Πρόσφατα και Προοπτικά δεδομένα 
Καθημερινής Κλινικής 
Πρακτικής από τη χρήση 
των νεότερων από του 
στόματος αντιπηκτικών 

Γεώργιος Ανδρικόπουλος, MD, PhD, FESC
Πρόεδρος ΙΜΕΘΑ
Διευθυντής Α Καρδιολογικού τμήματος κι 
Εργαστηρίου Ηλεκτροφυσιολογίας/Βηματοδότησης,
Ερρίκος Ντυνάν Hospital Center
The presenter has received honoraria for participation in lectures and advisory boards from the following pharmaceutical and biotechnology companies:

- AstraZeneca,
- Bard,
- Bayer Healthcare,
- Boehringer Ingelheim,
- Boston Scientific,
- Bristol-Myers Squibb,
- ELPEN,
- Galenica,
- Lilly,
- Medtronic,
- Menarini,
- MSD,
- Pfizer,
- Sanofi,
- Servier,
- StJude,
- Unifarma,
- Vianex.
### Stroke prevention in patients with atrial fibrillation (2)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).</td>
<td>IIb</td>
<td>A</td>
</tr>
</tbody>
</table>
Management of Atrial Fibrillation in Greece: the MANAGE-AF Study


603 consecutive patients with AF from 27 centers on a countrywide basis

6-month follow-up

Baseline status

AOC* 49%
APL 23%
No Drug 28%

68%
Background – Published GARFIELD-AF data show an increase in the prescribing of anticoagulant therapy over time.

Relative to NOACs, prescribing of VKAs has diminished since 2010.

![Bar chart showing the proportion of patients receiving different anticoagulant therapies over time.

Proportion of patients, %

Cohort 1 2010–11 (n=5311)
Cohort 2 2011–13 (n=11,562)
Cohort 3 2013–14 (n=11,343)
Cohort 4 2014–15 (n=10,923)
Cohort 5 2015–16 (n=11,372)

Camm et al. Heart 2016 (cohort 1–4); cohort 5 unpublished data

VKA, Vitamin K antagonist; NOAC, Non-VKA oral anticoagulant; AP, Antiplatelet

www.garfieldregistry.org
Medicines lifecycle: Development, Regulatory Requirements and Monitoring

Pre-clinical Phase
- Drug discovery
- Identification of candidate
- Non-clinical testing
- Safety and Efficacy tests

Clinical Trials
- Phase I
  The first human studies of a new drug - safety and dose-related side effects.
- Phase II
  The effectiveness for a specific therapeutic use in patients (whether the drug works in a certain disease or condition), safety evaluation.
- Phase III
  Sufficient information on the drug safety and efficacy to enable adequate assessment of the benefit/risk ratio for the drug and provide information for drug labeling.

Regulatory
- Submission of marketing authorisation request
- Approval after evaluation by authorities
- Availability and pricing dependent upon individual country

Post-marketing Activities
- Phase IV post-market monitoring process
  The sponsor is required to submit periodic updates to FDA/EMA; An ongoing post-market surveillance system to detect serious, unexpected adverse events and take actions as needed (e.g., the Sentinel Initiative designed by FDA), etc.
What are the differences and similarities between RWD and data from clinical trials?

Randomised clinical trials provide

- High level of evidence as a basis for approval of treatment
- Data from controlled, randomised, unbiased populations
- Basis for treatment guidelines

Real-world data provide

- Results as a basis for generating hypotheses* and interpreting results from clinical practice
- Data from non-randomised patients
- Additional data to help inform treatment decision-making

What does this mean?
Real-world data complement clinical trial results to provide additional information to assist in making treatment decisions

*Based on transferability of trial findings to clinical practice
Μητρώα ασθενών: Καλά, αλλά με περιορισμούς

♦ Ακόμη και οι πιο εξελιγμένες στατιστικές μέθοδοι δεν μπορεί να διορθώσουν τις διαφορές σε μη μετρήσιμους ή άγνωστους συγχυτικούς παράγοντες

♦ Ένας πιο απαιτητικός ασθενής μπορεί να λάβει περισσότερη παρακολούθηση ή πρόσθετη φροντίδα
Experience With Low-Dose NOACs From the Phase 3 AF Studies

![Bar chart showing the number of patients in different studies.]

