SAMUEL AND JEAN FRANKEL CARDIOVASCULAR CENTER
MICHIGAN MEDICINE

Optimal Antithrombotic Therapy in Peripheral Artery Disease

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2023 ACC CV Symposium

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Disclosures

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- Consulting Fees
  - Pfizer/Bristol-Myers Squib, Janssen, Bayer, Boston Scientific, Abbott Vascular
- Grant Funding
  - Boston Scientific
- Board of Directors
  - Anticoagulation Forum

Clinical Case

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- 66yo man presents to clinic for “leg pain”
- HPI:
  - Leg pain with exertion, improves with rest
  - Can’t keep up with wife or grandchildren
  - Difficulty grocery shopping
  - No rest pain or ulcerations

- PMH: DM2, CAD s/p PCI 3 years ago, HTN
- SH: Former smoker, quit 20 year ago
- Meds: ASA 75mg, atorvastatin, lisinopril, metformin, empagliflozin

- BP 132/72
- LE: hair loss below knee, no ulcers, no pallor/rubor. Palpable but weak PT pulses
- A1c 8.2%, Cr 0.9 mg/dL (GFR 75)
- Chol 195 mg/dL, HDL 45 mg/dL, LDL 130 mg/dL
- ABI 0.6 (R), 0.7 (L)

- Is he currently receiving guideline-recommended antithrombotic therapy?
- What anti-thrombotic strategy would be recommended if he undergoes LE angioplasty?

2016 ACC/AHA PAD Guidelines

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- Antiplatelet Therapy
  - ASA 75-325mg daily OR clopidogrel 75mg daily (Class I)
    - Reduce MI, stroke, vascular death in symptomatic PAD
  - ASA + clopidogrel to reduce cardiovascular events (Class II b)
    - Effectiveness is not well established

Circulation 2017;135:e726-e779

Anti-platelet Targets

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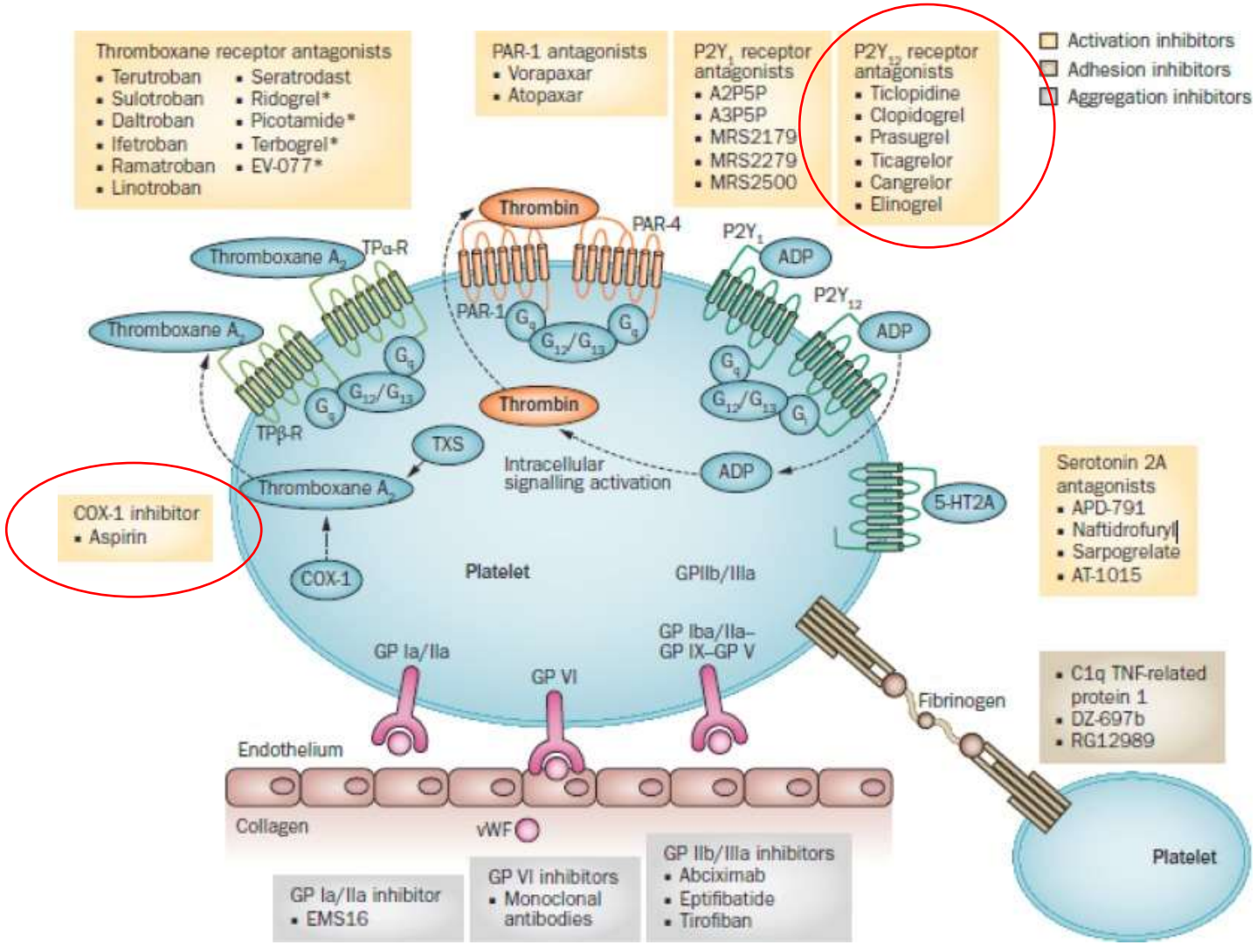

