

VOYAGER PAD

Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularizations for Peripheral Artery Disease

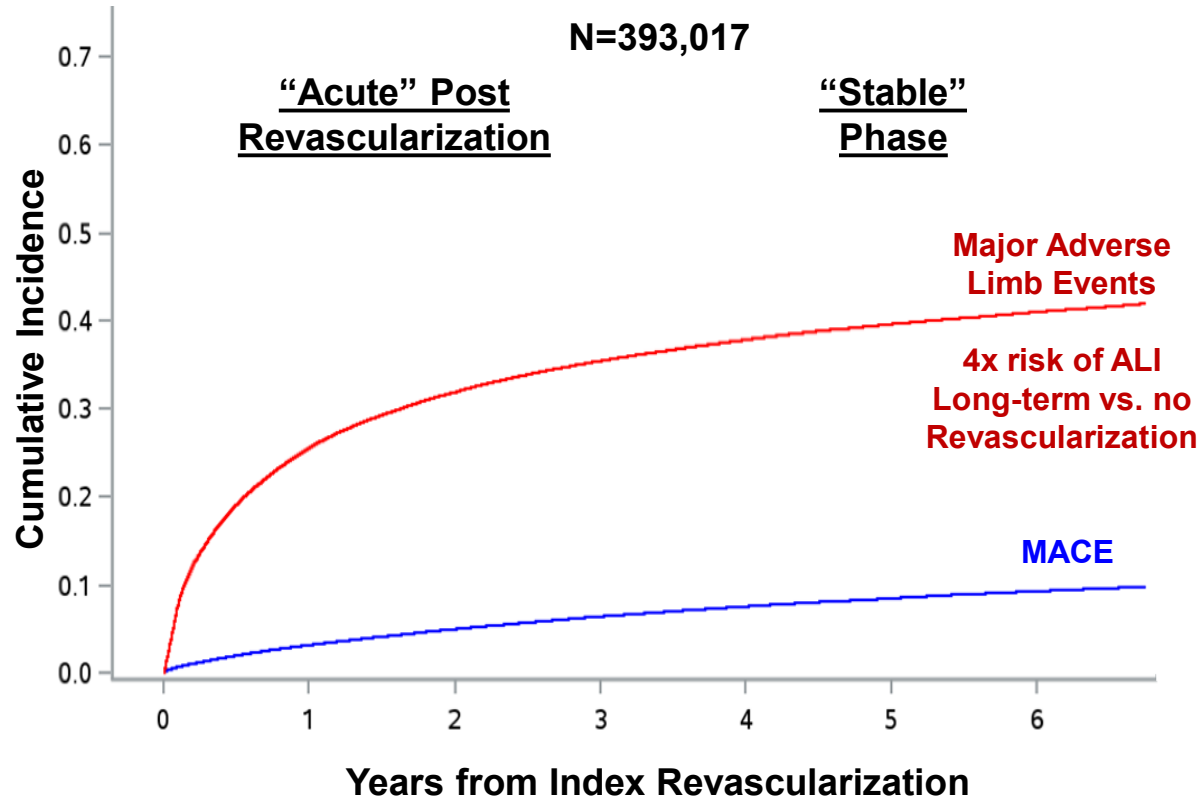
Marc P. Bonaca, Rupert M. Bauersachs, Manesh R. Patel,
Sonia S. Anand, Eike Sebastian Debus, Mark N. Nehler, Fabrizio
Fanelli, Warren H. Capell, Nicole Jaeger, Lihong Diao, Connie N. Hess, John
M. Kittelson, Lloyd P. Haskell, Scott D. Berkowitz, William R. Hiatt,
for the VOYAGER PAD Steering Committee & Investigators

*American College of Cardiology Virtual Scientific Sessions 2020
Late-Breaking Clinical Trial
March 28, 2020*



Background

Risk in Patients Undergoing Peripheral Revascularization



Outcomes in Patients with Acute Limb Ischemia

- Median hospitalization 8 days (IQR 5-15)
- ~4% die at presentation
- ~1/5 → major amputation
- ~1/3 → prolonged ICU stay
- ~3/4 → major surgery
- ***Outcomes after hospitalization are poor with ~15% disabled or dead***

Hess...Hiatt et al. JACC 2020

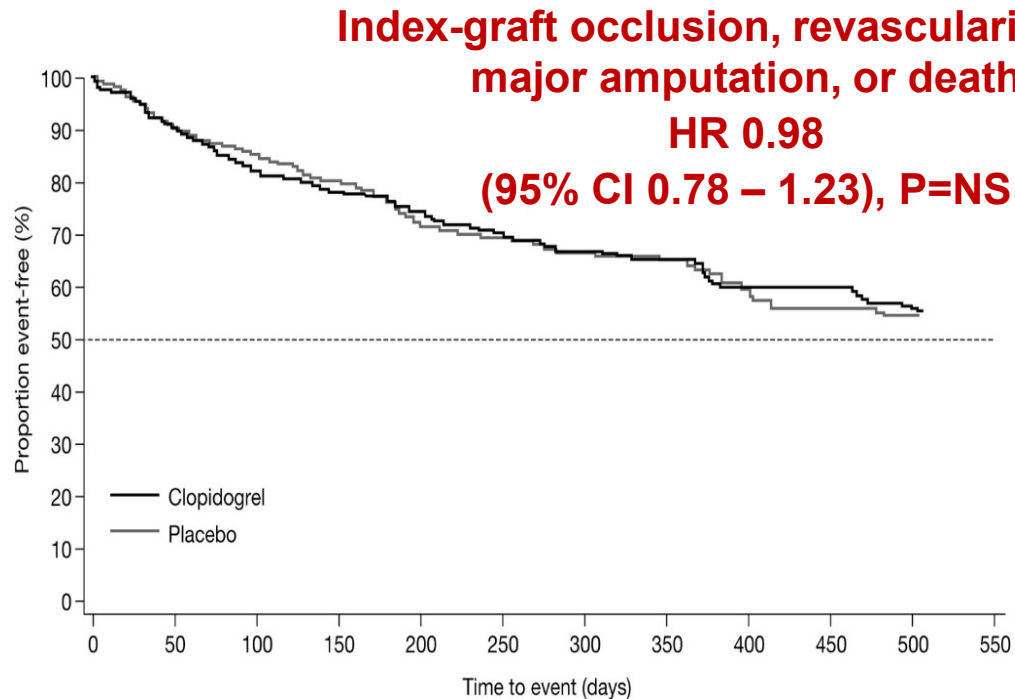
Jones...Fowkes et al. Circulation 2017

Bonaca...Sabatine et al. JACC 2017

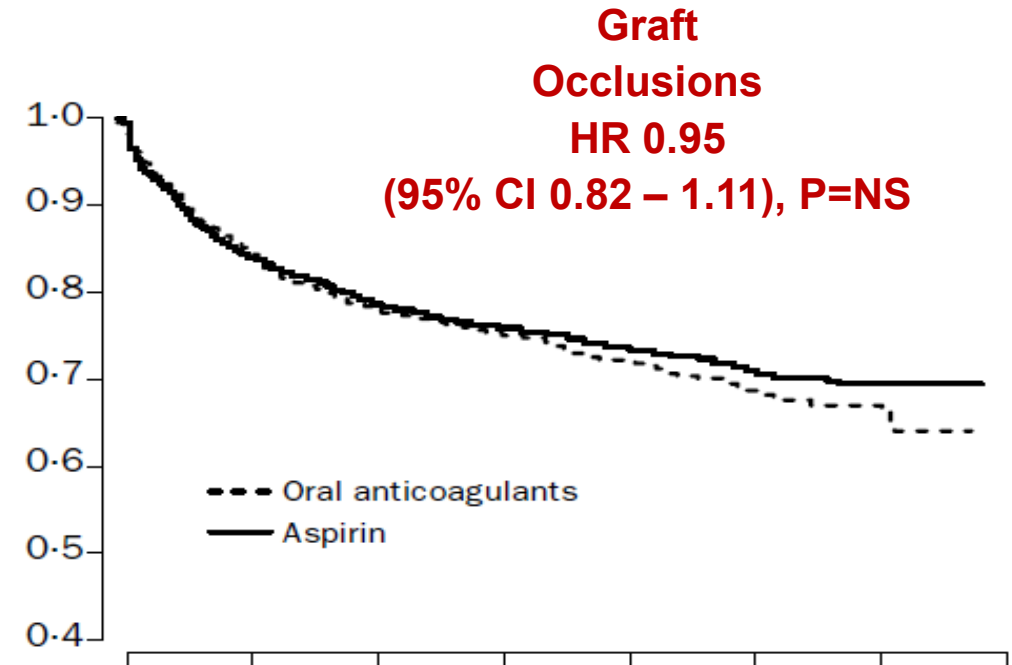
Bonaca...Morrow et al. Circulation 2016

Background

Despite the high risk, currently there is no proven antithrombotic strategy that has demonstrated efficacy for reducing major adverse limb and cardiovascular events after peripheral intervention for ischemia



DAPT with Aspirin and Clopidogrel
Increased GUSTO bleeding
HR 2.84 (1.32 – 6.08)



Full Intensity Oral anticoagulation
Increased risk of Hemorrhagic Stroke
HR 3.48 (1.14 – 10.60)

Trial Design

NCT02504216

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

**Ankle Brachial Index < 0.90 and Imaging Evidence of Occlusive Disease*

*ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion*

Randomized 1:1 Double Blind

**Rivaroxaban 2.5 mg
twice daily**

*Stratified by
Revascularization Approach
(Surgical or Endovascular)
and Use of Clopidogrel*

Placebo

Follow up Q6 Months, Event Driven, Median f/u 28 Months

Primary Efficacy Endpoint: Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

Principal Safety Outcome: TIMI Major Bleeding

Capell WH, Bonaca MP, Nehler MR...Hiatt WR. AHJ 2018

Objectives

In patients undergoing lower extremity revascularization for ischemic symptoms:

- Test whether **rivaroxaban 2.5 mg twice daily added to low dose aspirin** reduces the risk of major adverse limb and cardiovascular events compared to **aspirin alone**
- To evaluate the safety of **rivaroxaban 2.5 mg twice daily added to low dose aspirin** compared to **aspirin alone**

Inclusion & Exclusion

Inclusion

- Age \geq 50
- Documented PAD including:
 - Ischemic symptoms (functional limitation, rest pain or ischemic ulceration) AND
 - Imaging evidence of occlusion AND
 - Abnormal ABI
- Successful lower extremity revascularization for ischemia

Exclusion

- Revascularization for asymptomatic disease
- Recent revascularization (within 10 days) or ALI (2 weeks) or ACS (30 days)
- Current major tissue loss
- Need for antiplatelet or anticoagulant other than aspirin and/or clopidogrel
- Need for long-term DAPT (intended > 6 months)
- High risk for bleeding (significant bleeding in last 6 months, prior stroke or other high-risk condition)

Outcomes

Efficacy

Primary: acute limb ischemia (ALI), major amputation for vascular cause (amputation), myocardial infarction (MI), ischemic stroke or CV death

Secondary (hierarchical):

1. ALI, amputation, MI, ischemic stroke or coronary heart death
2. Unplanned index limb revascularization for ischemia
3. Vascular hospitalization for a coronary or peripheral event of thrombotic nature
4. ALI, amputation, MI, ischemic stroke or all-cause mortality
5. ALI, amputation, MI, all stroke or CV death
6. All-cause mortality
7. Venous thromboembolism

Safety

Principal: TIMI major bleeding

Secondary: ISTH major bleeding, BARC 3b or above

Trial Organization

Executive Committee

William R. Hiatt (Chair)

Marc P. Bonaca

Eike Sebastian Debus

Lloyd P. Haskell

Rupert M. Bauersachs (Co-Chair)

Sonia S. Anand

Mark R. Nehler

Scott D. Berkowitz

Manesh R. Patel

Fabrizio Fanelli

CPC Clinical Research

Warren H. Capell (ICAC Chair), Jennifer Armstrong (ICAC Member), Natalia Glebova, (ICAC Member), Connie N. Hess (ICAC Member), Mori Krantz (ICAC Member), Cecilia Low-Wang (ICAC Member), Lisa Cox (Executive Project Manager), Nicole Jaeger (Project Manager), Robin White (Director, Biostatistics and Programming), and Lihong Diao (Biostatistician).

Sponsors: Bayer & Janssen

Scott D. Berkowitz, Lloyd Haskell, Eva Muehlhofer, James Hung, Aneta Woroniecka-Osio MD, Uma Balasubramanian, Juliette Dehay, Alexandra Kley, Claudia Vogt, Akos Ferenc Pap

Independent Data Monitoring Committee

John Dormandy (Chair)*, Joshua Beckman (Chair), Scott Kinlay, Robert McLafferty, Robin Roberts, (Statistician), and William Robinson.

