VOYAGER-PAD Angiographic Core Lab:
Design and Initial Results

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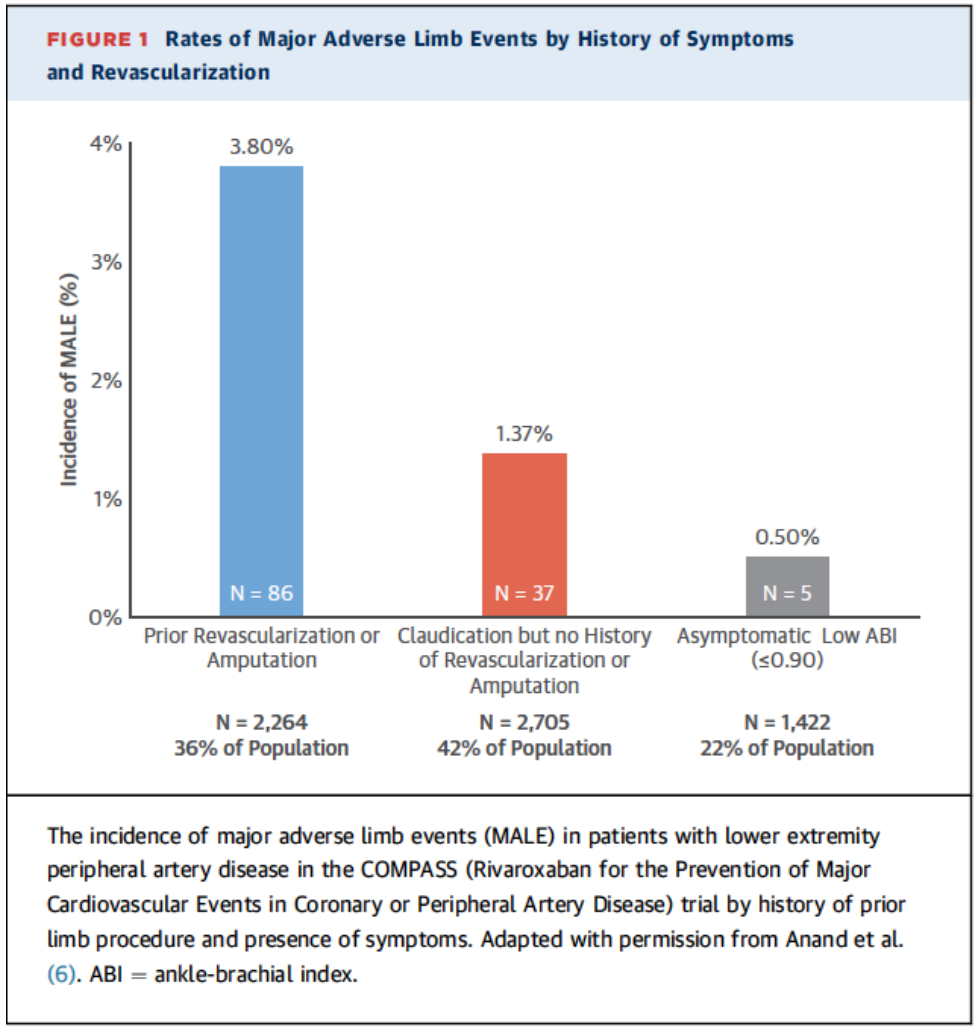
Background

PAD affects 230 million people worldwide and 10% suffer adverse cardiovascular events

PAD patients are heterogeneous



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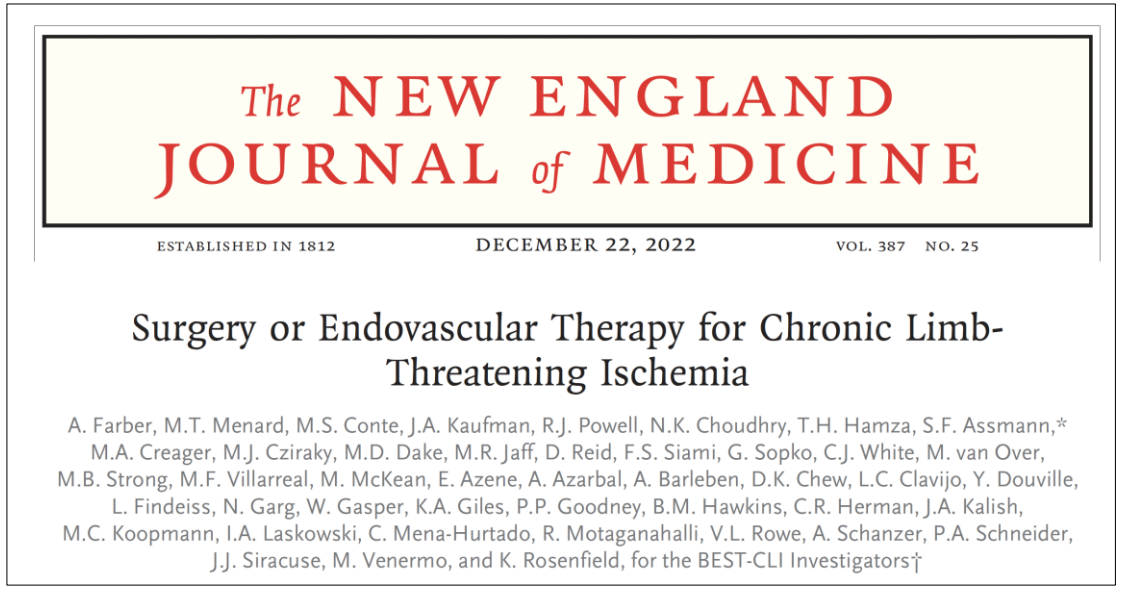
Fowkes et al *Nat Rev Cardiol*. 2017;14:156-170

Bonaca MP, Creager MA. *J Am Coll Cardiol*. 2018;71:2316-2318

PAD Patients with Prior Revascularization have High Major Adverse Limb Events

BEST-CLI



The NEW ENGLAND JOURNAL of MEDICINE

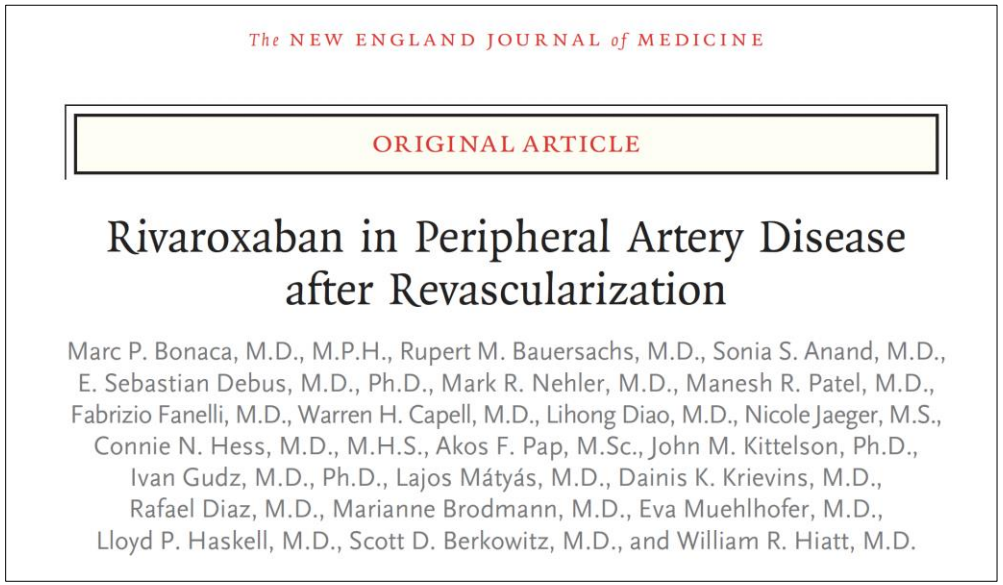
ESTABLISHED IN 1812 DECEMBER 22, 2022 VOL. 387 NO. 25

Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

A. Farber, M.T. Menard, M.S. Conte, J.A. Kaufman, R.J. Powell, N.K. Choudhry, T.H. Hamza, S.F. Assmann,* M.A. Creager, M.J. Cziraky, M.D. Dake, M.R. Jaff, D. Reid, F.S. Siami, G. Sopko, C.J. White, M. van Over, M.B. Strong, M.F. Villarreal, M. McKean, E. Azene, A. Azarbal, A. Barleben, D.K. Chew, L.C. Clavijo, Y. Douville, L. Findeiss, N. Garg, W. Gasper, K.A. Giles, P.P. Goodney, B.M. Hawkins, C.R. Herman, J.A. Kalish, M.C. Koopmann, I.A. Laskowski, C. Mena-Hurtado, R. Motaganahalli, V.L. Rowe, A. Schanzer, P.A. Schneider, J.J. Siracuse, M. Venermo, and K. Rosenfield, for the BEST-CLI Investigators†

Of 1813 CLTI patients, 888 (49%) experienced primary events (death, MALE)

VOYAGER-PAD



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., E. Sebastian 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, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., 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.

Of 6564 symptomatic PAD patients, 1092 (17%) experienced primary outcome (limb and CV events)

Farber. . . Rosenfield, et al. NEJM Nov 2022

Bonaca . . . Hiatt, et al NEJM March 2020

PAD Patients with Prior Revascularization have High Major Adverse Limb Events

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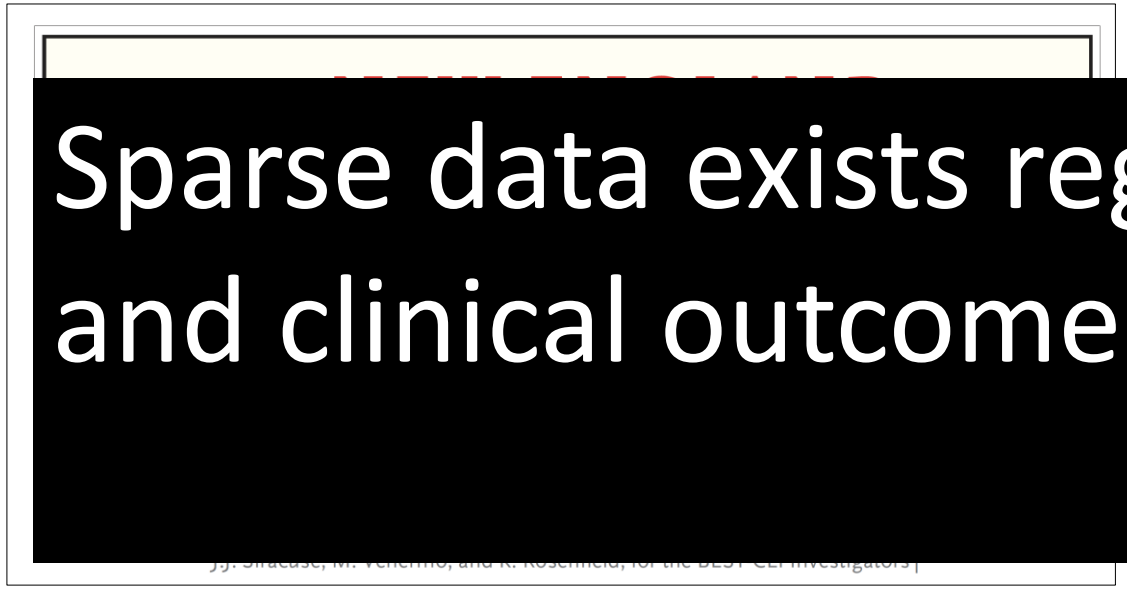

VOYAGER-PAD

Sparse data exists regarding PAD anatomy and clinical outcomes

Of 1813 CLTI patients, 888 (49%) experienced primary events (death, MALE)

Of 6564 symptomatic PAD patients, 1092 (17%) experienced primary outcome (limb and CV events)

