Efficacia e sicurezza di Edoxaban e Warfarin in pazienti con fibrillazione atriale e arteriopatia periferica

Insights dal trial ENGAGE AF-TIMI 48

Background

- Antithrombotic management in patients with atrial fibrillation (AF) and peripheral artery disease (PAD) is challenging because of the broad spectrum of ischemie risks in multiple vascular beds, heightened bleeding risks, and overlapping indications for anticoagulant and antiplatelet therapies.
- In patients with AF, full-dose oral factor (F)Xa inhibition has been associated with less bleeding than warfarin, but this advantage has been less clear in AF patients with comorbid PAD (subgroup analysis of the ROCKET-AF trial and ARISTOTLE trial).

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Background

- The COMPASS and VOYAGER trials demonstrated the efficacy and safety of very low dose of rivaroxaban (2.5 mg twice daily) plus aspirin versus aspirin alone, supporting lower intensity dual pathway inhibitor therapy for patients with PAD.
- Although patients with concomitant AF were excluded, the benefit of this strategy was particularly robust for stroke prevention, with a 46% reduction in those with PAD and although there was more bleeding with rivaroxaban, there appeared to be a favorable benefit-risk profile.
- Taken together, the benefit of low-doses of rivaroxaban and less favorable bleeding profile of full-dose anticoagulation in patients with PAD raise questions about the efficacy and safety of full-dose oral FXa inhibitor therapy in patients with concomitant AF and PAD.

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Ischemic and bleeding risk in atrial fibrillation with and without peripheral artery disease and efficacy and safety of full and half-dose Edoxaban vs. Warfarin: insights from ENGAGE AF-TIMI 48

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Methods

- Novel aspects of ENGAGE TIMI-48 include pharmacokinetic and pharmacodynamic testing and randomization to a low dose edoxaban regimen (50% reduction, 30/15 mg), which was not approved.
- Hypothesis: efficacy and safety of both dosing strategies of edoxaban versus warfarin, would be consistent regardless of PAD at baseline.
- Therefore, in this subanalysis the authors:
  - examined the efficacy and safety of edoxaban 60/30 mg relative to warfarin in ENGAGE TIMI-48 AF in relation to PK and PD in patients with and without concomitant PAD.
  - explored the efficacy and safety of edoxaban 60/30 mg versus edoxaban 30/15 mg and warfarin.

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Methods

- Of 21,105 patients with AF randomized to warfarin, edoxaban 60/30mg or edoxaban 30/15mg, 841 were identified with PAD.
- Endpoints included major adverse cardiovascular events (MACE), SSE, and major bleeding.

