

**CRITICAL LIMB ISCHEMIA (CLI) NON-RESPONDERS:
PATIENTS WHO DO NOT RESPOND TO REVASCULARIZATION,
FACTORS THAT IDENTIFY NON-RESPONSE
AND NON-RESPONDER PREVALENCE AND MARKETS**

Mary L. Yost
404-520-6652
THE SAGE GROUP

THE SAGE GROUP, LLC
RESEARCH AND CONSULTING
23 Ridge Rd
Beaufort SC 29907

Copyright Pending
2020

All rights reserved, including the right of reproduction
in whole or in part in any form.

Table of Contents

SUMMARY	7
RISK FACTORS ASSOCIATED WITH NON-RESPONSE	7
CRITICAL LIMB ISCHEMIA POPULATION: PREVALENCE OF RISK FACTORS FOR NON-RESPONSE	8
Microvascular Disease (MVD)	9
Presence of Chronic Kidney Disease Combined With Diabetes	9
Small Artery Disease (SAD) in the Foot	10
Non-Patent Pedal Arch	10
Renal Foot.....	10
Ischemic and Neuroischemic Ulcers and Wounds in Diabetics	11
Below-The-Ankle (BTA) Disease in Diabetics with Ischemic Ulcers	11
PREVALENCE OF NON-RESPONDERS: SUMMARY OF 2020 ESTIMATES...	12
Prevalence of Non-Responders Based on Presence of Microvascular Disease	13
Prevalence of Non-Responders Based on Presence of Chronic Kidney Disease Combined With Diabetes	13
Prevalence of Non-Responders Based on Presence of Small Artery Disease	14
Prevalence of Non-Responders Based on Presence of Non-Patent Pedal Arch	14
Prevalence of Non-Responders Based on Presence of Renal Foot.....	14
Prevalence of Non-Responders Based on Presence of Ischemic Ulcers and Wounds in Diabetics	14
Prevalence of Non-Responders Based on Presence of Below-The-Ankle (BTA) Disease in Diabetics with Ischemic Ulcers	15
RENAL FOOT—THE BEST ESTIMATE OF NON-RESPONSE PREVALENCE	15
Some Limitations	15
Need for Additional Data on Prevalence of Foot Disease in Those with Microvascular Disease	16
Small Artery Disease—New Data	16
MICROVASCULAR DYSFUNCTION: THE LINK BETWEEN FOOT ARTERY DISEASE, DIALYSIS AND DIABETES?	16
MARKET FOR NON-RESPONDERS: SUMMARY OF 2020 ESTIMATES	17
INTRODUCTION	18
Outcomes Defining Non-Response to Revascularization.....	18
SOME CRITICAL LIMB ISCHEMIA PATIENTS DO NOT RESPOND TO SUCCESSFUL REVASCULARIZATION	18
Ulcer Healing	18
Ulcer Healing Rates Lower than Limb Salvage Rates.....	19
Amputation	19
FREQUENCY OF RESTENOSIS AND REPEAT REVASCULARIZATION AFTER PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)	20
Restenosis	20
Repeat Revascularization.....	20
CRITICAL LIMB ISCHEMIC PREVALENCE	20
MICROVASCULAR DISEASE (MVD)	21
The Microcirculation	21

Microangiopathy	22
Impairs Perfusion and Oxygen Delivery to the Skin	22
Need for New Technologies to Measure Tissue Oxygenation and Perfusion	22
Diabetes and Chronic Ischemia Cause Microvascular Disease	22
Both Cause Neuropathy	22
Microvascular Disease Increases the Risk of Amputation Alone and in Combination with Peripheral Artery Disease	23
Higher Probability of Below Ankle Amputation	23
In Diabetics Microvascular Disease Predicts Ulceration and Amputation	23
Microvascular Dysfunction Likely Systemic.....	24
Polyvascular Phenomenon?	25
Prevalence of Any Microvascular Disease in Peripheral Artery Disease.....	25
NUMBER OF NON-RESPONDERS BASED ON THE PRESENCE OF ANY MICROVASCULAR DISEASE	26
Prevalence.....	26
Market.....	27
CAN THE PRESENCE OF ANY ONE MICROVASCULAR DISEASE PREDICT NON-RESPONSE?	27
ISCHEMIC PERIPHERAL NEUROPATHY (IPN).....	27
Critical Limb Ischemia Causes Ischemic Peripheral Neuropathy	27
Research Has Rarely Distinguished Between Diabetic Peripheral Neuropathy and Ischemic Peripheral Neuropathy	28
Ischemic Peripheral Neuropathy Data Inadequate to Predict Non-Responders	28
RETINOPATHY.....	28
Retinopathy and Peripheral Artery Disease	28
Retinopathy Predicts Amputation in Diabetics.....	28
Research on Retinopathy in Critical Limb Ischemia Inadequate to Predict Non-Responders.....	29
CHRONIC KIDNEY DISEASE (CKD)	29
Definition	29
Risk of Ulcers and Amputation.....	29
Prevalence in Critical Limb Ischemia.....	30
End-Stage Renal Disease (ESRD)	30
Limitations of Chronic Kidney Disease to Predict Non-Responders	30
CHRONIC KIDNEY DISEASE COMBINED WITH DIABETES.....	31
Diabetes and End-Stage Renal Disease (ESRD) Predict Wound Healing.....	31
Atherosclerotic Disease Pattern and Characteristics in Diabetes and Renal Failure ...	31
Severity of Renal Failure Predicts Distal Disease	31
Chronic Kidney Disease—More Disease Located in the Foot	32
Diabetes and Dialysis Combined Predict Below-the-Knee and Foot Artery Disease	32
Prevalence in Critical Limb Ischemia.....	32
NUMBER OF NON-RESPONDERS BASED ON THE COMBINED PRESENCE OF CHRONIC KIDNEY DISEASE AND DIABETES.....	32
Prevalence.....	33
Market.....	33

