ACKNOWLEDGEMENTS

During this journey of the compilation of my thesis, I have been helped, supported and encouraged by many, and I am feeling short of words to express my gratitude towards them.

I consider myself lucky to have ***Dr. Vishnu Motukuru, Consultant Vascular Surgeon,*** *Jain Institute of Vascular Sciences (JIVAS), as my supervisor and mentor. He has been a great teacher and a splendid personality. His clinical acumen, surgical skill and wisdom are well known and unparalleled. I will always cherish the time I spent under his guidance. He is, and will always remain as a source of inspiration for me.*

I am extremely thankful to my co-supervisors ***Dr. K.R. Suresh,*** *Director, JIVAS and* ***Dr. Umesh N.*** *Medical Director, Bhagwan Mahaveer Jain Hospital for their helping attitude and invaluable guidance that has helped me bring this work to its logical conclusion.*

I express my sincere thanks to ***Dr. Vivekanand, Dr. Sumanth Raj K B, Dr. Indushekar, Dr. Mamatha S H, Dr. Girija and Dr. Nikhil Dhanpal*** *Consultants, JIVAS for their valuable help and the encouragement and support they provided me, during my work.*

I would also like to thank ***Dr. Chethana*** *and* ***Dr. Poonam*** *for their valuable contribution towards patient counselling and timely follow-up.*

I sincerely thank all the patients who were part of the study for their cooperation.

I express my gratitude for the generous help and cooperation provided to me by my seniors ***Dr. Vaibhav, Dr. Surya Kiran, Dr. Pavan B K,*** *and my colleagues* ***Dr. Siddharth M. and Dr. (Lt Col) Vinay Nazareth*** *in completing my work. I am deeply indebted to my senior* ***Dr. Roshan Rodney*** *for taking time to assess my thesis and provide his valuable feedback despite his busy schedule. I would like to express my gratitude to* ***Dr. M. G. Sayyad*** *for his important contribution in writing materials and statistics during my work.*

I would like to express my gratitude to all our department staff Mrs. Hema, Mrs. Deepa, Mr. Sunil, Mr Ashok, Mr. Uday, Mr. Albert, Mrs. Prema, for their help in maintaining patient records and for data collection.

I would also like to express my gratitude to ***Dr. Vinod Naik*** *and* ***Dr. Shashank Shrotriya****, KEM Hospital Pune, who have been inspiring me throughout my journey of residency.*

I am very grateful to my family for their relentless love and affection towards me.

Last but not the least; I specially thank my husband ***Mr. Siddhant Sawant*** *for his constant support and cooperation along with the technical help that he has provided and my sister* ***Miss Tejal Melge*** *for her encouragement.*

Place: Bengaluru

August 2023

TABLE OF ABBREVIATIONS AND ACRONYMS:

ABI - Ankle-brachial index

AI - Aortoiliac

AKA - Above-knee amputation

AP - Ankle pressure

AT - Anterior tibial

BKA - Below-knee amputation

BMI - Body mass index

CAD - Coronary artery disease

CE-MRA - Contrast-enhanced MRA

CFA - Common femoral artery

CKD - Chronic kidney disease

CLI - Critical limb ischemia

CLTI - Chronic limb-threatening ischemia

CT - Computed tomography

CTA - Computed tomography angiography

CTO - Chronic total occlusion

CVD - Cardiovascular disease

DAPT - Dual antiplatelet therapy

DCB - Drug-coated balloon

DES - Drug-eluting stent

DFU - Diabetic foot ulcer

DM - Diabetes mellitus

DP - Dorsalis pedis

DSA - Digital subtraction angiography

DUS - Duplex ultrasound

EBR - Evidence-based revascularization

ESVS - European Society for Vascular Surgery

FP - Femoropopliteal

GLASS - Global Limb Anatomic Staging System

GSV - Great saphenous vein

GVG - Global Vascular Guidelines

HICs - High-income countries

IC - Intermittent claudication

IM - Inframalleolar

IP - Infrapopliteal

LBP - Limb-based patency

LDL-C - Low-density lipoprotein cholesterol

LMICs - Low- and middle-income countries

MACE - Major adverse cardiovascular event

MALE - Major adverse limb event

MRA - Magnetic resonance angiography

PAD - Peripheral artery disease

PBA - Plain balloon angioplasty

PFA - Profunda femoris artery

PLAN - Patient risk estimation, limb staging, anatomic pattern of disease

PSV - Peak systolic velocity

PT - Posterior tibial

PVR - Pulse volume recording

RCT - Randomized controlled trial

SFA - Superficial femoral artery

SVS - Society for Vascular Surgery

TAP - Target arterial path

TBI - Toe-brachial index

TcPO2 - Transcutaneous oximetry

TP - Toe pressure

WFVS - World Federation of Vascular Societies

WIfI - Wound, Ischemia, foot Infection

ABSTRACT

TITLE: "Validation of 'PLAN Concept' in patients with Critical Limb Threatening Ischemia (CLTI) undergoing infrainguinal revascularization."

AIMS and OBJECTIVES:

- Assessing patient outcome of an intervention suggested by PLAN Concept based on
  1. **P**atient risk,
  2. **L**imb severity, and
  3. **AN**atomic pattern of disease, in that order of priority.

- Assessment of validity of PLAN concept in assessing MALE and MACE outcome and wound healing rate post-revascularization for CLTI.

MATERIALS and METHODS: This is a single center, prospective, observational and longitudinal study carried out at Jain Institute of Vascular Sciences (JIVAS), Bhagwan Mahaveer Jain Hospital, Bangalore. Total of 318 patients with CLTI who underwent successful infrainguinal revascularization at JIVAS between January 2021 to December 2021 were included in the study and followed prospectively at 1, 3 and 6 months as per study protocol. The interventions i.e., endovascular or open bypass (including hybrid procedure), were carried out on the patients in accordance with established recommendations and the surgeon's personal preferences and judgment. At the end of the follow up period an analysis was made of whether or not the wound had successfully healed.

Patients were then divided into three groups: MATCHED GROUP i.e., patients in whom the procedure performed matched the procedure that PLAN Concept suggested, UNMATCHED GROUP i.e., patients in whom the procedure performed did not match the procedure the PLAN Concept suggested and INDETERMINATED GROUP i.e., patients in whom PLAN Concept suggestion was Indeterminate. At the end of the study, we assessed the outcomes, i.e., wound healing rates, rate of amputation and mortality and compared them between the matched and unmatched group. For the indeterminate group, the outcomes were compared between the patients who underwent endovascular intervention and those who underwent open bypass (including hybrid).

RESULTS: The study included 318 patients between the ages 30 to 92 with a mean age of 65.68 ± 11.08 years. 84.9% patients were males. Most common comorbidity noted was diabetes mellitus (90.9%) followed by hypertension (68..2%), CAD (37.7%), CKD (14.5%), COPD

(11.3%), dyslipidaemia (10.4%). 38.7% patients were smokers. According to Rutherford classification, we had 6.3% Category 4 patients, 67.3% category 5 patients and 26.4% category 6 patients. As per VQI mortality prediction model for infrainguinal revascularization, 94.3% of our patients were low-risk, 1.6% medium risk and 4.1% high risk. The number of patients with WIfI stage 1, 2, 3, and 4 was 0 (0%), 25 (7.9%), 77(24.2%) and 216 (67.9%) respectively. The number of patients with GLASS stage I, II, and III was 94 (29.6%), 125 (39.3%), and 99 (31.1%), respectively. Among the 318 patients, the number subject to bypass/hybrid surgery and endovascular therapy 56 (17.6%) and 262 (82.4%) respectively. PLAN Concept projected endovascular, bypass and indeterminate for 101 (31.76%), 89 (27.98%) and 128 (40.25%) respectively. At the end of 6 months, 187 patients (58.8%) had healed wounds, 31 (9.7%) died, 22 (6.9%) survived with major amputations and 30 (9.7%) were lost to follow-up. As segregated by PLAN concept, 135 (42.45%) underwent procedure that matched that suggested by PLAN, in 55 (17.29%) the procedure did not match and in 128 (40.25%) were indeterminate. The incidence of wound healing at the end of 6-month follow-up was significantly higher and the incidence of MALE/MACE outcomes was significantly lower in the matched cohort compared to the non-matched cohort with a P-value of 0.041 and <0.004 respectively. In the indeterminate cohort, both the wound healing rates and the MALE/MACE outcomes did not significantly differ between the endovascular and the bypass group.

CONCLUSIONS:

- Patients undergoing revascularization procedure that is in accordance with PLAN Concept, have better wound healing rates and lesser MALE/MACE outcomes.
- Both endovascular and bypass procedures will result in similar rates of wound healing and MALE/MACE outcomes for patients for whom the projection as per the PLAN Concept is indeterminate.
- In about 40% patients, the projection as per PLAN concept is indeterminate. This group requires further analysis and outcome data for a comprehensive idea of the ideal course of action.
- While planning a revascularization procedure for a patient with CLTI it is prudent to consider patient's comorbidities, complete clinical profile, wound status and vascular lesion in order to provide the best possible therapeutic option. PLAN Concept individualizes treatment option for every patient while taking into account all these parameters.

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1. INTRODUCTION

Chronic limb-threatening ischemia (CLTI) is highly morbid and advanced stage of peripheral vascular disease. Peripheral Arterial Disease affects more than 200 million people worldwide of which 11% have CLTI. It poses major burden on health care system while also deteriorating a patient's quality of life and hindering socio-economic growth [1,2].

Despite extensive educational programs and campaigns, the awareness regarding peripheral arterial disease remains dismal both among general public as well as doctors in developing countries.

CLTI management involves a multidisciplinary approach involving a vascular specialist, a podiatrist, a psychiatrist, a wound care nurse, a counsellor. Variability in practice patterns is also thereby high, contributing to a broad disparity in the utilization of treatments and clinical outcomes.

The choice of surgery or endovascular therapy as the initial treatment remains an ongoing debate among interventionalists worldwide. The patient's vascular disease pattern, surgical risk, the presence of an autogenous conduit for vein bypass, and patient preference are currently taken into consideration while planning an intervention, along with physician considerations like training, skill set, and treatment bias. [3,4,5] The extent to which this variability affects clinical outcomes in patients with CLTI is unknown. [3,5,6]

In an era of evidence-based medicine, such disparity is unacceptable as the basic goal of health care is to provide the best possible treatment to the patient. Hence in 2013 when the Global Vascular Guidelines were launched, the primary focus was CLTI. The goal was to improve the quality of care for patients with CLTI. This goal led to the development of Evidence Based Revascularization (EBR) which was a patient- and limb-centric approach rather than lesion-based treatment.

The PLAN concept of EBR stresses a structured management approach based on Patient risk, Limb severity, and ANatomic pattern of disease, in that order of priority.

To enhance the quality of the available evidence and attain EBR for patients with CLTI, the authors of GVG believe that adequate classification along these three distinct axes is clinically pertinent and essential.

2. REVIEW OF LITERATURE:

Atherosclerotic occlusive disease of arteries other than those supplying the heart and the brain is known as peripheral arterial disease (PAD). It is a major health concern that is physically, mentally and financially crippling for the patient.

Its prevalence rises with co-occurring diabetes, smoking, hypertension, and dyslipidemia in the aging population.

With an accompanying decreased quality of life for an aging population, it has grown to be a significant cause of death, morbidity, and an increasing financial burden on the patients and the healthcare industry.

Unfortunately, due to the high prevalence of atypical symptoms or pre-clinical disease, there is a dearth of precise data regarding the prevalence and incidence of PAD.

Additionally, when a patient first presents with these symptoms to a clinician, they do not always employ PAD screening methods.

As a result, epidemiologic data have been extrapolated from other measurable diseases (like diabetes) and outcomes (like amputation) with known relationships to underlying PAD, as well as from isolated community screening studies, data on symptomatic states like intermittent claudication. [7]

In patients with PAD, the arteries of the extremity are narrowed by atherosclerotic plaques with limit the blood flow in the limb distal to narrowing. This reduction in blood flow presents in many ways. While some patients present with no or atypical symptoms, most present with typical symptoms such as intermittent claudication, rest pain or tissue loss in the form of gangrene or non-healing ulcer.

PAD in often a marker of systemic atherosclerosis with high incidence of cardiovascular and cerebrovascular morbidity and mortality. Therefore, patients with PAD have an equivalent cardiovascular risk to patients with previous myocardial infarction and require aggressive risk factor modification to improve their long-term survival.

The management of PAD varies depending on the disease severity and symptom status. [8,9,10]

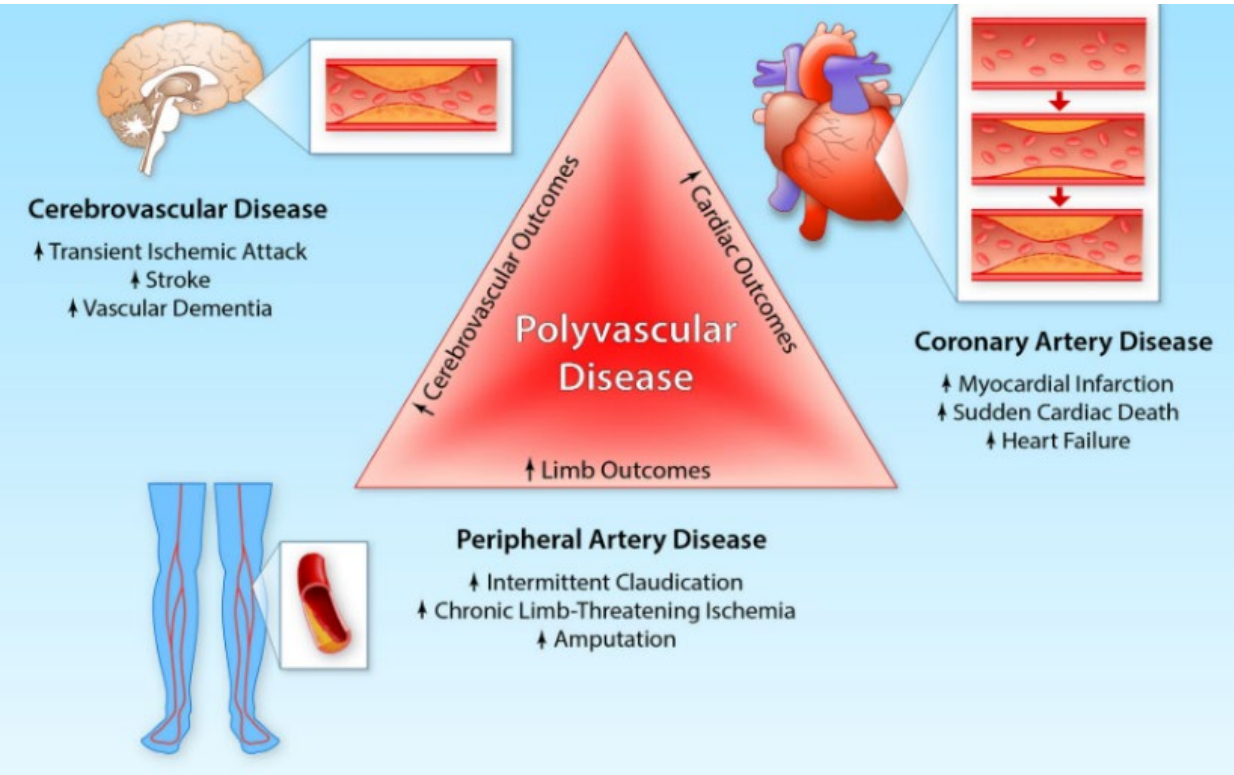


Figure 2.1: Polyvascular Nature of Atherosclerotic disease process [11]

Risk factors for PAD include:

1. Diabetes
2. Smoking
3. Obesity (a body mass index over 30)
4. High blood pressure
5. High cholesterol
6. Increasing age, especially after reaching 50 years of age
7. A family history of peripheral artery disease, heart disease or stroke
8. High levels of homocysteine, a protein component that helps build and maintain tissue

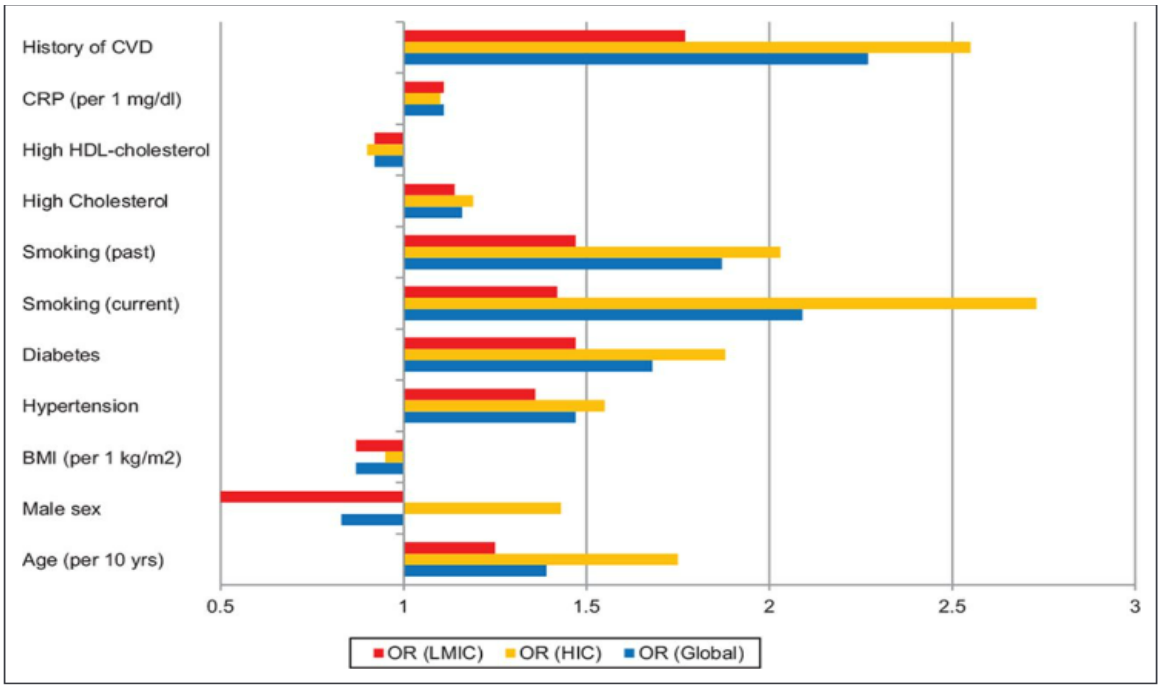
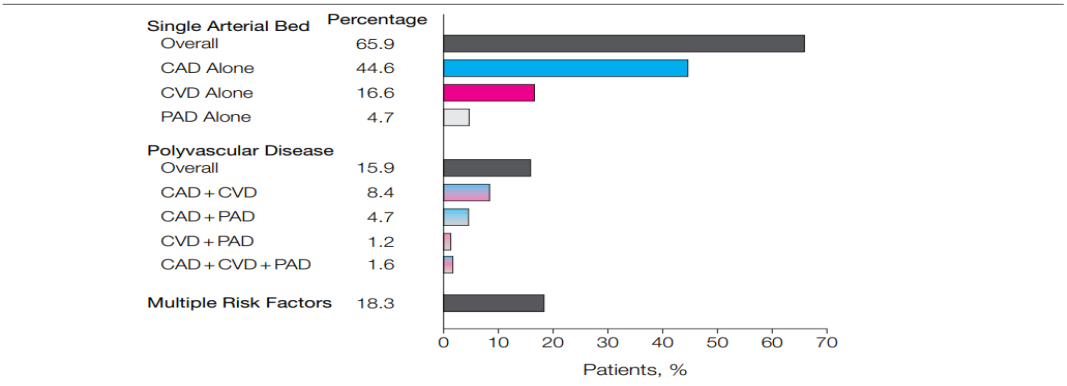


Figure 2.2: Odds ratio of PAD in high-income countries (HIC) and low to middle-income countries (LMIC) [1]

COPREVALENCE OF PAD AND OTHER ATHEROSCLEROTIC DISEASE:

The REACH Registry collected data on atherosclerotic risk factor prevalence and treatment in patients above 45years of age, from 44 countries. This study included 67888 patients and provided a real-world prevalence of Polyvascular disease which showed a 4.7% co-prevalence of PAD and CAD, 1.6% co-prevalence of PAD with CAD + CVD and 1.2% co-prevalence of PAD + CVD.



CAD indicates coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; REACH, Reduction of Atherothrombosis for Continued Health.

Figure 2.3: Co-prevalence of PAD and other Atherosclerotic disease

This registry also demonstrated that one of 6 patients with CAD, CVD, or PAD had symptomatic involvement of 1 or 2 other arterial beds. The degree of such overlap was estimated to be much greater in asymptomatic polyvascular disease, but this was not studied in this registry. This finding suggests that atherothrombosis is best managed as a systemic disease because of diffuse nature of the disease. But, despite the high prevalence of the atherosclerotic risk factors, the patient population under study utilized well-established medical treatments and lifestyle modification techniques far less than recommended. [12].

PREVALANCE OF PAD:

In 2010, a systemic review and meta-analysis by Fowkes FG et al estimated that >200 million people worldwide were living with PAD which was almost 23.5% increase since 2000.

This increase was believed to be largely attributable to increasing number of aging populations and the growing prevalence of risk factors, especially DM.