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Baseline characteristics

In PAD subgroup higher prevalence of CV risk factor and previous MACCE

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	No PAD (N=20255)	PAD (N=841)	P Value
Age - years, median (IQR)	72 (64-77)	74 (68-79)	<0.001
Weight - kilograms, median (IQR)	81.6 (70-95)	83 (72.6-95.3)	0.013
White Race - no. (%)	16322 (80.6)	737 (87.6)	<0.001
Region - no. (%)			
North America	4406 (21.8)	274 (32.6)	<0.001
Latin America	2599 (12.8)	62 (7.4)	
Western Europe	3115 (15.4)	121 (14.4)	
Eastern Europe	6843 (33.8)	294 (35.0)	
Asia-Pacific region and South Africa	3292 (16.3)	90 (10.7)	
Female - no. (%)	7826 (38.6)	207 (24.6)	<0.001
Smoking History - no. (%)			
Never smoker	12110 (59.8)	333 (39.6)	<0.001
Former smoker	6681 (33.0)	415 (49.4)	
Current smoker	1458 (7.2)	92 (11.0)	
History of Hypertension -no. (%)	18952 (93.6)	793 (94.3)	0.400
History of Dyslipidemia --no. (%)	10464 (51.7)	585 (69.6)	<0.001
History of Diabetes --no. (%)	7245 (35.8)	377 (44.8)	<0.001
Creatinine clearance <= 50 milliliters /minute --no. (%)	3864 (19.1)	210 (25.0)	<0.001
History of Carotid Disease --no. (%)	1042 (5.1)	253 (30.1)	<0.001
History of Coronary Artery Disease --no. (%)	6518 (32.2)	502 (59.7)	<0.001
Prior myocardial infarction --no. (%)	2221 (11.0)	211 (25.1)	<0.001
History of heart failure --no. (%)	11603 (57.3)	513 (61.0)	0.033
History of Stroke or transient ischemic attack--no. (%)	5703 (28.2)	267 (31.7)	0.023
CHA_2DS_2-VASc Score - mean (SD)	4.3 (1.4)	5.2 (1.3)	<0.001
Score > 3 – no. (%)	14139 (69.8)	773 (91.9)	<0.001
Without point for PAD, Mean (SD)	4.3 (1.4)	4.2 (1.3)	0.11
Score > 3 w/o point for PAD– no. (%)	14139 (69.8)	565 (67.2)	0.11
HAS-BLED Score - mean (SD)	2.5 (1.0)	2.8 (1.0)	<0.001
Score >= 3 – no. (%)	9300 (45.9)	498 (59.2)	<0.001
Peripheral Artery Disease History*			
Prior Endovascular Intervention	NA	160 (19.0)	
Prior Surgical Intervention	NA	183 (21.8)	
No prior Intervention	NA	516 (61.4)	
Aspirin use at randomization --no. (%)	5906 (29.2)	272 (32.3)	0.047
Thienopyridine use at randomization --no. (%)	434 (2.1)	53 (6.3)	<0.001
Lipid Lowering Therapy at randomization --no. (%)	9552 (47.2)	528 (62.8)	<0.001
Prior VKA use > 2 months -- no. (%)	11876 (58.6)	563 (66.9)	<0.001
Dose reduced at randomization --no. (%)	5097 (25.2)	258 (30.7)	<0.001

Efficacy of Edoxaban vs Warfarin

No interaction for efficacy with Edoxaban 60/30 mg

ITT cohort, Overall Study Period		Edoxaban (n=14063) 60/30 mg (n=7030) N	Edoxaban (n=14063) 60/30 mg (n=7030) Rate (%/year)	Edoxaban (n=14063) 30/15 mg (n=7033) n	Edoxaban (n=14063) 30/15 mg (n=7033) Rate (%/year)	Warfarin (n=7033) n	Warfarin (n=7033) Rate (%/year)	*Edoxaban 60/30 mg vs Warfarin* HR (95% CI)	*Edoxaban 60/30 mg vs Warfarin* Interaction p-value	*Edoxaban 30/15 mg vs Warfarin* HR (95% CI)	*Edoxaban 30/15 mg vs Warfarin* Interaction p-value
Major adverse cardiac event	**No PAD**	**780**	**4.32**	**857**	**4.80**	**864**	**4.83**	**0.89 (0.81- 0.98)**	**0.469**	**0.99 (0.90- 1.09)**	**0.324**
	PAD	**47**	**6.81**	**56**	**7.20**	**62**	**9.10**	**0.77 (0.53- 1.13)**		**0.82 (0.57- 1.18)**	
Stroke, systemic embolism, or cardiovascular death	No PAD	692	3.80	745	4.13	779	4.32	0.88 (0.79- 0.97)	0.330	0.95 (0.86- 1.05)	0.764
	PAD	36	5.09	51	6.46	52	7.48	0.70 (0.46- 1.08)		0.90 (0.61- 1.33)	
Stroke or Systemic Embolism	No PAD	288	1.59	362	2.01	330	1.83	0.86 (0.74- 1.01)	0.573	1.09 (0.94- 1.27)	0.039
	PAD	8	1.13	21	2.67	7	1.02	1.16 (0.42- 3.20)		2.73 (1.16- 6.43)	
Peripheral Vascular Interventions	No PAD	37	0.20	58	0.32	34	0.19	1.08 (0.68 – 1.72)	0.930	1.70 (1.11 – 2.60	0.694
	PAD	17	2.49	25	3.23	15	2.22	1.12 (0.56 – 2.26)		1.46 (0.77 – 2.76)	
Death											
Any cause	No PAD	731	3.93	687	3.69	783	4.22	0.93 (0.84- 1.03)	0.356	0.87 (0.79- 0.97)	0.751
	PAD	42	5.82	50	6.19	55	7.82	0.76 (0.50- 1.15)		0.82 (0.55- 1.21)	
Cardiovascular causes	No PAD	501	2.69	490	2.63	564	3.04	0.88 (0.78- 1.00)	0.143	0.86 (0.77- 0.98)	0.389
	PAD	29	4.02	37	4.58	47	6.68	0.61 (0.38- 0.98)		0.71 (0.46- 1.10)	

