Spital Thurgau

Hyperkalemia – a silent killer?

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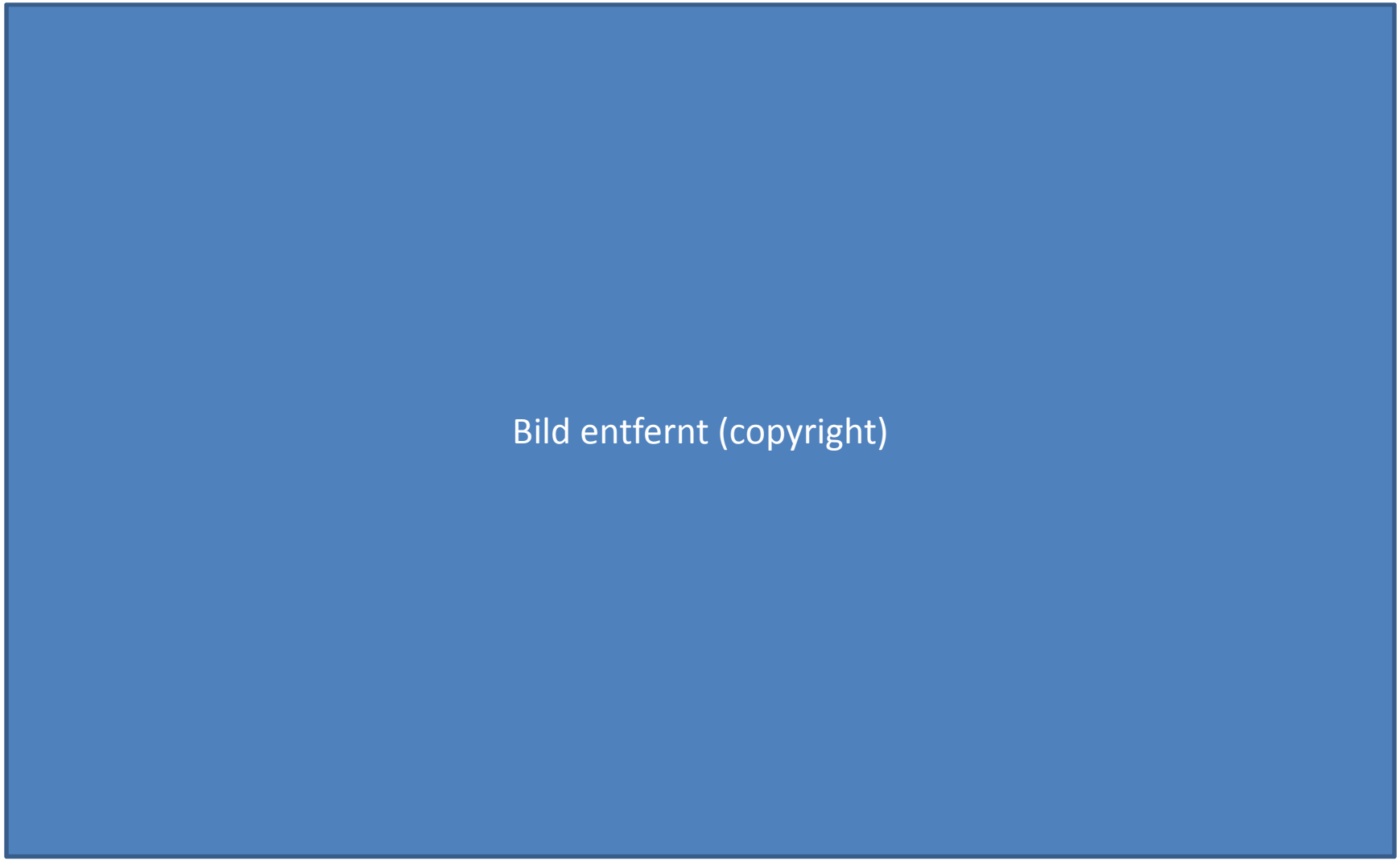
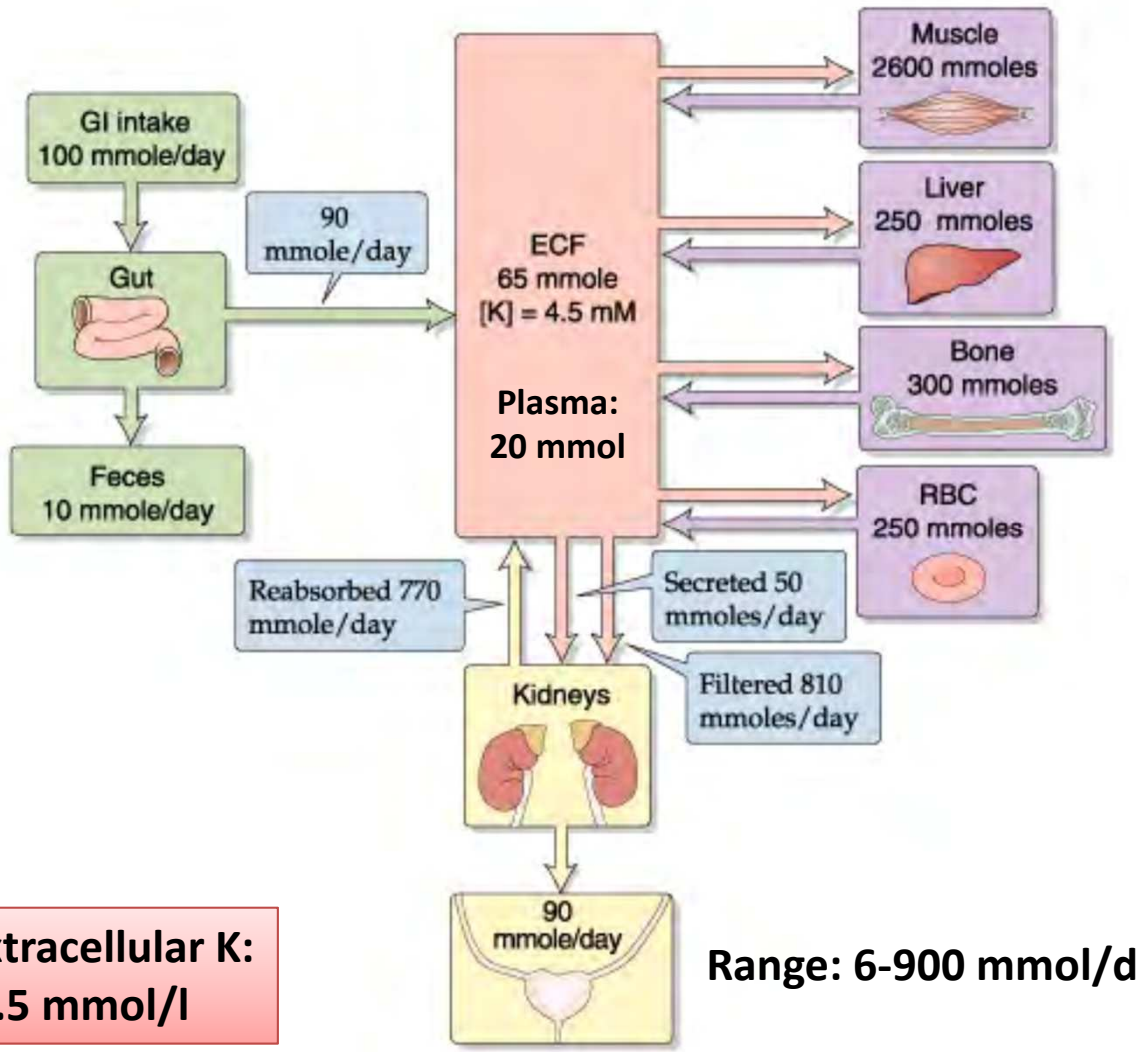
Mr. Hyper K. Lemia
charged with serial murder



