Assessing albuminuria

Methodological considerations with clinical impact

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Introduction

Albuminuria is a urinary biomarker that has been shown to be a predictor of renal and CV events.

As such albuminuria has a place in clinical practice: kDOQI stages 1 and 2 are defined by presence of micro-albuminuria.

There is strong lobby for standardisation of measurement serum creatinine (Cleveland Clinic / IDMS traceable) to obtain the most reliable GFR estimate.

Untill recently little attention has been paid to standardisation of albuminuria (*exception Miller et al, Clin Chem 2009;55:24-38*)

Micro-albuminuria
- Definition and classification -

	Spot urines (first morning void, or random)			24h urine	Overnight (timed)
	Albumin Concentration (mg/l)	Alb/creat ratio (mg/gram)		Albumin Excretion (mg/24h)	Albumin Excretion (μg/min)
Normal	**< 20**	**M** **F**	**< 17** **< 25**	**< 30**	**< 20**
Micro-albuminuria	**20 – 200**	**M** **F**	**17 - 170** **25 - 250**	**30 – 300**	**20 – 200**
Macro-albuminuria	**> 200**	**M** **F**	**> 170** **> 250**	**> 300**	**> 200**

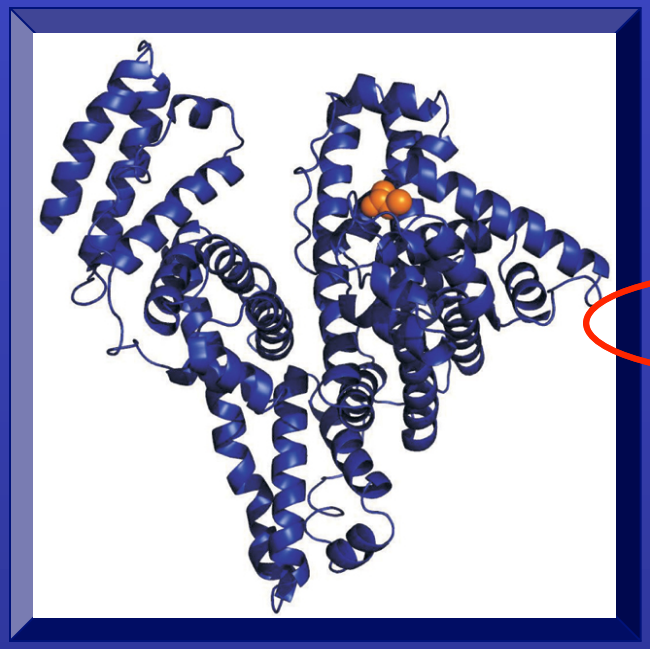
Assessment of albuminuria
Questions to address

1. What assay to use? (answer: immunochemistry polyclonal)
2. What urine sample to use?

   24hr urine collection, first morning void or a spot sample?
3. Which albuminuria measure to use: urinary albumin concentration, albumin/creatinine ratio, or 24hr albumin excretion?
4. Does it matter whether we use fresh urine samples or stored samples?
5. If we are going to use frozen urine samples, what is important?

   pre-storage handling, storage temperature, sample handling

Assessment of albuminuria
Which assay to use?



Polymerization

Dimerization

Monomer

Fragmentation

Loss of immunoreactivity ??

Type of assay

Colorimetric test strips

Immunochemistry based

Monoclonal AB

Polyclonal AB

Size exclusion (HPLC)

Bakker , Gansevoort et al, Curr Hypert Rep 2009;11:111-7

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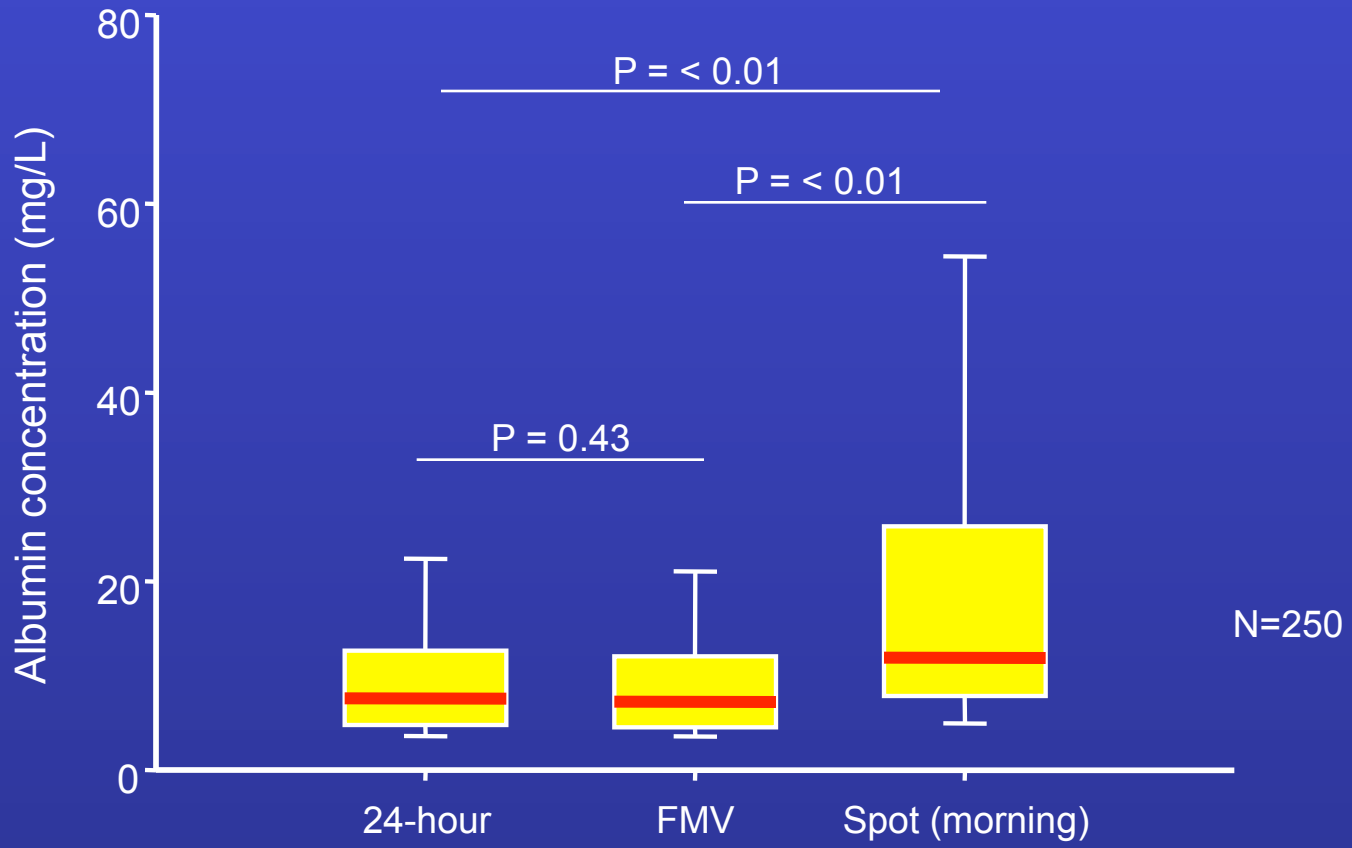
What urine samples to use ?

