Terapia anticoagulante per la prevenzione di eventi cardiovascolari nei pazienti con arteriopatia periferica

Risultati di una metanalisi

Background

- Peripheral arterial disease (PAD) remains a major cause of morbidity, mortality, and disability across the world despite the recent advancement in medical, endovascular, and surgical therapies.
- Current medical and surgical societal guidelines have advocated single or dual antiplatelet therapy (SAPT and DAPT)
- Recent RCTs have found superior outcomes with the addition of oral anticoagulation (AC) to antiplatelet (additional anti-ischemic benefit albeit at the cost of higher bleeding risk).
- More recent RCTs have shown a similar reduction of ischemic events with the addition of low-dose rivaroxaban to antiplatelet therapy

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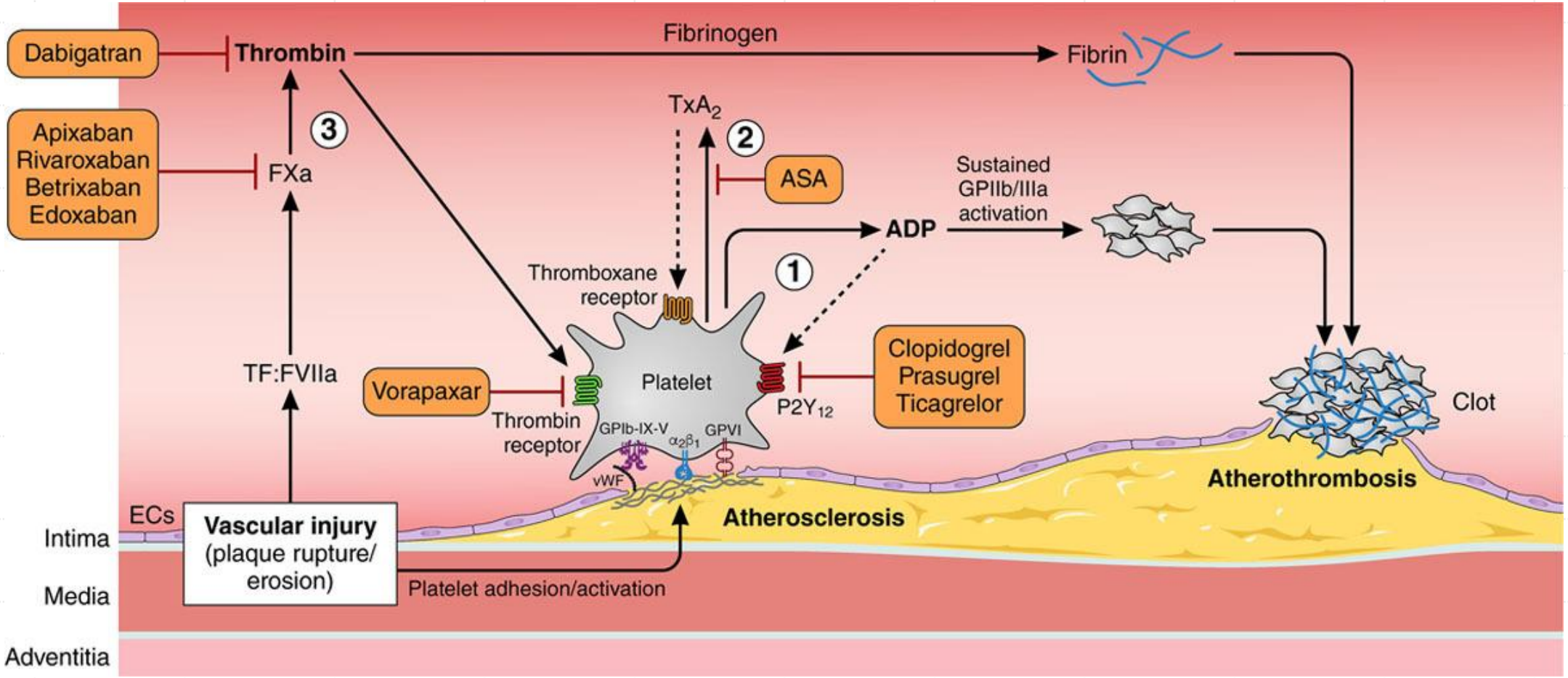

- Platelet activation and coagulation are stimulated by the interaction of flowing blood with injured vessel wall.
- 3 major pathways amplifying platelet activation
  - COX-1 pathway;
  - ADP-$P2Y_{12}$ pathway
  - thrombin pathway. inhibited by direct inhibition of thrombin, of thrombin generation by targeting FXa, and of PAR-1, the thrombin receptor.

