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# Edoxaban:
# The newest NOAC option for stroke prevention in AF

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14th Annual
Collingwood, Ontario,
February 10 -12, 2017

# Disclosures

- Relationships with commercial interests:
  - Speakers Bureau/Honoraria: Servier, Boehringer Ingelheim.
  - Research support: BMS; Pfizer; Bayer.

# Learning Objectives



- To describe edoxaban, a novel oral factor Xa inhibitor available in Canada, and its role in the treatment armamentarium for stroke prevention in atrial fibrillation

- To discuss key findings from clinical trials of edoxaban in stroke prevention in atrial fibrillation

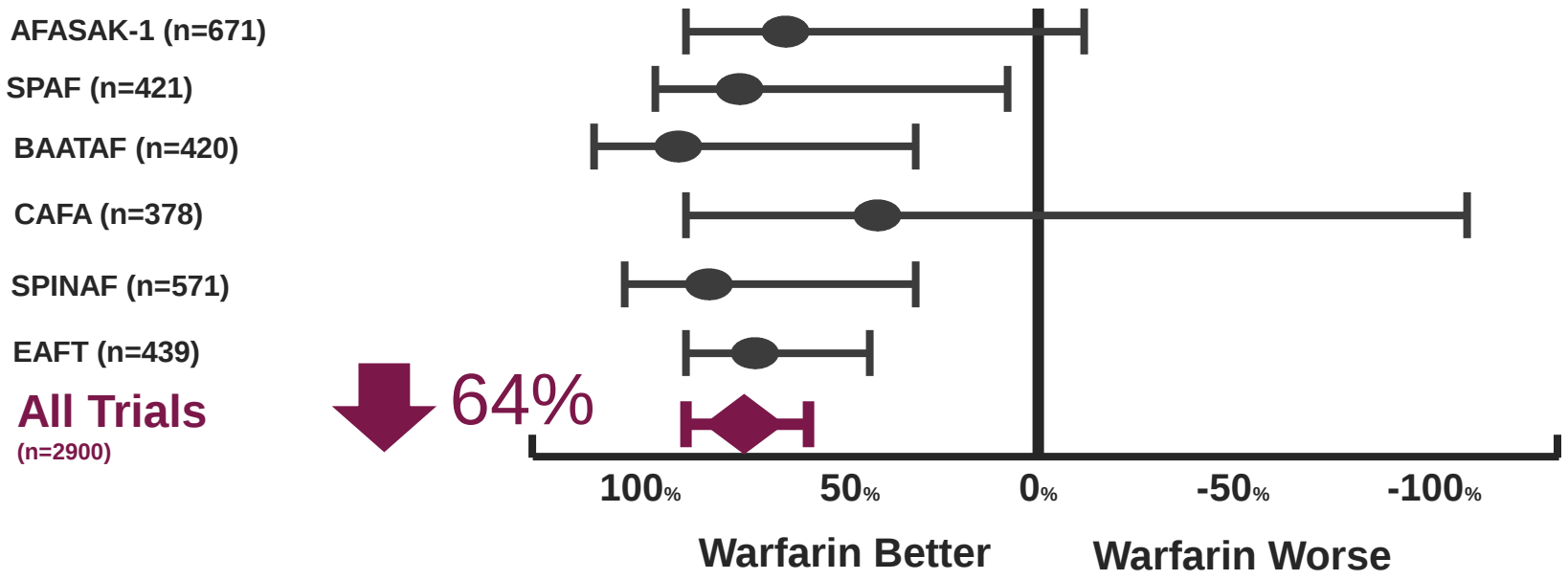
# Introduction

## Warfarin or NOACs for stroke prevention in AF?

# Warfarin Has Been Shown to Reduce Stroke Risk in AF



## Stroke Prevention in AF
### 6 Trials of Warfarin vs. Placebo




AFASAK: Atrial Fibrillation, Aspirin, AntiKoagulation; SPAF: Stroke Prevention in Atrial Fibrillation; BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA: Canadian Atrial Fibrillation Anticoagulation;
SPINAF: Stroke Prevention in Nonrheumatic Atrial Fibrillation; EAFT: European Atrial Fibrillation Trial

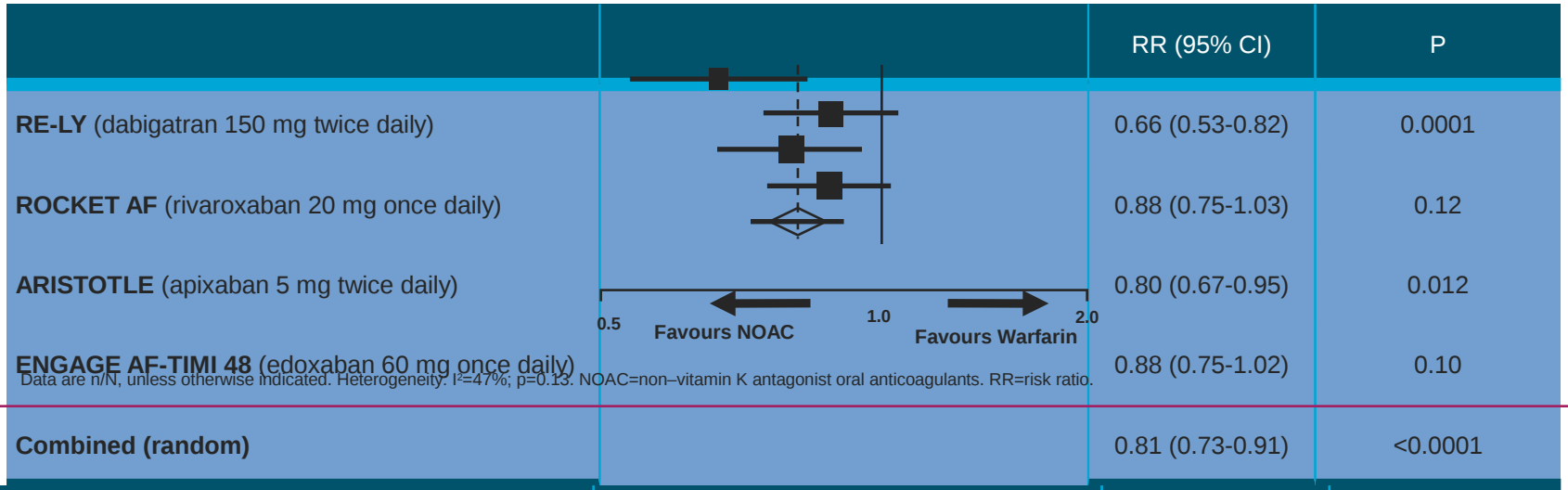


Hart RG, et al. *Ann Intern Med* 2007;146:857-67.

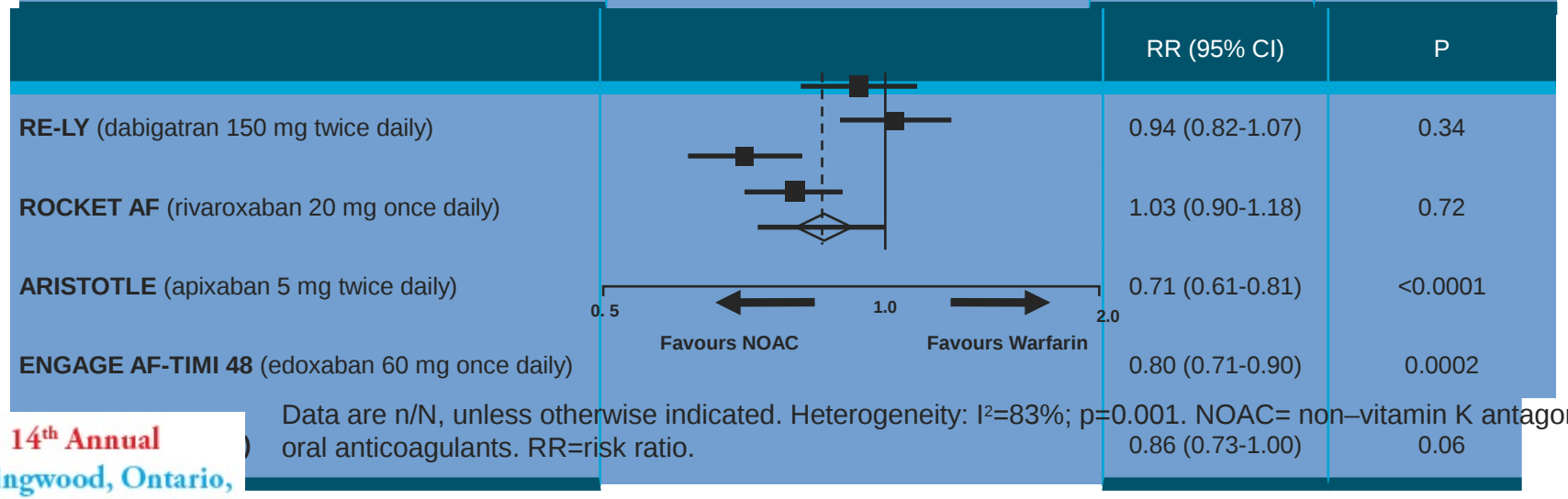
# Efficacy and Safety Benefits of NOACs vs. Warfarin from RCTs



## Stroke or systemic embolic events




Data are n/N, unless otherwise indicated. Heterogeneity: $I^2$=47%; p=0.13. NOAC=non–vitamin K antagonist oral anticoagulants. RR=risk ratio.




Data are n/N, unless otherwise indicated. Heterogeneity: $I^2$=83%; p=0.001. NOAC= non–vitamin K antagonist oral anticoagulants. RR=risk ratio.



Ruff CT, et al. *Lancet* 2014;383:955-62.

# Although Warfarin is Effective for Stroke Prevention in AF, NOACs are Becoming the Standard of Care

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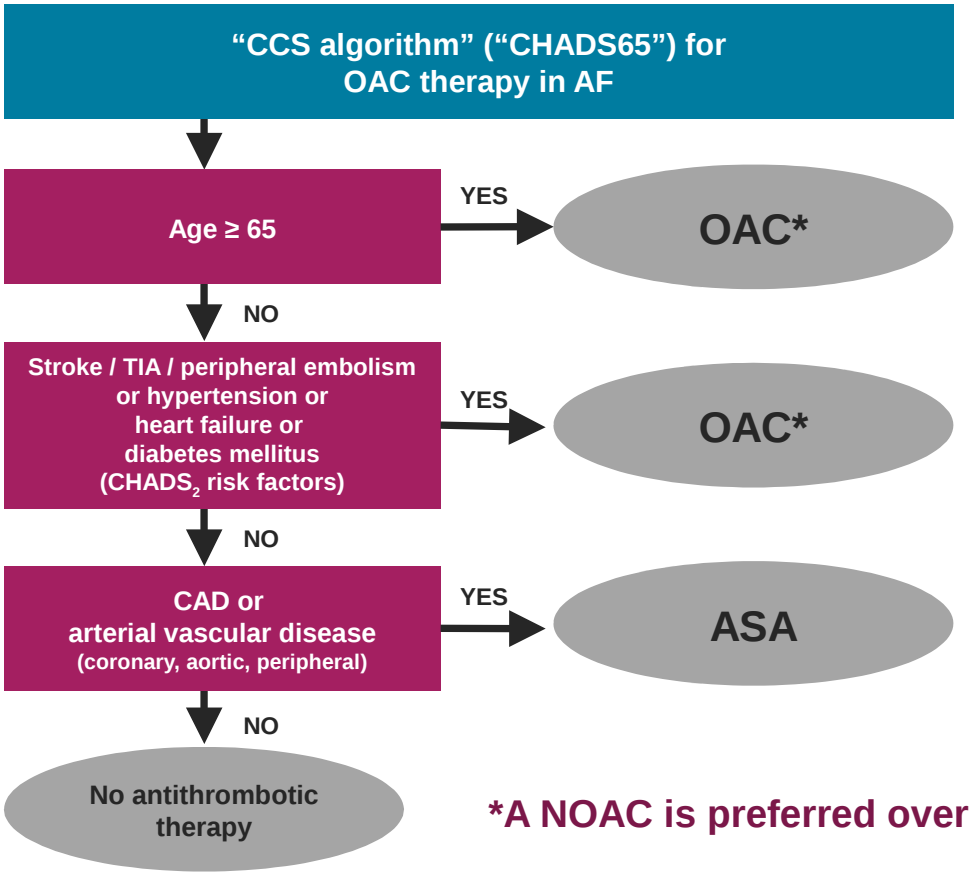
| 1950s…Warfarin | | 2000s…NOACs |
|---|---|---|
| • High risk of bleeding & hospitalization | → | • Less life-threatening bleeding and fewer hospitalizations with some NOACs |
| • Well documented drug/food/lifestyle interactions | → | • Fewer interactions |
| • Unpredictable pharmacokinetics | → | • Predictable pharmacokinetics |
| • Delayed onset and offset of action | → | • Rapid onset and offset of action |
| • Narrow therapeutic window (frequent INR monitoring) | → | • Wide therapeutic window (no monitoring required) |
| • Complexity for patient and doctor | → | • Simplicity for patient and doctor |
| • Poor adherence | → | • Better adherence |

# CCS Guidelines Prefer NOACs Over Warfarin For Non-valvular AF






**RECOMMENDATION:**

We recommend that when OAC therapy is indicated for patients with non-valvular AF, most patients should receive dabigatran, rivaroxaban, apixaban, or edoxaban…in preference to warfarin (Strong Recommendation, High-Quality Evidence).

