# Why is my patient bleeding again?

Update in management of anticoagulation in cardiovascular disease

“No Disclosures”

# Why was my patient bleeding? (2016)

- Focused on:
  - Afib:
    - definition of valvular Afib;
    - similar CVA risk in paroxysmal v permanent;
    - similar risk in Aflutter;
    - differences between CHADS2 v CHADSVASC score;
    - heparin bridging of warfarin therapy;
    - renal adjustment of and drug-drug interactions with NOACs;

**TABLE 4 Definitions of AF: A Simplified Scheme**

| Term | Definition |
|---|---|
| Paroxysmal AF | • AF that terminates spontaneously or with intervention within 7 d of onset.<br>• Episodes may recur with variable frequency. |
| Persistent AF | • Continuous AF that is sustained >7 d. |
| Long-standing persistent AF | • Continuous AF >12 mo in duration. |
| Permanent AF | • The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.<br>• Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.<br>• Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve. |
| Nonvalvular AF | • AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair. |

AF indicates atrial fibrillation.

# 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

***Developed in Collaboration With the Society of Thoracic Surgeons***

# Anticoagulation Regimen – Balancing Risks and Benefits

| Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **I** | **A** | **NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).** (What happened to mitral valve repair?)<br>**NEW**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding. |

# FDA Approval Afib Trials
# NOAC v warfarin

| | Pradaxa (dabigatran) | Xarelto (riveroxaban) | Eliquis (apixaban) | Savaysa (edoxaban) |
|---|---|---|---|---|
| Trial | RE-LY[1] | Rocket-AF[2] | ARISTOTLE[3] | Engage AF[4] |
| Stroke/embolism risk | 150 mg BID Superior | 20 mg daily Non-inferior | 5* mg BID Superior | 60 mg daily Non-inferior |
| Safety | | ↓ Fatal bleed | | |
| Major bleed | Similar | Similar | Reduced | Reduced |
| GI Bleed | Increased | Increased | Similar | Increased |
| IC Hge | Reduced | Reduced | Reduced | Reduced |

(*2.5 mg in high risk patients)


1. N Engl J Med, Volume 361(12):1139-1151. September 17, 2009
2. N Engl J Med, Volume 365(10):883-891. September 8, 2011
3. N Engl J Med, Volume 365(11):981-992. September 15, 2011
4. N Engl J Med, Volume 369(22):2093-2104. November 28, 2013

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

J Am Heart Assoc. 2016;5:e003725 doi: 10.1161/JAHA.116.00375

# 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

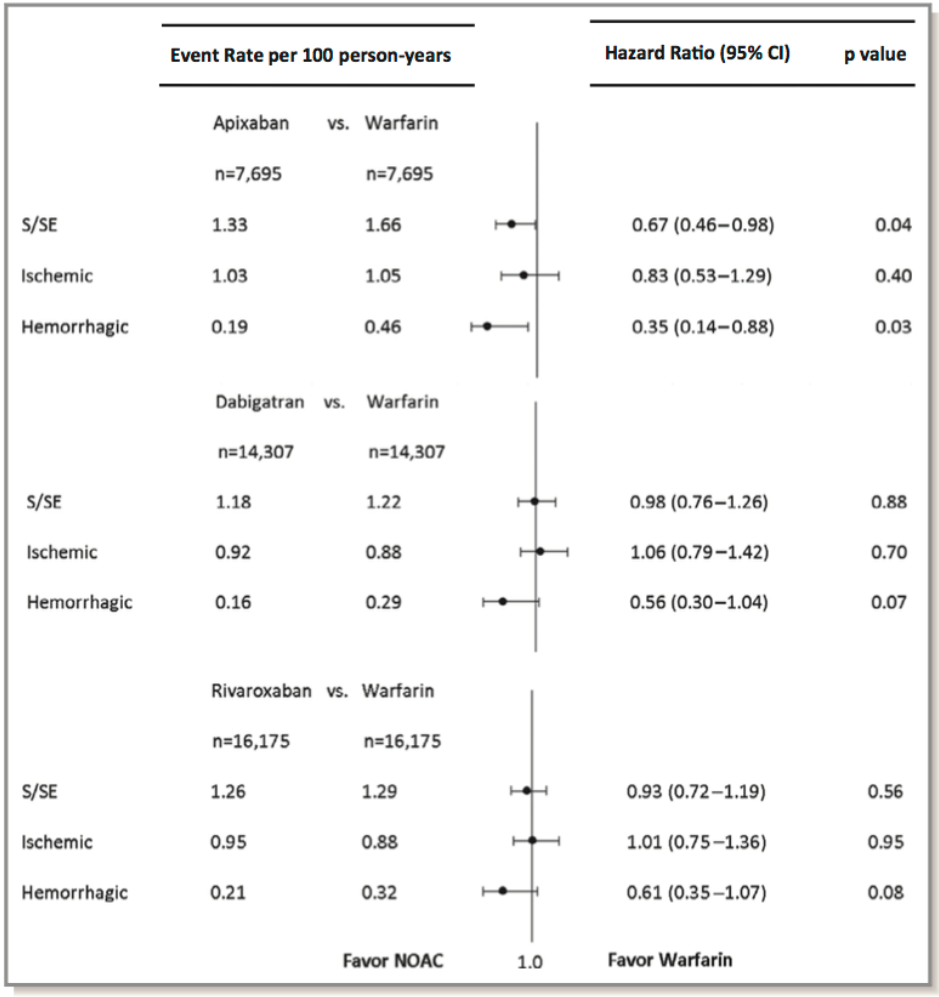



**Figure 2.** Forest plot depicting the hazard ratio for each pairwise propensity-matched medication comparison (dabigatran, rivaroxaban, and apixaban each vs warfarin) for stroke and systemic embolism (S/SE), ischemic stroke, and hemorrhagic stroke. NOAC, non–vitamin K oral anticoagulant.

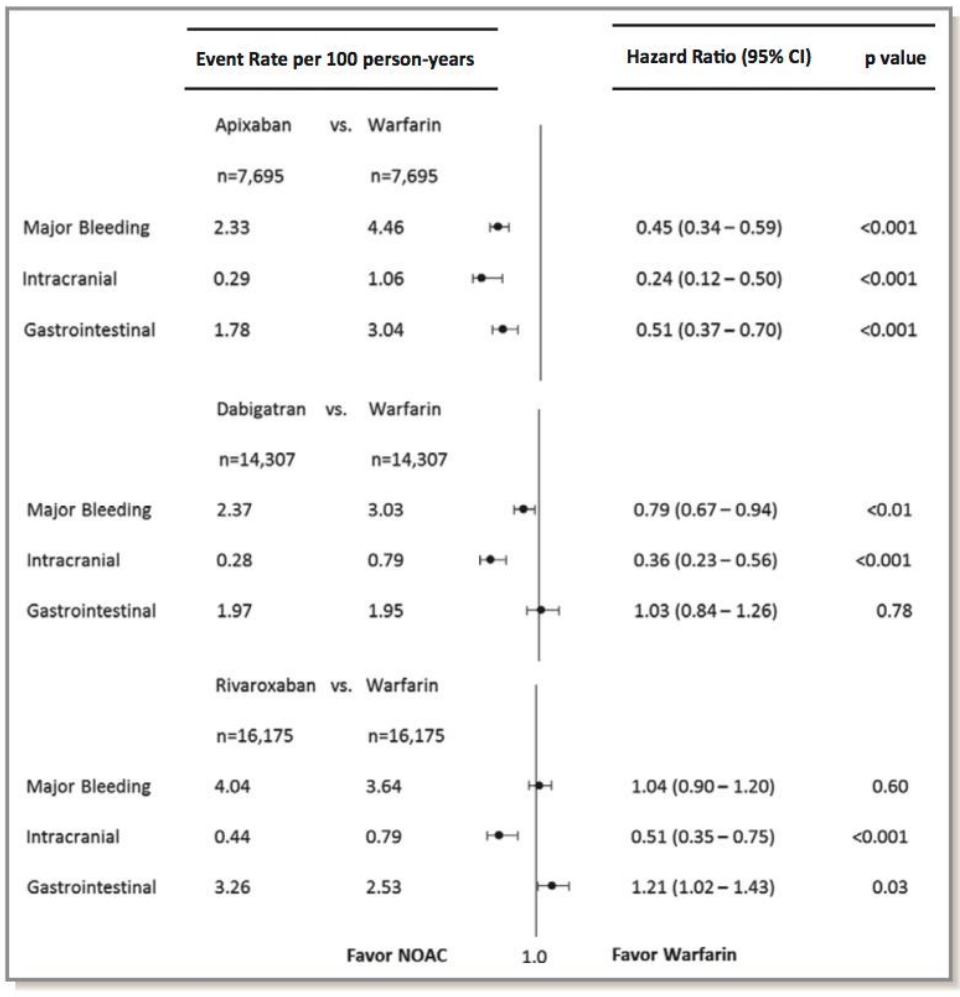
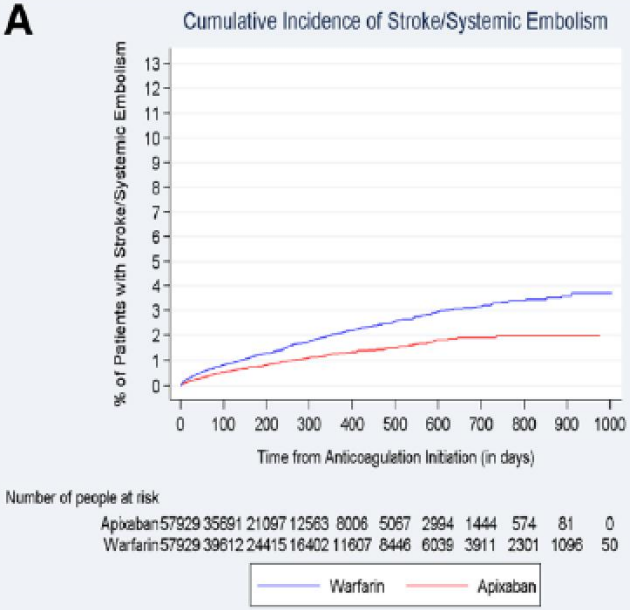
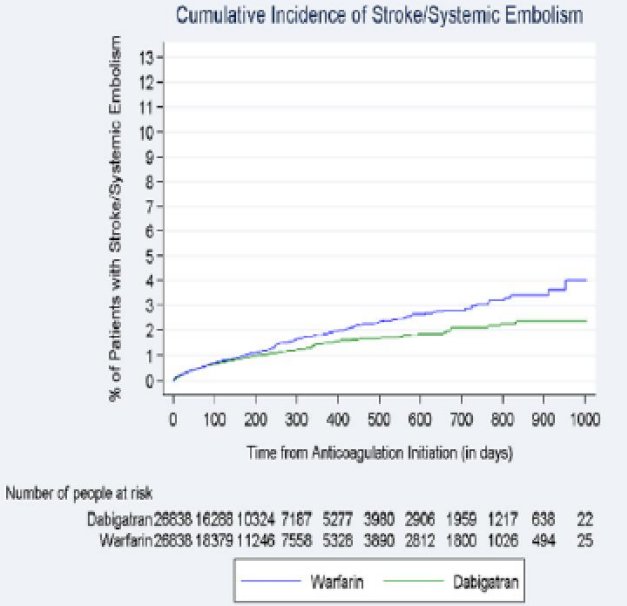


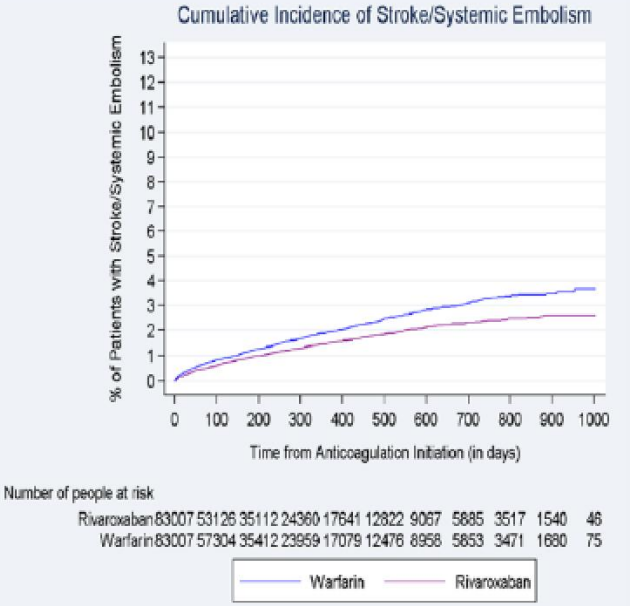

**Figure 3.** Forest plot depicting the hazard ratio for each pairwise propensity-matched medication comparison (dabigatran, rivaroxaban, and apixaban each vs warfarin) for major, intracranial, and gastrointestinal bleeding. NOAC, non–vitamin K oral anticoagulant.

