P2Y12 IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE , EUCLID TRIAL

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A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease (EUCLID)

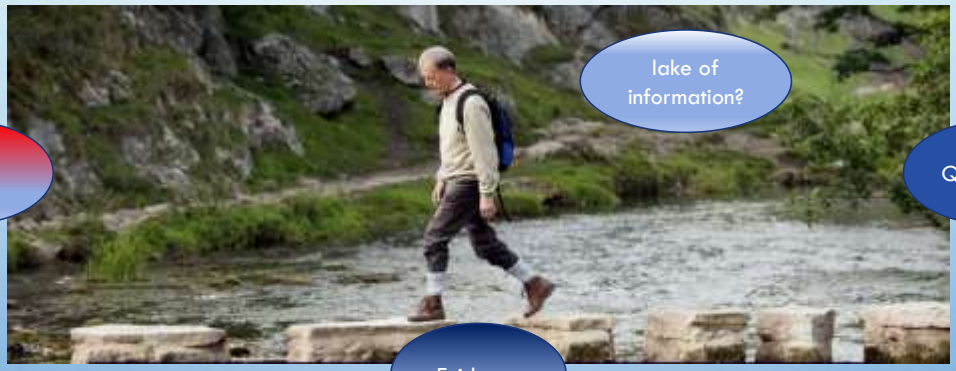
EUCLID

(EUCLID Examining Use of tiCagreLor In paD)

Prupose

- **Purpose** is to compare the effects of ticagrelor and clopidogrel in patients with Peripheral Artery Disease.

My aim



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Medical therapies:

Table 1. Effect of Medical Therapies in Subjects With Peripheral Artery Disease

	Symptomatic Improvement	Reduced Cardiovascular Risk
Exercise	+++	Not studied
Cilostazol	++	Neutral
Statins	+/−	+++
Antiplatelets	−	+++
L-Carnitine and propionyl-L-carnitine	++	Not studied
Pentoxifylline	++	Not studied
Naftidrofuryl	++	Not studied
Gene therapy	+/−	Neutral
Cell therapy	+/−	Not studied

***492 Circulation* July 24, 2012**

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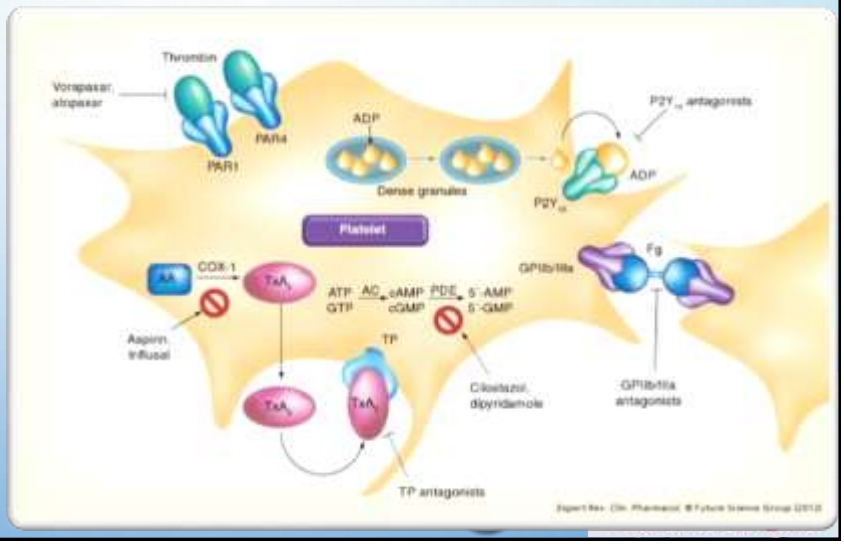
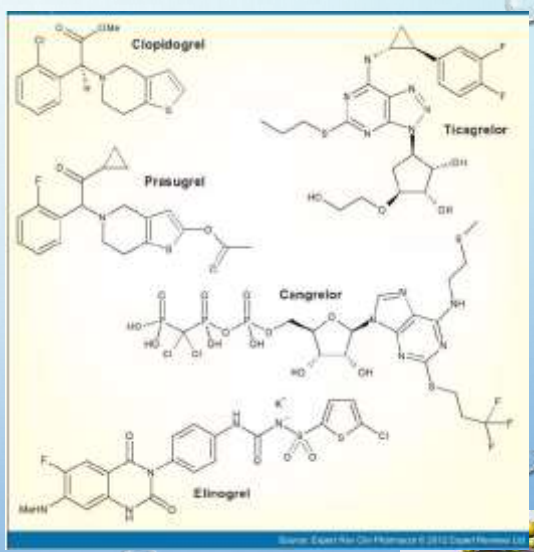
What is P2Y12 receptor antagonist



