# 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*

University of Colorado Anschutz Medical Campus

*An Academic Research Organization Affiliated with the University of Colorado School of Medicine*

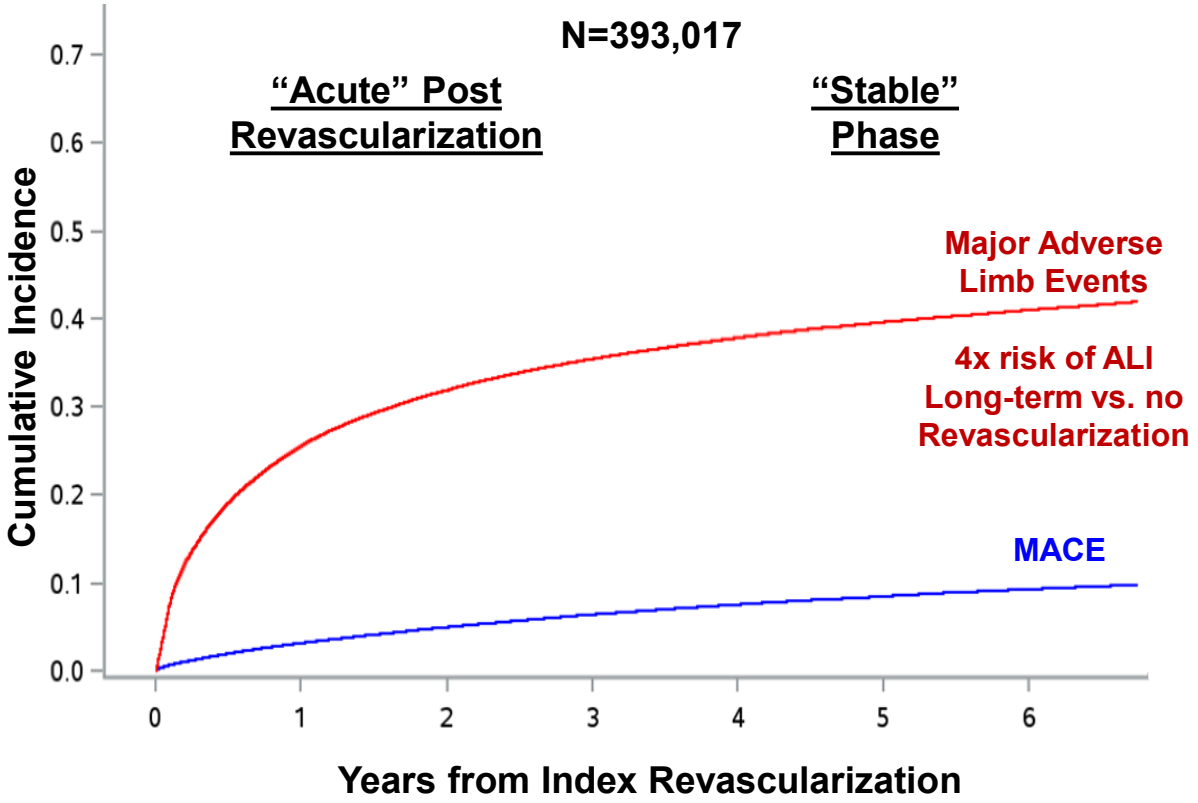
# Disclosures

**VOYAGER PAD was funded by Bayer & Janssen**

**Grant support to CPC Clinical Research from:**
**Amgen, Aralez, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk, Pfizer, Sanofi**

# Background

## Risk in Patients Undergoing Peripheral Revascularization




## Outcomes in Patients with Acute Limb Ischemia

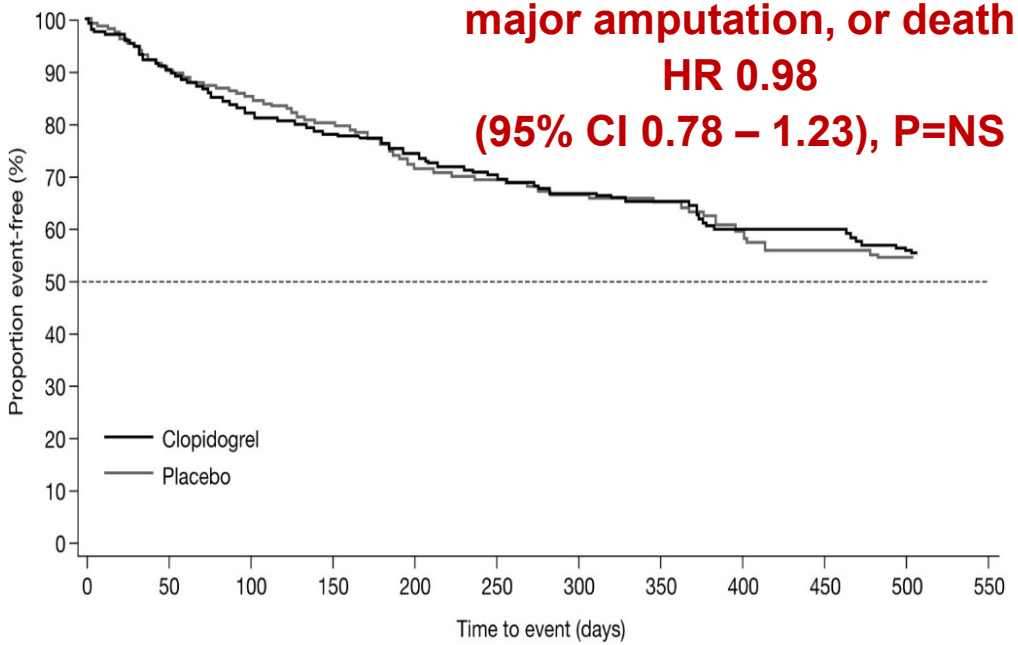
- Median hospitalization 8 days (IQR 5-15)
- ~4% die at presentation
- ~1/5 → major amputation
- ~1/3 → prolonged ICU stay
- ~3/4 → major surgery
- *Outcomes after hospitalization are poor with ~15% disabled or dead*


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

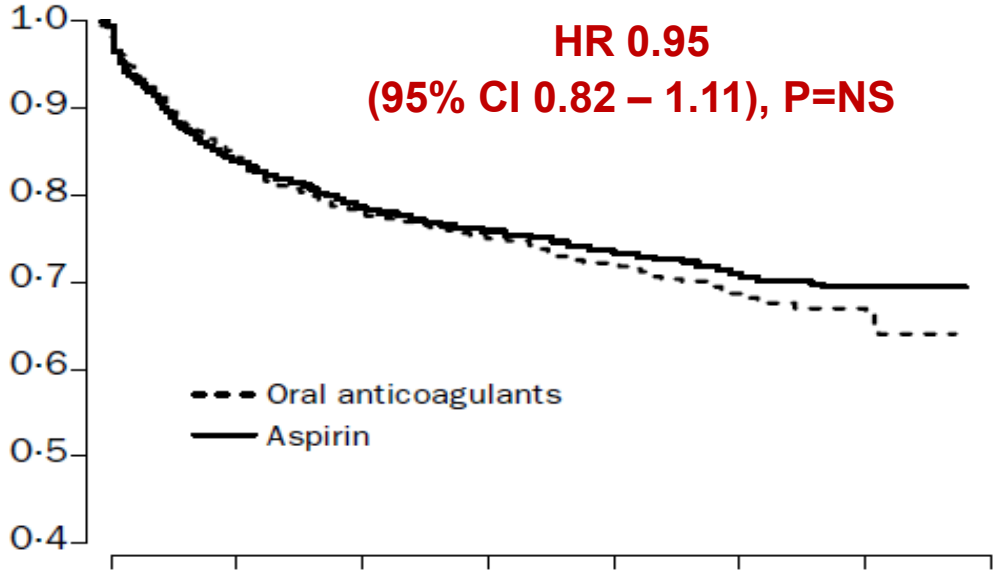
**Despite the high risk, currently there is no proven antithrombotic strategy that has demonstrated efficacy for reducing major adverse limb and cardiovascular events after peripheral intervention for ischemia**

**Index-graft occlusion, revascularization, major amputation, or death**
**HR 0.98**
**(95% CI 0.78 – 1.23), P=NS**




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

**Graft Occlusions**
**HR 0.95**
**(95% CI 0.82 – 1.11), P=NS**




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


Belch et al. Journal of Vascular Surgery. 2010
Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet. 2000

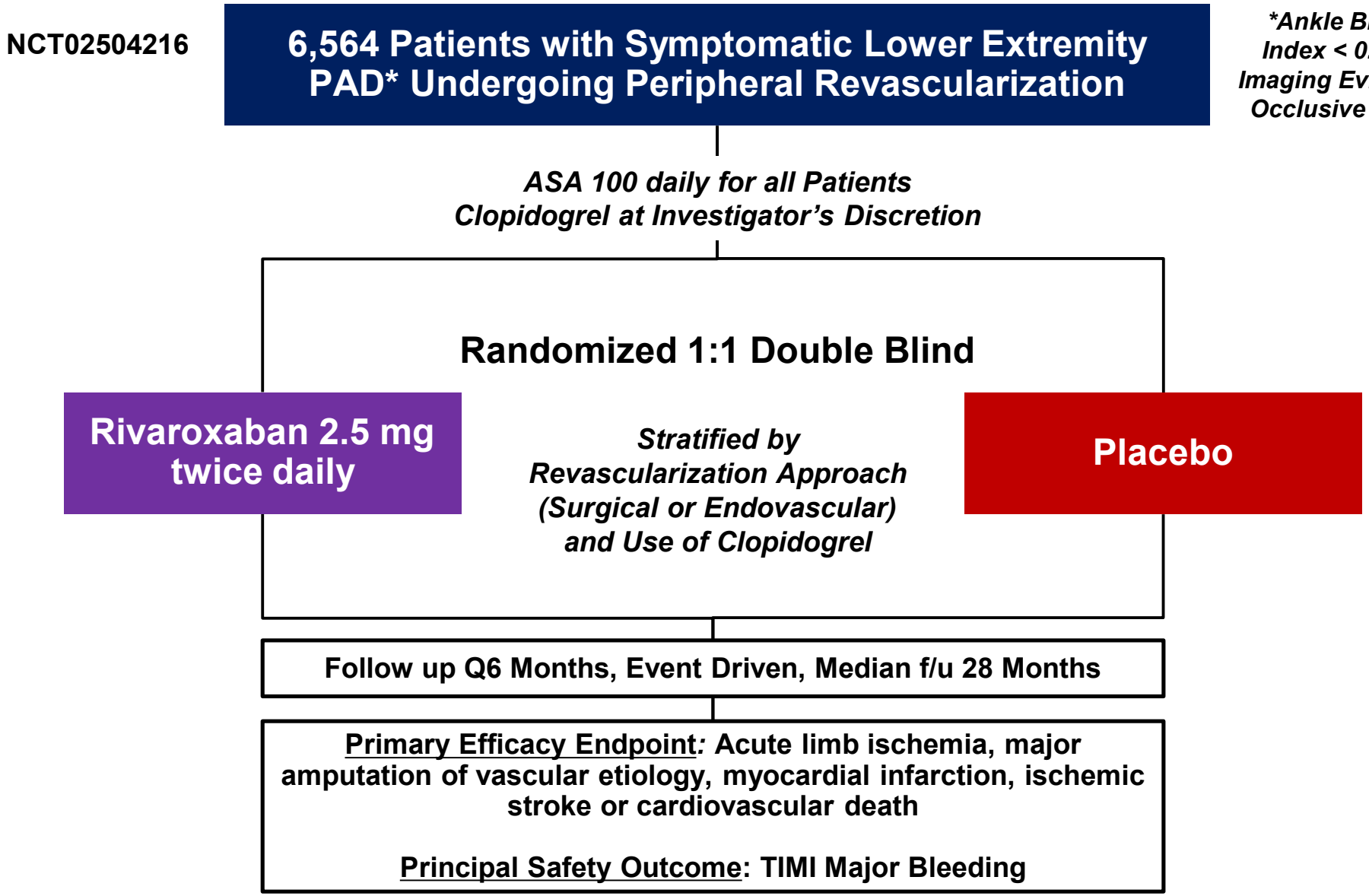
# Objectives

## In PAD 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

# Trial Design




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

# Inclusion & Exclusion

## Inclusion

- **Age ≥ 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

*CPC Clinical Events Committee (CEC) adjudicated all efficacy and safety events*

# 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. Chervenkoff
*Canada*
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*Czech Republic*
K. Roztocil
*China*
W. Fu / Z. Shi
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D. Krievins

