My ESVS Month Presentation

Debus Sebastian

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Disclosures

- ❑ X I have the following potential conflicts of interest to report:
  - ❑ X Receipt of grants/research support
  - ❑ X Receipt of honoraria and travel support in my task as executive member of the VOYAGER PAD Trial
  - ❑ Participation in a company sponsored speakers‘ bureau
  - ❑ Employment in industry
  - ❑ Shareholder in a healthcare company
  - ❑ Owner of a healthcare company

- ❑ I do not have any potential conflict of interest

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Effect of Rivaroxaban and Aspirin versus Aspirin alone in Patients with Peripheral Artery Disease undergoing surgical revascularization: Insights from the VOYAGER PAD trial

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

European Society for Vascular Surgery (ESVS) Virtual Scientific Sessions 2020
Late-Breaking Clinical Trial
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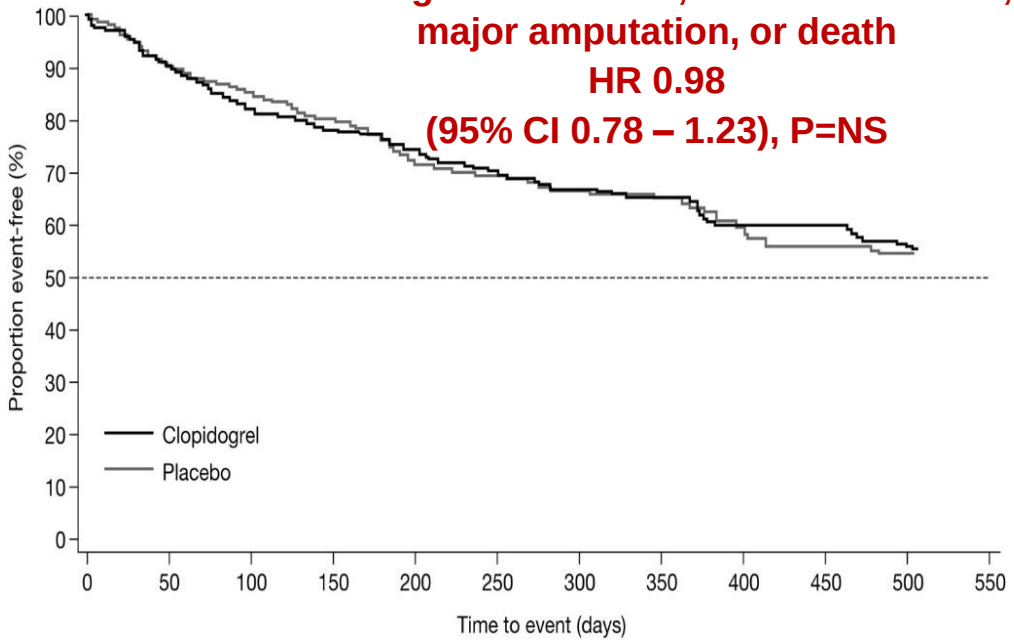
An Academic Research Organization Affiliated with the University of Colorado School of Medicine

Background

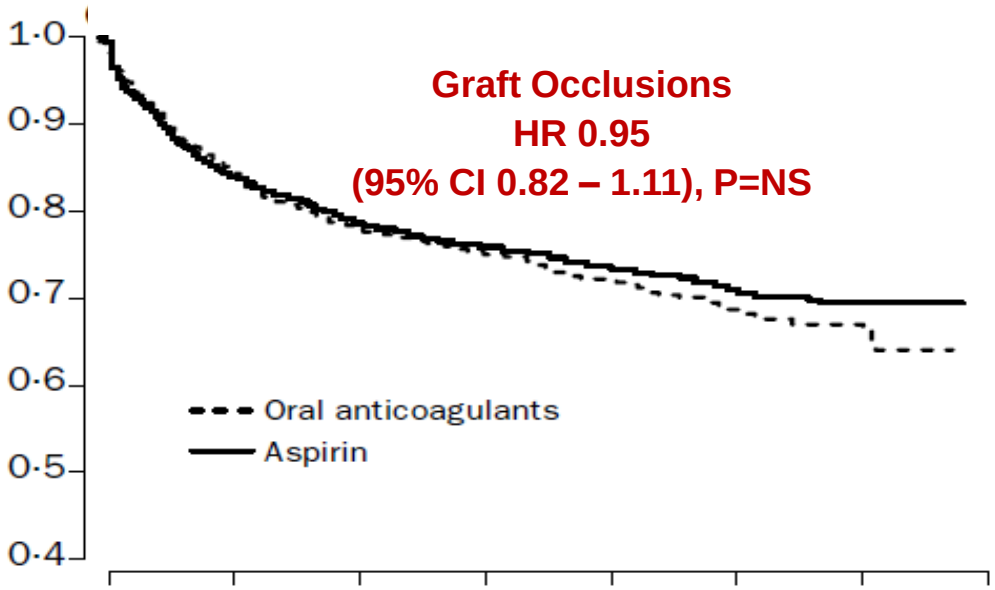
Despite high risk, <u>there is no proven antithrombotic strategy</u> that has demonstrated efficacy for <u>reducing major adverse limb and cardiovascular events after surgical revascularization for ischemia in symptomatic peripheral artery disease</u>

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



DAPT with Aspirin and Clopidogrel
GUSTO moderate or severe 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)

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

Trial Design: VOYAGER PAD

Vascular **O**utcomes Stud**Y** of **A**SA Alon**G** with Rivaroxaban in **E**ndovascular or Surgical Limb **R**evascularization for **PAD (VOYAGER PAD):**