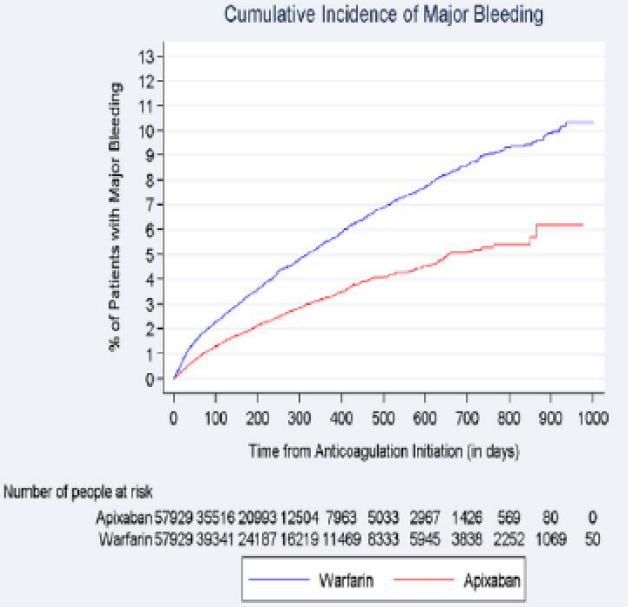
# The ARISTOPHANES Study

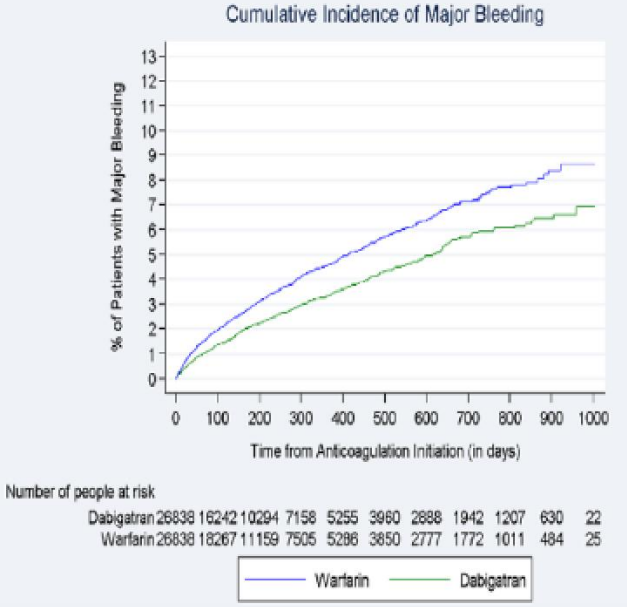
**A**

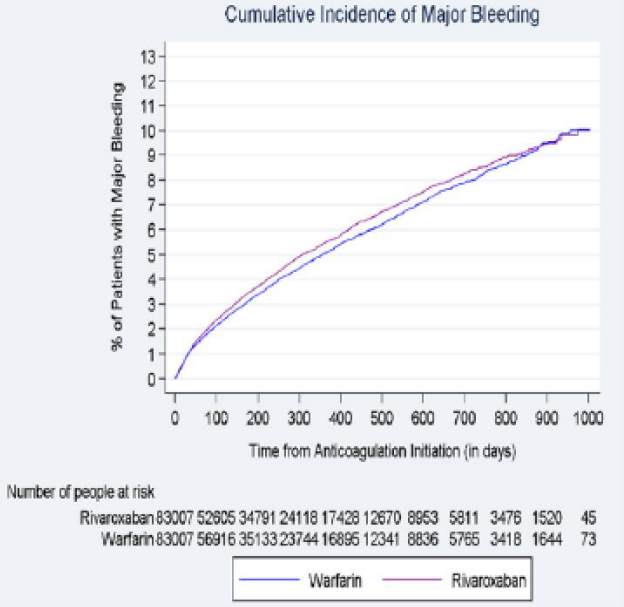


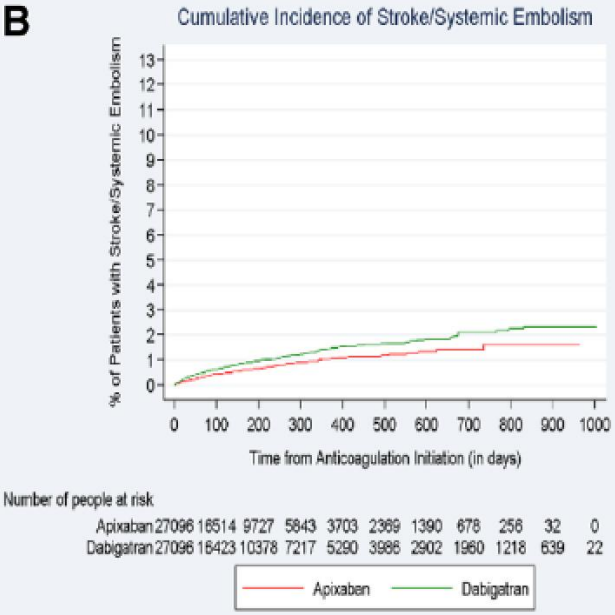



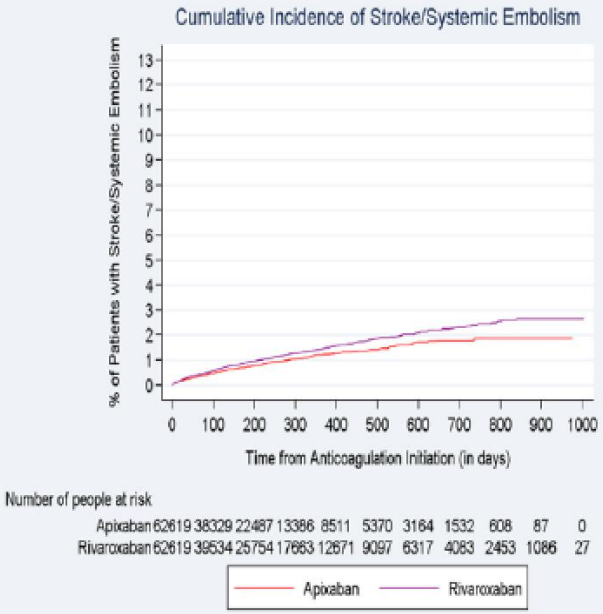



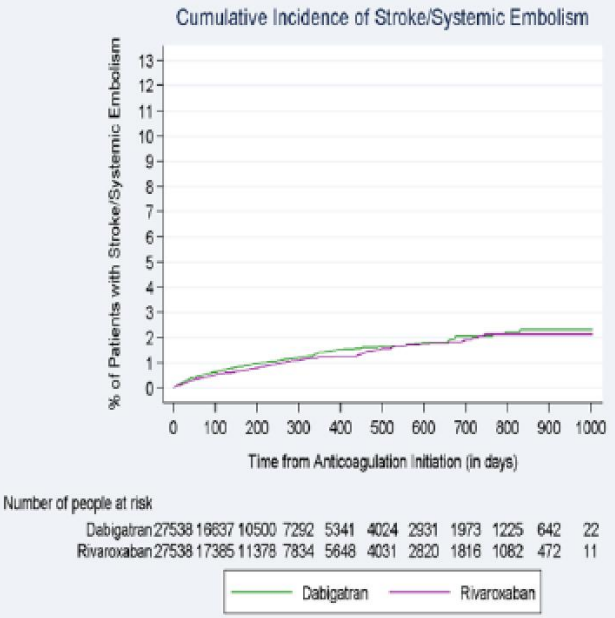

***Stroke. 2018;49:2933-2944.***

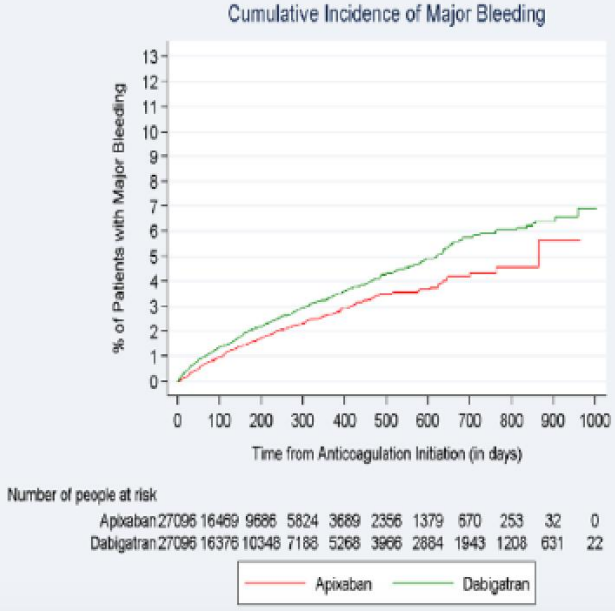
# The ARISTOPHANES Study

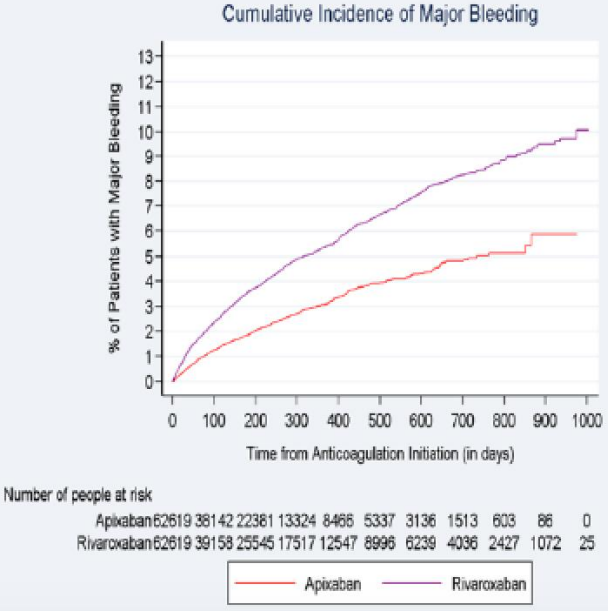
**B**

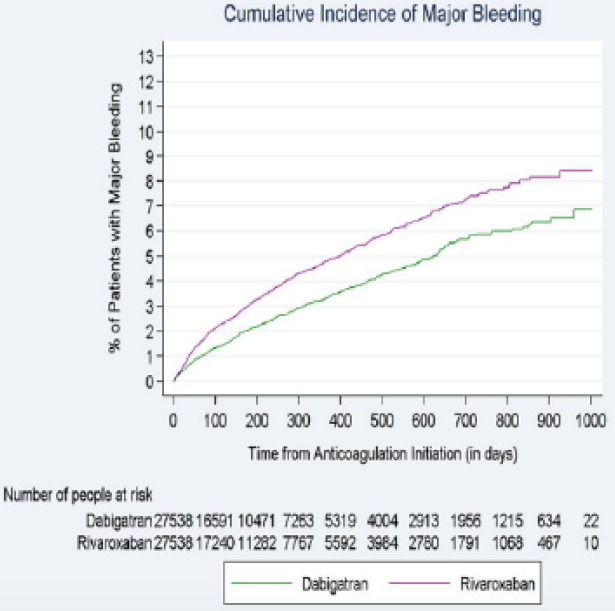



***Stroke. 2018;49:2933-2944.***

# Anticoagulation Regimen – Balancing Risks and Benefits

| Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **I** | **B** | **In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the $CHA_2DS_2$-VASc score is recommended for assessment of stroke risk.**<br>**MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. Patients with AF with bioprosthetic heart valves are addressed in the supportive text. (Section 4.1. in the 2014 AF guideline) |

# WHAT?

- 2014 Guideline: “Bioprosthetic heart valves have not been studied with any of the new anticoagulants.”
- 2019 Guideline:
  - “Patients with bioprosthetic heart valves were not included in studies validating the $CHA_2DS_2$-VASc scoring system.”
  - “Further study is needed before the routine long-term use of the $CHA_2DS_2$-VASc score can be recommended in AF patients with bioprosthetic heart valves.”
  - “In the ARISTOTLE (2015)(apixaban) and ENGAGE AF-TIMI 48 (2017, CHADS) (edoxaban) AF trials, small numbers (191, 82) of these patients (with mitral or aortic bioprosthetic valve implants) were included.
    - In these small subgroups, the findings suggested that apixaban and edoxaban appeared to be equitable alternatives to warfarin in patients with AF and remote bioprosthetic valve implantation.”

**TABLE 7** Comparison of the $CHADS_2$ and $CHA_2DS_2$-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

| Definition and Scores for $CHADS_2$ and $CHA_2DS_2$-VASc | | Stroke Risk Stratification With the $CHADS_2$ and $CHA_2DS_2$-VASc Scores | |
|---|---|---|---|
| | Score | | Adjusted Stroke Rate (% per y) |
| $CHADS_2$ | | $CHADS_2$* | |
| Congestive HF | 1 | 0 | 1.9 |
| Hypertension | 1 | 1 | 2.8 |
| Age ≥75 y | 1 | 2 | 4.0 |
| Diabetes mellitus | 1 | 3 | 5.9 |
| Stroke/TIA/TE | 2 | 4 | 8.5 |
| Maximum score | 6 | 5 | 12.5 |
| | | 6 | 18.2 |
| $CHA_2DS_2$-VASc | | $CHA_2DS_2$-VASc† | |
| Congestive HF | 1 | 0 | 0 |
| Hypertension | 1 | 1 | 1.3 |
| Age ≥75 y | 2 | 2 | 2.2 |
| Diabetes mellitus | 1 | 3 | 3.2 |
| Stroke/TIA/TE | 2 | 4 | 4.0 |
| Vascular disease (prior MI, PAD, or aortic plaque) | 1 | 5 | 6.7 |
| Age 65–74 y | 1 | 6 | 9.8 |
| Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| Maximum score | 9 | 8 | 6.7 |
| | | 9 | 15.20 |

# Anticoagulation Regimen – Balancing Risks and Benefits

| Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **IIa** | **B** | **For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a $CHA_2DS_2$-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy.**<br>**MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. (Section 4.1. in the 2014 AF Guideline) |

# Anticoagulation Regimen – Balancing Risks and Benefits

| Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **IIb** | **C- LD** | **For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a $CHA_2DS_2$-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered.**<br>**MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and evidence was added to support separate risk scores by sex. LOE was updated from C to C-LD. (Section 4.1. in the 2014 AF Guideline) |

2014: "With nonvalvular AF and a CHA2DS2-VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered."
ASPIRIN IS NOTE MENTIONED OUTSIDE OF MI/PCI IN THE 2019 DOCUMENT!

ORIGINAL RESEARCH ARTICLE

# Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation

## Should We Use a $CHA_2DS_2$-VA Score Rather Than $CHA_2DS_2$-VASc?

**Peter Brønnum Nielsen, MSc, PhD, Flemming Skjøth, MSc, PhD, Thure Filskov Overvad, MD, PhD, Torben Bjerregaard Larsen, MD, PhD, Gregory Y. H. Lip, MD**

Danish registry data, 239,671 patients, 1997-2015, primary discharge
Dx ischemic stroke or thromboembolism

| 5-year follow-up | MEN | | | WOMEN | | |
|---|---|---|---|---|---|---|
| 0 | 275 | 525.16 | 0.52 (0.47–0.59) | 143 | 342.31 | 0.42 (0.35–0.49) |
| 1 | 418 | 315.12 | 1.33 (1.21–1.46) | 362 | 274.45 | 1.32 (1.19–1.46) |
| 2 | 1051 | 386.25 | 2.72 (2.56–2.89) | 1569 | 497.89 | 3.15 (3.00–3.31) |
| 3 | 1076 | 273.03 | 3.94 (3.71–4.18) | 1683 | 397.81 | 4.23 (4.03–4.44) |
| 4 | 1151 | 173.49 | 6.63 (6.26–7.03) | 1670 | 218.21 | 7.65 (7.29–8.03) |
| 5 | 715 | 84.33 | 8.48 (7.88–9.12) | 1196 | 109.52 | 10.92 (10.32–11.56) |
| ≥6 | 438 | 44.22 | 9.90 (9.02–10.88) | 531 | 51.38 | 10.33 (9.49–11.25) |
| Overall | 5124 | 1801.60 | 2.84 (2.77–2.92) | 7154 | 1891.57 | 3.78 (3.70–3.87) |

Circulation. 2018;137:832-40.

# Sex

- Recent studies have suggested that female sex, in the absence of other AF risk factors (CHA2DS2-VASc score of 0 in males and 1 in females), carries a low stroke risk that is similar to males.
- The excess risk for females was especially evident among those with ≥2 non–sex-related stroke risk factors;
  - thus, female sex is a risk modifier and is age dependent
    - Adding female sex to the CHA2DS2-VASc score matters for age >65 years or ≥2 non–sex-related stroke risk factors

So female plus CHF, female plus HTN, or female plus DM, or female plus MI/PVD/aortic atheroma, or does NOT warrant anticoagulation.

# Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

**Table 3. Study Outcomes.**

| Outcome | No Bridging (N=918) | Bridging (N=895) | P Value |
|---|---|---|---|
| | *number of patients (percent)* | | |
| **Primary** | | | |
| Arterial thromboembolism | 4 (0.4) | 3 (0.3) | 0.01*, 0.73† |
| Stroke | 2 (0.2) | 3 (0.3) | |
| Transient ischemic attack | 2 (0.2) | 0 | |
| Systemic embolism | 0 | 0 | |
| Major bleeding | 12 (1.3) | 29 (3.2) | 0.005† |
| **Secondary** | | | |
| Death | 5 (0.5) | 4 (0.4) | 0.88† |
| Myocardial infarction | 7 (0.8) | 14 (1.6) | 0.10† |
| Deep-vein thrombosis | 0 | 1 (0.1) | 0.25† |
| Pulmonary embolism | 0 | 1 (0.1) | 0.25† |
| Minor bleeding | 110 (12.0) | 187 (20.9) | <0.001† |

* P value for noninferiority.
† P value for superiority.

# Interruption and Bridging Anticoagulation

| Recommendations for Interruption and Bridging Anticoagulation | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **I** | **C** | **Bridging therapy with unfractionated heparin or low-molecular-weight heparin is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding.** |
| **I** | **B-R** | **For patients with AF without mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated.**<br>**MODIFIED**: LOE was updated from C to B-R because of new evidence. (Section 4.1. in the 2014 AF Guideline) |

Mechanical valve, high risk (Afib+MS+CHF), prior embolic event on holding anticoagulant.

| | Pradaxa (dabigatran) | Xarelto (riveroxaban) | Eliquis (apixaban) | Savaysa (edoxaban) |
|---|---|---|---|---|
| Half-life (hold for)<br><br>(renal impaired CrCl < 50) | 12-17 h (1-2 days)<br><br>(3-5 days) | 5-13 h (>24 hours) | 9-14 h (>24 h low risk >48 h m-h risk) | 10-14 h (>24 h) |
| Excretion | 80% renal | 2/3 renal 1/3 hepatic | 25% renal 75% fecal | 50% renal |
| Dose | 150 mg BID¶ (pH dept absorpt)<br>¶ avoid p-gp inducers rifampin | 20 mg daily eve (with food) | 5 mg BID | 60 mg daily¶<br>¶ avoid p-gp inducers rifampin |
| Renal dose | CrCl 15-30 or CrCl 30-50 with p-gp inhibitors*: 75 mg BID<br>•Avoid dronederone, ketoconazole, verapamil | CrCl 15-50: 15 mg daily eve | [2.5 mg BID § if two of three:<br>Cr > 1.5<br>Age > 80<br>Kg < 60] | CrCl >95:CONTRA<br>CrCl 15-50: 30 mg daily |
| CrCl < 15 or Hemodialysis | Unknown/not rec | Unknown/not rec | See above | Unknown/not rec |
| Hepatic impairment | Mod: "[no change]" | Mod-severe: "avoid use" | M-m unchanged<br>S "not studied" | Mild unchanged<br>M-S "not rec" |

§ avoid combine 3A4/p-gp inhibitors ketoconizole, clarithromycin, rifampin, phenytoin, St. Johns

# Why was my patient bleeding? (2016)

- Focused on:
  - Afib: definition of valvular Afib; similar CVA risk in paroxysmal v permanent; similar risk in Aflutter; differences between CHADS2 v CHADSVASC score; heparin bridging of warfarin therapy; renal adjustment of and drug-drug interactions with NOACs; state of reversal agents (Praxbind)
  - Dosing of NOACs in other indications including prophylaxis or treatment of DVT/PE; state of reversal agents (Praxbind)

# NOAC Dose by Indication

| | Pradaxa (dabigatran) | Xarelto (riveroxaban) | Eliquis (apixaban) | Savaysa (edoxaban) |
|---|---|---|---|---|
| Non-prosthetic valve Afib | 150 mg BID | 20 mg daily | 5 mg BID | 60 mg daily* |
| DVT/PE risk reduction | 150 BID | 15 mg BID x 21d, then 20 mg daily | 2.5 mg BID | Not indicated |
| prophylaxis | (hip) 110 day 1, then 220 daily for 28-35 d | 10 mg daily x 35d(hip) 12d(knee) | 2.5 mg BID 35d(hip) 12d(knee) | Not indicated |
| DVT/PE | 150 BID post 5-10 d parenteral Rx | 15 mg BID x 21d, then 20 mg daily | 10 mg BID x 7 d then 5 mg BID | <60 kg 30 mg qd >60 kg 60 mg qd post 5-10 d parenteral Rx |
| Chronic DVT/PE | 150 BID | 20 mg daily | 2.5 mg BID | Not indicated |

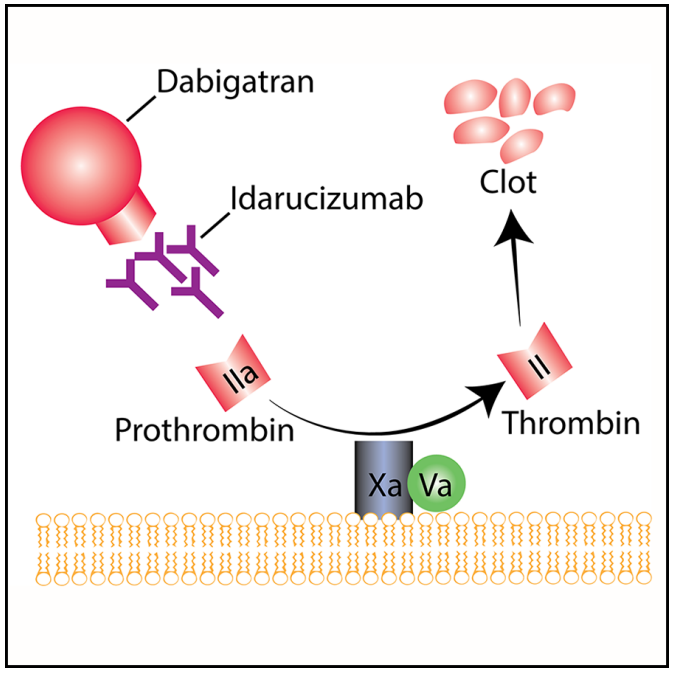
*not for use in moderate to severe mitral stenosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.


