

ISCHEMIA-CKD Trial Background and Design

Background

- 17% of US population (~26 million) have CKD¹
- By 2030 >2 million people with ESRD and many more with CKD projected²
- ~500 million worldwide with CKD
- ESRD and CKD associated with high risks of death from CAD³
- CKD patients are 5-10 times more likely to die than to develop ESRD

¹ 1999--2004 NHANES data

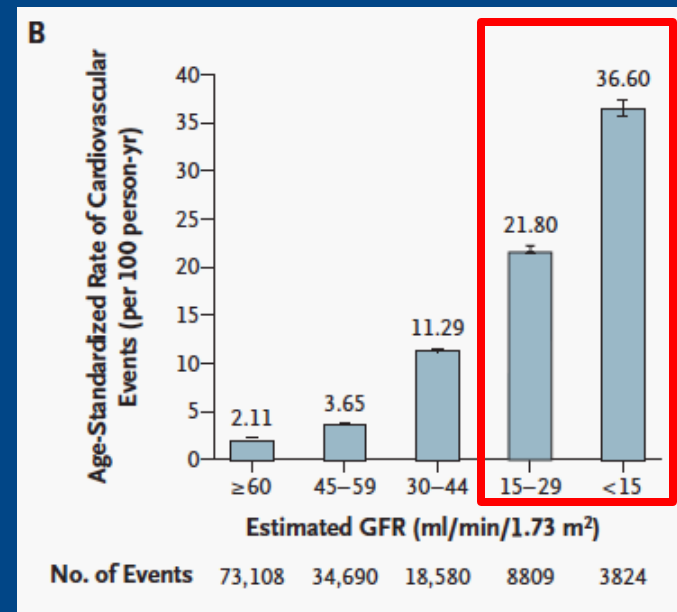
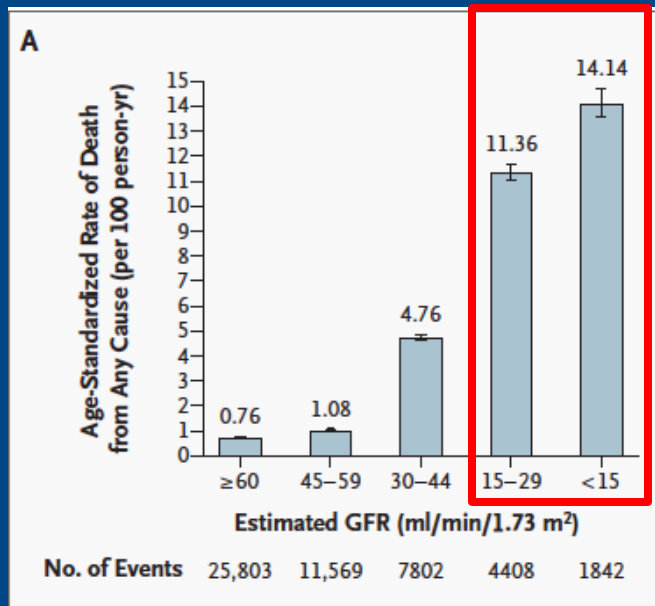
² Gilbertson et al. J Am Soc Nephrol 2003;14:F-PO881

³ Go et al. N Engl J Med 2004;351:1296–1305

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

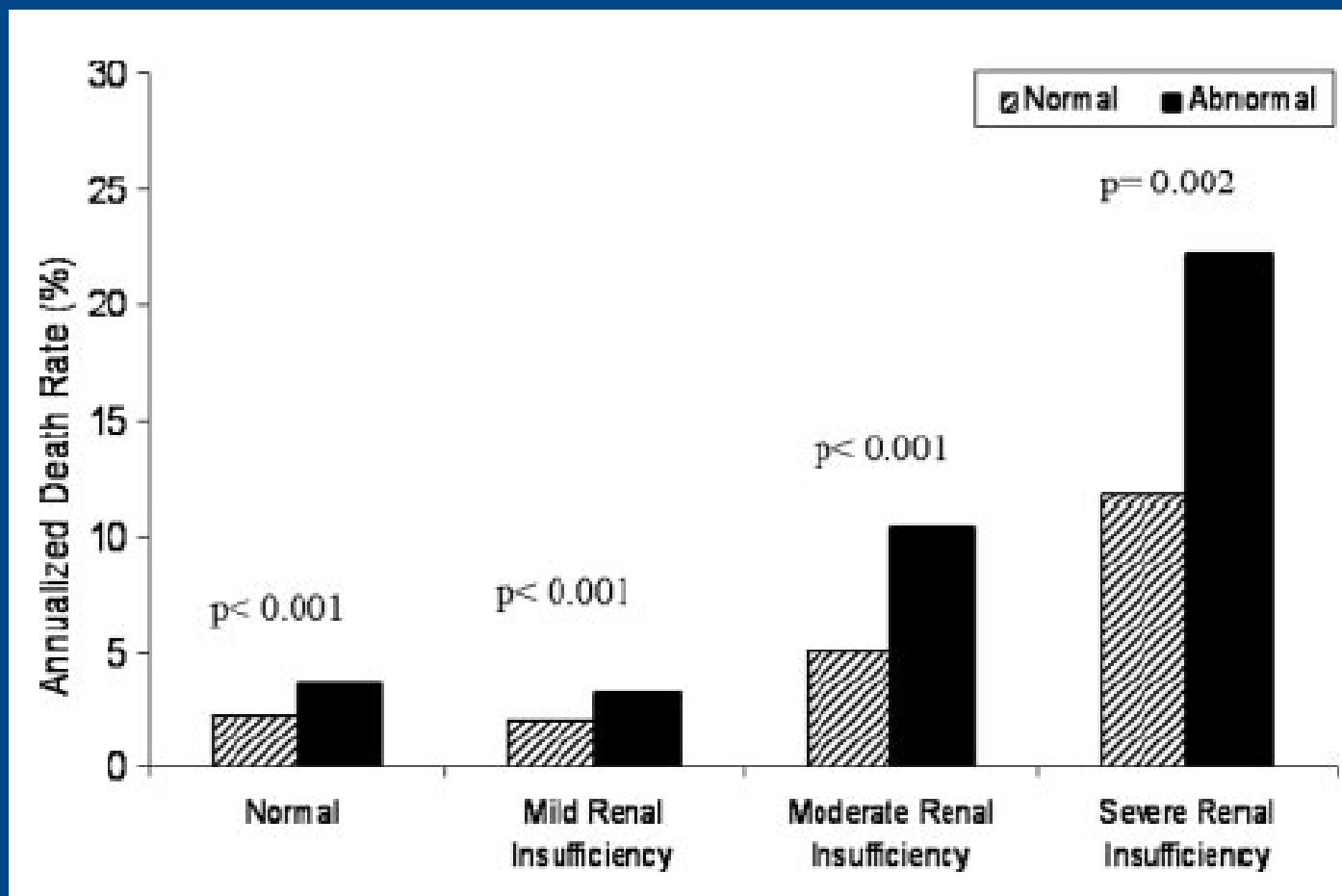
Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

