European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Peripheral Arterial Disease and Intermittent Claudication

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Recommendations

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Recommendation 1	**Class**	**Level of evidence**				
For patients with intermittent claudication, it is recommended that all revascularisation decisions are individualised and involve the patient in a shared decision-making process that consider available non-invasive therapies, expected treatment benefit, procedure-related risk and long-term patency.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Golledge, BJS, 2018	Prospective cohort study	Patients with intermittent claudication recruited at three hospitals in Australia; with mean (SD) follow-up of 5(3.4) years.	456, out of which 178 (39 %) underwent early revascularizati on and 278 (61 %) had initial conservative treatment.	N/A		The estimated 5-year major amputation rate was 6·2 and 0·7 per cent 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 (relative risk 5·40 to 4·22 in different models).
Kumakura, Eur Heart J Qual Care Clin Outcomes, 2017	Single-centre prospective cohort study	Patients with de novo intermittent claudication recruited at the Cardiovascular Hospital of Central Japan (Kitakanto Cardiovascular Hospital) from January 1990 to December 2014	1107 patients with de novo IC.	N/A		Revascularization did not improve mortality and MACE, and femoropopliteal revascularization increased MACLE (P < 0.05). There was no deterioration of claudication in 881 patients (79.6%). Worsening claudication was noted in 211 patients (14.8% per 5 years), and 15 patients (1.1% per 5 years) worsened to CLI. Diabetes and haemodialysis were independent predictors of CLI.

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Djerf, EJVES, 2020	Retrospective observational study based on prospectively collected registry data	All patients registered in the National Quality Registry for Vascular Surgery (Swedvasc) who underwent open or endovascular lower limb revascularisation for IC in Sweden between 12 May 2008 and 31 December 2012	5 860 patients revascularised for IC	N/A		The major amputation rate within one year of revascularisation for IC was 0.2% (n = 9/5860).

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Recommendation 3	**Class**	**Level of evidence**				
For clinically asymptomatic individuals without increased cardiovascular risk, screening for lower limb peripheral arterial disease with ankle-brachial index measurements is not recommended due to the lack of direct evidence for screening in the general population.	III	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Guirguis-Blake JM et al. JAMA 2018	Systematic review	PAD screening in General population		ABI		No population-based randomized trials of PAD screening were identified.
Alahdab et al JVS 2015	Systematic review	PAD screening in asymptomatic individuals.		ABI		The current available evidence does not support the benefit of routine ABI screening.
Andras et al Cochrane Database of Systematic Reviews 2014	Systematic review	PAD screening in General population		ABI		No RCTs were identified that met the inclusion criteria.
Lindholt et al, NEJM, 2022	RCT	Comprehensive screening study on subjects aged 65-74 recruited from the general population	46611	16736	29790	62.9% of invited screening subjects underwent screening. Screening included non-contrast electrocardiography-gated computed tomography to determine coronary artery calcium score and to detect aneurysms and atrial fibrillation, ABI measurements to detect peripheral artery disease and hypertension, and a blood sample to detect diabetes mellitus and hypercholesterolemia. The primary outcome was all- cause mortality. After approximately five years of follow-up, 2106 men (12.6%) in the invited group and 3915 men (13.1%) in the control group had died (hazard ratio, 0.95; 95% confidence interval [CI], 0.90 to 1.00; P=0.06) The hazard ratio for stroke in the invited group, as compared with the control group, was 0.93 (95% CI, 0.86 to 0.99); for myocardial infarction, 0.91 (95% CI, 0.81 to 1.03); for aortic dissection, 0.95 (95% CI, 0.61 to 1.49); and for aortic rupture, 0.81 (95% CI, 0.49 to 1.35). There were no significant between-group differences in safety outcomes

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Recommendation 4	**Class**	**Level of evidence**				
For clinically asymptomatic individuals at increased risk* of lower limb peripheral arterial disease, focused screening for peripheral arterial disease with ankle brachial index measurements based on the lowest recorded ankle pressure may be considered, to support secondary prevention strategies. *Individuals 65 years or older; individuals aged 50 to 64 years with risk factors for atherosclerosis (diabetes, history of smoking, hyperlipidemia, hypertension, chronic renal disease or family history of PAD); individuals younger than 50 years old with diabetes and one other risk factor for atherosclerosis; or those with known atherosclerotic disease in another vascular bed	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Lindholt et al. Lancet 2017	RCT	Randomly allocated (1:1) all men aged 65-74 years	50 156	Screening for abdominal aortic aneurysm, peripheral arterial disease, and hypertension, n=25078.	No screening, n=25078	After a median follow-up of 4·4 years (IQR 3·9-4·8), 2566 (10·2%) of 25 074 participants in the screening group and 2715 (10·8%) of 25 078 in the non-screening group had died. This finding resulted in a significant hazard ratio of 0·93 (95% CI 0·88-0·98; p=0·01), an absolute risk reduction of 0·006 (0·001-0·011), and a number needed to invite of 169 (89-1811). Incidences of diabetes (3995 per 100 000 person-years in the screening group vs 4129 per 100 000 person-years in the non-screening group), intracerebral haemorrhage (146 vs 140), renal failure (612 vs 649), cancer (3578 vs 3719), or 30 day mortality after cardiovascular surgery (44·57 vs 39·33) did not differ between groups.

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Shah et al International Angiology 2017	Systematic review			Using the ten WHO criteria for evaluation of a screening program, we analyzed the potential merits of conducting PAD screening, using ABI.		Randomized trials evaluating PAD screening in asymptomatic individuals at risk are needed a potential target population could include anybody aged 70 years or older and those aged 45-69 with at least one risk factor for PAD.
Matsushita et al. Lancet Diabetes Endocrinol 2017	Collaborative meta-analysis of international cohorts.	Individuals without a history of peripheral artery disease.	18 261 cases of PAD were recorded during follow-up, in 817 084 individuals without a history of PAD.			Clinical attention should be paid to the development of peripheral artery disease symptoms and signs in people with any stage of chronic kidney disease. Compared with an eGFR of 95 mL/min per 1·73 m^2, adjusted hazard ratios (HRs) for incident study-specific peripheral artery disease was 1·22 (95% CI 1·14-1·30) at an eGFR of 45 mL/min per 1·73 m^2 and 2·06 (1·70- 2·48) at an eGFR of 15 mL/min per 1·73 m^2. Even mild-to-moderate chronic kidney disease conferred increased risk of incident peripheral artery disease, with a strong association between albuminuria and amputation.
Sartipy et al, Eur J Vasc Endovasc Surg 2022	Prospective cohort study	Individuals between 60-90 years invited to ABI screening	n=4909, out of which 6% (Group 1) - 9.6% (Group 2) had PAD (depending on applied ABI measureme nt criteria) and the rest (Reference group) did not have PAD	N/A	N/A	The ten-year all-cause mortality for References and Groups 1 and 2 was 27.6%, 48.8%, and 67.2%, respectively. The overall age adjusted hazard ratio (95% confidence interval) for the composite outcome of CV mortality and a non-fatal CV event was 1.25 (1.06 - 1.49) for Group 1 and 2.11 (1.85 - 2.39) for Group 2.

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Lindholt et al, NEJM, 2022	RCT	Comprehensive screening study on subjects aged 65-74 recruited from the general population	46611	16736	29790	62.9% of invited screening subjects underwent screening. Screening included non-contrast electrocardiography-gated computed tomography to determine coronary artery calcium score and to detect aneurysms and atrial fibrillation, ABI measurements to detect peripheral artery disease and hypertension, and a blood sample to detect diabetes mellitus and hypercholesterolemia. The primary outcome was all- cause mortality. After approximately five years of follow-up, 2106 men (12.6%) in the invited group and 3915 men (13.1%) in the control group had died (hazard ratio, 0.95; 95% confidence interval [CI], 0.90 to 1.00; P=0.06) The hazard ratio for stroke in the invited group, as compared with the control group, was 0.93 (95% CI, 0.86 to 0.99); for myocardial infarction, 0.91 (95% CI, 0.81 to 1.03); for aortic dissection, 0.95 (95% CI, 0.61 to 1.49); and for aortic rupture, 0.81 (95% CI, 0.49 to 1.35). There were no significant between-group differences in safety outcomes

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Recommendation 5	**Class**	**Level of evidence**				
The ankle brachial index is recommended as the appropriate test to establish the diagnosis of lower limb peripheral arterial disease.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Donohue et al, Int Wound J. 2020	Review	PAD patients	1,847	ABI vs. Angiogram, DUS, MRA		ABI is sufficiently reliable and valid for PAD diagnosis
Aboyans et al, Circulation 2012	Review	PAD patients	2,833	ABI vs. Angiography, DUS	251	Sensitivity and specificity for ABI: 0.17-1.0 and 0.8-1.0.
Xu et al Can J Cardiol. 2013	Meta-analysis	PAD patients	569	ABI vs angiography		Pooled sensitivity and specificity for ABI: 0.75 (0.71-0.79) and 0.86 (0.83—0.90)
Crawford et al, Cochrane Database Syst Rev. 2016	Cochrane review	Patients with intermittent claudication	85	ABI vs DUS or angiography		Sensitivity and specificity for ABI: 0.97 (0.93-0.99) and 0.89 (0.67-0.95)
Weragoda et al Inter. J of Vasc Med. 2016.	Clinical trial	PAD patients	165	ABI vs DUS	68	Area under the curve of the ROC curve 0.91 (0.81-1.01)

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Recommendation 6	**Class**	**Level of evidence**				
It is recommended that an ankle brachial index cutoff value at ≤ 0.9 is used for lower limb peripheral arterial disease diagnosis, and that a value ≥1.4 be considered inconclusive.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Aboyans et al, Circulation 2012	Review	PAD patients	846	ABI cut- off <0.9 to detect 50% stenosis with imaging methods.		Sensitivity and specificity for ABI cut-off <0.9: 0.83-0.99 and 0.69-0.79.
Weragoda et al Inter. J of Vasc Med. 2016	Clinical trial	PAD patients	165	ABI vs DUS	68	Sensitivity and specificity for ABI at cut-off 0.89: 0.87 and 0.99.

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Recommendation 7	**Class**	**Level of evidence**				
When the ankle brachial index is used to estimate the severity of lower limb peripheral arterial disease in symptomatic patients or is being used during follow up after revascularisation, it is recommended to be calculated by dividing the highest systolic pressure at the ankle level by the highest systolic arm pressure.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Niazi et al Catheter Cardiovasc Interv. 2006	Observational study	PAD patients	208 limbs	Different ABI calculation method (highest- (HAP) or lowest ankle BP (LAP) was compared with angiogram		Sensitivity of high ankle pressure (HAP) and low ankle pressure (LAP): 0.69 vs 0.84. Specificity of HAP and LAP: 0.83 and 0.64. Accuracy of HAP and LAP was 0.72 and 0.80. The lower numerator has a better sensitivity and overall accuracy to diagnose PAD, while the higher has a higher specificity .
Schroder et al J Vasc Surg 2006	Observational study	PAD patients	216	HAP and LAP was compared with DUS.		Sensitivity of HAP and LAP: 0.68 vs 0.89. Specificity of HAP and LAP: 0.99 and 0.93. LAP is the superior method of calculating ABI to identify asymptomatic PAD and assess patient's cardiovascular risk, while HAP has a higher specificity
Klein et al Circulation. 2008	Review	Various		How to calculate the numerator		ABI should be calculated by using the mean ankle blood pressure of the crural vessels.

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Recommendation 8	**Class**	**Level of evidence**				
When the ankle brachial index is used as a cardiovascular risk marker, it is recommended that it is calculated by dividing the lowest recorded systolic pressure at the ankle level by the highest systolic arm pressure due to the higher sensitivity to detect peripheral arterial disease.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Espinola-Klein et al, Circulation 2008	Clinical trial	Coronary patients	831	The prognostic value for CV events of different methods of ABI calculation		PAD prevalence with use of highest ankle pressure (HAP) and lowest ankle pressure (LAP) 25.0 % and 35.8%. The hazard ratio for cardiovascular (CV) events was comparable for HAP and LAP (1.84 vs 1.72) when compared to patients without PAD. More patients at risk were identified by using the lowest ankle pressure (LAP).
Le Bevic et al, Vasc Med 2019	Clinical trial	Coronary patients	1.223	The prognostic value for CV events of different methods of ABI calculation		Hazard ratios for CV events among patients identified by LAP was 1.46 as compared 1.67 identified by HAP. Patients identified by LAP had significantly reduced survival and event-free survival ($p < 0.0001$ and $p = 0.008$) compared to patients without PAD. More patients at risk was identified. However, this cohort represents patients at already high risk.
O'Hare et al Circulation. 2006	Clinical trial	Various	53.246	Mortality and CV risk among the ABI spectrum		The LAP at baseline was used. adjusted HR for CV mortality and CV events for subjects with ABI <0.9: 2.20-2.62 and 1.09-3.81 as compared ABI>0.9<1.4: 0.9-2.12 and 1.00-1.53. Higher risk among patients with ABI<0.9, (measured by LAP) for CV events as compared to references.

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Pereira Fihlo et al Eur J Vasc Endovasc Surg. 2022	Observational study	General population	4909	Different ABI calculation methods (highest- (HAP) or lowest ankle BP (LAP) to estimate prevalence and risk for CV events.		PAD prevalence by using highest ankle pressure and lowes ankle pressure was 9.6% and 16%. Ten-years adjusted hazard ratios for CV mortality and non-fatal CV events for HAP and LAP: 2.11 (1.85 -2.39) and 1.25 (1.06 -1.49). By using LAP were 70% more patients with PAD at increased risk for a CV event diagnosed.

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Recommendation 9	**Class**	**Level of evidence**				
For individuals with a clinical suspicion of lower limb peripheral arterial disease but with inconclusive ankle brachial index recordings due to partly or completely incompressible arteries at the ankle level, the use of toe brachial index or absolute toe pressures should be considered as additional diagnostic tools to detect peripheral arterial disease.	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Herraiz-Adillo A Atherosclerosis 2020	Systematic Review	PAD patients	7,618 subjects	ABI vs. TBI	TBI: 1320 (1842 limbs) ABI: 6298 subjects (9662 limbs)	TBI exhibiting better sensitivities (but lower specificities) than ABI, especially in "challenging populations". TBI: sensitivity 81% (95% CI: 70-94), specificity = 77% (95% CI: 66-90), ABI sensitivity 61% (95% CI: 55-69), specificity = 92% (95% CI: 89-95) for detecting stenosis >50%.
Laivuori M, J Vasc Surg 2021	Cohort Study	PAD patients	Consecutive 6,784 patients	ABI vs. TP	-	In patients with normal ABI (defined as 0.9-1.3), 18.7% had a TP < 50mmHg. Low TP was significantly associated with lower survival and elevated cardiovascular mortality. TP <30mmHg: 10-year survival HR 2.0 (1.7-2.2), for TP<50mmHg: 10-year survival HR 1.6 (1.0-1.3)

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Recommendation 10	**Class**	**Level of evidence**				
For individuals with a clinical suspicion of lower limb peripheral arterial disease despite an ankle brachial index within the normal range, the use of toe brachial index or absolute toe pressures should be considered, to confirm peripheral arterial disease.	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Laivuori M, J Vasc Surg 2021	Cohort study	PAD patients	6784 consecutive patients	ABI vs. TP	-	In patients with normal ABI (defined as 0.9-1.3), 18.7% had a TP < 50mmHg. Low TP was significantly associated with lower survival and elevated cardiovascular mortality. TP <30mmHg: 10-year survival HR 2.0 (1.7-2.2), for TP<50mmHg: 10-year survival HR 1.6 (1.0-1.3)

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Recommendation 11	**Class**	**Level of evidence**				
For patients with suspected intermittent claudication and normal ankle brachial index at rest, a treadmill test with pre- and post-test measurements of the ankle brachial index* may be considered, to establish the peripheral arterial disease diagnosis and to quantify severity. * A post exercise ABI drop of ≥ 20% or ankle pressure decrease > 30 mmHg confirms the PAD diagnosis.	IIb	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Gardner A Med Sci Sports Exerc 1991	Comparative Study	PAD	10	Comparison of graded vs. continuous testing protocol including ABI measurement before and after exercise		Reliability of different treadmill protocols (graded vs. continuous workload and initial claudication distance vs. maximal walking distance) was assessed by intraclass correlation coefficient (ICC). Highest reliability was found for graded protocols (Maximal walking distance: continuous protocol ICC 0.55 vs. graded ICC 0.93). ABI was measured before and after exercise.
Birkett et al. PLOS One, 2021	Systematic Review	IC	3,881	Comparison of reporting standards in current protocols		High variation between different protocols. Maximal walking distance was reported using 14 different terminologies. 22 different treadmill protocols and 3 different corridor tests were employed to assess maximal walking distance.
Hoogeveen et al. Eur J Clin Invest, 2008	Cross-Section Study	Asymptomatic PAD	631	Investigation of ability to detect PAD by ABI after walking test		One-minute exercise test improves detection of PAD. PAD was confirmed by peak velocity curves and the potential of ABI after provocation was assessed to detect PAD. The cut-off for post-exercise ankle-pressure lowering was 30mmHg. The prevalence of PAD increased by 1.5% after exercise provocation.

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Recommendation 12	**Class**	**Level of evidence**				
When evaluating patients with suspected or confirmed intermittent claudication on a treadmill, the maximum walking distance observed during a graded treadmill test may be considered the most reliable treadmill parameter.	IIb	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Nicolai, J Vasc Surg, 2009	Meta-regression analysis of several diagnostic studies	PAD	658	Reliability of treadmill testing	N/A	Reliability of different treadmill protocols (graded vs. constant workload and initial claudication distance vs. maximal walking distance) was assessed by intraclass correlation coefficient (ICC). Highest reliability was found for the maximal walking distance by using the graded protocol (ICC: continuous protocol 0.9 (0.88-0.92) vs graded 0.95 (0.94-0.96), p<0.001).
Gardner A Med Sci Sports Exerc 1991	Comparative study	PAD	10	Comparison of graded versus constant testing protocol		Reliability of different treadmill protocols (graded vs. constant workload and initial claudication distance vs. maximal walking distance) was assessed by intraclass correlation coefficient (ICC). Highest reliability was found for graded protocols (Maximal walking distance: constant protocol ICC 0.55 vs. graded ICC 0.93).

