# Trattamento Anticoagulante Orale nella Fibrillazione Atriale Non Valvolare

# AVK .....meglio dei NOACs

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CONTROVERSIE SULL'USO DEI FARMACI ANTITROMBOTICI

# Non-vitamin K antagonist oral anticoagulants (NOACs): No longer new or novel

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Thrombosis and Haemostasis 111.5/2014

| Parametro | RELY<br>N = 18 113 | ROCKET-AF<br>N = 14 264 | ARISTOTLE<br>N = 18 201 | ENGAGE-AF<br>N = 21 105 |
|---|---|---|---|---|
| **Disegno dello studio:** | Multicentrico (951 centri), randomizzato, warfarin in aperto, dabigatran in doppia cecità (PROBE) | Multicentrico (1178 centri), randomizzato, doppia cecità, double dummy | Multicentrico (1030 centri), randomizzato, doppia cecità, double dummy | Multicentrico (1393 centri), randomizzato, doppia cecità, double dummy |
| **Dose** | **Dabigatran: 110 mg b.i.d.; 150 mg b.i.d.** | **Rivaroxaban: 20 mg o.d. (15 mg o.d. se VFG 30-49 cc/min)** | **Apixaban: 5 mg b.i.d. (2.5 mg o.d. se età > 80, peso <60 o creatininemia > 1.5 mg/dl)** | **Edoxaban: 60 mg od; 30 mg od. Dosi dimezzate se: VFG 30-50; peso <60, verapamil e/o chinidina** |
| **Endpoint primario** | Composito di ictus (ischemico / emorragico) ed embolia sistemica | Composito di ictus (ischemico / emorragico) ed embolia sistemica | Composito di ictus (ischemico ed emorragico) ed embolia sistemica | Composito di ictus (ischemico ed emorragico) ed embolia sistemica |
| **Durata follow-up** | 2.0 anni (mediana) | 1.8 anni (mediana) | 1.9 anni (mediana) | **2.8 anni** (mediana) |
| **Endpoint primario di sicurezza** | Sanguinamenti maggiori (inclusi i sanguinamenti pericolosi per la vita e quelli fatali) | Composito di sanguinamenti maggiori e non maggiori clinicamente rilevanti | Sanguinamenti maggiori (criteri ISTH) | Sanguinamenti maggiori (criteri ISTH) |
| **Età (anni)** | **71.5 (media)** | **73 (mediana)** | **70 (mediana)** | **72 (mediana)** |
| **$CHADS_2$ Score** | **2.1** | **3.5** | **2.1** | **2.8** |
| **TTR (medio%)** | **64** | **55** | **62** | **65** |
| **Analisi statistica** | Intention to treat | • Per protocol<br>• Intention to treat | Intention to treat | • Per protocol<br>• Intention to treat |

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

# 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

(*J Am Heart Assoc.* 2016;5:e003725 doi: 10.1161/JAHA.116.003725)

***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.

↓

Three 1:1 propensity score matched cohorts

Apixaban vs warfarin (n=15 390)

Dabigatran vs warfarin (n=28 614)

Rivaroxaban vs warfarin (n=32 350)

**Table 2.** Baseline Characteristics in Propensity Score–Matched NOAC or Warfarin Users

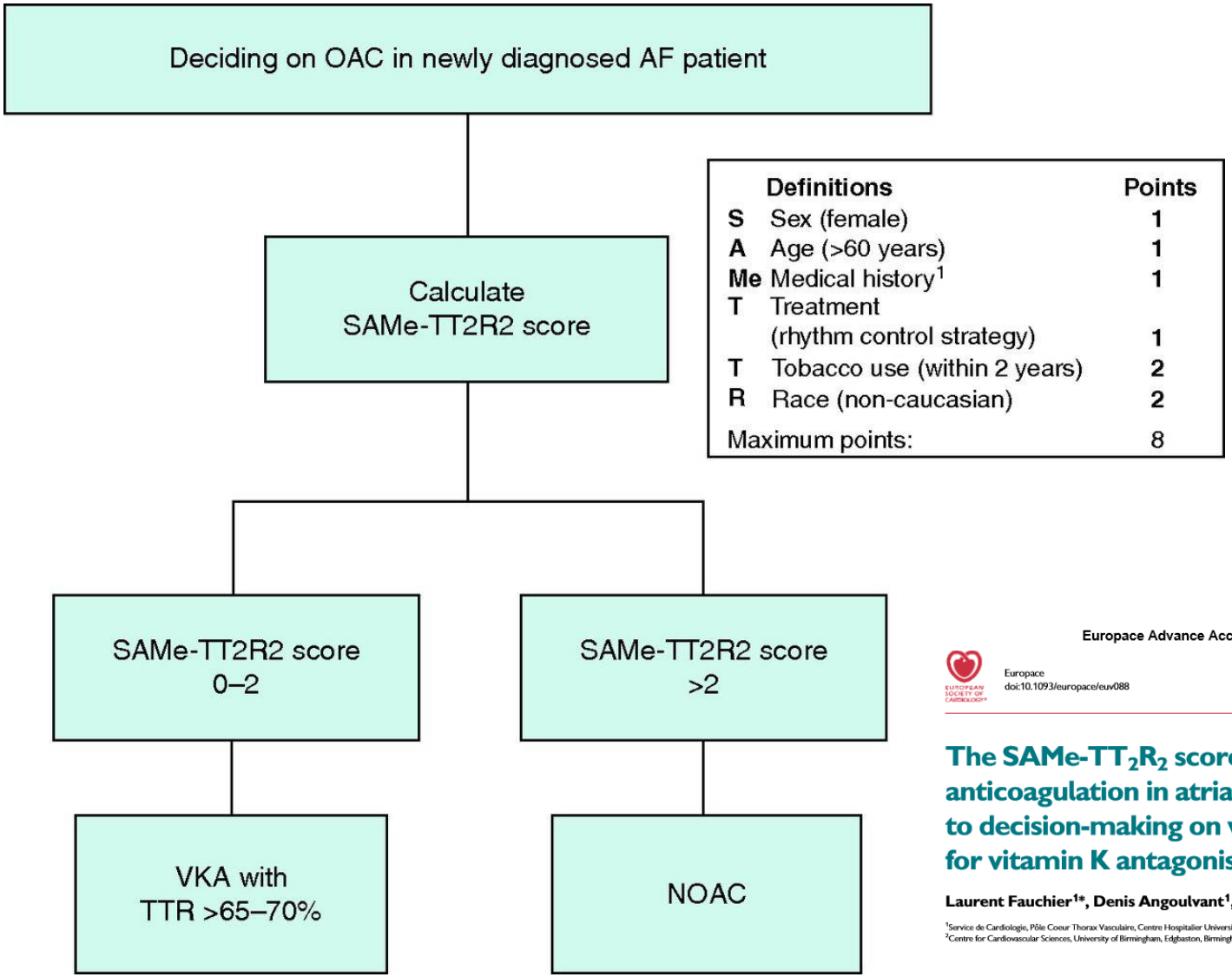
| | Apixaban (n=7695) | Warfarin (n=7695) | Dabigatran (n=14 307) | Warfarin (n=14 307) | Rivaroxaban (n=16 175) | Warfarin (n=16 175) |
|---|---|---|---|---|---|---|
| Age, y | | | | | | |
| Median (IQR) | 73 (66–81) | 73 (66–81) | 70 (62–78) | 70 (61–78) | 72 (64–79) | 72 (64–80) |
| 18–64 | 22.7 | 23.0 | 34.1 | 35.0 | 25.3 | 25.8 |
| 65–74 | 30.9 | 30.9 | 31.5 | 30.4 | 32.9 | 32.8 |
| ≥75 | 46.4 | 46.1 | 34.4 | 34.6 | 41.8 | 41.4 |
| Female | 46.9 | 46.8 | 39.7 | 40.4 | 43.2 | 43.7 |
| Nonwhite race | 20.2 | 20.4 | 18.9 | 19.3 | 19.9 | 20.4 |
| Medical history | | | | | | |
| Congestive heart failure | 31.4 | 31.9 | 27.2 | 27.3 | 28.9 | 29.5 |
| Hypertension | 87.5 | 87.5 | 85.2 | 84.9 | 85.7 | 85.9 |
| Diabetes mellitus | 35.0 | 34.3 | 34.0 | 34.0 | 34.6 | 35.1 |
| Stroke/TIA/SE | 15.1 | 15.5 | 13.8 | 14.2 | 14.0 | 14.4 |
| Vascular disease | 28.3 | 28.4 | 23.1 | 23.4 | 26.9 | 27.5 |
| Abnormal renal function | 10.1 | 10.1 | 5.6 | 5.6 | 7.4 | 7.3 |
| Abnormal liver function | 4.0 | 4.1 | 3.5 | 3.6 | 3.7 | 3.8 |
| Bleeding history or predisposition | 31.4 | 31.8 | 29.4 | 30.1 | 30.7 | 31.5 |
| Alcoholism | 2.8 | 2.7 | 2.6 | 2.6 | 2.9 | 3.1 |
| Pulmonary disease | 33.1 | 33.7 | 28.2 | 28.4 | 31.2 | 32.1 |
| Obesity | 19.6 | 19.9 | 17.6 | 17.3 | 18.3 | 18.9 |
| Smoking | 19.8 | 20.0 | 16.1 | 16.0 | 18.5 | 19.4 |

**Table 2.** Baseline Characteristics in Propensity Score–Matched NOAC or Warfarin Users

| | Apixaban (n=7695) | Warfarin (n=7695) | Dabigatran (n=14 307) | Warfarin (n=14 307) | Rivaroxaban (n=16 175) | Warfarin (n=16 175) |
|---|---|---|---|---|---|---|
| Medication use | | | | | | |
| Antiplatelets/NSAID | 12.1 | 12.5 | 10.3 | 10.2 | 11.6 | 11.6 |
| Amiodarone | 9.6 | 10.1 | 8.4 | 8.4 | 8.3 | 8.8 |
| Dronedarone | 2.8 | 2.6 | 3.7 | 4.2 | 2.4 | 2.6 |
| Other antiarrhythmic drugs | 11.1 | 10.7 | 12.8 | 12.9 | 11.0 | 11.2 |
| Digoxin | 8.9 | 9.1 | 13.6 | 13.6 | 10.8 | 11.1 |
| Diltiazem | 16.9 | 17.0 | 17.5 | 17.3 | 17.5 | 17.9 |
| Verapamil | 1.3 | 1.3 | 1.9 | 1.9 | 1.7 | 1.7 |
| Other calcium channel blockers | 16.6 | 16.3 | 13.3 | 13.4 | 14.9 | 14.7 |
| Statin | 45.6 | 46.7 | 41.5 | 41.2 | 43.0 | 43.9 |
| Other cholesterol reducers | 5.9 | 5.9 | 7.3 | 7.6 | 5.7 | 5.7 |
| β-Blockers | 47.5 | 47.8 | 44.6 | 44.5 | 45.6 | 45.0 |
| Renin angiotensin system antagonists | 47.1 | 47.2 | 45.4 | 45.0 | 45.5 | 46.0 |
| Diuretics | 32.3 | 31.8 | 28.5 | 28.5 | 29.6 | 29.6 |
| Metformin | 11.1 | 10.7 | 10.2 | 9.9 | 10.6 | 11.0 |
| Sulfonylureas | 6.0 | 6.0 | 6.0 | 5.9 | 6.0 | 5.9 |
| Thiazolidinedione | 0.8 | 0.8 | 1.5 | 1.3 | 0.9 | 0.9 |
| Insulin | 7.3 | 7.3 | 6.8 | 7.1 | 7.1 | 7.5 |
| Other diabetes drugs | 3.1 | 2.9 | 2.8 | 2.9 | 2.7 | 2.9 |
| Antiulcer agents | 21.9 | 21.4 | 18.4 | 18.4 | 20.3 | 21.2 |
| Antidepressant | 16.2 | 16.1 | 14.5 | 15.0 | 15.3 | 15.6 |