NCT02504216

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

**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 Endpoint: TIMI Major Bleeding

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

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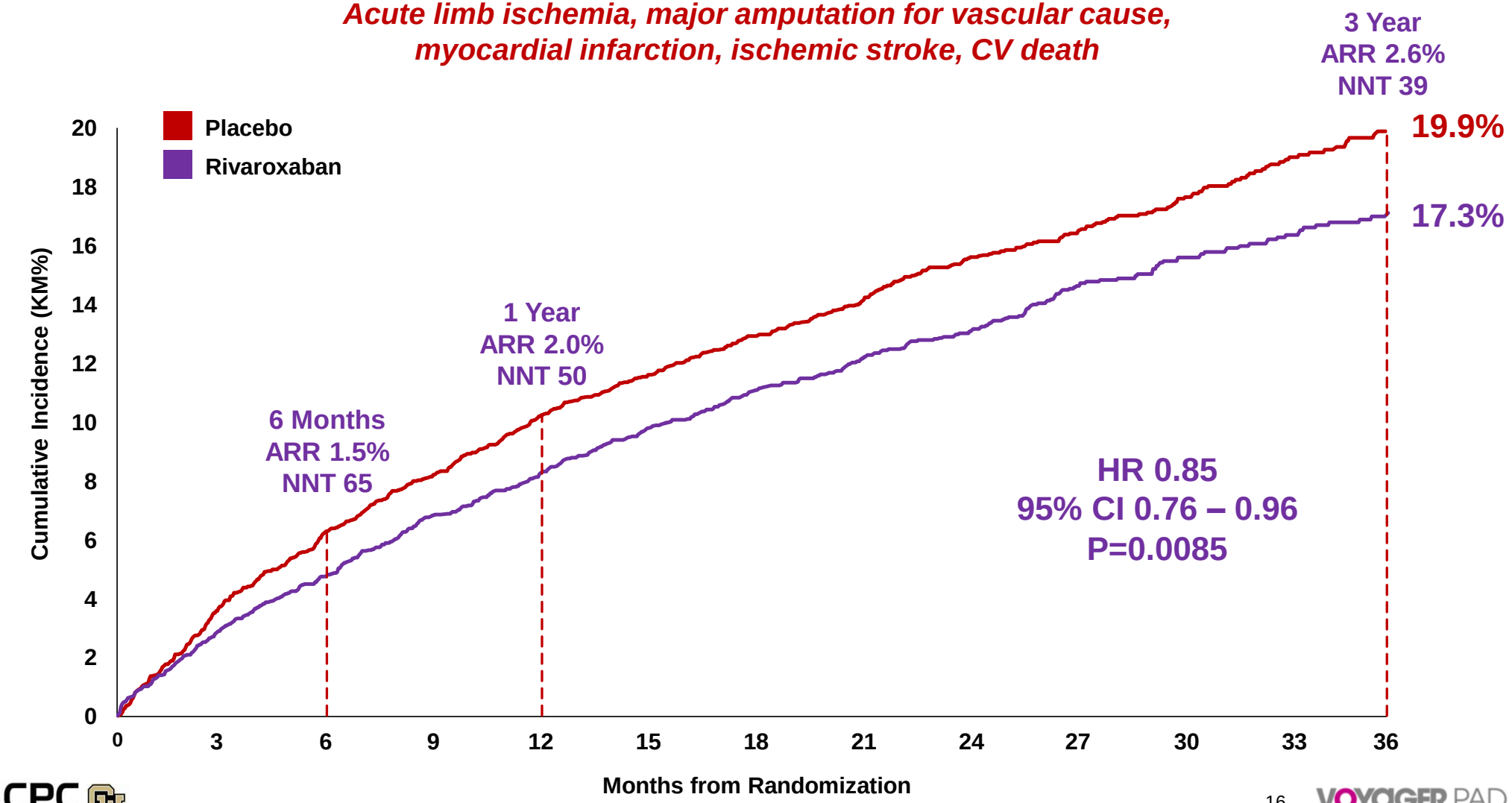
Primary Endpoint

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



ARR – absolute risk reduction, NNT number needed to treat

Bonaca MP…Hiatt WR. NEJM 2020

Objective and Methods

- To evaluate whether the efficacy and safety of rivaroxaban after revascularization for symptomatic PAD is consistent regardless of the approach to revascularization
- The approach (surgical vs. endovascular or hybrid) reported at randomization
- Primary efficacy outcome composite of acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, CV death, principle safety outcome TIMI major bleeding
- COX model with interaction terms to assess for heterogeneity of efficacy and safety of rivaroxaban by prior LER status

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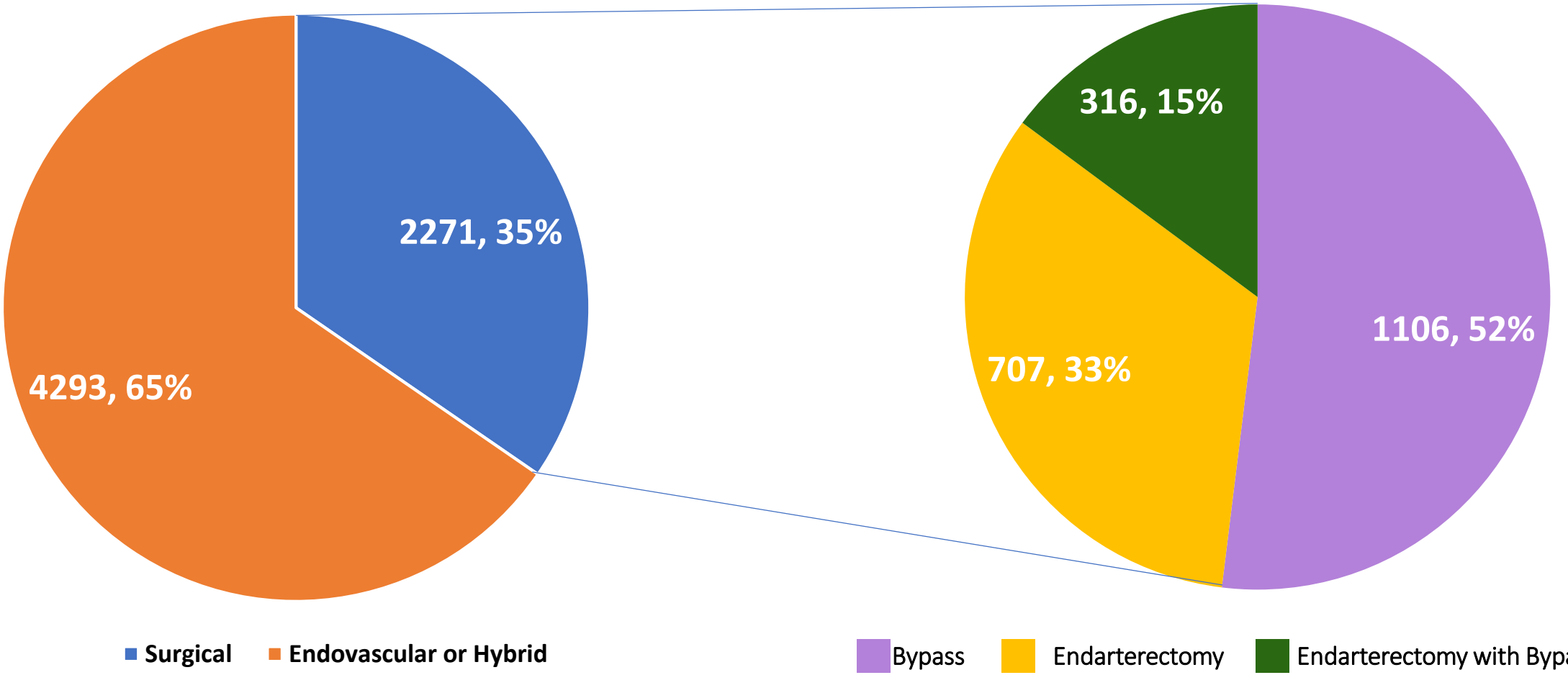
Distribution of Surgical Revascularizations