****Deceased***

Steering Committee and National Lead Investigators

Argentina

R. Diaz

Austria

M. Brodmann

Belgium

F. Vermassen

Brazil

D. Brasil

Bulgaria

V. Chervenkov

Canada

D. Szalay

Czech Republic

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J. Mills

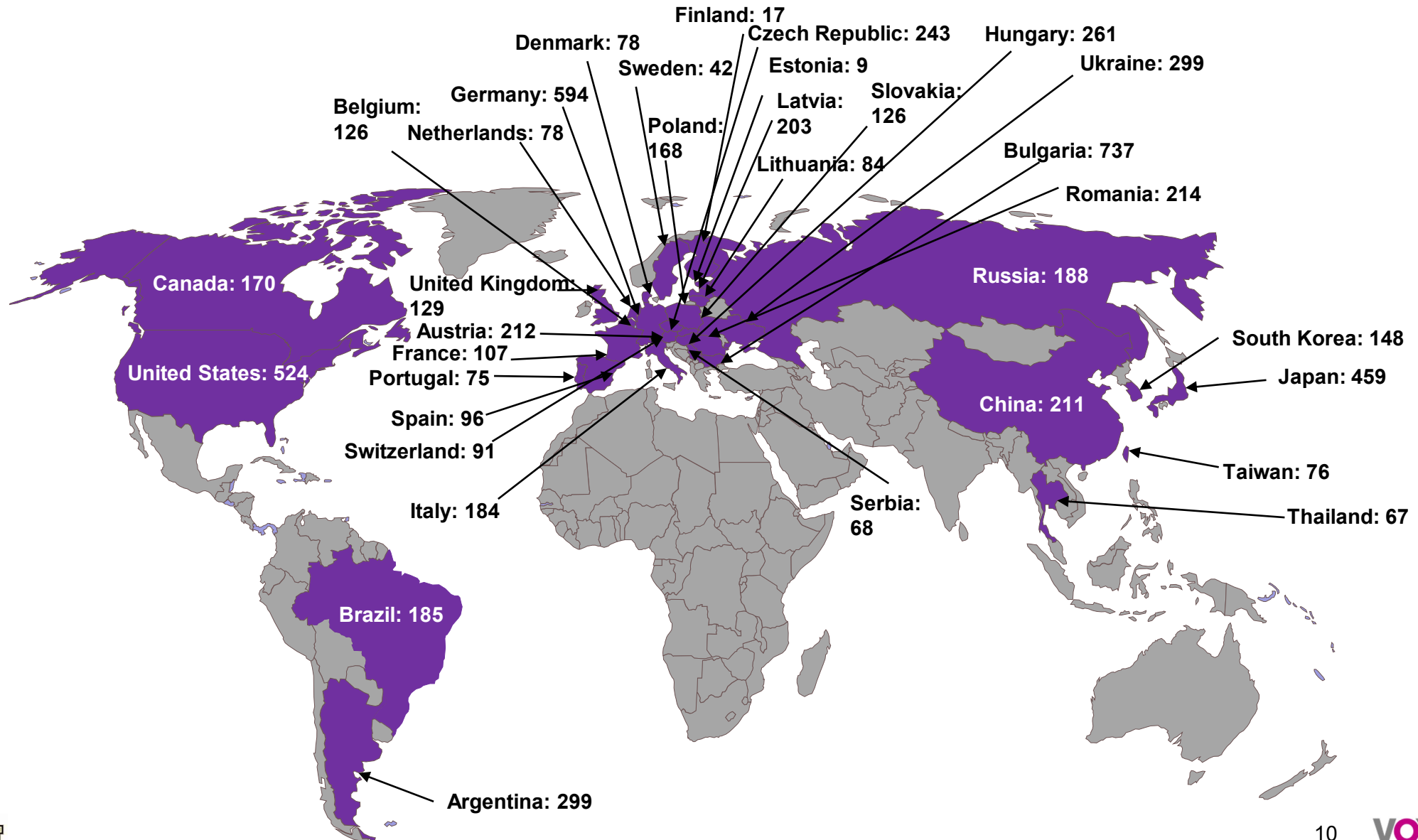
J. Mustapha

F. Saab

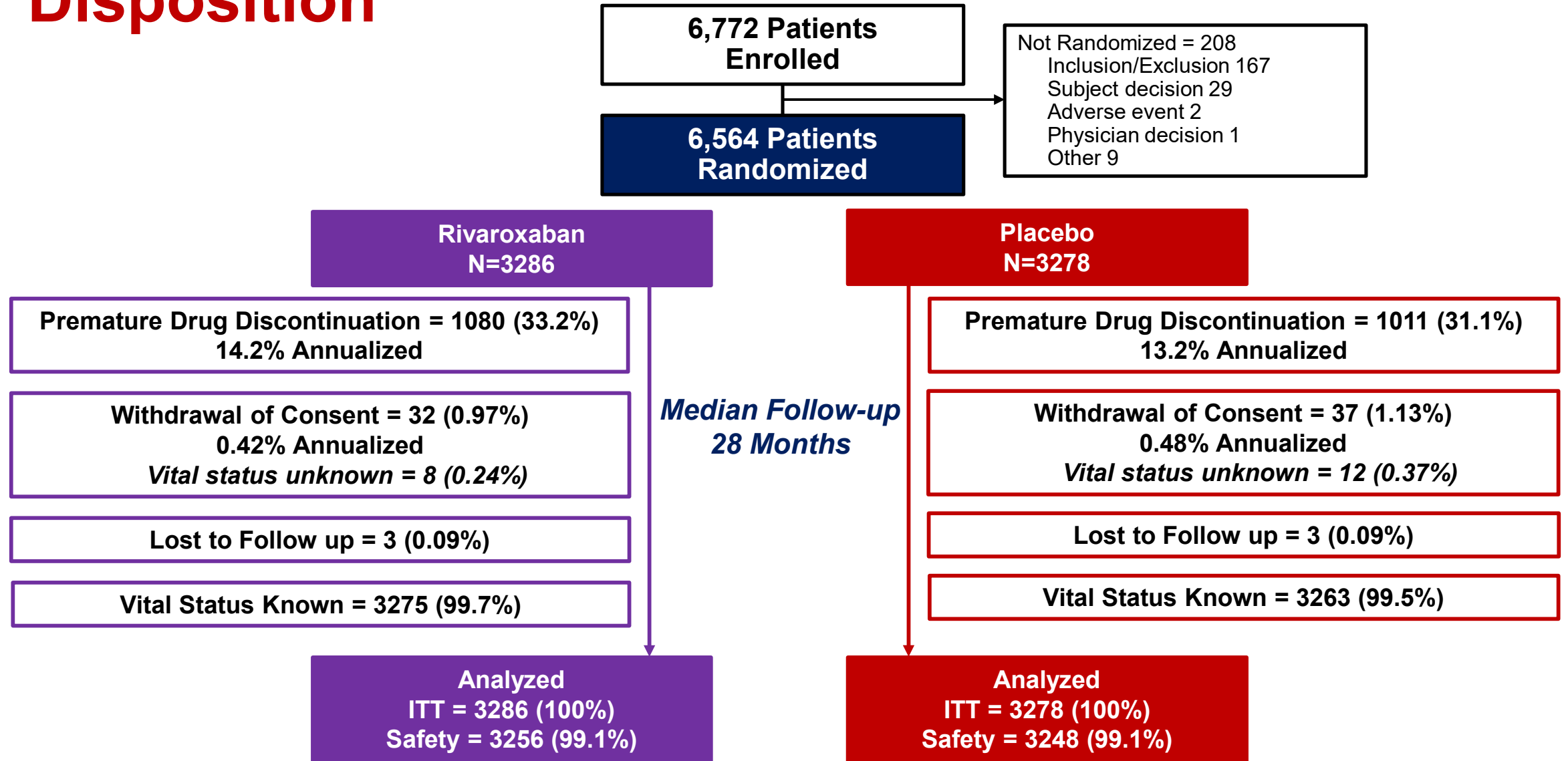
**Deceased*

Global Enrollment

6,564 patients randomized at 534 sites
in 34 countries between 7/2015 – 1/2018



Disposition



Complete primary efficacy and principal safety outcome ascertainment in 98.8% of potential patient-years of follow up

Baseline Characteristics

Characteristics at Randomization	Rivaroxaban 2.5 mg twice daily + aspirin N=3286 %	Placebo + aspirin N=3278 %
Age, Yrs Median	67	67
Female	26	26
Caucasian	81	81
Diabetes Mellitus	40	40
Current Smoking	35	35
COPD	11	11
eGFR < 60 ml/min/1.73m ²	20	20
Coronary Artery Disease	32	31
Prior MI	11	11
Known Carotid Stenosis	9	9
Clopidogrel	51	51
Statin	79	81
ACEi or ARB	64	63

P>0.05 for all comparisons

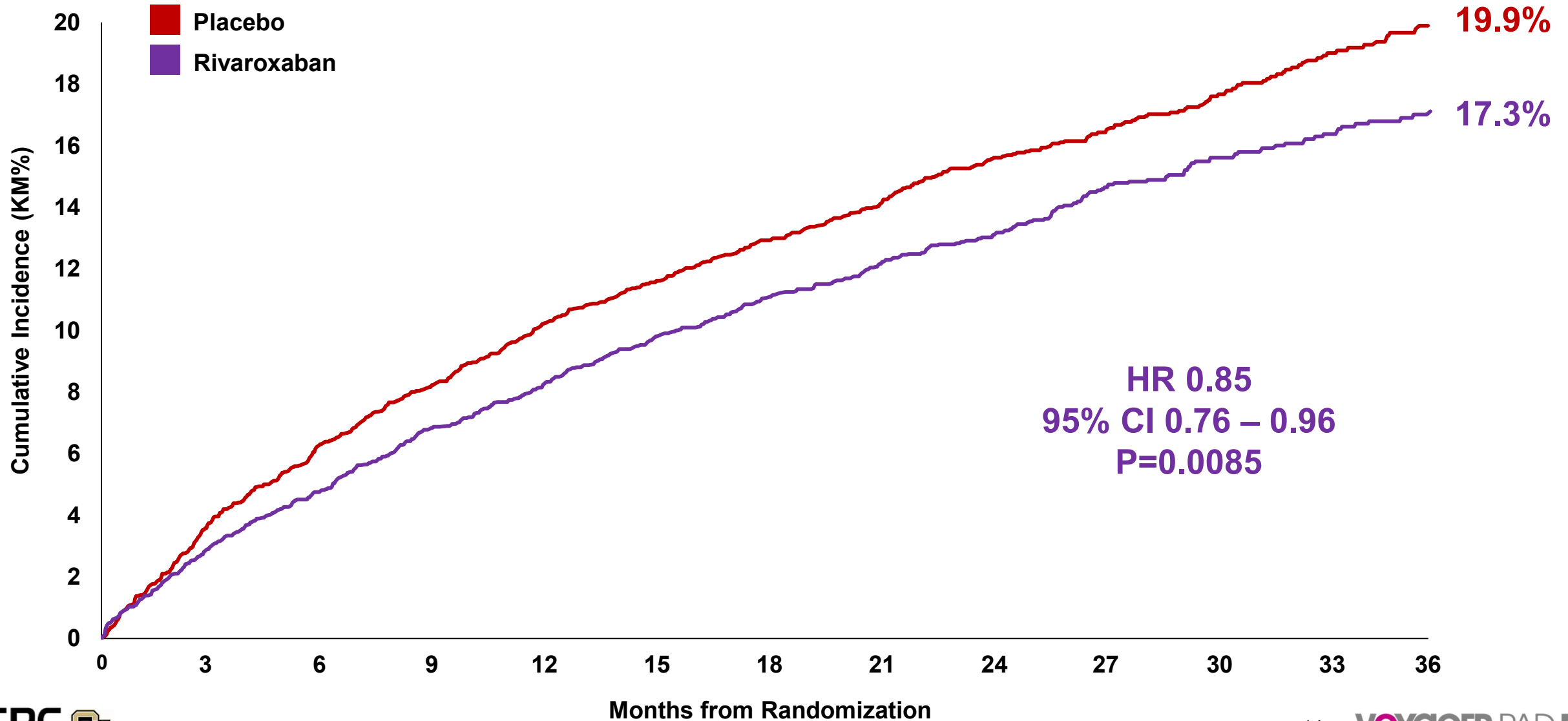
PAD & Procedural Characteristics

Characteristics at Randomization	Rivaroxaban 2.5 mg twice daily + aspirin N=3286 %	Placebo + aspirin N=3278 %
<i>Prior Peripheral Artery Disease History</i>		
History of Claudication	95	96
History of Revascularization	36	35
History of Amputation	6	6
Ankle Brachial Index, Median (IQR)	0.56 (0.42 – 0.67)	0.56 (0.42 – 0.67)
<i>Indication for Revascularization</i>		
Critical limb ischemia	23	24
Claudication	77	76
<i>Type of Revascularization</i>		
Surgical	35	35
Endovascular or Hybrid	66	65
Days from Procedure to Randomization Median, (IQR)	5 (2 – 7)	5 (2 – 7)

