# I Nuovi farmaci per la TAO:

## *novità terapeutiche nel controllo del rischio cardiovascolare*


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# LIMITATIONS OF CURRENT ANTICOAGULANTS

## WARFARIN

Drawbacks:

- Only oral
- Not for acute treatment
- Narrow therapeutic window
- Unpredictable response
- Requires frequent monitoring

## HEPARINS (UF + LMWH)

Drawbacks:

- Only injectable
- *Only for UF*: requires monitoring
- Not convenient for long-term use
- HIT

***NEW ANTICOAGULANTS NEEDED***
***SPECIFICALLY ORAL***

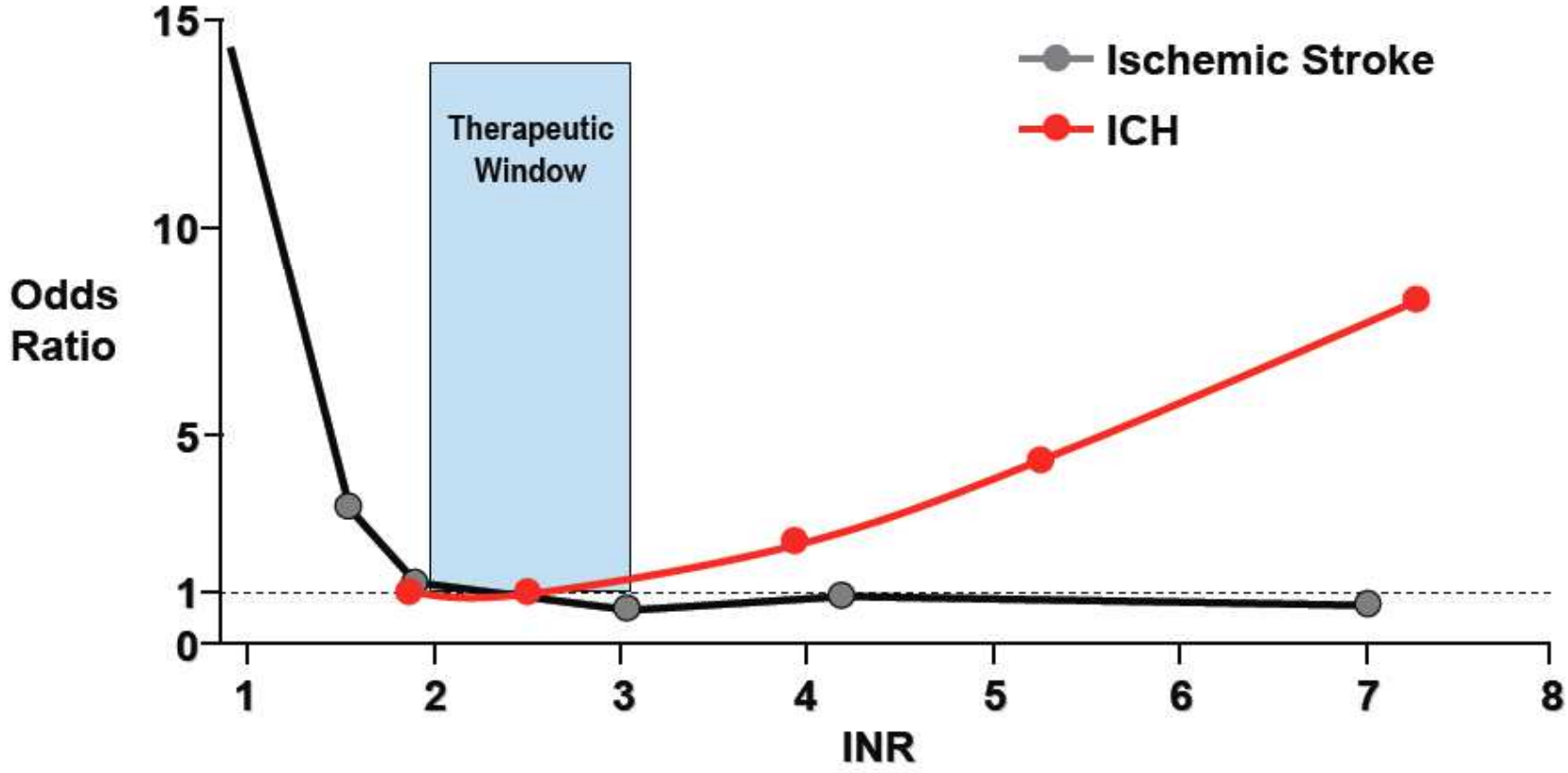
# Warfarin is One of the Most Common Drugs Associated With Adverse Events

- One of the 5 most common drug classes implicated in AEs
- One of the 5 most common drugs implicated in hospitalizations due to AEs
- Insulin and warfarin are implicated in 1 in every 7 estimated AEs treated in EDs
- In patients ≥ 65 yrs insulin, warfarin and digoxin are implicated in 1 in every 3 estimated AEs treated in EDs
- Insulin or warfarin is implicated in more than 25% of all estimated hospitalizations due to AEs

Budnitz et al. JAMA 2006;296:1858

# Warfarin Has a Narrow Therapeutic Window

## *Relationship Between Clinical Events and INR Intensity in Patients with Atrial Fibrillation*





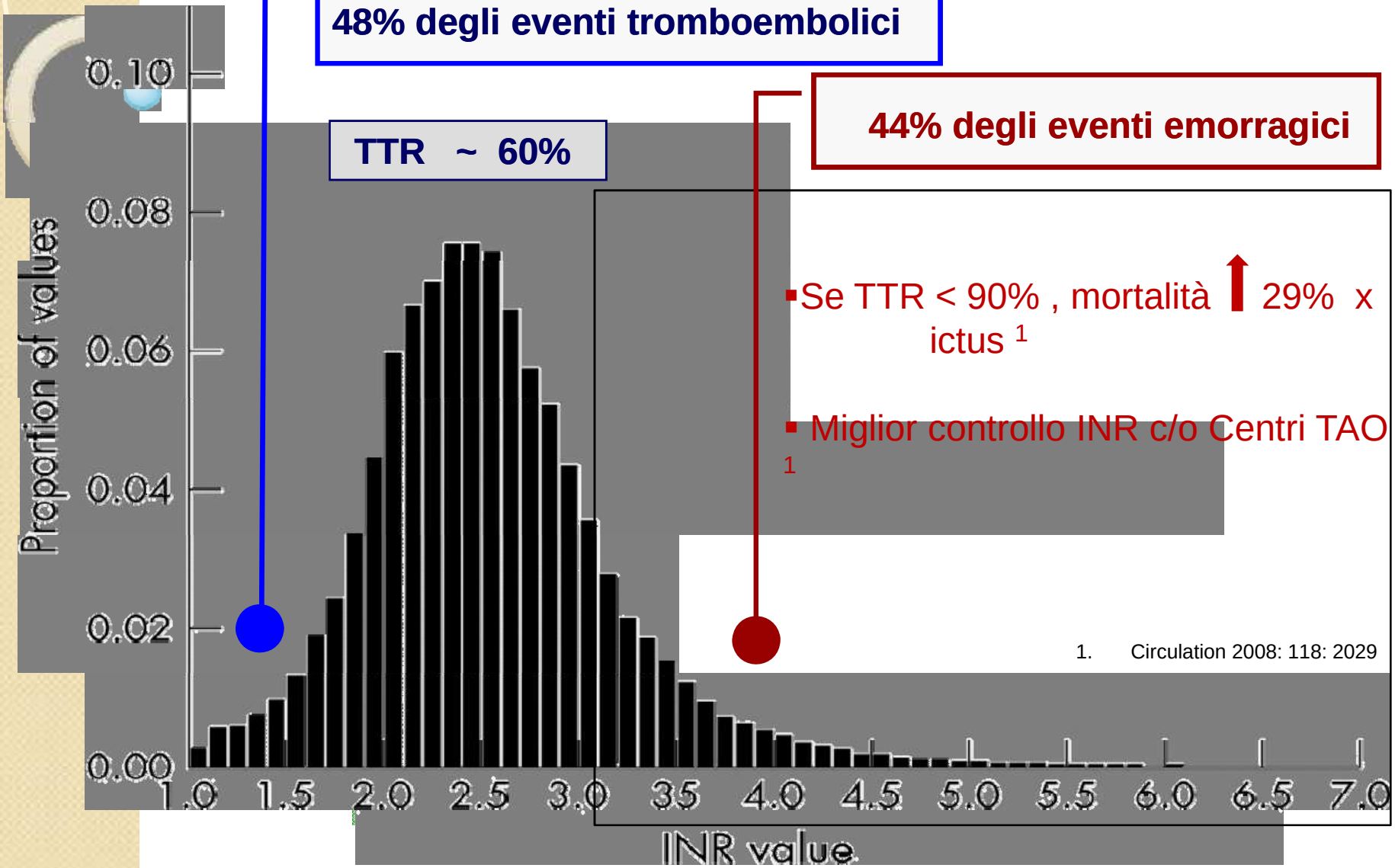
1. Hylek EM et al. *Ann Intern Med*. 1994;120:897.
2. Hylek EM et al. *N Engl J Med*. 1996;335:540.

# TEMPO in RANGE TERAPEUTICO

Frequency of adverse events in patients with poor anticoagulation: a meta-analysis

