

Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease

A Report from the Asian Pacific Society of Atherosclerosis and Vascular Disease Asia-Pacific Peripheral Artery Disease Consensus Statement Project Committee

Endorsed by the Atherosclerosis Committee of the Chinese Association of Pathophysiology, Indonesian Heart Association, Indonesian Society of Hypertension, Japanese College of Angiology, Korean Vascular Intervention Society, Philippine Society of Vascular Medicine, Society for Vascular and Endovascular Surgery of Singapore, and Vascular Society of India

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Background: Peripheral artery disease (PAD) is the most underdiagnosed, underestimated and undertreated of the atherosclerotic vascular diseases despite its poor prognosis. There may be racial or contextual differences in the Asia-Pacific region as to epidemiology, availability of diagnostic and therapeutic modalities, and even patient treatment response. The Asian Pacific Society of Atherosclerosis and Vascular Diseases (APSAVD) thus coordinated the development of an Asia-Pacific Consensus Statement (APCS) on the Management of PAD.

Objectives: The APSAVD aimed to accomplish the following: 1) determine the applicability of the 2016 AHA/ACC guidelines on the Management of Patients with Lower Extremity Peripheral Artery Disease to the Asia-Pacific region; 2) review Asia-Pacific literature; and 3) increase the awareness of PAD.

Methodology: A Steering Committee was organized to oversee development of the APCS, appoint a Technical Working Group (TWG) and Consensus Panel (CP). The TWG appraised the relevance of the 2016 AHA/ACC PAD Guideline and proposed recommendations which were reviewed by the CP using a modified Delphi technique.

Results: A total of 91 recommendations were generated covering history and physical examination, diagnosis, and treatment of PAD—3 new recommendations, 31 adaptations and 57 adopted statements. This Asia-Pacific Consensus Statement on the Management of PAD constitutes the first for the Asia-Pacific Region. It is intended for use by health practitioners involved in preventing, diagnosing and treating patients with PAD and ultimately the patients and their families themselves.

Key words: Peripheral artery disease, Intermittent claudication, Acute limb ischemia, Critical limb ischemia

Abbreviations:

AAA	Abdominal Aortic Aneurysm
AAI	Ankle-Arm Systolic Blood Pressure Index
AAV	Alternative Autologous Veins
ABI	Ankle-Brachial Index
ABP	Ankle Blood Pressure
ABPI	Ankle Brachial Pressure Index
ACAS	Asymptomatic Carotid Artery Stenosis
ACC	American College of Cardiology
ACD	Absolute Claudication Distance
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AFS	Amputation-Free Survival
AHA	American Heart Association
ALI	Acute Limb Ischemia
ALLHAT	Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial
APPADC	Asia-Pacific Consensus Statement on the Management of PAD Project
APSAVD	Asian Pacific Society of Atherosclerosis and Vascular Diseases

ARB	Angiotensin II Receptor Blockers
ARI	Absolute Risk Increase
ARIC	Atherosclerosis Risk in Communities Study
ARR	Absolute Risk Reduction
ASA	Acetylsalicylic Acid
AVD	Asymptomatic Vascular Disease
AWC	Aggressive Wound Care
AWD	Absolute Walking Distance
BASIL	Bypass versus Angioplasty in Severe Ischemia of the Leg
BID	Twice a Day
BK-Pop	Below-Knee Popliteal Bypass
BMI	Body Mass Index
BMS	Bare Metal Stenting
BMT	Best Medical Therapy
BP	Blood Pressure
BSX	Bypass Surgery
BTK	Below-the-knee
CAD	Coronary Artery Disease
CANVAS	Canagliflozin Cardiovascular Assessment Study

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CAPRIE	Clopidogrel Versus Aspirin In Patients At Risk Of Ischemic Events
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes
CAS	Carotid Artery Stenting
CCB	Calcium Channel Blocker
CCDU	Color Coded Doppler Ultrasound
CDT	Catheter Directed Thrombolysis
CFDS	Color Flow Duplex Surveillance
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLAU-S	Claudication Scale Questionnaire
CLEVER	Claudication: Exercise Versus Endoluminal Revascularization
CLI	Critical Limb Ischemia
COI	Conflict of Interest
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COR	Class of Recommendation
COPART	Characteristics and Outcome of patients hospitalized for lower extremity Peripheral Artery Disease Trial in France
CPG	Clinical Practice Guidelines
CRP	C-Reactive Protein
CT	Computerized Tomography
CTA	Computerized Tomography Angiography
CTO	Chronic Total Occlusion
CV	Cardiovascular
CVD	Cardiovascular Disease
DAPT	Dual Antiplatelet Therapy
DBP	Diastolic Blood Pressure
DCB	Drug-coated Balloon
DES	Drug-eluting Stent
DFU	Diabetic Foot Ulcer
DEB	Drug-eluting Balloon
DM	Diabetes Mellitus

DUET	Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accelerated Thrombolysis for thromboembolic infrainguinal disease
DUS	Duplex Ultrasound
E/I	Exposure/Intervention
EBM	Evidence-Based Medicine
EDTA	Ethylenediaminetetraacetic acid
EO	Expert Opinion
ER	Emergency Room
ESC	European Society of Cardiology
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
EURODIALE	European Study Group on Diabetes and the Lower Extremity
EV	Endovascular
EVT	Endovascular Therapy
FCD	Functional Claudication Distance
FLUVACS	Flu Vaccination in Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions Study
FMD	Flow-mediated Dilatation
FRIENDS	Freedom from Ischemic Events: New Dimensions for Survival
GDMT	Guideline-Directed Medical Therapy
GDP	Gross Domestic Product
GFR	Glomerular Filtration Rate
GMCB	Group-Mediated Cognitive Behavioral Intervention
GPIIb-IIIa	Glycoprotein IIb-IIIa
GSV	Great Saphenous Vein
HAP	Highest Ankle Pressure
HBA1c	Hemoglobin A1c
HBET	Home-based Exercise Therapy
HBOT	Hyperbaric Oxygen Therapy
HD	Hemodialysis
HePTFE	Heparin-bonded Expanded Polytetrafluoroethylene
HF	Heart Failure
HMDV	Hemashield Microvel Double Velour
HMO	Health Maintenance Organizations
HOPE	Heart Outcomes Prevention Evaluation
HPN	Hypertension
HR	Hazard Ratio
HR	Heart Rate
HRQOL	Health-related Quality of Life
HUV	Human Umbilical Vein

HVC	High-Velocity Criteria
IC	Intermittent Claudication
ICA	Internal Carotid Artery
ICAS	Internal Carotid Artery Stenosis
ICD	Intermittent Claudication Distance
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Disease Society of America
IEI	Endovascular Intervention
IFG	Impaired Fasting Glucose
INVEST	International Verapamil-Trandolapril Study
IPC	Intermittent Pneumatic Compression
IPMT	Isolated Pharmaco-Mechanical Thrombolysis/ Thrombectomy
ITT	Intention to Treat
IWGDF	International Working Group on the Diabetic Foot
LAP	Lowest Ankle Pressure
LD	Limited Data
LDL	Low-Density Lipoprotein
LEAP	Lower Extremity Assessment Project
LEB	Lower Extremity Bypass
LL	Lower Limb
LOE	Level of Evidence
LVC	Low-Velocity Criteria
MAC	Medial Arterial Calcification
MACE	Major Cardiovascular Events
MALE	Major Adverse Limb Events
MDC	Multidisciplinary Care
MGV	Midgraft Peak Velocity
MH-OR	Mantel-Haenzel Odds Ratio
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MWD	Maximal Walking Distance
NAC	Non-Autologous Conduit
NATALI	National Audit of Thrombolysis for Acute Leg Ischemia
NHMRC	National Health and Medical Research Council
NNH	Number Needed to Harm
NNHeS	National Nutrition and Health Survey
NNT	Number Needed to Treat
NOET	No Exercise Therapy
NPV	Negative Predictive Value
NPWT	Negative Pressure Wound Therapy
NR	Non-Randomized

NSTE-ACS	Non-ST Elevation Acute Coronary Syndrome
OAC	Oral Anticoagulant
OD	Once a Day
OLIVE	Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia Trial
OMC	Optimized Medical Care
OMT	Optimized Medical Therapy
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OR	Odds Ratio
PAD	Peripheral Artery Disease
PAOD	Peripheral Arterial Occlusive Disease
PAQ	Peripheral Artery Questionnaire
PCB	Paclitaxel-Coated Balloons
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical Examination
PEARL	Peripheral Use of AngioJet Rheolytic Thrombectomy with a Variety of Catheter Lengths
PEGASUS - TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54
PFWD	Pain-Free Walking Distance
PHIC	Philippine Health Insurance Corporation
PIOM	Patient or Population/Intervention or Exposure/Outcome(s)/Method
PMT	Pharmacomechanical Thrombectomy
POBA	Plain Old Balloon Angioplasty
POPADAD	Prevention Of Progression of Arterial Disease And Diabetes
PPI	Proton Pump Inhibitor
PPV	Positive Predictive Value
PROBE	Prospective Randomized Open Blinded End-Point
PSV	Peak Systolic Velocity
PTA	Percutaneous Transluminal Angioplasty
PTFE	Polytetrafluoroethylene
PVD	Peripheral Vascular Disease

PVI	Peripheral Endovascular Intervention
PVI	Percutaneous Vascular Intervention
PWT	Peak Walking Time
QALY	Quality-Adjusted Life Years
QOL	Quality of Life
RBFI	Regional Blood Flow Impairment
RCT	Randomized Controlled Trials
REACH	Reduction of Atherothrombosis for Continued Health
RENDEZVOUS	Retrospective Analysis for the Clinical Impact of Pedal Artery Revascularization Versus Non-Revascularization Strategy for Patients With Critical Limb Ischemia Registry
ROC	Receiver Operating Characteristic
rtPA	Recombinant Tissue Plasminogen Activator
SAFARI	Subintimal Arterial Flossing with Antegrade-Retrograde Intervention
SBP	Systolic Blood Pressure
SCRAPS	Sex, Comorbidities, Race, Age, Pathology, Socioeconomic Factors
SEP	Supervised Exercise Program
SET	Supervised Exercise Therapy
SFA	Superficial Femoral Artery
SGLT2	Sodium-Glucose Co-Transporter-2
SPP	Skin Perfusion Pressure
SPPB	Short Physical Performance Battery
ST	Stenting
ST+SE	Stenting + Supervised Exercise
STILE	Surgery versus Thrombolysis for Ischemia of the Lower Extremity
SV	Saphenous Vein
SVG	Saphenous Vein Graft
SWC	Standard Wound Care
TASC	Trans-Atlantic Intersociety Consensus
TBI	Toe-Brachial Index
TBPI	Toe Brachial Pressure Index
TCC	Total Contact Cast
TcPO2	Transcutaneous Oxygen Pressure
TER	Target Extremity Revascularization
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

TWG	Technical Working Group
UA	Unstable Angina
UCD	University of California Davis Medical Center
UFH	Unfractionated Heparin
UL	Upper Limb
US	Ultrasound
VKA	Vitamin K Antagonists
Vr	Velocity Ratio
WA	Walking Advice
WAR	Warfarin and Aspirin Group
WASA	Warfarin plus Aspirin
WIQ	Walking Impairment Questionnaire

Executive Summary

Background

Peripheral artery disease (PAD) is defined as an atherosclerotic vascular disease of the lower extremities. PAD is the most underdiagnosed, underestimated and undertreated of the atherosclerotic vascular diseases despite its poor prognosis. It was estimated that 70% of the 202 million people living with PAD were residing in low to middle income countries in 2010. This includes 54.8 million PAD patients in Southeast Asia and 45.9 million in the Western Pacific region¹.

PAD is a chronic medical condition. A comprehensive care plan for patients with PAD includes periodic clinical evaluation by a healthcare provider with experience in the care of vascular patients. Ongoing care focuses on cardiovascular risk reduction with medical therapy, exercise therapy, and, if indicated, revascularization. There may be racial or contextual differences in the Asia-Pacific region as to PAD epidemiology, availability of diagnostic and therapeutic modalities, physician practice patterns and even patient treatment response that may require a review of the applicability of international guidelines to this population.

Anticipating the November 2016 release of the American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease², the Asian Pacific Society of Atherosclerosis and Vascular Diseases (APSAVD) Executive Council found it an opportune time to coordinate the development of an Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease (PAD) and approved this project in July 2016. The Asia-Pacific Consensus Statement on PAD Project Committee (APPADC) was created to take charge of this project.

Objectives

The APPADC set out to accomplish the following objectives: 1) determine the applicability and relevance of the 2016 AHA/ACC guidelines to the management of PAD patients in the Asia-Pacific region, taking into consideration the epidemiology, physician practices, patient profile and patient response, and availability of therapies in the Asia-Pacific region; 2) retrieve and review literature from countries with APSAVD members; and 3) increase the awareness of PAD in these different countries.

Methodology

A Steering Committee was organized to oversee development of the consensus statement. The Steering

Committee appointed a Technical Working Group (TWG), composed of evidence review experts, to appraise the relevance of the 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease² to the Asia-Pacific region. For each 2016 AHA/ACC Statement, a research question in PICO (Patient or Population/Intervention or Exposure/Comparison/Outcomes) format was then drafted to frame the literature search for relevant research articles. Retrieved research articles were then appraised for directness, validity and applicability using the appraisal questions or checklist in chapters on Therapy and Diagnosis in *Painless Evidence-based Medicine* (2nd edition, 2017)^{3,4}.

The TWG aimed to include literature from APSAVD member countries not previously appraised nor cited in the AHA/ACC Guidelines, and derive data on Asia-Pacific populations from already cited articles. From these appraisals of additional and previously cited literature from the 2016 AHA/ACC PAD Guideline, evidence summaries were generated. The TWG then drafted proposed APPADC Recommendations which were reviewed by the Consensus Panel using a modified Delphi technique. Recommendations for which no consensus could be arrived at online were discussed and voted upon in an En Banc meeting on July 28, 2018 in Mandaluyong City, Philippines.

Results

A total of ninety-one (91) Recommendations were generated by the APPADC covering history and physical examination, diagnosis, and treatment of PAD. Three (3) recommendations were new, i.e. not based on 2016 AHA/ACC Statement but drafted de novo in the light of recent evidence, e.g. the COM-PASS trial⁵, EUCLID trial⁶--these are recommendations 18, 20 and 36. Thirty-one (31) recommendations were revisions or adaptations of the 2016 AHA/ACC Statements due to additional evidence obtained during the literature search, especially from countries relevant to the APSAVD, or for further emphasis or clarification. Out of these thirty-one recommendations, the Class of Recommendation was changed for 6 recommendations--downgraded in 5 (involving use of antiplatelet or anticoagulant therapy, prostanoids and influenza vaccination) and upgraded in 1 (foot examination in patients with diabetes and PAD). Furthermore, the level of evidence was changed for 10 recommendations. Fifty-seven (57) recommendations were adopted from the 2016 AHA/ACC Statements based on additional literature identified supporting their validity or in the absence of additional literature guiding a revision. Of the 57 adopted recommenda-

tions, four (4) had minor edits in wording, i.e. without bearing on the PICO nor direction of the recommendations. Some issues raised in the consensus panel discussions included the impact of certain adverse events of treatment, availability and cost-effectiveness of some diagnostic modalities, medical and interventional therapy, and long-term benefit of revascularization.

This Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease (APPADC) constitutes the first for the Asia-Pacific Region. It is intended for use by health practitioners involved in preventing, diagnosing and treating patients with PAD and ultimately the patients and their families themselves.

Introduction

In 2013, Fowkes *et al.* reported a systematic review of all PAD prevalence studies available worldwide where PAD was defined by an ankle-brachial pressure index less than or equal to 0.9¹⁾. 34 studies satisfied the inclusion criteria, 22 studies were from high income countries (HIC) including Hong Kong, Japan, Singapore, and South Korea and 12 studies were from low or middle income countries (LMIC) including China and Thailand. The included studies involved 112,027 participants, of which 9,347 had PAD. Overall, it was estimated that the number of people with PAD worldwide had increased from 164 million in 2000 to 201 million in 2010¹⁾. In HIC, the prevalence of PAD was 5.28% (95% CI 3.38–8.17%) in women and 5.41% (3.41–8.49%) in men, aged 45–49 years, and 18.38% (11.16–28.76%) in women and 18.83% (12.03–28.25%) in men, aged 85–89 years. PAD prevalence in men was lower in LMIC (2.89% [2.04–4.07%] at 45–49 years and 14.94% [9.58–22.56%] at 85–89 years). In LMIC, rates were higher in women than in men, especially at younger ages (6.31% [4.86–8.15%] of women aged 45–49 years)¹⁾.

Reported PAD prevalence rates in the Asia-Pacific region have ranged from 5% in the Philippines, 5.2% in Thailand to 8.2% in Singapore, 10.1% in Australia and 12.1% in Japan²⁻⁷⁾. The variation in prevalence rates may be accounted for by differences in the method of diagnosis and population subgroups studied. In populations of patients that had diabetes, for example, the PAD prevalence has been reported to range from 5.8% in Malays, to 19.4% in Chinese, 19.8% in Indians and 31.6% in Pakistanis⁸⁾.

The presentation symptoms of PAD vary from none (asymptomatic), atypical leg symptoms, intermittent claudication, ischemic rest pain to tissue loss⁹⁾. Irrespective of presentation, on objective testing, PAD

patients have walking impairment and also increased incidence of major cardiovascular events (MI, stroke or CV death) compared to age-matched members of the general population^{10, 11)}. Numerous reports have established that the incidence of major cardiovascular events among patients with symptomatic PAD is greater than those presenting with symptoms of coronary heart disease or prior stroke^{12, 13)}. Despite this, prescription of medications established to reduce major events has been repeatedly reported to be suboptimal in PAD patients⁵⁾.

In the REACH registry, it was reported that the incidence of CV death, MI, stroke or hospitalization from atherothrombotic events was highest among PAD patients (21.14% PAD vs. 15.2% CAD vs. 14.35% CVD)⁵⁾. In contemporary studies on populations with PAD and those with polyvascular disease, the medium-term incidence rates of major cardiovascular events ranged from around 10% to 20%. Moreover, despite the current availability of guideline-based preventive therapy, usage is not optimal and the adverse vascular events and related hospitalization rates remain high among PAD patients¹²⁻¹⁸⁾.

The economic burden of PAD is also substantial with a number of prior studies suggesting that the per patient costs of treating PAD are greater than those for other cardiovascular disease presentations^{19, 20)}.

Given the high social and economic burden of PAD, methods to establish evidence-based practice are important. The current document outlines recommendations for PAD management in the Asia-Pacific region. Anticipating the November 2016 release of Peripheral Artery Disease (PAD) Treatment Guidelines by the American Heart Association/American College of Cardiology, the Asian Pacific Society of Atherosclerosis and Vascular Diseases (APSADV) Executive Council decided to coordinate the development of an Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease (PAD) and approved this project in July 2016.

The Asia-Pacific Consensus Statement on PAD Project Committee (APPADC) set out to accomplish the following objectives: 1) determine the applicability and relevance of international PAD guidelines, specifically the 2016 AHA/ACC guidelines, to the management of PAD patients in the Asia-Pacific region, taking into consideration the epidemiology, physician practices, patient profile and patient response, and availability of therapies in the Asia-Pacific region; 2) retrieve and review literature from countries with APSADV members; and 3) increase the awareness of PAD in the Asia-Pacific region.

How to Use this Consensus Statement

This Consensus Statement provides selected practice recommendations on history and physical examination, diagnosis, and treatment of PAD patients. The recommendations were based on the appraised recommendations from the 2016 AHA/ACC PAD Guidelines¹⁾, best available evidence and expert opinion available at the time of the review. The consensus statement is designed to be used by any health practitioner involved in preventing, diagnosing and treating PAD including vascular medicine specialists, vascular surgeons, endocrinologists, wound care specialists, interventional radiologists, cardiologists, rehabilitation medicine specialists, internists and general medical practitioners, and ultimately the patients and their families themselves.

A tabulated Summary of Recommendations (**Table 1**) provides users with quick access to the individual consensus statement recommendations together with the corresponding Class (or strength) of the Recommendation (COR) and the Level of Evidence (LOE) the recommendation was based on. Recommendations are interpreted based on COR and LOE (**Table 2**).

The body of the document starts with the Introduction, which gives the historical background to this guideline, followed by the Consensus Statement Development Method, which contains the narrative of the processes of the development of the Consensus Statement.

The Results section lists the individual APPADC recommendations as follows: **Numbered APPADC Recommendation e.g. Recommendation 1 - 91**

2016 AHA/ACC Statement on which the recommendation was based. This refers to the numbered sections of the 2016 AHA/ACC Guideline and the statements that fall under each section.

For example:

10.1 Clinical Presentation of ALI: Recommendations

Recommendations for Clinical Presentation of ALI		
COR	LOE	Recommendations
I	C-EO	Patients with*
I	B-R	Angiography**

*The first recommendation was labeled as AHA/ACC Statement 10.1.1.

**The second recommendation was labeled as AHA/ACC Statement 10.1.2.

Summary of Evidence - for each recommendation, “additional or new” literature was appraised first followed by relevant references previously cited in the 2016 AHA/ACC Guidelines or when appropriate.

Delphi Issues - summarizing discussion on issues raised during the electronic/online review and votation by experts on the Consensus Panel

Consensus Issues - summarizing unsettled issues despite arrival at consensus.

References - each consensus statement recommendation may cite new/additional references and those previously cited in the 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity PAD

The recommendations in this Consensus Statement are based on the available evidence and opinion at the time of the consensus review. Fundamental to each of the recommendations is the foundation of a comprehensive history taking and physical examination. These principles will not be restated in every recommendation.

A. Background

Despite its worse cardiovascular prognosis, peripheral artery disease (PAD) is the most underdiagnosed, underestimated and undertreated of the atherosclerotic vascular diseases. According to global estimates of the prevalence of PAD in 2011, of the 202 million people living with PAD, 70% were residing in low to middle income countries, including 54.8 million in Southeast Asia and 45.9 million in the Western Pacific region¹⁾.

PAD is a lifelong chronic medical condition. A comprehensive care plan for patients with PAD includes periodic clinical evaluation by a healthcare provider with experience in the care of vascular patients. Ongoing care focuses on cardiovascular risk reduction with medical therapy, optimizing functional status with structured exercise, and, when indicated, revascularization. The care plan is further customized depending on whether the patient has undergone a revascularization procedure. There may be racial or contextual differences in the Asia-Pacific region as to PAD epidemiology, availability of diagnostic and therapeutic modalities, physician practice patterns and perhaps even patient treatment response that may require a review of the applicability of international guidelines.

To help address the need for greater awareness of PAD, the Asian Pacific Society of Atherosclerosis and Vascular Diseases (APSADV) held two special educational conferences—the 1st and 2nd Atherosclerotic

Table 1. Summary of APPADC Recommendations

(Text in bold font reflect modified recommendations from the 2016 AHA/ACC Guidelines and/or new recommendations)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
I. Clinical Assessment for PAD			
1	Patients at increased risk of PAD should undergo a comprehensive medical history and a review of symptoms to assess for typical symptoms such as exertional leg symptoms (intermittent claudication), ischemic rest pain and nonhealing wounds; and atypical symptoms related to PAD that may result in walking impairment.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
2	Patients at increased risk of PAD should undergo vascular examination, including palpation of lower extremity pulses (i.e., femoral, popliteal, dorsalis pedis, and posterior tibial), auscultation for femoral bruits, and inspection of the legs and feet.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
3	Patients with PAD should undergo noninvasive BP measurement in both arms at least once during the initial assessment in order to obtain the higher brachial systolic BP for ABI measurement, identify patients with subclavian (or innominate) artery stenosis and accurately measure BP for hypertension treatment.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
II. Diagnostic Testing for the Patient with Suspected Lower Extremity PAD			
A. Resting ABI for Diagnosing PAD			
4	4a. In patients with history or physical examination findings suggestive of PAD, the resting ABI is recommended to diagnose PAD.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
	4b. Segmental pressures and waveforms are used to localize the anatomic segments of PAD.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
5	Resting ABI should be reported as abnormal (ABI \leq 0.90), borderline (ABI 0.91 – 0.99), normal (ABI 1.00 – 1.40), or noncompressible (ABI $>$ 1.40).	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
6	In patients at increased risk of PAD but without history or physical examination findings suggestive of PAD, measurement of the resting ABI is reasonable.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
7	In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD, the ABI is not recommended.	Moderate (Class III) No Benefit Benefit = Risk	Moderate (Level B-NR)
B. Physiological Testing			
8	Toe-brachial index (TBI), where available , should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
9	Patients with exertional non-joint-related leg symptoms and normal or borderline resting ABI ($>$ 0.90 and \leq 1.40) should undergo exercise treadmill ABI testing to evaluate for PAD.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
10	In patients with PAD and an abnormal resting ABI (\leq 0.90), exercise treadmill ABI testing can be useful to objectively assess functional status.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
11	In patients with normal (1.00 – 1.40) or borderline (0.91 – 0.99) ABI in the setting of nonhealing wounds or gangrene, it is reasonable to diagnose CLI by using TBI with waveforms, transcutaneous oxygen pressure (TcPO ₂), or skin perfusion pressure (SPP).	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
12	In patients with PAD with an abnormal ABI (\leq 0.90) or with noncompressible arteries (ABI $>$ 1.40 and TBI \leq 0.70) in the setting of nonhealing wound or gangrene, TBI with waveforms, TcPO ₂ , or SPP can be useful to evaluate local perfusion.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
C. Imaging for Anatomic Assessment			
13	Duplex ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) of the lower extremities is useful to assess the anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
14	Invasive angiography is useful for patients with CLI in whom revascularization is being considered.	Strong (Class I) Benefit >>> Risk	Low (Level C-EO)
15	Invasive angiography is reasonable for patients with lifestyle-limiting intermittent claudication with an inadequate response to GDMT for whom revascularization is being considered.	Moderate (Class IIa) Benefit >> Risk	Low (Level C-EO)
16	Invasive and noninvasive angiography (i.e., CTA, MRA) should not be performed for the anatomic assessment of patients with asymptomatic PAD.	Strong (Class III Harm) Risk > Benefit	Moderate (Level B-NR)
D. Screening for Atherosclerotic Disease in Other Vascular Beds for the Patient with PAD			
17	A screening duplex ultrasound for abdominal aortic aneurysm (AAA) is reasonable in patients with symptomatic PAD.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
18	Patients with PAD should not be routinely screened for asymptomatic atherosclerosis in other arterial beds (coronary, carotid, renal arteries). (NEW)	Strong (Class III Harm) Risk > Benefit	Low (Level C-EO)
III. Medical Therapy for the Patient with PAD			
A. Antiplatelet Agents			
19	Antiplatelet therapy with aspirin alone (range 75 – 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.	Strong (Class I) Benefit >>> Risk	High (Level A)
20	Ticagrelor in comparison with clopidogrel is not recommended for patients with symptomatic PAD. (NEW)	Moderate (Class III) No Benefit Benefit = Risk	High (Level A)
21	In asymptomatic patients with PAD (ABI ≤ 0.90), suggesting antiplatelet therapy may be considered to reduce the risk of MI, stroke, or vascular death.	Weak (Class IIb) Benefit ≥ Risk	Low (Level C-EO)
22	In asymptomatic patients with borderline ABI (0.91 – 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.	Weak (Class IIb) Benefit ≥ Risk	Moderate (Level B-R)
23	The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.	Weak (Class IIb) Benefit ≥ Risk	Moderate (Level B-R)
24	DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.	Weak (Class IIb) Benefit ≥ Risk	Low (Level B-R)
25	Vorapaxar in addition to existing antiplatelet therapy in patients with symptomatic PAD is not recommended.	Strong (Class III Harm) Risk > Benefit	Moderate (Level B-R)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
B. Statin Agents			
26	Treatment with a statin medication is indicated for all patients with PAD.	Strong (Class I) Benefit >>> Risk	High (Level A)
C. Antihypertensive Agents			
27	Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death.	Strong (Class I) Benefit >>> Risk	High (Level A)
28	The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD.	Moderate (Class IIa) Benefit >> Risk	High (Level A)
D. Smoking Cessation			
29	Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.	Strong (Class I) Benefit >>> Risk	High (Level A)
30	Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (ie varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.	Strong (Class I) Benefit >>> Risk	High (Level A)
31	Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public spaces.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
E. Glycemic Control			
32	Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
33	Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
F. Oral Anticoagulation			
34	The use of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is of uncertain benefit and potentially harmful .	Strong (Class III Harm) Risk > Benefit	High (Level A)
35	Anticoagulation with vitamin K antagonists (VKA) should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD.	Strong (Class III Harm) Risk > Benefit	High (Level A)
36	The use of low dose aspirin (100 mg OD) and rivaroxaban (2.5 mg BID) may be considered to reduce the risk of MI, stroke, cardiovascular death and limb-related events in patients with symptomatic PAD, having considered the associated risk of bleeding. (NEW)	Weak (Class IIb) Benefit ≥ Risk	Moderate (Level B-R)
G. Cilostazol, Pentoxifylline, and Chelation Therapy			
37	Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with intermittent claudication.	Strong (Class I) Benefit >>>Risk	High (Level A)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
38	Pentoxifylline is not effective for treatment of intermittent claudication.	Moderate (Class III No Benefit) Benefit = Risk	Moderate (Level B-R)
39	Chelation therapy (e.g., ethylene- diaminetetraacetic acid) is not beneficial for treatment of intermittent claudication.	Moderate (Class III No Benefit) Benefit = Risk	Moderate (Level B-R)
H. Homocysteine Lowering			
40	B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended.	Moderate (Class III No Benefit) Benefit = Risk	Moderate (Level B-R)
I. Influenza Vaccination			
41	Annual influenza vaccination can be considered for patients with PAD especially if they have established coronary artery disease.	Moderate (Class IIA) Benefit >> Risk	Low (Level C-EO)
J. Structured Exercise Therapy			
42	In patients with intermittent claudication, a supervised exercise program is recommended to improve functional status and quality of life (QoL) and to reduce leg symptoms.	Strong (Class I) Benefit >>> Risk	High (Level A)
43	A supervised exercise program should be discussed as a treatment option for intermittent claudication before possible revascularization.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-R)
44	In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status.	Moderate (Class IIA) Benefit >> Risk	High (Level A)
45	In patients with intermittent claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate-to-maximum intermittent claudication while walking, can be beneficial to improve walking ability and functional status.	Moderate (Class IIA) Benefit >> Risk	High (Level A)
IV. Minimizing Tissue Loss in Patients with PAD			
46	Patients with PAD and diabetes mellitus should be counseled about self-foot examination and healthy foot behaviors aimed at reducing the risk of foot ulcers or amputation.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
47	In patients with PAD, prompt diagnosis and treatment of foot infection are recommended to reduce the risk of amputation.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
48	In patients with PAD and signs of foot infection, prompt referral to an interdisciplinary care team, when available, can be beneficial to reduce the risk of amputation and promote wound healing, in addition to administration of infection control measures.	Moderate (Class IIA) Benefit >>Risk	Low (Level C-LD)
49	It is reasonable to counsel patients with PAD without diabetes mellitus about self-foot examination and healthy foot behaviors to prevent amputations and ulcers.	Moderate (Class IIA) Benefit >> Risk	Low (Level C-EO)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
50	Among patients with PAD and diabetes mellitus, foot examination should be included in every clinic visit.	Strong (Class I) Benefit >>> Risk	Low (Level C-EO)
V. Revascularization for Intermittent Claudication			
51	Revascularization for intermittent claudication is a reasonable treatment for the patient with lifestyle-limiting intermittent claudication with an inadequate response to optimal guideline-directed medical therapy (GDMT).	Moderate (Class IIa) Benefit >>Risk	High (Level A)
A. Endovascular Revascularization for Intermittent Claudication			
52	Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting intermittent claudication and hemodynamically significant aortoiliac occlusive disease, although the long- term benefit of treatment is less clear.	Strong (Class I) Benefit >>> Risk	High (Level A)
53	Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting intermittent claudication and hemodynamically significant TASC A and B femoropopliteal disease, although the long-term benefit of treatment is less clear.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-R)
54	The usefulness of endovascular procedures as a revascularization option for patients with intermittent claudication due to isolated infrapopliteal artery disease is unknown.	Weak (Class IIb) Benefit ≥ Risk	Low (Level C-LD)
55	Endovascular procedures should not be performed in patients with asymptomatic PAD or stable intermittent claudication solely to prevent progression to critical limb ischemia.	Strong (Class III Harm) Risk > Benefit	Moderate (Level B-NR)
B. Surgical Revascularization for Intermittent Claudication			
56	When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material.	Strong (Class I) Benefit >>>Risk	High (Level A)
57	Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting intermittent claudication with inadequate response to GDMT, acceptable perioperative risk, in whom technical factors do not favor an endovascular-first approach.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-R)
58	Femoral-tibial artery bypasses should not be performed for the treatment of intermittent claudication.	Strong (Class III Harm) Risk > Benefit	Moderate (Level B-R)
59	Surgical procedures should not be performed in patients with PAD solely to prevent progression to CLI.	Strong (Class III Harm) Risk > Benefit	Moderate (Level B-NR)
VI. Management of CLI			
A. Revascularization for CLI			
60	In patients with CLI, revascularization should be performed when possible to minimize tissue loss.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
61	An evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI to minimize tissue loss.	Strong (Class I) Benefit >>> Risk	Low (Level C-EO)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
B. Endovascular Revascularization for CLI			
62	Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-R)
63	A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain.	Moderate (Class IIa) Benefit >> Risk	Low (Level C-LD)
64	Evaluation of the imaging findings of the PAD and correlation with clinical profile can be useful in selecting the endovascular approach for CLI.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-R)
65	Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene.	Weak (Class IIb) Benefit ≥ Risk	Moderate (Level B-NR)
C. Surgical Revascularization for CLI			
66	When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e., tibial, pedal) should be constructed with suitable autogenous vein.	Strong (Class I) Benefit >>> Risk	High (Level A)
67	Surgical procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
68	In patients with CLI for whom endovascular revascularization has failed and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries as a last resort in cases of limb salvage.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
69	A staged approach to surgical procedures is reasonable in patients with ischemic rest pain.	Moderate (Class IIa) Benefit >> Risk	Low (Level C-LD)
C.1. Wound Healing Therapies for CLI			
70	An interdisciplinary care team should evaluate and provide comprehensive care for patients with CLI and tissue loss to achieve complete wound healing and a functional foot.	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
71	In patients with CLI, wound care after revascularization should be performed with the goal of complete wound healing.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
72	The use of intermittent pneumatic compression (arterial pump) devices to augment wound healing and/or ameliorate severe ischemic rest pain is not well established.	Weak (Class IIb) Benefit ≥ Risk	Low (Level C-LD)
73	In patients with CLI, the effectiveness of hyperbaric oxygen therapy for wound healing is unknown.	Weak (Class IIb) Benefit ≥ Risk	Low (Level C-LD)
74	Prostanoids are not indicated in patients with CLI.	Strong (Class III Harm) Risk > Benefit	Moderate (Level B-R)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
VII. Management of Acute Limb Ischemia (ALI)			
A. Clinical Presentation of ALI			
75	Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
76	In patients with suspected ALI, initial clinical evaluation should rapidly assess limb viability and potential for salvage and does not require imaging.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
B. Medical Therapy for ALI			
77	In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
C. Revascularization of ALI			
78	In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology and degree of ischemia)	Strong (Class I) Benefit >>> Risk	Moderate (Level B-NR)
79	Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb.	Strong (Class I) Benefit >>> Risk	High (Level A)
80	Amputation should be performed as the first procedure in patients with a nonsalvageable limb.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
81	Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization.	Strong (Class I) Benefit >>> Risk	Low (Level C-LD)
82	In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-NR)
83	In patients with ALI due to embolism and with a salvageable limb, surgical thromboembolectomy can be effective.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-R)
84	The usefulness of ultrasound-accelerated catheter-based thrombolysis for patients with ALI with a salvageable limb is unknown.	Weak (Class IIb) Benefit ≥ Risk	Low (Level C-LD)
D. Diagnostic Evaluation for the Cause of ALI			
85	In the patient with ALI, a comprehensive history should be obtained to determine the cause of thrombosis and/or embolization.	Strong (Class I) Benefit >>> Risk	Low (Level C-EO)
86	In the patient with a history of ALI, testing for a cardiovascular cause of thromboembolism can be useful.	Moderate (Class IIa) Benefit >> Risk	Low (Level C-EO)

(Cont. Table 1)

No.	Recommendation	Class of Recommendation (COR)	Level (Quality) of Evidence (LOE)
VIII. Longitudinal Follow-up			
87	Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status.	Strong (Class I) Benefit >>> Risk	Low (Level C-EO)
88	Patients with PAD who have undergone lower extremity revascularization (surgical and/or endovascular) should be followed up with periodic clinical evaluation and ABI measurement.	Strong (Class I) Benefit >>> Risk	Low (Level C-EO)
89	Duplex ultrasound can be beneficial for routine surveillance of infrainguinal, autogenous vein bypass grafts in patients with PAD.	Moderate (Class IIa) Benefit >> Risk	Moderate (Level B-R)
90	Duplex ultrasound is reasonable for routine surveillance after endovascular procedures in patients with PAD.	Moderate (Class IIa) Benefit >> Risk	Low (Level C-LD)
91	The effectiveness of duplex ultrasound for routine surveillance of infrainguinal prosthetic bypass grafts in patients with PAD is uncertain.	Weak (Class IIb) Benefit ≥ Risk	Moderate (Level B-R)

PAD – peripheral artery disease; BP – blood pressure; ABI – ankle-brachial index; CLI – critical limb ischemia; GDMT – guideline-directed medical therapy; MI – myocardial infarction; TASC – Trans-Atlantic Inter-Society Consensus; ALI – acute limb ischemia

Table 2. Class of Recommendation and Level of Evidence

Class of Recommendation (CoR)*	Level (Quality) of Evidence*
STRONG Class I Benefit >>> Risk Class III: Harm Risk > benefit	HIGH Level A <ul style="list-style-type: none"> • high-quality evidence from more than 1 RCT • meta-analysis of high-quality RCTs • one or more RCTs corroborated by high-quality registry studies
MODERATE Class IIa Benefit >> Risk Class III: No Benefit Benefit = Risk	MODERATE Level B-R (Randomized) <ul style="list-style-type: none"> • moderate-quality evidence from one or more RCTs • meta-analysis of moderate-quality RCTs Level B-NR (Non-Randomized) <ul style="list-style-type: none"> • moderate-quality evidence from 1 or more well-designed, well-executed non-randomized studies, observational studies, or registry studies • meta-analysis of such studies
WEAK Class IIb Benefit ≥ Risk	LOW Level C-LD (Limited Data) <ul style="list-style-type: none"> • randomized or non-randomized observational or registry studies with limitations of design or execution • meta-analysis of such studies • physiological or mechanistic studies in human subjects Level C-EO (Expert Opinion) <ul style="list-style-type: none"> • consensus of expert opinion based on clinical experience

*Adapted from Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC Guidelines on the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, *Journal of the American College of Cardiology*, 2017; 69: e71-e126

PAD Fora, hosted by the Philippine Lipid and Atherosclerosis Society in 2011 and 2013, respectively. In anticipation of the November 2016 release of Peripheral Artery Disease (PAD) Treatment Guidelines by the American Heart Association/American College of Cardiology and that of the European Society of Cardiology (to be released in 2017), the APSAVD Executive Council found it opportune to coordinate the development of an Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease (PAD) and approved this project (Asia-Pacific Consensus Statement on the Management of PAD Project or APPADC) as proposed by Dr. Maria Teresa B. Abola and Prof. Rody Sy, during the business meeting in July 2016. Dr. Maria Teresa B. Abola was designated as the convener of the APPADC, coordinating the activities of the TWG, the Consensus Panel, and the secretariat, and reporting the progress of such to the Steering Committee.

