Supplementary Table (online only). Summary of Evidence

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendations 1.1 and 1.2					
de Graaff,[1] 2003	96 patients (128 legs) with clinically suspected CLI	Clinical judgment and AP	$TcPo_2$- and TP-guided management	Unblinded RCT. The randomization was performed by computer and was prestratified for the presence of DM and bilateral symptoms of CLI.	No significant difference was seen in terms of pain score, number of amputations, or death.
Wang,[2] 2016	Noninvasive screening tests for the prediction of wound healing and the risk of amputation in DFUs	Various tests	Various tests	Systematic review and meta-analysis of 37 observational studies	For the $TcPo_2$ test, the pooled DOR was 15.81 (95% CI, 3.36-74.45) for wound healing and 4.14 (95% CI, 2.98-5.76) for the risk of amputation. ABI was also predictive but to a lesser degree of the risk of amputations (DOR, 2.89; 95% CI, 1.65-5.05) but not of wound healing (DOR, 1.02; 95% CI, 0.40-2.64). It was not feasible to perform meta-analysis comparing the remaining tests. The overall quality of evidence was limited by the risk of bias and imprecision (wide CIs due to small sample size).
Brownrigg,[3] 2016	Prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in DM	Various tests	Various tests	Systematic review and meta-analysis of 11 observational studies on 9 markers of PAD	Skin perfusion pressure ≥40 mm Hg, TP ≥30 mm Hg (and ≥45 mm Hg), and $TcPo_2$ ≥25 mm Hg were associated with at least a 25% higher chance of healing. AP <70 mm Hg and fluorescein toe slope <18 units each increased the likelihood of major amputation by around 25%.
Beropoulis,[4] 2016	302 nondiabetic CLI patients treated by endovascular means	The prognostic value of WIfI	None	Retrospective unadjusted analysis of prospectively collected data	The AFS at 12 months was 87%, 81%, 81%, and 62% in the very-low-risk, low-risk, moderate-risk, and very-high-risk groups, respectively (P = .106). The difference was statistically significant between the very-low-risk and high-risk groups (HR, 3.4; 95% CI, 1.1-10.3; P = .029).
Ward,[5] 2017	93 patients who presented to a public hospital with CLI	The prognostic value of WIfI	None	Retrospective adjusted analysis	On multivariable analysis, increasing WIfI amputation score (OR, 1.84; 95% CI, 1.0-3.39) was associated with increased risk of 1-year major amputation rate.
Darling,[6] 2016	596 limbs of patients with a first-time lower extremity revascularization for CLTI	The prognostic value of WIfI	None	Retrospective adjusted analysis	WIfI mean score was predictive in the entire cohort (HR, 1.4; 95% CI, 1.1-1.7), the bypass-only cohort (HR, 1.5; 95% CI, 1.1-1.9), and the endovascular-only cohort (HR, 1.4; 95% CI, 1.0-1.8)

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendations 3.4, 3.5, and 3.6					
Lijmer,[7] 1996	441 patients with suspected PAD	Noninvasive tests for assessing PAD	None	Retrospective adjusted analysis with blinded readers	For assessing PAD (lesions ≥50%), determining an ABI is justified (ROC area, 0.95 ± 0.02). For disease localized to the AI segment, performing a single test, the femoral pulsatility index, is sufficient (ROC area, 0.80 ± 0.04). For disease including the FP and IP segments, a combination of tests is necessary.
Aboyans,[8] 2008	510 ambulatory patients (37% had DM)	Noninvasive tests for assessing PAD	None	Cross-sectional study, unblinded assessment, adjusted analysis	A strong association was found between DM and high ABI (OR, 16.0; $P < .001$). When ABI ranges were compared with TBI and Pk-PT results, those with ABI ≤0.9 and ABI ≥1.4 presented similar patterns of abnormalities. Pk-PT or TBI or both were abnormal in >80% of cases in both ABI ≤0.9 and ≥1.4 groups. The ABI vs TBI relationship appeared linear in nondiabetic patients but had an inverted J shape in diabetic patients, suggesting that high ABI masked leg ischemia.
Saluan,[9] 2018	556 patients from the Cohorte des Patients ARTériopathes hospitalized for PAD. Patients with CLI were enrolled according to the TASC II definition and followed up for at least 1 year.	Comparison of major amputation rate according to initial AP, systolic TP, and forefoot $TcPo_2$	3 comparative tests	The cohort selection was considered adequate (consecutive sampling) and low risk for selection bias, but outcome assessment was not adjusted or blinded.	AP failed to identify 42% of patients with CLI. After 1 year, 27% of medical and 17% of surgical patients had undergone major amputation. TP <30 mm Hg predicted major amputation in the whole sample and in the medical group (OR, 3.5 [1.7-7.1] and 5 [2-12.4], respectively), but AP did not. $TcPo_2$ <10 mm Hg also predicted major amputation (OR, 2.3 [1.5-3.5] and 3.8 [2.1-6.8]). The best predictive thresholds for major amputation were systolic TP <30 mm Hg and $TcPo_2$ <10 mm Hg. None of these methods performed before surgery was able to predict outcome in the revascularized patients.
Recommendations 3.7 and 3.8					
Larch,[10] 1997	50 patients with FP obstruction were examined immediately before planned PTA	Color DUS	DSA	Consecutive sample, 2 readers, cross-sectional design	The sensitivity of color DUS for detecting a hemodynamically relevant arterial lesion (stenosis or occlusion) was 100% in the PT artery, 78% in the AT artery, and 92% in the peroneal artery.

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Visser,[11] 2000	31 diagnostic studies	Gadolinium-enhanced MRA	Color-guided DUS	Diagnostic meta-analysis, medium risk of bias, adjusted analysis	Pooled sensitivity for MRA (97.5%; 95% CI, 95.7%-99.3%) was higher than that for DUS (87.6%; 95% CI, 84.4%-90.8%). Pooled specificities were similar: 96.2% (95% CI, 94.4%-97.9%) for MRA and 94.7% (95% CI, 93.2%-96.2%) for DUS.
Adriaensen,[12] 2004	73 patients with symptomatic PAD	CT	DSA	Randomized, unblinded	Further imaging was recommended more often after CT than after DSA ($P = .003$). Analysis of trends demonstrated increasing confidence in CT and stable confidence in DSA.
Collins,[13] 2007	Symptomatic lower limb PAD	DUS	MRA and CTA	Systematic review and meta-analysis of 113 observational studies of moderate quality	For the detection of stenosis >50% in the whole leg, MRA (14 studies) had the highest diagnostic accuracy, with sensitivity ranging from 92% to 99.5% and specificity from 64% to 99%. CTA (7 studies) was slightly inferior to MRA, with a sensitivity ranging from 89% to 99% and specificity from 83% to 97%, but better than DUS (28 studies), which had a sensitivity ranging from 80% to 98% and specificity from 89% to 99%.
Hingorani,[14] 2004	33 inpatients with chronic lower extremity ischemia	MRA	Contrast arteriography and duplex arteriography	Consecutive sample, prospective operative follow-up, unblinded	No differences were noted between intraoperative findings and arteriography. Two of the 3 differences between duplex arteriography and contrast arteriography were thought to be clinically significant, whereas 9 of the 12 differences between MRA and contrast arteriography were thought to be clinically significant. On the basis of these data in this series, MRA does not yet seem to be able to obtain adequate data on IP segments, at least not for this highly selected population. When severe tibial calcification or very low flow states are identified, contrast arteriography may be necessary for patients undergoing duplex arteriography.
Hingorani,[15] 2008	906 patients undergoing lower extremity revascularization	Duplex arteriography (207 intraoperatively, 699 preoperatively)	Contrast arteriography	Consecutive series, comparative, nonrandomized, low risk of bias overall	Additional contrast arteriography imaging was required for procedural planning in 102 patients. The areas not visualized well included iliac (73), femoral (26),

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					popliteal (17), and IP (221). Factors associated with increased need to obtain contrast arteriography included DM ($P < .001$), IP calcification ($P < .001$), older age ($P = .01$), and limb-threatening ischemia ($P < .001$).
Met,[16] 2009	957 patients with IC or CLI	CTA	DSA	Systematic review and meta-analysis of 20 nonrandomized studies of moderate quality	The sensitivity of CTA for detecting >50% stenosis or occlusion was 95% (95% CI, 92%-97%), and specificity was 96% (95% CI, 93%-97%). CTA correctly identified occlusions in 94% of segments, the presence of >50% stenosis in 87% of segments, and absence of significant stenosis in 96% of segments.
Recommendation 4.1					
The Study Group of Critical Chronic Ischemia of the Lower Extremities,[17] 1997	522 patients with chronic CLI	Various predictors	None	Prospective observational study with linkage to census information, unblinded	Besides age ≥70 years (RR, 1.94; 95% CI, 1.37-2.70), only a history of stroke (RR, 1.82; 95% CI, 1.19-2.79) and major amputation (RR, 1.90; 95% CI, 1.30-2.80) were significantly associated with mortality.
Recommendation 4.2					
Faglia,[18] 2014	553 diabetic patients admitted because of CLI	Various predictors, ACE and statin	None	Prospective observational study, consecutive sample	Multivariate analysis confirmed the independent role of age, history of stroke, renal insufficiency, and dialysis. Combined treatment with ACE and statin appeared to reduce mortality.
Armstrong,[19] 2014	739 patients with claudication or CLI who underwent diagnostic or interventional lower extremity angiography	Adherence to all four guideline-recommended therapies (aspirin, statins, ACE inhibitors, and smoking cessation)	Less adherence	Propensity weighting, consecutive cohort, and outcome adjustment; low risk of bias	After adjustment for baseline covariates, patients adhering to all four guideline-recommended therapies had decreased MACEs (HR, 0.64; 95% CI, 0.45-0.89), MALEs (major amputation, thrombolysis, or surgical bypass; HR, 0.55; 95% CI, 0.37-0.83), and mortality (HR, 0.56; 95% CI, 0.38-0.82) compared with patients receiving fewer than four of the recommended therapies.
Recommendation 4.3					
Antithrombotic Trialists' Collaboration,[20] 2002	Meta-analysis: 287 studies involving 135,000 patients in comparisons of antiplatelet therapy vs control and 77,000 in comparisons of different antiplatelet regimens	Antiplatelet	Control	Meta-analysis of randomized trials of various risk of bias	Allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one-quarter; nonfatal myocardial infarction was reduced by one-third, nonfatal stroke by one-