**48% degli eventi tromboembolici**

**44% degli eventi emorragici**



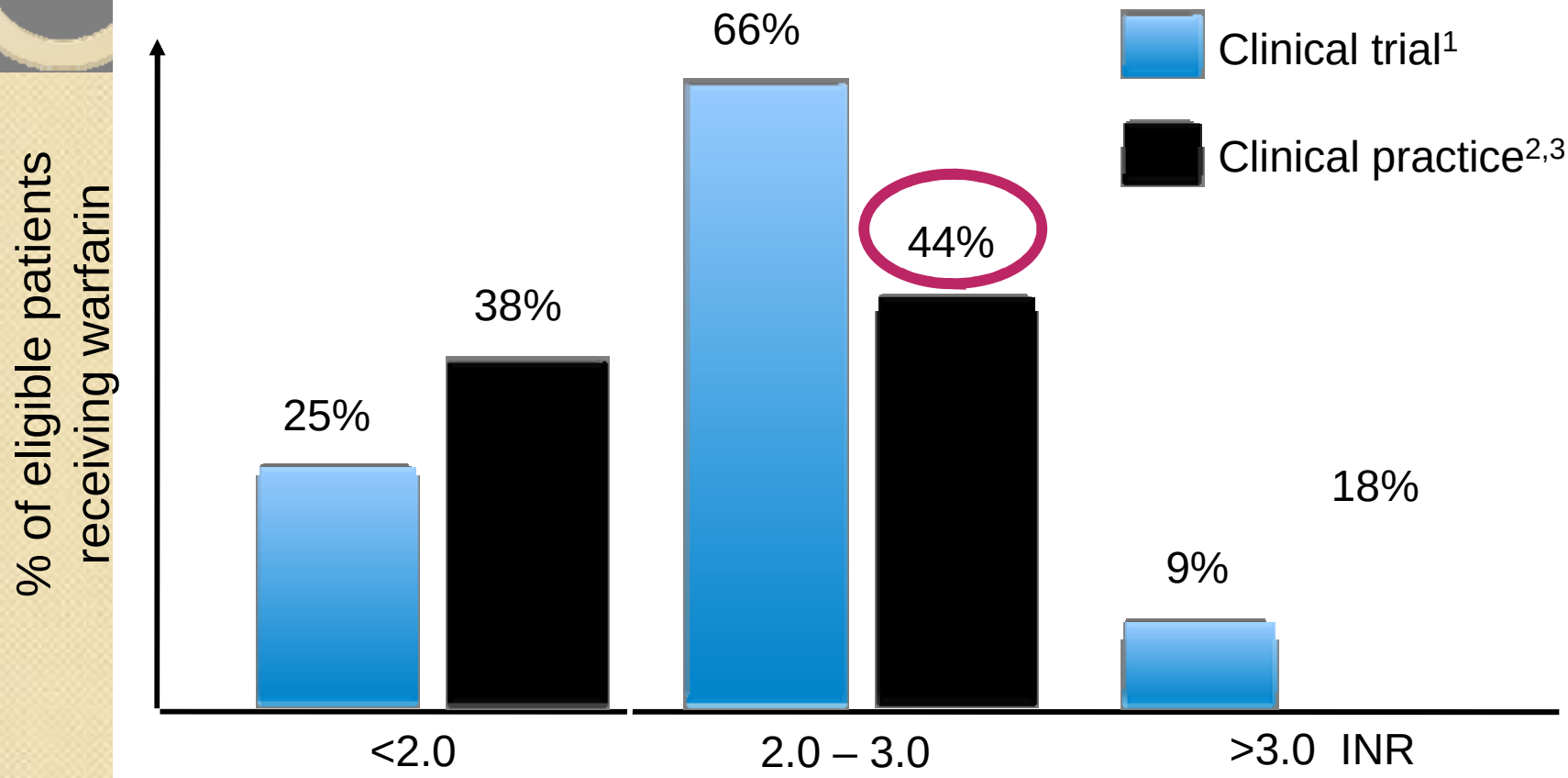

- Se TTR < 90% , mortalità ↑ 29% x ictus [1]
- Miglior controllo INR c/o Centri TAO [1]

1. Circulation 2008: 118: 2029

Oake N et al. CMAJ 2007;176:1589-94

# INR control: clinical trials v. clinical practice

INR* control in clinical trial versus clinical practice (TTR**)

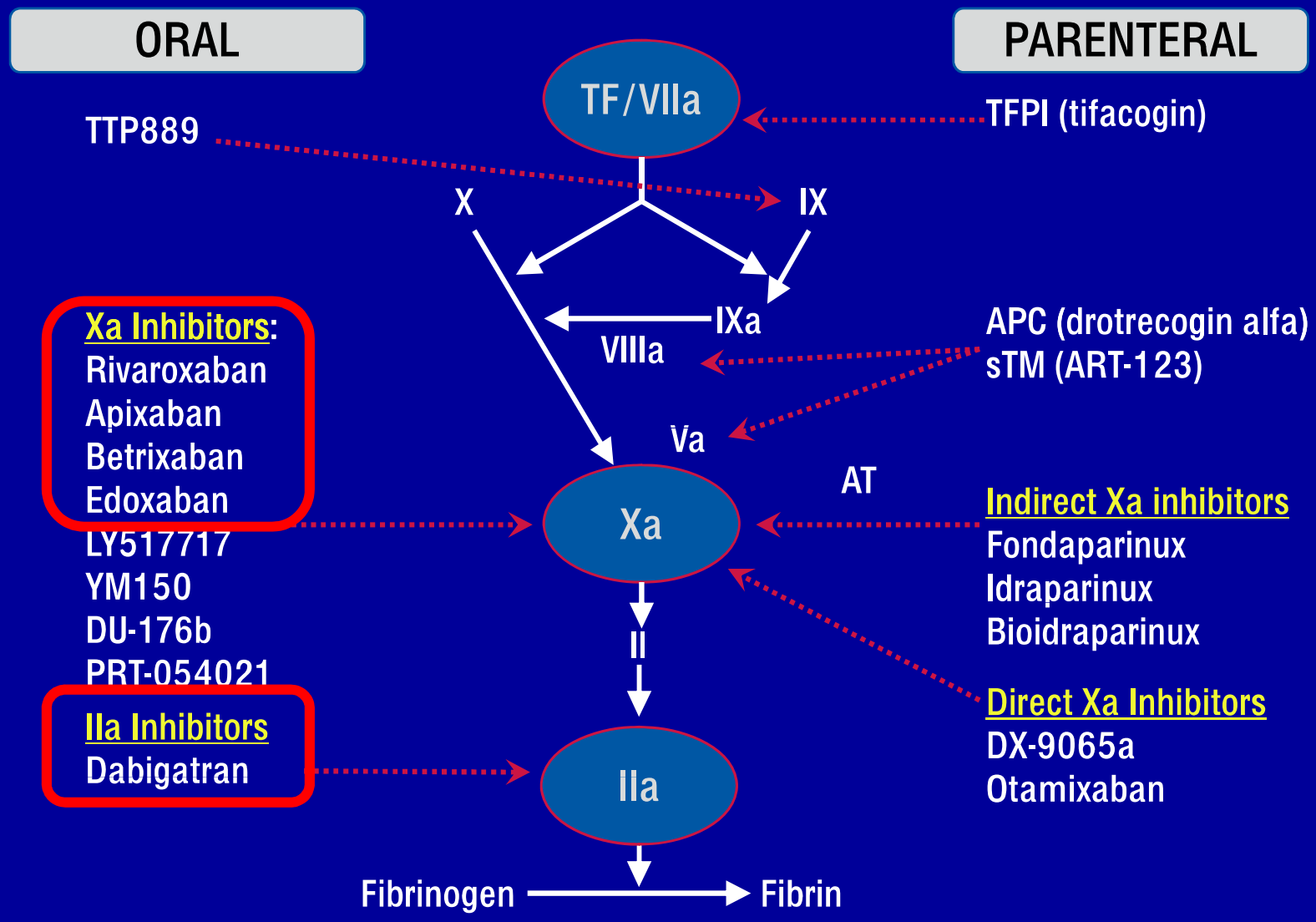



***INR = International normalized ratio**

**** TTR = Time in Therapeutic Range (INR2.0-3.0)**

1. Kalra L, et al. BMJ 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Samsa GP, et al. Arch Int Med 2000
3. Matchar DB, et al. Am J Med 2002; 113:42-51.

# Targets of New Anticoagulant Agents



# The RE-LY Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

## 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*

# CONCLUSIONS

## Prevention of stroke and systemic embolism

Dabigatran etexilate **110 mg** BID
non-inferior to well-controlled warfarin

RR 0.91 (95% CI: 0.74–1.11)

p<0.001 (non-inferiority) p=0.34 (superiority)

Dabigatran etexilate **150 mg** BID
superior to well-controlled warfarin

RR 0.66 (95% CI: 0.53–0.82)

p<0.001 (non-inferiority) p<0.001 (superiority)

# CONCLUSIONS

## Major Bleedings

Dabigatran etexilate **110 mg** BID
superior to well-controlled warfarin

RR 0.80 (95% CI: 0.69–0.93)

p=0.003 (superiority)

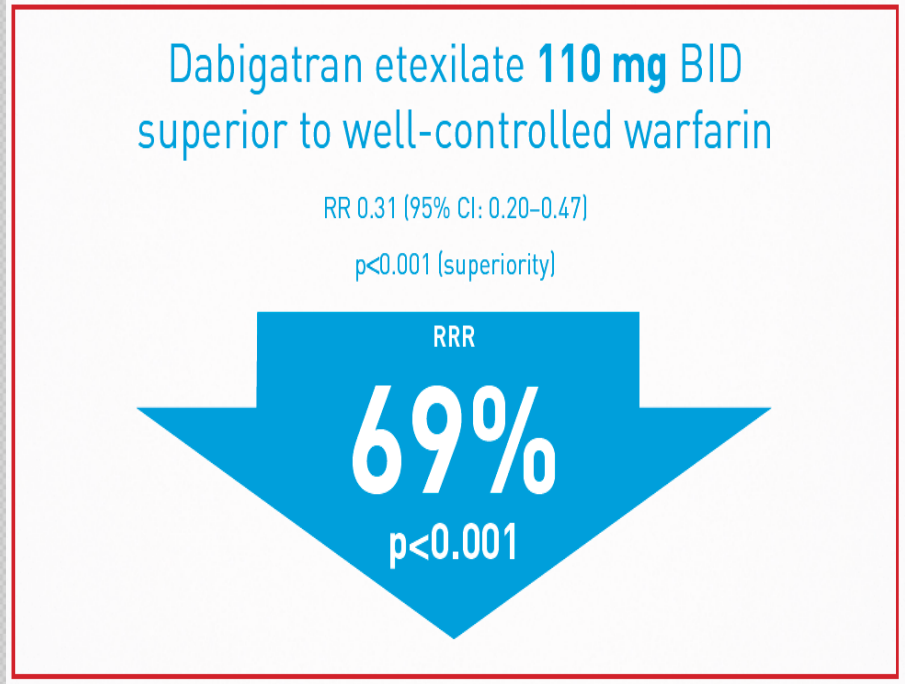

Dabigatran etexilate **150 mg** BID
non-inferior to well-controlled warfarin

RR 0.93 (95% CI: 0.81–1.07)

p=0.31 (superiority)

# CONCLUSIONS

## Reduction of Intra-cranial Bleedings




# Conclusions

**Both doses of dabigatran provide different and complementary advantages over warfarin**

- **150 mg BID has superior efficacy with similar bleeding**
- **110 mg BID has significantly less bleedings with similar efficacy**
- **Significant reduction in total bleeds, life threatening bleeds and intracranial bleeds**