FOOT OR BELOW-THE-ANKLE ATHEROSCLEROTIC DISEASE.....	34
Prevalence of Any Angiographic Foot Artery Disease in Critical Limb Ischemia	34
Diabetes and Chronic Kidney Disease—Higher Prevalence of Foot Artery Disease ..	35
CRITICAL LIMB ISCHEMIA—BIG ARTERY DISEASE AND SMALL	
ARTERY DISEASE OVERLAP IN THE FOOT.....	36
Disease in Multiple Territories—Primarily Below-The-Knee or Foot.....	36
Foot Artery Disease Associated with Below-the-Knee Disease and Critical Limb	
Ischemia	37
Dialysis Combined with Diabetes: Strongest Predictor of Below-the-Knee and Foot	
Disease	37
Medial Artery Calcification (MAC) and Small Artery Disease	38
NUMBER OF NON-RESPONDERS BASED ON THE PRESENCE OF SMALL	
ARTERY DISEASE IN THE FOOT	38
Prevalence	38
Market	39
NON-PATENT PEDAL ARCH.....	39
Noncompressible Arteries and Non-Patent Pedal Arch.....	40
Pedal Arch Patency Appears to Decline with Disease Severity	41
Severe Chronic Kidney Disease Predicts Loss of Patency	41
NUMBER OF NON-RESPONDERS BASED ON THE PRESENCE OF	
NON-PATENT PEDAL ARCH.....	41
RENAL FOOT	42
Severe Below-The-Knee and Foot Disease	42
Renal Foot Characteristics	42
Prevalence	43
NUMBER OF NON-RESPONDERS BASED ON THE PRESENCE OF RENAL	
FOOT	43
Prevalence	43
Market	44
ISCHEMIC AND NEUROISCHEMIC ULCERS.....	44
Peripheral Artery Disease Increases Risk of Diabetic Foot Ulcers (DFU).....	44
Peripheral Artery Disease Associated with Adverse Diabetic Foot Ulcer Outcomes ..	44
Severity of Ischemia Increases Risk of Adverse Outcomes	45
Ischemic and Neuroischemic Ulcers.....	45
Similar Skin Microvascular Abnormalities	45
Poorer Outcomes.....	45
NUMBER OF NON-RESPONDERS BASED ON THE PRESENCE OF	
ISCHEMIC AND NEUROISCHEMIC ULCERS.....	45
Prevalence	45
Market	46
BELOW-THE-ANKLE (BTA) DISEASE IN DIABETICS WITH ISCHEMIC	
AND NEUROISCHEMIC ULCERS.....	46
Prevalence	47

NUMBER OF NON-RESPONDERS BASED ON THE PRESENCE OF BELOW- THE-ANKLE (BTA) DISEASE IN PATIENTS WITH ISCHEMIC AND NEUROISCHEMIC ULCERS.....	47
Prevalence	47
Market	48
CONGESTIVE HEART FAILURE (CHF).....	49
APPENDIX I: CONSEQUENCES OF CHRONIC ISCHEMIA	50
Vessel Alterations, Tissue Damage, Systemic Effects and Neuropathy.....	50
Endothelial Dysfunction	50
Impaired Vasodilation.....	50
Also Affects the Microcirculation	51
Relationship to Disease Severity	51
The Common Link between Risk Factors and Atherosclerosis.....	51
Suppressed Collateral Vessel Growth.....	51
Factors Inhibiting Growth.....	51
Microcirculation Damaged by Low Blood Flow and Low Pressure	52
Constant Vasodilation and Unregulated Blood Flow	52
Excessive Blood Floods Capillaries.....	52
Edema	52
ISCHEMIC PERIPHERAL NEUROPATHY (IPN).....	53
Prevalence Increases with Severity of Ischemia.....	53
Other Neuropathies Frequently Present in Peripheral Artery Disease.....	53
APPENDIX II: DIABETES AND CRITICAL LIMB ISCHEMIA	54
Diabetic Abnormalities Promote Atherosclerosis and Thrombosis.....	54
Structural and Functional Vessel Abnormalities	54
Endothelial Dysfunction	55
Hypercoagulable State	55
Disease Located Below-the-Knee.....	55
Majority of Critical Limb Ischemia Patients Have Diabetes	55
APPENDIX III: THE NEUROISCHEMIC FOOT	56
Neuropathy.....	56
Caused by Microcirculatory Dysfunction and Metabolic Abnormalities	56
Exacerbated by Ischemia	56
Reduced Capillary Flow Leads to Skin Ischemia.....	56
A Biologically Compromised Foot Vulnerable to Ischemia.....	57
Propensity to Develop Ulcers, Infection and Gangrene.....	57
REFERENCES.....	58
INDEX OF TABLES	72

CONTACT INFORMATION

Mary L. Yost
President
Telephone (404) 520-6652
yost@thesagegroup.us