P>0.05 for all comparisons

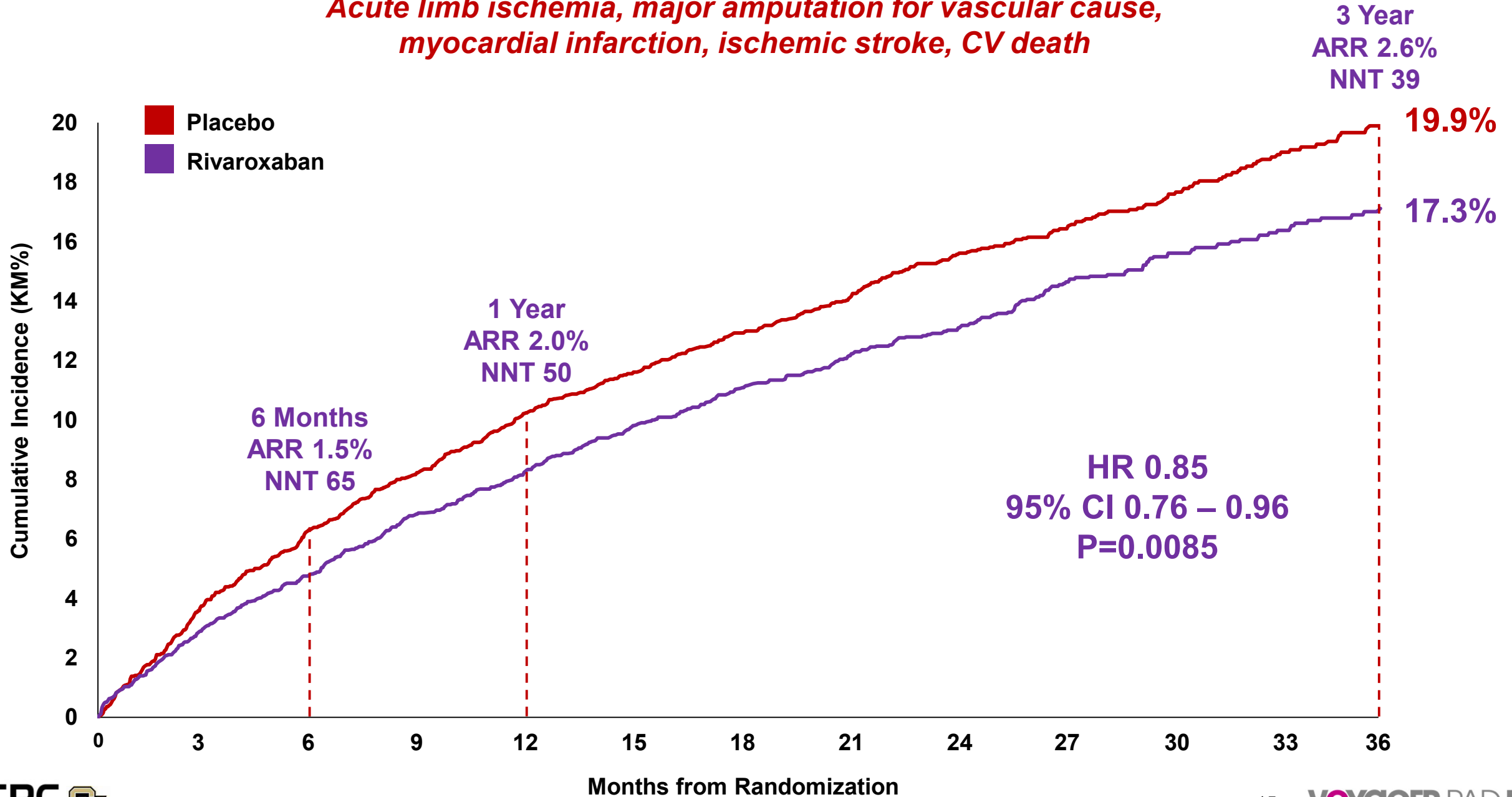
Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



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Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



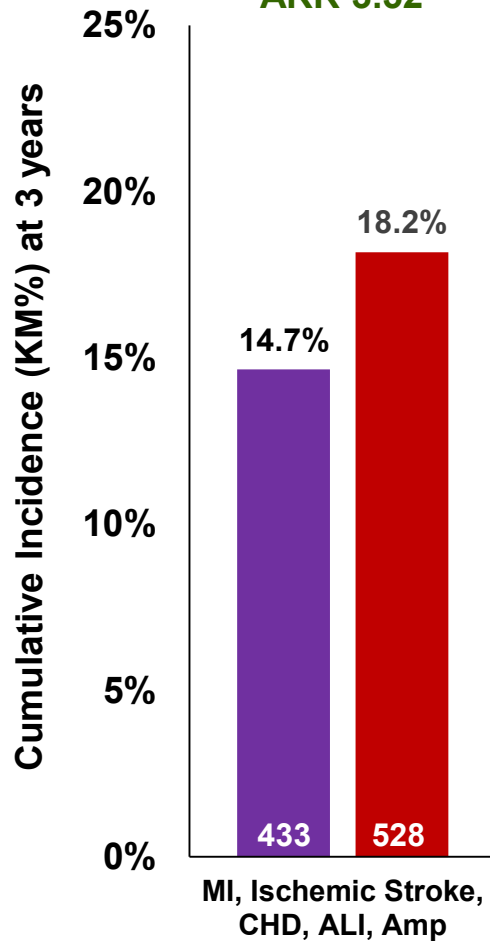
Primary Endpoint & Components

	KM% 3 Years (n) Rivaroxaban N=3286	KM% 3 Years (n) Placebo N=3278	HR (95% CI)
Primary Efficacy Outcome	17.3	19.9	0.85 (0.76 – 0.96)
Acute Limb Ischemia	5.24	7.74	0.67 (0.55 – 0.82)
Major Vascular Amputation	3.42	3.87	0.89 (0.68 – 1.16)
Ischemic Stroke	2.70	3.01	0.87 (0.63 – 1.19)
Myocardial Infarction	4.55	5.22	0.88 (0.70 – 1.12)
CV Death	7.05	6.43	1.14 (0.93 – 1.40)

