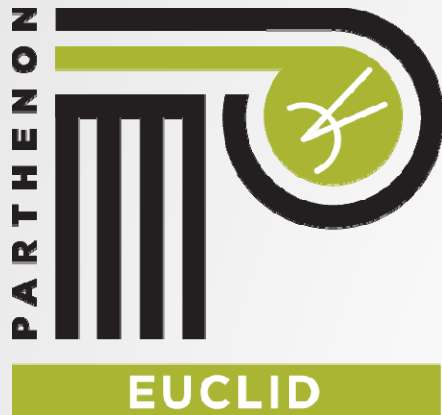




Manesh R. Patel, MD on behalf of the
EUCLID Executive and Steering Committee and Investigators

EUCLID Trial Primary Results
Late Breaking Clinical Trial Presentation
American Heart Association 2016
November 13th 2016



Disclosures

Member of Executive Committee: EUCLID trial

Research Support: AstraZeneca, CSI, HeartFlow, Janssen Research & Development, Johnson & Johnson, Maquet, Medtronic, National Heart, Lung, & Blood Institute

Consulting/Advisory Board: AstraZeneca, CSI, Genzyme, Bayer Corporation, Janssen Research & Development, Medtronic, Merck & Co.

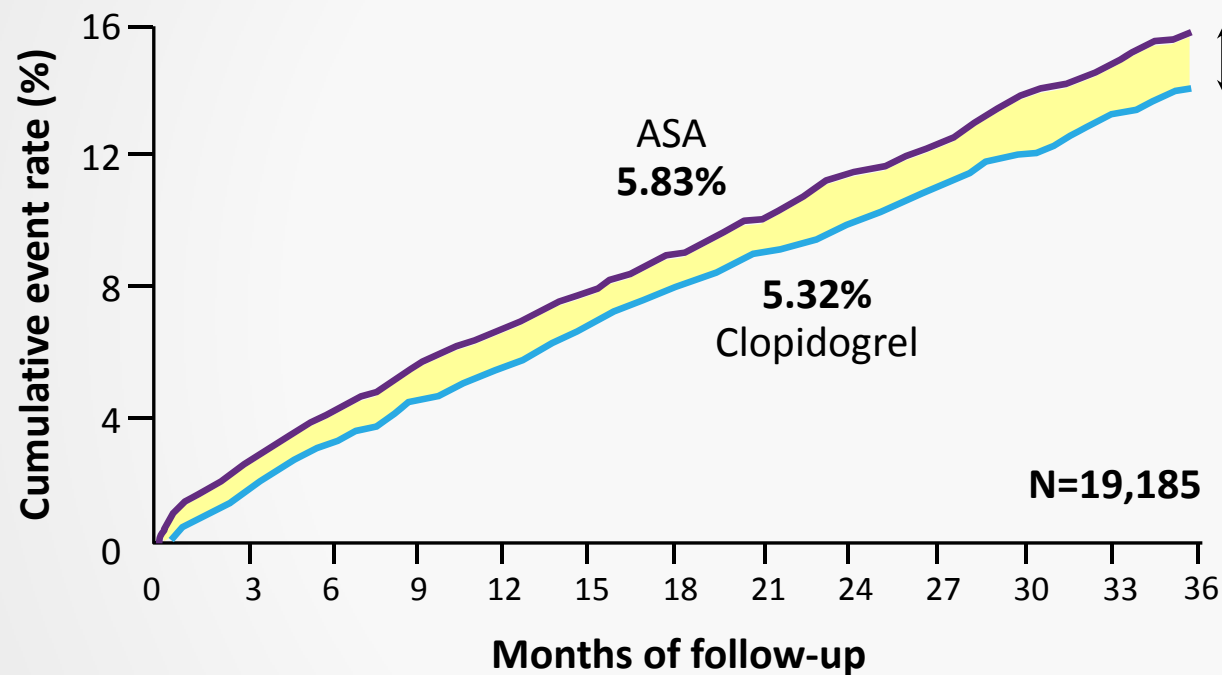
EUCLID was sponsored by AstraZeneca

Peripheral Artery Disease of the Lower Extremity



- Peripheral artery disease (PAD) is considered a systemic manifestation of atherosclerosis affecting over 200 million people worldwide.¹
- PAD is associated with both cardiovascular and limb morbidity and mortality.
- **Antiplatelet therapy is recommended for all patients with PAD.**