Farber. . . Rosenfield, et al. NEJM Nov 2022

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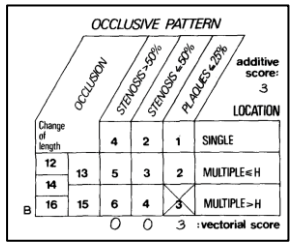
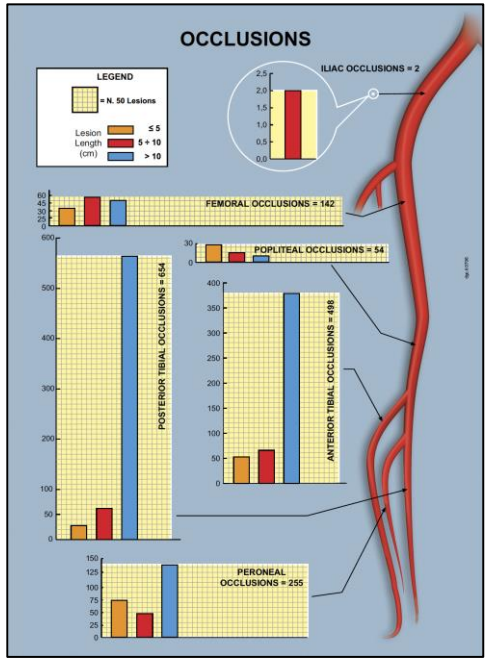
PAD Anatomic Classification Systems

BOLLINGER



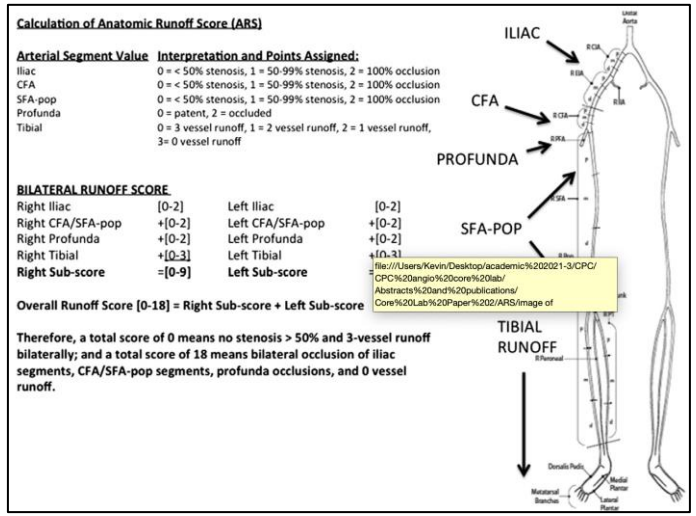
Earliest, 1981
Case-based

GRAZIANI



Angiographic anatomy of 417 CLTI patients with diabetes was characterized

ANATOMIC RUNOFF SCORE



Calculation of Anatomic Runoff Score (ARS)

Arterial Segment Value	Interpretation and Points Assigned:
Iliac	0 = < 50% stenosis, 1 = 50-99% stenosis, 2 = 100% occlusion
CFA	0 = < 50% stenosis, 1 = 50-99% stenosis, 2 = 100% occlusion
SFA-pop	0 = < 50% stenosis, 1 = 50-99% stenosis, 2 = 100% occlusion
Profunda	0 = patent, 2 = occluded
Tibial	0 = 3 vessel runoff, 1 = 2 vessel runoff, 2 = 1 vessel runoff, 3= 0 vessel runoff

BILATERAL RUNOFF SCORE

Right Iliac	[0-2]	Left Iliac	[0-2]
Right CFA/SFA-pop	+[0-2]	Left CFA/SFA-pop	+[0-2]
Right Profunda	+[0-2]	Left Profunda	+[0-2]
Right Tibial	+[0-3]	Left Tibial	+[0-3]
Right Sub-score	**=[0-9]**	**Left Sub-score**	

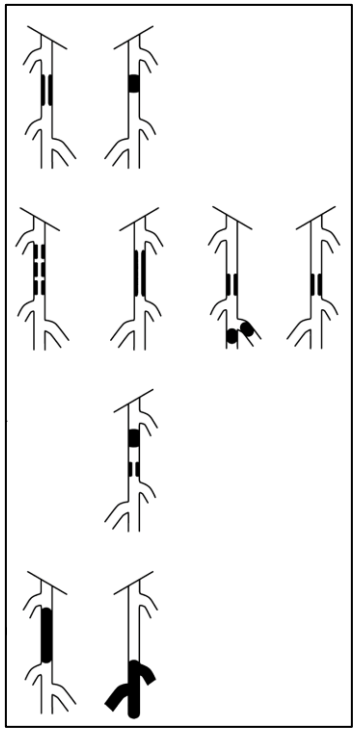
Overall Runoff Score [0-18] = Right Sub-score + Left Sub-score

Therefore, a total score of 0 means no stenosis > 50% and 3-vessel runoff bilaterally; and a total score of 18 means bilateral occlusion of iliac segments, CFA/SFA-pop segments, profunda occlusions, and 0 vessel runoff.

Angiogram reports of 908 patients were reviewed

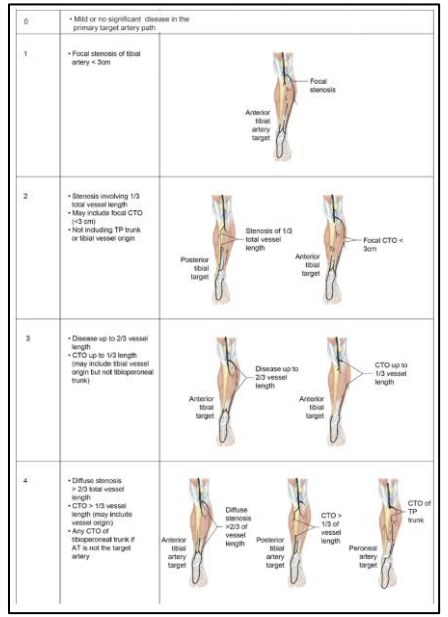
Association with traditional CV outcomes

TASC



Expert consensus to guide revascularization strategies for all PAD

GLASS



Created by expert consensus and systematic literature review to predict endovascular outcomes based on anatomy

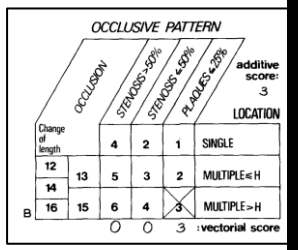
Bollinger et al. *Atherosclerosis*. 1981;38:339-346 Graziani et al. Eur J Vasc Endovasc Surg. 2007;33:453-460 Norgren, Hiatt et al. J Vasc Surg. 2007;45 Suppl S:S5-67 Jones et al. Am Heart J. 2015;170:400-408 *Conte et al. J Vasc Surg*. 2019;69:3S-125S e140

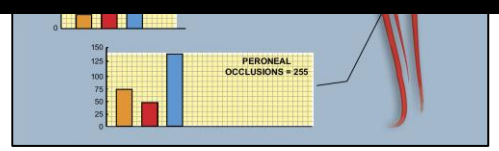
PAD Anatomic Classification Systems

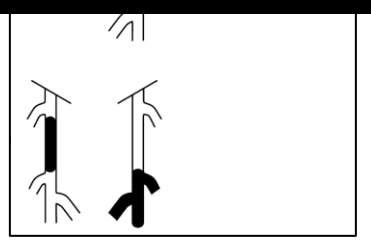
BOLLINGER

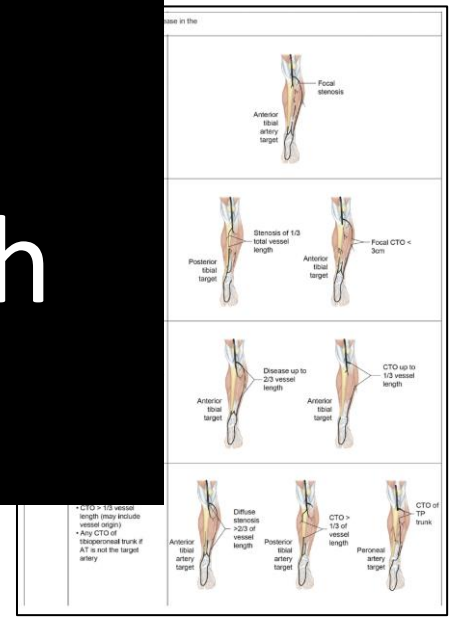
LASS

Current anatomic scores are based on expert opinion or are from datasets without associations with limb-specific outcomes









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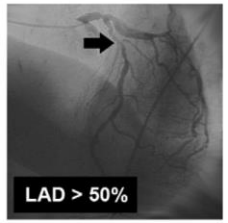
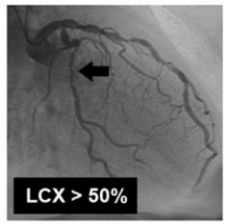
SYNTAX Score in CAD

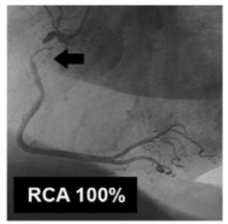
Lesion 1
Segment 5 — 10
Bifurcation Type A — 1
Lesion 1 score — **11**



Lesion 2
Segment 6 — 7
Length >20 mm — 1
Lesion 2 score — **8**



Lesion 3
Segment 13 — 1
Length >20 mm — 1
Heavy calcification — 2
Lesion 3 score — **4**



Lesion 4
Segment 1 — 5
Age T.O. is yes — 1
Blunt stump — 1
Bridging — 1
First segment visualised: 2 — 0
Lesion 4 score — **8**

SYNTAX SCORE — **31**

SYNTAX score correlates with anatomic complexity of CAD and is associated with adverse cardiovascular outcomes

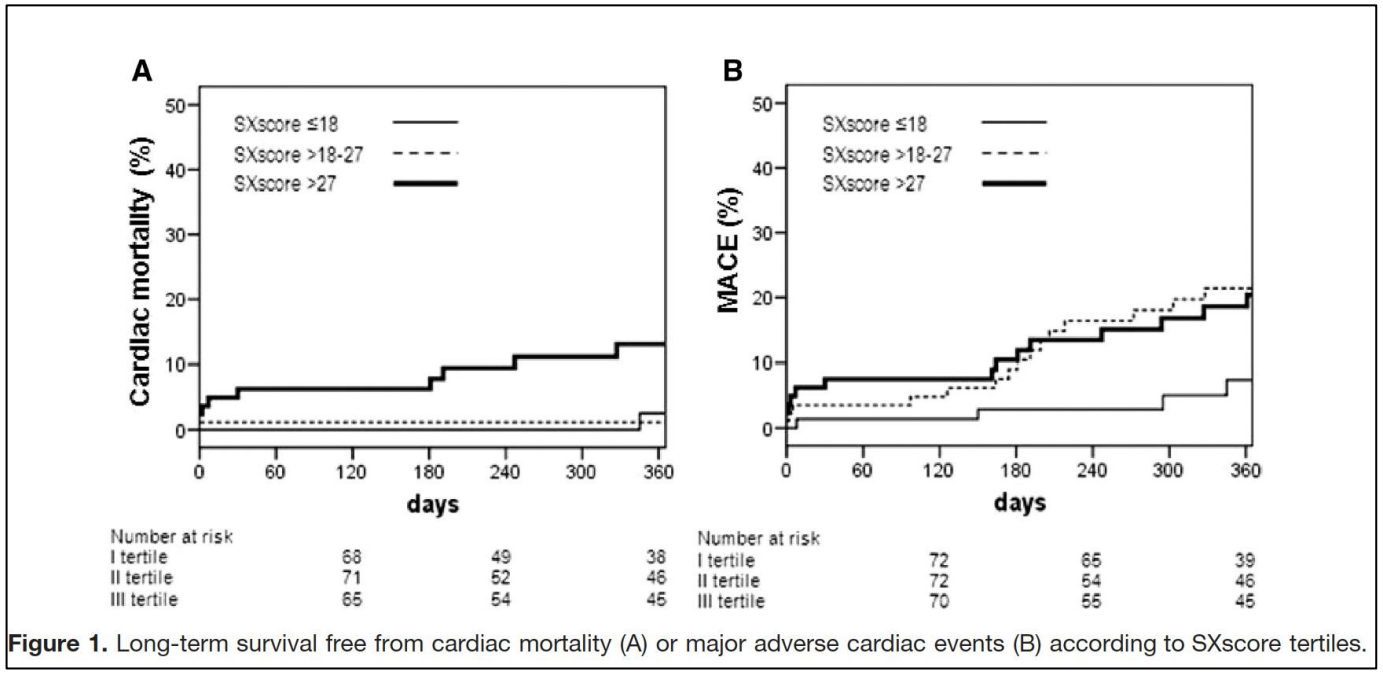


Figure 1. Long-term survival free from cardiac mortality (A) or major adverse cardiac events (B) according to SXscore tertiles.