- **Dabigatran RE-LY**:[a] 6076 once daily, 6015 twice daily.
- **Rivaroxaban ROCKET-AF**:[b] 5619 once daily, 1426 twice daily.
- **Apixaban ARISTOTLE**:[c] 8692 once daily, 428 twice daily.
- **Edoxaban ENGAGE AF**:[d] 5251 once daily, 1784 once daily, 5249 once daily, 1785 once daily.

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How Are NOACs Prescribed in the Real World?

<table>
<thead>
<tr>
<th>Country</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 mg</td>
<td>75 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>UK</td>
<td>63.7%</td>
<td>43.2%</td>
<td>75.7%</td>
</tr>
<tr>
<td>Germany</td>
<td>52.4%</td>
<td>37.3%</td>
<td>59.0%</td>
</tr>
<tr>
<td>France</td>
<td>55.7%</td>
<td>31.3%</td>
<td>58.4%</td>
</tr>
</tbody>
</table>

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

A. John Camm1*, Pierre Amarenco2, Sylvia Haas3, Susanne Hess4, Paulus Kirchhof5,6, Silvia Kuhrs7, Martin van Eickels4, and Alexander G.G. Turpie8, on behalf of the XANTUS Investigators

Figure 2 (A) Cumulative rates (Kaplan–Meier) for treatment-emergent all-cause death, major bleeding events, and stroke/systemic embolism.
(B) Event-free rate (Kaplan–Meier) for treatment-emergent all-cause death, major bleeding events, and stroke/systemic embolism. In total, 6,522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding, or stroke/systemic embolism.
Κύριες εκβάσεις αποτελεσματικότητας και ασφάλειας: ΧΑΝΤΟΥΣ και ROCKETF AF


*Events per 100 patient-years; †includes prior stroke, SE or TIA
Ασφάλεια του Rivaroxaban σε σχέση με τον βασικό θρομβοεμβολικό κίνδυνο στη ROCKET AF και σε καταγραφικές μελέτες

<table>
<thead>
<tr>
<th>Τυχαιοποιημένη κλινική μελέτη</th>
<th>Προοπτικό Μητρώο Καταγραφής</th>
<th>Αναδρομική βάση δεδομένων</th>
<th>Προοπτική μελέτη Παρατήρησης</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF&lt;sup&gt;1*&lt;/sup&gt; n=7111</td>
<td>Dresden NOAC&lt;sup&gt;2#&lt;/sup&gt; n=1200</td>
<td>US DoD PMSS&lt;sup&gt;3‡&lt;/sup&gt; n=27,467</td>
<td>XANTUS&lt;sup&gt;4*&lt;/sup&gt; n=6784</td>
</tr>
</tbody>
</table>

Σεβαρή αιμορραγία

<table>
<thead>
<tr>
<th>Επίπτωση/έτος</th>
<th>Μέσο CHADS&lt;sub&gt;2&lt;/sub&gt; score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6%</td>
<td>3.5</td>
</tr>
<tr>
<td>3.0%</td>
<td>2.4</td>
</tr>
<tr>
<td>2.9%</td>
<td>2.2&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.1%</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Ορισμός σοβαρής αιμορραγίας κατά ISTH; #τροποποιημένος ορισμός ISTH (περιλαμβάνει και χειρουργική επανεπέμβαση λόγω αιμορραγίας); ‡Ορισμός σοβαρής αιμορραγίας με τον αλγόριθμο Cunningham<sup>5</sup>; §Κοόρτη χωρίς σοβαρή αιμορραγία (αντιπροσωπεύει>98% του πληθυσμού της μελέτης)

Απόλυτη ετήσια επίπτωση ΑΕΕ ή καρδιοεμβολής στη ROCKET AF και σε καταγραφικές μελέτες

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study Name</th>
<th>n</th>
<th>Stroke/SE event rate/year</th>
<th>CHADS₂ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trial</td>
<td>ROCKET AF¹</td>
<td>7111</td>
<td>1.7%</td>
<td>3.5</td>
</tr>
<tr>
<td>Prospective registry</td>
<td>Dresden NOAC²</td>
<td>1204</td>
<td>1.7%*</td>
<td>2.4</td>
</tr>
<tr>
<td>Observational study</td>
<td>XANTUS³</td>
<td>6784</td>
<td>0.8%</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Includes transient ischaemic attack

Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation

DJ Graham, ME Reichman, M Wernecke, Y Hsueh, R Izem, MR Southworth, Y Wei, J Liao, MR Goulding, K Mott, Y Chillarige, TE MaCurdy, C Worrall, JA Kelman

