"Epidemiology, Diagnosis and Management of Renovascular Disease"

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KDIGO Controversies
Dublin, Ireland

February, 2020

Disclosures

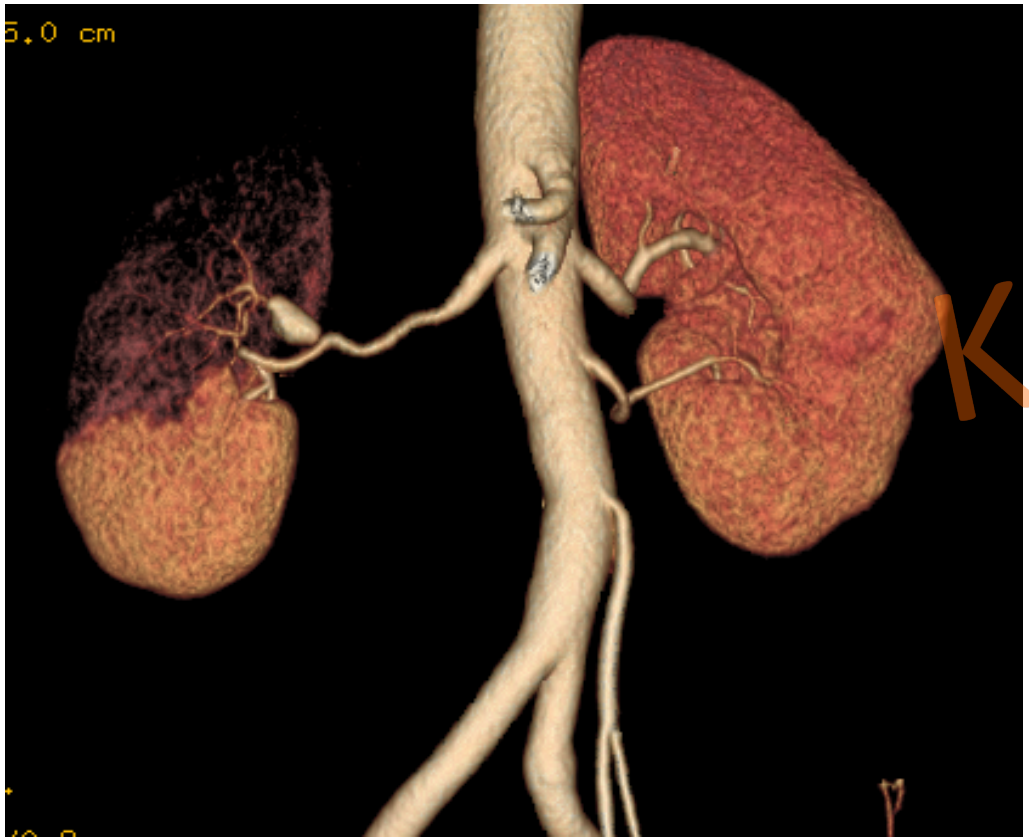
Site PI: CORAL Trial

NHLBI / NIDDK

Mayo Center for Regenerative Medicine

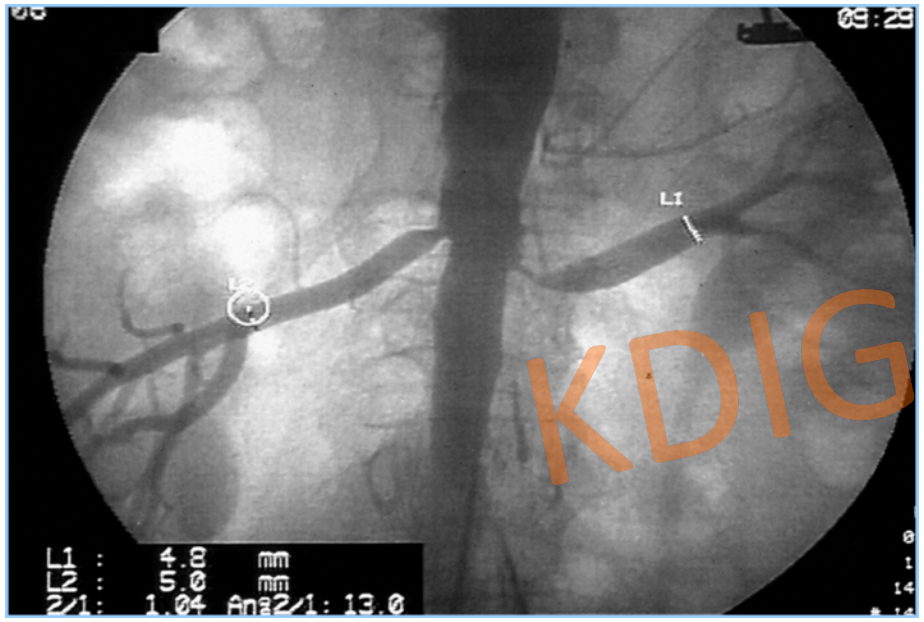
Section Editor: UpToDate

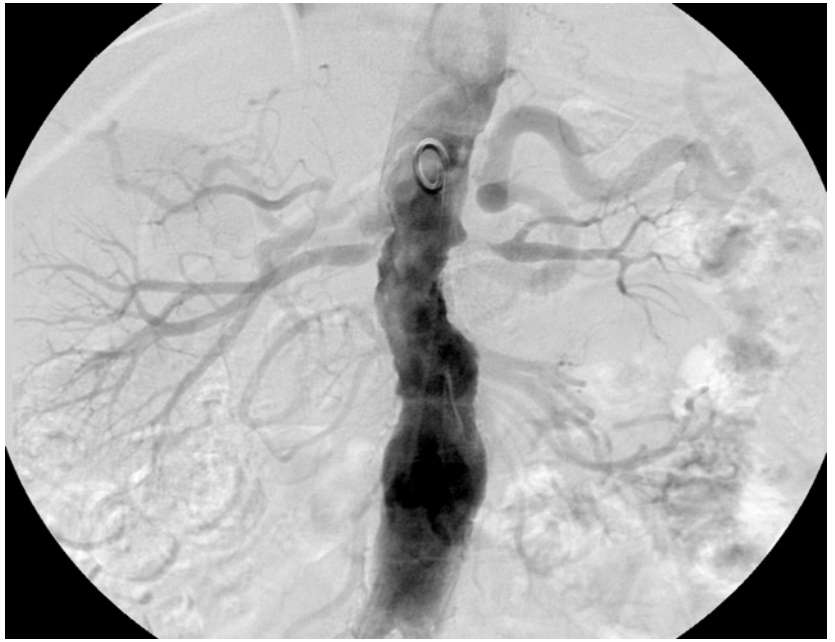
Renovascular Hypertension due to arterial occlusive lesions



- **Fibromuscular dysplasia**
- **Atherosclerotic disease**
- **Renal artery embolism**
- **Dissection / thrombosis**
- **Post-traumatic injury**
- **Aortic stent graft occlusion**

Spectrum of Renovascular Disease Manifestations :





Asymptomatic "Incidental RAS"

Renovascular Hypertension

Accelerated CV Disease
Congestive Heart failure
Stroke

Ischemic Nephropathy

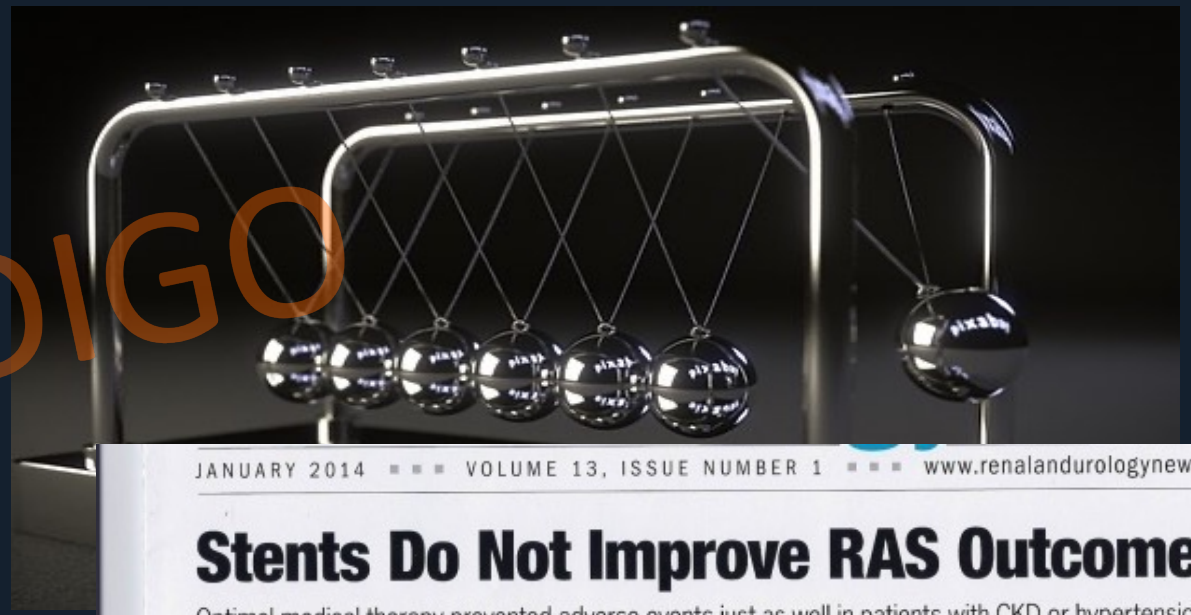
Note: This peripheral vascular disease threatens the kidney