The Royal College of Surgeons of England

P2Y12 receptor anatagonist

- In the field of purinergic signaling, the **$P2Y_{12}$** protein is found mainly but not exclusively on the surface of blood platelets, and is an important regulator in blood clotting.[4]
- $P2Y_{12}$ belongs to the Gi class of a group of G protein-coupled (GPCR) purinergic receptors[5] and is a chemoreceptor for adenosine diphosphate (ADP).[6][7] This P2Y receptor family has several receptor subtypes with different pharmacological selectivity, which overlaps in some cases, for various adenosine and uridine nucleotides. The P2Y12 receptor is involved in platelet aggregation and is thus a biological target for the treatment of thromboembolisms and other clotting disorders. Two transcript variants encoding the same isoform have been identified for this gene.[8]



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What drugs :

- **The drugs clopidogrel (Plavix),**
- **prasugrel (Efient, Effient),**
- **ticagrelor (Brilinta),**
- **cangrelor (Kengreal)**

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Where we are 2017

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AMERICAN COLLEGE of CARDIOLOGY

New Developments in Antiplatelet Therapies for Patients with Peripheral Artery Disease

Aug 22, 2016 | Subhash Banerjee, MD, FACC

Expert Analysis

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Basics of Antiplatelets in PAD

- APT has been shown to reduce the occurrence of MACE in patients with PAD, particularly atherothrombotic events occurring in the coronary and cerebral vasculature .
- Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. *(Class 1,Level of Evidence: A)*

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2/17/2017 New Developments in Antiplatelet Therapies for Patients with Peripheral Artery Disease American College of Cardiology

Basics of Antiplatelets in PAD

- Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. *(Class 1 ,Level of Evidence: B)*
- Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. *(Class 1,Level of Evidence: B)*

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Basics of Antiplatelets in PAD

- The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation of lower extremity ischemia and who are not at increased risk of bleeding and who are high perceived cardiovascular risk. *(Class IIb ,Level of Evidence: B)*

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criteria

- Inclusion criteria:
- Male and female patients 50 years old or older symptomatic peripheral artery disease
- Exclusion criteria:
- Patients needing dual anti-platlet drug treatment before start of study planned revascularisation or amputation
- Patients with known bleeding disorders
- Patients with a history of intracranial bleed
- Patients considered to be at risk of bradycardic events unless already treated with a permanent pacemaker

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Primary outcome measures :

- Primary Outcome Measures:
- Time from randomization to first occurrence of any event in the composite of cardiovascular death, myocardial infarction and ischemic stroke [Time Frame: Up to 40 months]

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Secondary outcome measures :

- **Secondary Outcome Measures:**
- **Time from randomisation to first occurrence of any event in the composite of CV death, MI, ischemic stroke and ALI [Time Frame: Up to 40 months]**
- **Time from randomization to occurrence of cardiovascular death [Time Frame: Up to 40 months]**
- **Time from randomization to occurrence of myocardial infarction [Time Frame: Up to 40 months]**
- **Time from randomization to occurrence of all-cause mortality [Time Frame: Up to 40 months]**

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Secondary outcome measures :

- **Time from randomization to occurrence of all-cause mortality [Time Frame: Up to 40 months]**
- **Time from randomization to occurrence of composite of cardiovascular death, myocardial infarction and all-cause stroke (ischaemic or haemorrhagic) [Time Frame: Up to 40 months]**
- **Time from randomisation to occurrence of ALI [Time Frame: Up to 40 months]**
- **Time from randomisation to occurrence of lower extremity revascularization [Time Frame: Up to 40 months]**
- **Time from randomisation to occurrence of any revascularisation (coronary, peripheral [limb, mesenteric, renal, carotid and other]) [Time Frame: Up to 40 months]**