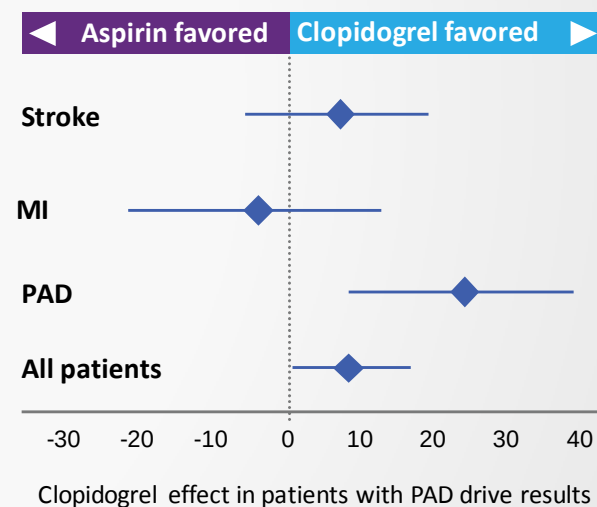
Efficacy of Clopidogrel vs. Aspirin for MI, Ischemic Stroke, or Vascular Death



ASA=aspirin.
Mean follow-up=1.91 years.
*ITT analysis.

CAPRIE Steering Committee. Lancet. 1996;348:1329-1339.

8.7%* P=0.043
Overall relative risk reduction



Background Conclusions

- PAD is common with a high risk for cardiovascular (CV) events.
- Clopidogrel is superior to aspirin in PAD and indicated.
- Ticagrelor is an antiplatelet agent that reduces CV death, myocardial infarction (MI), or stroke compared to clopidogrel in patients with acute coronary syndrome (ACS) and has proven benefits as chronic therapy in patients with prior MI.

