



Reduction in bleeding with edoxaban vs warfarin linked to lower all-cause mortality in 21,105 patients randomized in the ENGAGE AF-TIMI 48 trial

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

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

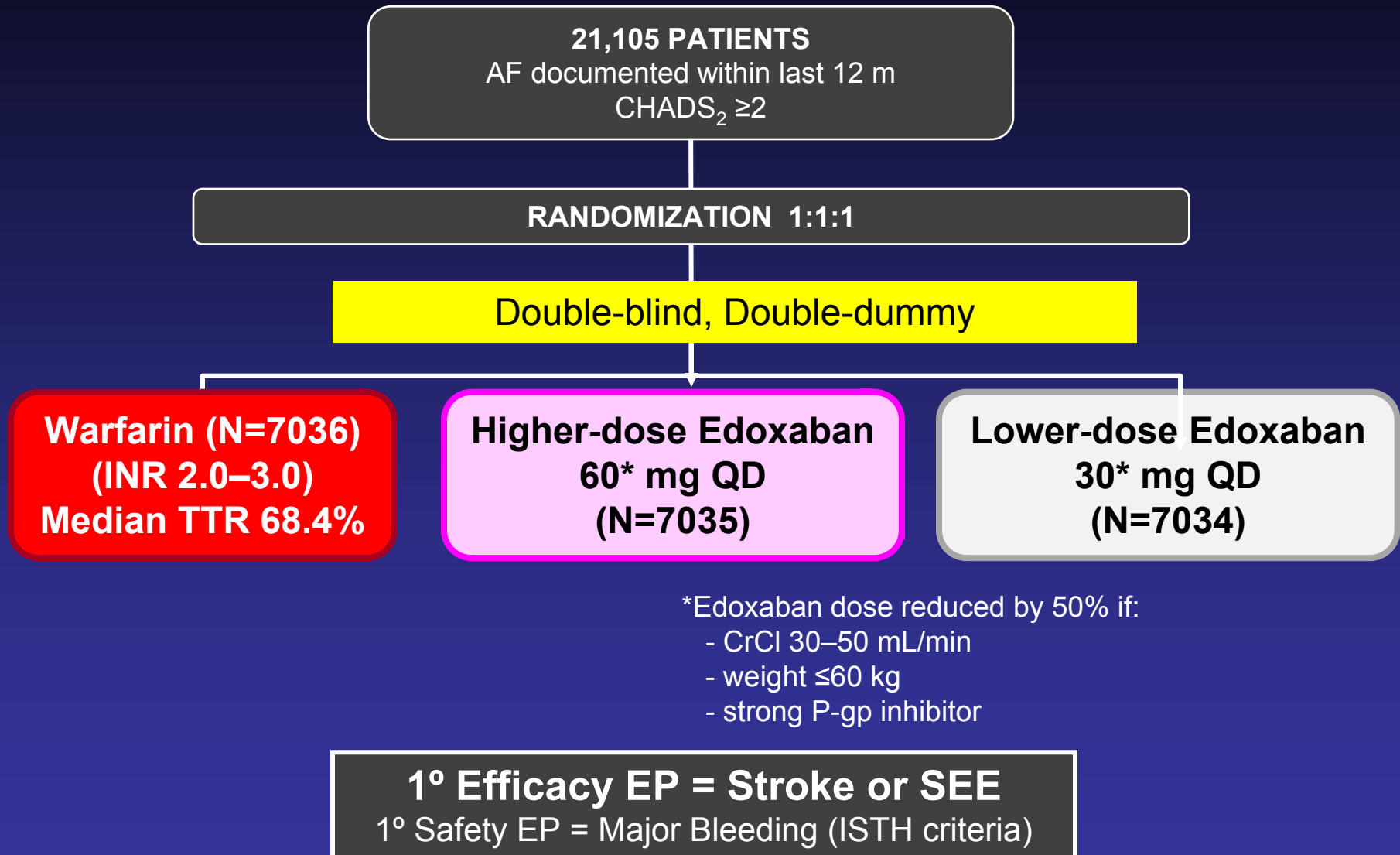
On behalf of the ENGAGE AF-TIMI 48