Active work on the consensus statement began in February 2017. There were three (3) groups of statements distributed by the TWG: History and Physical Examination, Diagnosis, and Treatment of the Patient with PAD. The consensus panel members submitted their votes of agreement or rejection of the statements from the TWG. Reasons for non-agreement were put forth and revised statements were proposed. There was another round of re-votes among the consensus panel members on selected issues with proposed revisions.

The highlights of the Consensus Statement were presented at the 11th APSAVD Biennial Congress, Iloilo City on February 27 – March 1, 2018. The presentation was well-received during the PAD Symposium on February 28, 2018. This provided a public forum during which additional comments from physicians in the audience were noted and included in the issues discussed by the consensus panel while deliberating on the corresponding statements.

B. Consensus Statement Development Methods

Organization of the Process

Creation of the Steering Committee

The Asia-Pacific Consensus Statement on the Management of PAD Project or APPADC convened a Steering Committee to provide oversight of the selection of the Consensus Panel members, the formulation process of the consensus statement, and the composition of the Technical Working Group (TWG). The APPADC Steering Committee was chaired by Professor Edward Janus (Australia) with members: Professor Shizuya Yamashita (Japan) and Professor Rody Sy, Dr. Fatima Collado and Dr. Florimond Gar-

cia (Philippines). The members were from the fields of General Medicine, Cardiology, Vascular Medicine, and Vascular Surgery.

Convening of the Consensus Panel

The Consensus Panel or simply the Panel was convened to participate in the development of the Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease by: providing literature from their respective countries on patient profiles, diagnosis, treatment, prevention and outcomes of PAD via email to be reviewed and appraised by the TWG; reviewing statements from the 2016 AHA/ACC Guidelines on the Management of PAD proposed by the TWG through the timely provision of comments and feedback via email; and reviewing and providing comment on the drafted Consensus Statement.

The Panel was an independent group of specialists and leaders recognized in the field of Vascular Medicine, Vascular Surgery, Cardiovascular Surgery and Cardiology/Internal Medicine created to develop the consensus statement. The Panel was chaired by Dr. Maria Teresa B. Abola with Panelists: Professor Jonathan Golledge (Australia), Dr. Jiang Zhisheng (China), Dr. Bryan Yan (Hong Kong), Dr. Rama Krishna Pinjala (India), Dr. Iwan Dakota, Dr. Salim Harris and Dr. Raden Suhartono (Indonesia), Dr. Yukihito Higashi, Dr. Hiroyoshi Yokoi and Dr. Tetsuro Miyata (Japan), Dr. Simonette Ganzon and Dr. Timothy Dy (Philippines), Dr. Pankaj Kumar Handa and Dr. Peter Robless (Singapore) and Dr. Seung-Woon Rha (South Korea). A patient with PAD and an interventional radiologist, Dr. Marvin Tamaña (Philippines), were also invited to join the Consensus Panel.

Creation of the Technical Working Group (TWG)

The APPADC Technical Working Group (TWG) was tasked to: a) appraise the 2016 AHA/ACC CPG on PAD; b) determine its applicability to the APSAVD member countries; c) revise the statements if needed; d) circulate the draft statements and ask the panel members to vote on the draft using the Modified Delphi technique. This TWG was chaired by Dr. Bernadette A. Tumanan-Mendoza, a cardiologist, clinical epidemiologist and health economist, together with other clinical epidemiologists, cardiologists, or vascular medicine specialists: Dr. Felix Eduardo R. Punzalan, Dr. Elmer Jasper B. Llanes, Dr. Noemi S. Pestaño, Dr. Elaine B. Alajar, Dr. Marjorie Gay Obrado-Nabablit and Dr. April Ann A. Bermudez-delos Santos.

Creation of the Evidence Base

The overall research question was:

How applicable is the 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease to the APSAVD member countries?

The first task of the TWG was to appraise the 2016 AHA/ACC Guidelines in its entirety. The overall appraisal of the CPG utilized the appraisal questions or checklist obtained from *Painless EBM* 2nd edition, 2017 (Chapter 7 Appraisal of Clinical Practice Guidelines)¹. The TWG then discussed the methods on appraisal of the individual AHA/ACC statements and search strategies. CPG guideline statements were converted to research/clinical questions, then appropriate literature -- particularly those applicable to APSAVD member countries - were searched for. The TWG opted to appraise the individual AHA/ACC CPG statements, search and appraise the applicable literature then propose whether to adopt or revise the specific AHA/ACC statement. The appraisal of the individual AHA/ACC Guideline statements likewise utilized the appraisal questions or checklist from *Painless Evidence Based Medicine* 2nd ed, 2017 (Chapters 2 and 3, on Therapy and Diagnosis respectively)^{2,3}.

Sample Research Question and Appraisal:

Among PAD patients with diabetes mellitus, how effective is counseling for self-foot examination and healthy foot behaviors in preventing the incidence of foot ulcers or amputations?

1. Appraising Directness:

For example:

P (Population/Patient) – PAD patients with diabetes mellitus

E/I (Exposure/Intervention) – counseling for self-foot examination and healthy foot behaviors

O (Outcome) – prevention of foot ulcers or amputations

M (Method) – RCTs/meta-analysis

2. Appraising Validity

Q: Were all important options and outcomes considered in making recommendations?

3. Appraising Results

Q1: What is the recommendation?

Q2: What is the level of evidence?

Q3: What is the strength of the recommendation?

4. Appraising Applicability: SCRAPS (Sex, Comorbidities, Race, Age, Pathology, Socioeconomic Factors)

The TWG divided the topics into several sections, i.e., according to some of the sections of the

AHA/ACC Guideline, to serve as a template for the draft. Economic evaluation studies related to PAD were also appraised.

Literature on the cost-effectiveness, cost-utility or cost-benefit of the different therapeutic options for PAD, i.e., effectiveness expressed as cost per quality-adjusted life years or disability adjusted life years or cost savings were also appraised. It should be borne in mind that applicability of the economic evaluations is limited to the study setting. Appraisal of the economic literature utilized the book, *Methods for the Economic Evaluation of Health Care Programmes* by Drummond *et al.* 3rd edition 2005⁴.

Internal discussions among TWG members were conducted on each AHA/ACC statement and corresponding research question, results of the appraisal, literature review, and whether the AHA/ACC statement should be adopted in full or revised depending on the evidence presented. When appropriate, a proposed alternative statement was voted upon. The resulting TWG proposed statements were then circulated to the Panel members for voting using a Modified Delphi technique.

Modified Delphi Technique

A number of TWG-proposed statements garnered comments and questions from the Panelists. These were then circulated to the Panelists electronically through a modified Delphi process to gather input on the TWG-proposed statements from Panel members for further discussion and to elicit their votes on the specific statements. This enabled the APPADC to gather consensus via email using an iterative process of definition of issues and discussion, feedback, revisions and reporting of conclusions without face-to-face discussions. A consensus vote was said to be reached if at least 75% of the Panelists were in agreement--panel members were asked to choose "YES" if they agree with the statement proposed by the TWG, and "NO" if they do not agree with the statement. Panelists were asked to send comments if they were not in agreement.

Formulation of the Recommendations

Stakeholder Consultations and Discussion of Issues

After these online discussions, most of the unsettled issues were clarified and the corresponding statements upheld.

As part of the consensus-generating process, APSAVD delivered a presentation during the PAD Symposium on February 28, 2018 at the 11th APSAVD Biennial Congress, Iloilo City (February 27 – March 1, 2018). The presentation was well-received. This served as a stakeholder consultation wherein

comments were collected from the audience. These included three issues: 1) the results of the recently released COMPASS trial⁵; 2) screening for atherosclerosis; and 3) modifying the definition and interpretation of the ABI to a more clinically relevant classification. Following the presentation, some of the Panelists present in the congress met to discuss the methodology used and the statements which achieved consensus. It was decided that an *en banc* face-to-face engagement with all or most of the Panelists should be held to achieve the following goals: 1) discuss two remaining statements with pending sensitive issues, 2) augment stakeholder participation by including additional interest groups, and 3) provide a forum for the “ratification” of all approved statements and discussion of future plans and other practical considerations related to the consensus statement.

En Banc Meeting

On July 28, 2018, members of the Steering Committee and the Consensus Panel convened in Mandaluyong City, Philippines for face-to-face discussions of unsettled consensus issues after the Delphi rounds.

This *en banc* meeting allowed for open exchange of viewpoints, discussions of the evidence and increased stakeholder participation via guest panelists (a Filipino patient with PAD and Dr. Marvin Tamaña, an interventional radiologist from the Philippines). The spirited discussions were skillfully moderated by a CPG methodologist, Dr. Leonila F. Dans of the Asia Pacific Center for Evidence-Based Healthcare (Philippines). The last two unsettled consensus issues were deliberated on, clarifications provided by the TWG and voted upon. Plans for authorship, dissemination, monitoring/evaluation and updating of the Consensus Statement were also discussed.

Funding Support

This project was conducted under the auspices of the APSAVD. The Philippine Lipid and Atherosclerosis Society provided the local coordination and secretariat to assist the Project Convenor/Coordinator, Dr. Maria Teresa B. Abola, and the TWG. Initial funding for the project was provided by the Philippine Heart Association (PHA), Philippine Society of Vascular Medicine and the APSAVD. The Communications Manager, Ms. Jennifer Seabrook, who is from the APSAVD Secretariat, was in charge of conducting the survey of responses of the panel members to the circulating statements and coordinating communications between the Steering Committee, Consensus Panel, TWG, and the APPADC coordinator. The Philippine Department of Health through the Philippine Heart

Center provided funds for the conduct of the *en banc* meeting and remaining project expenses.

Disclosure of Conflicts of Interest (COI)

All members of the Steering Committee, the Technical Working Group and the Consensus Panel were required to submit Disclosure of Conflicts of Interest forms (See DECLARATION OF CONFLICTS OF INTEREST on page 904). Those who participated in the *en banc* meeting verbally reiterated their disclosures, together with the members of the contracted Writing Group.

Assessment and Management of COI

Four members of the Panel declared relevant conflicts of interest. These panel members with COI's relevant to particular statements participated in but were recused from the relevant online votes. During the *en banc* meeting, similar handling of the COIs was performed. No other member declared relevant conflict of interests. The contracted Consensus Statement Writing Group was independent of both the APPADC and APSAVD, and likewise declared no COIs.

C. Results

Appraisal of the 2016 AHA/ACC Guidelines

An essential step prior to the evaluation of each guideline statement was the appraisal of the 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease. The evaluation of the quality and validity of this clinical guideline was performed by the TWG using the appraisal criteria described in Chapter 7, Appraisal of Clinical Practice Guidelines of Painless EBM 2nd ed, 2017 and was assessed to have complied with validity criteria¹.

The Research Questions

A total of ninety (91) research questions were generated from the above AHA/ACC guidelines and perceived gaps in knowledge. The research questions were framed in the Population/Patient-Intervention-Comparator-Outcome (PICO) or the Population/Patient-Exposure-Outcome (PEO) format.

Final Recommendations

The final recommendations were graded as to Class (whether strong, moderate or weak) using evidence categorized as strong (Level A), moderate (Level B) and weak (Level C), adapted from the 2016 AHA/ACC Guidelines².

A total of ninety-one (91) Recommendations were generated by the APPADC covering history and physical examination, diagnosis, and treatment of

Table 3. Patients at Increased Risk of PAD

- Age more than or equal to 65 years old
- Age 50-64, with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidemia, hypertension, and history of albuminuria or chronic kidney disease^{*}) or family history of PAD
- Age less than 50 years old, with diabetes mellitus and 1 additional risk factor for atherosclerosis
- Individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)
- Indigenous Australian ethnicity^{**}

Source: Adapted from 2016 AHA/ACC PAD guidelines (Table 4) (as Revised by the TWG & Consensus Panel)

^{*}History of albuminuria or chronic kidney disease is an additional risk factor for PAD^{5, 7, 12)}

^{**}Indigenous Australian ethnicity has been found to independently increase the risk of PAD (OR 3.29; 95% CI 1.55-6.97)^{14, 15)}

SEE REFERENCES for Recommendation 1 (Please see page 886-887)

PAD – peripheral artery disease; TWG – Technical Working Group; AAA – abdominal aortic aneurysm

PAD. Among these 91 Recommendations were three (3) new Recommendations, i.e. not based on the 2016 AHA/ACC Statements but drafted *de novo* in the light of recent evidence, e.g. the COMPASS trial³⁾, EUCLID trial⁴⁾. The 3 new Recommendations are:

Recommendation 18 Patients with PAD should not be routinely screened for asymptomatic atherosclerosis in other arterial beds (coronary, carotid, renal arteries)--Strong Recommendation (Class III Harm); Low Level of Evidence - Expert Opinion

Recommendation 20 Ticagrelor in comparison with clopidogrel is not recommended for patients with symptomatic PAD--Moderate Recommendation (Class III Moderate; High Level of Evidence - A)

Recommendation 36 The use of low-dose aspirin (100 mg OD) and rivaroxaban (2.5 mg BID) may be considered to reduce the risk of MI, stroke, cardiovascular death and limb-related events in patients with symptomatic PAD, having considered the associated risk of bleeding--Weak Recommendation (Class IIb); Moderate Level of Evidence - B-Randomized

Thirty-one (31) Recommendations were revised from the 2016 AHA/ACC Statement due to additional evidence obtained during the literature searches or for further emphasis or clarification⁵⁾. Out of these thirty-one recommendations, the Class of Recommendation was changed for six (6)⁶⁾ and the Level of Evidence (LOE) was changed for ten (10)⁷⁾ Recommendations.

Fifty-seven (57) Recommendations were adopted from the 2016 AHA/ACC Statement and supported by additional literature or maintained in the absence of additional literature to merit a revision⁸⁾. Of the 57 adopted recommendations, four (4) had minor edits in wording, i.e. without bearing on the PICO nor direction of the recommendations⁹⁾. As agreed upon, a general statement regarding the use of the phrase “where available” will be written as applicable when referring to the availability of recommended diagnos-

tic or therapeutic modalities.

D. Appraisal of AHA/ACC Guideline Statements and the APPADC Recommendations

I. Clinical Assessment for PAD

Recommendation 1:

Patients at increased risk of PAD should undergo a comprehensive medical history and a review of symptoms to assess for typical symptoms such as exertional leg symptoms (intermittent claudication), ischemic rest pain and non-healing wounds; and atypical symptoms related to PAD that may result in walking impairment.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 2.1.1 was adopted since a literature search did not suggest any differences in the clinical presentation of patients with PAD in the Asia-Pacific region. However, AHA/ACC Table 4 was revised to account for additional risk factors reported in data from Japan, Korea and Taiwan, i.e., a history of albuminuria or chronic kidney disease (CKD) (Table 3). **Moreover, the statement was reworded to include atypical symptoms that may lead to walking impairment among patients with PAD.** It has been reported that many PAD patients do not have typical symptoms of intermittent claudication, but rather have other non-joint-related limb symptoms or are asymptomatic¹⁶⁾ (Table 5).

Summary of Evidence:

In the 2016 AHA/ACC guidelines, patients at increased risk for PAD included: age \geq 65 years, age 50-64 years with risk factors for atherosclerosis (DM, smoking, hyperlipidemia, hypertension) or family history of PAD, age $<$ 50 with DM and 1 additional risk factor for atherosclerosis and individuals with known

Table 4. Prevalence of PAD and Associated Risk Factors reported in the Asia Pacific region

Countries	Prevalence	Risk Factors
Australia ¹⁾	REACH Registry: Prevalence 10.1%	Indigenous Australian status in the 50-64 year old group ^{14, 15)}
China ²⁾	IC: 11.4% AAI: 15.3% Both: 19.8% 40% asymptomatic (2006)	Higher prevalence in females Current smokers: 1.54 (95% CI 1.12 to 2.11)
Indonesia ³⁾	Case-control study on 40 elderly DM patients	Patients with PAD had increased age Lower waist circumference Lower triglyceride levels Higher homocysteine
Iran ⁴⁾	50 patients on hemodialysis PAD prevalence: 10%	Elevated LDL cholesterol
Japan ^{5, 6)}	REACH Registry: Prevalence 12.10% 583 patients with CKD - 10.3% had PAD - 32.9% eGFR <60 mL/min/1.73 m ² - In advanced CKD (eGFR <60) PAD prevalence 17.2% Hisayama study	PAD associated with advanced CKD [OR 1.85, CI 1.32–2.59, <i>p</i> <0.001], Age, male gender, systolic BP, and HBA1c. Multivariate logistic regression analyses: PAD independently predicted by the CKD stages (OR 1.498, CI 1.01–2.22, <i>p</i> =0.044). Greater urine albumin: Creatinine levels linearly associated with higher PAD prevalence, even within the range of normoalbuminuria
South Korea ⁷⁾	673 Diabetic Patients	Albuminuria significantly associated with PAD (OR 2.33, 95% CI 1.28–4.25 for normoalbuminuria vs. microalbuminuria and OR 3.28; 95% CI 1.40–7.66 for normoalbuminuria vs. macroalbuminuria)
Malaysia ⁸⁾	Cross-sectional study of 200 DM patients - Overall PAD prevalence 16% 5.8% in Malays, 19.4% in Chinese 19.8% in Indians	
New Zealand	No data retrieved	
Pakistan ⁹⁾	830 diabetic patients, the prevalence of PAD was 31.6%	No significant difference in gender Higher BMI Increased waist circumference
Philippines (2003 NNHES) ¹⁰⁾	ABI: 5% Validated Claudication Questionnaire (Edinburgh): 4.2%	Female (7.3% vs 2.9% in Males) Dyslipidemia IFG or DM Hypertension Smoking Obesity

(Cont. Table 4)

Countries	Prevalence	Risk Factors
Singapore (REACH registry) ¹¹⁾	8.17% of the REACH registry Singapore population	Mean age 66.1 years Males (73.6%) Diabetes (61.1%) Hypertension (79.2%) Hypercholesterolemia (76.4%) Abdominal obesity (46.5%) Smoking (61.1%)
Taiwan ¹²⁾	Case-control study of 11,817 PAD patients	Hypertension Diabetes Coronary Artery Disease Chronic Kidney Disease Hyperlipidemia Hyperuricemia Obesity Obstructive Sleep Apnea (OR 1.6)
Thailand ¹³⁾	Cross-sectional study in an urban population -overall PAD prevalence 5.2%	Multiple logistic regression analysis: hypertension (OR=1.7) female gender (OR=1.9) current smoking (OR=3.0) current alcohol drinking (OR=0.41) BMI > 25 kg/m ² OR=0.54

SEE REFERENCES for Recommendation 1 (Please see page 886-887)

PAD – Peripheral artery disease; REACH Registry– Reduction of Atherothrombosis for Continued Health Registry; IC – intermittent claudication; AAI - ankle-arm index; DM – Diabetes Mellitus; LDL – low-density lipoprotein; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; NNHeS – National Nutrition and Health Survey ABI – ankle-brachial index; IFG – impaired fasting glucose; BMI – body mass index

atherosclerotic disease in other vascular beds (coronary, carotid, subclavian, renal, mesenteric arteries or AAA).

After literature search, other risk factors were identified in the Asia-Pacific region (Table 4). Choi S, *et al.* reported that in Korean patients who have diabetes, albuminuria was significantly associated with PAD (OR 2.3, 95% CI 1.3–4.2 for normoalbuminuria vs. microalbuminuria and OR 3.3; 95% CI 1.4–7.7 for normoalbuminuria vs. macroalbuminuria)⁷⁾. In Japanese patients, multivariate logistic regression analyses suggested that PAD was independently predicted by the CKD stages (OR 1.5, CI 1.0–2.2, $p=0.044$)⁵⁾. In a case-control study of 11,817 patients in Taiwan, CKD was also suggested as a PAD risk factor¹²⁾.

Delphi Issues:

Another risk factor that could be added is indigenous Australian status in the 50-64 year old group. Based on the DRUID Study, the presence of diabetes among Indigenous Australians living in the urban setting (where healthcare access is better) increased the risk of developing PAD, both in patients with known

diabetes and those with new-onset diabetes. Furthermore, after comparing the results of the DRUID study with that of the AusDiab Study where patients included are those with diabetes in the general population, it appears that ethnicity further increases the risk of PAD (OR 3.3; 95% CI 1.6-6.9) after adjusting for common risk factors known to cause peripheral artery disease (age, diabetes duration, current smoker)¹⁴⁾. More importantly, indigenous Australians with PAD had almost a 5-fold greater risk of major cardiovascular events compared to non-indigenous Australians¹⁵⁾.

Recommendation 2:

Patients at increased risk of PAD should undergo vascular examination, including palpation of lower extremity pulses (i.e., femoral, popliteal, dorsalis pedis, and posterior tibial), auscultation for femoral bruits, and inspection of the legs and feet.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 2.1.2 did not include

Table 5. History and Physical Examination Findings Suggestive of PAD^{*5, 6)}

Findings in the History Suggestive of PAD	Physical Examination Findings Suggestive of PAD
<ul style="list-style-type: none"> • Intermittent Claudication • Other non-joint-related exertional lower extremity symptoms (not typical of claudication) • Impaired walking function • Ischemic rest pain 	<ul style="list-style-type: none"> • Abnormal lower extremity pulse examination • Vascular bruit • Non-healing lower extremity wound • Lower extremity gangrene • Other suggestive lower extremity physical findings (e.g., elevation pallor, dependency rubor)⁴⁾ • Extremity atrophy^{**} • Loss of hair^{**} • Brittle nails^{**}

*Adapted from Table 5 of the 2016 AHA/ACC PAD Guidelines

**Additional examination findings, as per recommendations of the TWG approved on consensus
SEE REFERENCES for Recommendation 2 (Please see page 886-887)

physical examination (PE) findings (e.g., extremity atrophy, loss of hair, brittle nails) that may be seen in patients with ischemic rest pain or critical limb ischemia. The AHA/ACC statement was adopted but the supporting Table 4 was adapted to account for additional PE findings that may be seen in patients with ischemic rest pain or critical limb ischemia. After a literature search, no additional data, nor differences among the APSAVD member countries regarding the statement were found (Table 5).

Summary of Evidence:

Additional findings of leg atrophy causing functional impairment were supported by another study by McDermott *et al.* in 2007 which measured ABI, calf muscle area, and intramuscular fat in a cross-sectional study including 439 patients with PAD¹⁾. Lower calf muscle area in the leg was associated with significantly poorer performance in usual- and fast-paced 4-meter walking speed and on the short physical performance battery (SPPB), adjusting for ABI, physical activity, percentage fat in calf muscle, muscle area in the leg, and other confounders ($p < 0.05$).

The other findings of hair loss and brittle nails were reported in additional references²⁻³⁾.

Delphi Issues:

A complete vascular examination and inspection of the lower extremities are important components of the assessment of PAD. The revised AHA/ACC Table 4 for additional examination findings (that may be suggestive of PAD) is shown on Table 5.

There were panel members who disagreed with including loss of hair and brittle nails in the list of physical examination findings because of the poor sensitivity for the detection of PAD⁵⁾.

Recommendation 3:

Patients with PAD should undergo noninvasive BP measurement in both arms at least once during the initial assessment in order to obtain the higher brachial systolic BP for ABI measurement, identify patients with subclavian (or innominate) artery stenosis and accurately measure BP for hypertension treatment.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 2.1.3 was adapted to highlight the importance of obtaining BP in both arms during the initial examination. These measurements are required for measurement of the ABI.

Summary of Evidence:

No additional data, nor differences among the APSAVD member countries regarding the statement were found. As determined in the 2016 AHA/ACC CPG, three outcomes were identified in making this recommendation: 1) Use of the highest brachial systolic pressure for the computation of the ABI; 2) Accurate measurement of the BP for the treatment of hypertension; and 3) Identifying an inter-arm BP of >15 mmHg to document subclavian or innominate artery stenosis. The TWG and Panel included these outcomes in the recommendation to emphasize the importance of obtaining BP in both arms during the initial examination.

II. Diagnostic Testing for the Patient with Suspected Lower Extremity PAD (Intermittent Claudication or CLI)

A. Resting ABI for Diagnosing PAD

Recommendation 4:

4a: In patients with history or physical examination findings suggestive of PAD, the resting ABI is recommended to diagnose PAD.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

4b: Segmental pressures and waveforms are used to localize the anatomic segments of PAD.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.1.1 was adopted but divided into two statements since resting ABI together with the history and PE are sufficient for the diagnosis of ABI while segmental pressure and waveforms are not necessary for the diagnosis of PAD, but instead are used to localize the site of stenosis or occlusion. No applicability issues were identified. ABI is an affordable method to diagnose PAD¹⁻⁶.

Summary of Evidence:

No additional literature was appraised.

Delphi Issues:

There were some panel members who reported that the measurement of segmental pressures was not usually requested because this procedure was not available in their vascular laboratories and there were concerns regarding its accuracy.

Recommendation 5:

Resting ABI should be reported as abnormal (ABI less than or equal to 0.90), borderline (ABI 0.91 – 0.99), normal (ABI 1.00 – 1.40), or non-compressible (ABI more than 1.40).

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 3.1.2 was adopted without revisions with no applicability issues identified.

Summary of Evidence:

ABI has good validity in the diagnosis of PAD, with sensitivities ranging from 68% to 84% and specificities ranging from 84% to 99%. The ABI cut-off value of ≤ 0.9 for the diagnosis of PAD is supported by several cross-sectional, prevalence and validation studies, some of which were performed in China¹⁻¹³. An important consideration is whether to use the

highest ankle pressure (HAP) or lowest ankle pressure (LAP) for the computation of ABI. Schroeder *et al.* reported that both methods were considered to have acceptable sensitivities and specificities using the ABI cutoff value of ≤ 0.90 for the diagnosis of PAD¹. LAP was noted to have modest specificity, but had higher positive predictive value (PPV) compared to HAP. Moreover, the incidence of false negative results in LAP was 12% (13/109) while HAP had 26% (36/138) false negative results. The current AHA guidelines do not specify whether to use the higher or lower of the two ankle arterial systolic pressures.

Studies examining the ability of an ABI of 0.91-0.99 to diagnose PAD have been limited¹⁴⁻²². Several studies have reported that this ABI range predicts the incidence of cardiovascular events and cardiovascular mortality. A recent meta-analysis reported that the HRs for cardiovascular events increased consistently with decreasing ABI for levels of ABI < 1.11 ²³. The ARIC study²¹⁻²³ as well as several Japanese observational studies¹⁴⁻¹⁹ have associated borderline ABI with increased risk of HF, coronary heart disease, carotid atherosclerosis, MI, all-cause death and cardiovascular death.

ABI values of > 1.4 indicate arterial incompressibility²³⁻³¹. This finding is common in patients with diabetes and chronic kidney disease (CKD), due to medial arterial wall calcification (MAC) and arterial stiffening. Aboyans *et al.* reported a strong association between diabetes mellitus and high ABI (> 1.40), OR = 15.97 (95% CI 3.2 – 66.1)³³. Additional tests are needed to diagnose PAD in people with incompressible vessels, such as toe-brachial pressure index.

Delphi Issues:

A Panel member commented that a significant proportion of Asian patients have diabetes and therefore would commonly have noncompressible tibial arteries and misleading ABIs. The recommendation should include a Buerger's test and the use of toe-brachial index (TBI) when the ABI is noncompressible > 1.4 . However, there were panel members who mentioned that measurement of TBI was not available in their vascular laboratories. Likewise, the absence of peripheral pulses warrants investigation by arterial duplex because the ABI is misleading in this group of patients with diabetes-associated tibial artery disease. In response to these points, another panel member commented that the sensitivity of Buerger's disease test for detecting vascular disease is 100%, with specificity of only 54% based on the critical review of physical findings (McGee *et al.*, *Arch Intern Med*; 1998)³³.

Recommendation 6:

In patients at increased risk of PAD but without history or physical examination findings suggestive of PAD, measurement of the resting ABI is reasonable.

**Moderate recommendation (Class IIa);
Moderate level of evidence
(Level B-NR)**

AHA/ACC Statement 3.1.3 was adopted without revisions with no issues on applicability identified. ABI is a relatively cheap, objective and reliable diagnostic modality for PAD.

Summary of Evidence:

The value of using ABI to screen for PAD (using a value of ≤ 0.90 for the diagnosis of PAD) among asymptomatic patients was assessed in terms of: accuracy and availability of the test, prevalence of the PAD diagnosis using this test, cost-effectivity and prognostic value. References cited in the 2016 AHA/ACC summary of evidence reported sensitivity of 79% to 95% and specificity of $>95\%$ for ABI <0.9 in diagnosing PAD. A meta-analysis¹⁾ reported a high accuracy rate supporting the use of resting ABI for the patients at increased risk but without examination findings of PAD. Another meta-analysis of 19 studies²⁾ evaluated the association between PAD identified through screening (most studies used ABI <0.90) and cardiovascular mortality and death. The pooled adjusted HR of PAD was 2.99 for all-cause mortality (95% CI, 2.16-4.12) and 2.35 for cardiovascular mortality (95% CI, 1.91-2.89). Overall, the summary of evidence of the 2016 AHA/ACC CPG and the additional references support the above recommendation.

Recommendation 7:

In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD, the ABI is not recommended.

**Moderate recommendation (Class III No benefit);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.1.4 was adopted without revisions with no issues on applicability identified.

Summary of Evidence:

Except for the references cited for the revisions in Tables 4 and 5 recommended in AHA/ACC statements 2.1.1 and 2.1.2, there were no other references that would lead to revision of the Statement.

B. Physiological Testing**Recommendation 8:**

Toe-brachial index (TBI), where available, should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.2.1 was adopted with no issues on applicability identified. Additional literature appraised (including a small study from Korea) supported the Statement.