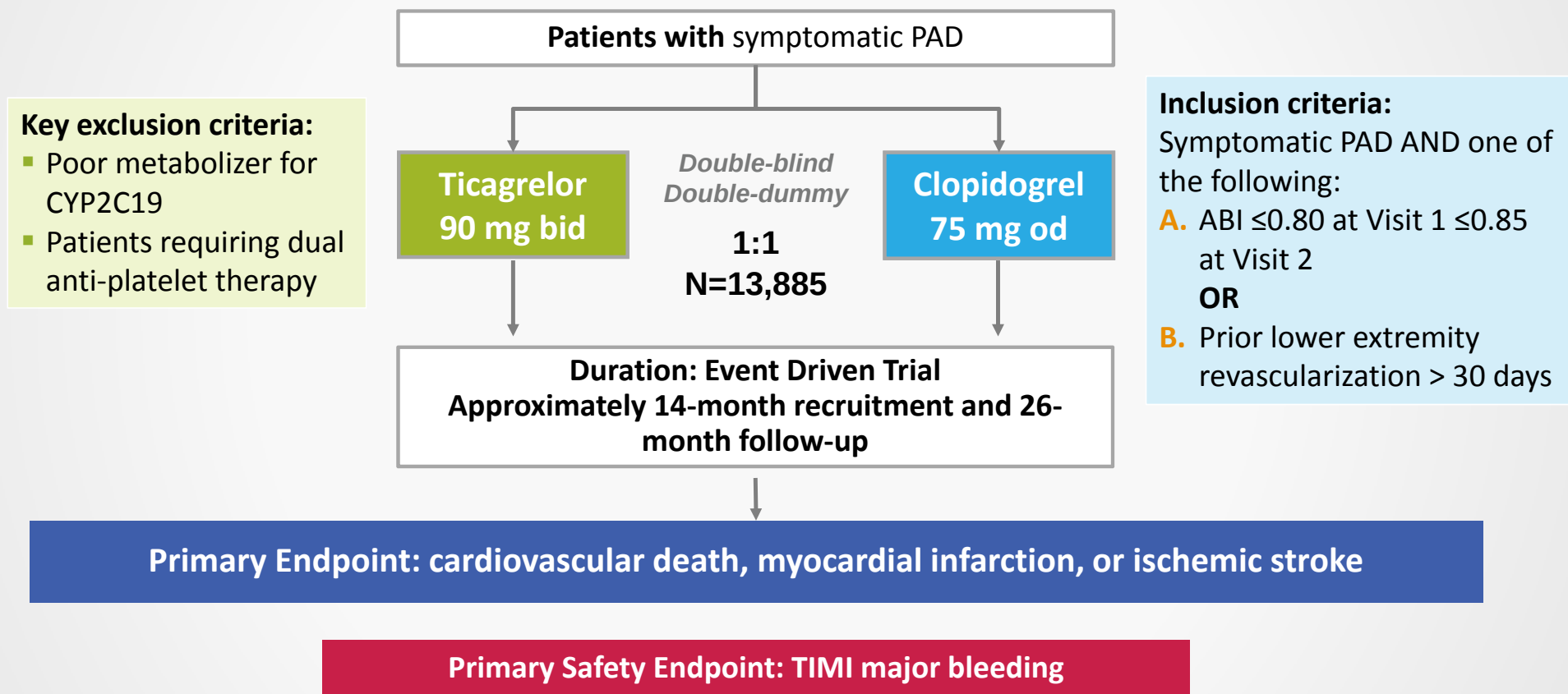
Primary Objective — EUCLID



The **primary objective** of the study is to determine if long-term monotherapy treatment with ticagrelor vs. clopidogrel reduces the rate of the composite of **CV death, MI, or ischemic stroke** in patients with symptomatic PAD.

First ordered **secondary endpoint**—primary endpoint plus acute limb ischemia (ALI) requiring hospitalization.

