Lithium toxicity

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Service de Néphrologie adulte

Hôpital Necker, Paris

Lithium

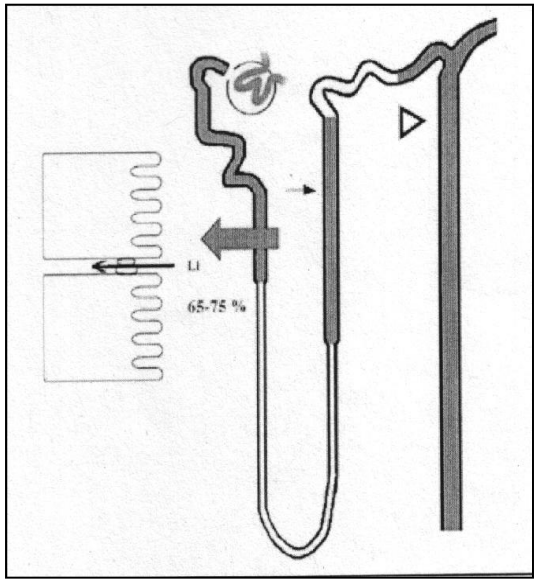
- Use of lithium salts as salt substitutes but recall from the marketplace in 1949

- Efficient in the treatment of acute mania, and in the prophylaxis of bipolar and unipolar affective disorders

- Alzheimer

Lithium

- Monovalent cation
  - Acts as sodium
- Freely filtered through the glomeruli
- 75% of the filtered load is reabsorbed in the proximal tubule
  - In case of sodium defect, additional 20% are reabsorbed in the large ascendant limb of Henle
- A small fraction is reabsorbed in the collecting duct
  - Through the apical sodium epithelial channel (ENaC)



Trepiccione et al, J Nephrol, 2010

Renal impact

- Reduced ability to concentrate the urines
  - After 8 weeks
- Chronic renal failure
  - After 10-20 years of treatment
- Hypercalcemia

Hypercalcemia

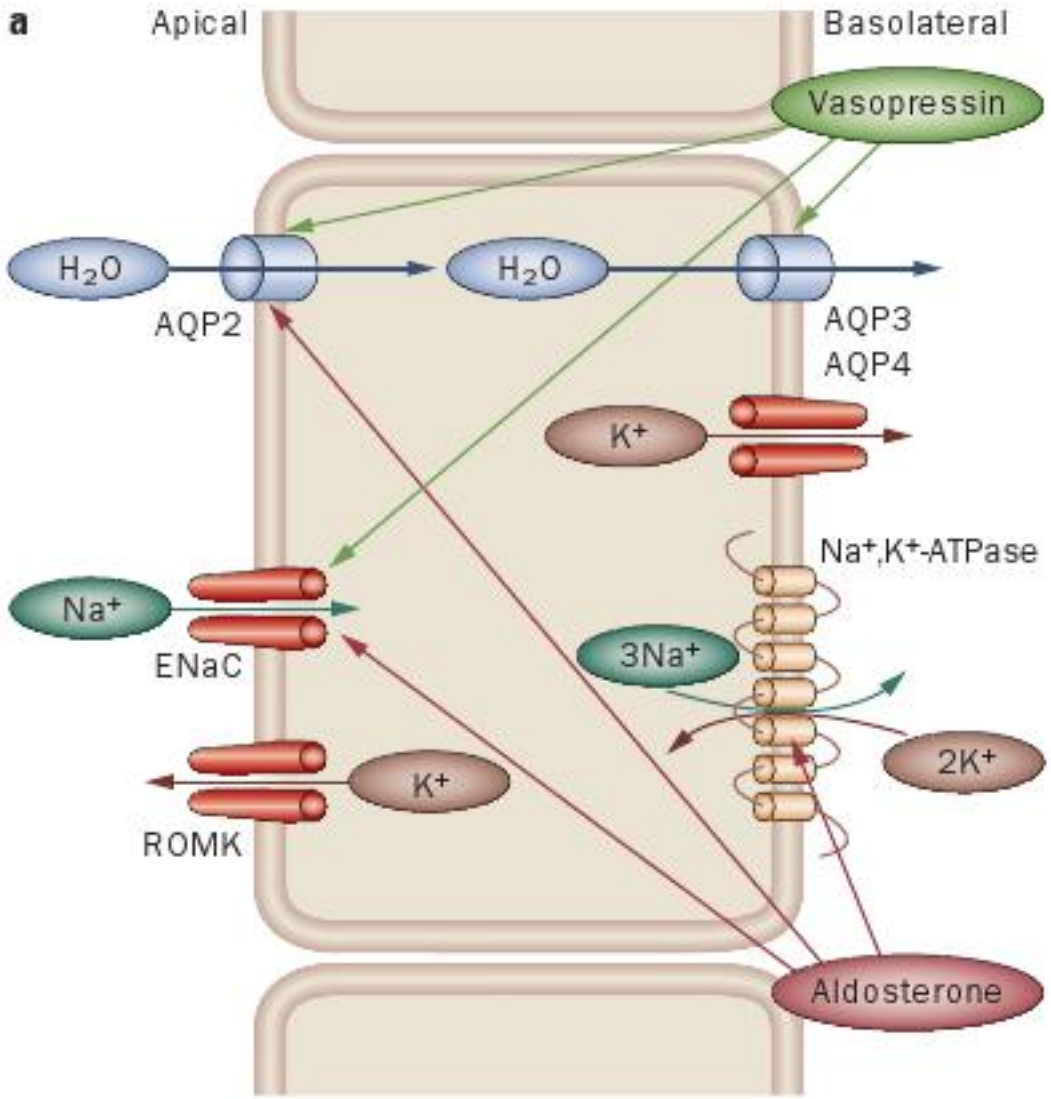
- False hypercalcemia due to dehydration
- Hyperparathyroidism
  - 10-15% if treatment >10 years
- Hypercalcemia usually moderate
- Risk of lithiasis and nephrocalcinosis (and osteoporosis)
- Adenoma 2/3 or hyperplasia 1/3
- Little impact of Li discontinuation
- Surgery if one adenoma
  - More difficult if hyperplasia
  - Risk of relapse
  - Calcimimetics?

Pathophysiology

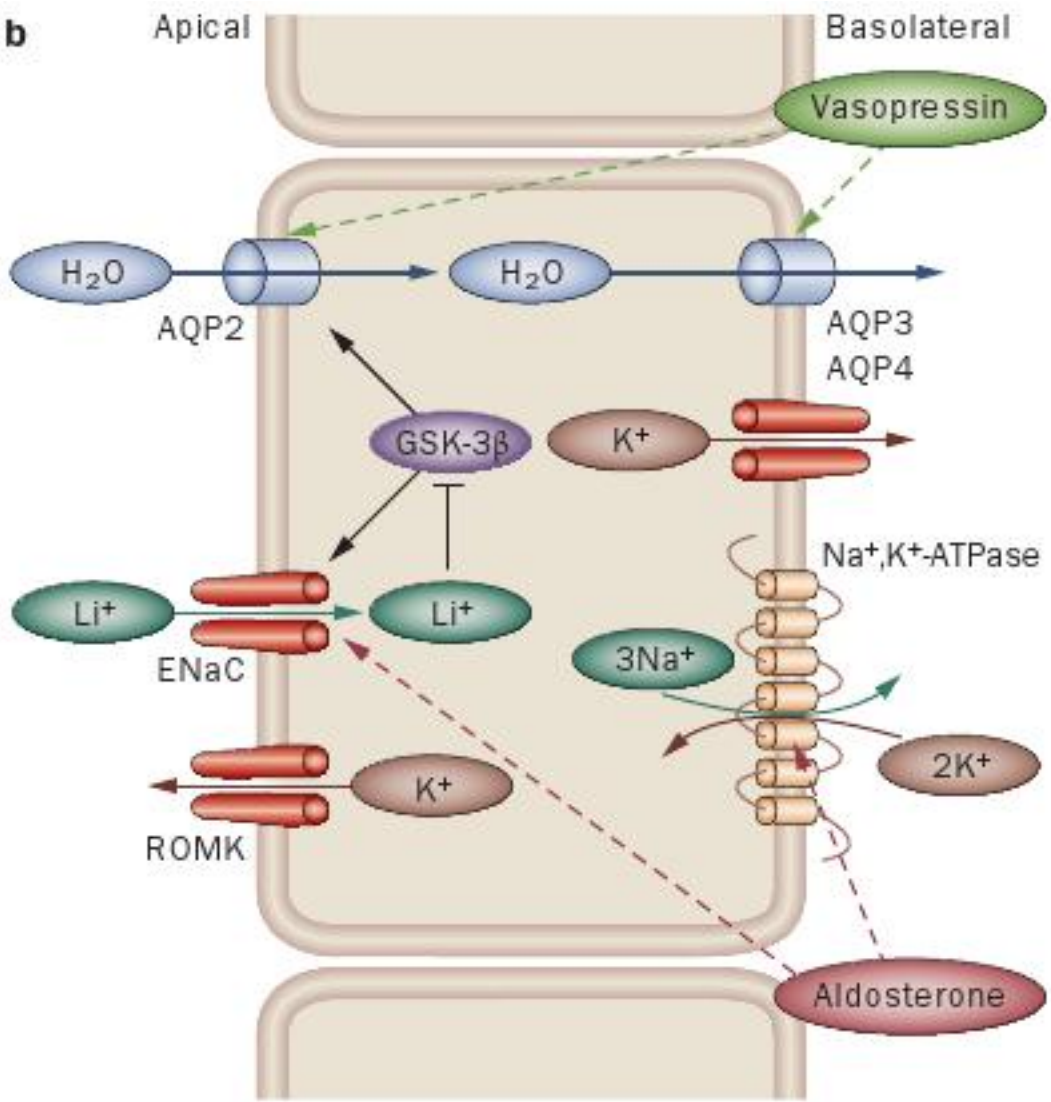
- Direct stimulation of PTH production by Li
- Or alteration of the sensibility of the calcium-sensing receptor
- Possible effect of Li on parathyroid tissue with increase of preexisting abnormal tissue

