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Predicting symptomatic recurrence of kidney stones

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Clinical Questions

- What is the risk of symptomatic recurrence in my patient with kidney stones?
  - Is everyone “50% recur in 10 years?”
  - What factors predict recurrence?
- What is the relationship between radiographic stone growth and symptomatic events?
  - Can we optimize how radiographic stone burden predicts symptomatic events?
- Are there clinical outcomes besides symptomatic recurrence with kidney stones?

Kidney stone presentation terminology

- Obstructing vs non-obstructing
  - Obstructing location: UVJ, ureter, UPJ, pelvic, or lower pole (intermittent obstruction)
  - Non-obstructing stones (occurs in 10% of living kidney donors)*
- Symptoms
  - Renal colic
  - Atypical abdominal/pelvic pain
  - Gross hematuria
  - Lower urinary tract symptoms (from UTI or the stone itself)
- Symptomatic stone episode
  - Symptomatic and stone in obstructing location (or passed and seen) or UTI from infected stone.
  - Not Suspected stone episode = Clinical diagnosis with no stone seen
  - Not Asymptomatic stone = non-obstructing on imaging and not infected.

*Lorenz EC et al, *Neph Dial Transpl*, 2011

All stone formers in Olmsted County

- All 4655 residents (1984-2003) with a new diagnosis of kidney stone in their chart were identified
- 2311 (50%) first-time symptomatic stone formers

- 2344 (50%) were excluded
  - Prevalent stone formers (19%)
    - 1st episode prior to 1984 or county residency
  - Only asymptomatic stones (8%)
  - Only “suspected stone episode” – no seen stone (11%)
  - Only bladder stones (3%)
  - No evidence of stone disease (7%)

Rule AD et al, JASN, 2014

Characteristics of first-time symptomatic stone formers

- Demographics: Mean age: 43 y
  Male: 62%
  BMI: 28.3 kg/m^2
- Incident stone event symptoms:
  - Renal Colic: 91%, Atypical pain: 6%, Gross Hem Only: 3%
  - Gross hematuria: 21%; Any hematuria: 78%; LUTS: 35%
  - Urinary tract infection: (3.4%)
- Imaging (only available in 93%):
  - Any obstructing stone: 85%
  - Any non-obstructing stone: 27%
- Comorbidities
  - Loose stools or Diarrhea: 9%,
  - Primary hyperparathyroidism: <1%

Rule AD et al, JASN, 2014

Characteristics of first-time symptomatic stone formers

- Treatments:
  - Urological Surgery: 32%
  - Diet: 19%
  - Medication: 3%
- Stone composition often not obtained:
  - Only 50% have stone analyzed
- 24-h urine chemistries often not obtained:
  - Only 31% volume, 28% calcium, 27% oxalate

Rule AD et al, JASN, 2014

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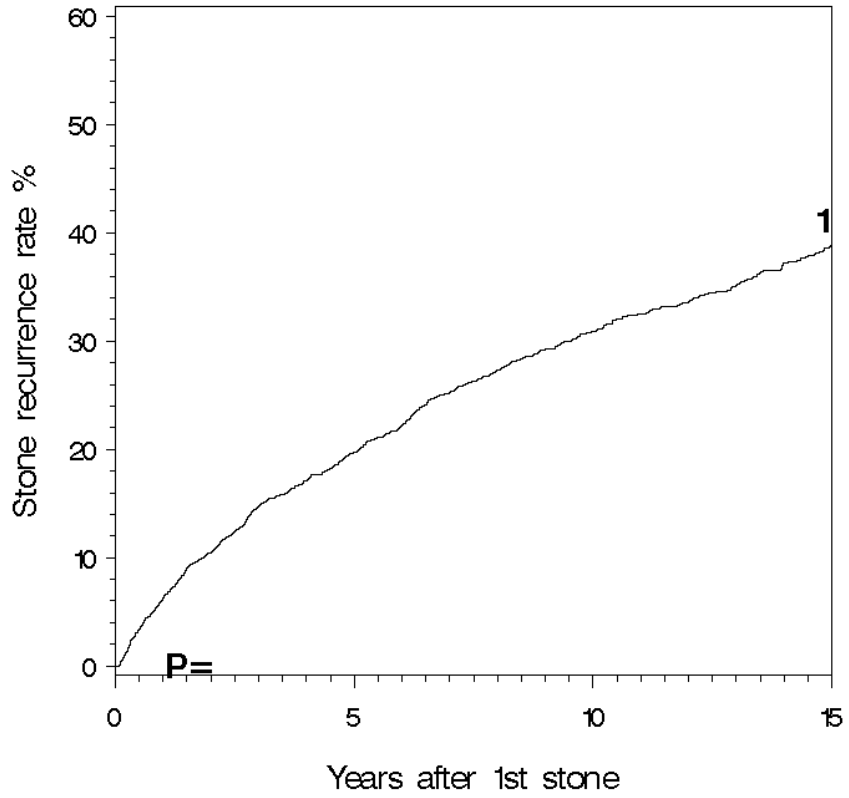
Stone Recurrence Rate

EJB4

- **The average recurrence was 30% at 10 years.**



- **Does recurrence rate differ by clinical characteristics at the first event?**

Rule AD et al, JASN, 2014

Slide 7

EJB4 Added Slide

Eric J Bergstralh, 9/18/2012

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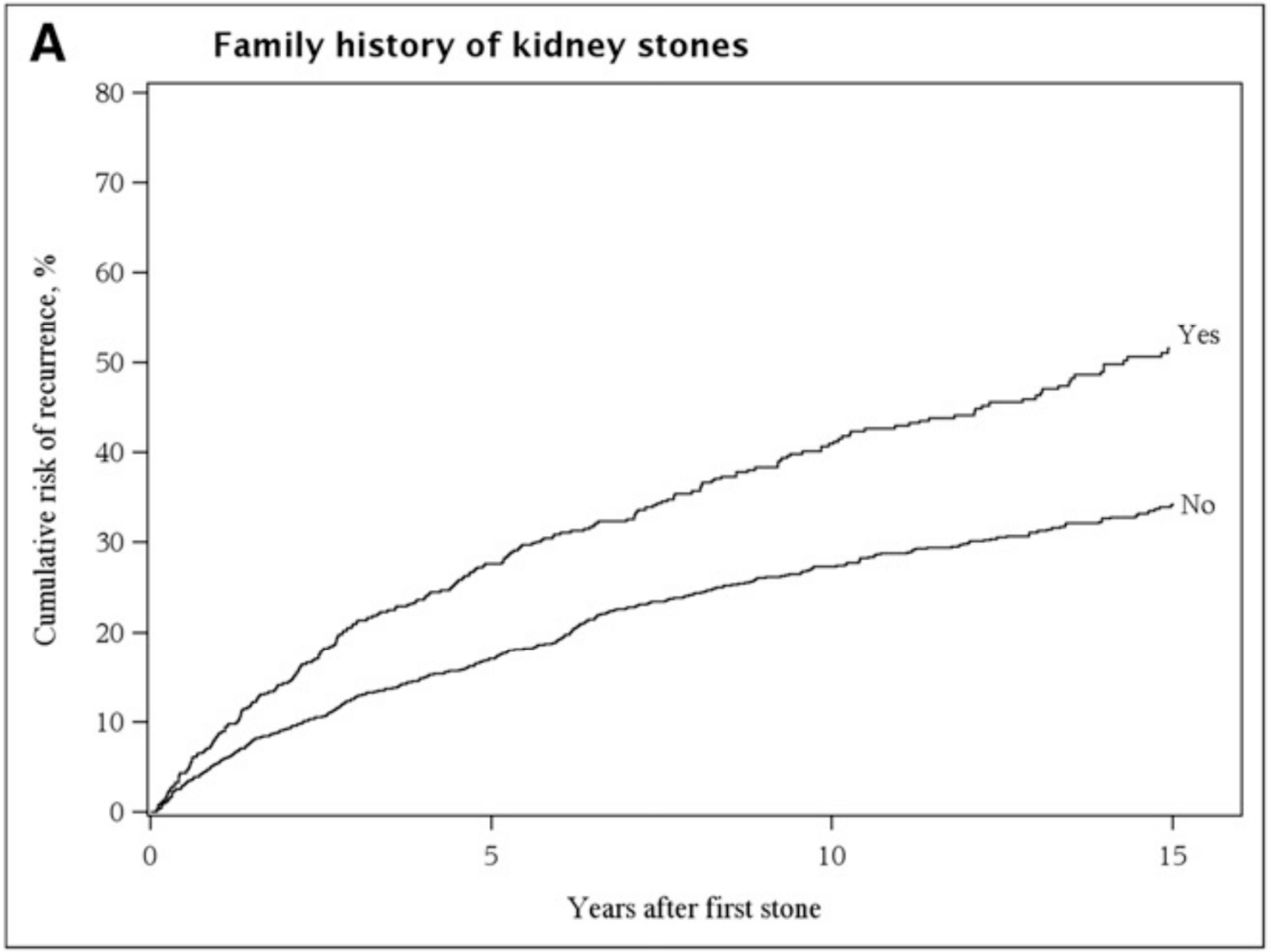
Family History of Stones (26%)



Rule AD et al, JASN, 2014

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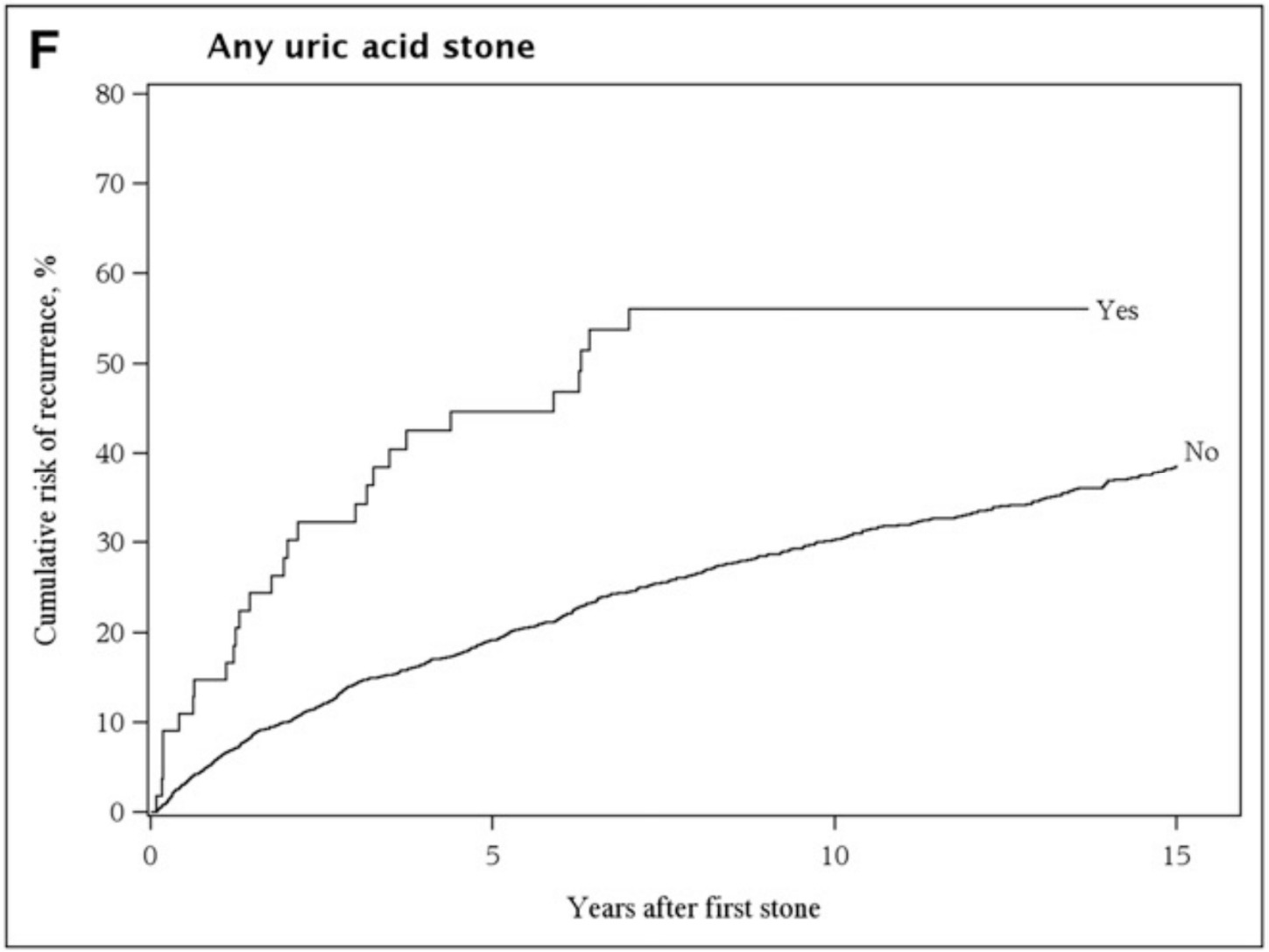
Stone Composition (5% Uric acid)



Rule AD et al, JASN, 2014

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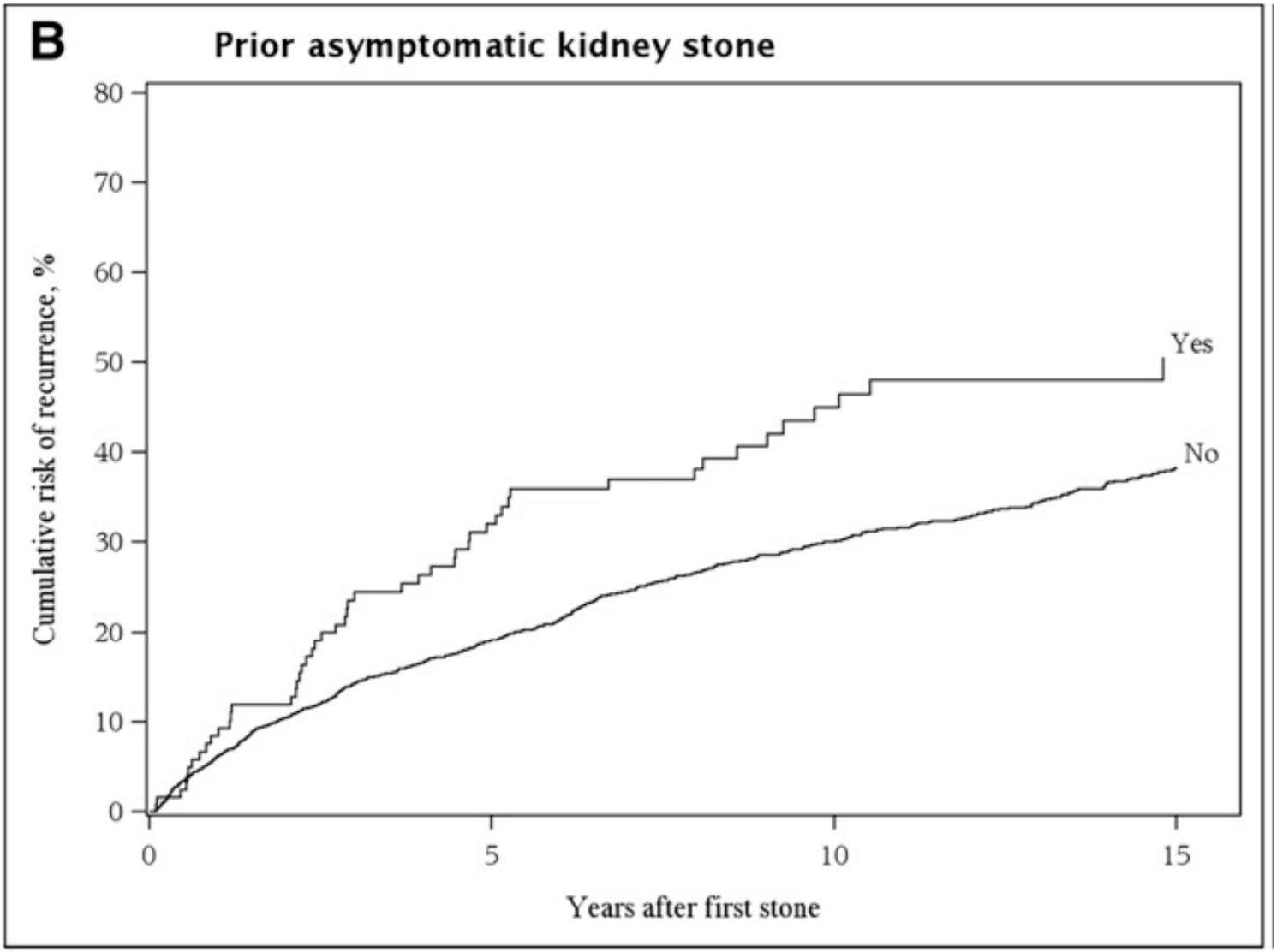
Past incidental asymptomatic stone (6%)



Rule AD et al, JASN, 2014

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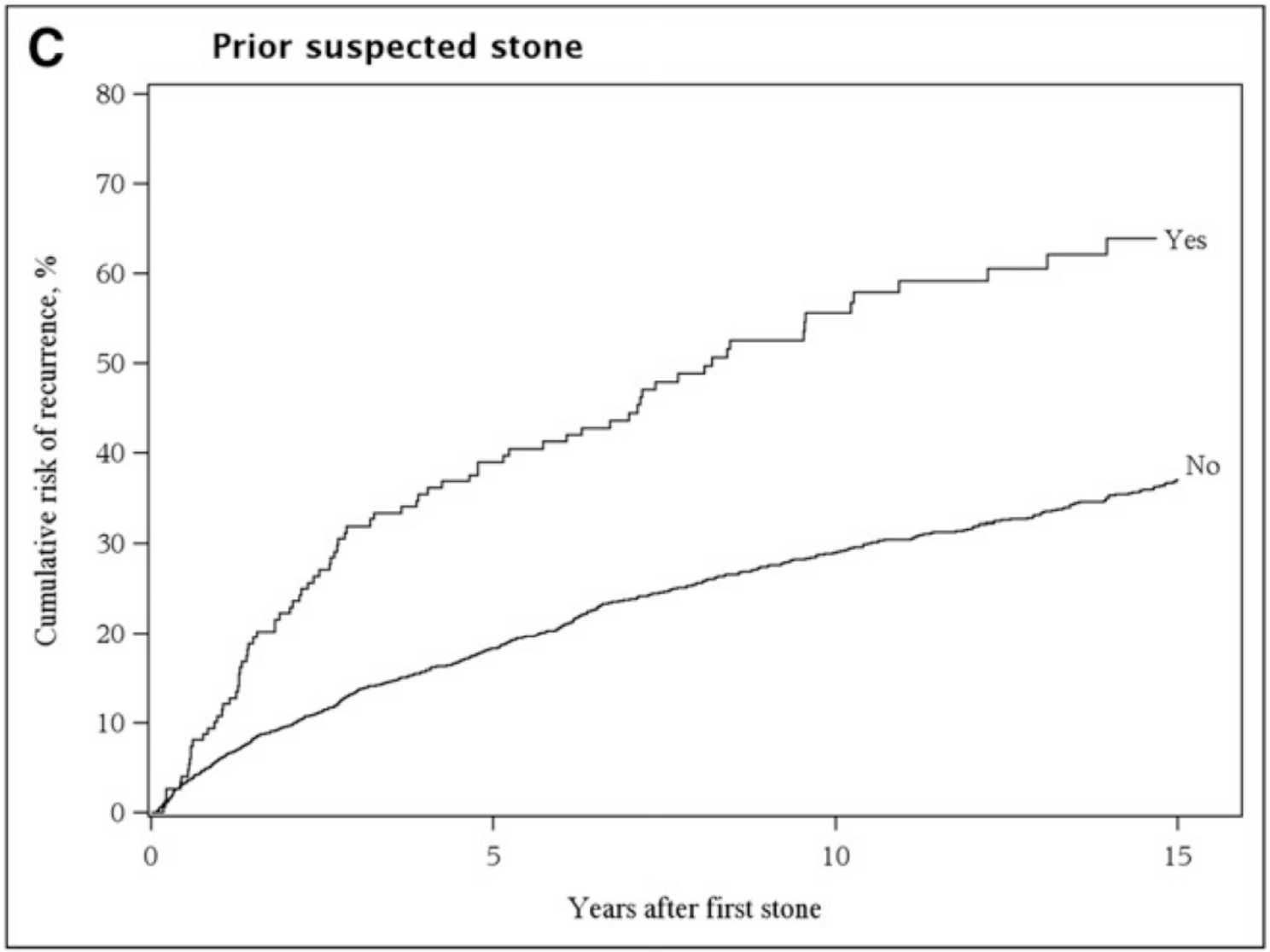
Past "suspected" stone event (7%)