Secondary Outcomes*

■ Placebo
■ Rivaroxaban

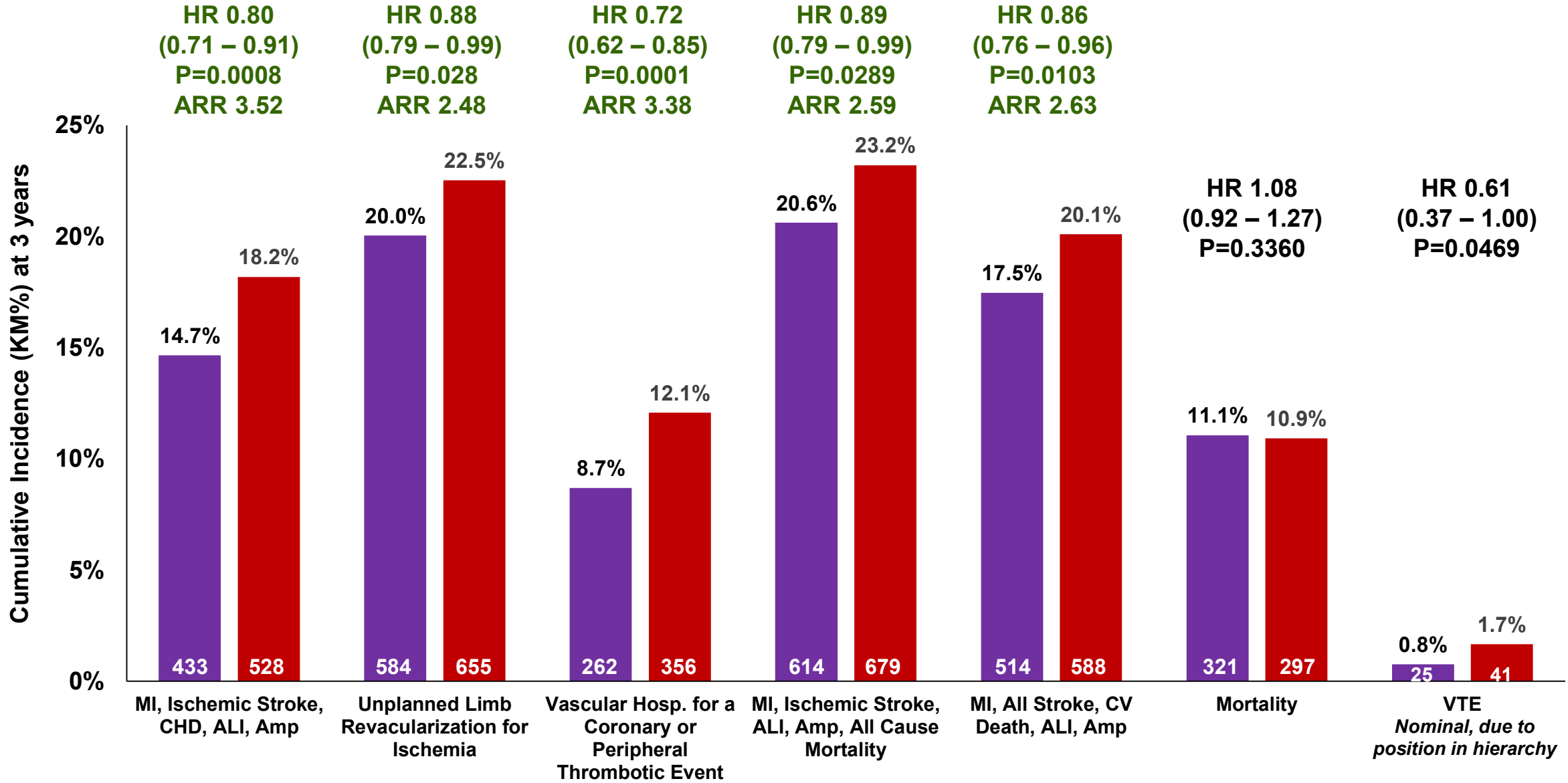
HR 0.80
(0.71 – 0.91)
P=0.0008
ARR 3.52



*Presented in order of hierarchy from left to right

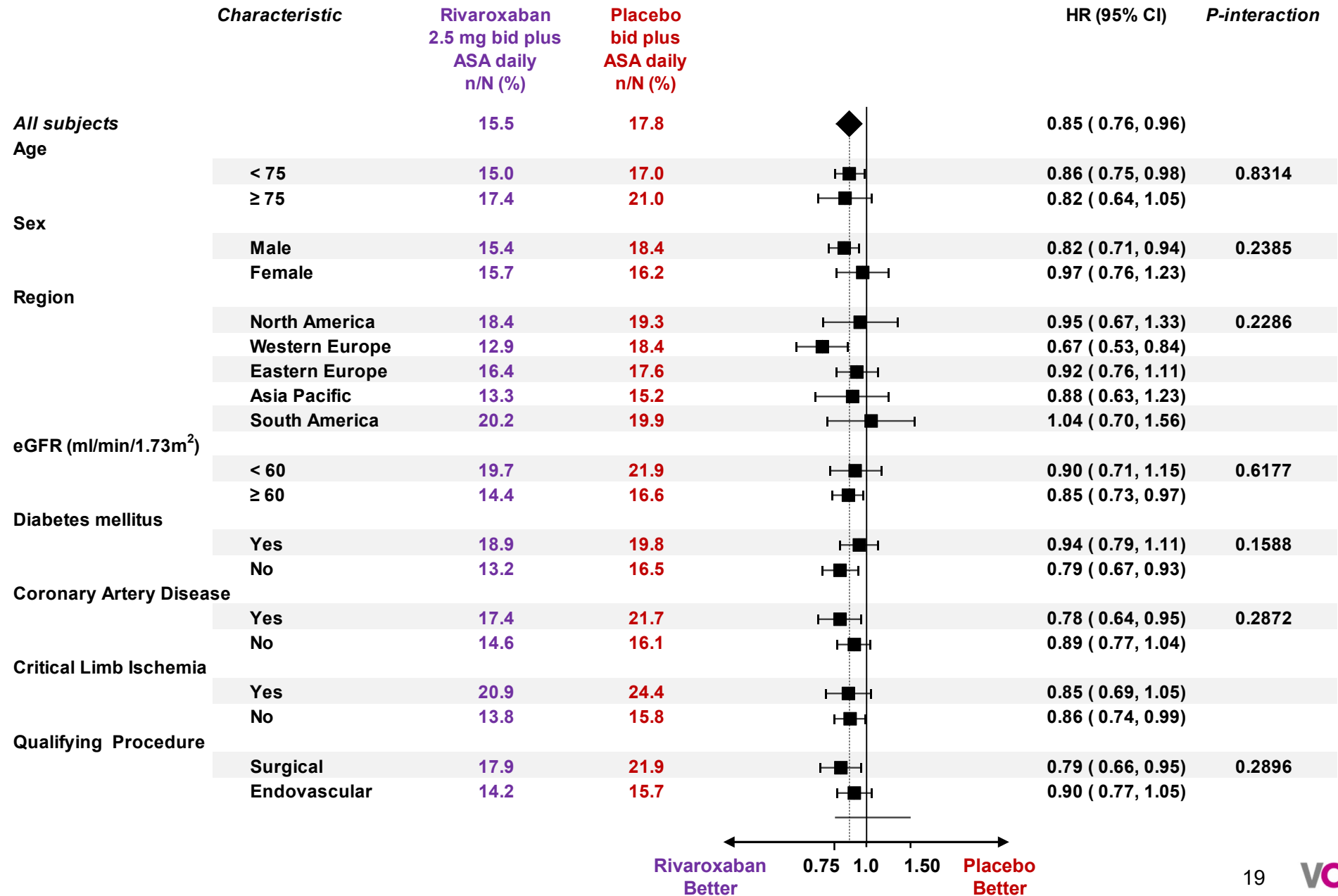
Secondary Outcomes*

Placebo
Rivaroxaban



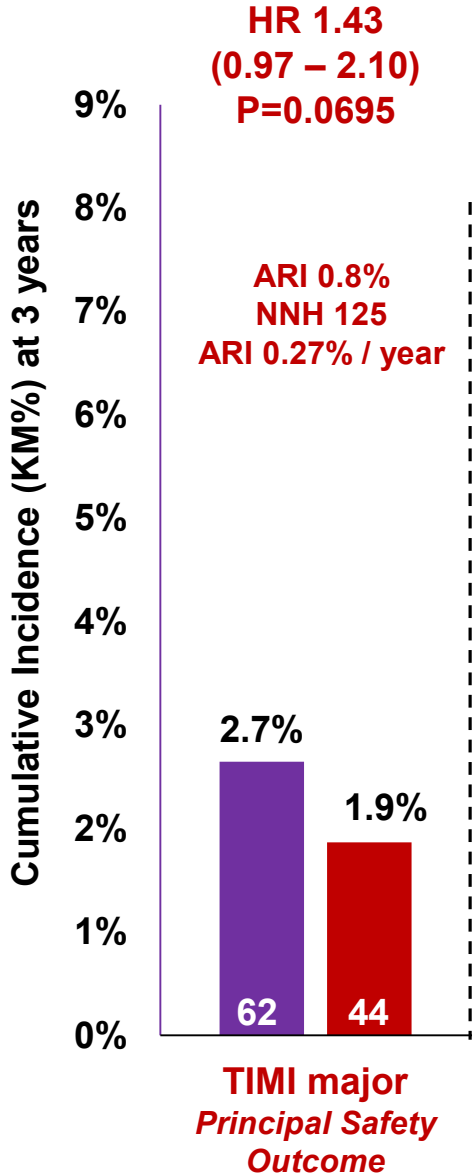
*Presented in order of hierarchy from left to right