Nephrogenic diabetes insipidus

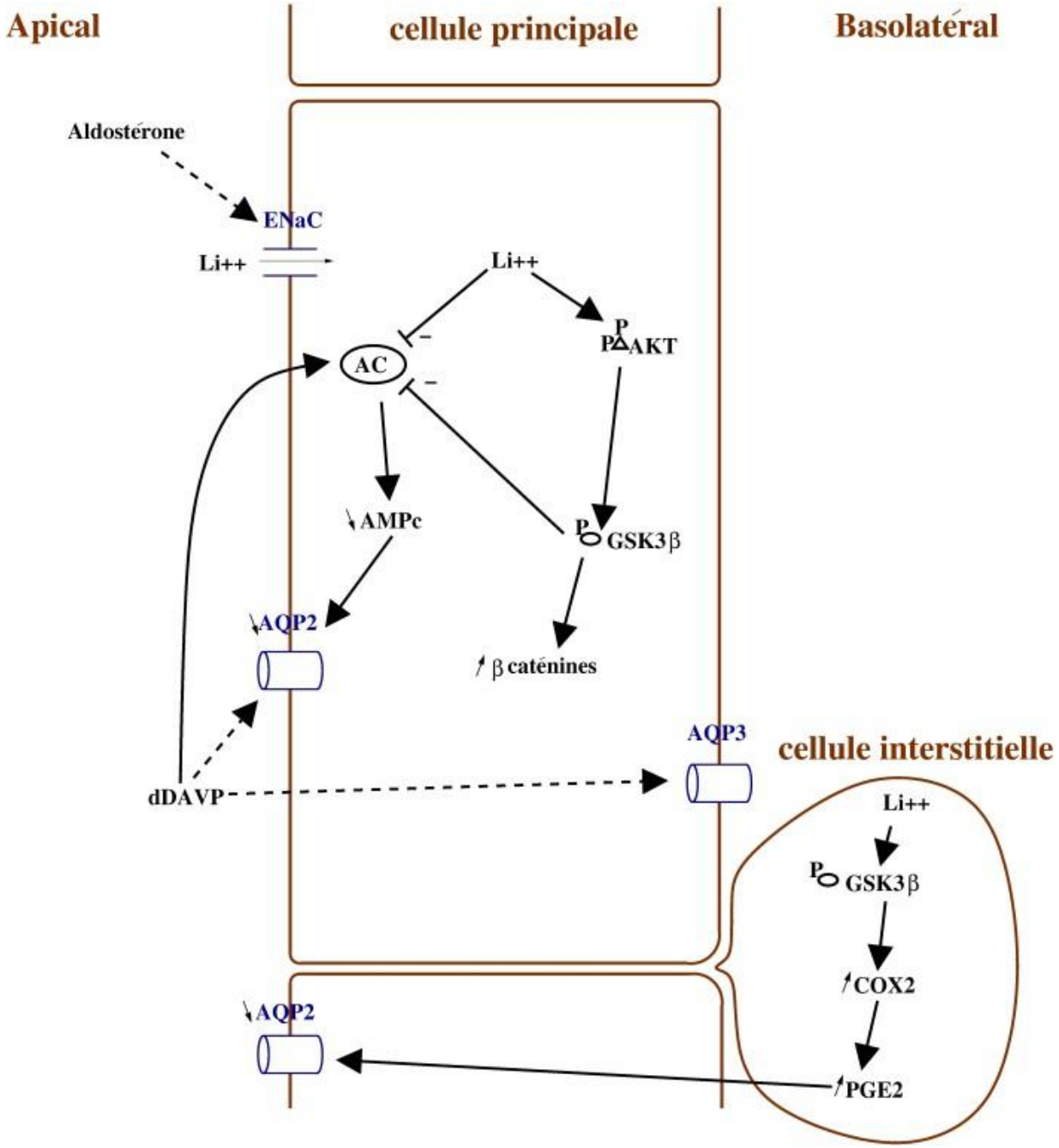
- 40-50% of patients
- Polyuro-polydipsic syndrome, up to 10l per day
- Less frequent with once day dosing
- Correlated to the duration of Li exposure
- May be irreversible, especially if >15 years

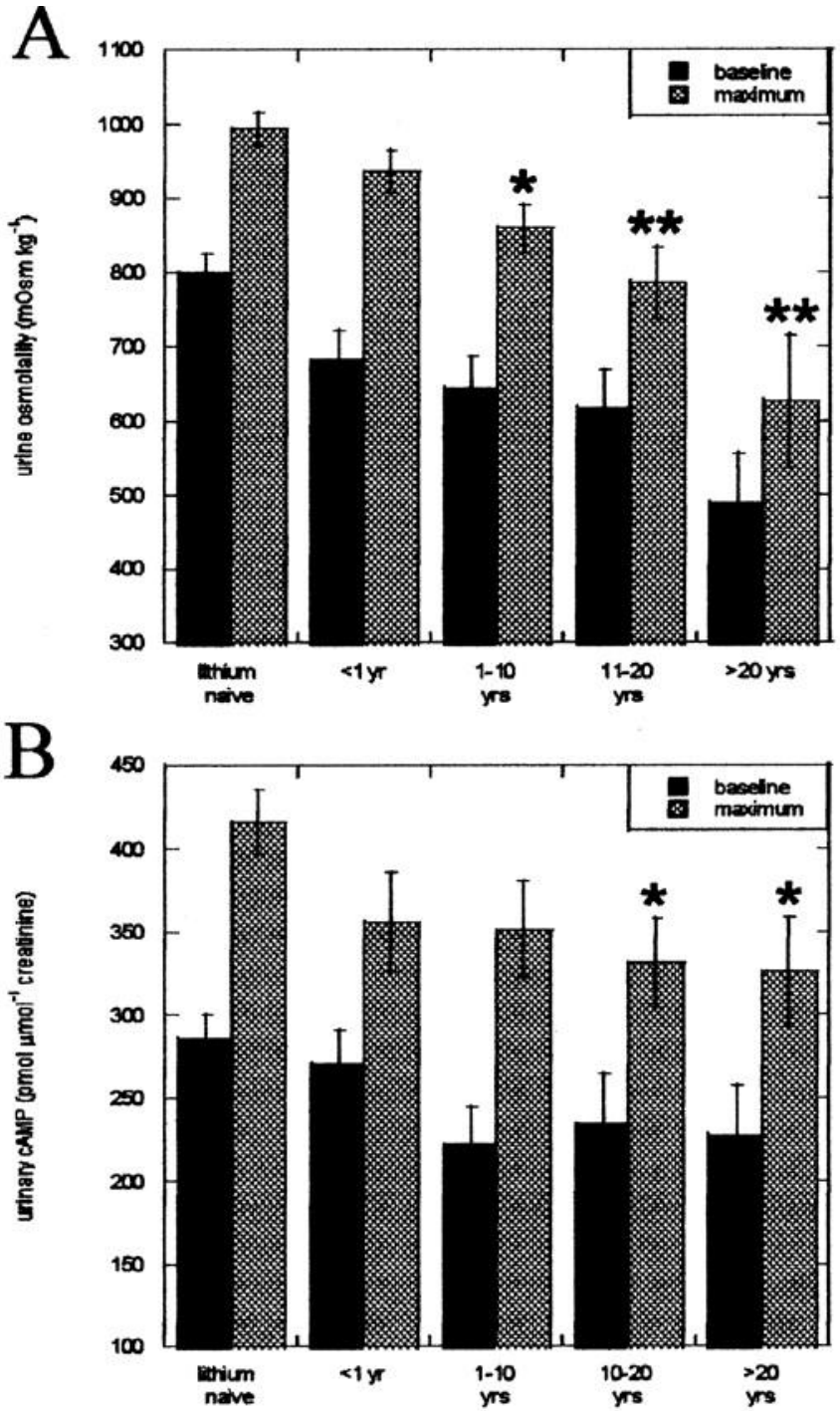


Grünfeld et al, Nat Rev Nephrol, 2009



Grünfeld et al, Nat Rev Nephrol, 2009


Apical
cellule principale
Basolatéral
Aldostérone
ENaC
Li++
Li++
AC
P
PAKT
AMPc
P
GSK3β
AQP2
β caténines
AQP3
cellule interstitielle
dDAVP
Li++
P
GSK3β
COX2
AQP2
PGE2



