What is the Best Medical Therapy for PAD? Do We Need Better?

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Conflicts of Interest

- Consultant
  - Abbott Vascular (non-compensated)
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  - Cardinal Health
  - Cordis Corporation (non-compensated)
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  - Medtronic (non-compensated)
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- Board Member
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
    - www.vivapvd.com
    - Intersocietal Accreditation Commission
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  - Access Closure, Inc
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  - PQ Bypass, Inc
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  - Sano V, Inc.
  - Vascular Therapies, Inc

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Adherence to Guideline-Recommended Therapy Is Associated With Decreased Major Adverse Cardiovascular Events and Major Adverse Limb Events Among Patients With Peripheral Arterial Disease

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Background—Current guidelines recommend that patients with peripheral arterial disease (PAD) cease smoking and be treated with aspirin, statin medications, and angiotensin-converting enzyme (ACE) inhibitors. The combined effects of multiple guideline-recommended therapies in patients with symptomatic PAD have not been well characterized.

Methods and Results—We analyzed a comprehensive database of all patients with claudication or critical limb ischemia (CLI) who underwent diagnostic or interventional lower-extremity angiography between June 1, 2006 and May 1, 2013 at a multidisciplinary vascular center. Baseline demographics, clinical data, and long-term outcomes were obtained. Inverse probability of treatment propensity weighting was used to determine the 3-year risk of major adverse cardiovascular or cerebrovascular events (MACE; myocardial infarction, stroke, or death) and major adverse limb events (MALE; major amputation, thrombolysis, or surgical bypass). Among 739 patients with PAD, 325 (44%) had claudication and 414 (56%) had CLI. Guideline-recommended therapies at baseline included use of aspirin in 651 (88%), statin medications in 496 (67%), ACE inhibitors in 445 (60%), and smoking abstinence in 528 (71%) patients. A total of 237 (32%) patients met all four guideline-recommended therapies. After adjustment for baseline covariates, patients adhering to all four guideline-recommended therapies had decreased MACE (hazard ratio [HR], 0.64; 95% CI, 0.45 to 0.89; P=0.009), MALE (HR, 0.55; 95% CI, 0.37 to 0.83; P=0.005), and mortality (HR, 0.56; 95% CI, 0.38 to 0.82; P=0.003), compared to patients receiving less than four of the recommended therapies.

Conclusions—In patients with claudication or CLI, combination treatment with four guideline-recommended therapies is associated with significant reductions in MACE, MALE, and mortality. (J Am Heart Assoc. 2014;3:e000697 doi: 10.1161/JAHA.113.000697)

Key Words: atherosclerosis • claudication • peripheral vascular disease • prevention • statins
Adherence to Guideline-Recommended Therapy: Study Design and Methods

• Retrospective study utilizing the PAD-UCD Registry
• Comparison of outcomes for patients receiving all 4 guideline recommended therapies with those receiving less than 4 guideline-recommended therapies

Definitions

• MACE- Major adverse cardiovascular or cerebrovascular event (myocardial infarction, stroke, death)
• MALE- Major adverse limb event (lower extremity amputation or surgical bypass)

Armstrong, J. Am Heart Assoc. 2014.
36% Reduction in MACE

Hazard ratio, 0.64; 95% CI, 0.45-0.89; P=0.009

45% Reduction in MALE

Hazard ratio, 0.55; 95% CI, 0.37-0.84; P=0.005

Armstrong, J. Am Heart Assoc. 2014.
Mechanisms of Functional Impairment in Peripheral Artery Disease

Oxygen Delivery

Arterial Obstruction
Endothelial Dysfunction
Increased Blood Viscosity
Mitochondrial Dysfunction
Ischemia and Free Radical Creation

Oxygen Utilization

Progressive Atherosclerosis
Loss of Muscle Mass
Claudication & Functional Limitation
Cardiovascular Deconditioning

Inflammation

Potential Mechanisms of Benefit of Exercise in Peripheral Artery Disease

Oxygen Delivery

Induction of Angiogenesis
Increased Endothelial Dependent Vasodilatation
Reduced Blood Viscosity
Improved Mitochondrial Energetics / Metabolism
Reduced Ischemia and Reactive Oxygen Species

Oxygen Utilization

Improvement In Atherosclerotic Risk Factors
Improved Muscle Function
Improved Functional Capacity and Exercise Pain Tolerance
Improved Cardiovascular Conditioning

Inflammation

Marc P. Bonaca, and Mark A. Creager Circulation Research. 2015;116:1579-1598
Effect of exercise on pain-free walking time in peripheral artery disease (PAD).

