Eventi ischemici periferici in pazienti con diabete mellito e aterosclerosi in terapia con ticagrelor e aspirina

Background

- Patients with type 2 diabetes mellitus (T2DM) are at heightened risk of developing PAD and experiencing MALE, and those who do experience a MALE event have a particularly poor prognosis.
- Multiple systemic medical therapies have demonstrated efficacy in reducing the risk of MALE including LDL-c lowering and antithrombotic therapies.
  - In **PEGASUS-TIMI 54** ticagrelor vs placebo on a background of aspirin reduced ALI by almost 50%.
  - **THEMIS** demonstrated that ticagrelor reduced major adverse cardiovascular events (MACE) in patients with stable coronary artery disease (CAD) and T2DM, and increased bleeding with a particularly favorable benefit/risk profile in those with a history of percutaneous intervention
- Understanding the effects of ticagrelor in this population with regards to limb ischemic events overall and in patients with known peripheral artery disease (PAD) may assist clinicians and patients in understanding benefit:risk balance, particularly in patients with T2DM with both CAD and PAD (polyvascular disease).

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Limb Outcomes With Ticagrelor Plus Aspirin in Patients With Diabetes Mellitus and Atherosclerosis

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Methods

- The results of prespecified analyses evaluating the effects of ticagrelor on limb ischemic events and the relative and absolute benefit and risk in patients with and without concomitant known PAD are presented as exploratory outcomes of THEMIS.
- Patients were randomized to ticagrelor or placebo on top of aspirin and followed for a median of 3 years.
- MACE (cardiovascular death, MI, or stroke), limb events (ALI, amputation, revascularization), and bleeding were adjudicated by an independent and blinded clinical events committee. The presence of PAD was reported at baseline.

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Baseline characteristics

- A total of 19,220 patients were randomized into THEMIS with a median F-UP of 3.3 years (Q1-Q3: 2.8-3.8 years).
- 1,687 (8.8%) had a known history of PAD
  - older, more frequently male, White, and enrolled in Europe, North America, or South America.
  - Risk factors were more frequent
  - The duration of T2DM and frequency of complications was greater
  - CAD was more severe

	PAD (n = 1,687)	No PAD (n = 17,533)	*P* Value
Age, y	68.0 (62.0-73.0)	66.0 (61.0-72.0)	<0.001
Female	455 (27.0)	5,576 (31.8)	<0.001
White race	1,401 (83.0)	1,2295 (70.1)	<0.001
Geographical region			<0.001
Asia and Australia	166 (9.8)	4,122 (23.5)	
Central and South America	209 (12.4)	1,969 (11.2)	
Europe and South Africa	994 (58.9)	8,765 (50.0)	
North America	318 (18.9)	2,677 (15.3)	
Hypertension	1,600 (94.8)	1,6176 (92.3)	<0.001
Hypercholesterolemia	1,557 (92.3)	15,196 (86.7)	<0.001
Current smoking	248 (14.7)	1,846 (10.5)	<0.001
eGFR	71.1 (56.1-85.6)	75.4 (61.0-90.1)	<0.001
Duration of diabetes mellitus, y	11.9 (6.0-19.0)	10.0 (5.0-16.0)	<0.001
Diabetes complications	683 (40.5)	4,227 (24.1)	<0.001
HbA1c, %	7.1 (6.4,8.1)	7.1 (6.4,8.1)	0.653
Multivessel coronary disease	1,168 (69.7)	10,767 (61.6)	<0.001
History of PCI	905 (53.6)	10,249 (58.5)	<0.001
History of CABG only	486 (28.8)	3,705 (21.1)	<0.001
Both PCI and CABG	162 (9.6)	1,184 (6.8)	<0.001
Neither PCI nor CABG	296 (17.5)	3,579 (20.4)	0.005