**Table 2.** Baseline Characteristics in Propensity Score–Matched NOAC or Warfarin Users

| | Apixaban (n=7695) | Warfarin (n=7695) | Dabigatran (n=14 307) | Warfarin (n=14 307) | Rivaroxaban (n=16 175) | Warfarin (n=16 175) |
|---|---|---|---|---|---|---|
| $CHA_2DS_2$-VASc | | | | | | |
| Median (IQR) | 4 (3–5) | 4 (3–5) | 3 (2–5) | 3 (2–5) | 4 (2–5) | 4 (2–5) |
| 0–1 | 9.9 | 10.0 | 15.9 | 16.6 | 12.2 | 12.1 |
| 2–3 | 33.2 | 33.0 | 38.2 | 36.9 | 35.6 | 35.6 |
| ≥4 | 56.8 | 57.0 | 45.9 | 46.5 | 52.2 | 52.3 |
| HAS-BLED | | | | | | |
| Median (IQR) | 2 (2–3) | 2 (2–3) | 2 (1–3) | 2 (1–3) | 2 (2–3) | 2 (2–3) |
| ≥3 | 41.5 | 41.9 | 33.7 | 33.9 | 38.6 | 39.1 |
| Charlson index | | | | | | |
| Median (IQR) | 2 (1–4) | 2 (1–4) | 2 (1–3) | 2 (1–3) | 2 (1–4) | 2 (1–4) |
| 0–1 | 37.7 | 37.9 | 45.5 | 45.3 | 41.3 | 40.6 |
| 2–3 | 32.0 | 32.1 | 30.4 | 30.4 | 30.8 | 30.5 |
| ≥4 | 30.3 | 30.0 | 24.1 | 24.3 | 27.9 | 28.9 |
| SAMe-$TT_2R_2$ | | | | | | |
| Median (IQR) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 2 (1–3) |
| ≥3 | 30.7 | 31.1 | 26.1 | 26.4 | 28.8 | 30.5 |
| Warfarin experienced | 20.2 | 20.4 | 37.8 | 38.6 | 24.4 | 25.0 |
| Reduced-dose NOAC | 18.1 | NA | 8.8 | NA | 21.5 | NA |

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EDITORIAL

## The SAMe-$TT_2R_2$ score and quality of anticoagulation in atrial fibrillation: a simple aid to decision-making on who is suitable (or not) for vitamin K antagonists

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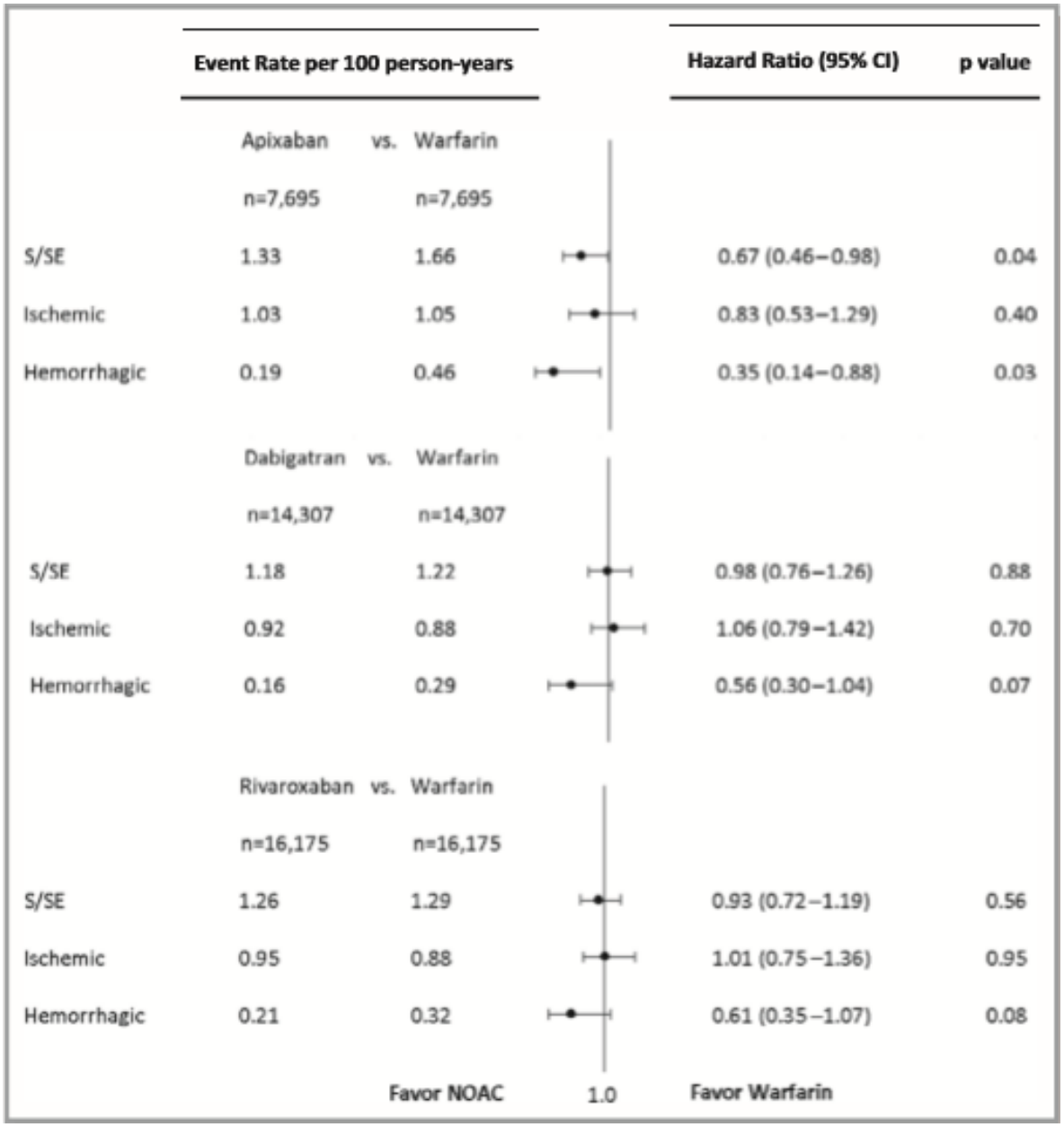


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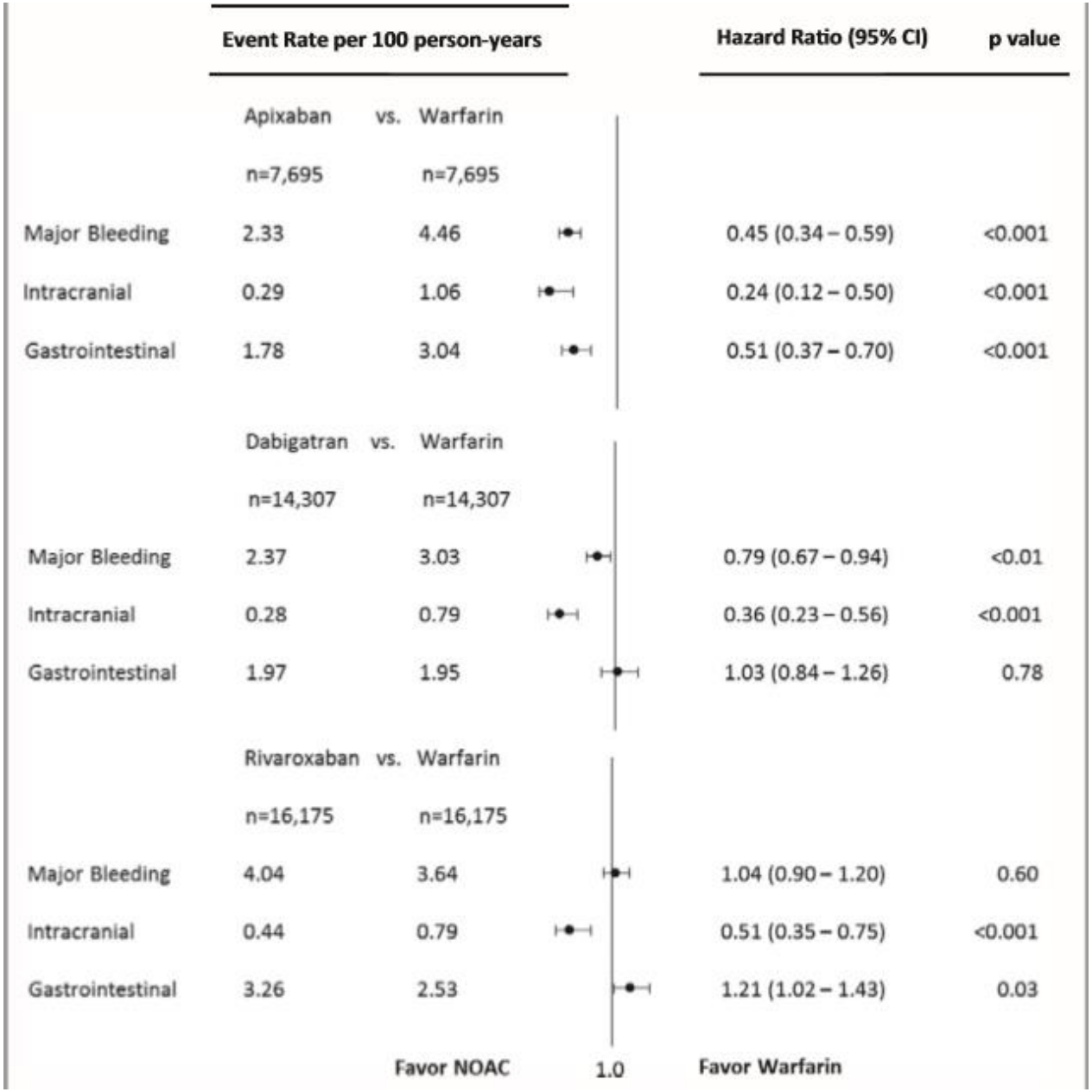


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American Heart Association | American Stroke Association

# Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

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in comparison to warfarin, 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. Our findings provide some reassurance of the effectiveness and safety of NOAC use in everyday practice and may facilitate clinical decision making. Nevertheless, the choice between NOACs and warfarin will ultimately depend on individual patient risk and preference.

Section Editors: Sean I. Savitz, MD, and Heinrich P. Mattle, MD

# Critique of Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation Trial

Roland Veltkamp, MD; Shyam Prabhakaran, MD, MS

The use of DOACs in AF now builds on experience in 5 megatrials with some 70 000 patients in primary and secondary stroke prevention.[3–6,10] Reassuringly, these trials consistently underscore the validity of the therapeutic principle rather than just the effectiveness of a single drug.

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# A Comparison of Oral Anticoagulant Use for Atrial Fibrillation in the Pre- and Post-DOAC Eras

Authors | Authors and affiliations

Joshua D. Brown, Anand R. Shewale, Parinita Dherange, Jeffery C. Talbert

Direct oral anticoagulants (DOACs) have seen rapid uptake for the prevention of stroke associated with non-valvular atrial fibrillation (NVAF). It is unclear whether use of DOACs represents direct therapeutic substitution over warfarin or if this coincides with an increase in overall treatment rates. This study sought to describe the difference in oral anticoagulant (OAC) use in the pre-DOAC and post-DOAC eras.

