

Efficacia di Ticagrelor nella
riduzione di eventi ischemici
periferici nei pazienti con
coronaropatia e diabete con
o senza arteriopatia periferica

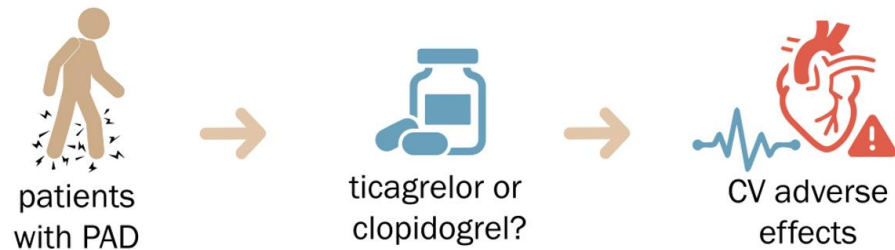
SUBANALISI DAL THEMIS TRIAL

EUCLID trial

EUCLID: Ticagrelor versus clopidogrel in symptomatic peripheral artery disease

Multicenter, double-blind, active-comparator randomized controlled trial

Objective: To assess if ticagrelor superior to clopidogrel in prevention of cardiovascular death, MI, or ischemic stroke in patients with symptomatic peripheral arterial disease.



13,885 patients (age >50 y) with symptomatic PAD (ABI 0.80 or less, TBI 0.60 or less if ABI ≥ 1.40)

ticagrelor
(90 mg twice daily)
(n=6930)



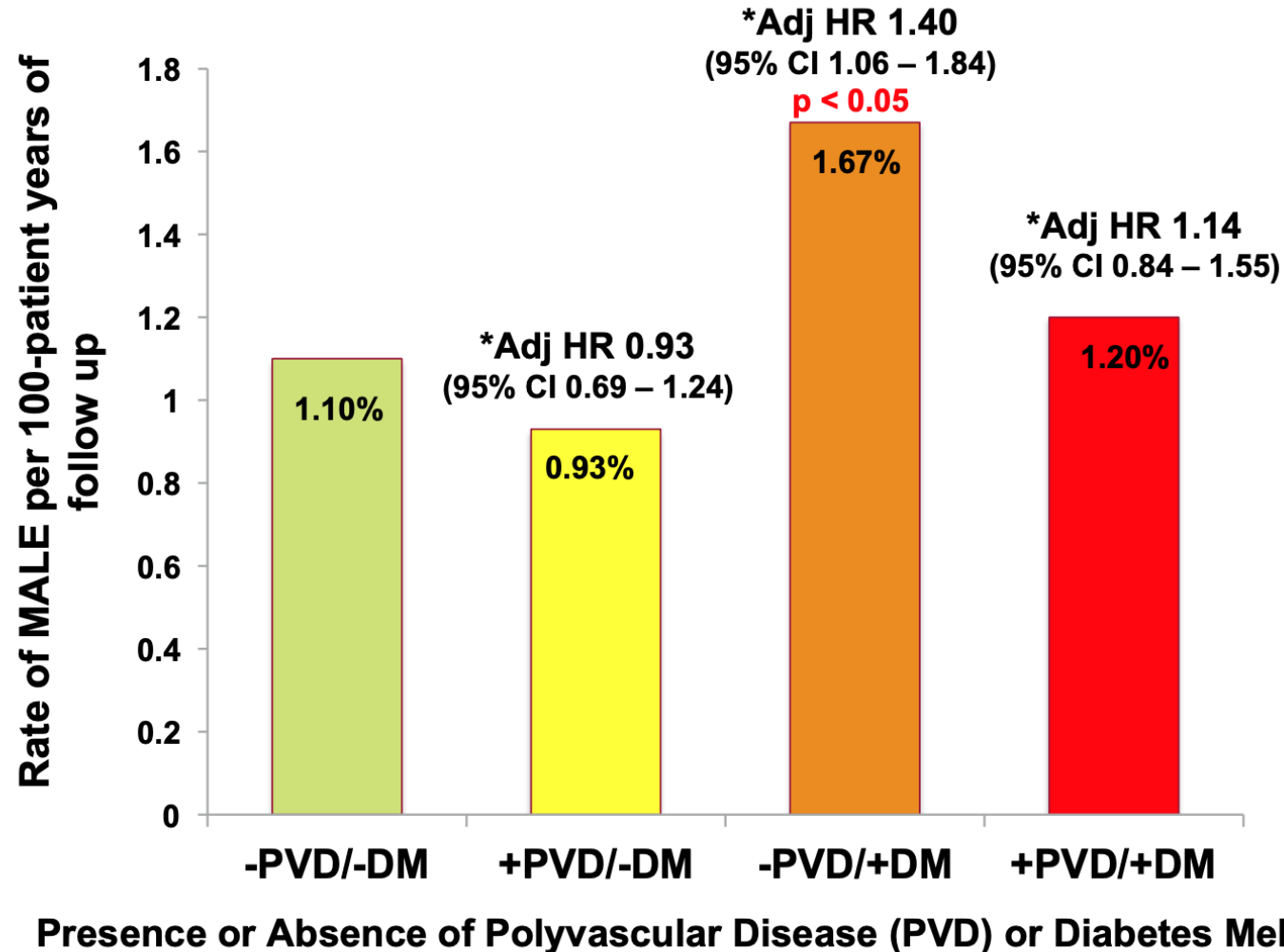
clopidogrel
(75 mg once daily)
(n=6955)