## Dosing Guide

To download the full Dosing & Reconstitution Guide CLICK HERE

### ANDEXXA Dosing Should Be Individualized

**ANDEXXA Has 2 Regimens Specific to FXa Inhibitors Used and Time of Last Dose**

- **≥8 Hours** since last dose of rivaroxaban or apixaban → ANDEXXA STANDARD DOSE
- **<8 Hours** since last dose of rivaroxaban or apixaban
  - rivaroxaban ≤10 mg — OR — apixaban ≤5 mg → ANDEXXA STANDARD DOSE
  - rivaroxaban >10 mg — OR — apixaban >5 mg → ANDEXXA HIGH DOSE
- **Unknown** administration (dose/time) of rivaroxaban or apixaban → ANDEXXA HIGH DOSE

### ANDEXXA Dosing Regimens

IV bolus followed by continuous infusion

**ANDEXXA Standard Dose**

| Initial IV Bolus | Follow-on IV Infusion |
|---|---|
| 400 mg at a target rate of 30 mg/min | 4 mg/min for up to 120 minutes |

**ANDEXXA High Dose**

| Initial IV Bolus | Follow-on IV Infusion |
|---|---|
| 800 mg at a target rate of 30 mg/min | 8 mg/min for up to 120 minutes |

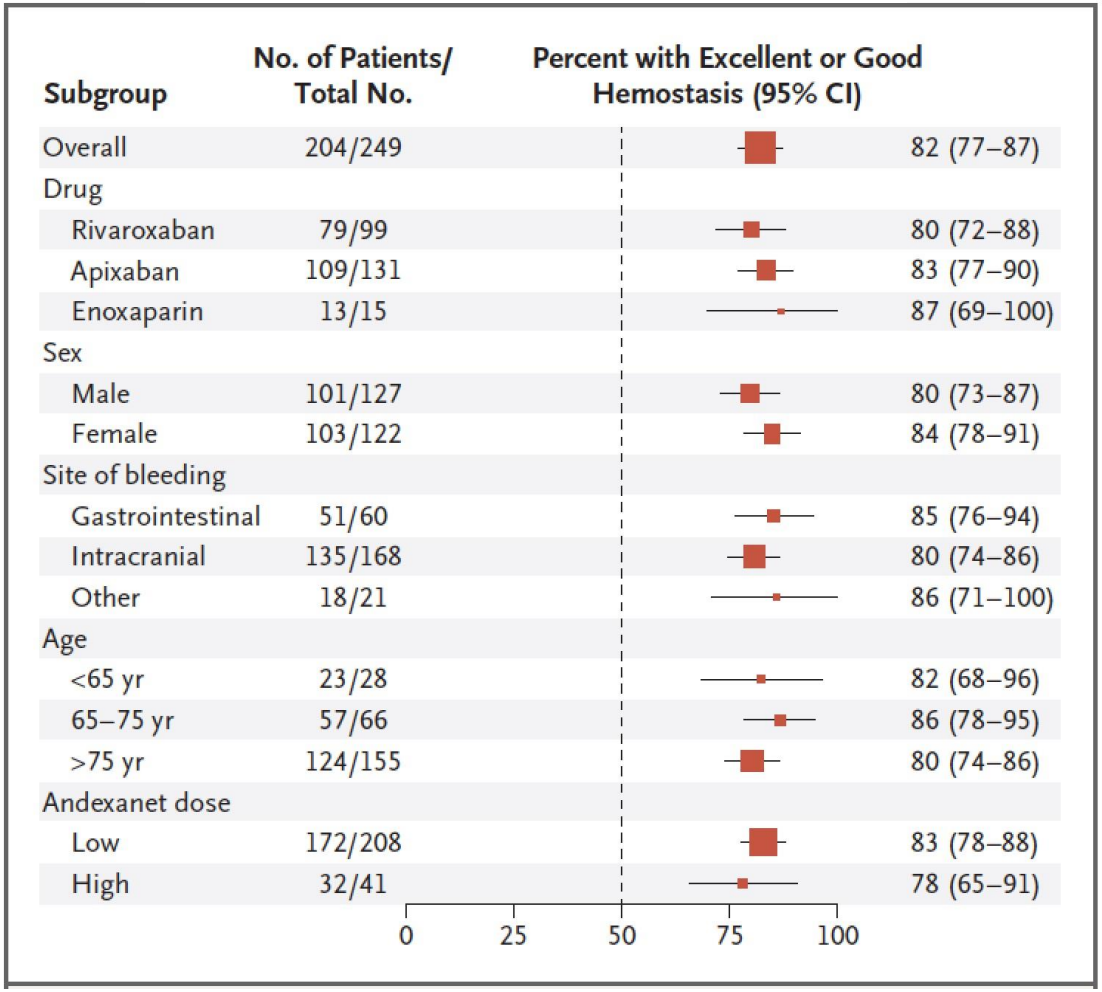
**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Safety Population (N=352) | Efficacy Population (N=254) |
|---|---|---|
| Age — yr | 77.4±10.8 | 77.1±11.1 |
| Male sex — no. (%) | 187 (53) | 129 (51) |
| White race — no. (%)† | 307 (87) | 222 (87) |
| Body-mass index‡ | 27.0±5.9 | 27.0±6.2 |
| Estimated creatinine clearance — no. (%)§ | | |
| <30 ml/min | 33 (9) | 27 (11) |
| 30 to <60 ml/min | 137 (39) | 104 (41) |
| ≥60 ml/min | 167 (47) | 113 (44) |
| Missing data | 15 (4) | 10 (4) |
| Primary indication for anticoagulation — no. (%)¶ | | |
| Atrial fibrillation | 280 (80) | 201 (79) |
| Venous thromboembolism‖ | 61 (17) | 46 (18) |
| Other | 11 (3) | 7 (3) |
| Medical history — no. (%) | | |
| Myocardial infarction | 48 (14) | 36 (14) |
| Stroke | 69 (20) | 57 (22) |
| Deep-vein thrombosis | 67 (19) | 53 (21) |
| Pulmonary embolism | 41 (12) | 28 (11) |
| Atrial fibrillation | 286 (81) | 204 (80) |
| Heart failure | 71 (20) | 56 (22) |
| Diabetes mellitus | 107 (30) | 80 (31) |
| Factor Xa inhibitor — no. (%)** | | |
| Rivaroxaban | 128 (36) | 100 (39) |
| Apixaban†† | 194 (55) | 134 (53) |
| Enoxaparin | 20 (6) | 16 (6) |
| Edoxaban | 10 (3) | 4 (2) |
| Site of bleeding — no. (%)‡‡ | | |
| Gastrointestinal | 90 (26) | 62 (24) |
| Intracranial | 227 (64) | 171 (67) |
| Other | 35 (10) | 21 (8) |

ORIGINAL ARTICLE

# Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*




This article was published on February 7, 2019, at NEJM.org.

# Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

**Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.***

| Variable | Safety Population (N=352) | | | |
|---|---|---|---|---|
| | Total | <6 Days after Bolus | 6–14 Days after Bolus | 15–30 Days after Bolus |
| | *number of patients (percent)* | | | |
| ≥1 Thrombotic event within 30 days† | 34 (10) | 11 | 11 | 12 |
| Myocardial infarction | 7 | 6 | 1 | 0 |
| Ischemic stroke or stroke of uncertain classification | 14 | 5 | 6 | 3 |
| Transient ischemic attack | 1 | 0 | 0 | 1 |
| Deep-vein thrombosis | 13 | 1 | 5 | 7 |
| Pulmonary embolism | 5 | 1 | 0 | 4 |
| Death within 30 days‡ | 49 (14) | 8 | 21 | 20 |
| Cardiovascular cause | 35 | 7 | 15 | 13 |
| Noncardiovascular cause | 12 | 1 | 5 | 6 |
| Uncertain cause | 2 | 0 | 1 | 1 |
| Restart of any anticoagulation§ | 220 (62) | 145 (41) | 46 (13) | 29 (8) |
| Thrombotic event before restart¶ | 26 (7) | | | |
| Thrombotic event after restart | 8 (2) | | | |
| Restart of oral anticoagulation‖ | 100 (28) | 31 (9) | 37 (11) | 32 (9) |
| Thrombotic event before restart¶ | 34 (10) | | | |
| Thrombotic event after restart | 0 | | | |

**WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS**

***See full prescribing information for complete boxed warning***

**Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including:**

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

**Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.**

# Why was my patient bleeding? (2016)

- Focused on:
  - Afib: definition of valvular Afib; similar CVA risk in paroxysmal v permanent; similar risk in Aflutter; differences between CHADS2 v CHADSVASC score; heparin bridging of warfarin therapy; renal adjustment of and drug-drug interactions with DOACs;
  - Dosing of NOACs in other indications including prophylaxis or treatment of DVT/PE; state of reversal agents (Praxbind)
  - CAD: P2Y12 pharmacokinetics, efficacy and bleeding risk, indications in NSTEMI v routine PCI, DAPT score and duration post NSTEMI PCI, long term ticagrelor (Brilinta) in CAD; unique antiplatelets like voxapar (Zontivity) (half-life!)

Table 2

## Key differences between oral P2Y12 receptor antagonists

| Feature | Clopidogrel | Prasugrel | Ticagrelor |
|---|---|---|---|
| Reversible platelet inhibition | No | No | Yes |
| Loading dose | 300-600 mg | 60 mg | 180 mg |
| Daily dose (wt >60 kg)[a] | 75 mg | 10 mg | 90 mg twice daily |
| Increased risk of non-CABG major bleeding[b] | – | Yes | Yes |
| Increased risk of CABG-related major bleeding[b] | – | Yes | No |
| Safe for use in patients with history of CVA | Yes | No | Yes |
| Prodrug | Yes | Yes | No |
| Dyspnea and ventricular pauses | No | No | Yes |

75 mg for ≥75-yo in lysis

Abbreviations: wt=patient body weight; CABG=coronary artery bypass graft; CVA=cerebrovascular accident

[a]The FDA recommends the option of a 5-mg daily dose of prasugrel in patients with body weight <60 kg

[b]Compared with clopidogrel

*Formulary*/Source: Refs 19,22, 23

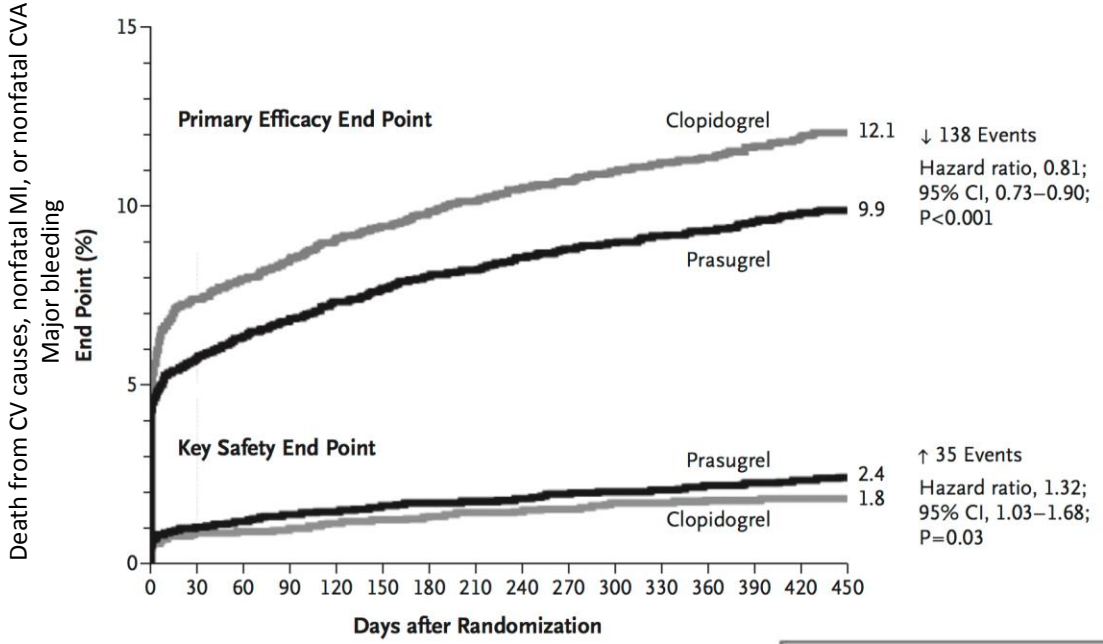
## Table. Comparison of the P2Y12 receptor antagonists

| | Clopidogrel | Prasugrel | Ticagrelor | Cangrelor |
|---|---|---|---|---|
| **Route** | Oral | Oral | Oral | Intravenous |
| **Onset** | 120-360 minutes | 60 minutes | 30 minutes | 2 minutes |
| **Offset** | 5 days | 7 days | 5 days | 60 minutes |
| **Reversible** | No | No | Yes | Yes |
| **Platelet Inhibition, IPA** | 20-60% | 60-80% | 70-95% | 95% |
| **Dosing for PCI** | LD: 600 mg<br>MD: 75 mg daily | LD: 60 mg<br>MD: 10 mg daily | LD: 180 mg<br>MD: 90 mg BID | LD: 30 mcg/kg<br>MD: 4 mcg/kg/min |
| **Dosing for Bridging** | | | | LD: none<br>MD: 0.75 mcg/kg/min |
| **Dosing Adjustments** | None | 5 mg/day if older than 75 years or <60 kg* | None | None |
| **Contraindications** | Active bleeding | Active bleeding; history of TIA or stroke | Active bleeding; ICH; severe hepatic impairment | Active bleeding |
| **Drug Interactions** | CYP2C19 inhibitors (eg, certain PPIs, azoles and SSRIs, cimetidine) | None identified | Avoid potent CYP3A4 inhibitors or inducers, caution with P-glycoprotein/CYP3A4 substrates (ie, simvastatin, lovastatin, digoxin) | Initiation of clopidogrel should be delayed until cangrelor infusion is stopped |

Source: Varnado et al.

IPA=Inhibition of platelet aggregation at Cmax with 5mM ADP (larger value indicates greater platelet inhibition); LD=loading dose; MD=maintenance dose; BID=twice daily; ICH=intracranial hemorrhage; TIA=transient ischemic attack; PPI=proton pump inhibitor; SSRI=selective serotonin receptor antagonist

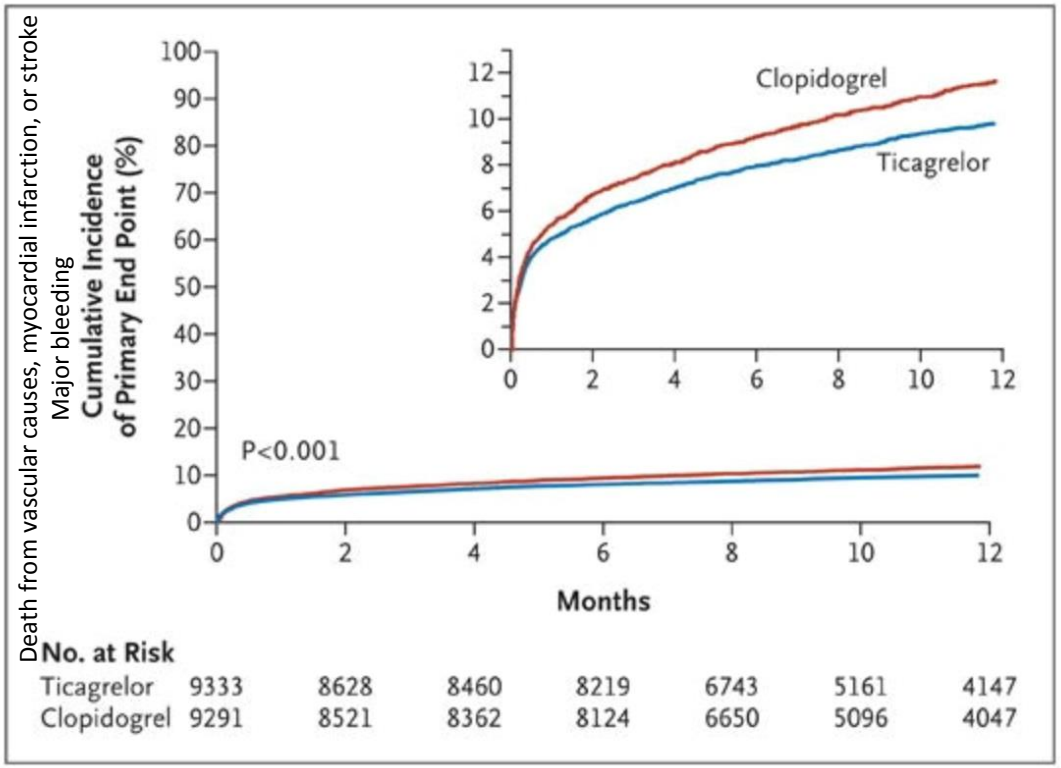
*The efficacy of this dose has not been studied for PCI




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Clopidogrel | 6795 6169 | 6036 | 5835 | 5043 | 4369 | |
| Prasugrel | 6813 6305 | 6177 | 5951 | 5119 | 4445 | |

Effient: 19% reduction
in primary end point

N Engl J Med 2007; 357:2001-2015




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9333 | 8628 | 8460 | 8219 | 6743 | 5161 | 4147 |
| Clopidogrel | 9291 | 8521 | 8362 | 8124 | 6650 | 5096 | 4047 |

Brilinta: 16% reduction
in primary end point

N Engl J Med 2009; 361:1045-1057

**Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.***

| End Point | Prasugrel (N=6741) | Clopidogrel (N=6716) | Hazard Ratio for Prasugrel (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| Non–CABG-related TIMI major bleeding (key safety end point) | 146 (2.4) | 111 (1.8) | 1.32 (1.03–1.68) | 0.03 |
| Related to instrumentation | 45 (0.7) | 38 (0.6) | 1.18 (0.77–1.82) | 0.45 |
| Spontaneous | 92 (1.6) | 61 (1.1) | 1.51 (1.09–2.08) | 0.01 |
| Related to trauma | 9 (0.2) | 12 (0.2) | 0.75 (0.32–1.78) | 0.51 |
| Life-threatening† | 85 (1.4) | 56 (0.9) | 1.52 (1.08–2.13) | 0.01 |
| Related to instrumentation | 28 (0.5) | 18 (0.3) | 1.55 (0.86–2.81) | 0.14 |
| Spontaneous | 50 (0.9) | 28 (0.5) | 1.78 (1.12–2.83) | 0.01 |
| Related to trauma | 7 (0.1) | 10 (0.2) | 0.70 (0.27–1.84) | 0.47 |
| Fatal‡ | 21 (0.4) | 5 (0.1) | 4.19 (1.58–11.11) | 0.002 |
| Nonfatal | 64 (1.1) | 51 (0.9) | 1.25 (0.87–1.81) | 0.23 |
| Intracranial | 19 (0.3) | 17 (0.3) | 1.12 (0.58–2.15) | 0.74 |
| Major or minor TIMI bleeding | 303 (5.0) | 231 (3.8) | 1.31 (1.11–1.56) | 0.002 |
| Bleeding requiring transfusion§ | 244 (4.0) | 182 (3.0) | 1.34 (1.11–1.63) | <0.001 |
| CABG-related TIMI major bleeding¶ | 24 (13.4) | 6 (3.2) | 4.73 (1.90–11.82) | <0.001 |

* The data shown are for patients who received at least one dose of the study drug and for end points occurring within 7 days after the study drug was discontinued or occurring within a longer period if the end point was believed by the local investigator to be related to the use of the study drug. Percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. CABG denotes coronary-artery bypass grafting.

† The most frequent sites of life-threatening bleeding were gastrointestinal sites, intracranial sites, the puncture site, and retroperitoneal sites.

‡ One patient in the clopidogrel group had a fatal gastrointestinal hemorrhage while receiving the study medication, but hemoglobin testing was not performed and, therefore, the criteria for TIMI major bleeding (including life-threatening and fatal bleeding) could not be applied and the data do not appear in this table.

§ Transfusion was defined as any transfusion of whole blood or packed red cells.

¶ For major bleeding related to CABG, the total number of patients were all patients who had received at least one dose of prasugrel or clopidogrel before undergoing CABG: 179 and 189, respectively. The ratio is the odds ratio, rather than the hazard ratio, and was evaluated with the use of the Cochran–Mantel–Haenszel test.