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*Poland*
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*Portugal*
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A. Hirsch (Co-Chair)*
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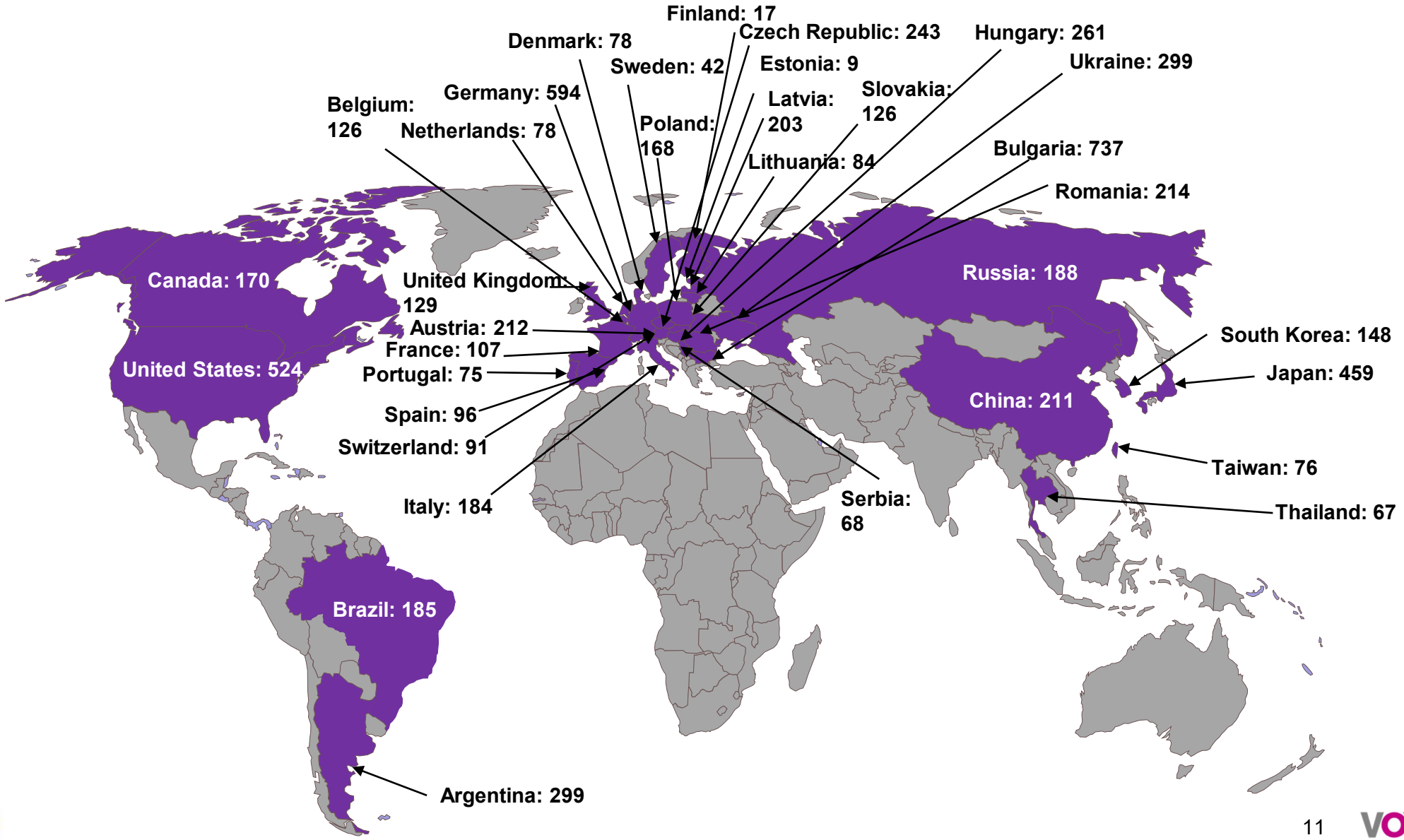
J. Chung
J. Kittelson (Biostatistician)
J. Mills
J. Mustapha
F. Saab

