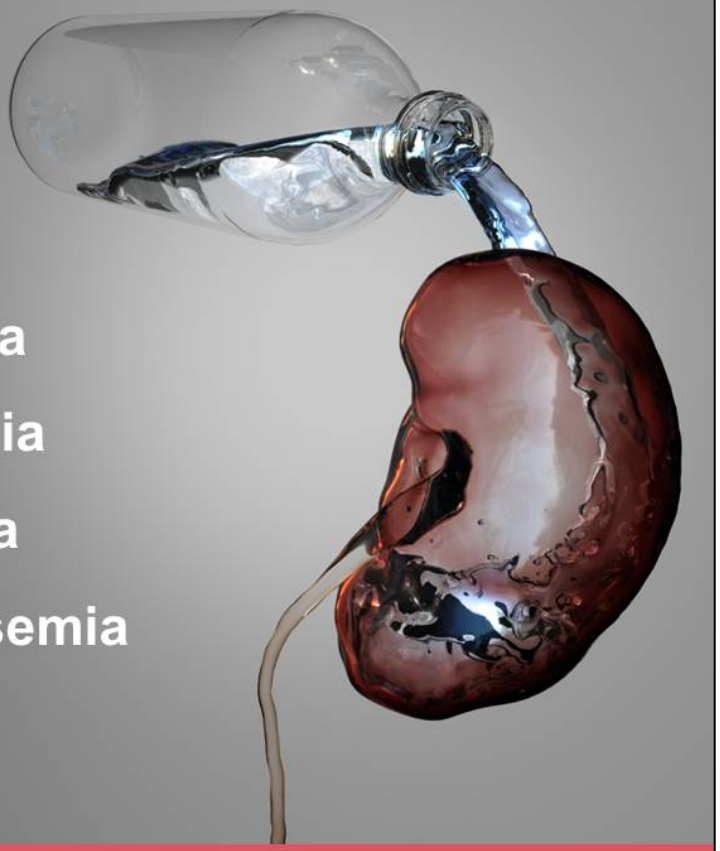
Nephro Update Europe 2019
20 – 21 September, Prague

Special Topic: Electrolyte Disorders

Ewout Hoorn, The Netherlands

Subtopics



- Hyponatremia
- Hypernatremia
- Hyperkalemia
- Hypomagnesemia

Take-Home Messages

Mechanism of disease

Diagnosis

Prognosis

Treatment

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Hyponatremia

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State of the Art: Hyponatremia

- Common electrolyte disorder – usually caused by disturbance in AVP-AQP2 axis
- European Hyponatremia Guideline (2014)
- Different treatment principle for acute/symptomatic vs. chronic hyponatremia
- Hyponatremia in CKD or dialysis?
- Water handling after kidney transplantation?

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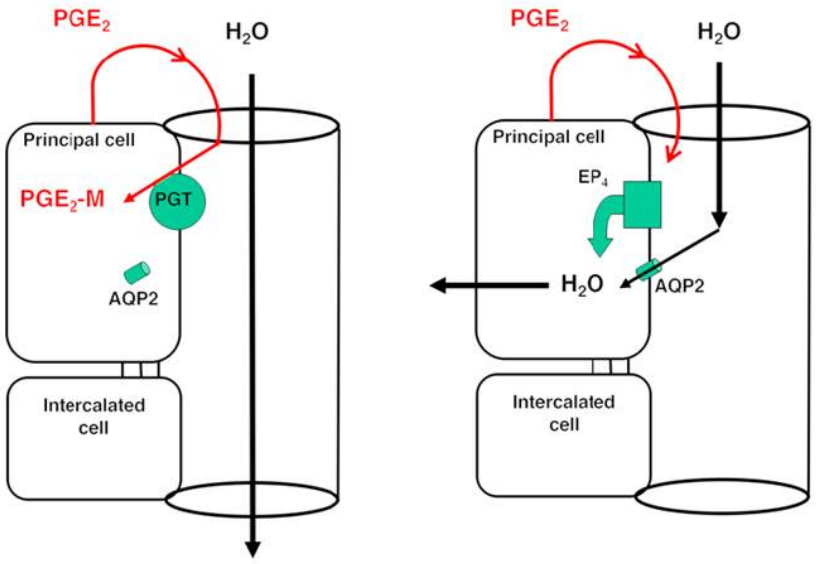
Mechanism of disease: thiazide-induced hyponatremia



Ware JS *et al.*, J Clin Invest 2017; 127: 3367-3374

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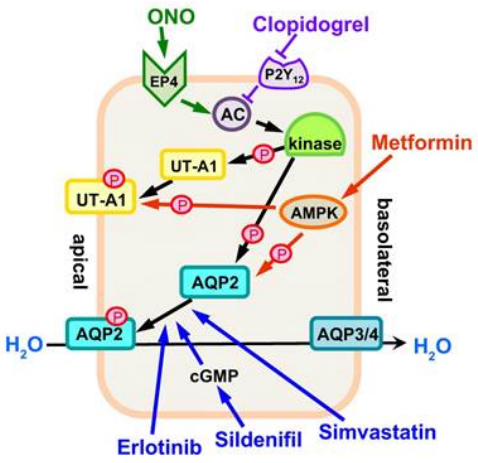
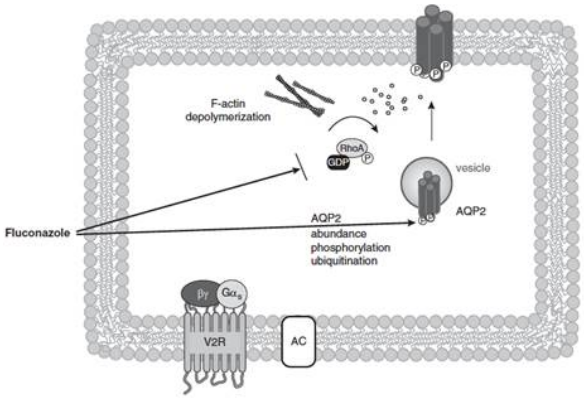
Other drugs activating aquaporin-2 independent of vasopressin





Sands JM *et al.*, Am J Physiol Renal Physiol 2016; 311: F1149-1152

Vukicevic T *et al.*, J Am Soc Nephrol 2019; 30: 795-810

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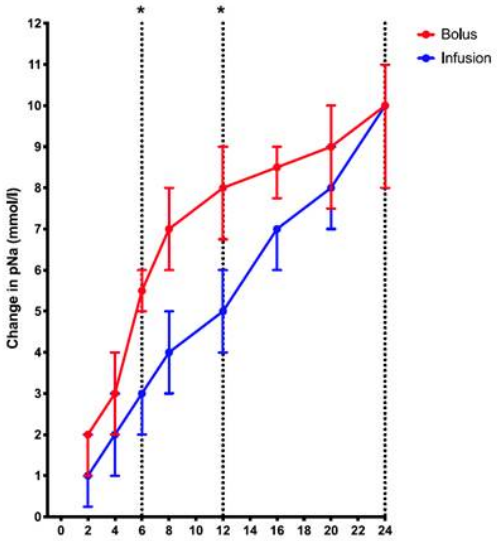
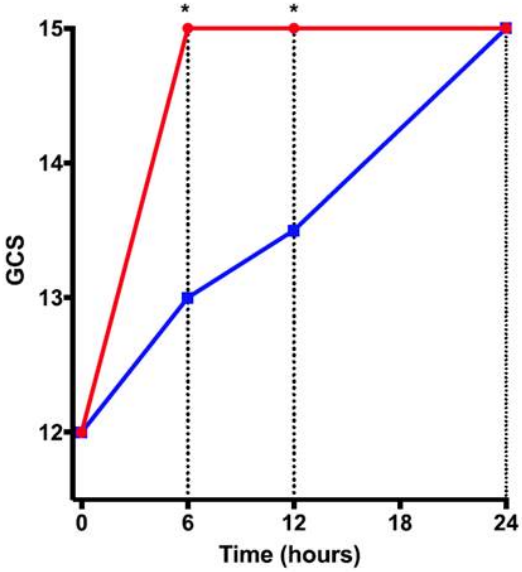
Treatment of acute hyponatremia: continuous *vs.* bolus hypertonic saline





