ACC Latin America Conference 2018

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TOP CLINICAL TRIALS of 2018 to Impact Your Practice - COMPASS

(Lower Extremity Peripheral Artery Disease)

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Disclosure of Potential Conflicts of Interest (David Brasil)

Categories of potential conflicts of interest	Company (2016, 2017 and 2018)
Sponsored in transport and/or hotel accommodations in Congresses/Conferences	**Servier**
Sponsored in clinical trials and/or in basic research funded by pharmaceutical companies	**Bayer - National Lead Investigator Voyager-PAD Clinical Trial**
Speaker in meetings sponsored by pharmaceutical companies	**Servier, LIBBS**
Participate in normative committees of scientific trials sponsored by pharmaceutical companies	**Bayer - National Lead Investigator & member of the International Steering Committee Voyager-PAD Clinical Trial**
Receive institutional support from pharmaceutical companies	–
Writing of educative materials sponsored by pharmaceutical companies	**LIBBS, Servier**
Provide training in evidence-based medicine for pharmaceutical company's personnel	**Vertex**
Hold stocks of pharmaceutical companies	–

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Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease

The COMPASS Trial

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- ✓ Multicenter, double-blind, randomized, placebo-controlled trial
- ✓ Rivaroxaban 2.5 mg twice daily + Aspirin **OR**
- ✓ Rivaroxaban 5 mg twice daily (Aspirin placebo) ***VERSUS*** Aspirin alone (Rivaroxaban placebo)
- ✓ Prevention of CV death, MI, or stroke (MACE) in patients with CAD or PAD

Anand *et al. J Am Coll Cardiol* 2018;71(20):2306-15.
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ORIGINAL ARTICLE

Eikelboom *et al. N Engl J Med* 2017;377(14):1319-1330.

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Age — yr	68.3±7.9	68.2±7.9	68.2±8.0
Female sex — no. (%)	2059 (22.5)	1972 (21.6)	1989 (21.8)
Body-mass index†	28.3±4.8	28.3±4.6	28.4±4.7
Blood pressure — mm Hg			
Systolic	136±17	136±18	136±18
Diastolic	77±10	78±10	78±10
Cholesterol — mmol/liter	4.2±1.1	4.2±1.1	4.2±1.1
Tobacco use — no. (%)	1944 (21.2)	1951 (21.4)	1972 (21.6)
Hypertension — no. (%)	6907 (75.5)	6848 (75.1)	6877 (75.4)
Diabetes — no. (%)	3448 (37.7)	3419 (37.5)	3474 (38.1)
Previous stroke — no. (%)	351 (3.8)	346 (3.8)	335 (3.7)
Previous myocardial infarction — no. (%)	5654 (61.8)	5653 (62.0)	5721 (62.7)
Heart failure — no. (%)	1963 (21.4)	1960 (21.5)	1979 (21.7)
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)
Peripheral arterial disease — no. (%)§	2492 (27.2)	2474 (27.1)	2504 (27.4)

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TABLE 1 Characteristics of Participants With Lower Extremity PAD

*** MALE - major adverse limb event**

	All Lower Extremity PAD	* MALE	* No MALE	p Value Univariable Predictor of MALE
No. randomized to treatment	6,391	128	6,263	
Age, yrs	67.6 ± 8.5	67.6 ± 8.3	67.6 ± 8.5	0.66
Women	1,786 (27.9)	24 (18.8)	1,762 (28.1)	0.03
Body mass index, kg/m^2	28.4 ± 4.9	27.9 ± 4.3	28.4 ± 4.9	0.19
Fontaine classification III or IV ischemia	234 (3.7)	22 (17.2)	212 (3.4)	<0.0001
History of coronary artery disease	4,145 (64.9)	68 (53.1)	4,077 (65.1)	0.0007
History of peripheral revascularization surgery or angioplasty	2,045 (32)	74 (57.8)	1,971 (31.5)	<0.0001
Previous amputation at baseline	335 (5.2)	26 (20.3)	309 (4.9)	<0.0001
Ankle-brachial index at baseline	0.90 ± 0.20	0.89 ± 0.24	0.90 ± 0.20	0.25
Ankle-brachial index <0.50	99 (1.5)	3 (2.3)	96 (1.5)	0.31
Current/former smoker	4,789 (74.9)	110 (85.9)	4,679 (74.7)	0.008
Diabetes	2,854 (44.7)	69 (53.9)	2,785 (44.5)	0.04
Hypertension	5,024 (78.6)	106 (82.8)	4,918 (78.5)	0.28
Renal insufficiency: eGFR <60%	1,783 (27.9)	37 (28.9)	1,746 (27.9)	0.84

