Iperkaliemia e ipokaliemia: corretta concentrazione di potassio nel dialisato, dieta e chelanti del potassio

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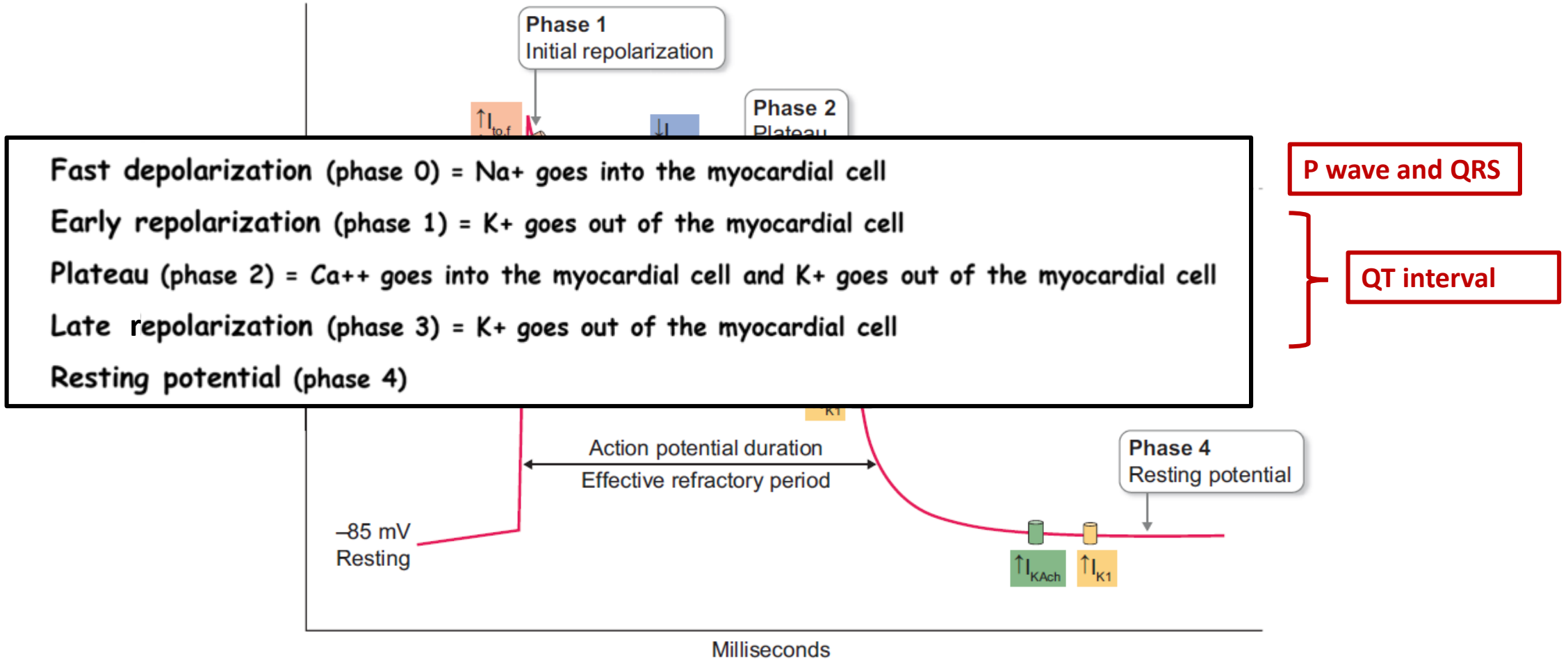
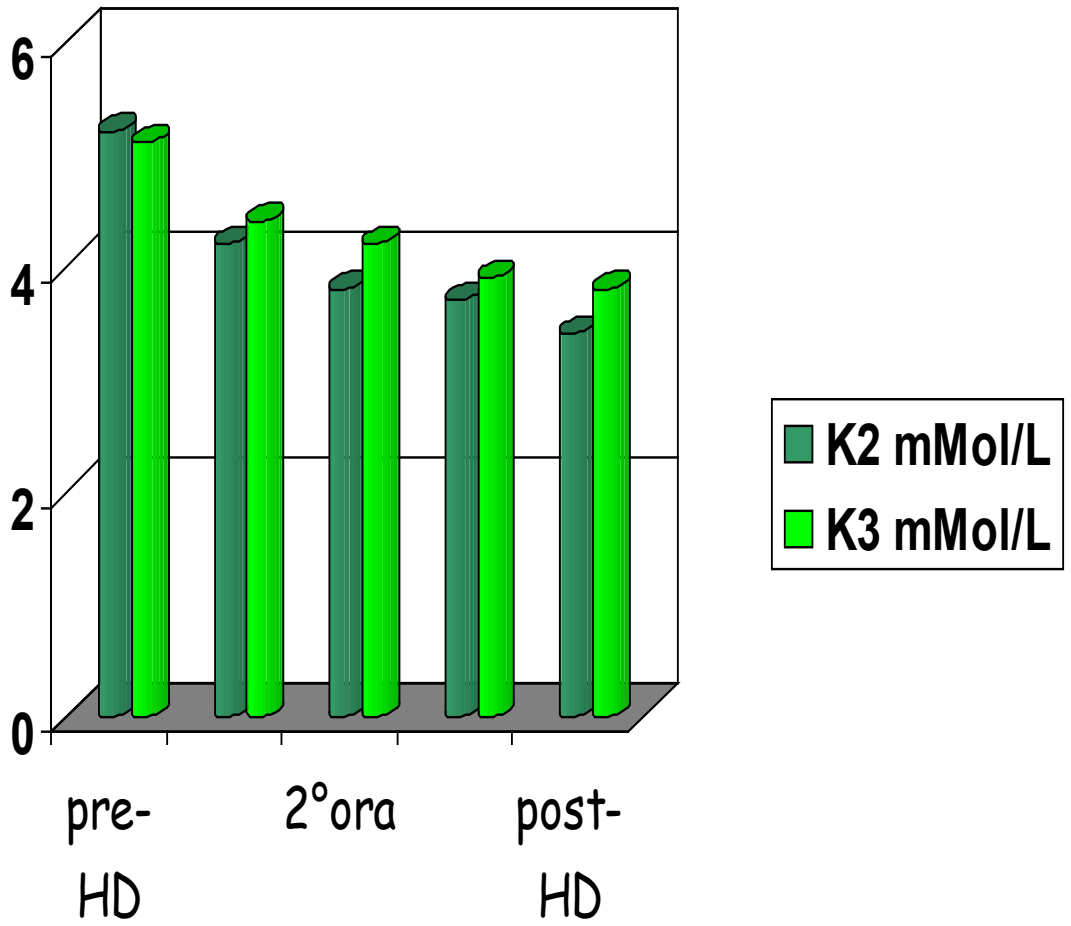
Clinica Nefrologia