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Recommendation 13	**Class**	**Level of evidence**				
For patients with intermittent claudication, the six minute walking test should be considered as the primary walking capacity test to determine the severity of intermittent claudication, as it is more representative than treadmill testing of everyday ambulatory function.	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
McDermott, MM, 2020	Methodological study based on data from 4 RCTs	Participants	467	N/A	N/A	Treadmill test and 6MWT are not comparable outcomes. The study compared relative changes in maximal treadmill walking distance versus 6-minute walk distance in response to a therapeutic intervention or control in randomized trials of participants with PAD. At the 6-month follow-up, participants with PAD randomized to control or placebo significantly declined in 6-minute walk distance (-10.2 m; 95% confidence interval, -18.2 to -2.2; P = .013), but improved maximal treadmill walking distance (+25.7 m; 95% CI, +6.0 to +45.3 m; P = .010). Among all participants, the presence (vs absence) of treadmill exercise training was associated with a 141.3-m greater improvement in maximal treadmill walking distance compared to 6-minute walk distance (95% CI, 88.2-194.4; P < .001), suggesting a benefit from treadmill training on the treadmill outcome.

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McDermott, MM, 2008	Cross sectional	Men and women	156	Treadmill vs. 6MWT	N/A	Participants completed a Gardner-Skinner treadmill protocol and the 6-minute walking test. Physical activity during daily life was measured continuously over 7 days with an accelerometer. Adjusted for age, gender, and race, higher levels of physical activity during daily life were associated with greater distance achieved in the 6-minute walk (P trend < .001). There was no significant correlation for physical activity level with maximum treadmill walking distance (p trend = 0.083).
McDermott, MM 2014	Review			Treadmill vs. 6MWT	N/A	Treadmill testing is particularly problematic for clinical trials that use supervised treadmill exercise as a therapeutic intervention, as there is a learning effect associated. Six-minute walk test better represents walking in daily life than treadmill walking.
Nordanstig, J 2014 J Vasc Surg	Observational study	Patients	49	Investigation of 6MWT vs. outdoor walking capacity	N/A	6MWT closely correlates to outdoor walking capacity (assessed by a global positioning system application for a smartphone). Correlation of the 6MWT to the outdoor walking capacity (r=0.78; P < .001) compared to self-reported maximum walking distance (r=0.56, p<0.001) and graded treadmill test (r=0.65, p<0.001)

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Recommendation 16	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease in whom imaging is indicated, duplex ultrasound, magnetic resonance angiography, or computed tomography angiography are recommended as primary imaging modalities, at the discretion of the treating physician.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Jens, Eur Radiol, 2013	Meta-analysis of 30 studies	1995-2012 Detection of at least 50% stenosis or occlusion.	1,404	MRA	DSA	Summary estimates sensitivity 93% (95% CI 91-95%), specificity 94% (95% CI 93–96%).
Menke, Ann of Int Med, 2010	Meta-analysis of 32 studies	1998-2009 Detection of at least 50% stenosis or occlusion.	1,022	MRA	DSA	Pooled sensitivity 95% (95% CI 92-96%), specificity 96% (95% CI 94-97%).
Collins, BMJ, 2007	Meta-analysis of 12 studies	1996-2005 Detection of at least 50% stenosis.	681	MRA	DSA	Median sensitivity 95% (95% CI 92-99.5%), specificity 97% (95% CI 64-99%).
Koelemay, JAMA, 2001	Meta-analysis of 34 studies	1985-2000 Detection of at least 50% stenosis or occlusion.	1,090	MRA	DSA	Estimated Q-points (sensitivity and specificity equal) 94% for 3D MRA, 90% for 2D MRA.
Nelemans, Radiology, 2000	Meta-analysis of 23 studies	1991-1999 Detection of at least 50% stenosis or occlusion.	597	MRA	DSA	Sensitivity ranged from 92% to 100%, specificity ranged from 91% to 99%.
Verma, European Radiology, 2022	Meta-analysis of 17 studies	Detection of at least 50% stenosis or occlusion.	459	Quiescent-interval-single-shot MRA	DSA/CE-MRA	Pooled sensitivity 88% (95% CI 85-91%), specificity 94% (95% CI 92-96%).

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Jens, Eur Radiol, 2013	Meta-analysis of 12 studies	1995-2012 Detection of at least 50% stenosis or occlusion.	673	CTA	DSA	Summary estimates sensitivity 96% (95% CI 93–98%), specificity 95% (95% CI 92–97%).
Met, JAMA 2009	Meta-analysis of 20 studies	1966-2008 Detection of at least 50% stenosis or occlusion.	957	CTA	DSA	Sensitivity 95% (95% CI 92-97%), specificity 96% (95% CI 93-97%).
Heijenbrok, Radiology, 2007	Meta-analysis of 12 studies	2000-2006 Detection of at least 50% stenosis.	436	CTA	DSA	Sensitivity 92% (95% CI 89-95%), specificity 93% (95% CI 91-95%).
Collins, BMJ, 2007	Meta-analysis of 6 studies	1996-2005 Detection of at least 50% stenosis.	245	CTA	DSA	Median sensitivity 91% (95% CI 89-99%), specificity 91 (95% CI 83-97%).
Sun, J Vasc Interv Radiol 2006	Systematic review of 10 studies	2003-2006 Detection of at least 50% stenosis or occlusion.	400	CTA	DSA	Pooled sensitivity 92% (95% CI 90-95%), specificity 91% (95% CI 87-95%).
Collins, BMJ, 2007	Meta-analysis of 7 studies	1996-2005 Detection of at least 50% stenosis.	369	Duplex ultrasound	DSA	Median sensitivity 88% (95% CI 80-98%), specificity 96% (95% CI 89-99%).
Visser, Radiology, 2000	Meta-analysis of 18 studies	1984-1998 Detection of at least 50% stenosis or occlusion.	1,059	Duplex ultrasound	DSA	Pooled sensitivity 88% (95% CI 84-91%), specificity 95% (95% CI 93-96%).

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Recommendation 17	**Class**	**Level of evidence**				
For patients with intermittent claudication, properly developed and tested patient-reported outcome measures should be considered to characterise functional status and health related quality of life when considering indications for treatment, outcome evaluation and for scientific purposes.	IIa	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Poku E, Health Qual Life Outcomes, 2019	Systematic review	Primary studies reporting psychometric properties of PROMs in English-speaking patients with various stages of PAD.	Data from 14 studies including 1594 patients that presented with symptomatic PAD.	N/A		The most frequently reported measure was the SF- 36 (*n* = 11 studies); others included the Walking Impairment Questionnaire (*n* = 8 studies), EQ-5D (*n* = 5 studies) and the Vascular Quality of Life Questionnaire (*n* = 3 studies). Studies included a diverse PAD population and varied in methodology, including approach to validation of PROMs. No study provided evidence of a full psychometric evaluation in the target population. Disease-specific measures were the only tools with reported content validity related to PAD.

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Mays R J Vasc Surg 2011	Systematic review	Systematic searches and evaluation of questionnaires that assessed functional status and/or general and disease-specific HRQOL in patients with PAD and symptoms of IC.	Six general questionnaires and 7 disease-specific questionnaires were included, with details about the number of domains covered and scored.	N/A		The Medical Outcomes Study Short Form 36 item questionnaire and Walking Impairment Questionnaire are currently the most used general and disease-specific questionnaires. Authors' conclusions: The use of tools which assess functional status and HRQOL has importance in both the clinical and research areas to assess treatment efficacy from the patient perspective. Therefore, assessing HRQOL in addition to treadmill-measured walking ability provides insight as to effects of treatments on patient outcomes and may help guide therapy.
Conijn A, Eur J Vasc Endovasc Surg, 2015	Systematic review	The study aim was to critically appraise, compare, and summarize the quality of the measurement properties of all available disease- specific patient- reported outcomes for IC, measuring health related QoL/health status or functional status. Medline and Embase was searched until November 18, 2013 using relevant search terms. Eligible studies were full text articles (a) about the development or validation of a disease specific PROM aiming to measure health related QoL, health status, or functional status (b) for patients with IC. The methodological quality of the included studies was assessed with the COSMIN checklist.	In total, 43 studies were included. Ten disease specific instruments measuring health related QoL/health status and two measuring functional status for patients with IC were identified	N/A		Measurement properties of the 12 studied instruments were evaluated in 43 studies only. Most of the evaluation studies were of poor quality according to the COSMIN checklist.

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Recommendation 18	**Class**	**Level of evidence**				
Trials and registries on the treatment of patients with intermittent claudication should consider using the Vascular Quality of Life six items survey (VascuQoL-6) to incorporate patient-reported outcome measures in a comparable way.	IIa	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Nordanstig, J Vasc Surg 2014	Prospective cohort study	Patients with intermittent claudication (n=129) and chronic limb-threatening ischemia (n=71)	200	N/A	N/A	Based on structured psychometric testing, the six most informative items from VascuQoL 25 were selected (VascuQoL-6) and tested versus the original VascuQoL-25. The correlation between VascuQoL-25 and VascuQoL-6 was r = 0.88 before intervention, r = 0.96 after intervention, and the difference was r = 0.91 (P < .001). The Cronbach α for the VascuQoL-6 was .85 before and .94 after intervention. Cognitive interviews indicated that the responders considered all six items to be relevant and comprehensible. Rasch analysis was used to reduce response options from seven (VascuQoL-25) to four (VascuQoL-6). VascuQol-6 was shown to have high precision and discriminative properties. Item fit was excellent, with both "infit" and "outfit" between 0.7 and 1.3 for all six items. The standardized response mean after intervention was 1.15, indicating good responsiveness to clinical change. VascuQoL-6 results correlated strongly (r = 0.72; P < .001) with the actual measured walking ability (n = 21).
Kumlien, Health Qual Life Outcomes, 2017	Prospective cohort study	Patients with peripheral arterial disease undergoing revascularisation (n=150) or treated conservately (n=50)	219	N/A	N/A	The validity and reliability of the VQ6, as tested in a target population without the surrounding 19 items from the original VascuQoL-25 survey, was high and a good fit to the Rasch model was observed. Further, an excellent internal consistency and significant correlations between comparable dimensions in the SF-

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						36 were demonstrated. In the test-retest analysis, the percentage agreement was somewhat poor (<70%) in the six items. However, no systematic disagreements between the two assessments were seen in any of the six items, and the test-retest assessment for the VQ6 sum score showed an acceptable intraclass correlation coefficient (0.86). Finally, all items in the VQ6 were considered as both understandable and relevant by the interviewed patients.
Arndt H Eur J Vasc Endovasc Surg 2022	Delphi consensus process among lower limb peripheral arterial disease medical experts and allied health professionals.	N/A	N/A	N/A	N/A	The participation rates in two Delphi rounds were 66% (31 participants of 47 invited) and 90% (54 of 60), respectively. Overall, 145 patient-reported outcome items were documented. Following the two Delphi rounds, 18 patient-reported quality indicators remained, all of which reached consensus regarding clinical relevance. The VascuQoL short form questionnaire (VascuQoL-6) includes a total of six items. Five of these six items also matched with high rated indicators identified in the Delphi study. Consequently, the panel recommended the use of the VascuQoL-6 survey as a preferred core PROM QI set (as well as an optional extension of 12 additional patient reported QIs that were also identified).

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Recommendation 21	**Class**	**Level of evidence**				
For all patients with lower limb peripheral arterial disease who smoke, it is recommended that both behavioural interventions and pharmacotherapy for smoking cessation are offered in order to provide the most effective means for successful smoking cessation.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Morgan GD, Preventive Medicine, 1996	RCT	Smokers 50-74 years old	659	279- physician-delivered brief quit smoking advice and counselling	380- control	Quit rate 15.4% for intervention versus 8.2% in control group at 6 months (P< .005)
Canga N, Diabetes care 2000	RCT	Diabetic smokers	280	147- nurse-led initial face-to- face interview, nicotine replacement therapy (optional), follow-up support program	133- control	Smoking cessation incidence at 6 months 17.0% in intervention group versus 2.3% in control. Difference 14.7% (95%CI 8.2 to 21.3%)
Weissfeld JL, Arch Int Med 1991	RCT	Male smokers	466	143- low intensity treatment (20-30 minute session with trained counsellor plus information booklet. 1 follow-up session. 150- high intensity treatment- comprehensive set of interventions in addition to low intensity group treatment	173- control group received pamphlet of risks of smoking and benefits of quitting	Quit smoking rate at 6 months were1.2% in control group, 6.3% in low intensity group and 6.0% in in high intensity group. Quit-smoking rate in control versus low intensity group, P= .014, relative rate 5.4; 95% CI, 1.2 to 25). Quit-smoking rate in control versus high intensity group, P= .017, relative rate 5.2; 95% CI, 1.1 to 23.8)

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Bock B, JMIR MHealth UHealth 2013	RCT	Adult smokers	60	30- individual 30 min counselling session by psychologist, given quit smoking guide and daily quit smoking text messages	30- individual 30 min counselling session by psychologist, given quit smoking guide and daily non-smoking related motivational text messages	Smoking cessation at 7 days improved in intervention group compared to control group (OR=4.52, 95% CI=1.24 to 16.53)
Smith BJ, Thorax, 2013, Carson-Chahhoud RV, PLOS ONE 2020	RCT: STOP trial	Adult smokers admitted with smoking-related illness (including PAD)	392	196- counselling sessions (mean number= 3.78) plus varenicline tartrate (C +VT)	196- counselling alone (C-alone)	Self-reported continuous smoking abstinence between 2 and 104 weeks 29.2% (C +VT) versus 18.8% (C-alone), (OR 1.78; 95% CI 1.10 to 2.86; p= .02)

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Recommendation 22	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease who smoke, counselling as part of intensive smoking cessation intervention is recommended.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
D. Hennrikus, et al. J Am Coll Cardiol 2010	RCT	PAD	124	Intensive tailored PAD-specific counselling intervention n=64	Minimal smoking cessation intervention n=60	Participants randomly assigned to the intensive intervention group were significantly more likely to be confirmed abstinent at 6-month follow-up: 21.3% versus 6.8% in the minimal intervention group (chi-square = 5.21, p = 0.023).

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Recommendation 23	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease who smoke, varenicline, either alone or in combination with nicotine replacement therapy, is recommended as the first line pharmacological smoking cessation treatment due to its higher effectiveness as compared to other pharmacological alternatives.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Barua RS et. al, JACC 2018	Systematic review	Smokers	N/A	varenicline	N/A	Evidence based guideline summarizing studies of varenicline
Anthenelli R et. al., Lancet 2016	RCT	Smokers	8144	Varenicline or bupropion	nicotine patch or placebo	Varenicline-treated participants achieved higher abstinence rates than those on placebo (OR 3.61, 95% CI 3.07 to 4.24), nicotine patch (OR 1.68, 1.46 to 1.93), and bupropion (OR 1.75, 95% CI 1.52 to 2.01).

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Recommendation 28	**Class**	**Level of evidence**				
For all patients with symptomatic lower limb peripheral arterial disease, high intensity statin treatment is recommended to reduce the subsequent risk for major cardiovascular events, limb events, and disease progression.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Antoniou et al., J Vasc Surg 2015	Meta-analysis	Patients who underwent noncardiac surgical or endovascular arterial reconstruction	675 (RCTs), 22,861 (observational studies)	Perioperative statin	No statin	Statin therapy is beneficial in improving operative and interventional outcomes and should be considered as part of the optimization strategy for prevention of adverse cardiovascular and cerebrovascular events and death.
Heart Protection Study Collaborative Group, J Vasc Surg 2007	RCT	Patients with PAD	6,748 (PAD) 13,788 (other high-risk participants)	Simvastatin 40 mg and anti-oxidant vitamins	Placebo and anti-oxidant vitamins	Benefits of cholesterol-lowering statin therapy in patients with PAD, regardless of their presenting cholesterol levels and other presenting features. Allocation to 40 mg simvastatin daily reduces the rate of first major vascular events by about one-quarter, and that of peripheral vascular events by about one-sixth.
Aung et al., Cochrane Database Syst Rev 2007	Meta-analysis of RCTs	Patients with PAD	10,049 from 11 RCTs	Lipid- lowering therapy	No lipid-lowering therapy	Lipid-lowering therapy is effective in reducing cardiovascular mortality and morbidity in people with PAD. It may also improve local symptoms. Until further evidence on the relative effectiveness of different lipid-lowering agents is available, use of a statin in people with PAD and a blood cholesterol level >/=3.5 mmol/L is most indicated
Kumbhani et al., Eur Heart J 2014	Retrospective observational	Patients with symptomatic PAD	5,861	Statin	No statin	Statin use was associated with an ~18% lower rate of adverse limb outcomes, including worsening symptoms, peripheral revascularization, and ischaemic amputations.

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Mohler et al., Circulation 2003	RCT	Patients with intermittent claudication	354	Atorvastatin 80mg, Atorvastatin 10mg	Placebo	Atorvastatin improves pain-free walking distance and community-based physical activity in patients with intermittent claudication.
Peters et al., J Am Heart Assoc 2020	Retrospective observational	Patients with symptomatic PAD who underwent revascularisation	22,208 (10,922 matched)	New statin therapy	No statins	Initiating statin therapy in patients with peripheral arterial occlusive disease after index revascularization is efficient and safe with an effect size comparable to earlier studies. In 10 922 matched patients, statin initiation was associated with lower all-cause mortality (chronic limb-threatening ischemia: hazard ratio [HR], 0.75 [95% CI, 0.68–0.84]; intermittent claudication: HR, 0.80 [95% CI, 0.70–0.92]), lower risk of major amputation in patients with chronic limb-threatening ischemia (HR, 0.73; 95% CI, 0.58–0.93) and lower risk of cardiovascular events (hazard ratio, 0.80; 95% CI, 0.70–0.92) in patients with intermittent claudication during 5 years of follow-up. Safety outcomes did not differ among the study groups.
Ramos et al., J Am Coll Cardiol 2016	Retrospective observational	Patients with an ABI ≤0.95 and without clinically recognised cardiovascular disease	5,480 matched	Statins	No statins	Statin therapy was associated with a reduction in MACE and all-cause mortality among participants without clinical CVD but with asymptomatic peripheral arterial disease, regardless of its low CVD risk.
Vogel et al., Circ Cardiovasc Interv 2013	Retrospective observational	Patients with symptomatic PAD	22,954	Statins	No statins	Preoperative statins were associated with improved 1-year limb salvage after lower extremity revascularization. The strongest association was found for patients with the diagnosis of claudication.