Internal and external K^+-balance



Total body K^+:
98% intracellular
2% extracellular

Normal extracellular K:
3.5 – 4.5 mmol/l

Range: 6-900 mmol/d

From: Giebisch *et al.* In: Medical Physiology 2017

Mechanisms leading to hyperkalemia

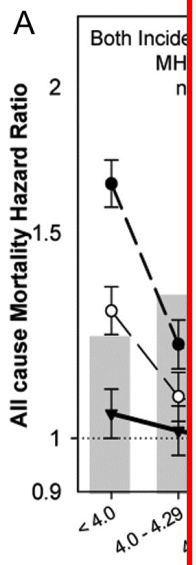
Excess potassium intake	Nutrition Potassium supplements
Reduced potassium excretion	Impaired renal function Impaired aldosterone secretion or action: - Renin-angiotensin-aldosterone system (RAAS) inhibitors - Adrenal insufficiency - Pseudohypoaldosteronism - Hyporeninemic hypoaldosteronism Low distal Na^+ delivery
Potassium redistribution	Acidosis Insulin deficiency or resistance Drugs Strenuous exercice Tissue breakdown (tumor lysis, rhabdomyolysis…) Hemolysis

Consequences of hyperkalemia

- Clinical consequences of hyperkalemia are caused by alterations in membrane excitability
- These consequences may be life-threatening, but symptoms are unspescific and often absent:
  - Neuromuscular: fatigue, weakness, muscle pain or tightness, paresthesias
  - Gastrointestinal: nausea, vomiting
  - Cardiac: palpitations

