Angiologie: les anti-thrombotiques, bonnes pratiques

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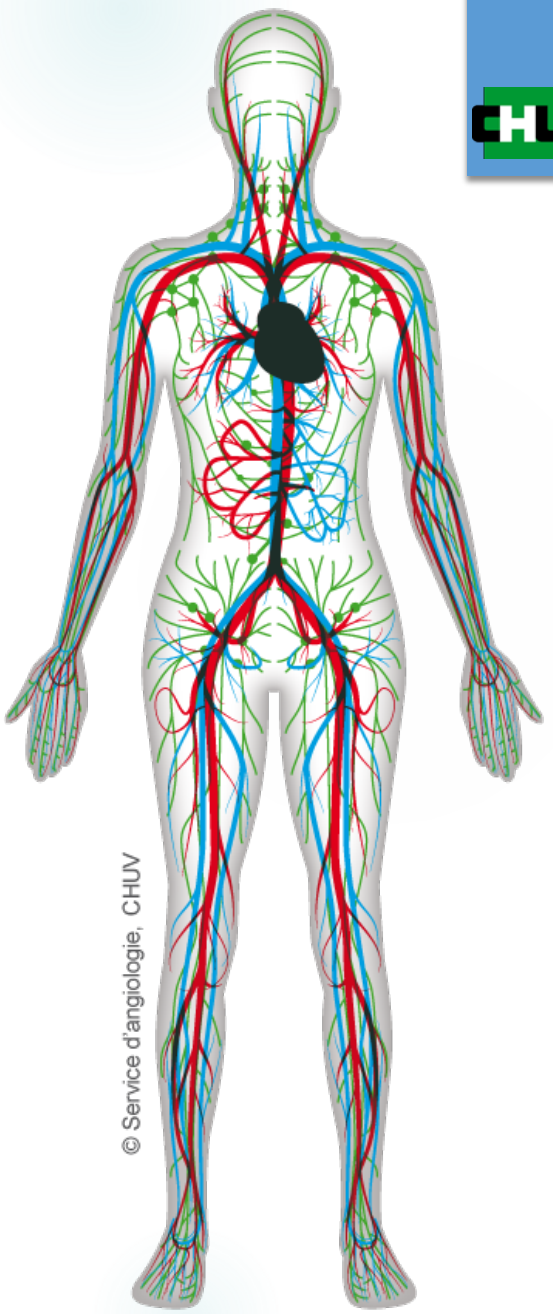
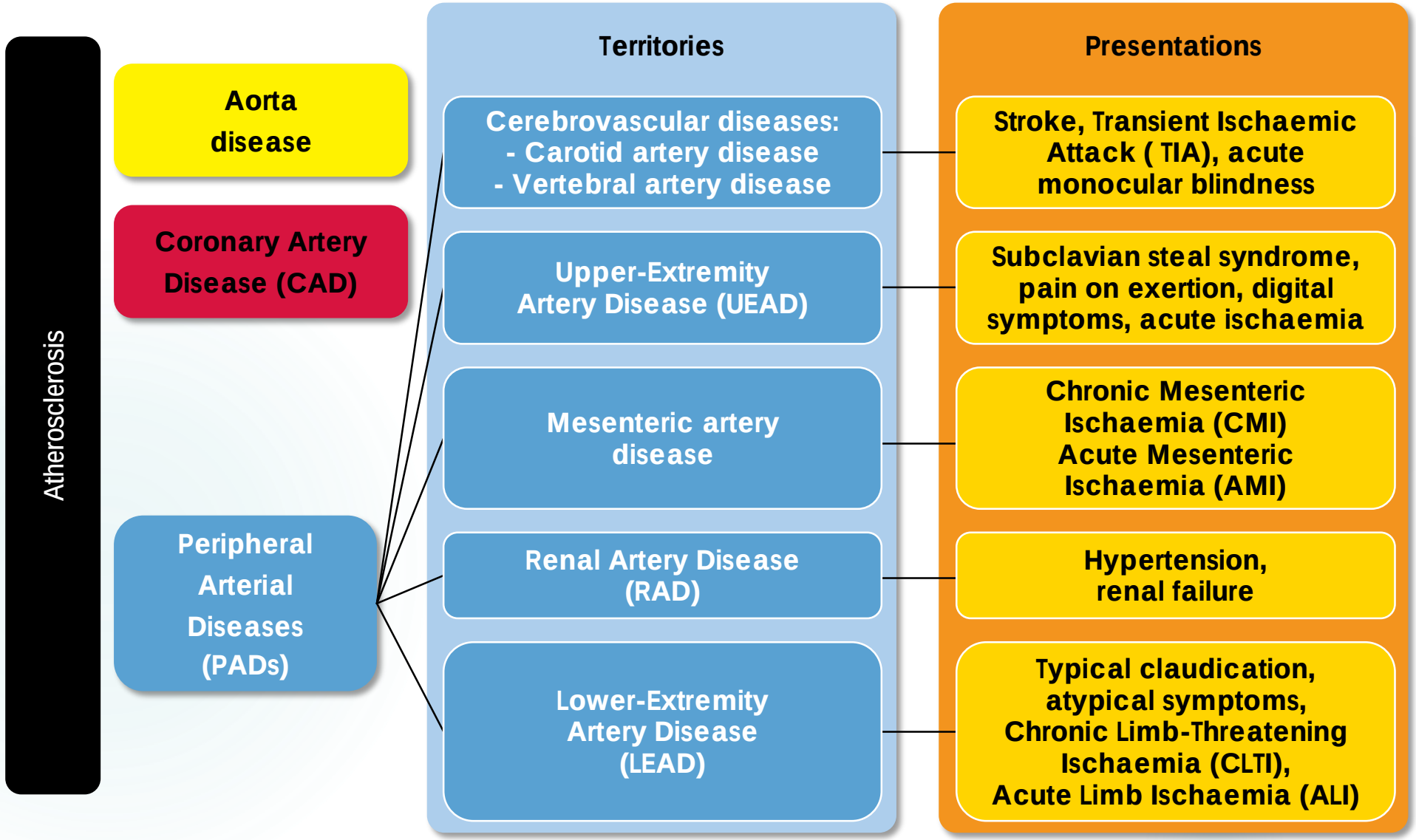


Presentations of Peripheral Arterial Diseases (PADs)

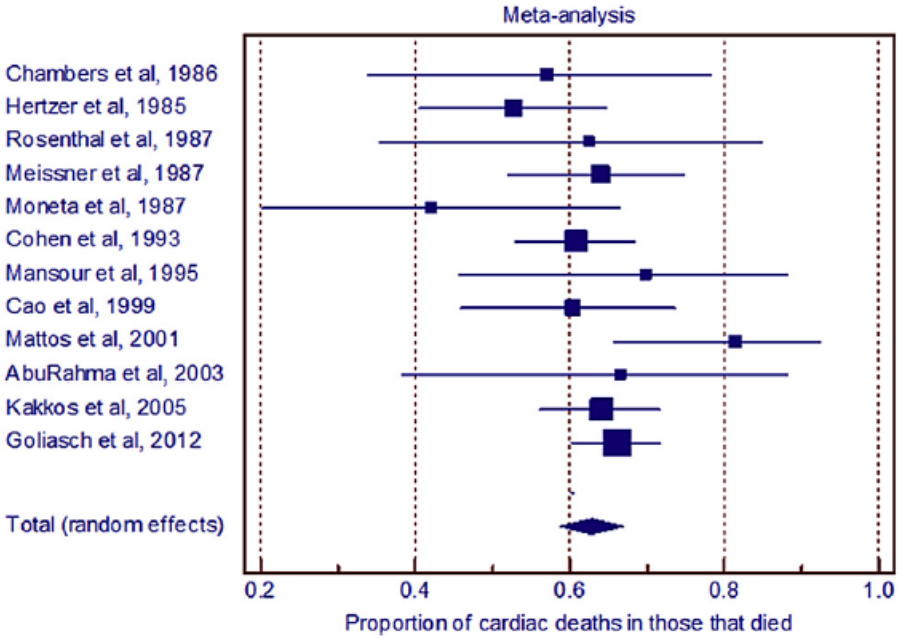


PADs and CVD risk

- Atherosclerosis is a generalized disease. Patients affected at one site are overall at risk for fatal and non-fatal cardiovascular events

Carotid artery stenosis

Systematic review including 11'391 pts with >50% asymptomatic carotid stenosis



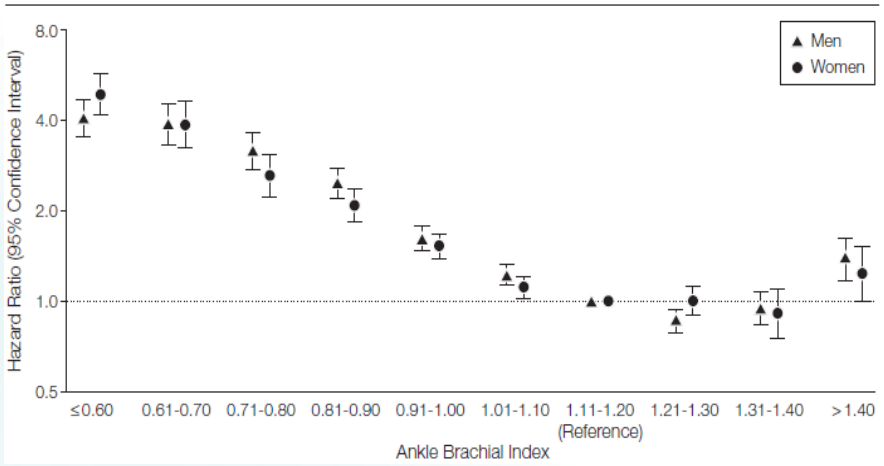
63% of late deaths related to cardiac events, mean cardiac-related mortality rate of 2.9%/yr

Giannopoulos K et al, EJVES, 2015

PADs and CVD risk

Lower extremity arterial disease (LEAD)