Median urinary albumin concentration



Median 24-hour	[IQ-range]	7.6 [4.8-12.7]
Median Overnight	[IQ-range]	7.2 [4.5-12.0]
Median Spot (morning)	[IQ-range]	11.9 [7.8-25.8]

Witte et al, JASN 2009;20:436-43

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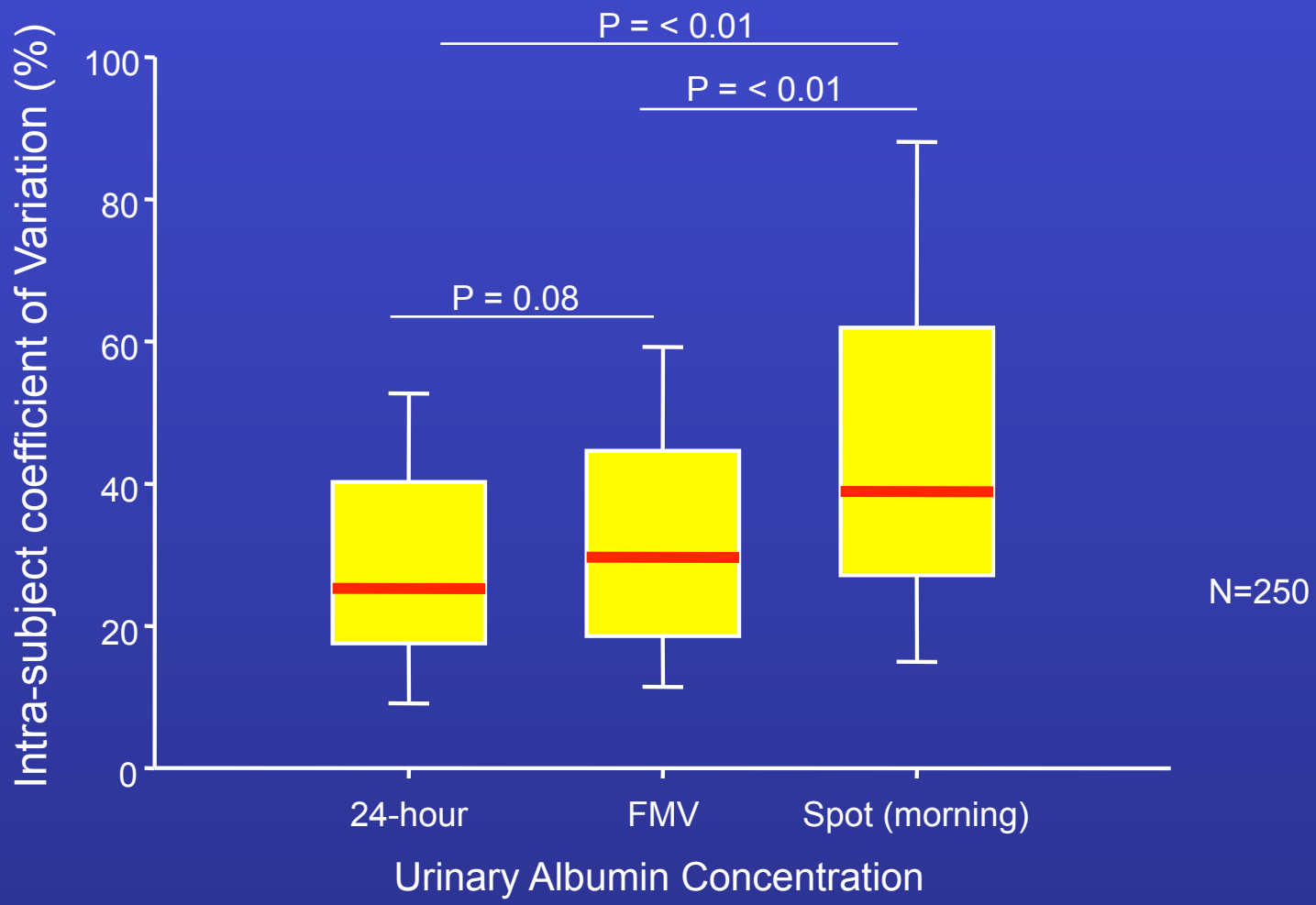
What urine samples to use ?

