#AHA23

Mount Sinai Hospital

# CLINICAL OUTCOMES IN TAVR PATIENTS RECEIVING ORAL ANTICOAGULATION ACCORDING TO RENAL FUNCTION: A PRESPECIFIED ANALYSIS OF THE ENVISAGE-TAVI AF TRIAL

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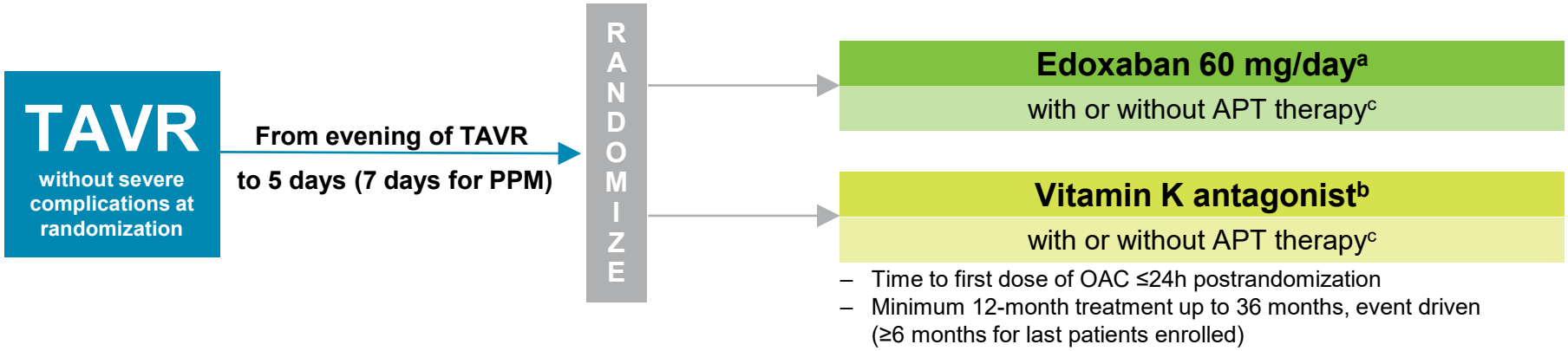
# BACKGROUND

- In the ENVISAGE-TAVI AF trial (NCT02943785), edoxaban was noninferior to VKA with respect to the composite primary outcome of NACE in patients with AF undergoing TAVR[1]
  - Nonetheless, edoxaban vs VKA treatment was associated with a higher incidence of major bleeding[1]
- Edoxaban is a direct oral factor Xa inhibitor that is 50% renally cleared, suggesting that renal function may influence the efficacy and safety of edoxaban treatment[2]
- Impaired kidney function is associated with higher rates of major bleeding among patients with AF receiving VKAs[3]
- The efficacy and safety of edoxaban vs VKA in patients with AF after TAVR across various levels of creatinine clearance has not been assessed

AF, atrial fibrillation; NACE, net adverse clinical events; TAVR, transcatheter aortic valve replacement; VKA, vitamin K antagonist.

1. Van Mieghem NM, et al. *N Engl J Med*. 2021;385(23):2150-60. 2. Matsushima N, et al. *Clin Pharmacol Drug Dev*. 2013;2(4):358-66. 3. Jun M, et al. *BMJ*. 2015;350:h246.

# ENVISAGE-TAVI AF STUDY DESIGN




[a]Edoxaban dose reduction to 30 mg in AF patients, if:
- Creatinine clearance ≤50 ml/min
- Body weight ≤60 kg[d]
- P-gp inhibitors per local label[d]

[d]No dose reduction criteria in the US for AF

[b]VKA patients target INR 2–3

In Japan: patients ≥70 yrs 1.6–2.6

[c]Stratification variable: specified use of APT

APT was allowed per the treating physician's discretion including
- DAPT up to 30 days after PCI, or
- SAPT indefinitely

AF, atrial fibrillation; APT, antiplatelet therapy; DAPT, dual antiplatelet therapy; INR, international normalized ratio; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; P-gp, P-glycoprotein; PPM, permanent pacemaker; SAPT, single antiplatelet therapy; TAVR, transcatheter aortic valve replacement; VKA, vitamin K antagonist.
Study Design: Van Mieghem NM, et al. *Am Heart J*. 2018;205:63-9.

