Efficacia dell'associazione tra rivaroxaban e aspirina nella prevenzione di complicanze vascolari maggiori nei pazienti con arteriopatia periferica degli arti inferiori: sottoanalisi dello studio COMPASS.

The Current ESC Guidelines for PAD Management Recommend Treatment of Symptomatic Peripheral Artery Disease (PAD)

2017 ESC guideline recommendations for antithrombotic therapies in patients with PAD

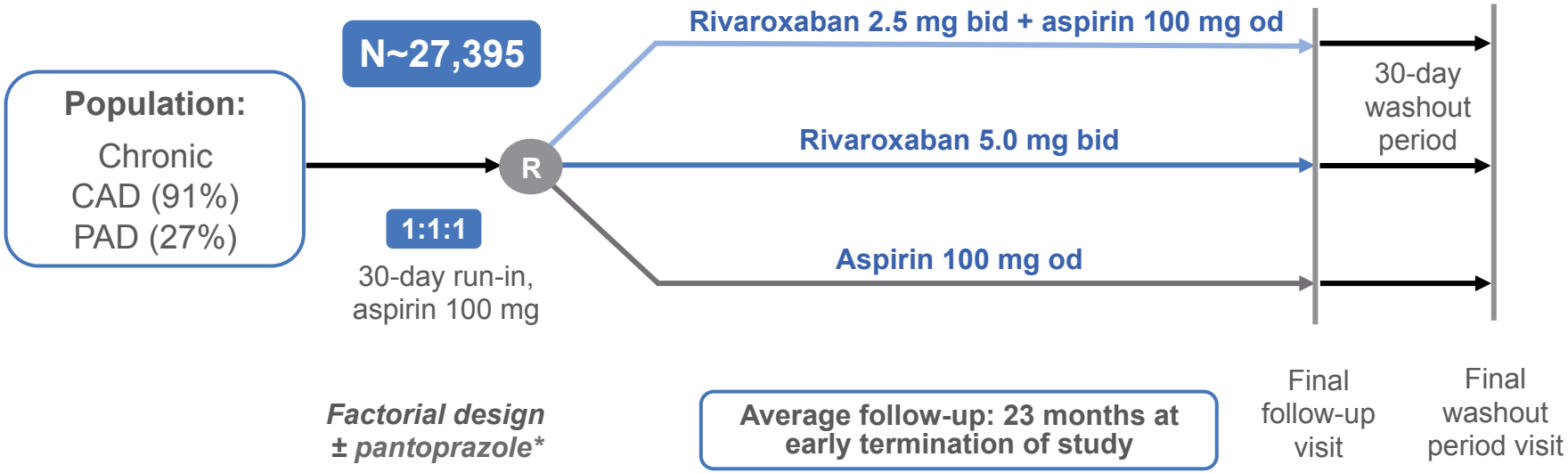
- SAPT is recommended for all patients with symptomatic PAD
- DAPT is recommended only for a limited period of time after certain revascularization procedures

Patients with…	Recommendation	Class
Symptomatic PAD	Antiplatelet therapy is recommended	Ic
Lower extremity PAD	In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin	IIb
	Anticoagulation with VKAs may be considered after autogenous vein infrainguinal bypass	IIb
	DAPT (aspirin plus clopidogrel) for ≥1 month should be considered after infra-inguinal stent implantation	IIa
	DAPT (aspirin plus clopidogrel) may be considered in the case of below-knee bypass with a prosthetic graft	IIb
	Long-term SAPT is recommended in all patients who have undergone revascularization	Ic
	SAPT is recommended after infrainguinal bypass surgery	Ia

1. Aboyans V *et al, Eur Heart* J 2017; doi: 10.1093/eurheartj/ehx095; 2. Aboyans V *et al*, *Eur J Vasc Endovasc Surg* 2017; doi:10.1016/j.ejvs.2017.07.018

A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in **COMPASS trial**

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban vascular dose 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al, N Engl J Med* 2017;377:1319-1330; 2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

COMPASS

Inclusion and Exclusion Criteria Ensure That Patients with Chronic PAD are Enrolled

