PAD Care Coordination

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  Massachusetts General Hospital, Boston, MA
Case for Care Coordination

Lower extremity PAD is prevalent, management is variable, and patient outcomes are suboptimal

• **CLI 1 year outcomes:**
  - 25% mortality rate
  - 30% amputation rate
  - 20% persistent CLI

• **PAD 5 year outcomes:**
  - 70-80% with stable claudication
  - 10-20% with worsening claudication
  - 5-10% with CLI
  - 20% non-fatal MI or CVA
  - 10-15% mortality rate

Norgren et al. Eur J Vasc Endovasc Surg 2007
Case for Care Coordination

Large economic burden on health care system

Mahoney et al. Circ Cardiovasc Qual Outcomes 2010
Mozaffarian et al. Circulation 2015
Multidisciplinary care in PAD
Moving toward a “team based” approach

Agrawal S et al. J Am Coll Cardiol 2016
Shishehbor et al. JACC 2016
Goals of Care Coordination

Increase awareness among patients and providers

- Asymptomatic
- Atypical pain
- Typical claudication

Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care

- Study designed to address feasibility of detecting PAD in primary care clinics, physician / patient awareness of PAD, and intensity of risk factor management
- Only 83% of patients and 49% of physicians aware of PAD diagnosis

Hirsch et al. JAMA 2001
Goals of Care Coordination
Improved screening of “at risk” patients

In CLI → 29% can have normal or near normal ankle brachial index (ABI)

- Toe brachial index (TBI) with waveforms
- Transcutaneous oximetry (TCPO2)
- Skin perfusion pressure (SPP)

ABI values in cohort of patients who underwent coronary angiography

Increased risk for PAD
- Age >65
- Age 50-64 with risk factors¹ or family history
  - HTN, HL, DM, tobacco
- Age <50 with DM and 1 other risk factor
- Known vascular disease elsewhere

¹HTN, HL, DM, tobacco

Crique et al. Circ Res 2015
Bunte et al. Vasc Med 2015
Lee et al. JACC Cardiovasc Interven 2013
Goals of Care Coordination

Improve risk factor control/guideline directed medical therapy

Antiplatelet agents:
- Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD
  - Meta-analysis of 135,000 high-risk patients with 22% odds reduction in favor of aspirin use
  - Clopidogrel may be superior to aspirin in PAD subgroup (CAPRIE)
  - Dual-antiplatelet therapy may have slight additional benefit with increased bleeding risk in PAD patients (CHARISMA substudies)
  - Novel agents have not shown significant net benefits (no benefit to ticagrelor in EUCLID, benefit vs bleeding risk for Vorapaxar)

Statin therapy:
- Treatment with a statin medication is indicated for all patients with PAD
  - Reduces claudication/improve walking distance, reduces noncoronary revascularization/amputation/PAD death (HPS)

Antihypertensive therapy:
- Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death
  - ACE and ARB can reduce cardiovascular ischemic events in patients with PAD (HOPE, ONTARGET)

Smoking cessation:
- Patients with PAD who smoke cigarettes or use other forms of tobacco should quit

Glycemic control:
- Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.