EUCLID Study Design



Global Participation

13,855 patients

811 sites

28 countries

NORTH AMERICA: 3044 PATIENTS

US: 2614

Canada: 430

LATIN AMERICA: 1740 PATIENTS

Argentina: 567

Brazil: 643

Chile: 161

Mexico: 369

EUROPE: 7499 PATIENTS

Bulgaria: 679

Czech Rep: 723

France: 371

Germany: 623

Hungary: 580

Italy: 285

Netherlands: 234

Poland: 609

Romania: 508

Russian Fed: 935

Slovakia: 419

Spain: 323

Sweden: 240

Turkey: 137

Ukraine: 536

UK: 297

ASIA-PACIFIC: 1602 PATIENTS

China: 423

Japan: 420

Philippines: 128

S. Korea: 214

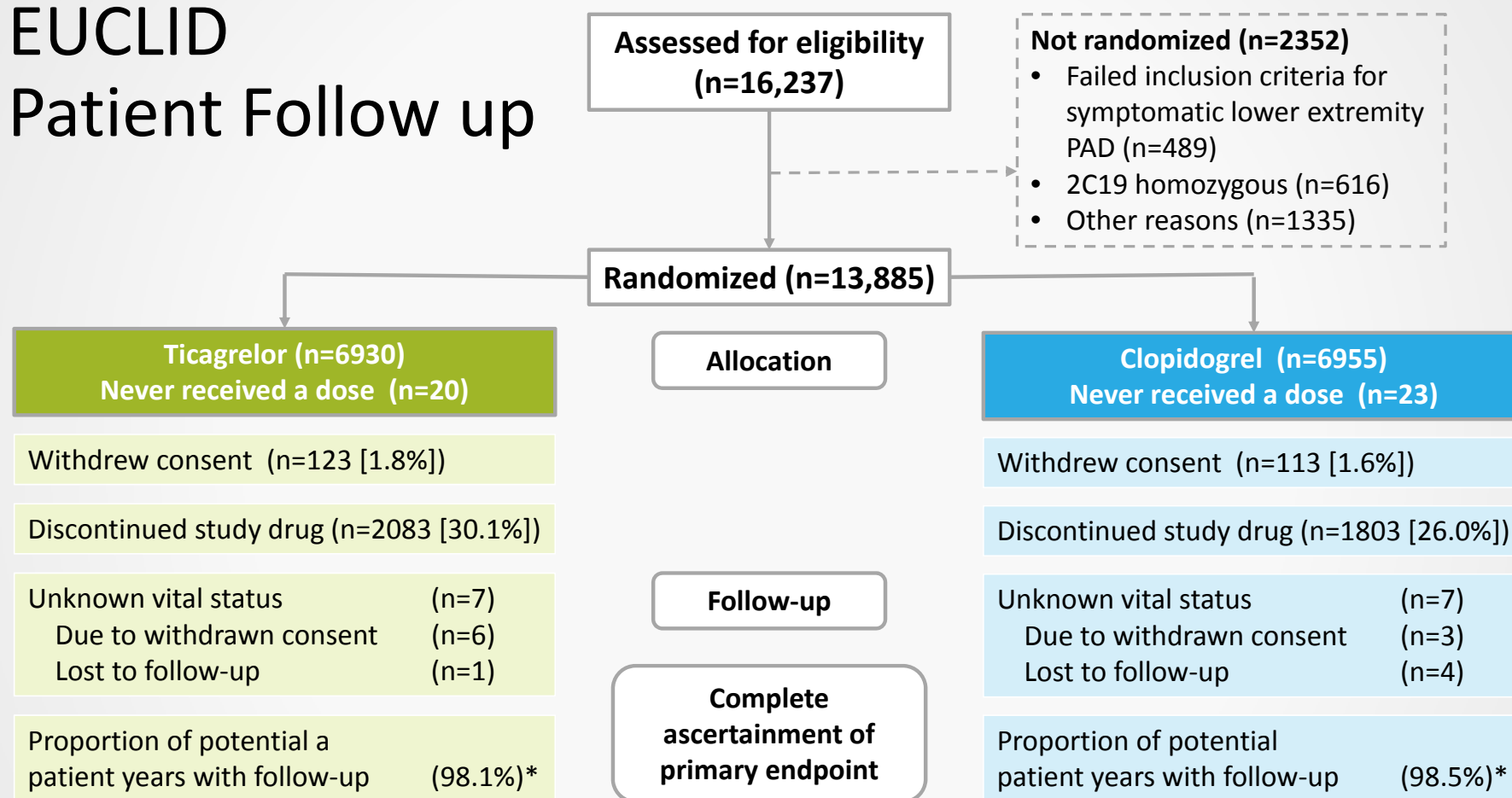
Thailand: 122

Vietnam: 295



EUCLID

Patient Follow up



*Time from randomization until first primary event, censoring or death, divided by total time until first primary event, death or primary analysis censoring date.