Nat Rev Cardiol 2015;12:30-47

Anti-platelet Targets

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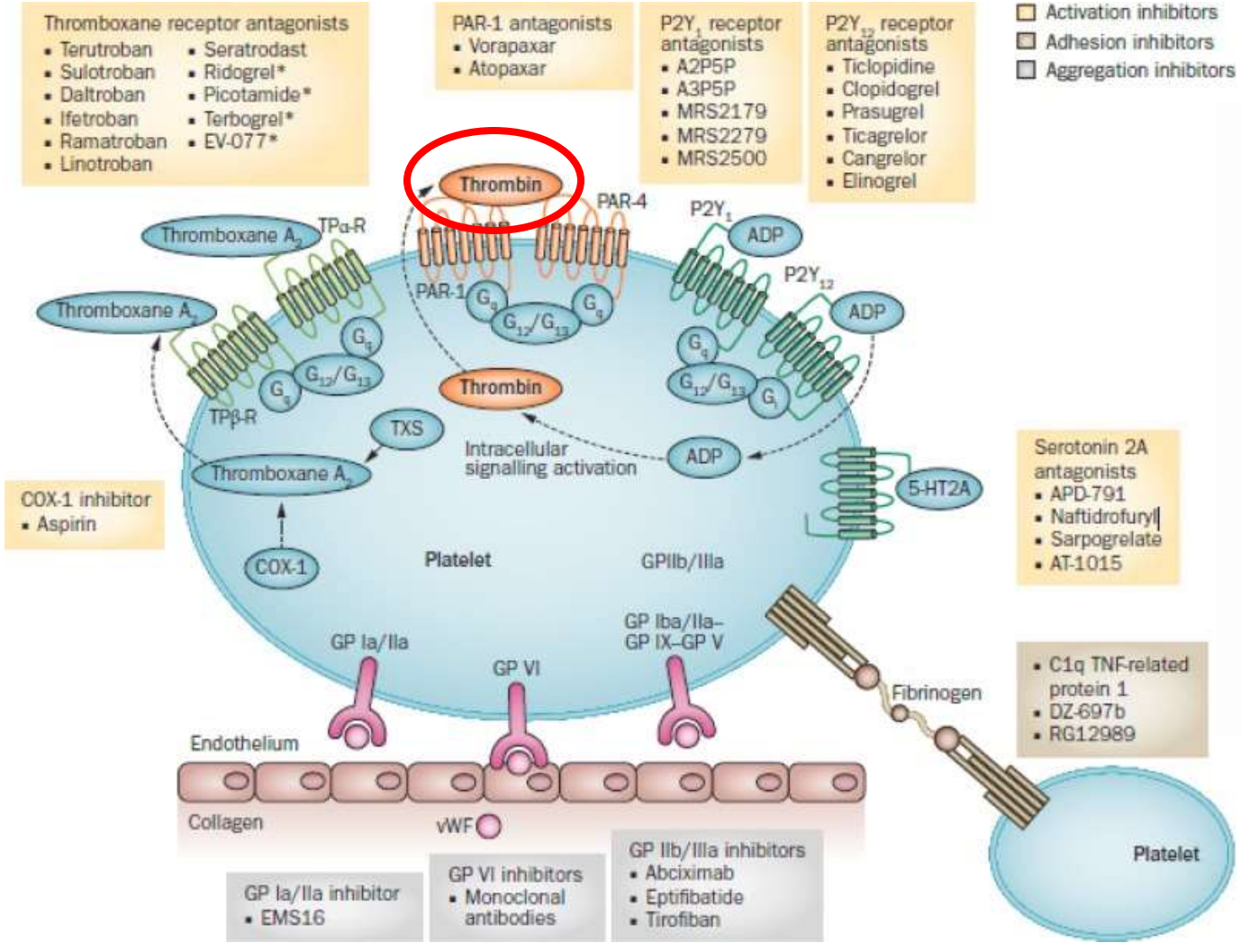

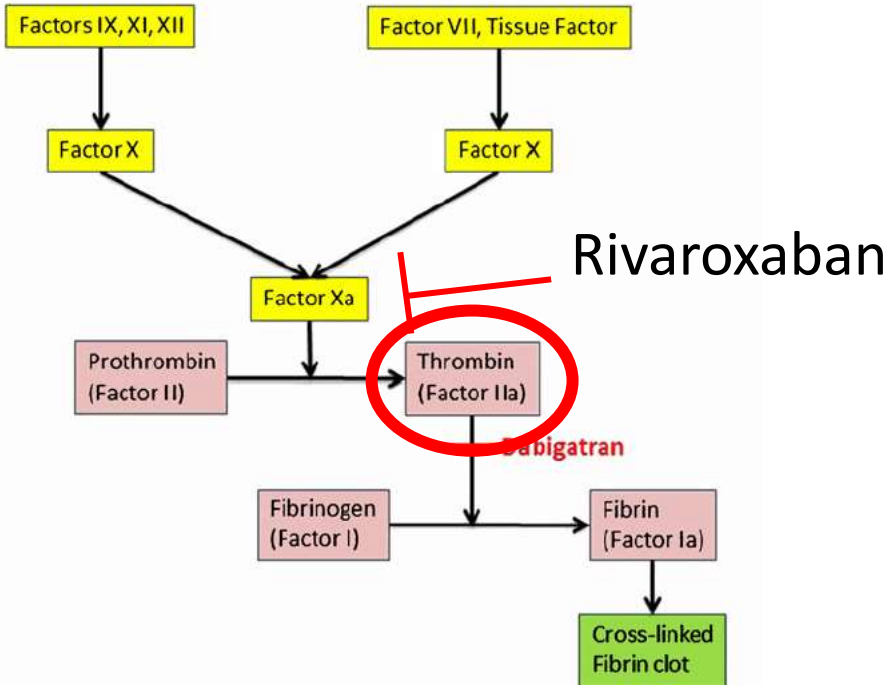

Nat Rev Cardiol 2015;12:30-47

Thrombosis and Severe PAD

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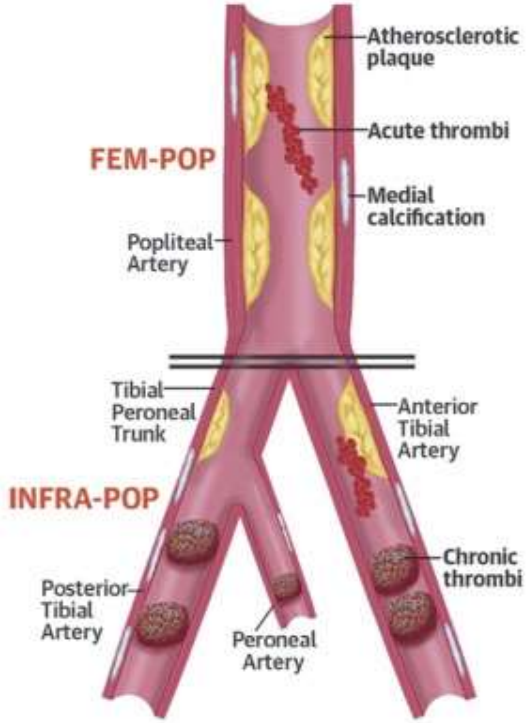
CENTRAL ILLUSTRATION Pathological Characterization of Large Arteries in Amputations for Critical Limb Ischemia



Narula, N. et al. J Am Coll Cardiol. 2018;72(18):2152-63.

