THEMIS: Ticagrelor Added to Aspirin in Patients with Stable Coronary Disease and Diabetes

Presented by Deepak L. Bhatt

Philippe Gabriel Steg,* Deepak L Bhatt,*

Tabassome Simon, Kim M. Fox, Shamir R. Mehta, Robert A. Harrington, Claes Held, Marielle Andersson, Anders Himmelmann, Wilhelm Ridderstråle, Maria Leonsson-Zachrisson, Yuyin Liu, Grzegorz Opolski, Dmitry Zateyshchikov, Junbo Ge, José Carlos Nicolau, Ramón Corbalán, Jan Hein Cornel, Petr Widimský, Lawrence A. Leiter
on behalf of the THEMIS Steering Committee and Investigators

*co-Chairs and co-Principal Investigators of THEMIS

European Society of Cardiology 2019

ClinicalTrials.gov registration: NCT01991795

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
BRIGHAM HEALTH BRIGHAM AND WOMEN'S HOSPITAL
Université de Paris
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

TICAGRELOR IN STABLE CAD AND T2D TREATED WITH ASA

PARTHENON THEMIS

Declaration of interest

- Research contracts (AstraZeneca)
- Research contracts (Amarin, Bayer, Sanofi, and Servier)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer-Ingelheim, Bristol-Myers-Squib Idorsia, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, Servier)

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, Afimmune, Amarin, Amgen, **AstraZeneca**, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda.

This presentation discusses off label and investigational uses of drugs.

THEMIS and THEMIS-PCI were funded by AstraZeneca.

The Baim Clinical Research Institute (Boston, MA) independently validated all data in this presentation.

Background

- Patients with both established coronary artery disease and type 2 diabetes mellitus are at increased risk of cardiovascular events.
- Platelet-mediated thrombosis is a major mechanism.
- Ticagrelor protects against CV events when added to aspirin in acute coronary syndromes and in patients with a history of prior myocardial infarction.
- Whether patients with diabetes and stable coronary artery disease without a history of prior MI or stroke also derive benefit from dual antiplatelet therapy with aspirin and ticagrelor is unknown.

CV=cardiovascular; MI=myocardial infarction

Methods

- THEMIS is a randomized, double-blind, placebo-controlled trial of ticagrelor versus placebo, on top of low-dose (75 to 150 mg) aspirin.
- Patients ≥ 50 years with type 2 diabetes receiving anti-hyperglycemic medications for at least 6 months, and with stable CAD (i.e., history of PCI, CABG, or angiographic stenosis ≥ 50% in at least 1 coronary artery) were enrolled.
- Patients with known prior MI or stroke were excluded.
- The initial dose of ticagrelor was 90 mg bid and was then changed to 60 mg bid due to emerging data on ticagrelor tolerability from PEGASUS-TIMI 54.

bid=twice daily; CAD=coronary artery disease; CABG=coronary artery bypass grafting; mg=milligrams; MI=myocardial infarction; PCI=percutaneous coronary intervention; PEGASUS-TIMI 54= Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54

Bhatt DL, Fox KM, Harrington RA, et al., and Steg PG. Clin Cardiol 2019 Feb 20. doi: 10.1002/clc.23164.

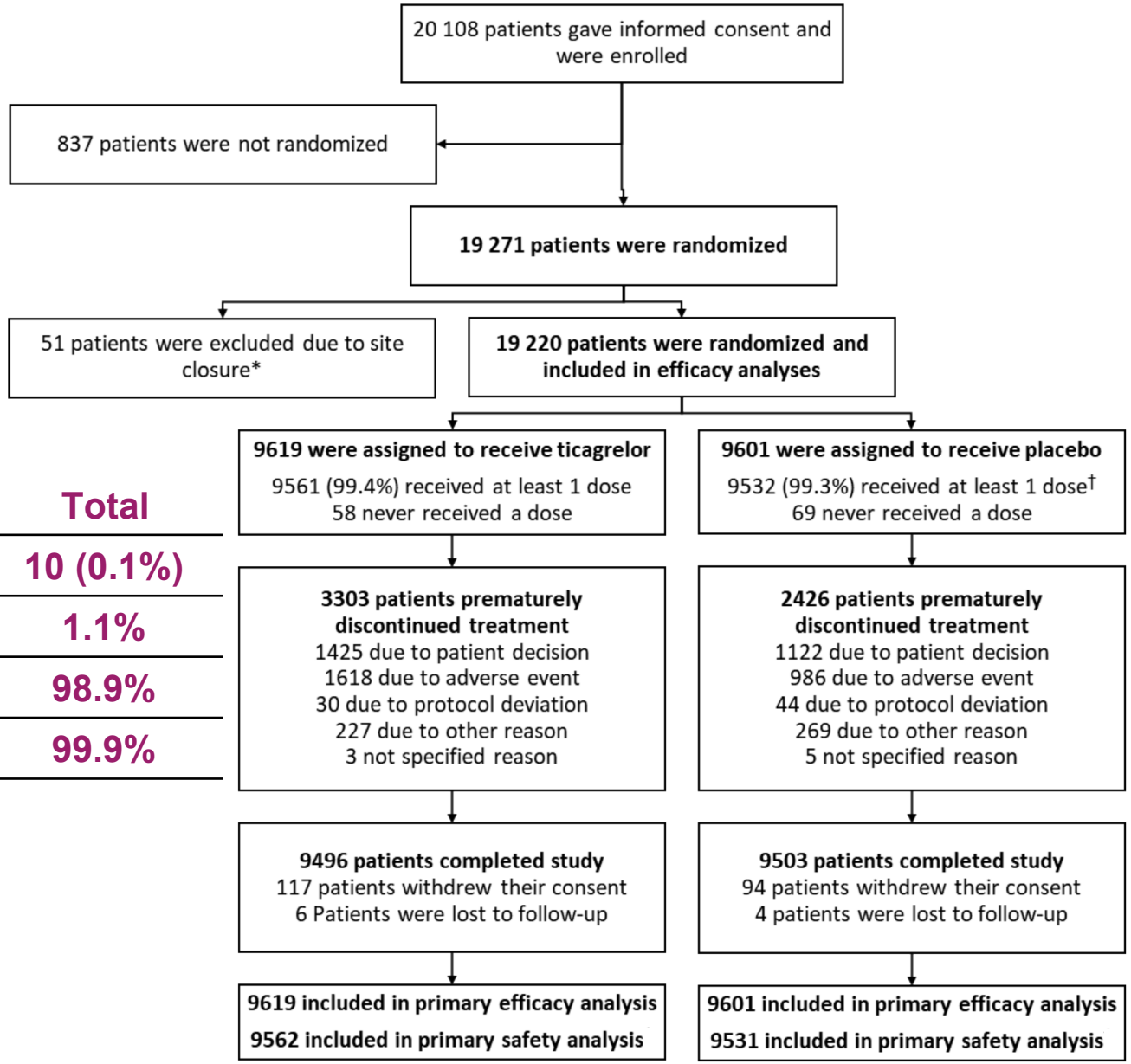
Endpoints

- The primary efficacy outcome was first occurrence of any event in the composite of cardiovascular death, MI, or stroke.
- Secondary efficacy outcomes were tested hierarchically according to the following sequence: CV death, MI, ischemic stroke, and all-cause death.
- The primary safety outcome was TIMI major bleeding.
- Efficacy and bleeding endpoints were independently adjudicated in a blinded manner.

CV=cardiovascular; MI=myocardial infarction; TIMI= thrombolysis in myocardial infarction

Bhatt DL, Fox KM, Harrington RA, et al., and Steg PG. Clin Cardiol 2019 Feb 20. doi: 10.1002/clc.23164.

Study Flow



	Ticagrelor	Placebo	**Total**
Lost to FU, n (%)	6 (0.1%)	4 (0.0%)	**10 (0.1%)**
Withdrew Consent	1.2%	1.0%	**1.1%**
Completed Study	98.7%	99.0%	**98.9%**
Known Vital Status	99.9%	99.9%	**99.9%**

The 51 excluded patients were due to inadequate adherence to good clinical practice at the site in a different study. One patient was randomized to placebo but only received ticagrelor tablets; this patient is included in the ticagrelor group in the safety analyses. FU= follow-up.

Baseline Characteristics

	Ticagrelor (N=9619)	Placebo (N=9601)
Median age (IQR) – years	**66.0 (61.0–72.0)**	**66.0 (61.0–72.0)**
Female – n (%)	**3043 (31.6)**	**2988 (31.1)**
Median body mass index (IQR) – kg/m²	29.0 (26.1–32.6)	29.1 (26.0–32.8)
Current smoker – n (%)	1056 (11.0)	1038 (10.8)
Race – n (%)		
Asian	**2211 (23.0)**	**2195 (22.9)**
Black or African American	205 (2.1)	198 (2.1)
Other	365 (3.8)	350 (3.6)
White	**6838 (71.1)**	**6858 (71.4)**
Geographic region – n (%)		
Asia and Australia	2145 (22.3)	2143 (22.3)
Central and South America	1100 (11.4)	1078 (11.2)
Europe and South Africa	**4884 (50.8)**	**4875 (50.8)**
North America	**1490 (15.5)**	**1505 (15.7)**

For all variables p>0.05 between treatment groups; Race reported by patients; IQR=interquartile range, kg=kilograms; m=meters; N=number of patients.

