Peripheral Artery Disease: Perspectives from the Kidney

Pranav S. Garimella, MD, MPH
Assistant Professor of Medicine
University of California San Diego

DISCLOSURES

- Otsuka Corp. (speaking fees)
- Kadmon LLC. (site PI for clinical trial)
- NIH K23 (research funding)

Content: PAD and CKD

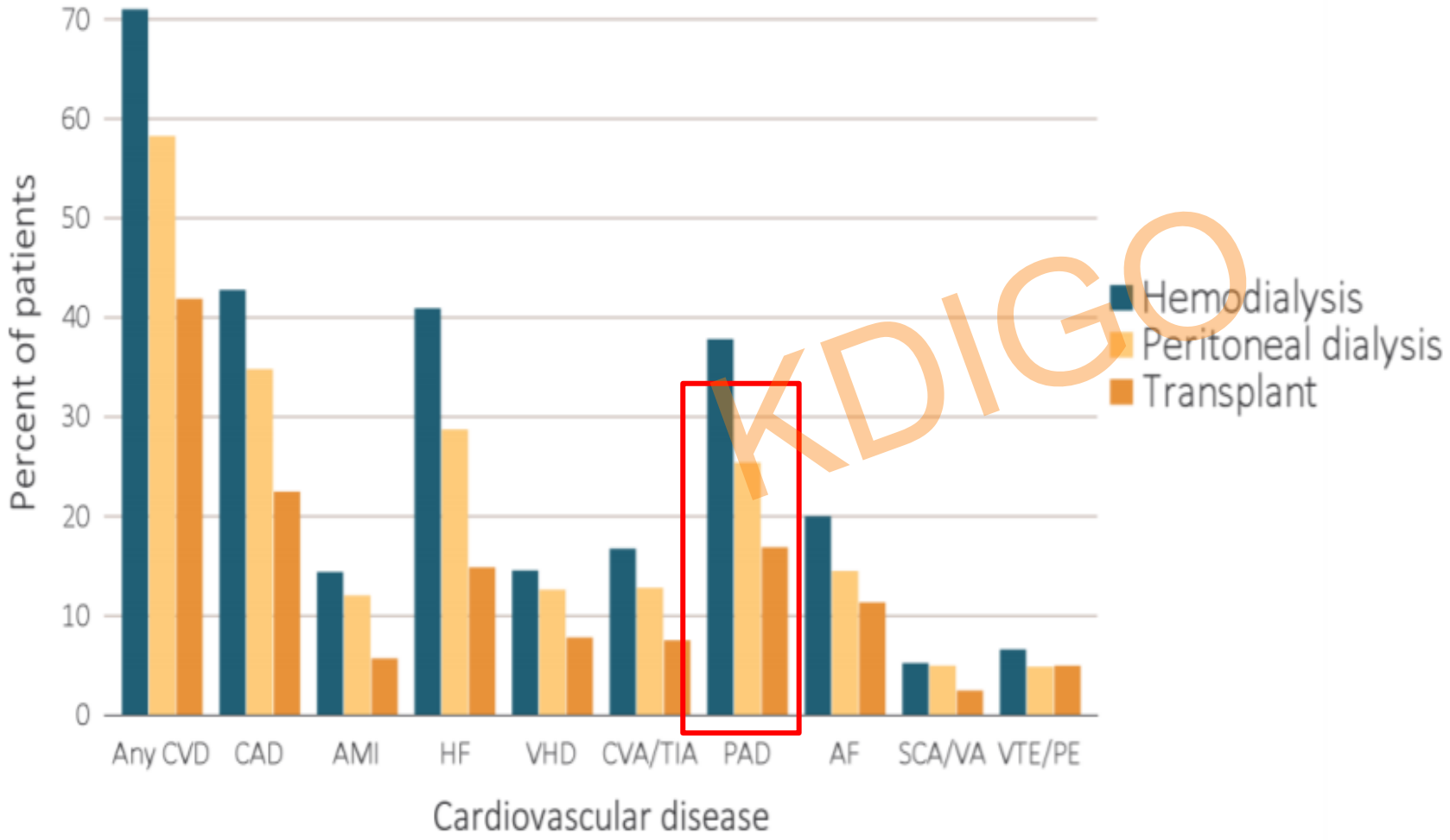
- Brief Epidemiology
- Diagnostic tests and differences in CKD
- PCSK9-inhibitors in PAD in CKD
- Prognosis and outcomes
- The need of the hour

Epidemiology of PAD in CKD

Study	Population	Prevalence (%)	Diagnostic criteria
Patients on dialysis			
USRDS	N=35,438 incident dialysis	38	Claims data
DOPPS	N=29,873 prevalent hemodialysis	25.3	Clinical
HEMO	N=936 prevalent hemodialysis	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	N=211 with CrCl < 60	24	ABI < 0.9
CRIC	N=3199 with eGFR < 60	7.4 15.9	Self reported history of PAD ABI < 0.9
CHS	N=648 with kidney disease	12	ABI < 0.9

Garimella et al. AJKD 2012.

PAD is more prevalent than CVA & MI in CKD



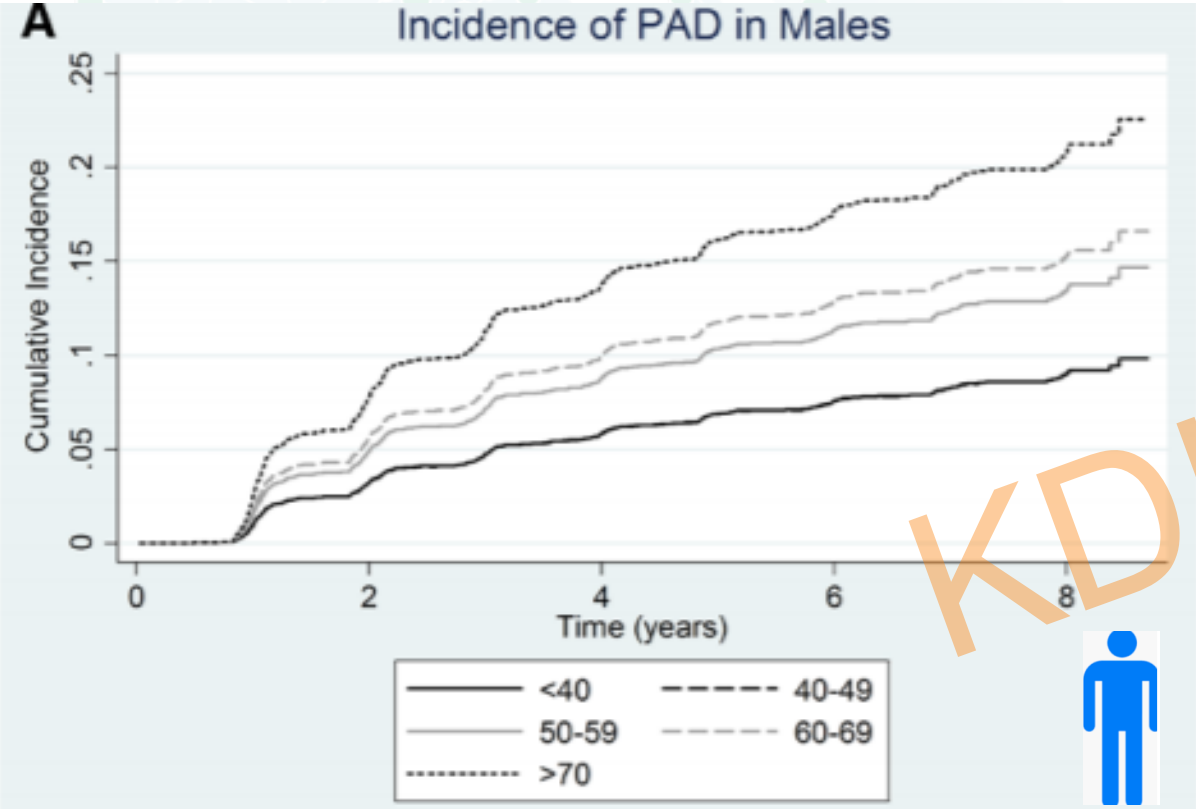
ASHD=atherosclerotic heart disease

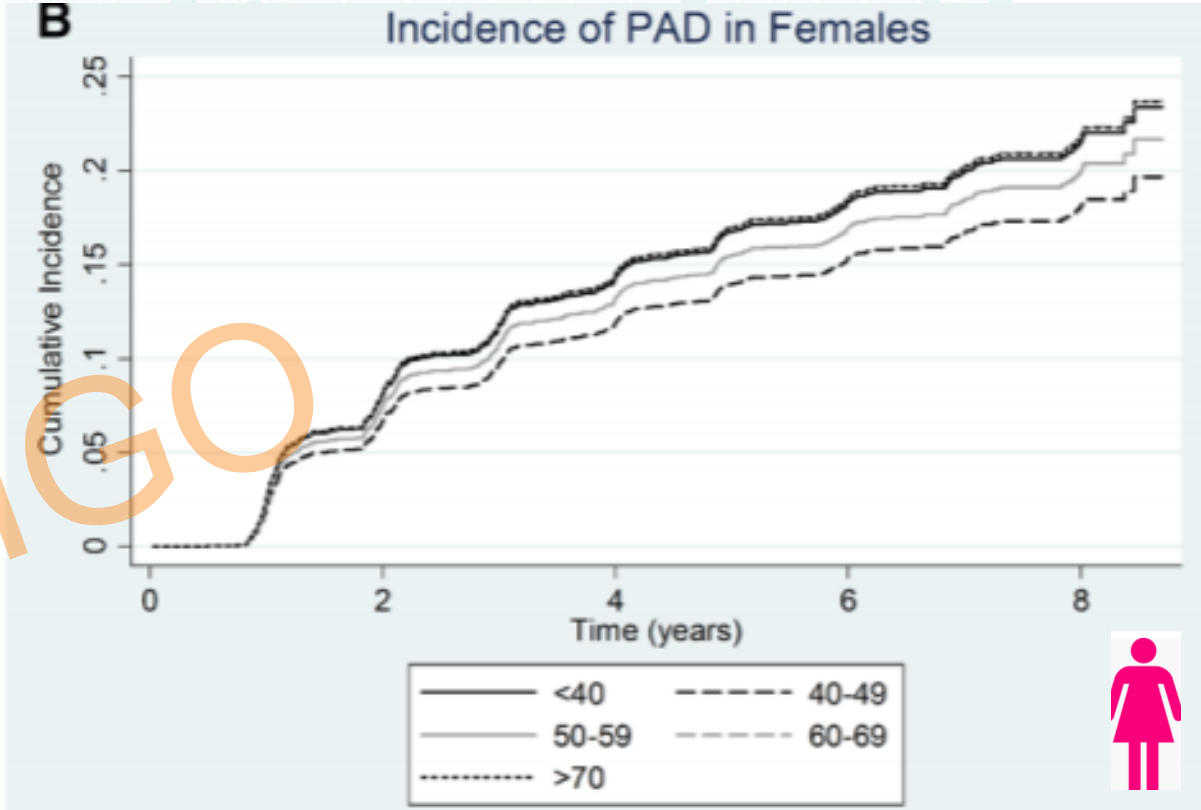
CVA=cerebrovascular accident

SCA=sudden cardiac arrest

USRDS Annual Data Report 2018

More young women with PAD and CKD than men



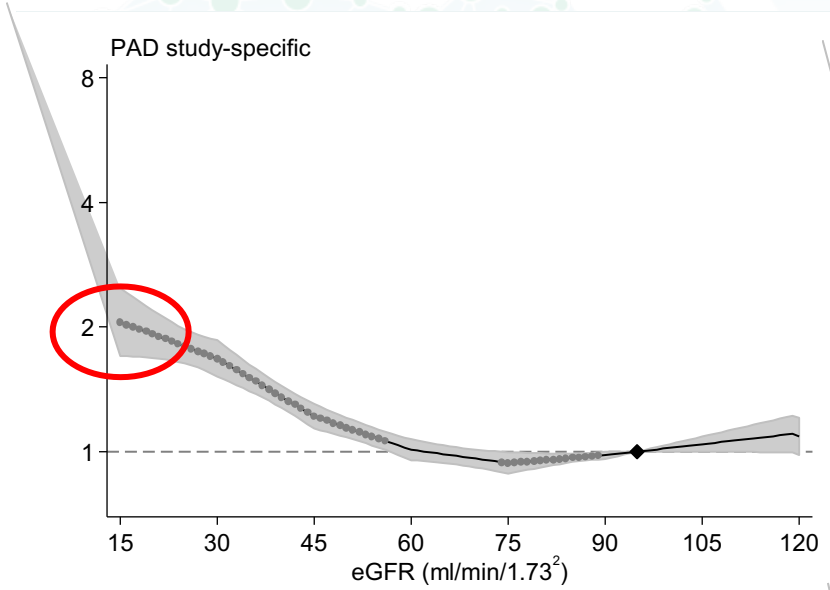


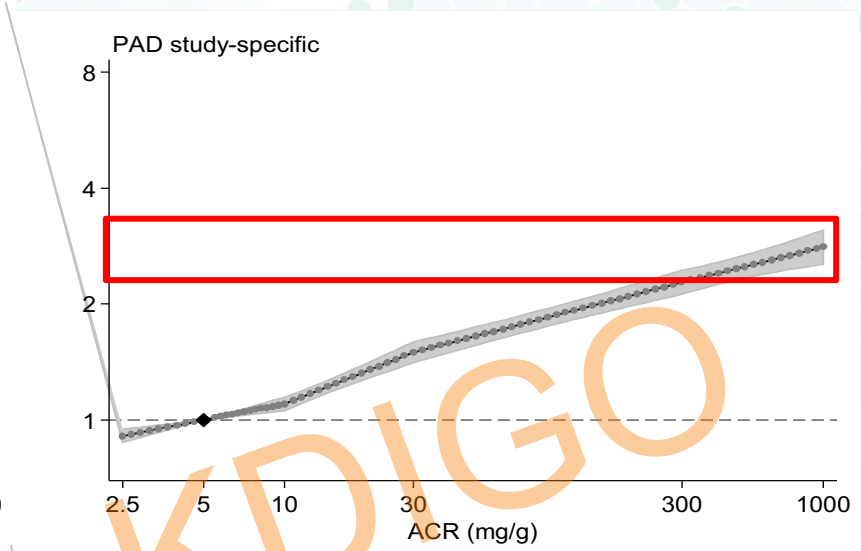
Women, compared to men, were at a markedly increased risk for PAD at younger ages

