Place des antithrombotiques dans le traitement de l'AOMI

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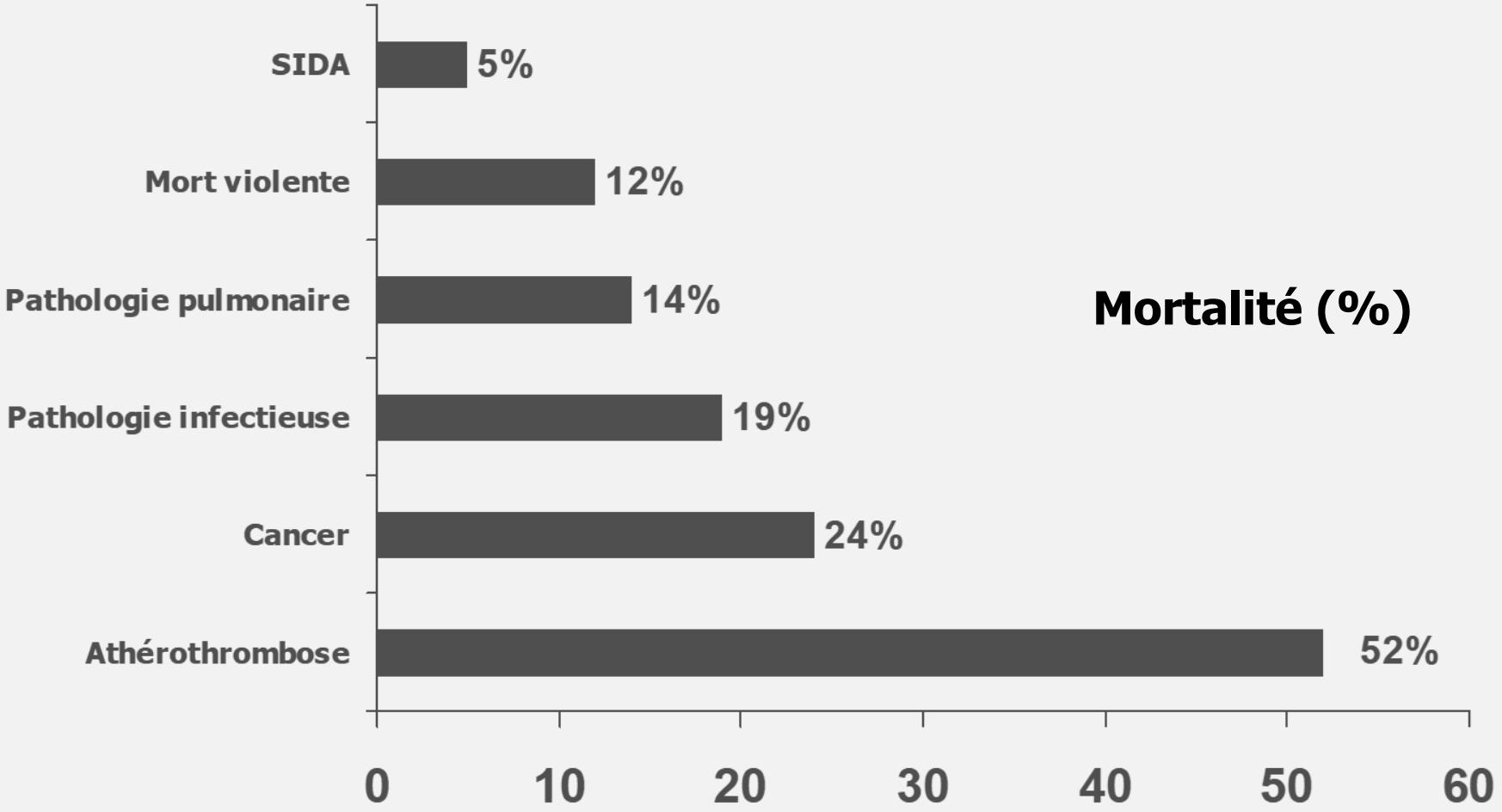
Libéral-Alger

L'ATHEROTHROMBOSE* EST UNE CAUSE MAJEURE DE DECES DANS LE MONDE[1]*

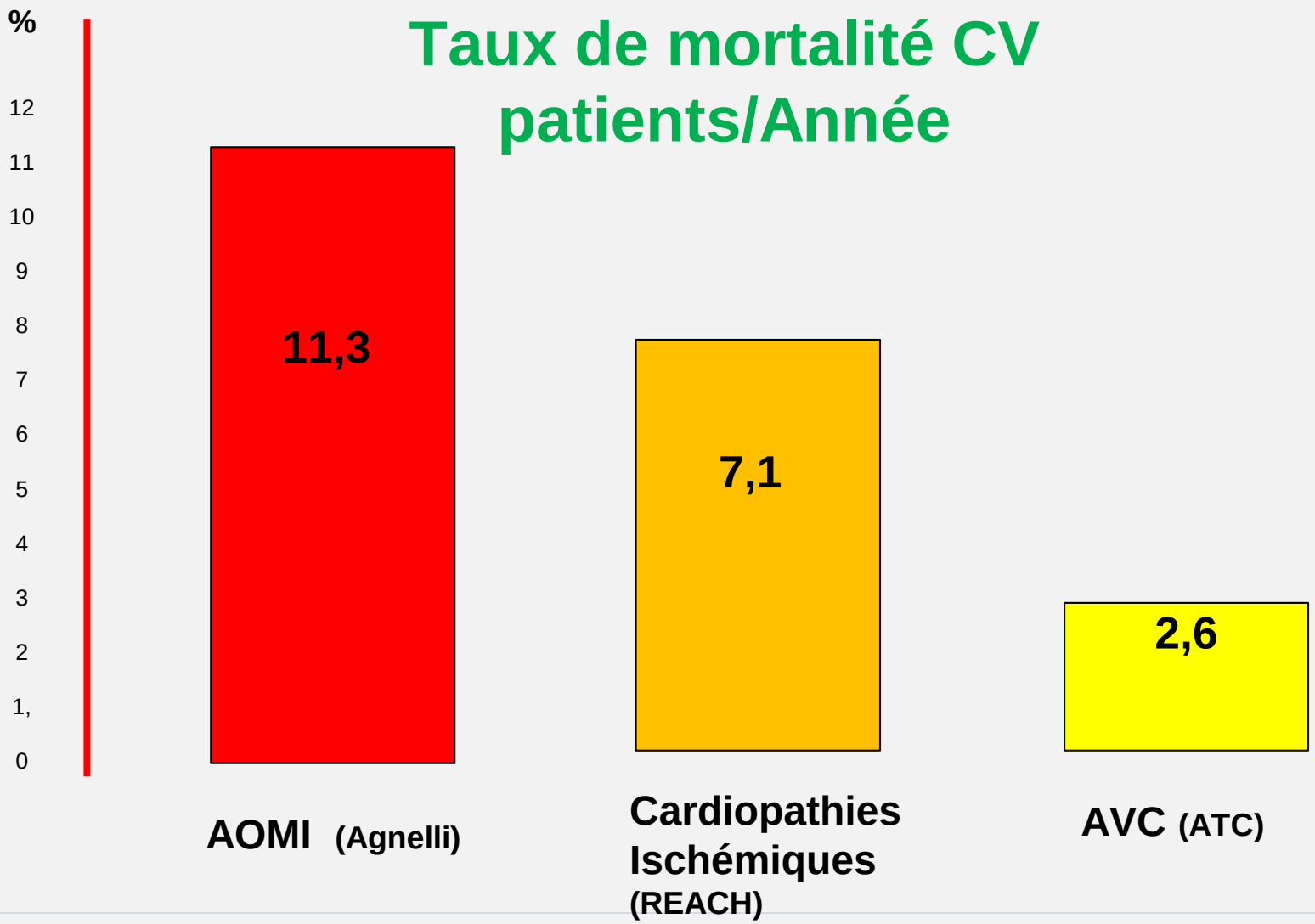


1. The World Health Report, 2000, WHO Geneva, 2000.

* Pathologie cardiovasculaire, cardiopathie ischémique et pathologie vasculaire cérébrale.

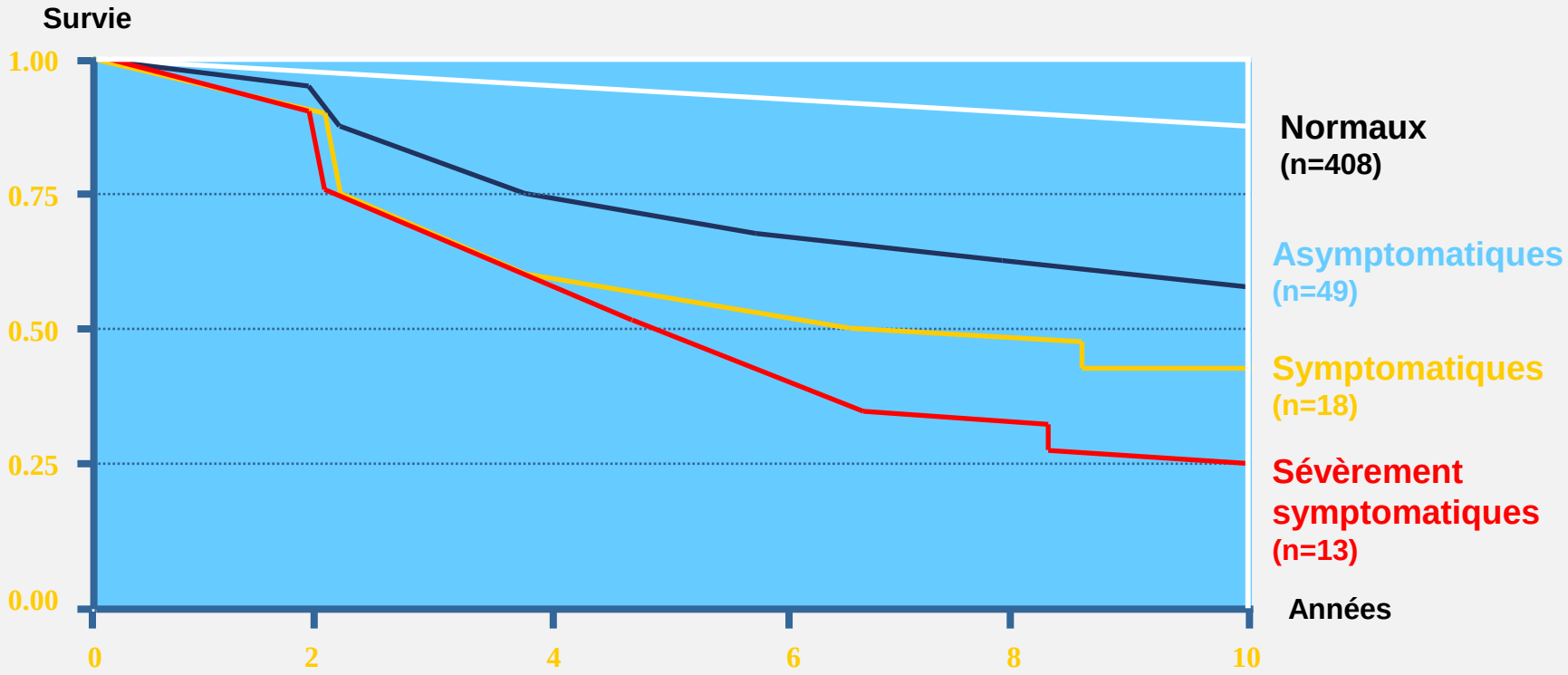
* états membres de l'OMS (Afrique, Amériques, Bassin Méditerranéen, Europe, Sud-Est Asiatique et Pacifique Ouest)

Risque de mortalité et AOMI



1: Agnelli G, Belch JJF, Baumgartner I, Giovas P, Hoffmann U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: Asystematic review. Atherosclerosis. 2020 Jan;293:94-100. doi:10.1016/j.atherosclerosis.2019.09.012.
2: Ducrocq G, Amarenco P, Labreuche J, Alberts MJ, Mas JL, Ohman EM, Goto S,Lavallée P, Bhatt DL, Steg PG. A history of stroke/transient ischemic attackindicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. Circulation. 2013 Feb 12;127(6):730-8.
3: Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L,Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, MeadeT, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individualparticipant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.