*This excludes 136 patients who underwent Endo/Hybrid procedures despite IxRS designation to Surgery (45 Endo, 91 Hybrid)

Baseline Characteristics

Characteristic	Surgical N=2271	Endovascular N=4293	P value
Age & Gender – n (%)			
Mean age – Yrs (SD)	66 (8.1)	68 (8.6)	<0.001
Female	466 (20.5)	1238 (28.8)	<0.001
Medical History – n (%)			
Hypertension	1825 (80.4)	3517 (81.9)	0.134
Diabetes Mellitus	709 (31.2)	1920 (44.7)	<0.001
Hyperlipidemia	1173 (51.7)	2766 (64.4)	<0.001
Chronic Kidney Disease	99 (4.4)	507 (11.8)	<0.001
Current Smoker	837 (36.9)	1442 (33.6)	<0.001
Cardiac Disease – n (%)			
Coronary Artery Disease	680 (29.9)	1387 (32.3)	0.054
Percutaneous Coronary Intervention	207 (9.1)	645 (15.0)	<0.001
Coronary Artery Bypass Graft	150 (6.6)	384 (8.9)	0.001
Heart Failure	219 (9.6)	320 (7.5)	0.003

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Baseline Medications	Surgical N=2271	Endovascular N=4293	P value
Medication – n/N (%)			
Aspirin (Non-Study)	1317 (58.0)	2951 (68.7)	0.056
Clopidogrel (Baseline)	568 (25.0)	3351 (78.1)	<0.001
Clopidogrel at Randomization	349 (15.4)	2964 (69.0)	<0.001
Dual Anti-Platelet Therapy	268 (11.8)	2299 (53.6)	<0.001
Beta-Blocker	917 (40.4)	1876 (43.7)	0.010
Statin	1740 (76.6)	3509 (81.7)	<0.001
ACE Inhibitor / ARB	1353 (59.6)	2806 (65.4)	<0.001

Geography			P value
Region – n/N (%)			<0.001
North America	152 (6.7)	542 (12.6)	
Western Europe	502 (22.1)	1324 (30.8)	
Eastern Europe	1283 (56.5)	1316 (30.7)	
Asia Pacific	174 (7.7)	787 (18.3)	
South America	160 (7.0)	324 (7.5)	

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PAD Characteristics	Surgical N=2271	Endovascular N=4293	P value
PAD Severity			
ABI at Screening, Mean (SD)	0.47 (0.19)	0.57 (0.18)	<0.001
ABI at 1 Mth Post-Procedure, Mean (SD)	0.87 (0.21)	0.93 (0.18)	<0.001
Critical Limb Ischemia – n/N (%)	696 (30.7)	837 (19.5)	<0.001
Prior Amputation – n (%)	130 (5.7)	260 (6.1)	0.622
Prior Major Amputation	25 (1.1)	40 (0.9)	0.514
Prior Minor Amputation	84 (3.7)	202 (4.7)	0.065
History of Prior Limb Revascularization – n (%)	673 (29.6)	1663 (38.7)	<0.001
Peripheral PTA	398 (17.5)	1510 (35.2)	<0.001
Surgical Bypass	379 (16.7)	283 (6.6)	<0.001
Initiation of Study Drug, Mean Days (SD)	6 (2.5)	4.5 (2.8)	<0.001
Target Lesion Length (cm)			
≥ 15	989 (45.5)	1263 (30.3)	<0.05
5 – < 15	814 (37.4)	1799 (43.1)	<0.05
< 5	373 (17.1)	1111 (26.6)	<0.05