Primary Outcome		
10.8%	CV death, MI, or ischemic stroke HR 1.02; 95% CI 0.92-1.13; P=0.65	10.6%
Secondary Outcome		
1.9%	Ischemic stroke HR 0.78; 95% CI 0.62-0.98; P=0.03	2.4%
5.2%	Cardiovascular death P=0.40	4.9%
1.6%	TIMI major bleeding P=0.49	1.6%
9.1%	All-cause mortality P=0.91	9.1%

In patients with symptomatic peripheral artery disease, ticagrelor was not superior to clopidogrel for the reduction of CV events. Major bleeding occurred at similar rates in both groups.

EUCLID trial

Behan S...Bonaca MP et al ACC 2020





*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use

THEMIS trial

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor in Stable Coronary Disease and Diabetes

MULTICENTER, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

19,220 Patients with type 2 diabetes and stable coronary artery disease	Ticagrelor 60 mg twice daily + low-dose aspirin 75–150 mg once daily  N=9619	Placebo + low-dose aspirin 75–150 mg once daily  N=9601
Cardiovascular death, MI, or stroke (median follow-up, 39.9 mo)	7.7% (N=736)	8.5% (N=818)
TIMI major bleeding	2.2% (N=206)	1.0% (N=100)

Ticagrelor + aspirin decreased ischemic cardiovascular events but increased major bleeding

THEMIS trial



Clinical Outcomes

	Ticagrelor (N=9619)		Placebo (N=9601)		Hazard Ratio (95% CI)	p-value
	Patients with events (%)	KM% at 36 mos	Patients with events (%)	KM% at 36 mos		
Primary: CV death/MI/stroke	736 (7.7%)	6.9%	818 (8.5%)	7.6%	0.90 (0.81–0.99)	0.038
Hierarchical Secondary End Points						
CV death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88–1.18)	0.79
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71–0.98)	0.029
Ischemic stroke	152 (1.6%)	1.5%	191 (2.0%)	1.8%	0.80 (0.64–0.99)	0.038
All cause death	579 (6.0%)	5.1%	592 (6.2%)	4.9%	0.98 (0.87–1.10)	0.68
Exploratory End Points						
All-cause death, MI, stroke	919 (9.6%)	8.5%	1018 (10.6%)	9.2%	0.90 (0.83–0.99)	0.025
All stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67–0.99)	0.044
Acute limb ischemia/ major amputation of vascular etiology	13 (0.1%)	0.1%	29 (0.3%)	0.3%	0.45 (0.23–0.86)	0.017
All-cause death/ MI/ stroke/ ALI/ major amputation of vascular etiology	927 (9.6%)	8.5%	1039 (10.8%)	9.4%	0.89 (0.82–0.97)	0.011
Coronary arterial revascularization	828 (8.6%)	8.2%	879 (9.2%)	8.9%	0.94 (0.86–1.04)	0.21

The analysis of all cause death includes data related to vital status in patients who withdrew consent (per the Statistical Analysis Plan); coronary revascularization is as reported by the investigator; event rate is calculated as number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100. Confidence intervals for secondary and exploratory efficacy end points were not adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. ALI=acute limb ischemia; CI=confidence interval; CV=cardiovascular; ICH=intracranial hemorrhage; KM=Kaplan-Meier; MI=myocardial infarction; mos=months; N=number of patients

THEMIS PAD- objectives

- ▶ To characterize limb events in the group overall and by the presence of PAD, including:
 - ▶ acute limb ischemia (ALI);
 - ▶ major amputation of vascular etiology;
 - ▶ peripheral revascularization (urgent, elective);
 - ▶ overall limb ischemia outcomes defined as composite of the individual events
- ▶ To evaluate the efficacy of adding ticagrelor to aspirin vs. aspirin alone to reduce limb ischemic events in patients with T2DM and CAD
- ▶ To evaluate whether this effect is similar in patients with and without PAD.

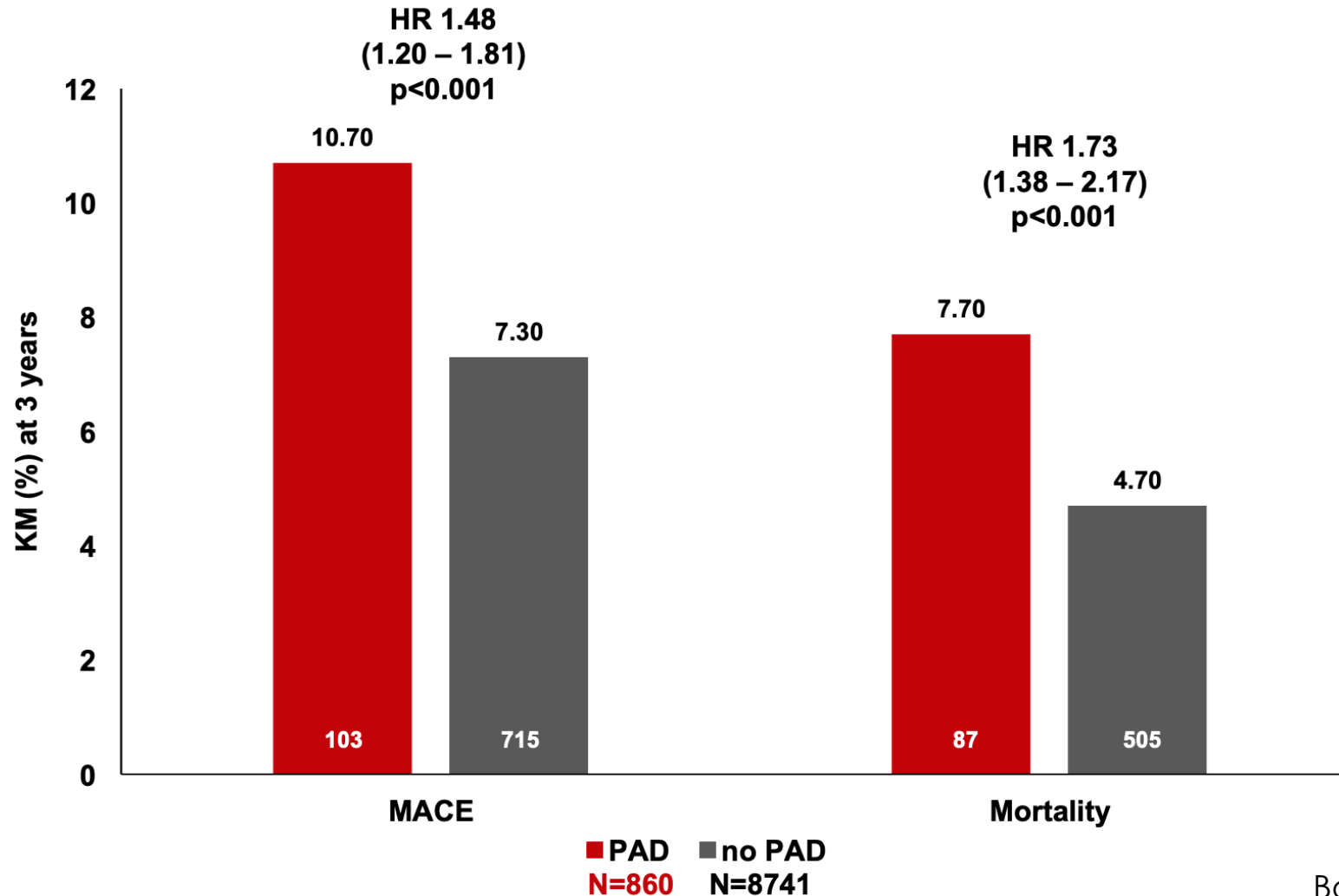
THEMIS-PAD methods

- ▶ Limb ischemic events were prospectively reported to an electronic data capture system
- ▶ Events were adjudicated using established definitions and by a blinded, independent clinical event committee
- ▶ The need for revascularization was investigator reported

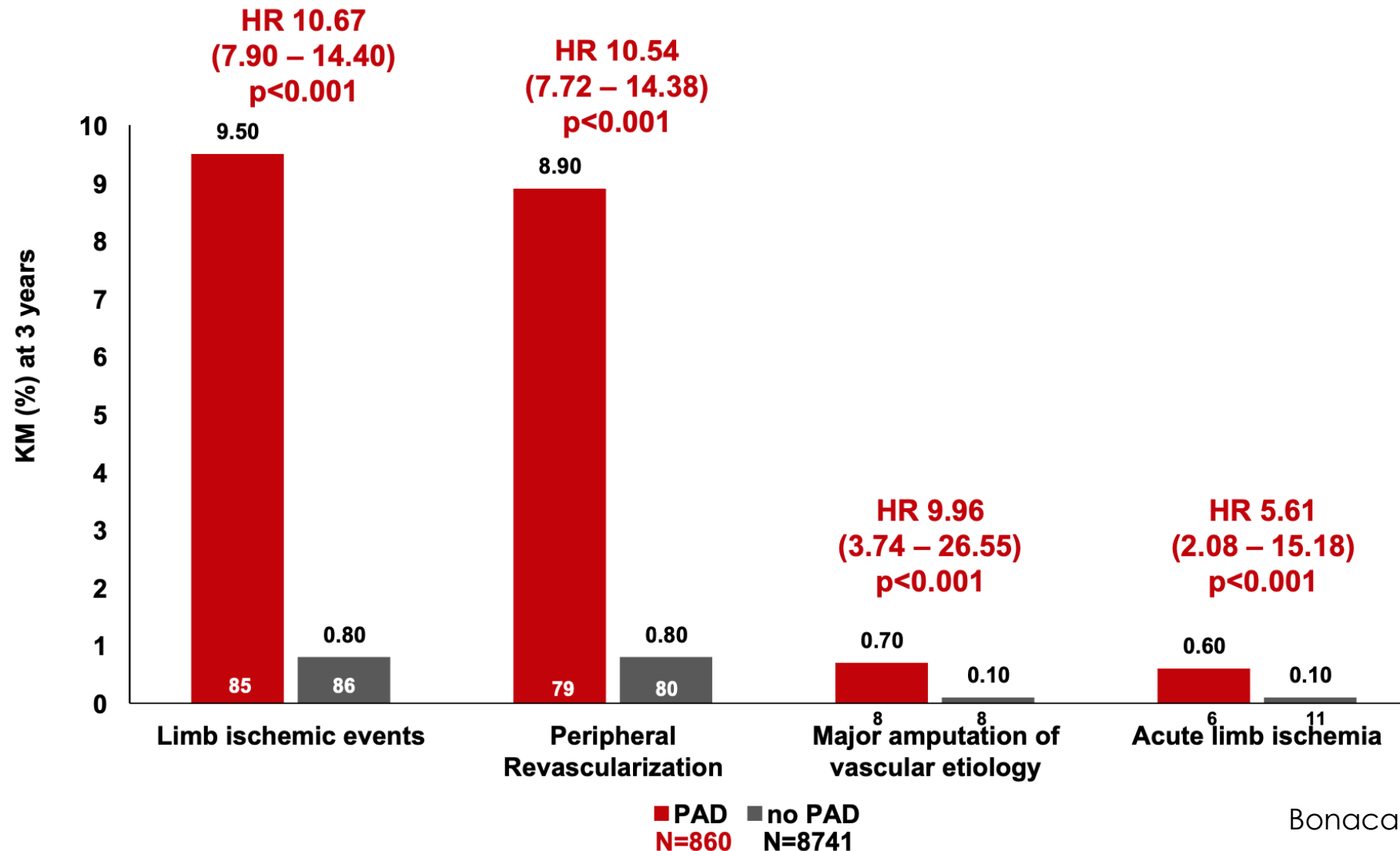
Baseline characteristics

Characteristic	PAD (N=1687)	No PAD (N=17533)	P-value
Age – median (IQR), yrs	68 (62 – 73)	66 (61 – 72)	<0.001
Female (%)	27	32	<0.001
Caucasian (%)	83	70	<0.001
Hypertension (%)	95	92	<0.001
Dyslipidemia (%)	92	87	<0.001
Duration of T2DM – median (IQR), yrs	12 (6 – 19)	10 (5 – 16)	<0.001
Diabetes complication (%)	41	24	<0.001
HbA1C – median (IQR), %	7.1 (6.4 – 8.1)	7.1 (6.4 – 8.1)	0.65
eGFR – median (IQR), mL/min/1.73m ²	71 (56 – 86)	75 (61 – 90)	<0.001
Coronary revascularization (%)	83	80	0.005

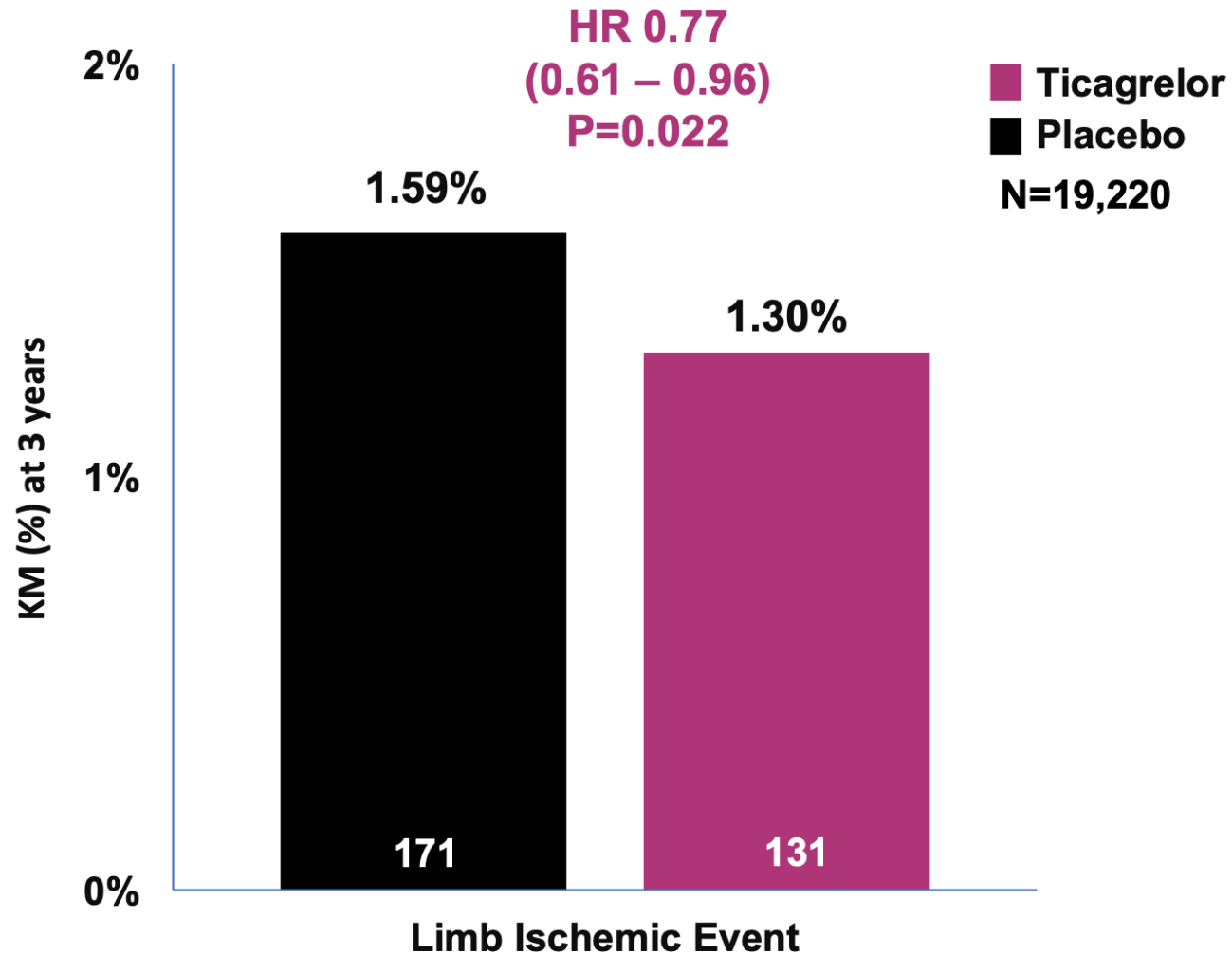
Outcome in placebo patients according to the presence of PAD



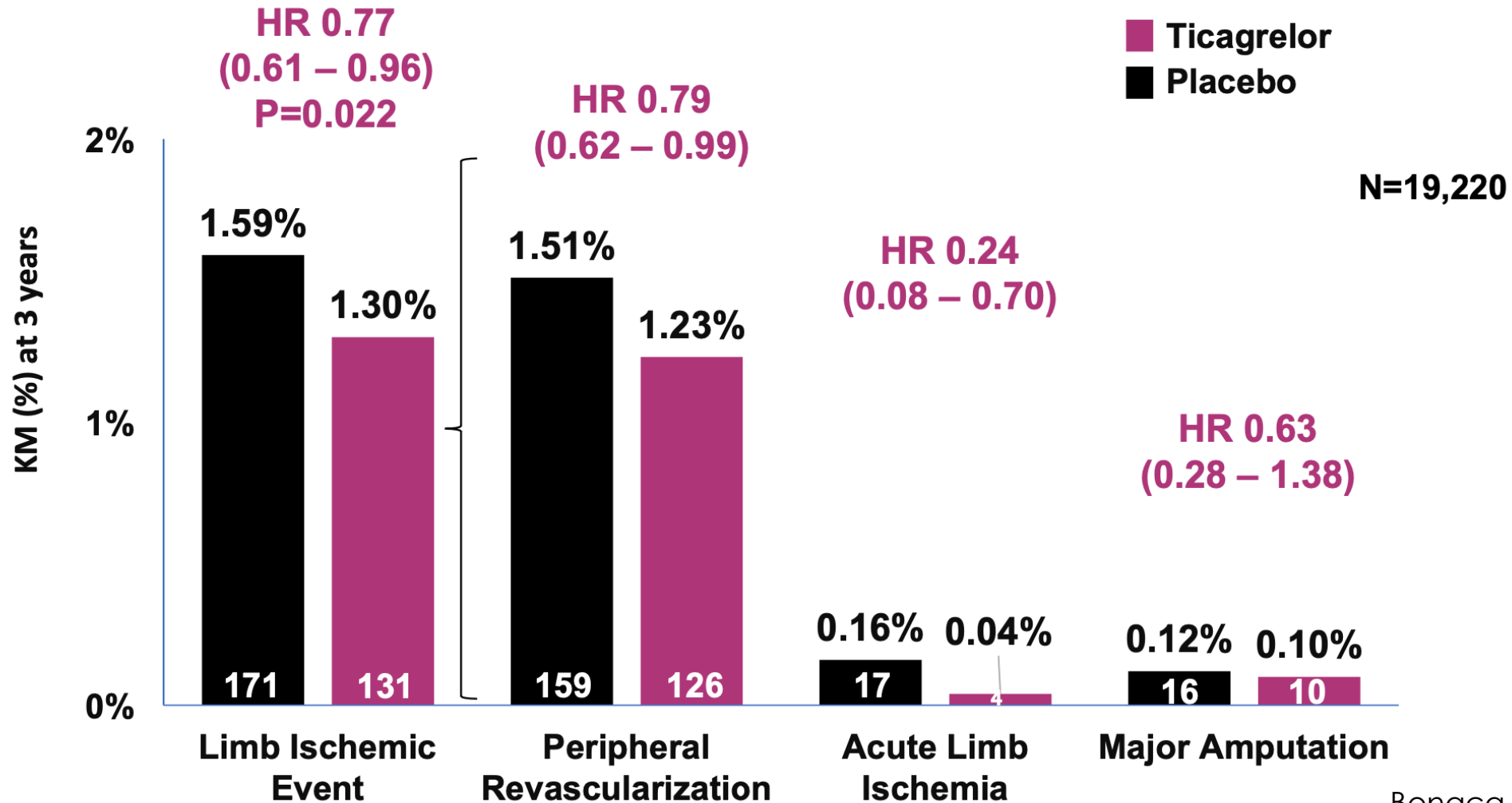
Outcome in placebo patients according to the presence of PAD



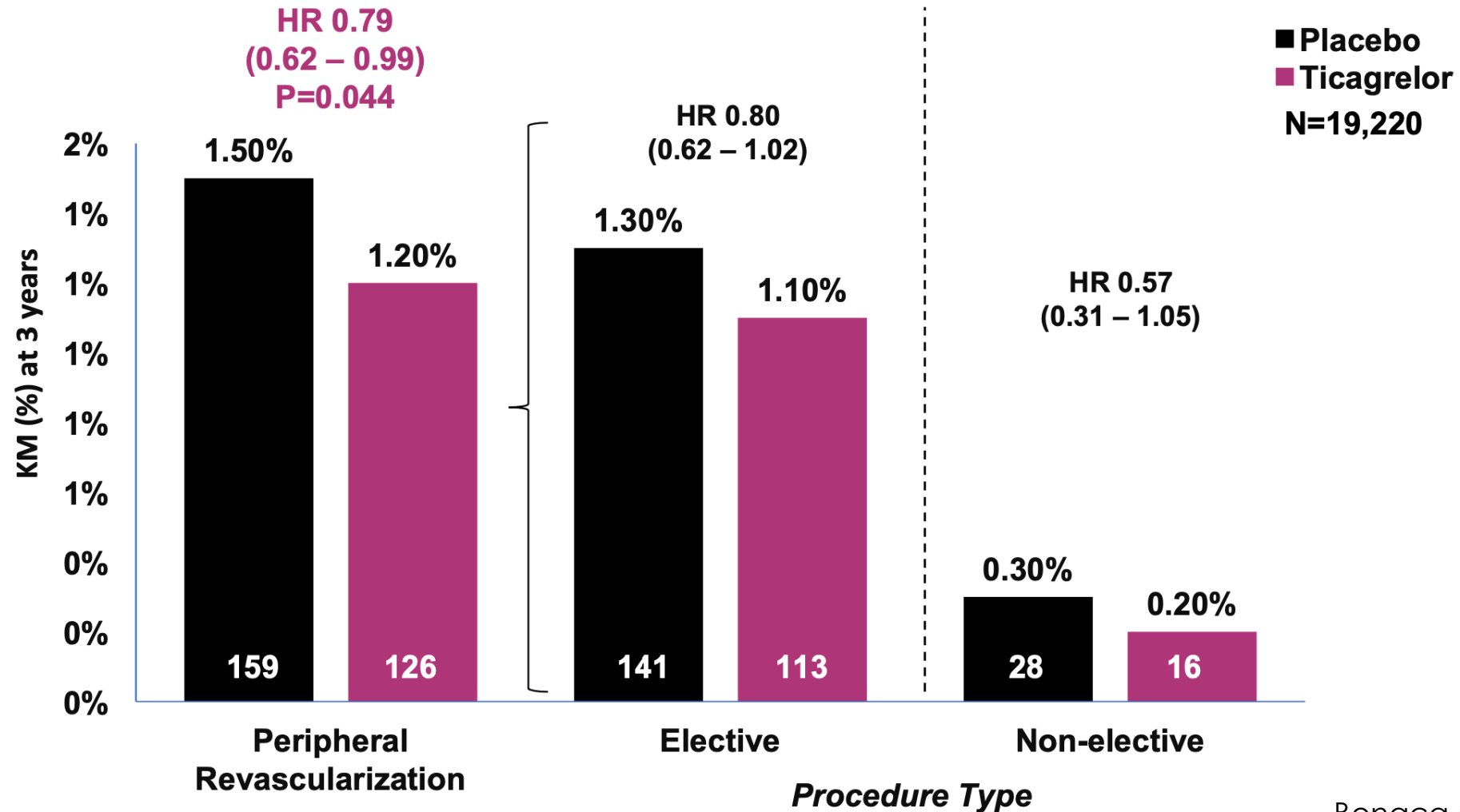
Limb ischemic outcomes with Ticagrelor vs. placebo



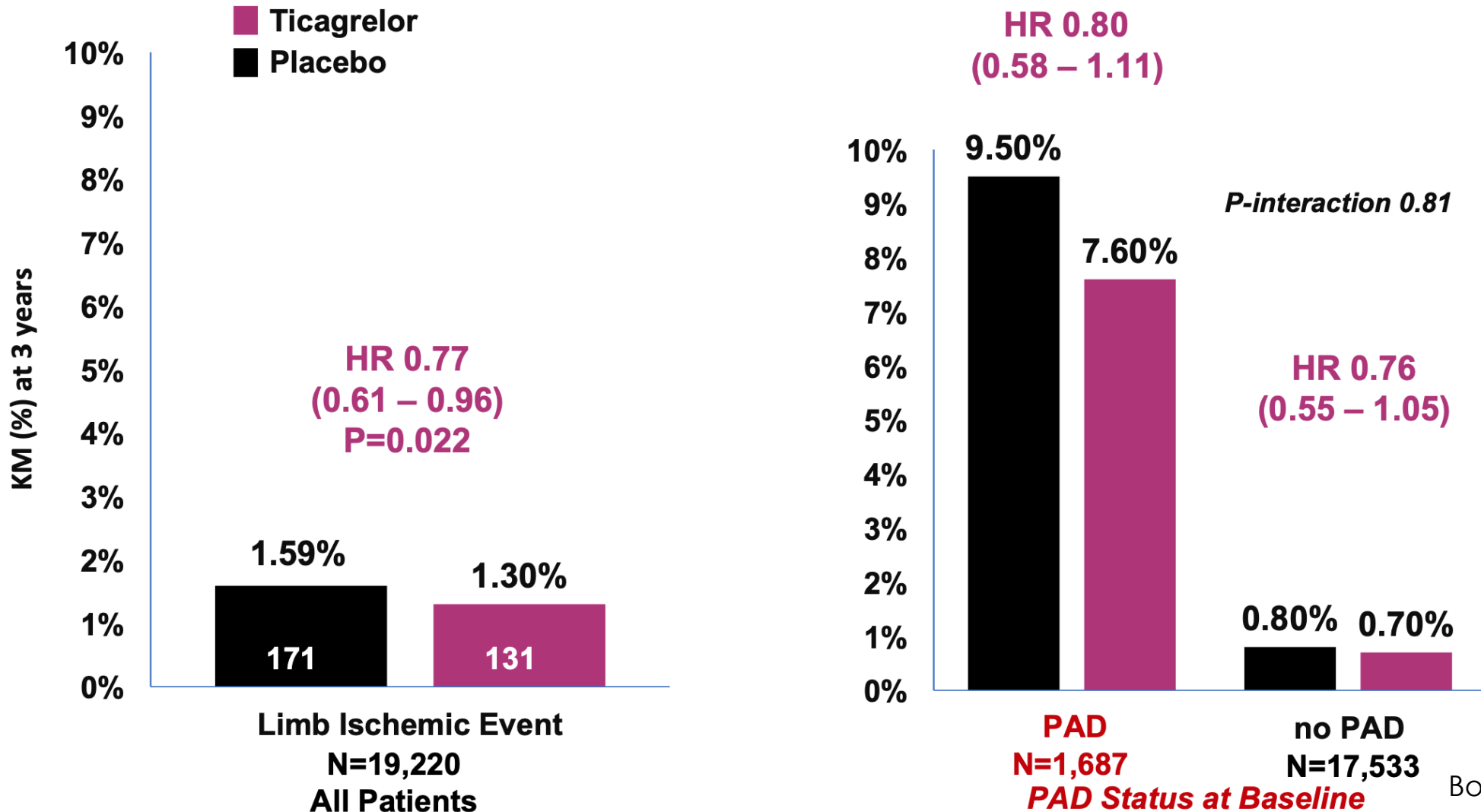
Limb outcomes by type with Ticagrelor vs. placebo



Peripheral revascularization with Ticagrelor vs. placebo



Limb outcomes with Ticagrelor vs. placebo according to PAD status



Summary

- **THEMIS demonstrated that ticagrelor plus aspirin versus aspirin alone reduces MACE and increases bleeding in patients with T2DM and stable CAD with consistent effects across major subgroups including PAD**
- **Ticagrelor reduced limb ischemic events with consistent effect across type of event including peripheral revascularization, acute limb ischemia, and amputation**
- **Among patients with T2DM and CAD, those with known PAD were at very high risk of limb events with a ~10-fold risk relative those with no known PAD**
- **The benefits of ticagrelor for limb outcomes were consistent regardless of PAD status at baseline, however, due to their higher risk profile, patients with PAD enjoyed a greater absolute benefit**

Conclusions

- **These findings suggest that patients with T2DM, CAD, and concomitant PAD may derive particular benefit from long-term ticagrelor when considering both adverse cardiovascular and limb outcomes**
- **Coupled with observations from PEGASUS-TIMI 54, these data further support the benefit of ticagrelor for limb ischemic events when added to aspirin in patients with stable atherosclerosis**
- **Future studies are needed to establish whether such a strategy is beneficial in patients selected on the basis of PAD and the safety of such a strategy after peripheral revascularization**