Appendix C. Comparison of antiplatelet, antihypertensive, and statin guidance across international guidelines for PAD.

Guideline, evidence grading	Antiplatelet	Antihypertensives	Statins
ACC/AHA 2005[1] **Class I:** Benefit >>> Risk. Procedure/ Treatment SHOULD be performed/ administered **Class IIa:** Benefit >> Risk. Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/ administer treatment **Class IIb:** Benefit ≥ Risk. Additional studies with broad objectives needed; Additional registry data would be helpful. Procedure/ treatment MAY BE CONSIDERED. **Class III:** Risk ≥ Benefit. No additional studies needed. Procedure/ treatment should not be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL **Level A:** Multiple (3-5) population risk strata evaluated. General consistency of direction and magnitude of effect. **Level B:** Limited (2-3) population risk strata evaluated. **Level C:** Very limited (1-2) population risk strata evaluated.	**Class I** 1. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level A**). 2. Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level A**) 3. Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (**Level B**) **Class III** Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD. (**Level C**)	**Class I** 1. Antihypertensive therapy should be administered to hypertensive patients with lower extremity PAD to achieve a goal of less than 140 mm Hg systolic over 90mm Hg diastolic (nondiabetics) or less than 130 mmHg systolic over 80 mm Hg diastolic (diabetics and individuals with chronic renal disease) to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death. (**Level A**) 2. Beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated inpatients with PAD. (**Level A**) **Class IIa** The use of angiotensin-converting enzyme inhibitors is reasonable for symptomatic patients with lower extremity PAD to reduce the risk of adverse cardio-vascular events. (**Level B**) **Class IIb** Angiotensin-converting enzyme inhibitors may be considered for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardio-vascular events. (**Level C**)	**Class I** Treatment with a hydroxymethyl glutaryl (HMG)coenzyme-A reductase inhibitor (statin) medication is indicated for all patients with PAD to achieve a target LDL cholesterol level of less than 100 mg per dL. (**Level B**) **Class IIa** 1. Treatment with an HMG coenzyme-A reductase inhibitor (statin) medication to achieve a target LDL cholesterol level of less than 70 mg per dL is reasonable for patients with lower extremity PAD at very high risk of ischemic events. (**Level B**) 2. Treatment with a fibric acid derivative can be useful for patients with PAD and low HDL cholesterol, normal LDL cholesterol, and elevated triglycerides. (**Level C**)
ACC/AHA 2016[2] **Class I:** Benefit >>> Risk (STRONG) **Class IIa:** Benefit >> Risk (MODERATE) **Class IIb:** Benefit ≥ Risk	**Class I** 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	**Class I** Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. (**Level A**)	**Class I** 1. Treatment with a statin medication is indicated for all patients with PAD. (**Level A**)

(WEAK) **Class 3: No benefit.** Benefit = Risk (MODERATE) **Class 3: Harm.** Risk > Benefit (STRONG) **Level A:** High-quality evidence from more than 1 RCT; meta-analyses of high quality RCTs; one or more RCTs corroborated by registry studies **Level B-R:** Moderate-quality evidence from 1 or more RCTs; meta-analyses of moderate-quality RCTs **Level B-NR:** Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies; meta-analyses of such studies **Level C-LD:** Randomized or nonrandomized observational or registry studies with limitations of design or execution; meta-analyses of such studies; physiological or mechanistic studies in human subjects **Level C-EO:** Consensus of expert opinion based on clinical experience	with symptomatic PAD. (**Level A**) **Class IIa** In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. (**Level C-EO**) **Class IIb** 1. 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. (**Level B-R**) 2. 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. (**Level B-R**) 3. DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization. (**Level C-LD**) 4. The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. (**Level B-R**)	**Class IIa** 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. (**Level A**)	
CCS Consensus Conference 2005[3] **Quality of Evidence** **I:** Evidence obtained from at least one properly randomized controlled trial or one large epidemiological study. **II:** Evidence based on at least one non-	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: Antiplatelets **Grade 1A** Lifelong antiplatelet therapy with aspirin (75 to 325 mg/d) or clopidogrel (75 mg/day) in patients with or without clinically	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: ACE inhibitors. There is evidence that ACE inhibitors may be effective irrespective of their blood pressure lowering effect, and therefore this class of drugs is a reasonable first	**Grade 1A** Medical therapies to reduce cardiovascular events in PAD: Statins