History of Disease at Baseline

	Ticagrelor (N=9619)	Placebo (N=9601)
Hypertension – n (%)	**8909 (92.6)**	**8867 (92.4)**
Dyslipidemia – n (%)	**8386 (87.2)**	**8367 (87.1)**
Angina pectoris – n (%)	5444 (56.6)	5357 (55.8)
Multi-vessel CAD – n (%)	5951 (61.9)	5984 (62.3)
Coronary arterial revascularization – n (%)	**7678 (79.8)**	**7667 (79.9)**
PCI – n (%)	**5558 (57.8)**	**5596 (58.3)**
CABG (no PCI) – n (%)	**2120 (22.0)**	**2071 (21.6)**
No history of revascularization	**1941 (20.2)**	**1934 (20.1)**
Median time since most recent CABG (IQR) – years	4.4 (1.6–9.2)	4.1 (1.5–9.3)
Median time since most recent PCI (IQR) – years	3.3 (1.5–6.7)	3.3 (1.5–6.6)
PAD – n (%)	827 (8.6)	860 (9.0)
History of poly-vascular disease – n (%)	1268 (13.2)	1311 (13.7)
Median duration of diabetes (IQR) – years	**10.0 (5.0–16.0)**	**10.0 (5.0–16.0)**
History of any diabetes complications – n (%)	2480 (25.8)	2430 (25.3)
Median HbA1c at baseline (IQR) – %	7.1 (6.4–8.1)	7.1 (6.4–8.1)
Median eGFR (MDRD) at baseline (IQR) – mL/min/1.73m²	75.1 (60.5–89.8)	75.0 (60.6–89.5)

For all variables p>0.05 between treatment groups; PCI is with or without stent; includes patients who also had a history of CABG; no history of revascularization is significant stenosis (at least 50% lumen stenosis) on coronary angiography but no revascularization; poly-vascular disease is arterial obstructive disease involving ≥2 vascular beds characterized by either 1) CAD (CAD, PCI, or CABG), 2) PAD, 3) carotid artery stenosis or cerebral revascularization; diabetes complications are at least one: retinopathy, autonomic neuropathy, peripheral neuropathy, and nephropathy. CABG=coronary artery bypass grafting; CAD=coronary artery disease; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin; IQR=interquartile range; MDRD=modification of diet in renal disease; mL=millilitres; min=minutes; N=number of patients; PAD=peripheral artery disease; PCI=percutaneous coronary intervention

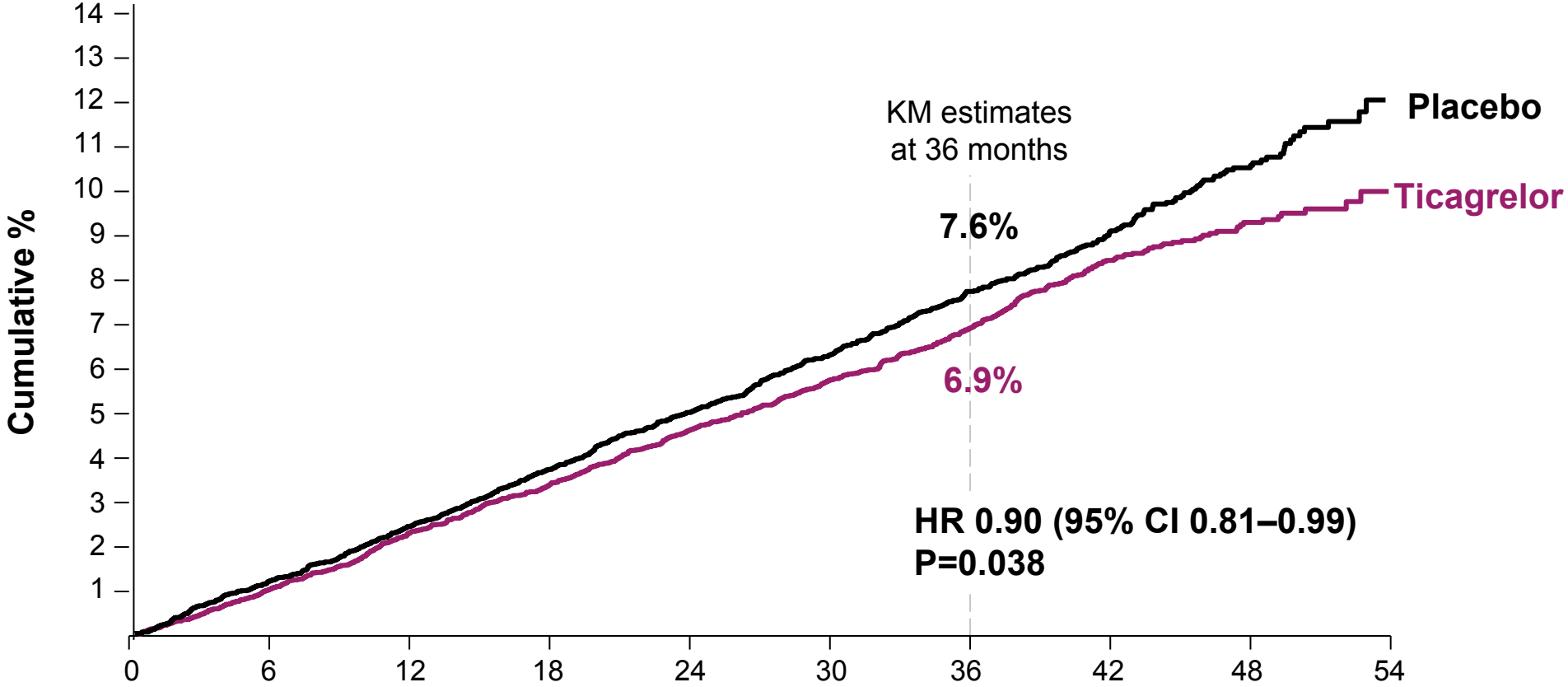
Medication Use at Baseline

	Ticagrelor (N=9619)	Placebo (N=9601)
Aspirin – n (%)	**9556 (99.3)**	**9548 (99.4)**
Median aspirin dose (IQR) – mg	100.0 (80.0–100.0)	100.0 (80.0–100.0)
Statin – n (%)	**8629 (89.7)**	**8637 (90.0)**
Ezetimibe – n (%)	536 (5.6)	499 (5.2)
Proton pump inhibitor – n (%)	2453 (25.5)	2448 (25.5)
ACE inhibitor or ARB – n (%)	**7558 (78.6)**	**7556 (78.7)**
ACE inhibitor – n (%)	4052 (42.1)	4094 (42.6)
ARB – n (%)	3627 (37.7)	3584 (37.3)
Beta-blocker – n (%)	**7058 (73.4)**	**7134 (74.3)**
Insulin – n (%)	2798 (29.1)	2710 (28.2)
Metformin – n (%)	7304 (75.9)	7310 (76.1)
SGLT2 inhibitor – n (%)	189 (2.0)	174 (1.8)
GLP1-R agonist – n (%)	203 (2.1)	210 (2.2)
DPP4-inhibitor – n (%)	1819 (18.9)	1795 (18.7)
Sulfonylurea – n (%)	3350 (34.8)	3416 (35.6)
Any diabetes medications – n (%)	**9586 (99.7)**	**9571 (99.7)**
1	4319 (44.9)	4291 (44.7)
2	3462 (36.0)	3448 (35.9)
3	1424 (14.8)	1468 (15.3)
>3	381 (4.0)	364 (3.8)

Medications used within 30 days of randomization, aspirin use captured on day of randomization; Metformin, SGLT2 inhibitor, GLP1-R agonist DPP4 inhibitor and sulfonylurea numbers include combination tablets. ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; DPP4= dipeptidyl peptidase 4; GLP1-R = glucagon-like peptide-1 receptor; IQR=interquartile range; mg=milligrams; N=number of patients; SGLT2=sodium-glucose co-transporter 2

