Impact of Low-dose Rivaroxaban plus Aspirin on Total Vascular Events in Fragile Patients with Peripheral Artery Disease: Insights from VOYAGER PAD

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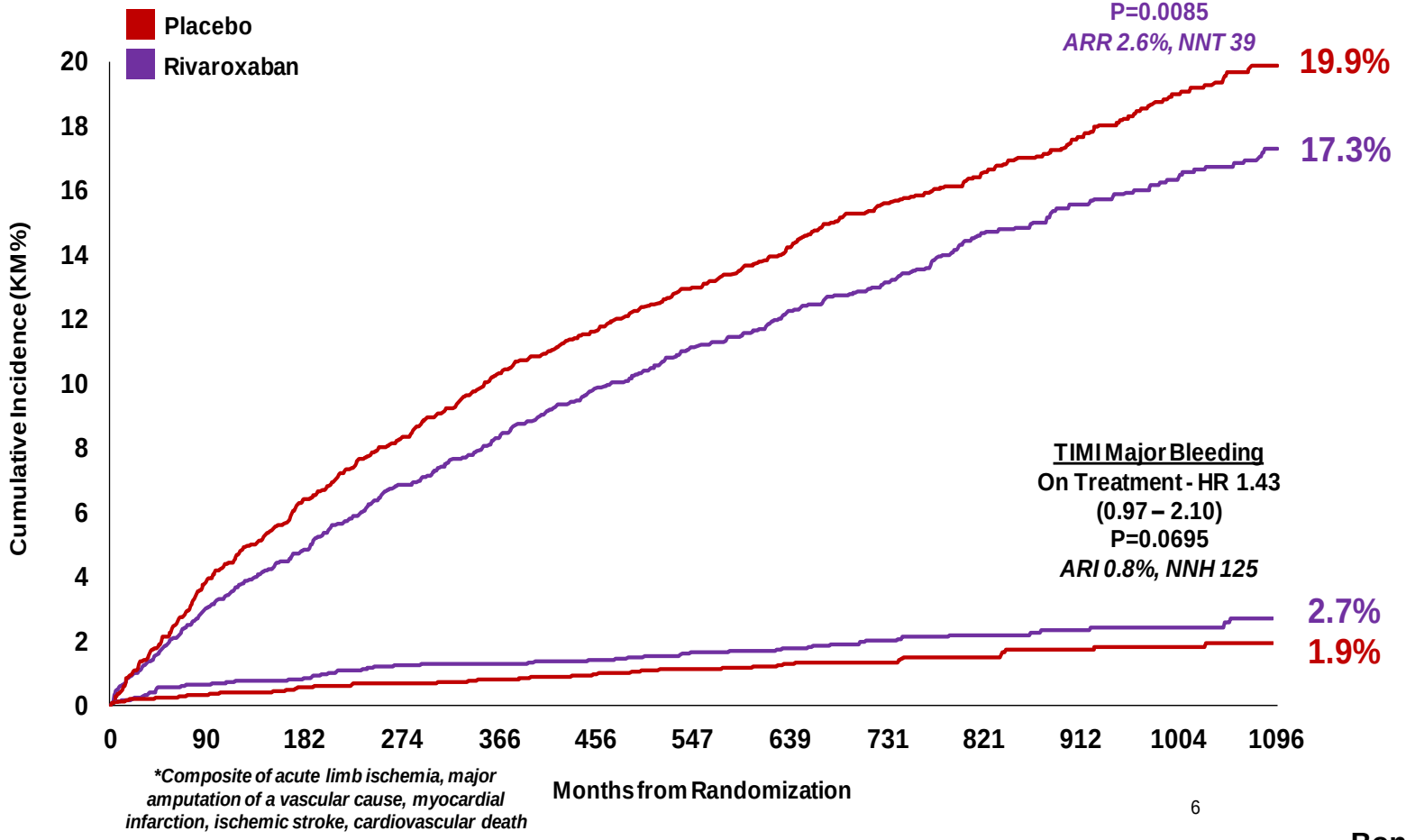
BACKGROUND

