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) | RCT  Multicenter  US  Funding: industry  Population  PAD patients with IC  Total N: 516  Mean Age: 64 to 65  N 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 mo  Individual  Mortality  MI  Stroke  QOL  Amputation  MWD  PFWD | Good  No limitations |
| Belcaro, 2002[16](#_ENREF_16) | RCT  Multicenter  Europe  Funding: NR  Population  PAD patients with IC  Total N: 60  Mean Age: 55 to 56  N 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 mo  Individual  MWD | Fair  Study interventions (active arm) were not similar to interventions used in routine clinical practice  Study'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) | RCT  Multicenter  US  Funding: NR  Population  PAD patients with IC  Total N: 81  Mean Age: 66 to 67  N 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 wk  Individual  ACD  ICD  Adverse events | Good  No limitations |
| Dawson, 2000[18](#_ENREF_18) | RCT  Multicenter  US  Funding: Otsuka America Pharmaceuticals  Population  PAD patients with IC  Total N: 698  Mean Age: 66  N 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 wk  Individual  MWD  PFWD  Change in ABI | Fair  No limitations |
| De Sanctis, 2002[19](#_ENREF_19),[20](#_ENREF_20)  Cesarone, 2002[21](#_ENREF_21) | RCT  Multicenter  Europe  Funding: independent  Population  PAD patients with IC  Total N: 194  Mean Age: 62 to 63  N 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 mo  Individual  Total Walking Distance | Fair  Study did not report participants' comorbid conditions  Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate  Study interventions (active arm) were not similar to interventions used in routine clinical practice  Study conducted solely outside the US |
| Hiatt, 2008[22](#_ENREF_22)  Stone, 2008[23](#_ENREF_23)  CASTLE Study | RCT  Multicenter  US  Funding: industry  Population  PAD patients with IC  Total N: 1435  Mean Age: 66  N 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 mo  Composite  (primary)  Stroke  TIA  Carotid revascularization  Individual  Mortality  Stroke  Adverse events | Good  No limitations |
| Hobbs, 2007[24](#_ENREF_24)  INEXACT Study | RCT  Single center  UK  Funding: NR  Population  PAD patients with IC  Total N: 38  Median Age: 67  N 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 mo  Individual  Adverse drug reaction  Change in ABI  ACD  ICD | Good  Study conducted solely outside the US  Study was conducted only at a single site |
| Money, 1998[25](#_ENREF_25) | RCT  Multicenter  US  Funding: NR  Population  PAD patients with IC  Total N: 239  Mean Age: 65  N 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 specified  Comparator  *Placebo* (N=120)  Concomitant therapy: None specified | Timing: 8 wk, 12 wk, 16 wk  Individual  Mortality  QOL  Adverse events  ACD | Fair  Study did not report participants' comorbid conditions |
| Soga, 2009[26](#_ENREF_26) | RCT  Multicenter  Asia  Funding: NR  Population  PAD patients with IC  Total N: 78  Mean Age: 71  N 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 mo  Composite  (secondary)  Total mortality  Cardiovascular mortality  Nonfatal MI  Stroke  Repeat revascularization  Major amputation  Minor amputation  Individual  Mortality  MI  Stroke  Repeat revascularization  Bleeding  Amputation | Good  No limitations |
| Strandness, 2002[27](#_ENREF_27) | RCT  Multicenter  US  Funding: industry  Population  PAD patients with IC  Total N: 394  Mean Age: 63 to 64  N 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 mo  Composite  (secondary)  Total mortality  Cardiovascular mortality  Individual  MWD  Adverse drug reactions | Fair  No limitations |
| ***Exercise training vs. usual care*** | | | | |
| Crowther, 2008[28](#_ENREF_28) | RCT  Single center  Australia  Funding: NR  Population  PAD patients with IC  Total N: 21  Mean Age: 67 to 71  N Female: 11  % Female: 52%  Race: NR | *Intervention*  Supervised Exercise (N=10)  Treadmill walking group: 3 times per wk for 12 mo  Concomitant therapy: Could include beta-blocker  *Comparator*  Control (N=11)  No specific instructions given  Concomitant therapy: Could include beta-blocker | Timing: 12 mo  Individual  PFWT | Fair  Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition  Study conducted solely outside the US  Study was conducted only at a single site |