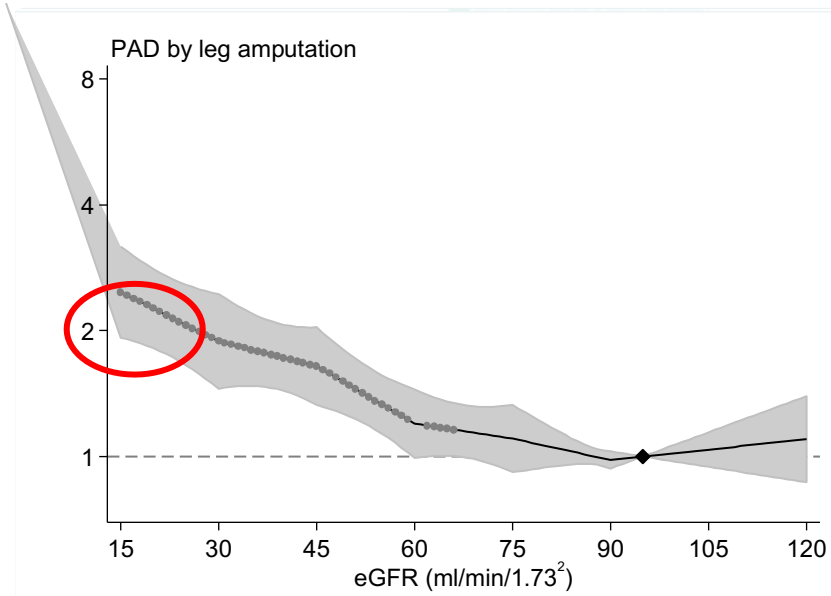
At ages greater than 70 years, the risk was similar across both sexes

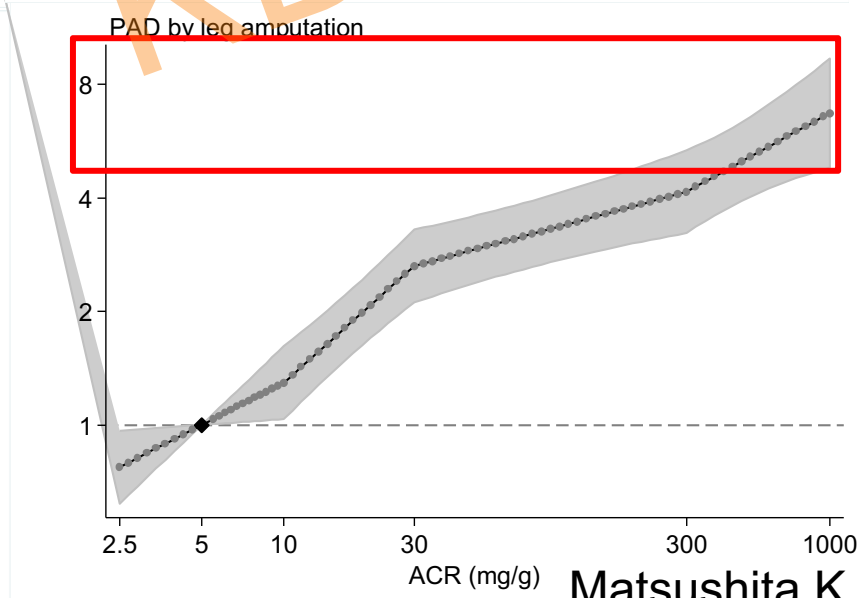
Wang et al. Circ Card Outcomes 2017

eGFR, albuminuria & risk of PAD and amputation









CKD Prognosis Consortium

21 cohorts (9 general, 8 high-risk, and 4 CKD) had data on incident PAD (mean follow-up 7.4 years)

N=817 084 without a history of PAD

18,261 incident PAD cases (1,754 amputation)

Matsushita K, et al. Lancet Diab & Endo. 2017

CKD risk factors associated strongly with amputation

Overall PAD

eGFR	ACR				overall
	<10	10-29	30-299	300+	
>90	Ref	**1.31** (1.19-1.45)	**1.82** (1.65-2.01)	**3.16** (2.61-3.84)	Ref
75-89	0.94 (0.87-1.01)	**1.22** (1.11-1.34)	**1.84** (1.68-2.03)	**3.14** (2.61-3.79)	0.95 (0.91-1.01)
60-74	0.97 (0.89-1.04)	**1.29** (1.18-1.41)	**1.87** (1.71-2.05)	**2.97** (2.54-3.48)	0.98 (0.93-1.04)
45-59	**1.24** (1.13-1.36)	**1.63** (1.46-1.81)	**2.07** (1.87-2.29)	**3.39** (2.93-3.92)	1.23 (1.16-1.31)
30-44	**1.78** (1.58-2.01)	**1.99** (1.72-2.30)	**2.51** (2.23-2.83)	**3.92** (3.36-4.58)	1.57 (1.46-1.70)
<30	**2.84** (2.28-3.53)	**2.84** (2.18-3.71)	**3.58** (3.06-4.19)	**5.76** (4.90-6.77)	2.42 (2.20-2.66)
overall	Ref	1.31 (1.25-1.37)	1.79 (1.71-1.86)	2.80 (2.62-3.00)	

Leg amputation

eGFR	ACR				overall
	<10	10-29	30-299	300+	
>90	Ref	**1.59** (1.21-2.08)	**2.17** (1.62-2.90)	**8.02** (5.45-11.80)	Ref
75-89	0.90 (0.72-1.13)	**1.94** (1.47-2.55)	**3.16** (2.44-4.11)	**7.21** (4.34-11.99)	1.04 (0.90-1.20)
60-74	1.02 (0.81-1.30)	**1.83** (1.36-2.48)	**3.25** (2.50-4.23)	**5.17** (3.02-8.86)	1.09 (0.93-1.27)
45-59	**1.54** (1.12-2.14)	**2.81** (1.95-4.06)	**3.96** (2.87-5.48)	**9.3** (6.11-14.15)	1.61 (1.32-1.96)
30-44	**2.12** (1.33-3.38)	**4.37** (2.84-6.74)	**4.43** (2.90-6.76)	**10.27** (6.03-17.50)	2.13 (1.68-2.69)
<30	**3.16** (1.67-5.99)	**5.77** (2.87-11.60)	**7.39** (4.72-11.57)	**10.61** (5.70-19.77)	2.59 (1.97-3.40)
overall	Ref	1.88 (1.64-2.16)	2.82 (2.47-3.23)	6.04 (4.97-7.35)	

HR <1.5 | HR 1.5-1.9 | HR 2.0-3.9 | HR ≥4.0

Matsushita K, et al. Lancet Diab & Endo. 2017

Who should be tested

- AHA/ACC Guidelines have recommended use of the resting ABI in
  - Any individual with abnormal ankle pulses, the presence of exertional leg symptoms suggestive of claudication
  - The presence of non-healing wounds or gangrene
  - High-risk populations
    - age 65 years and older or
    - 50 years and older with a history of smoking or diabetes

When to diagnose PAD in CKD patients

10.1 Diagnosis of PVD:

10.1a At the time of dialysis initiation, all patients should be evaluated for the presence of PVD. (C)

10.1b Evaluation should include physical examination including assessment of arterial pulse and skin integrity. (C)

10.1c Further specialized studies, such as duplex studies or invasive testing, should be undertaken if abnormalities are detected upon physical examination and interventions are considered. (C)

National Kidney Foundation® | KDOQI® Kidney Disease Outcomes Quality Initiative

KDIGO CKD Guideline 2012
NKF KDOQI Guideline 2005

4.3 CKD AND PERIPHERAL ARTERIAL DISEASE

There is a strong link between CKD and peripheral arterial disease (PAD). Symptoms of PAD may only be present in a minority of people who have clinical evidence of PAD.[579] It is therefore important to measure ankle-brachial index and perform regular systematic assessment of the lower limbs of people at high risk of PAD to identify bruits, loss of pulses, cool pale extremities, delay in venous filling, and skin ulceration.[580]

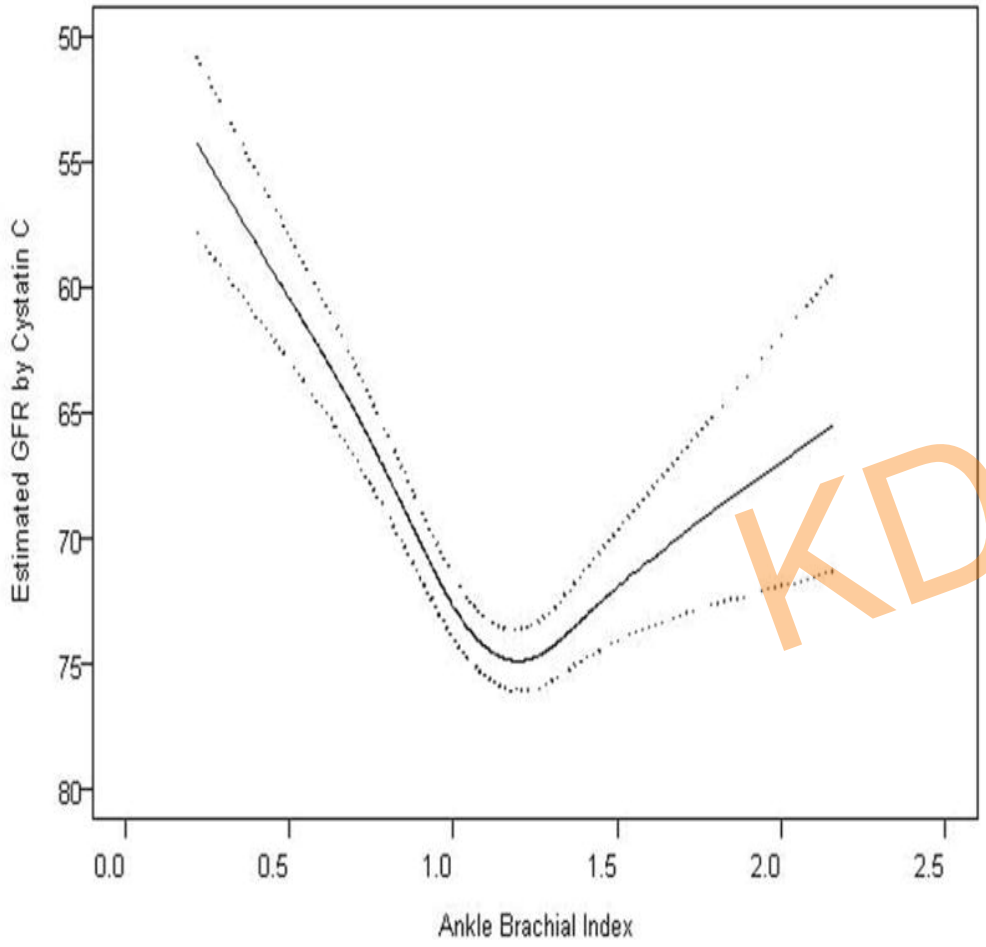
4.3.1: We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (*1B*)

How do you 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 (arthritis, neuropathy, etc.)
- **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 and vascular bruit**: Indicative of PAD (worth proceeding objective examinations such as ankle-brachial index [ABI])

Slide Courtesy Dr. Matsushita K

ABI (ankle-brachial index) in CKD

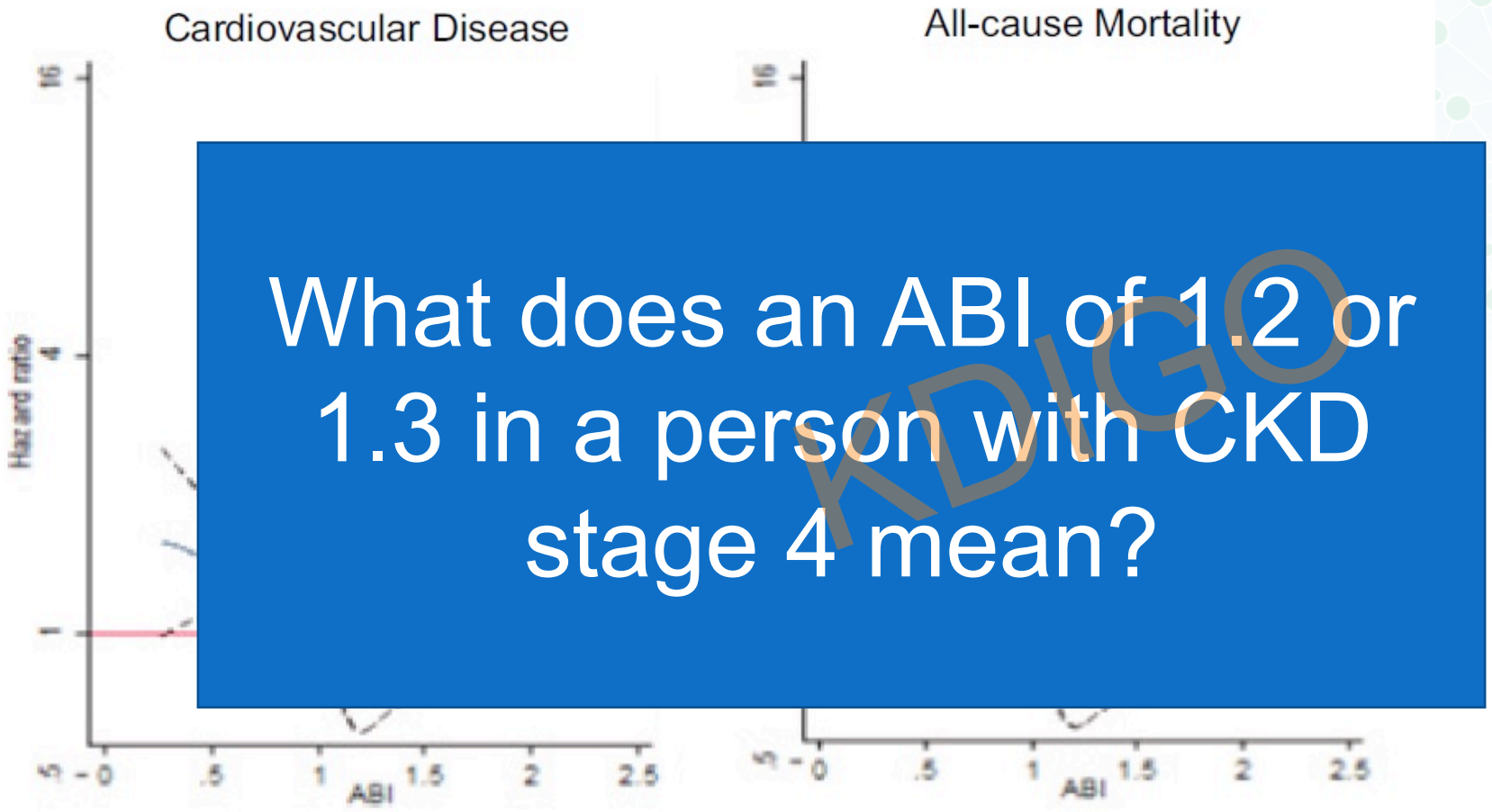


4,513 participants aged >69 years, 23% had CKD, all enrolled in the Cardiovascular Health Study