Coefficient of variation



Witte et al, JASN 09;20:436-43

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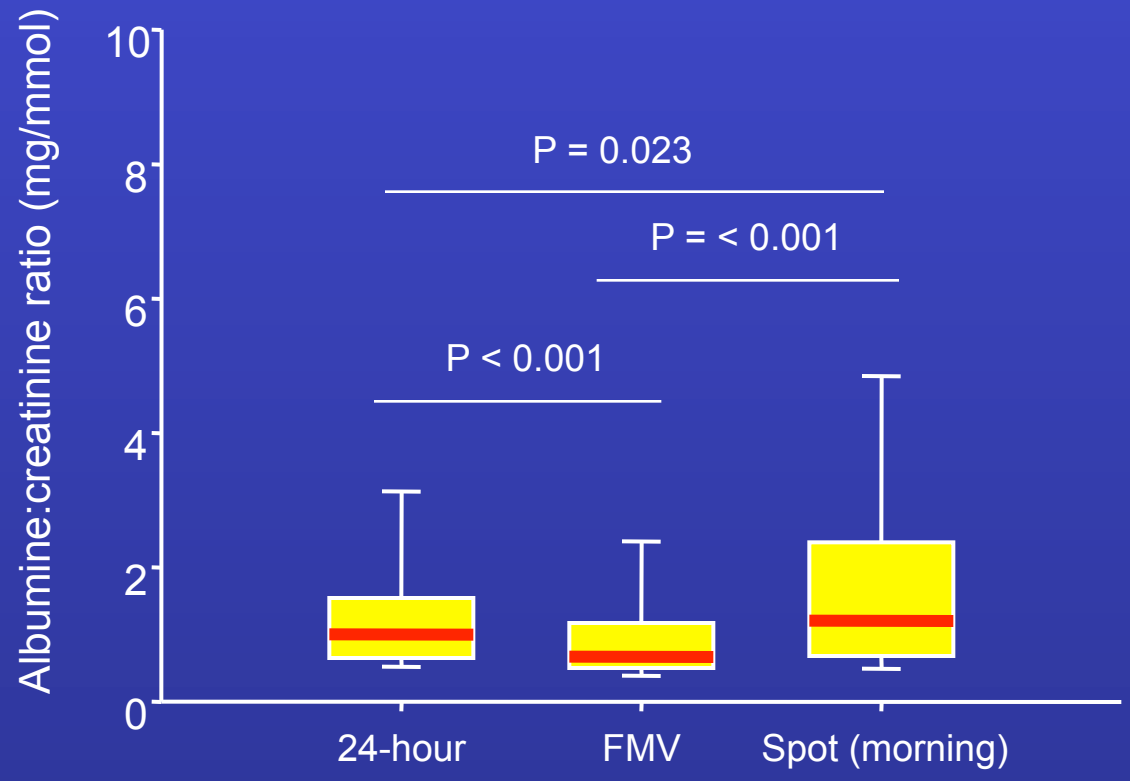
What urine samples to use ?

Median albumin:creatinine ratio



Median 24-hour	[IQ-range]	1.00 [0.65-1.54]
Median Overnight	[IQ-range]	0.67 [0.50-1.17]
Median Spot (morning)	[IQ-range]	1.21 [0.68-2.37]

