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

Presented by Deepak L. Bhatt, MD, MPH

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on behalf of the THEMIS Steering Committee and Investigators

*co-Chairs and co-Principal Investigators of THEMIS

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TICAGRELOR IN STABLE CAD AND T2D TREATED WITH ASA

PARTHENON THEMIS

Methods

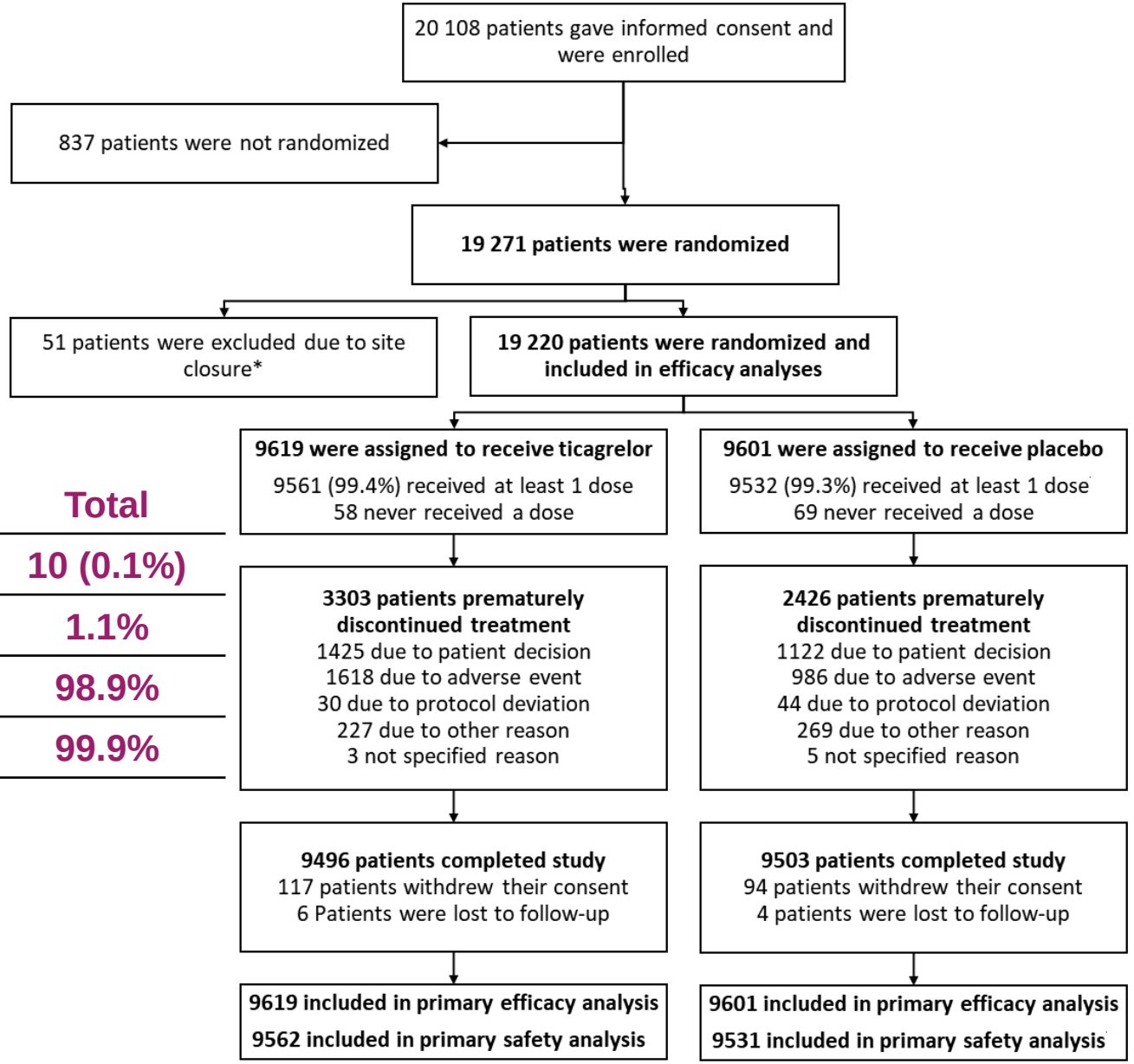
- THEMIS is a randomized, double-blind, placebo-controlled trial of ticagrelor versus placebo, on top of low-dose (75 to 150 mg) aspirin.
- Patients ≥ 50 years with type 2 diabetes receiving anti-hyperglycemic medications for at least 6 months, and with stable CAD (i.e., history of PCI, CABG, or angiographic 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.