- Decrease in the ability to concentrate the urines(osmolality), in the urinary excretion of AMPc and AQP2 correlated to the duration of Li exposure
- Decrease in the ability to react to vasopressin

Bedford J J et al. CJASN 2008

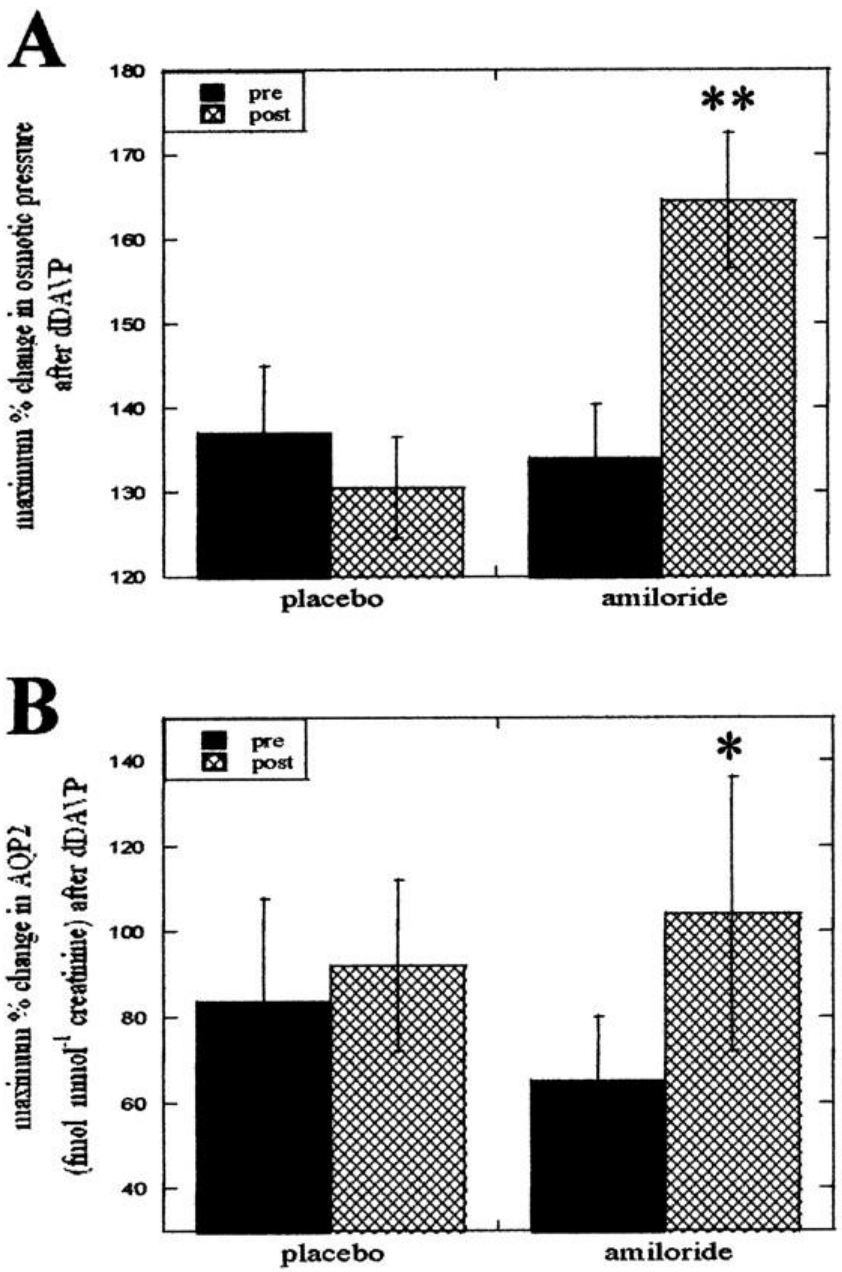
Treatment

Blockade of ENaC by amiloride

- Inhibition of Na+ and Li entry in principal cells

Cross-over study in Li-treated patients

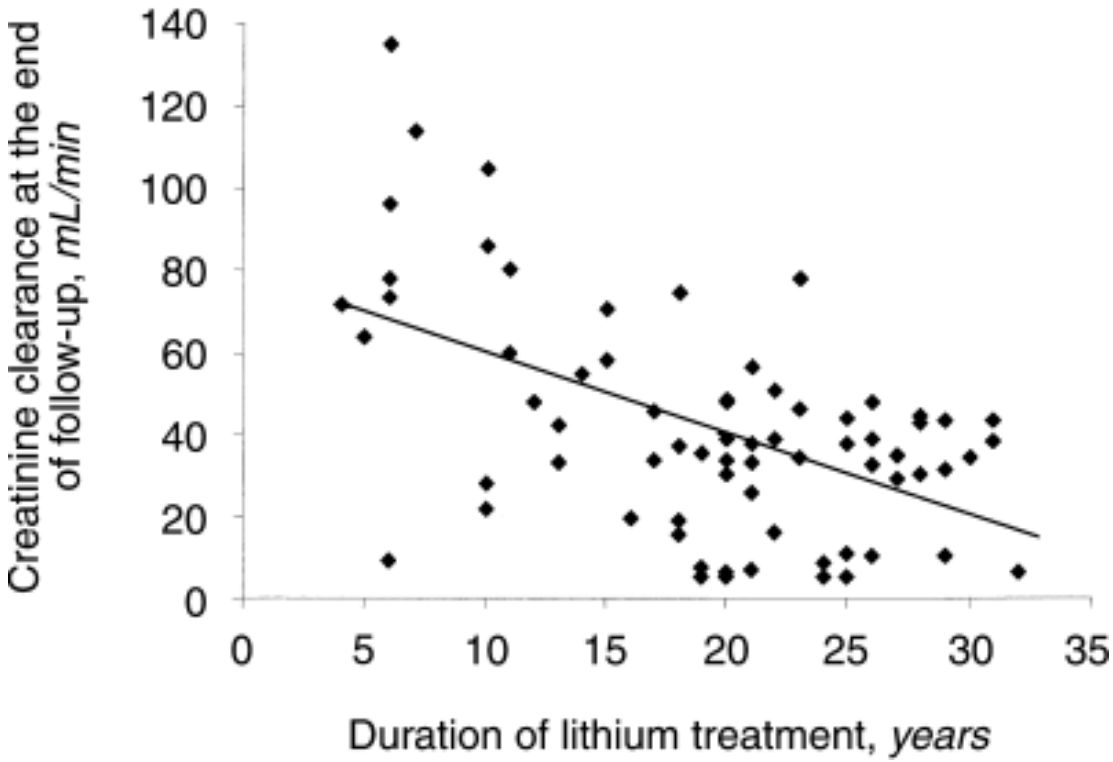
- Amiloride 10 mg/d 6 weeks
- Increase in urinary osmolality
- Treatment of polyuria
  - Batlle et al, NEJM, 1985
  - Bedford et al, CJASN, 2008



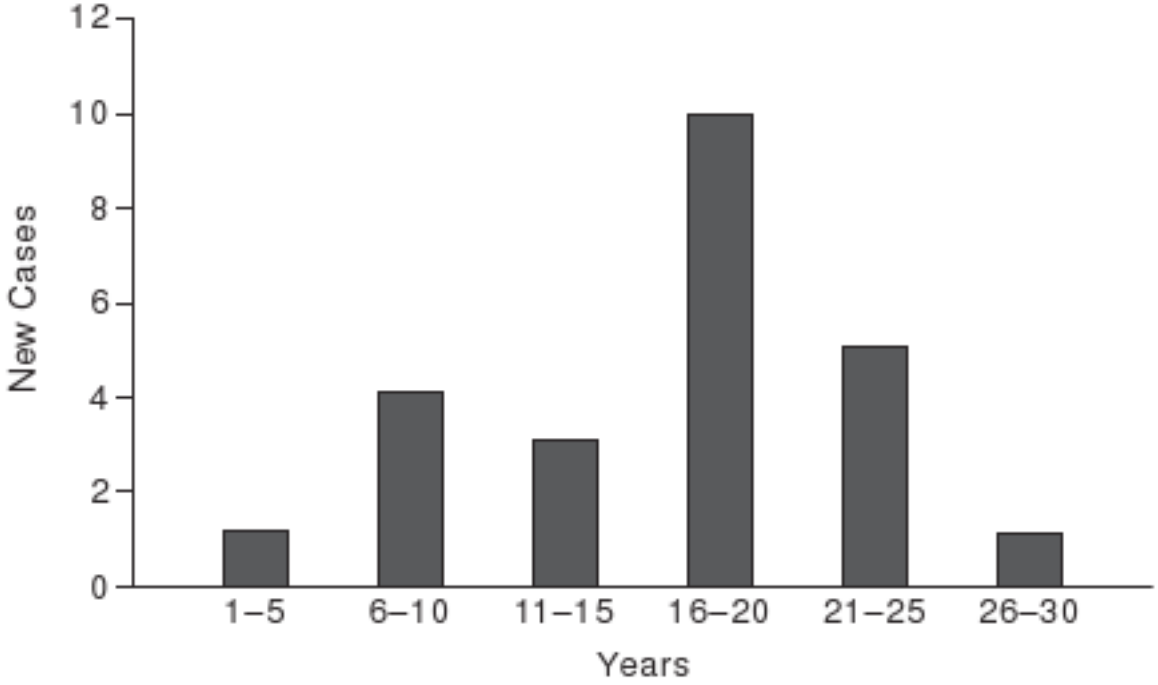
Bedford J J et coll. CJASN 2008

Li induced nephropathy

- Chronic renal failure in patients treated since 10-20 years
- Risk of CKD ~ 40 years