The study also showed that between the years 2000 and 2010, the number of individuals with PAD increased by 28.7% in low-income and middle-income countries and by 13.1% in high-income countries. [1]

The 2015 update of this study, which was published in 2019 in the Lancet, also revealed higher prevalence in LMICs than in HICs at younger ages, but greater increases with age in HICs than in LMICs, resulting in a higher prevalence in HICs than in LMICs at older ages.

It was also found that the prevalence of PAD in women in HICs was slightly higher than men up to the age of 75years, while no such difference was found in the LMICs.

This study concluded that globally, a total of 236·62 million people aged 25 years and older were living with peripheral artery disease in 2015, among whom 72·91% were in LMICs. [13]

PAD ASSOCIATED MORTALITY:

Due to the high frequency of risk factors in an aging population transitioning to a Western lifestyle, patients with PAD are at an increased risk of myocardial infarction and stroke [14]. This has a significant impact on the rising expense and burden of healthcare. [15]

According to the EUCLID trial, 1263 patients out of 13885 individuals passed away. 706 patients (55.9%) of the 1263 deaths were due to cardiovascular causes, and 522 patients (41.3%) died from causes other than cardiovascular causes.

The most frequent causes of death among patients who died from cardiovascular reasons were sudden cardiac death (20.1%) and unknown causes (19.2%). Ischemic stroke (3.2%), heart failure or cardiogenic shock (4.1%), acute myocardial infarction (5.2%), and other cardiovascular (5.7%) were additional cardiovascular causes of mortality.

Malignancy (11.9%), infection (11.9%), other non-cardiovascular causes (6.1%), pulmonary failure (2.7%), and non-intracranial hemorrhage (2.3%) were the most frequent non-cardiovascular causes of mortality. [16]

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS AND PAD:

Atherosclerosis is characterized by the presence of intimal lesions called atheromas (or atheromatous or atherosclerotic plaques). Atheromatous plaques are raised lesions composed of soft grumous lipid cores (mainly cholesterol and cholesterol esters, with necrotic debris) covered by fibrous caps.

The vessels most frequently affected by atherosclerosis include big elastic arteries (such as the aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (such as the coronary, renal, and popliteal arteries).

Accordingly, the heart, brain, kidneys, and lower extremities are where atherosclerosis is most likely to manifest as signs and symptoms of ischemia. The major clinical of atherosclerosis include myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral arterial disease (gangrene of the extremities).

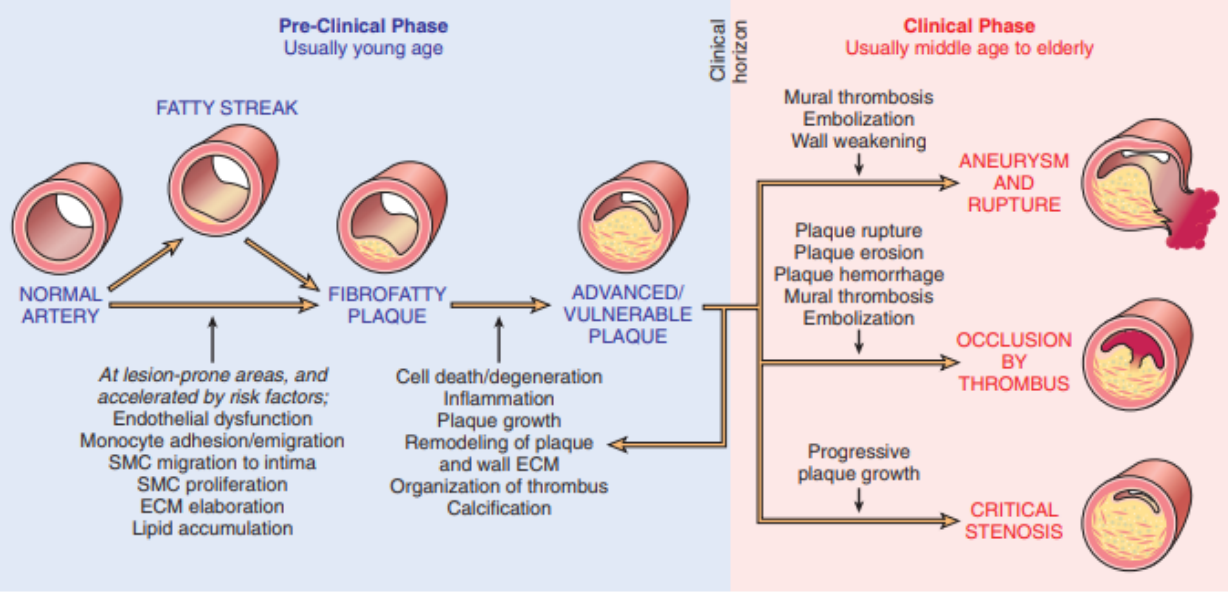


Figure 2.4: Natural History, morphologic features, main pathogenic events and clinical complications of atherosclerosis [17]

DUPLEX CLASSICICATION OF PAD: [18]

TABLE 2.1: DUPLEX CLASSIFICATION OF PAD

Stenosis Category	Peak Systolic Velocity (cm/s)	Velocity Ratio (V_r)	Distal Artery Spectral Waveform
Normal	<150	<1.5	Triphasic, Normal PSV
30%-49%	150-200	1.5-2	Triphasic, normal PSV
50%-75%	200-400	2-4	Monophasic, Reduced PSV
>75%	>400	>4	Dampened, monophasic reduced PSV

Occlusion	No flow, length of occlusion estimated by distance from exit and reentry collaterals	Dampened, monophasic reduced PSV

Classification based on Symptoms:

A. Fontaine classification [19]

Based solely on clinical symptoms, this was the first classification system published in 1954 by Fontaine et al. This system is not routinely used in patient care.

TABLE 2.2: FONTAINE CLASSIFICATION OF PAD:

Grade	Symptom
I	Asymptomatic, incomplete blood vessel obstruction
II	Mild claudication pain in limb
IIa	Claudication at a distance > 200 m
IIb	Claudication at a distance < 200 m
III	Rest pain, mostly in the feet
IV	Necrosis and/or gangrene of the limb

B. Rutherford Classification: [20,21]

Rutherford coined a symptomatic classification of PAD in 1986. He classified PAD into acute and chronic limb ischemia emphasizing on the fact the treatment for both is different.

The classification of chronic limb ischemia took into account the patient's symptoms along with an addition of objective non-invasive data.

TABLE 2.3: RUTHERFORD CLASSIFICATION OF PAD:		
Category	Clinical description	Objective criteria
0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
1	Mild claudication	Completes treadmill exercise: AP after exercise> 50 mm Hg a least 20mm Hg lower than resting value
2	Moderate claudication	Between categories 1 and 3
3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mm Hg
4	Ischemic rest pain	Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg
5	Minor tissue loss- nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg
6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

Abbreviations: AP- ankle pressure, PVR- pulse volume recording, TM- transmetatarsal, TP- toe pressure.

Angiosome Theory: [22]

Taylor and Palmer described a classification system based on arterial perfusion via angiosome. Six angiosomes were described in the lower extremity:

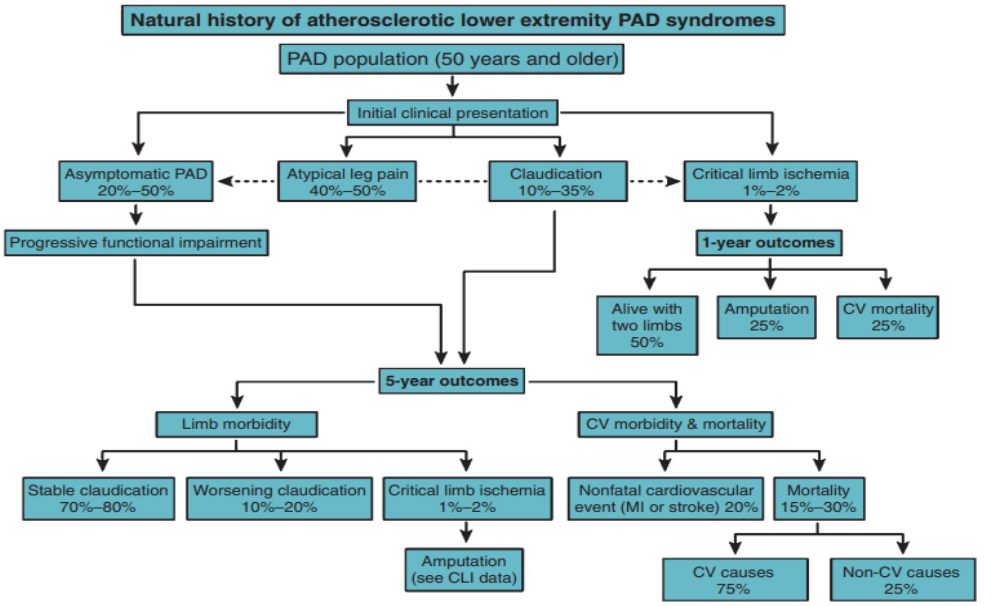
3 Posterior Tibial Angiosomes	• Medial Calcaneal Artery angiosome • Medial Plantar Antery angiosome • Lateral Plantar Artery angiosome
1 Anterior Tibial Angiosome	• Anterior tibial artery-Dorsalis Pedis Artery angiosome
2 Peroneal Artery angiosomes	• Lateral Calcaneal Artery angiosome • Anterior perforator Artery angiosome

The adjacent angiosomes can be feed by collateral vessels in the presence of necrosis, termed by Taylor as “choke vessels.”

Conventionally, the endovascular plan is to recanalize whichever vessel in easiest to recanalize and allowing collateral flow to heal the ulcer. However, according to a meta-analysis by Biancari and Juvonen that comprised nine studies A direct revascularization had higher rates of limb salvage, lower rates of amputation, and better wound healing rates. [23]

To yet, no randomized control studies have been conducted to support this theory.

DEFINITION AND NATURAL HISTORY OF PAD:



2-2 Outcomes of atherosclerotic peripheral arterial disease at 5 years. (From Hirsch AT, Haskal ZJ, Hertzer NR, et al; American Association for Vascular Surgery/Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines: ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease [lower extremity, renal, mesenteric, and abdominal aortic]: A collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines [writing committee to develop guidelines for the management of patients with peripheral arterial disease]—summary of recommendations. *J Vasc Interv Radiol* 17:1383–1397, 2006.)

Figure 2.5: Natural history of atherosclerotic lower extremity PAD syndromes

ASYMPTOMATIC DISEASE:

Fowkes et al in the Edinburgh Artery Study found the majority of PAD detected by non-invasive tests are asymptomatic. [39] Despite the lack of typical PAD symptoms, these patients still carry significant cardiovascular morbidity and mortality and associated functional decline.

The majority of individuals with PAD detected by noninvasive testing are asymptomatic. [24]

In a study of Mortality over 10years period in patients with PAD by Criqui et al in 1992, it was noted that individuals with asymptomatic PAD have 2.7-times greater risk of death from any cause and 4.7 times greater risk of death from a cardiovascular disease. [25]

Cause of Death	Unilateral LV-PAD (N = 34)	Bilateral LV-PAD (N = 30)	Asymptomatic LV-PAD (N = 49)	Symptomatic LV-PAD (N = 18)	Moderate LV-PAD (N = 49)	Severe LV-PAD (N = 18)	Isolated Posterior Tibial LV-PAD (N = 31)	Other LV-PAD (N = 33)
				relative risk (95% confidence interval)				
All causes	3.3 (1.9–5.9)	2.9 (1.5–5.5)	2.7 (1.6–4.5)	4.7 (2.3–9.6)	2.8 (1.6–4.8)	3.9 (1.9–8.0)	2.9 (1.6–5.4)	3.4 (1.9–6.0)
CVD	5.5 (2.5–12.1)	5.8 (2.5–13.3)	4.7 (2.3–9.8)	11.2 (4.5–27.9)	4.8 (2.3–10.3)	8.4 (3.4–20.8)	4.2 (1.7–10.4)	7.0 (3.2–14.9)
CHD	5.5 (2.0–15.2)	7.2 (2.6–19.7)	5.6 (2.3–13.5)	11.4 (3.6–35.8)	5.6 (2.2–14.2)	8.9 (3.0–26.8)	5.5 (1.8–16.7)	6.8 (2.7–17.5)

*CVD denotes cardiovascular disease, and CHD coronary heart disease. Relative risks have been adjusted for age, sex, number of cigarettes smoked per day, systolic blood pressure, HDL cholesterol level, LDL cholesterol level, logarithm of the triglyceride level, fasting plasma glucose level, body-mass index, and selection criterion.

Figure 2.6: Relative Risk of Death among subjects with various categories of Large-vessel PAD (LV-PAD)

INTERMITTENT CLAUDICATION:

Claudication is defined as pain, cramp or sense of fatigue in a muscle group of the lower extremity related to sustained exercise and relieved promptly by a few minutes of rest while standing evenly on both feet.

The word *claudication* is derived from the Latin word "*claudicare"* meaning "to limp".

Claudication is a frequent complaint mentioned by patients with PAD and is usually the first indication of a significant underlying occlusive disease.

The location of claudication pain can be used to predict the site of major arterial obstruction because the affected muscle group is typically one joint distal to the level of vascular occlusion.

TABLE 2.4: CLAUDICATION SITE AND LIKELY SITE OF OCCLUSION:

SITE OF CLAUDICATION PAIN	LIKELY SITE OF OCCLUSION
Calf	SFA or Popliteal
Thigh and Calf	Iliofemoral Segment

Buttock and distally	Aortoiliac Segment
Isolated foot	Buerger's or Tibial Arteritis (rare)
Confined to Trochanteric region or Buttock	Isolated internal iliac &/or profunda femoris insufficiency

Over 5 years, approximately 20% of patients with IC experience a major CV event and mortality ranges between 10% and 15% while 1-2% progress to critical limb ischemia. [26]

CLTI AND CLI: [2]

The term "critical limb ischemia" (CLI) was first coined at the Working Party of the International Vascular Symposium held in 1981.

Critical Limb Ischemia (CLI) is defined as:

1. Ischemic rest pain with an ankle pressure (AP) <40mmHg or
2. Tissue necrosis with AP <60mmHg in patient without diabetes.
3. ABI <0.5

This definition specifically excluded patients with diabetes because of the confounding effects of neuropathy and susceptibility to infection. This definition failed to include a large group of patients who were at risk of amputation. Hence in 2010 the term CLTI (Chronic Limb Threatening Ischemia) was proposed to include a wider cohort of patients who are at a risk of limb amputation owing to delayed wound healing due to varying degrees of ischemia.

Chronic limb-threatening ischemia (CLTI) was defined as objectively documented atherosclerotic PAD in association with ischemic rest pain or tissue loss (ulceration or gangrene), present for >2 weeks and associated with one or more abnormal hemodynamic parameters such as:

1. Ankle-brachial index (ABI) <0.8
2. Absolute highest AP 50mmHg, and

3. Absolute TP <30mmHg,
4. Transcutaneous partial pressure of oxygen (TcPO2) <30mmHg,
5. Flat or minimally pulsatile pulse volume recording (PVR) waveforms (equivalent to WIfI ischemia grade 3).

In patients with DM or ESRD, toe waveforms and systolic pressures are preferred.

CLTI affects a minority of individuals with PAD, variably estimated At 11% of the PAD population. The prevalence of CLTI has been estimated at 1.3% of an insured US adult population and 0.5% to 1.2% of Swedish adults older than 60 years.4,7 A recent meta-analysis estimated the prevalence of CLTI at 0.8% [27].

In a systematic review that examined the natural history of CLTI, summarizing data from 13 studies and 1527 patients who did not receive limb revascularization, the estimated 1-year mortality was 22% (12%–33%) and major amputation had occurred in 22% (2%–42%). [28]

TREATMENT OPTIONS FOR CLTI:

Physically and financially, CLTI is a severely morbid condition that uses up the vast bulk of treatment resources. Although far fewer patients present with CLTI than with intermittent claudication, CLTI patients consume the vast majority of treatment resources. As many as 25% CLTI end in amputation within 1year. Hence revascularization always take priority over medical therapy and exercise in patients presenting with CLTI. But the decision to proceed with revascularization is made more difficult by the fact that 25% of CLTI patients also experience cardiovascular death within a year of presenting. [29]

A. Medical Therapy Versus Revascularization:

Best medical therapy and aggressive risk factor modification are the keystones of medical management of CLTI. Aim of the treatment is both limb salvage as well and reduction of cardiovascular morbidity and mortality. [30,31]

Age and sex are two risk variables that cannot be modified, but others, such hyperlipidemia, hypertension, diabetes, smoking, and sedentary behavior, can.

Medical therapy for CLTI comprises of

1. Antithrombotic agents,
2. Lipid-lowering agents,
3. Diet and exercise therapy,
4. Effective management of comorbidities like diabetes and hypertension,
5. Lifestyle modification,
6. Smoking cessation and
7. Pain management.

After one year of follow-up, a systematic review of conservative treatment in CLTI patients found a 27% major amputation rate, an 18% all-cause mortality rate, and a 60% amputation-free survival rate [32].

There are no comparative studies that compare conservative management to revascularization. However, the overall rate of major amputation was lower in patients who have revascularization, ranging from 3% to 20% after one year of follow up vs. 27% for conservative treatment, according to a meta-analysis that compared the results of conservative management to those of revascularization. [33]

As suggested by evidence, revascularization is an essential component of CLTI management with medical therapy being an important adjunct. But, in cases where the disease is non-reconstructible i.e., no-option CLI and very high-risk patients, a trial of intensive wound care with medical therapy may yield some benefit in healing of small and superficial wounds.

B. Limb Amputation Versus Revascularization:

A significant proportion of CLTI patients present with severe disease, high grade infection or sepsis, or a non-reconstructible lesions. These three conditions have been listed as the traditional grounds for amputation:

a) Dead limb i.e., advanced gangrene,
b) Deadly-limb i.e., wet gangrene

c) Dead-loss limb i.e., severe rest pain with non-reconstructible CLTI. [34]

10-40% patients presenting with CLTI require primary amputation [35]. Failed revascularization due to disease progression, recurrent ischemia, or persistent infection or necrosis despite a patent revascularization account for secondary amputation.

Therefore, limb amputation with prosthetic rehabilitation is a great alternative for patients who present in this type of clinical scenario in order to accelerate functionality and early return to a decent QoL. The same ought to be a top priority for patients with significant tissue loss who are too ill or frail to benefit from limb revascularization [36].

C. Endovascular Treatment Versus Open Surgery:

The best revascularization plan for a patient with CLTI who is a candidate for revascularization has been an ongoing topic of debate in PAD management for a while now.

Although proponents of surgical bypass emphasize on its greater patency and increased durability [37], it has been associated with greater perioperative morbidity and mortality, a longer hospital stay, and depends on the availability of the ideal conduit [38, 39].

Those in favour of endovascular intervention argue that a shorter hospital stay will result in lower morbidity and death. [40]. Nonetheless, endovascular therapy is associated with patency rates that are inferior to open bypass along with limited reconstruction capability in high-risk lesions [40,41,42].

Thus, the choice between endovascular intervention and open bypass needs to be individualized for every patient depending on their risk profile, the condition of their wounds, and the type of vascular lesion while also taking into account the availability of a good-caliber GSV either from the same or the contralateral limb.

Evidence based revascularization (EBR) thus emerged to facilitate the clinician's decision making while offering the best possible treatment to the patient.

EVIDENCE BASED REVASCULARIZATION (EBR) AND "PLAN" CONCEPT: [2]

Effective revascularization is the cornerstone of limb salvage in CLTI. In 2013 when the Global Vascular Guidelines were launched, the primary aim was improvement of quality of care and reduction of disease burden of CLTI. The driving force behind this was the growing prevalence and increased health care costs around of CLTI worldwide.

CLTI is a highly morbid disease, incurring significant mortality, limb loss, pain, and diminished health-related quality of life (HRQL) among those afflicted.

Evidence Based Revascularization (EBR) was an important step towards improving quality of care of CLTI patients. The PLAN concept of EBR was thus designed to improve decision making, clinical outcomes, and cost-effectiveness.

PLAN is a three-step integrated approach based on

A. **P**atient risk estimation
B. **L**imb staging
C. **AN**atomic pattern of disease

A. PLAN: Patient Risk Estimation:

This is the first step in EBR and it entails assessing patient's candidacy limb salvage, peri-procedural risk and life expectancy. Multiple models have been proposed to assess this.