Rule AD et al, JASN, 2014

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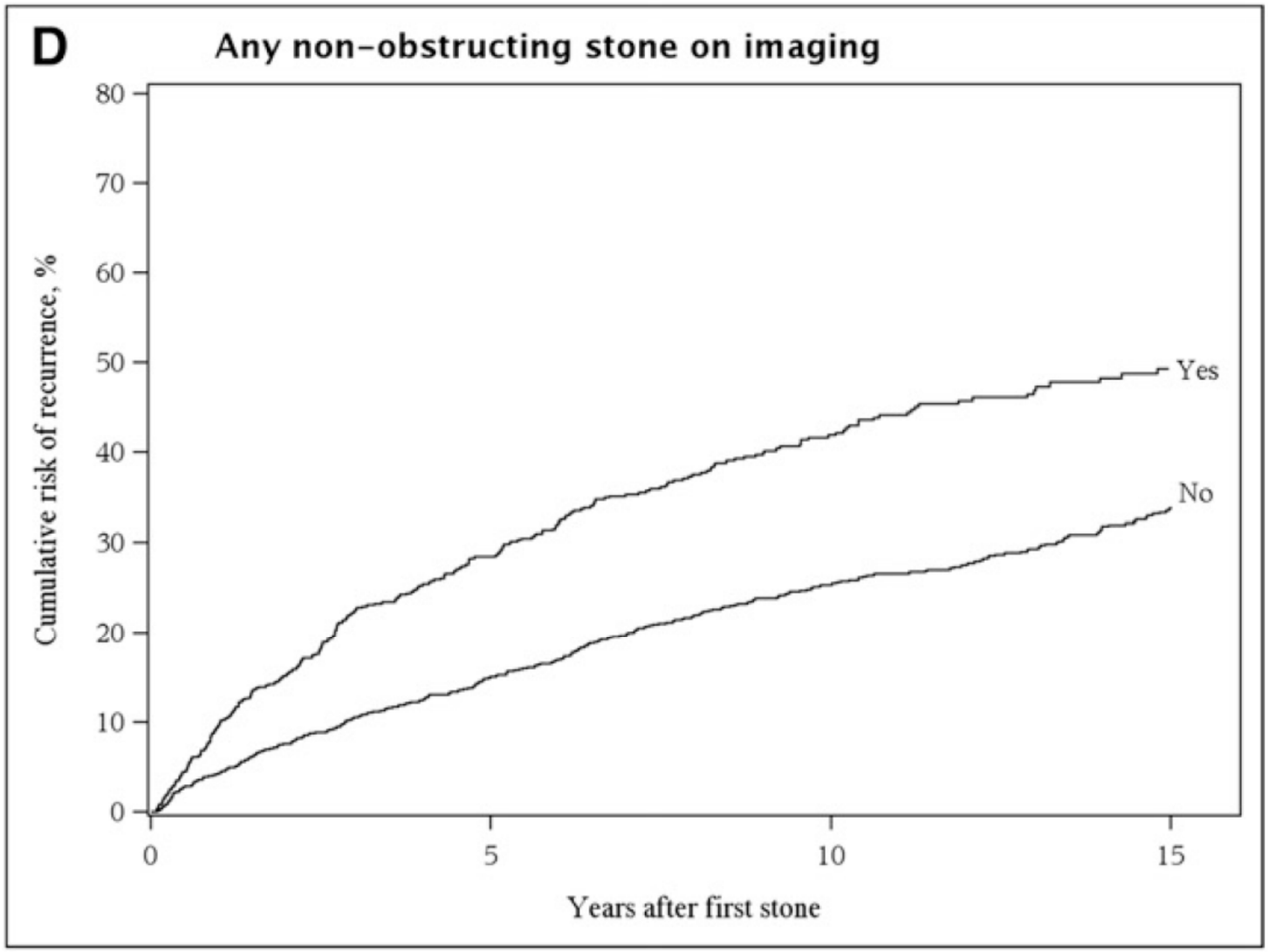
Any radiographic non-obstructing stone (27%)



Rule AD et al, JASN, 2014

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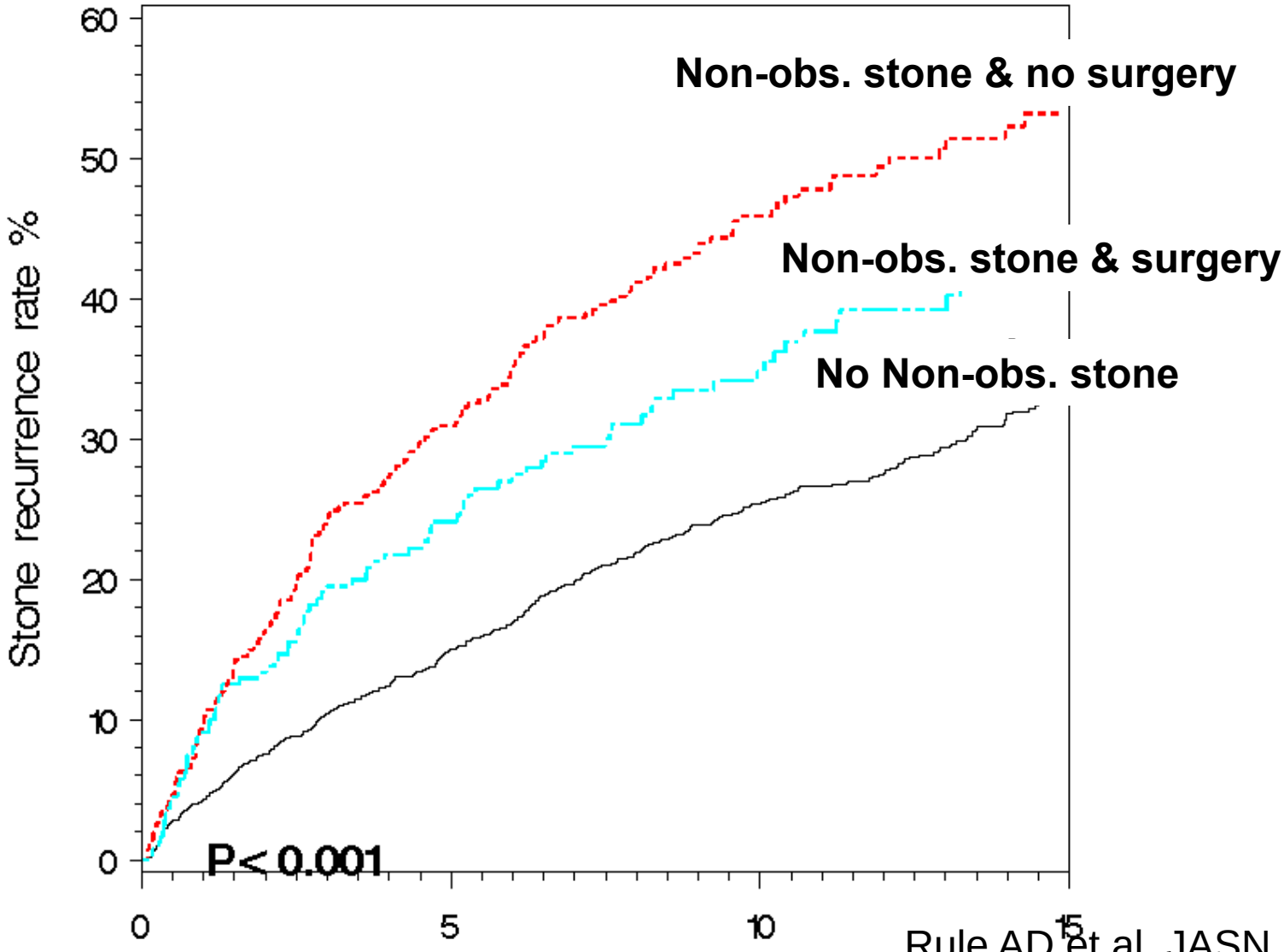
Non-obstructing stone (with or without surgery)



Rule AD et al, JASN, 2014

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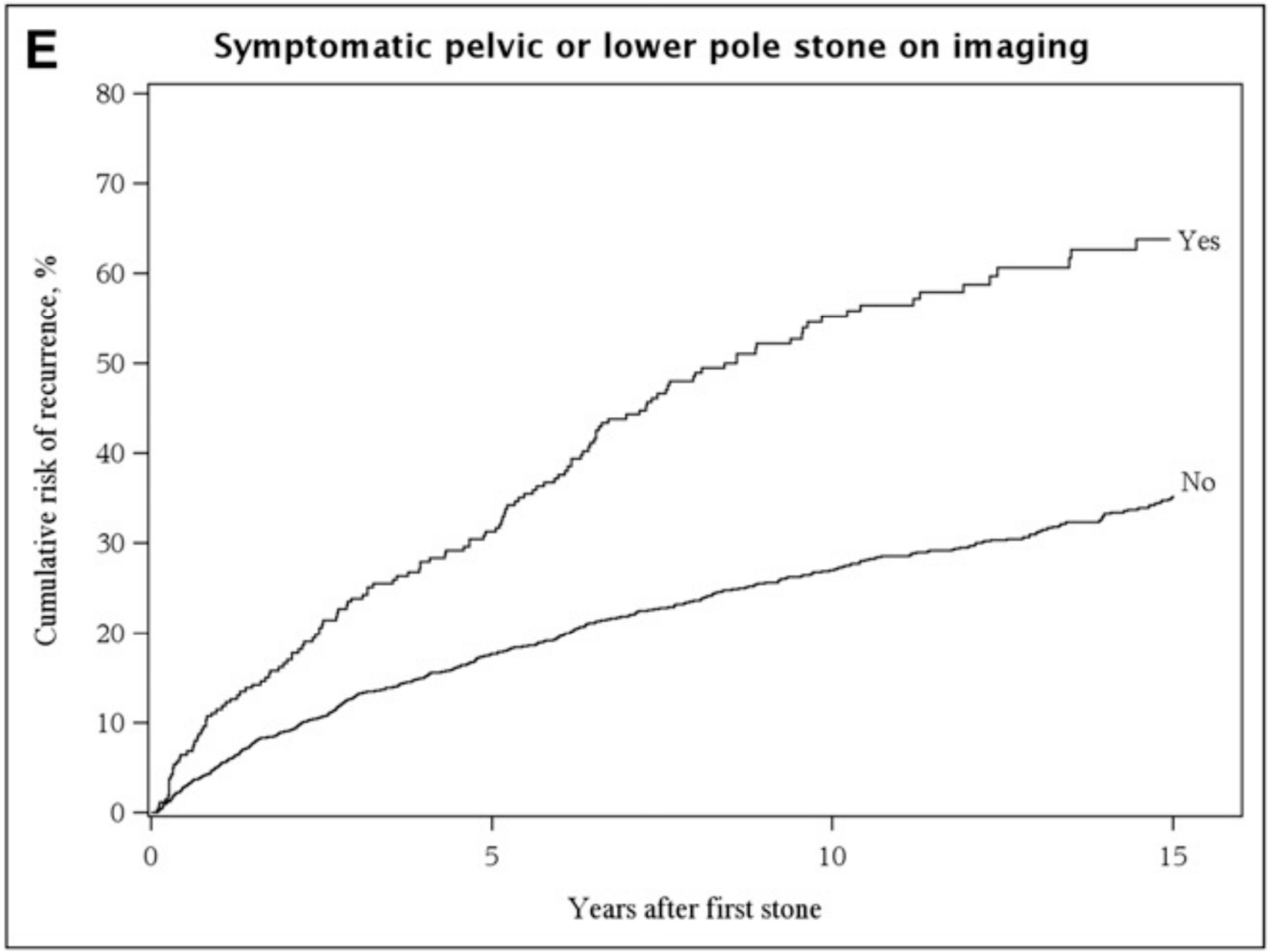
Renal pelvic or lower pole stone (13%)



Rule AD et al, JASN, 2014

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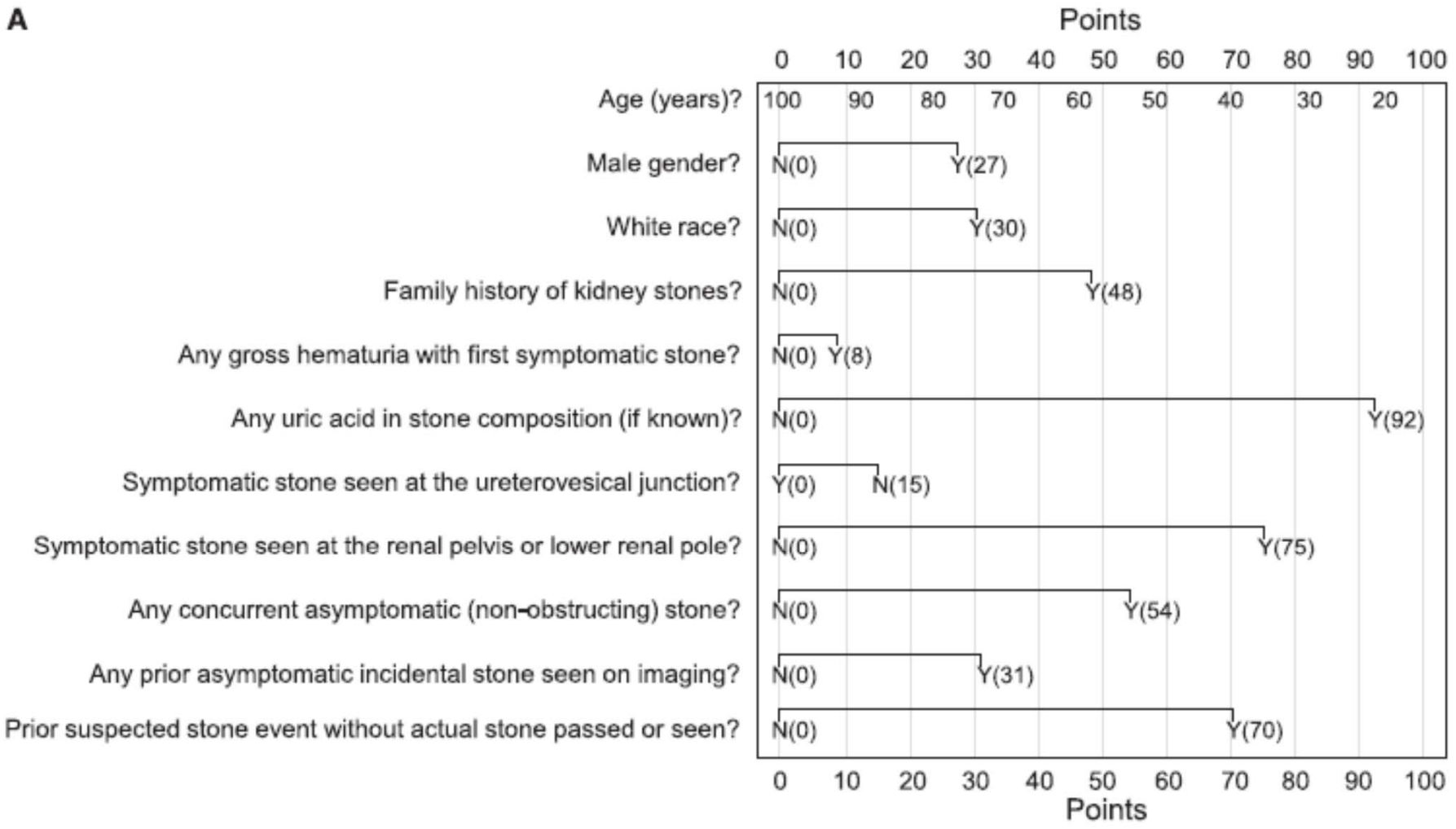
A
Points
0 10 20 30 40 50 60 70 80 90 100
Age (years)? 100 90 80 70 60 50 40 30 20
Male gender? N(0) Y(27)
White race? N(0) Y(30)
Family history of kidney stones? N(0) Y(48)
Any gross hematuria with first symptomatic stone? N(0) Y(8)
Any uric acid in stone composition (if known)? N(0) Y(92)
Symptomatic stone seen at the ureterovesical junction? Y(0) N(15)
Symptomatic stone seen at the renal pelvis or lower renal pole? N(0) Y(75)
Any concurrent asymptomatic (non-obstructing) stone? N(0) Y(54)
Any prior asymptomatic incidental stone seen on imaging? N(0) Y(31)
Prior suspected stone event without actual stone passed or seen? N(0) Y(70)
0 10 20 30 40 50 60 70 80 90 100
Points

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A 30 white F presents with renal colic and gross hematuria from a 10 mm L renal pelvic stone. Stone is uteroscopically removed and is 100% CaOx. A non-obstructing upper-pole 8 mm stone was also removed. Family history of stones, but this is her first stone event. She had similar symptoms 5 years ago, but they resolved on their own and no stone was ever seen.

- **What is her risk of future symptomatic stones?**

Recurrence Of Kidney Stone (2014)

By clicking on the "Submit" button below, you acknowledge that you have read, understand, and agree to be bound by the terms of the QxMD Online Calculator End User Agreement.

Use this calculator to predict the risk of a second symptomatic kidney stone after the first symptomatic stone.

First symptomatic stone?	Yes
Age (yrs)	
Gender	Female
Race	Not Caucasian
Family history of kidney stones?	No
Gross hematuria?	No
Uric acid composition?	No
Imaging performed?	No
Symptomatic ureterovesical junction stone (on imaging)	No
Symptomatic renal pelvic or lower pole stone? (on imaging)	No
Concurrent asymptomatic stone? (on imaging)	No
Prior incidental (asymptomatic) stone?	No
Prior suspect kidney stone event (no stone seen)	No

Submit

Use this calculator to predict the risk of a second symptomatic kidney stone after the first symptomatic stone.