***A NOAC is preferred over warfarin for non-valvular AF**

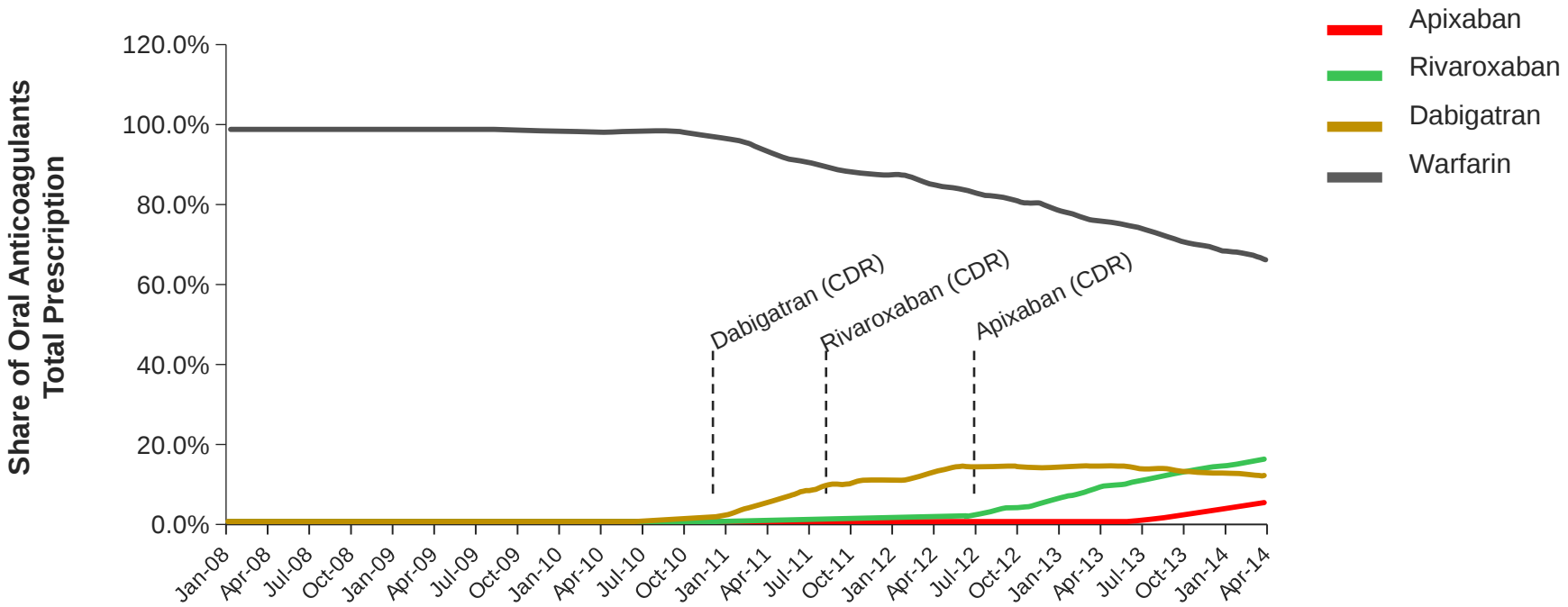


Macle L, et al. *Can J Cardiol* 2016;32:1170-85; Verma A, et al. *Can J Cardiol* 2014;30:1114-30.

# NOAC Use is Increasing in Canada, But these Agents May Still Be Underutilized



**All prescriptions filled by retail pharmacies from Alberta, Saskatchewan, Ontario, Quebec, Nova Scotia and New Brunswick between 2008 and 2014**




Dates of Common Drug Review (CDR) recommendations of each of the non–vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in patients with AF are shown.

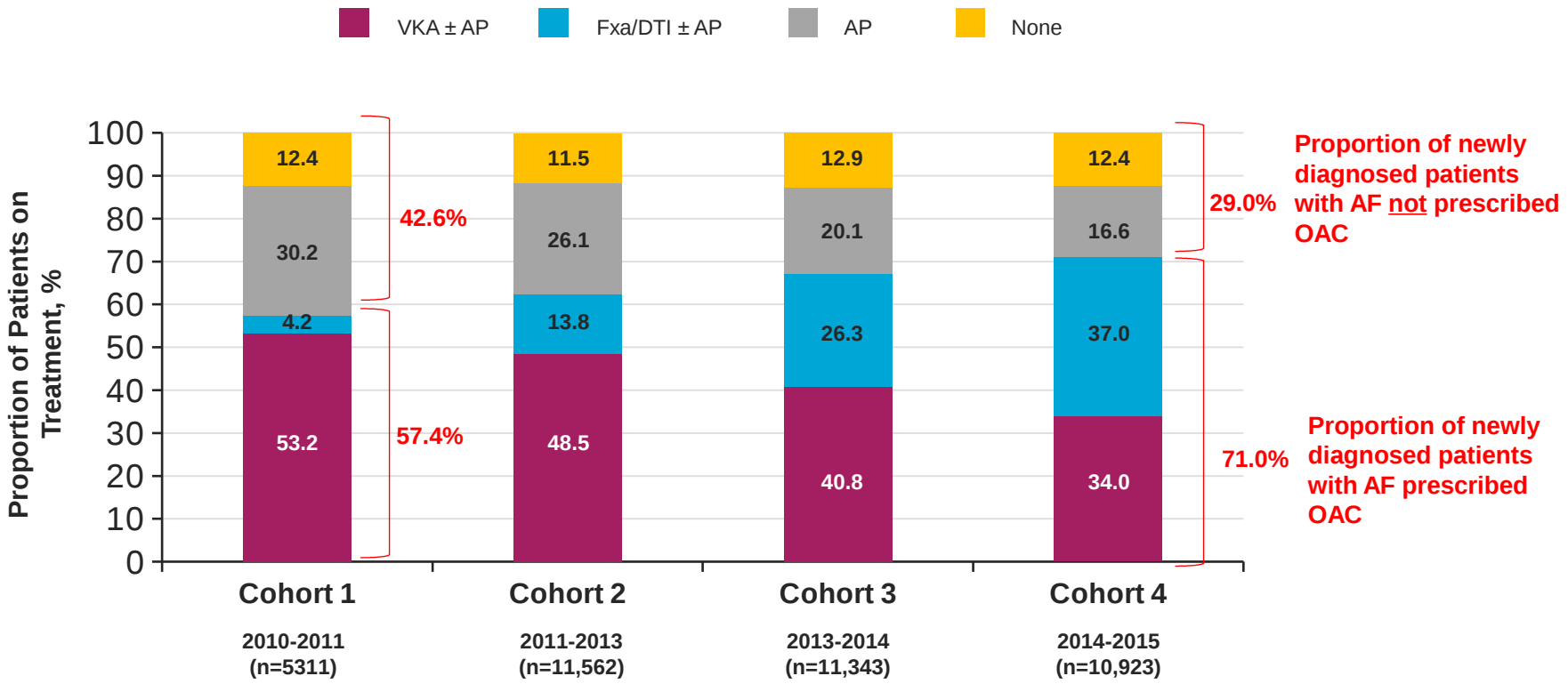


Weitz JI, et al. *Clin Ther* 2015;37:2506.

# Despite Increasing Use of NOACs in AF Globally, Many Patients Still Remain Untreated or Inappropriately Treated



## Evolution in Baseline Treatment for Patients Enrolled in Sequential Cohorts of GARFIELD-AF






Camm AJ, et al. *Heart* 2017;103:307-1

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# Edoxaban

## A Novel Oral Factor Xa Inhibitor

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# Edoxaban: A Novel Factor Xa Inhibitor in Canada

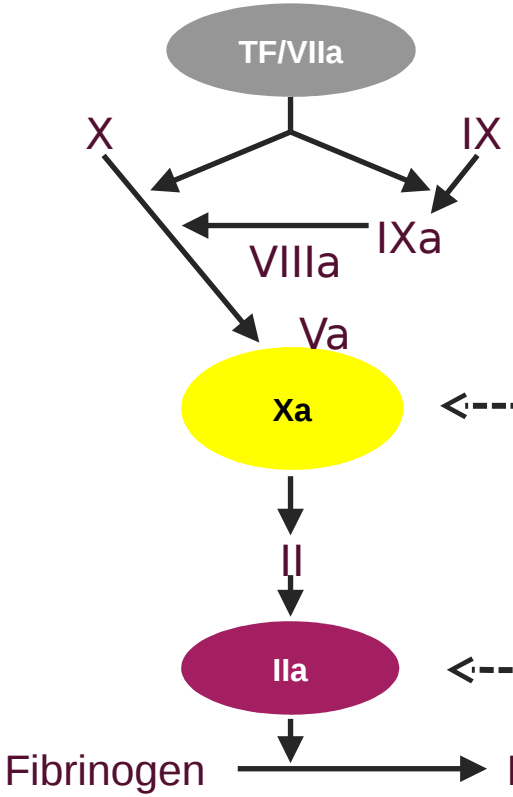


**Steps in Coagulation** | **Pathway** | **Drugs**

**Initiation**

**Propagation**

**Fibrin formation**




Rivaroxaban
Apixaban
Edoxaban

Dabigatran



Eriksson BI, et al. *Annu Rev Med* 2011;62:41–57; Ha
Eikelboom JW. *Circulation* 2011;123:1436-1450.

# Edoxaban: Pharmacologic Profile Compared With the Other NOACs



| | Dabigatran (Pradaxa®) | Rivaroxaban (Xarelto®) | Apixaban (Eliquis®) | Edoxaban (Lixiana®) |
|---|---|---|---|---|
| **Dosing frequency** | Twice daily | Once daily | Twice daily | Once daily |
| **Distribution volume (L)** | 50–70 | 50 | 21 | 107 |
| **Bioavailability** | 7% | 80% | 66% | 62% |
| **Hrs to $C_{max}$** | 1–2 (delayed by food) | 2–4 | 1–3 | 1–2 |
| **Half-life** | 12–14 h | 5–13 h | 8–15 h | 10–14 h |
| **CYP metabolism** | None | 66% | 15% | <4% |
| **Protein binding** | 35% | >90% | 87% | 55% |
| **Transporters** | P-gp | P-gp/BCRP | P-gp | P-gp |
| **Renal elimination** | 80% | 33%* | 25% | 50% |

*66% excreted in the urine with approximately 33% unchanged
BCRP = breast cancer resistance protein; CYP = cytochrome P450; NR = not reported; P-gp = P-glycoprotein



Adapted from: Gonzalez-Quesada CJ, Giugliano RP. *Am J Cardiovasc Drugs* 2014;14

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Engage AF
TIMI 48

# Edoxaban

## Summary of Efficacy and Safety in NVAF

## Main Findings

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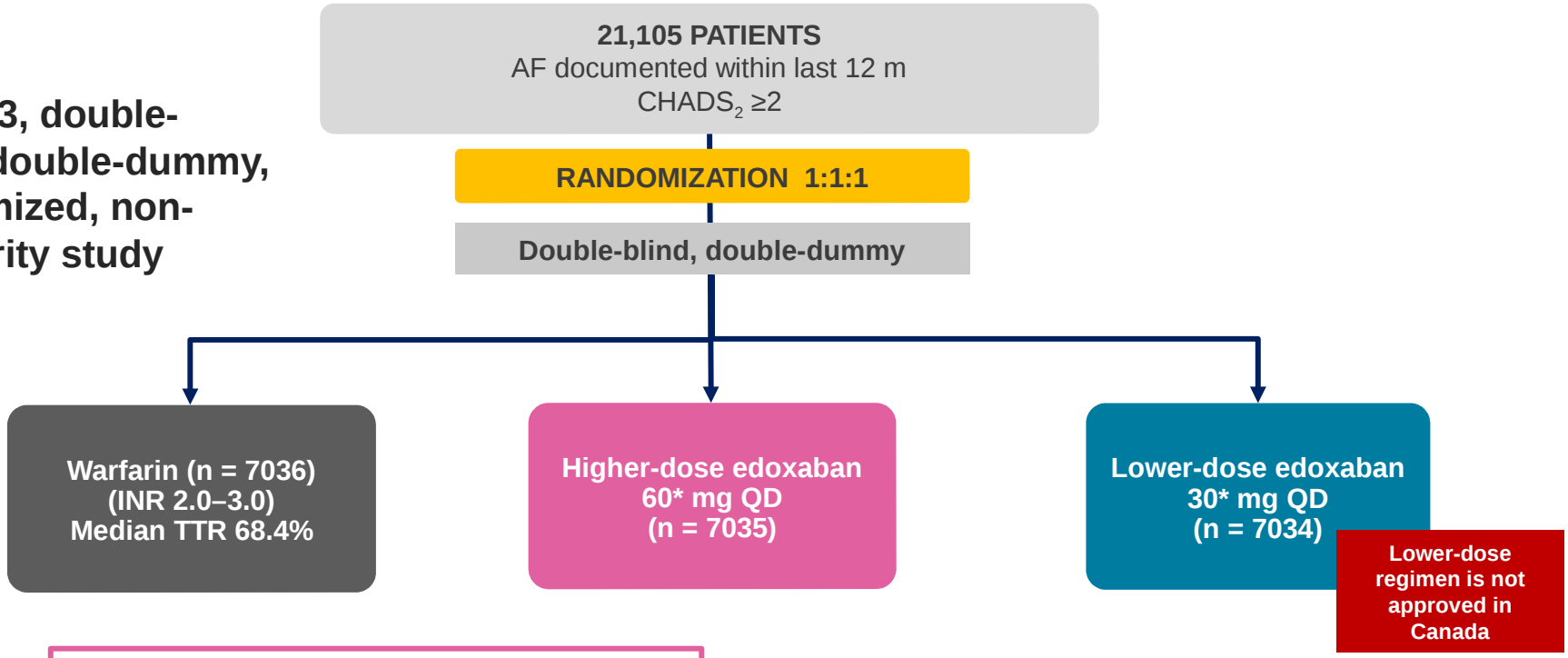
ENGAGE AF-TIMI 48: The Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation – Thrombolysis In Myocar Infarction study 48 NVAF: non-valvular atrial fibrillation

# Study Design



**Phase 3, double-blind, double-dummy, randomized, non-inferiority study**




***Edoxaban dose reduced by 50% if any of the following:**

- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

CrCl, creatinine clearance; P-gp, P-glycoprotein; QD: once daily



Ruff CR, et al. *Am Heart* J 2010;160:635-41.
Giugliano RP. *N Engl J Med* 2013;369:2093-104.

