# ARE ALL NOVEL ORAL CREATED ANTICOAGULANTS EQUAL ?

- Evidence from the recent literature

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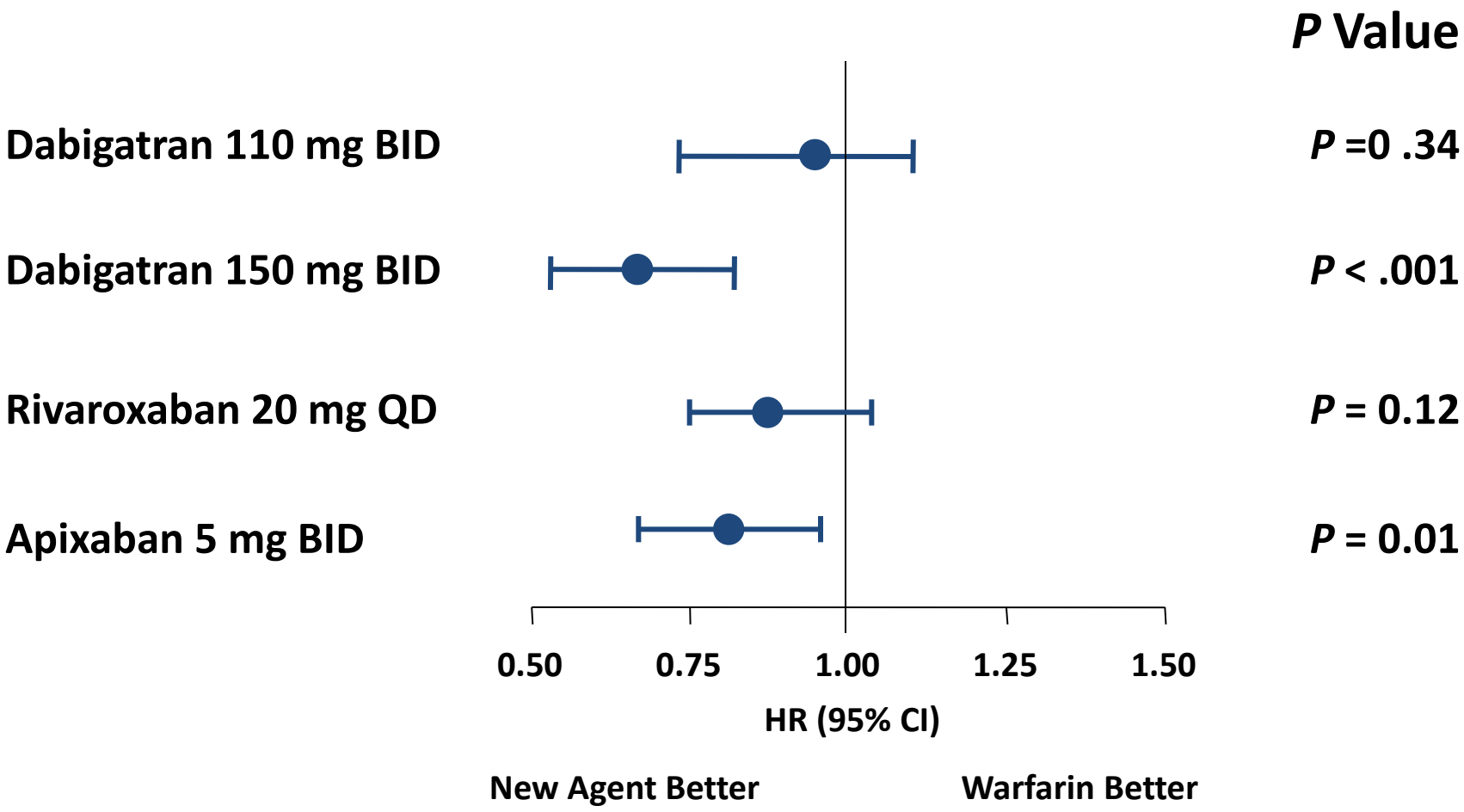
Ancona

# DISCLOSURES

- Speaker fee in the last 2 years from:
- Abbot,Bayer, Boheringer,Boston Scientific,Meda, Medico, Sanofi-Synthelabo, Sorin.

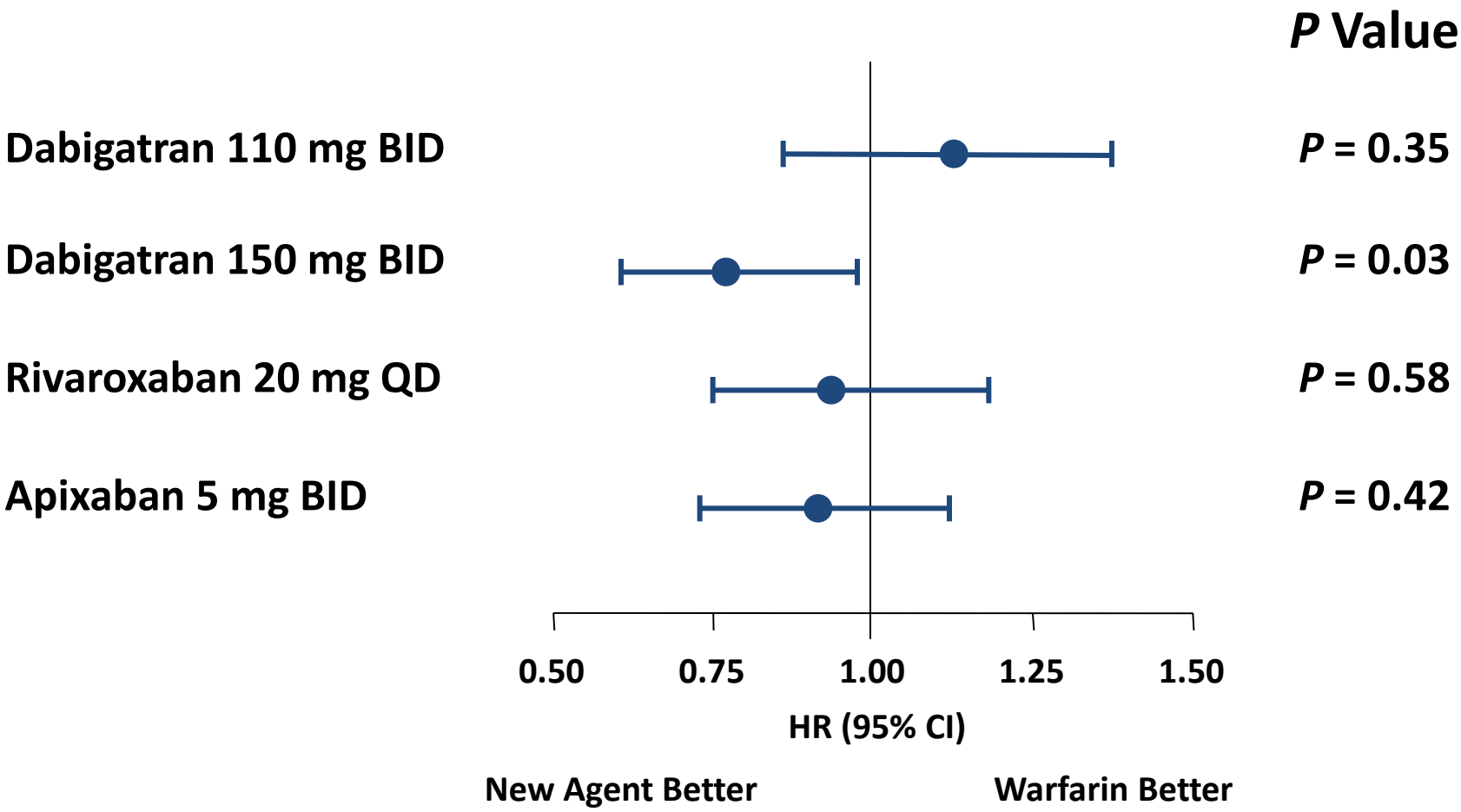
# DOACs vs warfarin: stroke and systemic embolism




**Not head to head comparison – For illustrative purposes only**

Connolly SJ, et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Patel MR, et al. N Engl J Med 2011;365:883–91; Granger C, et al. N Eng J Med 2011;365:981–92.

# DOACs vs warfarin: ischaemic stroke

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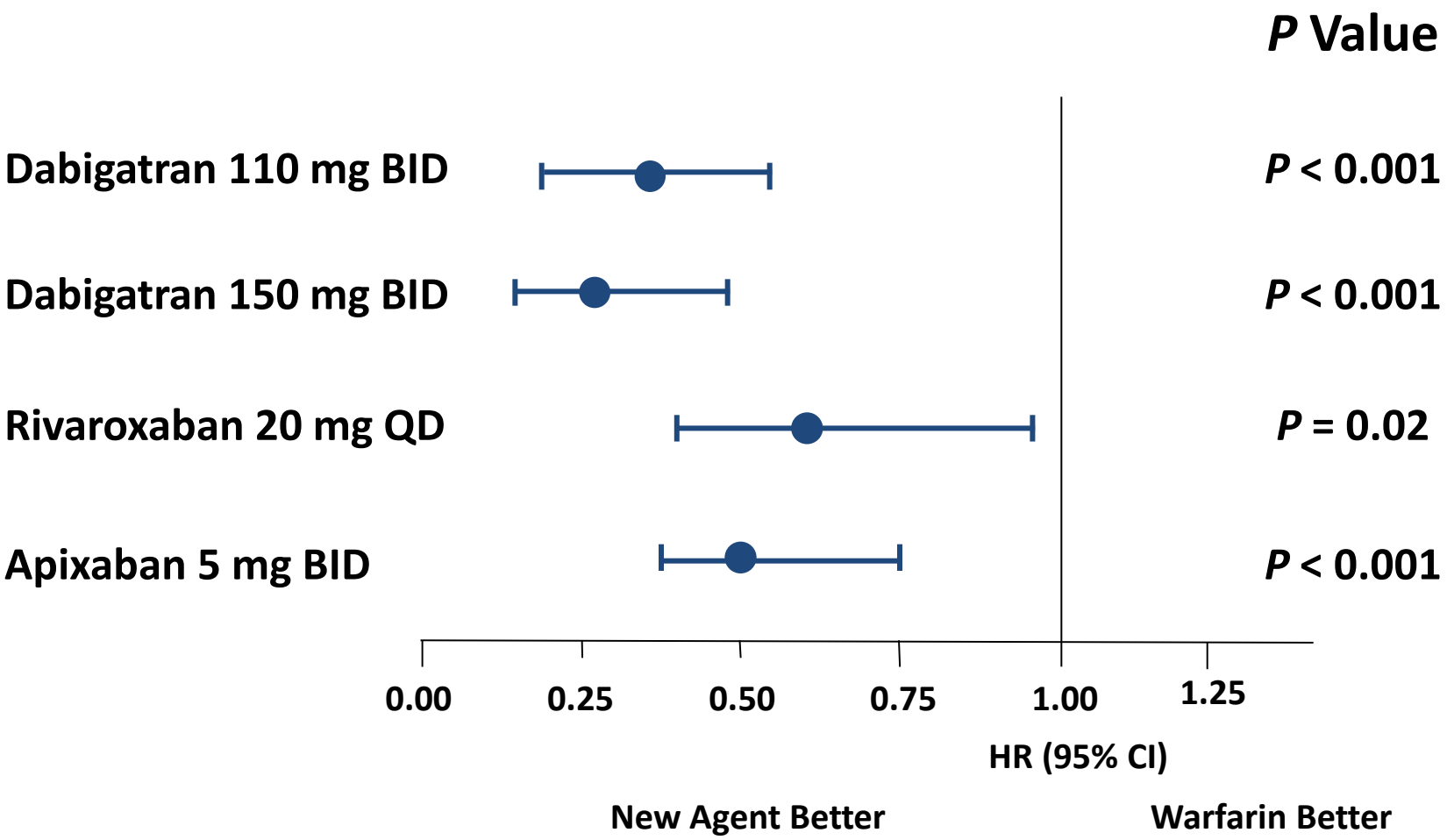
# DOACs vs warfarin: haemorrhagic stroke

