

Edoxaban in Atrial Fibrillation

Glenn Gormley, MD, PhD

Senior Executive Officer and
Global Head of R&D, Daiichi Sankyo Co., Ltd



Daiichi-Sankyo

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Background

- ◆ Based on the results of ENGAGE AF-TIMI 48, Daiichi Sankyo submitted a New Drug Application on January 8th, 2014 and is currently seeking approval from the FDA for the use of Edoxaban to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- ◆ During its review, FDA indicated some concerns about the results of sub-group analysis for renal function. FDA requested the Cardiovascular Renal Drug Advisory Committee (CRDAC) to discuss about their concerns

Roles of Advisory Committee

- ◆ The FDA regularly seeks the advice of its advisory committees as it reviews New Drug Applications (NDA)
- ◆ Purpose of the Advisory Committee meeting is to discuss any issues requested by FDA
- ◆ Advisory Committee makes a recommendation to FDA on whether the NDA should be approved or not
- ◆ FDA takes into account the advice of the committee when a final decision is made about the approval of any NDA

Outcome of the Meeting on Oct 30

- ◆ CRD Advisory Committee voted 9 to 1 to recommend approval of once-daily Edoxaban for the reduction in risk of stroke and systemic embolic events (SEE) in patients with non-valvular atrial fibrillation (NVAf)
- ◆ Daiichi Sankyo will work with the FDA during continued review of our New Drug Application

Features of ENGAGE AF-TIMI 48

- Largest NOAC trial (21,105 patients)
- Longest follow-up (2.8 years)
- Best follow-up (1 patient without vital status)
- Highest TTR (68.4%)
- 4-fold dose range (15 mg - 60 mg)
- Once-daily dosage