Sévérité de l'AOMI et mortalité



Courbe de survie (Kaplan Meyer) basée sur la mortalité toute cause chez des sujets normaux et des sujets présentant une AOMI symptomatique ou non

Criqui MH et al. Mortality over a period of 10 years in patients with peripheral arterial disease
N Eng J Med 1992; 326 : 381-6

Apport des AAP dans les AOMI

Athérothrombose et APTC *

Br Med J 1994; 308: 81-106.

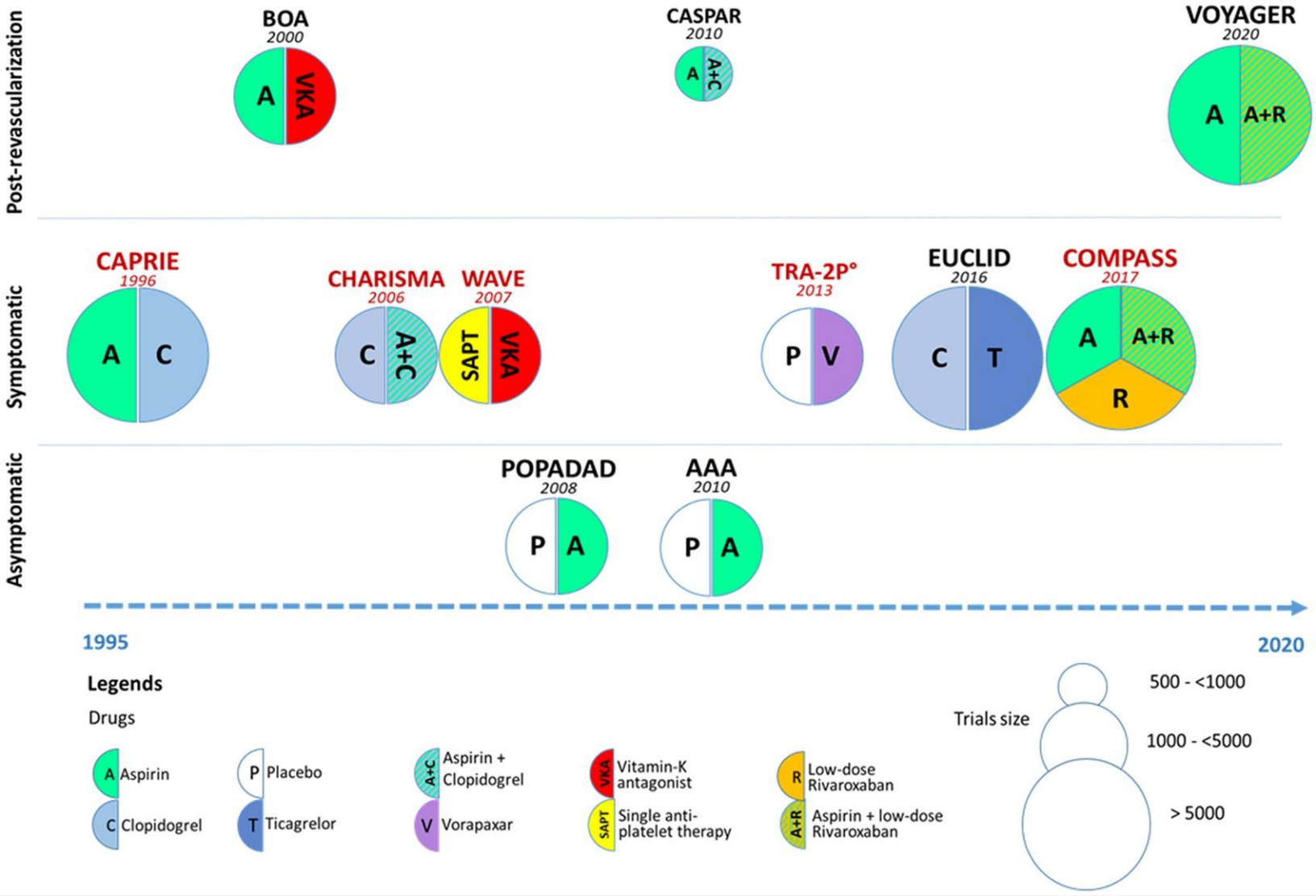
- APTC * (Antiplatelet Trialist's Collaboration 1994) :

  - Méta-analyse de 142 essais
  - Plus de 73 000 patients à haut risque :
    - IDM,
    - IDM en phase aiguë,
    - AVC,
    - AIT,
    - Autres conditions à risque vasculaire ischémique : angor instable ou stable, post-chirurgie et angioplastie, pathologies artérielles périphériques

Apport des AAP dans les AOMI

- **Résultats :**
  - **Les AAP en prévention secondaire :↓ 27 % des événements ischémiques majeurs versus placebo (critère combiné : IDM, AVC, mort vasculaire)**
  - **Aspirine : AAP le plus étudié (46 études, patients à haut risque) : ↓ 25 % des événements ischémiques majeurs versus placebo**
  - **Ticlopidine : ↓ 33 % des événements ischémiques majeurs versus placebo mais effets Ilaires ++++**

Major trials on antithrombotic therapies in lower-extremities artery disease including >500 patients.



Eur Heart J, Volume 42, Issue 39, 14 October 2021, Pages 4013–4024,

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

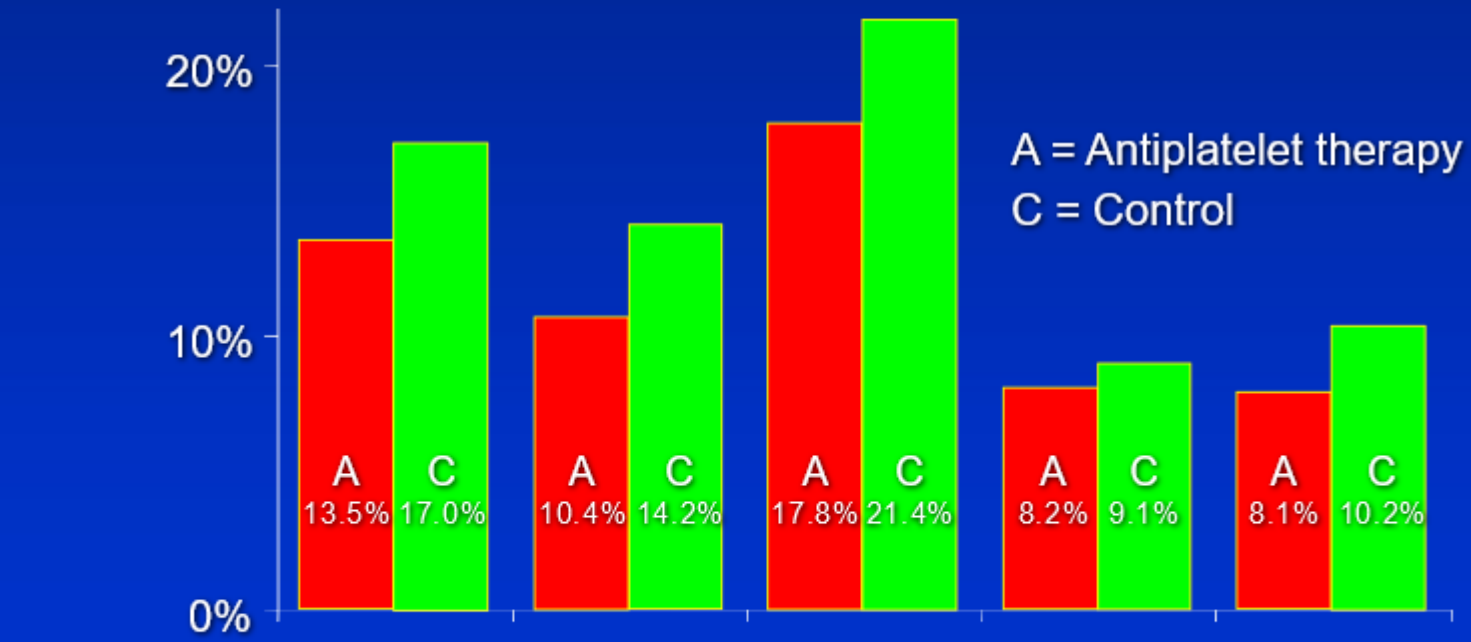
Antithrombotic Trialists' Collaboration

(N = 212,000 in 287 trials)

BMJ 324:71–86, 2002

Antithrombotic Trialists' Collaboration: Absolute effects on VASCULAR EVENTS

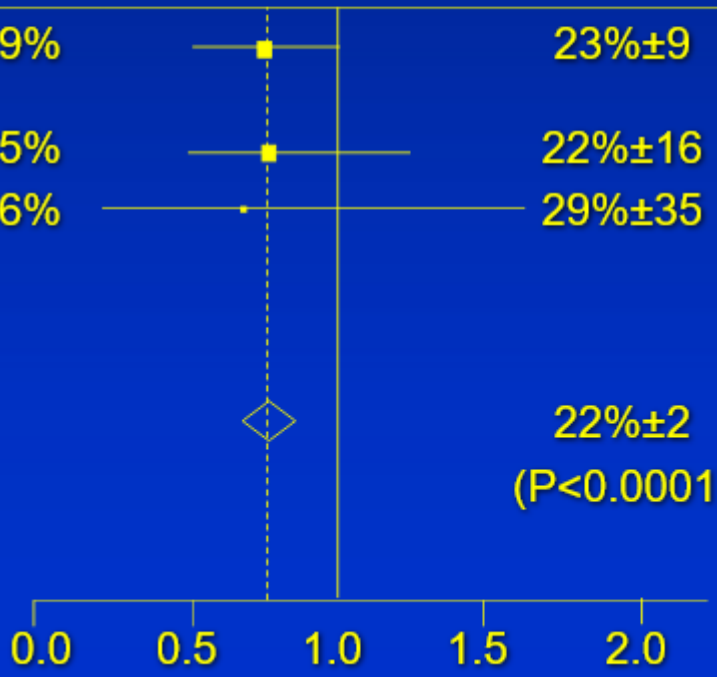
Benefit per 1000(SE):	36(5)	38(5)	36(6)	9(3)	22(3)
Average duration:	27 m	1m	29 m	0.7 m	22 m
P-value:	<0.0001	<0.0001	<0.0001	0.0009	<0.0001



Antithrombotic Trialists' Collaboration

Effects on VASCULAR EVENTS in patients with PERIPHERAL ARTERIAL DISEASE

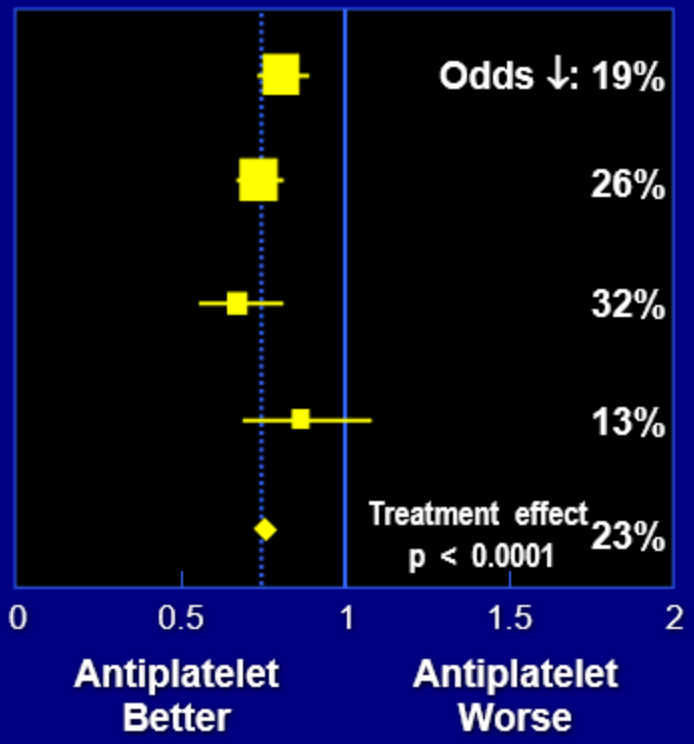
Category	APT	CTRL	Reduction
Intermittent claudication	6.4%	7.9%	23%±9
Peripheral graft	5.4%	6.5%	22%±16
Peripheral angioplasty	2.5%	3.6%	29%±35
All high-risk patients			22%±2 (P<0.0001)