# ENVISAGE-TAVI AF PRIMARY OUTCOMES[1]

## Primary efficacy outcome

NACE[a]

ITT population (all randomized patients)

## Primary safety outcome

Major bleeding (ISTH definition)

ITT population (all randomized patients)

[a]Composite of all-cause death, MI, ischemic stroke, systemic thromboembolic event, valve thrombosis, and major bleeding.
ISTH, International Society on Thrombosis and Haemostasis; ITT, intent-to-treat; MI, myocardial infarction; NACE, net adverse clinical events.
1. Van Mieghem NM, et al. *Am Heart J*. 2018;205:63–9.

# OBJECTIVE & METHODS

**Aim: To compare the efficacy and safety of edoxaban vs vitamin K antagonists in patients with AF and indication for chronic OAC therapy after successful TAVR, according to baseline creatinine clearance**

- Patients were stratified into 4 prespecified groups according to baseline creatinine clearance: <30 mL/min, ≥30 to <50 mL/min, ≥50 to <80 mL/min, and ≥80 mL/min

- Primary and secondary outcomes (relating to major bleeding[a] and separate components of the primary efficacy outcome) were analyzed in each treatment arm according to creatinine clearance levels
  - Results are presented as HRs with 2-sided 95% CIs based on Cox proportional hazards regression models
  - HRs were only calculated for outcomes with >5 events in both treatment groups

[a]International Society on Thrombosis and Haemostasis definition.
AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; OAC, oral anticoagulant; TAVR, transcatheter aortic valve replacement.

# BASELINE CHARACTERISTICS

| | Overall N = 1426 | Creatinine Clearance (mL/min) <30 n = 112 | ≥30–<50 n = 455 | ≥50–<80 n = 582 | ≥80 n = 224 | *P*-value[a] |
|---|---|---|---|---|---|---|
| **Age, years, mean (SD)** | 82.1 (5.4) | 85.5 (3.9) | 84.1 (4.6) | 81.6 (4.8) | 77.6 (5.9) | **<0.0001** |
| **Sex, male, n (%)** | 748 (52.5) | 41 (36.6) | 202 (44.4) | 335 (57.6) | 138 (61.6) | **<0.0001** |
| **Race, White, n (%)** | 1187 (83.2) | 72 (64.3) | 351 (77.1) | 512 (88.0) | 207 (92.4) | **<0.0001** |
| **Weight, kg, mean (SD)** | 75.3 (17.6) | 60.9 (13.6) | 67.3 (14.8) | 78.0 (14.9) | 91.6 (16.7) | **<0.0001** |
| **BMI, kg/m$^2$, mean (SD)** | 27.7 (5.5) | 24.3 (4.1) | 25.7 (4.5) | 28.2 (5.0) | 32.1 (6.3) | **<0.0001** |
| **CrCl, mL/min, mean (SD)** | 58.2 (24.1) | 23.8 (5.5) | 41.0 (5.6) | 62.8 (8.4) | 98.8 (20.3) | **<0.0001** |
| **HAS-BLED, mean (SD)** | 1.6 (0.8) | 1.7 (0.8) | 1.6 (0.8) | 1.6 (0.8) | 1.5 (0.7) | 0.06 |
| **$CHA_2DS_2$-VASc, mean (SD)** | 4.5 (1.3) | 4.6 (1.3) | 4.7 (1.3) | 4.4 (1.3) | 4.1 (1.4) | **<0.0001** |
| **Previous medical history** | | | | | | |
| Stroke or TIA, n (%) | 239 (16.8) | 12 (10.7) | 89 (19.6) | 105 (18.0) | 27 (12.1) | **0.02** |
| Hypertension, n (%) | 1304 (91.4) | 98 (87.5) | 410 (90.1) | 541 (93.0) | 205 (91.5) | 0.2 |
| Diabetes, n (%) | 527 (37.0) | 43 (38.4) | 148 (32.5) | 223 (38.3) | 90 (40.2) | 0.1 |
| Prior MB or predisposition to bleeding, n (%) | 125 (8.8) | 19 (17.0) | 39 (8.6) | 47 (8.1) | 14 (6.3) | **0.02** |

[a]Bolded *P*-values denote significance with a value of $P < 0.05$.
BMI, body mass index; $CHA_2DS_2$-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Stroke (doubled), Vascular disease, Age 65–74 years, Sex Category (female); CrCl, creatinine clearance; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; INR, international normalized ratio; MB, major bleeding; SD standard deviation; TIA, transient ischemic attack.