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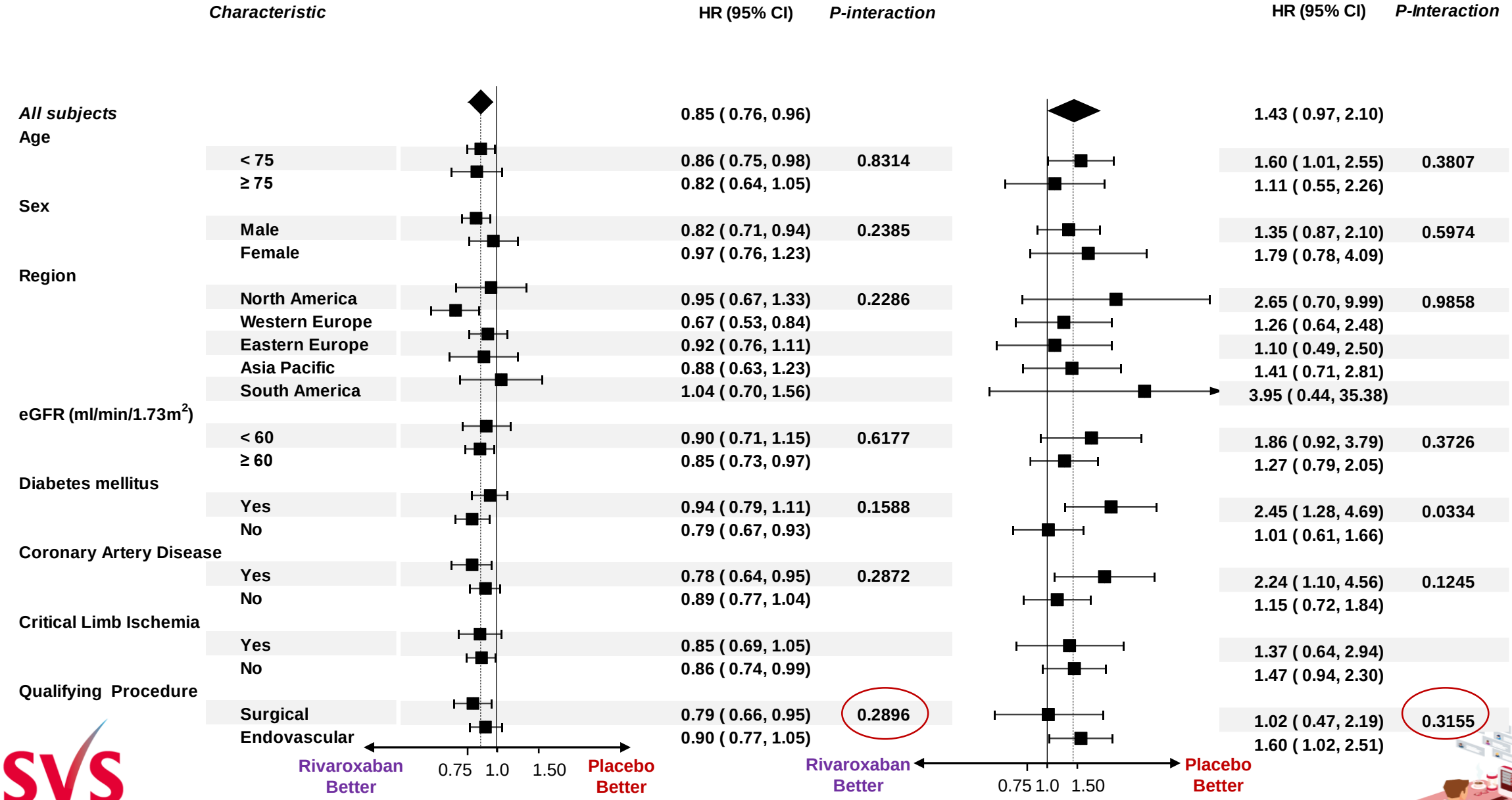
Primary Efficacy and Safety Outcomes by Qualifying Revascularization



Bonaca MP…Hiatt WR *et al. N Engl J Med* 2020;382:1994–2004

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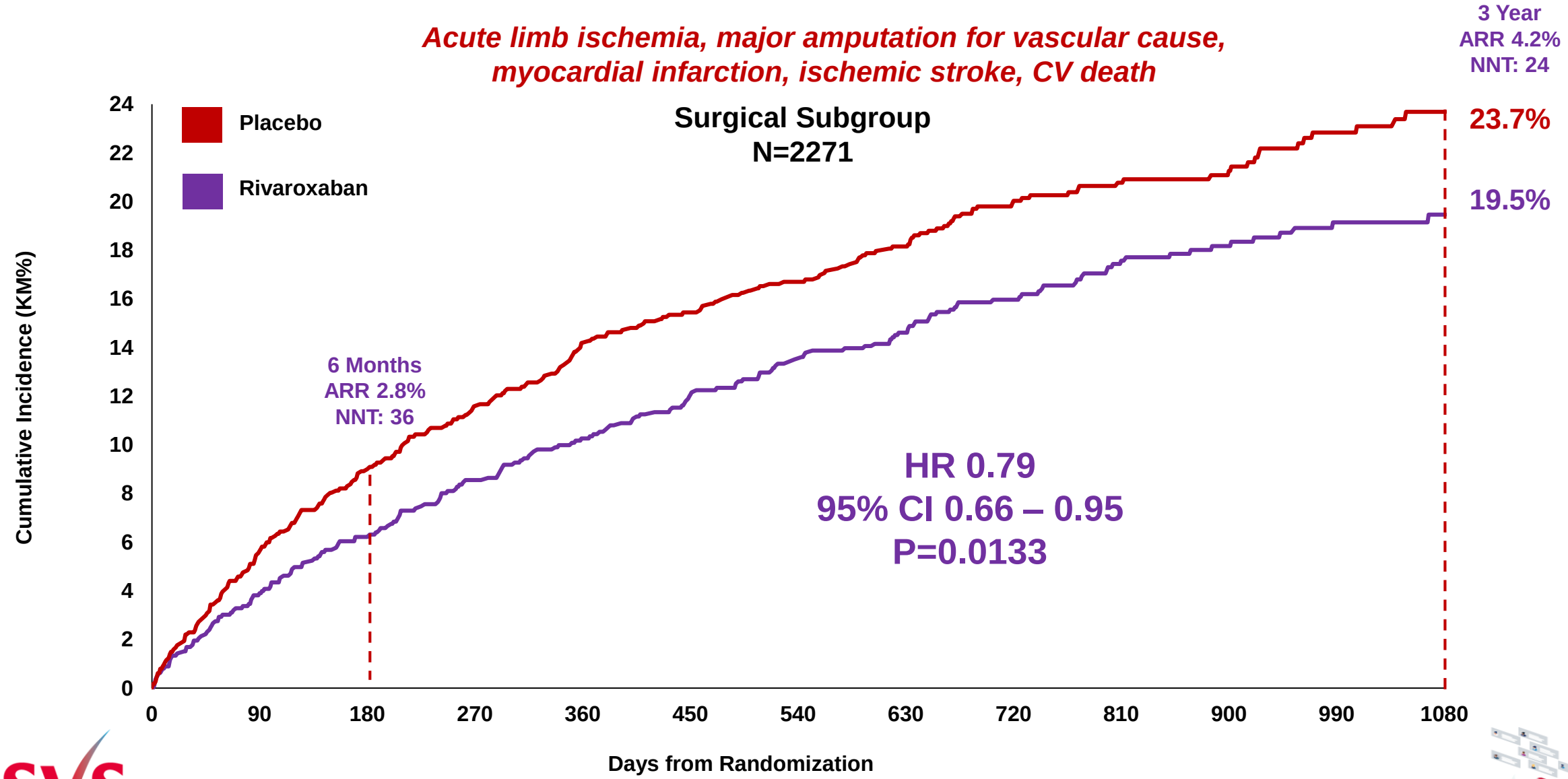
Primary composite endpoint in the Surgical Subgroup