Anticoagulation/Other:
- Cilostazol improves walking distance, whereas pentoxifylline does not
- Warfarin anticoagulation does not seem to be helpful in PAD patients; may be weak signal in autologous vein bypass grafts (BOA trial)
- Rivaroxaban anticoagulation may play a role in medical management of peripheral arterial disease (COMPASS)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Design</th>
<th>Pharmacologic Agents</th>
<th>Results</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td><strong>Antithrombotic Trialists’ Collaboration</strong>&lt;br&gt;2002</td>
<td>Meta Analysis – study effect of antiplatelet agents in patients at high risk for vascular events&lt;br&gt;N=135,000</td>
<td>1) Antiplatelet&lt;br&gt;2) Control</td>
<td>Nonfatal, MI, nonfatal CVA, vascular death:&lt;br&gt;5.8% vs. 7.1% (23% odds reduction in PAD cohort)</td>
<td>Included trials of antiplatelet vs. control or one antiplatelet vs. another one&lt;br&gt;In each subset, vascular benefit exceeded risk of major extracranial bleeding&lt;br&gt;Daily doses 75-150mg at least as effective as higher doses</td>
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<td><strong>CAPRIE</strong>&lt;br&gt;1996</td>
<td>RCT – Assess benefit of ASA vs. clopidogrel in reducing vascular events&lt;br&gt;Inclusion: recent ischemic CVA, MI, or symptomatic PAD&lt;br&gt;N=19,185&lt;br&gt;Mean follow up 1.91 years</td>
<td>1) Aspirin 325 mg daily&lt;br&gt;2) Clopidogrel 75mg daily</td>
<td>Primary outcome: composite of ischemic CVA, MI, or vascular death:&lt;br&gt;5.32% vs. 5.83% (p=0.043, RRR 8.7%) favoring clopidogrel in ITT analysis&lt;br&gt;Driven by 23.8% RRR in PAD group</td>
<td>Increased incidence of bleeding events in ASA group, primarily driven by GI bleed</td>
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<td><strong>CHARISMA</strong>&lt;br&gt;2006</td>
<td>RCT – Effect of DAPT in patients at high risk of atherothrombotic events&lt;br&gt;Inclusion: documented CAD, CVD, PAD, or multiple atherothrombotic risk factors&lt;br&gt;N=15,603&lt;br&gt;Median follow up 28 months</td>
<td>1) Aspirin 75-162 mg daily + clopidogrel 75 mg daily&lt;br&gt;2) Aspirin 75-162 mg daily + Placebo</td>
<td>Primary outcome: composite of MI, CVA, or CV death:&lt;br&gt;6.8% vs. 7.3% (p=0.22)&lt;br&gt;Severe bleeding:&lt;br&gt;1.7% vs. 1.3% (p=0.09)</td>
<td>Similar severe bleeding though increased moderate bleeding in DAPT group&lt;br&gt;Suggestion of benefit to DAPT with clinically evident atherothrombotic disease and harm if asymptomatic</td>
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<td><strong>EUCLID</strong>&lt;br&gt;2017</td>
<td>RCT – Evaluate outcomes with clopidogrel vs. ticagrelor in patients with PAD&lt;br&gt;Inclusion: symptomatic PAD with ABI≤0.8 or prior revascularization&lt;br&gt;N=13,885&lt;br&gt;Median follow up 30 months</td>
<td>1) Ticagrelor 90 mg BID&lt;br&gt;1) Clopidogrel 75mg daily</td>
<td>Primary outcome: composite of MI, CVA, or CV death:&lt;br&gt;10.8% vs. 10.6% (p=0.65)&lt;br&gt;Major bleeding:&lt;br&gt;1.6% in both groups</td>