Executive Committee and Investigators

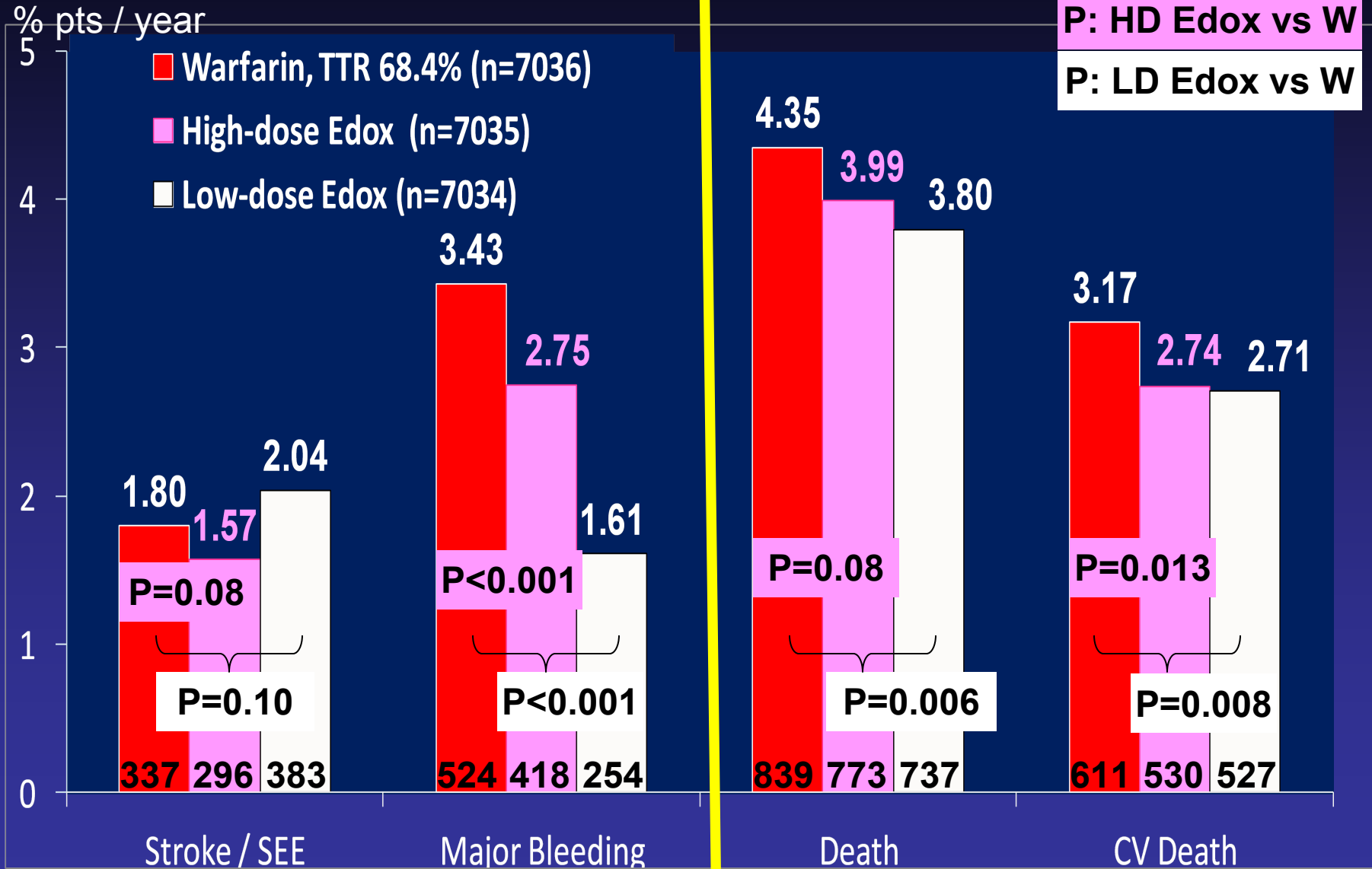
Disclosures

- **Research Grant Support**
 - Daiichi-Sankyo, Merck
- **Honoraria for Lectures/Consulting**
 - Daiichi-Sankyo, Merck, Janssen, Portola, Pfizer, Sanofi
- **NOTE: Dr. Giugliano plans to reference unlabeled/unapproved uses of drugs or products in his presentation.**