Renovascular Hypertension and Ischemic Nephropathy 2020

- Prevalence / Associated Disease
- Pathophysiology / Clinical manifestations
- Medical Rx: role of ACE / ARB
- Prospective Trials: low risk groups
- High-risk subsets
- Renal Revascularization 2020:

Renal Artery Stents: The Current Clinical Narrative

- Renal Revascularization: MAJOR Pendulum Swings



KDIGO

Editorial Comment

Open Renal Arteries Are Better Than Closed Renal Arteries

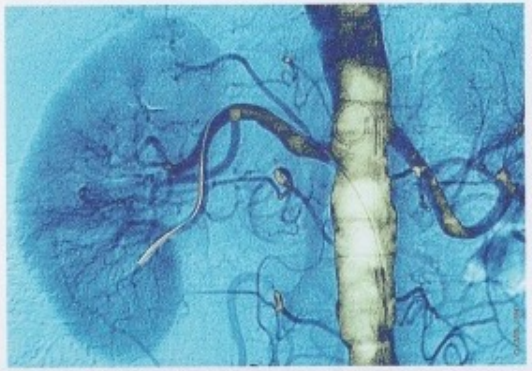
Christopher J. White, MD
Department of Cardiology,
Ochsner Clinic,
New Orleans, Louisiana

2000

JANUARY 2014 ▪▪▪ VOLUME 13, ISSUE NUMBER 1 ▪▪▪ www.renalandurologynews.com

Stents Do Not Improve RAS Outcomes

Optimal medical therapy prevented adverse events just as well in patients with CKD or hypertension



BY WAYNE KUZNAR

DALLAS—Renal artery stenting confers no additional benefit beyond optimal drug therapy for preventing adverse renal and cardiovascular events in patients with renal artery stenosis (RAS) and chronic kidney disease (CKD) or hypertension, a...data from a randomized cli...

The research findings fr... (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) study, presented by Christopher J. Cooper, MD, at the American Heart Association's Scientific Sessions 2013 and published online ahead of print in the *New England Journal of Medicine*, support those from other recent clinical trials of renal artery stenting and should prompt fur... ther restriction of its use. After initial enthusiasm in the late 1990s and early 2000s for renal artery stenting for patients with atherosclerotic RAS or hypertension, use of the intervention had already been declining based on studies published prior to CORAL, ...Creager, MD, Director of th... Center at Brigham and ...ospital in Boston.

"I hope [the CORAL study] does alter how people take care of patients. I think what it shows is, that with good medical therapy, the majority of patients can be managed without the need for a stent," said Dr. Cooper, Chairman of the Department of Medicine at the University of Toledo in Ohio.

continued on page 8

2014

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“Face Validity” Paradox: Internet Truth

- “Blood circulation is one of the most important functions in the body. It supplies oxygen to the brain and other organs.”

- It’s what makes our bodies work.”

Vital Proteins: Natural Whole Nutrition Blog

“The kidney needs blood”.

S C Textor

"The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review"

de Mast Q, Beutler JJ: J. Hypertens. 27:1333, 2009

N=40 Studies: 15, 879 patients (Population estimate: 6.8%)

"50% luminal" narrowing: Pooled Prevalence rates

- "Suspected Renovascular HTN" 14.1%
- Coronary Angiography: 10.5%
  - With HTN: 17.8%
- Peripheral vascular disease: 25.3%
- AAA: 33.1%
- ESRD: 40.8% ?
- Congestive Heart Failure: 54.1% ?

Trial results assure many Individuals with ARVD will be exposed to reduced renal blood flows for prolonged time periods.

Diagnosis of Renovascular Disease

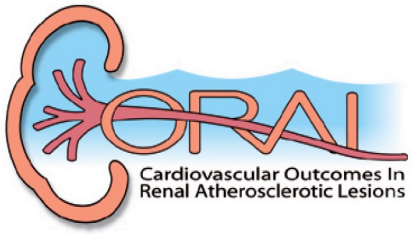
- Imaging: non-invasive
  - Renal artery duplex ultrasound
  - CT angiography
  - MR angiography
- Angiography
  - Translesional gradients / Functional Flow reserve
- Functional measures
  - Hormonal activation: renin-angiotensin system
  - Blood Oxygen Level Dependent (BOLD) MR

Clinical Features: Renovascular Hypertension

- Activated Renin-angiotensin-aldosterone system
- Paroxysmal symptoms: adrenergic activation
- Abnormal Circadian Rhythm
- Accelerated Target organ damage
  - Left Ventricular Hypertrophy
  - Microvascular disease
  - Renal injury: fibrosis/ ischemia

Medical Therapy of Renovascular Disease

- ACE / ARB as part of Regimen
  - Stability of GFR
  - Potassium
  - Adequacy of BP Control
- Calcium Channel Blockade
- Multiple Drug Regimens
- CV Risk: Statins, Aspirin, Smoking



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

Table 1. Baseline Characteristics of the Study Population, According to Treatment Group.*

Characteristic	Stenting plus Medical Therapy (N=459)	Medical Therapy Only (N=472)
Age (yr)	69.3±9.4	69.0±9.0
Male sex (%)	51.0	48.9
Race (%)†		
Black	7.0	7.0
Other	93.0	93.0
Body-mass index‡	28.2±5.3	28.7±5.7
Systolic blood pressure (mm Hg)	149.9±23.2	150.4±23.0
Blood pressure at target level (%)§	29.2	25.3
Estimated GFR (ml/min/1.73 m²)¶	58.0±23.4	57.4±21.7
Stage ≥3 chronic kidney disease (%)	49.6	50.4
Method of identification of stenosis (%)		
Angiography	68.4	68.6
Duplex ultrasonography	25.5	24.2
Computed tomographic angiography	4.4	5.3
Magnetic resonance angiography	1.7	1.9
Medical history and risk factors (%)		
Diabetes	32.4	34.3
Prior myocardial infarction	26.5	30.2
History of heart failure	12.0	15.1
Smoking in past yr	28.0	32.2
Hyperlipidemia	89.4	90.0
Angiographic findings‖		
% Stenosis, as assessed by core laboratory	67.3±11.4	66.9±11.9
% Stenosis, as assessed by investigator	72.5±14.6	74.3±13.1
Global ischemia (%)**	20.0	16.2
Bilateral disease (%)††	22.0	18.1

CORAL
Cardiovascular Outcomes In Renal Atherosclerotic Lesions

Baseline :

-*BP: reasonably controlled*

-*eGFR preserved*

-*Degree of stenosis*

-*overestimated on site*

-*fewer than 20% above 80%*

N.Engl.J.Med: 370: 13, 2014

Primary End-Point: CORAL

Cardiovascular Outcomes In Renal Atherosclerotic Lesions

Table 2. Clinical End Points.*

	Stenting plus Medical Therapy (N=459)	Medical Therapy Only (N=472)	Hazard Ratio (95% CI)	P Value
	no. (%)			
	161 (35.1)	169 (35.8)	0.94 (0.76–1.17)	0.58
	20 (4.4)	20 (4.2)		
	12 (2.6)	16 (3.4)		
	30 (6.5)	27 (5.7)		
	27 (5.9)	26 (5.5)		
	68 (14.8)	77 (16.3)		
	4 (0.9)	3 (0.6)		

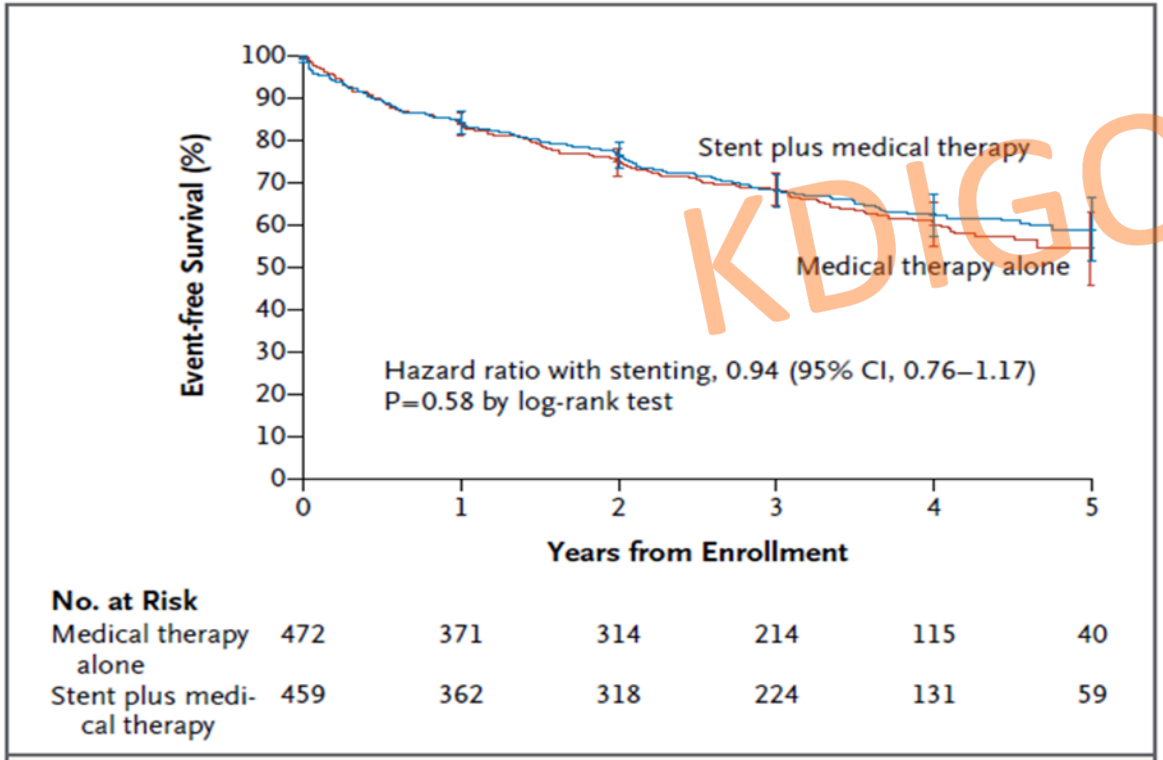


Figure 2. Kaplan–Meier Curves for the Primary Outcome.