Amputation Samples from 95 Patients

Atherosclerosis:

- Fem-pop (68%)
- Infra-pop (39%)

Fem-pop → acute thrombus
Infra-pop → chronic thrombus

PAD: High Risk for CV Mortality

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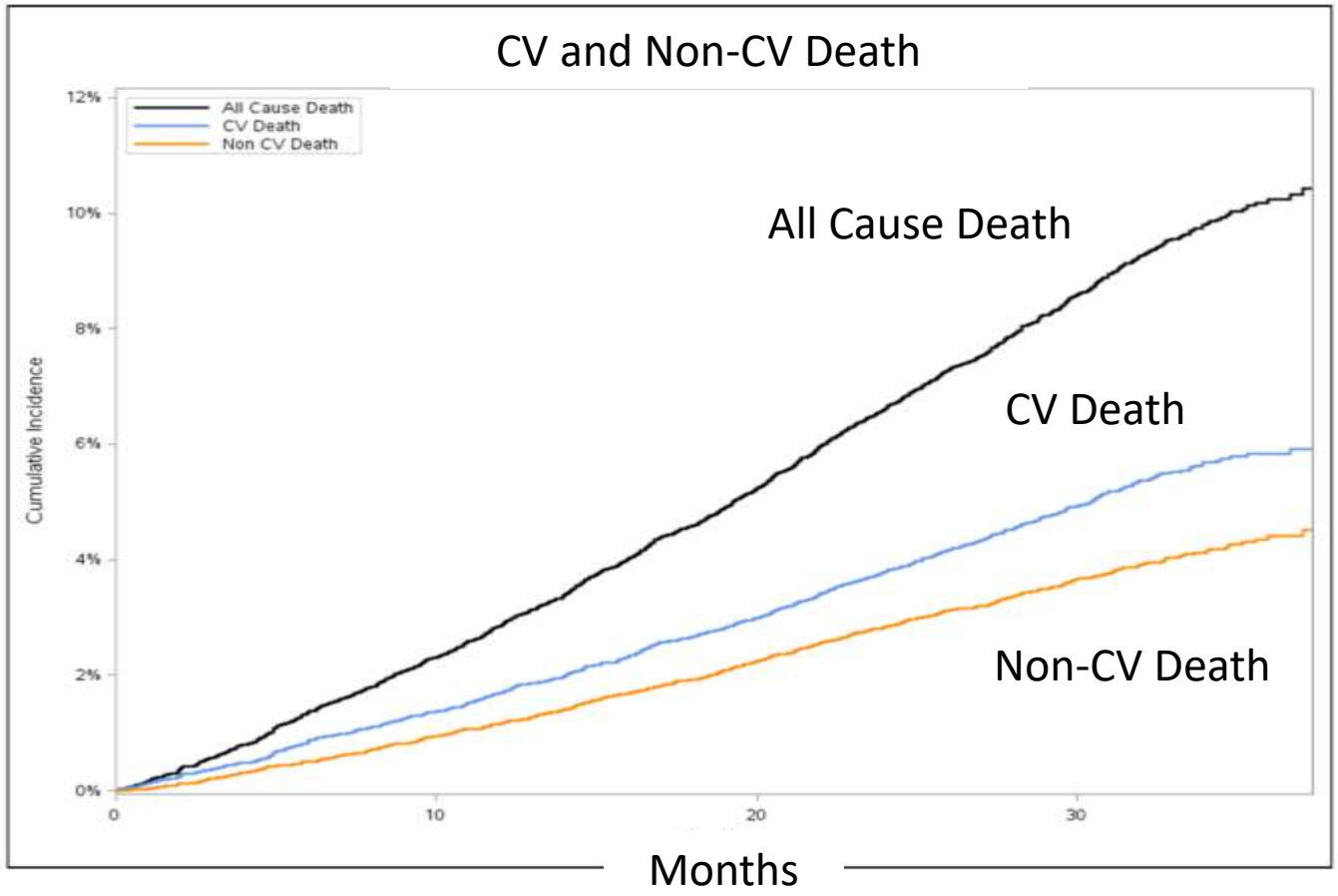
EUCLID Trial
13,885 pt with PAD

9.1% Mortality over median 30month f/u



~60% CV related death

Circ CQO 2020;13:e006550

VOYAGER PAD Study

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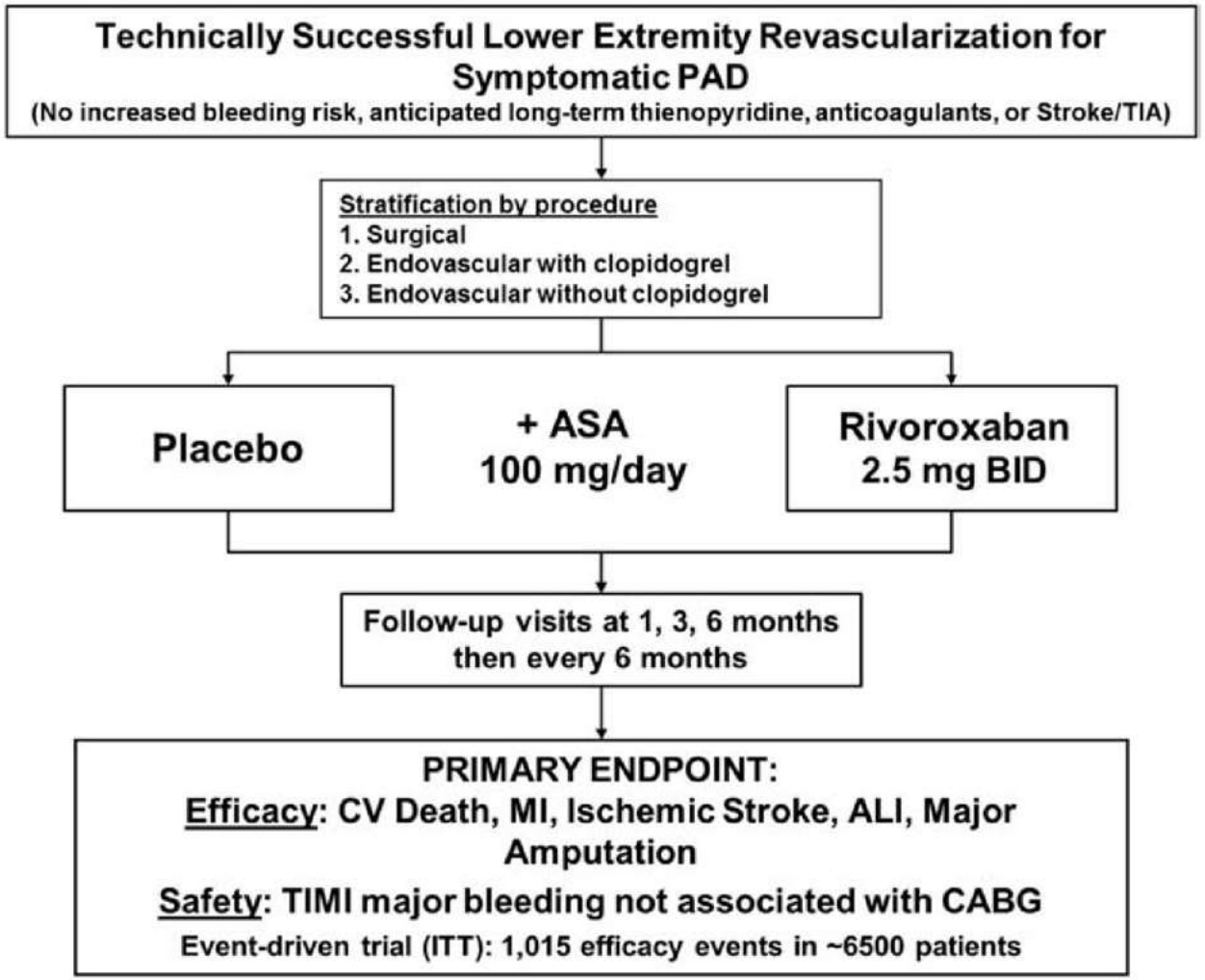

Figure 1. VOYAGER PAD study design.