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.

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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/1.73m^2	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

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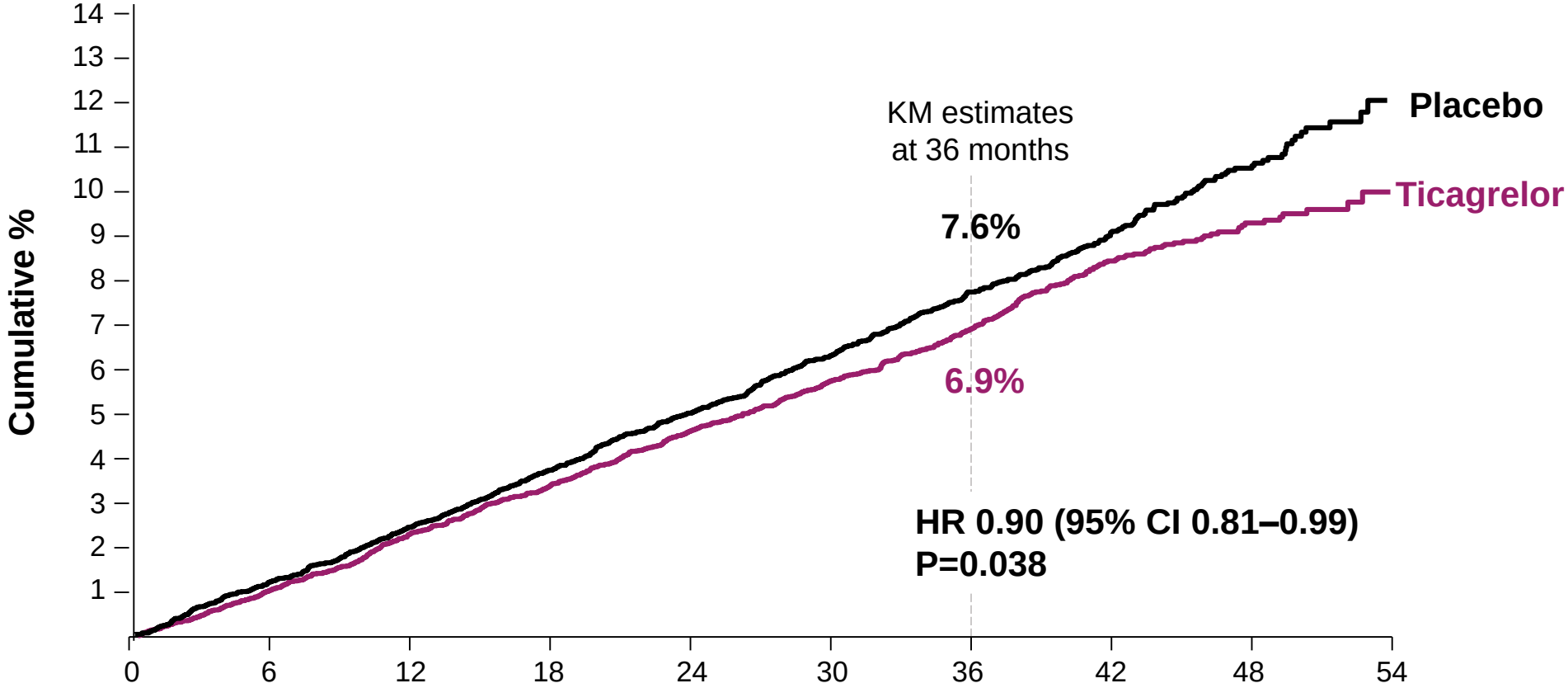
Primary Composite Endpoint