First symptomatic stone?	Yes
Age (yrs)	30
Gender	Female
Race	Caucasian
Family history of kidney stones?	Yes
Gross hematuria?	No
Uric acid composition?	No
Imaging performed?	Yes
Symptomatic ureterovesical junction stone (on imaging)	No
Symptomatic renal pelvic or lower pole stone? (on imaging)	Yes
Concurrent asymptomatic stone? (on imaging)	Yes
Prior incidental (asymptomatic) stone?	No
Prior suspect kidney stone event (no stone seen)	Yes
	Submit

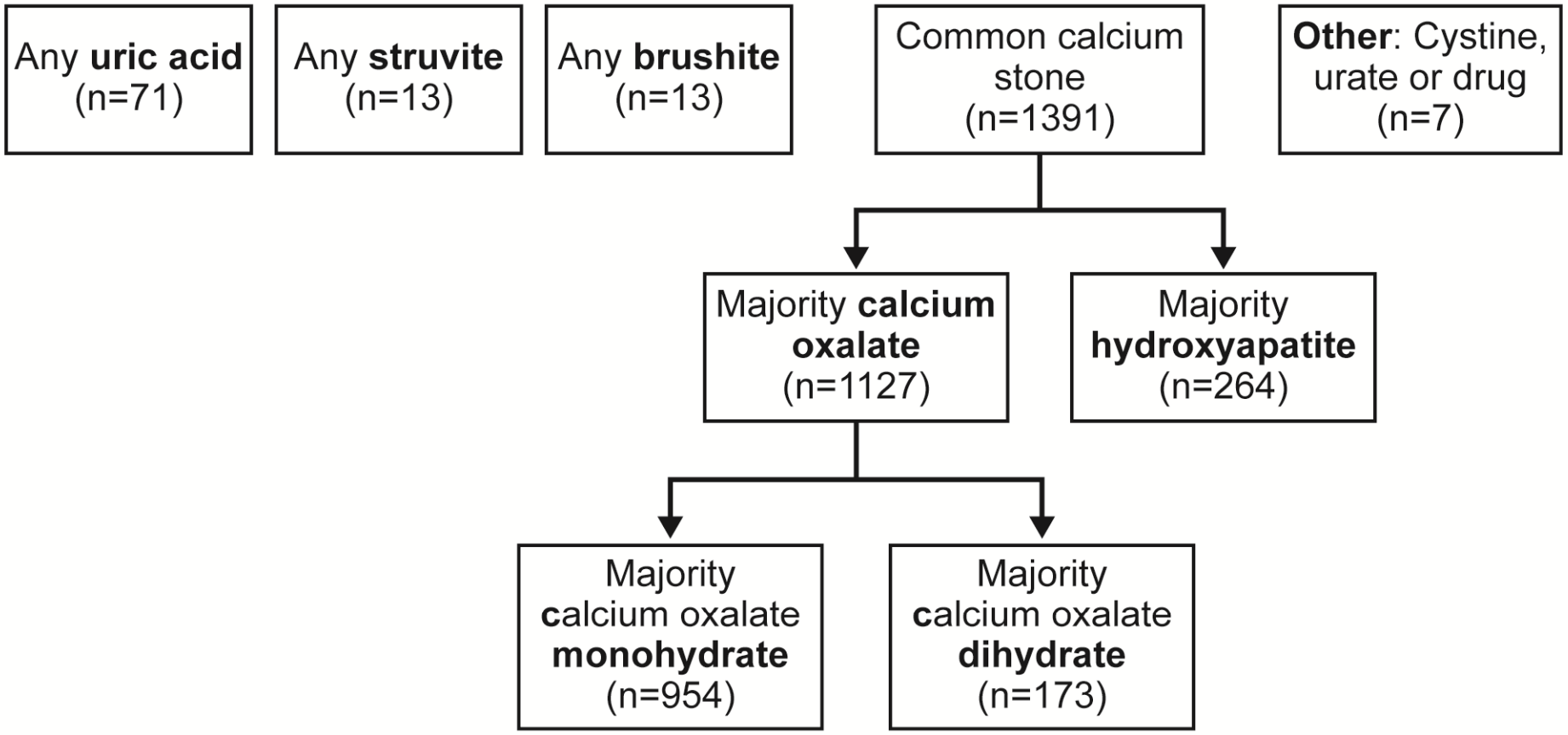
Risk of a second symptomatic kidney stone event at 2 years is 37.6%.

Risk of a second symptomatic kidney stone event at 5 years is 62.6%.

Risk of a second symptomatic kidney stone event at 10 years is 82.2%.

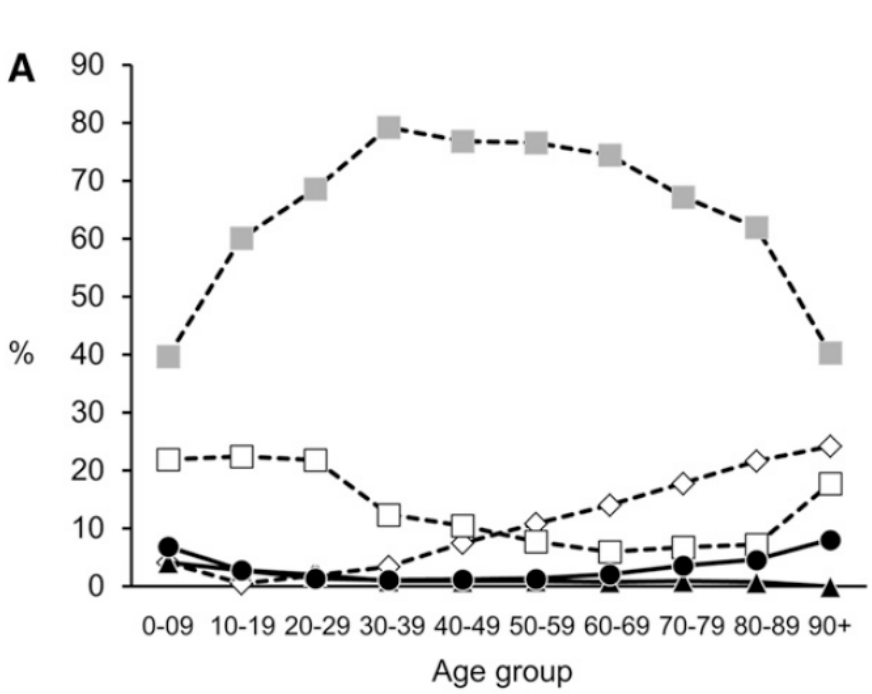
In comparison, the risk in the average first time symptomatic stone former is 11% at 2 years, 20% at 5 years and 31% at 10 years.

Stone Composition Classification

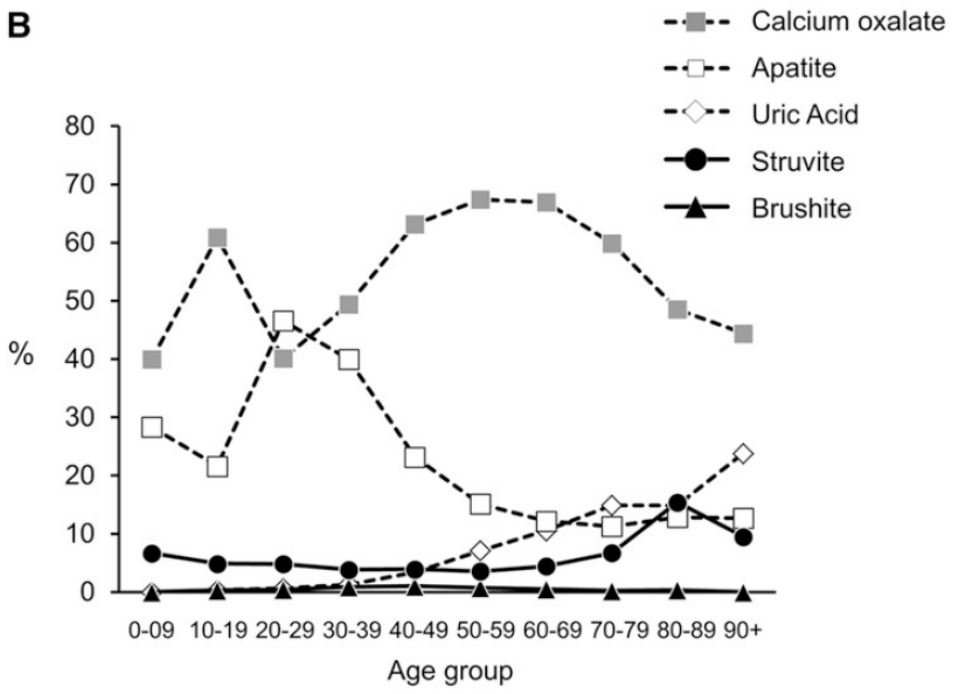


Stone composition – Mayo Clinic Lab

N = 43,545 stones in 2010



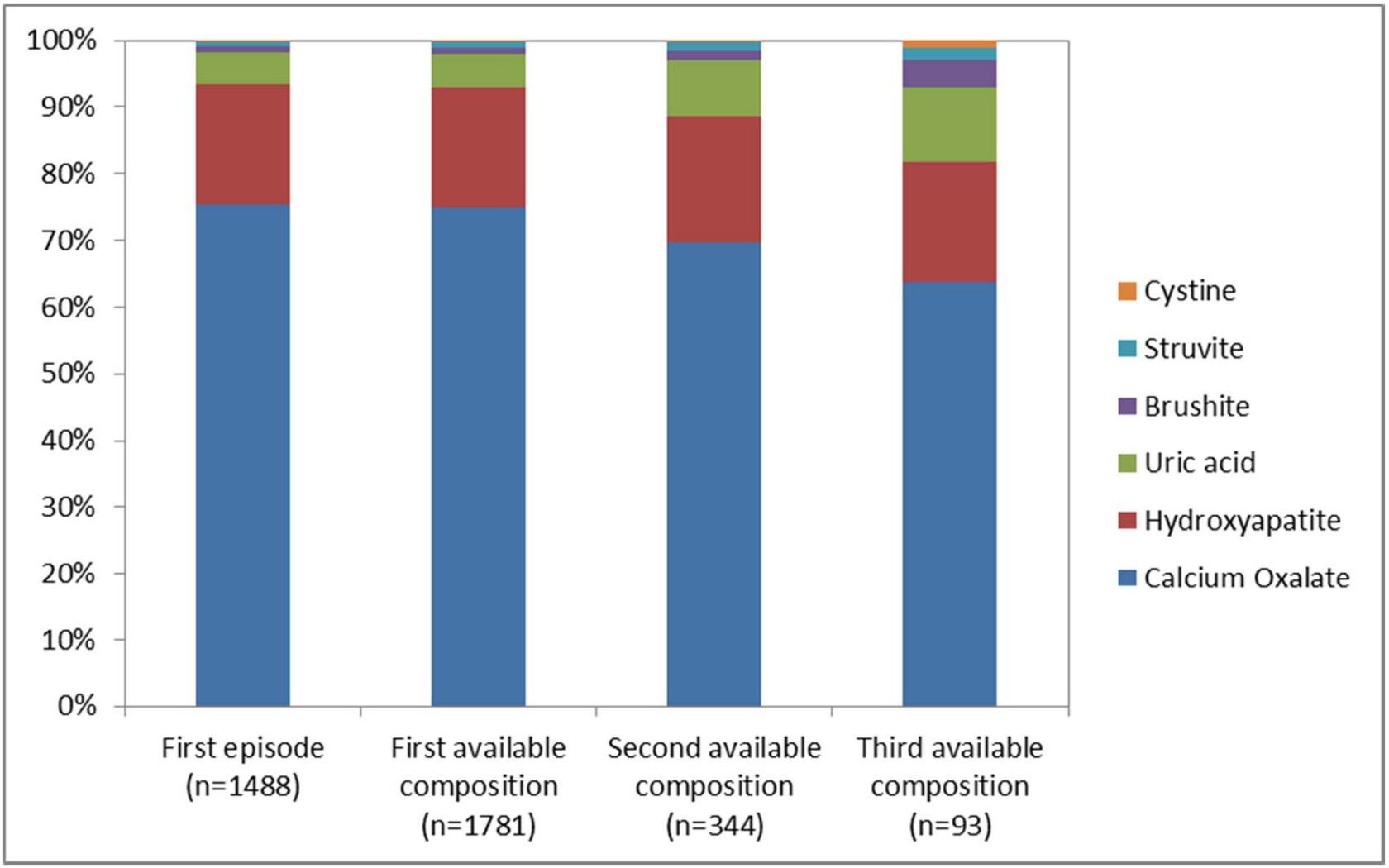
Male



Female

Lieske JC et al, CJASN, 2014

Stone Composition by episode in community



Singh P et al, Mayo Clin Proc, 2015

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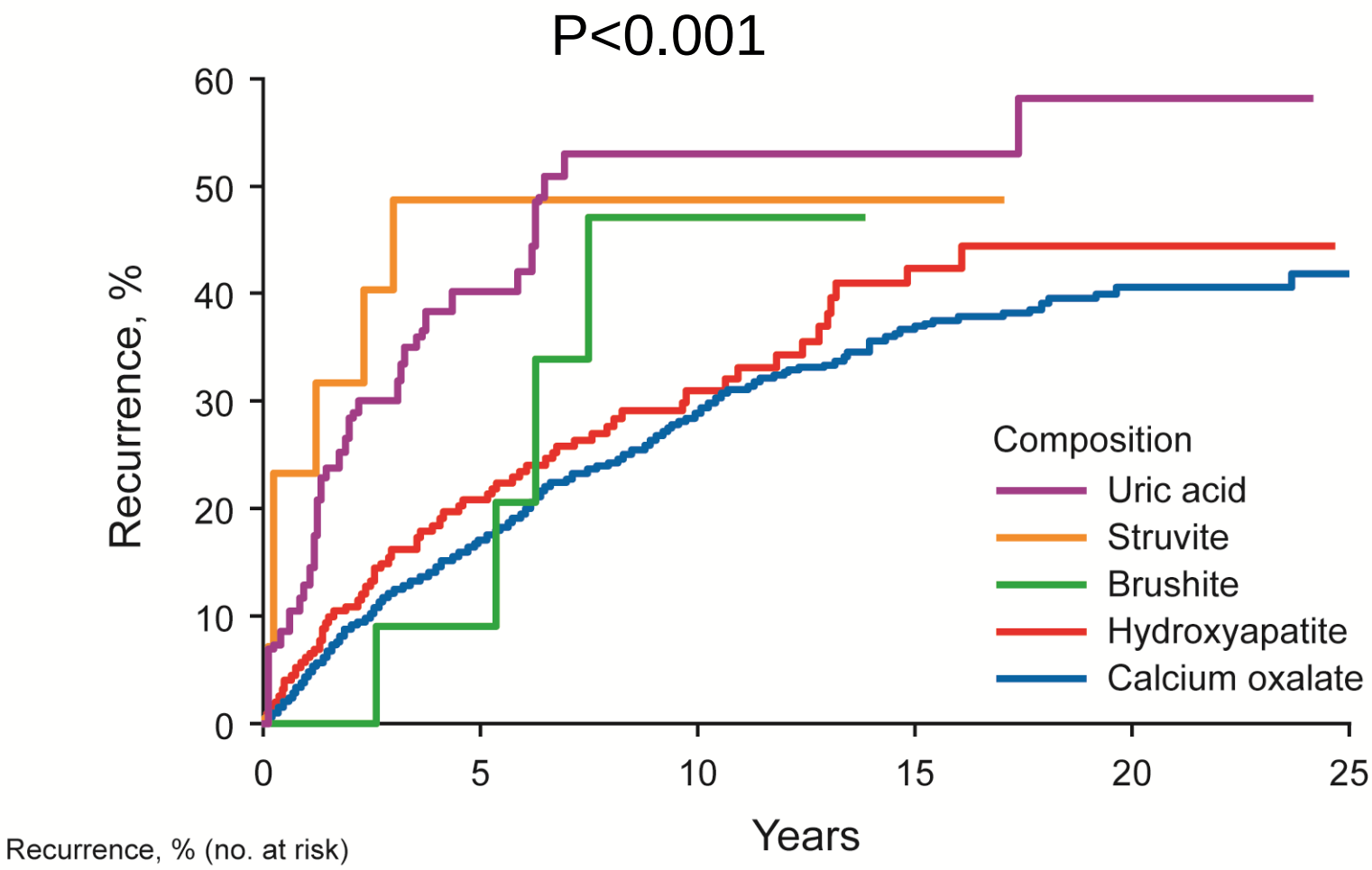
Recurrence by Stone Composition



Recurrence, % (no. at risk)

Singh P et al, Mayo Clin Proc, 2015

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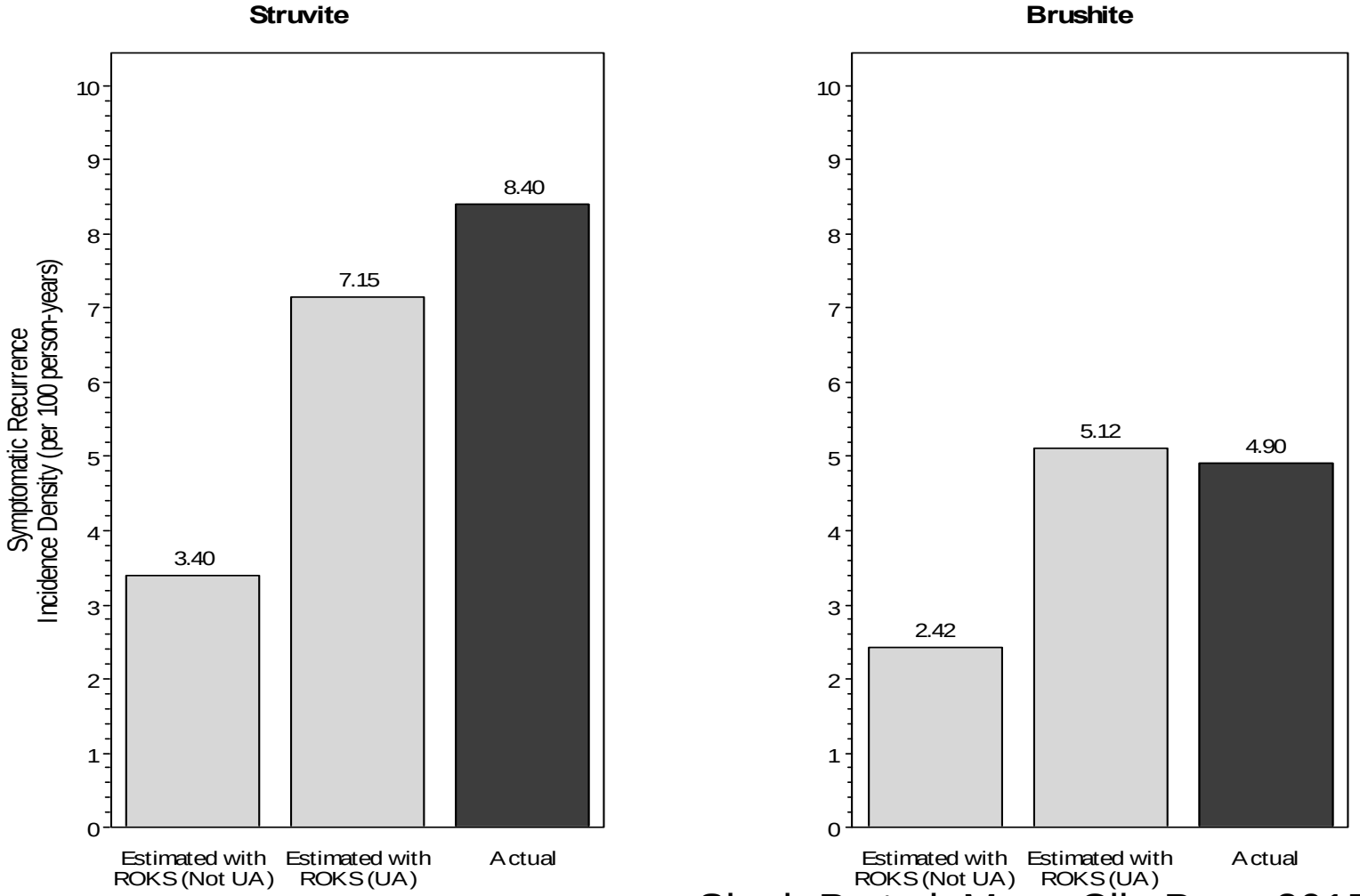
In the ROKS model, Struvite and Brushite stone recur at a high rate (similar to uric acid stones).