Am Heart J 2018;199:83-91

VOYAGER PAD

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	Rivaroxaban (n=3286)	Placebo (n=3278)
Median ABI	0.56 (0.42-0.67)	0.56 (0.42-0.67)
Prior Amputation	194 (5.9%)	196 (6.0%)
Claudication	3132 (95.3%)	3137 (95.7%)
CLI	1181 (35.9%)	1155 (25.3%)
Procedure for Claudication	2521 (76.7%)	2504 (76.4%)
Procedure for CLI	762 (23.2%)	771 (23.5%)
Endovascular	2153 (65.5%)	2140 (65.3%)
Surgical	1133 (34.5%)	1138 (34.7%)

NEJM 2020;382:1994-2004

VOYAGER PAD

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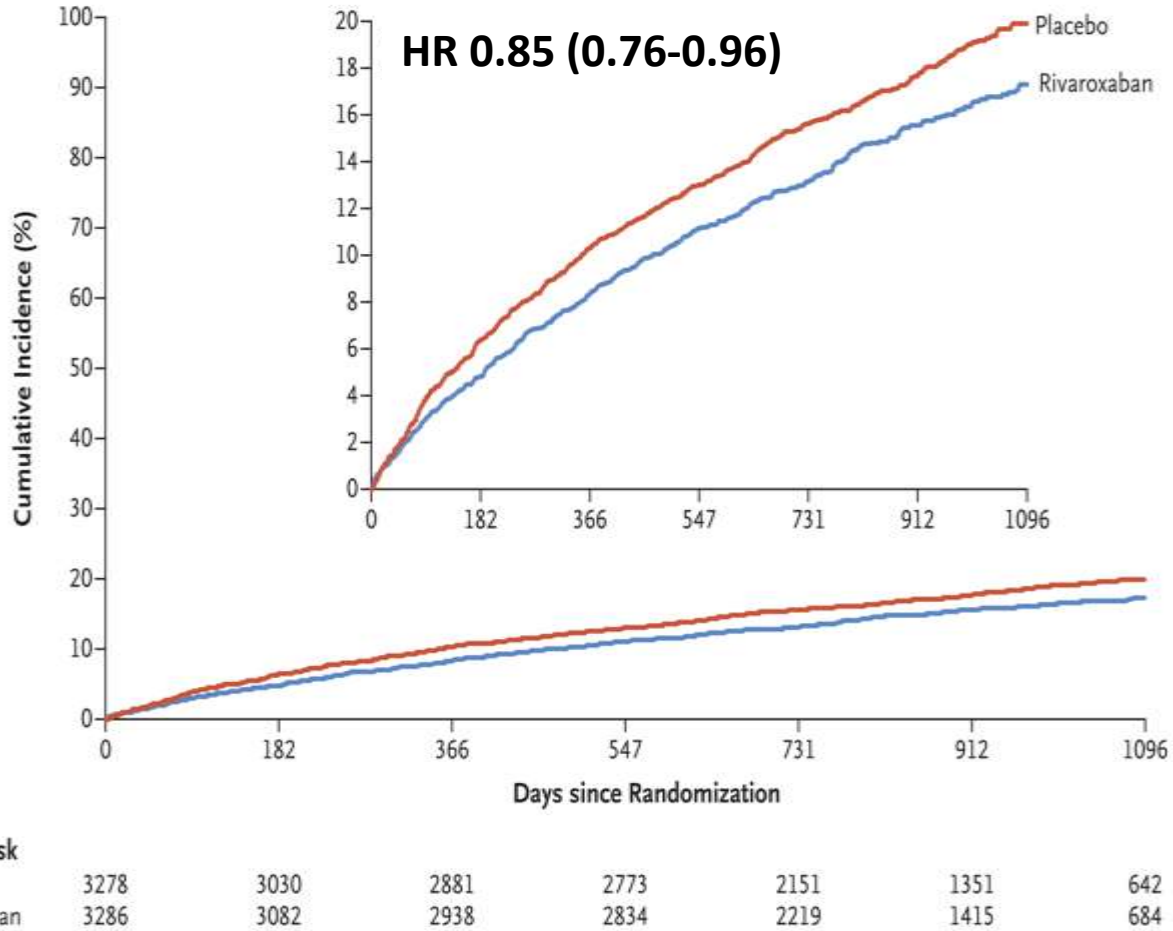
ALI, Major Amputation, MI, Ischemic Stroke, CV Death



	Riva (n=3286)	Placebo (n=3278)	HR (95% CI)
ALI	115 (4.7%)	227 (6.9%)	**0.67 (0.55-0.82)**
Amputation	103 (3.1%)	115 (3.5%)	0.89 (0.68-1.16)
MI	131 (4.0%)	145 (4.5%)	0.88 (0.70-1.12)
Stroke	71 (2.2%)	82 (2.5%)	0.87 (0.63-1.19)
CV Death	199 (6.1%)	174 (5.3%)	1.14 (0.93-1.40)

NEJM 2020;382:1994-2004

VOYAGER PAD

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Key Secondary Outcomes

	Riva (n=3286)	Placebo (n=3278)	HR (95% CI)
Unplanned revasc for recurrent ischemia	584 (17.8%)	655 (20.0%)	**0.88 (0.79-0.99)**
Hospitalization for CAD/PAD	262 (8.0%)	356 (10.9%)	**0.72 (0.62-0.85)**
All Cause Mortality	321 (9.8%)	297 (9.1%)	1.08 (0.92-1.27)

Safety Outcomes

	Riva (n=3286)	Placebo (n=3278)	HR (95% CI)
TIMI Major Bleeding	62 (1.90%)	44 (1.35%)	1.43 (0.97-2.10)
ICH	13 (0.40%)	17 (0.52%)	0.78 (0.38-1.61)
ISTH Major Bleeding	140 (4.30%)	100 (3.08%)	**1.42 (1.10-1.84)**
BARC Major Bleeding	93 (2.86%)	73 (2.25%)	1.29 (0.95-1.76)

