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Risk Stratification for Amputation in Patients with Symptomatic Peripheral Artery Disease After Lower Extremity Revascularization: Insights from VOYAGER PAD

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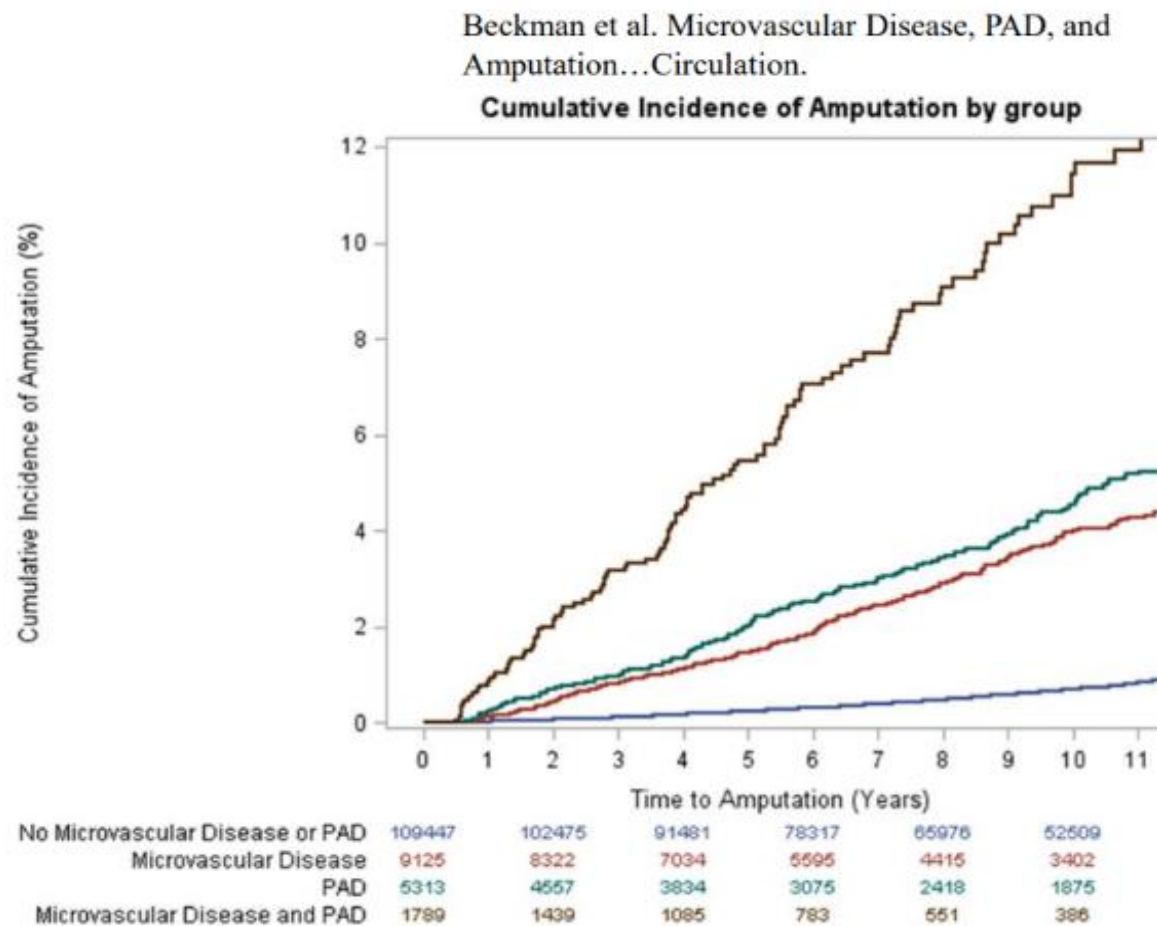
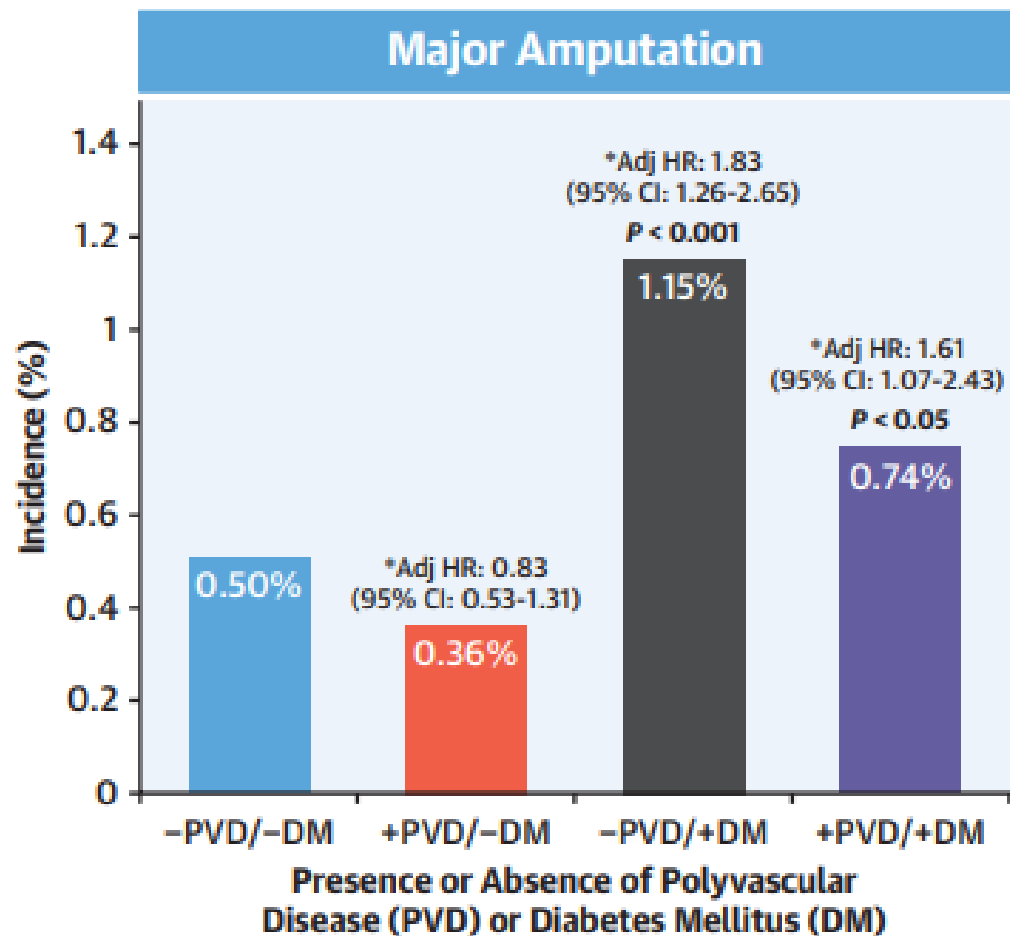