An independent FDA study of >118 000 Medicare patients compared dabigatran 150 mg BID with rivaroxaban 20 mg OD

**Outcomes**
- Thromboembolic stroke, ICH, major extracranial bleeding events including major GI bleeding, and mortality

**Methods**
- Retrospective analysis of Medicare database (Nov 2011–Jun 2014)
- Follow up until outcome of interest, death, end of study, treatment discontinuation (>3 day gap in anticoagulant supply), switching to different OAC
- Cox regression and inverse probability of treatment weighting based on propensity score

**Patients**
- New users of dabigatran 150 mg BID, or rivaroxaban 20 mg OD with NVAF, aged ≥65 years, average follow-up duration <4 months
- N=118 891 (52 240 dabigatran, 66 651 rivaroxaban)

**Limitations**
- No major limitations identified

**Funding**
- Interagency agreement between the CMS and FDA

A total of 52.240 dabigatran and 66.651 rivaroxaban initiators contributed 15.524 and 20.199 person-years of on-treatment follow-up (mean [range] duration, 108 [0-969] and 111 [0-923] days), respectively.

CMS, Centers for Medicare and Medicaid Services; ICH, intracranial haemorrhage; Graham et al. JAMA Intern Med 2016
An independent FDA study of >118 000 Medicare patients compared dabigatran 150 mg BID with rivaroxaban 20 mg OD

*Incidence rates are unadjusted; hazard ratios (HR) are adjusted HR (95% CI) comparing inverse probability of treatment-weighted new-user cohorts; bold values indicate statistical significance; average follow-up duration <4 months; ICH, intracranial haemorrhage; GI, gastrointestinal; Graham et al. JAMA Intern Med 2016

Λιγότερα αιμορραγικά συμβάντα με το Dabigatran
Λιγότερα ισχαιμικά ΑΕΕ με το Rivaroxaban

*Incidence rates are unadjusted; hazard ratios (HR) are adjusted HR (95% CI) comparing inverse probability of treatment-weighted new-user cohorts; bold values indicate statistical significance; average follow-up duration <4 months; ICH, intracranial haemorrhage; GI, gastrointestinal; Graham et al. JAMA Intern Med 2016
Prospective surveillance pilot of rivaroxaban safety within the US Food and Drug Administration Sentinel System


1Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA
2Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
3Kalmar Permanente Northern California, Oakland, CA, USA
4Biostatistics Unit, Group Health Research Institute and Department of Biostatistics, University of Washington, Seattle, WA, USA
5Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
6Center for Biologics Evaluation and Research, US Food and Drug, Rockville, MD, USA
7Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA
8Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA
9Office of Biometric and Statistical, Office of Biostatistics, Office of Biostatistics, Office of Translation Sciences, US Food and Drug Administration, Silver Spring, MD, USA
10Optum Epidemiology, Middleton, WI, USA
11Andrews, Blue Bell, PA, USA
12Humana Inc. Louisville, KY, USA
13HealthCore Inc. Alexandria, VA, USA

Methods: In patients with non-valvular atrial fibrillation, we sequentially compared outcomes for new users of rivaroxaban versus warfarin, employing propensity score matching and Cox regression. A total of 36,173 rivaroxaban and 79,520 warfarin initiators were variable-ratio matched within 2 monitoring periods.

Results: Statistically significant signals were observed for ischemic stroke (IS) (first period) and intracranial hemorrhage (ICH) (second period) favoring rivaroxaban, and gastrointestinal bleeding (GIB) (second period) favoring warfarin. In follow-up analyses using primary position diagnoses from inpatient encounters for increased definition specificity, the hazard ratios (HR) for rivaroxaban vs warfarin new users were 0.61 (0.47, 0.79) for IS, 1.47 (1.29, 1.67) for GIB, and 0.71 (0.50, 1.01) for ICH. For GIB, the HR varied by age: <66 HR = 0.88 (0.60, 1.30) and 66+ HR = 1.49 (1.30, 1.71).

Conclusions: This study demonstrates the capability of Sentinel to conduct prospective safety monitoring and raises no new concerns about rivaroxaban safety.