Summary of Evidence:

As mentioned in the Summary of Evidence for Recommendation 4, the ABI may be falsely elevated (>1.4) secondary to vessel incompressibility. In these cases, the measurement of great toe pressures is advocated because MAC less commonly affects the digital arteries of the great toe^{1,2)}. A small observational study ($n=30$) was done by Park SC *et al.* on patients with diabetes in Korea³⁾. The TWG derived accuracy measures from their data as follows: low sensitivity of ABI (27%) in identifying angiographically confirmed PAD, specificity of 89%, PPV and NPV of 60% and 68% respectively, whereas, TBI <0.6 was found to have 100% sensitivity and specificity.

Hoyer reviewed several cutoffs of TBI for diagnosing PAD. The review included seven studies where the accuracy of TBI was determined using contrast angiography as the reference standard⁴⁾. The sensitivity of TBI was 91-100%, while its specificity was 65 – 100% (PPVs and NPVs also reported), however, variations in the cutoff for the diagnosis of PAD was noted. The TBI used for the diagnosis of PAD ranged from <0.60 to <0.75 . Sample sizes of the studies included ranged from 30 to 100 limbs. The most notable study cited in relation to Statement 3.2.1 was the Weinberg study published in 2012. It included 100 limbs with ABI >1.4 , with cutoff for abnormal TBI of <0.70 . It reported a sensitivity of 100% but specificity was not reported.

Aboyans *et al.* demonstrated a strong association between DM and high ABI with an OR of 15.97⁵⁾. The higher prevalence of PAD among patients with CKD has been observed in several studies⁶⁻⁹⁾. The value of TBI in the diagnosis of PAD in CKD patients was supported by Suominen *et al.*, who reported that 62% of patients with an elevated ABI (>1.3) had PAD as diagnosed by TBI <0.6 ¹⁰⁾. Leskinen *et al.* reported an increased prevalence of PAD and medial arterial calcification in patients with CKD requiring dialysis and recommended measuring both ABI and TBI in patients with CKD⁸⁾. The NEFRONA study

also reported an increased incidence of high ABI in patients with advanced CKD⁹⁾.

The above studies emphasize the low accuracy of ABI in diagnosing PAD in DM and CKD patients due to vessel incompressibility. Alternative methods such as the TBI are of great value if clinical suspicion of PAD persists despite normal ABI values.

Recommendation 9:

Patients with exertional non-joint-related leg symptoms and normal or borderline resting ABI (greater than 0.90 and less than or equal to 1.40) should undergo exercise treadmill ABI testing to evaluate for PAD.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.2.2 was adopted without revisions with no issues on applicability identified. There were no references obtained that would change the Statement.

Summary of Evidence:

Intermittent claudication, a classical symptom of PAD, may be difficult to differentiate from pseudo-claudication (non-arterial in origin) in some cases. This is especially true for symptomatic patients with normal or borderline resting ABI. Treadmill exercise testing is an objective tool in establishing the diagnosis of lower extremity PAD in these cases. Gernigon *et al.*¹⁾ reported using exercise-transcutaneous oximetry (tcpO₂) on patients with borderline or normal ABI (0.91-1.4), where 46.2% of all patients had a significant abnormal tcpO₂ response (Regional Blood Flow Impairment or RBFi) during exercise consistent with a vascular origin of intermittent claudication. The percentage of RBFi was higher in the ABI-borderline (58.2%) than in the ABI-normal (35.4%) group, $p < 0.001$. Stein *et al.*²⁾ studied symptomatic patients suspected of having PAD, reporting 26 out of 84 (31%) with normal resting ABI developed abnormal ABI (< 0.9) after exercise. These studies suggest the value of exercise ABI in elucidating the etiology of exertional non-joint related leg symptoms in patients with ABI within the normal or borderline range.

Recommendation 10:

In patients with PAD and an abnormal resting ABI (less than or equal to 0.90), exercise treadmill ABI testing can be useful to objectively assess functional status.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.2.3 was adopted without revisions with no applicability issues identified.

Summary of Evidence:

For patients with PAD and an abnormal ABI (≤ 0.9), previous guidelines (2005, 2013) state that exercise treadmill tests are useful for providing the most objective evidence of the magnitude of the functional limitation in PAD patients, and can also be used to guide evaluation of response to treatment. Krudener¹⁾ studied the reliability of disease severity and functional impairment parameters such as pain-free walking distance (intermittent claudication distance, ICD), maximal walking distance (absolute claudication distance, ACD) and the distance at which a patient would prefer to stop because of claudication pain (Functional Claudication Distance or FCD) using two standardized treadmill exercise tests. Using the Rand-36 Questionnaire, FCD correlated significantly with five out of nine domains, namely physical function ($\rho = 0.571$), physical role ($\rho = 0.532$), vitality ($\rho = 0.416$), pain ($\rho = 0.416$) and health change ($\rho = 0.414$). De Liefde *et al.*²⁾, also reported a higher mortality risk among patients with known or suspected PAD who have an abnormal exercise test, with the highest mortality risk and cardiac death observed in PAD patients with a walking impairment together with an abnormal ankle BP response to treadmill exercise (HR 3.48 [2.22-5.46]). A 6-minute walk test is a reasonable alternative to treadmill ABI testing for assessment of functional status³⁾.

Delphi Issues:

One Panel reviewer questioned the applicability to an elderly population. Another reviewer commented that there is a need to highlight that the treadmill exercise protocol for diagnosing PAD is different from that used to determine functional status or walking capacity.

Recommendation 11:

In patients with normal (1.00 – 1.40) or borderline (0.91 – 0.99) ABI in the setting of nonhealing wounds or gangrene, it is reasonable to diagnose CLI by using TBI with waveforms, transcutaneous oxygen pressure (TcPO₂), or skin perfusion pressure (SPP).

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.2.4 was adopted without revision with no applicability issues identified.

Summary of Evidence:

TBI and Toe pressure may be discordant with

ABI values in some patients with diabetes mellitus and non-healing wounds. TBI of ≤ 0.70 is considered diagnostic of PAD in patients with medial arterial calcification because the digital arteries are infrequently noncompressible.

Yamada *et al.*¹⁾ retrospectively studied whether measurements of SPP (skin perfusion pressure) could assess the severity of limb ischemia and predict wound healing more accurately than other noninvasive examinations, such as ankle blood pressure (ABP), toe blood pressure (TBP), and the transcutaneous oxygen pressure (tcPO₂). SPP was more reliable than the measurement of ABP, TBP, or tcPO₂ in predicting wound healing. On the other hand, when SPP in combination with another measurement was studied, there was a strong correlation between SPP and TBP. Wound healing could be accurately predicted if the SPP was >40 mmHg and if the TBP was >30 mmHg. Castonuovo *et al.*²⁾ reported that SPP has a PPV of 75% and NPV of 85% for CLI. The sensitivity of SPP < 30 mm Hg as a diagnostic test of CLI was 85%, and the specificity was 73%, with an overall diagnostic accuracy of 79.3%.

Delphi Issues:

It was reemphasized that above measurements be done along with clinical assessment of the limb, as part and parcel of a good clinical history and physical examination.

Recommendation 12:

In patients with PAD with an abnormal ABI (≤ 0.90) or with noncompressible arteries (ABI >1.40 and TBI ≤ 0.70) in the setting of non-healing wound or gangrene, TBI with waveforms, TcPO₂, or SPP can be useful to evaluate local perfusion.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.2.5 was adopted without revisions with no applicability issues identified. There were no references obtained that changed the recommendation.

Summary of Evidence:

As discussed above, the ABI has diagnostic limitations in patients with noncompressible vessels. In such cases, alternative physiologic testing may be warranted especially in the setting of non-healing wound or gangrene among patients with high ABI (>1.40). In a study done by Aboyans *et al.*¹⁾ on patients with diabetes, 85.7% of patients with high ABI have low TBI and peak flow velocity of the posterior tibial artery. The TBI therefore is a reliable tool in assessing

the severity of PAD especially in the setting of high ABI.

On the other hand, a low ABI (<0.9) with low TBI (<0.7) can occur in the setting of non-healing wound or gangrene. In such cases, TBI with waveforms, TcPO₂ or SPP can be used to assess local perfusion. In a study done by Park SC on patients with CLI or non-healing wounds, no patient with a TBI > 0.6 demonstrated arterial insufficiency, nor did they have findings consistent with medial sclerosis²⁾. There were patients who demonstrated an ABI <0.9 but had a normal TBI, and the angiographic findings were also normal. These findings suggest that TBI is a useful and reliable tool in the assessment of severity of PAD in the setting of CLI or gangrene. However, larger studies are needed to verify these findings.

Yamada *et al.*³⁾ reported a significant correlation between SPP and ankle BP (ABP), SPP and toe BP (TBP), and SPP and the tcPO₂ ($P < .0001$, $r 0.75$; $P < .0001$, $r 0.85$; $P < .0001$, $r 0.62$; respectively). This implies that any of these non-invasive tests can be a reliable tool in assessing local perfusion in the setting of CLI or non-healing wounds. A threshold of 40 mm Hg for SPP has a sensitivity of 72% and specificity of 88% for predicting wound healing. Patients with TBP >30 mmHg has a 67% rate of local healing (sensitivity, 63%; specificity, 90%), while TcPO₂ threshold of 30 mmhg has a sensitivity of 60% and specificity of 87% for predicting local healing.

C. Imaging for Anatomic Assessment

Recommendation 13:

Duplex ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) of the lower extremities is useful to assess anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 3.3.1 was adopted with no issues on applicability identified. Additional references support the Statement.

Summary of Evidence:

In a metaanalysis¹⁾ of Duplex ultrasonography, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) for the diagnosis of PAD using contrast angiography as the gold standard, all of these 3 non-invasive imaging modalities were shown to have good sensitivity ranging from 80-90% and specificity (64-99%). One study using MRA reported low specificity (64%) and this was the

only study that included assessment of foot vessels²). Among the 3 modalities, contrast-enhanced MRA had the highest diagnostic accuracy. However, there are some drawbacks to MRA -- it cannot be used to evaluate the vascular wall for mural calcification. Metallic devices such as stents can greatly impede the evaluation of arteries and in-stent patency. A few years after this metaanalysis, newer generation CT scanners with thinner slice thickness were introduced. In a study using 64 multi-detector row CT, there was a higher degree of diagnostic accuracy owing to its better image resolution³). However evaluation of severely calcified lesions is difficult due to beam hardening artifacts.

Recommendation 14:

Invasive angiography is useful for patients with CLI in whom revascularization is being considered.

**Strong recommendation (Class I);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 3.3.2 was adopted. There was no new literature appraised on applicability to APSAVD member countries that would result to a revision of the Statement.

Summary of Evidence:

No new references were cited by the TWG.

Delphi Issue:

One Panel member commented that catheter-directed angiography is now rarely required for diagnosis of PAD.

Consensus Issues:

A strong Class 1 COR was given by the ACC/AHA PAD CPG panelists owing to the fact that there is an intent to revascularize a CLI patient for which invasive angiography is the only approach to do both diagnosis and subsequent revascularization. TWG confirmed that there were no new references retrieved for this statement.

Recommendation 15:

Invasive angiography is reasonable for patients with lifestyle-limiting intermittent claudication with an inadequate response to GDMT for whom revascularization is being considered.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 3.3.3. was adopted with no compelling applicability issues identified except for patients with comorbid conditions that greatly impair their functional capacity such as CHF, severe valvular heart disease, stroke, spinal cord problems, in which revascularization may not lead to a significant improvement in their current level of function. These issues are also applicable to patients in APSAVD member countries. Revascularization should be reserved for patients with lifestyle limiting claudication in whom a trial of conservative management has failed. There were no references obtained that would change the Statement.

Summary of Evidence:

No new references were cited by the TWG.

Recommendation 16:

Invasive and noninvasive angiography (i.e., CTA, MRA) should not be performed for the anatomic assessment of patients with asymptomatic PAD.

**Strong recommendation (Class III Harm);
Moderate level of evidence
(Level B-NR)**

AHA/ACC Statement 3.3.4 was adopted without revisions with no applicability issues identified. There were no additional references obtained that changed the recommendation. **The level of evidence was downgraded from B-R (randomized) to B-NR (nonrandomized).**

Summary of Evidence:

The evidence used were mainly case reports on adverse reactions related to the use of contrast material, i.e., contrast induced nephropathy and allergies¹⁻³).

*D. Screening for Atherosclerotic Disease in other Vascular Beds for the Patient with PAD
Screening for Abdominal Aortic Aneurysm*

Recommendation 17:

A screening duplex ultrasound for abdominal aortic aneurysm (AAA) is reasonable in patients with symptomatic PAD.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 4.1 was adopted without revision with no applicability issues identified. Additional references supported this statement. There were no references obtained from APSAVD countries that changed the recommendation.

Summary of Evidence:

The prevalence of AAA is 1-2% in men aged > 65 years¹. A meta-analysis by Xi Li, *et al.* including 56 studies reported a prevalence of AAA of 0.5% in Asia compared to 2.2% in America, 2.5% in Europe, and 6.7% in Australia¹. Most risk factors for atherosclerosis like hypertension and smoking were associated with AAA in Asian people. Risk factors for atherosclerosis as well as established atherosclerotic disease were associated with AAA in populations from other countries. Hypertension, smoking, coronary artery disease (CAD), dyslipidemia, respiratory disease, cerebrovascular disease, claudication and renal insufficiency were risk factors for AAA in European populations. Smoking and CAD were risk factors for AAA in America populations. Smoking, diabetes mellitus, CAD, dyslipidemia and respiratory disease were risk factors for AAA in Australian populations. Another study reported that the prevalence of AAA was higher in patients with of PAD and in people with advanced age and taller stature¹. The yield of screening can therefore be optimized through selection on the basis of patient characteristics.

Kurvers *et al.* reported that an AAA prevalence of 4% is required to render screening cost-effective. They investigated if screening for AAA is indicated in patients with atherosclerotic disease². 2274 patients referred to a vascular center with manifestation of atherosclerotic disease (i.e., PAD, TIA, stroke, ICAS, AAA, angina pectoris or MI) or risk factors for atherosclerotic disease (ie, diabetes mellitus, hypertension, hyperlipidemia) were screened for the presence of asymptomatic ICAS or AAA. In PAD patients, the overall prevalence of AAA was 5.6%. Including patients with advanced age increased the prevalence to 9.6%. In patients with TIA, stroke, or ICAS, overall prevalence of AAA was 5.6%. Including patients with advanced age only increased the prevalence to 8.2%, and selecting patients with taller stature only increased prevalence to 9.3%. In patients with both advanced age and taller stature, prevalence increased to 13.1%. Lindholt *et al.* estimated hospital costs and benefits of screening for AAA in 12,658 men (mean age 67.5 years) followed-up for an average of 5.13 years³. Screening for AAA reduced the frequency of urgent operations by 74%, and AAA-related hospital mortality by 68%.

Screening for Asymptomatic Atherosclerosis in Other Arterial Beds (Coronary, Carotid and Renal Arteries)**Recommendation 18:**

Patients with PAD should not be routinely screened for asymptomatic atherosclerosis in other arterial beds (coronary, carotid, renal arteries).

**Strong recommendation (Class III Harm);
Low level of evidence (Level C-EO)**

This is a new recommendation. The AHA/ACC PAD guideline included a section (Section 4.2) on “Screening for Asymptomatic Atherosclerosis in Other Arterial Beds (Coronary, Carotid and Renal Arteries” but did not make an explicit recommendation for reasons stated.

Summary of Evidence:

Symptomatic internal carotid artery (ICA) stenosis is an established major risk factor for stroke. In previous literature cited by the AHA/ACC, the risk of stroke was 21% at 2 weeks after the first TIA or minor stroke, and 32% at 12 weeks¹. Treatment of symptomatic carotid stenosis has been well established².

However, for asymptomatic carotid artery stenosis (ACAS), a more recent study showed stroke risks of around 0.5% per year for 70% to 99% ACAS patients³. The prevalence of ACAS in the general population appears lower (0.6 to 7.5%), hence screening of the general population may appear cost-ineffective. De Weerd *et al.*⁴, showed a prevalence of 0.2% in men aged < 50 years for moderate ACAS, to 7.5% in men aged ≥ 80 years. For women, this prevalence increased from 0% to 5.0%. Prevalence of severe ACAS ranged from 0.1% in men aged < 50 years to 3.1% in men aged ≥ 80. In a study of Korean PAD patients who underwent bypass surgery for chronic lower extremity ischemia, Woo-Sung *et al.* reported that preoperative screening carotid duplex scanning revealed a prevalence of 13.8% of asymptomatic > 70% ICA stenosis⁵. However, in another population of Iranian patients with significant PAD, Babil *et al.* found out that screening for significant ICA stenosis yielded a low prevalence of 4.2%⁶.

Studies report that the prevalence of asymptomatic atherosclerosis in other arterial beds is higher in patients with PAD than those without PAD⁷⁻⁹. However, at present, there is no evidence to demonstrate that screening all patients with PAD for asymptomatic atherosclerosis in other arterial beds improves clinical outcome. Kurvers *et al.*¹⁰ reported that in patients with PAD, overall prevalence of ICAS ≥ 70% was 12.5%. Selecting only patients with advanced age increased prevalence to 21.8%, and selecting only patients with lower diastolic BP increased prevalence

to 17.9%. In patients with both advanced age and lower diastolic BP, prevalence increased to 34.7%.

Sultan *et al.*¹¹⁾ looked at the prevalence and incidence of intervention required for concomitant asymptomatic vascular disease in patients undergoing their first elective peripheral arterial intervention. The prevalence of asymptomatic vascular disease was 13% PAD, 51% CAS and 8% AAA. Symptomatic and asymptomatic polyvascular disease patients had 11.4- and 8.16-fold increased likelihood for detection of asymptomatic CAS respectively ($P < 0.0001$) relative to the remaining study population. Asymptomatic polyvascular disease patients had 8.2-fold increased likelihood of asymptomatic AAA, $P < 0.0001$, compared to the remaining study population. The likelihood of requiring vascular intervention in asymptomatic polyvascular disease patients was OR 5.740 ($P = 0.044$) and for symptomatic polyvascular disease patients was OR 4.500 ($P < 0.001$). Asymptomatic AAA detected in both symptomatic and asymptomatic vascular disease patients, is the strongest predictive factor of intervention in 18 months follow-up. In asymptomatic polyvascular disease patients, CAS and AAA have the highest prevalence.

Delphi Issues:

The AHA stated that, “currently, there is no evidence to demonstrate that screening all patients with PAD for asymptomatic atherosclerosis in other arterial beds improves clinical outcome.” Instead, the AHA emphasized intensive treatment of risk factors through guideline-directed medical therapy (GDMT) to prevent “adverse cardiovascular ischemic events from asymptomatic disease in other arterial beds rather than doing routine screening. Literature appraisal on this issue led to adopting the same section from the AHA/ACC guideline. However, on further online discussion and questions raised during the Iloilo consultation, some of the panelist members and also stakeholders in the Iloilo consultation suggested that there still should be an explicit recommendation on this issue. To address this, the drafted proposed statement put forth for further online discussion was: **“All patients with PAD should not be routinely screened for asymptomatic atherosclerosis in other arterial beds”**.”

Although online consensus was reached to adopt AHA/ACC guideline section 4.2, additional literature emerged and was submitted for appraisal^{12, 13)}. This unsettled issue was then forwarded for discussion during the en banc meeting.

Consensus Issues:

In the en banc meeting, suggested additional articles were appraised to have directness issues (differ-

ent PEO) and thus had no bearing on the statement. The VIVA population (P) studied was different since it included Danish men mostly with no PAD. The VIVA exposure (E) or screening consisted of vascular screening with ABI and ultrasound of the abdominal aorta. There was also a questionnaire regarding lifestyle parameters, medical and smoking status, as well as laboratory determinations of cholesterol levels. Screening led to the diagnosis of PAD, abdominal aortic aneurysm, or hypertension and these patients received concomitant antiplatelet, or lipid lowering therapy. The VIVA primary outcome (O) was all-cause mortality or time to event or censoring, assessed five years after randomization rather than the outcomes (O) of interest for this recommendation - improvement in clinical outcomes, such as MACE or major adverse cardiovascular events^{12, 13)}.

Given the “richness” of the face-to-face discussions compared to the online discussions, it was agreed that despite the online consensus already arrived at which was to adopt AHA/ACC Guideline Section 4.2, the decision-making process would be repeated involving Panel members present. Firstly, it was agreed that an explicit statement/recommendation would be generated. Next, the wording of the Recommendation was carefully deliberated on given the “economic harm” incurred from an intervention lacking evidence of benefit¹⁴⁾. The proposed statement/recommendation from the panel during the *en banc* meeting was “Patients with PAD should not be routinely screened for asymptomatic atherosclerosis in other arterial beds (coronary, carotid, renal arteries)”; this was voted upon and approved. Finally, the COR and LOE were also agreed upon as COR Class III LOE Low - EO.

III. Medical Therapy for the Patient with PAD

A. Antiplatelet Agents

Recommendation 19:

Antiplatelet therapy with aspirin alone (range 75 – 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 5.1.1 was adopted with the addition of a statement regarding Ticagrelor (see Recommendation 20 below). After a literature search, no data specific to the APSAVD member countries, was found to support other recommendations regarding antiplatelet therapy in symptomatic PAD. The higher cost of clopidogrel as compared to ASA affects its affordability/usage. This is especially true in countries where healthcare services are usually paid through

out-of-pocket expenses, e.g., the Philippines.

Summary of Evidence:

In a meta-analysis by the Antithrombotic Trialists¹⁾ involving a total of 9,214 patients with PAD in a subgroup analysis, there was an 18% RRR in the group that was receiving antiplatelet drugs compared to those in the control group (ARR of 1.3% and NNT 77) with no significant difference in major extracranial bleeding. Moreover, in the subset of patients comparing ASA vs clopidogrel, there was an ARR of 1%, NNT of 100 in favor of clopidogrel. This study was valid but with reservation on the directness when it comes to interventions. There were 287 studies included with 195 studies on antiplatelet vs controls. However, no RCT evaluating efficacy of ASA exclusively in PAD patients was found. It was concluded that ASA or clopidogrel may be given to patients with PAD to prevent non-fatal MI, non-fatal stroke and vascular death.

Another trial on 366 outpatients with stage I-II PAD supports the use of ASA in PAD patients to reduce fatal and nonfatal vascular events²⁾. There were no directness or validity issues. The primary outcome was a combined incidence of fatal and nonfatal vascular events [MI, or stroke and pulmonary embolism (PE)]. There was a 64% RRR, ARR 7.2% and NNT of 14 with the use of ASA (100mg tablet per day) compared to placebo after 2 years of follow-up. However, actual sample size was much less than the computed sample size. It was stated that “... sample size should be 2000 but nontrial ASA use for concomitant diseases grew, the randomization rate diminished and recruitment was stopped. Hence, the study was too small to derive meaningful conclusions”.

Another meta-analysis by Berger *et al.*³⁾ looked specifically at PAD patients and compared ASA (100 mg – 1,500 mg per day) to placebo. There were no directness or validity issues. There was no significant difference between the two treatments arms as to the primary endpoint of cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death). However, in an individual endpoint of stroke comparing ASA and placebo alone (without concomitant dipyridamole), there was a 36% RRR, ARR 1.6%, and NNT of 62 in favor of the ASA group. The findings suggested that giving ASA to PAD patients may prevent stroke.

Trials also support the use of clopidogrel in patients with PAD⁴⁻⁵⁾. In the CAPRIE trial⁴⁾, clopidogrel was found to be more beneficial than ASA among PAD patients. The population included a mixture of patients with atherosclerotic vascular disease manifested including recent ischemic stroke, recent MI or

symptomatic PAD. In the subgroup of PAD patients, there was a 23% risk reduction with the use of clopidogrel compared to ASA, which also drove the overall results of the trial to a significant result in the composite outcome of ischemic stroke, MI or vascular death. The authors concluded that “long term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than ASA in reducing the combined risk of ischemic stroke, MI or vascular death.” TWG concluded that the benefit was driven mainly by the subgroup of patients with PAD. The findings suggest clopidogrel is more beneficial than ASA among PAD patients.

A systematic review by Katsanos *et al.*⁵⁾ supports the use of clopidogrel as monotherapy in PAD patients. This was a systematic review and a network meta-analysis of RCTs comparing different anti-platelets to placebo as reference treatment. Among the different anti-platelets used, only clopidogrel, ticagrelor and ticlopine showed risk reduction in MACE; with clopidogrel having “the most favorable benefit-harm profile” according to the authors. On the other aspect, ticlopidine, vorapaxar and combination of clopidogrel plus ASA showed a significant increase in severe bleeding events. The findings suggest that clopidogrel may be given as monotherapy to PAD patients.

Economic Evaluation:

Additional economic evaluations⁶⁻⁷⁾ using the Chinese healthcare perspective compared Clopidogrel (75 mg per day) with ASA (325 mg per day) among patients with established PAD⁷⁾. In that setting, it was shown that using Clopidogrel over ASA had an incremental cost-effectiveness ratio (ICER) of US\$ 9,890 per quality-adjusted life year (QALY). With a threshold ICER or willingness-to-pay ICER of US\$ 19,877 (3x per capita GDP of China in 2013), Clopidogrel was considered cost-effective for patients with PAD in comparison with ASA. However, sensitivity analyses showed that Clopidogrel was not likely to be cost-effective for patients aged 80 years old and treatment duration of more than 9 years.

In terms of cost applicability, the higher cost of clopidogrel as compared to ASA affects its affordability/ usage. This is especially true in countries where healthcare services are usually paid for through out-of-pocket expenses, e.g., the Philippines.

Delphi Issues:

Based on the clinical implications stated, there was a suggestion to mention clopidogrel before ASA in the statement but this was not approved, given the economic considerations for many of the countries included. ASA was advised as the first choice and

clopidogrel will only be recommended if the patient is not suitable for ASA (e.g., gastric ulcer, allergy).

Recommendation 20:

Ticagrelor in comparison with clopidogrel is not recommended for patients with symptomatic PAD.

**Moderate recommendation (Class III No Benefit);
High level of evidence (Level A)**

AHA/ACC Statement 5.1.1 was adopted with the addition of this **new APSAVD/APPADC recommendation** regarding Ticagrelor use compared to clopidogrel use. After a literature search, no data specific to the APSAVD member countries was found to support other recommendations regarding antiplatelet therapy in symptomatic PAD. The daily cost of ticagrelor is very much higher than clopidogrel, and this affects its affordability/usage. This is especially true in countries where healthcare services is usually largely paid for out-of-pocket, e.g., the Philippines.

Summary of Evidence:

Additional studies comparing ticagrelor and clopidogrel did not show superiority of ticagrelor over clopidogrel. The most recent study, Examining Use of ticagrelor In PAD (EUCLID)¹⁾, showed no statistically significant difference between Ticagrelor and Clopidogrel in the primary endpoint of cardiovascular death, MI or ischemic stroke. Considering the higher cost of ticagrelor compared to clopidogrel without additional clinical benefits, the TWG deemed it prudent not to recommend ticagrelor for patients with symptomatic PAD. This study involving 13,885 patients with almost 80% symptomatic PAD patients and interventions compared ticagrelor 90 mg BID as monotherapy vs clopidogrel 75 mg OD. There were no validity issues. In the primary composite endpoint of cardiovascular death, MI or ischemic stroke, there was no difference between the two treatment arms. For the individual endpoint of ischemic stroke, ticagrelor reduced the event by 22% compared to clopidogrel but the ARR was only 0.50% and the NNT was 200. Overall, the authors concluded that “in patients with symptomatic PAD, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups”. TWG agreed with the authors’ conclusion. This trial suggested ticagrelor has no additional benefit over clopidogrel among symptomatic PAD patients.

Delphi Issues:

The PEGASUS substudy²⁾ on the use of ticagrelor

versus placebo in PAD patients enrolled in the main PEGASUS Trial³⁾ compared ticagrelor to placebo, “all on a background of low-dose aspirin” (usage of ASA=99.9%). PEGASUS-TIMI 54 was a randomized, double-blind, placebo-controlled multinational clinical trial designed to evaluate the efficacy and safety of ticagrelor in addition to low dose ASA for long-term treatment of stable patients with a history of spontaneous MI.” The study compared dual therapy with ticagrelor plus aspirin versus monotherapy with aspirin among its included patients as opposed to comparison of monotherapies, the exposures (E) of interest in Recommendations 19 and 20 thus had directness issues.

Recommendation 21:

In asymptomatic patients with PAD (ABI less than or equal to 0.90), suggesting antiplatelet therapy may be considered to reduce the risk of MI, stroke, or vascular death.

**Weak recommendation (Class IIb);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 5.1.2 No additional literature from the APSAVD member countries appraised that would result in a revision of the Statement. The 3 studies previously appraised on asymptomatic patients with PAD did not show convincing evidence that ASA reduces cardiovascular events¹⁻³⁾. **The class of recommendation was downgraded from Class IIa to IIb.**

Summary of Evidence:

Evidence from the 3 studies previously appraised, where the issue raised was if ASA can reduce cardiovascular events on asymptomatic patients with PAD, was not convincing. Two of the studies cited did not show evidence that there was a reduction in MACE^{1,2)}. While the third study showed a reduction in MACE, the results apply to the overall population included, with only 22% of the total enrolled population being asymptomatic³⁾. PAD patients had more cardiovascular risk factors (e.g., HFN, DM) compared to patients without PAD. Patients with PAD also had higher incidence of MACE - 19.3% in patients with vs 8.4% in patients without PAD (PEGASUS - TIMI 54 study)⁴⁾. They also had higher rates of acute limb ischemia (1.0% vs 0.1%) and peripheral revascularization procedures (9.15% vs 0.46%)⁴⁾.

A randomized trial by Fowkes *et al.*¹⁾ suggested that ASA should not be recommended for patients with asymptomatic PAD and an ABI of ≤ 0.95 . There was no difference in the composite endpoints of initial fatal or nonfatal coronary event or stroke or revascularization between people allocated ASA or placebo.

There were no validity issues, however, there were issues in directness. First, the computation of the ABI used the lowest ankle pressure as the denominator, which may have overestimated the number of patients diagnosed with PAD. Second, based on the 2016 AHA guidelines, PAD should be defined by ABI of ≤ 0.90 . The study included patients with an ABI of < 0.95 , i.e. it included patients with an equivocal ABI. The incidence of major bleeding was not significantly greater in the ASA group. The findings suggest that ASA should not be recommended in patients with asymptomatic PAD and an ABI of ≤ 0.95 .

In another study, “Prevention of serious vascular events by ASA among patients with PAD”, a randomized, double-blind trial involving 366 patients with PAD, was identified however, the application of its overall results to asymptomatic PAD patients may be misleading²⁾. There were no validity issues but a limitation in the directness (population). The primary outcome was the combined incidence of fatal and nonfatal vascular events [MI, or stroke and pulmonary embolism (PE)] and CLI. There was a 64% RRR, HR 0.35 95% CI 0.15-0.82). However there are two important caveats to this trial: 1) Only 22% of the total enrolled population was asymptomatic; 2) There was no separate subgroup analysis for asymptomatic PAD. Application of the results to the asymptomatic PAD patients was unclear.

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD), a randomized placebo-controlled trial of ASA and antioxidants in patients with diabetes and asymptomatic PAD³⁾ consisted of 1276 adults with diabetes and ABI of ≤ 0.99 or less but asymptomatic cardiovascular disease. The authors concluded that “...the trial did not provide evidence to support the use of ASA ... in primary prevention of cardiovascular events and mortality in the population with diabetes studied”. TWG agreed with the authors’ conclusion and recommended to await bigger trial on this type of patient. There were no directness or validity issues.

Delphi Issues:

The presence of cardiovascular risk factors among patients with PAD should be highlighted, hence the following revisions: patients with PAD have more cardiovascular risk factors (e.g., HPN, DM, CHF) and have also been shown to have higher risks to develop MACE, i.e., 19.3% among PAD patients as compared to 8.4% to those without PAD as reported in the PEGASUS – TIMI 54 substudy⁴⁾. They also have higher rates of acute limb ischemia (1.0% vs 0.1%) and peripheral revascularization procedures (9.15% vs 0.46%)⁴⁾. In view of these high risk factors and risks

for MACE, the TWG recommended to consider giving antiplatelet therapy to asymptomatic patients with PAD despite the absence of convincing evidence that ASA can reduce cardiovascular events among asymptomatic patients with PAD based on the three studies cited above.

Recommendation 22:

In asymptomatic patients with borderline ABI (0.91 – 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.

**Weak recommendation (Class IIb);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.1.3 was adopted with no applicability issues identified. There was no literature from APSAVD member countries that would result in a revision of the Statement.

Summary of Evidence

No additional literature was appraised.

Recommendation 23:

The effectiveness of dual antiplatelet therapy (DAPT) (ASA and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.

**Weak recommendation (Class IIb);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.1.4 was adopted without revision with no applicability issues identified. There was no literature identified relevant to the APSAVD member countries that resulted in a revision of the Statement.

Summary of Evidence:

One study reported a reduction in MACE among patients who were given DAPT instead of ASA alone, but this was investigated in an observational cohort and the total population was relatively small (629 patients)¹⁾. The PAD subset of the CHARISMA trial^{2, 3)} included 3,096 patients with PAD (2,838 symptomatic and 258 asymptomatic) and randomized patients to clopidogrel plus ASA or ASA plus placebo. This did not show significant reduction in the primary endpoint (first occurrence of MI, stroke, or death from cardiovascular causes including hemorrhage); although there were reductions in some endpoints, e.g., MI. There was an increase in minor bleeding events among patients given DAPT instead of ASA.

Recommendation 24:

DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.

**Weak recommendation (Class IIb);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.1.5 was adopted because no additional data from APSAVD countries were identified. **In the light of additional literature appraised, the level of evidence was upgraded to B-R (randomized) from C-LD (limited data).**

Summary of Evidence:

Although there were additional references i.e., a network meta-analysis of 49 RCTs of several antiplatelet therapies¹⁾, 1 RCT with relatively small sample size and 1 open label prospective pilot trial^{2,3)}, these did not result in a change in the recommendation. One RCT was appraised but deemed to have directness issues as it was on dalteparin, rather than on clopidogrel³⁾.

A network meta-analysis by Katsanos *et al.*¹⁾ included 49 RCTs on patients with PAD randomized to receive antiplatelets or placebo or another antiplatelet therapy for prevention of cardiovascular events and/or amputations. Dual antiplatelet therapy with Clopidogrel plus ASA ranked highest (RR: 0.63, 95% CI: 0.35–1.15 indirect comparison to placebo) and it was the only treatment associated with a significant reduction of major amputations following leg revascularization (RR: 0.68, 95% CI: 0.46–0.99 direct comparison with ASA; NNT=94). This meta-analysis included both surgical (CASPAR), and endovascular (MIRROR and CHARISMA) trials.