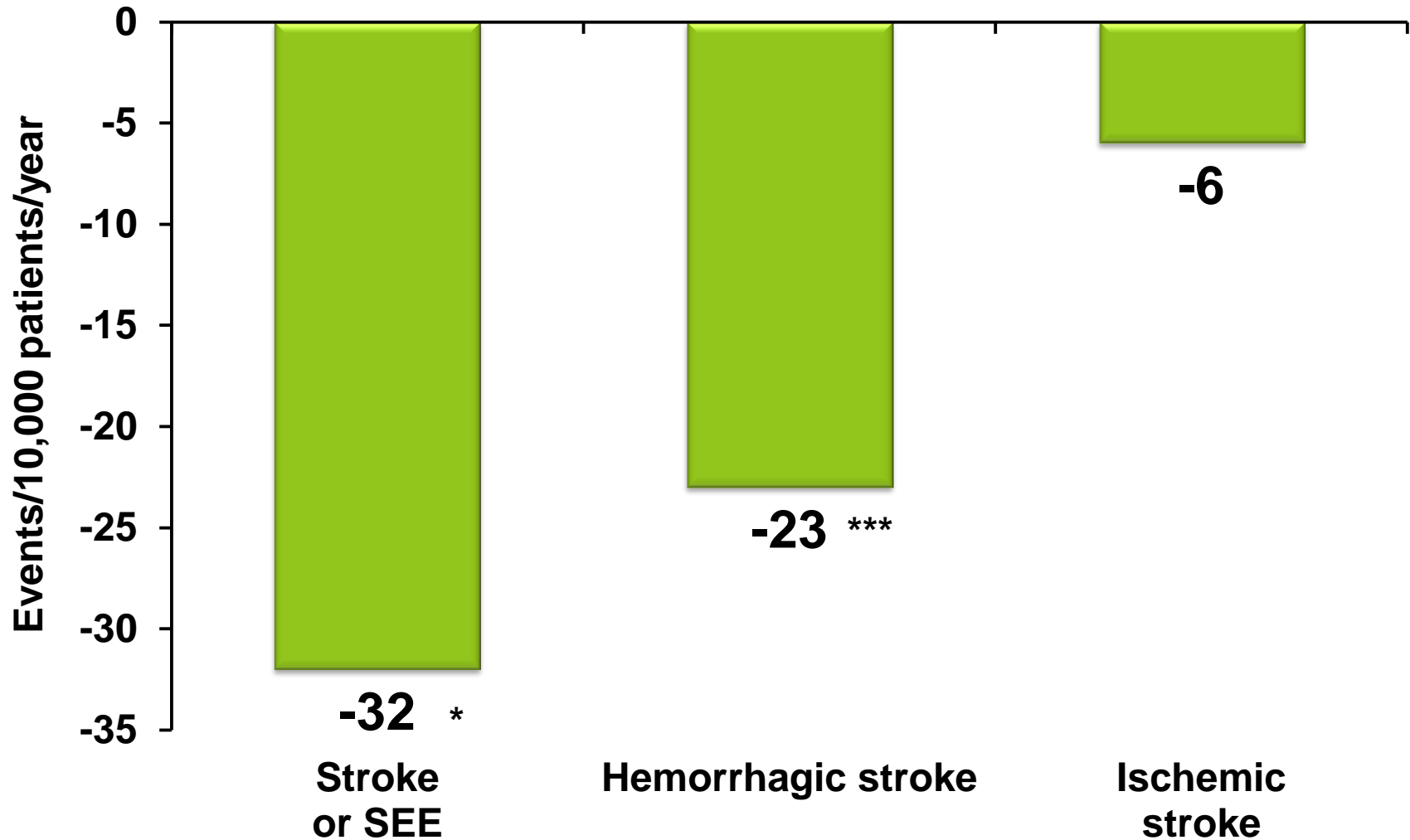
ENGAGE AF-TIMI 48 Trial Results

- ENGAGE met the primary efficacy endpoint of non-inferiority for stroke and SEE and superiority for the principal safety endpoint of major bleeding
- ENGAGE demonstrated significant benefit of Edoxaban compared with warfarin across all key secondary outcomes and predefined composite measures of net clinical outcome
- Many additional exploratory analysis have been conducted to better understand the results of ENGAGE that were not pre-defined in the protocol