Kaiser Permanente Renal Registry- 1,120,295 stable outpatients not on hemodialysis



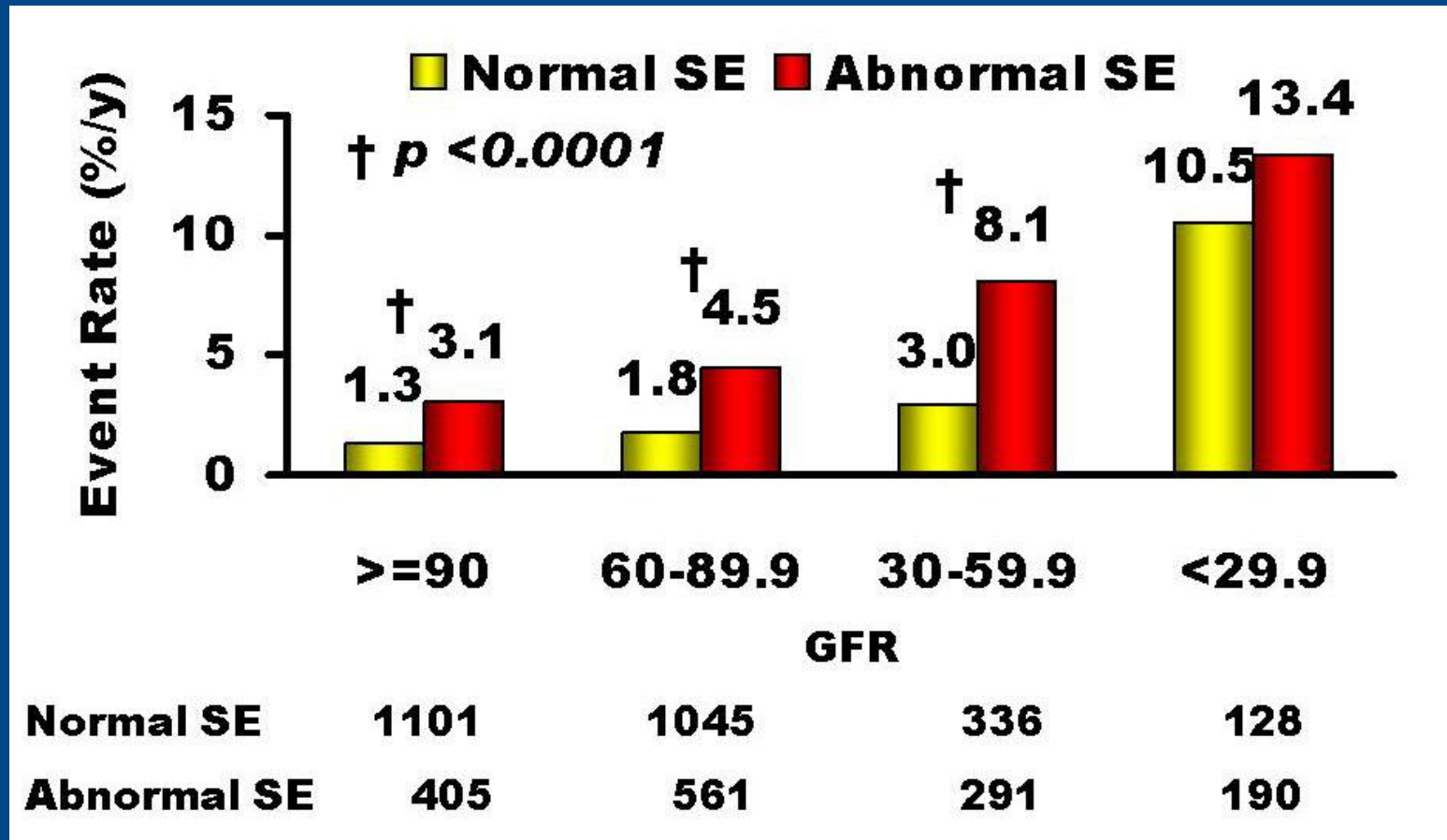
Exponential increase in death and CV events with GFR <30
4 year rates: Death 49%; CV events ~100%

Chronic Kidney Disease & SPECT



7348 consecutive patients without recent MI and referred for SPECT
88% mortality at 4-years in patients with GFR <30 and abnormal
SPECT