Garrahy A *et al.*
J Clin Endocrinol Metab 2019; 104: 3595-3602

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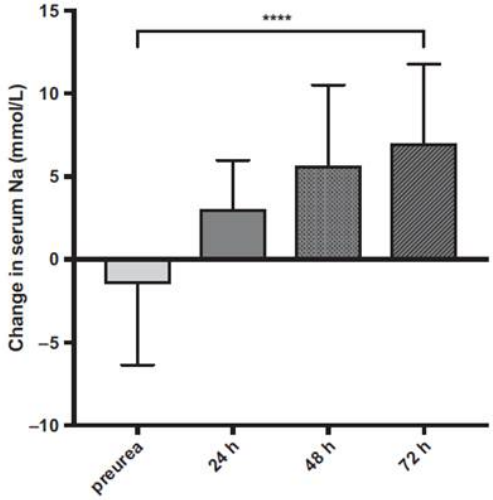
Urea for chronic hyponatremia in the syndrome of inappropriate antidiuresis



Lockett J *et al.*, Clin Endocrinol (Oxf) 2019; 90: 630-6

Urea for the Treatment of Hyponatremia

Helbert Rondon-Berrios,[1] Srijan Tandukar,[1] Maria K. Mor,[2,3] Evan C. Ray,[1] Filitsa H. Bender,[1] Thomas R. Kleyman,[1,4,5] and Steven D. Weisbord[1,3,6]

Clin J Am Soc Nephrol 2018; 13: 1627-32

Urea in cancer patients with chronic SIAD-induced hyponatremia: Old drug, new evidence

Alice Nervo[1] | Valentina D'Angelo[1] | Daniela Rosso[1] | Eleonora Castellana[2] Francesco Cattel[2] | Emanuela Arvat[1] | Emidio Grossi[1]

Clin Endocrinol (Oxf) 2019; 90: 842-8

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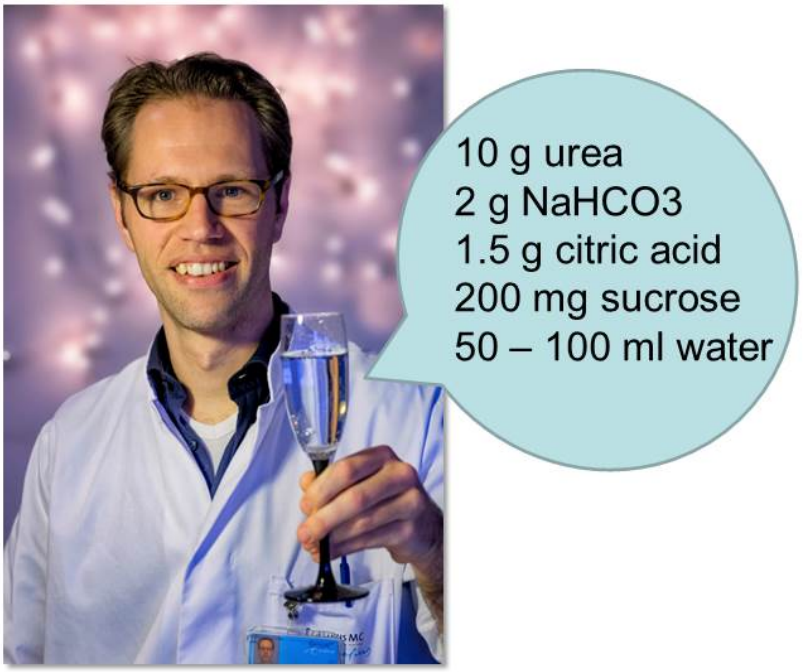
Urea: "Brussels champagne"



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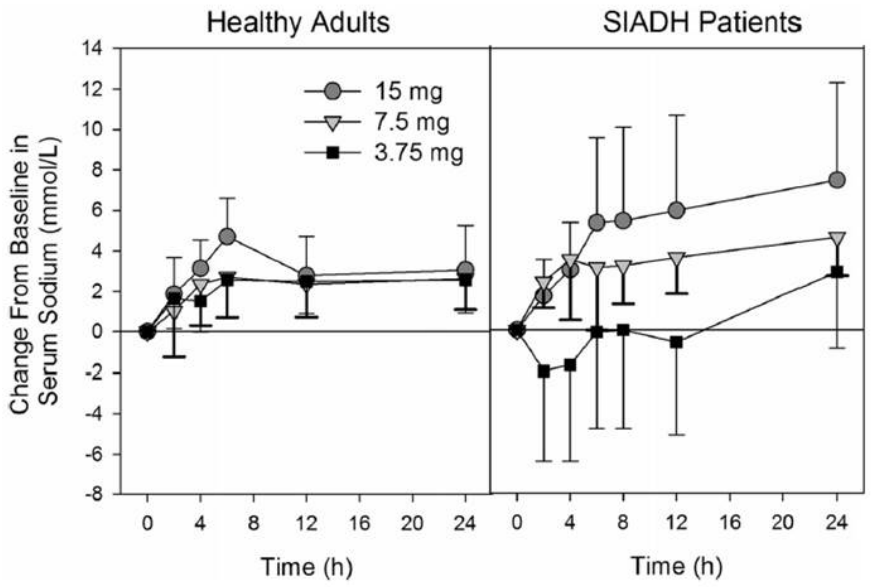
Pharmacodynamics of tolvaptan



Shoaf SE *et al.*, Eur J Pharmacol 2017; 73: 1399-1408

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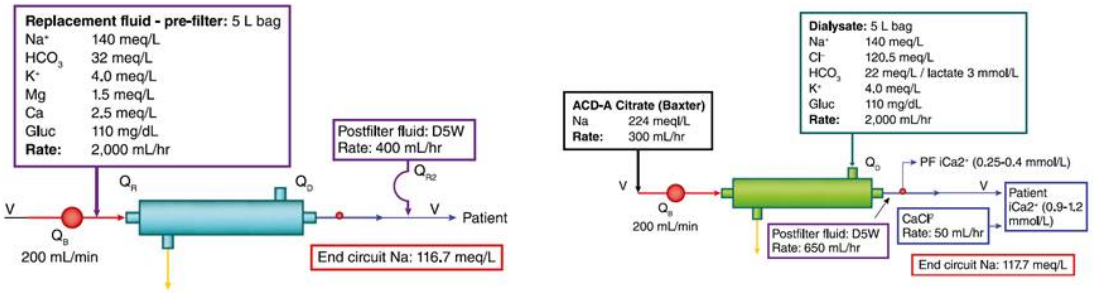
Management of severe hyponatremia with continuous renal replacement therapies



Rosner MH *et al.*, Clin J Am Soc Nephrol 2018; 13: 787-789

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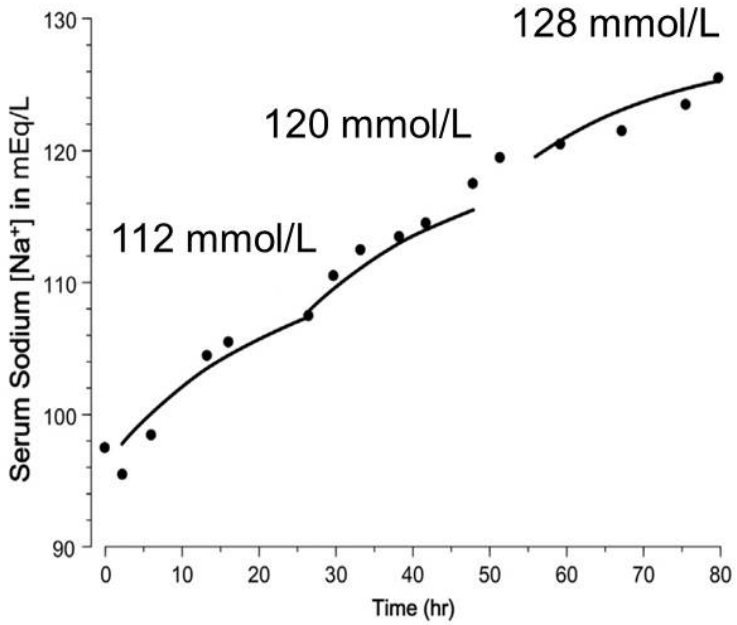
Low-sodium replacement fluid