Witte et al, JASN 09;20:436-43

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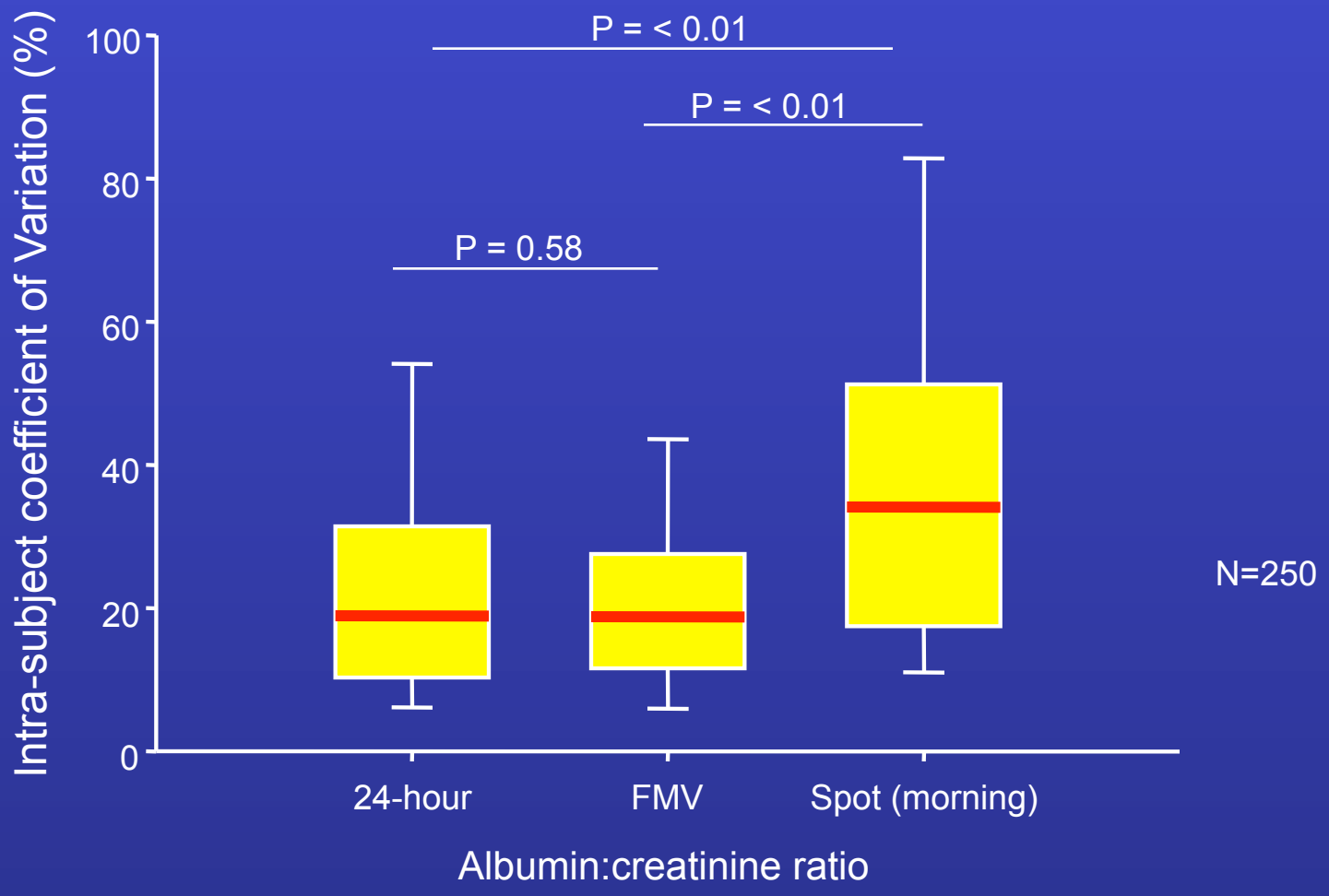
What urine samples to use ?

Coefficient of variation



Witte et al, JASN 09;20:436-43

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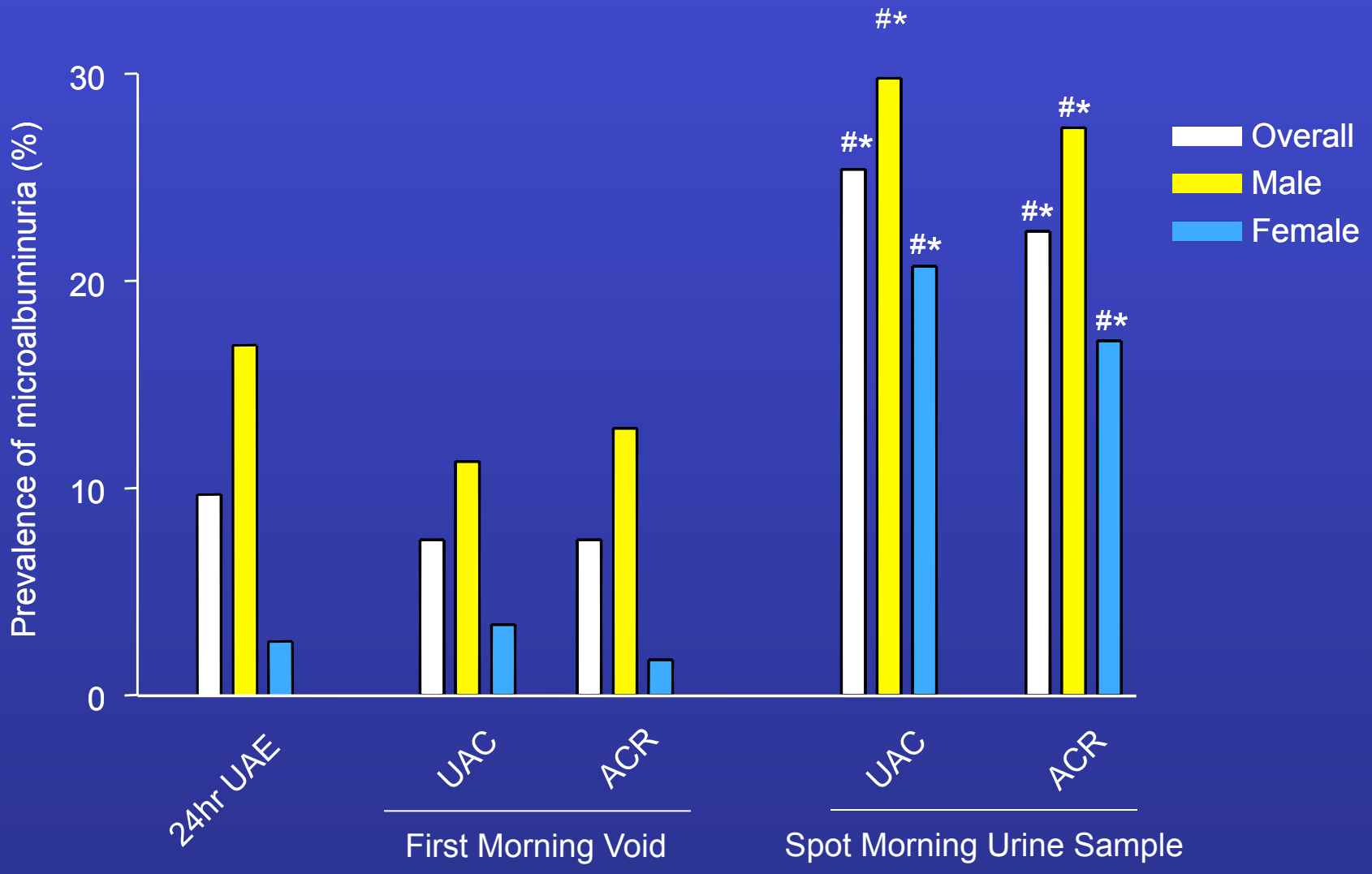
What urine samples to use ?