Presne et al, Kidney Int, 2003



Number of new cases of renal failure (114 patients)

Lepkifker et al. J Clin Psychiatry, 2004

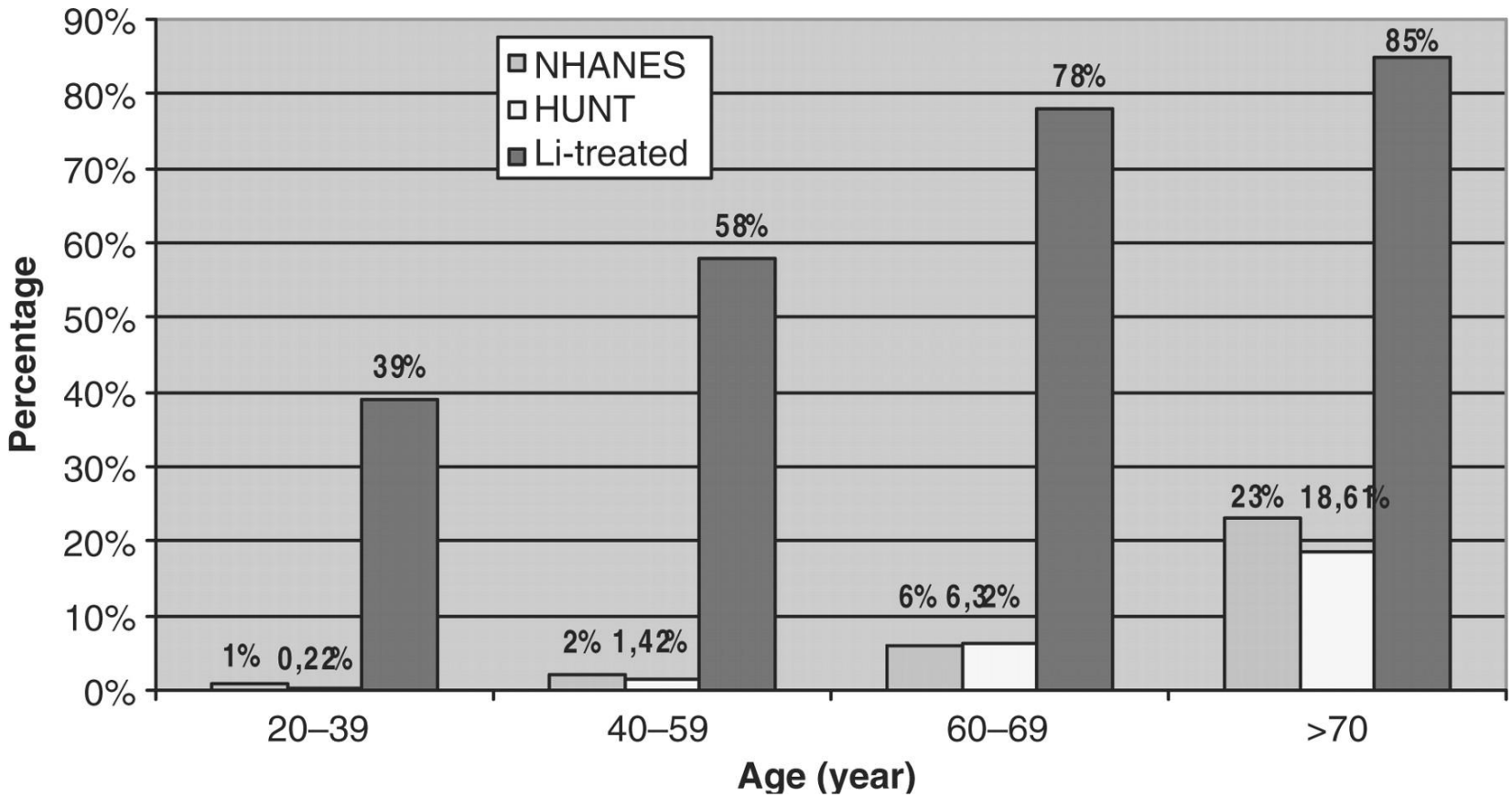
Prevalence

- After 6,5 years of treatment, 4% have creatininemia increase and after 19 years, 12%

  Bendz et al, NDT, 1994
- Patients treated 16,8 years: 21% creat>133µmol/l

  Lepkifker et al, J Clin Psychiatry, 2004
- Prevalence creatinine>150 µmol/l in Li treated population: 1.2% (ESRD excluded)

  Bendz et al, KI, 2010



GFR<60 in:

- 39% of patients between 20 and 39 years
- 85% if >70 years

Bassilios N et al. Nephrol. Dial. Transplant. 2008

Chronic renal failure in psychiatric population

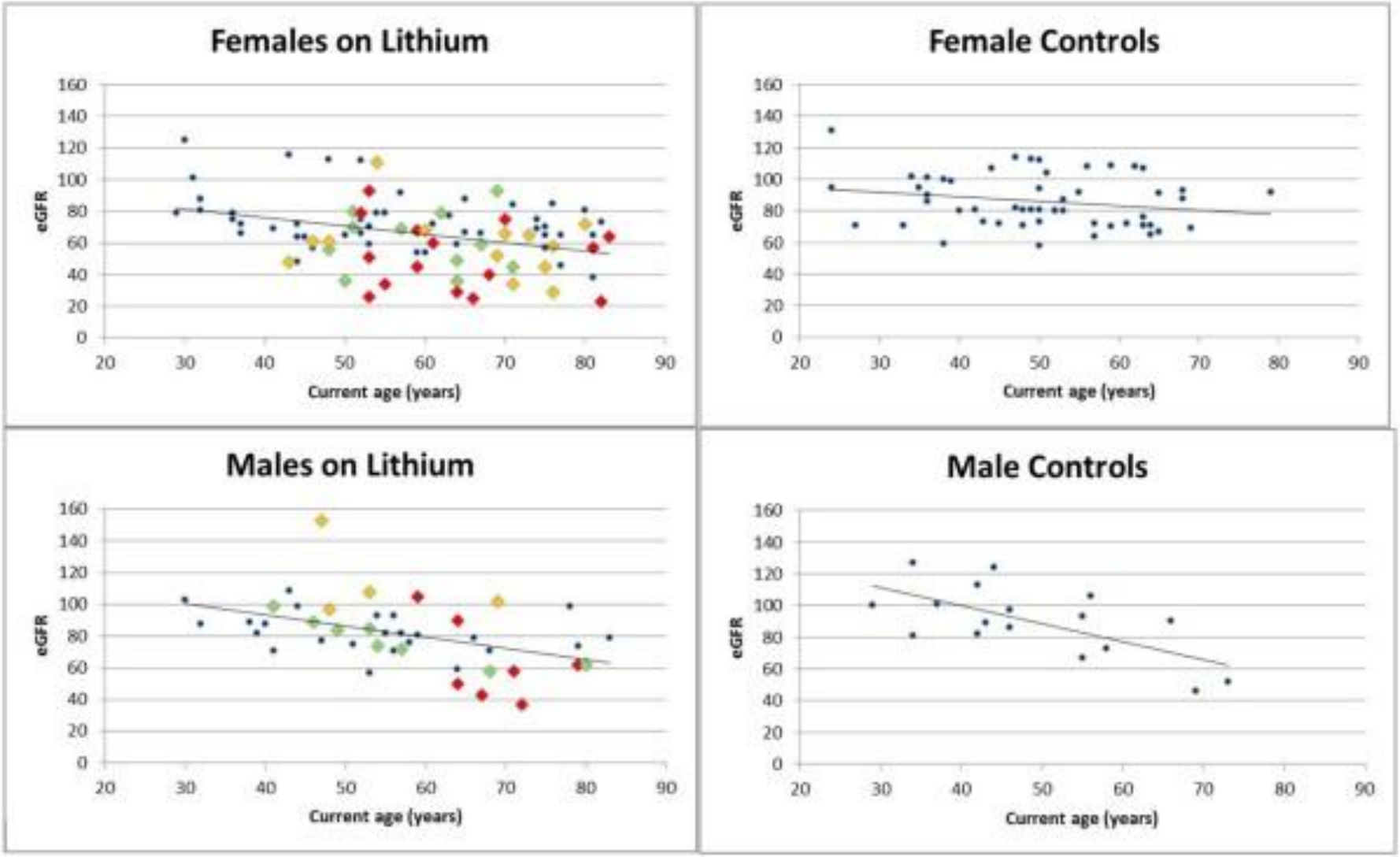
- In Great-Britain, lithium-treated patients with creatininemia dosage, compared to control group
- 422 patients
- 31% patients have no dosage of creatininemia (in 2 years)
- 17% cases with eGFR<60 vs 13% controls (OR 1.87, CI 1.10-3.8)