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					quarter, and vascular mortality by one-sixth (with no apparent adverse effect on other deaths). Absolute reductions in the risk of having a serious vascular event per 1000 were 36 among patients with previous myocardial infarction, 38 among patients with acute myocardial infarction, 36 among those with previous stroke or transient ischemic attack, 9 among those with acute stroke, and 22 among other high-risk patients.
Antithrombotic Trialists' Collaboration,[21] 2009	Meta-analysis of 6 primary prevention trials and 16 secondary prevention trials	Aspirin	No aspirin	Meta-analysis of individual participant data from randomized trials at varying risk of bias	In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0.51% aspirin vs 0.57% control per year; $P = .0001$). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0.10% vs 0.07% per year; $P < .0001$). In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6.7% vs 8.2% per year; $P < .0001$), with a nonsignificant increase in hemorrhagic stroke but reductions of about a fifth in total stroke (2.08% vs 2.54% per year; $P = .002$) and in coronary events (4.3% vs 5.3% per year; $P < .0001$). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women.
Recommendation 4.4					
CAPRIE Steering Committee,[22] 1996	19,185 patients with atherosclerotic vascular disease manifested as recent ischemic stroke, recent myocardial infarction, or symptomatic PAD	Clopidogrel (75 mg once daily)	Aspirin (325 mg once daily)	Randomized, blinded, international trial at low risk of bias	Patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, myocardial infarction, or vascular death compared with 5.83% with aspirin.
Hiatt,[23] 2017	13,885 patients with symptomatic PAD, with an ABI of ≤0.8 or prior revascularization of the lower limbs	Ticagrelor (90 mg twice daily)	Clopidogrel (75 mg once daily)	Double-blinded randomized trial at low risk of bias	Patients in both groups had similar rates of reduction in cardiovascular (CV) events (CV death, myocardial infarction, ischemic stroke) and rates of major bleeding. CV events occurred in 740 of 6955 (10.6%)

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					patients receiving clopidogrel (HR, 1.02; 95% CI, 0.92-1.13; $P = .65$), acute limb ischemia occurred in 1.7% of the patients (HR, 1.03; 95% CI, 0.79-1.33; $P = .85$), and major bleeding occurred in 1.6% (HR, 1.10; 95% CI, 0.84-1.43; $P = .49$).
Recommendation 4.5					
Anand,[24] 2018	7470 patients with PAD of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, IC (with objective evidence of PAD), of the carotid arteries (previous carotid artery revascularization or asymptomatic carotid artery stenosis of at least 50%) or CAD with an ABI of <0.9	Oral rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or aspirin once a day (100 mg and rivaroxaban placebo twice a day)	3 arms	Multicenter, blinded patients and investigators, RCT at low risk of bias	Rivaroxaban plus aspirin compared with aspirin alone reduced the composite end point of CV death, myocardial infarction, or stroke (126 [5%] of 2492 vs 174 [7%] of 2504; HR, 0.72; 95% CI, 0.57-0.90; $P = .0047$) and MALEs including major amputation (32 [1%] vs 60 [2%]; HR, 0.54; 95% CI, 0.35-0.82, $P = .0037$). Rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (77 [3%] of 2492 vs 48 [2%] of 2504; HR, 1.61; 95% CI, 1.12-2.31; $P = .0089$).
Recommendation 4.6					
Anand,[25] 2007	2161 patients with PAD	Antiplatelet agent + oral anticoagulant agent	Antiplatelet therapy alone	RCT	Treating 1000 patients with combination therapy compared with antiplatelet therapy alone for 3 years would lead to 24 fewer CV events but 28 more episodes of life-threatening bleeding, a net increase in serious adverse outcomes.
Recommendation 4.7					
Mills,[26] 2011	Meta-analysis of 10 RCTs enrolling 41,778 patients	High-dose statin	Low- or medium-dose statin	RCTs at low risk of bias	No difference in mortality or CV mortality. High dose reduced composite end points of CV death and nonfatal myocardial infarction and the composite of fatal and nonfatal stroke.
MRC/BHF Heart Protection Study,[27] 2002	20,536 adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or DM	40 mg simvastatin daily	Placebo	Blinded randomized trial	All-cause mortality was significantly reduced (1328 [12.9%] deaths among 10,269 allocated to simvastatin vs 1507 [14.7%] among 10,267 allocated to placebo; $P = .0003$) because of a highly significant 18% proportional reduction in the coronary death rate (587 [5.7%] vs 707 [6.9%]; $P =$

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					.0005), a marginally significant reduction in other vascular deaths (194 [1.9%] vs 230 [2.2%]; $P = .07$), and a nonsignificant reduction in nonvascular deaths (547 [5.3%] vs 570 [5.6%]; $P = .4$).
Meade,[28] 2002	1568 men (aged 35-92 years) with lower extremity arterial disease	400 mg bezafibrate daily	Placebo	Double-blinded randomized trial	Bezafibrate did not reduce the incidence of coronary heart disease and stroke (RR, 0.96; 95% CI, 0.76-1.21). There were 90 and 111 major coronary events in the active and placebo groups, respectively (RR, 0.81; 95% CI, 0.60-1.08), of which 64 and 65 were fatal (RR, 0.95; 0.66-1.37) and 26 and 46 were nonfatal (RR, 0.60; 95% CI, 0.36-0.99). Beneficial effects on nonfatal events were greatest in men aged <65 years at entry, in whom benefit was also seen for all coronary events (RR, 0.38, 95% CI, 0.20-0.72). There were no significant effects in older men. There were 60 strokes in those receiving active treatment and 49 in those receiving placebo (RR, 1.34; 95% CI, 0.80-2.01). There were 204 and 195 deaths from all causes in the two groups, respectively (RR, 1.03; 95% CI, 0.83-1.26). Bezafibrate reduced the severity of IC for up to 3 years.
Leng,[29] 2000	7 RCTs (698 patients with lower limb atherosclerosis)	Lipid-lowering therapy		Systematic review of 7 RCTs at low risk of bias	The follow-up period varied from 4 months to 3 years. The overall quality of the included trials was high. The trials were heterogeneous in terms of inclusion criteria, type of drugs used, and outcomes measured. Lipid-lowering therapy produced a marked but nonsignificant reduction in mortality (OR, 0.21; 95% CI, 0.03-1.17) but little change in nonfatal events (OR, 1.21; 95% CI, 0.80-1.83). In two trials, there was a significant overall reduction in disease progression on angiography (OR, 0.47; 95% CI, 0.29-0.77). The changes in ABI and walking distance were inconsistent, although trials showed a general improvement in symptoms that could not be combined in a meta-analysis.

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Aung,[30] 2007	18 randomized controlled trials (10,049 patients with PAD)	Lipid-lowering therapy		Systematic review of 18 RCTs	The pooled results from all eligible trials indicated that lipid-lowering therapy had no statistically significant effect on overall mortality (OR, 0.86; 95% CI, 0.49-1.50) or on total CV events (OR, 0.8; 95% CI, 0.59-1.09). However, subgroup analysis, which excluded PQRST, showed that lipid-lowering therapy significantly reduced the risk of total CV events (OR, 0.74; CI, 0.55-0.98). This was primarily due to a positive effect on total coronary events (OR, 0.76; 95% CI, 0.67-0.87). Greatest evidence of effectiveness came from the use of simvastatin in people with a blood cholesterol level ≥3.5 mmol/L (Heart Protection Study). Pooling of the results from several small trials on a range of different lipid-lowering agents indicated an improvement in total walking distance (WMD, 152 m; 95% CI, 32.11-271.88) and pain-free walking distance (WMD, 89.76 m; 95% CI, 30.05-149.47) but no significant impact on ABI (WMD, 0.04; 95% CI, −0.01 to 0.09).
Rodriguez,[31] 2017	509,766 patients (aged 21-84 years) in the Veterans Affairs health care system with two or more visits for atherosclerotic CVD in preceding 2 years	High-intensity statin therapy (n = 150,928) or low-intensity statin therapy (n = 33,920)	No statin (n = 92,625)	Retrospective cohort	During a mean follow-up of 492 days, there was a graded association between intensity of statin therapy and mortality, with 1-year mortality rates of 4.0% (5103/126,139) for those receiving high-intensity statin therapy, 4.8% (9703/200,709) for those receiving moderate-intensity statin therapy, 5.7% (1632/28,765) for those receiving low-intensity statin therapy, and 6.6% (4868/73,728) for those receiving no statin ($P < .001$). After adjustment for the propensity to receive high-intensity statins, the HR for mortality was 0.91 (95% CI, 0.88-0.93) for those receiving high- vs moderate-intensity statins. The magnitude of benefit of high- vs moderate-intensity statins was similar for an incident cohort HR of 0.93 (95% CI, 0.85-1.01). For patients aged 76 to 84 years, the HR was 0.91 (95% CI, 0.87-0.95). Patients treated with