Risk Stratification in PAD

- **Patients with PAD are at heterogenous risk of adverse limb events and specifically amputation**
- **Patient characteristics (e.g. diabetes mellitus) as well as limb/wound factors have been shown to be associated with amputation risk**
- **Risk stratification offers the opportunity to personalize assessment and the use of therapies to reduce the risk of amputation**



Amputation Risk independently elevated with microvascular disease



Behan...Bonaca et al. Impact of Polyvascular Disease and Diabetes on Limb and Cardiovascular Risk in Peripheral Artery Disease. JACC 2022

The Rutherford Classification System

- **Created in 1986**
- **Widely accepted**
- **Modified in 1997**
 - **Objective measures**

Rutherford Stage	Signs and Symptoms
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Rest pain
5	Ischemic ulcers of digits
6	Severe ischemic ulcers or gangrene

Rutherford R Bet al. Suggested standards for reports dealing with lower extremity ischemia. JVS 1986

WIFI – Wound Ischemia Foot Infection

Table 7. Assessment of the risk of amputation: the WIFI classification (for further details see Mills *et al*³¹⁷).

Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mmHg)	Toe pressure or TcPO ₂
	0	≥0.80	> 100	≥60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	<0.40	<50	<30
fi (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

Mills, Conte, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System...JVS 2014

Wfl – Stratified in clinical stages

Risk of major amputation at one year

	Ischemia - 0				Ischemia - 1			
W-0	VL	VL	L	M	VL	L	M	H
W-1	VL	VL	L	M	VL	L	M	H
W-2	L	L	M	H	M	M	H	H
W-3	M	M	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3
	Ischemia - 2				Ischemia - 3			
W-0	L	L	M	H	L	M	M	H
W-1	L	M	H	H	M	M	H	H
W-2	M	H	H	H	H	H	H	H
W-3	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3

Mills, Conte, et al. **The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System...JVS**
2014

Hypothesis using VOYAGER PAD population

- **Evaluate risk of amputation (major and minor)**
 - **Baseline Rutherford**
 - **Baseline Wlfl**
 - **Adding comorbid diabetes**
- **Examine the risk of minor and major amputation post LER stratified by baseline Rutherford and Wlfl score**
- **Determine whether the addition of comorbid diabetes to baseline Wlfl could strengthen the prediction model**

VOYAGER PAD

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

ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion (up to 6 months)

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg twice daily

Stratified by Revascularization Approach (Surgical or Endovascular with and without clopidogrel)