- ABI of ≤0.9 is diagnostic for PAD
- ABI 0.9-1.0 are "not normal" but **borderline low**
- Prevalence of an ABI >1.3 is high in CKD (23%) & ESRD (41%)
- Medial arterial calcification (MAC) results in decreased vessel compressibility → **FALSE NORMAL ABI or ELEVATED ABI**

Ix et al. JACC 2009

Low & high ABI associate with CVD risk in CKD



What does an ABI of 1.2 or 1.3 in a person with CKD stage 4 mean?

3,627 participants without clinical PAD in CRIC

Individuals with an ABI between 1.0 and <1.4 had the lowest risk of outcomes.-

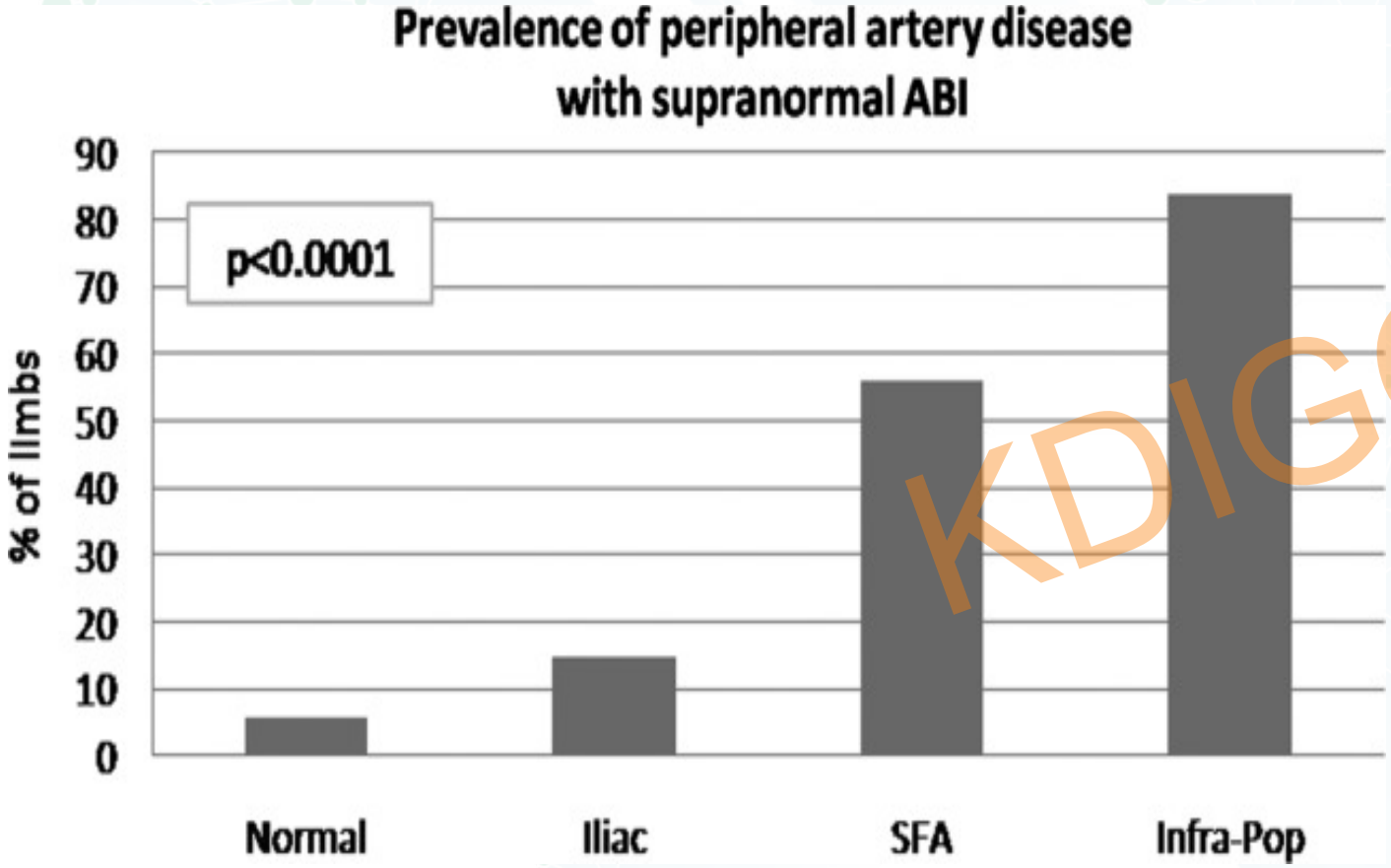
Chen et al. JAHA 2016

Other Diagnostic Tools

AHA/ACC 2016 PAD guideline recommends performing TBI when ABI >1.4

- **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 ultrasound**
- **Digital Subtraction Angio**
- **Conventional Angio**
- **MR Angio**

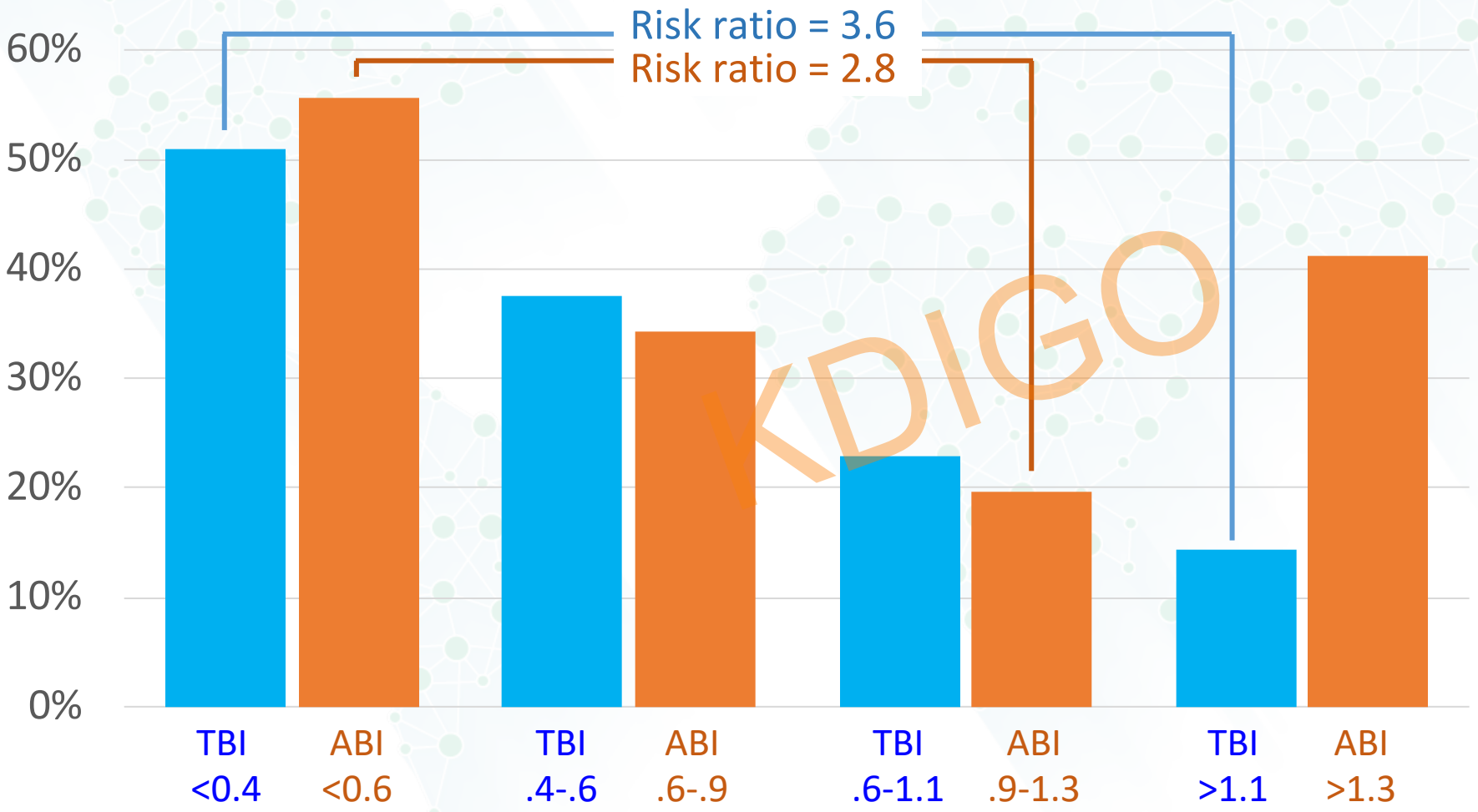
PAD is common even with a High ABI



- 92 symptomatic patients (116 limbs) with high ABI (>1.4) who underwent angiography
- 19.5% on dialysis
- Claudication 45%, CLI 52%
- Multilevel disease in 48.8%
- Toe brachial index **<0.7 was found in 92%**

Weinberg et al. Cath Card Int 2013

TBI vs. ABI and CVD mortality



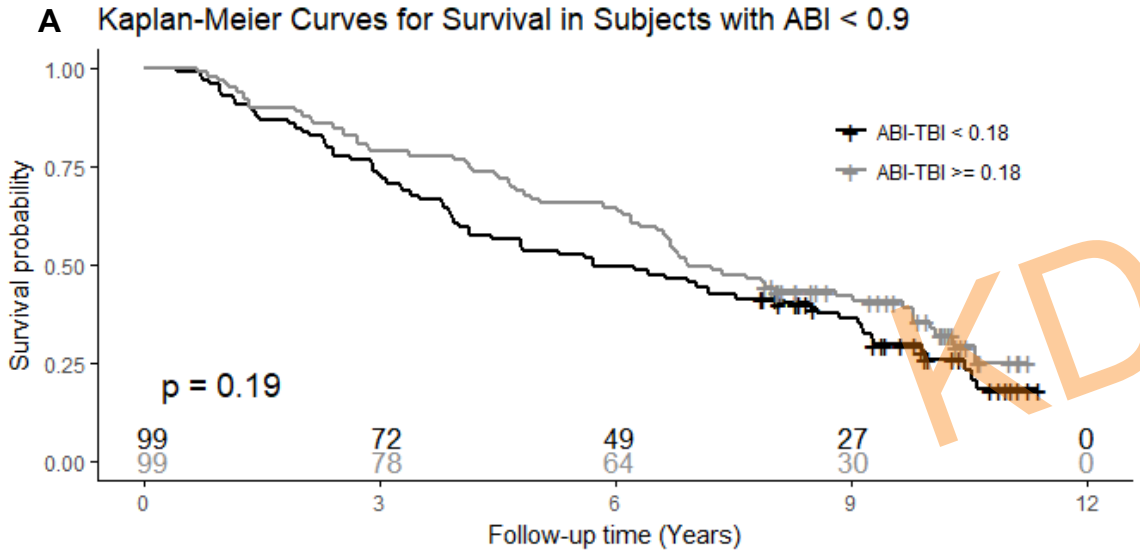
- 168 patients with diabetes
- 75 CVD deaths over a median 7 years
- J-shaped association with ABI, linear with TBI