**Table 4. Safety of the Study Drugs.***

| End Point | Ticagrelor Group | Clopidogrel Group | Hazard or Odds Ratio for Ticagrelor Group (95% CI)† | P Value |
|---|---|---|---|---|
| Primary safety end points — no./total no. (%) | | | | |
| Major bleeding, study criteria | 961/9235 (11.6) | 929/9186 (11.2) | 1.04 (0.95–1.13) | 0.43 |
| Major bleeding, TIMI criteria‡ | 657/9235 (7.9) | 638/9186 (7.7) | 1.03 (0.93–1.15) | 0.57 |
| Bleeding requiring red-cell transfusion | 818/9235 (8.9) | 809/9186 (8.9) | 1.00 (0.91–1.11) | 0.96 |
| Life-threatening or fatal bleeding, study criteria | 491/9235 (5.8) | 480/9186 (5.8) | 1.03 (0.90–1.16) | 0.70 |
| Fatal bleeding | 20/9235 (0.3) | 23/9186 (0.3) | 0.87 (0.48–1.59) | 0.66 |
| Nonintracranial fatal bleeding | 9/9235 (0.1) | 21/9186 (0.3) | | 0.03 |
| Intracranial bleeding | 26/9235 (0.3) | 14/9186 (0.2) | 1.87 (0.98–3.58) | 0.06 |
| Fatal | 11/9235 (0.1) | 1/9186 (0.01) | | 0.02 |
| Nonfatal | 15/9235 (0.2) | 13/9186 (0.2) | | 0.69 |
| Secondary safety end points — no./total no. (%) | | | | |
| Non–CABG-related major bleeding, study criteria | 362/9235 (4.5) | 306/9186 (3.8) | 1.19 (1.02–1.38) | 0.03 |
| Non–CABG-related major bleeding, TIMI criteria | 221/9235 (2.8) | 177/9186 (2.2) | 1.25 (1.03, 1.53) | 0.03 |
| CABG-related major bleeding, study criteria | 619/9235 (7.4) | 654/9186 (7.9) | 0.95 (0.85–1.06) | 0.32 |
| CABG-related major bleeding, TIMI criteria | 446/9235 (5.3) | 476/9186 (5.8) | 0.94 (0.82–1.07) | 0.32 |
| Major or minor bleeding, study criteria | 1339/9235 (16.1) | 1215/9186 (14.6) | 1.11 (1.03–1.20) | 0.008 |
| Major or minor bleeding, TIMI criteria‡ | 946/9235 (11.4) | 906/9186 (10.9) | 1.05 (0.96–1.15) | 0.33 |
| Dyspnea — no./total no. (%) | | | | |
| Any | 1270/9235 (13.8) | 721/9186 (7.8) | 1.84 (1.68–2.02) | <0.001 |
| Requiring discontinuation of study treatment | 79/9235 (0.9) | 13/9186 (0.1) | 6.12 (3.41–11.01) | <0.001 |
| Bradycardia — no./total no. (%) | | | | |
| Pacemaker insertion | 82/9235 (0.9) | 79/9186 (0.9) | | 0.87 |
| Syncope | 100/9235 (1.1) | 76/9186 (0.8) | | 0.08 |
| Bradycardia | 409/9235 (4.4) | 372/9186 (4.0) | | 0.21 |
| Heart block | 67/9235 (0.7) | 66/9186 (0.7) | | 1.00 |
| Holter monitoring — no./total no. (%) | | | | |
| First week | | | | |
| Ventricular pauses ≥3 sec | 84/1451 (5.8) | 51/1415 (3.6) | | 0.01 |
| Ventricular pauses ≥5 sec | 29/1451 (2.0) | 17/1415 (1.2) | | 0.10 |
| At 30 days | | | | |
| Ventricular pauses ≥3 sec | 21/985 (2.1) | 17/1006 (1.7) | | 0.52 |
| Ventricular pauses ≥5 sec | 8/985 (0.8) | 6/1006 (0.6) | | 0.60 |
| Neoplasm arising during treatment — no. of patients/ total no. (%) | | | | |
| Any | 132/9235 (1.4) | 155/9186 (1.7) | | 0.17 |
| Malignant | 115/9235 (1.2) | 121/9186 (1.3) | | 0.69 |
| Benign | 18/9235 (0.2) | 35/9186 (0.4) | | 0.02 |
| Increase in serum uric acid from baseline value — % | | | | |
| At 1 mo | 14±46 | 7±44 | | <0.001 |
| At 12 mo | 15±52 | 7±31 | | <0.001 |
| 1 Mo after end of treatment | 7±43 | 8±48 | | 0.56 |
| Increase in serum creatinine from baseline value — % | | | | |
| At 1 mo | 10±22 | 8±21 | | <0.001 |
| At 12 mo | 11±22 | 9±22 | | <0.001 |
| 1 Mo after end of treatment | 10±22 | 10±22 | | 0.59 |

* Plus–minus values are means ±SD. Data are shown for patients who received at least one dose of the study drug for events occurring up to 7 days after permanent discontinuation of the study drug. The percentages for the primary and secondary safety end points are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have more than one type of end point. CABG denotes coronary-artery bypass grafting.

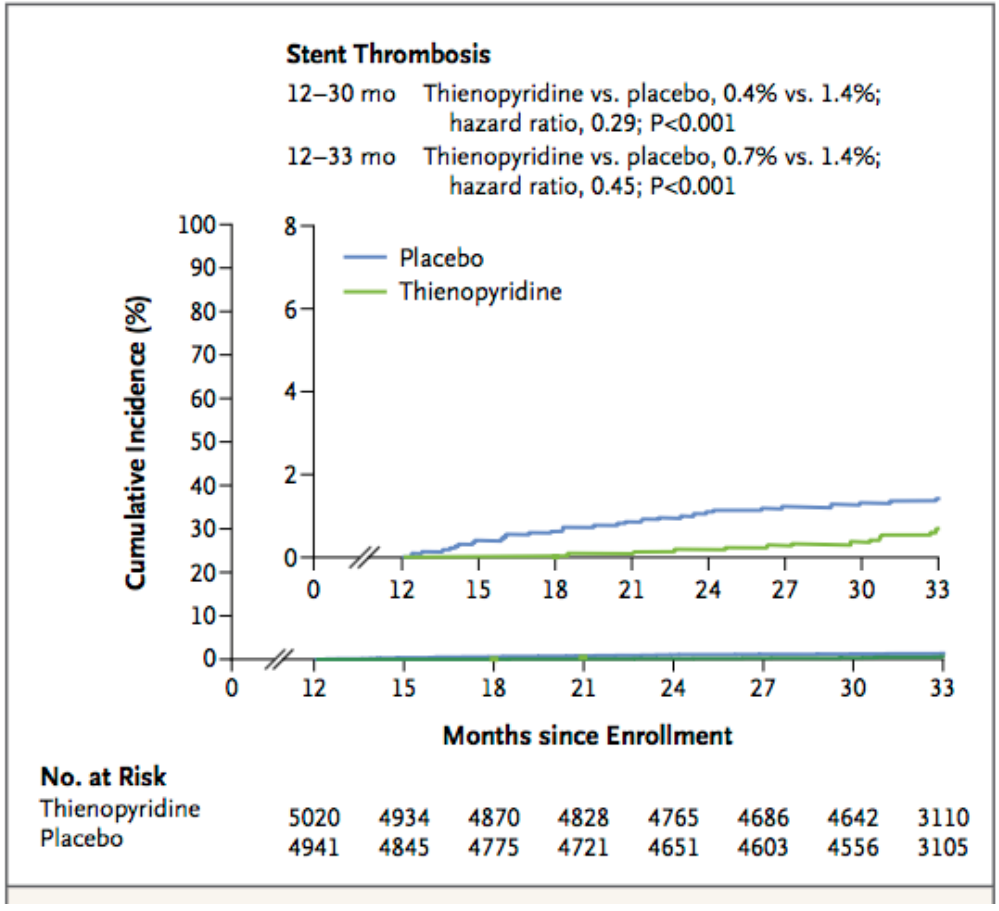
† Hazard ratios are shown for all safety end points except bleeding requiring red-cell transfusion, for which odds ratios are shown. P values for the odds ratios were calculated with the use of Fisher's exact test.

‡ Major bleeding and major or minor bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria refer to nonadjudicated events analyzed with the use of a statistically programmed analysis in accordance with previously used definitions.[10]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

# Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents



## TABLE 1. DAPT SCORE POINTS

| Variable | Points | Variable | Points |
|---|---|---|---|
| Age | | MI at presentation | 1 |
| ≥ 75 years | −2 | Previous PCI or previous MI | 1 |
| 65 to < 75 years | −1 | Stent diameter < 3 mm | 1 |
| < 65 years | 0 | CHF or LVEF < 30% | 2 |
| Current cigarette smoker | 1 | Vein graft PCI | 2 |
| Diabetes mellitus | 1 | Paclitaxel-eluting stent | 1 |

Abbreviations: CHF, congestive heart failure; DAPT, dual-antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

**Among patients who have not had a major ischemic or bleeding event within the first year after PCI:**

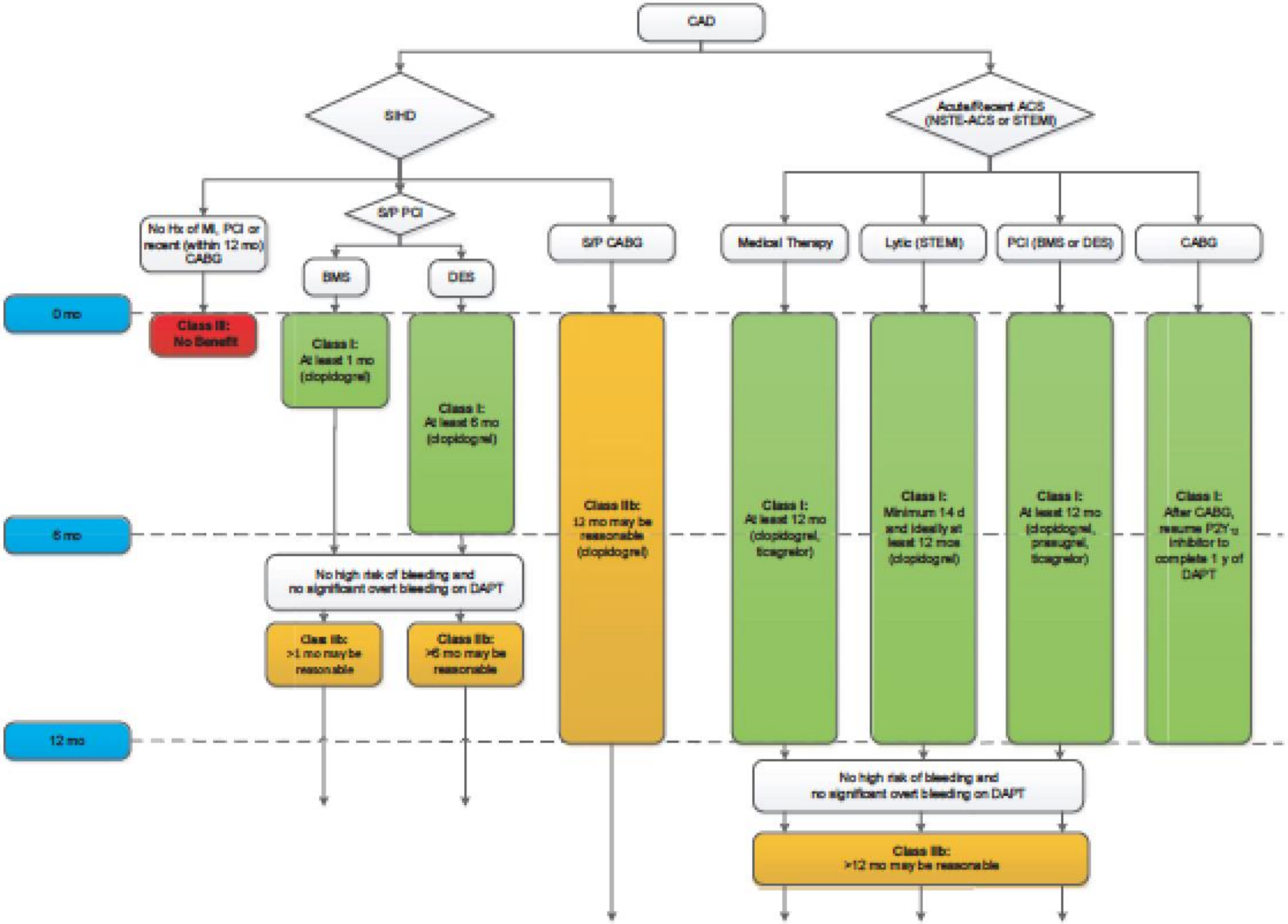
**The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, and patients for whom bleeding risks outweighed ischemic benefits.**

**Low DAPT Score (< 2)**
NNT to prevent ischemia = 153
NNH to cause bleeding = 64

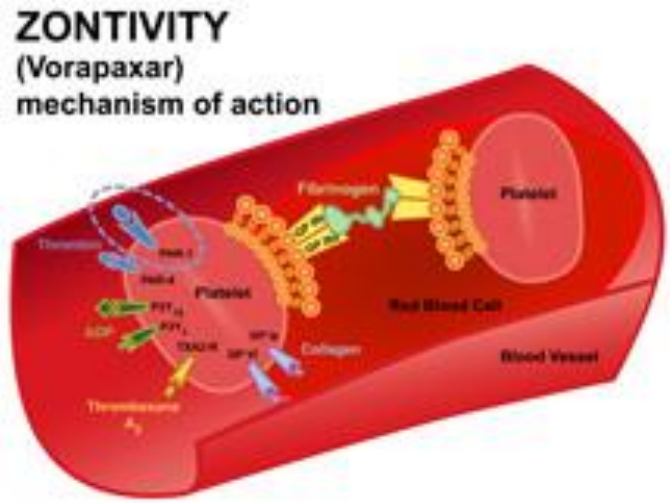
**High DAPT Score ≥ 2**
NNT to prevent ischemia = 34
NNH to cause bleeding = 272


**DAPT Score may help clinicians decide *who should, and who should not* be treated with extended DAPT**

**FIGURE 1** Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT



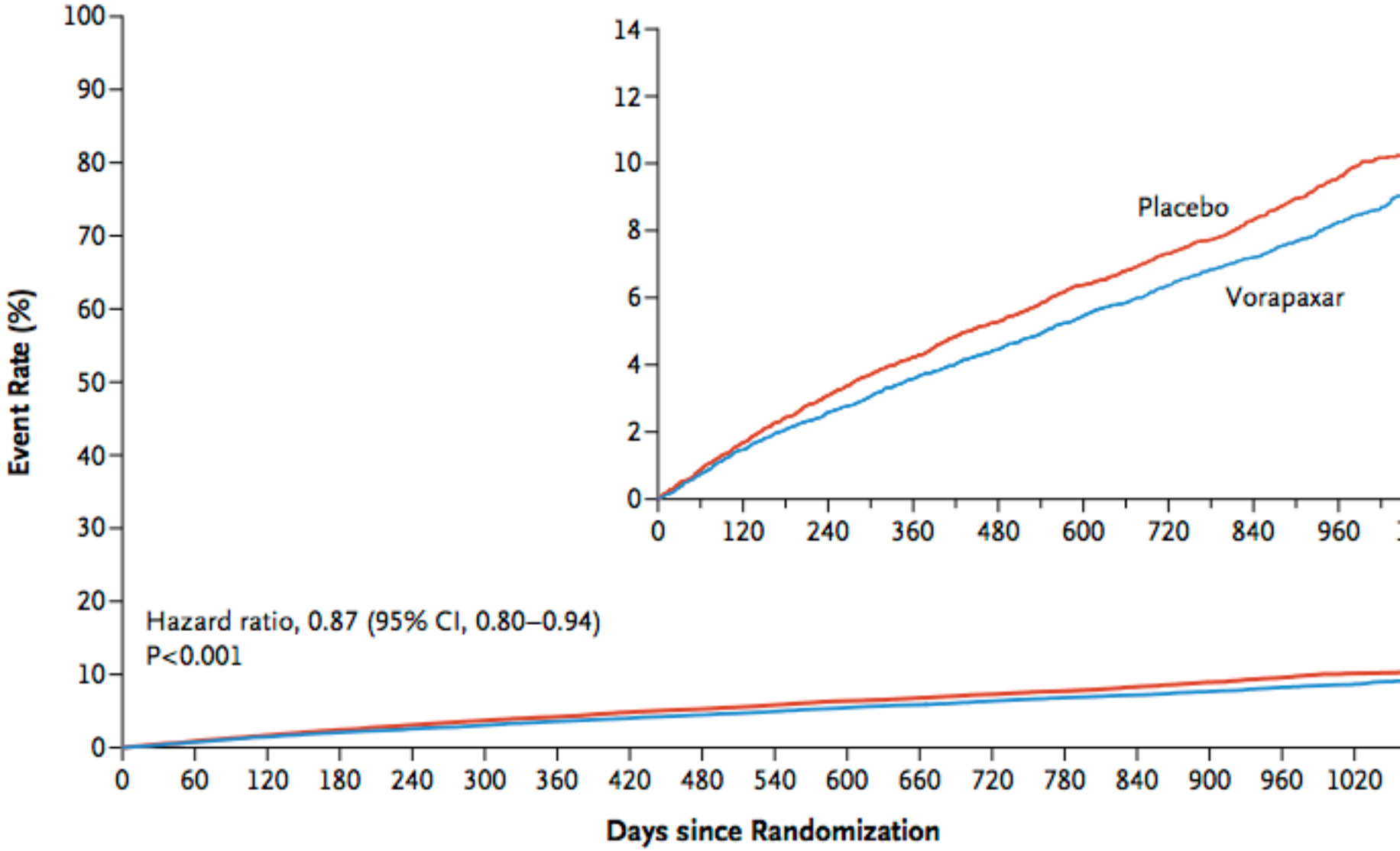
Thrombin potently activates platelets through the protease-activated receptor PAR-1. Vorapaxar is a novel antiplatelet agent that selectively inhibits the cellular actions of thrombin through antagonism of PAR-1.




- **Do not use ZONTIVITY in patients with a history of stroke, transient ischemic attack (TIA), or intracranial hemorrhage (ICH); or active pathological bleeding.**

ZONTIVITY is a protease-activated receptor-1 (PAR-1) antagonist indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD), with greater efficacy in diabetics than non-diabetics. ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.