Singh P et al, Mayo Clin Proc, 2015

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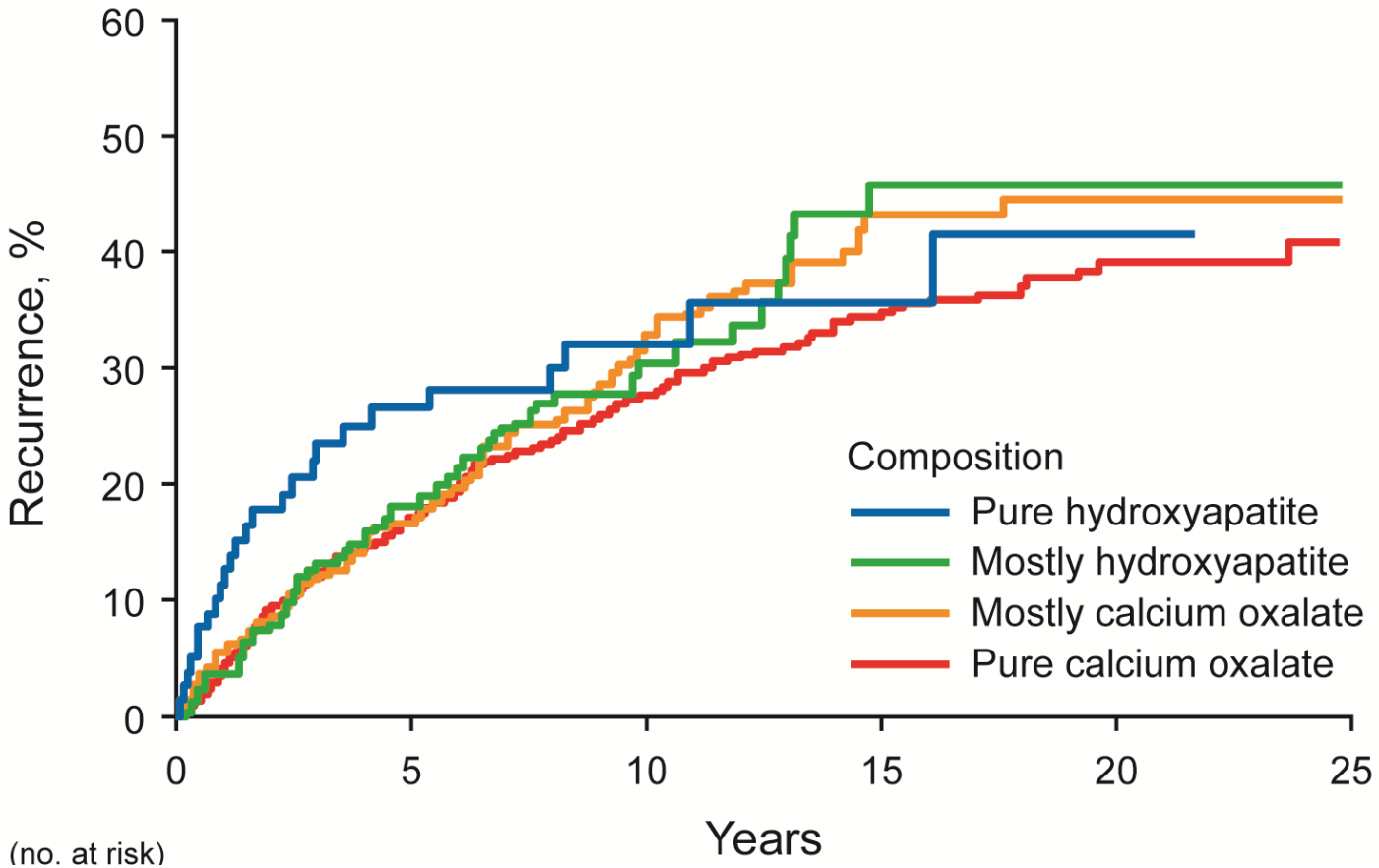
Ratio of CaOx to apatite is not predictive of recurrence

P-trend = 0.10



Recurrence, % (no. at risk)

Singh P et al, Mayo Clin Proc, 2015

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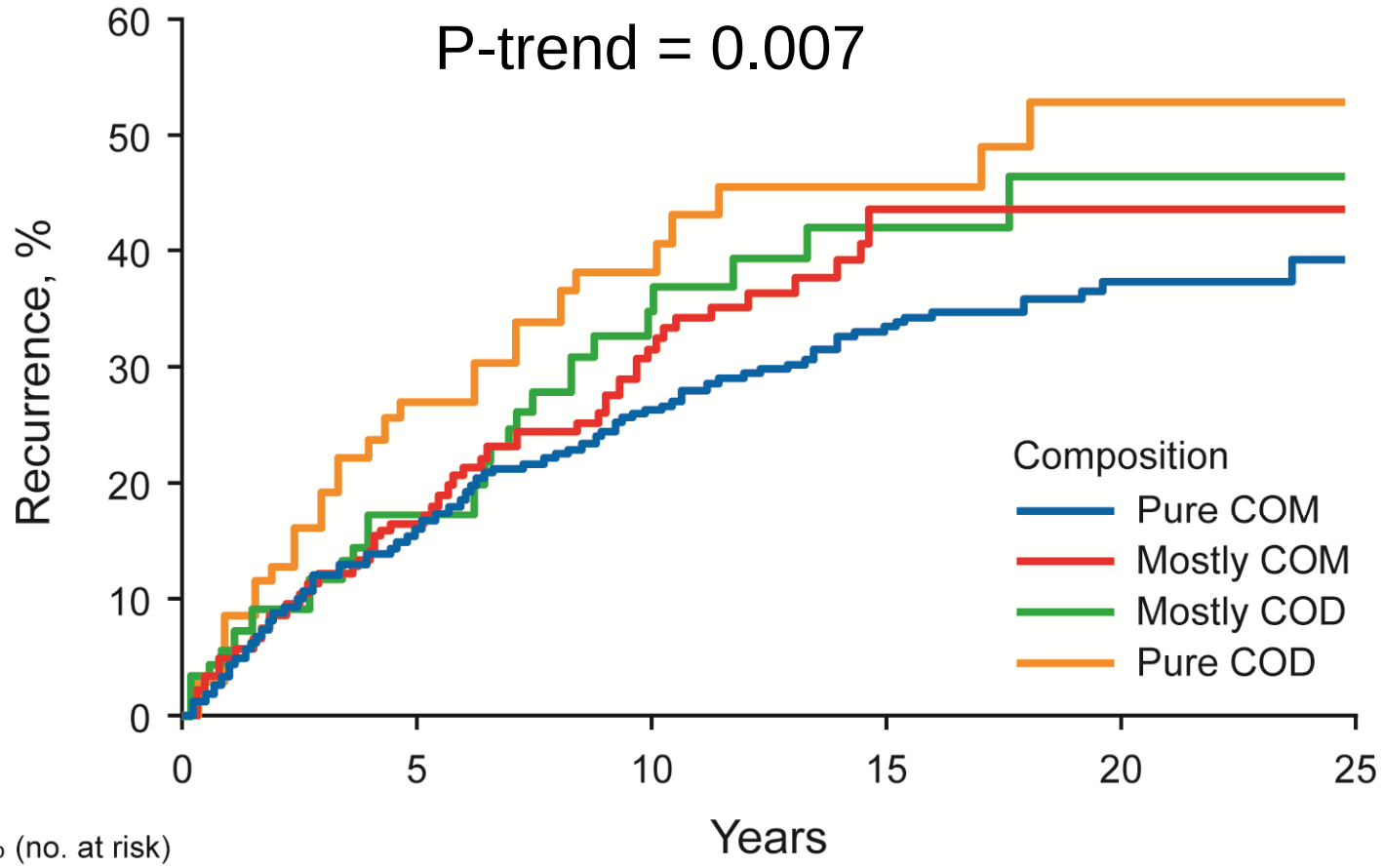
Ratio of COD to COM is predictive of recurrence



Recurrence, % (no. at risk)

Singh P et al, Mayo Clin Proc (In press)

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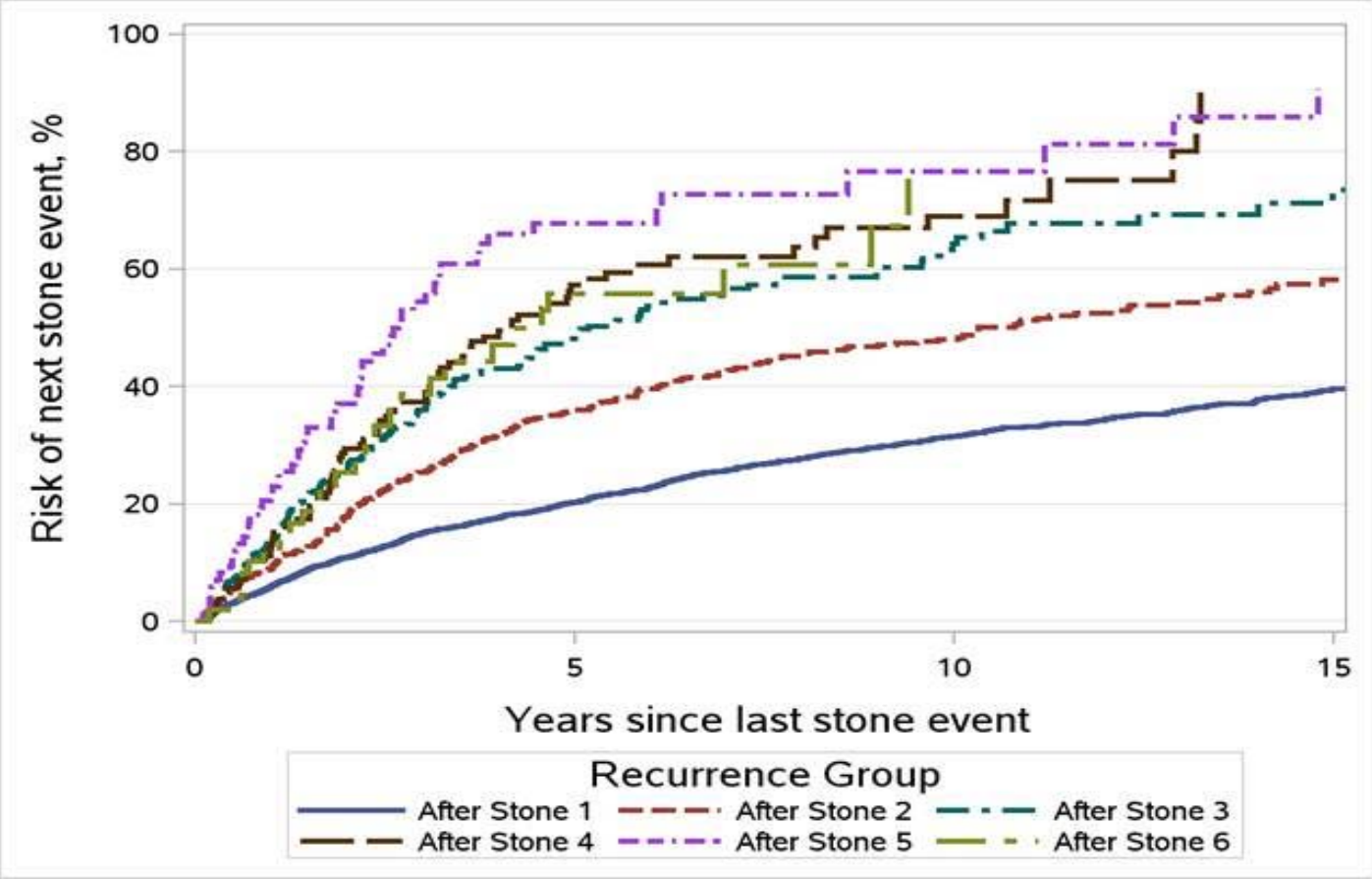
Number of prior episodes predicts higher risk of the next episode, until after about 5 episodes.



Patients learn to manage their stone episodes without clinical care.

CT scan as a surrogate for stone events

- **75 new symptomatic stone formers have a 5-year follow-up visit (while asymptomatic).**
  - CT scan (compared to baseline CT scan)

- **Left kidney CT Scan findings**
  - 43% have at least one non-obstructing stone at follow-up
  - 26% have a stone that is new or larger at follow-up

- **Right kidney CT Scan findings**
  - 43% have at least one non-obstructing stone at follow-up
  - 28% have a stone that is new or larger at follow-up

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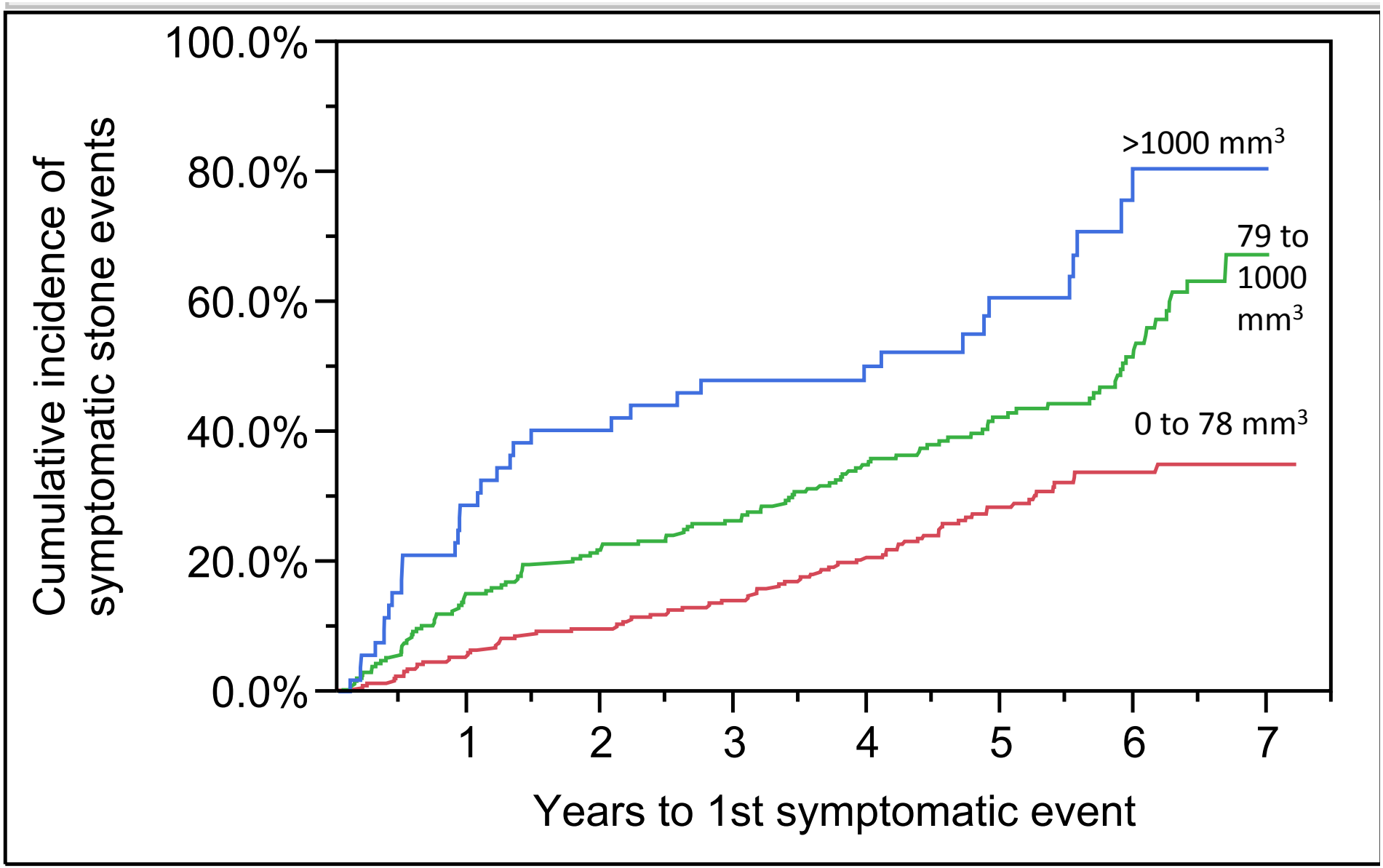
How should we characterize radiographic stone burden to predict risk of symptomatic recurrence?

- Largest stone diameter?
- Number of stones?
- Total volume occupied by all stones?

- 550 stone clinic patients with baseline CT scans (while asymptomatic).
- No kidney stone surgery
- 230 (42%) had as symptomatic stone event a median 5 years later.

Selby MG et al, Urology, 2014

Total stone volume as a predictor of symptomatic events



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CT Stone burden Characteristic	Hazard Ratio (95% CI)	P-value
Method of assessing CT stone burden (unadjusted)		
Total stone volume per quartile	1.40 (1.24 to 1.58)	**<0.001**
Number of stones per quartile	1.31 (1.17 to 1.46)	**<0.001**
Largest stone diameter per quartile	1.27 (1.13 to 1.42)	**<0.001**
Bilateral stone	1.81 (1.39 to 2.35)	**<0.001**
Total stone volume (per quartile)		
Unadjusted	1.40 (1.24 to 1.58)	**<0.001**
Adjusted for number of stones quartile, largest stone diameter quartile, and bilateral stones	1.35 (1.06 to 1.70)	**0.01**

Total stone volume was the only independent radiographic predictor of symptomatic stone events.

