctant

• Physicians’ overestimation of the risks of anticoagulation is the most consistently cited explanation for warfarin under-use

• Physicians’ risk perceptions may be influenced by their experiences with warfarin use
  – For example, in one small survey, physicians who reported having patients experience adverse events from anticoagulation were less likely to prescribe warfarin

• Different types of adverse events may have more influence on practice than others
  1. Bleeding in a patient to whom a physician prescribed warfarin
  2. Thromboembolic stroke in patient to whom a physician did not prescribe warfarin
Guidelines for Management of AF

- Is there a greater risk of stroke or bleeding?
Guidelines for Management of AF

HAS-BLED SCORE

Major Bleed:
Intracranial, intraocular, or retroperitoneal hemorrhage, death, clinically overt blood loss resulting in a decrease in hemoglobin of more than 2 g/dL
Transfusion of 2 or more units of packed RBCs or whole blood.

• 67% of the major bleeding events were gastrointestinal and 15% were intracranial.
# HAS-BLED Score

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong> Hypertension</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> Abnormal renal or liver function (1 each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>S</strong> Stroke</td>
<td>1</td>
</tr>
<tr>
<td><strong>B</strong> Bleeding</td>
<td>1</td>
</tr>
<tr>
<td><strong>L</strong> Labile INR</td>
<td>1</td>
</tr>
<tr>
<td><strong>E</strong> Elderly age</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong> Drugs or alcohol (1 each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Maximum Score** 9

Hypertension: SBP > 160 mmHg; Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine ≥ 200μmol/L; Abnormal liver function: Chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding: Previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Patients (n = 7329)</th>
<th>Adjusted stroke rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2</td>
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<tr>
<td>3</td>
<td>1730</td>
<td>3.2</td>
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<tr>
<td>4</td>
<td>1718</td>
<td>4.0</td>
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<tr>
<td>5</td>
<td>1159</td>
<td>6.7</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>294</td>
<td>9.6</td>
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<td>8</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HAS-BLED score</th>
<th>n</th>
<th>Bleeds, n</th>
<th>Bleeds/100 patients*</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>798</td>
<td>9</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1286</td>
<td>13</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>744</td>
<td>14</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>187</td>
<td>7</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>1</td>
<td>12.50</td>
</tr>
<tr>
<td>Any score</td>
<td>3071</td>
<td>48</td>
<td>1.56</td>
</tr>
</tbody>
</table>
Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCPC; Graham Nichol, MD, MPH, FRCPC; Anita Lau; Andreas Laupacis, MD, MSc, FRCPC

**Objective:** To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

**Design:** A Markov decision analytic model was used to determine the preferred treatment strategy (no antithrombotic therapy, long-term aspirin use, or long-term warfarin use) for patients with atrial fibrillation who are 65 years of age and older, are at risk for falling, and have no other contraindications to antithrombotic therapy. Input data were obtained by systematic review of MEDLINE. Outcomes were expressed as quality-adjusted life-years.

**Results:** For patients with average risks of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients' age or baseline risk of stroke, the risk of falling was not an important factor in determining their optimal antithrombotic therapy.

**Conclusions:** For elderly patients with atrial fibrillation, the choice of optimal therapy to prevent stroke depends on many clinical factors, especially their baseline risk of stroke. However, patients' propensity to fall is not an important factor in this decision.

*Arch Intern Med. 1999;159:677-685*
Accessing Risk in Patients with AF

Choosing Antithrombotic Therapy for Elderly Patients with AF Who are at Risk for Falls

- Persons taking Warfarin must fall about 295 times in 1 year for warfarin to not be the optimal therapy

- Since approximately 1 in 10 falls cause major injury, including fractures, persons who fall are much more likely to suffer other serious morbidity before developing brain hemorrhage

(Arch Intern Med. 1999; 159, 677-685)
Interruption of anticoagulation for surgery/procedures and bridging
A Bridge Too Far?

While bridge anticoagulation is common, it is also a common dilemma for health care providers treating patients on anticoagulation therapy. A review article published Sept. 14 in JACC raises the question of just when this course of action is necessary.

More than 35 million prescriptions for oral anticoagulants are written each year and 15-20% of patients will undergo an invasive procedure or surgery that interrupts their chronic oral anticoagulation, which puts them at risk for thromboembolism, hemorrhage, or death. Periprocedural anticoagulation is a common clinical dilemma and may lead to significant adverse events in patients. There is large agreement on three important principles surrounding bridging: (1) oral anticoagulants should not be interrupted for procedures with low bleeding risk; (2) patients at high risk for thromboembolism without excessive bleeding risk should consider bridging, while those at low thromboembolism risk should not be bridged; and (3) cases with intermediate risk should be managed by considering patient- and procedure-specific risk for bleeding and thromboembolism.

