Table C-2. Study characteristics table for KQ 2: Effectiveness and safety of exercise, medications, and endovascular and surgical revascularization for intermittent claudication

| **Study** | **Study Details** | **Intervention (N) and Comparator (N)** | **Timing and** **Outcomes Reported** | **Quality and****Limitations to Applicability** |
| --- | --- | --- | --- | --- |
| ***Medical therapy vs. usual care*** |
| Beebe, 1999[15](#_ENREF_15) | RCTMulticenterUSFunding: industryPopulationPAD patients with ICTotal N: 516Mean Age: 64 to 65N Female: 124% Female: 24% Race: 9.1% African American, 0.4% Asian, 88.6% White, 1.9% Other | *Intervention*Cilostazol 100 mg twice daily (N=175) 50 mg twice daily (N=171)Concomitant therapy: None specified*Comparator*Placebo (N=170)Concomitant therapy: None specified | Timing: 6 moIndividualMortality MI Stroke QOLAmputationMWDPFWD | GoodNo limitations |
| Belcaro, 2002[16](#_ENREF_16) | RCTMulticenterEuropeFunding: NRPopulationPAD patients with ICTotal N: 60Mean Age: 55 to 56N Female: 29% Female: 54.7% Race: NR | *Intervention*Pentoxifylline 400 mg four times daily (N=27)Concomitant therapy: Antiplatelet treatment 300 mg daily*Comparator*Placebo (N=26)Concomitant therapy: Antiplatelet treatment 300 mg daily | Timing: 2 wk, 3 mo, 6 moIndividualMWD | FairStudy interventions (active arm) were not similar to interventions used in routine clinical practiceStudy's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)Study conducted solely outside the US |
| Dawson, 1998[17](#_ENREF_17) | RCTMulticenterUSFunding: NRPopulationPAD patients with ICTotal N: 81Mean Age: 66 to 67N Female: 19% Female: 23.4% Race: 1% African American, 99% White | *Intervention*Cilostazol 100 mg twice daily (N=54)Concomitant therapy: Could include ACE inhibitors, beta-blockers, or calcium channel blockers*Comparator*Placebo (N=27)Concomitant therapy: Could include ACE inhibitors, beta-blockers, or calcium channel blockers | Timing: 2 wk, 4 wk, 8 wk, 12 wkIndividualACDICDAdverse events | GoodNo limitations |
| Dawson, 2000[18](#_ENREF_18) | RCTMulticenterUSFunding: Otsuka America PharmaceuticalsPopulationPAD patients with ICTotal N: 698Mean Age: 66N Female: 169% Female: 24.2% Race: 89% White, 9%Black, 2% Hispanic | *Intervention*Cilostazol 100 mg twice daily (N=227), pentoxifylline 400 mg three times daily (232 patients)Concomitant therapy: None specified*Comparator*Placebo (N=239)Concomitant therapy: None specified | Timing: 4 wk, 8 wk, 12 wk, 16 wk, 24 wkIndividualMWDPFWDChange in ABI | FairNo limitations |
| De Sanctis, 2002[19](#_ENREF_19),[20](#_ENREF_20)Cesarone, 2002[21](#_ENREF_21) | RCTMulticenterEuropeFunding: independentPopulationPAD patients with ICTotal N: 194Mean Age: 62 to 63N Female: 51% Female: 37.8% Race: NR | *Intervention*Pentoxifylline 600 mg three times daily (N=75)Concomitant therapy: None specified*Comparator*Placebo (N=60)Concomitant therapy: None specified | Timing: 6 mo, 12 moIndividualTotal Walking Distance | FairStudy did not report participants' comorbid conditionsParticipant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriateStudy interventions (active arm) were not similar to interventions used in routine clinical practiceStudy conducted solely outside the US |
| Hiatt, 2008[22](#_ENREF_22)Stone, 2008[23](#_ENREF_23)CASTLE Study | RCTMulticenterUSFunding: industryPopulationPAD patients with ICTotal N: 1435Mean Age: 66N Female: 495% Female: 34%Race: 79% White, 4% Hispanic, 16% African American, 1% Other | *Intervention*Cilostazol 100 mg twice daily (N=717)Concomitant therapy: Could include aspirin, clopidogrel, statin or warfarin*Comparator*Placebo (N=718)Concomitant therapy: Could include aspirin, clopidogrel, statin or warfarin | Timing: 36 moComposite(primary)StrokeTIACarotid revascularizationIndividualMortalityStrokeAdverse events | GoodNo limitations |
| Hobbs, 2007[24](#_ENREF_24)INEXACT Study | RCTSingle centerUKFunding: NRPopulationPAD patients with ICTotal N: 38Median Age: 67N Female: 7% Female: 20.6% Race: NR | *Intervention*Cilostazol 100 mg twice daily + best medical therapy (N=9)Best medical therapy: Smoking cessation via repeated advice and/or nicotine replacement/bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; treat/screen for diabetes; blood pressure <140/85; ACE-I considered for all patients; and written advice regarding exercise*Comparator*Best medical therapy (N=9)Best medical therapy: Smoking cessation via repeated advice and/or nicotine replacement/bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; treat/screen for diabetes; blood pressure <140/85; ACE-I considered for all patients; and written advice regarding exercise | Timing: 3 mo, 6 moIndividualAdverse drug reactionChange in ABIACDICD | GoodStudy conducted solely outside the USStudy was conducted only at a single site |