Survival curves are truncated at 5 years owing to instability of the curves because few participants remained in the study after 5 years.

N.Engl.J.Med: 370: 13, 2014

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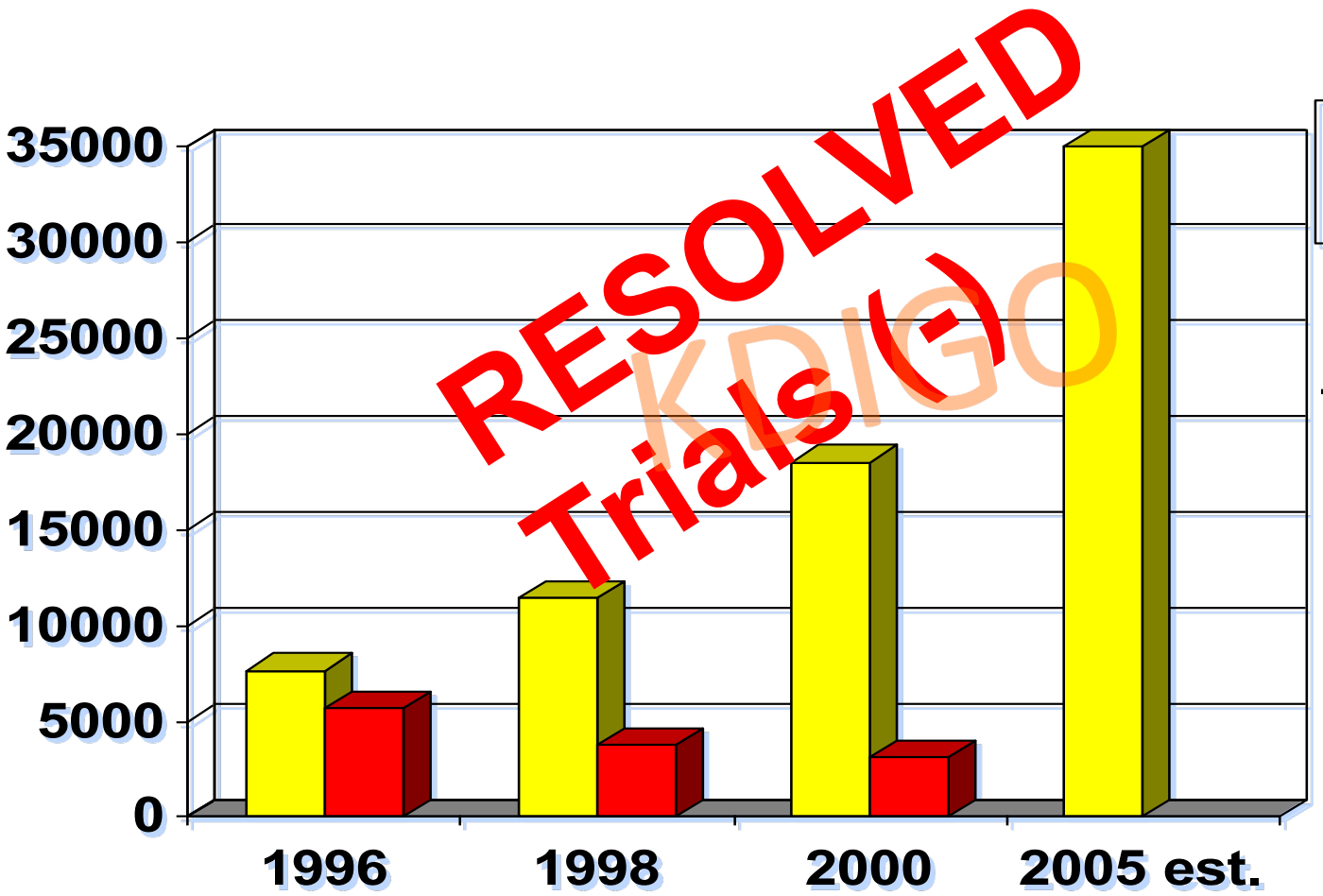
Utilization of Endovascular Renal Artery Stenting in Medicare Beneficiaries

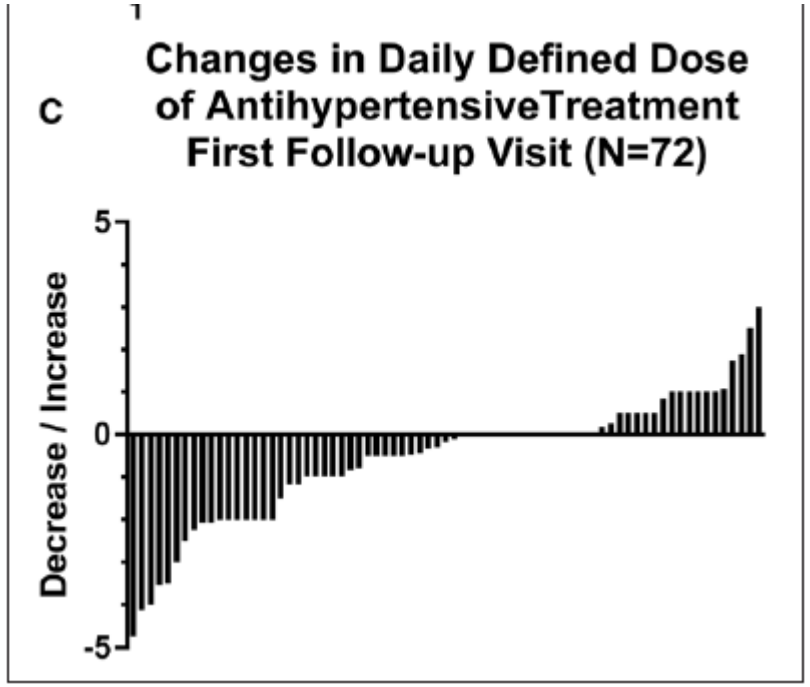


Trial results released during Period of increased use of Renal revascularization

Renal Artery Stenosis

Resistant Hypertension and Atherosclerotic Renal Artery Stenosis

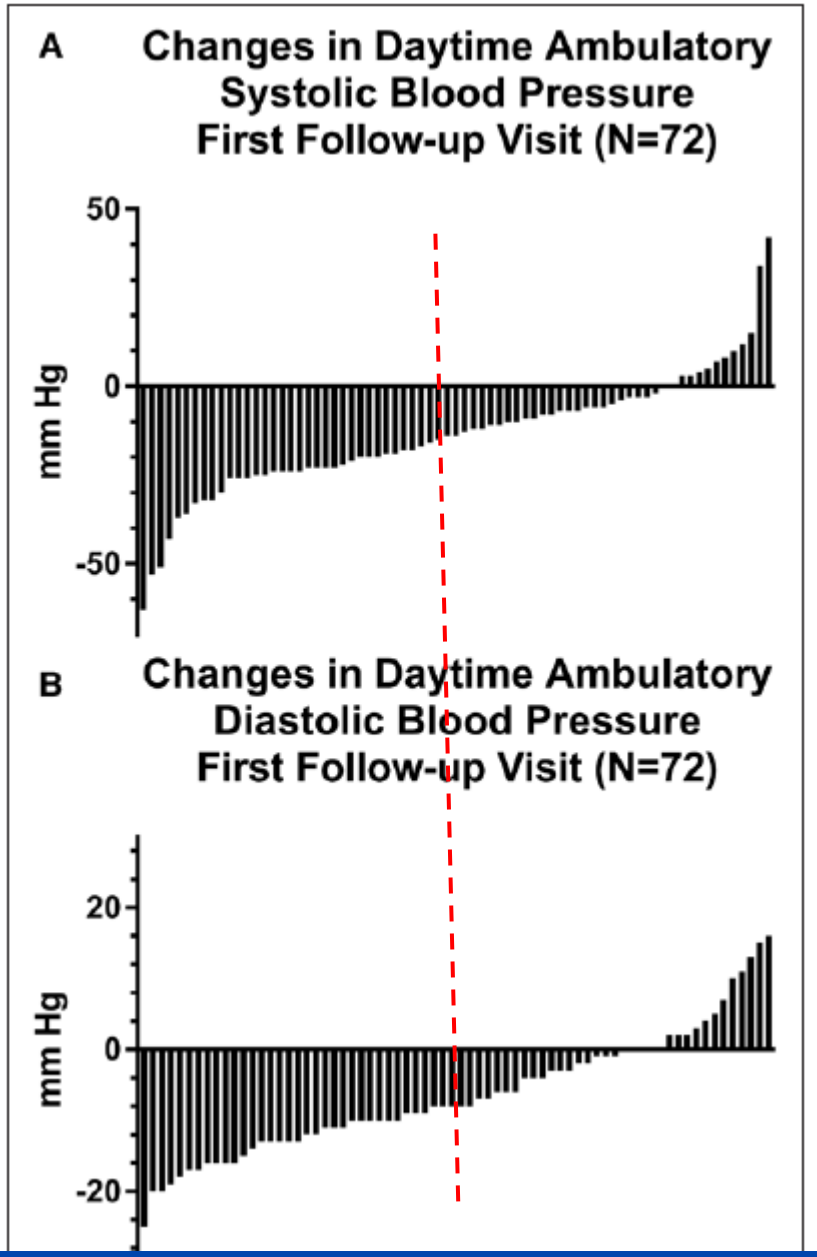
Effects of Angioplasty on Ambulatory Blood Pressure. A Retrospective Uncontrolled Single-Center Study