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Mills et al., QJM 2011	Meta-analysis of RCTs	Patients with and without prior coronary heart disease	170,255 (from 76 RCTs)	Statin	Placebo	Statin therapies offer clear benefits across broad populations. Statin therapy reduced all-cause mortality, Relative Risk (RR) 0.90 [95% confidence interval (CI) 0.86-0.94, P ≤ 0.0001, I(2)=17%]; cardiovascular disease (CVD) mortality (RR 0.80, 95% CI 0.74-0.87, P<0.0001, I(2)=27%); fatal myocardial infarction (MI) (RR 0.82, 95% CI 0.75-0.91, P<0.0001, I(2)=21%); non-fatal MI (RR 0.74, 95% CI 0.67-0.81, P ≤0.001, I(2)=45%); revascularization (RR 0.76, 95% CI 0.70-0.81, P ≤ 0.0001); and a composite of fatal and non-fatal strokes (0.86, 95% CI 0.78-0.95, P=0.004, I(2)=41%).
Rodriguez et al., JAMA Cardiol 2017	Retrospective observational	Patients with atherosclerotic cardiovascular disease	509,766	High- intensity statin therapy	Moderate- and low- intensity statin therapy	A graded association between intensity of statin therapy and mortality was found in a national sample of patients with atherosclerotic cardiovascular disease. High-intensity statins were associated with a small but significant survival advantage compared with moderate-intensity statins, even among older adults. Maximal doses of high-intensity statins were associated with a further survival benefit.
De Martino et al., J Vasc Surg 2014	Retrospective observational	Patients who underwent vascular surgery	14,489 (4,340 bypasses)	Statin	No statin	Statin therapy (along with antiplatelet therapy) preoperatively and at discharge was associated with reduced 30-day mortality and an absolute 18% improved 5-year survival after vascular surgery.
Cholesterol Treatment Trialists' Collaborators, Lancet 2005	Meta-analysis of RCTs	Patients	90,056 (from 14 RCTs)	Statins	Control	Statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL cholesterol, largely irrespective of the initial lipid profile or other presenting characteristics. The absolute benefit relates chiefly to an individual's absolute risk of such events and to the absolute reduction in LDL cholesterol achieved. There was a 12% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol (rate ratio [RR] 0.88, 95% CI 0.84-0.91; p<0.0001).

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Cholesterol Treatment Trialists' Collaborators, Lancet 2015	Meta-analysis of RCTs	Patients	174,149 (from 22 RCTs)	Statins	Control	In men and women at an equivalent risk of cardiovascular disease, statin therapy is of similar effectiveness for the prevention of major vascular events. The proportional reductions per 1·0 mmol/L reduction in LDL cholesterol in major vascular events were similar overall for women (rate ratio [RR] 0·84, 99% CI 0·78–0·91) and men (RR 0·78, 99% CI 0·75–0·81, adjusted p value for heterogeneity by sex=0·33) and also for those women and men at less than 10% predicted 5 year absolute cardiovascular risk (adjusted heterogeneity p=0·11).

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Recommendation 30	**Class**	**Level of evidence**				
For patients >80 years with lower limb peripheral arterial disease, it is recommended to offer treatment with statins for the same indications that apply to younger people, but caution should be exercised in patients who are under polypharmacy and or with severely impaired liver- or kidney function.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Ponce et al, J Clin Endocrinol Metab, 2019	Systematic review and meta-analysis of randomized clinical trials	Elderly patients (>65 years) receiving lipid-lowering therapy for primary or secondary prevention of cardiovascular events	60,194 elderly patients from 23 different RCTs that compared the effects of statins, fibrates, niacin, or different low- density lipoprotein (LDL) targets on cardiovascular outcomes in individuals aged 65 years or older. Experimental treatments were compared with placebo, usual care or active control. 17 trials compared statins with placebo in 50,322 participants.	Lipid- lowering agents, especially statin therapy	Placebo, usual care or active control	For secondary prevention, statins reduced all- cause mortality (RR: 0.80, 95% CI: 0.73 to 0.89), cardiovascular mortality (RR: 0.68, 95% CI: 0.58 to 0.79), CAD (RR: 0.68, 95% CI: 0.61 to 0.77), MI (RR: 0.68, 95% CI: 0.59 to 0.79), and revascularization (RR: 0.68, 95% CI: 0.61 to 0.77). Author's conclusions: high-certainty evidence supports statin use for secondary prevention in older individuals.

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Recommendation 31	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, it is recommended to monitor long-term prescription rates and longitudinal adherence to statin therapy to improve treatment concordance.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Kokkinidis et al., Vasc Med 2020	Meta-analysis	Patients with critical limb ischaemia	26,985 from 19 studies	Statin	No statin	Statins are associated with decreased risk for amputation, mortality, and MACCE, as well as increased overall patency rates among patients with CLI. Patients treated with statins were 25% less likely to undergo amputation (HR 0.75; 95% CI: 0.59-0.95; I2 = 79%) and 38% less likely to have a fatal event (HR 0.62; 95% CI: 0.52-0.75; I2 = 41.2%).
Pastori et al., Thromb Haemost 2020	Meta-analysis	Patients with PAD	138,060 from 51 studies (2 RCTs)	Statin	No statin	Statins reduce the incidence of MALE, all-cause, and CV mortality in patients with PAD. Statins reduced MALE incidence by 30% (pooled hazard ratio [HR]: 0.702; 95% confidence interval [CI]: 0.605-0.815) and amputations by 35% (HR: 0.654; 95% CI: 0.522-0.819), all-cause mortality by 39% (pooled HR: 0.608, 95% CI: 0.543-0.680), CV death by 41% (HR: 0.594; 95% CI: 0.455-0.777), composite CV endpoints by 34% (pooled HR: 0.662; 95% CI: 0.591-0.741) and ischemic stroke by 28% (pooled HR: 0.718; 95% CI: 0.620-0.831).
Peters et al., J Am Heart Assoc 2020	Retrospective observational	Patients with symptom atic PAD	22,208 (10,922 matched)	New statin therapy	No statin therapy	Initiating statin therapy in patients with peripheral arterial occlusive disease after index revascularization is efficient and safe with an effect size comparable to earlier studies. Statin initiation was associated with lower all-cause mortality (chronic limb-threatening ischemia: hazard ratio [HR], 0.75 [95% CI, 0.68–0.84]; intermittent claudication: HR, 0.80 [95% CI, 0.70–0.92]), lower risk of major amputation in patients

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						with chronic limb-threatening ischemia (HR, 0.73; 95% CI, 0.58–0.93) and lower risk of cardiovascular events (hazard ratio, 0.80; 95% CI, 0.70–0.92) in patients with intermittent claudication during 5 years of follow-up. Safety outcomes did not differ among the study groups.
Sigvant et al., Eur J Cardiovasc Prev Rehabil 2009	Retrospective observational	Patients with PAD	5,080	Preventive drug use	N/A	Statins were used by 17.5% (16.9-18.2), 29.4% (29.0-30.1), and 30.3% (29.9-30.8) of the patients with ASYMPTOMATIC PAD, IC, and CLI, respectively. Preventive drug use was more common in men with PAD. Compared with women they had an odds ratio of 1.3 (range 1.1-1.5) for lipid-lowering therapy.

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Recommendation 32	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, it is recommended to reduce the low density lipoprotein cholesterol concentrations to <1.4 mmol/L (<55 mg/dL) and decrease it by ≥50% if baseline values are within 55-110 mg/dL.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Mach et al., Eur Heart J 2019	Practice guidelines, systematic review					People with atherosclerotic cardiovascular disease, either clinical or unequivocal on imaging, including peripheral arterial disease should be acknowledged as very-high cardiovascular patients. In primary and secondary prevention for these patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4mmol/L (<55mg/dL) are recommended.
Cannon et al., NEJM 2015		Patients who had been hospitalised for an acute coronary syndrome	18,144	Combination of simvastatin (40mg) and ezetimibe (10mg)	Combination of simvastatin (40mg) and placebo	When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit.
Fulcher et al. for the Cholesterol Treatment Trialists Collaboration, Lancet 2010		Patients	174,149 (from 22 RCTs)	Statins	Control	In men and women at an equivalent risk of cardiovascular disease, statin therapy is of similar effectiveness for the prevention of major vascular events. The proportional reductions per 1·0 mmol/L reduction in LDL cholesterol in major vascular events were similar overall for women (rate ratio [RR] 0·84, 99% CI 0·78–0·91) and men (RR 0·78, 99% CI 0·75–0·81, adjusted p value for heterogeneity by sex=0·33) and also for those women and men at less than 10% predicted 5 year absolute cardiovascular risk (adjusted heterogeneity p=0·11).

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Sabatine et al., NEJM 2017		Patients with atherosclerotic cardiovascular disease	27,564	Statin therapy and evolocumab	Statin therapy and placebo	Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events.
Belch et. al., Vasa 2021	Consensus document					LDL-C should be lowered to <1.4mmol/L (<55mg/dL) and by >50% if pre-treatment values are 1.8-3.5mmol/L (70-135mg/dL).

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Recommendation 33	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease who are unable to achieve appropriate lipid targets despite following lifestyle advice and adherence to a high intensity statin therapy with appropriate doses of atorvastatin or rosuvastatin, the addition of ezetimibe is recommended, to reach recommended low density lipoprotein cholesterol target levels.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Cannon et al., N Engl J Med 2015	RCT	Patients who had been hospitalised for an acute coronary syndrome	18,144	Combina tion of simvastat in (40mg) and ezetimibe (10mg)	Combination of simvastatin (40mg) and placebo	When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit.

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Recommendation 35	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, it is recommended to reduce the blood pressure to ≤ 120-129/80 mmHg in patients <70 years and to ≤130-139/80 mmHg in patients ≥70 years to reduce the risk of major adverse cardiovascular events.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Unger et al., Am Heart Assoc 2020	Practice guidelines, systematic review					
Williams et. al., Eur Heart J 2018	Practice guidelines, systematic review					
Visseren, Eur Heart Journal, 2021	Practice guidelines, systematic review					The recommended ultimate SBP treatment target range for younger patients (18–69 years) is 120–130 mmHg, although some patients may safely achieve lower treated SBP levels than this and, if they are well tolerated, there is no need to back-titrate treatment. The ultimate target SBP for patients aged ≥70 years is <140 mmHg and down to 130 mmHg if tolerated.
Lewington et al., Lancet 2002	Meta-analysis	Studies providing data on blood pressure/ cholesterol/age /sex	958,074 from 61 prospective studies	N/A	N/A	Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

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Recommendation 36	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease and hypertension, it is recommended that antihypertensive pharmacotherapy follows a stepwise approach.* * Including angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) plus dihydropyridine calcium channel blocker ideally as one-pill low (step 1) or full dose combination (step 2). An escalation should be considered by adding a thiazide-like diuretic in step 3.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Visseren, Eur Heart Journal, 2021	Practice guidelines, systematic review					
Unger et al., Am Heart Assoc 2020	Practice guidelines, systematic review					
Yusuf et al., Lancet 2008	RCT	Patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage.	5,926	Telmisartan 80mg per day	Placebo	Telmisartan was well tolerated in patients unable to tolerate ACE inhibitors. Although the drug had no significant effect on the primary outcome of this study, which included hospitalisations for heart failure, it modestly reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke.
Ostergren et al., Eur Heart J 2004	RCT (Secondary analysis)	PAD patients included in the Heart Outcomes Prevention Evaluation (HOPE) study	3,099	ramipril 2.5mg daily for 7–10 days in a single blind fashion	Placebo	Ramipril reduced the risk of clinical outcomes in those with a clinical history of PAD as well as in the patients with subclinical PAD.

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Yusuf et al., N Engl J Med 2000	RCT	Patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure.	9,297	Ramipril 10mg per day	Placebo	Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure. Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1 percent, as compared with 8.1 percent in the placebo group; relative risk, 0.74; P<0.001), myocardial infarction (9.9 percent vs. 12.3 percent; relative risk, 0.80; P<0.001), stroke (3.4 percent vs. 4.9 percent; relative risk, 0.68; P<0.001), death from any cause (10.4 percent vs. 12.2 percent; relative risk, 0.84; P=0.005), revascularization procedures (16.3 percent vs. 18.8 percent; relative risk, 0.85; P<0.001), cardiac arrest (0.8 percent vs. 1.3 percent; relative risk, 0.62; P=0.02), [corrected] heart failure (9.1 percent vs. 11.6 percent; relative risk, 0.77; P<0.001), and complications related to diabetes (6.4 percent vs. 7.6 percent; relative risk, 0.84; P=0.03).

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Recommendation 37	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease and diabetes, it is recommended to reduce the blood glucose to near normal haemoglobin A1c values ≤ 7% (≤ 53 mmol/mol) to prevent vascular complications.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Cosentino et al., Eur Heart J 2019	Practice guidelines, systematic review					
American Diabetes Association 2021	Practice guidelines, systematic review					
UK Prospective Diabetes Study Group, Lancet 1998	Prospective observational	Patients with type 2 diabetes	4,075			Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycaemic attacks than are insulin and sulphonylureas, it may be the first-line pharmacological therapy of choice in these patients. Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13-47, p=0.002) for any diabetes-related endpoint, 42% for diabetes- related death (9-63, p=0.017), and 36% for all- cause mortality (9-55, p=0.011). Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032).

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Diabetes Control and Complications Trial Research Group 1993	RCT	Patients with insulin-dependent diabetes mellitus	1,441	External insulin pump	Three or more daily insulin injections	Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes mellitus.
Holman et al. 2008	RCT	Patients with newly diagnosed type 2 diabetes	5,102	Dietary restriction	Either sulfonylurea or insulin or metformin (overweight patients)	Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients. In the sulfonylurea- insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), and risk reductions for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007) emerged over time, as more events occurred. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause (27%, P=0.002).

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Recommendation 38	**Class**	**Level of evidence**				
Patients with lower limb peripheral arterial disease and type 2 diabetes, both sodium-glucose cotransporter 2 inhibitors or glucagon like peptide 1 receptor agonists are recommended as first line hypoglycaemic agents to reduce the risk of major cardiovascular and cardiorenal events.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Cosentino et al., Eur Heart J 2019	Practice guidelines, systematic review					These guidelines recommended both SGLT2 inhibitors (empagliflozin, canagliflozin, or dapagliflozin) or GLP-1 receptor agonists in patients with type 2 diabetes mellitus and cardiovascular disease to reduce cardiovascular events. Furthermore, the SGLT2 inhibitor empagliflozin or the GLP-1 receptor agonist liraglutide are recommended to reduce the risk of death in these patients.
American Diabetes Association 2021	Practice guidelines, systematic review					These guidelines recommended to treat patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure with SGLT2 inhibitors or GLP-1 receptor agonists.
Visseren et al., Eur Heart J 2021	Practice guidelines, systematic review					These guidelines recommended the use of GLP-1 receptor agonists or SGLT2 inhibitors in persons with type 2 diabetes mellitus and atherosclerotic cardiovascular disease to reduce cardiovascular and/or cardiorenal outcomes. Furthermore, the use of SGLT2 inhibitors is recommended in patients with chronic kidney disease to improve cardiorenal outcomes and with heart failure with reduced ejection fraction to lessen heart failure hospitalisations and cardiovascular death.

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Recommendation 39	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, an annual influenza vaccination is recommended, to reduce the risk of a severe influenza infection.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Peters et al., Eur J Vasc Endovasc Surg 2021	Retrospective observational	BARMER insured	100,000	Symptomatic PAD	Control group	The risk of inpatient hospital stay associated with influenza, ARDS, and acute respiratory disease was more than four times higher in patients with PAOD than in the control sample. Of 10 000 persons, 63.6 suffered from influenza, 8.3 from ARDS, and 734.3 from acute respiratory disease during one year follow up after index stay.
Ciszewski et al., Eur Heart J 2008	RCT	Patients with confirmed coronary artery disease	658	Influenza vaccine	Placebo	In optimally treated CAD patients influenza vaccination improves the clinical course of CAD and reduces the frequency of coronary ischaemic events.
Gurfinkel et al., Eur Heart J 2004	RCT	Patients with myocardial necrosis and planned percutaneous coronary interventions	200	Flu vaccination	No vaccination	Influenza vaccination may reduce the risk of death and ischaemic events in patients suffering from infarction and post-angioplasty during flu season. This effect was significantly evident at 1-year follow-up.

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Recommendation 40	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, full vaccination against COVID-19 disease is recommended due to the increased risk of hospitalisation with severe COVID-19 illness.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Smolderen et al, Curr Probl Cardiol, 2021	Registry study	Registry study on patients hospitalised for SARS- Cov-2 between March 1 and Nov 10 2020	n=3830, out of which 693 had PAD	N/A	N/A	PAD was independently associated with increased mortality (OR 1.45, 95% CI 1.11-1.88) and MACE (OR 1.48, 95% CI 1.16-1.87); after controlling for known risk factors.

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Recommendation 41	**Class**	**Level of evidence**				
For all patients with lower limb peripheral arterial disease (including asymptomatic stages) it is recommended to strive for at least 150-300 minutes a week of moderate intensity or 75-150 minutes a week of vigorous intensity aerobic physical activity, to reduce all cause and cardiovascular mortality and cardiovascular morbidity.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Powell et al, J Phys Act Health 2018	Review The Scientific Foundation for the Physical Activity Guidelines for Americans, including a review of systematic reviews and meta-analyses	General adult population	837 included articles for review	Different types of activity (e.g., aerobic, muscle strengthening, balance training), which tended to be of light to moderate intensity		All included reviews reported an inverse relationship between self-reported moderate-to vigorous physical activity and all-cause mortality, cardiovascular mortality and incidence. For more detailed information, please refer to the reference.
Kraus et al, Medicine & Science in Sports & Exercise 2019	Systematic umbrella review of systematic reviews, meta-analyses, and pooled analyses	General adult population	13 different papers were included, and up to 3.9 million participants in total were studied across these reviews and meta-analyses	Physical activity dose categories in metabolic equivalents of task (MET) for minutes or hours per week using quartiles or a variety of categories such as inactive and low, medium, and high amounts of physical activity, or high versus low amounts of physical activity		Follow-up for these studies ranged from 3.8 to more than 20 years. All 13 studies demonstrated a significant inverse dose–response relationship between moderate- to vigorous physical activity and all-cause mortality, cardiovascular mortality and incidence of CVD.. About 70% of the benefit was obtained by physical activity 150 minutes/week. The effects of moderate-to-vigorous physical activity on ischemic cardiovascular diseases, including coronary heart disease, ischemic stroke, and heart failure are very similar to those of all-cause mortality and CVD mortality. For more detailed information, please refer to the reference

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Recommendation 42	**Class**	**Level of evidence**				
For individuals with asymptomatic lower limb peripheral artery disease, supervised exercise programmes or structured home based exercise programmes may be considered, to improve maximum walking distance, health related quality of life, physical activity levels and self reported functional impairment.	IIb	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
McDermott et al, J Cardiopulm Rehabil, 2004	Pilot RCT	Asymptomatic PAD	N=32	Supervised treadmill walking program	Usual care	Maximum walking distance: NS 6MWT: NS WIQ: NS
Laslovich et al, Med Sci Sports Exerc, 2020	RCT	Asymptomatic PAD	N=38	Structured home-based exercise program	Attention control	6MWT: Intervention 354±98.5m to 467±100.6 m versus control 358 ± 90m to 364.6 ± 85 m, p<0.001. Total steps/day: Intervention 5976±2497 to 8431±250 versus control 6699±2046 to 6457±1880, p<0.001. Nonsleep sit/lie hours/day: Intervention 9.7±0.68 to 8.9±1.24 versus control 9.46±0.82 to 9.64±0.91, p<0.001 Sit-stand transitions/day: Intervention 45.7±11.7 to 52.8±10.4 versus control 41.3±11.5 to 39.9±10.8, p<0.001
Farhad et al, JPMA, 2019	Meta-analysis (RCTs)	PAD, with or without IC	9 studies, n=564	Supervised and structured exercise programs	Control	It was reported that maximal and pain-free walking distance, 6MWT improved more in the exercise group versus control group, p<0.05. No exact numbers were presented.