KEY POINTS

- In the study supporting rivaroxaban (Xarelto®) approval for stroke prevention in non-valvular atrial fibrillation, compared with warfarin, rivaroxaban had a similar effect on ischemic stroke, but decreased the risk of intracranial hemorrhage and increased the risk of major gastrointestinal bleeding.
- This study used new FDA Sentinel sequential monitoring capabilities to examine the safety of rivaroxaban among patients with atrial fibrillation during the drug’s early uptake period in 4 large Data Partners in the FDA Sentinel distributed database with diverse patient populations.
- An indication of a lower risk of ischemic stroke in the rivaroxaban group compared with warfarin was detected early and persisted with additional monitoring and sensitivity analysis.
Q: The effectiveness of NOACs in real-world setting

A: Any stroke or systemic embolism

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran*</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>0.66 (0.53-0.82)</td>
<td>0.88 (0.75-1.03)</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td></td>
<td>0.91 (0.74-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RWD Studies</td>
<td>0.93 (0.77-1.14)</td>
<td>0.87 (0.71-1.07)</td>
<td>0.67 (0.46-0.98)</td>
</tr>
<tr>
<td>n</td>
<td>n=2</td>
<td>n=2</td>
<td>n=1</td>
</tr>
<tr>
<td>I²</td>
<td>I² = 0%</td>
<td>I² = 0%</td>
<td>---</td>
</tr>
</tbody>
</table>

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

The effectiveness of NOACs in real-world setting

A: Ischemic stroke

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>0.76 (0.60-0.98)</td>
<td>0.94 (0.75-1.17)</td>
<td>0.92 (0.74-1.13)</td>
</tr>
<tr>
<td>1.11 (0.89-1.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RWD</td>
<td><strong>0.96 (0.80-1.16)</strong></td>
<td><strong>0.89 (0.76-1.04)</strong></td>
<td><strong>0.95 (0.75-1.19)</strong></td>
</tr>
<tr>
<td>Studies</td>
<td>n=12</td>
<td>n=5</td>
<td>n=3</td>
</tr>
<tr>
<td>I²</td>
<td>83%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

### Q: All-cause mortality in real-world setting

### A: All-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td>0.88 (0.77-1.00)</td>
<td>0.85 (0.70-1.02)</td>
<td>0.89 (0.80-0.998)</td>
</tr>
<tr>
<td></td>
<td>0.91 (0.80-1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RWD</strong></td>
<td><strong>0.63 (0.52-0.79)</strong></td>
<td>0.67 (0.35-1.30)</td>
<td>0.65 (0.56-0.75)</td>
</tr>
<tr>
<td>Studies</td>
<td>n=6</td>
<td>n=2</td>
<td>n=1</td>
</tr>
<tr>
<td></td>
<td><strong>I^2 = 83%</strong></td>
<td><strong>I^2 = 92%</strong></td>
<td>---</td>
</tr>
</tbody>
</table>

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

Q: The safety of NOACs in real-world setting

A: Major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran*</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>0.93 (0.81-1.07)</td>
<td>1.04 (0.90-1.20)</td>
<td>0.69 (0.60-0.80)</td>
</tr>
<tr>
<td></td>
<td>0.80 (0.69-0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RWD</td>
<td><strong>0.83 (0.65-1.05)</strong></td>
<td><strong>1.00 (0.92-1.08)</strong></td>
<td><strong>0.55 (0.48-0.63)</strong></td>
</tr>
<tr>
<td>Studies</td>
<td>n=15</td>
<td>n=8</td>
<td>n=4</td>
</tr>
<tr>
<td></td>
<td>I₂ = 93%</td>
<td>I₂ = 0%</td>
<td>I₂ = 0%</td>
</tr>
</tbody>
</table>

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

**Conclusion**

Our data indicate that overall persistence with rivaroxaban therapy is high, with a discontinuation rate of **15%** in the first year of treatment and few additional discontinuations thereafter.

**Table 3** Centrally adjudicated reasons for rivaroxaban discontinuation

<table>
<thead>
<tr>
<th>Reasons for rivaroxaban discontinuation</th>
<th>n (%) of all 223 discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding complications</td>
<td>67 (30.0)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>23 (10.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (7.2)</td>
</tr>
<tr>
<td>Bruising</td>
<td>9 (4.0)</td>
</tr>
<tr>
<td>Haematuria</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Suspected non-bleeding side effects</td>
<td>54 (24.2)</td>
</tr>
<tr>
<td>Vertigo/nausea/fatigue</td>
<td>17 (7.6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Eczema</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (7.2)</td>
</tr>
<tr>
<td>Stable sinus rhythm or LAA occlusion</td>
<td>22 (9.9)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>18 (8.1)</td>
</tr>
</tbody>
</table>

**Figure 1** Kaplan–Meier analysis of persistence to rivaroxaban treatment for all patients (top diagram) and for all patients who were observed for at least 12 months (bottom diagram), according to VKA pretreatment.

