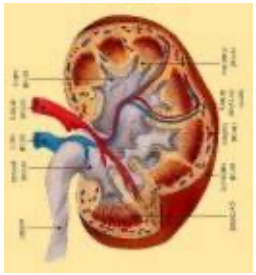


Province Wide Radiology Rounds
November 2016
Areas for Nephrology: Radiology Collaboration

What's the deal with renal sizes?
and
How toxic is IV contrast ?

M Bevilacqua and A Levin

UBC Division of Nephrology and

BC Provincial Renal Agency

Objectives: Renal imaging in polycystic disease

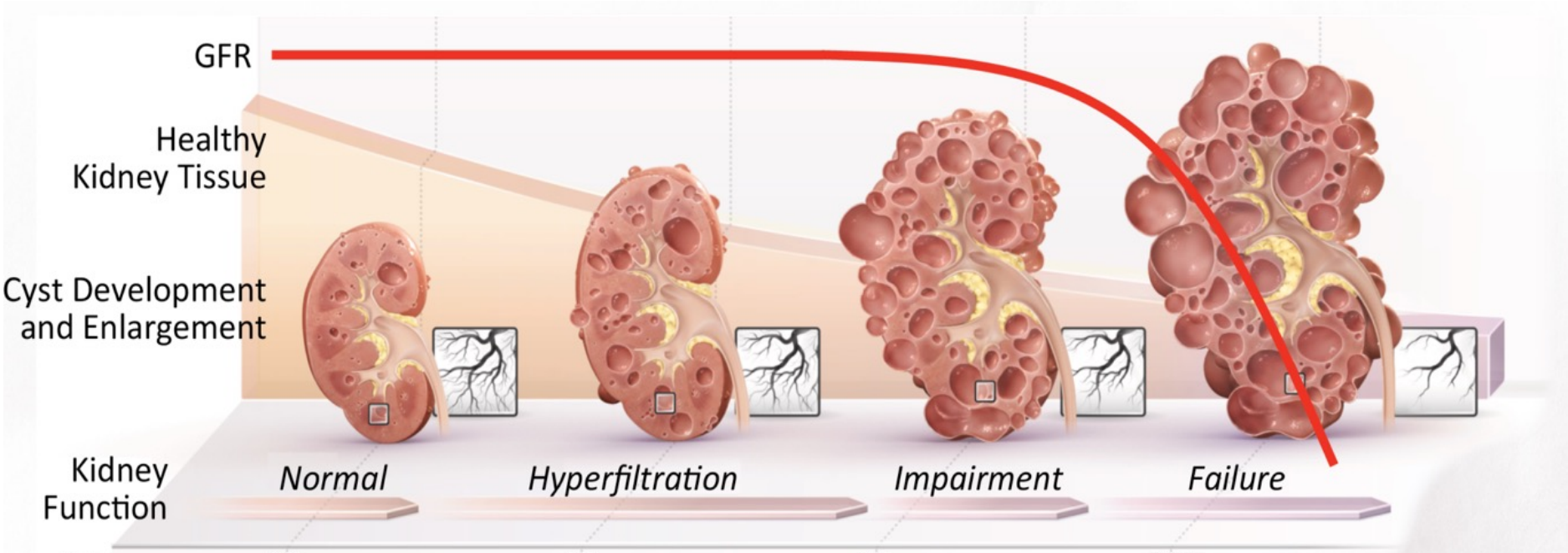
- Review natural history of Autosomal Dominant Polycystic Kidney Disease
- The challenge of prognostication in ADPKD
  - How renal imaging can address that challenge
- Role of standardization
  - Facilitate performance of complex imaging tests
  - Maximize utility of those tests

What's the deal with Polycystic Disease and kidney sizes?

Epidemiology

- Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting between 1-2.5/1000 live births
  - Approximately 4600 to over 10000 British Columbians living with the disease.
- Of patients with an identifiable etiology of ESRD, ADPKD is the 4th leading cause of ESRD in Canada

Natural history of PKD



Challenge #1: Diagnosis is not straightforward

Table 2. Ultrasound Criteria for Diagnosis of ADPKD

Age, y	PKD1	PKD2	Unknown ADPKD Gene Type
15-30	≥3 cysts*		
	PPV, 100%	PPV, 100%	PPV, 100%
	SEN, 94.3%	SEN, 69.5%	SEN, 81.7%
30-39	≥3 cysts*		
	PPV, 100%	PPV, 100%	PPV, 100%
	SEN, 96.6%	SEN, 94.9%	SEN, 95.5%
40-59	≥2 cysts in each kidney	PPV, 100%	
	PPV, 100%	SEN, 88.8%	PPV, 100%
	SEN, 92.6%		SEN, 90%

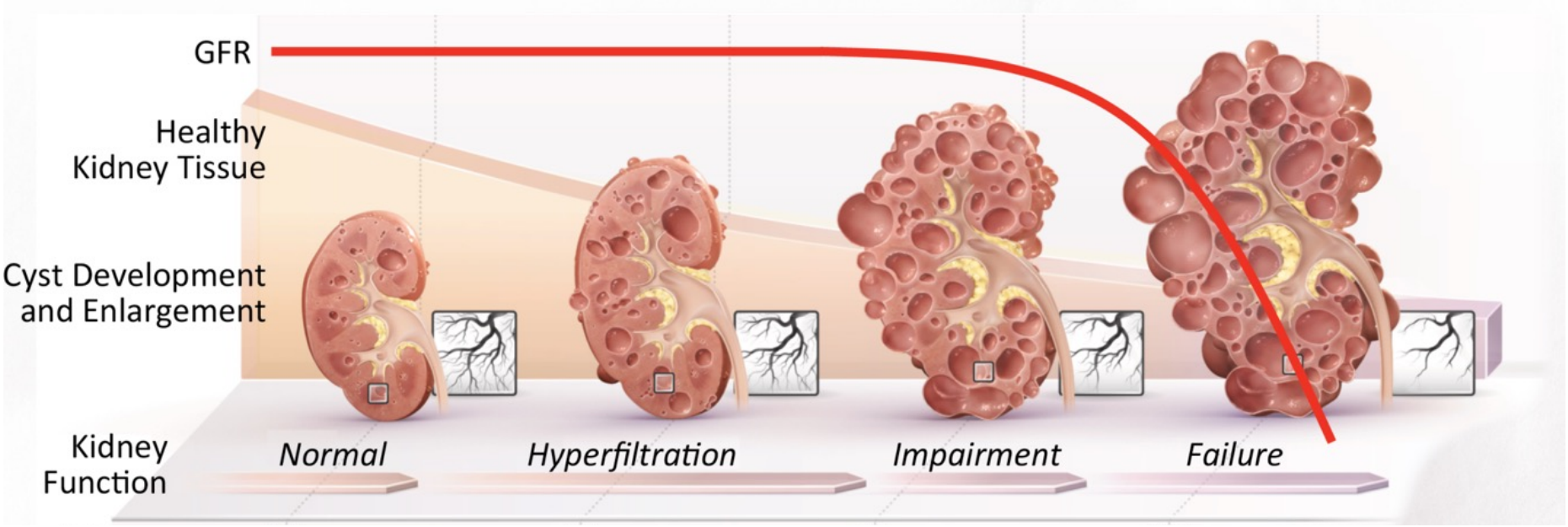
Table 3. Ultrasound Criteria for Exclusion of ADPKD

Age, y	PKD1	PKD2	Unknown ADPKD Gene Type
15-30	≥1 cyst		
	NPV, 99.1%	NPV, 83.5%	NPV, 90.8%
	SPEC, 97.6%	SPEC, 96.6%	SPEC, 97.1%
30-39	≥1 cyst		
	NPV, 100%	NPV, 96.8%	NPV, 98.3%
	SPEC, 96%	SPEC, 93.8%	SPEC, 94.8%
40-59	≥1 cyst		
	NPV, 100%	NPV, 100%	NPV, 100%
	SPEC, 93.9%	SPEC, 93.7%	SPEC, 93.9%

- Performance of diagnostic criteria depend on age
- Our ability to detect cysts is quite good, so it is easier to confirm the diagnosis than it is to rule it out
- There is a wider differential diagnosis of multiple bilateral renal cysts

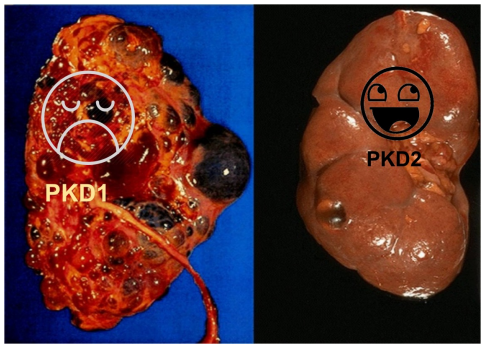
Barua M, Pei Y. Diagnosis of Autosomal-Dominant Polycystic Kidney Disease: An Integrated Approach. Semin Nephrol. 2010 Jul:30(4):356–65.

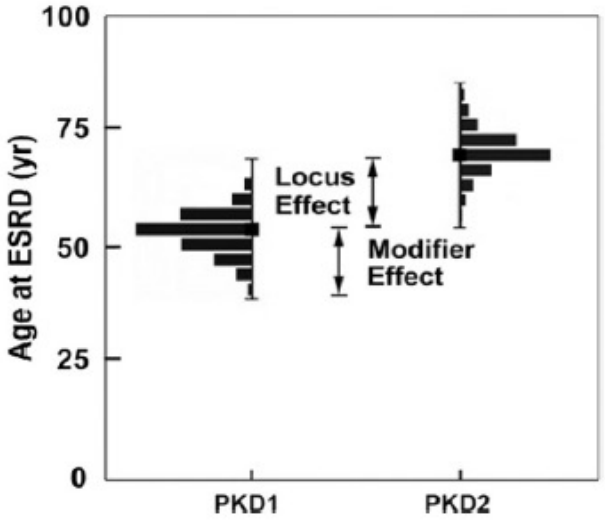
Challenge #2: Renal dysfunction is a late finding



By the time GFR changes, ***substantial irreversible disease progression has already occurred***

Challenge #3: Disease course is variable





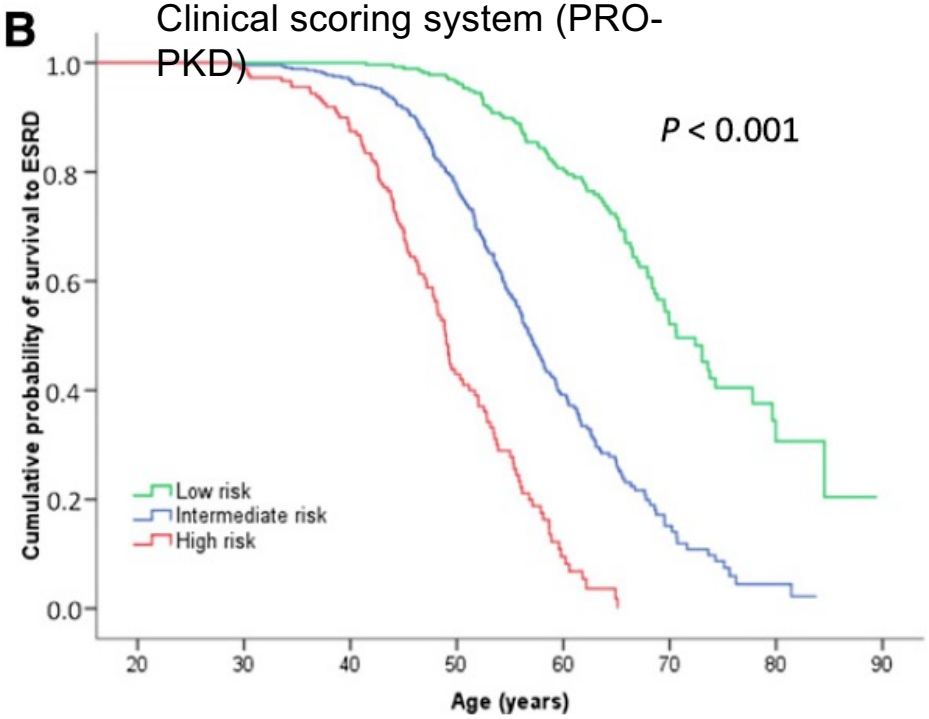
- Conventional wisdom was that there was a good (PKD2) and bad (PKD1) disease course

- The reality is more complicated and variability within and between families with PKD is a hallmark of PKD

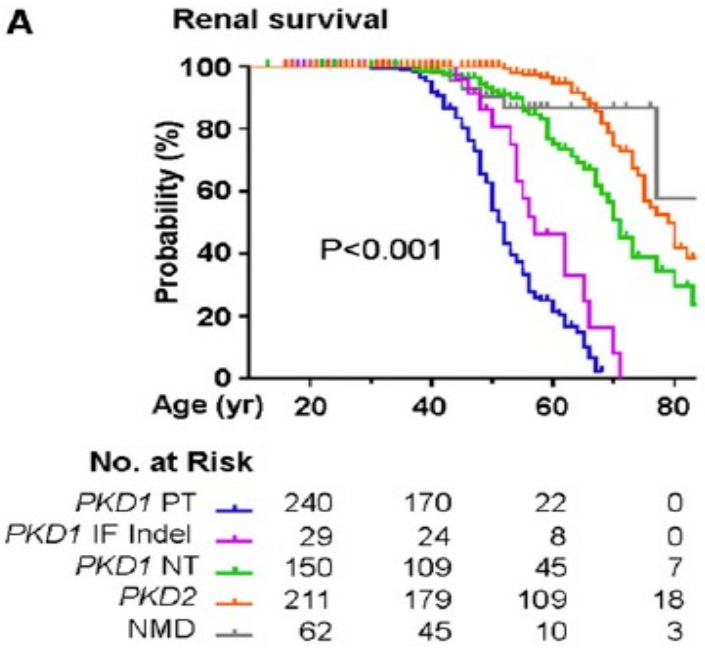
Barua M, Pei Y. Diagnosis of Autosomal-Dominant Polycystic Kidney Disease: An Integrated Approach. Seminars in Nephrology. 2010 Jul;30(4):356–65.