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					maximal doses of high-intensity statins had lower mortality (HR, 0.90; 95% CI, 0.87-0.94) compared with those receiving submaximal doses.
Recommendation 4.8					
SPRINT,[32] 2015	9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased CV risk but without DM	Systolic blood pressure target <120 mm Hg	Target of <140 mm Hg	Randomized trial at low risk of bias	Significantly lower rate of the primary composite (CV) outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs 2.19% per year; HR with intensive treatment, 0.75; 95% CI, 0.64-0.89; $P < .001$). All-cause mortality was also significantly lower in the intensive-treatment group (HR, 0.73; 95% CI, 0.60-0.90; $P = .003$).
Bavry,[33] 2010	2699 PAD patients observed for a mean of 2.7 years	Blood pressure target	NA		All-cause death, nonfatal myocardial infarction, or nonfatal stroke occurred least frequently among PAD patients treated to an average systolic blood pressure of 135 to 145 mm Hg and an average diastolic blood pressure of 60 to 90 mm Hg. PAD patients displayed a J-shaped relationship with systolic blood pressure and the primary outcome, although individuals without PAD did not. PAD patients may require a different target blood pressure than those without PAD.
ACCORD Study Group,[34] 2010	4733 participants with type 2 DM	Intensive therapy, targeting a systolic pressure of <120 mm Hg	Standard therapy, targeting a systolic pressure of <140 mm Hg	Low risk of bias, precise	Targeting a systolic blood pressure of <120 mm Hg compared with <140 mm Hg did not reduce the rate of a composite outcome of fatal and nonfatal major CV events.
Moise,[35] 2016	The objective of this study was to project the potential value of adding intensive systolic blood pressure goals in high-risk patients to the JNC7 or JNC8 guidelines in a contemporary population of untreated hypertensive individuals aged 35 to 74 years.	NA	NA	Simulation and state-transition (Markov cohort) model of incidence, prevalence, mortality, and costs of CVD	Adding intensive systolic blood pressure goals for high-risk patients prevents an estimated 43,000 and 35,000 annual CVD events incremental to JNC8 and JNC7, respectively. Intensive strategies save costs in men and are cost-effective in women compared with JNC8 alone. At a willingness to pay threshold of $50,000 per quality-adjusted life-years gained, JNC8 + intensive had the highest probability of cost-effectiveness in women (82%), and JNC7 +

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					intensive the highest probability of cost-effectiveness in men (100%). Assuming higher drug and monitoring costs, adding intensive goals for high-risk patients remained consistently cost-effective in men but not always in women.
Recommendation 4.9					
Nathan,[36] 2005	1441 patients with type 1 DM	Intensive therapy	Conventional therapy	Randomized trial at low risk of bias	Intensive treatment reduced the risk of any CVD event by 42% (95% CI, 9%-63%; $P = .02$) and the risk of nonfatal myocardial infarction, stroke, or death from CVD by 57% (95% CI, 12%-79%; $P = .02$).
van Dieren,[37] 2014	7768 patients with type 2 DM	Intensive glycemic control	Standard control	Randomized trial at low risk of bias	Feasible intensive control of DM There was no significant reduction in macrovascular disease, but a trend was seen toward fewer myocardial infarctions with more intensive glucose control.
Selvin,[38] 2004	13 observational studies (1699 patients with type 1 DM and 7435 patients with type 2 DM)	NA	NA	Meta-analysis of 13 prospective cohort studies	The pooled RR for CVD was 1.18; this represented a 1-percentage point increase in glycosylated hemoglobin level (95% CI, 1.10-1.26) in persons with type 2 DM. Results in persons with type 1 DM were similar but had a wider CI (pooled RR, 1.15; 95% CI, 0.92-1.43).
Recommendation 4.10					
Palmer,[39] 2016	301 clinical trials (1,417,367 patient-months)	Glucose-lowering drugs	Other glucose-lowering drugs	Meta-analysis of trials at overall low risk of bias	Compared with metformin, sulfonylurea (SMD, 0.18; 95% CI, 0.01-0.34), thiazolidinedione (SMD, 0.16; 95% CI, 0.00-0.31), dipeptidyl peptidase 4 inhibitor (SMD, 0.33; 95% CI, 0.13-0.52), and α-glucosidase inhibitor (SMD, 0.35; 95% CI, 0.12-0.58) monotherapy was associated with higher hemoglobin A1c levels. Sulfonylurea (OR, 3.13 [95% CI, 2.39-4.12]; RD, 10% [95% CI, 7%-13%]) and basal insulin (OR, 17.9 [95% CI, 1.97-162]; RD, 10% [95% CI, 0.08%-20%]) were associated with greatest odds of hypoglycemia.
Recommendation 4.11					
Nawaz,[40] 1998	33 inpatients receiving metformin	Contrast angiography		Retrospective case series	Twenty-nine patients had a normal serum creatinine concentration

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					before the procedure and none had a rise after angiography. Four patients had an abnormal serum creatinine concentration before angiography; all four patients showed significant deterioration and all four patients died, two of unrelated causes and two of acute renal failure and acidosis.
Goergen,[41] 2010	Systematic review of 5 CPGs on use of contrast medium in patients taking metformin	Contrast angiography	NA	NA	Recommendations were inconsistent regarding need to withhold metformin in patients with normal vs abnormal renal function. Not all guidelines included a specific time period. A 48-hour withholding period was the most common recommendation. Supporting evidence was of low quality, and connection between evidence and recommendations was unclear.
Recommendation 4.12					
Blomster,[42] 2016	20 countries worldwide participating in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial (6466 never-smokers, 1550 daily smokers, and 3124 former smokers)	Smoking	Nonsmoking	Prospective observation of a trial, low risk of bias	Daily smoking was associated with increased risk of major CV events and mortality. Men and women had similar HRs for most subcomponents of outcomes.
Newhall,[43] 2017	Vascular surgery practices	Brief smoking cessation intervention	Control sites	Cluster randomized trial at low risk of bias	Compared with usual care, patients in the intervention group were more likely to express interest in quitting and to acknowledge their addictive behaviors, and when resurveyed 3 months after intervention, they had larger declines in nicotine dependence and health effects domains.
Athyros,[44] 2013	1600 patients with established coronary heart disease, mean follow-up 3 years (RCT of statins)	Atorvastatin	No atorvastatin	Low risk, RCT	The relative effects of statins were similar in smokers and nonsmokers (absolute effects were higher in smokers).
Blomster,[42] 2016	11,140 patients with type 2 DM aged ≥55 years and in CV risk at the time of randomization.	NA	NA	Low risk, cohort	Daily smoking was associated with increased risk of all primary and secondary outcomes with the exception of major cerebrovascular disease.
Degenais,[45] 2005	8905 men and women in the Heart Outcomes Prevention	NA	NA	Observational cohort	Patients were observed for 4.5 years. Smokers, compared with never-

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
	Evaluation (HOPE) trial, with either CVD or DM with at least one additional risk factor (2728 never-smokers, 5241 former smokers, 936 current smokers)				smokers, had adjusted RRs for CV death of 1.65 (95% CI, 1.28-2.14), for myocardial infarction of 1.26 (95% CI, 1.01-1.58), for stroke of 1.42 (95% CI, 1.00-2.04), and for total mortality of 1.99 (95% CI, 1.63-2.44).
Recommendation 4.13					
Kondo,[46] 2011	25,464 healthy Japanese men, with no known diseases and not taking medications for hypertension, DM, or dyslipidemia	NA	NA	Observational cohort	Fewer total CVD events were observed with an increasing duration of quitting, with a statistically significant reduction in mortality with quitting for ≥4 years.
Newhall,[43] 2017	156 smokers at 8 vascular surgery clinics	Surgeon-delivered intervention protocol: cessation counseling, medications, and referral to quit line	Usual smoking cessation care	Cluster randomized trial without baseline assessment	More patients in the intervention group reported "a lot" or "some" interest in quitting after their initial appointment with the vascular surgeon (95.4% vs 85.7%; P = .05). At 3-month follow-up, 37% of those with a strong desire to quit were successful compared with 23% of those with a weak desire.
Recommendations 6.3, 6.4, and 6.5					
Schanzer,[47] 2008	Patients who underwent infrainguinal vein bypass surgery for CLI; two data sets were used: the PREVENT III randomized trial (n = 1404) and a multicenter registry (n = 716)	Infrainguinal vein bypass surgery	None	Retrospective analysis of prospectively collected data. For a given risk category, the AFS estimate was consistent between the derivation and validation sets.	Stratification of the patients in three risk categories yielded three significantly different Kaplan-Meier estimates for 1-year AFS (86%, 73%, and 45% for low-, medium-, and high-risk groups, respectively).
Bradbury,[48] 2010	2020 patients with severe lower limb ischemia due to infrainguinal disease who survived for 2 years after intervention (BASIL trial)	Bypass surgery first	Balloon angioplasty first	Multivariate Cox model based on RCT at low risk of bias evaluating the effect of baseline variables	Baseline factors that were significant were BASIL randomization stratification group, below-knee Bollinger angiogram score, BMI, age, DM, creatinine level, and smoking status. The factors that contributed to the Weibull predictive model were age, presence of tissue loss, serum creatinine concentration, number of AP measurements detectable, maximum AP measured, history of myocardial infarction or angina, history of stroke or transient ischemia attack, below-knee Bollinger angiogram score, BMI, and smoking status.
Meltzer,[49] 2013	4985 individuals after bypass surgery for CLI from the National Surgical Quality Improvement Program	Bypass surgery	None	Retrospective data analysis from a registry with adequate outcome and exposure ascertainment; derivatization and validation cohorts	Higher model scores were significantly associated with higher rates of mortality, all major morbidities, and 30-day major morbidity and mortality.