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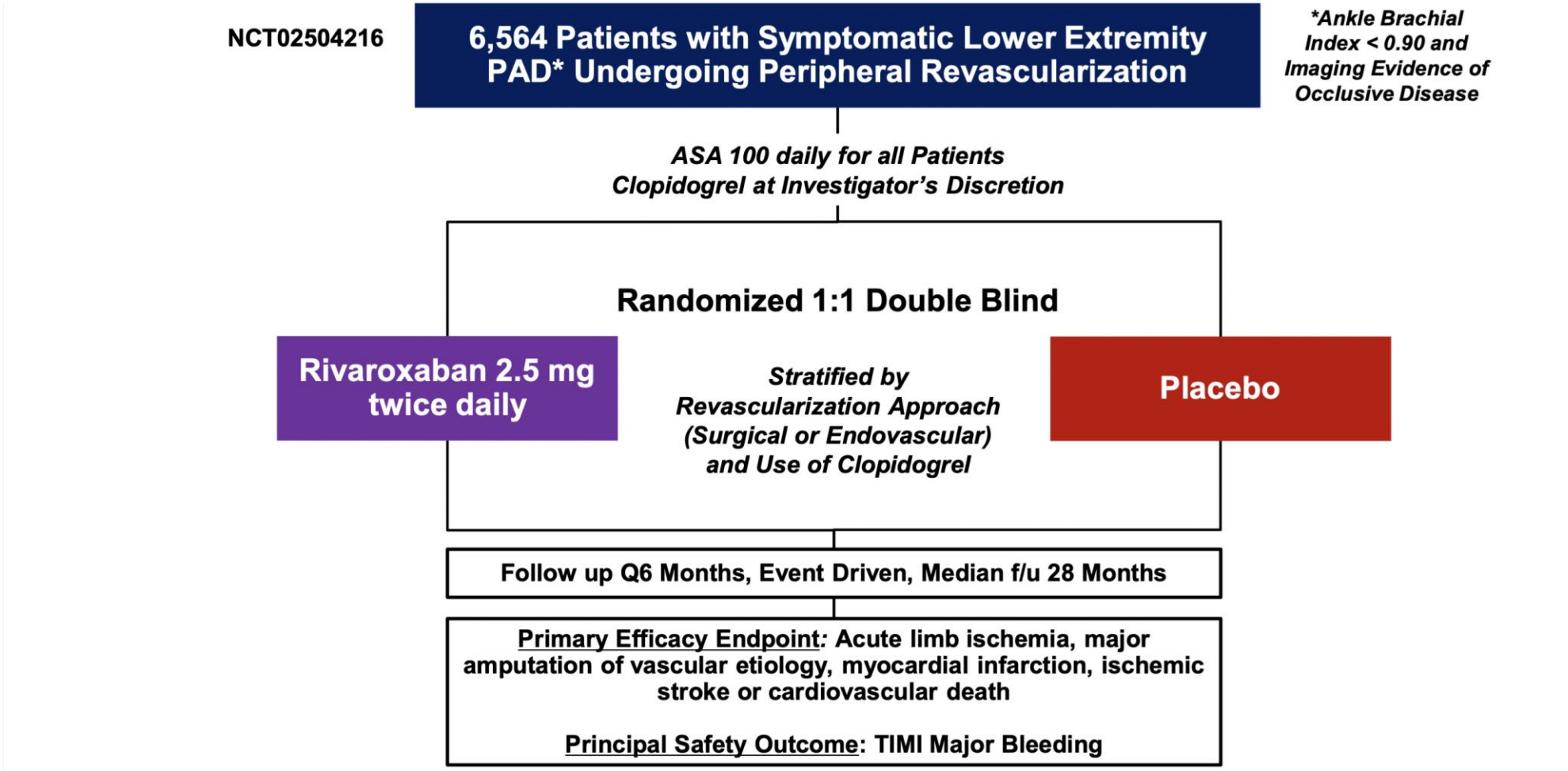
Capodanno et al. JACC Int Vol 2, No 8 2009

VOYAGER-PAD Trial Design



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

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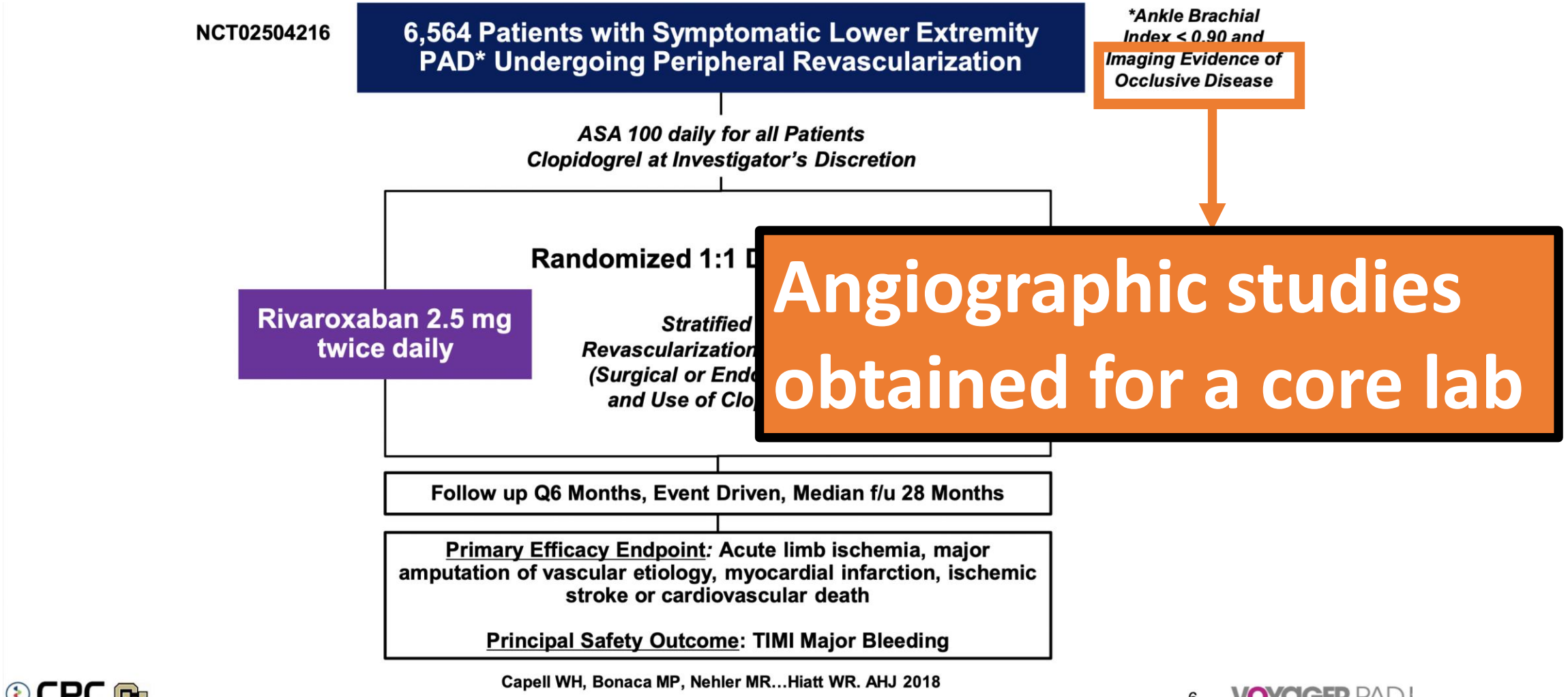

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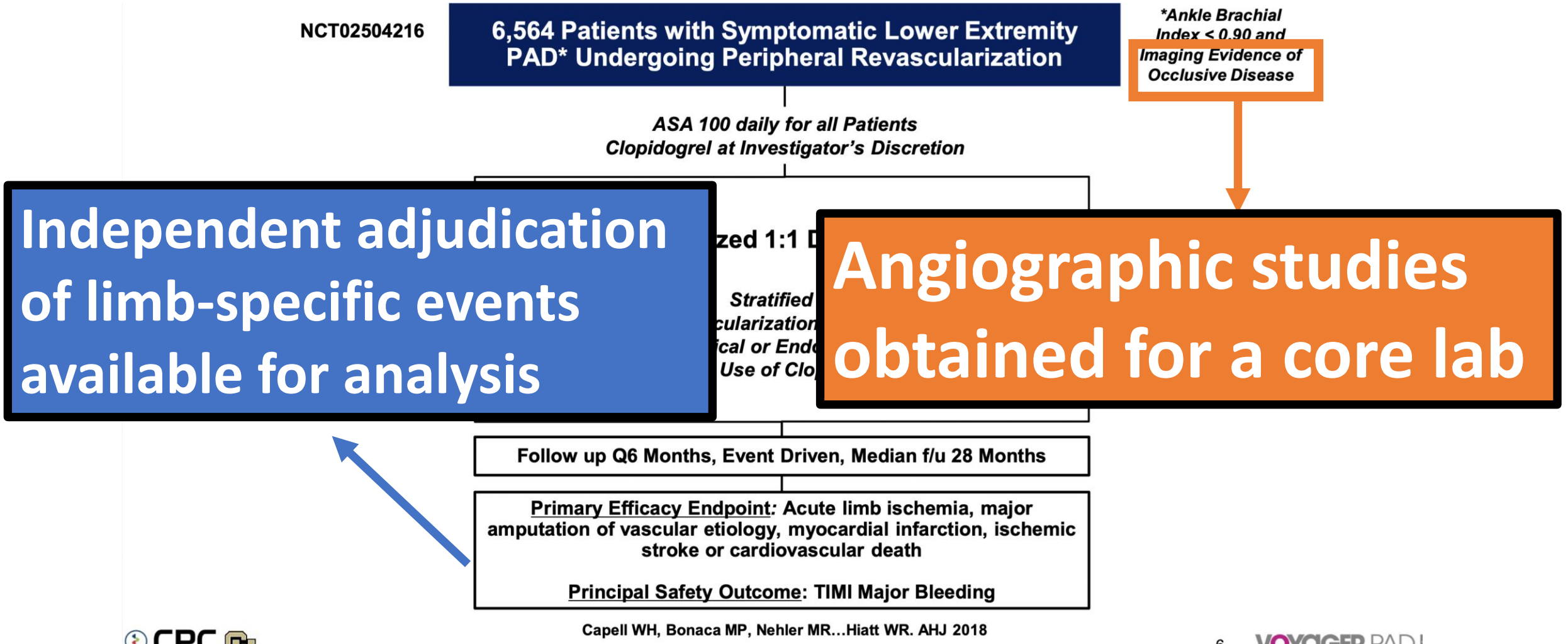
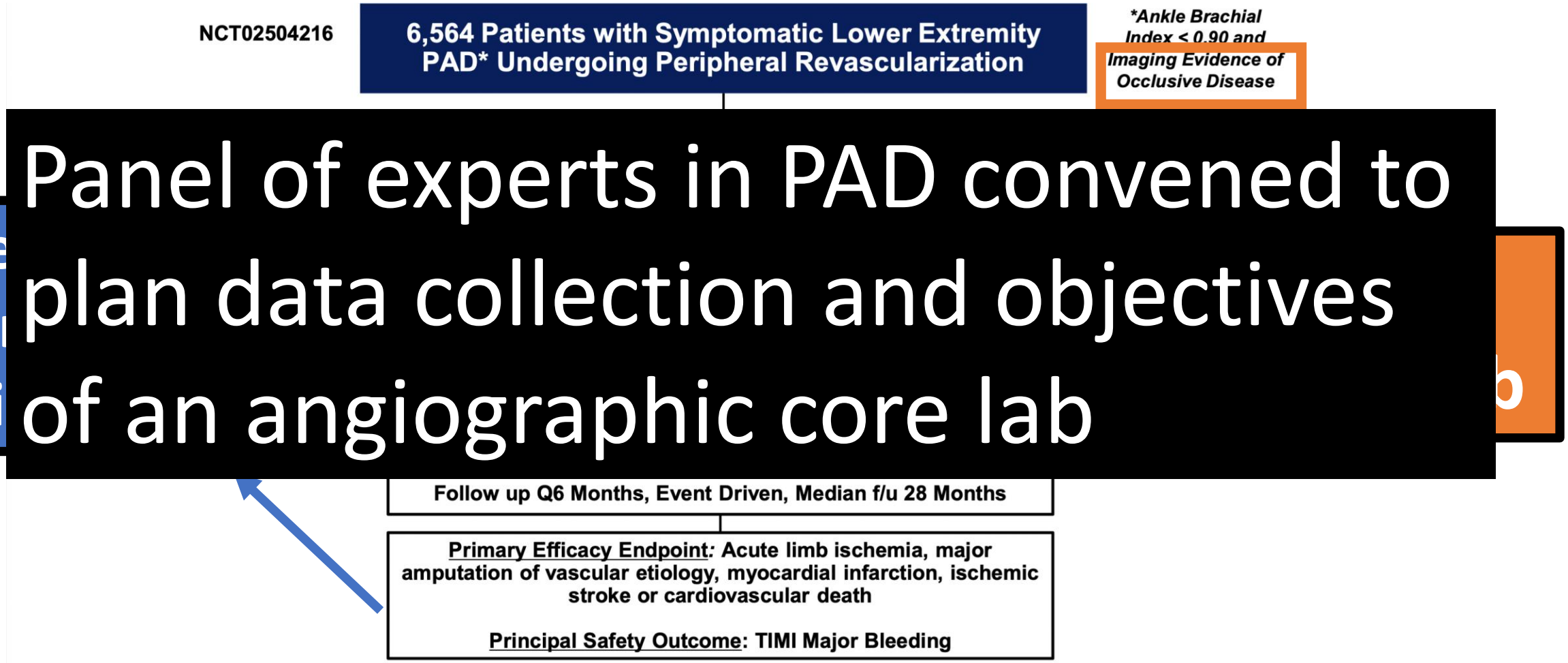