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Enrollment:	16415
Study Start Date:	December 2012
Study Completion Date:	September 2016
Primary Completion Date:	September 2016 (Final data collection date for primary outcome measure)

EUCLID Study Design

Patients with symptomatic PAD

Key exclusion criteria:
- Poor metabolizer for CYP2C19
- Patients requiring dual anti-platelet therapy

Ticagrelor 90 mg bid

Double-blind Double-dummy

1:1

N=13,885

Clopidogrel 75 mg od

Inclusion criteria:
Symptomatic PAD AND one of the following:
A. ABI ≤0.80 at Visit 1 ≤0.85 at Visit 2
OR
B. Prior lower extremity revascularization > 30 days

Duration: Event Driven Trial
Approximately 14-month recruitment and 26-month follow-up

Primary Endpoint: cardiovascular death, myocardial infarction, or ischemic stroke

Primary Safety Endpoint: TIMI major bleeding

Global Participation

13,855 patients
811 sites
28 countries

EUROPE: 7499 PATIENTS

Bulgaria: 679	Netherlands: 234	Sweden: 240
Czech Rep: 723	Poland: 609	Turkey: 137
France: 371	Romania: 508	Ukraine: 536
Germany: 623	Russian Fed: 935	UK: 297
Hungary: 580	Slovakia: 419	
Italy: 285	Spain: 323	

NORTH AMERICA: 3044 PATIENTS
US: 2614
Canada: 430

LATIN AMERICA: 1740 PATIENTS
Argentina: 567
Brazil: 643
Chile: 161
Mexico: 369

ASIA-PACIFIC: 1602 PATIENTS
China: 423
Japan: 420
Philippines: 128
S. Korea: 214
Thailand: 122
Vietnam: 295

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EUCLID Patient Follow up

Assessed for eligibility (n=16,237)

Not randomized (n=2352)
- Failed inclusion criteria for symptomatic lower extremity PAD (n=489)
- 2C19 homozygous (n=616)
- Other reasons (n=1335)

Randomized (n=13,885)

Allocation

Ticagrelor (n=6930)	Clopidogrel (n=6955)
Never received a dose (n=20)	Never received a dose (n=23)
Withdrew consent (n=123 [1.8%])	Withdrew consent (n=113 [1.6%])
Discontinued study drug (n=2083 [30.1%])	Discontinued study drug (n=1803 [26.0%])
Unknown vital status (n=7)	Unknown vital status (n=7)
Due to withdrawn consent (n=6)	Due to withdrawn consent (n=3)
Lost to follow-up (n=1)	Lost to follow-up (n=4)
Proportion of potential a patient years with follow-up (98.1%)*	Proportion of potential patient years with follow-up (98.5%)*

Follow-up

Complete ascertainment of primary endpoint

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

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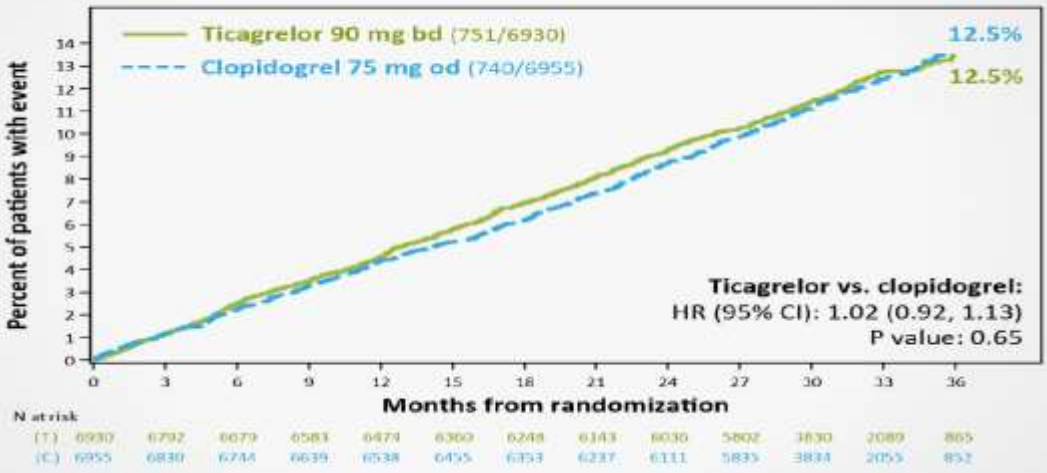
Results