| Gardner, 2002[29](#_ENREF_29) | RCT  Multicenter  US  Funding: Government  Population  PAD patients with IC  Total N: 61  Mean Age: 71 ro 72  N Female: NR  % Female: NR  Race: NR | *Intervention*  Exercise training (N=28)  Supervised treadmill walking 3 times per wk  Concomitant therapy: None specified  *Comparator*  Usual care (N=24)  Concomitant therapy: None specified | Timing: 6 mo, 18 mo  Individual  Total mortality  QOL - Walking impairment questionnaire  Major amputation  Exercise-related harms  Mean or 6-minute walking time  Absolute claudication distance  QOL - SF36  Initial Claudication Distance | Fair  No limitations |
| Gardner, 2011[30](#_ENREF_30) | RCT  Single center  US  Funding: Government  Population  PAD patients with IC  Total N: 119  Mean Age: 65 to 66  N 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 wk  Home treadmill walking group: 3 times per wk at self-selected pace for specified duration of time for 12 wk  Concomitant 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 wk  Individual  MI  Stroke  QOL  PWT  COT | Good  Study was conducted only at a single site |
| Gelin, 2001[31](#_ENREF_31)  Taft, 2001[32](#_ENREF_32) | RCT  Single center  Europe  Funding: Government  Population  PAD patients with IC  Total N: 264  Mean Age: 66 to 67  N 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 wk  Concomitant therapy: None specified  *Comparator*  Control (N=89)  Received no other specific advice or treatment apart from the general advice given to the two treatment groups  Concomitant therapy: None specified | Timing: 12 mo  Individual  Mortality  QOL  Vessel patency  Amputation  MWD | Fair  Study conducted solely outside the US  Study was conducted only at a single site |
| Gibellini, 2000[33](#_ENREF_33) | RCT  Study centers: NR  Location: NR  Funding: NR  Population  PAD patients with IC  Total N: 40  Mean Age: 67  N Female: 4  % Female: 10%  Race: NR | *Intervention*  Supervised exercise (N=20)  Treadmill walking training 5 times per wk for 4 wk  Concomitant therapy: ASA 325 mg daily  *Comparator*  Control (N=20)  No specific instructions given  Concomitant therapy: ASA 325 mg daily | Timing: 1 mo, 6 mo  Individual  ACD  ICD | Fair  Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate  Study eligibility criteria were poorly described or not appropriate  Study conducted solely outside the US  Study was conducted only at a single site |
| Hobbs, 2006[34](#_ENREF_34)  EXACT Study | RCT  Multicenter  UK  Funding: Government  Population  PAD patients with IC  Total N: 23  Median Age: 67  N 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 wk  Concomitant 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 mo  Individual  Adverse drug reaction  ACD  ICD | Fair  Study interventions (active arm) were not similar to interventions used in routine clinical practice  Study conducted solely outside the US  Study was conducted only at a single site |
| Hobbs, 2007[24](#_ENREF_24)  INEXACT Study | RCT  Single center  UK  Funding: NR  Population  PAD patients with IC  Total N: 38  Median Age: 67  N 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 wk  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  *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 mo  Individual  Adverse drug reaction  Change in ABI  ACD  ICD | Good  Study conducted solely outside the US  Study was conducted only at a single site |
| Lee, 2007[35](#_ENREF_35) | Observational  Single center  UK  Funding: NR  Population  PAD patients with IC  Total N: 70  Median Age: 67 to 69  N Female: 22  % Female: 31.4%  Race: NR | *Intervention*  Supervised exercise (N=33)  Circuit of exercises 3 times per wk for 12 wk  Concomitant 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 mo  Individual  MWD  ICD  QOL | Poor  Study did not report participants' baseline characteristics  Study did not report participants' comorbid conditions  Study conducted solely outside the US  Study was conducted only at a single site |
| Murphy, 2012[36](#_ENREF_36)  CLEVER Study | RCT  Multicenter  US, Canada  Funding: Government  Population  PAD patients with IC  Total N: 111  Mean Age: 62 to 65  N Female: 42  % Female: 37.8%  Race: NR | *Intervention*  Supervised Exercise + optimal medical therapy (N=43)  Exercises 3 times per wk for 26 wk  Concomitant 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 diet  Concomitant therapy: Could include ASA, thienopyridine, and statin | Timing: 30 days, 6 mo  Individual  PWT  COT  QOL  Change in ABI  Safety | 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) | Observational  Single center  Asia  Funding: NR  Population  PAD patients with IC  Total N: 100  Mean Age: 67  N 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 mo  Individual  ACD  Change in ABI | Poor  Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition  Comparator(s) not well described  Study conducted solely outside the US  Study was conducted only at a single site |