Independent adjudication of limb-specific events available for analysis

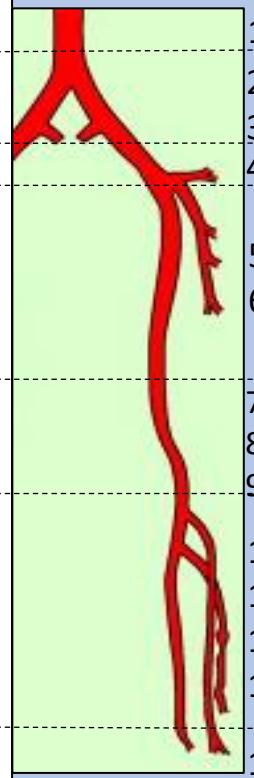
Angiographic studies obtained for a core lab

VOYAGER-PAD Trial Design



VOYAGER PAD Angiographic Core Lab

Anatomic and Flow Characteristics Across 16 Anatomic Segments from 2646 Angiograms in Core Lab Database



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2. Common iliac
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4. Common femoral
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Severity of stenosis
Length of Disease
Calcification
Prior stenting or bypass
Thrombus
Aneurysm
Revascularization

Adjudicated MACE and MALE outcomes and PROs (association with anatomy)

28-month median followup

Cross-sectional Analyses

PAD characteristics (Rutherford Category, ABI, CLTI) associations with anatomic features

Clinical characteristics (age, sex, diabetes, smoking, CKD) association with anatomic features

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Angiographic Reviewer Selection and Training

Eligible reviewer trained in Vascular Surgery, Interventional Radiology, or Interventional Cardiology with experience in angiographic peripheral vascular imaging

Reviewer undergoes standardization phase. >5 angiographic studies are reviewed. Results are compared among reviewers. Feedback provided to reviewers to promote inter-rater agreement.

Formal angiographic interpretations are performed

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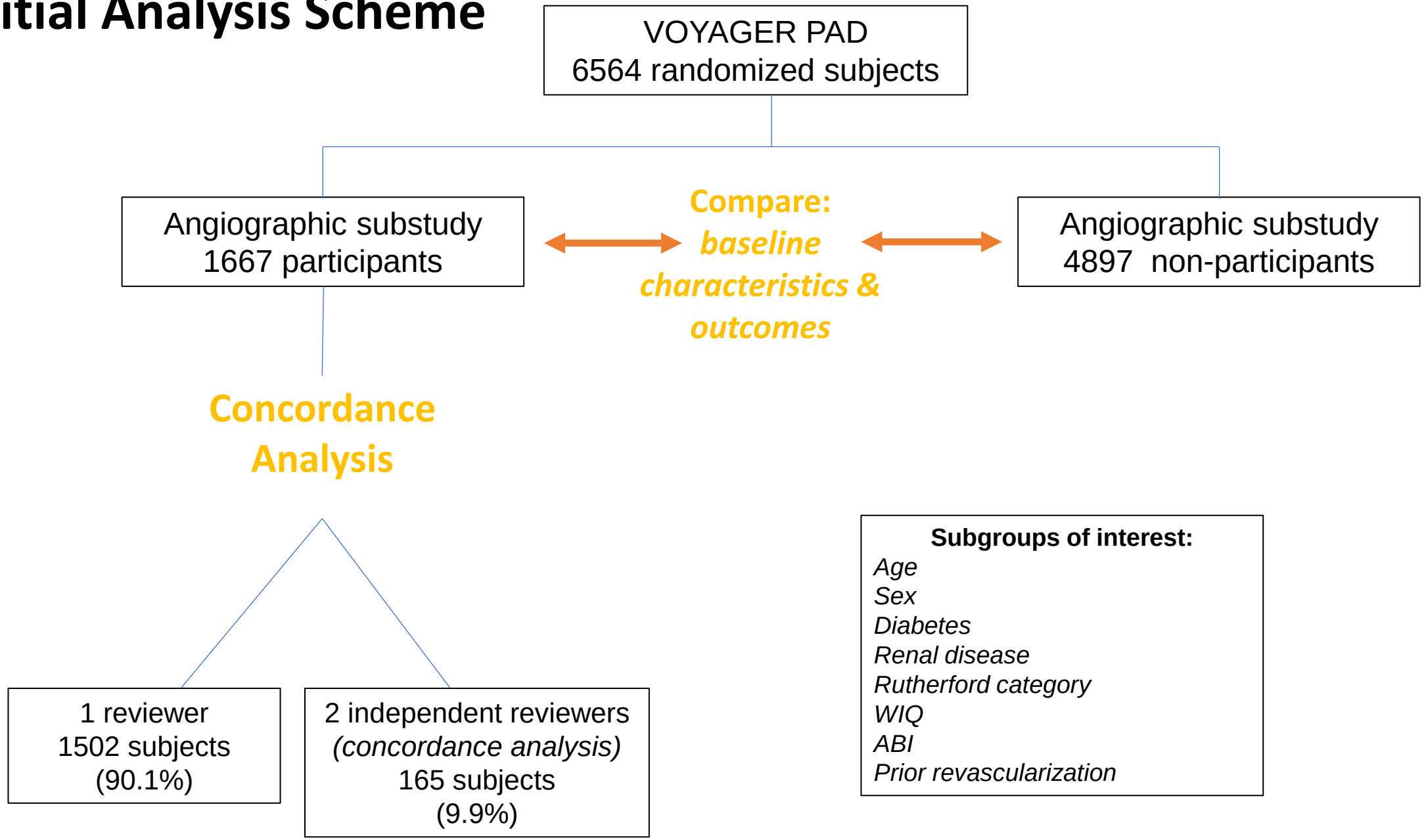
Initial Analysis Scheme



Subgroups of interest:

Age
Sex
Diabetes
Renal disease
Rutherford category
WIQ
ABI
Prior revascularization

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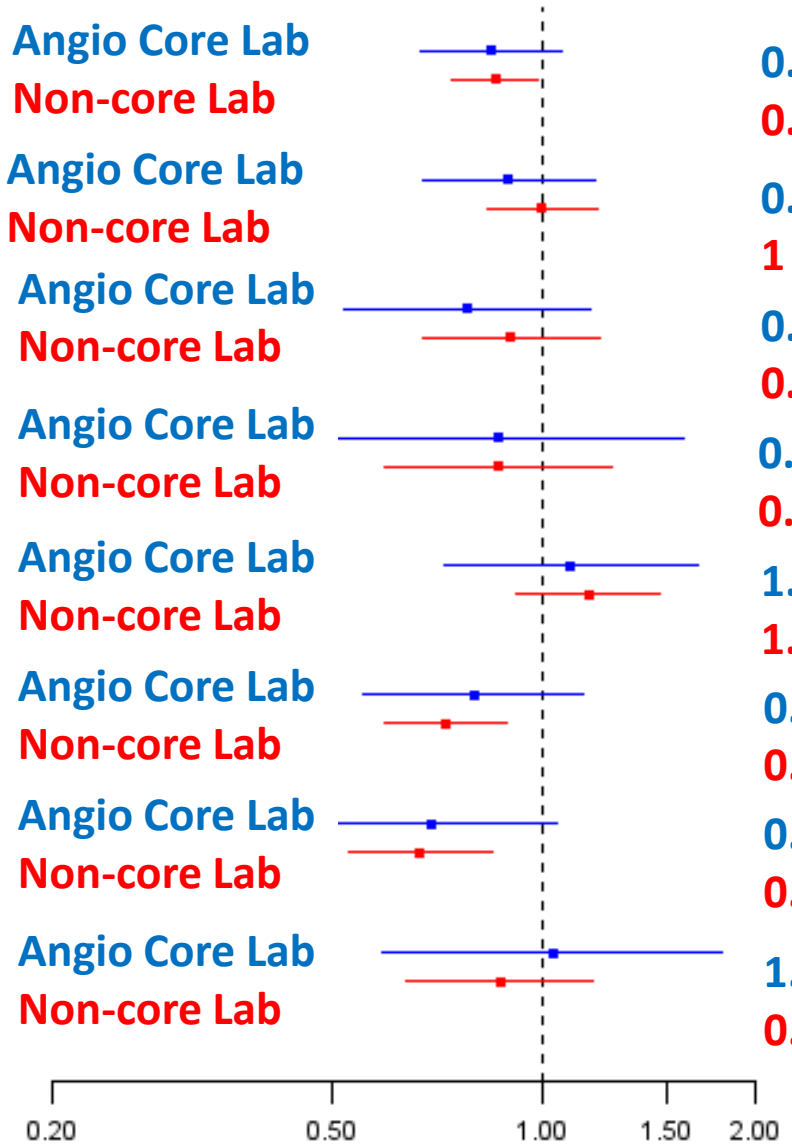
Demographics and Baseline Characteristics