# The ROCKET-AF Study

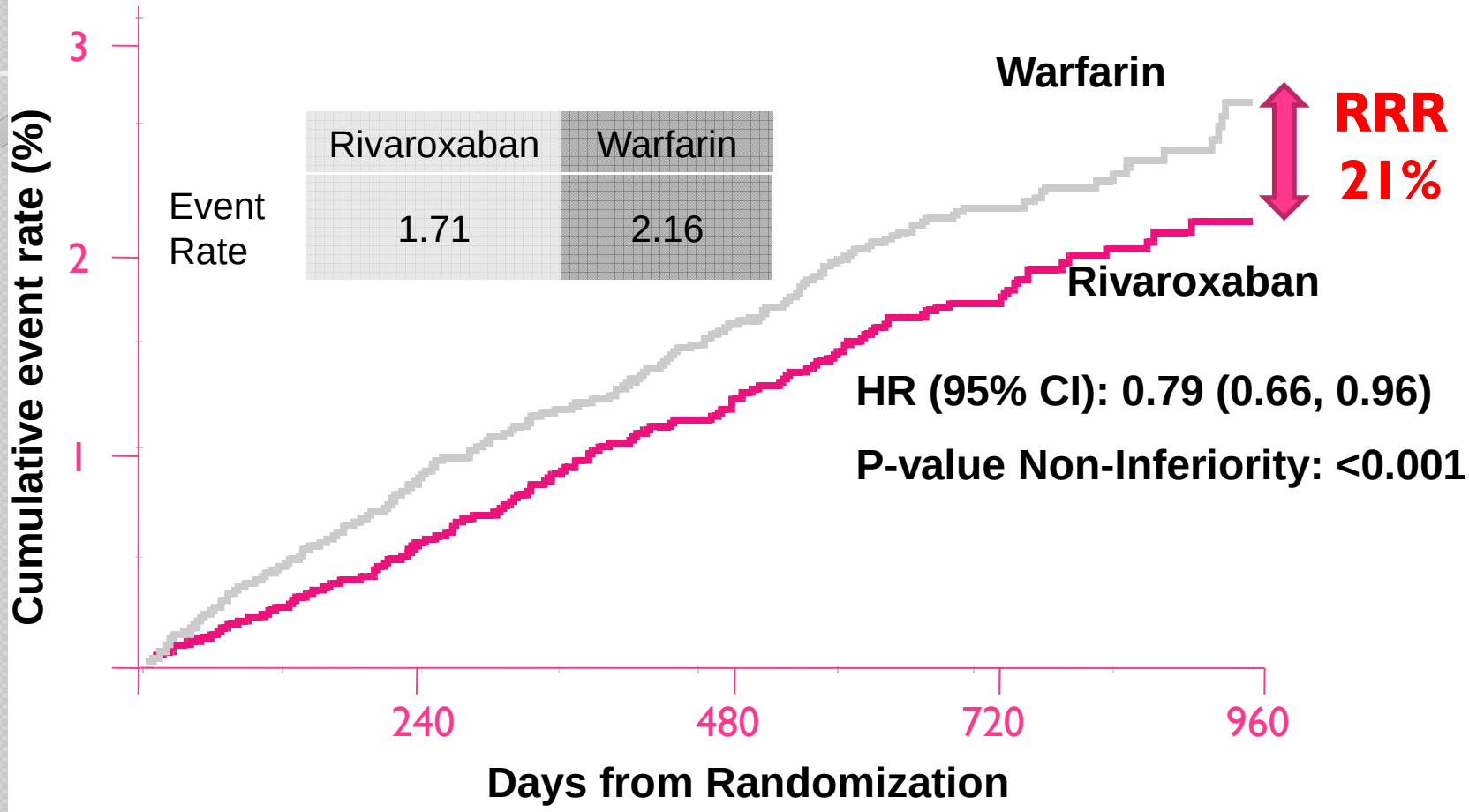
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

## Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

# Prevention of Stroke and Systemic Embolism




Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

# Primary Safety Outcomes

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

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

# Summary

**Efficacy**:

- Rivaroxaban was **non-inferior to warfarin** for prevention of stroke and non-CNS embolism.
- Rivaroxaban was **superior to warfarin** while patients were taking study drug.
- By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.

**Safety**:

- **Similar rates of bleeding** and adverse events.
- **Less ICH and fatal bleeding with rivaroxaban.**

**Conclusion**:

- **Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.**

# The ARISTOTLE Study

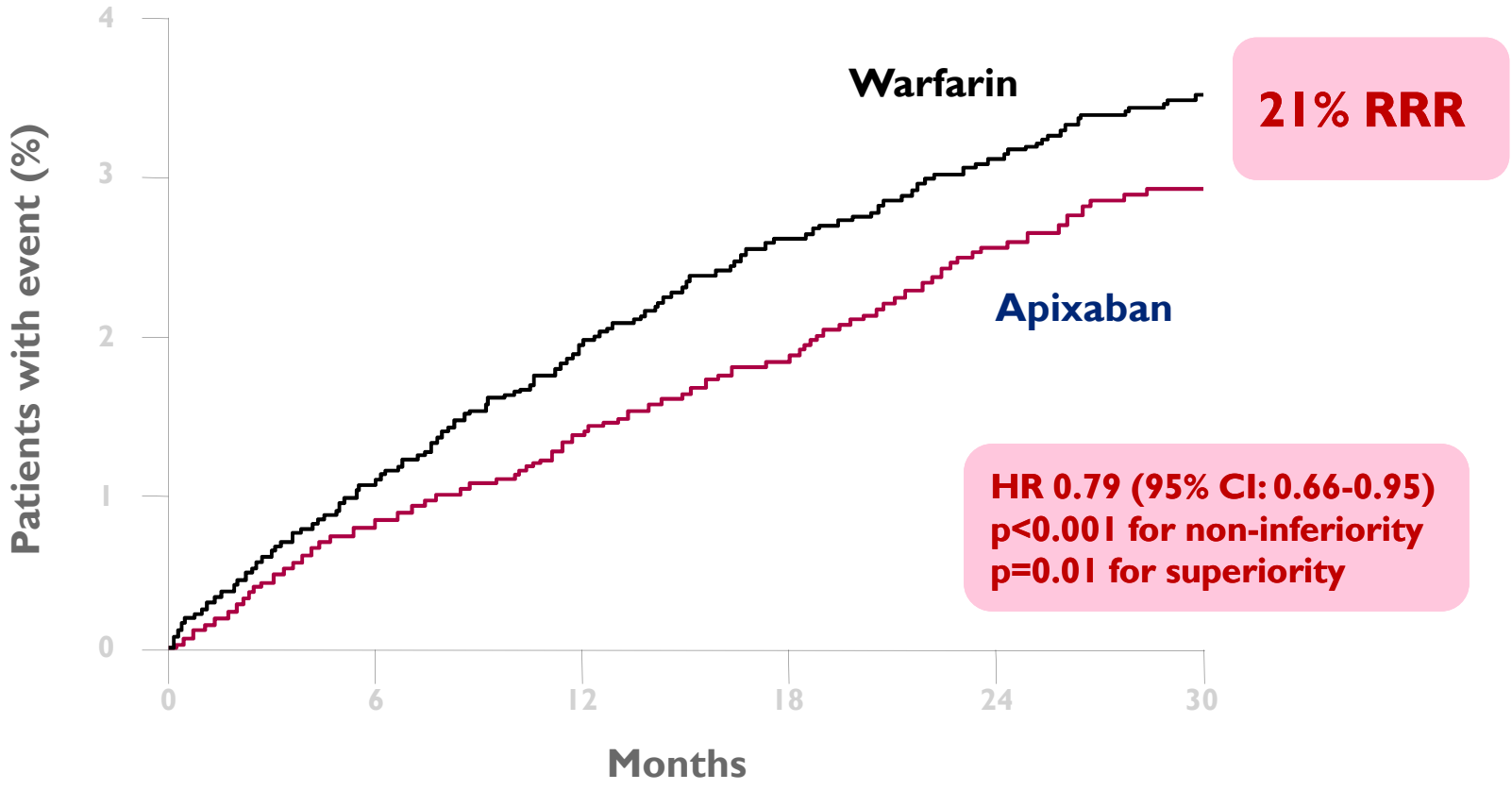
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

## Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

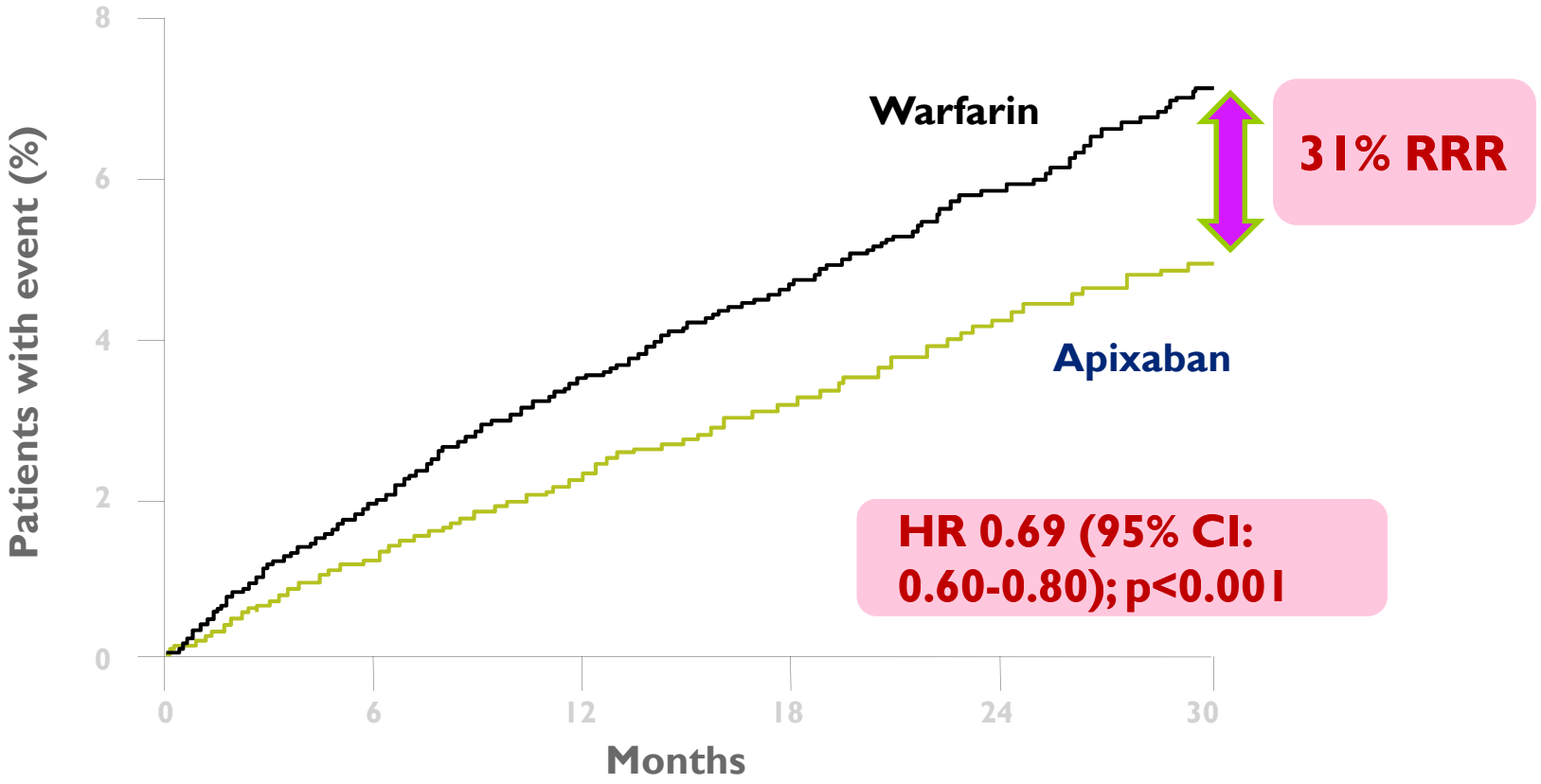
# ARISTOTLE: Apixaban **superior to warfarin** in preventing stroke or systemic embolism