Chronic Kidney Disease & Stress Echo



4147 SIHD patients undergoing Stress Echo

53.6% mortality at 4-years in patients with GFR $<$ 30 and abnormal stress echo

Event Rates in Patients with Advanced CKD and Abnormal Stress Test

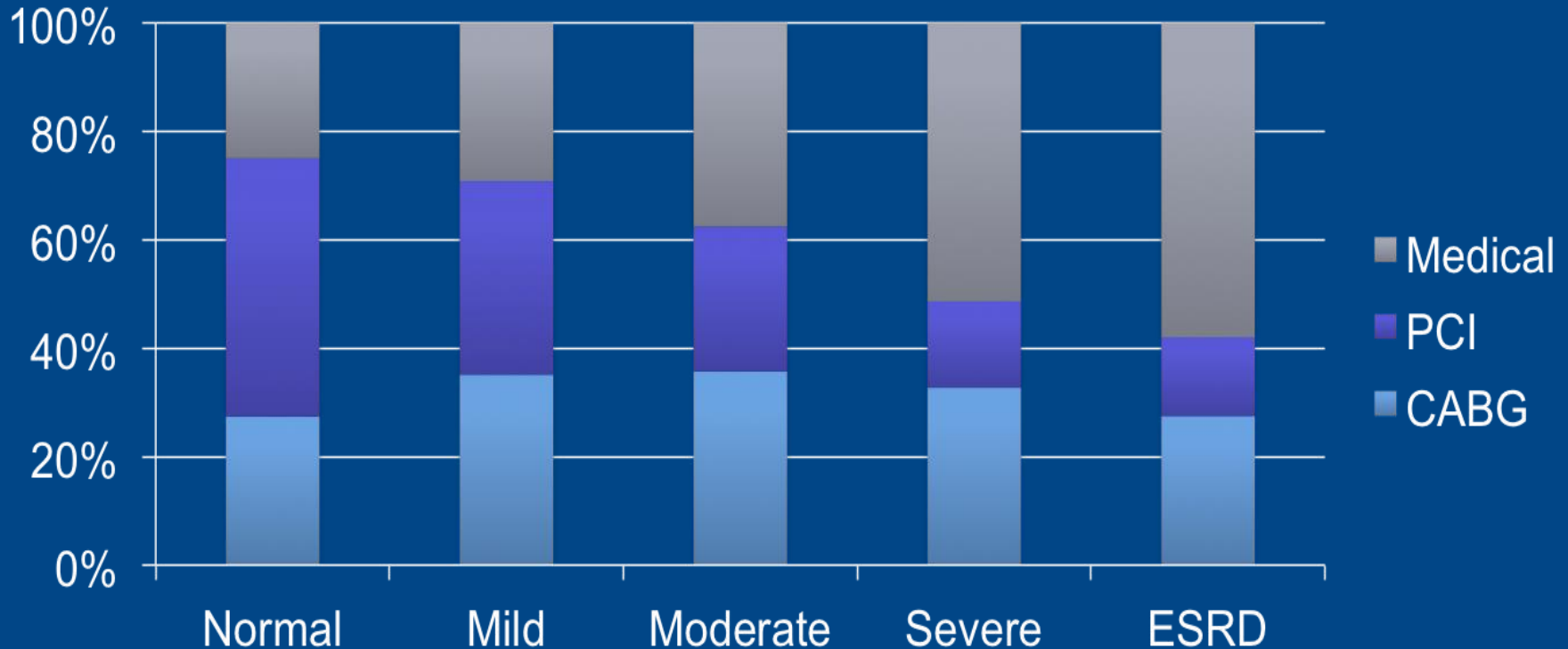
4-year projections

- Exponential increase in mortality
 - All cause mortality >50%
 - CD/MI rate >55%
 - Composite cardiovascular outcome rate >70%
- Prognosis worse than certain cancers

Treatment-Risk Paradox

CKD patients are undertreated with medical therapy and have lower rates of cath, revascularization & referral for stress testing than low risk patients

CKD Patients Undergo Less Revascularization



4584 patients with clinically significant CAD from Duke Database
<50% with severe CKD/ESRD undergo revascularization

Chest pain is a poor predictor of CAD in CKD patients

- Chest pain does not correlate well with CAD in CKD patients- Many are asymptomatic!!
 - likely because of autonomic dysfunction secondary to uremia and diabetes
- Silent CAD three times more prevalent than in the Framingham study population¹
- Most CKD patients lead a sedentary lifestyle
 - assessment of CAD on clinical grounds difficult
- Chest pain has poor sensitivity and specificity for predicting CAD in CKD patients (65% and 66% respectively)²

¹Margolis et al. Am J Cardiol. 1973 Jul; 32(1):1-7.