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Simons,[50] 2016	7754 patients with CLI from the national SVS VQI database	Bypass surgery	None	Retrospective data analysis from a registry with adequate outcome and exposure ascertainment	Three prediction models had similar discriminative performance: BASIL, Finland National Vascular (Finnvasc) registry, and modified PREVENT III. A novel VQI-derived model had improved discriminative ability with a C index of 0.71.
Biancari,[51] 2007	3925 patients status post infrainguinal surgical revascularization procedures	Infrainguinal surgical revascularization procedures	None	Retrospective data analysis from a registry with adequate outcome and exposure ascertainment; derivatization and validation cohorts	In the validation data set, the 30-day postoperative mortality/amputation rates in patients with scores of 0, 1, 2, 3, and 4 were 4.8%, 7.5%, 10.1%, 15.9%, and 22.2%, respectively ($P < .0001$); mortality rates were 0.7%, 2.3%, 4.2%, 5.5%, and 14.8%, respectively ($P < .0001$); and major amputation rates were 4.6%, 5.3%, 6.4%, 11.0%, and 14.0%, respectively ($P = .011$).
Recommendation 6.10					
Lavery,[52] 2008	162 patients with large, chronic, nonischemic diabetic foot wounds after partial foot amputation.	NA	NA	Reanalysis of RCT, moderate risk of bias	Early changes in percentage of wound area reduction were predictive of final healing at 16 weeks.
Sheehan,[53] 2003	203 patients with DFUs	NA	NA	Reanalysis of RCT, moderate risk of bias	The percentage change in foot ulcer area after 4 weeks of observation is a robust predictor of healing at 12 weeks.
Snyder,[54] 2010	250 control group patients from two RCTs of human fibroblast-derived dermal substitute for treating DFUs	NA	NA	Reanalysis of data from two RCTs	Regardless of baseline size category, DFUs with <50% persistent area of reduction at 4 weeks were less likely to heal by 12 weeks than DFUs with ≥50% persistent area of reduction ($P \leq .001$). Sensitivity and specificity were higher with cutoff of 4 weeks than weeks 1 to 3.
Cardinal,[55] 2008	241 DFUs from patients enrolled in RCTs on topical wound treatments	NA	NA	Reanalysis of data from two RCTs	Wound margin advance, initial healing rate, percentage wound surface area reduction, and wound healing trajectories (all $P < .001$) were powerful predictors of complete wound healing at 12 weeks. Wounds with poor healing progress by these criteria at 4 weeks were highly likely to remain unhealed after an additional 8 weeks of treatment.

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendation 6.11					
Abu Dabrh,[56] 2015	13 studies enrolling 1527 patients with CLI	Natural history	None	Meta-analysis of observational studies at increased risk of bias	During a median follow-up of 12 months, all-cause mortality rate was 22% (CI, 12%-33%) and major amputation rate was 22% (CI, 2%-42%). Worsened wound or ulcer was found at 35% (CI, 10%-62%). The quality of evidence was low because of increased risk of bias and inconsistency.
Recommendations 6.6, 6.12, 6.13, and 6.14					
Cull,[57] 2014	139 patients with foot wounds who presented for lower extremity revascularization	NA	NA	Retrospective analysis of prospectively collected data	The WIfI clinical stage was predictive of 1-year limb amputation (stage 1, 3%; stage 2, 10%; stage 3, 23%; stage 4, 40%) and wound nonhealing (stage 1, 8%; stage 2, 10%; stage 3, 23%; stage 4, 40%).
Zhan,[58] 2015	201 patients with threatened limbs	Amputation	Limb salvage	Retrospective cohort, consecutive sample, unadjusted analysis, no blinded outcome adjudication	The amputation group had a significantly higher prevalence of advanced stage 4 patients ($P <$ .001), whereas the limb salvage group presented predominantly as stages 1 to 3. Patients in clinical stages 3 and 4 had a significantly higher incidence of amputation ($P <$ .001), decreased AFS ($P <$ .001), and delayed wound healing time ($P <$ .002) compared with those in stages 1 and 2.
Darling,[59] 2015	596 limbs of patients undergoing an IP angioplasty for CLI	Angioplasty	NA	Retrospective cohort identified using administrative codes, consecutive sample, adjusted analysis, no blinded outcome adjudication	One-unit increase in the WIfI composite score is associated with a decrease in wound healing (HR, 1.2; 95% CI, 1.1-1.4) and an increase in the rate of stenosis (HR, 1.2; 95% CI, 1.1-1.4) and major amputations (HR, 1.4; 95% CI, 1.2-1.8).
Causey,[60] 2016	143 patients hospitalized for threatened limb	NA	NA	Retrospective analysis of prospectively gathered registry data of consecutive patients	Increased WIfI stage was associated with MALEs ($P = .018$), reduced limb salvage ($P = .037$), and decreased AFS ($P = .048$). PREVENT III risk score category was associated with mortality ($P <$ .001) and AFS ($P <$ .001).
Robinson,[61] 2017	280 threatened limbs.	NA	NA	Retrospective analysis of prospectively gathered registry data of consecutive patients, adjusted analysis	Increasing WIfI stage was associated with decreased 1-year Kaplan-Meier limb salvage (stage 1, 96%; stage 2, 84%; stage 3, 90%; and stage 4, 78%; $P = .003$) and AFS ($P = .006$).

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendation 6.17					
Seeger,[62] 1987	51 patients who had lower extremity revascularization	Real-time imaging of the saphenous and cephalic veins	Patients who had similar procedures in the 12 months before the use of vein mapping	Pre-post nonrandomized study	Preoperative mapping was found to be accurate in 50 of 51 patients (98%). Vein size as determined by B-mode ultrasound correlated well with angiograms, $R = 0.85$ overall with $R > 0.9$ in the last 7 months of the study. Wound complications occurred in 2% of the patients who had preoperative mapping and in 17% of the historical controls.
Wengerter,[63] 1990	239 IP reversed great saphenous vein graft bypasses placed for critical ischemia during a 7-year period	NA	NA	Nonrandomized prospective cohort study, unblinded	A pattern of increasing graft patency and limb salvage was noted as the minimum external diameter increased from <3.0 mm to ≥4.0 mm.
Schanzer,[64] 2007	1404 North American patients with CLI	Lower extremity bypass	NA	Secondary analysis of RCT	Vein diameter and conduit type were the dominant technical determinants of early and late graft failure.
Recommendations 6.20, 6.21, 6.22, 6.23, and 6.24					
Harward,[65] 1995	450 patients undergoing lower extremity arterial reconstruction	NA	NA	Retrospective unblinded cohort study	The majority of complications and deaths occurred in patients undergoing aortic inflow plus complex outflow procedures (profundaplasty or composite bypass conduits), in which the morbidity and mortality rates were 84.2% and 47.4%, respectively, compared with rates of 45.7% and 2.9% ($P < .01$) after all other inflow/outflow procedures. The increased difficulty of these complex procedures is reflected in the significantly greater blood loss and operative times (1853 mL and 10.0 hours) compared with similar values (1125 mL and 7.7 hours; $P < .01$) for all other inflow/outflow procedures.
Zukauskas,[66] 1995	1953 aortofemoral reconstructions were performed during a 6-year period	NA	NA	Retrospective unblinded cohort study	Single-stage multisegment reconstruction for multilevel arterial occlusive disease is a safe and effective method of treating critical limb ischemia.
Recommendation 6.25					
Jongkind,[67] 2010	Meta-analysis of 19 nonrandomized studies (1711 patients)	Endovascular approach	NA	Uncontrolled studies	Technical success was achieved in 86% to 100% of the patients. Clinical symptoms improved in 83% to 100%. Mortality was

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					described in seven studies and ranged from 1.2% to 6.7%. Complications were reported in 3% to 45% of the patients. The most common complications were distal embolization, access site hematomas, pseudoaneurysms, arterial ruptures, and arterial dissections.
Ye,[68] 2011	Meta-analysis of 16 endovascular treatment studies (958 patients)	Endovascular approach	NA	Retrospective, uncontrolled studies	Technical success was achieved in 92.8% of patients (95% CI, 89.8%-95.0%; 749 cases). Primary patency at 12 months was 88.7% (95% CI, 85.9%-91.0%; 787 cases). Subgroup analyses demonstrated a technical success rate of 93.7% (95% CI, 88.9%-96.5%) and a 12-month primary patency rate of 89.6% (95% CI, 84.8%-93.0%) for TASC C lesions. For TASC D lesions, these rates were 90.1% (95% CI, 76.6%-96.2%) and 87.3% (95% CI, 82.5%-90.9%), respectively.
Deloose,[69] 2017	120 patients with TASC II A and B iliac lesions	Endovascular treatment		Multicenter prospective cohort	The primary patency rate for the total patient population was 97.4%. The primary patency rates at 12 months for the TASC II class A and TASC II class B (C) lesions were, respectively, 98.3% and 96.6%.
Recommendation 6.26					
Indes,[70] 2013	Meta-analysis of 29 open bypass studies (3733 patients) and 28 endovascular treatment studies (1625 patients) in AI occlusive disease	Direct open bypass	Endovascular treatment	Mostly observational comparative studies	Mean length of hospital stay was 13 days for open bypass vs 4 days for endovascular treatment procedures ($P < .001$). The open bypass group experienced more complications (18.0% vs 13.4%; $P < .001$) and greater 30-day mortality (2.6% vs 0.7%; $P < .001$). At 1 year, 3 years, and 5 years, pooled primary patency rates were greater in the open bypass group vs the endovascular cohort (94.8% vs 86.0%, 86.0% vs 80.0%, and 82.7% vs 71.4%, respectively; all $P < .001$); the same was true for secondary patency (95.7% vs 90.0% [$P = .002$], 91.5% vs 86.5% [$P < .001$], and 91.0% vs 82.5% [$P < .001$], respectively).

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Chiu,[71] 2010	29 bypass studies	Bypass	Endovascular treatment	Systematic review of mostly observational studies	Operative mortality rate was 4.1% for AFB, 2.7% for IFB, and 2.7% for AI endarterectomy. Systematic morbidity rate was 16%, 18.9%, and 12.5%. Local morbidity rate was 6.3% for AFB, 5.7% for IFB, and 2.4% for AI endarterectomy. Graft-related morbidity/intervention failure rates were 3.1%, 4.2%, and 3.8%. Eight studies reported infection rates after AFB, with a combined rate of 0.4%. The 5-year patency rates for patients with CLI were 79.8% for AFB, 74.1% for IFB, and 81.7% for AI endarterectomy.
Ricco,[72] 2008	143 patients with unilateral iliac artery occlusive disease and disabling claudication	Crossover bypass	Direct bypass		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 after 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). Patency at 5 years after crossover bypass was significantly higher in patients presenting with no or low-grade SFA stenosis than in patients presenting with high-grade (≥50%) stenosis or occlusion of the SFA (74.0% ± 12% vs 62.5% ± 19%; $P = .04$). In both treatment groups, patency was comparable using polytetrafluoroethylene and polyester grafts. Overall survival was 59.5% ± 12% at 10 years.
Recommendation 6.27					
Kang,[73] 2008	65 limbs in 58 patients with occlusive disease of the CFA	CFA endarterectomy	NA	Retrospective, unblinded, adjusted analysis	Technical success was achieved in 100% of the cases. The 1- and 5-year primary patencies were 93% and 91%, respectively.
Ballotta,[74] 2010	117 patients	CFA endarterectomy	NA	Retrospective, unblinded, unadjusted analysis	There were no perioperative deaths or major complications. The 7-year rates of freedom from further revascularization and survival were 79% and 80%, respectively.