MALE defined as severe limb ischemia leading to an intervention or major vascular amputation.

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✓ ***OBJECTIVES***

Among LEPAD patients, investigate:

1. if hospitalizations, MACE, amputations, and deaths are ***higher after the first episode of MALE (?)*** compared with patients with PAD who do not experience MALE
2. the ***impact of treatment with low-dose rivaroxaban and aspirin*** compared with aspirin alone on the incidence of MALE, PVI, and all peripheral vascular outcomes over a median follow-up of 21 months

✓ **RESULTS**

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Vascular Amputation

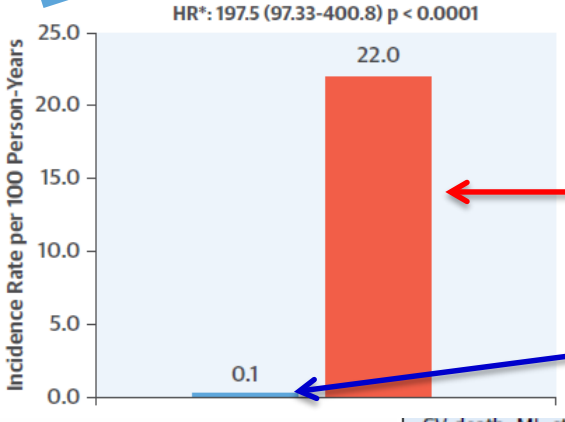

TABLE 3 Outcomes in Patients After MALE and Outcomes in Patients Before MALE

	Risk for Subsequent Outcomes in Patients After MALE During the Study (n = 128)				Risk for Outcomes Between Randomization and the Occurrence of MALE or End-of-Follow-Up (Whichever Came First) (n = 6,391)		
	No. of Patient-Years	n (%)	Rate/ 100-person yrs	1-Year Incidence Risk	No. of Patient-Years	n (%)	Rate/ 100-person-yrs
ion	65.59	79 (61.7)	120.5	61.5	9,346.09	1,903 (29.8)	20.4
nputation	113.74	25 (19.5)	22.0	20.5	11,409.48	15 (0.2)	0.1
ity	132.80	14 (10.9)	10.5	8.3	11,421.72	351 (5.5)	3.1
stroke	130.63	7 (5.5)	5.4	3.7	11,202.87	386 (6.0)	3.4
on	71.42	71 (55.5)	99.4	57.6	10,320.46	1,060 (16.6)	10.3
roke, total vascular	111.56	29 (22.7)	26.0	22.4	11,190.78	399 (6.2)	3.6
CV death, MI, stroke, major amputation	120.63	18 (14.1)	14.9	12.1	11,202.87	386 (6.0)	3.4

CV = cardiovascular disease; MALE = major adverse limb events; MI = myocardial infarction.

✓ ***RESULTS***

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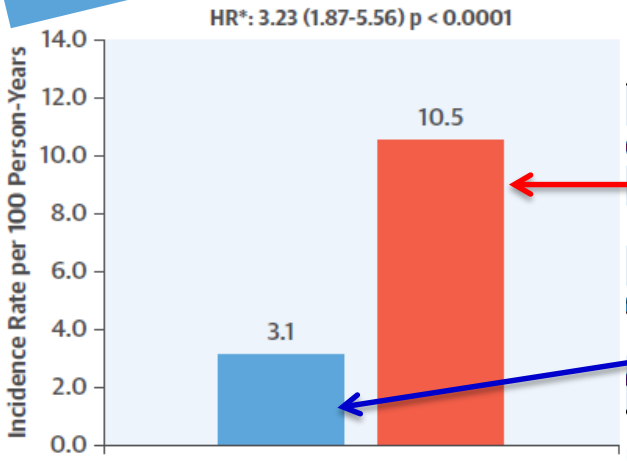
Death