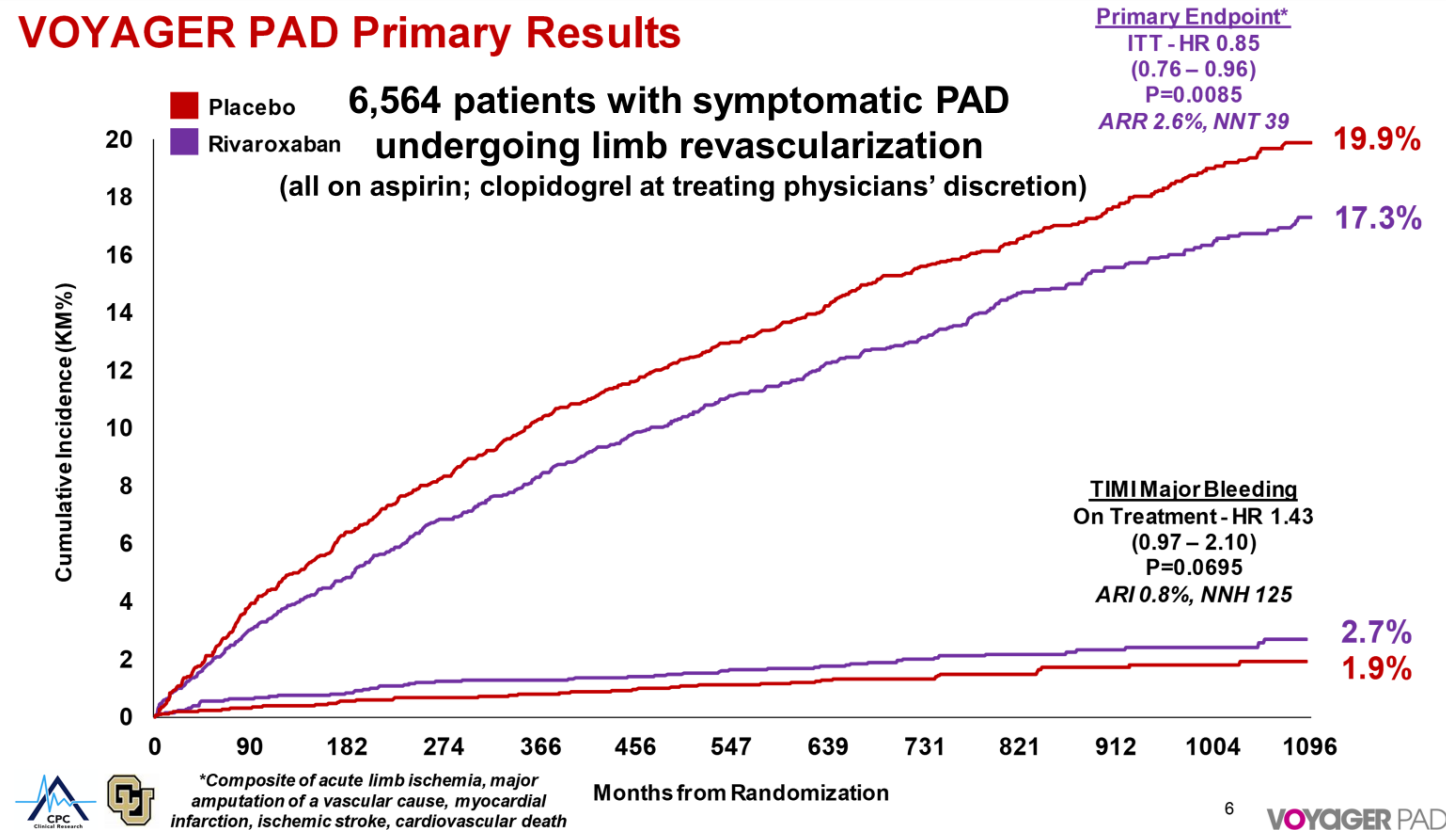
Placebo

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

VOYAGER PAD Primary Results



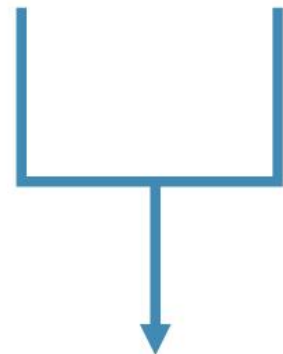
Methods

- **VOYAGER PAD population**
 - **Baseline Rutherford stage and Wifl scores recorded**
 - **Baseline Wifl stratified by presence of diabetes mellitus**
 - **Novel modified DM-Wifl score created**
 - **Amputation incidence (major and minor) at 3 years determined and risk stratified by these different risk prediction systems**

Rutherford Stage and
Wifl Score Determine



Rivaroxaban Placebo



Baseline
Rutherford/Wifl
Score

Revascularization

Randomization

Follow-up

Open,
Endovascular, or
Hybrid Procedure



Median 28 Months
Limb Events



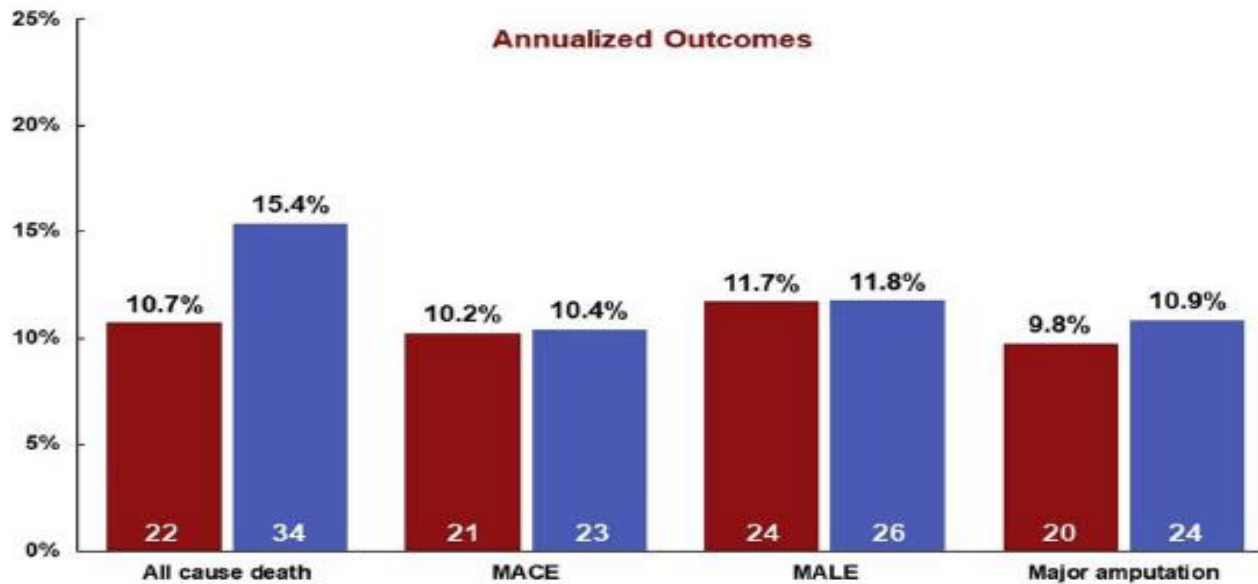
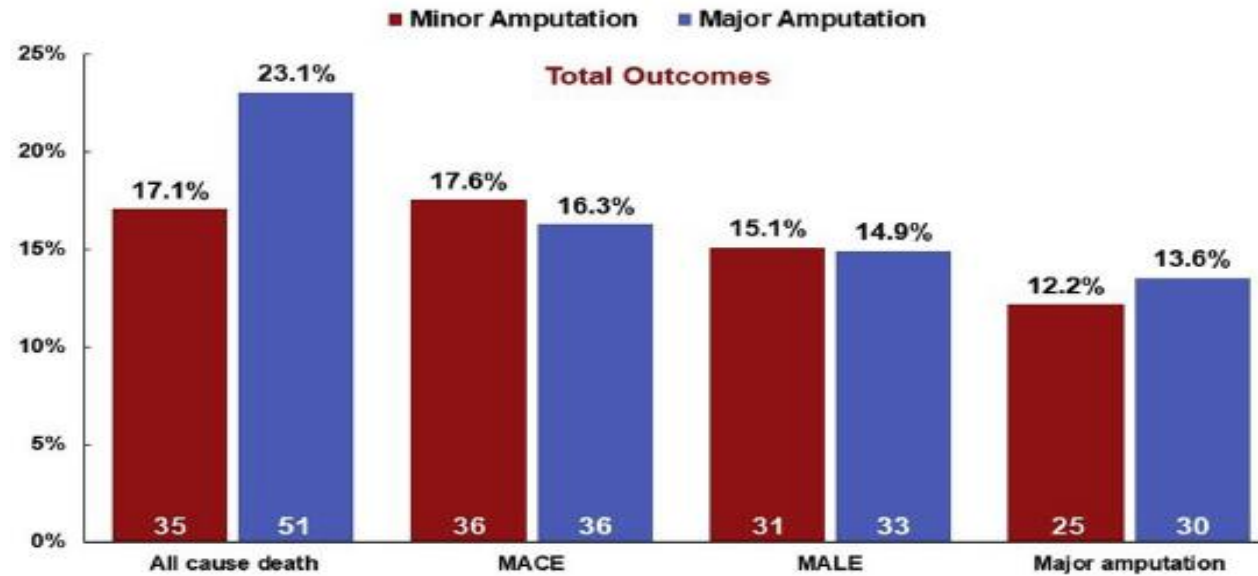
Why Diabetes?