Tan *et al.*²⁾ randomized 103 patients with PAD who underwent peripheral angioplasty and stenting to clopidogrel plus ASA versus control (anticoagulation). There were no significant differences in cardiovascular event rate and mortality 18 months after revascularisation between these two groups.

Finally, a prospective open-label pilot trial by Rocha-Singh *et al.*⁴⁾ which included 85 patients with severe intermittent claudication or CLI who underwent revascularization and received a single antiplatelet agent, ASA, and UFH prior to procedure and eptifibatide, was appraised. There were directness issues since the patients received single and not dual antiplatelet therapy.

Delphi Issue:

One of the reviewers suggested to include the duration of DAPT: 6 months DAPT, and then monotherapy for 5 years in separate statements. It was con-

cluded that further research is needed to determine the duration of DAPT and subsequent monotherapy.

Recommendation 25:

Vorapaxar in addition to existing antiplatelet therapy in patients with symptomatic PAD is not recommended.

**Strong recommendation (Class III Harm);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.1.6 was revised to make a recommendation against adding vorapaxar to existing antiplatelet because of evidence of harm from additional references appraised. **The class of recommendation was downgraded from IIb to III.** Vorapaxar is not yet available in all APSAVD-member countries.

Summary of Evidence:

Additional data from 1 meta-analysis (Katsanos *et al.*)¹⁾ and 1 RCT (Jones *et al.*)²⁾ suggested that Vorapaxar did not lead to a reduction in cardiovascular death, MI or stroke, but did lead to an increase in moderate to severe bleeding. The reported outcomes included: All-cause mortality, MI and stroke (RR 0.88 (0.69 – 1.1) $P=0.26$); cardiovascular death (RR 0.94 (0.65 to 1.35) $P=0.74$); non-fatal MI (RR 0.95 (0.67 to 1.36) $P=0.80$); and non-fatal stroke (RR 0.66 (0.39 to 1.08) $P=0.10$). Moreover, in the Katsanos network meta-analysis, the highest absolute rate of severe bleeding was noted with Vorapaxar plus ASA (2.0 events / 100 person-years). Severe bleeding was significantly increased with Vorapaxar (RR: 1.80; 1.22–2.69, NNT=130).

In a trial reported by Jones *et al.*²⁾ that randomized patients with NSTEMI-ACS with PAD to vorapaxar versus placebo, in addition to standard antiplatelet therapy, vorapaxar, when compared with placebo, did not statistically reduce the occurrence of the composite end point of cardiovascular death, MI, or stroke. Vorapaxar did increase the risk of moderate or severe bleeding in the overall trial, an effect that did not differ based on PAD diagnosis. The authors stated that there was a trend toward lower rates of peripheral revascularization and LE amputation in patients with PAD treated with vorapaxar compared with placebo. In the TRACER study, Vorapaxar on top of ASA compared to ASA led to a nonsignificant reduction in peripheral revascularization events and lower extremity amputation. In terms of harm, there was also statistically nonsignificant increase in GUSTO major bleeding or TIMI major bleeding but statistically significant increase in TIMI clinically significant bleeding.

B. Statins

Recommendation 26:

Treatment with a statin medication is indicated for all patients with PAD.

**Strong recommendation (Class I);
High level of evidence (Level A)**

ACC/AHA Statement 5.2 was adopted. Additional data on cost-effectiveness supported this statement.

Summary of Evidence:

There were no references identified that changed the Statement.

Economic Evaluation:

There is a dearth of economic evaluation studies on PAD especially among APSAVD member countries. In terms of statin therapy, one study looked into the assessment of cost-effectiveness of several pharmacological prevention measures among asymptomatic patients with PAD¹⁾. However, this study was done using the Swedish health service perspective, which is not applicable to any APSAVD member country. On the other hand, a study in Korea employed Markov modeling techniques to determine the cost-effectiveness of statin therapy²⁾. This study which used the Korean health care system perspective looked into statin use for primary prevention of cardiovascular disease, i.e., fatal or non-fatal MI and/or stroke. It did not consider statin use among those with PAD.

C. Antihypertensive Agents

Recommendation 27:

Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 5.3.1 was adopted with no issues on applicability identified. There were no references obtained that changed the recommendation.

Summary of Evidence:

The INVEST trial enrolled patients with hypertension and CAD¹⁾. They were assigned to either a CCB-based strategy (Verapamil SR + Trandolapril) or beta blocker-based strategy (Atenolol/Hydrochlorothiazide). Using a *post hoc* analysis, they were grouped into those with PAD and those without. Among hypertensive CAD patients, concomitant PAD carries a poor prognosis and increased the risk of major

adverse cardiovascular events including all-cause mortality, cardiovascular mortality, and total MI (fatal or non-fatal) over a mean follow-up of 2.7 years, compared with CAD alone. The incidence of the first occurrence of a vascular event was not significantly different between treatment strategies. PAD patients may require different BP targets compared to those without PAD wherein the best outcomes were observed with average treated systolic blood pressure of 135 to 145 mmHg. It was concluded that antihypertensive treatment among hypertensive patients with concomitant PAD and stable CAD is reasonable with either CCB- or beta blocker-based strategy.

Yusuf *et al.* (HOPE PAD)²⁾ suggested that: 1) The lower the ABI, the higher the rates of events (cardiovascular mortality, MI, stroke and all cause mortality); and 2) Treatment with Ramipril reduced the risk of events in those with a clinical history of PAD as well as in the patients with subclinical PAD.

The ALLHAT trial^{3, 4)} randomized 32,804 hypertensive patients to ACE-inhibitor, CCB, or an alpha receptor blocker compared with a thiazide. In a subgroup of participants who experienced clinically severe PAD, i.e., requiring hospitalizations or outpatient revascularization (2.5% of the study population), pre- and post-PAD nonfatal events and post-PAD total and cause-specific mortality did not differ in any treatment group (amlodipine vs. chlorthalidone or lisinopril vs. chlorthalidone). There were no differences in rates of MIs, strokes, heart failure, or coronary revascularization procedures in either the amlodipine vs. chlorthalidone or lisinopril vs. chlorthalidone treatment groups. Furthermore, the total mortality and cause-specific mortality (CVD, MI, stroke) among those with PAD did not differ in any of the treatment groups.

In the COPART registry⁵⁾, consisting of adults with a first hospitalization due to PAD, the overall mortality and cardiovascular mortality did not differ among PAD patients who were given beta blockers versus those who were not on beta blockers.

Recommendation 28:

The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD.

**Moderate recommendation (Class IIa);
High level of evidence (Level A)**

AHA/ACC Statement 5.3.2 was adopted with no issues on applicability identified. There were no references obtained that changed the Statement.

Summary of Evidence:

The INVEST trial which compared the effect of CCB + ACE-Inhibitor therapy with Beta blocker + thiazide treatment was cited earlier and did not show any significant difference in the risk for major adverse cardiovascular events¹⁾.

In the HOPE PAD trial^{2, 3)}, treatment with ramipril reduced the risk of clinical outcomes in those with a clinical history of PAD as well as in the patients with subclinical PAD.

Simultaneous treatment with an ACE-inhibitor and an angiotensin receptor blocker is not recommended, as shown in the ONTARGET trial⁴⁾. In this trial, the combination of ramipril plus telmisartan did not lead to additional benefit but resulted to more adverse events specifically hypotension, syncope and renal dysfunction. Telmisartan was not inferior to ramipril for both the prespecified primary outcome of death from cardiovascular causes, MI, stroke, or hospitalization for heart failure.

Although the INVEST study listed hypertension as one of the inclusion criteria, the two other studies included patients who were not hypertensive. The ONTARGET study included patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage were included. This study did not have hypertension as one of its inclusion criteria. On the other hand, the HOPE study patients were aged 55 years or greater and had existing cardiovascular disease (CAD, previous stroke, PVD), or diabetes and an additional coronary risk factor (smoking, hypertension, hypercholesterolemia, low HDL or microalbuminuria) but no heart failure or evidence of LV dysfunction. Hypertension is only listed as one of the additional risk factors for those with diabetes; those with existing cardiovascular disease may not be hypertensive.

Economic Evaluation:

In an assessment of the cost-effectiveness of 4 pharmacological interventions (ACE-I, statins, ASA & non-ASA antiplatelet therapy) among asymptomatic patients with PAD, the use of an ACE-I was associated with the largest reduction in events leading to the highest gain in Quality-Adjusted Life Years (QALYs). However, the study results cannot be applied to any APSAVD member country since it used the Swedish health care perspective⁵⁾.

D. Smoking Cessation**Recommendation 29:**

Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 5.4.1 was adopted with additional data coming from a population cross-sectional survey from an APSAVD member country (Lee et al.) showing strong supportive evidence¹⁾.

Summary of Evidence:

In a population-based cross-sectional survey of 2,517 Korean men aged >50 years old, the prevalence of PAD was increased amongst smokers compared to never smokers [adjusted OR 2.31 (95% CI 1.20-4.42) for former smokers and 4.30 (95% CI 2.13-8.66)]. The risk of PAD in current smokers was significantly higher than in former smokers (adjusted OR, 1.89; 95% CI, 1.19-3.01). The risk of PAD decreased with increasing years since quitting smoking in all models (*P*-trend=0.002, <0.001, and <0.001, respectively)¹⁾.

Recommendation 30:

Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 5.4.2 was adopted without revisions. There was no literature obtained from APSAVD member countries that resulted in a revision of the Statement.

Summary of Evidence:

In one trial, adults with PAD who were smokers were randomized to: 1) Delivery by physicians of very brief advice about smoking cessation; 2) Provision of a prescription for nicotine replacement therapy (NRT) to assist in smoking cessation, and 3) Active referral to telephone-based smoking cessation counseling. There were no significant differences in the number of patients who quit smoking between the control and the intervention groups, but this may be a result of the limited enrollment of patients¹⁾.

In the Philippines, bupropion is not available while varenicline's availability is limited.

Recommendation 31:

Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public spaces.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 5.4.3 was adopted with additional evidence supporting this Statement based on a population-based survey in China by He *et al.*

Summary of Evidence:

There was no literature obtained regarding applicability to APSAVD member countries that resulted in a revision of the Statement.

In a population-based cross-sectional survey by He, *et al.*¹⁾ of 2,334 participants aged ≥ 60 years, there was an increased risk of PAD with increasing second-hand smoke exposure. The prevalence of second-hand smoke exposure was 39.5% (477 subjects), with 414 (86.8%) exposed at home and 63 (13.2%) exposed in the workplace. Individuals exposed to second-hand smoke had a significantly higher risk of PAD than those unexposed. Adjusted odds ratios of PAD were 1.87 (95% CI, 1.30 to 2.68) for intermittent claudication, 1.47 (95% CI, 1.07 to 2.03) for ABI < 0.90 , and 1.67 (95% CI, 1.23 to 2.16) for either intermittent claudication or ABI < 0.90 . There was a significant dose-response gradient between the amount of second-hand smoke exposure and cumulative second-hand smoke exposure time and increasing risk of intermittent claudication, ABI < 0.90 , or overall prevalence of PAD (P for linear trend 0.048 to 0.001).

E. Glycemic Control**Recommendation 32:**

Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

ACC/AHA Statement 5.5.1 was adopted. Additional evidence from a retrospective cohort of Chinese patients supported the Statement. **The level of evidence was upgraded from C-EO to B-NR.**

Summary of Additional Evidence:

A retrospective cohort study by Wang *et al.*¹⁾ of 648 patients with diabetes-related foot ulcers examined the effect of introducing a multidisciplinary foot team (nurse, orthopedics, plastic surgery, vascular surgery, nutritional department, and endocrinology department). The authors reported a significant down-

ward trend in the duration of inpatient stay for diabetes-related foot ulcers after introduction of the service ($p=0.015$). The requirement for major amputation was reduced from 9.5-14.5% before 2006 to $< 5\%$ after introduction of the team. There was no literature obtained from APSAVD member countries that resulted in a revision of the AHA/ACC Statement.

Recommendation 33:

Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 5.5.2 was adopted with additional evidence supporting intensive glycemic control. There was no literature identified from APSAVD member countries that resulted in a revision of the Statement.

Summary of Evidence:

A recent umbrella systematic review by Hasan *et al.*¹⁾ included 9 RCT's that enrolled patients with diabetes without a history of foot ulcers and compared intensive glycemic control versus less intensive glycemic control. 10,897 patients aged 41-72 years old were included for an observation period of 2 to 10 years. Compared with less intensive glycemic control, intensive control was associated with a statistically significant decrease in the risk of amputation (RR, 0.65; 95% CI, 0.45-0.94; $I^2=0\%$). The risks of peripheral neuropathy (RR, 0.89; 95% CI, 0.75-1.05; $I^2=32\%$) and peripheral ischemia (RR, 0.92; 95% CI, 0.67-1.26; $I^2=0\%$) were not statistically significantly related to the intensity of glycemic control.

Delphi Issues:

Glycemic control with the SGLT2 inhibitor canagliflozin has been reported to increase the risk of lower extremity amputation (CANVAS trial)²⁾. Thus the type of diabetes treatment may also be important and this needs further investigation. However, in the light of other recent trials regarding conflicting results of specific oral hypoglycemic agents (OHAs) and their effect on MACE, e.g. trials on Saxagliptin and Sitagliptin (both of which neither increased or reduced the incidence of MACE), and the trial on Empagliflozin (which has a positive result in relation to MACE), review of the specific OHAs is beyond the scope of the PAD Consensus Statement. As such, the readers are referred to the specific CPGs for diabetes.

F. Oral Anticoagulation

Recommendation 34:

The use of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is of uncertain benefit and potentially harmful.

**Strong recommendation (Class III Harm);
High level of evidence (Level A)**

AHA/ACC Statement 5.6.1 was revised to emphasize not only potential harm but also uncertain benefit. No data specific to the Asia-Pacific region was found to support recommendations regarding the use of anticoagulation among PAD patients who underwent lower extremity autogenous vein or prosthetic bypass. **The class of recommendation was downgraded from IIb to III and the level of evidence was upgraded from B-R to A.**

Summary of Evidence:

The 3 studies and 1 meta-review used as evidence for this Statement did not show consistent and convincing benefit with the use of anticoagulants in improving patency after lower extremity autogenous vein or prosthetic bypass. There was evidence of harm especially in rates of bleeding and even mortality. An increase in mortality was reported in one trial, while increased rates of major bleeding rates were reported in two trials¹⁻⁴.

Sarac *et al.*¹ randomized 56 patients at high risk for graft failure to ASA or warfarin (WAR). Immediate postoperative primary graft patency rates were higher in the WAR group as compared with the ASA group (97.3% vs 85.2%) but the difference was not significant ($P=0.07$). The cumulative 3-year primary (uninterrupted duration of patency without intervention) and secondary patency rates (duration of patency that was restored to the same conduit after bypass graft occlusion) were significantly greater in the WAR group versus the ASA group. The warfarin plus ASA group also showed higher limb salvage rates. There was no significant difference between the two groups in terms of 30-day mortality. The incidence of postoperative hematomas was higher in the WAR group but this was not a major bleeding complication and authors attributed it to the use of heparin post-operatively. Based on the design of the trial, the findings may only be applicable to PAD patients at high-risk of graft occlusion. The trial suggests that oral anticoagulation may be considered in PAD patients at high risk of graft occlusion undergoing lower extremity autogenous vein bypass.

Another RCT² on 2,690 patients who had undergone infrainguinal grafting reported on bleeding

and mortality rates. Overall, there was no significant difference in the rates of graft occlusion between patients receiving oral anticoagulation (OAC) or ASA. In a sub-group analysis, there was significant reduction in graft occlusion with use of oral anticoagulation among patients using vein grafts; while ASA use was associated with a reduction in occlusion rates of prosthetic grafts. However, since the primary outcome was negative, interpretation of such sub-analyses is problematic. Most importantly the incidence of major bleeding was twice as high in the oral anticoagulation treatment group compared with the ASA group, with an ARI of 3.96%, NNH: 25. Overall this trial suggested that oral anticoagulation did not significantly reduce graft occlusion but increased the risk of major bleeding.

In a review by Bedenis *et al.*³ including 14 trials investigating the effect of anticoagulation on graft patency, no benefit of Vitamin K antagonists (VKA) was reported leading to the conclusion that the evidence for VKA in venous bypasses is weak and inconsistent. VKA may have a small advantage in terms of graft patency but there appears to be an increase in bleeding complications.

Finally, a multicenter trial on 831 patients who underwent peripheral arterial bypass surgery randomized patients to warfarin plus aspirin (WASA) versus ASA alone. The trial's primary outcome was graft patency. The secondary outcomes pertained to mortality (total mortality) and morbidity (risk of cerebral events, MI, thromboembolic events or need for hospitalization). Focusing on the outcomes of interest only, results showed that there was no benefit in the use of WASA over ASA alone in improving graft patency among patients who underwent bypass surgery with prosthetic or vein grafts. In fact, there was an increase in the risk of death in the WASA group, with ARI of 8.8% and a NNH of 11. Moreover, there was a significant increase in major bleeding events in the WASA group. This trial suggests that oral anticoagulation does not reduce graft occlusion among patients after lower extremity autogenous vein or prosthetic bypass but increases risks of death and major bleeding⁴.

Recommendation 35:

Anticoagulation with vitamin K antagonists (VKA) should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD.

**Strong recommendation (Class III Harm);
High level of evidence (Level A)**

AHA/ACC Statement 5.6.2 was revised to specify the class of anticoagulants (vitamin K antagonists) that the evidence base for the 2016

AHA/ACC Statement was focused on. There were no applicability issues identified.

Summary of Evidence:

The three studies on patients with PAD previously appraised by the AHA/ACC did not show a reduction in the risk of ischemic cardiovascular events amongst those allocated VKAs and there was increased risk of minor and major bleeding. Two RCTS^{1, 2)} on patients who had undergone infrainguinal grafting are discussed below.

The 2012 ACCP CPG on antithrombotic therapy in PAD³⁾ was also reviewed and this reported that anticoagulation, mainly warfarin, among PAD patients did not reduce risk of cardiovascular ischemic events. The authors of the CPG stated that “warfarin with or without ASA is associated with a significant increase in extracranial bleeding compared with ASA alone”.

Finally, a further trial by Anand *et al.*⁴⁾ randomized 2,161 patients with PAD (lower extremities, carotid or subclavian artery disease) to antiplatelet plus oral anticoagulant or antiplatelet alone. The authors’ concluded that “...combination therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications”. In fact, the use of anticoagulation therapy resulted in more life-threatening, moderate and minor bleeding compared to the use of antiplatelet alone. Moreover, in a sub-group analysis of the Chinese patients, there was an increased risk of MI, stroke, or death from cardiovascular causes. Overall oral anticoagulation using warfarin or acenocoumarol on top of antiplatelet therapy is not recommended for patients with PAD.

Delphi Issues:

The issue of the emerging evidence from the COMPASS trial on rivaroxaban (a selective direct factor Xa inhibitor) was raised, necessitating a revision of the AHA/ACC Statement to specify the class of anticoagulants studied in the evidence base for this statement⁵⁾. It was proposed and agreed upon to address separately the issue of rivaroxaban use. Two proposed statements were forwarded for discussions at the *En Banc* meeting.

Recommendation 36:

The use of low dose aspirin (100 mg OD) and rivaroxaban (2.5 mg BID) may be considered to reduce the risk of MI, stroke, cardiovascular death and limb-related events in patients with symptomatic PAD, having considered the associated risk of bleeding.

**Weak recommendation: (Class IIb);
Moderate level of evidence (Level B-R)**

This is a **new APSAVD/APPADC recommendation**; this issue was not discussed in the 2016 AHA/ACC Guidelines which was released prior to the release of the COMPASS trial results.

Summary of Evidence:

The COMPASS trial¹⁾ enrolled 7,470 patients with PAD from 558 hospitals, clinics or community practices in 33 countries, randomizing them to Rivaroxaban 2.5 mg BID + ASA 100 mg OD vs. ASA alone 100 mg OD vs. Rivaroxaban alone 5 mg BID. 6048 patients with symptomatic (81%) or asymptomatic (19%) PAD were included. The main reported result was that Rivaroxaban 2.5 mg BID + ASA 100 mg as compared to ASA 100 mg OD led to a significant ARR of 2% in major adverse cardiovascular events (composite endpoint of CV death, MI, or stroke). For the composite outcome of CHD death, ischemic stroke, MI or ALI, ARR was also 2%. The NNT for each of the composite outcomes was 50. For the pre-specified limb outcomes, the use of ASA + Rivaroxaban showed a 1.0% ARR for major adverse limb events and a 1.0% ARR for major adverse limb events plus major amputation. The NNT for each of the specified limb outcomes was 100. For the individual outcomes of MI, CV death and all cause death, the results were not significant (but the study was not powered to detect differences in the individual outcomes). However, in the individual outcome of stroke, there was an absolute risk reduction of 1.0%, with a NNT of 100.

Among the patients with PAD, the use of ASA + Rivaroxaban led to a 1.0% ARR for CV death, stroke, MI, or major adverse limb events and a 3.0% ARR for CV death, stroke, MI or major adverse limb events including major amputation. The NNTs for each of the specified limb outcomes were 100 and 33, respectively.

The risk of major bleeding (defined as composite of fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring operation, and bleeding that led to hospitalization) was increased by 1%, and was mostly gastrointestinal in nature. The risk of major bleeding increased by 61%,

ARH (Absolute Risk of Harm) of 1.0% and NNH (Number Needed to Harm) of 100. Fatal or critical organ bleeding was not significantly increased.

Based on the two prespecified net clinical benefit outcomes consisting of (1) CV death, MI, stroke and fatal or critical organ bleeding and (2) CV death, MI, stroke, or major adverse limb events, major amputation or fatal or critical organ bleeding, it was reported that “for every 1,000 patients treated, 27 major adverse CV events or major adverse limb events including major amputations would be prevented, while one fatal and one critical organ bleed would be caused over a 21-month period”. In view of these findings, the authors concluded that the “net clinical benefit favors the use of low-dose rivaroxaban plus aspirin”.

Dual therapy with Rivaroxaban 2.5 mg bid plus ASA 100 mg od, as compared with ASA 100 mg od, showed a significant reduction in major adverse cardiovascular and limb events among symptomatic patients with PAD. The risk for major bleeding was increased, but fatal or critical organ bleeding was not. However, it must be emphasized that the study enrolled high-risk symptomatic PAD patients, hence its applicability to this population and not to all symptomatic PAD patients. Furthermore, the 2.5 mg preparation of Rivaroxaban used in the study is not available in some APSAVD member countries.

Consensus Issues:

Two proposed statements were deliberated upon at the APPADC *En Banc* meeting on July 28, 2018: “The use of low-dose ASA and Rivaroxaban is reasonable to reduce the risk of limb-related events and cardiovascular events in patients at high risk of limb-related events, having considered the associated risk of bleeding” versus “The use of low-dose ASA and Rivaroxaban is reasonable to reduce the risk of MI, stroke, cardiovascular death and limb-related events in high risk patients with stable symptomatic PAD, having considered the associated risk of bleeding.”

After presentation of the appraisal of the COMPASS trial, it was emphasized that the discussion would focus on the Rivaroxaban 2.5 mg with ASA vs ASA alone data comparison. It was deemed to have no validity issues but directness and applicability issues in terms of the study population (P).

It was emphasized that participants from the Asia-Pacific region comprised only 14.4% of the entire COMPASS cohort. Issues were raised as to directness of the populations (P) studied. The study population recruited included high-risk symptomatic PAD patients (~81%), hence its applicability to high-risk populations, and not to symptomatic PAD patients

who are not high-risk. Also, the study included patients with symptomatic PAD and coronary artery disease with low ABI. It was pointed out that all included patients did not have lower limb PAD. Symptomatic PAD was defined as patients with previous aortofemoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac or infra-inguinal arteries, or previous limb or foot amputation for arterial vascular disease, or history of intermittent claudication and one or more of the following: ankle arm blood pressure ratio < 0.90 or significant peripheral arterial stenosis $\geq 50\%$ documented using angiography or duplex ultrasound or previous carotid revascularization or carotid artery stenosis of $\geq 50\%$ as diagnosed by duplex ultrasound or angiography and patients enrolled with CAD who had an ABI < 0.90). Baseline characteristics in the comparison groups were appraised to be similar. In the subgroup of *symptomatic* PAD patients, the low-dose Rivaroxaban and ASA combination therapy was favored in each outcome in the trial.

In terms of socioeconomic considerations, it was emphasized that the interventions used in the trial were Rivaroxaban 2.5 mg twice a day with 100 mg ASA once a day, compared with 100 mg ASA once a day alone. The prohibitive cost (e.g. \$2.20 per 2.5 mg tab in Singapore) and unavailability of the 2.5mg Rivaroxaban dose used in the study in most of the APSAVD countries were raised. Nevertheless, it was expressed that the unavailability of the 2.5 mg preparation of Rivaroxaban should not preclude the drafting of a guideline on its use, as having an explicit guideline on its use could drive countries to make it available.

It was agreed that the critical outcome of interest should be cardiovascular events (CV death, stroke or MI), thus guiding the wording of the proposed statement. It was agreed that the recommendation could not be a strong one, given that evidence was available from only one study with directness and applicability issues. In the overall analysis²⁾, but not in the subgroup of PAD alone, there was a subgroup for Asia-Pacific participants and the results show there was a reduction in the composite endpoint with the use of Rivaroxaban plus ASA. Further, in the main study, there was a significant 1% absolute risk increase (ARI) in major bleeding, with the use of Rivaroxaban and ASA, which was mostly gastrointestinal in origin. There was no significant difference in fatal or critical organ bleeding. For major bleeding, there was no subgroup analysis for the Asia-Pacific populations.

The viewpoint of the patient representative was sought. He described the physical and emotional

ordeal from a bleeding complication i.e. 3 days of hematuria arising from an accidental double dosing of his anticoagulant, warfarin. This served to drive home the important point of incorporating patients' values and preferences in the technical discussions.

The Panel members at the *en banc* meeting approved the statement "The use of low-dose Aspirin (100 mg OD) and Rivaroxaban (2.5 mg BID) may be considered to reduce the risk of MI, stroke, cardiovascular death and limb-related events in patients with symptomatic PAD, having considered the associated risk of bleeding. (Weak recommendation: (Class IIb); Moderate level of evidence (Level B-Randomized))

G. Cilostazol, Pentoxifylline, and Chelation Therapy

Recommendation 37:

Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with intermittent claudication.

**Strong recommendation: (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 5.7 was adopted. There was no literature from APSAVD member countries identified that required a revision of the AHA/ACC Statement.

Summary of Evidence:

It was reported in a meta-analysis of 8 studies by Bedenis *et al.*¹⁾ that cilostazol improved walking distance among patients with stable intermittent claudication. The analysis which compared cilostazol with either placebo or pentoxifylline suggested that patients given cilostazol (100 or 50 mg twice daily) had a significant improvement in initial claudication distance (ICD) compared with placebo (weighted mean difference or WMD 43 and 32 meters, respectively, $P=0.0007$). The treatment duration ranged from 6 to 26 weeks. No significant differences were observed between Cilostazol and Pentoxifylline. Cilostazol intake was associated with an increase in mild and treatable adverse side effects.

Cilostazol is available in some Asian countries but, in Australia, it is not available on the Pharmaceutical Benefits Scheme (PBS), a program of the Australian Government that provides subsidized prescription drugs to residents.

Recommendation 38:

Pentoxifylline is not effective for treatment of intermittent claudication.

**Moderate recommendation (Class III No Benefit);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.8 was adopted with no applicability issues identified. There was no literature identified from the APSAVD member countries that led to a revision of the AHA/ACC Statement 5.8. Appraisal of the references cited supported the statement.

Summary of Evidence:

The additional trials appraised¹⁻⁵⁾ also supported the recommendation that Pentoxifylline should not be used in patients with intermittent claudication because of the lack of benefit.

A 2011 meta-analysis by Squires H *et al.* included 26 RCTs comparing Pentoxifylline with placebo and Pentoxifylline with Cilostazol²⁾. This systematic review was not included in the citations within the AHA/ACC guideline. The majority of the trials comparing Pentoxifylline versus placebo did not show any significant benefit of the drug on mean walking distance, pain-free walking distance, ABPI or QoL. In comparison to Cilostazol, the effect of Pentoxifylline is uncertain since 1 study showed improvement with the former, 1 study showed improvement with the latter, while the others showed no significant difference.

Two trials by De Sanctis *et al.*^{3, 5)} which enrolled 120 and 194 patients with intermittent claudication randomized to either Pentoxifylline versus placebo showed that total walking distance improved significantly with Pentoxifylline compared with placebo at 6 and 12 months, with no reported adverse events. There was also a significant improvement in microcirculatory circulation with pentoxifylline compared to placebo. However, both trials had several validity issues, including potential for bias and high dropout rates.

A trial reported by Creager *et al.*⁴⁾ consisted of 430 patients with intermittent claudication and randomized patients between placebo, Iloprost (different doses) and Pentoxifylline. Although the trial specifically focused on the effects of Iloprost in patients with intermittent claudication, Pentoxifylline was used as one of the active treatment arms. There was a significant increase in absolute claudication distance in patients allocated Pentoxifylline compared to placebo, especially if the patient had a longer duration of PAD (12 months). However, the use of Pentoxifylline had no effect on initial claudication distance and overall quality of life.

A trial reported by Dawson *et al.*¹⁾ consisted of 699 patients with stable moderate to severe intermittent claudication randomized patients to Cilostazol versus Pentoxifylline versus placebo. The authors concluded that Cilostazol was significantly better than Pentoxifylline or Placebo in increasing walking dis-

tance in patients with intermittent claudication, with greater frequency of minor, self-limited side effects such as headache and diarrhea. Pentoxifylline was no better than placebo in increasing walking distance.

In the most recent meta-analysis by Salhiyyah K *et al.*⁶ which included 24 RCTs which enrolled 3,377 patients, due to the poor quality of published studies (no random sequence generation and allocation concealment, no clear report on blinding of assessors), large heterogeneity in interventions (dose and duration of treatment) and assessment of results (baseline walking distance and difference in baseline characteristics), the overall benefit of Pentoxifylline for intermittent claudication remained uncertain. In most studies, Pentoxifylline was shown to be well-tolerated, with mild nausea reported as the most common side effect.

Overall, in RCTs comparing Pentoxifylline with placebo, the effect of Pentoxifylline has been inconsistent. Also many of the trials had high risks of bias with respect to randomization of patients, blinding of patients, caregivers and outcome assessors and high dropout rates. Based on two systematic reviews it was concluded that Pentoxifylline did not significantly improve walking distance in patients with intermittent claudication^{2,6}.

Recommendation 39:

Chelation therapy (e.g., Ethylenediaminetetraacetic acid) is not beneficial for treatment of intermittent claudication. COR:

**Moderate recommendation (Class III No Benefit);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.9 was adopted with no applicability issues identified. No literature retrieved from the APSAVD member countries led to a revision of the Statement.

Summary of Evidence:

A meta-analysis by Villarruz *et al.*¹ which included 5 studies suggested no significant benefit with the use of EDTA chelation therapy in people with atherosclerotic cardiovascular disease. Moreover, the review reported a number of possible chelation therapy side effects such as faintness, gastrointestinal symptoms, proteinuria and hypocalcemia. Therefore, chelation is not recommended for patients with symptomatic PAD.

H. Homocysteine Lowering

Recommendation 40:

B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended.

**Moderate recommendation (Class III No Benefit);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 5.10 No literature specific to APSAVD member countries was found to support or refute the use of Vitamin B administration to lower homocysteine levels in PAD patients in order to prevent cardiovascular events.

Summary of Evidence:

Previously appraised evidence on the use of folic acid and Vitamin B supplementation to lower homocysteine levels among patients with PAD showed that it did not reduce cardiovascular events.

Randomized trials on patients with pre-existing CV disease or with diabetes and additional risk factors support that the use of Vitamin B supplementation to lower homocysteine level is not recommended in patients with PAD. Lonn *et al.*^{1, 2} studied 5,522 patients from 13 countries with preexisting CV disease or with diabetes and additional risk factors and compared combined folic acid, vitamin B6 and vitamin B12 with placebo. Although there were no validity issues, there was a limitation on directness since only 7.4% of the population had either intermittent claudication, surgical or endovascular revascularization for peripheral arterial disease. Nevertheless, the panel agreed with the authors' conclusion that the combination of folic acid, Vitamin B6 and B12 "had no beneficial effects on major vascular events in a high risk population with vascular disease."

In the meta-analysis cited by Khandappour³ in the AHA/ACC guideline, the outcomes were diverse, mostly mechanistic, with no report of cardiovascular events. Quality of studies included was also not mentioned. Hence, data from this analysis could not be used for a recommendation.

Overall, there is no evidence to support the use of Folate or B vitamin supplementation in PAD patients.

I. Influenza Vaccination

Recommendation 41:

Annual influenza vaccination can be considered for patients with PAD especially if they have established coronary artery disease.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 5.11 was revised because

of directness issues with the studies cited in the evidence for the AHA/ACC statement which involved patients with CAD or recent ACS. **The class of recommendation was downgraded from Class I to IIa.**

Summary of Evidence:

A trial in Thailand¹¹ as reported by Phromminitkul *et al.* randomized 439 patients with ACS to either influenza vaccine or placebo, and showed that vaccination reduced major adverse cardiovascular events. The trial however, did not include patients with PAD.

The studies cited in the evidence for the AHA/ACC recommendation involved patients with CAD or recent ACS¹⁻⁷. No patients with PAD were reported. However, although these trials did not specifically enroll participants with PAD, a majority of patients with PAD also have CAD³. A review of the literature revealed the following PAD population among CAD patients: a) PEGASUS TIMI 54⁸: 5% concomitant PAD among those with prior MI b) TRACER⁹: 7.2% patients with history of PAD among those with NSTEMI ACS and c) PLATO¹⁰: 6.1% PAD patients among those with ACS. The REACH registry, showed that among 40,258 patients with CAD, 4,298 (10.7%) had PAD¹¹. On the other hand, a case series of 78 patients by DJ Hur in 2012 showed that there was a 55% prevalence of significant CAD in patients with lower extremity PAD¹².

Two of the studies cited in the AHA/ACC statement had potential for bias, particularly that of the FLUVACS study¹³. One study in Korea looked into the cost-effectiveness of influenza vaccination among patients with acute coronary syndrome¹⁴. Using the Korean societal perspective, this study showed that vaccination among patients with ACS is highly cost-effective. However, the patient population also did not refer to patients with PAD, but those with acute coronary syndrome.