## Conclusions

There has been an overall increase in OAC use in the NVAF population, attributable to both favorable randomized trial results and aggressive marketing of DOACs in the USA.

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*Review Article*

# Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups

**Antonio Gómez-Outes,[1] Ana Isabel Terleira-Fernández,[2,3] Gonzalo Calvo-Rojas,[4] M. Luisa Suárez-Gea,[1] and Emilio Vargas-Castrillón[2,3]**

Table 1: Characteristics of the studies and treatments.

| Drug, trial | Dabigatran RE-LY [22, 48] | Rivaroxaban ROCKET [23, 49] | Apixaban ARISTOTLE [24, 50] |
|---|---|---|---|
| No. in sample | 18113 | 14264 | 18201 |
| Treatment characteristics | | | |
| Experimental drug | Dabigatran 150 mg or 110 mg twice daily | Rivaroxaban 20 mg or 15 mg once daily | Apixaban 5 mg or 2.5 mg twice daily |
| Experimental, *n* | 12091 | 7131 | 9120 |
| High-dose | 6076 | 5624 | 8702 |
| Low-dose | 6015 | 1597 | 428 |
| Control drug | Warfarin dose-adjusted to INR 2-3, once daily | Warfarin dose-adjusted to INR 2-3, once daily | Warfarin dose-adjusted to INR 2-3, once daily |
| Control, *n* | 6022 | 7133 | 9081 |
| TTR (%) | | | |
| Mean | 64.4 | 55.2 | 62.2 |
| Median | 67 | 58 | 66 |
| Trial phase | III | III | III |
| Design of randomised controlled trial | Multicentre, open-label PROBE | Multicentre, double-blind | Multicentre, double-blind |
| Adjudicating committee and blinded adjudication of outcomes | Yes | Yes | Yes |
| Interim analysis, *n* | 2 | 1 | 1 |
| Number of exclusion criteria | 14 | 31 | 19 |
| Main efficacy outcome | Stroke and SEE | Stroke and SEE | Stroke and SEE |
| Main analysis | Non-inferiority | Non-inferiority | Non-inferiority |
| Non-inferiority margin | Relative risk < 1.46 | Relative risk < 1.46 | Relative risk < 1.38 |
| Main population of analysis | Intent-to-treat | Per protocol | Intent-to-treat |
| Main period of analysis | Until notification of study termination | On-treatment plus 2 days | Until notification of study termination |
| Main safety outcome | Major bleeding | Clinically relevant bleeding | Major bleeding |
| Main population of analysis | Safety population | Safety population | Safety population |
| Main period of analysis | On-treatment plus 6 days* | On-treatment plus 2 days* | On-treatment plus 2 days* |
| Jadad Score | 3 | 5 | 5 |
| Median length follow-up (days) | 730 | 707 | 657 |

*After treatment discontinuation.
INR: international normalised ratio; PROBE: prospective, open-label, blinded endpoint; SEE: systemic embolic events; TTR: time in therapeutic range.

Table 2: Characteristics of the patients and events (overall study population).

| Drug, trial | Dabigatran RE-LY [22, 48] | Rivaroxaban ROCKET [23, 49] | Apixaban ARISTOTLE [24, 50] | $P$-value* |
|---|---|---|---|---|
| No in sample | 18113 | 14264 | 18201 | |
| Patients characteristics | | | | |
| Age (years) | 72 (mean) | 73 (median) | 70 (median) | — |
| Male gender | 11514 (64%) | 8604 (60%) | 5660 (65%) | <0.0001 |
| $CHADS_2$ (mean ± standard deviation) | 2.1 ± 1.1 | 3.46 ± 0.95 | 2.1 ± 1.1 | <0.0001 |
| $CHADS_2 \geq 2$ | 12337 (68%) | 14261 (≈100%) | 12018 (66%) | <0.0001 |
| $CHADS_2 = 1$ | 5775 (32%) | 3 (≈0%) | 6183 (34%) | <0.0001 |
| Prior stroke/transient ischemic attack | 3623 (20%) | 7468 (55%) | 3436 (19%) | <0.0001 |
| Congestive heart failure | 5793 (32%) | 8908 (63%) | 6451 (35%) | <0.0001 |
| Hypertension | 14283 (79%) | 12910 (91%) | 15916 (87%) | <0.0001 |
| Age ≥ 75 years | 7238 (40%) | 6229 (43%) | 5678 (31%) | <0.0001 |
| Diabetes | 4221 (23%) | 5695 (40%) | 4547 (25%) | <0.0001 |
| Prior myocardial infarction | 3005 (17%) | 2468 (17%) | 2585 (14%) | <0.0001 |
| Patients in centers with TTR ≥ 65% | 8950 (49%) | 3493 (24%) | 9046 (50%) | <0.0001 |
| Patients recruited in Europe | 6770 (37%) | 7582 (53%) | 7343 (40%) | <0.0001 |
| Patients with CrCl < 50 mL/min | 3505 (19%) | 2986 (21%) | 3017 (17%) | <0.0001 |
| Type of atrial fibrillation | | | | |
| Permanent-persistent | 12164 (67%) | 11548 (81%) | 15412 (85%) | <0.0001 |
| Paroxysmal | 5943 (33%) | 2514 (18%) | 2786 (15%) | <0.0001 |
| Antithrombotic treatment at baseline | | | | |
| VKA | 8989 (50%) | 8904 (62%) | 10401 (57%) | <0.0001 |
| Acetylsalicylic acid | 7198 (40%) | 5205 (37%) | 5632 (31%) | <0.0001 |
| Event rate in the control group | $N = 6022$ | $N = 7133$ | $N = 9081$ | |
| Total stroke or SEE | 202 (3.35%) | 306 (4.29%) | 265 (2.92%) | 0.0001 |
| Ischemic stroke | 143 (2.37%) | 226 (3.17%) | 175 (1.93%) | <0.0001 |
| Hemorrhagic stroke | 45 (0.75%) | 57 (0.80%) | 78 (0.75%) | 0.9968 |
| SEE | 16 (0.27%) | 25 (0.35%) | 15 (0.17%) | 0.2367 |
| Intracranial bleeding | 90 (1.49%) | 84 (1.18%) | 122 (1.34%) | 0.6421 |
| Major bleeding | 421 (6.99%) | 386 (5.41%) | 462 (5.09%) | <0.0001 |
| Death | 487 (8.09%) | 632 (8.86%) | 669 (7.37%) | 0.0168 |
| Treatment discontinuation† | 1150 (19%) | 2468 (35%) | 2732 (30%) | <0.0001 |

*Chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.
†Treated patients that received assigned study drug but did not complete study.
CrCl: creatinine clearance; SEE: systemic embolic event; TTR: time in therapeutic range; VKA: vitamin K antagonist.

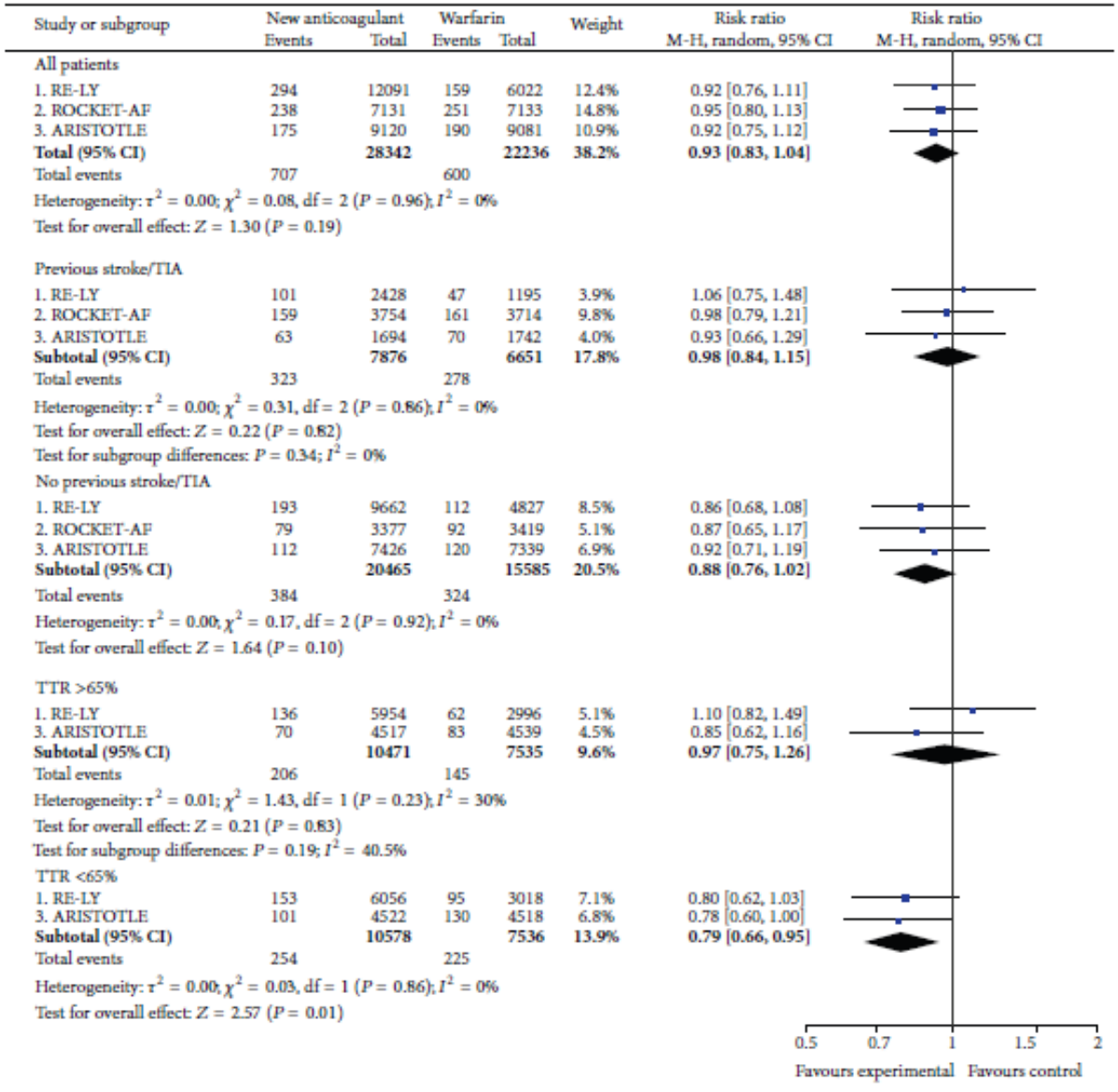


FIGURE 2: Nonhemorrhagic stroke and systemic embolic events.

