AMD
EMILIA ROMAGNA
ASSOCIAZIONE MEDICI DIABETOLOGI

LA PROTEZIONE CARDIOVASCOLARE COMPLETA

18 NOVEMBRE 2022

BOLOGNA

NH HOTEL BOLOGNA DE LA GARE - Piazza XX Settembre, 2

LA PROTEZIONE CARDIOVASCOLARE COMPLETA

La terapia antiaggregante e anticoagulante:

un'altra dimensione della protezione vascolare?

CardioASA in prevenzione primaria e secondaria studio COMPASS

dr.ssa Valentina Lo Preiato

Dichiarazione dei conflitti d'interesse

Ai sensi dell'art. 76 del Regolamento applicativo dell'Accordo Stato-Regioni 02.02.2017

La sottoscritta LO PREIATO VALENTINA

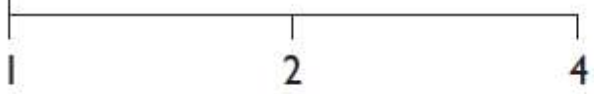
DICHIARA

che negli ultimi due anni ha ricevuto finanziamenti da: Eli-Lilly, Savio, Sanofi.

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario.

Diabete e rischio cardiovascolare

	Number of cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease*	26 505	2.00 (1.83–2.19)	64 (54–71)
Coronary death	11 556	2.31 (2.05–2.60)	41 (24–54)
Non-fatal myocardial infarction	14 741	1.82 (1.64–2.03)	37 (19–51)
Stroke subtypes*			
Ischaemic stroke	3 799	2.27 (1.95–2.65)	1 (0–20)
Haemorrhagic stroke	1 183	1.56 (1.19–2.05)	0 (0–26)
Unclassified stroke	4 973	1.84 (1.59–2.13)	33 (12–48)
Other vascular deaths	3 826	1.73 (1.51–1.98)	0 (0–26)



Emerging Risk Factors Collaboration et al. ***Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.*** Lancet 2010;375:2215–2222.

I diabetici a basso rischio CV non esistono!

ESC European Society of Cardiology
European Heart Journal (2020) 41, 255–323
doi:10.1093/eurheartj/ehz486
ESC GUIDELINES

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.

Diabete e prevenzione CV secondaria

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ESC GUIDELINES

6.5.1.2 Secondary prevention

The best available evidence for aspirin in secondary prevention remains that discussed in the 2013 ESC Guidelines on DM, pre-diabetes, and CVDs, developed in collaboration with the EASD[72] (see *section 7.1*).

Diabete e prevenzione CV secondaria

European Heart Journal (2013) 34, 3035–3087
doi:10.1093/eurheartj/eht108

ESC GUIDELINES

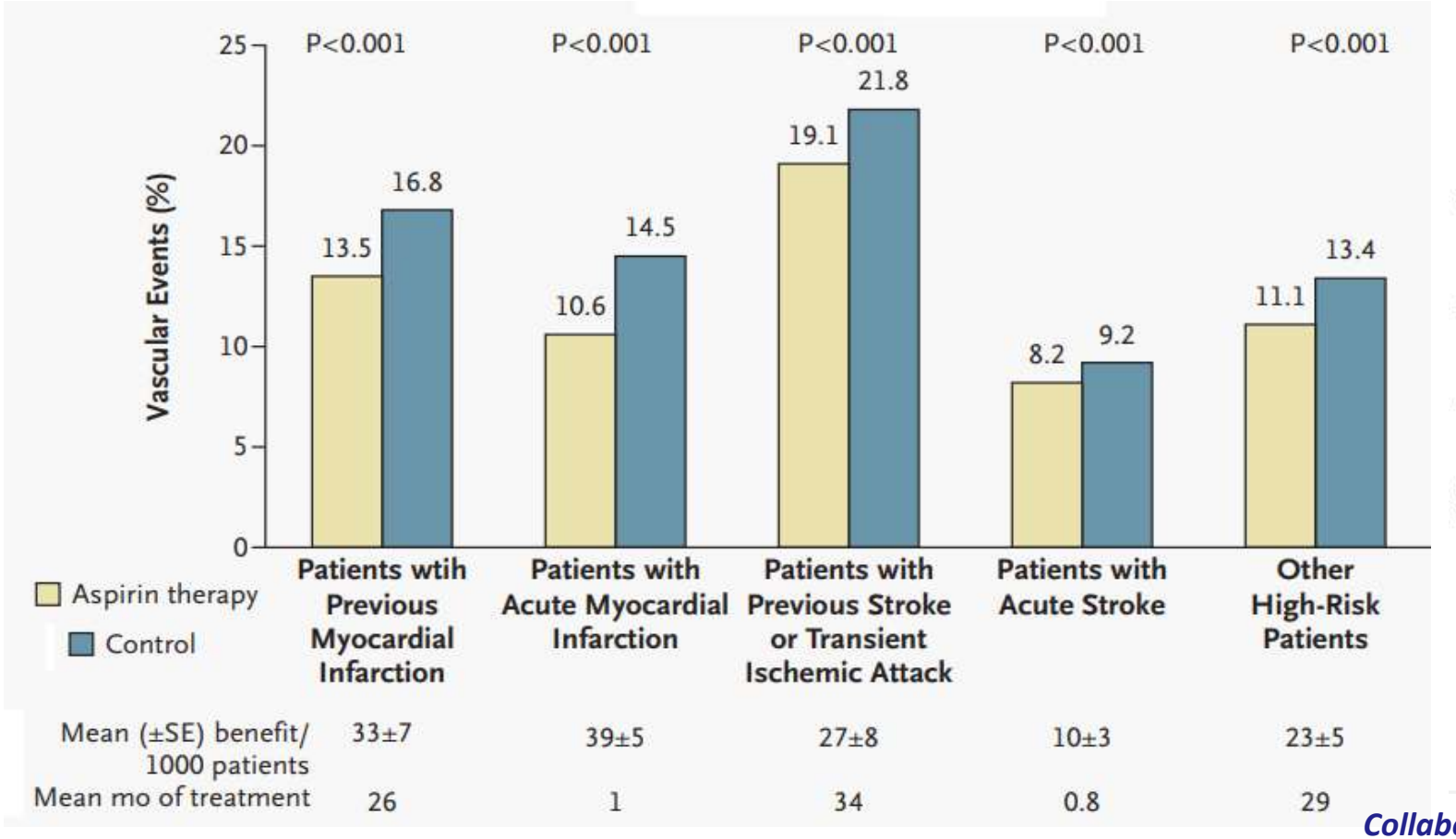
ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

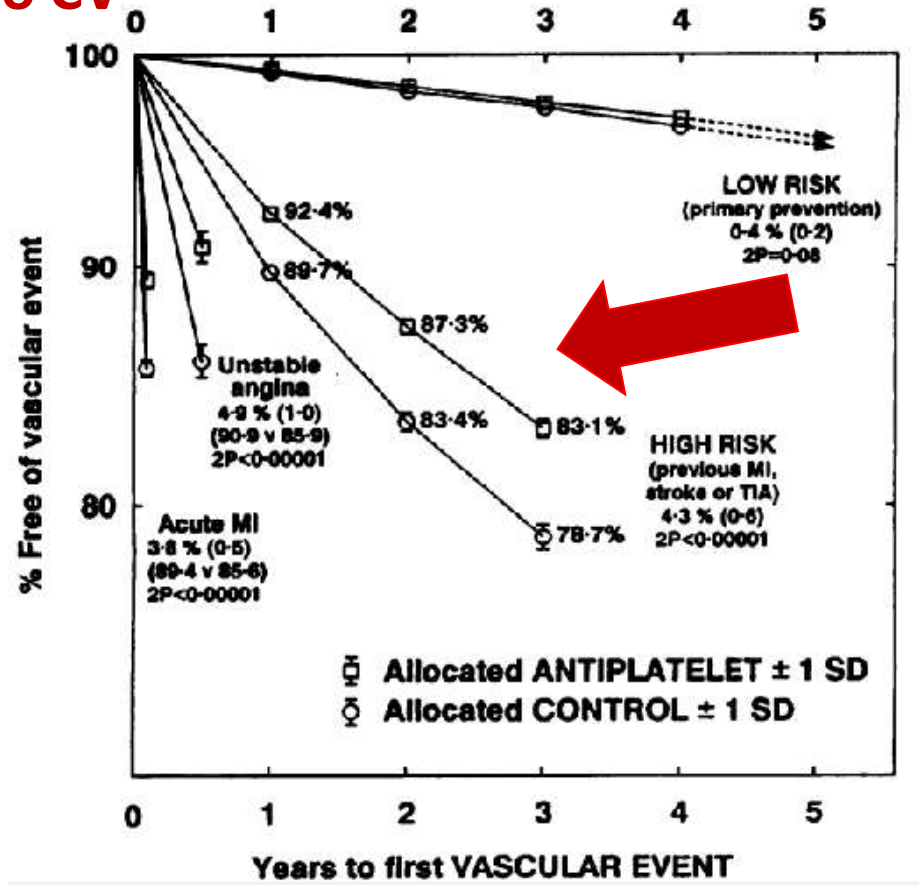
Therefore there is no apparent reason to treat patients with DM and CVD differently from non-DM patients and low-dose aspirin is uniformly recommended for both the acute treatment of ischaemic syndromes and their secondary prevention.[263]

Antiplatelet therapy in patients with diabetes			
Recommendations	**Class** [a]	**Level** [b]	**Ref.** [c]
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in DM.	I	A	270
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B	280, 285

Acido acetilsalicilico e prevenzione CV secondaria

70.000 pazienti ad alto rischio CV

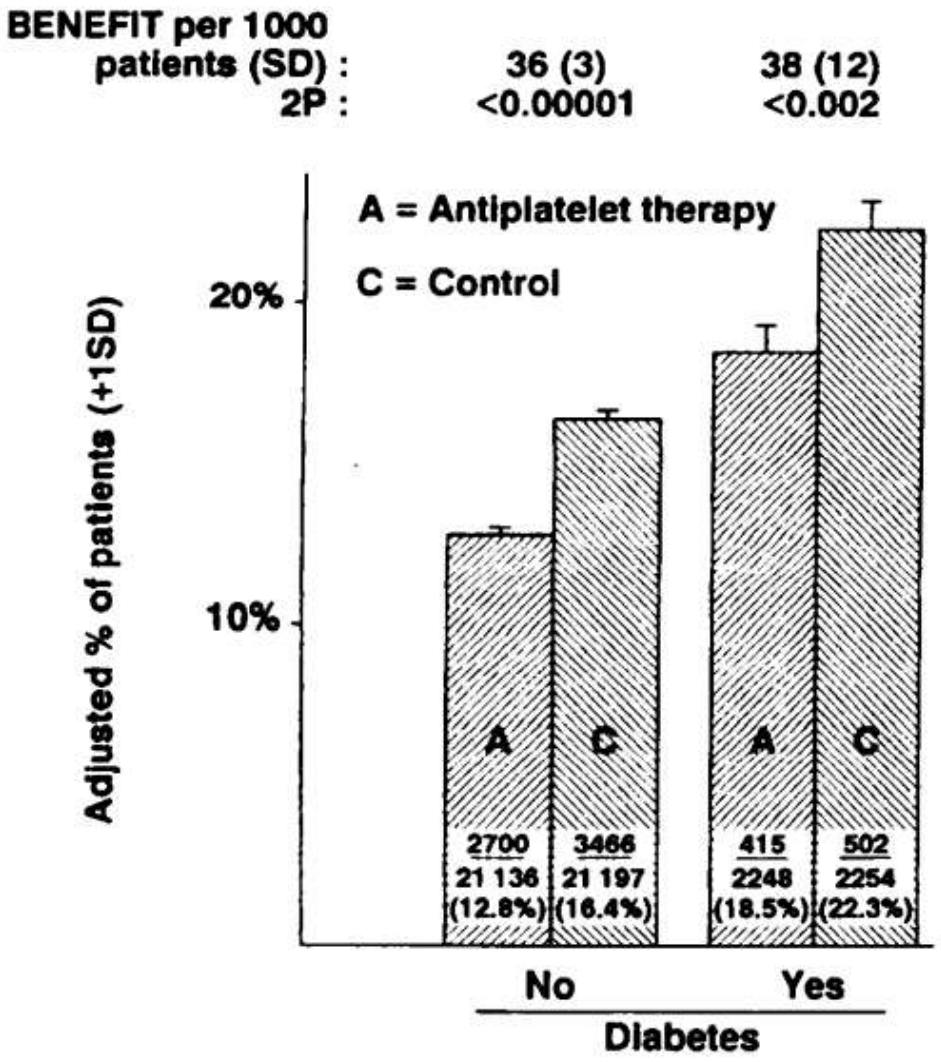




Patrono C et al. ***Low-dose aspirin for the prevention of atherothrombosis***. N Engl J Med 2005;353:2373–2383