Clinical and genetic criteria do not adequately prognosticate all PKD patients

Clinical scoring system (PRO-PKD)

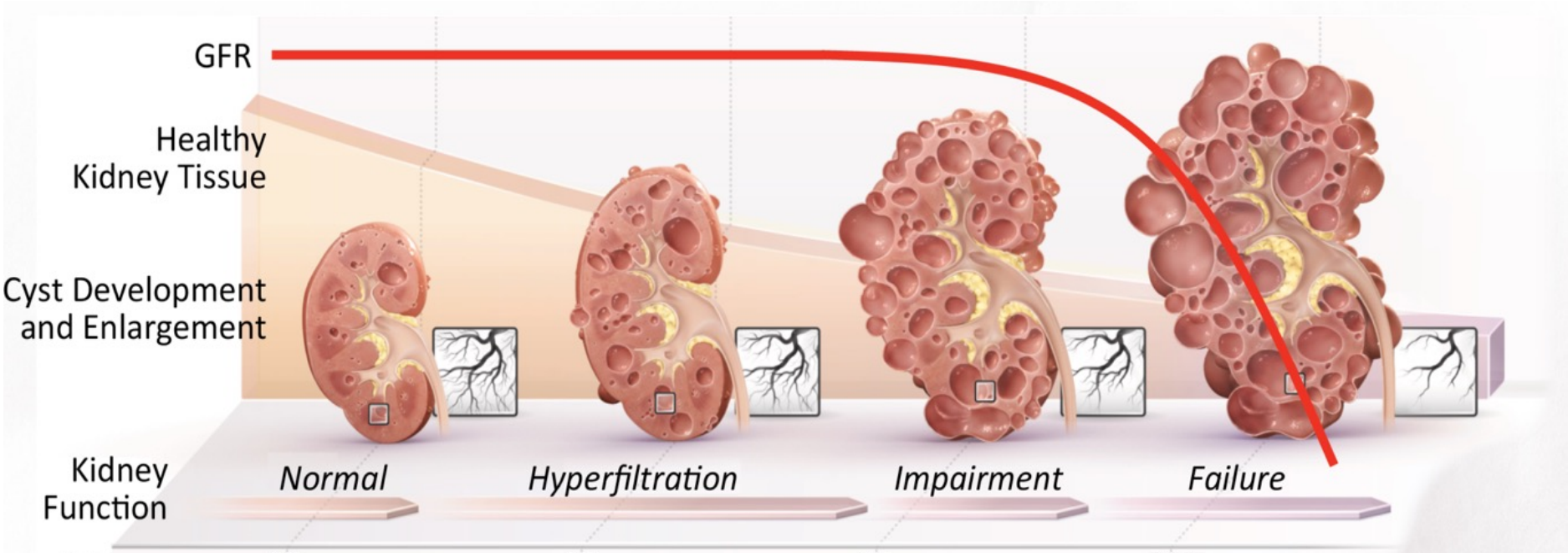


Genetic classification



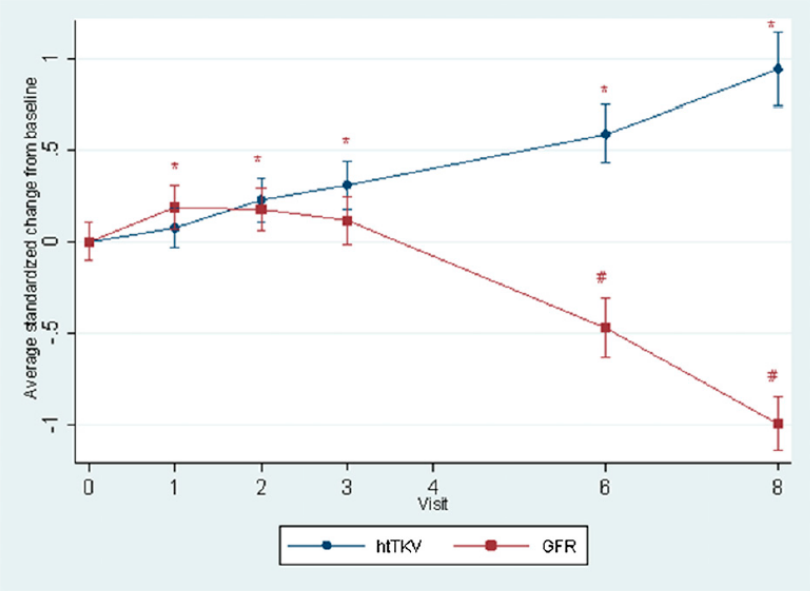
How can diagnostic imaging address these challenges?

Kidney growth in PKD



The rate of kidney growth is an expression of the ***individual PKD patient's phenotype***

Change in kidney size precedes change in renal function



It takes years before GFR changes, but changes in total kidney volume (TKV) were detectable at 1 year

Figure 2. | Average standardized change in htTKV and iothalamate GFR. htTKV determined at baseline and iothalamate GFR at baseline and five subsequent visits until year 8 (n=93 with complete data). P<0.01 based on paired t test comparing each year to baseline for htTKV (*) and GFR (#). htTKV, height-adjusted total kidney volume.

Clin J Am Soc Nephrol 7: 479–486, 2012.

TKV as a predictor of renal outcomes

Table 3. Baseline predictors of CKD stage 3 endpoint

Variable	AUC	Sensitivity	Specificity	Cut Point	95% CI of AUC	*P* Value*
htTKV (cc/m)	0.84	0.74	0.7	600	(0.79, 0.90)	
Serum creatinine (mg/dl)	0.75	0.58	0.81	1.1	(0.67, 0.82)	0.02
BUN (mg/dl)	0.76	0.63	0.79	16	(0.70, 0.83)	0.04
Urine albumin (mg/d)	0.70	0.66	0.67	30	(0.61, 0.78)	0.002
MCP-1 (pg/mg)	0.75	0.80	0.62	410	(0.68, 0.83)	0.02
Baseline age (yr)	0.66	0.60	0.65	35	(0.59, 0.74)	<0.001

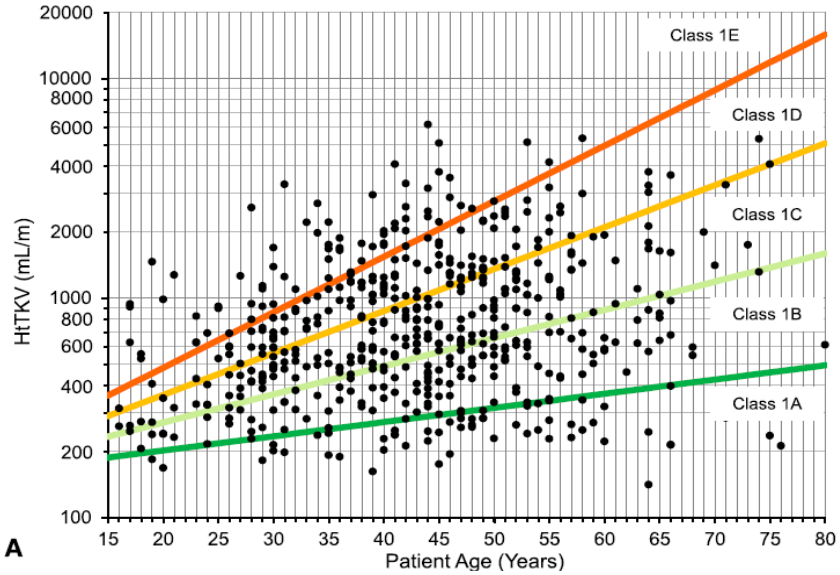
AUC, area under the curve; 95% CI, 95% confidence interval; htTKV, height-adjusted total kidney volume; MCP-1, monocyte chemotactic protein-1.

Total Kidney Volume (TKV) at baseline was is better predictor of risk of GFR <60 over 8 years than baseline age, baseline renal function or proteinuria

Clin J Am Soc Nephrol 7: 479–486, 2012.

Mayo classification categorizes rate of kidney growth

Class	Average annual change in TKV
1A	<1.5%
1B	1.5-3
1C	3-4.5
1D	4.5-6
1E	>6%

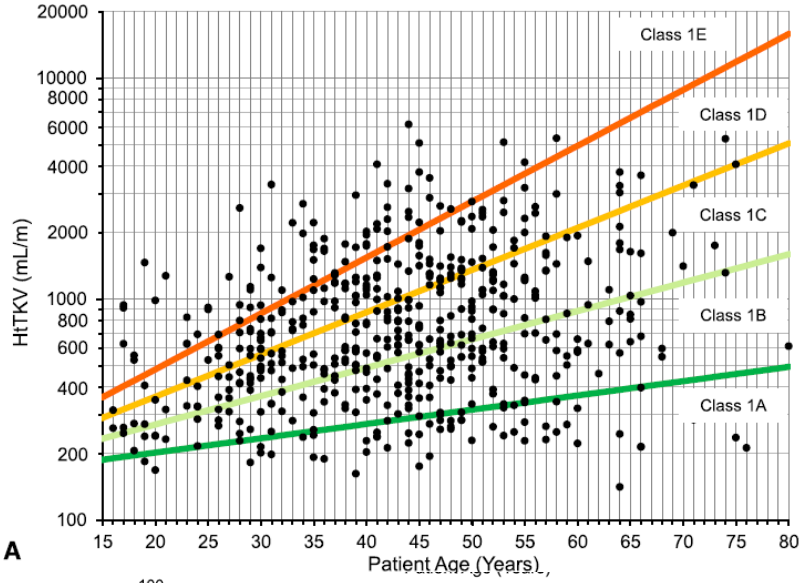


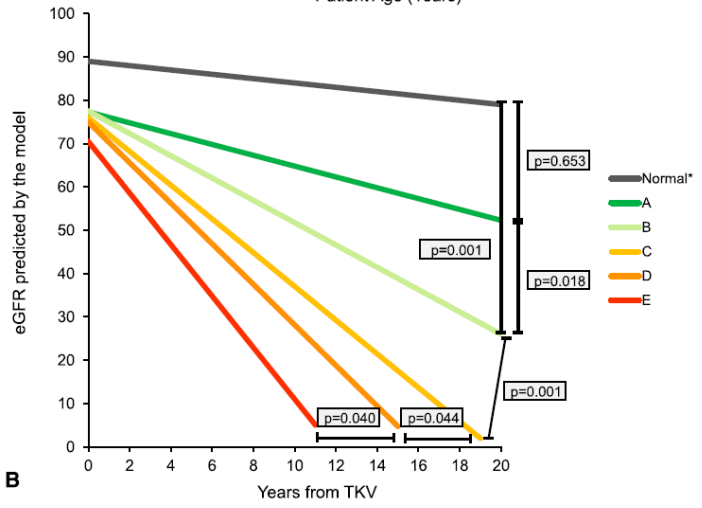
The 1A-1E classification is best thought of as a ***velocity of growth classification*** – the classes refer to the average annual growth in htTKV

J Am Soc Nephrol 26: 160–172, 2015.