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendation 6.28					
Chang,[75] 2008	171 patients (mean age, 67 ± 10 years; 38% female; 35% diabetic)	CFA endarterectomies and iliac stent/stent grafting	NA	Retrospective, noncomparative, nonblinded	Technical success occurred in 98% of patients. Clinical improvement was seen in 92% of patients. Mean ABI increased from 0.38 ± 0.32 to 0.72 ± 0.24. Median length of stay was 2 days (range, 1-51 days). The 30-day mortality was 2.3%, and 5-year survival was 60%. The 5-year primary, primary assisted, and secondary patencies were 60%, 97%, and 98%, respectively. Endovascular reintervention was required in 14% of patients; inflow surgical procedures were required in 10%. By logistic regression analysis, use of stent grafts compared with bare stents was associated with significantly higher primary patency (87% ± 5% vs 53% ± 7%; $P < .01$).
Recommendation 6.29					
Baumann,[76] 2011	98 patients with symptomatic obstructions of the CFA	Endovascular therapy	NA	Consecutive series, adjusted analysis	Primary sustained clinical improvement rates at 3, 6, 12, and 24 months were 55%, 55%, 40%, and 0% in CLI patients and 81%, 75%, 68%, and 52% in claudicants, respectively. Limb salvage rates at 24 months were 94% in CLI patients and 100% in claudicants.
Bonvini,[77] 2011	97 patients with symptomatic obstructions of the CFA	Endovascular therapy	NA	Prospectively maintained single-center database; retrospective analysis, unblinded and unadjusted	Failures—defined as a final angiographic result with a >30% residual stenosis—were observed on 26 occasions (7.2%). In-hospital major (ie, requiring surgery) and minor (ie, treated percutaneously or conservatively) complications occurred in 5 (1.4%) and 18 (5.0%) procedures, respectively.
Gouëffic,[78] 2017	117 patients with de novo atherosclerotic lesions of the CFA	Stenting	Surgery	Randomized trial, moderate risk of bias	Primary outcome (mortality and complications) occurred in 16 of 61 patients (26%) in the surgery group and 7 of 56 patients (12.5%) in the stenting group (OR, 2.5; 95% CI, 0.9-6.6; $P = .05$). The mean duration of hospitalization was significantly lower in the stenting group (3.2 ± 2.9 days vs 6.3 ± 3 days; $P < .0001$). At 24 months, the sustained clinical improvement, the primary patency

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					rate, and the target lesion and extremity revascularization rates were not different in the two groups.
Siracuse,[79] 2016	1014 patients with PAD	Isolated CFA intervention with or without a deep femoral artery intervention	NA	Retrospective unblinded, noncomparative	Survival was 92.9% at 1 year and 87.2% at 3 years. AFS, freedom from loss of patency or death, and reintervention-free survival were 93.5%, 83%, and 87.5% at 1 year, respectively. Multivariable predictors of mortality were tissue loss, COPD, ESRD, urgent case, and age, whereas aspirin use and nonwhite race were protective. Tissue loss, rest pain, COPD, ESRD, stent use, nonambulatory status, and female sex were predictive of major amputation, whereas aspirin use, P2Y12 antagonist use, statin use, and initial technical success were protective.
Recommendations 6.32, 6.40, and 6.41					
Almasri,[80] 2018	44 studies that enrolled 8602 patients with CLTI	All infrainguinal revascularization procedures	NA	Noncomparative meta-analysis	Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below-knee targets at 2 years and beyond. DESs demonstrated improved patency over BMSs in IP arteries (primary patency, 73% vs 50% at 1 year), which was at least comparable to balloon angioplasty (66% primary patency), albeit within an anatomically restricted cohort of CLTI patients. Survival, major amputation, and AFS at 2 years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss.
Recommendations 6.33, 6.34, 6.35, 6.36, and 6.37					
See Abu Dabrh,[56] 2015; Zhan,[58] 2015; Darling,[59] 2015; Causey,[60] 2016; Robinson,[61] 2017					
Recommendation 6.38					
Chae,[81] 2016	Meta-analysis of 727 patients with arterial occlusive disease in diabetic feet	Angiosome-targeted angioplasty	Non-angiosome-targeted angioplasty	Four non-randomized comparative studies at increased risk of bias	Overall limb salvage (OR, 2.209; $P = .001$) and wound healing rates (OR, 3.290; $P = .001$) were significantly higher in patients who received angiosome-targeted angioplasty. The revision rate was not significantly different (OR, 0.747; $P = .314$).

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Jongsma,[82] 2017	Meta-analysis of 19 cohort studies with 3932 patients with CLI	Direct revascularization according to the angiosome concept	Indirect revascularization	Nonrandomized studies at low risk of bias	Direct revascularization significantly improved wound healing (RR, 0.60; 95% CI, 0.51-0.71), major amputation (RR, 0.56; 95% CI, 0.47-0.67), and AFS rates (RR, 0.83; 95% CI, 0.69-1.00).
Biancari,[83] 2014	Systematic review and meta-analysis of 9 cohort studies (1290 legs)	Direct revascularization according to the angiosome concept	Indirect revascularization	Retrospective studies at increased risk of bias	The risk of unhealed wound was significantly lower after direct revascularization (HR, 0.64; 95% CI, 0.52-0.8; I^2, 0%; four studies included) compared with indirect revascularization. Direct revascularization was also associated with significantly lower risk of major amputation (HR, 0.44; 95% CI, 0.26-0.75; I^2, 62%; eight studies included). Pooled limb salvage rates after direct and indirect revascularization were 86.2% vs 77.8% at 1 year and 84.9% vs 70.1% at 2 years, respectively. The analysis of three studies reporting only on patients with DM confirmed the benefit of direct revascularization in terms of limb salvage (HR, 0.48; 95% CI, 0.31-0.75; I^2, 0%).
Sumpio,[84] 2013	Systematic review of 11 case series (1616 patients, 1757 limbs)	Revascularization		Mostly retrospective case series at increased risk of bias	Ten studies compared direct and indirect revascularization. Five studies reported that limb salvage rate was higher with direct revascularization than with indirect revascularization (93% vs 72%; $P =$ .02). Five of eight studies that reported wound healing rates found a significant increase with direct revascularization compared with indirect revascularization; however, length of follow-up varied between these studies. Mean time to healing was not significantly different in direct revascularization compared with indirect revascularization when analyzed by three studies. One study found a significant increase in AFS in direct revascularization compared with indirect revascularization (evaluated by three studies). Seven studies with a predominantly diabetic population reported limb salvage as a primary outcome, and

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					three found a significant increase with direct revascularization compared with indirect revascularization.
Azuma,[85] 2012	228 patients (249 limbs) with CLTI	Bypass	NA	Retrospective consecutive case series	The complete healing of ischemic wounds was achieved in 211 limbs (84.7%). ESRD (OR, 0.127; $P < .001$), DM (OR, 0.216; $P = .030$), Rutherford category 6 with heel ulcer/gangrene (OR, 0.134; $P < 0.001$), Rutherford category 6 except heel (OR, 0.336; $P = .025$), and low albuminemia (OR, 0.387; $P = .049$) were negative predictors of wound healing. Regarding the angiosome, the healing rate in the indirect revascularization group was slower than in the direct revascularization group, especially in patients with ESRD ($P < .001$). However, the healing rates of the direct and indirect revascularization groups were similar after minimizing background differences with propensity score methods ($P = .185$).
Recommendation 6.39					
Almasri,[80] 2018	44 studies that enrolled 8602 patients with CLTI	All infrainguinal revascularization procedures	NA	Noncomparative meta-analysis	Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below-knee targets at 2 years and beyond. DESs demonstrated improved patency over BMSs in IP arteries (primary patency, 73% vs 50% at 1 year), which was at least comparable to balloon angioplasty (66% primary patency), albeit within an anatomically restricted cohort of CLTI patients. Survival, major amputation, and AFS at 2 years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss.
Schillinger,[86] 2006	104 patients with severe claudication or CLTI due to stenosis or occlusion of the SFA	Stenting	Angioplasty	RCT	Secondary stenting was performed in 17 of 53 patients (32%) in the angioplasty group, in most cases because of a suboptimal result after angioplasty. At 6 months, the rate of restenosis on angiography

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					was 24% in the stent group and 43% in the angioplasty group ($P = .05$); at 12 months, the rates on DUS were 37% and 63%, respectively ($P = .01$). Patients in the stent group were able to walk significantly farther on a treadmill at 6 and 12 months than those in the angioplasty group.
Saxon,[87] 2008	197 patients with symptomatic PAD of SFA	PTA	Angioplasty plus stent graft	Multicenter RCT	The stent graft group had a significantly higher technical success rate (95% vs 66%; $P < .0001$) and 1-year primary vessel patency rate at DUS (65% vs 40%; $P = .0003$). A patency benefit was seen for lesions at least 3 cm long. At 12 months, chronic limb ischemia status was 15% further improved for the stent graft group ($P = .003$). There were no significant differences between treatment groups with regard to the occurrence of early or late major adverse events.
Dake,[88] 2011	474 patients with FP PAD (236 primary DES; 238 angioplasty)	DES	PTA, provisional BMS	Multinational RCT	There were 120 patients who had acute PTA failure and underwent secondary random assignment to provisional DES (n = 61) or BMS (n = 59). Primary end points were the 12-month rates of event-free survival and patency in the primary DES and PTA groups. Compared with the PTA group, the primary DES group exhibited superior 12-month event-free survival (90.4% vs 82.6%; $P = .004$) and primary patency (83.1% vs 32.8%; $P < .001$), satisfying the primary hypotheses. In the secondary evaluations, the primary DES group exhibited superior clinical benefit compared with the PTA group (88.3% vs 75.8%; $P < .001$); the provisional DES group exhibited superior primary patency (89.9% vs 73.0%; $P = .01$) and superior clinical benefit (90.5% and 72.3%; $P = .009$) compared with the provisional BMS group; and the stent fracture rate (both DES and BMS) was 0.9% (4/457).