Study Design



Primary and Mortality Endpoints



Objectives

In ENGAGE AF-TIMI 48 ITT cohort:

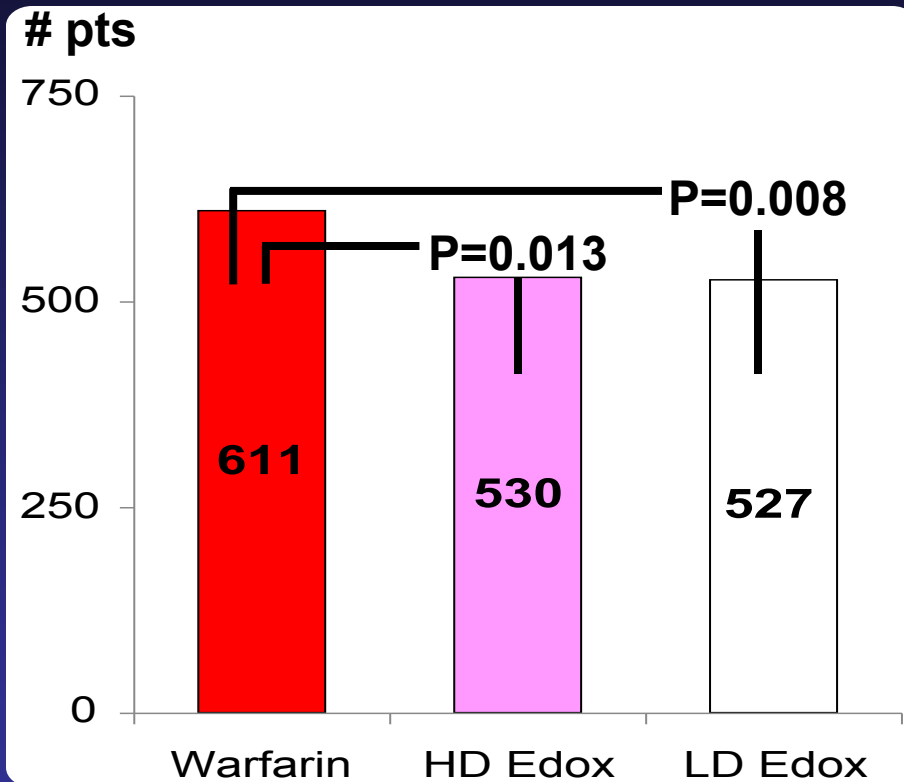
- To compare the causes of death by treatment group
- To explore reasons for differences in mortality rates by treatment group
- To explore the relationship between bleeding and death