<td>Primarily patients with claudication&lt;br&gt;4.6% CLI</td>
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<td><strong>TRA 2P-TIMI 50</strong>&lt;br&gt;2012</td>
<td>RCT – Determine safety/efficacy of vorapaxar in reducing atherothrombotic events in patients with known vascular disease on GDMT&lt;br&gt;Inclusion: prior MI, ischemic CVA, PAD&lt;br&gt;N=26,449&lt;br&gt;3-year follow up data reported</td>
<td>1) Vorapaxar 2.5 mg daily&lt;br&gt;2) Placebo</td>
<td>Primary outcome: composite of MI, CVA, or CV death:&lt;br&gt;9.3% vs. 10.5% (HR 0.87, p&lt;0.001)&lt;br&gt;Moderate or severe bleeding:&lt;br&gt;4.2% vs. 2.5% (HR 1.66, p&lt;0.001)&lt;br&gt;Intracranial hemorrhage:&lt;br&gt;1% vs. 0.5% (p&lt;0.001)&lt;br&gt;Net clinical outcome (efficacy outcome + bleeding):&lt;br&gt;11.7% vs. 12.1% (p=0.4)</td>
<td>Vorapaxar selectively inhibits thrombin via PAR-1 antagonism&lt;br&gt;94% on ASA at baseline. Minority on thienopyridine unless prior MI&lt;br&gt;DSMB recommended stopping study if history of CVA at 2 years due to increased ICH risk</td>
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<td>WAVE</td>
<td>RCT – Assess role of oral anticoagulants (OAC) in reducing CV events in PAD patients</td>
<td>1) Antiplatelet + warfarin • INR 2-3 2) Antiplatelet + control</td>
<td>Primary outcome: MI, CVA, CV death: 12.2% vs. 13.3% (p=0.48) Primary outcome: MI, CVA, CV death, severe ischemia leading to urgent revascularization: 15.9% vs. 17.4% (p=0.37) Life threatening bleeding: 4% vs. 1.2% (RR=3.41, p&lt;0.001)</td>
<td>1.3% ICH rate in oral anticoagulant group INR data: Mean 2.2 Therapeutic 62% Subtherapeutic 30.8% Supratherapeutic 7.2% Oral anticoagulants not indicated due to lack of benefit and increased bleeding</td>
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<td>BOA</td>
<td>RCT – Assess role of OAC compared with ASA in terms of preventing infrainguinal bypass graft occlusion</td>
<td>1) OAC • INR 3-4.5 2) ASA</td>
<td>Graft occlusion: 13.5% vs. 14.2% (p=NS) Major bleeding: 4.7% vs. 2.5%</td>
<td>0.6% ICH with OAC INR therapeutic ~50% of time Suggestion of benefit to OAC in vein graft subset No difference in vascular death, non-fatal MI, non-fatal CVA, or amputation</td>
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<td>COMPASS</td>
<td>RCT – Evaluate role of rivaroxaban alone or in combination with ASA in secondary prevention of CV events</td>
<td>1) ASA 100 mg daily + rivaroxaban 2.5 mg BID 2) Rivaroxaban 5 mg BID 3) ASA 100 mg daily</td>
<td>Primary outcome: composite of MI, CVA, or CV death: 4.1% vs. 5.4% for ASA + rivaroxaban vs. ASA (p=0.001) 4.9% vs. 5.4% for Rivaroxaban vs. ASA (p=NS)</td>
<td>Study terminated early by DSMB due to benefit in ASA + rivaroxaban group Also decrease in major amputation with ASA + rivaroxaban</td>
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<td></td>
<td>Substudy to look at limb events</td>
<td></td>
<td>PAD subgroup (ASA+rivaroxaban vs. ASA): MALE: 1% vs. 2% (HR 0.54, p=0.0054) Amputation: &lt;1% vs. 1% (HR 0.4, p=0.0069)</td>
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Goals of Care Coordination