Tool	End points	Critical factors	Reference
Taylor et al	Mortality, ambulatory failure (median follow-up of 2 years)	Age, race, ESRD, CAD, COPD, DM, dementia, baseline ambulatory status	Taylor,[409] 2006
Finnvasc	Perioperative (30-day) mortality, limb loss	DM, CAD, gangrene, urgent operation	Biancari,[63] 2007
PREVENT III	AFS (1 year)	ESRD, tissue loss, age >75 years, CAD, anemia	Schanzer,[64] 2008
BASIL	Survival (2 years)	Age, CAD, smoking, tissue loss, BMI, Bollinger score, serum creatinine concentration, AP (number measured and highest value), prior stroke/TIA	Bradbury,[65] 2010
CRAB	Perioperative (30-day) mortality, morbidity	Age >75 years, prior amputation or revascularization, tissue loss, ESRD, recent MI/angina, emergency operation, functional dependence	Meltzer,[66] 2013
Soga et al	Survival (2 years)	Age, BMI, nonambulatory status, ESRD, cerebrovascular disease, tissue loss, left ventricular ejection fraction	Soga,[225] 2014
VQI	AFS (1 year)	Age, tissue loss, DM, CHF, serum creatinine concentration, ambulatory status, urgent operation, weight, bypass conduit used	Simons,[67] 2016
VQI	Survival (30 days, 2 and 5 years)	Age, CKD, ambulatory status, CAD, CHF, COPD, tissue loss, diabetes, smoking, beta-blocker use	Simons,[412] 2018

AFS, Amputation-free survival; *AP*, ankle pressure; *BASIL*, Bypass vs Angioplasty in Severe Ischaemia of the Leg; BMI, body mass index; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *CRAB*, Comprehensive Risk Assessment for Bypass; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *MI*, myocardial infarction; *PREVENT III*, Project of Ex-vivo Vein graft Engineering via Transfection III; *TIA*, transient ischemic attack; *VQI*, Vascular Quality Initiative.

Figure 2.7: Comparison of various risk stratification models for CLTI patients.

B. PLAN: Limb Staging:

EBR recommends the used of SVS Threatened Limb Classification (WIfI) which integrates:

I. Wound (W)

II. Ischemia (I)

III. foot Infection (fI)

W: Wound:

SVS grades for rest pain and wounds/tissue loss (ulcers and gangrene): 0 (ischemic rest pain; no ulcer) 1 (mild) 2 (moderate) 3 (severe)

Table 2.5a: Wound Assessment

Grade	Ulcer	Gangrene
0	No ulcer	No gangrene
Clinical description: ischemic rest pain (requires typical symptoms + ischemia grade 3); no wound.		
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage		
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
Clinical description: major tissue loss salvageable with multiple digital amputations or standard TMA.		

3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer +/- calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis +/- calcaneal involvement
Clinical description: Extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect.		

*TMA- Trans-metatarsal amputation.

I: Ischemia:

Hemodynamics/perfusion: Measure TP or TcPO2 if ABI noncompressible (>1.3)

SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Table 2.5b: Ischemia Grades

Grade	ABI	Ankle Systolic Pressure	TP/TcPO2
0	≥ 0.80	> 100mmHg	> 60mmHg
1	0.6-0.79	70-100mmHg	40-59mmHg
2	0.4-0.59	50-70mmHg	30-39mmHg
3	≤ 0.39	< 50mmHg	< 30mmHg

ABI- Ankle-brachial index; PVR- pulse volume recording; TP- toe pressure; TcPO2- transcutaneous oximetry.

Patients with diabetes should have TP measurements.

fI: foot Infection:

SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe: limb and/or life-threatening)

Table 2.5c: Foot Infection Grades

Clinical manifestation of infection	Grade
No symptoms or signs of infection. Infection present, as defined by the presence of at least 2 of the following items: 1. Local swelling or induration. 2. Erythema > 0.5 to ≤2 cm around the ulcer. 3. Local tenderness or pain. 4. Local warmth. 5. Purulent discharge	0
Local infection involving only the skin and the subcutaneous tissue	1
Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis).	2
Local infection (as described above) with the signs of systemic inflammatory response syndrome (SIRS)	3

Amputation risk according to WIfI category

In the Delphi Consensus, each member was asked to assign a limb threat clinical stage to each of the 64 theoretical patient combinations that would correlate with risk of amputation (stage 1 - very low; stage 2 - low; stage 3 - moderate; and stage 4 - high).

In general, risk of amputation was believed to increase as one proceeds down and to the right (increasing severity of each of the individual WIfI score components).

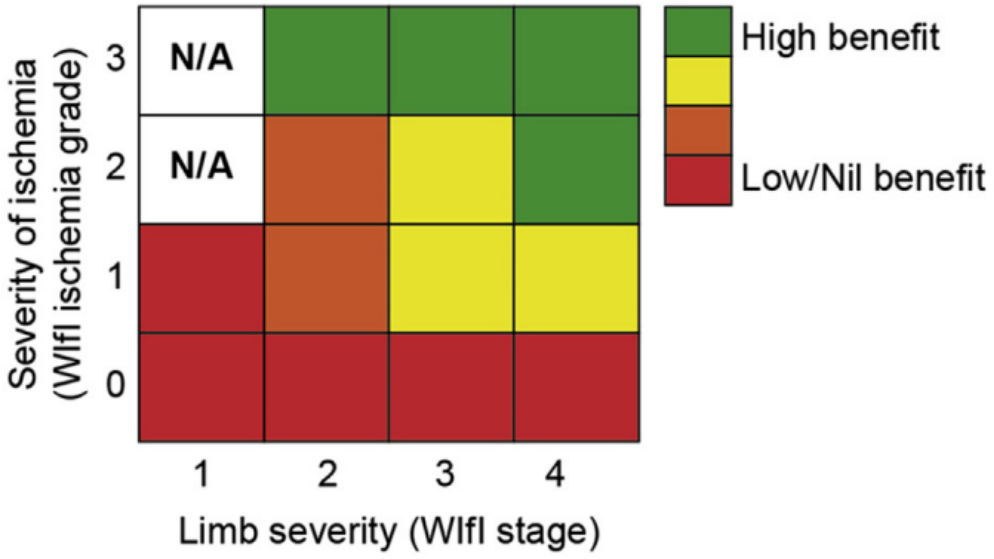
Table 2.5d: Amputation risk according to WIfI score

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Four classes: for each box, group combination into one of these four classes

Very low = VL = clinical stage 1
Low = L = clinical stage 2
Moderate = M = clinical stage 3
High = H = clinical stage 4
Clinical stage 5 would signify an unsalvageable foot

Table 2.5e: Presumed benefit of revascularization in CLTI is linked to both the severity of ischemia and the degree of limb threat:



Patients with lesser degree of tissue loss i.e., WIfI stage 1 to 3 with mild to moderate ischemia, can be given a trial of infection control and wound and podiatry care. Revascularization may be considered in these patients if the wound fails to heal after 4-5weeks despite appropriate limb care.

In cases with advanced tissue loss or infection i.e., WIfI stage 4 with moderate ischemia revascularization may be of some benefit.

All symptomatic patients with severe ischemia that corresponds to WIfI grade 3 should undergo revascularization if they are appropriate candidates for limb salvage.

C. PLAN: Anatomic pattern of disease (and conduit availability):

The anatomic pattern and complexity of the arterial disease in CLTI is defined by GLASS i.e., Global Limb Anatomic Staging System. Similar to the SYNTAX Score for Coronary artery disease, GLASS quantitatively characterizes the arterial vasculature of the lower limb quantitatively by taking into account the number, location, and complexity of the lesion as seen angiographically.

GLASS incorporates two novel and important concepts, the Target Arterial Path (TAP) and estimated limb-Based Patency (LBP). Based on appropriate angiographic imaging, the TAP is defined by the treating surgeon/interventionalist as the optimal arterial path to restore in-line flow to the ankle and foot, and resolve the clinical problem at hand. It may incorporate then either least diseased path or an angiosome-preferred strategy chosen by the clinician. The LBP is defined as maintenance of in-line flow throughout the entire length of the TAP, from groin to ankle. The complexity of disease traversed by the TAP from groin to ankle is integrated into the GLASS system. Femoropopliteal (FP) and Infrapopliteal (IP) arterial segments are individually graded on a scale from 0-4, and the grades are then combined into three GLASS stages for the limb, using a consensus-based patency. Using a consensus process, combinations of grade scores for the FP and IP segments are used to define **three GLASS stages** based on estimating the likelihood of immediate technical success [22] and 12-month LBP following endovascular intervention of the selected TAP. GLASS stages for the limb thus reflect a gradient of TAP complexity:

- **Stage I**: **Average Complexity Disease:** expected technical failure < 10% **AND** >70% 12-month LBP
- **Stage II**: **Intermediate Complexity Disease:** expected technical failure < 20% **AND** 12-month LBP 50-70%

- **Stage III**: **High Complexity Disease**: expected technical failure >20%; **OR** <50% 12-month LBP.

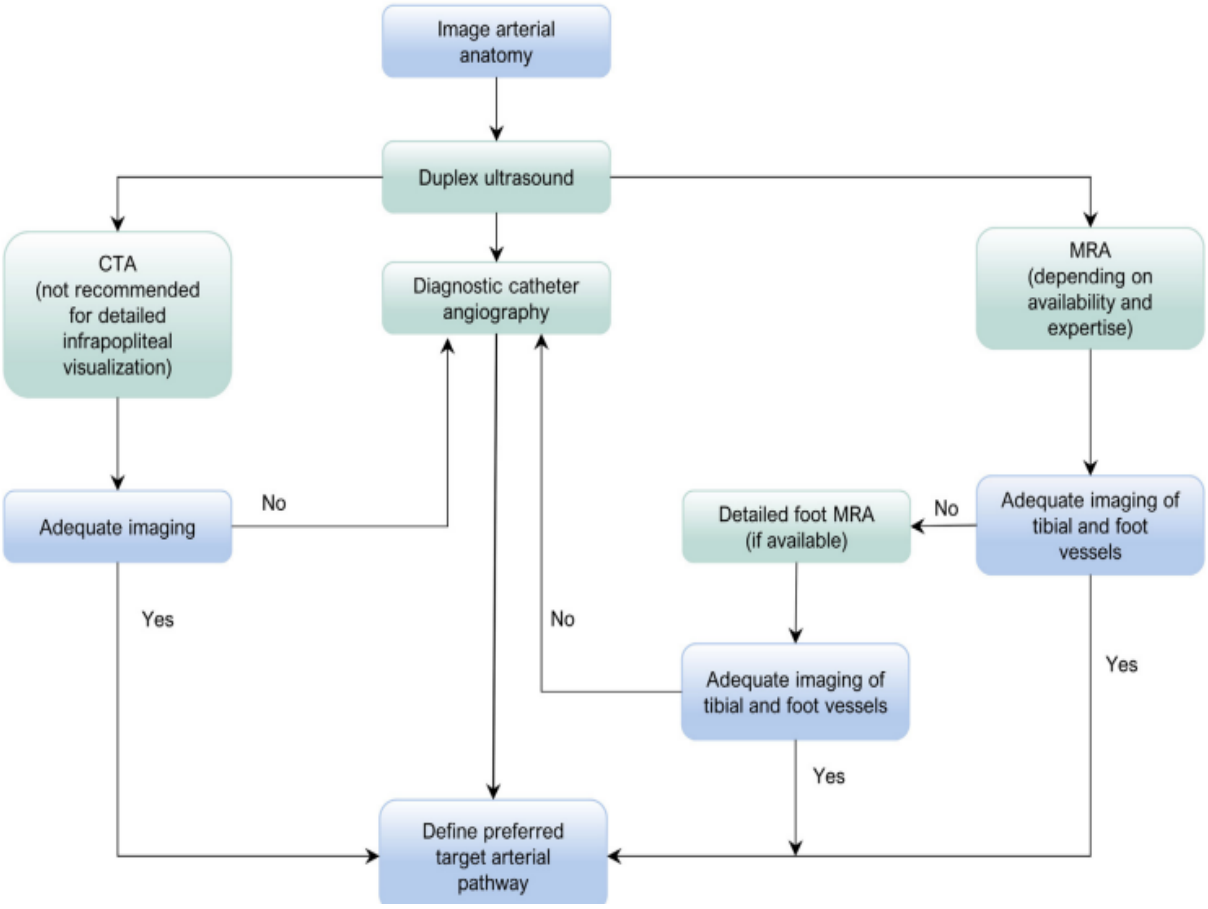


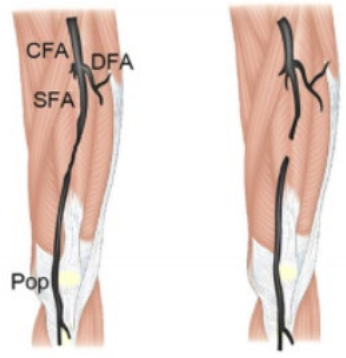
Figure 2.8: Algorithm suggested by GVG for anatomic imaging in patients with CLTI who are candidates for revascularization

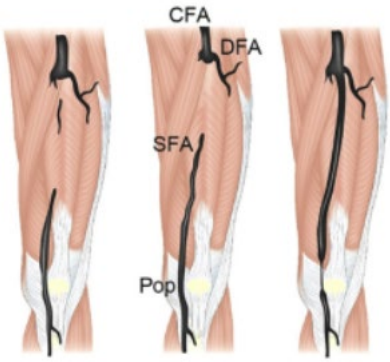
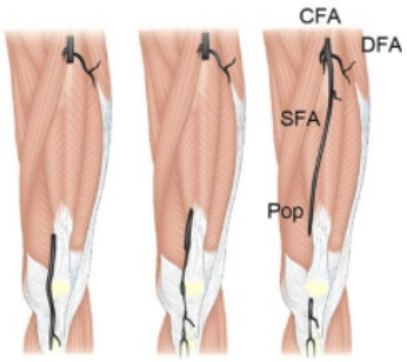
Key Definitions and Assumptions in GLASS:

1. Restoration of in-line flow to the ankle and foot is a primary goal.
2. Target arterial path (TAP): the selected continuous route of inline flow from groin to ankle. The TAP typically involves the least diseased IP artery but may be angiosome based
3. Limb-based patency (LBP): maintained patency of the TAP
4. Inflow disease (Aortoiliac and CFA) is considered separately and assumed corrected when using the infrainguinal staging system for clinical decision-making.

5. Grade within segment is determined by presence of any one of the defined descriptors within that grade (i.e., the worst disease attribute within the segment defines grade).
6. Calcification is considered only if severe; increases within segment grade by 1.
7. Inframalleolar (IM) disease (pedal) modifier: describes status of IM vessels (including terminal divisions of the peroneal artery) providing outflow into the foot.
8. The generic case of rest pain is used as a default for defining TAP as the least diseased IP artery, or a specific IP target artery based on clinical circumstances (e.g., angiosome directed in setting of wounds) may be selected by the clinician.

TABLE 2.6a. Description of femoro-popliteal anatomy grades.

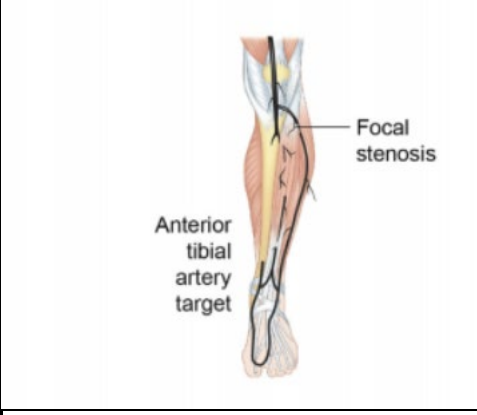
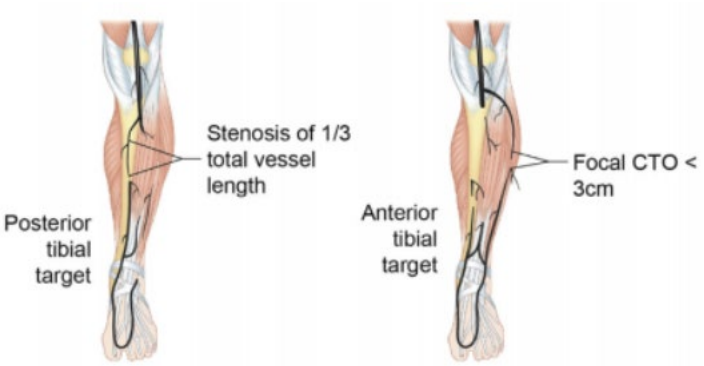
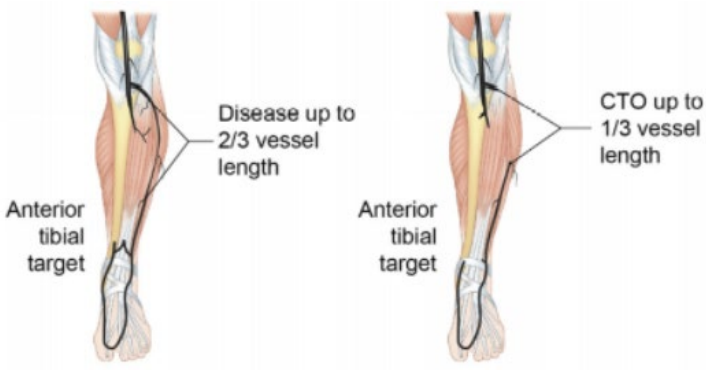
Femoro-popliteal (FP) Grading		
0	Mild or no significant (<50%) disease	
1	Total length SFA disease <1/3 (<10 cm); may include single focal CTO (< 5 cm) as long as not flush occlusion; popliteal artery with mild or no significant disease	
2	Total length SFA disease 1/3-2/3 (10-20 cm); may include CTO totaling < 1/3 (10 cm) but not flush occlusion; focal popliteal artery stenosis <2 cm, not involving trifurcation	

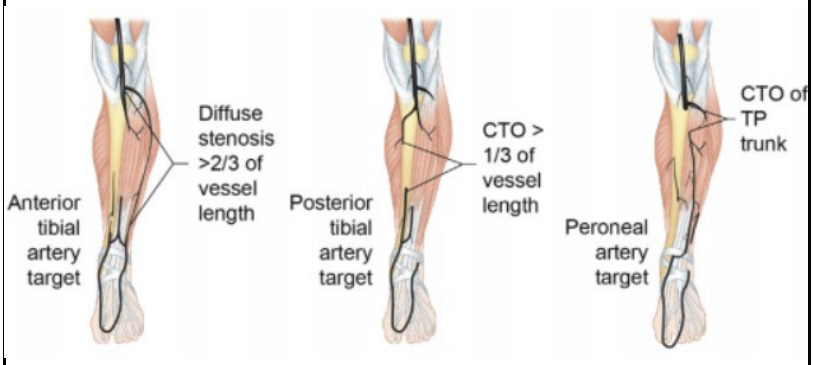
3	Total length SFA disease >2/3 (>20 cm) length; may include any flush occlusion <20 cm or non-flush CTO 10-20 cm long; short popliteal stenosis 2-5 cm, not involving trifurcation	
4	Total length SFA occlusion > 20 cm; popliteal disease >5 cm or extending into trifurcation; any Popliteal artery CTO	

*****involvement of trifurcation means disease includes the origin of either the anterior tibial or tibioperoneal trunk

*****severe calcification (e.g. >50% of circumference, diffuse, bulky, or "coral reef" plaques) within the TAP increases the within-segment **grade** by **+1**

TABLE 2.6b. Description of infra-popliteal anatomy grades

Infra-popliteal (IP) Grading		
0	Mild or no significant (<50%) disease	
1	Focal stenosis <3 cm not including TP trunk	
2	Total length of target artery disease < 1/3 (<10 cm); single focal CTO (< 3 cm not including TP trunk or target artery origin)	
3	Total length of target artery disease 1/3- 2/3 (10-20 cm); CTO 3-10 cm (may include target artery origin, but not TP trunk)	

4	Total length of target artery disease >2/3 length; CTO > 1/3 (>10 cm) of length (may include target artery origin); any CTO of TP trunk	

*IP grading is applied only to the primary selected vessel in the TAP

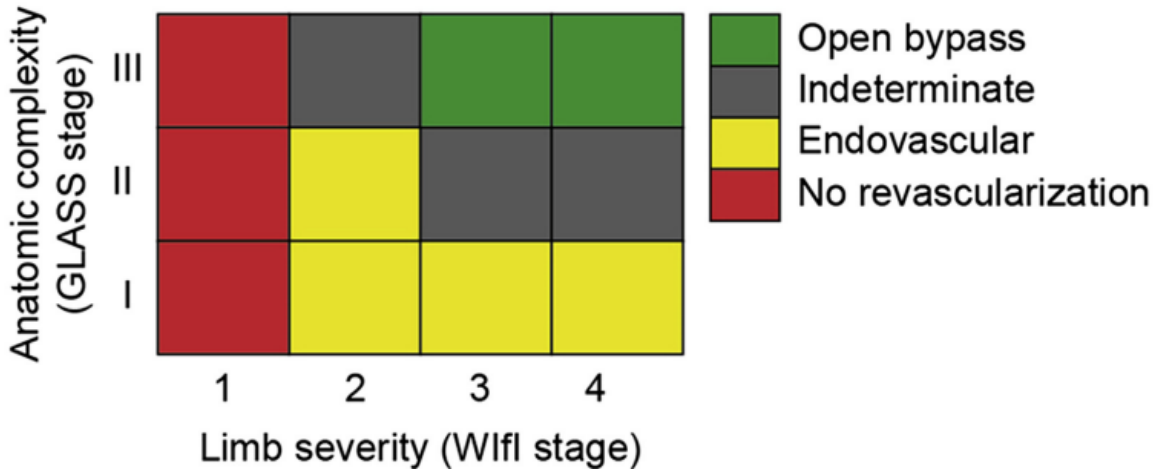
*severe calcification (e.g. >50% of circumference, diffuse, bulky, or “coral reef” plaques) within the TAP increases the within-segment **grade** by **+1**.

*TP trunk disease is only included if the TAP is the posterior tibial or peroneal artery.