Delphi Issues:

One reviewer suggested “Annual influenza vaccination can be considered for patients with PAD especially if they have established coronary artery disease.” The suggested revision was approved by the Panel members.

J. Structured Exercise Therapy

Recommendation 42:

In patients with intermittent claudication, a supervised exercise program is recommended to improve functional status and quality of life and to reduce leg symptoms.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 6.1. was adopted without revision with no applicability issues identified. The AHA guidelines looked into outcomes such as improved functional status, reduced leg symptoms and improved quality of life. However, outcomes such as improvement in ankle-brachial index and adverse events were not reported. Additional references supported the statement and there were no references obtained that required a revision.

Summary of Evidence:

RCTs have shown that a structured exercise program can improve walking ability and functional status by increasing maximal walking distance, claudication onset time, pain-free walking time and six-minute walk test results. One trial included questionnaire assessments and reported that a supervised exercise program decreased walking impairment and improved walking speed and distance and quality of life measures. However, there is a need to further validate these quality of life measures in more RCTs.

A systematic review and metaanalysis by Lyu *et al.*¹ which included 18 RCTs comparing intensive walking exercise with usual care in PAD patients showed that intensive walking exercise significantly improved maximal walking distance, pain-free walking distance, six-minute walk test and quality of life measures, with no increase in adverse events compared to usual standard of care. Improvement was best noted among patients who presented with intermittent claudication compared to those who had no symptoms of claudication.

A small trial reported by Delaney *et al.*², on 35 patients randomized to 12 weeks of treadmill only supervised exercise therapy (SET) versus combined treadmill and lower-limb resistance SET, showed that SET improved pain-free walking distance and 6-minute walking distance in patients with intermittent claudication. Addition of lower limb resistance training on top of SET did not result in a further increase in distance.

SET was also compared to No exercise (NOET) Walking advice (WA), Home based exercise (HB-ET) in a meta-analysis of 30 RCTs (1,406 patients with intermittent claudication)³. SET was superior to other forms of ET in improving maximal walking distance and pain-free walking distance in patients with intermittent claudication. However, at 6 months of follow-up, the efficacy of home-based programmes may be equal to SET. Also outcomes were mostly assessed through a treadmill walking test which the SET group had trained on and this may have biased findings in some of the trials.

Another small trial (16 patients with intermittent

claudication and PAD) done in Australia⁴⁾ showed that a 6-month supervised exercise program improved walking economy and fat metabolism during submaximal walking, and maximal walking performance of patients with claudication. A 6-month supervised exercise program was effective in increasing pain-free walking time and maximal walking time in patients with intermittent claudication.

Percutaneous vascular intervention (PVI) with SET was compared to SET alone in an RCT including 70 patients with PAD at Rutherford stage 1-4⁵⁾. Supervised exercise therapy after percutaneous vascular intervention improved absolute and functional claudication distance. However, additional therapy did not result in reduction in claudication, improvement in WIQ score, improvement in ABI and HRQOL, and prevention of reinterventions, restenosis and occlusions.

Economic Evaluation:

There are several cost-effectiveness studies on structured exercise for PAD patients, however, none of these studies used the perspective of any APSAVD member country⁶⁻¹²⁾. This leads to applicability problems of the study results to any APSAVD member country.

A meta-analysis by Parmenter *et al.*¹³⁾ which included 41 RCTs (1938 patients) compared exercise treatment for more than 2 weeks versus medical care with or without exercise advice. Exercise treatment in patients with PAD improved functional measures including peak VO₂, claudication distances using the Gardner treadmill protocol and the 6-minute walk test, although no significant improvement in physiologic parameters such as the ABI and FMD was noted.

Overall, these trials suggest that exercise treatment in patients with PAD and claudication is effective in improving functional capacity.

Recommendation 43:

A supervised exercise program should be discussed as a treatment option for intermittent claudication before possible revascularization.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 6.2 was adopted without revision. No literature related to the APSAVD member countries was found that required a revision.

Summary of Evidence:

Previous literature appraised for the 2016 AHA/ACC guidelines consisted of a meta-analysis and RCTs.

A systematic review of 11 RCTs¹⁾ assessed exercise therapy in conjunction with or in comparison with endovascular or open intervention. Exercise therapy was reported to be an effective method to improve walking distance in PAD, whether alone, or as an adjunct to endovascular procedures or surgery. However, only endovascular procedures or surgery led to an increase in the ABI. Study limitations included the small number of patients in the trials, and number of patients lost to follow-up. A meta-analysis was not done due to heterogeneity in the outcomes reported.

The CLEVER study²⁾ randomized 111 patients with moderate-to-severe claudication due to aortoiliac PAD into optimal medical care (OMC) versus OMC plus SE versus OMC plus stenting. This trial showed that supervised exercise (SE) and stenting (ST) improved functional status and quality of life for at least 18 months compared to OMC in patients with moderate to severe intermittent claudication due to aortoiliac peripheral arterial disease. Both SE and ST improved pain free walking time, claudication onset time and quality of life measures. When comparing SE and ST, there was no significant difference in improvement in pain-free walking time and claudication onset time, but ST provided significant improvement in mean ABI and some Peripheral Artery Questionnaire (PAQ) measures. The trial was not designed to compare improvement in symptoms with SE followed by ST versus ST alone. This trial suggested supervised exercise and stenting are effective in improving functional capacity of patients with intermittent claudication, by improving pain-free walking time and claudication onset time until 18 months of follow-up. Furthermore, since no difference in functional outcomes were observed between exercise and stenting, exercise can be offered to patients with intermittent claudication rather than percutaneous revascularization.

Another RCT reported by Fakhry *et al.*³⁾ randomized 151 patients with stable intermittent claudication to SET versus endovascular revascularization (ER). SET-first or ER-first treatment strategies were equally effective in improving functional performance and quality of life (QoL) in patients with intermittent claudication, 7 years after intervention. However, there were more invasive interventions in the ER-first group compared to SET-first treatment. Furthermore, major amputations were more common with the ER-first treatment strategy. Several limitations were noted in this study: a significant number of patients were lost to follow-up (more with SET); high mortality and attrition rate may have reduced the study's power to detect small differences between the 2 groups; those with ipsilateral multilevel disease (iliac and femoral)

were excluded to avoid multiple revascularization procedures (results may not be applicable to this subset) and no information was available on regular exercise performance of the patients after the trial.

Finally, an RCT⁴⁾ included 178 patients with symptomatic unilateral intermittent claudication compared PTA versus SEP versus PTA plus SEP. This trial (included in the AHA guidelines) showed that SEP, PTA and the combination improved symptoms and QoL measures in patients with intermittent claudication.

These trials support the value of supervised exercise in improving functional capacity in patients with claudication due to PAD. They also suggest that endovascular interventions can improve functional outcomes. Most of the trials have limited follow-up and there is some concern about the long-term durability of both therapies. There is a concern with endovascular therapy that because of durability issues many patients return for repeat intervention which can ultimately end up in major amputation for some patients. Thus interventional management of intermittent claudication should be limited to patients with lifestyle-limiting symptoms after a trial of all conservative therapies, including exercise therapy.

Recommendation 44:

In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status.

**Moderate recommendation (Class IIa);
High level of evidence (Level A)**

AHA/ACC Statement 6.3. was adopted without revision. No literature from APSAVD member countries was identified that required a revision of this statement.

Summary of Evidence:

Additional literature appraised consisted of a meta-analysis and a RCT. A systematic review by Fokkenrood et al included 14 RCTs¹⁾, involving 1002 patients with PAD, and reported that supervised exercise programs improved maximal walking distance and pain-free walking distance more significantly than non-supervised exercise programs. In the Asia-Pacific region, however, where supervised exercise programs are found infrequently, more studies are needed comparing the use of supervised exercise treadmill-based programs versus home-based exercise programs, specifically on functional outcomes, cost and long-term outcome.

A pilot RCT reported by Mays *et al.*²⁾ included

25 PAD patients and compared a comprehensive community-based walking exercise program with standard advice to walk. Peak walking time did not improve in patients with PAD but patient-reported outcomes such as claudication onset time and walking impairment improved significantly. However, due to the small sample size, use of community-based exercise programs in patients with PAD still needs to be studied in future trials.

RCTs included in the 2016 AHA/ACC Guidelines showed that structured community- or home-based exercise program with behavioral change techniques can improve walking ability and functional status by increasing maximal walking distance, claudication onset time, pain-free walking time and the six-minute walk test. Furthermore, walking impairment questionnaire speed and distance, and quality of life measures improved in one study. Further trials are needed to validate these findings.

Recommendation 45:

In patients with intermittent claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate-to-maximum claudication while walking, can be beneficial to improve walking ability and functional status.

**Moderate recommendation (Class IIa);
High level of evidence (Level A)**

AHA/ACC Statement 6.4 was adopted without revision. No literature from APSAVD member countries was identified. However, exercise programs are not readily available in some institutions/centers in APSAVD member countries.

Summary of Evidence:

Studies previously cited in 2016 AHA/ACC statement on the usage of exercise programs in PAD patients with intermittent claudication showed evidence that exercise programs improve walking ability and functional status.

A meta-analysis of 41 RCTs involving 1938 patients by Parmenter *et al.*¹⁾ compared exercise for more than 2 weeks to medical care with or without exercise. The analysis showed that exercise in patients with PAD improved functional measures (peak VO₂ and claudication distance), although no significant improvement in physiologic parameters (ABI, FMD) was noted. Based on subanalyses, the authors also proposed that exercising to mild pain may have better outcomes than exercising to moderate or maximal pain.

IV. Minimizing Tissue Loss in Patients with PAD

Recommendation 46:

Patients with PAD and diabetes mellitus should be counseled about self-foot examination and healthy foot behaviors aimed at reducing the risk of foot ulcers or amputation.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 7.1 was adopted but **reworded to specify the outcomes of interest for which limited data from additional literature was deemed to show benefit.** No issues on applicability were identified.

Summary of Evidence:

Additional literature by Ren *et al.*¹⁾ consisted of a prospective cohort of 185 patients at high risk for foot disease. After a median follow-up of 2 years, Intensive nursing education resulted in a decrease in the incidence of foot ulceration from 41.2% to 11.1%.

In the meta-analysis of 12 RCTs by Dorresteyn *et al.* which included patients with either type 1 or type 2 diabetes mellitus, only 5 trials reported the effect of patient education on foot ulceration or ulcer recurrence and amputation²⁾. A RCT of 354 patients by Malone *et al.*³⁾ showed benefit of an hour of group education by a podiatrist compared to usual care. The intervention reduced the incidences of foot ulceration and amputation by 69% and 67%, respectively. This approach needs to be further validated, however.

Recommendation 47:

In patients with PAD, prompt diagnosis and adequate treatment of foot infection are recommended to reduce risk of amputation.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 7.2 was **revised to emphasize the outcome of prevention of amputation.** A directness issue was raised since all patients in the studies cited had diabetes. There were no data from patients with PAD and no diabetes.

Summary of Evidence:

Additional literature appraised supported this Statement. A case-control study by Chiu *et al.*¹⁾ among 736 patients in Taiwan showed that patients in a Diabetic Foot Ulcer Treatment Program (DFUTP) had a lower amputation rate than the non-DFUTP group ($p=0.001$).

In another observational cohort reported by Pickwell *et al.*²⁾, which included 575 patients with

new foot ulcers, the incidence of amputation increased with increasing redness, peri-wound or pre-tibial edema, the presence of pus, lymphadenitis / lymphangitis, fever, elevated CRP levels, and increasing IWGDF category.

In a meta-analysis by Dinh *et al.*³⁾, of 9 cohort studies of DM patients with foot ulcers with suspicion of osteomyelitis, the presence of exposed bone or a positive probe-to-bone test were moderately predictive of osteomyelitis. MRI is the most accurate imaging test for diagnosis of osteomyelitis.

Recommendation 48:

In patients with PAD and signs of foot infection, prompt referral to an interdisciplinary care team, when available, can be beneficial to reduce the risk of amputation and promote wound healing, in addition to administration of infection control measures.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 7.3. was adopted but **reworded to specify the outcomes of interest.** No issues on applicability were identified. New references were appraised that further supported this statement.

Summary of Evidence:

In some institutions, a Diabetic foot ulcer (DFU) service is available; this is an integrated service that is primarily composed of a vascular surgeon, podiatrist, and endocrinologist as well as a physician assistant, prosthetist, and wound care nurse. Using this approach, Mathioudakis, *et al.* observed an enhanced ulcer healing time¹⁾.

A retrospective cohort study reported by Armstrong *et al.*²⁾, included 374 patients with diabetic foot complications requiring foot surgery or vascular intervention with Class 2 (prophylactic), class 3 (curative) and class 4 (emergency) procedures using the classification of non-vascular diabetic foot surgery. They found a significant reduction in surgery classified as urgent foot surgery after introduction of an integrated multidisciplinary team ($p<0.0001$).

In a trial reported by Chiu *et al.*³⁾, patients in Taiwan with infected diabetic foot ulcers with or without ischaemia were randomized to a diabetic foot ulcer treatment programme (DFUTP) group versus control. The treatment group had a lower amputation rate than the non-DFUTP group ($p=0.001$).

Recommendation 49:

It is reasonable to counsel patients with PAD without diabetes mellitus about self-foot examination and healthy foot behaviors to prevent amputations and ulcers.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 7.4. was revised to **include the outcome of interest.** No issues on applicability were identified.

Summary of Evidence

No references were found that required a different recommendation.

Recommendation 50:

Among patients with PAD and diabetes mellitus, foot examination should be included in every clinic visit.

**Strong recommendation (Class I);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 7.5 was revised to **emphasize that doing foot examinations in PAD patients with diabetes is important for detection of early signs of foot ulcers and prompt management. The class of recommendation was upgraded from Class IIa to Class I.** No issues on applicability were identified.

Summary of Evidence

No new evidence for this research question was retrieved.

Delphi Issues:

Experts emphasized that doing a foot examination in PAD patients with diabetes is essential for detection of early signs of foot ulcers and prompt management. Since the patients visit their clinicians regarding their blood sugar levels and other concerns, this visit should be an opportunity to also perform a foot examination.

A reference underscoring the need for preventive counseling was suggested by one of the Panel members. i.e. Berger JS, Ladapo JA Underuse of prevention and lifestyle counseling in patients with peripheral artery disease. *J Am Coll Cardiol*, 2017 May 9; 69(18): 2293-2300. doi: 10.1016/j.jacc.2017.02.064. The suggested reference refers to a survey of ambulatory visits over a period of 8 years. It described patterns of care of different healthcare providers (seeking to “evaluate trends in medical therapy and lifestyle counseling among PAD patients”). Since this study

did not directly address the Research Question it was not included in the list of References.

V. Revascularization for Claudication**Recommendation 51:**

Revascularization for intermittent claudication is a reasonable treatment for the patient with lifestyle-limiting intermittent claudication with an inadequate response to optimal guideline-directed medical therapy.

**Moderate recommendation (Class IIa)
High level of evidence (Level A)**

AHA/ACC Statement 8.1 was **adopted but reworded.** Most of the studies included in the 2017 meta-analysis by Pandey *et al.*¹⁾, (comparing endovascular therapy with SET) are from Europe. This may limit the generalizability of study findings to many APSAVD member countries.

Summary of Evidence:

Overall, prior clinical trials and metaanalyses suggest that both supervised exercise and endovascular therapy alone or together can improve walking distance during short-term follow-up in PAD patients. Prior trials do have a number of limitations including small sample sizes (range of $n=23-1435$)¹⁻³⁾. Heterogeneity in functional endpoints, single-arm observational study design, and poor subgroup reporting significantly limit comparative effectiveness analysis in PAD. Other limitations with past PAD studies like short follow-up periods and inconsistent medical management made it difficult to infer as to whether exercise therapy decreases long-term mortality.

A RCT showed primary invasive treatment strategy in combination with current best medical therapy (BMT) improved patient-reported HRQOL more than current BMT alone⁴⁾. Invasive treatment improved pain-free walking distance, but not MWD on the graded treadmill. Improved HRQOL by invasive treatment seems to be related mainly to an improved pain-free walking distance. However, compliance with BMT, which included smoking cessation, statin therapy, antiplatelet therapy, glucose-lowering treatment and nonsupervised exercise advice, was not optimal and persistent throughout the study duration in both groups.

A more recently published meta-analysis⁵⁾ reported that the combination of endovascular therapy with SET significantly improved maximal walking distance and lowered the risk of downstream revascularization or amputation. The authors recommend that revascularization can be considered as an adjunctive therapy to SET but not as a primary treatment

option for intermittent claudication.

On the other hand, another recent meta-analysis of RCTs updated the 2013 meta-analysis (of RCTs plus observational studies by the same author) showing that there was limited data on effectiveness of bypass surgery compared with other treatments^{6, 7}. Percutaneous Transluminal Angioplasty (PTA) was associated with decreased peri-interventional complications and shorter hospital stay and advisable in patients with significant comorbidity and high surgical risk.

A recent prospective cohort study⁸ followed outpatients with symptoms of intermittent claudication and a diagnosis of PAD for a mean(SD) of 5 (3.37) years. Based on variation in the practices of different vascular specialists, patients were either treated by early revascularization or received initial conservative treatment. The primary outcome was the requirement for major amputation. Thirty-nine percent underwent early revascularization while the rest had initial conservative treatment. The estimated 5-year major amputation rate was 6.2% and 0.7% in patients undergoing early revascularization and initial conservative treatment respectively ($P=0.003$). Early revascularization was associated with an increased requirement for major amputation in models adjusted for other risk factors. Patients presenting with intermittent claudication who underwent early revascularization appeared to be at higher risk of amputation than those who had initial conservative treatment. Hence, the management of patients with PAD using GDMT prior to revascularization appears to be the better approach.

Further studies may have to be done to address these differences in outcomes of different treatment options for intermittent claudication that may be due to heterogeneity in methodology.

Economic Evaluation:

There are no cost-effectiveness studies on revascularization and exercise therapy for claudication that are applicable to APSAVD member countries because of different study contexts – U.S., Netherlands, U.K. (population, societal or NHS perspectives).

A. Endovascular Revascularization for Claudication

Recommendation 52:

Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting intermittent claudication and hemodynamically significant aortoiliac occlusive disease, although the long-term benefit of treatment is less clear.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 8.1.1.1 was adopted but reworded to emphasize that only short-term outcomes have been reported in the available randomized trials. As noted earlier, most of the studies included in the 2017 meta-analysis by Pandey *et al.*, (compared endovascular therapy with SET) are from Europe¹. This may limit the generalizability of study findings to many APSAVD member countries.

Summary of Evidence:

Additional references further support the above AHA/ACC statements^{1, 2}.

In a 2017 meta-analysis by Pandey *et al.*¹, the combination of endovascular therapy with SET significantly improved maximal walking distance and lowered the risk of downstream revascularization or amputation. The authors recommended that initial revascularization be considered as an adjunctive therapy to SET but not as a primary treatment option in the initial management of intermittent claudication.

A RCT by Fakhry *et al.*² demonstrated that patients allocated to a combination of endovascular therapy plus supervised exercise exhibited significant improvement in maximum walking distance, pain-free walking distance, VasuQOL score and Sf-36 physical functioning score compared to supervised exercise alone.

Another RCT by Spronk *et al.*³ demonstrated that the revascularization group had clinical benefit compared to exercise shortly after the start of treatment. However, this benefit was lost over time. Revascularization reduced ipsilateral symptoms at 6 months, but this did not translate into improved clinical success, functional capacity, or quality of life when compared with exercise training. Endovascular revascularization or supervised hospital-based exercise in patients with claudication yielded similar benefits in terms of clinical success, functional capacity, and quality of life after 6 and 12 months of follow-up. One of the limitations was that balloon angioplasty rather than primary stent placement of the femoral artery was the initial approach to endovascular treatment in this study. Older generation stents without clopidogrel with inferior patency compared to newer generation stents (with clopidogrel) were also used. Exercise treatment was also noted to have an advantage because symptoms of the contralateral extremity are treated as well.

On the other hand, a RCT by Greenhalgh *et al.*⁴ showed statistically significant improvements in the PTA group for AWD, ICD, and SF36 physical score. Findings lend weight to the value of angioplasty for intermittent claudication for up to 24 months for either aortoiliac or femoropopliteal disease. However, the study was limited by small sample size.

In a RCT by Nylaende *et al.*⁵⁾, among patients with PAD, there were no differences in ABI from baseline in the OMT group compared to OMT+PTA group. Difference in changes between the two groups in terms of this outcome was statistically significant. PFW and MWD increased significantly for both groups compared to baseline, though significantly more in OMT+PTA group. Visual assessment scale for pain decreased significantly for both groups, although also significantly more in the OMT+PTA group. For QoL assessment, there was significant improvement on the domain of physical functioning after 24 months for the OMT+PTA group. INTRA-group, the reported health transition were improved up to 24 months for both groups ($p < 0.0001$). Notable difference in QoL between the groups were shown in the results from the CLAU-S form, but only up to 12 months (domain of pain during activity and pain severity). This difference disappeared after 12 months.

Delphi Issues:

One panelist challenged the statement on the uncertainty of long-term benefits of endovascular treatment. Additional references supporting 5-year durable outcomes for endovascular treatment of aortoiliac disease (>90% patency rate at 5 years) were proposed.

Recommendation 53:

Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting intermittent claudication and hemodynamically significant TASC A and B femoropopliteal disease although the long-term benefit of treatment is less clear.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 8.1.1.2 was adopted but reworded to emphasize that only short term outcomes have been reported in literature.

Summary of Evidence:

Previous literature for the 2016 AHA/ACC Statement 8.1.1.2 consisted of mostly RCTs plus one systematic review.

In a randomized trial by Nordanstig *et al.*¹⁾ including patients with lifestyle-limiting intermittent claudication, primary invasive treatment strategy (either open or endovascular) in combination with current BMT improved patient-reported HRQOL more than current BMT alone, [mainly owing to improved physical functioning, vitality and reduced pain among patients with either iliac or femoropopliteal

teal PAD)]. Invasive treatment improved pain-free walking distance, but not MWD on the graded treadmill. Improved HRQOL by invasive treatment seems to be related mainly to an improved pain-free walking distance. The observed improvement in pain-free treadmill walking distance seems to translate to an important benefit in terms of symptom reduction.

In another RCT by Hobbs *et al.*²⁾ comparing the adjuvant benefits of supervised exercise and PTA over BMT in patients with mild to moderate IC (defined as an absolute claudication distance [ACD] of 50-500 m on a treadmill), consistent improvement in the BMT+PTA group on ABI, ICD and ACD outcomes was noted. There were no significant symptomatic improvements in the supervised exercise group, although this may be a consequence of the design of the exercise program, its twice-weekly nature (augmented by unsupervised home exercise), and its 12-week duration. The lack of an observed treatment effect of BMT plus supervised exercise may be attributed to a type II statistical error.

In a RCT by Mazari *et al.*³⁾ comparing supervised exercise (SEP) vs angioplasty (PTA) vs SEP+PTA, the lack of a statistically significant difference between the treatments at 12 months in ICD and MWD was noted. This can be explained by a ceiling effect as a consequence of capping the treadmill test at 5 min (215 m). Although no statistically significant difference was observed between the three treatments after 12 months, the fact that no patient in the PTA plus SEP group deteriorated or required reintervention by 12 months is clinically significant. Restenosis rates in PTA and PTA plus SEP groups were comparable. Thus, combining SEP with PTA did not reduce the risk of restenosis, but prevented it from becoming symptomatic, leading to sustained clinical improvement. Limitations were inclusion of only patients with symptomatic, unilateral femoropopliteal arterial disease (representing only 15 – 20 % of patients with IC) as well as more than anticipated loss to follow-up in the SEP and PTA plus SEP groups due to patient withdrawal from hospital-based SEP.

In a systematic review of RCTs by Malgor *et al.*⁴⁾ comparing revascularization (either open or endovascular), exercise therapy, and medical management, blood flow parameters (e.g., ABI) improve faster and better with both forms of revascularization compared with nonsurgical management with exercise or medical management. These parameters, however, were not necessarily correlated with clinical improvement. Evidence supporting superiority of one of the three approaches is limited, although it seemed that the combination of SE and invasive revascularization may be superior to SE alone. However, endovascular inter-

ventions and surgical bypass come at a significant expense, can have limited durability, and may be associated with morbidity and mortality. Data on which intervention is best suited for a particular patient to obtain the best outcome are also lacking.

As earlier cited, Spronk *et al.*⁵⁾ reported that the clinical success observed in the revascularization group over exercise therapy was short-lived, with both groups experiencing similar benefits of clinical improvement after 6 and 12 months of follow-up.

A RCT by Gelin *et al.*⁶⁾ comparing SEP, Invasive treatment (open or endovascular) and observation (given general advice) showed that at 1 year follow-up, significant improvement was found for physiological parameters (maximum walking power, stopping distance, post-ischemic blood flow and big toe pressure) in the invasively treated group only (no delineation whether surgical or endovascular).

As cited earlier, Greenhalgh *et al.* reported clinical improvement in AWD and ICD after PTA which lasted for up to 24 months for either aortoiliac or femoropopliteal disease.

Nordanstig *et al.*⁸⁾ compared invasive (ASA or ticlopidine, hypertension management, smoking cessation advice + invasive: either endovascular or open) versus noninvasive (ASA or ticlopidine, hypertension management, smoking cessation advice) intervention. This study in unselected IC patients failed to show significantly improved maximal walking performance with a primary invasive versus a primary non-invasive treatment strategy. Invasive treatment resulted in moderate to large positive HRQOL effects regarding physical role function and pain. Evidence supports improved HRQOL with invasive treatment

Lastly, a RCT by Whyman *et al.*⁹⁾ comparing PTA (POBA) + medical treatment ($n=30$) versus control (medical treatment alone) ($n=32$) showed that in patients with claudication due to single discrete femoral artery lesions, PTA produces a greater short-term improvement in walking and quality of life than medical treatment alone and is associated with less progression of disease.

Delphi Issues:

One Panel reviewer commented that TASC A and B¹⁰⁾ are preferably treated by endovascular measures. TASC D lesions are preferably treated by surgical measures when cost-effectiveness issues are a concern in the relevant hospital. Another Panel reviewer questioned though whether TASC classification is still being used.

The suggestion to combine Statements 8.1.1.1 and 8.1.1.2 was reiterated however it was decided to keep the Recommendations separate because they

have different COR and LOE.

Recommendation 54:

The usefulness of endovascular procedures as a revascularization option for patients with intermittent claudication due to isolated infrapopliteal artery disease is unknown.

**Weak recommendation (Class IIb);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 8.1.1.3 was adopted with no applicability issues identified.

Summary of Evidence:

A RCT by Schulte *et al.*¹⁾ comparing self-expanding bare stents (nitinol) ($N=45$) versus PTA (POBA) ($N=47$) showed that based on their clinical observations and TLR, there is no evidence that primary stenting is superior to PTA with bailout stenting in short and medium infrapopliteal lesions.

Another RCT by Rastan *et al.*²⁾ comparing polymer-free sirolimus-eluting stents with a placebo-coated bare-metal stent found that stent treatment of focal infrapopliteal arterial lesions can be improved with the use of sirolimus-eluting stents compared with bare-metal stents.

A RCT by Siablis *et al.*³⁾ comparing paclitaxel-coated balloons (PCB) ($N=25$ arteries in 25 limbs) versus drug-eluting stents ($N=30$ arteries in 27 limbs) showed that infrapopliteal use of PCB, compared with DES, was associated with statistically significantly higher binary vascular restenosis at the 6-month time point. Use of DES is associated with significantly better immediate residual post-procedure stenosis and lower vessel restenosis than use of PCB when used in long infrapopliteal lesions.

Recommendation 55:

Endovascular procedures should not be performed in patients with asymptomatic PAD or stable intermittent claudication solely to prevent progression to critical limb ischemia.

**Strong recommendation (Class III Harm);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 8.1.1.4 was revised to **specify patients with asymptomatic PAD or stable intermittent claudication since the previous 3 recommendations applied to patients with PAD with lifestyle-limiting claudication.** No applicability issues were identified. There were no additional references obtained that would lead to a change in the Statement.

Summary of Evidence:

No additional literature was appraised aside from those cited in the AHA/ACC guidelines:

Leng *et al.*¹⁾ did a prospective cohort on 1592 subjects of the Edinburgh Artery Study, men and women aged 55-74, to check the natural history of PAD. After a 5-year study period, only 15.2% of the major asymptomatic group and 7.1% of the minor asymptomatic group developed claudication. Among patients with baseline claudication, only 8.2% underwent vascular surgery or amputation and 1.4% developed a leg ulcer.

Several studies have also demonstrated that peripheral endovascular procedures incur considerable costs and significant complications, which discourages their use in patients with asymptomatic PAD or stable intermittent claudication.

In a retrospective cohort, Sachs *et al.*²⁾ compared demographics, costs and comorbidities as well as in-hospital mortality and major amputation of patients who underwent PTA, peripheral bypass graft or aorto-femoral bypass from 1999-2007. They noted a three-fold increase in the number of patients undergoing PTA, with the average cost for PTA also increasing by 60%. Mortality was slightly lower with PTA but amputation rates for limb-threat patients appear higher. The mortality benefit with PTA may also be lost if multiple interventions are performed on the same patients.

A retrospective cohort by Shammam *et al.*³⁾ showed that clinically significant distal embolization requiring further mechanical or pharmacologic therapy occurs in approximately 2.4% of patients undergoing peripheral percutaneous interventions. Patients with TASC-D lesions, angiographic thrombus and prior history of amputation are at high risk of distal embolization.

B. Surgical Revascularization for Claudication**Recommendation 56:**

When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 8.1.2.1 was adopted with no applicability issues identified.

Summary of Evidence:

Additional literature appraised consists of 2 prospective cohort studies and 2 retrospective cohort studies supporting the recommendation that when

surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material. The RCT appraised, however, due to its limitations, did not reach a conclusion.

A noninferiority RCT by Midy *et al.*¹⁾ included patients who underwent above-knee femoropopliteal bypass using either autologous vein ($n=44$) or polyester or expanded polytetrafluoroethylene (PTFE) graft ($n=52$). Although recruitment could not reach the required numbers, the patency rate in the prosthetic group was nevertheless higher than that obtained in the autologous vein group, whatever the type of analysis carried out. Because of the number of patients who died or were lost to follow-up, it was not possible to reach a conclusion regarding the noninferiority of prosthetic bypasses compared with venous bypasses.

A prospective cohort study by Suckow *et al.*²⁾ comparing infrageniculate bypass with either single-segment saphenous vein or prosthetic conduit for CLI found that prosthetic infrapopliteal bypass grafts can perform competitively with single-segment saphenous vein grafts given appropriate patient selection.

Loh *et al.* conducted a single-center retrospective cohort involving³⁾ patients undergoing revascularization to below knee targets with using either Distaflor (ePTFE) grafts or rSVG. In the BK popliteal position, Distaflor grafts offer early patency comparable with rSVG but have significantly poorer mid- and long-term patency. Patency and limb salvage rates of the Distaflor bypasses were similar to those of standard PTFE bypasses.

A retrospective cohort study by Moreira *et al.*⁴⁾ included all patients who had undergone infrageniculate bypass originating from the common/superficial femoral artery for CLI. Conduit type did not affect outcomes for femoral to below-knee popliteal bypass for major adverse limb events and freedom from MALE, as well as primary patency loss. GSV is not significantly better for below-knee popliteal bypass than alternative autologous conduits. Non-autologous conduits are marginally better than alternative autologous conduits for below-knee popliteal bypass. This demonstrates that if the GSV is unavailable, choice of conduit for infrageniculate targets should depend on the location of the outflow anastomosis. Use of NAC to BK-Pop targets when GSV is unavailable was recommended due to similar outcomes but significantly lower blood loss compared with AAC.

Another retrospective cohort study by Avreginos *et al.*⁵⁾ categorized patients ($N=407$) into 3 groups, depending on the conduit used: GSV (great saphenous vein; primary conduit of choice; $N=255$), AAV (alternative autologous veins) (small saphenous veins,

arm veins, or spliced segments; $N=106$), or prosthetic (expanded polytetrafluoroethylene or heparin-bonded PTFE; $N=46$). Results showed AAV conduits may not offer any significant advantage over prosthetic bypass for below-knee targets at midterm follow-up. The authors also recommended a more thoughtful selection of candidates for AAV and rigorous ultrasonographic surveillance. Maintenance of long-term patency may also require frequent reinterventions.

A meta-analysis by Twine *et al.*⁶⁾, comparing different graft types for either above the knee or below the knee bypass grafting, showed that autologous vein grafts have long term patency benefits over synthetic polymers. In the long term (greater than two years), Dacron may confer a slight primary patency benefit over PTFE for above-knee bypass procedures. However, the authors reported that there was limited high quality evidence to indicate which graft type should be used for above the knee bypass procedures.

Another meta-analysis by Pereira *et al.*⁷⁾ which aimed to assess the long-term patency of femoropopliteal bypass grafts classified as above-knee PTFE, above-knee saphenous vein, or below-knee saphenous vein, found that great saphenous vein grafts performed better than PTFE in femoropopliteal bypass grafting.

Hunink *et al.*⁸⁾ in a meta-analysis compared PTA versus surgery. They found that saphenous vein grafts have better patency compared to PTA and PTFE grafts. In certain circumstances, equivalent patency between PTA and bypass surgery using PTFE was noted.

Recommendation 57:

Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting intermittent claudication with inadequate response to GDMT, acceptable perioperative risk, in whom technical factors do not favor an endovascular-first approach.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 8.1.2.2. was adopted but reworded; new evidence shows no advantage of endovascular therapy over surgical procedures for patients with intermittent claudication with acceptable perioperative risk in terms of primary vessel patency, and long-term amputation-free survival and patient survival. **The level of evidence was upgraded from B-NR to B-R (Randomized).** No issues on applicability were identified.

Summary of Evidence:

Additional relevant literature appraised consists

of a 2017 update¹⁾ to a 2013 meta-analysis and a retrospective cohort²⁾.

The 2017 meta-analysis of RCTs by Antoniou *et al.*¹⁾, updated the 2013 meta-analysis (of RCTs plus observational studies by the same author)³⁾ Meta-analysis of studies comparing bypass surgery vs. Percutaneous Transluminal Angioplasty (PTA) showed that a higher technical success rate was associated with bypass surgery but this was accompanied by a possible increase in post-interventional non-thrombotic complications. Peri-interventional complications were more frequently seen in patients with CLI undergoing bypass surgery rather than PTA. Primary patency rate was higher in bypass surgery at 1 year but this was not shown after 4 years. No difference in peri-procedural mortality, clinical improvement, amputation rates, reintervention rates or mortality rates within follow-up were identified. The authors observed that PTA was associated with decreased peri-interventional complications and shorter hospital stay and may be advisable for patients with significant comorbidity and high surgical risk.