Key inclusion criteria

- Previous peripheral artery revascularization
- Previous limb or foot amputation for arterial vascular disease
- Intermittent claudication plus:
  - Low ABI (<0.90), or
  - Significant peripheral artery stenosis (≥50%)
- Previous carotid revascularization, or asymptomatic carotid artery stenosis ≥50%
- CAD + low ABI (<0.90)

Key exclusion criteria

- High risk of bleeding
- Stroke within 1 month
- History of haemorrhagic/lacunar stroke
- Severe heart failure (ejection fraction <30%)
- eGFR <15 ml/min
- A need for dual antiplatelet therapy
- A need for non-aspirin antiplatelet therapy
- An indication for anticoagulation therapy

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

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PAD-Specific Limb Outcomes Were Added to Main Study Outcomes for COMPASS

- Primary cardiovascular outcome was MACE, defined as:
  - Composite of cardiovascular death, stroke or MI

- Key composite outcomes for PAD:
  - Primary limb outcome was major adverse limb events (MALE), defined as development of ALI or CLI and major amputations not included in ALI or CLI
  - The composite of MACE and MALE
  - The composite of MACE, MALE and major amputations not included in ALI or CLI

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

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Major Adverse Limb Events and Major Amputation Were Included in PAD-Specific Net Clinical Benefit

- Primary safety outcome: modified ISTH
  - Major bleeding defined as:
    - Fatal bleeding, or
    - Bleeding into a critical organ, or
    - Surgical site bleeding requiring reoperation, or
    - Bleeding requiring hospitalization

- Net clinical benefit outcome defined as:
  - MACE
  - MALE including major amputation
  - Fatal bleeding
  - Bleeding into a critical organ

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

COMPASS Included over 7000 Patients with Symptomatic PAD or Concomitant CAD and PAD

	Number of patients
All patients with PAD	7470
Symptomatic lower-extremity PAD	4129
Carotid disease	1919
CAD + asymptomatic PAD (ABI <0.90)	1422

- PAD was defined according to patient presentation at enrolment
- In addition, a patient could be defined as a PAD patient based on medical history and/or measurement of ABI at baseline visit
  - The latter category added patients with CAD and asymptomatic PAD patients into the overall PAD subgroup
- Median follow-up: 21 months

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

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Baseline Characteristics Were Consistent across Treatment Arms and in Line with Those Usually Seen in Patients with PAD

Characteristic	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504
Age, years, mean ± SD	67.9±8.5	67.8±8.5	67.8±8.5
Current smoker, n (%)	682 (27.4)	685 (27.7)	685 (27.4)
Former smoker, n (%)	1147 (46.0)	1154 (46.6)	1143 (45.6)
Diabetes, n (%)	1100 (44.1)	1083 (43.8)	1104 (44.1)
Hypertension, n (%)	1966 (78.9)	1939 (78.4)	2017 (80.6)
Prior CAD, n (%)	1656 (66.5)	1609 (65.0)	1641 (65.5)
Prior stroke, n (%)	171 (6.9)	177 (7.2)	154 (6.2)
Lipid lowering, n (%)	2088 (83.8)	2074 (83.8)	2074 (82.8)
ACE inhibitor/ARB, n (%)	1715 (68.8)	1757 (71.0)	1765 (70.5)

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced MACE by 28% Versus Aspirin Alone

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACE	126 (5)	149 (6)	174 (7)	0.72 (0.57–0.90)	0.0047	0.86 (0.69–1.08)	0.19
CV death	64 (3)	66 (3)	78 (3)	0.82 (0.59–1.14)	–	0.86 (0.62–1.19)	–
Stroke	25 (1)	43 (2)	47 (2)	0.54 (0.33–0.87)	–	0.93 (0.61–1.40)	–
MI	51 (2)	56 (2)	67 (3)	0.76 (0.53–1.09)	–	0.84 (0.59–1.20)	–

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

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Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Significantly Reduced Major Amputation by 70% Versus Aspirin Alone