Baseline Characteristics



	Ticagrelor (N=6930)	Clopidogrel (N=6955)
Age , median, (25th, 75th), years	66 (60, 72)	66 (60, 73)
Female sex , no. (%)	1908 (27.5)	1980 (28.5)
Weight , median (25th, 75th), kg	76.4 (66, 88)	76.5 (66, 88)
Tobacco use , no. (%)		
Never smoked	1481 (21.4)	1503 (21.6)
Current smoker	2125 (30.7)	2164 (31.1)
Former smoker	3281 (47.3)	3249 (46.7)

Medical History



	Ticagrelor (N=6930)	Clopidogrel (N=6955)
History of stroke, no. (%)	576 (8.3)	567 (8.2)
History of TIA, no. (%)	279 (4.0)	228 (3.3)
CAD, no. (%)	2019 (29.1)	2013 (28.9)
MI, no. (%)	1242 (17.9)	1280 (18.4)
Number of vascular beds[¶], no. (%)		
1	3874 (55.9)	3930 (56.5)
2	2333 (33.7)	2355 (33.9)
3	723 (10.4)	670 (9.6)
Diabetes mellitus (Type I & II), no. (%)	2639 (38.1)	2706 (38.9)
Hypertension, no. (%)	5437 (78.5)	5420 (77.9)
Hyperlipidemia, no. (%)	5229 (75.5)	5251 (75.5)

|| CAD is defined as prior MI, prior PCI, or prior CABG.

¶ A vascular bed is defined as either PAD, prior CAD (prior MI, prior PCI, or prior CABG), or prior cerebrovascular disease (prior stroke, prior TIA, prior carotid artery stenosis or prior carotid revascularization).

ABI indicates ankle-brachial index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation; TBI, toe-brachial index; TIA, transient ischemic attack.

PAD History—Inclusion Criteria for Randomization



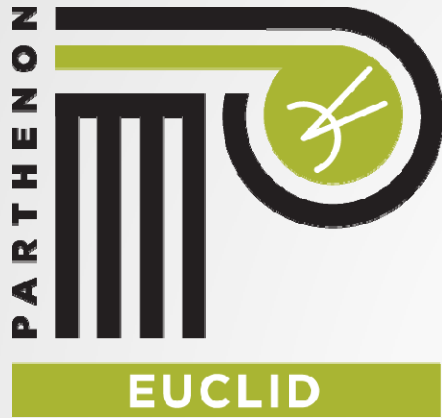
	Ticagrelor (N=6930)	Clopidogrel (N=6955)
Prior revascularization, no. (%)	3923 (56.6)	3952 (56.8)
ABI value, mean ($\pm$ SD)	0.78 ($\pm$ 0.23)	0.78 ($\pm$ 0.23)
ABI/TBI criterion, no. (%)[*]	3007 (43.4)	3003 (43.2)
ABI value, mean ($\pm$ SD)	0.63 ($\pm$ 0.15)	0.63 ($\pm$ 0.15)
TBI value, mean ($\pm$ SD)	0.49 ($\pm$ 0.14)	0.55 ($\pm$ 0.27)
Limb symptoms, no. (%)[†]		
Asymptomatic [‡]	1309 (18.9)	1292 (18.6)
Mild/moderate claudication	3674 (53.0)	3736 (53.7)
Severe claudication	1620 (23.4)	1608 (23.1)
Rest pain	186 (2.7)	192 (2.8)
Minor tissue loss (ischemic ulceration not exceeding ulcer of the digits of the foot)	107 (1.5)	100 (1.4)
Major tissue loss (severe ischemic ulcers or frank gangrene)	33 (0.5)	25 (0.4)
Prior major amputation above the ankle, no. (%)[§]	161 (2.3)	178 (2.6)

^{*}ABI (or TBI) is calculated from site-reported measurements in the CRF, and is calculated as the average of enrollment and randomization ABI (or TBI) measurements, where at each visit, the lowest of the right and left ABIs (or TBIs) is selected. Of those included based on ABI/TBI criteria, 82 (1.2%) patients in the ticagrelor group and 93 (1.3%) in the clopidogrel group were based on TBI criterion.

[†]Classified using Rutherford classification. Data missing for 1 patient in the ticagrelor group and 2 patients in the clopidogrel group.