NEJM 2020;382:1994-2004

VOYAGER PAD: Impact of Clopidogrel

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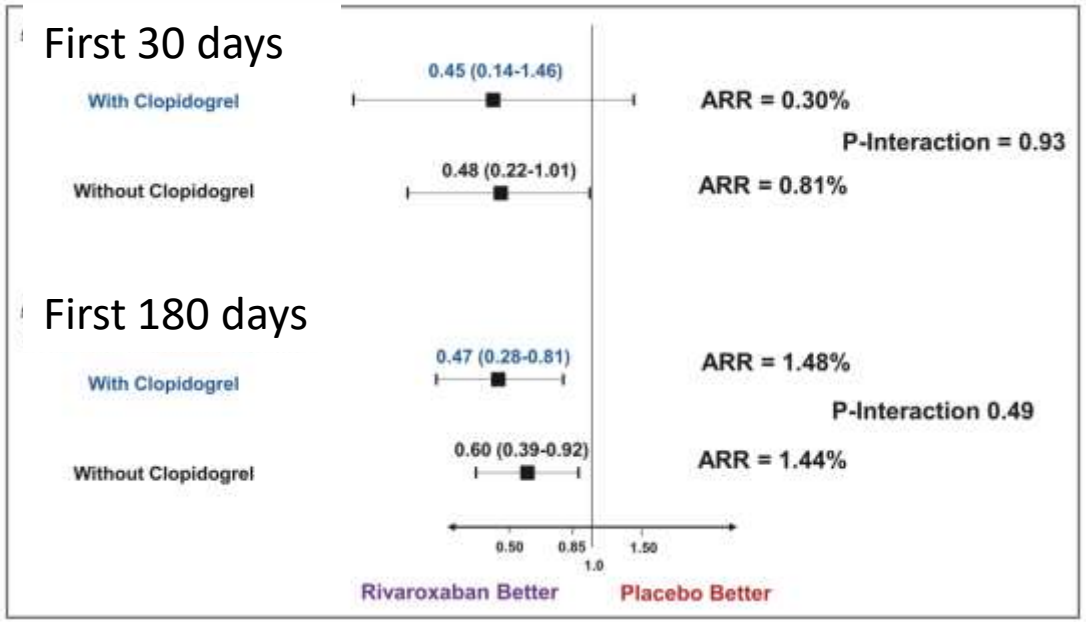
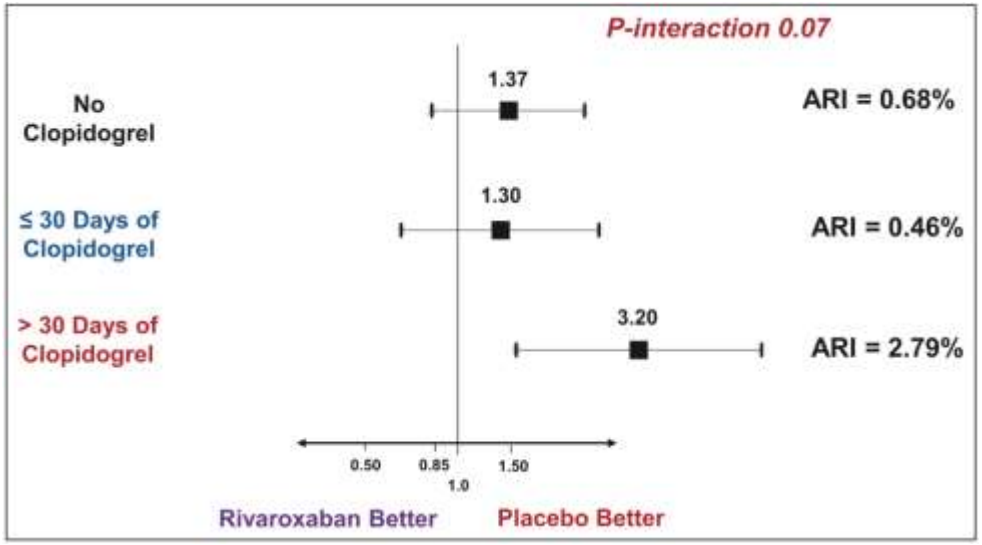
Clopidogrel Use:
Yes – 3313
No – 3234

Risk of ALI (Riva vs. Placebo)



Risk of ISTH Major Bleeding



Avoid bleeding risk: Use <30d clopidogrel

Circ 2020;142:2219-2230

COMPASS Trial (Rivaroxaban)

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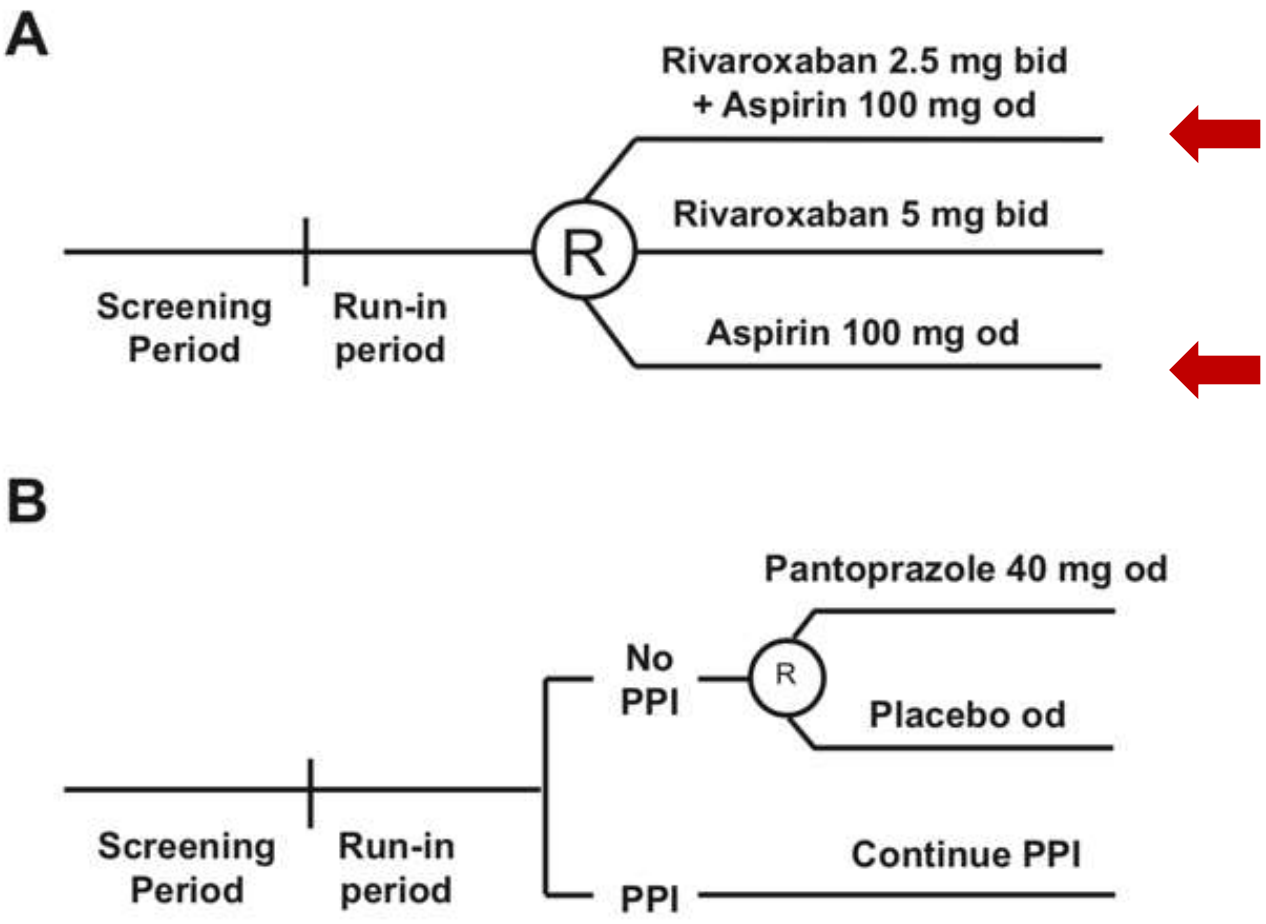
CAD Inclusion