Primary Composite Endpoint

Cardiovascular death/MI/stroke

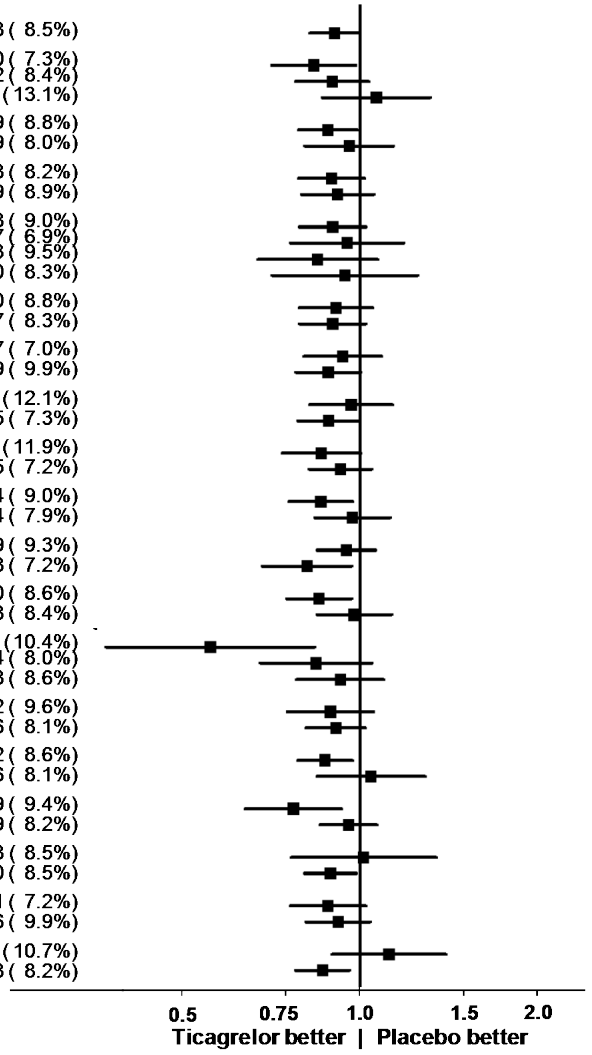


N at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

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

Primary Efficacy Endpoint – Subgroups

	N	Ticagrelor (%)	Placebo (%)	HR (95% CI)	P-value
Overall treatment effect	19220	736 (7.7%)	818 (8.5%)	0.90 (0.81, 0.99)	
Age (years)					
< 65	7934	243 (6.1%)	290 (7.3%)	0.83 (0.70, 0.98)	0.20
65 – 75	8890	330 (7.4%)	372 (8.4%)	0.89 (0.77, 1.03)	
> 75	2396	163 (13.6%)	156 (13.1%)	1.07 (0.86, 1.33)	
Sex					
Male	13189	505 (7.7%)	579 (8.8%)	0.88 (0.78, 0.99)	0.43
Female	6031	231 (7.6%)	239 (8.0%)	0.96 (0.80, 1.15)	
BMI (kg/m²)					
<= 30	10996	404 (7.3%)	448 (8.2%)	0.89 (0.78, 1.02)	0.81
> 30	8206	331 (8.1%)	369 (8.9%)	0.91 (0.79, 1.06)	
Geographic region					
Europe and South Africa	9759	392 (8.0%)	438 (9.0%)	0.89 (0.78, 1.02)	0.90
Asia and Australia	4288	139 (6.5%)	147 (6.9%)	0.95 (0.75, 1.20)	
North America	2995	119 (8.0%)	143 (9.5%)	0.84 (0.66, 1.07)	
Central and South America	2178	86 (7.8%)	90 (8.3%)	0.94 (0.70, 1.26)	
Aspirin dose at baseline (mg)					
<= 81	8135	324 (8.0%)	360 (8.8%)	0.91 (0.78, 1.05)	0.89
> 81	10785	401 (7.4%)	447 (8.3%)	0.89 (0.78, 1.02)	
HbA1c at baseline (%)					
<= 7	9108	295 (6.5%)	317 (7.0%)	0.93 (0.79, 1.09)	0.57
> 7	9642	420 (8.7%)	479 (9.9%)	0.88 (0.77, 1.00)	
eGFR (MDRD, mL/min/1.73 m²)					
<= 60	4549	266 (11.6%)	274 (12.1%)	0.96 (0.81, 1.14)	0.39
> 60	14338	461 (6.4%)	525 (7.3%)	0.88 (0.78, 1.00)	
Insulin use at baseline					
Yes	5508	286 (10.2%)	323 (11.9%)	0.85 (0.73, 1.00)	0.46
No	13712	450 (6.6%)	495 (7.2%)	0.92 (0.81, 1.05)	
History of angina					
Yes	10801	420 (7.7%)	484 (9.0%)	0.85 (0.75, 0.97)	0.21
No	8419	316 (7.6%)	334 (7.9%)	0.97 (0.83, 1.13)	
Multivessel coronary artery disease					
Yes	11935	523 (8.8%)	559 (9.3%)	0.95 (0.84, 1.07)	0.15
No	7232	211 (5.8%)	258 (7.2%)	0.81 (0.67, 0.97)	
History of PCI					
Yes	11154	404 (7.3%)	480 (8.6%)	0.85 (0.74, 0.97)	0.16
No	8066	332 (8.2%)	338 (8.4%)	0.98 (0.84, 1.14)	
Time since most recent PCI (years)					
< 1	1145	34 (5.8%)	58 (10.4%)	0.54 (0.36, 0.83)	0.07
1 – 3	4048	135 (6.7%)	164 (8.0%)	0.84 (0.67, 1.05)	
> 3	5959	235 (7.9%)	258 (8.6%)	0.92 (0.77, 1.10)	
History of CABG					
Yes	5537	236 (8.4%)	262 (9.6%)	0.89 (0.74, 1.06)	0.84
No	13683	500 (7.3%)	556 (8.1%)	0.91 (0.80, 1.02)	
History of coronary arterial revasc*					
Yes	15345	574 (7.5%)	662 (8.6%)	0.87 (0.77, 0.97)	0.14
No	3875	162 (8.3%)	156 (8.1%)	1.04 (0.84, 1.30)	
PPI use at baselline					
Yes	4901	175 (7.1%)	229 (9.4%)	0.76 (0.63, 0.93)	0.05
No	14319	561 (7.8%)	589 (8.2%)	0.95 (0.85, 1.07)	
Current smoker					
Yes	2094	90 (8.5%)	88 (8.5%)	1.01 (0.76, 1.36)	0.39
No	17125	646 (7.5%)	730 (8.5%)	0.89 (0.80, 0.98)	
Duration of diabetes (years)					
<= 10	9702	303 (6.3%)	351 (7.2%)	0.88 (0.75, 1.02)	0.68
> 10	9508	433 (9.0%)	466 (9.9%)	0.91 (0.80, 1.04)	
History of poly−vasc. disease†					
Yes	2579	148 (11.7%)	140 (10.7%)	1.12 (0.89, 1.42)	0.04
No	16627	587 (7.0%)	678 (8.2%)	0.86 (0.77, 0.96)	



Revascularization is PCI or CABG; Polyvascular disease is arterial obstructive disease involving at least 2 vascular beds characterized by either 1) CAD, PCI or CABG, 2) PAD, 3) carotid artery stenosis or cerebral revascularization. HRs are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable. p-value interaction was not calculated if the sum of events in all treatment groups was <12 in at least one subgroup category. BMI=body mass index; CABG=coronary artery bypass graft; CAD=coronary artery disease; CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; HbA1c=glycated hemoglobin; kg=kilograms; MDRD=modification of diet in renal disease; mg=milligrams; mL=milliliters; min=minutes; N=number of patients; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; poly-vasc=poly-vascular; PPI=proton pump inhibitor; revasc=revascularization

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

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

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

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

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

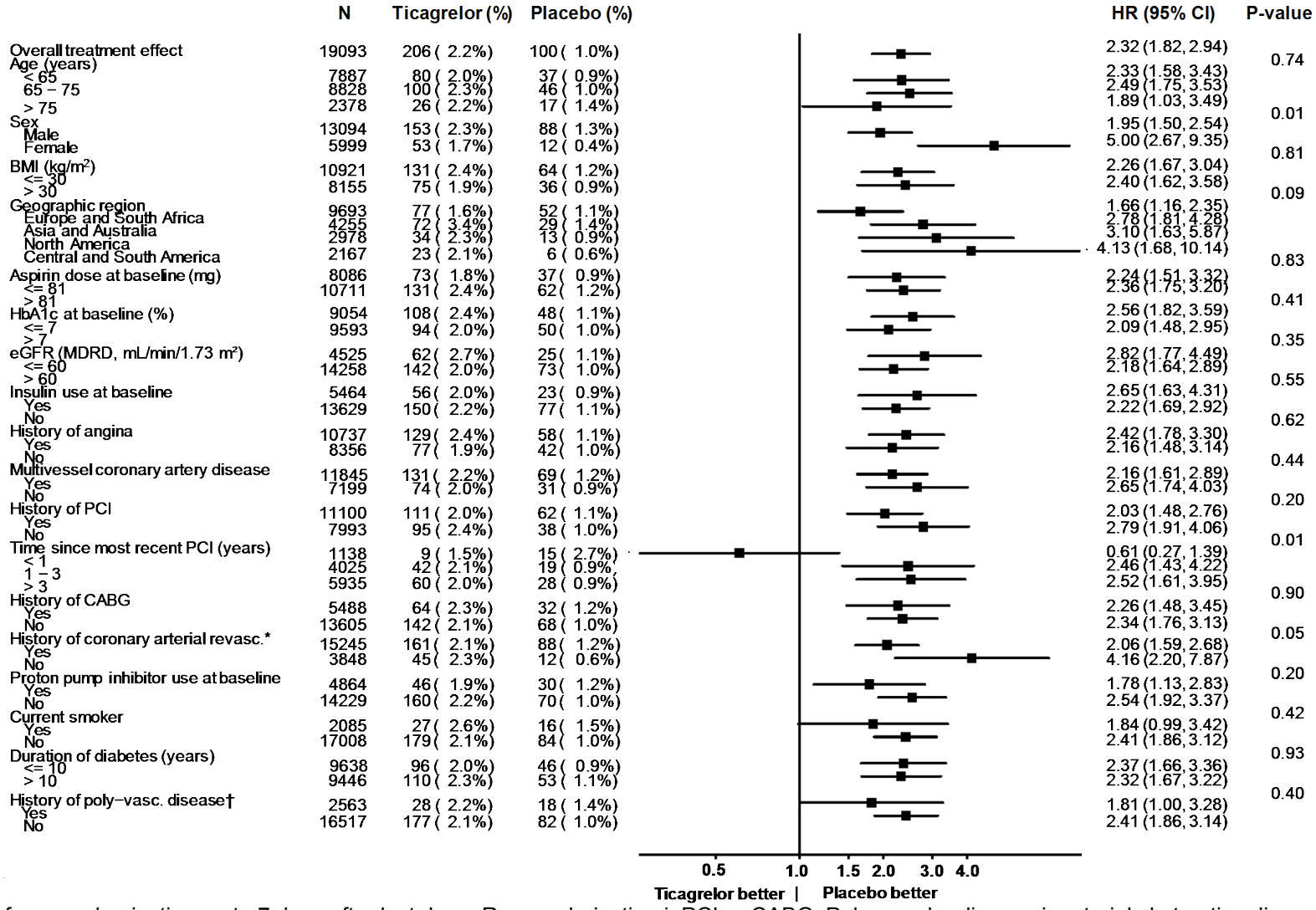
Bleeding Outcomes

	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 4, 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

TIMI Major Bleeding – Subgroups



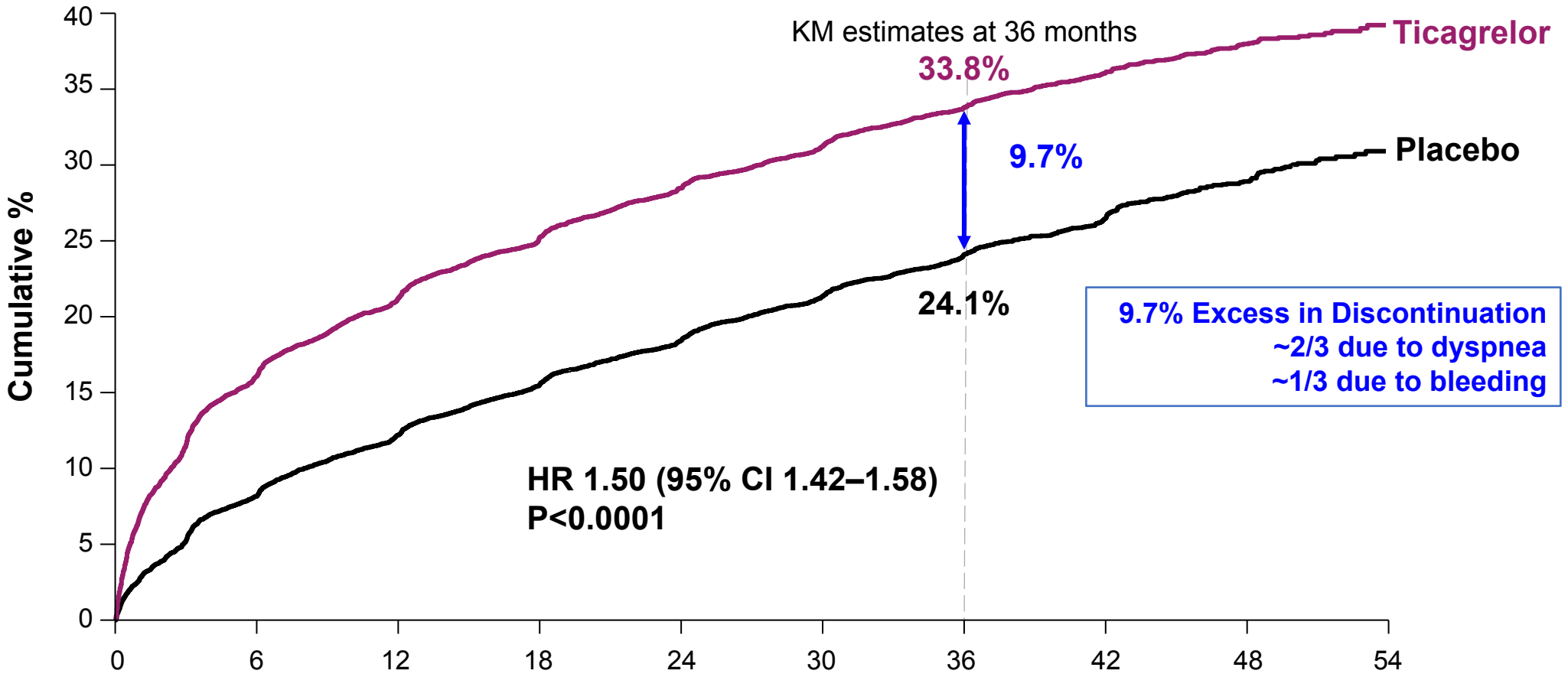
Includes events with onset from randomization up to 7 days after last dose. Revascularization isPCI or CABG; Polyvascular disease is arterial obstructive disease involving at least 2 vascular beds characterized by either 1) CAD, PCI or CABG, 2) PAD, 3) carotid artery stenosis or cerebral revascularization. HRs are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable. p-value interaction was not calculated if the sum of events in all treatment groups was <12 in at least one subgroup category. BMI=body mass index; CABG=coronary artery bypass graft; CAD=coronary artery disease; CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; HbA1c=glycated hemoglobin; kg=kilograms; MDRD=modification of diet in renal disease; mg=milligrams; mL=milliliters; min=minutes; N=number of patients; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; poly-vasc=poly-vascular; PPI=proton pump inhibitor; revasc=revascularization

