

CRITICAL LIMB ISCHEMIA UNITED STATES EPIDEMIOLOGY

TABLE OF CONTENTS

CRITICAL LIMB ISCHEMIA	1
CONCLUSION	9
U.S. CRITICAL LIMB ISCHEMIA PREVALENCE.....	9
MARKET OPPORTUNITY—ENDOVASCULAR	9
MARKET OPPORTUNITY—PHARMACEUTICAL.....	9
MARKET OPPORTUNITY—MECHANICAL THROMBECTOMY	10
MARKET FOR PATIENTS UNSUITABLE FOR REVASCLARIZATION	10
DIAGNOSTIC MARKET	10
NEW MARKET FOR ADJUNCT THERAPY IN REVASCLARIZED PATIENTS.....	10
<i>Restenosis Prevention Market</i>	10
OPTIMUM METHODS TO ESTIMATE CLI	10
INTRODUCTION	11
PURPOSE.....	12
2010 REVISED CRITICAL LIMB ISCHEMIA ESTIMATES	12
METHODS	12
PERIPHERAL ARTERIAL DISEASE (PAD)	13
INTERMITTENT CLAUDICATION	13
AN UNCOMMON SYMPTOM	13
LIMB ISCHEMIA	13
ACUTE LIMB ISCHEMIA (ALI)—LEG ATTACK	14
<i>Location</i>	14
<i>Occlusion Classification System</i>	14
CRITICAL LIMB ISCHEMIA (CLI)	15
SYMPTOMS	15
RISK FACTORS.....	15
<i>A Bilateral Disease</i>	15
<i>Multilevel Disease</i>	16
CLI—CLINICAL CLASSIFICATION	16
FONTAINE DISEASE CLASSIFICATION SYSTEM	16
RUTHERFORD CLASSIFICATION SYSTEM.....	16
CHRONIC ISCHEMIA	17
VESSEL ALTERATIONS, TISSUE DAMAGE AND SYSTEMIC EFFECTS	17
ENDOTHELIAL DYSFUNCTION.....	17
COLLATERAL VESSEL GROWTH SUPPRESSED.....	18
<i>Factors Inhibiting Growth</i>	18
MICROCIRCULATION DAMAGED BY INADEQUATE BLOOD FLOW AND PRESSURE.....	18
MALFUNCTION RESULTS IN STATE OF CONSTANT VASODILATION.....	19
<i>Flooded Capillaries</i>	19
EDEMA	19
SHORT-TERM CONSEQUENCES—DEATH AND LIMB LOSS	19
SIX MONTHS—20% MORTALITY AND 40% AMPUTATION	19

PATIENTS UNSUITABLE FOR REVASCLARIZATION	20
HIGH ONE-YEAR AMPUTATION RATE	20
ABI INVERSELY ASSOCIATED WITH AMPUTATION	20
OUTCOMES IN REVASCLARIZED PATIENTS	21
30-DAY MORTALITY AND AMPUTATION	21
<i>The Swedish Vascular Registry (Swedvasc)</i>	21
<i>Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) Trial</i>	22
<i>Project or Ex-Vivo Vein Graft Engineering via Transfection Study III (PREVENT III)</i>	23
THREE-MONTH OUTCOMES	23
ONE-YEAR OUTCOME	24
END-STAGE DISEASE—30% FIVE-YEAR SURVIVAL	24
FIVE-YEAR MORTALITY EXCEEDS MOST OTHER DEADLY DISEASES	24
DISEASE SEVERITY REDUCES SURVIVAL	24
FOUR-YEAR EVENT-FREE SURVIVAL DECLINES WITH DISEASE SEVERITY	24
LONG-TERM MORTALITY INCREASES WITH DISEASE SEVERITY	25
CAUSE OF DEATH.....	26
SERIOUS COMORBIDITIES	26
DIABETES.....	27
DIABETES DEFINED	27
<i>A Note on Diabetes Terminology</i>	27
PREDIABETES DEFINED	27
RISK FACTORS.....	27
MORTALITY.....	28
DIABETES AND PREDIABETES—AN EPIDEMIC	28
DIABETES AND PREDIABETES—42% OF THE U.S. ADULT POPULATION	28
DIABETES AND RACE/ETHNICITY	28
DIABETES PREVALENCE INCREASES WITH AGE	28
DIABETES AND PAD	29
PAD PREVALENT IN DIABETICS	29
DIABETIC ABNORMALITIES PROMOTE ATHEROSCLEROSIS AND THROMBOSIS.....	30
<i>Structural and Functional Vessel Abnormalities</i>	30
<i>Endothelial Dysfunction</i>	30
<i>Hypercoagulable State</i>	30
GREATER RISK OF DEVELOPING PAD	30
FACTORS THAT INCREASE RISK OF PAD IN DIABETICS.....	30
EXCESS CARDIOVASCULAR MORBIDITY AND MORTALITY	31
DISEASE LOCATED BELOW THE KNEE	31
THE NEUROISCHEMIC FOOT	31
NEUROPATHY IS COMMON	31
CAUSED BY MICROCIRCULATORY DYSFUNCTION AND METABOLIC ABNORMALITIES	31
A BIOLOGICALLY COMPROMISED FOOT VULNERABLE TO ISCHEMIA	32
PROPENSITY TO DEVELOP ULCERS, INFECTION AND GANGRENE.....	32
<i>Eurodiale—High Prevalence of PAD in Patients with Foot Ulcers</i>	32
FOOT ULCERS PRECEDE AMPUTATIONS	33
DIABETES AND CRITICAL LIMB ISCHEMIA	33
HIGHER RISK OF CLI AND MORE SEVERE DISEASE	34