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

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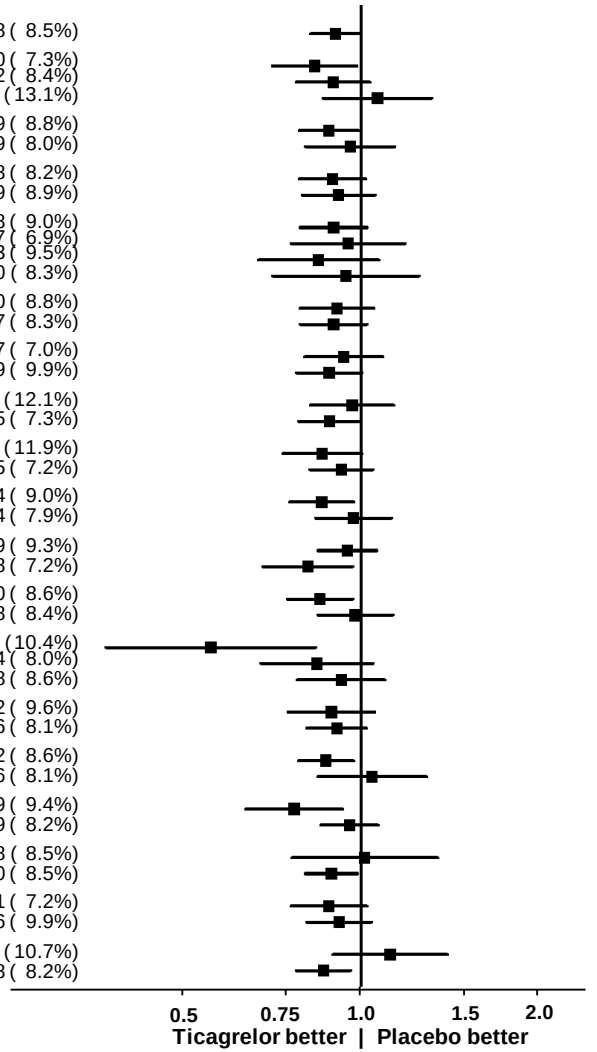
Primary Efficacy Endpoint – Subgroups

	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
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