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



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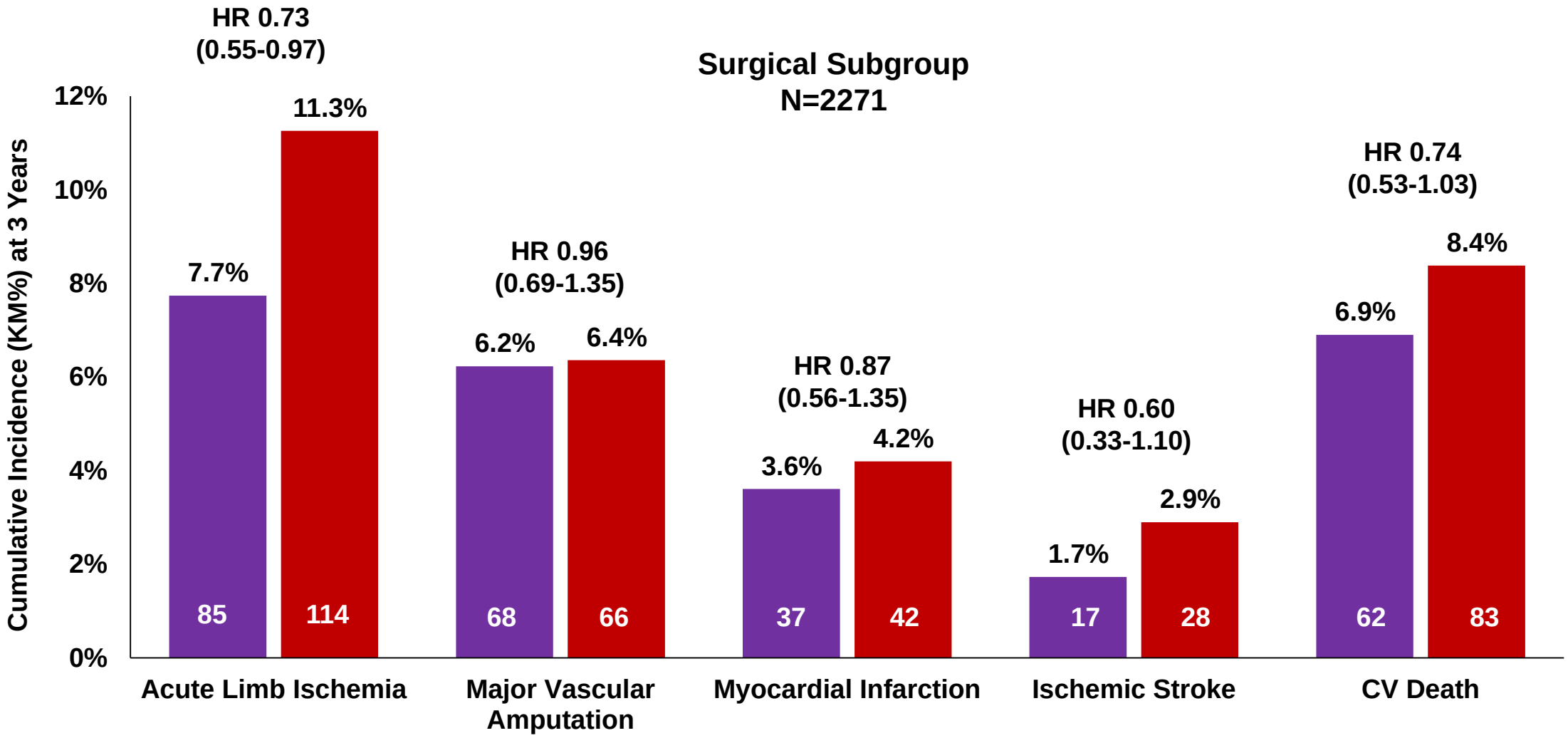
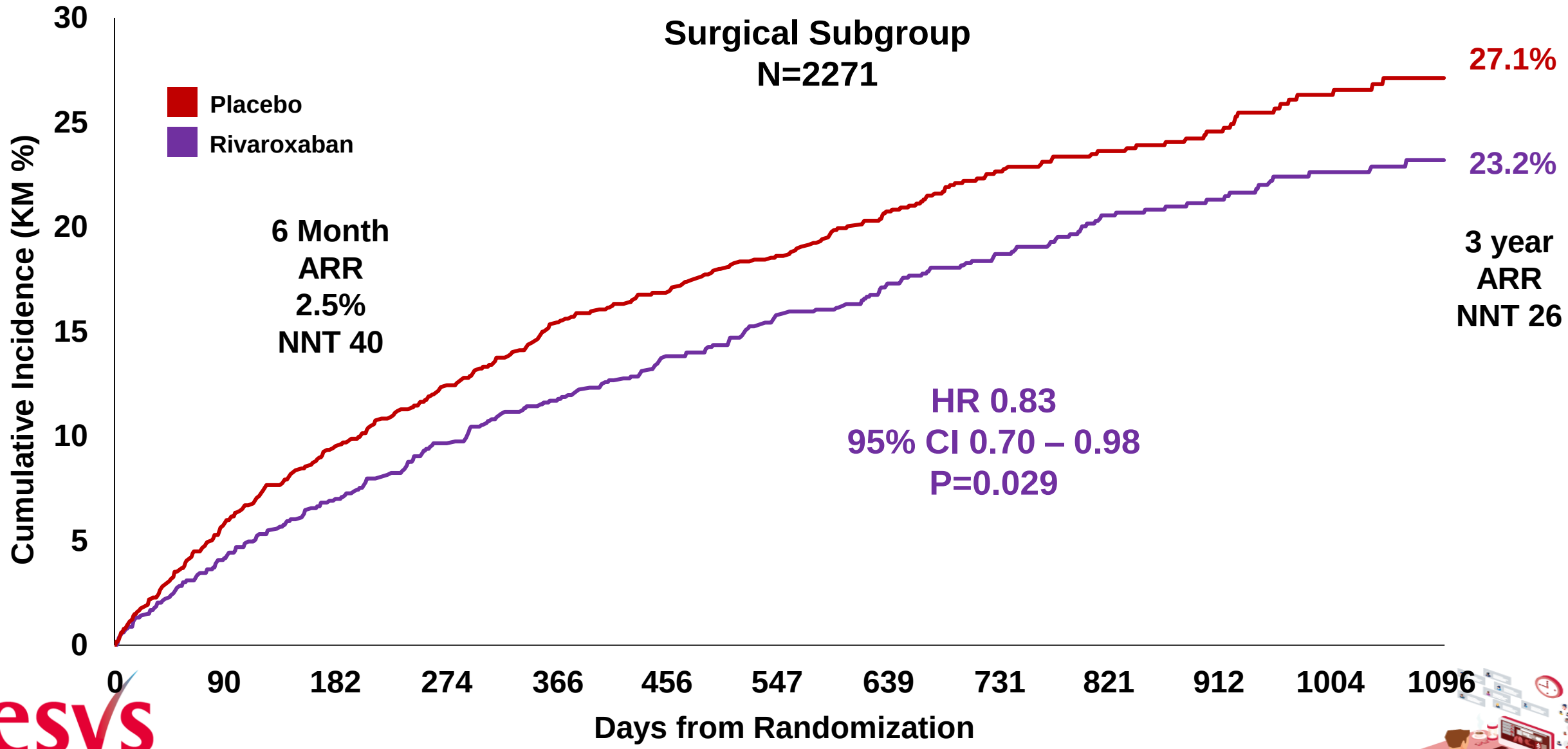
Primary Endpoint Components in the Surgical Subgroup