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McDermott et al. JAMA, 2009	RCT	Mixed population: Asymptomatic PAD (81%) and IC	156	Supervised treadmill exercise (1) or lower extremity resistance exercise (2)	Control (3)	6MWT: Group 1 increased their walking distance by 35.9m (95% CI 15.3-56.5), p<0.001, compared with group 3. Group 2 versus group 3, NS Treadmill walking time: Group 1 increased 3.44 min (95%CI 2.05-4.84), p<0.001, compared with group 3. Group 2 increased 1,9 min (95% CI 0.49-3.31), compared with group 3, p=0.009. Accelerometer measured physical activity: NS SF-36 physical functioning: Group 1 improved 7.5p (95% CI 0-15), p=0.02 more than group 3 Group 2 improved 7.5p (95% CI 0-15), p=0.04 more than group 3. Walking impairment distance score: Group 1 improved 10.7p (95% CI 1.56-19.9), p<0.02 more than group 3. Group 2 improved 6.9p (95% CI 1.1-12.8), p=0.02 more than group 3. Group 2 improved 10.4p (95% CI 0-20.8), p=0.03 more than group 3
McDermott et al. JAMA, 2013	RCT	Mixed population Asymptomatic PAD (72%) and IC	N=194	Home-based structured walking exercise	Control with health education sessions	6MWT: Intervention improved more than control: 42.4 (95%CI 27.9-56.8) versus -11.4 (95% CI -25.4 – 3.2), p<0.01. Total treadmill walking time: Intervention improved more than control: 1.54s (95%CI 0.87-2.20) versus 0.53s (0.87-2.20), p<0.04. WIQ distance and speed score: Intervention improved more than control: 11.1 (95%CI 3.9-18.1), p<0.003 and 10.4 (95%CI 3.4-17.4), p<0.004.

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Recommendation 43	**Class**	**Level of evidence**				
Patients with asymptomatic lower limb peripheral arterial disease without other contemporary indications for antithrombotic treatment should not be treated with aspirin as bleeding risk and side effects are likely to outweigh the benefit.	III	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Belch et al BMJ 2008	Multicenter RCT	DM type 1 or 2 and ABI<0.99, without CVD	1276	Aspirin (100 mg) tablet plus antioxidant capsule (n=320), Aspirin tablet plus placebo capsule (n=318),	Placebo tablet plus placebo capsule (n=318) Placebo tablet plus antioxidant capsule (n=320)	Primary end point: Composite: Death from coronary heart disease or stroke, or non-fatal myocardial infarction, stroke or above ankle amputation for critical limb ischemia. Primary events in treatment arm vs placebo: 0.98 (95% CI: 0.76-1.26) No evidence of reduction of CV events in this population by use of aspirin or anti-oxidants.
Fowkes et al JAMA 2010	RCT	ABI≤0.95, no CVD	28 980	Aspirin 100 mg	Placebo	Composite of initial fatal or nonfatal coronary event or stroke or revascularization: 13.7 events per 1000 person-years in the aspirin group vs 13.3 in the placebo group; hazard ratio [HR], 1.03; 95% CI, 0.84-1.27) Aspirin as compared placebo did not reduce vascular events
Ambler et al Br J Surg 2020	Review	Asymptomatic PAD	13 542	Aspirin	Placebo	Secondary prevention with aspirin did not significantly reduce non-fatal stroke (5 (95% CI 0–8) fewer per 1000 patients, p =0.055).

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Recommendation 44	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, even if asymptomatic, it is recommended to consider an ankle brachial index ≤0.9 or ≥1.4 a risk-enhancing factor for a cardiovascular event and for an increased all cause mortality.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Fowkes, European Heart Journal, 2006	Multi-center study	Mixed population: ABI <0.9 in 30.9% of at risk patients and 40.5% of with disease patients		8891		ABI <0.9 was associated with an increasing number of risk factors in at risk patients (r = 20.056, p = 0.02)
Hajibandeh 2017 vascular 2017	Meta-analysis	Symptomatic and asymptomatic PAD		Symptomatic PAD: 94,254 Asymptomatic PAD: 29.827		ABI <0.9 was risk of all-cause mortality (risk ratio: 2.52, 95% CI 2.26-2.82, P < 0.00001); cardiovascular mortality (risk ratio: 2.94, 95% CI 2.72-3.18, P < 0.00001); cerebrovascular event (risk ratio: 2.17, 95% CI 1.90-2.47, P < 0.00001); myocardial infarction (risk ratio: 2.28, 95% CI 2.07-2.51, P < 0.00001); fatal myocardial infarction (risk ratio: 2.81, 95% CI 2.33-3.40, P < 0.00001); fatal stroke (risk ratio: 2.28, 95% CI 1.80-2.89, P < 0.00001); The composite of myocardial infarction, stroke, and death (risk ratio: 2.29, 95% CI 1.87-2.81, P < 0.00001).
Heald; Atherosclerosis 2006	Review	Population-based: ABI<0.9 (symptomatic or asymptomatic PAD not specified)		44.590		ABI<0.9 was associated with an increased risk of subsequent all cause mortality (pooled RR 1.60, 95% CI 1.32-1.95), cardiovascular mortality (pooled RR 1.96, 95% CI 1.46-2.64), coronary heart disease (pooled RR 1.45, 95% CI 1.08-1.93) and stroke (pooled RR 1.35, 95% CI 1.10-1.65) after adjustment for age, sex, conventional cardiovascular risk factors and prevalent cardiovascular disease

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Qu, Cell Biochemistry & Biophysics 2015	Review	ABI<0.9 (symptomatic PAD or asymptomatic PAD not specified)		22,705		ABI of <0.90 was associated with an increased risk of all-cause mortality [odds ratio 2.74 (95 % confidence interval 2.03-3.68) cardiovascular., death, 3.23 (1.98-5.29) and 1.26] and non-cardiovascular mortality, 2.23 (1.40-3.55) and 1.29]
Sartipy, Int J cardiol Cardiovasc Risk and Prevention 2022 2018	Prospective cohort study	10-year follow-up of randomly selected citizens (with or without PAD, separated by PAD stage) aged 60-90 years in Sweden that underwent ABI measurements at baseline,	Total n=4659	Asymptomatic PAD n= 559	References n=4100	All cause mortality after 10 years was for references: 27,4% and ASYMPTOMATIC PAD 56,2% (CV mortality 8.6% vs 28,5%) Crude and age adjusted HR (95% CI) for fatal and non-fatal CV events was: 1.82 (1,72-1,93) and 1,48 (1,39-1,57).
Sigvant et al EJVES 2016	Review	ABI<0.9	Total subjects 95,205	Asymptomatic PAD: 1789 Symptomatic PAD: 57322 ABI<0,9 where symptomatic or asymptomatic PAD were not specified: 7636	References: 28,452	HR (95% CI) for ASYMPTOMATIC PAD vs references for all-cause mortality and CV mortality: 1.53 (1.18-1.99) and 1.94 (1.29-2.92)

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Recommendation 45	**Class**	**Level of evidence**				
For patients with intermittent claudication, a stepwise approach is recommended, providing risk factor management, best medical treatment, and exercise therapy as a first step, and revascularisation as a second step in compliant patients with continued disabling limb symptoms.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Fakhry et al. Circulation: cardiovascular interventions 2021	RCT (ERASE study)	Patients with intermittent claudication and aorta-iliac or femoropopliteal disease	212	Endovascular revascularisation (ER) + SET	SET	During 12 months follow up similar improvement in QoL (EQ-5D mean difference 0.012 [99% CI, −0.060 to 0.085). From a health care perspective, the estimated ICER for ER+SET versus SET was €34,810 per QALY gained.
Hageman et al, EJVS 2017	Population based study based on insurance data	Patients with intermittent claudication	1,690	SET first	first	Between 2009 and 2011 there was a 22% increase in adherence to SET as a first treatment strategy. In the same period, average costs of treatment per patient in 2011 were 6% lower than in 2009 (€6,885 vs €7,300; p = 0.020).
Van den Houten, BJS 2016	Markov model	Hypothetical cohort of patients with intermittent claudication	NA	SET first	ER first	SET is more cost-effective than ER. The mean costs of a SET-first treatment strategy over a 5- year interval were lower per patient, but there was no statistically significant difference in effectiveness. ER was associated with an additional €91600 per QALY gained compared with SET.
Reynolds et al, JAHA 2014	RCT (CLEVER study)	Patients with intermittent claudication and aorta-iliac disease	111	ER, SET	BMT	At 18 months, QALY was 1.20+-0.20 for ER and 1.16+-0.15 for SET (adjusted difference in means 0.02 (95% CI 0.04 to 0.08) p=0.59). The ICER for ER versus SET at 5 years was $122,600 per QALY gained.

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Fokkenrood et al EJVES 2014	Population based study based on insurance data	Patients with intermittent claudication	4,954	SET first	Intervention first (open or ER), Neither therapy	During 2 years follow up, 6.4% of SET patients received secondary intervention, 35.2% of ER patients received secondary intervention. Mean total costs per patient were €2,191, €9,851 and €824 for SET, intervention, and no therapy, respectively. Implementation of a stepped care model for patients with IC may lead to significant savings of health care resources.
Mazari et al, BJS 2013	RCT	Patients with intermittent claudication with femoropopliteal disease	178	SET+ER	SET, PTA	No difference between treatments in mean QALYs gained (PTA 0.62 (95%CI 0.59-0.65), SET 0.63 (95% CI 0.60-0.66), ER+SET 0.65 (95% CI 0.62-0.68). SET is the most cost-effective first-line treatment; compared to ER, ICER for SET was -€381,694/QALY and for SET + PTA -€13,450.
Spronk et al, JVS 2008	RCT	Patients with intermittent claudication with aorta-iliac or femoropopliteal disease	151	SET	ER	At 12 months functional capacity was similar for both groups (adjusted mean difference maximum walking distance 24m (99% CI -42-91, p-0.34)). QALY improvement was similar for both groups (mean difference 0.01 (99% CI 0.05-0.07, p=0.73)). ICER was €231,800/QALY for ER as compared to SET.
Treesak et al, Vasc Med 2004	Modelling study based on data from published papers	-	-	SET	ER (PTA without stent)	At 3 months, ER was more effective than SET and resulted in an additional 38 meters at an additional cost of $6719, for an ICER of $177/meter. At 6 months, however, exercise was more effective than PTA, resulting in an additional 137 meters walked, and costs less ($61 less per meter gained).
De Vries et al, Radiology 2002	Markov model	Hypothetical patients with intermittent claudication		SET	Intervention (ER or open)	ICER was $38,000/QALY for ER as compared to SET.

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Recommendation 46	**Class**	**Level of evidence**				
For patients with intermittent claudication, a supervised exercise program is recommended as first line therapy to improve maximum and pain free walking distance, health related quality of life and self reported functional impairment.	1	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Hageman et al, Cochrane report, 2018	Meta-analysis (RCTs)	IC	SET:635 HBET:320	SET	HBET	Maximum treadmill walking distance: SMD of 0.37 (95% CI 0.12 to 0.62; P = 0.004 (3 months) 0.68 (95% CI 0.07 to 1.30; P = 0.03) 6 months). This translates to a difference in favor of the SET group of approximately 120 meters in increased MWD. Pain-free treadmill walking distance: SMD 0.51 (95% CI 0.21 to 0.81; P = 0.0009) (3 months). SMD 1.13 (95% CI 0.63 to 1.63; P < 0.00001) (6 months). This translates to a difference in favor of the SET group of approximately 120 meters in increased MWD.

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Hageman et al, Cochrane report, 2018	Meta-analysis (RCTs)	IC	SET:635 WA: 445	SET	Unsupervised walk advise (WA)	Maximum treadmill walking distance: SMD of 0.80 (95% CI 0.53 to 1.07; P < 0.00001 (3 months). SMD of 0.75 (95% CI 0.44 to 1.05; P <0.00001. This translates to a difference in favor of the SET group of approximately 210 meters in increased MWD. Pain-free treadmill walking distance: SMD was increased to 0.74 (95% CI 0.56 to 0.93; P < 0.00001) (3 months). SMD of 0.60 (95% CI 0.39 to 0.82; P < 0.00001) (6 months). This translates to a difference in favor of the SET group of approximately 140 meters in increased PFWD. Health-related quality of life. At 9 months data show benefit of SET over WA for physical functioning (MD 8.40, 95% CI 2.91 to 13.89, p = 0.003), pain (MD 7.90, 95% CI 1.26 to 14.54, p=0.02), physical component summary (MD 3.0, 95% CI 0.51 to 5.49, 9=0.02). At 12 months, data show benefit of SET over WA for physical functioning (MD 5.59, 95% CI 1.09 to 10.08; p= 0.01), pain (MD 7.65, 95% CI 3.15 to 12.15; p=0.0009) and physical component summary (MD 2.76, 95% CI 0.43 to 5.09; p=0.02. There were no clear differences in any other subscale or time points. Self-reported functional impairment At 6 months, distance (MD 9.17, 95% CI 2.81 to 15.53, p= 0.005), stair (MD 6.51, 95% CI 0.07 to 12.95; p= 0.05), and combined scores (MD 5.99, 95% CI 0.56 to 11.42; p=0.03) showed improvement with SET over WA. At 9 months, distance (MD 10.00, 95% CI 1.50 to 18.50; p=0.02), speed (MD 12.00, 95% CI 6.38 to 17.62; p< 0.0001), and combined scores (MD 10.00, 95% CI 4.04 to 15.96; p=0.001) showed improvement with SET over WA. At 12 months, distance (MD 10.84, 95% CI 4.81 to 16.86; p=0.0004), speed (MD 9.32, 95% CI 3.64 to 15.00; p=0.001), and combined scores (MD 8.76, 95% CI 2.78 to 14.74; p = 0.004) showed clear improvement with SET There were no clear differences in any other subscale or time points.

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Parmenter et al, Sports Med, 2015	Meta-analysis (RCTs)	Diagnosed PAD	794	Treadmill-based SET	Usual medical care, with or without exercise advice	Maximum walking distance: Mean 41.0 m (95% CI 28.8-53.2m, p<0.001) (treadmill) in favor of SET. Maximum walking distance: Mean 34.9 m (95% CI 25.6-44.1 m, p<0.001) (6MWD) in favor of SET. Pain-free walking distance (treadmill). Mean 68.8 m, 95% CI 54.4-83.2 m, p<0.00001 in favor of SET. Pain-free walking distance (6MWT). Mean 52.7 m, 995% CI 24.7-80.6m, p<0.001 in favor of SET Health-related quality of life. Short-Form Physical Component Summary: A small improvement was observed in exercise training participants versus controls: MD 1.24 (95% CI 0.48 to 2.01, p=0.001). The one study that used resistance exercise did not improve SF-PCS score. Walking impairment questionnaire. WIQ speed: A significant improvement was observed in exercise versus control: MD 9.60 (95% cI 6.98 to 12.23, p< 0.00001). Both studies that used resistance exercise did not improve WIQ speed. WIQ distance: A significant improvement was observed in exercise versus control: MD 7.41 (95% CI 4.49 to 10-33, p<0.00001. The one study that used resistance exercise did not improve WIQ speed. WIQ stair climbing: an improvement was observed in exercise versus control: MD 5.07 (95% CI 3.16 to 6.99, p<0.00001). Both studies that used resistance exercise did not improve WIQ speed.
Vemulapalli et al, Am Heart J, 2015	Meta-analysis (RCTs)	IC	13 studies	SET, treadmill-based, circuit training, and walking exercises	UE, walking or exercise advice	Maximum treadmill walking distance: Mean 118 m (95% CI 55-179 m, p<0.001) (6 months follow- up) in favor of SET. Maximum treadmill walking distance: Mean 86 m (95% CI 52-118 m, p<0.001) (12 months follow- up) in favor of SET. Painfree treadmill walking distance at 6 months. Mean 35 m, 95% CI 22-48 m, p<0.001 for SE versus UE. Painfree treadmill walking distance at 12 months. Mean 23 m, 95% CI 23 m, CI 10-36 m, p<0.001 for SET versus UE
Gommans et al, Eur J Vasc Endovasc Surg, 2014	Meta-analysis (RCTs)	IC	1406	SET	No exercise control, walk advice	Maximum treadmill walking distance: SET results were superior with an SMD of 0.96 (95% CI 0.76- 1.16) (6 months follow-up) Pain-free treadmill walking distance: SET results were superior with an SMD of 0.89 (95% CI 0.65- 1.14) at 6 months follow-up

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Fokkenrood et al, Cochrane Report, 2013	Meta-analysis (RCTs)	IC	3 months: 592 6 months: 686	SET. Walking or training of lower limbs	Walk advice or structural home-based exercise programme	Maximum treadmill walking distance: Effect size 0.69 (95% CI 0.51 to 0.86) (3 months). This translates to a difference in favor of SET of approximately 180 m. Effect size of 0.48 (95% CI 0.32 to 0.64) (6 months) Pain-free treadmill walking distance: Effect size of 0.70 (95% CI 0.52 to 0.89) (3 months) This translates to a difference in favor of the supervised group of approximately 150 m in increased pain- free walking distance. Effect size of 0.52 (95% CI 0.35 to 0.69) (6 months) Health-related quality of life General health showed significant improvement with SET (ES 0.30, 95% CI 0.05 to 0.55) at 3 months follow-up. Role of pain showed significant improvement with SET. Effect size 0f 0.25, 95% CI 0.00 to 0.49 at 6 months
Fakhry et al, J Vasc Surg, 2012	Meta-analysis (RCTs)	IC	1054	SET, walking therapy	No intervention	Maximum treadmill walking distance: Mean 180 m (95% CI 130-230 m) in favor of SET Painfree treadmill walking distance: Mean 128 m, 95% CI, 92-165 m in favor of SET
Pymer et al, J Vasc Surg, 2021	Meta-analysis	IC	334 306	SET SET	HBET HBET	Maximum treadmill walking distance: MD 139m, 95% CI 45 to 232m, p = .004 in favor of SET Painfree treadmill walking distance: (MD 84m, 95% CI 25 to 143m, p = .005 in favor of SET