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NOACs= New oral anticoagulants

# Comparative PK/PD of DOACs

| | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| Target | IIa (thrombin) | Xa | Xa |
| Hours to $C_{max}$ | 1-3 | 2-4 | 3-4 |
| Half-life, hours | 12-17 | 5-13 | 12 |
| Renal Clearance, % | 80 | 33* | 27 |
| Transporters | P-gp | P-gp | P-gp |
| CYP Metabolism, % | None | 32 | <32 |

CYP = cytochrome P450; P-gp = P-glycoprotein *33% renally cleared; 33% excreted unchanged

Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2013
Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2011
ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK

# DOACs Phase III Trials

**Table 1: Overview of the phase III trials performed with the new oral anticoagulants* with study acronym and according to generic drug name.**

| Stroke prevention in atrial fibrillation | Acute coronary syndromes | Primary VTE prevention (orthopaedic surgery) | Primary VTE prevention (medically ill) | Initial treatment of VTE | Extended treatment of VTE |
|---|---|---|---|---|---|
| dabigatran<br>RE-LY | | dabigatran<br>RE-MODEL<br>RE-MOBILIZE<br>RE-NOVATE<br>RE-NOVATE II | | dabigatran<br>RE-COVER<br>RE-COVER II | dabigatran<br>RE-SONATE<br>RE-MEDY |
| rivaroxaban<br>ROCKET AF | rivaroxaban<br>ATLAS ACS-2 TIMI 51 | rivaroxaban<br>RECORD I<br>RECORD II<br>RECORD III<br>RECORD IV | rivaroxaban<br>MAGELLAN | rivaroxaban<br>EINSTEIN-DVT<br>EINSTEIN-PE | rivaroxaban<br>EINSTEIN-Extension |
| apixaban<br>AVERROES<br>ARISTOTLE | apixaban<br>APPRAISE-2 | apixaban<br>ADVANCE I<br>ADVANCE I<br>ADVANCE III | apixaban<br>ADOPT | apixaban<br>AMPLIFY | apixaban<br>AMPLIFY-Extension |
| edoxaban<br>TIMI 48-ENGAGE | | | | edoxaban<br>HOKUSAI-VTE | |

VTE, venous thromboembolism. *Studies with the oral thrombin inhibitor ximelagatran are not included since the drug was withdrawn from market in 2006.

Thromb Haemost 2014; 111: 575–582

# DOACs SPAF Trials

| | RE-LY | ROCKET-AF | ARISTOTLE |
|---|---|---|---|
| Drug | Dabigatran | Rivaroxaban | Apixaban |
| # Randomized | 18,113 | 14,264 | 18,201 |
| Dose (mg) | 150, 110 | 20 | 5 |
| Frequency | Twice Daily | Once Daily | Twice Daily |
| Dose Adjustment at baseline | No | 20 → 15 | 5 → 2.5 |
| Target INR (Warfarin) | 2.0-3.0 | 2.0-3.0 | 2.0-3.0 |
| Design | PROBE* | 2x blind | 2x blind |

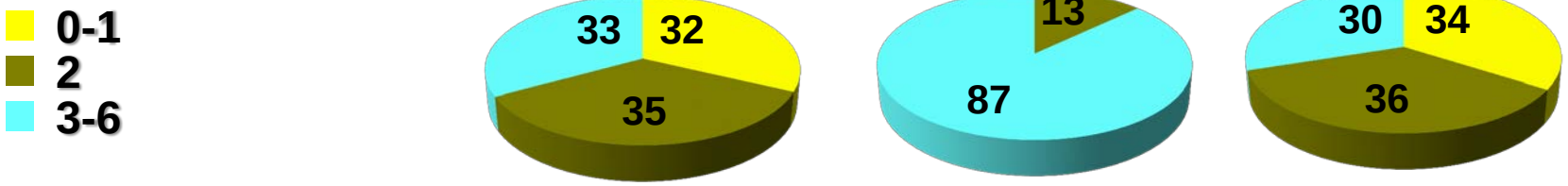
***PROBE = prospective, randomized, open-label, blinded end point evaluation**

*Connolly SJ, et al. N Engl J Med 2009;361:1139-1151*
*Patel MR, et al. N Engl J Med 2011;365:883-891*
*Granger CB, et al. N Engl J Med 2011;365:981-992*

# Baseline Characteristics

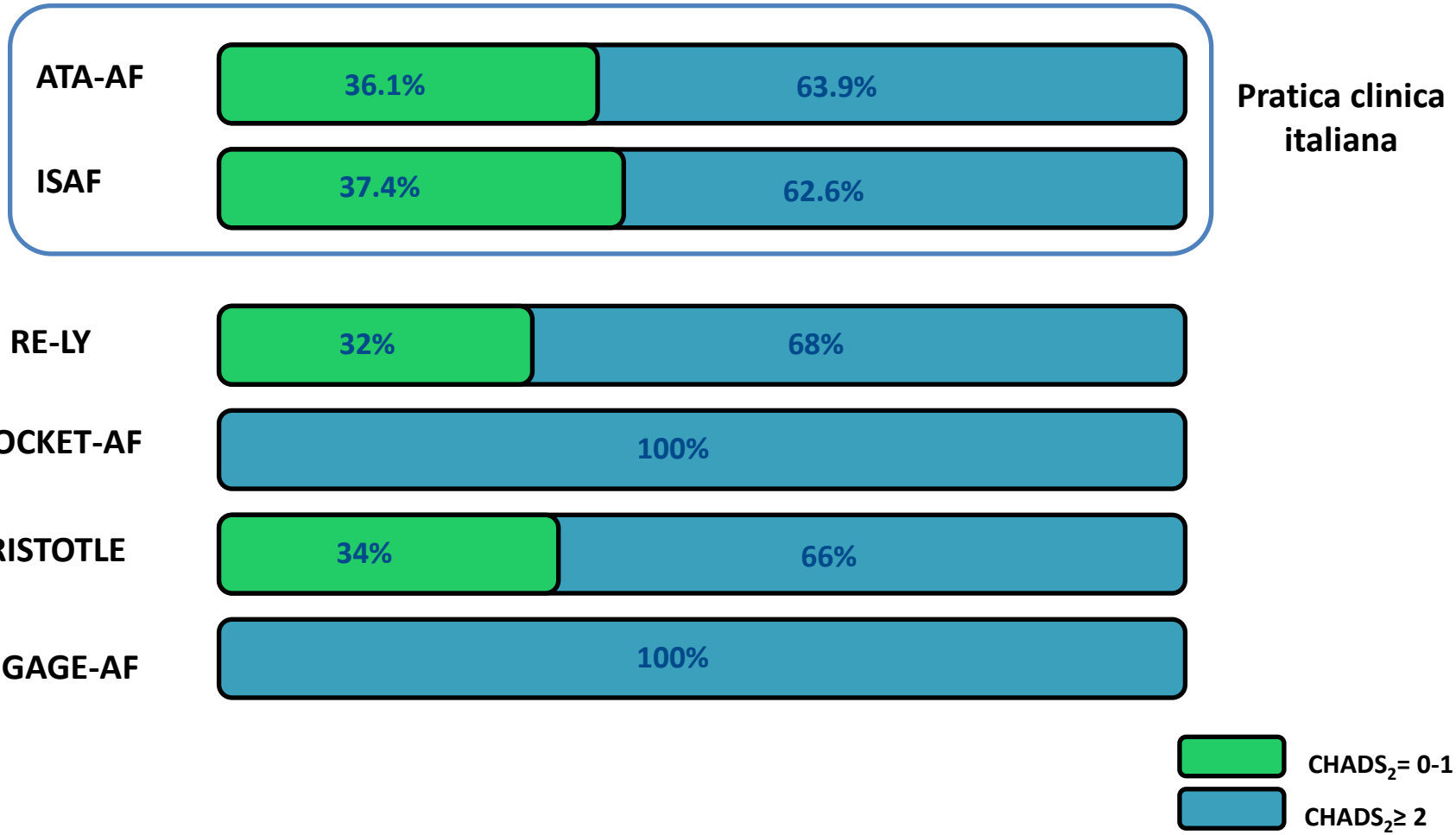
| | RE-LY (Dabigatran) | ROCKET-AF (Rivaroxaban) | ARISTOTLE (Apixaban) |
|---|---|---|---|
| # Randomized | 18,113 | 14,266 | 18,201 |
| Age, years | 72 ± 9 | 73 [65-78] | 70 [63-76] |
| Female, % | 37 | 40 | 35 |
| Paroxysmal AF | 32 | 18 | 15 |
| VKA naive | 50 | 38 | 43 |
| Aspirin Use | 40 | 36 | 31 |

$CHADS_2$




Connolly SJ, et al. N Engl J Med 2009;361:1139-1151
Patel MR, et al. N Engl J Med 2011;365:883-891
Granger CB, et al. N Engl J Med 2011;365:981-992

# Distribuzione del punteggio $CHADS_2$ in coorti di pazienti con FANV

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# Trial Metrics

| | RE-LY (Dabigatran) | ROCKET-AF (Rivaroxaban) | ARISTOTLE (Apixaban) |
|---|---|---|---|
| Median Follow-Up, years | 2.0 | 1.9 | 1.8 |
| TTR, % | 64 mean<br>67 median | 55 mean<br>58 median | 62 mean<br>66 median |
| Lost to Follow-Up, N | 20 | 32 | 90 |