Yessayan L *et al.*, Am J Kidney Dis 2014; 64: 305-310

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Severe Hyponatremia Overcorrection Risk (SHOR) score

Increased risk	Reduced risk
• Level of consciousness +2	• Volume overload –5
• Vomiting +2	• Chest tumor –5
• Severe hypokalemia +1	• Patient age –1/decade
• Hypotonic urine +4	
• Initial Na^+ < 110 mmol/l +4	

Woodfine JD *et al.*, Clin J Am Soc Nephrol 2019; 14: 975-982

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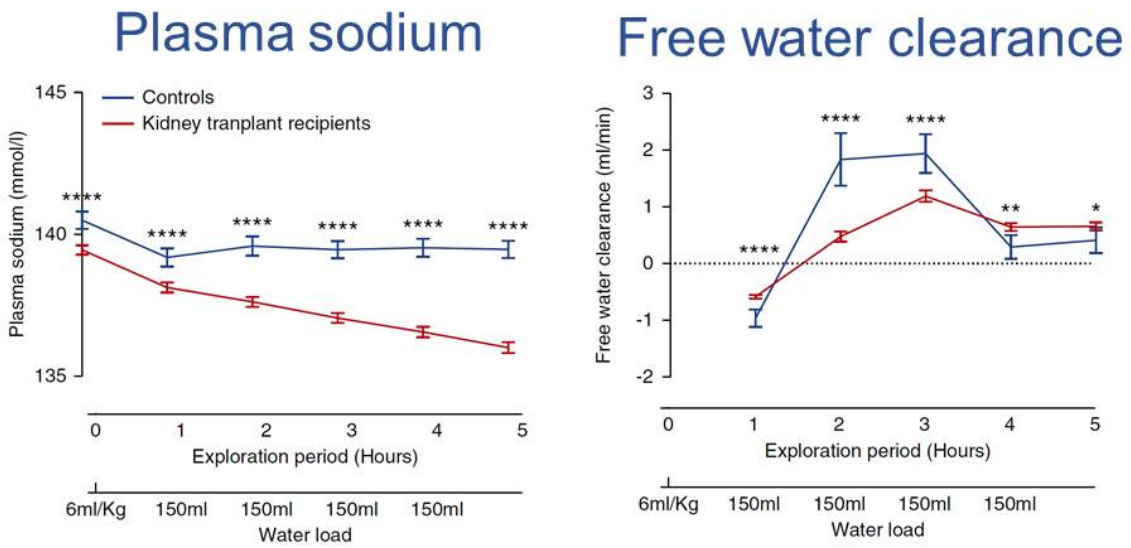
Osmoregulation performance and kidney transplant outcome



Mazloum M *et al.*, J Am Soc Nephrol 2019; 30: 1282-1293

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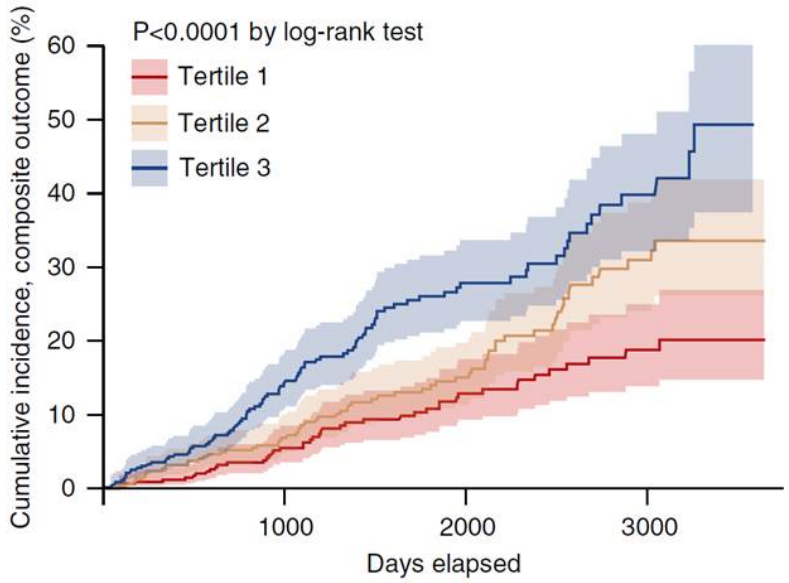
Steeper plasma sodium slopes associate with kidney transplant outcomes



Mazloum M *et al.*, J Am Soc Nephrol 2019; 30: 1282-1293

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Take-Home Messages: Hyponatremia

Mechanism of disease	Thiazide-induced hyponatremia
Diagnosis	
Prognosis	• Rapid correction • Kidney transplantation
Treatment	3% NaCl, urea, CRRT

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Hypernatremia

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State of the Art: Hypernatremia

- Hypernatremia is caused by unreplaced water loss, hypotonic polyuria, or an osmotic diuresis
- Complications rapid correction: less clear than for hyponatremia
- Hypotonic polyuria: diabetes insipidus or primary polydipsia
- The diagnostic test for hypotonic polyuria is the direct or indirect water deprivation test

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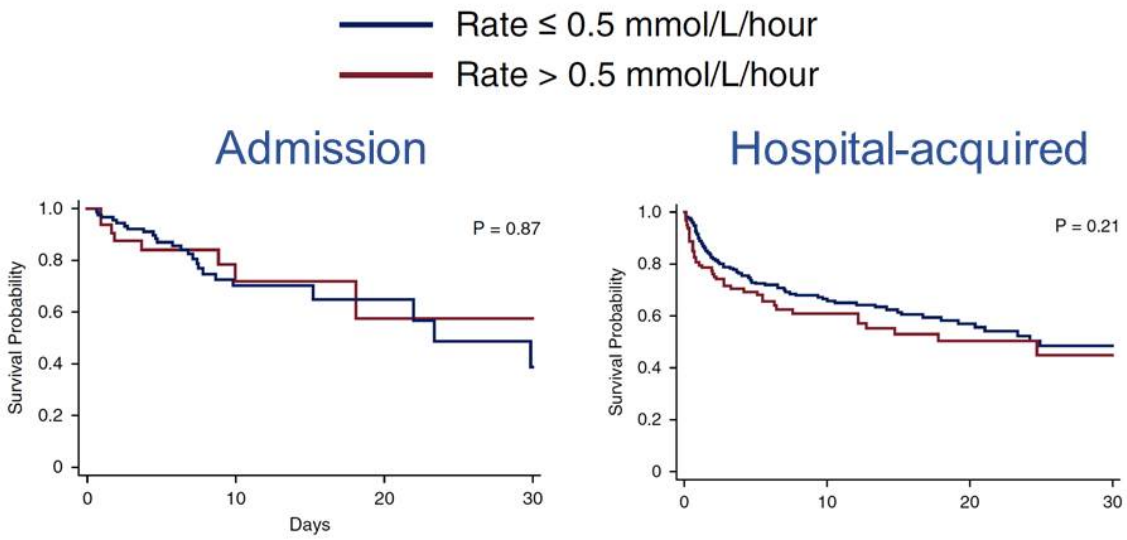
No difference in 30-day mortality of rapid *vs.* slow correction of hypernatremia