Antiplatelet Meta-Analysis

Endpoints: MI, Stroke, Vascular Death

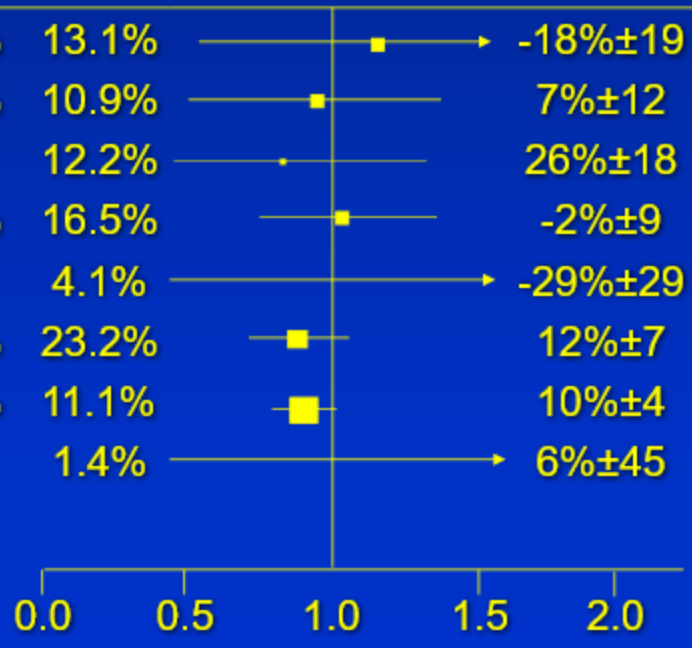
ASA Dose (mg)	No. of Trials	Odds Ratio & 95% CI	Anti-platelet	Control
500-1500	34	Odds ↓: 19%	14.5%	17.2%
160-325	19	26%	11.5%	14.8%
75-150	12	32%	10.9%	15.2%
< 75	3	13%	17.3%	19.4%
Any Aspirin	65	Treatment effect p < 0.0001 23%	12.9%	16.0%



Antithrombotic Trialists Collaboration, BMJ 324:71–86, 2002

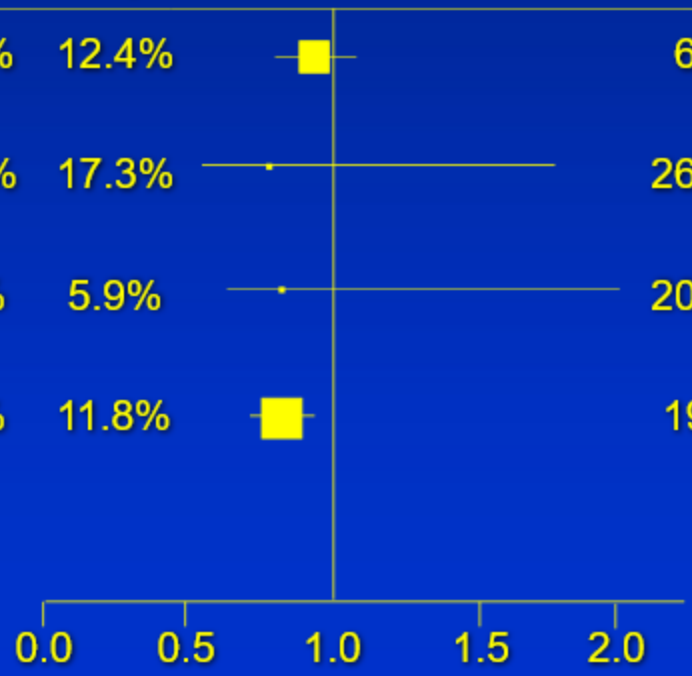
Antithrombotic Trialists' Collaboration
Other antiplatelet drugs vs aspirin

Comparison	APT	Asp	Redn	P-value
Sulphinpyrazone	16.2%	13.1%	-18%±19	NS
Triflusal	10.1%	10.9%	7%±12	NS
Ridogrel	9.6%	12.2%	26%±18	NS
Dipyridamole	16.7%	16.5%	-2%±9	NS
Indobufen	5.3%	4.1%	-29%±29	NS
Ticlopidine	21.1%	23.2%	12%±7	NS
Clopidogrel	10.1%	11.1%	10%±4	0.03
Other antiplatelet	1.3%	1.4%	6%±45	NS



Antithrombotic Trialists' Collaboration
Aspirin plus another antiplatelet vs aspirin

Comparison	APT	Asp	Reduction
Asp plus dipyridamole	11.8%	12.4%	6%±6
Asp plus sulphinpyrazone	13.4%	17.3%	26%±20
Asp+ ticlopidine	4.8%	5.9%	20%±24
Asp + iv IIb/IIIa-inhibitor	9.9%	11.8%	19%±4



Antithrombotic Trialists' Collaboration Conclusions

- Aspirin (or another antiplatelet drug) prevents serious vascular events in a wide range of high-risk patients, including people with intermittent claudication, stable angina, and—if oral anticoagulants are unsuitable—atrial fibrillation
- Low-dose aspirin (75-150mg daily) is as effective as higher aspirin doses for long-term use
- Clopidogrel is an effective alternative in patients with a contraindication to aspirin
- In some clinical circumstances, adding a second antiplatelet drug (e.g. clopidogrel or a GPIIb/IIIa antagonist) to aspirin may produce additional benefits

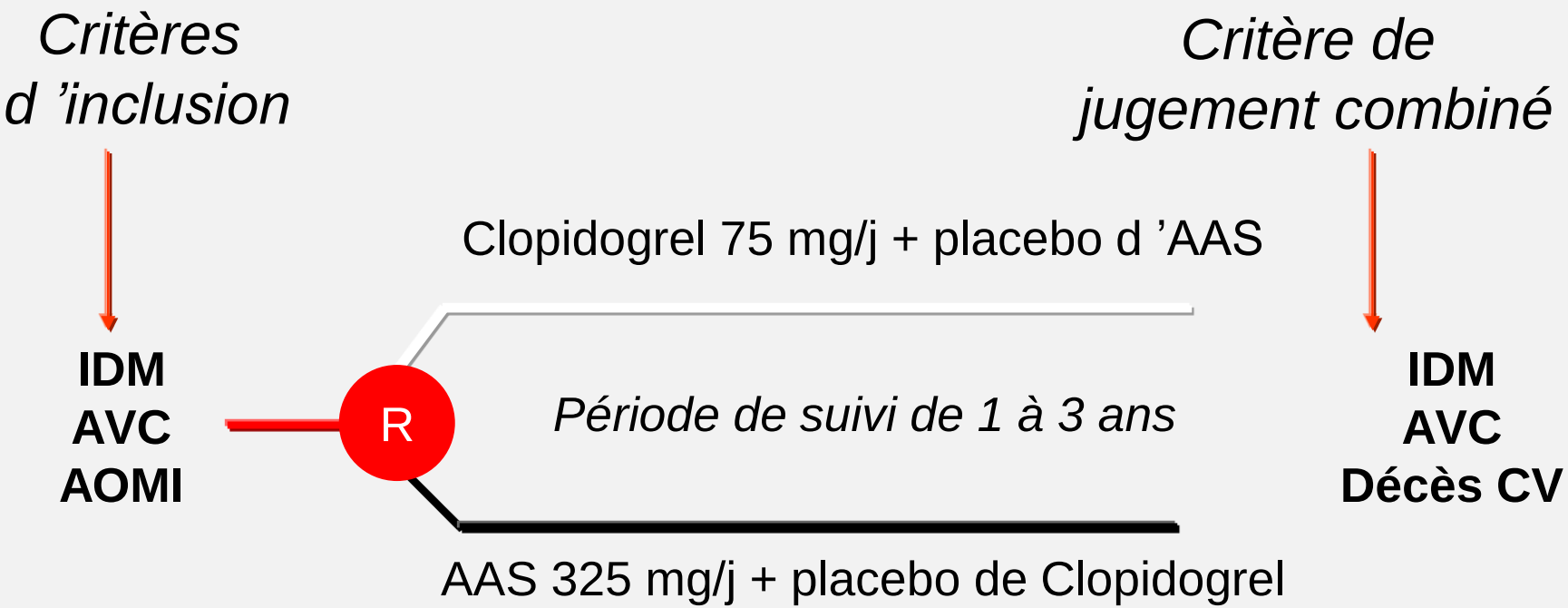
Clopidogrel versus Aspirin in Patients at Risk of Ischeamic Events

Méthodologie

- Étude prospective randomisée en double-aveugle controlée comparant ***le clopidogrel*** à ***l'aspirine.***
- **384** centres investigateurs dans 16 pays
- Durée de suivi 1 an minimum, 3 ans maximum

CAPRIE : final study report. Dossier D'AMM 1997

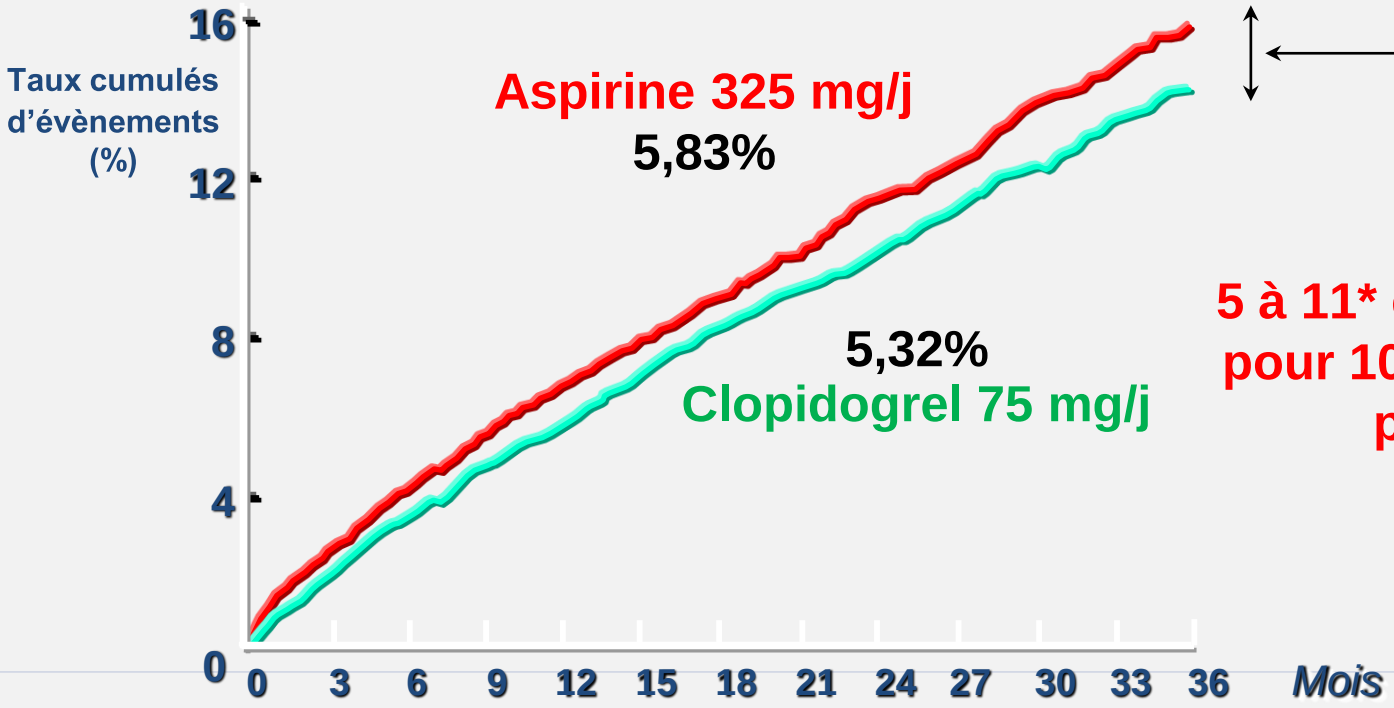
Schéma de l'étude



N = 19 185

Etude CAPRIE

- n = 19185, IDM < J35 (6302), AVC isch (6431), AOMI ≥ II (6452), suivi 1 à 3 ans
- Critère combiné : IDM, AVC, décès vasculaire