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Apixaban | 9,120 | 8,726 | 8,440 | 6,051 | 3,464 | 1,754 |
| Warfarin | 9,081 | 8,620 | 8,301 | 5,972 | 3,405 | 1,768 |

*Adapted from Granger et al. N Engl J Med 2011;365:981-92.*

# ARISTOTLE: Apixaban significantly reduced the risk of major bleeding* *vs.* warfarin




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Apixaban | 9088 | 8103 | 7564 | 5365 | 3048 | 1515 |
| Warfarin | 9052 | 7910 | 7335 | 5196 | 2956 | 1491 |

** Major bleeding was defined according to ISTH criteria*

*Adapted from Granger et al. N Engl J Med 2011;365:981-92.*

# ARISTOTLE: Apixaban significantly reduced the rate of bleeding irrespective of the bleeding definition used

| Outcome | Apixaban (N=9,088) Event Rate (%/yr) | Warfarin (N=9,052) Event Rate (%/yr) | HR (95% CI) | P value |
|---|---|---|---|---|
| Primary safety outcome: ISTH major bleeding | 2.13 | 3.09 | 0.69 (0.60, 0.80) | <0.001 |
| Intracranial | 0.33 | 0.80 | 0.42 (0.30, 0.58) | <0.001 |
| Other location | 1.79 | 2.27 | 0.79 (0.68, 0.93) | 0.004 |
| Gastrointestinal | 0.76 | 0.86 | 0.89 (0.70, 1.15) | 0.37 |
| Major or clinically relevant non-major bleeding | 4.07 | 6.01 | 0.68 (0.61, 0.75) | <0.001 |
| GUSTO severe bleeding | 0.52 | 1.13 | 0.46 (0.35, 0.60) | <0.001 |
| TIMI major bleeding | 0.96 | 1.69 | 0.57 (0.46, 0.70) | <0.001 |
| Any bleeding | 18.1 | 25.8 | 0.71 (0.68, 0.75) | <0.001 |

*Granger et al. N Engl J Med 2011;365:981-92.*

# ARISTOTLE: Conclusions

- In patients with AF and at least one additional risk factor for stroke, the use of apixaban, as compared with warfarin, significantly reduced the risk of:
  - Stroke or systemic embolism by 21% (p=0.01)
  - Major bleeding by 31% (p<0.001)
  - Death by 11% (p=0.047)
- The results were consistent in subgroups according to geographic region, status with respect to previous warfarin exposure, age, sex, and risk factors for stroke, as well as in other predefined subgroups
- Apixaban had an acceptable side-effect profile and a lower rate of study drug discontinuation than in the warfarin group

*Granger et al. N Engl J Med 2011;365:981-92.*

CHEST
Official publication of the American College of Chest Physicians

**Executive Summary : Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**

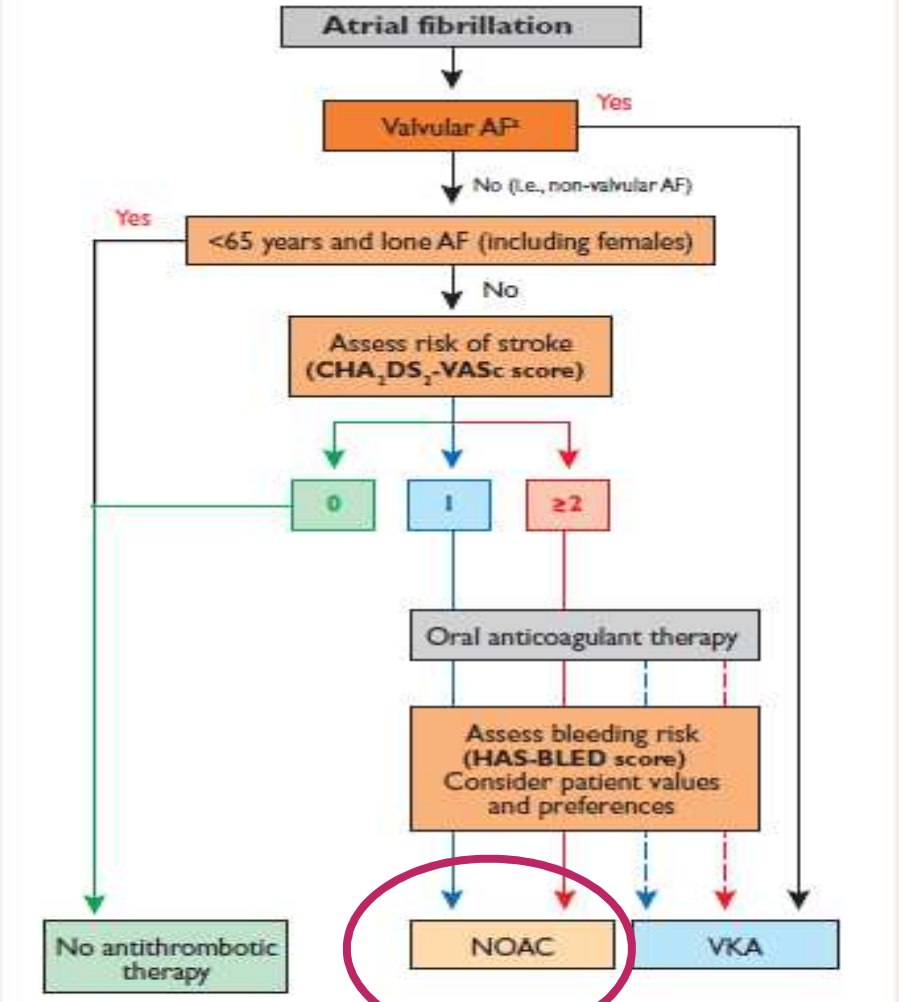
Gordon H. Guyatt, Elie A. Akl, Mark Crowther, David D. Gutterman, Holger J. Schünemann and for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel

*Chest* 2012;141;7S-47S
DOI 10.1378/chest.1412S3

**2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, $CHADS_2$ score = 2), we recommend oral anticoagulation rather than no therapy** (Grade 1A),

**2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0)** (Grade 2B).

*Remarks*: Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less). Clinicians should be aware that there is no antidote for dabigatran.




Antiplatelet therapy with aspirin plus dipyridamole, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.
Colour: $CHA_2DS_2$-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; $CHA_2DS_2$-VASc = see text; HAS-BLED = see text;
NOAC = novel oral anticoagulant; OAC = oral anticoagulant;
VKA = vitamin K antagonist.
*Includes rheumatic valvular disease and prosthetic valves.

**Figure 1** Choice of anticoagulant.

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

# RE-LY® – ROCKET-AF® – ARISTOTLE®
## Efficacia dei nuovi anticoagulanti orali: tutti non inferiori rispetto a warfarin

# Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation

## A Systematic Review and Meta-Analysis of the Literature

Francesco Dentali, MD; Nicoletta Riva, MD; Mark Crowther, MD; Alexander G.G. Turpie, MD; Gregory Y.H. Lip, MD; Walter Ageno, MD

***Background***—Novel oral anticoagulants (NOACs) have been proposed as alternatives to vitamin K antagonists for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Individually, NOACs were at least noninferior to vitamin K antagonists, but a clear superiority in overall and vascular mortality was not consistently proven.

***Methods and Results***—We performed a meta-analysis of phase II and phase III randomized, controlled trials comparing NOACs with vitamin K antagonists in patients with atrial fibrillation. The MEDLINE and EMBASE databases, supplemented with conference abstract books and www.clinicaltrials.gov, were searched up to the first week of July 2012 with no language restriction. Two reviewers performed independent article review and study quality assessment. Data on overall and cardiovascular mortality, stroke or systemic embolism, ischemic stroke, major and intracranial bleeding, and myocardial infarction were collected. NOACs were pooled to perform a comparison with vitamin K antagonists, calculating pooled relative risks (RRs) and associated 95% confidence intervals (CIs). We retrieved 12 studies (3 administering dabigatran, 4 administering rivaroxaban, 2 administering apixaban, and 3 administering edoxaban) enrolling a total of 54 875 patients. NOACs significantly reduced total mortality (5.61% versus 6.02%; RR, 0.89; 95% CI, 0.83–0.96), cardiovascular mortality (3.45% versus 3.65%; RR, 0.89; 95% CI, 0.82–0.98), and stroke/systemic embolism (2.40% versus 3.13%; RR, 0.77; 95% CI, 0.70–0.86). There was a trend toward reduced major bleeding (RR, 0.86; 95% CI, 0.72–1.02) with a significant reduction of intracranial hemorrhage (RR, 0.46; 95% CI, 0.39–0.56). No difference in myocardial infarction was observed.

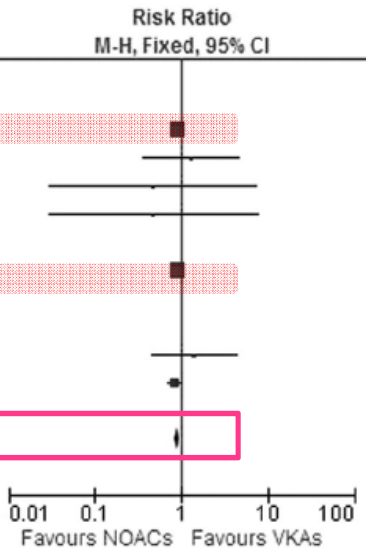
***Conclusions***—NOACs are associated with an overall clinical benefit compared with vitamin K antagonists. Additional research is required to confirm these findings outside the context of randomized trials. (*Circulation*. 2012;126:2381-2391.)