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Safety of Edoxaban vs. Warfarin

Safety cohort, On Treatment Study Period (with Interval Censoring)		Edoxaban (n=14008) 60/30 mg (n=7007) n	Edoxaban (n=14008) 60/30 mg (n=7007) Rate (%/year)	Edoxaban (n=14008) 30/15 mg (n=7001) n	Edoxaban (n=14008) 30/15 mg (n=7001) Rate (%/year)	Warfarin (n=7009) n	Warfarin (n=7009) Rate (%/year)	*Edoxaban 60/30 mg vs Warfarin* HR (95% CI)	*Edoxaban 60/30 mg vs Warfarin* Interaction p-value	*Edoxaban 30/15 mg vs Warfarin* HR (95% CI)	*Edoxaban 30/15 mg vs Warfarin* Interaction p-value
Major bleeding	**No PAD**	**395**	**2.70**	**241**	**1.60**	**500**	**3.39**	**0.80 (0.70- 0.91)**	**0.540**	**0.47 (0.40- 0.55)**	**0.906**
	PAD	**23**	**4.30**	**13**	**2.01**	**24**	**4.50**	**0.96 (0.54- 1.70)**		**0.45 (0.23- 0.89)**	
Major or clinically relevant nonmajor bleeding	No PAD	1461	11.01	1096	7.84	1684	12.89	0.86 (0.80- 0.92)	0.925	0.61 (0.57- 0.66)	0.450
	PAD	66	13.64	65	11.15	76	16.36	0.84 (0.61- 1.17)		0.70 (0.50- 0.97)	
Any overt bleeding	No PAD	1790	14.10	1419	10.54	2023	16.24	0.87 (0.82- 0.93)	0.516	0.66 (0.61- 0.70)	0.619
	PAD	74	15.81	80	14.06	89	20.38	0.79 (0.58- 1.07)		0.71 (0.53- 0.96)	