Safety 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
SAE	3049 (31.9%)	13.12	3210 (33.7%)	12.22	1.08 (1.03–1.13)	0.003
AE with outcome death	256 (2.7%)	1.10	309 (3.2%)	1.18	0.94 (0.79–1.11)	0.45
Any AE of bleeding	1446 (15.1%)	6.22	595 (6.2%)	2.26	2.77 (2.52–3.05)	<0.001
AE bleeding leading to treatment discontinuation	466 (4.9%)	2.01	125 (1.3%)	0.48	4.04 (3.32–4.92)	<0.001
Any AE of interest†	2562 (26.8%)	11.02	1302 (13.7%)	4.96	2.30 (2.15–2.46)	<0.001
AE dyspnea	2049 (21.4%)	8.82	700 (7.3%)	2.66	3.33 (3.06–3.63)	<0.001
AE dyspnea leading to treatment discontinuation	661 (6.9%)	2.84	75 (0.8%)	0.29	9.27 (7.30–11.77)	<0.001
AE gout	190 (2.0%)	0.82	159 (1.7%)	0.61	1.33 (1.08–1.64)	0.01
AE renal impairment	225 (2.4%)	0.97	220 (2.3%)	0.84	1.15 (0.96–1.39)	0.14
AE pneumonia	252 (2.6%)	1.08	263 (2.8%)	1.00	1.08 (0.91–1.28)	0.40
AE bradyarrhythmia	137 (1.4%)	0.59	120 (1.3%)	0.46	1.28 (1.01–1.64)	0.05

Includes events with onset from randomization up to 7 days after last dose. Events other than bleeding as reported by the investigator; any AE of interest includes dyspnea, gout, renal impairment, pneumonia or bradyarrhythmia; patients could have more than one category of event. AE=adverse event, CI=confidence interval; N=number of patients; SAE=serious adverse event

Permanent Treatment Discontinuation

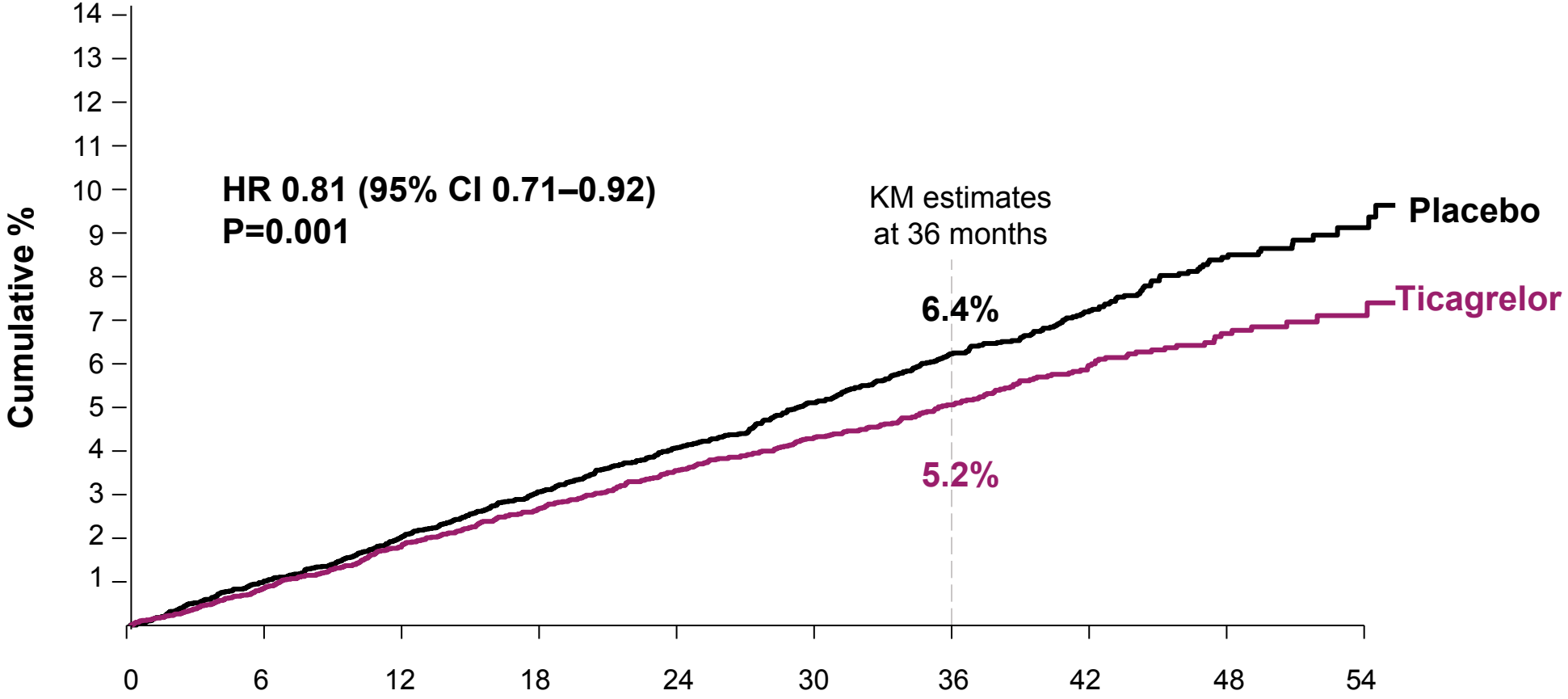


Number at risk										
Ticagrelor	9562	7904	7316	6831	6414	6029	4105	2483	1172	173
Placebo	9531	8660	8179	7772	7367	6974	4786	2959	1362	218

Discontinuation due to dyspnea 6.9% on ticagrelor vs. 0.8% on placebo (HR 9.27 [7.30-11.77] p <0.001); due to bleeding 4.9% vs 1.3% (HR 4.04 [3.32-4.92] p<0.001). CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier

Primary Composite Endpoint

Cardiovascular death/MI/stroke – on treatment



Number at Risk

Ticagrelor	9562	7891	7291	6799	6343	5962	4040	2431	1137	168
Placebo	9531	8639	8136	7702	7373	6875	4712	2904	1333	213

Patients censored 3 days after the last dose; CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

Limitations

- Dose of ticagrelor was changed from 90 mg bid to 60 mg bid during the trial, though efficacy and bleeding appeared to be consistent between doses.
- There was a significant increase in major bleeding, including traumatic intracranial bleeding (largely subdural), but not fatal bleeding
  - Practical advice would be to minimize the risk of head trauma (e.g., wear helmet while skiing, biking, etc.)
  - Ticagrelor reversal agent under development
- Higher rate of treatment discontinuation in the ticagrelor group
  - On treatment analyses show larger and more robust risk reductions, though with the usual caveats (only applies to adherent patients tolerating therapy)
- Subgroups not powered for efficacy
  - Though better net clinical benefit identified – stay tuned for **THEMIS-PCI**!

Conclusions

- In patients with stable coronary artery disease and diabetes, but without a prior history of myocardial infarction or stroke, compared with aspirin alone, the combination of ticagrelor plus aspirin reduced the primary endpoint of CV death, MI, or stroke.

- This benefit was achieved at the expense of increased major bleeding.

- This strategy of long-term DAPT may be beneficial in selected patients at low risk of bleeding but with a high risk of ischemic events.

CV = cardiovascular; DAPT= dual antiplatelet therapy; MI=myocardial infarction

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor in Patients with Stable Coronary Disease and Diabetes

P.G. Steg, D.L. Bhatt, T. Simon, K. Fox, S.R. Mehta, R.A. Harrington, C. Held, M. Andersson, A. Himmelmann, W. Ridderstråle, M. Leonsson-Zachrisson, Y. Liu, G. Opolski, D. Zateyshchikov, J. Ge, J.C. Nicolau, R. Corbalán, J.H. Cornel, P. Widimský, and L.A. Leiter, for the THEMIS Steering Committee and Investigators*

Full Details Available at www.NEJM.org

THEMIS-PCI: Ticagrelor Added to Aspirin in Patients with Diabetes and Stable Coronary Artery Disease with a History of Prior Percutaneous Coronary Intervention

Presented by P. Gabriel Steg

Deepak L. Bhatt,* Philippe Gabriel Steg,*

Shamir R. Mehta, Lawrence A. Leiter, Tabassome Simon, Kim Fox, Claes Held, Marielle Andersson, Anders Himmelmann, Wilhelm Ridderstråle, Jersey Chen, Yang Song, Rafael Diaz, Shinya Goto, Stefan K James, Kausik K. Ray, Alexander Parkhomenko, Mikhail N. Kosiborod, Darren K. McGuire, Robert A. Harrington,

on behalf of the THEMIS Steering Committee and Investigators

*co-Chairs and co-Principal Investigators of THEMIS

European Society of Cardiology 2019

ClinicalTrials.gov registration: NCT01991795

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

Université de Paris

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

TICAGRELOR IN STABLE CAD AND T2D TREATED WITH ASA

PARTHENON THEMIS

Disclosures

P. Gabriel Steg

- Research grants : Amarin, Bayer, Servier, Sanofi
- Speaker or consultant (including steering committees, DMCs and CECs): Amarin, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Idorsia, Merck, Novartis, Novo, Pfizer, Regeneron, Sanofi, Servier

THEMIS was supported by AstraZeneca.