Myocardial cell action potential

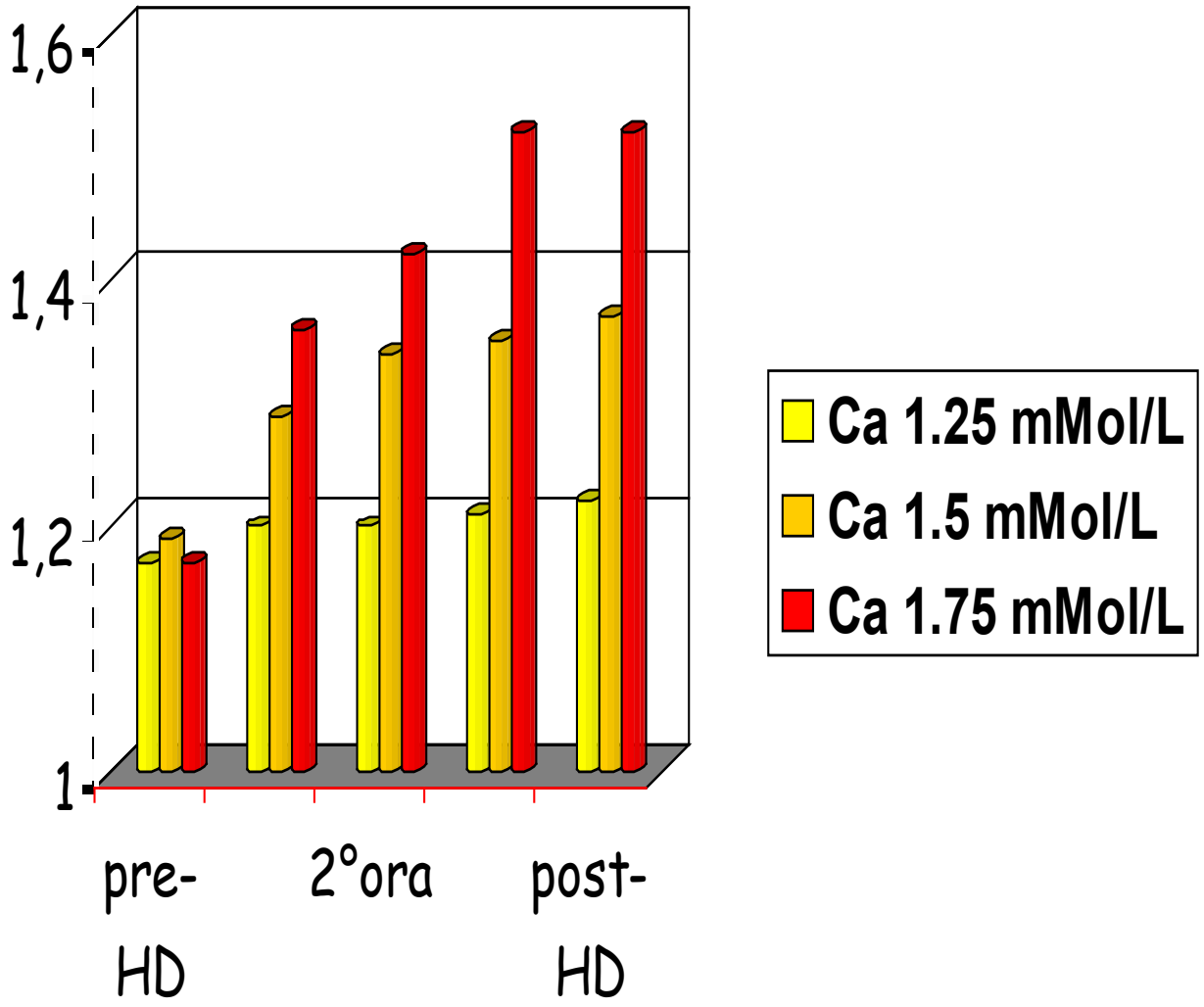


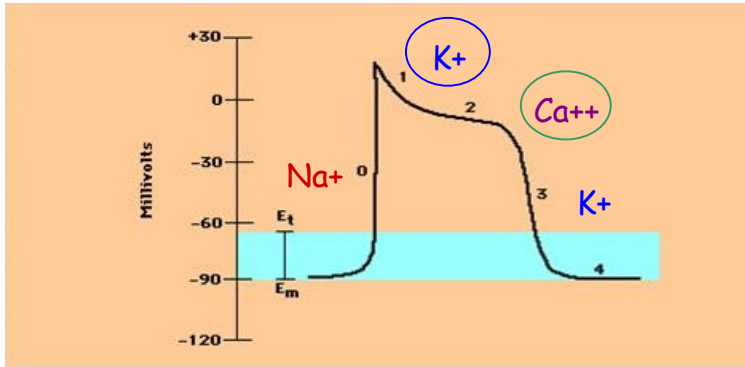
Genovesi, Nephrology Dialysis Transplantation 2023

Modificazione di K durante bicarbonato dialisi



Modificazione di Ca ionizzato durante bicarbonato dialisi





I livelli di potassio serico dipendono dal **pH**

↑ pH → ↑ shift di potassio da extra a intra cellulare

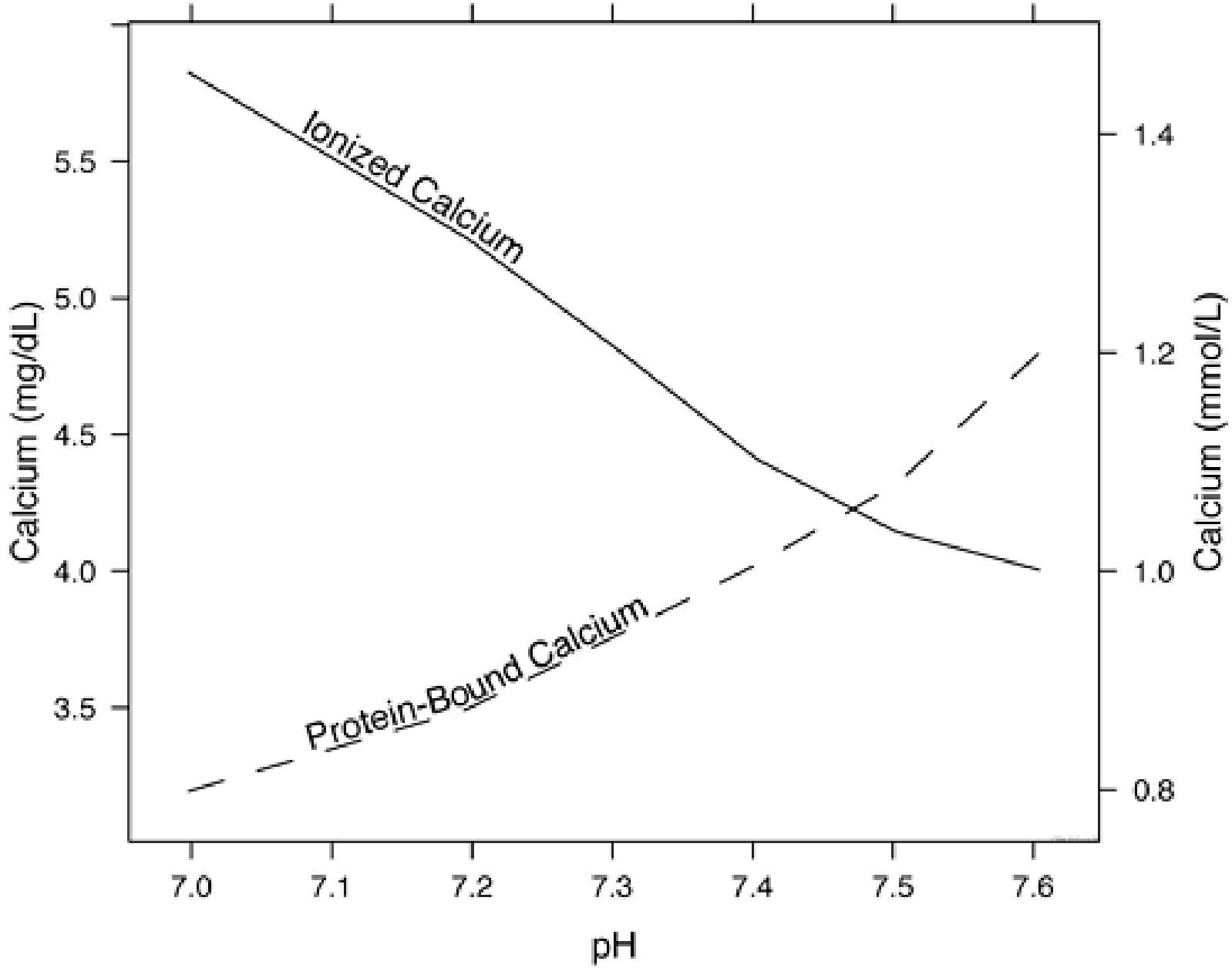
↓ pH → ↑ shift di potassio da intra a extra cellulare