Outcome	**Rivaroxaban 2.5 mg bid + aspirin N=2492**	**Rivaroxaban 5 mg bid N=2474**	**Aspirin N=2504**	**Rivaroxaban 2.5 mg bid + aspirin vs aspirin**		**Rivaroxaban 5 mg bid vs aspirin**	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MALE	30 (1)	35 (1)	56 (2)	0.54 (0.35–0.84)	0.0054	0.63 (0.41–0.96)	0.032
Major amputation	5 (<1)	8 (<1)	17 (<1)	0.30 (0.11–0.80)	0.011	0.46 (0.20–1.08)	0.068

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

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Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Significantly Reduced MACE and MALE Versus Aspirin Alone

Composite outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACE or MALE including major amputation	157 (6)	188 (8)	225 (9)	0.69 (0.56–0.85)	0.0003	0.83 (0.69–1.02)	0.077

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

Bleeding Increased but Low with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone, with No Differences Seen in Fatal and Intracranial Bleeding

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Major bleeding	77 (3)	79 (3)	48 (2)	1.61 (1.12–2.31)	0.0089	1.68 (1.17–2.40)	0.0043
Fatal	4 (<1)	5 (<1)	3 (<1)	–	–	–	–
Intracranial	5 (<1)	6 (<1)	9 (<1)	–	–	–	–
Fatal or symptomatic bleeding into a critical organ	21 (1)	26 (1)	19 (1)	1.10 (0.59–2.05)	-	1.39 (0.89–3.09)	-

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

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28% Reduction in Risk of the Composite Outcome with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone

Rates at median follow-up of 21 months	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Composite net clinical benefit outcome*	169 (7)	207 (8)	234 (9)	0.72 (0.59–0.87)	0.0008	0.89 (0.74–1.07)	0.23

- For every 1000 patients with PAD treated with rivaroxaban plus aspirin, 27 MACE or MALE (including major amputation) events would be prevented, and 1 fatal and 1 critical organ bleed would be caused over a 21-month period

*Defined as CV death, MI, stroke, MALE, major amputation, fatal bleeding or critical organ bleeding

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

COMPASS

Vascular Dose Rivaroxaban Showed Improved Outcomes for PAD Patients with a Need for Increased Vascular Protection

- Rivaroxaban vascular dose 2.5 mg BID plus aspirin reduced the composite endpoint of stroke, MI or CV death by 28%.
  - MALE by 46%
  - Major amputations by 70%
- Despite an expected increase in major bleeding events with Rivaroxaban 2.5 mg BID plus aspirin, no significant increase was observed in fatal or critical organ bleeding
- This dual pathway inhibition of Rivaroxaban vascular dose and aspirin represents a major advance in the management of PAD and is the only available therapeutic option to significantly reduce both MACE and MALE

*Defined as CV death, MI, stroke, MALE, major amputation, fatal bleeding or critical organ bleeding

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

JACC

J Am Coll Cardiol. 2018 Mar 7.
pii: S0735-1097(18)33502-2. doi: 10.1016/j.jacc.2018.03.008.

Original Investigations

Major Adverse Limb Events in Lower Extremity Peripheral Artery Disease: COMPASS Trial

Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, Verhamme P, Fox KAA, Cook-Bruns N, Lanius V, Connolly SJ, Yusuf S; COMPASS trial Investigators.

Objectives:

To investigate among participants with lower extremity PAD:

1) if hospitalizations, MACE, amputations, and deaths are higher after first episode of MALE compared with PAD patients who do not experience MALE;

2) the impact of treatment with low dose rivaroxaban and aspirin compared to aspirin alone on the incidence of MALE, peripheral vascular interventions, and all peripheral vascular outcomes over a median follow-up of 21 months.

