Medical management and exercise – Current state of the evidence in claudication

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Therapeutic Goals for PAD

• Reduce cardiovascular events
  – Statins
  – Smoking cessation
  – Anti-platelet therapy
  – Blood pressure control

• Increase pain-free walking distances
  – Supervised exercise
  – Revascularization
  – Medications

Statin Therapies to Reduce Cardiovascular Risk

• Statin medication is indicated for all patients with PAD to reduce cardiovascular risk
• Statins reduce risk of cardiovascular events by about 25%
Statin Therapies to Reduce Cardiovascular Risk in PAD
- Potent statins recommended at highest tolerated dose
  - Atorvastatin
  - Rosuvastatin
  - Simvastatin
- Generally safe and often well tolerated

Smoking Cessation
- Patients with PAD who smoke cigarettes or use other tobacco forms must be advised at every visit to quit smoking
- Develop a plan that includes pharmacotherapy
  - Varenicline
  - Bupropion
  - Nicotine replacement therapy
- Refer to a smoking cessation program

Anti-platelet therapy to reduce cardiovascular events
- Aspirin (75 to 325 mgs) or clopidogrel (75 mgs)
- Evidence does not support combined aspirin + clopidogrel to prevent CVD events in PAD
- Role of vorapaxar added to existing anti-platelet therapy for people with PAD is unclear

Vorapaxar
- Novel anti-platelet agent
- Antagonist of protease-activated receptor-1 (PAR-1)
- PAR-1 receptors exist on
  - Platelets (activation)
  - Vascular endothelium
  - Smooth muscle
Vorapaxar

- No effect on cardiovascular event rates in people with PAD
- Reduced rates of acute limb ischemia and lower extremity revascularization rates in PAD

Anti-coagulation to prevent cardiovascular events

- Anti-coagulation is not indicated to reduce cardiovascular events in patients with PAD.
- Associated with increased risk (bleeding)

Anti-Hypertensive Therapy

- Anti-hypertensive therapy should be administered to people with PAD and HTN to reduce risk of cardiovascular events.
- ACE Inhibitors and ARBs may be particularly effective in preventing cardiovascular events in PAD.

Medical Management to Improve walking ability in PAD patients with claudication
Cilostazol

- Phosphodiesterase type 3 inhibitor
- Vasodilator
- Anti-platelet properties
- Provides modest benefit- about 40% improvement in treadmill walking
- Side effects common
  - Headache, palpitations, diarrhea, lightheadedness

Cilostazol and Pentoxifylline for PAD


Supervised Treadmill Exercise for PAD

2012 meta-analysis

- 25 Randomized Clinical Trials
- Supervised treadmill exercise vs. control
- 1,054 patients with claudication
- Program length: 4-104 weeks

Characteristics of More Effective Supervised Walking Exercise Programs in PAD

- Exercise Frequency: > 3 times weekly.
- Exercise duration: > 30 minutes per session.
- Walking to maximal claudication pain may be best.
- Program duration of at least six months.

2017 Proposed Decision Memorandum from CMS

- “Evidence is sufficient to provide coverage for patients with symptoms of intermittent claudication to treat peripheral artery disease.”

CMS coverage of supervised exercise for claudication

- 12-week sessions
- Additional 36 sessions may be obtained with justification
- Three sessions/week
- Hospital or out-patient hospital setting
- Delivered by qualified personnel with basic and advanced cardiac life support training and training in exercise for PAD
- Must take place under direct supervision of a physician

What is needed to implement supervised treadmill exercise for claudication

- Treadmill for exercise training
  - Treadmills starting at 0.50 miles per hour
- Exercise physiologist or RN
- Cardiac rehabilitation programs can administer supervised exercise to PAD patients
- Cardiac stress test prior to exercise
Prescription for Supervised Treadmill Exercise

- Three times weekly exercise
- Start with 15 minutes of walking time per session
- Increase walking time each week by 5 minutes
- Goal is 45 to 60 minutes of treadmill walking per session

Summary:
Supervised Treadmill Exercise

- Supervised treadmill exercise improves treadmill walking performance in PAD
- Improvement is observed 4-12 weeks after onset of exercise
- Even with medical insurance, attendance three times weekly can be a challenge

2016 Clinical Practice Guidelines for Home-based exercise for PAD

- Practice Guidelines: Class IIA, Level of Evidence A
- Home based exercise is reasonable to prescribe to improve walking performance in PAD.

12-week home-based exercise program in PAD

- 180 participants.
- Randomized to supervised treadmill exercise, home-based walking exercise, or control.
- 12 week home-based walking exercise intervention
  - Three days walking per week.
  - Medical center visits once monthly
  - Step-counter used to provide feedback.