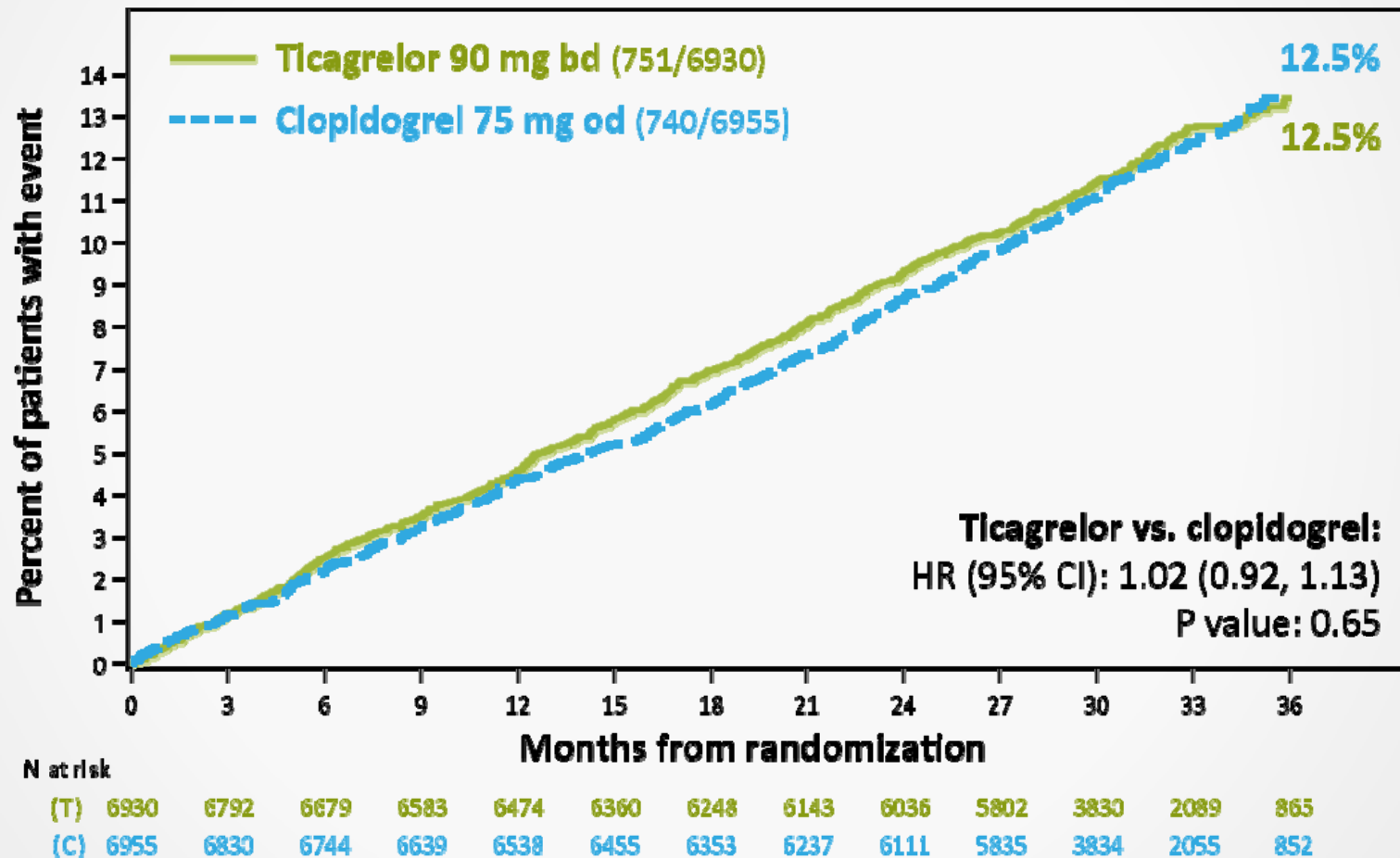
[‡]Symptom status at time of randomization (patients with a prior revascularization may have been asymptomatic at baseline).