Event Free Survival* with Rivaroxaban in Surgical Patients



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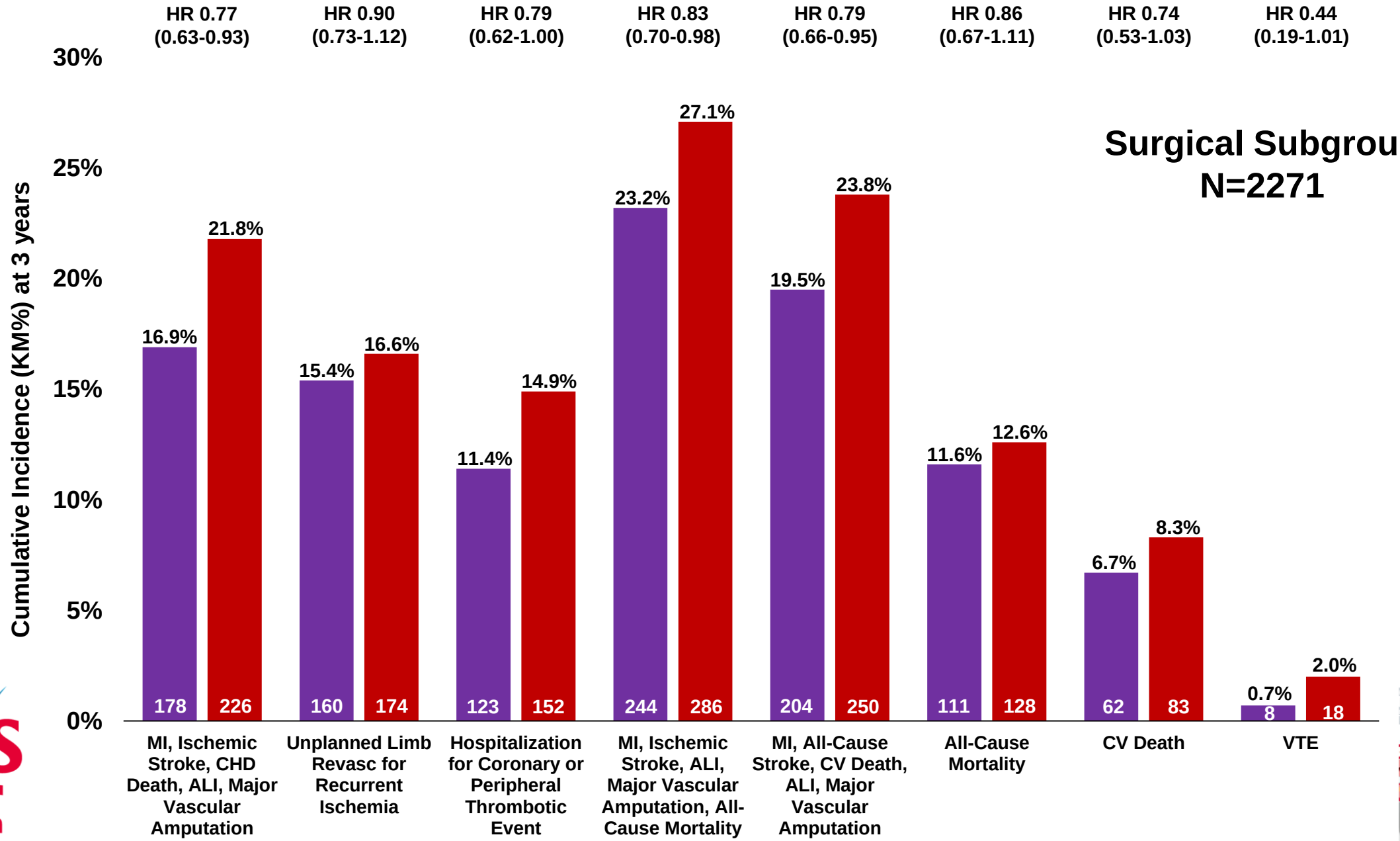
**Acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke or all cause mortality*