Circulation. 2019;139:2170–2185.

Meta-Analysis of Anticoagulation Therapy for the Prevention of Cardiovascular Events in Patients With Peripheral Arterial Disease

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Aim of the study

- Study level meta-analysis, comparing AC combination therapy to the current standard of care (SOC) antiplatelet therapy.
- To evaluate full-dose (FD) versus low-dose (LD) AC on safety and efficacy outcomes.

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Methods

- PUBMED, Medline, and Cochrane Library were searched through 2020 for randomized clinical trials comparing major adverse cardiovascular events (MACE) and risk of major bleeding (MB), between AC and standard of care (SOC) therapy, among patients with PAD.
- Meta-analysis was performed using weighted pooled absolute risk difference (RD) with 95% confidence interval (CI) and fixed effects model for overall and sub-groups of full dose (FD) and low dose (LD) AC therapies.

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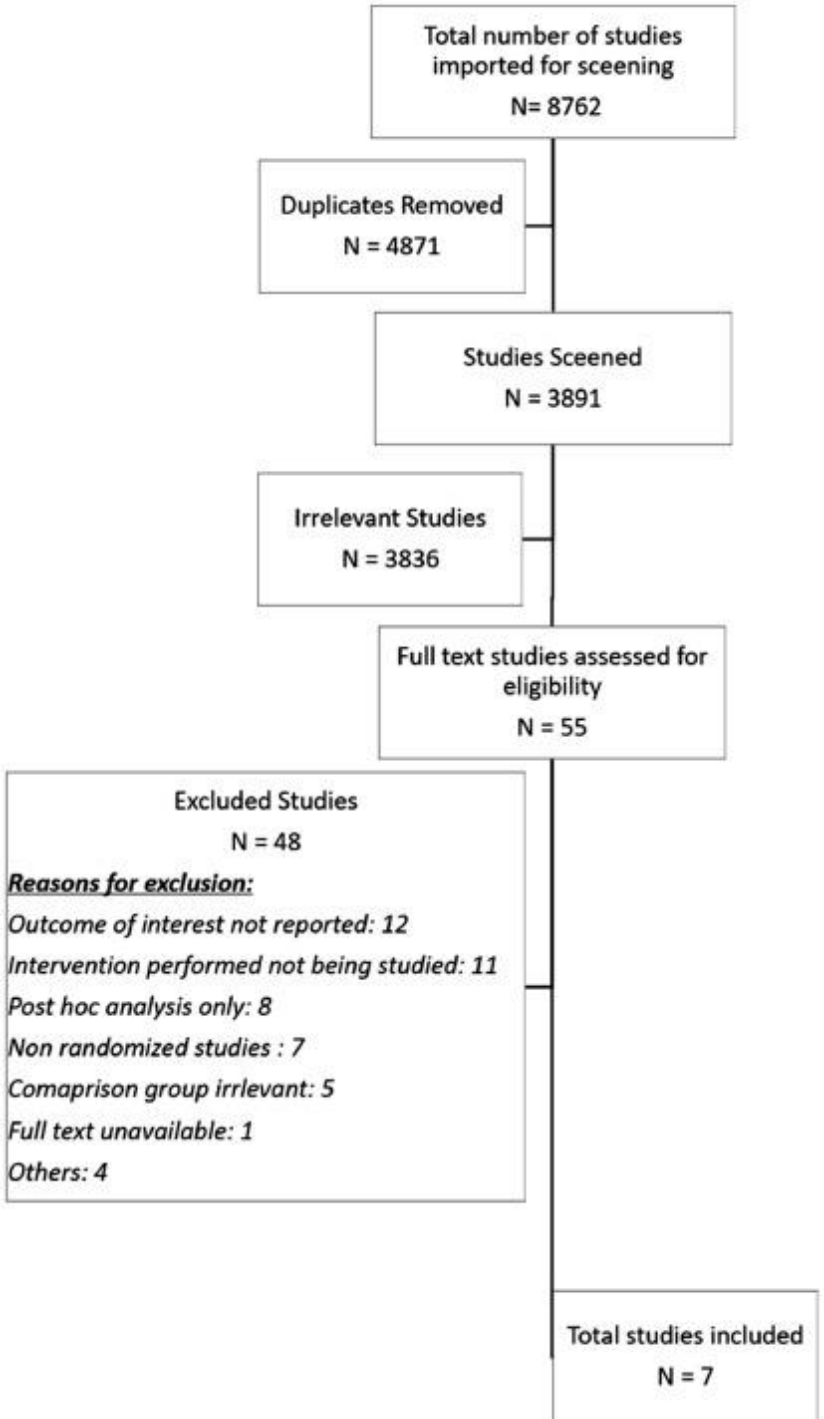
Study selection process

- Result: 17,684 patients from 7 different studies



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Summary of trial design and outcomes for the multicenter studies

All studies in the SOC arm used either single antiplatelet or dual antiplatelet (ePAD only), whereas the AC arm included AC with antiplatelet or without antiplatelet (Dutch BOA trial only).