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Rosenfield,[89] 2015	476 patients with symptomatic IC or ischemic pain while at rest and angiographically significant atherosclerotic lesions	Angioplasty with a paclitaxel-coated balloon	Standard angioplasty	Single-blinded, multicenter RCT	At 12 months, the rate of primary patency among patients who had undergone angioplasty with the drug-coated balloon was superior to that among patients who had undergone conventional angioplasty (65.2% vs 52.6%; $P = .02$). The proportion of patients free from primary safety events was 83.9% with the drug-coated balloon and 79.0% with standard angioplasty ($P = .005$ for noninferiority). There were no significant between-group differences in functional outcomes or in the rates of death, amputation, thrombosis, or reintervention.
Recommendation 6.42					
Mills,[90] 1992	214 consecutive infrainguinal bypass grafts (209 reversed vein and 5 polytetra fluoroethylene grafts)	DUS	NA	Prospective evaluation of consecutive sample, unblinded and not adjusted	The 30-day primary patency was 99% (129/130) for FP grafts and 93% (78/84) for femorodistal grafts. Secondary patency was 100% (130/130) and 96% (81/84), respectively. Primary patency was 89% (16/18) for those grafts that required intraoperative revision based on arteriographic findings.
Bandyk,[91] 1994	368 patients after carotid endarterectomy, infrainguinal vein bypass, or visceral or renal reconstruction	DUS	NA	Uncontrolled and nonrandomized series	DUS identified technical (residual plaque, stricture) or intrinsic defects (platelet thrombus, distal thrombosis) requiring revision in 37 (10%) of the reconstructions; low (<0.5%) complication rate.
Recommendation 7.1					
Ubbink,[92] 2013	Six studies comprising nearly 450 patients with inoperable chronic CLI	SCS	Standard care	Controlled nonblinded studies	Overall, no significantly different effect on ulcer healing was observed with the two treatments. Complications of SCS treatment consisted of implantation problems (9%; 95% CI, 4%-15%) and changes in stimulation requiring reintervention (15%; 95% CI, 10%-20%). Infections of the lead or pulse generator pocket occurred less frequently (3%; 95% CI, 0%-6%). Overall risk of complications with additional SCS treatment was 17% (95% CI, 12%-22%), indicating a number needed to harm of 6 (95% CI, 5-8). Average overall costs (one

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					study) at 2 years were €36,500 (SCS group) and €28,600 (conservative group). The difference (€7900) was significant ($P < .009$).
Recommendation 7.2					
Karanth,[93] 2016	Cochrane review showing no trials; critical lower limb ischemia due to nonreconstructible PAD	LS	Standard care	NA	No trials
Recommendation 7.3					
Abu Dabrh,[94] 2015	19 studies enrolling 2779 patients with CLI	Medical therapies (PGE1 and angiogenic growth factors) and devices (pumps and spinal cord stimulators)	Control interventions	Meta-analysis of randomized and nonrandomized studies at increased risk of bias	None of the non-revascularization-based treatments were associated with a significant effect on mortality. IPC (OR, 0.14; 95% CI, 0.04-0.55) and spinal cord stimulators (OR, 0.53; 95% CI, 0.36-0.79) were associated with reduced risk of amputation. The quality of evidence was low because of increased risk of bias and imprecision.
Recommendation 7.4					
Vietto,[95] 2018	33 randomized controlled trials with 4477 participants	Prostanoids	Other agents or placebo	Meta-analysis of randomized trials at increased risk of bias	Low-quality evidence suggests no clear difference in the incidence of CV mortality between patients receiving prostanoids and those given placebo (RR, 0.81; 95% CI, 0.41-1.58). High-quality evidence suggests that prostanoids have no effect on the incidence of total amputations compared with placebo (RR, 0.97; 95% CI, 0.86-1.09). Adverse events were more frequent with prostanoids than with placebo (RR, 2.11; 95% CI, 1.79-2.50; moderate-quality evidence).
Recommendation 7.5					
Smith,[96] 2012	8 trials enrolling 269 participants	Naftidrofuryl	Other agents or placebo	Meta-analysis of randomized trials at increased risk of bias	The effect of naftidrofuryl was statistically nonsignificant on pain, rest pain, skin necrosis, or mean ankle systolic pressure.
Recommendation 7.6					
Kranke,[97] 2015	12 trials enrolling 269 participants	HBOT	Usual care	Meta-analysis of randomized trials at increased risk of bias	HBOT increased ulcer healing rate in diabetics without significant effect on other outcomes. Data specifically in CLI were limited.

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Game,[98] 2016	Systematic review of 30 studies, including 13 HBOT trials	HBOT		11 RCTs and 2 retrospective cohort studies at increased risk of bias	Studies have conflicting results. It is not yet clear which patients would benefit from HBOT.
Santema,[99] 2018	120 patients with DM with an ischemic wound	HBOT	Usual care	RCT	After 12 months, 28 index wounds were healed in the standard care group vs 30 in the standard care with HBOT group (RD, 3%; 95% CI, −14 to 21). AFS was achieved in 41 patients in the standard care group and 49 patients in the standard care with HBOT group (RD, 13%; 95% CI, −2 to 28). In the standard care with HBOT group, 21 patients (35%) were unable to complete the HBOT protocol as planned. Those who did had significantly fewer major amputations and higher AFS (RD for AFS, 26%; 95% CI, 10-38).
Recommendation 8.1					
Abu Dabrh,[94] 2015	19 studies enrolling 2779 patients with CLI	Medical therapies (PGE1 and angiogenic growth factors) and devices (pumps and spinal cord stimulators)	Control interventions	Meta-analysis of randomized and nonrandomized studies at increased risk of bias	None of the non-revascularization-based treatments were associated with a significant effect on mortality. IPC (OR, 0.14; 95% CI, 0.04-0.55) and spinal cord stimulators (OR, 0.53; 95% CI, 0.36-0.79) were associated with reduced risk of amputation. The quality of evidence was low because of increased risk of bias and imprecision.
Peeters Weem,[100] 2015	Meta-analysis of 10 studies (499 patients)	Bone marrow-derived cell therapy	Placebo	Randomized controlled trials	No significant differences were observed in major amputation rates (RR, 0.91; 95% CI, 0.65-1.27), survival (RR, 1.00; 95% CI, 0.95-1.06), and AFS (RR, 1.03; 95% CI, 0.86-1.23) between the cell-treated and placebo-treated patients. The ABI (mean difference, 0.11; 95% CI, 0.07-0.16), $TcPo_2$ measurements (mean difference, 11.88; 95% CI, 2.73-21.02), and pain score (mean difference, −0.72; 95% CI, −1.37 to −0.07) were significantly better in the treatment group than in the placebo group.
Recommendation 9.1					
Elsherif,[101] 2018	223 diabetic patients who underwent either digital or transmetatarsal amputation	Transmetatarsal amputation	Digital amputation	Nonrandomized comparative observational study, consecutive sample	The median time to major amputation was (400 ± IQR 1205 days) in the digital amputation group compared with 690 ± IQR

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					891 days in the transmetatarsal amputation group ($P = .974$); 29.9% of digital amputations and 15.7% of transmetatarsal amputations in diabetic patients required minor amputations or revision procedures ($P = .04$). Median length of hospital stay was (20 days; IQR, 27 days) in the digital amputation group and (17 days; IQR, 17 days) in the transmetatarsal amputation group ($P = .17$). Need for readmission was 48.1% in digital amputation patients compared with 50% in transmetatarsal amputation patients ($P = .81$). Quality of time spent without symptoms of disease or toxicity of treatment was (315 days; IQR, 45 days) in the digital amputation group and (346 days; IQR, 48 days) in the transmetatarsal amputation patients (P = .099).
Recommendation 9.2					
Siracuse,[102] 2015	110,279 patients undergoing major vascular surgery	DNR status	No DNR	Nonrandomized sample from National Surgical Quality Improvement Program database; propensity score matching, no blinding	Compared with a matched cohort of high-risk non-DNR patients, those with DNR orders suffered equivalent rates of postoperative morbidity but markedly increased mortality.
Aziz,[103] 2015	16,678 patients underwent emergency vascular operations	DNR status	No DNR	Nonrandomized sample from National Surgical Quality Improvement Program database; propensity score matching, no blinding	DNR patients were more likely to have higher rates of graft failure (8.7% vs 2.4%; adjusted $P < .01$) and failure to wean from mechanical ventilation (14.9 % vs 9.9%; adjusted $P < .001$). DNR status was associated with a 2.5-fold rise in 30-day mortality (35.0% vs 14.0%; 95% CI, 1.7-2.9; adjusted $P < .001$).
Recommendation 9.3					
Reed,[104] 2008	33 Patients who had undergone BKA or AKA after failed lower extremity revascularization	NA	NA	Survey with 39% nonresponse rate	If faced with a similar scenario, 85% (28/33 patients) of amputees would do everything to save the leg; 54% (18/33) of patients actively used a prosthesis, and 91% (30/33) resided at home.
Recommendation 9.4					
Rollins,[105] 1985	54 patients underwent 56 profundaplasties for limb salvage	NA	NA	Uncontrolled surgical case series	After profundaplasty, ischemic ulcers healed in 9 of 17 (53%) patients. Rest pain was relieved in 6 of 19 (32%), and areas of ischemic