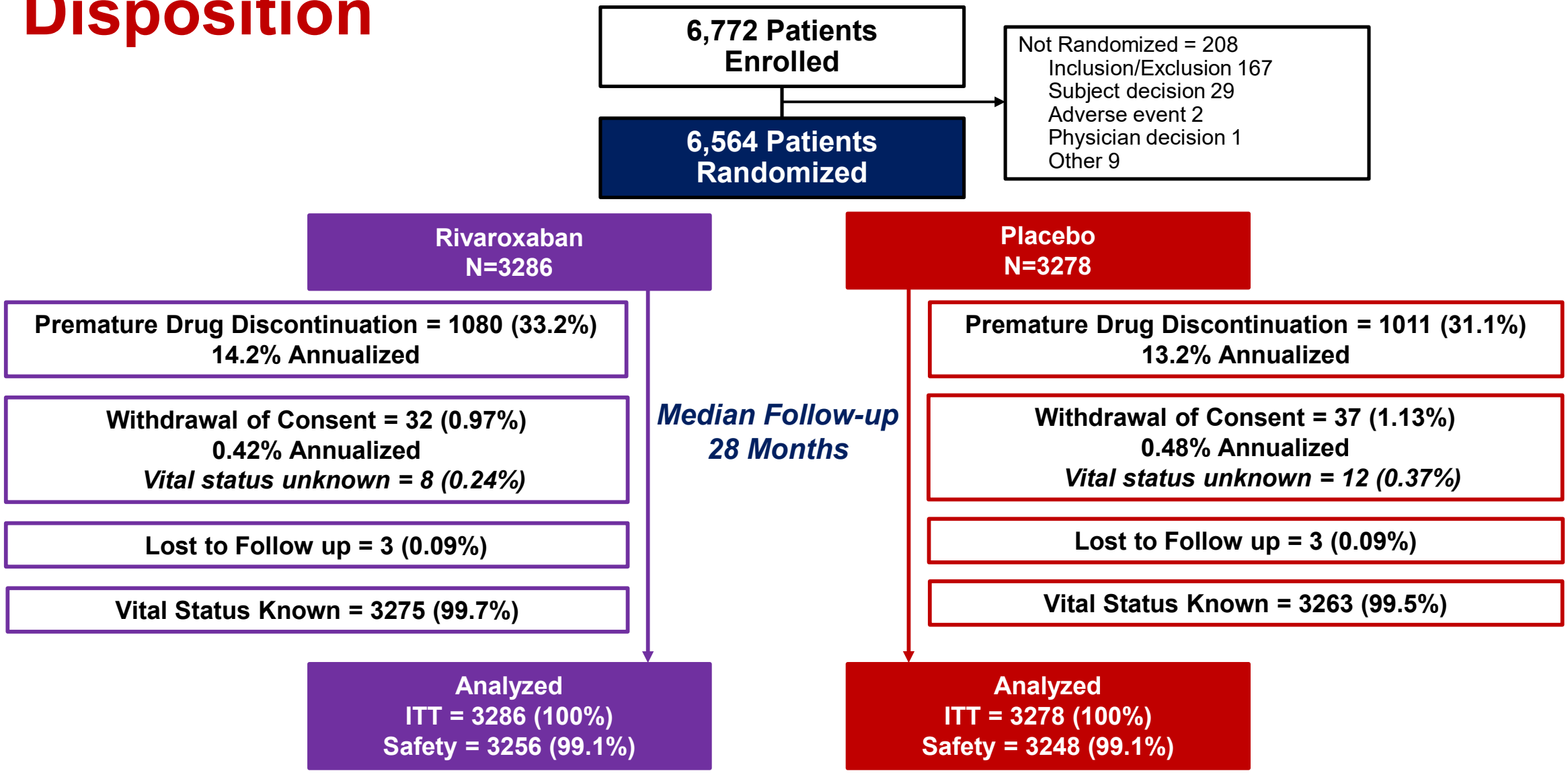
**Deceased*

# 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***

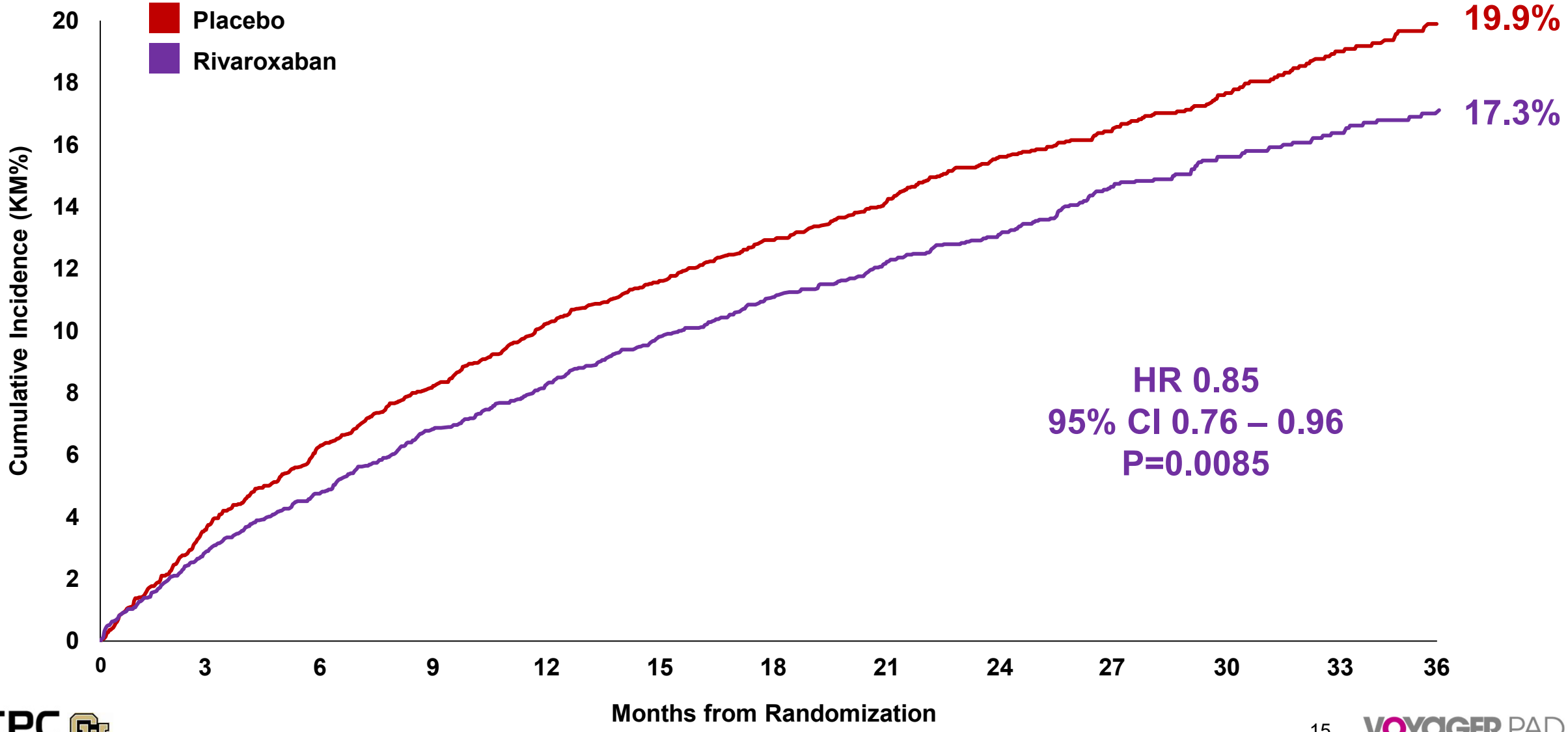
# PAD & Procedural Characteristics

| Characteristics at Randomization | Rivaroxaban 2.5 mg twice daily + aspirin N=3286 % | Placebo + aspirin N=3278 % |
|---|---|---|
| *Prior Peripheral Artery Disease History* | | |
| 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) |
| *Indication for Revascularization* | | |
| Critical limb ischemia | 23 | 24 |
| Claudication | 77 | 76 |
| *Type of Revascularization* | | |
| 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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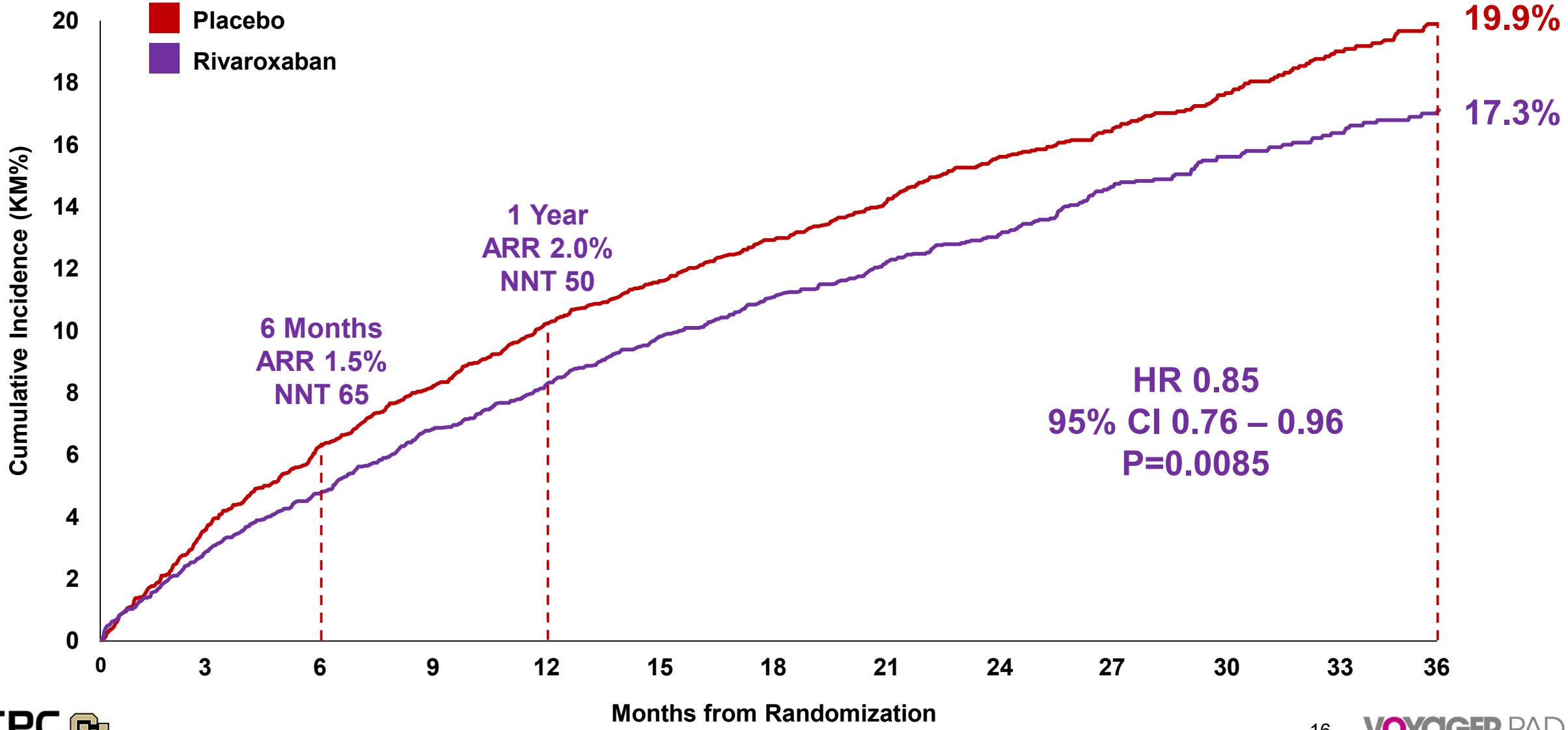
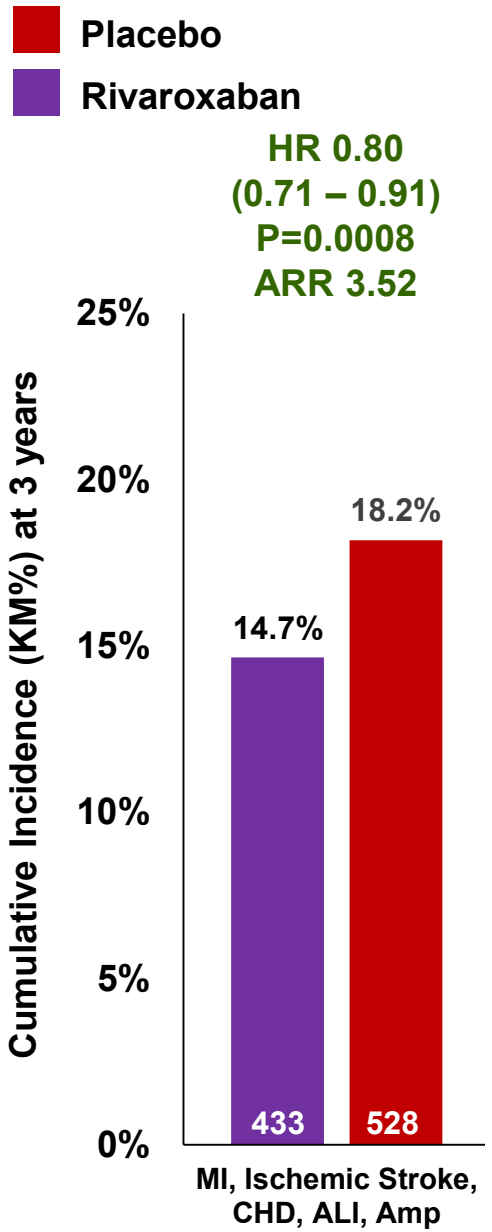



*ARR – absolute risk reduction, NNT number needed to treat*

# Primary Endpoint & Components

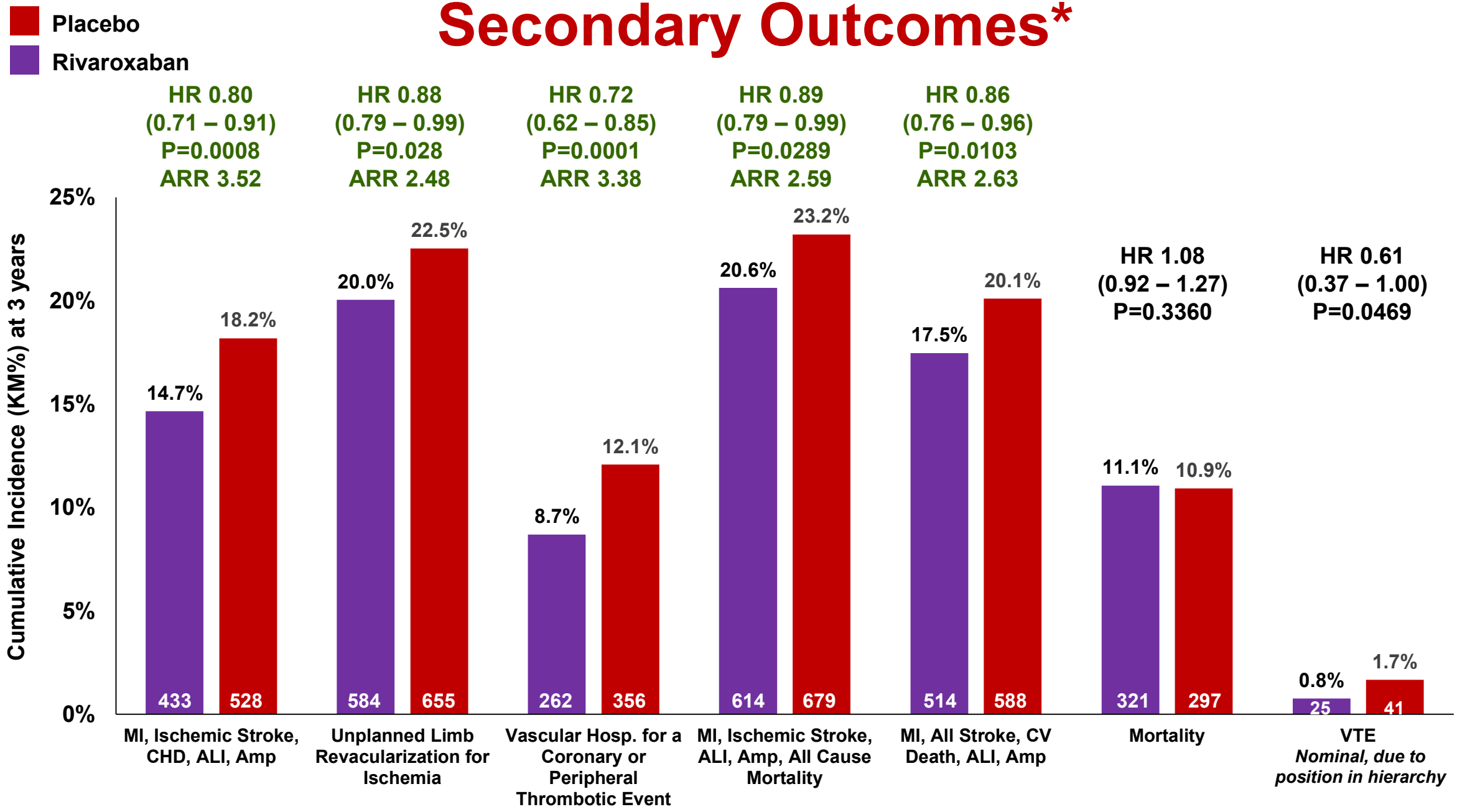
| | KM% 3 Years (n) Rivaroxaban N=3286 | KM% 3 Years (n) Placebo N=3278 | HR (95% CI) |
|---|---|---|---|
| Primary Efficacy Outcome | 17.3 | 19.9 | 0.85 (0.76 – 0.96) |
| Acute Limb Ischemia | 5.24 | 7.74 | 0.67 (0.55 – 0.82) |
| Major Vascular Amputation | 3.42 | 3.87 | 0.89 (0.68 – 1.16) |
| Ischemic 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*