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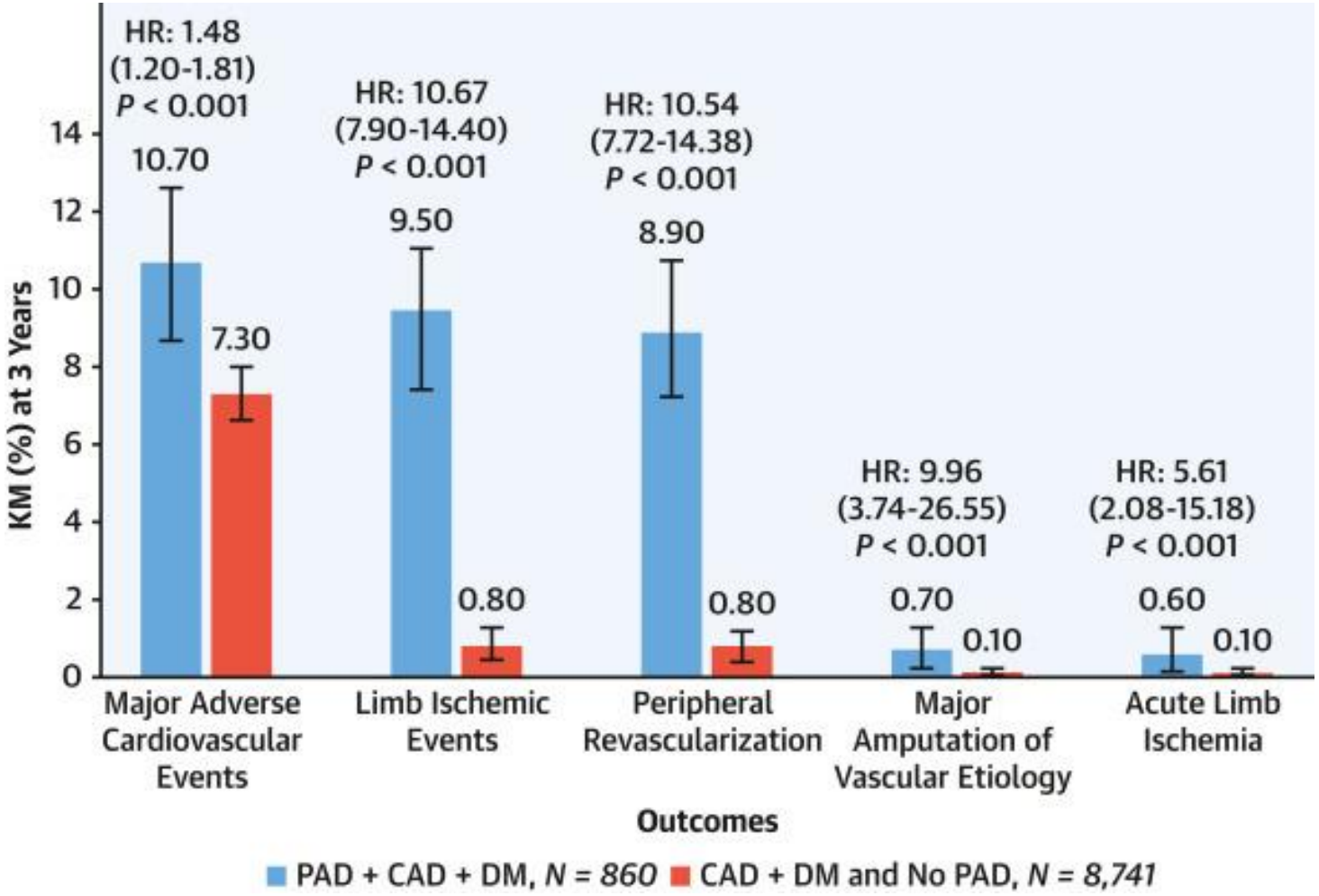
Ischemic Risk in Patients With and Without PAD Treated With Placebo



