Efficacy and Safety of Non-Vitamin-K Antagonist Oral Anticoagulants vs. Warfarin Across Body Mass Index and Body Weight: Insights from COMBINE-AF

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BACKGROUND
- NOACs preferred over W to prevent stroke in pts w/ AF.
- Guidelines & consensus statements advise caution with NOACs in obese pts → concern of lower drug exposure causing increased stroke risk.
- Conflicting data on outcomes across BMI/wgt; some studies suggest an “obesity paradox” → obese AF pts have better outcomes vs non-obese.
- Pt-level level data from COMBINE-AF (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, ROCKET-AF) analyzed.
- Lower-dose NOACs (Dabi 110, Edox 30/15) not approved for clinical use excluded.
- Outcomes analyzed across BMI & wgt by Cox models stratified by trial; interaction term for treatment by and BMI or treatment by and BMI or interaction term for BMI exposure causing increased stroke risk.
- Characteristics well-balanced by Rx across BMI groups.
- Stroke/SEE ↓ monotonically w/ NOAC and W as BMI ↑ (Fig 1).

METHODS
- Of 57,866 pts, 39% and 5% had BMIs ≥ 30 and ≥ 40 kg/m².
- Pts w/ higher BMI (≥40 vs. <25 kg/m²) were:
  o 9 yrs younger on average (65 vs. 74 yrs)
  o Had more CV risk factors (HTN: 95% vs. 80%, DM: 55% vs. 20%), but lower rates of prior stroke/TIA (18% vs 35%), p <0.001 for each.
- Characteristics well-balanced by Rx across BMI groups.
- Stroke/SEE ↓ monotonically w/ NOAC and W as BMI ↑ (Fig 1).

RESULTS (Continued)
- Overall, NOAC ↓ stroke/SEE by 19% vs W, w/ Rx effect consistent across range of BMI (Fig 1).
- ISTH major bleeding ↓ monotonically w/ ↑ BMI with W, but rates similar across BMI for NOAC (Fig 2).
- Overall, NOAC ↓ major bleeding by 14% vs W, esp in lower BMI pts (Fig 2).
- ICH ↓ with higher BMI for both NOAC and W.
- Overall, NOAC ↓ ICH by 55% vs W, with highly consistent Rx effect across BMI (Fig 3).
- NCO ↓ monotonically for W, but ↑ w/ NOAC at very high BMIs (Fig 3).
- Overall, NOAC ↓ NCO by 9% (Fig 4), but at BMI ≥40 kg/m², NCO favored W (HR 1.28 [95% CI 1.04-1.58]), driven by excess mortality (3.6% vs. 2.8%/y) with NOAC.
- Excess in deaths driven by SCD (39% vs 26%) & HF death (19% vs 7%); no differences in vascular death (inclusive of ischemic and bleeding events; 5% vs. 7%).
- Findings similar when assessed by wgt.

CONCLUSIONS
- ↓ event rates in obese AF pts may be due to differences in characteristics across BMI (e.g., age).
- NOACs ↓ stroke/SEE, major bleeding, and ICH across range of BMI & wgt.
- NOACs ↓ risk of NCO, except possibly in pts w/ BMI ≥40 (but not due to higher rates of ischemic or bleeding events).
- Thus, NOACs seem generally preferable to W across BMI & wgt.
- Further data needed to better understand findings on mortality in pts w/ BMI ≥40 kg/m².

FIGURES
- Event Probabilities of Clinical Outcomes Across BMI
- Fig 1: Stroke/Systemic Embolic Event
- Fig 2: ISTH Major Bleeding
- Fig 3: Intracranial Hemorrhage
- Fig 4: Net Clinical Outcome

- NCO = Stroke/SEE, ISTH Major Bleeding, All-Cause Mortality
- HR 0.91 (95% CI 0.87-0.95) p<0.001