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

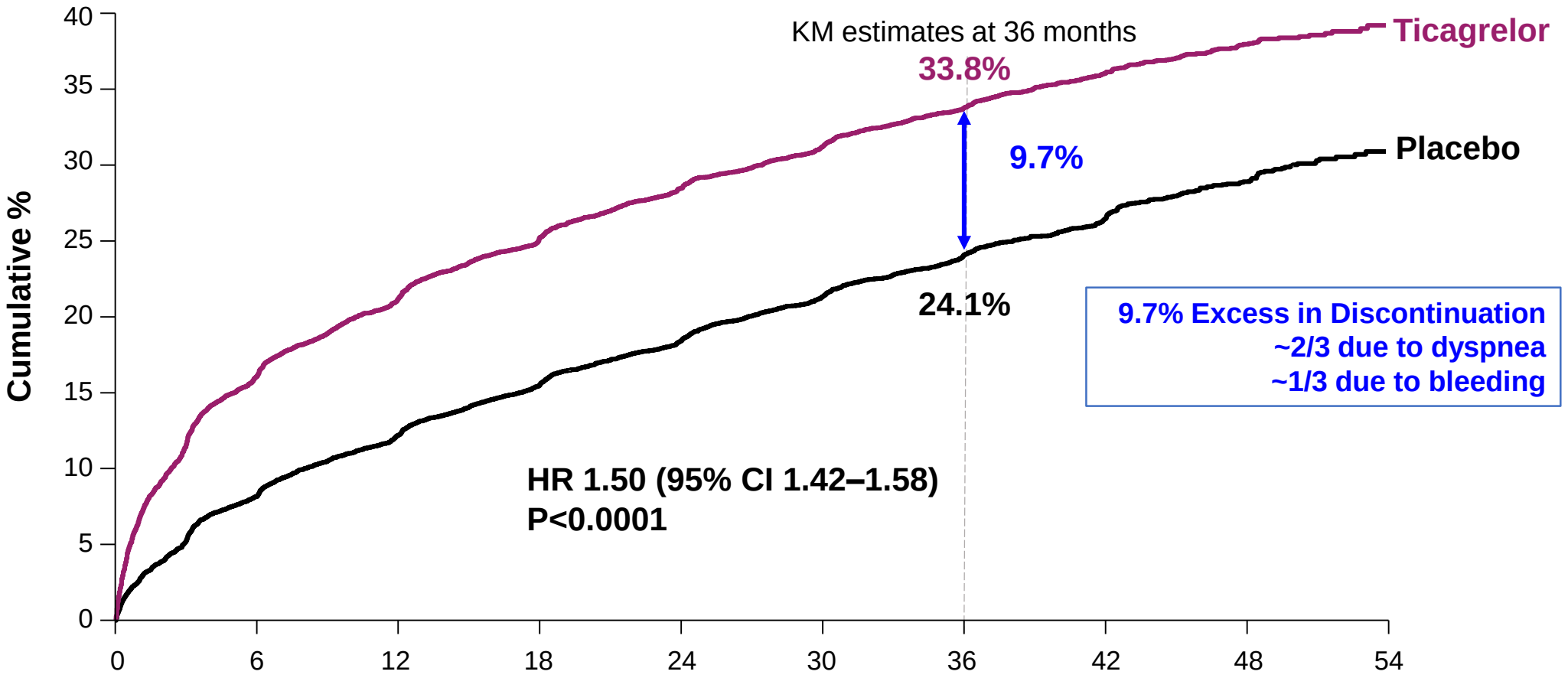
Bleeding Outcomes

	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

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

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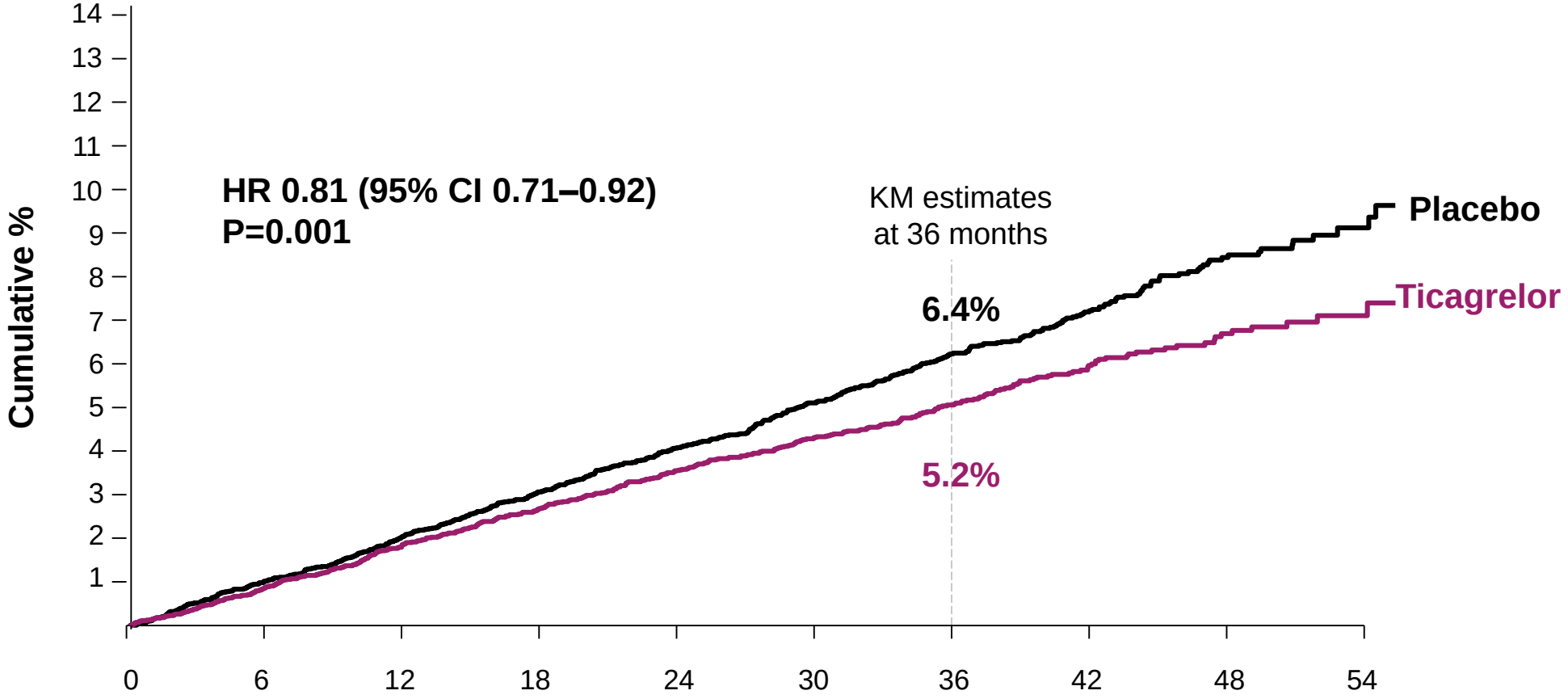
Primary Composite Endpoint