*TTR, time in therapeutic range

Connolly SJ, et al. N Engl J Med 2009;361:1139-1151
Patel MR, et al. N Engl J Med 2011;365:883-891
Granger CB, et al. N Engl J Med 2011;365:981-992

# INTERAZIONI FRA FARMACI

# Possible drug-drug interactions – effect on DOAC plasma levels

| | | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| Atorvastatin | P-gp/ CYP3A4 | +18% | no data yet | no effect | no effect |
| Digoxin | P-gp | no effect | no data yet | no effect | no effect |
| Verapamil | P-gp/ wk CYP3A4 | +12–180% (reduce dose) | no data yet | + 53% (SR) (reduce dose 50%) | minor effect |
| Diltiazem | P-gp/ wk CYP3A4 | no effect | +40% | No data | minor effect |
| Quinidine | P-gp | +50% | no data yet | +80% (reduce dose 50%) | +50% |
| Amiodarone | P-gp | +12–60% | no data yet | no effect | minor effect |
| Dronedarone | P-gp/CYP3A4 | +70–100% | no data yet | +85% (reduce dose 50%) | no data yet |
| Ketoconazole; itraconazole; voriconazole; posaconazole | P-gp and BCRP/ CYP3A4 | +140–150% | +100% | no data yet | up to +160% |

Red = contraindicated; Orange = adapt dose; Yellow = consider dose reduction if two concomitant yellow interactions present

Heidbuchel H et al. Europace 2013;15:625–51

# Possible drug-drug interactions – effect on DOAC plasma levels

| | Interaction | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| Fluconazole | CYP3A4 | no data | no data | no data | +42% |
| Cyclosporin; tacrolimus | P-gp | no data | no data | no data | +50% |
| Clarithromycin; erythromycin | P-gp/ CYP3A4 | +15–20% | no data | no data | +30–54% |
| HIV protease inhibitors | P-gp and BCRP/ CYP3A4 | no data | strong increase | no data | up to +153% |
| Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital | P-gp and BCRP/ CYP3A4/CYP2J2 | -66% | -54% | -35% | up to -50% |
| Antacids | GI absorption | -12–30% | no data | no effect | no effect |

Heidbuchel H et al. Europace 2013;15:625–51

# MULTAQ … efficacia nella **vita reale**

## Dabigatran–dronedarone interaction in a spontaneous reporting system

**Pranav K. Gandhi, William M. Gentry, and Michael B. Bottorff**

*J Am Pharm Assoc.* 2013;53:414–419.

- Obiettivo dello studio era di quello di indagare sui potenziali sanguinamenti associati alla concomitante somministrazione di dabigatran e dronedarone …

***Objectives:*** To investigate the risk of bleeding events associated with concurrent administration of dabigatran–dronedarone compared with dabigatran standalone therapy using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and to identify the characteristics of patients with bleeding events associated with concurrent use of dabigatran and dronedarone.

# MULTAQ … efficacia nella **vita reale**

## Dabigatran–dronedarone interaction in a spontaneous reporting system

**Pranav K. Gandhi, William M. Gentry, and Michael B. Bottorff**

*J Am Pharm Assoc.* 2013;53:414–419.

**Table 2.** Reporting odds ratios concerning the occurrence of bleeding events in index and reference groups

| | Bleeding cases | Nonbleeding cases | OR (95% CI) |
|---|---|---|---|
| Concomitant use of dabigatran and dronedarone | 51 | 57 | 13.80 (9.45–20.14) |
| Dabigatran but not dronedarone | 1,819 | 1,747 | 16.06 (15.00–17.19) |
| Dronedarone but not dabigatran | 82 | 779 | 1.62 (1.29–2.04) |
| Neither dabigatran nor dronedarone | 12,961 | 199,866 | 1 |

Abbreviation used: OR, odds ratio.

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# MULTAQ … efficacia nella **vita reale**

## Dabigatran–dronedarone interaction in a spontaneous reporting system

Pranav K. Gandhi, William M. Gentry, and Michael B. Bottorff

***Conclusion:*** The likelihood of reporting bleeding events to FAERS among patients using dabigatran only was similar to that among patients using dabigatran and dronedarone concomitantly.

- **Negli USA le segnalazioni alla FDA di sanguinamenti nei pazienti trattati solo con dabigatran erano simili a quelle rilevate nei pazienti trattati con dabigatran associato a Multaq**

# Possible drug-drug interactions – effect on DOAC plasma levels (III)

| | | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| Aged ≥80 years | Increased plasma level | | | | |
| Aged ≥75 years | Increased plasma level | | | | |
| Weight ≤60 kg | Increased plasma level | | | | |
| Renal function | Increased plasma level | | | | |

Other increased bleeding risk

Pharmacodynamic interactions – antiplatelet drugs, NSAIDs

Systemic steroid therapy

Other anticoagulants

Recent surgery on critical organ (brain, eye)

Thrombocytopenia (e.g. chemotherapy)

HAS-BLED ≥3

Red = contraindicated; Orange = adapt dose; Yellow = consider dose reduction if two concomitant yellow interactions present

NSAIDs = non-steroidal anti-inflammatory drugs

Heidbuchel H et al. Europace 2013;15:625–51

# NAO E CARDIOVERSIONE

# Cardioversion during Phase III trials

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.
Learn and Live.

**Dabigatran Versus Warfarin in Patients With Atrial Fibrillation: An Analysis of Patients Undergoing Cardioversion**

Rangadham Nagarakanti, Michael D. [illegible], James Oldgren, Sean Yusuf, Michael Chernick, Timothy H. Aikens, Greg Parekh, Paul A. Reilly,

*Circulation* pu
DOI: 10.1161/CIR
Circulation is published by the American



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Vol. 61, No. 19, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.025

**Heart Rhythm Disorders**

## Outcomes After Cardioversion and Atrial Fibrillation Ablation in Patients Treated With Rivaroxaban and Warfarin in the ROCKET AF Trial

Jonathan P. Piccini, MD, MHS,* Susanna R. Stevens, MS, Manesh R. Patel, MD,* Jonathan L. Halperin, MD,† Dani Graeme J. Hankey, MD,§ Werner Hacke, MD, PHD,‖ Ric Christopher C. Nessel, MD,¶ Kenneth W. Mahaffey, MD, Robert M. Califf, MD,** Günter Breithardt, MD†† for the & Investigators

*Durham, North Carolina; New York, New York; Boston, Mass Heidelberg and Münster, Germany; Raritan, New Jersey; and*

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http://dx.doi.org/10.1016/j.jacc.2013.09.062

**Antithrombotic Therapy**

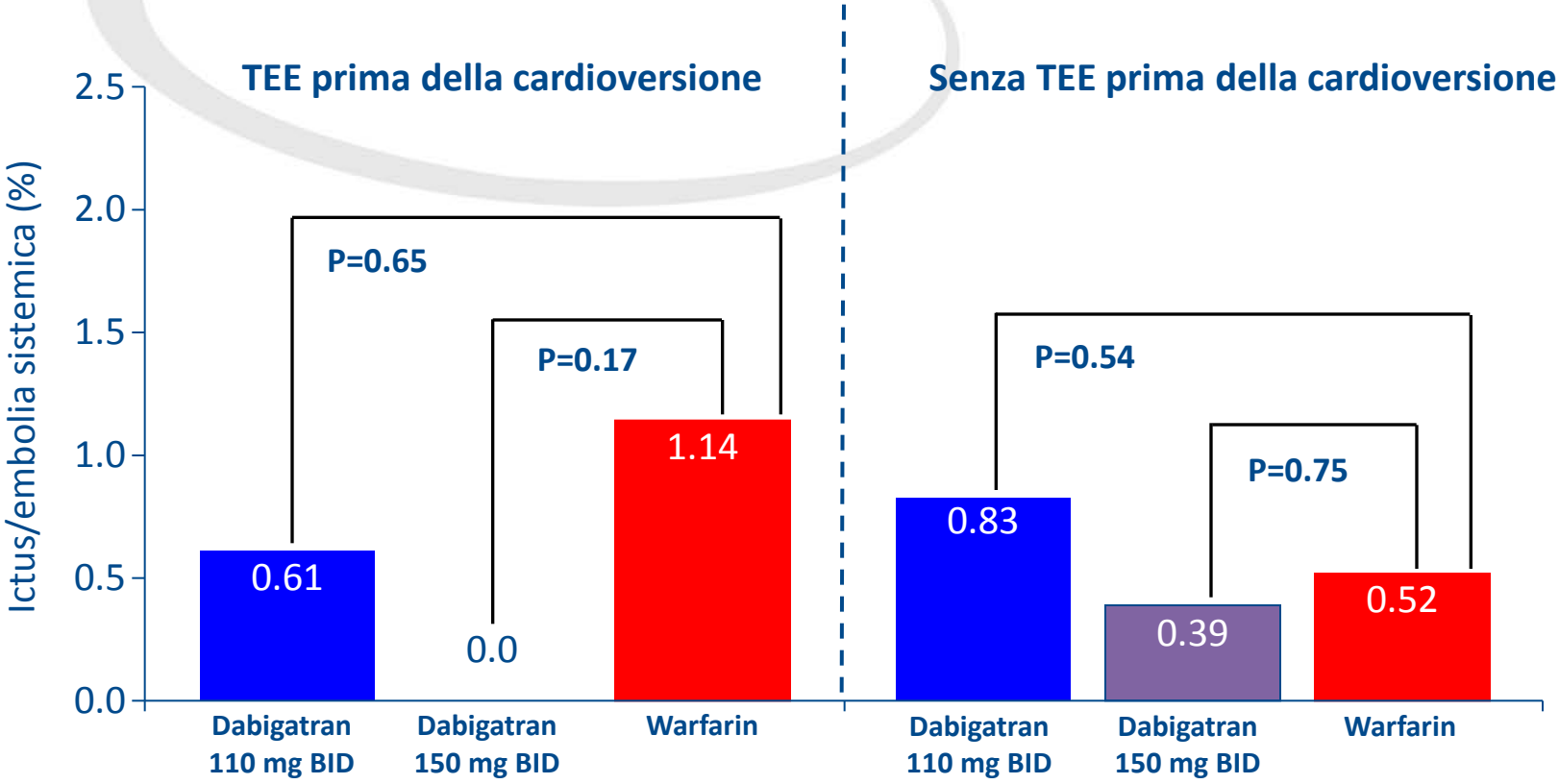
## Efficacy and Safety of Apixaban in Patients After Cardioversion for Atrial Fibrillation