| Money, 1998[25](#_ENREF_25) | RCTMulticenterUSFunding: NRPopulationPAD patients with ICTotal N: 239Mean Age: 65N Female: 59% Female: 24.7% Race: 9% African American, 0.4% Asian, 87% White, 3.6% Other | *Intervention*Cilostazol 100 mg twice daily (N=119)Concomitant therapy: None specifiedComparator*Placebo* (N=120)Concomitant therapy: None specified | Timing: 8 wk, 12 wk, 16 wkIndividualMortalityQOLAdverse eventsACD | FairStudy did not report participants' comorbid conditions |
| Soga, 2009[26](#_ENREF_26) | RCTMulticenterAsiaFunding: NRPopulationPAD patients with ICTotal N: 78Mean Age: 71N Female: 13% Female: 16.7% Race: NR | *Intervention*Cilostazol 100 mg twice daily (N=39)Concomitant therapy: Percutaneous transluminal angioplasty ± stent ASA 81-100 mg daily ± ticlopidine 200 mg daily (in some stent patients)Also could include statin, beta-blocker, ACE inhibitor or ARB*Comparator*Placebo (N=39)Concomitant therapy: Percutaneous transluminal angioplasty ± stent ASA 81-100 mg daily ± ticlopidine 200 mg daily (in some stent patients)Also could include statin, beta-blocker, ACE inhibitor or ARB | Timing: 24 moComposite(secondary)Total mortalityCardiovascular mortalityNonfatal MIStrokeRepeat revascularizationMajor amputationMinor amputationIndividualMortalityMI Stroke Repeat revascularization Bleeding Amputation | GoodNo limitations |
| Strandness, 2002[27](#_ENREF_27) | RCTMulticenterUSFunding: industryPopulationPAD patients with ICTotal N: 394Mean Age: 63 to 64N Female: 94% Female: 24% Race: 86.3% White, 11.2% Black, 1.5% Hispanic, .5% Asian, .5% Other | *Intervention*Cilostazol 100 mg twice daily (N=133)50 mg twice daily (N=132)Concomitant therapy: None specified*Comparator*Placebo (N=129)Concomitant therapy: None specified | Timing: 6 moComposite(secondary)Total mortalityCardiovascular mortalityIndividualMWDAdverse drug reactions | FairNo limitations |
| ***Exercise training vs. usual care*** |
| Crowther, 2008[28](#_ENREF_28) | RCTSingle centerAustraliaFunding: NRPopulationPAD patients with ICTotal N: 21Mean Age: 67 to 71N Female: 11% Female: 52% Race: NR | *Intervention*Supervised Exercise (N=10)Treadmill walking group: 3 times per wk for 12 moConcomitant therapy: Could include beta-blocker*Comparator*Control (N=11)No specific instructions givenConcomitant therapy: Could include beta-blocker | Timing: 12 moIndividualPFWT | FairStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the conditionStudy conducted solely outside the USStudy was conducted only at a single site |
| Gardner, 2002[29](#_ENREF_29) | RCTMulticenterUSFunding: GovernmentPopulationPAD patients with ICTotal N: 61Mean Age: 71 ro 72N Female: NR% Female: NRRace: NR | *Intervention*Exercise training (N=28)Supervised treadmill walking 3 times per wkConcomitant therapy: None specified*Comparator*Usual care (N=24)Concomitant therapy: None specified | Timing: 6 mo, 18 moIndividualTotal mortalityQOL - Walking impairment questionnaire Major amputationExercise-related harmsMean or 6-minute walking timeAbsolute claudication distanceQOL - SF36Initial Claudication Distance | FairNo limitations |
| Gardner, 2011[30](#_ENREF_30) | RCTSingle centerUSFunding: GovernmentPopulationPAD patients with ICTotal N: 119Mean Age: 65 to 66N Female: 62% Female: 52% Race: 57% White | *Intervention*Supervised exercise (N=40); Home exercise (N=40)Supervised treadmill walking group: 3 times per wk at specified pace for specified duration of time for 12 wkHome treadmill walking group: 3 times per wk at self-selected pace for specified duration of time for 12 wkConcomitant therapy: None specified*Comparator*Control (N=39)Encouraged to walk more on their own but did not receive specific recommendations about an exercise program during the study. Concomitant therapy: None specified | Timing:12 wkIndividualMIStrokeQOLPWTCOT | GoodStudy was conducted only at a single site |
| Gelin, 2001[31](#_ENREF_31)Taft, 2001[32](#_ENREF_32) | RCTSingle centerEuropeFunding: GovernmentPopulationPAD patients with ICTotal N: 264Mean Age: 66 to 67N Female: 90% Female: 34.1% Race: NR | *Intervention*Supervised exercise (N=88)Treadmill walking training 3 times per wk for 6 mo, then 2 times per wkConcomitant therapy: None specified*Comparator*Control (N=89)Received no other specific advice or treatment apart from the general advice given to the two treatment groupsConcomitant therapy: None specified | Timing: 12 moIndividualMortalityQOLVessel patencyAmputationMWD | FairStudy conducted solely outside the USStudy was conducted only at a single site |