A retrospective cohort by Wiseman *et al.*⁴⁾, which included patients over age 65 years who underwent an open or endovascular lower extremity revascularization procedure, found that endovascular approach is associated with improved long-term amputation-free survival. For patients with intermittent claudication, there is no significant difference between endovascular or surgical intervention in terms of combined 30-day post-op amputation or mortality, and amputation, and mortality rates.

Darling²⁾, in a retrospective cohort, showed that bypass-first approach was associated with improved wound healing, fewer restenosis and interventions, increased total hospital length of stay and wound infection, perioperative mortality and amputation rates were similar. On this basis, for appropriately selected patients, bypass may be preferred in the mid-term and long term in relatively fit patients expected to live >2 years, the apparent improved durability and reduced reintervention rate of open surgical bypass could outweigh the short-term considerations of increased morbidity, especially in those with an available and suitable single-segment great saphenous vein conduit

A meta-analysis by Antoniou *et al.*³⁾ comparing endovascular versus open surgery for the treatment of femoropopliteal arterial occlusive disease concluded that endovascular-first approach may be advisable in patients with significant comorbidity, for fit patients with a longer-term perspective, bypass procedure may be offered as a first-line interventional treatment.

Another meta-analysis by Fowkes *et al.*⁵⁾ included

all randomised controlled trials of bypass surgery versus control, or any other regimen (angioplasty, exercise therapy, and medical treatment) and compared surgical bypass versus other types of intervention (medical, exercise therapy, or angioplasty). They found that for patients with intermittent claudication, on the outcome of primary patency: surgery may be considered. For the outcome of mortality in 30-days, no pooled analysis could be obtained. There is a trend towards less mortality using endovascular intervention. No pooled analysis was obtained for outcomes on progression to amputation and complications of intervention. Thus, evidence for the effectiveness of bypass surgery for intermittent claudication is lacking.

Recommendation 58:

Femoral-tibial artery bypass should not be performed for the treatment of intermittent claudication.

**Strong Recommendation (Class III Harm);
Moderate level of Evidence (Level B-R)**

AHA/ACC Statement 8.1.2.3. was adopted but reworded. The appraised additional evidence supported the Recommendation.

Summary of Evidence:

A prospective cohort study authored by Loh *et al.*¹⁾ compared infrainguinal bypasses using either precuffed expanded polytetrafluoroethylene (ePTFE) grafts ($N=101$) versus reversed great saphenous vein grafts (rSVG) ($N=47$). However, only 5.9% and 14.9% of the patients had precuffed ePTFE graft surgery and vein graft surgery, respectively, for intermittent claudication as the indication for revascularization. In the tibial position, Distaflo graft performed significantly worse compared with vein grafts at all time points. Limb salvage rates were lower compared with the vein group. Patency and limb salvage rates of the Distaflo bypasses were similar to those of standard PTFE tibial bypasses reported historically.

A retrospective cohort by Avreginos *et al.*²⁾ included patients who were categorized in three groups, depending on the conduit used: ($N=407$), GSV (great saphenous vein; primary conduit of choice) ($N=255$), AAV (alternative autologous veins) (small saphenous veins, arm veins, or spliced segments) ($N=106$), and prosthetic (expanded polytetrafluoroethylene or heparin-bonded PTFE) ($N=11\%$). However, the indication for surgery was critical limb ischemia in 96%. They found that AAV conduits may not offer any significant advantage over prosthetic bypass for below-knee targets at midterm follow-up. More thoughtful selection of candidates for AAV,

including patients needing a distal infrapopliteal bypass (good life expectancy and low risk for a perioperative complication, or those with active infection). Rigorous ultrasonographic surveillance is essential for success and frequent reinterventions should be anticipated to maintain long-term patency.

Previous literature consisted of 1 RCT and cohort studies. Veith *et al.*³⁾ randomized patients to autologous saphenous vein (ASV) versus polytetrafluoroethylene (PTFE) grafts for intermittent claudication. Results fail to support the routine preferential use of PTFE grafts for either femoropopliteal or more distal bypasses. This graft may be used preferentially in selected poor-risk patients for femoropopliteal bypasses, particularly those that do not cross the knee.

Recommendation 59:

Surgical procedures should not be performed in patients with PAD solely to prevent progression to CLI.

**Strong recommendation (Class III Harm);
Moderate level of evidence (Level B-NR)**

ACC/AHA Statement 8.1.2.4 was adopted since additional literature supported the Statement.

Summary of Evidence:

Additional literature appraised consisted of a systematic review and a retrospective cohort:

In a systematic review by Van Den Maijer¹⁾ which included patients who had undergone above or below the knee femoropopliteal bypasses in which complications within the first 30 days post-op, overall morbidity rate was 37%. However, according to reviewers, there was inconsistent reporting of morbidities. There is no part in the study that defines what the symptoms of the patients are, except to surmise the symptoms from the Rutherford class. The statement specifically says “for peripheral artery disease” patients “to prevent progression to critical limb ischemia.” This study includes patients with Rutherford 4/5/6 (31%), with 33% unspecified. Only 36% belongs to Class 3. There is no delineation per class as to percentage of morbidities.

A retrospective cohort by Collins *et al.*²⁾ evaluated patients with PAD diagnosed by ABI of <0.90 and observed for all-cause mortality following lower extremity bypass surgery or lower extremity amputation (above or below knee major procedures only). PAD severity was a marker for mortality following lower limb revascularization. Those ≥ 70 years had increased risk for mortality following lower extremity bypass surgery. Again, the majority of patients included had moderately severe to critical PAD.

Delphi Issues:

Issues were raised that the proposed statement “Surgical procedures should not be performed in patients with asymptomatic PAD or stable claudication. COR: III (Harm) LOE: B-NR” could be confusing being that “patients with PAD” include both asymptomatic PAD, patients with stable claudication and those with lifestyle-limiting claudication. Since the research question was worded as “Among patients with PAD with or without claudication, what is the association of surgical bypass procedures to mortality and adverse events (bleeding, adverse limb outcomes, major adverse cardiovascular events)?”, proposed revisions to the Statement were not approved.

VI. Management of Critical Limb Ischemia**A. Revascularization for CLI****Recommendation 60:**

In patients with CLI, revascularization should be performed when possible to minimize tissue loss.

**Strong Recommendation (Class I);
Moderate Level of Evidence (Level B-NR)**

AHA/ACC Statement 9.1.a was adopted. The evidence quoted for this research question is for the natural history of untreated CLI. A literature search showed only evidence comparing surgical versus endovascular treatment revascularization, which is not a direct answer for this question. No issues on applicability were identified.

Summary of Evidence:

A meta-analysis by Abu Dabrh *et al.*¹⁾ included 13 studies (8 RCTs included only the placebo or untreated arms plus 5 case series). Enrolled patients must have rest pain, tissue loss, ulcer, or gangrene; meet the criteria for Rutherford class 4 to 6; or have an ankle pressure <70 mm Hg, toe pressure <50 mm Hg, flat pulse volume recording, or transcutaneous oxygen pressure <40 mm Hg. They found that mortality and major amputations are common in those patients who have untreated CLI.

Recommendation 61:

An evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI to minimize tissue loss.

**Strong recommendation (Class I);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 9.1.b was revised to specify the outcome of the interest. No issues on applicability were identified. There are no/additional

references that would support a different statement/recommendation.

Summary of Evidence:

There is no direct evidence for this research question.

Delphi Issues:

It would be useful to describe the composition of the interdisciplinary team, as this interdisciplinary team may not be feasible in all centers. Two additional studies were suggested by a Panel reviewer: 1) a retrospective study by Chung J, Modrall G, Ahn C, *et al.*, entitled “Multidisciplinary care improves amputation-free survival in patients with chronic critical limb ischemia. *J Vasc Surg*, 2015; 61: 162-169,” compared multidisciplinary team approach (MDC) to standard wound care (SWC) among CLI patients irrespective of whether or not revascularization will be done 2) Suzuki H, Maeda A, Maezawa H, *et al.* “The efficacy of a multidisciplinary team approach in critical limb ischemia. *Heart Vessels*, 2017 Jan; 32(1): 55-60. doi: 10.1007/s00380-016-0840-z. Epub 2016 Apr 22. PMID: 27106919” did not have a comparator group, i.e., all patients in the study were provided the multidisciplinary team approach. Nevertheless, both had directness issues and thus were not added to the evidence base, and the LOE was maintained at EO rather than revised to LD, as suggested.

B. Endovascular Revascularization for CLI**Recommendation 62:**

Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 9.1.1.1 was adopted with no revisions. No issues on applicability were identified. Studies done in the Asia-Pacific region also support the Statement.

Summary of Evidence:

One meta-analysis of moderate quality RCTs, one systematic review of one RCT and 22 observational studies, one systematic review of 3 RCTs and 6 cohort studies, and moderate-quality evidence from one RCT, the BASIL trial, were appraised¹⁾. Based on the BASIL trial, both endovascular and surgical revascularization can establish in-line blood flow to the foot in patients with CLI, including those with non-healing wounds or gangrene, with endovascular intervention best suited for patients whose life expectancy

is approximately two years. Over time, surgical revascularization using a vein conduit is a better option. In the meta-analysis, systematic review, registries and cohort studies, endovascular revascularization had a high technical success rate, increased patency rate, improvement in ankle-brachial index (ABI), time to wound healing and amputation-free survival during the immediate post-procedural period and up to several years of follow-up. Some studies also showed shorter hospital and intensive care unit stay, with low complication rates.

A meta-analysis by Xiaoyang *et al.*²⁾ included 7 RCTs of angioplasty versus bypass for CLI. There was no significant difference between angioplasty and bypass surgery in amputation-free survival and leg salvage at 1 year, 3 years and 5 years from the intervention. Although mortality within 30 days from intervention was significantly lower in the angioplasty group, the significant difference was not noted at subsequent follow-ups in 1, 3 and 5 years. The limitations include small sample size, randomization and double-blinding, with some trials terminated early due to poor enrollment. They reported that, in patients with CLI, angioplasty was not more effective than bypass surgery in amputation free survival and leg salvage from the first to fifth year of intervention. However, angioplasty has a lower mortality rate during the first month of intervention compared to bypass surgery.

A systematic review by Abu Dabrh *et al.*³⁾ included 9 studies on 3071 subjects with CLI. The 3 RCTs and 6 cohort studies suggest that bypass surgery and endovascular intervention in patients with CLI may have similar effects on mortality and major amputation, while better primary and primary assisted patency can be expected with surgery. This review however was limited by significant heterogeneity between studies. It was concluded that, in patients with CLI, endovascular revascularization and bypass surgery were equally effective in establishing in-line blood flow to the foot, which can result in reduction in major amputation, with better patency rates with surgery.

A systematic review by Jones *et al.*⁴⁾ included 23 studies comparing endovascular versus surgical revascularization among patients with CLI. There were no significant differences in mortality or limb outcomes between endovascular and surgical revascularization in patients with CLI. The review was also limited by the inclusion of only 1 RCT and several observational studies. In this review, among patients with CLI, an endovascular procedure is not more effective than surgical revascularization in establishing in-line blood flow to the foot. Both procedures showed the same mortality and limb outcome rates. Further RCTs need to be done to compare the two procedures.

A prospective cohort study by Iida *et al.*⁵⁾ in 2015 included 314 patients with CLI and investigated stenting w/ nitinol stents on femoral artery lesions and balloon angioplasty alone on infrapopliteal lesions (DES and balloons for femoropopliteal lesions and atherectomy devices for femorotibial lesions not available during the study). This was a 3-year outcome registry of Japanese patients with CLI who underwent EVT. Although initial success rate was high, only half of patients will have an amputation-free survival in 3 years, with increased age, low BMI, dialysis and Rutherford class 6 as predictors of initial hazard rates during the first 6 months of intervention of the index limb. Furthermore, wound recurrence rate was high, especially for isolated BTK lesions. Although the study evaluated outcomes of patients who had common clinical conditions, it also had several limitations: it was a single-arm study rather than a RCT versus bypass surgery; it only included Japanese patients, and ulcer recurrence at 1 to 3 years was not evaluated at a central lab. Among patients with critical limb ischemia due to infrainguinal lesions, endovascular therapy was effective in establishing in-line blood flow to the foot during the immediate intervention period. However, there was a high reintervention rate over time, with reduced amputation-free survival in 3 years, particularly in high-risk patients, including those with increased age, low BMI, on hemodialysis, and with Rutherford Classification 6.

Another prospective cohort study by May *et al.* in Singapore in 2014⁶⁾ included 229 symptomatic limbs and compared angioplasty with or without stenting when feasible versus bypass surgery for patients contraindicated for angiogram, with arterial obstruction not feasible for endovascular intervention or unsatisfactory revascularization after endovascular treatment. Although patients included were a mix of CLI and claudication, majority of the patients were those who presented with ulcer or gangrene. Satisfactory clinical outcomes were achieved with the use of an endovascular strategy, with acceptable limb salvage rates and survival at 1 and 2 years. Among patients with CLI, an endovascular procedure was effective in establishing in-line blood flow to the foot for up to 2 years, and can result in acceptable limb salvage and amputation-free survival rates.

A prospective cohort study by Tan *et al.*⁷⁾ in 2010 included 46 patients with CLI enrolled into the PTA treatment arm of the LEAP study done in Singapore. PTA in diabetic patients with CLI had a high technical success rate, and resulted in improvement in ankle-brachial index, reduction in pain and improvement in ulcer healing during the perioperative period, with a 66% limb salvage rate at 3 years of follow-up.

The limitations include potential confounders (adherence to diabetic regimes and risk factor modification shown to be important in altering the outcome in CLI), lack of anatomical evidence for long-term patency and the relatively short-term follow-up of 3 years. Among diabetic patients with CLI, PTA was effective in establishing in-line blood flow to the foot during the immediate postoperative period and up to three years of follow-up.

Another prospective multicenter study by Iida *et al.*⁸⁾ in 2013 included 312 Japanese patients with *denovo* CLI and investigated an EVT strategy left to the discretion of the treating physicians at each center. SFA lesions were treated with provisional nitinol stenting, whereas popliteal and below-the-knee (BTK) lesions were treated with balloon angioplasty without stenting. In patients with CLI due to below the knee lesions, EVT was successful during the immediate period post-intervention, with a high amputation free survival rate at 6 months and 12 months. Low BMI, heart failure and wound infection were identified as risk factors for amputation. Reintervention rate was also high, with low BMI and wound infection identified as risk factors. Among patients with CLI, endovascular procedures were effective in establishing in-line blood flow to the foot during the immediate postoperative period. However, patients with low BMI, heart failure and wound infection were at risk for lesser amputation-free survival rates and reintervention.

In a retrospective review by Tay *et al.*⁹⁾, 40 patients with CLI with chronic total occlusions (CTO) had endovascular retrograde intervention in Singapore. Retrograde SAFARI technique in those with chronic total occlusions was safe and feasible, with a high technical success and limb salvage rates. In patients with nonhealing wounds or gangrene, retrograde endovascular procedure using the SAFARI technique may be effective in establishing in-line blood flow to the foot, which can result in high limb salvage rates.

A retrospective cohort study by Nakama *et al.* in 2017¹⁰⁾ focused on patients with CLI with infrapopliteal arterial disease who underwent EVT at 5 centers in Japan. Patients who underwent pedal artery angioplasty had significantly higher rate of wound healing and shorter time to wound healing compared to those who did not undergo the procedure. Independent predictors of delayed wound healing included: nonambulatory status, wound depth, and daily hemodialysis. Among patients presenting with CLI, endovascular intervention, particularly pedal artery angioplasty, was effective in establishing in-line blood flow to the foot and resulted in improvement in ABI, higher wound healing rates and shorter time to wound healing, with

no significant increase in peri-procedural complications.

A retrospective cohort study by Katib *et al.* in 2015¹¹⁾ done in Australia showed that an endovascular-first treatment strategy was associated with fewer major amputation and shorter length of hospital and ICU stays. In patients who had major amputations, renal disease, more severe Rutherford category, use of tobacco, and dementia were identified as independent predictors for limb loss. In those with CLI, endovascular-first strategy was effective in establishing in-line blood flow to the foot during immediate and postoperative period up to 8 years, resulting in less major amputations and shorter hospital stay.

A retrospective cohort study published by Bae *et al.* in 2013¹²⁾ included 189 limbs of 152 Korean patients (mean age 67 year-old), including rest pain (category 4) in 45 (24%) limbs and non-healing wound (category 5, 6) in 144 (76%) limbs. Endovascular revascularization was effective in wound healing in patients with CLI and can be performed without significant complications. Although recurrence rate is high, limb salvage rates are also high after 1 and 3 years of follow-up. Since patients with CLI have several comorbidities, endovascular revascularization should be considered as first-line therapy in patients with CLI. In patients with nonhealing wounds or gangrene, endovascular procedures was effective in establishing in-line blood flow to the foot, which can result in high limb salvage rates.

Nakano *et al.* in 2013¹³⁾ included 406 patients with CLI with isolated infrapopliteal artery lesions in 465 limbs in a retrospective registry of Japanese patients with endstage renal disease who underwent balloon angioplasty for CLI. Although hemodialysis (HD) patients have a higher repeat revascularization rate and lower major amputation-free survival compared to non-HD patients, isolated infrapopliteal balloon angioplasty was an effective treatment in this subgroup of patients. Non-ambulatory status, presence of gangrene and higher CRP levels are strong predictors of poor prognosis and amputation or death after endovascular treatment in HD patients with CLI. This study is limited by its non-randomized, retrospective design and treatment strategies offered included only balloon angioplasty. Furthermore, primary patency was not assessed because majority of patients had TASC D lesions and calcified vessels, which are difficult to evaluate with duplex ultrasound, so TER rate was evaluated instead. Balloon angioplasty may offer technical success resulting in effective in-line flow to the foot during the immediate stage of intervention in dialysis patients with CLI. This however was counter-

acted by higher rates of reintervention, amputation and death, especially in those who are non-ambulatory, with gangrene and with high CRP levels.

Park *et al.*¹⁴⁾ included 616 patients who had infrainguinal intervention in Korea. EVT including balloon angioplasty with or without stent placement for CLI in diabetic patients with CTO of the BTK arteries resulted in high limb salvage rate despite discrepancies in patency rates, with no significant 30-day complication rate. Limitations included its retrospective case review nature, short-term follow-up and evaluation rate; Doppler ultrasound and transcutaneous pre and postoperatively were not performed during follow-up. Among diabetic patients with CLI and CTO of the BTK arteries, balloon angioplasty with or without stent deployment was effective in establishing in-line blood flow to the foot during the immediate 30-day postoperative period, resulting in high limb salvage rate.

Another retrospective cohort study by Khandolkar in 2016¹⁵⁾ included 34 patients who had endovascular reconstruction of popliteal and/or infrapopliteal arteries for CLI and >70% stenosis on DSA, with clinical follow-up of at least 3 months. This was a study performed in a hospital in India. Endovascular revascularization of popliteal and infrapopliteal arteries was feasible, safe and effective for the treatment of CLI, with majority of patients enrolled, achieving successful limb salvage. In this study, among patients with nonhealing wounds or gangrene, endovascular revascularization was effective in establishing in-line blood flow to the foot, which can result in successful wound healing, clinical improvement and limb salvage

Recommendation 63:

A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 9.1.1.2 was adopted with no revisions. No issues on applicability were identified despite the absence of a specific trial which studied patients with ischemic rest pain who underwent endovascular intervention in the Asia-Pacific region. For the intervention (I) of endovascular procedures, most outcomes (O) in the evidence obtained only centered on patency rates, amputation rates, rates of repeat revascularization, which are not the only outcomes of interest in patients with ischemic rest pain. Outcomes such as reduction in pain and improvement in quality of life were not regularly reported.

Summary of Evidence:

Additional literature consisted of 1 RCT and 5 cohort studies with issues in directness because population studied were patients with CLI in general, and only a small population of patients with ischemic rest pain were included. Based on the available RCT and cohorts, it is reasonable to use a staged approach and address inflow disease first in patients with ischemic rest pain, as part of the spectrum of patients with CLI. However, not all clinically significant outcomes were addressed. Outcomes focused on good patency and limb salvage rates while reduction in pain and improvement in quality of life were not addressed.

A recent RCT by Spreen *et al.*¹⁾ randomized 144 limbs in 137 patients into DES arm ($N=74$ patients, 75 limbs) versus PTA-BMS ($N=67$ patients, 69 limbs) and concluded that long-term amputation and event-free survival in CLI due to infrapopliteal lesions is more favorable after DES treatment compared with conventional endovascular strategy of PTA-BMS, with higher patency rates with DES use. The trial was limited by the fact that a number of patients were physically unable to undergo sonography of the treated limb. Although the trial included patients with ischemic rest pain, there was no subgroup analysis to determine improved outcome in this subset, hence, it is not certain whether the results can be extrapolated to this group. Among patients with CLI, including those with ischemic rest pain, the use of DES was more effective in reducing amputation and major event rates compared to bare metal stents. Due to limited analysis of patients with ischemic rest pain, however, more studies need to be performed to test the effectiveness of DES in this subgroup.

Another recent RCT by Spreen *et al.*²⁾ randomized 144 limbs in 137 patients Rutherford category 4 to PTA+/-BMS versus DES. There was a significant reduction in residual stenosis after DES compared to PTA +/-BMS among patients with CLI attributable to infrapopliteal artery disease. However, this did not result in significant reduction in major amputation and survival rates. Although minor amputation was significantly reduced during the initial 6 months after the procedure, this result was not sustained beyond 6 months. Periprocedural complications and adverse events were similar in both endovascular interventions. Only a small percentage of the population presented with ischemic rest pain. Among patients with ischemic rest pain whose inflow lesions have been addressed, both PTA using either BMS or DES have good patency rates. Whether this would result in reduction in pain and improvement in quality of life needs to be studied further.

A registry by Tsai *et al.*³⁾ included 883 patients

undergoing peripheral endovascular intervention (PVI) versus 975 patients undergoing Lower Extremity Bypass (LEB). In PAD patients undergoing revascularization, endovascular intervention was associated with higher rates of reintervention at 1 and 3 years after the procedures compared to bypass. However, there were lower rates of complications noted immediately after the procedure, until 30 days of follow-up. In terms of amputation rates, no significant difference between the two was noted. The study has an observational design and potential bias may be seen in the intervention applied. Also, drug-eluting stents and advanced retrograde tibial techniques were not widely used yet during the trial, and both techniques may potentially improve outcome of endovascular intervention. Furthermore, patency rates does not necessarily translate to symptom improvement, an outcome of interest particularly in patients presenting with ischemic rest pain. In patients with ischemic rest pain, a staged endovascular procedure to address inflow lesions is effective in reducing amputation rates, with lower morbidity during the immediate postoperative period, at the expense of higher rates of repeat intervention. Based on the results, it is not known whether improvement in patency rates translated to improvement in clinical outcomes such as reduction in rest pain and improvement in quality of life. Hence, more trials need to be done specifically to address this subgroup of patients.

A prospective cohort by Rocha *et al.*⁴⁾ investigated percutaneous transluminal angioplasty (PTA) with stent using Xpert™ self-expanding nitinol stent in 120 target limbs. In patients with CLI, angioplasty with stenting using nitinol stents resulted in a high periprocedural success rate, with relatively acceptable rates of freedom from target lesion revascularization. The study limitations were its cohort nature, short-term follow-up and only a small percentage of patients with rest pain, but data were analysed separately according to Rutherford class and 60% of patients included were reported to have their inflow lesions addressed first. All patients with ischemic rest pain had amputation-free survival and freedom from major amputation. Furthermore, pain was significantly reduced after 6 months and 12 months of treatment. In patients with ischemic rest pain, a staged endovascular procedure to address inflow lesions first then subsequent angioplasty with stenting using a nitinol stent can result in reduction of pain and reduce risk of amputation.

A prospective cohort by Dorros *et al.*⁵⁾ investigated tibioperoneal vessel angioplasty. Angioplasty of inflow and infrapopliteal arterial lesions in patients with CLI resulted in immediate periprocedural high patency rates. Five years after revascularization,

patients presenting with rest pain required fewer surgical revascularization and amputation compared to patients presenting with ulceration and gangrene. Furthermore, there was a higher event-free 5 year-survival among Fontaine Class III patients compared to Fontaine Class IV patients, reiterating the fact that with more severe peripheral arterial disease, the higher risk for mortality. Among patients with CLI, a staged endovascular procedure to address inflow lesions first was effective in reducing the degree of stenosis. In patients with ischemic rest pain, angioplasty to reduce inflow and subsequent tibioperoneal disease will reduce the need for surgical bypass and amputation.

A retrospective cohort by Ryer *et al.*⁶⁾ investigated angioplasty +/- stent used as a first-line therapy for all with stenosis >50% or occlusion of an infringuinal vessel in CLI. Patients with CLI who underwent PTA with or without stenting showed that this intervention can result in high rates of long-term patency and no significant morbidity and mortality. Lower patency rates were seen among those with TASC D lesions, gangrene/ulcers and diabetes. An initial failed endovascular intervention also did adversely affect the ability to perform a second endovascular procedure or surgical bypass. However, only a small proportion of patients (12%) included presented with rest pain. Furthermore, outcomes such as reduction in pain and improvement in quality of life were not assessed in the study. Among patients with CLI, a staged endovascular procedure to address inflow lesions first was effective in reducing the degree of stenosis, which can persist over time, unless the patient has a TASC D lesion, with ulcer or gangrene or with diabetes. Further studies on patients with ischemic rest pain need to be performed to see reduction in pain and improvement in quality of life.

A prospective cohort by Gray *et al.*⁷⁾ included 23 patients and investigated Laser-assisted angioplasty w/ balloon dilation and stenting. The population included patients presenting with ulceration or gangrene, and not patients with ischemic rest pain. Endovascular treatment resulted in a high technical success rate during the immediate postoperative period, with improvement in ABI, reduction in ulcer area, and improvement in symptoms and limb salvage. However, since no patients presenting with ischemic rest pain alone were included, the results cannot be translated to this subset of patients. Only a small number of patients were enrolled, and angiography was not routinely performed at follow-up so durability of arterial patency could not be investigated. Among patients with nonhealing wounds or gangrene, an endovascular procedure was effective in establishing in-line blood flow to the foot, which can result in improvement of ABI,

reduction in ulcer area, limb salvage and improvement of symptoms. However, further studies need to be done on patients with ischemic rest pain alone.

Delphi Issues:

A “staged approach” to endovascular procedures was clarified to mean that in patients with ischemic rest pain, a staged endovascular procedure to address inflow lesions first then subsequent angioplasty with stenting of more distal lesions can result in reduction of pain and reduce the risk of amputation.

Recommendation 64:

Evaluation of the imaging findings of peripheral artery disease and correlation with clinical profile can be useful in selecting the endovascular approach for CLI.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 9.1.1.3 was revised for clarity. No issues on applicability were identified.

Summary of Evidence:

There was moderate quality evidence from three RCTs and two cohort studies (one of these cohort studies, the OLIVE Registry was done in Japan). Based on the available RCT and cohorts, it is reasonable to evaluate lesion characteristics in patients with critical limb ischemia before selecting whether balloon angioplasty alone or balloon angioplasty with stenting should be performed. Although better patency rates were seen with drug eluting stents, this did not consistently translate into important clinical outcomes such as reduction in amputation rates, better wound healing and improvement in pain. Most outcomes in the evidence obtained focused on patency rates, amputation rates and rates of repeat revascularization, while other important outcomes such as reduction in pain and improvement in quality of life were not regularly reported.

A RCT by Spreen *et al.*¹⁾ included 144 limbs and compared DES arm versus PTA-BMS. Long-term amputation and event-free survival in CLI due to infrapopliteal lesions were more favorable after DES treatment compared with conventional endovascular strategy of PTA-BMS, with higher patency rates with DES use. Among patients with CLI, use of DES was more effective in reducing amputation and major event rates compared to bare metal stents.

Another RCT, also by Spreen *et al.*²⁾ showed a significant reduction in residual stenosis after DES compared to PTA +/-BMS among patients with CLI attributable to infrapopliteal artery disease. However,

this did not result in significant reduction in major amputation and survival rates. Although minor amputation was significantly reduced during the initial 6 months after the procedure, this result was not sustained beyond 6 months. Periprocedural complications and adverse events were similar in both endovascular interventions. The study limitations included the following: (1) not all had reduced ABI (significant number of patients have diabetes, which may cause arterial calcification, hence, a falsely elevated ABI); (2) lesions were assessed by CTA and not conventional angiography, (3) patients who had amputation of the index limb or died from progressive ischemia were considered treatment failures. Finally, only a small percentage of the population presented with ischemic rest pain. Although DES resulted in better patency rates in patients with CLI due to infrapopliteal arterial occlusive disease, this did not translate into any significant clinical outcomes.

A randomized study by Francesco *et al.*³⁾ (with PROBE design) showed that angioplasty with drug eluting balloon stenting of tibial vessels in patients with CLI showed a significant reduction in binary stenosis, target lesion revascularization and vessel occlusion at 12 months. Although major amputation was not significantly reduced (which may be due to low rates of amputation seen in the study), use of DEB resulted in faster and more complete ulcer healing rates. However, this study was done in a single, high-volume center which may have a specific interventional technique; moreover the investigator was not blinded. Use of drug eluting stents after balloon angioplasty resulted in better patency rates, less target lesion revascularization and better wound healing rates in patients with diabetes and CLI with complex anatomic lesions.

A prospective cohort study by Iida *et al.*⁴⁾ described earlier included patients with CLI without major amputation whose lesions were limited to infrainguinal artery and investigated stenting with nitinol stents on femoral artery lesions and balloon angioplasty alone on infrapopliteal lesions. This was a 3-year outcome registry of Japanese patients with CLI who underwent EVT. Only around half of the patients had amputation-free survival in 3 years. The study group was a sicker population with around half on maintenance dialysis.

A prospective cohort study by Feiring *et al.*⁵⁾ investigated BTK stenting to establish straight-line flow to the foot in one tibial vessel. This prospective cohort showed that use of DES is safe and effective in preventing major amputations and relieving symptoms in patients with CLI attributable to below the knee lesions. However, the study was a nonrandom-

ized, single-center and single-operator trial, which may introduce potential bias. The study was also not designed to evaluate angiographic restenosis.

Delphi Issues:

A panel reviewer suggested addition of two references: 1) from Japan: Ohki T, Kichikawa K, Yokoi H, *et al.* Outcomes of the Japanese multicenter Viabahn trial of endovascular stent grafting for superficial femoral artery lesions. *Vasc Surg*, 2017 Jul; 66(1): 130-142.e1. and 2) Darling JD, McCallum JC, Soden PA, *et al.* Results for primary bypass versus primary angioplasty/stent for lower extremity chronic limb-threatening ischemia. *J Vasc Surg*, 2017 Aug; 66(2): 466-475. Epub 2017 Mar 6. 3) Antoniou GA, Georgiadis GS, Antoniou SA, *et al.* Bypass surgery for chronic lower limb ischaemia. *Cochrane Database Syst Rev*, 2017 Apr 3; 4: CD002000.

Suggested articles were not included due to directness issues. Although the statement is about evaluation of lesion characteristics to assist in planning for the endovascular approach, the papers do not directly answer the statement.

Recommendation 65:

Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene.

**Weak recommendation (Class IIb);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 9.1.1.4 was adopted. No issues on applicability were identified despite scarcity of references among the APSAVD member countries. Additional references (including the study in Japan by Nakayama *et al.*) support the above recommendation.

Summary of Evidence:

Additional literature appraised consists of a systematic review and cohort studies supporting the use of angiosome-directed endovascular therapy in CLI with nonhealing wounds or gangrene since it has been shown to be effective in improving wound-healing rates. Several cohort studies showed conflicting data regarding amputation rates. Although the systematic review done recently by Jongsma *et al.* showed both faster wound healing rates and reduction in amputation rates, the studies included were cohort studies.

A recent systematic review by Jongsma *et al.*¹⁾ investigated direct revascularization versus indirect revascularization. This systematic review concluded that direct revascularization significantly improves wound healing and major amputation rates after endovascular treatment in CLI. The results however,

are less applicable to bypass surgery because the bypass is anastomosed to the least affected artery, with runoff passing the ankle to maintain patency. Despite the high quality of studies included, most of these studies were retrospective case series and may be at risk for selection bias. Direct revascularization through angiosome-directed treatment via endovascular intervention can be effective in improving wound healing and reducing major amputation rates in patients with CLI, particularly those with ulceration and gangrene.

A recent multicenter retrospective cohort by Nakama *et al.*²⁾ investigated an EVT procedure – Dual-antiplatelet (ASA 100 mg/d and clopidogrel 75 mg/d or cilostazol 200 mg/d) given before EVT and continued as long as possible. This retrospective study was done in Japan and showed that patients who underwent pedal artery angioplasty had significantly higher rate of wound healing and shorter time to wound healing compared to those who did not undergo the procedure. Independent predictors of delayed wound healing included: nonambulatory status, wound depth, and daily hemodialysis. Among patients presenting with critical limb ischemia, endovascular intervention, particularly pedal artery angioplasty, can be beneficial in wound healing with no significant increase in periprocedural complications.

A retrospective analysis by Iida *et al.*³⁾ investigated angiosome-oriented direct revascularization versus indirect revascularization. This propensity matching analysis of this retrospective cohort study in patients with CLI showed that there was a significantly better wound-healing rate in those who were treated through angiosome-directed revascularization. However, major amputation and reintervention rates were not reduced compared to indirect revascularization. These results are not applicable to diabetic patients presenting with infection, a high-risk group of patients who often present with CLI. In patients with CLI, direct revascularization via angiosome-directed treatment can be beneficial in wound healing but does not affect amputation rates.

Lastly, Aerden *et al.*, in a cohort study⁴⁾ discussed the use of angiosomes to identify areas, which need revascularization. The database used was a registry of patients scheduled for below-the-knee revascularization. The paper concludes that there is difficulty in using angiosomes to guide revascularization due to the “ambiguity in wound stratification” and “heterogenous presentation of diabetic foot wounds.” Although the conclusion of the paper does not directly support the statement, it agrees that angiosomes “may be reasonable” to be used for some but not all patients.

C. Surgical Revascularization for CLI

Recommendation 66:

When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e., tibial, pedal) should be constructed with suitable autogenous vein.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 9.1.2.1 was adopted without revisions and with no issues on applicability identified.

Summary of Evidence:

Additional literature consists of a systematic review, RCT, and three retrospective cohort studies that support the recommendation for patients who underwent surgery for CLI to have bypass to the popliteal or infrapopliteal arteries with a suitable autogenous vein to ensure better patency rates during the perioperative period up to three to five years after revascularization. Limitations include not analyzing other outcomes such as limb survival and improvement in quality of life.

