Clinical outcomes in patients receiving oral anticoagulation stratified by the presence of dose reduction criteria and older age: A subanalysis of ENVISAGE-TAVI AF

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BACKGROUND

- In the ENVISAGE-TAVI AF trial (NCT02943785), edoxaban was noninferior to vitamin K antagonists (VKAs) for preventing net adverse clinical events (NACE) but was associated with increased major bleeding (MB) in patients with atrial fibrillation (AF) after transcatheter aortic valve implantation (TAVI)[1]
- The edoxaban dose was reduced in patients who met the dose reduction criteria (DRC) set in the trial (body weight ≤60 kg, creatinine clearance [CrCl] 15–50 mL/min, and concomitant use of selected P-glycoprotein inhibitors); presence of the DRC indicate a more vulnerable patient phenotype[1]
- It is unknown if there are differences in clinical outcomes between patients who meet the DRC vs those who do not and if age has an effect on these outcomes

OBJECTIVE

- To compare baseline patient characteristics and clinical outcomes between patients from the ENVISAGE-TAVI AF trial who met the edoxaban DRC and those who did not, stratified by anticoagulation strategy and age

METHODS

- In the randomized, controlled ENVISAGE-TAVI AF trial, patients who met 1 or more of the DRC were indicated to receive 30 mg once daily, while all others not meeting the DRC were to receive 60 mg once daily[1]
- This subanalysis included all randomised patients who received ≥1 dose of the study drug (safety analysis set)
  - Outcome parameters included NACE (composite all-cause death, myocardial infarction, ischaemic stroke, systemic thromboembolic event, valve thrombosis, or MB), MB, major gastrointestinal bleeding (MGIB), ischaemic stroke, intracranial haemorrhage, all-cause death, cardiovascular (CV) death, and non-CV death
- Baseline characteristics and clinical outcomes were compared in patients who met the edoxaban DRC vs those who did not, with further subanalyses comparing clinical outcomes between patients receiving edoxaban vs VKAs and age (<80 or ≥80 years of age)

RESULTS

Patients meeting the DRC vs those who did not

- Of 1377 patients, 637 met the DRC and 740 did not (**Table 1**)
- At baseline, patients who met the DRC had lower means for body weight and CrCl (*P* <0.0001 each), higher mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack, Vascular disease, Age 65 to 74 years, Sex category [female]) scores (*P* <0.0001), less frequent use of VKAs pre-TAVI (*P* = 0.008), and more frequent use of non–vitamin K oral anticoagulants pre-TAVI (*P* = 0.03) compared with those who did not meet the DRC (**Table 1**)
- Patients with vs without the DRC had significantly higher rates of NACE (*P* = 0.04) and all-cause death (*P* = 0.01) and similar rates for MB and MGIB (**Figure 1**)

Clinical outcomes for edoxaban vs VKAs stratified by DRC and age

- For patients <80 years of age, there was no significant interaction for the presence or absence of DRC and the type of treatment received (**Figure 2A**)
- For patients ≥80 years of age, there was a significant interaction for the presence or absence of DRC and treatment type for NACE (*P* = 0.03) and all-cause death events (*P* = 0.03; **Figure 2B**)
  - Among patients who met the DRC, those receiving edoxaban vs VKAs had lower rates of NACE and all-cause death (**Figure 2B**)
- Among patients ≥80 years of age, MB event rates were similar between patients who received edoxaban vs VKAs for both patients who did and did not meet the DRC (**Figure 2B**)
- For patients ≥80 years of age who did not meet the DRC, there was a higher rate of MGIB with edoxaban vs VKAs; however, for those who met the DRC, the rate of MGIB with edoxaban was comparable to that with VKAs (**Figure 2B**)

CONCLUSIONS

Overall, patients who met the DRC were a more vulnerable group with higher risk of NACE and all-cause death compared with patients who did not meet the DRC

For patients aged <80 years, there was a similar risk of clinical outcomes with edoxaban vs VKAs for patients who met the DRC and those who did not

Patients aged ≥80 years who met the DRC had lower risk of NACE and all-cause death and similar risk of major bleeding with edoxaban vs VKAs compared with those who did not meet the DRC

In this subanalysis of the ENVISAGE-TAVI AF trial, patients who were ≥80 years of age and met the DRC had lower risk of NACE and all-cause death and similar risk of major bleeding with edoxaban vs VKAs.

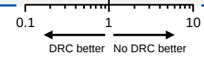
Table 1. Patient demographics and baseline clinical characteristics

	DRC n = 637	No DRC n = 740	*P*-value
Age, years, mean ± SD	83.8 ± 4.8	80.5 ± 5.5	**<0.0001**
Sex, male	262 (41.1)	457 (61.8)	**<0.0001**
Weight, kg, mean ± SD	66.6 ± 16.6	82.8 ± 14.9	**<0.0001**
BMI, kg/m², mean ± SD	25.6 ± 4.9	29.5 ± 5.4	**<0.0001**
Race, White	465 (73.0)	681 (92.0)	**<0.0001**
CrCl (Cockcroft-Gault), mL/min, mean ± SD	42.0 ± 14.1	72.3 ± 22.1	**<0.0001**
CHA_2DS_2-VASc, mean ± SD	4.7 ± 1.3	4.3 ± 1.4	**<0.0001**
HAS-BLED, mean ± SD	1.6 ± 0.8	1.5 ± 0.8	0.05
Prior major bleeding or predisposition to bleeding	61 (9.6)	58 (7.8)	0.3
Pre-TAVI use of VKAs	268 (42.1)	365 (49.3)	**0.008**
Pre-TAVI use of NOACs	196 (30.8)	188 (25.4)	**0.03**
No pre-TAVI use of VKAs or NOACs	173 (27.2)	187 (25.3)	0.5

Data are presented as n (%) unless otherwise noted.
Bolded *P*-values are significant.
BMI, body mass index; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack, Vascular disease, Age 65 to 74 years, Sex category (female); CrCl, creatinine clearance; DRC, dose reduction criteria; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drug/alcohol usage; NOAC, non–vitamin K oral anticoagulant; SD, standard deviation; TAVI, transcatheter aortic valve implantation; VKA, vitamin K antagonist.