VOYAGER-PAD – Primary efficacy & Safety outcomes

The NEW ENGLAND JOURNAL of MEDICINE

VOYAGER PAD Primary Results



ORIGINAL ARTICLE

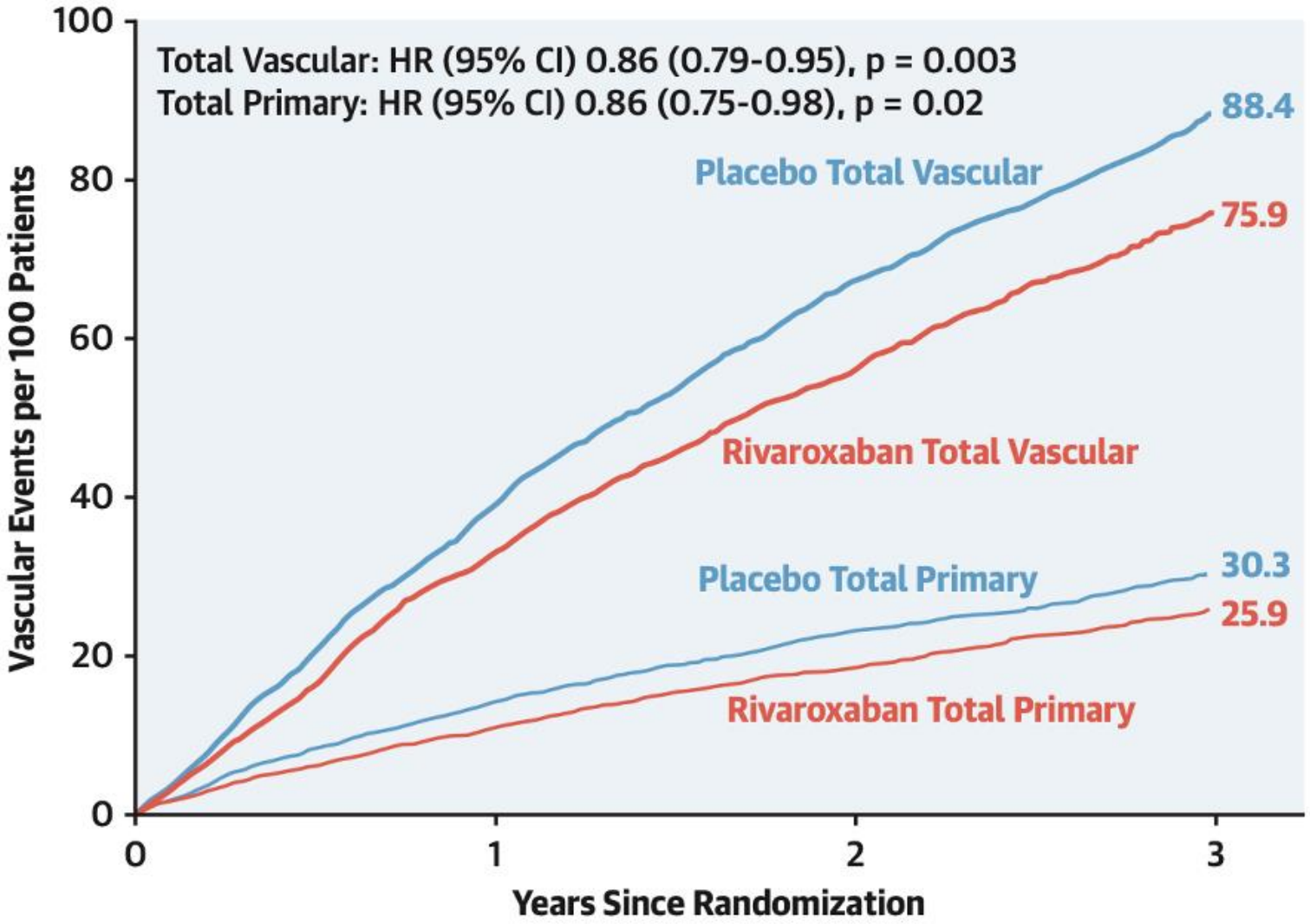
Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., E. Sebastian Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D., Dainis K. Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D., Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and William R. Hiatt, M.D.

Bonaca MP, et al. N Engl J Med. 2020 May 21;382(21):1994-2004.

BACKGROUND

VOYAGER-PAD – Primary and Total Vascular Events



Bauersachs RM, et al. J Am Coll Cardiol. 2021 Jul 27;78(4):317-326.

AIM & METHODS

The aim was to assess the safety and efficacy of rivaroxaban on major adverse limb events (MALE) and total vascular events in fragile patients with symptomatic PAD undergoing lower extremity revascularization.

- **Fragile was pre-specified subgroup including criteria such as age >75 yr, or weight ≤ 50 kg or baseline eGFR < 50 mL/min/1.73^2.**
- **MALE was defined as acute limb ischemia or major amputation.**
- **Total vascular events (first and subsequent) for components of the primary endpoint as well as additional vascular events including peripheral revascularizations and venous thromboembolism.**

RESULTS

Baseline Characteristics

Baseline Characteristics	Fragile N=1669	Non-Fragile N=4677	P-value
Median age (IQR) – yr	77 (72 – 81)	64 (59 – 69)	<0.0001
Female (%)	41	21	< 0.0001
White Caucasian (%)	67	85	< 0.0001
Hypertension (%)	88	80	<0.0001
Diabetes Mellitus (type 2) (%)	46	38	<0.0001
Hyperlipidemia (%)	59	60	0.50
eGFR < 60 ml/min.1.73m^2 (%)	53	9	<0.0001
Prior MI (%)	12	10	0.17
Carotid stenosis ≥ 50% (%)	10	8	0.003
History of heart failure (%)	10	8	<0.0001