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					necrosis healed in 7 of 20 (35%). Cumulative patency of the deep femoral artery was 49% at 3 years but fell to 21% at 5 years, whereas cumulative limb salvage was 49% and 36%, respectively. Eleven of the required 28 amputations were performed in the immediate postoperative period. Profundaplasty was used to lower the amputation level and to preserve the knee joint in six patients. The other five early amputations occurred in severely ischemic limbs without distal vessels suitable for bypass. The profundaplasty remained patent in all 19 patients who underwent BKA, and 16 (84%) became ambulatory with a prosthesis.
Miksic,[106] 1986	282 PFA reconstructions	NA	NA	Uncontrolled surgical case series	An inflow correction was necessary in 60.3% of PFA reconstructions. Factors that bear on the success or failure of profundaplasty were evaluated. These were AI inflow, extent of disease in the PFA, runoff in the distal popliteal-tibial system, and extent of the ischemic lesion. Of the failures, most were due to established gangrene, obstructions throughout the whole length of the PFA, or poor popliteal-tibial runoff system. The cumulative limb salvage at 2 years was 86.8% in limbs subjected to an inflow correction procedure and profundaplasty but only 56.5% in repair of the PFA alone.
Recommendation 9.5					
Ayoub,[107] 1993	32 patients with TKAs for ischemia	NA	NA	Uncontrolled consecutive surgical case series	Average length of stay was 8.7 days. One patient required a revision to AKA. There were no other major complications.
Taylor,[108] 2008	309 BKA patients	NA	NA	Uncontrolled consecutive surgical case series	Patients with CAD (OR, 0.465; 95% CI, 0.289-0.747), cerebrovascular disease (OR, 0.389; 95% CI, 0.154-0.980), and impaired ambulatory ability before BKA (OR, 0.310; 95% CI, 0.154-0.623) were less likely to have a successful outcome (wound healing, maintenance of

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					ambulation, and survival for at least 6 months) with BKA. Patients with impaired ambulation combined with another factor had only a 20% to 23% probability of successful outcome, and patients with all three had a 10.4% probability of success.
Recommendation 9.6					
Webster,[109] 2012	Individuals undergoing their first major lower limb amputation because of vascular disease or DM	NA	NA	Uncontrolled surgical case series	At 4 months, unsuccessful prosthetic fitting was significantly associated with depression, prior arterial reconstruction, DM, and pain in the residual limb. At 12 months, 92% of all patients were fitted with a prosthetic limb, and individuals with transfemoral amputation were significantly less likely to have a prosthesis fitted. Age older than 55 years, diagnosis of a major depressive episode, and history of renal dialysis were associated with fewer hours of prosthetic walking.
Recommendation 9.7					
Glaser,[110] 2013	1715 patients undergoing lower extremity amputation (exclusive of trauma or tumor)	NA	NA	Uncontrolled surgical case series	Cox proportional hazards regression analysis revealed that ESRD (HR, 3.9; 95% CI, 2.3-6.5), chronic renal insufficiency (HR, 2.2; 95% CI, 1.5-3.3), atherosclerosis without diabetic neuropathy (HR, 2.9; 95% CI, 1.5-5.7), atherosclerosis with diabetic neuropathy (HR, 9.1; 95% CI, 3.7-22.5), and initial major amputation (HR, 1.8; 95% CI, 1.3-2.6) were independently predictive of subsequent contralateral major amputation.
Bradley,[111] 2006	107 vascular amputees (mean age, 70 years) referred for prosthesis provision	NA	NA	Cross-sectional study, unblinded unadjusted	On analysis, 41% were prescribed a statin and 39% were prescribed a statin and 60% an antiplatelet agent. Whereas 39% of these patients were receiving both drugs, 32% had been prescribed neither.
Recommendations 10.1, 10.2, 10.3, 10.4, and 10.5 (also see evidence for 4.7 and 4.8)					
Bedenis,[112] 2015	16 studies with 5683 randomized participants Nine different treatment groups were evaluated: aspirin or aspirin and dipyridamole (DIP) vs placebo or nothing (six	Antiplatelets	Other approaches	Meta-analysis of trials at low to moderate risk of bias	Graft patency was improved in the aspirin or aspirin-DIP treatment group (OR, 0.42; 95% CI, 0.22-0.83; $P = .01$; 952 participants).

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
	studies); aspirin or aspirin-DIP vs pentoxifylline (two studies); aspirin-DIP vs indobufen (one study); aspirin or aspirin-DIP vs vitamin K antagonists (two studies); aspirin-DIP vs low-molecular-weight heparin (one study); ticlopidine vs placebo (one study); aspirin vs PGE1 (one study); aspirin vs naftidrofuryl (one study); and clopidogrel and aspirin vs aspirin alone (one study).				
Abbruzzese,[113] 2004	172 patients underwent 189 primary autogenous infrainguinal arterial reconstructions	Statins	No statins	Retrospective comparative study, not blinded, adjusted analysis	Perioperative mortality (2.6%) and major morbidity (3.2%) were not different between groups. There was no difference in primary patency (74% ± 5% vs 69% ± 6%; $P = .25$), limb salvage (92% ± 3% vs 90% ± 4%; $P = .37$), or survival (69% ± 5% vs 63% ± 5%; $P = .20$) at 2 years. However, patients taking statins had higher primary-revised (94% ± 2% vs 83% ± 5%; $P < .02$) and secondary (97% ± 2% vs 87% ± 4%; $P < .02$) graft patency rates at 2 years. Of all factors studied by univariate analysis, only statin use was associated with improved secondary patency ($P = .03$) at 2 years. This was confirmed by multivariate analysis.
Henke,[114] 2004	293 patients (338 infrainguinal bypass procedures	NA	NA	Retrospective case series	Statin drugs were taken by 56% of patients, ACE inhibitors by 54% of patients, and antiplatelet agents or warfarin sodium (Coumadin) by 93% of patients. Statin drug use was independently associated with increased graft patency (OR, 3.7; 95% CI, 2.1-6.4) and with decreased amputation rate (OR, 0.34; 95% CI, 6.15-0.77). Kaplan-Meier analysis showed that only ACE inhibitors were associated with lower mortality ($P = .05$).
Suckow,[115] 2015	2067 infrainguinal bypass patients, from the Vascular Study Group of New England registry (67% with CLTI)	NA	NA	Retrospective analysis of prospectively collected data	Despite higher comorbidity burdens, long-term survival was better for patients taking statins in crude (RR, 0.7; $P < .001$), adjusted (HR, 0.7; $P = .001$), and propensity-matched analyses (HR, 0.7; P = .03). In

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					subgroup analysis, a survival advantage was evident in patients taking statins with CLI (5-year survival rate, 63% vs 54%; log-rank, $P = .01$) but not with claudication (5-year survival rate, 84% vs 80%; log-rank, $P = .59$). Statin therapy was not associated with 1-year rates of major amputation (12% vs 11%; $P = .84$) or graft occlusion (20% vs 18%; $P = .58$) in CLI patients. Perioperative myocardial infarction occurred more frequently in patients taking a statin in crude analysis (RR, 2.2; $P = .01$) but not in the matched cohort (RR, 1.9; $P = .17$).
Brown,[116] 2008	Systematic review of randomized and nonrandomized studies of patients undergoing infrainguinal bypass surgery	Antiplatelet treatment	No antiplatelet treatment	Moderate risk of bias overall	The administration of a variety of platelet inhibitors resulted in improved venous and artificial graft patency compared with no treatment. However, analyzing patients for graft type indicated that those patients receiving a prosthetic graft were more likely to benefit from administration of platelet inhibitors than patients treated with venous grafts.
Willigendael,[117] 2005	Meta-analysis of data from 29 studies	NA	NA	Moderate risk of bias overall	The effect of smoking on graft patency in the randomized clinical trials and other prospective studies had a 3.09-fold (2.34-4.08; $P < .00001$) increase in graft failure. There is a dose-response relationship, with decreased patency in heavy smokers compared with moderate smokers. Smoking cessation restores patency rates toward the never-smokers group.
Hobbs,[118] 2003	Review of systematic reviews on smoking cessation strategies	Smoking cessation interventions	Usual care	Moderate risk of bias overall	Cochrane reviews have shown benefits of nicotine replacement therapy as well as a small but significant benefit from brief physician advice compared with no advice (OR, 1.69). More frequent advice may be marginally more effective.
Belch,[119] 2010	851 patients undergoing unilateral, below-knee bypass graft	Clopidogrel plus aspirin	Placebo plus aspirin	Randomized placebo-controlled multinational trial	The primary efficacy end point was a composite of index graft occlusion or revascularization, above-ankle

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					amputation of the affected limb, or death. In the overall population, the primary end point occurred in 149 of 425 patients in the clopidogrel group vs 151 of 426 patients in the placebo (plus aspirin) group (HR, 0.98; 95% CI, 0.78-1.23). In a prespecified subgroup analysis, the primary end point was significantly reduced by clopidogrel in prosthetic graft patients (HR, 0.65; 95% CI, 0.45-0.95; P = .025) but not in venous graft patients (HR, 1.25; 95% CI, 0.94-1.67; not significant). A significant statistical interaction between treatment effect and graft type was observed (P [interaction] = .008). Although total bleeds were more frequent with clopidogrel, there was no significant difference between the rates of severe bleeding in the clopidogrel and placebo (plus aspirin) groups (2.1% vs 1.2%).
Gassman,[120] 2014	165 bypasses in patients with multiple comorbidities (79% CLTI)	Preoperative aspirin	NA	Case series	Preoperative and postoperative aspirin use was associated with increased 2-year secondary prosthetic graft patency over control (preoperative, 78% vs 44% [$P < .002$]; postoperative, 72% vs 50% [$P < 0.01$]). Preoperative aspirin use was associated with an improvement in the rate of amputation (OR, 0.44; 95% CI, 0.198-0.997) and stenosis (OR = 0.45; 95% CI, 0.217-0.956).
Bhatt,[121] 2006	15,603 patients with clinically evident CVD or multiple risk factors	Clopidogrel plus low-dose aspirin	Placebo plus low-dose aspirin	Large randomized controlled trial	The primary efficacy end point was a composite of myocardial infarction, stroke, or death from CV causes. The rate of the primary efficacy end point was 6.8% with clopidogrel plus aspirin and 7.3% with placebo plus aspirin (RR, 0.93; 95% CI, 0.83-1.05; $P = .22$). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7% and 17.9% (RR, 0.92; 95% CI, 0.86-0.995; $P = .04$), and the rate of severe bleeding was