Figure 1. Clinical outcomes stratified by the presence or absence of DRC

Endpoint	Event rate, %/yr (no. of patients/total no.)	Hazard ratio (95% CI)	*P*-value[a]
NACE			
DRC	19.17 (161/637)		**0.04**
No DRC	14.87 (161/740)		
Major bleeding			
DRC	8.90 (77/637)		0.6
No DRC	7.95 (88/740)		
Major GI bleeding			
DRC	3.99 (36/637)		0.7
No DRC	4.16 (47/740)		
Ischaemic stroke			
DRC	2.66 (24/637)		0.6
No DRC	2.25 (26/740)		
ICH			
DRC	1.53 (14/637)		0.4
No DRC	1.97 (23/740)		
All-cause death			
DRC	9.98 (92/637)		**0.01**
No DRC	6.88 (81/740)		
CV death			
DRC	5.32 (49/637)		0.06
No DRC	3.57 (42/740)		
Non-CV death			
DRC	4.67 (43/637)		0.1
No DRC	3.31 (39/740)		

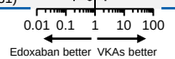


[a]*P*-values represent the comparison between the DRC and no DRC groups; bolded *P*-values are significant.
CI, confidence interval; CV, cardiovascular; DRC, dose reduction criteria; GI, gastrointestinal; ICH, intracranial haemorrhage; NACE, net adverse clinical events.

Figure 2. Clinical outcomes in patients receiving edoxaban vs VKAs stratified by DRC and age (A) <80 years old or (B) ≥80 years old

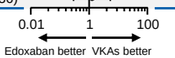
A)

Endpoint	Event rate, %/yr (no. of patients/total no.)		Hazard ratio (95% CI)[a]	*P*-value[b]
	Edoxaban	VKAs		
NACE				
DRC	26.80 (18/52)	11.87 (7/46)		0.06
No DRC	11.11 (23/131)	13.23 (27/131)		
Major bleeding				
DRC	10.86 (8/52)	4.92 (3/46)		0.5
No DRC	7.11 (15/131)	5.13 (11/131)		
Major GI bleeding				
DRC	5.18 (4/52)	3.28 (2/46)		0.9
No DRC	4.21 (9/131)	2.76 (6/131)		
Ischaemic stroke				
DRC	1.25 (1/52)	1.62 (1/46)		0.7
No DRC	1.37 (3/131)	3.20 (7/131)		
ICH				
DRC	0.0 (0/52)	1.57 (1/46)		NC
No DRC	0.91 (2/131)	1.79 (4/131)		
All-cause death				
DRC	11.13 (9/52)	7.83 (5/46)		0.7
No DRC	4.53 (10/131)	4.41 (10/131)		
CV death				
DRC	9.89 (8/52)	6.26 (4/46)		0.9
No DRC	2.72 (6/131)	1.76 (4/131)		
Non-CV death				
DRC	1.24 (1/52)	1.57 (1/46)		0.9
No DRC	1.81 (4/131)	2.64 (6/131)		



B)

Endpoint	Event rate, %/yr (no. of patients/total no.)		Hazard ratio (95% CI)[a]	*P*-value[b]
	Edoxaban	VKAs		
NACE				
DRC	16.93 (62/267)	21.29 (74/272)		**0.03**
No DRC	19.30 (66/242)	13.65 (45/236)		
Major bleeding				
DRC	9.56 (36/267)	8.47 (30/272)		0.4
No DRC	11.20 (39/242)	6.89 (23/236)		
Major GI bleeding				
DRC	4.58 (18/267)	3.24 (12/272)		0.1
No DRC	7.05 (25/242)	2.04 (7/236)		
Ischaemic stroke				
DRC	2.56 (10/267)	3.25 (12/272)		0.8
No DRC	2.14 (8/242)	2.34 (8/236)		
ICH				
DRC	1.51 (6/267)	1.89 (7/272)		1.0
No DRC	2.11 (8/242)	2.63 (9/236)		
All-cause death				
DRC	7.46 (30/267)	12.80 (48/272)		**0.03**
No DRC	9.15 (35/242)	7.48 (26/236)		
CV death				
DRC	3.73 (15/267)	5.87 (22/272)		0.1
No DRC	4.97 (19/242)	3.74 (13/236)		
Non-CV death				
DRC	3.73 (15/267)	6.93 (26/272)		0.1
No DRC	4.19 (16/242)	3.74 (13/236)		



[a]Hazard ratios and *P*-values for subgroups with ≤5 events should be interpreted with caution; [b]*P*-values represent the interaction effect between the DRC and oral anticoagulant type; bolded *P*-values are significant.
CI, confidence interval; CV, cardiovascular; DRC, dose reduction criteria; GI, gastrointestinal; ICH, intracranial haemorrhage; NACE, net adverse clinical events; NC, not calculated; VKA, vitamin K antagonist.

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REFERENCES
1. Van Mieghem NM, et al. *N Engl J Med*. 2021;385(23):2150–60.

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