| Treat-Jacobson, 2009[38](#_ENREF_38)  Bronas, 2011[39](#_ENREF_39) | RCT  Single center  US  Funding: American Heart Association  Population  PAD patients with IC  Total N: 41  Mean Age: 68  N Female: 12  % Female: 29%  Race: 85% White | *Intervention*  Supervised exercise (N=20)  Treadmill walking group: 3 times per wk for 12 wk  Arm-ergometry cycle training group: 3 times per wk for 12 wk  Concomitant 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 exercise  Concomitant therapy: Could be on cilostazol, antiplatelet agent, lipid-lowering agent, beta-blocker or ACE inhibitor at discretion of physician | Timing: 12 wk, 24 wk  Individual  MWD  PFWD | Good  No limitations |
| Tsai, 2002[40](#_ENREF_40) | RCT  Multicenter  Asia  Funding: NR  Population  PAD patients with IC  Total N: 64  Mean Age: 76  N Female: 9  % Female: 17%  Race: NR | *Intervention*  Supervised exercise (N=27)  Treadmill walking 3 times per wk for 12 wk  Concomitant therapy: None specified  *Comparator*  Control (N=26)  No specific instructions noted  Concomitant therapy: None specified | Timing: 3 mo  Individual  PWT  COT  QOL | Poor  Study did not report participants' comorbid conditions  Study conducted solely outside the US  Study was conducted only at a single site |
| ***Endovascular intervention vs. usual care*** | | | | |
| Feinglass, 2000[41](#_ENREF_41) | Observational  Multicenter  US  Funding: Government  Population  PAD patients with IC  Total N: 526  Mean Age: 69  N Female: 105  % Female: 20%  Race: 16% African American | *Intervention*  Endovascular revascularization (N=44)  Angioplasty  Concomitant therapy: Could include ASA, statin, pentoxifylline, warfarin, diuretics, ACE inhibitors, vasodilators, nitrates, calcium channel blockers and beta-blockers  *Comparator*  Medical therapy (N=277)  Not defined  Concomitant therapy: Could include ASA, statin, pentoxifylline, warfarin, diuretics, ACE inhibitors, vasodilators, nitrates, calcium channel blockers and beta-blockers | Timing: 18 mo  Individual  Cardiovascular mortality  Stroke  QOL  Major amputation  Change in ABI | Fair  Study exclusion criteria were poorly described or not appropriate  Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition  Diagnostic or therapeutic advances have been made in routine practice since the study was conducted  Comparator(s) not well described |
| Gelin, 2001[31](#_ENREF_31)  Taft, 2001[32](#_ENREF_32) | RCT  Single center  Europe  Funding: Government  Population  PAD patients with IC  Total N: 264  Mean Age: 66 to 67  N Female: 90  % Female: 34.1%  Race: NR | Intervention  Endovascular revascularization (N=87)  No description of endovascular procedures  Concomitant therapy: Not specified  Comparator  Control (N=89)  No specific information given  Concomitant therapy: Not specified | Timing: 12 mo  Individual  Mortality  QOL  Vessel patency  Amputation  MWD | Fair  Study conducted solely outside the US  Study was conducted only at a single site |
| Giugliano, 2012[42](#_ENREF_42) | Observational  Single center  Europe  Funding: NR  Population  PAD patients with IC  Total N: 479  Mean Age: 64 to 66  N Female: 89  % Female: 18.6%  Race: NR | *Intervention*  Endovascular revascularization (N=264)  Percutaneous transluminal angioplasty  Concomitant therapy: None specified  *Comparator*  Conservative medical therapy (N=215)  Concomitant therapy: None specified | Timing: 21 mo (median followup)  Composite (total events)  Cardiovascular mortality  Nonfatal MI  Nonfatal stroke  PTCA  CABG  Carotid PTA  Composite (total cardiovascular mortality)  Sudden death  Fatal MI  Fatal stroke  Individual  Fatal MI  Nonfatal MI  Fatal stroke  Nonfatal stroke  PTCA  CABG  Carotid PTA | Fair  Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition  Comparator(s) not well described  Study was conducted solely outside the US  Study was conducted only at a single site |