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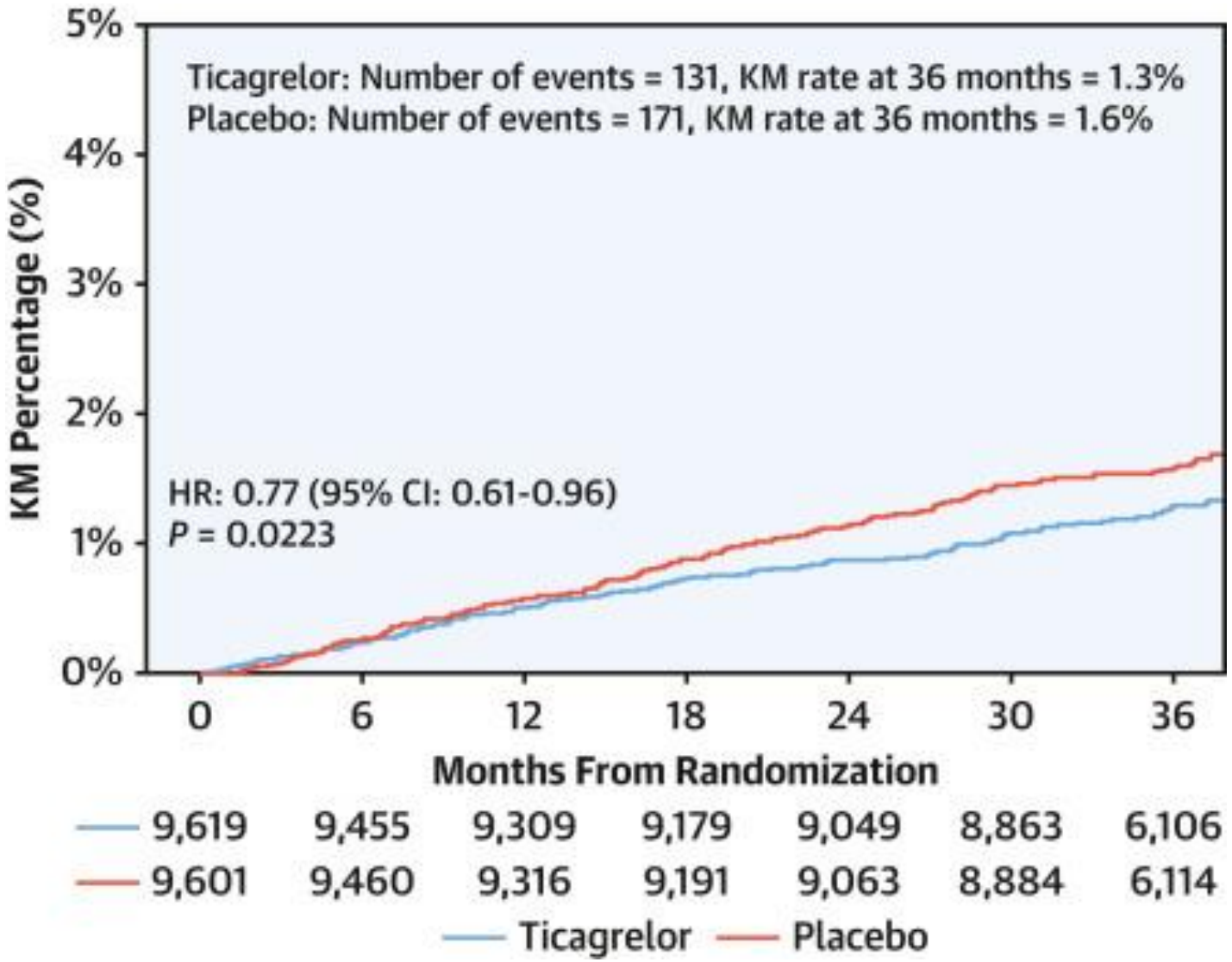
Limb Ischemic Events Over Follow-Up With Ticagrelor vs Placebo