Systematic review including 24955 men and 23339 women from general population with ABI measure at baseline



ABI ≤0.90 associated with twice the 10-yr total mortality, CV mortality, and major coronary event rate compared with the overall rate in each Framingham risk score category

Ankle Brachial Index Collaboration, JAMA, 2008

In the overall stable population with arterial disease, ~1 in 7 pts with atherosclerosis will experience CV death, MI, stroke or hospitalization within 1 yr

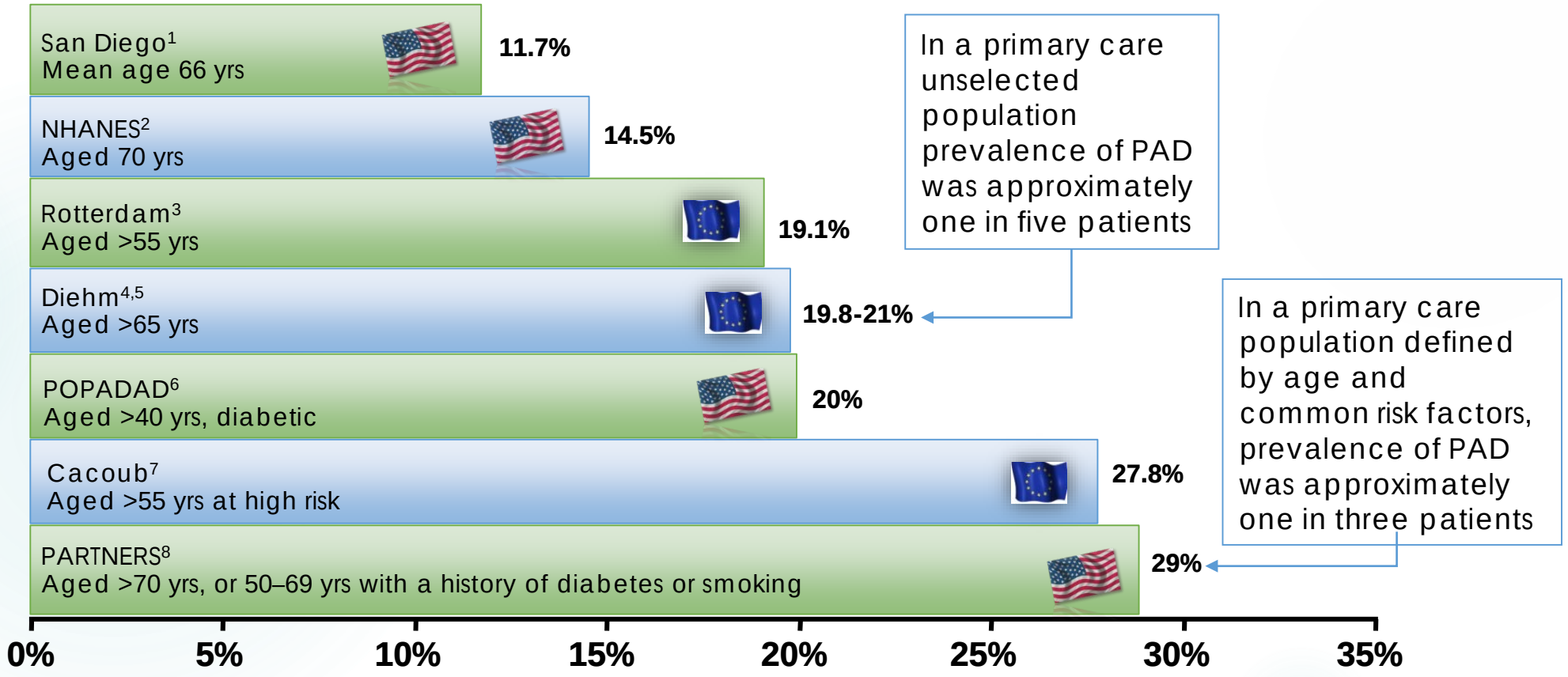
LEAD (n= 858)	21.1% 1 in ~5	
CAD (n=38602)	15.2% 1 in ~6	
CVD (n=18013)	14.5% 1 in ~7	

Steg et al, JAMA, 2007 (REACH registry)

L’artériopathie périphérique des MI

La prévalence de l'AOMI est élevée chez les patients consultant les praticiens

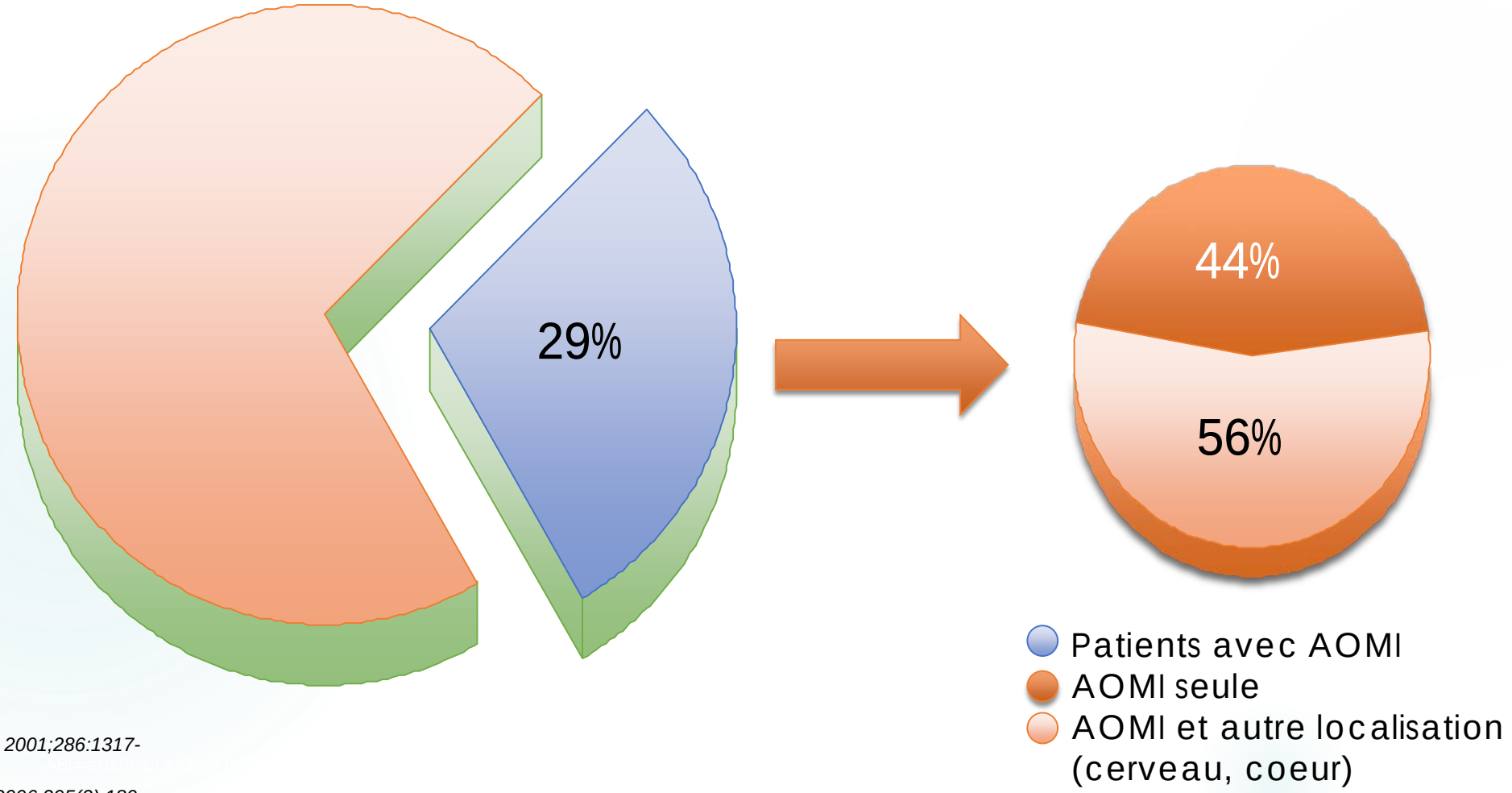
Prévalence élevée dans le monde entier, dans tous les groupes ethniques, chez les hommes comme chez les femmes



1. Criqui MH, et al. *Circulation* 1985. 2. Selvin E, Erlinger TP. *Circulation*. 2004. 3. Meijer WT, et al. *Arterioscler Thromb Vasc Biol* 1998. 4. Diehm C, et al. *Atherosclerosis* 2004. 5. Diehm C. et al. *Circulation* 2009. 6. Newman et al. *Arterioscler Thromb Vasc Biol* 1999. 7. Cacoub P. et al. *Clinical practice* 2009. 8. Hirsch AT, et al. *JAMA* 2001.

Environ 60% des patients avec AOMI* présentent une atteinte vasculaire diffuse

*Diagnostiquée avec la mesure de l'ABI



Hirsch, AT et al. JAMA. 2001;286:1317-24.