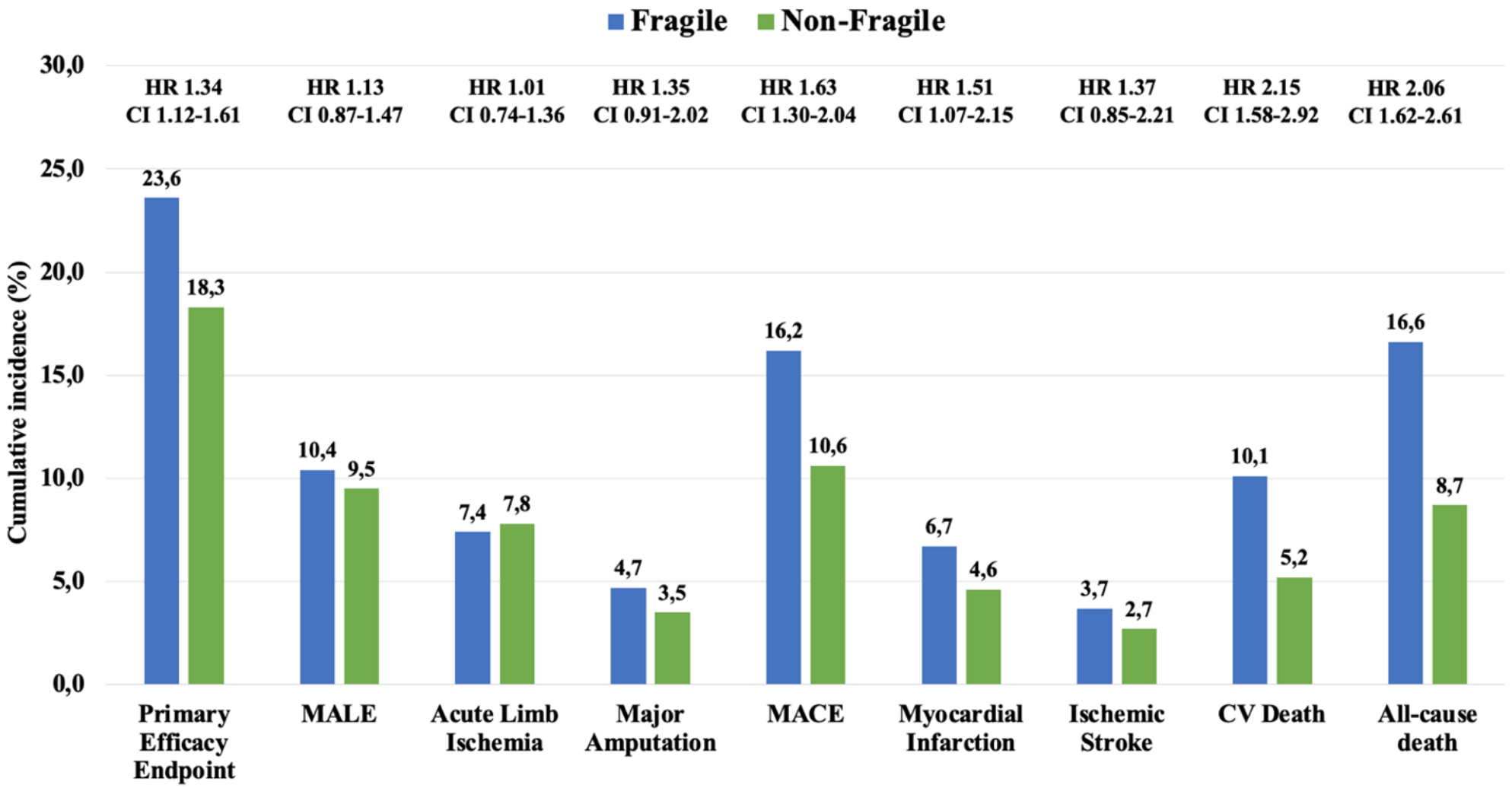
RESULTS

Baseline Characteristics

Baseline Characteristics	Fragile N=1669	Non-Fragile N=4677	P-value
Qualifying revascularization			**<0.0001**
Surgical (%)	27	37	
Endovascular (%)	73	63	
PAD Characteristics			
Prior limb revascularization (%)	34	33	0.74
Prior Major Amputation (%)	7	5	0.005
Medications			
Statins (%)	77	81	0.002
ACE/ARB (%)	66	62	0.005
Clopidogrel at randomization (%)	55	52	0.034

RESULTS

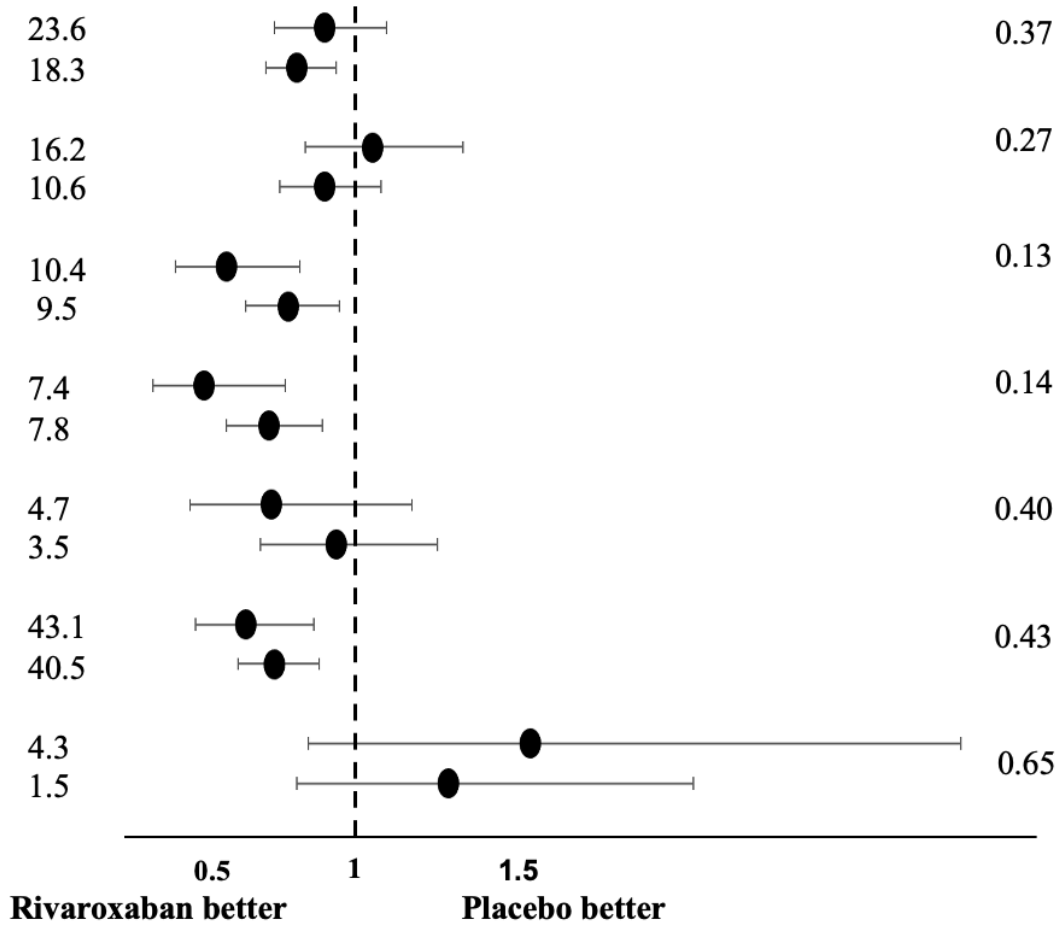
Fragile vs Non-Fragile in Placebo Group



RESULTS - ITT, FIRST EVENTS

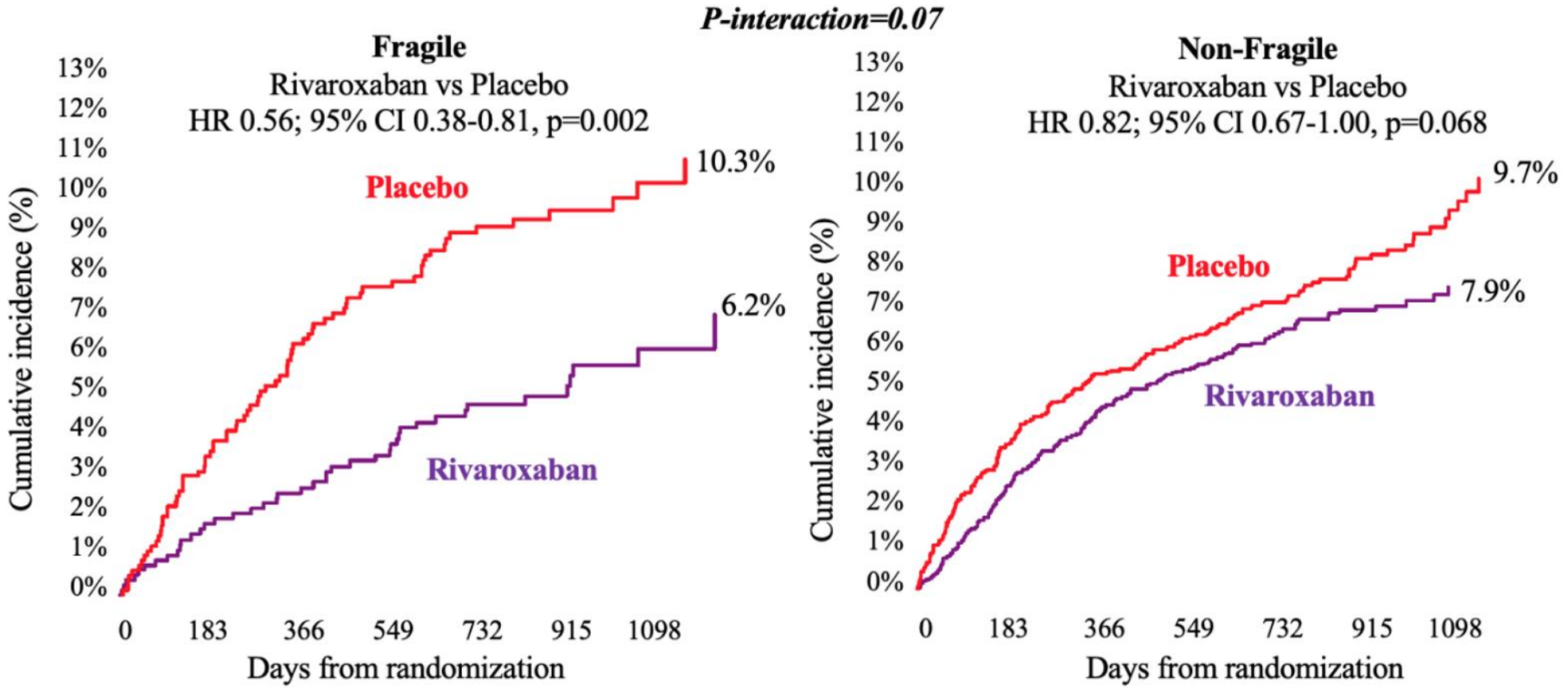
Efficacy and Safety Outcomes Rivaroxaban vs Placebo