Hyun et al. J Vasc Surg. 2014

Slide Courtesey Dr Kuni Matsushita

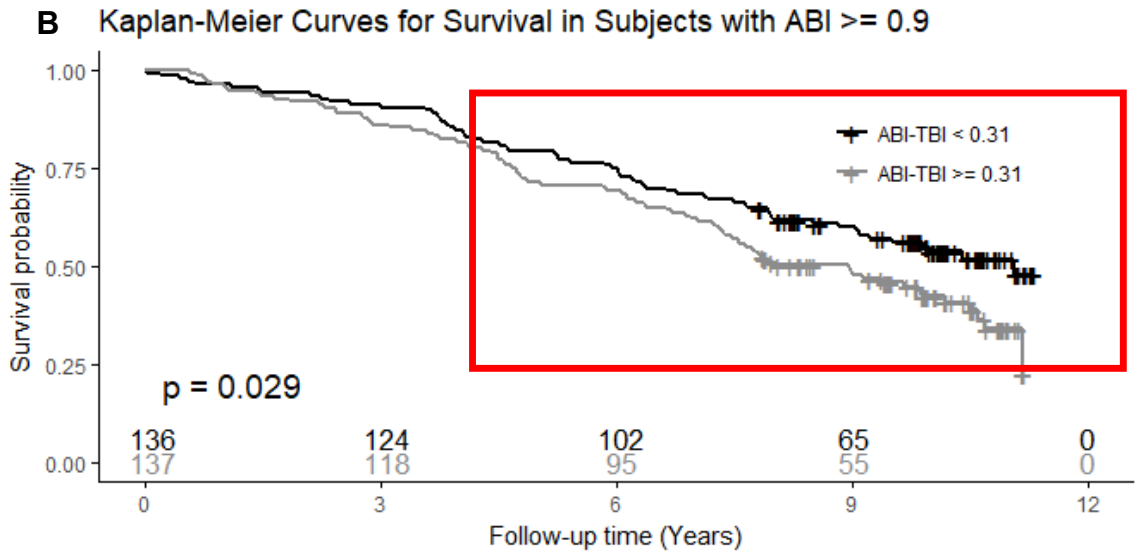
Association of Ankle-Brachial and Toe-Brachial Indexes With Mortality in Patients With CKD

- Capturing both atherosclerosis and vascular stiffness: ABI-TBI differential



471 patients referred for vascular testing

Baseline ABI-TBI and Mortality over 7 years

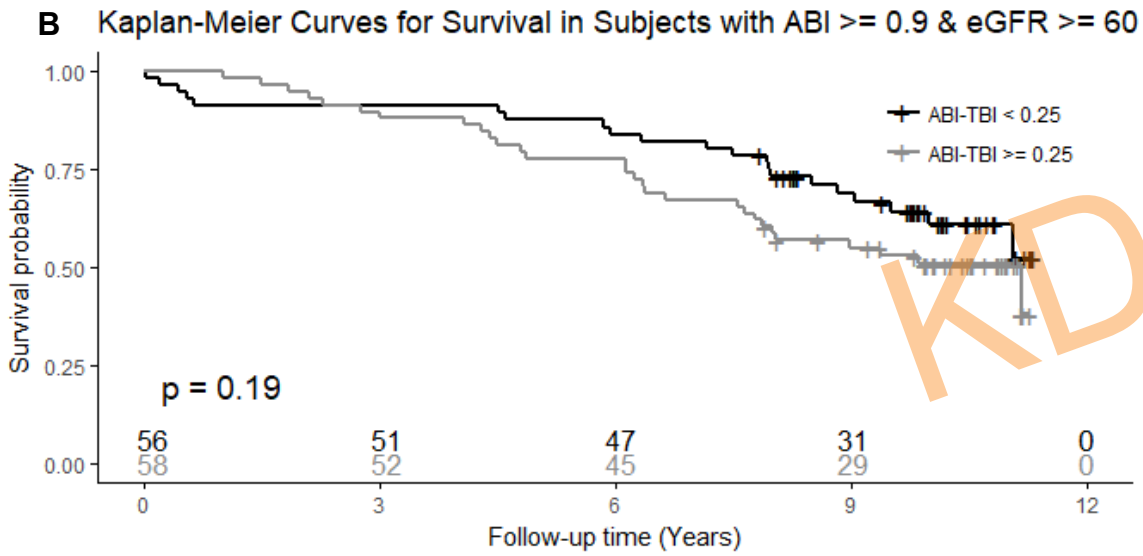


Stratified by ABI value ≥ or <0.9

Kamath et al. *Kidn Med. 2020*

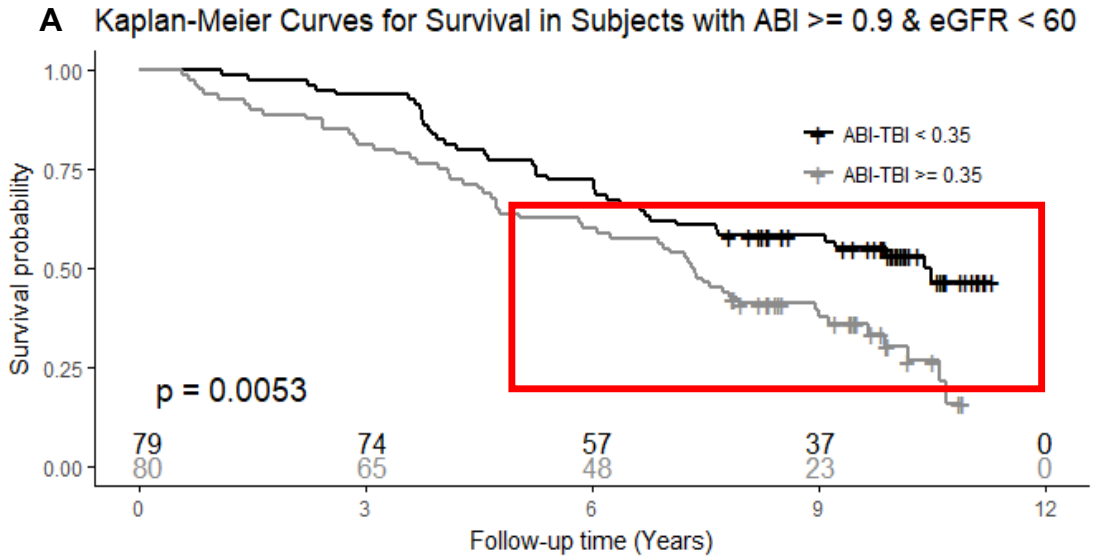
Association of Ankle-Brachial and Toe-Brachial Indexes With Mortality in Patients With CKD

- Capturing atherosclerosis and vascular stiffness: ABI-TBI a possibility?



471 patients referred for vascular testing

Baseline ABI-TBI and its association with all-cause mortality over 7 years



Stratified by CKD status

Kamath et al. *Kidn Med. 2020*

Treatment of PAD
Therapies Based Upon Symptoms

Intermittent Claudication

- Exercise Therapy
- Drugs
  - Pentoxifylline
  - Cilostazol
- Revascularization
  - *Severe disability*

Goal to provide relief of symptoms

Critical limb ischemia

- Wound care
- Antibiotics
- Revascularization
  - Endovascular
  - Surgery

Goal to promote limb survival

Treatment of PAD
Prevent Ischemic Events

Risk factor modification

- **Smoking cessation**
  - Goal: complete cessation
- **Lipid management**
  - Target LDL < 70 mg/dL
- **Blood pressure control**
  - Goal <130/85 mm Hg
- **Blood sugar control**
  - Goal: HbA_{1c} 7-8%

Antiplatelet therapies

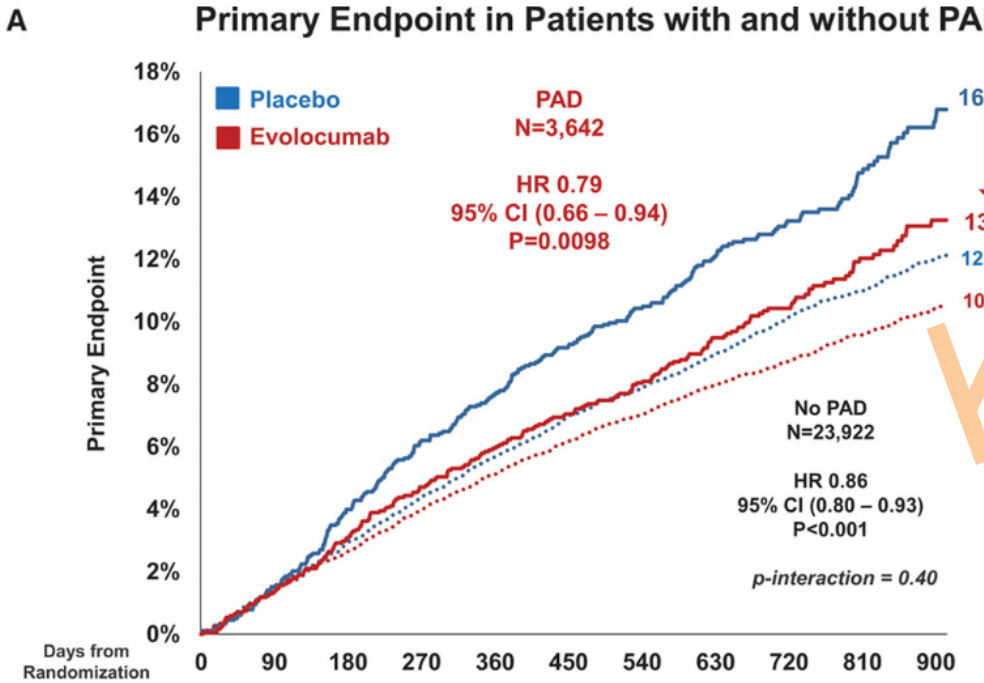
- **Aspirin or Clopidogrel**

Antithrombotic therapies

- **Rivaroxaban**
  - Goal: reduction in risk of MI, stroke, and vascular death

PCSKi and MACE

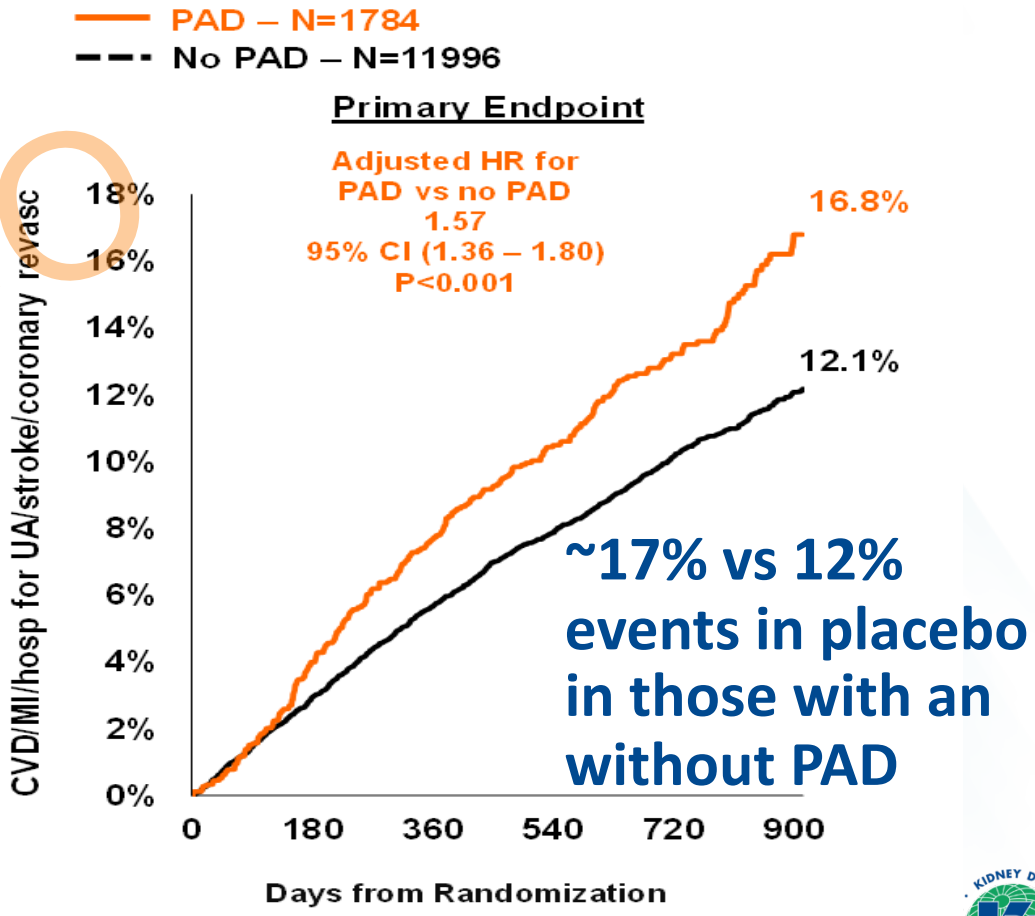
Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease



Number at risk

Placebo PAD	1784	1749	1700	1654	1617	1588	1536	1281	973	695	432
Evolocumab PAD	1858	1827	1790	1753	1726	1701	1651	1378	1050	749	460
Placebo no PAD	11996	11793	11582	11390	11217	11039	10400	8759	6864	5173	3443
Evolocumab no PAD	11926	11736	11568	11384	11224	11081	10486	8807	6972	5242	3476