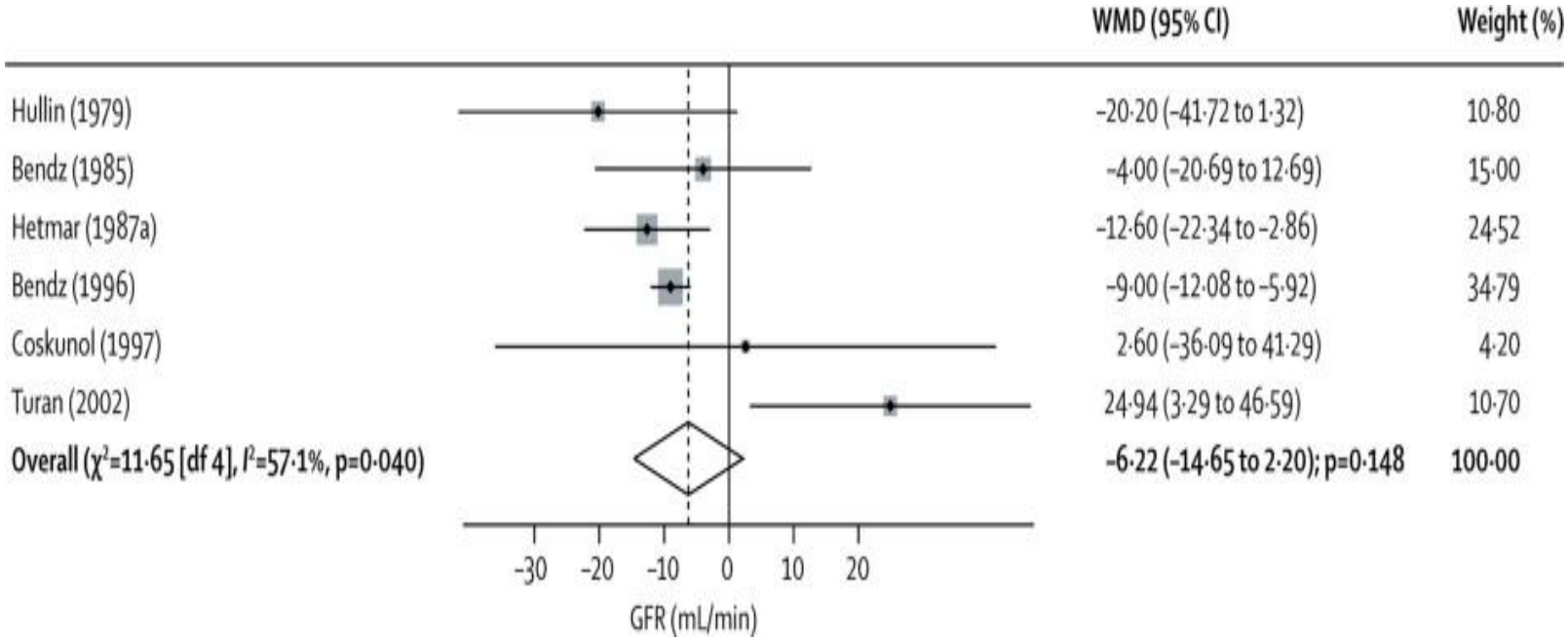
Minay J et al, Gen Hosp Psychiatry, 2013

Chronic renal failure in psychiatric population

- 139 Li-treated patients (1 to 33 years) compared to 70 patients treated with other psychotropic drugs
- eGFR <60 ml/min more frequent if Li-treated
  - 38/139 = 27.3% versus 4/70 = 5.7% (P = 0.0002)
  - But Li patients are older
- In multivariate analysis: lower eGFR associated with Li exposure duration, age and female

Bocchetta et al, BMC Med, 2013


Females on Lithium
Female Controls
Males on Lithium
Male Controls
eGFR
Current age (years)
0
20
40
60
80
100
120
140
160
20
30
40
50
60
70
80
90



Meta-analysis of case-control studies: comparison of GFR of Li-treated patients versus controls
eGFR reduced of 5 ml/min but for a one year period of observation!

McKnight et al, Lancet, 2012

End stage renal disease

- 18 patients with Li-induced ESRD among 3369 Li-treated patients:
  - prevalence among Li-treated patients : 0.53%
  - 6x general population

- Li-treated patients:
  - >46 years at ESRD
  - Mean duration of treatment 23 years
  - Lithium discontinuation 10 years before ESRD in 10 patients

Bendz et al, Kidney Int, 2010

End stage renal disease

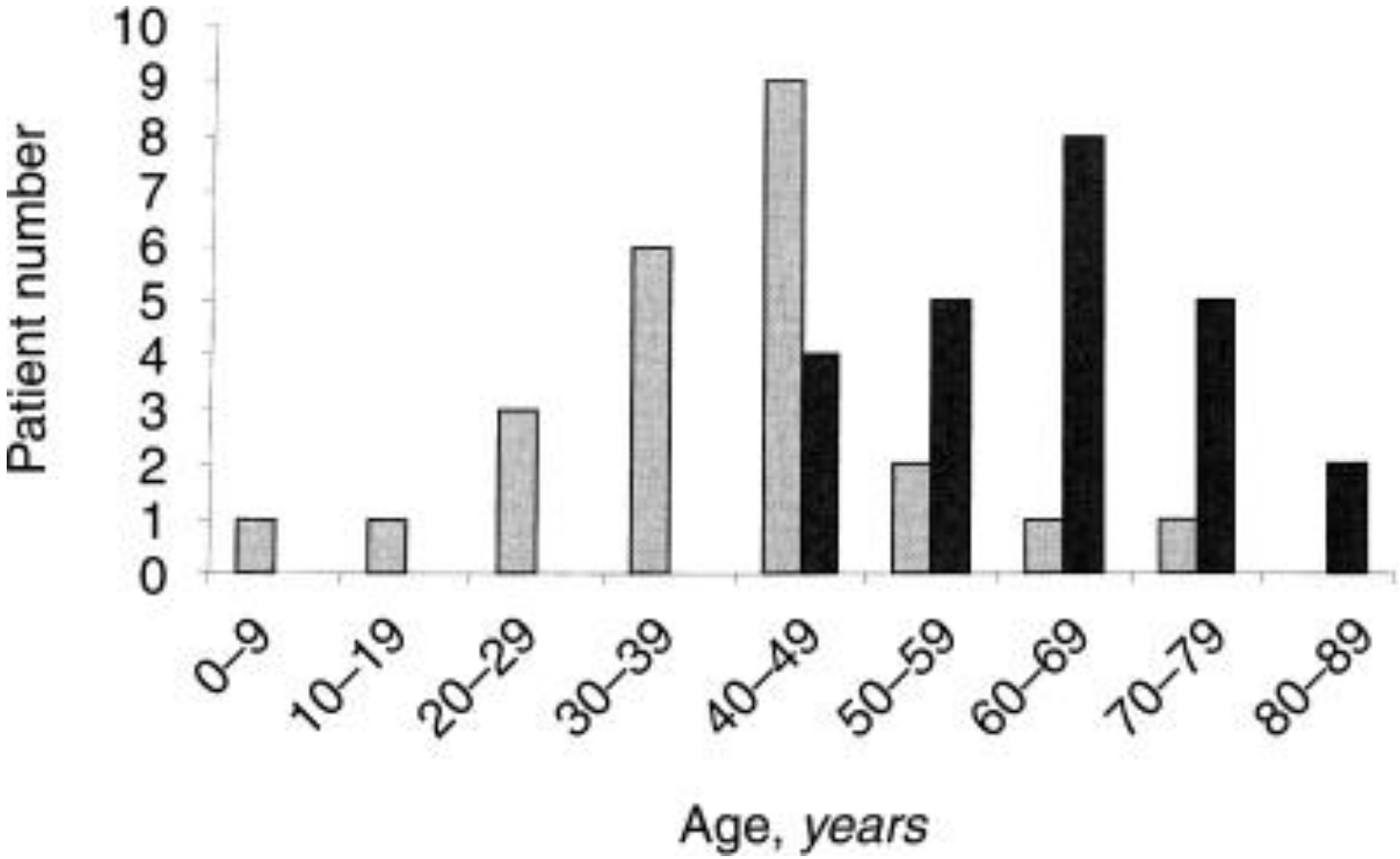
- 30 patients with Li-induced ESRD among 1995 Li patients (>55 years)
- Prevalence of ESRD among Li patients: 1.5%
  - If Li = only cause: 0.7%
  - Relative risk of ESRD in the Li-treated population compared to the general population x 8
- Among these 30 patients, Li is the only (14) or the main (10) cause of ESRD in 24:
  - Age at ESRD 66 years (46–82),
  - Duration of Li 27 years (12–39) including 22 >15 years
  - 15 have discontinuated, 8 years before

Aiff et al, Eur Neuropsychopharmacol, 2014

	All	ESRD	Others	p
N Patients	74	12	62	NS
Sex F/M	46/28	6/6	40/22	NS
Age Li	43	40	43	NS
Li duration	20	22	19	NS
Initial GFR	63	39	67	0,002
Final GFR	41	7	48	<0,0001
Follow-up	10	9	10	NS
Li discontinuation	25	6	19	NS

Same lithiemia!