Bhatt DL et al,. JAMA 2006;295(2):180-189

Clinical stages of LEAD

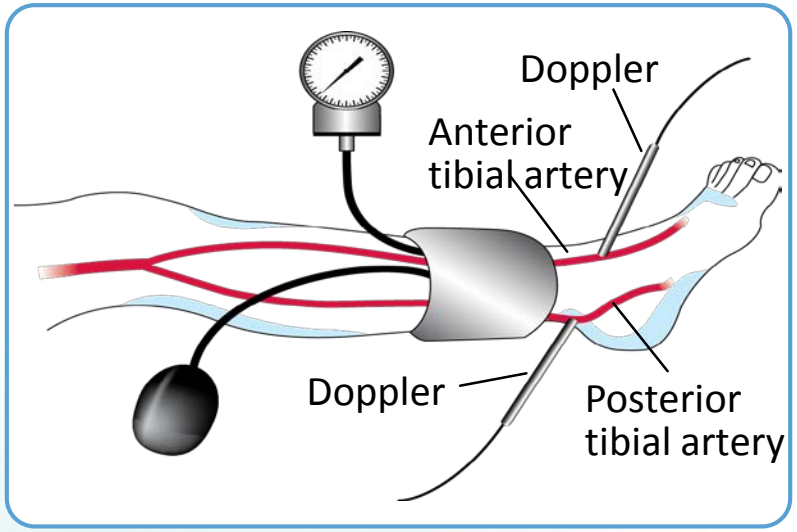
Concept of **« Masked LEAD »** in

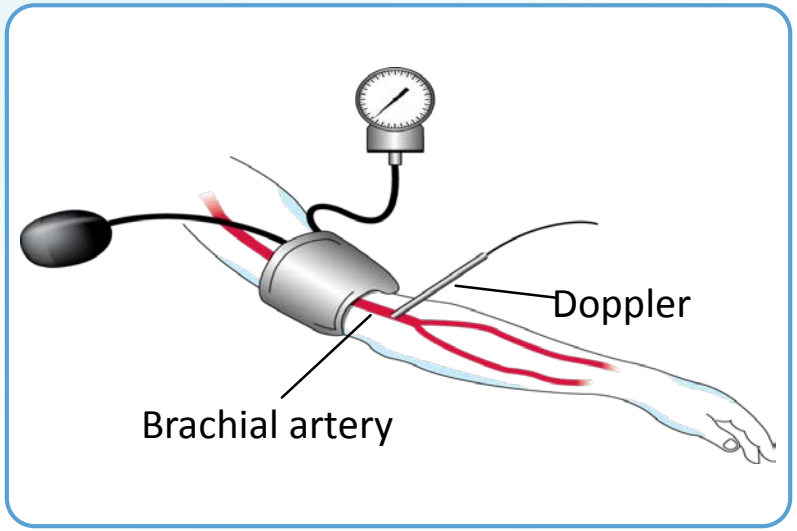
- Aging
- Frailty
- Neuropathy
- Joint disease
- Heart failure
- COPD

…. with limited/no walking

Fontaine classification		
Stage		Symptoms
I		Asymptomatic
II	IIa	Non-disabling intermittent claudication
	IIb	Disabling intermittent claudication
III		Ischaemic rest pain
IV		Ulceration or gangrene

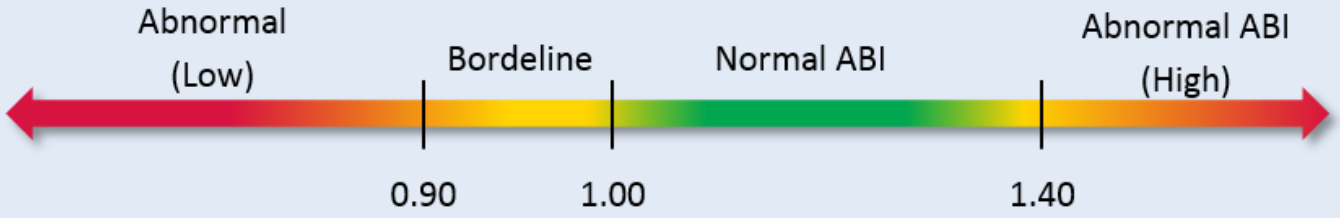
Ankle Brachial Index





3. How to interpret the ABI?

- For diagnosis of LEAD interpret each leg separately (one ABI per leg).
- For the CV risk stratification: take the lowest ABI between the two legs.
- Interpretation:



Aboyans V. et al, ESC guidelines, EHJ, 2017

Quel patient devrait bénéficier d'une mesure de l'ABI en pratique clinique ?

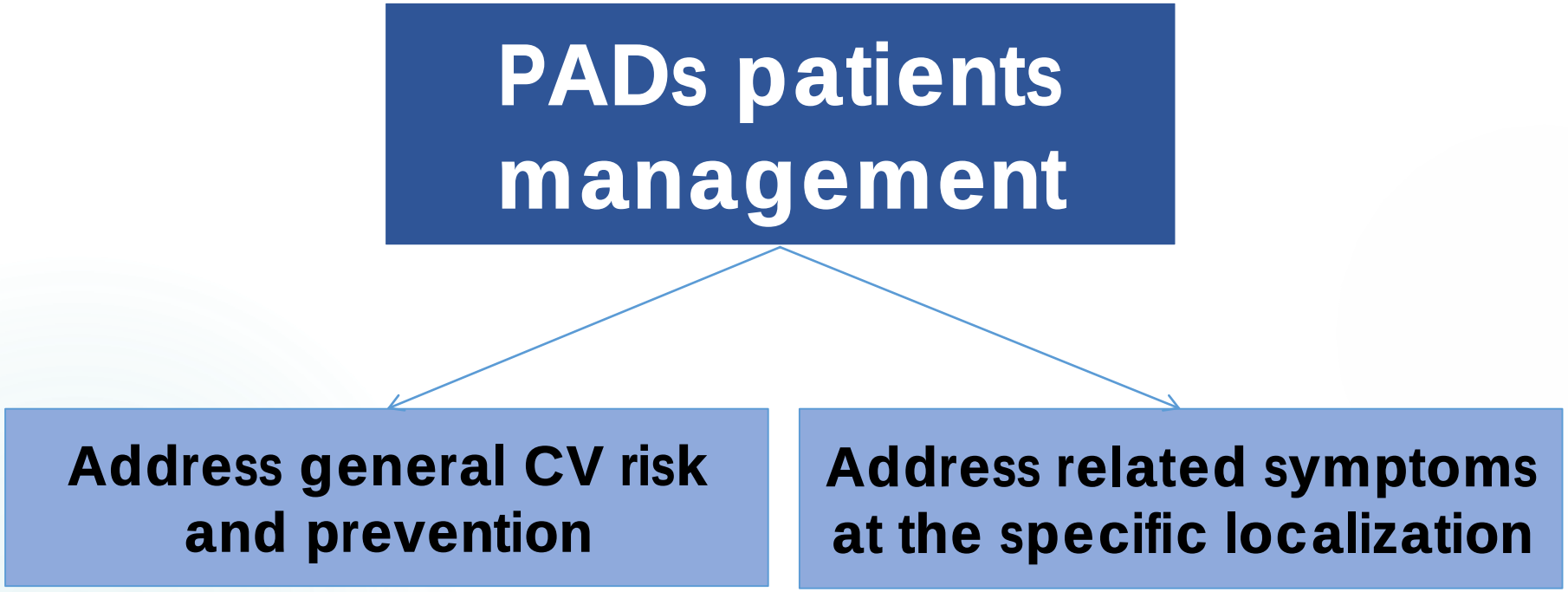
- Patients avec suspicion clinique d'AOMI:
  - Absence de pouls et/ou présence d'un souffle artériel
  - Claudication intermittente typique ou tout symptôme suggérant une AOMI
  - Absence de cicatrisation d'une ulcération des MI

- Patients à risque d'AOMI:
  - Dans un contexte d'athérosclérose: maladie coronarienne, toute atteinte artérielle périphérique
  - Autres conditions: AAA, IRC, arrêt cardiaque

- Patients asymptomatiques libres de tout signe clinique mais à risque de développer une AOMI:
  - Hommes et femmes âgés >65 ans,
  - Hommes et femmes âgés <65 ans classés à haut risque CV risque selon les Guidelines ESC,
  - Hommes et femmes âgés >50 ans avec antécédents familiaux d'AOMI

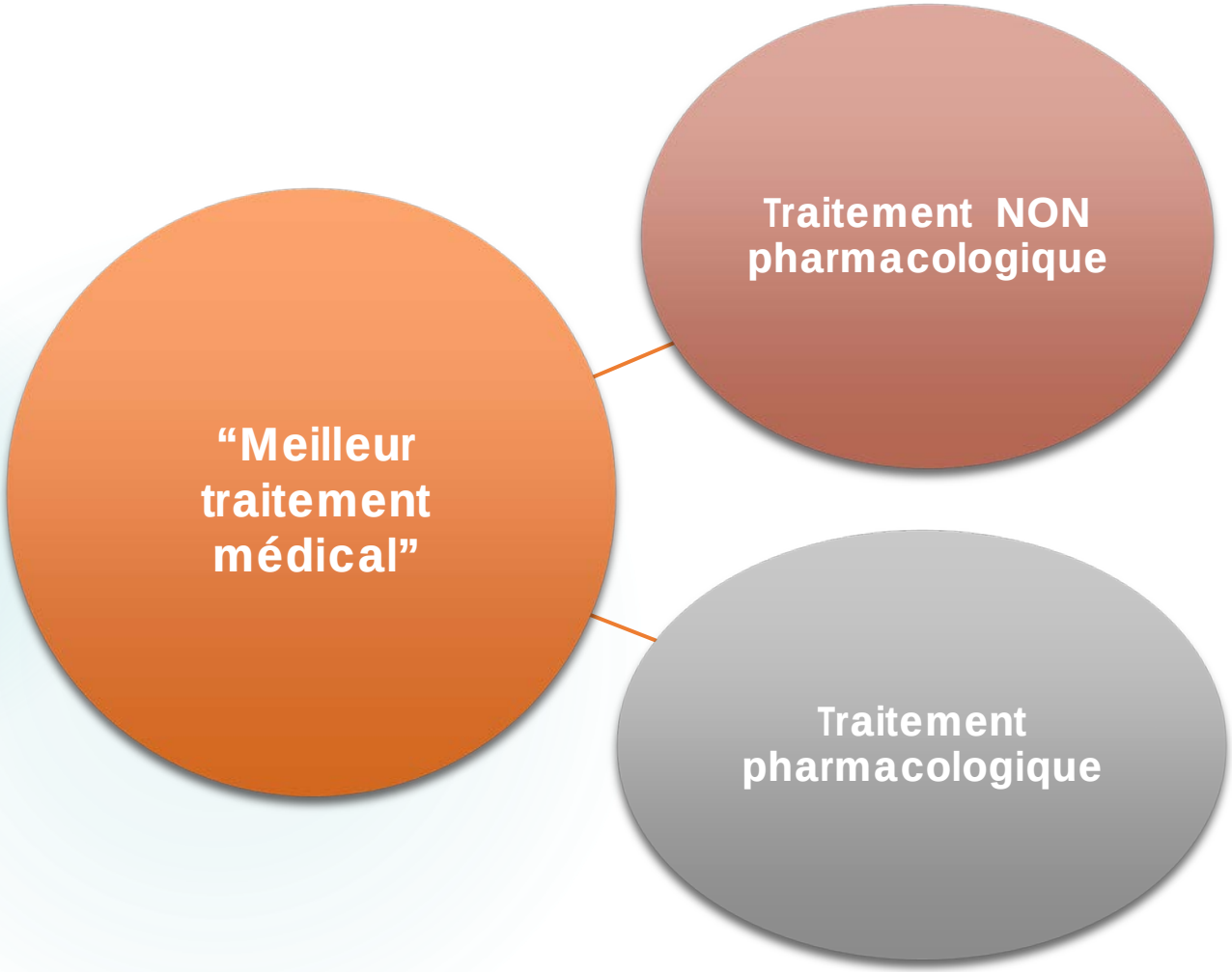
Aboyans V. et al, ESC guidelines, EHJ, 2017