	% VOYAGER ITT population
Type 2 DM	38%
Female	26%
Smoking (current/former)	80%
Prior amputation	6%
Statin use ay baseline	80%

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Age	1	-0.0106	0.00592	3.2329	0.0722
DM II	1	0.9105	0.0978	86.6618	<.0001
Gender	1	0.0690	0.1134	0.3701	0.5430
Ever Smoking	1	-0.1252	0.1211	1.0683	0.3013
Statin baseline	1	-0.2291	0.1159	3.9075	0.0481
Prior amputation	1	0.000679	0.00358	0.0361	0.8494

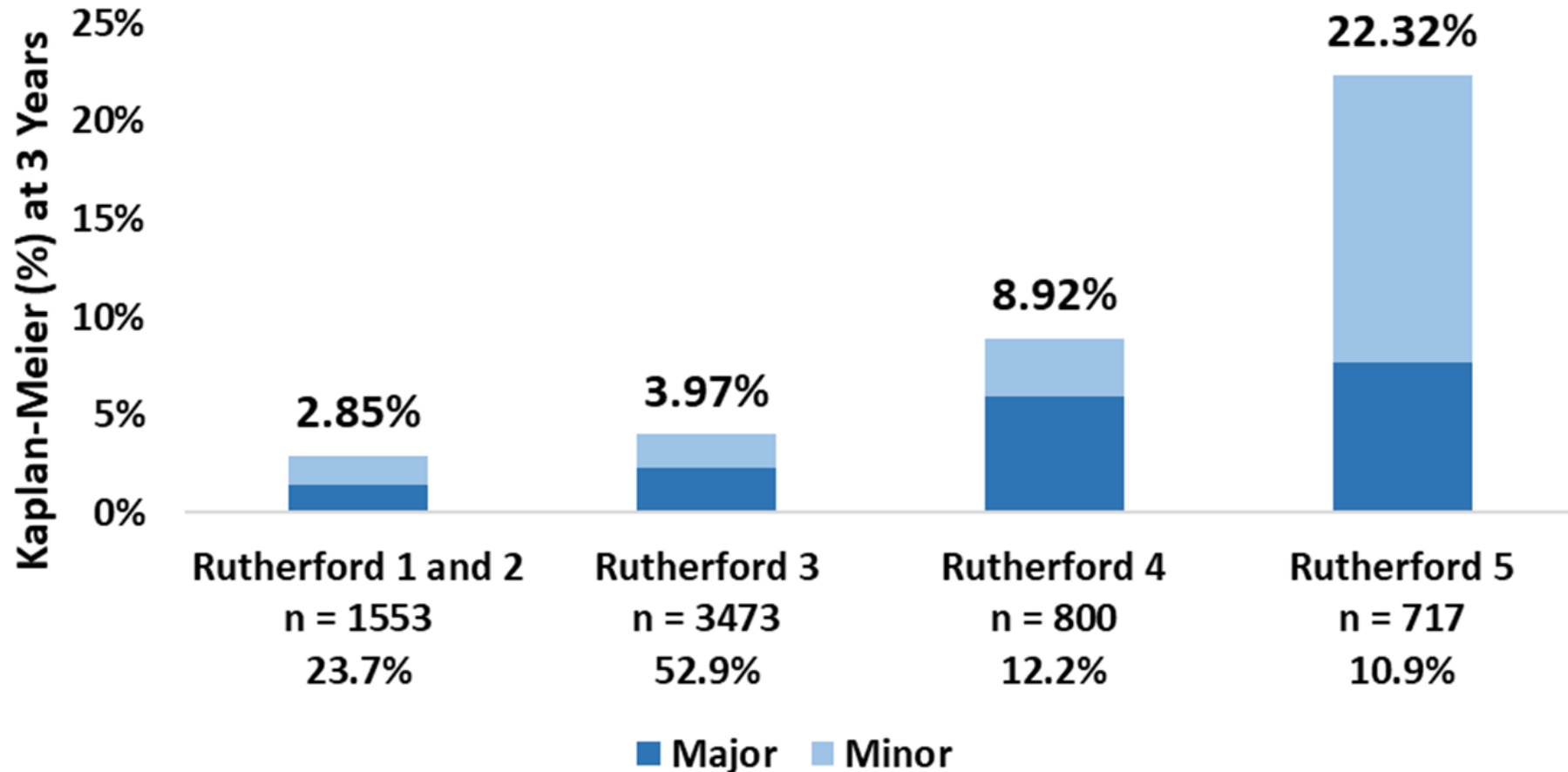
Why Minor and major amputations?