### Insights From the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)

Greg Flaker, MD,* Renato D. Lopes, MD, PHD,† Sana M. Al-Khatib, MD, MHS,† Antonio G. Hermosillo, MD,‡ Stefan H. Hohnloser, MD,§ Brian Tinga, MS,† Jun Zhu, MD,‖ Puneet Mohan, MD, PHD,¶ David Garcia, MD,# Jozef Bartunek, MD, PHD,** Dragos Vinereanu, MD, PHD,†† Steen Husted, MD, DMSc,‡‡ Veli Pekka Harjola, MD, PHD,§§ Marten Rosenqvist, MD,‖‖ John H. Alexander, MD, MHS,† Christopher B. Granger, MD,† for the ARISTOTLE Committees and Investigators

*Columbia, Missouri; Durham, North Carolina; Tlalpan, Mexico; Frankfurt, Germany; Beijing, China; Princeton, New Jersey; Albuquerque, New Mexico; Aalst, Belgium; Bucharest, Romania; Århus, Denmark; Helsinki, Finland; and Stockholm, Sweden*

# Sottoanalisi cardioversione: ictus o embolia sistemica con o senza TEE




Percentuali analoghe di ictus o embolia sistemica con/senza TEE prima della cardioversione

BID = due volte al giorno; TEE = ecocardiografia transesofagea

Nagarakanti R et al. Circulation 2011;123:131–6

# X-VeRT: primary efficacy endpoints

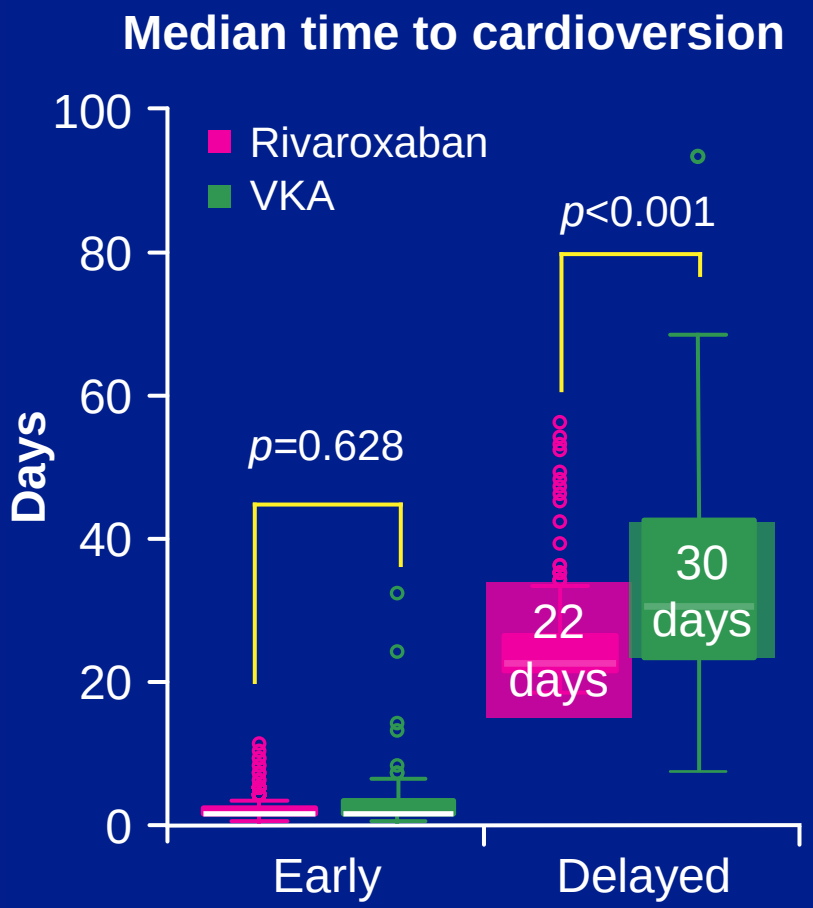
| | Rivaroxaban (N=978) | | VKA (N=492) | | Risk ratio (95% CI) |
|---|---|---|---|---|---|
| | % | n* | % | n* | |
| **Primary efficacy endpoint** | **0.51** | **5** | **1.02** | **5** | **0.50 (0.15–1.73)** |
| Stroke | 0.20 | 2 | 0.41 | 2 | |
| Haemorrhagic stroke | 0.20 | 2 | | 0 | |
| Ischaemic stroke | | 0 | 0.41 | 2 | |
| TIA | | 0 | | 0 | |
| Non-CNS SE | | 0 | 0.20 | 1 | |
| MI | 0.10 | 1 | 0.20 | 1 | |
| Cardiovascular death | 0.41 | 4 | 0.41 | 2 | |

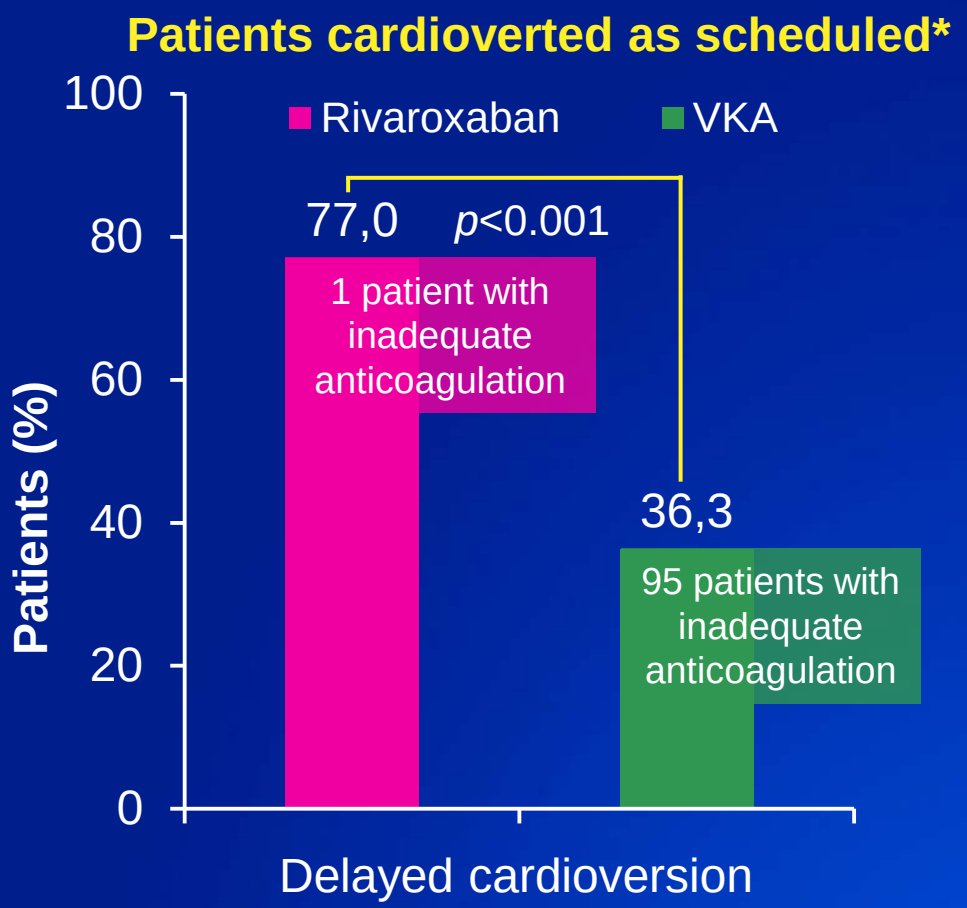
*Number of patients with events; patients may have experienced more than one primary efficacy event
mITT population

Cappato R *et al. Eur Heart J* 2014: doi: 10.1093/eurheartj/ehu367

X-VeRT

# X-VeRT: time to cardioversion by cardioversion strategy




*Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA)

Cappato R *et al. Eur Heart J* 2014: doi: 10.1093/eurheartj/ehu367

X-VeRT

# RE-LY® ROCKET-AF® ARISTOTLE®

## Popolazioni studiate

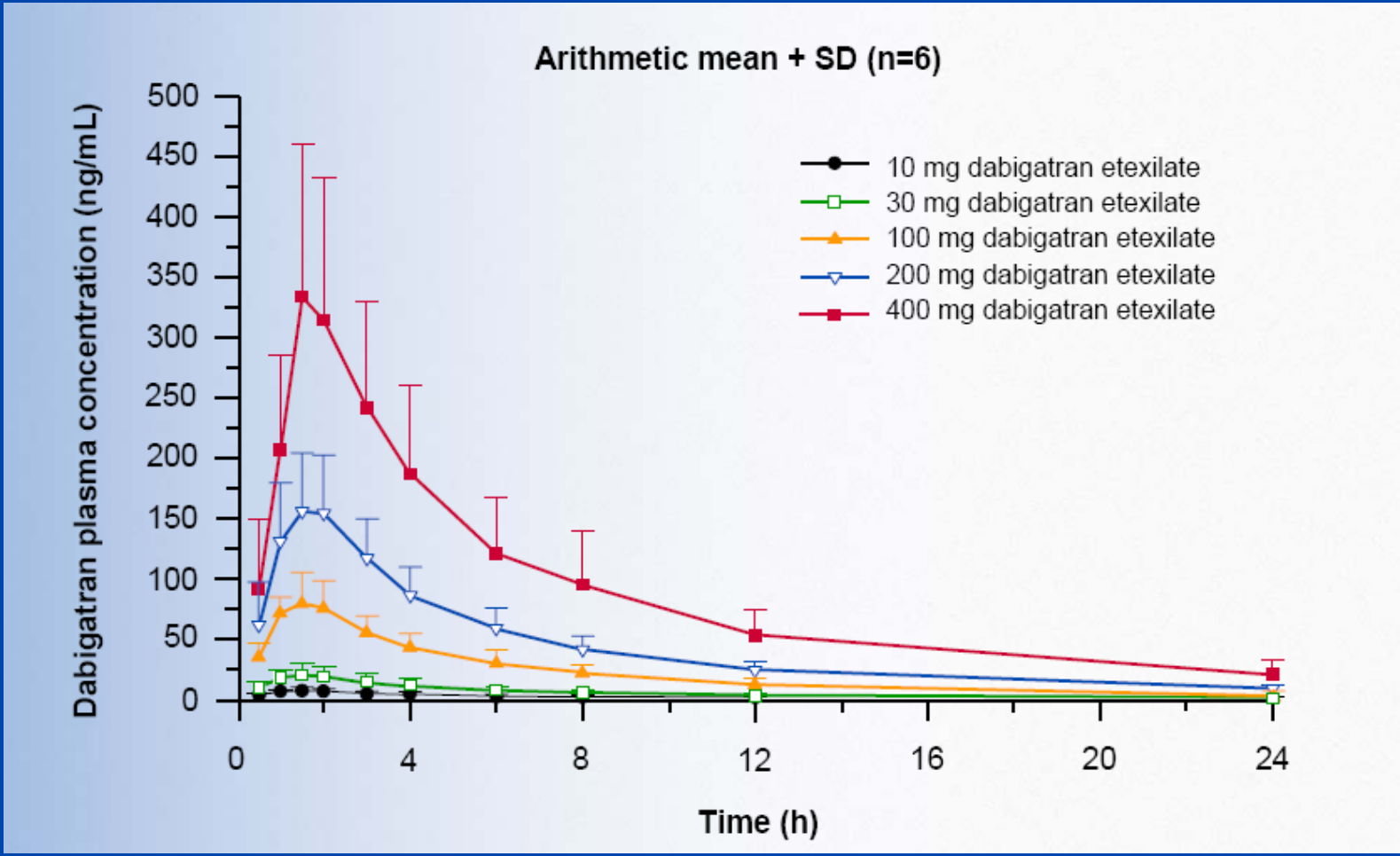

Connolly et al. NEJM 2009; 361:1139-51; Patel et al. NEJM 2011; 365:883-91; Granger et al. NEJM 2011; 365:981-92; Fox et al. European Heart Journal 2011; 32:2387-2394