Selby MG et al, Urology, 2014

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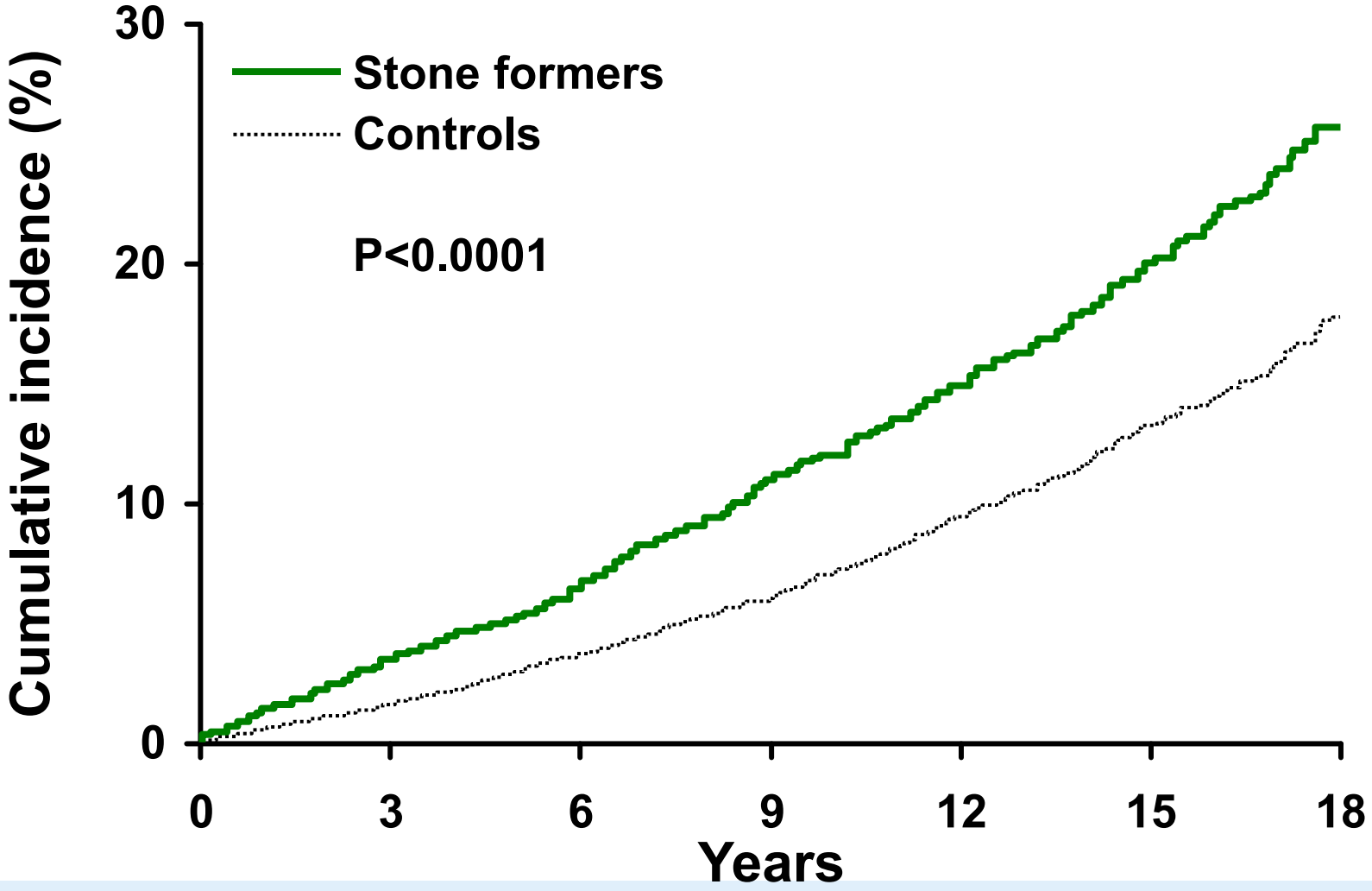
Stone outcomes besides symptomatic recurrence

- Chronic kidney disease
  - Established in rare forms of stone disease
  - Less clear in the “occasional” stone former
- Cardiovascular disease?

Risk of CKD (clinical diagnosis-ICD9)



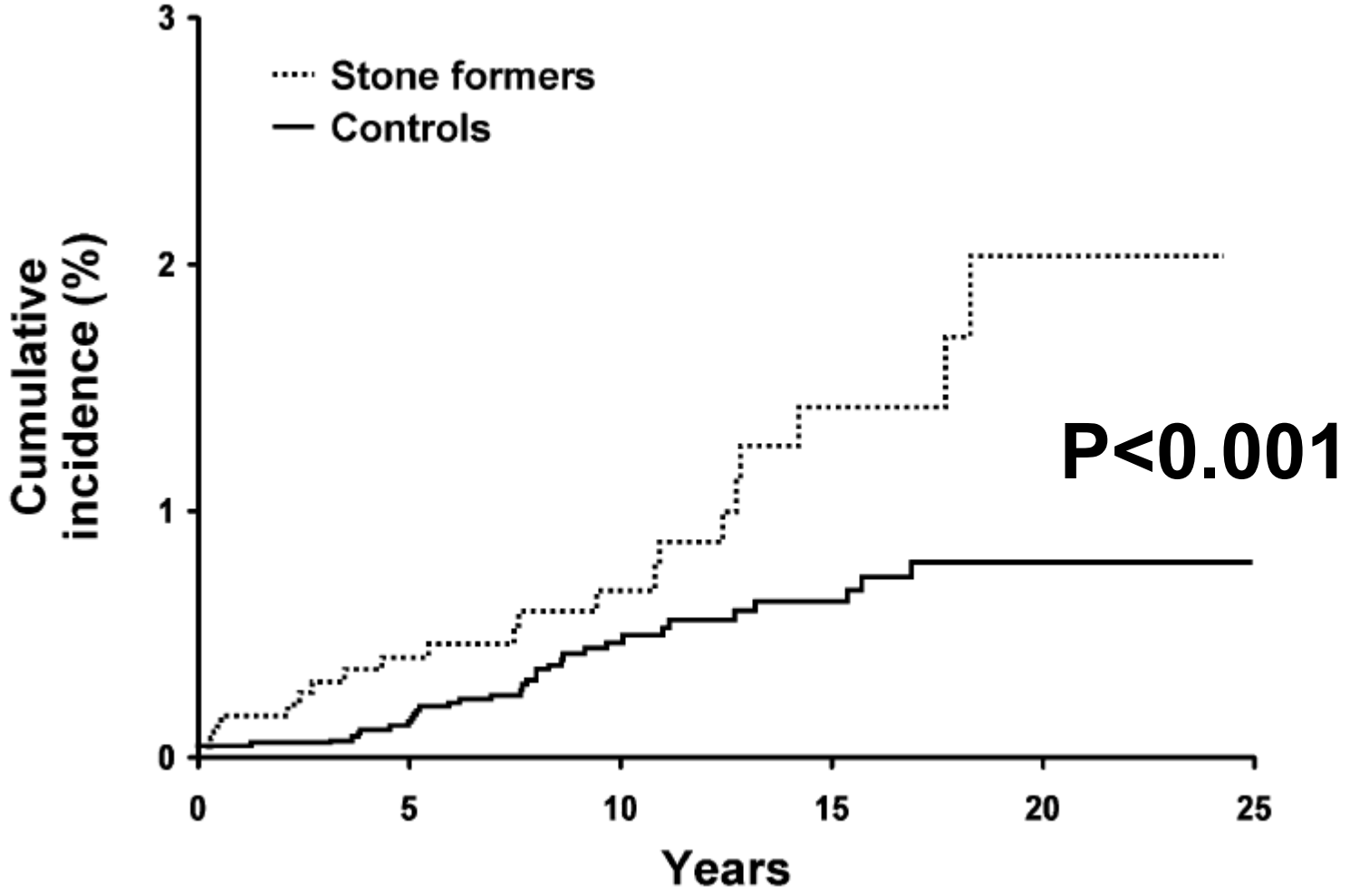
Rule AD et al, CJASN, 2009

Risk of CKD with kidney stones independent of co-morbidities

CKD Definition	Unadjusted HR (95%CI)	Co-morbidity Adjusted HR (95%CI)
Clinical CKD by Diagnostic code	1.67 (1.48, 1.88)	1.56 (1.39, 1.77)
Sustained elevated SCr (censor at last clinic visit)	1.46 (1.22, 1.74)	1.36 (1.13, 1.62)
Sustained elevated SCr (censor at last SCr level)	1.26 (1.05, 1.51)	1.25 (1.04, 1.49)

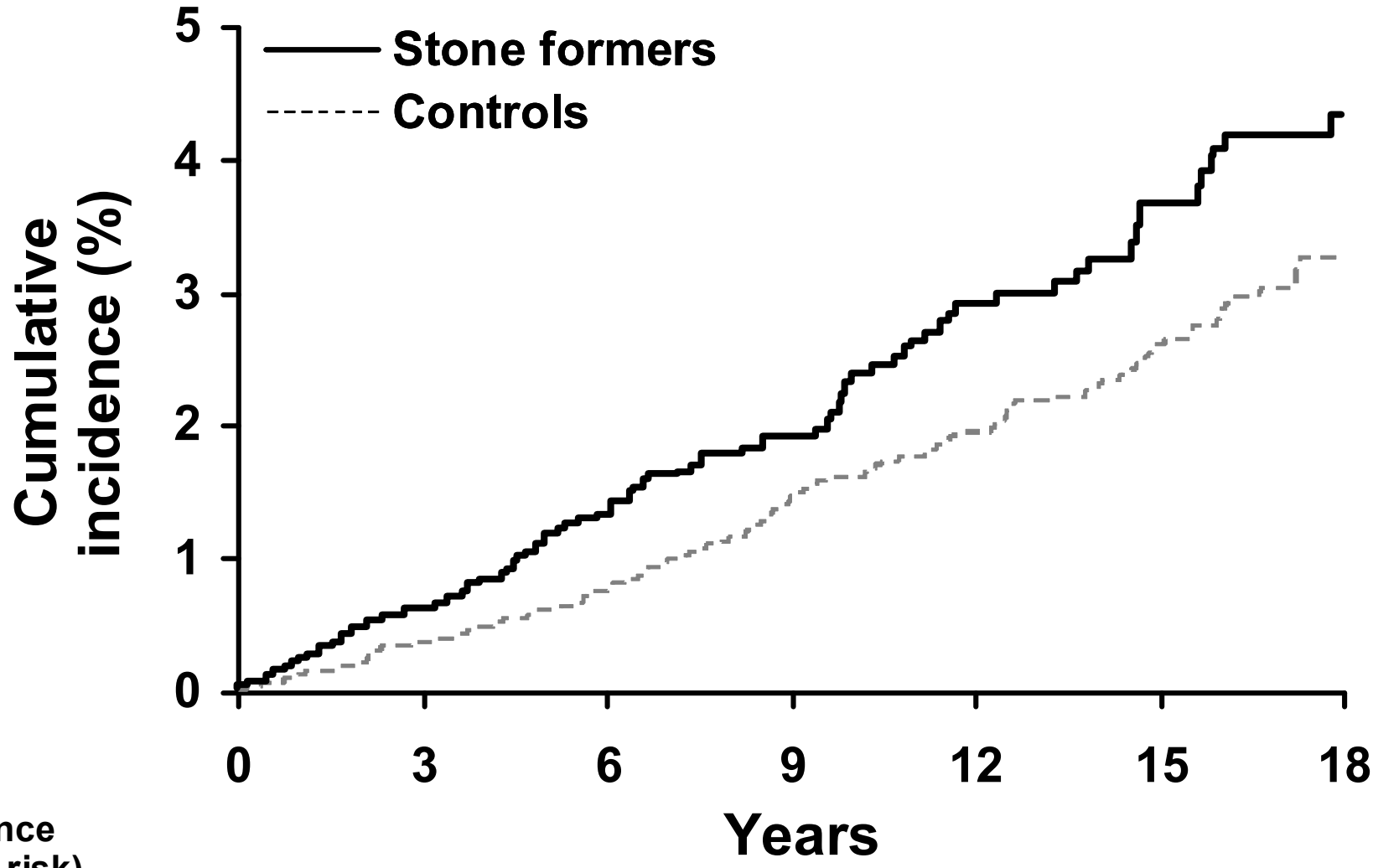
Rule AD et al, CJASN, 2009

Risk of ESRD in symptomatic stone formers



El-Zoghby ZM et al, CJASN, 2012

Risk of myocardial infarction in stone formers?



Incidence (no. at risk)				
Controls	0 (10,860)	0.8 (6,689)	2 (3,184)	4.2 (1,010)
Stone formers	0 (4,564)	1.3 (2,686)	3 (1,276)	5.2 (404)

Rule AD et al, *JASN*, 2010

Findings from Project 3

- Kidney stone symptomatic recurrence occurs in 30% by 10 years.
  - Clinical and laboratory characteristics can be used to predict those at highest risk for recurrence (ROKS)
- Stone composition informs risk of recurrence:
  - High risk: cystine, uric acid, brushite, struvite
  - Moderate risk: COD
  - Low risk: COM, hydroxyapatite
- Total stone volume is more informative of recurrence risk than # stones or largest stone diameter.
- Stone formers at increased risk for CKD/ESRD and MI.

Mayo Clinic Urology O'Brien Center – Project 3 Team

Co-Investigators

- John Lieske (Neph)
- Amy Krambeck (Urology)
- Felicity Enders (Stats)
- Lisa Vaughan (Stats)
- Terri Vrtiska (Radiology)
- Cynthia McCollough (Radiology)
- Bill Haley (Neph – Jacksonville)

Core Study Personnel

- Cynthia Nosek (Nurse Abstractor)
- Ruth Kraft (Study Coordinator)
- Samuel Edeh (Lab Tech)
- Zejfa Haskic (Lab Tech)
- Ramila Mehta (Stat Programmer)

Research Fellow

- Jay Wonngarm (Neph)

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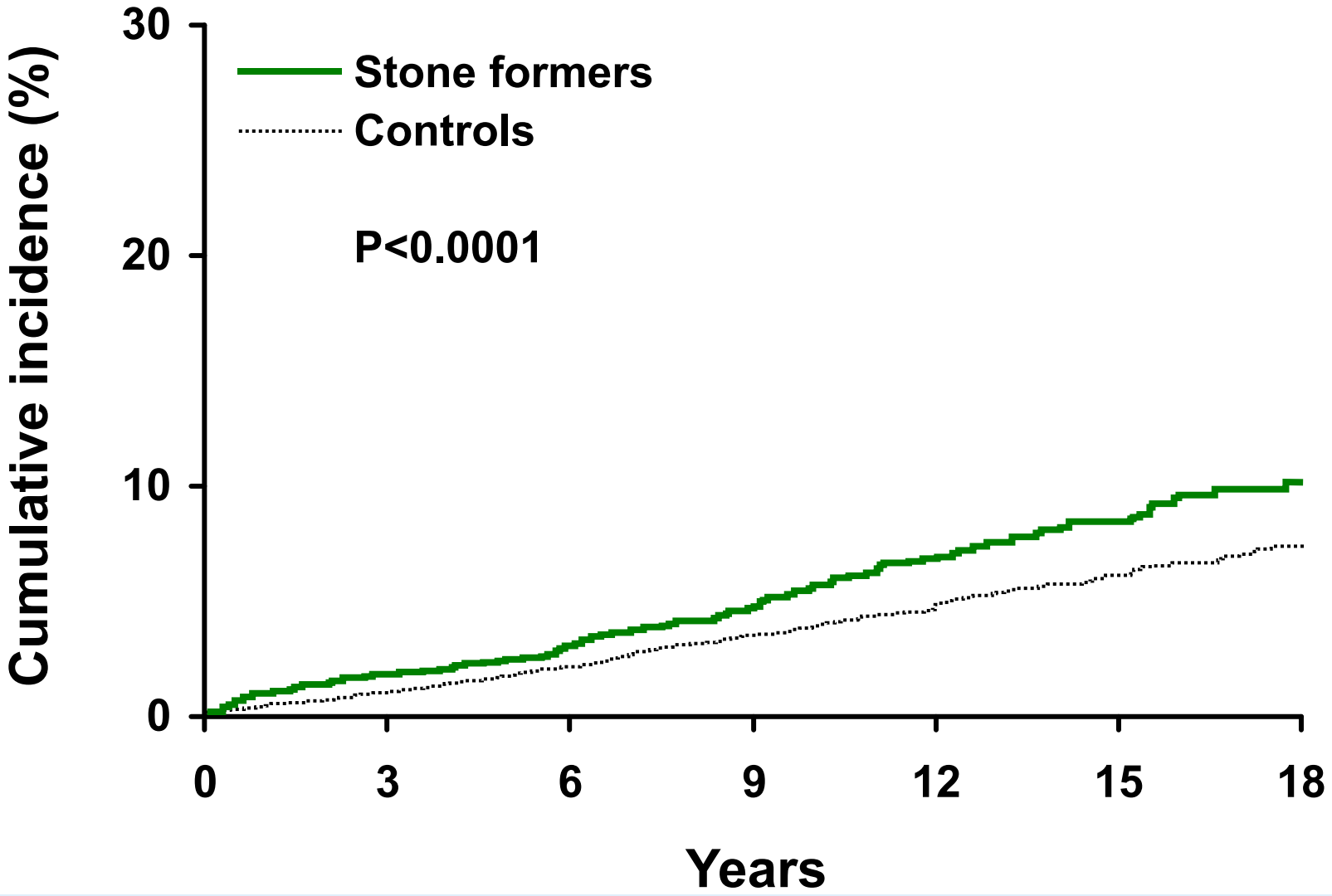
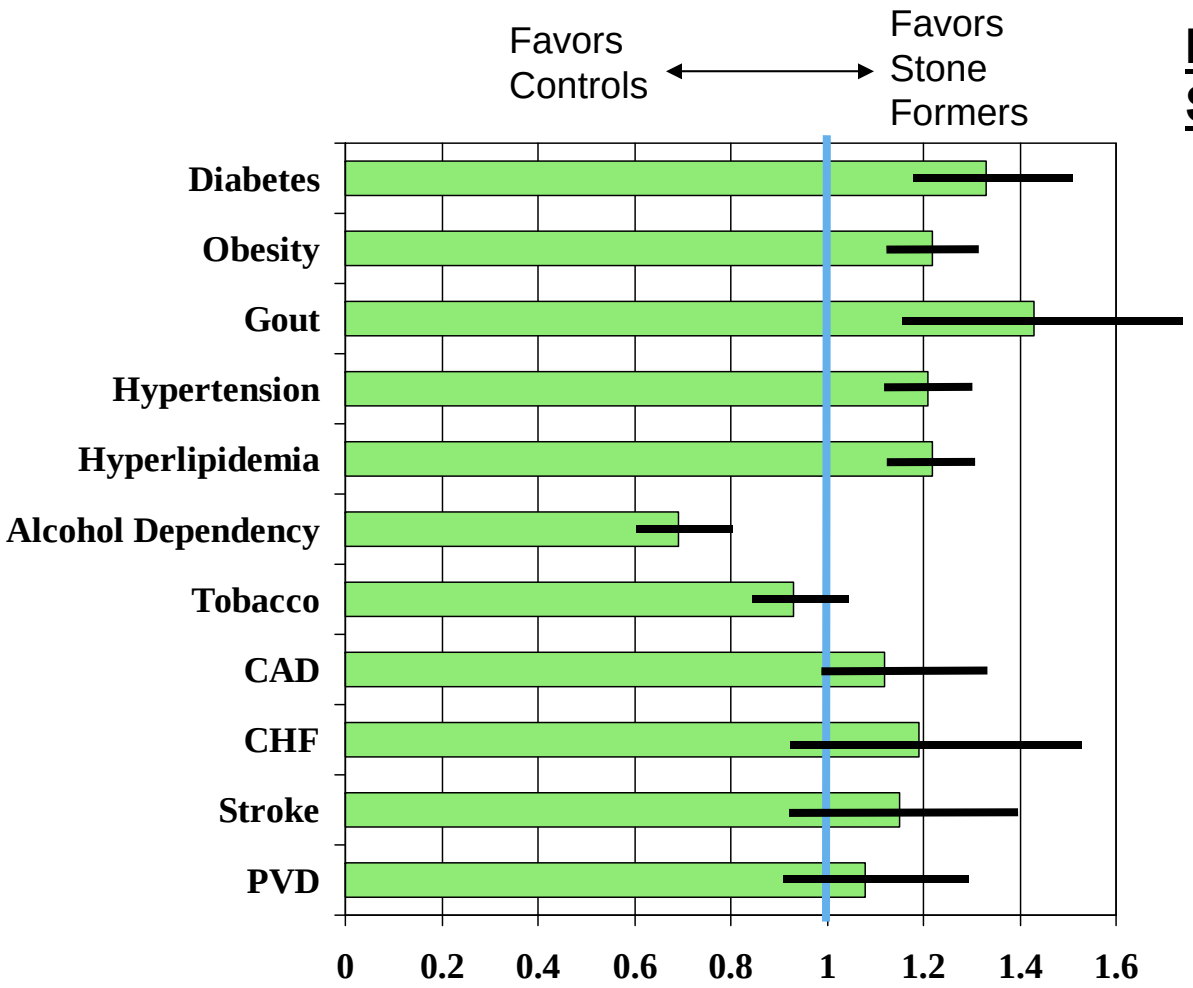
Risk of sustained ↑SCr (>1.3 M, >1.1 F)