Thrombosis
Volume 2013, Article ID 640723,

| Study or subgroup | New anticoagulant Events | Total | Warfarin Events | Total | Weight | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| All patients | | | | | | |
| 1. RE-LY | 741 | 12091 | 421 | 6022 | 5.8% | 0.88 [0.78, 0.98] |
| 2. ROCKET-AF | 395 | 7131 | 386 | 7133 | 5.5% | 1.02 [0.89, 1.17] |
| 3. ARISTOTLE | 327 | 9120 | 462 | 9081 | 5.4% | 0.70 [0.61, 0.81] |
| **Total (95% CI)** | | **28342** | | **22236** | **16.7%** | **0.86 [0.70, 1.05]** |
| Total events | 1463 | | 1269 | | | |
| Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 14.29$, df = 2 ($P = 0.0008$); $I^2 = 86\%$ | | | | | | |
| Test for overall effect: $Z = 1.49$ ($P = 0.14$) | | | | | | |
| TTR >65% | | | | | | |
| 1. RE-LY | 387 | 5954 | 194 | 2996 | 5.0% | 1.00 [0.85, 1.19] |
| 2. ROCKET-AF | 135 | 1689 | 115 | 1839 | 4.0% | 1.28 [1.01, 1.62] |
| 3. ARISTOTLE | 201 | 4517 | 245 | 4529 | 4.8% | 0.82 [0.69, 0.99] |
| **Subtotal (95% CI)** | | **12160** | | **9364** | **13.8%** | **1.01 [0.80, 1.27]** |
| Total events | 723 | | 554 | | | |
| Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 8.35$, df = 2 ($P = 0.02$); $I^2 = 76\%$ | | | | | | |
| Test for overall effect: $Z = 0.06$ ($P = 0.95$) | | | | | | |
| Test for subgroup differences: $P = 0.09$; $I^2 = 66.0\%$ | | | | | | |
| TTR <65% | | | | | | |
| 1. RE-LY | 347 | 6056 | 225 | 3018 | 5.1% | 0.77 [0.65, 0.90] |
| 2. ROCKET-AF | 249 | 5252 | 271 | 5284 | 5.0% | 0.92 [0.78, 1.09] |
| 3. ARISTOTLE | 125 | 4522 | 217 | 4518 | 4.3% | 0.58 [0.46, 0.71] |
| **Subtotal (95% CI)** | | **15830** | | **12820** | **14.4%** | **0.75 [0.58, 0.96]** |
| Total events | 721 | | 713 | | | |
| Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 11.53$, df = 2 ($P = 0.003$); $I^2 = 83\%$ | | | | | | |
| Test for overall effect: $Z = 2.27$ ($P = 0.02$) | | | | | | |

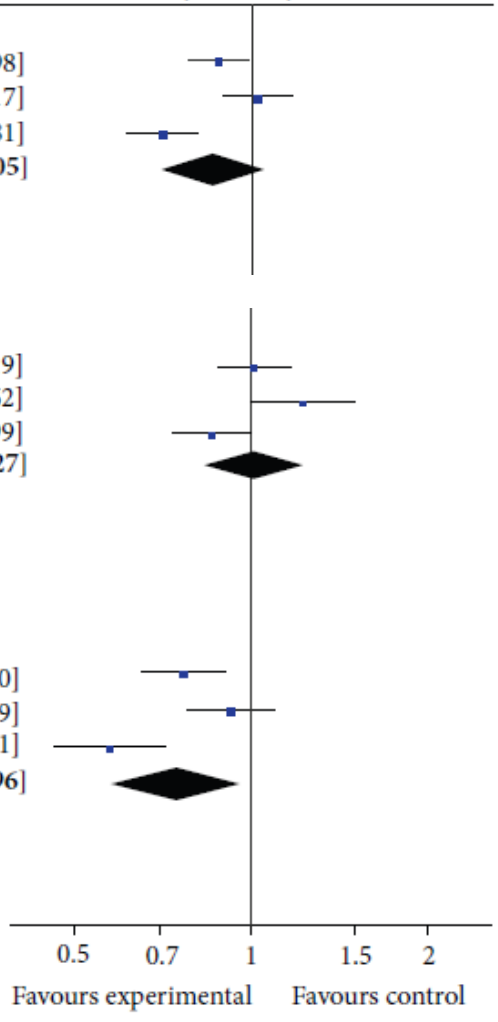




FIGURE 6: Major bleeding.

| Study or subgroup | New anticoagulant Events | Total | Warfarin Events | Total | Weight | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| All major gastrointestinal bleedings | | | | | | |
| 1. RE-LY | 385 | 12091 | 149 | 6022 | 14.0% | 1.29 [1.07, 1.55] |
| 2. ROCKET-AF | 224 | 7131 | 154 | 7133 | 13.7% | 1.45 [1.19, 1.78] |
| 3. ARISTOTLE | 105 | 9120 | 119 | 9081 | 12.5% | 0.88 [0.68, 1.14] |
| **Total (95% CI)** | | **28342** | | **22236** | **40.2%** | **1.20 [0.92, 1.56]** |
| Total events | 714 | | 422 | | | |
| Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 9.25$, df = 2 ($P = 0.010$); $I^2 = 78\%$ | | | | | | |
| Test for overall effect: $Z = 1.31$ ($P = 0.19$) | | | | | | |
| Upper gastrointestinal bleeding | | | | | | |
| 1. RE-LY | 103 | 12091 | 54 | 6022 | 11.0% | 0.95 [0.68, 1.32] |
| 2. ROCKET-AF | 151 | 7131 | 104 | 7133 | 12.8% | 1.45 [1.13, 1.86] |
| 3. ARISTOTLE | 66 | 9120 | 85 | 9081 | 11.2% | 0.77 [0.56, 1.06] |
| **Subtotal (95% CI)** | | **28342** | | **22236** | **34.9%** | **1.03 [0.70, 1.52]** |
| Total events | 320 | | 234 | | | |
| Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 10.26$, df = 2 ($P = 0.006$); $I^2 = 80\%$ | | | | | | |
| Test for overall effect: $Z = 0.17$ ($P = 0.87$) | | | | | | |
| Lower gastrointestinal bleeding | | | | | | |
| 1. RE-LY | 91 | 12091 | 18 | 6022 | 7.6% | 2.52 [1.52, 4.17] |
| 2. ROCKET-AF | 49 | 7131 | 32 | 7133 | 8.7% | 1.53 [0.98, 2.39] |
| 3. ARISTOTLE | 39 | 9120 | 36 | 9081 | 8.5% | 1.08 [0.69, 1.70] |
| **Subtotal (95% CI)** | | **28342** | | **22236** | **24.8%** | **1.59 [0.99, 2.54]** |
| Total events | 179 | | 86 | | | |
| Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 6.08$, df = 2 ($P = 0.05$); $I^2 = 67\%$ | | | | | | |
| Test for overall effect: $Z = 1.94$ ($P = 0.05$) | | | | | | |

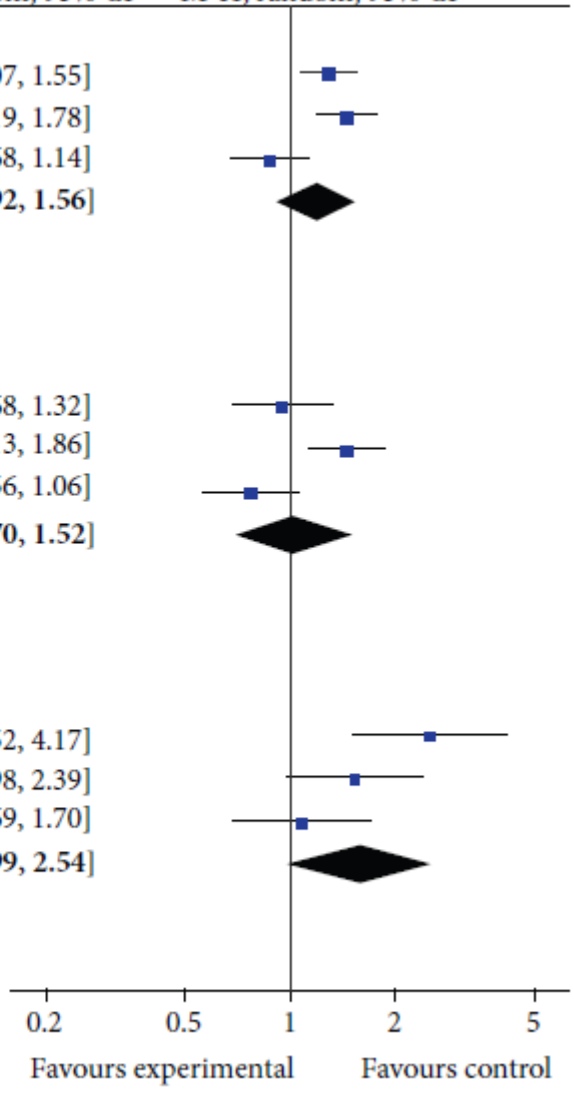




FIGURE 7: Major gastrointestinal bleeding.

Although this review shows that the overall net clinical benefit of the NOAC versus warfarin is favourable, the magnitude of such benefit may be however influenced by a number of factors, as suggested by subgroup analyses. In RE-LY and ARISTOTLE, superiority in the composite of all strokes and SEE was mainly gained at expenses of events that occurred in non-European countries (e.g., South America, Asia, and Africa), while all the NOAC were consistently not superior to warfarin in Europe. In the ROCKET study, with a higher proportion of European patients, these differences were not apparent. It is hard to believe that geography itself influences treatment effect, but it may influence the way patients are managed in clinical practice [59, 60]. Potential interaction factors accounting for geographic differences may comprise the quality of oral anticoagulation and control of associated risk factors for thrombosis (e.g., hypertension, diabetes, and heart failure). The benefit of oral anticoagulation is largely dependent on the quality of INR control achieved by centers and countries as measured by TTR [61, 62]. The use of center-based TTRs as a proxy for individual-level INR control is a matter of controversy, but it may be considered a reasonable approach in clinical trials comparing the NOAC and warfarin

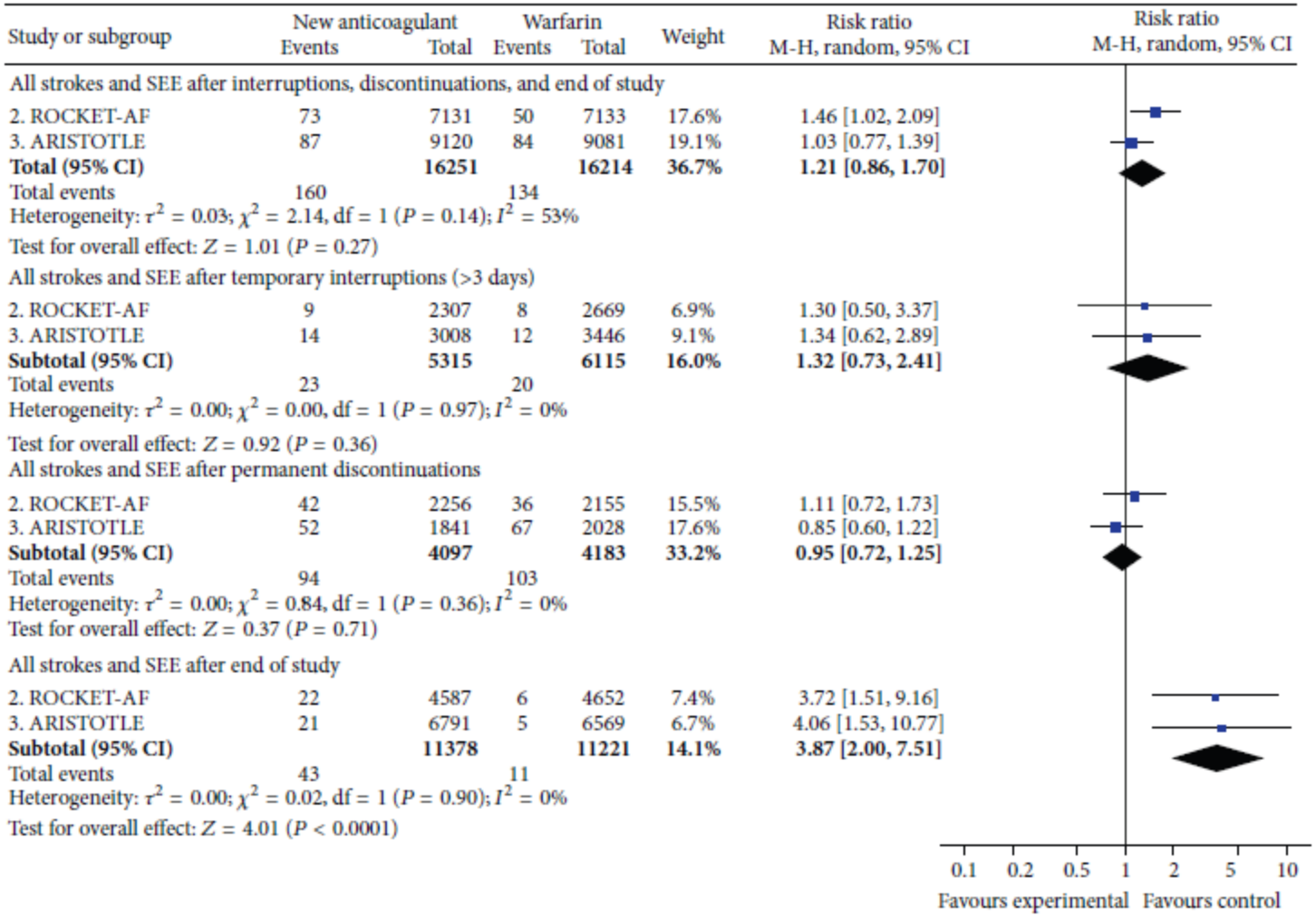


FIGURE 5: All strokes and systemic embolic events after study drug discontinuation.