Edoxaban 60/30 mg vs Warfarin

Risk Differences for 10,000 Patients per Year

Primary Endpoints—mITT On-Treatment

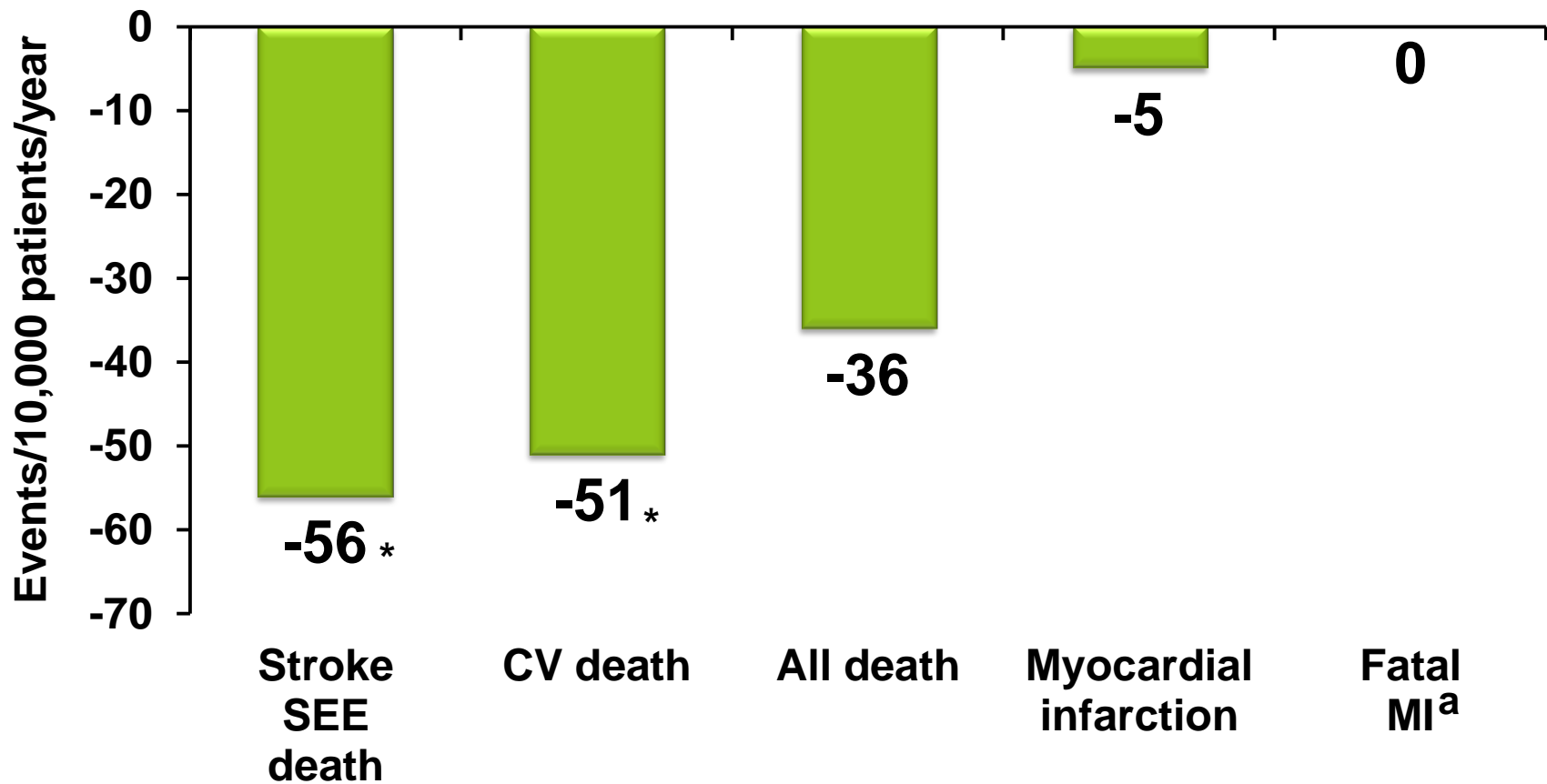


* $p < 0.05$
*** $p \leq 0.001$

Edoxaban 60/30 mg vs Warfarin

Risk Differences for 10,000 Patients per Year

Secondary End Points—ITT Overall



^aFatal MI were 9 in 60/30 group and 9 in warfarin group. No difference between treatment

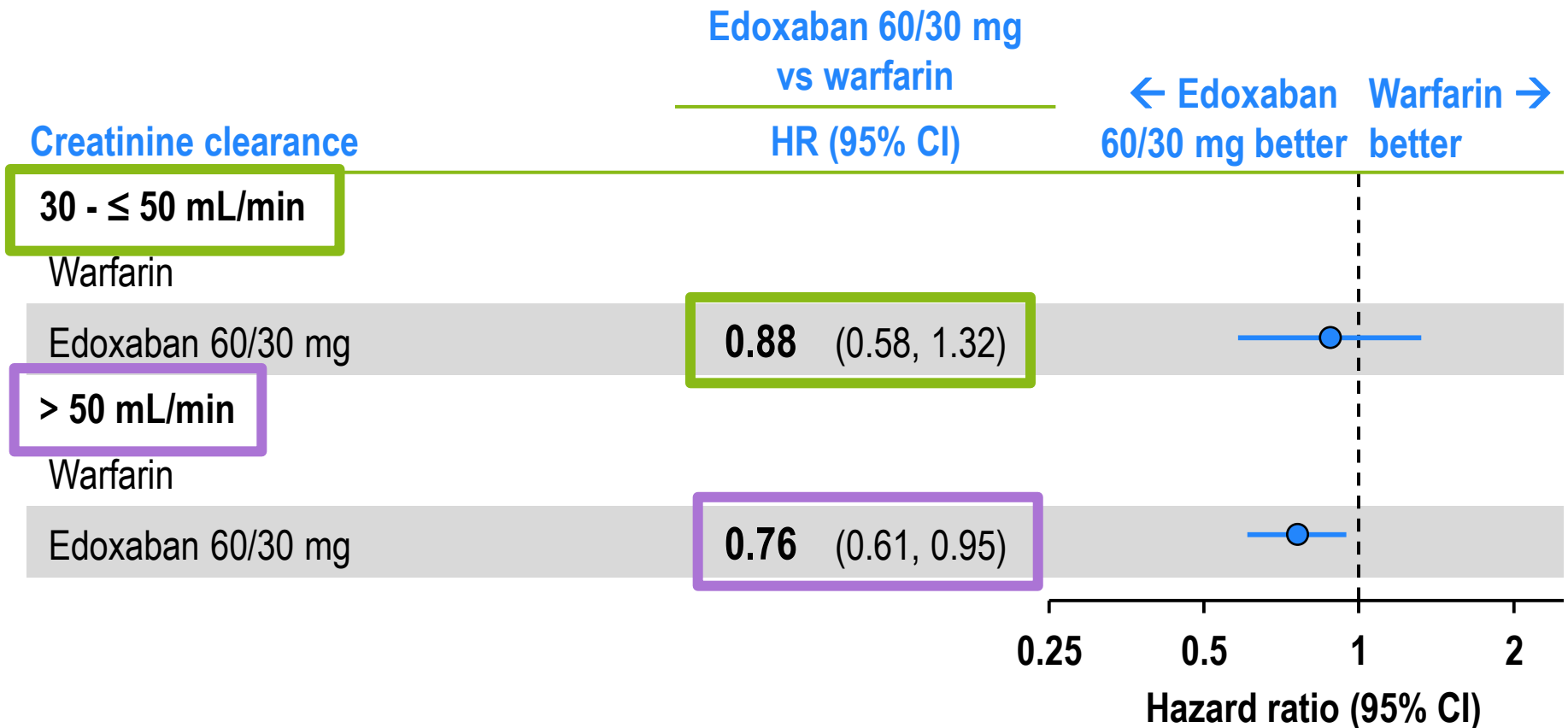
Focus of FDA Advisory Committee Subgroup Analyses