ABPM: Average Fall 14/6 mmHg

BP Meds: fell from 4.0 to 3.6

No Change in GFR



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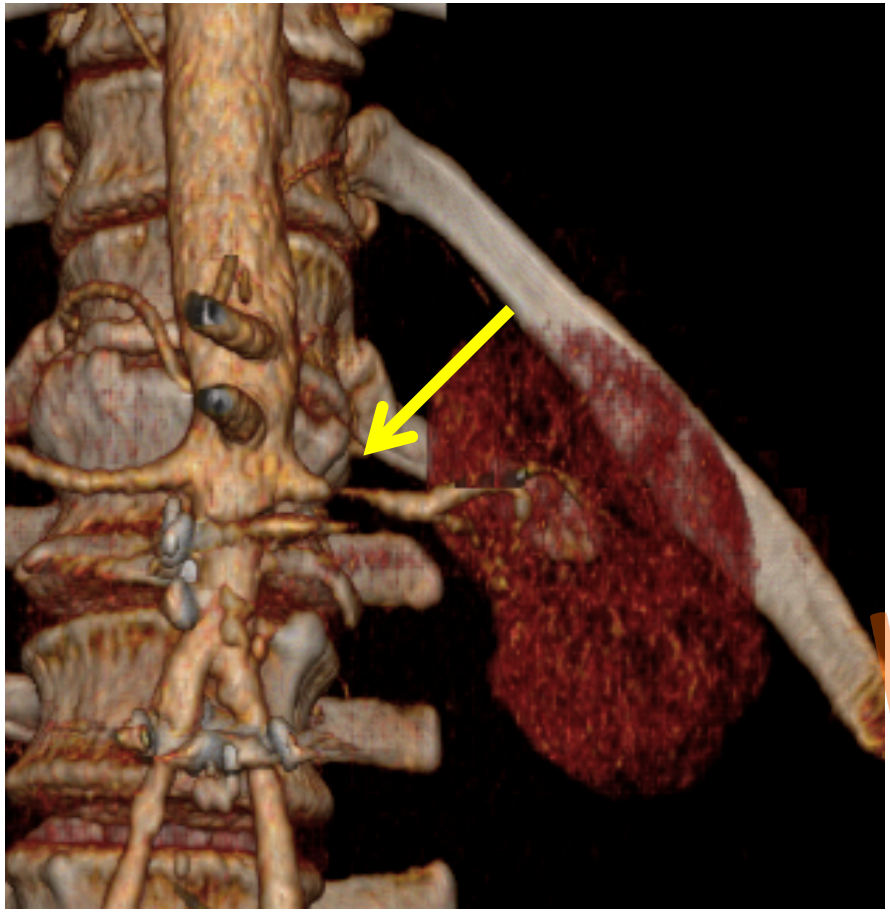
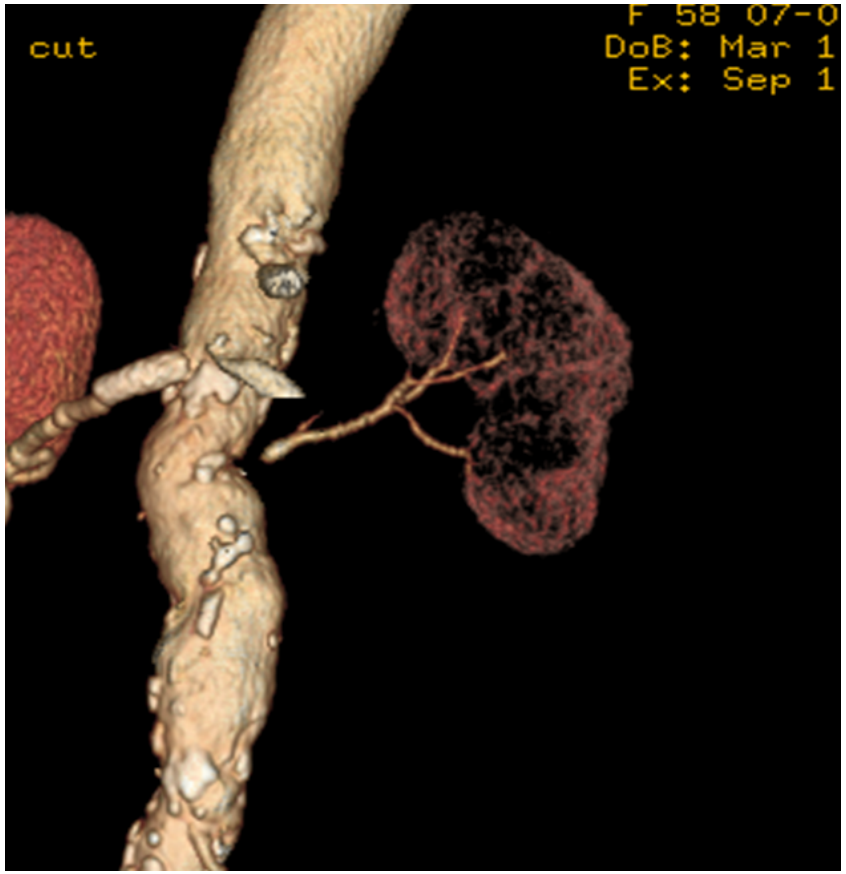
Courand, et.al: Hypertension, 74: 1516, 2019



“Ischemic nephropathy” Definition

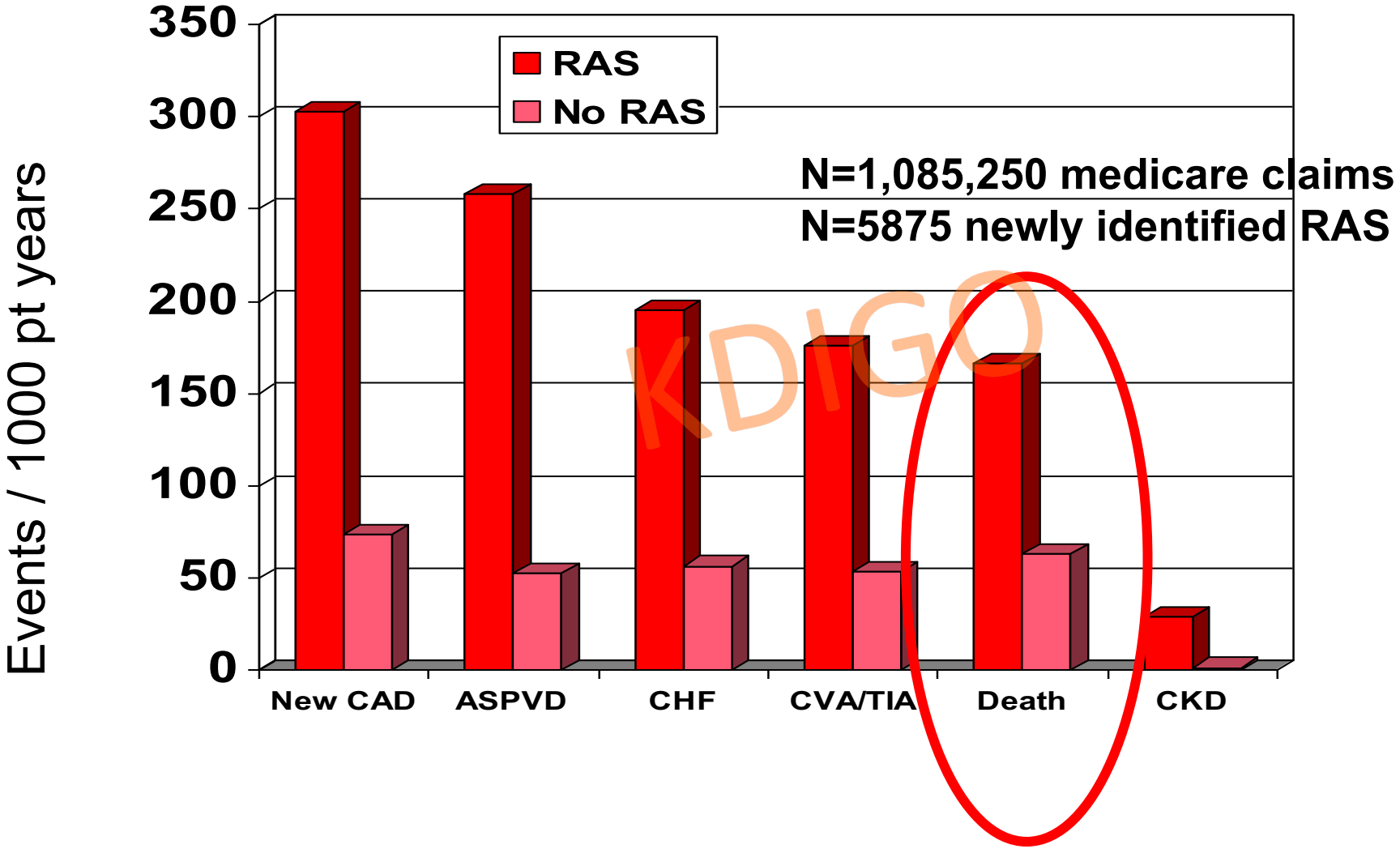
KDIGO



1. “Hemodynamically significant” main renal artery disease
2. Loss of function (GFR) due to vascular insufficiency
3. ?”ischemia”