Methods:

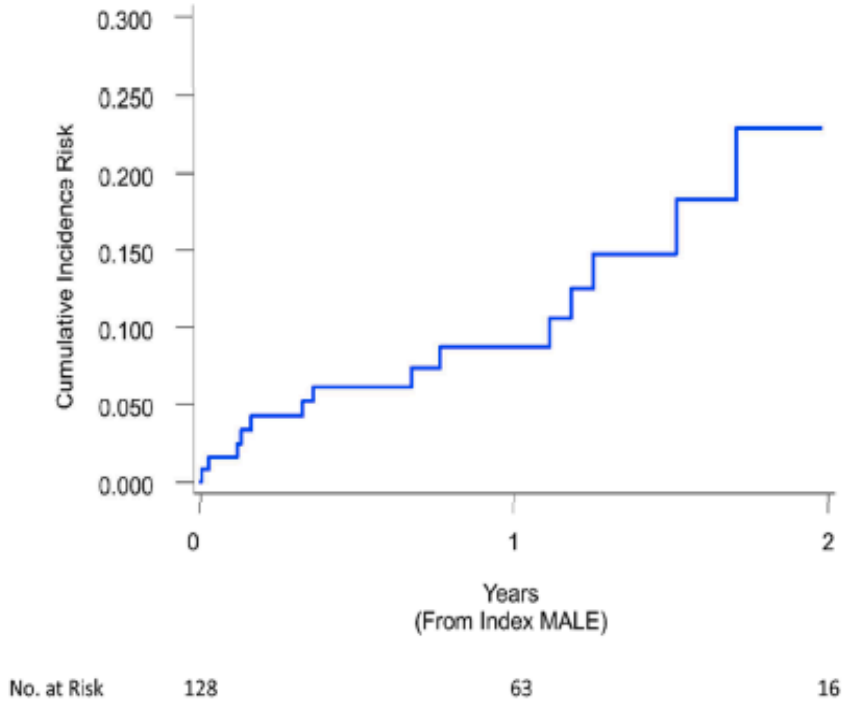
- Outcomes were analyzed in **6,391 patients** with lower extremity PAD who were enrolled in the COMPASS trial.
- MALE was defined as severe limb ischemia leading to an intervention or major vascular amputation.

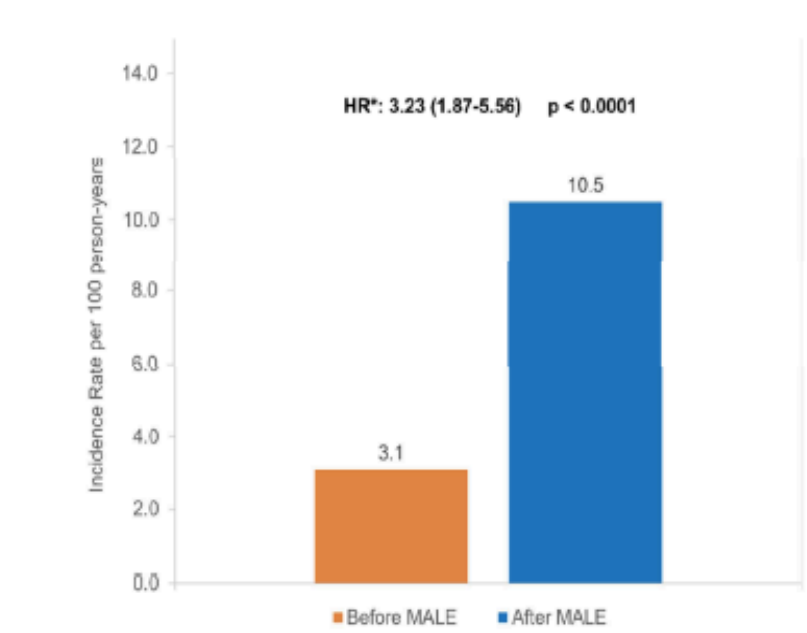
J Am Coll Cardiol. 2018 Mar 7.
pii: S0735-1097(18)33502-2. doi: 10.1016/j.jacc.2018.03.008.

Results:

A. **The cumulative incidence risk of death following MALE** (line graph). This shows the cumulative incidence risk of death following index MALE in PAD patients who suffered a MALE.

B. The bar graph shows **Pre-MALE and Post MALE incidence rates for death** with the Hazard Ratio (95% confidence interval) for the index MALE.