| Gibellini, 2000[33](#_ENREF_33) | RCTStudy centers: NRLocation: NRFunding: NRPopulationPAD patients with ICTotal N: 40Mean Age: 67N Female: 4% Female: 10% Race: NR | *Intervention*Supervised exercise (N=20)Treadmill walking training 5 times per wk for 4 wkConcomitant therapy: ASA 325 mg daily*Comparator*Control (N=20)No specific instructions givenConcomitant therapy: ASA 325 mg daily | Timing: 1 mo, 6 moIndividualACDICD | FairParticipant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriateStudy eligibility criteria were poorly described or not appropriateStudy conducted solely outside the USStudy was conducted only at a single site |
| Hobbs, 2006[34](#_ENREF_34)EXACT Study | RCTMulticenterUKFunding: GovernmentPopulationPAD patients with ICTotal N: 23Median Age: 67N Female: 7% Female: 30.4% Race: NR | *Intervention*Supervised Exercise + best medical therapy(N=7)Circuit of moderate intensity exercises 2 times per wk for 12 wkConcomitant therapy: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent*Comparator*Best medical therapy (N=7)Best medical therapy: Not defined but could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent | Timing: 3 mo, 6 moIndividualAdverse drug reactionACDICD | FairStudy interventions (active arm) were not similar to interventions used in routine clinical practiceStudy conducted solely outside the USStudy was conducted only at a single site |
| Hobbs, 2007[24](#_ENREF_24)INEXACT Study | RCTSingle centerUKFunding: NRPopulationPAD patients with ICTotal N: 38Median Age: 67N Female: 7% Female: 30.4% Race: NR | *Intervention*Supervised exercise + best medical therapy (N=9)Circuit of moderate intensity exercises 2 times per wk for 12 wkBest medical therapy: Smoking cessation via repeated advice and/or nicotine replacement / bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; treatment/screen for diabetes; blood pressure < 140/85; ACE-I considered for all patients; and written advice regarding exercise*Comparator*Best medical therapy (N=9)Best medical therapy: Smoking cessation via repeated advice and/or nicotine replacement / bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; treatment/screen for diabetes; blood pressure <140/85; ACE-I considered for all patients; and written advice regarding exercise | Timing: 3 mo, 6 moIndividualAdverse drug reactionChange in ABIACDICD | GoodStudy conducted solely outside the USStudy was conducted only at a single site  |
| Lee, 2007[35](#_ENREF_35) | ObservationalSingle centerUKFunding: NRPopulationPAD patients with ICTotal N: 70Median Age: 67 to 69N Female: 22% Female: 31.4% Race: NR | *Intervention*Supervised exercise (N=33)Circuit of exercises 3 times per wk for 12 wkConcomitant therapy: Prescribed an antiplatelet, received smoking cessation advice and support (including nicotine replacement therapy), and risk factor modification (appropriate management of hypertension, hypercholesterolemia and diabetes. All patients also received an advice leaflet regarding exercise.*Comparator*Conservative medical therapy (N=37)Prescribed an antiplatelet, received smoking cessation advice and support (including nicotine replacement therapy), and risk factor modification (appropriate management of hypertension, hypercholesterolemia and diabetes. All patients also received an advice leaflet regarding exercise. | Timing: 6 moIndividualMWDICDQOL | PoorStudy did not report participants' baseline characteristicsStudy did not report participants' comorbid conditionsStudy conducted solely outside the USStudy was conducted only at a single site |
| Murphy, 2012[36](#_ENREF_36)CLEVER Study | RCTMulticenterUS, Canada Funding: GovernmentPopulationPAD patients with ICTotal N: 111Mean Age: 62 to 65N Female: 42% Female: 37.8% Race: NR | *Intervention*Supervised Exercise + optimal medical therapy (N=43)Exercises 3 times per wk for 26 wkConcomitant therapy: Could include ASA, thienopyridine, and statin*Comparator*Optimal medical therapy (N=22)Optimal medical therapy: Cilostazol 10 0 mg twice daily; advice about home exercise and dietConcomitant therapy: Could include ASA, thienopyridine, and statin | Timing: 30 days, 6 moIndividualPWTCOTQOLChange in ABISafety | Good Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition |
| Sugimoto, 2010[37](#_ENREF_37) | ObservationalSingle centerAsiaFunding: NRPopulationPAD patients with ICTotal N: 100Mean Age: 67N Female: 5% Female: 5% Race: NR | *Intervention*Supervised exercise + medical therapy (N=61)Treadmill walking 2 times per day for 3 wk plus medical therapy which could include the following medications or combinations: Cilostazol alone or with beraprost, warfarin, or aspirin; beraprost alone or with aspirin or ticlopidine; limaprost alone or with aspirin + ticlopidine; sarpogrelate alone or with ethyl icosapentate or aspirin; aspirin alone or with ticlopidine; warfarin alone*Comparator*Medical therapy (N=39)Could include the following medications or combinations: Cilostazol alone or with beraprost, warfarin, or aspirin; beraprost alone or with aspirin or ticlopidine; limaprost alone or with aspirin + ticlopidine; sarpogrelate alone or with ethyl icosapentate or aspirin; aspirin alone or with ticlopidine; warfarin alone | Timing: 6 moIndividualACDChange in ABI | PoorStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the conditionComparator(s) not well describedStudy conducted solely outside the USStudy was conducted only at a single site |
| Treat-Jacobson, 2009[38](#_ENREF_38)Bronas, 2011[39](#_ENREF_39) | RCTSingle centerUSFunding: American Heart AssociationPopulationPAD patients with ICTotal N: 41Mean Age: 68N Female: 12% Female: 29% Race: 85% White | *Intervention*Supervised exercise (N=20)Treadmill walking group: 3 times per wk for 12 wkArm-ergometry cycle training group: 3 times per wk for 12 wkConcomitant therapy: Could be on cilostazol, antiplatelet agent, lipid-lowering agent, beta-blocker or ACE inhibitor at discretion of physician*Comparator*Control (N=8) Instructed to follow care given by their physician, received written instructions on how to exercise independently if they chose to do so and were asked to keep a daily record of any exerciseConcomitant therapy: Could be on cilostazol, antiplatelet agent, lipid-lowering agent, beta-blocker or ACE inhibitor at discretion of physician | Timing: 12 wk, 24 wkIndividualMWDPFWD | GoodNo limitations |
| Tsai, 2002[40](#_ENREF_40) | RCTMulticenterAsiaFunding: NRPopulationPAD patients with ICTotal N: 64Mean Age: 76N Female: 9% Female: 17% Race: NR | *Intervention*Supervised exercise (N=27)Treadmill walking 3 times per wk for 12 wkConcomitant therapy: None specified*Comparator*Control (N=26)No specific instructions notedConcomitant therapy: None specified | Timing: 3 moIndividualPWTCOTQOL | PoorStudy did not report participants' comorbid conditionsStudy conducted solely outside the USStudy was conducted only at a single site |
| ***Endovascular intervention vs. usual care*** |
| Feinglass, 2000[41](#_ENREF_41) | ObservationalMulticenterUSFunding: GovernmentPopulationPAD patients with ICTotal N: 526Mean Age: 69N Female: 105% Female: 20% Race: 16% African American | *Intervention*Endovascular revascularization (N=44)AngioplastyConcomitant therapy: Could include ASA, statin, pentoxifylline, warfarin, diuretics, ACE inhibitors, vasodilators, nitrates, calcium channel blockers and beta-blockers*Comparator*Medical therapy (N=277)Not definedConcomitant therapy: Could include ASA, statin, pentoxifylline, warfarin, diuretics, ACE inhibitors, vasodilators, nitrates, calcium channel blockers and beta-blockers | Timing: 18 moIndividualCardiovascular mortalityStrokeQOLMajor amputationChange in ABI | FairStudy exclusion criteria were poorly described or not appropriateStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the conditionDiagnostic or therapeutic advances have been made in routine practice since the study was conductedComparator(s) not well described |
| Gelin, 2001[31](#_ENREF_31)Taft, 2001[32](#_ENREF_32) | RCTSingle centerEuropeFunding: GovernmentPopulationPAD patients with ICTotal N: 264Mean Age: 66 to 67N Female: 90% Female: 34.1% Race: NR | InterventionEndovascular revascularization (N=87)No description of endovascular proceduresConcomitant therapy: Not specifiedComparatorControl (N=89)No specific information givenConcomitant therapy: Not specified | Timing: 12 moIndividualMortalityQOLVessel patencyAmputationMWD | FairStudy conducted solely outside the USStudy was conducted only at a single site |
| Giugliano, 2012[42](#_ENREF_42) | ObservationalSingle centerEuropeFunding: NRPopulationPAD patients with ICTotal N: 479Mean Age: 64 to 66N Female: 89% Female: 18.6%Race: NR | *Intervention*Endovascular revascularization (N=264)Percutaneous transluminal angioplastyConcomitant therapy: None specified*Comparator*Conservative medical therapy (N=215)Concomitant therapy: None specified | Timing: 21 mo (median followup)Composite (total events)Cardiovascular mortalityNonfatal MINonfatal strokePTCACABGCarotid PTAComposite (total cardiovascular mortality)Sudden deathFatal MIFatal strokeIndividualFatal MINonfatal MIFatal strokeNonfatal strokePTCACABGCarotid PTA | FairStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the conditionComparator(s) not well describedStudy was conducted solely outside the USStudy was conducted only at a single site |