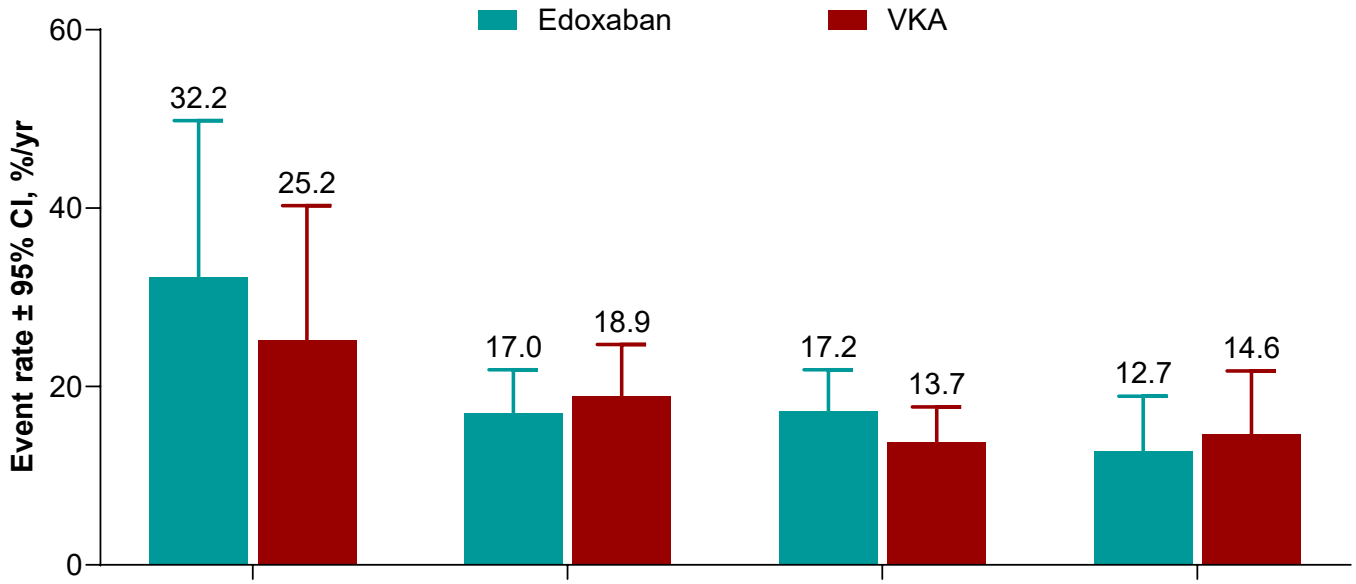
# OVERALL CLINICAL OUTCOMES

| Outcome[a] | Creatinine Clearance (mL/min) <30 n = 112 | ≥30–<50 n = 455 | ≥50–<80 n = 582 | ≥80 n = 224 | *P*-value[b] |
|---|---|---|---|---|---|
| **NACE** | 28.6 (20.10, 39.35) | 17.8 (14.67, 21.44) | 15.4 (12.78, 18.31) | 13.6 (10.03, 18.04) | **0.007** |
| **Major bleeding** | 16.2 (10.03, 24.77) | 8.3 (6.24, 10.84) | 7.3 (5.62, 9.43) | 8.1 (5.43, 11.63) | **0.04** |
| **All-cause death** | 17.8 (11.65, 26.12) | 8.6 (6.56, 11.11) | 7.4 (5.69, 9.40) | 5.8 (3.60, 8.71) | **0.0002** |
| **Cardiovascular death** | 10.3 (5.76, 16.96) | 4.4 (2.95, 6.25) | 3.6 (2.48, 5.13) | 3.7 (2.00, 6.14) | **0.007** |
| **All stroke** | 0.7 (0.02, 3.82) | 3.3 (2.06, 4.98) | 3.5 (2.36, 4.99) | 3.0 (1.47, 5.27) | 0.4 |
| **Ischemic stroke** | 0.7 (0.02, 3.82) | 2.5 (1.47, 4.05) | 2.8 (1.79, 4.15) | 2.1 (0.92, 4.21) | 0.5 |
| **Intracranial hemorrhage** | 0.7 (0.02, 3.85) | 1.9 (1.02, 3.28) | 1.7 (0.96, 2.82) | 2.1 (0.92, 4.18) | 0.7 |
| **Fatal major bleeding** | 1.4 (0.17, 4.96) | 0.7 (0.24, 1.70) | 1.3 (0.62, 2.23) | 0.5 (0.06, 1.89) | 0.6 |
| **Major GI bleeding** | 7.7 (3.86, 13.83) | 3.1 (1.93, 4.77) | 4.0 (2.79, 5.63) | 4.6 (2.70, 7.42) | 0.1 |