randomized cohort comparison or multi-centre study, chronological series or extra ordinarily results from large non-randomized studies. **III:** Opinions of respective authorities, based on clinical experience, descriptive studies or reports of expert committees. **Classification and Recommendations** **A:** Evidence sufficient for universal use (usually based on randomized clinical trials). **B:** Evidence acceptable for widespread use, evidence less robust, but based on randomized clinical trials. **C:** Evidence not based on randomized clinical trials.	manifest coronary or cerebrovascular disease. **Grade 1B** Aspirin or Clopidogrel recommended over ticlopidine **Grade 1B** Cilostazol is recommended for patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention **Grade 2B** Pentoxyfilline is not recommended **Grade 2B** Anticoagulant therapy (vitamin K antagonists) is not recommended	choice if blood pressure lowering is required. **No Grade assigned** <u>Blood Pressure Lowering</u> The evidence of the effectiveness of BP lowering in other vascular subgroups (…) taken together with the emerging data of its effectiveness in PAD patients allows us to advocate for aggressive BP lowering in this high-risk subgroup.	
CCS The Use of Antiplatelet Therapy in the Outpatient Setting 2011[4] **Class I:** Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective **Class IIa:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the weight of evidence in favour **Class IIb:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the	**Class I** For patients with symptomatic PAD with overt CAD or cerebrovascular disease, antiplatelet therapy as indicated for the CAD and/or cerebrovascular status is recommended (**Level A**). **Class IIa** 1. For patients allergic or intolerant to ASA, use of clopi- dogrel is suggested (**Level B**). 2. For all infrainguinal reconstructions, low-dose ASA (75- 162 mg daily) should be given (**Level B**). 3. Long-term antiplatelet therapy with ASA 75-162 mg daily should be given to patients who undergo lower-extremity balloon angioplasty with or without stenting for	**N/A**	**N/A**

usefulness/ efficacy less well established **Class III:** Evidence that the treatment is not useful and in some cases may be harmful **Level A:** Data derived from multiple randomized clinical trials or meta-analyses **Level B:** Data derived from a single randomized clinical trial or large nonrandomized studies **Level C:** Consensus of opinion by experts and/or small studies, retrospective studies, and registries	chronic symptomatic PAD (**Level C**). **Class IIb** 1. For patients with symptomatic PAD without overt CAD or cerebrovascular disease, low-dose ASA (75-162 mg daily) or clopidogrel 75 mg daily is recommended, provid- ing the risk for bleeding is low (**Level B**). The choice of drug may depend on patient preference and cost considerations. 2. For patients with intermittent claudication, using clopidogrel 75 mg daily in addition to ASA 75-162 mg daily is not recommended unless the patient is judged to be at high vascular risk along with a low risk of bleeding (**Level B**). 3. For patients with asymptomatic PAD with an ABI < 0.9, low-dose ASA (75-162 mg daily) may be considered for those at high risk because of associated atherosclerotic risk factors in the absence of risk factors for bleeding (**Level C**). 4. In those with infrainguinal grafts and a high risk of thrombosis or limb loss, combination therapy with a vitamin K antagonist and ASA may be of benefit (**Level C**). 5. Low-dose ASA (75-162 mg daily) may be considered for all patients with an AAA, particularly those with clinical or subclinical PAD (**Level C**). **Class III** 1. For patients with symptomatic PAD with an indication for oral anticoagulation such as		

	atrial fibrillation, venous thromboembolism, heart failure, or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (**Level A**). 2. For patients with symptomatic PAD without compelling indications for oral anticoagulation such as atrial fibrillation or venous thromboembolism, oral anticoagulation should not be added to antiplatelet therapy (**Level B**). 3. Anticoagulation with heparin or vitamin K antagonists should be avoided in this setting (**Level B**). 4. For patients with intermittent claudication, dipyridamole should not be used in addition to ASA (**Level C**).		
CCS 2022 (PAD Guideline)[5] **Strength of Recommendation:** **Strong:** guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). **Weak:** the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention)	1. We recommend against routine antithrombotic therapy (antiplatelet or anticoagulant) for patients with isolated asymptomatic lower extremity PAD (**Strong Recommendation; High-Quality Evidence**). 2. We recommend treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) for management of patients with symptomatic lower extremity PAD who are at high risk for ischemic events (high-risk comorbidities such as polyvascular disease, diabetes, history of heart failure, or renal insufficiency) and/or high-risk limb presentation post peripheral revascularization, limb amputation, rest pain, ischemic ulcers) and at low bleeding risk (**Strong**	1. We suggest that the approach to initiation and titration of antihypertensive agents should follow the Hypertension Canada guidelines (**Weak Recommendation; Low-Quality Evidence**). 2. We suggest treating hypertension to a target of less than 140/90 mm Hg in patients with PAD without compelling indications for specific agents or targets (**Weak Recommendation; Low-Quality Evidence**). 3. We recommend that PAD patients with hypertension be treated with ACE inhibitors or ARBs as the first choice in the absence of contraindications (**Strong Recommendation; Moderate-Quality Evidence**).	1. We recommend that patients with PAD qualify as statin-indicated patients and should receive lipid-modifying therapy for the reduction of death, CV death, nonfatal MI, nonfatal stroke (MACE), and MALE concordant with the recommendations in the 2021 Canadian Cardiovascular Society (CCS) guide- lines for the management of dyslipidemia (**Strong Recommendation; High-Quality Evidence**). a. Maximally tolerated dose of statin therapy b. Statin add-on therapies (ezetimibe and/or PCSK-9 inhibitors) if receiving maximally tolerated dose of statin therapy and the low-density lipoprotein cholesterol is ≥ 1.8 mmol/L, non-high-density lipoprotein cholesterol ≥ 2.4 mmol/L or apolipoprotein B100 ≥ 0.7 mg/dL.