Collaborative overview of randomised trials of antiplatelet therapy: I: Prevention of death, myocardialinfarction and strokeby prolonged antiplatelet therapyin various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106.

Diabete e ASA in prevenzione CV secondaria



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Diabete e ASA in prevenzione CV primaria

European Heart Journal (2013) 34, 3035–3087
doi:10.1093/eurheartj/eht108

ESC GUIDELINES

Antiplatelet therapy in patients with diabetes		
Recommendations	**Class** [a]	**Level** [b]
Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb	C

ESC European Society of Cardiology
European Heart Journal (2020) 41, 255–323
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

Recommendations	Class[a]	Level[b]
In patients with DM at high/very high risk,[c] aspirin (75 - 100 mg/day) may be considered in primary prevention in the absence of clear contraindications.[d 231]	IIb	A
In patients with DM at moderate CV risk,[c] aspirin for primary prevention is not recommended.	III	B
Gastric protection		
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.[232,235]	IIa	A

Diabete e ASA in prevenzione CV primaria

The NEW ENGLAND JOURNAL of MEDICINE

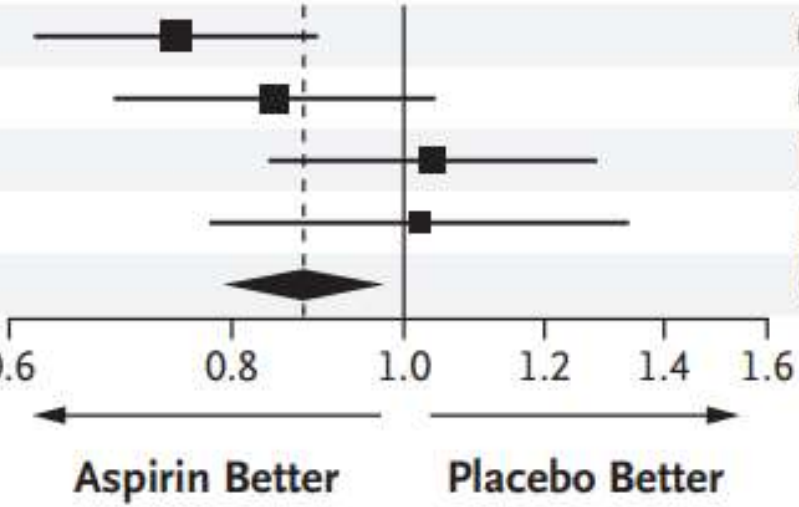
ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

15.480 pazienti diabetici

Year of First Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
<3	201 (2.6)	269 (3.5)	0.74 (0.62–0.89)	
3 to <5	169 (2.3)	198 (2.7)	0.85 (0.69–1.04)	
≥5 to <7	180 (2.5)	171 (2.4)	1.04 (0.84–1.28)	
7	108 (2.7)	105 (2.7)	1.02 (0.78–1.33)	
All	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**



Diabete e ASA in prevenzione CV primaria: sicurezza

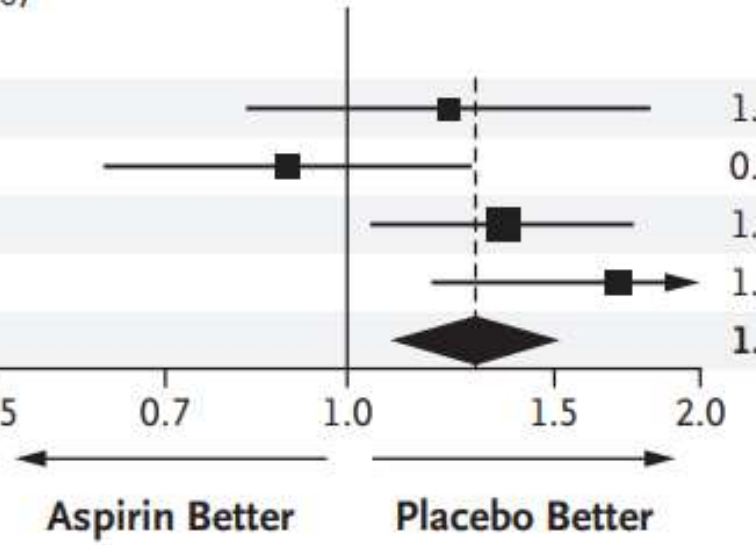
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



Diabete e ASA in prevenzione CV primaria: sicurezza

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Approximately half the excess of bleeding was in the gastrointestinal tract, with approximately one third in the upper gastrointestinal tract. However, even near the end of the trial in 2016, only approximately one quarter of participants were receiving proton-pump inhibitors (PPIs). It is possible that bleeding rates among aspirin users might be lower if PPIs were routinely used in these persons

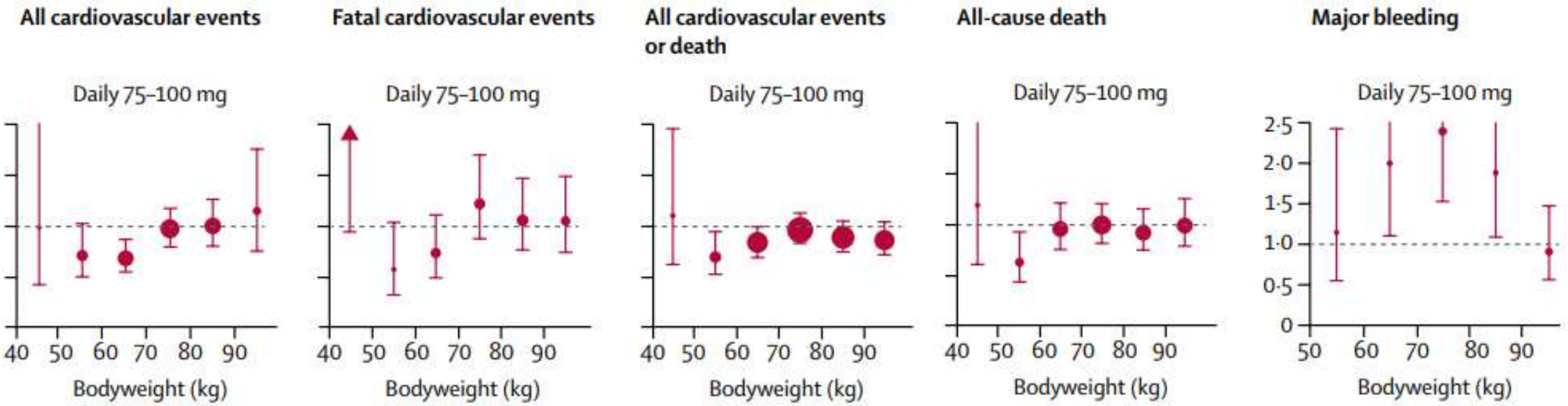
CONCLUSIONS

The absolute benefits were largely counterbalanced by the bleeding hazard.

Diabete e ASA nella prevenzione CV: tutto risolto?

Dose fissa indipendente dal peso del paziente?

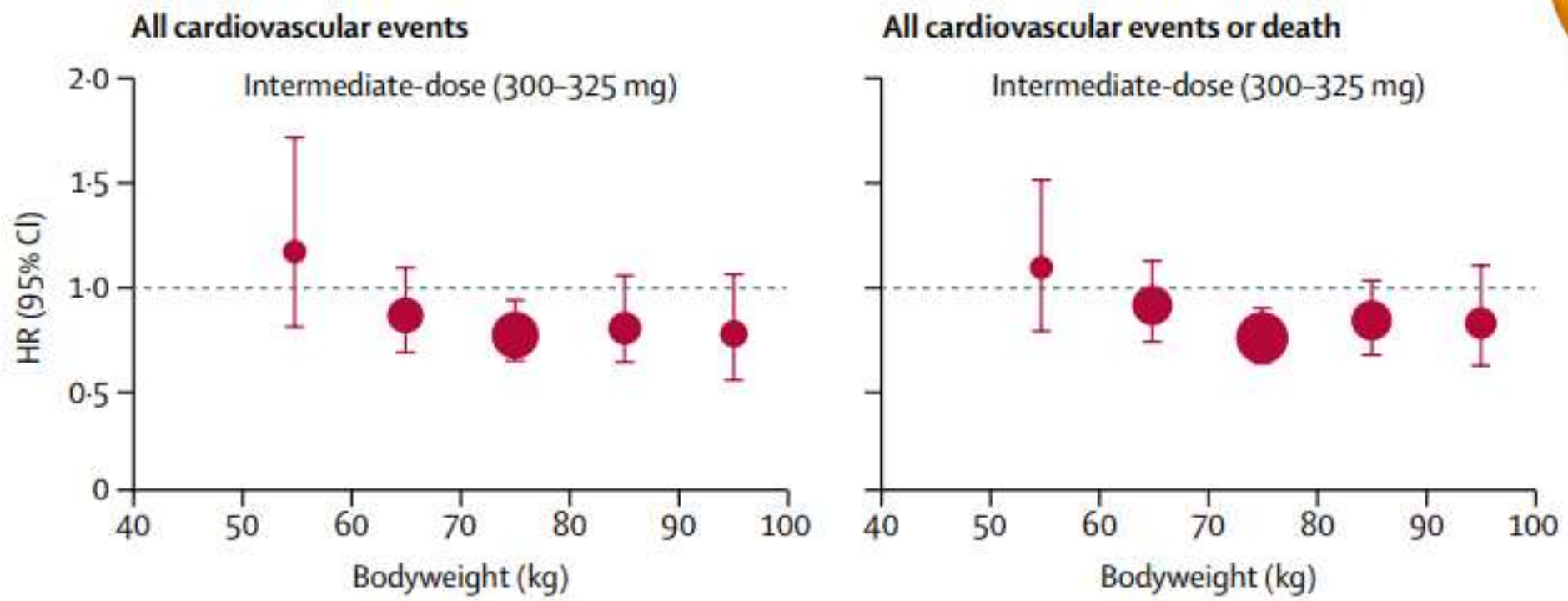
10 trials - 117.279 pazienti



Rothwell PM et al. ***Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials***. Lancet 2018;392:387399

Diabete e ASA nella prevenzione CV: tutto risolto?