PADs patients management



Recommendations	Class	Level
In healthcare centres, it is recommended to set up a multi-disciplinary **Vascular Team** to make decisions for the management of patients with PADs.	I	C

General CV prevention



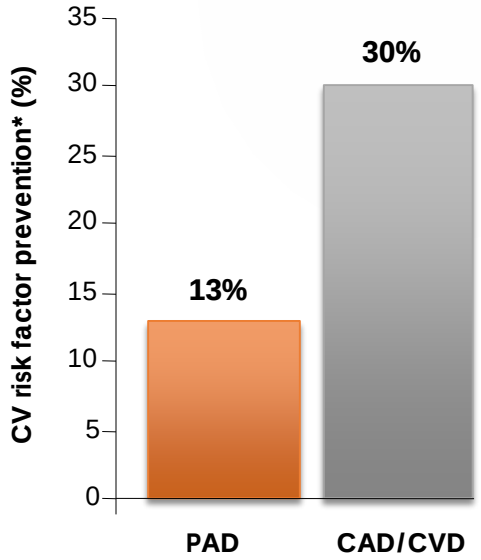
- Arrêt du tabagisme
- Diète saine
- Contrôle du poids
- Exercice physique régulier

- Antihypertenseurs
- Hypolipémiants
- Contrôle optimale du glucose chez les pts diabétiques
- Antithrombotiques

Réduction de la morbidité / mortalité: Le contrôle étroit des facteurs de risque demeure une étape essentielle

- Arrêt du tabagisme
- Modification du taux de cholestérol
- Contrôle des valeurs tensionnelles
- Réduction de l'obésité
- Contrôle du diabète

8'475 patients with at least one site of proven atherosclerosis disease (primary French care practices)



* antihypertensive, antiplatelet, lipid lowering drugs

Blacher et al J Vasc Sur, 2006

Antithrombotic agents in LEAD

- Antihrombotic therapy is part of **best medical treatment** for symptomatic PADs

- In LEAD patients, antiplatelet agents are used to:
  - Prevent limb-related events
  - Prevent CV events

Antithrombotic therapy in patients with **asymptomatic** LEAD

Recommendations	Class	Level
Lower extremity artery disease		
Because of a lack of proved benefit, antiplatelet therapy is not routinely indicated in patients with isolated* **asymptomatic** LEAD.	III	A

- Randomized trials are negative (POPADAD[1], AAA[2])
- There are safety issues

* Without any other clinical CV condition requiring antiplatelet therapy (e.g. CHD or other multisite artery disease)

[1] *The Prevention of Progression of Arterial Disease and Diabetes trial, BMJ, 2008*
[2] *The Aspirine fo Asymptomatic Atherosclerosis trial, JAMA, 2010*

Antithrombotic therapy in patients with **symptomatic** LEAD

Recommendations	Class	Level
Lower extremity artery disease		
Long-term SAPT* is recommended in **symptomatic** patients	I	A

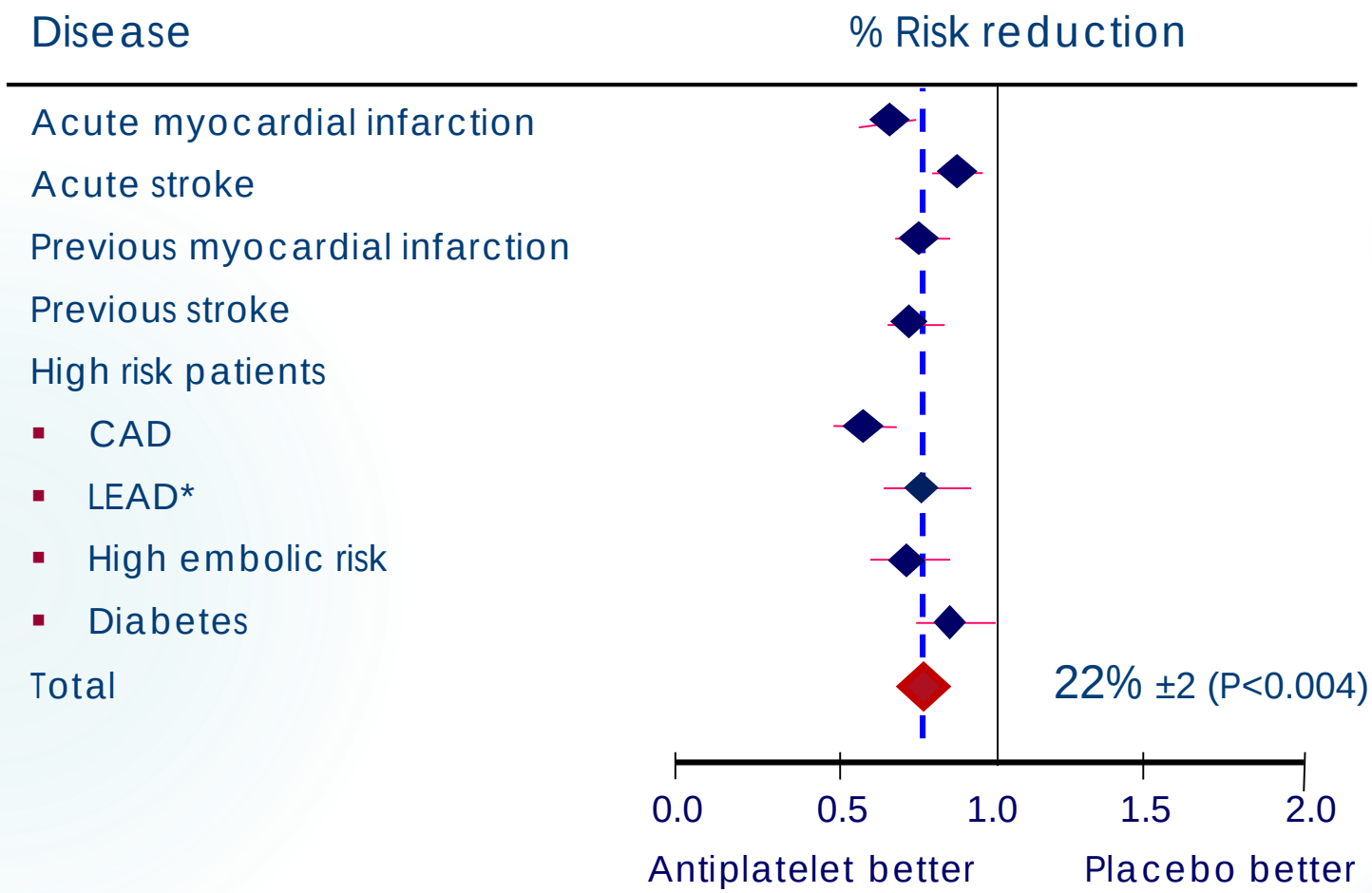
- To date, data proving superiority of dual antiplatelet treatment (DAPT) over aspirine alone, to reduce CV events in patients with LEAD, are lacking → No recommandation in 2017

**SAPT: single antiplatelet treatment;*

Antithrombotic trialists' Colaboration. BMJ 2002; CAPRIE, Lancet 1996; Aspirine for the prevention of CV events in patients with PAD, JAMA 2009

Antithrombotic Trialists' Collaboration

Risk for cardiovascular events (myocardial infarction, stroke, cardiovascular death)



Antithrombotic Trialists' Collaboration. BMJ 2002; 324: 71–86.