**Risk factors for discontinuation of rivaroxaban therapy**

To evaluate potential risk factors for rivaroxaban discontinuation, a Cox proportional hazard analysis was performed (Table 4). A history of chronic heart failure (HR 1.43; 95% CI 1.09–1.87; P = 0.009) or diabetes (HR = 1.39; 95% CI 1.06–1.82; P = 0.018) were the only statistically significant baseline risk factors for rivaroxaban discontinuation.

**Funding**

The NOAC registry is supported by the Gesellschaft für Technologie- und Wissenstransfer der TU-Dresden (GWT-TUD GmbH), Germany (sponsor), by research funds of the University Hospital Carl Gustav Carus, Dresden, Department of Vascular Medicine and by grants from Bayer HealthCare, Boehringer Ingelheim, and Pfizer. All authors declare no conflicts of interest.
Efficacy and safety of rivaroxaban compared with warfarin in patients with carotid artery disease and nonvalvular atrial fibrillation: Insights from the ROCKET AF trial

Conclusions: Patients with CD in ROCKET AF had similar risk of stroke/SE compared with patients without CD. Additionally, there was no interaction between CD and the treatment effect of rivaroxaban or warfarin for stroke prevention or safety endpoints.

Η επίπτωση τόσο της ΚΜ όσο και της ΧΝΝ αυξάνει με την ηλικία

Οι πληθυσμοί με νεφρική δυσλειτουργία ήταν διαφορετικοί στις μελέτες

- Κατανομή των CHADS<sub>2</sub> των ασθενών με μέτρια νεφρική δυσλειτουργία (CrCl 30–49 ml/min)

1. Χαρτί ARISTOTLE<sup>1</sup> apixaban
2. Χαρτί RE-LY<sup>2</sup> dabigatran
3. Χαρτί ROCKET AF<sup>3</sup> Rivaroxaban

Μέσο CHADS<sub>2</sub> 2,6

- 45% ≤1
- 38% 2
- 17% 3–6

Το μέσο CHADS<sub>2</sub> δεν έχει δημοσιευθεί

Μέσο CHADS<sub>2</sub> 3,7

- 91% ≤1
- 9% 2

CHADS<sub>2</sub> score

Μεταβολισμός και κάθαρση του Rivaroxaban

- Περίπου το 1/3 της χορηγούμενης δόσης απεκκρίνεται άμεσα από τους νεφρούς ως αμετάβλητη δραστική ουσία
- 2/3 υφίσταται μεταβολική αποδόμηση στο ήπαρ
  - 50% αποβάλλεται από τους νεφρούς
  - 50% αποβάλλεται από την ηπατοχολική οδό

Οδοί κάθαρσης του rivaroxaban και αποβολή ανενεργών μεταβολιτών

Σκεπτικό για ειδική νεφρική δόση στη μελέτη ROCKET AF στους ασθενείς με Μέτρια Νεφρική Δυσλειτουργία (CrCl 30–49 ml/min)

Rivaroxaban (10 mg*) exposure is increased in patients with renal impairment compared with healthy controls

*Rivaroxaban was given as a single oral dose of 10 mg (two 5 mg tablets).

**Official study title:** Factor XA – inhibition in RENal patients with non-valvular atrial fibrillation Observational registry

**Objective:** To assess CKD progression and safety of anticoagulation strategies in NVAF patients with eGFR 15–49 ml/min /1.73 m² in routine clinical practice

**Study population:**
Patients with NVAF (N=2500) and eGFR/CrCl 15–49 ml/min

**Pre-study phase**
- Rivaroxaban for ≥3 months
- VKA for ≥3 months
- No OAC (ASA or no treatment) for ≥3 months

**Follow-up phase**
- n≥1000
- n≥1000
- n<500

**Day 0** 90 180 270 … … 720

**InVESTigators to collect data at initial visit, at 3 months and then quarterly**

**Short design:** Observational, open-label, active-controlled, multicentre study (N=2500)

[www.clinicaltrials.gov/ct2/show/NCT02663076](http://www.clinicaltrials.gov/ct2/show/NCT02663076)
All NOACs are recommended for stroke prevention in patients with eligible patients with AF in preference over a VKA\textsuperscript{1}