[§] Major amputation included above the knee and transtibial amputations.



Overall Primary Trial Results

Primary Efficacy Endpoint (CV Death, MI, or Ischemic Stroke)



Efficacy Outcomes



	Ticagrelor (N=6930)	Clopidogrel (N=6955)	HR (95% CI)	P Value
Primary outcome: Composite of CV death, MI, or ischemic stroke, no. (%)	751 (10.8)	740 (10.6)	1.02 (0.92–1.13)	0.65
CV death, no. (%)	363 (5.2)	343 (4.9)	1.07 (0.92–1.23)	0.40
MI, no. (%)	349 (5.0)	334 (4.8)	1.06 (0.91–1.23)	0.48
Ischemic stroke, no. (%)	131 (1.9)	169 (2.4)	0.78 (0.62–0.98)	0.03
Key secondary efficacy outcome: Composite of CV death, MI, ischemic stroke, or ALI requiring hospitalization, no. (%)	839 (12.1)	833 (12.0)	1.02 (0.92–1.12)	0.74

ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Other Secondary Outcomes



	Ticagrelor (N=6930)	Clopidogrel (N=6955)	HR (95% CI)	P Value
All-cause mortality , no. (%)	628 (9.1)	635 (9.1)	0.99 (0.89–1.11)	0.91
Composite of CV death, MI, or all-cause stroke (ischemic or hemorrhagic), no. (%)	766 (11.1)	759 (10.9)	1.02 (0.92–1.13)	0.72
Hospitalization for ALI , no. (%)	117 (1.7)	115 (1.7)	1.03 (0.79–1.33)	0.85
Lower extremity revascularization , no. (%)	846 (12.2)	892 (12.8)	0.95 (0.87–1.05)	0.30
Composite of all revascularizations (coronary and peripheral [limb, mesenteric, renal, carotid, or other]), no. (%)	1211 (17.5)	1250 (18.0)	0.97 (0.90–1.05)	0.46

ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

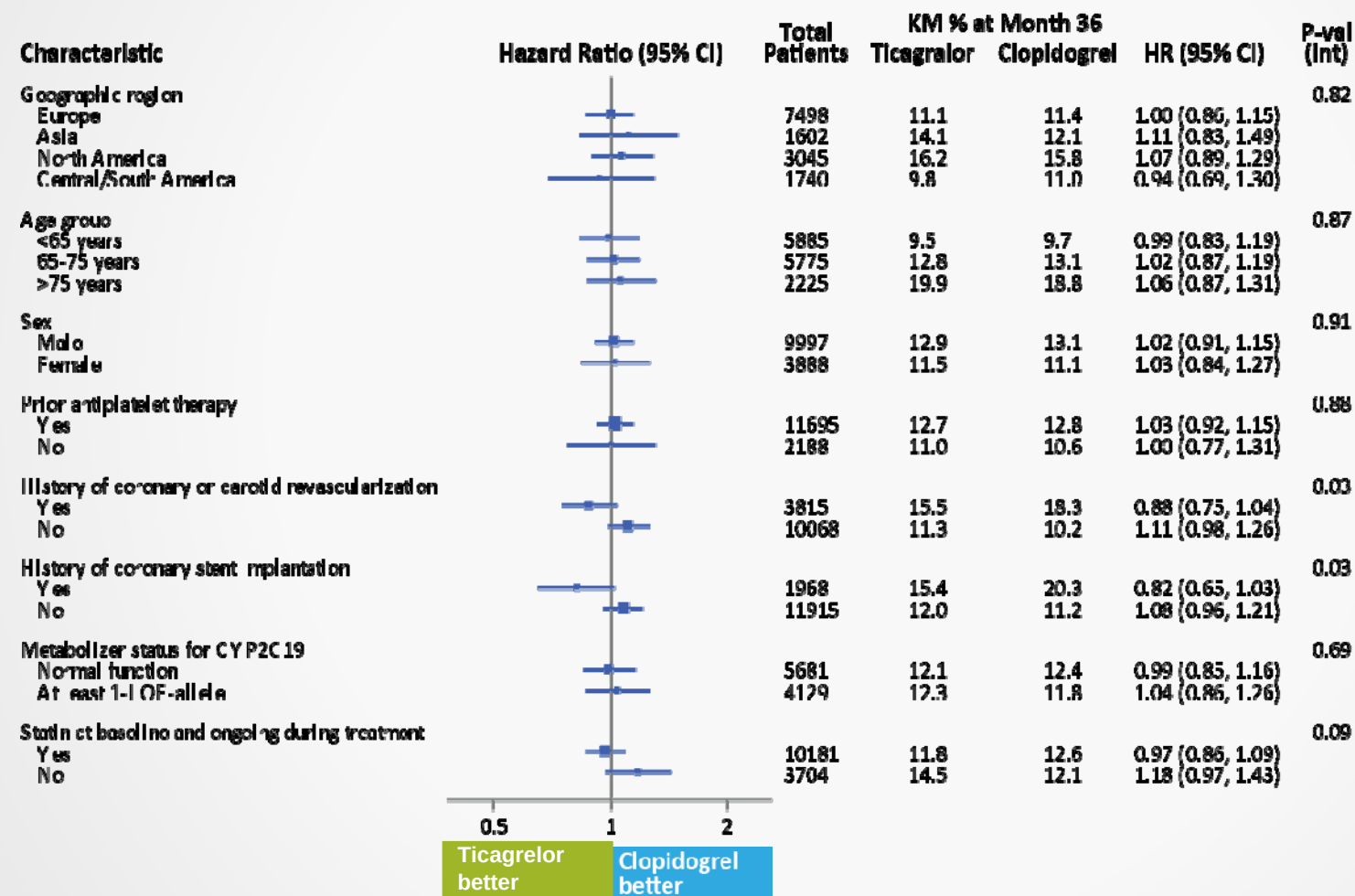
Safety Outcomes



	Ticagrelor (N=6910)	Clopidogrel (N=6932)	HR (95% CI)	P Value
Primary safety outcome:				
TIMI major bleeding, no. (%)	113 (1.6)	109 (1.6)	1.10 (0.84–1.43)	0.49
Intracranial bleeding	34 (0.5)	34 (0.5)	1.06 (0.66–1.70)	0.82
Fatal bleeding	10 (0.1)	20 (0.3)	0.53 (0.25–1.13)	0.10
TIMI minor bleeding, no. (%)	84 (1.2)	67 (1.0)	1.32 (0.96–1.83)	0.09
Adverse events leading to discontinuation, no. (%)	1063 (15.4)	766 (11.1)		
Dyspnea leading to discontinuation	330 (4.8)	52 (0.8)		<0.001
Bleeding leading to discontinuation	168 (2.4)	112 (1.6)		<0.001

CI indicates confidence interval; HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction.

Primary Efficacy Endpoint



Conclusions



In patients with symptomatic peripheral artery disease:

- Ticagrelor was not superior to clopidogrel for the reduction of cardiovascular events;
- Major bleeding occurred at similar rates in patients treated with ticagrelor and clopidogrel.

Clinical Interpretation and Future Directions



- Limited antithrombotic medical options for patients with PAD.
- The active comparator in this trial, clopidogrel monotherapy, is effective antiplatelet therapy in PAD.
 - Ticagrelor has comparable efficacy and safety
- Caution extrapolating evidence from coronary artery disease patients to peripheral artery disease:
 - Individual studies in PAD patients are needed.

EUCLID Study Committees



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Colin Baigent
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Peter Held (AstraZeneca)
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Christopher White, Alan Hirsch, **Vietnam:** Dinh Thi Thu Huong

Thank you to the Team and Patients who agreed to participate!





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ORIGINAL ARTICLE

Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease

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