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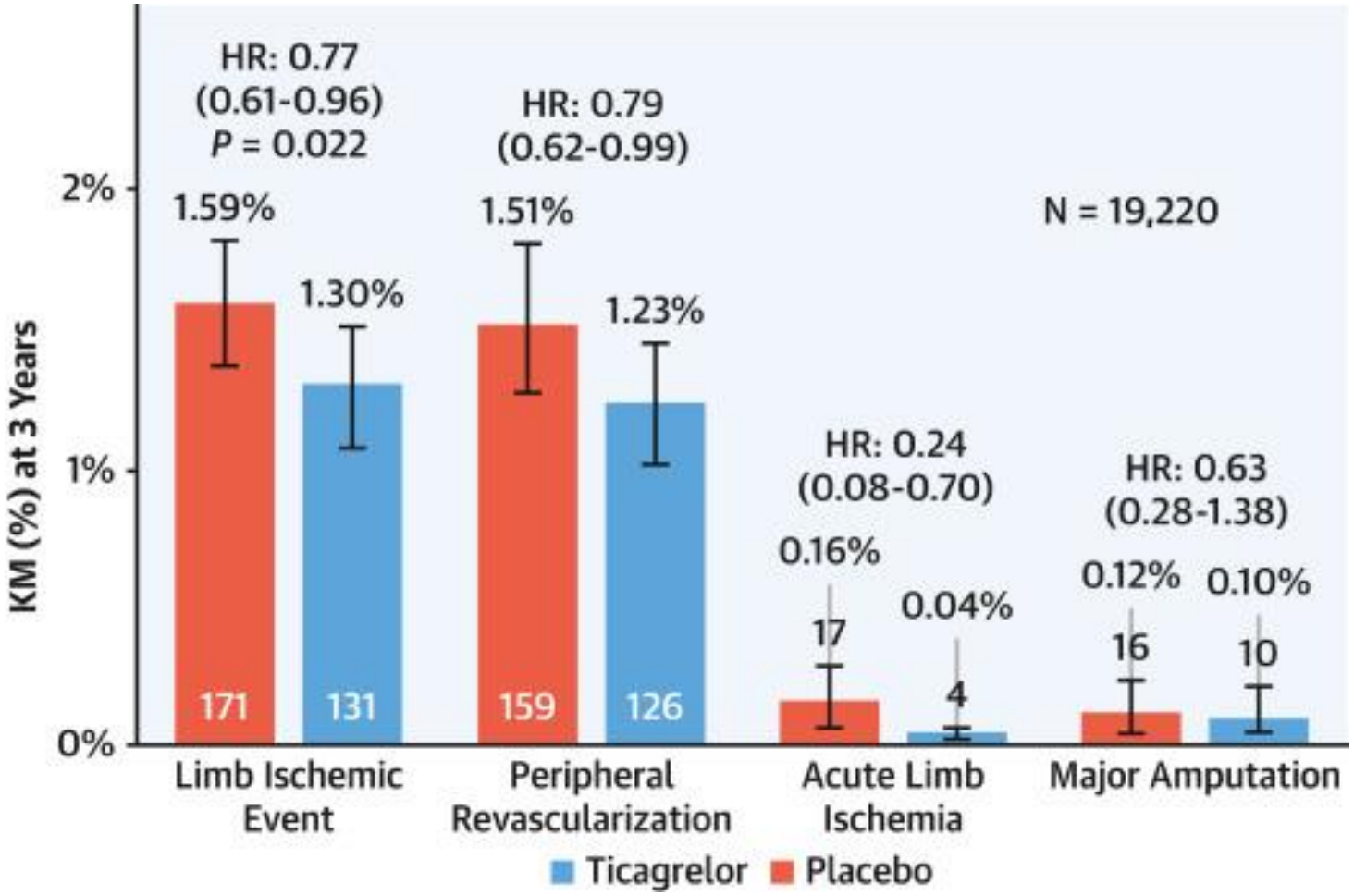
Limb Ischemic Events and Individual Components With Ticagrelor vs Placebo