# Primary Efficacy and Safety Endpoints



## Primary efficacy:

- Time to first stroke (ischemic or hemorrhagic) or systemic embolic event (SEE)

  (mITT analysis)

## Primary safety:

- Major bleeding as defined by ISTH (with minor modification for Hb decrease and blood transfusion requirements)
  - Fatal bleeding, and/or
  - Symptomatic bleeding in critical area or organ, and/or
  - Bleeding causing fall in Hb > 2 g/dL (1.24 mmol/L), adjusted for transfusions

  (ITT analysis)

**All efficacy and safety outcomes were adjudicated by a clinical endpoint committee**

ISTH, International Society on Thrombosis and Hemostasis; P-gp, P-glycoprotein; Hb: hemoglobin



Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.
Schullman et al. *J Thromb Haemost* 2005;3:692-94.

# Edoxaban Dose Regimens



- **Two once-daily dosing regimens:**
  - Higher-dose regimen (60/30): 60 mg, dose-reduced to 30 mg
  - Lower-dose regimen (30/15): 30 mg, dose-reduced to 15 mg
    - Lower-dose regimen is not approved in Canada
- **Doses reduced at randomization for:**
  - CrCl: 30-50 mL/min
  - Weight ≤60 kg
  - Cardiac medications that are strong P-gp inhibitors (e.g., verapamil or quinidine)
- **Continued dose adjustment after randomization if above items change**

CrCl: creatinine clearance; P-gp: P-glycoprotein



Ruff CR, et al. *Am Heart J* 2010; 160:635-41
Salazar DE et al. *Thromb Haem* 2012;107:925-34.

# Baseline Characteristics



| | |
|---|---|
| Median age [IQR] | 72 [64, 78] |
| Female sex | 38% |
| Paroxysmal atrial fibrillation | 25% |
| $CHADS_2$ (mean ± SD) | 2.8 ± 1.0 |
| $CHADS_2 \geq 3$ | 53% |
| $CHADS_2 \geq 4$ | 23% |
| Prior CHF | 57% |
| Hypertension | 94% |
| Age ≥ 75 years | 40% |
| Diabetes mellitus | 36% |
| Prior stroke or TIA | 28% |
| Dose reduced at randomization | 25% |
| Prior VKA experience | 59% |
| Aspirin at randomization | 29% |
| Amiodarone at randomization | 12% |

**No differences across treatment groups**



Giugliano RP. *N Engl J Med* 2013;369:2093-104.

# Trial Quality Metrics



- **99.6% of randomized patients received treatment**
  - 25.3% in mITT population received reduced dose of edoxaban/placebo at randomization
  - After randomization:
    - Dose reductions in 7.1%
    - Dose increases in 1.2%
  - Rates of dose adjustments similar across groups at and after randomization
- **Median duration of treatment exposure**: 907 days (2.5 years) excluding interruptions
- **Median follow-up**: 1022 days (2.8 years)
- **Median TTR for warfarin**: 68.4% (interquartile range 56.5–77.4%)*



mITT: modified intent-to-treat; TTR: time in therapeutic range

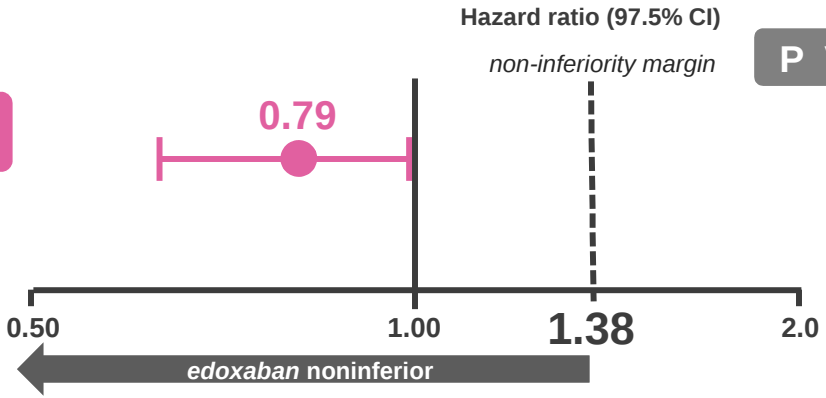
*TTR was calculated using the method of Rosendaal et al.

Giugliano RP, et al. *N Engl J Med* 2013;369:2093–2104.
Rosendaal et al. *Thromb Haemost* 1993;69:236–239.

# Primary Endpoint: Stroke / SEE

## Noninferiority Analysis (mITT, On Treatment)

Higher-dose edoxaban* (n=7012) vs warfarin (n=7012)

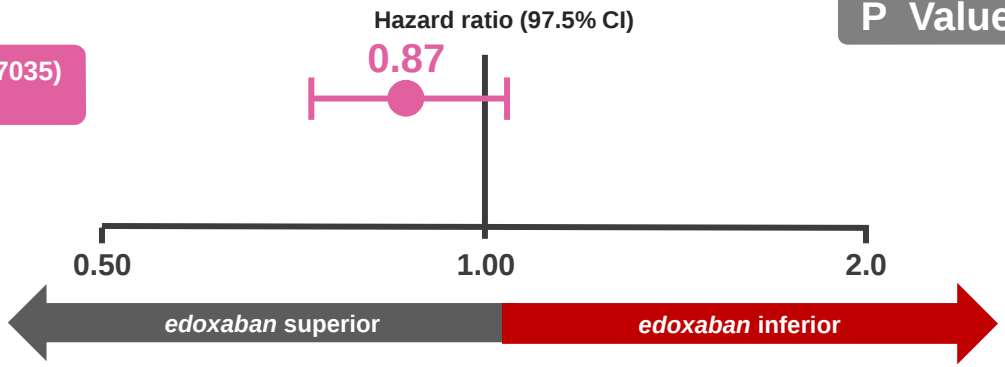



**P Value for Non-inferiority**

P<0.001

## Superiority Analysis (ITT, Overall)

Higher-dose edoxaban* (n= 7035) vs warfarin (n=7036)




**P Value for Superiority**

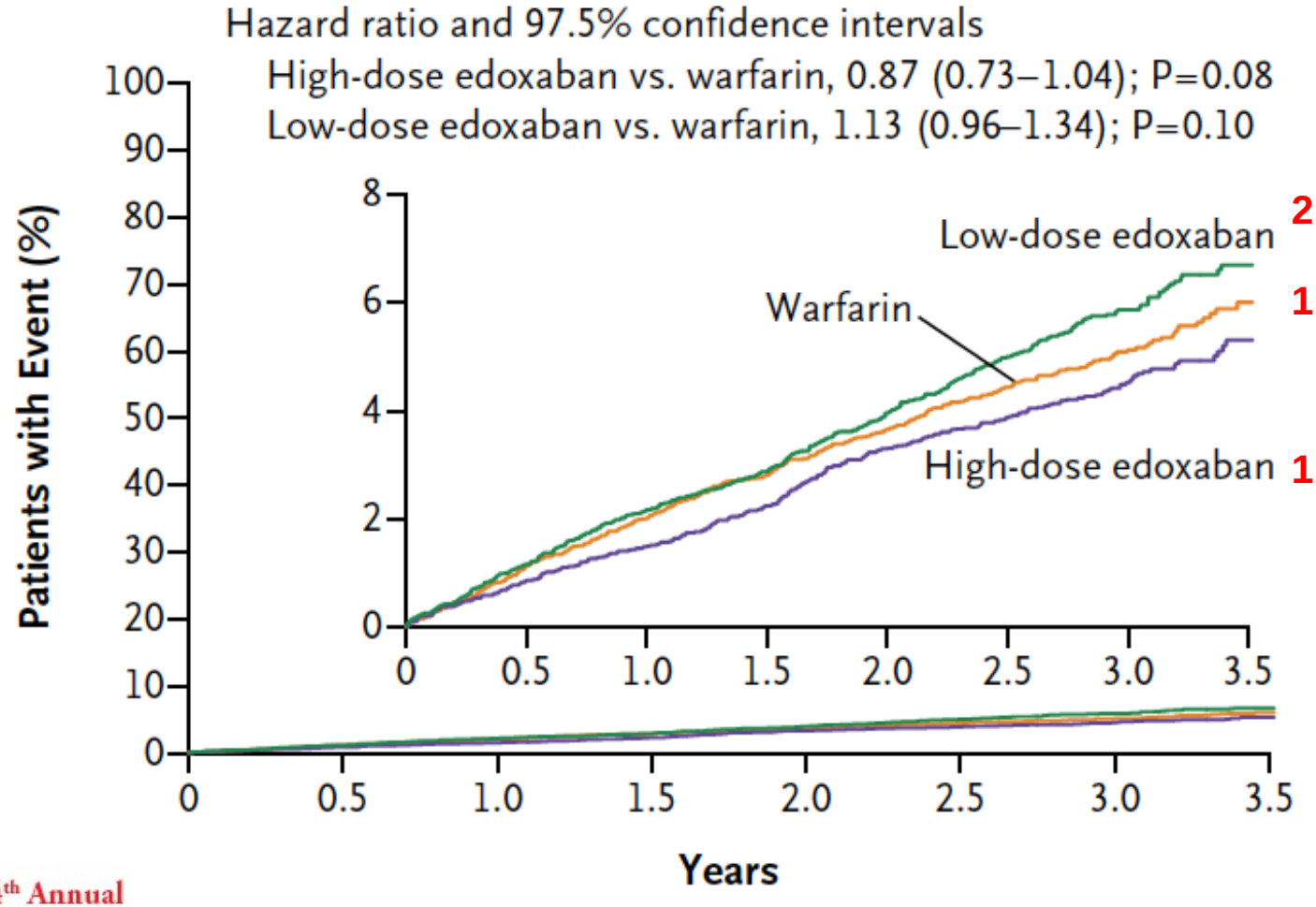
P=0.08

*Dose reduced by 50% in selected pts



Giugliano RP, et al. *N Engl J Med* 2013;369:2093–2104.

# Primary Efficacy Outcome: Stroke or SEE (Superiority Analysis)




**ITT vs. mITT**

**2.04 vs. 1.61%/yr**

**1.80 vs. 1.50%/yr**

**1.57 vs. 1.18%/yr**

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Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Primary Safety Outcome: Major Bleeding
## Safety On-Treatment

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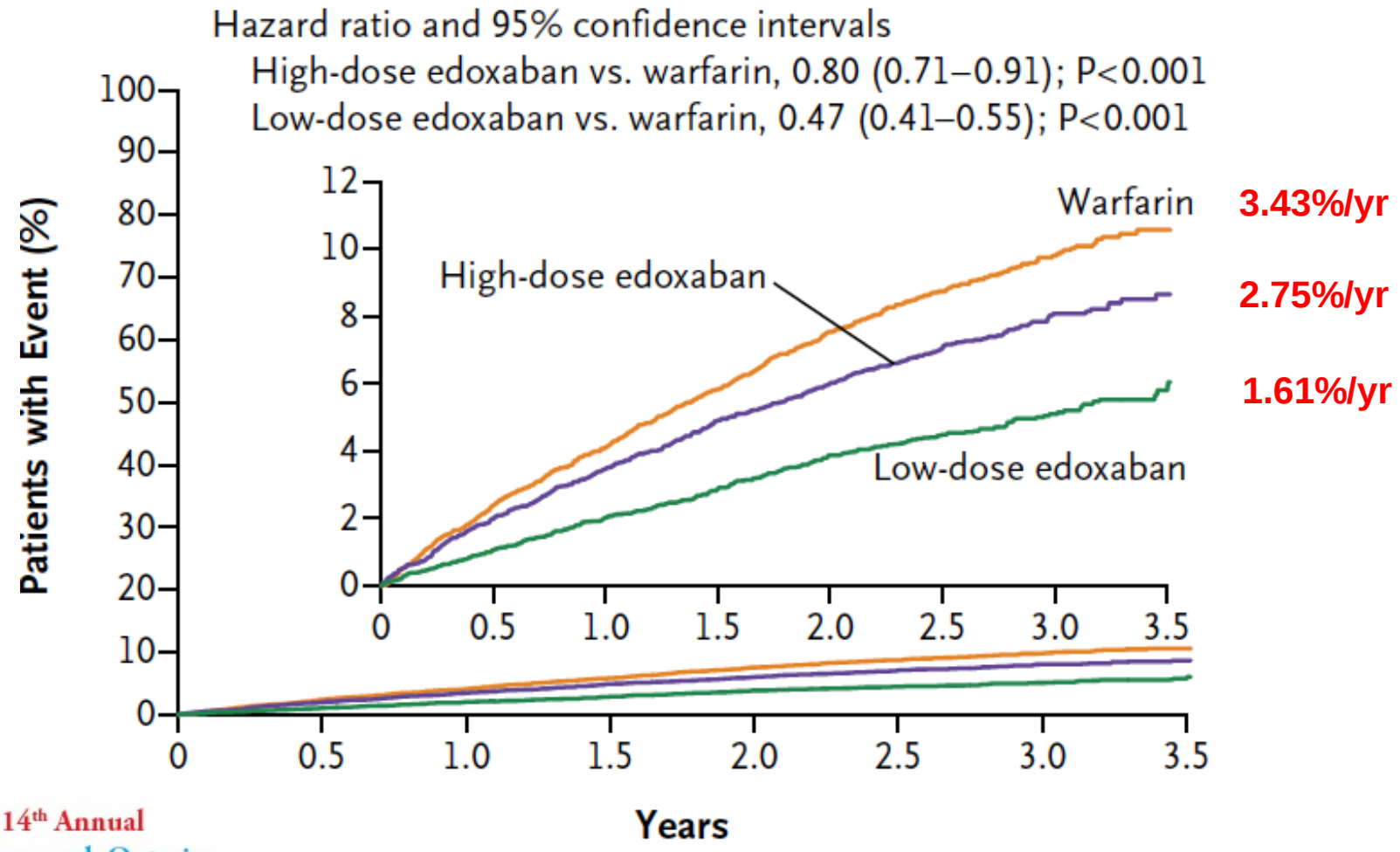