Gardner RE et al. J Am Heart Assoc
2014;3:e001107
Change in peak treadmill walking time by supervised vs. home-based exercise

![Graph showing change in peak treadmill walking time (seconds) for control, supervised, and home conditions.](image)

Overall P value < 0.001*  
P < 0.05 vs. control  
P < 0.05 vs. control


Home based exercise improves six minute walk distance more than supervised exercise

![Graph showing 6MWT total distance (m) for control, supervised, and home conditions.](image)

Overall P value = 0.028*  
P < 0.05 vs. control  
P < 0.05 vs. supervised


Summary: Home-based walking exercise

- Growing evidence suggests that home-based exercise has benefit for PAD
- Successful programs incorporate behavioral change strategies
- Effective programs have patients return to the medical center at least once monthly for feedback

How to Implement Home-Based Exercise in PAD

- Advise participants to walk for exercise at least three – preferably 4/5 days per week
- Start with 10-15 minutes per session of exercise
- Increase walk time by 5 minutes each week
- Set goals
- Monitor progress
- Activity monitor may help
Home-based exercise: Additional considerations

- Successful home-based programs require behavioral change interventions
- Requires more self-motivation
- Not as easy to ‘prescribe’
- Improves over ground walking more than supervised treadmill exercise
- Benefits may be more durable than supervised exercise

Summary: Exercise for PAD

- Walking exercise is effective for patients with PAD
  - Supervised
  - Home-based
- CMS coverage likely coming soon for supervised exercise
- Home-based therapies require behavioral change techniques
  - Important long-term therapeutic option

Strength Training in PAD

- Improves treadmill walking in PAD
- Not as effective as walking exercise
- Improves quality of life and patient perceived walking

SILC Trial: Changes in 6 minute walk performance by group among PAD participants with and without intermittent claudication

- Pair-wise P-value (diet vs. strength)
- Pair-wise P-value (diet vs. treadmill)

SILC Results: Change in treadmill walking performance among PAD participants with and without claudication

<table>
<thead>
<tr>
<th>Change in Performance (Meters)</th>
<th>Diet N=39</th>
<th>Strength N=41</th>
<th>Treadmill N=45</th>
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<tr>
<td>* P-value = 0.001</td>
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Pair-wise P-value (diet vs. strength); Pair-wise P-value (diet vs. treadmill)

Upper and Lower Extremity Ergometry Exercise in PAD

Randomized Controlled Trial: Upper Limb Ergometry in Peripheral Arterial Disease Patients

- 104 patients with PAD
- Randomized:
  - to upper-limb aerobic ergometry exercise
  - lower limb aerobic ergometry exercise
  - control
- 24 week follow-up
  - Outcomes measured every six weeks
- Primary outcomes:
  - Absolute walking distance
  - Time to onset of claudication

Statistical significance:
* P < .05; ** P < .01: indicates significantly higher than control patients;
*†† P < .01: indicates significantly higher than baseline

Ergometry improves maximum walking distance in PAD patients with claudication (N=104)
Conclusions Ergometry Exercise

- Arm and leg ergometry exercise improve treadmill walking performance in PAD participants.
- Mechanism may be related to improved oxygen uptake and delivery to muscle.

Novel Medical Therapies for Claudication

- Angiotensin Receptor Blockers (Telmisartan)
- Granulocyte macrophage colony stimulating factor (GM-CSF)
- Epicatechin-rich cocoa
- Metformin

In pre-clinical models, telmisartan...

- Improves skeletal muscle contractile properties
  - Increases PPARδ
  - Regulates myofiber metabolic and contractile activity
- Improves skeletal muscle mitochondrial function.
  - Increases AMPK
- Increases muscle perfusion

Pilot study of telmisartan for PAD

- 36 patients with PAD
  - Stage Fontaine II
- Randomized:
  - Telmisartan 40/80 mg once daily
  - Placebo
- 12 month follow-up
- Primary Endpoint:
  - Maximal treadmill walking distance
- Secondary Endpoints
  - Flow-mediated vasodilation (FMD)
  - Ankle-brachial index (ABI)
  - Disease-related quality of life (DRQL)

**Telmisartan vs. placebo for intermittent claudication**

Primary Outcome: Change in Maximum Treadmill Walking Distance (P<0.001)

![Graph showing change in maximum treadmill walking distance over time for treatment groups Telmisartan and Placebo.]


**Summary Telmisartan**

- A pilot study of telmisartan suggests benefit for patients with PAD
  - Improves treadmill walking performance.
  - Improves brachial artery flow-mediated dilation.
- More evidence is needed.

**Granulocyte Macrophage Colony Stimulating Factor for PAD**

- Increases circulating progenitor cells
  - Progenitor cells promote vascular repair
  - Progenitor cells improve endothelial function
  - Progenitor cells promote angiogenesis

**GM-CSF for Peripheral Artery Disease**

- 159 participants with PAD and claudication randomized to GM-CSF vs. placebo
- GM-CSF delivered subcutaneously
  - 3 x weekly
  - 4 weeks
  - Self-administered
- Outcomes measured at 3 and 6 month F/Up
- Primary Outcome: Maximal treadmill walking time

**GM-CSF vs. Placebo: Maximal Treadmill Walking Time (N=159)**

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<th>GM-CSF</th>
<th>PLACEBO</th>
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<td>6 Month</td>
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**GM-CSF for Claudication**

- Improved WIQ distance score in GM-CSF group at 3-month follow-up (P=0.047)
- Improved SF-36 physical functioning score at 3 month follow-up (P=0.03).
- No improvement from GM-CSF for WIQ stair climbing or walking speed.
- No improvements in WIQ scores or quality of life at 6 month follow-up.


**ALDH Bright Cells are not effective for Claudication**

**ALDH Bright Cells for Claudication**

Post-hoc analyses suggested increases in collateral vessels in patients with occluded femoral arteries

GM-CSF CONCLUSIONS

• Current data on G-CSF/GM-CSF for PAD are largely negative (no benefit)

• PROPEL trial to test combination of exercise + GM-CSF- results available in 2017

CONCLUSIONS

• Medications can reduce cardiovascular event rates effectively.

• More medical therapies for improving functioning in PAD are needed.

• Exercise is the most effective medical therapy for PAD

• CMS coverage of supervised exercise likely coming soon.