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Recommendation 47	**Class**	**Level of evidence**				
For patients with intermittent claudication, a structured home based exercise programme with behaviour intervention strategies should be considered, to improve maximum and pain free walking distance, when supervised exercise therapy is not possible	IIa	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Golledge et al, Br J Surg, 2019	Meta-analysis (RCTs)	PAD	Treadmill test: 524 6MWT: 441	HBET	WA	Maximum walking distance: SMD 0.32 (95% CI 0.15 to 0.50, p<0.001 (treadmill test) in favor of HBET. SMD 0.28 95% CI 0.09 to 0.47, p=0.004 (6MWT) in favour of HBET Pain-free walking distance: SMD 0.45 (95% CI 0.27 to 0.62, p<0.001 (treadmill test) in favor of HBET
Pymer et al, J Vasc Surg, 2021	Meta-analysis	IC	334 306	HBET HBET	SET SET	Maximum treadmill walking distance: MD 139m, 95% CI 45 to 232m, p = .004 in favor of SET Painfree treadmill walking distance: (MD 84m, 95% CI 25 to 143m, p = .005 in favor of SET
Pymer et al, J Vasc Surg, 2021	Meta-analysis	IC	137 109	HBET HBET	Basic exercise advice Basic exercise advice	Maximum treadmill walking distance: MD 39.0m, 95% CI -123.1 to 201.1m, p = .64 Pain-free walking distance: MD 64.5m, 95% CI 14.1 to 114.8m, p = .01, in favor of HBET
Pymer et al, J Vasc Surg, 2021	Meta-analysis	IC	100	HBET	No exercise controls	Maximum treadmill walking distance: MD 136m, 95% CI -2 to 273m, p = .05

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Recommendation 48	**Class**	**Level of evidence**				
For patients with intermittent claudication, alternative modes of supervised exercise programs, including arm ergometry, strength training, cycling, aerobic exercise, Nordic walking, and combinations of exercise should be considered, to improve maximum and pain free walking distance, when supervised walking exercise is not possible.	IIa	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Jansen et al, Cochrane report, 2020	Meta-analysis (RCTs)	IC	N=412	Supervised exercise programs, including arm ergometry, strength training, cycling, aerobic exercise, Nordic walking, or combinations of exercise	Supervised walking exercise	Maximum walking distance: SMD of -0.11, 95% CI -0.33 to 0.11, p=0.32 (at end of exercise program) Pain-free walking distance: SMD of -0.06, 95% CI -0.30 to 0.17, p=0.59 (at end of exercise program)

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Recommendation 49	**Class**	**Level of evidence**				
For patients with intermittent claudication, participation in an exercise based cardiac rehabilitation program may be considered, to improve maximum walking distance and self reported functional impairment when supervised exercise therapy is not possible.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Siercke et al, Eur J Vasc Endovasc Surg, 2021	RCT	IC	118	Supervised exercise program as part of a comprehensive cardiac rehabilitation program	Best medical treatment and walk advice	Maximum walking distance: 350.5 m versus 253 m, favoring the intervention group, p=0.005. VascuQoL-6 score: 17.3 points versus 15.6 points, favoring the intervention group, p=0.002

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Recommendation 50	**Class**	**Level of evidence**				
For patients with intermittent claudication who have undergone a revascularisation procedure, it is recommended to initiate or continue with supervised exercise therapy to increase walking capacity and health related quality of life and to decrease the need for secondary revascularisation procedures.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Saratzis A, JACC Cardiovasc Interv, 2019	Network meta-analysis of randomized controlled trials	Network meta-analysis comparing all possible therapeutic modalities to improve limb symptoms in patients with intermittent claudication.	2,983 patients with intermittent claudication	Four distinct treatment modalities were compared against each other: best medical therapy (BMT) alone, supe rvised exercise therapy (SET), PTA, and PTA combined with supervised exercise therapy.		Compared with BMT alone, PTA plus SET outperformed other treatment strategies, with a maximum walking distance gain of 290 m (95% credible interval: 180 to 390 m; $p < 0.001$). QoL assessments were reported in 15 trials; PTA plus SET was superior to other treatments (Cohen's D = 1.8; 95% credible interval: 0.21 to 3.4).

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Klaphake S, J Cardiovasc Surg (Torino), 2018	Systematic review of RCTs	Patients with aortoiliac or femoropopliteal in seven RCTs comparing supervised exercise therapy (SET) + endovascular revascularization (EVR) versus EVR and SET only	n=637 (from five different trials included in the systematic review); 387 were males.	SET + EVR	SET or EVR alone	SET + EVR was associated with a greater MWD at 6 months compared to EVR only or SET only, with a standardized mean difference (SMD) of 0.86 (95% CI: 0.15, 1.57) and 0.41 (95% CI: 0.17, 0.66), respectively. At twelve months no significant difference in maximum walking distance was observed between combination treatment compared to EVR (SMD 0.96 [95% CI: -0.44, 2.37]) or SET (SMD 0.52 [95% CI: -0.17, 1.20]). Compared to EVR only, the combination treatment was associated with a greater PFWD walking distance at 12 months (SMD 0.73 [95% CI 0.01, 1.45]). Most included studies reported only minor differences in quality of life in favor of the combination treatment, or no difference at all.
Meneses AL, Sports Med, 2017	Systematic review	Data from eight trials comparing the effectiveness of lower limb revascularisation in combination with supervised exercise therapy (SET) versus lower limb revascularization or SET alone.	726 patients	SET + lower limb revascularisation	SET or lower limb revascularisation alone	Combined therapy resulted in greater improvements in pain-free (mean difference [MD] range 38–408 m) and maximal walking distances (MD range 82–321 m) compared with revascularisation or supervised training alone.
Aherne T, Surg Res Pract, 2015	Systematic review	Data from 15 papers reporting outcomes of 11 RCTs that directly compare supervised exercise with various invasive interventions.	969 patients, out of which 514 patients were included in the comparison of combination therapy versus single intervention (SET or revascularization) alone	SET + (open and endo) revascularisation	SET or (open and endo) revascularisation alone	A combination of revascularisation and SET offered superior outcomes to monotherapy across multiple studies. Two trials assessed open surgery with adjunctive SET with both suggesting significant benefits in walk distances in the combination therapy group. All four trials assessing endovascular intervention in conjunction with SET compared to monotherapy reported greater improvements in the walking distances when combination therapy was used.

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Fakhry F, Cochrane Database Syst Rev, 2018	Systematic review	Data from 3 RCTs that compared endovascular revascularization in combination with SET versus SET alone in intermittent claudication.	432 patients with intermittent claudication (305 patients were available with regard to the pain-free walking distance (PFWD) endpoint; and 106 patients for long term follow-up of maximal walking distance (MWD)	SET + endovascular revascularisation (EVR)	SET	No clear differences between groups for MWD (SMD 0.26, 95% CI -0.13 to 0.64; 3 studies; 432 participants; moderate-quality evidence) and PFWD (SMD 0.33, 95% CI -0.26 to 0.93; 2 studies; 305 participants; moderate-quality evidence). Long-term follow-up in one study (106 participants) revealed a large effect on MWD (SMD 1.18, 95% CI 0.65 to 1.70; low-quality evidence) in favour of the combination therapy.
Doshi R, Eur J Intern Med, 2021	Systematic review	Data from 4 RCTs comparing the effectiveness of EVR + SET versus SET alone with regard to maximal walking distance and need for secondary revascularisation procedures	Not reported	SET + EVR	SET	SET + EVR as compared with SET alone was associated with a significantly higher maximum walking distance at 6 [Mean difference: 91.53, 95% CI 13.03-170.04) and 12 months [Mean difference: 73.04, 95% CI 12.05-134.04] follow up. SET + EVR as compared with SET alone was also associated with a lower risk of revascularization procedures in future [RR: 0.31, 95% CI: 0.15-0.67].
Bo E, Int J Environ Res Public Health, 2013	RCT	An comparison of supervised exercise therapy (SET) after percutaneous transluminal angioplasty (PTA) compared to PTA alone on physical function, limb hemodynamics and health-related quality of life (HRQoL) in patients with intermittent claudication.	50	PTA + SET	PTA	During the 12 months' follow-up, the intervention group had significantly better walking distance than the control group. The intervention group also had a significantly higher HRQoL score in the physical component score of the SF-36, and the domains of physical function, bodily pain and vitality

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Fakhry F, JAMA, 2015	RCT	A comparison of the effectiveness of endovascular revascularization plus supervised exercise for intermittent claudication compared with supervised exercise only.	212	EVR + SET	SET	EVR + SET was associated with larger improvement in maximum walking distance (mean difference between groups, 282 m; 99% CI, 60-505 meters); and in pain-free walking distance (mean difference, 408 m; 99% CI, 195-622 m). The EVR + SET group also demonstrated significantly greater improvement in the disease-specific VascuQol score (mean difference, 0.62 [99% CI, 0.20-1.03]) and in the score for the SF-36 physical functioning (mean difference, 9.8 [99% CI, 1.4-18.2]).
Thanigaimani S, J Am Heart Assoc, 2021	Network meta- analysis	A comparison of the relative efficacy of cilostazol, home exercise therapy, supervised exercise therapy (SET), endovascular revascularization (ER), and ER plus SET (ER+SET) in improving maximum walking distance (MWD) over short- (<1 year), moderate- (1 to <2 years), and long-term (≥2 years) follow-up in people with intermittent claudication.	46 clinical trials involving a total of 4256 patients were included. Fourteen trials involving 1327 patients reported maximal walking distance at moderate term follow-up.			At moderate-term follow-up, SET (MD, 201.1; 95% CrI, 89.8–318.3) and ER+SET (MD, 368.5; 95% CrI, 195.3–546.9), but not home exercise therapy (MD, 99.4; 95% CrI, −174.0 to 374.9) or ER (MD, 84.2; 95% CrI, −35.3 to 206.4), significantly improved MWD (in meters) compared to controls.
Kruidenier, J Vasc Interv Rad 2011	RCT	Patients with in termittent claudication, the majority were treated for aorto-iliac lesions	70	Endovasc revasc + SET	EVR	The mean difference in absolute claudication distance at 6 months of follow-up was 271.3 m (95% confidence interval [CI] 64.0-478.6, P = .011) in favor of EVR +SET.

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Recommendation 51	**Class**	**Level of evidence**				
For patients with lifestyle-limiting intermittent claudication who are adherent to best medical treatment including exercise therapy, cilostazol or naftidrofuryl oxalate should be considered, to improve walking distance, but treatment should be stopped after three to six months of therapy if no improvement has been noted.	IIa	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Bedenis et al. 2014	Systematic review of 15 RCTs	Patients with stable intermittent claudication		Cilostazol	Placebo or other antiplatelet agents	Cilostazol has been shown to be of benefit in improving walking distance in people with intermittent claudication secondary to PAD. Although there is an increase in adverse side effects, they are generally mild and treatable. There is currently insufficient data on whether taking cilostazol results in a reduction of all-cause mortality and cardiovascular events or an improvement in quality of life.
Stevens et al. 2012	Systematic review of 26 RCTs and meta-analysis of 11 RCTs	Patients with intermittent claudication due to peripheral arterial disease				Naftidrofuryl oxalate and cilostazol are both effective treatments for claudication; naftidrofuryl oxalate is likely to be the most effective, with minimal serious adverse events. Naftidrofuryl oxalate was ranked first for both MWD and PFWD (probability of 0·947 and 0·987, respectively, of being the best treatment) followed by cilostazol and pentoxifylline. For naftidrofuryl oxalate, cilostazol and pentoxifylline, MWD increased by 60 (95 per cent credible interval 20 to 114) per cent, 25 (11 to 40) per cent and 11 (-1 to 24) per cent respectively relative to placebo, and PFWD increased by 49, 13 and 9 per cent.
Salhiyyah et al. 2015	Systematic review of 24 RCTs	Patients with IC Fontaine				Given the generally poor quality of published studies and the large degree of heterogeneity

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		stage II.				evident in interventions and in results, the overall benefit of pentoxifylline for patients with Fontaine class II intermittent claudication remains uncertain. Pentoxifylline was shown to be generally well tolerated. Of 17 studies comparing pentoxifylline with placebo, 14 reported TWD and 11 reported PFWD; the difference in percentage improvement in TWD for pentoxifylline over placebo ranged from 1.2% to 155.9%, and in PFWD from -33.8% to 73.9%.
Salhiyyah et al. 2012	Systematic review of 23 RCTs	Patients with stable intermittent claudication, Fontaine stage II.				Given the generally poor quality of the published studies and the large degree of heterogeneity in the interventions and the results, the overall benefit of pentoxifylline for patients with Fontaine class II intermittent claudication remains uncertain. Pentoxifylline is generally well tolerated. In a total of 17 studies which compared pentoxifylline with placebo, of which 14 reported TWD and 11 reported PFWD, the difference in percentage improvement in TWD for pentoxifylline over placebo ranged from 1.2% to 155.9%, and for PFWD the difference ranged from -33.8% to 73.9%.
Dawson et al. 2000	RCT	Patients with moderate-to-severe claudication	698	Cilostazol	Pentoxifylline, placebo	Cilostazol was significantly better than pentoxifylline or placebo for increasing walking distances in patients with intermittent claudication, but was associated with a greater frequency of minor side effects. Pentoxifylline and placebo had similar effects.

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Recommendation 52	**Class**	**Level of evidence**				
For patients with intermittent claudication, prostanoids are not recommended to improve walking distance.	III	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Salhiyyah et al. 2012	Systematic review of 23 RCTs	Patients with stable intermittent claudication, Fontaine stage II.				Given the generally poor quality of the published studies and the large degree of heterogeneity in the interventions and the results, the overall benefit of pentoxifylline for patients with Fontaine class II intermittent claudication remains uncertain. Pentoxifylline is generally well tolerated. In a total of 17 studies which compared pentoxifylline with placebo, of which 14 reported TWD and 11 reported PFWD, the difference in percentage improvement in TWD for pentoxifylline over placebo ranged from 1.2% to 155.9%, and for PFWD the difference ranged from -33.8% to 73.9%.
Robertson et al. 2013	Systematic review of 18 RCTs	People with intermittent claudication				Whilst results from some individual studies suggested a beneficial effect of PGE1, the quality of these studies and of the overall evidence available is insufficient to determine whether or not patients with intermittent claudication derive clinically meaningful benefit from the administration of prostanoids.

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Recommendation 54	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation, balloon angioplasty with selective bare metal stent placement should be considered as the primary approach for iliac artery stenoses due to similar effectiveness and safety compared with primary stenting.	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	N=396	Primary bare metal stenting	Balloon angioplasty	Two trials compared primary BMS implantation to balloon angioplasty with provisional BMS in 396 patients with short iliac lesions. The Dutch Iliac Stent Trial provided data on patency, reintervention, mortality and amputation rates up to 72 months post-intervention with no differences in outcomes at all follow-up times. In the STAG trial for treatment of iliac occlusions (length 54.1±15.8 mm), patency rates did not differ through 2-year 1 follow-up. The study was however halted early due to increased major complications for provisional versus primary stenting (20% vs 5%, 3 p=0.01), driven by distal embolization.
Klein, Radiology 2006	Randomized trial DUTCH Iliac Stent Trial	Patients with short iliac lesions (<10cm)	279 patients (95.2% IC)	Primary bare-metal stenting group (n=143)	PTA with selective bare-metal stenting group (n=136)	No significant difference in primary patency (HR 1.3, 95% CI 0.8-2.1); reintervention rate (HR 1.1, 95% CI 0.6-1.9) and all-cause mortality (HR 1.3, 95% CI 0.7-2.2) after 72 months follow-up, respectively.
Goode, Br J Surg 2013	Randomized trial STAG Trial	Patients with iliac occlusive disease (occlusion length < 8 cm)	112 patients (89.3% IC)	Primary stenting group (n=57)	PTA group (n=55)	Technical success: 98% vs 84% (p=0.007) Procedural complications: 5% vs 2°% (p=0.01) predominantly distal embolization* No differences in primary or secondary patency at 1 and 2 years

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Jongsma, Cochrane Database Syst Rev 2020	Meta-analysis of DUTCH and STAG Trials					Insufficient evidence to make general conclusions about effects of PTA with selective stent placement versus primary stenting for stenotic or occlusive lesions of the iliac artery. Primary stenting may result in lower distal embolization rates in iliac artery occlusions.

* STAG trial was stopped prematurely due to the significant increase in major complications when iliac occlusions were treated by PTA rather than by initial stent placement. The majority of these events were due to distal embolization, all managed successfully by endovascular techniques or open surgery, without limb loss.

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Recommendation 55	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation, primary bare metal stenting is recommended over primary balloon angioplasty for iliac artery occlusions due to the lower risk of distal embolisation.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ, 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	N=396	Primary bare metal stenting	Balloon angioplasty	Two trials compared primary BMS implantation to balloon angioplasty with provisional BMS in 396 patients with short iliac lesions. In the STAG trial for treatment of iliac occlusions (length 54.1±15.8 mm), patency rates did not differ through 2-year 1 follow-up. The study was however halted early due to increased major complications for provisional versus primary stenting (20% vs 5%, 3 p=0.01), driven by distal embolization.
Klein, Radiology 2006	Randomized trial: DUTCH Iliac Stent Trial	Patients with short iliac lesions (<10cm)	279 patients (95.2% IC)	Primary bare-metal stenting group (n=143)	PTA with selective bare- metal stenting group (n=136)	No significant difference in primary patency (HR 1.3, 95% CI 0.8-2.1); reintervention rate (HR 1.1, 95% CI 0.6-1.9) and all-cause mortality (HR 1.3, 95% CI 0.7-2.2) after 72 months follow-up, respectively.
Goode, Br J Surg 2013	Randomized trial: STAG Trial	Patients with iliac occlusive disease (occlusion length < 8 cm)	112 patients (89.3% IC)	Primary stenting group (n=57)	PTA group (n=55)	Technical success: 98% vs 84% (p=0.007) Procedural complications: 5% vs 2°% (p=0.01) predominantly distal embolization No differences in primary or secondary patency at 1 and 2 years
Jongsma, Cochrane Database Syst Rev 2000	Meta-analysis of DUTCH and STAG Trials					Insufficient evidence to make general conclusions about effects of PTA with selective stent placement versus primary stenting for stenotic or occlusive lesions of the iliac artery. Primary stenting results in lower distal embolization rates in iliac artery occlusion.