Antithrombotic therapy in patients with **symptomatic** LEAD

Recommendations	Class	Level
Lower extremity artery disease		
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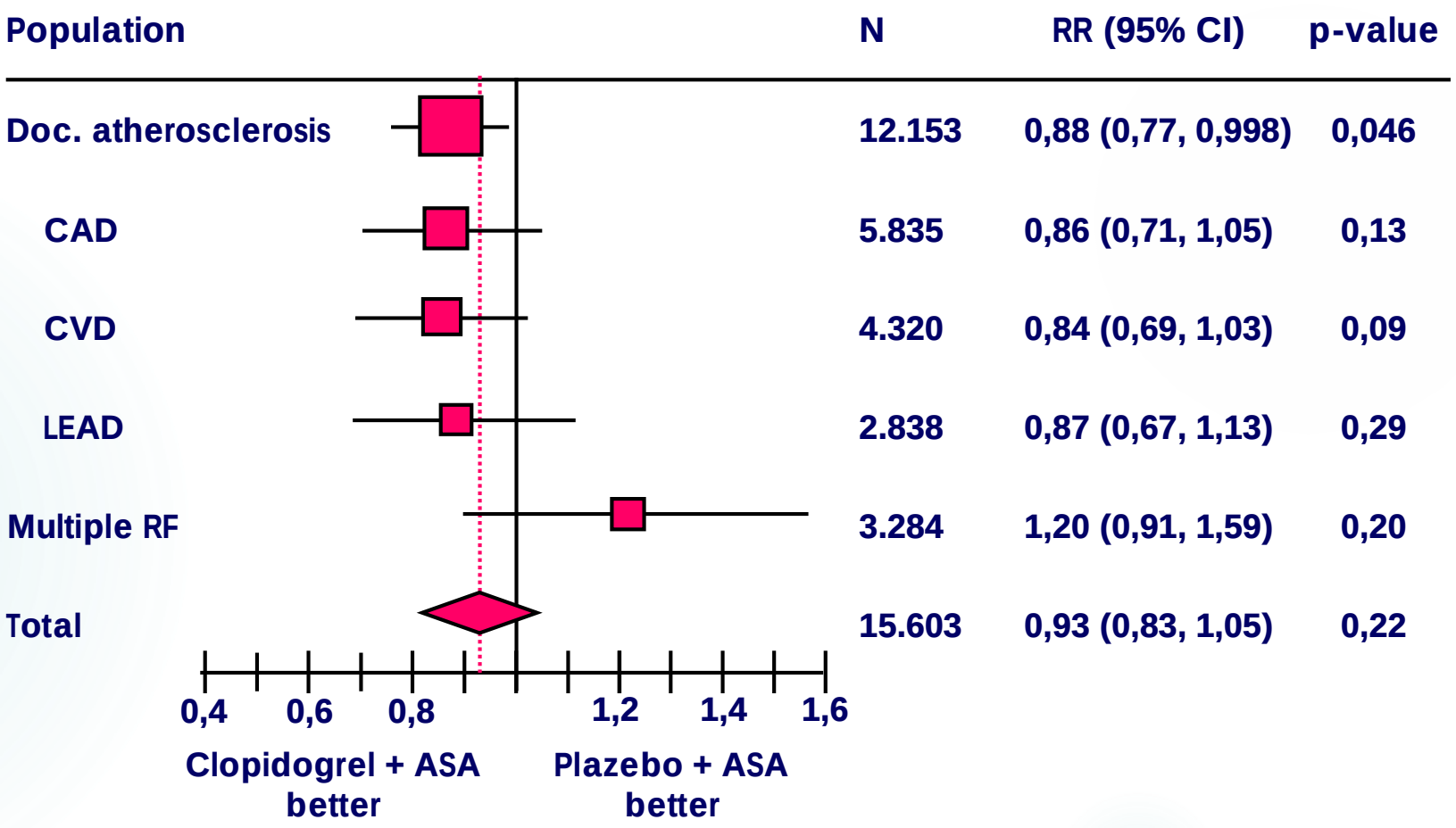
Antithrombotic trialists' Colaboration. BMJ 2002; CAPRIE, Lancet 1996; Aspirine for the prevention of CV events in patients with PAD, JAMA 2009

CHARISMA

(Clopidogrel + ASA vs ASA)



Bhatt D.L., N Engl J Med 2006; 354:1706-17

Antithrombotic therapy in patients with **symptomatic** LEAD *(continued)*

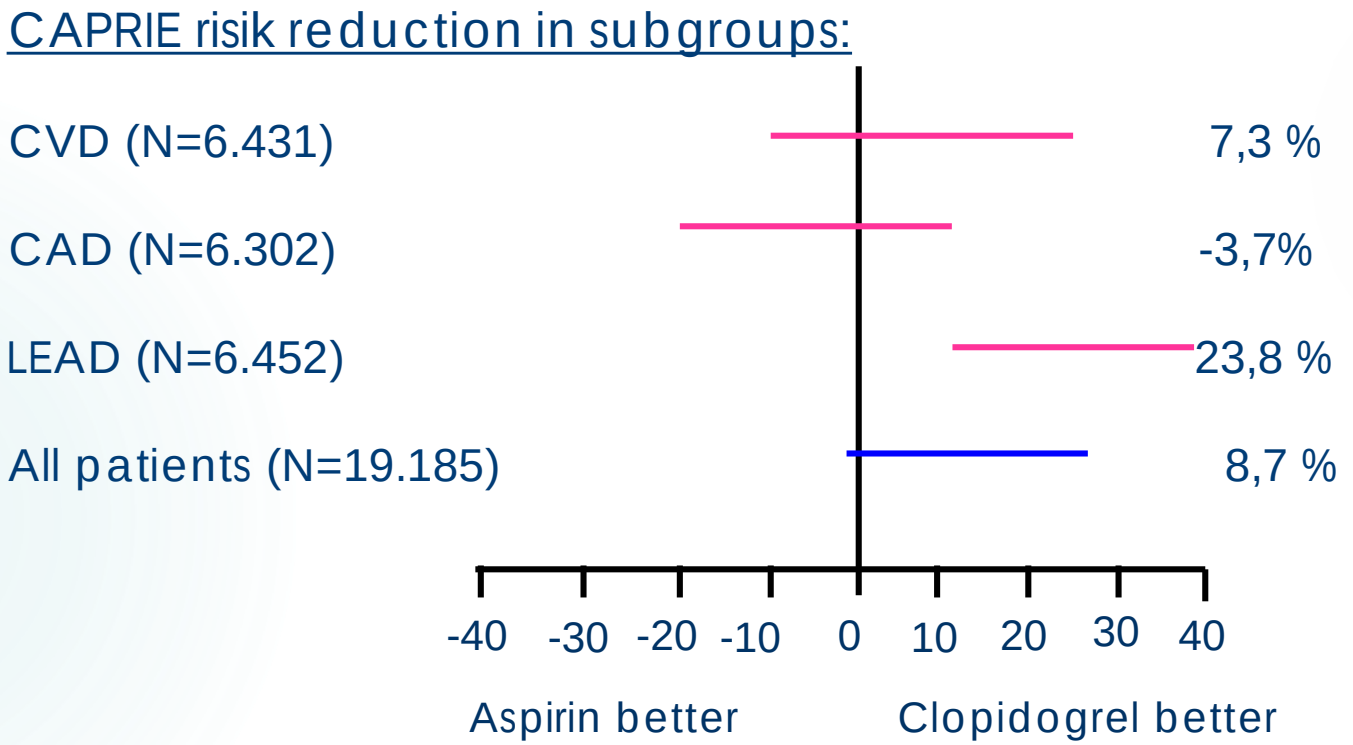
Recommendations	Class	Level
Lower extremity artery disease *(continued)*		
In patients requiring antiplatelet therapy, **clopidogrel** may be preferred over aspirin.	**IIb**	**B**

- **CAPRIE study**: Clopidogrel was superior to aspirine in the subgroup of patients with clinical LEAD → significant reduction in CV mortality and MACE

CAPRIE steering committee, Lancet 1996

CAPRIE

Efficacy of Clopidogrel vs. ASA in MI, stroke or vascular death

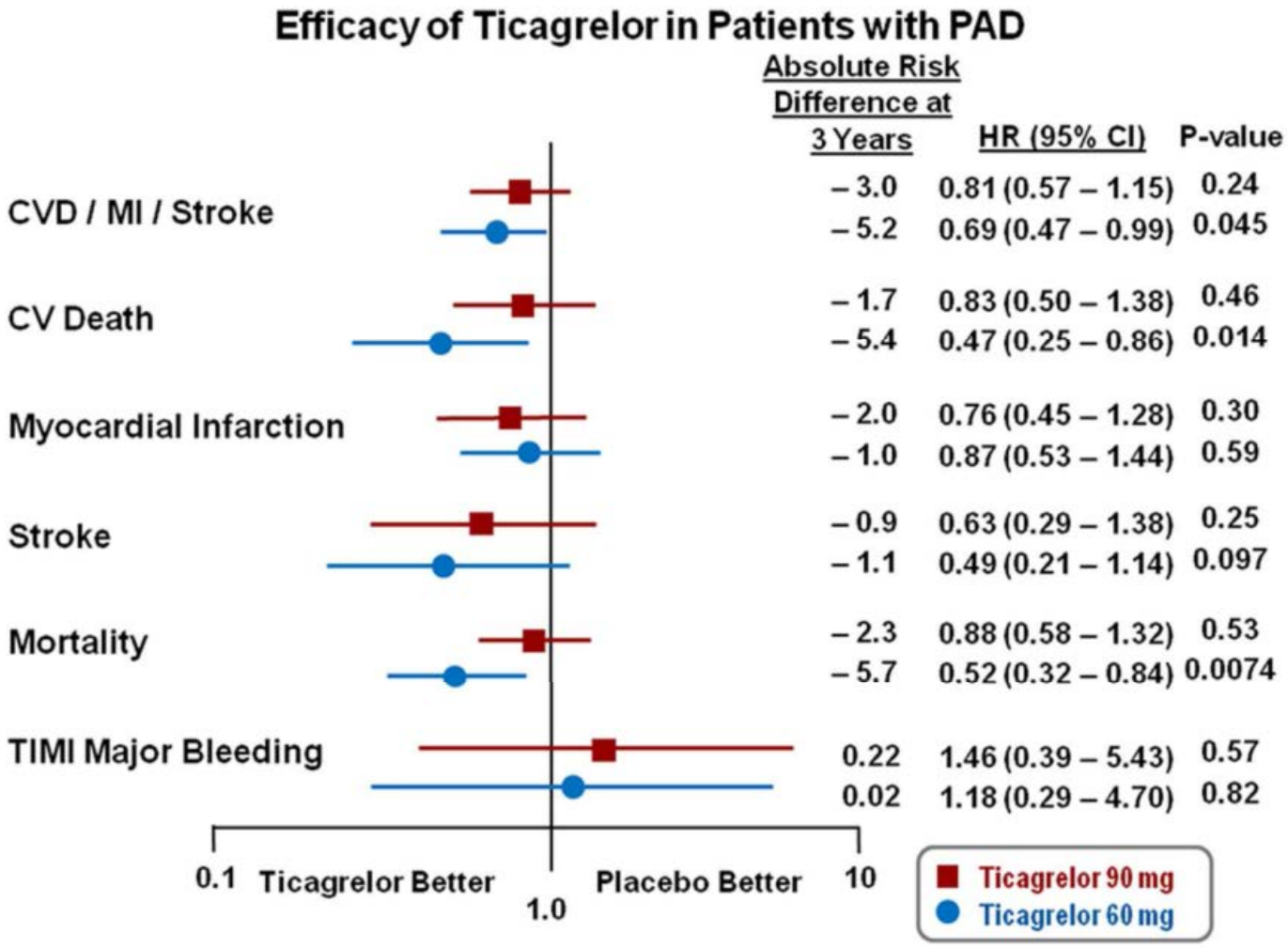


CAPRIE Lancet 1996; 348: 1329–39.