~3.5% vs 2.1% ARR with Evolocumab in those with and without PAD

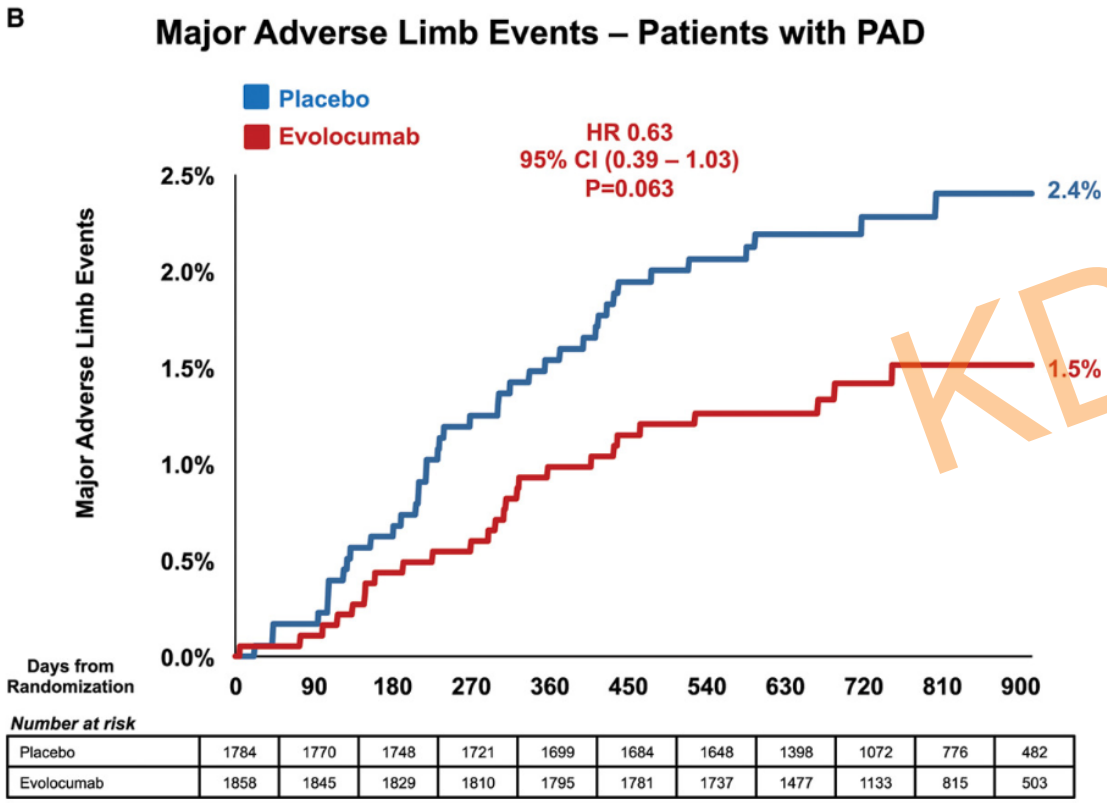


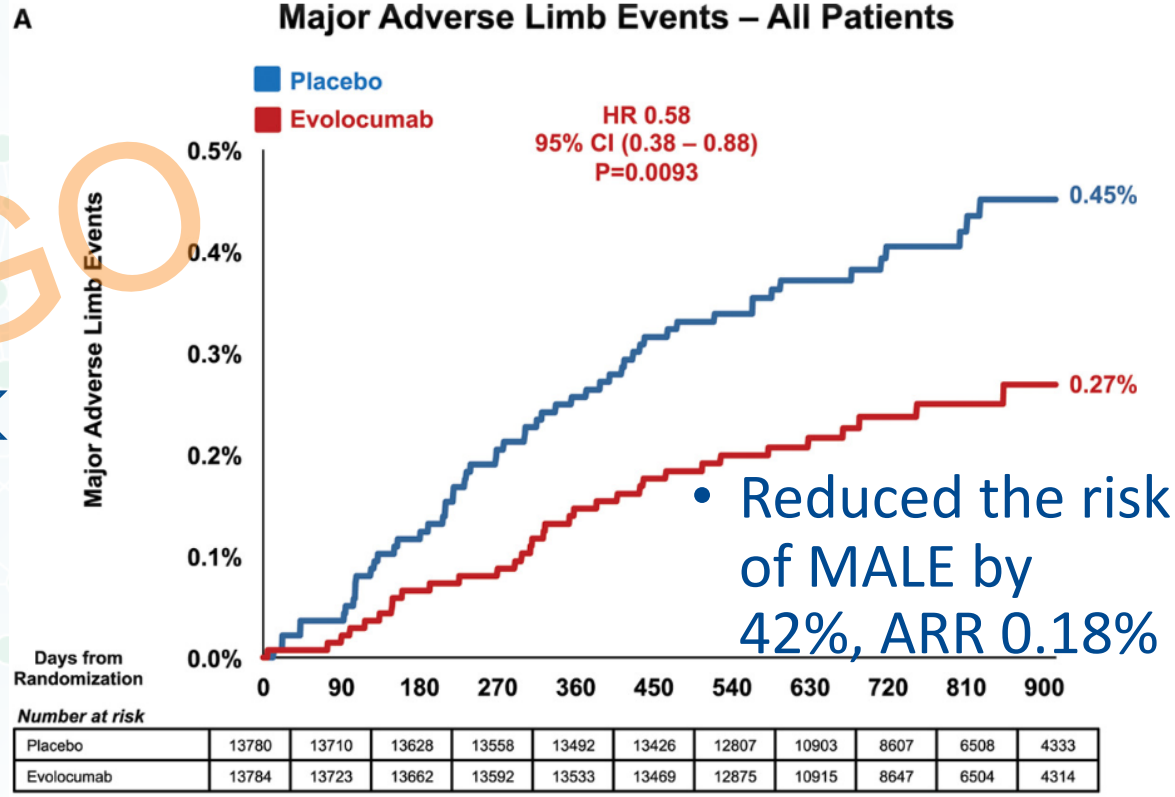
~17% vs 12% events in placebo in those with an without PAD

Bonaca et al. *Circulation 2017*

PCSKi and MALE

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease





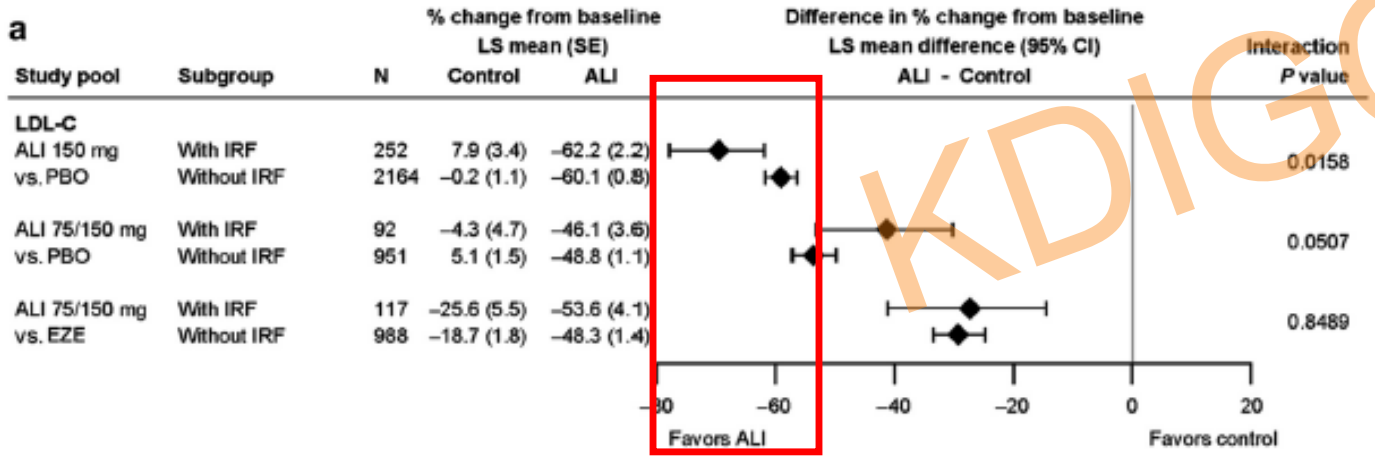
- Reduced the risk of MALE by 42%, ARR 0.18%

Bonaca et al. *Circulation 2017*

PCSK9 inhibitors in kidney disease

www.kidney-international.org

Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease

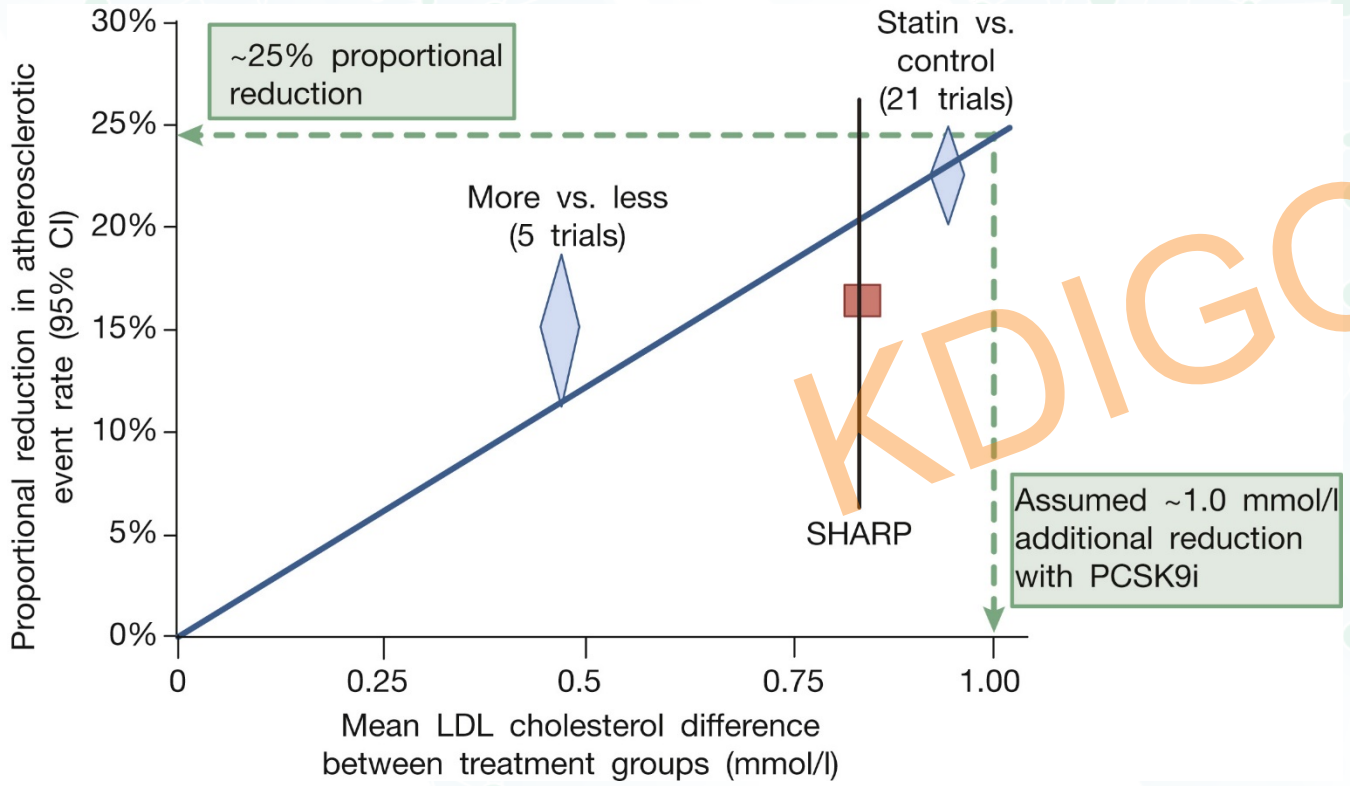


- 8 trials of alirocumab 150mg q 2 compared to ezetimibe or placebo
- 4690 participants overall
- 10% (470) with kidney disease
- 99% on statins
- Only biochemical and safety endpoints

LDL-C reduction was ~60%, with similar effects among patients with or without impaired renal function.

Toth et al *Kidn Int 2018*

Relationship of absolute reduction in LDL-C and proportional MACE risk reduction



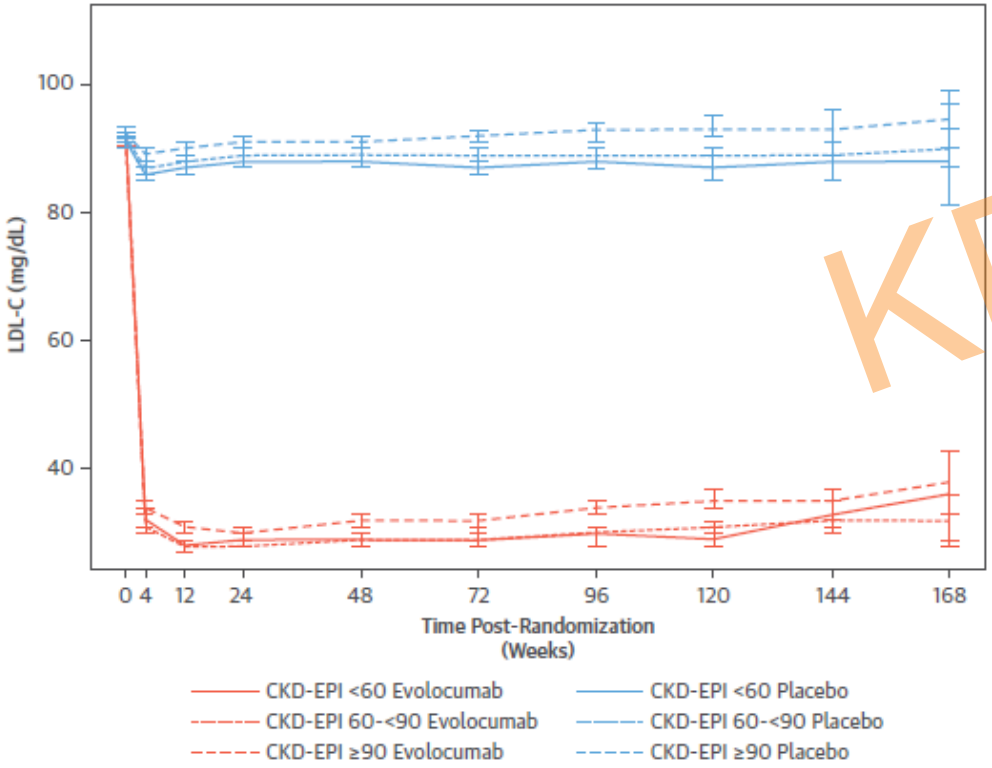
- Assuming statin-based is already common in CKD
- Target LDL-C of ~1.7 mmol/l
- Additional 60% reduction (with PCSK9i use) would equate to a ~1.0 mmol/l reduction.