	VOYAGER PAD[8]	COMPASS[7]	ePAD[9]	Wave[10]	Jivegard[13]	Johnson[12]	Dutch BOA[11]
Year	2020	2018	2018	2007	2005	2002	2000
Sample size	6,564	4,996	203	2,161	284	831	2,690
Median follow-up, (years)	2.3	1.7	0.5	2.9	1	3	1.8
Age, (years)	67 ± 6	67.6 ± 8.5	67.3 ± 9.5	64	73.5 ± 9	64 ± 8	69 ± 10
Male	74%	71%	71%	73.6%	55.2%	99%	63%
Aspirin dose	100 mg	100 mg	100 mg	81-325 mg	75 mg	325 mg	80 mg
AC type and dose	Rivaroxaban (2.5mg)	Rivaroxaban (2.5mg)	Edoxaban (60mg)	VKA (INR 2-3)	Dalteparin (5000 IU)	VKA (INR 1.4-2.8)	VKA (INR: 3-4.5)
Composite primary efficacy outcome (MACE)	CVD, CVA, MI, ALI, AMP	CVD, CVA, MI, ALI	CVD, CVA, MI, TLR, AMP	CVD, CVA, MI, ALI, AMP	(-)	(-)	CVD, CVA, MI, AMP
Primary safety outcome (major bleeding)	+	+	+	+	+	+	+

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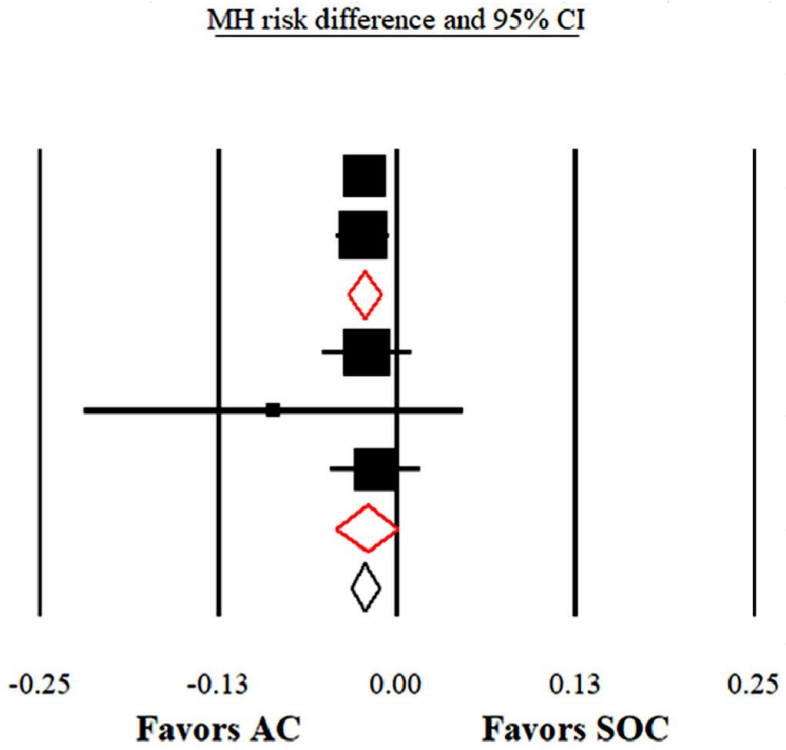
Primary efficacy outcomes: MACE between anticoagulation and SOC therapy

Study name	Subgroup within study	MH risk difference	Lower limit	Upper limit	Z-Value	p-Value	MACE / Total AC	MACE / Total SOC
COMPASS [7] 2018	LD	-0.0221	-0.0360	-0.0081	-3.1042	0.0019	142 / 2492	198 / 2504
VOYAGER[8] 2020	LD	-0.0236	-0.0416	-0.0056	-2.5641	0.0103	508 / 3286	584 / 3278
		-0.0229	-0.0348	-0.0111	-3.7852	0.0002	650 / 5778	782 / 5782
Dutch BOA[11] 2000	FD	-0.0207	-0.0510	0.0096	-1.3375	0.1811	248 / 1326	275 / 1324
ePAD [9] 2018	FD	-0.0859	-0.2183	0.0465	-1.2722	0.2033	32 / 100	41 / 101
Wave Trial[10] 2007	FD	-0.0147	-0.0461	0.0168	-0.9143	0.3606	172 / 1080	188 / 1081
		-0.0207	-0.0423	0.0009	-1.8745	0.0609	452 / 2506	504 / 2506
		-0.0223	-0.0328	-0.0117	-4.1321	0.0000	1102 / 8284	1286 / 8288