Variable	Included in Angiographic Core Lab (N=1667)	Non-Angiographic Core Lab (N=4897)	p-value
Demographics and General Descriptors			
Mean age (SD), years	67.2 (8.4)	67.0 (8.5)	0.4527
Female, no. (%)	463 (27.8%)	1241 (25.3%)	0.0504
Race			
White	1448 (86.9%)	3855 (78.7%)	<0.0001
Black or African American	66 (4.0%)	89 (1.8%)	
Asian	107 (6.4%)	859 (17.5%)	
American Indian Alaska Native	3 (0.2%)	2 (0.0%)	
Mean BMI (kg/m2)	26.9	26.3	<0.0001
Geographic region			
North America	**329 (19.7%)**	**365 (7.5%)**	**<0.0001**
Western Europe	**618 (37.1%)**	**1208 (24.7%)**	
Eastern Europe	**519 (31.1%)**	**2080 (42.5%)**	
Asia Pacific	**100 (6.0%)**	**861 (17.6%)**	
South America	**101 (6.1%)**	**383 (7.8%)**	

Demographics and Baseline Characteristics

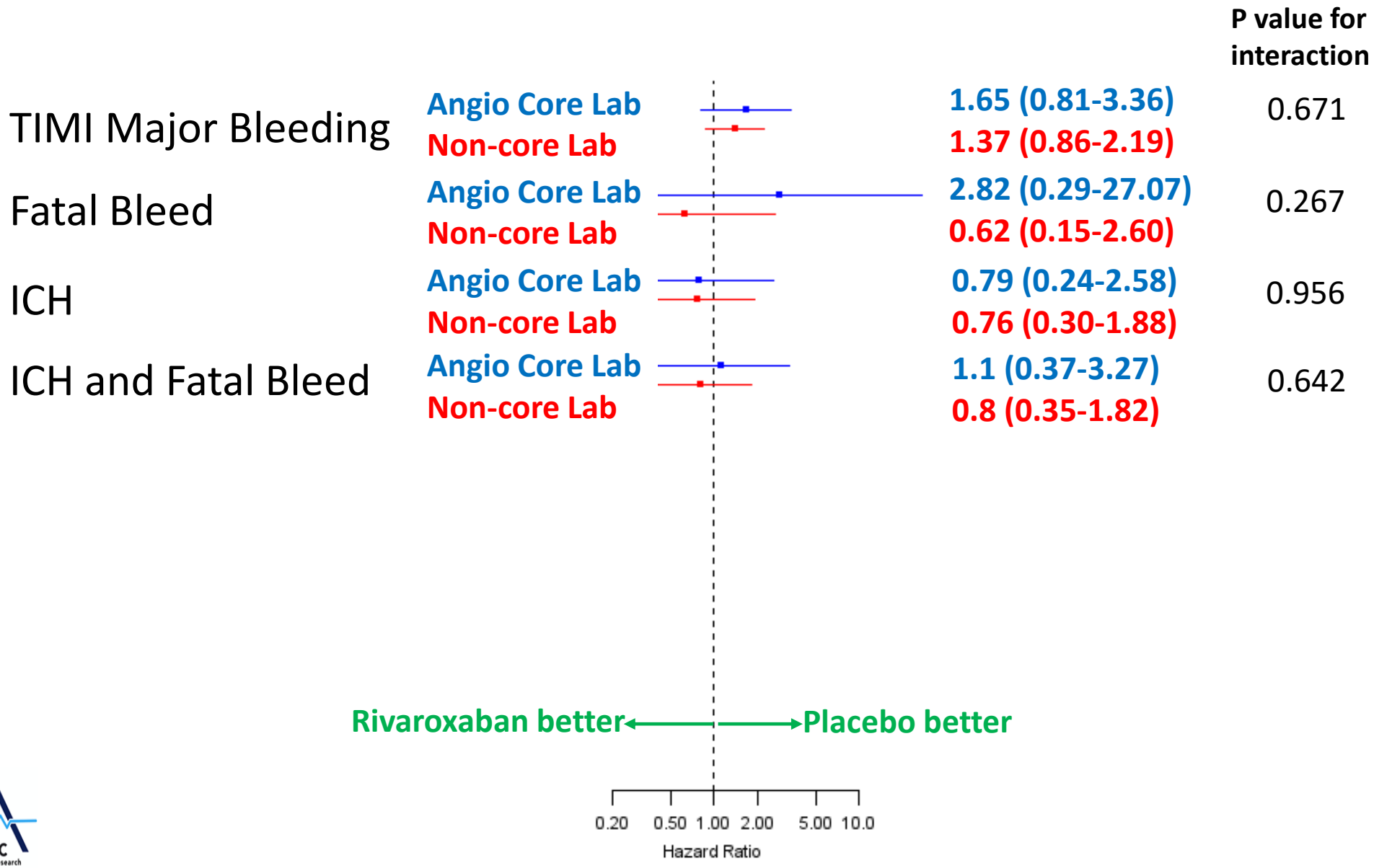
Variable	Included in Angiographic Core Lab (N=1667)	Non-Angiographic Core Lab (N=4897)	p-value
Type of qualifying revascularization procedure			
Endovascular	1273 (76.4%)	2818 (57.5%)	<0.0001
Hybrid	47 (2.8%)	241 (4.9%)	
Surgical	347 (20.8%)	1838 (37.5%)	
Risk Factors			
eGFR group 2 (ml/min/1.73m2)			<0.0001
< 30	10 (0.6%)	33 (0.7%)	
≥30 to < 60	369 (22.1%)	915 (18.7%)	
≥ 60	1183 (71.0%)	3809 (77.8%)	
Diabetes mellitus, no. (%)	697 (41.8%)	1932 (39.5%)	0.1717
Smoking status			
Never	302 (18.1%)	1049 (21.4%)	0.0152
Former	752 (45.1%)	2179 (44.5%)	
Current	613 (36.8%)	1666 (34.0%)	
Clopidogrel used at baseline, no. (%)	1150 (69.0%)	2769 (56.5%)	<0.0001

Efficacy Outcomes: Core Lab versus Non-core lab



			P value
Primary composite	Angio Core Lab	0.84 (0.67-1.06)	0.934
	Non-core Lab	0.85 (0.74-0.98)	
MACE	Angio Core Lab	0.89 (0.67-1.18)	0.508
	Non-core Lab	1 (0.83-1.19)	
MI	Angio Core Lab	0.78 (0.52-1.17)	0.567
	Non-core Lab	0.9 (0.67-1.21)	
Stroke	Angio Core Lab	0.86 (0.47-1.58)	0.996
	Non-core Lab	0.86 (0.59-1.25)	
CV death	Angio Core Lab	1.09 (0.72-1.65)	0.797
	Non-core Lab	1.16 (0.92-1.47)	
MALE	Angio Core Lab	0.8 (0.56-1.14)	0.651
	Non-core Lab	0.73 (0.59-0.89)	
ALI	Angio Core Lab	0.7 (0.46-1.05)	0.869
	Non-core Lab	0.67 (0.53-0.85)	
Major Amputation	Angio Core Lab	1.03 (0.59-1.79)	0.588
	Non-core Lab	0.87 (0.64-1.18)	

Safety Outcomes: Core Lab versus Non-core lab



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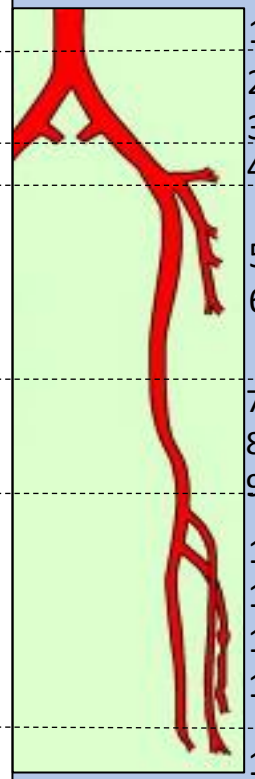

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Length of Disease
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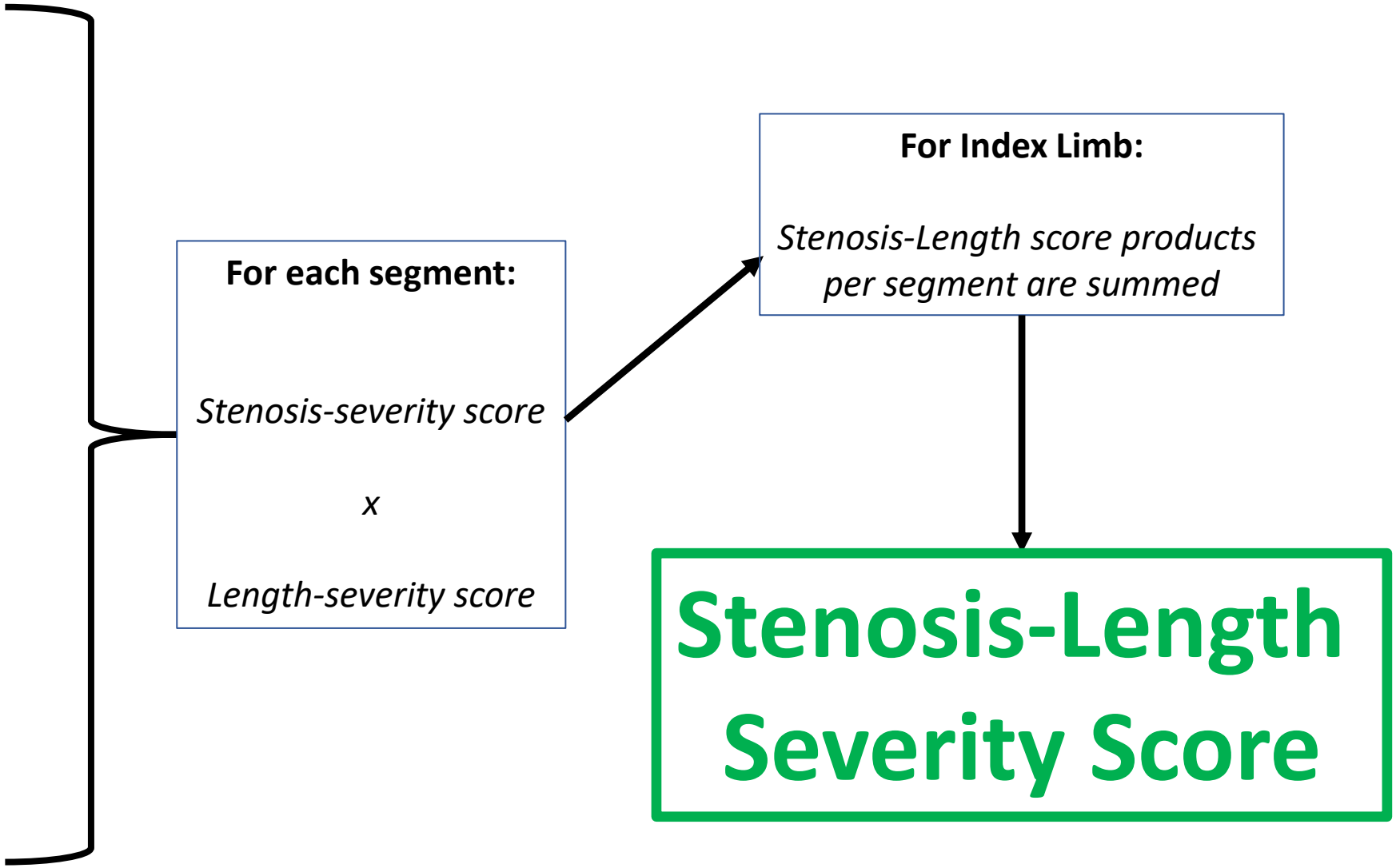
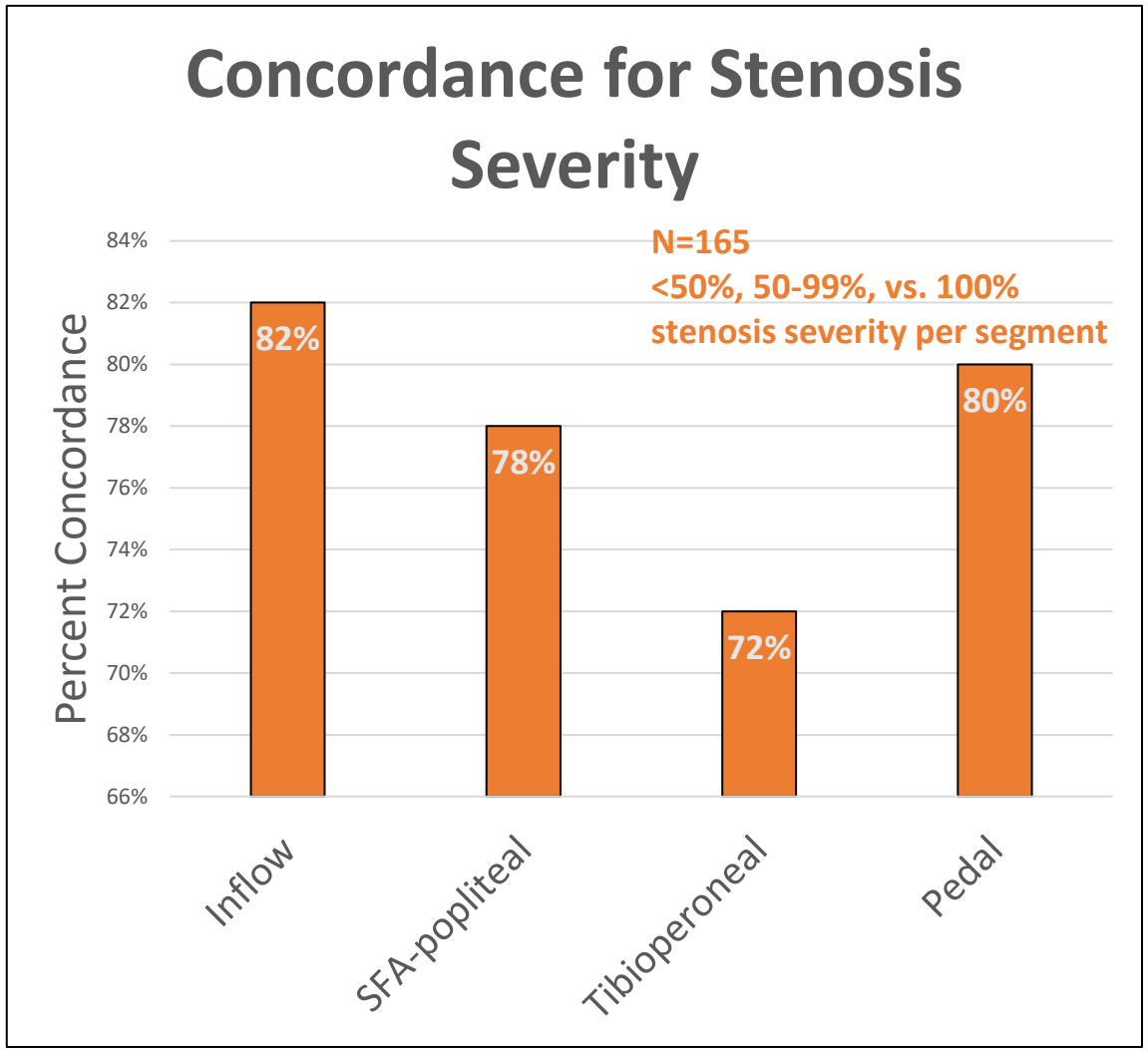
Generation of Stenosis-Length Severity Score