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✓ **RESULTS**

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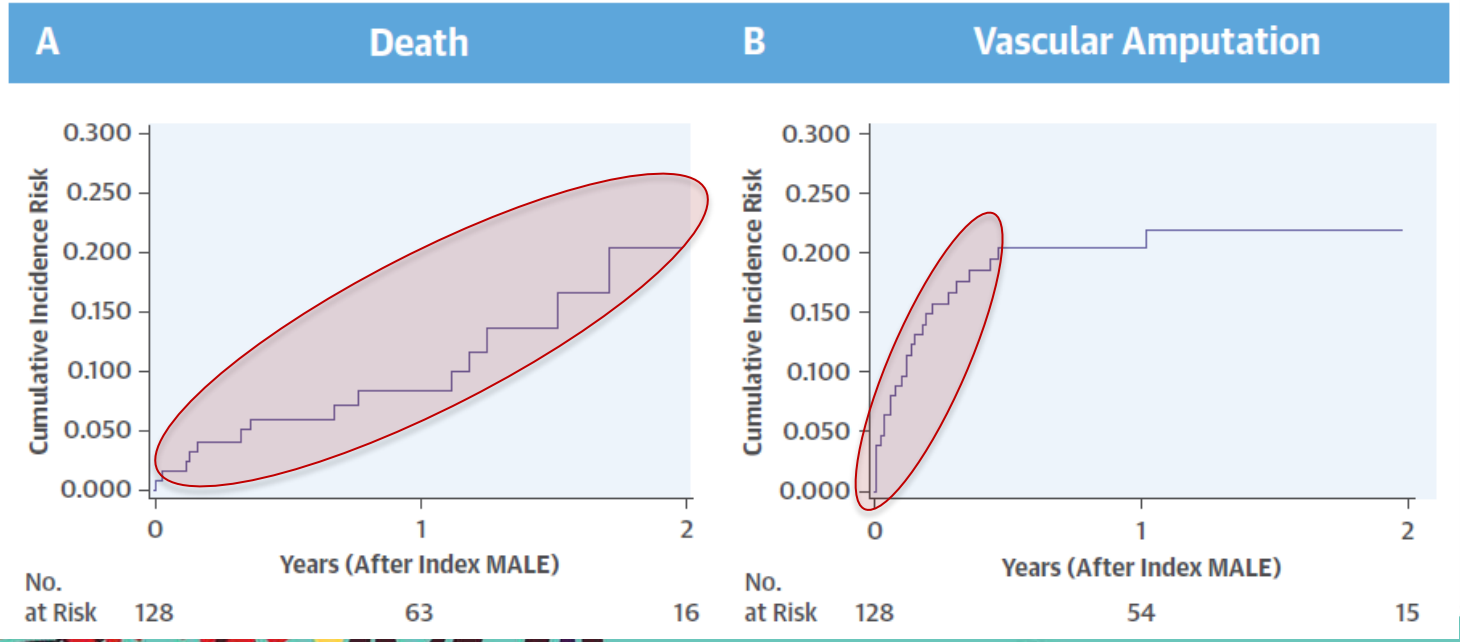
CENTRAL ILLUSTRATION High Mortality and Vascular Amputation After MALE in Peripheral Artery Disease



Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease

The COMPASS Trial

✓ ***RESULTS***

TABLE 4 Impact of MALE Index Event on Outcomes of Interest

	HR (95% CI)	p Value
Any hospitalization*	7.21 (5.51-9.43)	<0.0001
Total vascular amputation*	197.5 (97.33-400.8)	<0.0001
All-cause mortality	3.23 (1.87-5.56)	<0.0001
CV death, MI, stroke	1.52 (0.72-3.24)	0.27
CV hospitalization*	11.72 (9.04-15.21)	<0.0001
MACE or vascular amputation*	7.56 (5.14-11.12)	<0.0001
MACE or major amputation*	4.23 (2.62-6.84)	<0.0001

Index MALE event modeled as a time-dependent covariate in the Cox proportional hazards model. *Considering only those outcomes that did not occur on the same day as the index MALE.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); other abbreviations as in Table 3.