The **Baim Clinical Research Institute** (Boston, MA) independently validated all the data in this presentation.

Background

- THEMIS was a randomized, double-blind, placebo-controlled trial of ticagrelor versus placebo, on top of low-dose aspirin (75 to 150 mg) in patients with type 2 diabetes mellitus receiving anti-hyperglycemic medications for at least six months, and with stable CAD.

- We hypothesized that THEMIS patients with prior PCI, (who have been previously treated with DAPT), would be the group most likely to have a favorable balance of efficacy and safety.

CAD=coronary artery disease; DAPT=dual antiplatelet therapy; mg=milligrams; PCI=Percutaneous Coronary Intervention

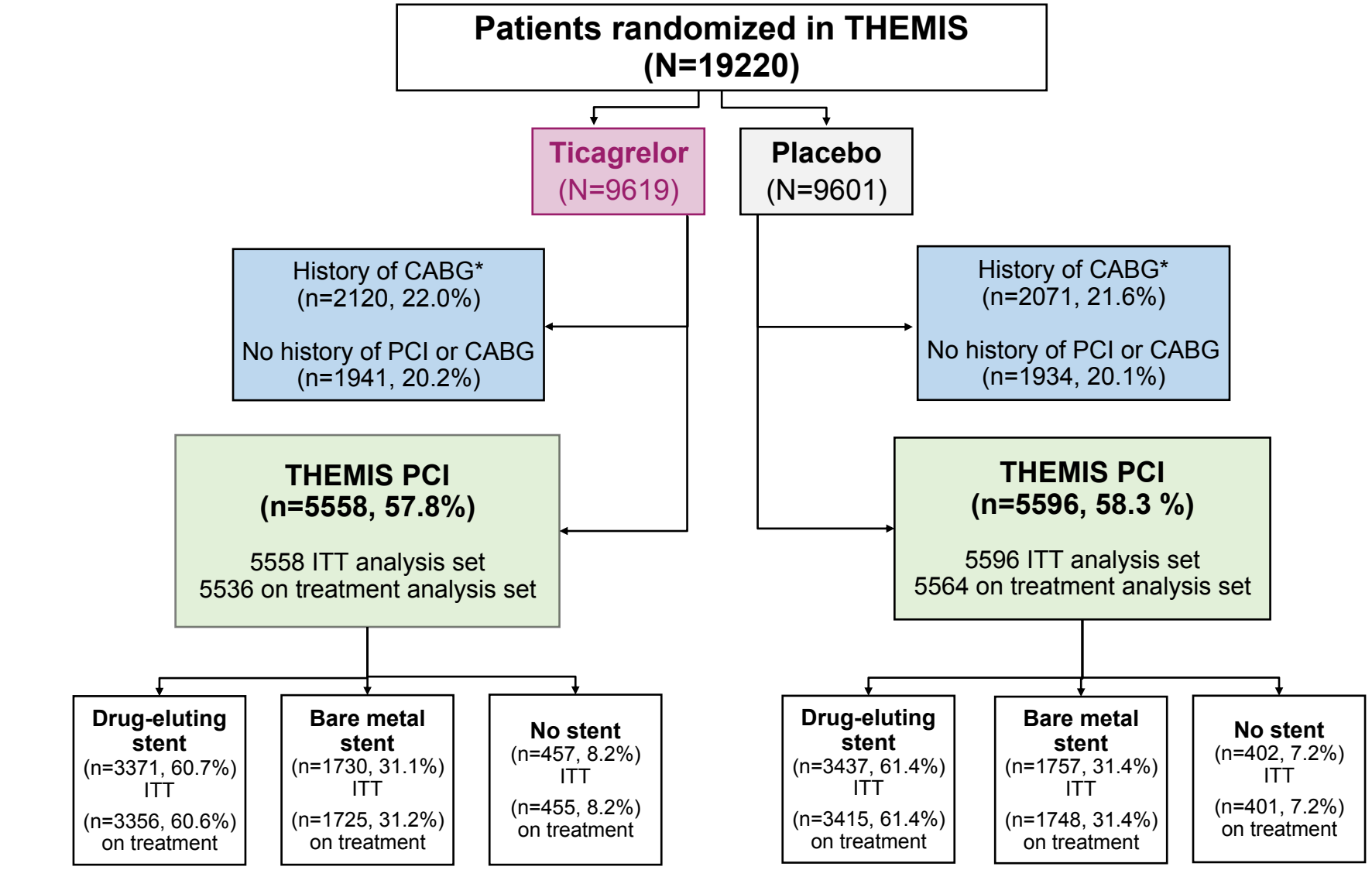
Methods

- In THEMIS, ticagrelor produced a 10% relative risk reduction (HR 0.90, 95% CI 0.81-0.99, P=0.038) over placebo in the primary endpoint of CV death, MI, or stroke in 19,220 patients with CAD and type 2 diabetes mellitus.

- THEMIS PCI is a prespecified subgroup analysis of patients with a history of PCI, a large subgroup (58% of THEMIS), corresponding to a major inclusion criterion.

CAD=coronary artery disease; CI=Confidence Interval; CV=Cardiovascular; HR=hazard ratio; ICH=intracranial hemorrhage; MI=Myocardial Infarction; PCI=Percutaneous Coronary Intervention

Study Flow



*excludes patients with a history of PCI; CABG=coronary artery bypass graft; ITT=intention to treat; PCI=percutaneous coronary intervention

THEMIS Baseline Characteristics

by History of PCI

	History of PCI (N=11154)	No history of PCI (N=8066)
Median age (IQR) – year	66.0 (61.0–72.0)	66.0 (61.0–72.0)
Female sex – n (%)	3436 (30.8)	2595 (32.2)
Current smoker – n (%)	1334 (12.0)	760 (9.4)
Geographic region – n (%)		
Asia and Australia	2894 (25.9)	1394 (17.3)
Central and South America	1166 (10.5)	1012 (12.5)
Europe and South Africa	5427 (48.7)	4332 (53.7)
North America	1667 (14.9)	1328 (16.5)
Hypertension – n (%)	10263 (92.0)	7513 (93.1)
Dyslipidemia – n (%)	9889 (88.7)	6864 (85.1)
Angina pectoris – n (%)	6606 (59.2)	4195 (52.0)
Multi-vessel coronary artery disease – n (%)	6310 (56.6)	5625 (69.7)
PCI with stent – n (%)	**10295 (92.3)**	–
PCI with drug-eluting stent – n (%)	**6808 (61.0%)**	–
CABG – n (%)	1346 (12.1)	4191 (52.0)
Median time since most recent PCI (IQR) – years	3.3 (1.5–6.6)	–
PAD – n (%)	905 (8.1)	782 (9.7)
Polyvascular disease – n (%)	1339 (12.0)	1240 (15.4)
Median duration of diabetes (IQR) – years	10.0 (5.1–16.0)	10.0 (5.0–16.0)
Median HbA1c at baseline (IQR) – %	7.1 (6.4–8.1)	7.1 (6.4–8.1)
Median eGFR (MDRD) at baseline (IQR) – mL/min/1.73m²	75.6 (60.9–90.1)	74.3 (60.1–89.1)

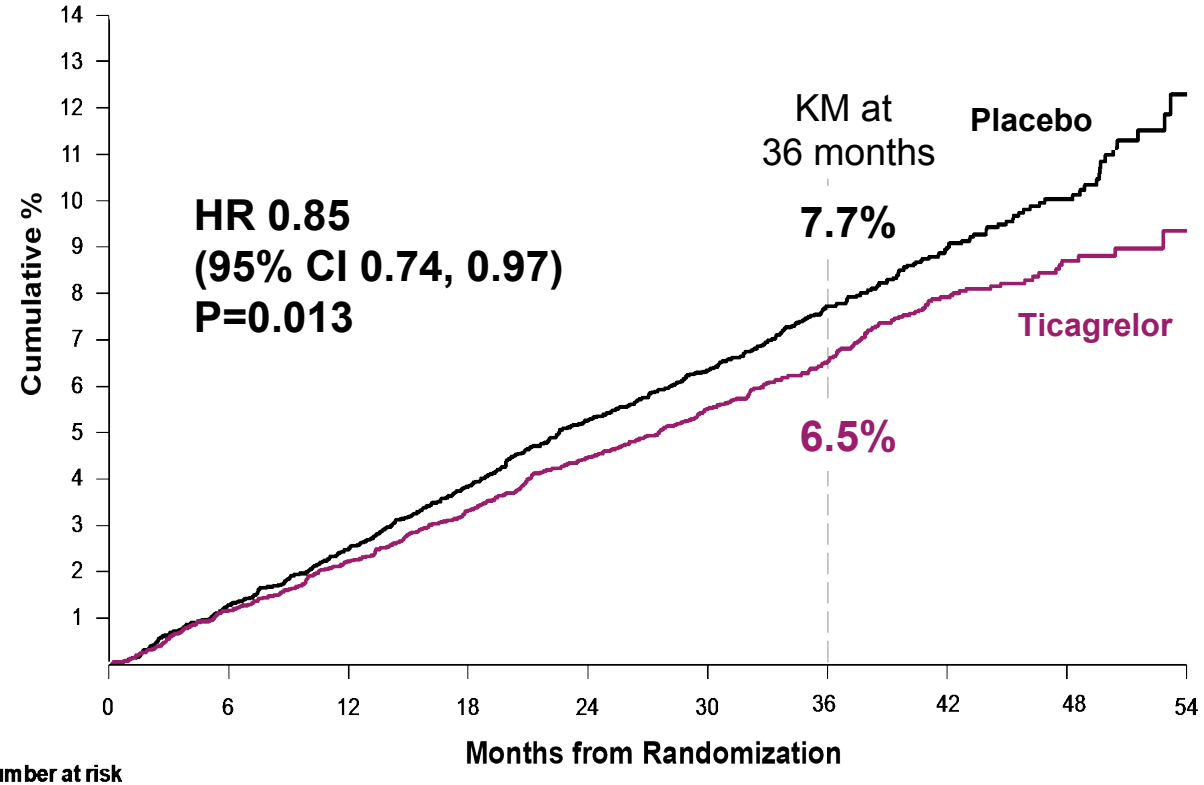
. Polyvascular disease is arterial obstructive disease involving at least 2 vascular beds where vascular bed involvement is characterized by either 1) CAD, PCI or CABG, 2) PAD, 3) carotid artery stenosis or cerebral revascularization.
CABG=coronary artery bypass grafting; CAD= coronary artery disease; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin; IQR=interquartile range; MDRD=modification of diet in renal disease; m=meters; mL=milliliters; min=minutes; N=number of patients; PAD=peripheral artery disease; PCI=percutaneous coronary intervention