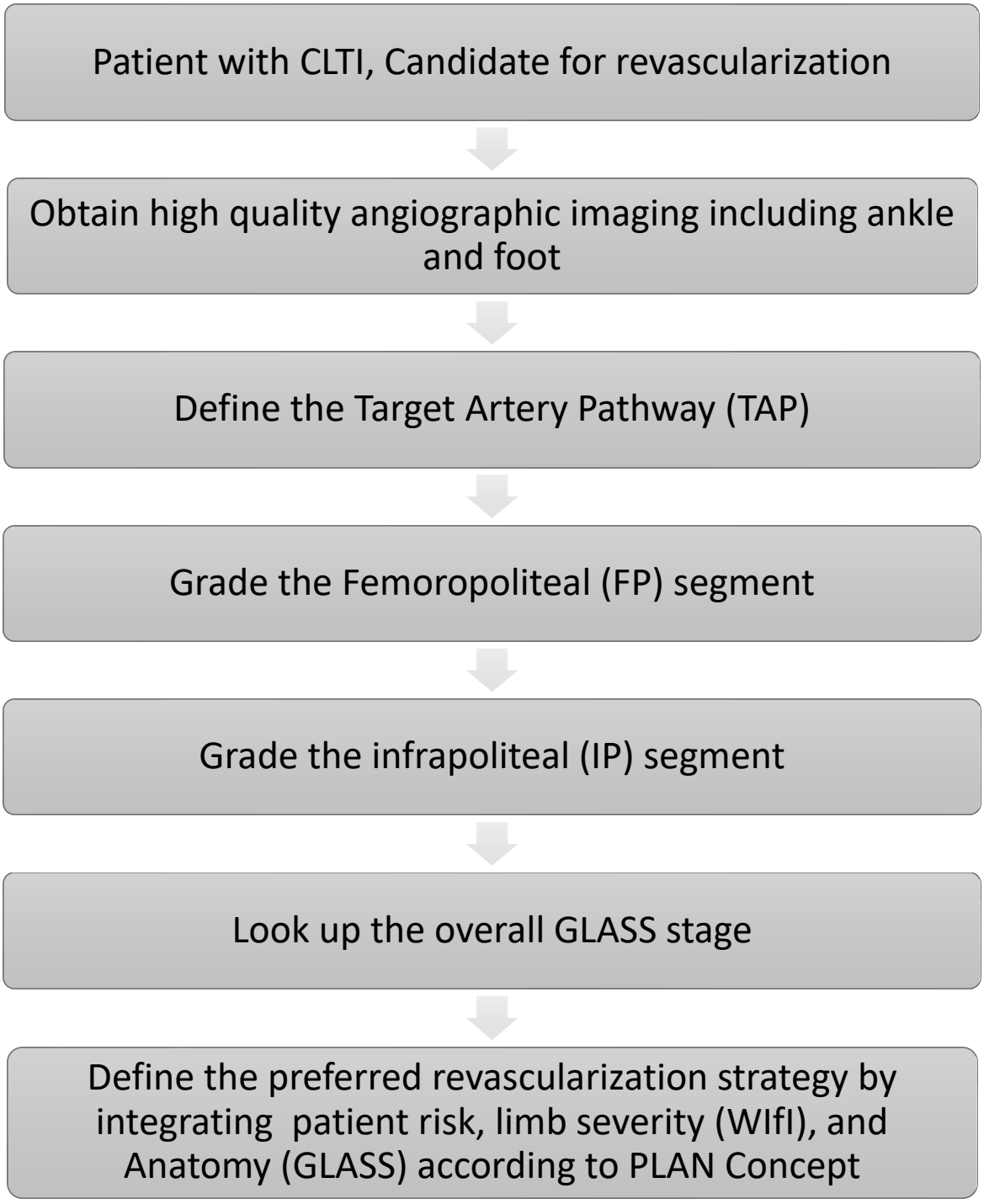
TABLE 2.6c: Patterns of infrainguinal disease: assignment of overall GLASS stage for the limb based on combination of segmental (FP and IP) grades.

		INFRAINGUINAL GLASS STAGE				
FP Grade	**4**	**III**	**III**	**III**	**III**	**III**
	3	**II**	**II**	**II**	**III**	**III**
	2	**I**	**II**	**II**	**II**	**III**
	1	**I**	**I**	**II**	**II**	**III**
	0	**NA**	**I**	**I**	**II**	**III**
		0	**1**	**2**	**3**	**4**
		IP Grade				

TABLE 2.7: Preferred Initial revascularization for infrainguinal disease:



Flowchart of application of GLASS to stage infrainguinal disease pattern in CLTI:



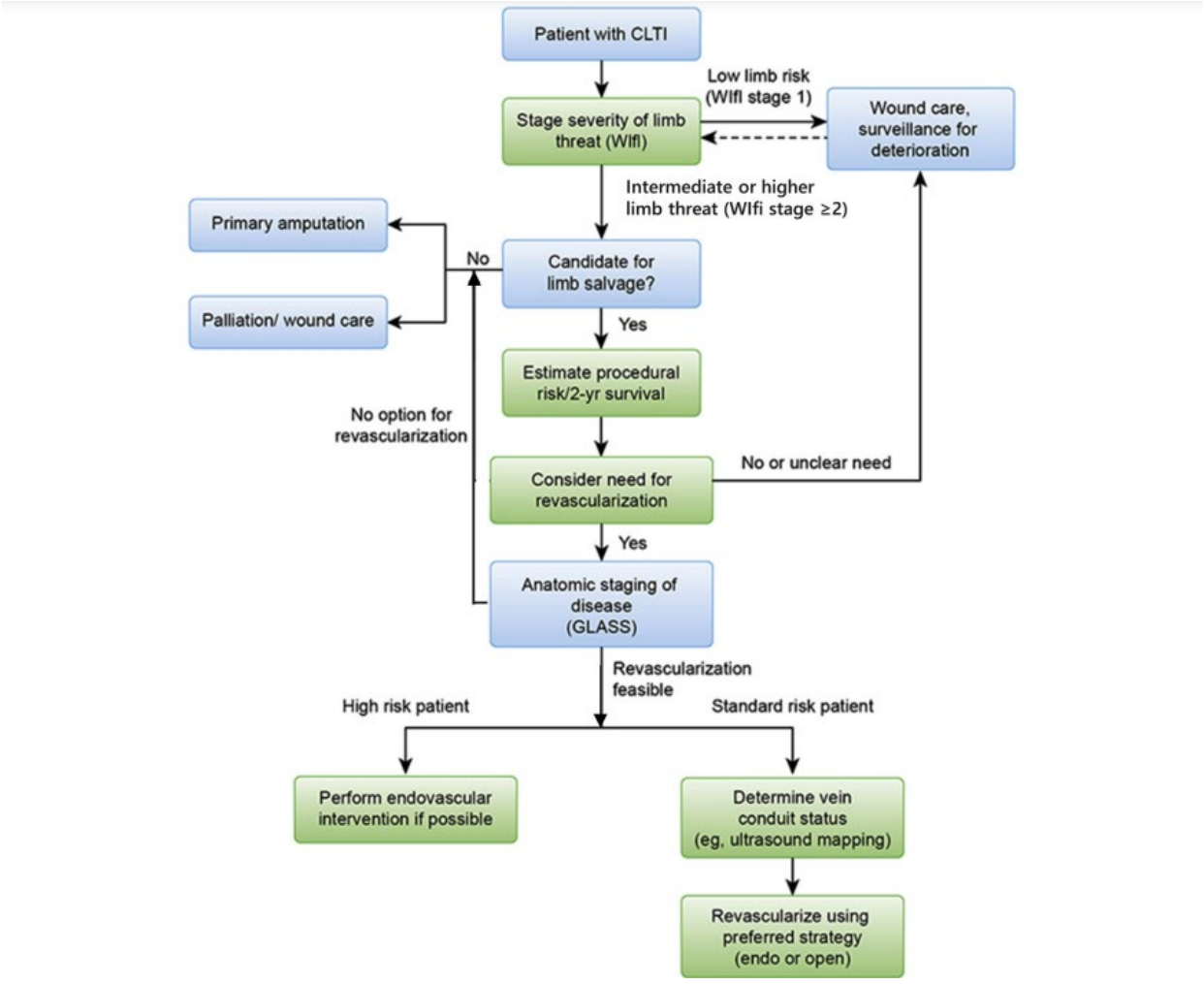


Figure 2.9: PLAN Framework for clinical decision making in CLTI with infraingiunal disease:

3. AIMS AND OBJECTIVES

- Assessing patient outcome of an intervention suggested by PLAN Concept based on
  1. Patient risk,
  2. Limb severity, and
  3. ANatomic pattern of disease, in that order of priority.

- Assessment of validity of PLAN concept in assessing MALE and MACE outcome and wound healing rate post-revascularization for CLTI.

4. MATERIALS AND METHODS

Study site

This study was carried out at Jain Institute of Vascular Sciences (JIVAS), Bhagwan Mahaveer Jain Hospital, Bangalore.

Study population

Total of 318 patients admitted with Chronic Limb Threatening Ischemia (CLTI) underwent successful infrainguinal revascularization at JIVAS between January 2021 to December 2021 i.e., 12months. All of them were included in the study.

Study design

A single center, prospective, observational and longitudinal study.

Sample size calculation

The sample size was calculated using Open Epi software at 95% confidence interval (CI). The calculated sample size was 123. Assuming 20% non-response rate the estimated sample size was 123 + 24= 147. However, 318 subjects were enrolled in the present study.

Time frame for study

Patients were enrolled from January 2021 to December 2021 and were followed prospectively at 1, 3 and 6 months as per study protocol.

Inclusion criteria

Adult patients (i.e.,18years and above) with chronic limb threatening ischemia (CLTI) who have undergone successful infrainguinal revascularization.

CLTI is defined as a patient presenting with any of the following clinical signs or symptoms:

1. Ischemic rest pain
2. Gangrene involving any part of lower limb or foot
3. Non-healing ulcer on any part of the lower limb or foot

   In addition to the following:

   a) With ABI </= 0.8

   b) With decreased arterial flow documented by hemodynamic and imaging studies.

Exclusion Criteria:

1. Patients having uncorrected aorto-iliac significant disease (>50%)
2. Patients having uncorrected common femoral artery stenosis (>50 %)
3. Pure venous ulcers without arterial component
4. Traumatic arterial injury
5. Acute limb ischemia (symptoms present for 2 weeks or less)
6. Embolic disease
7. Non-atherosclerotic chronic vascular conditions of the lower extremity (eg, Vasculitis, Buerger disease, Radiation Arteritis)

The primary endpoints: Wound Healing rate

The secondary endpoints: MALE and MACE outcomes

5. STUDY METHODOLOGY

Patient enrollment

- This is a single center observational study, done over a period of 18 months.
- Study period: January 2021- June 2022
  - Recruitment period: 12months
  - Follow up period: 6months

Demographic data of the patients was recorded with history and physical examination findings pre operatively in form of chief complaints, personal history of smoking and tobacco if any. They were assessed for medical risk factors like diabetes mellitus, hypertension, coronary artery disease (CAD), chronic kidney disease (CKD), Dyslipidemia, and Chronic Obstructive Pulmonary Disease (COPD). In all patients' general, local examination were carried out with careful documentation of vascular status of both lower limbs along with ankle brachial index (ABI) and pulse volume recording (PVR). Preoperative imaging was based on clinical findings and was performed in the form of arterial duplex, CT angiography or MR angiography or Digital Subtraction Angiography (DSA). All patients who had infrainguinal revascularization (Bypass or angioplasty / stenting) were enrolled for the study.

Patient Classification

Patient were then analyzed as per PLAN Concept according to which the following were assessed:

A. **P**atient risk as calculated by VQI for Infrainguinal revascularization (open or PVI) for CLTI: 30 day and 2-year survival,
B. **L**imb Severity stage assessed as per WIfI (Wound Ischemia and foot Infection) stages.
C. **AN**atomical severity of the infrainguinal arterial disease as per Global Limb Based Anatomical Staging System (GLASS).

Revascularization Procedures

The interventions i.e., endovascular or open bypass (including hybrid procedure), were carried out on the patients in accordance with established recommendations and the surgeon's personal preferences and judgment. Post procedure pulse/Doppler signal status were noted and the PVR/ABI

recorded on the first post operative day. Wound status at the time of discharge was noted for comparison at follow-up.

Secondary Procedures

Patients with infected ulcers or gangrene underwent wound debridement and toe amputation following revascularization either at the time of primary admission or when felt necessary at the time of follow-up.

Follow up

All patients were counseled about the life style modification regarding foot wear and foot care and were regularly followed up at 1, 3 and 6 months clinically. In a few cases, where clinical follow-up was ergonomically difficult, telephonic follow-up was done. Wound status of the patient in terms of healed or not healed were noted periodically.

Analysis:

At the end of the follow up period an analysis was made of whether or not the wound had successfully healed.

Patients were then divided into three groups:

a) **MATCHED GROUP**: Patients in whom the procedure performed matched the procedure that PLAN Concept suggested
b) **UNMATCHED GROUP**: Patients in whom the procedure performed did not match the procedure the PLAN Concept suggested
c) **INDETERMINATED GROUP**: Patients in whom PLAN Concept suggestion was Indeterminate.

   At the end of the study, we assessed the outcomes, i.e., wound healing rates, rate of amputation and mortality and compared them between the matched and unmatched group. For the indeterminate group, the outcomes were compared between the patients who

underwent endovascular intervention and those who underwent open bypass (including hybrid).

Statistical Analysis

The data on categorical variables is shown as n (% of cases) and the data on continuous variables is presented as mean and standard deviation (SD). The inter-group statistical comparison of distribution of categorical variables is tested using Chi-Square test or Fisher's exact probability test if more than 20% cells have expected frequency less than 5. All results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly.

In the entire study, the p-values less than 0.05 are considered to be statistically significant. The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS ver 24.0, IBM Corporation, USA) for MS Windows. [43,44,45]

Ethic committee and scientific committee approval

Present study design is approved by ethic and scientific committee of Bhagwan Mahaveer Jain Hospital, Bengaluru.

6. OBSERVATIONS AND RESULTS

Present study was a prospective observational study which was undertaken to study the surgical outcome of application of PLAN concept and outcome analysis in the Infrainguinal revascularization for chronic limb threatening ischemia (CLTI). The study was carried out in the department of Surgery, JIVAS, BMJH, Bangalore during the period January 2021 to June 2022.

A total of 318 cases that satisfied inclusion/exclusion criteria as per the study protocol were included in the study. The mean age of cases studied was 65.68 ± 11.08 years and the age range was 30 – 92 years, with inclusion of both the genders (male to female sex ratio was 5.62: 1.00).

The following section shows the detailed statistical analysis along interpretation and the graphical representation of the available data.

Table 6.1) Age distribution of the study population:

Age group (years)	No. of cases	% of cases
30 – 39	9	2.8
40 – 49	14	4.4
50 – 59	55	17.3
60 – 69	127	39.9
70 – 79	75	23.6
80 – 89	37	11.6
>90	1	0.3
Total	**318**	**100.0**

Age distribution of the study population:

Out of 318 cases studied, 9 cases (2.8%) were between 30 – 39 years, 14 cases (4.4%) between 40 – 59 years, 55 (17.3%) between 50 – 59 years, 127 (39.9%) between 60 – 69 years, 75 (23.6%) between 70 – 79 years, 37 cases (11.6%) between 80 – 89 years, 1 (0.3%) was above 90 years.

The mean age of the study population was 65.68 ± 11.08 years and the age range was 30 – 92 years.

Graph 6.1) Age distribution of the study population (%).

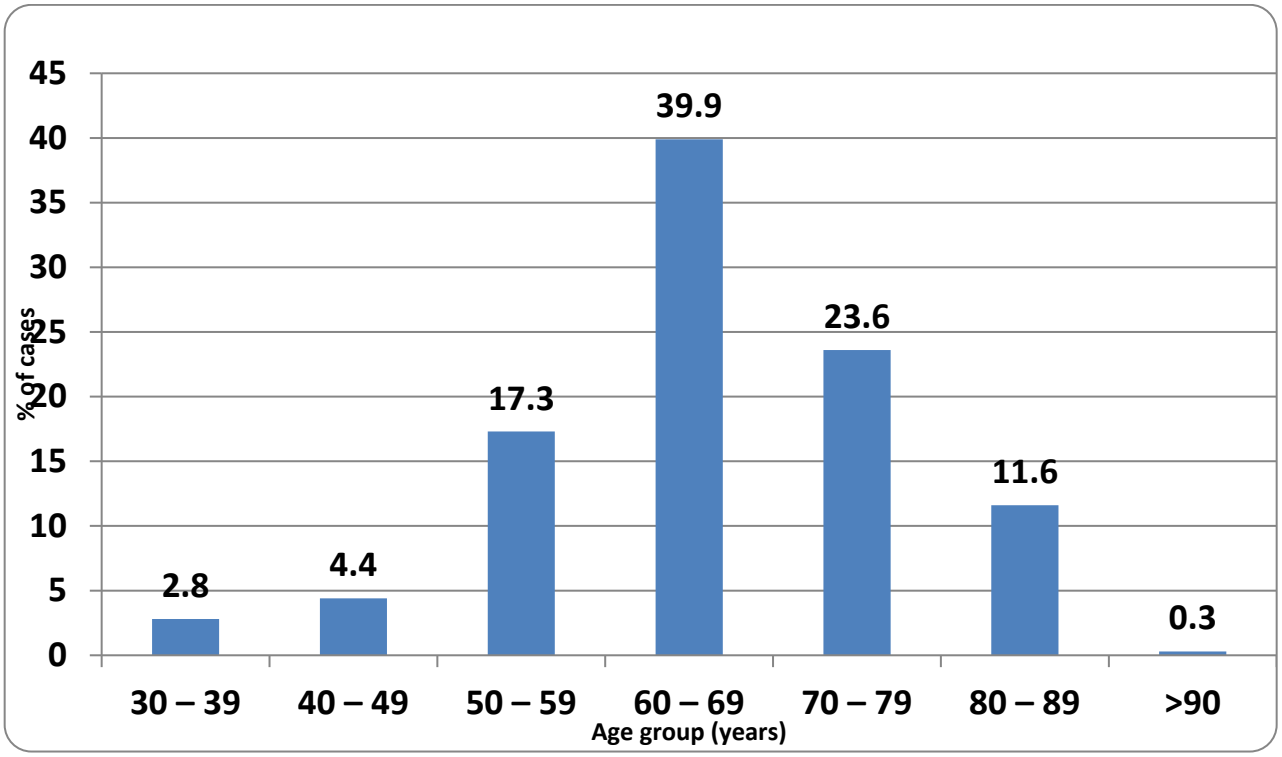
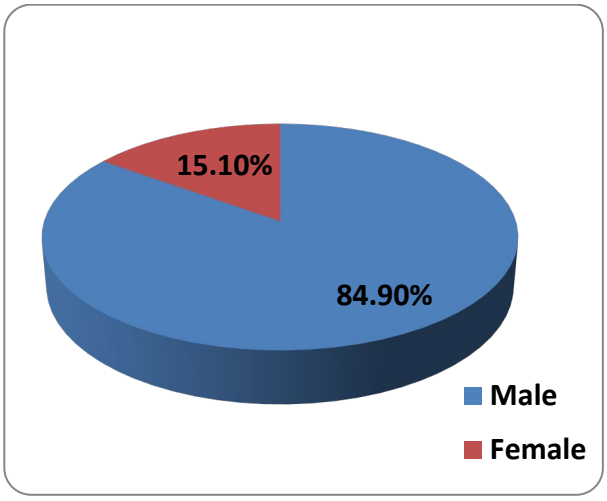


Table 6.2) Sex distribution:

Sex	No. of cases	% of cases
Male	270	84.9
Female	48	15.1
Total	**318**	**100.0**

Graph 6.2) Sex distribution (%):



Sex distribution: Out of 318 patients recruited, 270 (84.9%) were male and 48 (15.1%) were female. The male to female sex ratio was 5.62:1 in the study group.

Table 6.3) Distribution of co-morbidities in the study population:

Co-morbidity	No. of cases	% of cases
Diabetes mellitus	289	90.9
Hypertension	217	68.2
Coronary artery disease (CAD)	120	37.7
Chronic kidney disease (CKD)	46	14.5
Chronic obstructive pulmonary disease	36	11.3
Dyslipidaemia	33	10.4

Distribution of co-morbidities in the study population:

Out of 318 cases studied, 289 (90.9%) had diabetes mellitus, 217 (68.2%) had hypertension, 120 (37.7%) had coronary artery disease (CAD), 46 cases (14.5%) had chronic kidney disease (CKD), 36 cases (11.3%) had Chronic obstructive pulmonary disease (COPD) and 33 cases (10.4%) had dyslipidaemia. All co-morbidities were non-exclusive, meaning same case had multiple co-morbidities.

Graph 6.3) Distribution of co-morbidities among the study population (%).