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

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

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

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
  - 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**!

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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

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

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 Ph. Gabriel Steg, MD

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on behalf of the THEMIS Steering Committee and Investigators

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TICAGRELOR IN STABLE CAD AND T2D TREATED WITH ASA

PARTHENON THEMIS

Methods

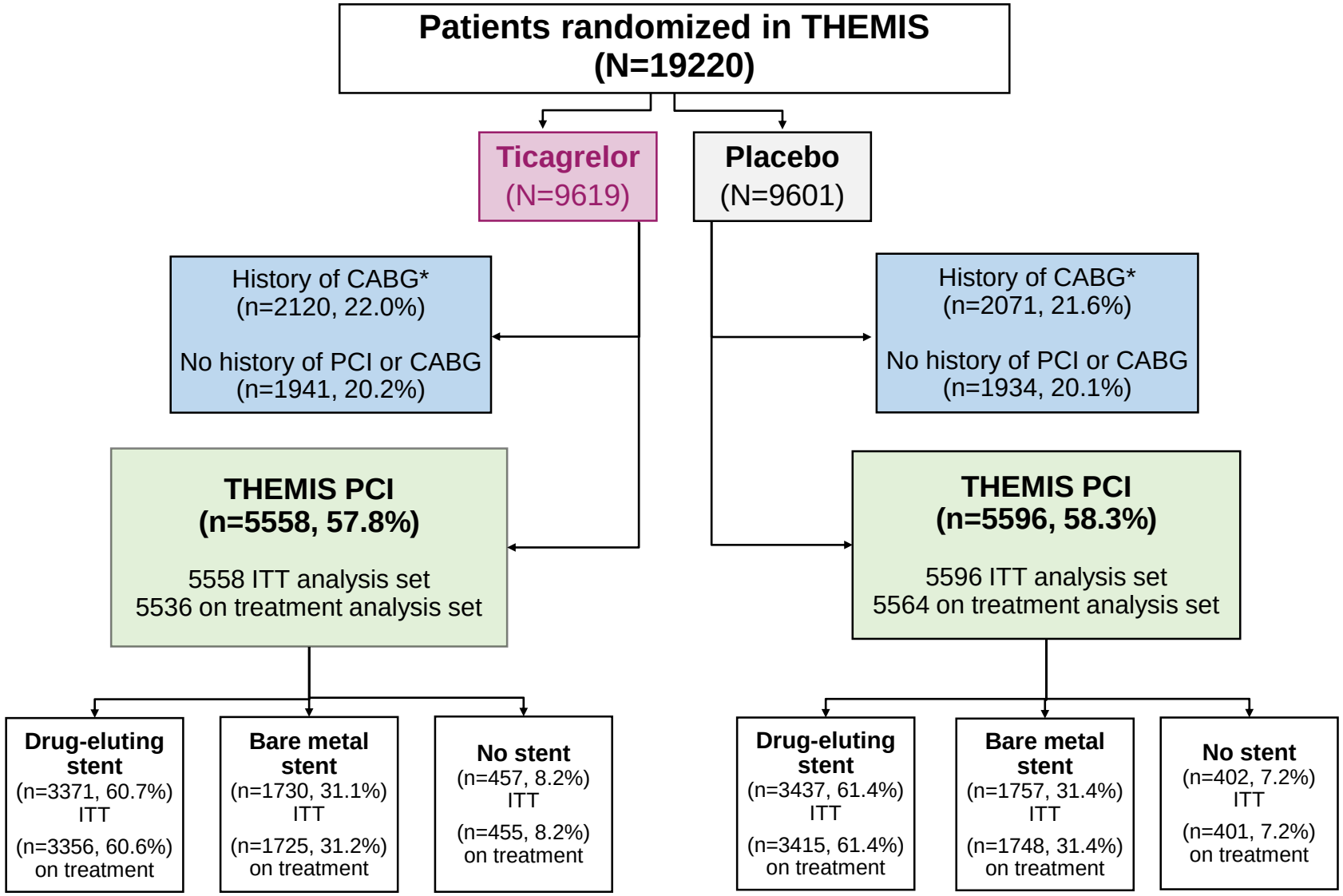
- In THEMIS, ticagrelor produced a 10% relative risk reduction (HR 0.90, 95% CI 0.81-0.99, P=0.038) over placebo in the primary endpoint of CV death, MI, or stroke in 19,220 patients with CAD and type 2 diabetes mellitus.

