Risk of Limb Events and Effect of Ticagrelor in Patients with and without Peripheral Artery Disease: Insights from the THEMIS Trial

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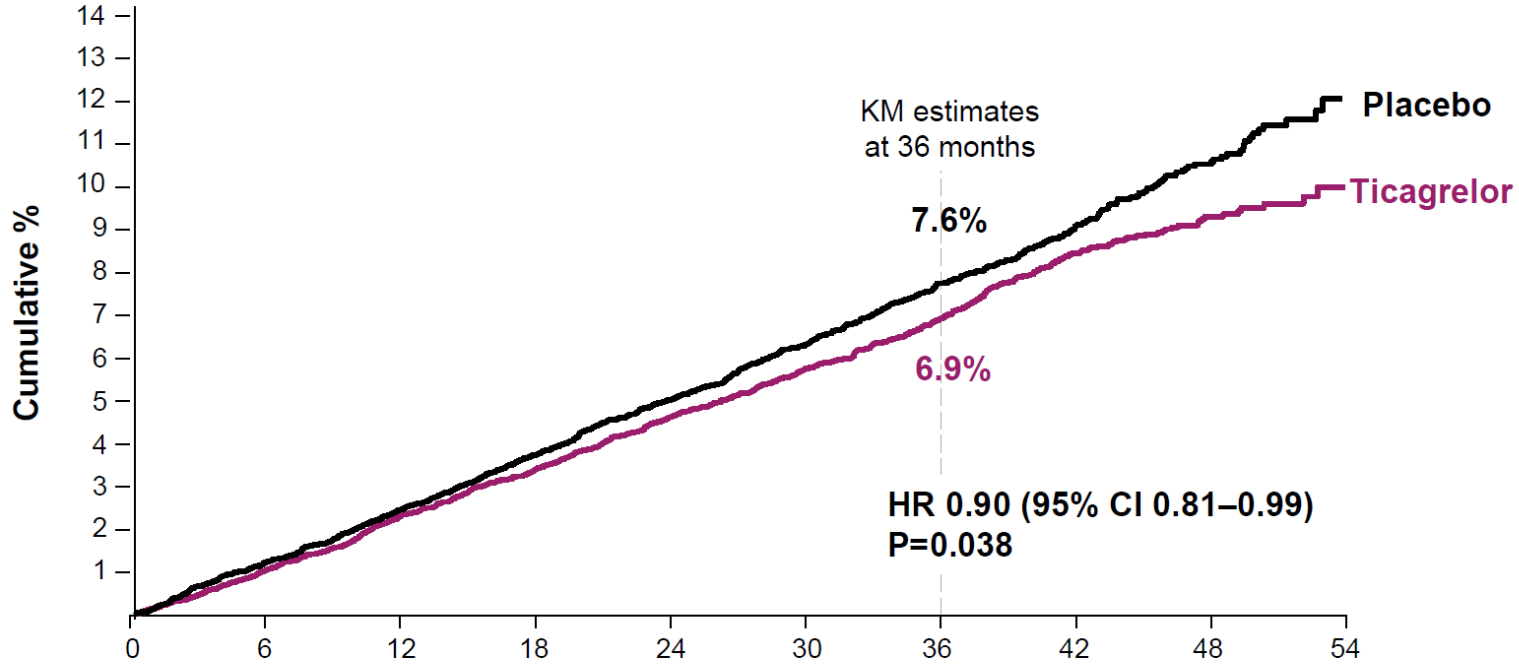
Disclosures

- THEMIS funded through a grant from AstraZeneca
- Marc P. Bonaca reports grant support to CPC Clinical Research from Amgen, AstraZeneca, Bayer, Janssen, Merck

Ticagrelor with Aspirin Reduces MACE in Diabetes and CAD

Primary Composite Endpoint

Cardiovascular death/MI/stroke



N at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

No heterogeneity for the primary efficacy outcome on the basis of PAD

NCT01991795

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Ticagrelor with Aspirin Increases Bleeding in Diabetes and CAD

Bleeding Outcomes

	Ticagrelor (N=9562)		Placebo (N=9531)			
	Patients with events (%)	Event rate/ 100 patient years)	Patients with events (%)	Event rate/ 100 patient years)	Hazard Ratio (95% CI)	p-value
TIMI major bleeding	206 (2.2%)	0.89	100 (1.0%)	0.38	2.32 (1.82–2.94)	<0.001
TIMI major or minor bleeding	285 (3.0%)	1.23	129 (1.4%)	0.49	2.49 (2.02–3.07)	<0.001
TIMI major, minor, or requiring medical attention	1072 (11.2%)	4.61	485 (5.1%)	1.85	2.51 (2.26–2.80)	<0.001
PLATO major bleeding	310 (3.2%)	1.33	145 (1.5%)	0.55	2.41 (1.98–2.93)	<0.001
BARC bleeding						
5 (fatal bleeding)	17 (0.2%)	0.07	10 (0.1%)	0.04	1.90 (0.87–4.15)	0.11
5 or 4	17 (0.2%)	0.07	11 (0.1%)	0.04	1.73 (0.81–3.69)	0.16
5, 4 or 3	341 (3.6%)	1.47	163 (1.7%)	0.62	2.36 (1.96–2.84)	<0.001
Intracranial hemorrhage	70 (0.7%)	0.30	46 (0.5%)	0.18	1.71 (1.18–2.48)	0.005
Spontaneous	28 (0.3%)	0.12	27 (0.3%)	0.10	1.17 (0.69–1.98)	0.57
Procedural	1 (0.0%)	0.00	3 (0.0%)	0.01		
Traumatic	41 (0.4%)	0.18	16 (0.2%)	0.06	2.87 (1.61–5.12)	<0.001

Includes events with onset from randomization up to 7 days after last dose. BARC bleeding was defined according to a score of 3 to 5 as follows: type 3, bleeding with a decrease in the hemoglobin of more than 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; type CABG-related bleeding; and type 5, fatal bleeding. Traumatic ICH: 27 (66%) on ticagrelor and 6 (38%) on placebo reported as subdural bleeding by investigators.