| Hobbs, 2006[34](#_ENREF_34)EXACT Study | RCTMulticenterUKFunding: GovernmentPopulationPAD patients with ICTotal N: 23Median Age: 67N Female: 7% Female: 30.4% Race: NR | *Intervention*Endovascular revascularization + best medical therapy (N=9)Percutaneous transluminal angioplasty Best medical therapy: Not definedConcomitant therapy: None specified*Comparator*Best medical therapy (N=7)Best medical therapy: Not definedConcomitant therapy: None specified | Timing: 6 moIndividualACDICD | FairStudy interventions (active arm) were not similar to interventions used in routine clinical practiceStudy conducted solely outside the USStudy was conducted only at a single site |
| Koivunen, 2008[43](#_ENREF_43) | ObservationalSingle centerEuropeFunding: Academy of FinlandPopulationPAD patients with ICTotal N: 180Mean Age: 67N Female: 62% Female: 34.4% Race: NR | *Intervention*Endovascular revascularization (N=85)Percutaneous transluminal angioplasty Concomitant therapy: None specified*Comparator*Conservative treatment (N=64)Lifestyle modification and medicationConcomitant therapy: None specified | Timing: 12 moIndividualQOLPFWD | Poor Comparator(s) not well describedStudy did not use a clinically relevant surrogate outcome where applicableStudy conducted solely outside the USStudy was conducted only at a single site |
| Murphy, 2012[36](#_ENREF_36)CLEVER Study | RCTMulticenterUS, Canada Funding: GovernmentPopulationPAD patients with ICTotal N: 111Mean Age: 62 to 65N Female: 42% Female: 37.8% Race: NR | *Intervention*Endovascular revascularization + optimal medical therapy (N=46)Revascularization with stent (not otherwise specified)Optimal medical therapy: Cilostazol 100 mg bid; advice about home exercise and dietConcomitant therapy: Could include ASA, thienopyridine, and statin*Comparator*Optimal medical therapy (N=22)Optimal medical therapy: Cilostazol 100 mg twice daily; advice about home exercise and dietConcomitant therapy: Could include ASA, thienopyridine, and statin | Timing: 30 days, 6 moIndividualPWTCOTQOLChange in ABISafety | GoodStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition |
| Nylaende, 2007[44](#_ENREF_44)OBACT Study | RCTSingle centerEuropeFunding: industryPopulationPAD patients with ICTotal N: 56Mean Age: 68 to 69N Female: 25% Female: 44.6% Race: NR | *Intervention*Endovascular revascularization + optimal medical therapy (N=28)Percutaneous transluminal angioplasty ± stentOptimal medical therapy: Nicotine plaster and bupropion prescribed to smokers if not contraindicated; instructions for a home-based exercise training program; nutritional advice given; ASA 160 mg daily (or Plavix in patients with history of peptic ulcer; statins for patients with hypercholesterolemia; individualized hypertension treatment*Comparator*Optimal medical therapy (N=28)Optimal medical therapy: Nicotine plaster and bupropion prescribed to smokers if not contraindicated; instructions for a home-based exercise training program; nutritional advice given; ASA 160 mg daily (or Plavix in patients with history of peptic ulcer); statins for patients with hypercholesterolemia; individualized hypertension treatment | Timing: 3 mo, 12 mo, 24 moIndividualMortalityQOLMWDPFWD | GoodStudy conducted solely outside the USStudy was conducted only at a single site |
| Pell, 1997[45](#_ENREF_45) | ObservationalMulticenterEuropeFunding: GovernmentPopulationPAD patients with ICTotal N: 201Mean Age: 67 N Female: 78% Female: 38.8% Race: NR | *Intervention*Endovascular revascularization (N=19)Percutaneous transluminal angioplastyConcomitant therapy: None specified*Comparator*Conservative treatment (N=119)No description providedConcomitant therapy: None specified | Timing: 6 moIndividualMortalityQOL | FairStudy did not report participants' baseline characteristicsStudy did not report participants' comorbid conditionsStudy exclusion criteria were poorly described or not appropriateComparator(s) not well describedStudy conducted solely outside the US |
| Whyman, 1997[46](#_ENREF_46)Whyman, 1996[47](#_ENREF_47) | RCTSingle centerUKFunding: GovernmentPopulationPAD patients with ICTotal N: 62Mean Age: 61 to 63N Female: 11% Female: 17.7% Race: NR | *Intervention*Endovascular revascularization + conventional medical therapy (N=30) Percutaneous transluminal angioplastyConventional medical therapy: Low dose aspirin plus advice on smoking and exercise*Comparator*conventional medical therapy (N=32)Conventional medical therapy: Low dose aspirin plus advice on smoking and exercise | Timing: 6 mo, 24 moIndividualMWDICDChange in ABI | FairStudy conducted solely outside the USStudy was conducted only at a single site |