Methods

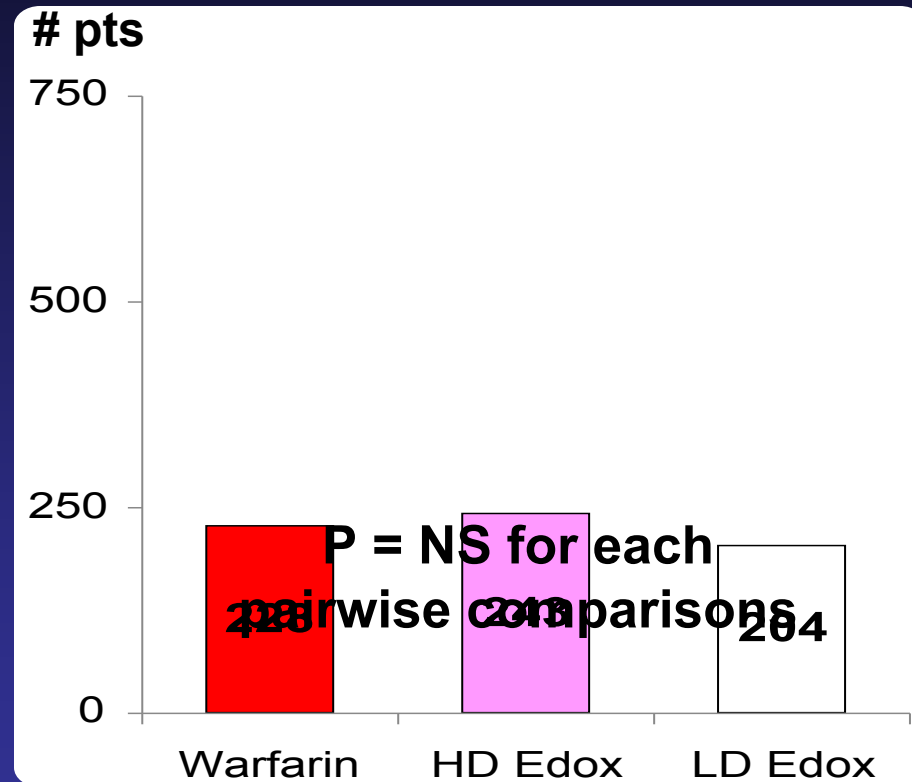
- All deaths, CV and bleeding events were adjudicated by an independent, blinded committee using prospective definitions:
 - Death: Cardiovascular (CV) vs Non-CV
Subcategories of each
NOTE: Bleeding deaths classified as CV
 - Bleeding: ISTH* criteria
 - Fatal bleeds (directly caused death \leq 7d)
 - Bleeding contributed to death (bleed on causal pathway to death within 30d)