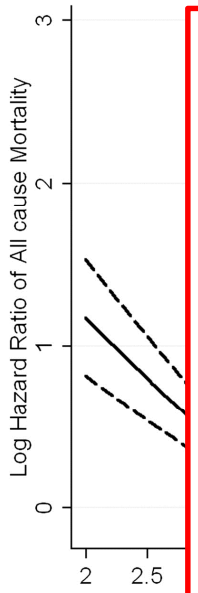
Serum-K^+ and mortality

Predialysis K^+ and mortailty in HD



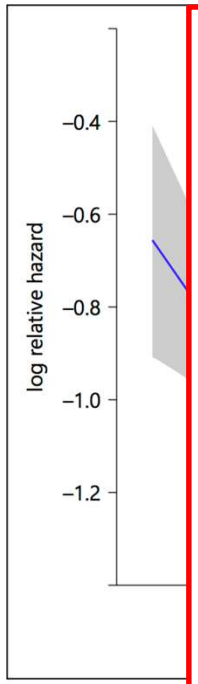
Kovesdy

Time-averaged K^+ and mortailty in PD



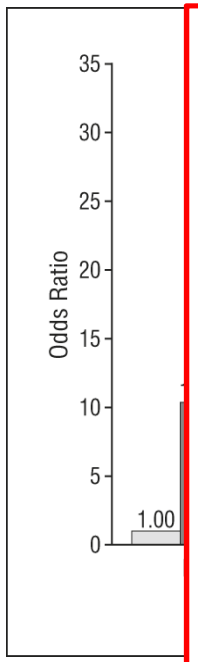
Torlen,

K^+ and mortailty in CKD



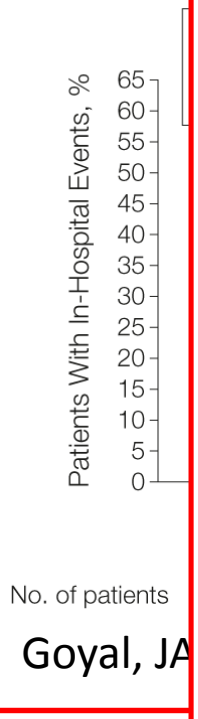
Nakhoul,

K^+ and mortailty in CKD



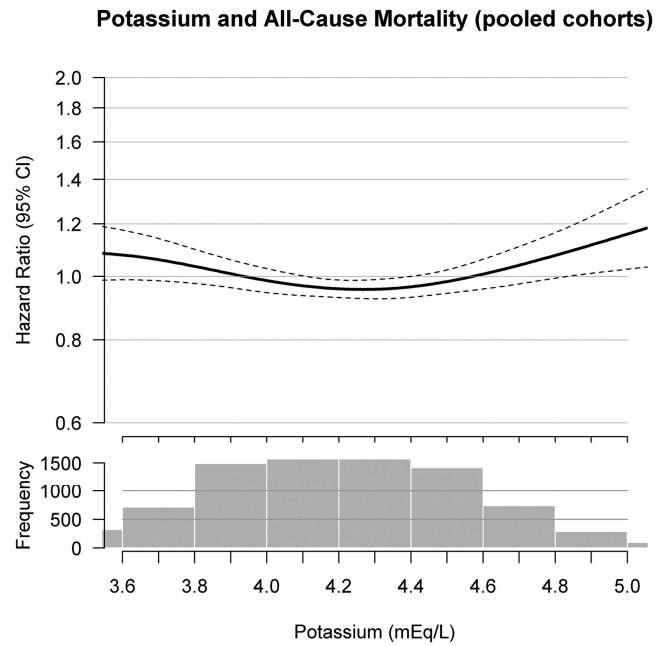
Einhorn,

Mean in-hospital K^+ and mortality after MI



Goyal, JA

Community-based K^+ and mortality



Hughes-Austin, CJASN 2017

Serum-K^+ and mortality

- Hyperkalemia is associated with higher mortality across a spectrum of diseases
- But: association = causality?
- Clinical consequences of hyperkalemia depend not only on the K^+-level, but:
  - rapidity of onset
  - presence of concomitant electrolyte abnormalities
  - Medications
  - other comorbidities

➔***Hence, there is no clear cut off for a „critically elevated“ an also no upper limit for a „safe“ K^+-level!***

Consequences of hyperkalemia

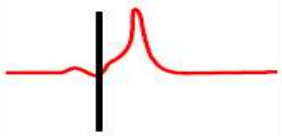
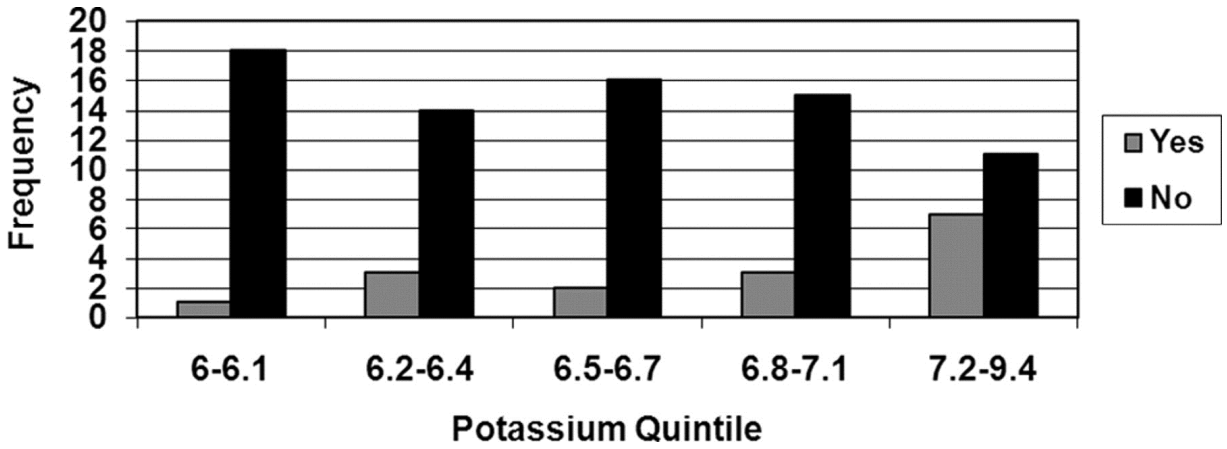
Serum Potassium	Typical ECG Appearance	Possible ECG Abnormalities
Mild (5.5-6.5 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5-8.0 mEq/L)		Loss of P wave Prolonged QRS complex
Severe (> 8.0 mEq/L)		