Mayo class predicts rate of GFR loss

Class	Average annual change in TKV	Average annual decrease in eGFR
1A	<1.5%	0.23
1B	1.5-3	1.33
1C	3-4.5	2.63
1D	4.5-6	3.48
1E	>6%	4.78



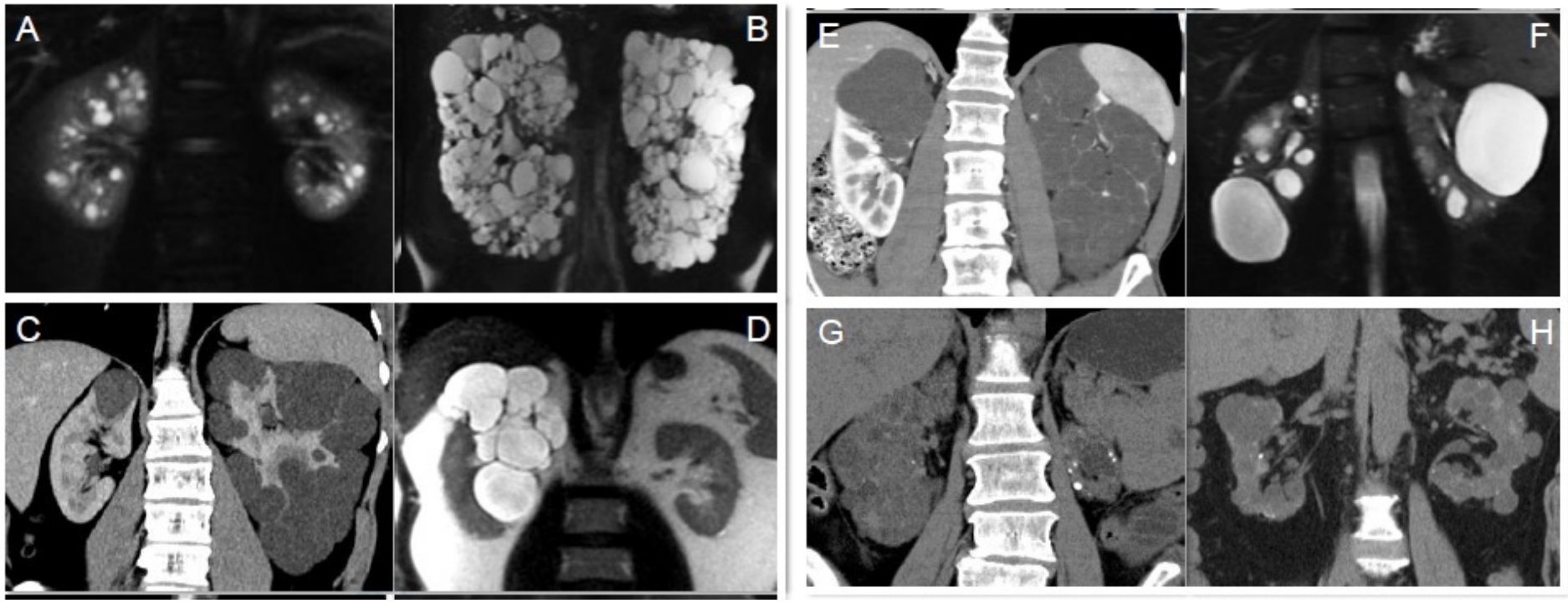


At present, this appears to be the best predictor of renal progression for ***early stage*** PKD

J Am Soc Nephrol 26: 160–172, 2015.

How do we measure kidney size?

Step 1: determine ‘typical’ vs ‘atypical’ morphology



Step 2: Pick an imaging method

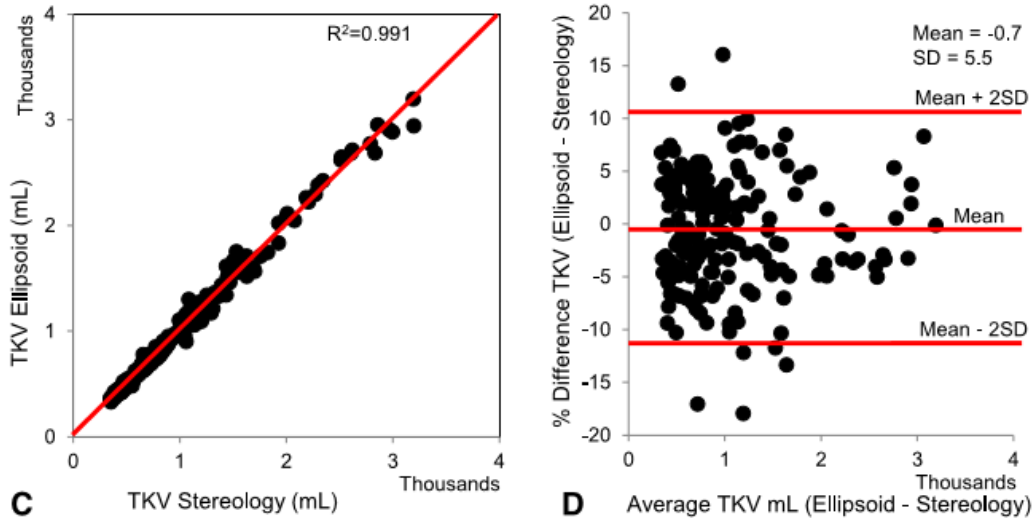
There are two main methods:

- Ultrasound determination of size
- Cross-sectional assessment of total kidney volume (TKV) done with either CT or MRI

MRI/CT

- The gold standard for TKV measurement remains manual stereology
  - This is time consuming – on average 45 min per scan
- Several techniques exist with sufficient accuracy that are less time consuming
  - Ellipsoid
  - Mid-slice
  - Automated (based on automated thresholding and boundary refinement)

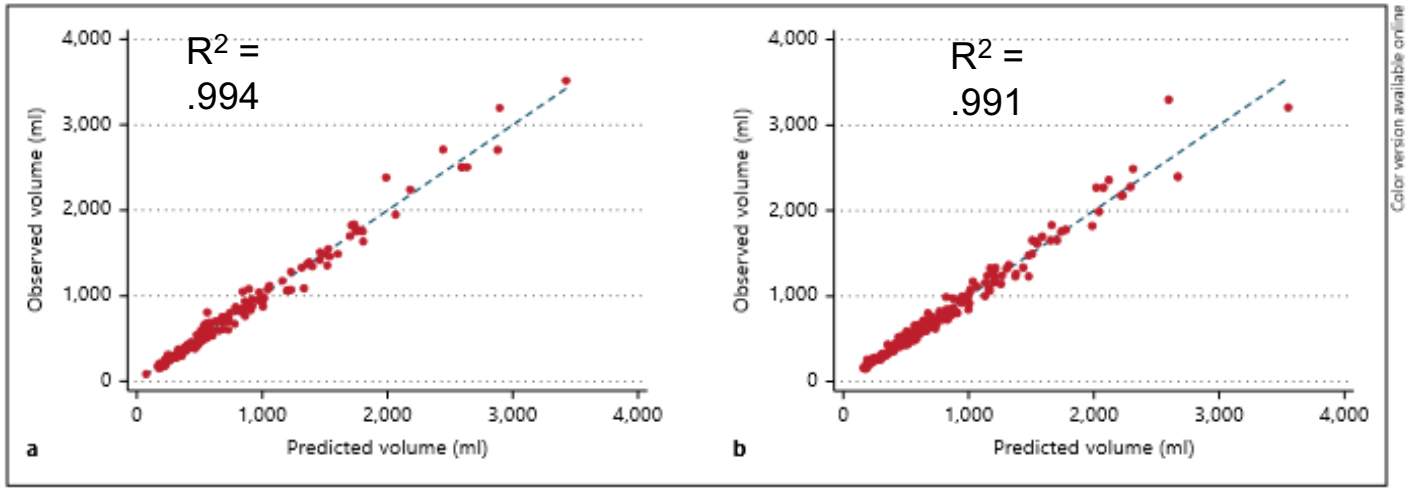
MRI - ellipsoid



From the CRISP cohort and a longitudinal cohort followed at the Mayo, ellipsoid estimates of TKV were very comparable to manual stereology and on average took 7 min compared to 45 min to read

Irazabal MV, Rangel LJ, Bergstralh EJ, Osborn SL, Harmon AJ, Sundsbak JL, et al., the CRISP Investigators. Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials. J Am Soc Nephrol. 2015 Jan 1;26(1):160–72.

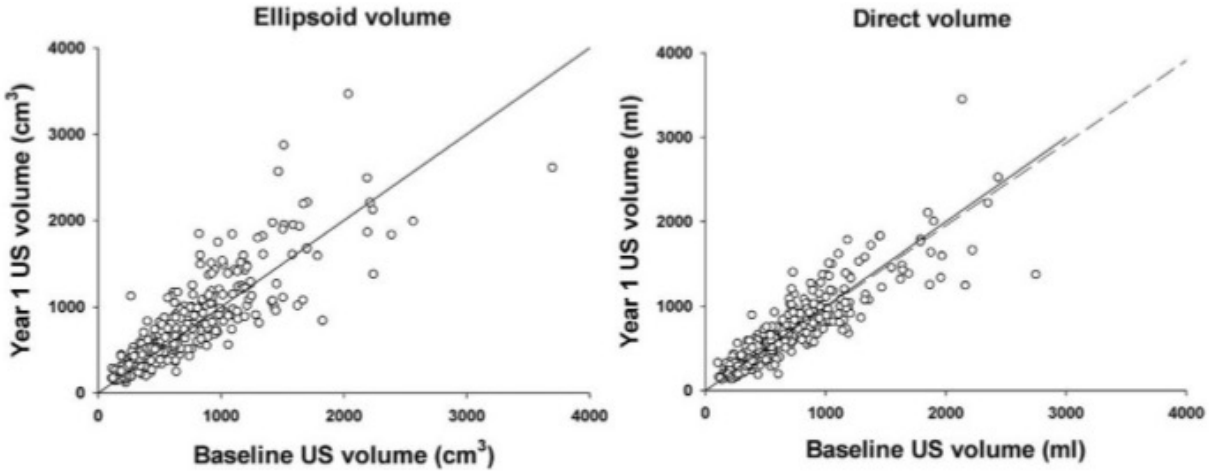
Estimation based on single slice area



A single mid-coronal slice can be used to estimate size – area is calculated and a linear transformation is applied that yields values highly correlated with stereology

Bae KT, Tao C, Wang J, Kaya D, Wu Z, Bae JT, et al. Novel Approach to Estimate Kidney and Cyst Volumes Using Mid-Slice Magnetic Resonance Images in Polycystic Kidney Disease. Am J Nephrol. 2013;38(4):333–41.

Ultrasound measurement of TKV

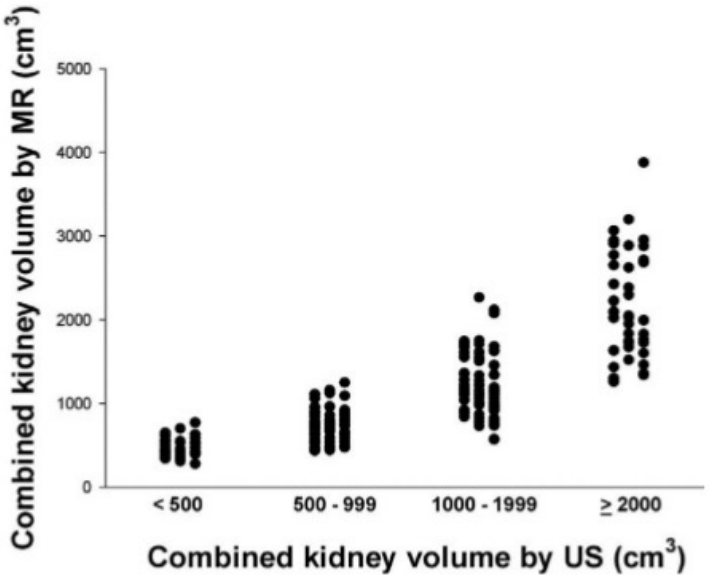


Compared to MRI, there is much higher variability in TKV measurement either for ellipsoid (21-35%) or stereology (18-42%).

This and other studies have shown that US tends to consistently overestimate size

O'Neill WC, Robbin ML, Bae KT, Grantham JJ, Chapman AB, Guay-Woodford LM, et al. Sonographic Assessment of the Severity and Progression of Autosomal Dominant Polycystic Kidney Disease: The Consortium of Renal Imaging Studies in Polycystic Kidney Disease (CRISP). Am J Kidney Dis. 2005 Dec;46(6):1058–64.