RRR = 8.7%
P = 0.043

5 à 11* événements évités pour 1000 patients traités pendant 1 an

*Critère élargi : IDM, AVC, décès vasculaire, hospitalisation pour ischémie ou saignement

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

AAP : BENEFICE DANS l'AOMI

Critère principal : IdM, AVC, décès vasculaire

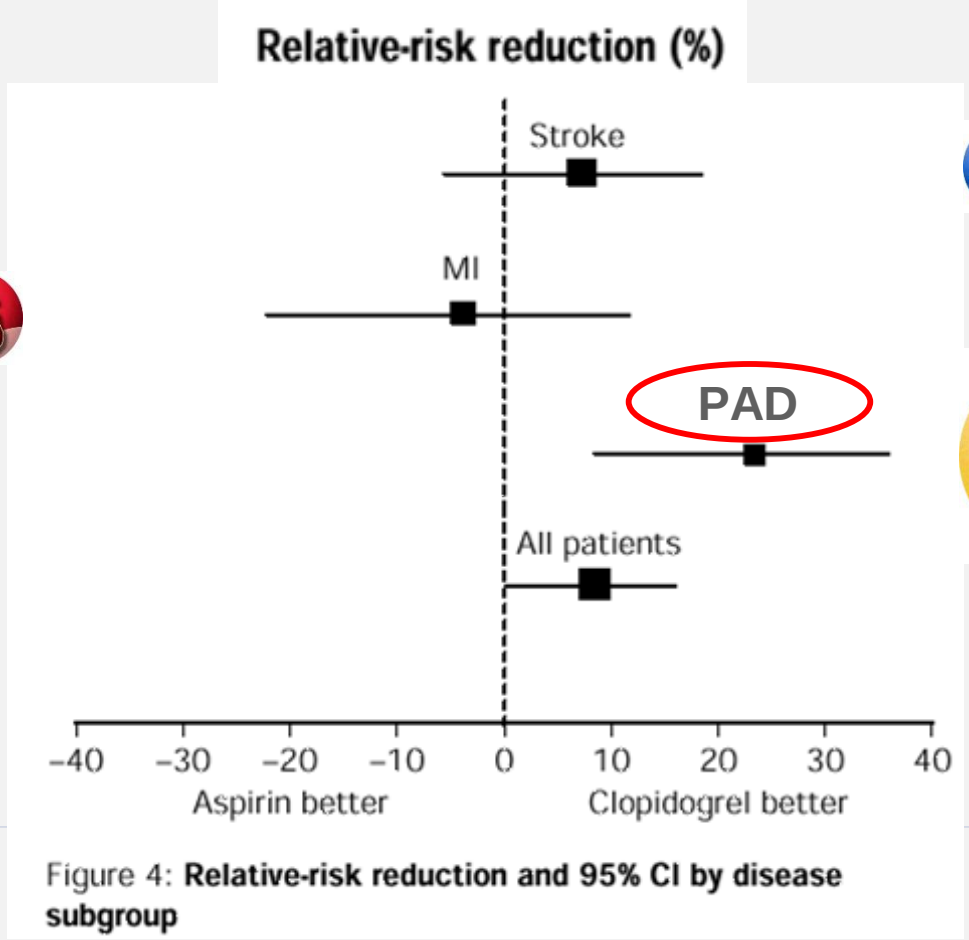
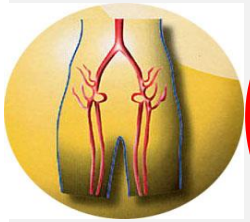


Figure 4: **Relative-risk reduction and 95% CI by disease subgroup**

-3,7%
p = NS

+7,3%
p = NS



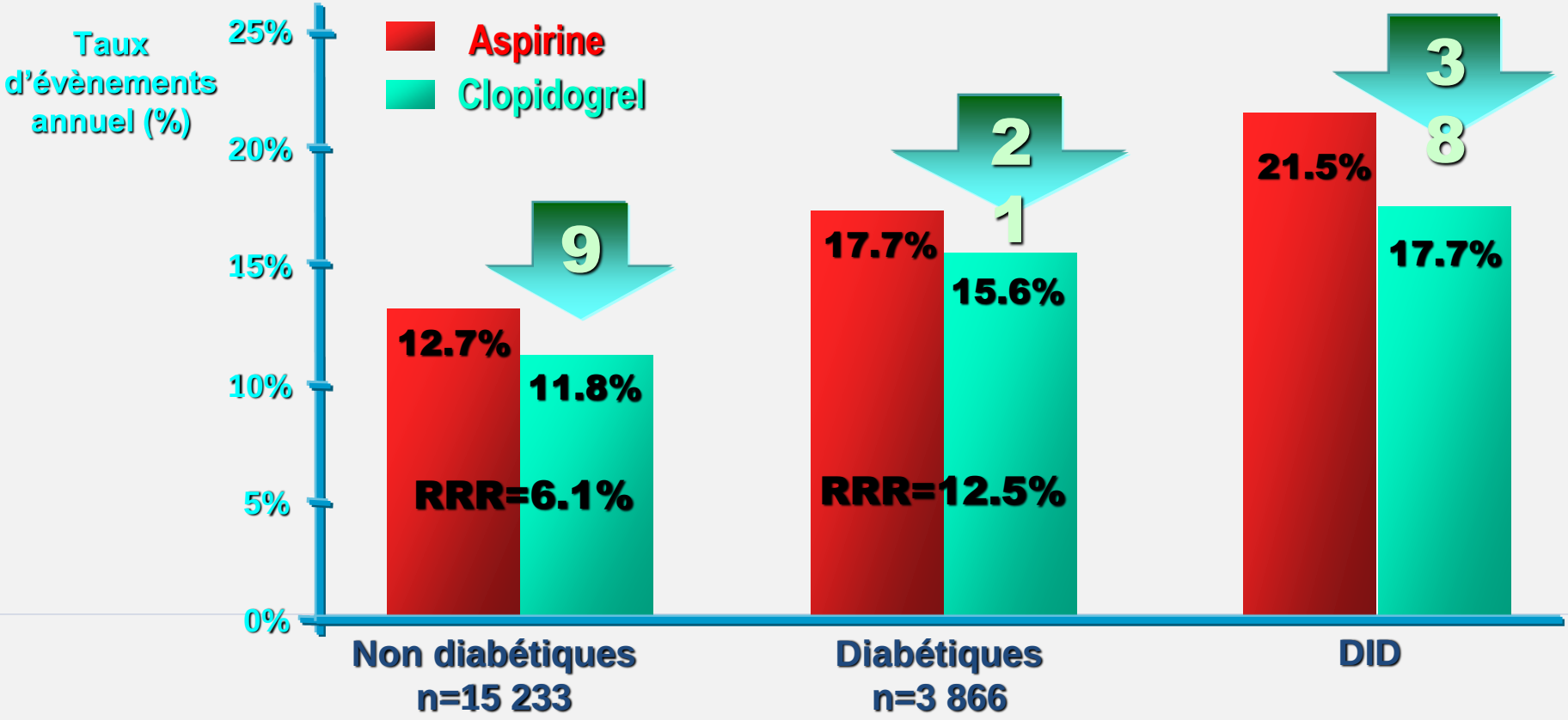
+23,8%
p = 0,0028

Lancet 1996;348:1329-39

AAP : BENEFICE CHEZ LES PATIENTS DIABETIQUES

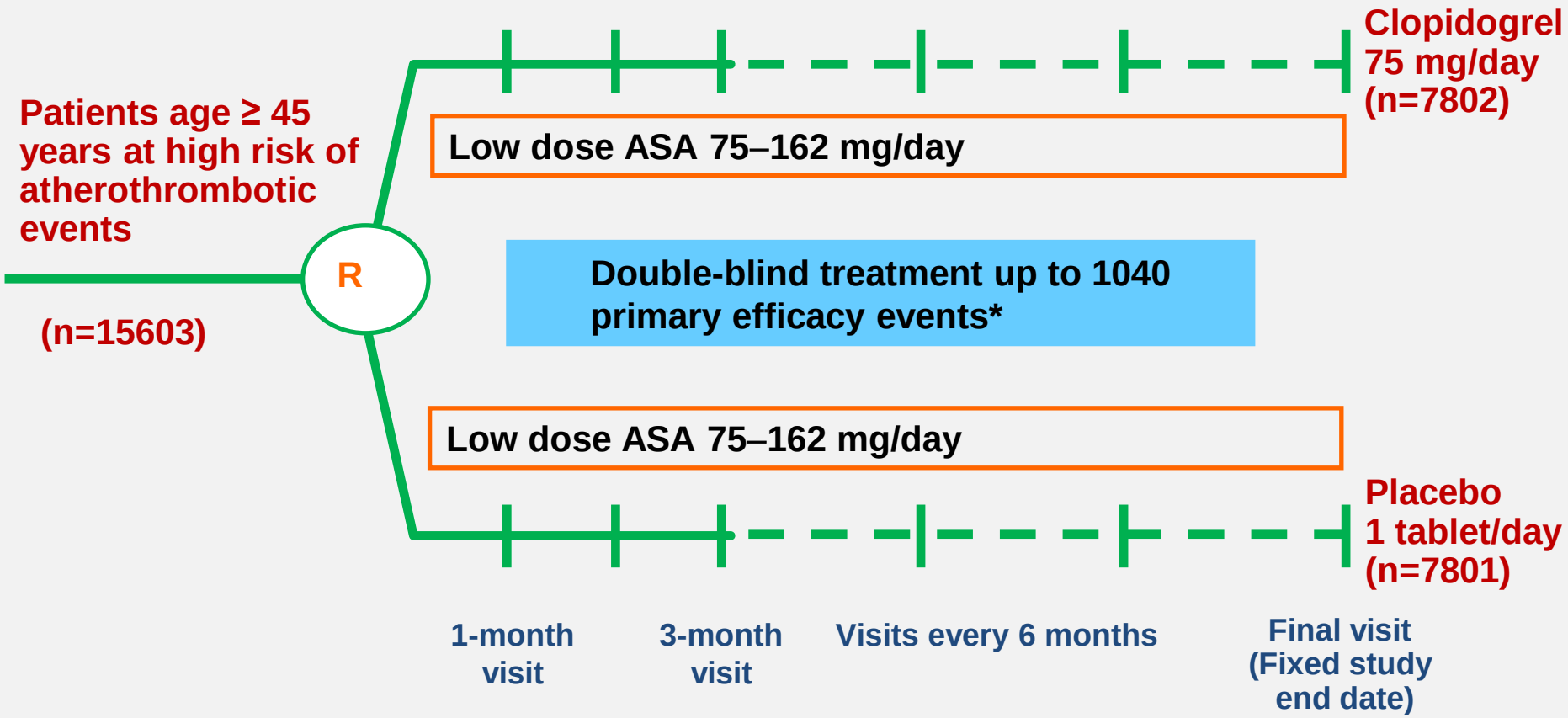
Evénements : Mortalité CV, IDM, AVC, Hosp pour ischémie ou saignements