| Hobbs, 2006[34](#_ENREF_34)  EXACT Study | RCT  Multicenter  UK  Funding: Government  Population  PAD patients with IC  Total N: 23  Median Age: 67  N Female: 7  % Female: 30.4%  Race: NR | *Intervention*  Endovascular revascularization + best medical therapy (N=9)  Percutaneous transluminal angioplasty  Best medical therapy: Not defined  Concomitant therapy: None specified  *Comparator*  Best medical therapy (N=7)  Best medical therapy: Not defined  Concomitant therapy: None specified | Timing: 6 mo  Individual  ACD  ICD | Fair  Study interventions (active arm) were not similar to interventions used in routine clinical practice  Study conducted solely outside the US  Study was conducted only at a single site |
| Koivunen, 2008[43](#_ENREF_43) | Observational  Single center  Europe  Funding: Academy of Finland  Population  PAD patients with IC  Total N: 180  Mean Age: 67  N 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 medication  Concomitant therapy: None specified | Timing: 12 mo  Individual  QOL  PFWD | Poor  Comparator(s) not well described  Study did not use a clinically relevant surrogate outcome where applicable  Study conducted solely outside the US  Study was conducted only at a single site |
| Murphy, 2012[36](#_ENREF_36)  CLEVER Study | RCT  Multicenter  US, Canada  Funding: Government  Population  PAD patients with IC  Total N: 111  Mean Age: 62 to 65  N 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 diet  Concomitant 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 diet  Concomitant therapy: Could include ASA, thienopyridine, and statin | Timing: 30 days, 6 mo  Individual  PWT  COT  QOL  Change in ABI  Safety | Good  Study 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 | RCT  Single center  Europe  Funding: industry  Population  PAD patients with IC  Total N: 56  Mean Age: 68 to 69  N Female: 25  % Female: 44.6%  Race: NR | *Intervention*  Endovascular revascularization + optimal medical therapy (N=28)  Percutaneous transluminal angioplasty ± stent  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  *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 mo  Individual  Mortality  QOL  MWD  PFWD | Good  Study conducted solely outside the US  Study was conducted only at a single site |
| Pell, 1997[45](#_ENREF_45) | Observational  Multicenter  Europe  Funding: Government  Population  PAD patients with IC  Total N: 201  Mean Age: 67  N Female: 78  % Female: 38.8%  Race: NR | *Intervention*  Endovascular revascularization (N=19)  Percutaneous transluminal angioplasty  Concomitant therapy: None specified  *Comparator*  Conservative treatment (N=119)  No description provided  Concomitant therapy: None specified | Timing: 6 mo  Individual  Mortality  QOL | Fair  Study did not report participants' baseline characteristics  Study did not report participants' comorbid conditions  Study exclusion criteria were poorly described or not appropriate  Comparator(s) not well described  Study conducted solely outside the US |
| Whyman, 1997[46](#_ENREF_46)  Whyman, 1996[47](#_ENREF_47) | RCT  Single center  UK  Funding: Government  Population  PAD patients with IC  Total N: 62  Mean Age: 61 to 63  N Female: 11  % Female: 17.7%  Race: NR | *Intervention*  Endovascular revascularization + conventional medical therapy (N=30)  Percutaneous transluminal angioplasty  Conventional 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 mo  Individual  MWD  ICD  Change in ABI | Fair  Study conducted solely outside the US  Study was conducted only at a single site |
| ***Surgical revascularization vs. usual care*** | | | | |
| Mori, 2002[48](#_ENREF_48) | Observational  Single center  Asia  Funding: NR  Population  PAD patients with IC  Total N: 427  Mean Age: 64 to 66  N Female: 54  % Female: 13%  Race: NR | *Intervention*  Surgical Revascularization (N=259)  Surgical bypass, percutaneous transluminal angioplasty or stent  Concomitant therapy: None specified  *Comparator*  Usual Care (N=168)  Concomitant therapy: None specified | Timing: 3 yr, 5 yr  Individual  Total mortality  Vessel patency  Symptom improvement | Low  Study eligibility/exclusion criteria were poorly described or not appropriate  Study's cointerventions did not adequately reflect routine clinical practice  Diagnostic or therapeutic advances have been made in routine practice since the study was conducted  Comparator(s) not well described  Study conducted solely outside the US  Study was conducted only at a single site |
| ***Endovascular intervention vs. exercise training*** | | | | |