Dose fissa indipendente dal peso del paziente?



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Diabete e ASA nella prevenzione CV: tutto risolto?

ESC European Society of Cardiology
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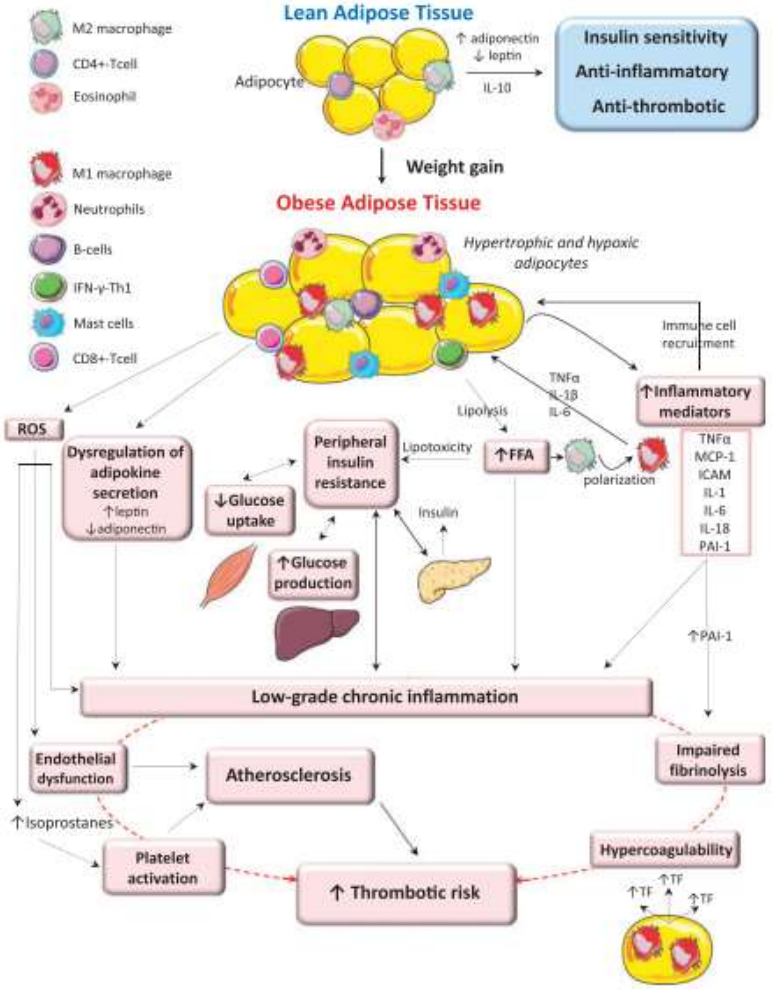
ESC GUIDELINES

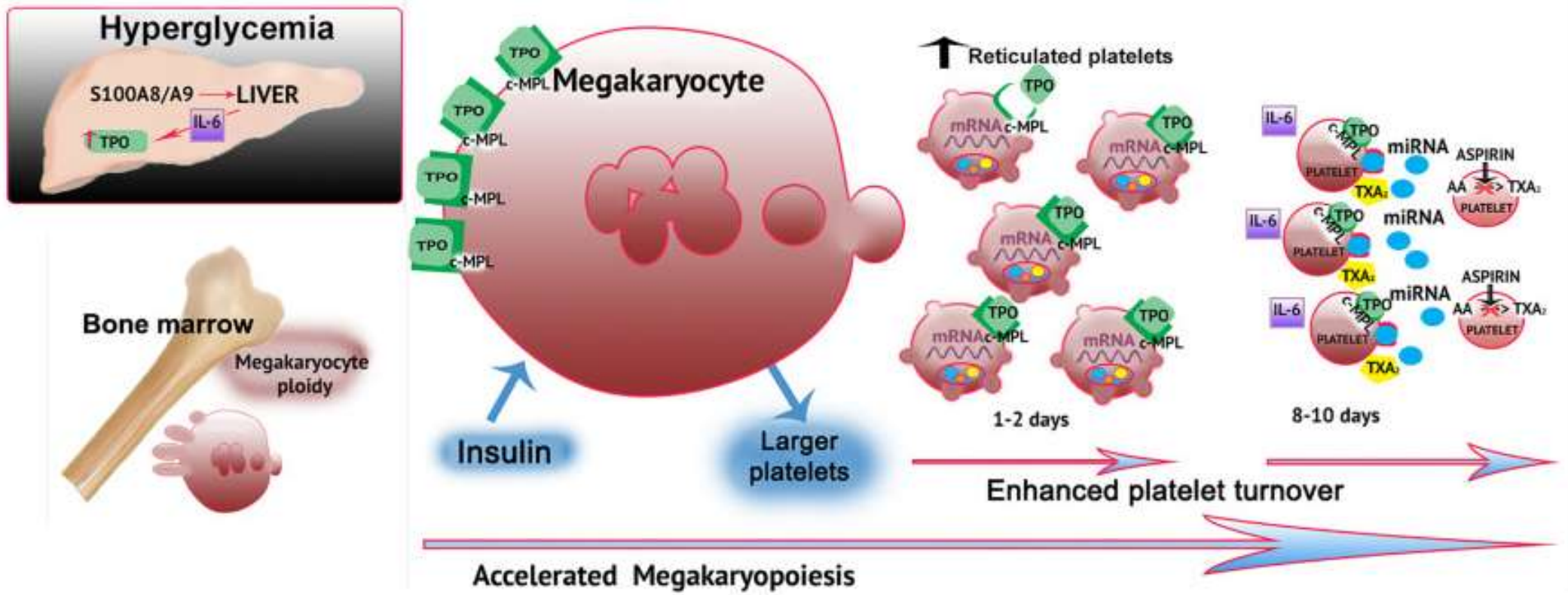
It has been recently suggested that body weight[233] or size can lower responsiveness to aspirin, as well as to clopidogrel, requiring higher daily doses.[234] Pharmacokinetic data suggest a lower degree of platelet inhibition, especially in moderate-to-severely obese patients.[234] However, the benefit of intensified antiplatelet regimens in obese DM patients remains to be established.



Rocca B et al. ***Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis***. Eur Heart J 2018;39:16721686f

Diabete e ASA nella prevenzione CV: tutto risolto?

Alterata megacariocitopoiesi

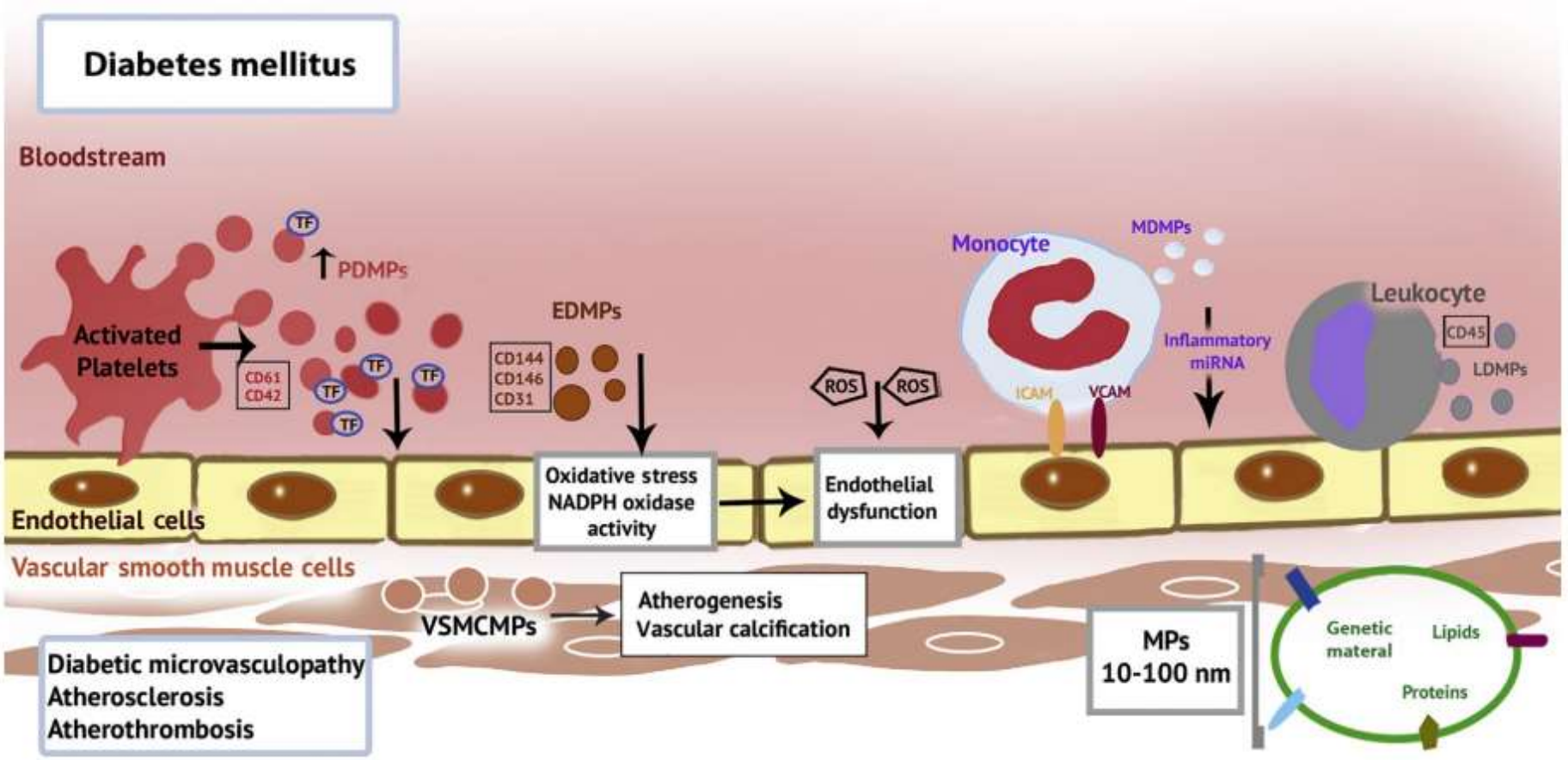


- **Turnover accelerato**
- **Piastrine reticolate**

The Role of Platelets in Diabetes Mellitus https://doi.org/10.1016/B978-0-12-813456-6.00027-8

Diabete e ASA nella prevenzione CV: tutto risolto?