Marc P. Bonaca, and Mark A. Creager Circulation Research. 2015;116:1579-1598
Schematic of oral antiplatelet therapies and their targets.

Marc P. Bonaca, and Mark A. Creager Circulation Research. 2015;116:1579-1598
Effects of Vorapaxar in PAD

Limb Vascular Events in Symptomatic* PAD Patients at 3 Years in TRA²P-TIMI 50

Vorapaxar vs Placebo

HR 0.84 (0.73 – 0.97)
HR 0.58 (0.39 – 0.86)

82% on Statin
97% on background Antiplatelet therapy

Marc P. Bonaca, and Mark A. Creager Circulation Research.
2015;116:1579-1598
Smoking cessation and incident peripheral artery disease (PAD).

Marc P. Bonaca, and Mark A. Creager Circulation Research.
2015;116:1579-1598
Smoking and PAD

• Smoking is the single most important risk factor for the development and progression of PAD
• Among patients with PAD, 80% report being a current or past smoker
• Risk of PAD among smokers is 3 to 6 times higher than among nonsmokers
• PAD patients who achieve abstinence have far higher survival rates than those who do not
Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease

Ehrin J. Armstrong, MD, MS, a Julie Wu, BS, b Gagan D. Singh, MD, b David L. Dawson, MD, c William C. Pevec, MD, c Ezra A. Amsterdam, MD, b and John R. Laird, MD, b Aurora, Colo; and Sacramento, Calif

Objective: Although smoking cessation is recommended for all patients with peripheral artery disease, there are little data regarding the prevalence of smoking among patients at the time of angiography or the effect of smoking cessation on clinical outcomes.

Methods: Consecutive patients with claudication or critical limb ischemia who underwent peripheral angiography from 2006 to 2013 were included in an observational cohort analysis. Smoking status was assessed at the time of angiography and during follow-up clinic visits. Kaplan-Meier analysis was used to assess the relationship between smoking cessation, mortality, and amputation-free survival.

Results: Among 739 patients (423 men and 316 women; mean age, 60 ± 12 years), 204 (28%) remained active smokers at the time of lower extremity angiography. At the time of angiography, the mean number of cigarettes smoked per day was 16 ± 10, and the mean pack-years was 40 ± 25. During the course of the subsequent year, 61 patients (30%) successfully quit smoking and maintained continued abstinence. Baseline medication use between groups did not differ significantly. The mean ankle-brachial index was also similar for quitters vs nonquitters (0.53 ± 24 vs 0.49 ± 0.22; P = .3). During follow-up to 5 years, patients who quit smoking had significantly lower all-cause mortality (14% vs 31%; hazard ratio, 0.40; 95% confidence interval, 0.18-0.90) and improved amputation-free survival (81% vs 60%; hazard ratio, 0.43, 95% confidence interval, 0.22-0.86) compared with patients who continued smoking, with most of the difference driven by reduced mortality among patients who quit smoking. The findings remained significant on multivariable analysis.

Conclusions: Approximately one-third of active smokers with peripheral artery disease successfully quit smoking within 1 year after lower extremity angiography. Patients who quit smoking have lower mortality and improved amputation-free survival compared with patients who continue smoking. (J Vasc Surg 2014;60:1565-71.)
Smoking Cessation

**UCD PAD Registry**

- Among 739 patients with claudication or CLI, 204 (28%) remained active smokers at the time of LE angiography
- Mean number of cigs/day 16, mean pack-years 40
- In subsequent year, 61 (30%) patients successfully quit smoking
Dramatic difference in survival for patients with critical limb ischemia!

