# PERIPHERAL ARTERY DISEASE IN CKD/ESRD

## *What The Nephrologist Ought To Know*

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## CONFLICT OF INTERESTS/DISCLOSURES

- None

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## Audience Response Question

- **Which Month Has Been Denoted PAD Awareness Month?**
- A) January
- B) March
- C) July
- D) September
- E) PAD doesn't have a month

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## Our Clinical Practice

- A 62 yo man on dialysis tells his nephrologist about a history of nonspecific right-leg pain and a non-healing ulcer on his foot. ESRD was due to HTN
- Before the start of of dialysis therapy 1 years ago, his ankle-brachial index (ABI) was 1.2 and further testing was not pursued given the absence of an ulcer and concerns regarding gadolinium and contrast exposure
- CT angiography- multi-segment right leg PAD, not amenable to revascularization
- After 6 months of wound care, analgesics, non–weight bearing, and antibiotics to treat wound infections, the ulcer fails to heal and progresses to gangrene, and the patient requires amputation of his foot.

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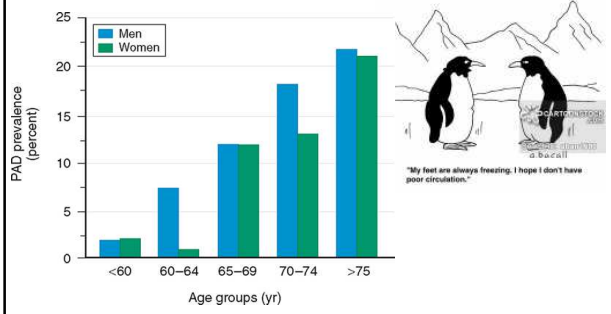
## WHAT IS PAD







AHA and Stroke Statistics—2004.
CDC Statistics 2007

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## EPIDEMIOLOGY OF PAD IN CKD AND ESRD

| Study | Population | Prevalence (%) | Diagnostic criteria |
|---|---|---|---|
| **Patients on dialysis** | | | |
| USRDS | 35,438 incident dialysis patients | 45.9 | Claims data |
| DOPPS | 29,873 prevalent hemodialysis patients | 25.3 | clinical* |
| HEMO | 936 prevalent hemodialysis patients | 23 | clinical* |
| Fishbane | 132 prevalent hemodialysis patients | 35 | ABI < 0.9 |
| Testa | 226 prevalent hemodialysis patients | 33 | ABI < 0.9 |
| **Patients with CKD stage 3 or more** | | | |
| NHANES | 211 participants with CrCl < 60mL/min/1.73 $m^2$ | 24 | ABI < 0.9 |
| CRIC | 3199 participants with eGFR < 60 mL/min/1.73 $m^2$ | 7.4<br>15.9 | Self reported history of PAD<br>ABI < 0.9 |
| CHS | 648 participants with kidney disease** | 12 | ABI < 0.9 |
| ARIC [24] | 376 participants with eGFR < mL/min/1.73$m^2$ | 8.6 incident cases/1000 person-years | clinical* and ABI <0.9 |

*Garimella et al, AJKD 2012*

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## PAD IS MORE PREVALENT THAN CVA OR A.FIB IN PERSONS ON DIALYSIS


- **Persons with ESRD and PAD are:**
  - More likely to die or lose limbs than GP
  - Less likely to be referred to specialists
  - Less likely to be considered for revasc.
  - Likely to do better with treatment despite all the above

Data Source: USRDS Annual Data Report 2014

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## RISK FACTOR FOR PAD IN CKD

- **Traditional Risk Factors**
  - Male sex
  - Smoking
  - Diabetes
  - Hypertension
  - Hyperlipidemia
- **Unique CKD risk factors**
  - Low eGFR
  - Albuminuria
  - Chronic Inflammation
  - Oxidative Stress
  - Homocysteine
  - Lipoprotein A
  - Ca x Phos
  - Arterial Stiffness

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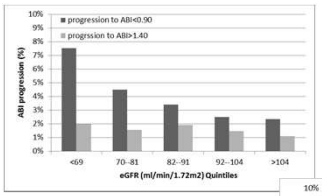
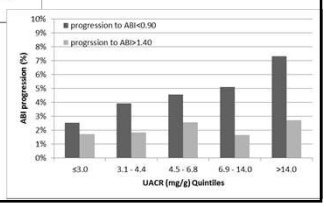
## KIDNEY DYSFUNCTION AND ALBUMINURIA INCREASE RISK OF PAD