Thrombosis
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The NOAC seem no more effective than warfarin in preventing nonhemorrhagic stroke and SEE in NVAF. However, they are generally associated with a lower risk of ICB than warfarin. The net benefit of the NOAC seems better than that of warfarin in situations in which quality of oral anticoagulation is poor, given that thromboembolic complications, major bleeding, and mortality may be decreased, as well as patients with prior stroke or transient ischemic attack, as the absolute risk reduction in ICB may be particularly significant. However, the absolute benefit of the NOAC tends to be of a lesser magnitude in Europe than in other regions, which might be due to regional differences in quality of oral anticoagulation and overall management of associated risk factors for thrombosis. These findings would deserve further investigation.

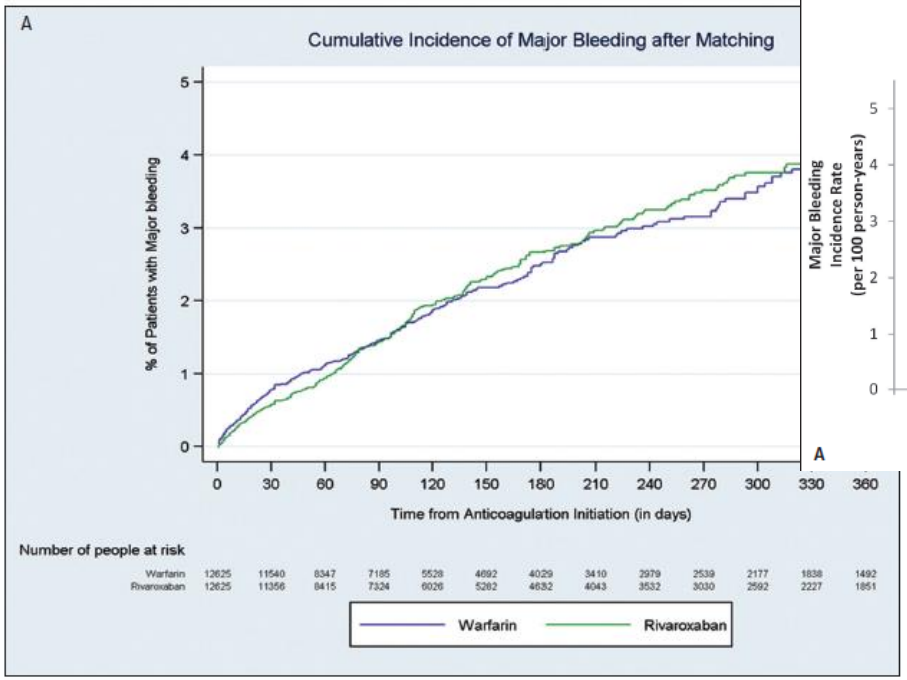
# Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin

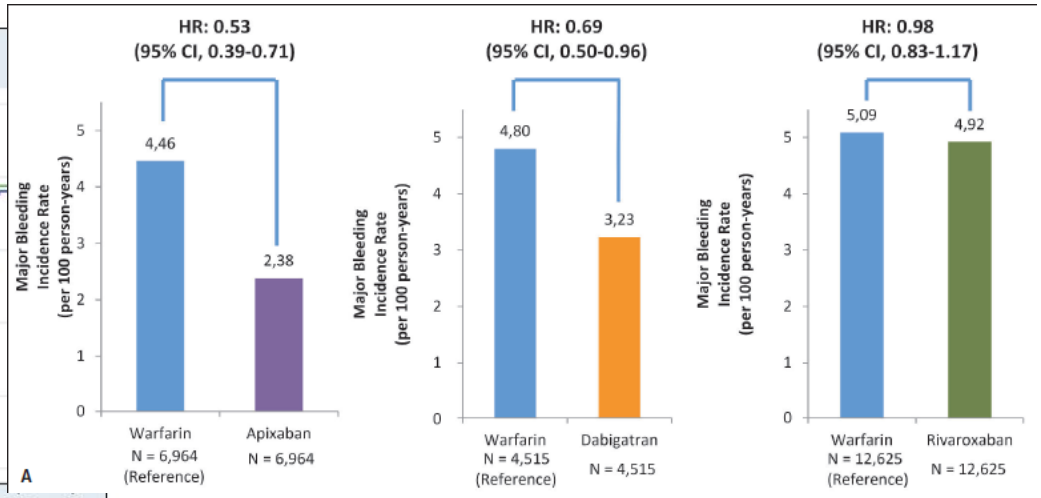
Thrombosis and Haemostasis 116.5/2016

## A propensity score matched analysis

Gregory Y. H. Lip[1,2]; Allison Keshishian[3]; Shital Kamble[4]; Xianying Pan[4]; Jack Mardekian[5]; Ruslan Horblyuk[5]; Melissa Hamilton[4]

[1]University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK; [2]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [3]STATinMED Research, Ann Arbor, Michigan, USA; [4]Bristol-Myers Squibb Company, Princeton, New Jersey, USA; [5]Pfizer, Inc., New York, New York, USA




This 'real-world' observational study using propensity score matched cohorts demonstrates that apixaban and dabigatran initiation was associated with significantly lower risk of major bleeding compared to warfarin initiation among newly anticoagulated NVAF patients in the real world setting amongst US patients. When comparisons were made between NOACs, rivaroxaban initiation was associated with significantly higher risk of major bleeding compared to apixaban initiation.

# Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Torben Bjerregaard Larsen,[1,2] Flemming Skjøth,[2,3] Peter Brønnum Nielsen,[2]
Jette Nordstrøm Kjældgaard,[2] Gregory Y H Lip[2,4]

## WHAT IS ALREADY KNOWN ON THIS TOPIC

The use of non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) has been increasing since their introduction

Based on data from clinical practice, however, limited evidence exists on effectiveness and safety of NOACs compared with warfarin

## WHAT THIS STUDY ADDS

No significant difference in risk of ischaemic stroke was evident between NOACs and warfarin

Rivaroxaban was associated with a lower risk of ischaemic stroke or systemic embolism than warfarin, but with comparable major bleeding rates

Dabigatran and apixaban had non-significant hazard ratios compared with warfarin for ischaemic stroke or systemic embolism, whereas major bleeding rates were significantly lower with reference to warfarin

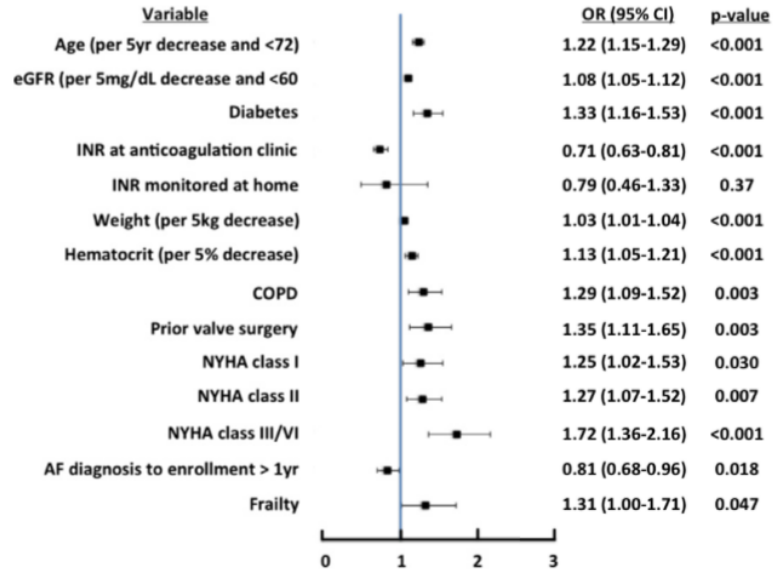
thebmj | *BMJ* 2016;353:i3189 | doi: 10.1136/bmj.i3189

## Conclusions

All NOACs are generally safe and effective alternatives to warfarin in a clinical care setting.

# Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry

Sean D. Pokorney, MD, MBA,[a,b] DaJuanicia N. Simon, MS,[b] Laine Thomas, PhD,[b] Gregg C. Fonarow, MD,[c] Peter R. Kowey, MD,[d] Paul Chang, MD,[c] Daniel E. Singer, MD, MA,[f] Jack Ansell, MD,[g] Rosalia G. Blanco, BA,[b] Bernard Gersh, MB, ChB, DPhil,[h] Kenneth W. Mahaffey, MD,[i] Elaine M. Hylek, MD, MPH,[j] Alan S. Go, MD,[k] Jonathan P. Piccini, MD, MHS,[a,b] and Eric D. Peterson, MD, MPH[a,b], for the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators *Durham, NC; Los Angeles, Oakland, CA; Wynnewood, PA; Raritan, NJ; Boston, MA; New York, NY; and Rochester, MN*




eGFR = estimated glomerular filtration rate by MDRD. COPD = chronic obstructive pulmonary disease

Factors associated with TTR in the lowest quartile (≤53%).

Our analysis did show that INR management by an anticoagulation clinic was protective against low TTR with an odds ratio of 0.71 (95% CI 0.63-0.81), whereas TTR in anticoagulation clinics was slightly higher than that of non-anticoagulation clinics (69% vs 66%). Anticoagulation clinics may be serving a self-selected group of patients. The increased use and homogeneity of anticoagulation clinics in Europe[26] may, at least in part, explain the higher TTR values of 68% in Germany,[27] 76% in Sweden,[28] and 83% in Denmark.[24] Patients with multiple factors associated with low TTR may not be ideal candidates for warfarin therapy, and these patients should be considered for a NOAC.