		3-year KM rates % Rivaroxaban	Placebo	P-interaction
Primary efficacy outcome				
Fragile	0.93 (0.75-1.15)	20.8	23.6	0.37
Non-Fragile	0.83 (0.72-0.97)	14.3	18.3	
MACE				
Fragile	1.10 (0.86-1.42)	17.4	16.2	0.27
Non-Fragile	0.93 (0.77-1.13)	10.2	10.6	
MALE				
Fragile	0.58 (0.40-0.84)	6.2	10.4	0.13
Non-Fragile	0.80 (0.65-0.98)	7.9	9.5	
Acute limb ischemia				
Fragile	0.50 (0.32-0.79)	2.2	7.4	0.14
Non-Fragile	0.73 (0.58-0.92)	4.9	7.8	
Major amputation				
Fragile	0.74 (0.45-1.24)	3.4	4.7	0.40
Non-Fragile	0.97 (0.70-1.33)	2.7	3.5	
CAD/PAD hospitalization				
Fragile	0.65 (0.47-0.89)	36.5	43.1	0.43
Non-Fragile	0.75 (0.62-0.91)	37.9	40.5	
TIMI major bleeding				
Fragile	1.54 (0.82-2.91)	4.6	4.3	0.65
Non-Fragile	1.37 (0.84-2.23)	2.1	1.5	