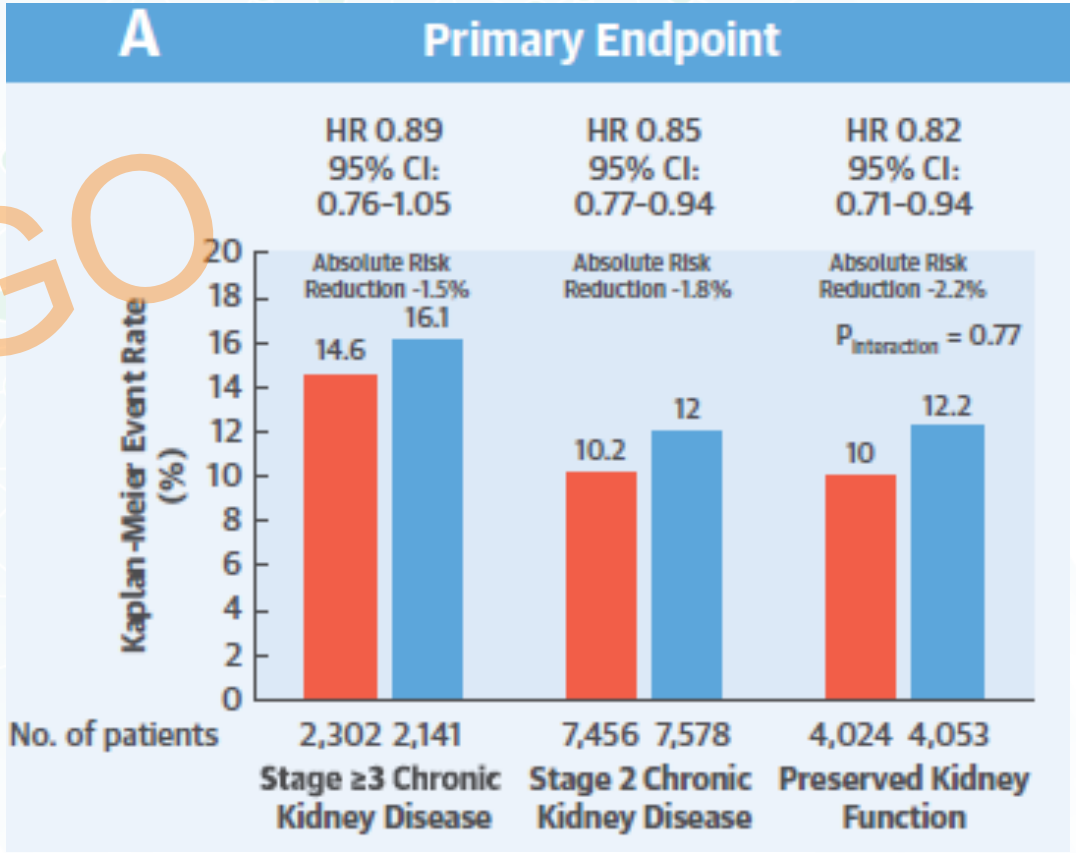
~25% proportional reduction in ASCVD risk with PCSK9i

Mahfam et al *Kidn Int 2019*

PCSK9 inhibitors in kidney disease

Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial





Charytan et al. *JACC 2019*

PCKS9i in Kidney Disease and PAD

Lack of data on PAD therapy in CKD

Trial and Intervention	Primary Outcome	Population Studied	Comments
Heart Protection Study (HPS) Simvastatin vs. placebo	Myocardial infarction, coronary death, stroke, or revascularization	20,536 participants with PAD and other vascular disease	Excluded severe kidney disease
Atorvastatin vs. placebo	Change in maximal walking time	354 patients with claudication	1255 diabetic patients on dialysis
UKPDS 33: Intense BP control in type 2 diabetics	All cause mortality, adverse CV events	3,867 newly diagnosed patients with type 2 diabetes	Excluded patients with serum creatinine > 2mg/dL
Exercise training	Improving walking distance	25 men with claudication	Excluded diabetes due to severe and distal PAD
Supervised exercise vs. control group	6-minute walk test and the short physical performance battery	156 participants with ABI < 0.95	CKD not mentioned
Antithrombotic Trialists' Collaboration Antiplatelet therapy vs. control	Non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause	135, 640 participants of which 9214 had PAD	2632 patients on dialysis but 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 CVD including symptomatic PAD	Excluded patients with severe kidney disease, uncontrolled hypertension
Cilostazol vs. placebo	Maximal walking distance	Meta-analyzing 2,702 patients with claudication	CKD not mentioned

Garimella et al *AJKD 2012*

CKD Patients Often Excluded From Trials

http://www.kidney-international.org original article

The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease

D Charytan[1] and RE Kuntz[2]

PLOS ONE

RESEARCH ARTICLE

Representation and reporting of kidney disease in cerebrovascular disease: A systematic review of randomized controlled trials

Ioannis Konstantinidis[1☯*], Shanti Patel[2], Marianne Camargo[2], Achint Patel[2], Priti Poojary[3], Steven G. Coca[2☯], Girish N. Nadkarni[2☯]

Research Letter

January 2016

Representation of Patients With Kidney Disease in Trials of Cardiovascular Interventions

An Updated Systematic Review

Ioannis Konstantinidis, MD[1]; Girish N. Nadkarni, MD, MPH, CPH[2]; Rabi Yacoub, MD[2]; et al

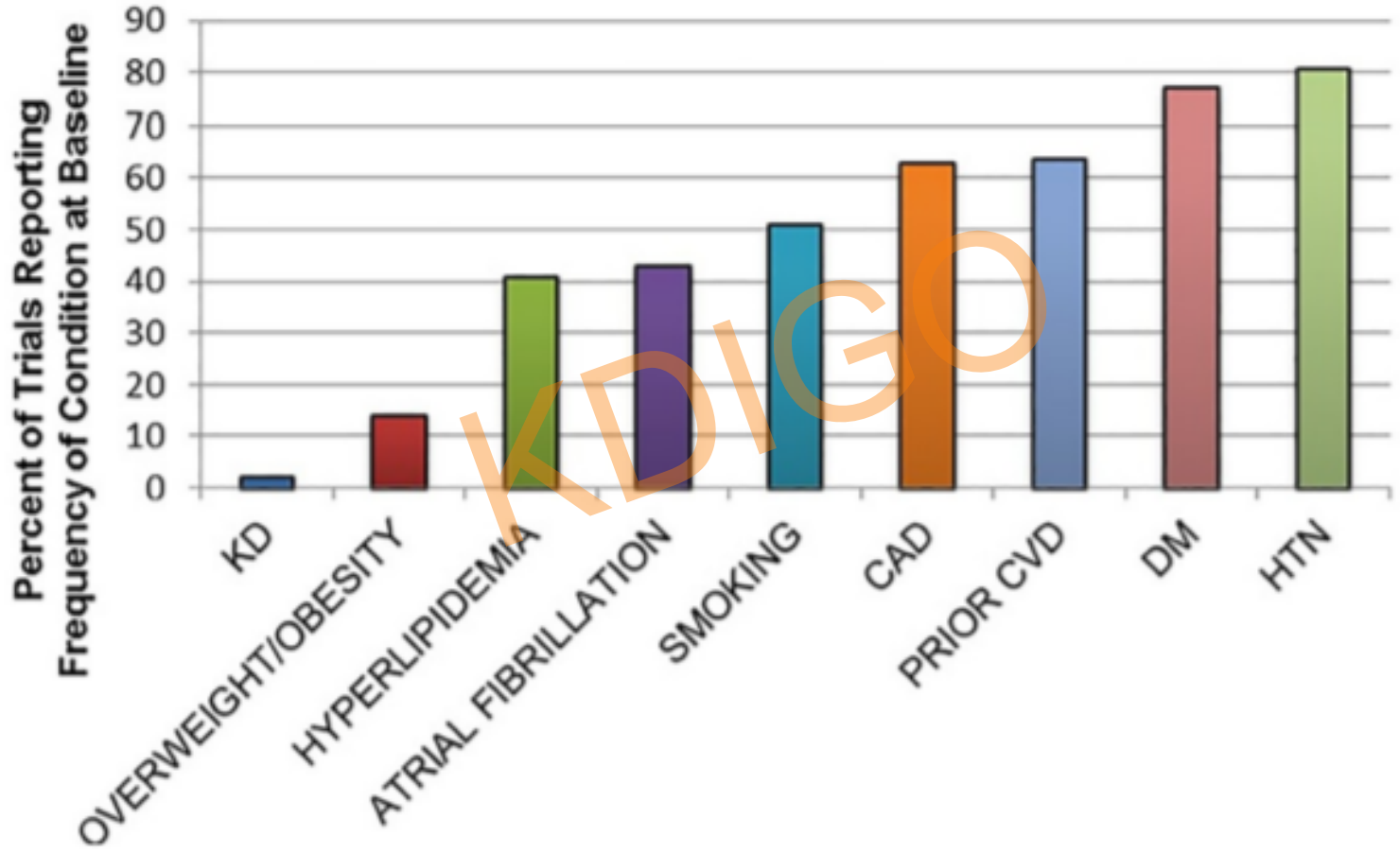
Research Letter

June 19, 2018

Representation of Patients With Chronic Kidney Disease in Trials of Cancer Therapy

Abhijat Kitchlu, MD, FRCPC[1,2]; Joshua Shapiro, BSc[2]; Eitan Amir, MD, PhD[3]; Amit X. Garg, MD, PhD[4]; S. Joseph Kim, MD, PhD[1]; Ron Wald, MDCM, MPH[2]; Ziv Harel, MD, MSc[2]

In trials of Cerebrovascular Disease ~ 3% reported kidney Function



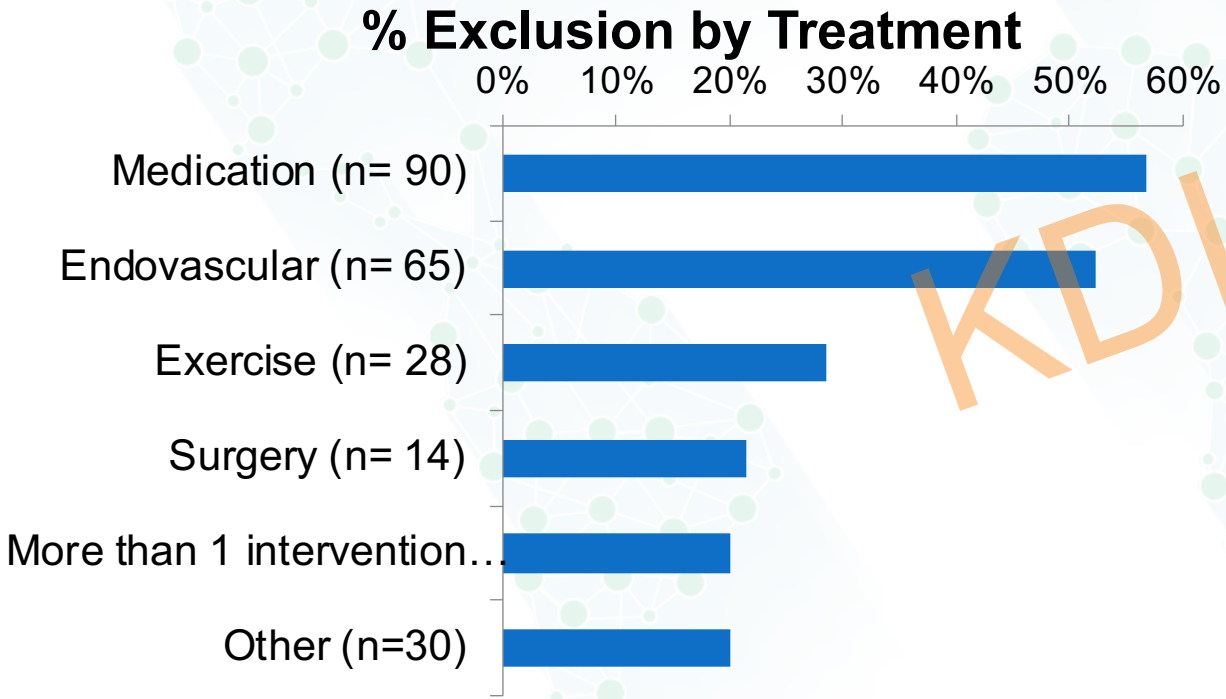
Konstantinidis PLoS One. 2017

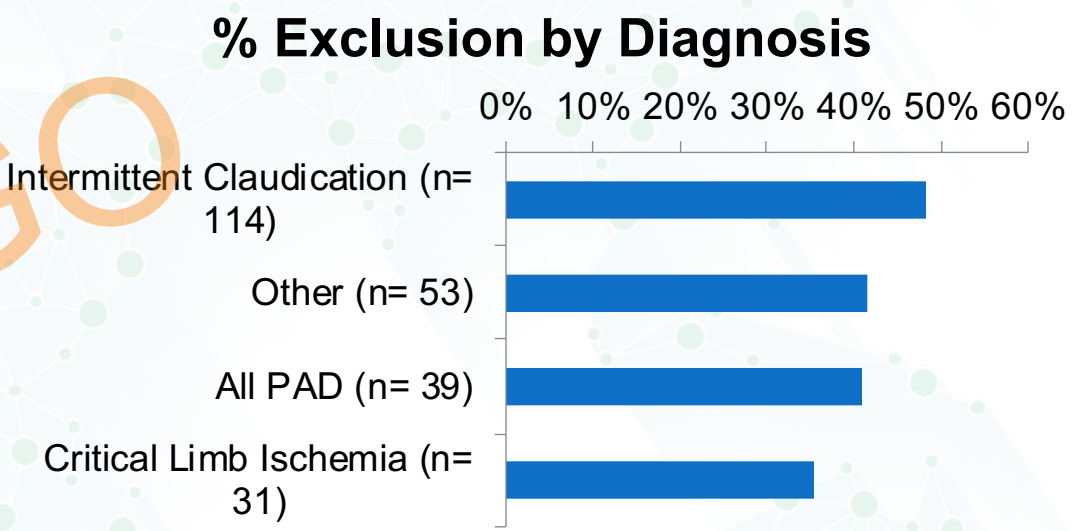
NEED TO INCLUDE PERSONS WITH CKD IN PAD TRIALS

Exclusion of Persons with Kidney Disease in Trials of Peripheral Artery Disease

A Systematic Review of Randomized Trials

CJASN ePress.