Figure from McCullough PA, et al. *Rev Card*

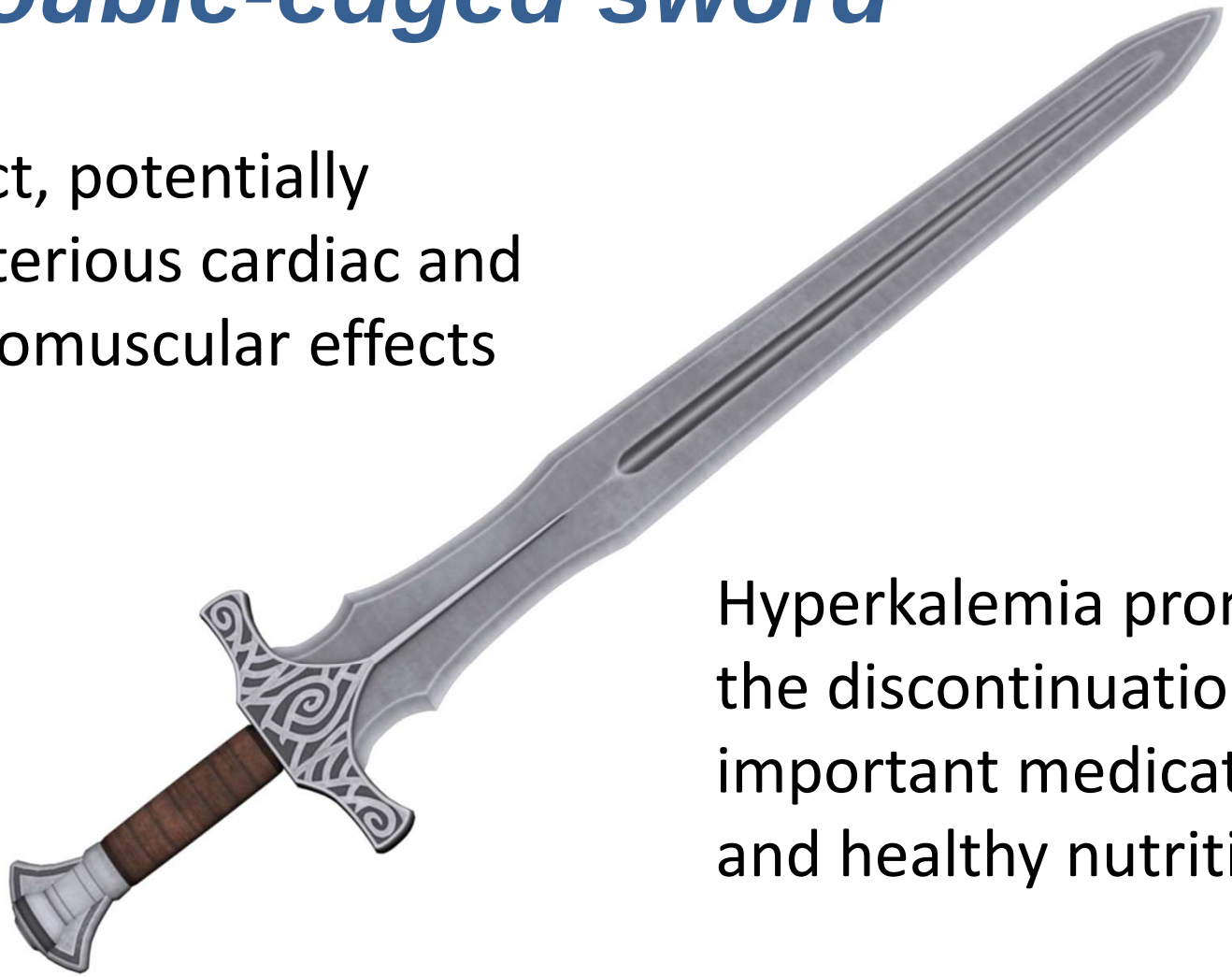
Frequency of ECG changes



Montague, CJASN 2008

Hyperkalemia: a double-edged sword

Direct, potentially deleterious cardiac and neuromuscular effects



Hyperkalemia prompts the discontinuation of important medications and healthy nutrition

Guideline recommendations for RAASi treatment

Table 1 | Guideline recommendations for RAASi treatment of heart failure, chronic kidney disease, and diabetes mellitus[a]