- 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

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

Study Flow



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

Bhatt DL, Steg PG, et al. *Lancet* 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

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

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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	
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

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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

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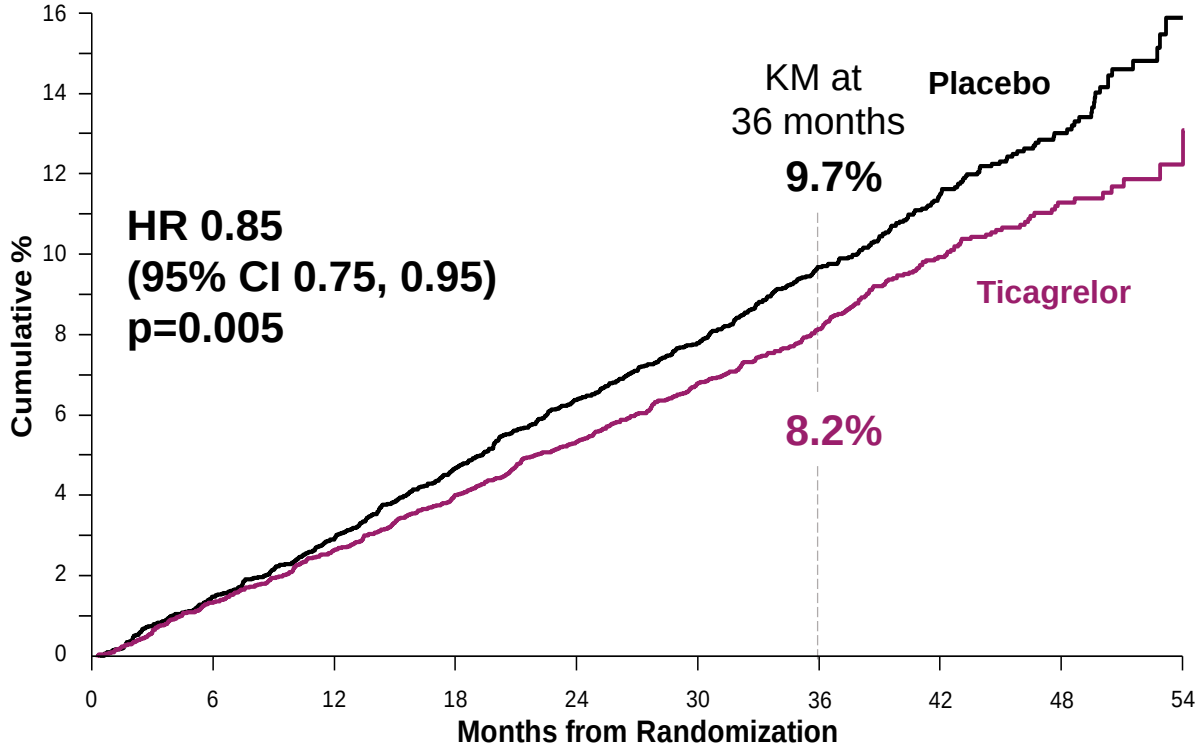
Net Clinical Benefit