Chauhan K *et al.*, Clin J Am Soc Nephrol 2019; 14: 656-663

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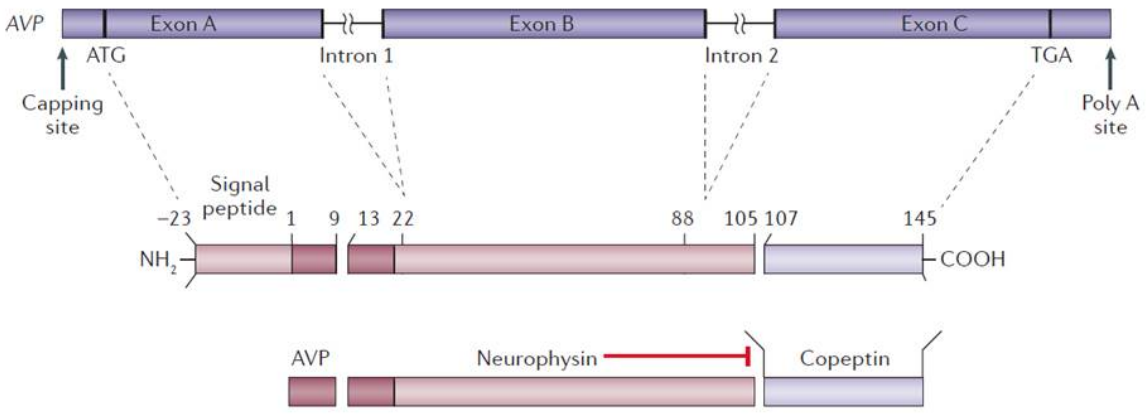
Copeptin is the C-terminal part of the pre-pro-hormone of arginine vasopressin



Christ-Crain *et al.*, Nat Rev Nephrol 2016; 12: 168-76

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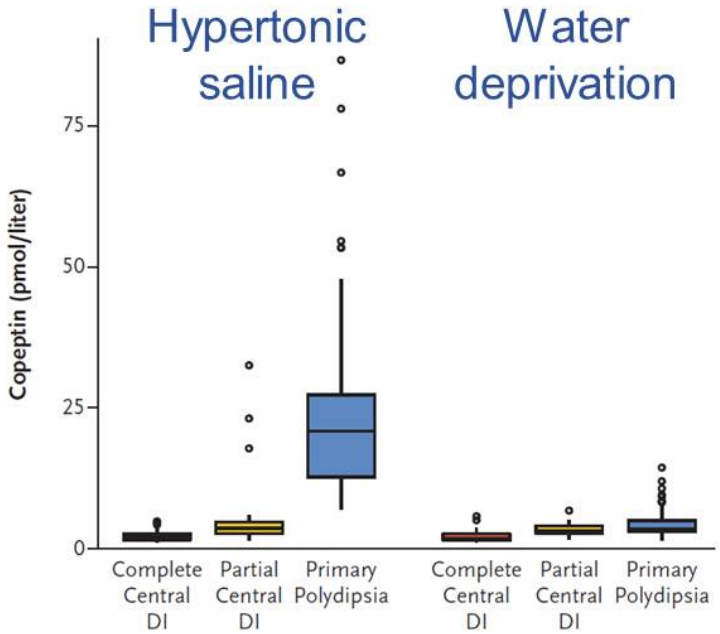
Copeptin response to hypertonic saline



Fenske W *et al.*, N Engl J Med 2018; 379: 428-439

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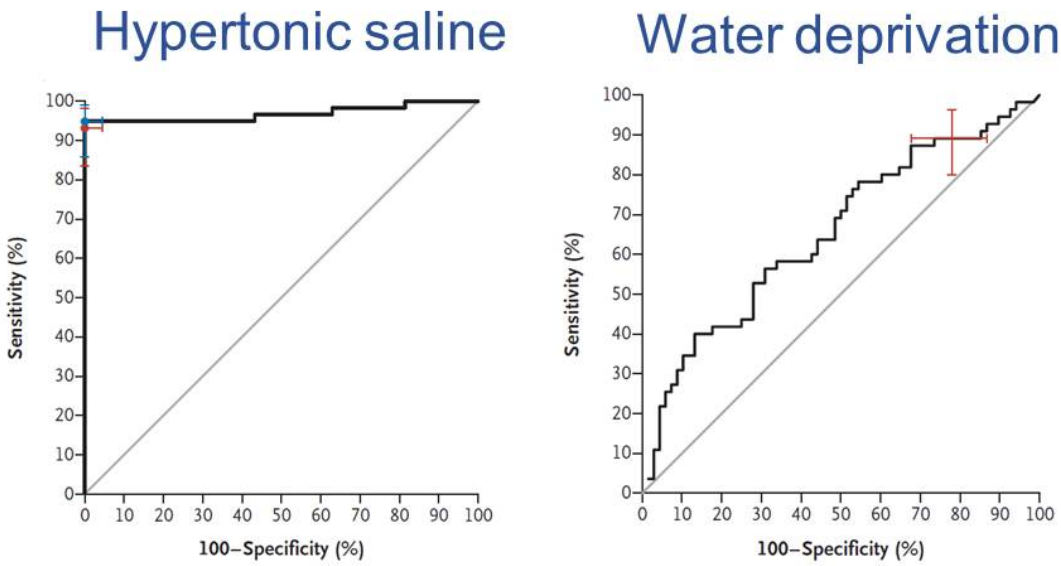
The hypertonic saline test outperforms the indirect water deprivation test



Fenske W *et al.*, N Engl J Med 2018; 379: 428-439

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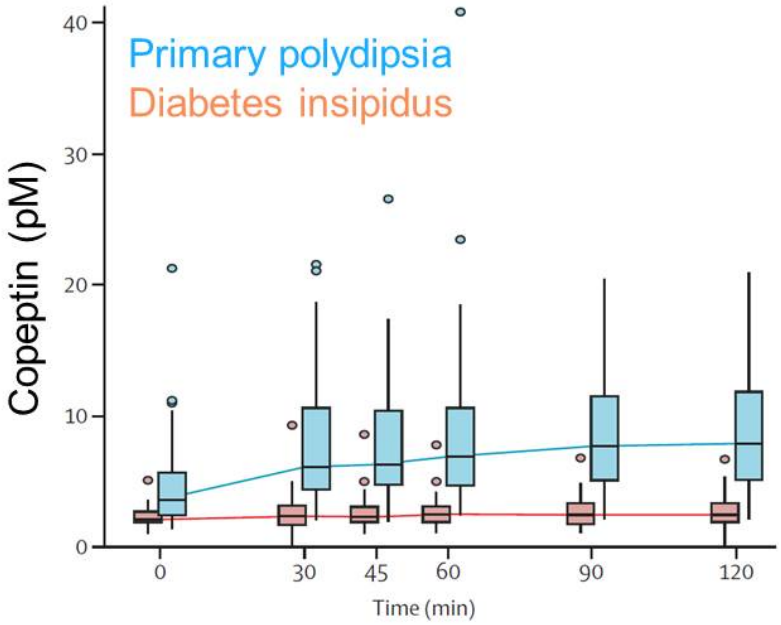
Copeptin response to arginine