BARC=Bleeding Academic Research Consortium, CABG=coronary artery bypass grafting; CI=confidence interval; N=number of patients; PLATO=PLATelet inhibition and patient outcomes; TIMI=Thrombolysis in Myocardial Infarction

No heterogeneity for the principal safety outcome on the basis of PAD

NCT01991795

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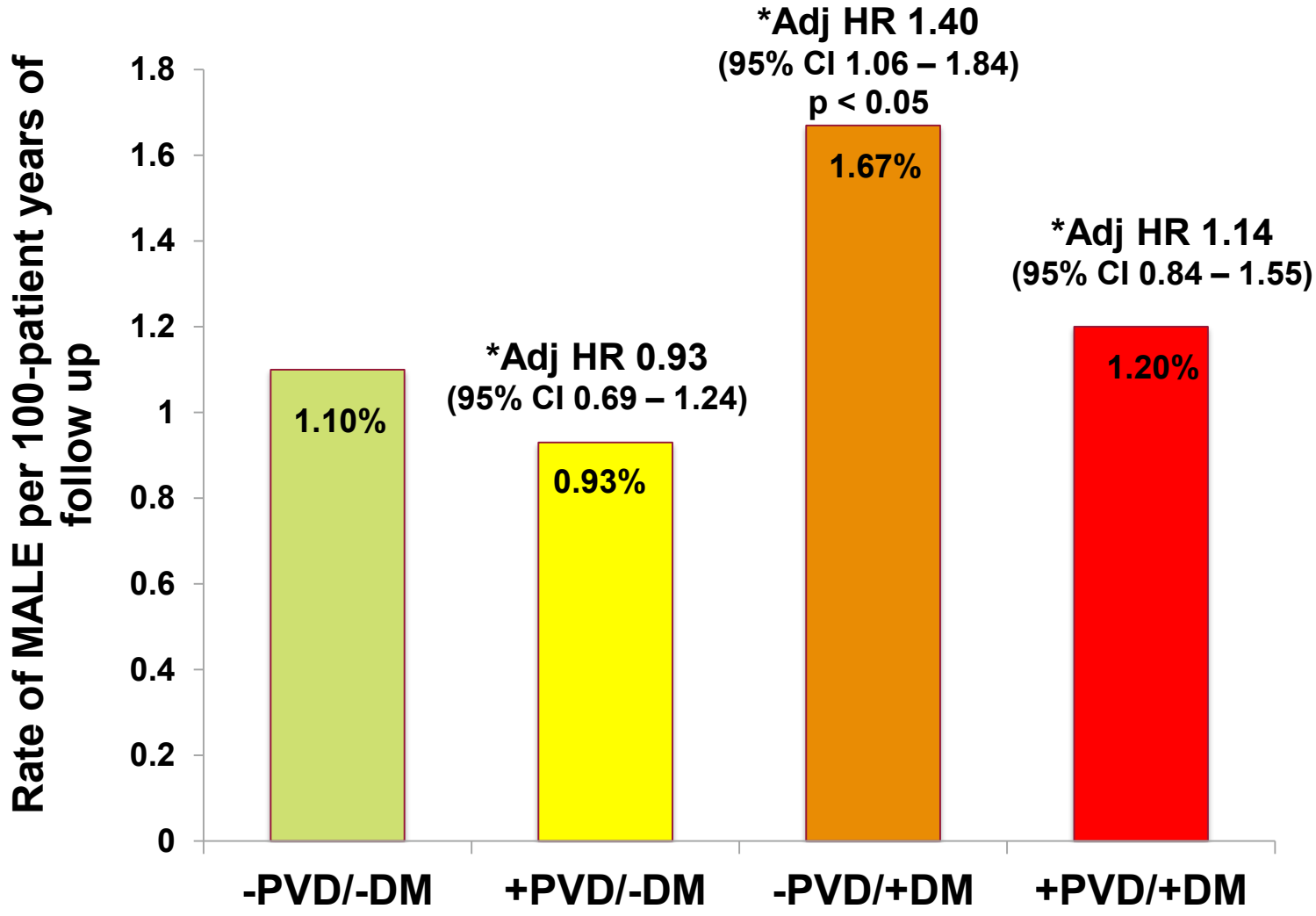
Diabetes Associated with Increased Risk of Adverse Limb Events