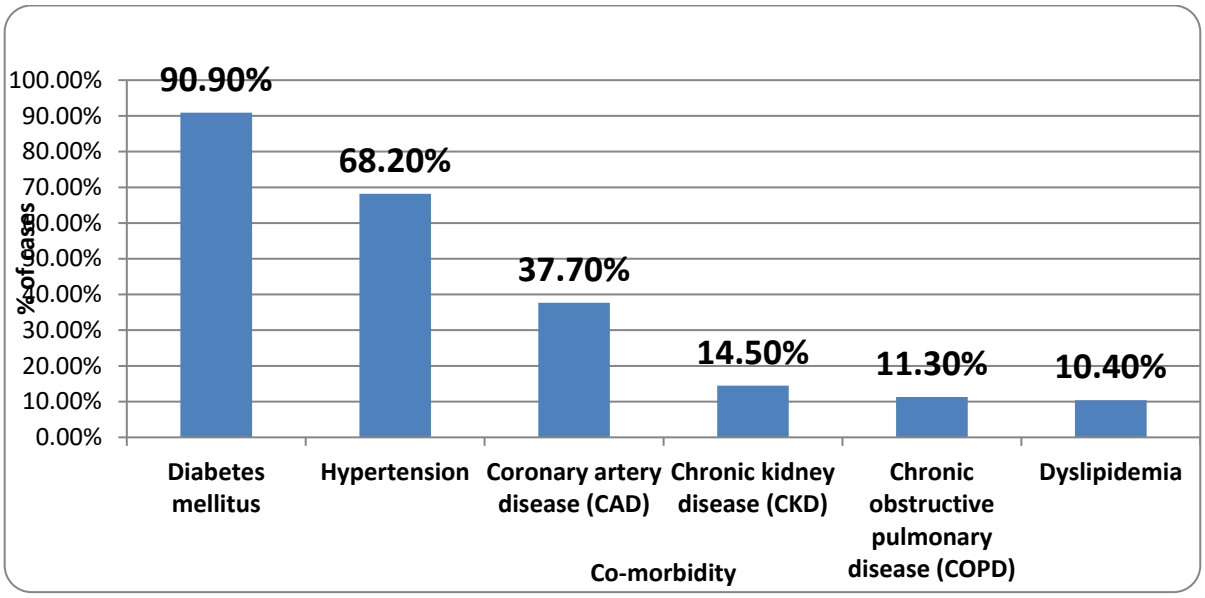
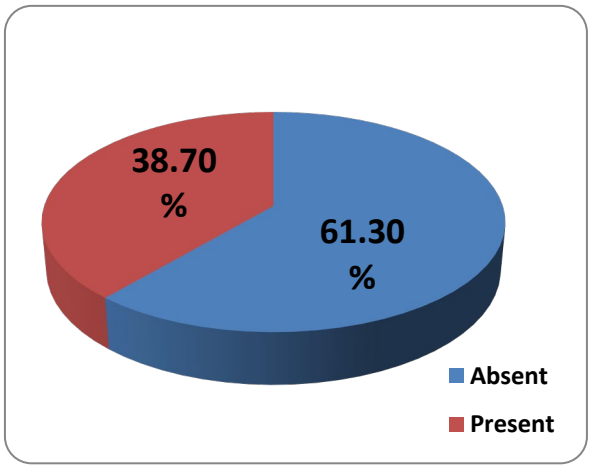


Table 6.4) Distribution of smoking habit: **Graph 6.4) Distribution of smoking habit (%)**

Smoking status	No. of cases	% of cases
Absent	195	61.3
Present	123	38.7
Total	**318**	**100.0**



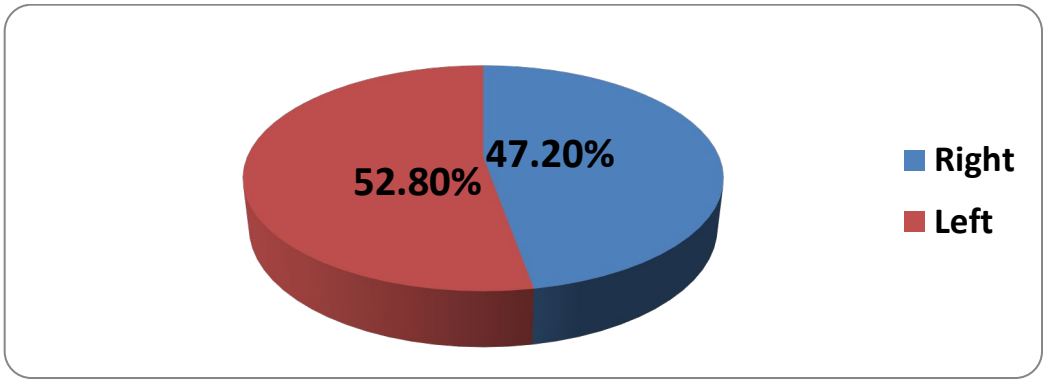
Distribution of smoking status:

Out of 318 cases studied, 123 cases (38.7%) were current or ex-smokers and 195 (61.3%) were non-smokers as per the clinical history.

Table 6.5) Distribution of laterality of index limb involved:

Index limb*	No. of cases	% of cases
Right	150	47.2
Left	168	52.8
Total	**318**	**100.0**

Graph 6.5) Distribution of laterality of index limb involved (%):

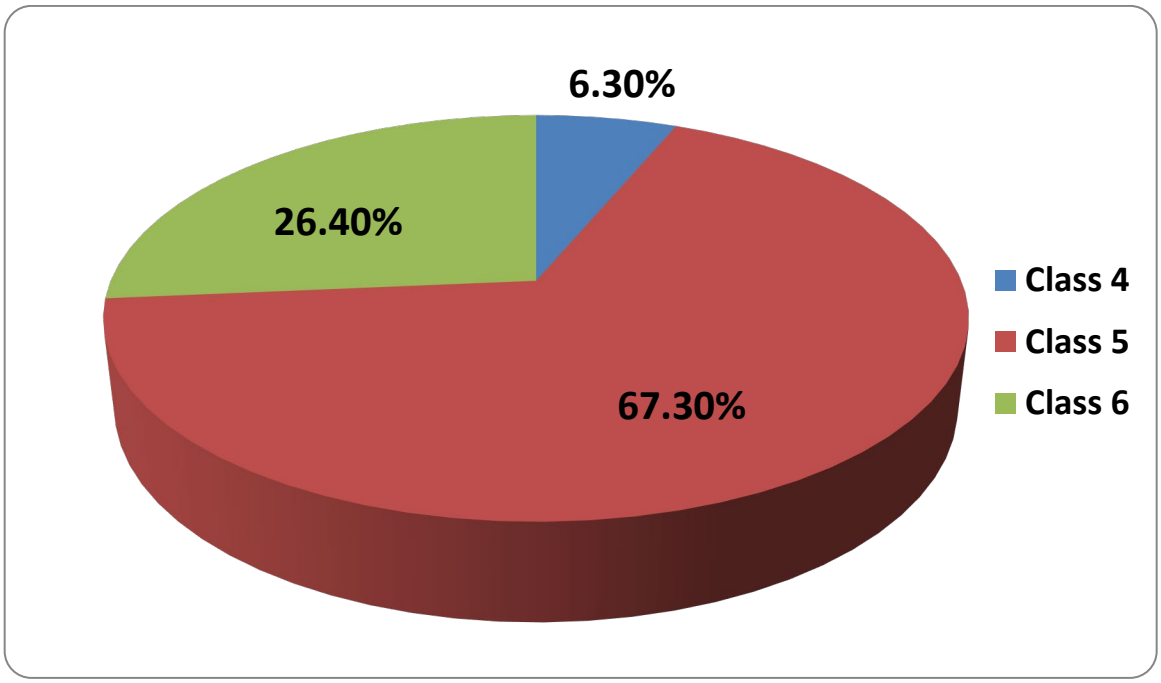


*One patient underwent bilateral revascularization, which was considered as two separate events.

Table 6.6) Distribution of cases according to Rutherford/SVS classification:

Rutherford class	No. of cases	% of cases
Class 4	20	6.3
Class 5	214	67.3
Class 6	84	26.4
Total	**318**	**100.0**

Graph 6.6) Distribution of cases according to Rutherford/SVS classification



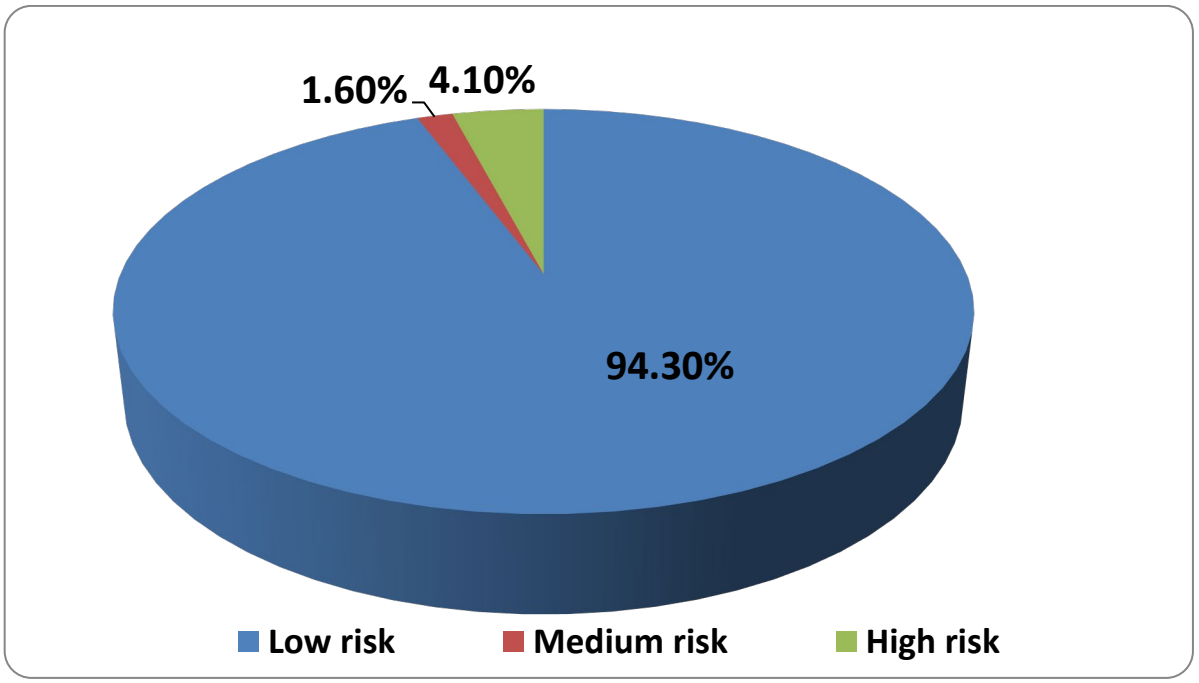
Distribution of cases according to Rutherford/SVS classification:

Out of 318 cases, 20 cases (6.3%) were Rutherford category 4, majority of cases i.e. 214 cases (67.3%) Rutherford category 5, 84 cases (26.4%) Rutherford category 6.

Table 6.7) Distribution of patient risk profile as per VQI:

Risk	No. of cases	% of cases
Low risk	300	94.3
Medium Risk	05	1.6
High risk	13	4.15
Total	**318**	**100.0**

Graph 6.7) Distribution of patient risk profile as per VQI (%):



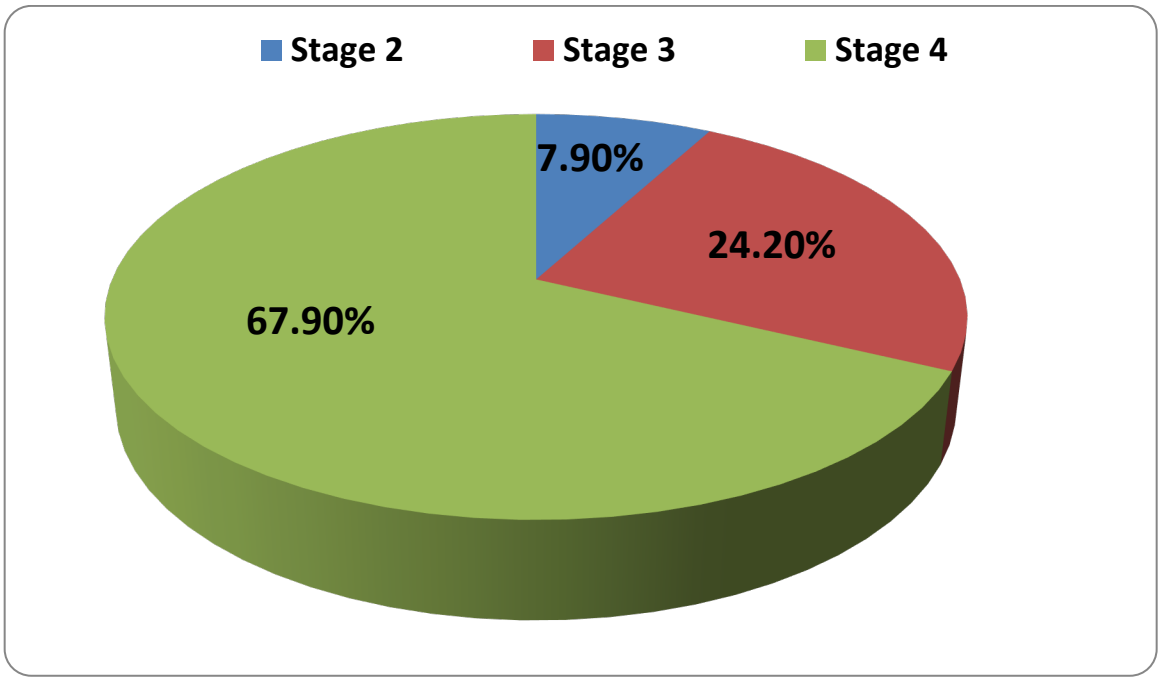
Distribution of patient risk profile:

Out of 318 cases studied, majority of cases i.e., 300 cases (94.3%) had low risk, 5 cases (1.6%) medium risk and 13 cases (4.15%) had high risk profile at the time of surgical intervention.

Table 6.8) Distribution of WIfI stage:

WIfI stage	No. of cases	% of cases
Stage 2	25	7.9
Stage 3	77	24.2
Stage 4	216	67.9
Total	**318**	**100.0**

Graph 6.8) Distribution of WIfI stage:



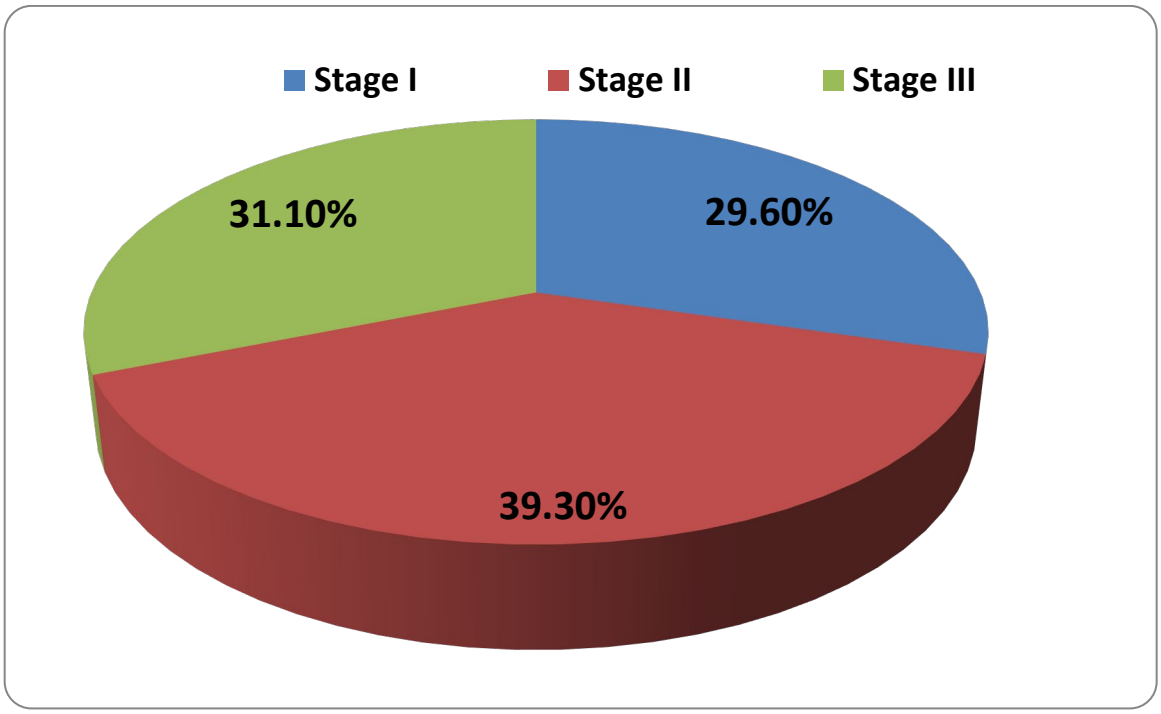
Distribution of WIfI stage

Out of 318 cases studied, 25 cases (7.9%) had WIfI Stage 2, 77 cases (24.2%) Stage 3 and majority of cases i.e., 216 cases (67.9%) Stage 4.

Table 6.9) Distribution of GLASS stage:

GLASS stage	No. of cases	% of cases
Stage I	94	29.6
Stage II	125	39.3
Stage III	99	31.1
Total	**318**	**100.0**

Graph 6.9) Distribution of GLASS stage:



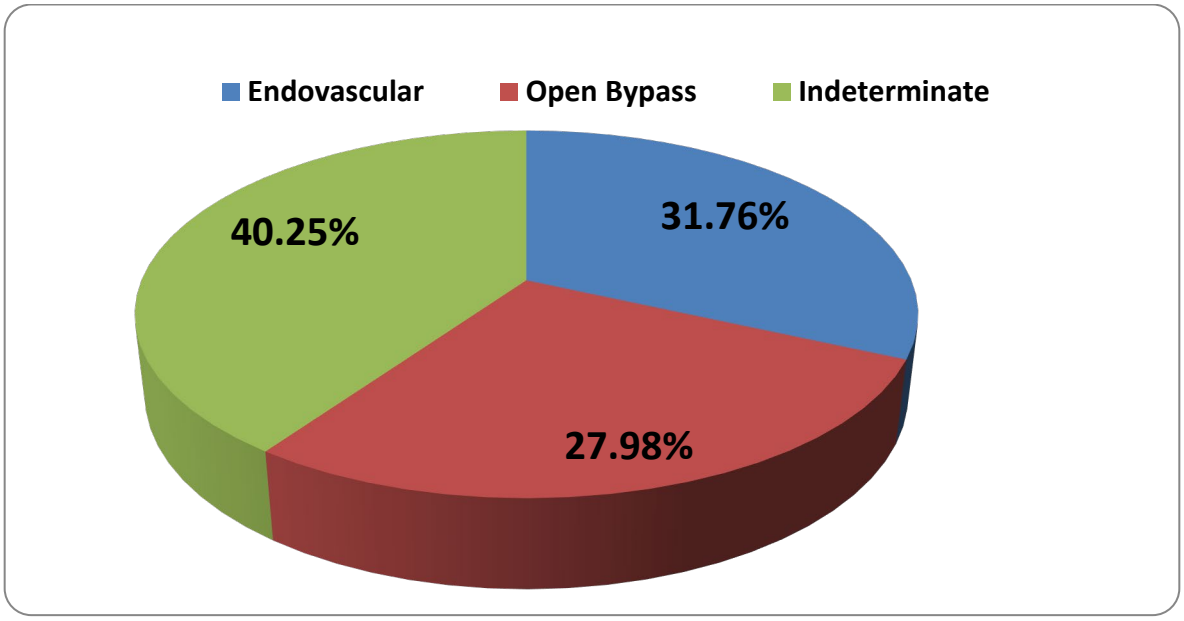
Distribution of GLASS stage

Out of 318 cases studied, 94 cases (29.6%) had GLASS Stage I, majority of cases i.e., 125 cases (39.3%) GLASS Stage II and 99 cases (31.1%) GLASS stage III in the study group.

Table 6.10) Distribution of type of revascularization procedure as projected by PLAN Concept:

Type of procedure as projected by PLAN	No. of cases	% of cases
Endovascular	101	31.76
Open Bypass	89	27.98
Indeterminate	128	40.25
Total	**318**	**100.0**

Graph 6.10) Distribution of type of revascularization procedure as projected by PLAN Concept



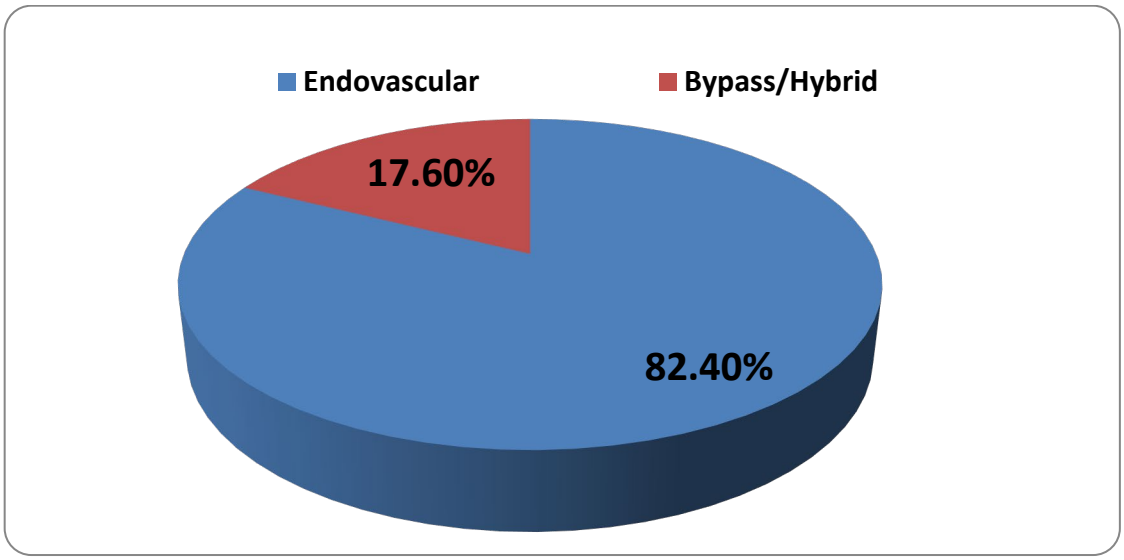
Distribution of type of revascularization procedure as projected by PLAN Concept:

Out of 318 cases studied, PLAN projected Endovascular in 101 cases (31.76%), Open Bypass in 89 cases (27.98%) and in majority of cases PLAN projection was indeterminate i.e., in 128 cases (40.25%).