Results: Causes of Death

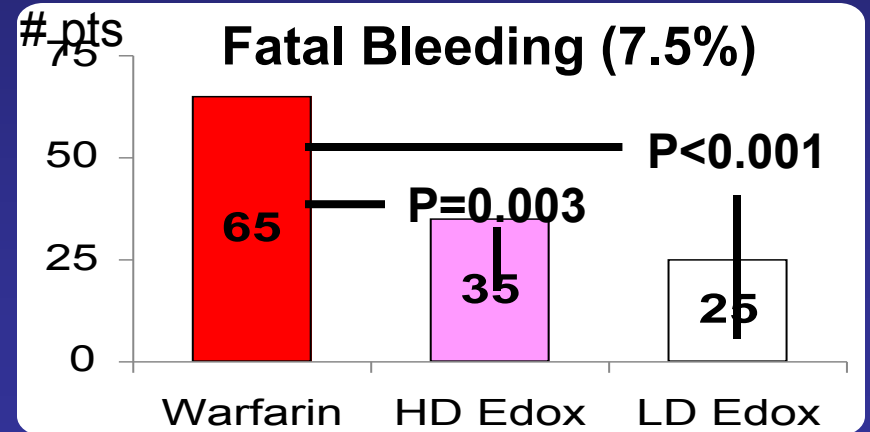
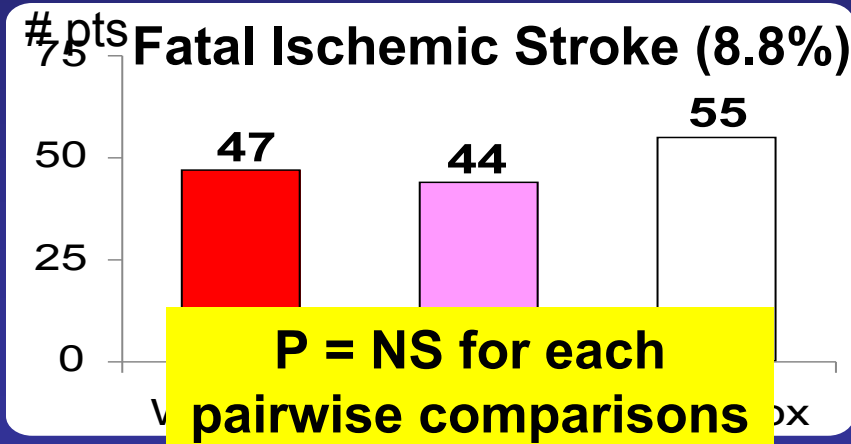
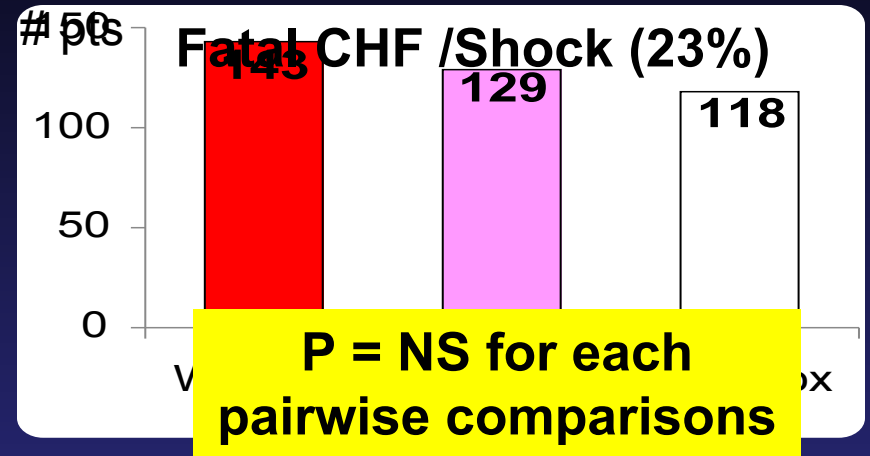
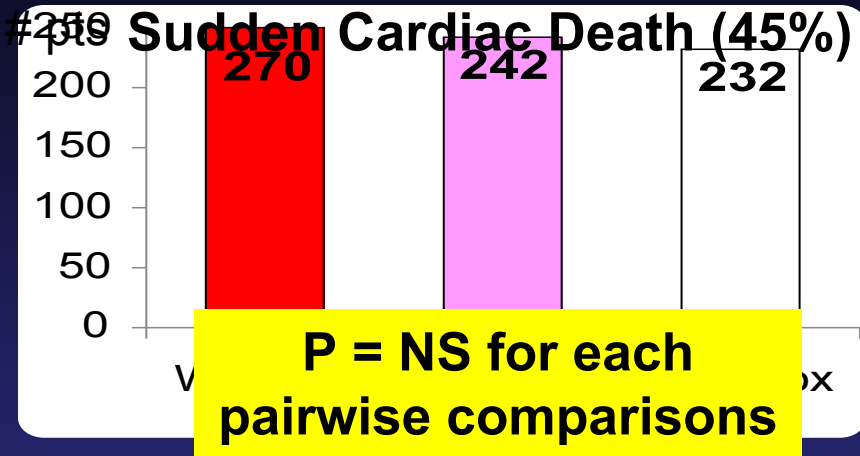
Cardiovascular (71%)