- A test for heterogeneity was used to evaluate whether observed treatment effects were consistent across various subgroups
- 2 out of 20 different subgroups evaluated demonstrated a significant interaction for efficacy
 - Protocol defined analysis by Region
 - Exploratory analysis by 3 categories of baseline CrCL

Stroke or SEE by Baseline CrCL

mITT On-Treatment

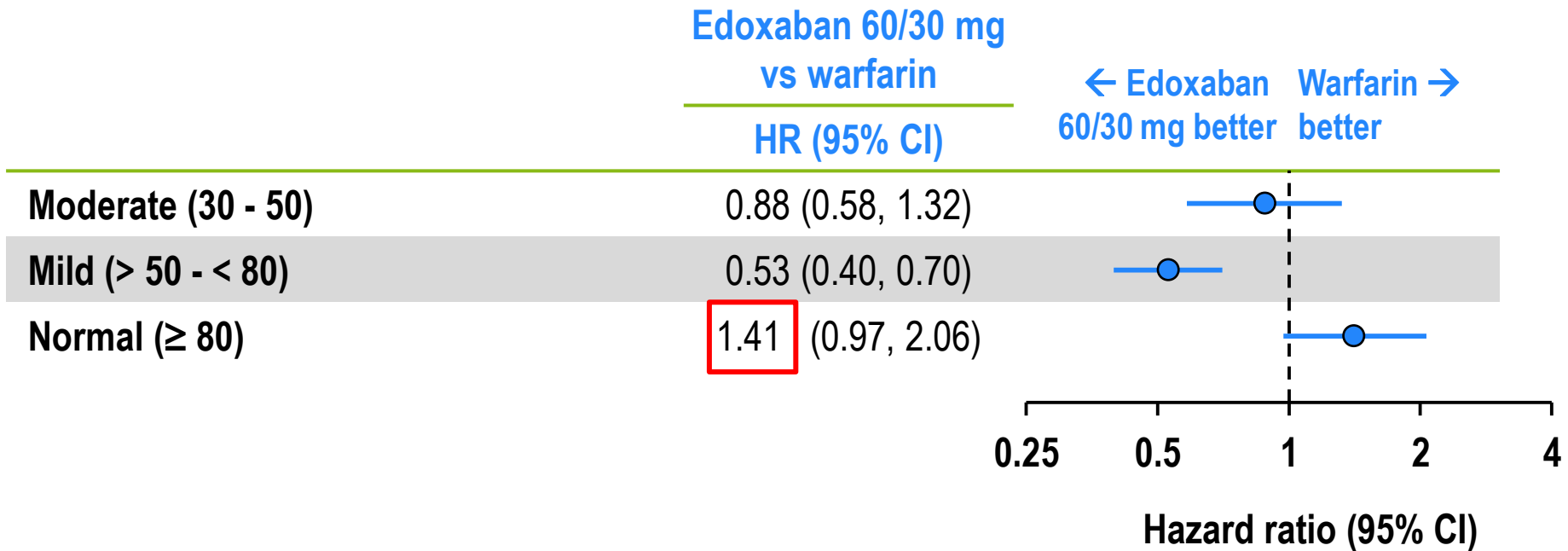
Pre specified subgroup analysis (defined in Protocol)