Note: “ischemic nephropathy ≠ “renal artery stenosis”

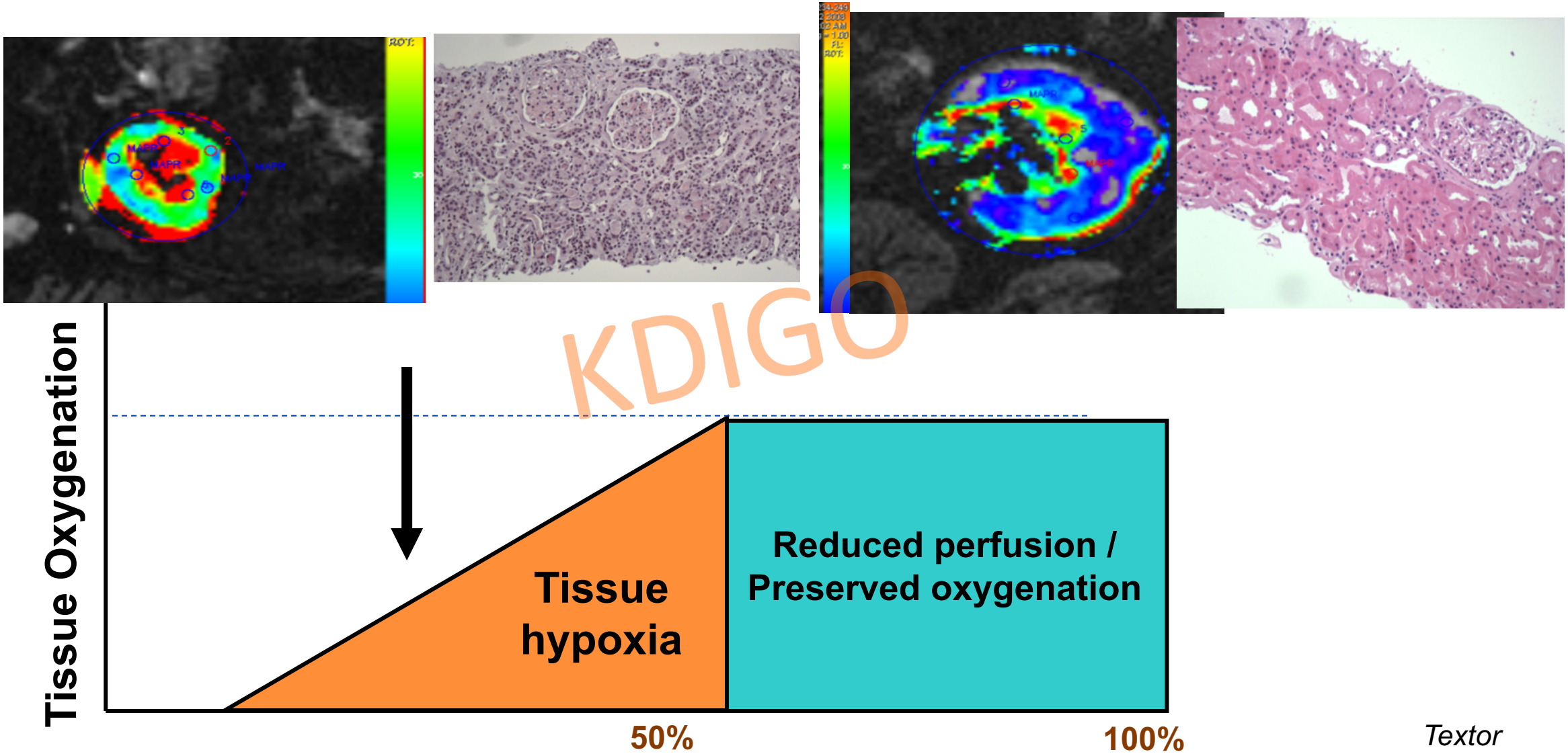
New Onset Clinical Events after Dx of Atherosclerotic Renovascular Disease



MAYO CLINIC

Kalra, et.al: Kidney Int: 68: 2005

Renovascular Disease and Tissue Oxygenation



Case: 74 y.o. Male: Referred for:

1. **Hypertension management**
2. **Advice re: ?renal transplant?**

Hx: 20+ years : moderate hypertension
Longstanding smoker
AAA: aortobifemoral bypass 12 y. ago

Hospitalized: 1 year ago: "TIA" left weakness
BP 210/150 mm Hg

2 mos. Ago: Hospitalized: 230 /140 mmHg
Encephalopathy:
Creatinine from 1.3 mg to 2.5 mg/dL

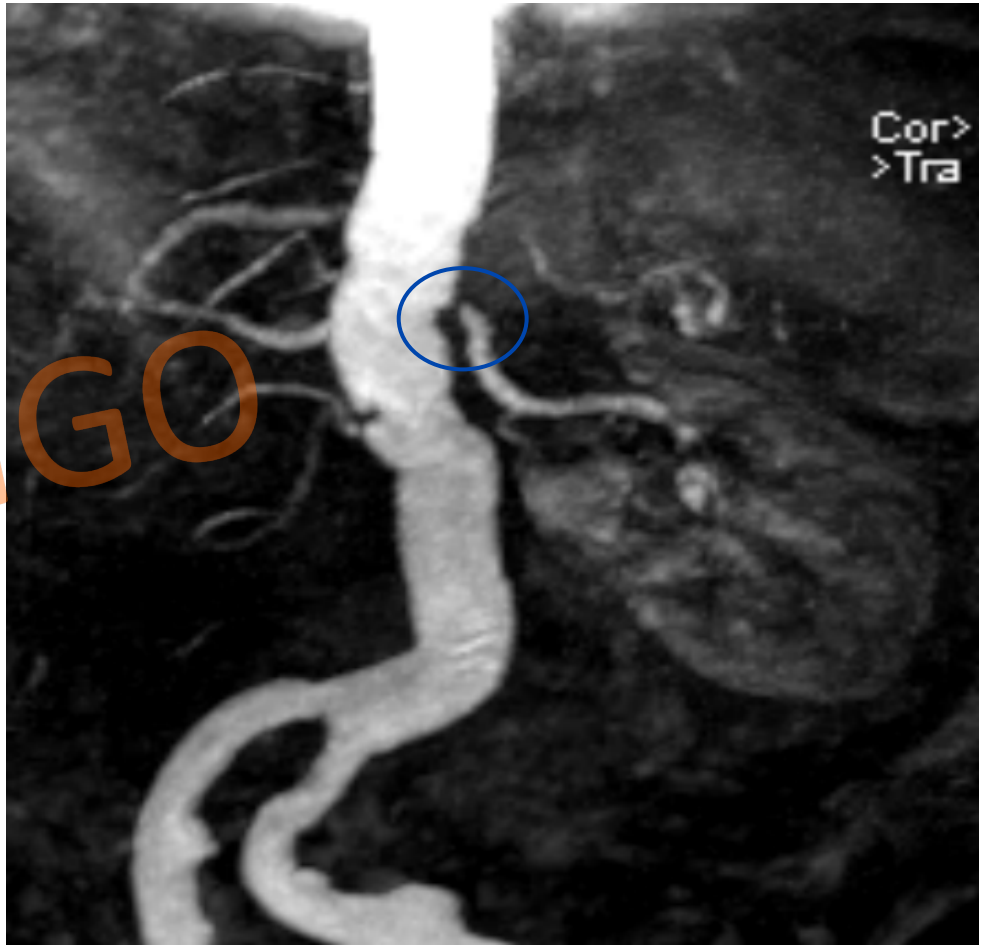
74 y.o. Male: Medical Regimen:

Valsartan (Diovan) 320 mg
Carvedilol (CoReg) 25 mg bid
Furosemide (Lasix) 80 / 40 mg
Clonidine 0.3 mg QID
minoxidil 2.5 mg bid
Darbopoeitin weekly
Aliskiren (Tekturna) 150 mg