Low eGFR is linearly associated with increased risk of developing low ABI




Albuminuria is a risk factor for both low ABI and high ABI

*Garimella et al, AJKD 2014*

## WHEN TO DIAGNOSE PAD
### Audience Response Question

- **According to current Kidney Guidelines, patients should be evaluated for PAD:**
- A) When they initiate dialysis
- B) Regularly
- C) When they complain of leg pain
- D) After development of critical limb ischemia
- E) No guidelines exist on evaluation of PAD in persons with Kidney Disease

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## WHEN TO DIAGNOSE PAD
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## HOW TO DIAGNOSE PAD

- Intermittent claudication: muscle pain or discomfort brought on by exercise and relieved by rest
  - Present in less than 15% who have PAD
  - Numerous confounding causes of pain in PAD (neuropathy, RLS)
- Poor lower extremity skin and hair integrity have been used in teaching to define an increased
  - Presence or absence is both insensitive and not specific
- **Abnormal pulses: provides adequate data for any clinician to proceed to establish a PAD diagnosis**

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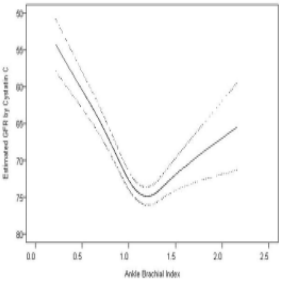
## ABI IN CKD AND ESRD



**U Shaped Association of GFR and ABI in the population**

*Ix*, JACC 2009

ABI of <0.9 are diagnostic for PAD

Values in the range of 0.9-1.0 are "not normal"

Prevalence of an ABI >1.3 is high in CKD (23%), ESRD (41%) and Tx (24%)

Medial arterial calcification (MAC) results in decreased vessel compressibility

**MAC can give a FALSE NORMAL ABI or ELEVATED ABI**

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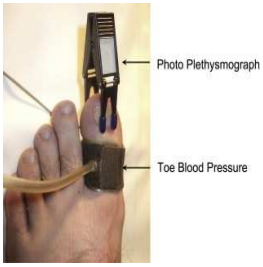
## OTHER DIAGNOSTIC MODALITIES




**TASCII and AHA/ACC guidelines recommend performing TBI when ABI >1.3**

- **Toe Brachial Index**
  - Toe arteries less effected by MAC
  - May be useful in ruling out disease or detecting distal small vessel PAD
  - Studies show high ABI and PAD can co-exist
- **Duplex USG**
- **Digital Subtraction Angio**
- **Conventional Angio**
- **MR Angio**
- **Skin perfusion**

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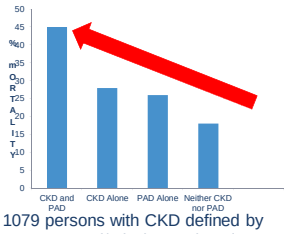
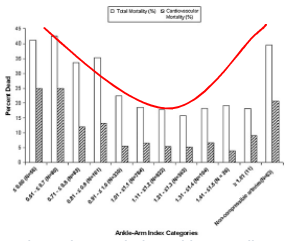
## PAD AND CKD: A DEADLY COMBINATION




1079 persons with CKD defined by eGFR < 60ml/min (MDRD) and PAD (ABI <0.9)

Increasing 6 year mortality with both CKD and PAD



U Shaped association with mortality and ABI in general population

How about in CKD and ESRD?