What about other antithrombotics ?

PEGASUS

Long-term therapy with Ticagrelor (90 or 60 mg vs. placebo + ASA 100 after myocardial infarction (Total: N=21,162; subgroup LEAD: N=1,143)

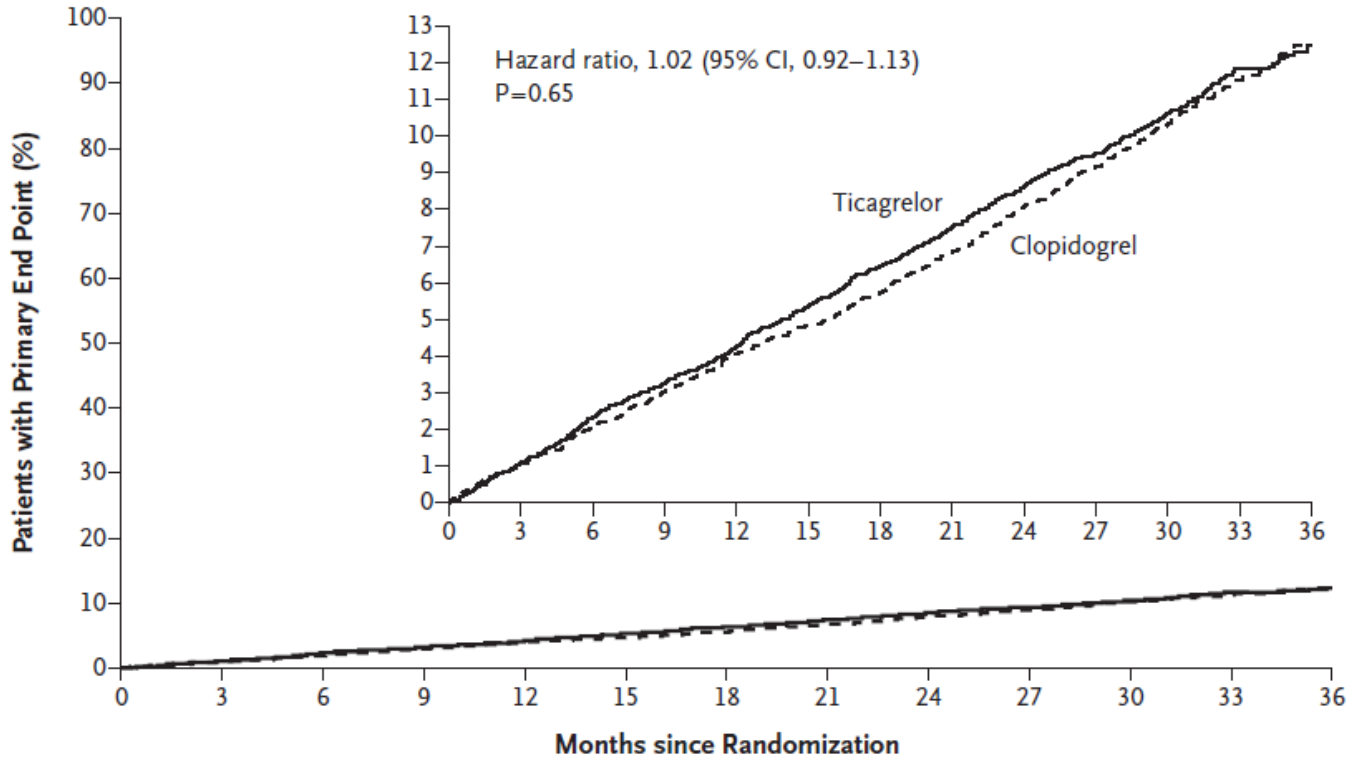


Bonaca MP et al., J Am Coll Cardiol 2016; 67: 2719-28

EUCLID

- Ticagrelor vs Clopidogrel in pts with LEAD
- No reduction in MACE nor MALE
- No decrease in mortality
- No increase in major bleeding

Primary endpoint: cv death, MI, stroke



No. at Risk													
Ticagrelor	6930	6792	6679	6583	6474	6360	6248	6143	6036	5802	3830	2089	865
Clopidogrel	6955	6830	6744	6639	6538	6455	6353	6237	6111	5835	3834	2055	852

Hiatt WR et al., N Engl J Med. 2017; 376: 32-40.

TRA2°P

N=26.449 patients after MI, LEAD or stroke* (*study arm was early stopped); Subgroup LEAD: N=3.787

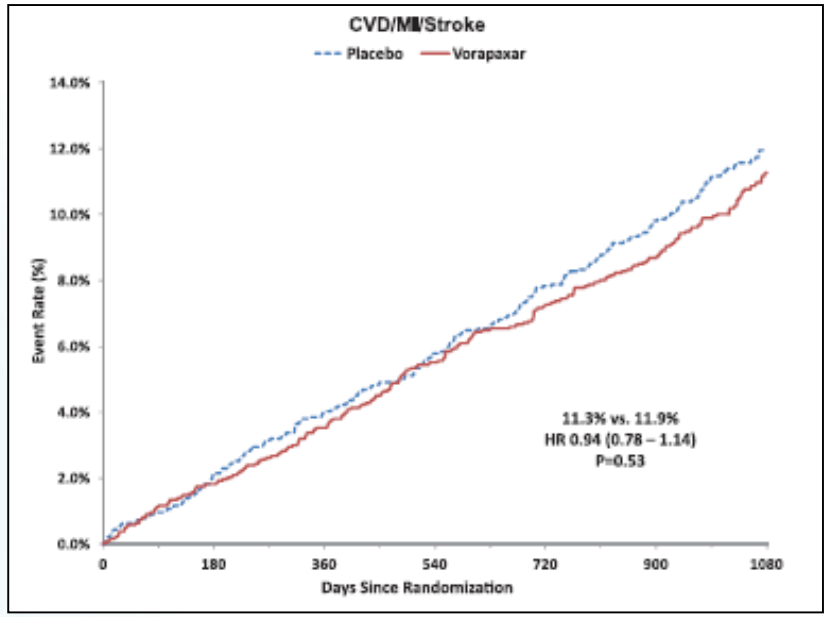
Vorapaxar + ASA vs ASA in pts with stable symptomatic LEAD

No reduction in MACE

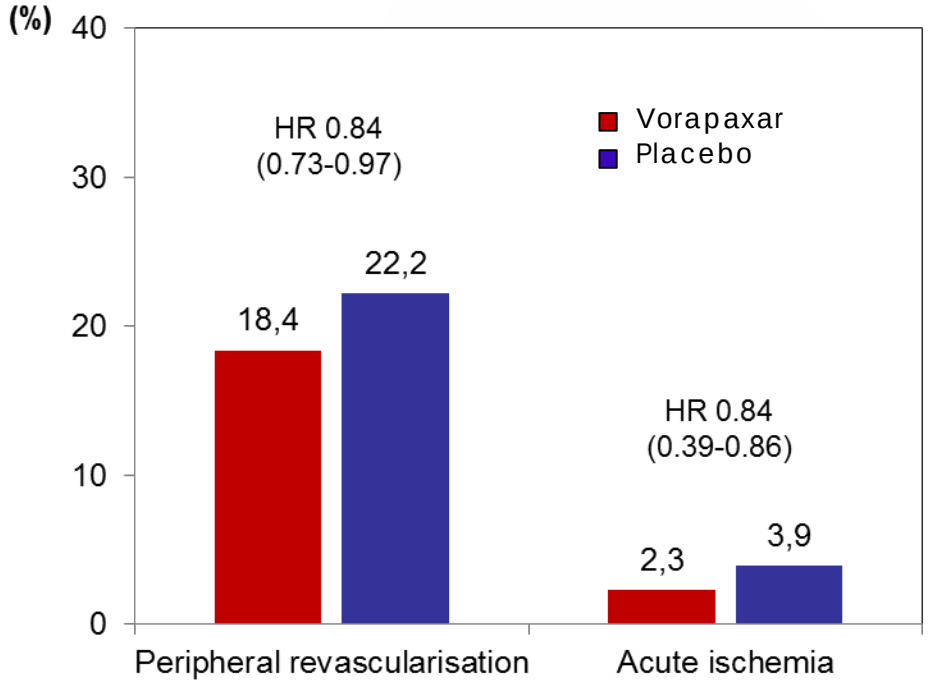
⇩ Hospitalisation for ALI of 42%

⇧ Major bleeding 1.5x

Primary endpoint TRA2°P
(cv death, MI, stroke)