Winzeler B *et al.*, Lancet 2019; 394: 587-595

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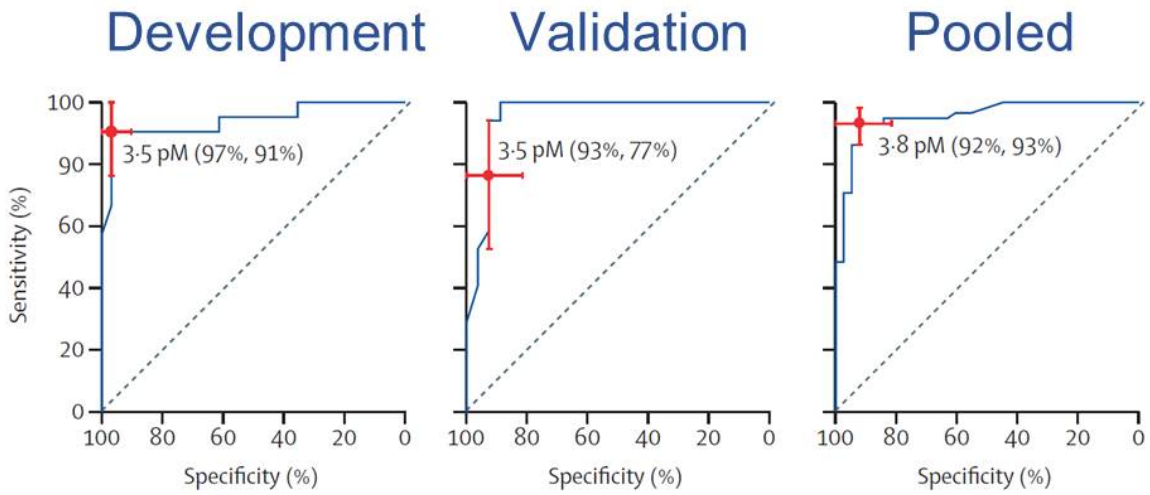
Diagnostic performance of arginine



Winzeler B *et al.*, Lancet 2019; epub 11 July

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Take-Home Messages: Hypernatremia

Mechanism of disease

Diagnosis → Hypertonic saline, arginine, copeptin

Prognosis → Rapid *vs.* slow correction

Treatment

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Hyperkalemia

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State of the Art: Hyperkalemia

- Hyperkalemia is common in CKD and associated with poor outcomes
- "Old" binders (sodium and calcium polystyrene sulfonate) *vs.* "new" binders (patiromer, zirconium siclocilicate)
- Risks of hyperkalemia *vs.* low K^+ intake?

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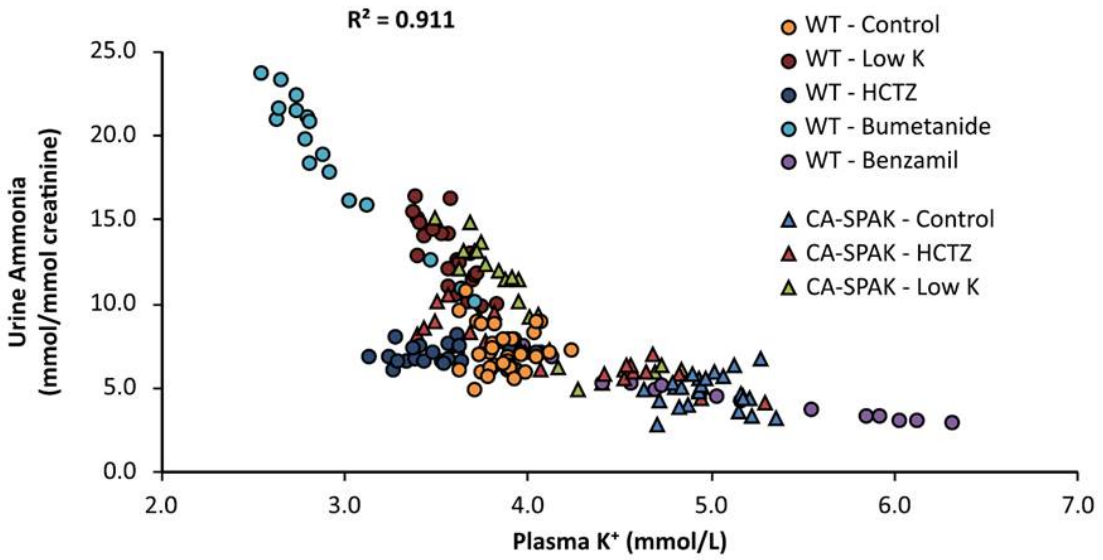
Mechanism of disease: hyperkalemia-induced acidosis



Harris AN *et al.*, J Am Soc Nephrol 2018; 29: 1411-1425

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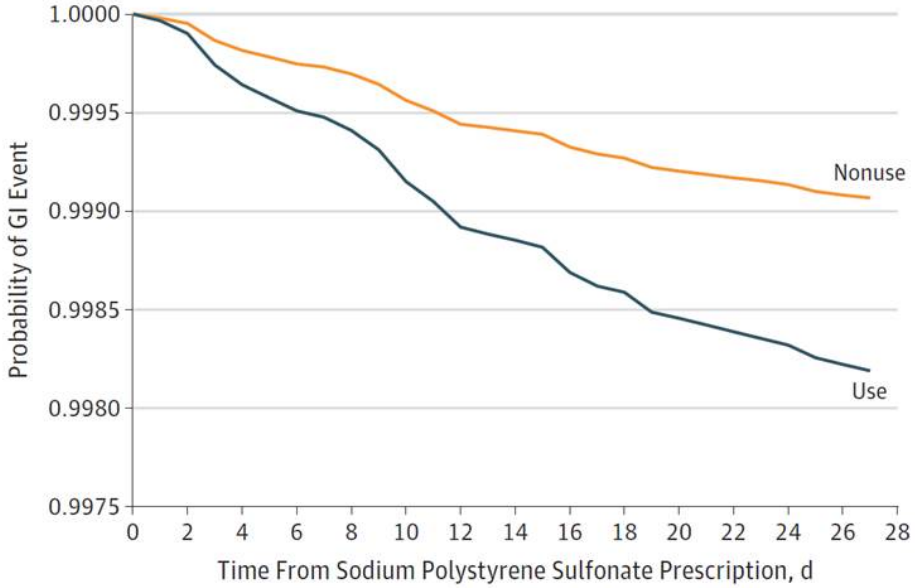
Risk of gastrointestinal injury with sodium polystyrene sulfonate



Noel JA *et al.*, JAMA Intern Med 2019; epub 10 June

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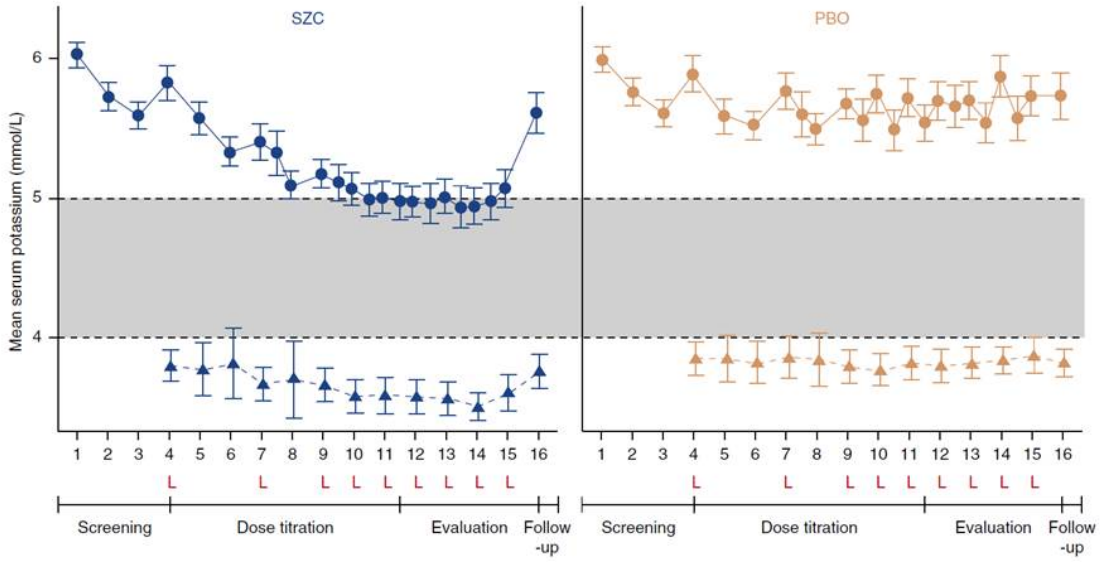
Sodium zirconium cyclosilicate for predialysis hyperkalemia