Primary Efficacy Endpoint

CV death, MI or stroke (ITT)

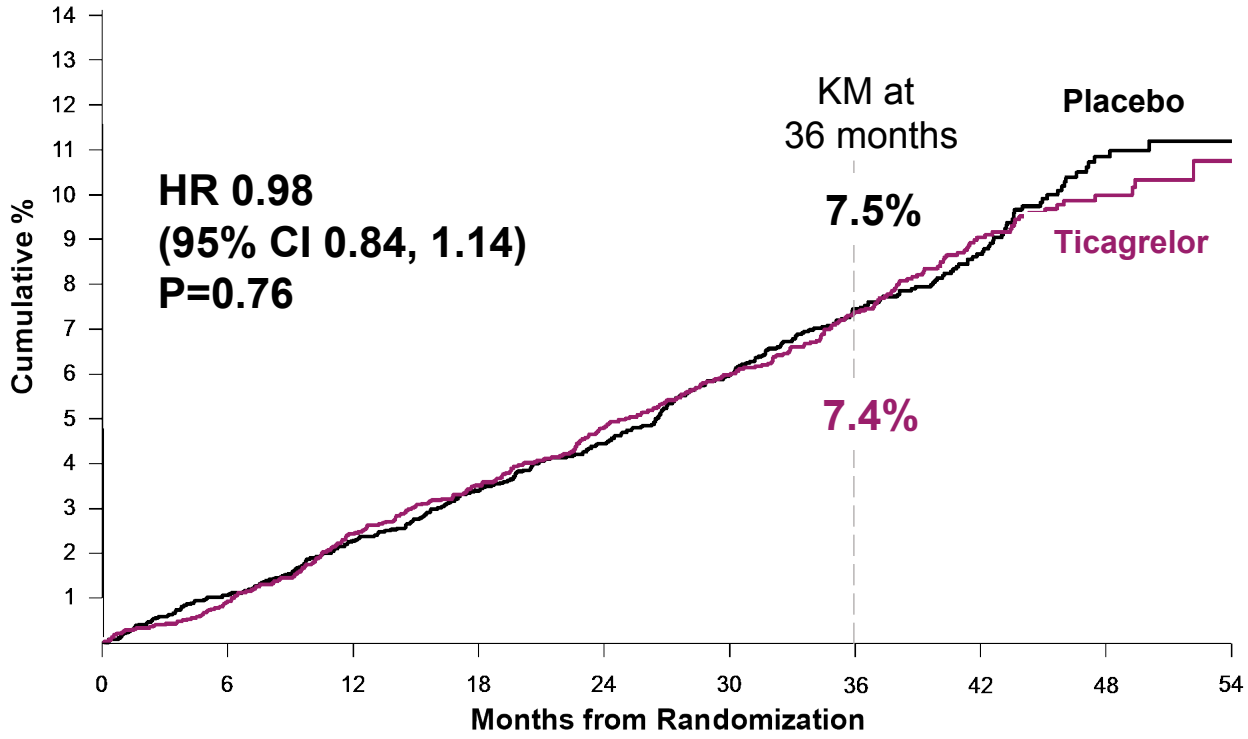
Interaction p=0.16

History of PCI



Number at risk										
Ticagrelor	5558	5436	5347	5251	5165	5054	3492	2128	984	102
Placebo	5596	5484	5387	5278	5169	5062	3476	2131	995	103

No History of PCI



Number at risk										
Ticagrelor	4061	3980	3890	3823	3744	3638	2482	1536	700	68
Placebo	4005	3930	3859	3798	3740	3630	2458	1551	690	71

CI=Confidence Interval; CV=cardiovascular; HR=hazard ratio; KM=Kaplan-Meier; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

Efficacy Endpoints

ITT Population

	Subgroup	Ticagrelor (N=9619) N	Ticagrelor (N=9619) Patients with events (%)	Placebo (N=9601) N	Placebo (N=9601) Patients with events (%)	Hazard Ratio (95% CI)	P-value	P-interaction
CV death/MI/stroke (Primary)	History of PCI	5558	404 (7.3%)	5596	480 (8.6%)	0.85 (0.74–0.97)	0.013	0.16
	No history of PCI	4061	332 (8.2%)	4005	338 (8.4%)	0.98 (0.84–1.14)	0.76	
All-cause death/MI/stroke	History of PCI	5558	494 (8.9%)	5596	603 (10.8%)	0.82 (0.73–0.93)	0.0014	0.021
	No history of PCI	4061	425 (10.5%)	4005	415 (10.4%)	1.02 (0.89–1.17)	0.80	
All-cause death/MI/stroke/ ALI/ major amputation, vascular etiology	History of PCI	5558	500 (9.0%)	5596	616 (11.0%)	0.82 (0.72–0.92)	0.0007	0.023
	No history of PCI	4061	427 (10.5%)	4005	423 (10.6%)	1.00 (0.88–1.15)	0.97	
CV death	History of PCI	5558	174 (3.1%)	5596	183 (3.3%)	0.96 (0.78–1.18)	0.68	0.41
	No history of PCI	4061	190 (4.7%)	4005	174 (4.3%)	1.08 (0.88–1.33)	0.44	
All-cause death*	History of PCI	5558	282 (5.1%)	5596	323 (5.8%)	0.88 (0.75–1.03)	0.11	0.059
	No history of PCI	4061	297 (7.3%)	4005	269 (6.7%)	1.09 (0.93–1.29)	0.29	
MI	History of PCI	5558	171 (3.1%)	5596	216 (3.9%)	0.80 (0.65–0.97)	0.027	0.42
	No history of PCI	4061	103 (2.5%)	4005	112 (2.8%)	0.91 (0.70–1.19)	0.51	
STEMI	History of PCI	5558	16 (0.3%)	5596	51 (0.9%)	0.32 (0.18–0.55)	<0.0001	0.85
	No history of PCI	4061	6 (0.1%)	4005	21 (0.5%)	0.28 (0.11–0.70)	0.007	
Stroke	History of PCI	5558	96 (1.7%)	5596	131 (2.3%)	0.74 (0.57–0.96)	0.024	0.26
	No history of PCI	4061	84 (2.1%)	4005	90 (2.2%)	0.93 (0.69–1.25)	0.62	
Coronary arterial revascularization†	History of PCI	5558	599 (10.8%)	5596	645 (11.5%)	0.93 (0.84–1.04)	0.22	0.72
	No history of PCI	4061	229 (5.6%)	4005	234 (5.8%)	0.97 (0.81–1.16)	0.75	
ALI /major amputation of vascular etiology	History of PCI	5558	7 (0.1%)	5596	15 (0.3%)	0.47 (0.19–1.15)	0.099	0.88
	No history of PCI	4061	6 (0.1%)	4005	14 (0.3%)	0.43 (0.16–1.11)	0.080	

Hazard ratios, p-values calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as the only explanatory variable. * Includes deaths based on publicly available vital status data in patients who withdrew consent. ALI=acute limb ischemia; CI=confidence interval; CV=cardiovascular; ITT=intention to treat; MI=myocardial infarction; N=number of patients; PCI=percutaneous coronary intervention; STEMI=ST segment elevation MI

Bleeding Endpoints

Safety Population

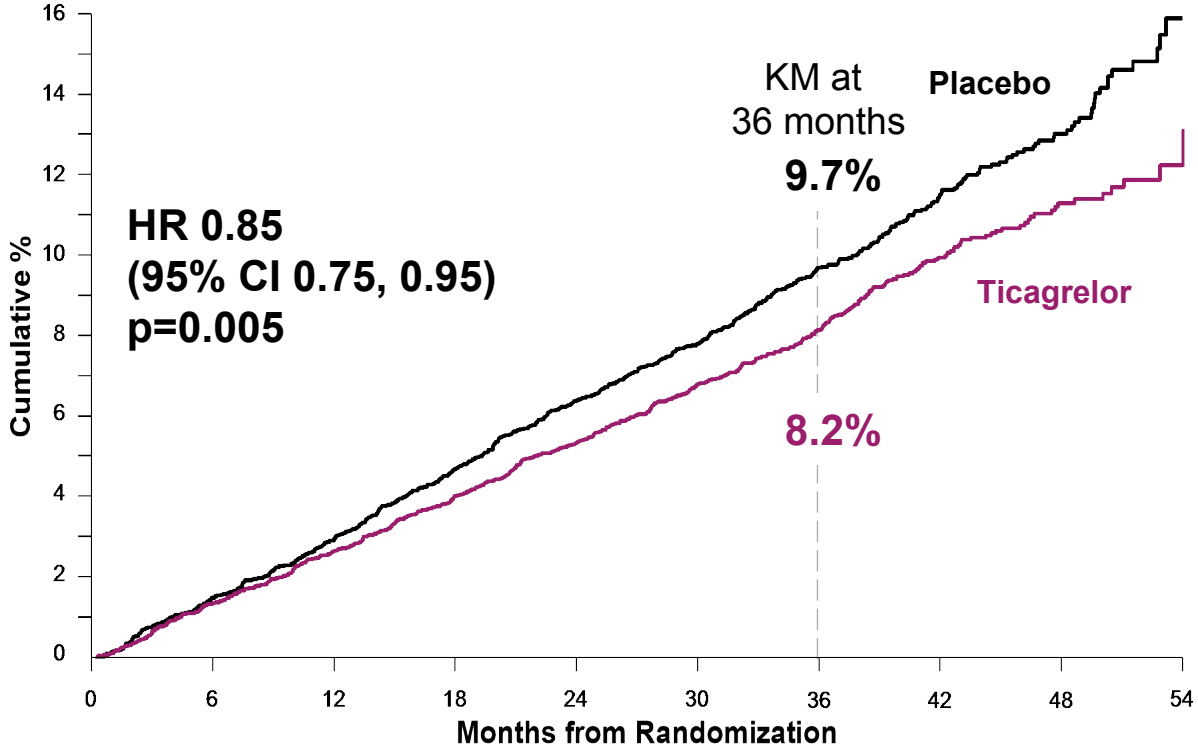
	Subgroup	Ticagrelor N	Ticagrelor Patients with events (%)	Placebo N	Placebo Patients with events (%)	Hazard Ratio (95% CI)	P-value	P-interaction
TIMI major bleeding	History of PCI	5536	111 (2.0%)	5564	62 (1.1%)	2.03 (1.48–2.76)	<0.0001	0.20
	No history of PCI	4026	95 (2.4%)	3967	38 (1.0%)	2.79 (1.91–4.06)	<0.0001	
BARC type 2, 3, 4 or 5	History of PCI	5536	632 (11.4%)	5564	313 (5.6%)	2.32 (2.02–2.65)	<0.0001	0.041
	No history of PCI	4026	453 (11.3%)	3967	176 (4.4%)	2.89 (2.43–3.44)	<0.0001	
Fatal bleeding (BARC type 5)	History of PCI	5536	6 (0.1%)	5564	6 (0.1%)	1.13 (0.36–3.50)	0.83	0.22
	No history of PCI	4026	11 (0.3%)	3967	4 (0.1%)	3.04 (0.97–9.55)	0.057	
Intracranial hemorrhage	History of PCI	5536	33 (0.6%)	5564	31 (0.6%)	1.21 (0.74–1.97)	0.45	0.036
	No history of PCI	4026	37 (0.9%)	3967	15 (0.4%)	2.74 (1.51–5.00)	0.00098	

Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as the only explanatory variable.
BARC=Bleeding Academic Research Consortium; CI=confidence interval; PCI=percutaneous coronary intervention; TIMI=thrombolysis in myocardial infarction

Net Clinical Benefit

All cause death, MI, stroke, fatal bleed or ICH (ITT)*

History of PCI

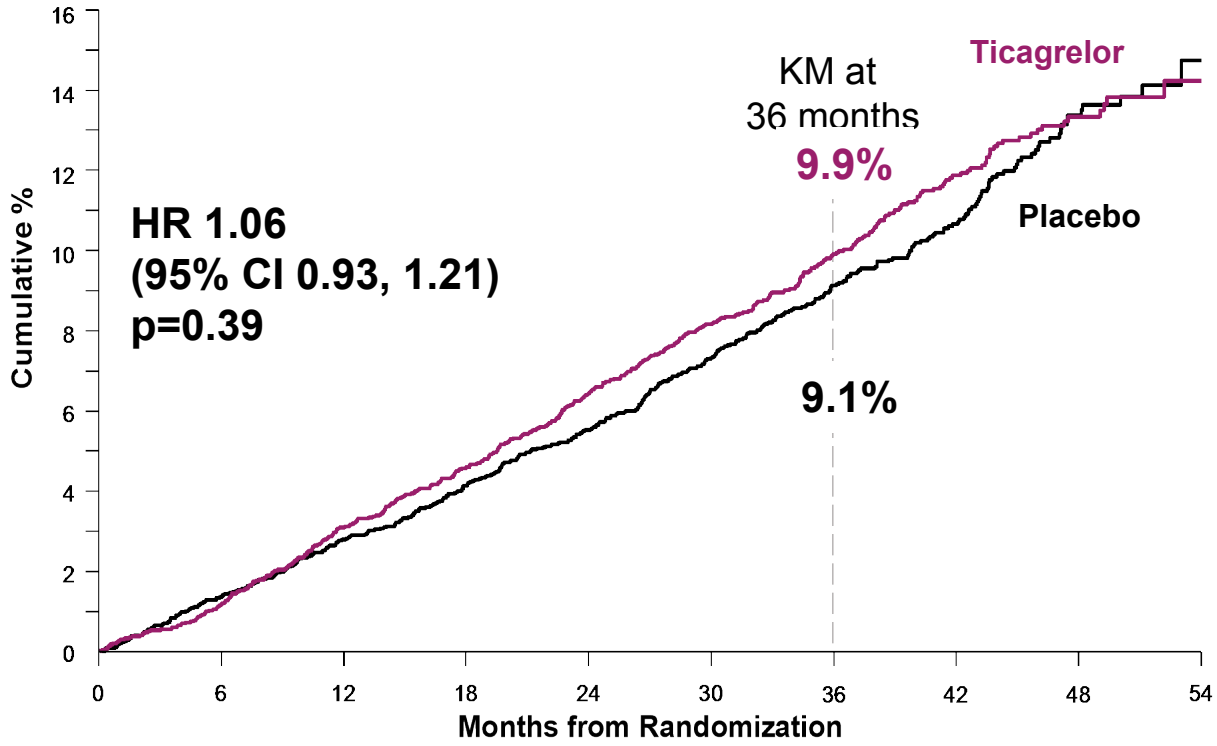


Number at risk

Ticagrelor	5558	5433	5339	5240	5153	5037	3484	2124	981	100
Placebo	5596	5480	5390	5274	5166	5060	3470	2128	993	102

Interaction p=0.012

No history of PCI



Number at risk

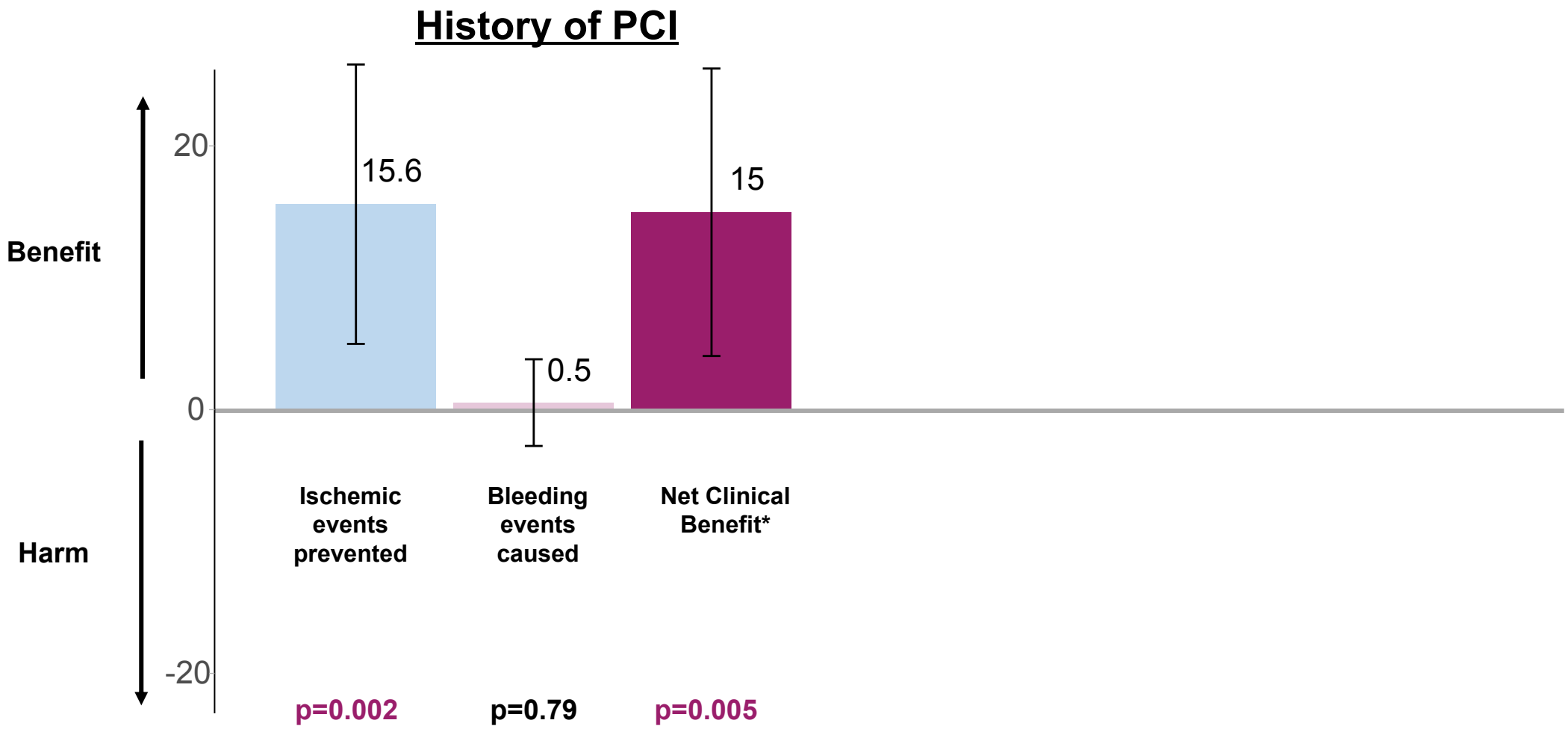
Ticagrelor	4061	3978	3881	3813	3728	3620	2471	1527	696	68
Placebo	4005	3932	3859	3799	3737	3628	2455	1549	690	70

*Prespecified definition of net clinical benefit.

CI=confidence interval; HR=hazard ratio; ICH=intracranial hemorrhage; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

Events Prevented or Caused

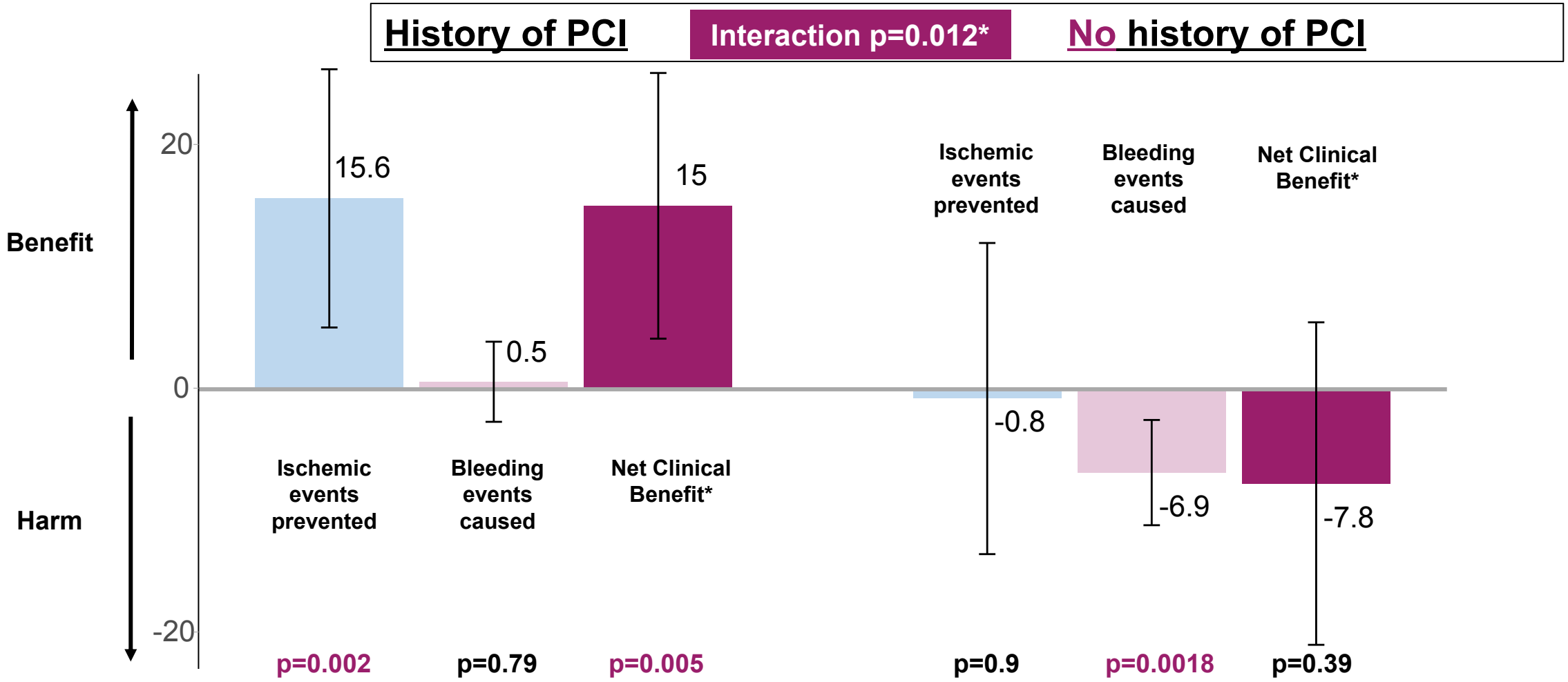
for 1000 Patients Treated 3 Years with Ticagrelor