Despite these recommendations, surveys show that 30% of physicians choose to bridge patients at low risk of thromboembolism and bridging, including the recent BRIDGE trial. They note that recent data suggest that 40-60% of oral anticoagulant interruptions may be unnecessary, and furthermore, that the interruption and re-initiation of warfarin can be associated with an increased incidence of stroke. Additionally, certain operations like orthopedic surgeries may tolerate the continuation of anticoagulants.

Overall, their review found that the rate of periprocedural thromboembolism for unbridged oral anticoagulation interruption is rare, at an estimated 0.53% from over 23,000 interruptions in 17 studies between 1966 and 2015. The rate of thromboembolism for patients who are bridged is only slightly higher at 0.92%. Rates of bleeding and thromboembolism vary by oral anticoagulation indication. The risk of thromboembolism with mechanical heart valves is around 1%. In left ventricular assist devices, where the management of anticoagulants is complex and lacking consensus, data show a 1.5% risk of thromboembolism. Most recent studies show a periprocedural bleeding to thrombosis ratio of 13:1 with bridging and 5:1 without bridging, "suggesting that the net effect of bridging is unbalanced toward bleeding." In one study, 14 atrial fibrillation (AF) patients on oral anticoagulants died after heparin bridging compared to no deaths in the control group without heparin.

The bridged group should have had higher scores. The study also found that bridging was associated with a 4-fold increased risk of bleeding.

The BRIDGE trial, recently published in the New England Journal of Medicine, "provides the most compelling evidence that routine bridging in moderate risk patients is harmful," according to Rechmacher and Fang. In the study, AF patients undergoing a procedure with planned warfarin interruption were randomized to anticoagulation bridging with low-molecular weight heparin, dalteparin or placebo. A large majority (89.4%) of the patients were designated as low bleeding risk. The rate of thromboembolism in the placebo group was noninferior to the bridging group, while major and minor bleeding in the placebo group was significantly less in the non-bridging group.

Moving forward, Rechmacher and Fang note that the upcoming PERIO2 study may help to answer the question about whether to bridge patients with AF and a high CHADS2. They also point out that "novel anticoagulants may also offer a safer and simpler periprocedural management strategy than warfarin" in the future. However, more studies are needed to determine the safety of interrupting and restarting these new therapies.

"While awaiting the results of additional randomized trials, physicians should carefully reconsider the practice of routine bridging and whether periprocedural anticoagulation interruption is even necessary," they write. They recommend avoiding interruptions strategies should be considered.

"This excellent comprehensive review by Rechmacher et al provides further evidence that physicians need to be more careful regarding the use of bridging anticoagulation around the time of procedures," says Robert P. Giugliano, MD, associate professor of medicine and Brigham and Women's Hospital and the editorial lead of the ACC's Anticoagulant Community. "This paper further supports the notion that we should use bridging anticoagulation less frequently, reserving it only for patients at the highest risk for thromboembolism."

He adds that it is important to avoid the easy comparison of exchanging one bleed for one stroke. "If you use bridging, you are likely to have a better net outcome, but you don't want to be doing it needlessly."
## ACCP 2012 Bridging Guidelines

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Indication for VKA Therapy</th>
<th>Mechanical Heart Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CHADS(_2) score of 5 or 6</td>
<td>Recent (within 3 mo) VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recent (within 3 mo) stroke or transient ischemic attack</td>
<td>Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rheumatic valvular heart disease</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td>CHADS(_2) score of 3 or 4</td>
<td>VTE within the past 3-12 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active cancer (treated within 6 mo or palliative)</td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
<td>CHADS(_2) score of 0 to 2 (assuming no prior stroke or transient ischemic attack)</td>
<td>VTE &gt; 12 mo previous and no other risk factors</td>
</tr>
</tbody>
</table>
ACCP 2012 Bridging Guidelines

- In patients with a mechanical heart valve, Afib, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation during interruption of VKA therapy (Grade 2C)
  - CHADS<sub>2</sub> 5-6, < 3 months CVA/TIA, or rheumatic valve disease
- In patients at moderate risk for thromboembolism, the bridging or no bridging approach is based on individual patient- and surgery-related risk factors
  - CHADS<sub>2</sub> 3-4
- In patients at low risk, we suggest no bridging during interruption of VKA therapy (Grade 2C)
  - CHADS<sub>2</sub> 0-2, no TIA/CVA
Mayo 2013 Bridging Guidelines