Stroke or SEE by Baseline CrCL

mITT On-Treatment

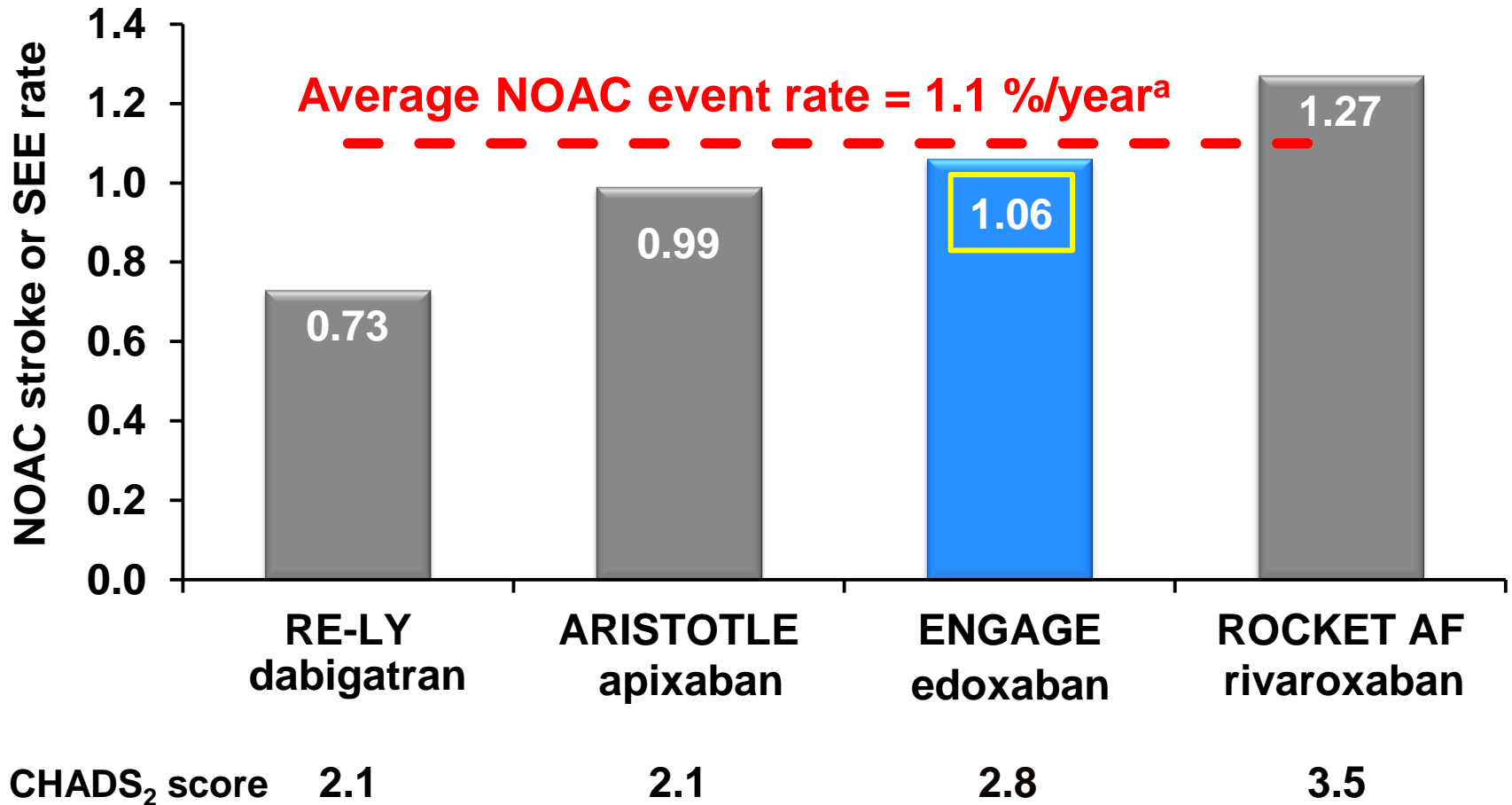
Exploratory subgroup analysis (not pre specified)



NOAC Stroke or SEE Rates in Contemporary Trials

Normal Renal Function Subgroup (CrCL ≥ 80 mL/min)