Only 11% trials reported baseline kidney function

Garimella et al. *CJASN. 2020*

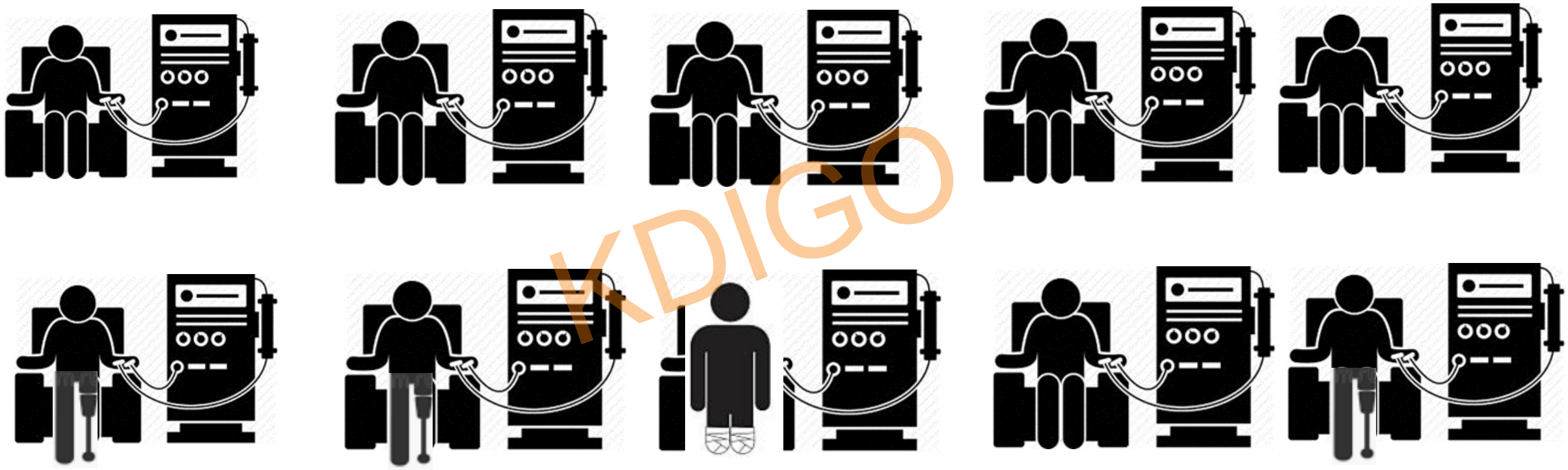
Where we left off….KDIGO Guidelines 2012

- ……ongoing debate as to the timing and use of specific diagnostic criteria for identification of PAD in people with CKD and no studies have examined the utility of conventional methods in early detection of PAD in CKD.

- The use of specific medical and surgical management strategies in people with CKD and PAD has not been evaluated.

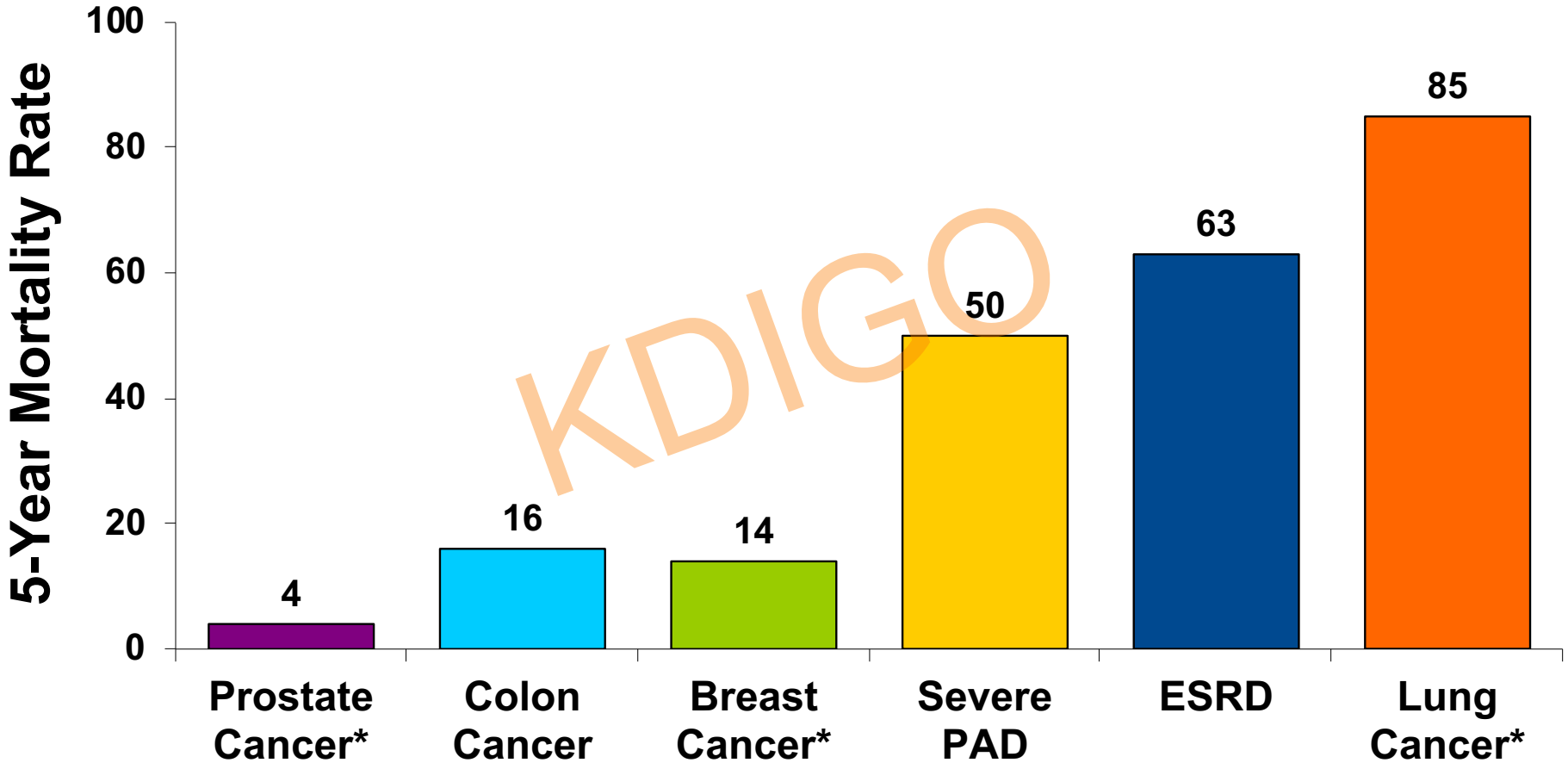
- There is no reason to believe that treatment strategies should differ, though risks of diagnostic testing (such as angiography) remain real.

Why Do We Need to Care?



More heads than feet in the dialysis units

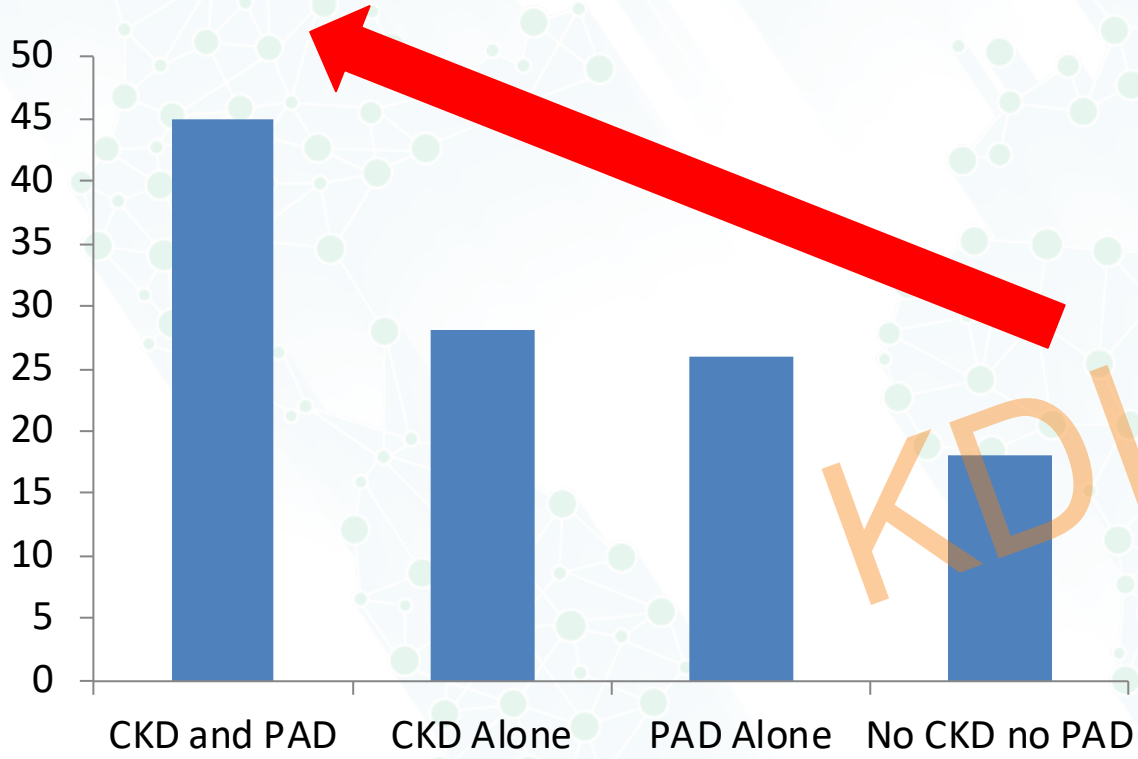
5-year mortality across different conditions



Cancer Registry Ontario, 2012
Criqui et al. N Engl J Med. 1992;326:381-6

Slide courtesy Dr. Alan Hirsch

PAD and CKD: deadly together

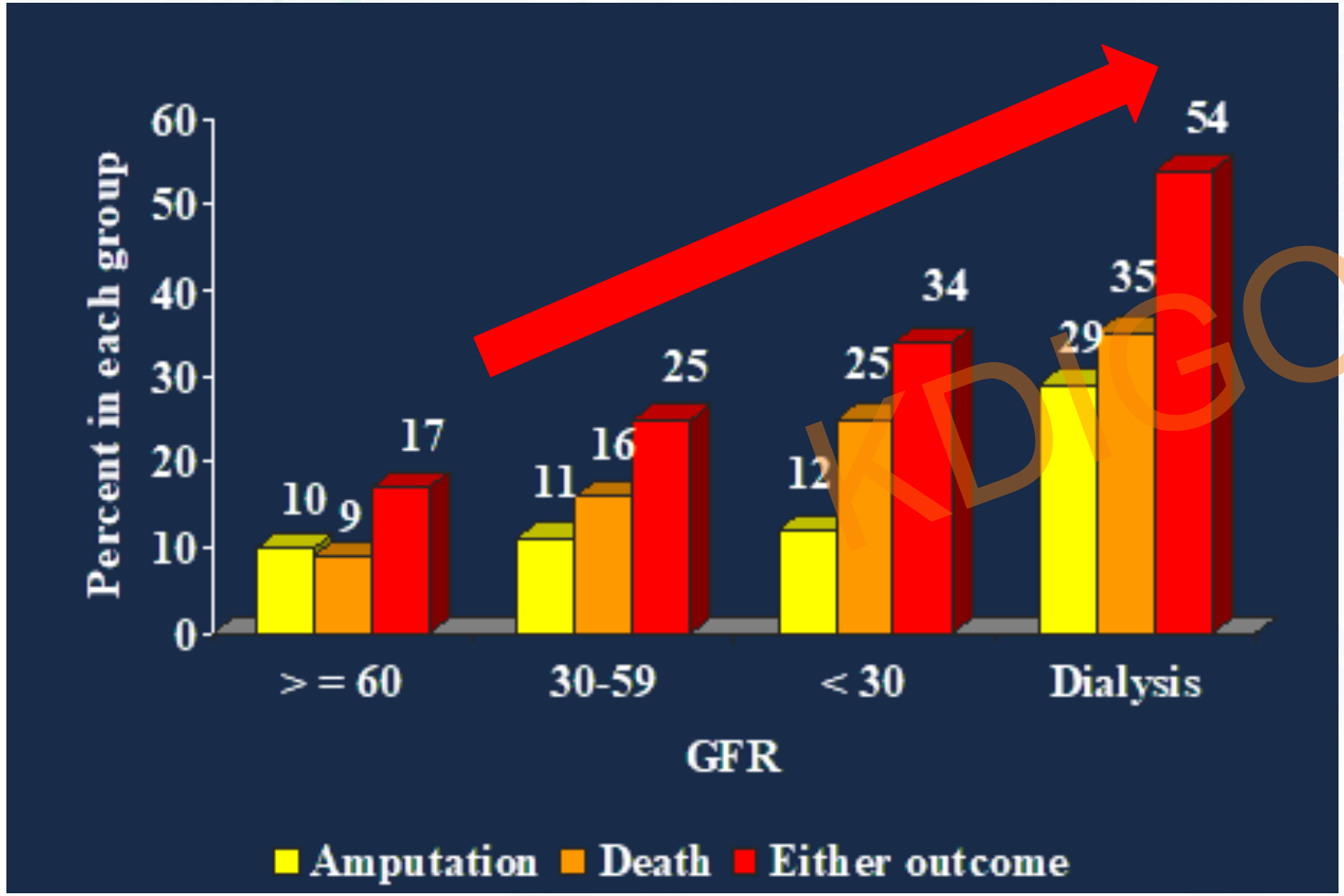


- 1079 persons with CKD defined by eGFR < 60 and PAD (ABI <0.9)
- Increasing 6 year mortality with both CKD and PAD