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bridging Therapy Required</th>
<th>No Bridging Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical heart valve</td>
<td>Mitral-valve replacement, two or more mechanical valves, non-bileaflet aortic-valve replacement, or aortic-valve replacement with other risk factors</td>
<td>Aortic-valve replacement, bileaflet prosthesis, and no additional risk factors</td>
<td>Other risk factors include prior stroke, TIA, intracardiac thrombus, or cardioembolic event</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>Prior stroke or embolic event, cardiac thrombus, or CHADS&lt;sub&gt;2&lt;/sub&gt; score of ≥4</td>
<td>No prior stroke or embolic event, absence of cardiac thrombus, or CHADS&lt;sub&gt;2&lt;/sub&gt; score of &lt;4</td>
<td>Prior stroke, TIA, intracardiac thrombus, or cardioembolic event increases risk</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Venous thromboembolism within previous 3 mo or severe thromboembolus</td>
<td>Venous thromboembolism &gt;3 mo previously or no additional risk factors (e.g., active cancer and nonsevere thromboembolism)</td>
<td>Consider inferior vena cava filter if venous thromboembolism occurred &lt;1 mo previously, if urgent or emergency surgery is required, or if there is a contraindication to anticoagulation therapy</td>
</tr>
</tbody>
</table>

Differences with ACCP:
- **No uncertainty with moderate risk group**
- Anyone with stroke/TIA was high risk regardless of timing of index event
- Includes cardiac thrombus
- Excludes valvular afib

New Data Regarding Bridge Therapy

- BRIDGE investigators RCT (2015)

- 1884 non-valvular atrial fibrillation patients
  - *May not apply to valvular afib, mechanical valves, LVADs, recently diagnosed thromboembolism (<3 months), Afib patients with CHF, post ACS setting etc.*

- Elective endoscopic and surgical procedures
- Randomized to bridging vs. no bridging
- Bridging Group (when compared to no bridging)
  - More major bleeding (3.2% vs. 1.3%)
  - No difference in thromboembolism risk (0.3% vs. 0.4%)

Douketis et al. NEJM 2015;373:823-833
Neena S. Abraham MD, MSc . Presentation- Antithrombotics and Endoscopy: Advice for Endoscopy Nurses from Cardiogastroenterology Clinic Mayo Clinic
Current Practice

- In high-risk patients (particularly those with mechanical valves, prior stroke, TIA, or systemic embolism), or when a series of procedures requires interruption of oral anticoagulant therapy for longer than a 10 day period, low-molecular-weight heparin may be administered subcutaneously.
Discontinuation of Oral Anticoagulation
New Data Regarding Discontinuation of OAC

Interventions NOT necessarily requiring discontinuation of anticoagulation

Dental interventions
  Extraction of one to three teeth
  Paradontal surgery
  Incision of abscess
  Implant positioning
Ophthalmology
  Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
## Temporary interruption of NOAC prior to endoscopic procedure

<table>
<thead>
<tr>
<th>Drug (Creatinine Clearance)</th>
<th>Last dose prior to low–risk endoscopic procedure *</th>
<th>Last dose prior to high–risk endoscopic procedure **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (&gt;50 mL/min)</td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>Dabigatran (31- 50 mL/min)</td>
<td>2 days</td>
<td>4 days</td>
</tr>
<tr>
<td>Dabigatran (&lt;30 mL/min)</td>
<td>4 days</td>
<td>6 days</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban/Edoxaban (&gt;50 mL/min)</td>
<td>1 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban/Edoxaban (31 to 50 mL/min)</td>
<td>1-2 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban/Edoxaban (&lt; 30 mL/min)</td>
<td>2 days</td>
<td>4 days</td>
</tr>
</tbody>
</table>

* A low-risk procedure has a 48 hour risk of major bleeding of 0% to 2%; a high-risk procedure ** has a 48 hour risk of major bleeding of 2% to 4%
Use of Direct Oral Anticoagulants in Patients with Bioprosthetic Valves
Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

Giulia Renda, MD, PhD, a Fabrizio Ricci, MD, a Robert P. Giugliano, MD, SM, b Raffaele De Caterina, MD, PhD a

ABSTRACT

BACKGROUND Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist. Phase III trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin excluded patients with moderate/severe mitral stenosis or mechanical heart valves, but variably included patients with other VHD and valve surgeries.