A systematic review by Twine *et al.*¹⁾ investigated at least two graft types selected from autologous vein (reversed or *in situ*), HUV, PTFE, Dacron, composite grafts and heparin bonded grafts. Autologous vein compared to synthetic materials had significantly better primary patency rates when used as conduit for above knee bypasses. Dacron showed a primary patency benefit over PTFE above knee bypass after long term follow-up. PTFE with a vein cuff showed better primary patency rates compared to PTFE for below the knee bypass. The study only looked into patency rates and did not analyze outcomes such as limb survival and improvement in quality of life. As alternatives, Dacron followed by PTFE with a vein cuff may be secondary choices. However, more RCTs are needed to study the latter. The study had several limitations: it was a non-randomized, retrospective trial; there were more prior bypass surgeries in the HePTFE group compared to the vein group, and the lengths of the HePTFE bypasses had to bridge were greater than the vein bypasses. Therefore, in patients with CLI who will undergo tibial or peroneal bypass surgery, bypass should be constructed with a suitable autologous vein to ensure better patency rates during the perioperative period to 3 years after revascularization.

A RCT by Klinkert *et al.*²⁾ investigated reversed saphenous venous bypass vs polytetrafluoro-ethylene (PTFE) bypass among 151 above-knee femoropopliteal bypasses. In patients with severe intermittent clau-

dication, rest pain or ulceration requiring surgical bypass, use of saphenous veins compared to PTFE had significantly better patency rates at all time intervals up to five years of follow-up, with fewer reoperations observed.

A retrospective cohort study by Arhuidese *et al.*³⁾ investigated autogenous conduit (59%) versus prosthetic conduit (41%) among 9,739 infrainguinal open bypass in hemodialysis patients during a 5-year study period. This study showed that the use of autogenous conduits compared to prosthetic conduits for surgical bypass in patients on hemodialysis and PAD resulted in better patency rates and lesser acute graft infection and acute limb loss within the immediate 30-day perioperative period. Long-term outcomes at the fifth year after intervention also showed significantly better primary and secondary patency rate, with younger age, diabetes, impaired functional status and tissue loss as observed predictors of limb loss.

Another retrospective cohort by Uhl *et al.*⁴⁾ investigated autologous vein graft (reversed, non-reversed) versus heparin-bonded expanded polytetrafluoroethylene (HePTFE) conduit. In patients with CLI who underwent tibial or peroneal bypass surgery, autologous veins compared to PTFE grafts showed better primary and secondary graft patency and limb salvage rates, within the immediate perioperative period, and at 1 and 3 years of follow-up. The study, however, had several limitations: it was a non-randomized, retrospective trial; there were more prior bypass surgeries in the HePTFE group compared to the vein group, and the lengths of the HePTFE bypasses had to bridge were greater than the vein bypasses.

Lastly, a retrospective cohort by Arvela *et al.*⁵⁾ showed that arm vein conduits are superior to prosthetic grafts in terms of midterm assisted primary patency, secondary patency and leg salvage in infrapopliteal bypasses for CLI.

Recommendation 67:

Surgical procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 9.1.2.2 was adopted with no revisions. No issues on applicability were identified. Studies done in the Asia-Pacific region also support the recommendation.

Summary of Evidence:

One systematic review of nonrandomized trials (includes two cohort studies of Japanese patients) and several cohort studies with limitations in design were

appraised. Although several cohort studies on the use of surgical revascularization in patients with CLI, either in comparison to endovascular intervention or through surgical bypass comparing different grafts, showed that in-line blood flow to the foot can be established, this outcome was measured differently in these studies. Furthermore, although the population included patients with CLI, analysis for patients with ischemic rest pain compared to those with ulceration and gangrene were not done separately.

A systematic review by Hinchliff *et al.*¹⁾ investigated bypass surgery or endovascular therapy or both. Included nonrandomized studies in diabetic patients with PAD presenting with foot ulceration showed that revascularization improved limb salvage rates compared to no revascularization. Note however that there was heterogeneity of studies due to different baseline characteristics and outcomes measured, and several trials were at high risk for bias. Hinchliff *et al.* did not give a definite conclusion as to which revascularization method is better.

A RCT by Popplewell *et al.*²⁾ investigated Vein Bypass ($n=56$) versus Plain Balloon Angioplasty ($n=48$) among 108 patients with infrapopliteal disease. Based on this subgroup analysis of patients in the BASIL trial who presented with CLI secondary to infrapopliteal disease, there was no significant difference between vein bypass and endovascular intervention in terms of overall survival, time to amputation and time to healing of ischemic tissue loss. However, there was a significant reduction in rest pain in those who underwent surgical bypass. Although perioperative morbidity within 30 days from intervention was higher in the bypass group, mortality rates between the two groups did not differ. Thus, in patients with CLI presenting with nonhealing wound or gangrene, lower extremity bypass is as effective as percutaneous balloon angioplasty in establishing in-line blood flow to the foot. Additionally, more RCTs comparing the two interventions on outcomes of limb survival, reduction in amputation and time to wound healing should be performed.

A propensity-matched cohort study by Mehaffey *et al.*³⁾ investigated lower extremity bypass (LEBs) versus endovascular intervention (IEIs) among 13,294 LEBs and IEIs with 8,066 cases performed for CLI. There was a significantly lower risk-adjusted 30-day MALE rate compared with IEI, with significant reduction in amputation rates. Despite inherent risks with surgical procedures, there was no difference in 30-day MACE rate between LEB and IEI.

Another propensity score matching study by Shiraki *et al.*⁴⁾ in Japan investigated Bypass Surgery ($n=68$) versus Endovascular Therapy ($n=178$) among

246 HD patients with CLI who had infrainguinal revascularization. In hemodialysis patients with CLI who underwent infrainguinal revascularization, there was no significant difference in survival, major adverse limb events and major amputation between bypass surgery and endovascular intervention. Note however that the study was a retrospective analysis with small sample size and inadequate information of anatomic details of the lesions.

A retrospective cohort study by Ohmine *et al.*⁵⁾ investigated EVT First (E group, 118 legs in 102 patients) versus Below-the-knee-ankle joint bypass First (B group, 51 legs in 48 patients) in 169 legs in 150 patients. In patients with CLI, there was no significant difference between endovascular intervention first versus bypass first in terms of amputation-free survival, limb salvage and overall survival. However, surgical bypass was more effective in terms of improving hemodynamic parameters and also showed significantly fewer repeat revascularization procedures compared to endovascular treatment. Identified risk factors for death in the cohort included older age, nonambulatory condition, presence of coronary artery disease and congestive heart failure. The limitations of the study include its non-randomization, small sample size and short duration of follow-up.

Lastly, another retrospective cohort study by Soga *et al.*⁶⁾ in Japan investigated Bypass Surgery (BSX) versus Endovascular Intervention (EVT) among 460 CLI patients who underwent revascularization. There was no significant difference in amputation free survival, limb salvage and overall survival between endovascular and surgical intervention. However, there was a significantly higher rate of major adverse limb events and repeat revascularization in the endovascular treatment group. Note however that the study was a retrospective analysis with limited evaluation of more complex arterial lesions and underutilization of medical therapy in patients treated with endovascular intervention.

Recommendation 68:

In patients with CLI for whom endovascular revascularization has failed and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries as a last resort in such cases for limb salvage.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 9.1.2.3 was revised to specify its application for cases requiring limb salvage. No issues on applicability were identified.

Summary of Evidence:

The cohort studies showed that although patency rates were significantly higher with the use of autogenous veins, in patients in whom an autogenous vein is not available and endovascular revascularization is not possible, prosthetic materials were acceptable, with primary patency rates around 64-74% after one year. Over time however, lower patency rates were noted.

A prospective cohort by Suckow *et al.*¹⁾ investigated below-knee bypass using prosthetic graft below the knee popliteal artery or more distal target in 1,227 patients who underwent below-knee bypass for CLI. One-year outcomes for below-knee prosthetic bypass grafting can be comparable to those for greater saphenous vein conduit. In this study however, use of cryopreserved vein, upper extremity vein, spliced or composite vein grafts, or prosthetic grafts with a venous cuff were not analyzed. Additionally, the patient cohort studied was predominantly Caucasian and may not be applicable to the Asia-Pacific region. Furthermore, the database evaluated patients at one-year follow-up, limiting the assessment of more long-term outcomes in patency and limb salvage. Lastly, analysis of bleeding complications was limited to short-term occurrences.

A retrospective cohort by Uhl *et al.*²⁾ investigated 198 bypasses for CLI (Rutherford category 4-6). In patients with CLI who underwent tibial or peroneal bypass surgery because of unsuitability for endovascular intervention, autologous veins compared to PTFE grafts showed better primary and secondary graft patency and limb salvage rates, within the immediate perioperative period, and at one and three years of follow-up. However, in case a suitable autogenous vein is not available, use of prosthetic bypass grafts may result in a 64% and 34% patency rates at one and three years, respectively.

Lastly, another retrospective cohort by Jin *et al.*³⁾ investigated 11 infrainguinal arterial bypass surgeries using PTFE+GSV ($n=10$) versus PTE+arm vein ($n=1$). Use of PTFE grafts combined with autogenous vein for surgical revascularization to below the knee popliteal or tibial arteries had acceptable primary patency and amputation-free survival rates in two years. Note though that the study had a small sample size, short follow-up period and retrospective design. This needs to be further studied in a larger RCT.

Recommendation 69:

A staged approach to surgical procedures is reasonable in patients with ischemic rest pain.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 9.1.2.4 was adopted with

no revisions. No issues on applicability were identified. New and additional references support the above statement. This includes a cohort study among Japanese patients.

Summary of Evidence:

Additional literature appraised consists of cohort studies on patients with CLI, though only a small part of the population included patients presenting with ischemic rest pain. Furthermore, there was no analysis of outcomes specifically for this subgroup. Patency rates and hemodynamic parameters improved after revascularization in the CLI group, however, reduction in pain and improvement in quality of life in patients with PAD Rutherford Category 4 still needs to be established in further trials.

A retrospective cohort by Akamatsu *et al.* in Japan¹⁾ investigated inflow repair and staged runoff repair. This included approximately 31% of patients with ischemic rest pain in the total population and showed that rest pain significantly improved after inflow repair and thus, did not require additional infrainguinal revascularization. When analyzed together as a group of patients with CLI, limb salvage rates were noted to be at 89%, 89% and 74% at 1, 3 and 5 years of follow-up, while freedom from major adverse limb events was 75%, 75% and 56% in the same follow-up years. The study however was a retrospective observational study with inherent biases and small sample size. Additionally, patients were treated according to their presentation and medical condition.

Another retrospective cohort by Dosluoglu *et al.*²⁾ investigated endovascular (EV group, $N=356$ patients, 436 limbs) versus open bypass (OPEN group, $N=207$ patients, 226 limbs) versus combination of the two (HYBRID group, $N=91$ patients, 108 limbs). In patients with chronic PAD, Rutherford category 3-6, hybrid procedures can be effective for multilevel revascularization in high-risk patients, with favorable patency and limb salvage rates. Although there were high perioperative morbidity and mortality rates seen in the hybrid group, this may reflect the fact that patients in this group were considered to be at higher risk compared to those in the endovascular only or bypass only group. Note, however, the study's limitations include its retrospective nature and heterogeneity of the population included.

Lastly, another retrospective cohort by Antoniou *et al.*³⁾ of patients with multilevel atherosclerotic arterial disease, including 23% of patients who presented with ischemic rest pain, showed that hybrid open and endovascular procedures done at a single setting were effective in maintaining good primary patency rates and limb salvage rates, and improving ankle-brachial

index. Whether this translated to reduction in rest pain was not included as part of the outcome studied. Note, however, the study's limitations include its retrospective nature, heterogeneity of the study population, and short follow-up period. Thus, randomized studies on reduction in pain and improvement in quality of life must be done.

C.1. Wound Healing Therapies for CLI

Recommendation 70:

An interdisciplinary care team should evaluate and provide comprehensive care for patients with CLI and tissue loss to achieve complete wound healing and a functional foot.

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 9.2.1 was adopted with no issues on applicability identified.

Summary of Evidence:

Data from one additional study¹⁾ supported the 2016 AHA/ACC guideline based on previous literature appraised²⁻⁵⁾. In the appraised study of Mii *et al.*¹⁾, a multidisciplinary team of specialists was in charge of wound care and this included specialists in vascular surgery, radiology, cardiology, cerebrovascular neurology, diabetes, renal disease, infection, rehabilitation, prosthetics and orthotics who held weekly conferences regarding patients with CLI.

In this study of Japanese patients, on top of the multidisciplinary care provided by the team of specialists, an anesthesiologist joined the team to perform sciatic nerve block at bedside to facilitate surgical debridement. Furthermore, skin grafting performed by a dermatologist was done as necessary. The authors reported that aggressive wound care with a multidisciplinary team appeared to shorten the time to wound healing and increase the wound-healing rates. Study limitations, however, were described, among which were the study's retrospective single-center design with a small population and that the standard wound care group was comprised of historical controls. Also, only some patients in the aggressive wound care group required sciatic nerve block and skin grafting.

Recommendation 71:

In patients with CLI, wound care after revascularization should be performed with the goal of complete wound healing.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 9.2.2 was adopted with

no issues on applicability identified.

Summary of Evidence:

Wound healing was the primary focus of the recommendation. Cohort data on patients with CLI who underwent revascularization showed that limb salvage and survival are higher among patients with wound care but the quality of the evidence was a mixture of low and high risk for bias (weak). Though the evidence is rather weak (C-LD), the importance of wound care (wound cleaning, etc.) is emphasized through a Class I recommendation.

Mii *et al.*¹⁾ reviewed 126 consecutive patients undergoing infrainguinal bypass for tissue loss. Prior to March 2013, standard wound care (SWC) and negative pressure wound therapy (when necessary) was done by vascular surgeons. Thereafter, in addition to SWC, aggressive wound care (AWC) including intense daily bedside surgical debridement under a sciatic nerve block by an anesthesiologist and active skin grafting by a dermatologist, if necessary, was performed. Wound healing and major amputation were defined as the end points. Wound healing of the AWC group was superior to that of the SWC group (AWC versus SWC, 1-year wound healing rate: 92% vs. 80%; mean wound healing time: 48 days vs. 82 days; $p=0.011$). The authors then recommended adequate ("aggressive") wound management to achieve complete wound healing.

A multicenter randomized trial by Armstrong *et al.*²⁾ investigated negative pressure wound therapy (NPWT) versus control. However, imbalance in baseline characteristics and unblinded caregiver (clinician-investigators) in the control group was allowed to change the treatment based on their clinical judgment and based on published guidelines. This is a bias in favor of the controls because it provided high proportion of healed wounds in the control group. In spite of this, the treatment group still showed higher proportion of wound healing. The authors concluded that "treatment with NPWT resulted in higher proportion of wounds that healed, faster healing rates and potentially fewer re-amputations (though study not powered to detect this outcome) than with standard treatment."

Lastly, a meta-analysis by Bus *et al.*³⁾ included patients with diabetes mellitus type 1 or 2, and foot ulcer. Best available evidence from this review is for use of non-removable devices, either TCC (Total Contact Cast) or irremovable walkers for healing of neuropathic plantar forefoot ulcers. The population included only patients with diabetes and most studies had a high risk of bias. Hence, drawing robust recommendations and external generalizability to other pop-

ulations may not be possible. High-quality controlled studies are thus recommended. The authors then recommended the use of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure, which may be helpful.

Recommendation 72:

The use of intermittent pneumatic compression (arterial pump) devices to augment wound healing and/or ameliorate severe ischemic rest pain is not well established.

**Weak recommendation (Class IIb);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 9.2.3 was revised to indicate that the effectiveness of the intervention was uncertain and not yet well-established due to the paucity of available data. The lack of availability and relatively high cost of the device limit applicability of the statement to some APSAVD member countries.

Summary of Evidence:

Limited data with low quality evidence due to validity issues erring on high risk of bias were appraised from a meta-analysis, a systematic review (no meta-analysis performed) and a randomized trial.

A meta-analysis by Moran *et al.*¹⁾ consisting of two controlled before-and-after studies and six case series investigated intermittent pneumatic compression IPC (single or sequential) plus standard medical care versus standard medical care only. All the studies included in this systematic review were evaluated to have high risks of bias based on their study designs. Moreover, combining case series with controlled before-and-after studies to come up with a meta-analysis is also problematic (“combining apples and oranges”). Results may suggest that IPC devices may be associated with improved limb salvage, wound healing and pain management. However, confidence intervals on the outcomes of limb salvage and wound healing were wide due to small sample size ($N=48$; 24 in each arm). Its effect on pain management may be considered but study quality was with high risk of bias and sample size was also small (total sample size=31), with skewed sample sizes in each group, i.e., 23 in the intervention and 8 in the control arm. The authors recommended that until additional well-designed analytical studies examining the effect of IPC, the treatment effects of IPC remain unproven. Overall, there is “lack of high-quality evidence demonstrating its effectiveness.”

Williams *et al.*²⁾ also conducted a systematic review consisting of nine trials on IPC. All nine trials

except for one had no controls for comparison. Although the search was thorough, no assessment of included trials was done. Moreover, due to non-randomized study design, no meta-analysis was done. The trial which compared active treatment ($n=24$) with controls ($n=24$) (Kavros 2008), showed 58% (IPC) vs 17% (control) had complete healing and limb salvage ($p<0.01$) after 18 months. In spite of this limitation, the authors concluded that “the evidence presented suggests that IPC reduces pain and increases limb salvage in CLI...”. Still, there is no convincing evidence that IPC is beneficial in promoting wound healing and/or in ameliorating severe ischemic rest pain.

Alvarez *et al.*³⁾ randomized patients ($n=34$) with symptomatic PAD or CLI to high pressure IPC (60 minutes twice daily for 16 weeks) versus standard care with an exercise regimen (20 minutes twice a day for 16 weeks). Primary endpoint was peak walking time (PWT). Results showed that high-pressure IPC improved PWT significantly. It also reduced rest pain, improved healing rates, physical function and bodily pain. However, the study has a small sample size.

Recommendation 73:

In patients with CLI, the effectiveness of hyperbaric oxygen therapy for wound healing is unknown.

**Weak recommendation (Class IIb);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 9.2.4 was adopted with no issues on applicability identified. No additional references were found that would support a different recommendation.

Summary of Evidence:

There is insufficient evidence from previous literature below that shows the effectiveness of hyperbaric oxygen therapy in wound healing, particularly for patients with CLI presenting with arterial ulcers.

A meta-analysis by Kranke *et al.*¹⁾ investigated Hyperbaric Oxygen Therapy (HBOT) versus No HBOT (with or without placebo) in patients with diabetic foot ulcers and venous ulcers. HBOT was found to significantly improve healing of ulcers at six weeks (for diabetic and venous ulcers) and at 18 weeks (for venous ulcers only) but not at long-term follow-up at one year. The trials included also had various flaws in design and/or reporting.

A double blind RCT by Abidia *et al.*²⁾ included only 18 diabetic patients with ischemic, non-healing lower extremity ulcers (1 to 10 cm in diameter that had not shown signs of healing >6 weeks since pre-

sentation). The authors concluded that HBOT has the potential to enhance the healing of ischemic, non-healing diabetic leg ulcers and may be used as a valuable adjunct to conventional therapy when reconstructive surgery is not possible. However, it must be considered that the study is limited to a small sample size with significant loss to follow-up. The outcome of interest was wound healing. Its effect on more significant outcomes like reduction of amputation and mortality rates was not evaluated.

Recommendation 74:

Prostanoids are not indicated in patients with CLI.

**Strong recommendation (Class III Harm);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 9.2.5 was adopted with no issues on applicability identified. The recommendation was supported by data from a recent meta-analysis. No additional studies were found that would support a different recommendation. **However, the class of recommendation was downgraded from Class III No Benefit to Class III Harm.**

Summary of Evidence:

Prostanoids did not provide reduction in amputations and mortality but resulted in more adverse events, hence, their use is not recommended.

In a recent (2016) meta-analysis by Vitale *et al.*¹⁾, prostanoids reduced major amputations but not total amputations. Of the 18 trials, only 11 and 10 trials reported data on total and major amputations, respectively. Prostanoids were associated with a significantly lower risk of major MH-OR 0.77 (0.63;0.93), $p=0.007$], but not total amputations. Healing rate (available only in seven trials) was not significantly augmented by prostanoid use. Authors stated that “the available data are not sufficient to support an extensive use of prostanoids in patients with CLI, as an adjunct to revascularization or an alternative to major amputation in cases which cannot undergo revascularization.” There were no directness or validity issues. The results showed benefit in reducing major amputations. However, they did not show a statistically significant effect in reducing total amputations, mortality and MACE. Note that mortality and MACE incidence was very small due to the limited sample size and often not reported in some trials. Instead, there were significantly more adverse events (nausea, headache and flushing) with prostanoid use. In spite of the foreseen benefits, the authors advised caution due to clinical heterogeneity (Note: I^2 was not reported in the forest plot of the individual result) and moderate risk of bias

of the included studies. Although prostanoids provided reduction in major amputations, the evidence used were not of high quality and the use of prostanoids did not provide reduction in total amputations, mortality and MACE. More trials with better quality and greater number of people and perhaps longer follow-up are recommended to establish its efficacy and safety.

Another 2010 meta-analysis by Ruffolo *et al.*²⁾ included 20 RCTs with patients presenting with CLI, without chance of rescue or reconstructive intervention. Prostanoids were compared with placebo or other pharmacological control treatments. No directness or validity issues were identified. Prostanoids were found to be effective in providing rest-pain relief and ulcer healing. However, they did not show a statistically significant effect in reducing amputations and mortality. Instead, there were more statistically significant adverse events with the use of prostanoids. Authors advised caution due to clinical heterogeneity and moderate risk of bias of the included studies.

Delphi Issues:

One Panel reviewer suggested appraisal of Mahapatra *et al.*³⁾. The trial could not be used to support the AHA/ACC statement primarily because it involved a different outcome i.e. a change in ABI whereas the TWG’s outcomes of interest were reducing limb amputation, cardiovascular mortality, total mortality and the risk of having adverse events. Due to this directness issue (difference in outcome (O) of interest), further appraisal of the article was not done.

VII. Management of Acute Limb Ischemia (ALI)

A. Clinical Presentation of ALI

Recommendation 75:

Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

Recommendation 76:

In patients with suspected ALI, initial clinical evaluation should rapidly assess limb viability and potential for salvage and does not require imaging.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 10.1.1 was adopted with no issues on applicability identified. **The Level of Evidence (LOE) was revised from Expert Opinion to limited data on review of literature and appraisal of recent cohort studies^{1, 2)}, the data of which sup-**

ported the Statement.

AHA/ACC Statement 10.1.2 was adopted with no issues on applicability identified.

Summary of Evidence:

Seven observational studies were appraised, including one prospective cohort conducted in Thailand²⁻⁷). These cohorts demonstrate that initial clinical evaluation, if done promptly, can reduce limb loss and mortality. Prompt recognition and management of ALI may prevent adverse outcomes, particularly in limb viability, limb salvage, major adverse cardiovascular events, and mortality. A prospective study by Multirangura *et al.* 2008²) suggests that among Thai people with acute embolism, successful outcome (i.e., resolution of limb pain and restoration of limb viability without major amputation or death within six months after the treatment) was higher among patients (87.1%) that were promptly addressed with primary revascularization. This study suggests the generalizability of benefit to an Asian population with regards early recognition and prompt treatment of acute embolism.

Other cohorts reviewed included that of Morriss-Stiff *et al.* in 2009³) which investigated all emergency operations performed during the period 1993-2003 from theatre registry and demonstrated that a delay from symptom onset to surgery is a major determinant of outcome and a good clinical acumen in establishing a diagnosis and commencing appropriate surgery is probably the most important factor in improving results in ALI. The longer the delay, the higher the mortality and the amputation rates. A cohort by Baril *et al.* in 2013⁴) demonstrated that patients with acute lower extremity ischemia who undergo lower extremity bypass, when compared with patients undergoing elective bypass, represent a distinct group who are at higher risk for both perioperative adverse events and worse outcomes, specifically mortality and limb loss, at 1 year. However, this trial reported only on outcomes following surgical bypass and did not include patients with ALI who were treated with either thromboembolectomy alone or with endovascular techniques. A registry from the FRIENDS study by Duval *et al.* 2014⁵) focused on 200 patients with limb threatening PAD. Authors concluded that, for individuals with ischemic symptoms less than 14 days, prolonged limb ischemia is associated with higher 30-day and 1-year amputation, systemic ischemic event rates, and worse amputation-free survival. Data implied that “prompt diagnosis and revascularization might improve outcomes for patients with ALI.”

One of the cohorts reviewed extends the benefit

of prompt and correct identification of limb ischemia in promoting limb salvage rate to patients ages 90-100 years old. Saarinen *et al.* in 2015⁶) demonstrated that the median survival and amputation free survival rates were low (between 44-51%) but the limb salvage rate was good. This may imply that regardless of age, initial and rapid identification and evaluation of ALI can provide good limb salvage rate. Though the study dealt with the prognosis of patients with limb ischemia, and not specifically on the effect of initial clinical evaluation of limb viability and potential for salvage, the study was able to establish the burden of illness among nonagenarian patients. Authors, however, emphasized that assessing frailty and cognition pre-operatively in order to predict adverse post-operative outcomes, is an important determinant in choosing the best treatment for each patient, especially in this age group. Limitations of this cohort include a lack of a control group and the heterogeneity of the study population as the study included CLI and ALI.

Clinical evaluation leads to a shortened time delay to revascularization than the time spent for patients who underwent imaging procedures before revascularization. This was concluded from a prospective cross-sectional study by Londero *et al.* 2014⁷) which investigated a fast track program among patients who came in the ED due to pain in the extremity or those suspected of ALI. The largest time delay was between onset of symptoms and first contact to a medical doctor. The authors emphasized that it is of great importance that patients with suspected ALI are referred to a hospital with vascular specialists immediately. The results showed that the in-hospital time delay for all three groups needing vascular intervention (from specialist assessment to revascularization) were as follows: 1) Operation alone: 325 minutes (median time); 2) with CT/MR and operation: 822 minutes; and 3) Thrombolysis or endovascular treatment: 5621 minutes. Patients who went for imaging before further intervention had an almost 8.5 hours longer in-hospital delay than patients who needed immediately operation. Certain issues from this study may limit the generalizability of the results, such as a small sample size and only one practice in one hospital was studied.

Delays in the recognition and treatment of ALI need to be identified to be able to deploy strategic approaches to lessen such problems and with the intent of improving survival and limb viability. A single center retrospective study by Normahani *et al.* 2017¹) focused on identification of delays in the acute limb ischemia pathway via retrospective review of in-patient records. Majority of the cases who presented with ALI were embolic in nature. Longest delay was

the time interval from onset of symptoms to arrival at the emergency department (11.5 hours), followed by the time interval from arrival to ED to revascularization/intervention (10.2 hours). The delay in imaging from the arrival of patient to ED is 4.8 hours. Of all the imaging studies for ALI, DUS was significantly shorter than time to angiography (2.5 hours versus 12 hours). Time to CTA vs angiography was not statistically significant. Mortality was higher among elderly patients and for those diagnosed to have an embolus. There was no description on the comparison of mortality for those whose interventions were done later compared to those who underwent early intervention. Overall major amputation rate was 14.9% and 30% of these were performed as a primary amputation and the remaining following revascularization. Patients who underwent amputation presented significantly later than those who did not require amputation.

B. Medical Therapy for ALI

Recommendation 77:

In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 10.2 was adopted with no issues on applicability identified. **The Level of Evidence (LOE) was revised from expert opinion (EO) to limited data (LD) upon review of literature.**

Summary of Evidence:

Studies have shown that the initial treatment of choice for ALI patients when limbs are viable or not threatened is systemic anticoagulation with heparin in combination with other interventions, unless contraindicated.

In a prospective cohort by Blaisdell *et al.*¹⁾, 54 patients with acute arterial ischemia were treated with selective management in an attempt to minimize deaths and to salvage the maximum number of limbs using the following interventions depending on patient status: 1) High-dose heparin therapy; 2) Operative removal of the clot; and 3) Amputation of the limb. There was a significant decrease in mortality rate with no corresponding increase in limb loss using selective management. The following considerations were used: 1) If the patient presents within 6 to 8 hours of the onset of acute arterial occlusion and if paralysis or anesthesia is present, then ultimate limb loss is likely. Therapeutic choices are high-dose heparin therapy, operative removal of the clot, or amputation of the limb, the ultimate choice being dependent

on patient status; 2) If sensation and motor function are present, limb viability is not threatened, and good results can be obtained by utilizing anticoagulation and delayed elective revascularization, if the latter is indicated; 3) Revascularization attempts after 10 to 12 hours of severe ischemia often are unsuccessful, and ischemia is followed by either recurrent thrombosis and ultimate limb loss, or by death from the systemic effects of reperfusion of ischemic tissue. This type of limb is managed best by using high-dose heparin therapy if viable, or by amputation if it is not. Another 20-year retrospective non-randomized study by Tawes *et al.*²⁾ investigated the following: 1) Heparin; 2) Embolectomy; and 3) Heparin & embolectomy. The use of combined heparin and embolectomy resulted in improved limb salvage rate and survival rate.

At the time that this literature review was being conducted, there have been no randomized studies to determine if low molecular weight heparin is better (or comparable) to unfractionated heparin.

C. Revascularization for ALI

Recommendation 78:

In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology and degree of ischemia)

**Strong recommendation (Class I);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 10.3.1 was adopted with no issues on applicability identified. **The Level of Evidence (LOE) was revised from C-limited data to B-Non-randomized on review of literature.**

Summary of Evidence:

Evidence base for the AHA/ACC 2016 Guideline consisted of a 1978 prospective cohort by Blaisdell *et al.*¹⁾ and a 1996 randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts in 124 patients by Comerota *et al.*²⁾. The Blaisdell cohort, which included 54 patients with ALI, concluded that revascularization strategies should primarily depend on patient status to minimize deaths and to salvage the maximum number of limbs. Considerations for this are cited in the Summary of Evidence for Recommendations 75 and 77.

Additional literature appraised was a 10-year prospective cohort from 11 centers (NATALI) by Earnshaw *et al.*³⁾ that investigated thrombolysis among patients with ALI. Factors that increased the risk for death included sex (women were less likely to survive; $P=0.006$), increasing age ($P<0.001$), ischemic heart disease ($P<0.001$), native vessel occlusion ($P<0.001$),

and occlusion caused by embolus ($P=0.02$). On the other hand, factors that increased the risk for amputation were male sex, younger age, increasing Fontaine grade ($P=0.02$), graft occlusion, and occlusion caused by thrombosis. Amputation free-survival (AFS) deteriorated progressively with age, and was reduced to 66% in patients with diabetes ($P=0.003$). On the other hand, AFS improved in the group taking warfarin ($P=0.04$). The pretreatment factors that remained significantly related to AFS were age, diabetes, duration of ischemia, Fontaine grade ($P=0.001$), and presence of a neurosensory deficit ($P=0.004$).

Recommendation 79:

Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb.

**Strong recommendation (Class I);
High level of evidence (Level A)**

AHA/ACC Statement 10.3.2 was adopted with no further revisions and no issues on applicability identified. New/additional reference further supports the above statement.

Summary of Evidence:

A recent meta-analysis by Enezate *et al.*¹⁾ of six studies (5 randomized prospective and 1 observational retrospective) compared endovascular versus surgical treatment for ALI and demonstrated that among patients with ALI who presented with less than 2 weeks duration from the onset of symptoms, there were no differences in mortality, limb amputation at 1 month, 6 months and 1 year, as well as in the incidence of recurrent ischemia with endovascular versus operative treatment.

Intraarterial thrombolytic therapy was also compared with surgery in some randomized trials reviewed. Ouriel *et al.*²⁾ compared intraarterial thrombolytic therapy with operative revascularization in the initial treatment of ALI and found that thrombolytic therapy was associated with a significant improvement in 30-day event-free survival rate, with amputation or death in 14% versus 30% ($p=0.04$). The differences in the 30-day requirement for amputation (9% vs 14%) and 30-day mortality rate 12% vs 18% though did not attain statistical significance. The 12-month survival rate was 84% in the thrombolytic treatment arm and 58% in the operative arm. The mortality difference was higher in the operative group which could be attributed to the higher rates of in-hospital cardiopulmonary complications in the operative group. On the other hand, more major bleeding occurred in the thrombolytic group although this did not reach statistical significance (11% vs 2%, $P=0.06$). This included

one patient with intracranial hemorrhage leading to uncal herniation and death. Limb salvage was similar in each group averaging 82% at 1 year. Thrombolytic therapy was associated with a reduction in incidence of in-hospital cardiopulmonary complications and a corresponding increase in patient survival rates. It has better short term (30-day) and 1-year outcome as compared to operative treatment, though there was a trend towards more bleeding episodes but it didn't reach statistical significance. Although this trial has a randomized prospective design, the sample size is too small to draw a definitive conclusion.

Another RCT by Ouriel *et al.*³⁾ found that initial thrombolytic therapy was not superior to operative intervention with respect to the major end points of survival and limb salvage. The amputation-free survival rate in the surgical group did not differ with the urokinase group. There were no differences in amputation-free survival rates and mortality rates between the thrombolysis and operative group, but an initial strategy of thrombolysis reduces the number of open procedures required for acute ischemia of the lower leg. Major hemorrhage was significantly higher in the thrombolysis group as compared to the operative group; therefore, identification of risk factors for hemorrhage will be of value in future studies to improve selection of candidates for thrombolysis.

The STILE Trial⁴⁾ compared intraarterial thrombolytic therapy with operative revascularization for patients who require revascularization for lower limb ischemia caused by non-embolic arterial and graft occlusion. Composite clinical outcome at 1 month was significantly higher in the thrombolysis group, driven by the significantly higher recurrent/ ongoing ischemia and complications (life threatening hemorrhage and vascular complications) in the thrombolysis group. At 6-month follow-up, although there were no overall differences in mortality or major amputation, acutely ischemic patients (less than 14 days) have a higher amputation-free survival in patients who underwent thrombolysis ($p=0.01$) because of improved limb salvage ($p=0.02$), compared with surgical patients. Based on this study, patient related factors (duration of onset of symptom, Fontaine grade) should be always considered in creating a treatment strategy that will translate to a better patient care/clinical outcome.