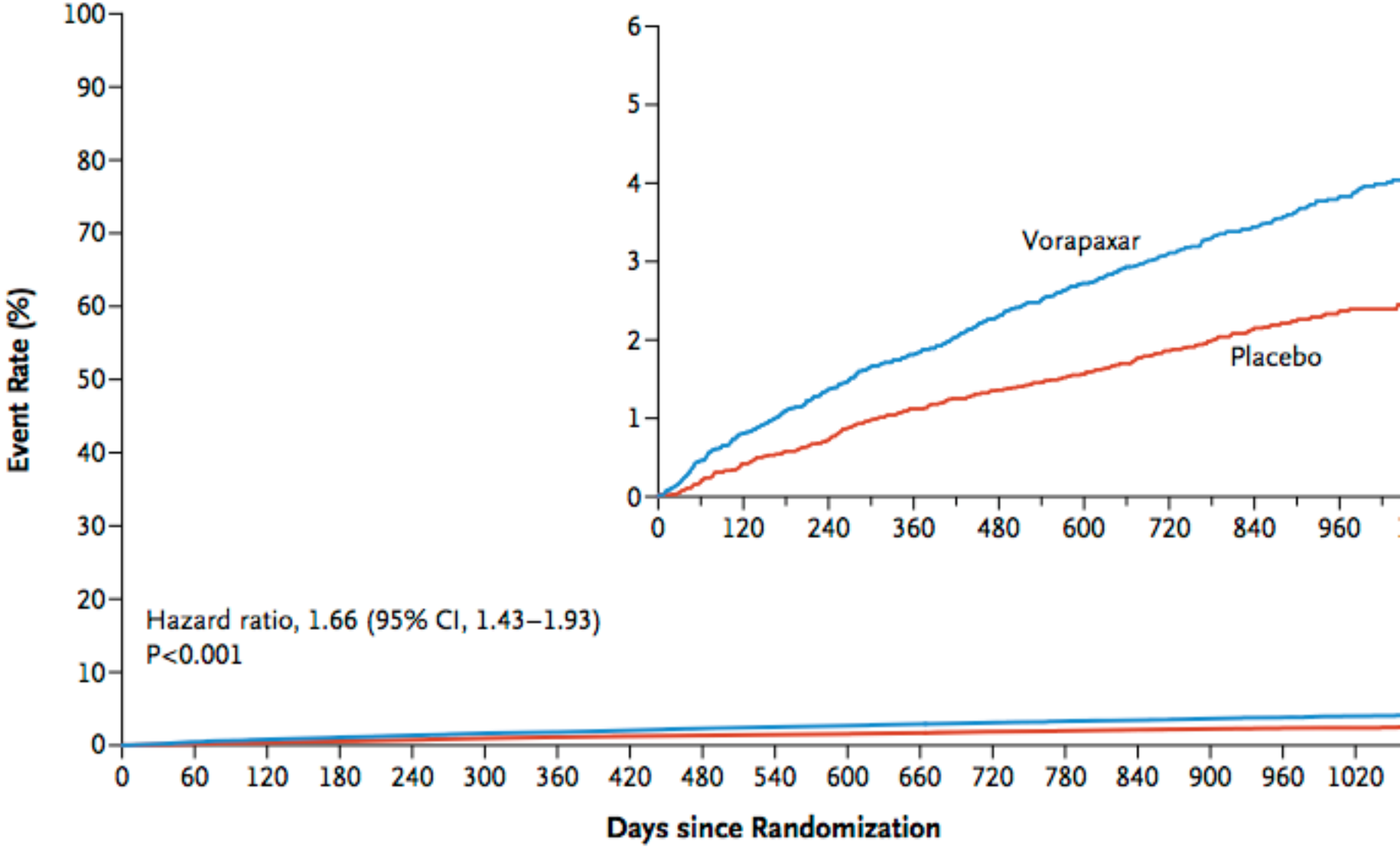
eath from Cardiovascular Causes, Myocardial Infarction, or Stroke




. at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| cebo | 13,224 | 12,727 | 12,365 | 12,013 | 9,366 | 6,239 |
| apaxar | 13,225 | 12,784 | 12,479 | 12,162 | 9,463 | 6,287 |

USTO Moderate or Severe Bleeding




. at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| cebo | 13,166 | 12,311 | 11,620 | 11,120 | 9,334 | 6,039 |
| rapaxar | 13,186 | 12,235 | 11,570 | 10,997 | 9,174 | 5,963 |

The apparent terminal elimination half-life for vorapaxar is approximately **8 days** (range 5-13 days) and is similar for the active metabolite. Inhibition of TRAP-induced platelet aggregation at a level of 50% can be expected at 4 weeks after discontinuation of daily doses of ZONTIVITY 2.08 mg, consistent with the terminal elimination half-life of vorapaxar

N Engl J Med 2012; 366:1404-1413

**Table 2. Efficacy and Bleeding End Points at 3 Years.***

| End Point | Vorapaxar | Placebo | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *number (percent)* | | | |
| **Efficacy** | 13,225 | 13,224 | | |
| Cardiovascular death, myocardial infarction, or stroke | 1028 (9.3) | 1176 (10.5) | 0.87 (0.80–0.94) | <0.001 |
| Cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization | 1259 (11.2) | 1417 (12.4) | 0.88 (0.82–0.95) | 0.001 |
| Cardiovascular death or myocardial infarction | 789 (7.3) | 913 (8.2) | 0.86 (0.78–0.94) | 0.002 |
| Cardiovascular death | 285 (2.7) | 319 (3.0) | 0.89 (0.76–1.04) | 0.15 |
| Myocardial infarction | 564 (5.2) | 673 (6.1) | 0.83 (0.74–0.93) | 0.001 |
| Stroke | | | | |
| Any stroke | 315 (2.8) | 324 (2.8) | 0.97 (0.83–1.14) | 0.73 |
| Ischemic stroke | 250 (2.2) | 294 (2.6) | 0.85 (0.72–1.01) | 0.06 |
| Urgent coronary revascularization | 279 (2.5) | 316 (2.6) | 0.88 (0.75–1.03) | 0.11 |
| Death from any cause | 540 (5.0) | 565 (5.3) | 0.95 (0.85–1.07) | 0.41 |
| **Bleeding** | 13,186 | 13,166 | | |
| GUSTO moderate or severe | 438 (4.2) | 267 (2.5) | 1.66 (1.43–1.93) | <0.001 |
| TIMI | | | | |
| Clinically significant | 1759 (15.8) | 1241 (11.1) | 1.46 (1.36–1.57) | <0.001 |
| Non–CABG-related major | 287 (2.8) | 198 (1.8) | 1.46 (1.22–1.75) | <0.001 |
| CABG-related major† | 11 (7.6) | 10 (6.1) | 1.13 (0.48–2.66) | 0.79 |
| Fatal | 29 (0.3) | 20 (0.2) | 1.46 (0.82–2.58) | 0.19 |
| Intracranial | 102 (1.0) | 53 (0.5) | 1.94 (1.39–2.70) | <0.001 |
| Intracerebral | 89 (0.8) | 41 (0.4) | 2.19 (1.51–3.17) | <0.001 |
| Subdural or epidural | 12 (0.1) | 10 (0.1) | 1.20 (0.52–2.79) | 0.67 |
| Unknown | 1 (<0.1) | 2 (<0.1) | | |
| **Net clinical outcome** | 13,186 | 13,166 | | |
| Cardiovascular death, myocardial infarction, stroke, or GUSTO moderate or severe bleeding | 1315 (11.7) | 1358 (12.1) | 0.97 (0.90–1.04) | 0.40 |
| Cardiovascular death, myocardial infarction, stroke, urgent coronary revascularization, or GUSTO moderate or severe bleeding | 1526 (13.4) | 1593 (14.0) | 0.96 (0.89–1.02) | 0.20 |
| Death from any cause, myocardial infarction, stroke, or GUSTO severe bleeding | 1322 (11.9) | 1436 (12.8) | 0.92 (0.85–0.99) | 0.02 |

* Percentages are cumulative Kaplan–Meier event rates at 3 years. The stroke component in all efficacy end points included all ischemic and hemorrhagic strokes, unless otherwise specified. Urgent coronary revascularization was defined by recurrent ischemia leading to urgent coronary revascularization. CABG denotes coronary-artery bypass grafting, GUSTO Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.
† CABG-related major bleeding was assessed in 175 patients in the vorapaxar group and 201 patients in the placebo group.

# Why was my patient bleeding? (2016)

- Focused on:
  - Afib: definition of valvular Afib; similar CVA risk in paroxysmal v permanent; similar risk in Aflutter; differences between CHADS2 v CHADSVASC score; heparin bridging of warfarin therapy; renal adjustment of and drug-drug interactions with DOACs; state of reversal agents (Praxbind)
  - Dosing of NOACs in other indications including prophylaxis or treatment of DVT/PE
  - CAD: P2Y12 pharmacokinetics, efficacy and bleeding risk, indications in NSTEMI v routine PCI, DAPT score and duration post NSTEMI PCI, long term ticagrelor (Brilinta) in CAD; unique antiplatelets like voxapar (Zontivity) (half-life!)
  - Combined use of Coumadin plus antiplatelets for CAD plus Afib:
    - Double v triple therapy: WOEST Trial

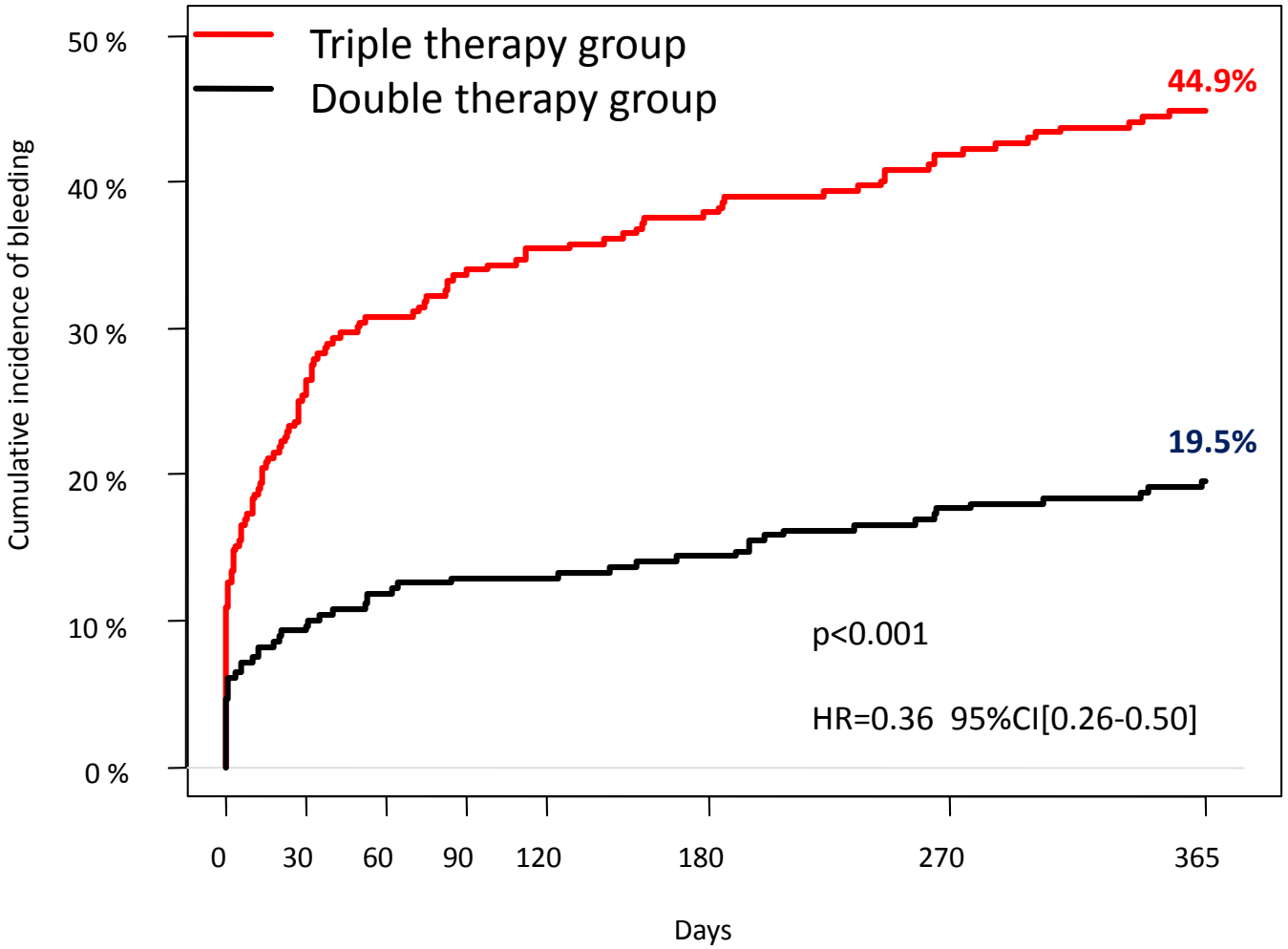
# The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet, Jurriën ten Berg

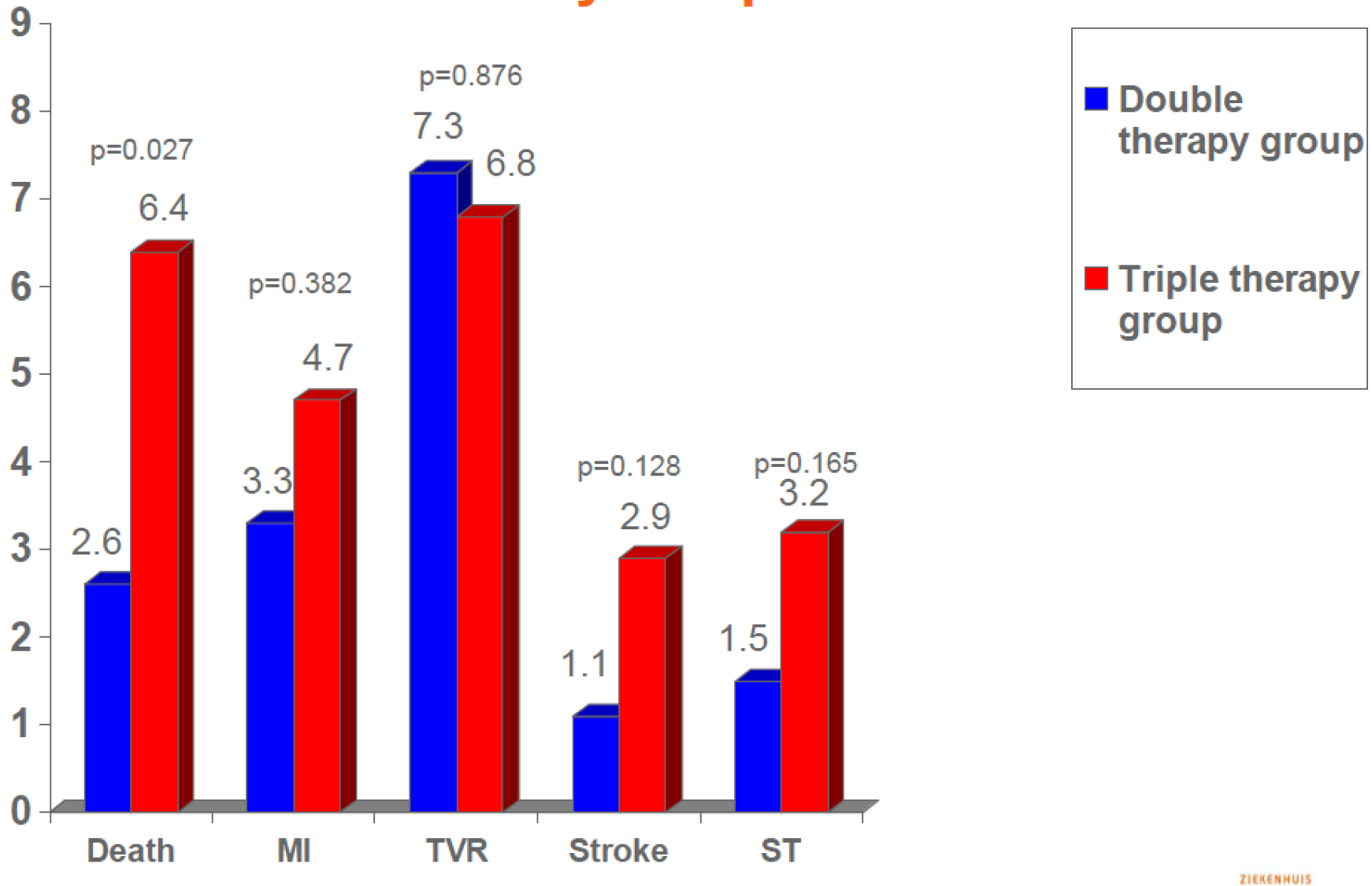
The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing (clinicaltrials.gov NCT00769938)