Inoltre ….. il legame del calcio con l'albumina dipende dal **pH:**

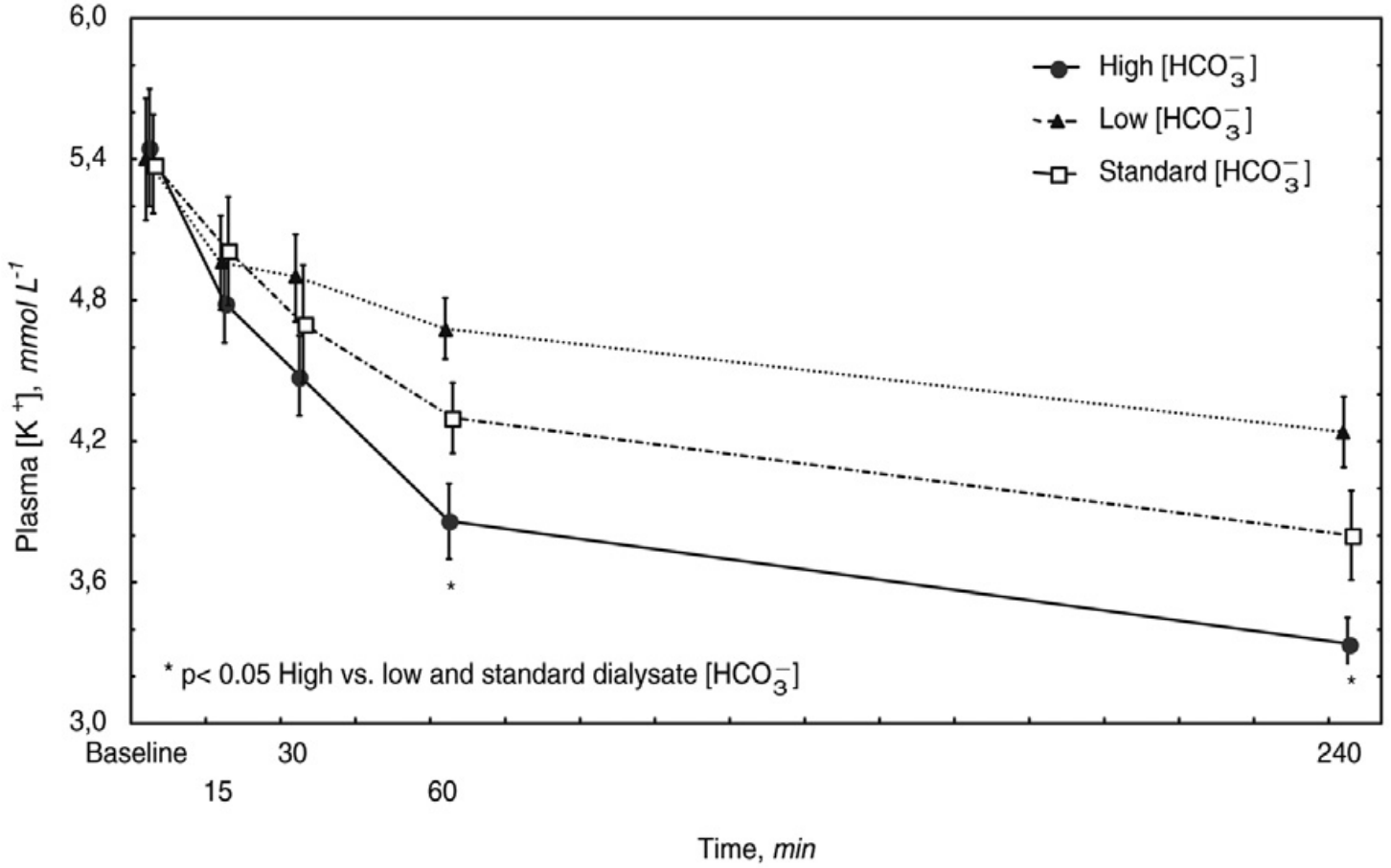
↑ pH → ↑ legame con Albumina → ↑ Calcio Tot → ↓ Calcio Ionizz

↓ pH → ↓ legame con Albumina → ↓ Calcio Tot → ↑ Calcio Ionizz

grossolanamente, per ogni diminuzione di 0.1 di pH
il calcio ionizzato aumenta di 0.05 mmol/l (0.2 mg/dl).