# Differenze

- **Dabigatran** (dati da RE-LY trial):
  - efficace e sicuro in associazione a clopidogrel e/o ASA (unico con dati)
  - meglio di Warfarin su ictus ischemico (unico)
  - efficace e sicuro nella cardioversione(sottostudio)
  - due dosaggi: 150 mgx2 (maggior efficacia) e 110 mgx2 (maggior sicurezza), randomizzazione 1:1 ai due dosaggi
- **Rivaroxaban** (dati da ROCKET-AF trial):
  - mono somministrazione (unico con dati)
  - dose ridotta di ¼ (a 15 mg) in pazienti con insufficienza renale moderata (ClCr 30-49 ml): 21 % del totale dei pazienti
  - Efficace e sicuro nella CV (Xvert)
- **Apixaban** (dati da ARISTOTLE trial):
  - unico che ha direttamente dimostrato superiorità ad ASA (AVERROES trial)
  - meglio di W come efficacia (ictus) e sicurezza (emorragie maggiori)
  - ridurre a metà dose (2,5 mg x2) in pazienti con 2 fra età ≥ 80, peso<60 kg, Cr ≥1.5 mg/dl): 4.6 % del totale dei pazienti

# BID vs monosomministrazione

# Reproducible PK Profile




- PK profile is **reproducible** across a wide range of doses[1,2]

[1]Stangier *et al. Br J Clin Pharmacol* 2007:64:292-303
[2]Stangier *Clin Pharmacokinet* 2008;47:285-295

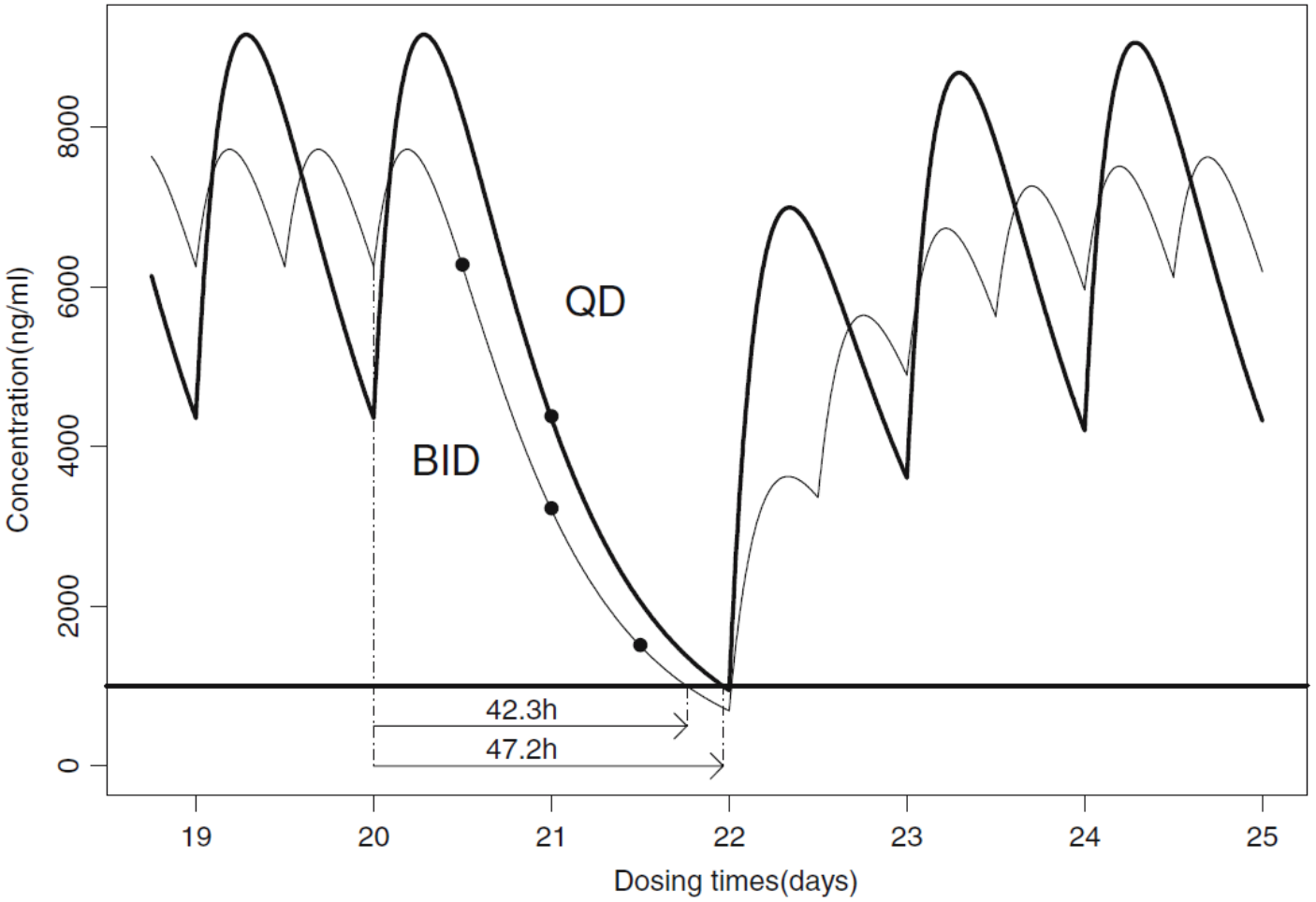
# Twice daily dosing of dabigatran for stroke prevention in atrial fibrillation. A pharmacokinetic justification

A PK simulation study derived from a population PK model supplemented with data from 9522 patients enrolled in RE-LY supports the BID dosing regimen in patients with AF.

The results show that BID dosing leads to more stable plasma concentrations, thereby minimizing the risks of both bleeding and thrombosis. The predicted consequences of a missed dose with BID dosing are less than for QD dosing, where trough levels may decrease to the point where they do not provide sufficient anticoagulation.


Clemens A *et al. Curr Med Res Opin* 2012;28:195–201.

# Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics




Comtè L *et al. J Pharmacokinet Pharmacodyn* 2007 34:549–558.

# Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics

A key point is that the pharmacokinetic equivalent of a single missed once-daily dose is between two and three sequentially omitted twice-daily doses. Thus, an important parameter is the probability of two or three twice-daily doses being *sequentially* omitted, versus the probability of missing a single once-daily dose. An extensive body of electronically compiled dosing history data shows that the probability of sequential omission of 2–3 twice daily doses is half the probability of omission of a single once daily dose. For that reason, a twice-daily regimen is likely to prove to be superior to a once-daily regimen in maintaining drug concentrations within a therapeutically desirable range.

(Comtè, 2007)

# Dati a lungo termine

# RELY-ABLE®: goal and design

- To provide additional information on the long-term effects of D150 and D110 in patients completing RE-LY®
- Patients eligible at completion of RE-LY® study if still receiving study dabigatran and being followed at centre participating in RELY-ABLE®
  - Dabigatran continued blinded in RELY-ABLE® for 2.3 years, when combined with RE-LY®: **maximum of 4.3 years' follow-up**
- Patients in countries where dabigatran was not yet approved continued to receive blinded dabigatran: **maximum of 6.7 years' follow-up**
- Descriptive analysis of outcomes: stroke, SE, MI, vascular mortality, total mortality, bleeding (major, life-threatening, minor, and total), DVT and net clinical benefit

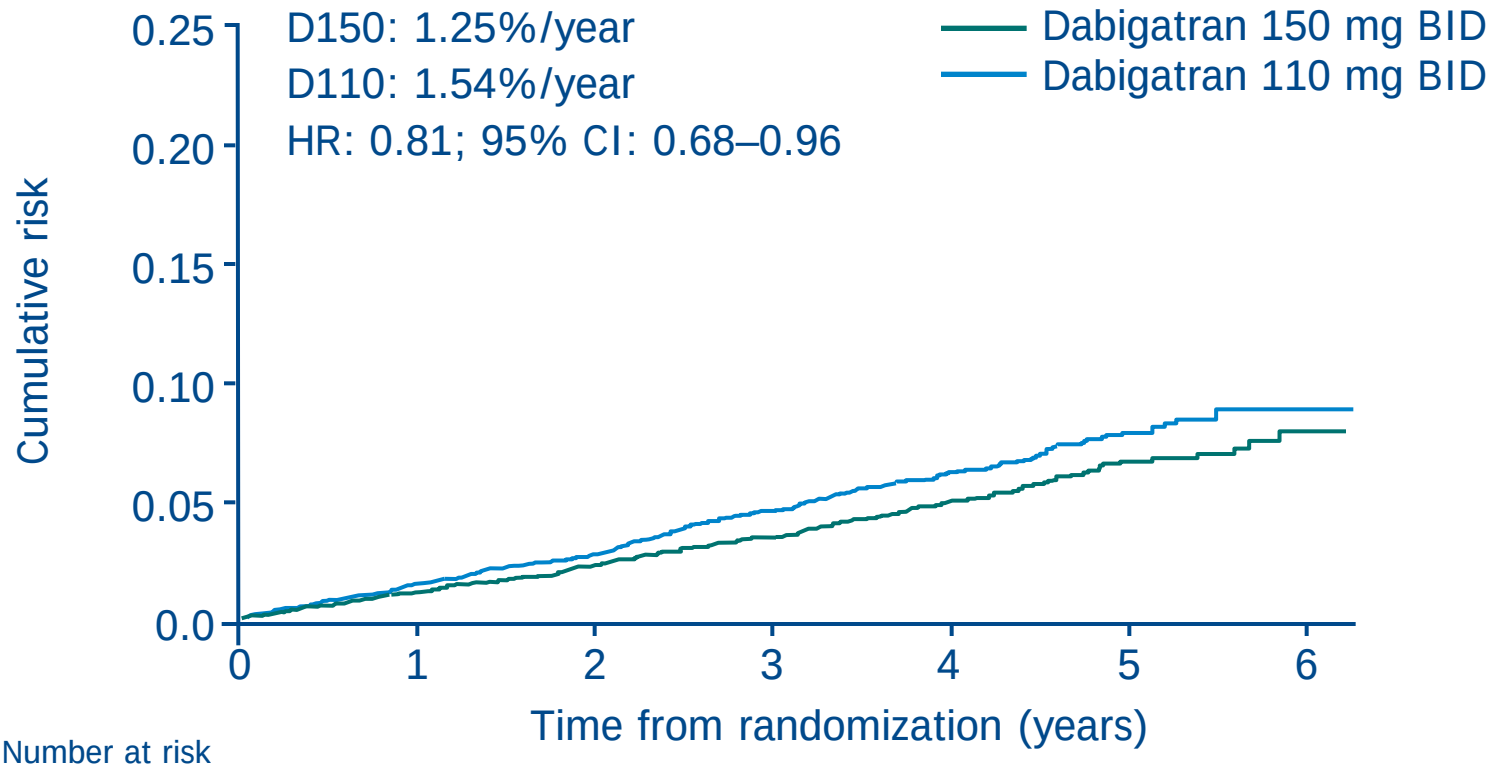
D150 and D110 = dabigatran 150 and 110 mg twice daily, respectively; DVT = deep vein thrombosis; MI = myocardial infarction; SE = systemic embolism