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Recommendation 56	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation who need stent placement for iliac artery lesions, the application of self expanding bare metal stents rather than balloon expandable stents may be considered due to the lower risk of re-stenosis and target lesion revascularisation compared with balloon expandable stents.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	n=660	Self-expanding stents (SES)	Balloon-expandable stents BES)	The ICE trial allocated 660 patients to primary self-expanding BMS or balloon-expandable BMS implantation for common or external iliac artery lesions (length 37.5±30.0mm). Mid-term patency (OR 2.69, 95%CI 1.31- 5.52) and TLR risk (OR 0.41, 95%CI 0.17-0.97) favoured self-expanding stents with safety endpoints remaining equivocal.
Krankenberg, JACC Cardiovasc. Interv. 2017	RCT	Patients with single common or external iliac artery lesions	660 patients (96.4% IC)	Self-expanding BMS group (n=340	Balloon-expandable BMS group (n=320)	Higher primary patency for intervention group at 12 months (94.5% vs 87%, p=0.03). Lower TLR for intervention group (3% vs 6.9%, p=0.04). No difference in index limb amputation and all-cause mortality.

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Recommendation 57	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation who have Trans-Atlantic Inter-Society Consensus Document II C/D iliac lesions, covered stent placement may be considered over bare metal stents due to higher patency rates.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	n=125	Covered stents	Bare-metal stents	In the COBEST trial, covered stenting resulted in advantageous mid-term patency compared to BMS (OR 3.15, 95%CI 1.29-7.66). Patency benefits for covered stenting were sustained on five-year post- hoc analysis, while no differences in mortality and amputation were observed. The COBEST trial demonstrated high risk of bias.
Mwipatayi, J Vasc Surg 2016	RCT	125 patients with aortoiliac disease (50% had TASC II C & D lesions)	168 iliac lesions (78.4% of study participants had IC)	Covered stents group (n=83)	Non-covered stents group (n=85)	Aortoiliac lesions treated with a covered stent were significantly more likely to remain free from binary restenosis than those that were treated with a bare- metal stent (hazard ratio [HR], 0.35; 95% confidence interval (CI), 0.15-0.82; *P* = .02). Freedom from occlusion was also higher in lesions treated with covered stents than in those treated with a bare-metal stent (HR, 0.28; 95% CI, 0.07-1.09); however, this did not reach statistical significance (*P* = .07). Subgroup analyses demonstrated a significant difference in freedom from binary restenosis for covered stents in TASC C and D lesions compared with a bare stent (HR, 0.136; 95% CI, 0.042-0.442). This difference was not demonstrated for TASC B lesions (HR, 0.748; 95% CI, 0.235-2.386).

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Bekken, EJVES 2022	RCT	Patients with aortoiliac disease and principal treatment target in the common iliac artery of moderate anatomic complexity, 71 % had intermittent claudication (Rutherford 1-3)	n=174	Covered stent	Bare metal stent	One hundred and seventy-four limbs were studied according to the intention to treat principle; with 87 limbs in each group. Freedom from binary restenosis after two years of follow up was 84.7% (95% CI 76.7 to 92.7%) in the BMS group and 89.1% (95% CI 82.4 to 95.8%) in the CS group (p=0.40). Freedom from occlusion was 95.0% (95% CI 90.3 to 95.7%) in the BMS group and 96.4% (95% CI 92.5 to 100%) in the CS group (p=0.66). Freedom from target lesion revascularisation was 91.1% (95% CI 84.8 to 97.3%) and 95.2% (95% CI 90.7 to 99.7%), respectively (p=0.31). Technical success, complications, haemodynamic success, and clinical success were also comparable between both groups. Per-protocol analysis did not affect the outcomes of the study.

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Recommendation 58	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularization who are considered as low risk with long life expectancy, open surgery may be considered for Trans-Atlantic Inter-Society Consensus Document II C/D lesions that include the iliac arteries as well as the aorta up to the renal arteries, due to favourable primary and secondary patency rates compared with endovascular approaches.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Salem, Cardiovasc Intervent Radiol 2021	Meta-analysis of observational studies	Patients with TASC II C/D aorto-iliac occlusive disease	66 studies, 9319 patients. Number of patients with IC not specified	Open surgery: n=5875	Standard endovascular: n=3204 CERAB: n=240	Higher primary patency with open surgery (1 and 3 year), comparable secondary patency. Thirty-day mortality rate was 0.79% (95% CI 0.3-1.3%) for standard endovascular treatment, 0% for CERAB and 3% (95% CI 2-3%) for open surgery. Thirty-day morbidity was 9% % (95% CI 6-12%) for standard endovascular treatment, 10% for CERAB (95% CI 1-26%) and 15% (95% CI 11-20%) for open surgery. Local complications not reported
Premaratne, J Vasc Surg 2020	Meta-analysis of observational studies	Patients with TASC C/D aorto- iliac occlusive disease	11 studies, 4030 patients (56.8% IC)	Open surgery: n=1679 (60.5% IC)	Endo/hybrid surgery: n=2351 (54.1% IC)	No difference concerning ABPI change, 30-day mortality, 30-day graft/stent thrombosis between both groups. Higher primary patency with open surgery (50 months), but younger patients. Higher primary patency with hybrid than endo alone. Local complications not reported

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Indes, J Endovasc Ther 2013	Meta-analysis of observational studies	Patients with TASC II C/D aorto-iliac occlusive disease	57 studies, 5358 patients (61.4% IC)	Open surgery: n=2053 (55% IC)	Endo surgery: n=1138 (76% IC)	Mean length of hospital stay was 13 days for open surgery group versus 4 days for endovascular treatment procedures (p<.001). The open surgery group experienced more complications (18.0% versus 13.4%, p<.001) and greater 30-day mortality (2.6% versus 0.7%, p<.001). At 1, 3 and 5 years, pooled primary patency rates were greater for open surgery group versus the endovascular cohort (94.8% versus 86.0%, 86.0% versus 80.0%, 82.7% versus 71.4% respectively, p<.001), as well as secondary patency (95.7% versus 90.0%, 91.5% versus 86.5%, 91.0% versus 82.5%, p<.001).
Starodubtsev, EJVES 2022	RCT	Patients with iliac and CFA artery disease	202 patients randomized in open or hybrid repair	Open repair: 100 patients (85% IC)	Hybrid repair: 102 patients (86% IC)	The average hospital length of stay was shorter in the HR group 8.2 (4.2) days HR group vs. 15.7 (6.9) days OR group, p < .001); the 30 day peri-operative morbidity rate was 8.8% in the HR group vs. 21% in the OR group (p = .030). There was no significant difference in the 36-month mortality rate (p=0.16). The cumulative primary patency rates were 93% (HR) vs. 93% (OR) at 12 months and 91% (HR) vs. 89% (OR) at 36 months (p 1⁄4 .38).

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Recommendation 59	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation who are not suitable for iliac endovascular, hybrid or surgical anatomical revascularization, femorofemoral crossover bypass grafting may be considered, as an alternative for aorto-iliac occlusive lesions.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Capoccia, Ann Vasc Surg, 2010	Review of 3 observational studies and 3 RCTs	Patients with aorto-iliac occlusive disease	6 studies included, 675 patients	Femoro-femoral crossover bypass, n=675 (100% IC)	NA	1-year PP: 71.6-96.0% 5-year PP: 49.4-72.0% Local complications 0.4-13.4%
Eiberg, EJVES 2006	Randomized controlled trial	Patients with aorto-iliac occlusive disease	126 patients	PET Femoro-femoral crossover bypass, n=60 (100% IC)	PTFE Femoro-femoral crossover bypass, n=66	2-year PP 90% 2-year Freedom from symptoms: 76% No difference concerning graft material 7% experiences infectious complications
Ricco JVS 2008	Randomised controlled trial	Patients with unilateral iliac artery occlusive disease, disabling claudication and TASC C/D lesions	143 patients	Direct surgical revascularisation	Femoro-femoral crossover bypass grafting	Median follow-up was 7.4 years One patient in the direct bypass group died postoperatively. Primary patency at 5 years was higher in the direct bypass group than in the crossover bypass group (92.7 +/- 6.1% vs 73.2 +/- 10%, P = .001). Assisted primary patency and secondary patency at 5 years were also higher after direct bypass than crossover bypass (92.7 +/- 6.1% vs 84.3 +/- 8.5%, P = .04 and 97.0 +/- 3.0% vs 89.8 +/- 7.1%, P = .03, respectively).

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Recommendation 60	**Class**	**Level of evidence**				
For fit patients with disabling intermittent claudication at low risk for groin complications and with common femoral artery bifurcation stenosis or occlusion undergoing revascularisation, open surgery is recommended due to expected higher long term patency rates compared with endovascular approaches.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Ballotta, Surgery 2010	Retrospective cohort study single center	Occlusive CFA disease	117 PAD patients (73 IC)	Open CFA endarterectomy	-	No perioperative deaths or major complications, 6.6% local complications. 7-year PP, APP, and limb salvage rates were 96%, 100%, and 100%, respectively; the 7-year rates of freedom from further revascularization and survival were 79% and 80%
Kang, J Vasc Surg 2008	Retrospective cohort study, single center	Occlusive CFA disease	65 PAD patients (44 IC)	Open CFA endarterectomy	-	5% major complications requiring reintervention, no perioperative mortality or amputation. 1- and 5-year primary patencies: 93% and 91%

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Recommendation 61	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation, with common femoral artery stenosis or occlusion not extending down to the femoral bifurcation, endovascular treatment may be considered as an alternative to open surgery due to similar midterm patency rates compared with open surgery in non-complex common femoral artery lesions.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Changal, J Interv Cardiol 2019	Meta- analysis of 26 observational single centre studies and 2 RCTs	Patients with steno-occlusive lesions of the common femoral artery	28 studies included, 2684 patients	Common femoral endarterectomy: n=1930 (53.7% IC)	Endovascular treatment with routine stenting: n=306 (66.1% IC) Endovascular treatment with selective stenting: n=678 (64.8% IC)	Similar 1-year primary patency. Similar primary patency at maximum follow-up for endovascular treatment with routine stenting and common femoral artery endarterectomy
Boufi, J Vasc Surg 2021	Meta- analysis of 2 RCTs	Patients with steno-occlusive lesions of the common femoral artery	197 patients	Endovascular management of common femoral artery lesions: n=96 (71.1% IC)	Common femoral endarterectomy: n=95 (79.9% IC)	Technical failure rates were similar for endovascular group versus open surgical group (OR=1.55; 95% CI 0.11-14.45). Cumulative 30-day mortality did not differ statistically (OR=1.54; 95% CI 0.11-20.42). Post-operative morbidity was improved in endovascular group (0R=0.059; 95% CI 0.01-0.26; p<.001).No difference in early reintervention rate (OR=3.53; 95%CI 0.36-34.68). Similar 1-year primary patency (OR=0.49; 95% CI 0.29-3.06). Subgroup analysis showed that neither claudication nor associated lesions influence surgical results with regard to patency.

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Recommendation 63	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication due to femoropopliteal steno-occlusive disease, a careful selection for revascularization is recommended where the treatment indication is weighed against the degree of disability, results of non-invasive therapies, concomitant comorbidities, procedural risks, and expected procedural patency, due to remaining uncertainty about sustained clinical benefits and risks.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Djerf, Circulation: Cardiovasc Interv 2020	RCT	Patient with mild to severe intermittent claudication	158	79 (invasive treatment	79 (conservative treatment)	Improved quality of life within 2 years, not maintained at 5 years
Gunnarsson, SAGE Open Med 2020	Registry study	Infrainguinal lesions in IC patients	775 patients	Invasive treatment: n=775	NA	Between 79% and 99% of patients need hospitalization each year (most common causes of hospitalization were cerebrovascular and ischemic heart diseases)
Howard, JVS 2022	Registry study	Femoropopliteal bypass in IC patients	325 bypasses	NA	NA	Of 325 total reviews, surgeons stated they would not have recommended bypass in 134 reviews (41%) and deemed bypass inappropriate in 122 reviews (38%). The most common reason for inappropriateness was lack of pre-operative medical and lifestyle therapy, which was present in 63% of reviews where bypass was deemed appropriate and 39% of reviews where bypass was deemed inappropriate ($P < .001$). Surgeons stated they would have recommended additional preoperative therapy in 65% of reviews where bypass was deemed inappropriate and 35% of reviews where bypass was deemed appropriate ($P < .001$).

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Recommendation 64	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularization who have Trans-Atlantic Inter-Society Consensus Document II A/B femoropopliteal lesions, the adjunctive use of paclitaxel coated balloon angioplasty should be considered after optimal balloon angioplasty without the need for stenting.	IIa	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	21 studies, 3896 patients	Drug-coated balloon group (n=2332)	Uncoated balloon group (n=1564)	Drug-coated balloon angioplasty was associated with a higher likelihood of primary patency at short-term (OR 3.21, 95% CI 2.44-4.24), mid-term (OR 2.75, 95% CI 2.14-3.52) and long-term (OR 2.47, 95% CI 1.93-3.16) follow-up. Drug-coated balloon angioplasty was associated with a lower risk of target-lesion revascularization at short-term (OR 0.33, 95% CI 0.22-0.49), mid-term (OR 0.31, 95% CI 0.23-0.41) and long-term (OR 0.43, 95% CI 0.32-0.59) follow-up. Similar risk estimates for all-cause mortality between groups at short-term (OR 1.03, 95% CI 0.50-2.13), mid-term (OR 0.90, 95% CI 0.57-1.42) and long-term (OR 0.96, 95% CI 0.67-1.39) follow-up.

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Recommendation 66	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation, selective drug eluting stent placement should be considered if femoropopliteal plain balloon angioplasty leads to suboptimal results i.e., residual stenosis or dissection.	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	3 studies; 471 patients	Drug-eluting stent (DES) group (n=236)	Bare-metal stent group (n=235)	No difference in the likelihood of primary patency (OR 1.64, 95% CI 0.89-3.03) and target-lesion/vessel revascularization (OR 0.5, 95% CI 0.22-1.11) at mid-term follow-up.
Dake, Circulation 2016	Randomised trial: Zilver-PTX trial	Patients with femoro-popliteal lesions	479 patients (91% IC)	Drug-eluting stent group (n=241)	PTA with selective stenting group (n=238)	Higher primary patency rate for overall DES group compared to standard care (66.4% vs 43.4%, p<0.01) through 5-year follow-up. Higher primary patency rate for provisional DES compared to provisional BMS (72.4% vs 53%, p=0.03). Higher freedom from TLR for overall DES group compared to standard care (83.1% vs 67.6%, p<0.01). Higher freedom from TLR for provisional DES compared to provisional BMS (84.9% vs 71.6%). Higher all-cause mortality for primary DES group compared to PTA (16.9% vs 10.2%, p=0.03).
Goueffic, JACC Cardiovasc. Interv. 2020	Randomised trial: BATTLE trial	Patients with femoro-popliteal lesions	181 patients (80.7% IC)	Drug-eluting stent group (n=90)	Bare-metal stent group (n=91)	No difference in primary patency and TLR at 2 years. No difference in all-cause mortality (1.2% vs 6.4%, p=0.06)
Bausback, J Am Coll Cardiol 2019	Randomised trial: REAL-PTX trial	Patients with femoro-popliteal lesions	150 patients (86.7% IC)	Drug-eluting stent group (n=75)	Drug-coated balloon group (n=75)	No difference in primary patency at 3 years (56.7% vs 42.4%, p=0.17). No difference in TLR (68.9% vs 71.3%, p=0.74). No difference in all-cause mortality (4% vs 10.7%, p=0.12).

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Liistro, J Am Coll Cardiol 2019	Randomised trial (subgroup analysis): DRASTICO trial	Patients with intermittent claudication and femoro-popliteal lesions	192 patients, including 67 claudicants	Drug-eluting stent group (n=39)	Drug-coated balloon group (n=28)	No difference in binary restenosis at 1 year (17% vs 26%, p=0.4)
Gouëffic, Circulation, 2022	Randomised trial (2:1 DES:BMS)	Patient with femoropopliteal lesions, 96% had intermittent claudication, mean lesion length were 75.6 mm (DES group) and 72.2 mm (BMS group).	775 patients	Drug-eluting stent n=508	Bare metal stent (BMS) n=267	12-month incidence of primary patency was superior for DES (83.2%) than for BMS (74.3%), p<0.01). Incidence of primary sustained clinical improvement was greater among patients treated with DES than BMS (83.0% versus 76.6%; p=0.045). The health-related quality of life dimensions of mobility and pain/discomfort improvement did not differ significantly between treatment arms (66.4% and 53.6% of DES-treated and 64.2% and 58.1% for BMS- treated patients, respectively). At 12 months, no statistical difference was observed in all-cause mortality between patients treated with the DES or BMS (2.7% versus 1.1% relative risk, 2.4 [95% CI, 0.69–8.36]; p=0.15).