Ischemic events: All-cause death (excluding fatal bleeds), non-fatal myocardial infarction, non-fatal ischemic stroke. Bleeding events: Fatal bleeds and non-fatal intracranial hemorrhage.
*Prespecified definition of net clinical benefit: all cause death, myocardial infarction, stroke, fatal bleed or intracranial hemorrhage (Intention to treat).
P-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model.

Events Prevented or Caused

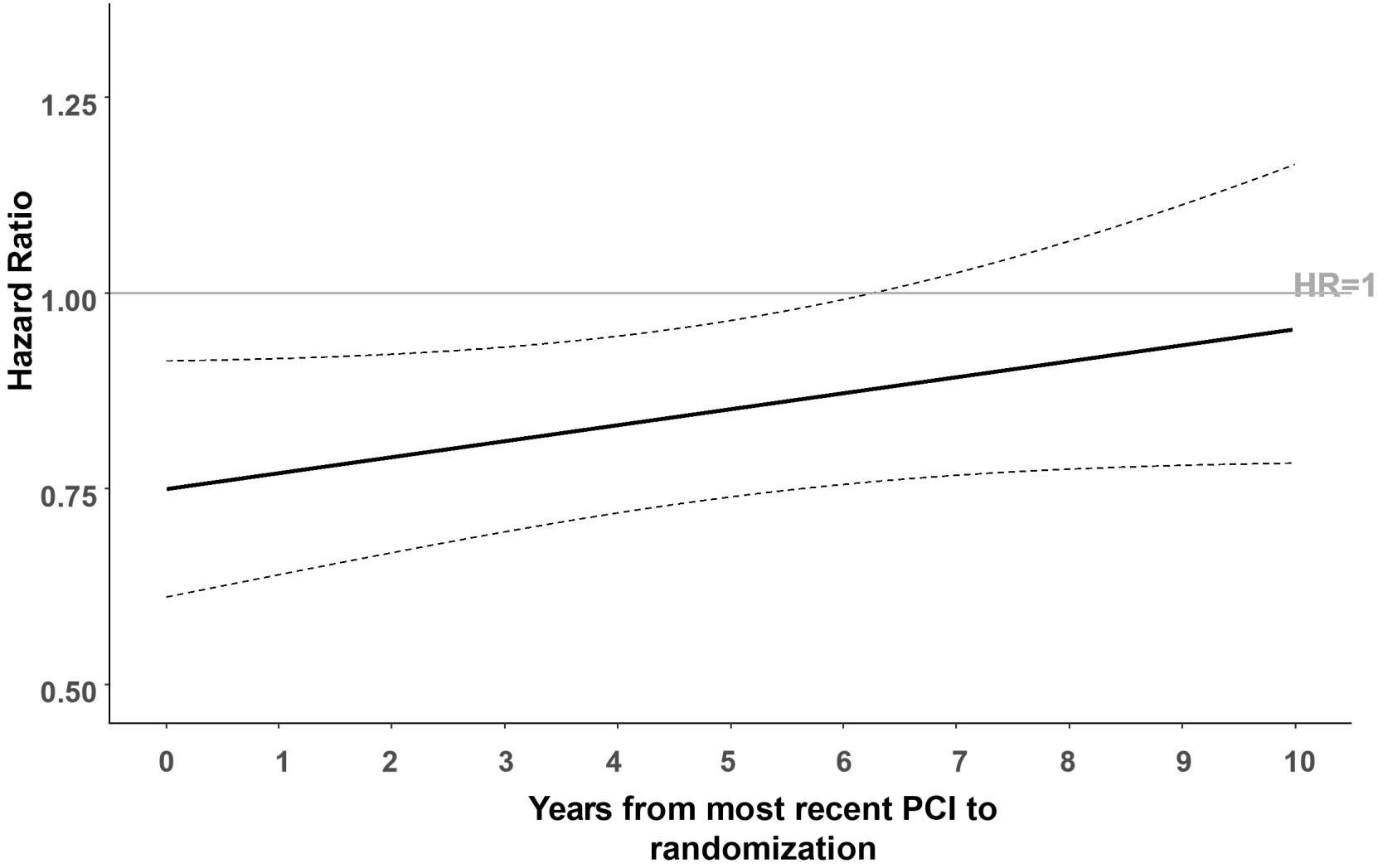
for 1000 Patients Treated 3 Years with Ticagrelor



Ischemic events: All-cause death (excluding fatal bleeds), non-fatal myocardial infarction, non-fatal ischemic stroke. Bleeding events: Fatal bleeds and non-fatal intracranial hemorrhage.
*Prespecified definition of net clinical benefit: all cause death, myocardial infarction, stroke, fatal bleed or intracranial hemorrhage (Intention to treat).
P-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model.

Benefit of Ticagrelor vs Placebo

as a Function of Time between PCI and randomization



Dotted lines signify 95% confidence interval; HR=hazard ratio; PCI=percutaneous coronary intervention

Primary and Secondary Efficacy Endpoints

On treatment

		Ticagrelor (N=9562)		Placebo (N=9531)				
	Subgroup	N	Patients with events (%)	N	Patients with events (%)	Hazard Ratio (95% CI)	p-value	p-interaction
CV death/ MI/stroke	History of PCI	5536	225 (4.1%)	5564	347 (6.2%)	**0.73 (0.62–0.87)**	**0.0003**	**0.036**
	No history of PCI	4026	200 (5.0%)	3967	233 (5.9%)	0.96 (0.80–1.16)	0.70	
All-cause death/ MI/ stroke	History of PCI	5536	242 (4.4%)	5564	378 (6.8%)	**0.73 (0.62–0.85)**	**<.0001**	**0.01**
	No history of PCI	4026	222 (5.5%)	3967	250 (6.3%)	1.00 (0.83–1.20)	0.99	
All-cause death/ MI/ stroke/ ALI/ major amputation of vascular etiology	History of PCI	5536	244 (4.4%)	5564	387 (7.0%)	**0.71 (0.61–0.84)**	**<.0001**	**0.011**
	No history of PCI	4026	224 (5.6%)	3967	258 (6.5%)	0.98 (0.82–1.17)	0.78	
CV death	History of PCI	5536	60 (1.1%)	5564	85 (1.5%)	0.81 (0.58–1.12)	0.20	0.15
	No history of PCI	4026	86 (2.1%)	3967	87 (2.2%)	1.11 (0.83–1.50)	0.48	
All-cause death*	History of PCI	5536	77 (1.4%)	5564	118 (2.1%)	**0.74 (0.56–0.99)**	**0.044**	**0.021**
	No history of PCI	4026	110 (2.7%)	3967	105 (2.6%)	1.18 (0.90–1.54)	0.22	
MI	History of PCI	5536	109 (2.0%)	5564	177 (3.2%)	0.70 (0.55–0.88)	0.003	0.21
	No history of PCI	4026	69 (1.7%)	3967	86 (2.2%)	0.90 (0.66–1.24)	0.51	
STEMI	History of PCI	5536	9 (0.2%)	5564	39 (0.7%)	0.26 (0.13–0.54)	0.0003	0.76
	No history of PCI	4026	3 (0.1%)	3967	16 (0.4%)	0.21 (0.06–0.73)	0.014	
Stroke	History of PCI	5536	65 (1.2%)	5564	99 (1.8%)	0.74 (0.54–1.02)	0.062	0.38
	No history of PCI	4026	62 (1.5%)	3967	76 (1.9%)	0.91 (0.65–1.28)	0.59	
ALI/major amputation of vascular etiology	History of PCI	5536	3 (0.1%)	5564	9 (0.2%)	0.38 (0.10–1.39)	0.14	0.65
	No history of PCI	4026	5 (0.1%)	3967	10 (0.3%)	0.55 (0.19–1.61)	0.27	

Hazard ratios and P-values calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as the only explanatory variable. Includes events with onset date at or after randomization day up to 7 days after the last dose; only patients who took at least 1 dose of study drug are included. The number of first events for the components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

*Includes deaths based on publicly available vital status data in patients who have withdrawn consent.

ALI= acute limb ischemia; CI=confidence interval; CV=cardiovascular; MI=myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation MI

Conclusions

- In stable CAD patients with diabetes and prior PCI, ticagrelor added to aspirin reduced cardiovascular death, MI, and stroke, although with increased major bleeding. Ticagrelor provided a favorable net clinical benefit in patients with prior PCI.

- This suggests that long term therapy with ticagrelor in addition to aspirin is a new option for patients with diabetes and a history of PCI who have tolerated antiplatelet therapy, have high ischemic risk, and low bleeding risk.

Full details available at www.thelancet.com

PARTHENON
THEMIS

THE LANCET

Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial

Deepak L Bhatt, Philippe Gabriel Steg*, Shamir R Mehta, Lawrence A Leiter, Tabassome Simon, Kim Fox, Claes Held, Marielle Andersson, Anders Himmelmann, Wilhelm Ridderstråle, Jersey Chen, Yang Song, Rafael Diaz, Shinya Goto, Stefan K James, Kausik K Ray, Alexander N Parkhomenko, Mikhail N Kosiborod, Darren K McGuire, Robert A Harrington, on behalf of the THEMIS Steering Committee and Investigators†*