Disease state	Recommendation	Source of recommendation	Level of recommendation	Strength of evidence
Heart failure with reduced ejection fraction	In patients with history of MI and reduced EF, ACEIs or ARBs should be used to prevent HF	ACC/AHA[18]	I	A
	ACEIs are recommended in patients with HFrEF (LVEF ≤40%) and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality	ESC[19] ACC/AHA[18]	I	A
	ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACEI-intolerant, unless contraindicated, to reduce morbidity and mortality	ESC[19] ACC/AHA[18]	I	A
	Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACEI and a beta-blocker in whom an aldosterone antagonist is not indicated or tolerated	ESC[19] ACC/AHA[18]	IIb	A
	MRAs are recommended in patients with NYHA class II to IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality	ESC[19] ACC/AHA[18]	I	A
	MRAs are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF ≤40% who develop HF symptoms or who have a history of DM, unless contraindicated	ACC/AHA[18]	I	A
Chronic kidney disease	For prevention of CKD progression, suggest an ARB or ACEI be used in diabetic adults with CKD and UAE 30 to 300 mg/24 h	KDIGO[20,21]	2	D
	For prevention of CKD progression, recommend an ARB or ACEI be used in both diabetic and nondiabetic adults with CKD and UAE >300 mg/24 h	KDIGO[20,21]	1	B
	Do not routinely discontinue RAASi (ACEI, ARB, MRA, direct renin inhibitor) in people with GFR <30 ml/min/1.73 m^2 as they remain nephroprotective	KDIGO[22,23]	NA	NA
	In the population ≥18 years of age with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status	JNC 8[24,25]	Moderate recommendation	B
Diabetes mellitus	Pharmacological therapy for patients with DM and HTN should comprise a regimen that includes either an ACEI or an ARB	ADA[26]		B
	Either an ACEI or ARB is suggested for the treatment of diabetic nephropathy patients with modestly elevated UAE (30–299 mg/day) and is recommended for those with UAE >300 mg/day	ADA[27]		B: UAE 30–299 mg/day A: UAE >300 mg/day
Resistant hypertension	MRAs should be considered, if no contraindication exists	ESH/ESC[28] JNC 8[24]	IIa	B

ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction; ESC, European Society of Cardiology; ESH, European Society of Hypertension; GFR, glomerular filtration rate; HF, heart failure; HFrEF, HF with reduced EF; HTN, hypertension; JNC, Joint National Committee; KDIGO, Kidney Disease Improving Global Outcomes; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; UAE, urine albumin excretion.

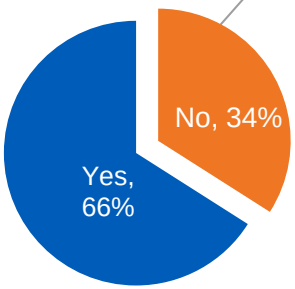
[a]Recent data suggest ACEIs are possibly superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD.[15]

RAASi use in the real world setting

- Several studies have shown underutilization of RAASi compared to guideline recommendations
- When RAASi are prescribed, they are often used in submaximal doses

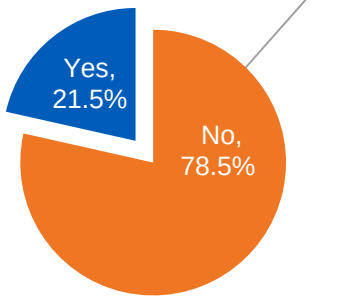
Reasons for withholding RAASi therapy

ACEi



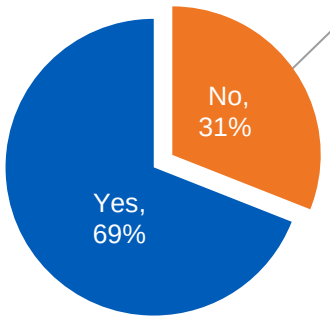
Contraindicated	**22.3%**
Not tolerated	**62.5%**
Reasons	
Cough	55.9%
Hypotension	22.5%
Worsening renal function	11.8%
Hyperkalaemia	**3.9%**
Other reasons	**15.2%**

ARB



Not indicated	**79.1%**
Contraindicated	**6.6 %**
Not tolerated	**6.4%**
Reasons	
Hypotension	48.1%
Worsening renal function	26.7%
Cough	7.2%
Hyperkalaemia	**5.5%**
Other reasons	**7.9%**