Govsyeyev et al. Etiology and outcomes of amputation in patients with peripheral artery disease in the EUCLID trial. JVS 2022

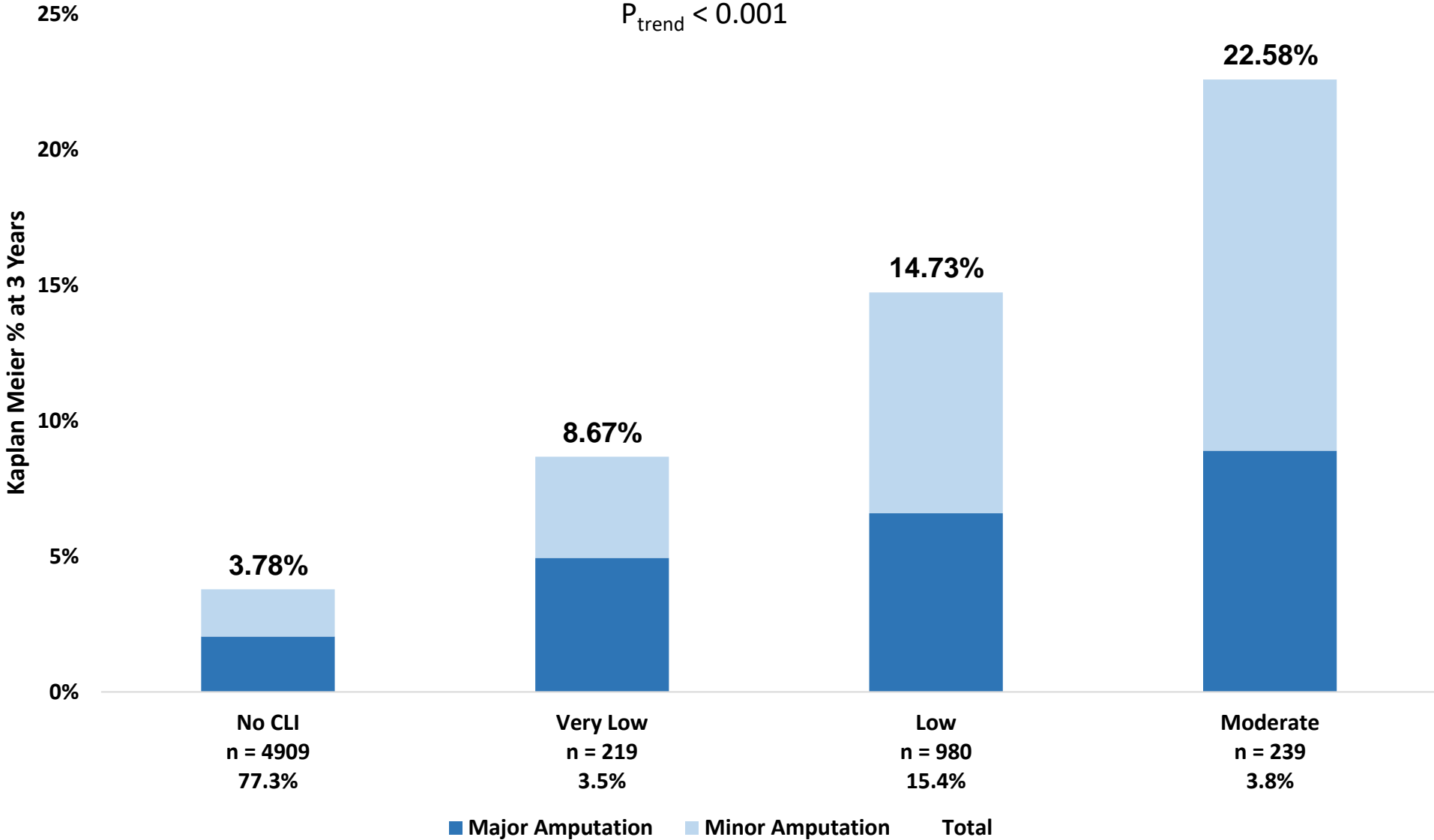
Incidence of Amputation at 3 Years By Rutherford Classification