*Presented in order of hierarchy from left to right

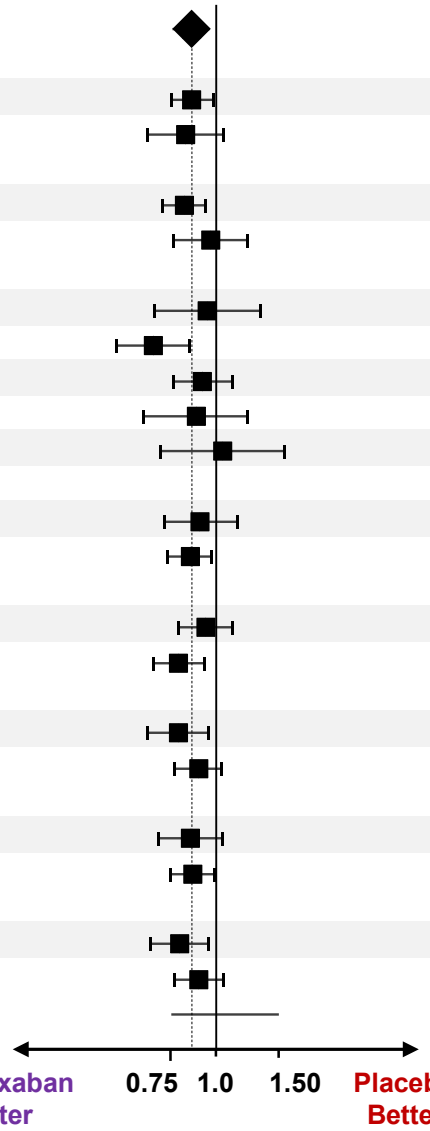
# Secondary Outcomes*



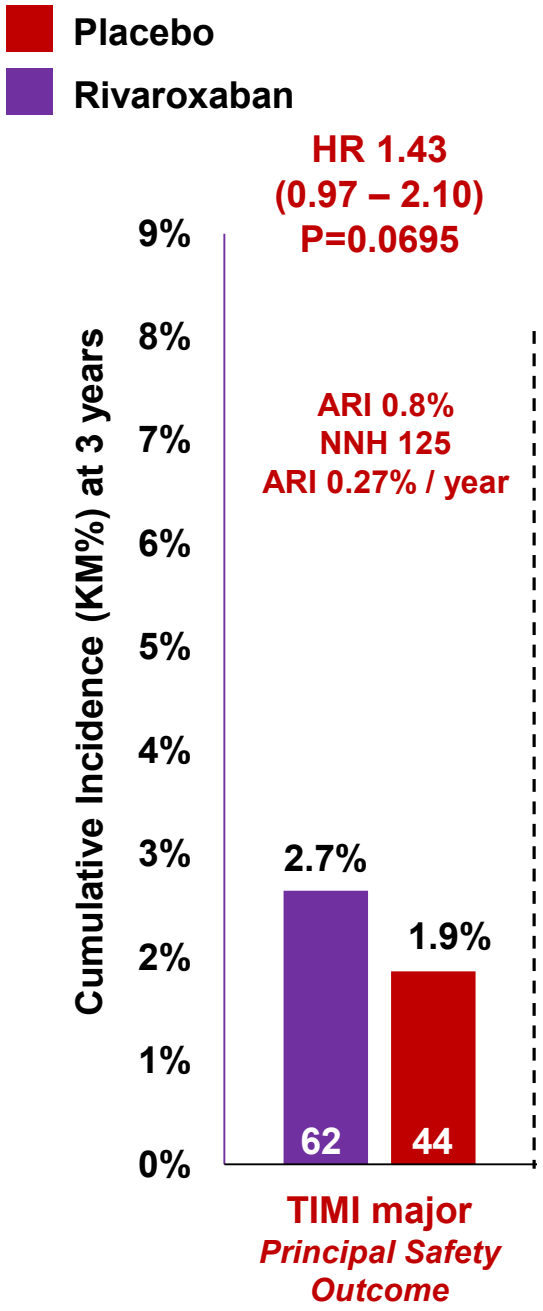

*Presented in order of hierarchy from left to right

# Primary Efficacy Outcome in Selected Subgroups

| *Characteristic* | | Rivaroxaban 2.5 mg bid plus ASA daily n/N (%) | Placebo bid plus ASA daily n/N (%) | HR (95% CI) | *P-interaction* |
|---|---|---|---|---|---|
| *All subjects* | | 15.5 | 17.8 | 0.85 ( 0.76, 0.96) | |
| Age | | | | | |
| | < 75 | 15.0 | 17.0 | 0.86 ( 0.75, 0.98) | 0.8314 |
| | ≥ 75 | 17.4 | 21.0 | 0.82 ( 0.64, 1.05) | |
| Sex | | | | | |
| | Male | 15.4 | 18.4 | 0.82 ( 0.71, 0.94) | 0.2385 |
| | Female | 15.7 | 16.2 | 0.97 ( 0.76, 1.23) | |
| Region | | | | | |
| | North America | 18.4 | 19.3 | 0.95 ( 0.67, 1.33) | 0.2286 |
| | Western Europe | 12.9 | 18.4 | 0.67 ( 0.53, 0.84) | |
| | Eastern Europe | 16.4 | 17.6 | 0.92 ( 0.76, 1.11) | |
| | Asia Pacific | 13.3 | 15.2 | 0.88 ( 0.63, 1.23) | |
| | South America | 20.2 | 19.9 | 1.04 ( 0.70, 1.56) | |
| eGFR (ml/min/1.73m$^2$) | | | | | |
| | < 60 | 19.7 | 21.9 | 0.90 ( 0.71, 1.15) | 0.6177 |
| | ≥ 60 | 14.4 | 16.6 | 0.85 ( 0.73, 0.97) | |
| Diabetes mellitus | | | | | |
| | Yes | 18.9 | 19.8 | 0.94 ( 0.79, 1.11) | 0.1588 |
| | No | 13.2 | 16.5 | 0.79 ( 0.67, 0.93) | |
| Coronary Artery Disease | | | | | |
| | Yes | 17.4 | 21.7 | 0.78 ( 0.64, 0.95) | 0.2872 |
| | No | 14.6 | 16.1 | 0.89 ( 0.77, 1.04) | |
| Critical Limb Ischemia | | | | | |
| | Yes | 20.9 | 24.4 | 0.85 ( 0.69, 1.05) | |
| | No | 13.8 | 15.8 | 0.86 ( 0.74, 0.99) | |
| Qualifying Procedure | | | | | |
| | Surgical | 17.9 | 21.9 | 0.79 ( 0.66, 0.95) | 0.2896 |
| | Endovascular | 14.2 | 15.7 | 0.90 ( 0.77, 1.05) | |