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Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Primary Safety Outcome: Major Bleeding
## Safety On-Treatment

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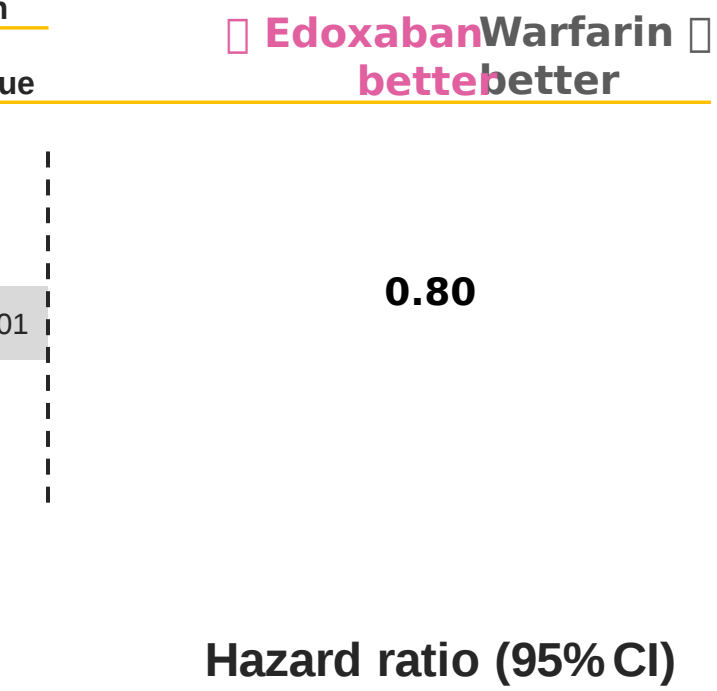
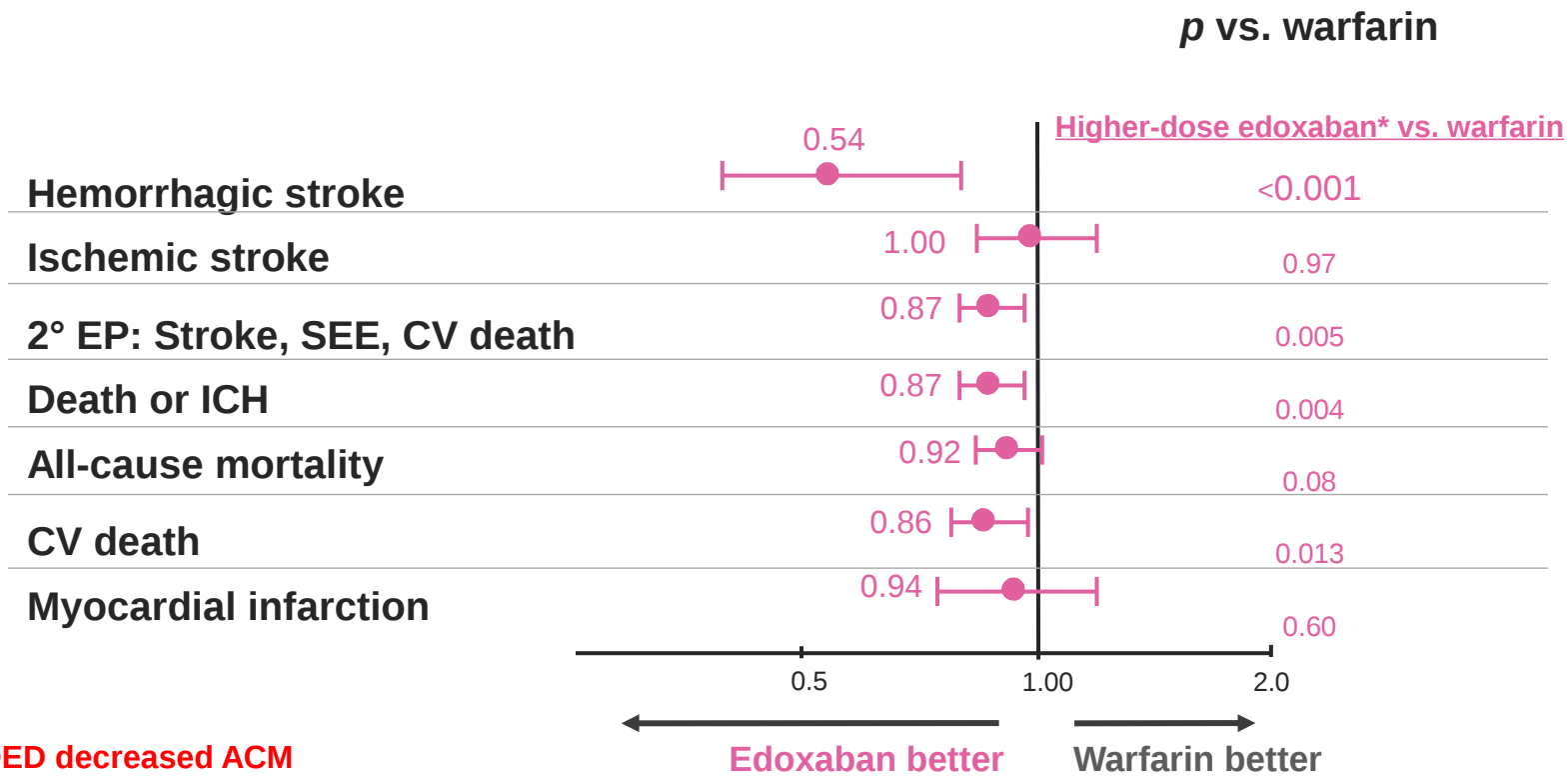
| Outcome Treatment | n | Event rate, %/yr | Edoxaban vs warfarin HR (95% CI) | P value |
|---|---|---|---|---|
| **Major bleed** | | | | |
| Warfarin | 524 | 3.43 | — | — |
| Higher-dose edoxaban | 418 | 2.75 | 0.80 (0.71, 0.91) | < 0.001 |






Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Key Secondary Outcomes




***LDED decreased ACM**
**HR 0.87 CI 0.79-0.96 p=0.006**

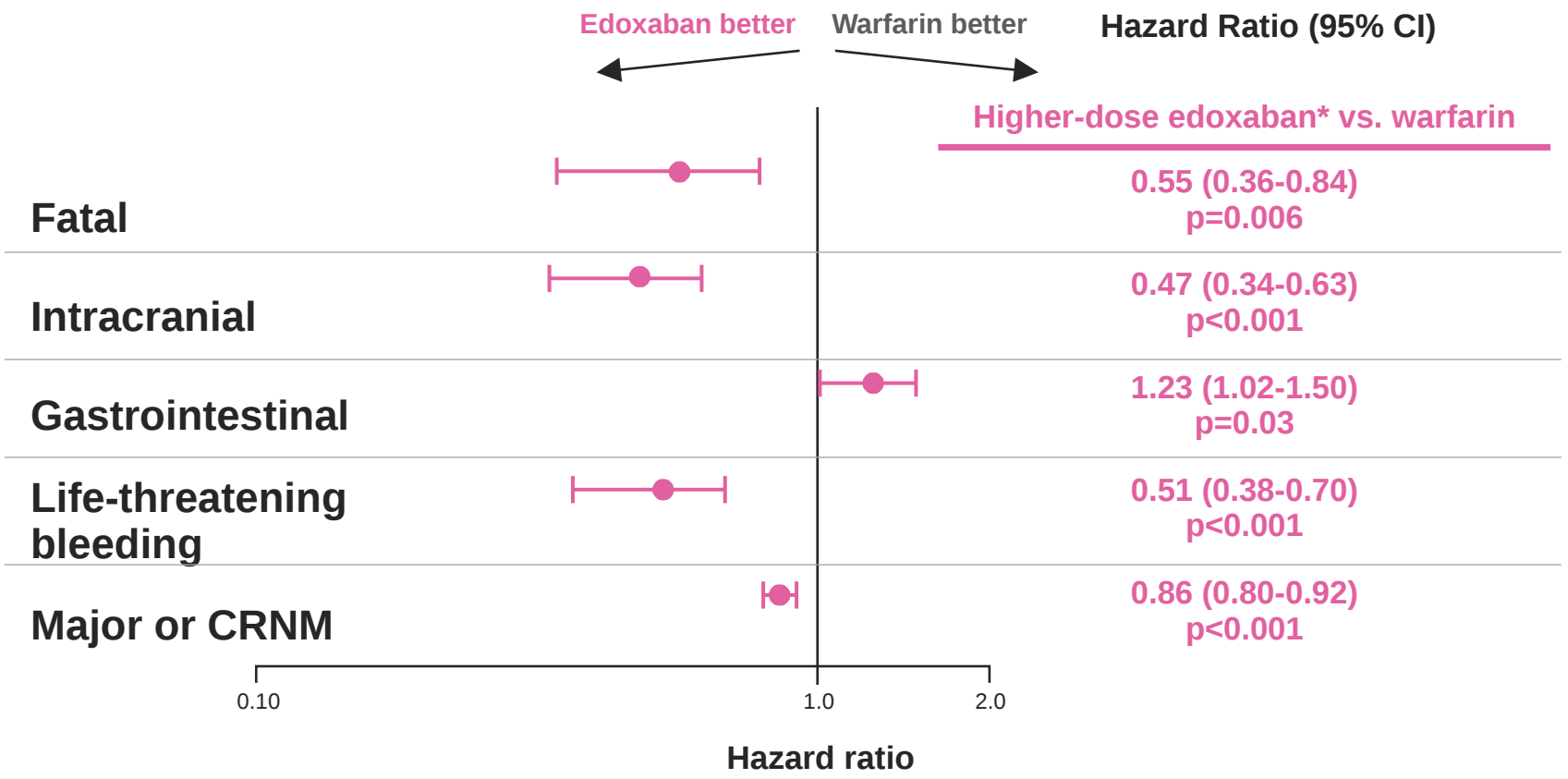
*Dose reduced by 50% in selected pts

EP: endpoint; SEE: systemic embolic event; CV: cardiovascular; ICH: intracranial hemorrhage



Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Other Bleeding Outcomes

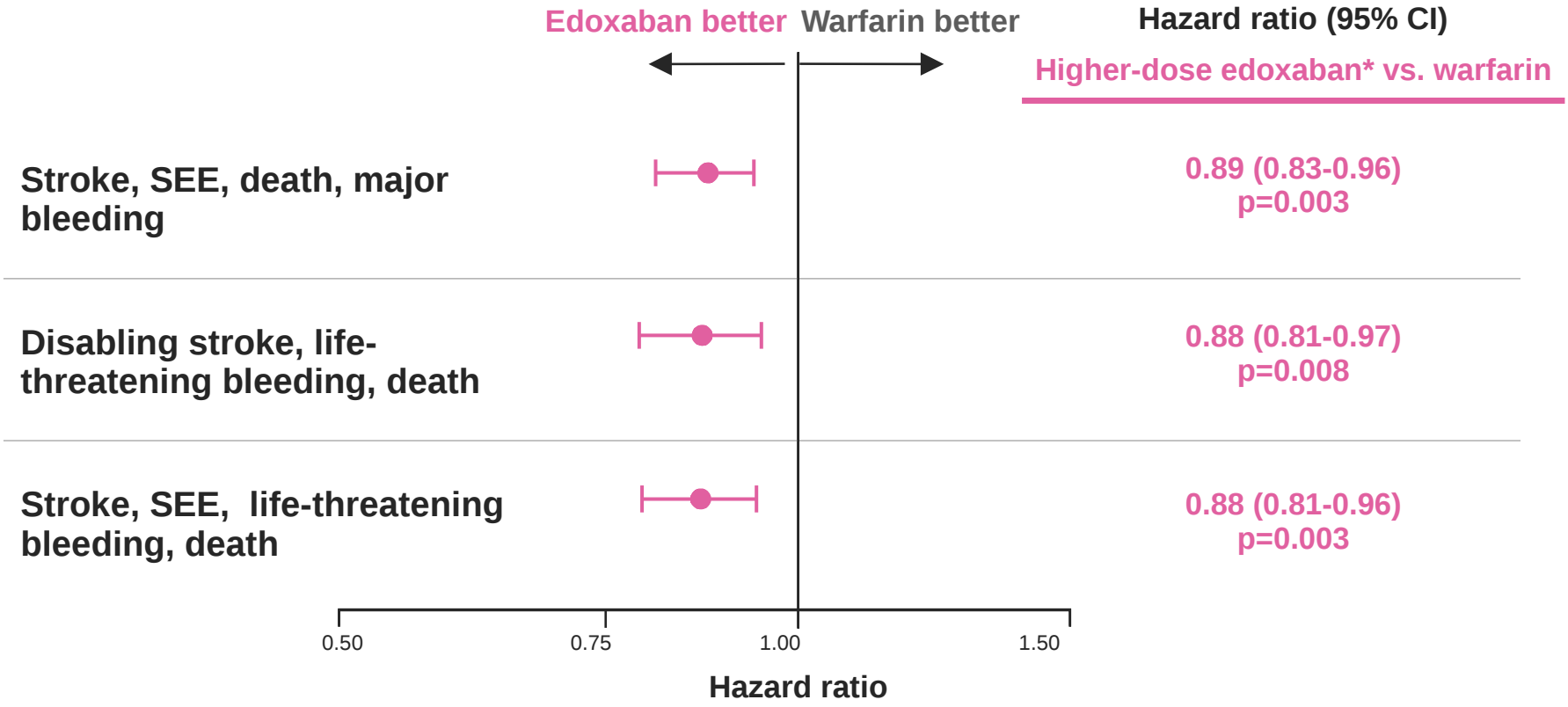



*Dose reduced by 50% in selected pts

CRNM: clinically relevant nonmajor bleeding

Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Net Clinical Outcomes

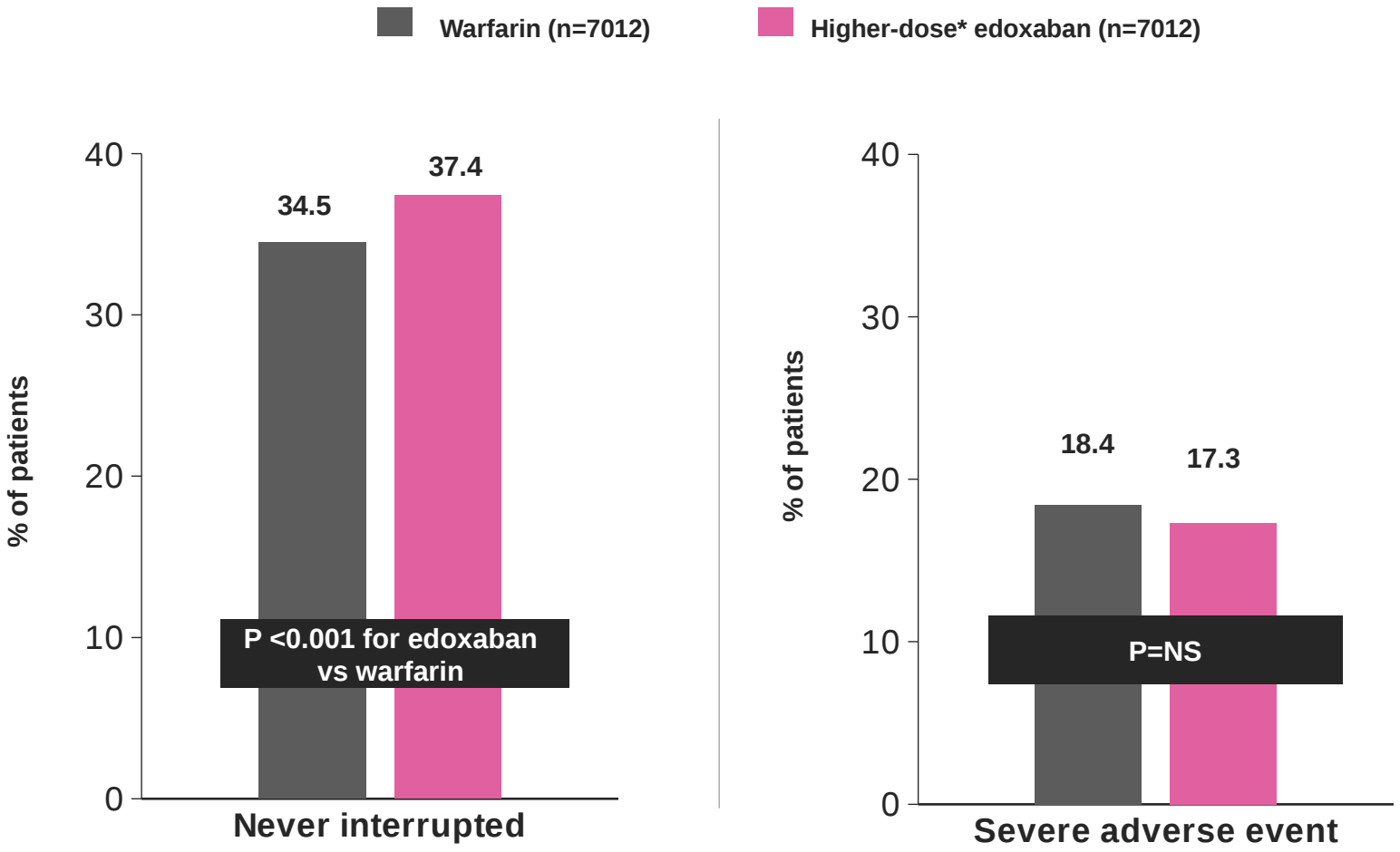



*Dose reduced by 50% in selected pts

SEE: systemic embolic event

Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Tolerability and Adverse Events




*Dose reduced by 50% in selected pts



Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Primary Efficacy Results (Stroke/SEE) in Pre-specified Subgroups of Patients

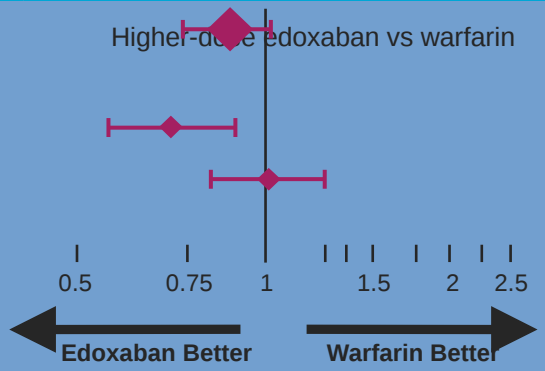


## Prespecified subgroups

- **Age:**
- **Prior stroke or TIA:**

Only significant interaction (P<0.05) was in following subgroup: previous receipt of a VKA

| Subgroup | Patients | Higher-dose edoxaban | Warfarin | Hazard ratio with High (95% CI) | Interaction P-value |
|---|---|---|---|---|---|
| **All Patients** | 21105 | 1.57 | 1.80 | | |
| **VKA Naïve** | | | | | 0.03 |
| Yes | 8663 | 1.49 | 2.12 | | |
| No | 12441 | 1.62 | 1.60 | | |




- **AF type:**
  - Paroxysmal
  - Persistent

– > 3

– ≤ 66.4%

manent



Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Primary Safety Results (Major Bleeding) in Pre-specified Subgroups of Patients

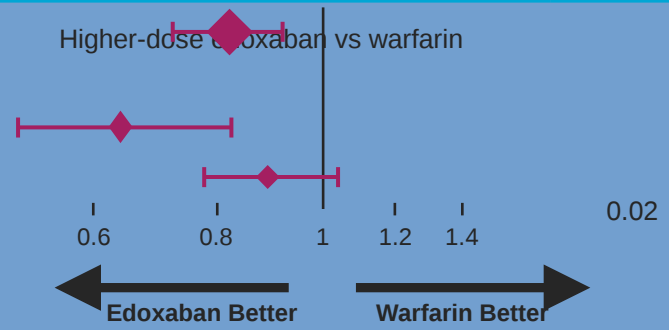


## Prespecified subgroups

- **Age:**
- **Prior stroke or TIA:**
- **Prior MI:**

Only significant interaction (P<0.05) was in the subgroup that was dose reduced at baseline

| Subgroup | Patients | Higher-dose Edoxaban | Warfarin | Hazard Ratio with High (95% CI) | Interaction P-value |
|---|---|---|---|---|---|
| **All Patients** | 21026 | 2.75 | 3.43 | | |
| **Dose Adjusted** | | | | | 0.02 |
| Yes | 5330 | 3.05 | 4.85 | | |
| No | 15696 | 2.66 | 3.02 | | |




- Non-white

- **CHADS2 score:**
  - ≤ 3
  - > 3

- **Centre level TTR:**
  - > 66.4%
  - ≤ 66.4%

- **AF type:**
  - Paroxysmal
  - Persistent
  - nanent



Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Relative Efficacy and Safety of Edoxaban vs. Warfarin by Dose Reduction Status

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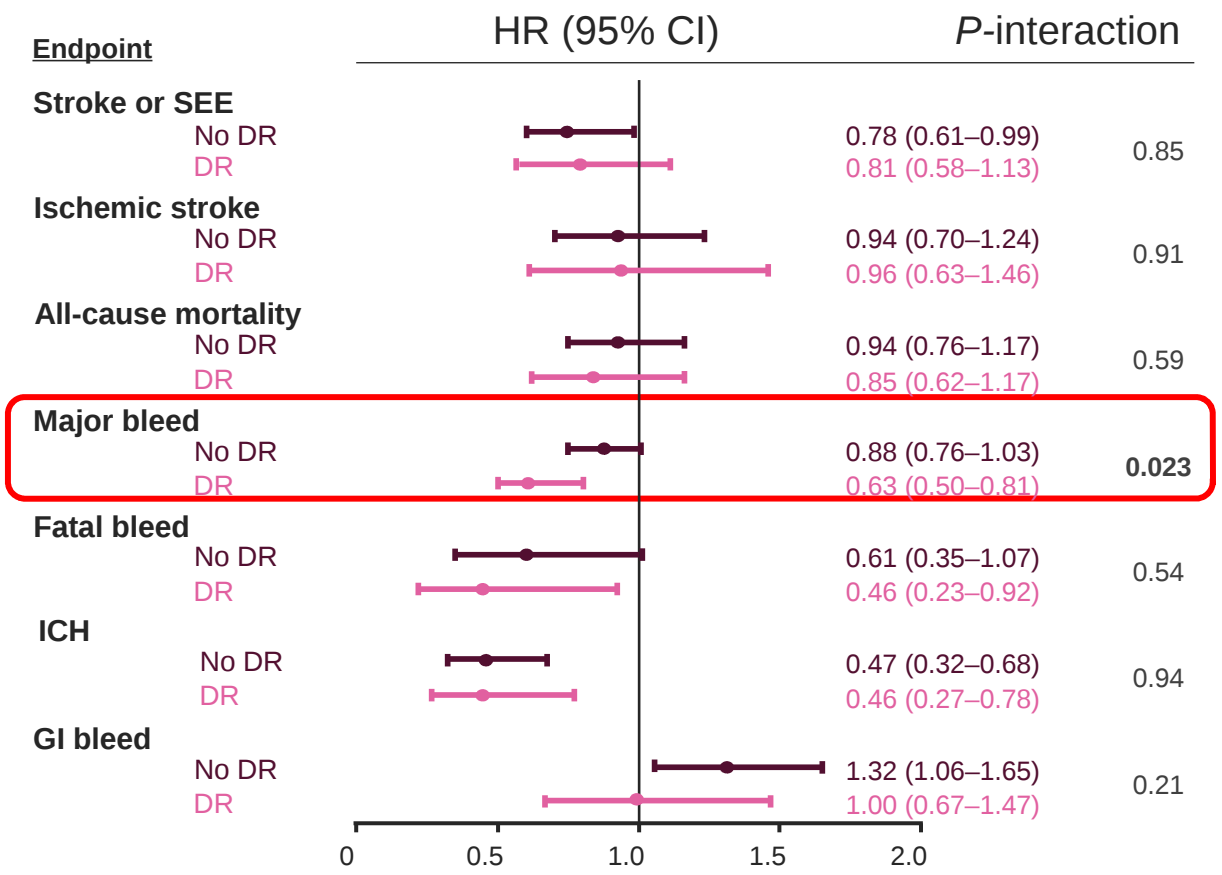
## Higher-dose edoxaban vs. warfarin

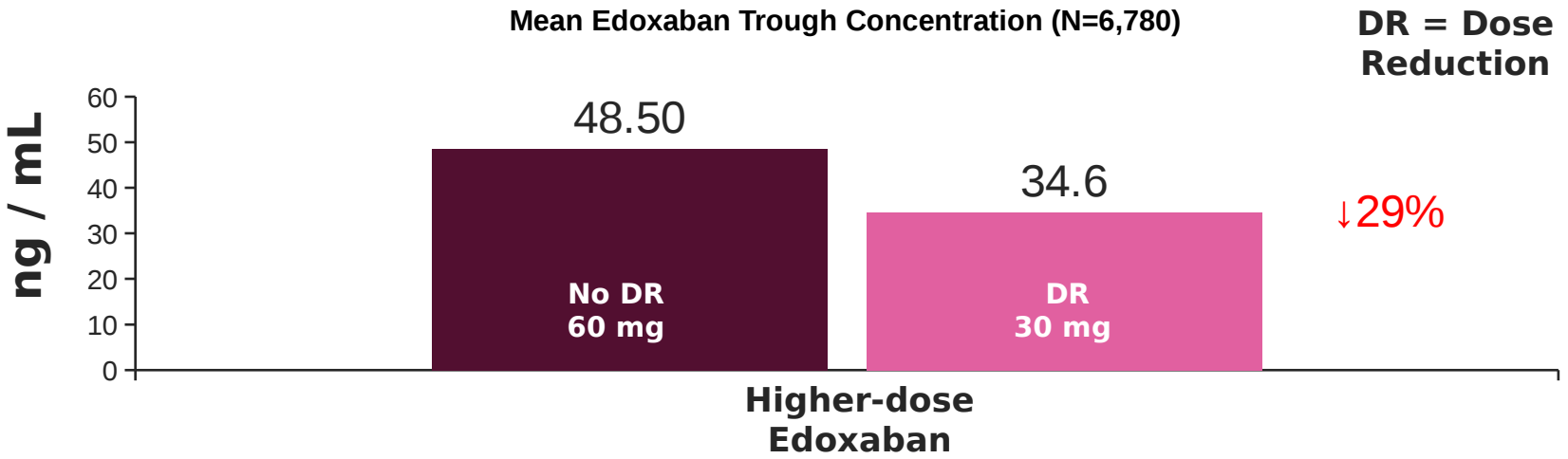


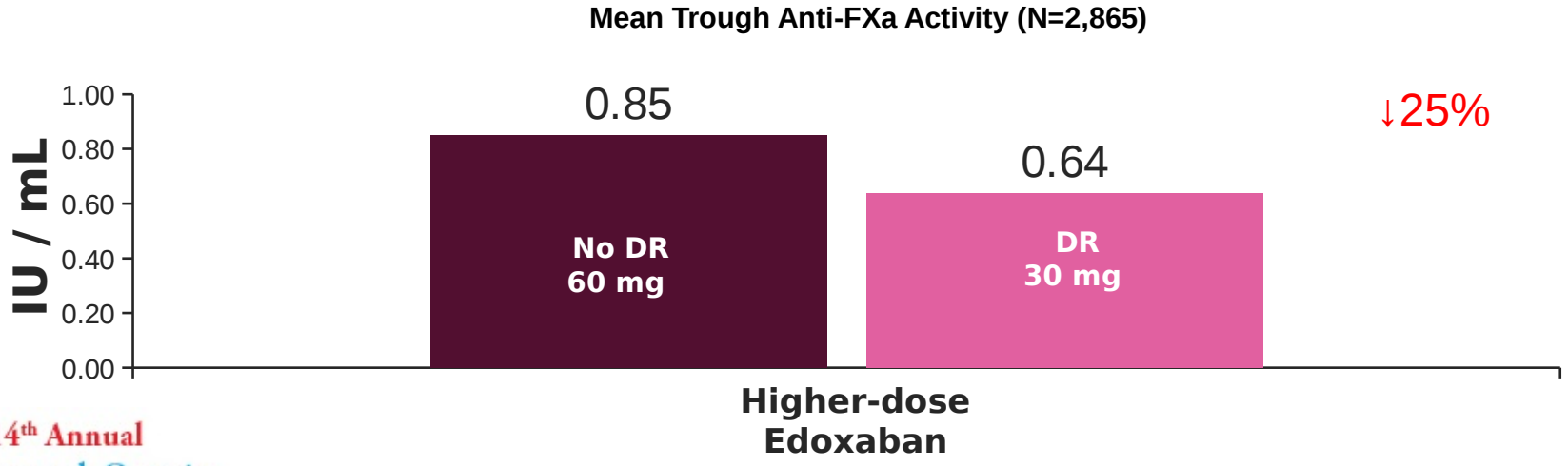

CI, confidence interval; DR, dose reduction; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; SEE, systemic embolic event.



Ruff CT, et al. *Lancet* 2015;385:2288-95.

# Edoxaban Concentration & Anti-FXa Activity

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Ruff CT et al. *Lancet* 2015;385:2288-95.

# Stroke/SEE in Patients With and Without Dose Reduction

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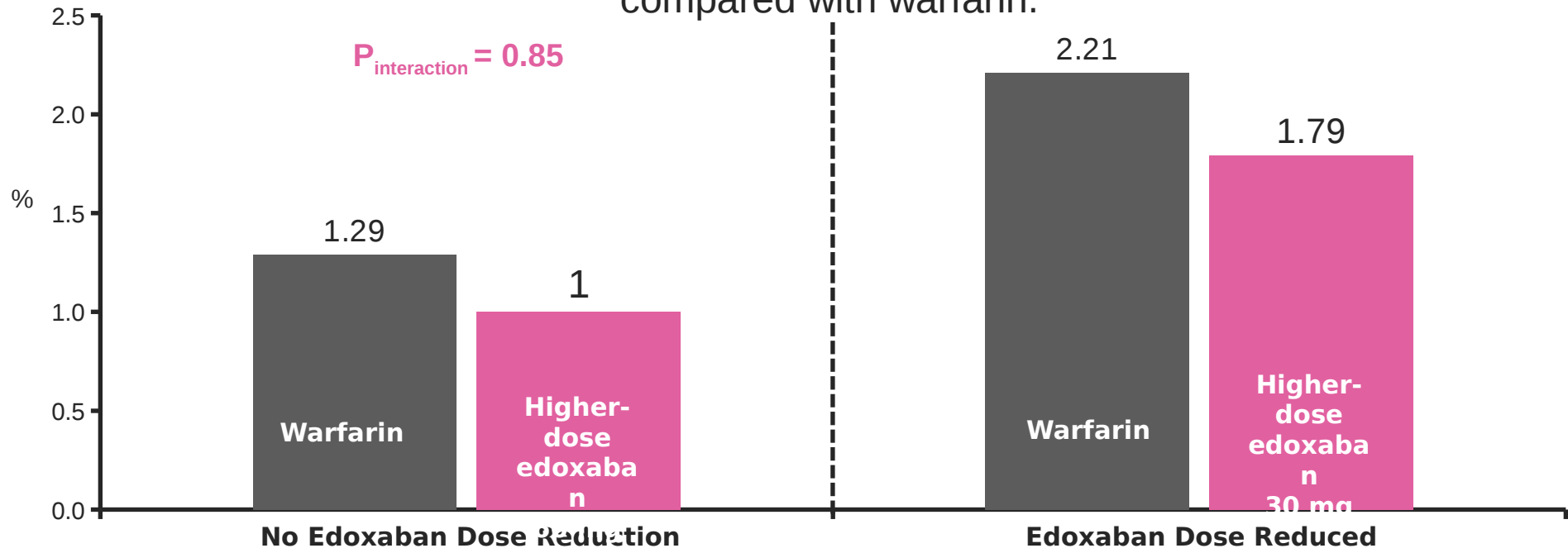
**Higher-dose edoxaban vs. warfarin**
**No Dose Reduction:** HR 0.78 (0.61–0.99)
**Dose Reduction:** HR 0.81 (0.58–1.13)

Despite the lower anti-FXa activity, dose reduction preserved the efficacy of edoxaban compared with warfarin.




| | | | | |
|---|---|---|---|---|
| **Edox Conc (ng/mL)** | **NA** | **48.5** | **NA** | **34.6** |
| **Anti-Fxa (IU/mL)** | **NA** | **0.85** | **NA** | **0.64** |



Ruff CT, et al. *Lancet* 2015;385:2288-95.

# Major Bleeding in Patients With and Without Dose Reduction

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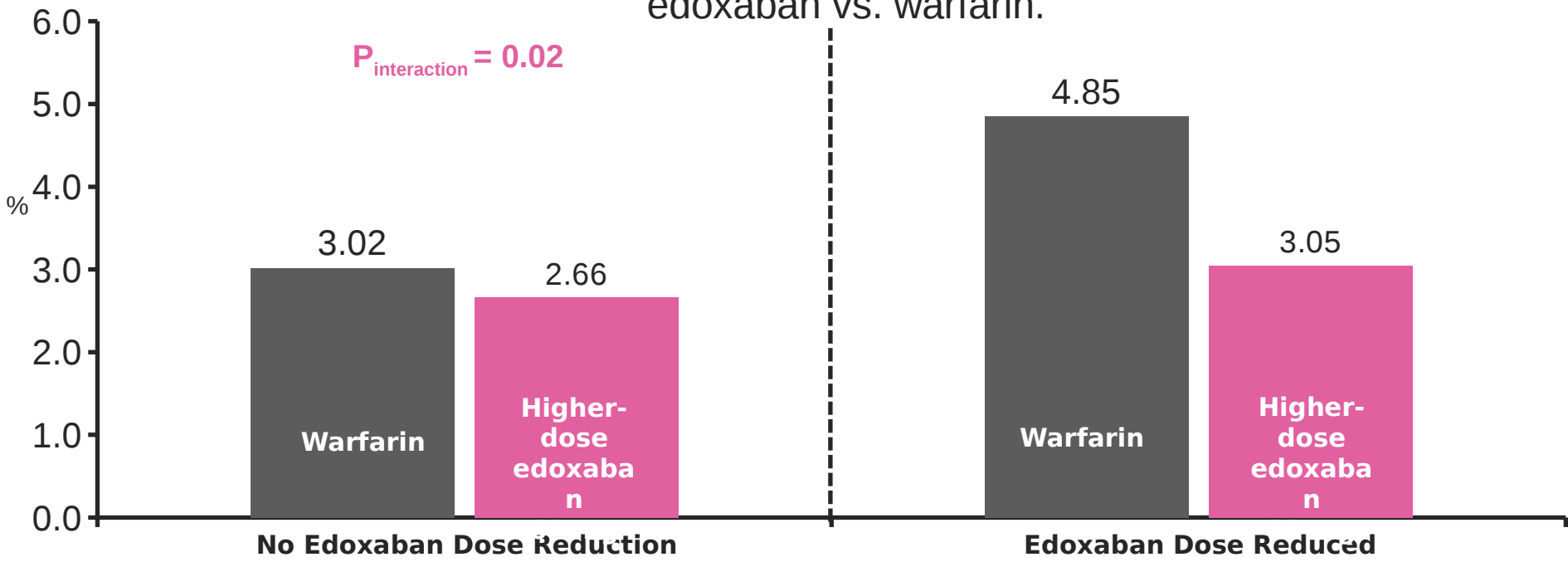
**Higher-dose edoxaban vs. warfarin**
**No Dose Reduction:** HR 0.88 (0.76–1.03)
**Dose Reduction:** HR 0.63 (0.50–0.81)

- Despite the lower anti-FXa activity, dose reduction provided even greater safety with edoxaban vs. warfarin.




| | | | | |
|---|---|---|---|---|
| **Edox Conc (ng/mL)** | **NA** | **48.5** | **NA** | **34.6** |
| **Anti-Fxa (IU/mL)** | **NA** | **0.85** | **NA** | **0.64** |

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Ruff CT, et al. *Lancet* 2015;385:2288-95.

# Edoxaban Trough Concentration and Outcomes

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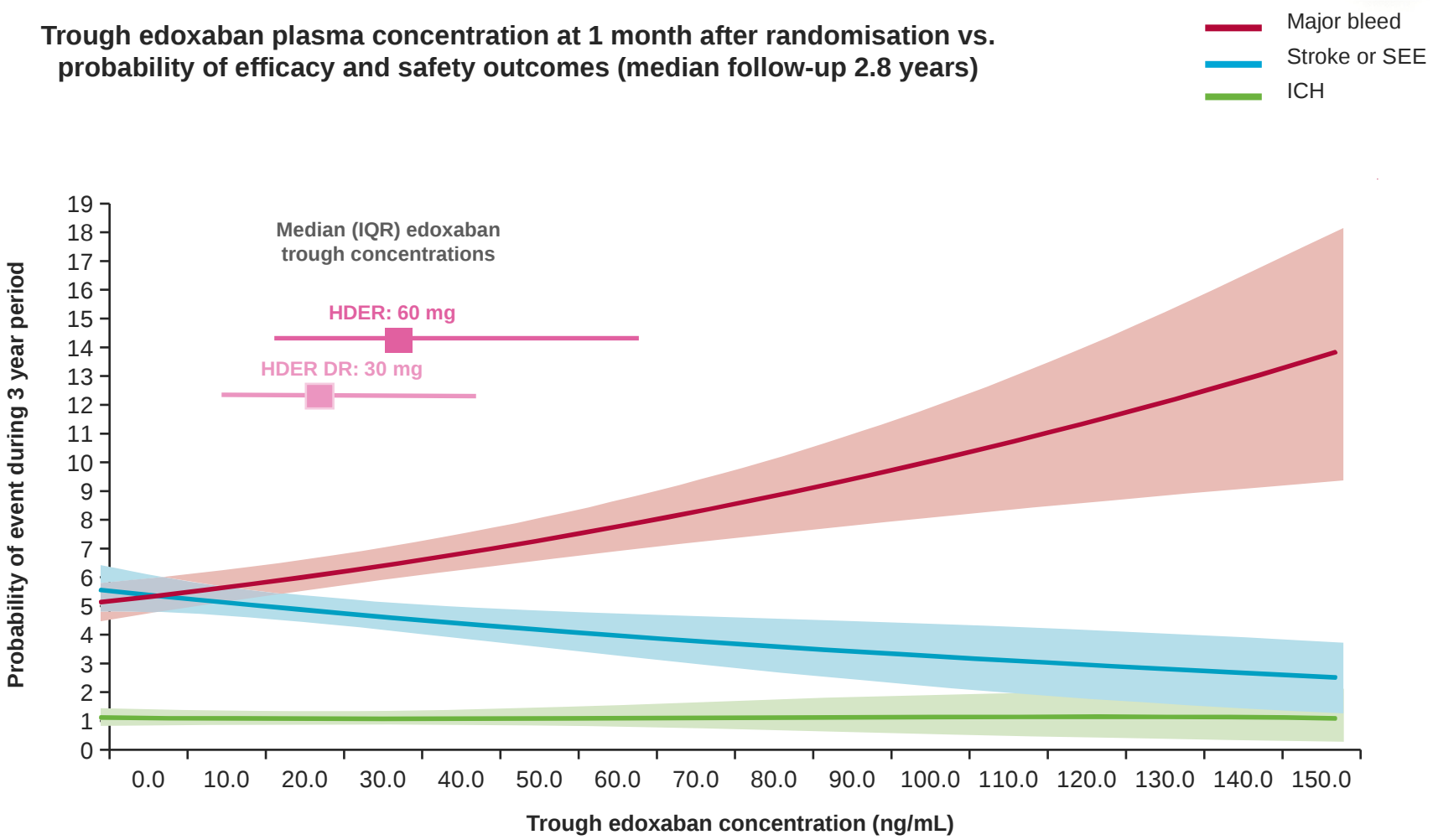
**Trough edoxaban plasma concentration at 1 month after randomisation vs. probability of efficacy and safety outcomes (median follow-up 2.8 years)**




Modelled data with confidence intervals
HDER: higher-dose edoxaban regimen; DR: dose reduced



Ruff CT, et al. *Lancet* 2015;385:2288-95.

# Conclusions: Main Trial



**Compared to well-managed warfarin (TTR 68.4%), once-daily edoxaban:**

- Non-inferior for stroke/systemic embolic event (both regimens)
  - Trend toward reduced stroke/systemic embolic event in ITT analysis
- Both regimens significantly reduced:
  - Major bleeding
  - ICH
  - Hemorrhagic stroke
  - CV death
- Superior net clinical outcomes



Giugliano RP, et al. *N Engl J Med* 2013;369:2093-104.

# Conclusions: Edoxaban Dose Adjustment



**Reducing the dose of edoxaban based on clinical features alone:**

- Maintained the balance between ischemic and bleeding events without measuring drug levels or anticoagulant activity

**The therapeutic window (dose response curve) of edoxaban:**

- Major bleeding – most sensitive to dose concentration
- Stroke or SEE – less sensitive to dose concentration
- ICH – least sensitive to dose concentration



Ruff CT, et al. *Lancet* 2015;385:2288-95.