*Liew et al*, CJASN 2008
Sutton-Tyrrell, Stroke 2008

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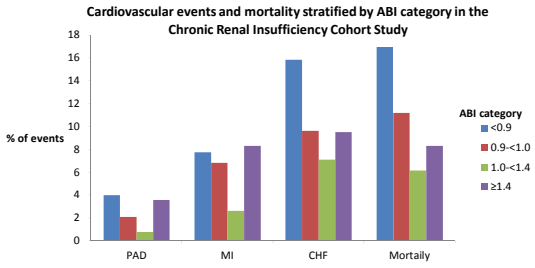
## HIGH AND LOW ABI ARE ASSOCIATED WITH ADVERSE OUTCOMES IN CKD




*Chen, Garimella et al, ASN 2012*

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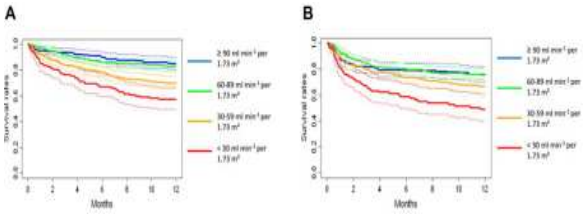
## MORTALITY AND AMPUTATIONS IN PATIENTS HOSPITALIZED FOR PAD




- 1010 patients admitted with Rutherford >3 class PAD
- Mortality rates 16%, 18%, 31.7%, and **44.3%** (p<0.001)
- Amputation rates 23.7%, 21.5%, 28%, and **40.2%** (p<0.001)

*Lacroix et al*, J Vas Surg 2013

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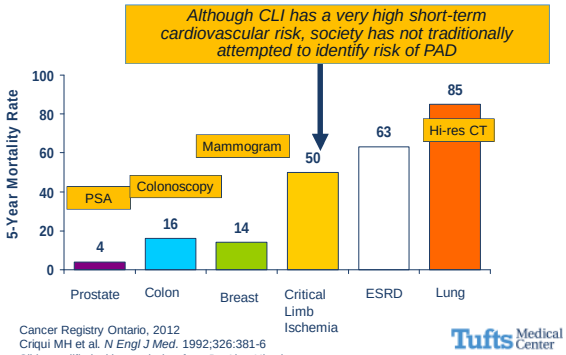
## RELATIVE 5-YEAR MORTALITY RATES




Cancer Registry Ontario, 2012
Criqui MH et al. *N Engl J Med*. 1992;326:381-6
Slide modified with permission from Dr. Alan Hirsch

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## TREATMENT OF PAD IN CKD/ESRD (all extrapolated from the general population)

- **Secondary Prevention of CVD in Patients with PAD**
  - Antiplatelet medications (any kind). No anticoagulants
  - **SMOKING CESSATION**
  - Diabetes and hypertension management
  - Statin therapy
  - Physical activity
- **Claudication and Critical Limb Ischemia Therapies**
  - Supervised exercise programs (Class IA) for symptomatic PAD (limitations: arthritis, COPD, HF)
  - Cilostazol (only 2% use in ESRD patients with PAD)
  - When above fail, consider revascularization therapy

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## REVASCULARIZATION THERAPY

- First line treatment in Critical Limb Ischemia (rest pain, non-healing wounds or ulcers, and/or gangrene)
- **CLI + CKD**: less likely treated with revascularization
- Both endovascular and open surgical options
- CKD/ESRD lesions are usually more distal
- Current AHA/ACC guidelines: surgical revascularization should be first line revascularization therapy in persons with a life expectancy greater than 2 years
- Persons on dialysis have increased risk of infection, graft loss, amputations and mortality

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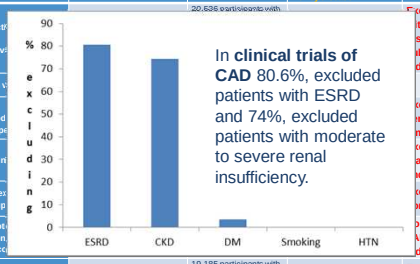
## LACK OF DATA ON PAD THERAPY IN CKD/ESRD

| Trial and Intervention | Primary Outcome | Population Studied | Included patients with kidney disease | Comments |
|---|---|---|---|---|
| Heart Protection Study (HPS) Simvastatin vs. | | 20,536 participants with | | Excluded individuals with severe kidney disease or evidence of substantially impaired kidney function |
| Atorvastatin vs. | | | | |
| UKPDS 33 Intense blood control in type | | | | Excluded patients with serum creatinine > mg/DL |
| Exercise traini | | | | Excluded patients with diabetes due to severe and distal PAD in them |
| Supervised ex control group | | | | Excluded patients with normal ABI |
| Antithrombot Collaboration therapy vs. co | | | | No separate data on PAD patients with kidney disease |
| CAPRIE Clopidogrel vs. aspirin [6] | All cause, CVD mortality, non fatal CVD events, leg amputation | 19,185 participants with ischemic stroke, myocardial infarction, or symptomatic PAD | Not reported | Excluded patients with severe kidney disease, uncontrolled hypertension |
| Cilostazol vs. placebo | Maximal walking distance | Meta-analysis of RCTs of 2,702 patients with claudication | Not reported | - |