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					1.7% and 1.3% (RR, 1.25; 95% CI, 0.97-1.61; $P = .09$). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel and 5.5% with placebo (RR, 1.2; 95% CI, 0.91-1.59; $P = .20$), and the rate of death from CV causes also was higher with clopidogrel (3.9% vs 2.2%; $P = .01$). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR, 0.88; 95% CI, 0.77-0.998; $P = .046$).
Cassar,[122] 2005	132 patients with claudication undergoing endovascular revascularization	Clopidogrel plus aspirin	Placebo plus aspirin	Double-blinded, placebo-controlled RCT	Clopidogrel plus aspirin inhibits platelet function more than aspirin alone. Platelet function in the clopidogrel group was significantly suppressed compared with baseline at 1 hour, 24 hours, and 30 days after endovascular intervention (stimulated fibrinogen binding by 53.9%, 51.7%, and 57.2%, respectively; all $P < .001$).
Strobl,[123] 2013 Tepe,[124] 2012	80 patients with PAD endovascularly treated	Preinterventional and postinterventional therapy with aspirin and clopidogrel	Aspirin and placebo	Blinded trial at low risk of bias	At 6 months, clopidogrel patients had significantly lower rates of target lesion revascularization compared with placebo patients (2 [5%] vs 8 [20%]; $P = .04$). After stopping clopidogrel-placebo after 6 months, there was no significant difference in target lesion revascularization at 12 months after treatment (9 [25%] clopidogrel vs 12 [32.4%] placebo; $P = .35$). Mortality was 0 vs 1 in the placebo group at 6 months ($P = .32$) and 0 vs 3 at 12 months ($P = .08$). Dual antiplatelet therapy reduces peri-interventional platelet activation and improves functional outcome without higher bleeding complications.
Cassar,[122] 2005	132 patients after lower limb angioplasty	Clopidogrel and aspirin	Placebo and aspirin	Blinded trial at low risk of bias	Clopidogrel and aspirin inhibited platelet function more than aspirin alone in patients with claudication before and after angioplasty.

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendation 10.10					
Mills,[125] 2001	156 autogenous infrainguinal vein grafts in 142 patients	DUS surveillance	NA	Uncontrolled and not blinded	The incidence of graft thrombosis was 3% per year (mean follow-up, 27.5 months). Intermediate lesions developed in 32 grafts (20%). Among these 32 grafts with intermediate stenoses, 63% progressed to critical and were revised, and 32% resolved or stabilized.
Recommendation 10.11					
Landry,[126] 2002	330 surgical graft revisions were performed on 259 extremities in 245 patients	Reversed lower extremity vein grafts	NA	Retrospective noncomparative analysis	The assisted primary patency rate of all grafts, the limb salvage rate for patients undergoing surgery for limb salvage indications, and the survival rate of all patients were 87.4%, 88.7%, and 72.4%, respectively, 5 years after the original bypass grafting procedure; 85.7%, 83.4%, and 67.8%, respectively, 7 years after the original bypass grafting procedure; and 80.4%, 75.4%, and 53.4%, respectively, 10 years after the original bypass grafting procedure. A total of 180 revisions (55%) were performed during the first year, 110 revisions (33%) were performed between the first year and the fifth year, and 40 revisions (12%) were performed on grafts older than 5 years. Lower extremity vein grafts revised within the first year after bypass grafting had lesions within the graft in 78%, in the native arterial inflow in 10%, and in the native arterial outflow in 12%. This differed significantly from the location of lesions in revisions performed between 1 year and 5 years and after 5 years (graft, 63% and 62%; inflow, 20% and 19%; outflow, 17% and 19% ($P > .05$, χ^2 test).
Nguyen,[127] 2004	188 vein grafts, from a total series of 1260 bypasses, undergoing revision of stenotic lesions	Revision procedures performed for repair of stenotic lesions in infrainguinal vein bypass grafts	NA	Retrospective noncomparative series	There was no difference in patency rate for different revision procedures, type of vein graft, indication for the original procedure, or patients with DM or renal disease. The overall limb salvage rate was 83.2% ± 3.5% 5

Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
					years after graft revision. With Cox proportional hazards analysis of time to failure of the revision procedure, the outflow level of the original bypass and the time of revision proved to be important predictors of durability of the graft revision. Revision of popliteal bypass grafts resulted in a 60% 5-year primary patency rate, whereas revision of tibial grafts resulted in a 42% 5-year primary patency rate ($P = .004$; HR, 2.06). Five-year secondary patency rates were 90% and 76%, respectively ($P = .009$; HR = 3.43). The timing of the graft revision proved to be an additional predictor. Grafts revised within 6 months of the index operation had lower primary patency than those with later revisions (42.9% vs 80.7%; HR, 1.754; $P = .0152$).
Recommendation 10.12					
Bui,[128] 2012	94 limbs (85 patients) underwent endovascular therapy for SFA-popliteal disease	NA	NA	Prospective nonrandomized study, consecutive sampling, unblinded	The initial scan findings were normal in 61 limbs (65%), and serial DUS results remained normal in 38 (62%). In 17 limbs (28%), progressive stenoses were detected during surveillance. The rate of thrombosis in this subgroup was 10%. Moderate stenoses were detected in 28 (30%) limbs at initial scans; of these, 39% resolved or stabilized, 47% progressed to severe, and occlusions developed in 14%. Five (5%) limbs harbored severe stenoses on initial scans, and 80% of lesions resolved or stabilized. Progression to occlusion occurred in one limb (20%). The last DUS showed that 25 limbs harbored severe stenoses; of these, 13 (52%) were in symptomatic patients and thus required reintervention regardless of DUS findings. Eleven limbs (11%) eventually occluded. Sensitivity and specificity of DUS to predict occlusion were 88% and 60%, respectively.

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Supplementary Table (online only). Continued.

Study	Population	Intervention	Comparison	Methodologic quality	Results
Recommendation 10.13					
Humphries,[129] 2011	122 infrainguinal interventions for CLI in 113 patients (53% male; mean age, 71 years)	Early DUS	Normal DUS	Nonrandomized prospective comparative study, unblinded or adjusted	There were 50 patients who had an abnormal finding on early DUS and 40 patients who had a normal finding. In patients with a normal DUS finding, the amputation rate was 5% vs 20% in the group with an abnormal finding ($P = .04$). Primary patency was 56% in the group with a normal finding and 46% in the group with an abnormal finding ($P = .18$). Early DUS was able to identify a residual stenosis not seen on completion angiography in 56% of cases.
Recommendations 10.14 and 10.15					
Elraiyah,[130] 2016	19 interventional studies, of which 13 were randomized controlled trials, including data from 1605 patients with DFUs using an offloading method	Offloading approaches	Usual care	The risk of bias in the included studies was moderate.	This analysis demonstrated improved wound healing with total contact casting over removable cast walker, therapeutic shoes, and conventional therapy. There was no advantage of irremovable cast walkers over total contact casting. There was improved healing with half-shoe compared with conventional wound care. Therapeutic shoes and insoles reduced relapse rate in comparison with regular footwear. Data were sparse regarding other offloading methods.

ABI, Ankle-brachial index; *ACE,* angiotensin-converting enzyme; *AFB,* aortofemoral bypass; *AFS,* amputation-free survival; *AI,* aortoiliac; *AKA,* above-knee amputation; *AP,* ankle pressure; *AT,* anterior tibial; *BASIL,* Bypass vs Angioplasty in Severe Ischaemia of the Leg; *BKA,* below-knee amputation; *BMI,* body mass index; *BMS,* bare-metal stent; *CAD,* coronary artery disease; *CFA,* common femoral artery; *CI,* confidence interval; *CLI,* critical limb ischemia; *CLTI,* chronic limb-threatening ischemia; *COPD,* chronic obstructive pulmonary disease; CPGs, clinical practice guidelines; *CT,* computed tomography; *CTA,* computed tomography angiography; *CV,* cardiovascular; *CVD,* cardiovascular disease; *DES,* drug-eluting stent; *DFUs,* diabetic foot ulcers; *DIP,* dipyridamole; *DM,* diabetes mellitus; *DNR,* do not resuscitate; *DOR,* diagnostic odds ratio; *DSA,* digital subtraction angiography; *DUS,* duplex ultrasound; *ESRD,* end-stage renal disease; *FP,* femoropopliteal; *HBOT,* hyperbaric oxygen therapy; *HR,* hazard ratio; *IC,* intermittent claudication; *IFB,* iliofemoral bypass; *IP,* infrapopliteal; *IPC,* intermittent pneumatic compression; *IQR,* interquartile range; *JNC,* Joint National Committee; *LS,* lumbar sympathectomy; *MACEs,* major adverse cardiac events; *MALEs,* major adverse limb events; *MRA,* magnetic resonance angiography; *NA,* not applicable; *OR,* odds ratio; *PAD,* peripheral artery disease; *PFA,* profunda femoris artery; *PGE1,* prostaglandin E1; *Pk-PT,* posterior tibial artery peak flow velocity; *PREVENT III,* Project of Ex-vivo Vein graft Engineering via Transfection III; *PT,* posterior tibial; *PTA,* percutaneous transluminal angioplasty; *RCT,* randomized controlled trial; *RD,* risk difference; *ROC,* receiver operating characteristic; *RR,* relative risk; *SCS,* spinal cord stimulation; *SFA,* superficial femoral artery; *SMD,* standardized mean difference; *SVS,* Society for Vascular Surgery; *TASC II,* TransAtlantic Inter-Society Consensus II; *TBI,* toe-brachial index; *$TcPo_2$,* transcutaneous oximetry; *TKA,* through-knee amputation; *TP,* toe pressure; *VQI,* Vascular Quality Initiative; *WIfI,* Wound, Ischemia, and foot Infection; WMD, weighted mean difference.

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