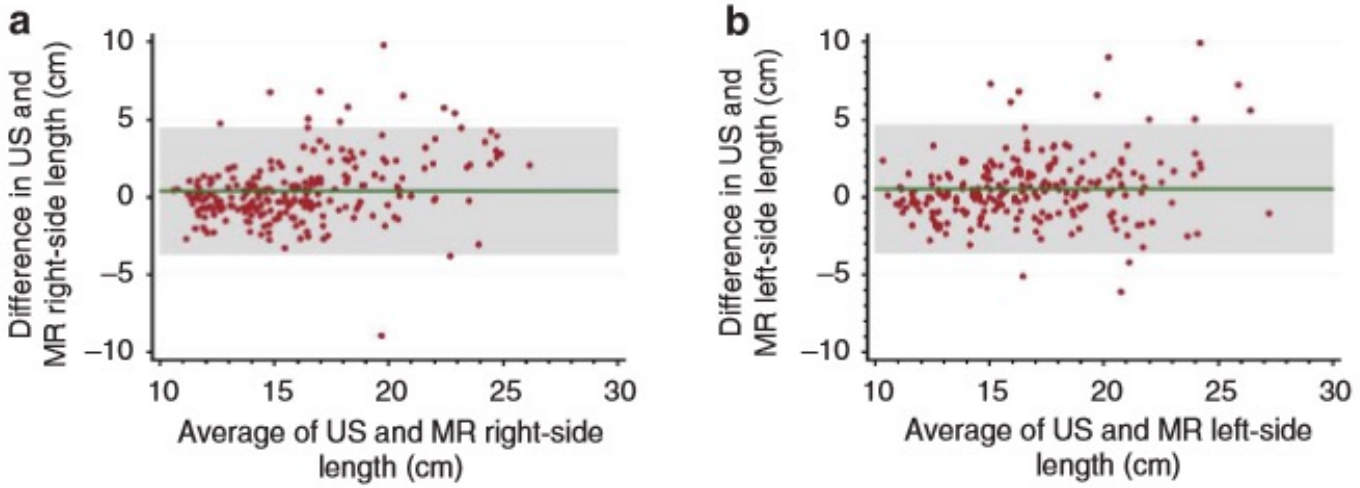
Does ultrasound have value in PKD?



- If you just need a broad idea of kidney size, ultrasound performance is good in that setting

O'Neill WC, Robbin ML, Bae KT, Grantham JJ, Chapman AB, Guay-Woodford LM, et al. Sonographic Assessment of the Severity and Progression of Autosomal Dominant Polycystic Kidney Disease: The Consortium of Renal Imaging Studies in Polycystic Kidney Disease (CRISP). Am J Kidney Dis. 2005 Dec;46(6):1058–64.

Kidney length



This is the least variable sonographic measurement, and in the right setting gives just as much prognostic info as cross-sectional TKV

Bhutani H, Smith V, Rahbari-Oskoui F, Mittal A, Grantham JJ, Torres VE, et al. A comparison of ultrasound and magnetic resonance imaging shows that kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. Kidney Int. 2015 Jul;88(1):146–51.

Maximizing the utility of imaging in PKD

Standardization is key

Our **first in Canada** standardized ultrasound reporting

Old report
Kidneys are enlarged and display multiple bilateral cysts consistent with polycystic kidney disease The largest cyst on the right is 3.6cm by 2.4cm and is unchanged in size. There is no dominant cyst on the left.

New report
Study confirms phenotypic diagnostic criteria for polycystic kidney disease Typical morphology of cyst involvement with diffuse bilateral cystic expansion. Right kidney 17.8cm, left kidney 18cm in long axis. Measurement of renal length is less precise at lengths exceeding 17cm. If more accurate determination of renal size is required, suggest cross-sectional imaging.

Benefits of US standardization

- Maximize the information from tests already performed
- Ensure accuracy and comparability of diagnostics for PKD patients across BC
  - Equitable access to care in all areas of the province
- High quality US reporting will eliminate the need for some cross-sectional imaging

Coming soon: Standardized TKV measurement and reporting

With the department of radiology at SPH we are conducting a pilot study of different methods of TKV measurement and calculation

This will be another first in Canada and will:

- Bring a powerful tool from the research world into everyday clinical care
- Provide British Columbians with PKD unmatched access to state of the art diagnostics
- Standardization will facilitate image acquisition, interpretation and maximize information available to clinicians

- How toxic is IV contrast ?

Objectives: Contrast Nephropathy

- Current definitions, names and controversies associated with Contrast and Acute Kidney Injury (CIN vs CAN vs CA-AKI)
- Review lower-mainland research project aimed at reducing the incidence of Contrast associated nephropathy
  - True incidence and impact of strategies
- Evidence for current prophylaxis practices
- Recommendations

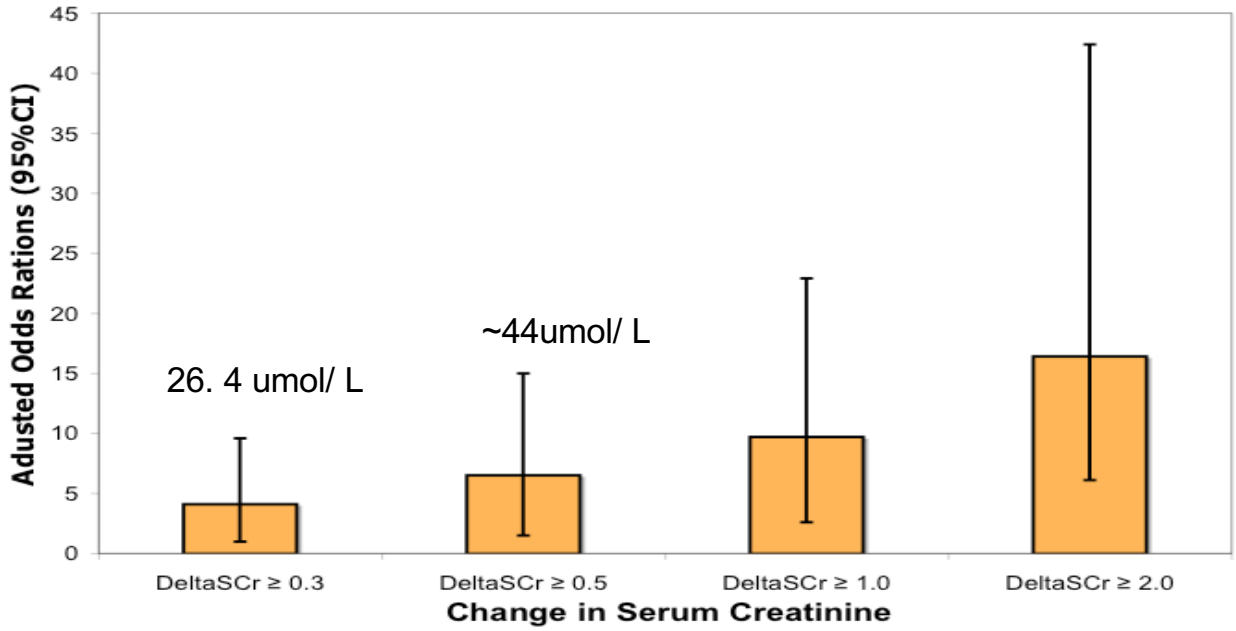
Contrast-Induced Nephropathy (CIN) or Contrast Associated Nephropathy

- Estimated incidence varies widely (1% to 30%)
- 3rd most common cause Acute Kidney Injury (AKI) in hospitalized patients
- Clinical definitions and diagnostic criteria vary:
  - Post intra-arterial or intravenous administration of contrast rise in serum SCr of >44 micromol/L and/or >25% within 48-96 hours of contrast exposure
  - Newer definitions of AKI (KDIGO 2012): increase in SCR by >26.6 micromol/L within 48 hours or a change in SCr >1.5x baseline or urine volume <0.5 mL/kg/hr for 6 hours
- Misclassification of cause of AKI and confounding in problematic in assessment

Acute Kidney Injury: impact on short term and long term outcomes

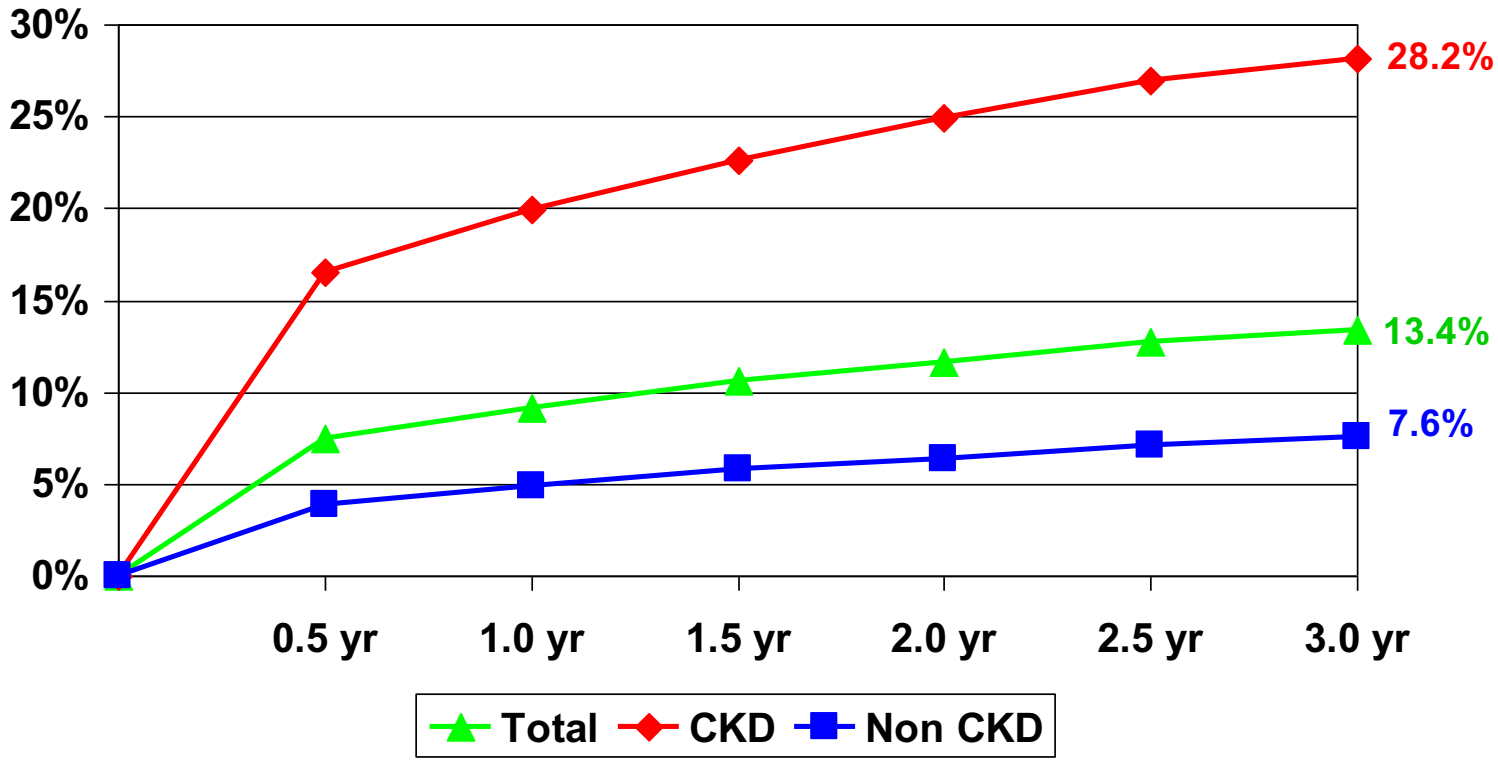
Adjusted OR of Inpatient Death with Changes in Serum Creatinine