Primary Efficacy Outcome in Selected Subgroups



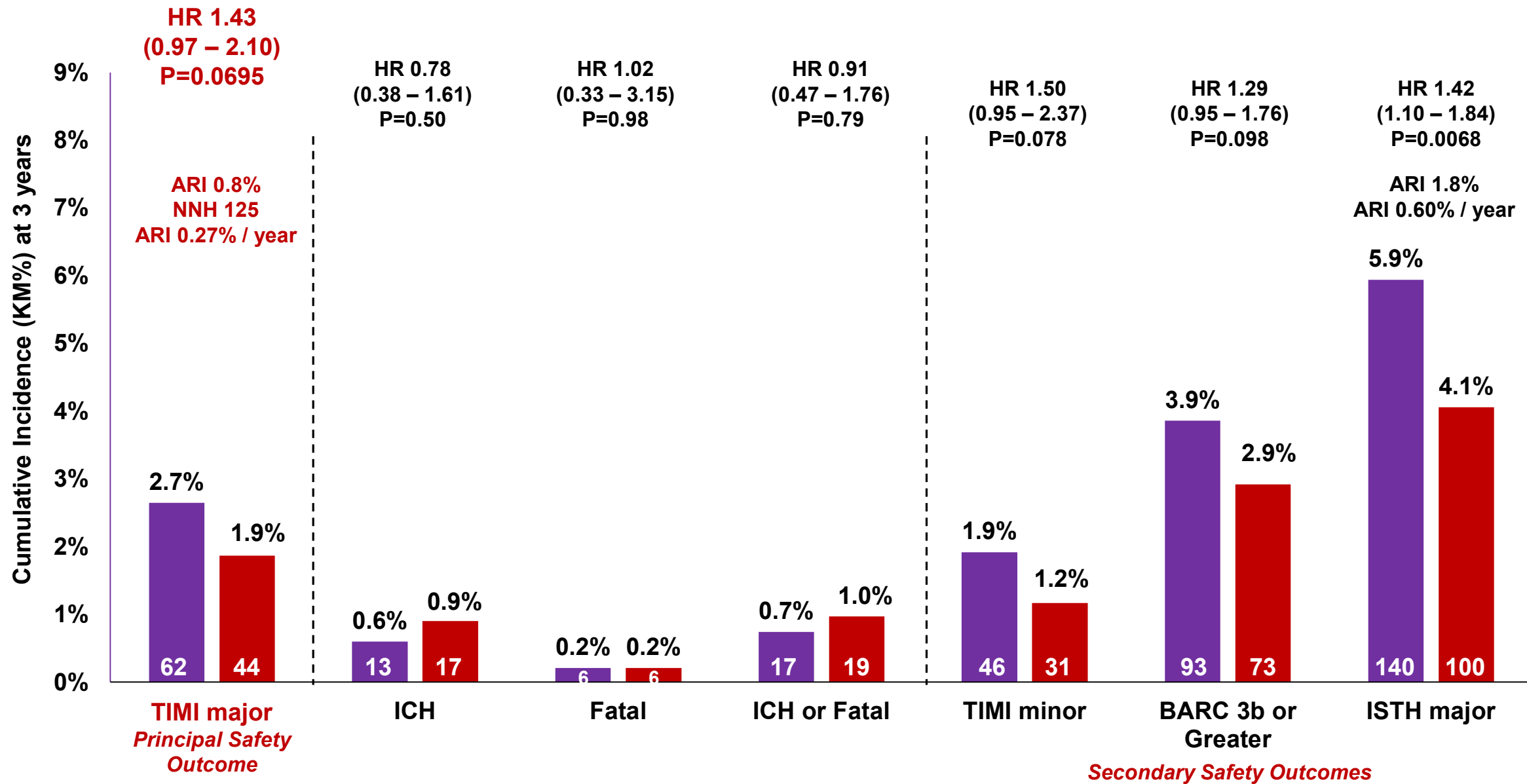
Safety

Placebo
Rivaroxaban

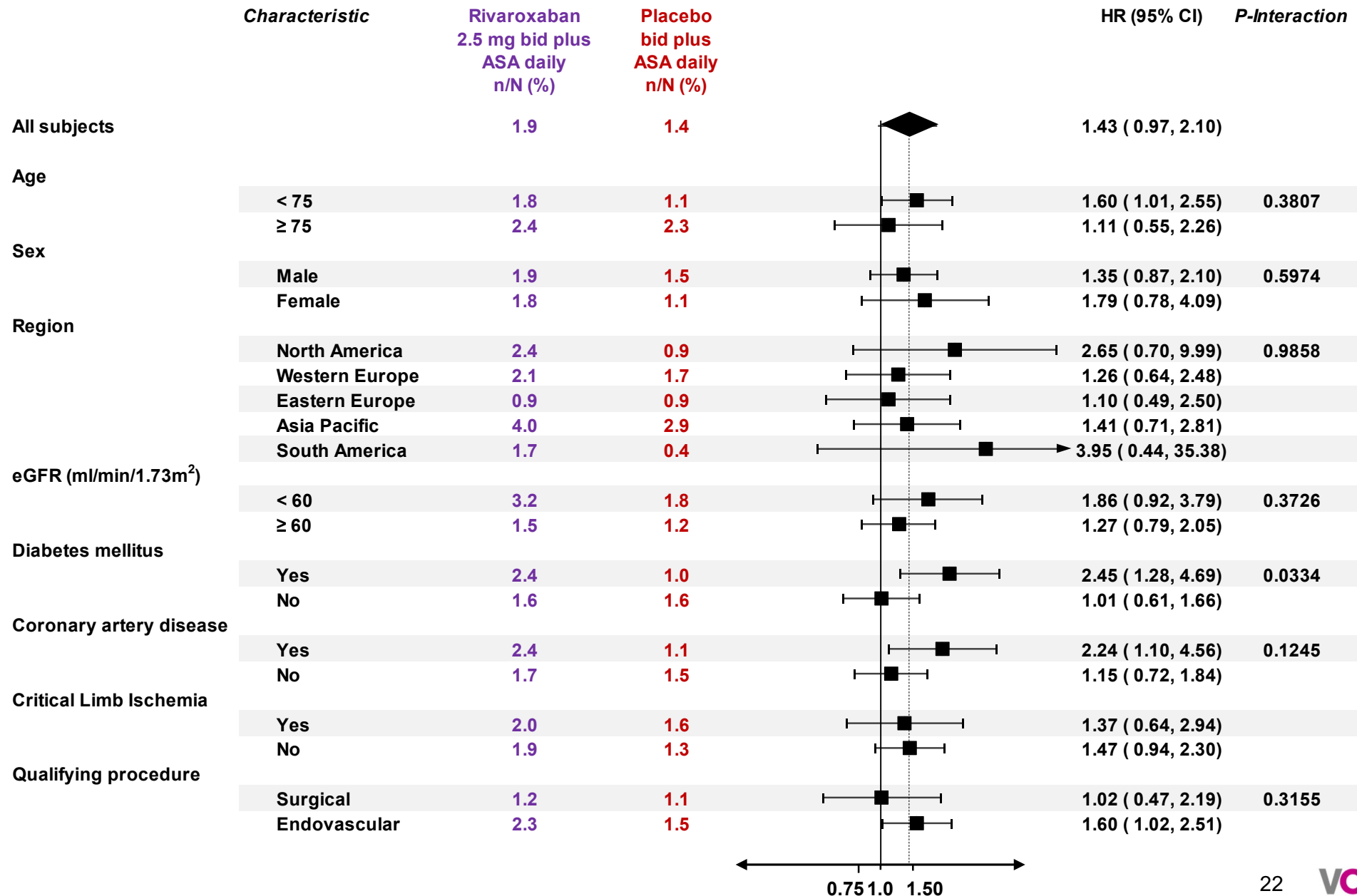


Safety

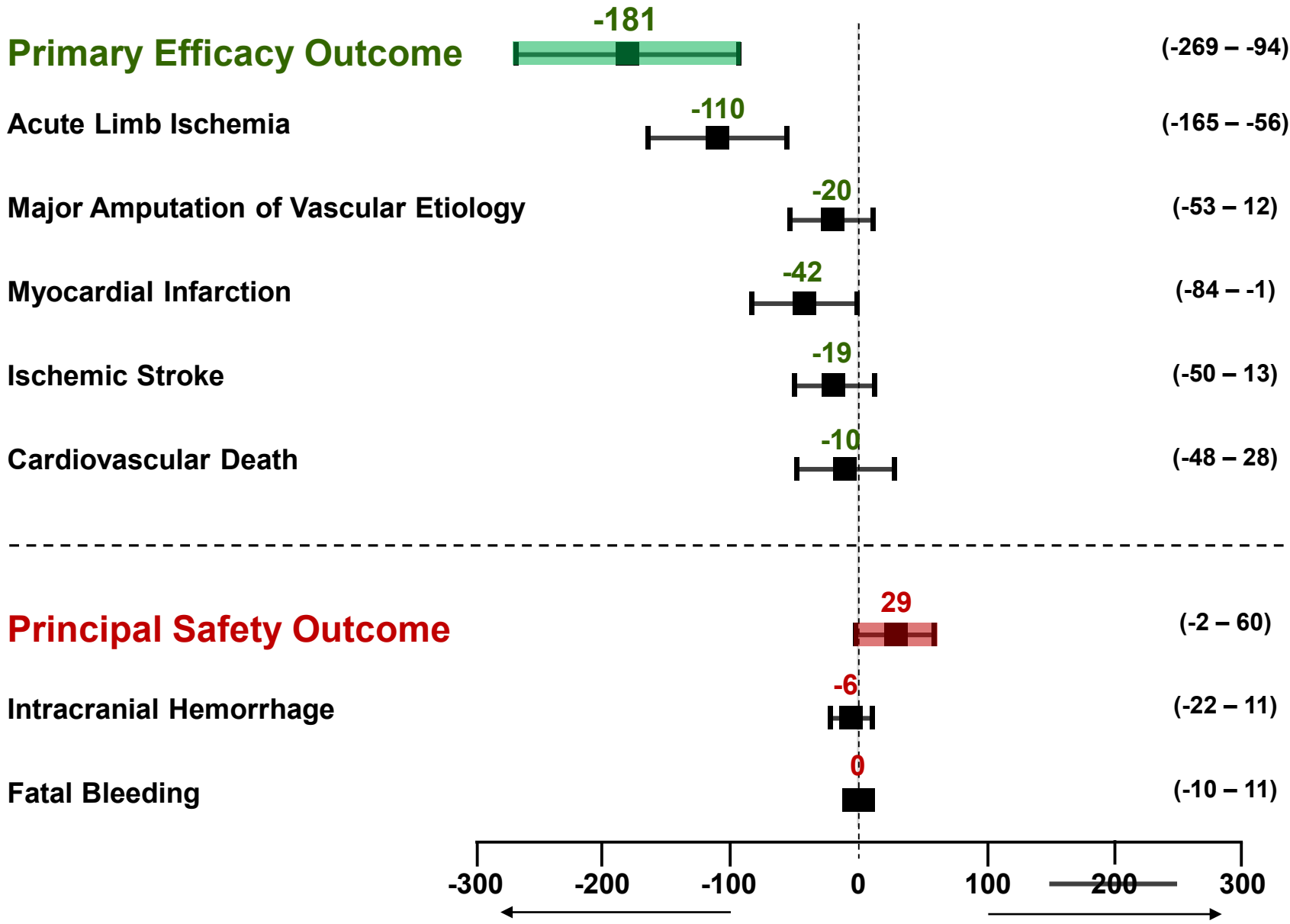
Placebo
Rivaroxaban



Principal Safety Outcome in Selected Subgroups



First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year



Summary & Conclusion

- **In symptomatic PAD after revascularization, ~1 in 5 have acute limb ischemia, major amputation of vascular etiology, MI, ischemic stroke or cardiovascular death at 3 years**
- **In this population and setting, rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone:**
 - ✓ **Significantly reduces this risk with...**
 - **Benefits apparent early and continued over time**
 - **Consistent benefit across major subgroups**
 - **Broad benefits including reductions in unplanned index limb revascularization**
 - ✓ **Increases bleeding, in VOYAGER PAD there was a numerical increase in TIMI major bleeding and significantly increased ISTH major bleeding but no excess in intracranial or fatal bleeding**
 - ✓ **Prevents ~6 times as many ischemic events relative to bleeds caused in PAD patients after revascularization**



ORIGINAL ARTICLE

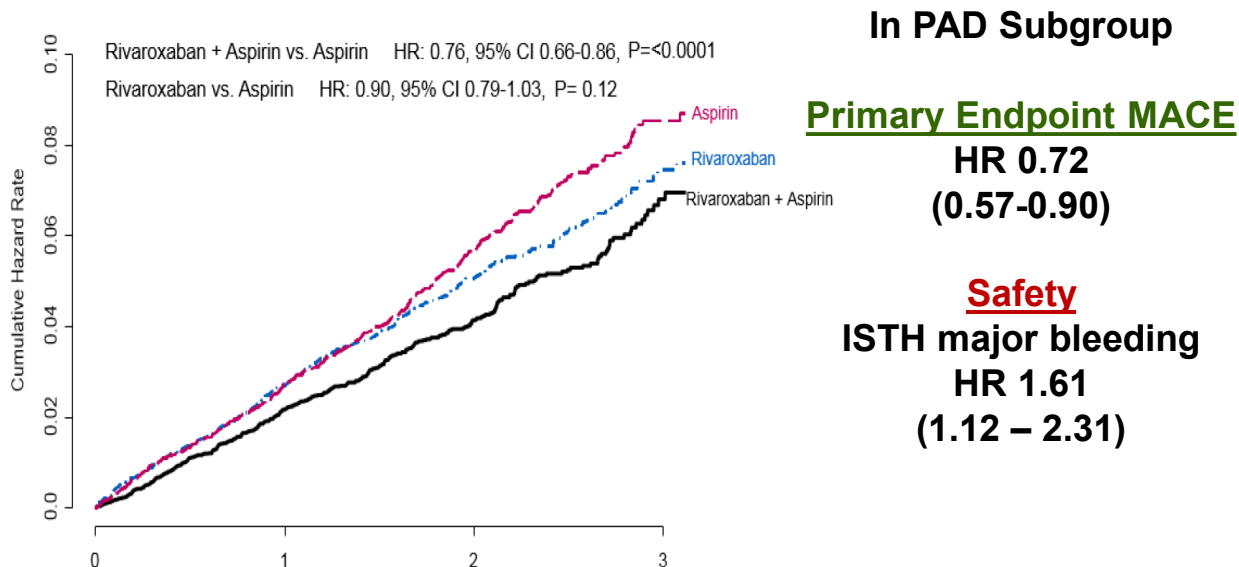
Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D.,
Sonia S. Anand, M.D., Eike S. Debus, M.D., Ph.D., Mark R. Nehler, M.D.,
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Lihong Diao, , Nicole Jaeger, , Connie N. Hess, M.D., M.H.S., Akos F. Pap, ,
John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D.,
Dainis K Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D.,
Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and
William R. Hiatt, M.D.

Backup Slides

Designed as a PAD Intervention Study:

- **Population: symptomatic lower extremity PAD undergoing intervention, without further enrichment for risk**
 - 4-fold risk of ALI long-term vs no revascularization
 - ALI outcomes after hospitalization 15% disabled or dead
- **Setting: post-intervention (particularly high risk for limb and bleeding complications)**
- **Treatment: rivaroxaban on top of standard of care, including clopidogrel**
- **Primary efficacy outcome: severe limb & cardiovascular events**

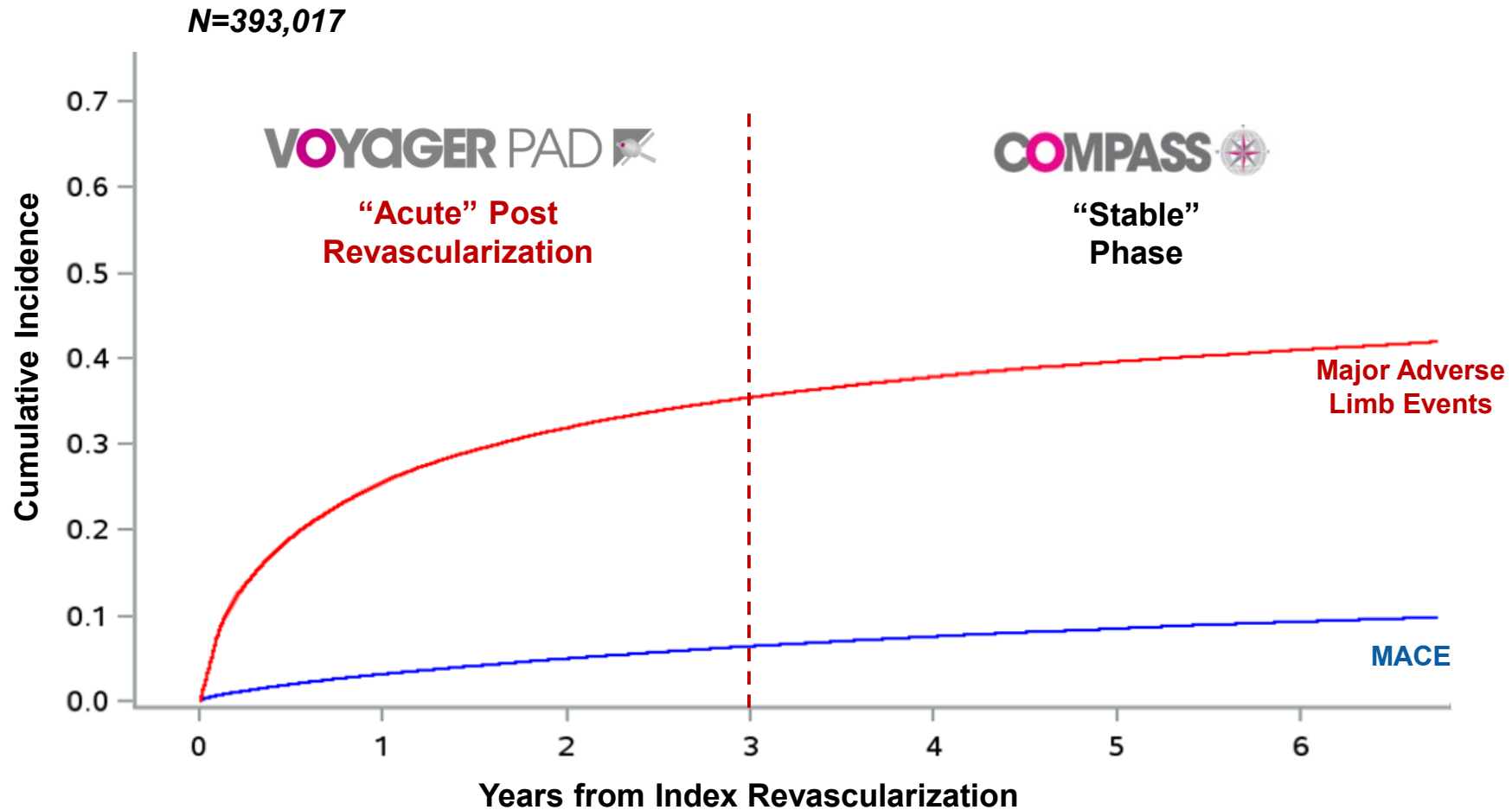


- Enriched for polyvascular disease (e.g. CAD in ~66%)
- Broad definition of PAD (including asymptomatic low ABI)
- Stable setting
- MACE primary outcome
- Clopidogrel not allowed