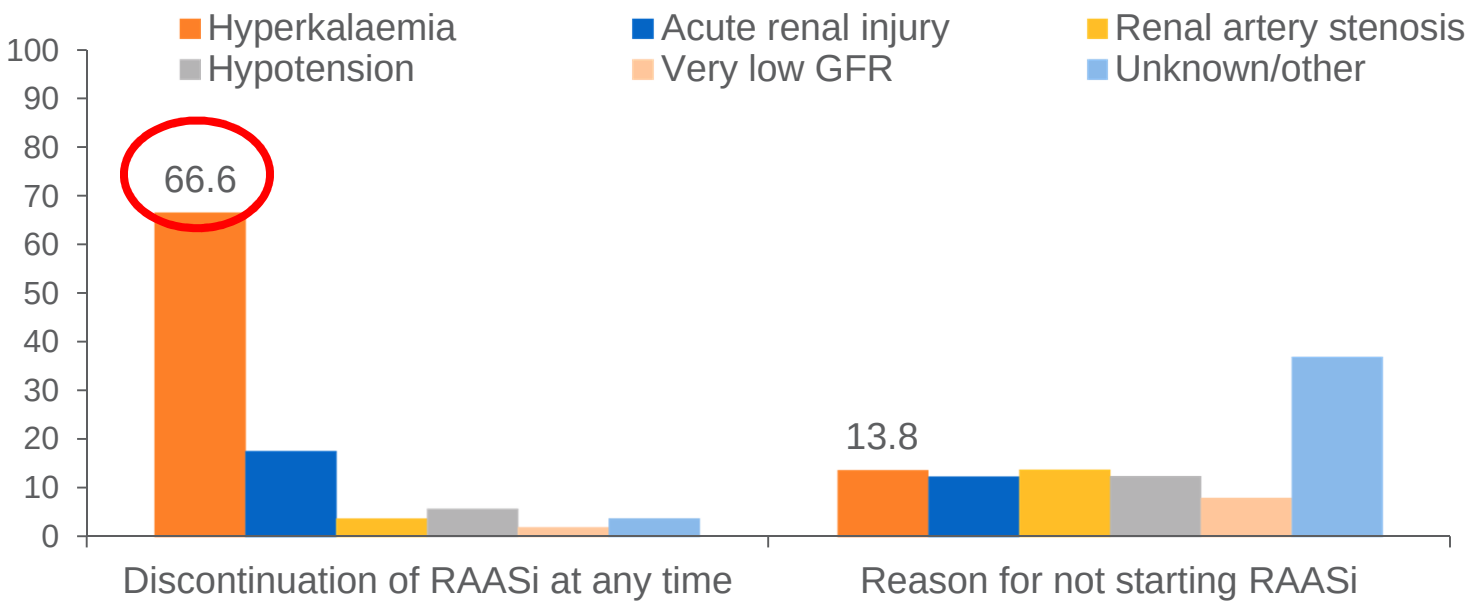
MRA



Not indicated	**61.8%**
Contraindicated	**18.9%**
Not tolerated	**14.9%**
Reasons	
Renal dysfunction	51.2%
Hyperkalaemia	**31.4%**
Gynecomastia	15.3%
Other reasons	**4.5%**

Komajda M, et al. *Eur J Heart Fail*. 2016;18:514–22.

Reasons for withholding RAASi therapy

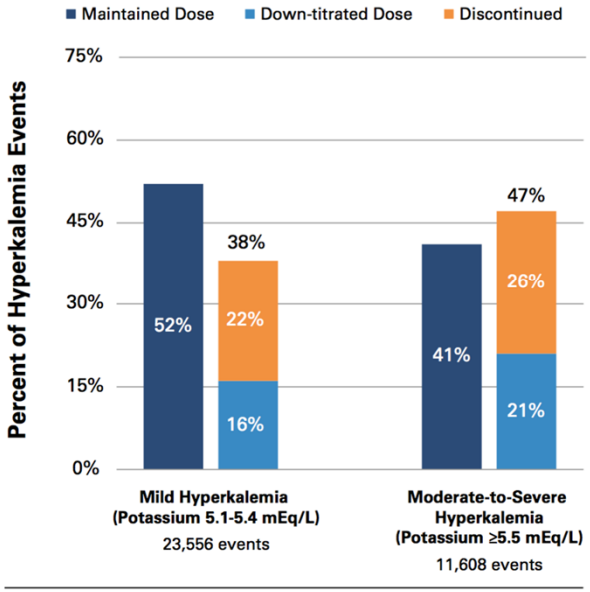


Yildirim, Ren Fail 2012

Ironically, patients with risk factors for hyperkalemia are also those who receive the greatest absolute benefit from RAASi.

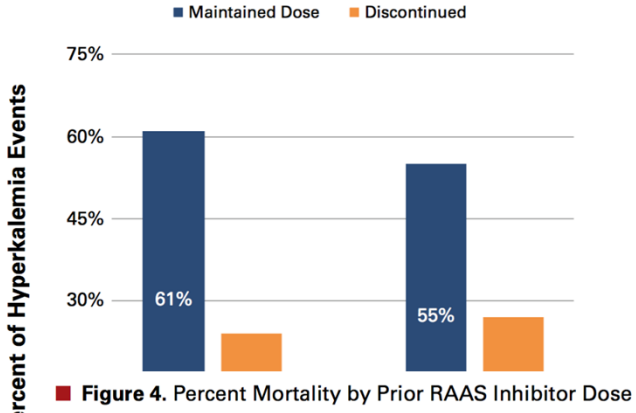
Hyperkalemia, subsequent RAASi adaptation and mortailty

Figure 2A. *Among Patients on RAAS Inhibitor at Maximum Dose*



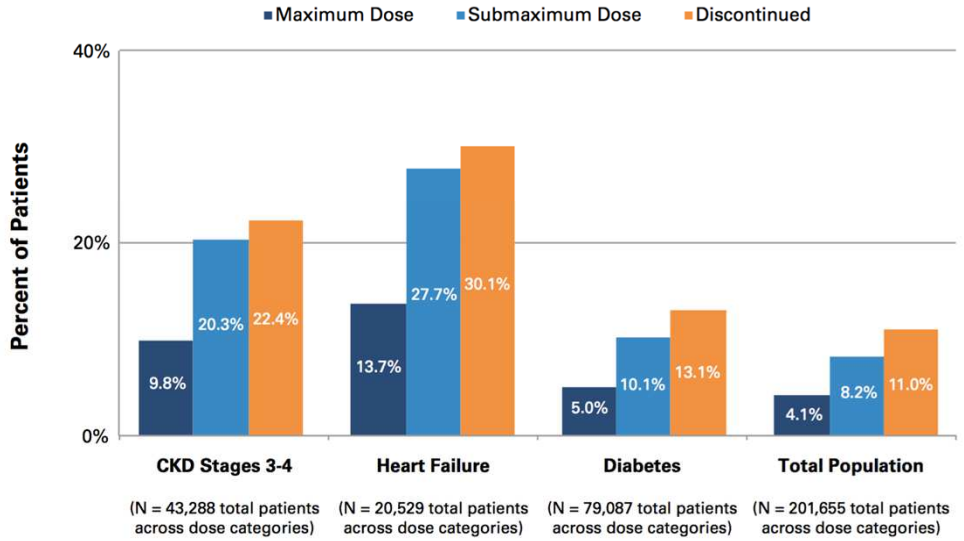
RAAS indicates renin-angiotensin-aldosterone system.