*Adjusted for age, sex, severity, CKD



Chertow et al. JASN November, 2005

AKI leads to progression to ESRD, especially if CKD pre-exists



Slide courtesy of A. Levin

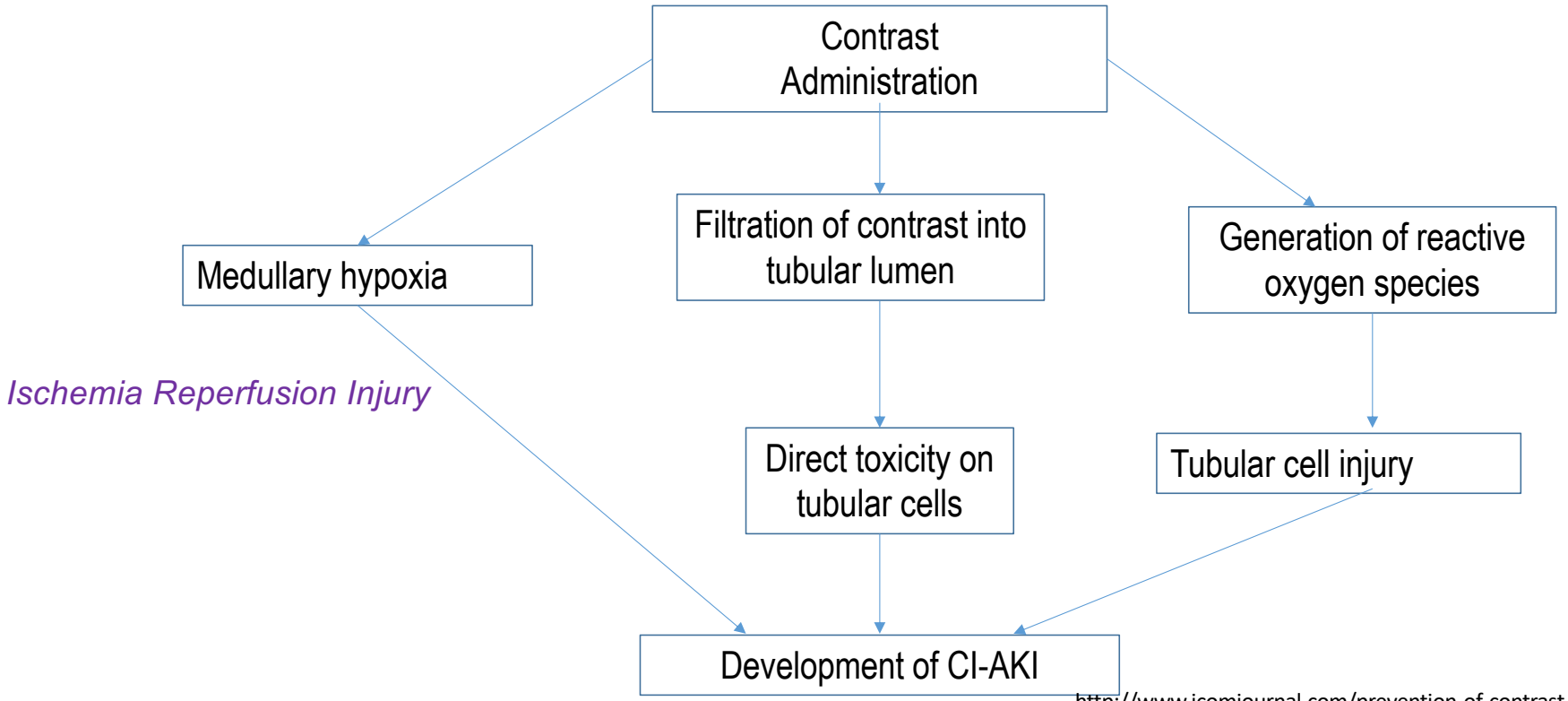
Pathophysiology of AKI: what we do know

Patho-physiological processes (common pathways):

- persistent vasoconstriction
- Tubular obstruction
- Cellular structural and metabolic alterations
- Inflammation

- Morphological alterations
  - Cell death
  - De-differentation of viable cells
  - Proliferation
  - Re-differentiation
  - Restitution of normal epithelieum

Pathophysiology :
Does contrast cause tubular damage? YES



http://www.jcomjournal.com/prevention-of-contrast-induced-acute-kidney-injury/

Table 1. Factors Increasing Susceptibility to Renal Hypoperfusion.

Failure to decrease arteriolar resistance
Structural changes in renal arterioles and small arteries
Old age
Atherosclerosis
Chronic hypertension
Chronic kidney disease
Malignant or accelerated hypertension
Reduction in vasodilatory prostaglandins
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Afferent glomerular arteriolar vasoconstriction
Sepsis
Hypercalcemia
Hepatorenal syndrome
Cyclosporine or tacrolimus
Radiocontrast agents
Failure to increase efferent arteriolar resistance
Angiotensin-converting–enzyme inhibitors
Angiotensin-receptor blockers
Renal-artery stenosis

There are a number of factors which increase Susceptibility to Renal Hypoperfusion:

Modifiable and non modifiable

History and Physical should allow you to determine how many of these factors exist

Abuelo J. N Engl J Med 2007;357:797-805

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Causes of Low-Perfusion States.

Hypovolemic causes

Fluid loss to the third space

- Tissue damage (e.g., pancreatitis)
- Hypoalbuminemia (e.g., the nephrotic syndrome)
- Bowel obstruction

Blood loss

Fluid loss to the outside

- Gastrointestinal causes
- Renal causes (e.g., diuretics, adrenal insufficiency, hypercalcemia)
- Dermal causes (e.g., burns, sweating)

Cardiovascular causes (congestive heart failure)

Myocardial causes (e.g., infarction, cardiomyopathy)

Pericardial causes (e.g., tamponade)

Pulmonary vascular causes (e.g., embolism)

Arrhythmia

Valvular disease

Distributive causes (reduced vascular resistance)

Sepsis

Hepatorenal syndrome

Overdose of drugs (e.g., barbiturates)

Vasodilators (e.g., nitrates, antihypertensive agents)

Local renal hypoperfusion

Renal-artery stenosis (atherosclerosis or fibromuscular hyperplasia)

Malignant hypertension

Causes of Low-Perfusion States

The NEW ENGLAND JOURNAL of MEDICINE

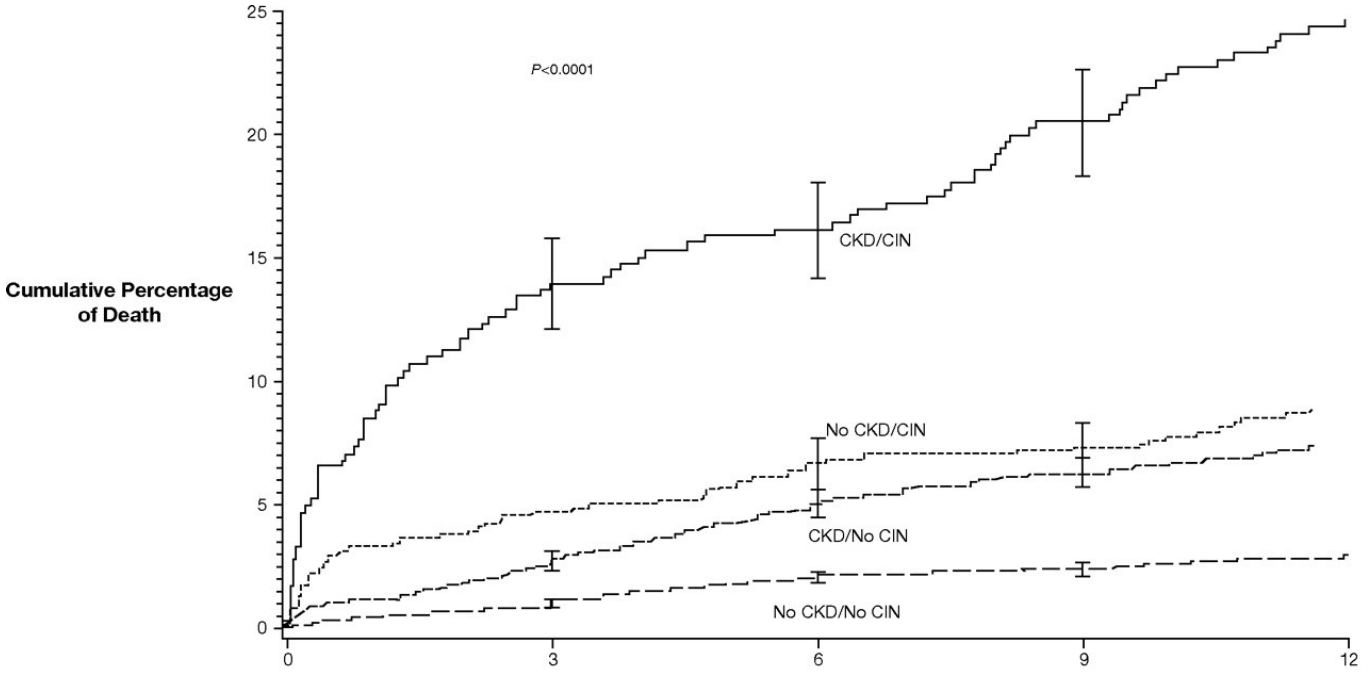
Reported Mortality with 'CIN' rates vary (3-54%)

Reference	No. of Patients and Type of Contrast Procedures	CIN Definition (Size of Increase in SCr from Baseline)	In-Hospital Mortality Rates: CIN vs No CIN	Long-Term Mortality Rates: CIN vs No CIN
McCullough *et al.*, 1997 (5)	1826 in a derivation set, 2251 in a validation set; PCI	>25% during first 5 days	7.1% vs 1.1%;35.7% for dialysis-dependent ($P < 0.0000001$)	—
Rihal *et al.*, 2002 (3)	254 with CIN, 6890 without CIN; PCI	>0.5 mg/dl during first 48 h	22.0% vs 1.4% ($P < 0.001$)	12.1% vs 3.7% ($P < 0.0001$) (1-yr hospital survivors);44.6% vs 14.5% ($P < 0.0001$) (5-yr hospital survivors)
Gruberg *et al.*, 2000 (8)	439 with CKD (SCr ≥1.8 mg/dl) not dialysis-dependent; PCI	≥25% during first 2 days or needing dialysis	14.9% vs 4.9%;22.6% for dialysis-dependent ($P < 0.001$)	37.7% vs 19.4% ($P = 0.001$) (1-yr cumulative rate)
Gruberg *et al.*, 2001 (9)	7741; PCI	Requiring dialysis	27.5% vs 1.0% ($P < 0.001$)	54.5% vs 6.4% ($P < 0.0001$) (1-yr cumulative rate)
Dangas *et al.*, 2005 (4)	5250 CKD(+), 1980 CKD(−); PCI	≥25% or ≥0.5 mg/dl during first 48 h	6.3% vs 0.8% (CKD(+), $P < 0.0001$);2.5% vs 0.1% (CKD(−), $P < 0.0001$)	22.6% vs 6.9% (CKD(+); $P < 0.0001$)8.0% vs 2.7% (CKD(−); $P < 0.0001$) (1-yr cumulative rate)
Levy *et al.*, 1996 (11)	183 with CIN, 183 matched control subjects; various procedures (about half angiography)	≥25% to ≥2 mg/dl during first 2 days	34% vs 7% ($P < 0.001$)	—

Different populations
With and without CKD
PCI or variable procedures, including angiography

Rudnick et al. CJASN 2008 Jan;3(1):263-72.

One-year survival after percutaneous coronary intervention in patients with or without CKD and with or without CIN (4).



Number at risk

CKD/CIN	364	313	305	289	251
CKD/No CIN	1641	1599	1560	1539	1378
No CKD/CIN	637	608	595	591	542
No CKD/No CIN	4906	4858	4805	4786	4375

Dangas *et al.* Am J Cardiol. 2005:95:13-19
Rudnick *et al.* CJASN 2008;3:263-272

Radiological Contrast studies vs PCI

- Not equivalent
- Extrapolations may or may not be relevant

- Data on risk of contrast toxicity with non-PCI imaging studies equally variable
  - Definitions
  - Incidence

- But, AKI as a predictor of poor outcomes is consistent

Is all AKI post contrast due to contrast ?

Controversies with Contrast Studies and AKI :CIN/ CAN/

- Available literature has consistently shown that patients who develop CIN have a higher mortality rate
- However, most studies on CIN are observational cohort studies
- Although data demonstrates a temporal association between CIN-AKI and death, it does not prove a causal relationship
- Observational studies are prone to confounding bias
  - Perhaps hidden variables explain the causal link between predictor and outcomes better than the observed temporal relationship

Growing body of evidence suggests that contrast may not be the primary cause of AKI in patients who receive a contrast scan

Risk of Nephropathy after Intravenous Administration of Contrast Material: A Critical Literature Analysis[1]

ARTICLE | January 1985

Renal Function Following Infusion of Radiologic Contrast Material

A Prospective Controlled Study

Benvon C. Cramer, MD; Patrick S. Parfrey, MD; Tom A. Hutchinson, MD; Dana Baran, MD; Denis M. Melanson, MD; Romeo E. Ethier, MD; John F. Seely, MD

Intravenous Contrast Material Exposure Is Not an Independent Risk Factor for Dialysis or Mortality[1]

Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

ORIGINAL RESEARCH CONTRIBUTION

Does the Current Definition of Contrast-induced Acute Kidney Injury Reflect a True Clinical Entity?