Patients should have regular follow-up visits to test their renal function among other checks\textsuperscript{2}

<table>
<thead>
<tr>
<th>Frequency of visits</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly</td>
<td>All patients with AF to test hemoglobin, renal and liver function</td>
</tr>
<tr>
<td>6-monthly</td>
<td>If CrCl 30–60 ml/min or if on dabigatran and aged &gt;75 years or fragile</td>
</tr>
<tr>
<td>3-monthly</td>
<td>If CrCl 15–30 ml/min</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Kirchhof P et al, Eur Heart J 2016; doi:10.1093/eurheartj/ehw210; \textsuperscript{2} Heidbuchel H et al, Europace 2013;15:625–651
Χαρακτηριστικά Αντικαρδικών Φαρμάκων

Xarelto (Rivaroxaban) Tablets

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

May 2016

Use in Patients with Renal Impairment

Patients with End-Stage Renal Disease on Dialysis (addition)

- Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.
15.5 Anticoagulation in patients with severe chronic kidney disease

The use of NOACs has not been tested in patients with creatinine clearance $<30$ mL/min, and there is very little evidence on the effects of OAC in patients on haemodialysis or on other forms of renal replacement therapy. Studies evaluating OAC in patients with severe CKD are needed to inform the best management in this patient group at high risk for stroke and bleeding.
The Effect of Rivaroxaban with Aspirin on Stroke Outcomes in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial

Mike Sharma MD, On behalf of the COMPASS Steering Committee and Investigators
January 25, 2018
Hazard ratio with rivaroxaban plus aspirin, 0.58  
(95% CI, 0.44-0.76), P<0.0001
Hazard ratio with rivaroxaban alone, 0.82  
(95% CI, 0.65-1.05), P=0.12

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
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<tbody>
<tr>
<td>Rivaroxaban plus aspirin</td>
<td>0 6 12 18 24 30 36</td>
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<tr>
<td>9152</td>
<td>9067</td>
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<tr>
<td>Rivaroxaban alone</td>
<td>9117</td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>9126</td>
</tr>
</tbody>
</table>
Ischemic/Uncertain Stroke

A Ischemic or Uncertain Stroke

HR Rivaroxaban plus aspirin
0.51
(95% CI, 0.38-0.69)

HR Rivaroxaban alone
0.66
(95% CI, 0.50-0.88)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban plus aspirin</td>
<td>9152</td>
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<tr>
<td></td>
<td>2259</td>
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<tr>
<td></td>
<td>673</td>
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<tr>
<td>Rivaroxaban alone</td>
<td>9117</td>
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<tr>
<td></td>
<td>2231</td>
</tr>
<tr>
<td></td>
<td>693</td>
</tr>
</tbody>
</table>
Hemorrhagic Stroke

**B  Hemorrhagic Stroke**

HR Riva plus aspirin  
1.49  
(95% CI, 0.67-3.31)

HR Riva alone  
2.70  
(95% CI, 1.31-5.58)

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
<th>HR Riva plus aspirin</th>
<th>HR Riva alone</th>
<th>HR Aspirin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9152</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>6</td>
<td>9082</td>
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<td>0.005</td>
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<td>24</td>
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<tr>
<td>30</td>
<td>2279</td>
<td>0.025</td>
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<tr>
<td>36</td>
<td>1.49</td>
<td>0.030</td>
<td>2.70</td>
<td>6.79</td>
</tr>
</tbody>
</table>

(95% CI, 0.67-3.31)

HR Riva alone  
2.70  
(95% CI, 1.31-5.58)
Conclusions

• Rivaroxaban 2.5 mg BID + aspirin compared to aspirin
  • Reduced ischemic stroke by 49%  
    • Without a significant increase in ICH  
    • Or hemorrhagic conversion  

• Major effect in secondary prevention*
  • Stroke: ARR 2.7%  
    \[ \text{NNT} = 37 \]  

• Reduced early disability
  • Commensurate with decrease in stroke occurrence  

• A significant advance in stroke prevention for those with CAD/PAD without AF

* Stroke within 1 month exclusion
### Current Lifecycle of Medical Products Expenditures