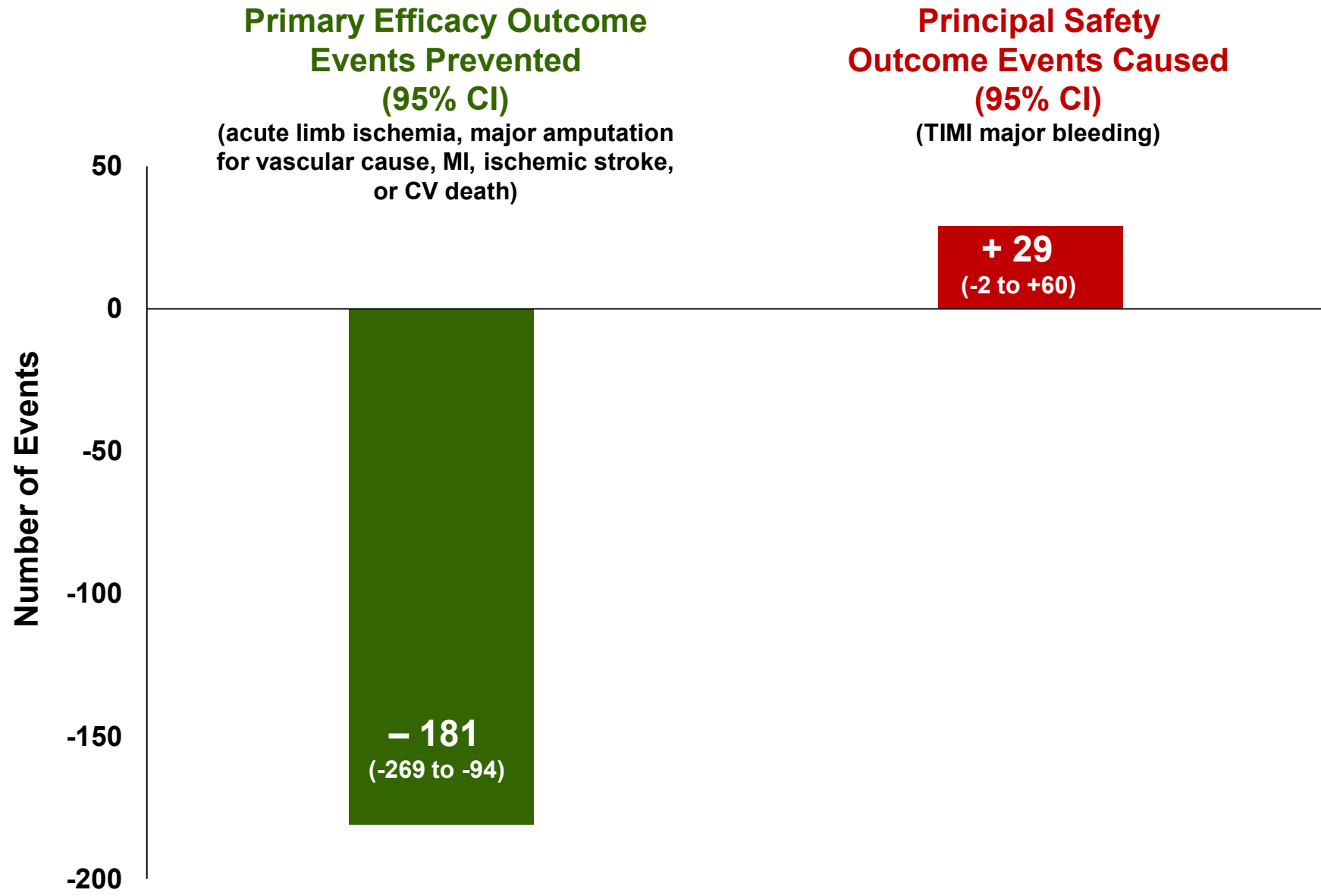
Anand SA et al. Lancet 2017

Perspective

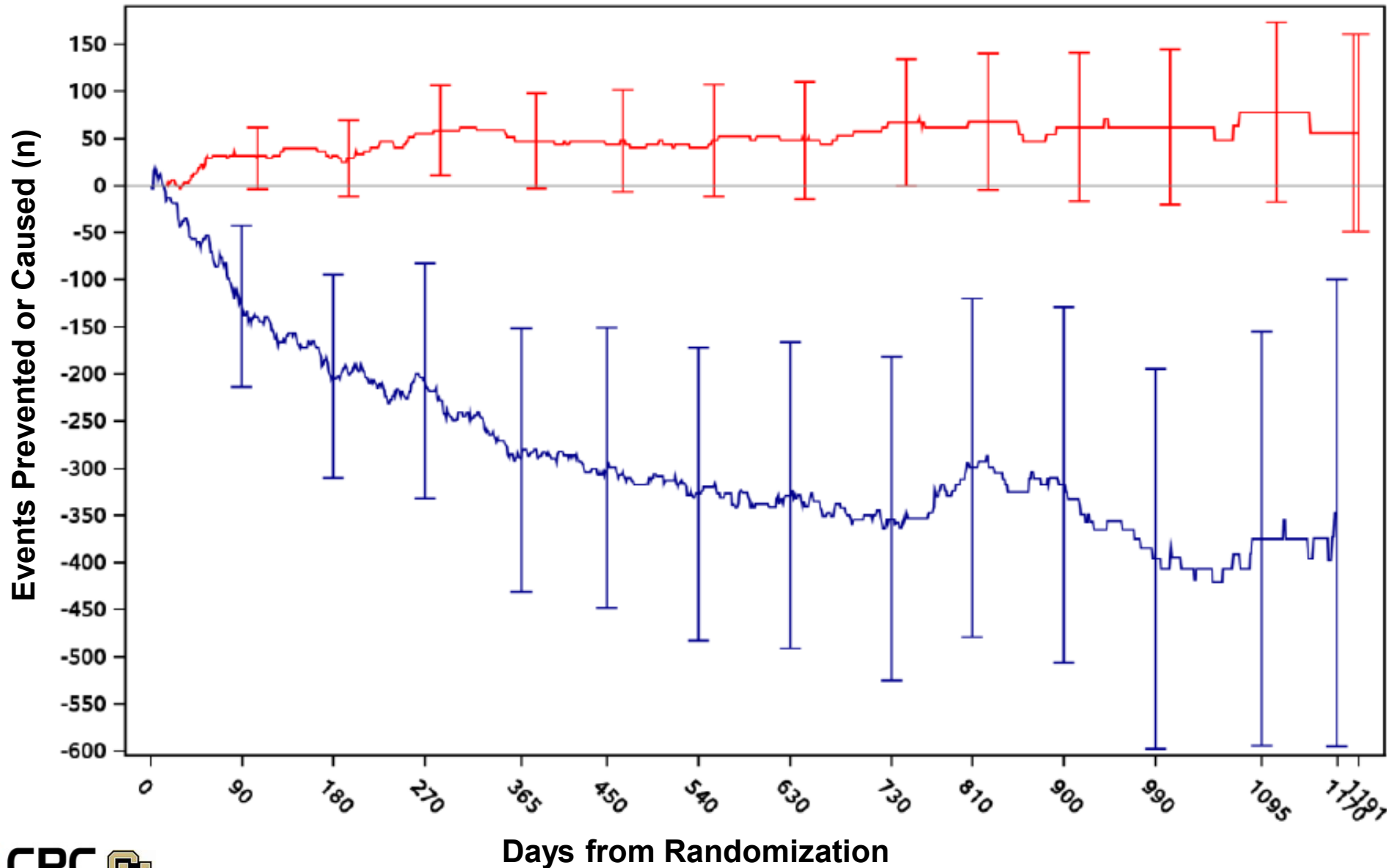
A regimen of rivaroxaban 2.5 mg twice daily added to aspirin reduces the risk of major adverse limb and cardiovascular outcomes from acute intervention to long-term secondary prevention



First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year



Risk & Benefit Over Time

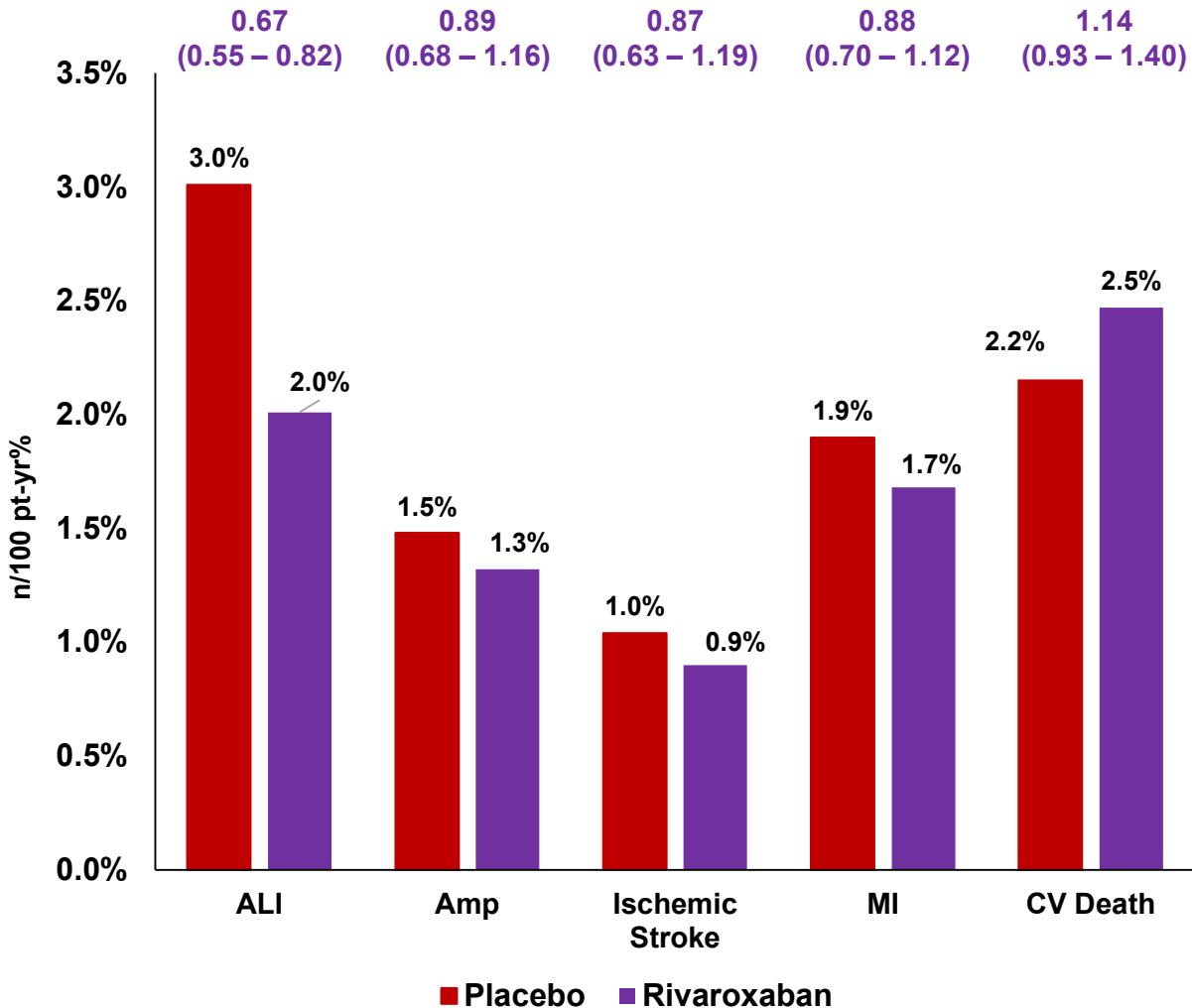


**TIMI major
bleeding**

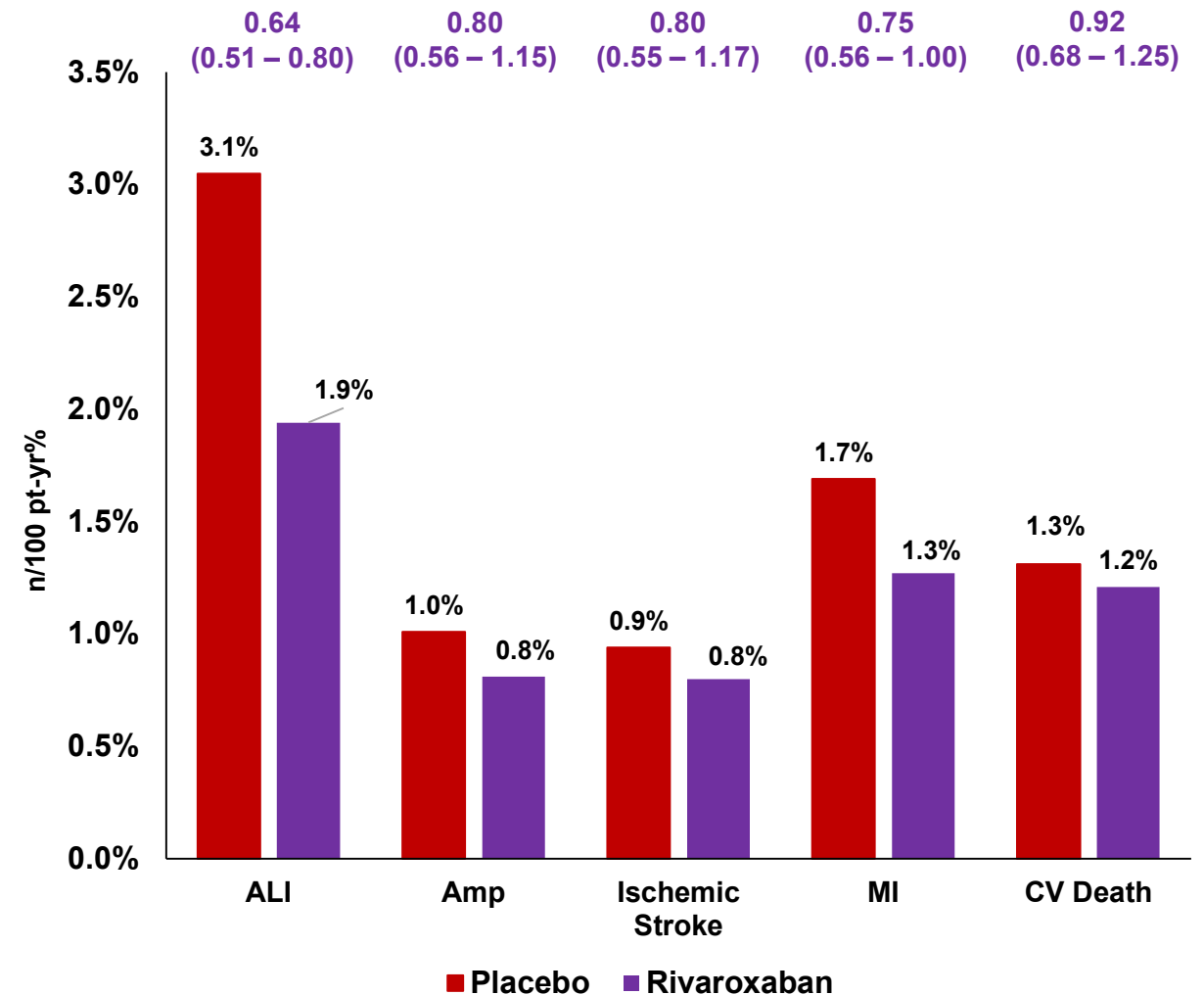
**Primary endpoint
composite of acute limb
ischemia, major
amputation of vascular
cause, MI, ischemic
stroke or CV death**