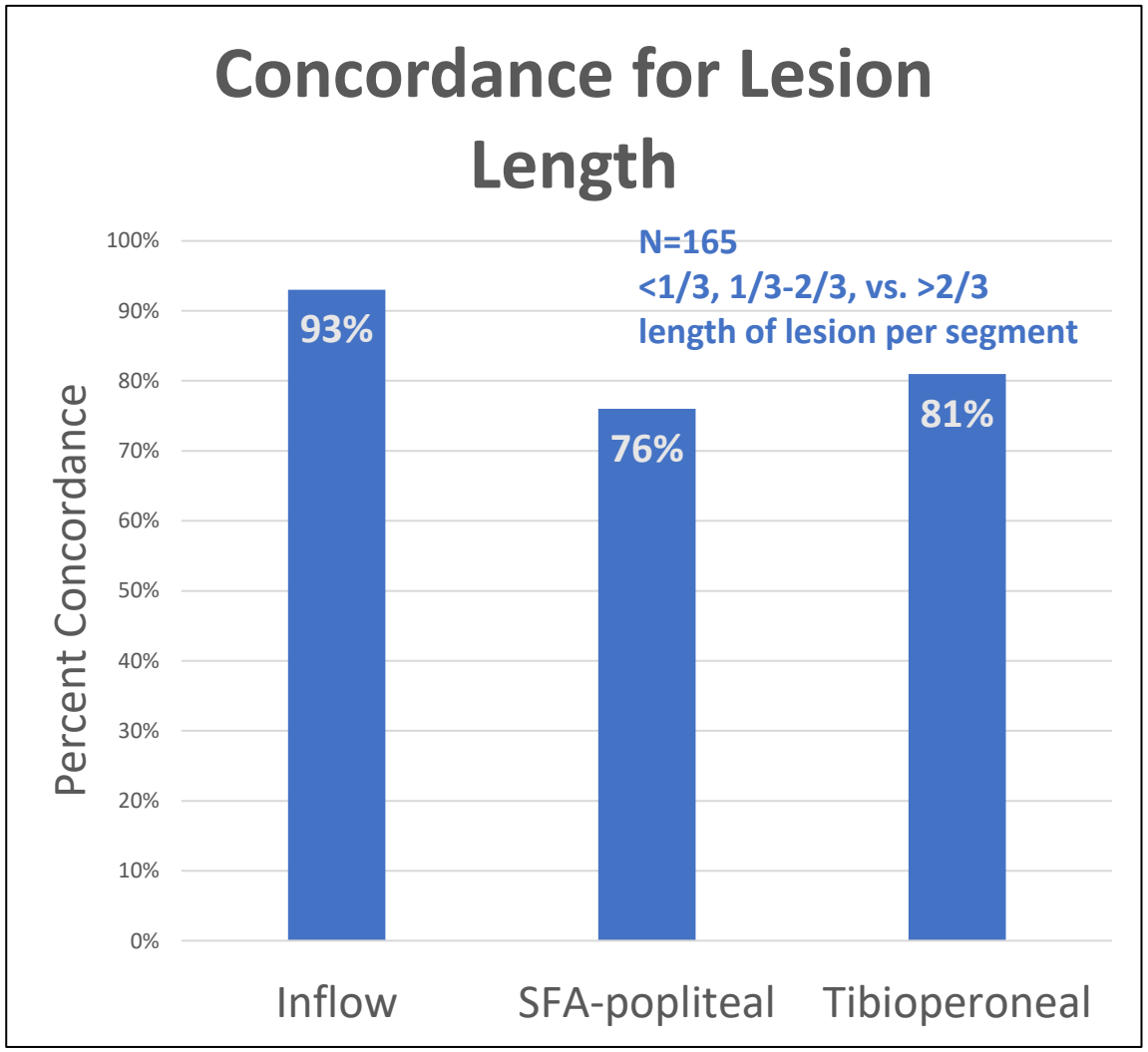
Stenosis severity of segment	Stenosis-severity Score
<50%	0
50-69%	1
70-99%	2
100%	3

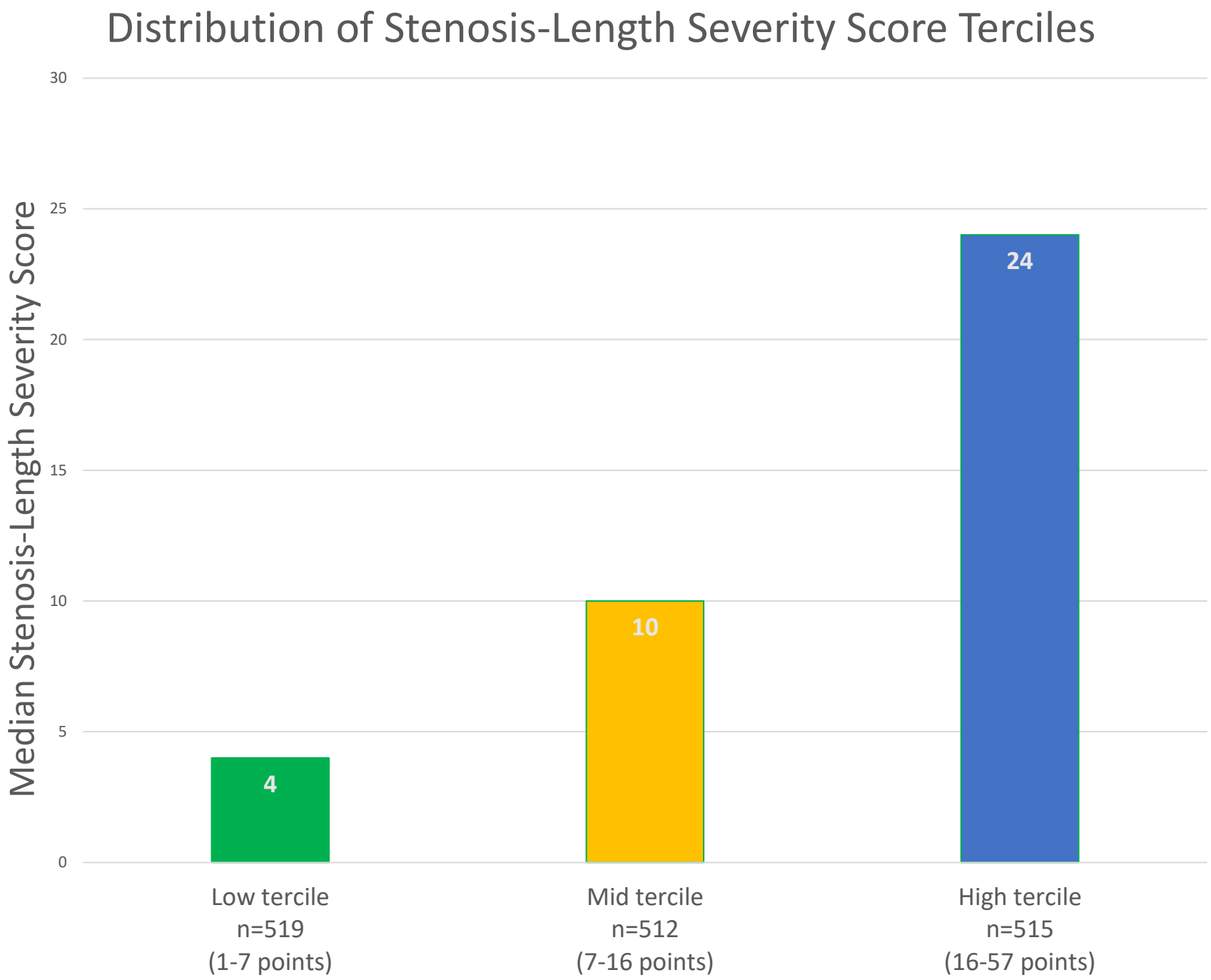
Length severity of segment	Length-severity Score
<1/3	1
1/3-2/3	2
>2/3	3