Figure 2B. *Among Patients on RAAS Inhibitor at Submaximum Dose*



RAAS

Figure 4. Percent Mortality by Prior RAAS Inhibitor Dose



Epstein, Am J Manag Care 2015

Hyperkalemia – really of concern?

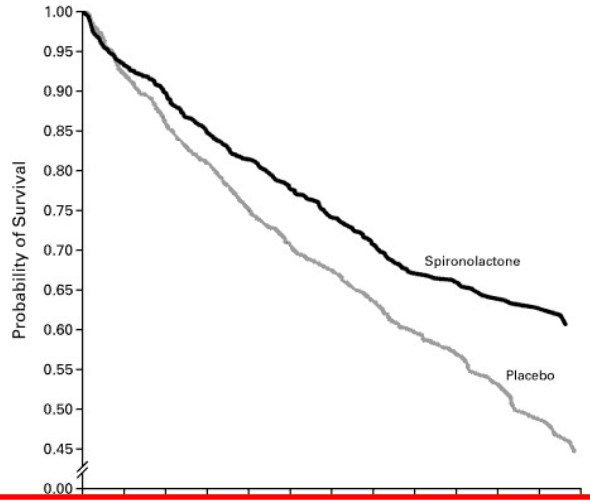
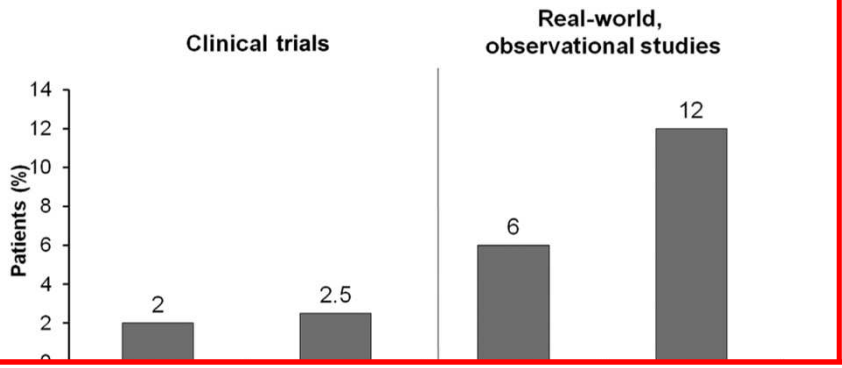


TABLE 4. ADVERSE EVENTS.

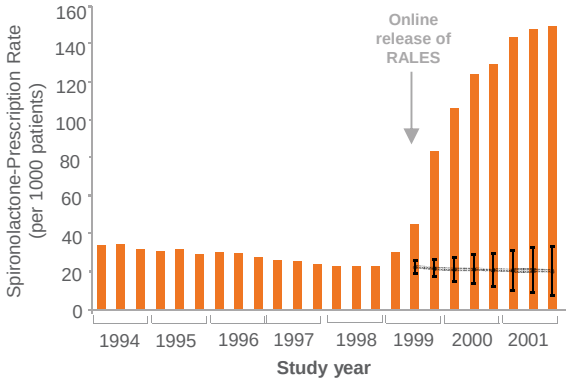
ADVERSE EV

Serious hyp

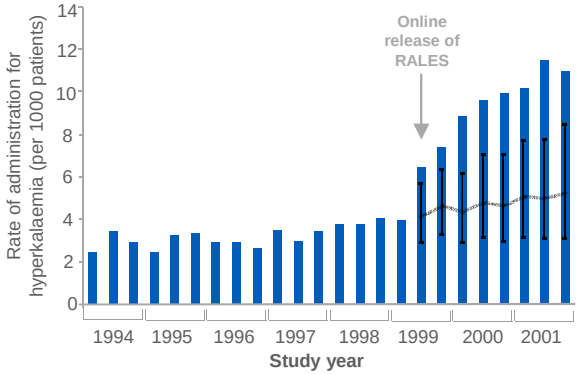
RALES:



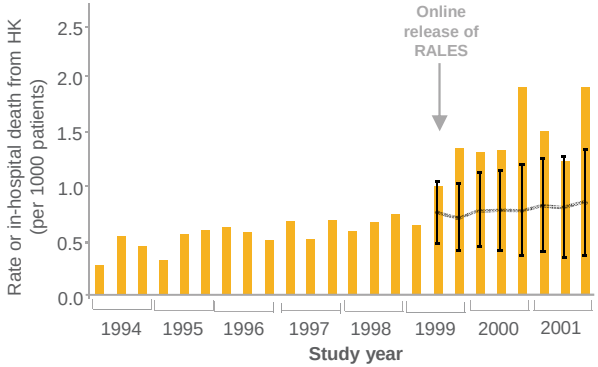
Spironolactone-prescription rate (per 1,000 patients)