**Key Words:** anticoagulants ■ atrial fibrillation ■ meta-analysis ■ mortality ■ stroke

## A Total mortality

| | Study or Subgroup | NOACs Events | NOACs Total | VKAs Events | VKAs Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| D | NCT01136408 (D) | 0 | 104 | 0 | 62 | | Not estimable |
| D | PETRO | 0 | 166 | 0 | 70 | | Not estimable |
| D | RE-LY | 884 | 12091 | 487 | 6022 | 41.1% | 0.90 [0.81, 1.01] |
| E | WEITZ | 11 | 713 | 3 | 250 | 0.3% | 1.29 [0.36, 4.57] |
| E | CHUNG | 1 | 159 | 1 | 75 | 0.1% | 0.47 [0.03, 7.44] |
| E | YAMASHITA | 1 | 260 | 1 | 125 | 0.1% | 0.48 [0.03, 7.62] |
| A | ARISTOTLE-J | 0 | 148 | 0 | 74 | | Not estimable |
| A | ARISTOTLE | 603 | 9120 | 669 | 9081 | 42.4% | 0.90 [0.81, 1.00] |
| R | NCT00973245 (R1) | 0 | 75 | 0 | 27 | | Not estimable |
| R | NCT00973323 (R2) | 0 | 50 | 0 | 26 | | Not estimable |
| R | J-ROCKET-AF | 7 | 637 | 5 | 637 | 0.3% | 1.40 [0.45, 4.39] |
| R | ROCKET-AF | 208 | 7061 | 250 | 7082 | 15.8% | 0.83 [0.70, 1.00] |
| | Total (95% CI) | | 30584 | | 23531 | 100.0% | 0.89 [0.83, 0.96] |
| | Total events | 1715 | | 1416 | | | |

Heterogeneity: Chi² = 1.91, df = 6 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.24 (P = 0.001)



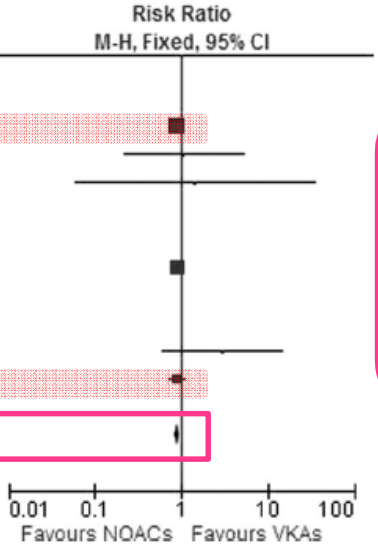

**NNT 244**

**apixaban**
**dabigatran**
**rivaroxaban**

## B Cardiovascular mortality

| Study or Subgroup | NOACs Events | NOACs Total | VKAs Events | VKAs Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| NCT01136408 (D) | 0 | 104 | 0 | 62 | | Not estimable |
| PETRO | 0 | 166 | 0 | 70 | | Not estimable |
| RE-LY | 563 | 12091 | 317 | 6022 | 43.8% | 0.88 [0.77, 1.01] |
| WEITZ | 6 | 713 | 2 | 250 | 0.3% | 1.05 [0.21, 5.18] |
| CHUNG | 1 | 159 | 0 | 75 | 0.1% | 1.43 [0.06, 34.57] |
| YAMASHITA | 0 | 260 | 0 | 125 | | Not estimable |
| ARISTOTLE-J | 0 | 148 | 0 | 74 | | Not estimable |
| ARISTOTLE | 308 | 9120 | 344 | 9081 | 35.7% | 0.89 [0.77, 1.04] |
| NCT00973245 (R1) | 0 | 75 | 0 | 27 | | Not estimable |
| NCT00973323 (R2) | 0 | 50 | 0 | 26 | | Not estimable |
| J-ROCKET-AF | 6 | 637 | 2 | 637 | 0.2% | 3.00 [0.61, 14.81] |
| ROCKET-AF | 170 | 7061 | 193 | 7082 | 19.9% | 0.88 [0.72, 1.08] |
| Total (95% CI) | | 30584 | | 23531 | 100.0% | 0.89 [0.82, 0.98] |
| Total events | 1054 | | 858 | | | |

Heterogeneity: Chi² = 2.36, df = 5 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)



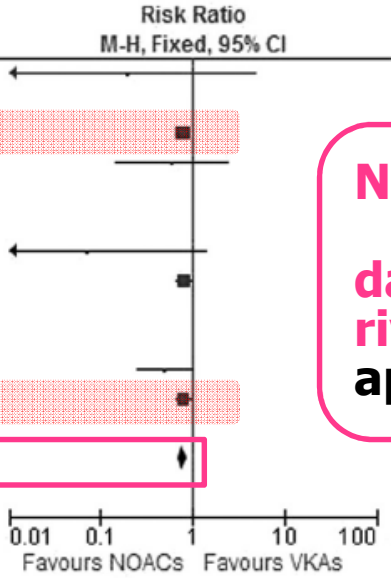

**NNT 500**

**dabigatran**
**rivaroxaban**
**apixaban**

## A Stroke or Systemic Embolism

| Study or Subgroup | NOACs Events | NOACs Total | VKAs Events | VKAs Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| NCT01136408 (D) | 0 | 104 | 1 | 62 | 0.2% | 0.20 [0.01, 4.84] |
| PETRO | 0 | 166 | 0 | 70 | | Not estimable |
| RE-LY | 317 | 12091 | 202 | 6022 | 33.4% | 0.78 [0.66, 0.93] |
| WEITZ | 5 | 713 | 3 | 250 | 0.5% | 0.58 [0.14, 2.43] |
| CHUNG | 0 | 159 | 0 | 75 | | Not estimable |
| YAMASHITA | 0 | 260 | 0 | 125 | | Not estimable |
| ARISTOTLE-J | 0 | 148 | 3 | 74 | 0.6% | 0.07 [0.00, 1.37] |
| ARISTOTLE | 212 | 9120 | 265 | 9081 | 32.9% | 0.80 [0.67, 0.95] |
| NCT00973245 (R1) | 0 | 75 | 0 | 27 | | Not estimable |
| NCT00973323 (R2) | 0 | 50 | 0 | 26 | | Not estimable |
| J-ROCKET-AF | 11 | 637 | 22 | 637 | 2.7% | 0.50 [0.24, 1.02] |
| ROCKET-AF | 188 | 7081 | 240 | 7090 | 29.7% | 0.78 [0.65, 0.95] |
| Total (95% CI) | | 30604 | | 23539 | 100.0% | 0.77 [0.70, 0.86] |
| Total events | 733 | | 736 | | | |

Heterogeneity: Chi² = 4.90, df = 6 (P = 0.56); I² = 0%
Test for overall effect: Z = 4.94 (P < 0.00001)



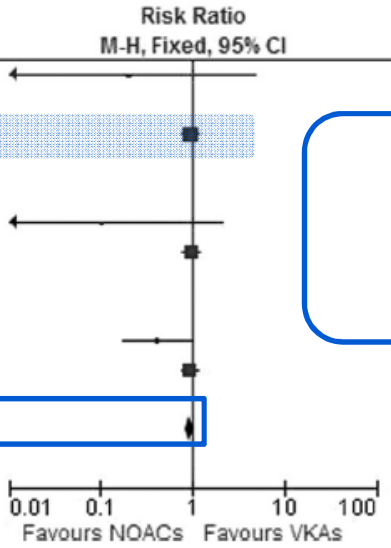

**NNT 173**

**dabigatran**
**rivaroxaban**
**apixaban**

## B Ischemic stroke

| Study or Subgroup | NOACs Events | NOACs Total | VKAs Events | VKAs Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| NCT01136408 (D) | 0 | 104 | 1 | 62 | 0.4% | 0.20 [0.01, 4.84] |
| PETRO | 0 | 166 | 0 | 70 | | Not estimable |
| RE-LY | 255 | 12091 | 134 | 6022 | 34.6% | 0.95 [0.77, 1.17] |
| CHUNG | 0 | 159 | 0 | 75 | | Not estimable |
| YAMASHITA | 0 | 260 | 0 | 125 | | Not estimable |
| ARISTOTLE-J | 0 | 148 | 2 | 74 | 0.6% | 0.10 [0.00, 2.07] |
| ARISTOTLE | 149 | 9120 | 155 | 9081 | 30.0% | 0.96 [0.77, 1.20] |
| NCT00973245 (R1) | 0 | 75 | 0 | 27 | | Not estimable |
| NCT00973323 (R2) | 0 | 50 | 0 | 26 | | Not estimable |
| J-ROCKET-AF | 7 | 637 | 17 | 637 | 3.3% | 0.41 [0.17, 0.99] |
| ROCKET-AF | 149 | 7061 | 161 | 7082 | 31.1% | 0.93 [0.74, 1.16] |
| Total (95% CI) | | 29871 | | 23281 | 100.0% | 0.92 [0.81, 1.04] |
| Total events | 560 | | 470 | | | |

Heterogeneity: Chi² = 6.40, df = 5 (P = 0.27); I² = 22%
Test for overall effect: Z = 1.35 (P = 0.18)




**n.s.**

# RE-LY® – ROCKET-AF® – ARISTOTLE®

## Efficacia dei nuovi anticoagulanti orali: tutti non inferiori rispetto a warfarin

### Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran*, *Rivaroxaban*, *Apixaban*) Versus *Warfarin* in Patients With Atrial Fibrillation

Corey S. Miller, BA[a,c], Sonia M. Grandi, MSc[a], Avi Shimony, MD[a,b,d], Kristian B. Filion, PhD[a], and Mark J. Eisenberg, MD, MPH[a,b,c,*]

| Characteristic | Trial | | | | | |
|---|---|---|---|---|---|---|
| | ARISTOTLE | | RE-LY | | ROCKET AF | |
| | Apixaban (n = 9,120) | Warfarin (n = 9,081) | Dabigatran (n = 6,076) | Warfarin (n = 6,022) | Rivaroxaban (n = 7,131) | Warfarin (n = 7,133) |
| Dose (mg) | 5 twice daily* | Target INR of 2.0–3.0 | 150 twice daily | Target INR of 2.0–3.0 | 20/day† | Target INR of 2.0–3.0 |
| Drug discontinuation rate | 25.3% | 27.5% | 21.2% | 16.6% | 23.7% | 22.2% |
| Median length of follow-up (days) | 657 | | 730 | | 707 | |
| Mean time in therapeutic range | NA | 62% | NA | 64% | NA | 55% |
| Age (years), mean ± SD or median (IQR) | 70 (63–76) | 70 (63–76) | 71.5 ± 8.8 | 71.6 ± 8.6 | 73 (65–78) | 73 (65–78) |
| Women | 35.5% | 35.0% | 36.8% | 36.7% | 39.7% | 39.7% |
| AF type | | | | | | |
| Persistent or permanent | 84.9% | 84.4% | 67.4% | 66.2% | 81.1% | 80.8% |
| Paroxysmal | 15.1% | 15.5% | 32.6% | 33.8% | 17.5% | 17.8% |
| New | NA | | NA | | 1.4% | 1.4% |
| $CHADS_2$ score, mean ± SD | 2.1 ± 1.1 | 2.1 ± 1.1 | 2.2 ± 1.2 | 2.1 ± 1.1 | 3.5 ± 0.94 | 3.5 ± 0.95 |
| 0 or 1 | 34.0% | 34.0% | 32.2% | 30.9% | ~0% | ~0% |
| 2 | 35.8% | 35.8% | 35.2% | 37.0% | 13.0% | 13.1% |
| 3–6 | 30.2% | 30.2% | 32.6% | 32.1% | 87.0% | 86.9% |
| Previous VKA use‡ | 57.1% | 57.2% | 50.2% | 48.6% | 62.3% | 62.5% |
| Previous stroke or transient ischemic attack§ | 19.2% | 19.7% | 20.3% | 19.8% | 54.9% | 54.6% |
| Heart failure‖ | 35.5% | 35.4% | 31.8% | 31.9% | 62.6% | 62.3% |
| Diabetes mellitus | 25.0% | 24.9% | 23.1% | 23.4% | 40.4% | 39.5% |
| Hypertension | 87.3% | 87.6% | 78.9% | 78.9% | 90.3% | 90.8% |

* Subjects who, at baseline, were ≥80 years of age, had body weights ≤60 kg, or had serum creatinine levels ≥1.5 mg/dl (133 μmol/L) received apixaban 2.5 mg twice daily.