Prevalence of microalbuminuria



Witte et al, JASN 09;20:436-43

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Which albuminuria measure to use?

Predicting CV outcome

AUC ROC curve

		24 hr urine	First morning void	
		UAE (mg/24hr)	UAC (mmol/L	ACR (mg/mmol)
Overall		0.65	0.62	0.66*
Subgroups	Male	0.64	0.62	0.68*
	Female	0.66	0.59#	0.66*
	<47 yr	0.58	0.52	0.52
	>47yr	0.65	0.64	0.64

* p < 0.05 vs UAC, # p < 0.05 vs UAE

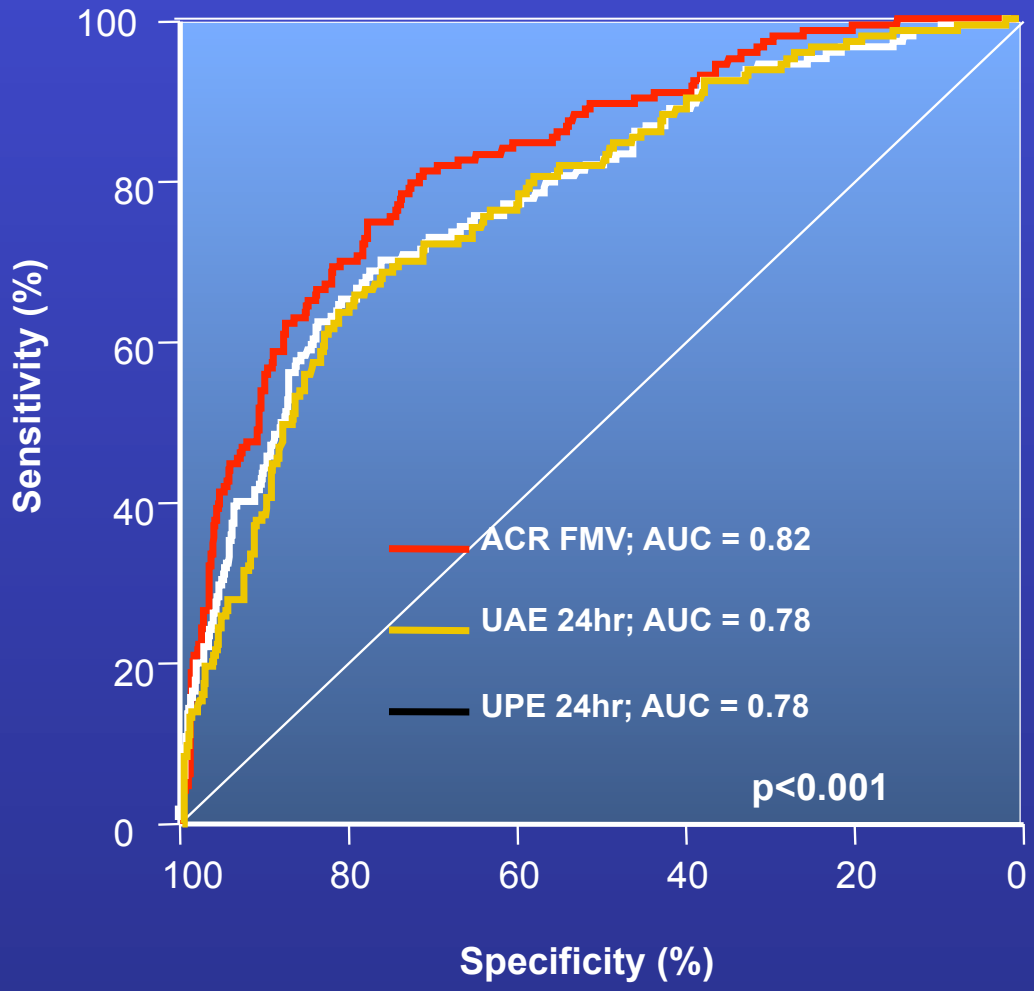
N=3432

Random sample of the general population

Lambers-Heerspink et al, Am J Epidemiol 08;168:897-905

Which albuminuria measure to use?