**Conclusions** Among patients with AF in US clinical practices, TTR on warfarin is suboptimal, and those at highest predicted risks for stroke and bleeding were least likely to be in therapeutic range. (Am Heart J 2015;170:141-148.e1.)

| Variable | Overall, N = 5,210 | Quartile 1 (TTR 0%-53%), N = 1,131 | Quartile 2 (TTR 54%-67%), N = 1,267 | Quartile 3 (TTR 68%-79%), N = 1,353 | Quartile 4 (TTR 80%-100%), N = 1,259 | *P* |
|---|---|---|---|---|---|---|
| Demographics | | | | | | |
| Age, mean (SD) | 75 (10) | 74 (11) | 75 (10) | 75 (9) | 75 (9) | .51 |
| Female sex | 2,218 (43%) | 595 (45%) | 579 (46%) | 570 (42%) | 474 (38%) | <.001 |
| White race | 4,714 (90%) | 1,166 (88%) | 1,146 (90%) | 1,234 (91%) | 1,168 (93%) | .003 |
| College education | 1,552 (30%) | 336 (25%) | 376 (30%) | 423 (31%) | 417 (33%) | <.001 |
| Insurance status | | | | | | <.001 |
| Medicare | 3,666 (70%) | 902 (68%) | 904 (71%) | 975 (72%) | 885 (70%) | |
| Medicaid | 216 (4%) | 87 (7%) | 57 (5%) | 40 (3%) | 32 (3%) | |
| Private | 1,096 (21%) | 289 (22%) | 248 (20%) | 278 (21%) | 281 (22%) | |
| Past medical history | | | | | | |
| Anemia | 975 (19%) | 296 (22%) | 255 (20%) | 217 (16%) | 207 (16%) | <.001 |
| Frailty | 276 (5%) | 99 (7%) | 82 (6%) | 55 (4%) | 40 (3%) | <.001 |
| Chronic obstructive pulmonary disease | 868 (17%) | 279 (21%) | 234 (18%) | 198 (15%) | 157 (12%) | <.001 |
| Hypertension | 4,475 (86%) | 1,162 (87%) | 1,084 (86%) | 1,162 (86%) | 1,067 (85%) | .30 |
| Diabetes | 1,587 (30%) | 486 (37%) | 409 (32%) | 355 (26%) | 337 (27%) | <.001 |
| Chronic kidney disease | 1,898 (36%) | 548 (41%) | 469 (37%) | 488 (36%) | 393 (31%) | <.001 |
| Prior gastrointestinal bleed | 424 (8%) | 133 (10%) | 97 (8%) | 106 (8%) | 88 (7%) | .031 |
| Obstructive sleep apnea | 980 (19%) | 274 (21%) | 260 (21%) | 248 (18%) | 198 (16%) | .004 |
| Peripheral vascular disease | 737 (14%) | 219 (16%) | 189 (15%) | 190 (14%) | 139 (11%) | <.001 |
| Prior cerebrovascular event | 915 (18%) | 251 (19%) | 232 (18%) | 229 (17%) | 203 (16%) | .24 |
| Heart failure | 1,866 (36%) | 582 (44%) | 466 (37%) | 462 (34%) | 356 (28%) | <.001 |
| Risk stratification | | | | | | |
| $CHADS_2$ score, mean (SD) | 2.4 (1.2) | 2.6 (1.3) | 2.5 (1.3) | 2.4 (1.2) | 2.3 (1.2) | <.001 |
| $CHA_2DS_2$-VASc score, mean (SD) | 4.1 (1.6) | 4.3 (1.7) | 4.2 (1.7) | 4.1 (1.6) | 3.9 (1.6) | <.001 |
| ATRIA bleeding score, mean (SD) | 2.8 (1.9) | 3.0 (2.0) | 2.9 (1.9) | 2.8 (1.9) | 2.7 (1.8) | <.001 |
| Site characteristics | | | | | | |
| Anticoagulation clinic | 2,545 (49%) | 577 (43%) | 624 (49%) | 685 (51%) | 659 (52%) | <.001 |

(Am Heart J 2015;170:141-148.e1.)

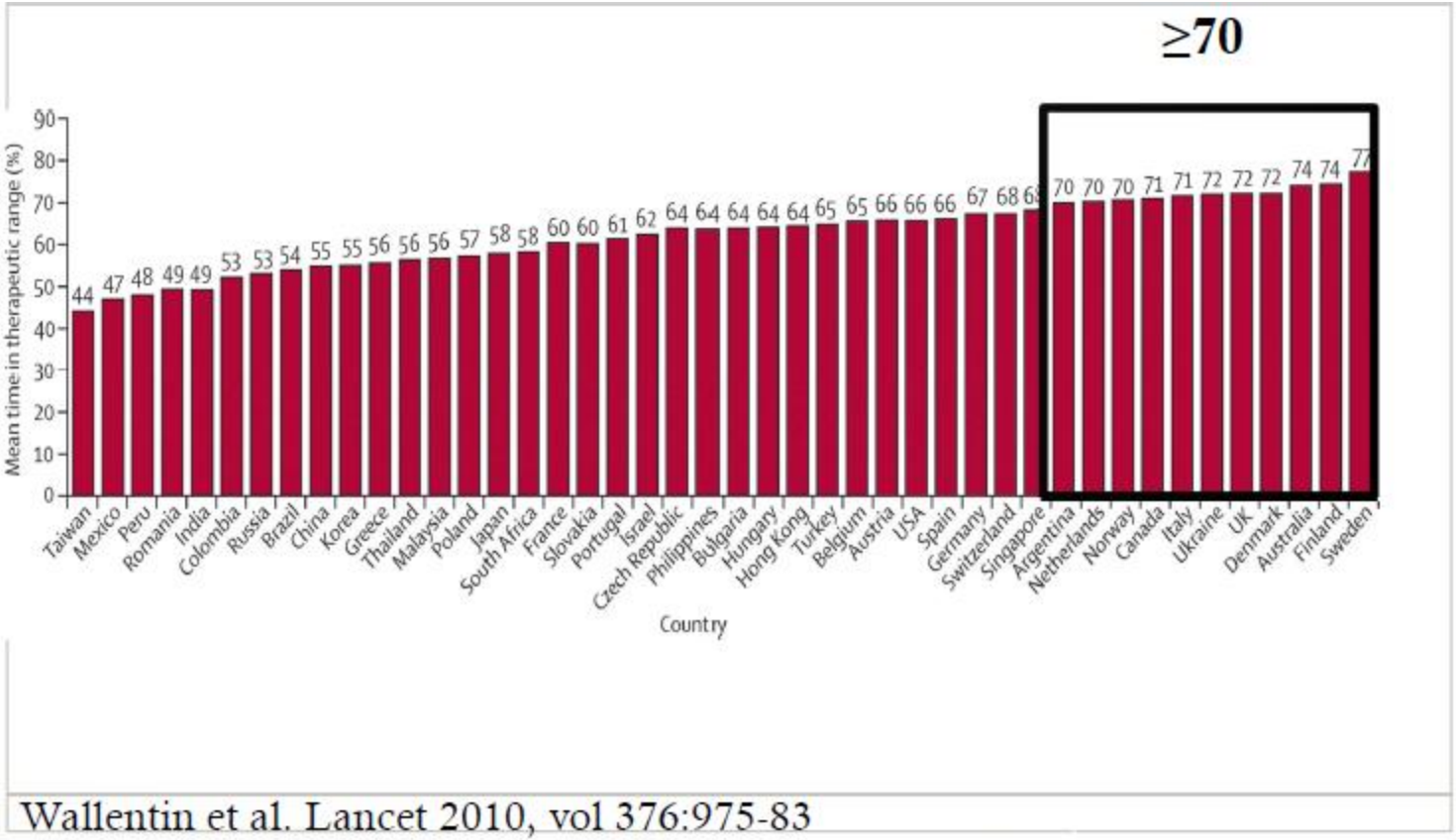
# Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA

Mattias Wieloch[1,2*], Anders Själander[3], Viveka Frykman[4], Mårten Rosenqvist[5], Niclas Eriksson[6], and Peter J. Svensson[1,7]

**Table 2** Complication frequency and estimated risk per patient-year in 4273 patients from the AuriculA subgroup with 95% CI in parenthesis

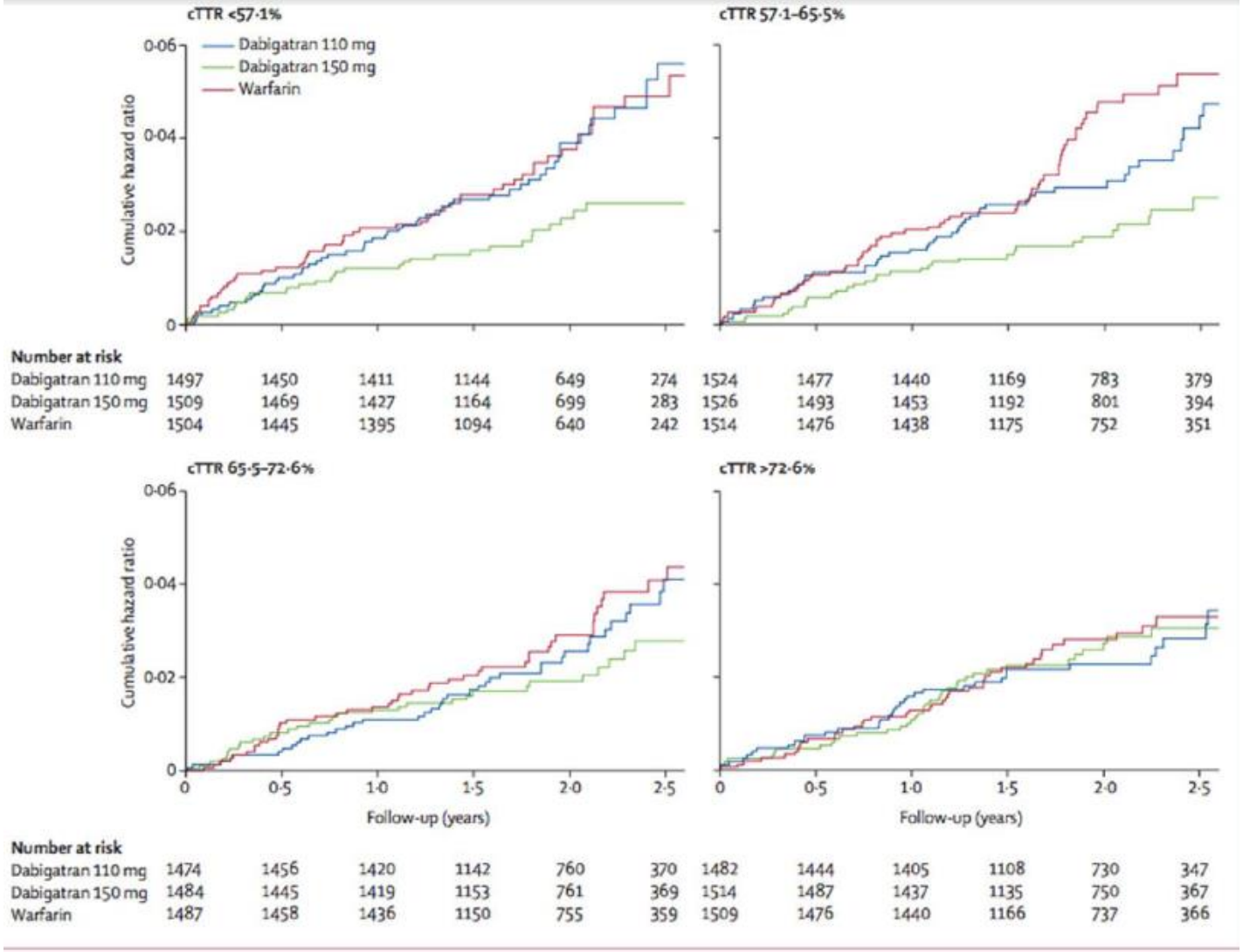
| Indication | Total (*n*) | Mean age | Treatment years | Bleeding (*n*) | Thrombosis (*n*) | Bleeding risk/ patient-year (%) | Thrombosis risk/ patient-year (%) | Mean TTR (%) |
|---|---|---|---|---|---|---|---|---|
| Whole population | 4273 | 70 | 3377 | 87 | 58 | 2.6 (2.0–3.1) | 1.7 (1.3–2.2) | 74.9 |
| no. of men | 2425 | 69 | 1906 | 46 | 31 | 2.4 (1.7–3.1) | 1.6 (1.1–2.2) | 74.9 |
| no of women | 1848 | 73 | 1471 | 41 | 27 | 2.8 (1.9–3.6) | 1.8 (1.1–2.5) | 74.8 |
| Atrial fibrillation | 2491 | 74 | 2043 | 53 | 29 | 2.6 (1.9–3.3) | 1.4 (0.9–1.9) | 75.8 |
| Heart valve dysfunction | 597 | 67 | 519 | 12 | 14 | 2.3 (1.0–3.6) | 2.7 (1.3–4.1)[a] | 76.0 |
| Venous thrombo-embolism | 1146 | 66 | 802 | 21 | 14 | 2.6 (1.5–3.7) | 1.8 (0.8–2.7) | 72.6 |
| Other | 267 | 65 | 213 | 4 | 2 | 1.9 (0.0–3.7) | 0.9 (0.0–2.2) | 74.7 |

# Mean time in therapeutic range (TTR) in worldwide




Wallentin et al. Lancet 2010, vol 376:975-83

# Effectiveness TTR




Wallentin et al. Lancet 2010, vol 376:975-83

Prof. Hugo ten Cate
Maastricht University Medical Centre
Maastricht the Netherlands

- TTR of ≥70% is recommended in the European Society of Cardiology guidelines[1]
- **Mean TTR ranged from 55–65% in the warfarin arm of key trials of non-VKA oral anticoagulants[2-4]**

1. Camm AJ et al. Eur Heart J. 2012. 2.Patel MR et al. N Engl J Med. 2011.
3. Connolly SJ et al. N Engl J Med. 2009 4. Granger CB et al. N Engl J Med. 2011.