Disfunzione endoteliale

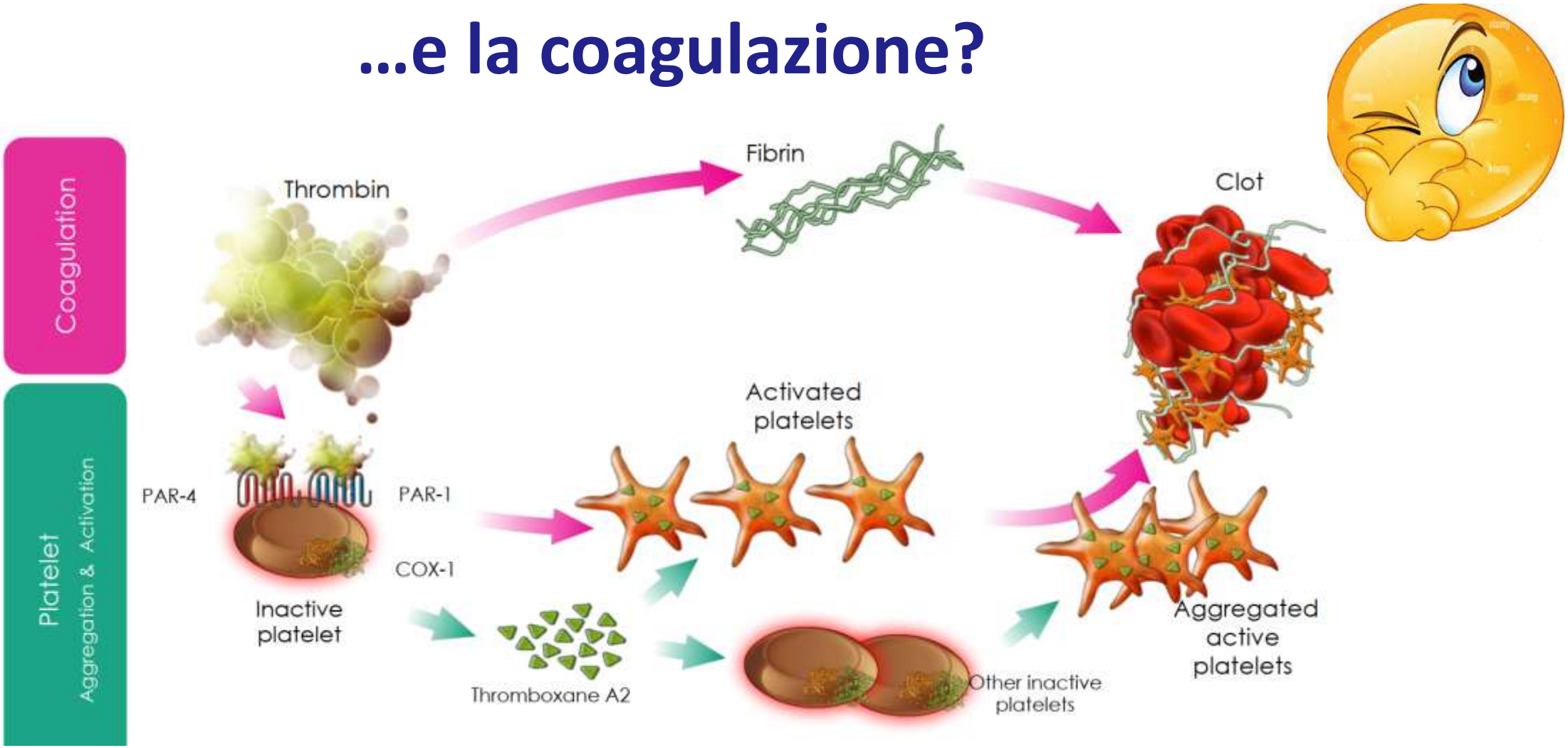


Moniciti e macrofagi fonte extrapiastrinica di TXA2

The Role of Platelets in Diabetes Mellitus https://doi.org/10.1016/B978-0-12-813456-6.00027-8

Diabete e ASA nella prevenzione CV: nessuna possibilità?

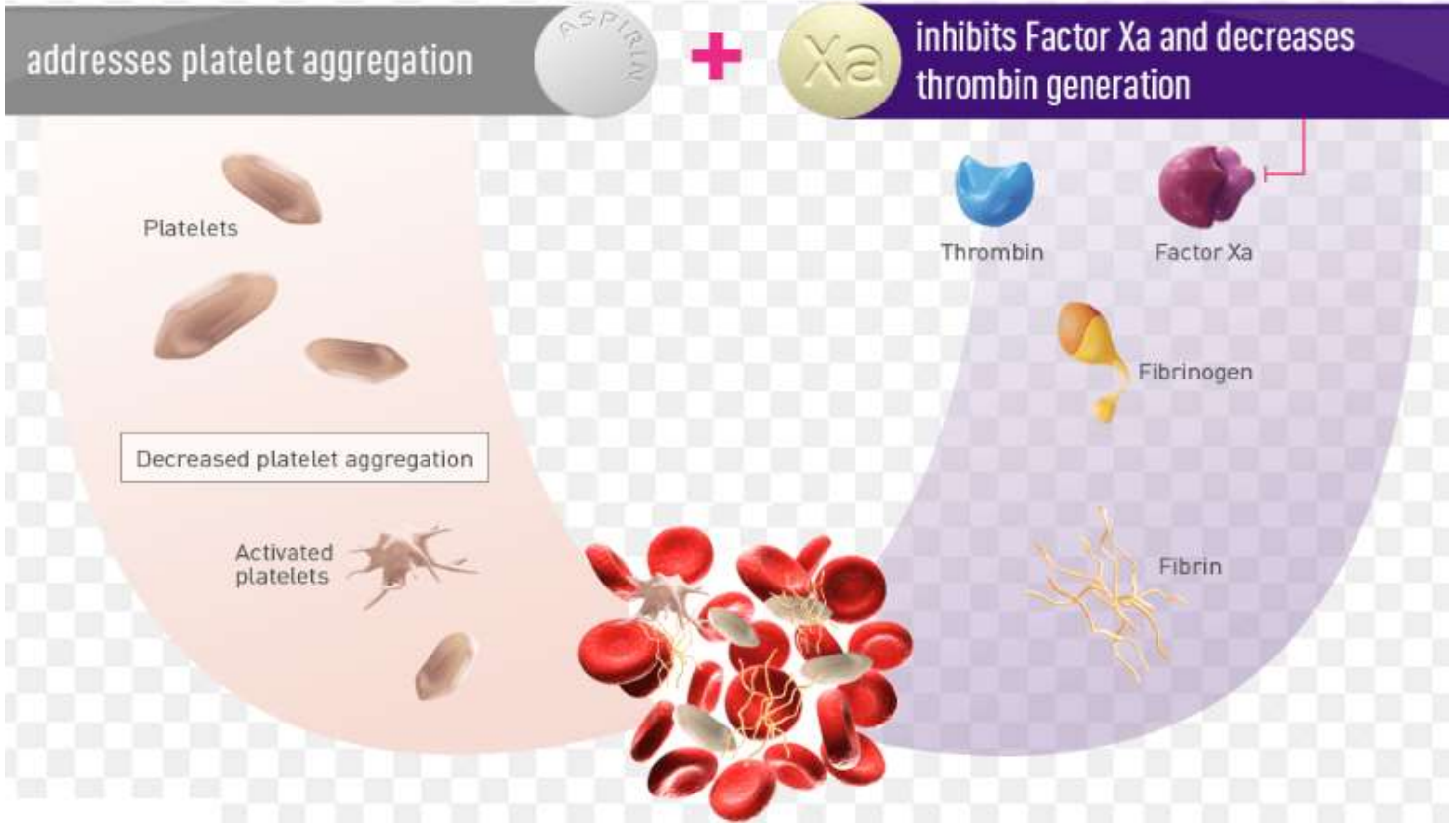
…e la coagulazione?



La doppia inibizione

AGGREGAZIONE

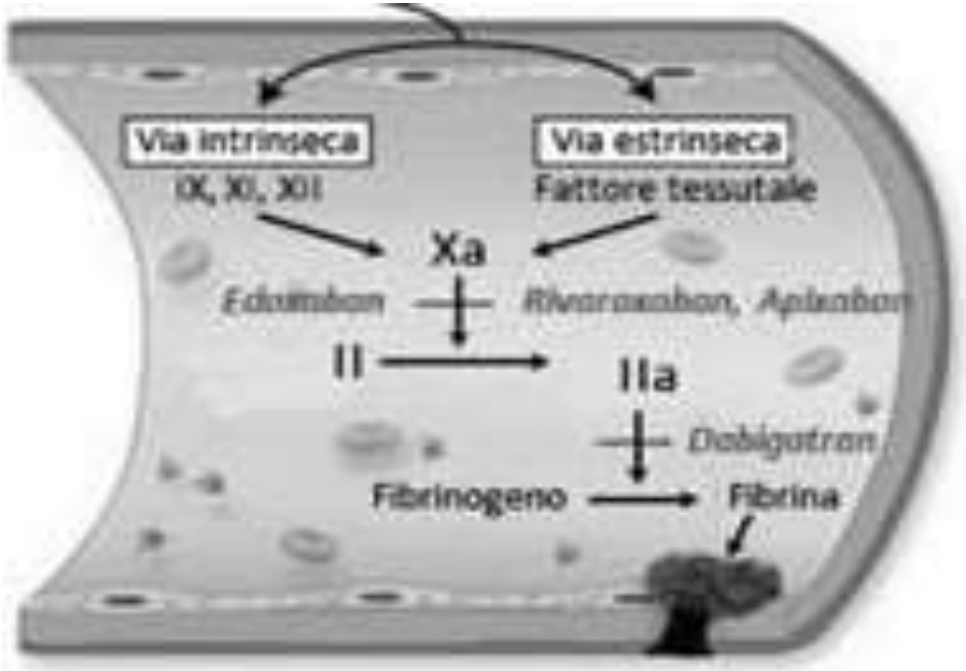
COAGULAZIONE



Rivaroxaban: chi è?

Rivaroxaban è un inibitore diretto e altamente selettivo del fattore Xa.