Fishbane S *et al.*, J Am Soc Nephrol 2019; epub 14 June

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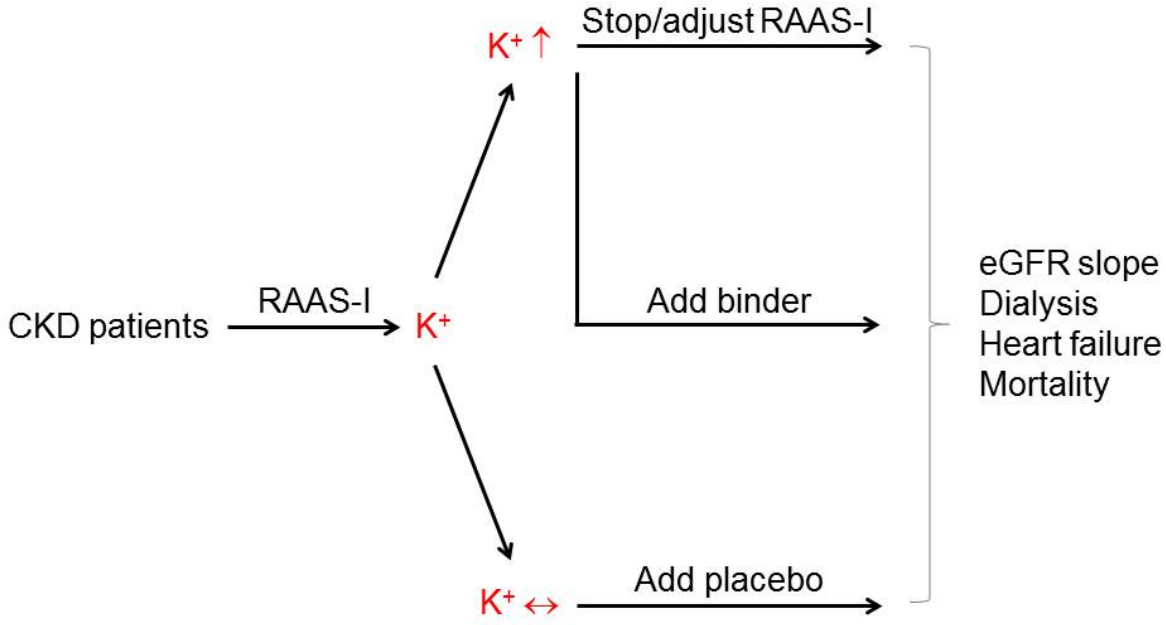
Is potassium just a surrogate marker?



with thanks to Felix Knauf

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K^+ in CKD…

To bind or to bond?

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Cohort studies on the association between urinary K^+ and renal outcomes

1. ONTARGET & TRANSCEND (Smith *et al.*, Kidney Int 2014)
2. CRIC (He *et al.*, J Am Soc Nephrol 2015)
3. Shiga (Araki *et al.*, Clin J Am Soc Nephrol 2015)
4. PREVEND (Kannegieter *et al.*, Kidney Int 2016)
5. MDRD (Leonberg-Yoo *et al.*, Am J Kidney Dis 2017)
6. KNOW-CKD (Kim *et al.*, Clin J Am Soc Nephrol 2019)
7. Amsterdam (Van Noordenne *et al.*, under review)

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RCT with K^+ supplementation in CKD

Inclusion	Run-in phase	Randomized phase	Endpoints
eGFR 15-45 ml/min	KCl	Placebo	ΔeGFR
Hypertension		KCl	ABPM
Progressive CKD		KCitrate	Proteinuria

Gritter M *et al.*, Nephron 2018; 140: 48-57
ClinicalTrial.gov NCT03253172

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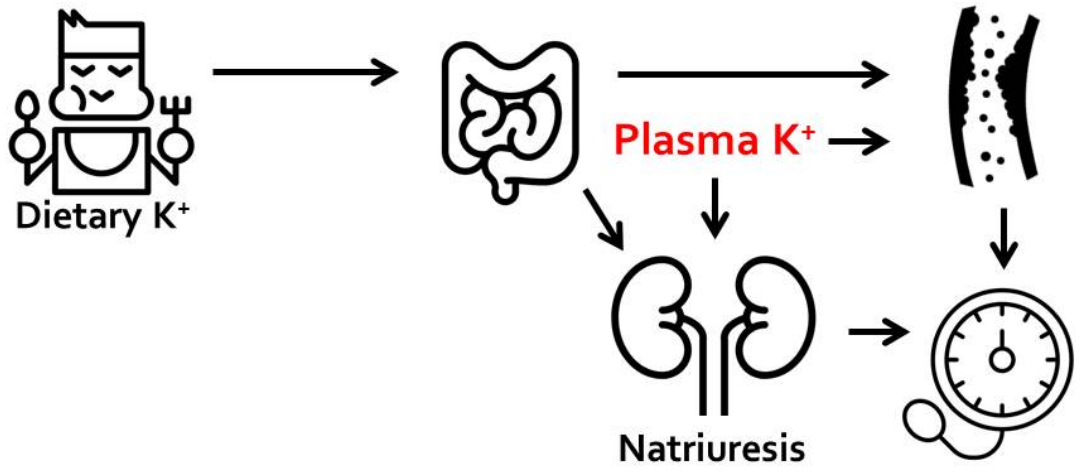
Possible mechanisms for the renoprotective effects of K^+



Gritter M *et al.*, Hypertension 2019; 73: 15-23

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Take-Home Messages: Hyperkalemia

Mechanism of disease	Type 4 RTA
Diagnosis	
Prognosis	• GI side effects of SPS • Urine K^+ > renal outcomes
Treatment	• Old *vs.* new binders • K^+ supplementation?

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Hypomagnesemia

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State of the Art: Hypomagnesemia

- Etiology: GI vs. urinary losses, genetic causes (e.g. Gitelman syndrome), drug-induced causes (PPIs, CNIs)
- Associated with increased risk of diabetes (including PTDM) and cardiovascular disease
- Role of hypomagnesemia and magnesium supplementation in CKD?

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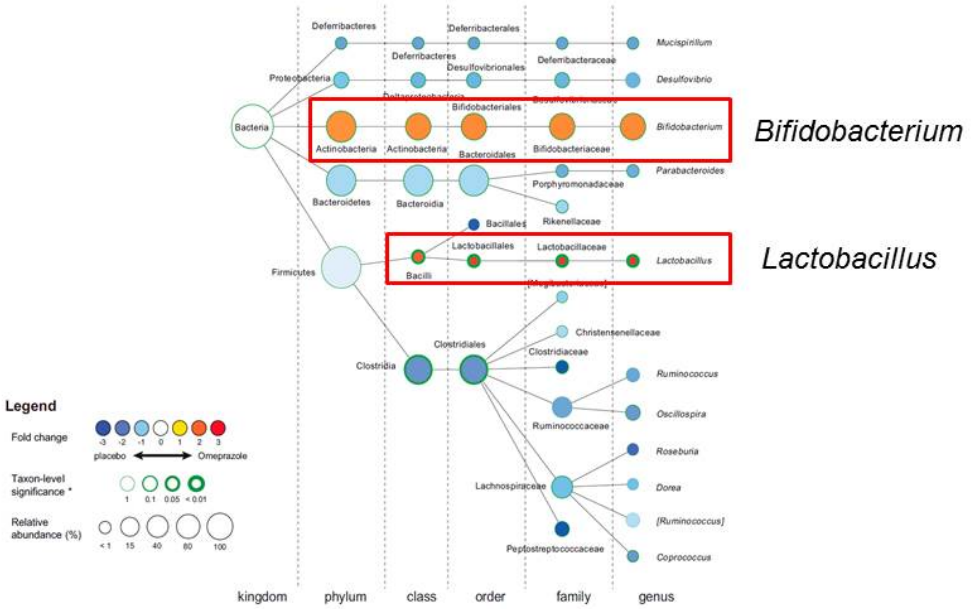
PPI-induced hypomagnesemia: low gut microbiota diversity