![Graph showing survival rates for continued smoking and quitting smoking over a follow-up period of 1000 days. The graph indicates a significant difference in survival rates, with a hazard ratio (HR) of 0.34 (95% CI 0.13 - 0.88).]
From the Peripheral Vascular Surgery Society

Statin therapy is associated with superior clinical outcomes after endovascular treatment of critical limb ischemia

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Objective: The aim of this study was to determine if statin therapy improves clinical outcomes after endovascular intervention in patients with critical limb ischemia (CLI).

Methods: A retrospective review of all patients undergoing endovascular treatment for CLI was performed. Two groups were created according to whether they were receiving statin therapy at the time of intervention. Demographics, lesion morphology, overall mortality, primary and secondary patency, and limb salvage were compared between these groups. Analysis was performed using multivariate regression and Kaplan-Meier analysis.

Results: Between 2004 and 2009, 646 patients, 319 receiving statin therapy and 327 without, underwent an endovascular intervention for CLI. The statin group had significantly higher rates of diabetes mellitus, coronary artery disease, congestive heart failure, previous myocardial infarction, and coronary artery bypass grafting (P < .05). The two groups had similar lesion length, location, lesion type, TransAtlantic Inter-Society Consensus (TASC) classification, and primary procedure. At 24 months, the statin-treated group had higher rates of primary patency (43% vs 33%; P = .007), secondary patency (66% vs 51%; P = .001), limb salvage (83% vs 62%; P = .001), and overall survival (77% vs 62%; P = .038). Statin therapy was also independently associated with improved limb salvage by multivariate regression analysis (hazard ratio, 2.55; P < .001).

Conclusions: Patients who were receiving statin therapy when they underwent interventions to treat CLI had significantly improved overall survival, primary and secondary patency, and limb salvage rates. Our findings suggest that statins should be part of the periprocedural treatment regimen and support further investigation into the beneficial effects of statins in patients undergoing endovascular treatment of CLI. (J Vasc Surg 2012;55:371-80.)
Association Between Statin Medications and Mortality, Major Adverse Cardiovascular Event, and Amputation-Free Survival Rates in Patients With Critical Limb Ischemia

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Objectives
The aim of this study was to determine the associations between statin use and major adverse cardiovascular and cerebrovascular events (MACCE) and amputation-free survival in critical limb ischemia (CLI) patients.

Background
CLI is an advanced form of peripheral arterial disease associated with nonhealing arterial ulcers and high rates of MACCE and major amputation. Although statin medications are recommended for secondary prevention in peripheral arterial disease, their effectiveness in CLI is uncertain.

Methods
We reviewed 380 CLI patients who underwent diagnostic angiography or therapeutic endovascular intervention from 2006 through 2012. Propensity scores and inverse probability of treatment weighting were used to adjust for baseline differences between patients taking and not taking statins.

Results
Statins were prescribed for 246 (65%) patients. The mean serum low-density lipoprotein (LDL) level was lower in patients prescribed statins (75 ± 28 mg/dl vs. 96 ± 40 mg/dl, p < 0.001). Patients prescribed statins had more baseline comorbidities including diabetes, coronary artery disease, and hypertension, as well as more extensive lower extremity disease (all p values < 0.05). After propensity weighting, statin therapy was associated with lower 1-year rates of MACCE (stroke, myocardial infarction, or death; hazard ratio [HR]: 0.53; 95% confidence interval [CI]: 0.28 to 0.99), mortality (HR: 0.49, 95% CI: 0.24 to 0.97), and major amputation or death (HR: 0.53, 95% CI: 0.35 to 0.98). Statin use was also associated with improved lesion patency among patients undergoing infrapopliteal angioplasty. Patients with LDL levels >130 mg/dl had increased HRs of MACCE and mortality compared with patients with lower levels of LDL.

