

# **Edoxaban versus Warfarin in Atrial Fibrillation Patients with Low, Mid and High Body Weight: Analysis of Outcomes in the ENGAGE AF TIMI 48 Trial**

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**Background:** Impact of extremes of body weight on outcomes with NOACs in patients with AF has not been well-characterized.

**Aim:** To analyse the pharmacokinetic, pharmacodynamics, and outcomes of pts at the extremes of weight from a large RCT of pts with AF.

**Methods:** In ENGAGE AF-TIMI 48, 21,105 pts with CHADS<sub>2</sub> ≥2 were randomized to warfarin or edoxaban and followed for 2.8 years (median).

3 subgroups identified according to weight at baseline:

- **Low body weight (0-5th percentile): ≤ 55 kg**
- **Middle body weight (45-55th percentile): 79.8-84 kg (reference)**
- **High body weight (95-100th percentile): ≥ 120 kg**

**NOTE:** Edoxaban dose was ↓50% if CrCl ≤ 50 ml/min, body weight ≤ 60 kg, or strong P-gp inhibitor used

## Baseline Characteristics by Weight Category

<u>Weight category</u>	<b>Low (0-5th percentile) ≤ 55 kg</b>	<b>Middle (45-55th percentile) 79.8-84 kg</b>	<b>High (95-100th percentile) ≥ 120 kg</b>	<u>Weight category</u>	<b>Low (0-5th percentile) ≤ 55 kg</b>	<b>Middle (45-55th percentile) 79.8-84 kg</b>	<b>High (95-100th percentile) ≥ 120 kg</b>
Number of pts	1082	2153	1093	Number of pts	1082	2153	1093
Age (median)	76	73	62				
Women (%)	76	35	18	<b>Risk factors (%)</b>			
Region (%)				- Age ≥75 yr	57	46	10
- N America	10	19	53	- Hx stroke /TIA	41	29	17
- Asia/Pac/SAF	56	11	4	- CHF	53	56	63
- W Europe				- Diabetes	19	35	62
- E Europe				- HTN	83	95	97
- Latin Am							
				<b>CrCl ≤ 50 ml/min</b>			
CHADS <sub>2</sub> 4–6 (%)	27	25	13	<b>Weight ≤ 60 kg</b>			
Median CrCl (ml/min)	45	70	130	<b>P-gp therapy</b>			
VKA naive (%)	51	41	29	<b>Dose reduced* (%)</b>	99.8	16	4

P <0.001 for all 3-way comparisons

\* Edoxaban dose was ↓50% if CrCl ≤ 50 ml/min, body wgt ≤ 60 kg, or strong P-gp inhibitor used

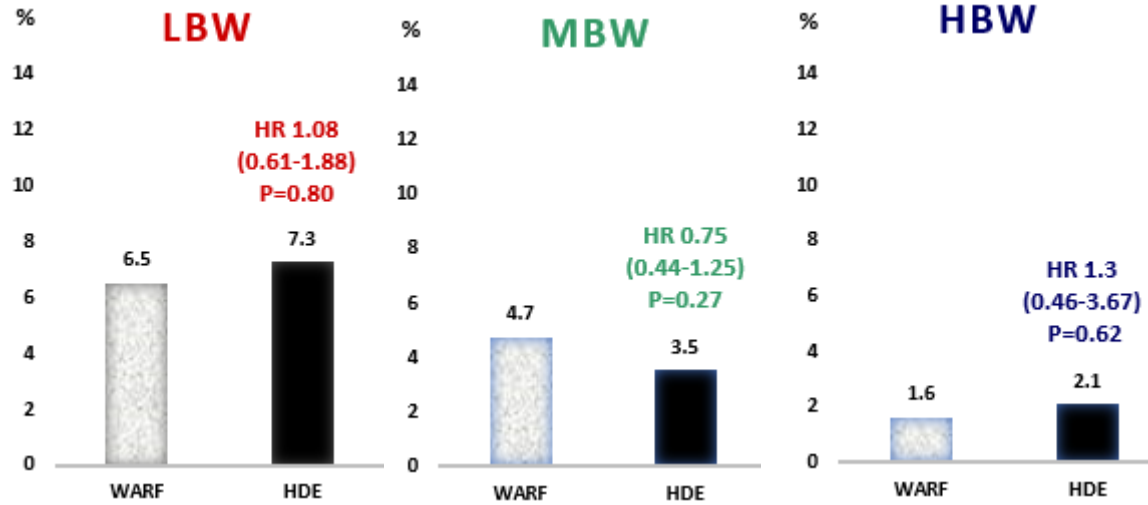
Very large differences between **lightest 5%** and **heaviest 5%**