Presne et al, Kidney Int, 2003



Age at lithium start and at dialysis: 20 years

Presne et al, Kidney Int, 2003

Prevalence in dialysis

- Among 130 dialysis centers
  - 24 cases of Li-induced ESRD among 10 726 patients (40% of the French dialysis patients)
  - prevalence 0.22%

Presne et al, Kidney Int, 2003

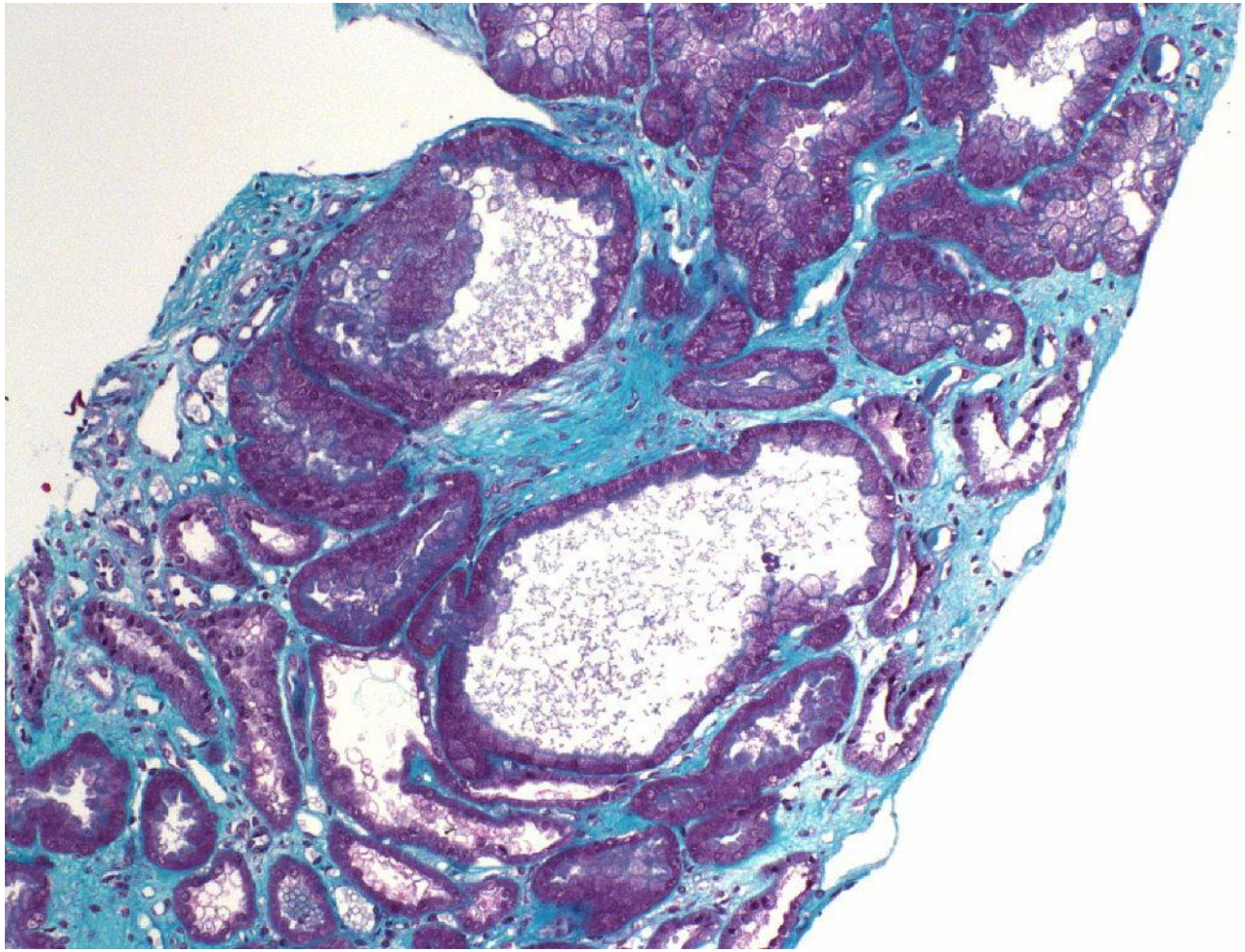
- Australian and New Zeland registries: 187/38316 between 1991 and 2011
  - Increase of the incidence rate of Li-induced ESRD: 0.14 cases/million inhabitant/year in 1992-1996 to 0.78 in 2007-2011
  - Proportion of incident patients : 0.19% in 1992–1996 to 0.70% in 2007–2011

Roxanas et al, Med J Aust. 2014

Histology

- Chronic tubulo-interstitial nephropathy
- Interstitial fibrosis may be present after 5 years of treatment

  Presne et al, KI, 2003
- Glomerulosclerosis lesions may be associated
- Renal cysts



Chronic tubulointerstitial nephropathy with diffuse interstitial fibrosis, tubular atrophy but normal glomeruli.
Cysts and tubular dilatations.

Photo: Dr M Rabant

Clinical presentation and risk factors

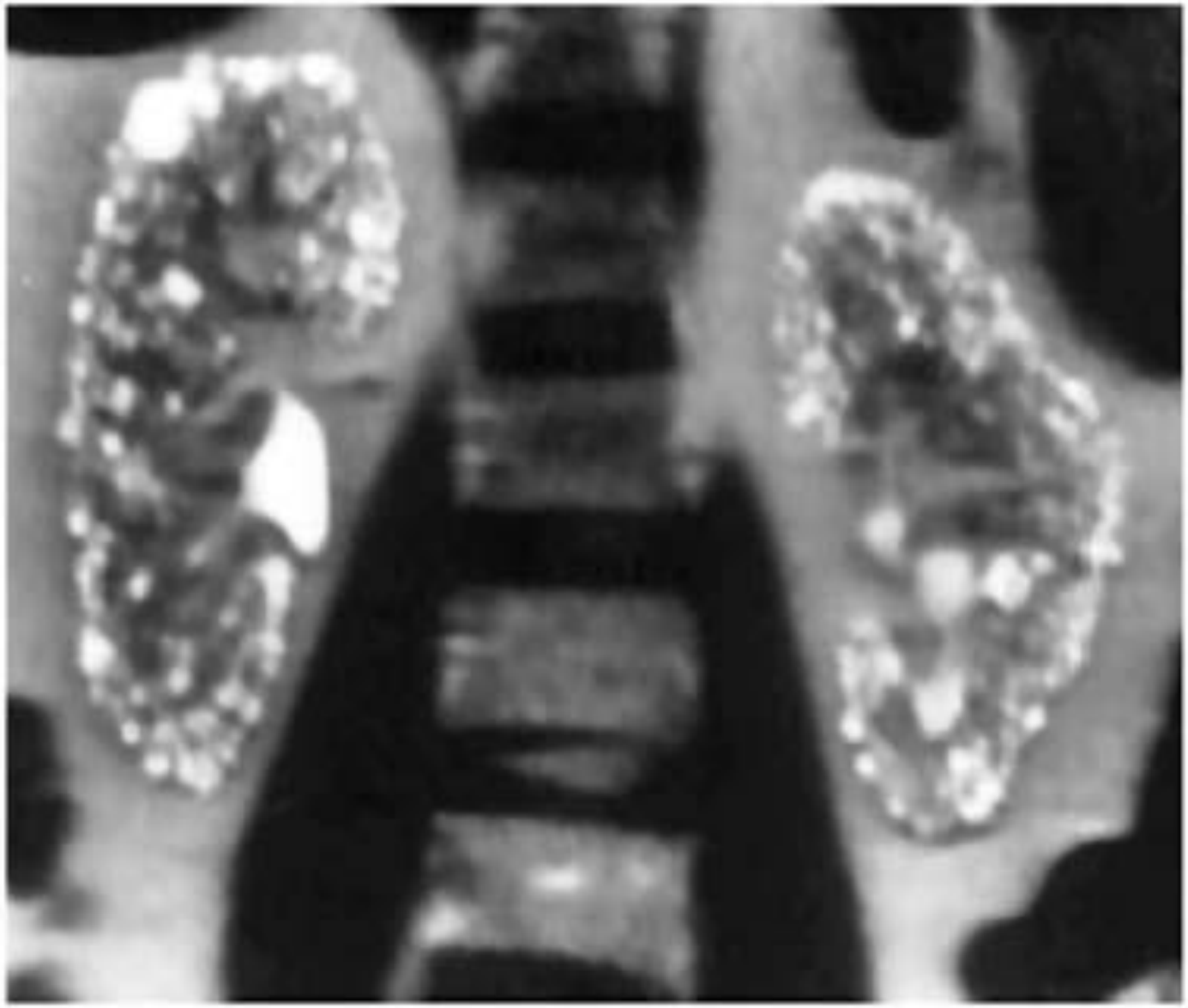
- Asymptomatic
- No hypertension
- No proteinuria
- Very rare nephrotic syndromes (26 cases)

  Markowitz, JASN, 2000
- Urinary concentration defect often associated
- Risk factor: Li exposition duration
- Co-morbidities?, Li intoxication episodes?, once day vs twice day dosing?