Disclosures/Conflict of interest: none

# Primary Endpoint: Total number of TIMI bleeding events



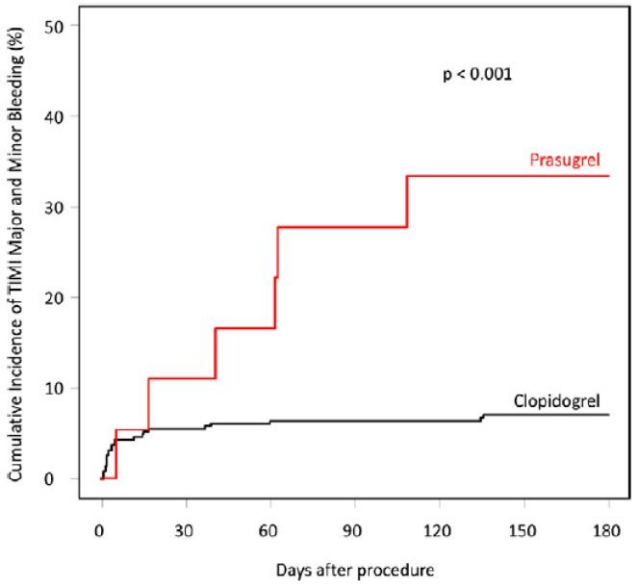
# Secondary Endpoint

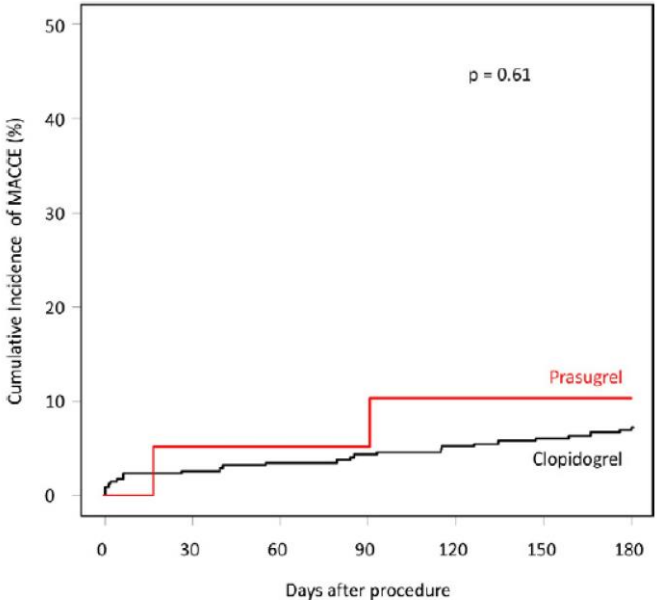



MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

ZIEKENHUIS ST ANTONIUS

# Prasugrel v clopidogrel in Triple Therapy

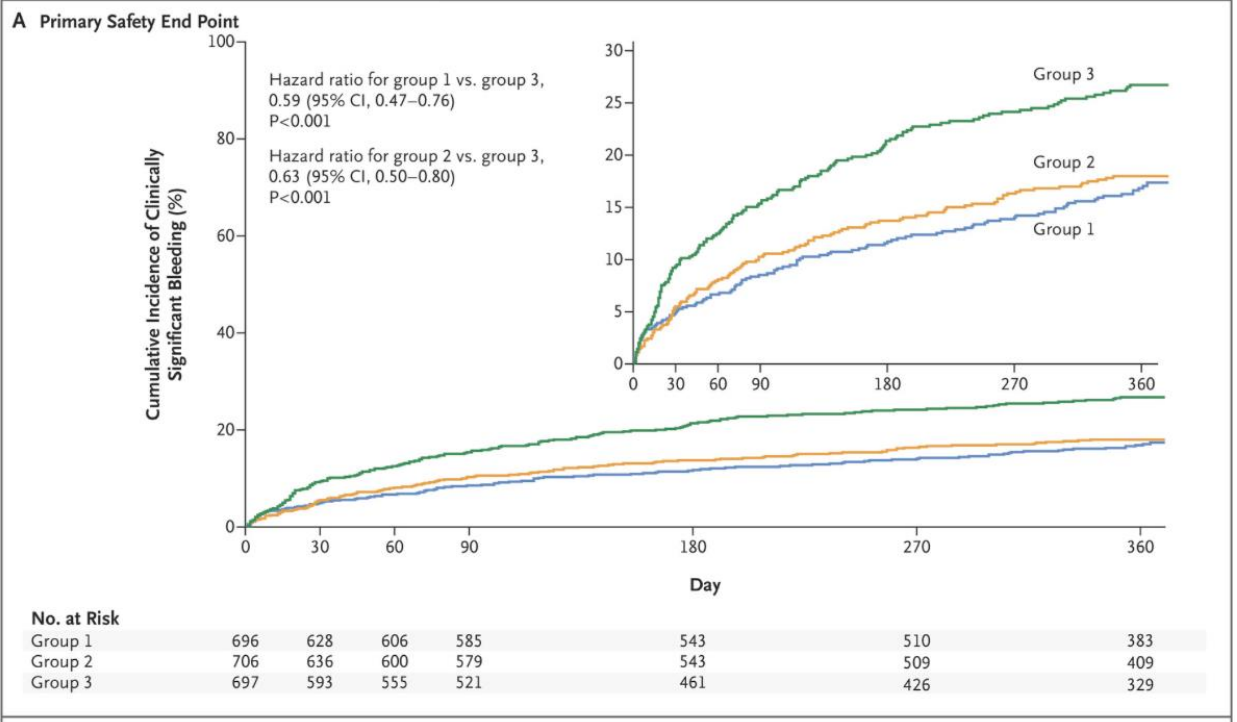


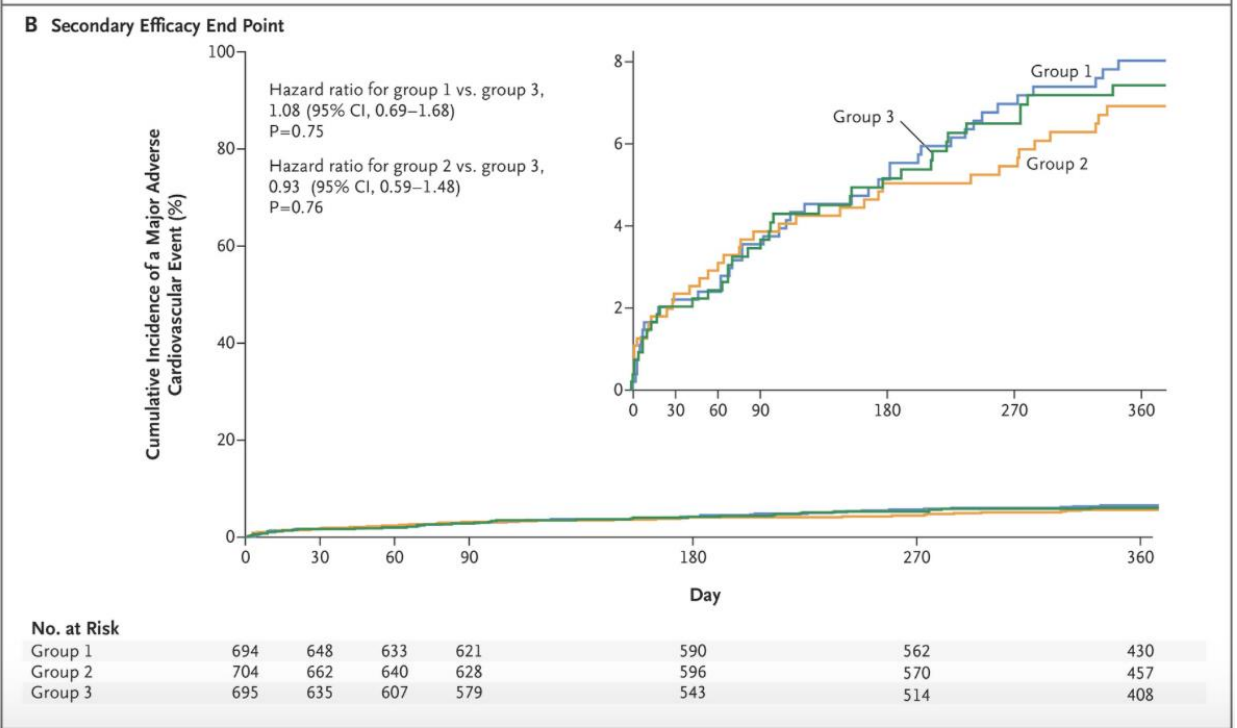




- 377 patients:
  - drug-eluting stent implantation with an indication for oral anticoagulation (VKA) and were treated with a 6-month regimen of aspirin and oral anticoagulation with either prasugrel or clopidogrel.
- Primary endpoint:
  - composite of Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding at 6 months.
- Secondary endpoint:
  - was a composite of death, myocardial infarction, ischemic stroke, or definite stent thrombosis.

(J Am Coll Cardiol 2013;61:2060–6)

From this time forth P2Y12 in triple therapy means clopidogrel/ticagrelor.



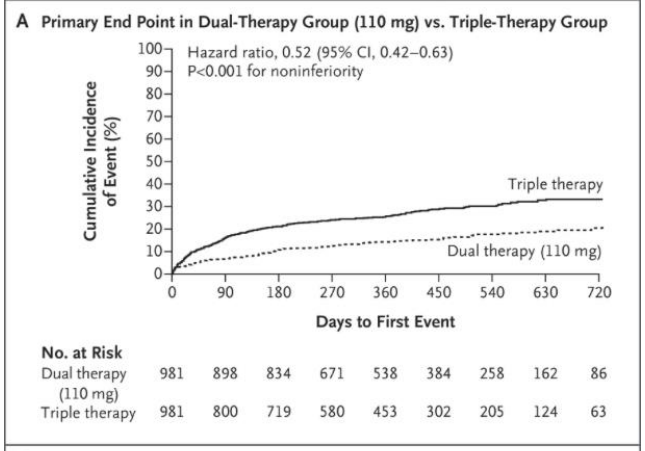

# Pioneer AF-PCI

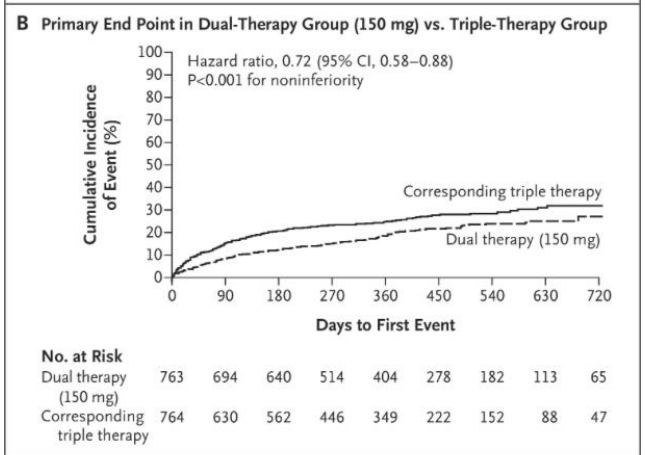
- Group 1:
  - P2Y12 plus rivaroxiban 15 mg daily for 12 mo;
- Group 2:
  - DAPT plus rivaroxaban 2.5 BID for 1,6 or 12 mo;
- Group 3:
  - DAPT plus VKA for 1, 6 or 12 mo.
- Primary end point:
  - “clinically significant bleeding”
- Secondary endpoint:
  - CV death, MI, CVA

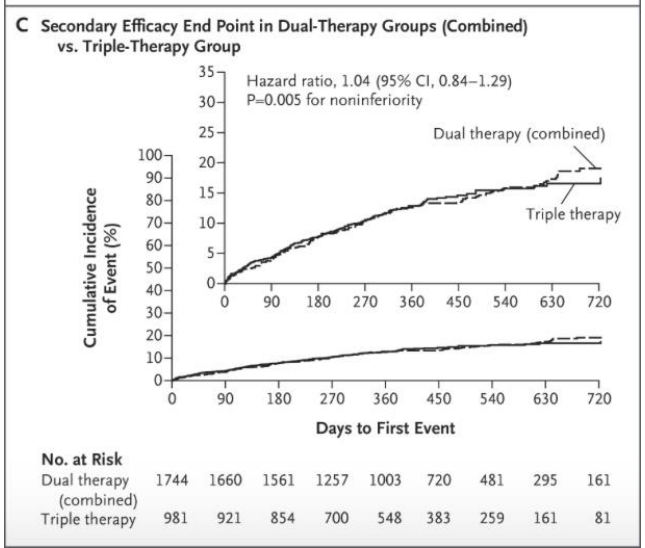
N Engl J Med 2016; 375:2423-2434

# AF Complicating ACS

| Recommendations for AF Complicating ACS | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **IIa** | **B-R** | **In patents with AF at increased risk of stroke (based on $CHA_2DS_2$-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy.**<br>**NEW**: New RCT data and data from 2 registries and a retrospective cohort study are available. |
| **IIa** | **B-R** | **In patients with AF at increased risk of stroke (based on $CHA_2DS_2$-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with $P2Y_{12}$ inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy.**<br>**NEW**: New published data are available. |



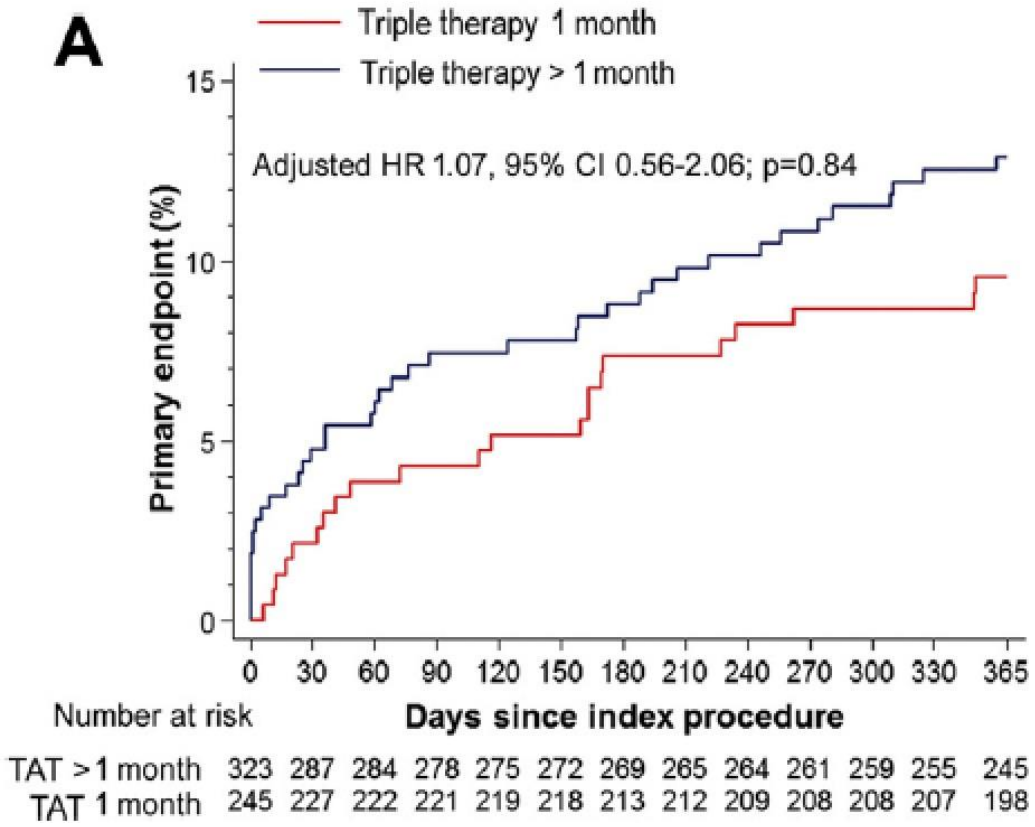




# RE-DUAL PCI Trial

- VKA plus P2Y12 (clopidogrel or ticagrelor) plus ASA versus dabigatran (110 or 150 BID) plus P2Y12 without ASA.
- Primary end point “major or clinically relevant bleeding.”
- Secondary endpoint thromboembolic events (MI, CVA, SE), death or unplanned revascularization.

N Engl J Med 2017; 377:1513-1524




## Bern PCI Registry

- 568 patients with indications for oral anticoagulation, who under went BMS(21%)/DES(79%) stenting:
  - 245 (43%) were discharged on a regimen of 1-month TAT and
  - 323 (57%) on a regimen >1-month TAT (mean 5.1±3.3 months, median 3 months).

- Primary endpoint:
  - composite of cardiac death, myocardial infarction, stroke, definite stent thrombosis, or TIMI (Thrombolysis in Myocardial Infarction) major bleeding within 1 year.

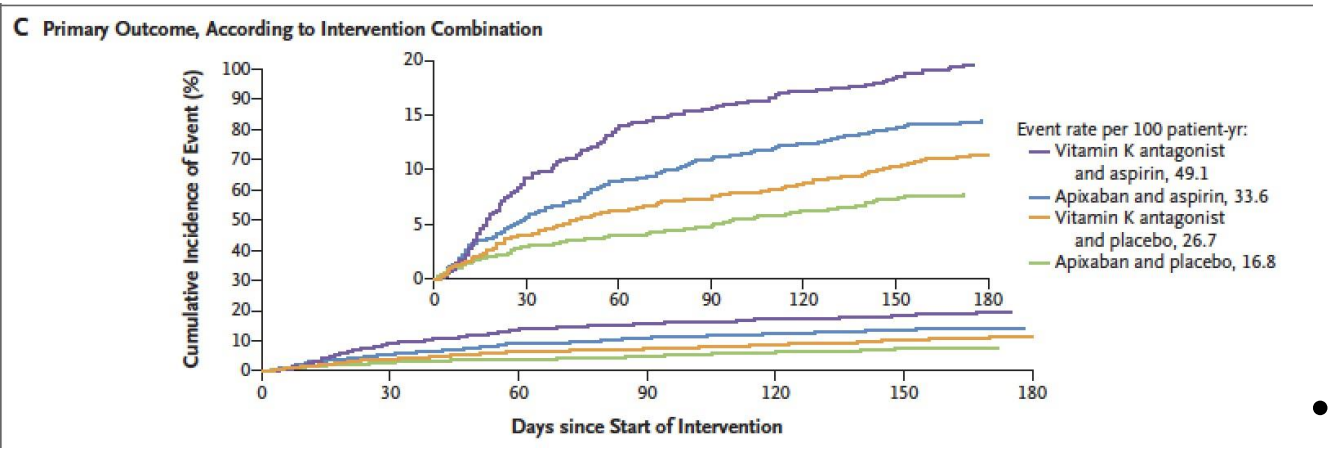
(J Am Coll Cardiol Intv 2016;9:1473–83)

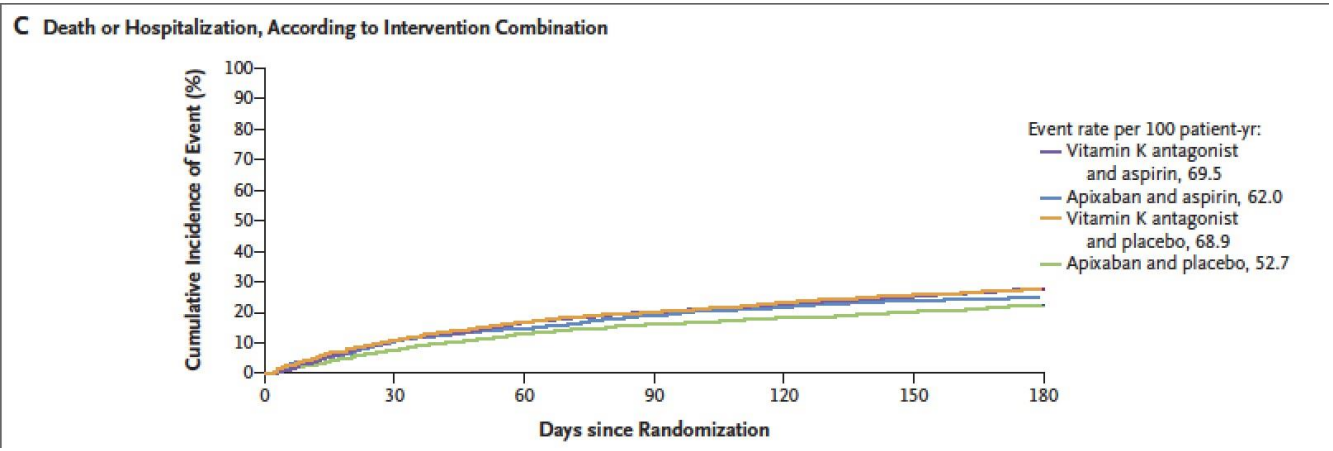
# AF Complicating ACS

| Recommendations for AF Complicating ACS | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **IIa** | **B-R** | **In patients with AF at increased risk of stroke (based on $CHA_2DS_2$-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy.**<br>**NEW**: New published data are available. |
| **IIb** | **B-R** | **If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF who are at increased risk of stroke (based on $CHA_2DS_2$-VASc risk score of 2 or greater) and who have undergone PCI with stenting (drug eluting or bare metal) for ACS, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at 4 to 6 weeks may be considered.**<br>**NEW**: New published data are available. |

# AGUSTUS

4614 patients, Afib and ACS or stable PCI, taking P2Y12…



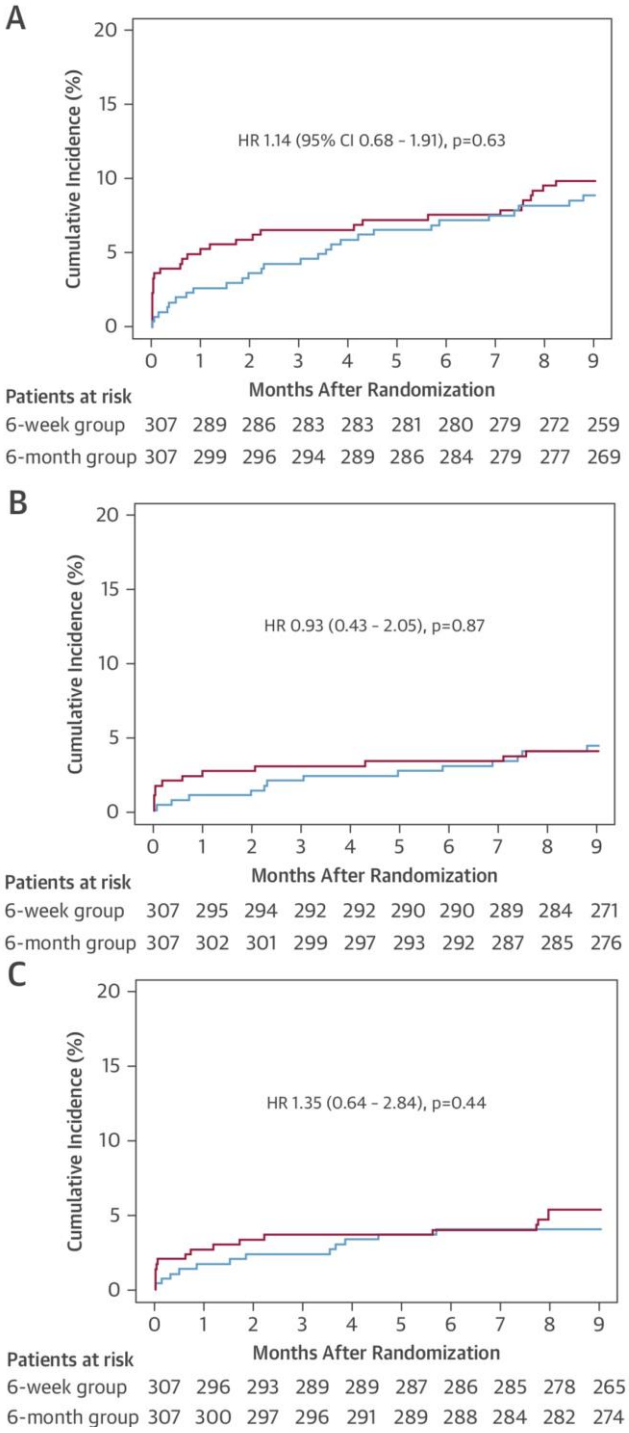




- Two-by-two factorial design:
  - of apixaban or a VKA and to receive aspirin or matching placebo for 6 months
- Primary outcome:
  - major or clinically relevant nonmajor bleeding

Secondary outcomes

- included death or hospitalization and a composite of ischemic events

This article was published on March 17, 2019, at NEJM.org.