²Schmidt A et al. Am J Kidney Dis. 2001; 37(1):56-63

CKD and CVD: Summary

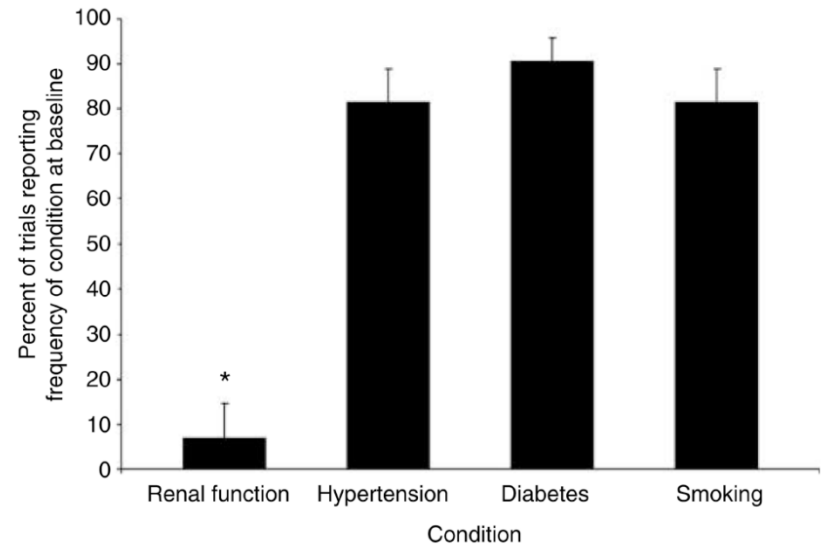
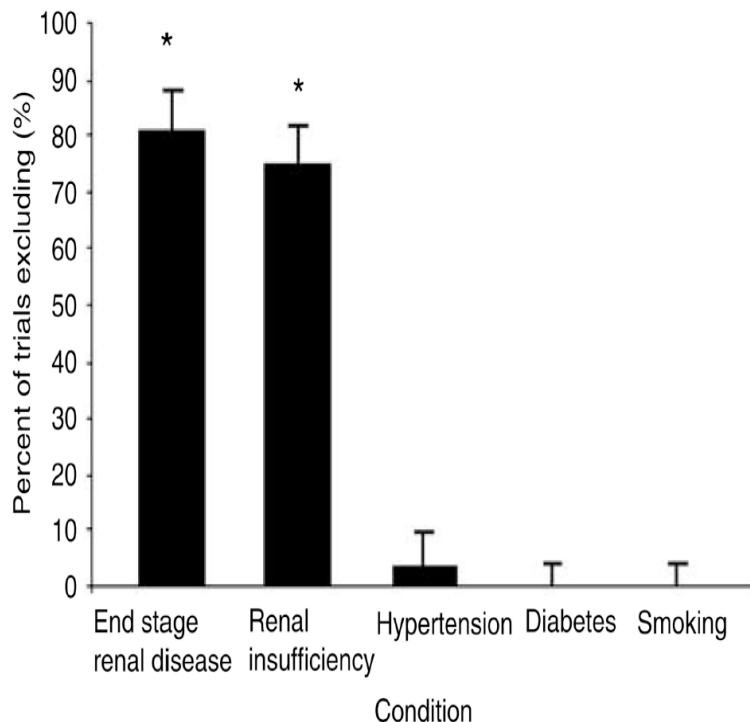
Patients with CKD are at the “highest risk” for CVD
(KDOQI guidelines)

All patients with CKD should undergo routine assessment for CVD because regular screening may help identify CKD patients who would benefit from interventions to reduce CVD risk

Stress testing in CKD patients provides for appropriate risk stratification and prognostication and guides further management to reduce cardiac risk