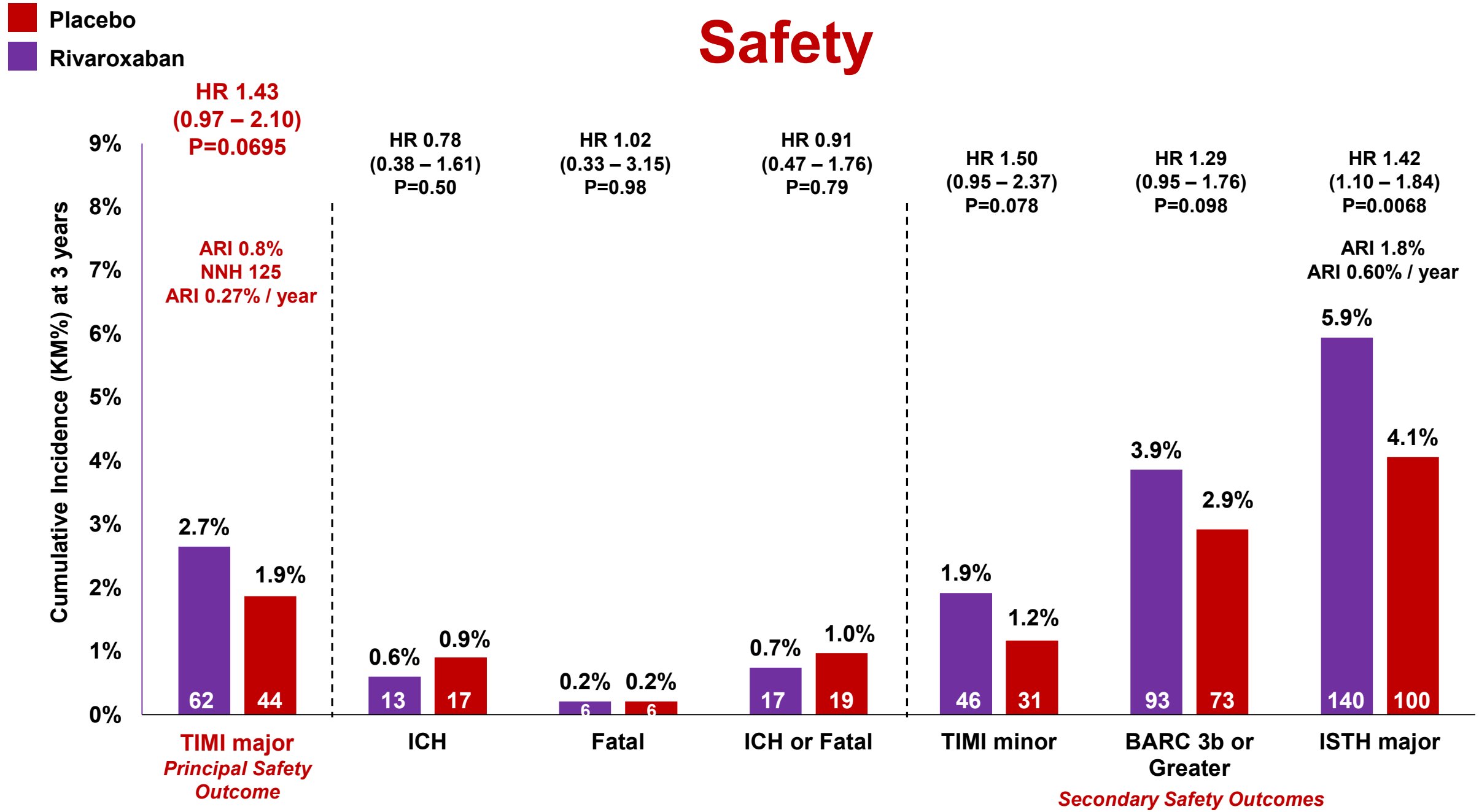


# Safety




*ARI – absolute risk increase, NNH number needed to harm*

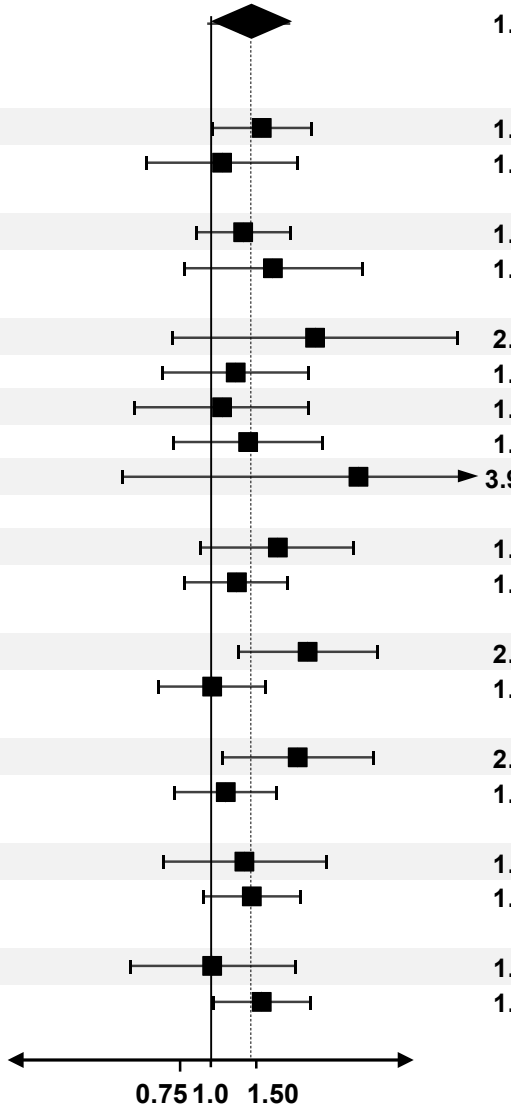
# Safety



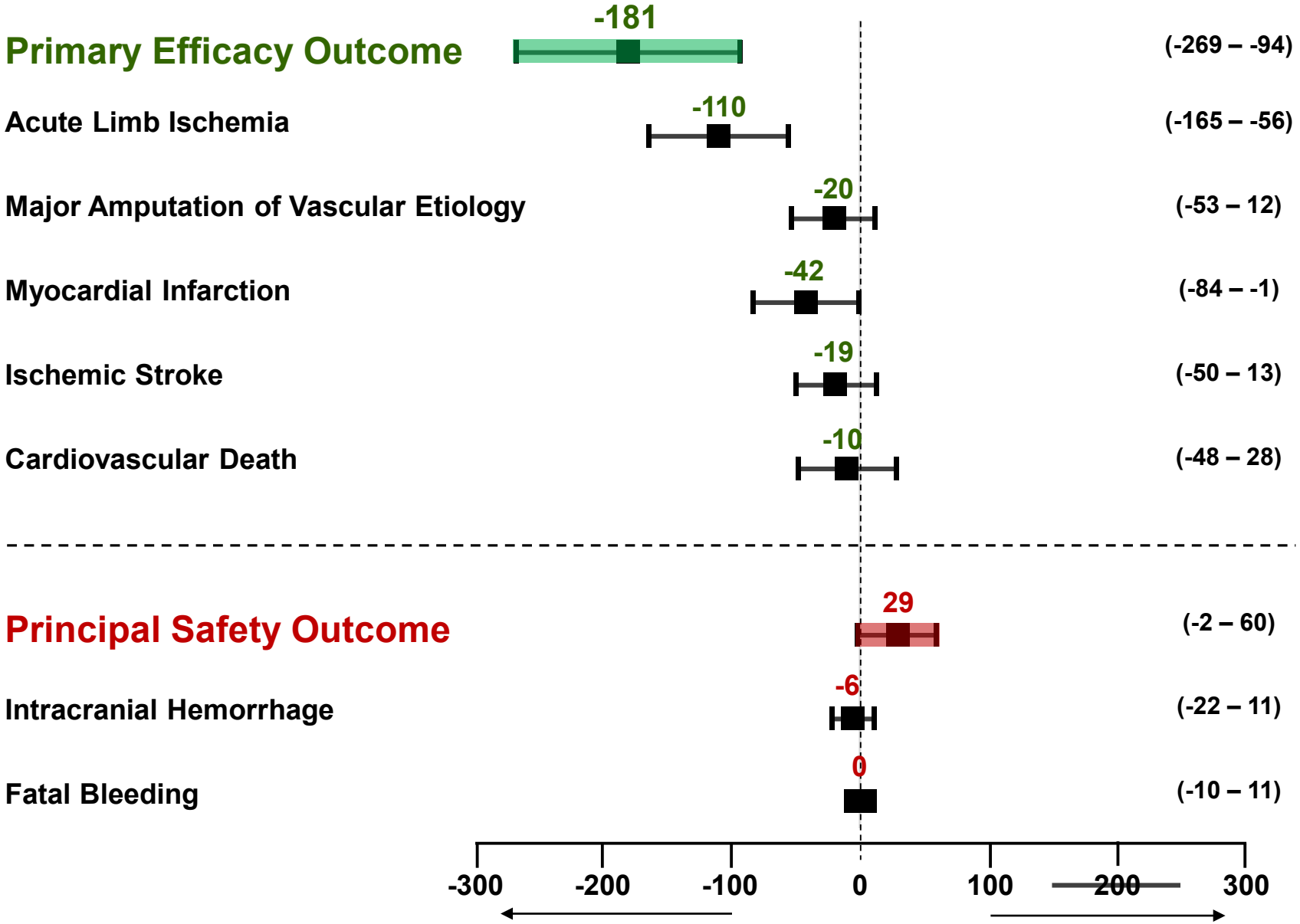

*ARI – absolute risk increase, NNH number needed to harm*

# Principal Safety Outcome in Selected Subgroups

| *Characteristic* | | Rivaroxaban 2.5 mg bid plus ASA daily n/N (%) | Placebo bid plus ASA daily n/N (%) | HR (95% CI) | *P-Interaction* |
|---|---|---|---|---|---|
| All subjects | | 1.9 | 1.4 | 1.43 ( 0.97, 2.10) | |
| Age | | | | | |
| | < 75 | 1.8 | 1.1 | 1.60 ( 1.01, 2.55) | 0.3807 |
| | ≥ 75 | 2.4 | 2.3 | 1.11 ( 0.55, 2.26) | |
| Sex | | | | | |
| | Male | 1.9 | 1.5 | 1.35 ( 0.87, 2.10) | 0.5974 |
| | Female | 1.8 | 1.1 | 1.79 ( 0.78, 4.09) | |
| Region | | | | | |
| | North America | 2.4 | 0.9 | 2.65 ( 0.70, 9.99) | 0.9858 |
| | Western Europe | 2.1 | 1.7 | 1.26 ( 0.64, 2.48) | |
| | Eastern Europe | 0.9 | 0.9 | 1.10 ( 0.49, 2.50) | |
| | Asia Pacific | 4.0 | 2.9 | 1.41 ( 0.71, 2.81) | |
| | South America | 1.7 | 0.4 | 3.95 ( 0.44, 35.38) | |
| eGFR (ml/min/1.73m$^2$) | | | | | |
| | < 60 | 3.2 | 1.8 | 1.86 ( 0.92, 3.79) | 0.3726 |
| | ≥ 60 | 1.5 | 1.2 | 1.27 ( 0.79, 2.05) | |
| Diabetes mellitus | | | | | |
| | Yes | 2.4 | 1.0 | 2.45 ( 1.28, 4.69) | 0.0334 |
| | No | 1.6 | 1.6 | 1.01 ( 0.61, 1.66) | |
| Coronary artery disease | | | | | |
| | Yes | 2.4 | 1.1 | 2.24 ( 1.10, 4.56) | 0.1245 |
| | No | 1.7 | 1.5 | 1.15 ( 0.72, 1.84) | |
| Critical Limb Ischemia | | | | | |
| | Yes | 2.0 | 1.6 | 1.37 ( 0.64, 2.94) | |
| | No | 1.9 | 1.3 | 1.47 ( 0.94, 2.30) | |
| Qualifying procedure | | | | | |
| | Surgical | 1.2 | 1.1 | 1.02 ( 0.47, 2.19) | 0.3155 |
| | Endovascular | 2.3 | 1.5 | 1.60 ( 1.02, 2.51) | |



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




*Efficacy and safety on-treatment

# 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***

The NEW ENGLAND JOURNAL of MEDICINE

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., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., 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.

**Slides for Download at:**
**https://cpcclinicalresearch.org/ @cpcresearch**

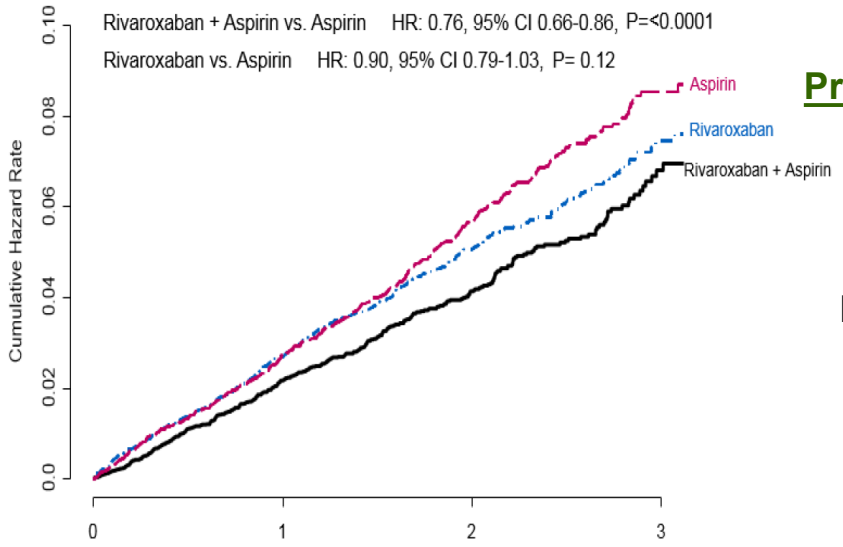
# Backup Slides

VOYAGER PAD

COMPASS

## 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***




**In PAD Subgroup**

**Primary Endpoint MACE**
**HR 0.72**
**(0.57-0.90)**

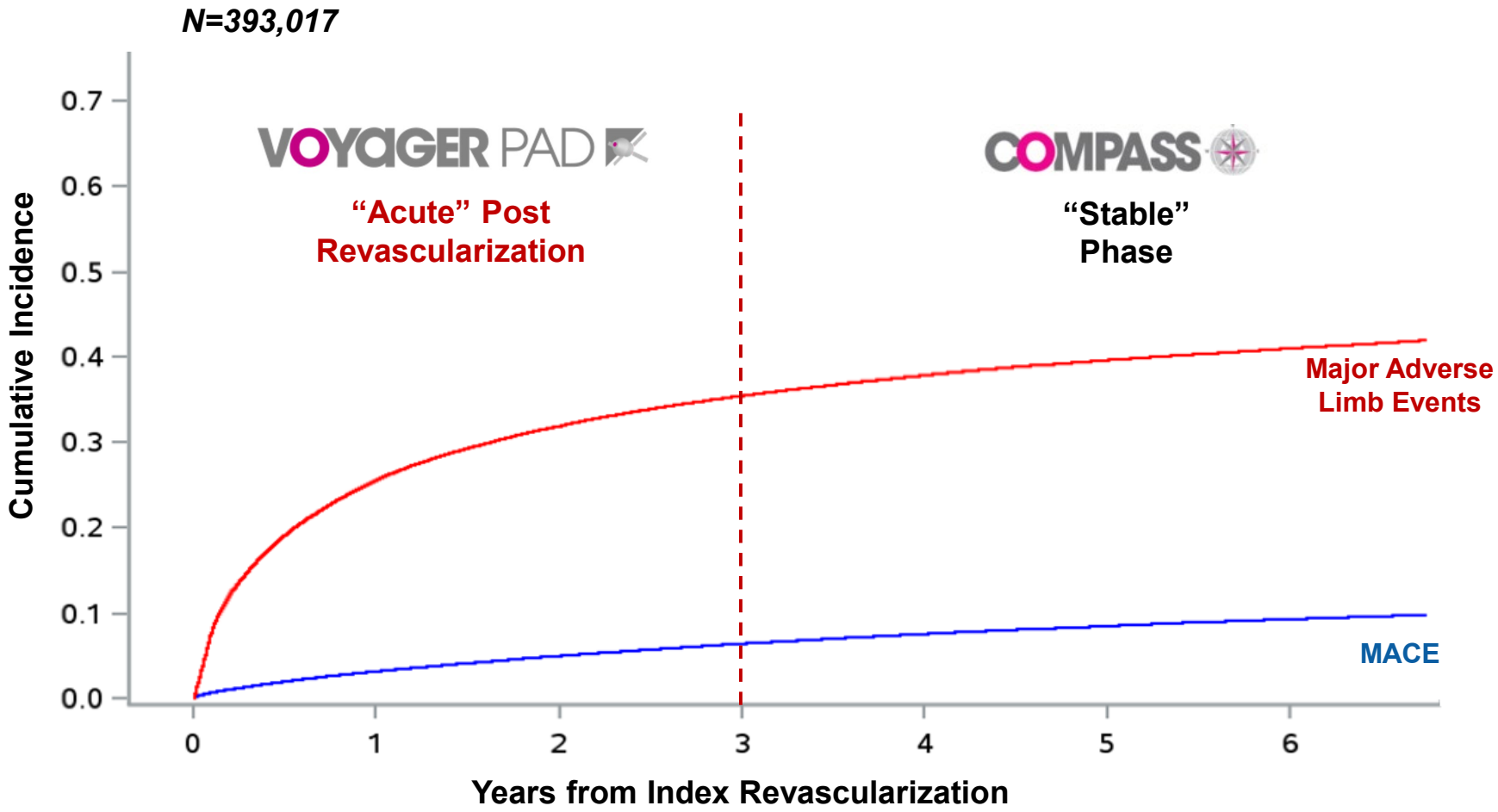
**Safety**
**ISTH major bleeding**
**HR 1.61**
**(1.12 – 2.31)**