Efficacy – Intention To Treat versus & Treatment

Intention To Treat



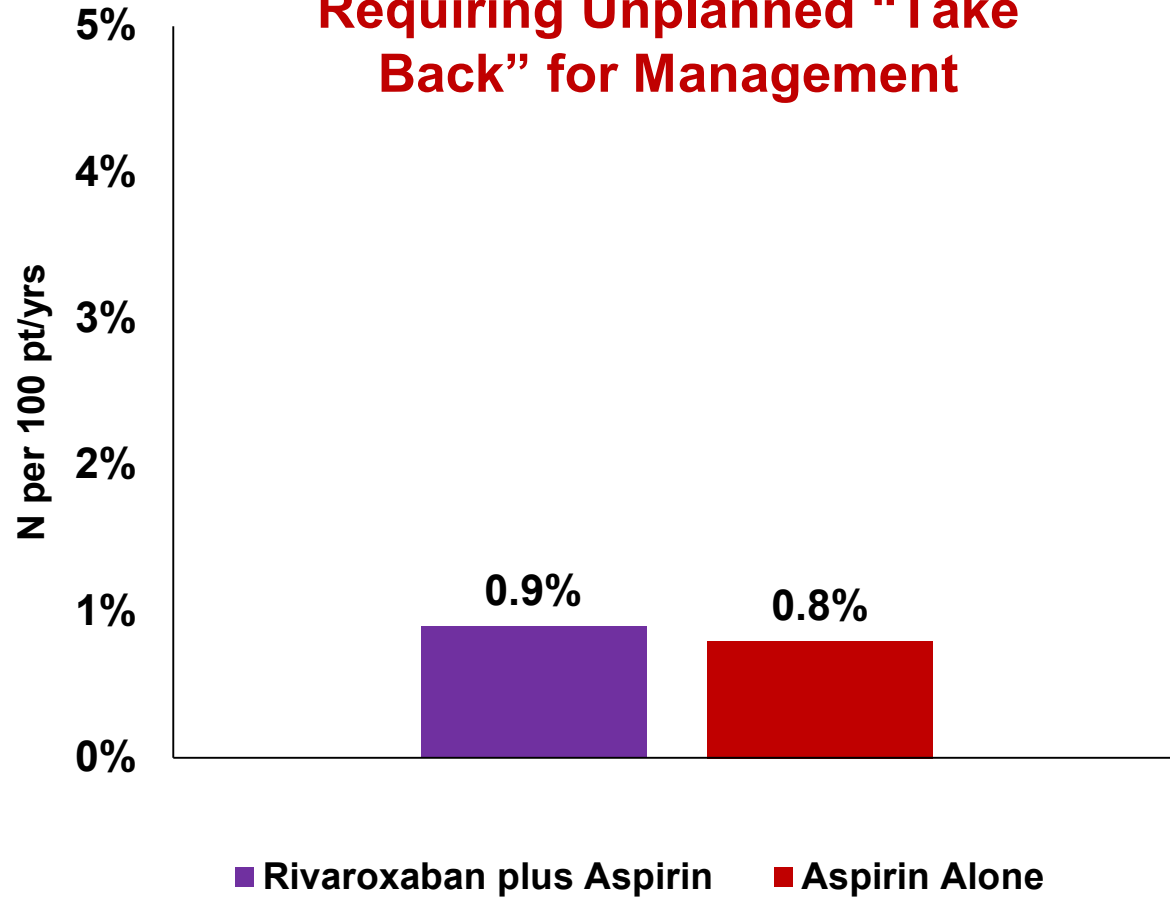
On Treatment*



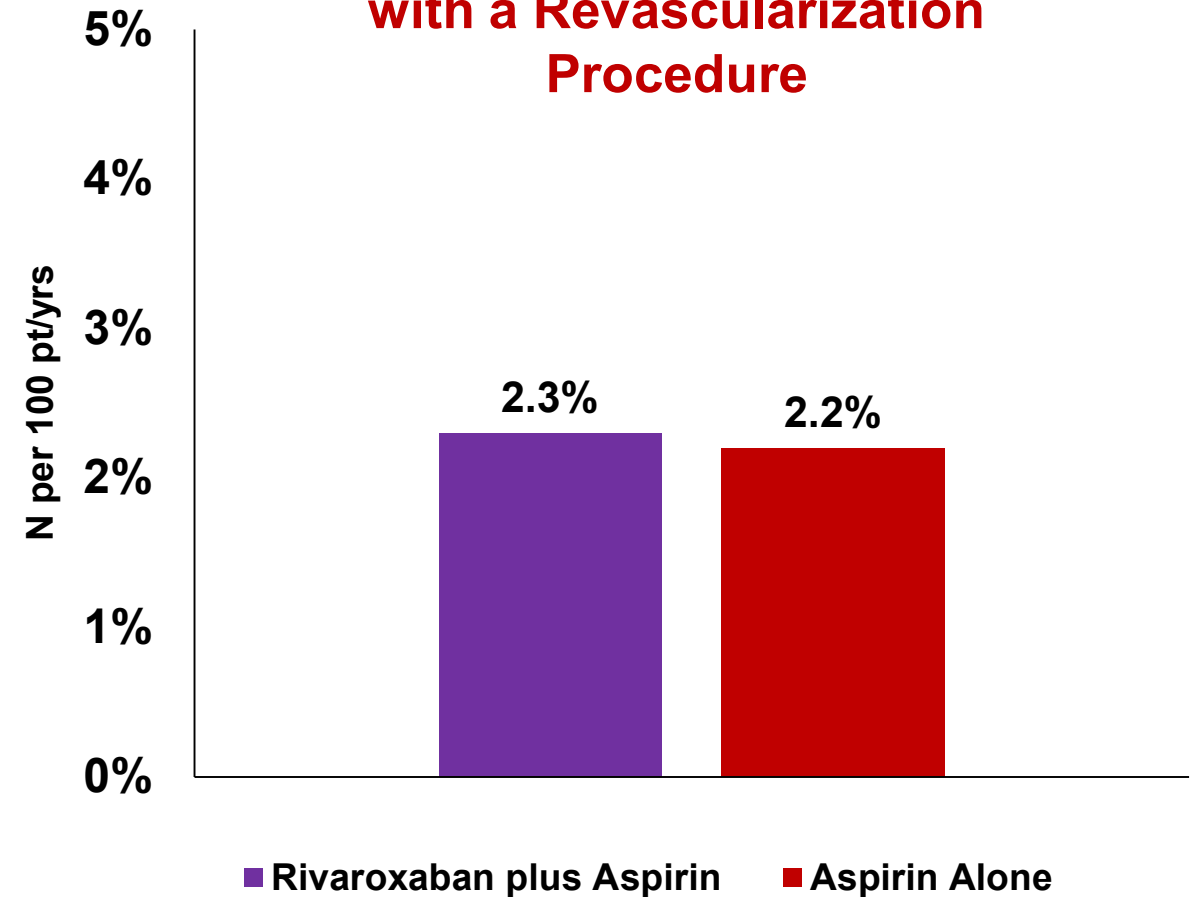
*includes events from randomization until 2 days following permanent drug discontinuation

Procedural Bleeding

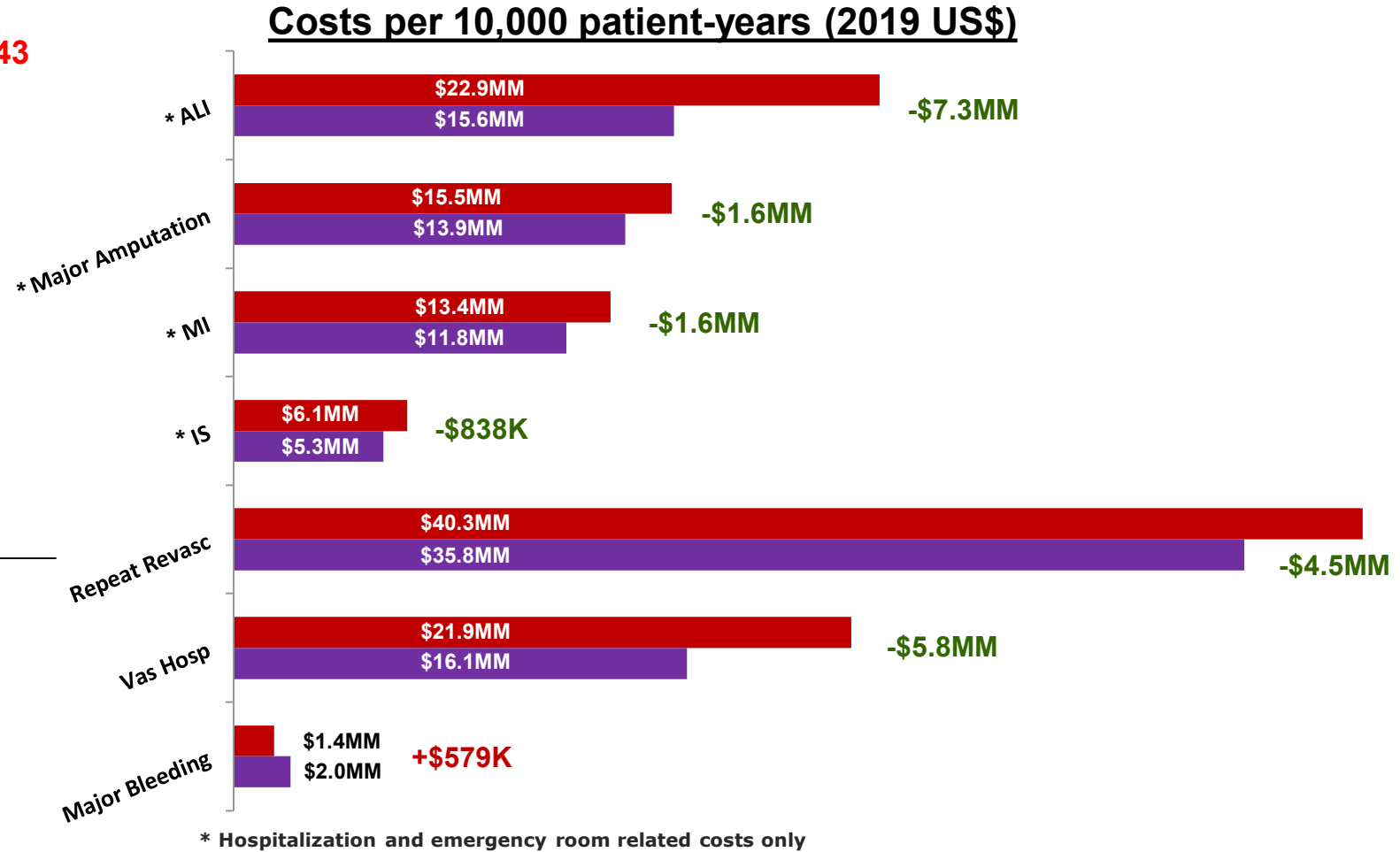
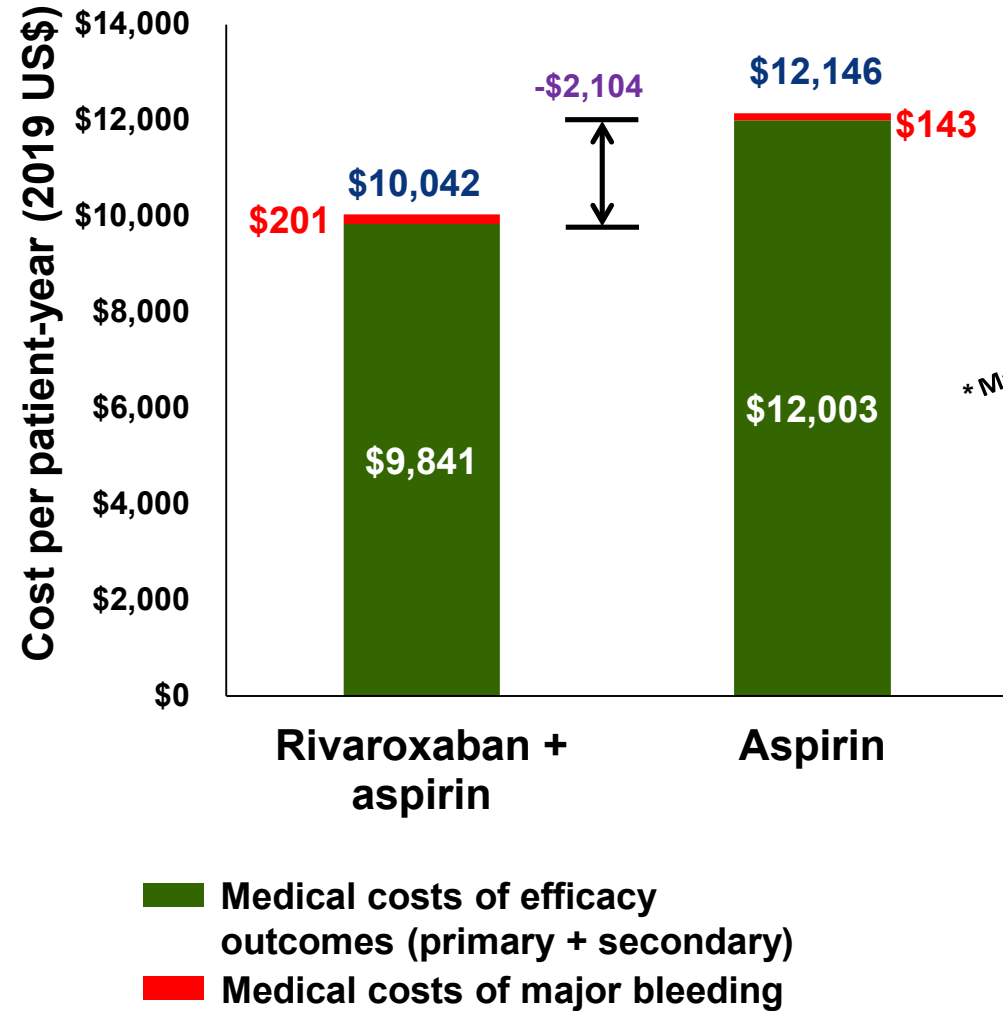
Post-Procedural Bleeding Requiring Unplanned “Take Back” for Management