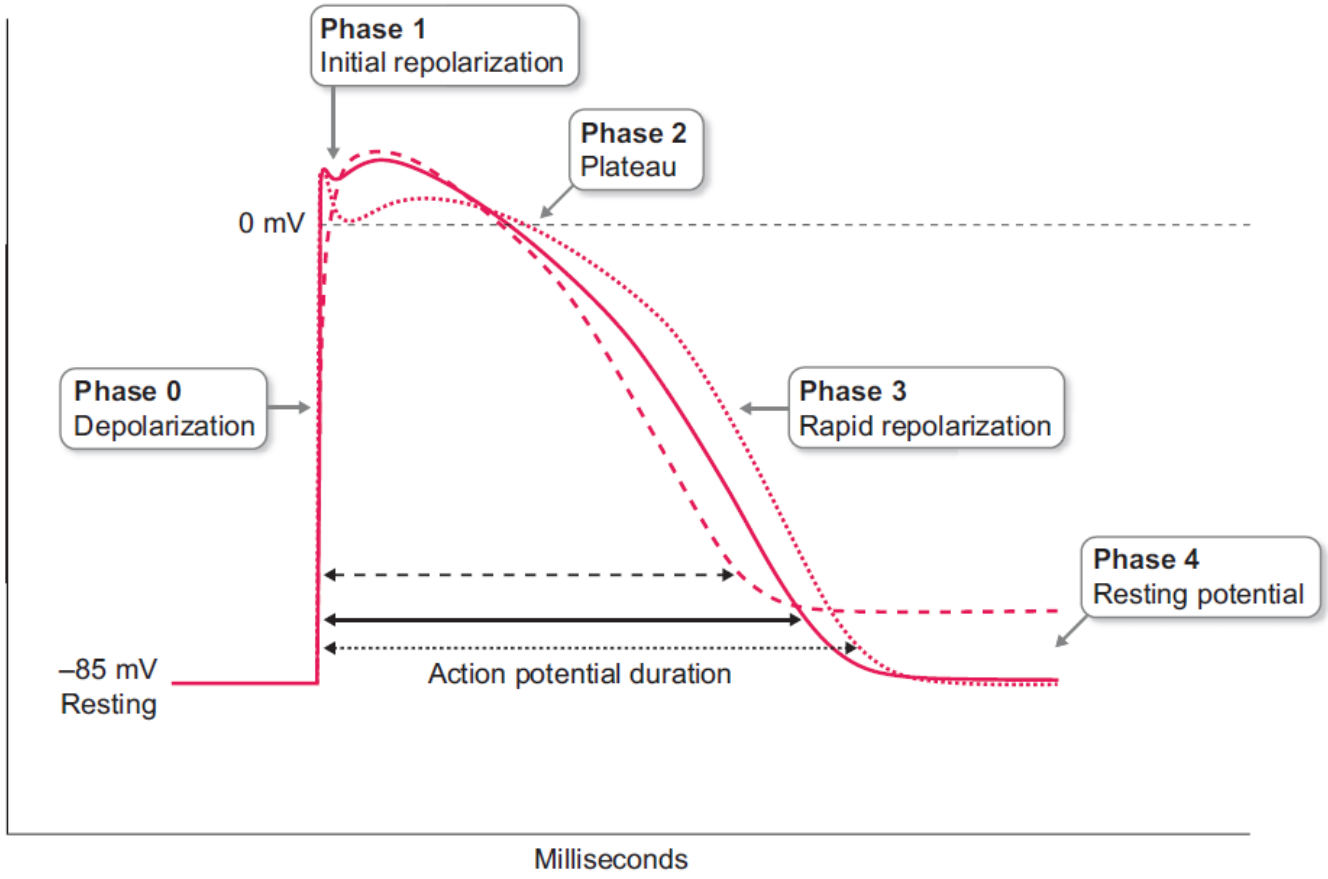

Ionized Calcium
Protein-Bound Calcium
Calcium (mg/dL)
5.5
5.0
4.5
4.0
3.5
Calcium (mmol/L)
1.4
1.2
1.0
0.8
7.0
7.1
7.2
7.3
7.4
7.5
7.6
pH

Bicarbonate concentrations and potassium-lowering effect in chronic haemodialysis



Heguilen, NDT 2005

Effect of electrolytes on myocardial action potential



Normal K+ and Ca++

Hyperkalemia and Hypercalcemia

Hypocalcemia and Hypokalemia

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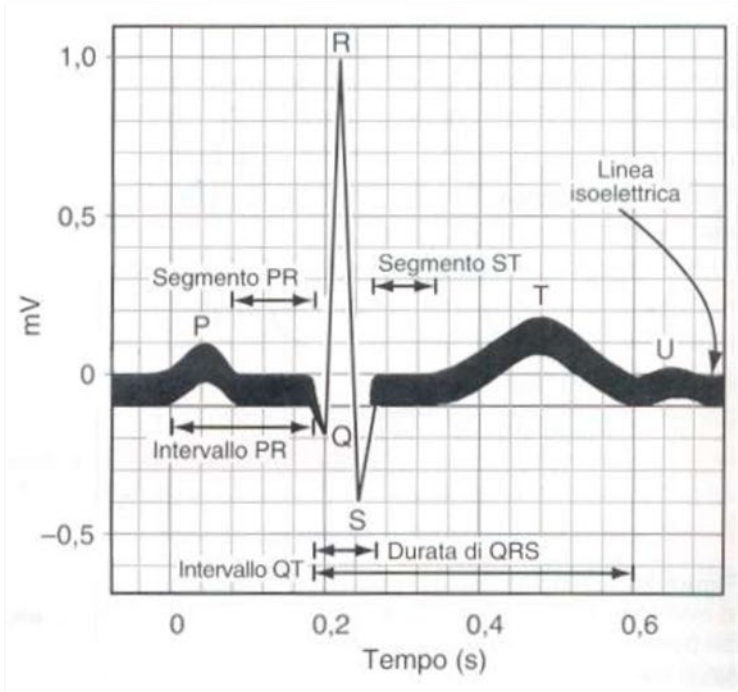
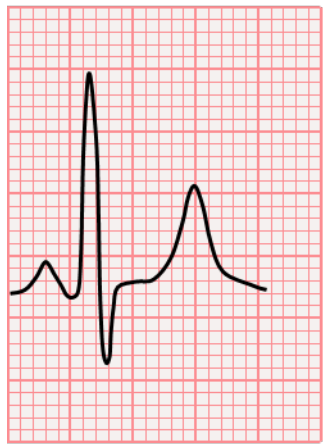
The QT interval of the ECG represents the ventricular cell repolarisation time. If ventricular repolarisation time increases, QT interval increases.



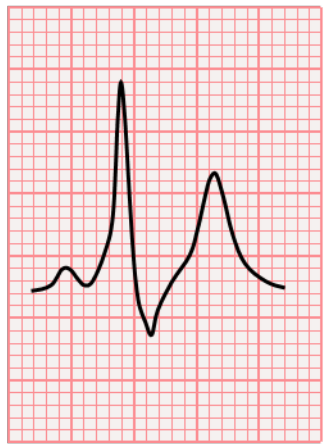
A decrease in plasma potassium and calcium levels induces a QTc increment, while an increase in kalemia and calcemia shortens the QT interval.