**Lightest pts: 4x female, most from Asia, 2x prior stroke/TIA, CrCl median 45 ml/min, 2x VKA naïve**

**Heaviest pts: 14 years younger, most from NA, 3x higher rate of DM, CrCl median 130 ml/min**

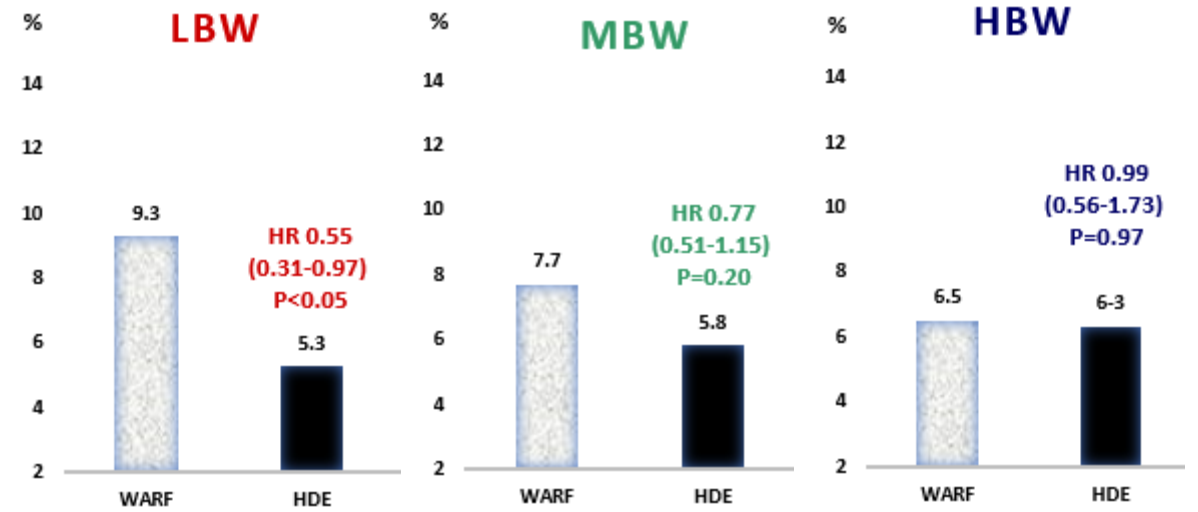
PRIMARY EFFICACY END POINT: STROKE/SEE

P int=0.52



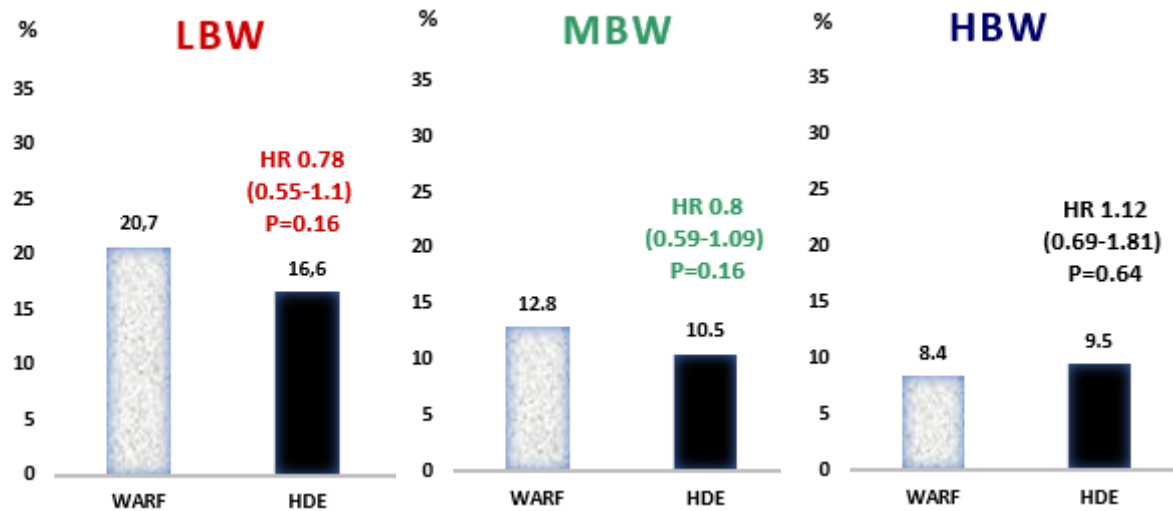
PRIMARY SAFETY END POINT: MAJOR BLEEDING