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

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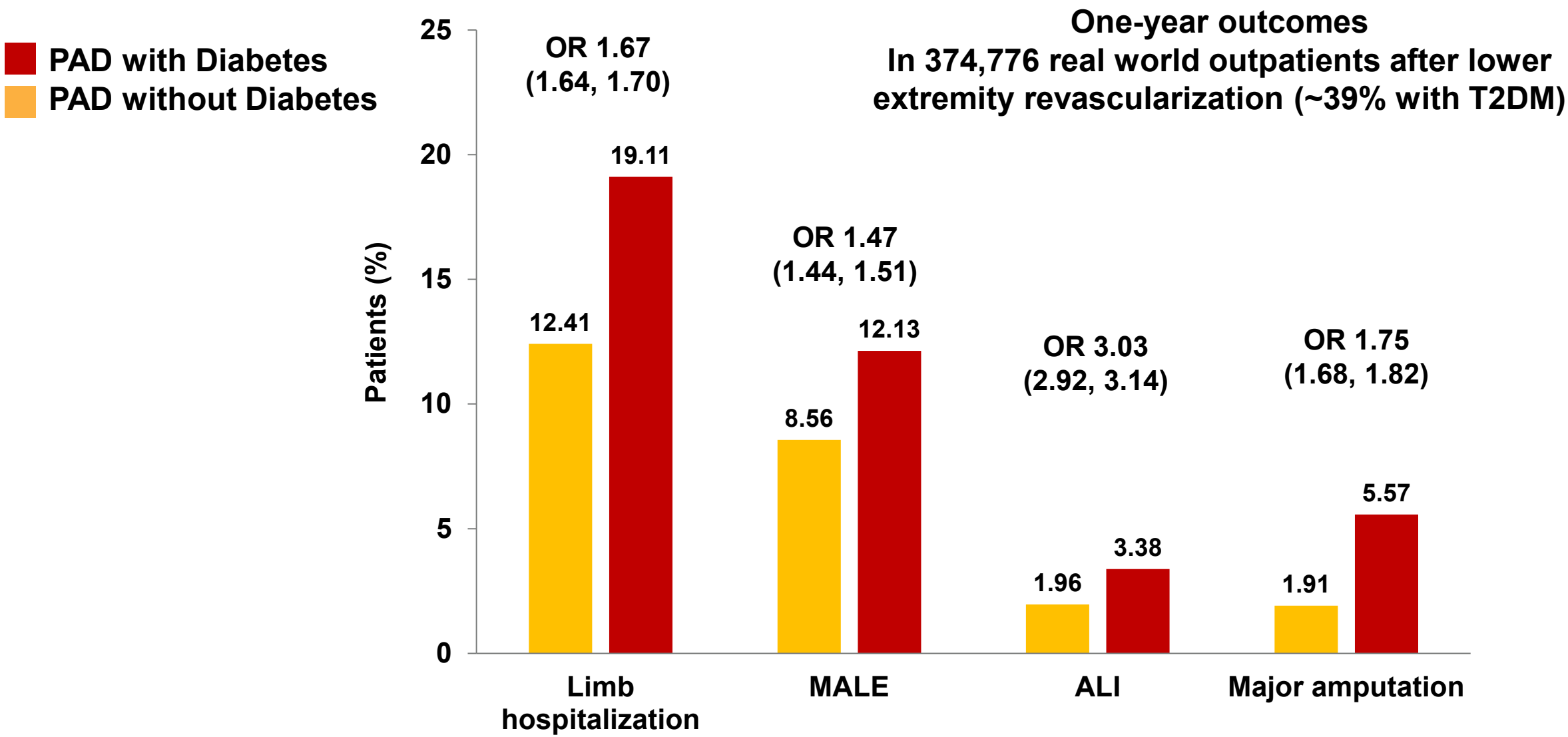
Diabetes Increases the Risk of Major Adverse Limb Events



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Objectives

- To characterize the spectrum of limb ischemic events in patients with Type 2 diabetes mellitus (T2DM) and CAD overall and based on the presence of concomitant peripheral artery disease (PAD) :
  - Acute limb ischemia (ALI)
  - Major amputation of vascular etiology
  - Peripheral revascularization (urgent and elective)
  - Overall limb ischemic outcomes defined as composite of ALI, major amputation of vascular etiology, and peripheral revascularization
- To evaluate the efficacy of ticagrelor + ASA vs. ASA alone for reducing limb ischemic events in patients with T2DM and CAD
- To evaluate whether the effect of ticagrelor on limb events was consistent in those with and without concomitant PAD

Methods

- **THEMIS was a large, multi-center, international trial randomizing patients to ticagrelor vs. placebo on a background of low dose aspirin**
  - **Patients with DM with CAD (incl. prior PCI) without history of MI or Stroke**
  - **Patients at high risk of bleeding or requiring anticoagulation excluded**

- **Sites prospectively reported limb ischemic events in an electronic data capture system**