Predicting renal outcome



N=701

Lambers Heerspink et al, submitted

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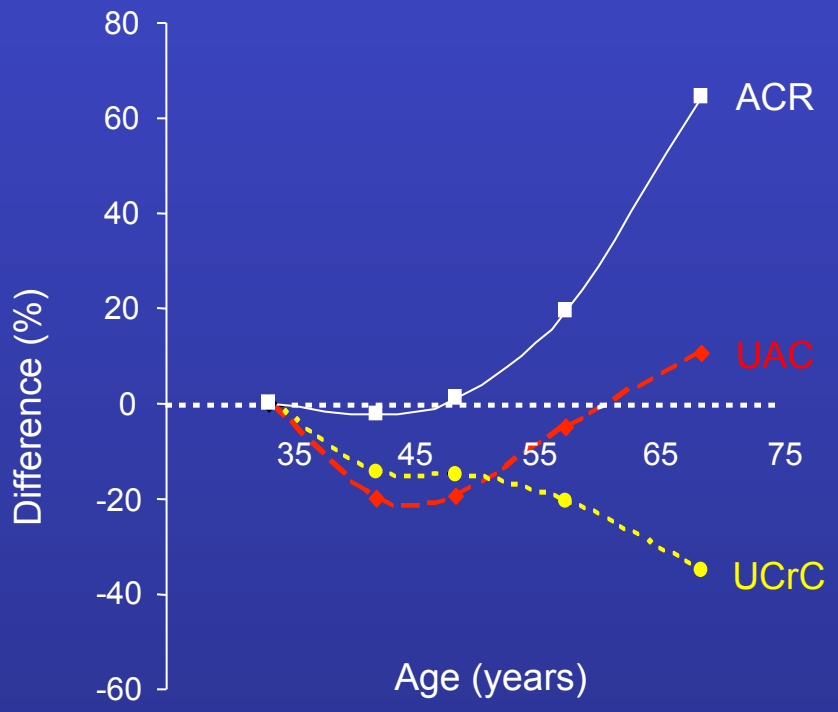
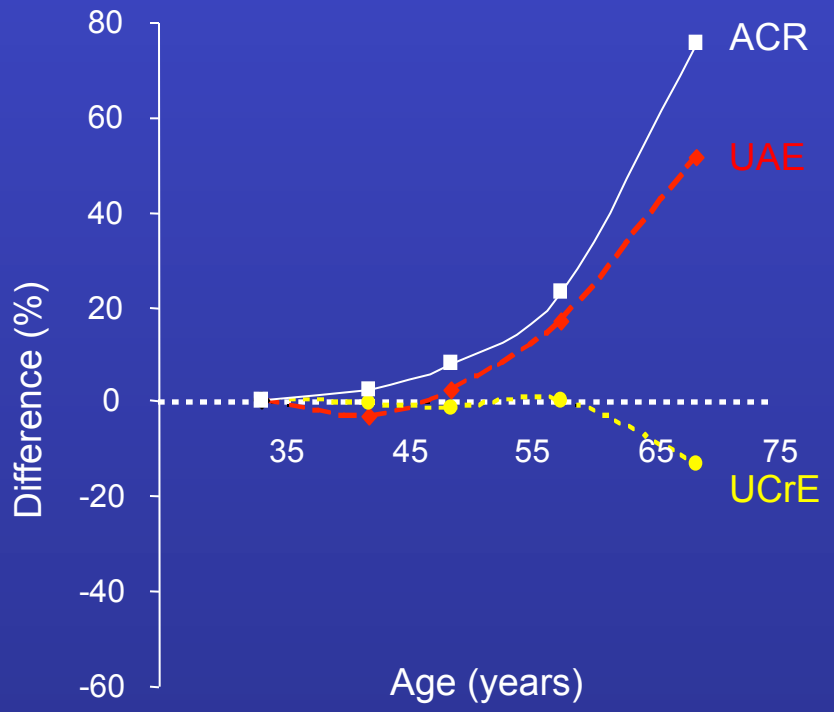
Which albuminuria measure to use?

ACR "incorporates" the influence of age

First morning void



24-hour urine collection



Lambers-Heerspink, Gansevoort et al, Am J Epidemiol 2008;168:897-905

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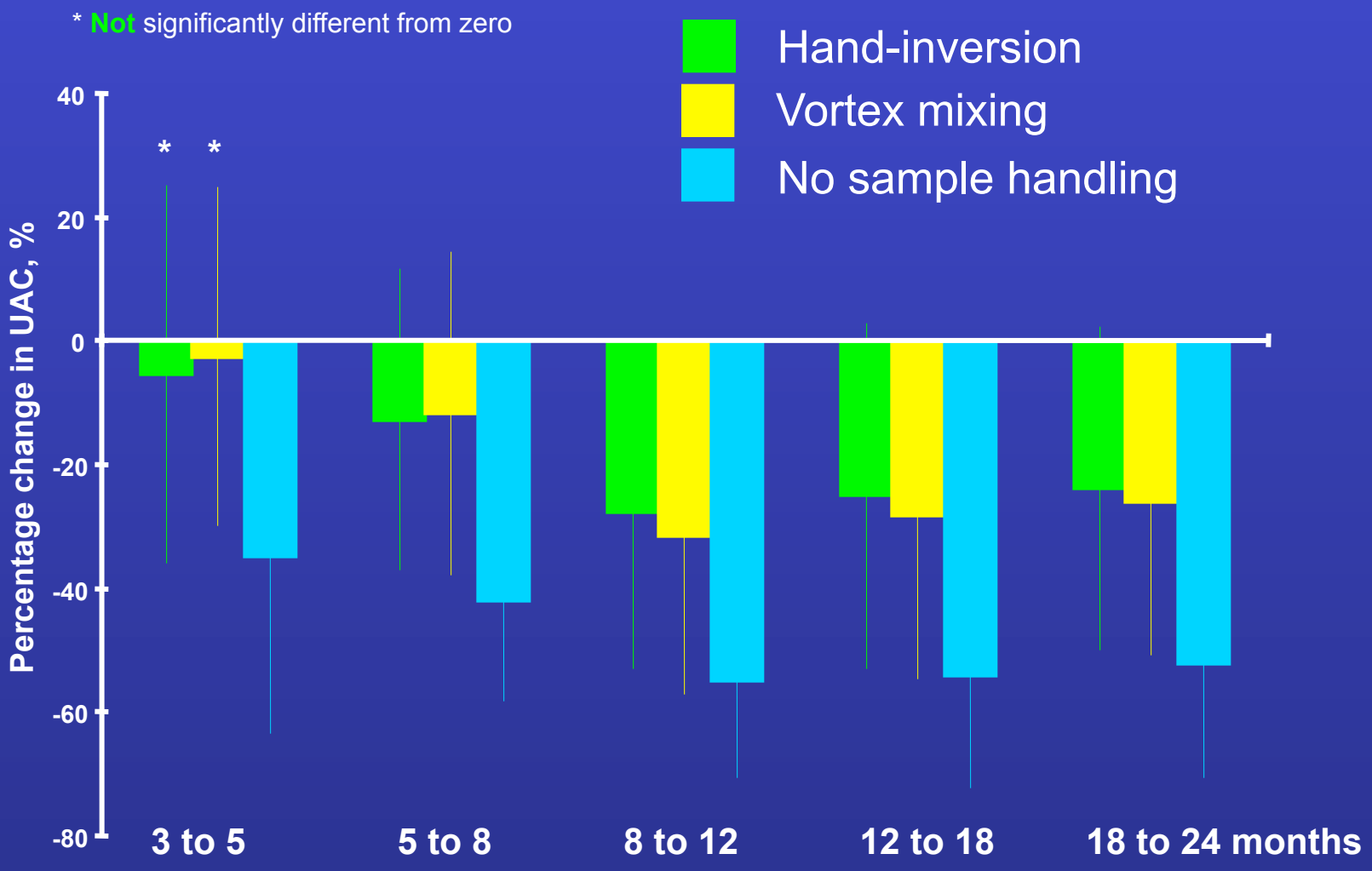
Frozen storage (-20 C) of urine samples