P int=0.35



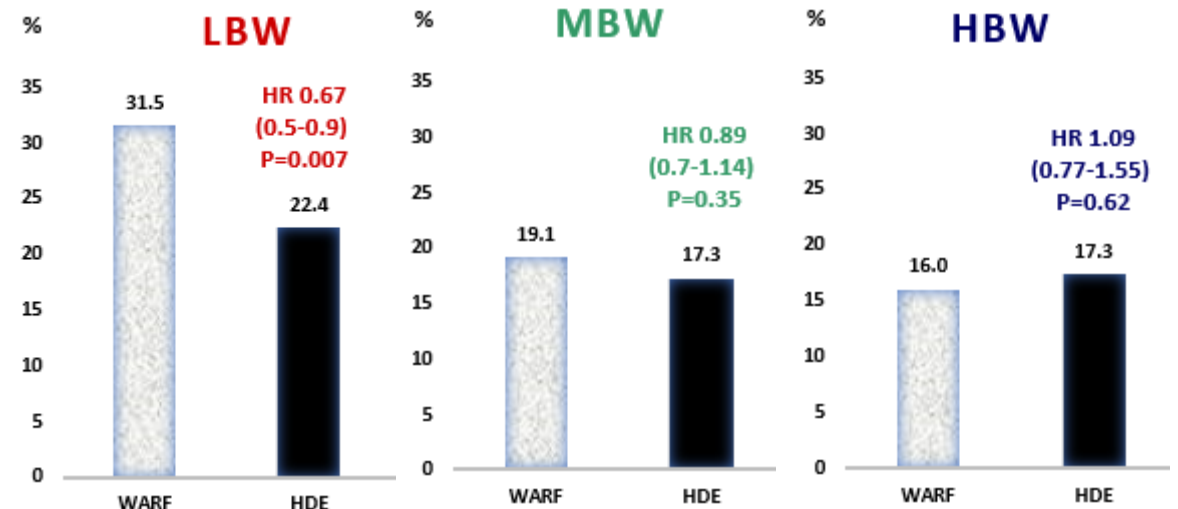
MACE: MI/stroke/SEE/CV death

P int=0.39



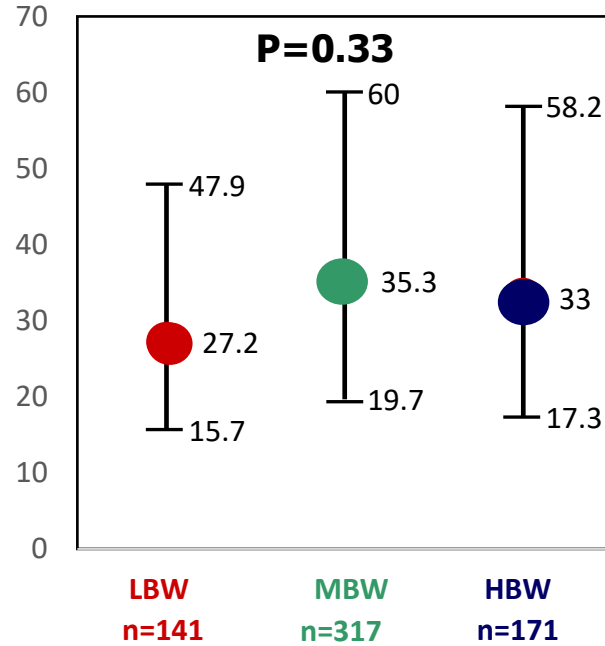
NET CLINICAL OUTCOME: Stroke/SEE/Major Bleeding/Death