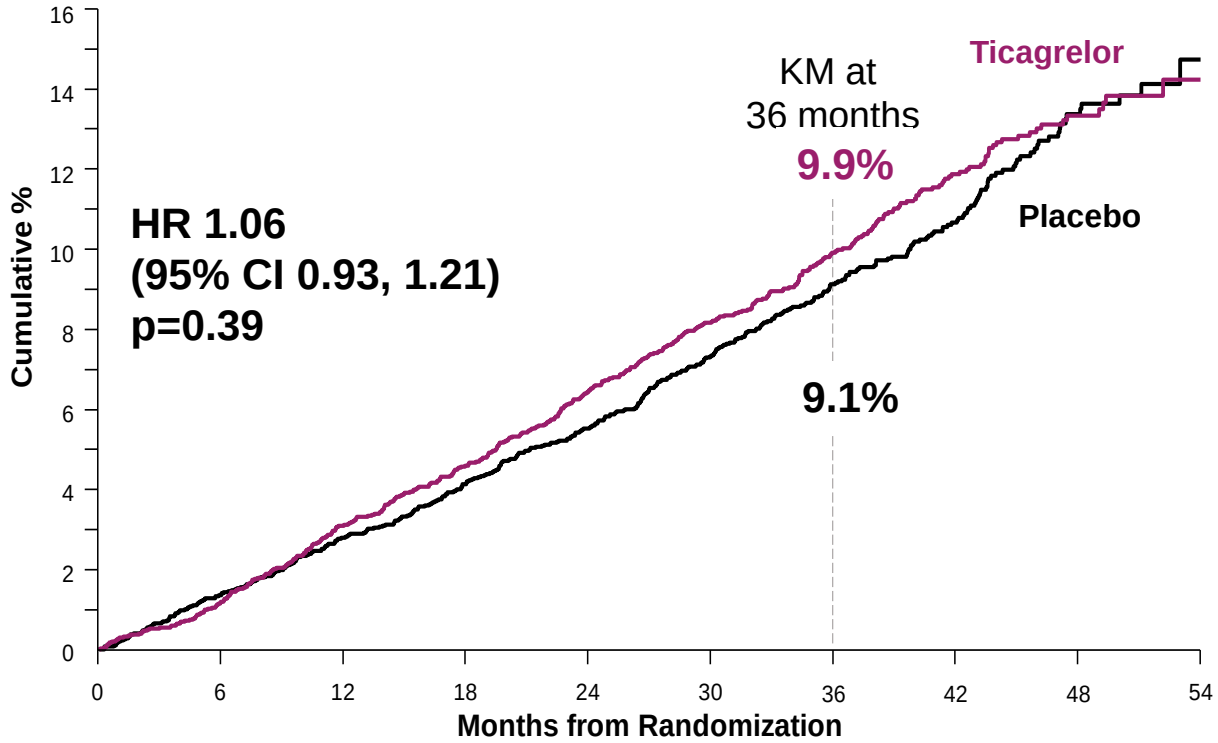
All cause death, MI, stroke, fatal bleed, or ICH (ITT)*

History of PCI

Interaction p=0.012

No 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

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

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