Influence of duration of storage and sample handling



Brinkman et al, Clin Chem 2005;51:2181-3

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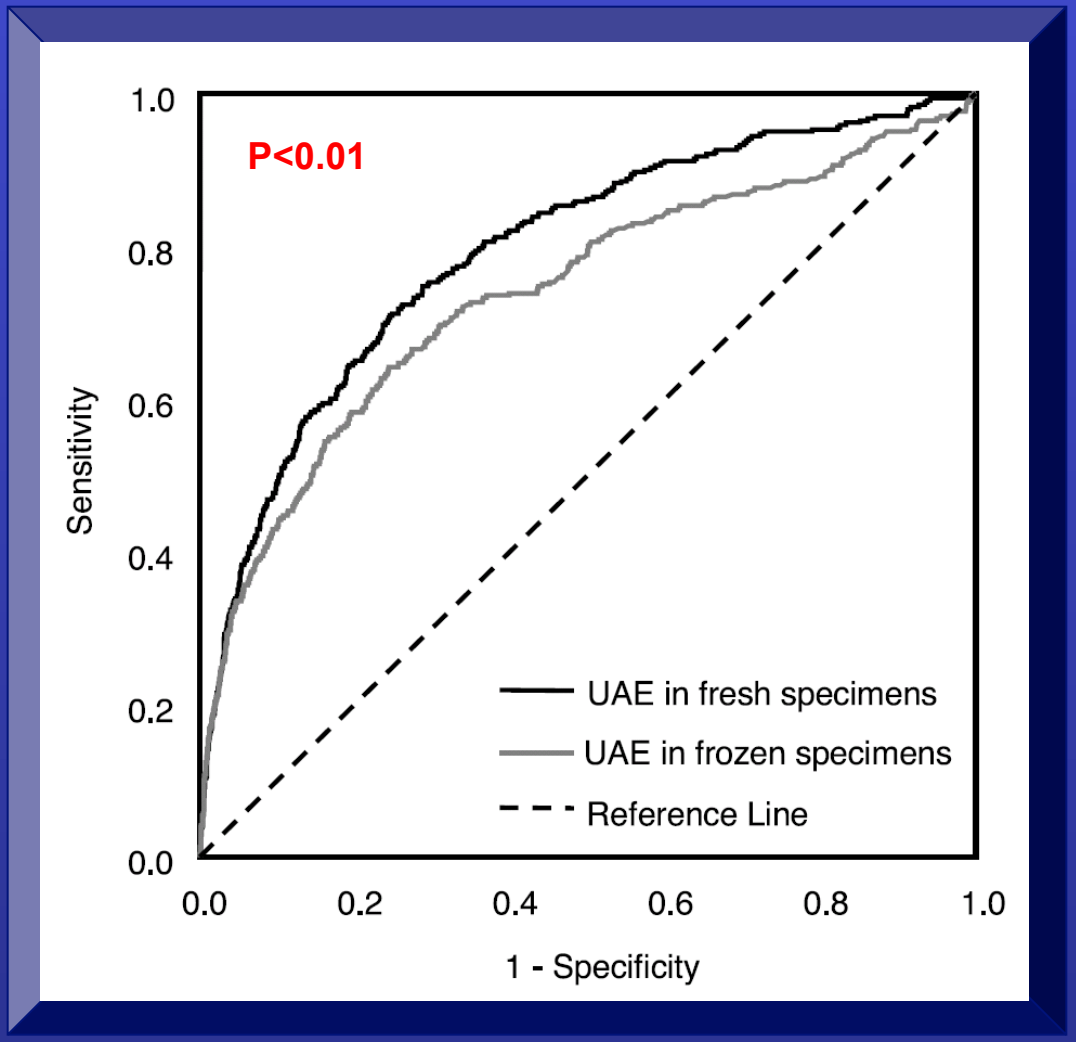
Predictive value of albuminuria

Does it matter when urine has been stored frozen ?