CKD Patients are Underrepresented in Clinical Trials

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

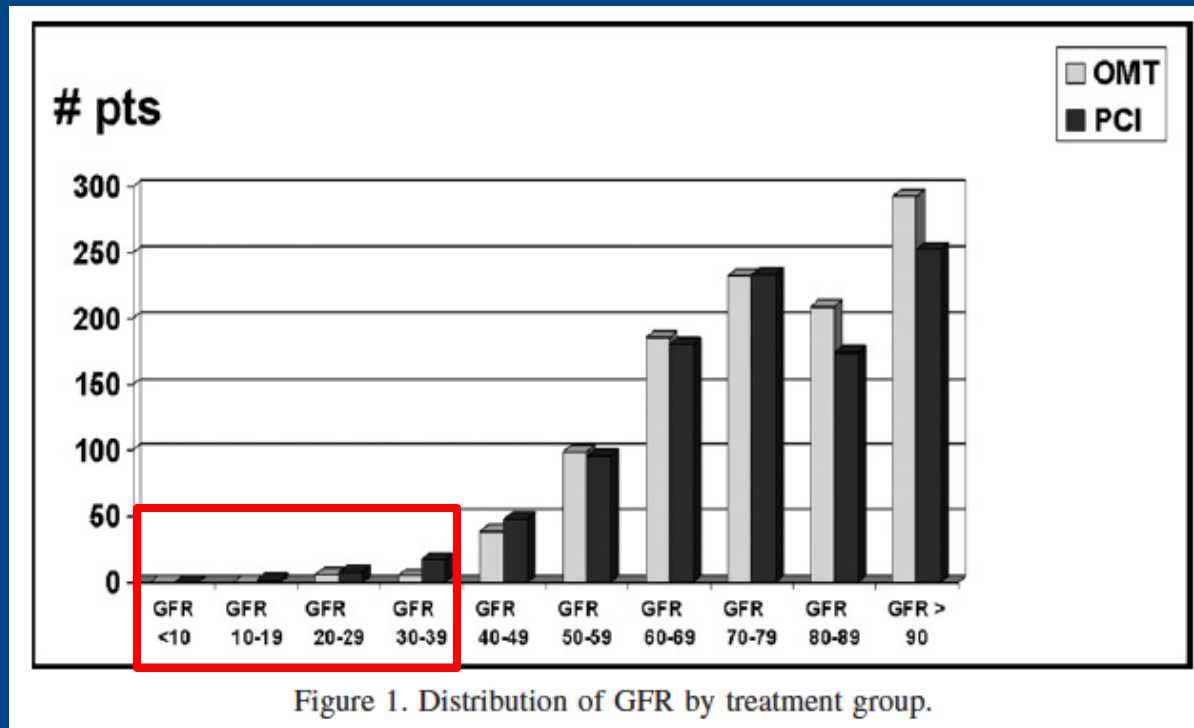


Data from 86 trials randomizing 411 633 subjects

Majority (~80%) of CAD trials exclude CKD/ESRD patients

CKD Under-Represented in Contemporary Revascularization vs. Medicine SHD trials

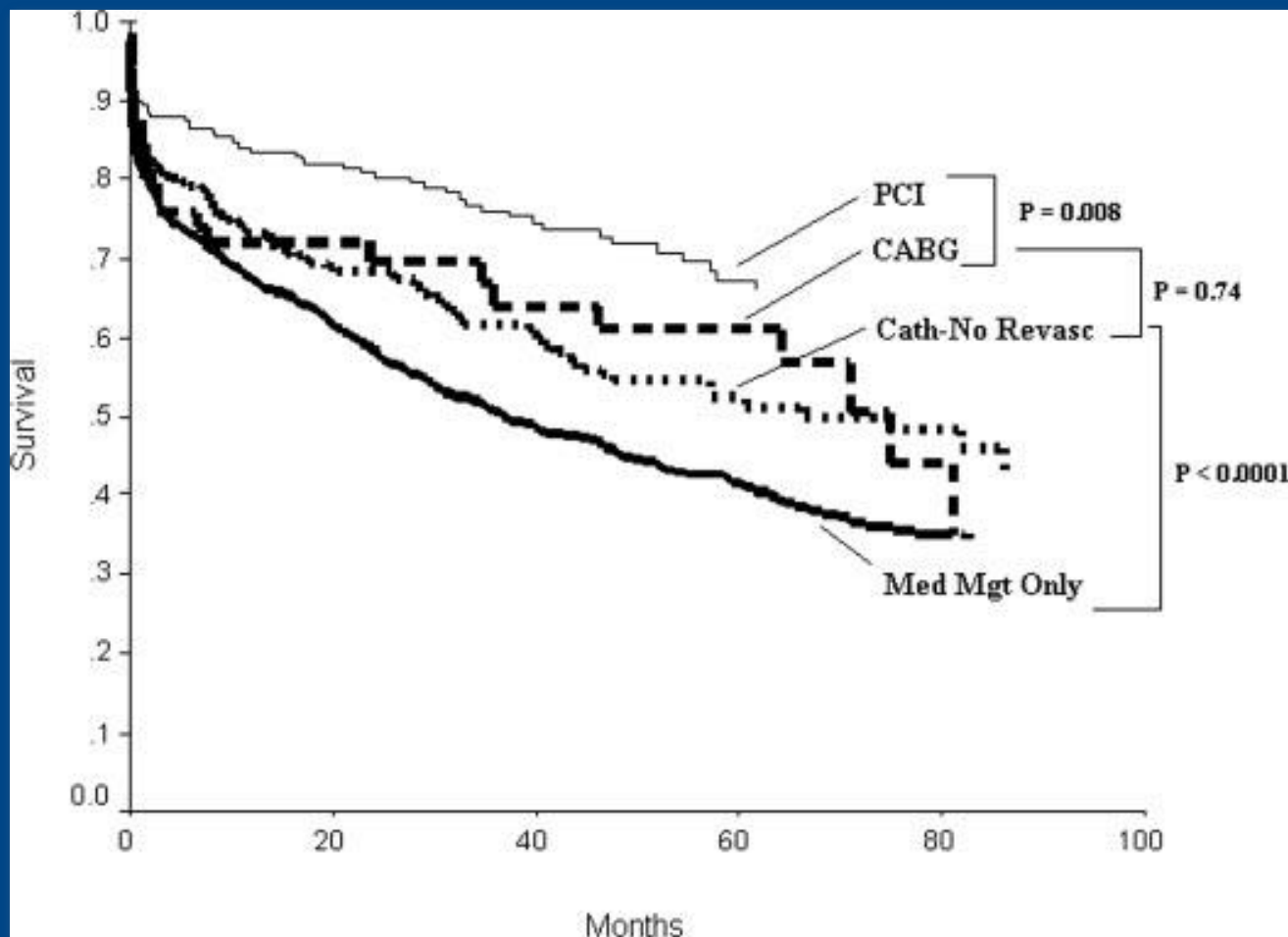
- BARI-2D: Subjects with creatinine >2 mg excluded
- COURAGE: Only 16 patients with GFR <30



ISCHEMIA-CKD Trial

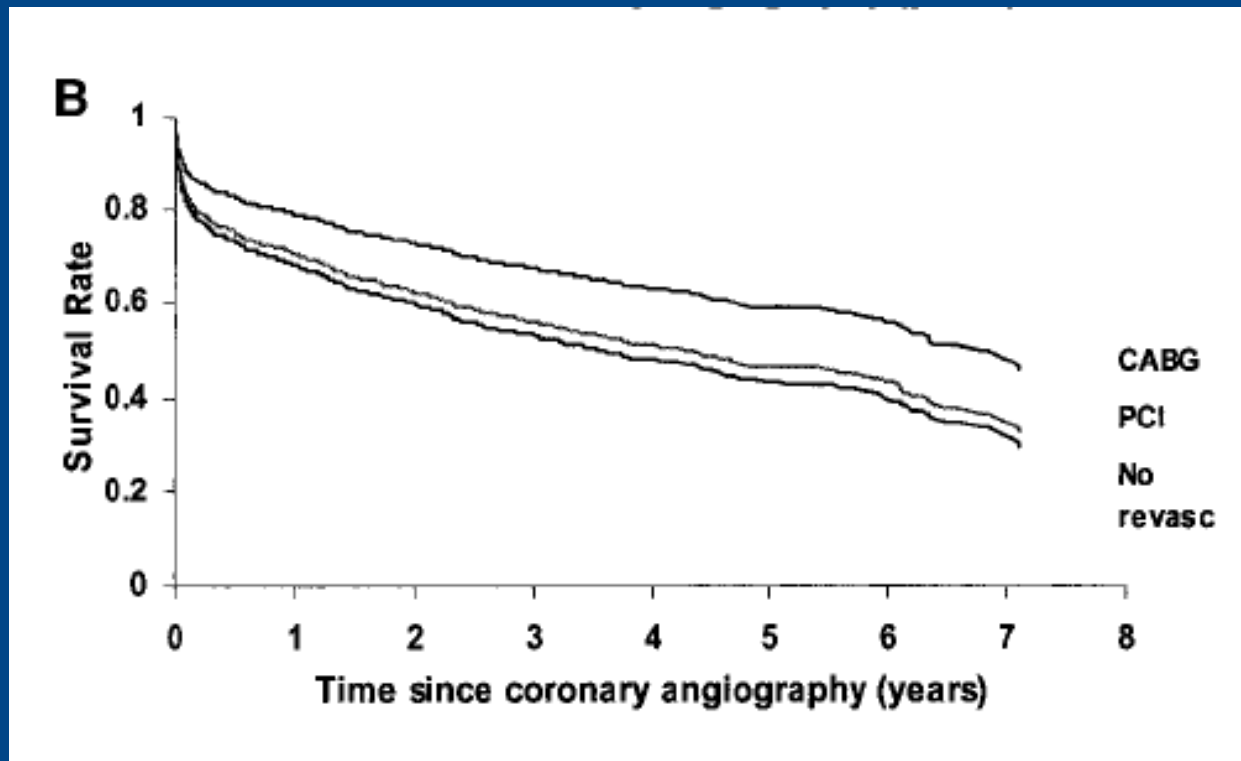
Revascularization vs. Medical Therapy in CKD Patients