<table>
<thead>
<tr>
<th></th>
<th>Pre-Clinical Studies</th>
<th>Clinical Trials</th>
<th>Regulatory Review</th>
<th>Post-Market Monitoring</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>1 y</td>
<td>1.65 y</td>
<td>2.53 y</td>
<td>2.56 y</td>
<td>6.74 y</td>
</tr>
<tr>
<td>Cost*</td>
<td>$182 M</td>
<td>$375 M</td>
<td>$542 M</td>
<td>$689 M</td>
<td>$1.6 B</td>
</tr>
</tbody>
</table>

*FDA

- **Overall trend in Research & Development Efficiency (inflation-adjusted)***

The proportion of phase III trials started for CVD therapies:
- 21% in 1990 ➔ 7% in 2012.

The proportion of CVD drugs among new launches:
- 13% in mid-1990s ➔ 6% after 2012.

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1. The BPC (Bipartisan Policy Center) initiative: Health Innovation Safe Effective Cures.
Πρόγραμμα κλινικών μελετών Rivaroxaban

- Registries
  N=~90,000
- NIS
  N=~47,000
- Phase IV
  N=~3,900
- Phase II/III
  N=~51,000
- Completed Phase I, II & III
  N=~86,000

Over 275,000 patients expected
Evidence leads to multiple new indications

<table>
<thead>
<tr>
<th>Indication/areas of use</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
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</thead>
<tbody>
<tr>
<td>DVTx</td>
<td>EINSTEIN DVT</td>
<td>AMPLIFY</td>
<td>RE-COVER I</td>
<td>HOKUSAI VTE</td>
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<tr>
<td>PEx</td>
<td>EINSTEIN PE</td>
<td>AMPLIFY EXT</td>
<td>RE-COVER II</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention of VTE</td>
<td>EINSTEIN EXT</td>
<td>RE-SONATE</td>
<td>RE-MEDY</td>
<td></td>
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<tr>
<td>SPAF</td>
<td>ROCKET AF</td>
<td>AVERROES</td>
<td>RE-LY</td>
<td>ENGAGE-AF TIMI 48</td>
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<tr>
<td></td>
<td>J-ROCKET AF</td>
<td>ARISTOTLE</td>
<td></td>
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</tr>
<tr>
<td>VTEp OS</td>
<td>RECORD1</td>
<td>ADVANCE-1 (US)</td>
<td>RE-MOBILIZE (US)</td>
<td>STARS E-3</td>
</tr>
<tr>
<td>Hip</td>
<td>RECORD2</td>
<td>ADVANCE-2</td>
<td>RE-NOVATE</td>
<td>STARS J-4</td>
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<tr>
<td>Knee</td>
<td>RECORD3</td>
<td>ADVANCE-3</td>
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<td>RE-MODEL</td>
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<tr>
<td>ACSsp</td>
<td>ATLAS ACS 2-TIMI 51</td>
<td>APPRAISE-2 (stopped)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medically ill</td>
<td>MAGELLAN</td>
<td>ADOPT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Green dot**: Licensed
- **Orange dot**: Licensed ex-US only
- **Gray dot**: Licensed Japan only
- **Yellow dot**: Ongoing Phase III study
- **Red dot**: Phase III study failed
- **Black dot**: No study ongoing/known
- **White dot**: Phase III complete/no license
1. Mechanical Prosthetic Valves and Rheumatic Mitral Valve Disease
2. Cancer-Associated Thrombosis
3. Treatment of Cancer-Associated Acute Venous Thromboembolism
4. Prevention of Venous Thromboembolism in the Hospital Setting
5. Primary Prevention of Venous Thromboembolism in the Ambulatory Setting
6. Antiphospholipid Syndrome
7. Other Hypercoagulable States
8. End-Stage Renal Disease
9. Pediatric Patients
10. Pregnancy

Sources of Funding
This work was funded by the National Institutes of Health: 1RO1NS070307 (Hylek), 5T32HL007227-42 (Aronis).

Aronis K, Hylek E. Journal of the American Heart Association, January 28, 2018
Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study

Dietary intake of 135 335 pts from 18 countries with a median follow-up of 7.4 years

Implications of all the available evidence
Removing current restrictions on fat intake but limiting carbohydrate intake (when high) might improve health. Dietary guidelines might need to be reconsidered in light of consistent findings from the present study, especially in countries outside of Europe and North America.

Why does it seem that, when the results of an observational study support what we want to hear, people are also more willing to embrace the findings?