Richard Sinert, DO, Ethan Brandler, MD, Ramanand Arun Subramanian, PhD, and Andrew C. Miller, MD

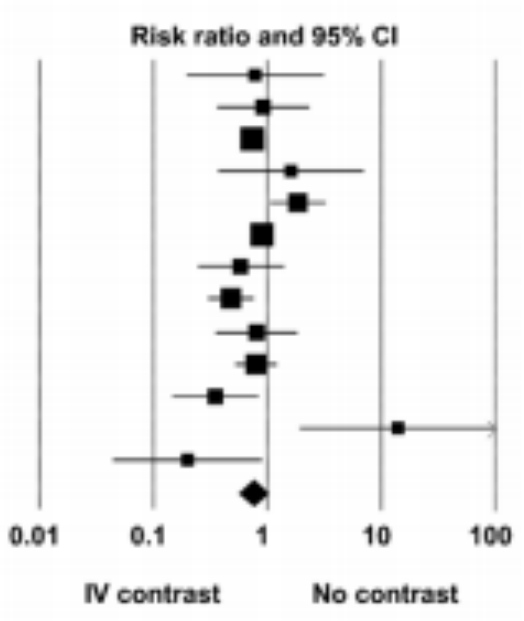
Frequency of Acute Kidney Injury Following Intravenous Contrast Medium Administration: A Systematic Review and Meta-Analysis[1]

Jennifer S. McDonald, PhD
Robert J. McDonald, MD, PhD
Jules Comin, MD
Eric E. Williamson, MD
Richard W. Katzberg, MD
M. Hassan Murad, MD, MPH
David F. Kallmes, MD

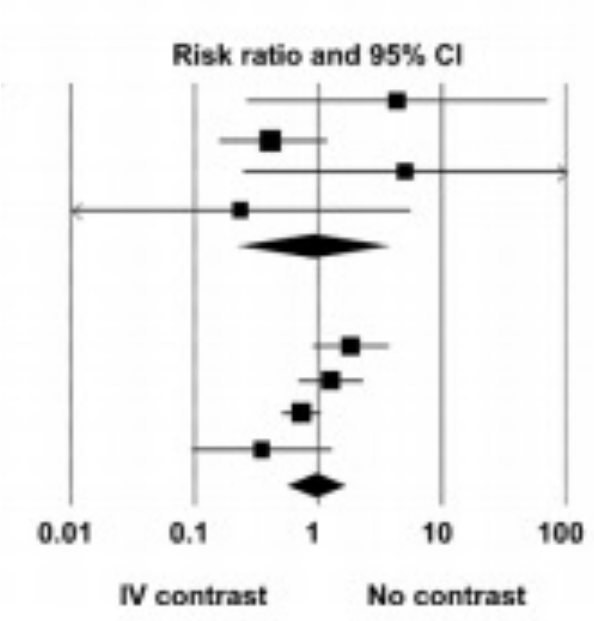
Purpose: To perform a systematic review and meta-analysis of controlled studies examining the incidence of acute kidney injury (AKI) and other outcomes in patients exposed to intravenous (IV) contrast medium compared with patients who underwent an imaging examination without contrast medium or were otherwise unexposed (control group).

McDonald et al. RSNA 2013:267(1): 119-128

Incidence of AKI, death and dialysis similar in patients who received IV contrast and who did not



AKI Incidence



Incidence of death or dialysis

Current state:

- There is increasing questioning of the true incidence and relationship of contrast to AKI in hospitalized pts

- Most studies in the literature are retrospective observational cohort studies
- Few prospective CIN studies available, especially in hospitalized patients

The BC experience: understanding incidence of CIN

Hemmett *et al. Canadian Journal of Kidney Health and Disease* (2015) 2:38
DOI 10.1186/s40697-015-0073-6

Canadian Society of Nephrology/
Société canadienne de néphrologie

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

ORIGINAL RESEARCH ARTICLE Open Access

Time to revisit the problem of CIN? The low incidence of acute kidney injury with and without contrast in hospitalized patients: an observational cohort study

Juliya Hemmett[1], Lee Er[2], Helen H. L. Chiu[2], Christopher Cheung[3], Ognjenka Djurdjev[2] and Adeera Levin[2,3*]

The Environment

- 100,000 CT scans are performed annually within Fraser Health Authority (FHA)
  - Baseline incidence of CIN is unknown
- Variability exists in protocols to mitigate CIN risk
- Recent guidelines (2011) suggest need for CIN prevention protocols to reduce incidence
  - Lower mainland and provincial interest in harmonized protocol for all radiology departments

Applying Robust Research Methodology and CQI

- Implementation of standardized protocols in lower mainland
- What is baseline incidence of CIN / AKI Post contrast?
- What is incidence of CIN/ AKI post contrast, after implementation of protocols?

Purpose of the Lower Mainland CIN Prevention Initiative

- Improve patient safety and decrease incidence of contrast induced nephropathy (CIN) in at-risk patients through a multipronged approach:

1. Develop a CIN prevention protocol based on the most recent Radiology guidelines
2. Describe the incidence of CIN using robust definitions, and all available data, both pre and post-protocol implementation, with a large local health authority (Fraser Health Authority)
3. Describe the current issues related to reporting of incidence of CIN
4. Develop a plan for future roll out of the protocol throughout the province

Timeline of CQI Initiative

- Sept 2012-May 2013: Design of CIN-AKI prevention protocol within FHA
- Dec. 2012 – Measuring incidence of CIN-AKI at FHA pre-protocol implementation
- June 2013 – Protocol goes live
- Oct. 2013 – Measuring incidence of CIN-AKI at FHA post-protocol implementation

eGFR greater or equal to 60 mLs/min	eGFR 30 to 59 mLs/min	eGFR less than 30 mLs/min
• Avoid dehydration • No specific intervention needed. Proceed with examination	• Avoid dehydration • Hold nephrotoxic drugs (NSAIDs, ACEi, ARB's and diuretics) for 24 to 48 hours prior to IV contrast • Stop Metformin therapy for 48 hours following intravascular contrast injection • Follow up SCr and eGFR in 48 to 72 hrs • Metformin therapy can be restarted if renal function is similar to baseline (less than 25% decrease from baseline) • Consider alternate imaging examinations not involving contrast media • Minimize contrast volume • Avoid repeat iodinated contrast exams within 48 hrs	• Avoid dehydration • Hold nephrotoxic drugs (NSAIDs, ACEi, ARB's and diuretics) for 24 to 48 hours prior to IV contrast • Stop Metformin therapy for 48 hours following intravascular contrast injection • Follow up SCr and eGFR in 48 to 72 hrs • Metformin therapy can be restarted if renal function is similar to baseline (less than 25% decrease from baseline • Consider alternate imaging examinations not involving contrast media • Minimize contrast volume • Avoid repeat iodinated contrast exams within 48 hrs • IV hydration recommended • Radiologist to discuss examination with referring physician

- Inclusion criteria:
  - In-patients within 4 hospitals in the FHA who had a CT scan performed
    - Pre-protocol implementation: Dec 1-12, 2012
    - Post-protocol implementation: October 1-13, 2013

  - Creatinine measurements available
    - 7 days before the scan *and* within 7 days of the scan

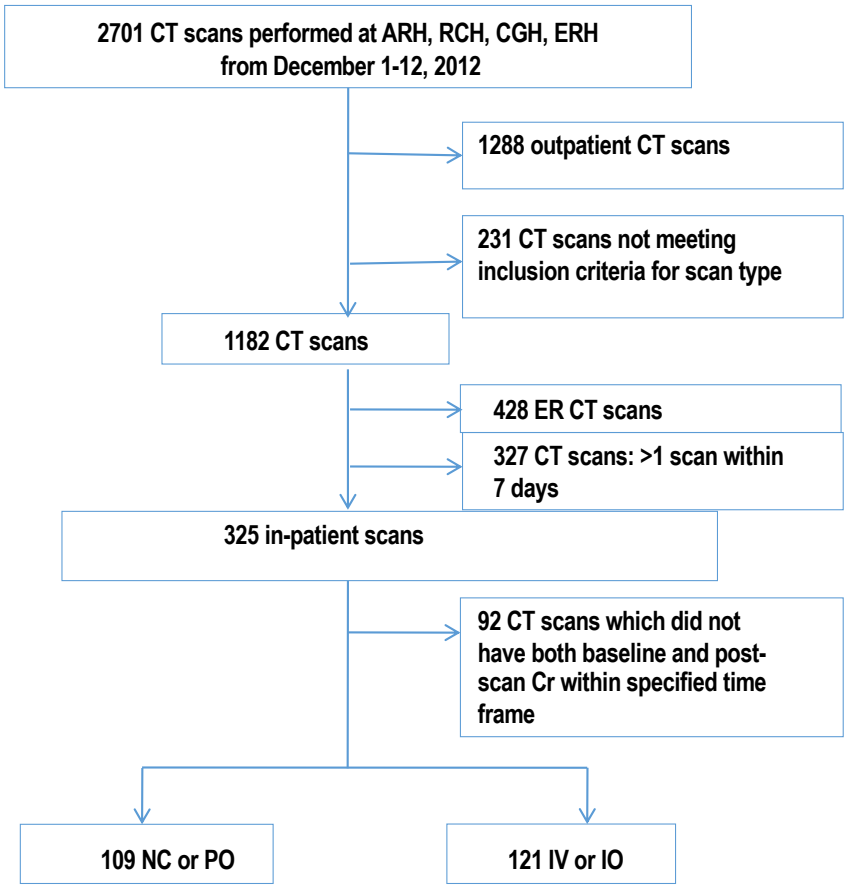
- Exclusion criteria:
  - Intra-arterial contrast scans
  - Patients >1 CT scan within 7 days
  - CT scans of extremities
    - Ie: non head, spine, chest, abdomen or pelvis

Data Collection

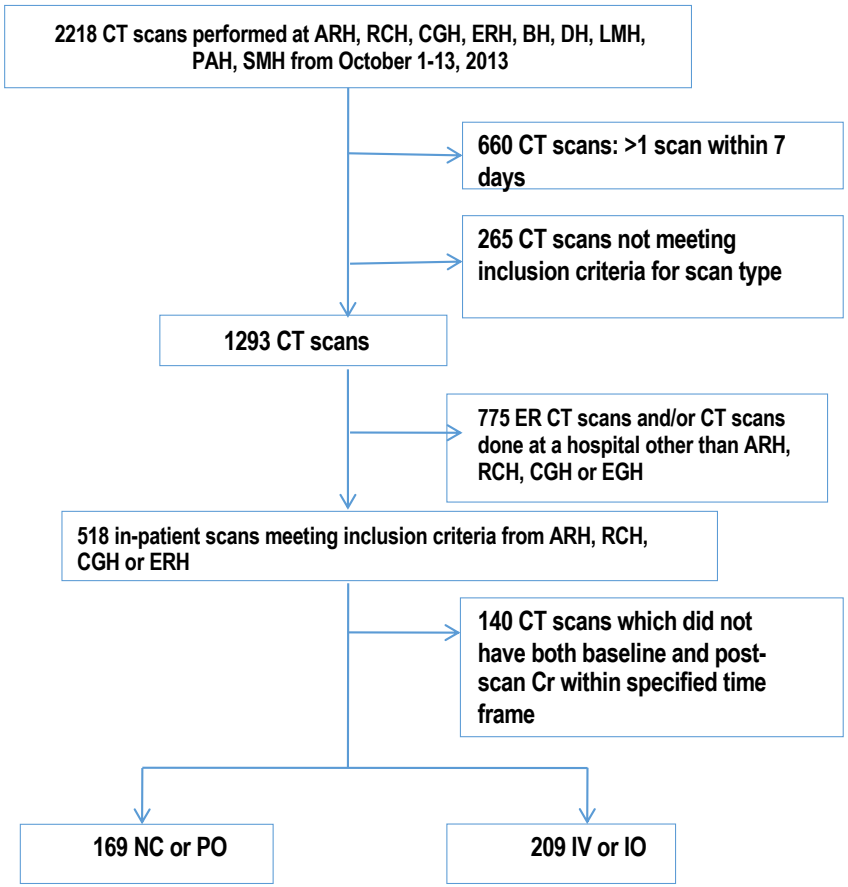
- Over **5000 CT** scan reports from the FHA radiology department individually read (JH, CC)
  - Ascertainment of details of scan
- Radiology data linked to laboratory data from MediTech
- Data collected:
  - patient demographics
  - type of CT scan, type of contrast
  - creatinine ascertainment within 7 days pre- and post-CT scan

Baseline Data :