[a]All outcomes reported as event rates, %/yr (95% CI). [b]Bolded *P*-values denote significance with a value of $P < 0.05$.
CI, confidence interval; GI, gastrointestinal; NACE, net adverse clinical events.

# TREATMENT EFFECTS

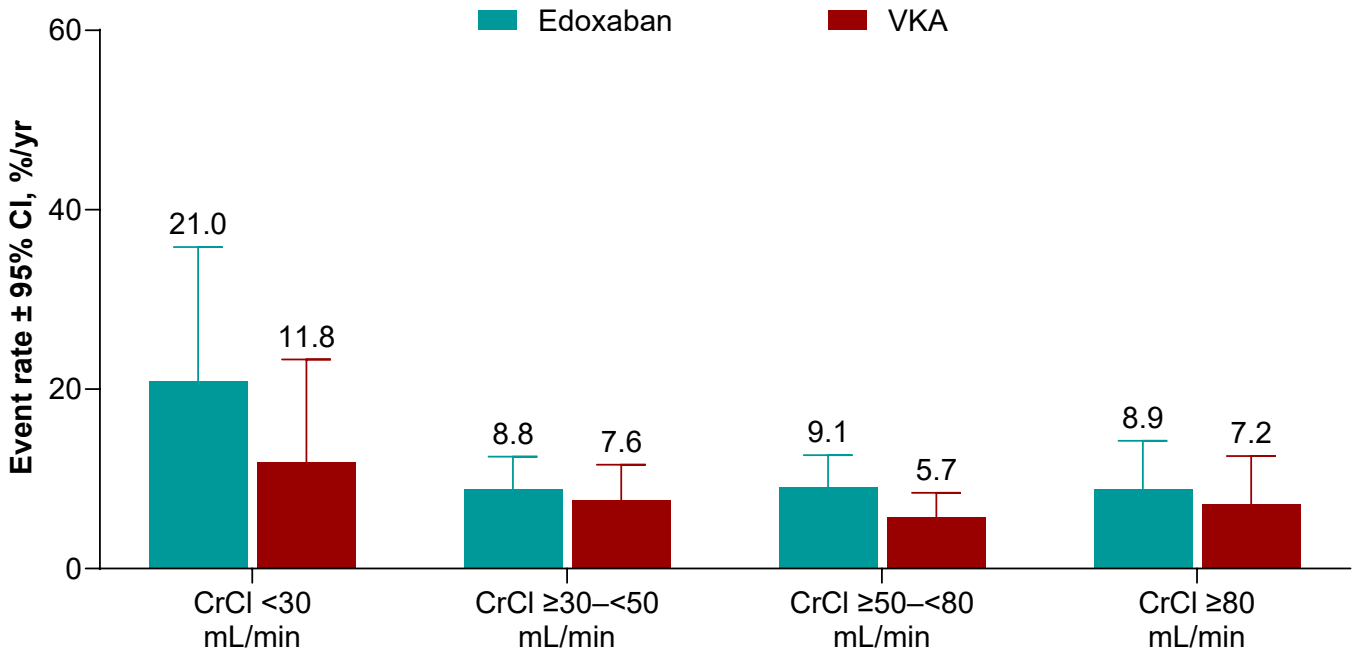
## NACE[a]




[a]Composite of all-cause death, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, and major bleeding.
CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; NACE, net adverse clinical events; VKA, vitamin K antagonist.