Evénements prévenus / 1000 patients par an versus aspirine



Bhatt DL. Am J Cardiol 2002;90:625-628

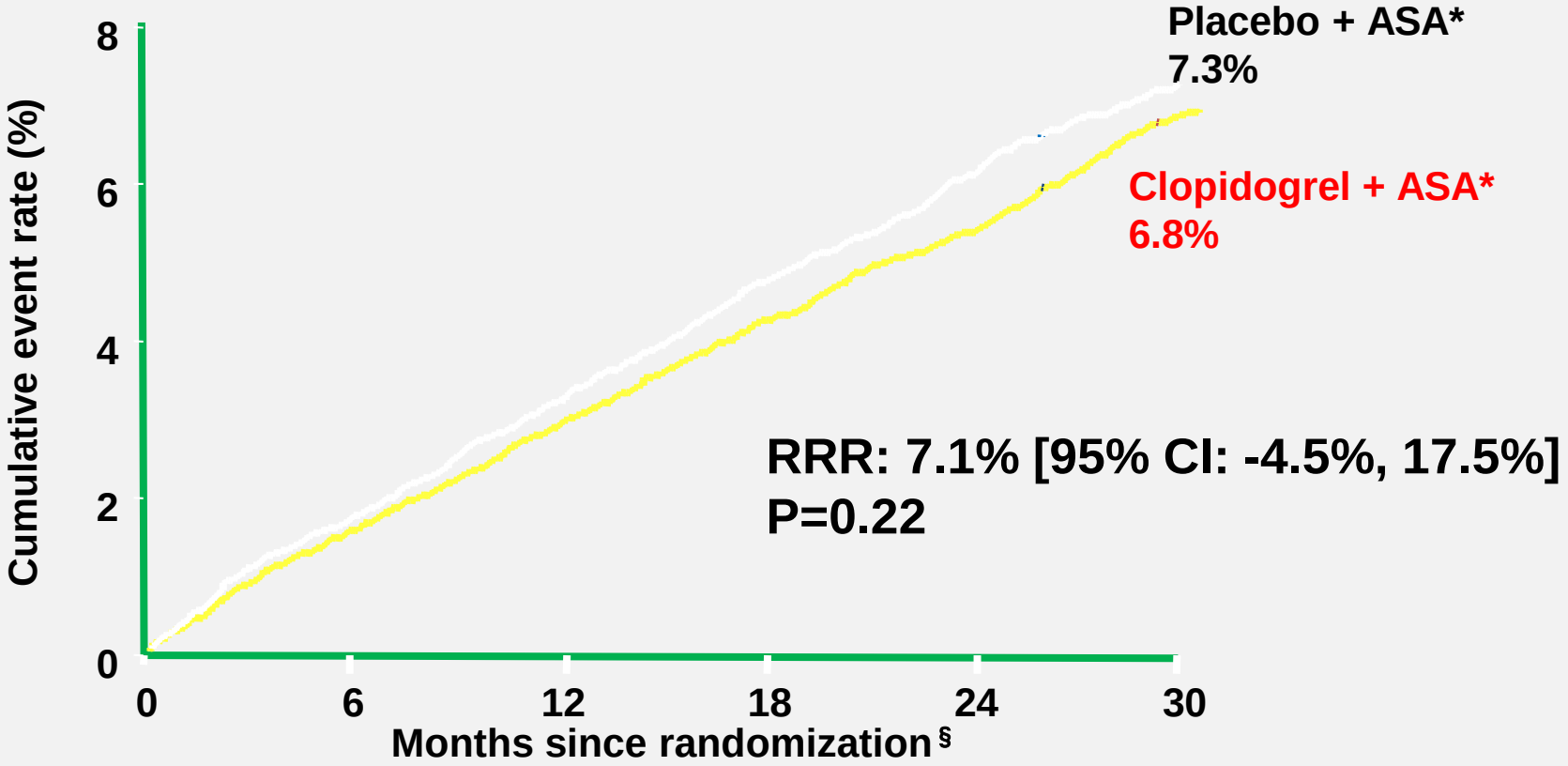
CHARISMA Trial Design



* MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death; event-driven trial

Bhatt DL, Topol EJ, et al. Am Heart J 2004; 148: 263–268.

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†



† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

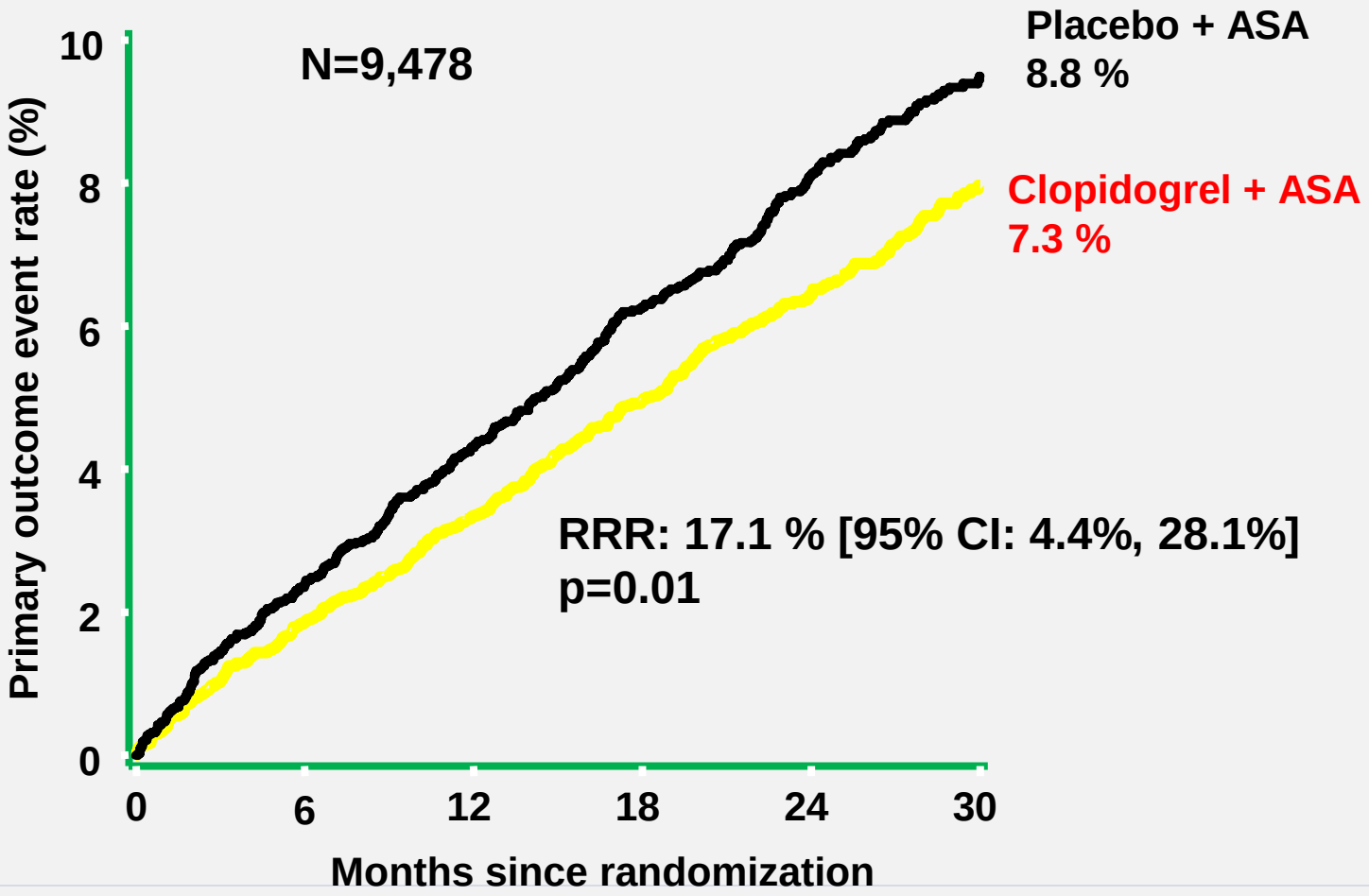
*All patients received ASA 75-162 mg/day

§ The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Bhatt DL, Fox KA, Hacke W, et al. 2006, in press.

Primary Endpoint (MI/Stroke/CV Death) in Patients with Previous MI, IS, or PAD

"CAPRIE-like Cohort"

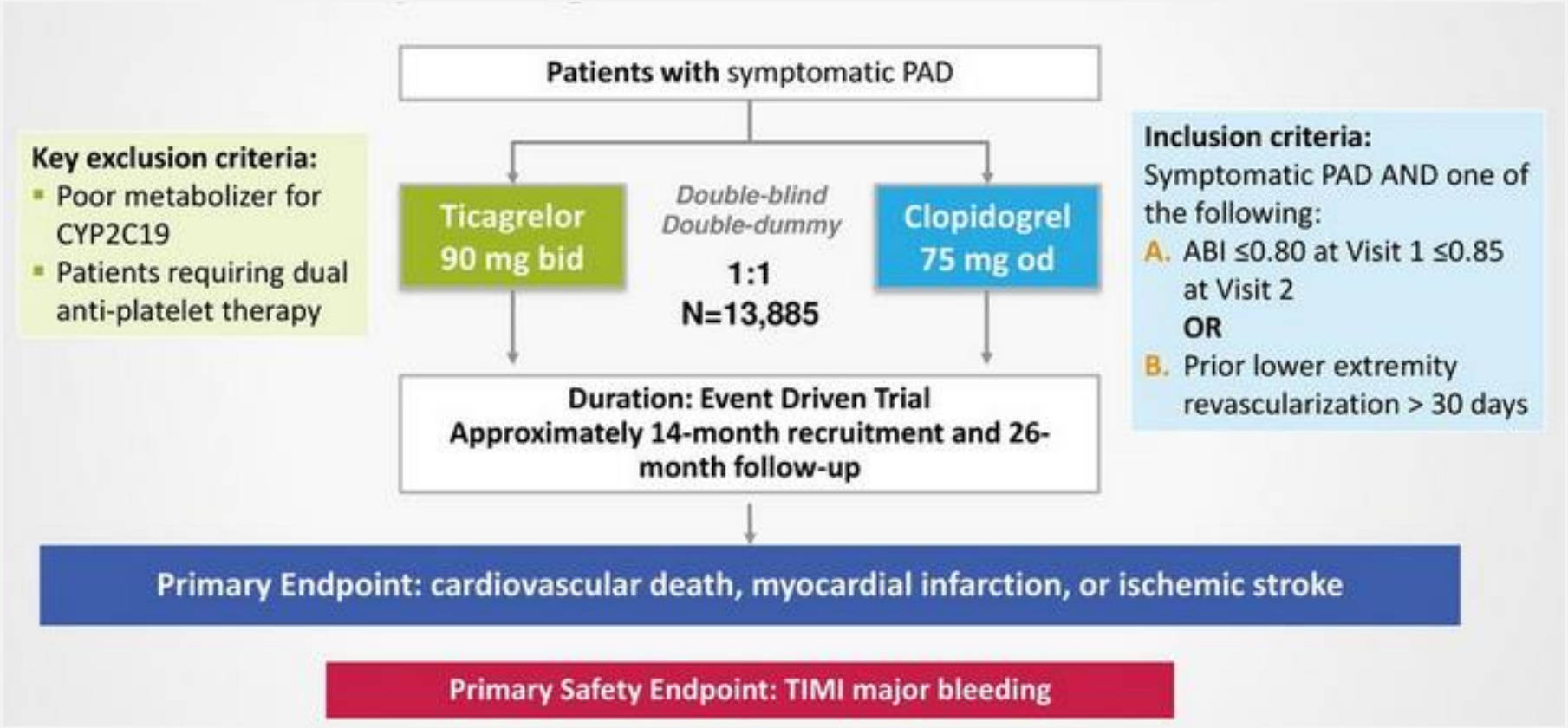


Bhatt DL. Presented at ACC 2006.