| Gelin, 2001[31](#_ENREF_31)  Taft, 2001[32](#_ENREF_32) | RCT  Single center  Europe  Funding: Government  Population  PAD patients with IC  Total N: 264  Mean Age: 66 to 67  N 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 mo  Concomitant therapy: None specified | Timing: 12 mo  Individual  Mortality  QOL  Vessel patency  Amputation  MWD | Fair  Study conducted solely outside the US  Study was conducted only at a single site |
| Greenhalgh, 2008[49](#_ENREF_49)  MIMIC Study | RCT  Multicenter  UK  Funding: Government  Population  PAD patients with IC; 93 patients with femoropopliteal disease,34 patients with aortoiliac disease  Total N: 127  Mean Age: 63 to 69  N Female: 46  % Female: 36.2%  Race: NR | *Intervention*  Endovascular revascularization (N=67)  Percutaneous transluminal angioplasty ± stent  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.  *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 mo  Individual  Mortality  MI  Stroke  Repeat revascularization  QOL MWD  ICD | Fair  No limitations |
| Hobbs, 2006[34](#_ENREF_34)  EXACT Study | RCT  Multicenter  UK  Funding: Government  Population  PAD patients with IC  Total N: 23  Median Age: 67  N 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 wk  Best medical therapy: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent  *Comparator*  Endovascular revascularization + best medical therapy (N=9)  Percutaneous transluminal angioplasty  Best medical therapy: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent | Timing: 6 mo  Individual  ACD  ICD | Fair  Study interventions (active arm) were not similar to interventions used in routine clinical practice  Study conducted solely outside the US  Study was conducted only at a single site |
| Kruidenier, 2011[50](#_ENREF_50) | RCT  Single center  Europe  Funding: NR  Population  PAD patients with IC  Total N: 70  Mean Age: 62  N Female: 27  % Female: 38.6%  Race: NR | *Intervention*  Endovascular revascularization (N=35)  Consisted of iliac  angioplasty with selective stent placement for iliac stenoses,  angioplasty with primary stent placement for superficial  femoral artery stenoses, or recanalization with primary  stent placement for iliac and femoral occlusions  Concomitant 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 mo  Concomitant therapy: None specified | Timing: within 3 wk of procedure, 3 mo, 6 mo  Individual  ACD  QOL  Change in ABI  Vessel patency  Repeat revascularization | Good  Study conducted solely outside the US  Study was conducted only at a single site |
| Mazari, 2012[51](#_ENREF_51)  Mazari, 2010[52](#_ENREF_52) | RCT  Single center  UK  Funding: European Society of Vascular Surgery  Population  PAD patients with IC  Total N: 178  Median Age: 70  N Female: 71  % Female: 39.9%  Race: NR | *Intervention*  Endovascular revascularization (N=60),  Endovascular revascularization + supervised exercise (N=58)  Endovascular therapy: Percutaneous transluminal angioplasty  Supervised exercise therapy: Circuit of exercises 3 times per wk for 12 wk  Concomitant 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 wk  Concomitant 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 mo  Individual  Repeat revascularization  Periprocedural complications  QOL  Vessel patency  MWD  ICD | Good  Comparator(s) not well described  Study conducted solely outside the US  Study was conducted only at a single site |
| Murphy, 2012[36](#_ENREF_36)  CLEVER Study | RCT  Multicenter  US, Canada  Funding: Government  Population  PAD patients with IC  Total N:111  Mean Age: 62 to 65  N Female: 42  % Female: 37.8%  Race: NR | *Intervention*  Supervised exercise + optimal medical therapy (N=43)  Exercises 3 times per wk for 26 wk  Optimal medical therapy: Cilostazol 100 mg bid; advice about home exercise and diet  Concomitant 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 diet  Concomitant therapy: Could include ASA, thienopyridine, and statin | Timing: 30 days, 6 mo  Individual  PWT  COT  QOL  Change in ABI  Safety | Good  Study 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) | RCT  Multicenter  Europe  Funding: Government  Population  PAD patients with IC  Total N: 201  Mean Age: 68  N 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 mo  Individual  Mortality  Repeat revascularization  QOL  Vessel patency  Major amputation  MWD | Good  Study conducted solely outside the US |