p < 0.0001
trend

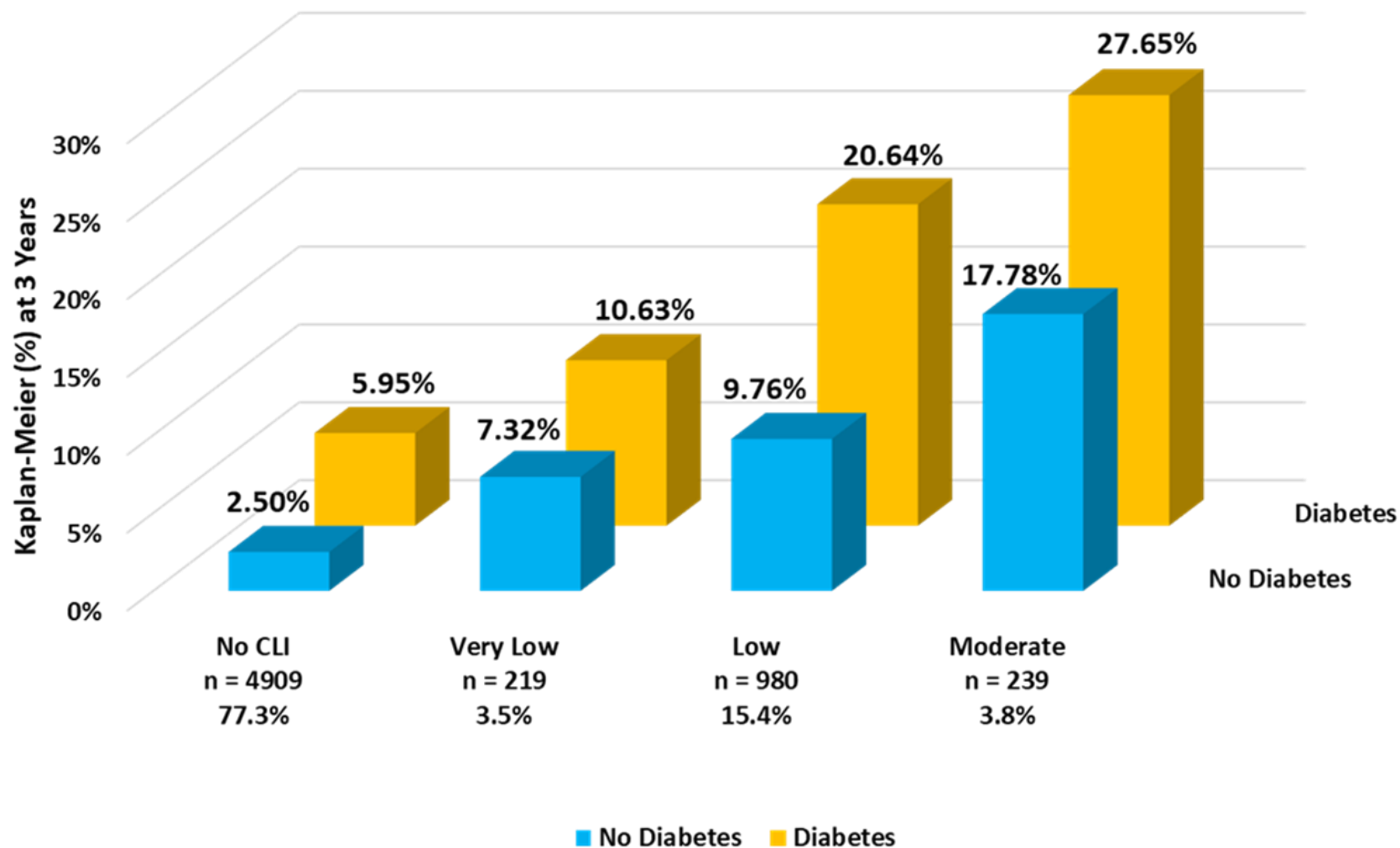


Incidence of All Amputations by Wifl Score at 3 Years

$P_{\text{trend}} < 0.001$



Incidence of Amputation at 3 Years by Wifl in Patients With and Without Diabetes Mellitus



Original Wifi Score

	Ischemia - 0				Ischemia - 1			
W-0	VL	VL	L	M	VL	L	M	H
W-1	VL	VL	L	M	VL	L	M	H
W-2	L	L	M	H	M	M	H	H
W-3	M	M	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3
	Ischemia - 2				Ischemia - 3			
W-0	L	L	M	H	L	M	M	H
W-1	L	M	H	H	M	M	H	H
W-2	M	H	H	H	H	H	H	H
W-3	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3

Modified DM-Wifi Score (patients without diabetes)

	Ischemia - 0				Ischemia - 1			
W-0	L	L	L	M	L	L	M	H
W-1	L	L	L	M	L	L	M	H
W-2	L	L	M	H	M	M	H	H
W-3	M	M	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3
	Ischemia - 2				Ischemia - 3			
W-0	L	L	M	H	L	M	M	H
W-1	L	M	H	H	M	M	H	H
W-2	M	H	H	H	H	H	H	H
W-3	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3