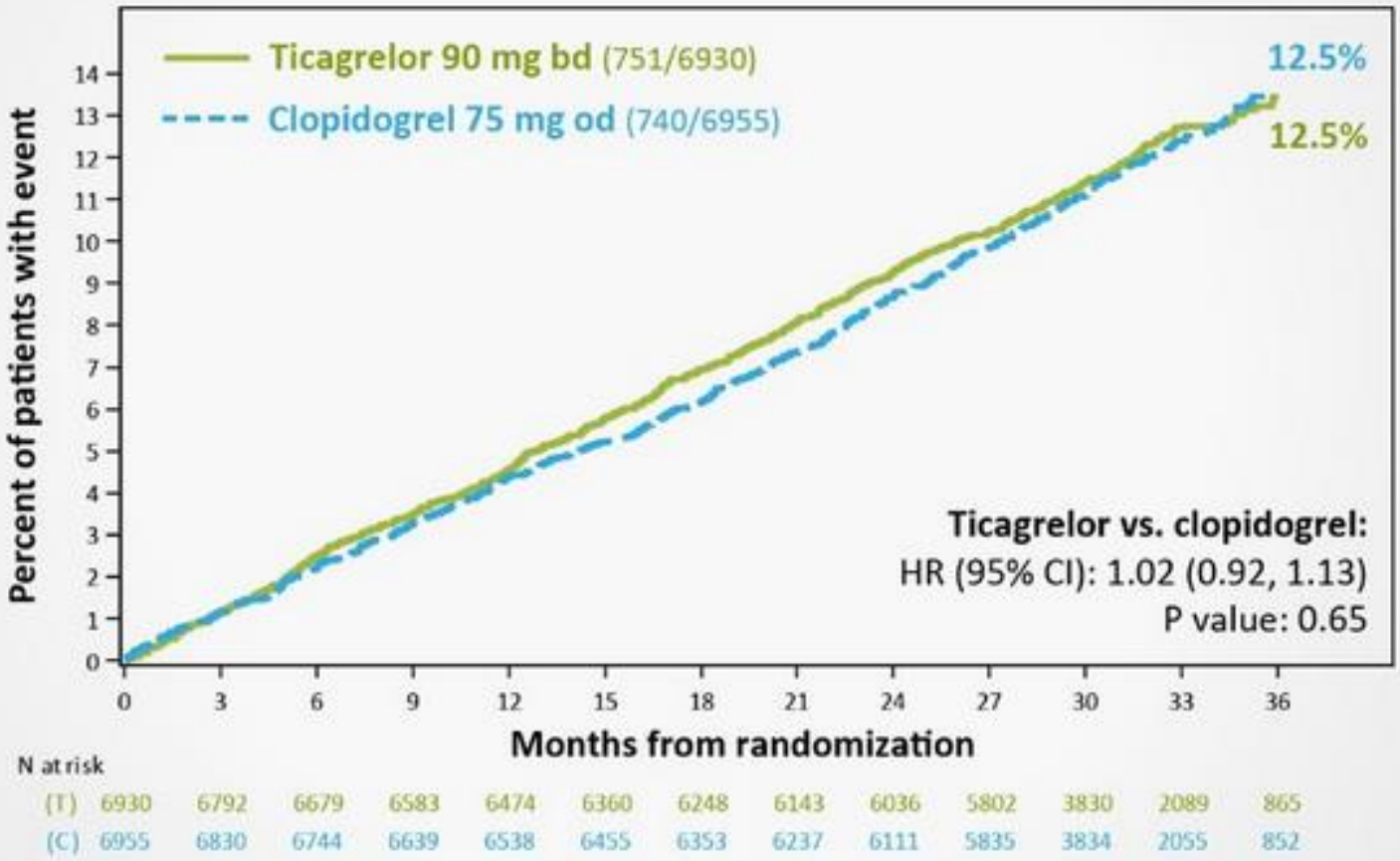
Conclusions

- In patients with multiple risk factors only, without clearly established CV disease, dual antiplatelet was not beneficial - excess in CV mortality as well as an increase in bleeding
- In patients with documented CV disease (CAD, CVD, or PAD) long-term clopidogrel plus ASA resulted in a significant 12.5% RRR in MI/Stroke/CV Death with no significant increase in severe bleeding compared to ASA alone

EUCLID Study Design



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



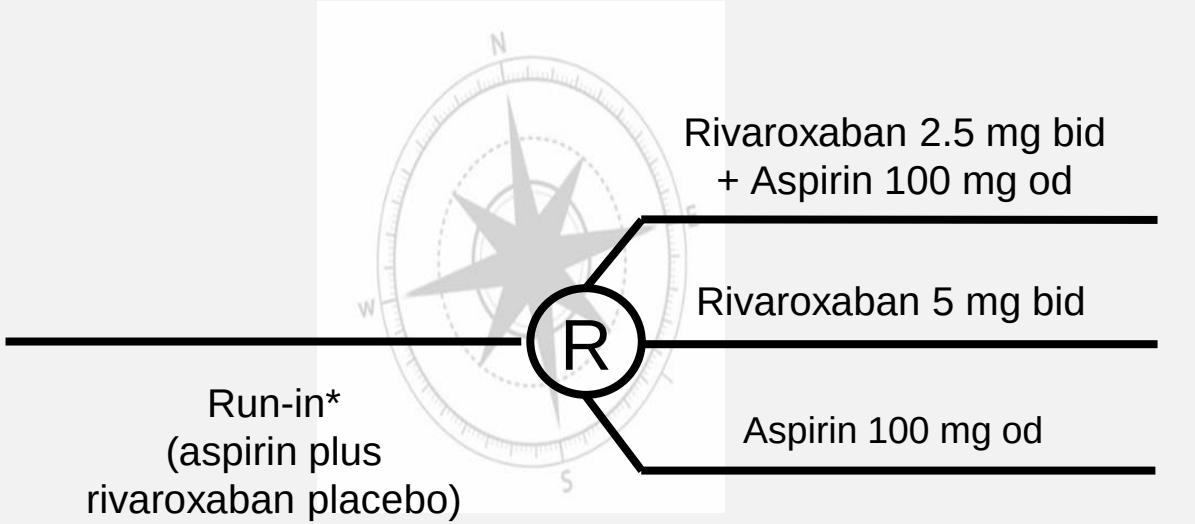
Conclusions

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.

COMPASS Study Design

n=27,395 Chronic CAD or PAD
2,200 participants with a primary outcome event

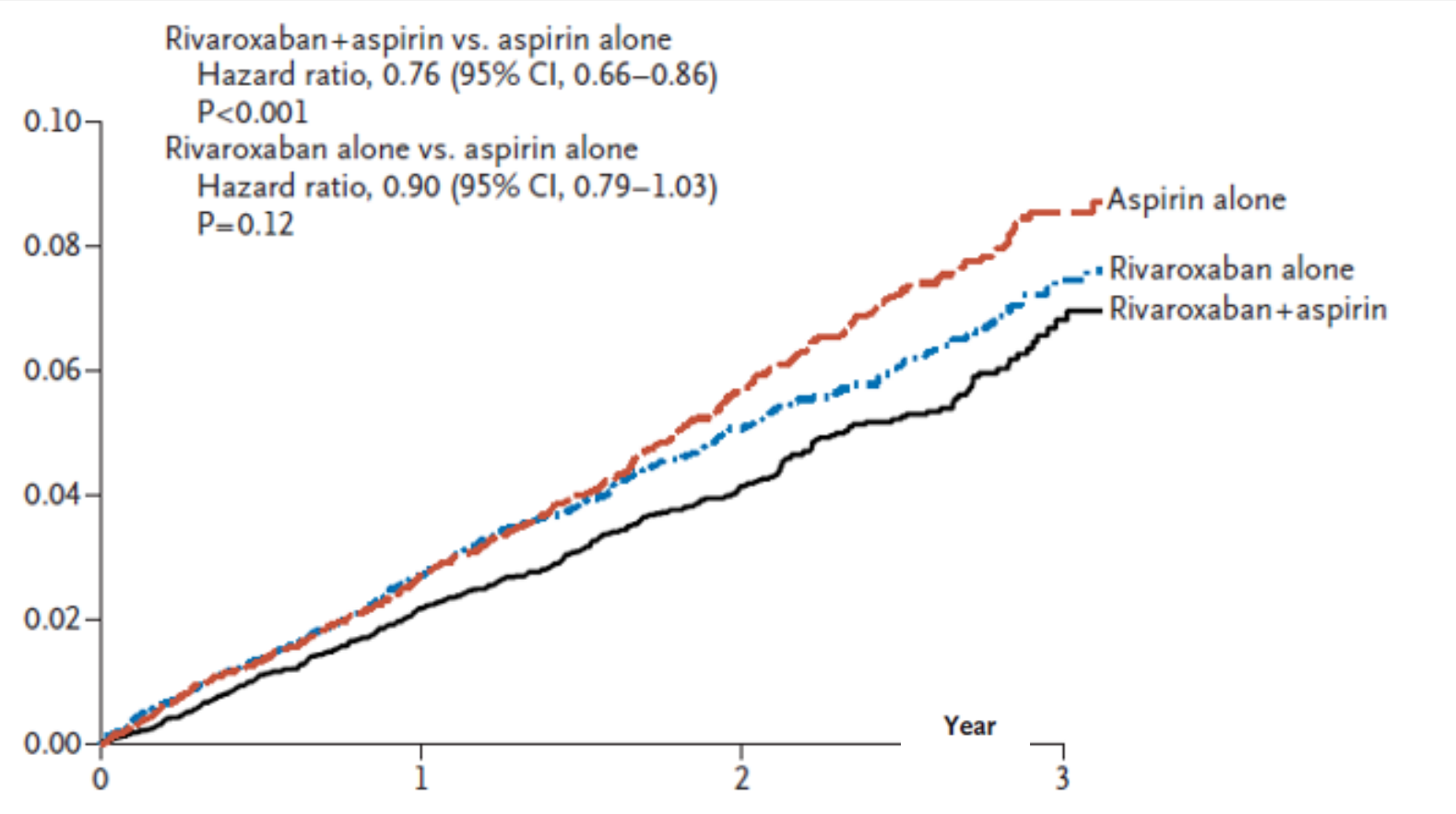


Expected mean follow up: 3-4 years

*excluding patients enrolled 4-14 days post CABG

Bosch JJ, et al. *Can J Cardiol* 2017; 33: 1027-1035.

COMPASS: patients with chronic CAD or PAD (n=27,395)



Eikelboom JW, et al. *N Engl J Med* 2017; 377: 1319-30.