P int=0.087

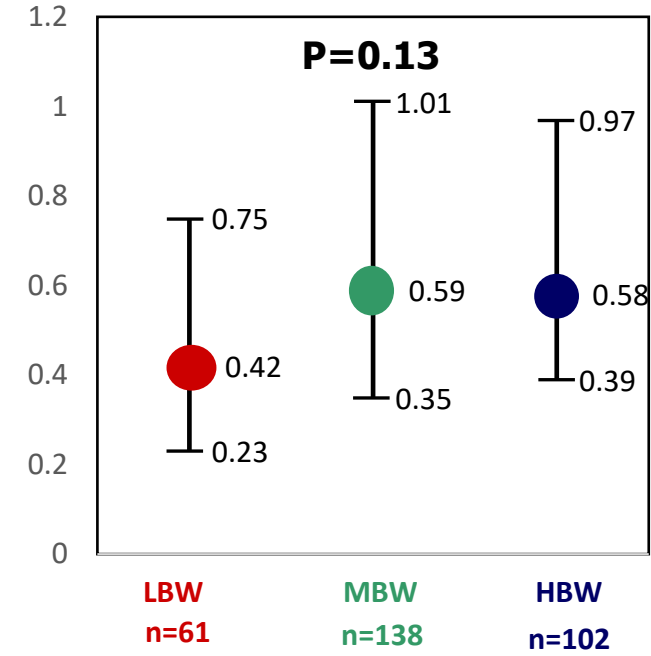


# Pharmacokinetics and Pharmacodynamics of Higher Dose Edoxaban Regimen by Weight Groups

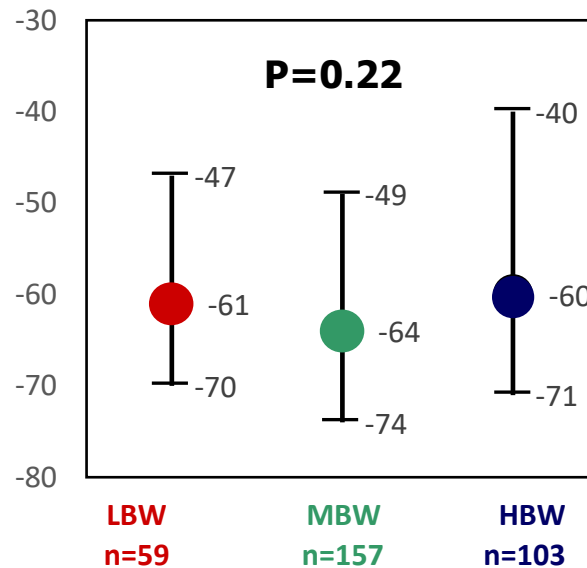
## Trough Edoxaban concentrations (ng/mL)



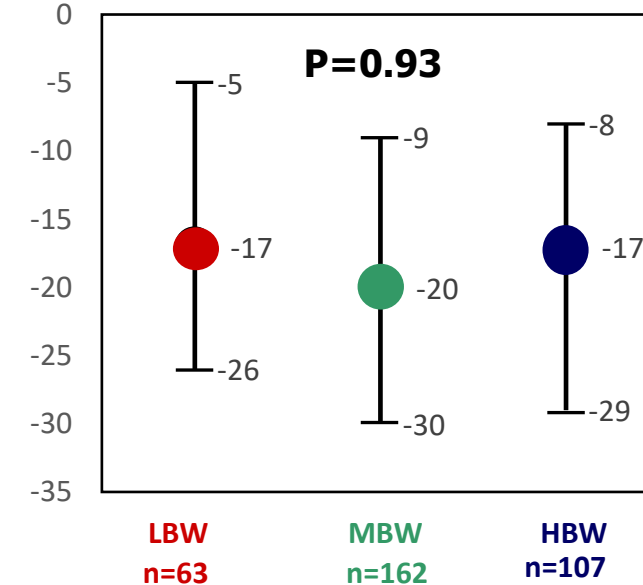
## Trough Exogenous Anti-Factor Xa Activity (IU/ml)



## % Inhibition Endogenous FXa activity at Peak (Day 29)



## % Inhibition Endogenous FXa activity at Trough (Day 29)



# **Conclusions**

**In an analysis of extremes of body weight from the ENGAGE AF-TIMI 48 trial:**

- Low body weight subjects (<55kg) were older, with more risk factors, consistent with a more fragile clinical status, and had higher rates of stroke, bleeding, CV events, and death.**
- Approved edoxaban regimen (60/30 mg o.d.) achieved similar efficacy regardless of weight, while bleeding and net outcomes were most favourable in pts with low body weight, compared to warfarin**
- Use of recommended criteria for edoxaban dose adjustment resulted in consistent drug concentrations and inhibition of Factor Xa across extremes of body weight**