FDA Briefing Document, table 65, page 156

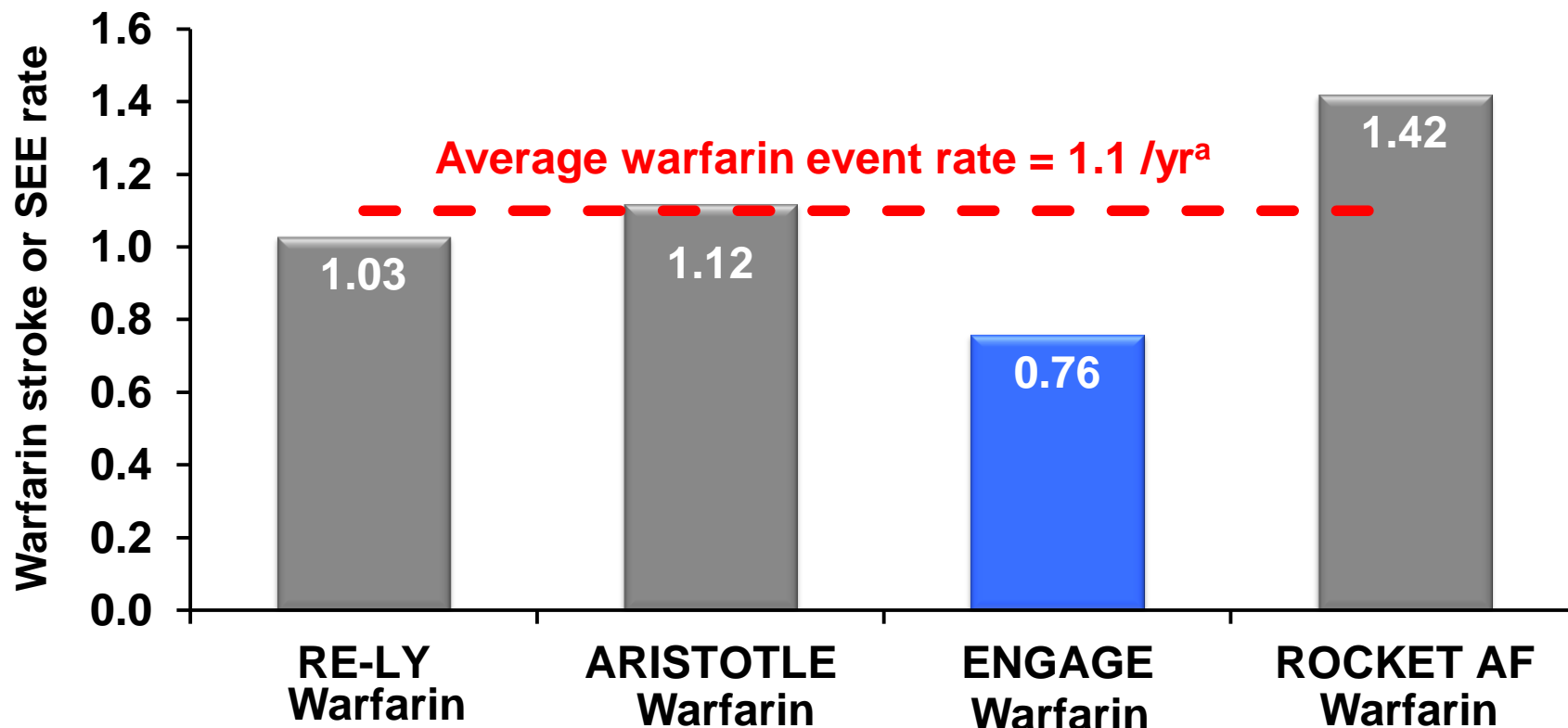


^a Ruff C, et al. *Lancet*. 2014;383:955-962.

Warfarin Stroke or SEE Rates in Contemporary Trials

Normal Renal Function Subgroup (CrCL \geq 80 mL/min)