OBJECTIVES This study aimed to determine relative safety and efficacy of NOACs in patients with VHD.

METHODS We performed a meta-analysis of the 4 phase III AF trials of the currently available NOACs versus warfarin in patients with coexisting VHD to assess pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for stroke/systemic embolic events (SSEE), major bleeding, intracranial hemorrhage (ICH), and all-cause death.

RESULTS Compared with warfarin, the rate of SSEE in patients treated with higher-dose NOACs was lower and consistent among 13,585 patients with (RR: 0.70; 95% CI: 0.58 to 0.86) or 58,098 without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; interaction p = 0.13). Major bleeding in patients on higher-dose NOACs versus warfarin was similar and consistent among patients with (RR: 0.93; 95% CI: 0.68 to 1.27) or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02; interaction p = 0.63 for VHD/no-VHD difference). Intracranial hemorrhage was lower with higher-dose NOACs than with warfarin irrespective of VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and 0.49; 95% CI: 0.41 to 0.59, respectively; interaction p = 0.91). No protective effect of higher-dose NOACs in preventing all-cause death seemed to be present in patients with VHD versus without VHD (RR: 1.01; 95% CI: 0.90 to 1.14 vs. RR: 0.88; 95% CI: 0.82 to 0.94, respectively; interaction p = 0.03).

CONCLUSIONS High-dose NOACs provide overall efficacy and safety similar in AF patients with or without VHD.

(J Am Coll Cardiol 2017;69:1363–71) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Guidelines for Management of AF

- In patients with AF and VHD (other than moderate/severe mitral stenosis or mechanical heart valves) NOACs are attractive alternatives to VKAs because the coexistence of VHD does not affect the overall relative efficacy or safety of NOACs in terms of prevention of SSEE and major bleeding. Current definitions of “valvular” and “nonvalvular” AF are misleading, and the use of NOACs should be permitted in most patients with VHD.

- The recently proposed term “MARM-AF,” standing for “Mechanical And Rheumatic Mitral valvular AF” could be useful to identify the true high risk AF patients for whom VKAs are the anticoagulants of choice.
**CENTRAL ILLUSTRATION:** SSEE and Major Bleeding in Patients Without and With VHD, Treated With Higher-Dose NOACs or Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Study or Subgroup</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO VHD</strong></td>
<td></td>
<td><strong>NO VHD</strong></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td>ARISTOTLE</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (Higher Dose)</td>
<td>0.84 (0.75-0.95)</td>
<td>ENGAGE AF-TIMI 48 (Higher Dose)</td>
<td>0.85 (0.70-1.02)</td>
</tr>
<tr>
<td>RE-LY (Higher Dose)</td>
<td></td>
<td>RE-LY (Higher Dose)</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</td>
<td></td>
<td>ROCKET AF</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>RR (95% CI)=0.84 (0.75-0.95)</td>
<td><strong>Subtotal</strong></td>
<td>RR (95% CI)=0.85 (0.70-1.02)</td>
</tr>
<tr>
<td><strong>VHD</strong></td>
<td></td>
<td><strong>VHD</strong></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td>ARISTOTLE</td>
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</tr>
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<td>ENGAGE AF-TIMI 48 (Higher Dose)</td>
<td>0.93 (0.68-1.27)</td>
</tr>
<tr>
<td>RE-LY (Higher Dose)</td>
<td></td>
<td>RE-LY (Higher Dose)</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</td>
<td></td>
<td>ROCKET AF</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>RR (95% CI)=0.70 (0.58-0.86)</td>
<td><strong>Subtotal</strong></td>
<td>RR (95% CI)=0.93 (0.68-1.27)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>RR=0.81 (0.73-0.89)</td>
<td><strong>Total (95% CI)</strong></td>
<td>RR=0.88 (0.75-1.02)</td>
</tr>
</tbody>
</table>

### Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO VHD</td>
<td>-0.755</td>
<td>0.1804</td>
<td>19.5%</td>
<td>0.47 [0.33, 0.67]</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>-0.734</td>
<td>0.1612</td>
<td>21.8%</td>
<td>0.48 [0.35, 0.66]</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (higher dose)</td>
<td>-0.844</td>
<td>0.2189</td>
<td>15.6%</td>
<td>0.43 [0.28, 0.66]</td>
<td></td>
</tr>
<tr>
<td>RE-LY (higher dose)</td>
<td>-0.5276</td>
<td>0.1983</td>
<td>17.6%</td>
<td>0.59 [0.40, 0.87]</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>74.5%</td>
<td>0.49 [0.41, 0.59]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.30$, df = 3 ($P = 0.73$); $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 7.67$ ($P &lt; 0.00001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### VHD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE VHD</td>
<td>-1.273</td>
<td>0.3537</td>
<td>7.8%</td>
<td>0.28 [0.14, 0.56]</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 VHD (higher dose)</td>
<td>-0.9416</td>
<td>0.4875</td>
<td>4.5%</td>
<td>0.39 [0.15, 1.01]</td>
<td></td>
</tr>
<tr>
<td>RE-LY VHD (higher dose)</td>
<td>-1.0217</td>
<td>0.3828</td>
<td>6.8%</td>
<td>0.36 [0.17, 0.76]</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF VHD</td>
<td>0.239</td>
<td>0.3999</td>
<td>6.4%</td>
<td>1.27 [0.58, 2.78]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>25.5%</td>
<td>0.47 [0.24, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 8.94$, df = 3 ($P = 0.03$); $I^2 = 66%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.17$ ($P = 0.03$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

| Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 10.33$, df = 7 ($P = 0.17$); $I^2 = 32\%$ | 100.0% | 0.48 [0.39, 0.60] |                               |
| Test for overall effect: $Z = 6.65$ ($P < 0.00001$) | 100.0% | 0.48 [0.39, 0.60] |                               |
| Test for subgroup interactions: $\chi^2 = 0.01$, df = 1 ($P = 0.91$), $I^2 = 0\%$ | 100.0% | 0.48 [0.39, 0.60] |                               |
### All-cause death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO VHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>-0.1744</td>
<td>0.0716</td>
<td>16.8%</td>
<td>0.84 [0.73, 0.97]</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (higher dose)</td>
<td>-0.1278</td>
<td>0.0615</td>
<td>22.7%</td>
<td>0.88 [0.78, 0.99]</td>
<td></td>
</tr>
<tr>
<td>RE-LY (higher dose)</td>
<td>-0.1393</td>
<td>0.0757</td>
<td>15.0%</td>
<td>0.87 [0.75, 1.01]</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>-0.0943</td>
<td>0.0657</td>
<td>19.9%</td>
<td>0.91 [0.80, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>74.5%</td>
<td>0.88 [0.82, 0.94]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.69, df = 3 (P = 0.87); I^2 = 0$

Test for overall effect: $Z = 3.87 (P = 0.0001)$

<table>
<thead>
<tr>
<th>VHD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE VHD</td>
<td>0.01</td>
<td>0.094</td>
<td>9.7%</td>
<td>1.01 [0.84, 1.21]</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 VHD (higher dose)</td>
<td>0.1222</td>
<td>0.1161</td>
<td>6.4%</td>
<td>1.12 [0.90, 1.42]</td>
<td></td>
</tr>
<tr>
<td>RE-LY VHD (higher dose)</td>
<td>-0.0943</td>
<td>0.1339</td>
<td>4.8%</td>
<td>0.91 [0.70, 1.18]</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF VHD</td>
<td>-0.0202</td>
<td>0.1365</td>
<td>4.6%</td>
<td>0.98 [0.75, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>25.5%</td>
<td>1.01 [0.90, 1.14]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 1.59, df = 3 (P = 0.66); I^2 = 0$

Test for overall effect: $Z = 0.22 (P = 0.82)$

| Total (95% CI)                  |                 |      | 100.0% | 0.91 [0.86, 0.96]             |                               |

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 6.90, df = 7 (P = 0.44); I^2 = 0$

Test for overall effect: $Z = 3.23 (P = 0.001)$

Test for subgroup interactions: $\chi^2 = 4.62, df = 1 (P = 0.03), I^2 = 78.4$

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Giulia Renda et al. JACC 2017;69:1363-1371
Device Based Solutions
Unable To Take Warfarin or DOAC?

- Frail, numerous falls
- GI bleeds
- Cerebral bleeds
- Stroke despite therapeutic warfarin
- Non-compliant / labile INR
- (Do not want warfarin or DOAC)
Introducing the WATCHMAN™ LAAC Device

A first-of-its-kind, proven alternative to long-term warfarin therapy for stroke risk reduction in patients with non-valvular AF

Most studied LAAC therapy, only one proven with long-term data from randomized trials or multi-center registries

Comparable stroke risk reduction, and statistically superior reductions in hemorrhagic stroke, disabling stroke and cardiovascular death compared to warfarin over long-term follow-up⁴,²

The WATCHMAN™ Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS$_2$ or CHA$_2$DS$_2$-VASc scores and are recommended for anticoagulation therapy;

- Are deemed by their physicians to be suitable for warfarin; and

- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.
WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
  - IC/EP or IC&EP, TEE, General Anesthesia, Surgical Back-up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein
  (Does not require open heart surgery)

- General anesthesia*
- 1 hour procedure*
- 1-2 day hospital stay

* Typical to patient treatment in U.S. clinical trials
WATCHMAN™ Device Endothelialization

Canine Model – 30 Day

Canine Model – 45 Day

Human Pathology – 9 Months Post-implant (Non-device related death)

Images on file at Boston Scientific Corporation.
Results in animal models may not necessarily be indicative of clinical outcomes.
Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke or SE</td>
<td>0.79</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.95</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.56</td>
<td>0.21</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.48</td>
<td>0.006</td>
</tr>
</tbody>
</table>

| All-cause death                               | 0.73  | 0.07    |
| Major bleed, all                              | 1.00  | 0.98    |
| Major bleeding, non procedure-related         | 0.51  | 0.002   |

Source: Holmes DR, et al. Holmes, DR et al. JACC 2015; In Press. Combined data set of all PROTECT AF and PREVAIL WATCHMAN patients versus chronic warfarin patients
WATCHMAN™ Device Reduces Ischemic Stroke Over No Therapy

* Imputation based on published rate with adjustment for CHA²DS²-VASc score (3.0); Olesen JB. Thromb Haemost (2011)
Device Based Solutions

• Biggest difference is recommended anti-platelet regimen.

• After treatment of a LAA occlusion device, patients are treated with oral anticoagulation (OAC) plus aspirin for 45 days followed by clopidogrel plus aspirin out to six months. Aspirin is continued for life.

• If OAC contraindicated- clopidogrel plus aspirin for six months.
Cryptogenic CVA
Background

- 30% of ischemic strokes are of unknown mechanism (Cryptogenic stroke)

- Detection of AF usually prompts long term anticoagulation instead of antiplatelet therapy

- Optimal monitoring duration to detect AF is currently undetermined

- AF may be paroxysmal, occur rarely, and be asymptomatic, making detection with routine methods difficult.
EMBRACE Study – also published in NEJM

- Canadian Study
- N = 572
- Subjects were ≥55 years old
- Two arms
  - 30 day event-triggered recorder
  - Standard care (24 hour Holter)
- Primary Outcome
  - AF episodes of 30 seconds or longer within 90 days
- Secondary Outcomes
  - AF episodes of 2.5 minutes or longer within 90 days
  - Anticoagulation status at 90 days
EMBRACE Results

• Primary Outcome
  – Event recorder detected AF episodes ≥30 seconds in **16.1%** of patients vs. **3.2%** in control arm

• Secondary Outcome
  – Event recorder detected AF episodes ≥2.5 minutes in **9.9%** of patients vs. **2.5%** in control arm

OAC prescribed in **18.6%** of patients in event recorder arm vs. **11.1%** in control arm
Objectives of CRYSTAL-AF

- To assess whether a long-term cardiac monitoring strategy with an implantable cardiac monitor (ICM) is superior to standard monitoring for the detection of AF in patients with Cryptogenic stroke.

- Determine the proportion of patients with cryptogenic stroke that have underlying AF.

- Determine actions taken after patient is diagnosed with AF.

- **Primary endpoint:** Detection of AF at 6 months
Comparison of Monitoring Strategies

Continuous Monitoring Arm: Implantation of REVEAL® XT

- Minimally invasive outpatient procedure
- Local anesthetic and no leads or fluoroscopy
- 15-30 minute procedure
- Device can be followed remotely
- MRI conditional
- 3 year device longevity
- Automatic AF detection algorithm

Standard Monitoring Arm

- Cardiac monitoring performed according to local standards, after mandated testing completed
- Symptoms consistent with AF were evaluated by study physicians

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), Richard Bernstein, MD, Ph.D., et al. NEJM June 26, 2014
Patient Follow-up

- Patients in both arms received scheduled follow-up visits at:
  - 1 month
  - 6 months
  - 12 months
  - Every 6 months thereafter until study closure

- Follow-up visits recorded:
  - Cardiac symptoms
  - Treatment modifications
  - Recurrence of stroke or TIA
  - Modified Rankin Scale
  - Health status (EQ-5D)
Primary Endpoint: DETECTION OF AF AT 6 MONTHS