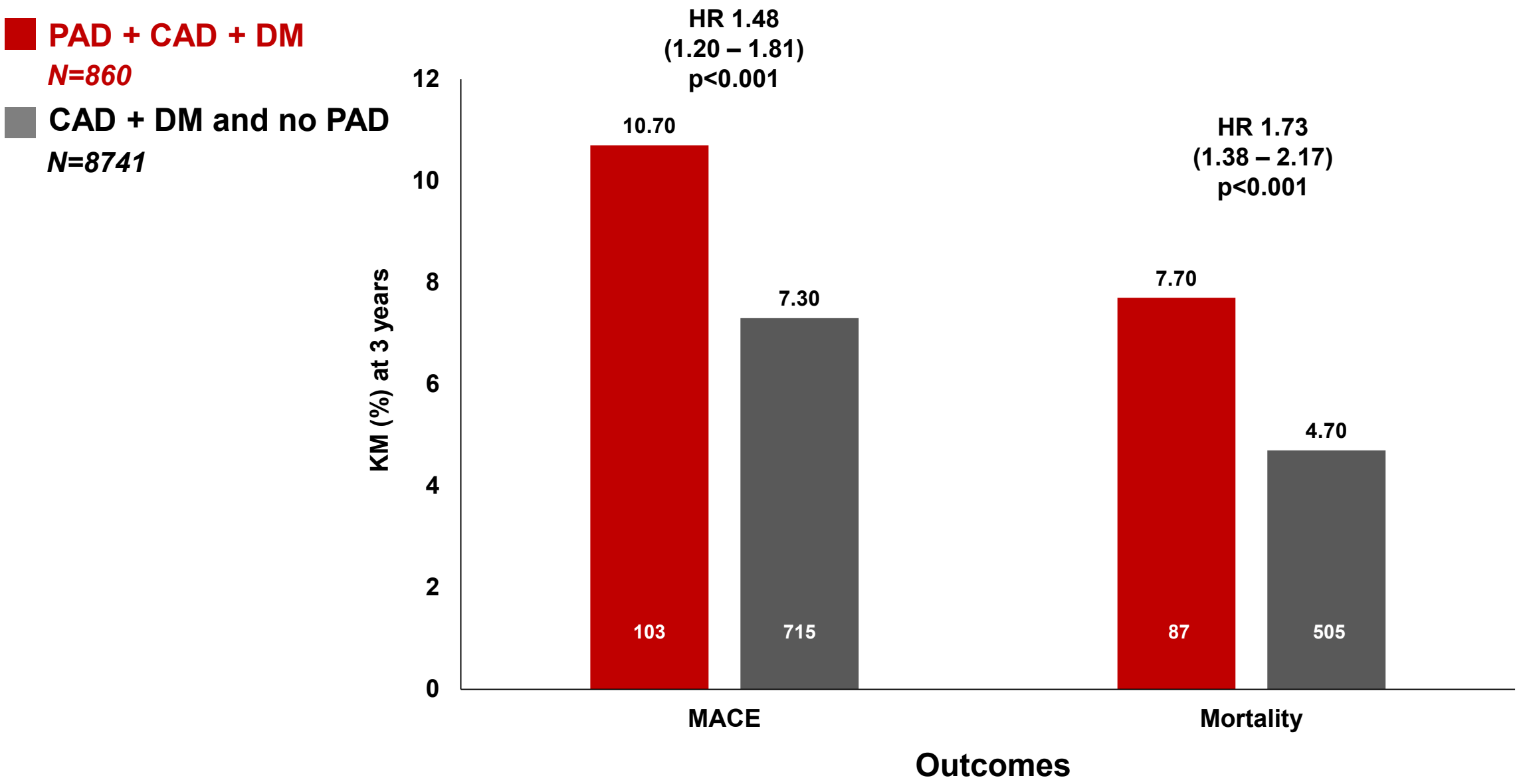
- **Major adverse limb events (MALE) prospectively adjudicated including:**
  - ***Acute limb ischemia* – *acute thrombotic occlusion of a lower extremity artery threatening or resulting in tissue loss***
  - ***Major amputation of a vascular etiology* – *amputation above the foot with impaired perfusion as a primary etiology, including chronic critical limb threatening ischemia***

- **The need for peripheral revascularization was investigator reported and categorized as urgent or elective**