No interaction for safety with Edoxaban 60/30 mg

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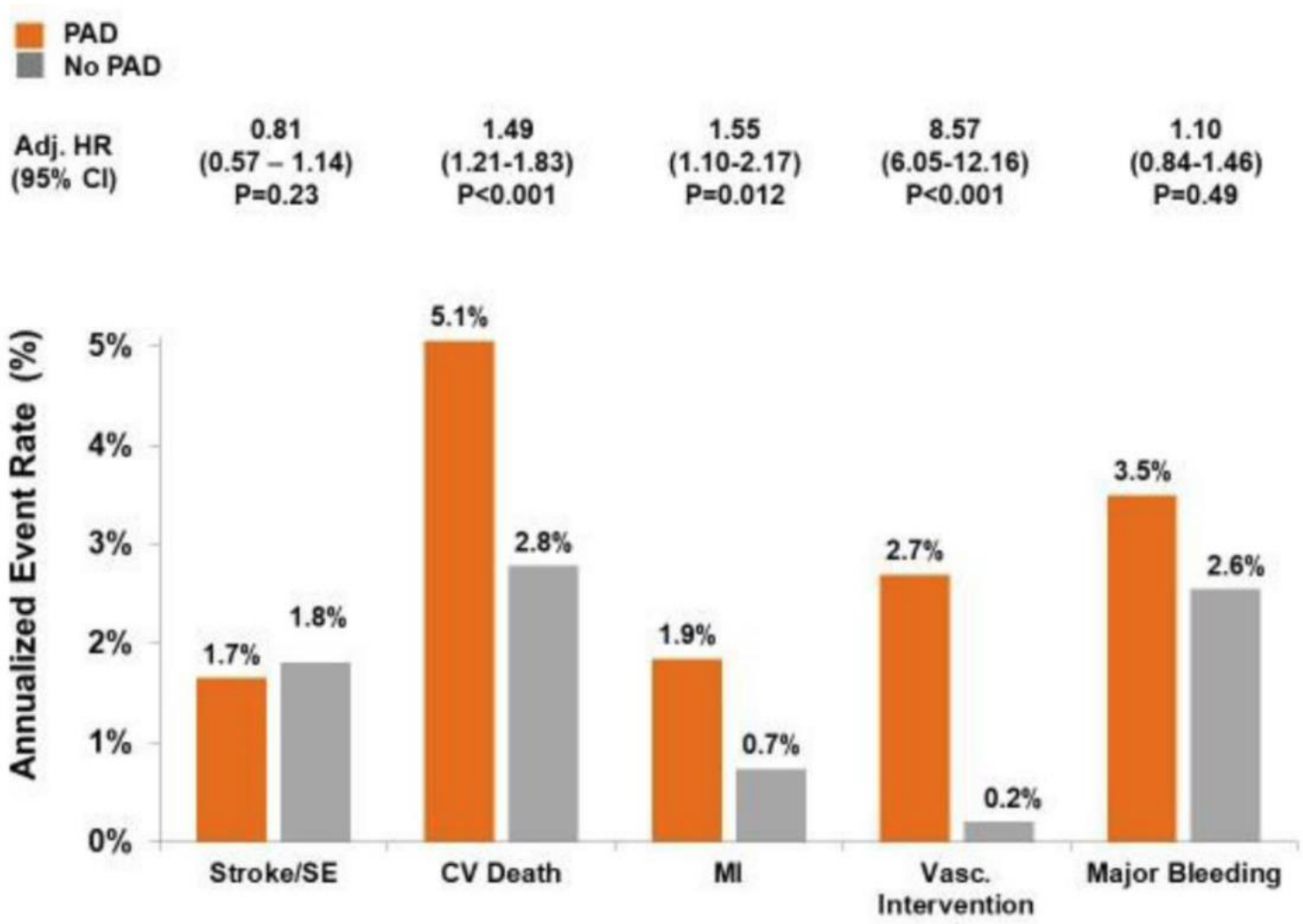
Outcomes in AF patients with or without PAD