Diagnosis

- Li treatment more than 10 years
- Chronic tubulointerstitial nephropathy
- No other etiology
- Slow decrease of eGFR 2.2 ml/min/year

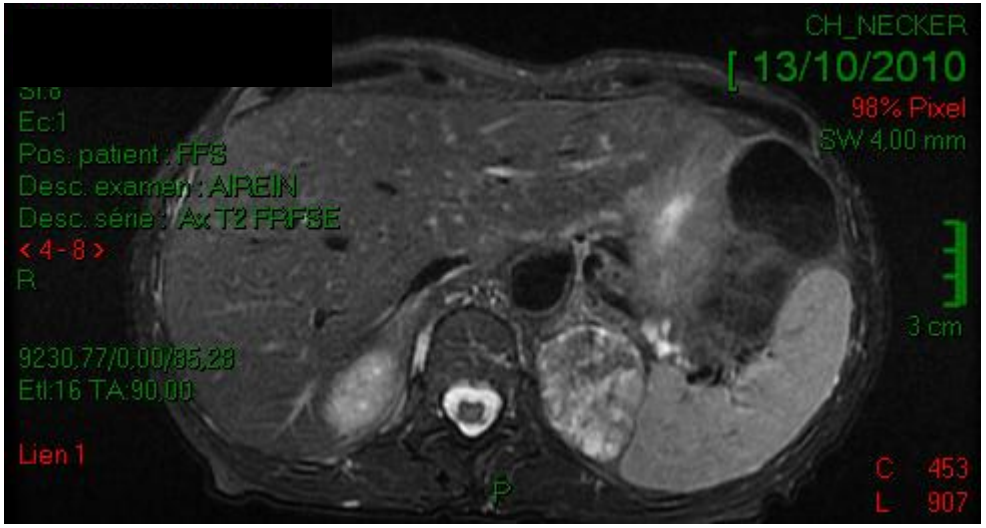
  Presne, KI, 2003
- Cysts (ultrasound, RMN)
  - Cortical and medullar microcysts
  - Normal size kidneys



Farres et al,
Radiology, 2003

Renal tumors and lithium

A



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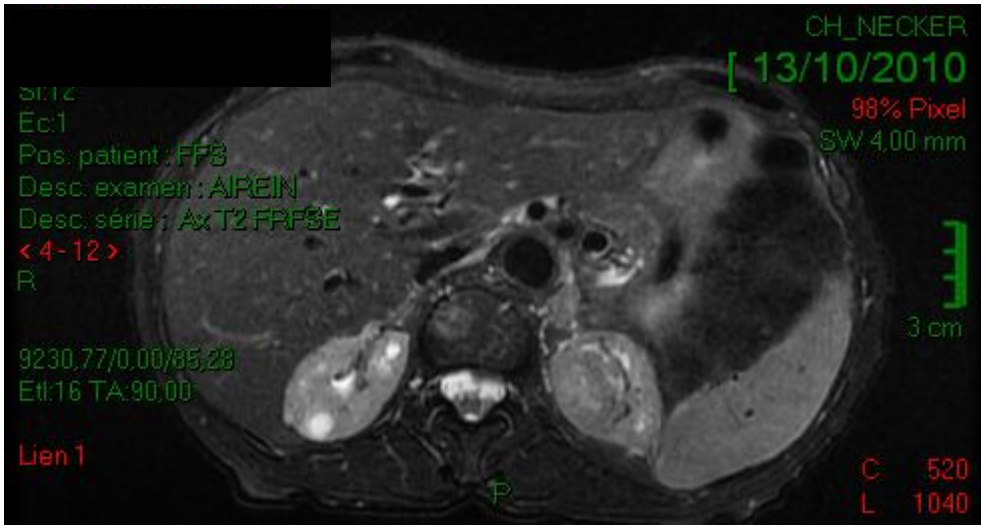


Renal RMN in a patient treated with Li during 31 years but stopped since 5 years at the time of the investigations.

A. Lesion of the left kidney : histology= clear cell renal cell carcinoma.

B. Renal cysts in the same patient.

Renal tumors and lithium

- Cohort of 170 Li-treated patients
  - 14 cases of renal tumors
  - 7 (4,1%) malignant tumors
  - 7 (4,1%) benign tumors
- Mean duration of Li exposure at diagnosis: 21,5±10,3 years
- Comparison to 340 age, sex and eGFR matched control patients: percentage of renal tumors, particularly cancers and oncocytomas increased in Li-treated patients

Zaidan et al, Kidney Int, in press

Renal tumors and lithium

- Comparison to the French general population : Standardized Incidence Ratio of renal cancer significantly increased in Li-treated patients:
  - 7,51 (95%IC[1,51-21,95]) and 13,69 (95%IC[3,68-35,06]) in men and women, respectively.
- Increased risk of renal timors in Li-treated patients.

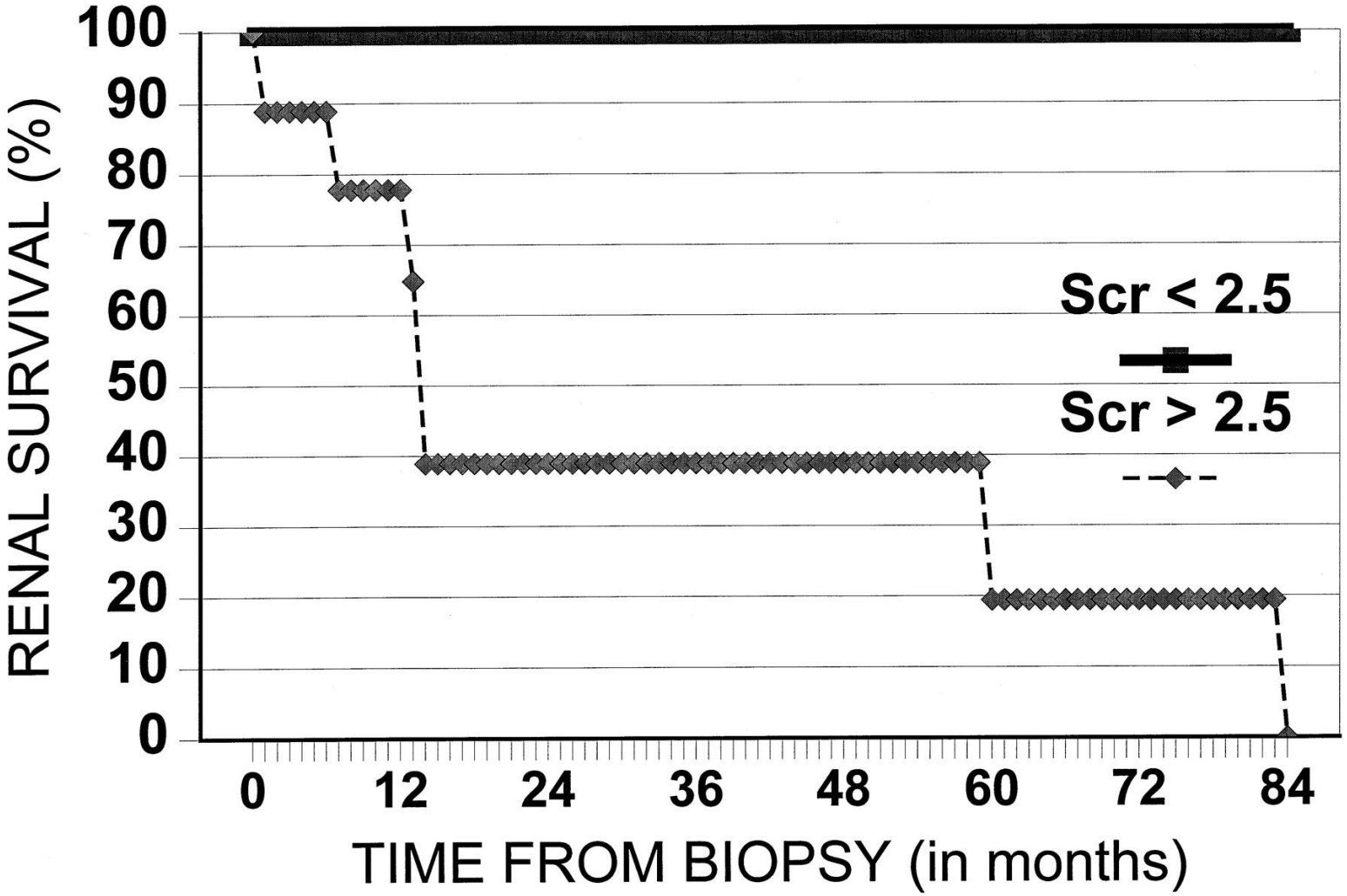
Pathophysiology hypothesis

- Accumulation of Li in distal nephron and collecting duct cells via ENaC
- Inhibitory phosphorylation of GSK3β and activation Wnt/β-catenin signaling
- Interference with several signaling pathways which regulate tubular cells proliferation, differentiation and apoptosis.
- Onset of tubular dilatations, cysts, and tumoral lesions.