TRA2°P: leg perfusion

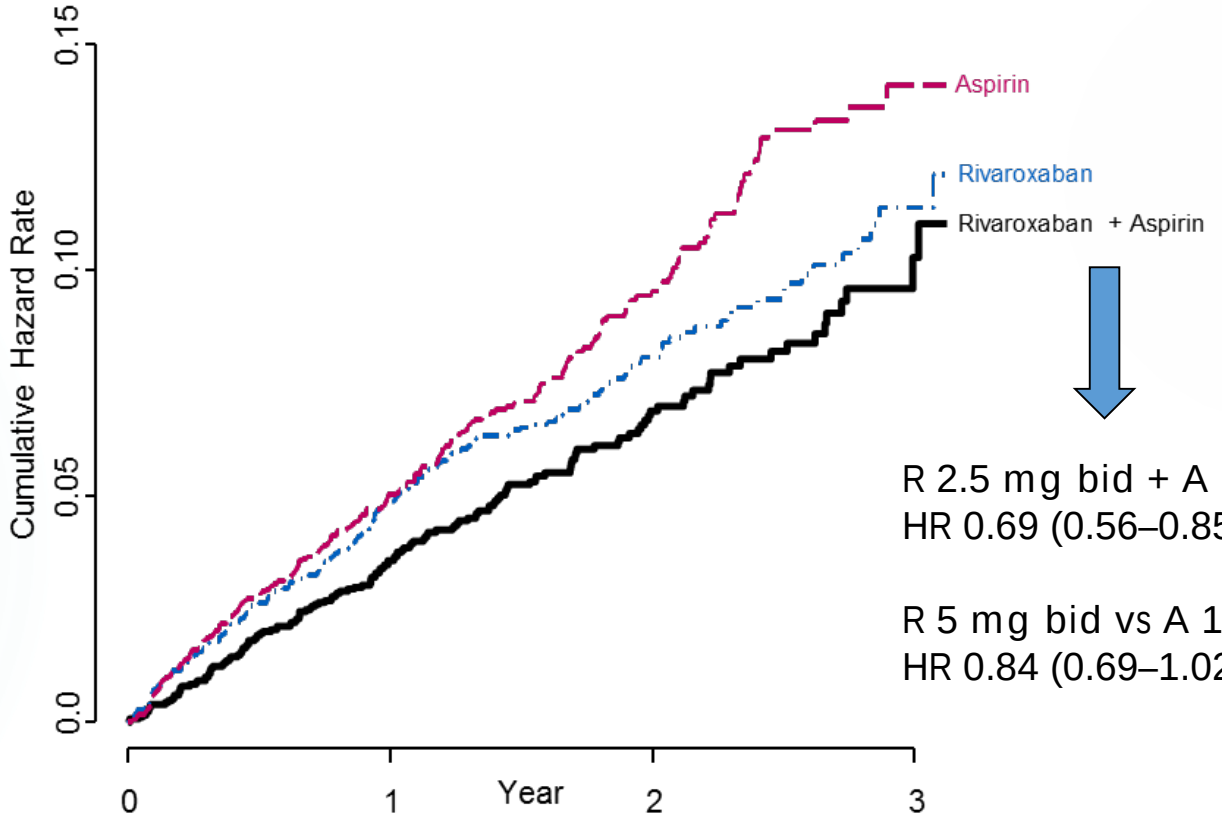


Bonaca MP, J Am Coll Cardiol. 2014; 64: 2309-2317

COMPASS

Cardiovascular OutcoMes for People Using Anticoagulation StrategieS

Cardiovascular death/stroke/MI or MALE including major amputation



R 2.5 mg bid + A 100 mg vs A 100 mg:
HR 0.69 (0.56–0.85), *p*=0.0003

R 5 mg bid vs A 100 mg:
HR 0.84 (0.69–1.02), *p*=0.08

Anand SS et al. ESC 2017, Abs 1157; Anand SS et al. Lancet 2017;In Press

Antithrombotic therapy in patients with LEAD following revascularization

- Improve graft patency, decrease amputation rate, increase survival
- Acceptable bleeding risk

Recommendations	Class	Level
Lower extremity artery disease *(continued)*		
Long-term SAPT is recommended in all patients who have undergone revascularization	I	C

Antithrombotic therapy in patients with LEAD following **bypass-grafting**

Recommendations	Class	Level
Lower extremity artery disease *(continued)*		
SAPT is recommended after infra-inguinal bypass surgery	I	A
Vitamin K antagonists may be considered after autologous **vein** infra-inguinal bypass[1]	IIb	B
DAPT with aspirin and clopidogrel may be considered in **below-knee bypass** with **prosthetic** graft[2]	IIb	B

- No difference between aspirin vs. aspirin plus clopidogrel was found regarding graft occlusion, revascularization, above-ankle amputation, or death
- 35% reduction in primary end-point with DAPT in BTK prosthetic grafts

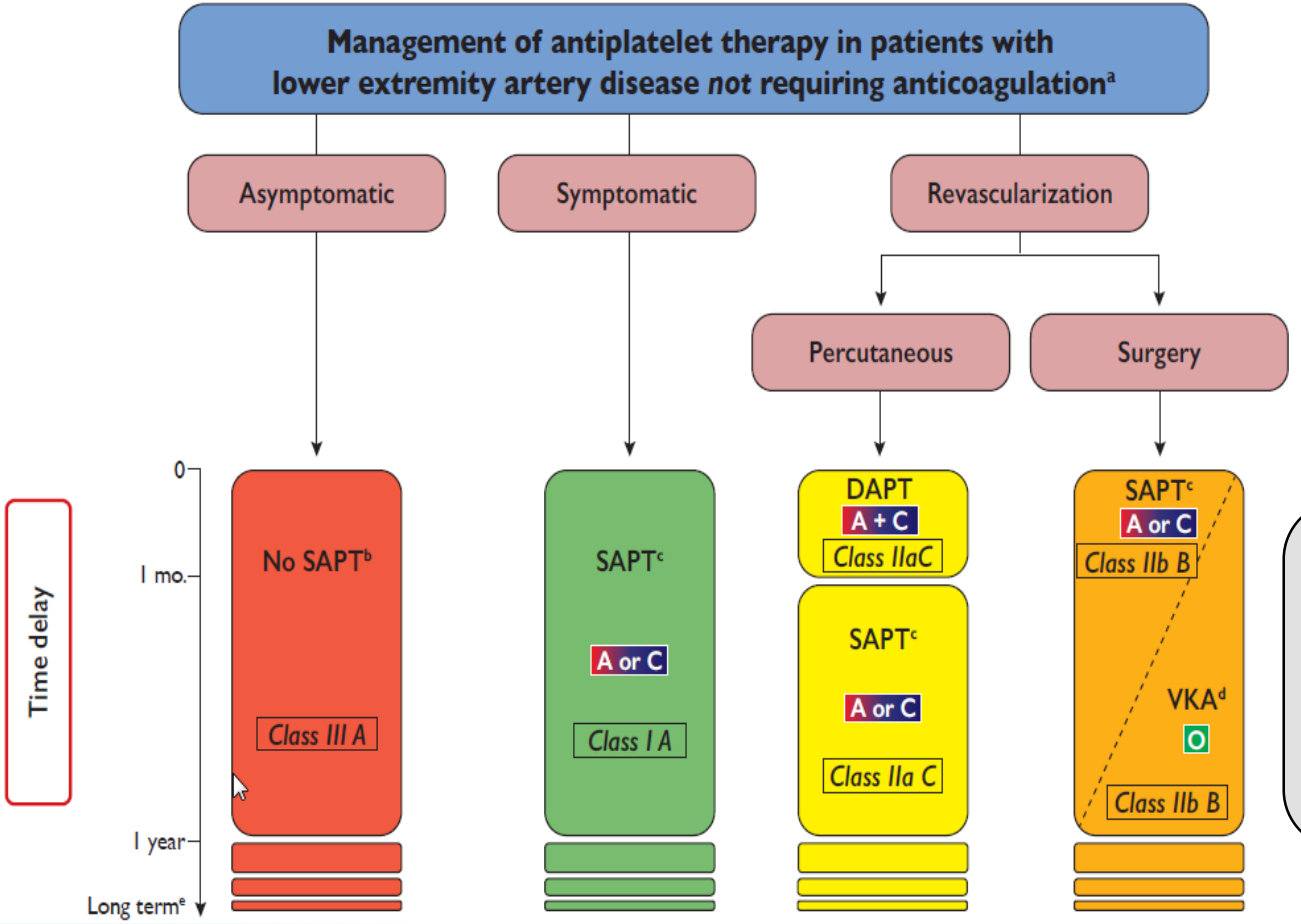
[1]The Dutch Bypass oral Anticoagulants or Aspirin Study, Lancet 2000; [2]CASPAR trial, J Vasc Sur 2010

Antithrombotic therapy in patients with LEAD following **endovascular treatment**

Recommendations	Class	Level
Lower extremity artery disease *(continued)*		
DAPT with aspirin and clopidogrel for **at least one month** should be considered after infra-inguinal stent implantation.	**IIa**	C

- Irrespective of stent type
- No specific evidence for prolonging antiplatelet therapy in below-the-knee stenting
- Anticoagulation did not improve patency while increased bleeding

Summary: patients NOT requiring AC



A Aspirin 75-100 mg/day

C Clopidogrel 75 mg/day

O Oral Anticoagulation

[b]SAPT should be considered if CAD/CAS

[c]DAPT may be considered if ACS/PCI<1 year or complex PCI

[d]Evidence is weak and bleeding doubles as compared to SAPT.