In **clinical trials of CAD** 80.6%, excluded patients with ESRD and 74%, excluded patients with moderate to severe renal insufficiency.

Garimella et al, AJKD 2012
Charytan, KI 2006

## IMPORTANT QUESTIONS TO ANSWER

| Key clinical questions | Clinical practice recommendations | Suggested research |
|---|---|---|
| What is the best modality to establish the diagnosis of PAD in patients with CKD/ESRD? | Clinical history and physical examination, with targeted use of the ABI<br>**If ABI non-diagnostic, consider other PAD physiologic or imaging tests**<br>Consider CTA or /MRA if planning a revascularization procedure | **Define the accuracy of the ABI compared to, and in combination with, other physiologic PAD testing modalities (e.g. TBI,)** |
| Should diagnostic tests other than ABI be utilized routinely in patients with CKD? | **If the ABI is elevated (>1.3), or pedal arteries are non-compressible, or clinical suspicion persists despite a normal ABI, consider performing an exercise ABI/TBI or other imaging** | **Prospective evaluation of ABI test characteristics in a cohort of CKD** patients to determine the association of abnormal ABI values by eGFR; |
| Which pharmacologic, exercise, risk factor modification, or revascularization strategies of care are efficacious in patients with CKD and PAD? | Aggressive management of diabetes, lipids and BP control, smoking cessation, antiplatelet therapy<br>**Prescription of a supervised exercise program in patients with claudication**<br>Revascularization if CLI is present or if above interventions not beneficial | **Retrospective analysis of existing cohort**<br>**RCT to evaluate efficacy of drug therapies in CKD populations** |
| Are preventive interventions such as podiatrist evaluation, special fitting shoes useful in prevention of progression to CLI/amputations? | Consider podiatric evaluation in patients with CLI, infections to reduce risk of amputation | **Prospective study to evaluate clinical and economic implications of CLI and progression to amputation in CKD/ESRD populations** |

*Garimella et al*, AJKD 2012

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## TAKE HOME MESSAGES

- **KNOW THAT PAD IS MORE COMMON** IN CKD/ESRD THAN OTHERS
- CURRENT NON-INVASIVE TESTING MAY BE **INADQUATE TO DIAGNOSE AND RISK STRATIFY**
- **UNIQUE RISK FACTORS** IN CKD/ESRD LEAD TO BOTH HIGH AND LOW ABI (BOTH ARE BAD)
- NEED TO 'FACILITATE DIAGNOSIS' BY HAVING A **LOW SUSPICION THRESHOLD**
- IF NON INVASIVE TESTING IS NEGATIVE, CONSIDER INVASIVE TESTING
- **REFER TO A SPECIALIST**

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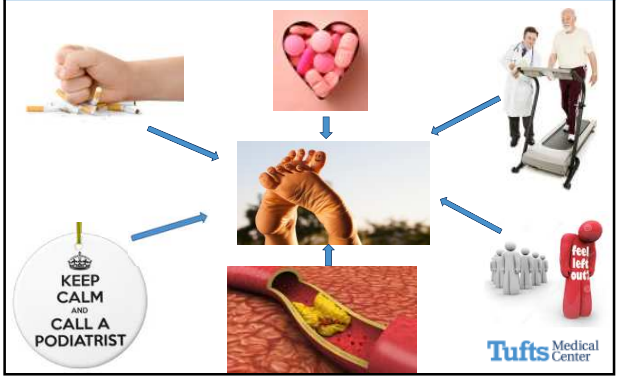
## TAKE HOME MESSAGES- PREVENTION & TREATMENT

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## WE NEED TO DO MORE

**AN INCH OF BLOOD FLOW**

**CAN MAKE A FOOT OF DIFFERENCE**


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