Treatment discontinuation?

- First line treatment, risk of suicide and relapse
- Discussion between patient, nephrologist, psychiatrist
- Probability of renal improvement only if moderate renal failure:
  - eGFR>40 ml/min
  - If not, risk of decrease of eGFR despite Li discontinution

Presne et al, Kidney Int, 2003



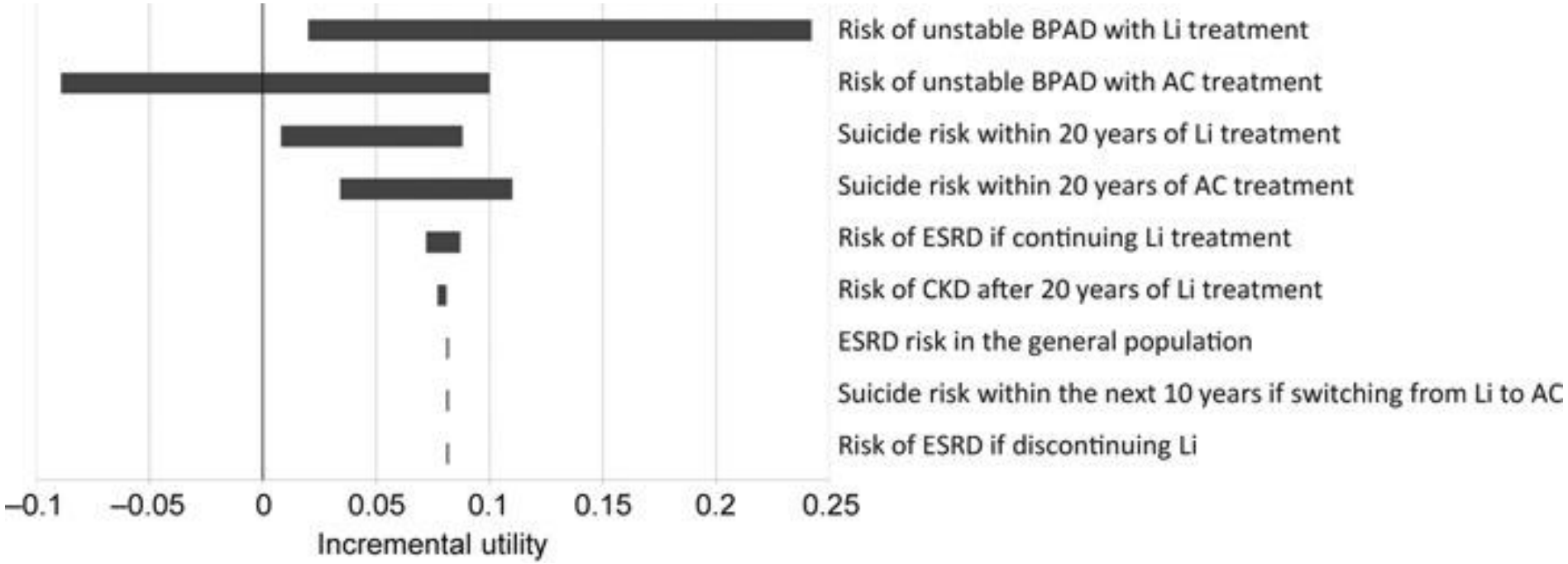
The only predictive factor of ESRD is initial creatininemia

MARKOWITZ G S et al. JASN, 2000

Treatment discontinuation?

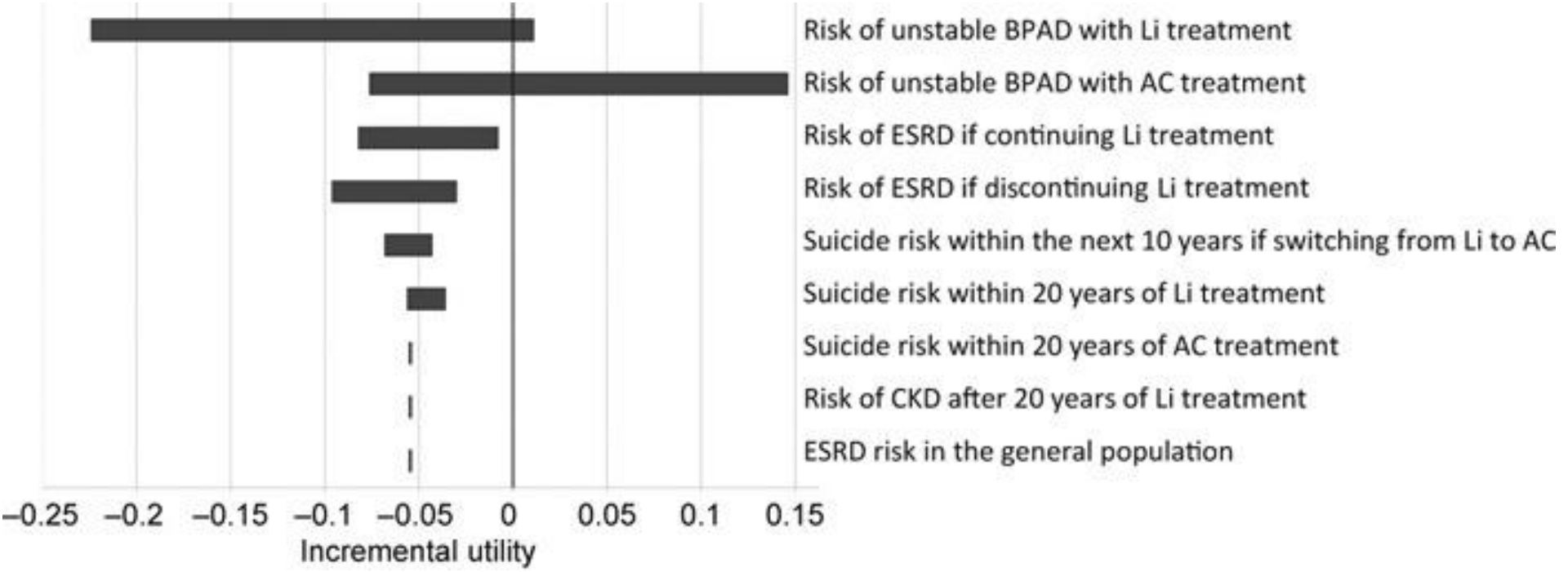
- Mortality
  - 1411 patients in a psychiatry department
  - Mortality due to renal failure 2/201
  - Suicide after Li discontinuation 42/201

    Boccheta, J Clin Psychopharmacol, 2007



At the initiation of the treatment, the risk of renal failure is unimportant in the decision to start treatment

Werneke et al, Acta Psychiatr Scand, 2012



After 20 years of treatment, the psychiatric risk is the most important variable of the model

Li remain the treatment of choice in 97 % of cases

Werneke et al, Acta Psychiatr Scand, 2012

Estimated GFR (MDRD or CKD-EPI)

>60 mL/min	60>eGFR>40 mL/min	40>eGFR>25 mL/min	< 25 mL/min
-Creatinine, calcemia/ 6 months or if any intercurrent event, dehydatation	-Discuss therapeutic alternatives, especially in young patients -Nephrologic check-up,renal ultrasound -Creatininemia, calcemia/6 months -Lithiemia < 0.4-0.6 mmol/l -Mood follow-up	-eGFR may continue to decrease even if lithium is stopped - Nephrologic check-up, renal ultrasound -Creatininemia, calcemia/4 months -Lithiemia<0.4- 0.6 mmol/l -Mood follow-up	-The interruption of lithium is not very useful since renal lesions are irreversible -Nephrologic follow-up -Creatininemia, calcemia /3 months -Lithiemia <0.4-0.6 mmol/l -Mood follow-up

Conclusion

- Nephrogenic diabetes insipidus
  - in 40-50% of patients
  - may be irreversible, especially if >15 years
- Chronic tubulointerstitial nephropathy
  - 1,2% of Li-treated patients
  - But risk of ESRD
  - Risk correlated to the duration of exposition