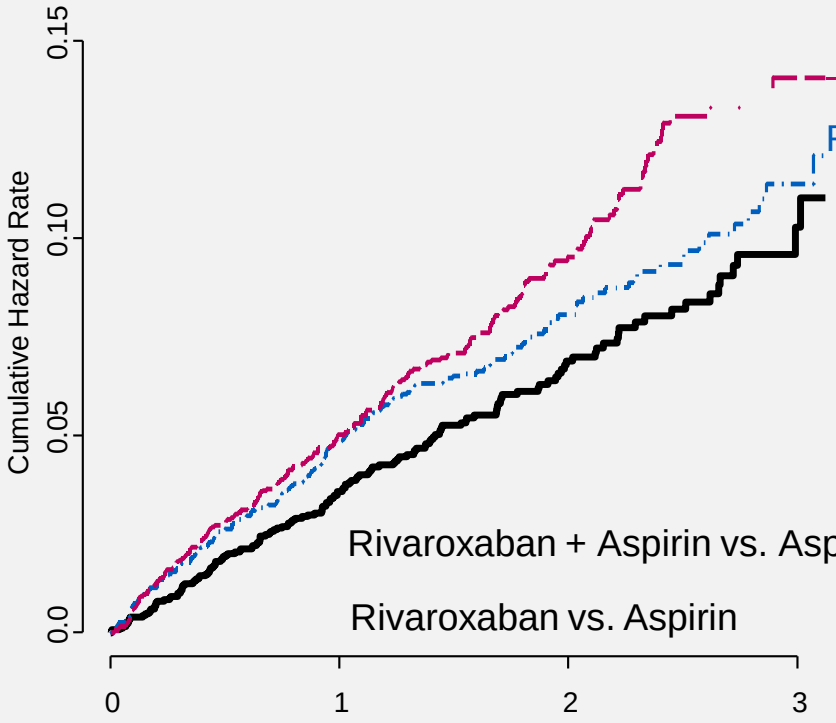
PAD Patients in COMPASS

PAD Groups	Number of patients
All Patients	7,470
Symptomatic PAD Limbs	4,129
Carotid Disease	1,919
CAD + Low ABI (<0.90) only	1,422

Mean Follow-up: 21 months

COMPASS PAD

MACE or MALE or Major Amputation



Rivaroxaban + Aspirin vs. Aspirin HR: 0.69 (0.56-0.85) P=0.0003

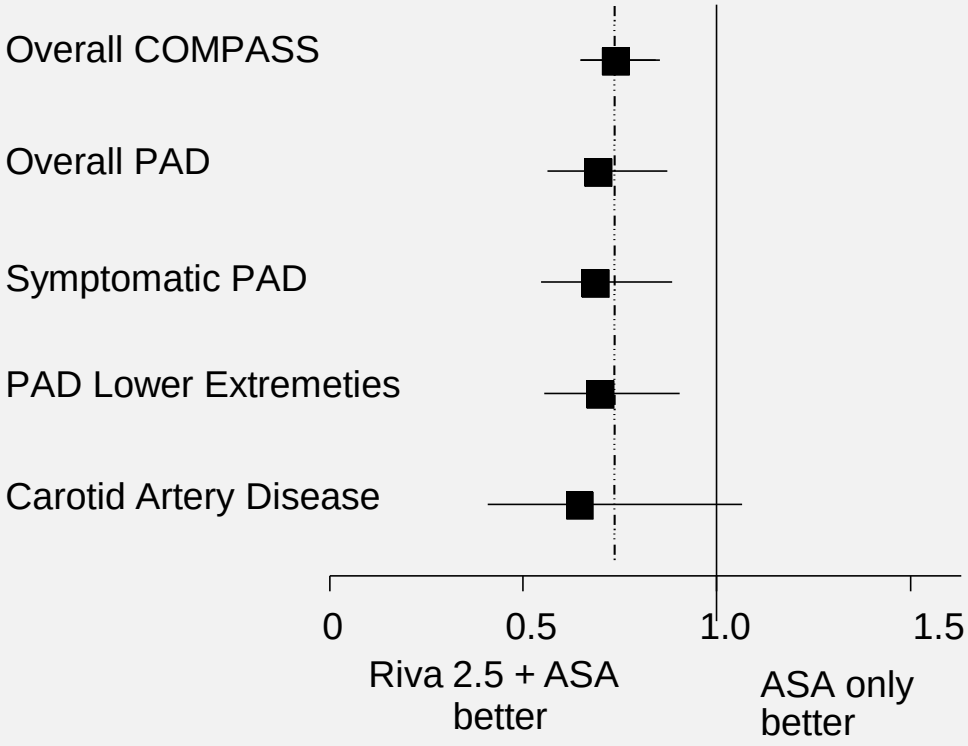
Rivaroxaban vs. Aspirin HR: 0.84 (0.69-1.02) P=0.08

No. at Risk

Riva + ASA	**2492**	**2069**	**893**	**124**
Riva	**2474**	**2023**	**864**	**147**
ASA	**2504**	**2034**	**911**	**113**

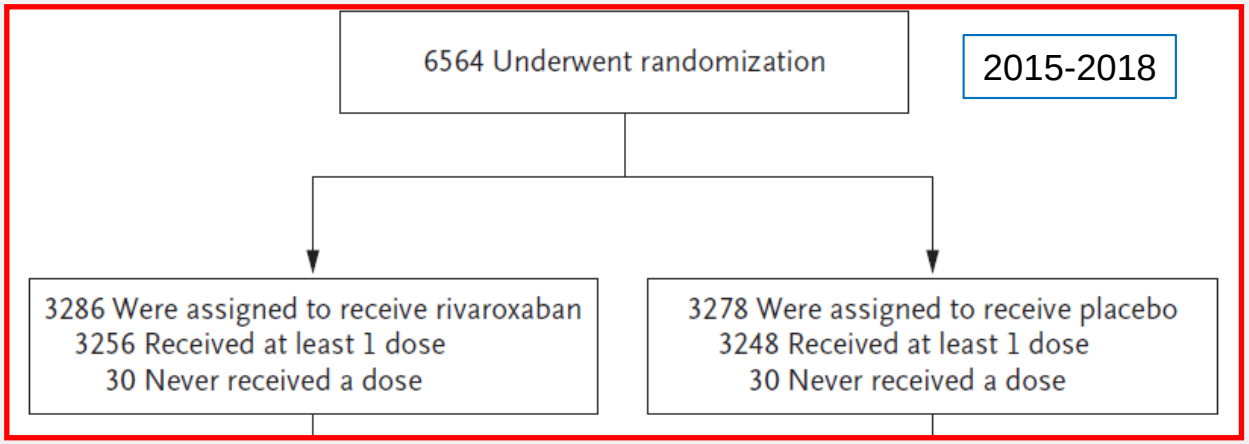
COMPASS PAD

MACE, MALE or Major Amputation



After PAD Revascularization: VOYAGER-PAD

ASA + Rivaroxaban 2.5mg BID vs ASA alone



Qualifying revascularization (within 10 days):
- Endovascular: 65%
- Surgical: 35%

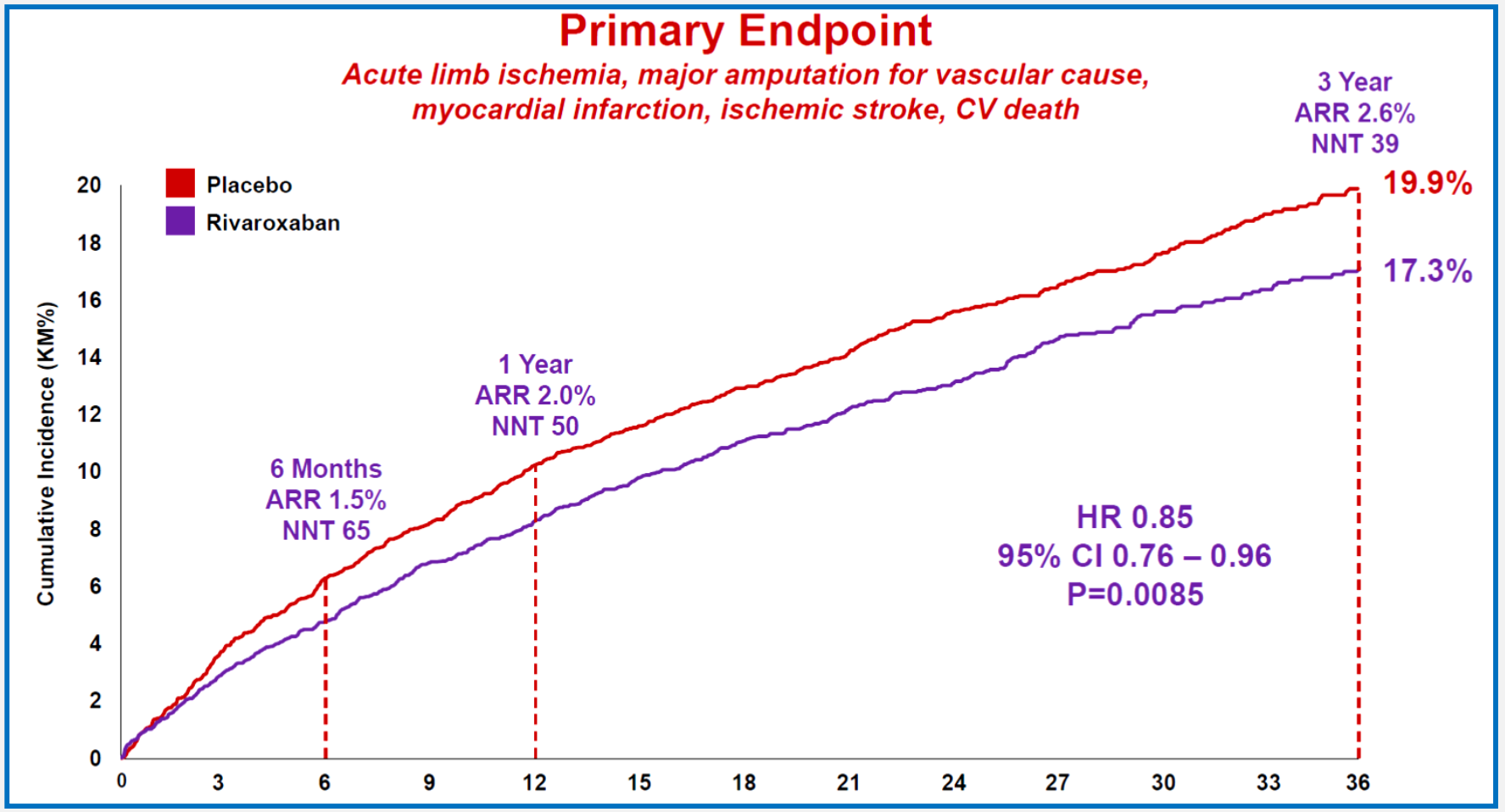
Indication:
- Claudication: 77%
- CLI: 23%

Primary outcome: Composite of ALI, major amputation (vascular), MI, ischemic stroke, CV death

Bonaca MP, et al. NEJM 2020

Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



Months from Randomization

VOYAGER PAD : Bleeding Outcomes

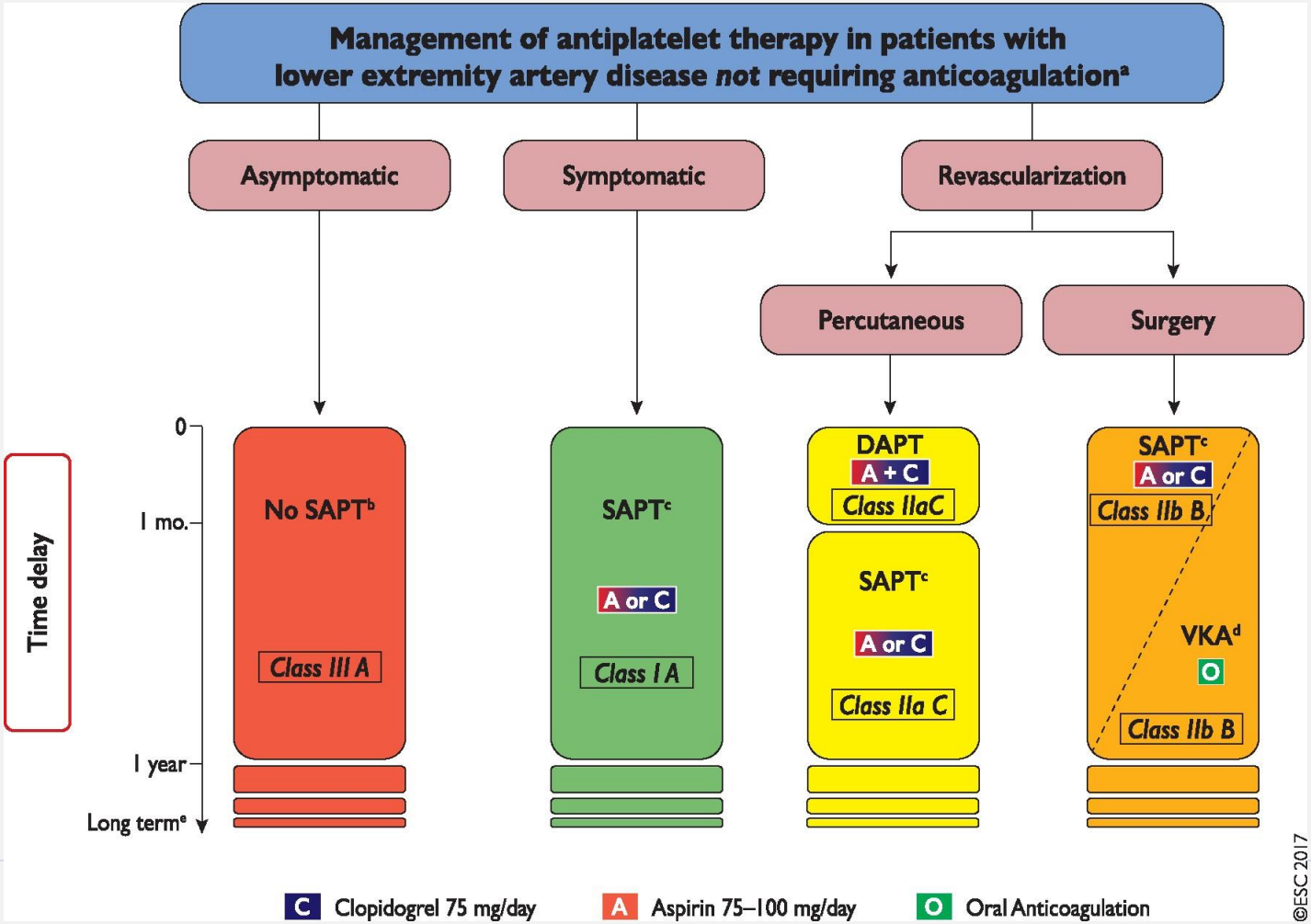
	ASA + Riva 2.5mg	ASA alone	HR (95% CI)	P-value
TIMI major bleeding	62	44	1.43 (0.97-2.10)	0.07
Fatal	6	6	1.02 (0.33-3.15)	-
Intracranial	13	17	0.78 (0.38-1.61)	-
ISTH major bleeding	140	100	1.42 (1.10-1.84)	0.007