Fig 2 (A) Heterogeneity (Q: 1.14, df: 4, I^2: 0%, P=0.89)



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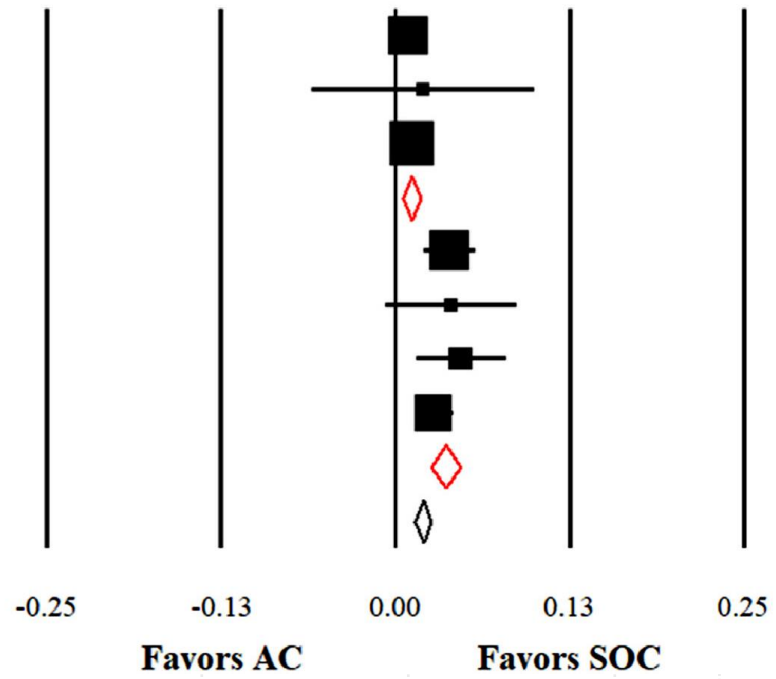
Primary safety outcomes: risk of major bleeding between anticoagulation and SOC therapy

Study name	Subgroup within study	Statistics for each study					MB / Total	
		MH risk difference	Lower limit	Upper limit	Z-Value	p-Value	AC	SOC
COMPASS[7] 2018	LD	0.0097	0.0018	0.0176	2.4031	0.0163	64 / 2492	40 / 2504
Jivegard[13] 2005	LD	0.0204	-0.0586	0.0994	0.5064	0.6126	20 / 141	17 / 140
VOYAGER[8] 2020	LD	0.0122	0.0031	0.0214	2.6135	0.0090	140 / 3256	100 / 3248
		0.0113	0.0050	0.0177	3.4990	0.0005	224 / 5889	157 / 5892
Dutch BOA[11] 2000	FD	0.0392	0.0209	0.0574	4.1972	0.0000	108 / 1326	56 / 1324
ePAD[9] 2018	FD	0.0401	-0.0068	0.0870	1.6765	0.0936	5 / 100	1 / 101
Johnson[12] 2002	FD	0.0474	0.0153	0.0795	2.8946	0.0038	35 / 418	15 / 413
Wave Trial[10] 2007	FD	0.0278	0.0144	0.0411	4.0800	0.0000	43 / 1080	13 / 1081
		0.0362	0.0254	0.0470	6.5634	0.0000	191 / 2924	85 / 2919
		0.0196	0.0140	0.0251	6.9051	0.0000	415 / 8813	242 / 8811

Fig 2 (B) Heterogeneity (Q: 17.93, df: 6, I^2: 66.5%, P=0.006)