TABLE 5 Peripheral Vascular Disease Outcomes and Treatment Effect With Rivaroxaban and Aspirin or Rivaroxaban Alone Compared With Aspirin Alone

	Rivaroxaban 2.5 mg b.i.d. Plus Aspirin 100 mg (n = 2,139)	Rivaroxaban 5 mg b.i.d. Plus Aspirin Placebo (n = 2,129)	Aspirin 100 mg Plus Rivaroxaban Placebo (n = 2,123)	Rivaroxaban 2.5 b.i.d. Plus Aspirin 100 mg		Rivaroxaban 5 mg b.i.d. vs. Aspirin 100 mg once-daily	
				HR (95% CI)	p Value	HR (95% CI)	p Value
MALE*	32 (1.5)	40 (1.9)	56 (2.6)	0.57 (0.37-0.88)	0.01	0.71 (0.47-1.06)	0.10
Total vascular amputation	11 (0.5)	17 (0.8)	26 (1.2)	0.42 (0.21-0.85)	0.01	0.65 (0.35-1.19)	0.16
Major vascular amputation	5 (0.2)	8 (0.4)	15 (0.7)	0.33 (0.12-0.92)	0.03	0.52 (0.22-1.22)	0.13
All amputations	19 (0.9)	24 (1.1)	36 (1.7)	0.52 (0.30-0.91)	0.02	0.66 (0.39-1.10)	0.11
Vascular interventions†	117 (5.5)	119 (5.6)	150 (7.1)	0.76 (0.60-0.97)	0.03	0.78 (0.62-1.00)	0.05
Total outcomes for peripheral artery disease complications‡	132 (6.2)	138 (6.5)	169 (8.0)	0.76 (0.61-0.96)	0.02	0.81 (0.64-1.01)	0.06
Major bleeding	68 (3.2)	66 (3.1)	42 (2.0)	1.61 (1.09-2.36)	0.01	1.60 (1.09-2.36)	0.02
Severe bleeding§	24 (1.1)	23 (1.1)	18 (0.8)	1.32 (0.71-2.42)	0.38	1.30 (0.70-2.40)	0.41

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✓ RESULTS

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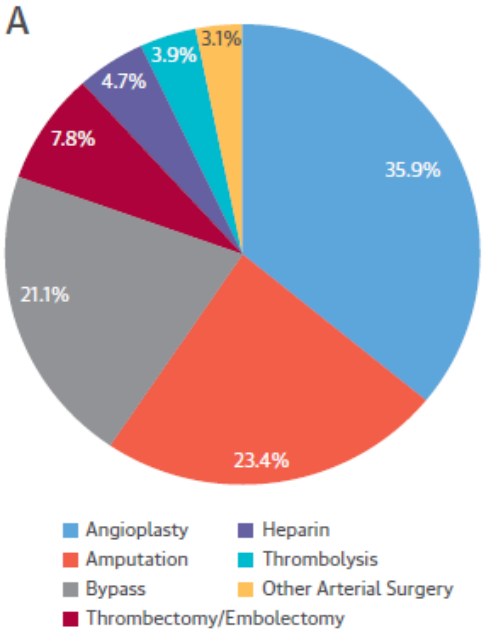
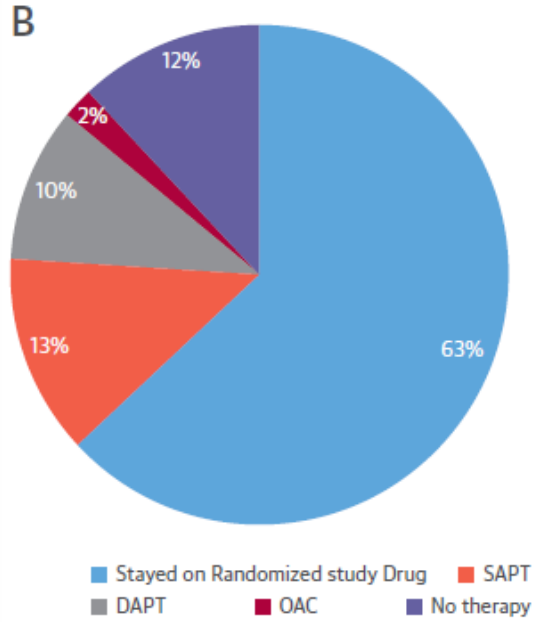
Types of interventions MALE patients underwent after the diagnosis with CLI