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Recommendation 67	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation, routine use of atherectomy for the treatment of femoropopliteal lesions is not recommended due to the lack of superiority of atherectomy over conventional endovascular therapies in terms of efficacy and safety endpoints.	III	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta- analysis of RCTs	Patients with foremost intermittent claudication	N=514	Atherectomy	Conventional endovascular therapy with balloon angioplasty or bare metal stenting	Seven RCTs including 514 patients examined atherectomy use for femoropopliteal disease (length 88.1mm, IQR 68.9-106.3mm; 24.5% occlusions, IQR 12.5-48.6%).32,58-63 Risk of bias was considered intermediate-to-high for all studies. Two early trials allocated 103 patients with IC to directional atherectomy or balloon angioplasty, finding trends towards lower 1-year (OR 0.24, 95% CI 0.05-1.12)61 and 2-year (OR 0.38, 95% CI 0.13-1.12) patency with atherectomy use. Adjunctive balloon angioplasty with upfront atherectomy was evaluated by two RCTs. Shammas et al assigned 58 patients to atherectomy plus BA or BA alone, finding no differences in mid-term TLR (OR 0.30, 95%CI 0.05-1.88).Distal macroembolization (within embolic protection devices) occurred more frequently with atherectomy (64.7% vs 0%, p<0.001). In the COMPLIANCE 360 study, atherectomy with adjunctive balloon angioplasty produced no additional benefits in freedom from mid-term restenosis or TLR. The ISAR-STATH trial allocated 155 patients to three treatment arms: atherectomy with provisional BMS, plain or DCB angioplasty with adjunctive BMS, respectively. Compared to DCB with BMS, likelihood of primary patency at 6 months was significantly lower (OR

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						0.25, 95%CI 0.09-0.71) and TLR risk at 24 months significantly higher (OR 5.49, 95%CI 2.04-14.75) with atherectomy use. Long-term TLR risk numerically favoured BA with BMS over atherectomy (OR 0.52, 95%CI 0.23-1.18) without statistical significance being reached.
Vroegindeweij, Eur J Vasc Surg 1992	RCT	Patients with intermittent claudication and short femoropopliteal lesions	30 patients (100% IC)	Atherectomy group (n=16)	PTA group (n=14)	Lower patency for the intervention group at 1 year (25% vs 77%, p=0.02).
Tielbeek, J Vasc Interv Radiol 1996	RCT	Patients with intermittent claudication and short femoropopliteal lesions	73 patients (100% IC)	Atherectomy group (n=38)	PTA group (n=35)	No difference in patency at 2-year follow-up (44% vs 67%, p=0.06)
Shammas, J Vasc Interv Radiol 2011	RCT	Patients with infrainguinal lesions (79% femoropopliteal)	58 patients (79.3% IC)	Atherectomy with adjunctive PTA group (n=29)	PTA group (n=29)	No difference in TLR at 1 year (11.1% vs 16.7%). No difference in amputation rates (0% vs 4.2%). No difference in all-cause mortality (7.7% vs 14.8%). Higher rate of distal macroembolization in the intervention group (64.7% vs 0%, p=0.001)
Dattilo, J Invasive Cardiol 2014	RCT: COMPLIANCE 360 trial	Patients with femoropopliteal lesions	50 patients (90% IC)	Atherectomy with adjunctive PTA group (n=25)	PTA group (n=25)	No difference in freedom from TLR or restenosis at 1 year (81.2% vs 78.3%, p=0.99)
Ott, Circulation 2017	RCT: ISAR-STATH trial	Patients with SFA lesions	155 patients (94.2% IC)	Atherectomy with selective bare-metal stenting group (n=55)	PTA plus bare-metal stenting group (n=52); drug-coated balloon angioplasty plus bare- metal stenting group (n=48)	Higher restenosis rate in the intervention group compared to DCB + BMS at 6 months (54% vs 23%, p<0.017). No difference in restenosis for atherectomy vs PTA + BMS at 6 months (54% vs 52%). Higher TLR rate in the intervention group compared to DCB + BMS at 2 years (53% vs 17%, p<0.017). No difference in all-cause mortality between groups at 2 years.

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Zeller, Circ Cardiovasc Interv 2017	RCT: DEFINITIVE-AR trial	Patients with femoropopliteal lesions	102 patients (98.4% IC)	Atherectomy with adjunctive drug-coated balloon angioplasty group (n=48)	Drug-coated balloon angioplasty group (n=54)	No difference in primary patency at 6 months (95% vs 88.9%) and 1 year (84.6% vs 81.3%). No difference in TLR at 6 months (4.7% vs 3.9%) and 1 year (7.3% vs 8%). No amputation were performed for the duration of the study.
Cai, Ann. Vasc. Surg. 2020	RCT	Patients with femoropopliteal lesions	94 patients (70.2% IC)	Atherectomy with adjunctive drug-coated balloon angioplasty group (n=45)	Drug-coated balloon angioplasty group (n=49)	No difference in primary patency at 1 year (80.5% vs 75.7%) and 2 years (67.1% vs 55.1%). No difference in TLR at 1 year. No difference in all-cause mortality at 2 years (0% vs 4.1%) No amputations performed during the study.

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Recommendation 68	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing revascularisation, covered stents may be considered an alternative to bare metal stents in the treatment of long (>20 cm) femoropopliteal lesions due to favourable patency rates.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Koeckerling, EHJ 2023	Systematic review and meta-analysis of RCTs	Patients with foremost intermittent claudication	N=486	Covered stents	Balloon angioplasty or bare metal stenting	Three RCTs applied covered stenting in femoropopliteal arteries (length 180mm, IQR 125- 181mm; 58.8% occlusions, IQR 41.9-65.6%). Saxon et al compared covered stenting to balloon angioplasty with provisional bare metal stenting in 197 intermediate-length femoropopliteal lesions (70±40mm), observing superior 1-year patency results (OR 2.77, 95%CI 1.42-5.40) in the intervention group. Long-term outcomes of covered versus uncovered stenting were explored by two RCTs including 289 patients with complex femoropopliteal lesions. The VIBRANT trial reported equivalent patency (OR 0.92, 95%CI 0.26-3.34) and TLR risks (OR 1.02, 95%CI 0.52-2.02) at three years post- intervention.65 Mortality was numerically higher in the experimental arm (OR 3.28, 95% CI 0.83- 12.91), while no amputations were registered. In the VIASTAR trial, 1-year patency results were equivocal, but favoured covered stenting at two years (OR 2.49, 95% CI 1.06-5.88). However, long-term TLR risk did not differ between groups (OR 0.76, 95% CI 0.31-1.84).
Saxon, J Vasc Interv Radiol 2008	RCT	Patients with SFA lesions	197 limbs (88.8% IC)	Covered stenting group (n=97)	PTA with selective BMS group (n=100)	Higher primary patency in the intervention group at 1 year (65% vs 40%, p=0.0003).No difference in all-cause mortality and amputation at 1 year.The trial was terminated early owing to the requirement for modifying the device itself and redefining originally specified endpoints

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Geraghty, J. Vasc. Surg. 2013	RCT: VIBRANT trial	Patients with SFA lesions	148 patients (92.6% IC)	Covered stenting group (n=72)	BMS group (n=76)	No difference in primary patency at 3 years (24.2% vs 25.9%). No difference in freedom from first reintervention at 3 years. All-cause mortality for covered stent vs BMS group at 3 years: 12.5% vs 3.9%.
Lammer, CardioVasc. Interv. Radiol. 2015	RCT: VIASTAR trial	Patients with femoropopliteal lesions	141 patients (81.6% IC)	Covered stenting group (n=72)	BMS group (n=69)	No difference in primary patency (70.9% vs 55.1%, p=0.11) and freedom from TLR (84.6% vs 77%, p=0.37) at 1 year. Higher primary patency in the intervention group at 2 years (63.1% vs 41.2%, p=0.04). No difference in freedom from TLR at 2 years (79.4% vs 73%, p=0.37).

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Recommendation 70	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication undergoing femoropopliteal bypass, autologous vein grafts are recommended over prosthetic grafts due to the favourable long term patency rates.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Ambler, Cochrane Database Sys Rev 2018	Systematic review of randomized trials	Patients requiring above the knee bypass Mixed IC/CLI populations	4 studies: n=422	Autologous vein: number not specified	Prosthetic materials: number not specified	For above-knee bypass, there was moderate- quality evidence that autologous vein grafts lower the risk for loss of primary patency compared to prosthetic grafts by 60 months (Peto odds ratio (OR) 0.47, 95% confidence interval (CI) 0.28 to 0.80; 3 studies, 269 limbs; P = 0.005). No difference between polyester and ePTFE grafts (OR 1.67, 95% CI 0.96-2.90, 2 studies, 247 limbs)
Vossen, Vascular 2022	Meta-analysis	Patients requiring above the knee bypass for IC	6 studies: n=524	Autologous vein: number not specified	PTFE: number not specified	Average patency rates at one and 5 years were 88% and 76% vs 81% and 68% in the ASV and the PTFE groups, respectively. One and five-year patency was not statistically different between the groups (OR 5.21; 95% CI 0.60-45.36 and OR 2.10; 95% CI 0.88-5.01). In a mixed population of patients with IC and CLI (84% IC patients), 1 year patency was comparable (OR 1.40; 95% CI 0.87- 2.25). However, after a follow-up of over 3 years, this mixed group had significantly higher patency rates in favour of the ASV (OR 2.06; 95 % CI 1.30-3.26).

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Kim, J Surg Res 2022	Retrospective review	Patients requiring above or below the knee femoro-popliteal bypass for IC	282 patients	NA	NA	A total of 282 patients underwent femoropopliteal bypass surgery for IC. Me- dian age was 68 y (interquartile range, 61-73 y). Bypass conduits included great saphenous vein (GSV) (48.2%), prosthetic grafts (48.9%), and non-GSV autogenous grafts (2.8%). Distal bypass target was above-knee in 62.1% and below-knee in 37.9% of patients. The most common postoperative complications were wound infections (14.2%) followed by unplanned 30-d hospital readmissions (12.4%). Mortality rates were low at 0.4% (30 d) and 3.2% (1 y). Five-year primary patency rates trended highest for claudicants undergoing above- knee bypass with GSV conduit (log-rank P 1⁄4 0.065). Five-year amputation-free survival rates were highest using GSV conduit regardless of distal bypass target (log-rank P 1⁄4 0.017). On a multivariable analysis, age (HR 1.02 [1.00-1.04], P 1⁄4 0.023) and active smoking (HR 1.48 [1.06- 2.06], P 1⁄4 0.021) were identified as risk factors for diminished primary graft patency. Risk factors for amputation-free survival included age (HR 1.03 [1.01-1.05], P < 0.001) and GSV conduit type (HR 0.65 [0.46-0.90], P 1⁄4 0.011).
Sharrock, Angiology 2019 (comment from a reviewer)	Meta-analysis	Patients requiring above the knee bypass	8 RCTs, 1271 grafts, 1132 patients	608 saphenous vein (number of IC not specified)	663 prosthetic (number of IC not specified)	At 5 years, the vein group had significantly higher primary patency (odds ratio [OR]: 1.73, 95% confidence interval [CI]: 1.17-2.55, *P* = 0.006), primary assisted patency (OR: 4.02, 95% CI: 2.84-5.70, *P* < 0.0001), and secondary patency (OR: 1.83, 95% CI: 1.20-2.80, *P* = 0.005) rates compared with the prosthetic group. The vein group required significantly fewer reinterventions (OR: 0.33, 95% CI: 0.18-0.60, *P* = 0.0003). There was no significant difference in 30-day mortality (risk difference: -0.01, 95% CI: -0.02 to 0.01, *P* = 0.34), 30-day morbidity (OR: 1.58, 95% CI: 0.61-4.06, *P* = 0.35)

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Recommendation 72	**Class**	**Level of evidence**				
In the extreme scenario of highly selected patients with disabling intermittent claudication, where endovascular revascularization of below the knee lesions is deemed necessary, balloon angioplasty with selective drug eluting stent placement may be considered.	IIb	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Zeller, JACC Cardiovasc Interv 2015	RCT (sub-group analysis)	Patients with infrapopliteal lesions	72 patients, including 16 patients with intermittent claudication	Paclitaxel coated balloon angioplasty: n= 8	Uncoated balloon angioplasty: n=8	No difference between both arms
Rastan, J Am Coll Cardiol 2012	RCT (sub-group analysis)	Patients with infrapopliteal lesions	161 patients, including 86 patients with intermittent claudication	Sirolimus eluting stents: n=40	Bare metal stents: n=46	Higher primary patency in intervention group at 1 year (85.3% vs 55%, p=0.006). No difference in TLR at 1 year (5.9% vs 20%, p=0.09). Lower target-vessel revascularization in intervention group at 33 months (7.9% vs 25%, p=0.04). No difference in all-cause mortality (18.4% vs 18.2%, p=1) and amputation rates (0% vs 4.7%, p=0.19) at 33 months.

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Recommendation 73	**Class**	**Level of evidence**				
In the extreme scenario of highly selected patients with disabling intermittent claudication who require stent placement for short below the knee lesions, the use of drug eluting stents rather than bare metal stents may be considered due to the favourable patency rates of drug eluting stents.	IIb	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Rastan, J Am Coll Cardiol 2012	RCT (sub- group analysis)	Patients with infrapopliteal lesions	161 patients, including 86 patients with intermittent claudication.	Sirolimus luting stents: n=40	Bare metal stents: n=46	Higher primary patency in intervention group at 1 year (85.3% vs. 55%, p=0.006). No difference in TLR at 1 year (5.9% vs. 20%, p=0.09). Lower target-vessel revascularization in intervention group at 33 months (7.9% vs 25%, p=0.04) No difference in all-cause mortality (18.4% vs 18.2%, p=1) and amputation rates (0% vs 4.7%, p=0.19) at 33 months.

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Recommendation 74	**Class**	**Level of evidence**				
For patients with disabling intermittent claudication, open surgical treatment of isolated below knee lesions is not recommended for the majority of patients due to the risk of harm from tibial revascularization.	III	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Levin, J Vasc Surg 2021	Observational study	Infrainguinal bypasses for claudication: tibial versus popliteal	5347 limbs	1173 tibial bypasses	4184 popliteal bypasses	Tibial bypasses were associated with poor outcomes, including amputations. Tibial bypass was associated with increased risk of : Occlusion/death (HR 1.65, 95% CI 1.28-2.11). Major ipsilateral amputation/death (HR 1.6, 95% CI 1.12-2.19) Ipsilateral reintervention/amputation/death (HR 1.51 95% CI 1.28-1.79)
Fashandi, J Vasc Surg 2018	Observational study	Infrainguinal open or endo procedures for intermittent claudication	3925 limbs	2155 open surgery	1170 endovascular surgery	Tibial revascularization was a predictor of 30-day MALEs (OR 2.16, 95% CI 1.47-3.18)

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Recommendation 75	**Class**	**Level of evidence**				
In rare circumstances for patients with disabling intermittent claudication due to below knee lesions, bypass grafting with a venous graft may be considered if exhaustive non-invasive treatment and endovascular therapy is not an alternative option.	IIb	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Kobayashi, Vasc Endovasc Surg 2021	Retrospective single center study	Tibial bypass for IC	43 patients	49 tibial bypasses	Compared to CLTI group	Surgical site infection: 10% Primary and secondary patency rates in IC patients were 79% and 94% at 1 year, 71% and 90% at 3 years, 65% and 90% at 5 years, which were significantly higher than those of critical limb threatening ischemia patients. Graft failure: 31% Amputation-free survival rates in IC patients were 100% at 1 year, 93% at 3 years and 90% at 5 years, which was significantly higher than in critical limb threatening patients. Daily activity at discharge and at last visit showed maintained daily activity.

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Recommendation 78	**Class**	**Level of evidence**			
For patients with intermittent claudication who have undergone an infra-inguinal endovascular intervention and have no increased bleeding risk*, low dose aspirin (75-100 mg once daily) in combination with low dose rivaroxaban (2.5 mg twice daily) should be considered, to reduce the risk of secondary cardiovascular and major limb events. *Medical history or active clinically noteworthy bleeding, lesions, or conditions within the last six months considered to be a major risk of major bleeding (including current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known oesophageal varices, vascular aneurysms of the large arteries or major intraspinal or intracerebral vascular abnormalities), any known hepatic disease associated with coagulopathy or bleeding risk, major trauma, or accidents within 30 days, any medically documented history of intracranial hemorrhage, stroke or TIA, known active malignancy (excluding basal or squamous cell carcinoma) (VOYAGER criteria).	IIa	B			
Reference	**Study type**	**Patient population / setting, *n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Bonaca et al., New England Journal of Medicine, 2020	Multi-centre RCT	6564 patients with peripheral arterial disease who underwent revascularization (both endovascular and open- surgery)	Aspirin + plus Rivaroxaban 2.5mg twice a day	Aspirin + placebo	Treatment with Rivaroxaban (2.5mg twice daily) and aspirin combined, compared to aspirin alone reduced the primary composite efficacy outcome (acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes) (HR=0.85, 95%CI: 0.76–0.96) during a median follow-up of 28 months. Subgroup analysis by treatment strategy showed that the positive primary efficacy outcome was driven by the surgical subgroup (HR 0.79 95% CI 0.66 to 0.95) while the endovascular subgroup difference did not reach significance (HR 0.90 95% CI 0.77 to 1.05). Moreover, the incidence of major bleeding was significantly higher in the rivaroxaban group after endovascular treatment (HR 1.60, 95% CI 1.02-2.51) but not after surgical treatment (HR 1.02, 95% CI 0.47-2.19)

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Recommendation 79	**Class**	**Level of evidence**			
In the rare post-revascularisation scenario where triple antithrombotic therapy is deemed necessary on clinical grounds, patients with intermittent claudication not at high risk for bleeding who have undergone endovascular intervention and receive post-procedural treatment with aspirin (75-100 mg once daily) in combination with low dose rivaroxaban (2.5 mg twice daily) should not have clopidogrel (75 mg) for longer than 30 days as the bleeding risk is likely to outweigh the benefit.	III	C			
Reference	**Study type**	**Patient population / setting, *n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Hiatt et al Circulation 2021	Subgroup analysis of multicentre RCT	6564 patients with peripheral arterial disease who underwent revascularization (both endovascular and open-surgery). Clopidogrel was used in 3313 patients in addition to the primary therapy	Aspirin plus Rivaroxaban 2.5mg twice a day plus clopidogrel (1658)	Aspirin plus placebo plus clopidogrel (1655)	The addition of clopidogrel did not improve any clinical outcome but led to significantly more ISTH major bleeding (HR 2.24 95% CI 1.24 to 4.03). This trend was evident when clopidogrel use exceeded 30 days.

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Recommendation 80	**Class**	**Level of evidence**				
For patients with intermittent claudication who have undergone infra-inguinal endarterectomy or bypass surgery and have no increased bleeding risk*, low dose aspirin in combination with low dose rivaroxaban should be considered to reduce the risk of secondary cardiovascular and major limb events. *Medical history or active clinically noteworthy bleeding, lesions or conditions within the last six months considered to be a major risk of major bleeding (including current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known oesophageal varices, vascular aneurysms of the large arteries or major intraspinal or intracerebral vascular abnormalities), any known hepatic disease associated with coagulopathy or bleeding risk, major trauma or accidents within 30 days, any medically documented history of intracranial hemorrhage, stroke or TIA, known active malignancy (excluding basal or squamous cell carcinoma) (VOYAGER criteria).	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Bonaca et al 2020	RCT	Patients with peripheral artery disease who have undergone lower-extremity revascularization.	6564	Rivaroxaban 2.5mg and aspirin, n=3286	Placebo and aspirin, n=3278	Rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone.

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Debus et al 2021	RCT subgroup analysis	Patients with peripheral artery disease who have undergone infrainguinal surgical lower-extremity revascularizati on (endarterectomy or bypass surgery)	2185	Rivaroxaban 2.5mg and aspirin, n=1084	Placebo and aspirin, n=1101	After surgical revascularisation, the primary efficacy outcome (acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes) occurred in 199 (18.4%) patients in the rivaroxaban group and 242 (22.0%) patients in the placebo group with a cumulative incidence at 3 years of 19.7% and 23.9%, respectively (hazard ratio, 0.81 [95% CI, 0.67–0.98]; *P*=0.026). The principal safety outcome (TIMI major bleeding) occurred in 11 (1.0%) patients in the rivaroxaban group and 13 (1.2%) patients in the placebo group and the composite of fatal bleeding or intracranial hemorrhage and postprocedural bleeding requiring intervention was not significantly increased in the rivaroxaban treatment arm.