2700 CT scans : 109 vs 121 -/+ contrast



3 Months After Protocol Implementation : 2200 CT scans:166 vs 209 -/+ Contrast



Similar patients underwent CT scans in both time periods

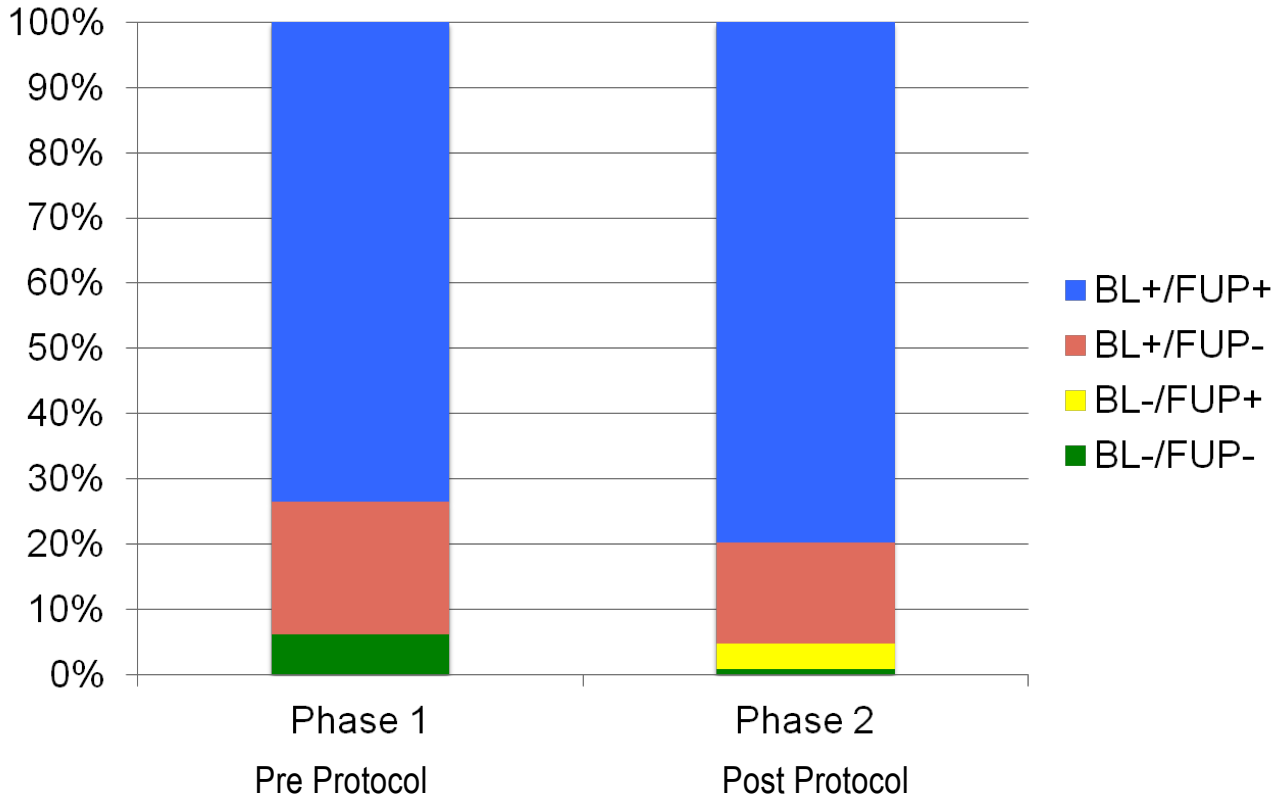
Strict	NC/PO		IV/IO		P-value for ScanType
	Phase 1	Phase 2	Phase 1	Phase 2	
# Patients	109	165	121	205	
Age (median [IQR])	70 [59, 81]	74 [60, 84]	68 [54, 77]	65 [51, 76]	<0.001
Male (n; %)	57 (53%)	97 (59%)	64 (53%)	121 (59%)	0.96
BL eGFR (median [IQR])	66 [43, 94]	64 [37, 87]	72 [58, 104]	74 [58, 96]	<0.001
BL eGFR>60 (n; %)	62 (57%)	89 (54%)	85 (70%)	147 (73%)	<0.001

There were significant differences between those who did and did not receive contrast (BL eGFR, and age)
There were no significant differences between those in Pre and Post implementation of protocol

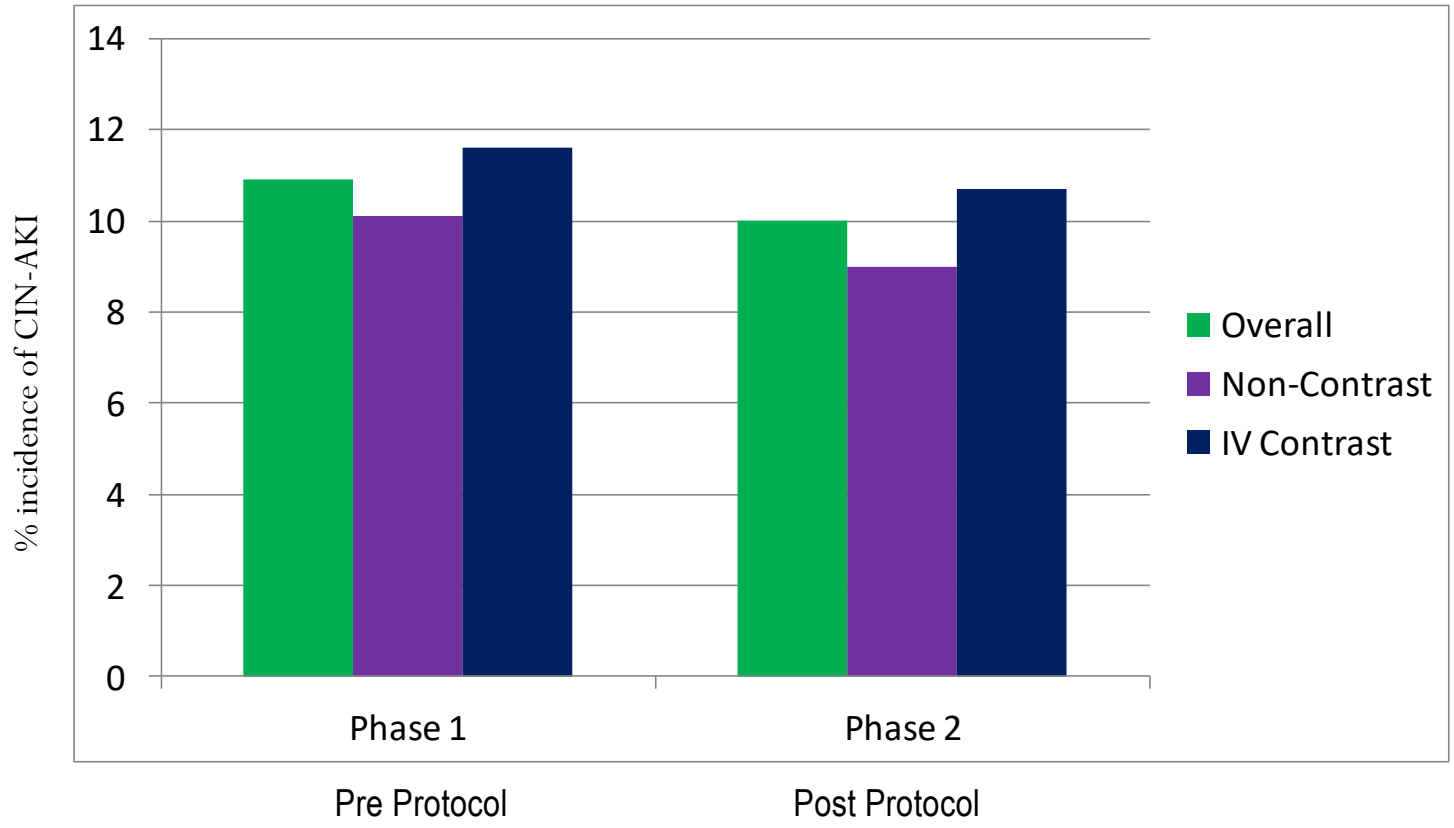
Pre-/Post sCr availability by study phase and scan type: Some improvement in post protocol determinations of sCr in patients that underwent contrast CT scans

Strict	Serum Creatinine Availability			
	BL+, FUP+	BL+, FUP-	BL-, FUP+	BL-, FUP-
Phase 1				
NC/PO	110 (69.6%)	39 (24.7%)	1 (0.6%)	8 (5.1%)
IV/IO	123 (73.6%)	34 (20.4%)	0 (0.0%)	10 (6.0%)
Phase 2				
NC/PO	169 (66.0%)	49 (19.1%)	32 (12.5%)	6 (2.4%)
IV/IO	209 (79.8%)	41 (15.6%)	10 (3.8%)	2 (0.8%)

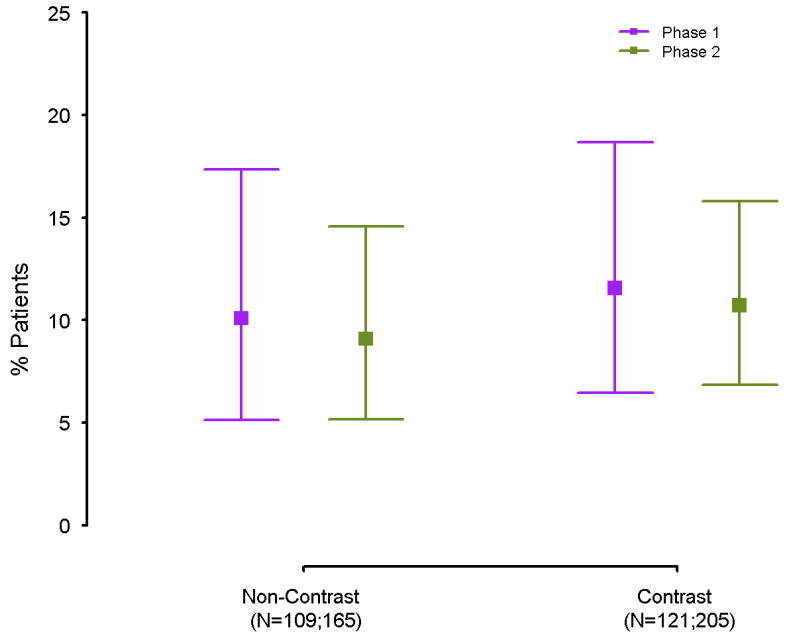
After protocol implementation, more patients receiving IV contrast had Pre-/Post sCr available :
20% still did not have both Pre and Post-scan sCr measured



Incidence of CIN-AKI FHA before and after protocol implementation remained unchanged



Incidence of CIN-AKI before and after protocol implementation: Incidence is similar in Non-Contrast Vs Contrast Scans (10-12%)



Lessons Learned

- True incidence of AKI within FHA in-patients receiving CT scan is low: ~10%
- AKI incidence is similar in those with and without contrast CT scans
- Our CIN-AKI prophylaxis protocol did not improve incidence of AKI in patients who received contrast CT scans despite improved monitoring of SCr
  - Adherence; implementation etc may be problematic
- Serum creatinine is not routinely ordered pre and post contrast even in in-patients 20%
- There may be a bias against ordering contrast studies in older patients, and those at risk for CIN: appropriateness of this practice is not clear

Updated literature : JASN October 2016

Estimating the risk of Radiocontrast Induced Nephropathy

- US Nationwide In-Patient Sample (29 M)
  - Stratified for +/- 12 common conditions
  - Logistic regression models with adjustments for Comorbidity and severity of illness

  - AKI rates = 5.5% and 5.6 % (with and without contrast)

"Risk of radiocontrast associated nephropathy may be overstated in literature and overestimated by clinicians…

More accurate AKI risk estimates may improve clinical decision making and balance benefits of contrast enhanced imaging vs risk of AKI"

Wilhelm-leen; Montez-Rath and Chertow JASN 2016 doi 10.1681/ASN.2016010021

Practical considerations

- At risk populations
- Prevention/ attention
- What does work and what does not work

Risk factors

Patient Related:

- Pre-existing CKD
  - eGFR <60 or uACr >30
- Diabetes mellitus
- Proteinuria
- Intravascular volume depletion
- Decreased cardiac output
- Nephrotoxins

Procedure Related:

- Type of contrast
- Dose of contrast
- Multiple procedures within 72h
- Intra-arterial administration

Prevention Strategies

- Choose non-contrast study if appropriate
- Avoid concomitant drugs that can harm the kidneys
- *Selection of contrast media*
  - *HOCM vs LOCM*
  - *LOCM vs IOCM*
  - *Limit volume of contrast*
- Hydration administration
  - IV vs oral
  - Saline vs bicarbonate
- NAC: yes or no?
- Dialysis: NO

Avoidance of concomitant nephrotoxins

- Drugs that impair autoregulation / exacerbate ischemis
  - NSAIDs
  - Cyclosporine, tacrolimus (CNI)
  - Diuretics
  - ACEi/ ARBs

- CAVEAT:
  - Metformin is NOT toxic, but does accumulate in AKI leading to lactic acidosis

Volume administration

- The rationale
  - Dampen vaso-constrictive effects of contrast on renal medulla
  - Decreases concentration of contrast in tubular lumen
  - Decreases viscosity of contrast in tubular lumen

- The evidence
  - Saline or bicarbonate?
  - Preferred route of administration: IV or oral?