Comerota *et al.*⁵⁾ randomized 124 patients (68% male) with lower limb bypass graft occlusion (46 autogenous and 78 prosthetic) to surgery ($n=46$) or intra-arterial catheter-directed thrombolysis ($n=78$) with rt-PA or urokinase. Composite outcome including death, amputation, ongoing/recurrent ischemia, and major morbidity was analyzed on an intent-to-

treat basis at 30 days and 1 year. Overall, there was a better composite outcome at 30 days ($P=0.023$) and 1 year ($P=0.04$) in the surgical group compared with lysis, due predominantly to a reduction in ongoing/recurrent ischemia, most notable in autogenous grafts. However, following successful catheter placement, patency was restored by lysis in 84%, and 42% had a major reduction in planned operations. One-year results of successful lysis compared favorably with the best surgical procedure, which was new graft placement. Acutely ischemic patients randomized to lysis demonstrated a trend toward a lower major amputation rate at 30 days ($P=0.074$) and significantly at 1 year ($P=0.026$) compared with surgical patients, while those with more than 14 days ischemia showed no difference in limb salvage but higher ongoing/recurrent ischemia in lytic patients ($P<0.001$). Patients with occluded prosthetic grafts had greater major morbidity than did those with occluded autogenous grafts ($P<0.02$).

Delphi Issue:

One panel member expressed his concern that the recommendation may be misleading. Sometimes ALI occurs due to embolism of organized thrombus or tumor thrombus. In such cases, the thrombus cannot be dissolved by catheter-based thrombolysis.

Recommendation 80:

Amputation should be performed as the first procedure in patients with a non-salvageable limb.

**Strong recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 10.3.3 was adopted with no further revisions and no issues on applicability identified.

Summary of Evidence:

Patients having irreversible limb ischemia, defined as major tissue loss or permanent nerve damage, a profoundly anesthetic and paralyzed limb, with rigor and inaudible signals, usually require amputation¹⁾. It is apparent that skeletal muscle is the predominant tissue in the limb but also the tissue that is most vulnerable to ischemia. Physiological and anatomical studies show that irreversible muscle cell damage starts after 3 hours of ischemia and is nearly complete at 6 hours. In the setting of reperfusion injury in which the process involves the bulk of the lower extremity, amputation rather than attempts at revascularization may be the most prudent course to prevent the toxic product in the ischemic limb from entering the systemic circulation²⁾. The metabolic consequences

are variable and are related to the severity of injury which depend on the duration of ischemia and the effects of reperfusion. These can range from transient symptoms in the lower extremity to systemic inflammation with multiple organ dysfunction. Tissue damage and inflammation can lead to pain, swelling, and the possibility of compartment syndrome; while inflammatory mediators of the local response to ischemia-reperfusion injury can also have widespread systemic effects that could lead to acute lung injury, myocardial dysfunction, and acute renal failure which are significantly associated with morbidity and mortality³⁾.

Prolonged limb ischemia is a known risk factor for poorer outcomes. In the FRIENDS registry by Duval *et al.*⁴⁾ of patients with limb threatening disease in individuals with ischemic symptoms <14 days, prolonged limb ischemia was associated with higher 30-day and 1-year amputation, systemic ischemic event rates, and worse amputation-free survival. Duration of limb ischemia of <12, 12 to 24, and >24 hours in patients with ALI was associated with much higher rates of first amputation. A retrospective study by Normahani *et al.*⁵⁾ focused on identification of delay in the ALI pathway via retrospective review of in-patient records. Among patients who presented with ALI, the overall major amputation rate was 14.9%. Patients who underwent amputation presented significantly later than those who did not require amputation.

Recommendation 81:

Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization.

**Strong Recommendation (Class I);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 10.3.4 was adopted with no further revisions and no issues on applicability identified.

Summary of Evidence:

The lower extremity muscles reside in compartments, surrounded by fascia and bones. Reperfusion to ischemic muscles can cause cellular edema, resulting in increased compartment pressure. When compartment pressure is >30 mmHg (i.e., compartment syndrome), there is capillary and venule compression that leads to malperfusion of the muscle. Studies have demonstrated that irreversible muscle cell damage starts after 3 hours of ischemia and is nearly complete at 6 hours. In most instances of reperfusion, which follows thrombotic or embolic occlusion, there will be

a variable degree of ischemic damage in the zone where collateral blood flow is possible. The extent of this region will determine the magnitude of the inflammatory response, whether local or systemic. Only in this region will therapy be of any benefit, whether fasciotomy to prevent pressure occlusion of the microcirculation, or anticoagulation to prevent further microvascular thrombosis. In instances in which the process involves the bulk of the lower extremity, amputation rather than attempts at revascularization may be the most prudent course to prevent the toxic product in the ischemic limb from entering the systemic circulation¹.

Revascularization of a limb after a severe and prolonged period of ischemia may be associated with high rates of mortality and amputation because of the development of a postrevascularization syndrome. This “revascularization” syndrome includes several complications, both local (explosive swelling of the limb, compartment syndrome and skeletal muscle infarction (rhabdomyolysis) and general (acidosis, hypercalcemia, hypovolemic shock, renal, hepatointestinal and pulmonary failures, arrhythmias and cardiac arrest (multiple organ dysfunction). Therapies are directed against complications after they occurred, once revascularization is completed: fasciotomy, mannitol and diuretics administration for forced diuresis, fluid administration to correct hypovolaemia, use of resins, insulin and glucose or haemodialysis to deal with hypercalcemia, administration of buffers to correct acidosis, control of hypercalcaemia with orthophosphates and calcitonin²). The tolerance of tissue for ischemia varies with the specific tissue type and/or the presence or absence of collateral flow. Skeletal muscle is known to be most vulnerable to ischemia³. Because muscle comprises the primary tissue mass in the extremities, damage to muscle remains the most critical aspect of limb reperfusion syndrome. Although the degree of skeletal muscle injury is known to correlate directly with the severity and duration of the ischemia^{4, 5}.

A prospective cohort by Khan *et al.*⁶ included all patients with a diagnosis of late-presenting, acute lower extremity arterial occlusion, who were operated on. Among 206 patients who presented with arterial occlusion of 72 hours or more, the most common revascularization intervention done was femoral artery exploration with embolectomy. Fasciotomy was performed in 45.6% cases for existing or impending compartment syndrome. Of those patients presenting with late-onset limb ischemia who received pre-emptive fasciotomy, 17 required amputation. Of those patients on whom embolectomy was performed, 34 required embolectomy due to failure of revasculariza-

tion and 22 required re-embolectomy (10.68%) while 17 were found to have life-threatening ongoing ischemia despite fasciotomy and required amputation (13.1%). Mortality was 5.8%. This study suggests that late revascularization may require additional surgery like fasciotomy and re-embolectomy to reduce amputation and mortality rates.

Recommendation 82:

In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-NR)**

AHA/ACC Statement 10.3.5 was adopted with no further revisions and no issues on applicability identified. Additional reference further supports the above statement.

Summary of Evidence:

Acute and subacute ischemia of the lower limb are still a common reason for amputation. Surgical thrombectomy has declined in importance due to the increased incidence of perioperative complications, while local intra-arterial lysis is also associated with an increased rate of hemorrhagic complications¹. Various mechanical thrombectomy systems have been available over the past few years which have low rates of complications, accompanied by a high technical success rate and low amputation rate.

Wissgot *et al.*² reviewed various percutaneous mechanical thrombectomy systems and concluded that these appear to be an effective alternative in the therapy of acute and subacute arterial occlusions in infrainguinal vessel regions (compared with established vascular surgery and local lysis procedures). These systems are available for use by a trained interventional team within a few minutes and are relatively easy to handle. In particular, patients with contraindications for lysis therapy or an increased surgical risk can be rapidly revascularized.

Recommendation 83:

In patients with ALI due to embolism and with a salvageable limb, surgical thromboembolectomy can be effective.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 10.3.6 was adopted with no issues on applicability identified. **The level of evidence was revised from C-limited data (LD) to B-Randomized on review of additional literature.**

Summary of Evidence:

A recent meta-analysis by Enezate *et al.*¹⁾ of six studies (5 randomized prospective and 1 observational) compared endovascular versus surgical treatment for ALI. The mean age was 67 years and 65% of patients were male. Among patients with ALI who presented with less than 2 weeks duration from the onset of symptoms, there were no differences in mortality, limb amputation at 1 month, 6 months and 1 year, as well as in the incidence of recurrent ischemia with endovascular versus operative treatment.

Additional references support operative management of salvageable limbs with ALI due to embolism. A prospective cohort by Kempe *et al.*²⁾ included patients undergoing lower extremity embolectomy of the aorta, iliac, or infrainguinal arteries. Femoral artery exploration with embolectomy was the most common procedural management in 86% of patients. Six percent (6%) required bypass for limb salvage during the initial operation. Fasciotomies were performed in 39%, and unexpected return to the operating room occurred in 24%. The 5-year amputation freedom and survival estimates were 80% and 41%, respectively. Another retrospective chart review by Zaraca *et al.*³⁾ included 490 thromboembolectomies performed in 468 patients. Surgical intervention for lower limb ischemia was associated with high 2-year mortality but offers good 2-year limb salvage.

In a retrospective chart review done by Ender *et al.*⁴⁾ on ALI patients on whom thromboembolectomy was done, the following risk factors for limb loss should be considered: thromboembolectomy failure, high ischemic stage, high level of plasma creatinine kinase and compartment syndrome on admission.

Recommendation 84:

The usefulness of ultrasound-accelerated catheter-based thrombolysis for patients with ALI with a salvageable limb is unknown.

**Weak recommendation (Class IIb);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 10.3.7 was adopted with no further revisions and no issues on applicability identified. Data from the additional 2015 RCT did not support a revision of the statement nor change in COR and LOE.

Summary of Evidence:

Thrombolytic therapy for thrombosed infrainguinal native arteries and bypass grafts has been increasingly used over the years. The main limitation of thrombolysis is the occurrence of bleeding compli-

cations. Low intensity ultrasound (US) has been hypothesized to accelerate enzymatic thrombolysis, thereby reducing therapy time. Schrijver *et al.*¹⁾ randomized 60 patients to urokinase with ultrasound accelerated thrombolysis (UST) compared to standard thrombolysis (ST) groups and studied a mechanistic endpoint (i.e., thrombolysis time as its primary endpoint). Authors concluded that the thrombolysis time was significantly reduced by UST as compared with ST in patients with recently thrombosed infrainguinal native arteries or bypass grafts. The reduction in thrombolysis time did not translate to significant differences in technical success nor hard endpoints, like combined 30-day death and severe adverse event rate (ST had more patients achieving technical success and less 30-day death & severe adverse event rates but the differences were not statistically significant). The number of bleeding complications were substantial in both groups. There were moderate 30-day patency rates in both treatment groups (82% in ST, 71% in UST but difference is not statistically significant). Although there was a reduction in thrombolysis time and use of urokinase with UST compared to ST, this did not translate to achieving higher success rate, nor reduction in 30-day death and severe adverse events for UST.

D. Diagnostic Evaluation for the Cause of ALI**Recommendation 85:**

In the patient with ALI, a comprehensive history should be obtained to determine the cause of thrombosis and/or embolization.

**Strong recommendation (Class I);
Low level of evidence (Level C-EO)**

Recommendation 86:

In the patient with a history of ALI, testing for a cardiovascular cause of thromboembolism can be useful.

**Strong recommendation (Class IIA);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 10.4.1 and 10.4.2 were adopted with no further revisions and no issues on applicability identified. No references were found that would support a revision of the Statement.

Summary of Evidence:

ALI may be related to underlying PAD (including prior lower extremity bypass graft) or may be related to other conditions that can result in ALI through either thrombotic (e.g., hypercoagulable state) or embolic mechanisms. Management should not be delayed for testing for the underlying cause of

limb ischemia because delay from symptom onset to revascularization is a major determinant of outcome^{1,2}.

The evaluation of a cardiovascular (i.e., embolic) cause for ALI is most useful in the patient without underlying PAD and can be completed after revascularization. Heart rhythm monitoring (e.g., electrocardiogram, Holter monitoring) may be done to detect arrhythmias such as atrial fibrillation. Cardiac imaging may be done to detect prior myocardial infarction, valvular vegetations, intracardiac shunts or thrombi, all of which may provide a setting for thromboembolism.

VIII. Longitudinal Follow-up

Recommendation 87:

Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status.

**Strong recommendation (Class I);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 11.1 was adopted with no further revisions and no issues on applicability identified. No references were found that would support otherwise.

Summary of Evidence:

No new references were found that would support a revision in the Statement.

Recommendation 88:

Patients with PAD who have undergone lower extremity revascularization (surgical and/or endovascular) should be followed up with periodic clinical evaluation and ABI measurement.

**Strong recommendation (Class I);
Low level of evidence (Level C-EO)**

AHA/ACC Statement 11.2 was adopted with no further revisions and no issues on applicability identified. No references were found that would support a revision of the statement.

Summary of Evidence:

No new references were cited.

Recommendation 89:

Duplex ultrasound (DUS) can be beneficial for routine surveillance of infrainguinal, autogenous vein bypass grafts in patients with PAD.

**Moderate recommendation (Class IIa);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 11.3 was adopted with no further revisions and no issues on applicability identified. Additional references (including a 2017 meta-analysis) further support the statement.

Summary of Evidence:

It is well documented that the duplex findings of a stenosis correlate well with both the angiographic findings and direct hemodynamic measurements¹⁻³. Autogenous vein of good quality is the conduit of choice for infrainguinal bypass grafting. However, good initial success may be threatened by the development of intrinsic vein-graft stenosis, which accounts for approximately 60% of graft thromboses^{4,5}.

DUS can be beneficial, possibly only secondary to ABI and clinical examination. A recent meta-analysis of randomized and nonrandomized comparative studies by Abu Dabrh in 2017⁶ enrolled patients who underwent infrainguinal arterial reconstruction and received DUS surveillance for follow-up compared with any other method of surveillance. Although the search strategy utilized was thorough, the trials included had high risk of bias and were of low quality (many were non-randomized; while those randomized did not report allocation concealment and blinding). Results were imprecise, having estimates with wide confidence intervals. DUS surveillance was not associated with a significant change in primary, secondary, or assisted primary patency or mortality in comparison with ankle-brachial index and clinical examination. DUS surveillance was associated with a non-statistically significant reduction in amputation rate (OR 0.70 [95% CI, 0.23-2.13]).

In addition, a retrospective analysis by Tinder, *et al.*⁷ investigated Duplex ultrasound surveillance and Doppler ankle derived pressure. The natural history of 141 (40%) bypasses with an abnormal first duplex scan differed from “normal” grafts by more frequent (51% vs 24%, $P < 0.001$) and earlier (7 months vs 11 months) graft revision for severe stenosis and a lower 3-year assisted primary patency (68% vs 87%; $P < 0.001$). In 52 (15%) limbs, the bypass graft failed and 20 (6%) limbs required amputation. The efficacy of duplex scan surveillance after infrainguinal vein bypass may be enhanced by having a more intensive surveillance for bypasses with higher risk for stenosis.

Recommendation 90:

Duplex ultrasound (DUS) is reasonable for routine surveillance after endovascular procedures in patients with PAD.

**Moderate recommendation (Class IIa);
Low level of evidence (Level C-LD)**

AHA/ACC Statement 11.4 was adopted with no further revisions and no issues on applicability identified. As only retrospective analyses have been found to support this statement, more robust studies are needed to strengthen this recommendation. No new/additional references were found that would change the statement.

Summary of Evidence:

A retrospective analysis by Baril *et al.*¹⁾ included patients with PAD who underwent SFA stenting and monitored by duplex imaging. A total of 330 limbs underwent femoropopliteal angioplasty and stenting. Patients were seen in follow-up at 1, 3, and 6 months after their procedure. After this initial 6-month period, patients were then evaluated at 6-month intervals indefinitely. Angiograms were reviewed independently from the DUS findings. ROC curves were used to compare angiographic stenosis with PSV and Vr to establish optimal criteria for determining $\geq 50\%$ and $\geq 80\%$ stenosis. Out of 330 limbs who underwent SFA Stenting, 78 limbs met the criteria and 59 limbs underwent re-intervention. Of the 59 limbs that underwent reintervention, 37 (63%) were symptomatic, and 22 (37%) underwent reintervention based on DUS findings alone. Another retrospective cohort by Troutman *et al.*²⁾ included patients with PAD who underwent stenting and monitored by duplex imaging. Follow-up DUS surveillance was found to be able to predict failure of stent grafts placed for lower extremity occlusive disease. DUS imaging was done 1 week after the procedure, then every 3 months the first year, and every 6 months thereafter. Majority of those with abnormal DUS findings that underwent prophylactic intervention were those with abnormal findings in the femoro-popliteal arteries. The sensitivity of DUS for the total cohort was 58% and the specificity was 97%. The negative predictive value and positive predictive value was 78% and 93%, respectively.

Another retrospective cohort by Back *et al.*³⁾ included patients with PAD who underwent stenting and serial DUS after stent graft placement. The surveillance algorithm included aortoiliac duplex scanning within 1 month and serial limb pressure measurements and femoral artery waveform analyses during follow-up. Iliac systems with a peak systolic velocity >300 cm/s and velocity ratio >2.0 by duplex and/or symptomatic or hemodynamic deterioration were considered failing and an indication for angiography. DUS surveillance after iliac stenting was able to localize stenotic segments. Indirect clinical indicators found 17 (20%) suspected failing iliac systems, in which DUS correctly identified 5 of 6 (83%) recur-

rent iliac stenoses and facilitated secondary endovascular intervention. Three (4%) stent occlusions occurred in the treated iliac systems despite surveillance. During follow-up ranging to 36 months after stent placement (mean 12 months), life table primary, assisted primary, and secondary patency rates for the treated iliac systems were 78%, 90%, and 98%, respectively, at 18 months.

Delphi Issues:

It was proposed that the LOE be revised from C-LD to B-NR on the basis of 2 recent retrospective studies^{4,5)}. Upon appraisal by the TWG though, there were directness issues and limitations arising from retrospective study design and criteria needed for prospective validation. Said references were not added by the TWG and LOE was not revised to B-NR.

Recommendation 91:

The effectiveness of duplex ultrasound (DUS) for routine surveillance of infrainguinal prosthetic bypass grafts in patients with PAD is uncertain.

**Weak recommendation (Class IIb);
Moderate level of evidence (Level B-R)**

AHA/ACC Statement 11.5. was adopted with no further revisions and no issues on applicability identified. No additional references were found that would lead to a change in the recommendation.

Summary of Evidence:

A retrospective review of databases by Brumberg *et al.*¹⁾ investigated patients who underwent infrainguinal prosthetic bypass graft and routine surveillance using DUS. Despite this surveillance, 51 (39%) bypasses occluded during follow-up [i.e., 30 single thrombotic events and 21 multiple (recurrent) thromboses]. Secondary interventions were performed for 32 (63%) occlusions, 3-year primary, assisted, and secondary patency rates were 39%, 43%, and 59%, respectively, for all bypasses, with no difference noted between above-knee and below knee grafts ($P=0.5$). At 3 years, freedom from limb loss was 75%, and patient survival was only 70%, with no adverse effect on survival imparted by amputation. Sixty-nine total adverse events occurred as a result of thrombotic occlusion ($n=51$), duplex scan-detected stenosis ($n=13$), or graft infection ($n=5$). Forty-nine percent of all initial graft occlusions eventually led to amputation. Twenty-three patients (27% of 86 patients) maintained on chronic warfarin were subtherapeutic at time of occlusion. Use of a distal anastomotic adjunct with below knee bypasses reduced graft thrombosis (35% with versus 60% without) but did

not reach significant patency advantage ($P=0.07$).

In another retrospective review of databases by Stone *et al.*²⁾, patients with PAD who underwent femoro-femoral bypass and routine surveillance using DUS of all femoro-femoral bypass (vein and prosthetic) grafts were included. Vascular laboratory surveillance after femoro-femoral bypass using DUS imaging of the inflow iliac artery and graft accurately identified failing grafts. A duplex-detected identified stenosis with a PSV >300 cm/s correlated with failure, and repair of identified lesions was associated with excellent 5-year patency. The primary graft patency at 1, 3, and 5 years was 86%, 78%, and 62%, respectively. Correction of duplex-detected stenosis resulted in assisted-primary patency of 95% at 1 year and 88% at 3 and 5 years ($P<0.0001$, log-rank). Secondary graft patency was 98% at 1 year and 93% at 3 and 5 years.

A RCT by Lundell *et al.*³⁾ included patients post-infrainguinal bypass who were randomized to intensive ($n=79$) or routine surveillance ($n=77$) after operation. The primary patency and secondary patency rates of femoro-popliteal bypass grafts after 1 year were similar with both the intensive and routine surveillance group, but better with the intensive surveillance group than routine surveillance group at 3 years. Intensive surveillance identified failing vein grafts leading to a significantly higher cumulative assisted primary and secondary patency compared with routine follow-up examination at 3 years. On the other hand, intensive surveillance group versus routine follow-up group among on PTFE grafts has comparable assisted primary and secondary patency rate at 1 year.

E. Research Implications

The APPADC identified important knowledge gaps that need to be addressed through primary research:

- Frequency of follow-up of PAD patients - There are currently no studies that determine the most appropriate frequency for follow-up among patients with PAD.
- Duration of antiplatelet/antithrombotic therapy
- Role of new therapy for glycemic control and lipid-lowering drugs
- Ticagrelor vs. Placebo with background aspirin therapy on symptomatic PAD patients with prior MI (dual therapy)
- Value of Hyperbaric Oxygen Therapy
- Interventions for Intermittent Claudication
- Novel therapies for critical limb ischemia
- Cost-effectiveness of specific therapies and interventions in the Asia-Pacific population

F. Dissemination for the Members of the APSAVD

Planning for Dissemination and implementation

It is the hope of the APSAVD and APPADC that the dissemination and use of this Consensus Statement that is more relevant and applicable to patients in our region will help improve the management and outcomes of our PAD patients.

As a regional statement, it is recognized that there will be differences in each country that would require further contextualization or customization in the dissemination, implementation and applicability of these guidelines, i.e. differences in health systems structures as well as in the cost and availability of services and medicines. Each APSAVD member country is then charged with developing specific plans to efficiently disseminate and implement the recommendations in these guidelines to their fellow physicians.

The Consensus Statement will be presented during the APSAVD Annual Meeting. Before the meeting, copies would have been mailed to the members for their perusal. Comments and questions will be elicited during the discussion period for the purpose of clarifying the recommendations. A copy of the consensus document will be available at the APSAVD website after this is published.

Endorsement to the ministry of health of each member country and other relevant general and subspecialty societies in the management of PAD at the regional and local/country level will also be done.

Dissemination to the Training Institutions

APSAVD members will be asked to endorse the Consensus Statement to their respective national institutions of health. Then, copies of the Consensus Statement with the said endorsement will be sent to the heads of hospital-based Sections of Cardiology, Cardiovascular Surgery, training institutions and medical schools and libraries so as to incorporate the recommendations in their teaching and training curricula, with the support of consultants, mentors and other educational influentials.

Dissemination to Industry Partners, Regulatory Agencies, and Payors

The Consensus Statement will be transmitted to national health insurance corporations, health maintenance organizations (HMOs), pharmaceutical industry partners, development partners and civil society organizations through formal communications by the APPADC in cooperation with national health ministries or departments.

Dissemination to the Patients and the Public in General

A simplified or 'laymanized' version of the Consensus Statement shall be formatted and made available to the APSAVD members in a format that will be ready for reproduction and dissemination to their patients in their clinics. The same will be available for interested parties who might browse the APSAVD website.

G. Implementation and Monitoring

There is currently no data on the current practices in the management of PAD of Asia-Pacific countries. The APSAVD Research Committee will track changes in practice by doing a survey on baseline patient characteristics and physician practices before and after dissemination of the guidelines. This could help monitor and evaluate the impact of the guidelines on current practice as well as identify areas for improvement in terms of its use and acknowledge other research gaps to be investigated. Potential research questions include: Have the guidelines been well-disseminated? What proportion of patients get the recommended examination/treatments? Are there barriers to implementation that need to be further addressed? Are there issues on applicability? What are the boosters in practice that help eliminate gaps in management? What are the indicators to say people are following the guideline?

H. Updating of the Guidelines

The APSAVD/APPADC plans to update this Consensus Statement within five (5) years. The recommendations herein shall hold until such time that technology, patient and provider preferences, or new evidence drive the need to revisit and update the Consensus Statement.

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Executive Summary

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Chapters

A. Background

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B. Consensus Statement Development Methods

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C. Results

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- 6) COR changed for: Recommendations 21 (IIa to IIb), 25 (IIb to III Harm), 34 (IIb to III Harm), 41 (I to IIa), 50 (IIa to I), 74 (III-No benefit to III-Harm)
- 7) LOE changed for: Recommendations 16 (B-R to B-NR), 24 (C-LD to B-R), 32 (C-EO to B-NR), 34 (B-R to A), 57 (B-NR to B-R), 72 (B-NR to CLD), 75 (C-EO to C-LD), 77 (C-EO to C-LD), 78 (C-LD to B-NR), 83 (C-LD to B-R)
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D. Appraisal

I. Clinical Assessment for PAD

Recommendation 1 (other articles are cited in Table 4)

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II. Diagnostic Testing for the Patient with Suspected Lower Extremity PAD (Intermittent Claudication or CLI)

A. Resting ABI for Diagnosing PAD

Recommendation 4:

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Recommendation 5:

References for ABI Cutoff ≤ 0.90

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B. Physiological Testing

Recommendation 8:

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D. Screening for Atherosclerotic Disease in Other Vascular Beds for the Patient with PAD**Screening for Abdominal Aortic Aneurysm****Recommendation 17:**

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Screening for Asymptomatic Atherosclerosis in Other Arterial Beds (Coronary, Carotid and Renal Arteries)**Recommendation 18:**

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III. Medical Therapy for the Patient with PAD

A. Antiplatelet Agents

Recommendation 19:

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V. Revascularization for Claudication

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VI. Management of Critical Limb Ischemia

A. Revascularization for CLI

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C.1. Wound Healing Therapies for CLI

Recommendation 70:

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VII. Management of Acute Limb Ischemia (ALI)

A. Clinical Presentation of ALI

Recommendations 75 and 76:

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B. Medical Therapy for ALI

Recommendation 77:

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C. Revascularization for ALI

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Recommendation 81:

- 1) Blaisdell W. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. 2002; 10: 620-630
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Recommendation 84:

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D. Diagnostic Evaluation for the Cause of ALI

Recommendations 85 and 86:

- 1) Duval S, Keo HH, Oldenburg NC, Baumgartner I, Jaff MR, Peacock JM, Tretinyak AS, Henry TD, Luepker RV, Hirsch AT. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: the FRIENDS registry. *Am Heart J*, 2014; 168: 577-587
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VIII. Longitudinal Follow-up

Recommendation 89:

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Recommendation 91:

- 1) Brumberg RS, Back MR, Armstrong PA, Cuthbertson D, Shames ML, Johnson BL, Bandyk DF. The relative importance of graft surveillance and warfarin therapy in infrainguinal prosthetic bypass failure. *J Vasc Surg*, 2007; 46: 1160-1166
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- 3) Lundell A, Lindblad B, Bergqvist D, Hansen F. Femoropopliteal-crural graft patency is improved by an intensive surveillance program: a prospective randomized study. *J Vasc Surg*, 1995; 21: 26-33

DECLARATION OF CONFLICTS OF INTEREST

Table 1. Steering Committee Members

Given name	Employment/ Consultancy	Grant received	Payment as study investigator	Support for travel to meetings for the study, or other purposes	Fees for participation in activities such as data monitoring boards and others	Payment for lectures including service on speakers' bureaus	Stock/stock options	Expert testimony	Patents (planned, pending or issued)	Royalties	No conflicts of interest to declare
Edward Janus	None	None	None	MSD and AMGEN	None	MSD AMGEN	None	None	None	None	
Rody Sy	None	Pfizer, Sanofi, MSD, Novartis, Servier	Pfizer, Sanofi, MSD, Novartis, Servier	MSD, Pfizer, Servier, LRI	None	None	None	None	None	None	
Shizuya Yamashita	None	Kowa, Nippon Boehringer Ingelheim, Otsuka, Shionogi, Bayer, MSD, Kyowa Mede, Takeda, Sanwaka-gaku, Astellas, Daiichi-Sankyo, Mochida, Astra Zeneca, Hayashibara, Teijin, Kaken Kissei	None	None	None	Kowa, Otsuka, Bayer, MSD, Takeda, Sanwaka-gaku, Toa Eiyoun, Ono, Astellas-Amgen Biopharma, Sanofi, Bristol-Myers, Daiichi-Sankyo, Astra Zeneca, Sky-light Biotech, Kaken, Pfizer, Aegerion.	None	None	None	None	
Fatima Colado	None	None	Astra-Zeneca	None	None	None	None	None	None	None	
Florimond Garcia											Yes

Table 2. Consensus Panel Members

Given Name/ Country	Employment/ Consultancy	Grant received	Payment as study investigator	Support for travel to meetings for the study, or other purposes	Fees for participation in activities such as data monitoring boards and others	Payment for lectures including service on speakers' bureaus	Stock/stock options	Expert testimony	Patents (planned, pending or issued)	Royalties	No conflicts of interest to declare
Maria Teresa Abola (Chair) Philippines	None	None	Astra-Zeneca, Bayer, Novartis	Astra, Bayer, Corbridge, Novartis, Pfizer, Servier, LRI-Therapharma	None	Aspen, Astra, Bayer, Corbridge, Menarini, Pfizer, Servier	None	None	None	None	
Jonathan Golledge Australia	Public hospital and university (The Townsville Hospital and James Cook University/ Consultant for Amgen and Reven	Grants from national funding bodies e.g. NHMRC, Queensland Government	None	I have received support to speak at some national and international meetings	I have occasionally been given fees for giving advice in relation to vascular disease from companies (e.g. Reven)	Amgen	None relevant	None	None	None	
Jiang Zhisheng China											Yes
Bryan Yan Hongkong	None	None	None	Boston Scientific, Medtronic, Cook Medical	None	Boston Scientific, Medtronic, Cook Medical	None	None	None	None	

Asia-Pacific PAD Management Consensus Statement

Ramakrishna Pinjala India												Yes
Iwan Dakota Indonesia												Yes
Salim Harris Indonesia												Yes
Raden Suhartono Indonesia												Yes
Yukihito Higashi Japan	None	Teijin Pharma Limited, Boehringer Ingelheim GmbH, Merck Sharp & Dohme Corp., Sanofi Kabushiki Kaisya, Astra Zeneca Kabushiki Kaisya, Kyowa Hakko Kirin Company Limited, Takeda Pharmaceutical Company Limited, Astella Pharma Incorporated, Daiichi Sankyo Company Limited, Mochida Pharmaceutical Company Limited, Nihon Kohden Corporation, Shionogi Company Limited, Nippon Sigma Company Limited, Sanwa Kagaku Kenkyusho Company Limited, Unex Corporation, and Kao Corporation.	None	Radiometer Limited, Omron Corporation, Sumitomo Dainippon Pharma Company Limited, Otsuka Pharmaceutical Company Limited, Torii Pharmaceutical Company Limited, Kowa Company Limited, Fujiyaku Company Limited, Amgen Astellas BioPharma Kabushiki Kaisya, Nippon Shinyaku Company Limited, Itamar Medical Limited, Bayer Holding Limited, Eli Lilly Kabushiki Kaisya, and Ono Pharmaceutical Company Limited	None	Teijun Pharma Limited, Boehringer Ingelheim GmbH, Merck Sharp & Dohme Corporation, Sanofi Kabushiki Kaisya, AstraZeneca Kabushiki Kaisya, Kyowa Hakko Kirin Company Limited, Takeda Pharmaceutical Company Limited, Astellas Pharma Incorporated, Daiichi Sankyo Company Limited, Mochida Pharmaceutical Company Limited, Nihon Kohden Corporation, Shionogi Company Limited, Nippon Sigma Company Limited, Sanwa Kagaku Kenkyusho Company Limited, Unex Corporation, Kao Corporation, Radiometer Limited, Omron Corporation, Sumitomo Dainippon Pharma Company Limited, Otsuka Pharmaceutical Company Limited, Torii Pharmaceutical Company Limited, Kowa Company Limited, Fujiyaku Company Limited, Amgen Astellas BioPharma Kabushiki Kaisya, Nippon Shinyaku Company Limited, Itamar Medical Limited, Bayer Holding Limited, Eli Lilly Kabushiki Kaisya, and Ono Pharmaceutical Company Limited	None	None	None	None		

Tetsuro Miyata Japan	None	Daiichi Sankyo Co, Sanofi K.K.	None	None	None	Kaken Pharmaceutical Co. Ltd., Astella Pharma Inc., Taisho Toyama Pharmaceutical Co.Ltd., Mitsubishi Tanabe Pharma Co., Amgen Astellas BioPharma K.K., Daiichi Sankyo Co.Ltd., Otsuka Pharmaceutical Co. Ltd., Pfizer Inc., Nippon Shinyaku Co. Ltd., LeMaitre Vascular GK., Cardinal Health Japan, Bristol-Myers Squibb, W.L. Gore & Associates, Toray Industries Inc., Bayer Yakuhin Ltd., Mochida Pharmaceutica Co. Ltd., Sanofi K.K.	None	None	None	None	
Hiroyoshi Yokoi Japan						Daiichi Sankyo Co.					
Marie Simonette Ganzon Philippines	None	None	None	Bayer, Corbridge, Servier	None	Bayer, Corbridge, Servier	None	None	None	None	
Timothy Dy Philippines											Yes
Pankaj Kumar Handa Singapore											Yes
Peter Ashley Robless Singapore	None	Nil	None	Nil	Nil	Nil	Nil	Nil	Nil	Nil	
Seung-Woon Rha South Korea											Yes

Table 3. Technical Working Group Members

Given name	employment/ Consultancy	Grant received	Payment as study inves- tigator	Support for travel to meet- ings for the study, or other purposes	Fees for par- ticipation in activities such as data moni- toring boards and others	Payment for lectures including ser- vice on speak- ers' bureaus	Stock/stock options	Expert testi- mony	Patents (planned, pending or issued)	Royalties	No conflicts of interest to declare
Bernadette Tumanan- Mendoza (Chair) Philippines											Yes
Elaine Alajar Philippines	None	None	CAROLINA trial	Pascual Pharma Cor- poration; MSD	None	Boehringer- Ingelheim, MSD, Pascual Pharma Cor- poration, Ser- vier, Pharma- link, Unilab	None	None	None	None	
April Bermudez- delos Santos Philippines											Yes
Elmer Jasper Llanes Philippines	None	None	None	McGraw, LRI-Ther- apharma, Ser- vier, Bayer, MSD	None	MSD, Servier, Bayer, Sanofi, Novartis, Boehringer- Ingelheim, Menarini	None	None	None	None	
Gay Marjorie Obrado Philippines											Yes
Noemi Pestaño Philippines											Yes
Felix Eduardo Punzalan Philippines											Yes