**ISAR Triple Trial:**

614 stable CAD patients with DES, clopidogrel for 6 weeks or 6 months, plus VKA plus ASA:

- Primary endpoint (A):
  - composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months.
- Secondary endpoints:
  - (B): combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke;
  - (C) TIMI major bleeding.

(Why bother using BMS in Afib patients?)

J Am Coll Cardiol 2015;65:1619–29

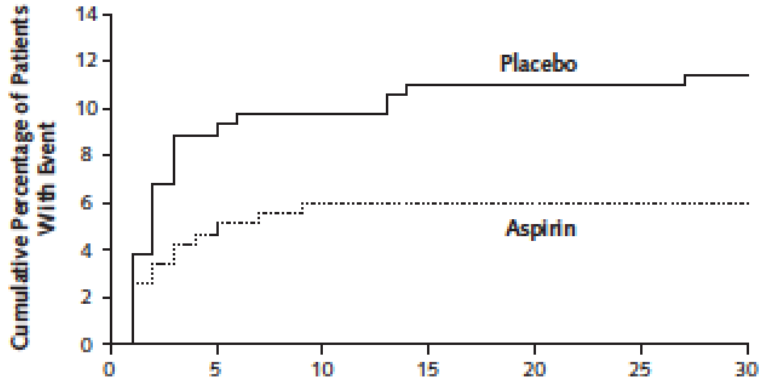
Annals of Internal Medicine

ORIGINAL RESEARCH

# Aspirin in Patients With Previous Percutaneous Coronary Intervention Undergoing Noncardiac Surgery

Michelle M. Graham, MD; Daniel I. Sessler, MD; Joel L. Parlow, MD, MSc; Bruce M. Biccard, MBChB, MMedSci, PhD; Gordon Guyatt, MD, MSc; Kate Leslie, MBBS, MD, MEpi; Matthew T.V. Chan, MBBS, PhD; Christian S. Meyhoff, MD, PhD; Denis Xavier, MD, MSc; Alben Sigamani, MBBS, MD; Priya A. Kumar, MD; Marko Mrkobrada, MD, MSc; Deborah J. Cook, MD, MSc; Vikas Tandon, MD; Jesus Alvarez-Garcia, MD, PhD; Juan Carlos Villar, MD, PhD; Thomas W. Painter, MBChB; Giovanni Landoni, MD; Edith Fleischmann, MD; Andre Lamy, MD, MSc; Richard Whitlock, MD, PhD; Yannick Le Manach, MD, PhD; Meylin Aphang-Lam, MD; Juan P. Cata, MD; Peggy Gao, MSc; Nicolaas C.S. Terblanche, MD, MMed; Pamidimukkala V. Ramana, MBBS; Kim A. Jamieson, MBChB; Amal Bessissow, MD, MSc; Gabriela R. Mendoza, MD; Silvia Ramirez, MD; Pierre A. Diemunsch, MD, PhD; Salim Yusuf, MD, DPhil; and P.J. Devereaux, MD, PhD

*Figure 2.* Effect of aspirin on risk for composite of death and nonfatal myocardial infarction among patients with a history of percutaneous coronary intervention.

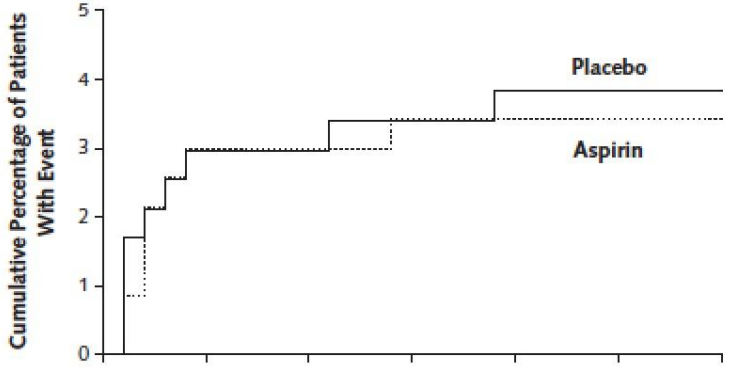



Patients at risk, *n*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 236 | 215 | 212 | 209 | 209 | 209 | 208 |
| Aspirin | 234 | 223 | 221 | 221 | 221 | 221 | 221 |

*P* for interaction = 0.036.

*Figure 3.* Effect of aspirin on risk for major bleeding among patients with a history of percutaneous coronary intervention.




Patients at risk, *n*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 236 | 228 | 225 | 224 | 223 | 223 | 223 |
| Aspirin | 234 | 228 | 227 | 226 | 226 | 226 | 226 |

*P* for interaction = 0.73.

*Ann Intern Med.* doi:10.7326/M17-2341
This article was published at Annals.org on 14 November 2017.

Original Investigation

FREE

February 2017

# Assessment of Use vs Discontinuation of Oral Anticoagulation After Pulmonary Vein Isolation in Patients With Atrial Fibrillation

Sara Själander, MD, PhD[1]; Fredrik Holmqvist, MD, PhD[2,3]; J. Gustav Smith, MD, PhD[3,4]; et al

» Author Affiliations | Article Information

*JAMA Cardiol.* 2017;2(2):146-152. doi:10.1001/jamacardio.2016.4179

From: **Assessment of Use vs Discontinuation of Oral Anticoagulation After Pulmonary Vein Isolation in Patients With Atrial Fibrillation**

JAMA Cardiol. 2017;2(2):146-152. doi:10.1001/jamacardio.2016.4179

**Table 2. Cardiovascular Events per Year of Follow-up After PVI**

| $CHA_2DS_2$-VASc Score | Events While Taking Warfarin Sodium, No. (% per Year) | | | Events While Not Taking Warfarin Sodium, No. (% per Year) | | |
|---|---|---|---|---|---|---|
| | Ischemic Stroke | Intracranial hemorrhage | Death | Ischemic Stroke | Intracranial hemorrhage | Death |
| <2 | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 | 1 (0.1) |
| ≥2 | 4 (0.3) | 2 (0.2) | 6 (0.5) | 5 (1.6)[a] | 0 | 3 (0.9) |

Abbreviations: $CHA_2DS_2$-VASc, congestive heart failure, hypertension, age 75 years or older (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 years, sex category (female); PVI, pulmonary vein isolation.

[a] $P = .046$ comparing patients taking and not taking warfarin.

Table Title:

Cardiovascular Events per Year of Follow-up After PVI

"These findings indicate that discontinuation of warfarin treatment is not safe after PVI in high risk patients, especially those who have previously experienced an ischemic stroke."

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

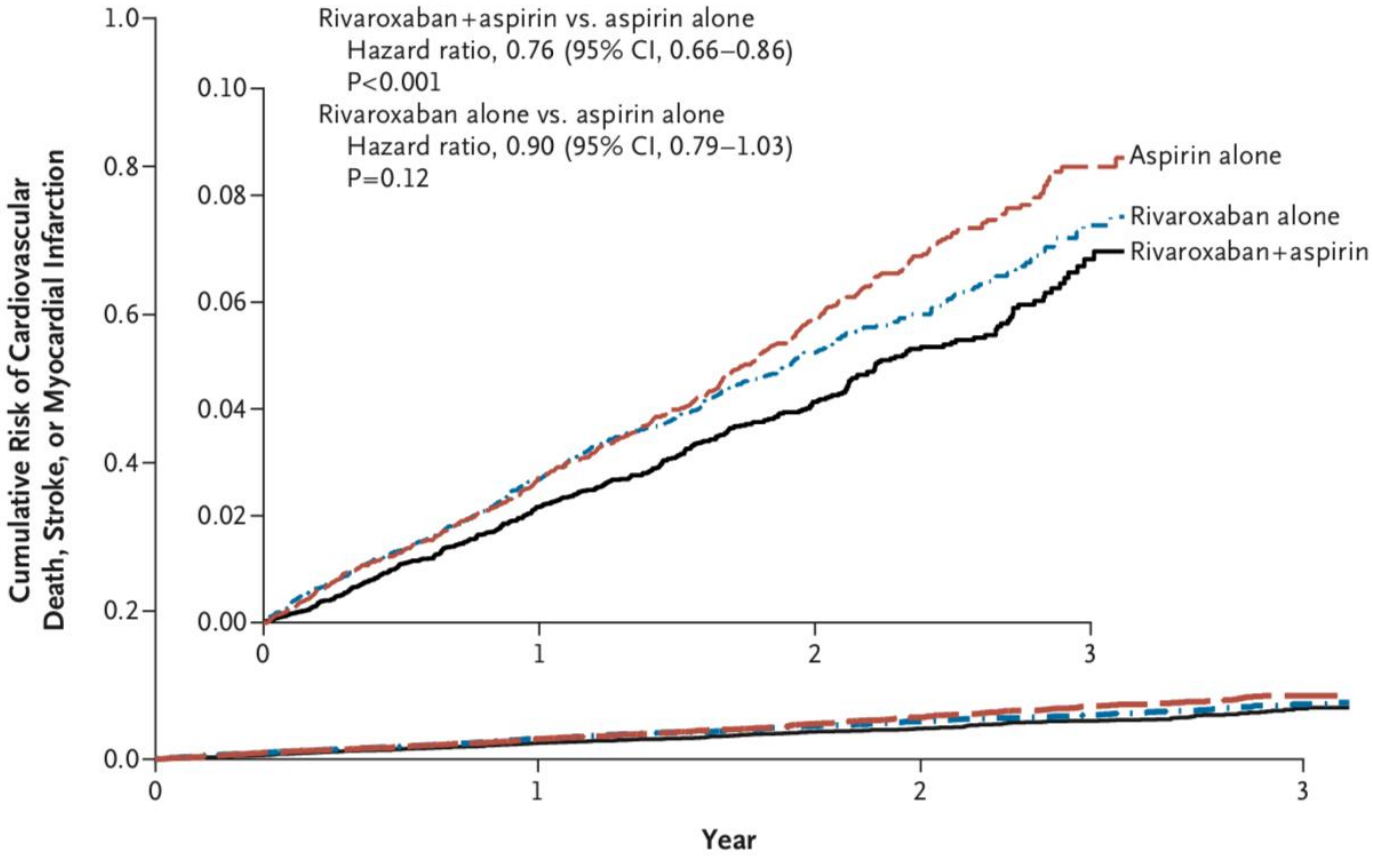
# Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A.K. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

- 27,395 participants with stable coronary artery disease, peripheral arterial disease, or both to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily) for mean follow-up of 23 months.
- The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction.

**Table 1. Baseline Characteristics of the Participants.***

| Characteristic | Rivaroxaban plus Aspirin (N=9152) | Rivaroxaban Alone (N=9117) | Aspirin Alone (N=9126) |
|---|---|---|---|
| Age — yr | 68.3±7.9 | 68.2±7.9 | 68.2±8.0 |
| Female sex — no. (%) | 2059 (22.5) | 1972 (21.6) | 1989 (21.8) |
| Body-mass index† | 28.3±4.8 | 28.3±4.6 | 28.4±4.7 |
| Blood pressure — mm Hg | | | |
| Systolic | 136±17 | 136±18 | 136±18 |
| Diastolic | 77±10 | 78±10 | 78±10 |
| Cholesterol — mmol/liter | 4.2±1.1 | 4.2±1.1 | 4.2±1.1 |
| Tobacco use — no. (%) | 1944 (21.2) | 1951 (21.4) | 1972 (21.6) |
| Hypertension — no. (%) | 6907 (75.5) | 6848 (75.1) | 6877 (75.4) |
| Diabetes — no. (%) | 3448 (37.7) | 3419 (37.5) | 3474 (38.1) |
| Previous stroke — no. (%) | 351 (3.8) | 346 (3.8) | 335 (3.7) |
| Previous myocardial infarction — no. (%) | 5654 (61.8) | 5653 (62.0) | 5721 (62.7) |
| Heart failure — no. (%) | 1963 (21.4) | 1960 (21.5) | 1979 (21.7) |




| No. at Risk | | | | |
|---|---|---|---|---|
| Aspirin alone | 9126 | 7808 | 3860 | 669 |
| Rivaroxaban alone | 9117 | 7824 | 3862 | 670 |
| Rivaroxaban+aspirin | 9152 | 7904 | 3912 | 658 |

**Figure 1. Cumulative Incidence of the Primary Efficacy Outcome among Participants Receiving Rivaroxaban plus Aspirin, Rivaroxaban Alone, or Aspirin Alone.**

Participants in the rivaroxaban-plus-aspirin group received 2.5 mg of rivaroxaban twice daily and 100 mg of aspirin once daily. Participants in the rivaroxaban-alone group received 5 mg of rivaroxaban twice daily and an aspirin-matched placebo once daily. Participants in the aspirin-alone group received 100 mg of aspirin once daily and a rivaroxaban-matched placebo twice daily. The inset shows the same data on an expanded y axis.

**Table 3. Bleeding Events and Net Clinical Benefit.***

| Outcome | Rivaroxaban plus Aspirin (N=9152) | Rivaroxaban Alone (N=9117) | Aspirin Alone (N=9126) | Rivaroxaban plus Aspirin vs. Aspirin Alone | | Rivaroxaban Alone vs. Aspirin Alone | |
|---|---|---|---|---|---|---|---|
| | | | | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value |
| | | *number (percent)* | | | | | |
| Major and minor bleeding | | | | | | | |
| Major bleeding | 288 (3.1) | 255 (2.8) | 170 (1.9) | 1.70 (1.40–2.05) | <0.001 | 1.51 (1.25–1.84) | <0.001 |
| Fatal bleeding† | 15 (0.2) | 14 (0.2) | 10 (0.1) | 1.49 (0.67–3.33) | 0.32 | 1.40 (0.62–3.15) | 0.41 |
| Nonfatal symptomatic ICH† | 21 (0.2) | 32 (0.4) | 19 (0.2) | 1.10 (0.59–2.04) | 0.77 | 1.69 (0.96–2.98) | 0.07 |
| Nonfatal, non-ICH, symptomatic bleeding into critical organ† | 42 (0.5) | 45 (0.5) | 29 (0.3) | 1.43 (0.89–2.29) | 0.14 | 1.57 (0.98–2.50) | 0.06 |
| Other major bleeding† | 210 (2.3) | 164 (1.8) | 112 (1.2) | 1.88 (1.49–2.36) | <0.001 | 1.47 (1.16–1.87) | 0.001 |
| Fatal bleeding or symptomatic ICH | 36 (0.4) | 46 (0.5) | 29 (0.3) | 1.23 (0.76–2.01) | 0.40 | 1.59 (1.00–2.53) | 0.05 |
| Fatal bleeding or symptomatic bleeding into critical organ | 78 (0.9) | 91 (1.0) | 58 (0.6) | 1.34 (0.95–1.88) | 0.09 | 1.58 (1.13–2.19) | 0.006 |
| Major bleeding according to ISTH criteria | 206 (2.3) | 175 (1.9) | 116 (1.3) | 1.78 (1.41–2.23) | <0.001 | 1.52 (1.20–1.92) | <0.001 |
| Transfusion within 48 hr after bleeding | 87 (1.0) | 66 (0.7) | 44 (0.5) | 1.97 (1.37–2.83) | <0.001 | 1.50 (1.03–2.20) | 0.03 |
| Minor bleeding | 838 (9.2) | 741 (8.1) | 503 (5.5) | 1.70 (1.52–1.90) | <0.001 | 1.50 (1.34–1.68) | <0.001 |
| Site of major bleeding | | | | | | | |
| Gastrointestinal | 140 (1.5) | 91 (1.0) | 65 (0.7) | 2.15 (1.60–2.89) | <0.001 | 1.40 (1.02–1.93) | 0.04 |
| Intracranial | 28 (0.3) | 43 (0.5) | 24 (0.3) | 1.16 (0.67–2.00) | 0.60 | 1.80 (1.09–2.96) | 0.02 |
| Skin or injection site | 28 (0.3) | 28 (0.3) | 12 (0.1) | 2.31 (1.18–4.54) | 0.01 | 2.34 (1.19–4.60) | 0.01 |
| Urinary | 13 (0.1) | 30 (0.3) | 21 (0.2) | 0.61 (0.31–1.23) | 0.16 | 1.43 (0.82–2.50) | 0.20 |
| Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ | 431 (4.7) | 504 (5.5) | 534 (5.9) | 0.80 (0.70–0.91) | <0.001 | 0.94 (0.84–1.07) | 0.36 |

* ICH denotes intracranial hemorrhage, and ISTH International Society on Thrombosis and Haemostasis.
† If a participant had more than one event of major bleeding, only the most serious bleeding event was counted in these analyses.