DIABETIC PATIENTS PRESENT WITH ADVANCED ISCHEMIA	34
CLI DEVELOPS SUDDENLY	34
DIABETES INCREASES THE RISK OF AMPUTATION	34
<i>Risk of Amputation Related to Severity of Diabetes</i>	35
HIGHER MORTALITY	35
ADDITIONAL RISK FACTORS INCREASE SEVERITY	35
<i>Diabetes and Smoking—A Deadly Combination</i>	35
CHRONIC KIDNEY DISEASE (CKD)	36
DEFINITIONS	36
DRAMATIC INCREASE IN U.S. ESRD PATIENTS	36
ESRD ASSOCIATED WITH HIGH INCIDENCE OF CARDIOVASCULAR MORBIDITY AND MORTALITY	36
<i>Morbidity and Mortality Increase with Severity of CKD</i>	37
CALCIFICATION	37
<i>Present in 40% to 70% of ESRD Patients</i>	38
<i>Associated with Diabetes</i>	38
PAD AND CHRONIC KIDNEY DISEASE	38
PAD COMMON IN DIALYSIS PATIENTS	38
DIALYSIS OUTCOMES AND PRACTICE PATTERNS STUDY (DOPPS)	38
CKD INCREASES THE RISK FOR DEVELOPING PAD	39
<i>PAD Incidence and Prevalence Higher in More Severe Disease</i>	39
ABI PREDICTS MORTALITY IN ESRD	40
KIDNEY DISEASE, DIABETES AND PAD—A LIFE AND LIMB THREATENING COMBINATION	40
HIGH PREVALENCE OF PAD IN PATIENTS WITH BOTH CHRONIC KIDNEY DISEASE AND DIABETES	40
PATIENTS WITH KIDNEY FAILURE CAUSED BY DIABETES—PAD PRESENT IN 36%	40
PAD INCIDENCE HIGHEST IN PATIENTS WITH DIABETES AND KIDNEY DISEASE	41
SIGNIFICANTLY INCREASED RISK OF AMPUTATION	42
CRITICAL LIMB ISCHEMIA AND CHRONIC KIDNEY DISEASE	42
CRITICAL LIMB ISCHEMIA IS COMMON IN ESRD PATIENTS	42
CLI SEVERITY RELATED TO SEVERITY OF KIDNEY DYSFUNCTION	42
MORTALITY	43
<i>Critical Limb Ischemia Predicts All-Cause Mortality in Dialysis Patients</i>	43
<i>Renal Dysfunction Predicts Mortality in Critical Limb Ischemia Patients</i>	43
AMPUTATION MORE LIKELY IN DIALYSIS PATIENTS	44
<i>Concurrent with Revascularization</i>	44
<i>Poor Amputation-Free Survival</i>	45
DISEASE LOCATED BELOW THE KNEE	45
CLI—A PRIMARY CAUSE OF DEATH IN ESRD?	46
ESTIMATING THE PREVALENCE OF CLI	47
METHODS	47
INCIDENCE AND PREVALENCE DEFINED	47
SUMMARY OF INCIDENCE ESTIMATES	48
INCIDENCE—OVERVIEW OF METHODS	48
PROGRESSION FROM IC	49
2010 INCIDENCE ESTIMATE	49
LIMITATIONS	49
NUMBER OF HOSPITALIZATIONS OR REVASCULARIZATION PROCEDURES	49
LIMITATIONS	49