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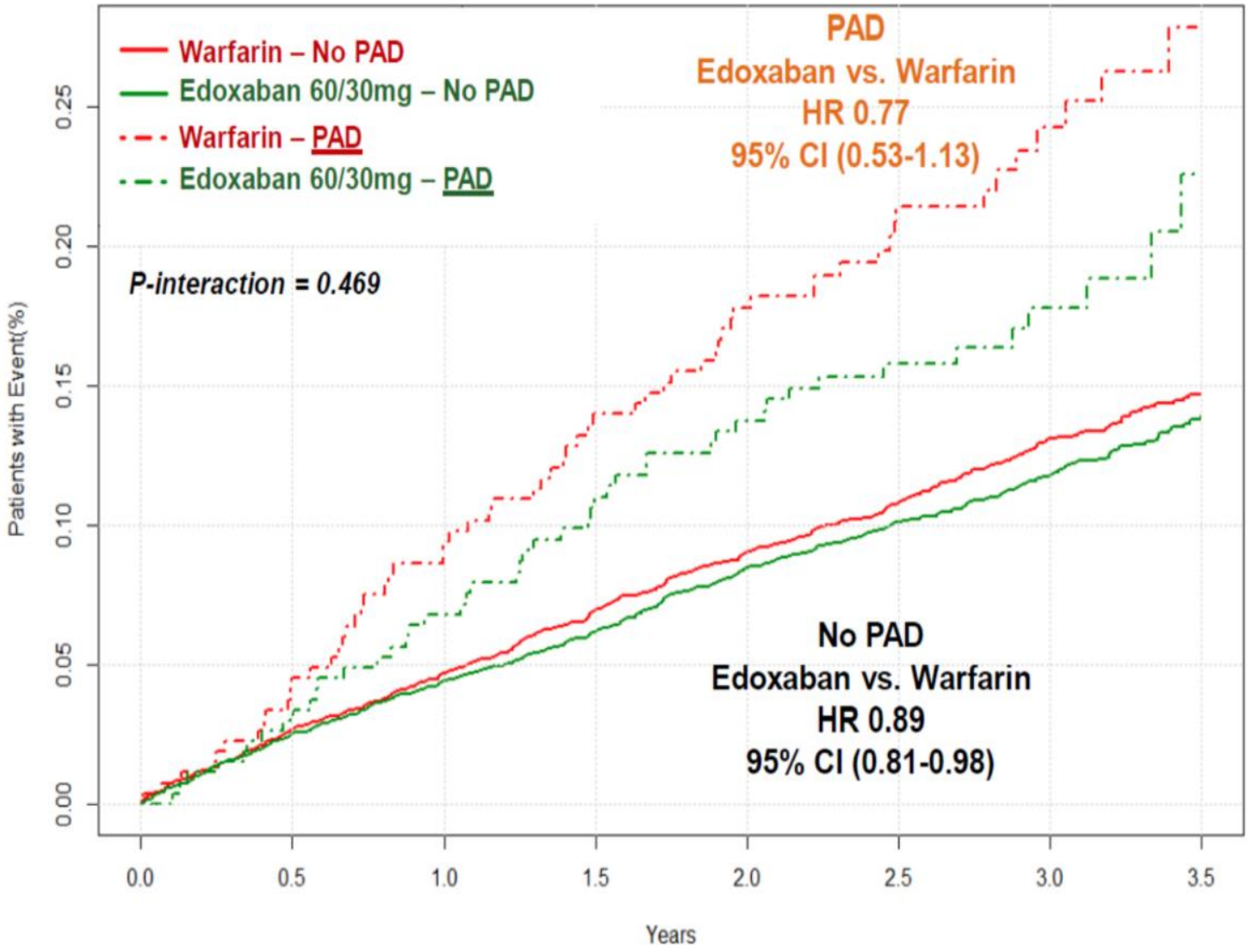
Cardiovascular Death, MI or ischemic stroke and history of PAD