Revasc vs. Medical Therapy: Mortality



ACS patients with CKD (eGFR <60 or on HD)

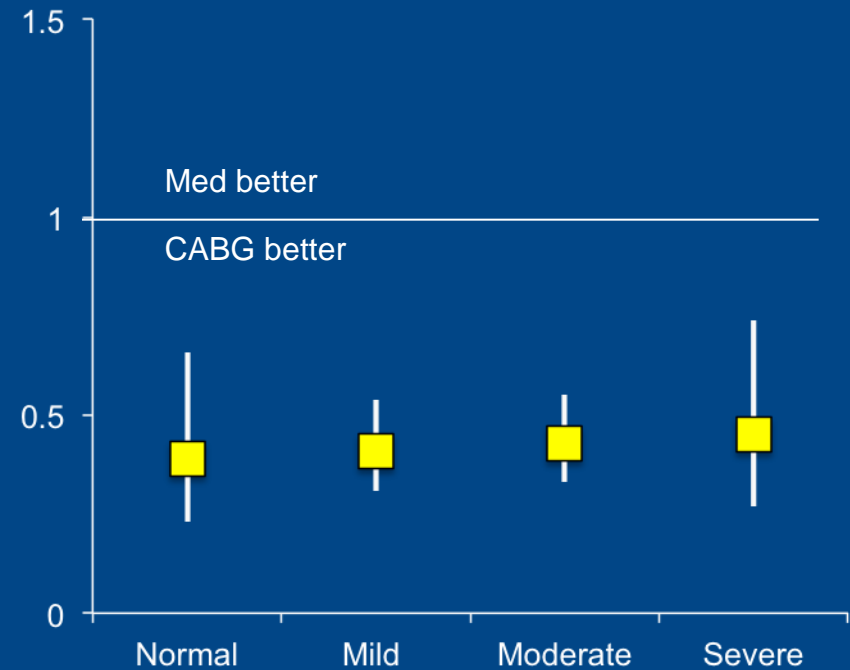
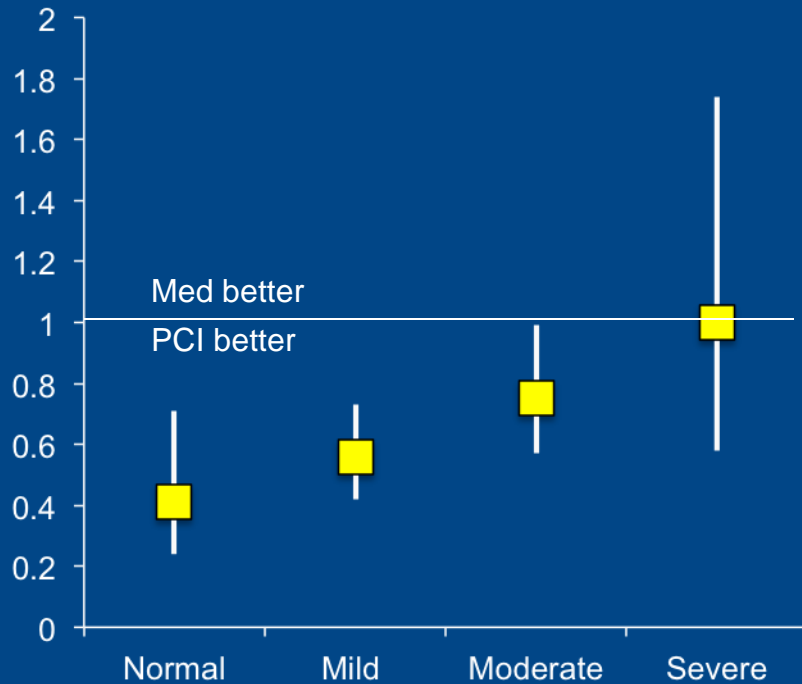
Revasc vs. Medical Therapy: Mortality



APPROACH Registry: 750 non-dialysis dependent CKD patients with or without ACS undergoing cardiac cath

Better outcomes with CABG when compared with PCI or no revasc

Revasc vs. Medical Therapy: Mortality



4584 patients with clinically significant CAD from Duke Database

Revasc vs. Medical Therapy for CKD Patients: Observational Studies

- Potential benefit of PCI vs. medical therapy
- Potential benefit of CABG vs. medical therapy
- However quality of medical therapy unknown
- Selection and ascertainment bias driving the results
- Despite the data, <50% of CKD patients undergo cath

ISCHEMIA-CKD Trial Trial Design

Patients with site determined
ischemia and eGFR <30 or on
dialysis¹

No CCTA

Simplified criteria
for ETT/expanded
def of ischemia

RANDOMIZE
N = 1000

INVASIVE Strategy
OMT² + Cath +
Optimal Revascularization

CONSERVATIVE Strategy
OMT² alone
Cath reserved for OMT failure

Average 4 Years of Follow-up
Primary Endpoint: Composite of Death and MI

¹ Low probability of significant left main disease based on assessment by PI

² OMT=Optimal medical therapy

Overview

- Primary objective: to determine whether the INV strategy reduces the incidence of death or nonfatal MI compared with CON in participants with advanced CKD (eGFR <30 or on dialysis)
- 500 patients with advanced CKD will be randomized in ISCHEMIA-CKD
- Designed to run seamlessly with the main ISCHEMIA study
- ISCHEMIA-CKD will be the largest treatment strategy trial in advanced CKD patients with stable ischemic heart disease