Connolly S et al. Circulation 2013;128:237–43; Ezekowitz M. AHA 2013; abstr 10684

Maximum of 6.7 years' follow-up

# RELY-ABLE® extended follow-up: stroke or systemic embolism

- Rates of stroke and systemic embolism remained low during the extended follow-up period



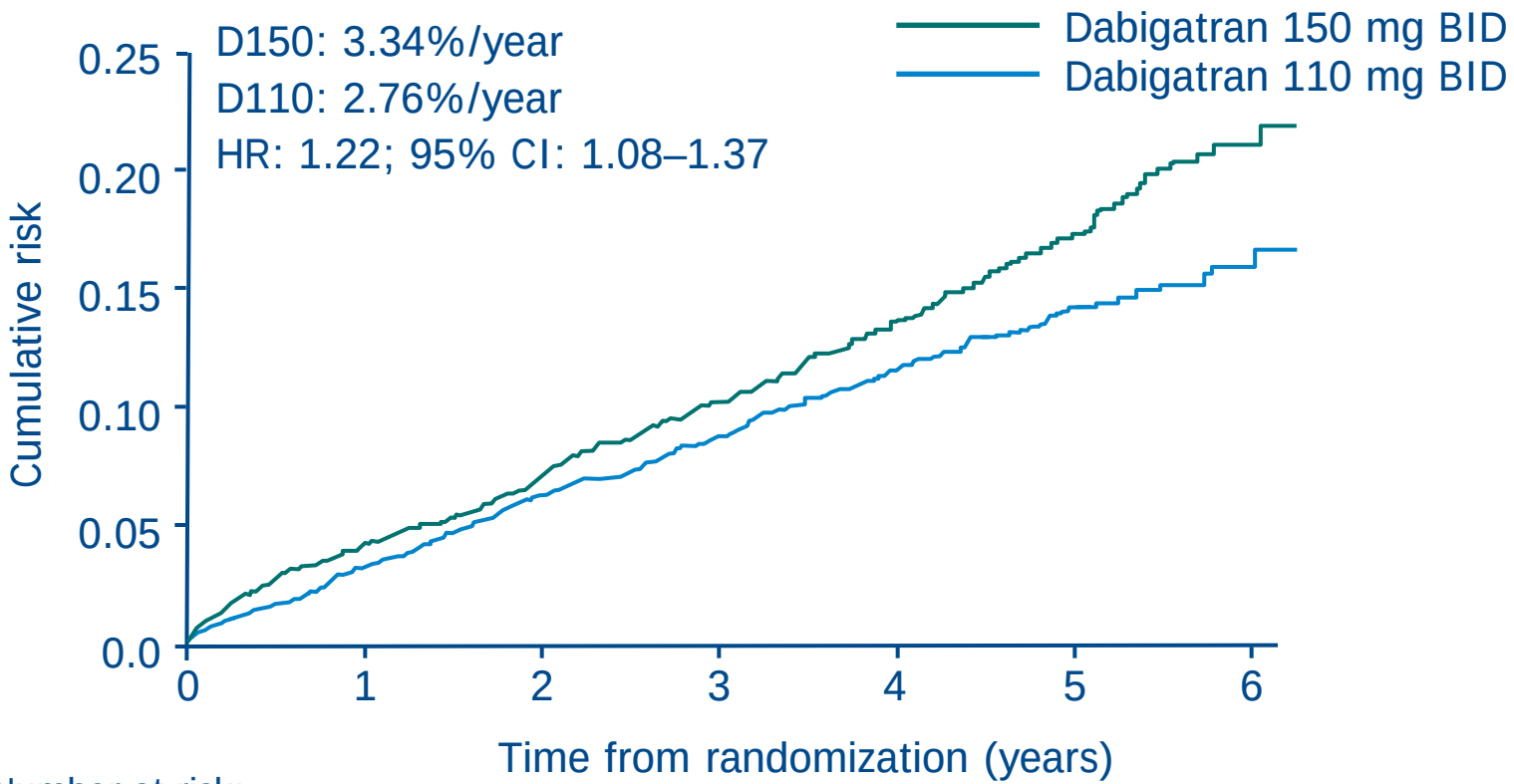

Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5706 | 4190 | 2737 | 2147 | 929 | 157 |
| D150 | 6076 | 5774 | 4276 | 2753 | 2181 | 953 | 149 |

Ezekowitz M. AHA 2013; abstr 10684

# RELY-ABLE® extended follow-up: major bleeding

- Rates of major bleeding remained consistent over 6.7 years of follow-up



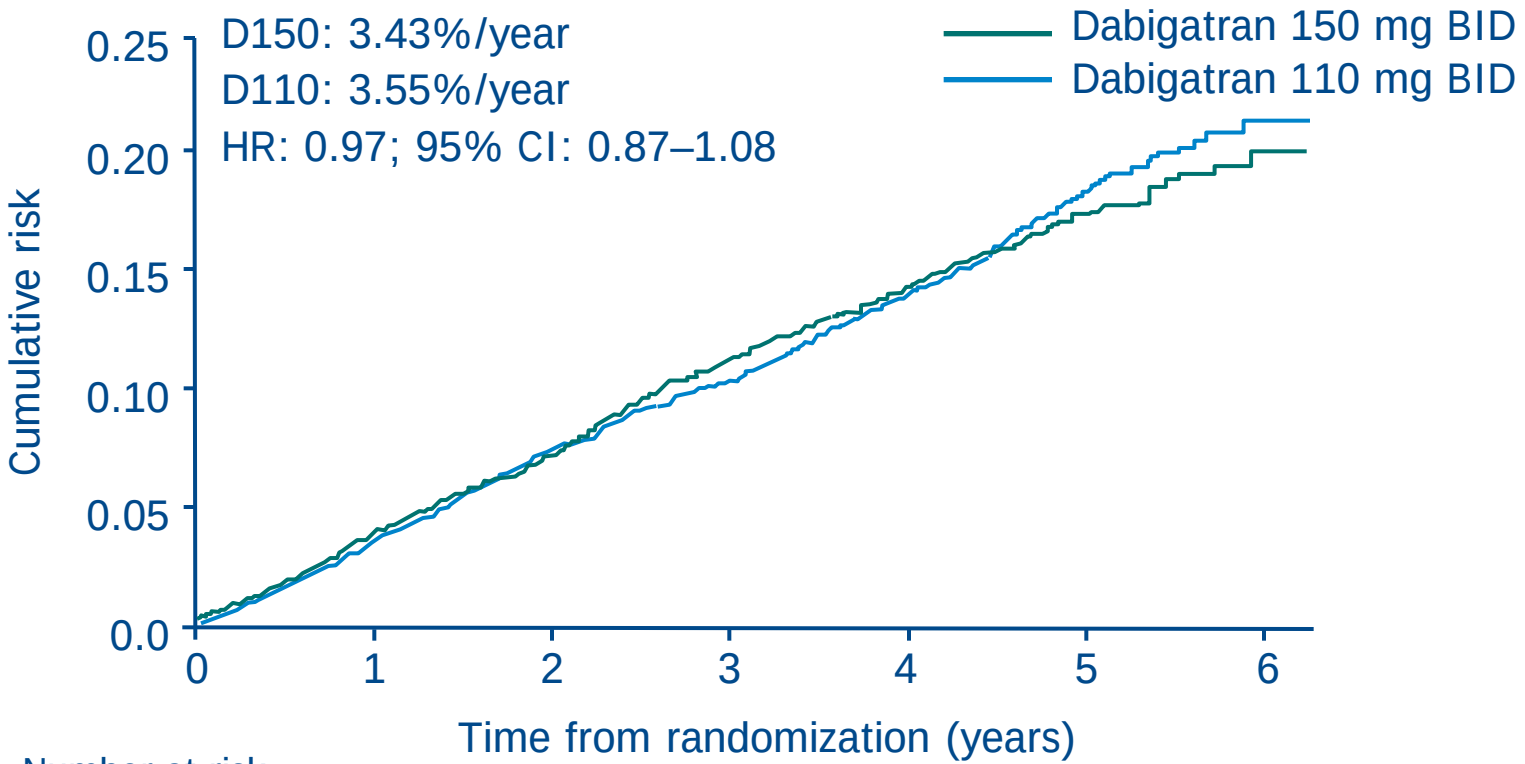

Number at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5616 | 4075 | 2658 | 2085 | 903 | 158 |
| D150 | 6076 | 5622 | 4130 | 2638 | 2077 | 910 | 146 |

Ezekowitz M. AHA 2013; abstr 10684

# RELY-ABLE® extended follow-up: total mortality

- Total mortality remained comparable for both doses during extended follow-up




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5772 | 4266 | 2798 | 2211 | 957 | 165 |
| D150 | 6076 | 5824 | 4340 | 2786 | 2226 | 980 | 155 |