| ***Surgical revascularization vs. usual care*** |
| Mori, 2002[48](#_ENREF_48) | ObservationalSingle centerAsiaFunding: NRPopulationPAD patients with ICTotal N: 427Mean Age: 64 to 66N Female: 54% Female: 13%Race: NR | *Intervention*Surgical Revascularization (N=259)Surgical bypass, percutaneous transluminal angioplasty or stentConcomitant therapy: None specified*Comparator*Usual Care (N=168)Concomitant therapy: None specified | Timing: 3 yr, 5 yrIndividualTotal mortalityVessel patencySymptom improvement | LowStudy eligibility/exclusion criteria were poorly described or not appropriateStudy's cointerventions did not adequately reflect routine clinical practiceDiagnostic or therapeutic advances have been made in routine practice since the study was conductedComparator(s) not well describedStudy conducted solely outside the USStudy was conducted only at a single site |
| ***Endovascular intervention vs. exercise training*** |
| Gelin, 2001[31](#_ENREF_31)Taft, 2001[32](#_ENREF_32) | RCTSingle centerEuropeFunding: GovernmentPopulationPAD patients with ICTotal N: 264Mean Age: 66 to 67N Female: 90% Female: 34.1% Race: NR | *Intervention*Endovascular revascularization (N=87)A variety of procedures were performed.Concomitant therapy: None specified*Comparator*Supervised exercise (N=88)Treadmill walking training 3 times per wk for 6 moConcomitant therapy: None specified | Timing: 12 moIndividualMortalityQOLVessel patencyAmputationMWD | FairStudy conducted solely outside the USStudy was conducted only at a single site |
| Greenhalgh, 2008[49](#_ENREF_49)MIMIC Study | RCTMulticenterUKFunding: GovernmentPopulationPAD patients with IC; 93 patients with femoropopliteal disease,34 patients with aortoiliac diseaseTotal N: 127Mean Age: 63 to 69N Female: 46% Female: 36.2% Race: NR | *Intervention*Endovascular revascularization (N=67)Percutaneous transluminal angioplasty ± stentConcomitant therapy: Counseling regarding smoking cessation and nicotine replacement therapy was prescribed where necessary. Optimal medical management of hypertension, hyperlipidemia, diabetes, and medication management including antiplatelet therapy was coordinated through the patient’s primary physician.*Comparator*Supervised exercise (N=60)Walking circuit interspersed with seven lower limb training stations at least 1 times per wk for 6 mo.Concomitant therapy: Counseling regarding smoking cessation and nicotine replacement therapy was prescribed where necessary. Optimal medical management of hypertension, hyperlipidemia, diabetes, and medication management including antiplatelet therapy was coordinated through the patient’s primary physician. | Timing: 6 mo, 12 mo, 24 moIndividualMortalityMIStrokeRepeat revascularizationQOLMWDICD | FairNo limitations |
| Hobbs, 2006[34](#_ENREF_34)EXACT Study | RCTMulticenterUKFunding: GovernmentPopulationPAD patients with ICTotal N: 23Median Age: 67N Female: 7% Female: 30.4% Race: NR | *Intervention*Supervised Exercise + best medical therapy (N=7)Circuit of moderate intensity exercises 2 times per wk for 12 wkBest medical therapy: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent*Comparator*Endovascular revascularization + best medical therapy (N=9)Percutaneous transluminal angioplastyBest medical therapy: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent | Timing: 6 moIndividualACDICD | FairStudy interventions (active arm) were not similar to interventions used in routine clinical practiceStudy conducted solely outside the USStudy was conducted only at a single site |
| Kruidenier, 2011[50](#_ENREF_50) | RCTSingle centerEuropeFunding: NRPopulationPAD patients with ICTotal N: 70Mean Age: 62N Female: 27% Female: 38.6% Race: NR | *Intervention*Endovascular revascularization (N=35)Consisted of iliacangioplasty with selective stent placement for iliac stenoses,angioplasty with primary stent placement for superficialfemoral artery stenoses, or recanalization with primarystent placement for iliac and femoral occlusionsConcomitant therapy: None specified*Comparator*Endovascular revascularization + supervised exercise (N=35)Endovascular intervention as per intervention plus a nonspecified exercise program 2 times per wk for 6 moConcomitant therapy: None specified | Timing: within 3 wk of procedure, 3 mo, 6 moIndividualACDQOLChange in ABIVessel patencyRepeat revascularization | GoodStudy conducted solely outside the USStudy was conducted only at a single site |