Hyperkalemia

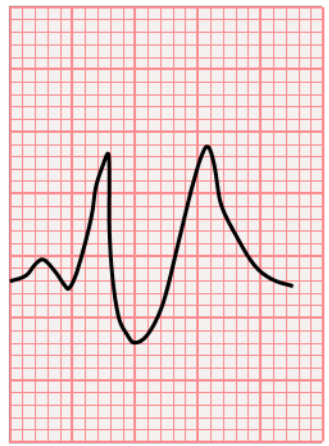
K = 6.5 mEq/L



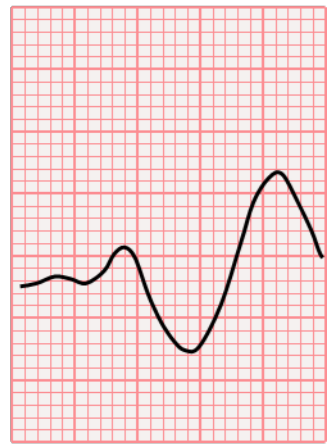
K = 7.0 mEq/L



K = 8.0 mEq/L

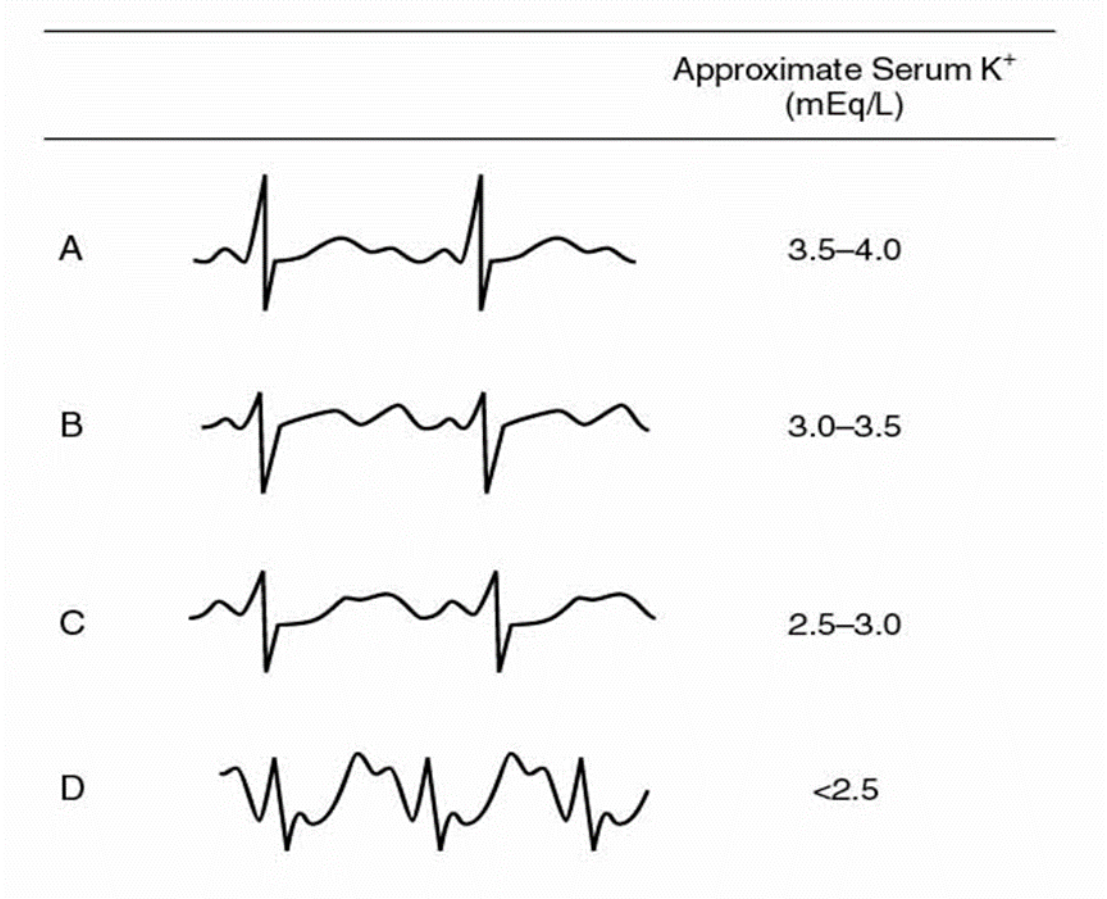


K = 9.0 mEq/L



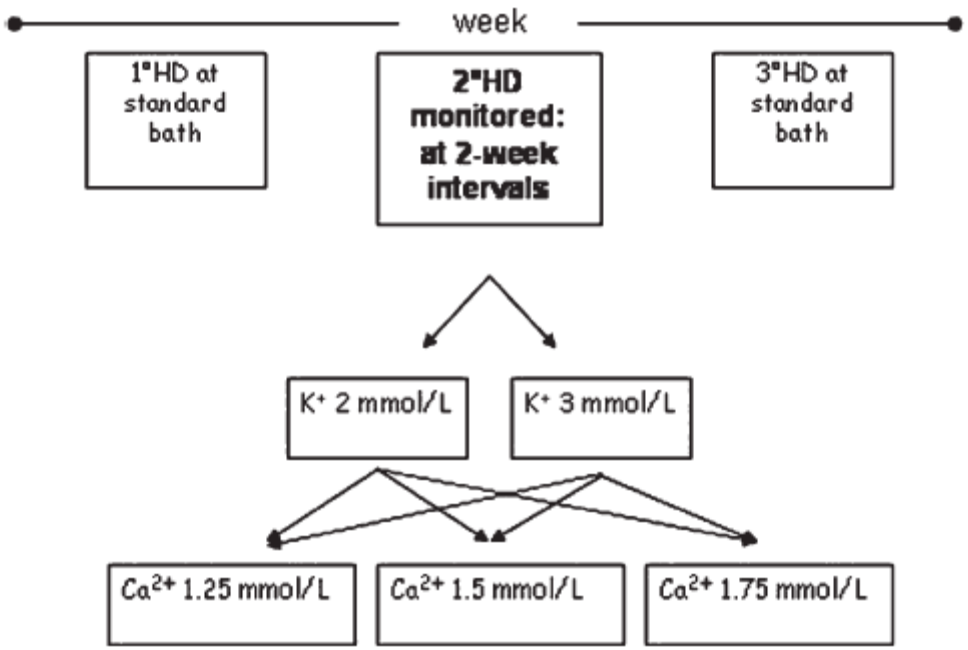
Asystole and Cardiac Arrest

Hypokalemia



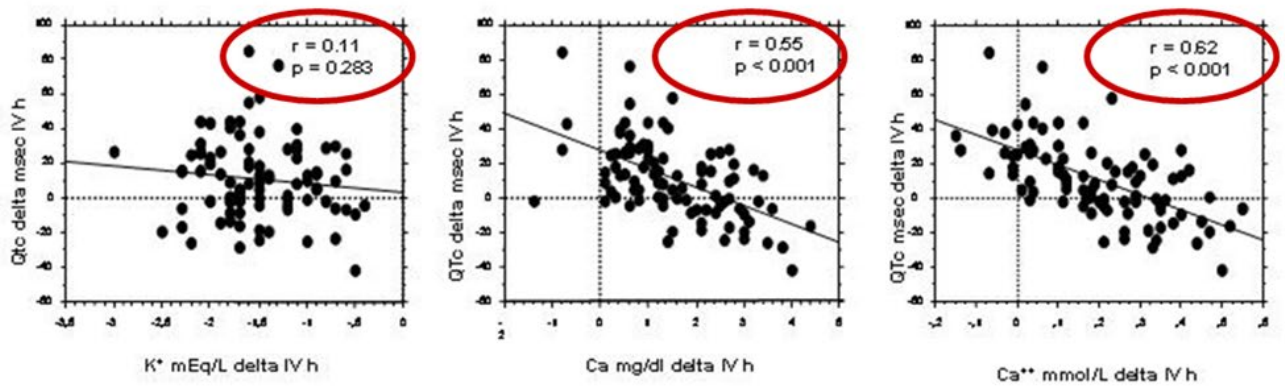
QT interval prolungation and ventricular fibrillation

QT interval and HD bath composition



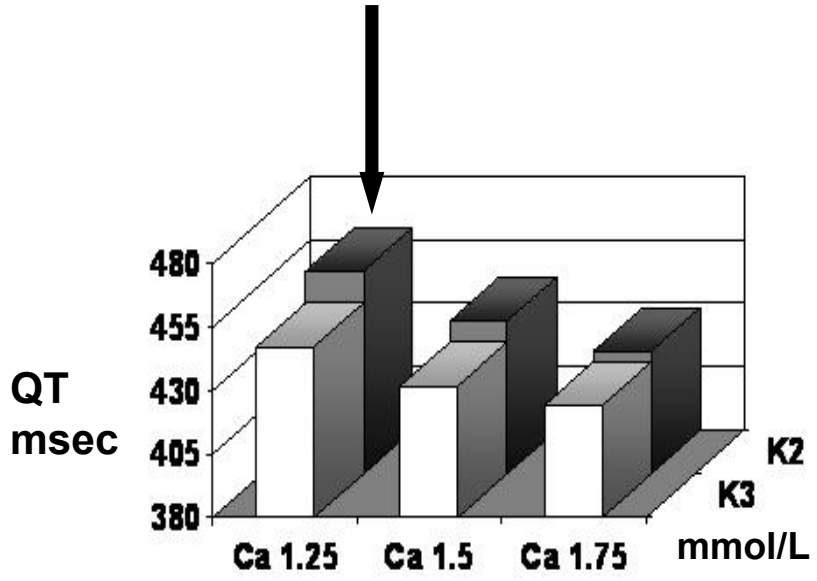
Genovesi *Europace* 2008

The correlation between QTc and calcium intra-dialysis modifications is closer than the relation between QTc and intradialytic potassium changes.