Brinkman et al, Clin Chem 2007;53:153-4

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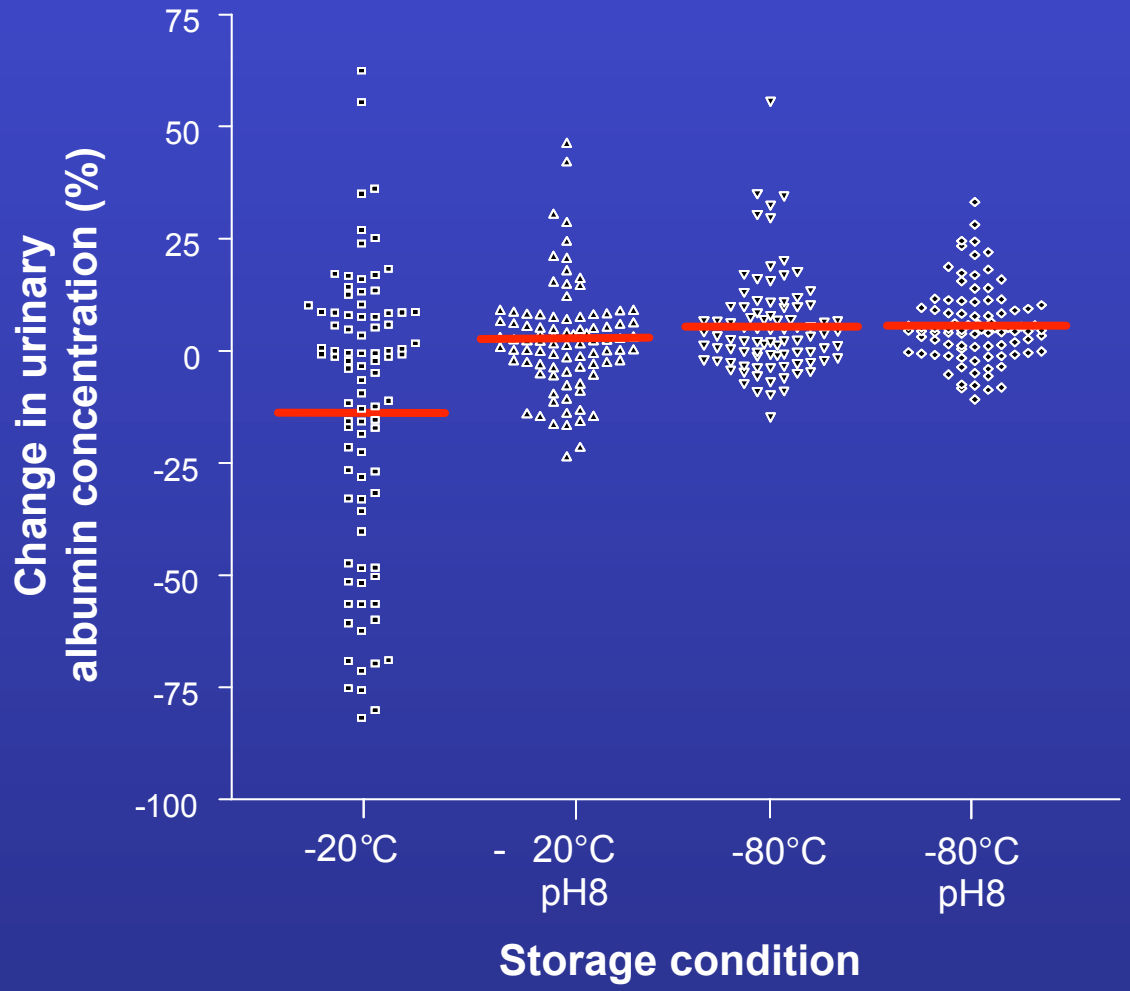
Frozen storage of urine samples

Does urinary pH matter ?



Lambers Heerspink et al, Diabetic Med 2009;26:556-9

Screening for albuminuria
The past (1892)

ALBUMINURIA

IN

HEALTH AND DISEASE

WITH TWO APPENDICES

(1) A CONTRIBUTION TO THE THEORY OF URINARY SECRETION.

(2) THE HYGIENIC TREATMENT OF ALBUMINURIA.

BY

DR. H. SENATOR,

PROFESSOR EXTRAORDINARY OF MEDICINE; PHYSICIAN TO THE ROYAL CHARITÉ HOSPITAL, AND TO THE AUGUSTA HOSPITAL OF BERLIN.

WITH ONE LITHOGRAPHED ILLUSTRATION.

TRANSLATED BY

DR. T. P. SMITH.

Gansevoort and Ritz, Nephrol Dial Transplant 2008

Conclusions

When assessing the clinical impact of urinary biomarkers it is essential to take into consideration methodological issues

1. Which assay was used? Polyclonal? Intra- and interassay CV?
2. What urine samples were used? Preferably 24hr collections or first morning voids
3. In case first morning void samples are used, normalise for creatine concentration
4. Fresh or frozen? Preferably use fresh urine samples.
5. If frozen, what were storage conditions and how was sample handling? Frozen at -80 ^{0}Celsius, pH adjustment (or protease inhibitors?), vortexing?