Improve adherence to guideline-directed therapies

- Supervised Exercise Programs (SEP) has shown demonstrable benefit in parameters of functional status, QOL, and cost-effectiveness
- Improved functional status, in turn, has been linked to preservation of mobility in longitudinal follow up

➢ YET

- Availability and utilization remains low
  ➢ In predominantly European survey only 30% of patients had access to SEP and <50% of providers referred more than half their eligible patients

- May improve with recent approval for CMS reimbursement

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<thead>
<tr>
<th>Treatment</th>
<th>Adherence</th>
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<tr>
<td>ASA</td>
<td>88%</td>
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<tr>
<td>Statin</td>
<td>67%</td>
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<tr>
<td>ACE</td>
<td>60%</td>
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<tr>
<td>Tobacco abstinence</td>
<td>71%</td>
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</tbody>
</table>

Adherence associated with significant reduction in MACE and MALE
Goals of Care Coordination
Create programs and facilitate referrals to exercise programs

• Level 1 evidence supporting exercise programs (SEP)¹
  • Supervised exercise program – takes place in a hospital or outpatient facility
  • Structured community- or home-based exercise program – takes place in the personal setting of the patient rather than in a clinical setting

• Supervised exercise program design
  • Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest. Minimum of 30 to 45 min per session, at least 3 times/wk for a minimum of 12 wk (36-46). Goal is to progress to these levels over time.¹

• Randomized data to support. CMS recently approved
  • CLEVER, ERASE studies²,³
  • Home-based walking exercise programs can be effective⁴

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¹ Gerhard-Herman MD et al. 2016 AHA/ACC Guidelines
² Murphy TP et al. Circ 2012
³ Fakhry F et al. JAMA 2015
⁴ McDermott MM et al. JAMA 2013
Goals of Care Coordination

Development of “Centers of Excellence” for CLI care

Clinical Outcomes vs. LER Volume

LER Volume vs. Distance

Clinical Outcomes vs. Distance

Amputation Odds Ratio

30 Day Mortality

LER Quintile

Medhekar et al. J Vasc Surg 2017
Prompt revascularization is imperative
Efficient high-quality care saves lives and limbs

- Having vascular interventionalists (cardiologist, vascular medicine practitioners, radiologists, surgeons) with expertise is essential
- 40% of medically-managed CLI patients will require amputation at 6 months
- 30% major amputation and 25% mortality 1 year following CLI diagnosis
  - Reduced drastically by prompt revascularization and initiation of CV risk reduction therapies
    - 91% reduction in amputation rates when patients received diagnostic angiogram¹
    - Significant MACE/MALE reduction with adherence to guideline-directed therapies²
- Billions of dollars in Medicare expenditures allocated to managing complications of CLI

Goodney et al. Circ Cardiovasc Quality Outcomes 2012
Averting Amputation is Important

*High mortality, re-intervention, and loss of mobility*

- Approximately 25% of patients with CLI get primary amputation
  - Vary by race, ethnicity, socioeconomic status
  - Higher incidence with Medicare, Medicaid, and uninsured status
- Why important:
  - High morbidity/mortality after amputation
    - 70% mortality at 3 years
  - High rates of recurrent amputation
    - Up to 30% at 2 years
  - Decreased mobility / QOL
    - Only 40% regain full mobility
  - Huge economic burden:
    - Cost exceeding $4.3 billion annually

Goals of Care Coordination

Employ strategies to promote efficient wound healing

➢ 56% readmission rate
➢ 14% within 30 days

➢ Result:
  ➢ Increased MALE/mortality
  ➢ Increased cost

Reed et al. JAHA 2016
Wound care

Overview

- Arterial and venous ulcers share some pathophysiology
- Effective wound healing decreases amputation rate
- Multidisciplinary Team approach
  - Vascular Surgery
  - Vascular Medicine
  - Vascular Interventionist
  - Infectious Disease specialists
  - Orthopedic surgery
  - Endocrinology
  - Internal Medicine
  - Podiatry
  - Wound Clinic (RNs, NPs)

- Gerhard-Herman MD et al. 2016 AHA/ACC Guidelines
Wound Healing

Another argument for multidisciplinary care coordination

- Most (limited) data derive from patients with venous disease.
  - Major difference in arterial wounds is the need to address optimizing perfusion first.
- WIFI classification can be a useful tool to predict limb salvage and wound healing\(^1\)
- There are many strategies for wound care.
  - Data supporting any particular strategy are weak
  - There are marked variations in wound care\(^2\)
  - Efforts should focus on assessing products and practices and shifting resource from those with little/no evidence to evidence-based strategies\(^2\)
- Care coordination/Multidisciplinary wound care seems superior
  - Involving multiple disciplines, such as podiatry, in wound care clinic seems more effective than “standard” wound care\(^3,4\)
  - Improves wound healing, reduces amputation\(^3,4\)
- Hyperbaric oxygen therapy remains debated, but approved in diabetic foot ulcers\(^5,6\)