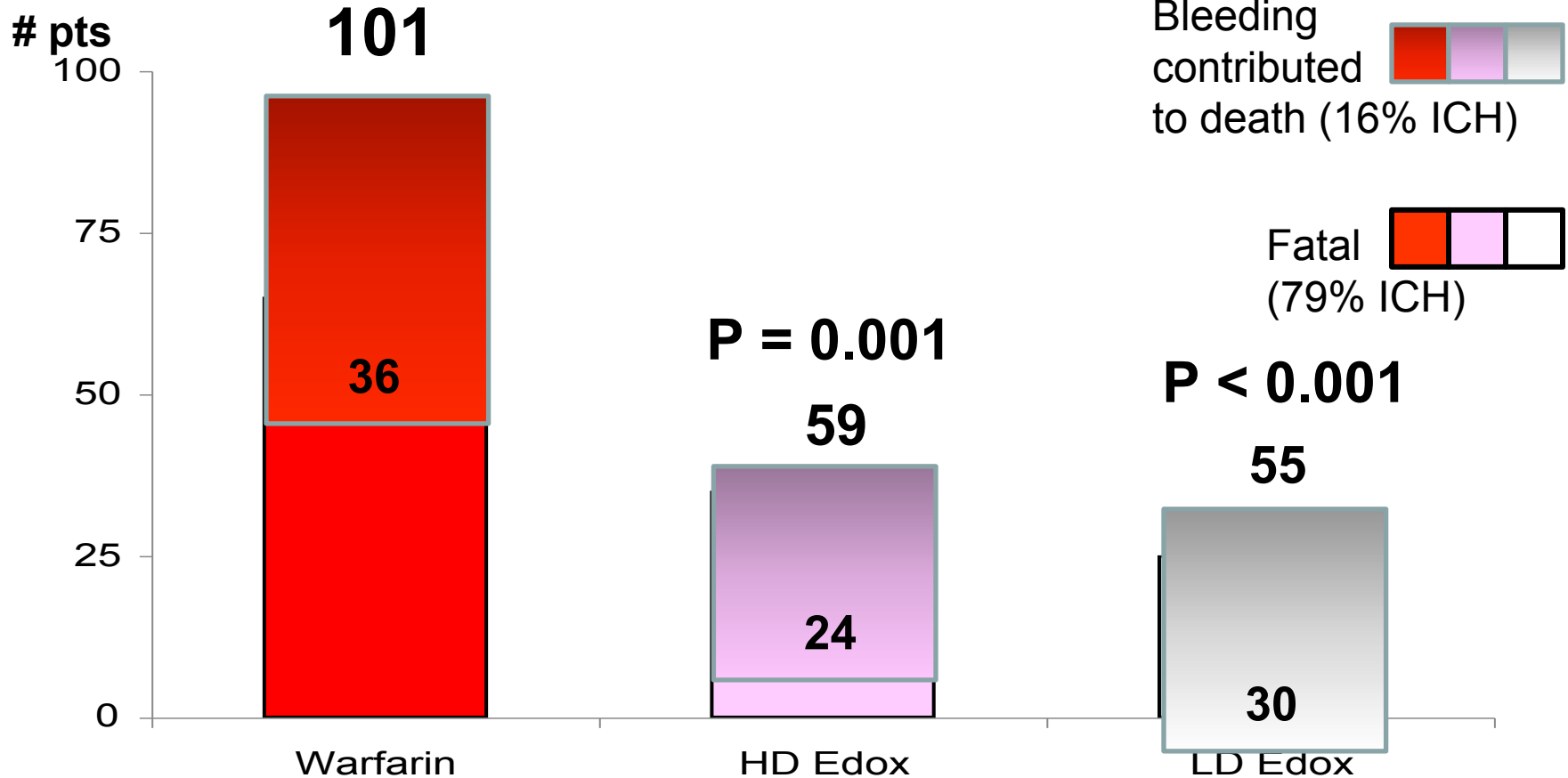
Non-Cardiovascular (29%)