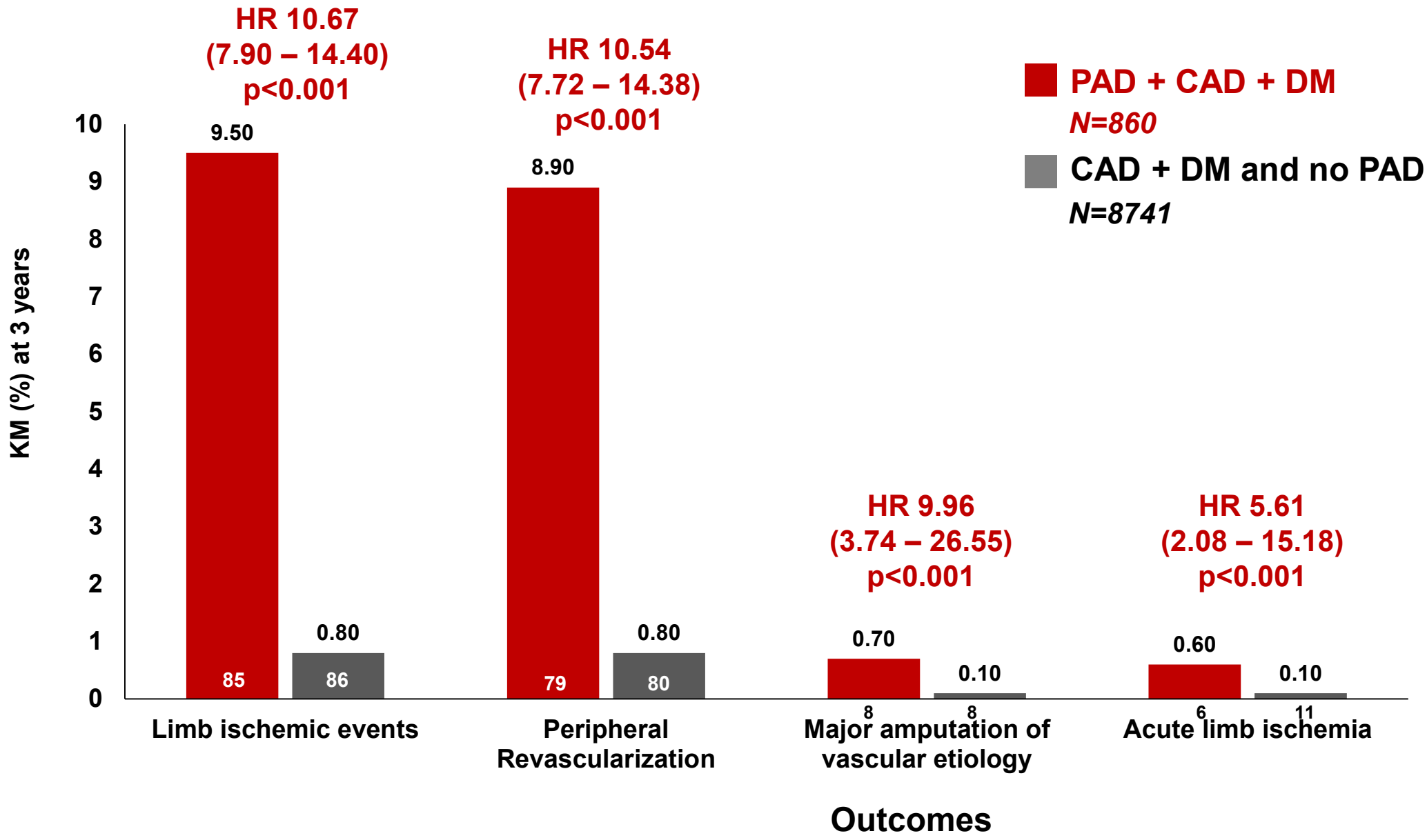
Baseline Characteristics

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
Current Smoking (%)	15	11	<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

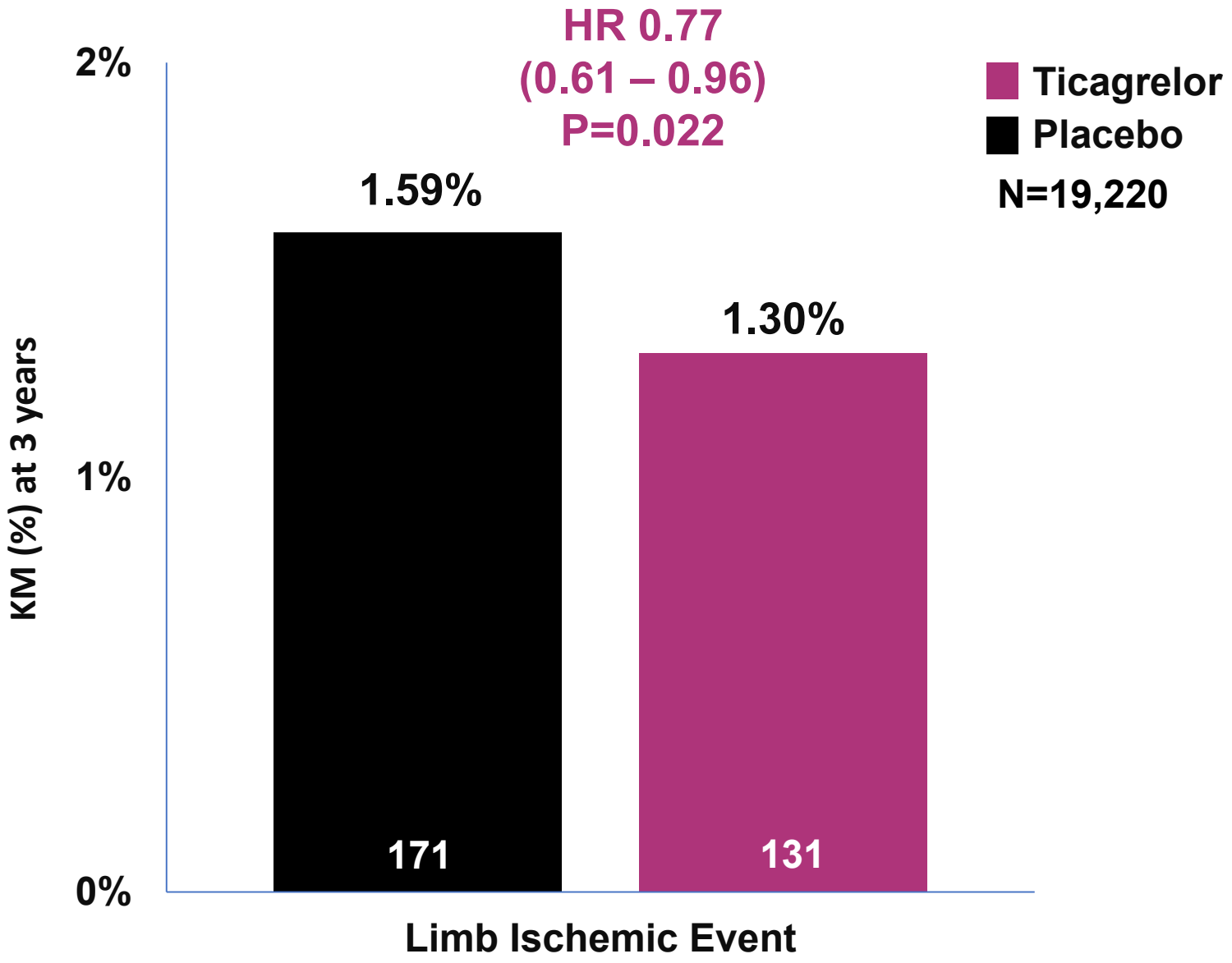
Outcomes in Placebo Patients with PAD versus no PAD