1 Zhan et al, J Vasc Surg 2015
2 Gray TA et al, BMJ Open 2018
4 Driver VR et al, J Am Podiatr Med Assoc 2010
5 Stoekenbroek R et al, Eur J Vasc Endovasc Surg 2014
6 DAMO2CLES Study, Santenana KTB et al, Diabetes Care 2018
Andersen CA et al, J Vasc Surg 2010
Wound Healing

Wound, Ischemia, and foot Infection (WIFI Classification)

Wound*

0: no ulcer and no gangrene
1: small ulcer and no gangrene
2: deep ulcer or gangrene limited to toes
3: extensive ulcer or gangrene

Ischemia**

Grade | ABI | Ankle Systolic Pressure | Toe pressure/TCPO2
0  | ≥0.8 | >100mmHg | ≥260mmHg
1  | 0.6-0.79 | 70-100mmHg | 40-59mmHg
2  | 0.4-0.59 | 50-70mmHg | 30-39mmHg
3  | ≤0.39 | <50mmHg | <30mmHg

Foot infection***

0: noninfected
1: mild (<2cm cellulitis)
2: moderate (>2cm cellulitis / purulence)
3: severe (systemic response / sepsis)

a. Estimate risk of amputation at 1 year for each combination

b. Estimate likelihood of benefit of requirement for revascularization (assuming infection can be controlled first)

FL. Foot Infection; I. Ischemia; W. Wound.

Premises:
1. Increase in wound class increases risk of amputation (based on PEDIS, UT, and other wound classification systems)
2. PAD and infection are synergistic (Eurodiab): infected wound + PAD increases likelihood revascularization will be needed to heal wound
3. Infection 3 category (systemic/metabolic instability): moderate to high-risk of amputation regardless of other factors (validated IDSA guidelines)

Four classes: for each box, group combination into one of these four classes

Very low = VL = clinical stage 1
Low = L = clinical stage 2
Moderate = M = clinical stage 3
High = H = clinical stage 4

Clinical stage 5 would signify an unsalvageable foot

Lower Extremity Ulcers

Diverse etiology with need for specialized management more important than type of treatment

**Local factors:**
- Wound Infection
- Traumatized Tissue
- Foreign Bodies
- Pressure
- Ongoing Maceration
- Ischemia
- Contamination (Urine/Feces)

**Systemic factors:**
- Diabetes
- Anemia
- Malnutrition
- Immunodeficiency
- Stress
- Smoking
- Age
- Chronic Diseases (Anemia)

Gray TA et al. BMJ Open 2018
Post-Procedure Surveillance

Significant variability among providers. One possible strategy.

• **Prior to Discharge:**
  - ABI / PVR and/or DUS
  - Consider use of toe brachial index (TBI) with waveforms, transcutaneous oximetry (TCPO2), or skin perfusion pressure (SPP)
  - Correction of clinically relevant issues prior to discharge

• **After discharge:**
  - Clinical assessment and duplex US at 1 month, q6 months for 1st year, then yearly
    - Guideline-driven recommendation for infrainguinal autogenous vein bypass grafts
      - Identify high-grade stenosis (PSV >300 cm/sec or PSV ratio >3.5) or impending graft failure (PSV <40 cm/sec)
    - Lack of consensus for endovascular intervention or prosthetic bypass grafts
      - Reasonable to individualize based on patient factors, lesion location, type of intervention, and complexity
    - Prompt re-assessment for new or non-healing wound or change in symptom status

Gerhard-Herman MD et al. 2016 AHA/ACC PAD Guidelines
Post-Procedure Surveillance

Protocol

• Effective screening integrates comprehensive clinical assessment with imaging
  • Multiple options for imaging including DUS, ABI/PVR, TBI, SPP, TCPO2

• Goals:
  • Ensure adequate revascularization
  • Detection of procedural complications
  • Detection of ISR and new lesions that may compromise limb

• Modify based upon clinical situation:
  • Non healing wounds
  • New clinical symptoms