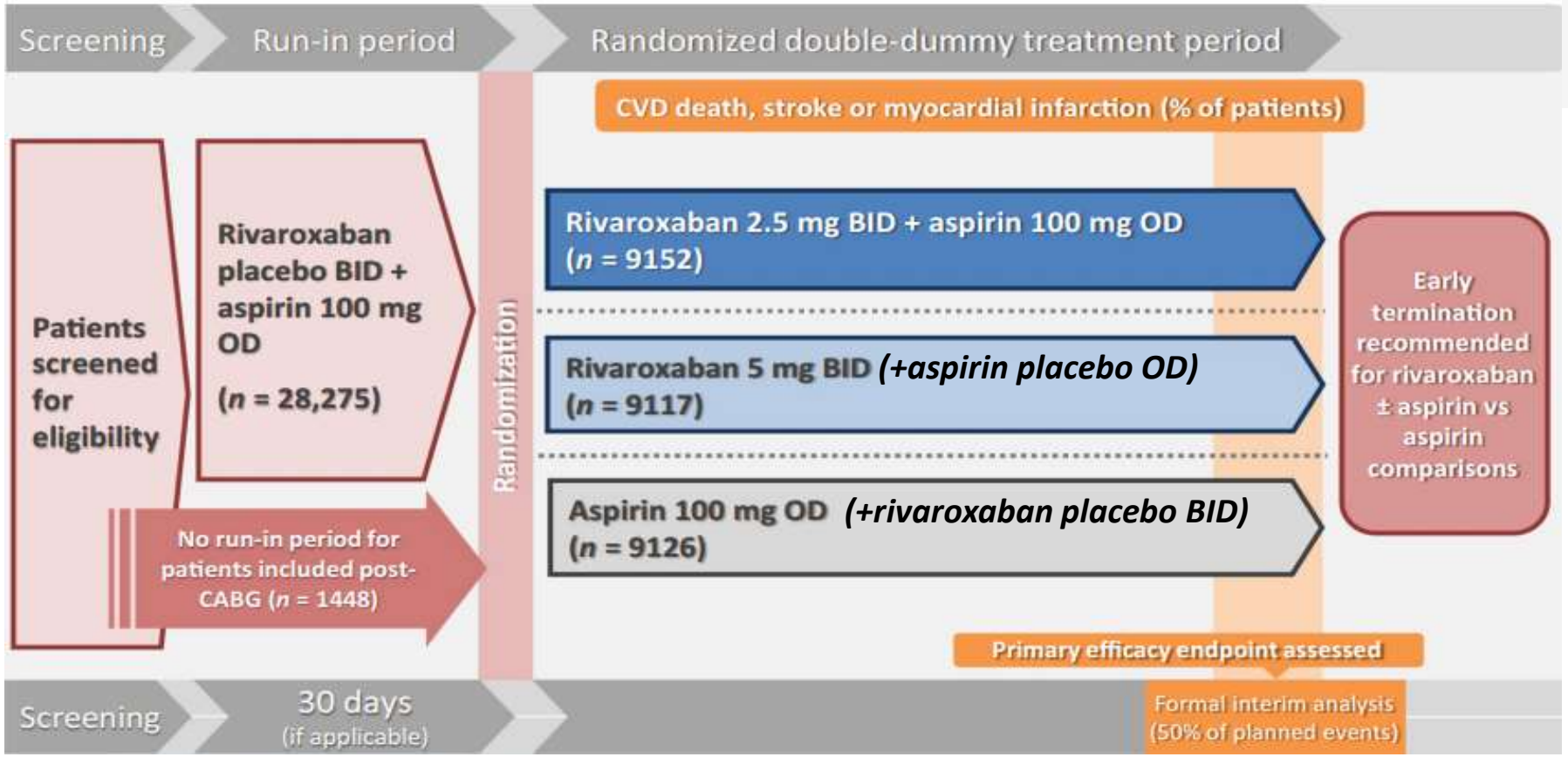
L'inibizione del fattore Xa interrompe le vie intrinseca ed estrinseca della cascata della coagulazione e inibisce la formazione di trombina.



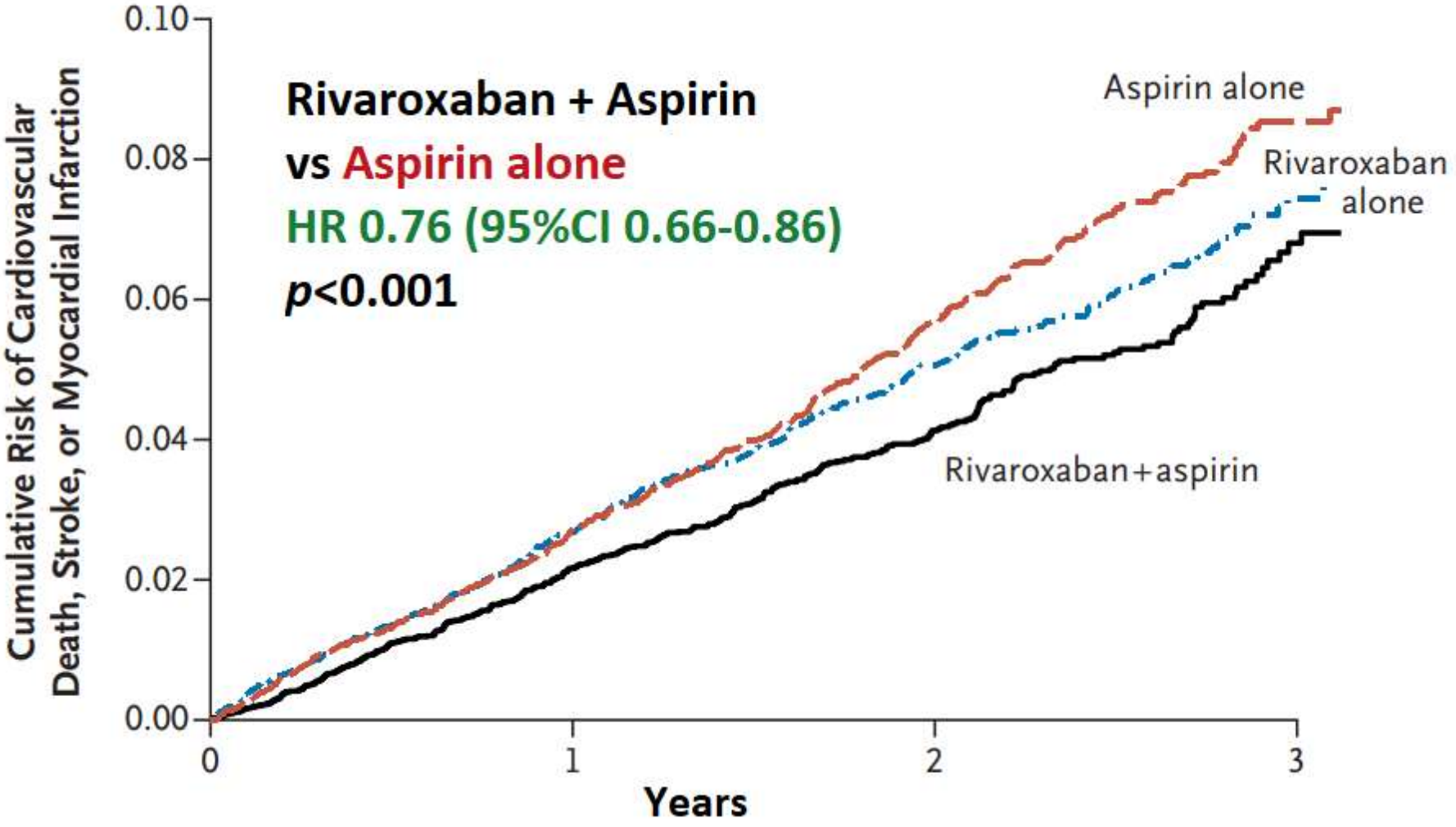
Rivaroxaban: studio COMPASS

Obiettivo: **valutazione del trattamento con Rivaroxaban da solo o in associazione ad ASA rispetto alla sola ASA nella prevenzione di IMA, ictus cerebrale e mortalità CV in pazienti con cardiopatia ischemica o arteriopatia periferica.**

27.395 pazienti



Studio COMPASS: risultati



-24%
MACE

Studio COMPASS: risultati a confronto

Rivaroxaban: -24% MACE

RRR/RRI	Rivaroxaban 2.5 mg BID + aspirin[1]	Lipid lowering (1 mmol/L)[2,3]	BP lowering (10 mmHg)[4]	ACEi[5]	Empagliflozin[6]	Alirocumab[7]
MACE	–24%	–21%	–20%	–18%	–14%	–14%
All-cause mortality	–18%	–9%	–13%	–14%	–32%	–15%

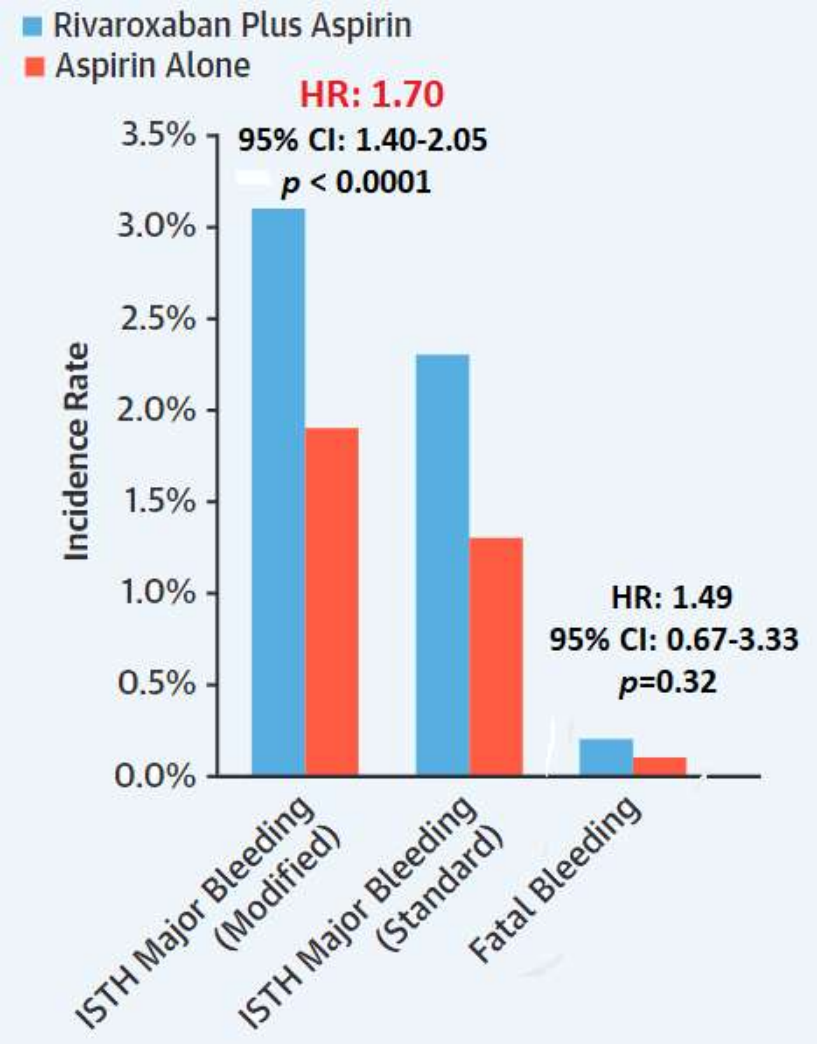
1- Eikelboom JW et al. N Engl J Med 2017;377:1319–1330; 2- CTT Collaboration. Lancet 2015;385:1397–1405