Table 6.11) Distribution of type of revascularization procedure performed by us at JIVAS:

Type of procedure done	No. of cases	% of cases
Endovascular	262	82.4
Bypass/Hybrid	56	17.6
Total	**318**	**100.0**

Graph 6.11) Distribution of type of revascularization procedure performed by us at JIVAS:



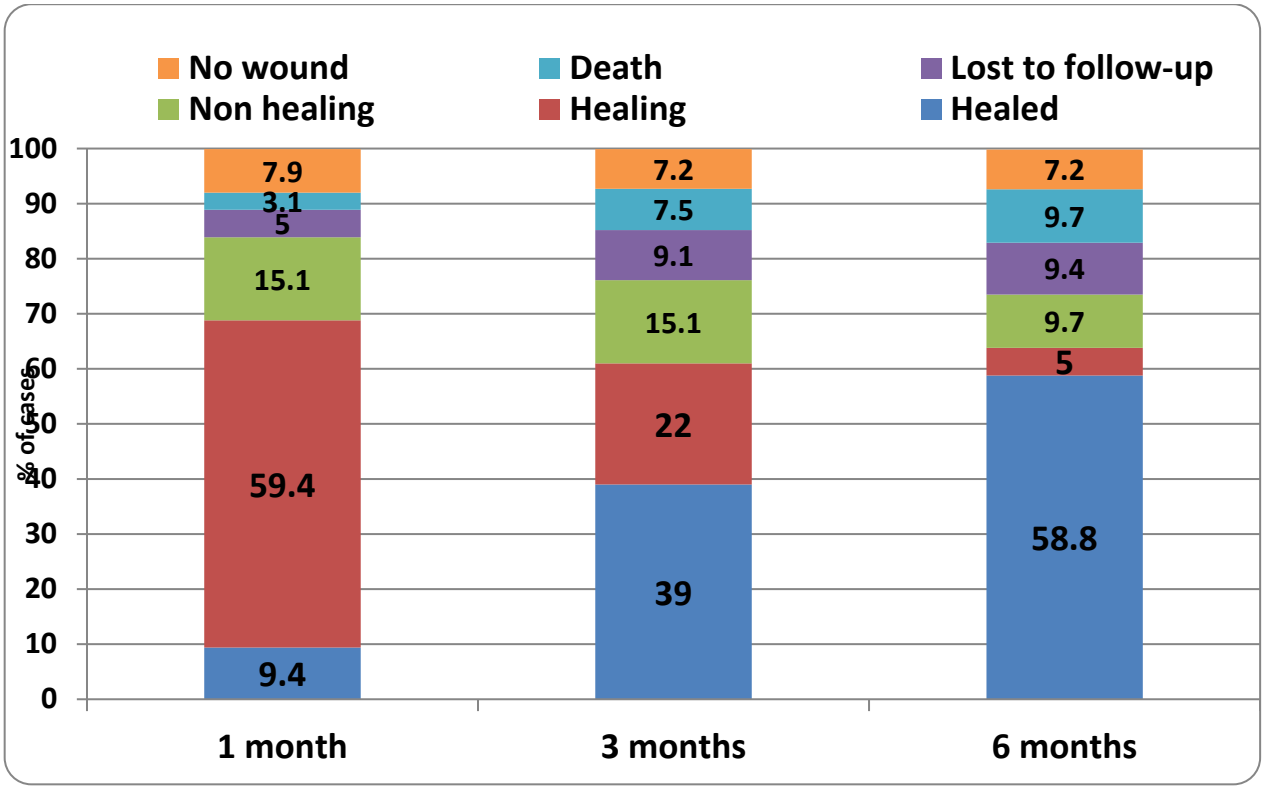
Distribution of type of revascularization procedure performed by us at JIVAS:

Out of 318 cases studied, majority of cases i.e., 262 cases (82.4%) had Endovascular procedure done and 56 cases (17.6%) had Bypass/Hybrid procedure done in the study group. The hybrid procedures were clubbed with the bypass group as their number was small i.e., 8 cases.

Table 6.12) Distribution of wound healing status among the entire study cohort:

Wound healing status	1 month		3 months		6 months	
	n	%	n	%	n	%
Healed	30	9.4	124	39.0	187	58.8
Healing	189	59.4	70	22.0	16	5.0
Non healing	48	15.1	48	15.1	31	9.7
Lost to follow-up	16	5.0	29	9.1	30	9.4
Death	10	3.1	24	7.5	31	9.7
No wound	25	7.9	23	7.2	23	7.2
Total	**318**	**100.0**	**318**	**100.0**	**318**	**100.0**

Graph 6.12) Distribution of wound healing status among the entire study cohort:



Distribution of wound healing status **among the entire study cohort:**

Out of 318 cases studied, 30 cases (9.4%) had healed wound, 189 (59.4%) were in healing phase, 48 (15.1%) had non healing status, 16 (5.0%) were lost to follow-up, 10 (3.1%) died and 25 cases (7.9%) had no wound at the time of post-op 1 month follow-up.

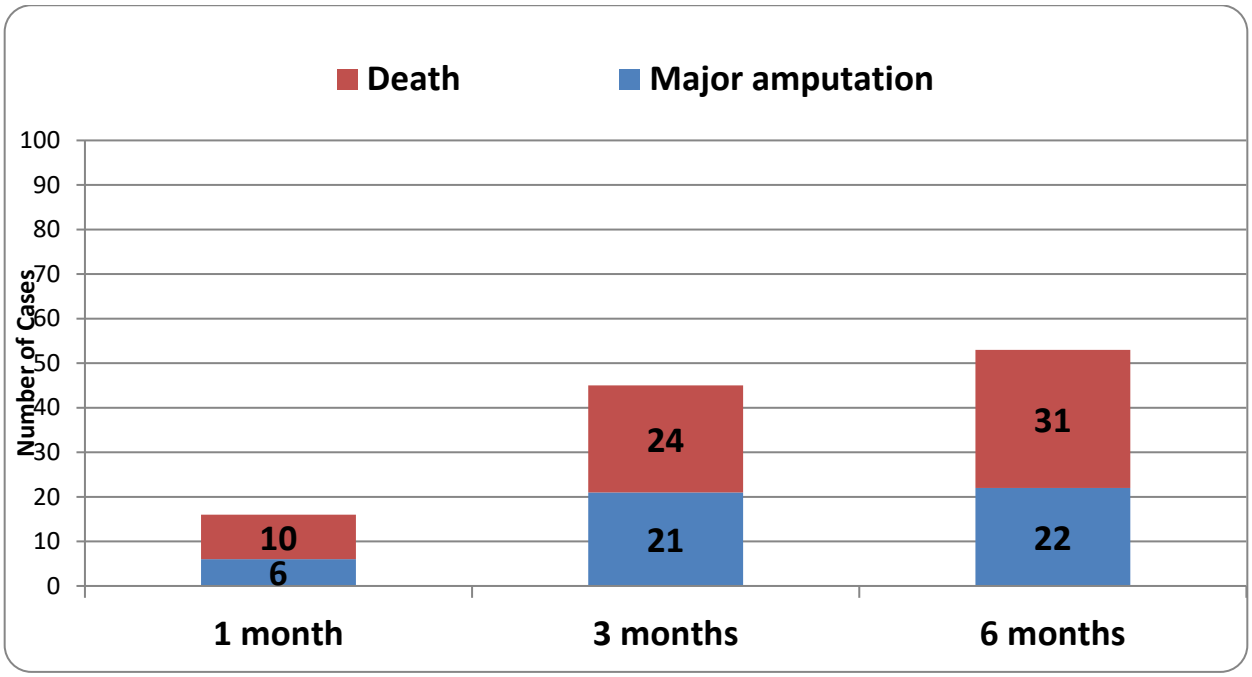
Out of 318 cases studied, 124 cases (39.0%) had healed wound, 70 (22.0%) were in healing phase, 48 (15.1%) had non healing status, 29 (9.1%) were lost to follow-up, 24 (7.5%) died and 23 cases (7.2%) had no wound at the time of post-op 3-month follow-up.

Out of 318 cases studied, 187 cases (58.8%) had healed wound, 16 (5.0%) were still in healing phase, 31 (9.7%) had non healing status, 30 (9.4%) were lost to follow-up, 31 (9.7%) died and 23 cases (7.2%) had no wound at the time of post-op 6-month follow-up.

Table 6.13) Distribution of total Major Adverse Limb Events (MALE) and Major Adverse Cardiovascular Events (MACE) outcome among the entire study cohort.

MALE and MACE	1 month	3 months	6 months
Survived with major amputation	6	21	22
Death	10	24	31
Total	**16**	**45**	**53**

Graph 6.13) Distribution of MALE/MACE outcome among the entire study cohort:



Distribution of Major Adverse Limb Events (MALE) and Major Adverse Cardiovascular Events (MACE) outcome among the entire study cohort:

At 1-month follow-up total 16 out of the 318 cases had adverse events (6 survived with major amputation and 10 died).

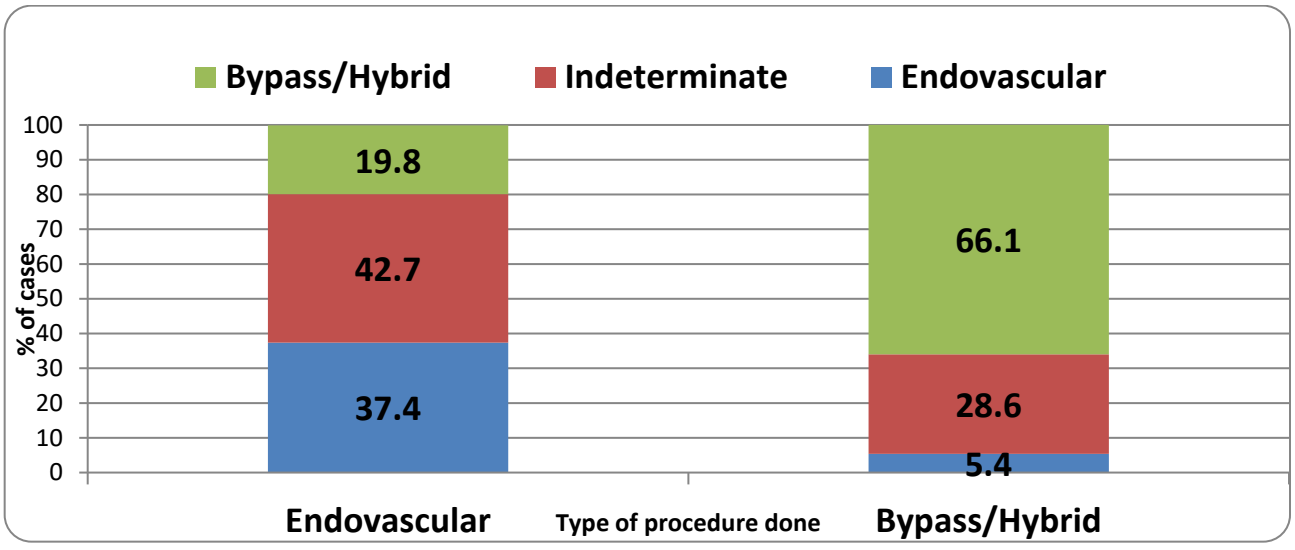
At 3-month follow-up total 45 cases had adverse events (21 survived with major amputation and 24 died).

At 6-month follow-up total 53 cases had adverse events (22 survived with major amputation and 31 died).

Table 6.14) Distribution of agreement between revascularization procedure performed and the type of procedure projected by PLAN.

	Type of procedure done					
	Endovascular		**Bypass/Hybrid**		**Total**	
Type of procedure as per PLAN	n	%	n	%	n	%
Endovascular	98	37.40	3	5.4	101	31.76
Indeterminate	112	42.74	16	28.6	128	27.98
Bypass	52	19.84	37	66.1	89	40.25
Total	**262**	**100.0**	**56**	**100.0**	**318**	**100.0**

Graph 6.14) Distribution of agreement between revascularization procedure performed and the type of procedure recommended by PLAN.



Distribution of agreement between revascularization procedure performed and the type of procedure recommended by PLAN:

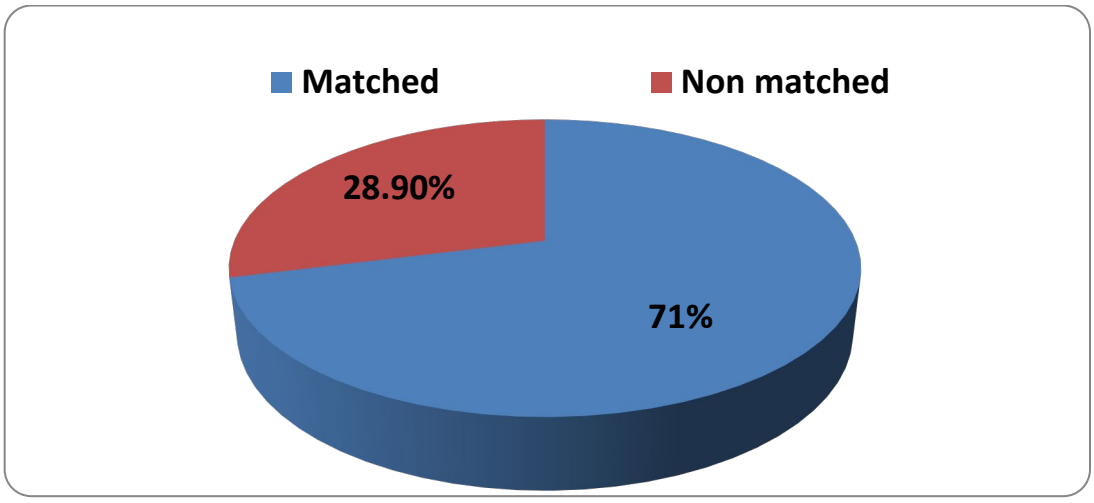
Out of 262 cases who underwent Endovascular procedure, PLAN recommended Endovascular in only 98 (37.4%). Amongst the others, PLAN recommended Bypass in 52 (19.84%) and was indeterminate in 112(42.74%).

Out of 56 cases who underwent Bypass procedure (includes hybrid procedure), PLAN recommended Bypass in 37(66.1%). Amongst the others, PLAN recommended Endovascular in 3 (5.4%) and was indeterminate in 16(28.6%).

Table 6.15) Distribution of revascularization procedure matching status between performed procedure and procedure as per PLAN (Excluding indeterminate procedures).

Procedure matching status	No. of cases	% of cases
Matched	135	71.0
Non matched	55	28.9
Total	185	100.0

Graph 6.15) Distribution of revascularization procedure matching status between performed and procedure as per PLAN (Excluding indeterminate procedures).



Distribution of revascularization procedure matching status between performed and procedure as per PLAN (Excluding indeterminate procedures)

Out of 318 cases, PLAN recommendation was indeterminate in 128. These 128 were not included to determine the matching status between the performed procedures and the procedures recommended by PLAN. Out of the remaining 190 cases, 135 cases (71.4%) fell into the matched cohort and 55 cases (28.6%) fell into the non-matched cohort.

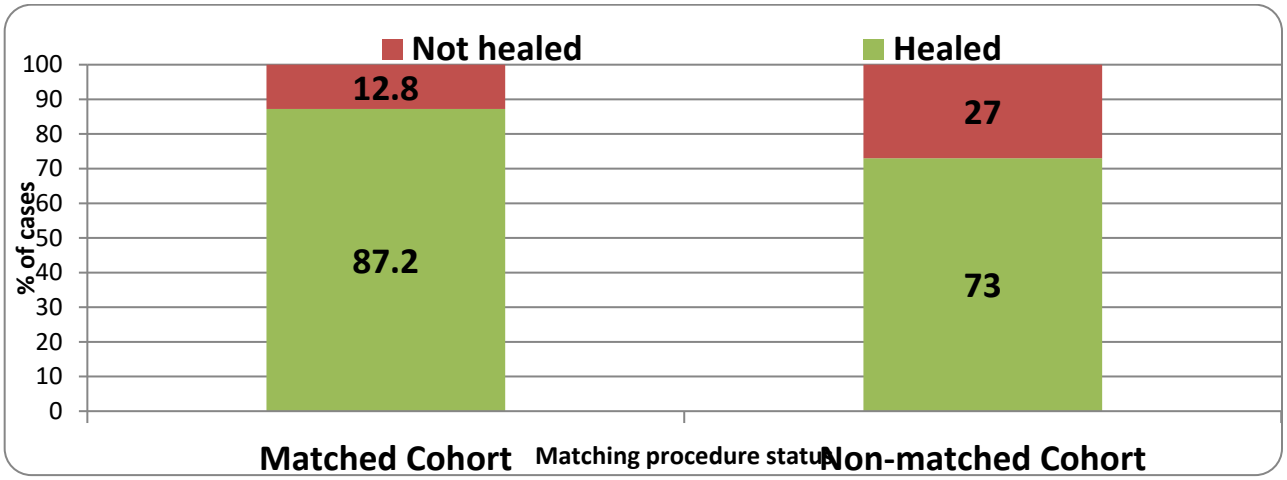
A. Analysis of wound healing between the matched and the non-matched cohort:

Out of 318 cases, 128 cases from the indeterminate cohort were excluded in this wound healing assessment. Out of the remaining 190 cases, there were 135 patients in the matched cohort and 55 patients in the non-matched cohort. In the matched cohort, 117 were followed up to 6months, while 8 died and 10 were lost to follow-up. In the non-matched cohort, 37 were followed up to 6months, 11 died and 7 were lost to follow-up.

Table 6.16) Comparison of wound healing between the matched and the non-matched cohort at the end of 6months:

	Matched cohort (117)		**Non-matched cohort (37)**		**P-value**
Wound status at 6 months	n	%	n	%	
Healed	102	87.2	27	73.0	0.041*
Not healed	15	12.8	10	27.0	
Total	**117**	**100.0**	**37**	**100.0**	
P-value by Chi-Square test. P-value<0.05 is considered to be statistically significant.					

Graph 6.16) Comparison of wound healing between the matched and the non-matched cohort at the end of 6months (%):



Comparison of wound healing between the matched and the non-matched cohort at the end of 6months:

Out of 117 cases from the matched cohort, 102 (87.2%) had healed wounds at 6-month follow-up and in 15 cases (12.8%) wounds failed to heal.

Out of 37 cases with non-matched cohort, 27 (73.0%) had healed wounds at 6-month follow-up and in 10 cases (27.0%) wounds failed to heal.

The incidence of wound healing at the end of 6-month follow-up was significantly higher in the matched cohort compared to the non-matched cohort (P-value 0.041).

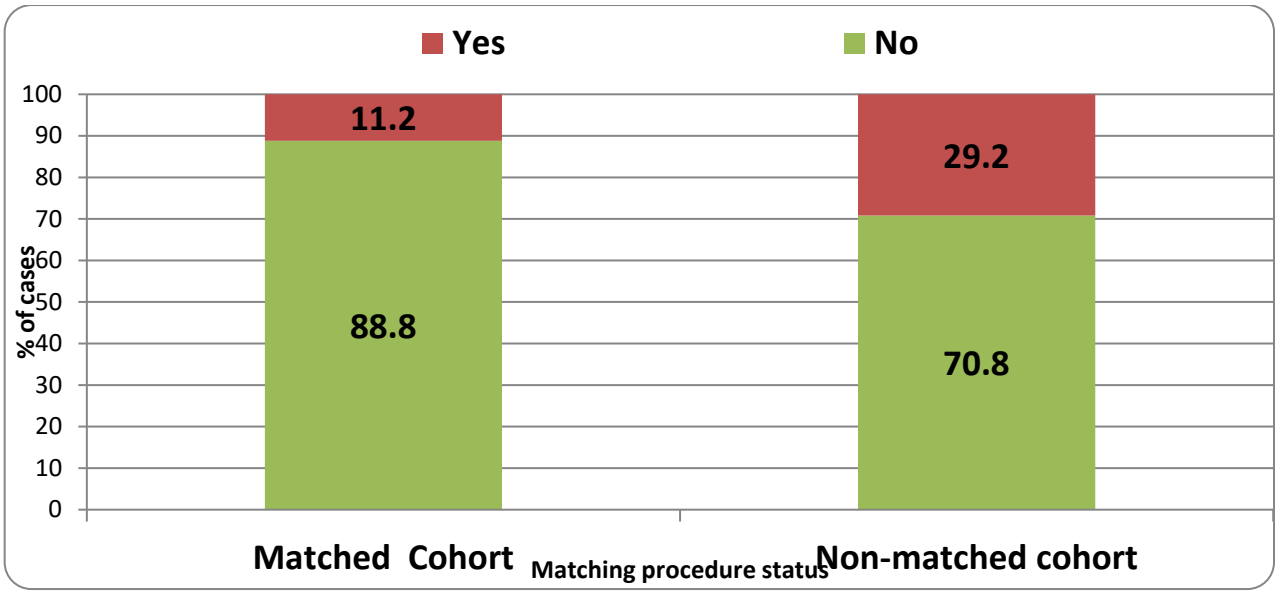
B. Analysis of MALE/MACE outcome between matched and non-matched cohort at the end of 6 months.