Exam: 174 / 71 mm Hg P: 72
s/p AAA repair
No carotid bruits 1+ edema

Lab: Hgb 11.7 g/dL Creatinine: 3.8 mg/dL
K+: 5.1 Na+: 138 mEq/L HCO3: 29 mEq/L

Renal MR angio

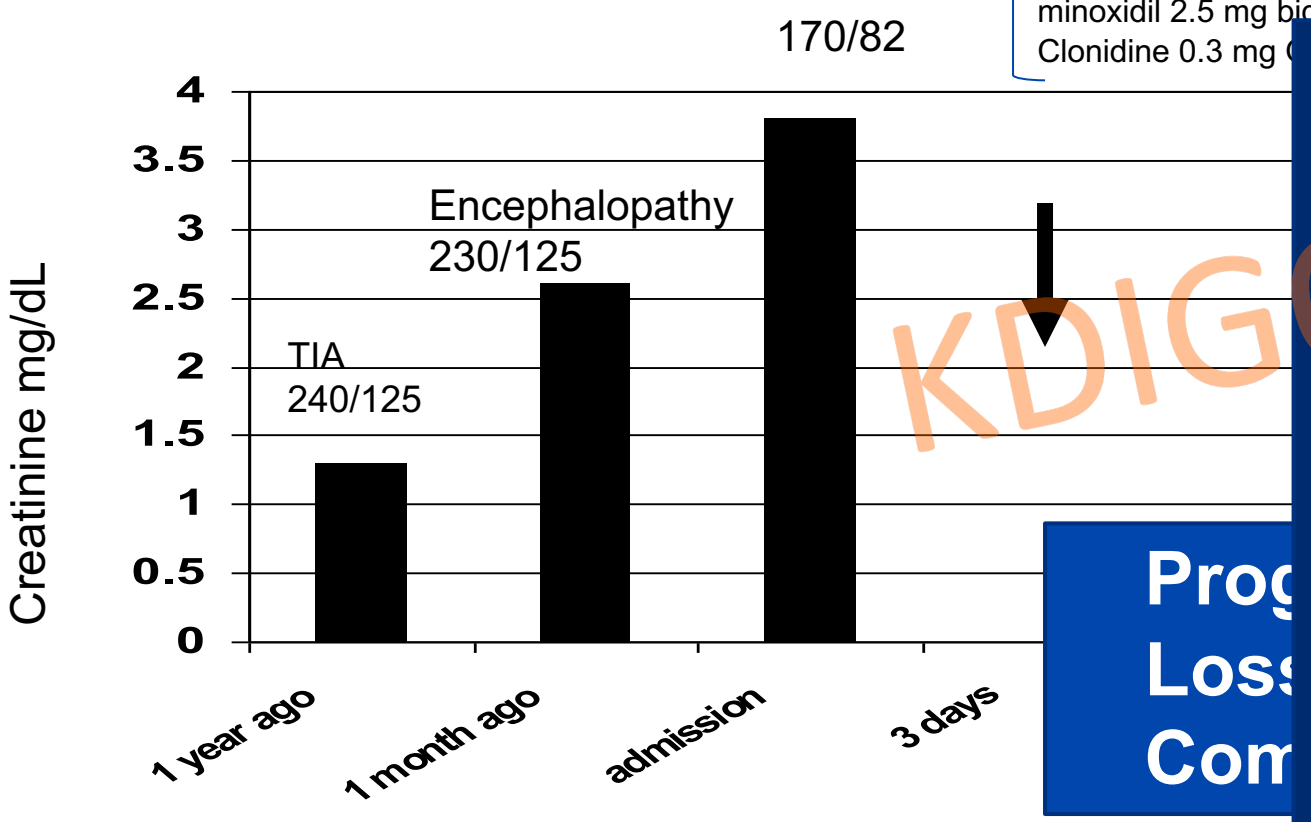


Attending Rounds: A Patient with Accelerated Hypertension and an Atrophic Kidney

Stephen C. Textor

Clin. J. Am.Soc. Nephrol. 2014

Aliskiren (Tekturna) 150 mg
Valsartan (Diovan) 320 mg
Carvedilol (CoReg) 25 mg bid
Furosemide (Lasix) 80 / 40 mg
minoxidil 2.5 mg bid
Clonidine 0.3 mg



Prog
Loss
Com

When is the damage irreversible?

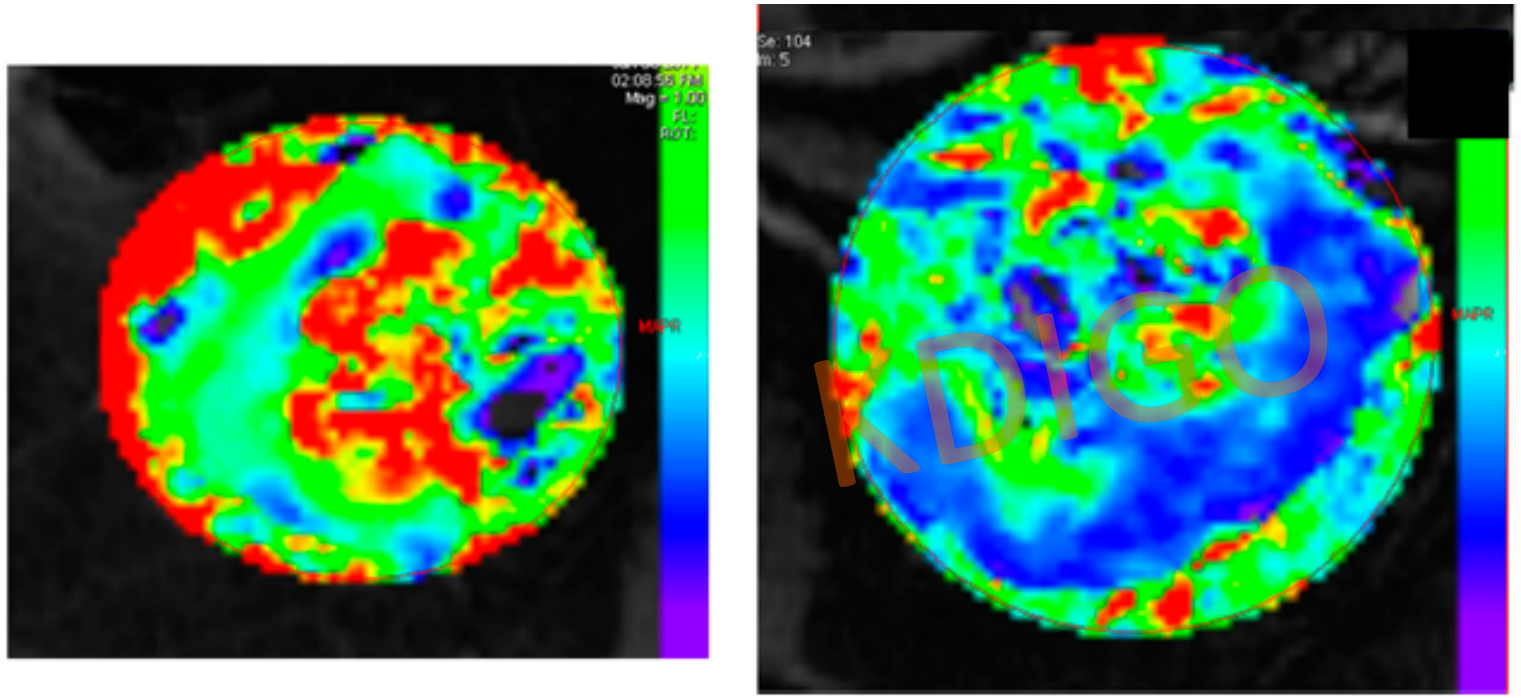
How should this be evaluated?
?imaging
?lab evaluation

When to undertake renal revascularization?

MAYO CLINIC

Clin. J. Am.Soc. Nephrol. 2014

Blood Oxygen Level Dependent (BOLD) MR imaging 74 y.o. male: Bilateral RAS and CKD



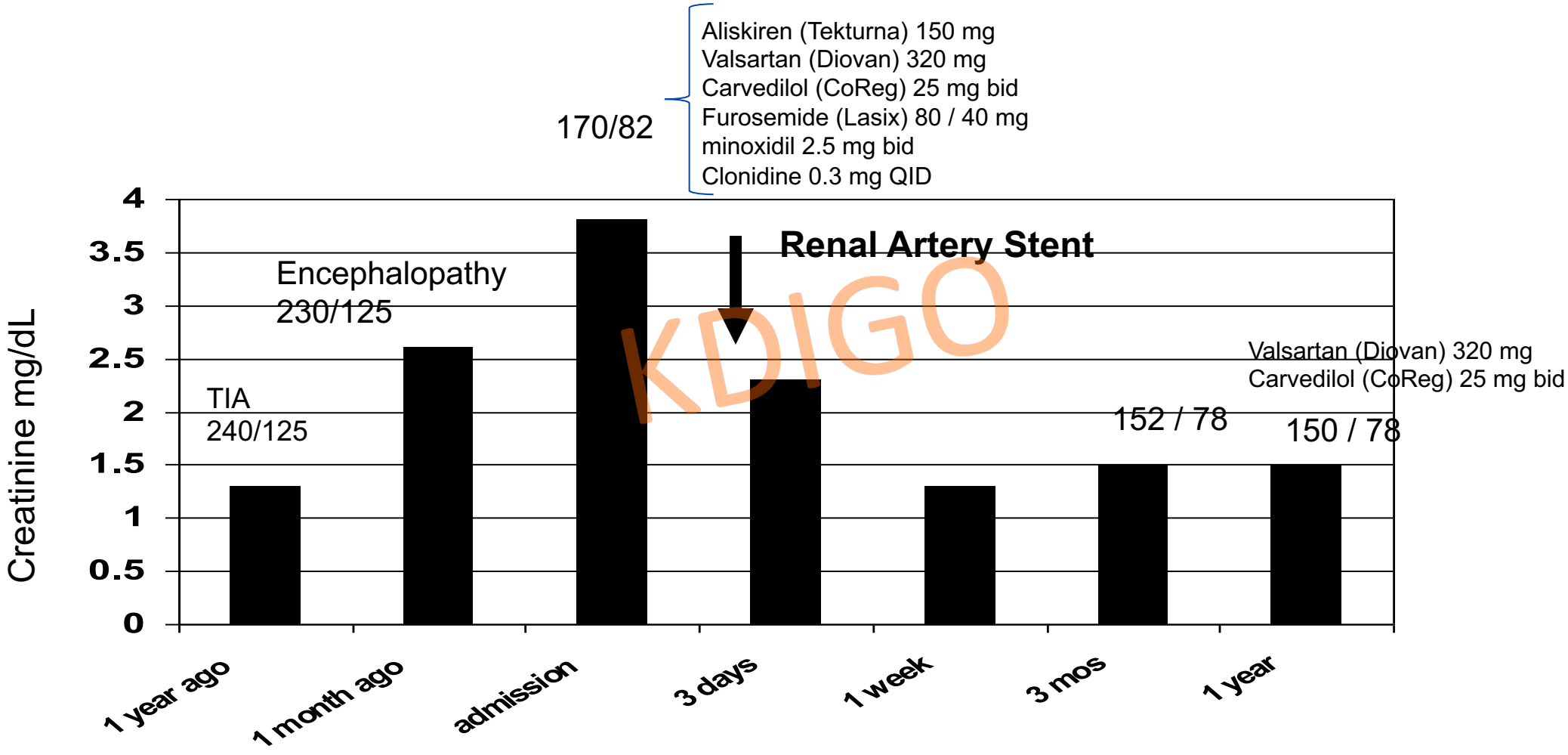
Axial Maps of R2 reflect tissue levels of deoxyhemoglobin*