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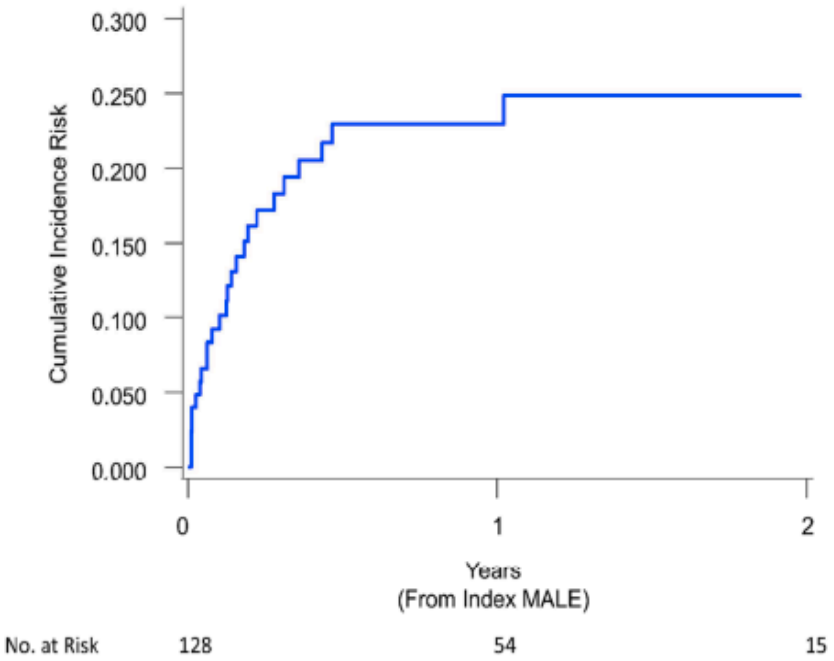
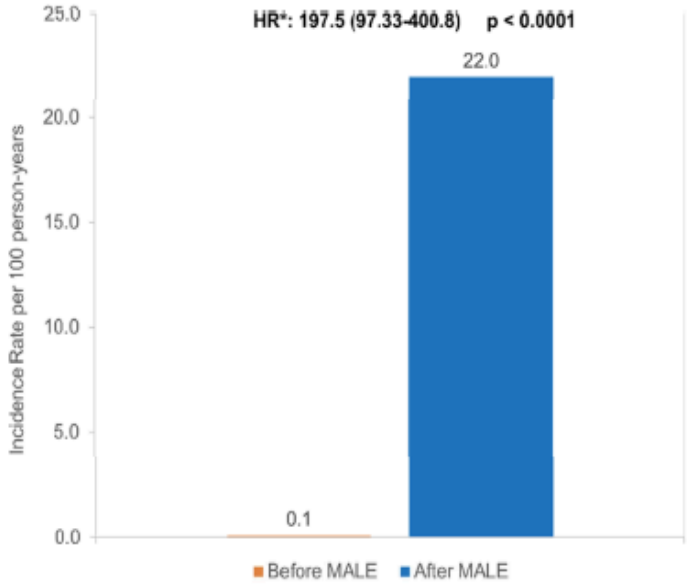
Results:

A.



B.