Any Bleeding Associated with a Revascularization Procedure

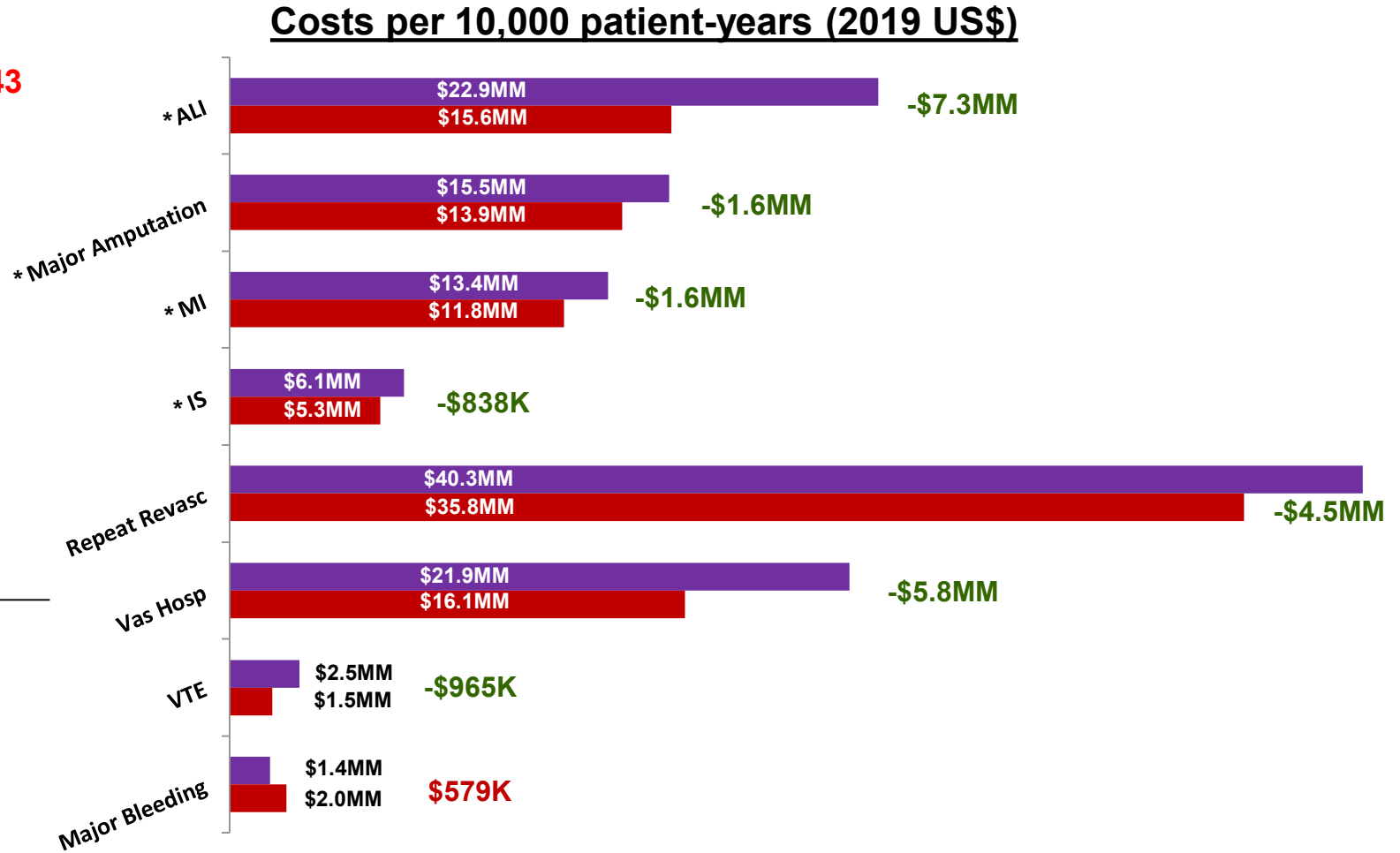
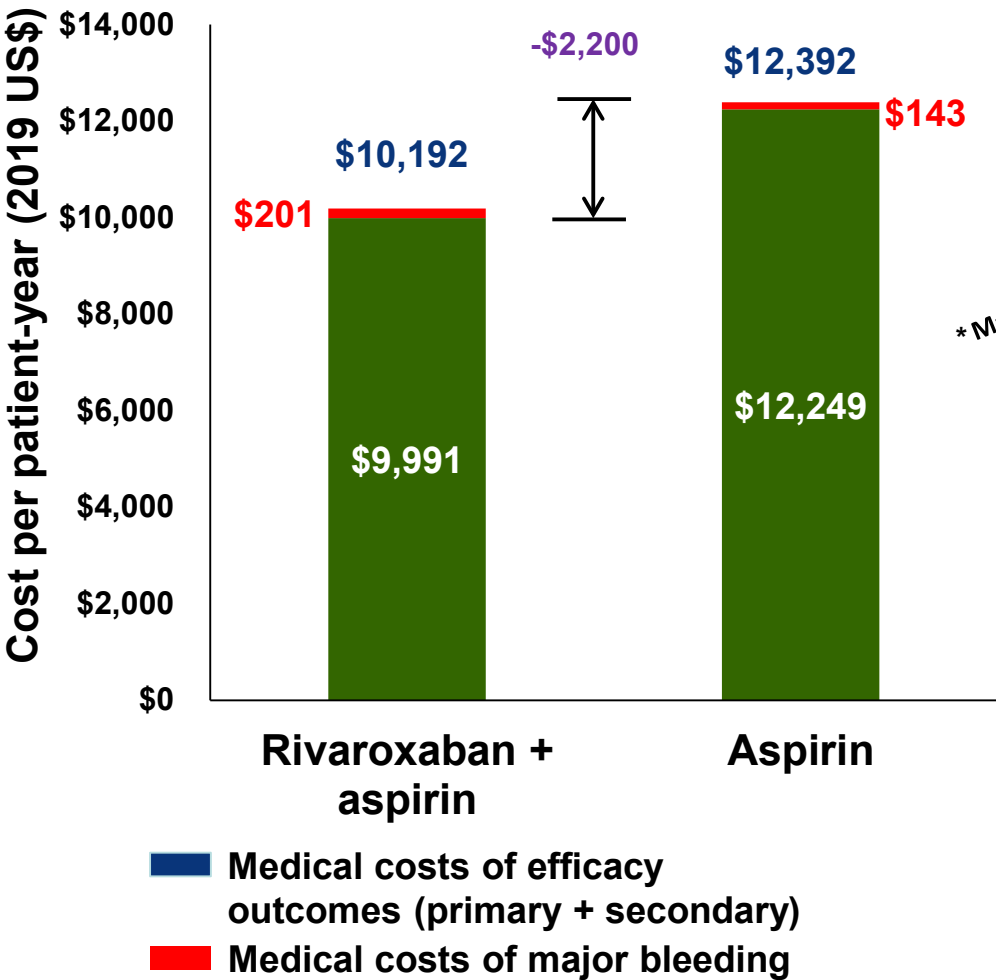


Medical Cost Reduction with Rivaroxaban versus Placebo Per Year



Total medical costs reduced = \$21MM per 10,000 patient-years

Medical Cost Reduction with Rivaroxaban versus Placebo Per Year

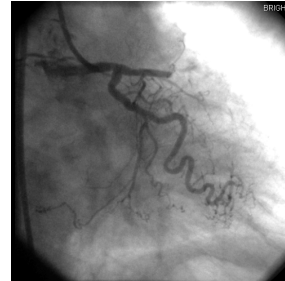
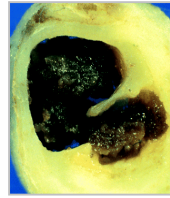


Total medical costs reduced = \$22MM per 10,000 patient-years

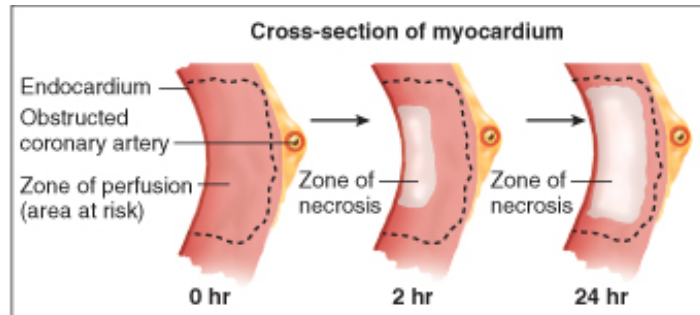
* Hospitalization and emergency room related costs only

Cost of rivaroxaban for 30-day supply = \$470 (@25% discount = \$352.5)
 Most patients pay between \$0 and \$47 per month depending on health insurance plan
<https://www.xarelto-us.com/xarelto-cost/co-pay-and-list-price>

STEMI



- Acute thrombotic occlusion of an artery threatening tissue loss
- **“Time Is Muscle”**
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication

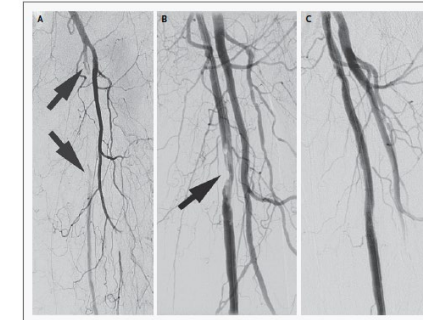


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- **Mortality at 1 year 8.1%¹**
- **Recurrent MACE at 1 year 3.4%¹**
- **HF at 1 year 7.4%¹**

1. Zeymer et al. EORP EU STEMI Registry 2019

ALI



- Acute thrombotic occlusion of an artery threatening tissue loss
- **“Time Is Muscle”**
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication



0 Hour

→ 24 Hour

- **Mortality at 1 year 12.1%²**
- **MACE 11.7%, Recurrent ALI 24% (1 yr)²**
- **Amputation at 1-year 27%²**

2. Bonaca et al. Circulation 2016