Rule AD et al, CJASN, 2009

Prevalent Co-morbidities



	Incident Stone Formers	Controls
Diabetes	10%	7%
Obesity	24%	21%
Gout	3.4%	2.4%
Hypertension	20%	17%
Hyperlipidemia	21%	18%
Alcohol Dependency	5.5%	7.8%
Tobacco	15%	16%
CAD	7.4%	6.7%
CHF	2.3%	1.9%
Stroke	3.1%	2.8%
PVD	4.6%	4.3%

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Rule AD et al, CJASN, 2009

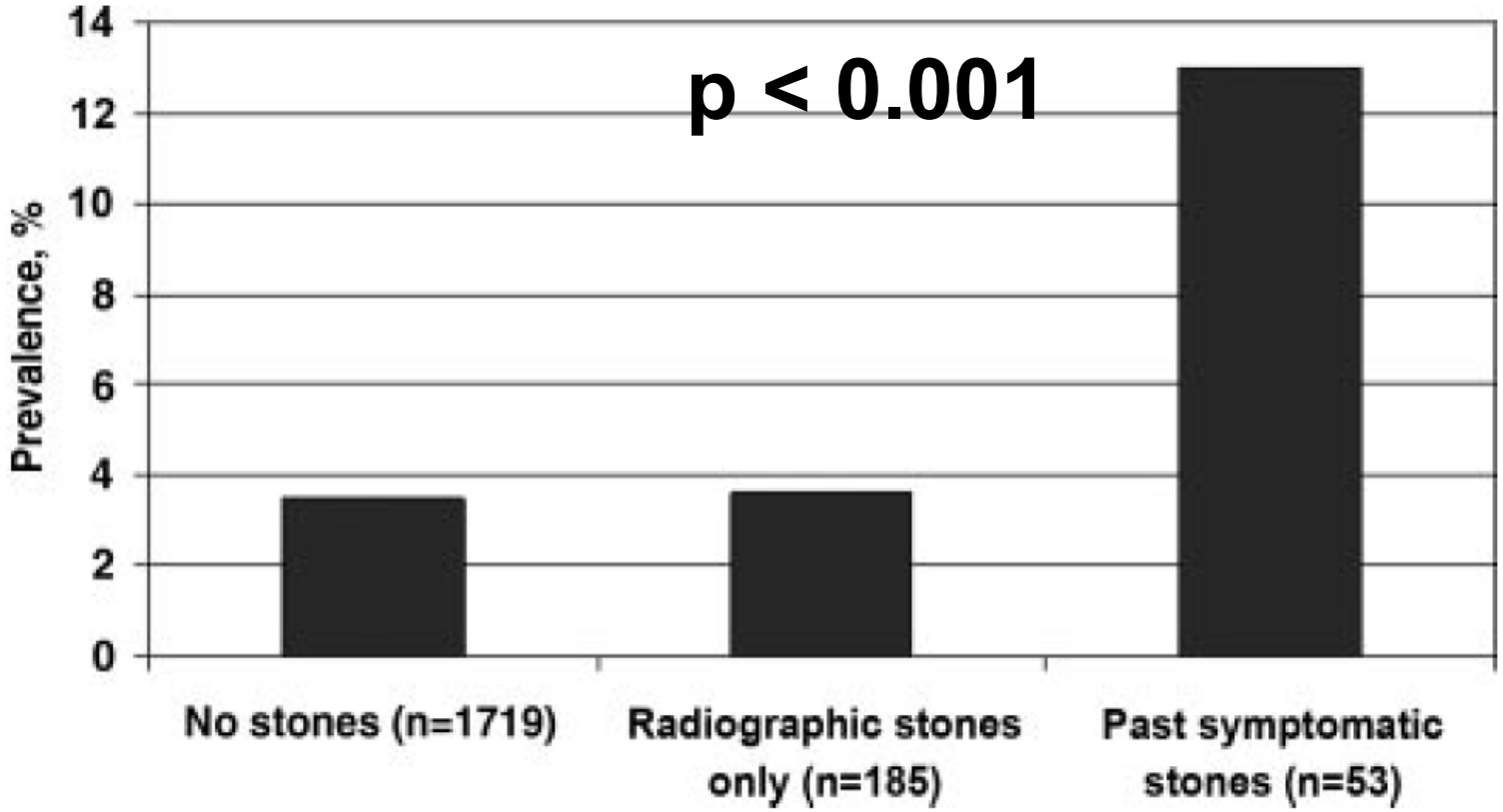
CKD predictors among stone formers in Olmsted County, Minnesota.

Table 3. Predictors of CKD in a Multivariable Model

Predictor	Odds Ratio (95% confidence interval)	*P*
Hypertension	1.53 (0.46-5.57)	0.6
Diabetes	3.49 (1.13-12.92)	0.03
Body mass index > 30 kg/m^2	0.93 (0.31-2.69)	0.9
Ileal conduit	1.49 (0.91-∞)	0.8
≥6 Urinary tract infections (vs < 6)	4.83 (1.00-34.90)	0.05
Struvite stone type (vs all others)	4.52 (0.45-∞)	0.2
Allopurinol	7.86 (1.79-52.95)	0.003

Saucier NA et al, AJKD, 2009

Albuminuria in potential kidney donors



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Lorenz EC et al, *Neph Dial Transpl*, 2011

Potential pathways…

Stones causal:

Obstructive uropathy
(AKI leads to CKD, not always symptomatic)
Duct of Bellini crystal plugs
Parenchymal injury from stone surgery

Other factors causal:

Urinary tract infections
Chronic diarrhea
Hypercalcuria
(nephrocalcinosis)
Uric acid nephropathy
Ureteral reflux
(ileal conduits, neurogenic bladder)

Do stone formers develop CKD after their 1st stone event (V1 mean 75 days & V2 mean 180 days after)

Characteristic	Stone Formers (n=390)	Controls (n=458)	P-value*
V1 Serum creatinine, mg/dl	0.87	0.84	0.13
V2 Serum creatinine, mg/dl	0.85	0.81	0.09
V1 Cystatin C, mg/l	0.83	0.72	<0.0001
V2 Cystatin C, mg/l	0.82	0.72	<0.0001
V1 24-h urine protein, mg	35	23	0.06
V2 24-h urine protein, mg	36	26	0.19
V1 24-h urine albumin, >5 mg	33%	19%	<0.0001
V2 24-h urine albumin, >5 mg	19%	15%	0.01

***Adjusted for age & sex**

Stone formers have higher BMI, more HTN, more UTIs, more diarrhea, & more dehydration than controls.

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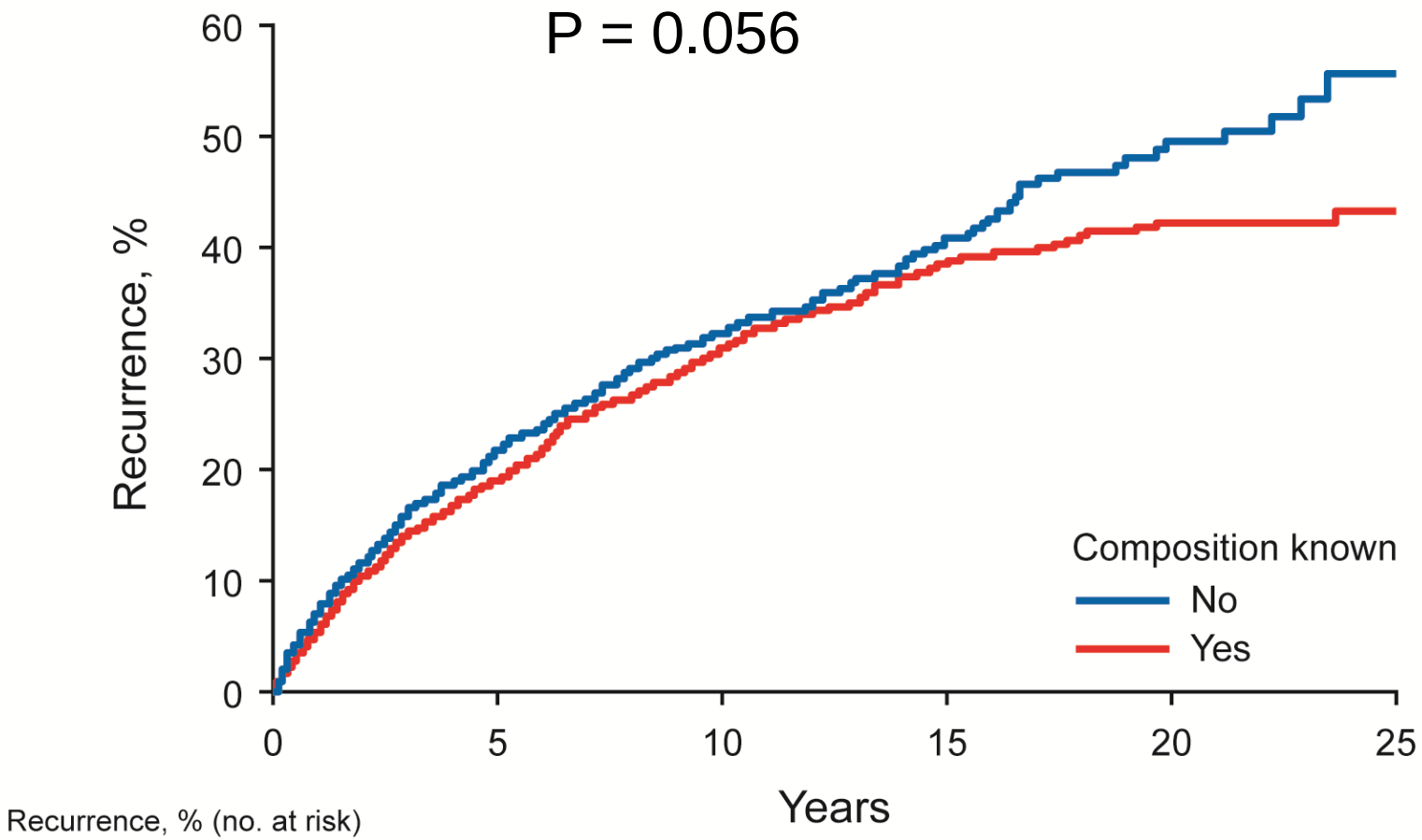
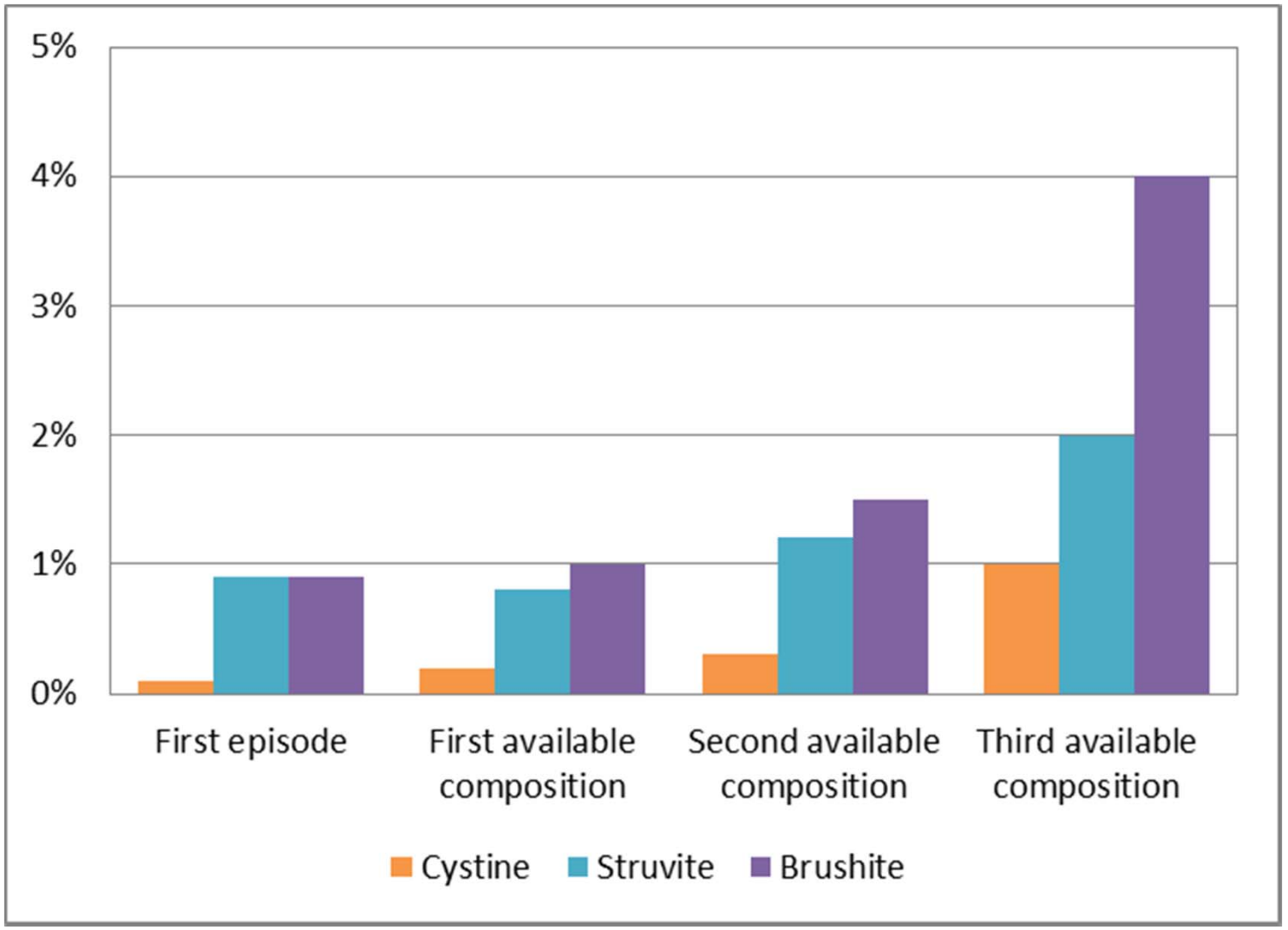
Knowing composition of first stone and risk of recurrence



Singh P et al, Mayo Clin Proc (In press)

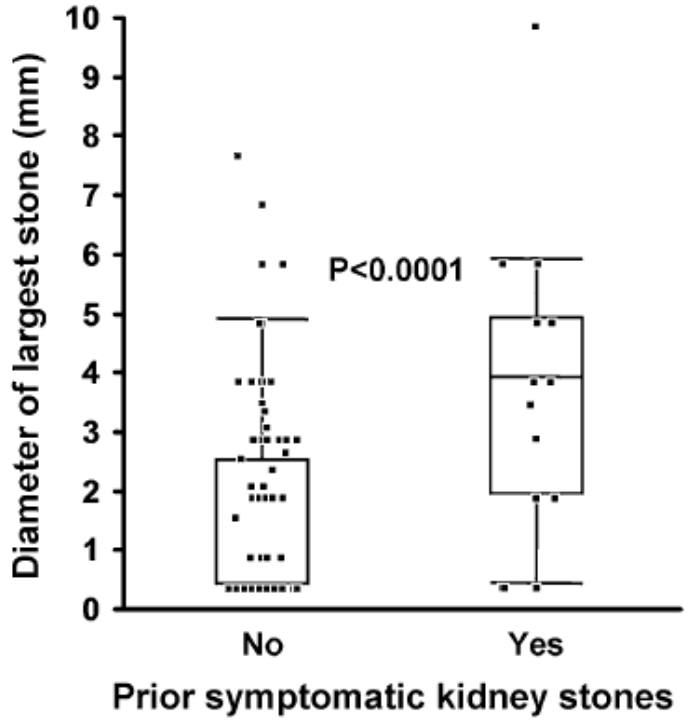
Stone Composition by episode



Singh P et al, Mayo Clin Proc (In press)

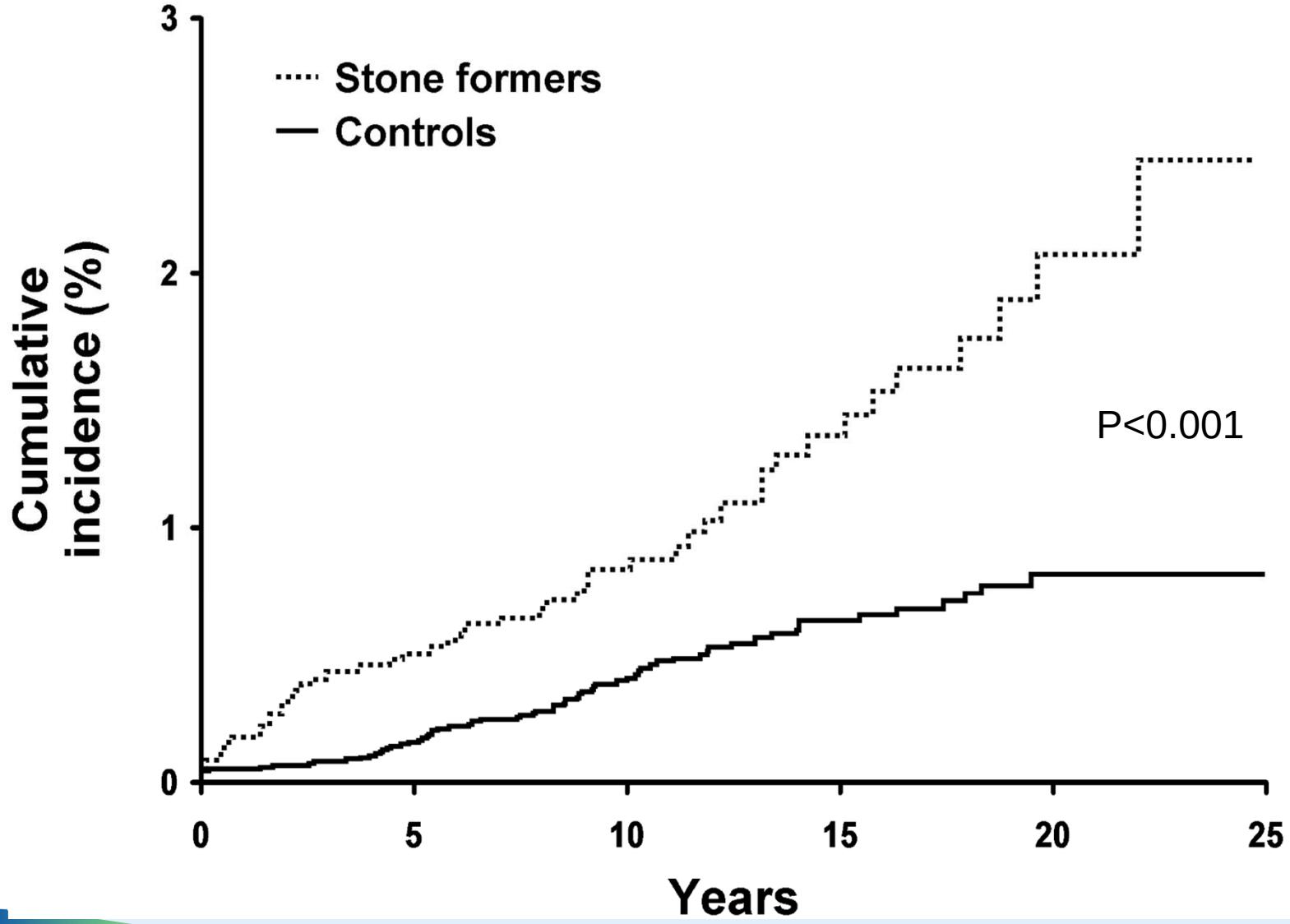
Characteristics of stones in living donors