Gommers LMM *et al.*, FASEB J 2019; epub 12 July

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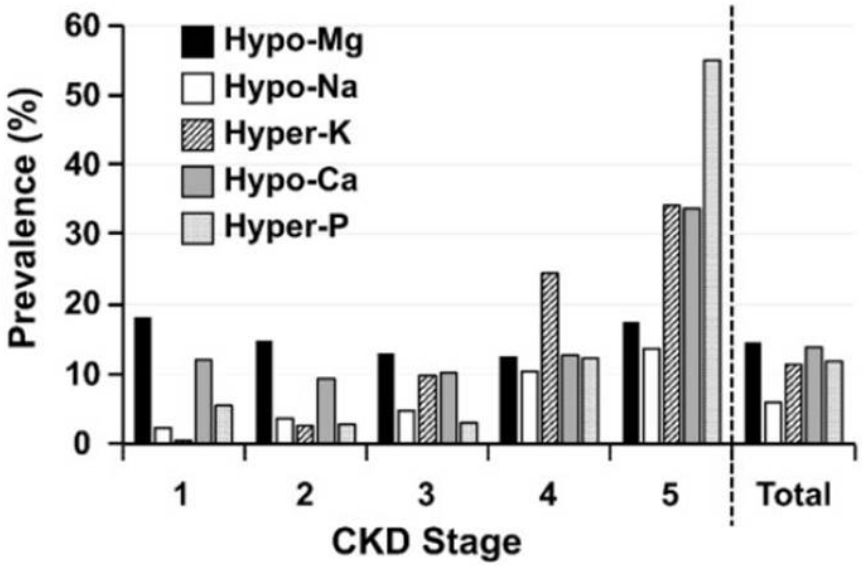
Hypomagnesemia is the most common electrolyte disorder in CKD



Oka *et al.*, Nephrol Dial Transplant 2019; 34: 1154-1162

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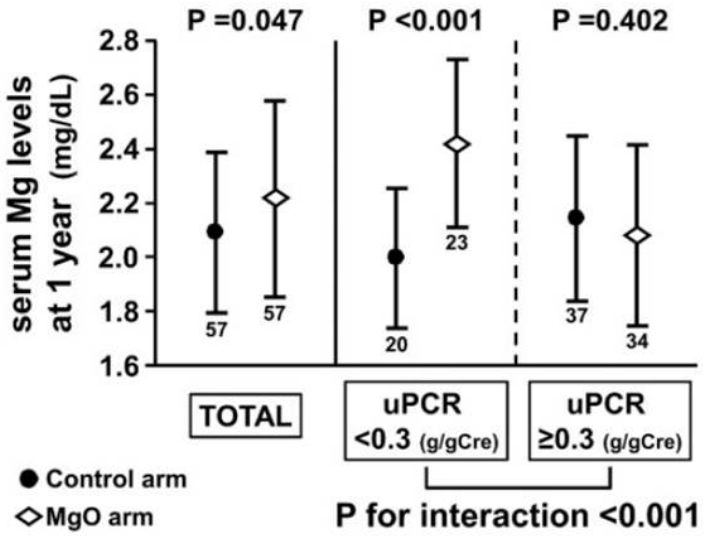
Hypomagnesemia in proteinuric CKD is resistant to Mg^{2+} supplementation



Oka *et al.*, Nephrol Dial Transplant 2019; 34: 1154-1162

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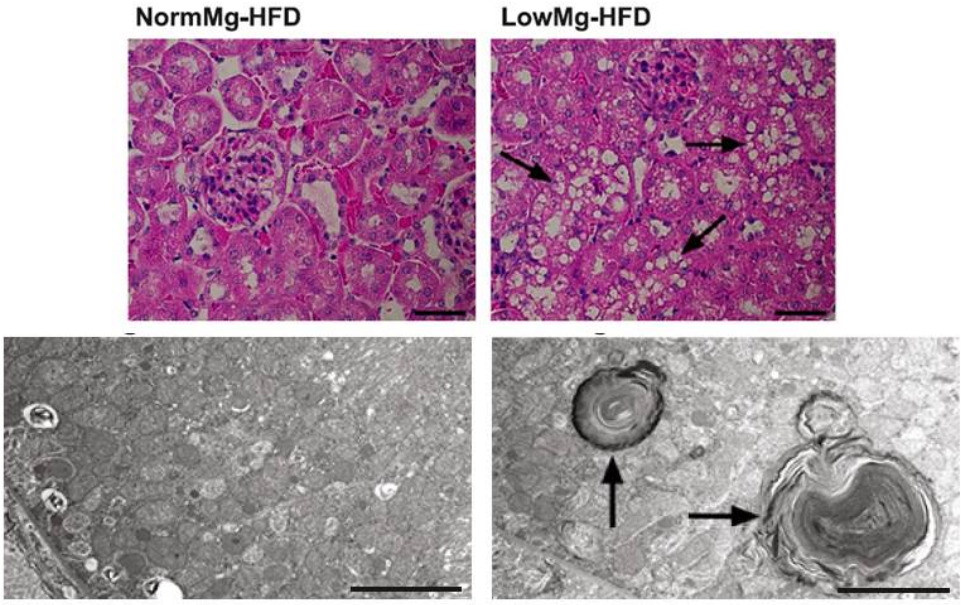
High fat–low Mg^{2+} diet causes HypoMg, phospholipidosis and albuminuria



Kurstjens *et al.*, FASEB J 2019; 33: 7192-7201

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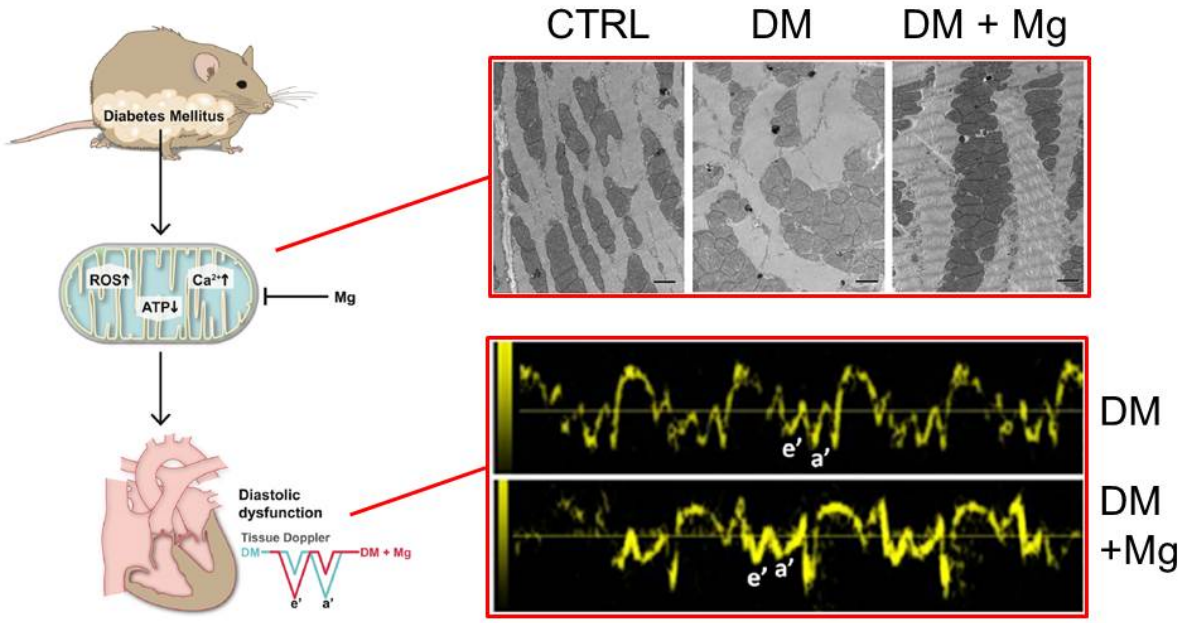
Mg^{2+} supplementation improves diabetic mitochondrial and cardiac diastolic function