Out of the 135 patients in the matched cohort, 10 were lost to follow-up, hence 125 were included in analysis of MALE/MACE outcomes. Similarly in the non-matched, 7 out of 55 were lost to follow-up, hence 48 were included in analysis of MALE/MACE outcomes.

Table 6.17) Comparison of MALE/MACE outcome between matched and non-matched cohort at the end of 6 months.

	Matched cohort (125)		**Non matched cohort (48)**		**P-value**
MALE/MACE outcome	n	%	n	%	
No	111	88.8	34	70.8	0.004**
Yes	14	11.2	14	29.2	
Total	**125**	**100.0**	**48**	**100.0**	
P-value by Chi-Square test. P-value<0.05 is considered to be statistically significant. **P-value<0.01.					

Graph 6.17) Comparison of MALE/MACE outcomes between Matched and non-matched cohort at the end of 6 months.



Comparison of MALE/MACE outcome between matched and non-matched cohort at the end of 6 months.

Out of 125 cases from matched cohort, 111 (88.8%) did not have MALE/MACE outcome at and 14 (11.2%) had MALE/MACE outcome at 6-month follow-up.

Out of 48 cases from non-matched cohort, 34 (70.8%) did not have MALE/MACE outcome and 14 (29.2%) had MALE/MACE outcome at 6-month follow-up.

The incidence of MALE/MACE outcome at the end of 6-month follow-up was significantly lower in group of cases with matched procedures compared to the group of cases without the matched procedures (P-value<0.004).

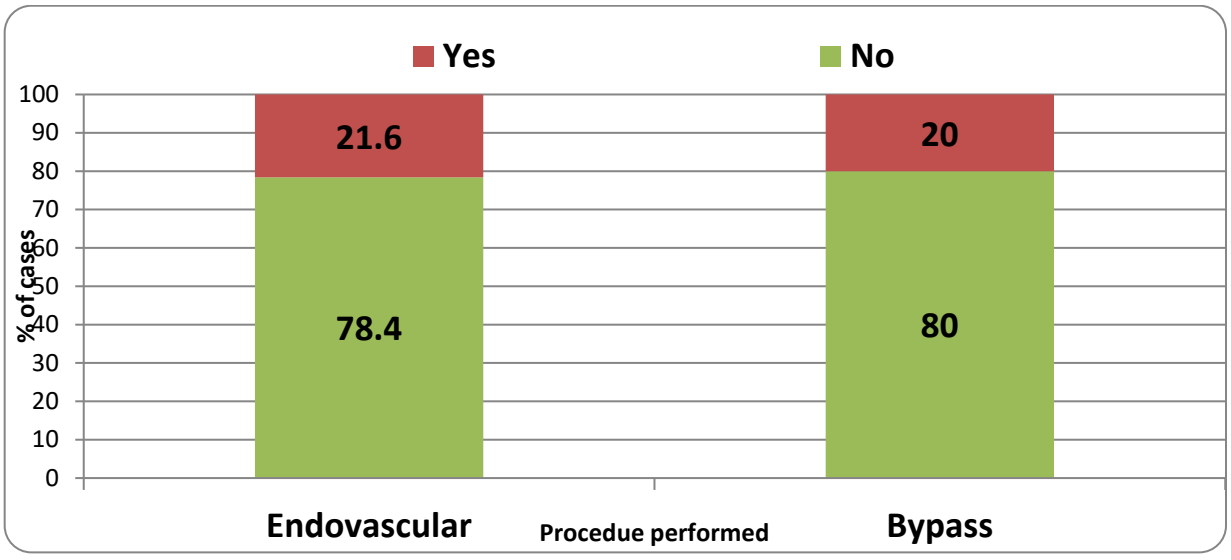
C. Analysis of the indeterminate cohort for wound healing:

Out of the 128 patients in indeterminate cohort, 12 patients died and 13 were lost to follow-up. Excluding these, 103 patients were followed up to 6 months and analysed for assessing wound healing.

Table 6.18) Comparison of wound healing at the end of 6-month follow-up between the procedure performed in group of cases from indeterminate cohort:

	Procedure performed				
	Endovascular (88)		**Bypass (15)**		**P-value**
Wound healing at 6 months	n	%	n	%	
Healed	69	78.4	12	80.0	0.999[NS]
Not healed	19	21.6	3	20.0	
Total	**88**	**100.0**	**15**	**100.0**	
P-value by Chi-Square test. P-value<0.05 is considered to be statistically significant. NS – Statistically non-significant.					

Graph 6.18) Comparison of wound healing at the end of 6-month follow-up between the procedure performed in group of cases from indeterminate cohort:



Comparison of wound healing at the end of 6-month follow-up between the procedure performed in group of cases from indeterminate cohort:

Out of 88 cases from the indeterminate cohort who underwent Endovascular procedure, 69 (78.4%) had healed wounds at 6 month follow-up and in 19 cases (21.6%) wounds did not heal.

Out of 15 cases from indeterminate cohort who underwent Bypass procedure done, 12 (80.0%) had healed wounds at 6-month follow-up and in 3 cases (20.0%) wounds did not heal.

The incidence of wound healing at the end of 6-month follow-up did not differ significantly between groups (P-value-0.999).

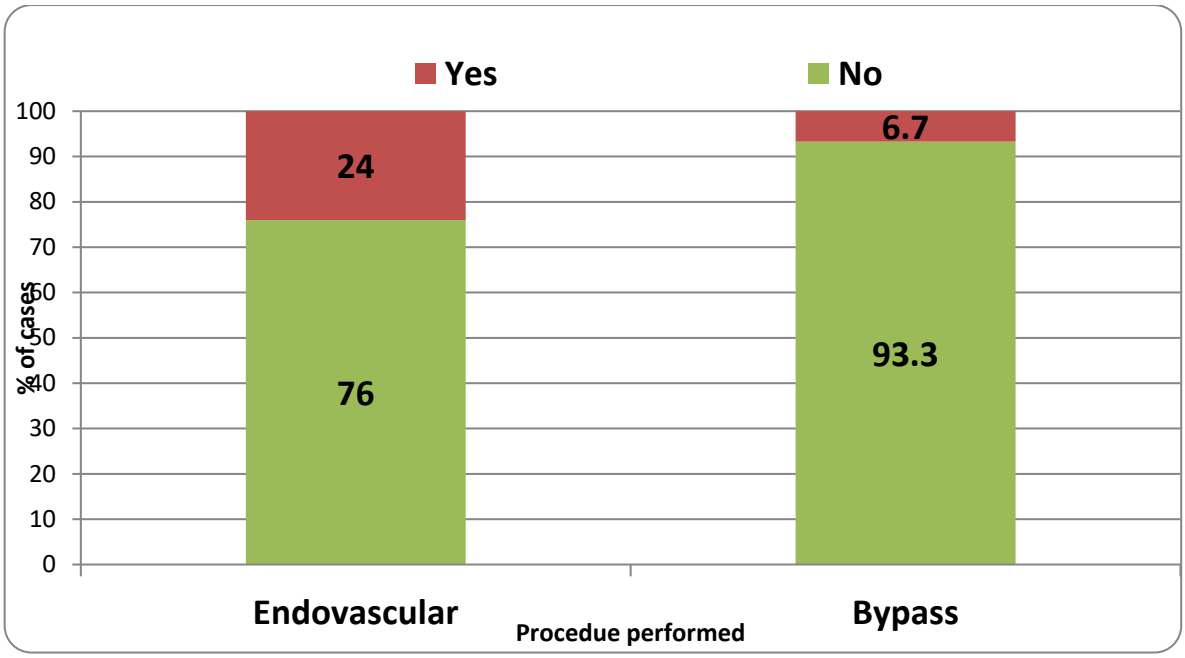
D. Analysis of the indeterminate cohort for MALE/MACE outcomes:

Out of 128 patients in indeterminate cohort, 13 were lost to follow-up, hence 115 were included in MALE/MACE outcome analysis.

Table 6.19) Comparison of MALE/MACE outcome at the end of 6-month follow-up between the procedure performed in group of cases from indeterminate cohort:

	Procedure performed				
	Endovascular (100)		**Bypass (15)**		**P-value**
MALE/MACE outcome	n	%	n	%	
No Yes	76 24	76.0 24.0	14 1	93.3 6.7	0.185^{NS}
Total	**100.0**	**100.0**	**15**	**100.0**	
P-value by Chi-Square test. P-value<0.05 is considered to be statistically significant. NS – Statistically non-significant.					

Graph 6.19) Comparison of MALE/MACE outcome at the end of 6 month follow-up between the procedure performed in group of cases from indeterminate cohort:



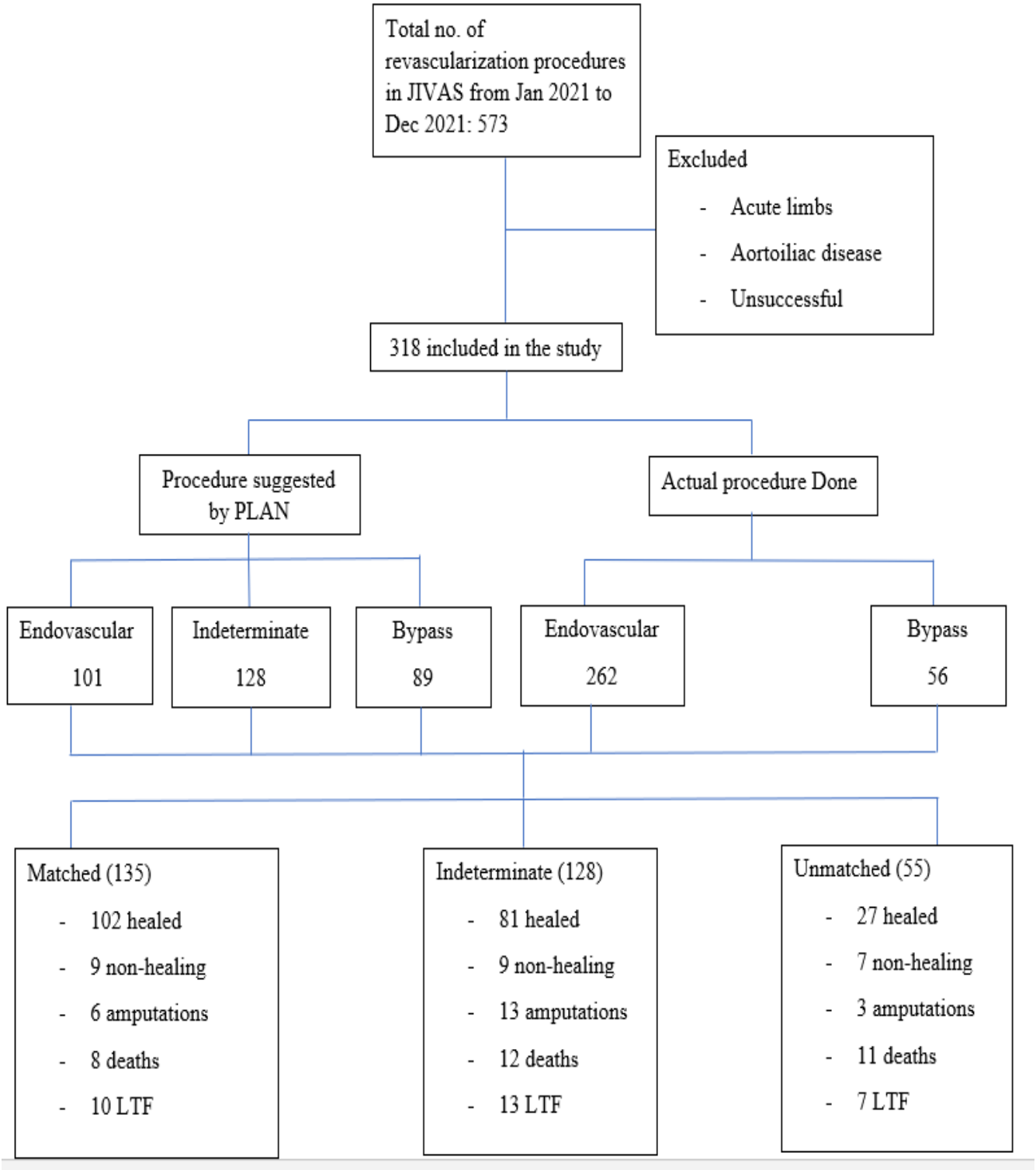
Incidence of MALE/MACE outcome at the end of 6-month follow-up according to the procedure performed in group of cases with indeterminate procedure by PLAN.

Out of 100 who underwent Endovascular procedure, 76 (76.0%) did not have MALE/MACE outcome at 6-month follow-up and 24 cases (24.0%) had MALE/MACE outcome.

Out of 15 cases who underwent Bypass procedure, 14 (93.3%) did not have MALE/MACE outcome at 6-month follow-up and only 1 case (6.7%) had MALE/MACE outcome.

The incidence of MALE/MACE outcome at the end of 6-month follow-up did not differ significantly between group of cases (P-value 0.185).

STUDY FLOWCHART:



7. DISCUSSION

Present study was a prospective observational study which was undertaken to study the surgical outcome of application of PLAN concept and its validation in the Infrainguinal revascularization for chronic limb threatening ischemia (CLTI). The study was carried out in the department of Surgery, JIVAS, Bangalore during the period January 2021 to June 2022.

A total of 318 cases that satisfied inclusion/exclusion criteria as per the study protocol were included in the study.

Patients underwent infrainguinal revascularization as per standard current protocols and were followed for six months. We calculated clinical outcomes in terms of wound healing and limb salvage as well as MACE outcomes.

To the best of our knowledge there is no study so far that validates PLAN for application in Evidence Based Revascularization. Hence this study was undertaken to assess its applicability. Very few studies have actually included WIfI and GLASS classification but none take into account all three parameters i.e., Patient Risk (VQI), WIfI stage and GLASS classification, in planning the most suitable procedure for the patient that will reduce the morbidity and mortality in these patients. This prospective study will give us an idea about the limb salvage and wound healing rates along with Major Adverse Events (MAEs) outcomes in when PLAN is taken into account while planning revascularization.

In our institute, 318 patients underwent infrainguinal revascularization for CLI between months of January 2021 to June 2022 that were included in the study. At the end of the six months 30 patients were lost to follow up and 31 patients died.

Demographics:

The mean age of cases studied was 65.68 ± 11.08 years and the minimum – maximum age range was 30 – 92 years, with 80.8% patients between the age group of 50-79years.

This correlated with the data published on demographics and prevalence peripheral arterial disease in Northern India by Sawan Sharma et al [46] which found 78.2% patients within the age group of 51 to 80years.

With an inclusion of both the genders the male to female ratio was 5.62:1).

Studies done by Cull et al [47], William Robinson et al [48], Bala Ramanan et al [49] also had predominantly male population while the north Indian data by Sharma et al [46] had a M:F ratio of 6:1.

Distribution of Comorbidities:

Out of 318 cases studied, 289 (90.9%) had diabetes mellitus, 217 (68.2%) had hypertension, 120 (37.7%) had coronary artery disease (CAD), 46 cases (14.5%) had chronic kidney disease (CKD), 36 cases (11.3%) had Chronic obstructive pulmonary disease (COPD) and 33 cases (10.4%) had dyslipidemia. All co-morbidities were non-exclusive, meaning same case could have multiple co-morbidities.

Table 7.1: Comparison of co-morbidities with other studies in major journals:

Comorbidities	JIVAS No (%)	Sharma et al [46]	Ramanan et al [49]	Mathioudakis et al [50]	Robinson et al [48]
DM II	289 (90.9%)	108 (39.3%)	118 (75%)	206 (94.9%)	163(83.7%)
HTN	217 (68.2%)	119 (43.3%)	132 (85%)	177 (81.6%)	229 (89%)
CKD	46 (14.5%)	--	37 (24%)	39 (18%)	184 (72%)
CAD	120 (37.7%)	61 (22.3%)	75 (48%)	51 (23.5%)	115 (45%)
Dyslipidemia	33 (10.4%)	47 (17.1%)	111 (71%)	106 (48.9%)	190 (74%)
COPD	36 (11.3%)	--	20 (13%)	23 (10.6%)	36 (14%)

Diabetes was less common in Sharma et al (39.3%) [46] as compared to our study (90.9%) while the other studies matched the statistics that were shown by our study.

Hypertension was seen in 68.2% patients in our study which was slightly more than the incidence seen in the study by Sharma et al but less than that seen in Ramanan et al [49], Mathioudakis et al [50] and Robinson et al [48].

CAD was found to be affecting 37.7% of our study population, which was close to the prevalence noted in the other studies mentioned.

Dyslipidemia prevalence was 10.4% in our study which is at par with that found by Sharma et al (17.1%) [46]. Higher prevalances were noted in Ramanan et al (71%) [49], and Robinson et al (74%) [48] studies.

Distribution of smoking status among the cases studied

Out of the 318 patients in our study, 38.7% were smokers compared to 80.4% in the Northern India study by Sharma et al [46] and 31% in a study from Southern India by Krishnan et al [51] and 14-21% in the western population [37,52,53]

Pre-op Rutherford Category distribution compared to other studies:

In our study only Rutherford category 4 and above were selected. Numbers of patients with Rutherford Category 4 were 20 (6.3%), category V were 214 (67.3%) and Category 6 were 84 (26.4%). This also reflects that patients getting admitted in our department with infra-inguinal disease predominantly have tissue loss, majority being minor tissue loss.

This Rutherford Category, i.e., Category 4-6, of disease represents the majority of the PAD patients who seek medical help. This is also the category that is at a higher risk of MAEs within 2 years. Kaplan-Meyer estimates of freedom from major amputation at 36 months were found to be 98.5% in Rutherford Categories 2-3, 94.0% in Categories 4-5, and 79.9% in Categories 6 in a study by S. Giannopoulos et al [54], indicating that the focus of revascularization should be on the Rutherford category 4-6 patients.

Distribution of patient risk profile

Out of 318 cases studied, majority of cases i.e., 300 cases (94.3%) were stratified into low-risk group, 5 cases (1.6%) medium-risk and 13 cases (4.15%) in high-risk group as per VQI mortality prediction model for infrainguinal revascularization which predicts the likelihood of survival for the first 30 days, and that over the first two years postoperatively. Low, medium, and high risk is defined by 30-day mortality estimates of ≤3%, 3%-5%, or >5% and 2-year mortality estimates of ≤30%, 30%-50%, or ≥50%, respectively. [55]

Pre-operative WIfI classification compared to other studies:

In WIfI classification, no patients presented with WIfI stage I, 25 cases (7.9%) presented in WIfI stage II, 77 cases (24.2%) in WIfI stage III and majority of cases i.e. 216 cases (67.9%) in WIfI stage IV. Cull et al [47], Zhan et al [56], Darling et al [57] and other studies also noted very less patients in WIfI stage I. Ward et al had a high representation of WIfI stage IV (59.1%), while all the other studies had majority of representation from WIfI stage II and III. This is reflective of the fact that most patients presenting at JIVAS present at an advanced stage of wound severity that are difficult to treat owing to high infection burden.

Table 7.2: Comparison of Stage of Presentation According to WIfI

Study (Yr): Number Of limbs at risk	Stage 1 No (%)	Stage 2 No (%)	Stage 3 No (%)	Stage 4 No (%)
JIVAS Study: 318	0 (0%)	25 (7.9%)	77 (24.2%)	216(67.9%)
Zhan et al [56] (2015):201	39(19.4)	50(24.8)	53(26.3)	59(29.3)
Cull et al [47] (2014):151	37(24.5)	63(41.7)	43(28.4)	8(5.2)

Causey et al [58] (2016):160	21(13.1)	48(30)	42(26.2)	49(30.62)
Beropoulis et al [59] (2016):126	29(23)	42(33.3)	29(23)	26(20.6)
Ward et al [60] (2017):98	5(5.1)	21(21.4)	14(14.2)	58(59.1)
Darling et al [57] (2017):992	12(1.2)	293(29.5)	249(24)	438(43)
Robinson et al [48] (2017):280	48(17.14)	67(23.9)	64(22.8)	83(29.6)
Tokuda et al [61] (2017):163	16(9.81)	30(18.4)	56(34.3)	61(37.4)

Pre operative GLASS classification:

All the patients admitted in JIVAS for revascularization were classified as per GLASS for the assessing the Anatomical stage of the disease. Out of total 318 patients, 94 cases (29.6%) were in Stage I of GLASS classification, majority of cases i.e., 125 cases (39.3%) in GLASS stage II and 99 cases (31.1%) were in stage III. This classification of patients was based on intra-operative DSA or pre-operative MR Angiography or CT angiography (if DSA was not done).