| Mazari, 2012[51](#_ENREF_51)Mazari, 2010[52](#_ENREF_52) | RCTSingle centerUKFunding: European Society of Vascular SurgeryPopulationPAD patients with ICTotal N: 178Median Age: 70N Female: 71% Female: 39.9% Race: NR | *Intervention*Endovascular revascularization (N=60), Endovascular revascularization + supervised exercise (N=58)Endovascular therapy: Percutaneous transluminal angioplastySupervised exercise therapy: Circuit of exercises 3 times per wk for 12 wkConcomitant therapy: All patients were prescribed antiplatelet therapy (aspirin and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation program), and risk factor modification (target oriented management of hypertension, hypercholesterolemia, and diabetes. All patients also received an advice leaflet regarding exercise.*Comparator*Supervised exercise (N=60)Supervised exercise therapy: Circuit of exercises 3 times per wk for 12 wkConcomitant therapy: All patients were prescribed antiplatelet therapy (aspirin and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation program), and risk factor modification (target oriented management of hypertension, hypercholesterolemia, and diabetes. All patients also received an advice leaflet regarding exercise. | Timing: 3 mo, 6 mo, 12 moIndividualRepeat revascularizationPeriprocedural complicationsQOLVessel patencyMWDICD | GoodComparator(s) not well describedStudy conducted solely outside the USStudy was conducted only at a single site |
| Murphy, 2012[36](#_ENREF_36)CLEVER Study | RCTMulticenterUS, Canada Funding: GovernmentPopulationPAD patients with ICTotal N:111Mean Age: 62 to 65N Female: 42% Female: 37.8% Race: NR | *Intervention*Supervised exercise + optimal medical therapy (N=43)Exercises 3 times per wk for 26 wkOptimal medical therapy: Cilostazol 100 mg bid; advice about home exercise and dietConcomitant therapy: Could include ASA, thienopyridine, and statin*Comparator*Endovascular revascularization + optimal medical therapy (N=46)Revascularization with stent (not otherwise specified)Optimal medical therapy: Cilostazol 100 mg bid; advice about home exercise and dietConcomitant therapy: Could include ASA, thienopyridine, and statin | Timing: 30 days, 6 moIndividualPWTCOTQOLChange in ABISafety | GoodStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition |
| Nordanstig, 2011[53](#_ENREF_53) | RCTMulticenterEuropeFunding: GovernmentPopulationPAD patients with ICTotal N: 201Mean Age: 68N Female: 74% Female: 37% Race: NR | *Intervention*Revascularization (surgical or endovascular) + optimal medical therapy (N=100)Revascularization: In general, aorto-iliac TASC A and B lesions were treated endovascularly and TASC C and D lesions with surgery. Femoropopliteal TASC A lesions were offered angioplasty, whereas TASC BeD lesions usually were treated surgically. For lesions in the common femoral artery, endarterectomy with or without patch angioplasty was used.Optimal medical therapy: ASA 75 mg daily (or ticlopidine if contraindication to aspirin). Smokers were offered participation in a smoking cessation support programme and received verbal and written information with smoking cessation advice. Hypertension, diabetes and hyperlipidemia were managed according to national guidelines.Verbal training advice and a written training programme for IC. Instructed to walk at least 1 h/day and to walk up to their maximal claudication distance as often as possible and to perform an additional exercise programme at home several times a day.*Comparator*Optimal medical therapy (N=100)Optimal medical therapy: ASA 75 mg daily (or ticlopidine if contraindication to aspirin). Smokers were offered participation in a smoking cessation support programme and received verbal and written information with smoking cessation advice. Hypertension, diabetes and hyperlipidemia were managed according to national guidelines.Verbal training advice and a written training programme for IC. Instructed to walk at least 1 h/day and to walk up to their maximal claudication distance as often as possible and to perform an additional exercise programme at home several times a day. | Timing: 24 moIndividualMortalityRepeat revascularizationQOLVessel patencyMajor amputationMWD | GoodStudy conducted solely outside the US |
| Perkins, 1996[54](#_ENREF_54) | RCTSingle centerUKFunding: Oxford Direct Research CommitteePopulationPAD patients with ICTotal N: 56Mean Age: 63N Female: 6% Female: 10.7%Race: NR | *Intervention*Endovascular revascularization (N=30)Percutaneous transluminal angioplastyConcomitant therapy: None specified*Comparator*Supervised exercise (N=26)Dynamic leg exercises 2 times per wk for 6 moConcomitant therapy: None specified | Timing: 3 mo, 6 mo, 9 mo, 12 mo, 15 mo, 6 yrIndividualMortalityRepeat revascularizationMWDPeriprocedural complications | FairStudy exclusion criteria were poorly described or not appropriateDiagnostic or therapeutic advances have been made in routine practice since the study was conductedStudy conducted solely outside the USStudy was conducted only at a single site |