Liu M *et al.*, JCI Insight 2019; 4: e123182

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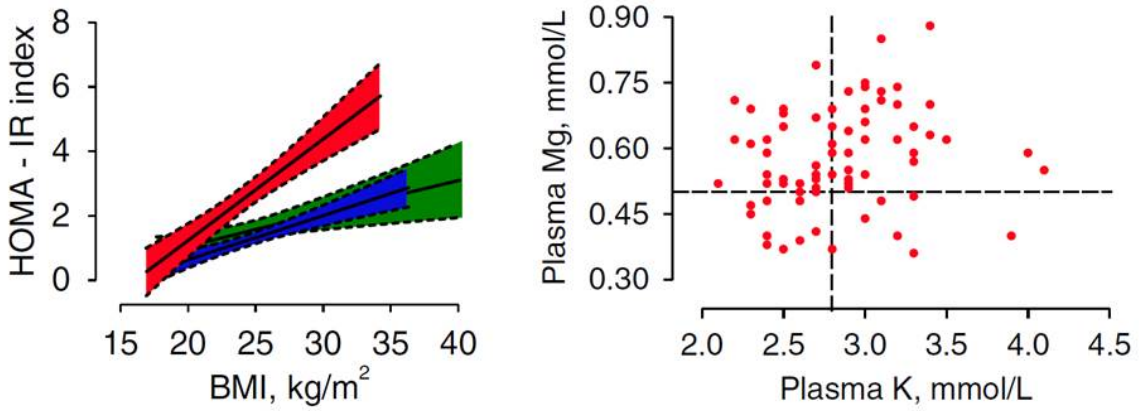
Resistance to insulin in patients with Gitelman syndrome



Blanchard *et al.*, J Am Soc Nephrol 2019; epub 8 July

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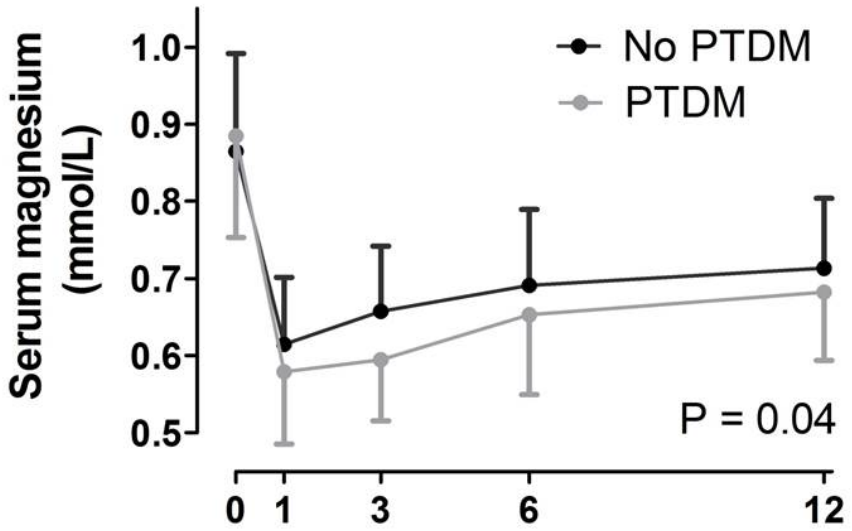
A lower plasma Mg^{2+} independently predicts post-transplant diabetes mellitus



Van der Burgh AC *et al.*, Nephrol Dial Transplant 2019; epub 30 July

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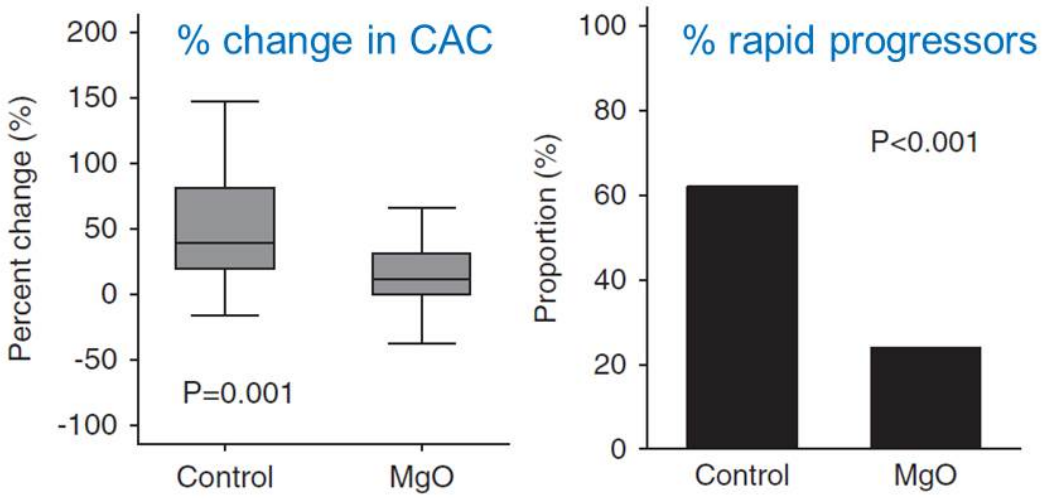
Magnesium oxide reduces coronary artery calcification in predialysis CKD



Sagakuchi Y *et al.*, J Am Soc Nephrol 2019; 30: 1073-1085

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Take-Home Messages: Hypomagnesemia

Mechanism of disease	• PPI-induced HypoMg • Kidney damage?
Diagnosis	
Prognosis	Diabetes, CV disease
Treatment	Mg^{2+} supplementation?

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List of References (1)

Before 2018

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2. Christ-Crain *et al.*, Nat Rev Nephrol 2016; 12: 168-76
3. Sands JM *et al.*, Am J Physiol Renal Physiol 2016; 311: F1149-1152
4. Shoaf SE *et al.*, Eur J Pharmacol 2017; 73: 1399-1408
5. Ware JS *et al.*, J Clin Invest 2017; 127: 3367-3374

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2. Rosner MH *et al.*, Clin J Am Soc Nephrol 2018; 13: 787-789
3. Gritter M *et al.*, Nephron 2018; 140: 48-57
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5. Fenske W *et al.*, N Engl J Med 2018; 379: 428-439
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3. Lockett J *et al.*, Clin Endocrinol (Oxf) 2019; 90: 630-6
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8. Sagakuchi Y *et al.,* J Am Soc Nephrol 2019; 30: 1073-1085
9. Mazloum M *et al.,* J Am Soc Nephrol 2019; 30: 1282-1293
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13. Fishbane S *et al.,* J Am Soc Nephrol 2019; epub 14 June
14. Blanchard *et al.*, J Am Soc Nephrol 2019; epub 8 July
15. Winzeler B *et al.*, Lancet 2019; epub 11 July
16. Gommers LMM *et al.*, FASEB J 2019; epub 12 July
17. Van der Burgh AC *et al.*, Nephrol Dial Transplant 2019; epub 30 July

List of Abbreviations

- AQP2, aquaporin-2
- AVP, arginine vasopressin
- CKD, chronic kidney disease
- CNI, calcineurin inhibitor
- CRRT, continuous renal replacement therapy
- GI, gastro-intestinal
- K^+, potassium
- Mg^{2+}, magnesium
- PGE2, prostaglandin E2
- PPI, proton pump inhibitor
- PTDM, post-transplantation diabetes mellitus
- RTA, renal tubular acidosis
- SPS, sodium polystyrene sulfonate

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