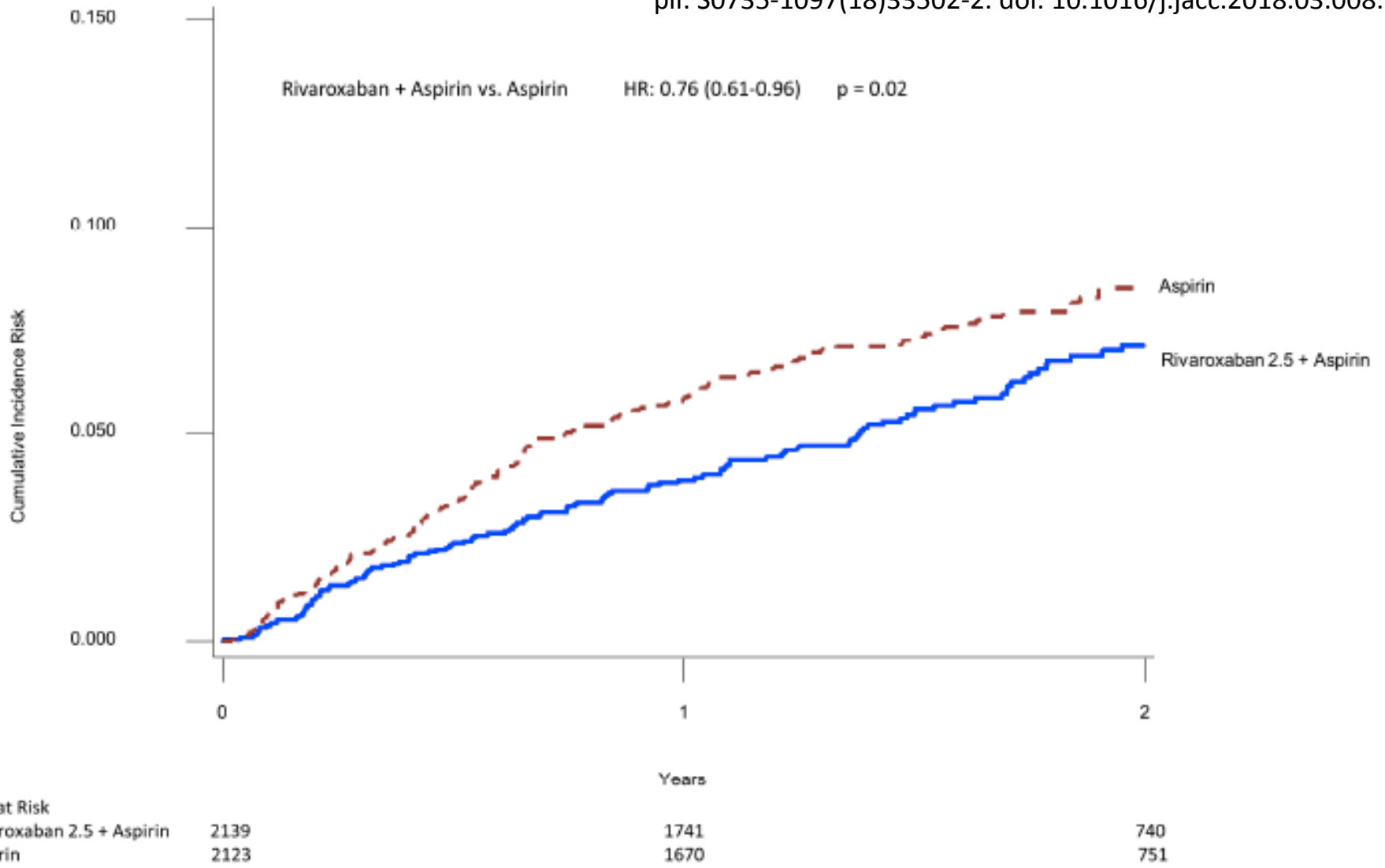
A. The cumulative incidence of subsequent total vascular amputation following MALE (line graph).

B. B. The bar graph shows **Pre-MALE and Post MALE incidence rates for vascular amputation** with the Hazard Ratio (95% confidence interval) for the index MALE.

J Am Coll Cardiol. 2018 Mar 7.
pii: S0735-1097(18)33502-2.
doi: 10.1016/j.jacc.2018.03.008.

Results: The cumulative incidence risk of **peripheral artery outcomes** in trial participants treated with rivaroxaban and aspirin compared to aspirin alone.

J Am Coll Cardiol. 2018 Mar 7.
pii: S0735-1097(18)33502-2. doi: 10.1016/j.jacc.2018.03.008.



Conclusions:

- Among individuals with lower extremity PAD, the development of MALE is associated with a poor prognosis, making its prevention of utmost importance.

- The combination of rivaroxaban 2.5 mg bid and aspirin significantly lowers the incidence of MALE and its related complications and should be considered as an important therapy for patients with PAD.

J Am Coll Cardiol. 2018 Mar 7.
pii: S0735-1097(18)33502-2. doi: 10.1016/j.jacc.2018.03.008.