Rate of detection in ICM arm was 8.9% vs 1.4% in control arm

CRYptogenic STroke and underlying Atrial Fibrillation (CRYSTAL AF), Richard Bernstein, MD, Ph.D., et al. NEJM June 26, 2014
## 6 Month Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time from Randomization to AF Detection</td>
<td>41 days</td>
<td>32 days</td>
</tr>
<tr>
<td>Patients found to have AF</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>% Asymptomatic Episodes</td>
<td>74%</td>
<td>33%</td>
</tr>
<tr>
<td>Oral Anticoagulation Usage, overall</td>
<td>10.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>OAC use in patients with detected AF</td>
<td>94.7%</td>
<td>66.7%</td>
</tr>
</tbody>
</table>
| Testing required to detect AF | Automatic AF detection | 88 ECGs  
20 24-hour Holters  
1 event recorder |
Secondary Endpoint: Detection of AF at 12 months

Rate of detection in ICM arm was 12.4% vs 2.0% in control arm

CRYptogenic STroke and underlying Atrial Fibrillation (CRYSTAL AF), Richard Bernstein, MD, Ph.D., et al. NEJM June 26, 2014
Detection of AF at 3 years

Rate of detection in ICM arm was **30.0% vs 3.0%** in control arm
Conclusions

- ICM is superior to standard monitoring in detection of AF at 6 months (HR = 6.43), 12 months (HR=7.32), and 36 months (HR=8.78) in patients with cryptogenic stroke.

- AF was detected in 8.9%, 12.4%, and 30% of patients at 6 months, 12 months, and 36 months in the ICM arm.

- 92.3% of patients with AF in the ICM arm had a day with greater than 6 minutes of AF.

- Detection of AF changed management to anticoagulation in 97% of patients.

- Long-term continuous monitoring should be performed in patients with cryptogenic stroke.
“Triple Therapy” Recommendations and the Risk of Bleeding
“Triple therapy” in patients with CAD/AF/ACS

To date, only two trials, WOEST and ISAR-TRIPLE, randomized patients requiring chronic anticoagulation and undergoing PCI to triple therapy (i.e. aspirin, clopidogrel, and VKA) or dual therapy (clopidogrel plus VKA).

In WOEST, almost 70% received OAC because of AF, but only a minority of patients had an ACS. WOEST demonstrated that triple therapy (continued for a full year) doubles the risk of bleeding complications compared with a single antiplatelet (SAPT) agent (clopidogrel) plus VKA. Although this small open-label study was underpowered for evaluation of efficacy outcomes, clopidogrel plus VKA was associated with an intriguing significantly lower mortality rate, the mechanism of which remains elusive.

Of note, no data are available on how SAPT therapy with aspirin + VKA would have performed. In ISAR-TRIPLE, 6 weeks of triple therapy (i.e. aspirin + VKA + clopidogrel) was compared with a 6-month strategy with the same therapy in patients exclusively treated with a DES. There was no significant difference in both bleeding or thrombotic events, or their combination, between the two strategies.
“Triple therapy” in patients with CAD/AF/ACS

There are currently three ongoing large-scale outcome studies evaluating combinations of NOAC or VKA and antiplatelets in patients with AF that undergo a PCI with stenting (elective or due to an ACS), providing hope that within the next few years there will be more evidence in this field.

1. The PIONEER AF PCI study (NCT01830543) evaluates the safety of two different rivaroxaban treatment strategies vs. VKA: (i) 15 mg rivaroxaban OD plus clopidogrel; (ii) 2.5 mg BID plus low-dose aspirin 75–100 mg plus clopidogrel, prasugrel or ticagrelor, followed by rivaroxaban 15 mg OD (or 10 mg for subjects with moderate renal impairment) plus aspirin for 12 months; or (iii) VKA treatment strategy utilizing similar combinations of antiplatelet therapy.

2. The RE-DUAL PCI study (NCT02164864) evaluates dual antithrombotic therapy regimens of (i) 110 mg dabigatran BID plus clopidogrel or ticagrelor, or (ii) 150 mg dabigatran BID plus clopidogrel or ticagrelor, with (iii) a triple antithrombotic therapy combination of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin for 1–3 months.

3. Finally, apixaban will be evaluated vs. VKA in AF patients with a recent ACS in the AUGUSTUS trial (NCT02415400). All patients will be receiving a P2Y12 inhibitor and will be randomized in a 2 × 2 factorial design to 6 months of apixaban 5 mg BID vs. VKA, and aspirin vs. placebo.