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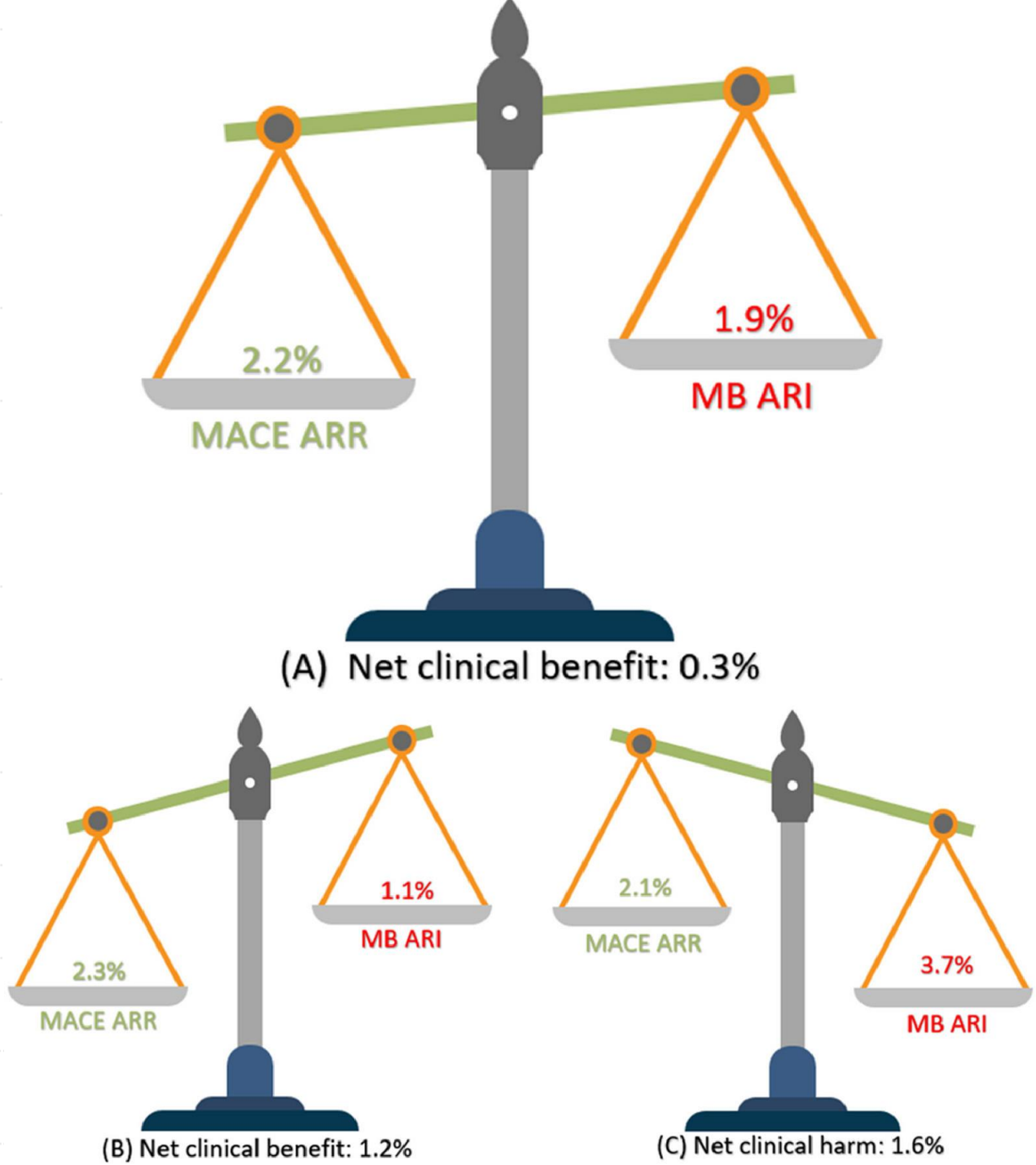
Net clinical benefit and harm

A) Overall,
B) Low dose,
C) Full dose anticoagulation therapy.



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Limitations

- Variations in the type and dose of AC between the studies.
- Bleeding definition were highly variable → attempted to standardize by using either ISTH or the individual trial definition.
- Some trials designed to assess safety or major adverse limb events (MALE) and not MACE.
- Variability in the duration and follow-up, → the long-term efficacy and safety of AC remains uncertain.
- The majority of the FD AC trials were of relatively small sample size, and only one trial was powered to detect statistically significant differences in cardiovascular and ischemic endpoints.
- Age distribution 64 - 74 ± 10years→ results cannot be directly extrapolated to patients < 55 or > 85
- FD AC with warfarin is considered SOC for patients who underwent bypass surgery utilizing vein grafts, based on subgroup analyses of the Dutch BOA study. No sufficiently powered studies have been performed to investigate graft patency with LD AC → results cannot be extrapolated for this particular subset of patients

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Conclusions

- The addition of AC to SOC antiplatelet therapy in patients with PAD is associated with a lower risk for ischemic cardiovascular events but at the cost of higher bleeding risk.
- LD, compared to FD AC, has a favorable safety/efficacy ratio and should be applied in patients if bleeding risk is low.

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