In the study done by Takahiro Tokuda et al [62], in which 154 patients were studied, and 34.4% patients presented with GLASS Stage I disease, 24.6% with GLASS Stage II disease and 40.90% with GLASS Stage III disease. Our study correlated well with this study published in 2021.

Wound healing at 6th month

Out of total 318 patients, 31 patients died and 30 patients were lost to follow-up. Of the remaining 257 patients, 23(7.2%) presented with only rest pain and no wounds. Out of the remaining 234 patients, 187 patients (58.8%) had healed wounds and 22 patients (6.9%) had undergone a major amputation by the end of 6months while the remaining 25 (7.86%) continued to have non-healing wounds.

The wound healing percentage progressively increased for 9.4% (30 patients) at the end of one month, 38.9% (124 patients) by the end of 3months and 58.8% (187 patients) by the end of 6 months.

Distribution of type of revascularization procedure done

Out of 318 cases who underwent successful infrainguinal revascularization, majority of cases i.e., 262 cases (82.4%) underwent Endovascular procedure and 56 cases (17.6%) underwent open bypass procedure as was decided by the operating surgeon based on WIfI stage and GLASS stage of the patient.

In a study by Morisaki K et al [63], in which 69.5% underwent bypass, 20.5% underwent endovascular therapy and 10.0% underwent hybrid procedure, it was noted that only WIfI stage and inframalleolar disease were risk factors for major amputation and impaired wound healing. Although, GLASS stage was found to be prognostic factor for poor overall survival, it played no role in predicting limb-salvage or wound healing. Nevertheless, GLASS was useful in deciding between bypass surgery and endovascular therapy.

A systemic review and meta-analysis by Vangelis Bontinis et al [64], demonstrated that patients with CLTI undergoing endovascular interventions classified as GLASS stage III had almost a four-fold risk increased risk for immediate technical failure and 1.84 times increased risk for major amputation compared with stages I and II thereby proving the importance of GLASS staging of every PAD patient who is a candidate for revascularization.

Taking into consideration the available evidence, we planned the patient's procedure based on the patient's WIfI staging and GLASS staging.

Distribution of wound healing status at 1month, 3months and 6months:

Patients were reviewed at 1, 3 and 6motnhs and wound healing status was noted.

The percentage of wound healing showed a progressive increase from 9.4% in 1st month to 39% in 3rd month to 57.9% at 6months.

Accordingly, the percentage of wounds in healing stage went down from 59.4% in 1st month to 22% in 3rd month to 5% in 6th month.

25 patients had no wounds and presented with rest-pain. 2 of these patients were lost to follow-up, while the other 23 continued to remain wound and pain free at the 6th month follow-up.

16 patients (5%) were lost to follow-up at 1st month. This number increased to 29 (9.1%) at 3months and 31 (9.7%) at 6months.

Distribution of Major Adverse Limb Events (MALE) and Major Adverse Cardiovascular Events (MACE) outcome

There was a total of 53 MAEs in the study. This accounts for 16.6% of the study population.

The total MACE events were 9.74% and MALE events were 6.9% of the study population (318).

16 of these MAEs occurred in the 1st month, 29 occurred between 1st to 3rd month and 8 occurred between 3rd to 6th month.

The total number major amputations were 6 at the end of 1st month, then it gradually increased to 21 by 3rd month and 22 by 6months.

Most amputations i.e., 15(68%) occurred between 1st to 3rd month of follow-up.

Speaking of MACE (all-cause mortality) incidents, 10 occurred at the end of the first month, 24 at the end of three months, and 31 at the end of six months.

32.2% of the total mortality occurred in the peri-operative period (mortality within 30days of procedure).

A registry by Weissler et al [65] compared 1758 (49.7%) patients undergoing CLTI-PVI with 1779 (50.3%) undergoing non-CLTI-PVI. By the end of the first year, MACE occurred in 29.5% of CLTI

patients and MALE in 34.0% of CLTI patients. In the non-CLTI group, MACE was 8.2% and MALE was 26.1% by the end of 1 year.

Distribution of type of revascularization procedure as suggested by PLAN

When the PLAN concept was applied to the 318 cases studied, PLAN suggested Endovascular procedure for 101 cases (31.76%), Bypass procedure for 89 cases (27.98%) and was indeterminate in majority of cases i.e., 128 cases (40.25%).

Distribution of agreement between revascularization procedure performed and the type of procedure suggested by PLAN concept:

Out of 262 cases of Endovascular repair, PLAN concept suggested Endovascular approach in 37.4% (98 cases), Open Bypass in 19.8% (52 cases) and was indeterminates in 42.7% (112 cases).

Out of 56 cases who underwent Open Bypass procedure, PLAN suggested Endovascular approach in 5.4% (3 cases), Open Bypass in 66.1% (37 cases) and remained indeterminate in 28.6% (16 cases).

In both groups, representation of Indeterminate procedure as per PLAN was significant, i.e., 42.7% in the Endovascular group and 28.6% in Open Bypass group.

Distribution of revascularization procedure matching status between procedure performed and procedure as projected by PLAN (Excluding indeterminate procedures)

Out of 318 cases 128 had indeterminate procedure by PLAN so were not included to determine the matching status between the performed procedures and the procedures by PLAN. Out of the remaining 190 cases, procedure suggested by PLAN concept and that actually performed at JIVAS matched in 135 cases (71.0%). This group is referred to as ‘MATCHED COHORT’. In 55 cases (28.9%), the procedure suggested by PLAN and that actually performed at JIVAS did not match. This group is referred to as ‘NON-MATCHED COHORT’.

Comparison of wound healing status at the end of 6-month follow-up between the matched and non-matched cohorts:

Out of the 135 patients in the matched cohort, 8 died and 10 were lost to follow-up by 6-month follow-up. Therefore, 117 patients from this cohort were included in the wound healing analysis.

Similarly, in the non-matched cohort, which consisted of 55 patients, 11 died and 7 were lost to follow-up. Hence, 37 patients were included in the wound healing analysis from this cohorts.

Out of 117 cases from the matched cohort, 102 (87.2%) had healed wounds at 6-month follow-up while in 15 cases (12.8%) the wounds failed to heal. Of these 15 patients whose wounds failed to heal, 6 underwent major amputations.

Out of 37 cases from the non-matched cohort, 27 (73.0%) had healed wounds at 6-month follow-up and in 10 cases (27.0%) the wounds failed to heal. Of these 10 patients in whom the wounds failed to heal, 3 underwent major amputations.

The incidence of wound healing at the end of 6 months was significantly higher in the MATCHED COHORT compared to the NON-MATCHED COHORT.

While the healing percentage in matched cohort was 87.2%, in the non-matched cohort it was 73%. This difference was statistically significant with a P-value of 0.041 (<0.05).

Comparison of MALE/MACE outcome at the end of 6-month follow-up between the matched and the non-matched cohort:

Of the 135 patients in the matched cohort, 10 were lost to follow-up, hence 125 patients were analyzed for MALE/MACE outcomes. In the non-matched cohort, 7 out of 58 were lost to follow-up. Hence 48 were included in the MALE/MACE outcome analysis.

In the matched cohort, 6 patients underwent major amputation and 8 patients died. This gave a total of 14 patients which amounts to 11.2% MALE/MACE outcome.

In the non-matched cohort, 3 patients underwent major amputations and 11 patients died. This was a total of 14 patients i.e., 29.2% MALE/MACE outcome.

The NON-MATCHED COHORT showed a higher incidence of MALE/MACE outcomes (29.2%) compared to the MATCHED COHORT (11.2%)

This difference was statistically significant with a p-value of 0.004 (<0.05)

Comparison of wound healing at the end of 6-month follow-up according to the procedure performed in group of cases with indeterminate procedure by PLAN:

Out of the 128 patients in indeterminate cohort, 12 patients died and 13 were lost to follow-up. Excluding these, 103 patients were analysed for assessing wound healing.

Of these 103 patients, 88 underwent endovascular intervention and 15 underwent bypass.

Out of the 88 patients in the endovascular group, 69 patients i.e., 78.4% had healed wounds by 6months follow-up.

Similarly, in the bypass group 12 out of 15 patients i.e., 80% had healed wounds at 6-month follow-up.

While there was a slightly higher wound healing rate in the bypass group, this difference was not found to be statistically significant (p-value: 0.999).

Comparison of MALE/MACE outcome at the end of 6 month follow-up according to the procedure performed in group of cases with indeterminate procedure by PLAN:

Out of 128 patients in indeterminate cohort, 13 were lost to follow-up, hence 115 were included in MALE/MACE outcome analysis.

Of these 115 patients, 100 underwent endovascular intervention and 15 underwent bypass.

In the endovascular group, there were 12 major amputations and 12 deaths which was a total of 24 patients, i.e., 24% MALE/MACE outcome.

In the bypass group, there was 1 major amputation and no death which amounted to 6.7% MALE/MACE outcome.

Although there was a significant difference between the MALE/MACE outcomes between the patients who underwent endovascular v/s those who underwent bypass (24% v/s 6.7%) in the indeterminate group, this difference was not statistically significant (p-value: 0.185).

8. CONCLUSION

Peripheral Arterial Disease is a growing health problem, especially in diabetic and CKD patients. The primary aim of the vascular specialist is to relieve the patient's discomfort and heal his/her wound by means of revascularization. The choice between open bypass and endovascular intervention for revascularization has been the longest running debate among vascular specialists with many studies trying to prove the superiority of one over the other. In the past, multiple scoring systems have tried to resolve this conflict. But, none of the currently available systems (like TASC, GLASS, WIfI etc.) suggest intervention based on either the vascular lesion characteristics or the patients' wound burden. None of these systems consider the patients' complete clinical profile that includes his/her fitness to undergo an intervention, longevity, wound stage as well as vascular lesion characteristics.

To address this issue, the GVG proposed PLAN Concept of Evidence Based Revascularization (EBR) which not only takes into account all the patient characteristics, but also acts as guide to create the in-line flow across the foot (either by bypass or endovascular procedure) in an attempt to offer the best-possible treatment option to the patient.

Apart from the diseased infrainguinal arterial segments we found, that the burden of the wound and patient's comorbidities and longevity are also equally important considerations that need to be paid attention to, while planning a revascularization.

In our study, when the patient underwent revascularization that matched the suggestion made by the PLAN concept, the results have been demonstrated to be better in terms of better wound healing rates with fewer MALE/MACE outcomes.

In some circumstances, the PLAN concept also makes an "INDETERMINATE" suggestion. In this group of patients, there has been no difference in outcomes of wound healing or MALE/MACE when either endovascular or open bypass procedure is performed.

We believe that this 'INDETERMINATE' GROUP is the Achilles heel of the PLAN concept. This group represents almost 40% of the study population and PLAN concept does not define the ideal procedure for this group of patients. Further studies are required to validate the ideal procedure for this group of patients.

From our findings, we conclude that the PLAN concept of EBR is a beneficial tool for determining the appropriate revascularization procedure for a patient in order to provide the best course of treatment.

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10. DEFINITIONS:

Diabetes mellitus: defined as baseline fasting blood glucose levels of > 126mg/dl, HbA1c (>6.5%) or the need for glucose lowering treatment according to the World Health Organization Criteria. [1]

Hypertension: defined as having high blood pressure (systolic blood pressure > 140mg Hg and /or diastolic blood pressure >90 mm Hg) and/or receiving antihypertensive treatment for at least 1 year before inclusion in study.[2]

Coronary artery disease (CAD): defined as a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations.[3]

Cerebro-vascular disease (CVD): defined as a history of stroke, transient ischemic attack, or carotid artery revascularization. [4]

Chronic kidney disease (CKD): defined as serum creatinine >1.5 mg/dL 24 hrs before surgery. [5]

Smoking habit: defined as active smoker when the patient smoked at the time of the inclusion or gave up the habit in a period lower than 6 months. [6]

Technical success: defined as presence of antegrade flow through treated lesion in native vessel at end of procedure [7,8,9] or the presence of less than 25% to 30% residual stenosis, lack of flow limiting dissection by angiography at the termination of the procedure. [10,11,12,13]

Hemodynamic success: defined as an ABI increase of at least 0.15, TBI increase of at least 0.10, TcPO2 increase by 10. [14,15]

Wound healing: Complete wound healing was defined by the achievement of complete epithelialisation of all wounds in their affected limbs. The duration from the initial revascularization to complete epithelialisation was defined as the healing time. If the ulcer

recurred within 2 months after epithelialisation, the diagnosis of complete healing was rescinded; otherwise, the observation of wounds was terminated for the calculation of the wound healing time. The 'end' point of this study was clinical success defined by complete wound healing.

Primary patency: defined as the duration of follow-up in which there is an absence of occlusion or significant restenosis within the treated segment as detected by ABI,TBI,TcPO2. [16]

Limb salvage: defined as prevention of major amputation. Major amputation was defined as limb loss below or above the knee level, while minor amputation was defined as a transmetatarsal or more distal level amputation of the lower extremity. [17,18]

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ANNEXURE - 1

STUDY PROFORMA

DEMOGRAPHIC DATA

NAME :

ADDRESS :

AGE/SEX :

HOSPITAL No. :

TELEPHONE :

DATE OF ADMISSION :

Comorbidities:

Diabetes - Duration

Yes ☐ No ☐ Treatment - OHA Insulin

Duration On medication ☐ ☐

Hypertension	☐	Yes	☐	No		
CKD	☐	Yes	☐	No	☐	☐
Dyslipidaemia	☐	Yes	☐	No	☐	☐
CAD	☐	Yes	☐	No	☐	☐

Social History:

Tobacco: ☐ No ☐ Yes Duration ☐ Ex- ☐

DIAGNOSIS

Laboratory Investigations:

Complete blood count	
Urea	
Creatinine	
PT-INR, APTT	
2 D ECHO	

ABI	
TBI	
TCPO2	
MRI Angiography /CT Angiography/Digital Subtraction Angiography	

Procedure performed-

COHORT 1: Patients in whom the procedure performed matched the procedure projected by PLAN concept.

COHORT 2: Patients in whom the procedure performed did not match the procedure projected by PLAN concept.

INDETERMINATE COHORT: Patients in whom the procedure the procedure projected by PLAN concept is indeterminate.

Follow Up

	Postoperative	1-month	3-month	6-month
CLINICAL EXAMINATI				
Wound Healing status				
Death				
Major amputations				

ANNEXURE - 2

PATIENT INFORMATION SHEET

1. What is the background to and purpose of the study?

   The purpose of the study is to assess the validity of PLAN concept in predicting outcome and success rate of revascularization for Chronic Limb Threatening Ischemia (CLTI) and hence, testing its applicability in Evidence Based Revascularization (EBR).

2. Do I have to take part?

   Yes, it is necessary for you to actively participate in the study as your regular follow up and strict adherence to the given instructions is necessary for a comprehensive analysis of result.

3. What will happen to me if I take part?

   Your treatment or plan of intervention and further follow up and care will, in no way, be affected.

4. What do I have to do?

   You will be given a set of instructions regarding medications, follow-up visits, follow-up PVRs, wound care etc. which you have to follow scrupulously. These instructions are in accordance to the standard protocol of patient-care at our institute. You also have to notify us when you have any worsening of symptoms or deterioration of wound status (if any).

5. What are the possible side effects, risks and discomforts of taking part?

   No additional intervention or extra tests are being performed on you. Hence, participation in this study has no possible side-effects, risks or discomforts.

6. What are the possible benefits of taking part?

   NA

7. How will my personal data be used?

   Your personal data will be used only for the purpose of study and strict confidentiality will be maintained about the same.

8. Will there be provision for free treatment for research related injury?
   There is no possible research related injury, hence, no compensation is necessary.

9. Will compensation be paid to the subjects if disability or death results from such study?
   As there is no change in standard of patient care or intervention, there is no possibility of study related disability or death.

10. Whom should I contact if I need more information or help?
    You can contact me i.e. Dr.Pranjal, for further information or help.

Contact Details:

Dr. Pranjal Melge

Mobile No: 9420267221

NAME OF GUIDE: **Dr. Vishnu Motukuru**

Department of Vascular and Endovascular
surgery Bhagwan Mahaveer Jain Hospital,
Bangalore Mobile No: 984513711

Dr.M.D Marker
Member Secretary
Ethical Committee of Bhagwan Mahaveer Jain Hospital,
Bangalore Mobile No: 9845081000

Critical limb ischemia may be considered the most severe pattern of peripheral artery disease, being associated with high risk of major amputation, cardiovascular events and death. CLI is defined by presence of chronic ischemic rest pain, ulceration or gangrene attributable to arterial occlusive disease. Usually the impairment of peripheral perfusion is a long chronic process that

occurs along months or years in relation to age, and risk factors including smoke, diabetes, hypertension, dyslipidemia, chronic kidney disease, hypercoagulable states and hyperhomocysteinemia. The diagnosis of CLI id defined by clinical findings associated with objective peripheral examinations such as ankle brachial index and transcutaneous oxygen pressure.

CLTI is managed by revascularization and medical intervention for pain management, control of underlying co-morbidities, and secondary prevention of future cardiac or limb events with statins, antiplatelets and antithrombotic agents.

To diagnose and treat this disease you may be subjected to some blood tests and peripheral examination. You will be treated by doctors specialized in this field and you will be given treatment as per your main problem. You will undergo surgery suited best for you. You should comply with the post-operative advice which includes - taking the medications as directed by the specialist doctor correctly and prompt follow up visits.

The details of the treatment will be recorded by me for research purpose. This research work will only be observational and will not interfere with the treatment course or procedure and will not cause any risk to your health or extra expenditure. Secrecy will be maintained regarding the nature of your disease and the treatment you will be undergoing and your identity will not be disclosed.

ANNEXURE-3

INFORMED CONSENT FORM:

Study title: VALIDATION OF "PLAN CONCEPT" IN PATIENTS WITH CRITICAL LIMB THREATENING ISCHEMIA (CLTI) UNDERGOING INFRAINGUINAL REVASCULARIZATION

Study site: Bhagwan Mahaveer Jain Hospital, Bangalore.

I have been explained about the nature of the study. I have read about and understand the purpose of the study, type of study, risk and benefits associated with my involvement. I have been given the opportunity to ask questions regarding various aspects of the study. I understand that confidentiality is maintained in patient details. The information collected is only for research. I also understand that I am free to withdraw from the study at any point of time and standard of care provided to me does not change if I am quitting to take part in the study.

I the undersigned agree to voluntarily participate in this study and authorize the collection and disclosure of my personal information for the purpose of research.

		SUBJECT INITIAL BOX
1	The content of the above consent form and the procedure has been explained to me in a language ---------- known to me and I have understood the same.	
2	I understood that my participation in the study is voluntary and that I am free to withdraw any time, without my medical care or legal rights being affected.	
3	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose (s).	

4	I agree to take part in the above study.	
5	I have received a copy of the signed and dated informed Consent Form.	

Subject name and signature/ thumb impression: **Date:**

Name and signature/ thumb impression of witness: **Date:**

Name and signature of person obtaining consent: **Date**

Doctors name and signature: **Date:**

ANNEXURE-4

SCIENTIFIC COMMITTEE APPROVAL LETTER:

SCIENTIFIC COMMITTEE

APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Scientific Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **APPLICATION OF PLAN CONCEPT AND OUTCOME ANALYSIS IN INFRAINGUINAL REVASCULARIZATION FOR CLTI** Conducted by **DR.PRANJAL MELGE** Department of **VASCULAR SURGERY** under the guidance of **DR. VISHNU MOTUKURU** approximate period of study is from **JUNE 2021 to MAY 2022.**

Scientific Committee meeting held on **8/06/2021.**

Date : 22/07/2021

Dr. (Wg Cdr) M.D.Marker
Medical Director
BMJH Scientific Committee

Dr. (Wg Cdr) M.D. Marker
Medical Director
BHAGWAN MAHAVEER JAIN HOSPITAL
Bangalore-560 052

ANNEXURE-5

ETHICAL COMMITTEE APPROVAL LETTER:

ETHICS COMMITTEE ON HUMAN RESEARCH
BHAGWAN MAHAVEER JAIN HOSPITAL
A UNIT OF BHAGWAN MAHAVEER MEMORIAL JAIN TRUST
Millers Road, Vasanthnagar, Bangalore - 560 052.
✆ : 4087 5555 (30 Lines), 4110 0550, Fax: 080 2226 1153
e-mail : bmjh.mdoffice@gmail.com

APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Ethics Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **APPLICATION OF PLAN CONCEPT AND OUTCOME ANALYSIS IN INFRAINGUINAL REVASCULARIZATION FOR CLTI** Conducted by **DR.PRANJAL MELGE** Department of **VASCULAR SURGERY** under the guidance of **DR. VISHNU MOTUKURU** approximate period of study is from **JUNE 2021 to MAY 2022.**

Ethics Committee meeting held on **8/06/2021.**

Dr. (Wg Cdr) M.D.Marker
Member Secretary
BMJH Ethics Committee

Member Secretary
Ethics Committee on Human Research
Bhagwan Mahaveer Jain Hospital
Millers Road, Vasanthnagar
Bangalore-560 052

Date : 22/07/2021

ANNEXURE-6

MASTERCHART