Secondary Endpoints in order of Hierarchy



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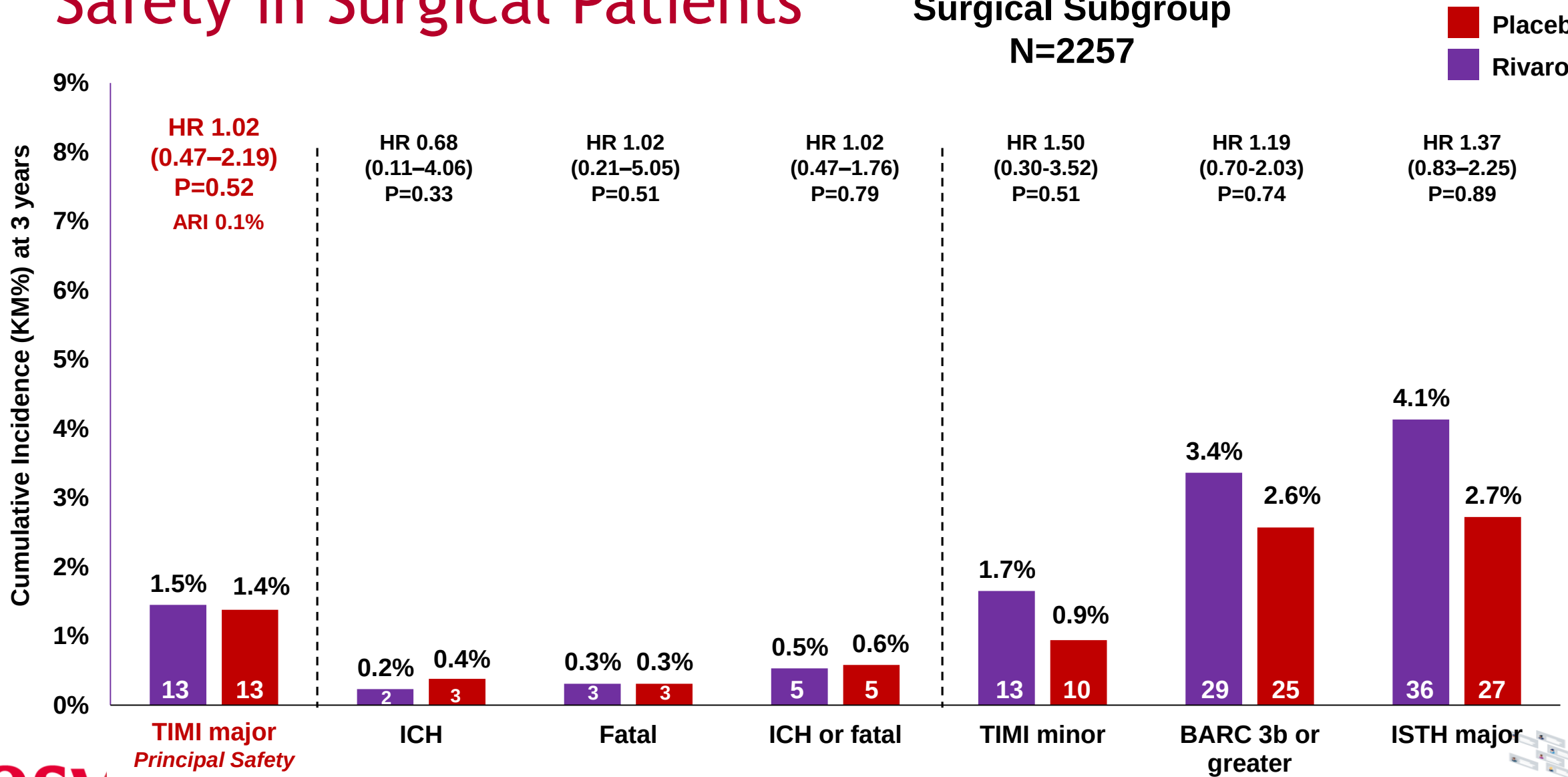
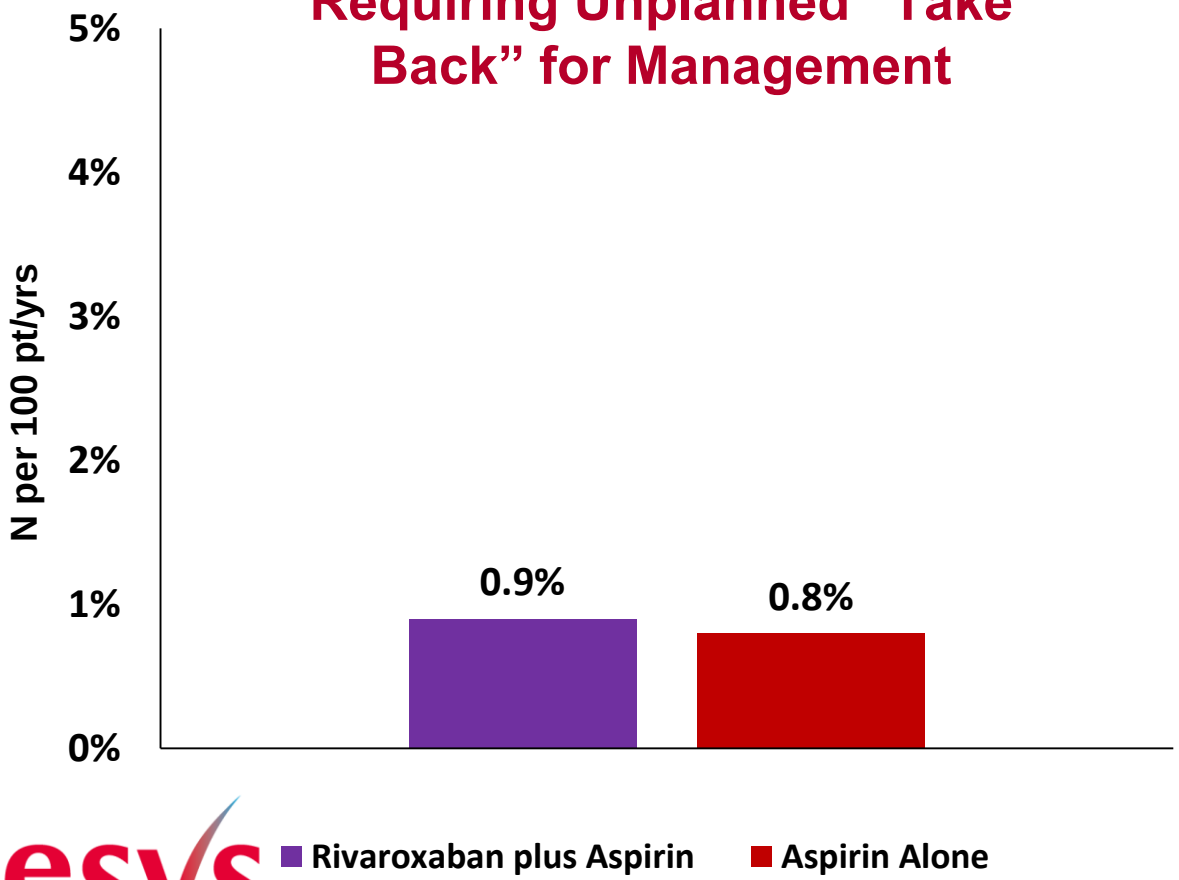
Safety in Surgical Patients