Prof. Hugo ten Cate
Maastricht University Medical Centre
Maastricht the Netherlands

# Point up

- TTR > 70% offers greater protection against TE stroke (and mortality) than poorly controlled VKA
- At TTR > 70% bleeding complications are acceptable (in Sweden)
- In NOAC trials the average comparator (warfarin) had a rather modest TTR (55-64%)
- So, why are we satisfied with non-inferior or limited superiority of NOAC as compared to suboptimal warfarin.
- **Implication is that NOAC therapy should be improved!**

ONE
SIZE
FITS
ALL


ONE SIZE DOES
NOT FIT ALL
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Antithrombotic Therapy

# The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

## The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PHD,* Thorsten Lehr, PHD,†‡ Sebastian Haertter, PHD,† Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPHIL,§ John W. Eikelboom, MB BS,§ Michael D. Ezekowitz, MD, PHD,‖ Gerhard Nehmiz, PHD,† Susan Wang, PHD,* Lars Wallentin, MD, PHD,¶ on behalf of the RE-LY Investigators

**Table 1** Plasma Concentrations of Total Dabigatran After Oral Administration of Dabigatran 110 or DE 150, and Dose-Normalized Concentrations

| | DE 110 (ng/ml) | | DE 150 (ng/ml) | | DE 110 + DE 150 (ng/ml/mg) | |
|---|---|---|---|---|---|---|
| | $C_{pre,ss}$ (n = 4,227) | $C_{2,ss}$ (n = 4,583) | $C_{pre,ss}$ (n = 4,222) | $C_{2,ss}$ (n = 4,600) | $C_{pre,ss}$ (n = 8,449) | $C_{2,ss}$ (n = 9,183) |
| gMean | 64.7 | 126 | 91 | 175 | 0.795 | 1.54 |
| gCV, % | 79.9 | 75.3 | 81.9 | 74.1 | 80.9 | 74.7 |
| Median | 65.9 | 133 | 93 | 184 | 0.811 | 1.62 |
| P10 | 28.2 | 52 | 39.8 | 74.3 | 0.349 | 0.648 |
| P90 | 155 | 275 | 215 | 383 | 1.9 | 3.36 |
| Min | 1.15 | 1.07 | 1.04 | 2.3 | 0.00923 | 0.0129 |
| Max | 608 | 745 | 809 | 1,000 | 7.36 | 9.02 |

bid = twice daily; $C_{2,ss}$ = 2-h post-dose plasma concentration at steady state; $C_{pre,ss}$ = pre-dose plasma concentration at steady state; DE = dabigatran etexilate; DE 110 = dabigatran etexilate 110 mg twice daily; DE 150 = dabigatran etexilate 150 mg twice daily; gCV = geometric coefficient of variation; gMean = geometric mean; P10 = 10th percentile; P90 = 90th percentile.

**Table 2** Dose-Normalized Plasma Concentrations (ng/ml/mg) of Dabigatran According to Demographic Characteristics in the RE-LY Trial

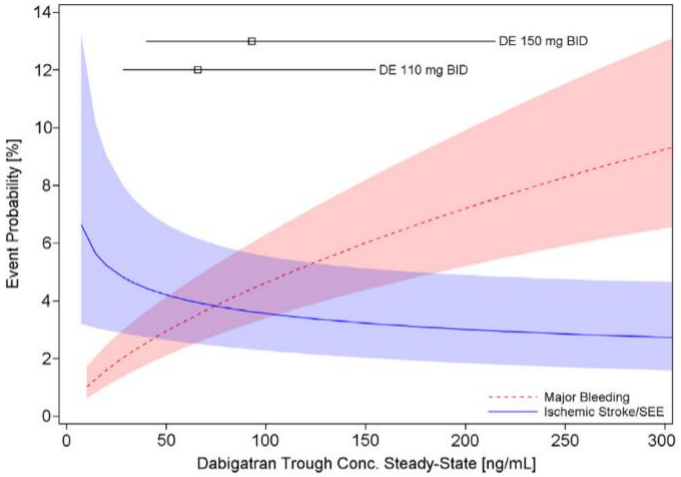
| Characteristic | Measure | Subgroup 1 | Subgroup 2 | Subgroup 3 | Subgroup 4 |
|---|---|---|---|---|---|
| Sex | | Male (n = 5,524) | Female (n = 2,925) | | |
| | gMean | 0.727 | 0.942 | — | — |
| | gCV, % | 78.2 | 69.3 | — | — |
| | Median | 0.736 | 0.967 | — | — |
| | P10 | 0.324 | 0.419 | — | — |
| | P90 | 1.7 | 2.21 | — | — |
| Age, yrs | | <65 (n = 1,466) | 65 to <75 (n = 3,787) | ≥75 (n = 3,196) | |
| | gMean | 0.586 | 0.749 | 0.982 | — |
| | gCV, % | 86 | 75.2 | 76 | — |
| | Median | 0.595 | 0.761 | 0.994 | — |
| | P10 | 0.241 | 0.341 | 0.45 | — |
| | P90 | 1.43 | 1.69 | 2.22 | — |
| Weight, kg | | <50 (n = 163) | 50 to <100 (n = 6,852) | ≥100 (n = 1,433) | |
| | gMean | 0.998 | 0.824 | 0.652 | — |
| | gCV, % | 83.8 | 80.6 | 77.1 | — |
| | Median | 1.01 | 0.84 | 0.66 | — |
| | P10 | 0.41 | 0.365 | 0.281 | — |
| | P90 | 2.63 | 1.94 | 1.56 | — |

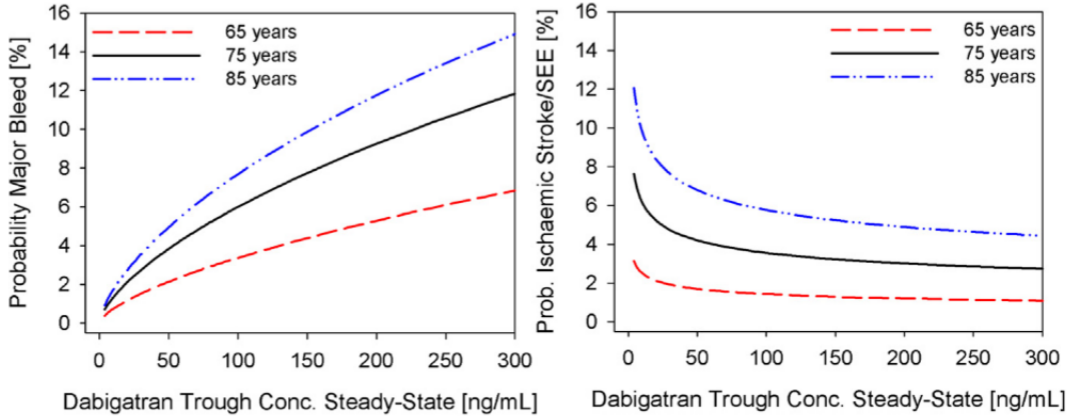
| CrCl, ml/min | | <30 (n = 18) | 30 to <50 (n = 1,512) | 50 to <80 (n = 3,937) | ≥80 (n = 2,690) |
|---|---|---|---|---|---|
| | gMean | 1.87 | 1.29 | 0.828 | 0.564 |
| | gCV, % | 51.9 | 78 | 71.7 | 70.2 |
| | Median | 2.11 | 1.33 | 0.857 | 0.582 |
| | P10 | 0.905 | 0.601 | 0.395 | 0.262 |
| | P90 | 3.16 | 2.83 | 1.77 | 1.2 |
| $CHADS_2$ | | 0–1 (n = 2,783) | 2 (n = 2,964) | 3+ (>2) (n = 2,702) | |
| | gMean | 0.688 | 0.808 | 0.908 | — |
| | gCV, % | 76.4 | 79.2 | 83.5 | — |
| | Median | 0.706 | 0.820 | 0.932 | — |
| | P10 | 0.318 | 0.355 | 0.390 | — |
| | P90 | 1.527 | 1.935 | 2.191 | — |
| $CHA_2DS_2$-VASc | | 0–1 (n = 282) | 2 (n = 1,663) | 3+ (>2) (n = 6,504) | |
| | gMean | 0.499 | 0.624 | 0.863 | — |
| | gCV, % | 82.4 | 73.5 | 79.6 | — |
| | Median | 0.513 | 0.636 | 0.887 | — |
| | P10 | 0.218 | 0.284 | 0.380 | — |
| | P90 | 1.115 | 1.376 | 2.10 | — |
| HAS-BLED | | 0–1 (n = 5,201) | 2+ (>1) (n = 3,248) | | |
| | gMean | 0.701 | 0.972 | | |
| | gCV, % | 76.5 | 81.3 | | |
| | Median | 0.715 | 0.989 | | |
| | P10 | 0.316 | 0.415 | | |

**Table 3** Trough Concentrations of Dabigatran (ng/ml/mg) Grouped by Outcome Event Occurrence

| | Major Bleed (n = 323) | Any Bleed (n = 2,319) | No Bleed (n = 5,899) | Stroke/SEE (+) (n = 129) | No Stroke/SEE (−) (n = 8,250) | Stroke/SEE/Death (+) (n = 387) | No Stroke/SEE/Death (−) (n = 7,789) | CV Events* (+) (n = 391) | No CV Events (−) (n = 7,865) |
|---|---|---|---|---|---|---|---|---|---|
| gMean | 113 | 86.9 | 72.8 | 76.6 | 76.5 | 88.5 | 75.4 | 87.8 | 75.6 |
| gCV, % | 79.8 | 81.4 | 84 | 84.1 | 83.9 | 84.7 | 83.3 | 89.5 | 83.1 |
| Median | 116 | 88.2 | 75.3 | 80.6 | 78.3 | 91.4 | 77.6 | 90.7 | 77.6 |
| P10 | 46.7 | 35.7 | 30.7 | 26.4 | 32.1 | 33.1 | 31.8 | 31.2 | 32 |
| P90 | 269 | 211 | 175 | 185 | 186 | 226 | 181 | 229 | 182 |

*Cardiovascular (CV) events include stroke, systemic embolism, pulmonary embolism, myocardial infarction, and vascular deaths.