Concordance for Components of SLS Score



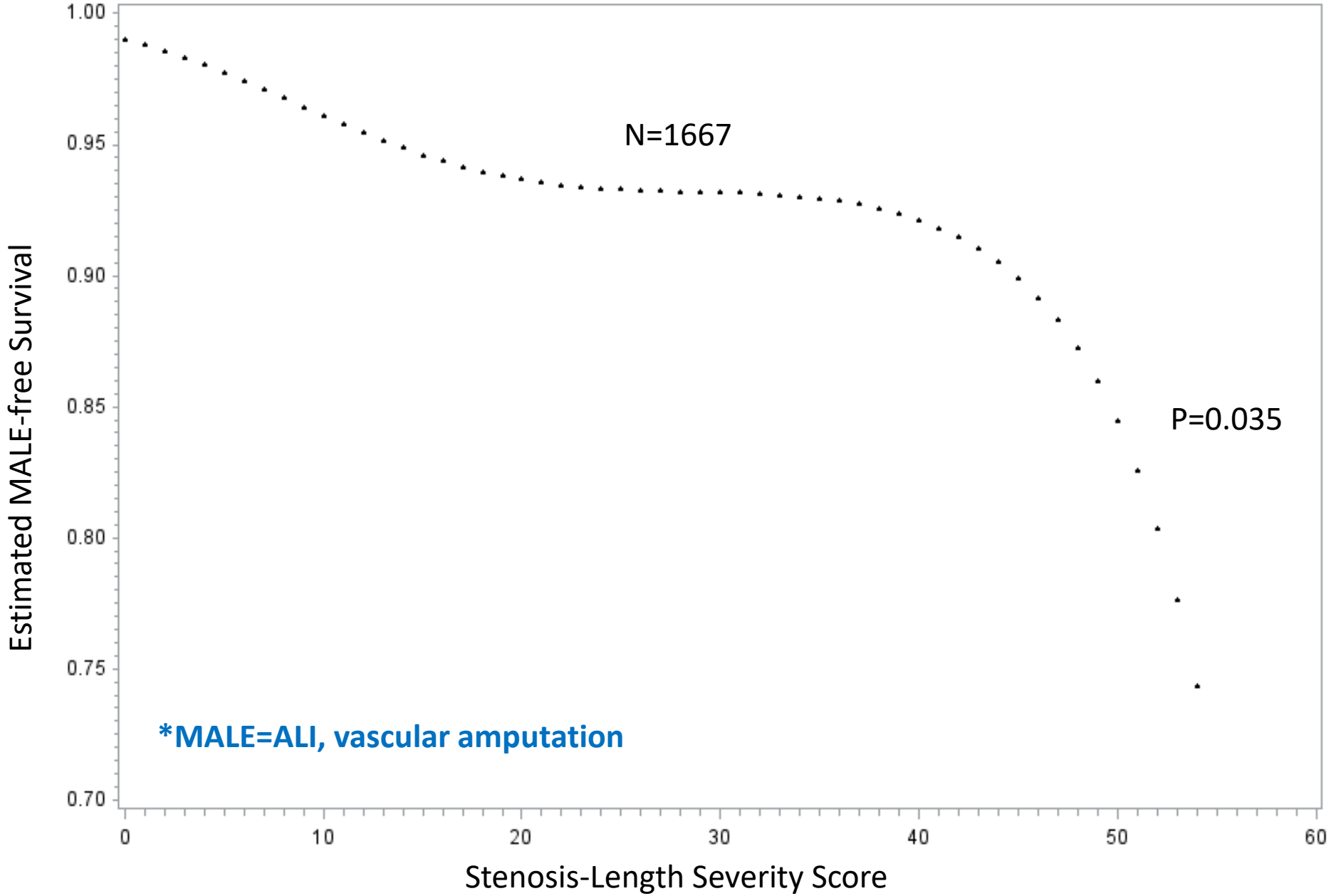



Distribution of Stenosis-Length Severity Score Terciles
Median Stenosis-Length Severity Score
30
25
20
15
10
5
0
4
10
24
Low tercile
n=519
(1-7 points)
Mid tercile
n=512
(7-16 points)
High tercile
n=515
(16-57 points)

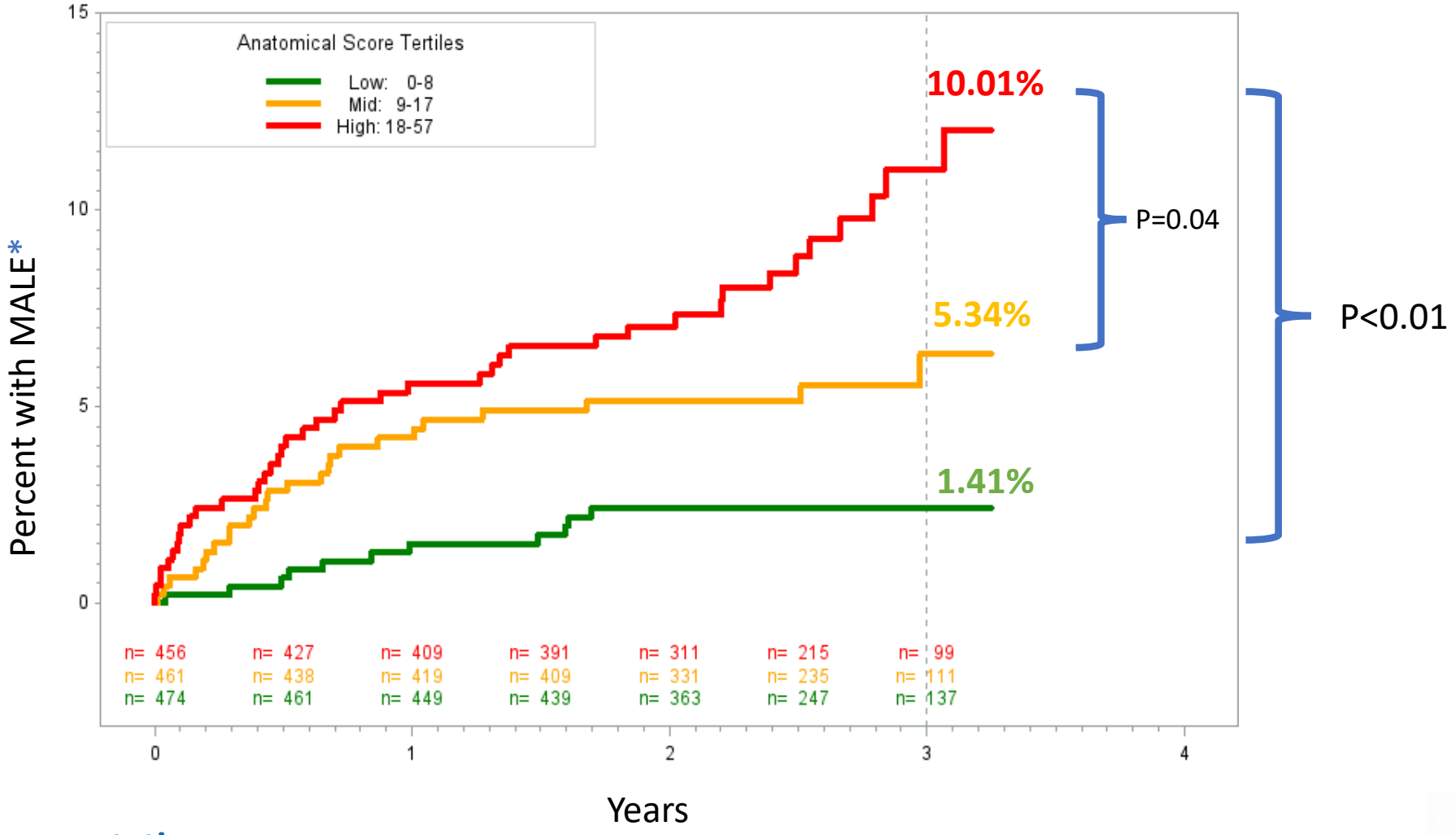
Baseline Characteristics by Stenosis-Length Severity Score Terciles

Variable	Low Tertile n=519	Mid Tertile n=496	High Tertile n=522	P value tertile 1 vs. 2	P value tertile 2 vs. 3	P value tertile 1 vs. 3
Age, years (mean, SD)	66.6 (8.3)	67 (8.3)	68 (8.5)	0.49	0.05	0.01
Sex, female (n, %)	154 (29.7%)	148 (29.8%)	129 (24.7%)	0.95	0.07	0.07
Black (n, %)	17 (3.3%)	21 (4.2%)	24 (4.6%)	0.28	0.07	0.02
BMI (mean, Kg/m2)	27.6	26.8	26.3	<0.01	0.07	<0.01
CKD, yes (n, %)	62 (11.9%)	56 (11.3%)	60 (11.5%)	0.74	0.92	0.82
Diabetes, yes (n, %)	208 (40.1%)	197 (39.7%)	248 (47.5%)	0.91	0.01	0.02
Smoking, never (n, %)	67 (12.9%)	83 (16.7%)	115 (22.0%)	0.14	0.09	<0.01
Index leg ABI at screen (mean, SD)	0.6 (0.16)	0.6 (0.18)	0.5 (0.20)	<0.01	<0.01	<0.01

Cubic Spline of Stenosis-Length Severity Score and MALE*



Survival Plot of MALE* by Stenosis-Length Severity Score Terciles



*MALE=ALI, vascular amputation

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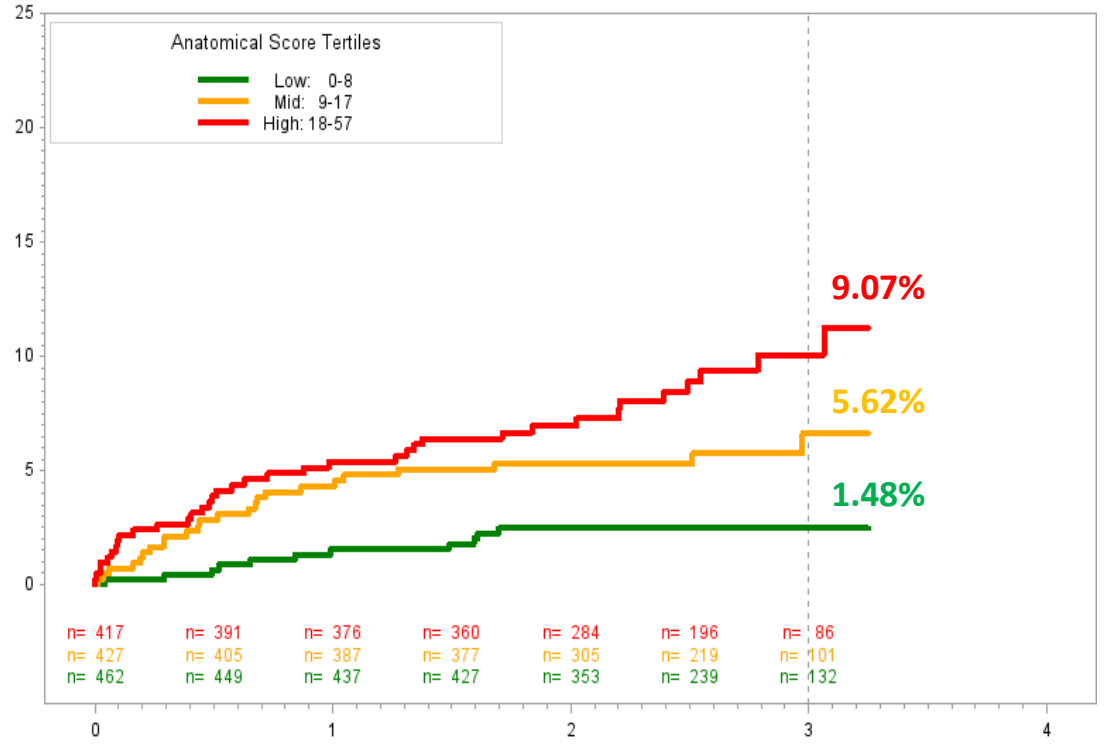
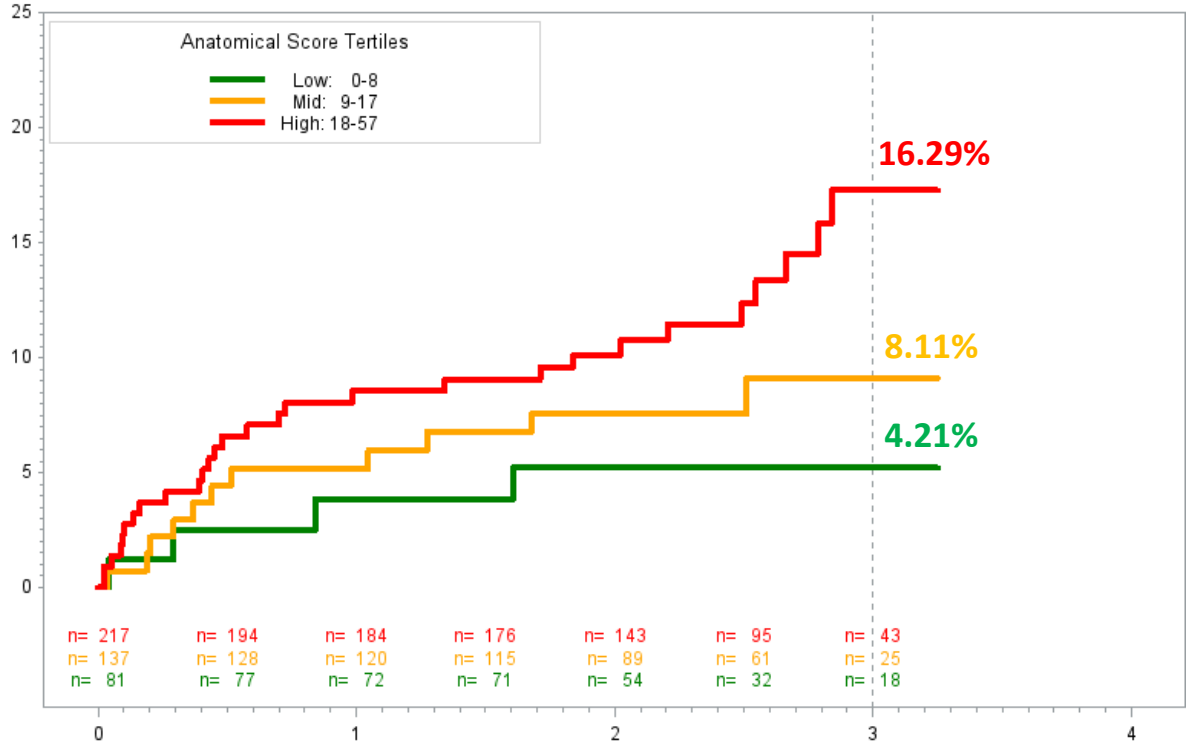
Survival Plot of MALE* by Stenosis-Length Severity Score Terciles