- 11% (210 of 1957) candidate living kidney donors had radiographic stones



Lorenz EC et al, *Neph Dial Transpl*, 2011

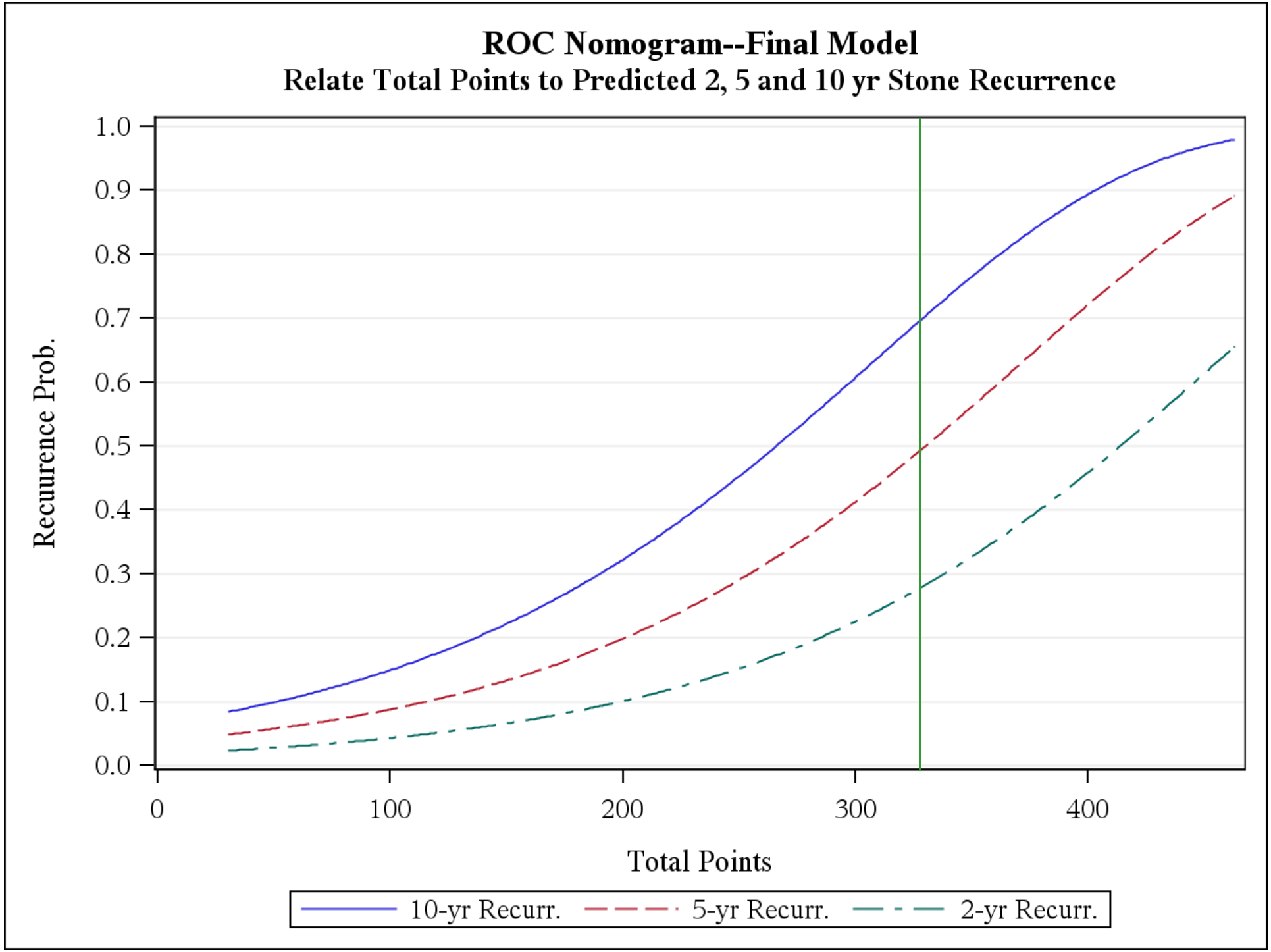
Risk of ESRD in coded stone formers



El-Zoghby ZM et al, CJASN, 2012

Project 3 – Specific Aims

- **Aim 1** – Develop a model to optimally predict symptomatic stone events among historical stone formers in the general population.
- **Aim 2** – Validate and improve this model using prospective stone formers with a baseline detailed survey and urine chemistries.
- **Aim 3** – Determine if models that predict symptomatic stone events also predict asymptomatic radiographic stone growth in stone formers.
- **Aim 4** – Identify specific risk factors for chronic kidney disease among stone formers.


ROC Nomogram--Final Model
Relate Total Points to Predicted 2, 5 and 10 yr Stone Recurrence
Recuurence Prob.
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
Total Points
10-yr Recurr.
5-yr Recurr.
2-yr Recurr.

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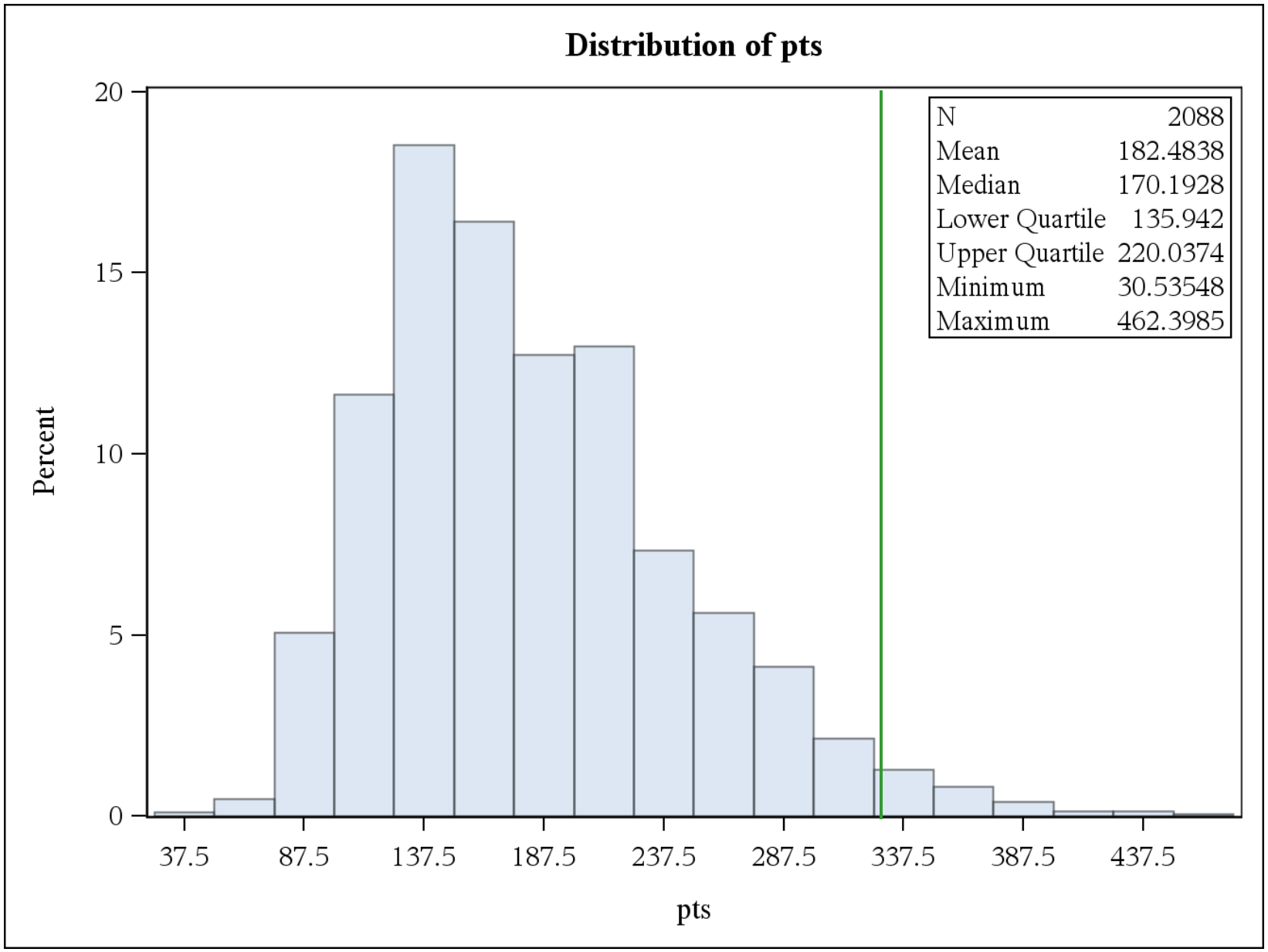
Distribution of pts
Percent
20
15
10
5
0
37.5
87.5
137.5
187.5
237.5
287.5
337.5
387.5
437.5
pts
N 2088
Mean 182.4838
Median 170.1928
Lower Quartile 135.942
Upper Quartile 220.0374
Minimum 30.53548
Maximum 462.3985

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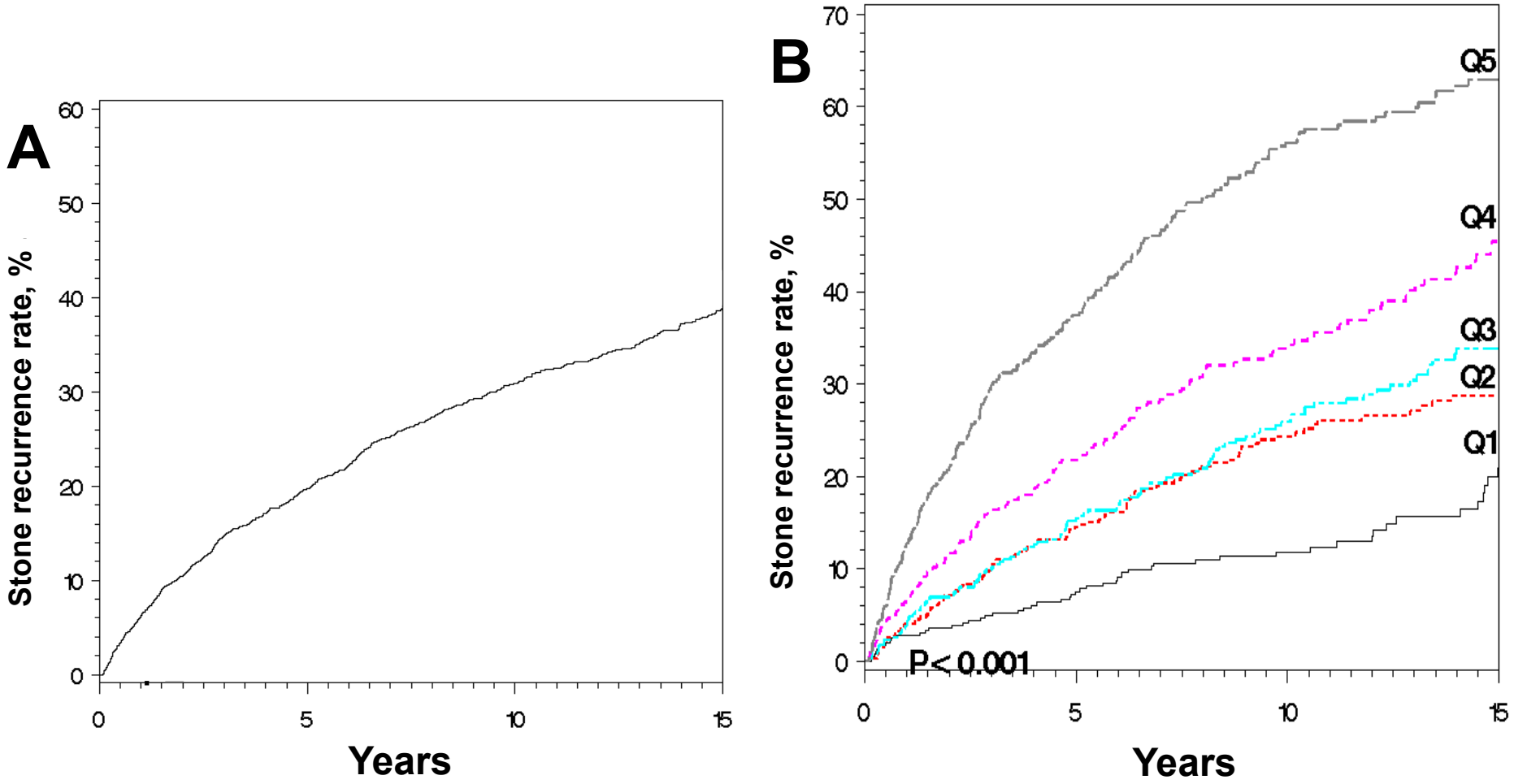
Multivariable Analysis

ROC Score Quintiles Plot



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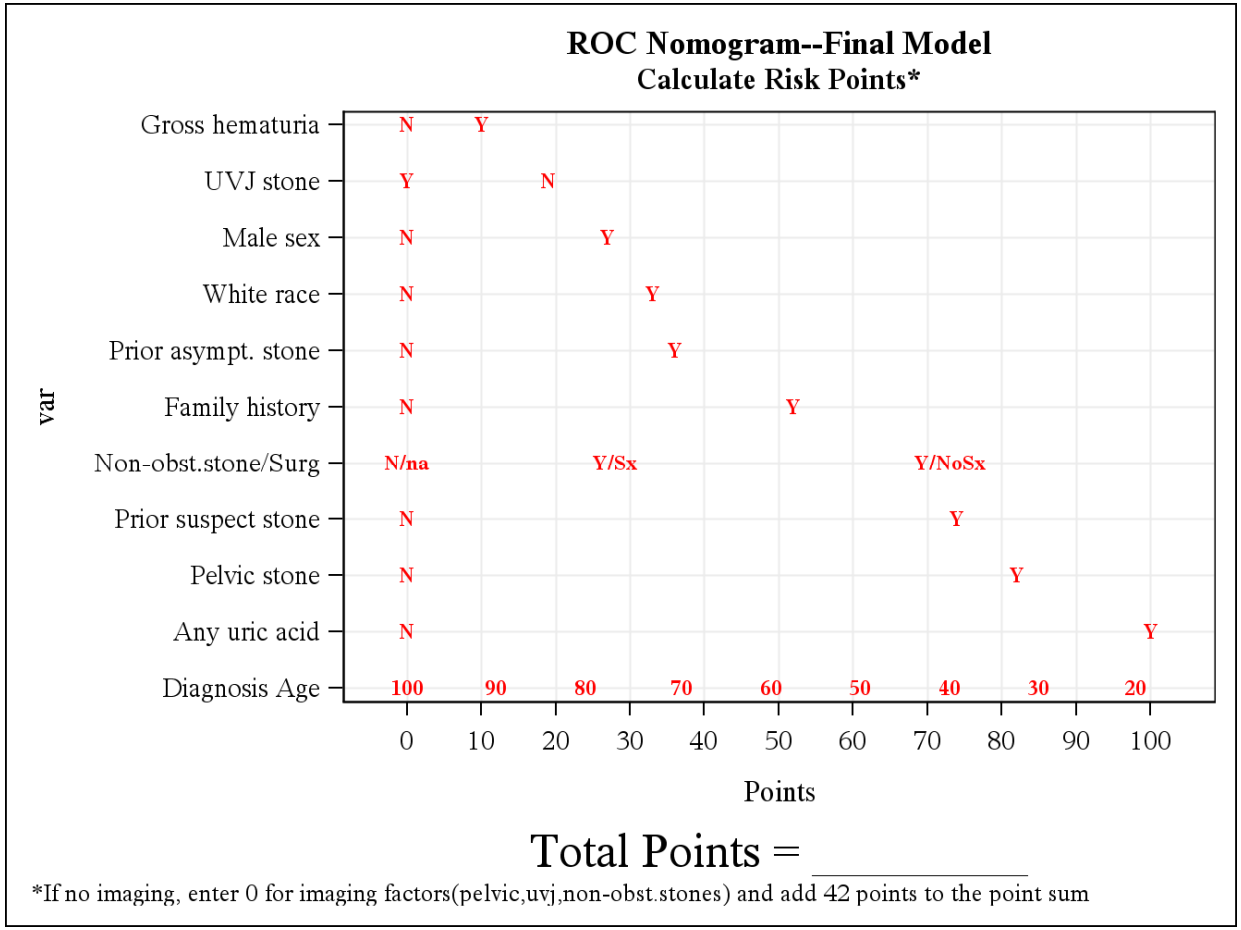
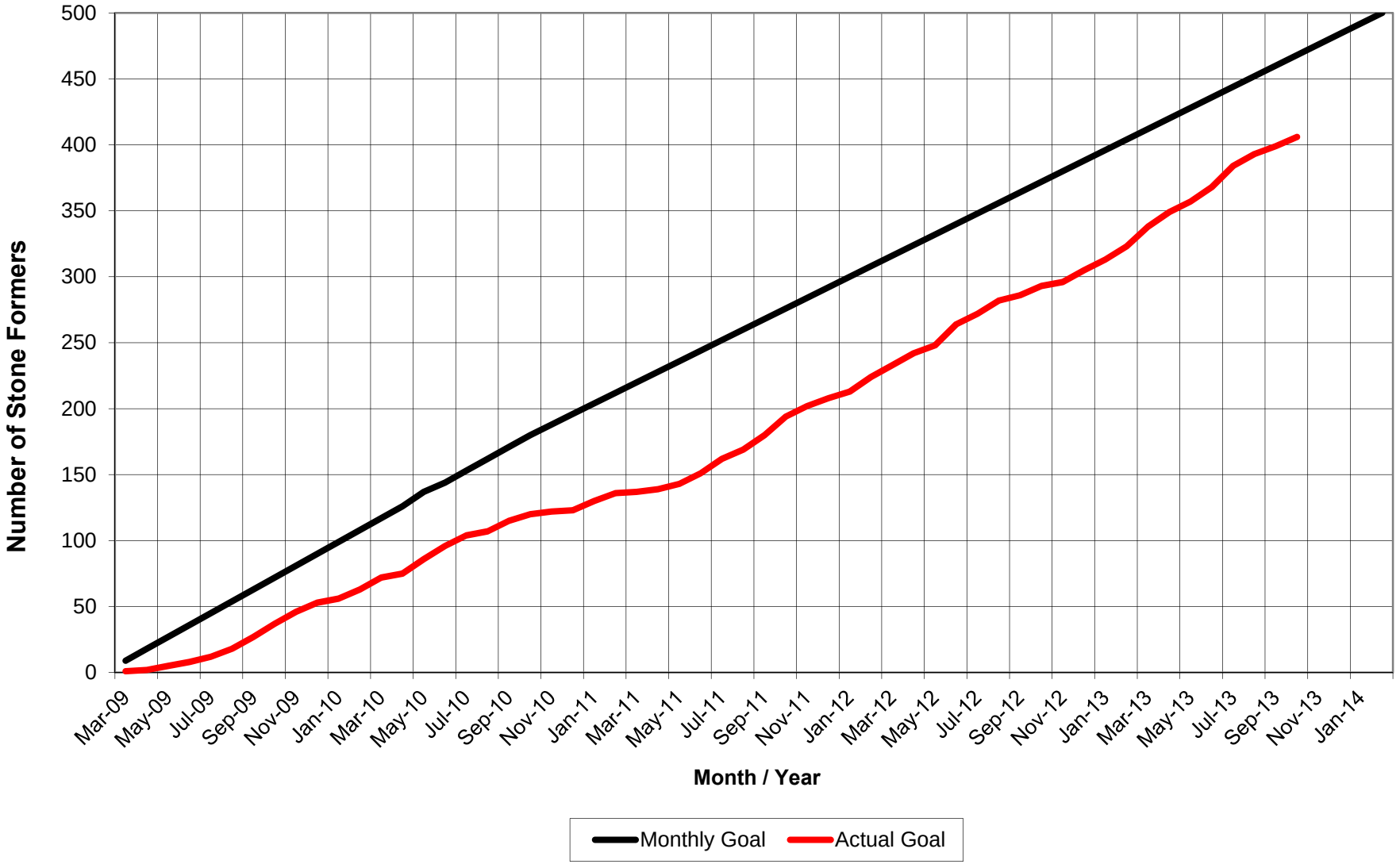
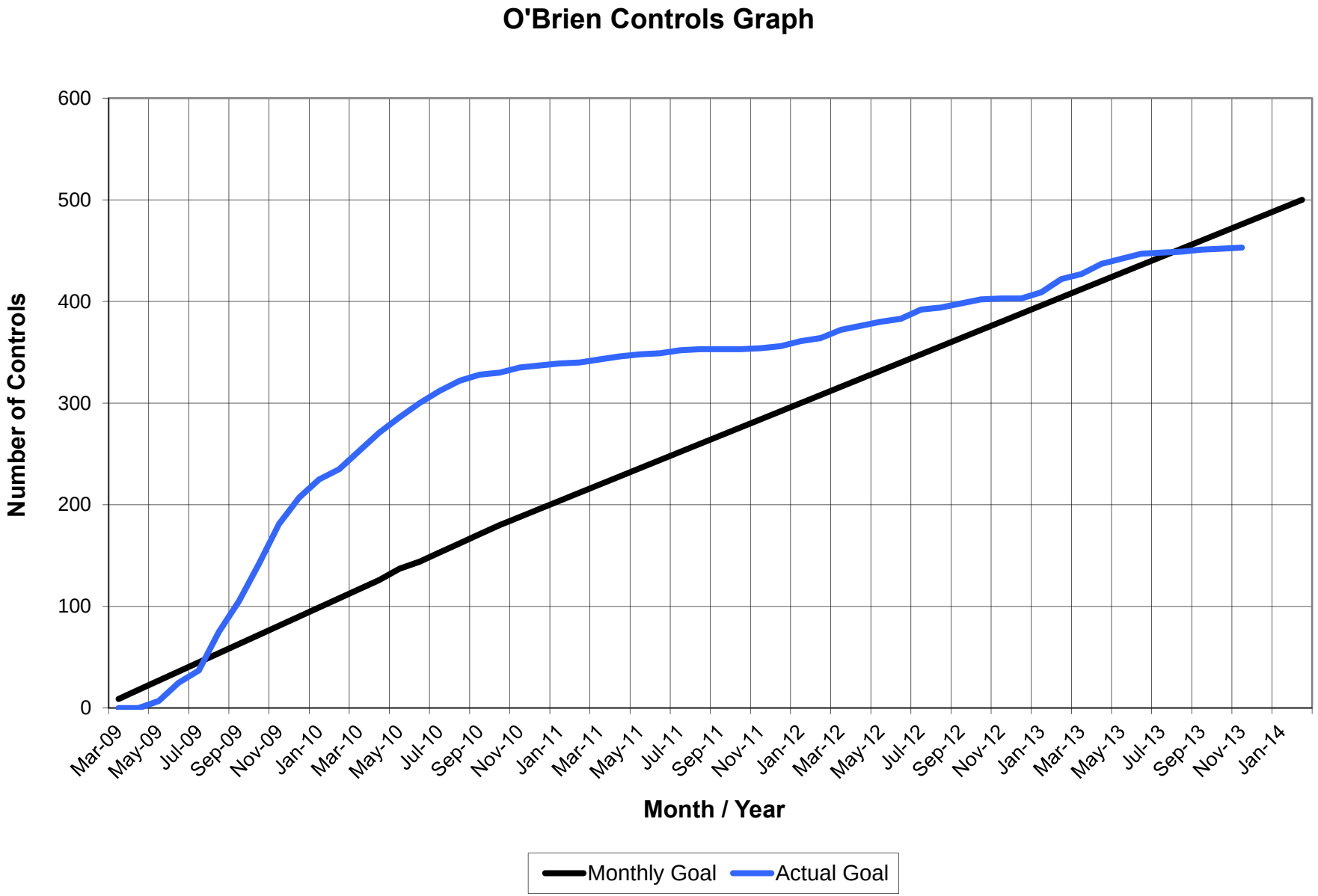
Aim 1 – Develop a model to better predict symptomatic stone recurrence using 4680 chart validated symptomatic stone formers in Olmsted County(1984-2016)