- MI
- Multi-vessel CAD, PCI, CABG
- Age 65+
- ≤65 plus tobacco, DM, CKD, CHF, or prior stroke

PAD Inclusion

- Bypass or Angioplasty
- Prior amputation
- Claudication plus
  - ABI <0.9
  - ≥50% stenosis
  - Prior carotid revascularization or ≥50% carotid disease



Can J Cardiol 2017;33:1027-1035

CAD and/or PAD

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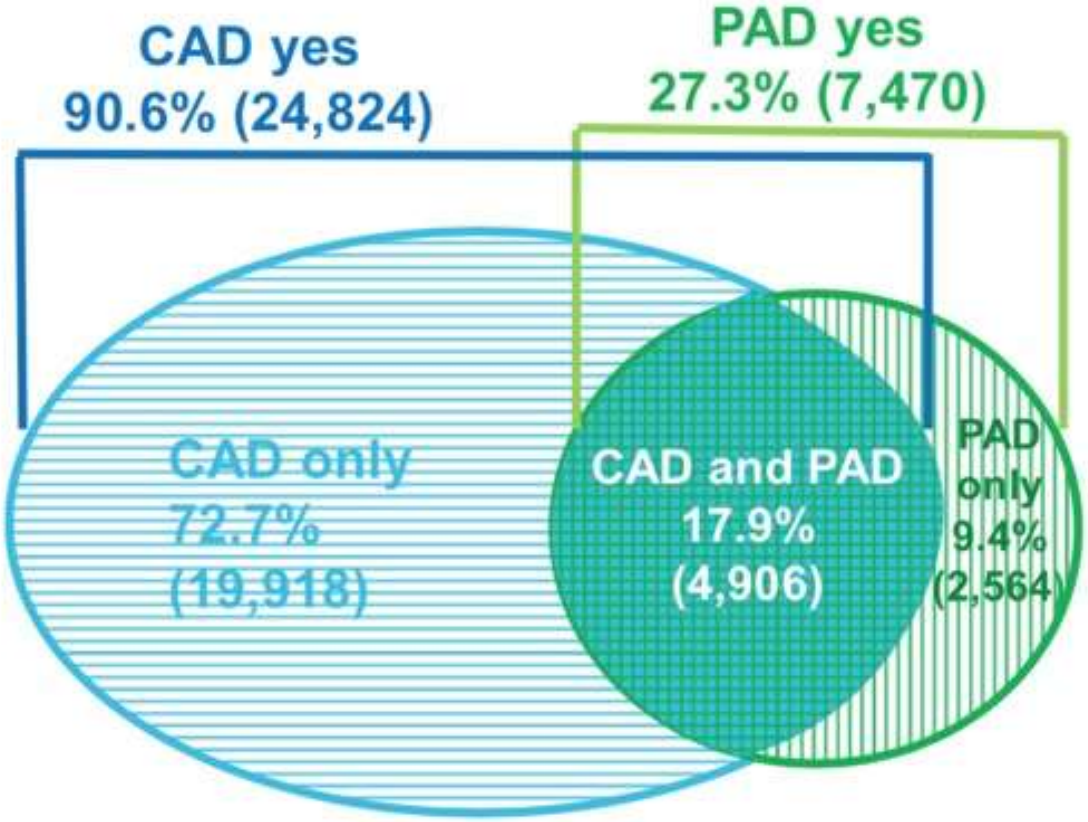

Many of your CAD patients have PAD!

Lancet 2018;391:205-218

COMPASS Trial

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Riva + ASA vs. ASA only
HR 0.74 (0.65-0.86)

	Riva + ASA	ASA Only	HR
ISTH Major Bleed	2%	1%	**1.77 (1.39-2.24)**
GI Major Bleed	2%	1%	**2.13 (1.57-2.88)**
Minor Bleed	9%	6%	**1.74 (1.55-1.95)**

Lancet 2018;391:205-218

COMPASS Trial: PAD Subgroup

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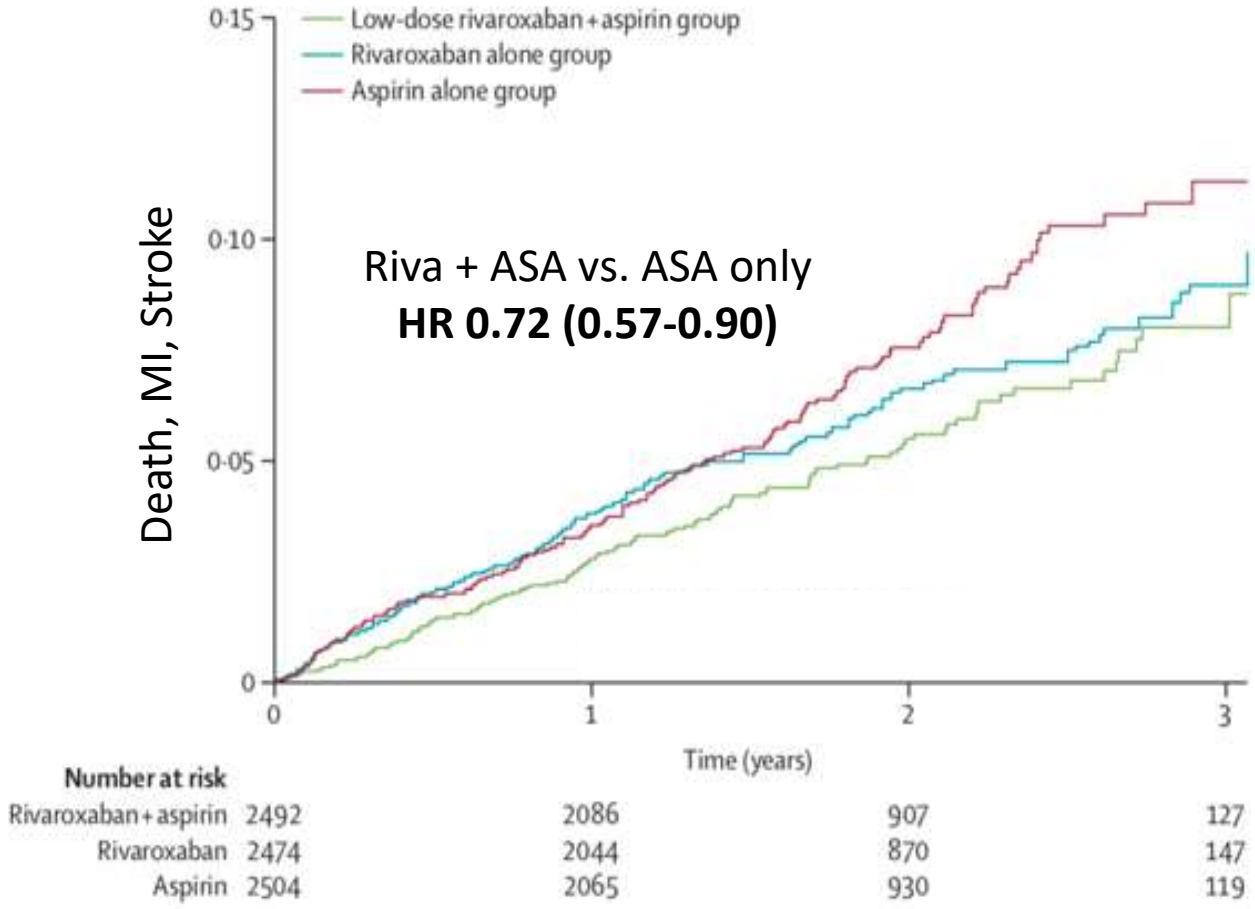