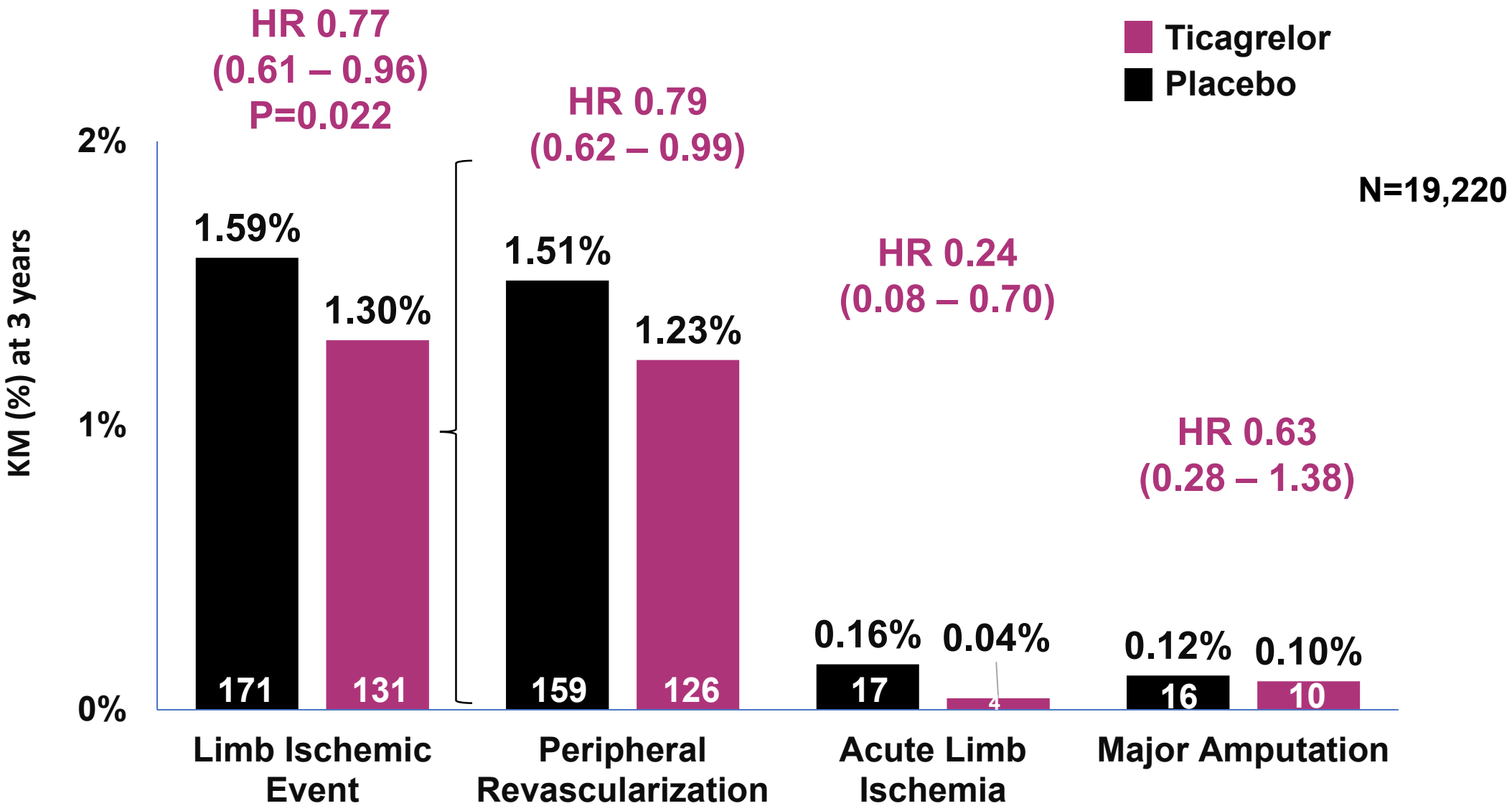
Outcomes in Placebo Patients with PAD versus no PAD