- **Prevalent instead of just incident symp. stone formers**
- **Asymptomatic and suspect stone formers**
- **Impact of surgery and medications on risk.**



O'Brien Prospective Stone Formers Graph

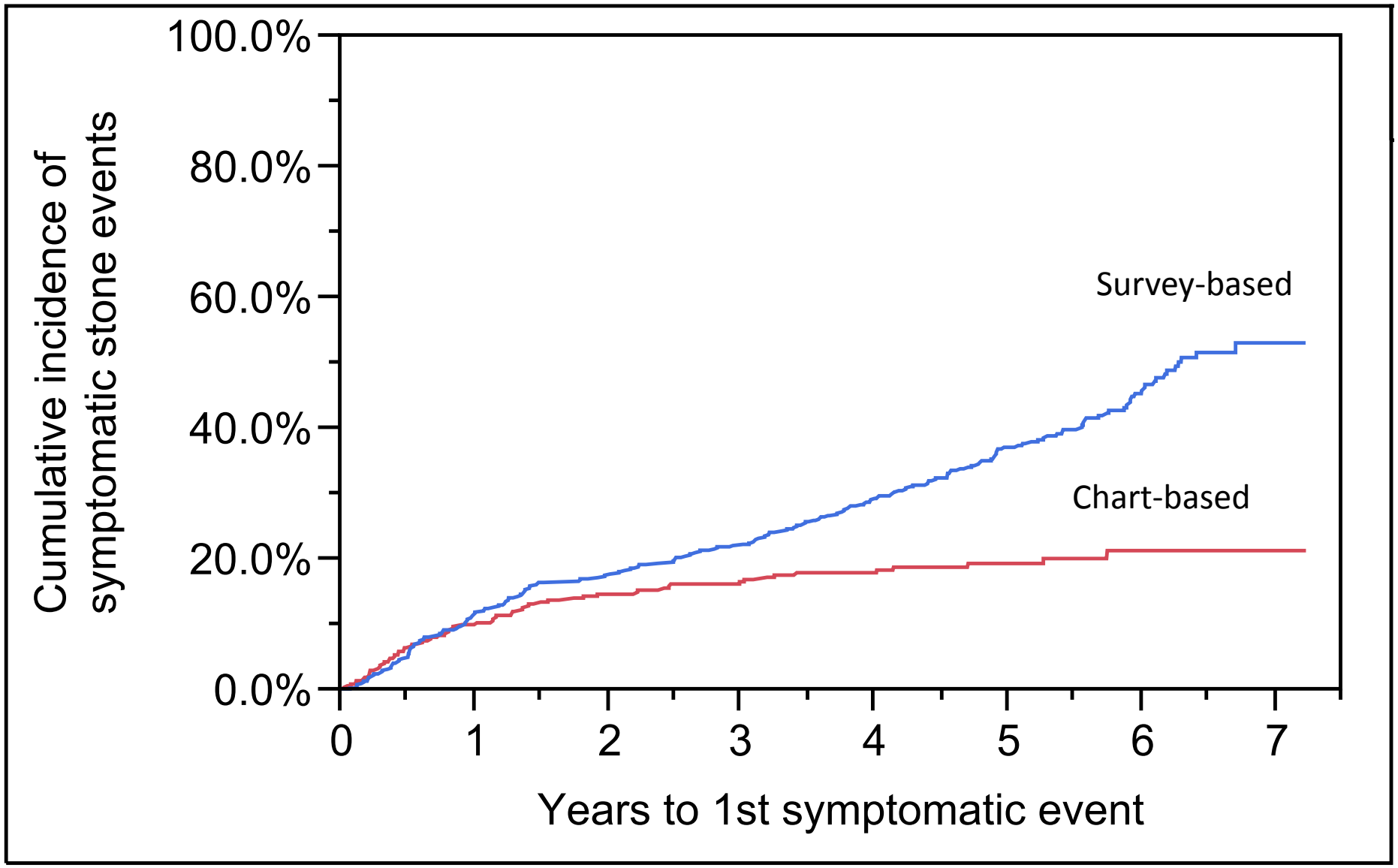



O'Brien Controls Graph
Number of Controls
600
500
400
300
200
100
0
Mar-09
May-09
Jul-09
Sep-09
Nov-09
Jan-10
Mar-10
May-10
Jul-10
Sep-10
Nov-10
Jan-11
Mar-11
May-11
Jul-11
Sep-11
Nov-11
Jan-12
Mar-12
May-12
Jul-12
Sep-12
Nov-12
Jan-13
Mar-13
May-13
Jul-13
Sep-13
Nov-13
Jan-14
Month / Year
Monthly Goal
Actual Goal

Survey results (1st visit)

	Stone Formers	Controls
Male	53%	53%
Mean Age	46 y	46 y
Family history of kidney stones	38%	20%
Chronic diarrhea	10%	6%
Restrict fluid to avoid bathroom	17%	8%
Nocturia	29%	11%
Pain from stone	99.6%	
Stone surgery	49%	
Hospitalized	31%	
Stone medication	4%	
Altered diet for stones	40%	

Importance of the survey for stone events



Resources for these questions

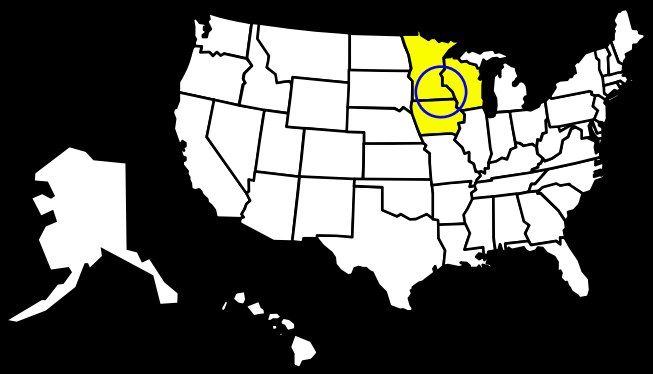
- Rochester Epidemiology Project (population-based)
  - Historical cohort study of incident symptomatic stone formers in Olmsted County from 1984 to 2012 (n=6735 charts validated and abstracted so far).
  - Prospective cohort study of incident symptomatic stone formers in SE Minnesota from 2009 (goal n=700, but 486 enrolled so far)
    - 5-year follow-up visit with a CT scan in 250.
- Mayo Clinic stone clinic (referral-based)
  - Serial CT scans in stone formers while asymptomatic (every 1 to 2 years)

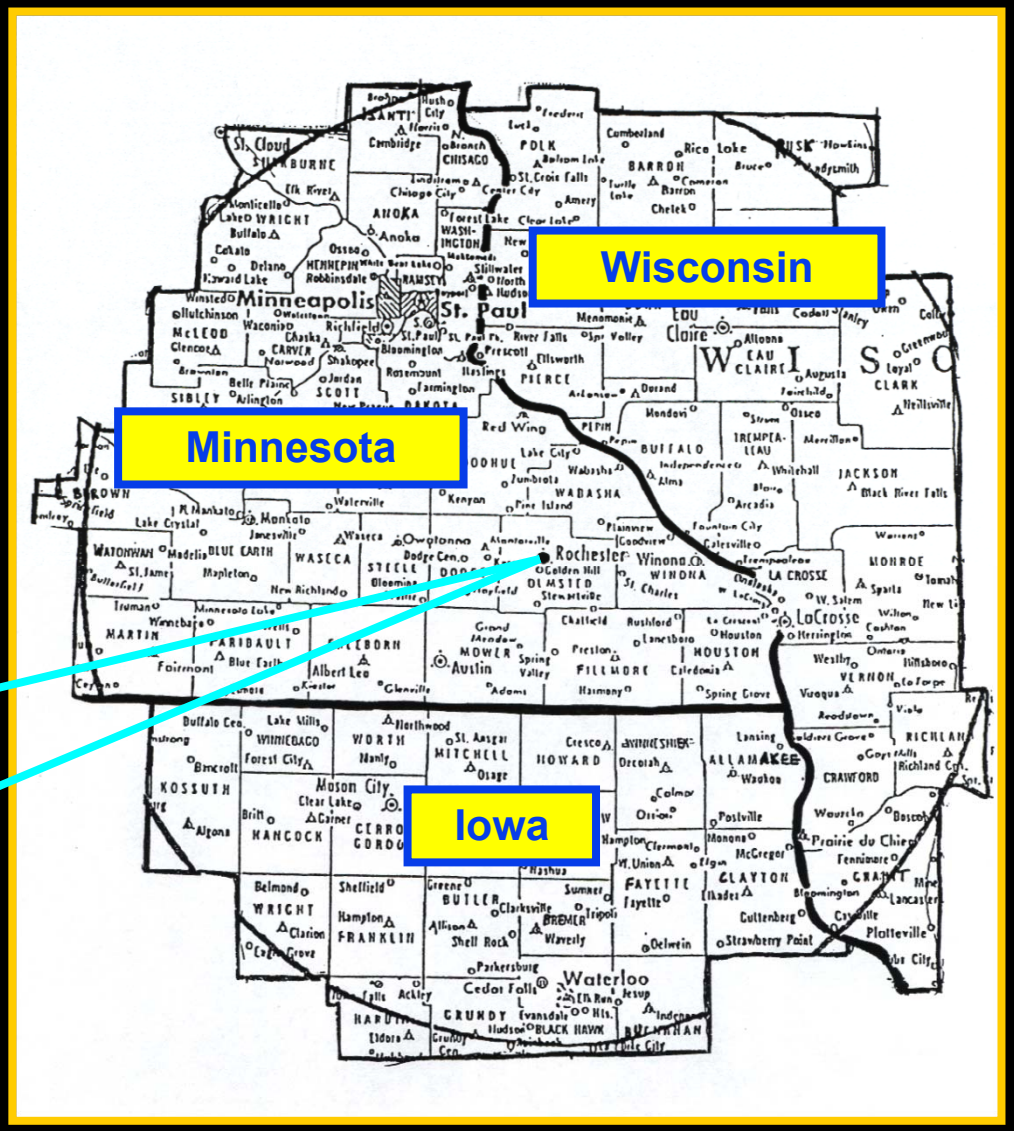
Rochester Epidemiology Project

- Used for our population based cohort studies.
- Unique and unparalleled records linkage infrastructure for research:
  - Data Covering 1966 to Present
  - Inpatient and outpatient medical records linked
  - Birth to death coverage
- 95% of the Olmsted County population has at least one clinic visit every 2-3 years!
- Ideal for population-based cohort studies that require long-term follow-up.
- Granular data from entire medical record

Melton J, Mayo Clin Proc, 1996

Geography of REP





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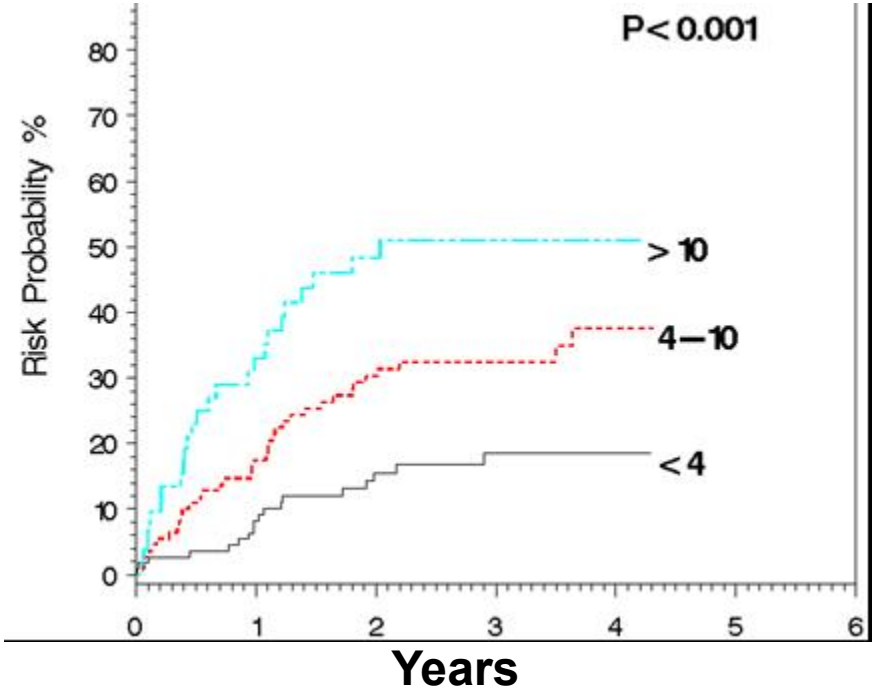
Aim 3 – Determine if models that predict symptomatic recurrence predict stone formation & growth on a 5-year CT scan among 250 stone formers in our prospective cohort.

- Is CT scan a reasonable surrogate for symptomatic events?
- Eventually will relate new stone growth on CT to symptomatic stone events
  (Need longer follow-up)

Risk of symptomatic events by radiographic stone diameter (mm)



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Prospective cohort study

Clinic visit	**Kidney stone questionnaire and Medical record review**	**Food Frequency Questionnaire; One day diet diary**	**24-hr urine**	**Blood sample (20 ml) for renal function, electrolytes and DNA extraction**
Blood pressure	Family history	Dietary potassium	24-hr calcium	Serum creatinine x 2
Height, weight,	Physical Activity Score	Dietary animal protein	24-hr oxalate	Cystatin C x 2
Waist/hip circumference	Dehydration Score	Dietary calcium	24-hr citrate	Total Calcium
	Diabetes history	Dietary oxalate	24 hr UA	Phosphorous
	Stone type(s)	Dietary sodium	24 hr volume	DNA extraction
	Stone treatments	Dietary sucrose	24 hr CaOx SS	Plasma oxalate
		Dietary phytate Dietary fluid Dietary animal fat	24 hr CaP SS $(ULM\text{-}SS)_{CaOx}$ $(ULM\text{-}SS)_{CaP}$	**Spot AM urine (at 90 day follow-up)** Albumin
		Dietary vegetable fat	Albumin Creatinine	Creatinine

Stone composition

Population-based incident vs Referral-based prevalent

	Olmsted County First available after incident stone	Mayo Clinic Referral Lab in 2000 (Lieske, CJASN, 2014)	VA Referral Lab 1983-2002 (Mandel N, J Urology, 2003)	Stone clinic (Pak C, Amer J Medicine, 2003)
Only Calcium Oxalate and/or Apatite	93%	88%	71%	85%
Any Brushite	1.0%	1.3%	4%	2%
Any Uric Acid	5%	10%	14%	8%
Any Struvite	1.0%	0.5%	10%	3%
Other	<0.5%	1%	1%	2%