Liew et al, CJASN 2008

Tarantino, Pulp Fiction 1992

CKD increases risk of amputation and mortality after revascularization



- **>16,000** patients with revascularization or amputation for CLI
- Derived from VA National Surgical Quality Improvement Program
- Outcomes:
  - Morbidity or Mortality within 30 days of procedure
  - Stratified by GFR

O'Hare, Johansen et al. J Vasc Surg 2004

PAD is intervened upon late in CKD patients

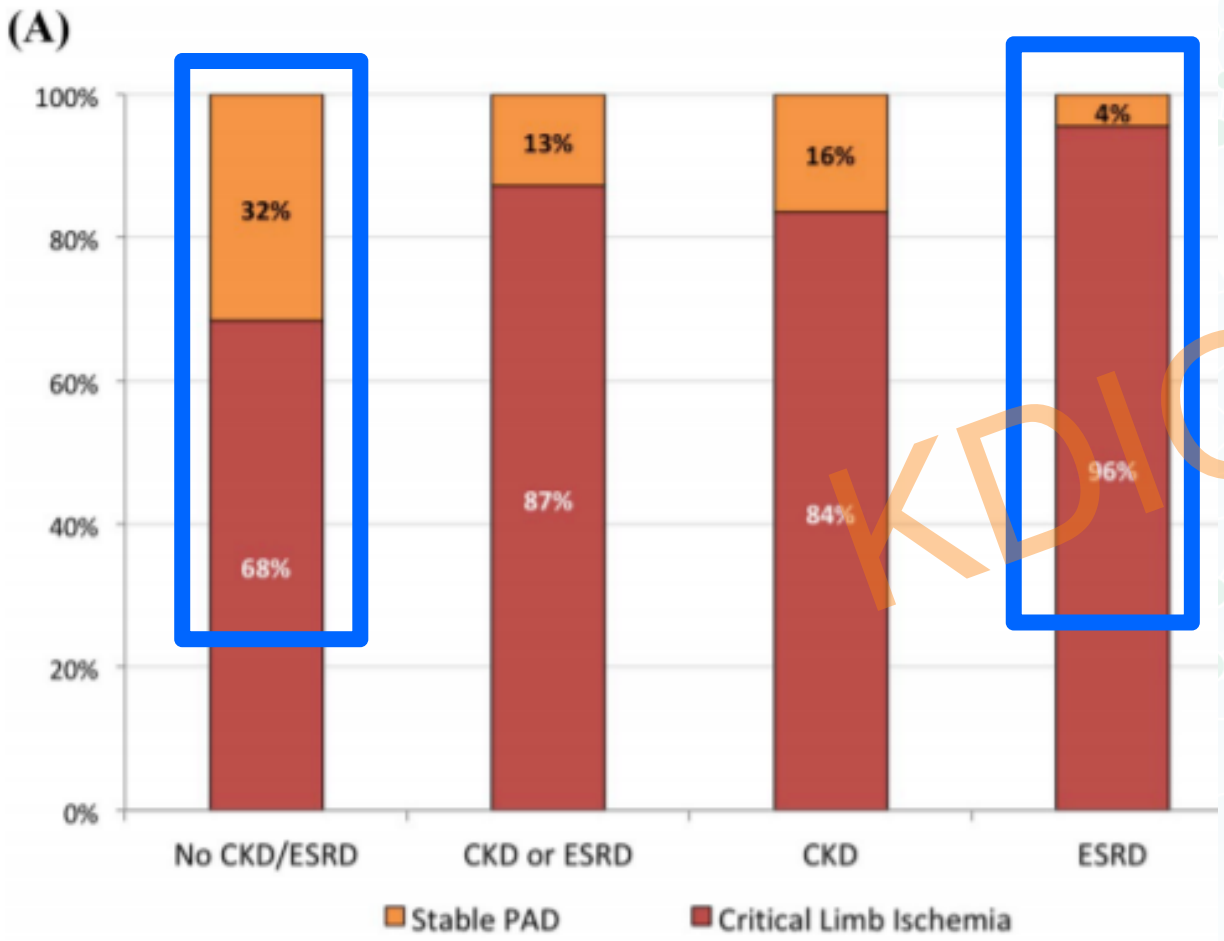
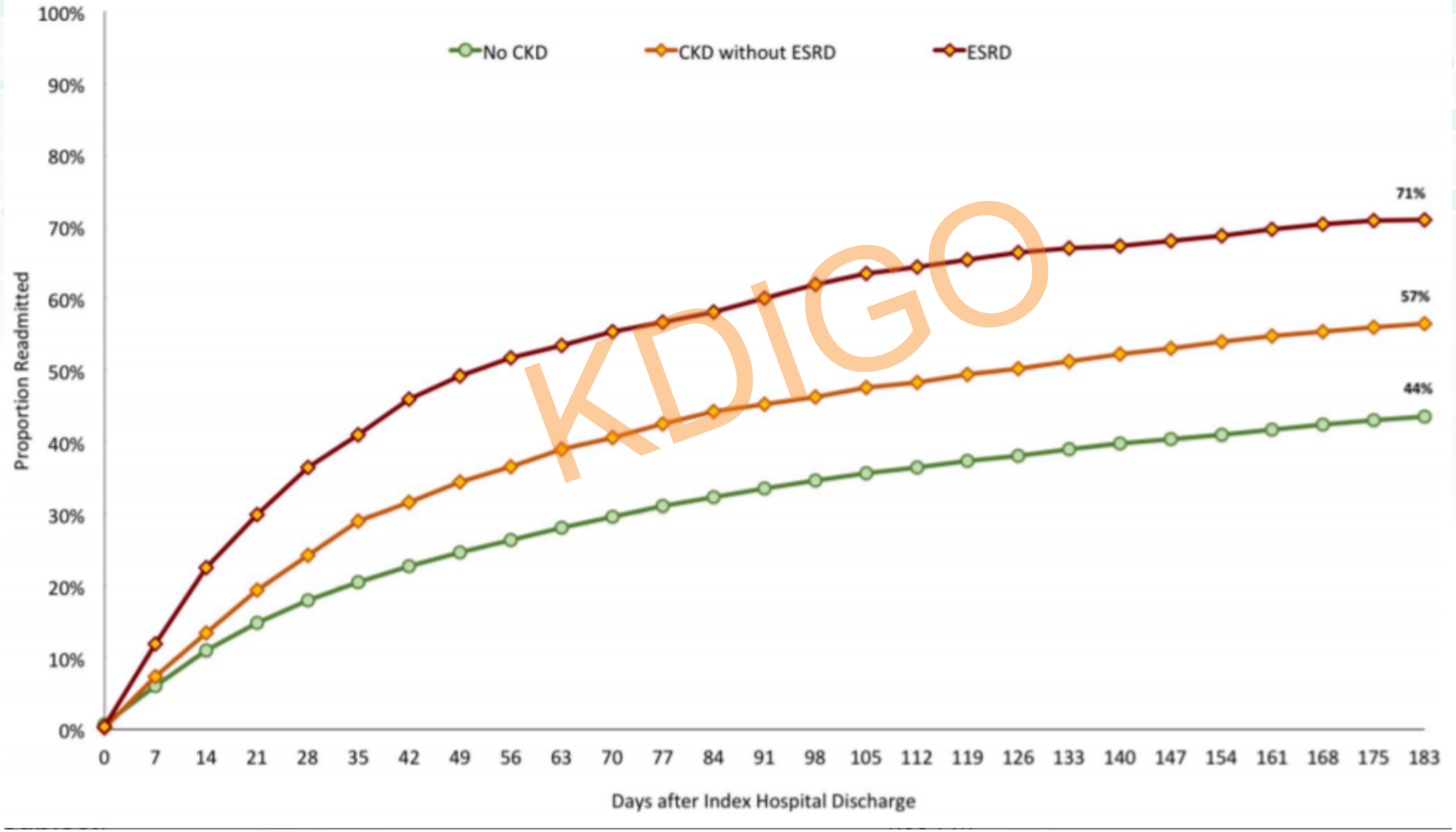


Fig. 1. Characteristics of the index hospitalization by CKD/ESRD status.

- Nationwide Readmission Database
- 39,441 patients with PAD hospitalized for revascularization
- 10,530 (26%) had kidney disease of whom 31% had ESKD

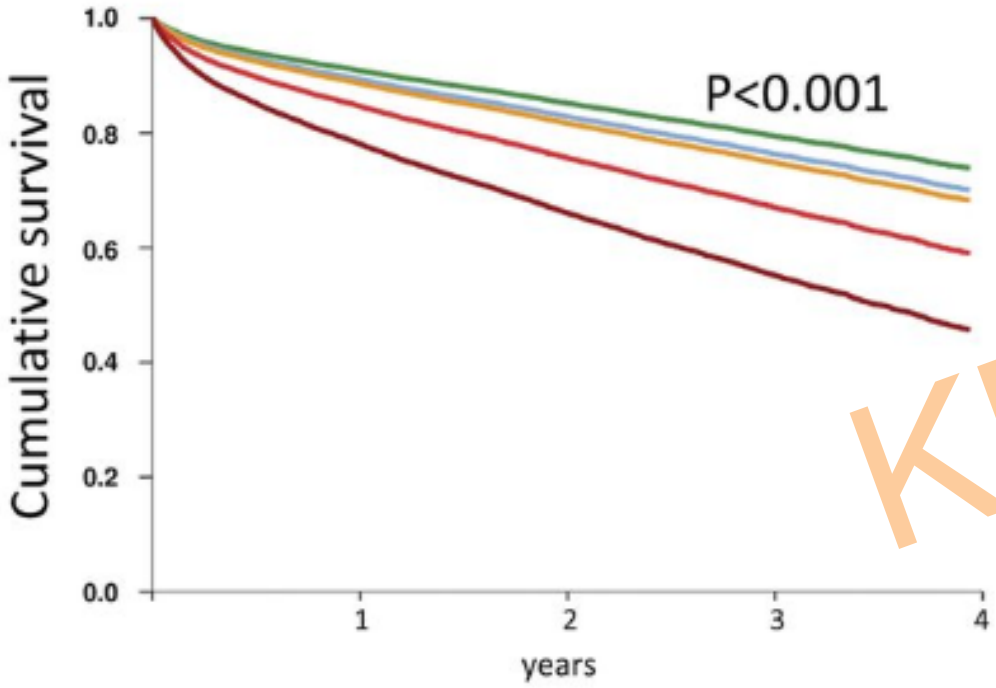
Bhandari, Atherosclerosis 2019

High Readmission & Readmission Rate with PAD and CKD



Bhandari, Atherosclerosis 2019

PAD outcomes in non dialysis CKD remain poor after hospitalizations



no CKD	29,162	18,701	9,285	6
CKD stage 2	1,715	1,124	597	0
CKD stage 3	2,959	1,707	766	0
CKD stage 4	572	289	116	0
CKD stage 5	797	410	183	0

- 41,882 patients in Germany with PAD who had an index hospitalization
- Those with CKD
  - **underwent significantly fewer revascularizations**
  - **Higher amputations**
  - More sepsis and infections
  - Higher MI incidence
  - Greater mortality
- Mortality rates after 4 years were 27% in patients without CKD and 46%, 52%, 72%, and 78% in those with CKD stages 2, 3, 4, and 5

However, we are doing something right…

Trends in Mortality for Endovascular vs. Surgery for PAD in HD Patients

- Used Nationwide Inpatient Sample data between 2002-2012
- Prevalent dialysis patients
- 77,049 endovascular procedures for PAD
- 29,556 surgical procedures for PAD

Garimella et al. JACC: Cardiovascular Interventions 2017

Summary

- PAD is common, prevalence increases with CKD stage
- Outcomes are worse for patients with ANY degree of CKD
- Recognize CKD as PAD risk factors
- Limitations of common diagnostic tests (ABI)
- Include CKD patients (stage 4-5) in trials
- Develop multi-disciplinary approach to PAD care in CKD

The Need of the Hour

Key clinical questions	Practice recommendations	Suggested research
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 and TBI test characteristics in a cohort of CKD**
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 **Prescription of a supervised exercise program in patients with claudication** Revascularization if CLI is present or if above interventions not beneficial	**Meta-analysis of existing RCT and cohort** **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**

Garimella & Hirsch, Adv Chr Kid Dis 2015

Re-Evaluating Peripheral Artery Insufficiency in Renal disease: A call to *REPAIR*

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Associate Professor,
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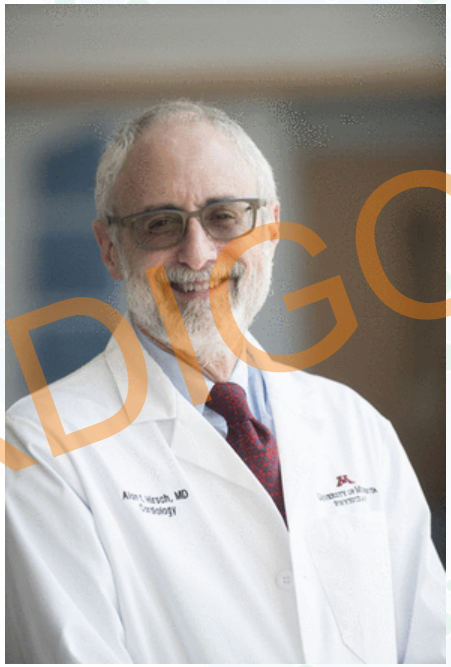

Alan T. Hirsch (1954-2017)
University of Minnesota

Michael Criqui, MD
Emeritus Professor
UCSD

Mark Sarnak, MD, MS
Chief of Nephrology,
Professor, Tufts