† Subjects with creatinine clearance of 30 to 40 ml/min at baseline received rivaroxaban 15 mg/day.

‡ Defined as patients who used VKAs for ≥61 and 30 days in RE-LY and ARISTOTLE, respectively. Unspecified for ROCKET AF.

§ For ROCKET AF and ARISTOTLE, these data include patients who had systemic embolisms.

‖ For ROCKET AF and ARISTOTLE, these data include patients with left ventricular ejection fractions <35% and <40%, respectively.

(Am J Cardiol 2012;110:453–460)

# RE-LY® – ROCKET-AF® – ARISTOTLE®

## Sicurezza dei nuovi anticoagulanti orali

**A Major bleeding**

| Study or Subgroup | NOACs Events | NOACs Total | VKAs Events | VKAs Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| NCT01136408 (D) | 1 | 104 | 1 | 62 | 0.1% | 0.60 [0.04, 9.36] |
| PETRO | 0 | 166 | 0 | 70 | | Not estimable |
| RE-LY | 741 | 12091 | 421 | 6022 | 38.8% | 0.88 [0.78, 0.98] |
| WEITZ | 6 | 713 | 1 | 250 | 0.1% | 2.10 [0.25, 17.39] |
| CHUNG | 0 | 159 | 2 | 75 | 0.2% | 0.10 [0.00, 1.95] |
| YAMASHITA | 2 | 260 | 0 | 125 | 0.0% | 2.41 [0.12, 49.90] |
| ARISTOTLE-J | 0 | 143 | 1 | 75 | 0.1% | 0.18 [0.01, 4.27] |
| ARISTOTLE | | | | | | |
| NCT00973245 (R | | | | | | |
| NCT00973323 (R | | | | | | |
| J-ROCKET-AF | | | | | | |
| ROCKET-AF | | | | | | |
| Total (95% CI) | | | | | | |
| Total events | | | | | | |
| Heterogeneity: Ch | | | | | | |
| Test for overall eff | | | | | | |

**NNT 137**

***Myocardial Infarction***

MI occurred in 394 of 30 584 patients (1.29%) treated with NOACs and in 304 of 23 531 patients (1.29%) treated with VKAs (Figure 4). There was no difference in the risk of developing MI between NOACs and VKAs (RR, 0.99; 95% CI, 0.85–1.15; $I^2$=55%).

**B Intracranial**

| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| NCT01136408 (D) | 0 | 104 | 0 | 62 | | Not estimable |
| PETRO | 0 | 166 | 0 | 70 | | Not estimable |
| RE-LY | 64 | 12091 | 90 | 6022 | 35.4% | 0.35 [0.26, 0.49] |
| WEITZ | 3 | 713 | 0 | 250 | 0.2% | 2.46 [0.13, 47.47] |
| CHUNG | 0 | 159 | 0 | 75 | | Not estimable |
| YAMASHITA | 1 | 260 | 0 | 125 | 0.2% | 1.45 [0.06, 35.30] |
| ARISTOTLE-J | 0 | 143 | 1 | 75 | 0.6% | 0.18 [0.01, 4.27] |
| ARISTOTLE | 52 | 9088 | 122 | 9052 | 36.0% | 0.42 [0.31, 0.59] |
| NCT00973245 (R1) | 0 | 75 | 0 | 27 | | Not estimable |
| NCT00973323 (R2) | 0 | 50 | 0 | 26 | | Not estimable |
| J-ROCKET-AF | 5 | 639 | 10 | 639 | 2.9% | 0.50 [0.17, 1.45] |
| ROCKET-AF | 55 | 7111 | 84 | 7125 | 24.7% | 0.66 [0.47, 0.92] |
| Total (95% CI) | | 30599 | | 23548 | 100.0% | 0.46 [0.39, 0.56] |
| Total events | 180 | | 307 | | | |

Heterogeneity: Chi² = 9.15, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 8.22 (P < 0.00001)

0.01 0.1 1 10 100
Favours NOACs Favours VKAs

**NNT 141**

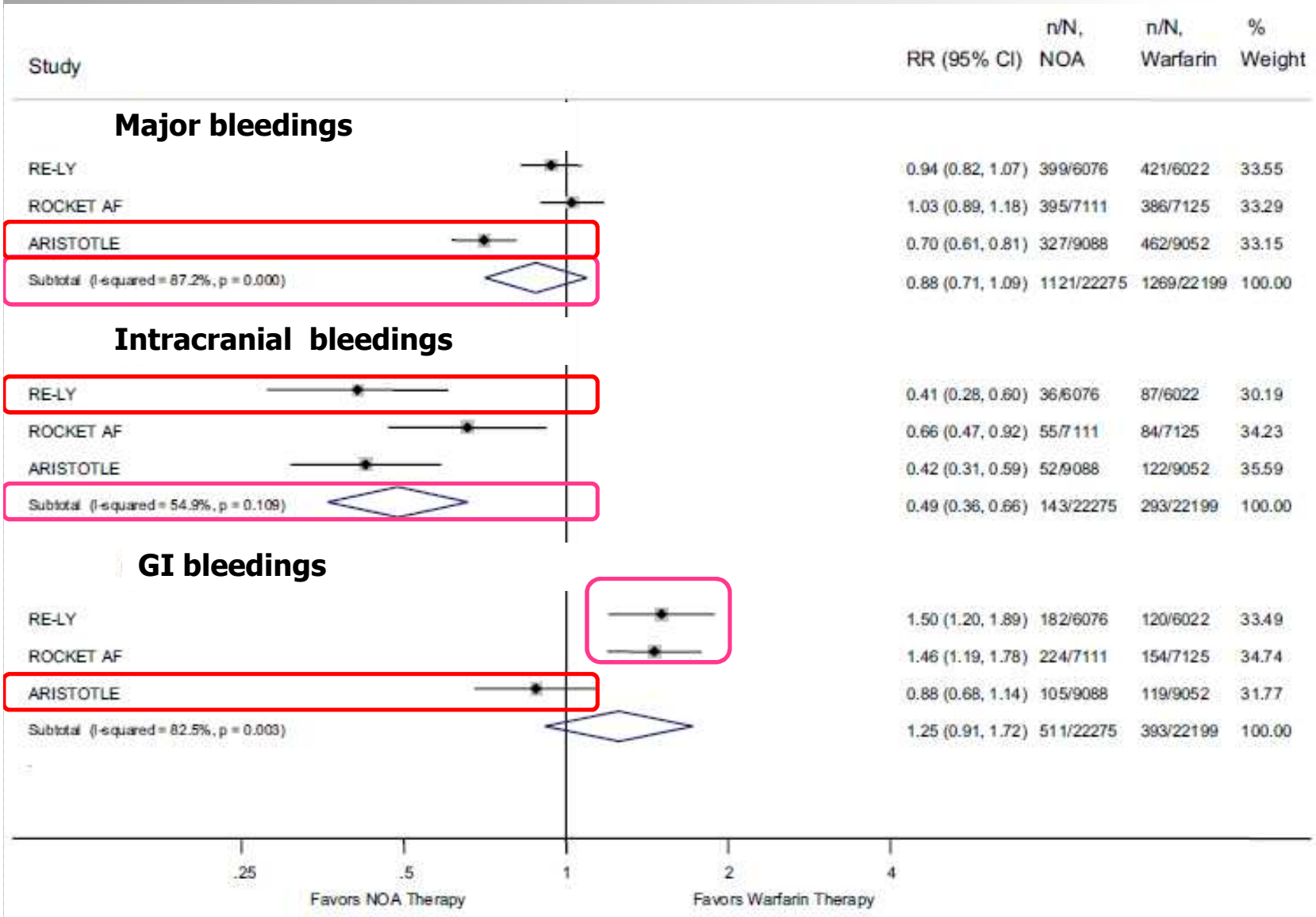
**dabigatran**
**apixaban**
**rivaroxaban**

**Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation : A Systematic Review and Meta-Analysis of the Literature**

Francesco Dentali, Nicoletta Riva, Mark Crowther, Alexander G.G. Turpie, Gregory Y.H. Lip and Walter Ageno

# RE-LY® – ROCKET-AF® – ARISTOTLE®

## Sicurezza dei nuovi anticoagulanti orali




**Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran, Rivaroxaban, Apixaban*) Versus *Warfarin* in Patients With Atrial Fibrillation**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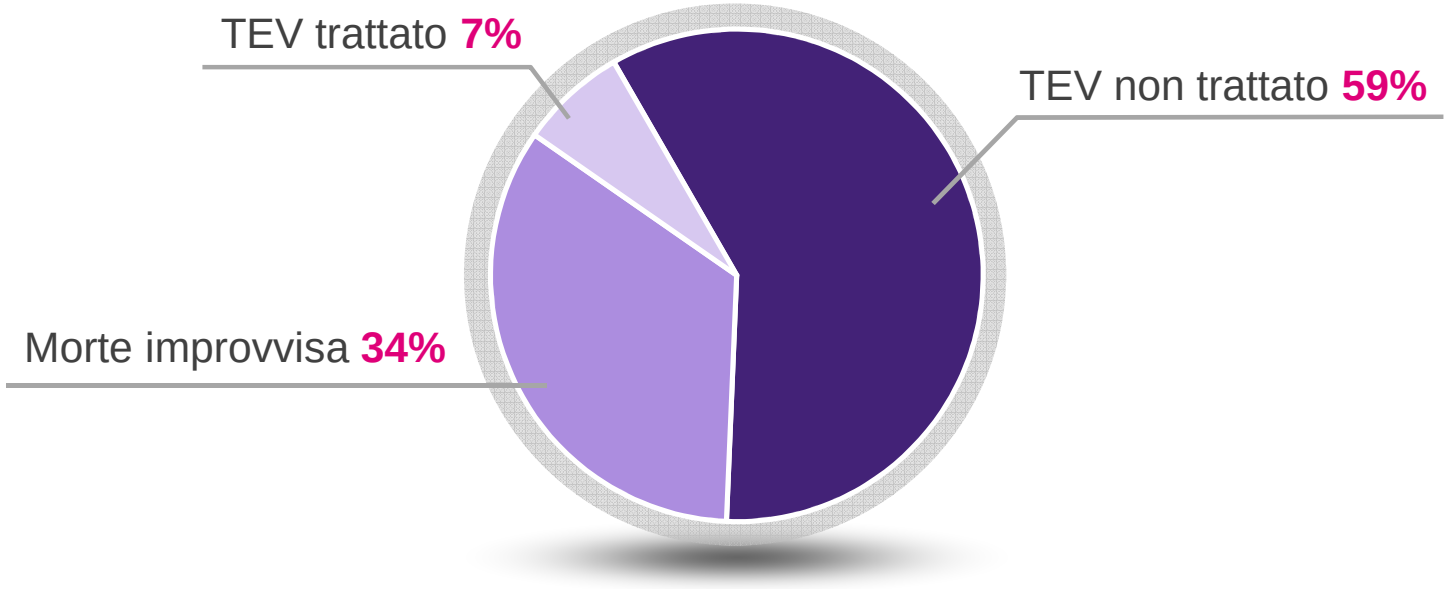
# Valutazione dell'impatto del TEV in Europa