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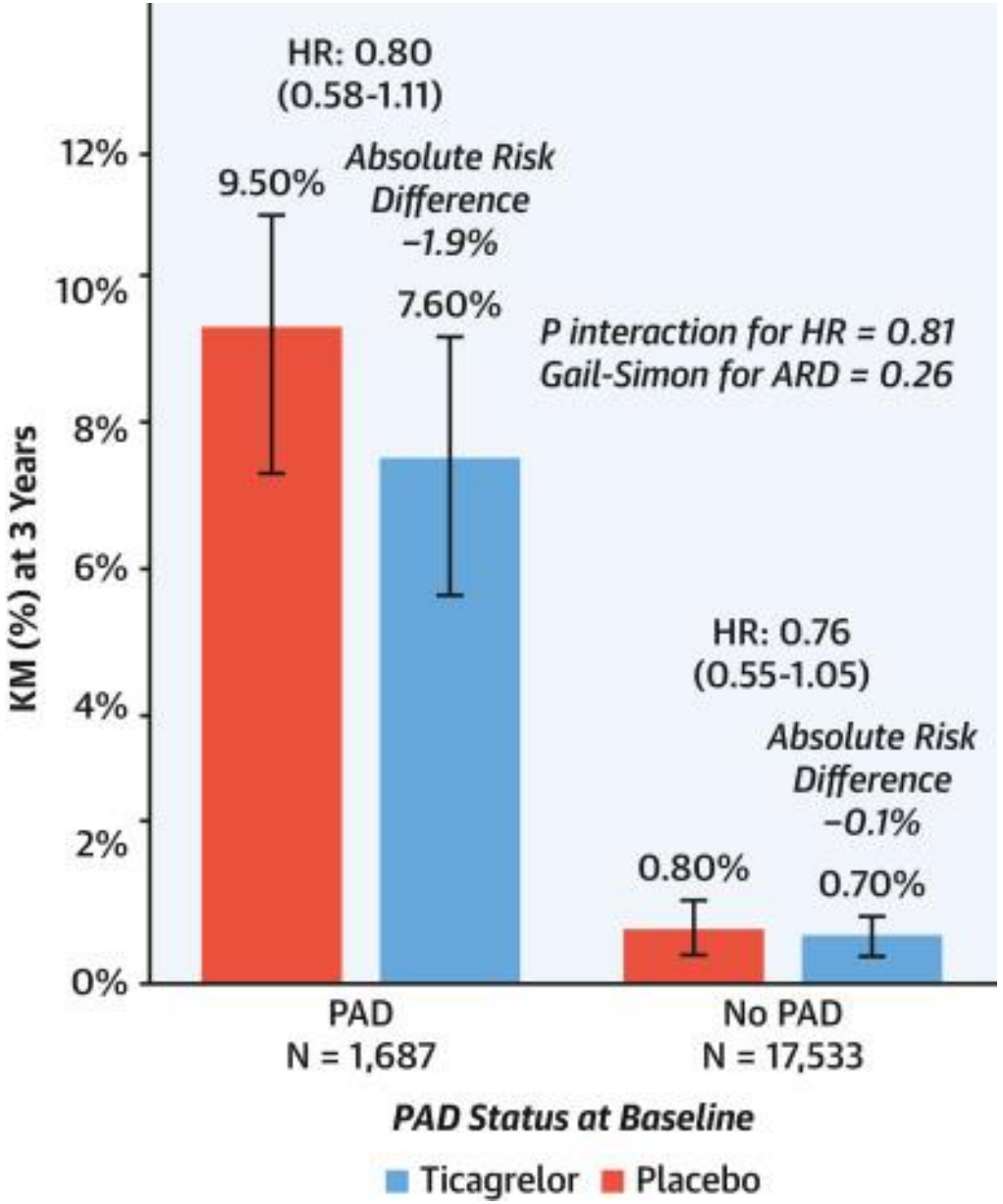
Limb Events With Ticagrelor Based on PAD History



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Ischemic Events With Ticagrelor vs Placebo in Patients With and Without PAD

	PAD				No PAD				
	Ticagrelor (N = 827) n, (Kaplan-Meier % at 3 Years)	Placebo (N = 860) n, (Kaplan-Meier % at 3 Years)	Absolute Risk Difference	HR (95% CI), *P* Value	Ticagrelor (N = 8,792) n, (Kaplan-Meier % at 3 Years)	Placebo (N = 8,741) n, (Kaplan-Meier % at 3 Years)	Absolute Risk Difference	HR (95% CI), *P* Value	*P* Interaction
Limb ischemic events	65 (7.6)	85 (9.5)	−1.9	0.80 (0.58-1.11), 0.19	66 (0.7)	86 (0.8)	−0.1	0.76 (0.55-1.05), 0.10	0.81
Major adverse limb events	8 (1.0)	13 (1.3)	−0.3	0.65 (0.27-1.58), 0.35	5 (0.1)	16 (0.2)	−0.1	0.31 (0.11-0.85), 0.023	0.27
Acute limb ischemia	3 (0.4)	6 (0.6)	−0.2	0.53 (0.13-2.13), 0.37	1 (0.0)	11 (0.1)	−0.1	0.09 (0.01-0.70), 0.022	0.16
Major amputation[a]	6 (0.8)	8 (0.7)	0.1	0.81 (0.28-2.35), 0.70	4 (0.0)	8 (0.1)	−0.1	0.50 (0.15-1.65), 0.26	0.54
Peripheral revascularization	60 (6.9)	79 (8.9)	−2.0	0.79 (0.57-1.11), 0.18	66 (0.7)	80 (0.8)	−0.1	0.81 (0.59-1.13), 0.22	0.92
Elective	55 (6.3)	74 (8.3)	−2.0	0.78 (0.55-1.10), 0.16	58 (0.6)	67 (0.6)	0.0	0.85 (0.60-1.21), 0.38	0.72
Urgent	5 (0.6)	13 (1.3)	−0.7	0.41 (0.15-1.15), 0.0902	11 (0.1)	15 (0.2)	−0.1	0.72 (0.33-1.58), 0.42	0.38
MACE	97 (11.3)	103 (10.7)	0.6	1.01 (0.76-1.33), 0.97	639 (6.5)	715 (7.3)	−0.8	0.89 (0.80-0.99), 0.029	0.40
Cardiovascular death	57 (6.7)	51 (5.8)	0.9	1.19 (0.81-1.73), 0.38	307 (3.0)	306 (2.9)	0.1	1.00 (0.85-1.17), 0.97	0.38
Myocardial infarction	34 (4.0)	37 (4.4)	−0.4	0.98 (0.61-1.56), 0.93	240 (2.4)	291 (3.2)	−0.8	0.82 (0.69-0.97), 0.024	0.47
Stroke	22 (2.5)	28 (2.8)	−0.3	0.85 (0.48-1.48), 0.56	158 (1.7)	193 (2.0)	−0.3	0.82 (0.66-1.01), 0.057	0.91
Mortality	92 (10.0)	87 (7.7)	2.3	1.13 (0.85-1.52), 0.40	487 (4.7)	505 (4.7)	0.0	0.96 (0.84-1.08), 0.48	0.29