Genovesi *Europace* 2008

Electrolyte concentration during haemodialysis and QT interval prolongation in uraemic patients



Genovesi *Europace* 2008

QTc interval duration and bicarbonate concentration in dialysate

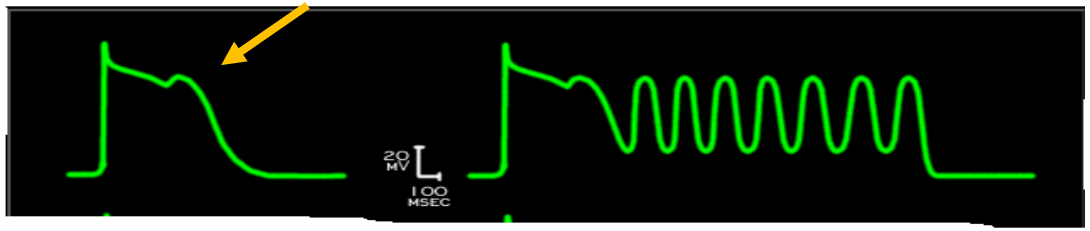
TABLE III
PREDICTORS OF INCREASE IN QTc AT MULTIVARIATE REGRESSION ANALYSIS

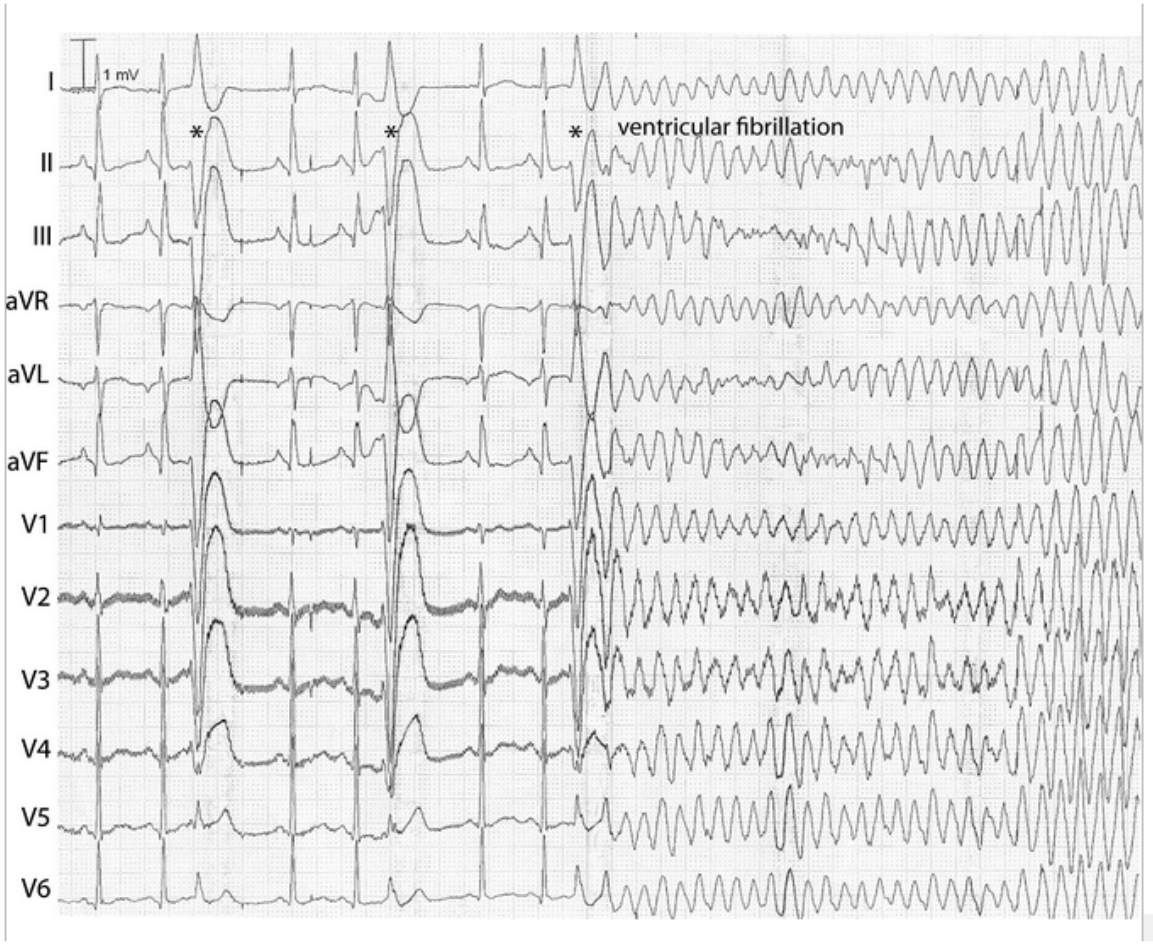
	Hazard ratio	95% Confidence interval	p Value
Low K	1.57	1.21-1.97	0.001
Low Ca	1.64	1.31-1.77	0.01
High bicarbonate	1.54	1.25-1.68	0.001
Low K and low Ca	2.21	1.94-2.55	0.0001
Low K and low Ca and high bicarbonate	3.33	2.58-3.93	0.00001

Di Iorio, JNEP 2012

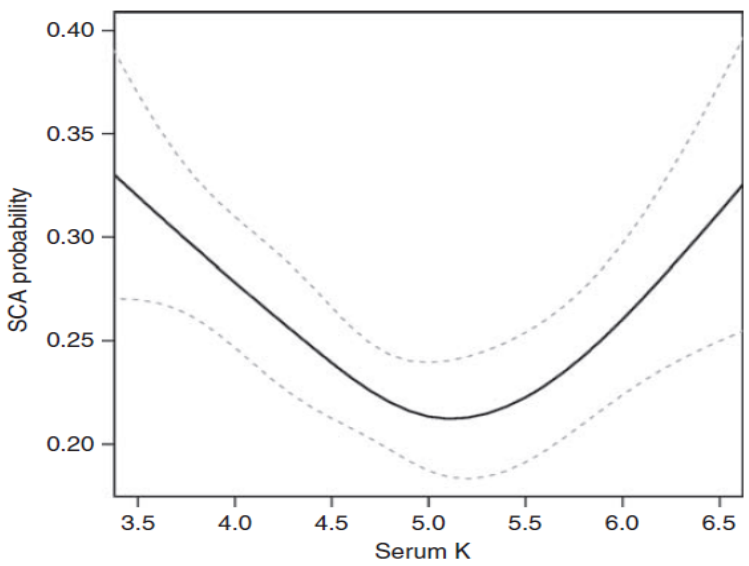
A severe prolongation of ventricular repolarisation time can cause early after-depolarizations that may “trigger” tachy-arrhythmias