NUMBER OF AMPUTATIONS.....	50
2010 INCIDENCE ESTIMATE	50
LIMITATIONS	50
COMBINATION METHODS—ITALIAN STUDY	50
2010 INCIDENCE ESTIMATE	50
SURVEY OF VASCULAR SURGEONS IN GREAT BRITAIN AND IRELAND.....	50
CLI INCIDENCE ESTIMATE.....	51
STUDY DESCRIPTION	51
UNDERESTIMATES NUMBER WITH CLI.....	51
OXVASC—POPULATION-BASED INCIDENCE BY AGE AND SEX	52
DESCRIPTION.....	52
INCIDENCE BY AGE AND SEX.....	52
2010 INCIDENCE ESTIMATE	53
LIMITATIONS	53
PREVALENCE ESTIMATED FROM INCIDENCE.....	53
SUMMARY OF CLI PREVALENCE ESTIMATES.....	54
DISEASE PROGRESSION IN IC PATIENTS	55
2010 PREVALENCE ESTIMATE	55
LIMITATIONS ASSOCIATED WITH DISEASE PROGRESSION FROM IC	55
<i>Based on the Minority of PAD Patients</i>	<i>55</i>
<i>Excludes Non-IC Patients.....</i>	<i>55</i>
SHORTCOMINGS IN OLDER STUDIES THAT MEASURED PROGRESSION.....	56
AS MANY AS HALF OF CLI PATIENTS DEVELOP CLI WITHOUT PRIOR SYMPTOMS	56
IC MAY PROGRESS TO CLI AT HIGHER RATES	56
PREVALENCE BASED ON POPULATION SURVEYS	57
HUNT STUDY.....	57
DESCRIPTION.....	57
RESULTS BY AGE AND SEX.....	57
2010 PREVALENCE ESTIMATE	58
LIMITATIONS	58
2010 PREVALENCE ADJUSTED FOR POPULATION 70 YEARS AND OLDER.....	58
<i>Based on 60%-80% CLI Occurring in Population Age 70 and Older.....</i>	<i>58</i>
<i>Based on 5%-10% of Population Age 70-79 with CLI.....</i>	<i>58</i>
NEW SOUTH WALES RURAL COMMUNITY STUDY	59
RESULTS.....	59
2010 PREVALENCE ESTIMATE	60
CLI PREVALENCE ESTIMATED FROM PAD POPULATION.....	60
PAD PROJECTIONS	60
METHOD —PAD POPULATION BY DISEASE SEVERITY	61
2010 CLI PREVALENCE	61
CLI PREVALENCE ESTIMATED FROM HIGH RISK GROUP—DIABETICS.....	61
A NOTE ON PAD DIAGNOSTIC METHOD	61
<i>Limitations of ABI < 0.90</i>	<i>61</i>
<i>Abnormally High ABI May Also Indicate Disease.....</i>	<i>62</i>
PAD PREVALENCE IN DIABETES.....	62

CARDIOVASCULAR HEALTH STUDY	64
THE HOORN STUDY	64
SEATTLE STUDY OF DIABETIC AND NONDIABETIC VOLUNTEERS AGE 12-90	65
NEWLY DIAGNOSED DIABETICS IN ITALY	66
KRISTIANSTAD POPULATION-BASED STUDY	66
FREMANTLE DIABETES STUDY	66
DIABETICS IN A MICHIGAN HMO	67
SMALL PILOT STUDY IN ENGLISH HOSPITAL CLINIC	67
DIABETICS IN HELSINKI.....	67
THE ‘MEN BORN IN 1914’ STUDY	67
POPULATION IN EAST DORSET, ENGLAND	68
GERMAN EPIDEMIOLOGICAL TRIAL ON ANKLE BRACHIAL INDEX (GETABI)	68
NHANES II—PHYSICIANS EXAMINATION.....	69
NHANES 1999-2000	69
NHANES 1999-2002—ELDERLY DIABETICS	69
CLI ESTIMATES BASED ON THE DIABETES METHOD.....	70
ESTIMATION METHODS AND ASSUMPTIONS	71
POPULATION AGE 65 AND OLDER	71
<i>Glucose Status by Sex</i>	71
<i>PAD Prevalence by Glucose Status</i>	72
<i>Critical Limb Ischemia by Glucose Category</i>	72
POPULATION AGE 45-64.....	73
<i>Glucose Status</i>	73
<i>PAD Prevalence by Glucose Status</i>	74
<i>Critical Limb Ischemia by Glucose Status</i>	74
PAD AND CLI ESTIMATES BASED ON INCREASING PREVALENCE OF DIABETES	75
CLI PROJECTIONS.....	75
CRITICAL LIMB ISCHEMIA—MARKET OPPORTUNITIES	77
ENDOVASCULAR MARKET	77
METHODS AND ASSUMPTIONS—CURRENT MARKET.....	77
METHODS AND ASSUMPTIONS—POTENTIAL MARKET	79
<i>Actual CLI Treatment Pathway Often Differs from the Ideal</i>	80
IMPACT OF NEW ENDOVASCULAR TECHNOLOGIES.....	80
GREATER SHARE OF LIMBS TREATED.....	81
SIGNIFICANT INCREASE IN MARKET VALUE.....	81
STENTS.....	82
CURRENT STENT MARKET.....	82
IMPACT OF NEW STENT TECHNOLOGY ON MARKET POTENTIAL	82
PHARMACEUTICAL THERAPIES	83
RISK FACTOR MODIFICATION	83
ANTIHYPERTENSIVES	83
ANTILIPIDS	84
ANTIPLATELETS	85
NO REVASCUARIZATION PATIENTS	86
DIAGNOSTIC MARKET	86

ADJUNCT THERAPY IN REVASCULARIZED PATIENTS	86
RESTENOSIS PREVENTION IN BYPASS PATIENTS	87
RESTENOSIS TREATMENTS IN ENDOVASCULAR PATIENTS	87
THROMBOLYTICS	87
MECHANICAL THROMBECTOMY	87
APPENDIX A: COMPARISON OF PAD ESTIMATES WITH PREVIOUS ESTIMATES	89
REFERENCES	90
INDEX OF TABLES	103
INDEX OF FIGURES	105
GLOSSARY	106
DISCLOSURE STATEMENT	147
CONTACT INFORMATION	148