| Perkins, 1996[54](#_ENREF_54) | RCT  Single center  UK  Funding: Oxford Direct Research Committee  Population  PAD patients with IC  Total N: 56  Mean Age: 63  N Female: 6  % Female: 10.7%  Race: NR | *Intervention*  Endovascular revascularization (N=30)  Percutaneous transluminal angioplasty  Concomitant therapy: None specified  *Comparator*  Supervised exercise (N=26)  Dynamic leg exercises 2 times per wk for 6 mo  Concomitant therapy: None specified | Timing: 3 mo, 6 mo, 9 mo, 12 mo, 15 mo, 6 yr  Individual  Mortality  Repeat revascularization  MWD  Periprocedural complications | Fair  Study exclusion criteria were poorly described or not appropriate  Diagnostic or therapeutic advances have been made in routine practice since the study was conducted  Study conducted solely outside the US  Study was conducted only at a single site |
| Spronk, 2009[55](#_ENREF_55)  Spronk, 2008[56](#_ENREF_56) | RCT  Single center  Europe  Funding: NR  Population  PAD patients with IC  Total N: 151  Median Age: 65 to 66  N Female: 67  % Female: 44.4%  Race: NR | *Intervention*  Endovascular revascularization (N=75)  Percutaneous transluminal angioplasty ± stent  Concomitant therapy: ASA 100 mg daily  *Comparator*  Supervised exercise (N=75)  Hospital based treadmill exercise 2 times per wk for 24 wk  Concomitant therapy: ASA 100 mg daily | Timing: 6 mo, 12 mo  Individual  Mortality  QOL MWD PFWD  Change in ABI | Fair  Study conducted solely outside the US  Study was conducted only at a single site |
| ***Surgical revascularization vs. exercise + medical therapy*** | | | | |
| Drozdz, 2001[57](#_ENREF_57) | Observational  Single center  Europe  Funding: NR  Population  PAD patients with IC  Total N: 127  Mean Age: 58  N 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 prostheses  Concomitant therapy: None specified | Timing: 6 wk, 12 wk  Individual  MWD  COT  ABI | Fair  Study eligibility/exclusion criteria were poorly described or not appropriate  Study's cointerventions did not adequately reflect routine clinical practice  Study conducted solely outside the US  Study was conducted only at a single site |
| ***Endovascular intervention vs. surgical revascularization*** | | | | |
| Feinglass, 2000[41](#_ENREF_41) | Observational  Multicenter  US  Funding: Government  Population  PAD patients with IC  Total N: 526  Mean Age: 69  N Female: 105  % Female: 20%  Race: 16% African American | *Intervention*  Endovascular revascularization (N=44)  Percutaneous transluminal angioplasty  Concomitant therapy: None specified  *Comparator*  Surgical revascularization (N=60)  Bypass grafting ± angioplasty  Concomitant therapy: None specified | Timing: 18 mo  Individual  Cardiovascular mortality  Stroke  QOL  Major amputation  Change in ABI | Fair  Study exclusion criteria were poorly described or not appropriate  Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition  Diagnostic or therapeutic advances have been made in routine practice since the study was conducted  Comparator(s) not well described |
| Koivunen, 2008[43](#_ENREF_43) | Observational  Single center  Europe  Funding: Academy of Finland  Population  PAD patients with IC  Total N: 180  Mean Age: 67 to 68  N Female: 62  % Female: 34.4%  Race: NR | *Intervention*  Endovascular revascularization (N=85)  Percutaneous transluminal angioplasty ± stent  Concomitant therapy: None specified  *Comparator*  Surgical revascularization (N=31)  Surgical bypass or endarterectomy  Concomitant therapy: None specified | Timing: 12 mo  Individual  QOL  PFWD | Poor  Comparator(s) not well described  Study did not use a clinically relevant surrogate outcome where applicable  Study conducted solely outside the US  Study was conducted only at a single site |
| Pell, 1997[45](#_ENREF_45) | Observational  Multicenter  Europe  Funding: Government  Population  PAD patients with IC  Total N: 201  Mean Age: 67  N Female: 78  % Female: 38.8%  Race: NR | *Intervention*  Endovascular revascularization (N=19)  Percutaneous transluminal angioplasty  Concomitant therapy: None specified  *Comparator*  Surgical revascularization (N=19)  Arterial reconstruction  Concomitant therapy: None specified | Timing: 6 mo  Individual  Mortality  QOL | Fair  Study did not report participants' baseline characteristics  Study did not report participants' comorbid conditions  Study exclusion criteria were poorly described or not appropriate.  Comparator(s) not well described  Study 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