**Probability of Clinical Outcomes Versus Dabigatran Plasma Concentrations**

# Drug Adherence and Persistence Results

National Primary Care Database in England (The Health Improvement Network, THIN).

| | Dabigatran | Rivaroxaban | Apixaban | Warfarin |
|---|---|---|---|---|
| Adherence at 1 y, % | 83.5 | 84.1 | 83.6 | 88.7 |
| Persistence at 1 y, % | 59.1 | 64.1 | 67.0 | 87.5 |
| Crossover to warfarin, % | 12.1 | 3.4 | 1.9 | -- |
| Crossover to another NOAC, % | 7.3 | 3.4 | 1.5 | -- |

- **In this large UK population base of AF patients, persistence with DOACs was lower than has been observed in clinical trials.**
- **Analyses of DOAC side effects profiles and real word acceptability should be conducted**

Banerjee A, et Al. ESC 2016.

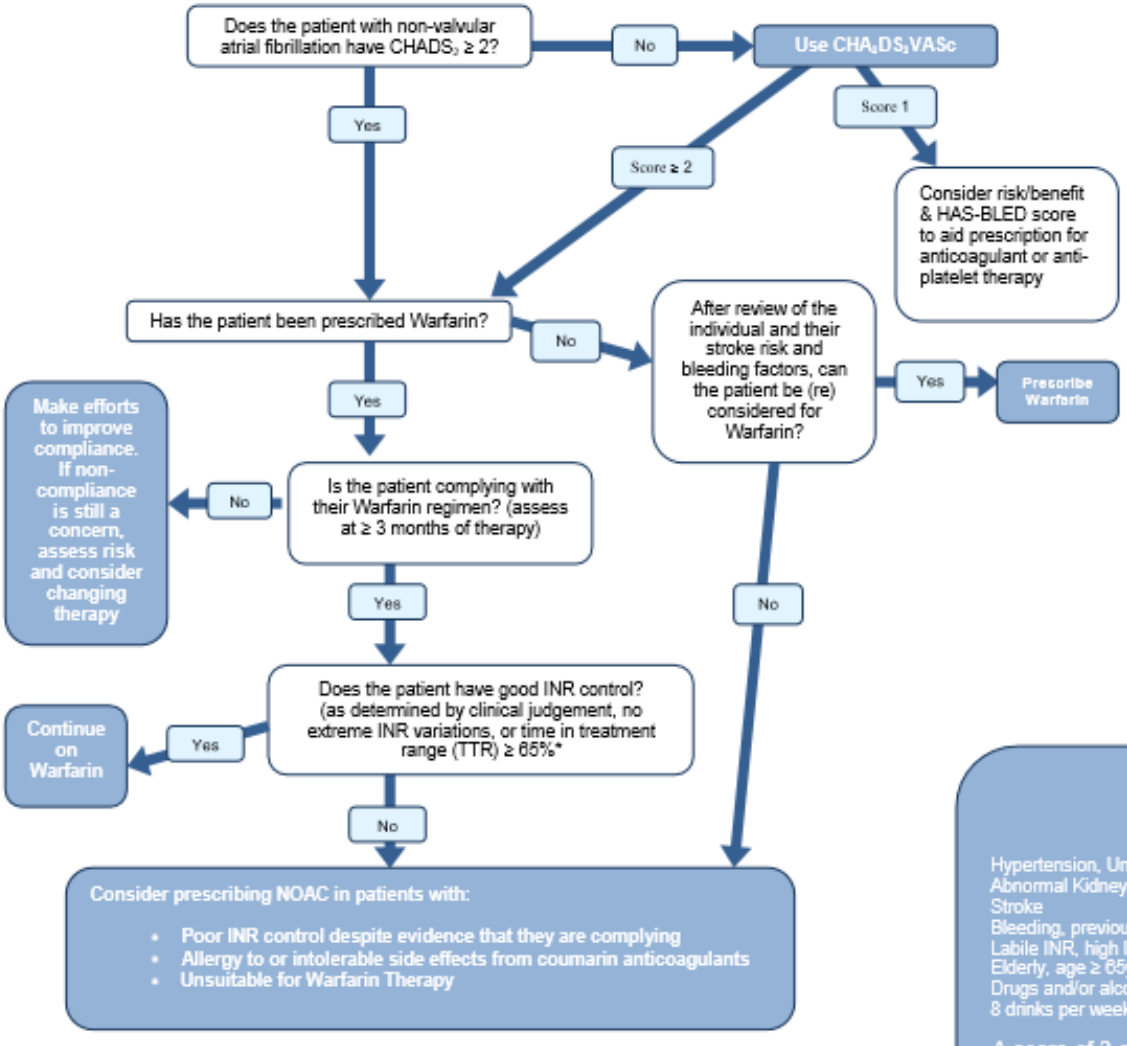
# Persistence of DOACs by Cohort Among DOAC- Naive Patients


| LaCoin L, et Al | Apixaban (N =1736) | Rivaroxaban (N =3447) | Dabigatran (N =1030) |
|---|---|---|---|
| Availability of follow-up (months) | | | |
| Median (interquartile range) | 8.1 (4.7, 13.3) | 9.6 (5.3, 15.8) | 15.1 (9.4, 25.0) |
| Persistence* % (95% CI) [N at risk] | | | |
| at 3 months | 90.5 (89.1, 91.9) N = 1374 | 87.3 (86.2, 88.4) N = 2689 | 82.8 (80.5, 86.1) N = 817 |
| at 6 months | 86.6 (84.8, 88.2) N = 945 | 81.6 (80.2, 82.9) N = 1921 | 73.2 (70.4, 75.9) N = 610 |
| at 12 months | 81.9 (79.6, 84.0) N = 401 | 74.8 (73.1, 76.5) N = 957 | 64.8 (61.7, 67.9) N = 398 |

# Effect on NOACs plasma level of drug-drug interaction

| | | 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% |

**On balance of risks and benefits, Warfarin should be considered for moderate or high risk atrial fibrillation patients (CHADS$_2$ ≥ 2)**




*(*Connolly et al. 2009. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM/ Vol. 361 no.12.Healy et al.2007. Oral Anticoagulation in Atrial Fibrillation. ACTIVE.W )*

Final Version May 2013

**CHADS$_2$ Score**

| | |
|---|---|
| Congestive Heart failure | 1 |
| Hypertension | 1 |
| Age ≥ 75 | 1 |
| Diabetes | 1 |
| Previous Stroke or TIA | 2 |

Consider anticoagulation if ≥ 2

Use CHA$_2$DS$_2$VASc assessment tool if < 2

**Annual Stroke Risk vs CHADS$_2$ Score**

| | |
|---|---|
| 0 | 1.9% |
| 1 | 2.8% |
| 2 | 4.0% |
| 3 | 5.9% |
| 4 | 8.5% |
| 5 | 12.5% |
| 6 | 18.2% |

**CHA$_2$DS$_2$VASc Score**

| | |
|---|---|
| Congestive Heart Failure/ LVD | 1 |
| Hypertension | 1 |
| Age ≥ 75 years | 2 |
| Diabetes mellitus | 1 |
| Stroke/TIA/TE | 2 |
| Vascular disease (MI, PAD or aortic plaque) | 1 |
| Age between 65 and 74 years | 1 |
| Sc - Sex category - Female | 1 |

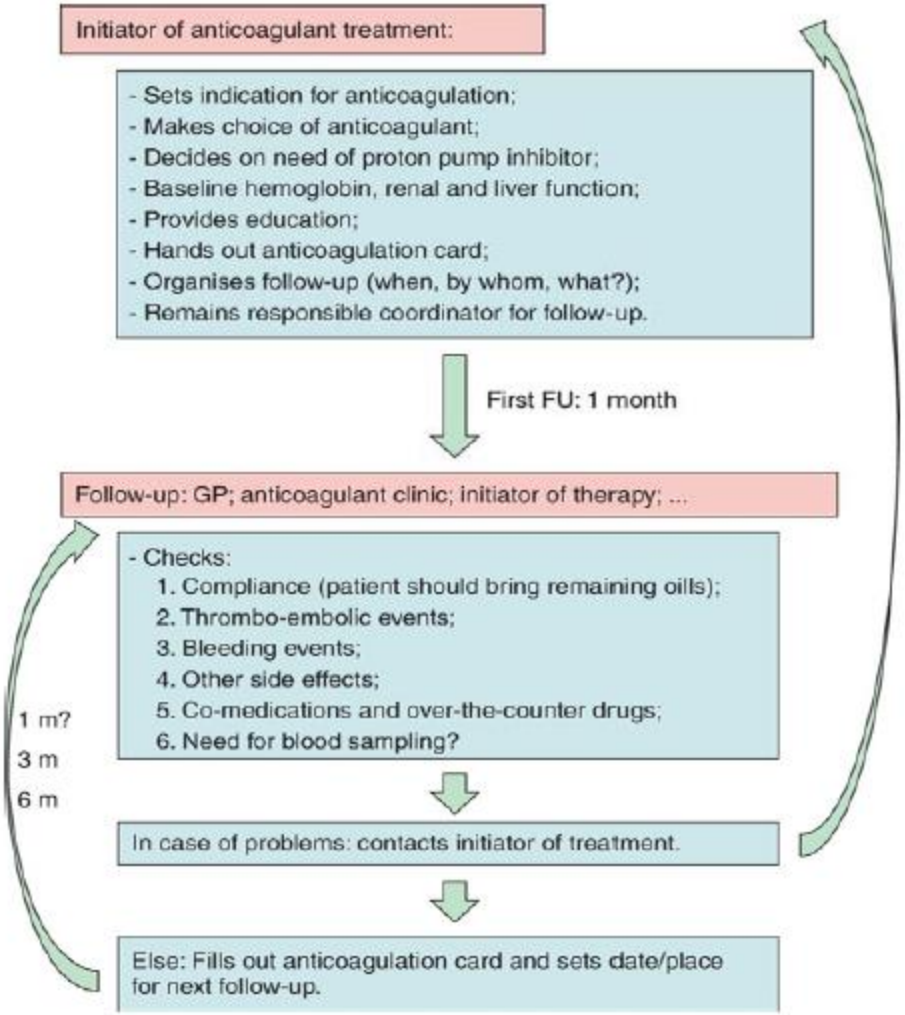
Score of ≥ 2 anticoagulation therapy

Score of 1 consider risk/benefit and HAS-BLED score to aid decision for anticoagulation or antiplatelet therapy

**HAS-BLED Score**

| | | score | Annual Risk % |
|---|---|---|---|
| Hypertension, Uncontrolled Sys >160mmHg | 1pt | 0 | 1.1 |
| Abnormal Kidney (Cr > 200) and/or liver function | 1pt each | 1 | 1.0 |
| Stroke | 1pt | 2 | 1.9 |
| Bleeding, previous history, anaemia or predisposition | 1pt | 3 | 3.7 |
| Labile INR, high INR or poor time in Therapeutic range | 1pt | 4 | 8.7 |
| Elderly, age ≥ 65yrs | 1pt | 5 | 12.5 |
| Drugs and/or alcohol, antiplatelets, more than 8 drinks per week | 1pt each | | |

A score of 3 or more is not a contraindication to oral anticoagulation but these patients require extra care.




**Structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake.**

# Grazie per l'attenzione

*Giuseppe Rescigno*

Centro Emostasi e Trombosi

DEA *"Umberto I - A.Tortora"*

Nocera Inferiore-Pagani (SA)

INR: 8.0  ha preso farmaci? Ha cambiato farmaci?