Rate of admission for hyperkalaemia (per 1,000 patients)



Rate of in-hospital death from hyperkalaemia (per 1,000 patients)



Juurlink, NEJM 2004

Current management of hyperkalemia

Potassium redistribution	Insulin – Glucose Beta-agonists Bicarbonate
Facilitate renal potassium excretion	Reduce / stop RAASi Loop diuretics Rehydration if volume depleted / less sodium restriction Fludrocortisone
Restrict potassium intake	Nutritional restrictions
Facilitate intestinal potassium excretion	Potassium binders
Extracorporeal removal	Dialysis

Potassium-binders available and under evaluation

	Sodium polystyrene sulfonate (SPS), Resonium®	Patiromer Calcium Sorbitex, Veltassa®	Sodium zirconium cyclosilicate, ZS-9
Exchange Ion	Na^+	Ca^{2+}	Na^+
Onset of action	variable, 2 – 6 hours[1]	7 hours[3]	1 – 6 hours[1]
Effect duration	variable, 6 – 24 hours[1]	12 – 24 hours[3]	unclear, 4 – 12 hours[1]
Preparation and administration	powder, 15g in 100mL water[2]	powder, 8.4/16.8 g in 80mL water, apple juice, cranberry juice[15]	powder, 5/10/15 g in 240mL water[1]
Dosing	3 – 4 x daily[2]	chronic: 1 x daily with meal[15]	subacute: 3 x daily with meal[1] chronic: 1 x daily with meal[1]
Setting	sub-acute (contraindicated at serum K^+ < 5.0 mmol/L)[2]	chronic (should not replace emergency treatment)[15]	subacute or chronic[1]
Clinical studies performed	1961: observational study[12] 2014: randomized, single-blind, SPS vs. CPS (3d)[13] 2015: randomized, double-blind, placebo-controlled (7d)[14]	RLY5016-103: Onset of action (12d)[3] RLY5016-201: HD patients (1w)[4] RLY5016-202: PEARL (4w)[5] RLY5016-205: AMETHYST (52w)[6] RLY5016-301: OPAL (12w)[7] RLY5016-401: TOURMALINE(4w)[8]	ZS-002: Phase II (2/4d) ZS-003: Phase III (3w)[9] ZS-004: HARMONIZE (4w)[10] ZS-005: long-term (52w)[11]
Safety profile	hypomagnesemia, anemia, edema, nausea, vomiting, constipation, diarrhea, GI tract ulceration or necrosis[2]	common: hypomagnesemia, constipation, diarrhea, abdominal pain, flatulence uncommon: nausea, vomiting[15]	hypertension, peripheral edema, urinary tract infection, nausea, constipation, anemia, upper respiratory tract infection[11]
Availability	US: approved since 1958 France: 1980	US: approved since October 2015 EU: approved since July 2017 CH: under review	US: under review EU: under review

1. Beccari MV, Meaney CJ. *Core Evidence* 2017; 12:11-24. 2. Fachinformation Resonium, www.swissmedicinfo.ch 3. Bushinsky DA, et al. *Kidney International* 2015;88:1427–1433. 4. Bushinsky DA, et al. *Am J Nephrol* 2016;44:404–410. 5. Pitt B, et al. *Eur Heart J* 2011;32(7):820-828. 6. Bakris G, et al. *JAMA* 2015;314:151-61. 7. Weir MR, et al. *N Engl J Med* 2015;372(3):211-221. 8. Pergola PE, et al. *Am J Nephrol* 2017;46:323-332. 9. Packham DK, et al. *N Engl J Med* 2015;372(3):222-231. 10. Kosiborod M, et al. *JAMA* 2014;312(21):2223-2233. 11. Fishbane S, et al. ZS-005 data, poster presented at ASN Kidney Week 2017; November 2017; New Orleans, #2759765. 12. Scherr L, et al. *N Engl J Med* 1961;264(39):115-119. 13. Nasir K, Ahmad A. *J Ayub Med Coll Abbottabad* 2014;26(4):455-458 14. Lepage L, et al. *Clin J Am Soc Nephrol* 2015;10:2136-2142 15. Patiromer professional information, www.ema.europa.eu

Conclusions

- Hyperkalemia is consistently associated with mortality across a wide range of clinical situations
- Other factors modulate the „cardiac toxicity“ of hyperkalemia and there is no threshold for mortality risk
- Apart from its direct potentially fatal consequences, hyperkalemia is often responsible for underprescription of RAASi

Spital Thurgau

Thank you for your attention

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Physiological role of K^+

intracellular

- Cell volume
- pH
- Enzymatic functions

extracellular

Resting membrane potential

→Neuromuscular function

→Cardiac rhythm

→Vascular tone

Mechanisms leading to hyperkalemia

Excess potassium intake	Nutrition Potassium supplements
Potassium redistribution	Acidosis Insulin deficiency or resistance Drugs Strenuous exercice Tissue breakdown (tumor lysis, rhabdomyolysis…) Hemolysis
Reduced potassium excretion	Impaired renal function Impaired aldosterone secretion or action: - Renin-angiotensin-aldosterone system (RAAS) inhibitors - Adrenal insufficiency - Pseudohypoaldosteronism - Hyporeninemic hypoaldosteronism Low distal Na^+ delivery