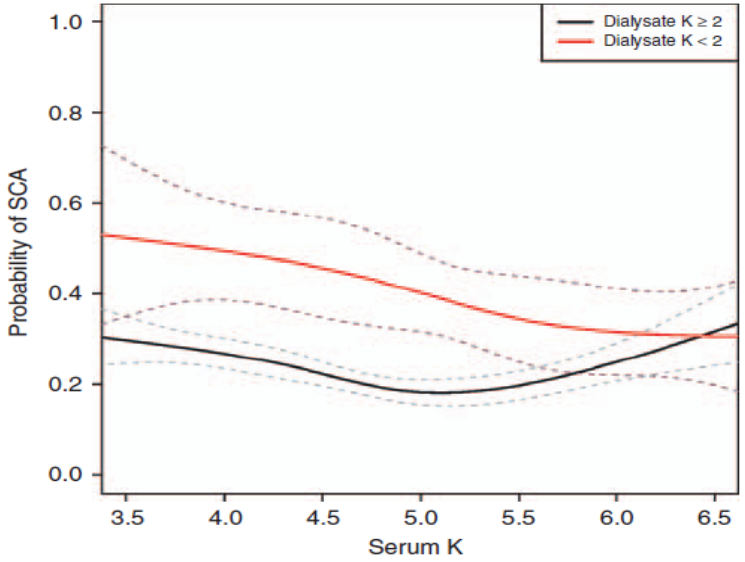
EAD





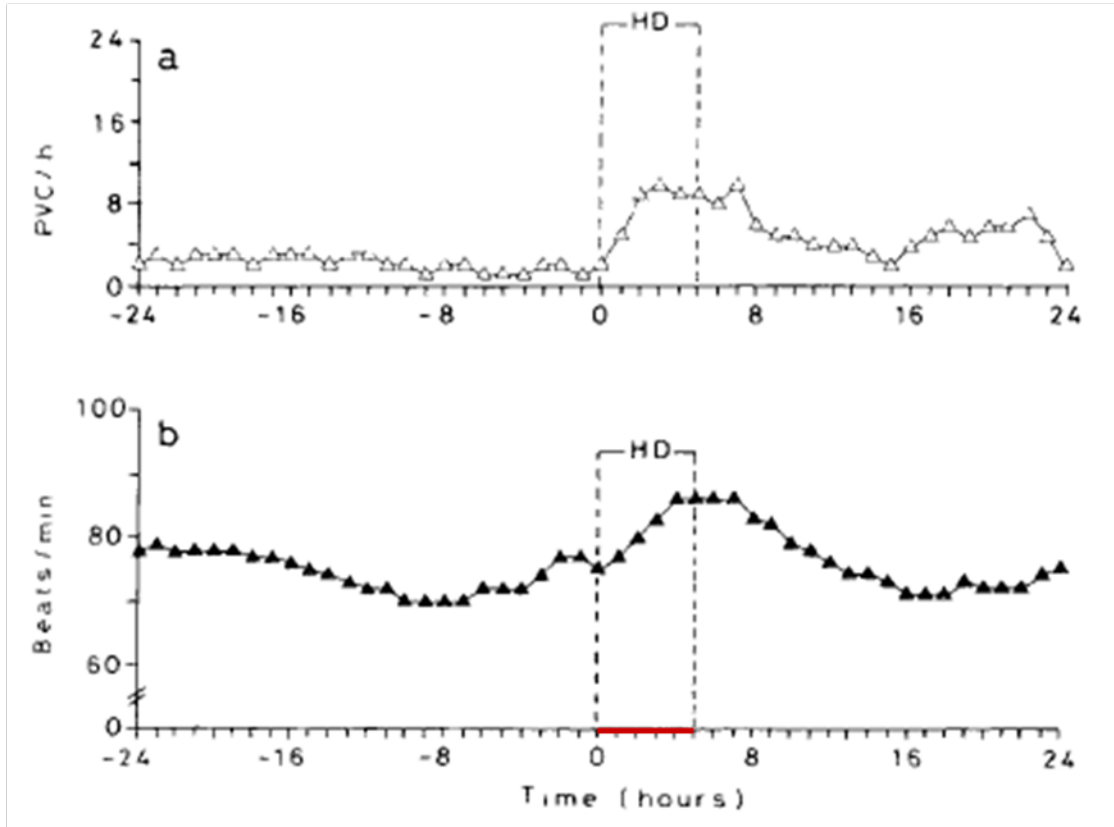
Potassium dialysate concentration and intra-dialytic sudden cardiac arrest





Pun, Kidney International 2011

The hemodialysis session increases ventricular arrhythmias



Gruppo emodialisi e Patologie Cardiovascolari *Lancet* 1988

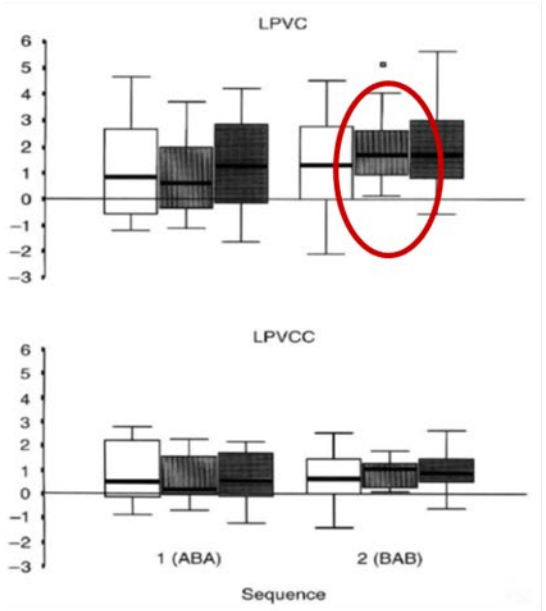
Mortality is not increased in patients with increased intra-dialytic arrhythmia

UNIVARIATE AND MULTIVARIATE RISK FACTORS FOR TOTAL 4-YEAR MORTALITY (36/128)

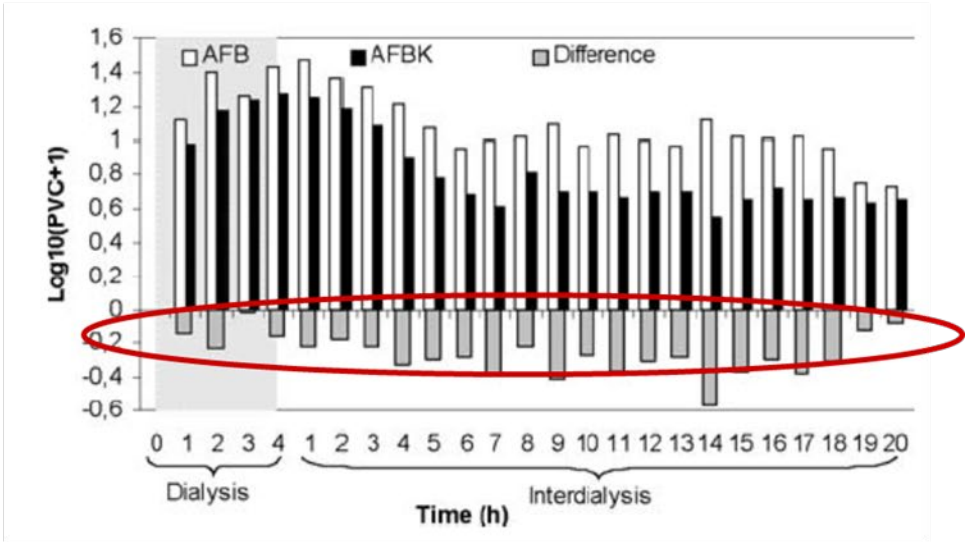
Factor*	% mortality†	Univariate analysis RR (95% CI)	Univariate analysis p‡	Multivariate analysis RR (95% CI)	Multivariate analysis p‡
Age ⩾ 55 yr (2)	40 (33/82)	8·85 (3·23–24·21)	0·0001	8·24 (2·53–16·22)	0·001
PVC ⩾2/h	40 (15/37)	1·76 (1·01–3·07)	0·047		
IHD (2)	61 (11/18)	2·75 (1·53–4 93)	0·0007	2·32 (1·05–3 55)	0·040
LV hypertrophy (18)	34 (16/47)	1·95 (1·01–3·76)	0·046		
Lown class 4A or B	44 (12/27)	1 87 (0·97–3·59)	NS	..	..
LV dysfunction (15)	28 (6/21)	1·14 (0·53–2·44)	NS	..	..
Kidney transplant (13)	11 (1/9)	0·38 (0·03–4 03)	NS	..	..
Digitalis (9)	35 (7/20)	1·30 (0 43–3·89)	NS	..	..
Antiarrhythmics (9)	55 (5/9)	2·13 (0·80–5·67)	NS	..	..

