Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation – TIMI 48

Primary Results

Robert P. Giugliano, MD, SM, FAHA, FACC

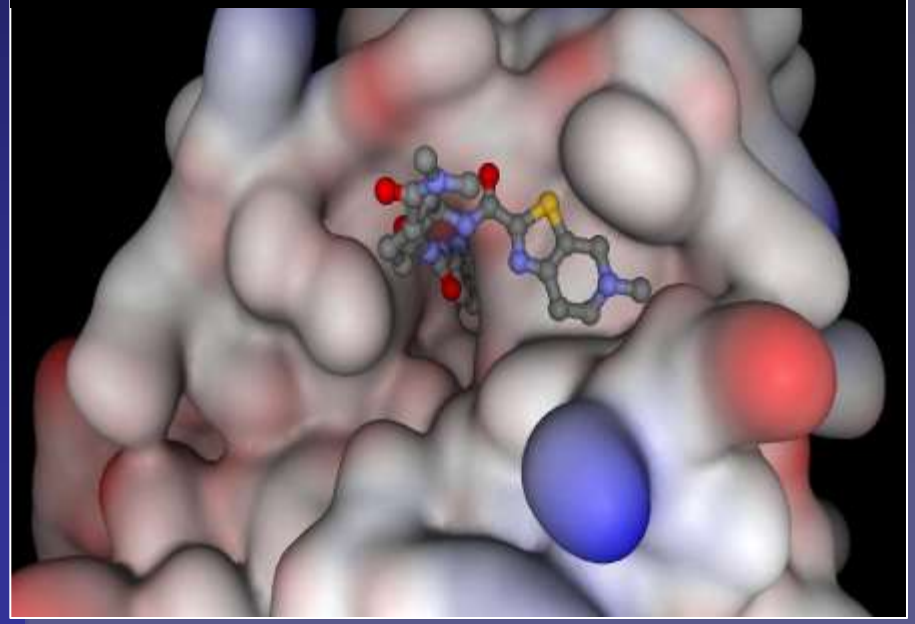
On behalf of the ENGAGE AF-TIMI 48

Executive Committee and Investigators

Background

- Warfarin in AF: ↓stroke 64% vs placebo
- Warfarin ↑bleeding and has well-known limitations
- 3 NOACs at least as effective; ↓hem. stroke by 51%[1]

Edoxaban seated in Factor Xa catalytic center



Direct oral FXa inhibitor

62% oral bioavailability

Peak 1-2h

$t_{1/2}$ ~10-14h

***Once* daily**

~50% renal clearance

Dose↓ 50%[2] if:
- **CrCl 30-50 mL/m**
- **Weight ≤ 60kg**
- **Strong P-gp inhib**

AF=atrial fibrillation; CrCl=creatinine clearance; FXa=Factor Xa; NOAC=new oral anticoagulant; P-gp=p-glycoprotein

1. Dogliiotti A et al. Clin Cardiol 2013;36:61-7.
2. Salazar DE et al. Thromb Haemost 2012;107:925-36.

Study Design

21,105 PATIENTS
AF on electrical recording within last 12 m
$CHADS_2$ ≥2

RANDOMIZATION
1:1:1 randomization is stratified by $CHADS_2$ score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

Warfarin (INR 2.0–3.0)	High-dose Edoxaban 60* mg QD	Low-dose Edoxaban 30* mg QD

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

1º Efficacy EP = Stroke or SEE
2º Efficacy EP = Stroke or SEE or CV mortality
1º Safety EP = Major Bleeding (ISTH criteria)

Non-inferiority
Upper 97.5% CI <1.38

CI = confidence interval; CrCl = creatinine clearance; ISTH=International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE=systemic embolic event

Ruff CR et al. Am Heart J 2010; 160:635-41.

Trial Organization

TIMI Study Group

Eugene Braunwald (Study Chair)
Elliott M. Antman (Principal Investigator)
Robert P. Giugliano (Co-Investigator)
Christian T. Ruff (Co-Investigator)
Suzanne Morin (Director)
Stephen D. Wiviott (CEC)
Sabina A. Murphy (Statistics)
Naveen Deenadayalu (Statistics)
Laura Grip (Project Director)
Abby Cange (Project Manager)

Executive Committee

Eugene Braunwald
Elliott M. Antman
Robert P. Giugliano
Michele Mercuri
Stuart Connolly
John Camm
Michael Ezekowitz
Jonathan Halperin
Albert Waldo

Sponsor: Daiichi Sankyo

Michele Mercuri
Hans Lanz
Indravadan Patel
Minggao Shi
James Hanyok

CRO: Quintiles

Maureen Skinner
Shirali Patel
Dean Otto
Joshua Betcher
Carmen Reissner

Data Safety Monitoring Board

Freek W. A. Verheugt (Chair)
Jeffrey Anderson
J. Donald Easton
Allan Skene (Statistician)
Shinya Goto
Kenneth Bauer

Population/Analysis Definitions

Populations	Analyses
mITT*, On-Treatment†	Primary efficacy (Non-inferiority)
Intent-to-Treat (ITT) All randomized	Superiority All events
Safety, On-Treatment†	Principal Safety Major Bleeding (ISTH definition)

*** mITT = All patients who took at least 1 dose**
† On-Treatment = 1st dose → last dose +3 days or end of double-blind treatment
ISTH=International Society on Thrombosis and Haemostasis

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

CHF=congestive heart failure; IQR=interquartile range; TIA=transient ischemic attack; VKA=vitamin K antagonist

21,105 Patients, 1393 Centers, 46 Countries

UNITED STATES (3907) | CHINA (469) | DENMARK (219) | CROATIA (127)

Key Trial Metrics	
Received drug / enrolled	**99.6%**
Completeness of follow-up	**99.5%**
Final visit or died / enrolled	**99.1%**
Off drug (patients per yr)	**8.8%**
Withdrew consent, no data	**0.9%**
Lost to follow-up	**n=1**
Median time in therapeutic range [Interquartile range]	**68.4% [56.5-77.4]**

INDIA (690) *B. SomaRaju*

TAIWAN (234) *S. Chen*

GUATEMALA (136) *G. Sotomora*

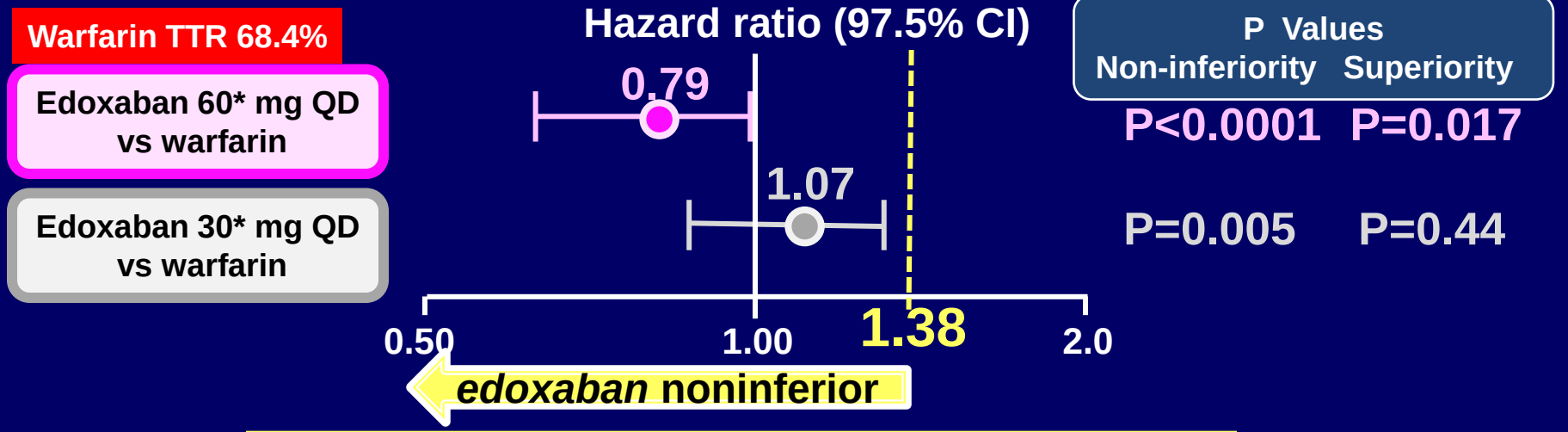
BULGARIA (520) *A. Goudev*

SOUTH KOREA (230) *N. Chung*

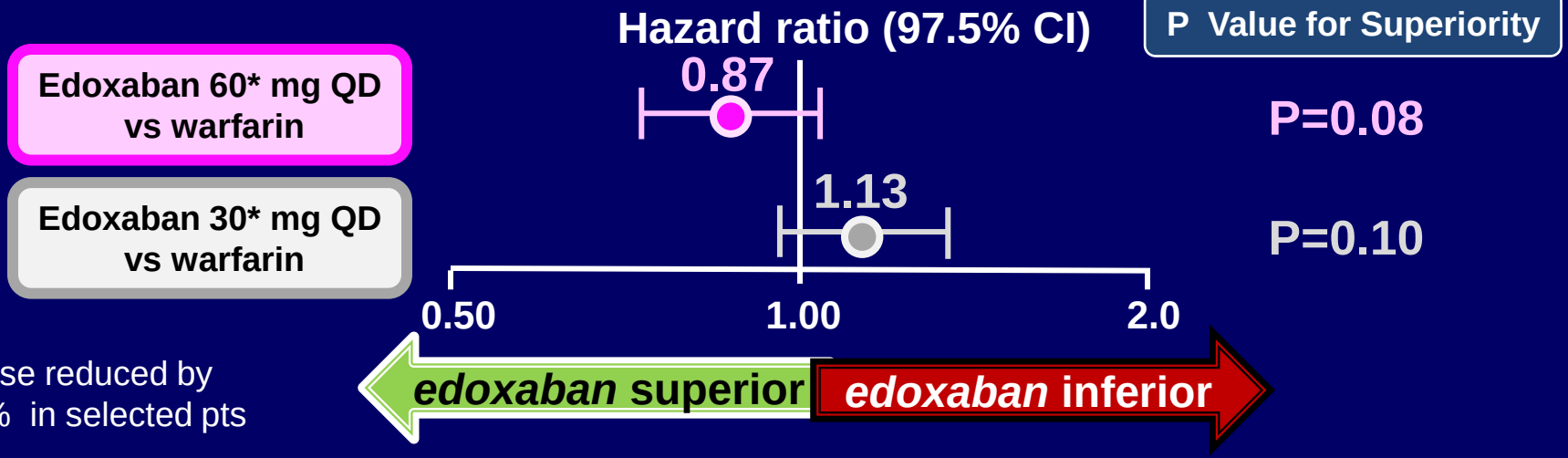
NEW ZEALAND (131) *H. White*

Primary Endpoint: Stroke / SEE
(2.8 years median f/u)

Noninferiority Analysis (mITT, On Treatment)

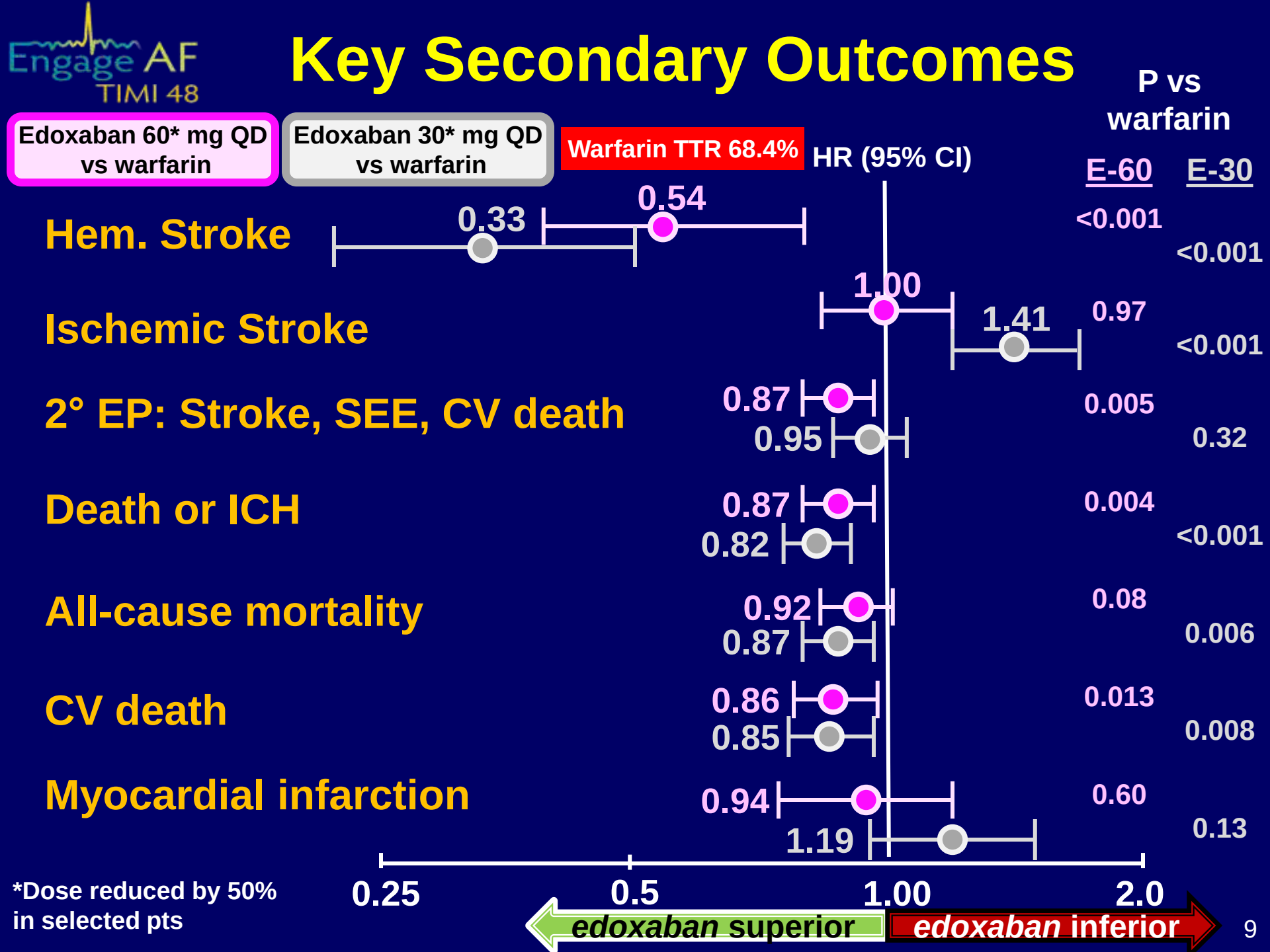


Superiority Analysis (ITT, Overall)



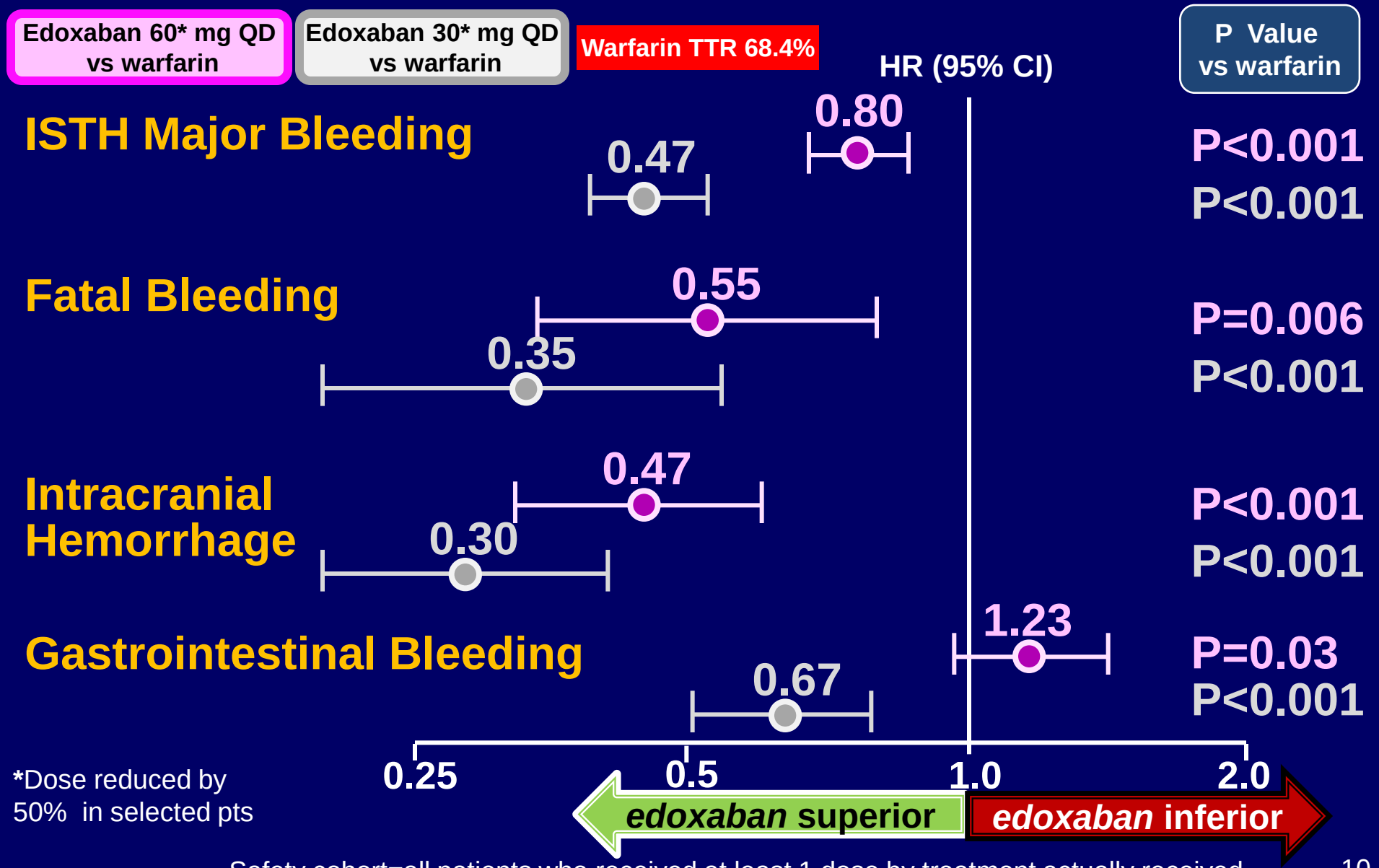
*Dose reduced by 50% in selected pts

Key Secondary Outcomes



*Dose reduced by 50% in selected pts

Main Safety Results
- Safety Cohort on Treatment -

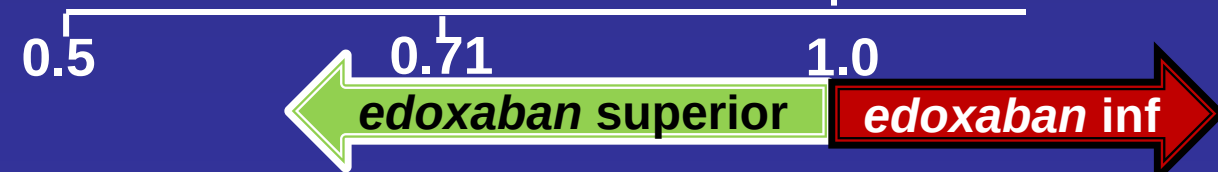


*Dose reduced by 50% in selected pts

Safety cohort=all patients who received at least 1 dose by treatment actually received

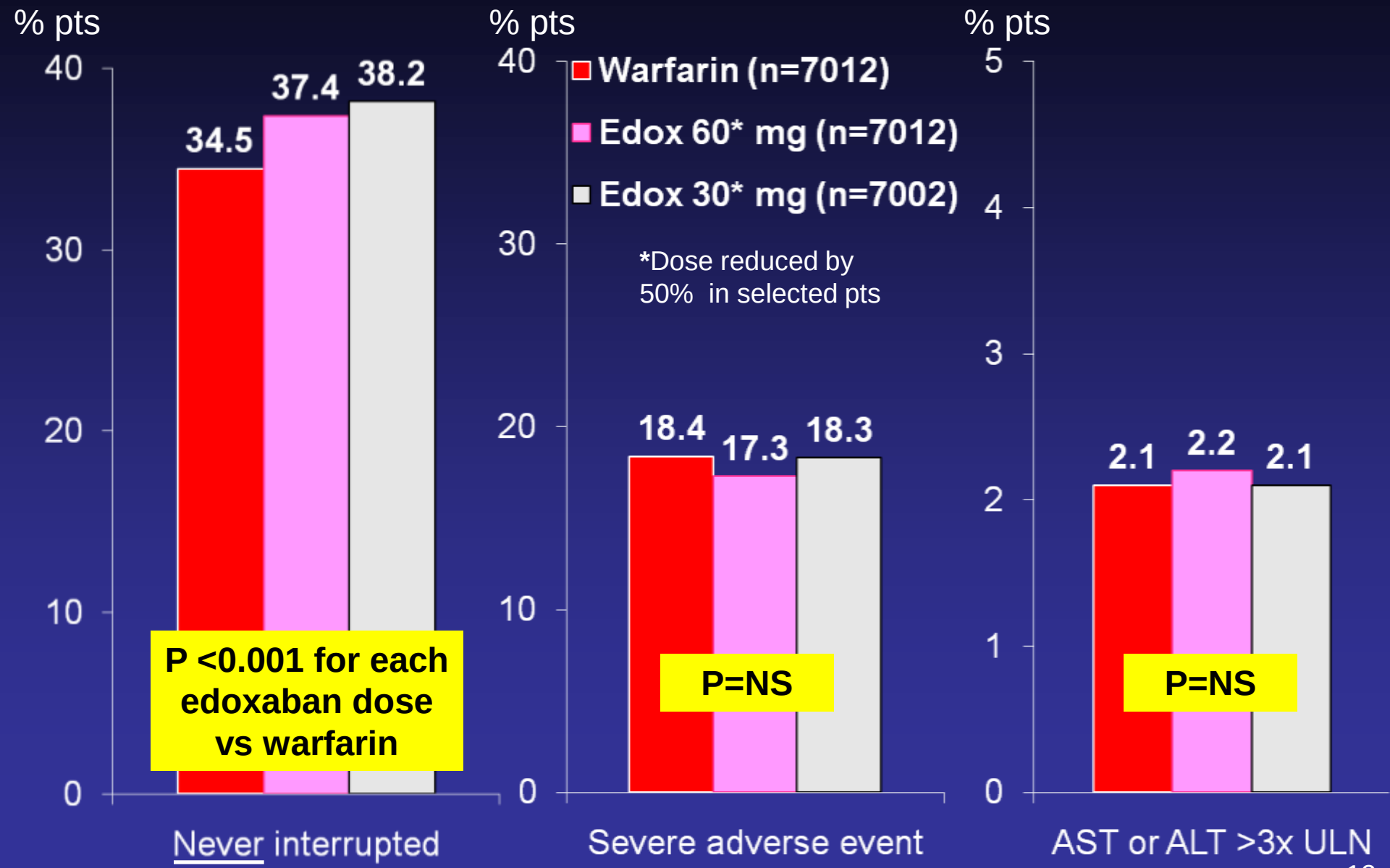
Net Clinical Outcomes

	Edoxaban 60* mg QD vs warfarin	Edoxaban 30* mg QD vs warfarin	Warfarin TTR 68.4%	Hazard ratio (95% CI)	P Value vs warfarin
Stroke, SEE, death, major bleeding	0.89	0.83			P=0.003 P<0.001
Disabling stroke, life-threatening bleeding, death	0.88	0.83			P=0.008 P<0.001
Stroke, SEE, life-threatening bleeding, death	0.88	0.89			P=0.003 P=0.007



*Dose reduced by 50% in selected pts
SEE=systemic embolic event

Tolerability and Adverse Events



Transition Period Outcomes

- All pts transitioned → VKA or NOAC
- If VKA: Frequent INRs, overlapped VKA + edox (30 or 15 mg) for ≤ 2 wks until INR ≥ 2.0
- If NOAC: start when INR < 2.0

Events After Transition to Open-label Anticoagulant	Warfarin (n=4503)	High-dose Edoxaban (n=4526)	Low-dose Edoxaban (n=4613)
Stroke or SEE* through 30d	7 (0.16%)	7 (0.15%)	7 (0.15%)
Major Bleeds through 14d	6 (0.13%)	4 (0.09%)	5 (0.11%)

Data shown include all patients on blinded study drug at the end of the treatment period

SEE=systemic embolic event. No SEEs occurred during the 30-day transition period.

Summary

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

- **Non-inferior for stroke/SEE (both regimens)**
  - **High dose ↓stroke/SEE on Rx (trend ITT)**
- **Both regimens *significantly* reduced:**
  - **Major bleeding (20%/53%)**
  - **ICH (53%/70%)**
  - **Hem. stroke (46%/67%)**
  - **CV death (14%/15%)**
- ***Superior* net clinical outcomes**

No excess in stroke or bleeding during transition → oral anticoagulant at end of trial

The NEW ENGLAND JOURNAL of MEDICINE

www.nejm.com DOI:10.1056/NEJMoa1310907

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D.,

THE LANCET Articles

Comprehensive Meta-Analysis Comparing the Efficacy and Safety of NOACs with Warfarin in AF

Ruff CT, et al. [in press]

European Heart Journal

Left Atrial Structure and Function in Atrial Fibrillation: ENGAGE AF-TIMI 48
Gupta D et al.
EHJ (in press)

Thank you to our patients, investigators and coordinators, data safety committee members, clinical endpoint committee members, core laboratories, operational teams, monitors, Quintiles, and Daiichi Sankyo