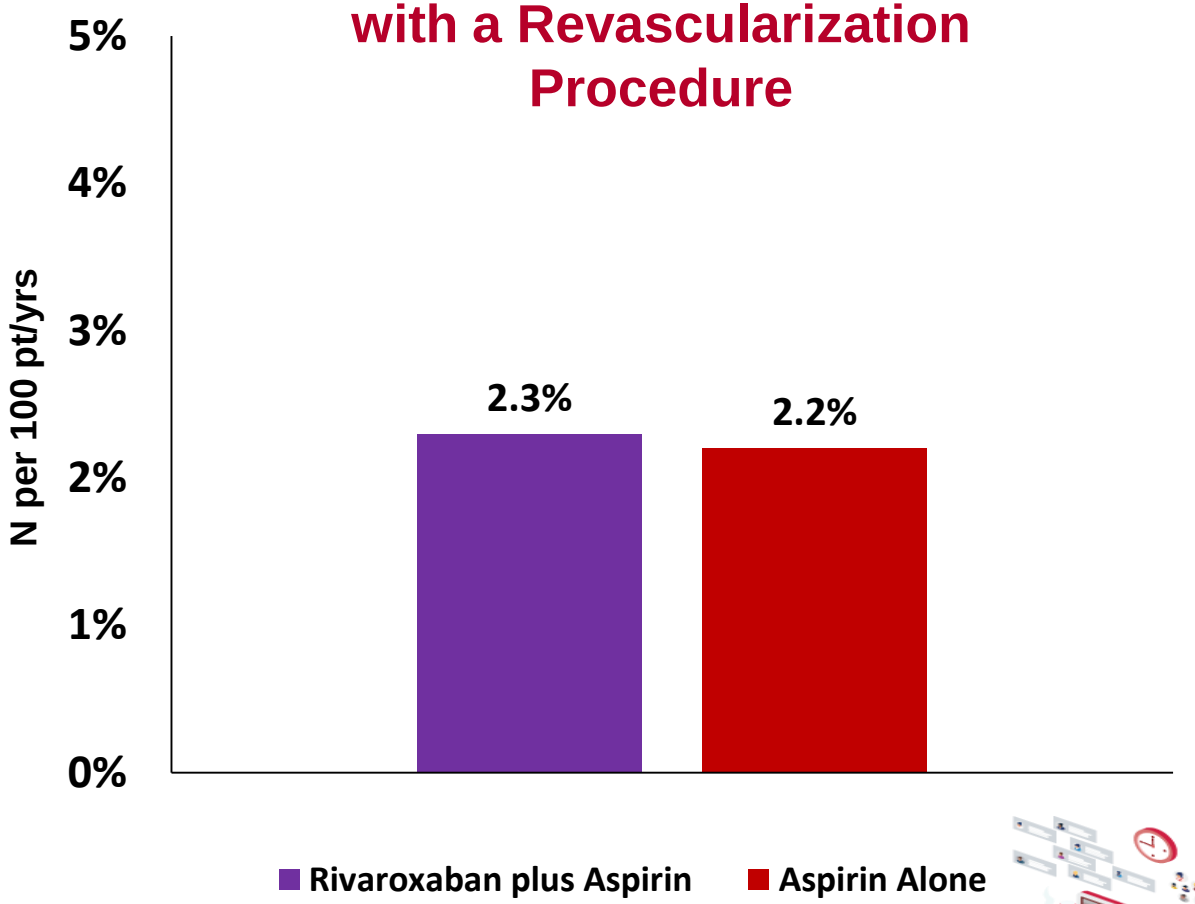
ARI, absolute risk increase;
NNH, number needed to harm

Procedural Bleeding

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



Any Bleeding Associated with a Revascularization Procedure



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Summary

- In symptomatic PAD after revascularization, ~1 in 5 have acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death at 3 years
- in patients treated surgically, that risk is higher approaching ~1 in 4 having a first event at 3 years.

- Following Surgical Revascularization, Rivaroxaban 2 x 2.5 mg with aspirin compared to aspirin alone:

  ✓ *Significantly reduces this risk with…*
  - *Robust Benefits apparent early and consistent over time with a NNT at 3 years of 24*
  - *Reduces a broad range of thrombotic complications including unplanned index limb revascularization and event free survival (NNT of 26 at 3 years)*

  ✓ *Increases bleeding with a numerical increase in TIMI major bleeding and a NNH in surgical patients of ~1000, and no increase in fatal bleeding or intracranial hemorrhage and no apparent increase in procedural or take back bleeding*

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Conclusion

- Symptomatic PAD patients undergoing surgical revascularization are at very high risk of irreversible harm events of the limb, heart and brain in spite of available medical therapies

- A strategy of rivaroxaban 2.5 mg twice daily added to aspirin should be considered in patients who are not at high risk of bleeding
  - Initiated after hemostasis is achieved
  - Continued long-term with benefit demonstrated from VOYAGER PAD to COMPASS

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