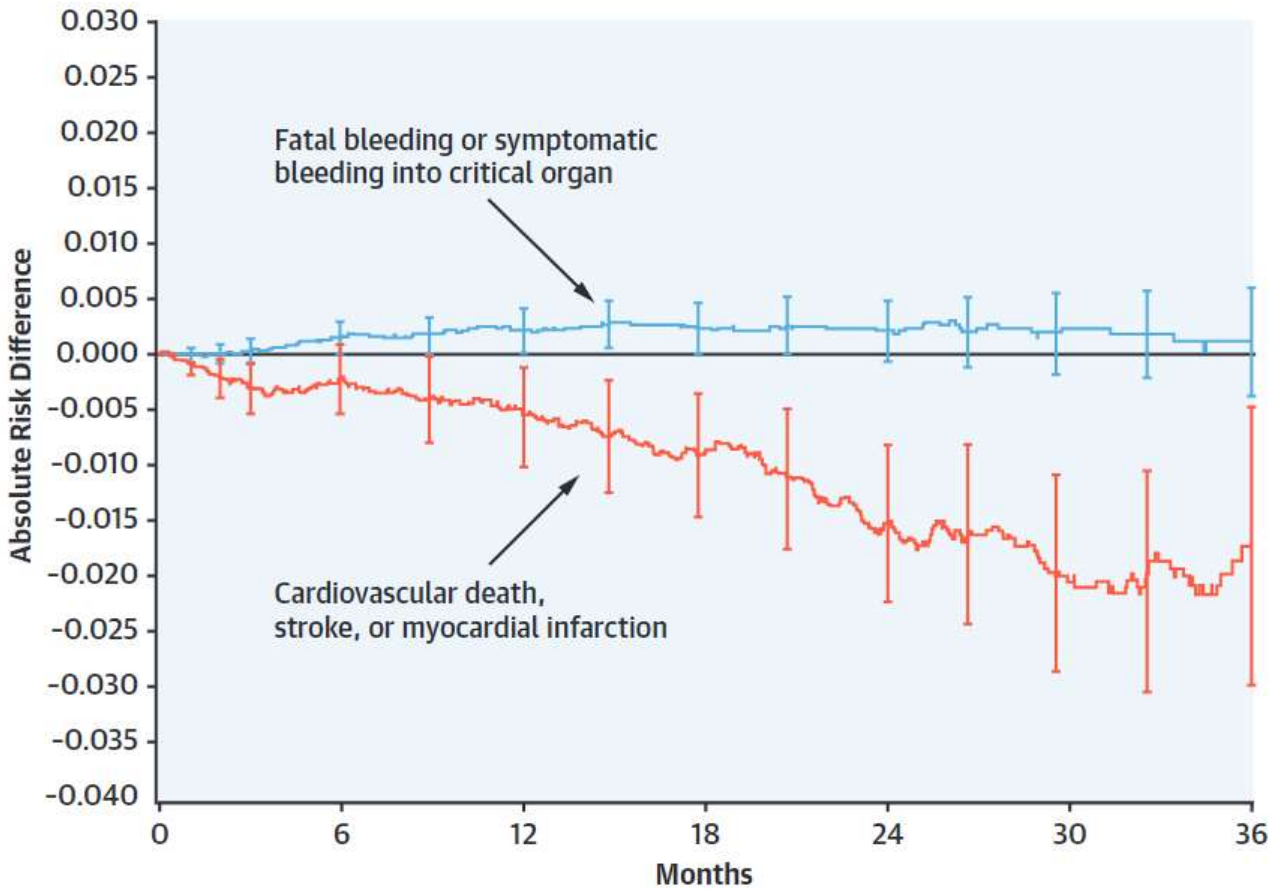
3- Collins R et al. Lancet 2016;388:2532–2561; 4- Ettehad D et al. Lancet 2016;387:957–967

5- Dagenais GR et al. Lancet 2006;368:581–588; 6- Zinman B et al. N Engl J Med 2015;373:2117–2128

7- Schwartz GG et al. N Engl J Med 2018;379:2097–2107

Studio COMPASS: sicurezza

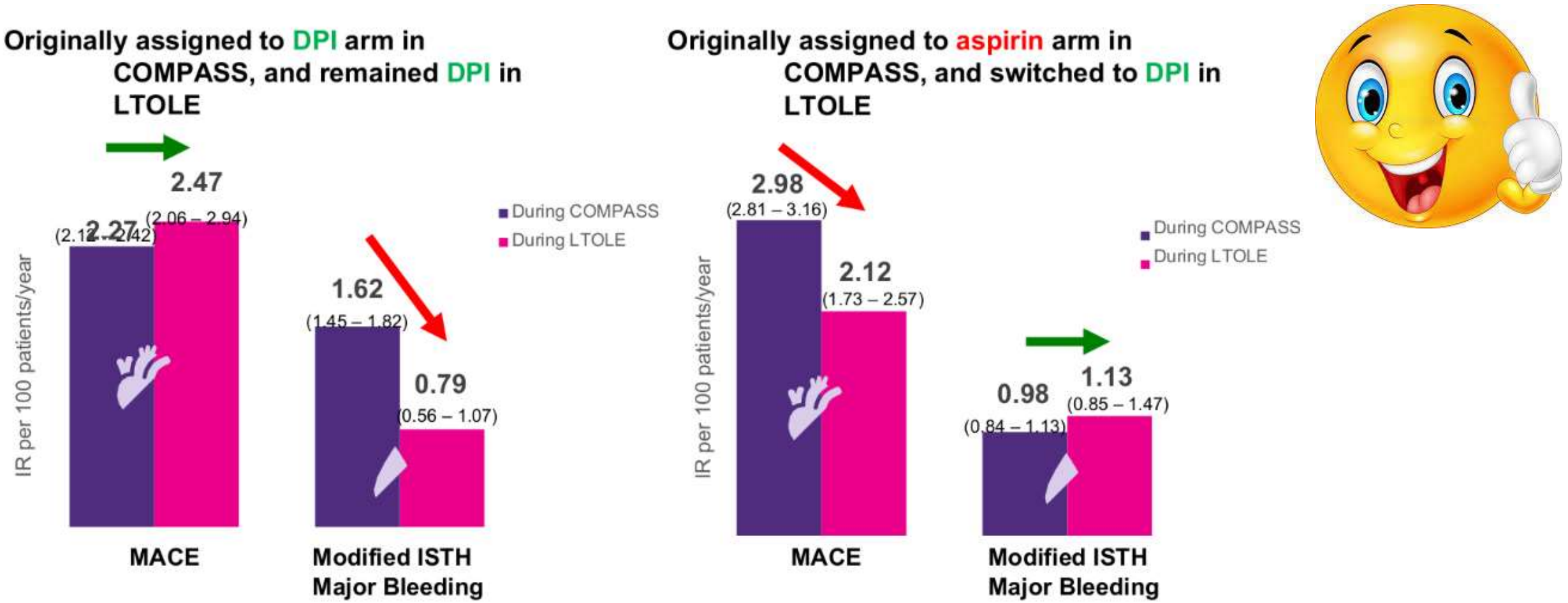




Pazienti ≥75 anni:
rischio CV: HR 0,89 (IC 95% 0,7-1,1)
rischio emorragico: HR 2,12 (IC 95% 1,5-3,0)

Pazienti < 75 anni:
rischio CV: HR 0,70 (IC 95% 0,6-0,8)
rischio emorragico: HR 1,53 (IC 95% 1,2-1,9)

Studio COMPASS: estensione open label



Long-Term Treatment with the Combination of Rivaroxaban and Aspirin in Patients with Chronic Coronary or Peripheral Artery Disease: Outcomes During the Open Label Extension of the COMPASS trial European Heart Journal - Cardiovascular Pharmacotherapy (2022) 0, 1–10 https://doi.org/10.1093/ehjcvp/pvac023

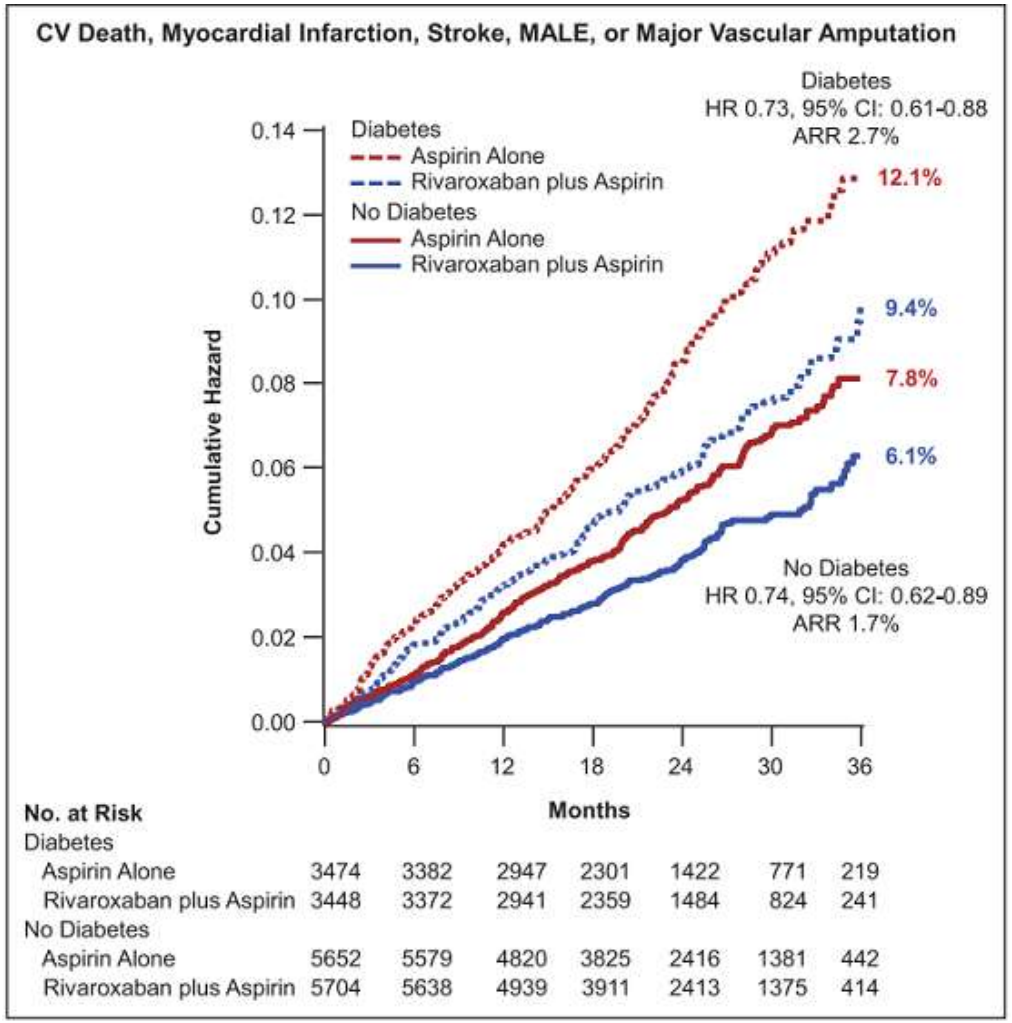
Studio COMPASS: subanalisi pazienti diabetici

6.922 pazienti con diabete mellito vs 11.356 pazienti senza diabete mellito

Characteristic	No Diabetes Mellitus (n=11356)	Diabetes Mellitus (n=6922)	*P* Value
Age, y	69.0±7.7	67.0±8.2	<0.0001
Female	2370 (20.9)	1678 (24.2)	<0.0001
Body mass index, kg/m^2	27.7±4.3	29.3±5.2	<0.0001
Previous stroke	343 (3.0)	343 (5.0)	<0.0001
Previous myocardial infarction)	7220 (63.6)	4155 (60.0)	<0.0001
Heart failure	2328 (20.5)	1614 (23.3)	<0.0001
Coronary artery disease	10491 (92.4)	6083 (87.9)	<0.0001
Peripheral artery disease	2792 (24.6)	2204 (31.8)	<0.0001
Estimated glomerular filtration rate, mL/min			
<30	64 (0.6)	99 (1.4)	<0.0001
30–<60	2357 (20.8)	1648 (23.8)	<0.0001
≥60	8932 (78.7)	5174 (74.8)	<0.0001

Studio COMPASS: subanalisi pazienti diabetici

6.922 pazienti con diabete mellito vs 11.356 pazienti senza diabete mellito



-27%

MACE + MALE

Sanguinamenti maggiori:

No DM: 4.4% vs 3.2%

HR 1.69 [95% CI, 1.33–2.15]; p<0.0001

DM: 4.5% vs 3.4%

HR, 1.69 [95% CI, 1.33-2.15]; p=0.0006

Studio COMPASS: subanalisi PAD

7.470 pazienti

	Low-dose rivaroxaban plus aspirin versus aspirin alone	
	HR (95% CI)	p value
Primary and secondary outcomes		
Cardiovascular death, stroke, myocardial infarction*	0·72 (0·57–0·90)	0·0047
Coronary heart disease death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	0·68 (0·53–0·86)	0·0011
Cardiovascular death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	0·71 (0·57–0·88)	0·0019
Prespecified limb outcomes		
Acute limb ischaemia‡	0·56 (0·32–0·99)	0·042
Major adverse limb event‡	0·54 (0·35–0·84)	0·0054
All vascular amputations	0·40 (0·20–0·79)	0·0069
Major amputation‡	0·30 (0·11–0·80)	0·011

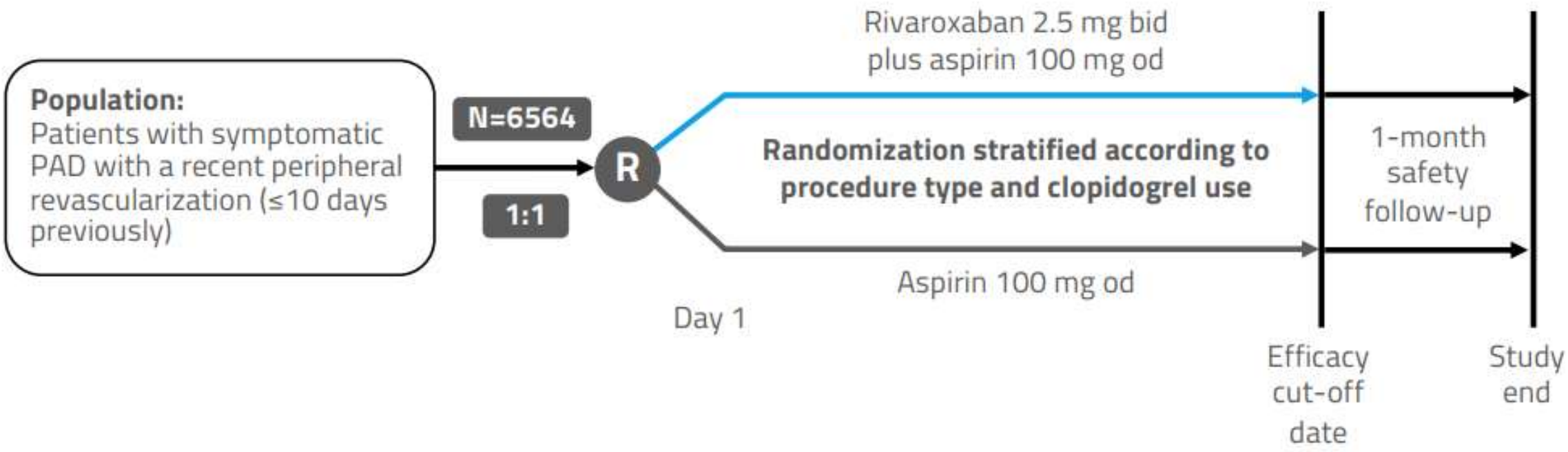
-28% MACE

-46% MALE

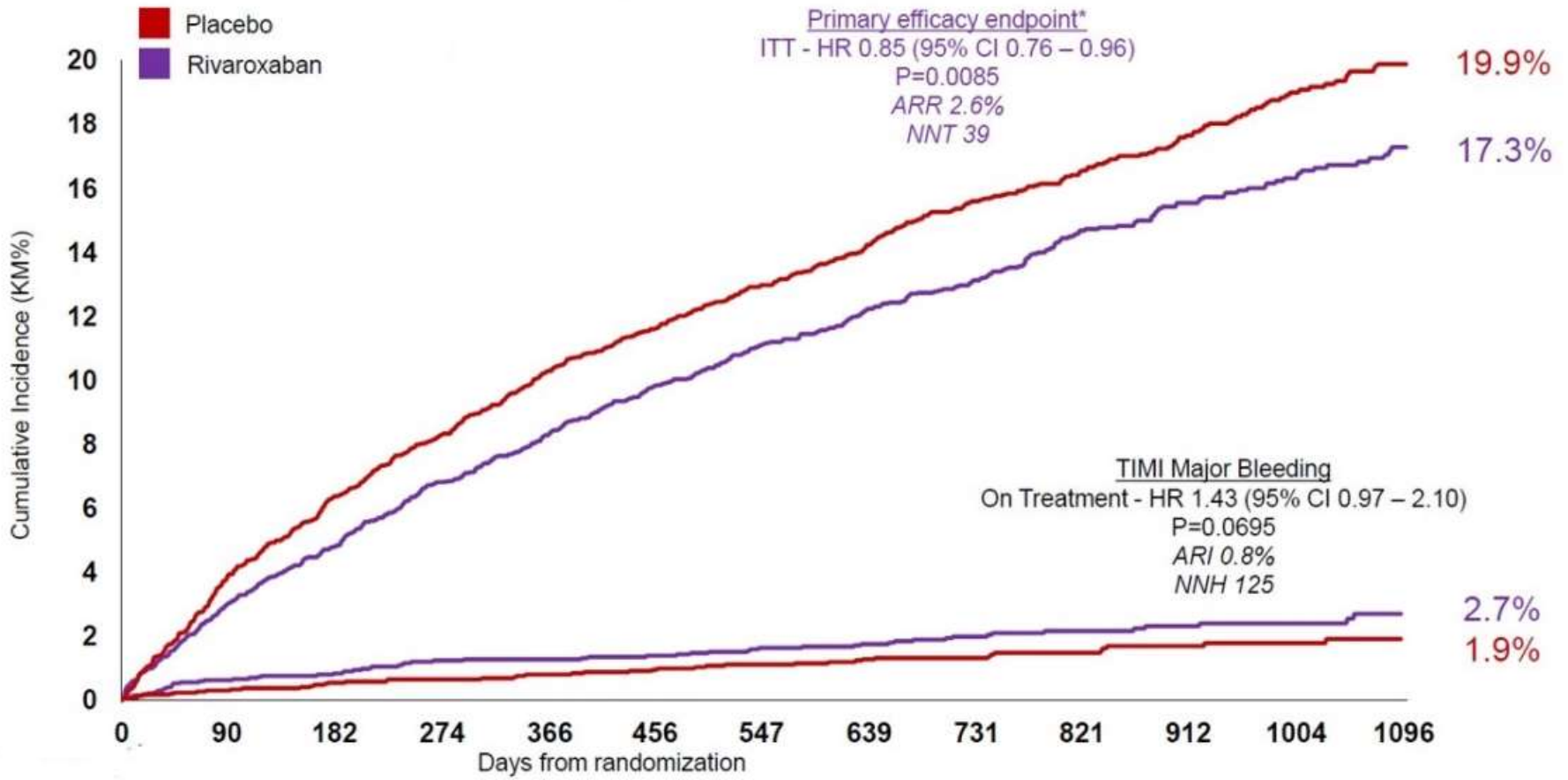
-70%
Amputazioni maggiori

Studio VOYAGER PAD

Obiettivo: **valutazione del trattamento con Rivaroxaban in pazienti sottoposti a rivascolarizzazione periferica nella prevenzione di ischemie acute, amputazioni maggiori per cause vascolari, infarto miocardico, ictus ischemico, morte CV.**