Saline vs bicarbonate: heterogeneous studies

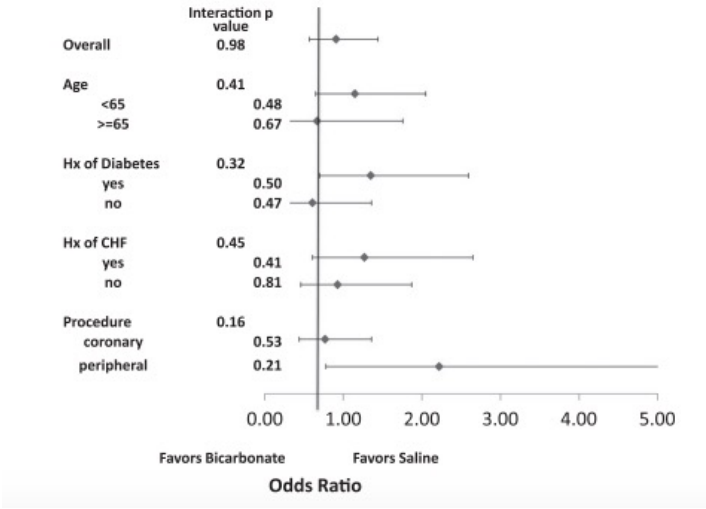
	Number of Patients	Baseline SCr (mg/dL)	Definition of 1° Outcome	Frequency of CIAKI Bicarbonate	Frequency of CIAKI Saline	Assumed Effect Size of Bicarbonate
Positive studies						
Briguori et al	219	2.0	↑ SCr ≥ 25%	1.9%	9.9%	86%
Masuda et al	59	1.3	↑ SCr ≥ 0.5mg/dL or ≥ 25%	6.6%	34.5%	85%
Merten et al	119	1.7–1.9	↑ SCr ≥ 25%	1.7%	13.6%	66%
Ozcan et al	176	1.4	↑ SCr ≥ 0.5mg/dL or ≥ 25%	4.2%	16.6%	NR
Pakfetrat et al	192	1.1	*	4.2%	12.5%	NR
Recio-Mayoral et al	111	1.0	↑ SCr ≥ 0.5mg/dL	1.8%	21.8%	85%
Neutral studies						
Adolph et al	145	1.5–1.6	↑ SCr ≥ 0.5mg/dL or ≥ 25%	4.2%	2.7%	87%
Brar et al	353	1.5	↓ eGFR ≥ 25%	13.3%	14.6%	66%
Maioli et al	502	1.2	↑ SCr ≥ 0.5mg/dL	10%	11.5%	50%
Vasheghani et al†	265	1.6–1.6	↑ SCr ≥ 0.5mg/dL or ≥ 25%	7.4%	5.9%	71%

*Three definitions of CIAKI assessed; differences between bicarbonate and saline based on ↑ SCr ≥ 0.3 mg/dL.

BOSS: no difference in CI-AKI between saline and bicarbonate-treated groups (elective angio)

Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD

Richard Solomon, Paul Gordon,† Steven V. Manoukian,‡ J. Dawn Abbott,§ Dean J. Kereiakes,‖ Allen Jeremias,¶ Michael Kim,** Harold L. Dauerman,* on behalf the BOSS Trial Investigators*



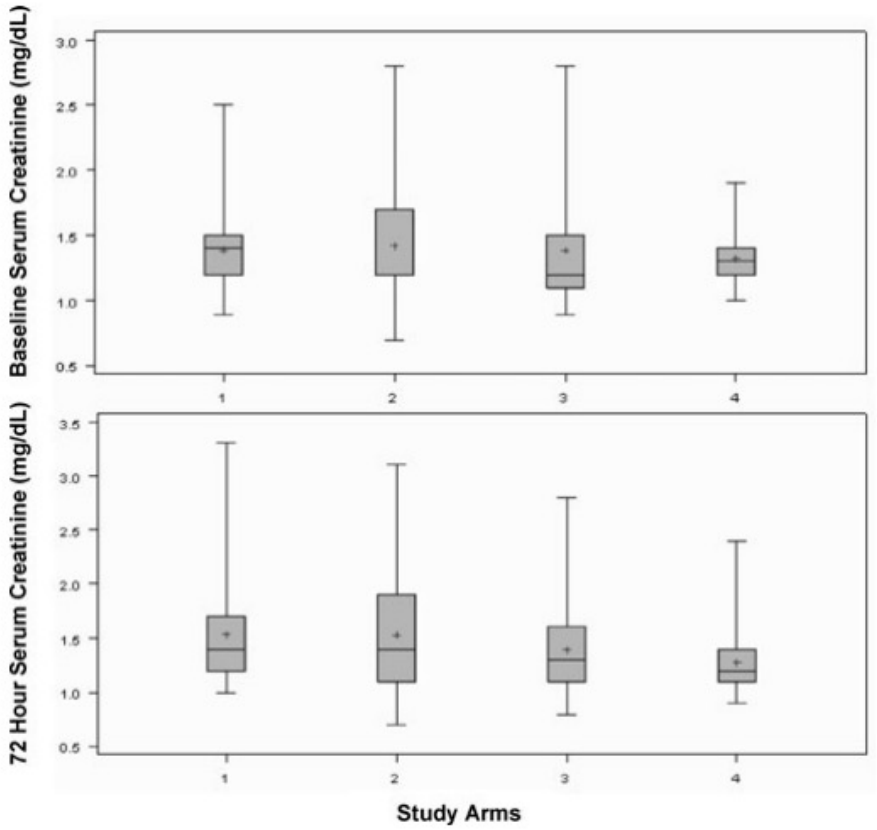
Solomon et al. CJASN 2015 10(9): 1519-24

Oral vs IV:
Randomized prospective trial of IV saline versus oral hydration demonstrates significantly higher rate of CIN in oral hydration arm

- 53 patients on day of non-emergent cath randomized to NS or unrestricted fluids
- Baseline SCr ~106
- 19% developed AKI, much lower in NS group (1/27) than in oral hydration group (9/26); RR 0.11
- However, small sample size, no control for oral intake

Trivedi et al. Nephron Clin Pract 2003;93:C29-C34.

Oral hydration and alkalinization non-inferior to IV hydration: HYDRATE trial (angio, CKD)



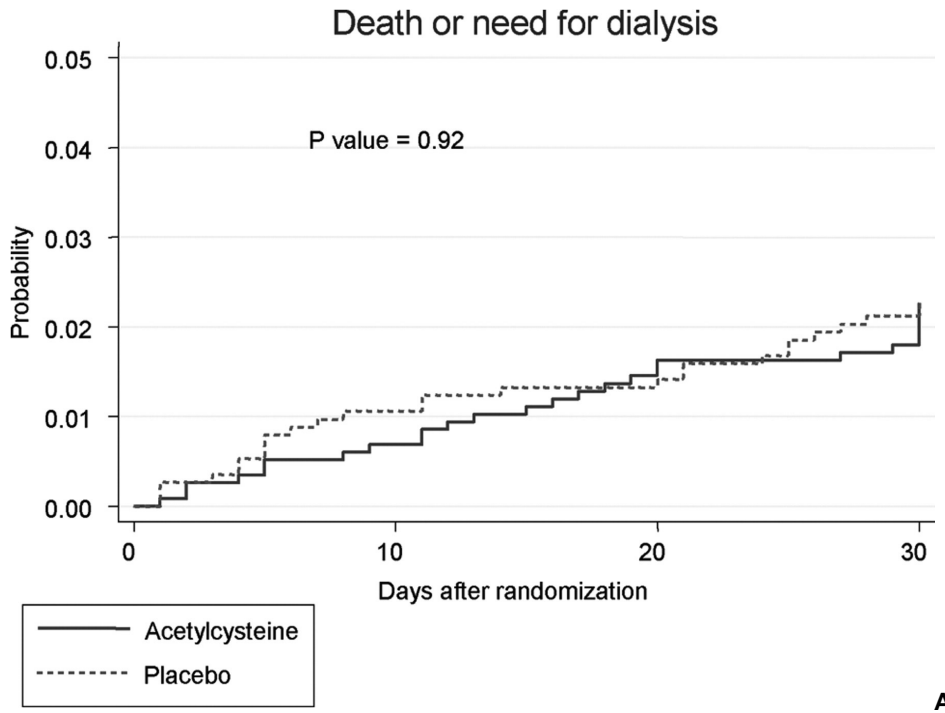
Group 1: IV NS
Group 2: IV NaHCO3
Group 3: Oral hydration alone
Group 4: Oral hydration with oral bicarbonate

Cho et al. Journal of Interventional Cardiology. 2010. 23:5:460-466

The NAC story

ACT Trial:

Probability of death or need for dialysis is the same in NAC vs placebo groups



ACT Investigators Circulation. 2011;124:1250-1259

Probability of death or need for dialysis from the day of randomization (day 0) to day 30 among patients in the acetylcysteine and placebo groups.

IV NAC ineffective at preventing CIN in high-risk patients with impaired renal function undergoing cardiac catheterization (SPH study)

A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: Lack of effect

John G. Webb, MD,[a] Gordon E. Pate, MB, MSc,[a] Karin H. Humphries, MBA, DSc,[a] Christopher E. Buller, MD,[b] Stephen Shalansky, PharmD,[a] Ali Al Shamari, MD,[a] Anton Sutander, MD,[a] Tracey Williams,[a] Rebecca S. Fox, MSc,[b] and Adeera Levin, MD[a] *Vancouver, British Columbia, Canada*

Table III. Per Protocol Analysis

End point	N-acetylcysteine (n = 194)	Placebo (n = 204)	P
Primary end point			
≥ 5 mL/min decline in creatinine clearance (Cockcroft-Gault formula)	23.7%	21.1%	.55
Secondary end points			
≥ 5 mL/min decline in glomerular filtration rate (MDRD formula)	24.7%	22.5%	.64
≥ 44 μmol/L increase in serum creatinine	7.2%	5.9%	.69
≥ 25% increase in serum creatinine	11.9%	10.8%	.75

n = 398; 40 patients with no follow-up creatinine, 38 with follow-up outside 2–8 day window, 11 protocol violations. *MDRD*, Modification of diet in renal disease.

Webb et al. Am Heart J 2004;148:422-9

NAC studies do not convincingly demonstrate effective CIN prophylaxis

- NAC always given with volume; not controlled for
- Confounders including heterogeneous populations
- Low risk patients in multiple trials
- Small changes in SCr as end-point
- Incongruent meta-analyses
- Incongruent guideline recommendations

In summary:

- NAC is not likely beneficial alone; does not replace other interventions

Prophylactic hemodialysis not useful for preventing CIN-AKI

- Small trials performed
- Most show no benefit, or even greater incidence of CIN in patients who receive prophylactic hemodialysis

Prophylactic dialysis or hemofiltration

CM can be easily removed with hemodialysis, however there is no evidence that this removal reduces the risk of CIN. Reduction of CIN with dialysis is also not biologically plausible since the CM would reach the kidneys within one or two cardiac cycles and subsequent removal of CM is unlikely to stop the cascade of renal injury, which would have already begun. Though one study[45] did show a reduction in CIN with hemofiltration, this result has not been reproduced by

Patients on dialysis

Patients undergoing hemodialysis need not be fluid loaded prior to contrast administration. Coordination of contrast administration with the timing of hemodialysis is unnecessary. Nephrotoxicity remains a concern in patients who retain residual function and in these patients renal protective measures may be considered.

CAR 2011 Consensus Guidelines on Prevention of CIN

Summary of recommendations for prevention

- Identify high-risk patients (eGFR and uACR)
- Discontinue NSAIDS and other nephrotoxins (24-48h)
- Use low-osmolar or iso-osmolar contrast in high risk groups
- Volume expansion: practical aspects (in hospital vs out patient)
  - isotonic saline or sodium bicarbonate
  - Oral hydration
- NAC unlikely to be useful alone
- Hemodialysis, hemofiltration is not useful and is not necessary

Summary: The bottom line

- Does Contrast associated nephropathy exist?
  - Yes, should be considered in high risk patients (in-pts and out-pts)
  - Likley less frequent than previously documented (5-10%)
- All increases in serum creatinine post contrast are not necessarily CIN
  - Especially in-patients; ? change terminology to CAN (Contrast Associated nephropathy)
- Minimize volume contraction :
  - oral hydration practical in OP ; No evidence for extensive IV hydration
- Avoid nephrotoxins/ drugs which impair autoregulation or which might be dangerous if AKI occurs
- No NAC is needed
- No dialysis is needed pre or post

Unanswered questions

- Who should be responsible for monitoring kidney function post contrast study?

- What mechanisms should we put in place to track AKI post imaging ?
  - Pre-printed orders (in and out-patient) ?
  - Letters to pts and GPs/ MD ordering imaging ?
  - Feedback and audit ?

Overall summary

- Nephrology and Radiology collaborations
    - Accurate and meaningful patient diagnoses
    - Ensuring patient safety
    - Evidence informed care : best test to answer the question

Thank you for all current collaborations…

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