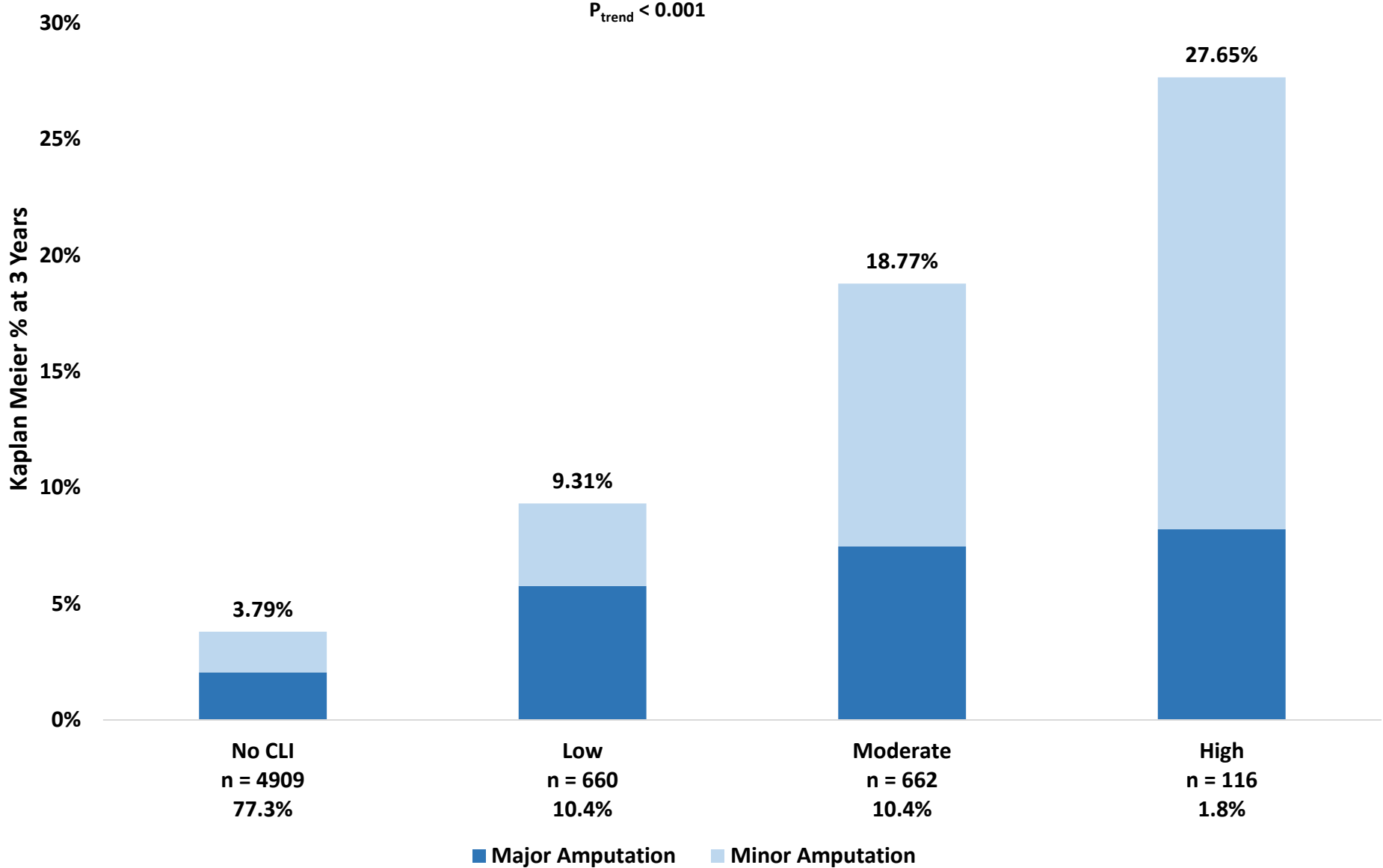
Original Wifi Score

	Ischemia - 0				Ischemia - 1			
W-0	VL	VL	L	M	VL	L	M	H
W-1	VL	VL	L	M	VL	L	M	H
W-2	L	L	M	H	M	M	H	H
W-3	M	M	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3
	Ischemia - 2				Ischemia - 3			
W-0	L	L	M	H	L	M	M	H
W-1	L	M	H	H	M	M	H	H
W-2	M	H	H	H	H	H	H	H
W-3	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3

Modified DM-Wifi Score (with Diabetes)

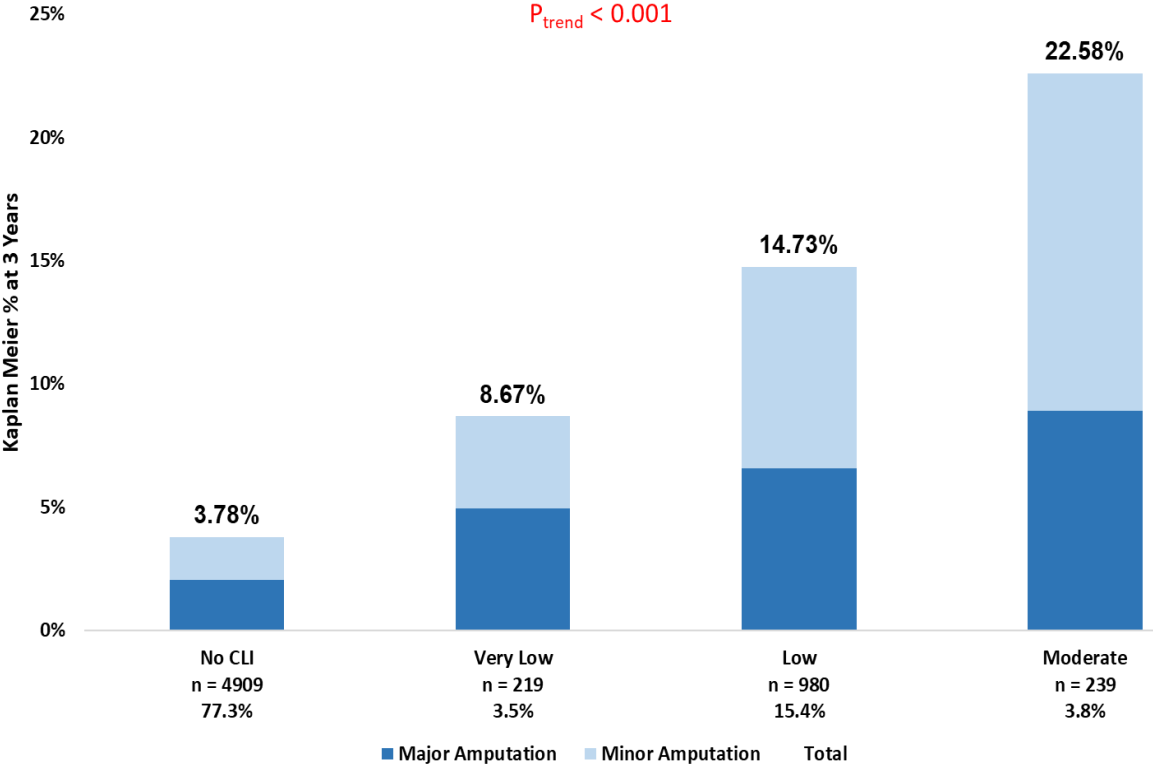
	Ischemia - 0				Ischemia - 1			
W-0	M	M	M	H	M	M	H	H
W-1	M	M	M	H	M	M	H	H
W-2	M	M	H	H	H	H	H	H
W-3	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3
	Ischemia - 2				Ischemia - 3			
W-0	M	M	H	H	M	H	H	H
W-1	M	H	H	H	H	H	H	H
W-2	H	H	H	H	H	H	H	H
W-3	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3