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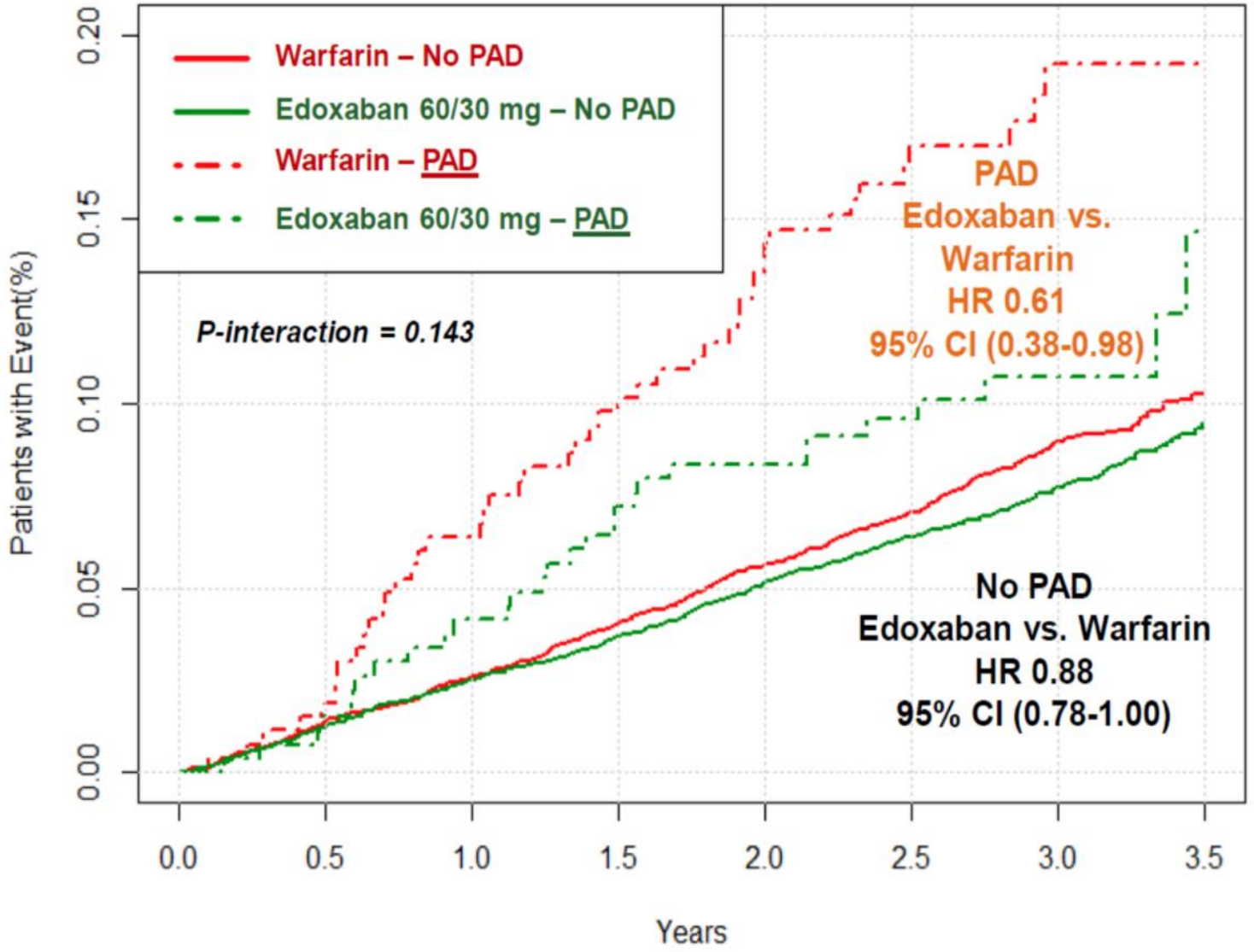
Cardiovascular death by treatment and history of PAD