RESULTS - ITT FIRST EVENTS

3-year KM rates for MALE in Fragile and non-Fragile

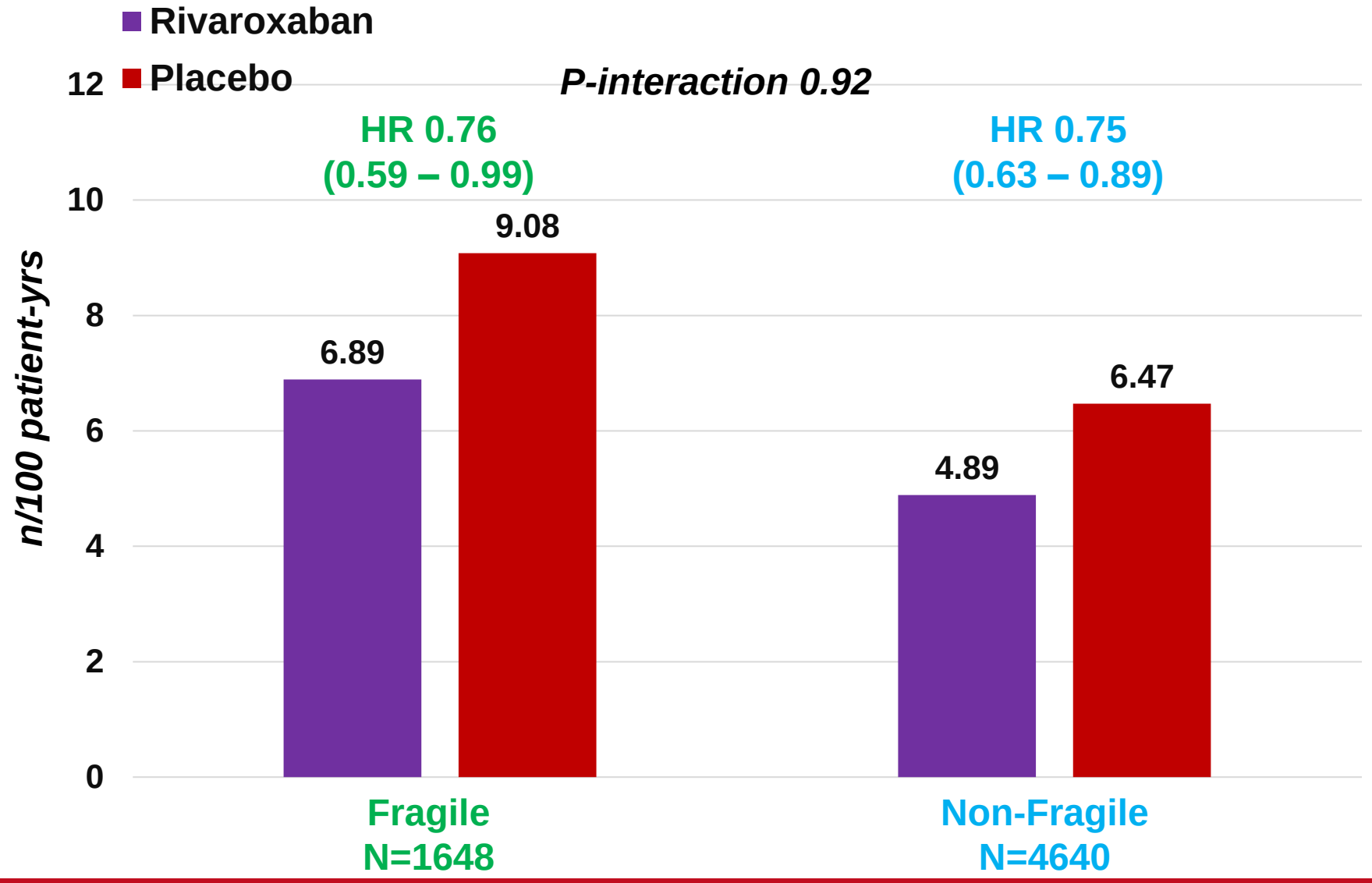


No. at risk							
Placebo	838	783	739	705	554	341	172
Rivaroxaban	831	778	747	712	563	333	158

No. at risk							
Placebo	2335	2194	2116	2064	1611	1023	471
Rivaroxaban	2342	2232	2154	2095	1639	1070	521