| Spronk, 2009[55](#_ENREF_55)Spronk, 2008[56](#_ENREF_56) | RCTSingle centerEuropeFunding: NRPopulationPAD patients with ICTotal N: 151Median Age: 65 to 66N Female: 67% Female: 44.4% Race: NR | *Intervention*Endovascular revascularization (N=75)Percutaneous transluminal angioplasty ± stentConcomitant therapy: ASA 100 mg daily*Comparator*Supervised exercise (N=75)Hospital based treadmill exercise 2 times per wk for 24 wkConcomitant therapy: ASA 100 mg daily | Timing: 6 mo, 12 moIndividualMortalityQOLMWDPFWDChange in ABI | FairStudy conducted solely outside the USStudy was conducted only at a single site |
| ***Surgical revascularization vs. exercise + medical therapy*** |
| Drozdz, 2001[57](#_ENREF_57) | ObservationalSingle centerEuropeFunding: NRPopulationPAD patients with IC Total N: 127Mean Age: 58N Female: 28% Female: 22%Race: NR | *Intervention*Exercise training (N=83)Treadmill 3 times a week for 12 weeks Concomitant therapy: 600mg pentoxifylline orally twice daily*Comparator*Surgical revascularization (N=44)Vascular bypass prosthesesConcomitant therapy: None specified | Timing: 6 wk, 12 wkIndividualMWDCOTABI | FairStudy eligibility/exclusion criteria were poorly described or not appropriateStudy's cointerventions did not adequately reflect routine clinical practiceStudy conducted solely outside the USStudy was conducted only at a single site |
| ***Endovascular intervention vs. surgical revascularization*** |
| Feinglass, 2000[41](#_ENREF_41) | ObservationalMulticenterUSFunding: GovernmentPopulationPAD patients with ICTotal N: 526Mean Age: 69N Female: 105% Female: 20% Race: 16% African American | *Intervention*Endovascular revascularization (N=44)Percutaneous transluminal angioplastyConcomitant therapy: None specified*Comparator*Surgical revascularization (N=60)Bypass grafting ± angioplastyConcomitant therapy: None specified | Timing: 18 moIndividualCardiovascular mortalityStrokeQOLMajor amputationChange in ABI | FairStudy exclusion criteria were poorly described or not appropriateStudy selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the conditionDiagnostic or therapeutic advances have been made in routine practice since the study was conductedComparator(s) not well described |
| Koivunen, 2008[43](#_ENREF_43) | ObservationalSingle centerEuropeFunding: Academy of FinlandPopulationPAD patients with ICTotal N: 180Mean Age: 67 to 68N Female: 62% Female: 34.4% Race: NR | *Intervention*Endovascular revascularization (N=85)Percutaneous transluminal angioplasty ± stentConcomitant therapy: None specified*Comparator*Surgical revascularization (N=31)Surgical bypass or endarterectomyConcomitant therapy: None specified | Timing: 12 moIndividualQOLPFWD | PoorComparator(s) not well describedStudy did not use a clinically relevant surrogate outcome where applicableStudy conducted solely outside the USStudy was conducted only at a single site |
| Pell, 1997[45](#_ENREF_45) | ObservationalMulticenterEuropeFunding: GovernmentPopulationPAD patients with ICTotal N: 201Mean Age: 67N Female: 78% Female: 38.8% Race: NR | *Intervention*Endovascular revascularization (N=19)Percutaneous transluminal angioplastyConcomitant therapy: None specified*Comparator*Surgical revascularization (N=19)Arterial reconstructionConcomitant therapy: None specified | Timing: 6 moIndividualMortalityQOL | FairStudy did not report participants' baseline characteristicsStudy did not report participants' comorbid conditionsStudy exclusion criteria were poorly described or not appropriate.Comparator(s) not well describedStudy conducted solely outside the US |

**Abbreviations:** ABI=ankle brachial index; ACE=angiotensin converting enzyme; ASA=acetylsalicylic acid (aspirin); CI=confidence interval; CLI=critical limb ischemia; COT=claudication onset time; CV=cardiovascular; DVT=deep vein thrombosis; GI=gastrointestinal; HR=hazard ratio; IC=intermittent claudication; ICD=initial claudication distance; IU=international units; LMWH=low molecular weight heparin; MI=myocardial infarction; mo=month/months; MWD=maximal walking distance; MWT=maximal walking time; N=number of patients; NR=not reported; NS=not significant; PAD=peripheral artery disease; PFWD=pain-free walking distance; PTA=percutaneous transluminal angiography; PUD=peptic ulcer disease; PWD=peak walking distance; PWT=peak walking time; QOL=quality of life; RCT=randomized controlled trial; SD=standard deviation; TIA=transient ischemic attack; UFH=unfractionated heparin; wk=week/weeks; yr=year/years