Claudication



Chronic Limb-Threatening Ischemia



*MALE=ALI, vascular amputation

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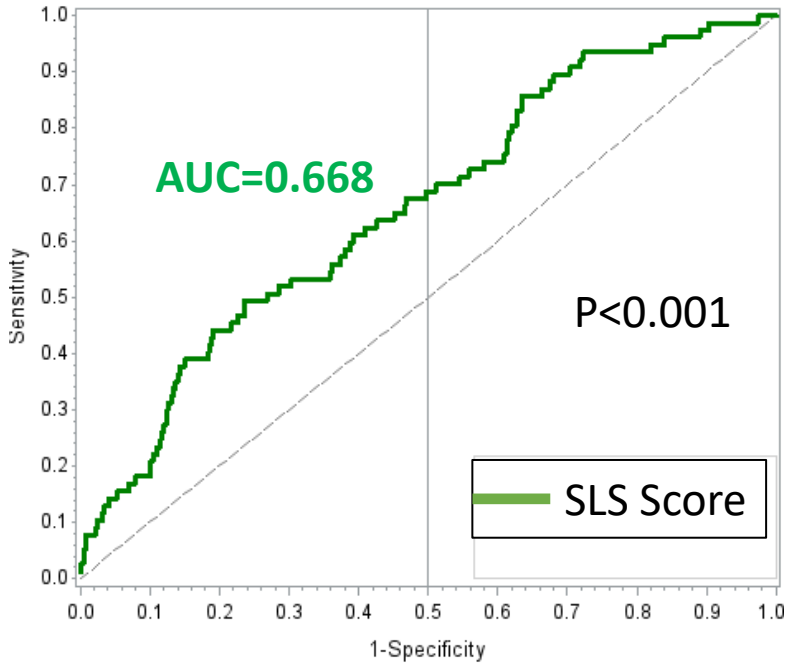
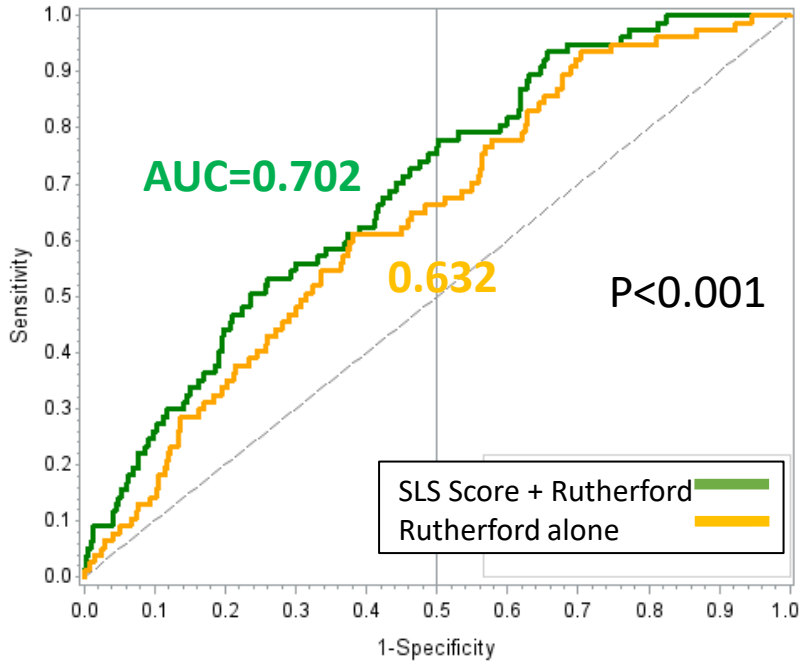
ROC Analysis for SLS Severity Score, ABI, and Rutherford for MALE*

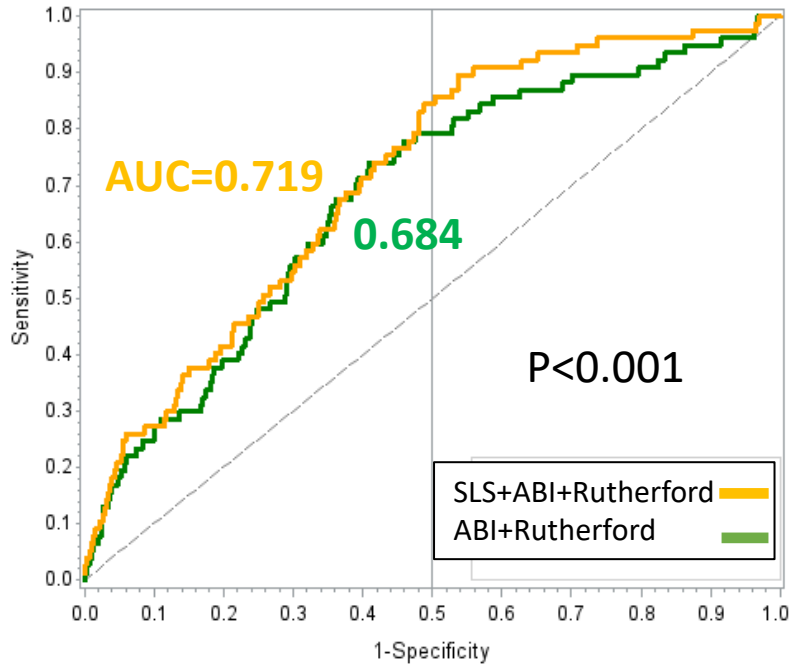
ROC Curve for SLS Score alone



ROC for SLS Score+Rutherford & Rutherford Alone



ROC for SLS+ABI+Rutherford & ABI+Rutherford



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*MALE=ALI, vascular amputation

Conclusions

PAD is prevalent and confers increased risk of limb events

Understanding how PAD anatomy contributes to risk may improve outcomes (as in CAD)

VOYAGER-PAD Angiographic Core lab offers an opportunity to better understand the relationships with anatomy, outcomes, and PAD subgroups

The stenosis-length severity score seems to add incremental predictive value for major adverse limb events to ABI and Rutherford category

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Thank you!

Questions?

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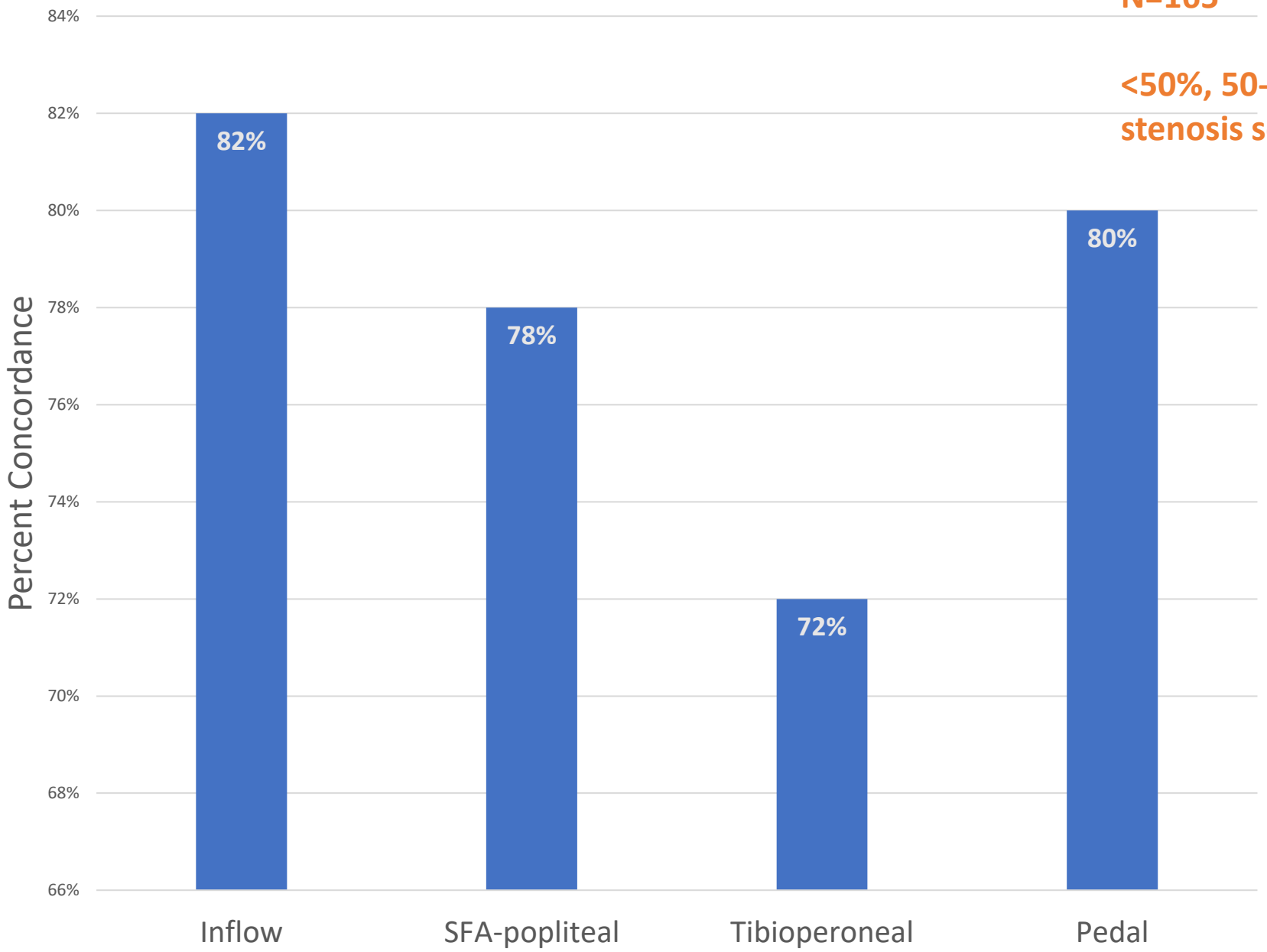
Concordance for Stenosis Severity

N=165

<50%, 50-99%, vs. 100% stenosis severity per segment



Concordance for Lesion Length

N=165

<1/3, 1/3-2/3, vs. >2/3 length of lesion per segment