Antithrombotic therapy used after the diagnosis of MALE



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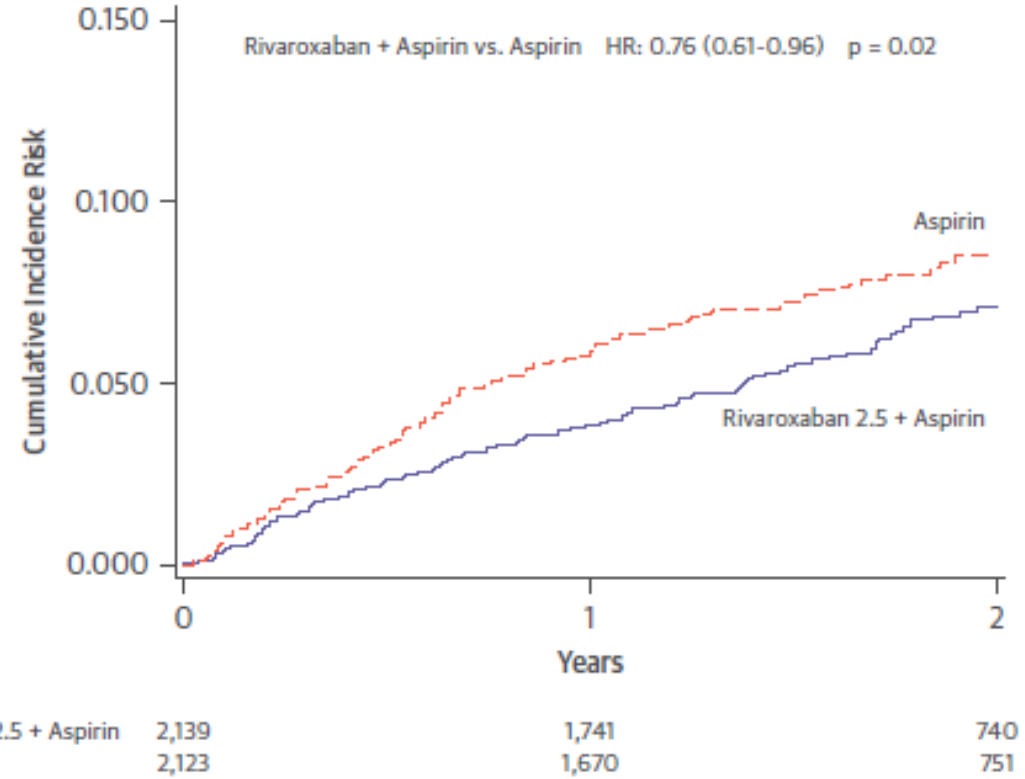
✓ **RESULTS**

All types of peripheral artery outcomes in trial participants treated with **Rivaroxaban and Aspirin** *versus* **Aspirin Alone**



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✓ *HIGHLIGHTS FOR DISCUSSION*

The MALE index event significantly increased the risk of:

- Subsequent Hospitalizations (HR 7.21; *p*<0.0001)
- Subsequent Amputations (HR 197.5; *p*<0.0001)
- Death (HR 3.23; p<0.001)

Rivaroxaban 2.5 mg/2x daily and Aspirin *versus* Aspirin Alone (incidence)**:**

- ☑ MALE ↓ 43% (*p*=0.01)
- ☑ Total vascular amputations ↓ 58% (*p*=0.01),
- ☑ Peripheral vascular interventions ↓ 24% (*p*=0.03)
- ☑ All types of peripheral artery outcomes ↓ 24% (*p*=0.02)

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