Figure 4. | Axial image slices from blood oxygen level–dependent MR for right and left kidneys. Left panel depicts the R2* map (reflecting the level of deoxyhemoglobin) of the right kidney, showing a hypoxic cortical zone and widespread areas of elevated deoxyhemoglobin in the medullary segments (red). Right panel depicts the R2* map in the left kidney, with a lower (blue) cortical zone and more gradual development of deeper medullary areas of hypoxia. This near-normal appearance of the corticomedullary oxygen gradient with the human kidney appeared despite reduced blood flow from renovascular occlusive disease (in the text).

Prognosis: Major Predictors of Renovascular Disease Outcomes: 74 y.o male

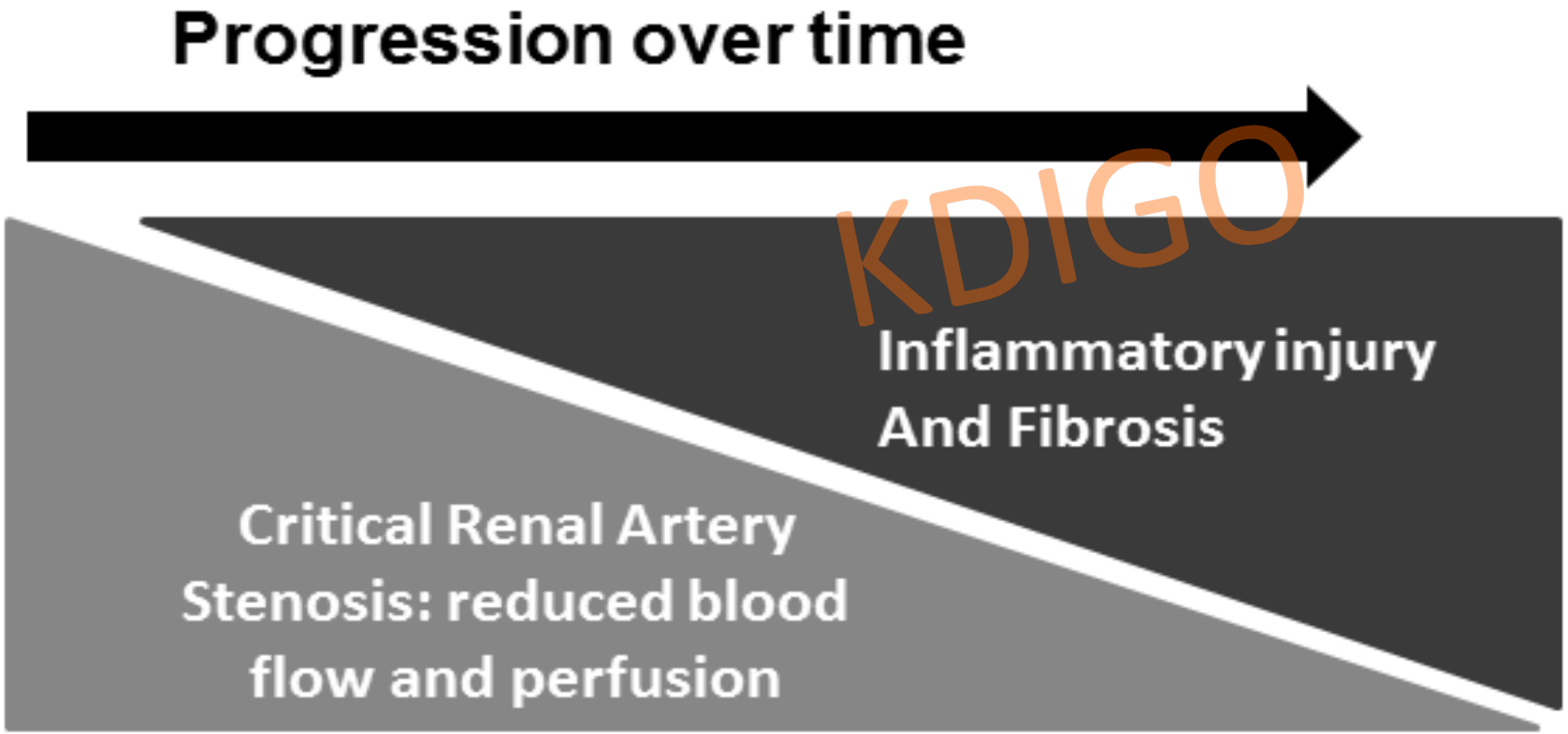
- Size/GFR — *Normal kidney size on left/ recent creatinine below 1.5 mg/dL*
- Proteinuria — *none*
- Evident tissue hypoxia: ?functional (FSOC)
  - *Elevated Cortical and Fraction>30 sec-1*
  - *Both fall after furosemide*
- Rapidity of onset and change
  - Months? — *@ 12-18 months*
  - Years?
  - Decades?

Recovery of Renal Function after stent revascularization:

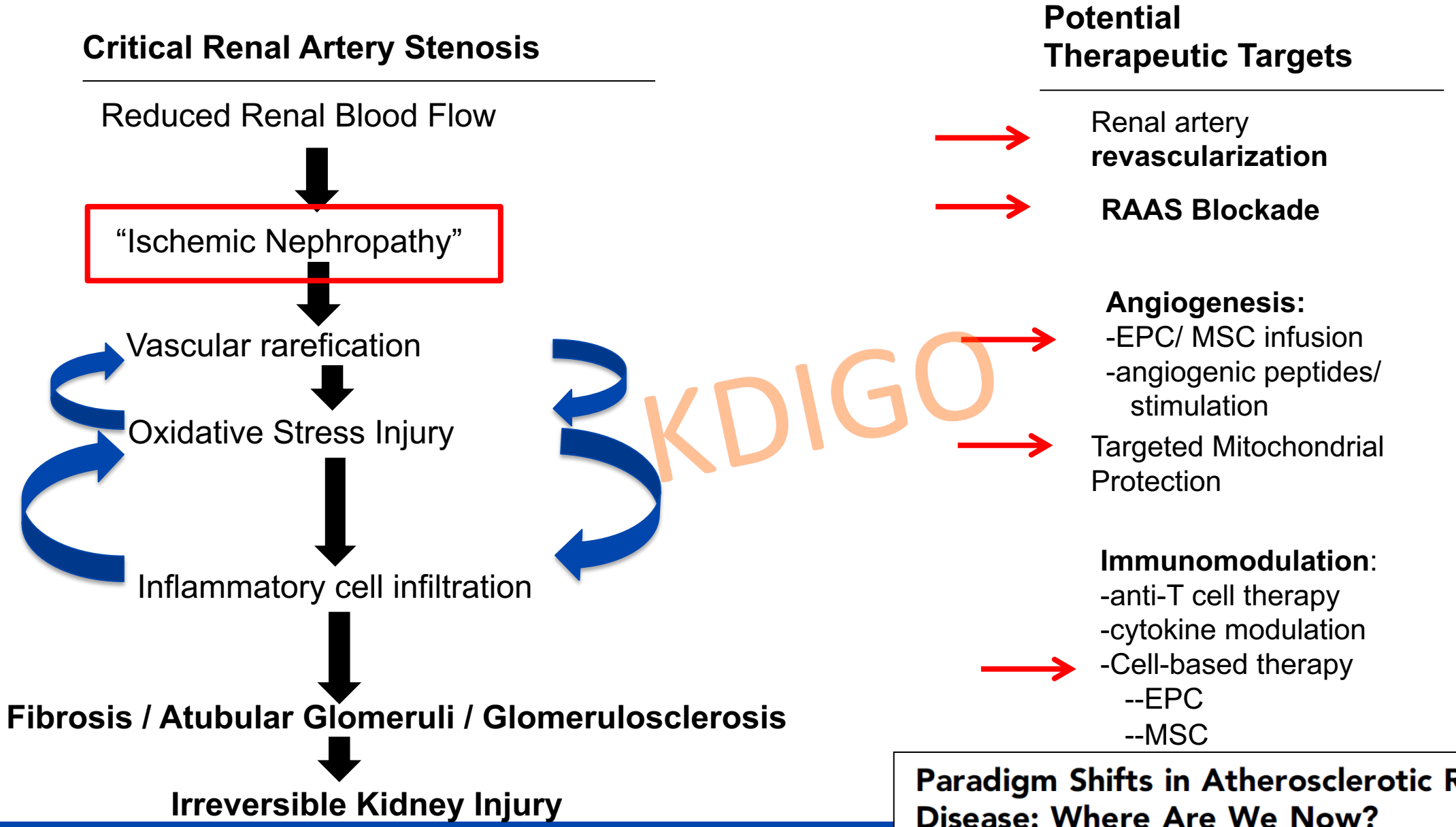


CJASN: Jan. 2014

Renovascular Disease 2020:
Transition from hemodynamic to inflammatory injury



Injury pathways and targets in Atherosclerotic Renovascular Disease

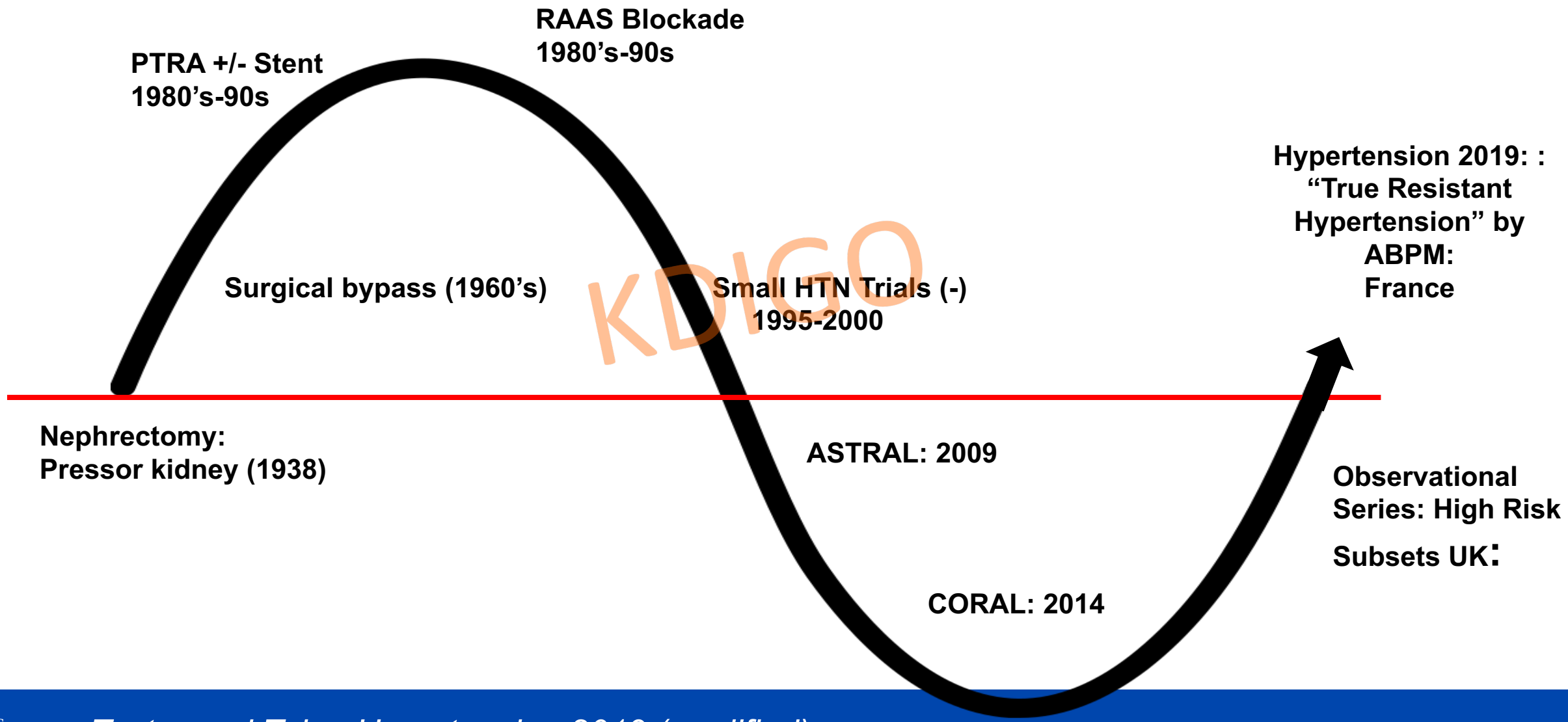


Paradigm Shifts in Atherosclerotic Renovascular Disease: Where Are We Now?

Stephen C. Textor and Lilach O. Lerman

JASN 26: 2074, 2015

Management of Renovascular Disease: Enthusiasm for renal revascularization



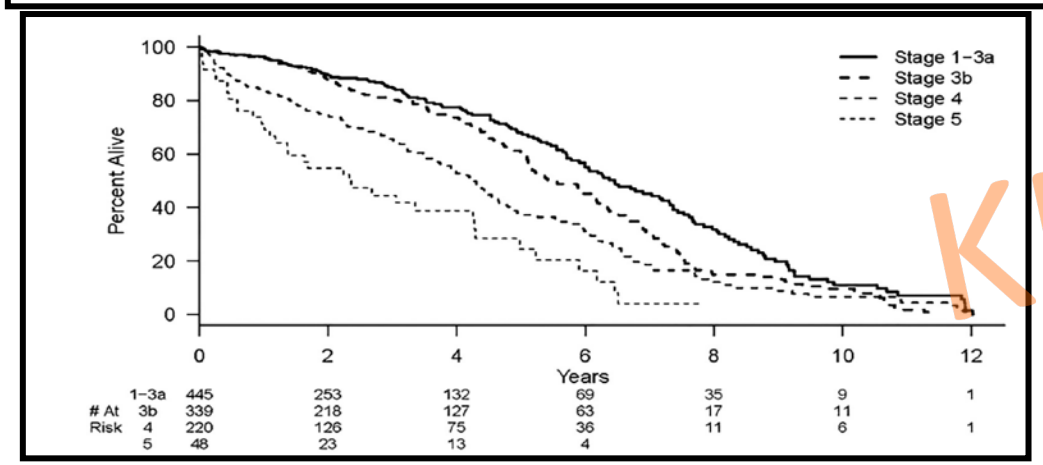
Textor and Taler, Hypertension 2019 (modified)

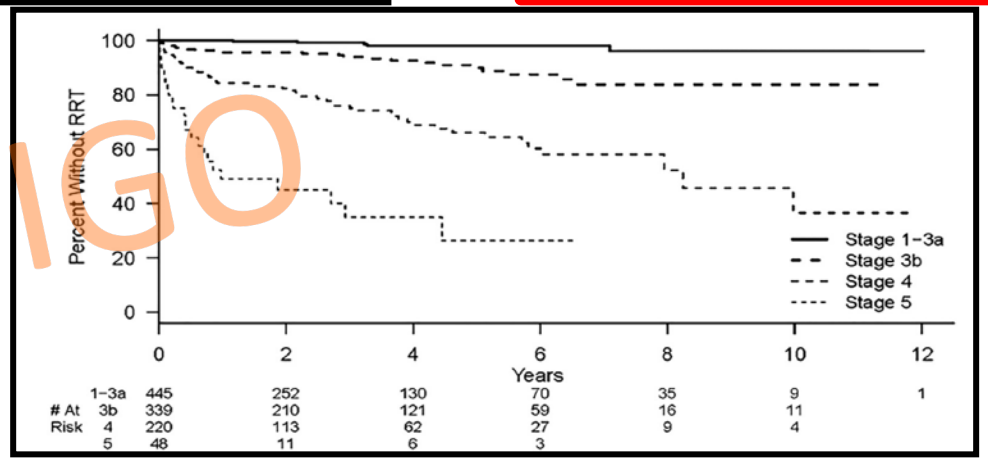
Mortality and Renal Replacement Therapy after Renal Artery Stent Placement for Atherosclerotic Renovascular Disease

Sanjay Misra, MD, Ankaj Khosla, MD, Jake Allred, MS, William S. Harmsen, MS, Stephen C. Textor, MD, and Michael A. McKusick, MD

N=1052 patients
1996-2009

F/U: 37% died
10.6% RRT





Predictors: Death
--CKD stage
--DM
--Carotid disease
--proteinuria

Predictors: Renal Replacement Therapy
--CKD stage
--proteinuria
--smoker
--ACEI (-)

J. Vasc. Interv. Radiol.: 2016

Renovascular Hypertension and Ischemic Nephropathy 2020

- Prevalence / Associated Disease
- Pathophysiology / Clinical manifestations
- Medical Rx: role of ACE / ARB
- Prospective Trials: low risk groups
- High-risk subsets
- Renal Revascularization 2020: Competing risk
  - ?Adjunctive therapy

Is Renovascular Disease "lost" or becoming an "orphan Disease"?

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