Studio VITAE (VTE Impact Assessment Group in Europe)

**Mortalità in Germania, Italia, Francia, Regno Unito, Spagna e Svezia**

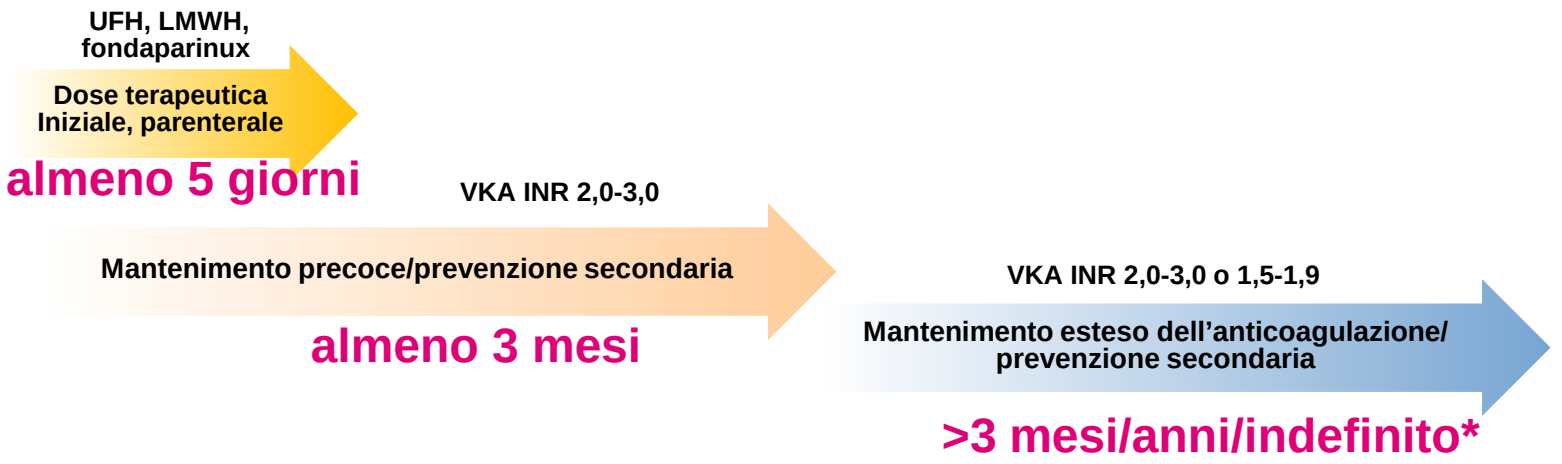



- **Incidenza TVP** (primo episodio e TVP ricorrente) = ***1.5 su 1000*** persone/anno, di cui 65/100.000 acquisita in comunità e 83/100.000 acquisita in ambito ospedaliero.
- **Incidenza EP** = ***1 su 1000*** persone/anno, di cui 28/100.000 acquisita in comunità e 67/100.000 in ambito ospedaliero.

Cohen AT, et al. *Thromb Haemost* 2007;98(4):756-64.

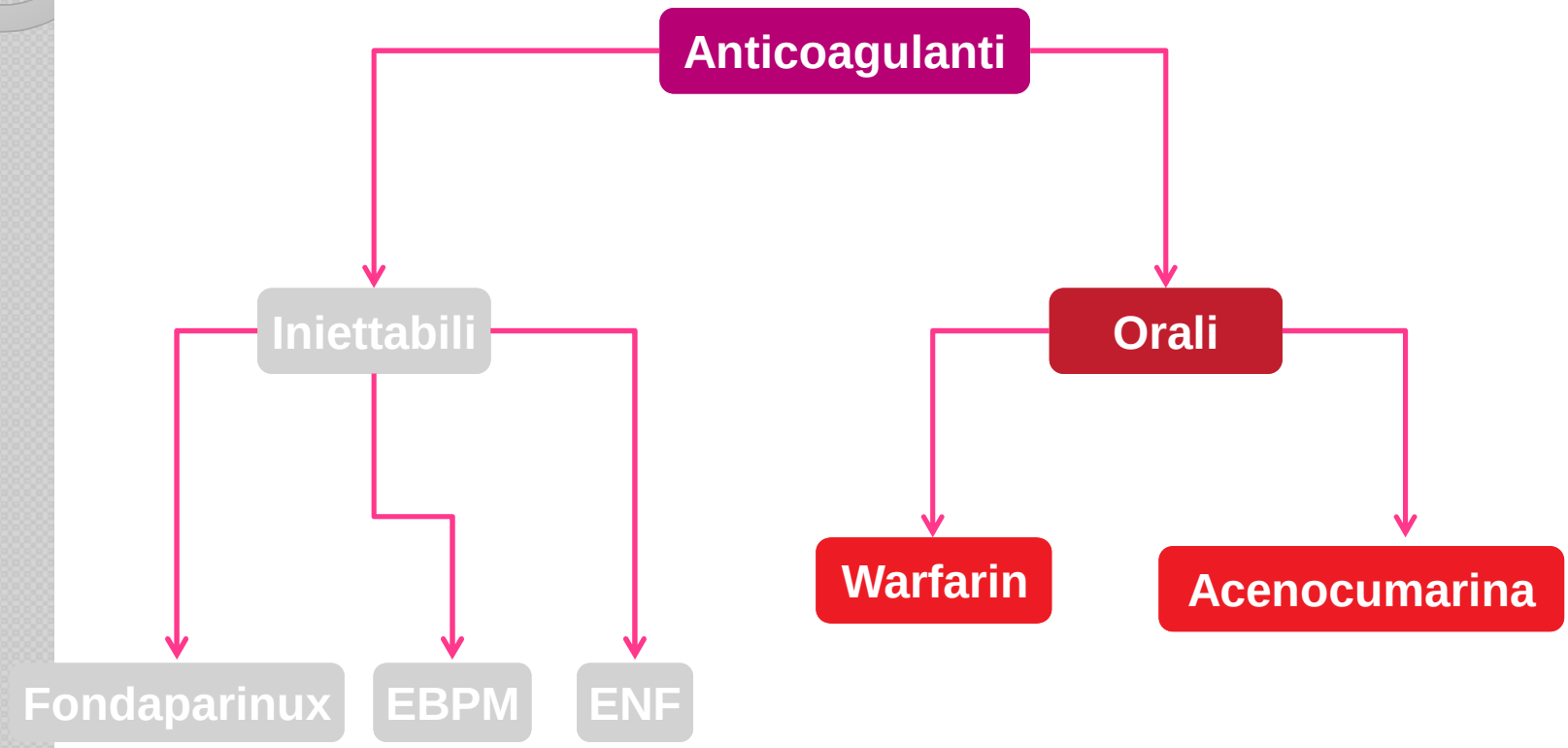
# Fasi della patologia e opzioni terapeutiche attuali

- **Tipologie e intensità dei trattamenti anticoagulanti convenzionali**




*Con rivalutazione del rapporto rischio/beneficio individuale a intervalli periodici.

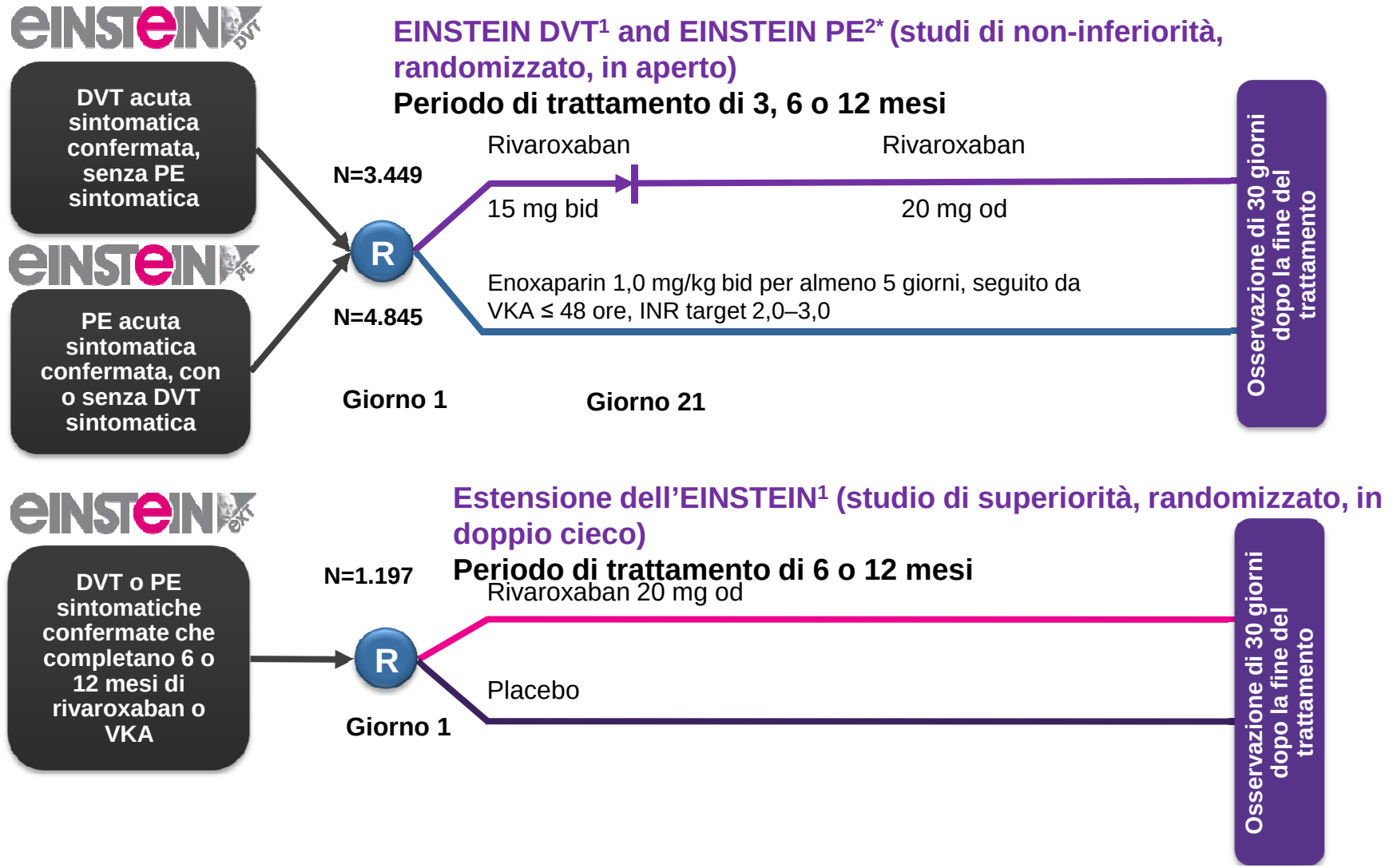
# Trattamento medico "tradizionale" della TVP