Ezekowitz M. AHA 2013; abstr 10684

# RELY-ABLE®: conclusions

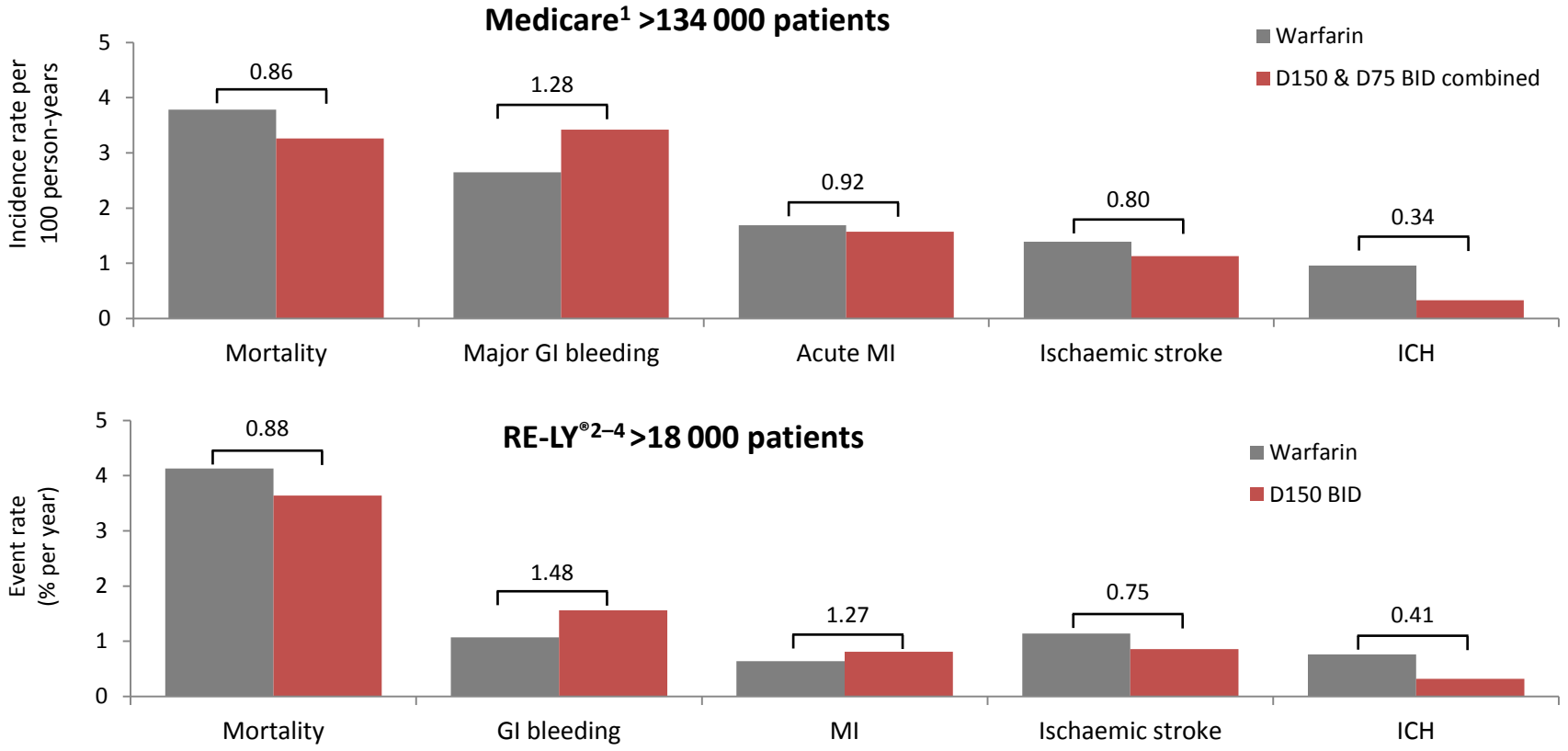
- Dabigatran is the only NOAC with long-term follow-up data extending up to 6.7 years
  - No new safety signals were observed during this period
- RELY-ABLE® provides additional safety information for a large cohort of patients continuing the same dose of dabigatran as assigned in the RE-LY® trial
- Rates of major events were consistent with RE-LY®
  - Low rates of intracranial bleeding were sustained throughout the RELY-ABLE® study period

The results from RELY-ABLE® support the long-term safety of dabigatran in patients with NVAF and contribute to the growing body of data reinforcing dabigatran as an important advance in the treatment of patients with AF

NVAF = nonvalvular AF

Connolly S et al. Circulation 2013;128:237–43; Ezekowitz M. AHA 2013; abstr 10684

# Independent FDA Medicare analysis findings are consistent with findings from RE-LY®




Independent FDA analysis confirmed the favourable benefit–risk profile of dabigatran in clinical practice

**In the USA, the licensed doses for Pradaxa ® are: Pradaxa® 150 mg BID and Pradaxa ® 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF**

Numbers on bars denote HRs vs warfarin. D75 = dabigatran 75 mg; D150 = dabigatran 150 mg

**1.** Available at http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm; accessed September 2014; **2.** Connolly SJ et al. N Engl J Med 2009;361:1139–51; **3.** Connolly SJ et al. N Engl J Med 2010;363:1875–6; **4.** Pradaxa®: EU SPC, 2014

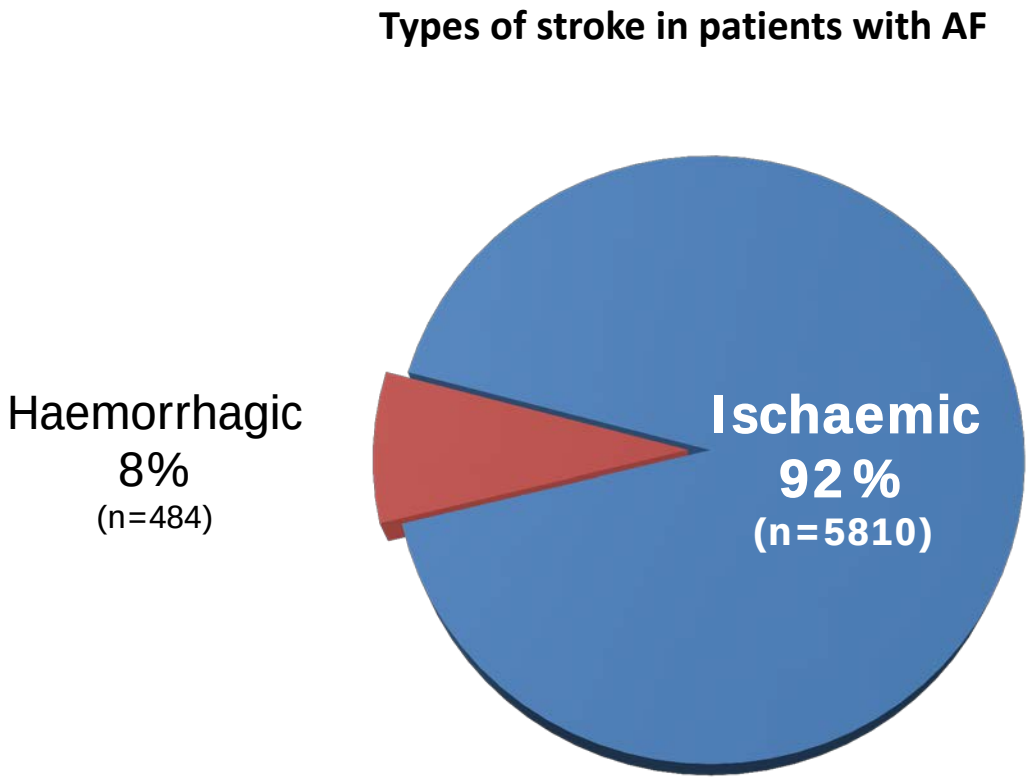
Tableau 5 Persistance au traitement aux deux mois chez les nouveaux utilisateurs de dabigatran ou de warfarine du 20 avril 2011 au 19 avril 2012 ayant une FANV* et assurés en continu par le régime public d'assurance médicaments

| Persistance au traitement | DABIGATRAN | | | | WARFARINE |
|---|---|---|---|---|---|
| | 110 mg 2x /jr | 150 mg 2x /jr | Autres posologies | TOTAL | |
| | % | % | % | % | % |
| 2 mois | 81,1 | 82,8 | 87,0 | 82,4 | 72,6 |
| 4 mois | 81,4 | 82,7 | 83,5 | 82,2 | 66,6 |
| 6 mois | 78,9 | 81,0 | 82,2 | 80,2 | 63,9 |
| 8 mois | 78,3 | 80,8 | 81,4 | 79,7 | 59,5 |
| 10 mois | 75,0 | 77,6 | 80,8 | 76,8 | 55,9 |
| 12 mois | 76,1 | 78,7 | 80,2 | 77,7 | 55,7 |

* Définie comme une occurrence d'un diagnostic de fibrillation auriculaire dans les six mois précédant la date d'amorce du dabigatran ou de la warfarine sans atteinte valvulaire.

INESS, Marzo 2013

# Most strokes associated with AF are ischaemic



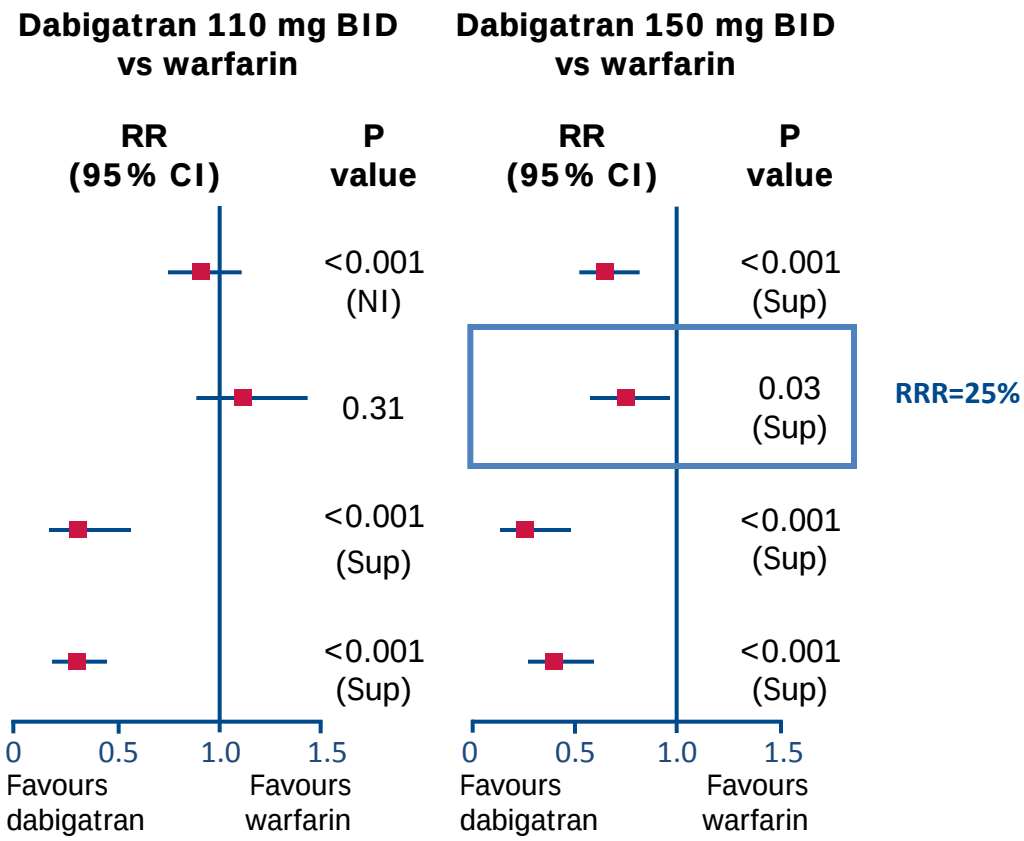

Based on data collected in the Danish National Indicator Project for 39 484 patients hospitalized for stroke (80% of all stroke admissions in Denmark) including 6294 patients with AF; OAC use not recorded