Major Inclusion/Exclusion Criteria

Major Inclusion Criteria

- Site-determined ischemia on an ischemia test
- eGFR <30 or on dialysis

Major Exclusion Criteria

- LVEF < 35%
- Acute coronary syndrome within the previous 2 months
- PCI within the previous 12 months
- Prior CABG unless the anatomy is known to be suitable for complete revascularization

Enrollment and Randomization Process

- Similar to main trial patients with eGFR 30-59 (eg, no CCTA) with some exceptions:
 - Enrollment and randomization based exclusively on site determined ischemia, therefore pre-enrollment ischemia verification is NOT available for ISCHEMIA-CKD
 - ETT criteria does not require CCTA performance
 - Expanded definition of moderate ischemia requires site read ischemia that is less than moderate plus either heart rate $\leq 75\%$ of predicted maximum or peak workload not to exceed stage 2 or 7 Mets
 - Other ancillary criteria for moderate ischemia are outlined in the FAQs (age, duration of dialysis etc)

Eligibility of Patients on List for Renal Transplant

Patients on the renal transplantation list may be particularly suitable for the trial because:

- The average wait time for renal transplantation is ~5-7 years. Most patients can be enrolled into the trial and still go on to receive renal transplantation.
- There is a 50% chance of not receiving cath and thus preventing exposure to contrast.
- Participants randomized to the CON arm (optimal medical therapy only) can cross over to cath closer to the time of renal transplantation, if cath is the standard of care prior to renal transplant.
- Patients with CKD have increased risk of restenosis and need for repeat revascularization after PCI or CABG. If the usual practice is for CKD patients to undergo cath when they are listed, they may need another cath prior to their renal transplant in 5-7 years. It may therefore be best to allow them to participate in the trial and revascularize closer to transplantation.

Impact of Revascularization on Outcome Prior to Non- Cardiac Surgery (including renal transplant): Review of Evidence

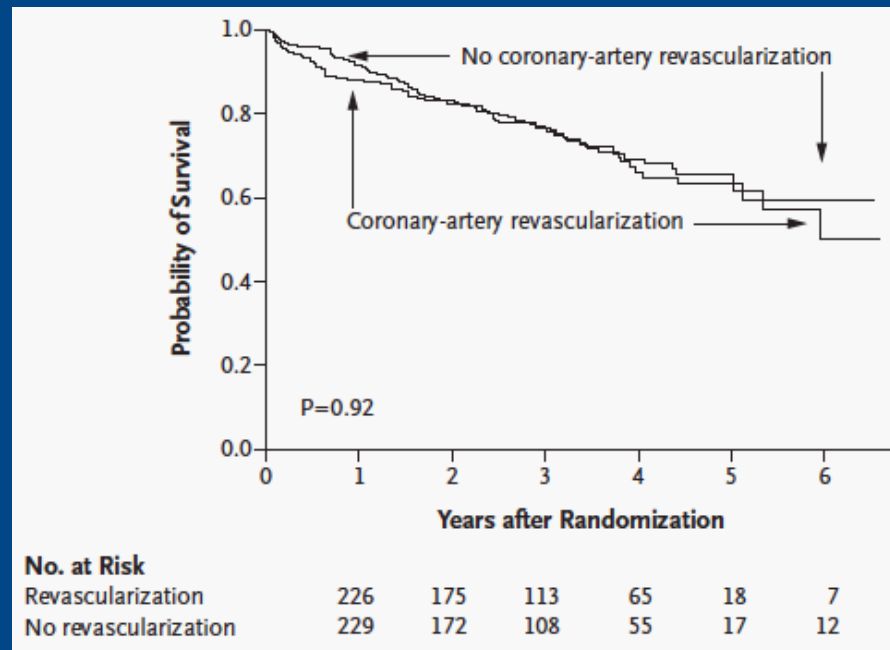
The NEW ENGLAND JOURNAL of MEDICINE

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Coronary-Artery Revascularization before Elective Major Vascular Surgery