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Bleeding Events With Ticagrelor vs Placebo in Patients With and Without PAD

	PAD			No PAD			
	Ticagrelor (N = 825) n, (Kaplan-Meier % at 3 Years)	Placebo (N = 849) n, (Kaplan-Meier % at 3 Years)	HR (95% CI), *P* Value	Ticagrelor (N = 8,737) n, (Kaplan-Meier % at 3 Years)	Placebo (N = 8,682) n, (Kaplan-Meier % at 3 Years)	HR (95% CI), *P* Value	*P* Interaction
TIMI major bleeding	17 (2.4)	12 (1.8)	1.62 (0.77-3.39) 0.20	189 (2.7)	88 (1.2)	2.41 (1.87-3.11) <0.001	0.4511
Fatal bleeding	1 (0.2)	1 (0.1)	1.15 (0.07-18.35) 0.92	16 (0.3)	9 (0.1)	1.98 (0.88-4.49) 0.10	0.6699
Nonfatal intracranial hemorrhage	7 (0.9)	5 (0.8)	1.63 (0.52-5.15) 0.40	63 (0.9)	41 (0.5)	1.72 (1.16-2.55) 0.0068	0.9801

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Limitations

- Protocolized screening for PAD was not performed at enrollment; therefore, it is likely that some patients with PAD that was not clinically evident were misclassified as not having PAD.
  - This factor may explain the occurrence of limb ischemic events and reduction in MALE risk with ticagrelor in the subgroup without known PAD.
- The lack of granularity regarding PAD history limits the generalizability of the findings to specific patients with PAD, especially considering the heterogeneity of this population.
- The PAD subgroup was modest in size at approximately 9% of the overall population.
- The effects observed of ticagrelor are in patients selected on the basis of stable CAD and T2DM; therefore, the efficacy and safety and benefit:risk balance may not translate to patients selected on the basis of PAD alone or in a periprocedural setting.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with T2DM who have CAD and lower extremity PAD, therapy with aspirin plus ticagrelor decreases the incidence of major adverse limb outcomes compared with aspirin alone, but increases the risk of bleeding.

TRANSLATIONAL OUTLOOK:

Further studies are needed to compare the safety and efficacy of DAPT with ticagrelor plus aspirin in patients with PAD with other strategies, including dual-pathway inhibitor combinations of antiplatelet and target-specific anticoagulant agents.

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Conclusions

- Patients with T2DM and comorbid CAD and PAD are at heightened risk of limb ischemic events.
- Long-term ticagrelor added to aspirin deceases MACE and limb ischemic events in this population but increases bleeding.
- Identifying comorbid PAD in patients with CAD and T2DM may identify a population who may derive benefits with long-term ticagrelor including limb outcomes.
- Future trials evaluating the combination of ticagrelor and aspirin for the reduction of MACE and MALE would further elucidate benefit/risk ratio of such therapy in patients with PAD, including those without CAD.

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