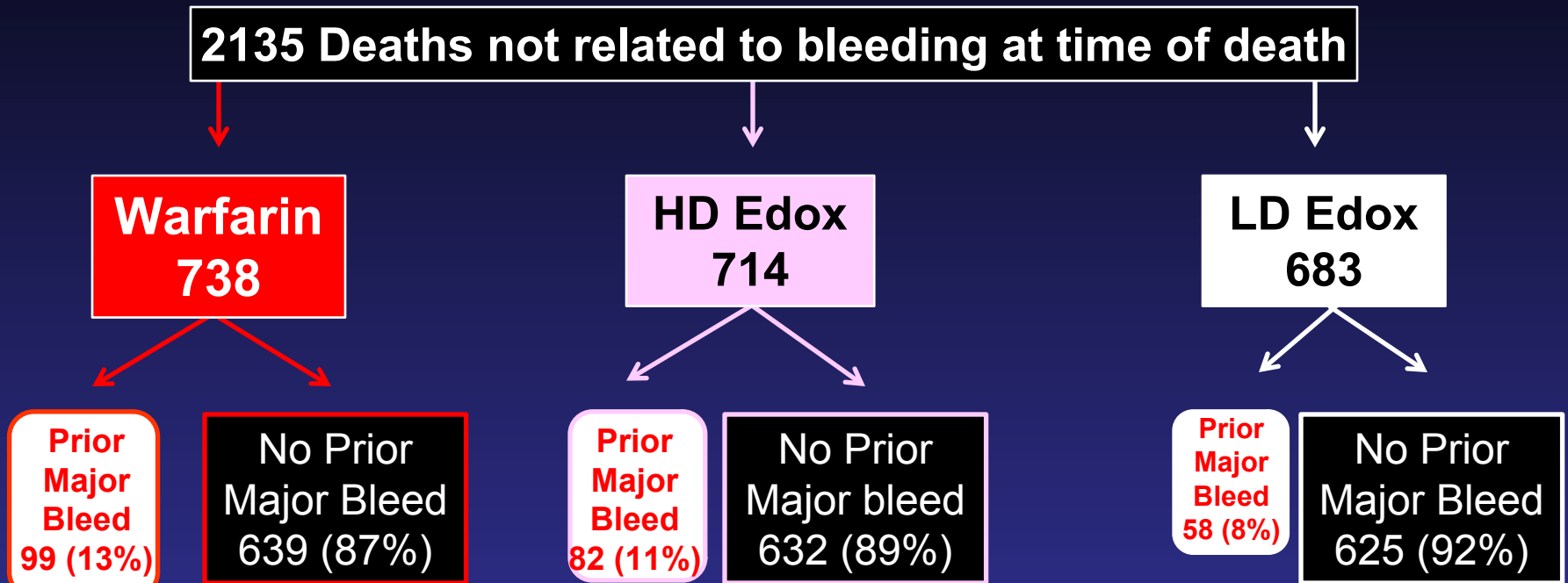
Top 4 Subclasses of CV Death



Bleeding Related to Death



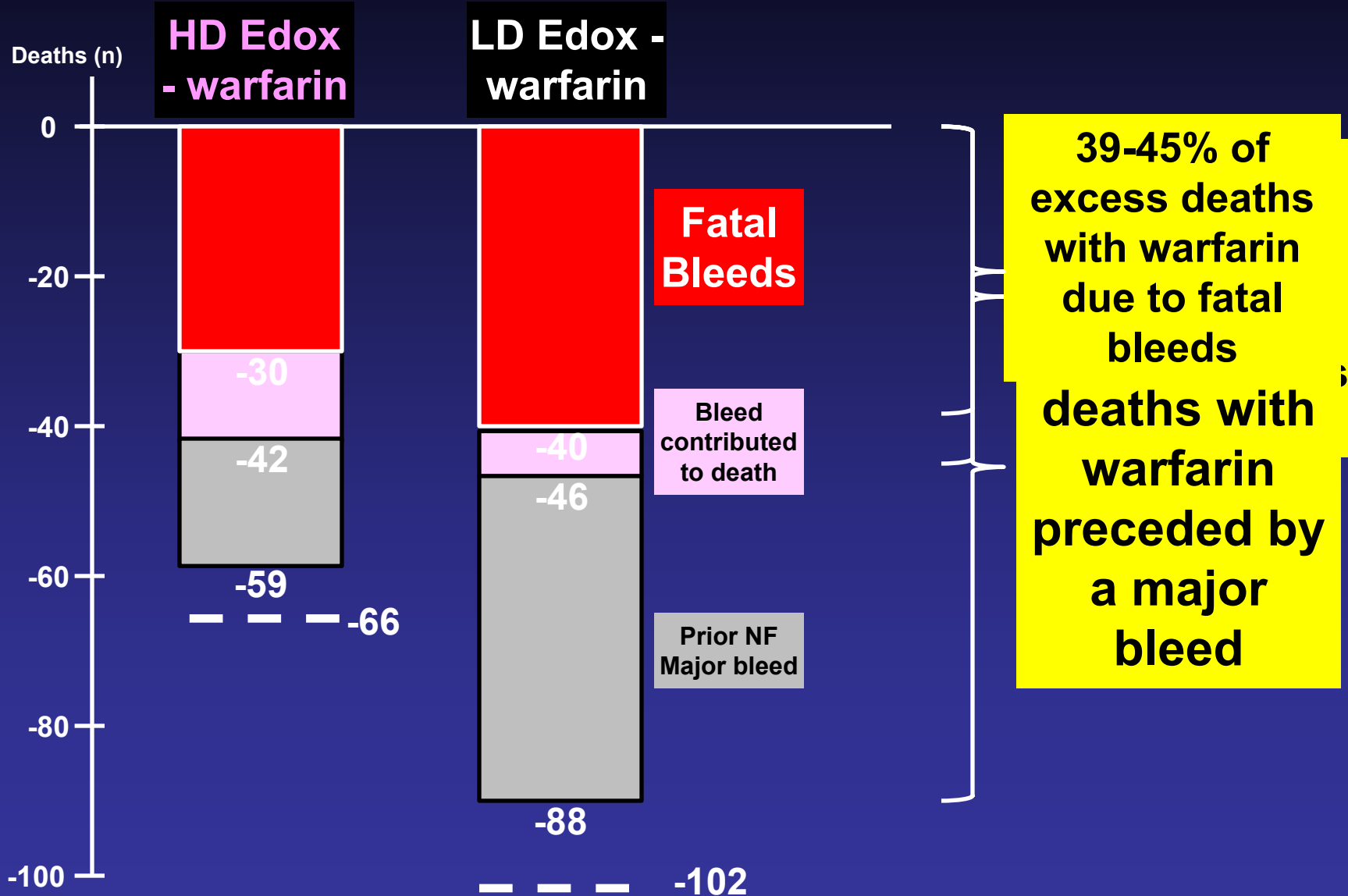
Deaths “not due” to bleeding



After a Non-Fatal Major Bleed

- Risk of death was increased by 1.7-fold (vs no major bleed)
- 91% of patients interrupted study anticoagulant >3d
 - 61% never rechallenged with any anticoagulant
- Ischemic CV death (W=32, HDE=16, LDE=20) and fatal ischemic stroke (W=10, HDE=4, LDE=6) ↑~2x warfarin group

Breakdown of Excess Deaths in the Warfarin Group



Summary

- 1. Compared to well-managed warfarin (TTR 68.4%), once-daily edoxaban:**
 - **Reduced bleeding (incl. fatal bleeding)**
 - **Reduced mortality**
- 2. Fewer fatal bleeds and bleeding contributing to death account for ~50% of reduction in total mortality with edox.**
- 3. Better tolerability with edoxaban may have reduced deaths not directly due to active/recent bleeding**