FDA Briefing Document Table 65, p 156



CHADS₂ score

2.1

2.1

2.8

3.5

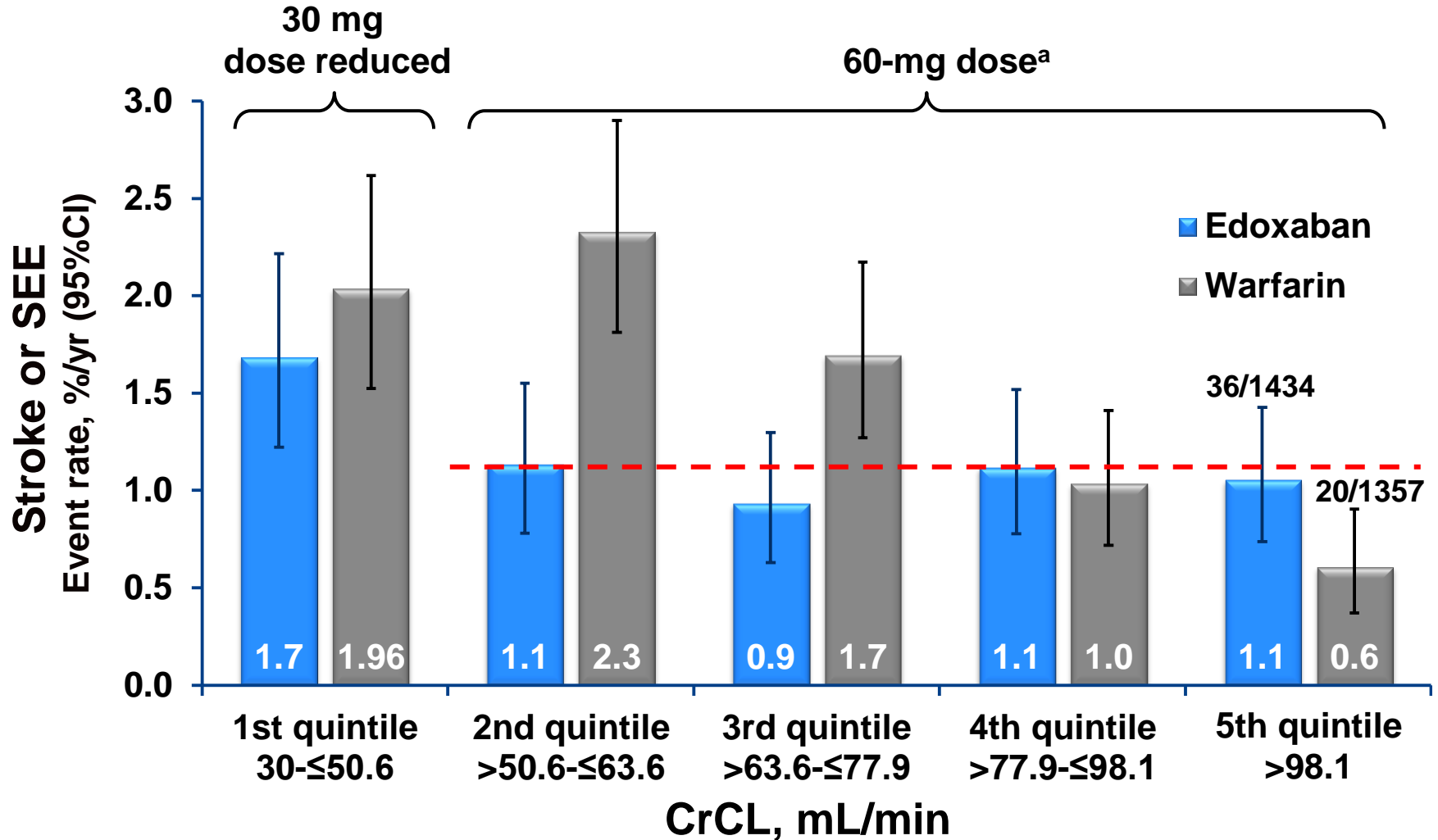
Entire study population.

^a Ruff C, et al. *Lancet*. 2014;383:955-962.

Stroke or SEE by CrCL Quintiles

mITT On-Treatment

Post-hoc subgroup analysis by CrCL quintiles



^a Unless patients met prespecified criteria for dose reduction.

Summary

- ENGAGE met the primary efficacy endpoint of non-inferiority for stroke and SEE and superiority for major bleeding
- ENGAGE demonstrated significant benefit of Edoxaban compared with warfarin across all key secondary outcomes and predefined composite measures of net clinical outcome
- In patients with normal renal function ($\text{CrCL} \geq 80 \text{ mL/min}$), Edoxaban performed similar to other NOACS with an event rate = 1.06%/yr,
- In the 5th quintile of CrCL, ($>98 \text{ mL/min}$), regional variability in warfarin effect and small sample size resulted in a numerical difference in event rates with overlapping confidence intervals

Conclusion

- The use of the Edoxaban 60/30 mg dose regimen for the proposed indication is safe and effective across the entire population of patients studied, including patients with normal renal function, and should be approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation