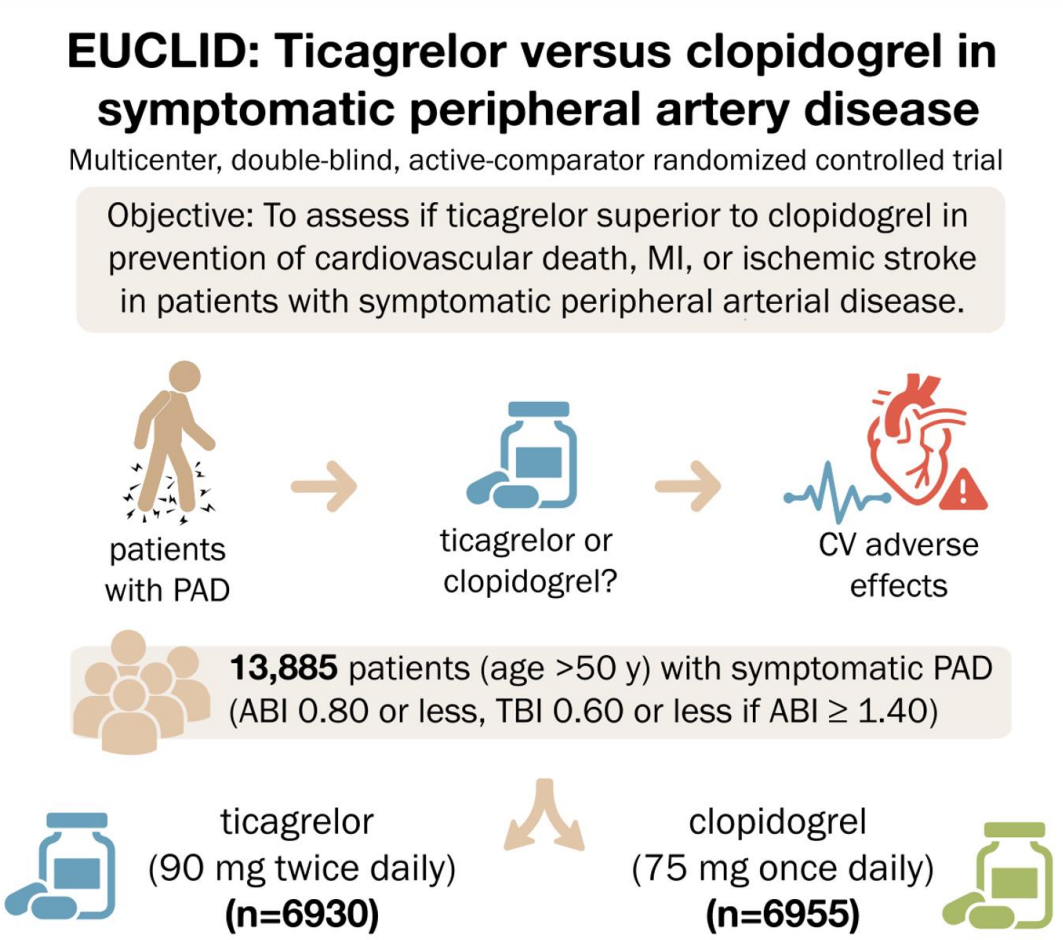
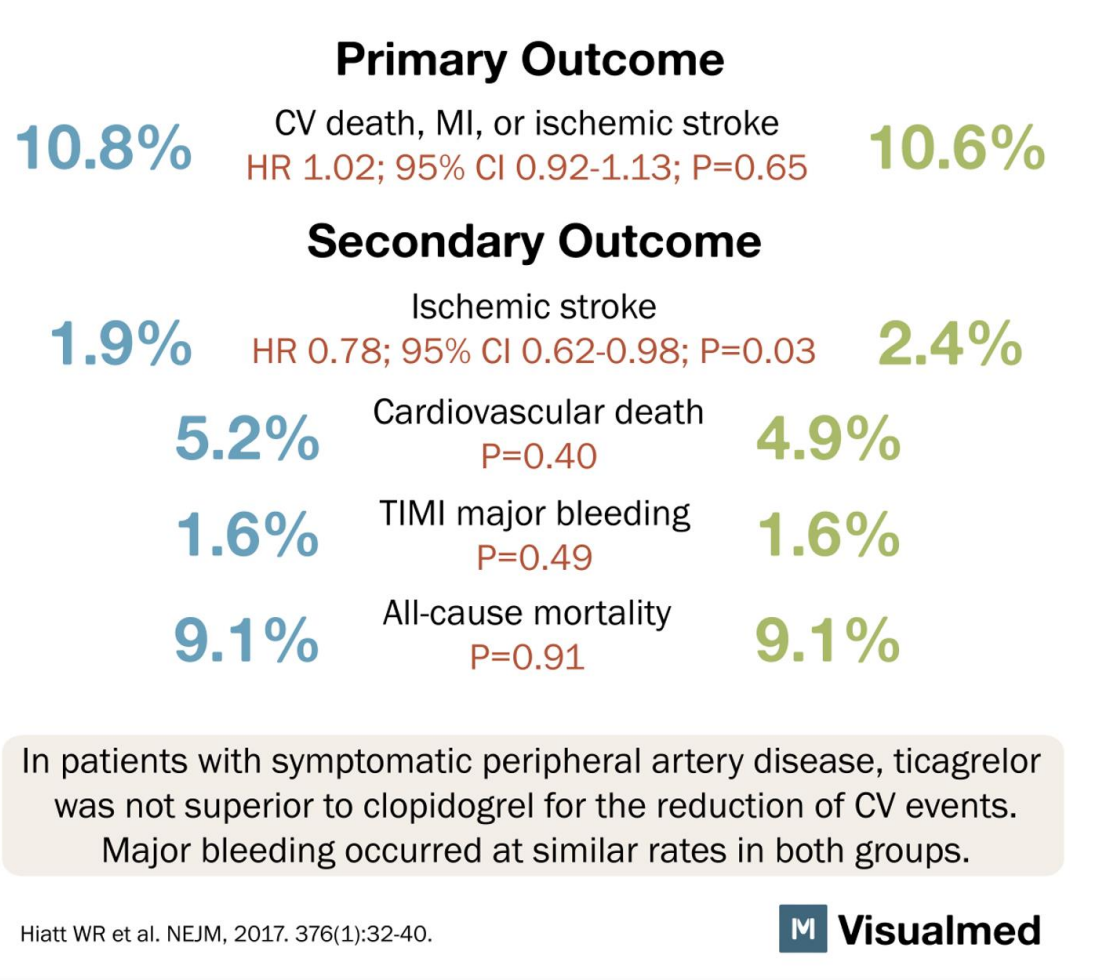
Efficacia di Ticagrelor nella riduzione di eventi ischemici periferici nei pazienti con coronaropatia e diabete con o senza arteriopatia periferica

SUBANALISI DAL THEMIS TRIAL

EUCLID trial





EUCLID trial

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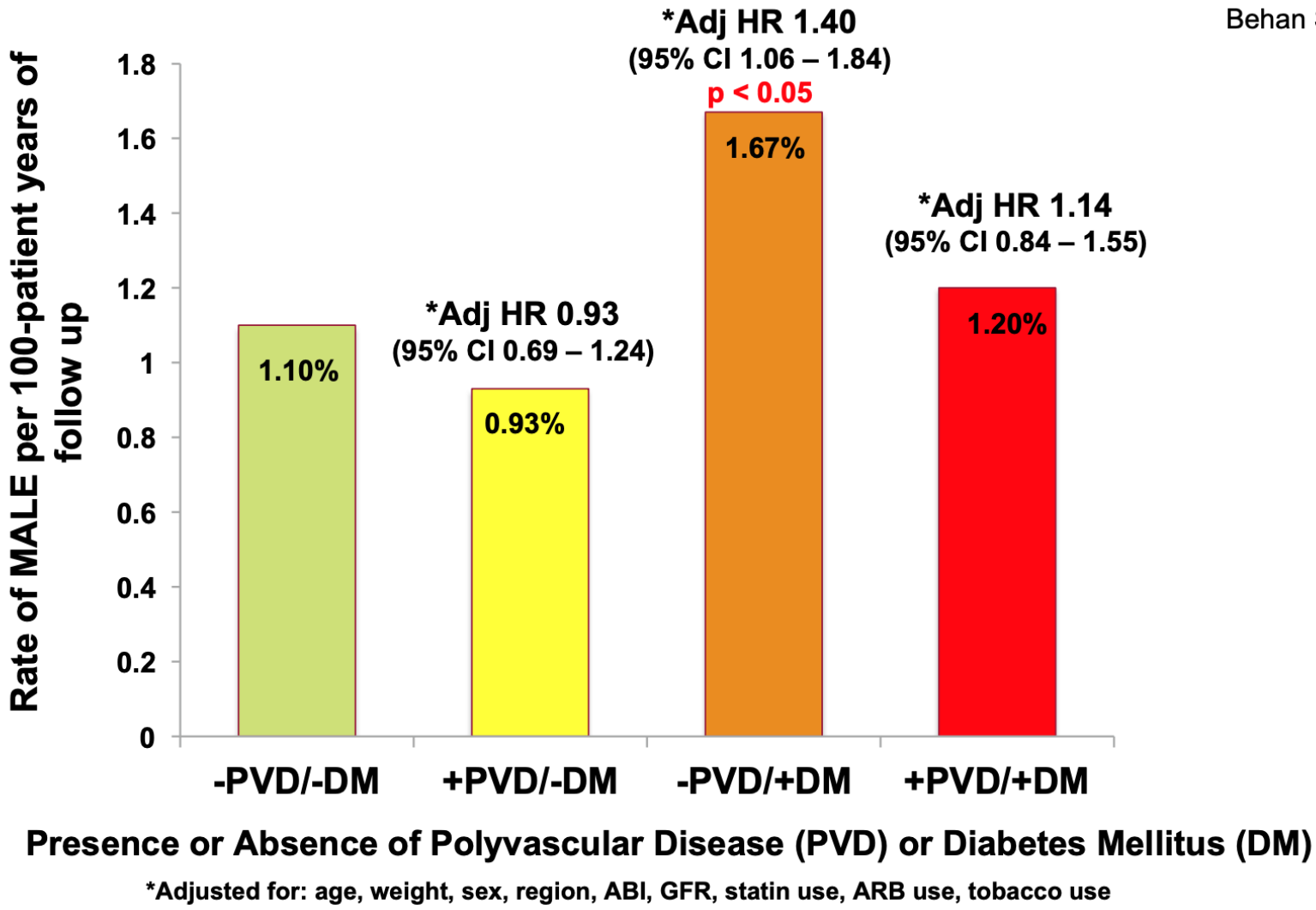
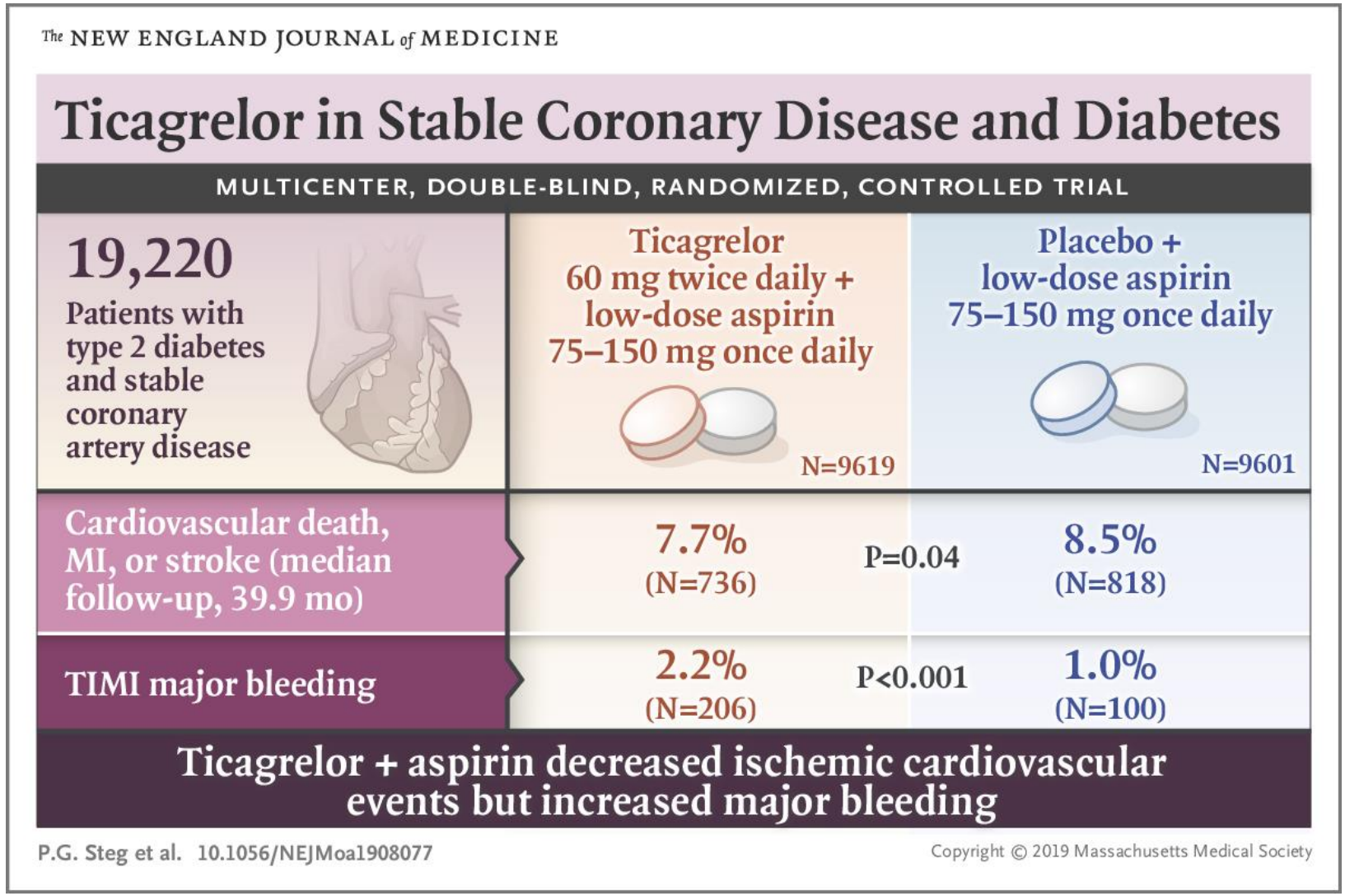


THEMIS trial



THEMIS trial

Clinical Outcomes

	Ticagrelor (N=9619)		Placebo (N=9601)			
	Patients with events (%)	KM% at 36 mos	Patients with events (%)	KM% at 36 mos	Hazard Ratio (95% CI)	p-value
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. aspiirin 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.

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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, indipendent clinical event committee
- The need for revascularization was invistigator reported

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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

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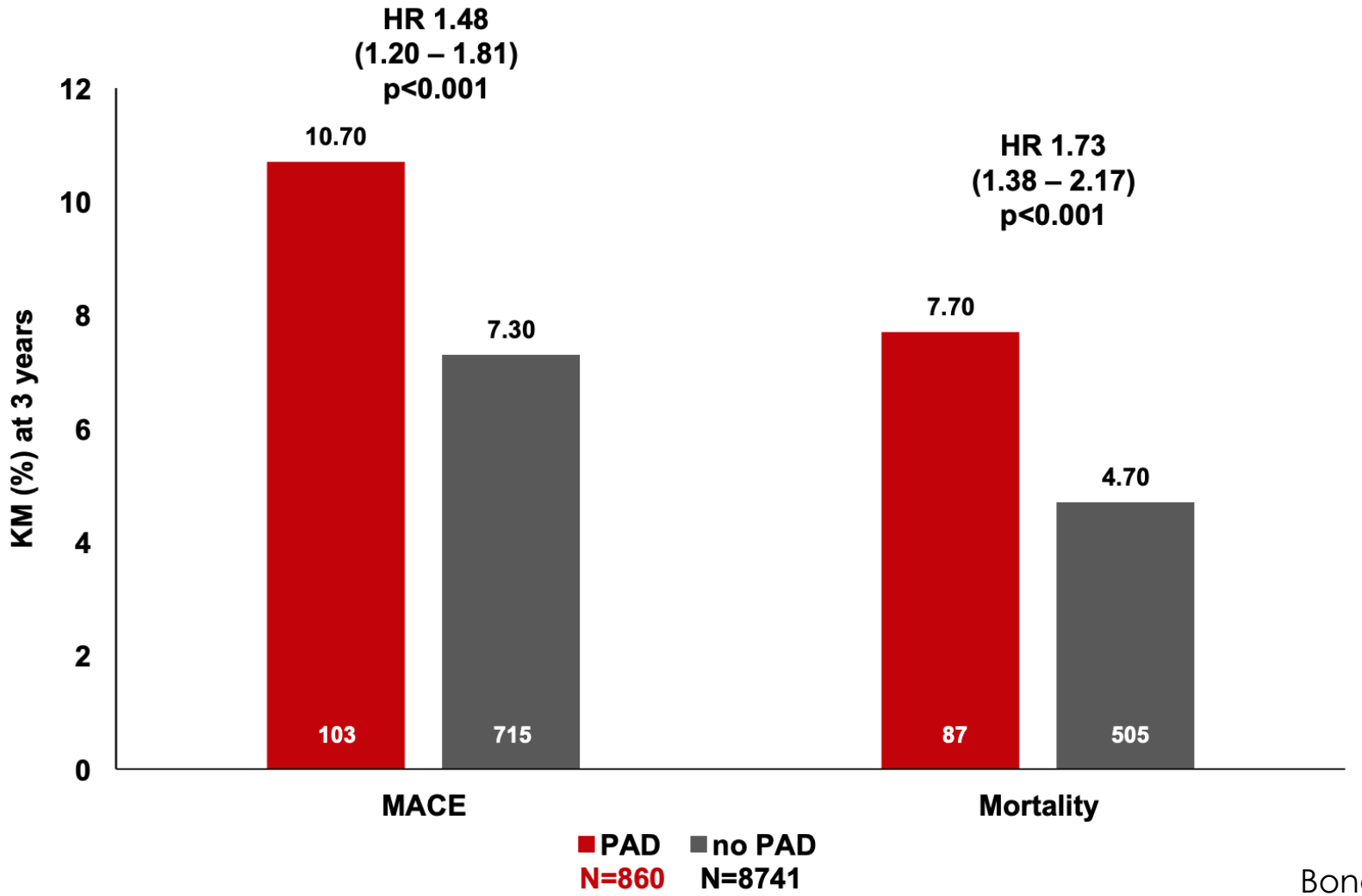
Outcome in placebo patients according to the presence of PAD



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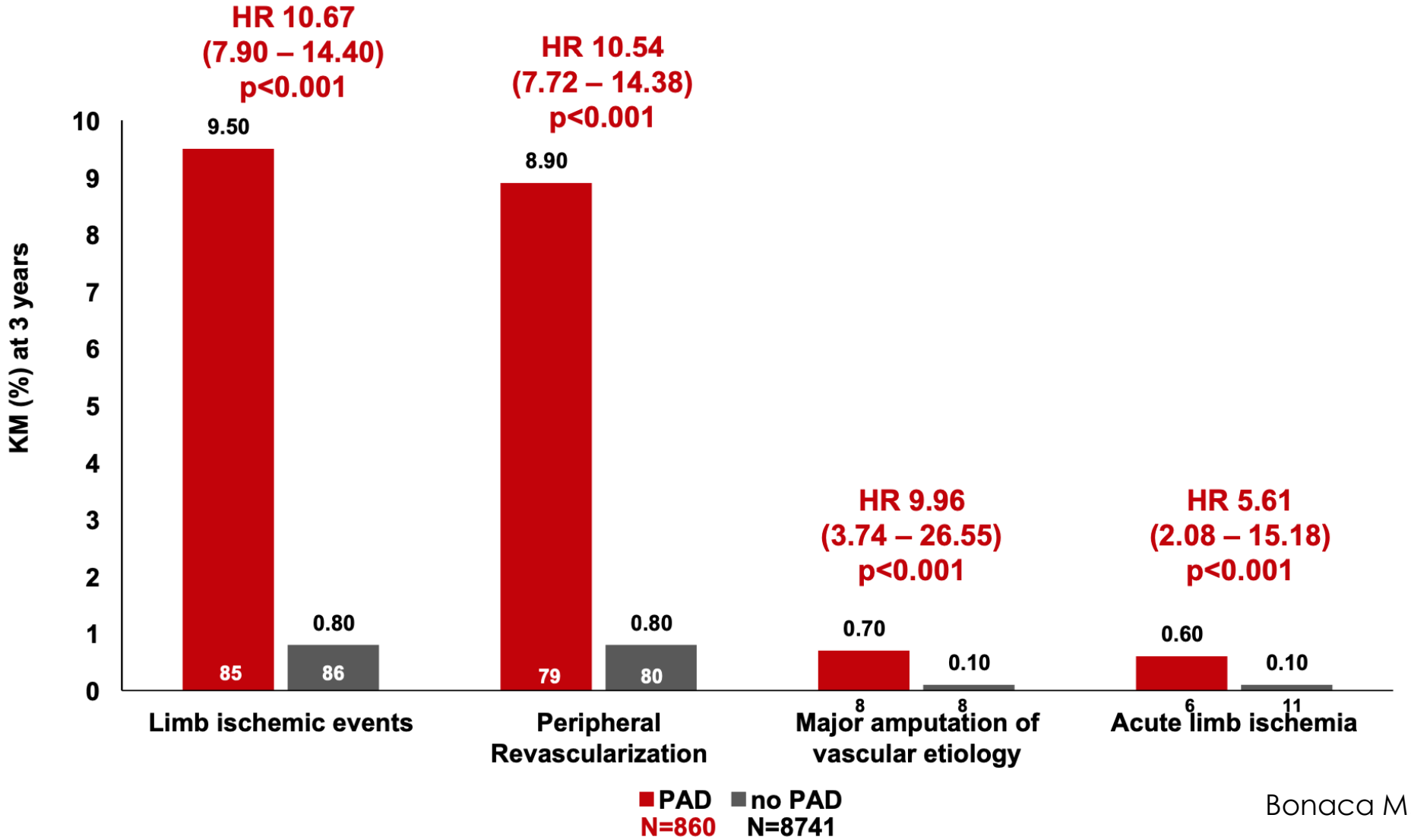
Outcome in placebo patients according to the presence of PAD



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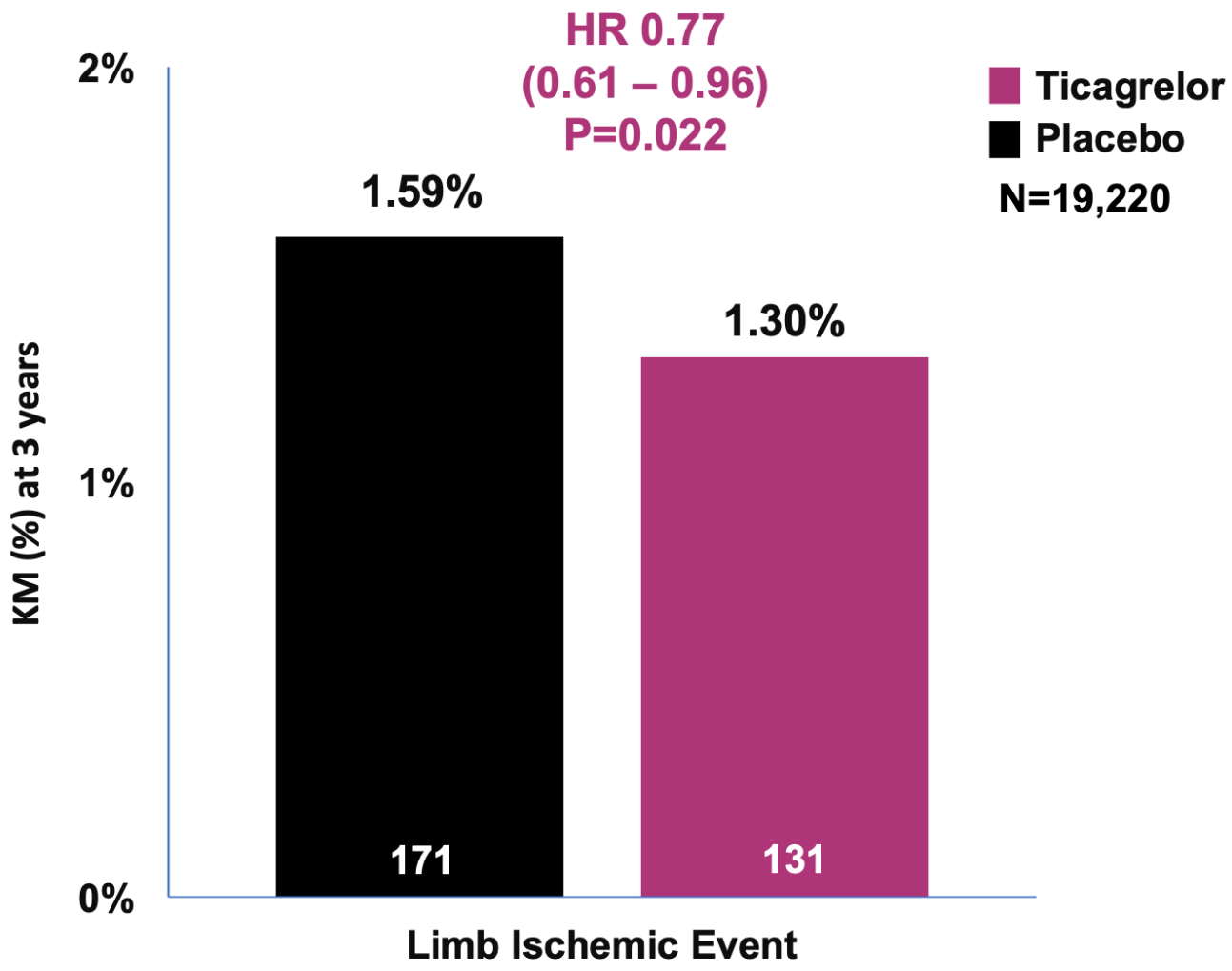
Limb ischemic outcomes with Ticagrelor vs. placebo



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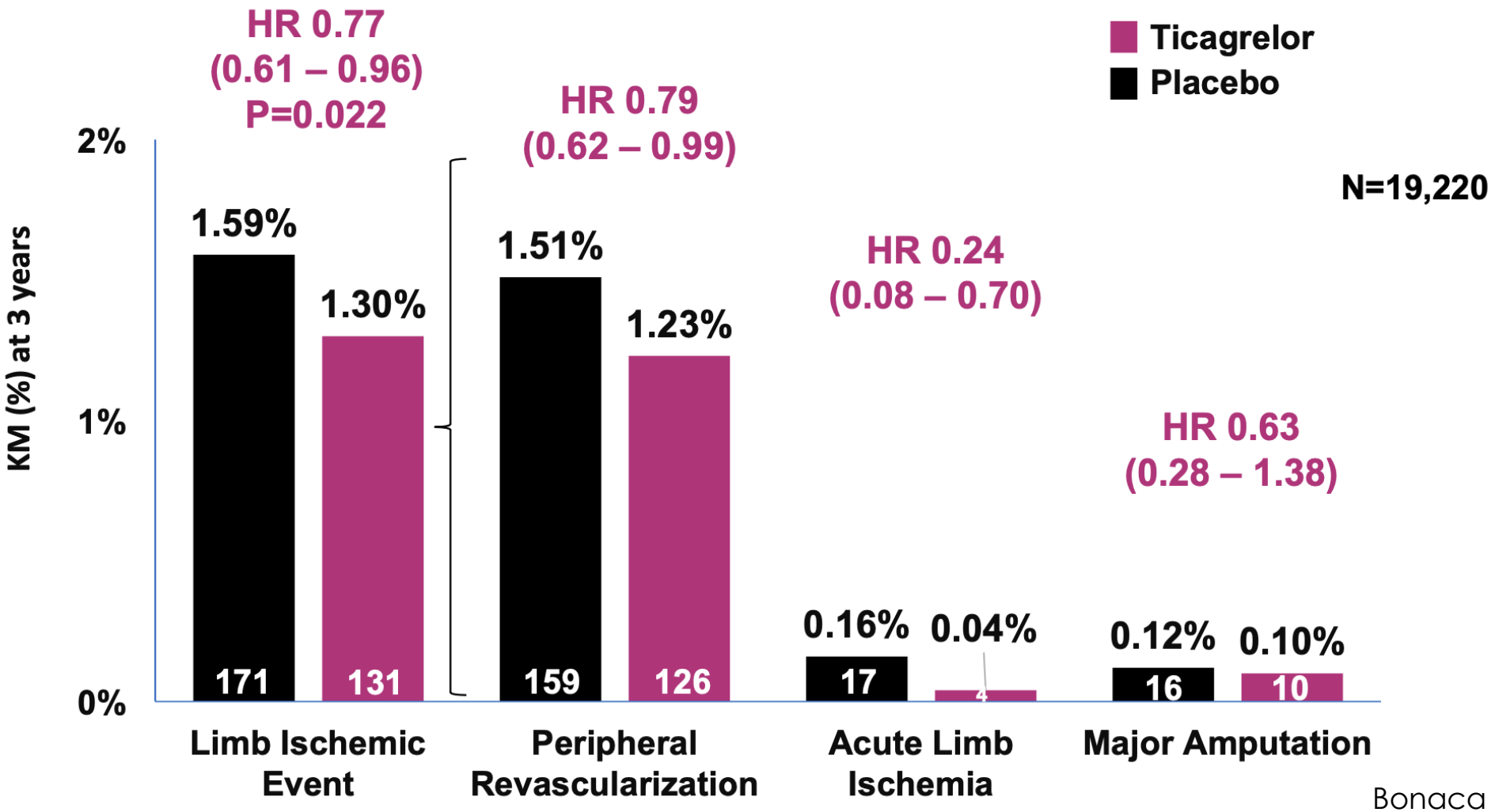
Limb outcomes by type with Ticagrelor vs. placebo



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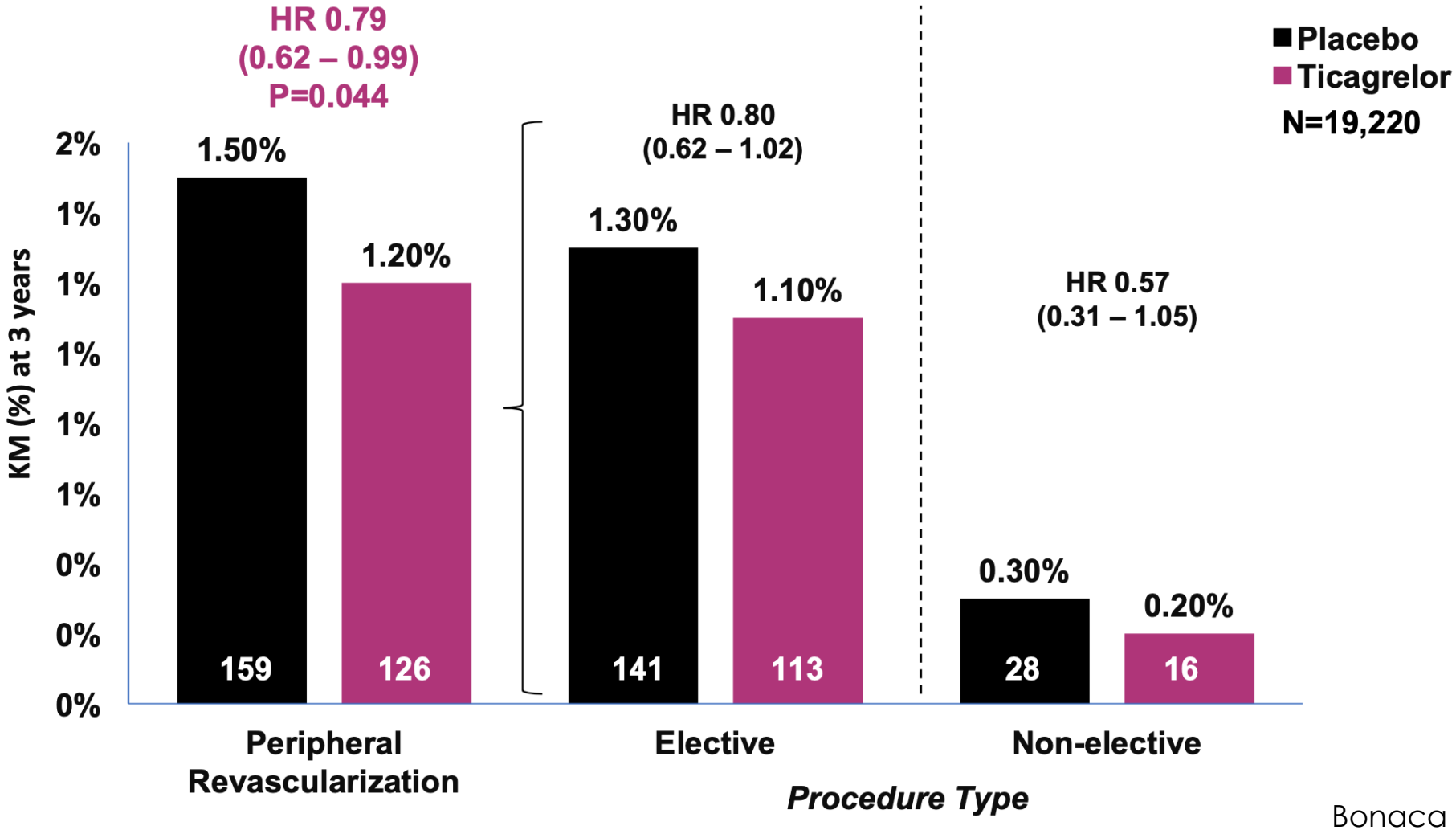
Peripheral revascularization with Ticagrelor vs. placebo



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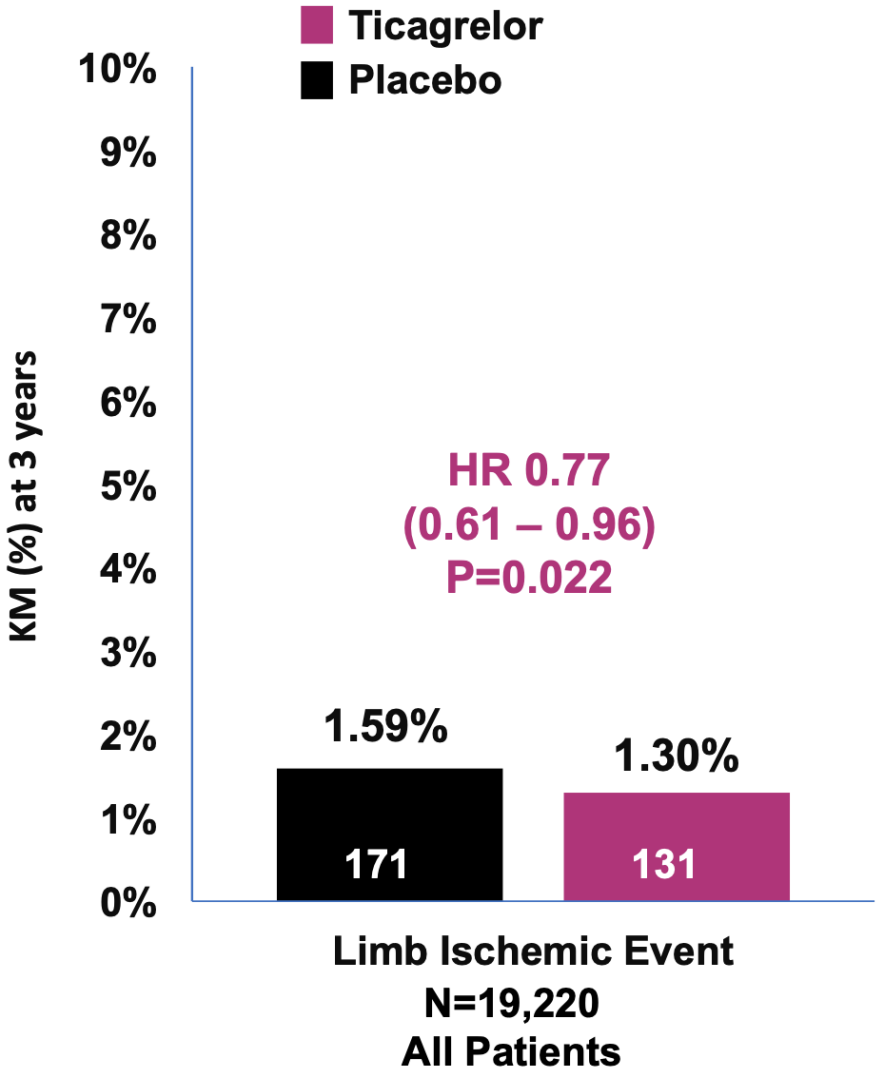
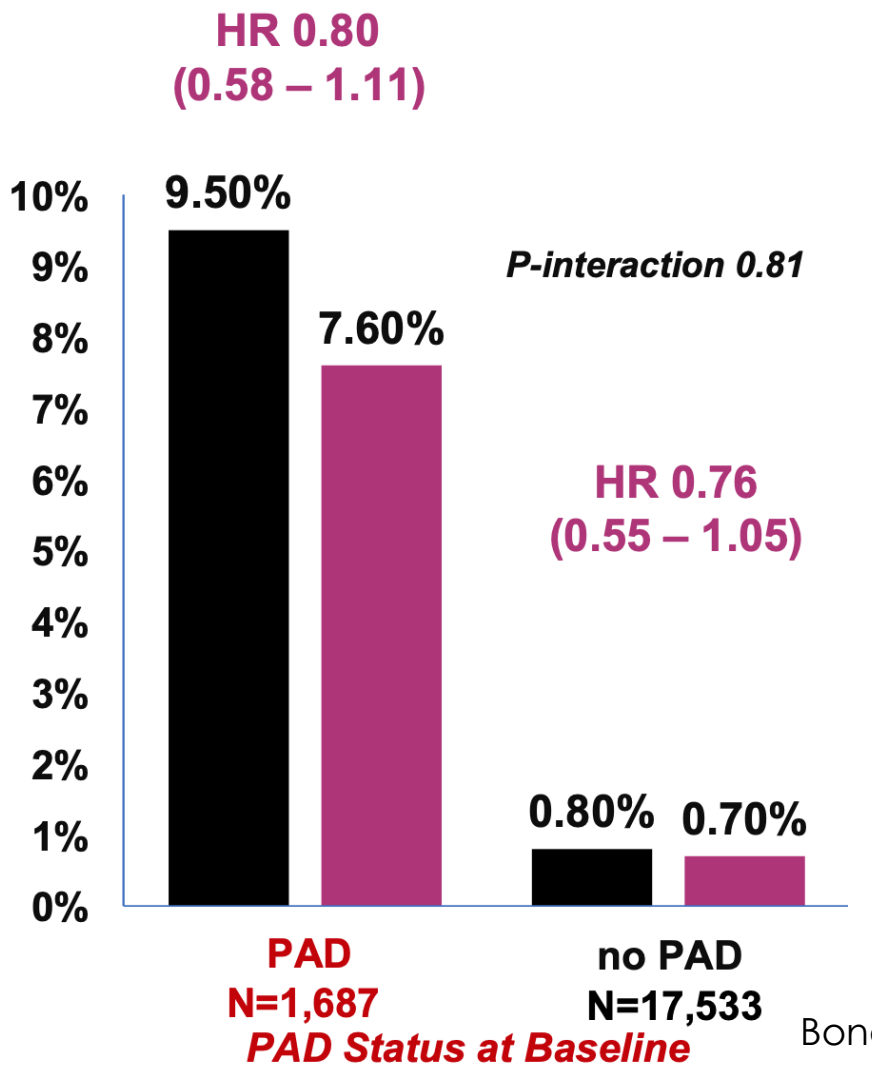
Limb outcomes with Ticagrelor vs. placebo according to PAD status





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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**

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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**

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