4. A similar trial with edoxaban, EVOLVE-AF-PCI, is likely to start.
Management of Bleeding
Management of DOAC Bleeding

Initial Assessment and Risk Stratification: The ABC’s
A= Airway; B= Breathing; C= Circulation

Mild Bleeding
- Delay next dose
- Anticoagulant effect dissipates 24 h (with no renal failure)
- T1/2= 12-17 h

Moderate-Severe Bleeding
- Correct hemodynamics to perfuse kidneys
- Blood-product transfusion
- Endoscopic evaluation
- +/- hemodialysis with renal failure
- Oral charcoal (if ingestion <2h)*; PPI probably helpful if recent ingestion (decreases absorption)

Life-Threatening Bleeding
- Consider rFVIIa or **PCC
- Charcoal filtration

Neena S. Abraham MD, MSc.
Presentation- Antithrombotics and Endoscopy: Advice for Endoscopy Nurses from Cardiogastroenterology Clinic Mayo Clinic

*Recommendations based on limited nonclinical data
** PCC= prothrombin concentrate complex

Antithrombotics and Endoscopy: Advice for Endoscopy Nurses from Cardiogastroenterology Clinic Antithrombotics and Endoscopy: Mayo Clinic
Management of Factor Xa Inhibitor Bleeding

- Hold drug(s)
- *No Vit K*
- Resuscitation (i.v. access, fluid administration, blood product transfusion)
- Maintain diuresis to clear drug
- Mechanical compression and surgical methods to stop bleeding
DOAC reversal agents

- **Idarucizumab (Praxbind®)**

  - Humanized monoclonal antibody with high affinity for dabigatran; binds free and thrombin-bound dabigatran
  - Clinical outcomes (Pollock CV et al. NEJM 2015):
    - N=90 bleeding patients on Dabigatran or with need for surgery.
    - 2.5 gram bolus IV X 2 normalized dilute thrombin time in 93-98% of patients.
    - Cessation of bleeding in 11.4 hours; normal surgical hemostasis in 92%
  - Approved 10/16/15 by FDA for “life threatening hemorrhage/need for emergency surgery or procedures”; REVERSE-AD trial ongoing (N=450)
DOAC reversal agents: In Development

• **Andexanet alpha**
  - Phase II study in healthy volunteers
  - Decreased anti-Xa activity and plasma concentration of free apixaban
  - Future studies required in the setting of major hemorrhage

• **Aripazine (PER977)**
  - Synthetic molecule binds to heparin, LMWH and DOACs in animals
  - Whole blood clotting time (*in vitro*) show reduction of edoxaban effect within 10 minutes of IV infusion (restoration to 10% over baseline)
  - Needs human studies and clinical trials
Dose-dependent reversal of Apixaban-induced Anti-FactorXa activity correlates with reduction in Apixaban plasma free fraction
Patients with warfarin-associated GIB and indications for continued long-term antithrombotic therapy should resume anticoagulation within the first week following hemorrhage.

Warfarin therapy resumption within 4-7 days of GI bleeding associated with lower risk of all-cause death: HR 0.31 (0.15-0.62)
Use of the Direct Oral Anticoagulants in Obese Patients
The use of anticoagulants in morbidly obese patients

Justyna Domienik-Karlowicz, Piotr Pruszczyk

Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Poland

Abstract

Due to its constantly growing incidence, obesity is an increasingly serious social and medical problem. Available data on the use of novel oral anticoagulants in morbidly obese and obese patients are very limited. However, we tried to summarize the available knowledge on the use of anticoagulants in this subpopulation of patients in everyday clinical practice. Studies on the clinical use of anticoagulants provide a poor basis for any adjustment of doses in obese patients as compared to patients with normal body weight. In our opinion, further studies are required in this particular population. (Cardiol J 2016; 23, 1: 12–16)
Conclusions

• Atrial Fibrillation is significantly underestimated
• CHADS-2 VASC scoring system allows for a more accurate method of assessing risk and appropriate treatment
• DOACs provide opportunity to minimize growing burden of potentially preventable thromboembolism (especially AF)
• Reductions in both stroke and bleeding translate into important benefits for patients
• Most bleeding can be managed without specific antidotes
• Specific antidotes in development will provide reassurance to physicians
• Device based approaches to detecting the incidence of AF and reducing the risk of thromboembolism are readily available.
Thank You for your attention!
References

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SH230-609-AD June 201
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