No benefit of revascularization prior to major vascular surgery

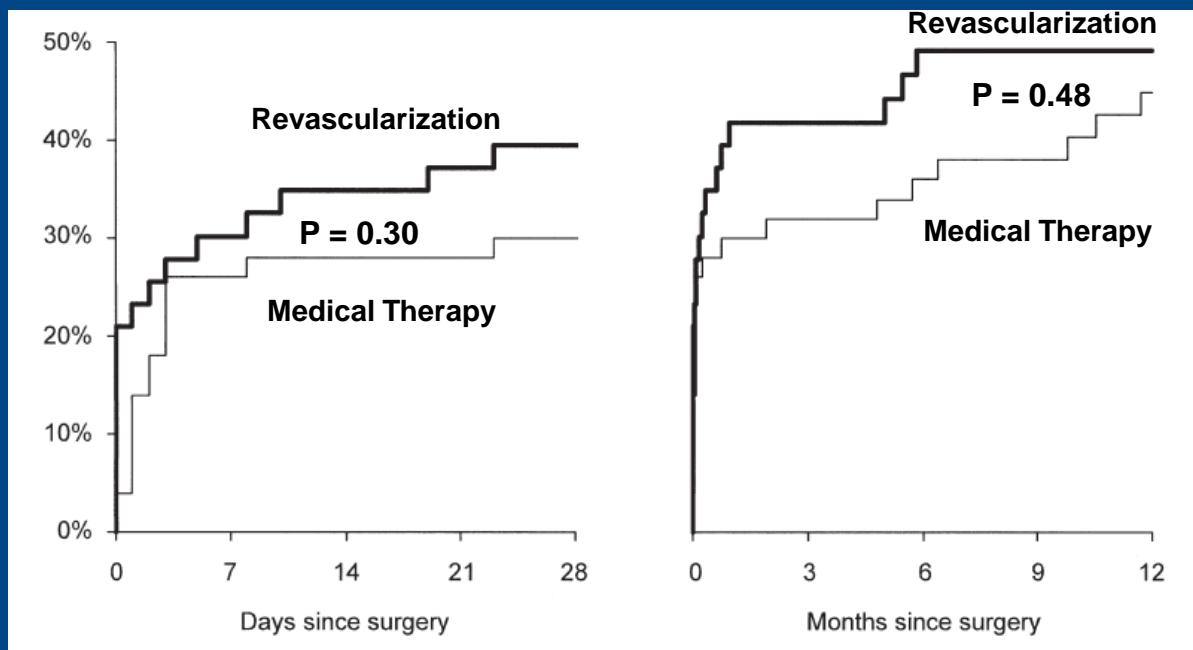
N Engl J Med 2004;351:2795-804

ISCHEMIA
CKD

Aug.01.2015

A Clinical Randomized Trial to Evaluate the Safety of a Noninvasive Approach in High-Risk Patients Undergoing Major Vascular Surgery

The DECREASE-V Pilot Study



- Patients with extensive stress-induced ischemia (5 segments or 3 walls)
- 46% with Angina
- Preoperative coronary revascularization in high-risk patients was not associated with an improved outcome (numerically higher events)

J Am Coll Cardiol 2007;49:1763–9

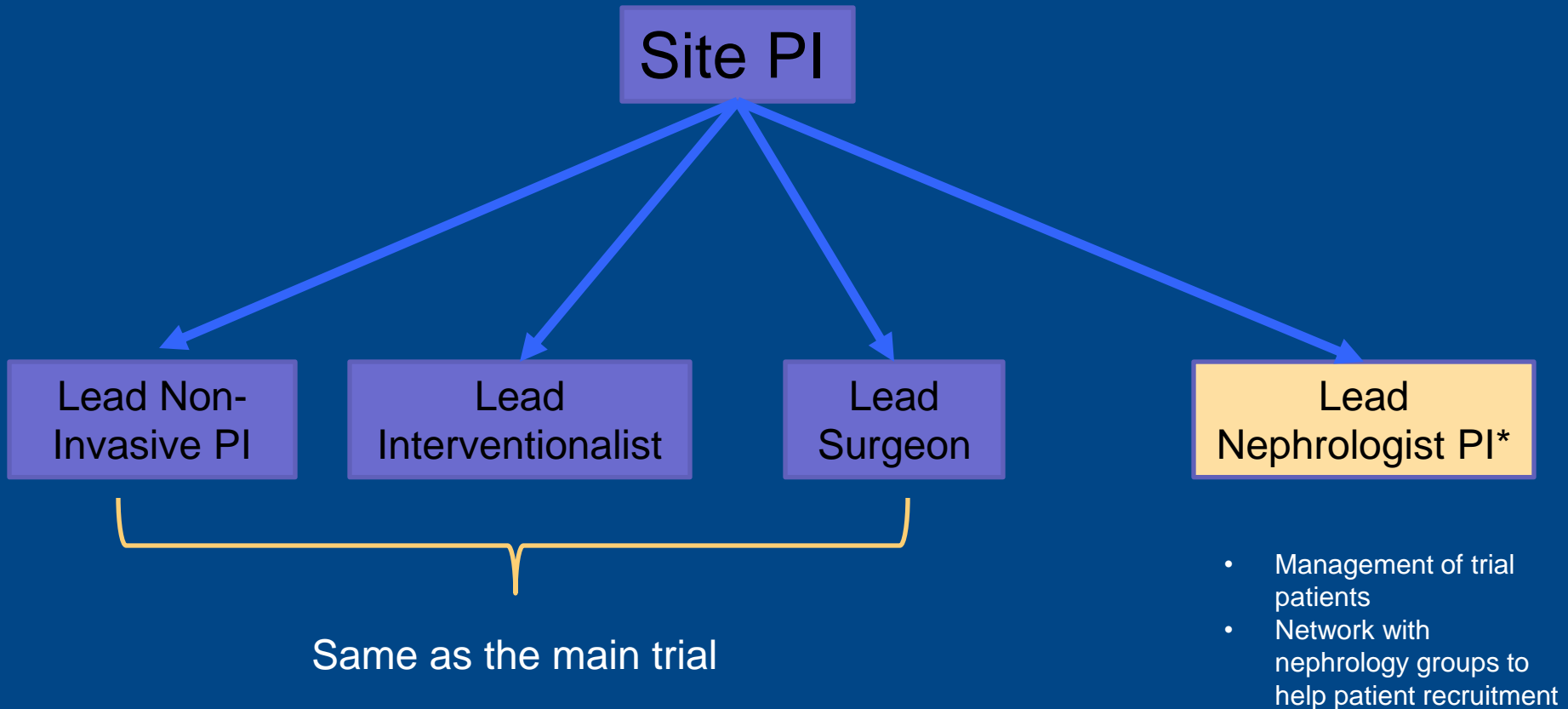
Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates

A Scientific Statement From the American Heart Association and the
American College of Cardiology Foundation

*Endorsed by the American Society of Transplant Surgeons,
American Society of Transplantation, and National Kidney Foundation*

There is no evidence to support prophylactic
preoperative percutaneous revascularization in
patients with asymptomatic ischemia or stable angina

Site Organization



* May vary based on local practice and for certain sites the role could be consultant/advisory only

Unique Design Reduces Contrast Exposure

- Contrast exposure risk in the CKD trial:
 - **No contrast exposure**: 50% of patients (OMT arm)
 - **Some contrast exposure**: ~25% of patients (diagnostic cath+CABG)
 - **Contrast exposure**: ~25% of patients (diagnostic cath+PCI)