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Recommendation 81	**Class**	**Level of evidence**			
In the rare post-revascularisation scenario where triple antithrombotic therapy is deemed necessary on clinical grounds, patients with intermittent claudication not at high risk for bleeding who have undergone lower limb surgical revascularisation and receive post-procedural treatment with aspirin (75-100 mg once daily) in combination with low dose rivaroxaban (2.5 mg twice daily) should not have clopidogrel (75 mg) for longer than 30 days as the bleeding risk is likely to outweigh the benefit.	III	C			
Reference	**Study type**	**Patient population / setting, *n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Hiatt et al Circulation 2021	Subgroup analysis of multicentre RCT	6564 patients with peripheral arterial disease who underwent revascularization (both endovascular and open- surgery). Clopidogrel was used in 3313 patients in addition to the primary therapy	Aspirin plus plus Rivaroxaban 2.5mg twice a day plus clopidogrel (1658)	Aspirin plus placebo plus clopidogrel (1655)	The addition of clopidogrel did not improve any clinical outcome but led to significantly more ISTH major bleeding (HR 2.24 95% CI 1.24 to 4.03). This trend was evident when clopidogrel use exceeded 30 days.

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Recommendation 82	**Class**	**Level of evidence**				
For patients with intermittent claudication who have undergone infra-inguinal bypass surgery with autologous vein and without increased bleeding risk, vitamin K antagonists with an international normalised ratio range at 2.0-2.5 may be considered to improve graft patency.	IIb	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Geraghty et al. 2011, Cochrane database of systematic reviews	Systematic review of 14 trials	Patients undergoing femoro-popliteal or femoro-distal bypass grafting for the treatment of IC and CLI.	4970	Trials in which participants were randomly allocated to receive either anticoagulant therapy versus placebo, one anticoagulant regimen versus another, or anticoagulant therapy versus an alternative treatment. The type of therapy, dosage, time of starting in relation to surgery (pre or postoperatively), and duration of therapy were recorded.		Patients undergoing infrainguinal venous bypass are more likely to benefit from treatment with VKA than platelet inhibitors. Patients receiving an artificial graft benefit from platelet inhibitors (aspirin). However, the evidence is not conclusive. Randomised controlled trials with larger patient numbers are needed in the future to compare antithrombotic therapies with either placebo or antiplatelet therapies.

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Bedenis et al. 2015, Cochrane database of systematic reviews	Systematic review of 16 trials	Patients with symptomatic PAD undergoing infrainguinal bypass surgery		Antiplatelet agents		Antiplatelet therapy with aspirin had a slight beneficial effect on the patency of peripheral bypasses, but seemed to have an inferior effect on venous graft patency compared with artificial grafts. The effect of aspirin on cardiovascular outcomes and survival was mild and not statistically significant; this might be due to the fact that the majority of patients receiving a peripheral graft have an advanced stage of PAD with critical ischaemia. These patients are usually seriously ill with respect to cardiovascular diseases with high mortality rates of 20% per year. Additionally, the number of patients included in this analysis might still be too small to reach a statistically significant effect for mortality and cardiovascular morbidity.
Monaco et al. 2012	RCT	Patients who underwent femoro-popliteal surgery	341	Clopidogrel 75mg plus Warfarin	Clopidogrel 75mg plus Aspirin 100mg	Efficacy (graft patency, severe arterial ischemia): overall 8-year patency rates 44.4% vs. 30.4% (p=0.026), freedom from severe arterial ischemia 77.6% vs. 63.9% (p=0.044) Safety: no differences in life-threatening bleeding, 2.85% vs. 1.37% in bleeding not requiring hospitalization (p=0.03)
Tangelder et al. 2000, Lancet Van Hattum et al. 2009, Circulation	RCT	Patients who required an infrainguinal bypass graft for obstructive arterial disease were eligible for inclusion	2,690	Phenproc oumon or Acenocou marol (INR 3.0-4.5)	Aspirin 100mg	Efficacy incidence (graft occlusion, secondary: composite event of vascular death, non-fatal MI, non- fatal stroke, or amputation) at 2287 patient years were 308 vs. 322 events (HR 0.95, 0.82-1.11*n.s.). Better outcomes in vein grafts (HR 0.69, .54-0.88), composite 248 vs. 275 events (HR 0.89, 0.75-1.06*n.s.) - Safety incidence at 1 year were 108 vs 56 events (HR 1.96, 0.14-2.7)

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De Smit et al. 1992	RCT	Patients <70y with conservative or surgical treatment with symptoms of intermittent claudication	300	Phenprocoumon	Placebo	Efficacy (disease progression): at 5 years disease progression rate was 9% vs. 29% ($p<0.001$) Safety: 44 vs. 8 bleeding complications

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Recommendation 83	**Class**	**Level of evidence**				
For patients with intermittent claudication who have undergone infra-inguinal bypass surgery with a prosthetic conduit, single antiplatelet therapy may be considered to improve graft patency.	IIb	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Bedenis et al. 2015, Cochrane database of systematic reviews	Systematic review of 16 trials.	Patients with lower limb atherosclerosis undergoing femoropopliteal or femorodistal bypass grafting	5683	Different antithrombotic treatment regimens	Placebo, no treatment or other active antithrombotic therapy treatment	Compared with placebo or no treatment, ASPIRIN or ASPIRIN + dipyramidole improved primary graft patency. This improvement was evident in those that received prosthetic grafts, but not in those that received venous grafts. The comparison of ASPIRIN or ASPIRIN + dipyramidole versus vitamin K antagonists included two studies with more than 2000 participants. There were no differences between treatment for primary graft patency at three, six, 12 or 24 months, and there was also no evidence of a difference for limb amputation, cardiovascular events or mortality. One large study evaluated clopidogrel and ASPIRIN versus ASPIRIN alone, and there was no evidence of a difference in primary patency at 24 months.There was evidence that DAPT increased total bleeding events but there was no difference in severe or fatal bleeding.

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Geraghty et al. 2011, Cochrane database of systematic reviews	Systematic review of 14 trials.	Patients undergoing femoropopliteal or femorodistal bypass grafting for the treatment of IC and CLI. Patients undergoing bypass surgery for trauma were excluded. Patients undergoing bypass procedures using autologous vein grafts, synthetic (polytetrafluoro ethylene (PTFE) or Dacron) grafts, treated human umbilical vein, or a combination of these materials were included.	4970	Trials in which participants were randomly allocated to receive either anticoagulant therapy vs. placebo, one anticoagulant regimen vs. another, or anticoagulant therapy vs. an alternative treatment. The type of therapy, dosage, time of starting in relation to surgery (pre or postoperatively), and duration of therapy were recorded.		Patients undergoing infrainguinal venous bypass are more likely to benefit from treatment with VKA than platelet inhibitors. Patients receiving an artificial graft benefit from platelet inhibitors (aspirin). However, the evidence is not conclusive. Randomised controlled trials with larger patient numbers are needed in the future to compare antithrombotic therapies with either placebo or antiplatelet therapies.
Lassila et al. 1991	RCT	Patients with first arterial reconstruction due to peripheral vascular disease (Fontaine II, III, IV)	144	Aspirin 250mg	No antiplatelet	Efficacy (death or new cardiovascular events, local arterial adverse event): incidence at follow- up not different. Local arterial events: 15 vs. 31 patients ($p<0.01$).
Belch et al. 2010, Clin Res Stud	RCT, Multi-center, double-blind, 1:1	Patients undergoing unilateral below-the-knee bypass grafting for atherosclerotic peripheral arterial disease	851	Clopidogrel 75mg plus aspirin 75-100mg	Placebo plus aspirin	Efficacy incidence (composite of index graft occlusion or revascularization, above-ankle index amputation, or death) at 2 years were 35.1% vs. 35.4% (HR 0.98, 0.78-1.23*) Safety incidence (severe bleeding) at 2 years were 2.1% vs. 1.2% (n.s.), mild bleeding: 10.8% vs. 5.0% ($p=0.002$)

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McCollum et al. 1991, J Vasc Surg	RCT, Multi-center, double-blind	Patients with femoropopliteal vein bypasses	549	Dipyrida mole 150mg plus aspirin 300mg	Placebo	Efficacy (graft patency, cardiovascular events (composite of myocardial infarction and stroke)): graft patency at 36 months was 52% vs. 47% (p=0.43), cardiovascular events 35 vs. 53 per 1000 patient years (p=0.004) Safety: cardiovascular symptoms 98.3 vs. 163.8 per 1000 patient years (p=0.004), other adverse events not different
Clyne et al. 1987, Br J Surg	Single-center RCT	Patients with lower extremity femorodistal bypass grafts	140	Aspirin 300mg plus dipyridamole 200mg twice daily	No treatment	Overall results showed higher patency in the treated group (P =0.012) which was entirely accounted for by the difference between prosthetic dipyridamole and aspirin group (85 per cent patency) and prosthetic control group (53 per cent patency, P =0405) and arose during the first postoperative month. A six-week perioperative course of dipyridamole and aspirin allows the patency of prosthetic femorodistal bypass to approach that of autogenous vein, and the regimen therefore is recommended for patients who may require a prosthetic graft.

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Recommendation 85	**Class**	**Level of evidence**				
For all patients with lower limb peripheral arterial disease who have undergone lower limb revascularisation, disease specific health related quality of life instruments, preferably with established thresholds for minimally important clinical difference should be considered, to evaluate the treatment results.	IIa	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Cassar K Eur J Vasc Endovasc Surg 2003	Systematic review	A review of studies (out of which 5 were RCTs) of exercise- based interventions which assessed Quality of Life (QoL) of patients with IC as either a primary or secondary endpoint.	In total 1850 studied patients. The majority of included studies had relatively small sample sizes.	N/A		Compared with generic HRQoL instruments, disease specific measures were more responsive to QoL improvements and detected changes across a range of domains following both supervised and home-based exercise.
Donker J Vascular 2016	Systematic review	The review included 23 articles that described quality of life in approximately 4600 patients suffering from peripheral arterial disease.	4600	N/A		Invasive treatment generally results in better quality of life scores (at a maximum of 2 years of follow-up), compared with non-invasive treatment.
Peri-Okonny PA Circ Cardiovasc Qual Outcomes 2021		Patients presenting to vascular clinics with new or worsened claudication in the US cohort of the PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease:		N/A		The crude minimal clinically important difference (MCID) for the PAQ summary scale improvement and worsening were 8.7 (2.9-14.5) and -11.0 (-18.6 to -3.3), respectively. After multivariable adjustment, these were 8.9 (3.0-14.8) and -11.2 (-18.2 to -4.2), respectively.

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		Investigating Trajectories) registry who completed baseline and follow-up PAQ assessments along with the Global Assessment of Functioning scale were included				
Gardner AW, Vasc Med 2018	Exploratory analysis within a three-armed RCT	Patients with intermittent claudication were recruited from vascular laboratories and vascular clinics at the University of Oklahoma HSC.	n=180	Supervised exercise therapy n=60 Home-based exercise n=80	Attention control n=80	The MCID for the WIQ distance score was approximately a 6% change from baseline when evaluated with a distribution-based method, and 5% when evaluated with an anchor-based approach.
Conijn AP Cardiovasc Intervent Radiol 2015	Prospective multicenter cohort study	Patients with intermittent claudication	294 patients with IC			For the MCID analyses of the VascuQol (25 items) and the WIQ questionnaires, 163 and 134 patients were analysed, respectively. The MCID values for the VascuQol were 0.87 for improvement and 0.23 for deterioration. For the WIQ, the MCID values were 0.11 and -0.03 for improvement and deterioration, respectively.
Nordanstig J Eur J Vasc Endovasc Surg 2017	Populati on- based registry study	Revascularised patients with intermittent claudication and chronic limb- threatening ischemia in the National Quality Registry for Vascular Surgery (Swedvasc)	A total of 3194 revascularised PAD patients with complete VQ-6 baseline recordings (intermittent claudication (IC) n=1622 and critical limb ischaemia (CLI) n=1572) were studied, of which 2996 had complete VQ-6 recordings 30 days and 1092 a year after the vascular intervention	N/A		For the VascuQoL-6 questionnaire, the MCID one year after revascularisation for IC patients ranged from 1.7 to 2.2 scale steps, depending on the method of analysis. ROC analyses demonstrated that the VQ-6 discriminative properties for a substantial clinical benefit was excellent for IC patients (area under curve (AUC) 0.87, sensitivity 0.81, specificity 0.76). An optimal VQ-6 threshold for a substantial clinical benefit was determined at 3.5 scale steps among IC patients

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Recommendation 86	**Class**	**Level of evidence**				
For patients with lower limb peripheral arterial disease, it is recommended that a continuous assessment of suitable indicators of quality of treatment (including survival, functional status, surgical complications and major adverse cardiovascular and limb events) is organised and maintained to improve the care delivered to those patients.	I	C				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Bellmunt 2014	Systematic review of systematic reviews of high methodological quality	Patients with PAD				Six indicators were finally generated: four on pharmacological interventions, antiplatelet agents, naftidrofuryl, cilostazol, and statins; and two lifestyle interventions, exercise and tobacco cessation. No indicators were derived for diagnostic tests or surgical techniques. Most indicators targeted patients with intermittent claudication.
Olin 2010	Consensus document					
Rieß 2018	Delphi consensus study					After two Delphi rounds, 12 indicators (27.9 %) achieved the limit of agreement for relevance and four (9.3 %) for practicability. Major adverse limb events (MALE), major amputation, and major re- intervention (or re-operation) were consented as both highly relevant and practicable. Additionally, major adverse cardiovascular events (MACE), myocardial infarction, stroke or transient ischaemic attack, all-cause death, all re- intervention (or re-operation), wound infection, vascular access-related major complication, walking distance, and Rutherford-classification were consented as highly relevant. Ankle-brachial-index was consented as highly practicable.

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Hischke 2019	Systematic review	Patients with PAD				This study revealed a lack of published evidence based quality indicators concerning invasive treatment for PAOD in the literature. A total of three process quality indicators matched the search criteria: one on pharmacological intervention, another on smoking cessation, and a third on surveillance of lower extremity vein bypass grafts. The grey literature search revealed an additional 31 structure, process, and outcome quality indicators from the databases of professional societies and organisations have not been incorporated in prior guidelines. Interestingly, no indicator related to patient reported outcomes could be identified from either high quality sources or grey literature.

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Recommendation 87	**Class**	**Level of evidence**				
It is recommended to pay attention to a balanced proportion of women and men in clinical studies, with a proportional representation of both sexes according to the sex specific frequency of the disorder or the intervention under study.	I	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Mayor et al, J Vasc Surg, 2022	Review	Data from ClinicalsTrials.gov 2008-2020	Included trials on PAD: 68			The participation-to-prevalence ratios (PPR) (dividing the percentage of women among trial participants by the percentage of women in the disease population) = 0.65 (IQR 0.53-0.77). PPR did not vary significantly over time
Jelani et al, Current Atherosclerosis Reports 2018	Review		Included studies: 32			In more than half of reviewed PAD studies did women comprise <35%. In reviewed RCTs women represented 22%. In included cardiovascular risk trials represented women 27% of the total population (n= 412048) without major change over time.
Hirsch, Circulation 2012	Scientific statement					The American Heart Association recommends: Future clinical trials for PAD treatment including pharmacological treatment, life-style interventions and revascularization procedures to be powered for detection of gender-based differences.

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Recommendation 88	**Class**	**Level of evidence**				
In postmenopausal women, hormone replacement therapy with oestrogen or progestin is not recommended for prevention of cardiovascular disease due to the lack of proven cardiovascular benefits.	III	A				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Rossouw JE et al. 2002 JAMA	RCT	postmenopausal women	16608	8506	8102	Estrogen plus progestin vs. placebo should not be used for prevention of coronary heart disease (HR for CHD 1.29 (1.02-1.63)) as the adverse effect of developing breast cancer exceeded, therefore risks exceeded benefit.
Grady D et al 2002 JAMA	RCT	Postmenopausal women	2763	1380	1383	After 6.8 years, hormone therapy (estrogene and progesterone) did not reduce risk of cardiovascular events in women with CHD (HR 0.99 (0.81-1.17)). Postmenopausal hormone therapy should not be used to reduce risk for CHD events in women with CHD.

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Recommendation 89	**Class**	**Level of evidence**				
It is recommended to offer similar evidence based cardiovascular primary and secondary preventive strategies to men and women with peripheral arterial disease.	I	B				
Reference	**Study type**	**Patient population / setting**	***n***	**Intervention**	**Control group (if any)**	**Relevant findings**
Jain RK e Curr Diab Rep 2015	Review	Women with diabetes and cardiovascular disease	20 studies included RCT, metanalyses, and Cohort studies			Women with diabetes and cardiovascular disease are treated less aggressively with life-style changes and pharmacological therapy. These disparities should be recognized and addressed.
Srivaratharajah, Candian J of Cardiology 2018	Review	PAD patients				Lower rate of preventive strategies is used in women. Greater efforts in treatment in women is needed.
Hirsch et al, Circulation 2012	Scientific Statement					Physical activity programs demonstrate a meaningful response, but only one in four of the reports included women.
Peters, Eur J Vasc Surg 2020	Observational	Health Insurance Claim Data, inpatient and outpatient care for IC (54%) and CLI 46%.	83 867 (Women = 38 421)			Prescription rate of optimal pharmacological treatment defined as lipid lowering drugs, anti-thrombotics, and antihypertensives among men and women: 42.7% vs 37.0%, Adjusted OR 0.89 (0.86-0.92) with similar gender gap over study period (2010-2018). Sex gap in treatment pattern
Makowski, Atherosclerosis, 2021	Observational	Claims data in patient treatment for IC	42 197 (Women = 13 677)			Statin and anti-platelet use among men and women: 75% vs 72% ($p<0.001$) and 76% vs74% ($p=0.003$).Sex gap in treatment pattern
Teodorescu J Vasc Surg 2013	Review					No meta-analysis available. Men more likely to receive preventive medication as compared women.
Ramkumar Circ Cardiovasc Interv 2018	Observational	Registry Study Vascular Quality Initiative Claudication: 53%	23 820 (women = 9 885)			Women were significantly less treated with statins, B-blockers, anti-coagulation and aspirin as compared men. Sex gap in treatment pattern

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Messiha Eur J Vasc Endovasc Surg 2022	Observational	Nationwide ambulatory claims data covering 87% of the German population: IC and CLTI	N= 17, 633 970 Women: 47%			IC the group 48.5% of the male and 41% of the female patients received statin therapy. During 2009-2016, the gender gap in statin prescription rates increased to 8% (p>0.05) among IC patients. Sex gap in treatment pattern.

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