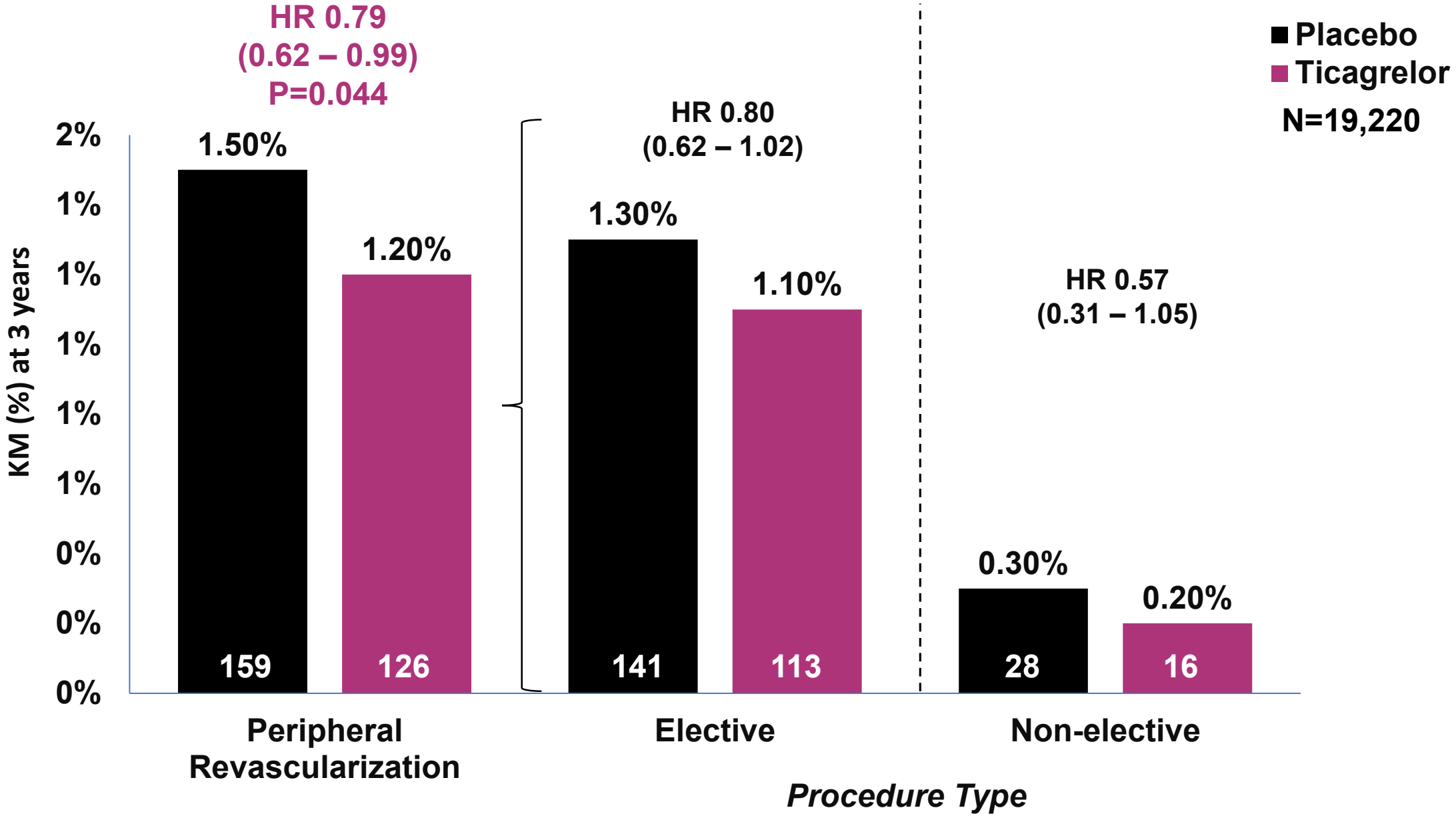
Overall Limb Ischemic Outcomes with Ticagrelor versus Placebo



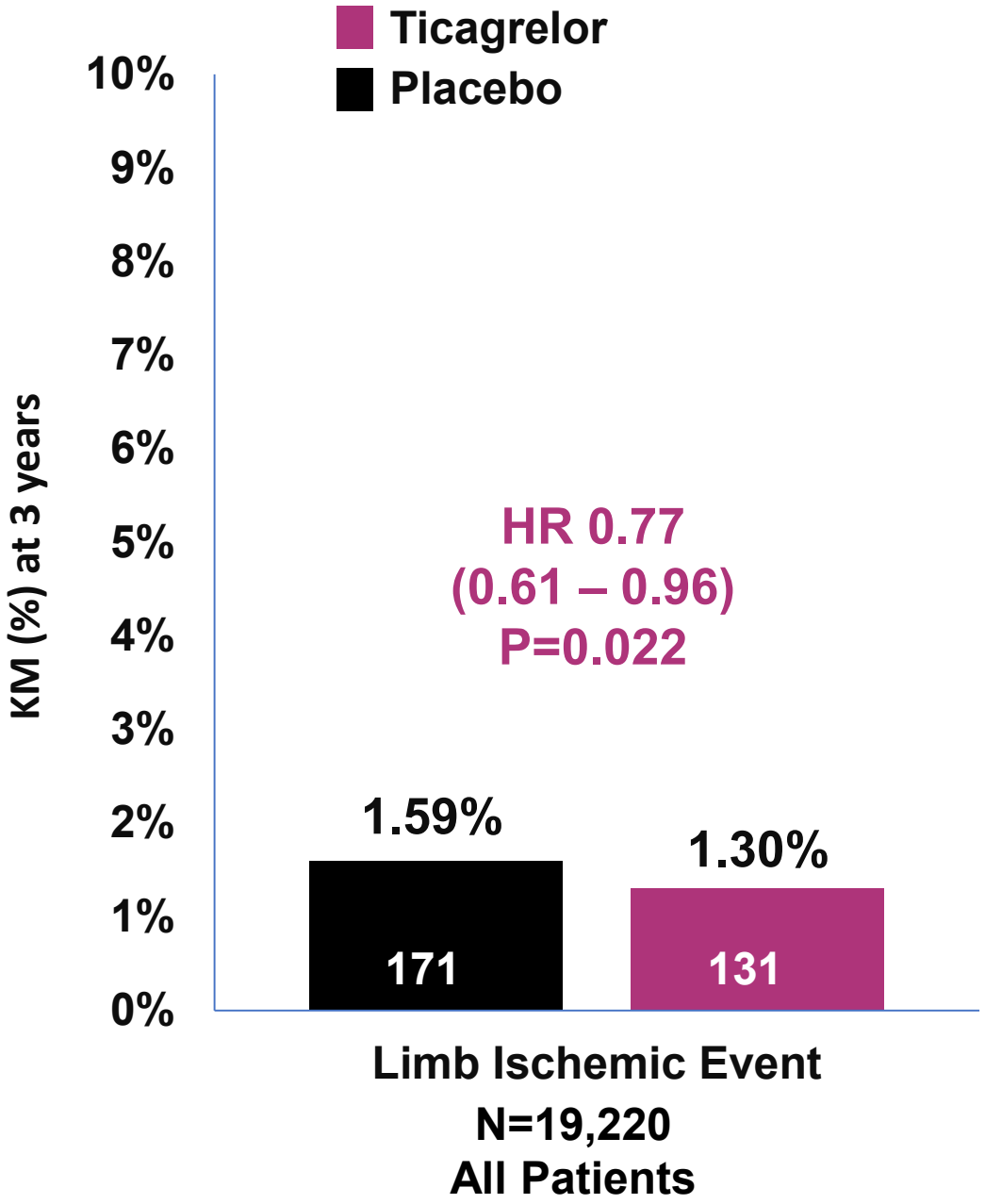
Limb Outcomes by Type with Ticagrelor versus Placebo