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# Summary

## High-Risk Populations

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# Efficacy of Higher-dose Edoxaban (HDER) in High-Risk Populations

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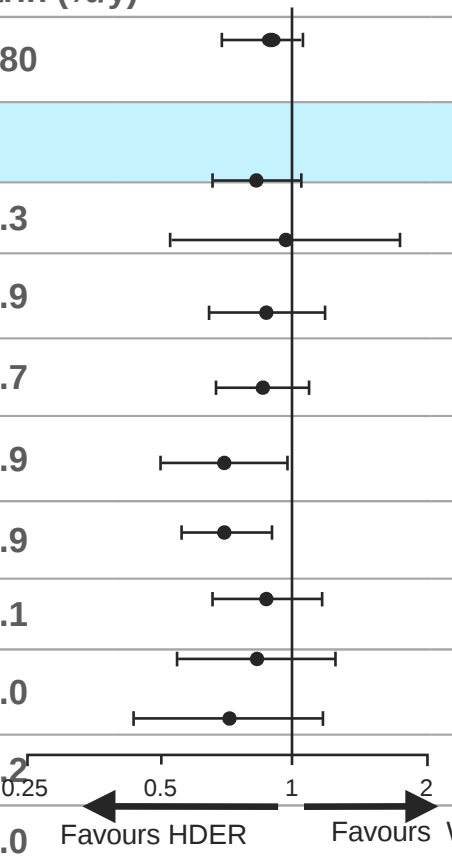
| | HDER (%/y) | Warfarin (%/y) | HR (95% CI) |
|---|---|---|---|
| Stroke/SEE (Overall Population)[1] | 1.57 | 1.80 | 0.87 (0.73–1.04)[a] |
| **Stroke/SEE in High-Risk Populations** | | | |
| Elderly (Age ≥75 years)[2] | 1.9 | 2.3 | 0.83 (0.66–1.04) |
| Increased Risk of Falling[3] | 2.8 | 2.9 | 0.96 (0.53–1.75) |
| Moderate Renal Dysfunction (CrCl 30–50 mL/min)[4] | 2.3 | 2.7 | 0.87 (0.65–1.18) |
| Prior Ischemic Stroke or TIA[5] | 2.4 | 2.9 | 0.86 (0.67–1.09) |
| Concomitant Single Antiplatelet Therapy[6] | 1.3 | 1.9 | 0.70 (0.50–0.98) |
| VKA Naïve[7] | 1.5 | 2.1 | 0.71 (0.56–0.90) |
| Female Sex[8] | 1.8 | 2.0 | 0.87 (0.66–1.17) |
| Heart Failure (NYHA class III–IV)[9] | 1.8 | 2.2 | 0.83 (0.55–1.25) |
| Valvular Heart Disease[10] | 1.4 | 2.0 | 0.69 (0.44–1.07) |




[a] CI = 97.5%

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1. Giugliano et al. *N Engl J Med* 2013; 369:2093–104. 2. Kato et al. *J Am Heart Assoc* 2016;5:e003432.
3. Steffel et al. J Am Coll Cardiol 2016 ;68:1169-78. 4. Bohula et al. *Circulation* 2016; 134:24–36.
5. Rost et al. *Stroke* 2016; 47:2075–82. 6. Xu et al. *J Am Heart Assoc* 2016;5:e002587.
7. O'Donoghue et al. *Euro Heart J*. 2015;36:1470–7. 8. Giugliano et al. *Presented at Venice Arrhythmias, 2015*.
9. Magnani et al. *Eur J Heart Fail* 2016 ;18:1153-61. 10. Renda et al. *J Am Coll Cardiol* 2016;67(13_S):2194

# Safety of Higher-Dose Edoxaban (HDER) in High-Risk Populations

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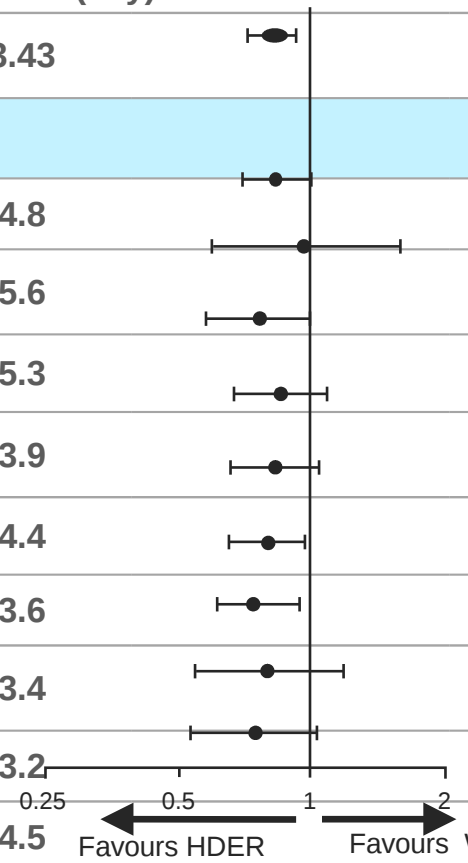
| | HDER (%/y) | Warfarin (%/y) | HR (95% CI) |
|---|---|---|---|
| Major Bleeding (Overall Population)[1] | 2.75 | 3.43 | 0.80 (0.71–0.91) |
| **Major Bleeding in High-Risk Populations** | | | |
| Elderly (Age ≥75 years)[2] | 4.0 | 4.8 | 0.83 (0.70–0.99) |
| Increased Risk of Falling[3] | 5.4 | 5.6 | 0.96 (0.59–1.56) |
| Moderate Renal Dysfunction (CrCl 30–50 mL/min)[4] | 4.0 | 5.3 | 0.76 (0.58–0.98) |
| Prior Ischemic Stroke or TIA[5] | 3.3 | 3.9 | 0.84 (0.67–1.06) |
| Concomitant Single Antiplatelet Therapy[6] | 3.6 | 4.4 | 0.82 (0.65–1.04) |
| VKA Naïve[7] | 2.9 | 3.6 | 0.80 (0.65–0.97) |
| Female Sex[8] | 2.5 | 3.4 | 0.74 (0.59–0.92) |
| Heart Failure (NYHA class III–IV)[9] | 2.5 | 3.2 | 0.79 (0.54–1.17) |
| Valvular Heart Disease[10] | 3.3 | 4.5 | 0.74 (0.53–1.02) |

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# How to Use Edoxaban

## Review of the Canadian Product Monograph

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# Edoxaban: Indications



## Edoxaban is indicated for the:

- **Prevention of stroke and systemic embolic events in patients with atrial fibrillation, in whom anticoagulation is appropriate**
- Treatment of venous thromboembolism (VTE) (deep vein thrombosis [DVT], pulmonary embolism [PE]) and the prevention of recurrent DVT
  and PE



LIXIANA® (Edoxaban) Product Monograph. Daiichi Sankyo, Inc. November 2016.

# Edoxaban Dosing Recommendations for Stroke Prevention in AF

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**Usual Recommended Dose:** 60 mg once daily

***can be taken with or without food***

**If any of the following:**

- **Moderate renal impairment (CrCl 30- 50 mL/min )**
- **Low body weight ≤ 60 kg (132 lbs)**
- **Concomitant use of P-gp inhibitors, except amiodarone and verapamil**

**Dose Reduction:** 30 mg once daily



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# Use of Edoxaban in Special Patient Populations

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## Patients with renal impairment

| | Edoxaban dose OD |
|---|---|
| Mild renal impairment (CrCl 50-80 mL/min) | 60 mg |
| Moderate renal impairment (CrCl 30-50 mL/min) | 30 mg |
| Severe renal disease or on dialysis (CrCl <30 mL/min) | Not recommended |

## Patients with hepatic impairment impairment

| | Edoxaban dose OD |
|---|---|
| Mild to moderate hepatic impairment | 60 mg |
| Severe hepatic impairment | Not recommended |
| Hepatic disease associated with intrinsic coagulation abnormalities | Contraindicated |

## Elderly

**No dose adjustment generally required**



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# Precision Medicine: The Right Drug and the Right Dose

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- NOACs in general have a favorable efficacy and safety profile compared with VKAs
- However, optimal anticoagulant selection requires consideration of **individual patient characteristics** and important **differences among the agents**

**Drug Factors:**

- Dose schedule (once vs. twice daily)
- Drug interactions
- Efficacy and safety vs. warfarin in important patient subgroups

**Patient Characteristics:**

- Age
- Renal function
- Comorbidities (e.g., CVD)
- Relative risks of stroke vs. bleeding
- Patient adherence or preference for once-daily vs. twice-daily dosing

# Summary

- Dose-adjusted edoxaban therapy offers a favorable efficacy and safety profile compared with warfarin
  - non-inferior to warfarin with respect to stroke prevention
  - Lower rates of bleeding and death from CV causes

- Another option in the NOAC armamentarium → tailored stroke prevention therapy

# Thank You!
# Questions?

# Back-up Slides

# Edoxaban: Contraindications



- Clinically significant active bleeding, including GI bleeding
- Lesions or conditions at increased risk of clinically significant bleeding, e.g.:
  - Recent cerebral infarction (hemorrhagic or ischemic)
  - Active peptic ulcer disease with recent bleeding
  - Spontaneous or acquired impairment of hemostasis
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Hypersensitivity to edoxaban or to any ingredients of the formulation
- Concomitant treatment with any other anticoagulant, including
  - UFH, except at doses used to maintain a patent central venous or arterial catheter
  - LMWH (e.g., enoxaparin and dalteparin)
  - Heparin derivatives (e.g., fondaparinux)
  - Oral anticoagulants (e.g., warfarin, dabigatran, apixaban, rivaroxaban) except under circumstances of switching therapy to or from edoxaban
- Pregnancy
- Nursing Women



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# Use of Edoxaban in Patients Taking Concomitant Medications

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## Pharmacokinetic drug interactions

| Concomitant medications | Recommendation |
|---|---|
| **P-gp inhibitors/substrates** (e.g., cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine)* | • Dose reduction to edoxaban 30 mg daily |
| **Strong CYP 3A4 and P-gp inducers** (e.g., rifampicin) | • Should generally be avoided since edoxaban efficacy may be compromised |

## Pharmacodynamic drug interactions

| Concomitant medications | Recommendation |
|---|---|
| **Anticoagulants** | • Contraindicated due to increased bleeding risk |
| **ASA** | • May be co-administered with low-dose ASA (≤100 mg/day)<br>• Assess bleeding risk before co-administration and use with caution if necessary |
| **Thienopyridines** (e.g., clopidogrel) | • May increase risk of bleeding, use with caution |
| **NSAIDS** (naproxen) | • Chronic use of NSAIDs not recommended with edoxaban |

*Except verapamil and amiodarone – no dose adjustment required with these agents



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# Information on Switching To Edoxaban



| Switching from: | To Edoxaban |
|---|---|
| VKA | • Discontinue VKA and start edoxaban when INR ≤ 2.5 |
| Dabigatran, rivaroxaban, apixaban | • Discontinue non-VKA oral anticoagulant<br>• Start edoxaban at the time of the next non-VKA dose |
| Subcutaneous anticoagulant | • Discontinue subcutaneous anticoagulant<br>• Start edoxaban at time of next scheduled subcutaneous anticoagulant dose |
| Unfractionated heparin | • Discontinue infusion and start edoxaban 4 hours later |



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# Information on Switching From Edoxaban

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| Switching from edoxaban to: | |
|---|---|
| **VKA oral option:** | • Administer edoxaban 30 mg (15 mg for patients on a reduced dose for one or more of the following: moderate to severe renal impairment [CrCL 15– 50 mL/min], low body weight, or use with P-gp inhibitors [except amiodarone and verapamil]), together with an appropriate VKA dose<br>• Measure INR at least weekly and just prior to daily edoxaban dose to minimize influence on INR measurements<br>• Once stable INR ≥ 2.0 achieved, discontinue edoxaban |
| **Parenteral anticoagulant and VKA option:** | • Discontinue edoxaban and administer parenteral anticoagulant and VKA at time of next scheduled edoxaban dose<br>• Once stable INR ≥ 2.0 achieved, discontinue parenteral anticoagulant and continue VKA |
| **Oral anticoagulants other than VKA:** | • Discontinue edoxaban<br>• Start non-VKA anticoagulant at time of next scheduled edoxaban dose |
| **Parenteral anticoagulants:** | • Discontinue edoxaban<br>• Start the parenteral anticoagulant at time of next scheduled edoxaban dose |



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# Temporary Discontinuation

- Edoxaban should be taken regularly, as prescribed, to ensure optimal effectiveness
- All temporary discontinuations should be avoided, unless medically indicated



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# Perioperative Considerations with Edoxaban

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## Pre-Operative Phase

| | |
|---|---|
| Invasive procedure or surgical intervention | Stop edoxaban at least 24 hours before intervention |
| In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required | Consider stopping edoxaban at least 48 hours before surgery |



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# Perioperative Considerations with Edoxaban (continued)



## Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture

- Use of indwelling catheters ↑ risk of epidural or spinal hematoma in patients treated with antithrombotics
  - Remove indwelling epidural or intrathecal catheters at least 5 hours prior to first dose of edoxaban
- If traumatic puncture occurs → delay edoxaban for 24 hours
- Monitor frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction)
  - If neurological deficits noted → urgent diagnosis and treatment necessary
- Before neuraxial intervention:
  - Consider potential benefit vs. risks
  - Use edoxaban only when benefits clearly outweigh possible risks
- Do not withdraw epidural catheter earlier than 24 hours after last administration of edoxaban



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# Postoperative Considerations with Edoxaban

Restart edoxaban as soon as adequate hemostasis has been established and the clinical situation allows in order to avoid unnecessary increased risk of thrombosis



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# Edoxaban Overdose



- In cases of overdose (and depending on clinical situation), stop edoxaban or delay next dose, taking into account the half-life of edoxaban
  (10-14 hours)
- In cases of bleeding, initiate appropriate measures such as packed RBCs and/or hemostasis
- A specific reversal agent for edoxaban is not available
- Consider the following for reversal of the anticoagulant effect of edoxaban:
  - 3- or 4-factor PCC
  - aPCCs
  - Recombinant Factor VIIa