- **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




Hess…Hiatt et al. JACC 2020

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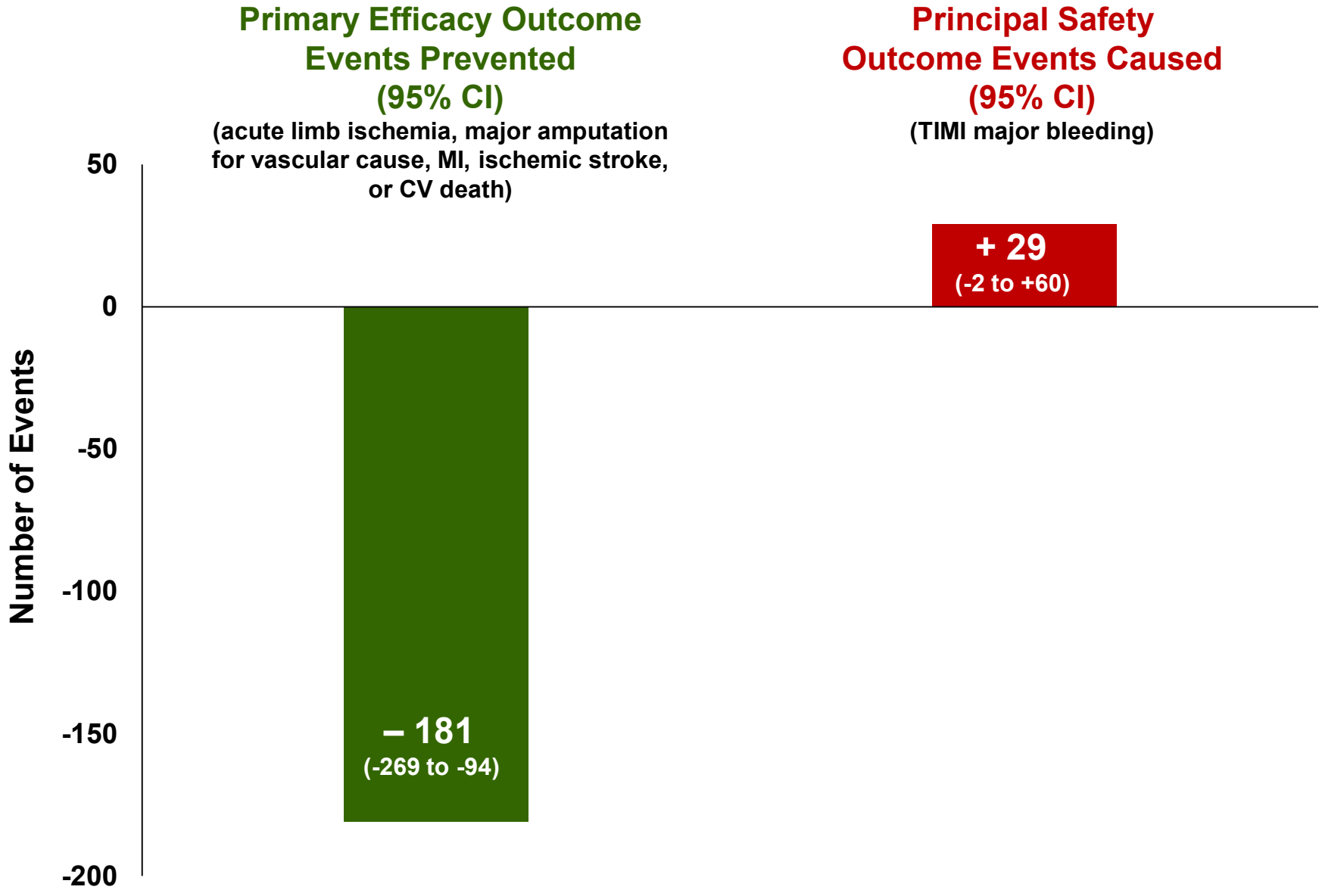
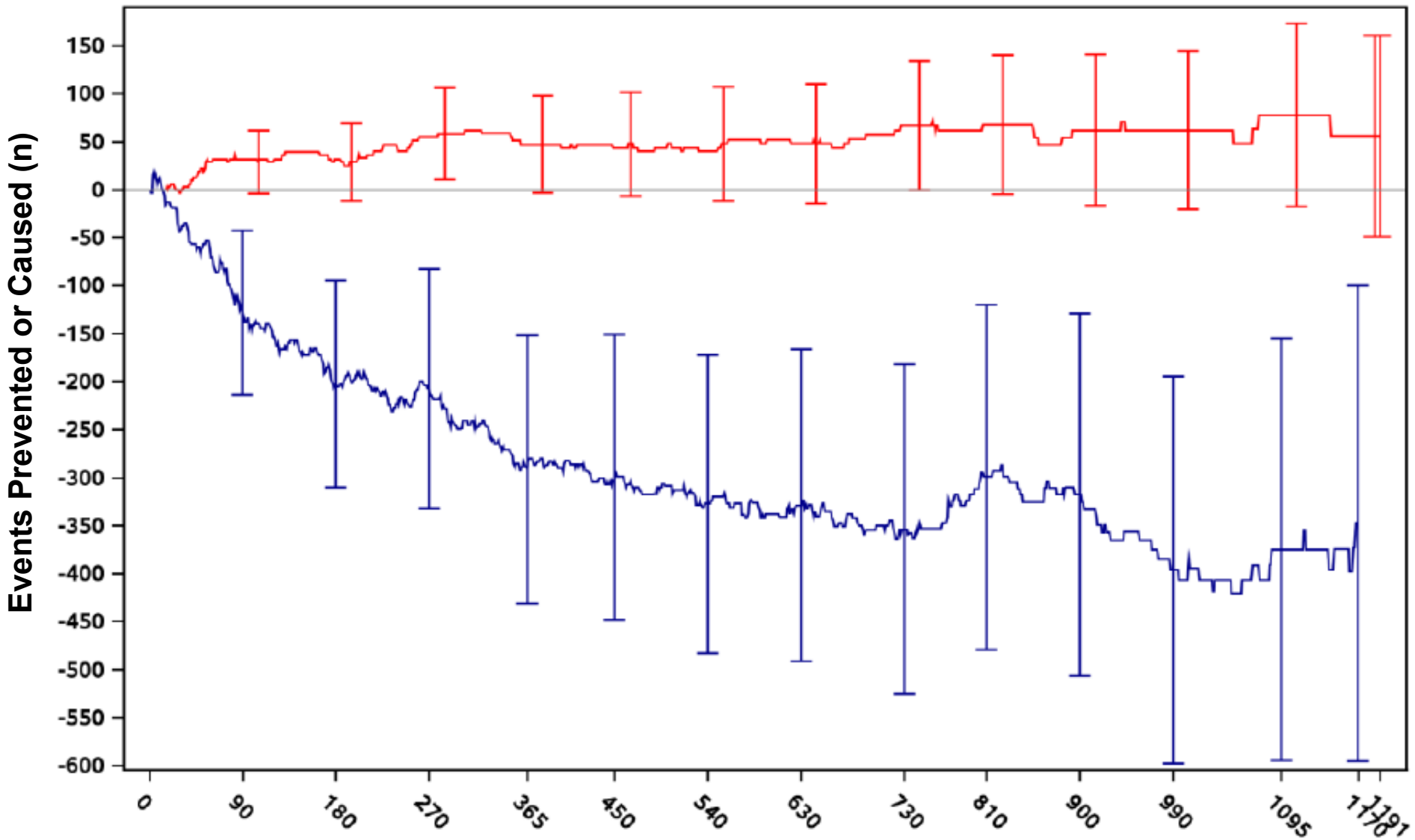



*Efficacy and safety on-treatment

# Risk & Benefit Over Time

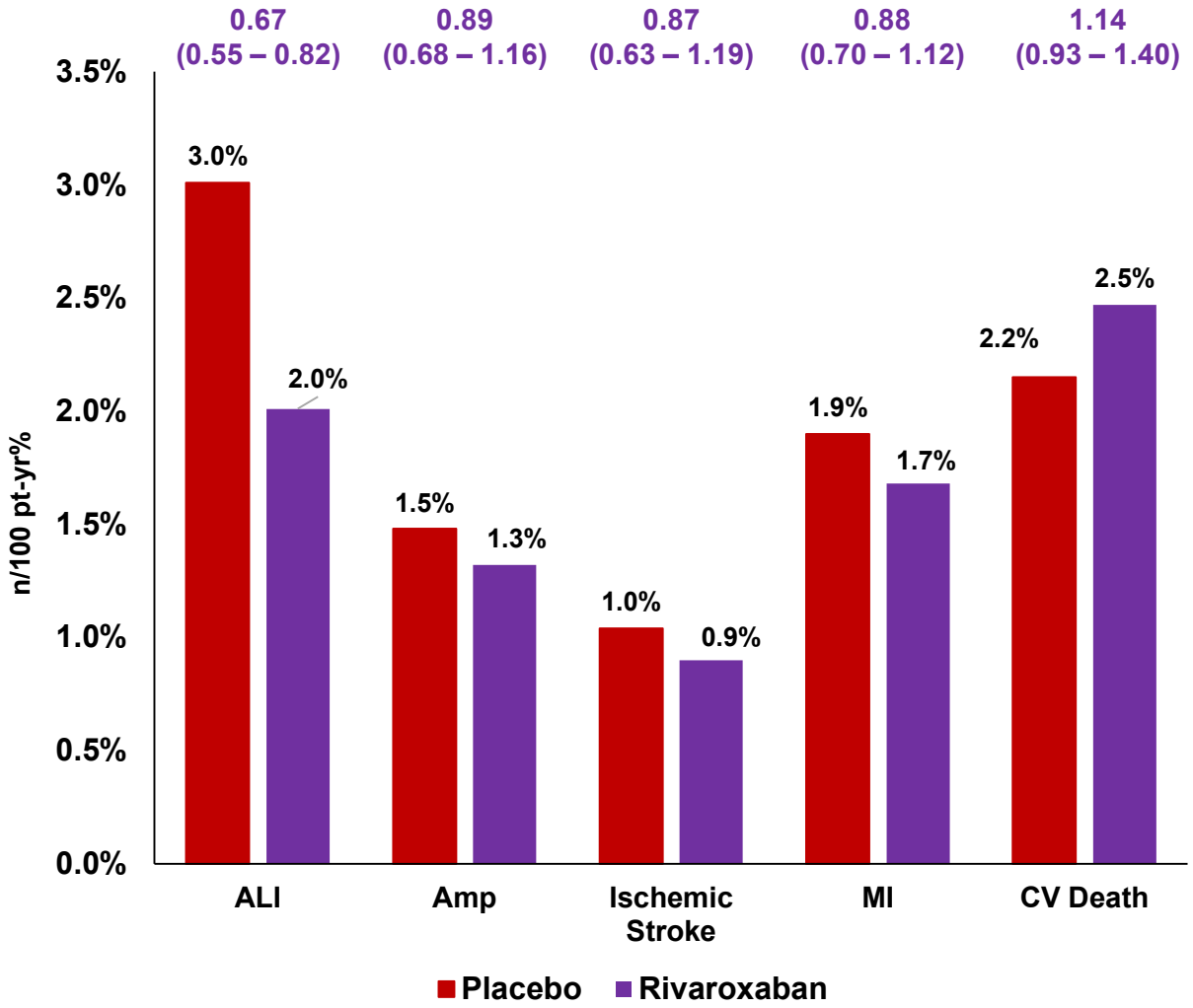



**TIMI major bleeding**

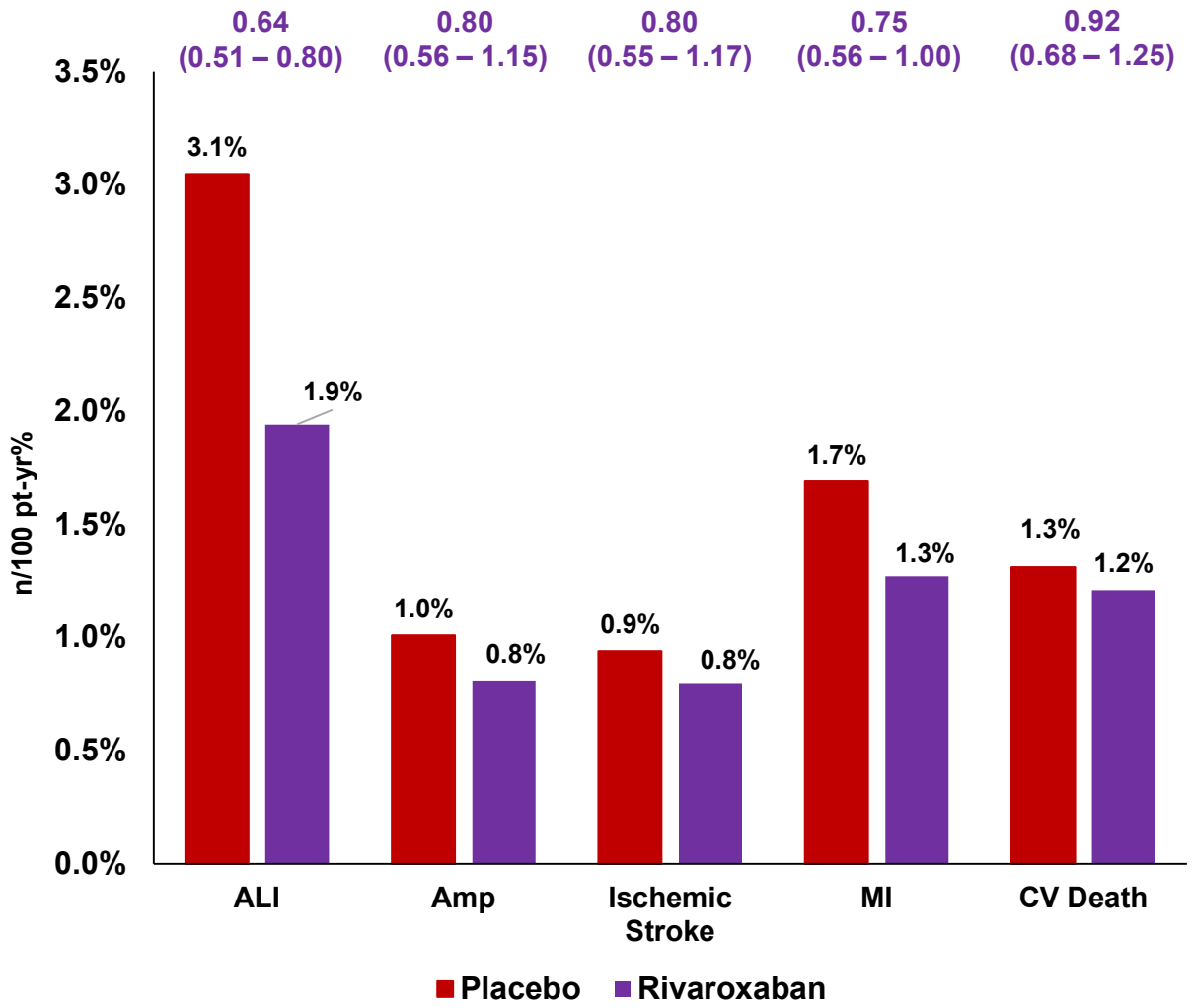
**Primary endpoint composite of acute limb ischemia, major amputation of vascular cause, MI, ischemic stroke or CV death**