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

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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

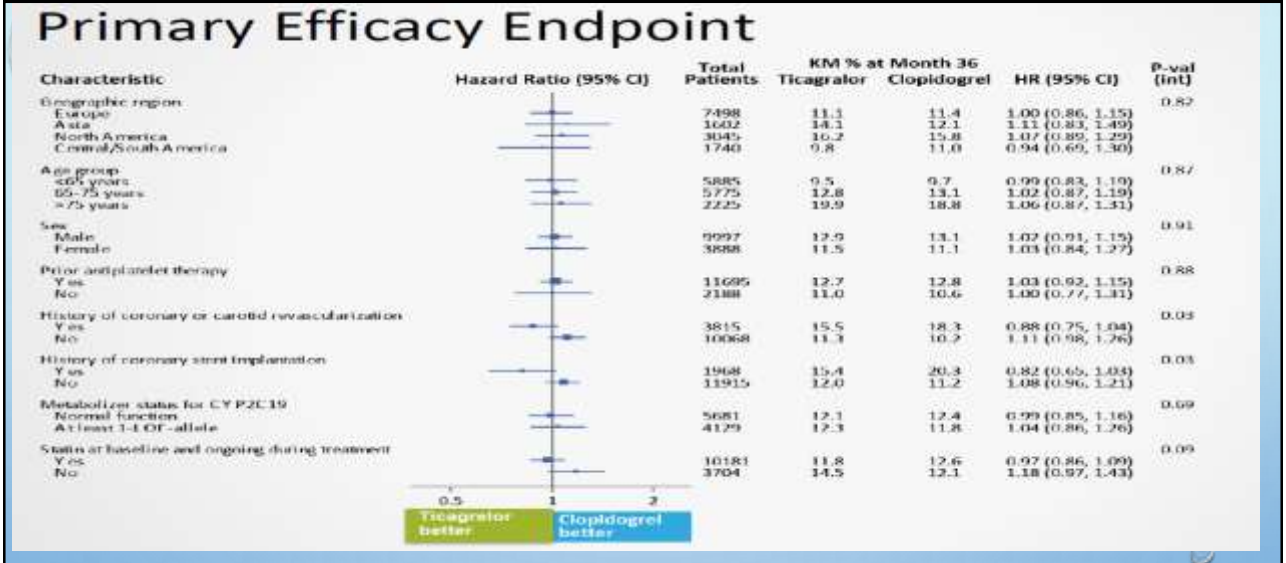
ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

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



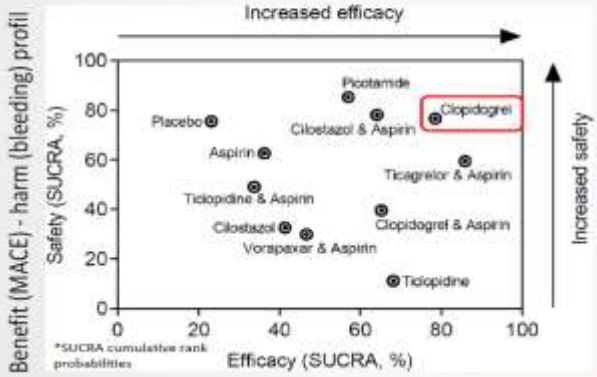
Conclusions :

- **In patients with symptomatic PAD**
- **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**

The Magic slide ?

Efficacy & Safety of Antiplatelet Agents for Prevention of MACE and Leg Amputations in PAD

Systematic Review and Network Meta- Analysis (49 RCT)



surgical & endovascular revascularization

- *3 RCT (of 49 RCT analysed)*
- *3.527 patients*
- *> 8.000 person-years of follow up*

short-term DAPT reduces major amputations after revascularization

PLOS ONE 10 (8),1-19,2015

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Thank you

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