but appreciable uncertainty exists. **Quality of Evidence:** **High:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect**.** **Very Low:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	**Recommendation; High-Quality Evidence**). 3. We recommend combination treatment with rivaroxaban 2.5 mg twice daily and aspirin or single antiplatelet therapy for patients with symptomatic lower extremity PAD and low bleeding risk in the absence of high-risk limb presentation or high-risk comorbidities (**Strong Recommendation; High-Quality Evidence**). 4. We recommend single antiplatelet therapy with either aspirin (75-325 mg) or clopidogrel (75 mg) be considered for patients with symptomatic lower extremity PAD at high bleeding risk who remain eligible for antithrombotic therapy (**Strong Recommendation; High-Quality Evidence**). 5. We suggest that clopidogrel (75 mg daily) should be the preferred agent when single antiplatelet therapy is deemed to be the optimal antithrombotic choice (**Weak Recommendation; Moderate-Quality Evidence**). 6. We suggest that dual antiplatelet therapy(DAPT; aspirin and clopidogrel or aspirin and ticagrelor) be used for patients with symptomatic lower extremity PAD at high risk for vascular events, at low bleeding risk, and who have contraindications to rivaroxaban (**Weak Recommendation; Moderate-Quality Evidence**). 7. We recommend against the additional use of full-dose anticoagulation with antiplatelet therapy for the		2. We recommend that patients with PAD, who, despite maximally tolerated dose of statin therapy have a triglyceride level of 1.5-5.6 mmol/L, should be considered for use of icosapent ethyl for the reduction CV death, nonfatal MI, and nonfatal stroke concordant with the recommendations in the 2021 CCS guidelines for the management of dyslipidemia (**Strong Recommendation; Moderate-Quality Evidence**).

	purpose of decreasing MACE and MALE events in patients with stable lower extremity PAD (**Strong Recommendation; High-Quality Evidence**).		
ESC 2011[6] **Class I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. **Class II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy. **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. **Class III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. **Level A:** Data derived from multiple randomized clinical trials or meta-analyses. **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies. **Level C:** Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.	**Class I** Antiplatelet therapy is recommended in patients with symptomatic PAD. (**Level C**)	**Class I** All patients with PAD should have their blood pressure controlled to ≤140/90 mmHg. (**Level A**) **Class IIa** ß-Blockers are not contraindicated in patients with LEAD, and should be considered in the case of concomitant coronary artery disease and/or heart failure (**Level B**)	**Class I** All patients with PAD should have their LDL cholesterol lowered to <2.5 mmol/L (100 mg/dL), and optimally to <1.8 mmol/L (70 mg/dL), or ≥ 50% when the target level cannot be reached. (**Level C**)
ESC-ESVS 2017[7]	**Class I** 1. Antiplatelet therapy is recommended in patients	**Class I** In patients with PADs and hypertension, it is	**Class I** 1. Statins are recommended in all

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. **Class II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy. **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. **Class III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. **Level A:** Data derived from multiple randomized clinical trials or meta-analyses. **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies. **Level C:** Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.	with symptomatic PADs. (Level C) 2. Long-term SAPT is recommended in symptomatic patients. (**Level A**) **Class IIb** In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin. (**Level B**) **Class III** Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD. (**Level A**)	recommended to control blood pressure at <140/90 mmHg. (**Level A**) **Class IIa** ACEIs or ARBs should be considered as first-line therapyc in patients with PADs and hypertension. (**Level B**)	patients with PADs. (**Level A**) 2. In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by >_50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). (**Level C**)
NICE 2012[8]	Offer all people with peripheral arterial disease information, advice, support and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance on: - smoking cessation - diet, weight management and exercise - lipid modification and statin therapy - the prevention, diagnosis and management of diabetes - the prevention, diagnosis and management of high blood pressure - antiplatelet therapy		

ACC: American College of Cardiology, AHA: American Heart Association, CCS: Canadian Cardiovascular Society, ESC: European Society of Cardiology, ESVS: European Society for Vascular Surgery, NICE: National Institute for Health and Care Excellence, COR: class of recommendation, ABI: ankle-brachial index, ACEi: ace-inhibitor, ARB:

angiotensin II receptor blocker, BP: blood pressure, CAD: coronary artery disease, DAPT: dual-antiplatelet therapy, HDL: high-density-lipoprotein, LDL: low-density-lipoprotein, MI: myocardial infarction, PAD: peripheral artery disease, LEAD: lower extremity artery disease, SAPT: single-antiplatelet therapy, MACE: major adverse cardiovascular events, MALE: major adverse limb events

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