Conclusions
Statins are associated with lower rates of mortality and MACCE and increased amputation-free survival in CLI patients. (J Am Coll Cardiol 2014;63:682–90) © 2014 by the American College of Cardiology Foundation
Decreased Hazard of MACCE in Statin Group


Very high LDL is bad!

Unadjusted Propensity Weighted HR 0.51 (95% CI 0.28 - 0.94)
Statin Therapy in PAD

Limb Vascular Events in Symptomatic* PAD Patients at 4 Years in the REACH Registry

<table>
<thead>
<tr>
<th>Event</th>
<th>No Statin</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.83</td>
<td>0.64</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.72–0.95)</td>
<td>(0.48–0.86)</td>
</tr>
<tr>
<td>Kaplan-Meier (%) at 4 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Perip. Revasc</td>
<td>18.2</td>
<td>21.7</td>
</tr>
<tr>
<td>Amputation</td>
<td>3.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Marc P. Bonaca, and Mark A. Creager Circulation Research. 2015;116:1579-1598
Association of dual-antiplatelet therapy with reduced major adverse cardiovascular events in patients with symptomatic peripheral arterial disease

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Objective: This study was conducted to determine whether there is additive benefit of dual-antiplatelet therapy (DAPT) with aspirin (acetylsalicylic acid [ASA]) and clopidogrel compared with ASA monotherapy among patients with symptomatic peripheral arterial disease.

Methods: This was an observational cohort analysis that included 629 patients with claudication or critical limb ischemia. The prevalence of patients taking ASA monotherapy vs DAPT was assessed monthly for up to 3 years. A propensity model was constructed to adjust for baseline demographic characteristics and to assess the effect of DAPT on major adverse cardiovascular events (MACEs) and major adverse limb events.

Results: At baseline, 348 patients were taking DAPT and 281 were taking ASA monotherapy. During 3 years of follow-up, 50 events (20%) occurred in the DAPT group vs 59 (29%) in the ASA monotherapy group. After propensity weighting, DAPT use was associated with a decreased risk of MACEs (adjusted hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.44-0.96) and overall mortality (adjusted HR, 0.55; 95% CI, 0.35-0.89). No association was found between DAPT use and the risk of major amputation (adjusted HR, 0.69; 95% CI, 0.37-1.29). In a subgroup of 94 patients who underwent point-of-care platelet function testing, 21% had decreased response to ASA and 55% had a decreased response to clopidogrel. No association was found between a reduced response to ASA or clopidogrel and adverse events at 1 year.

Conclusions: DAPT may be associated with reduced rates of MACEs and death among patients with symptomatic peripheral arterial disease. (J Vasc Surg 2015;62:157-65.)
Adjusted HR 0.65 (95% CI 0.44-0.96)

What Is Best Medical Therapy in PAD?

- **Asymptomatic PAD**
  - No Symptoms + No history of Peripheral Revascularization
  - ABI < 0.90

- **Symptomatic PAD**
  - Current Symptoms + ABI < 0.85 Peripheral Revasc.
  - History of Symptoms +

**Therapies for MACE Reduction**
- Lifestyle Modification
- Tobacco Cessation Therapies
- Statin therapy
- Blood Pressure control (ACEi or ARB preferred)
- Antiplatelet monotherapy may be beneficial in selected patients

**Therapies for Limb Vascular Event Risk Reduction**
- Statin therapy may be beneficial
- PAR-1 Antagonist for selected patients

**Therapies for Symptom Improvement**
- Exercise
- Cilostazol
- Statin therapy may be beneficial
- Revascularization

Marc P. Bonaca, and Mark A. Creager Circulation Research. 2015;116:1579-1598
Summary

• Appropriate medical care in patients with PAD is critically important to reduce the risk of major adverse cardiovascular events

• Adherence to guidelines based therapy does make a difference!

• We need more focused data on PAD patients specifically:
  – Post Endovascular Intervention
  – In addition to Endovascular Intervention
  – For symptomatic patients with PAD who do not need a revascularization
What is the Best Medical Therapy for PAD? Do We Need Better?

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