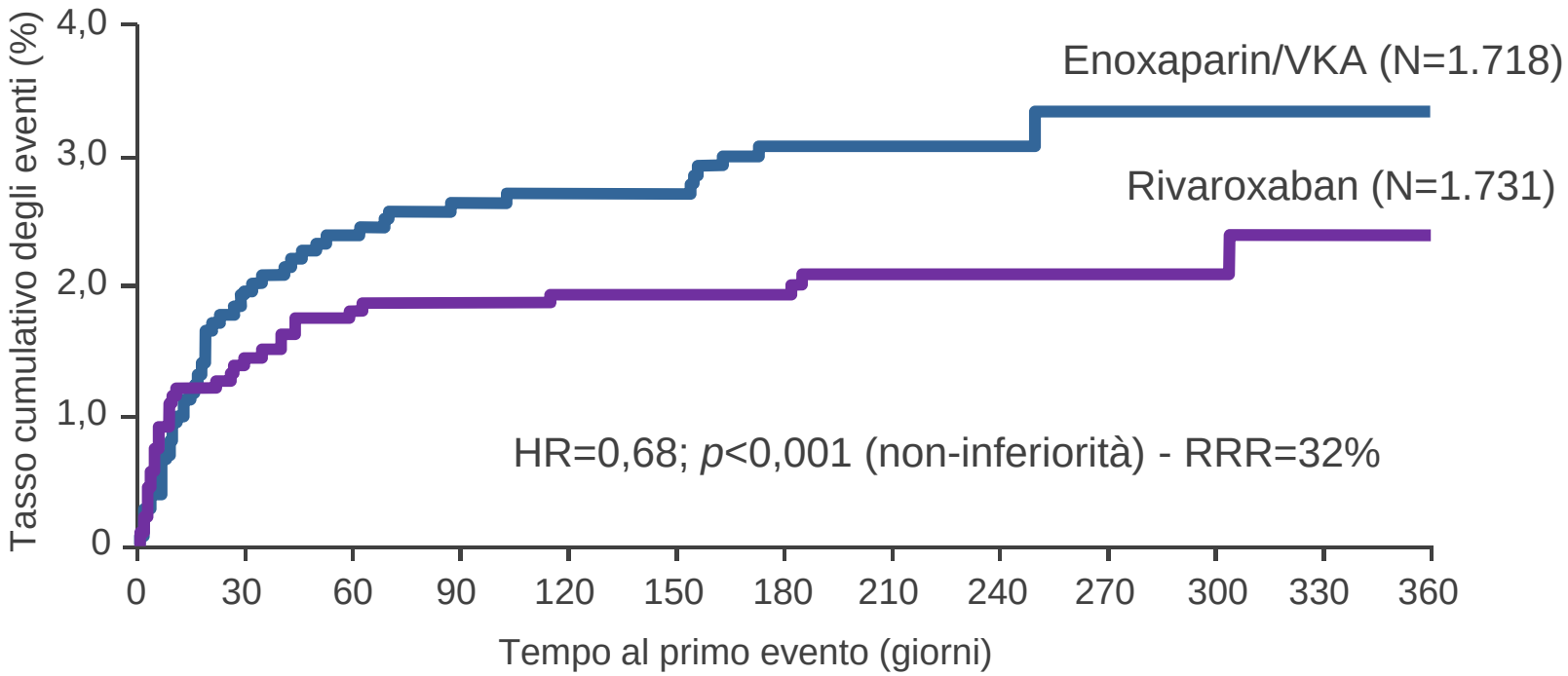
# *Il nuovo standard terapeutico per il trattamento della TVP*

## Il “*single drug approach*”

# Rivaroxaban EINSTEIN fase III: disegni di studio

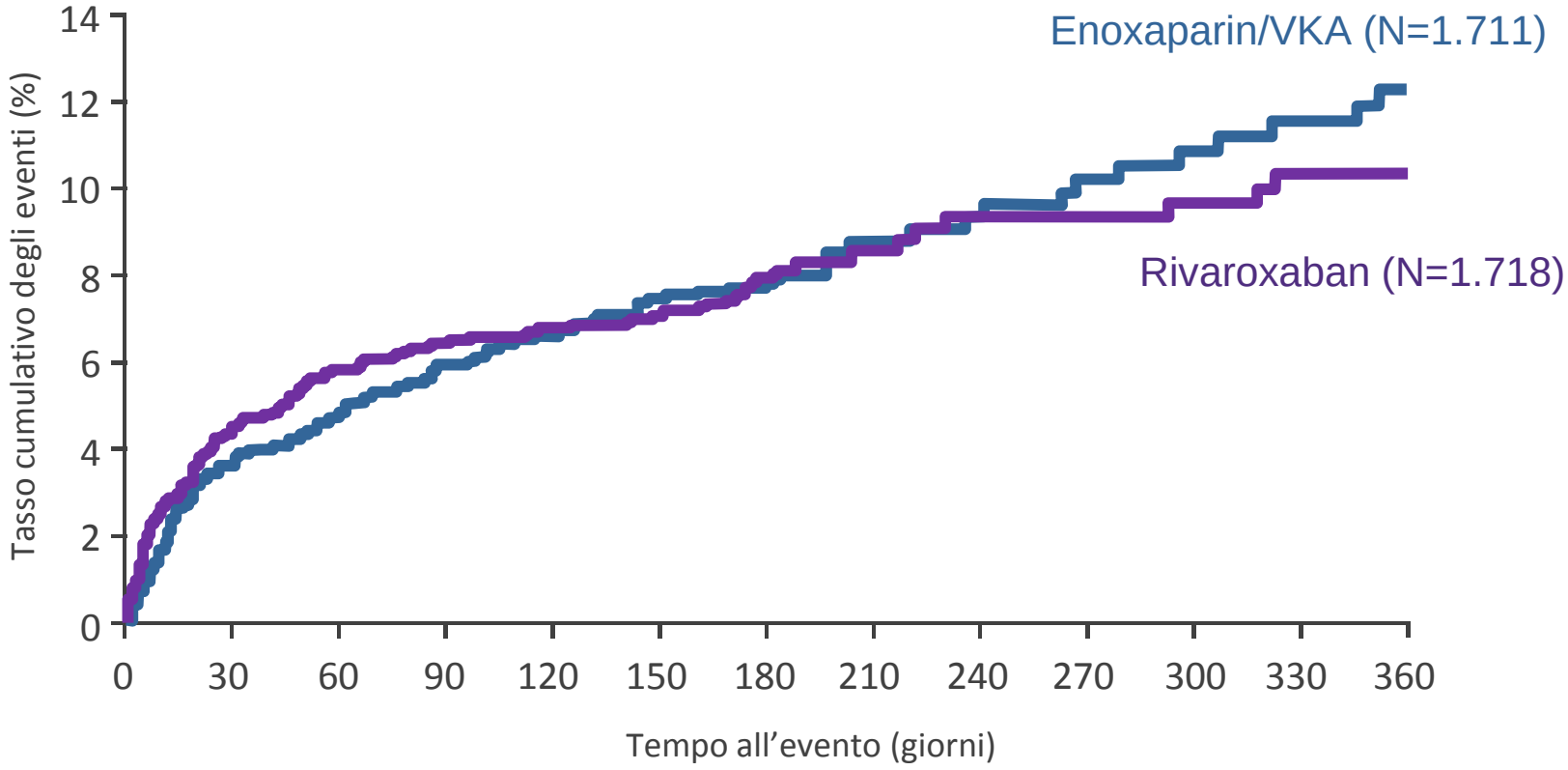


# End-Point Primario di Efficacia




**End-point primario a 21 giorni**, 1,2% rivaroxaban vs 1,7% terapia standard

# End point primario di Sicurezza



# EINSTEIN DVT: conclusioni

- Nei pazienti che avevano DVT acuta sintomatica prossimale, senza PE sintomatica, rivaroxaban ha mostrato:
  - Non-inferiorità vs LMWH/VKA per l'efficacia (HR=0,68; 95% CI 0,44–1,04; p<0,001), sfiorata la superiorità
  - Risultati simili per l'outcome principale di sicurezza tra i due gruppi (HR=0,97; 95% CI 0,76–1,22; p=0,77)
  - Efficacia confermata e risultati di sicurezza sovrapponibili indipendentemente dall'età, dal peso corporeo, dal sesso, dalla clearance della creatinina e dalla presenza di cancro
  - Nessuna evidenza di tossicità epatica

- **Rivaroxaban orale, 15 mg bid per 3 settimane seguito da rivaroxaban 20 mg od, fornisce ai medici ed ai pazienti un approccio semplice e con un unico farmaco per il trattamento acuto della DVT e migliora potenzialmente il profilo di rischio-beneficio del trattamento anticoagulante.**

Agenzia Italiana del Farmaco

AIFA

**26/09/2012**

# AIFA CONCEPT PAPER

## I nuovi anticoagulanti orali nella prevenzione di ictus e tromboembolismo sistemico in pazienti con fibrillazione atriale non valvolare.

Questo documento illustra i criteri di selezione al trattamento anticoagulante/antitrombotico dei pazienti con fibrillazione atriale non valvolare (FANV) nella prevenzione di ictus e tromboembolismo sistemico. Il documento si basa principalmente sulle più recenti evidenze scientifiche e sulle recenti Linee guida fornite dalla comunità scientifica internazionale con particolare riferimento a quelle della Società Europea di Cardiologia, essendo queste ultime più pertinenti alla realtà Italiana.

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In conclusione, tenendo conto di tutte le considerazioni sopra, nonostante gli evidenti vantaggi dei NOACs ci sono diverse priorità in base alle quali decidere quali gruppi trattare per primi con i nuovi anticoagulanti, cominciando ovviamente, dai pazienti nuovi che stanno appena iniziando il trattamento; quelli non ben gestiti con warfarin; quelli con valori labili di INR; quelli ai quali warfarin è stato sconsigliato a causa dei rischi di emorragia intracranica (come per esempio le categorie particolari come gli ipertesi).

**26/09/2012**

**AIFA CONCEPT PAPER**


# ATTENZIONE AI FACILI ENTUSIASMI !!!