ESC 2017

Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with PADs.[27,28]	I	B
Healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.[31,32]	I	A
In patients with PADs, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by ≥50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).[25]	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.[51]	I	C[d]
In patients with PADs and hypertension, it is recommended to control blood pressure at <140/90 mmHg.[41,42,52]	I	A
ACEIs or ARBs should be considered as first-line therapy[c] in patients with PADs and hypertension.[47,53]	IIa	B

Lower extremities artery disease		
Long-term SAPT is recommended in symptomatic patients.[51,54,68]	I	A
Long-term SAPT is recommended in all patients who have undergone revascularization.[72]	I	C
SAPT is recommended after infra-inguinal bypass surgery.[72,88,89]	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin.[51,69]	IIb	B
Vitamin K antagonists may be considered after autologous vein infra-inguinal bypass.[73]	IIb	B
DAPT with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation.	IIa	C
DAPT with aspirin and clopidogrel may be considered in below-the-knee bypass with a prosthetic graft.[64]	IIb	B
Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated[d] asymptomatic LEAD.[66, 67]	III	A

Antiplatelet therapy in patients with lower extremity artery disease.



Eur Heart J, Volume 39, Issue 9, 01 March 2018, Pages 763–816

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2024

CLINICAL PRACTICE GUIDELINE

2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease

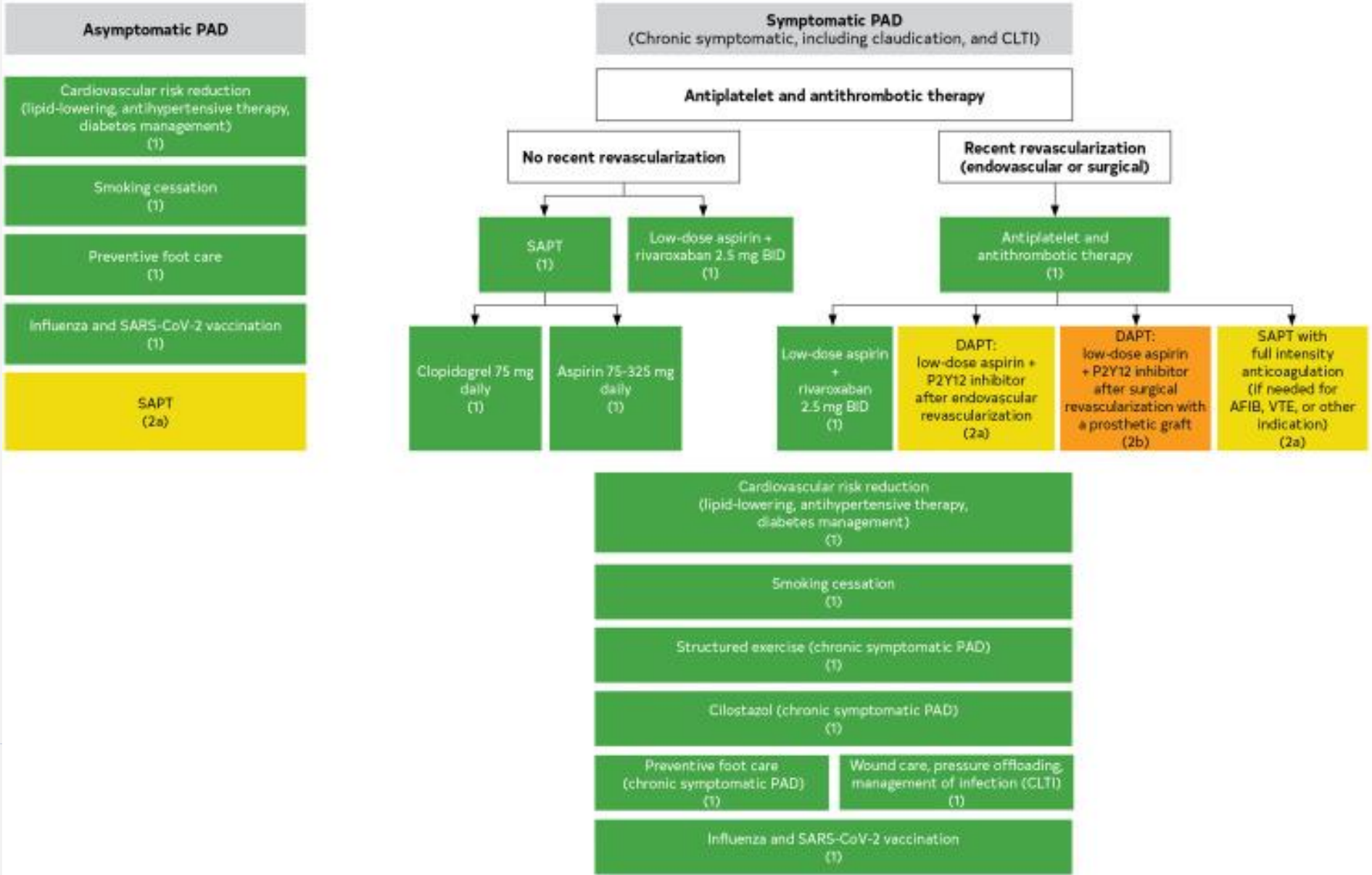
A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Podiatric Medical Association, Association of Black Cardiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, Society of Interventional Radiology, and Vascular & Endovascular Surgery Society

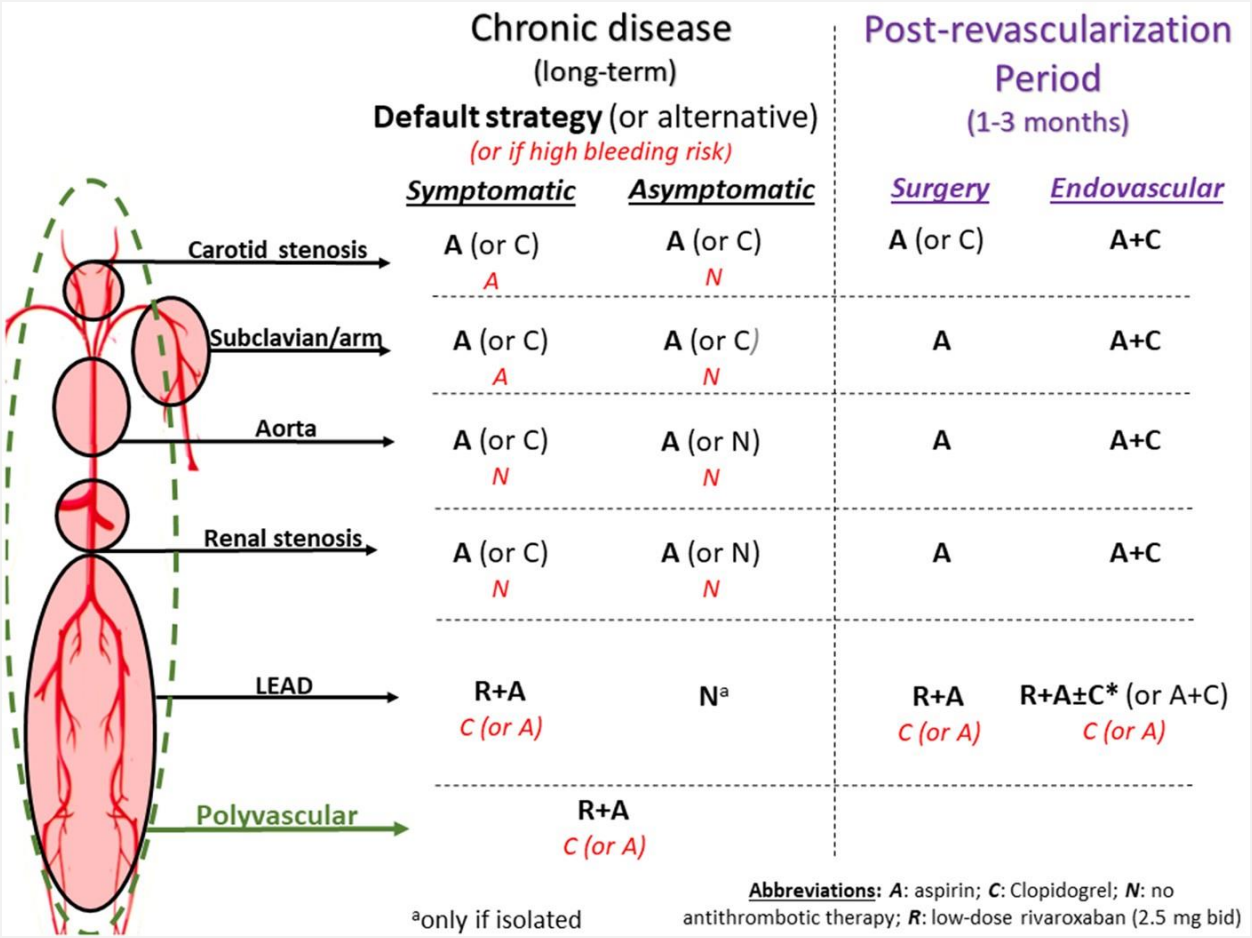
2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with symptomatic PAD, single antiplatelet therapy is recommended to reduce the risk of MACE.[1-4]
1	B-R	2. In patients with symptomatic PAD, single antiplatelet therapy with clopidogrel alone (75 mg daily) is recommended to reduce the risk of MACE.[4]
1	C-LD	3. In patients with symptomatic PAD, single antiplatelet therapy with aspirin alone (range, 75-325 mg daily) is recommended to reduce the risk of MACE.[1-3]
1	A	4. In patients with symptomatic PAD, low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is effective to reduce the risk of MACE and MALE.[5,6]
1	B-R	5. After endovascular or surgical revascularization for PAD, antiplatelet therapy is recommended.[1,7-9]
1	A	6. After endovascular or surgical revascularization for PAD, low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is recommended to reduce the risk of MACE and MALE.[7]

2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease



Summary of optimal and alternative antithrombotic strategies in patients with peripheral arterial disease. ...



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Merci pour votre attention