RBCs: red blood cells
PCC: prothrombin complex concentrate
aPCCs: activated prothrombin complex concentrates



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# Monitoring and Testing



- No need to monitor anticoagulation effect of edoxaban during routine clinical practice
- However, assessment of anticoagulant effect of edoxaban may be appropriate in certain infrequent clinical situations, such as:
  - Overdosage
  - Acute bleeding
  - Urgent surgery
  - Cases of suspected non-compliance
- Calibrated quantitative anti-FXa assay may be useful to inform clinical decisions in these circumstances



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# Conclusions

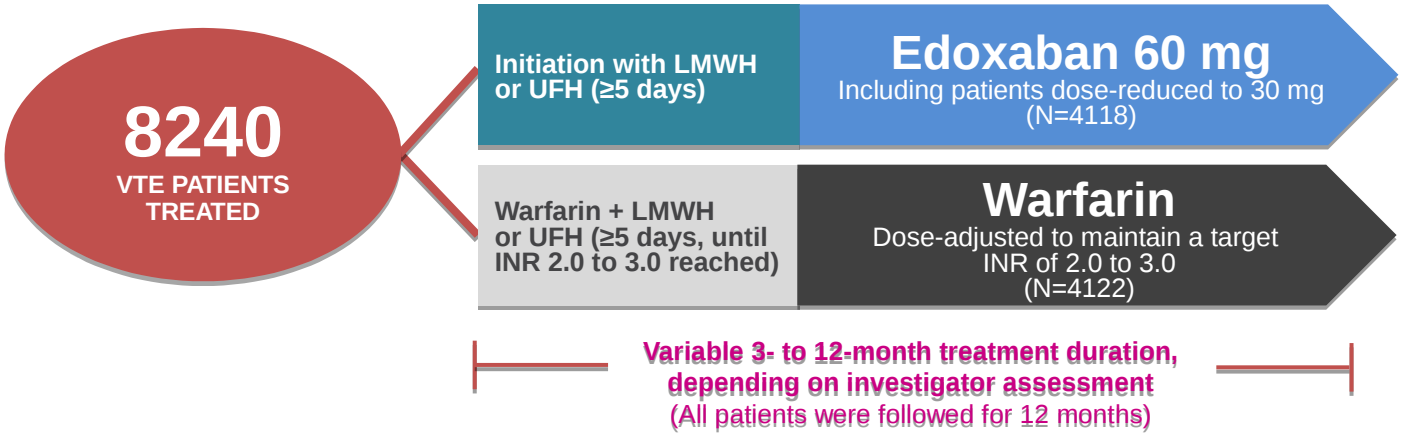
Hokusai VTE

Summary of Efficacy and Safety in Venous Thromboembolism (VTE)

# EDOXABAN

# Study Design






**Primary Endpoints:**

**Primary efficacy:**

Incidence of adjudicated symptomatic recurrent VTE, defined as a composite of DVT or nonfatal or fatal PE

**Primary safety:**

Incidence of adjudicated clinically relevant bleeding, defined as the composite of major or CRNM

- A total of 8240 patients (N=4118 for edoxaban and N=4122 for warfarin) received study drug and were included in the mITT population (patients who received at least one dose of study medication)
- Patients randomized to edoxaban received 30 mg once daily if they met one or more of the following criteria:
  - CrCl 30 to 50 mL/min
  - Body weight ≤60 kg/132 lb
  - Concomitant use of certain P-gp inhibitors



CrCl: creatinine clearance; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CRNM: clinically relevant non-major bleeding

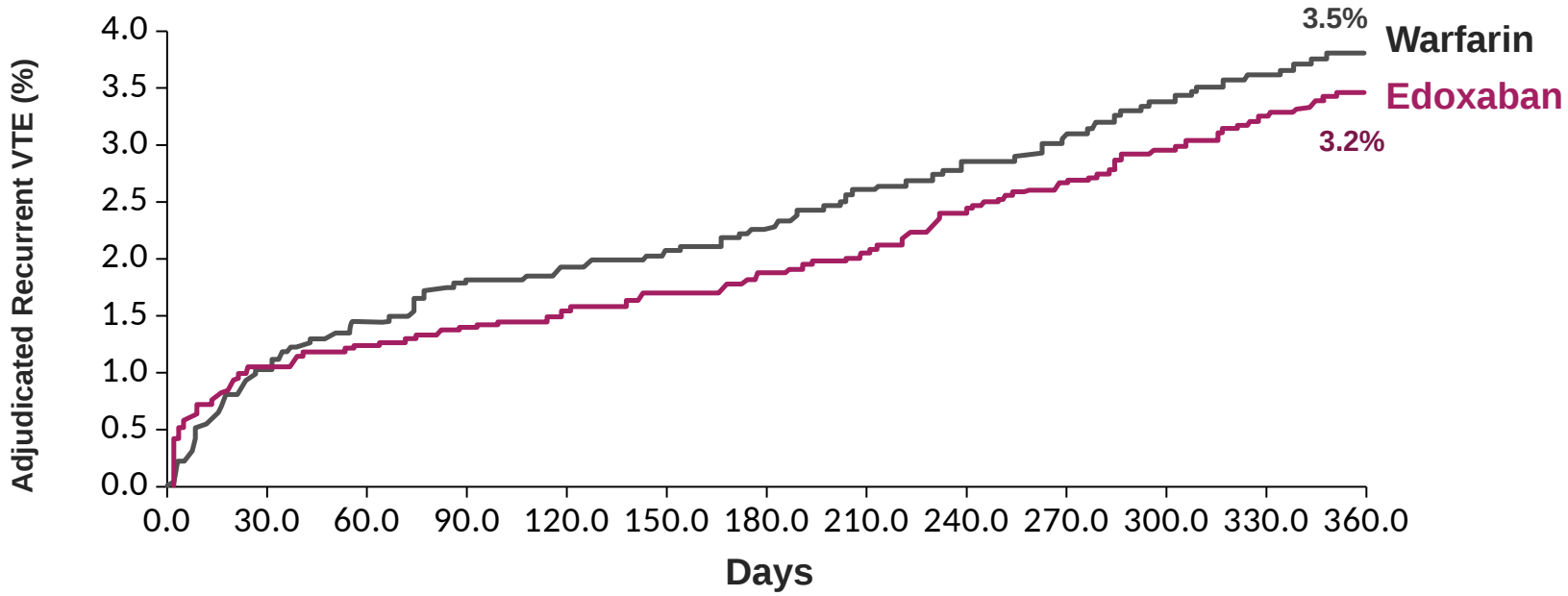
The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415.

# Primary Efficacy Outcome: Recurrent VTE



## Kaplan-Meier Cumulative Event Rates for Adjudicated Recurrent VTE

**Hazard ratio (95% CI) with edoxaban: 0.89 (0.70–1.13); P<0.001 for non-inferiority**





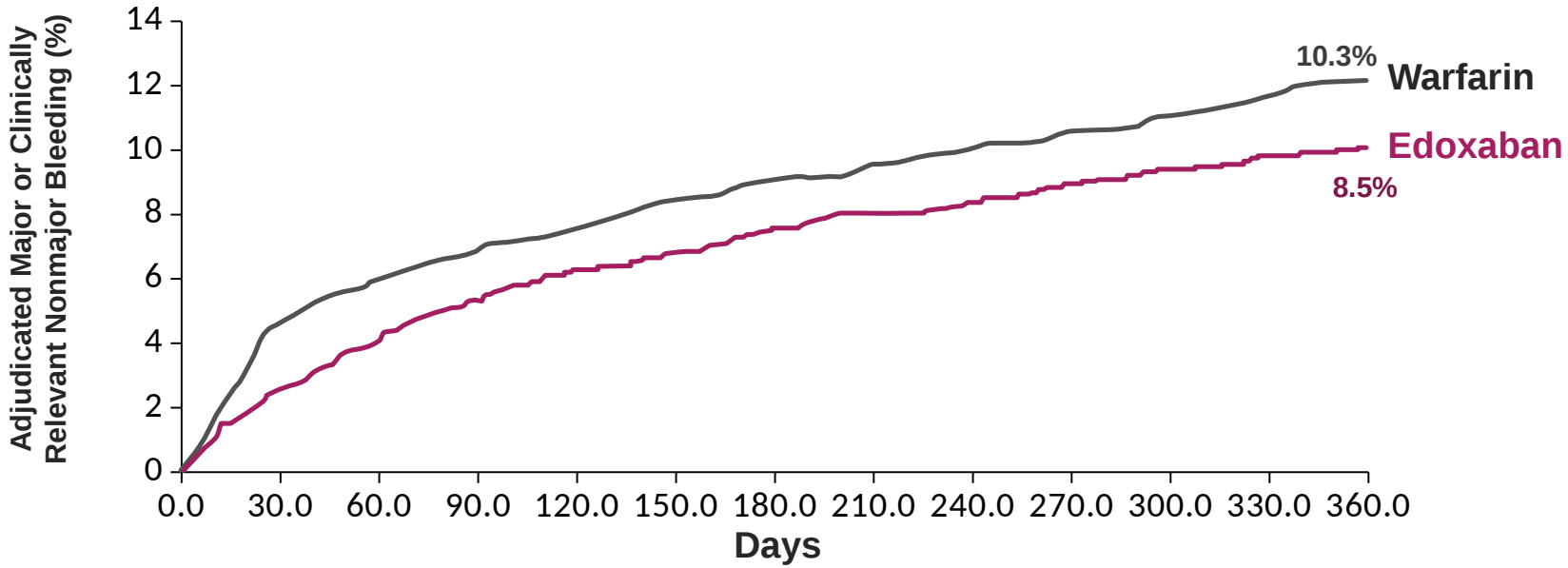

The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415

# Primary Safety Outcome: Major or Clinically-Relevant Non-Major Bleeding



## Kaplan-Meier Cumulative Event Rates for Adjudicated Major or Clinically Relevant Non-major Bleeding

**Hazard ratio (95% CI): 0.81 (0.71–0.94); P=0.004 for superiority**






The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415

# Conclusions



## Edoxaban after initial treatment with heparin:

- Non-inferior to high-quality standard therapy for preventing recurrent VTE
- Consistent efficacy in patients with DVT and PE
- Clinically significant reduction in recurrent VTE in right ventricular dysfunction subgroup
- Significantly less bleeding in a broad spectrum of patients with VTE, including those with severe PE



The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415

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Hokusai VTE

# Back-up Slides

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# Patient Characteristics



| Patient Characteristic[a] | Edoxaban (N=4118) | Warfarin (N=4122) |
|---|---|---|
| **Age** | | |
| Mean – yr | 55.7 ± 16.3 | 55.9 ± 16.2 |
| ≥75 yr – no. (%) | 560 (13.6) | 544 (13.2) |
| **Male sex – no. (%)** | 2360 (57.3) | 2356 (57.2) |
| **Weight – no. (%)** | | |
| ≤60 kg | 524 (12.7) | 519 (12.6) |
| >100 kg | 611 (14.8) | 654 (15.9) |
| **CrCl 30-50 mL/min – no. (%)** | 268 (6.5) | 273 (6.6) |
| **Patients receiving 30 mg of edoxaban at randomization – no. (%)** | 733 (17.8) | 719 (17.4) |
| **Causes of DVT or PE – no. (%)[b]** | | |
| Unprovoked | 2713 (65.9) | 2697 (65.4) |
| Temporary risk factor | 1132 (27.5) | 1140 (27.7) |
| Cancer | 378 (9.2) | 393 (9.5) |
| Previous VTE | 784 (19.0) | 736 (17.9) |

[a]Plus–minus values are means ±standard deviation. There were no significant differences between the treatment groups in any of the characteristics listed.
[b]A patient could have multiple risk factors. Temporary risk factors included recent surgery, trauma, immobilization, or use of estrogen.



The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415

# Primary Efficacy Outcome: Recurrent VTE or VTE-Related Death

| | Edoxaban (N=4118) | Warfarin (N=4122) | Hazard ratio (95% CI) | P Value |
|---|---|---|---|---|
| **First recurrent VTE or VTE-related death- no. (%)** | | | | |
| Overall study period | 130 (3.2) | 146 (3.5) | 0.89 (0.70-1.13) | <0.001 noninferiority |
| Patients with index DVT* | 83 (3.4) | 81 (3.3) | 1.02 (0.75-1.38) | |
| Patients with index PE** | 47 (2.8) | 65 (3.9) | 0.73 (0.50-1.06) | |
| On-treatment period | 66 (1.6) | 80 (1.9) | 0.82 (0.60-1.14) | <0.001 noninferiority |
| Subgroup severe PE (RV dysfunction ProBNP) n/N (%) | 15/454 (3.3) | 30/485 (6.2) | 0.52 (0.28-0.98) | |

*Denominator is number of patients with index DVT: 2468 and 2453 in edoxaban and warfarin group respectively
**Denominator is number of patients with index PE : 1650 and 1669 in edoxaban and warfarin group respectively



The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415

# Safety Outcomes



| | Edoxaban (N=4118) | Warfarin (N=4122) | Hazard ratio (95% CI) | P Value |
|---|---|---|---|---|
| **First major or clinically relevant non major bleeding – no. (%)** | 349 (8.5) | 423 (10.3) | 0.81 (0.71-0.94) | 0.004 superiority |
| Major bleeding – no. (%) | 56 (1.4) | 66 (1.6) | 0.84 (0.59-1.21) | 0.35 superiority |
| Fatal | 2 (<0.1) | 10 (0.2) | | |
| Intracranial | 0 | 6 (0.1) | | |
| Non-fatal in critical sites | 13 (0.3) | 25 (0.6) | | |
| Intracranial | 5 (0.1) | 12 (0.3) | | |
| Non-fatal in non-critical sites | 41 (1.0) | 33 (0.8) † | | |
| Clinically relevant non-major bleeding – no. (%) | 298 (7.2) | 368 (8.9) | 0.80 (0.68-0.93) | 0.004 superiority |

† some patients have more than 1 bleeding



The Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406-1415

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# Summary

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# Thank You!
# Questions?

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