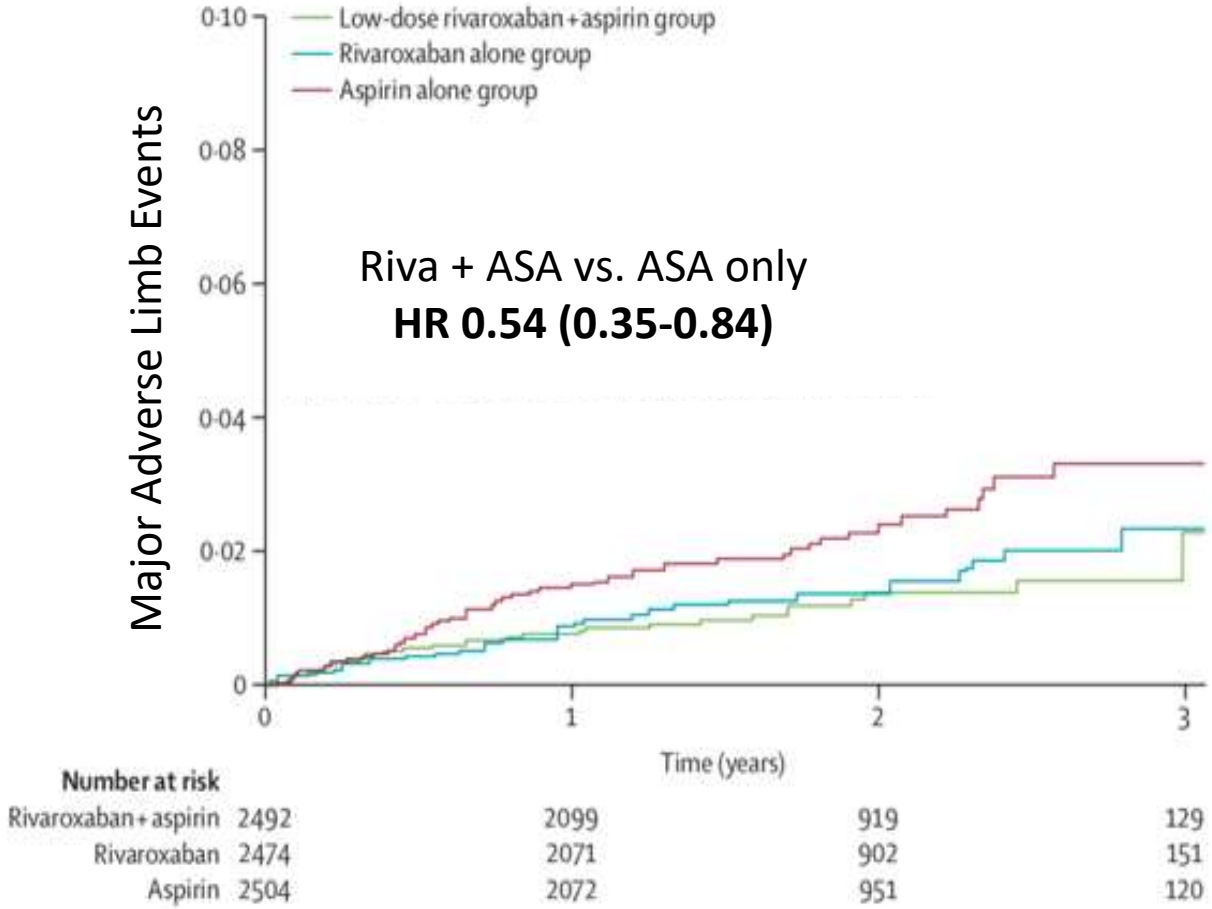

ISTH Major Bleed: 3% vs 2% (HR 1.61, 1.08-2.39)

Lancet 2018;391:219-229

Who Should Receive Rivaroxaban?