Incidence of All Amputations by Modified-DM Wifi Score at 3 Years



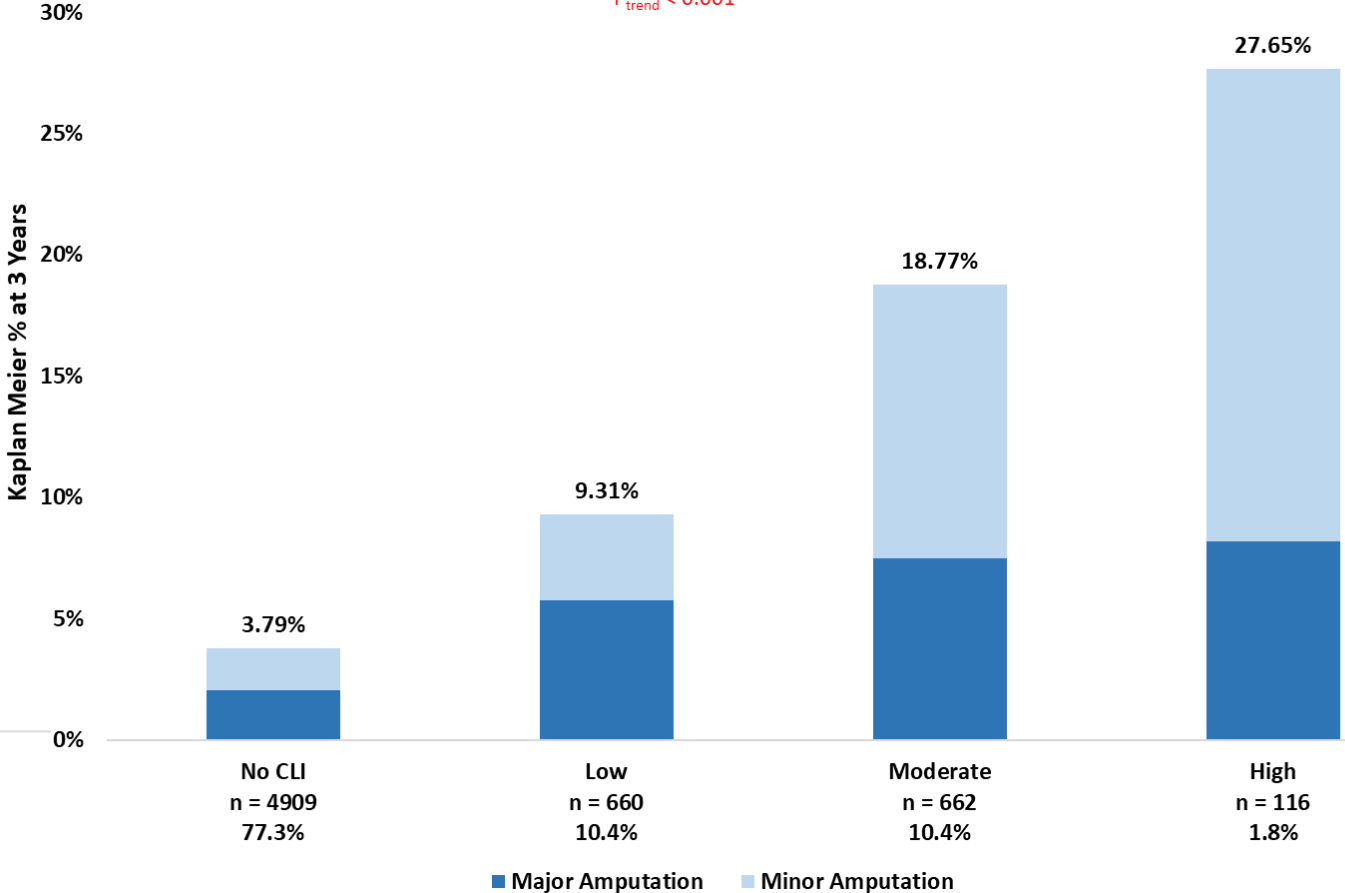
Incidence of All Amputations by Wifi Score at 3 Years

$P_{trend} < 0.001$



Incidence of All Amputations by Modified-DM Wifi Score at 3 Years

$P_{trend} < 0.001$



Conclusion

- **Stratifying amputation risk**
 - **Rutherford significantly associated with future amputation risk even after successful revascularization**
 - **Wifl associated with amputation risk, however, when stratified by Diabetes Mellitus, risk is increased across categories**
 - **A Novel DM-Wifl score can stratify risk in a different manner by including comorbid diabetes. This may make risk labels more appropriate and offer a more complete picture for our patients with diabetes.**