# Efficacy – Intention To Treat versus & Treatment

## Intention To Treat



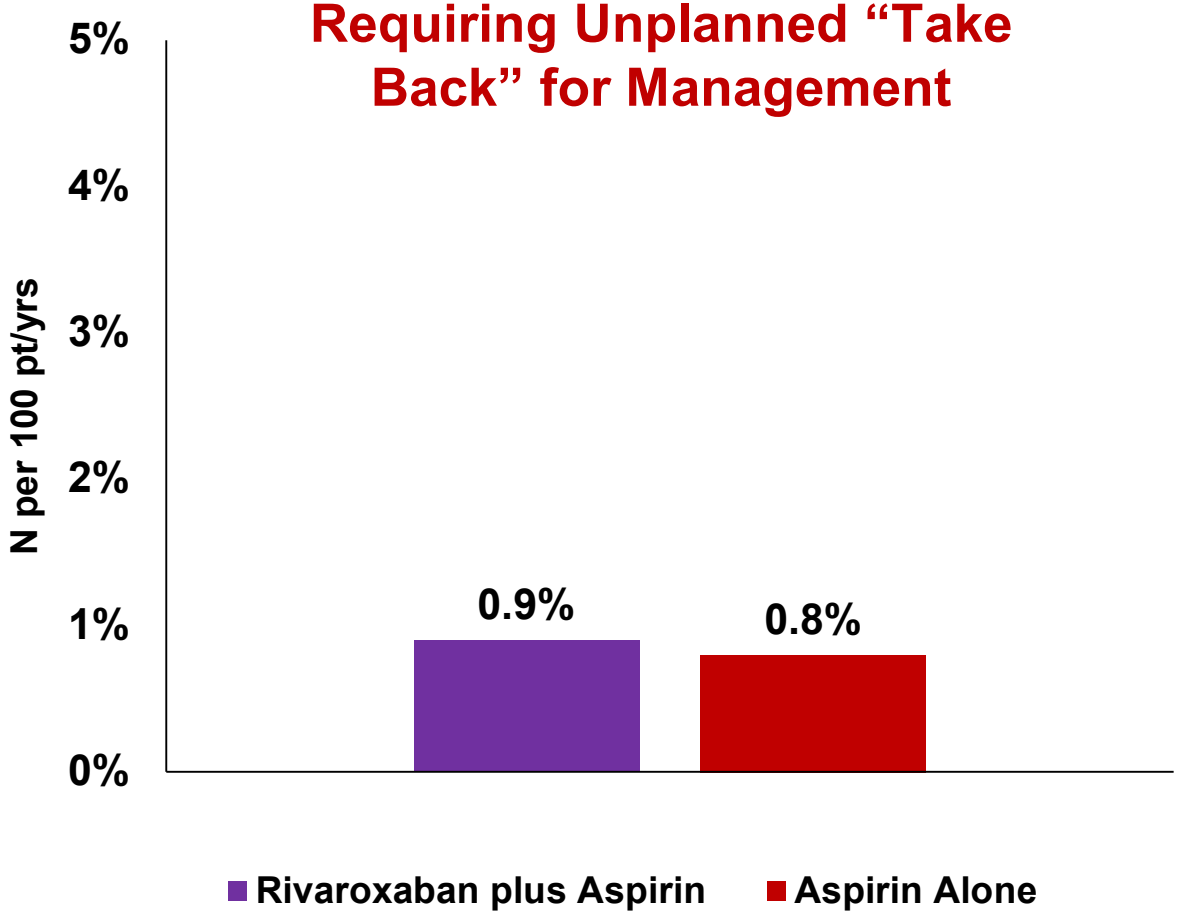

## On Treatment*



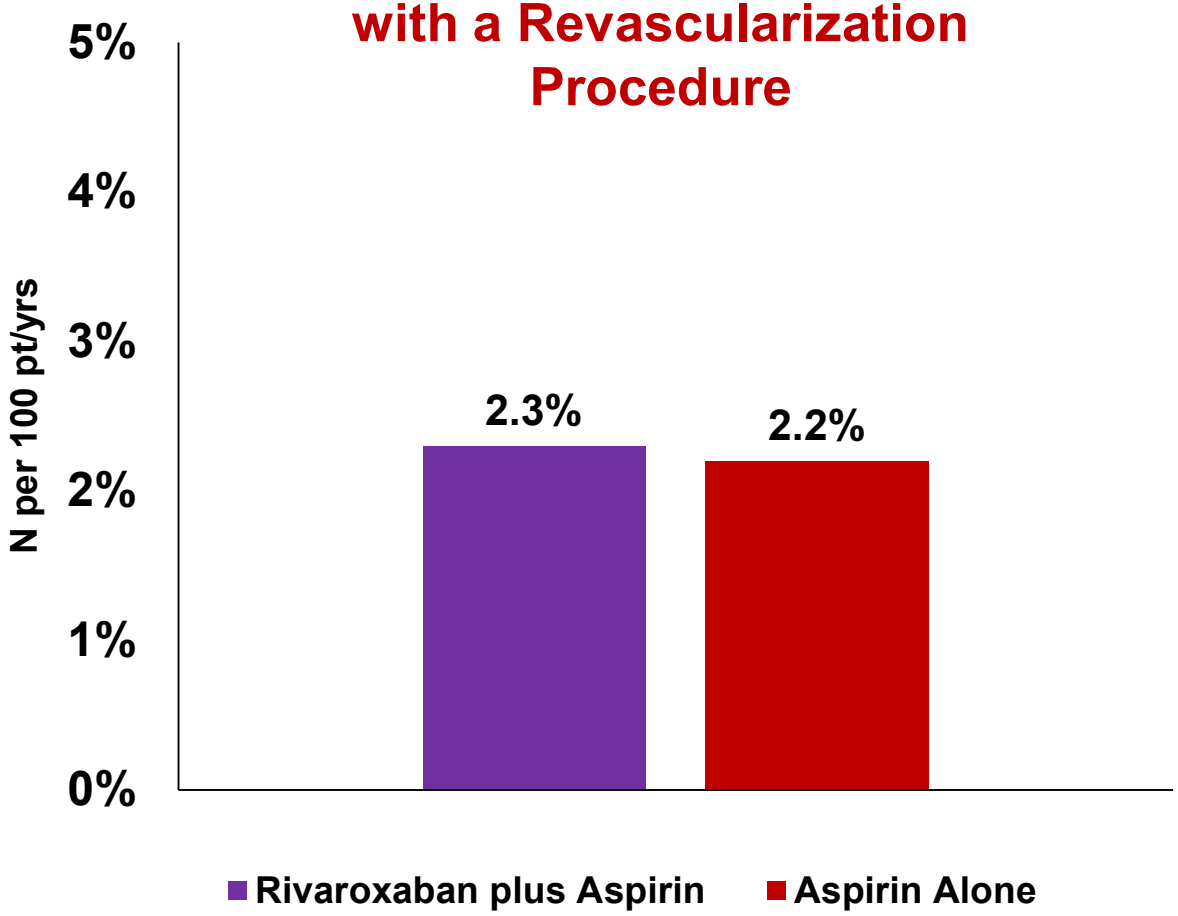

**includes events from randomization until 2 days following permanent drug discontinuation*

# Procedural Bleeding

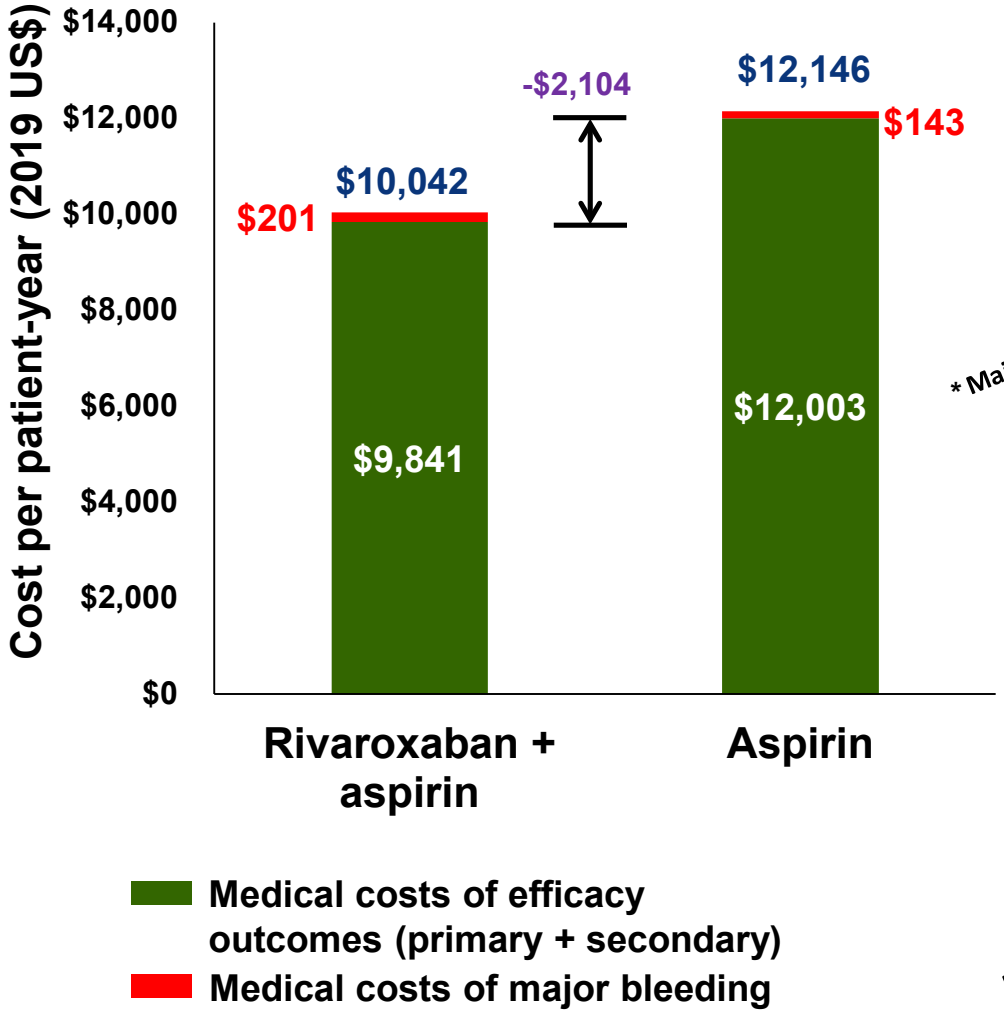
## Post-Procedural Bleeding Requiring Unplanned "Take Back" for Management