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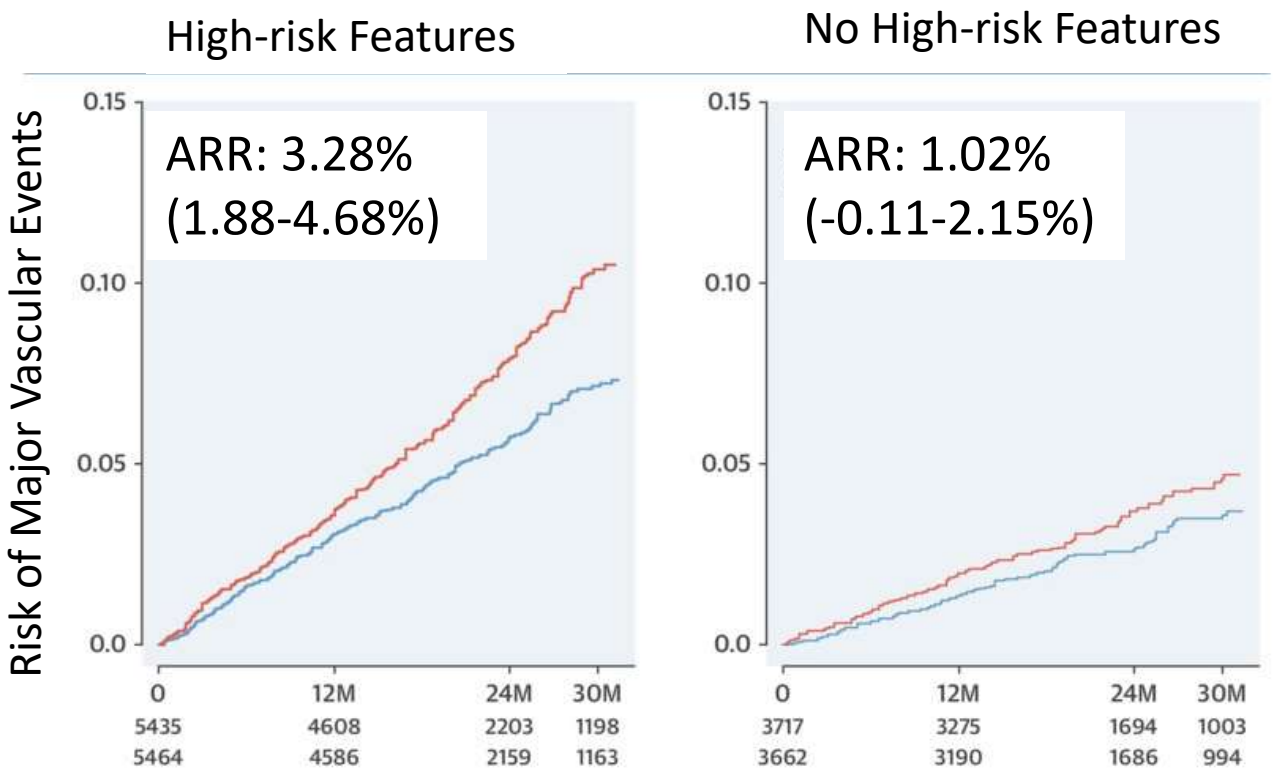
Risk of Vascular Events (Highest-Lowest)

- Multi-vessel Vasc Dz & eGFR<60
- Multi-vessel Vasc Dz & CHF
- CHF
- DM
- eGFR <60
- Age >75



Analysis of COMPASS trial

JACC 2019;73:3271-80

ESC Guidelines

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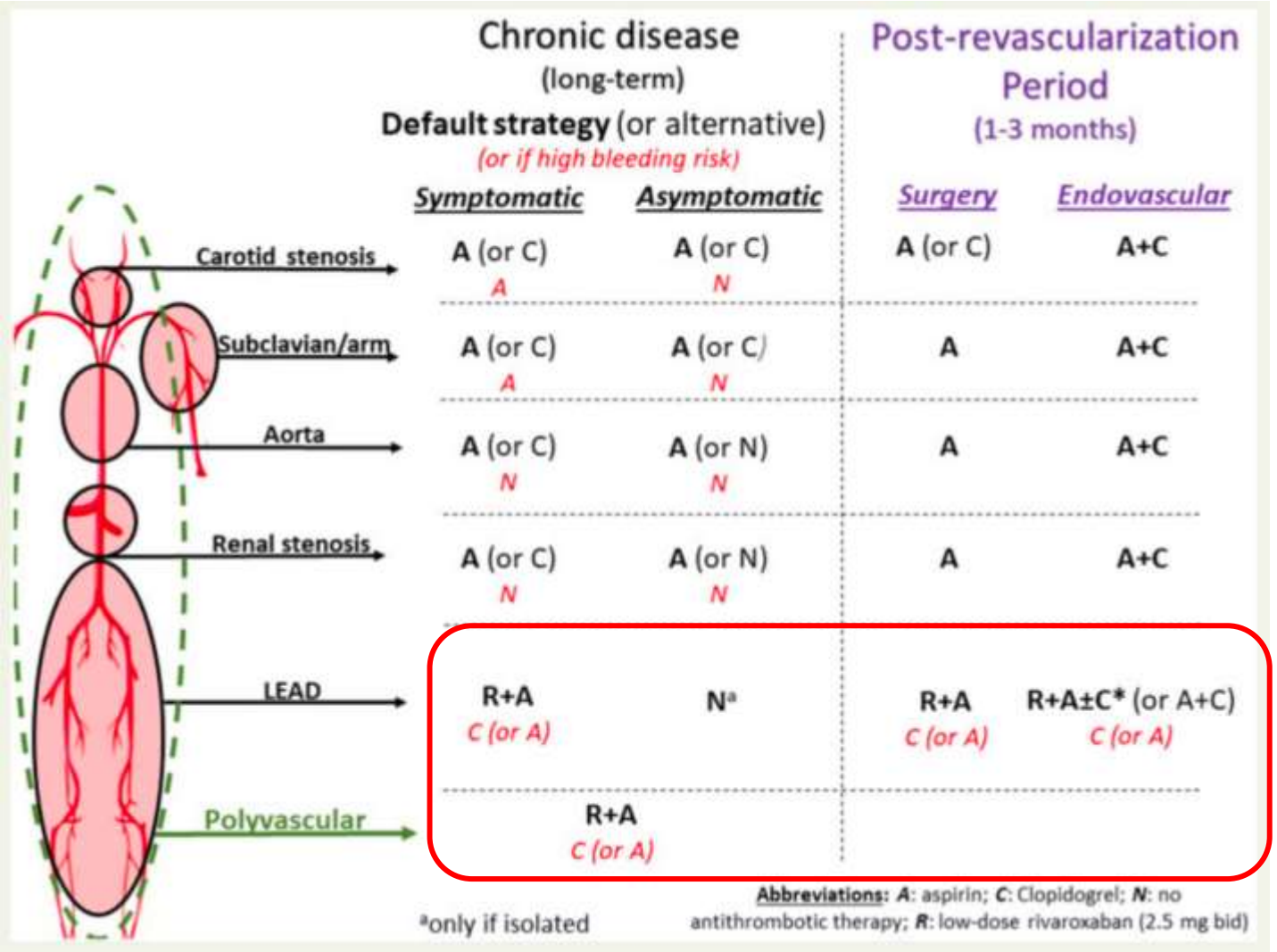

Updated ACC/AHA guidelines coming in 2023!!

Eur Heart J 2021;42:4013-4024

Return to Clinical Case

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- 66yo man presents to clinic for “leg pain”
- Moderate PAD, DM2, known CAD

- Receiving guideline-recommended antithrombotic meds?
  - Yes per ACC/AHA 2016 (ASA 75mg)
    - Guidelines now outdated
  - No per ESC (should be on rivaroxaban 2.5mg BID + ASA 75mg)
- Other anti-thrombotic strategy?
  - Add rivaroxaban 2.5mg BID + ASA 75mg (multi-vessel disease, DM2)
  - If revascularization → < 30days of clopidogrel (minimize bleed)

Thank you!

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