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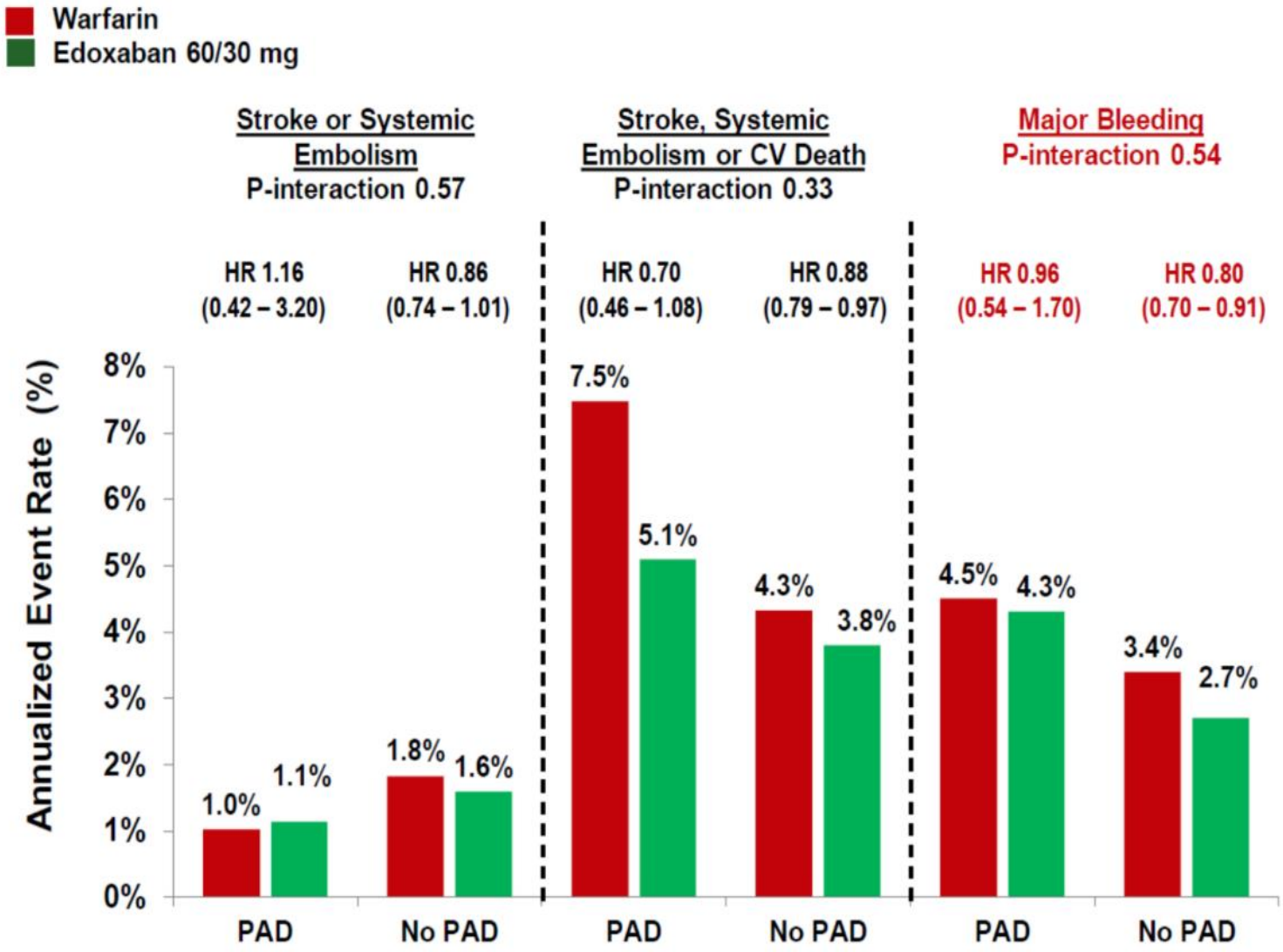
Edoxaban vs. Warfarin in AF with or without PAD



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Limitations

- First, PAD at baseline was identified by site investigators without routine testing. Therefore, patients with unrecognized PAD may have been miscategorized as «no PAD».
- Second, the number of patients in the PAD subgroup was modest (~4% of the overall trial and 841 patients), and the number of outcomes events was small, particularly for limb outcomes.
    - However, both the number of patients and number of primary efficacy events is similar to previously reported PAD subgroups from pivotal trials of other Factor Xa inhibitors.
- Because the trial was not powered for subgroup analyses, the findings should be considered exploratory and conclusions regarding risk and treatment effects should be considered hypothesis generating.
- Although comparisons were adjusted for other baseline variables, there may be other, unrecognized sources of confounding.
- Patients in clinical practice may behave differently from those in a randomized trial, and results should not be generalized to patients who would not have been eligible for participation in the ENGAGE AF-TIMI 48, such as those with CHADS scores 0 or 1, severe kidney disease, or patients receiving DAPT.
- Both dosing regimens of edoxaban significantly reduced CV mortality in the overall trial and there was no significant interaction on the basis of PAD for CV mortality. As such, observation regarding differences by dosing strategy on this endpoint with respect to PAD should be regarded as hypothesis generating.

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Conclusions

Key question(s)

Use of anticoagulants at varying doses has expanded in patients with Peripheral Artery Disease raising question as to the optimal dosing in patients with PAD and comorbid atrial fibrillation

Key finding(s)

In ENGAGE AF TIMI 48, patients with PAD were at heightened risk of MACE and CV death versus those without PAD. The approved "full dose" of edoxaban showed consistent efficacy and safety versus warfarin, however, a lower dose was inferior for stroke prevention.

Take-home message

Patients with PAD and AF are at high ischemic and bleeding risk and the efficacy and safety of edoxaban 60/30 mg is consistent. Although lower intensity anticoagulation reduces MACE in PAD without AF, in those with AF, lower doses are not sufficient for stroke prevention.

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