Antithrombotic therapy for LEAD patients requiring oral AC

- First step is to reassess indication for OAC

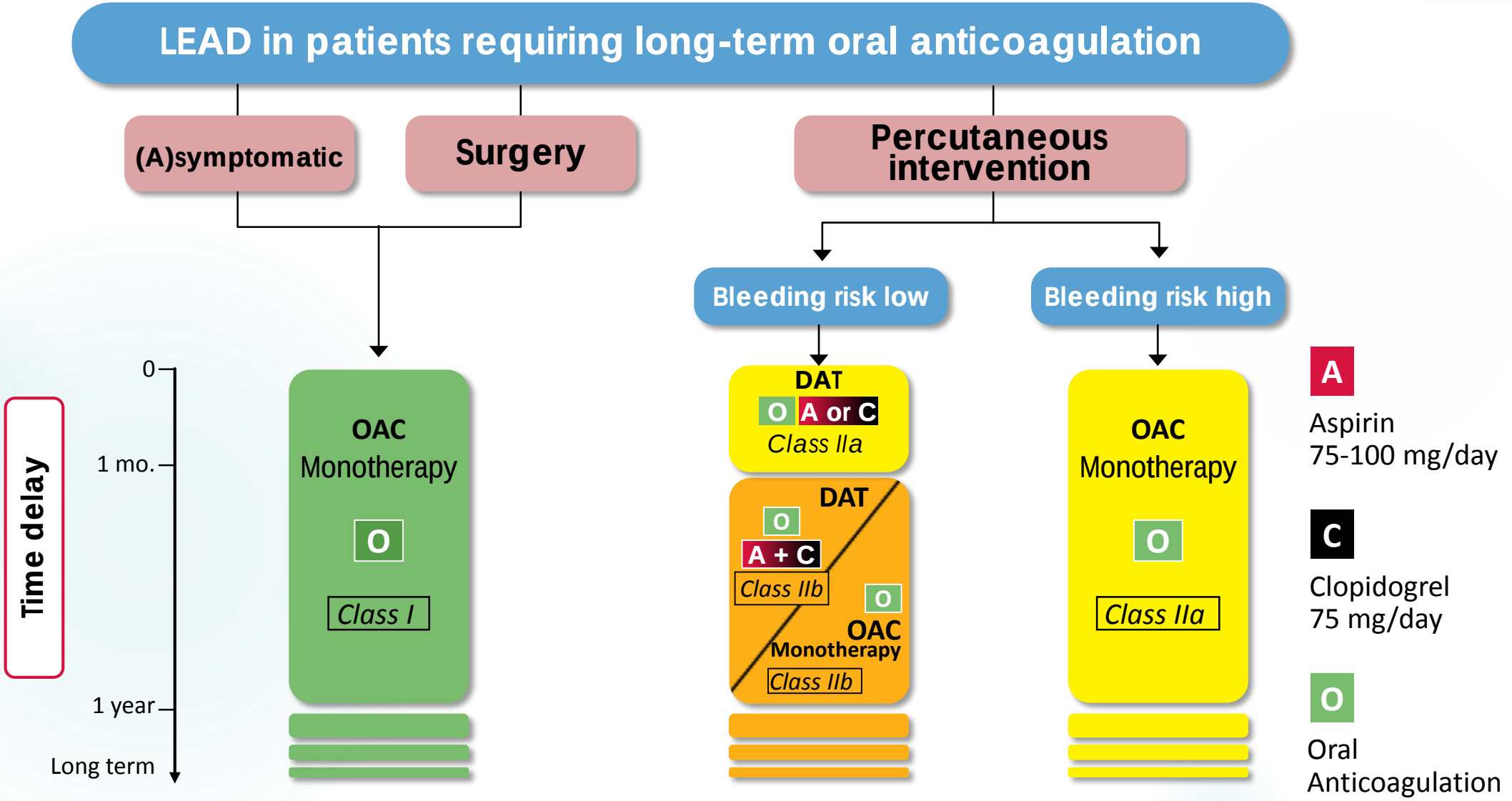
Recommendations	Class	Level
Lower extremity artery disease *(continued)*		
In patients with PADs and AF, oral anticoagulation:		
• is recommended when CHA_2DS_2-VASc score ≥2,	I	A
• should be considered in all other patients.	IIa	B
In patients with PADs who have an indication for OAC (e.g. AF or mechanical prosthetic valve), oral anticoagulants **alone** should be considered.	IIa	B

Antithrombotic therapy for LEAD patients requiring oral AC

Recommendations	Class	Level
After endovascular revascularization, aspirin or clopidogrel should be considered **in addition** to OAC for **at least 1 month** if the bleeding risk is low compared to the risk of stent/graft occlusion.	IIa	C
After endovascular revascularization, OAC **alone** should be considered if the bleeding risk is high compared to the risk of stent/graft occlusion.	IIa	C
OAC and SAPT may be considered **beyond one month** in high ischaemic risk patients or when there is another firm indication for long-term SAPT.	IIb	C

- Duration of combined therapy should be as limited as possible depending on clinical indication and bleeding risk
- With the exception of BTK stenting, or complex lesions at very high risk of thrombosis, triple therapy is discouraged in this setting
- Gastric protection with a proton pump inhibitor is recommended

Summary: Patients requiring oral AC



Gaps in evidence

- Optimal duration for DAPT after stenting, as well as the potential benefit of its long-term use in patients with chronic limb-threatening ischemia, should be further investigated

- Role of direct oral anticoagulants in LEAD needs to be assessed

- Need for trials assessing antiplatelet strategies in the full spectrum of LEAD (asymptomatic, intermittent claudication, chronic limb-threatening ischaemia)

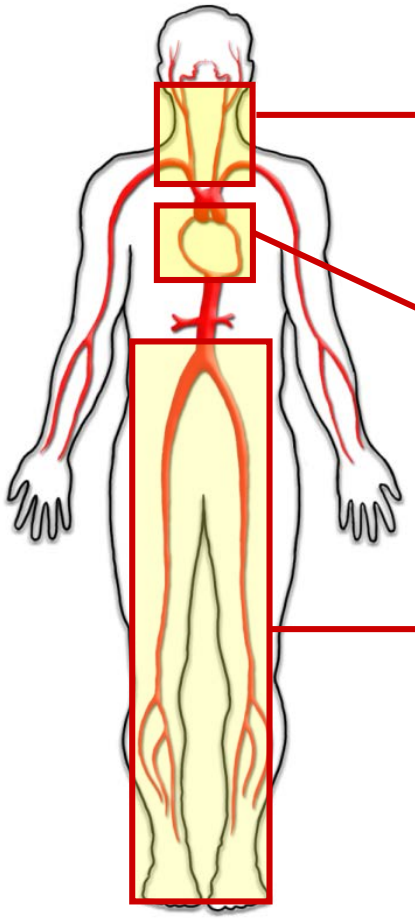
- A number of antiplatelet strategies are available → their specific indications remain unclear

- Optimal strategy of antithrombotic treatment in patients with atrial fibrillation and LEAD requires specific RCTs

Key messages

- Single antiplatelet therapy is indicated only if LEAD patients are symptomatic or have undergone revascularization
- Clopidogrel is the preferred antiplatelet drug in LEAD patients
- Chronic anticoagulation therapy is given only if there is a concomitant indication and may be combined with single antiplatelet therapy when there is a recent revascularisation procedure

Patient I.E, 67 years (05/99 - 06/17)



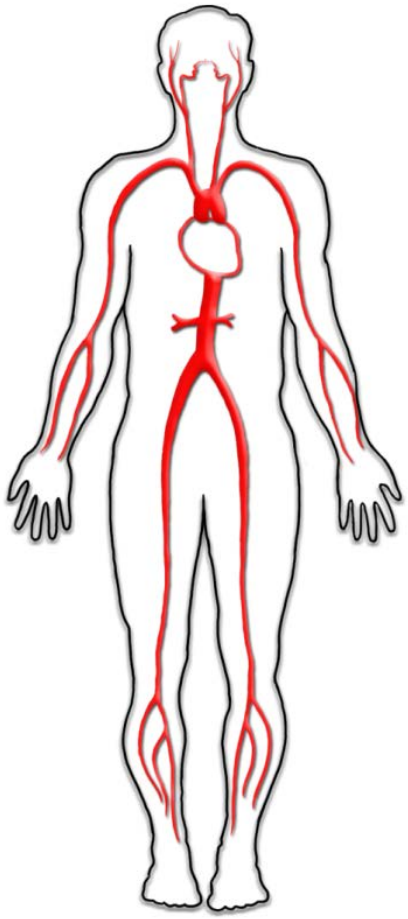
CVD
- CEA internal carotid artery 1999 + 2000
- 06/17: no restenosis by duplex sonography

CAD
- PCI RCA 2005, PCI LAD 2015
- 06/17: stress echo with normal response

Symptomatic LEAD
- angioplasty both SFA 2000
- re-intervention left side 2014
- 06/17: intermittent claudication Rutherford 2

At present: Stable multisite PAD

Patient I.E, 67 years (05/99 - 06/17)



Cardiovascular risk factors:

1. **Smoking (at this time 4 cigarettes/d)**
2. **Hyperlipidemia**
3. **Arterial Hypertension**
4. **Diabetes mellitus (Insulin therapy)**

Multiple Choice Question 1

Which antithrombotic treatment would you use in this patient?

a) Aspirin 100 mg od
b) Clopidogrel 75 mg od
c) Aspirin 100 mg od and Clopidogrel 75 mg od
d) Rivaroxaban 5 mg bid
e) Rivaroxaban 2.5 mg bid and Aspirin 100 mg od

Multiple Choice Question 3

Which treatment regime would you use if the patient developed atrial fibrillation while on ASA 100 mg od?

a) Switch to OAC only
b) Keep Aspirin 100 mg od only
c) Switch to ASA + Clopidogrel 75 mg od
d) Switch to OAC + Aspirin 100 mg od
e) Switch to OAC + Clopidogrel 75 mg od

Merci !

What about other antithrombotics ?

CHARISMA (subgroup analysis)	TRA2°P-TIMI50 (subgroup analysis)	EUCLID	PEGASUS (subgroup analysis	
Clopidogrel +ASA vs ASA in pts with prior MI, stroke or symptomatic LEAD	Vorapaxarl +ASA vs ASA in pts with stable symptomatic LEAD	Ticagrelor vs Clopidogrel in pts with LEAD	Ticagrelor + ASA vs ASA in pts with prior MI +LEAD	
			60 mg	**90 mg**
⇩ MACE of 17%	No reduction in MACE	No reduction in MACE nor MALE	⇩ MACE of 31% no decrease in MALE	No reduction in MACE ⇩ MALE (51%)
No decrease in mortality	⇩ Hospitalisation for ALI of 42%	No decrease in mortality	⇩ Decrease in mortality (48%)	No decrease in mortality
No increase in severe bleeding	⇧ Major bleeding 1.5x	No increase in major bleeding	No increase in major bleeding	