Andersen KK et al. Stroke 2009;40:2068–72

# Dabigatran 150 mg is the only new-generation agent to also reduce the risk of ischaemic stroke vs warfarin

- In addition to a significant reduction in stroke/SE, haemorrhagic stroke, and ICH

| | Event rate (%/yr) | | |
|---|---|---|---|
| | D110 | D150 | Warfarin |
| Stroke/SE | 1.54 | 1.11 | 1.71 |
| Ischaemic stroke | 1.28 | 0.86 | 1.14 |
| Haemorrhagic stroke | 0.12 | 0.10 | 0.38 |
| ICH | 0.23 | 0.32 | 0.76 |




ICH = intracranial haemorrhage; NI = non-inferiority;
RR = relative risk; RRR = relative risk reduction; SE = systemic embolism; Sup = superiority

Connolly SJ et al. N Engl J Med 2010;363:1875–6; Pradaxa®: EU SmPC, 2012

# Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis

Yan Xu BSc, Anne M. Holbrook MD PharmD MSc, Christopher S. Simpson MD, Dar Dowlatshahi MD PhD, Ana P. Johnson PhD

See related commentary in *CMAJ* by Coppens and colleagues at www.cmaj.ca/lookup/doi/10.1503/cmaj.131291.

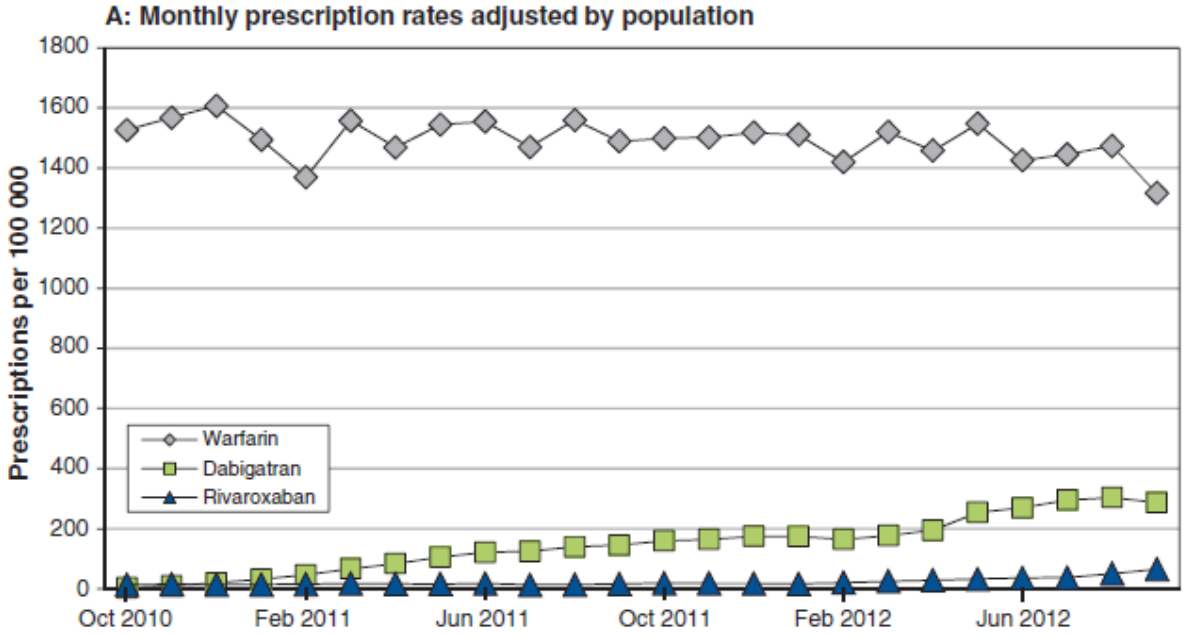
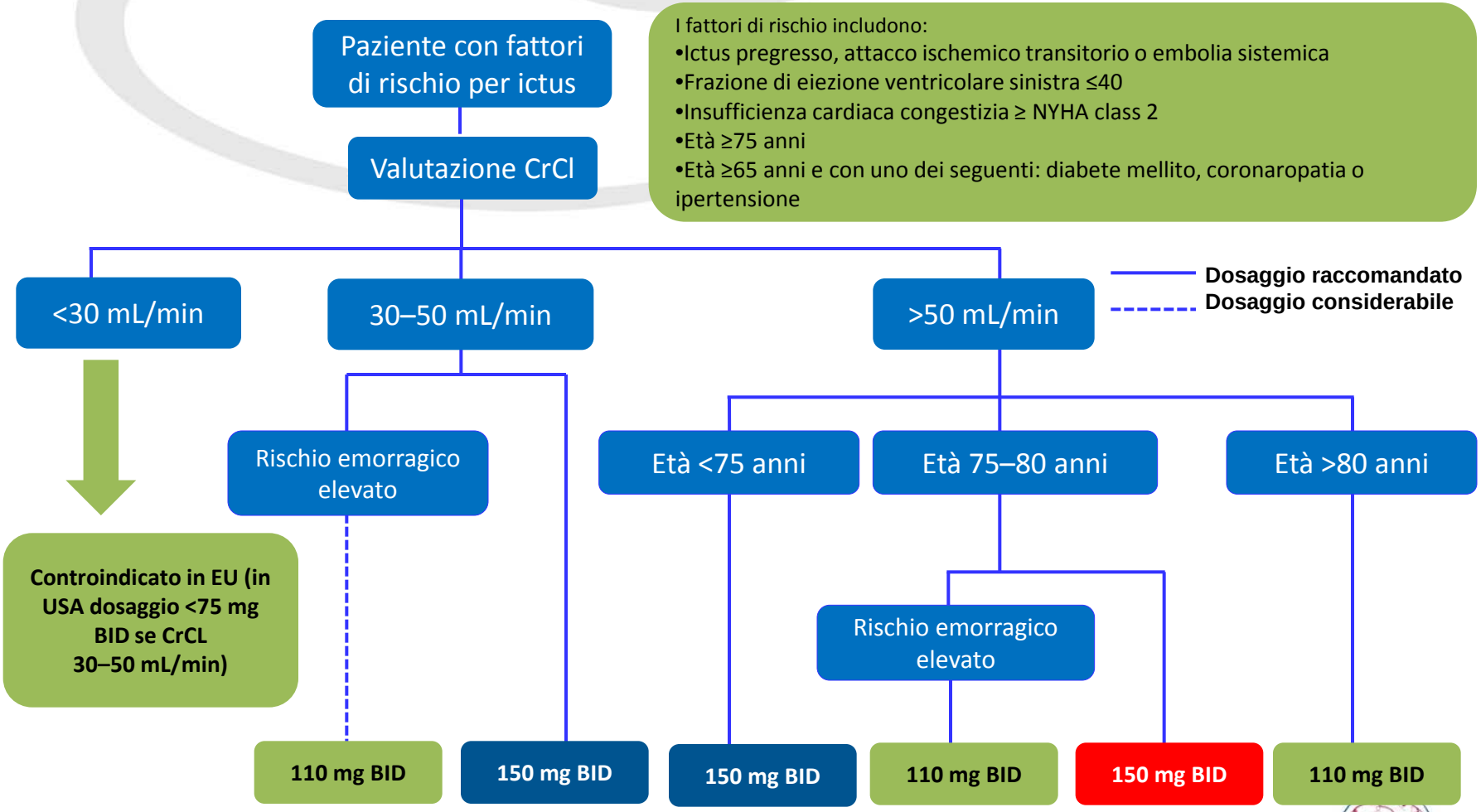



**Figure 1:** Monthly prescription rates for warfarin, dabigatran and rivaroxaban in Ontario among adults aged ≥ 20, adjusted by population (A) and proportion of prescription rates by type of anticoagulant (B).

# Dabigatran nella prevenzione dell'ictus in pazienti con FA: risolvere le incertezze nella pratica quotidiana




La funzionalità renale deve essere valutata in tutti i pazienti prima di iniziare la terapia con dabigatran

BID = due volte al giorno; CrCl = clearance della creatinina; NYHA = New York Heart Association

Adapted from: Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

# Stroke prevention in older adults with atrial fibrillation

Michiel Coppens MD PhD, Robert G. Hart MD, John W. Eikelboom MBBS

See related research article by Xu and colleagues in *CMAJ Open* at www.cmajopen.ca/content/1/3/E115

## KEY POINTS

- Older patients with atrial fibrillation have a higher risk of stroke and worse outcomes after stroke than younger patients, but many do not receive recommended anticoagulation treatment.
- Subgroup analyses of data for more than 19 100 patients aged 75 years or older enrolled in phase III trials suggest that the new oral anticoagulants dabigatran, rivaroxaban and apixaban offer consistent benefits over warfarin in older patients with atrial fibrillation.
- The rate of intracranial bleeding, the most feared complication of anticoagulation, is related to age and is sharply reduced by the new anticoagulants relative to warfarin, making these agents particularly attractive for older patients.
- Uptake of new oral anticoagulants in Canada has been rapid. Their use in older patients is consistent with guideline recommendations and is supported by the results of clinical trials.
- Ongoing surveillance by regulatory authorities and postmarketing studies of the use of new oral anticoagulants will help to inform uptake of the medications and related outcomes among older patients in clinical settings.

*CMAJ* 2013. DOI:10.1503/cmaj.131291