# TREATMENT EFFECTS

## MAJOR BLEEDING[a]

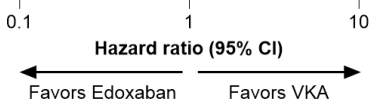



[a]International Society on Thrombosis and Haemostasis definition.
CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; VKA, vitamin K antagonist.

# TREATMENT EFFECTS

## SECONDARY OUTCOMES

| CrCl, mL/min | Edoxaban vs VKA | Hazard ratio[a] | n/N (%/yr) Edoxaban | VKA | *P*-value[b] |
|---|---|---|---|---|---|
| **All-cause death** | | | | | |
| <30 | | 1.02 | 13/58 (18.07) | 13/54 (17.60) | 1.0 |
| ≥30–<50 | | 0.67 | 27/240 (7.05) | 32/215 (10.60) | 0.1 |
| ≥50–<80 | | 1.19 | 34/276 (8.01) | 31/306 (6.78) | 0.5 |
| ≥80 | | 0.73 | 10/118 (4.84) | 12/106 (6.82) | 0.5 |
| **CV death** | | | | | |
| <30 | | 0.88 | 7/58 (9.73) | 8/54 (10.83) | 0.8 |
| ≥30–<50 | | 1.03 | 17/240 (4.44) | 13/215 (4.31) | 0.9 |
| ≥50–<80 | | 1.22 | 17/276 (4.01) | 15/306 (3.28) | 0.6 |
| ≥80 | | 0.88 | 7/118 (3.39) | 7/106 (3.98) | 0.8 |
| **Any stroke** | | | | | |
| <30 | | NA | 0/58 | 1/54 (1.35) | NA |
| ≥30–<50 | | 0.56 | 9/240 (2.40) | 13/215 (4.42) | 0.2 |
| ≥50–<80 | | 0.93 | 14/276 (3.39) | 16/306 (3.60) | 0.8 |
| ≥80 | | 1.00 | 6/118 (2.97) | 5/106 (2.92) | 1.0 |
| **Intracranial hemorrhage** | | | | | |
| <30 | | NA | 1/58 (1.41) | 0/54 | NA |
| ≥30–<50 | | 0.68 | 6/240 (1.58) | 7/215 (2.35) | 0.5 |
| ≥50–<80 | | 0.53 | 5/276 (1.18) | 10/306 (2.21) | 0.2 |
| ≥80 | | NA | 4/118 (1.96) | 4/106 (2.32) | NA |
| **Major GI bleeding** | | | | | |
| <30 | | NA | 7/58 (10.16) | 4/54 (5.44) | NA |
| ≥30–<50 | | 1.31 | 13/240 (3.46) | 8/215 (2.69) | 0.5 |
| ≥50–<80 | | 3.09 | 25/276 (6.28) | 9/306 (2.02) | **0.004** |
| ≥80 | | 1.63 | 11/118 (5.62) | 6/106 (3.51) | 0.3 |




[a]Hazard ratios were only calculated for outcomes with ≥5 events in both treatment groups. [b]Bolded *P*-values denote significance with a value of $P < 0.05$.
CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; GI, gastrointestinal; NA, not available; VKA, vitamin k antagonist.

# LIMITATIONS

- The open-label design of the study includes a risk of reporting bias regarding the trial outcomes
- Trial results apply only to an older population of patients with AF undergoing TAVR, intermediate operative risk, and symptomatic aortic stenosis
- Creatinine clearance does not provide a full assessment of renal function; other pertinent variables reflective of kidney function were not collected
- Results for outcomes with low event rates should be interpreted with caution

AF, atrial fibrillation; TAVR, transcatheter aortic valve replacement.

# CONCLUSIONS

- In this ENVISAGE-TAVI AF subanalysis, baseline creatinine clearance appeared to influence rates of adverse outcome parameters more than OAC strategy as there were numerically higher rates of NACE and major bleeding in patients with creatinine clearance <30 mL/min vs other subgroups and no significant effect of treatment on these outcomes
- Physicians should consider baseline creatinine clearance when deciding OAC treatment for patients with AF after TAVR

AF, atrial fibrillation; NACE, net adverse clinical events; OAC, oral anticoagulant; TAVR, transcatheter aortic valve replacement.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## DISCLOSURES

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# THANK YOU



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