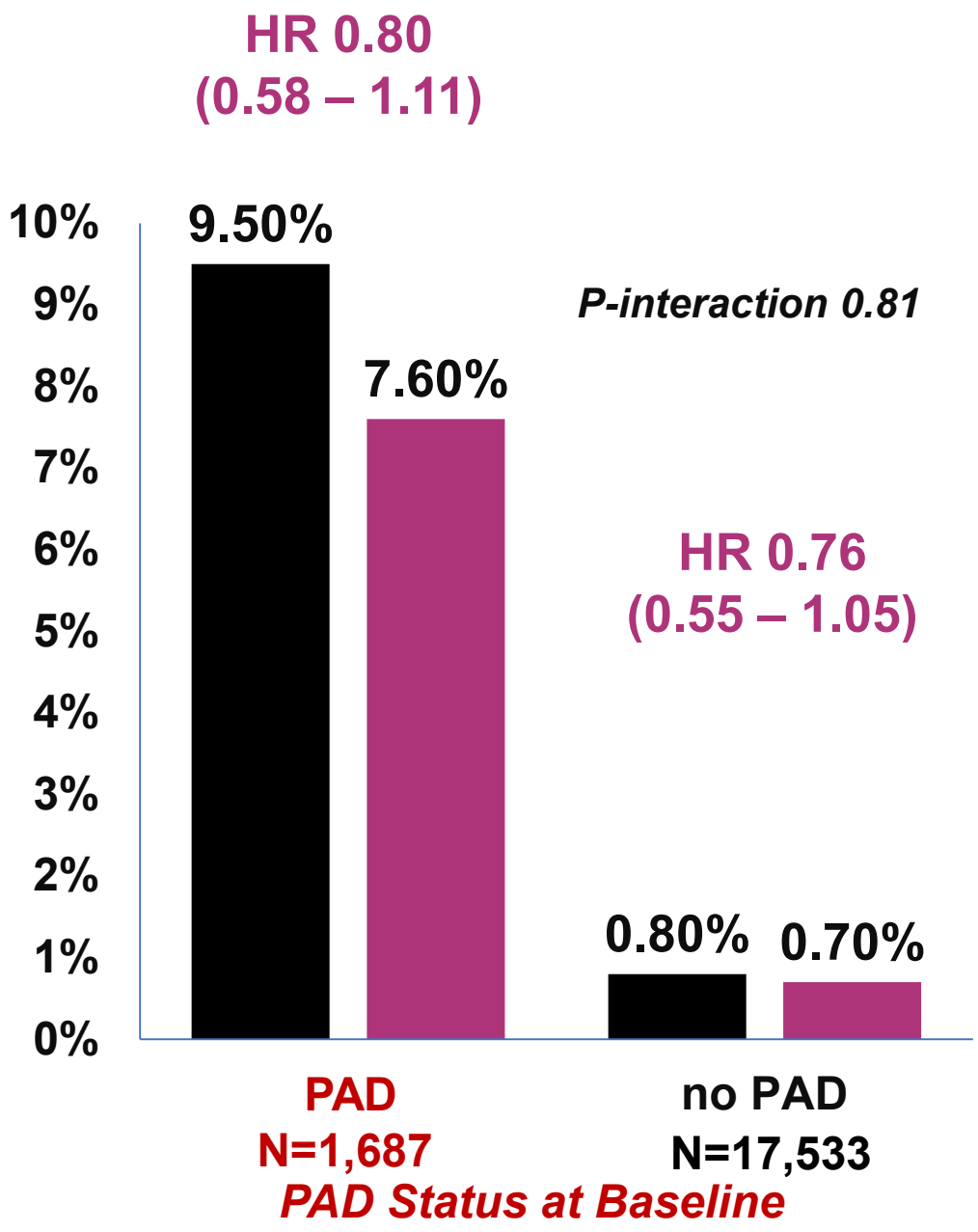


Peripheral Revascularization with Ticagrelor versus Placebo



Limb Events with Ticagrelor versus Placebo in PAD vs. no PAD





Summary

- **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**

- **In patients enrolled in THEMIS, ticagrelor reduced limb ischemic events including:**
  - **~50% reduction in major adverse limb events (ALI, amputation of vascular etiology)**
  - **~20% reduction in peripheral revascularization, including elective**

- **These benefits were consistent regardless of PAD status, however, due to their higher risk profile, patients with PAD enjoyed a greater absolute benefit**

Conclusion

- 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

- Future studies are needed to establish whether such a strategy is beneficial in patients selected for PAD and the safety after peripheral revascularization