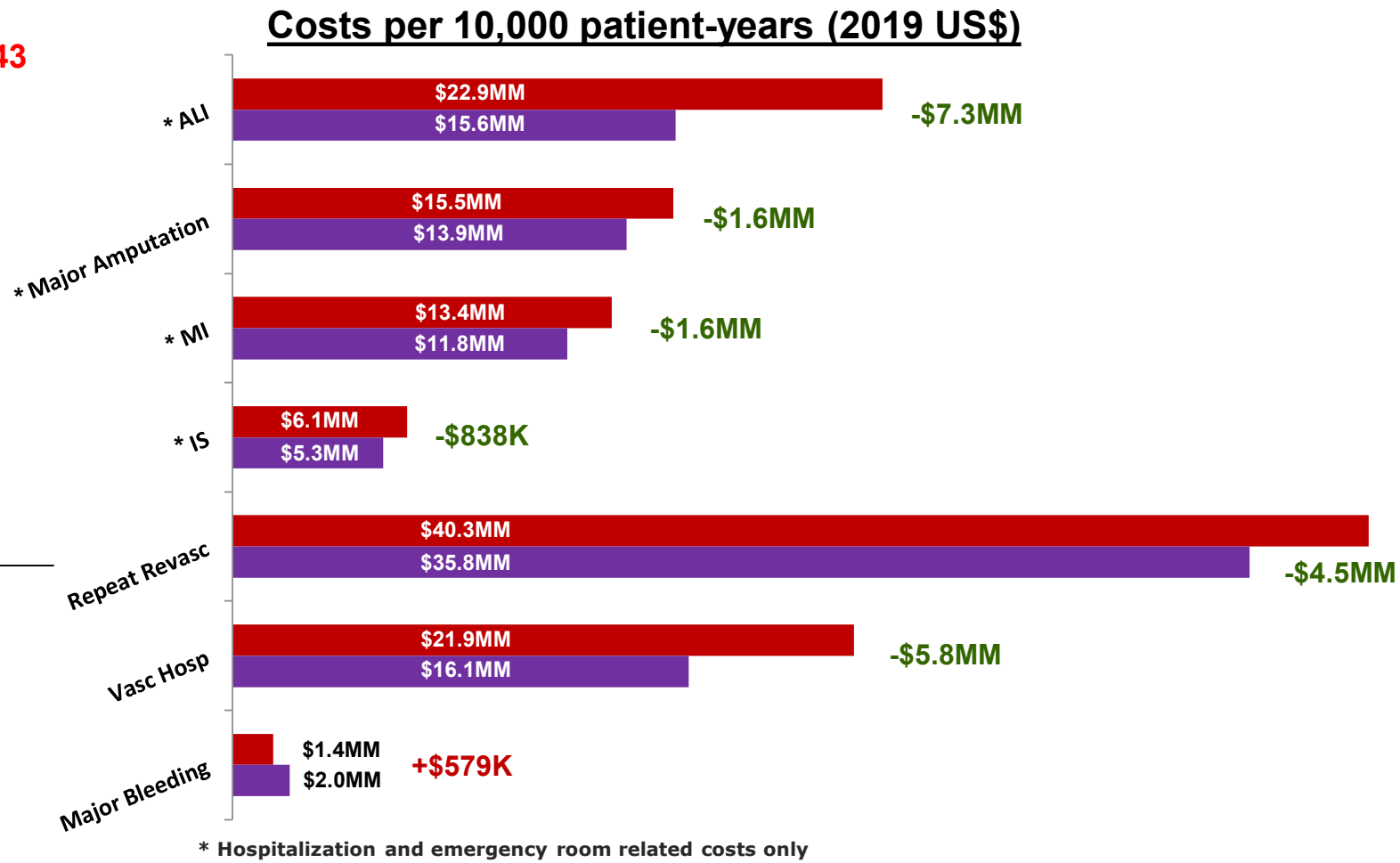



## Any Bleeding Associated with a Revascularization Procedure



# Medical Cost Reduction with Rivaroxaban versus Placebo Per Year



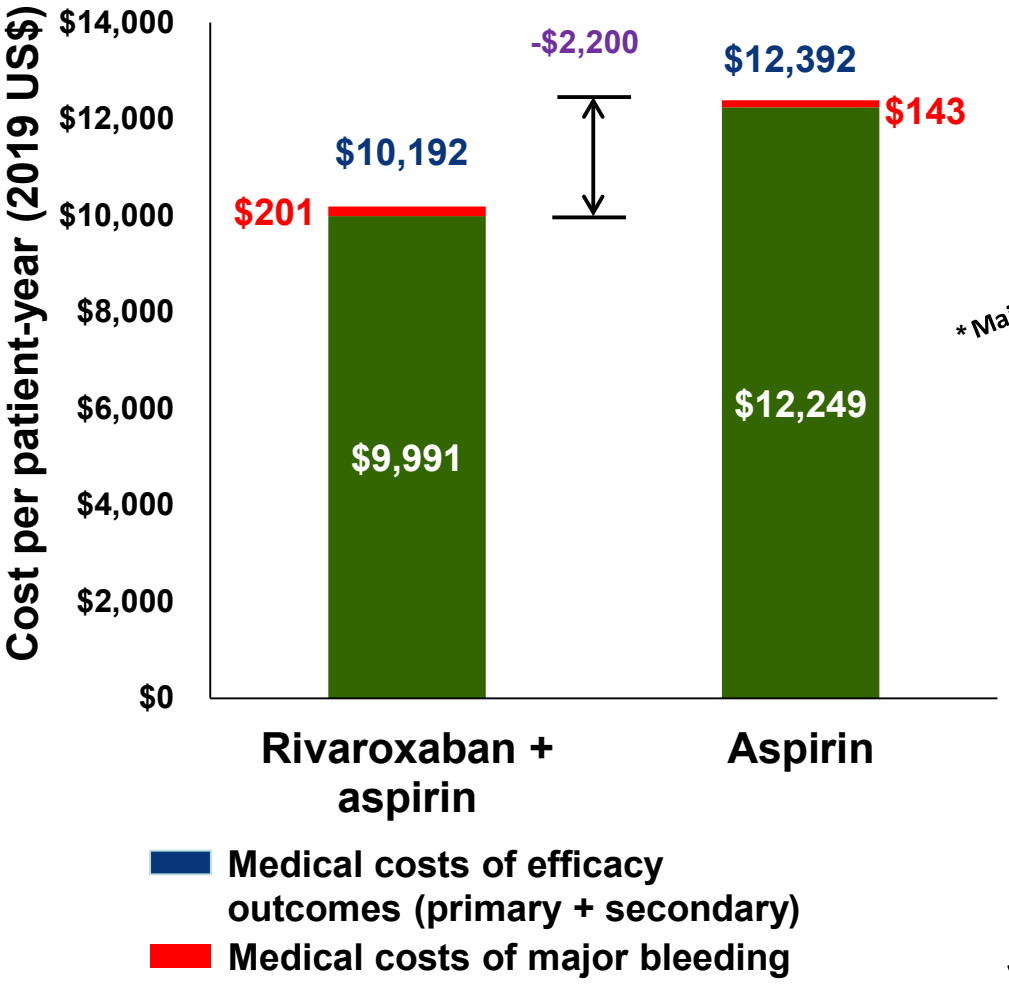

* Hospitalization and emergency room related costs only

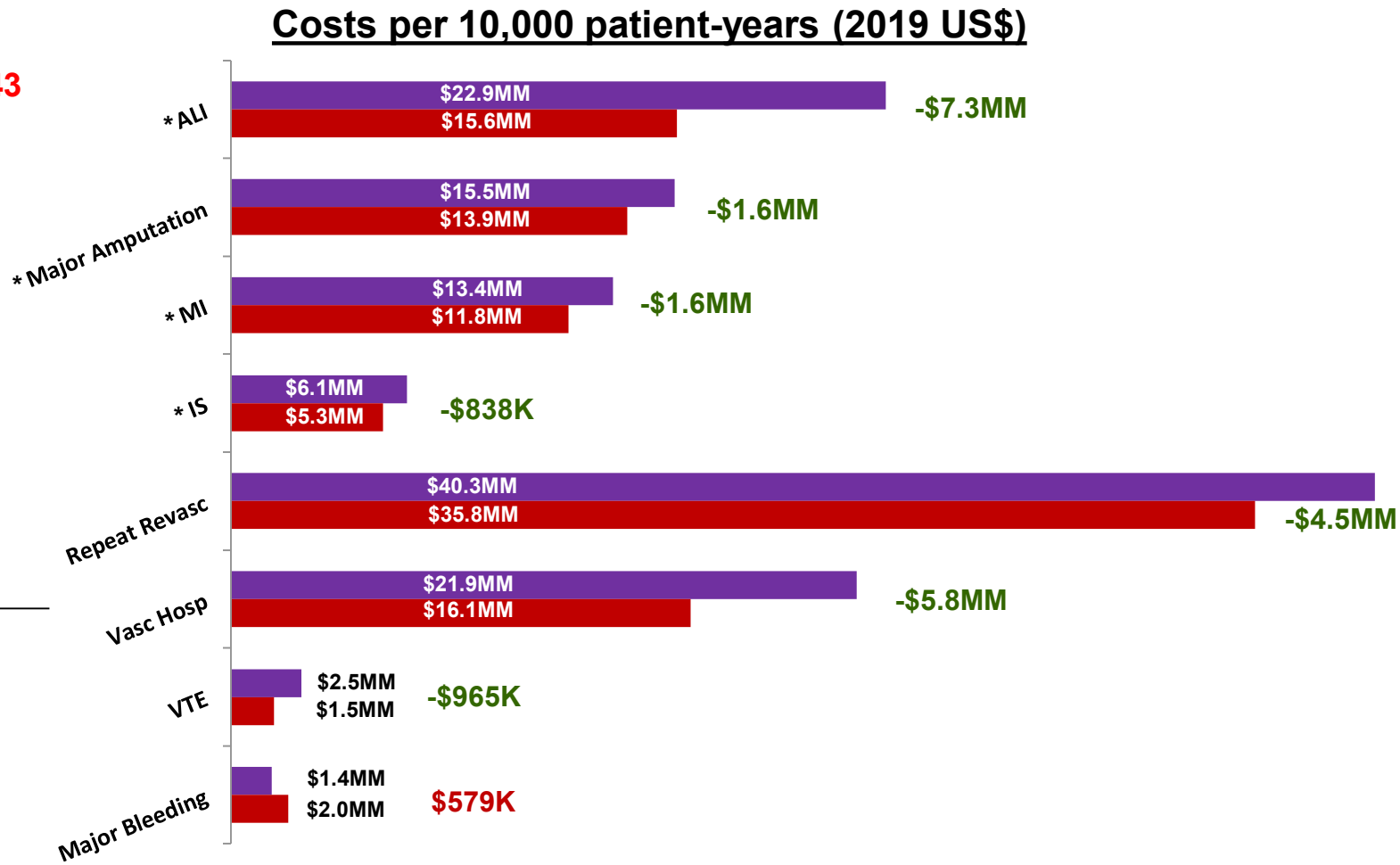
**Total medical costs reduced = $21MM per 10,000 patient-years**

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

PAD, peripheral artery disease; ALI, acute limb ischemia; MI, myocardial infarction; IS, ischemic stroke; Revasc, revascularization; Vas Hosp, vascular hospitalization; WAC, wholesale acquisition cost.

# Medical Cost Reduction with Rivaroxaban versus Placebo Per Year

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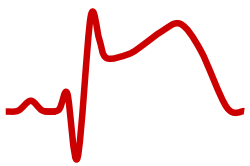
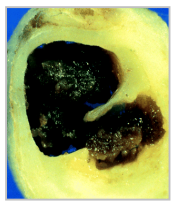
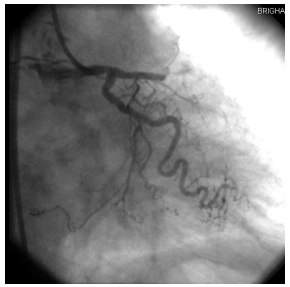
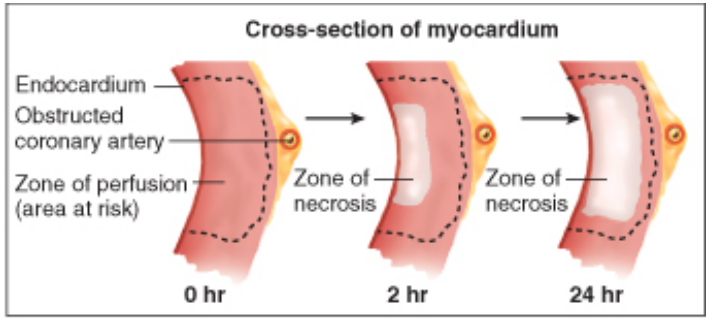
# STEMI







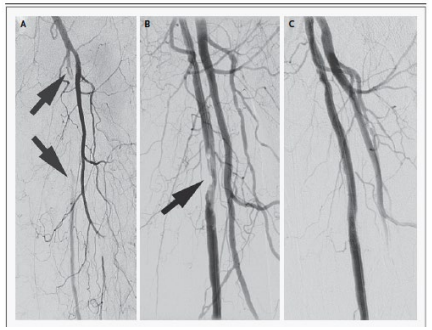
- Acute thrombotic occlusion of an artery threatening tissue loss
- "Time Is Muscle"
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication






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

# 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]

1. Zeymer et al. EORP EU STEMI Registry 2019

2. Bonaca et al. Circulation 2016