**TABLE 4** Graft Failure Rates by Treatment Group and Type of Conduit

| | Rivaroxaban Plus Aspirin (N = 396) | | Rivaroxaban Alone (N = 381) | | Aspirin Alone (N = 362) | | Rivaroxaban Plus Aspirin vs. Aspirin Alone | | Rivaroxaban Alone vs. Aspirin Alone | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N With Graft | N With Graft Occluded | N With Graft | N With Graft Occluded | N With Graft | N With Graft Occluded | OR (95% CI) | p Value | OR (95% CI) | p Value |
| All grafts together | 1,242 | 113 (9.1) | 1,166 | 91 (7.8) | 1,154 | 92 (8.0) | 1.13 (0.82–1.57) | 0.45 | 0.95 (0.67–1.33) | 0.75 |
| Veins | 804 | 84 (10.5) | 741 | 63 (8.5) | 747 | 74 (9.9) | 1.05 (0.72–1.53) | 0.79 | 0.82 (0.55–1.22) | 0.32 |
| Radial artery | 38 | 5 (13.2) | 25 | 2 (8.0) | 30 | 1 (3.3) | 4.09 (0.42–39.4) | 0.22 | 2.41 (0.17–33.5) | 0.50 |
| LIMA | 379 | 18 (4.8) | 362 | 17 (4.7) | 347 | 14 (4.0) | 1.17 (0.57–2.40) | 0.66 | 1.15 (0.55–2.41) | 0.71 |
| RIMA | 21 | 6 (28.6) | 36 | 9 (25.0) | 27 | 3 (11.1) | 3.20 (0.66–15.5) | 0.14 | 2.64 (0.51–13.7) | 0.24 |
| Cryopreserved | 0 | 0 (0.0) | 2 | 0 (0.0) | 3 | 0 (0.0) | — | — | — | — |

Values ar
CI = co

**TABLE 6** Clinical Outcomes at the End of the Study

| | Rivaroxaban Plus Aspirin (n = 502) | Rivaroxaban Alone (n = 483) | Aspirin Alone (n = 463) | Rivaroxaban Plus Aspirin vs. Aspirin Alone | | Rivaroxaban Alone vs. Aspirin Alone | |
|---|---|---|---|---|---|---|---|
| | | | | Hazard Ratio (95% CI) | p Value | Hazard Ratio (95% CI) | p Value |
| Primary outcome* | 12 (2.4) | 16 (3.3) | 16 (3.5) | 0.69 (0.33–1.47) | 0.34 | 0.99 (0.50–1.99) | 0.98 |
| CV death | 5 (1.0) | 6 (1.2) | 2 (0.4) | 2.36 (0.46–12.1) | 0.29 | 2.77 (0.56–13.7) | 0.19 |
| Stroke | 5 (1.0) | 5 (1.0) | 7 (1.5) | 0.66 (0.21–2.09) | 0.48 | 0.71 (0.23–2.25) | 0.56 |
| Myocardial infarction | 4 (0.8) | 7 (1.4) | 7 (1.5) | 0.53 (0.16–1.81) | 0.30 | 1.03 (0.36–2.94) | 0.96 |
| Other outcomes | | | | | | | |
| PCI and/or redo CABG | 13 (2.6) | 20 (4.1) | 10 (2.2) | 1.25 (0.55–2.86) | 0.59 | 2.05 (0.96–4.38) | 0.06 |
| Heart failure | 12 (2.4) | 12 (2.5) | 8 (1.7) | 1.43 (0.58–3.49) | 0.44 | 1.45 (0.59–3.56) | 0.41 |
| Venous thromboembolism | 1 (0.2) | 1 (0.2) | 5 (1.1) | 0.19 (0.02–1.59) | 0.08 | 0.19 (0.02–1.62) | 0.09 |
| Hospitalization for CV causes | 64 (12.7) | 77 (15.9) | 54 (11.7) | 1.11 (0.77–1.60) | 0.57 | 1.44 (1.02–2.04) | 0.04 |

Values are n (%) unless otherwise indicated. *Primary outcome for COMPASS: CV death, stroke, or myocardial infarction.

CABG = coronary artery bypass grafting; COMPASS = Cardiovascular OutcoMes for People Using Anticoagulation StrategieS; CV = cardiovascular; PCI = percutaneous coronary intervention.

**TABLE 7** Bleeding Results per Treatment Groups

| Outcome | Rivaroxaban Plus Aspirin (n = 502) | Rivaroxaban Alone (n = 483) | Aspirin Alone (n = 463) | Rivaroxaban Plus Aspirin vs. Aspirin Alone | | Rivaroxaban Alone vs. Aspirin Alone | |
|---|---|---|---|---|---|---|---|
| | | | | Hazard Ratio (95% CI) | p Value | Hazard Ratio (95% CI) | p Value |
| ≤30 days after CABG surgery | | | | | | | |
| Major bleeding | 2 (0.4) | 1 (0.2) | 5 (1.1) | 0.37 (0.07–1.88) | 0.21 | 0.19 (0.02–1.61) | 0.09 |
| Minor bleeding | 10 (2.0) | 6 (1.2) | 7 (1.5) | 1.32 (0.50–3.47) | 0.57 | 0.82 (0.28–2.44) | 0.72 |
| Fatal bleeding | 0 (0.0) | 0 (0.0) | 0 (0.0) | – | – | – | – |
| Bleeding into a critical organ | 1 (0.2) | 0 (0.0) | 1 (0.2) | 0.92 (0.06–14.7) | 0.95 | – | – |
| Surgical site bleeding requiring reoperation | 0 (0.0) | 0 (0.0) | 0 (0.0) | – | – | – | – |
| Bleeding leading to hospitalization | 2 (0.4) | 1 (0.2) | 5 (1.1) | 0.37 (0.07–1.88) | 0.21 | 0.19 (0.02–1.61) | 0.09 |
| >30 days after CABG surgery | | | | | | | |
| Major bleeding | 12 (2.4) | 19 (3.9) | 8 (1.7) | 1.41 (0.58–3.45) | 0.45 | 2.43 (1.06–5.54) | 0.03 |
| Minor bleeding | 31 (6.2) | 22 (4.6) | 21 (4.5) | 1.40 (0.80–2.43) | 0.23 | 1.01 (0.56–1.84) | 0.97 |
| Fatal bleeding | 1 (0.2) | 1 (0.2) | 0 (0.0) | – | – | – | – |
| Bleeding into a critical organ | 3 (0.6) | 4 (0.8) | 1 (0.2) | 2.73 (0.28–26.3) | 0.36 | 3.89 (0.44–34.8) | 0.19 |
| Surgical site bleeding requiring reoperation | 0 (0.0) | 0 (0.0) | 0 (0.0) | – | – | – | – |
| Bleeding leading to hospitalization | 12 (2.4) | 17 (3.5) | 7 (1.5) | 1.61 (0.63–4.08) | 0.31 | 2.49 (1.03–6.01) | 0.04 |

Values are n (%) unless otherwise indicated.

CABG = coronary artery bypass grafting; CI = confidence interval.

(J Am Coll Cardiol 2019;73:121–30)

# Points to remember

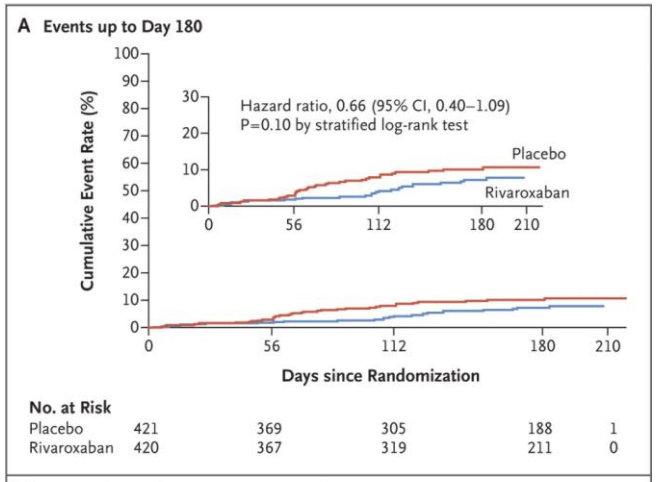
- Afib with valvular heart disease means
  - Moderate-to-severe mitral stenosis or mechanical MVR, period.
- DOAC still not indicated for afib with bioprosthetic valve, MV repair probably OK.
- CHADSVA v CHADSVASc? Being female is a risk modifier….
  - Female ≥ 65 or female ≥ 2 other points gets AC
- DOAC's are preferred over warfarin in afib.
- Know the right DOAC dose by renal function and by indication.
- Prasugrel and ticagrelor improve CV death and MI comp to clopidogrel: prasugrel increases bleeding, ticagrelor not so much but has unique side effects.
- Don't use prasugrel in ≥75-years, ≤60 kg or prior CVA. Don't use vorapaxor Hx CVA/TIA/ICH.
- DAPT for 30 months is only in ACS, elective PCI/DES only needs DAPT 6 months.
- Never include prasugrel in triple therapy for Afib/PCI.
- If using triple therapy post PCI (?STEMI) cut it back in 4-6 weeks.
- Warfarin plus clopidogrel is better and less risky than triple therapy.
- DOAC plus clopidogrel/ticagrelor is better than warfarin plus P2Y12.
- Rivaroxiban and vorapaxor are indicated additional anticoagulant therapy in chronic CAD, both reduce CV events, both increase risk of bleeding.
- There is still no good evidence to suggest that anticoagulation can be discontinued after PV ablation in patients at risk for stroke.

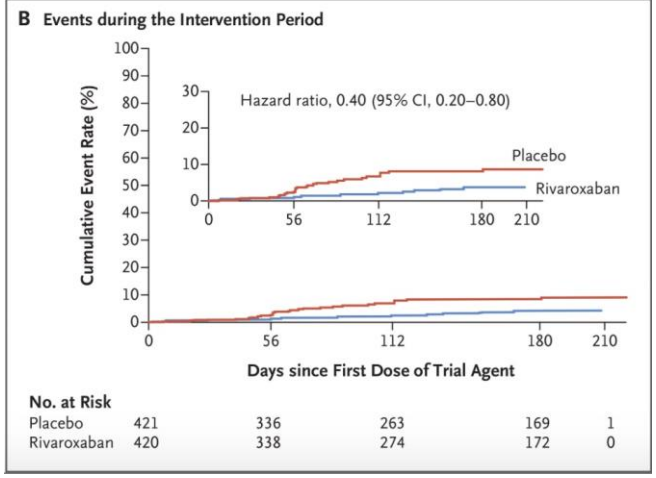

**Treatment for: Deep Vein Thrombosis Prophylaxis after Knee Replacement Surgery, Deep Vein Thrombosis Prophylaxis after Hip Replacement Surgery, Prevention of Thromboembolism in Atrial Fibrillation, Coronary Artery Disease, Peripheral Arterial Disease, Deep Vein Thrombosis, Pulmonary Embolism, and we tried CHF, Bypass Grafts, and coming soon…DVT prophylaxis in cancer!**

# Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

Alok A. Khorana, M.D., Gerald A. Soff, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Saroj Vadhan-Raj, M.D., M.H.C.M., C.M.Q., Hanno Riess, M.D., Ph.D., Ted Wun, M.D., Michael B. Streiff, M.D., David A. Garcia, M.D., Howard A. Liebman, M.D., Chandra P. Belani, M.D., Eileen M. O'Reilly, M.D., Jai N. Patel, Pharm.D., et al., for the CASSINI Investigators*

(hazard ratio, 0.66; 95% [CI], 0.40 to 1.09; P=0.10)




(hazard ratio, 0.40; 95% CI, 0.20 to 0.80)

- Double-blind, randomized trial involving high-risk ambulatory patients with cancer
- 841 patients without DVT at screening to rivaroxaban (10 mg) or placebo daily for up to 180 days
- primary efficacy end point:
  - composite of objectively confirmed proximal deep-vein thrombosis in a lower limb, pulmonary embolism, symptomatic deep-vein thrombosis in an upper limb or distal deep-vein thrombosis in a lower limb, and death from venous thromboembolism and was assessed up to day 180
- The same end point was assessed during the intervention period (first receipt of trial agent to last dose plus 2 days).

**Table 3. Primary Safety End Points, According to Trial Group.***

| End Point | Placebo (N=404) | Rivaroxaban (N=405) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients with event (%)* | | | |
| Primary safety end point: major bleeding | 4 (1.0) | 8 (2.0) | 1.96 (0.59–6.49) | 0.26 |
| Secondary safety end point: clinically relevant nonmajor bleeding | 8 (2.0) | 11 (2.7) | 1.34 (0.54–3.32) | 0.53 |
| Major and clinically relevant nonmajor bleeding | 12 (3.0) | 19 (4.7) | 1.54 (0.75–3.17) | 0.24 |

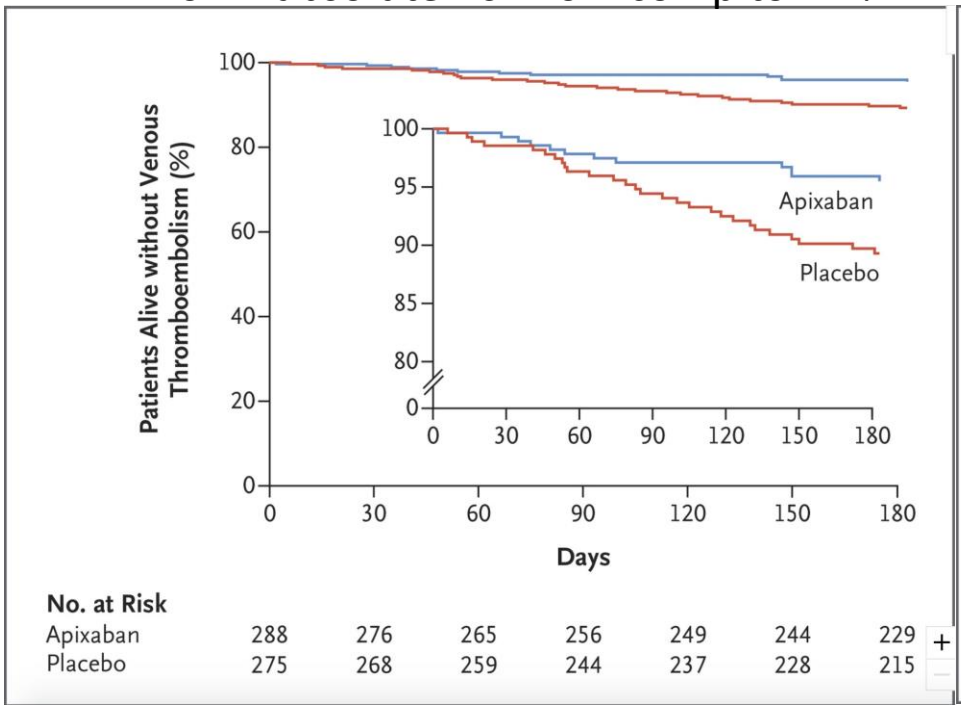
N Engl J Med 2019; 380:720-728

# Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

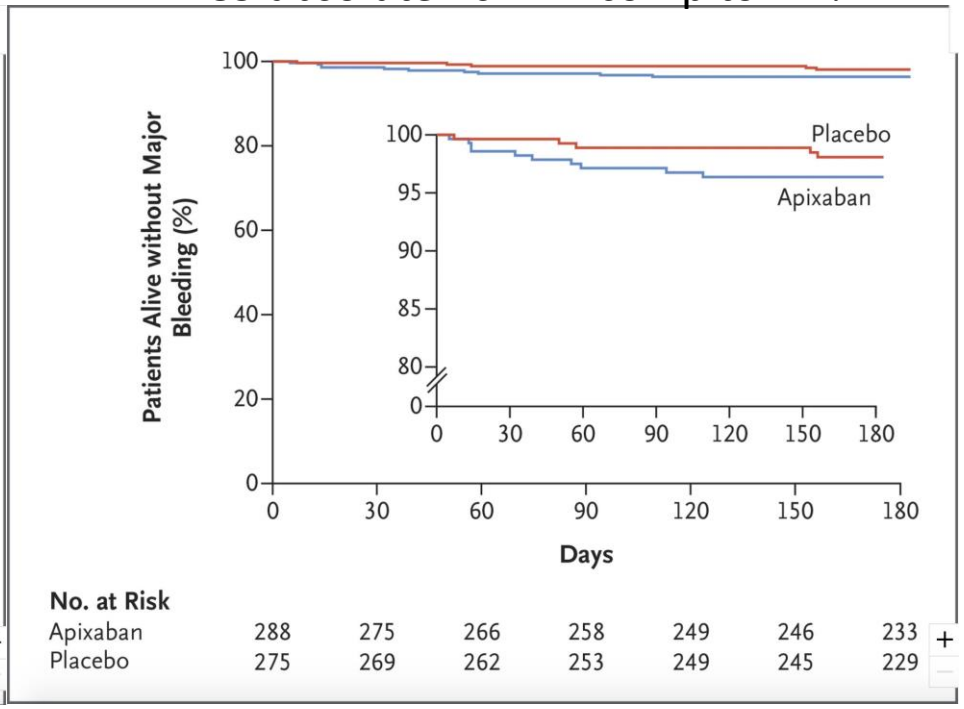
Marc Carrier, M.D., Karim Abou-Nassar, M.D., Ranjeeta Mallick, Ph.D., Vicky Tagalakis, M.D., Sudeep Shivakumar, M.D., Ariah Schattner, M.D., Philip Kuruvilla, M.D., Danny Hill, M.D., Silvana Spadafora, M.D., Katerine Marquis, M.D., Mateya Trinkaus, M.D., Anna Tomiak, M.D., et al., for the AVERT Investigators*

- Randomized, placebo-controlled, double-blind clinical trial 563 patients
- apixaban (2.5 mg twice daily) for thromboprophylaxis in ambulatory patients with cancer who were at intermediate-to-high risk for venous thromboembolism and were initiating chemotherapy.

HR 0.41 absolute risk 10.2 comp to 4.2%




HR 1.89 absolute risk 2.1 comp to 1.1%




N Engl J Med 2019; 380:711-719

| Risk Factor | Score | HAS-BLED Score | Bleeding Rate (%/year) |
|---|---|---|---|
| Hypertension | 1 | 0 | 1.13 |
| Abnormal renal/hepatic function | 1 (each) | 1 | 1.02 |
| Stroke | 1 | 2 | 1.88 |
| Bleeding | 1 | 3 | 3.74 |
| Labile INRs | 1 | 4 | 8.70 |
| Elderly (≥ 65 years) | 1 | ≥5 | Insufficient data |
| Drugs or alcohol use | 1 (each) | | |

Table 5. Definition of the SAMe-$TT_2R_2$ Score, Used to Aid Initial Decision Making Between Vitamin K Antagonist (With Good Quality Anticoagulation Control) and a Non–Vitamin K Antagonist Oral Anticoagulant[a]

| Definitions | Points |
|---|---|
| Sex (female) | 1 |
| Age (<60 y) | 1 |
| Medical history[b] | 1 |
| Treatment (interacting drugs, eg, amiodarone for rhythm control) | 1 |
| Tobacco use (within 2 y) | 2 |
| Race (not white) | 2 |
| **Maximum points** | 8 |

[a] The SAMe-$TT_2R_2$ score is proposed as a means to help with decision making, to identify those newly diagnosed nonanticoagulated AF patients who have a probability of doing well while taking a vitamin K antagonist (VKA) (with SAMe-$TT_2R_2$ score, 0-2) and achieve a time in therapeutic range (TTR) of at least 65% or 70%. In contrast, a SAMe-$TT_2R_2$ score of more than 2 suggests that such patients are unlikely to achieve a good TTR while taking a VKA, and a non-VKA oral anticoagulant should be used upfront, without a "trial of warfarin" period.

[b] Two of the following: hypertension, diabetes mellitus, coronary artery disease or myocardial infarctions, peripheral artery disease, congestive heart failure , previous stroke, pulmonary disease, or hepatic or renal disease.