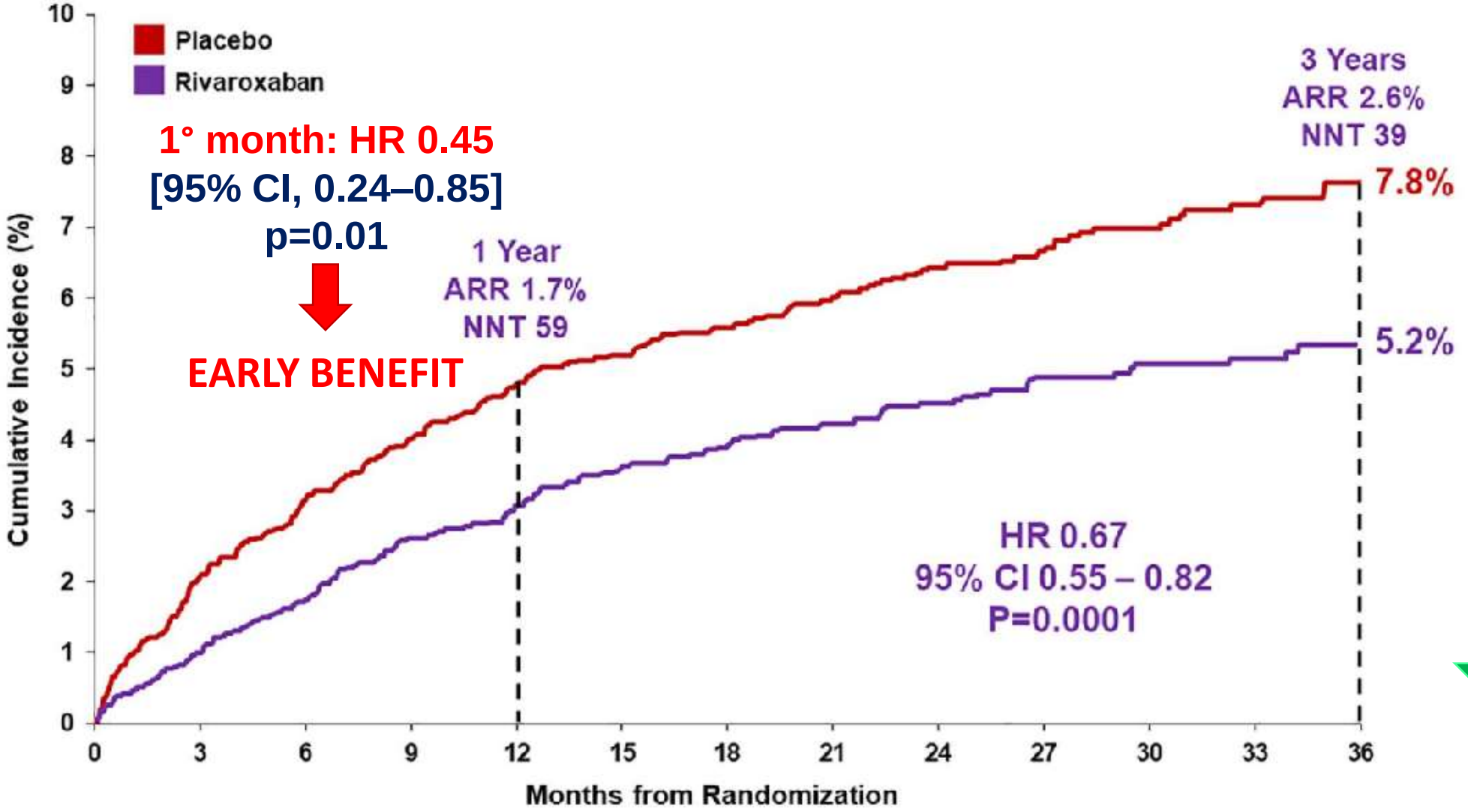
Studio VOYAGER PAD



-15%

Endpoint 1°

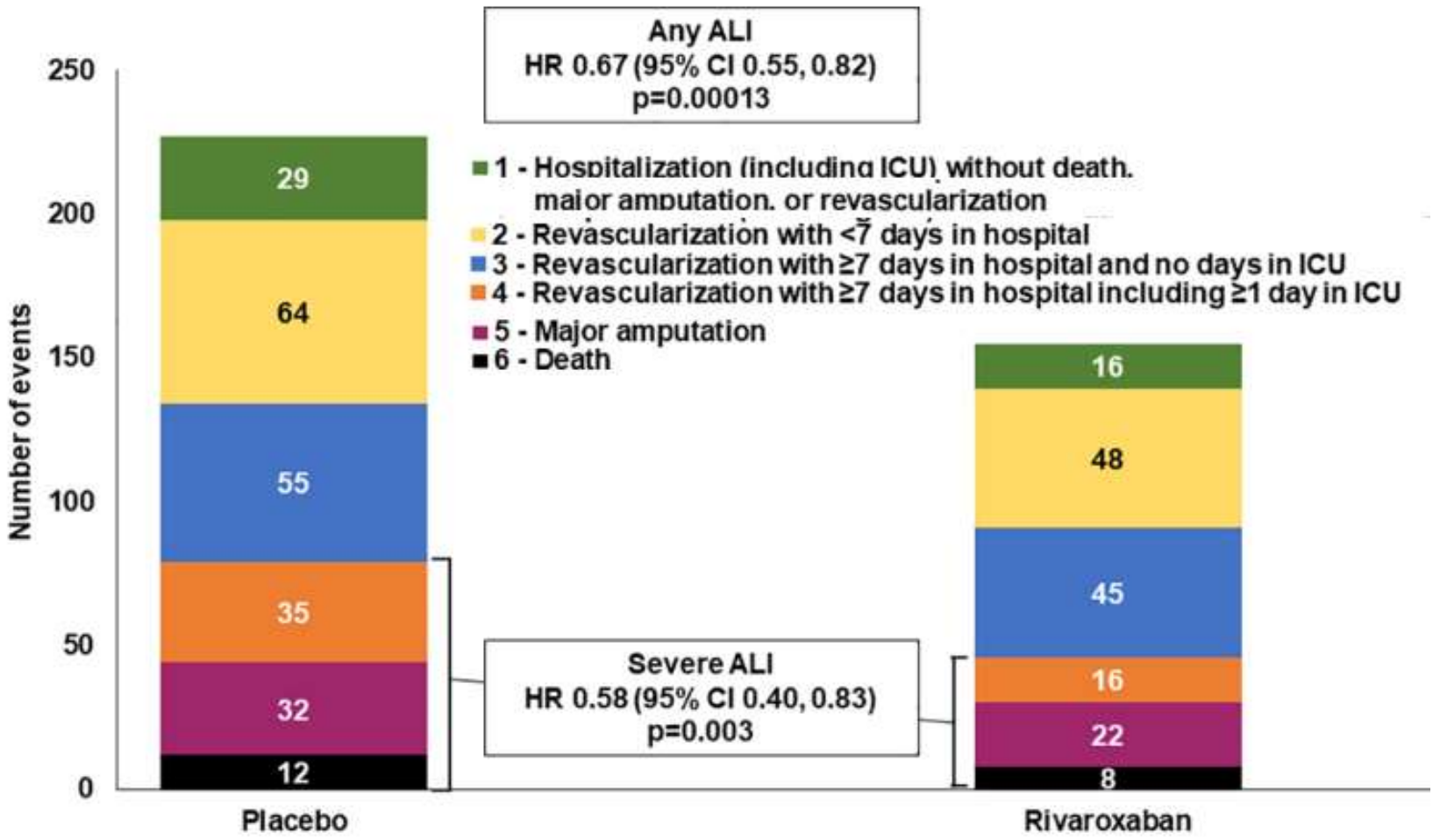
Studio VOYAGER PAD: subanalisi ALI



HR 0.71
[95% CI, 0.57–0.88]
p=0.002

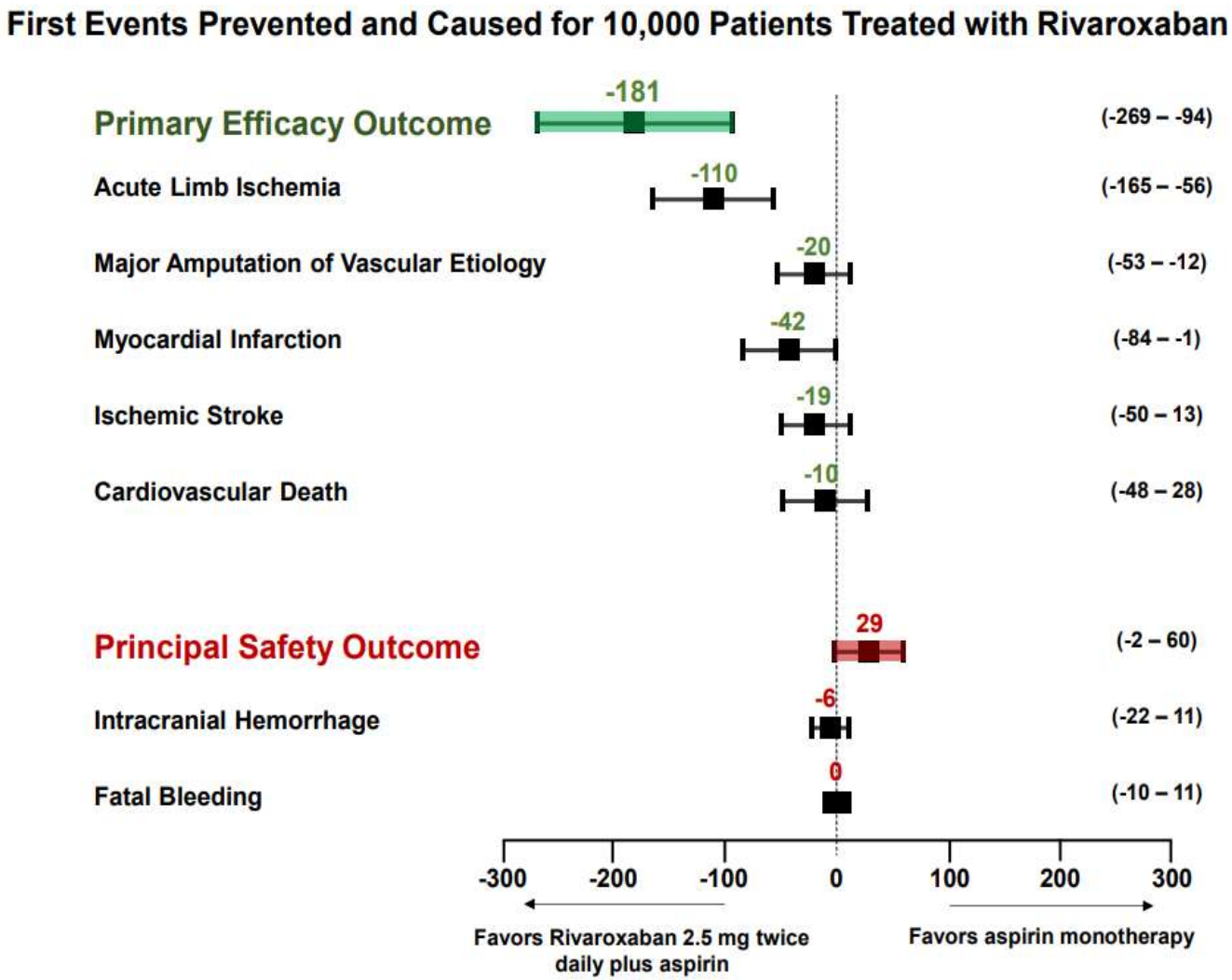
-29%
ALI

Studio VOYAGER PAD: subanalisi ALI



-42%
Severe ALI

Studio VOYAGER PAD: sicurezza



Ogni 10000 pazienti trattati per 1 anno:

-181 eventi

vs

29 eventi emorragici

(0 fatali, 6 emorragie intracraniche)

Rivaroxaban: scheda tecnica

Indicazione: **Rivaroxaban, somministrato con acido acetilsalicilico (ASA), è indicato per la prevenzione di eventi aterotrombotici in pazienti adulti, ad alto rischio di eventi ischemici, che presentano coronaropatia o arteriopatia periferica sintomatica.**

Posologia**: la dose raccomandata è 2,5 mg due volte al giorno.**

Compromissione renale: **i limitati dati clinici relativi ai pazienti con grave compromissione renale (clearance della creatinina 15 - 29 mL/min) indicano che le concentrazioni plasmatiche di rivaroxaban aumentano in misura significativa. Rivaroxaban pertanto deve essere usato con cautela in questi pazienti.**
Non è raccomandato l'uso in pazienti con clearance della creatinina < 15 mL/min.

Compromissione epatica: **Nei pazienti cirrotici Child Pugh A sono state osservate solo lievi variazioni della farmacocinetica di rivaroxaban (aumento medio di 1,2 volte dell'AUC), pressoché paragonabili a quelle del gruppo sano di controllo.**
Nei pazienti cirrotici Child Pugh B, l'AUC media di rivaroxaban è risultata significativamente aumentata (2,3-2,6 volte). Questi pazienti presentavano anche ridotta eliminazione renale di rivaroxaban.
Non sono disponibili dati relativi ai pazienti con grave compromissione epatica. Rivaroxaban è quindi controindicato nei pazienti con patologie epatiche associate a coagulopatia e rischio emorragico clinicamente significativo, compresi i pazienti cirrotici con Child Pugh B e C.

Popolazione anziana: **non è previsto aggiustamento della dose, tuttavia porre attenzione al fatto che il rischio emorragico aumenta con l'aumentare dell'età.**

Rivaroxaban: rimborsabilità AIFA

AGENZIA ITALIANA DEL FARMACO

La rimborsabilità a carico del SSN è limitata a pazienti:

- **con diagnosi di arteriopatia periferica sintomatica**
- **che NON necessitino di doppia terapia anti-aggregante o di terapia anticoagulante a dose piena o altra terapia anti-aggregante diversa dalla aspirina**
- **in aggiunta ad acido acetilsalicilico.**

Arteriopatia periferica sintomatica

- **Pregresso By-pass aorto-femorale**
- **Pregresso by-pass dell'arto inferiore**
- **Pregressa rivascolarizzazione mediante angioplastica AAII**
- **Pregressa amputazione per malattia vascolare**
- **Claudicatio intermittens associata a :**
  - **rapporto pressione arteriosa caviglia/braccio < 0.90**
  - **stenosi arteriosa periferica > 50%**
  - **stenosi carotidea sottoposta a rivascolarizzazione o stenosi carotidea sintomatica > 50%**

AMD
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ASSOCIAZIONE MEDICI DIABETOLOGI

Grazie!

18 NOVEMBRE 2022

BOLOGNA

NH HOTEL BOLOGNA DE LA GARE - Piazza XX Settembre, 2