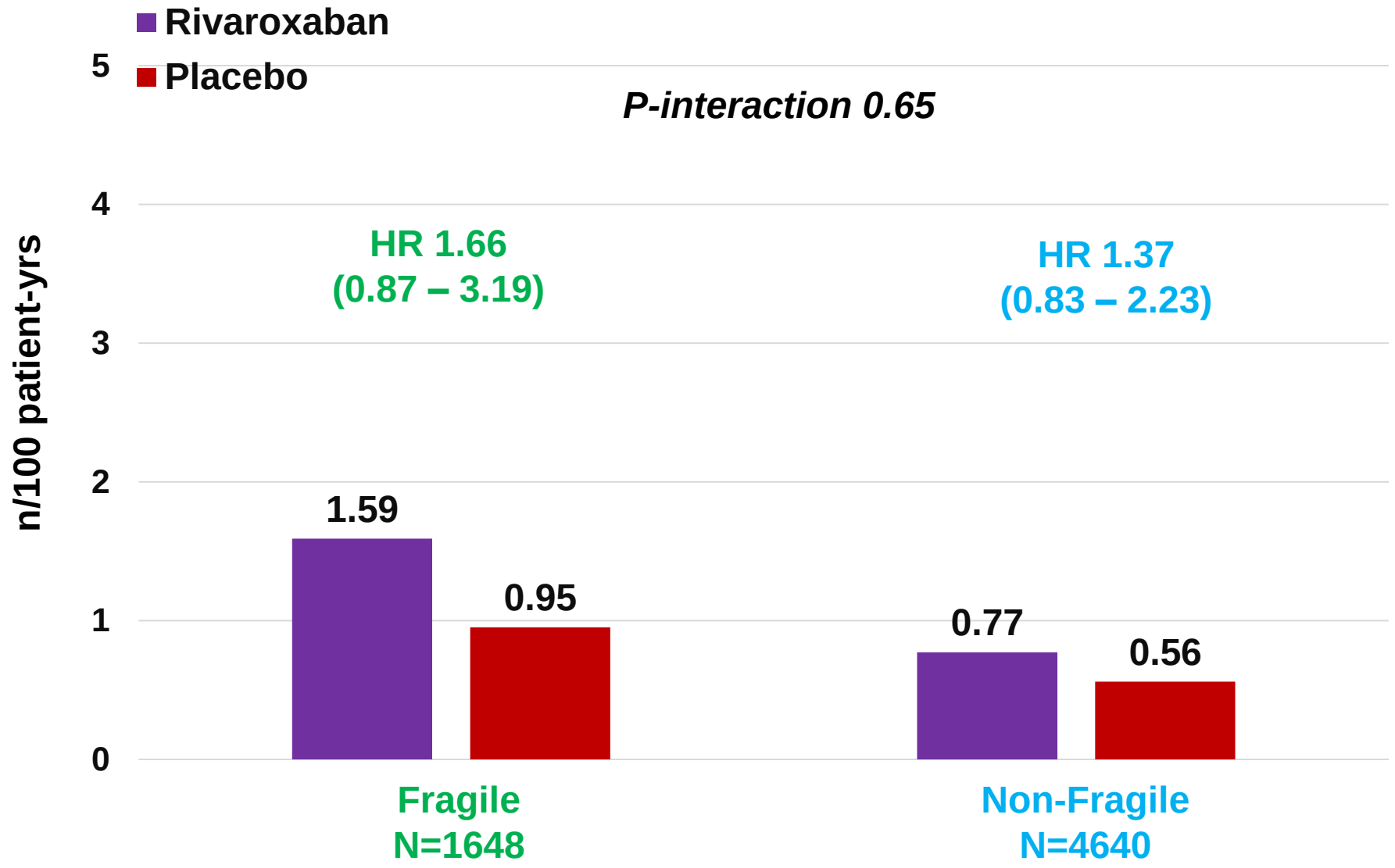
RESULTS - ON TREATMENT

Primary Efficacy Endpoint by Fragile Status



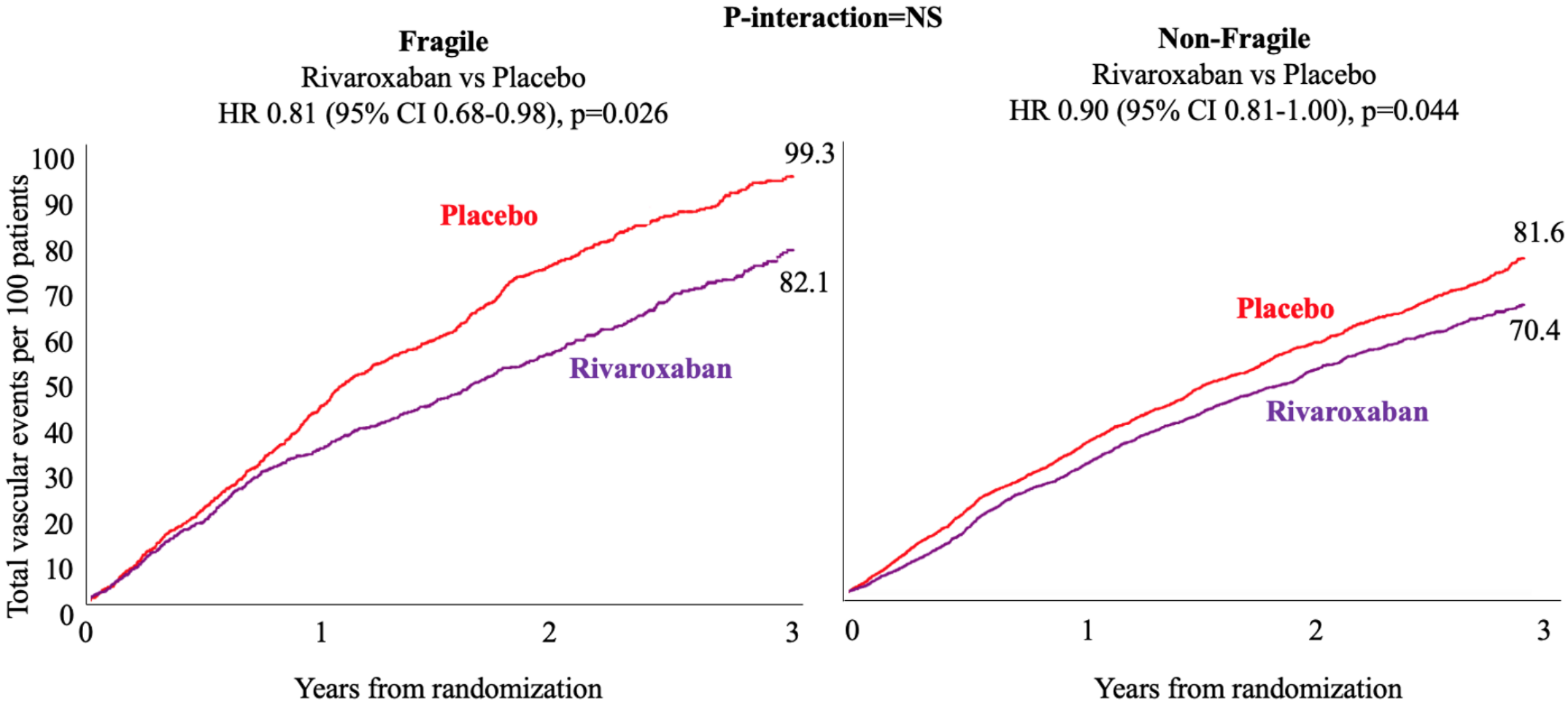
RESULTS - ON TREATMENT

TIMI Major Bleeding by Fragile Status



RESULTS

Total Vascular Events in Fragile and non-Fragile



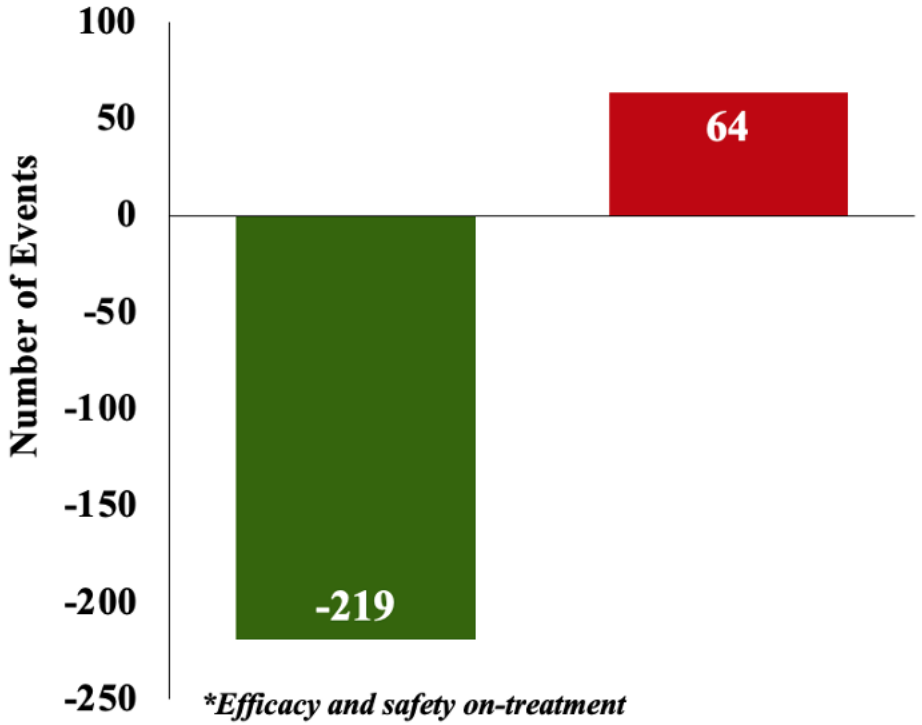
RISK / BENEFIT: ON TREATMENT

First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year

FRAGILE

Primary Efficacy Outcome
Events Prevented
HR 0.76
(95% CI 0.59-0.99)

Principal Safety Outcome
Events Caused
HR 1.54
(95% CI 0.82-2.91)

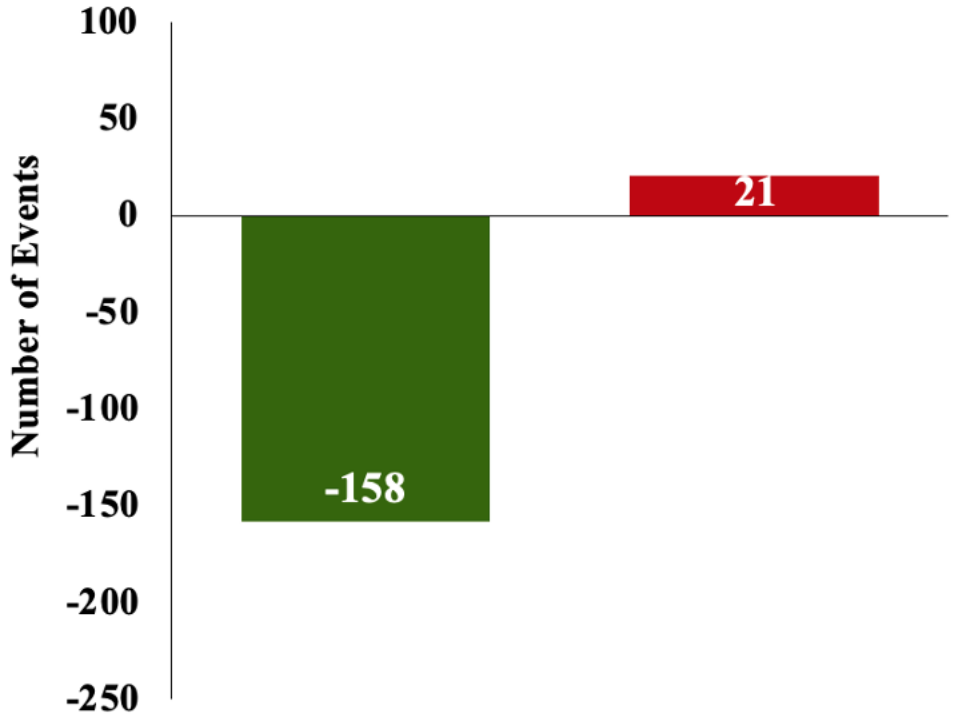


*Efficacy and safety on-treatment

NON-FRAGILE

Primary Efficacy Outcome
Events Prevented
HR 0.75
(95% CI 0.63-0.89)

Principal Safety Outcome
Events Caused
HR 1.37
(95% CI 0.84-2.23)



SUMMARY & CONCLUSION

- Fragile patients showed higher risk of MACE+MALE and all-cause death compared to non-fragile
- Overall, VOYAGER PAD demonstrated that rivaroxaban 2.5 mg twice daily added to low dose aspirin (+/- clopidogrel) in fragile patients:
  - Reduces irreversible harm events in particular MALE and total vascular events.
  - Increases bleeding but not fatal bleeding with benefit risk ratio 4:1.

- In patients with symptomatic PAD after LER, rivaroxaban should be considered regardless of frailty and future studies should consider novel approaches to bleeding risk stratification in this population.

An Affiliate of:

THANK YOU

American Heart Association.

Scientific Sessions

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