Sforzini *Lancet* 1992

Potassium profiled hemodialysis can decrease intradialytic ventricular arrhythmias

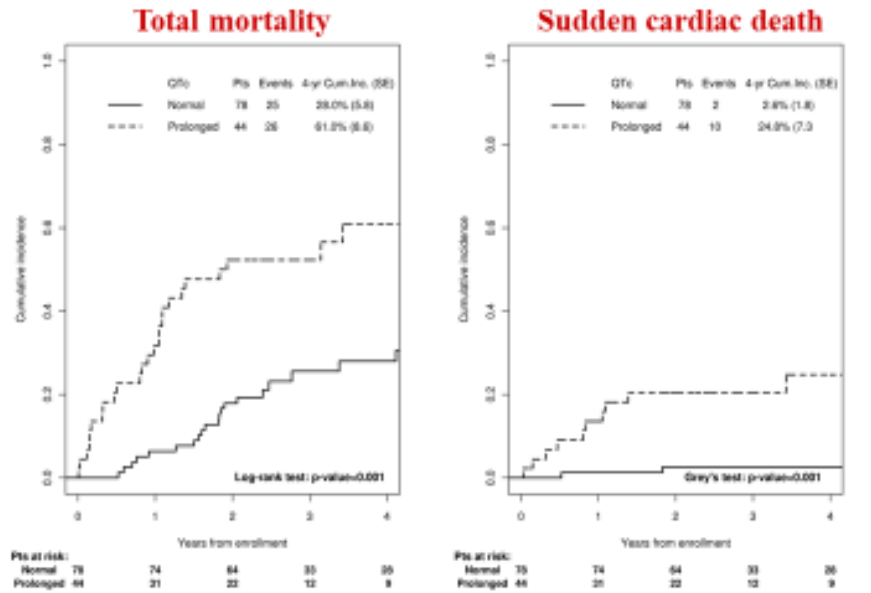


Radaelli *Kidney Int* 1996



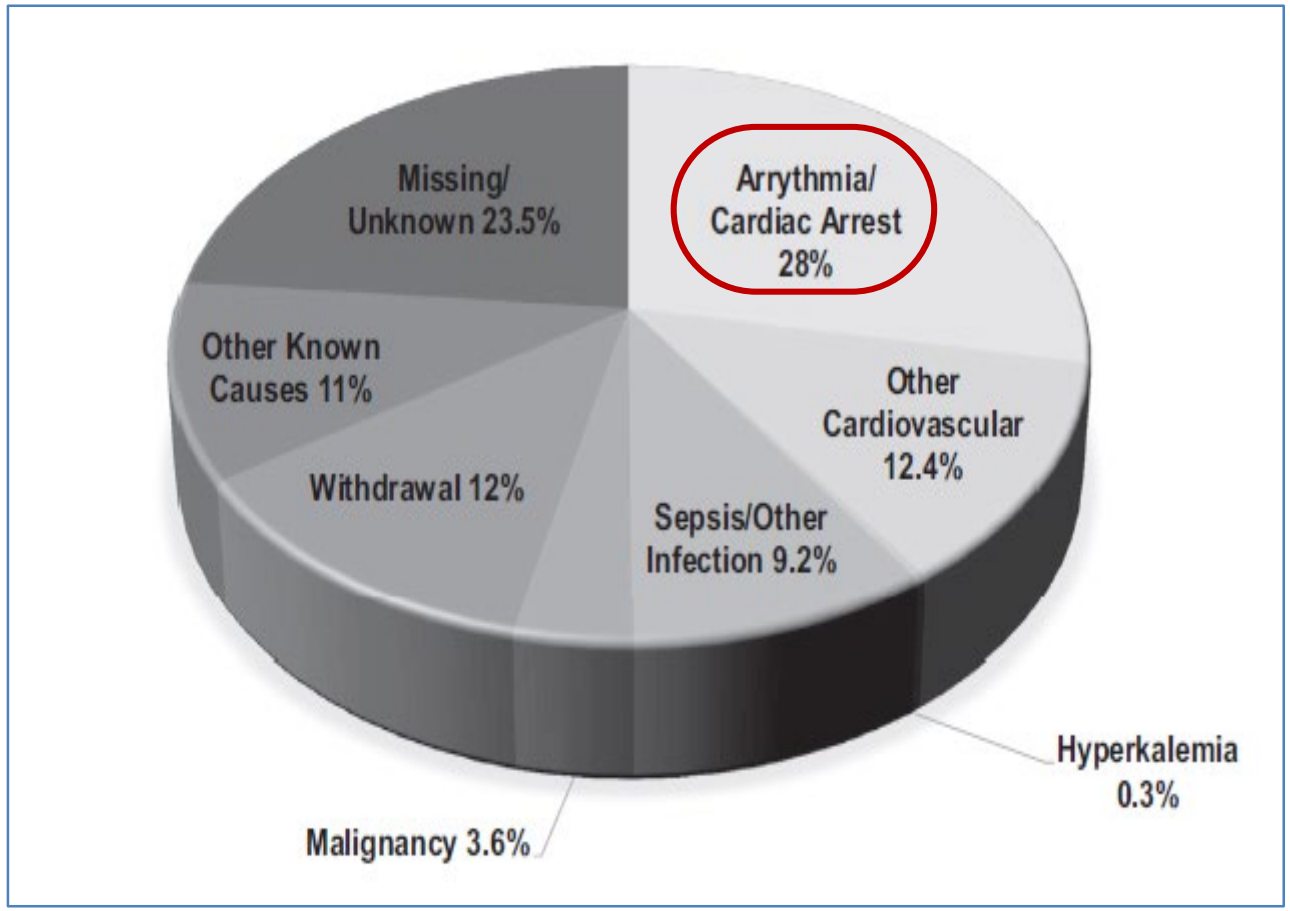
Santoro NDT 2008

Increased QT duration is associated with an increase in both total and sudden cardiac mortality in hemodialysis patients



Genovesi, Europace 2013

Causes of death among dialysis patients (2011 to 2013)



Renal Data System, 2015 Annual Data Report, Fig 9.1b.

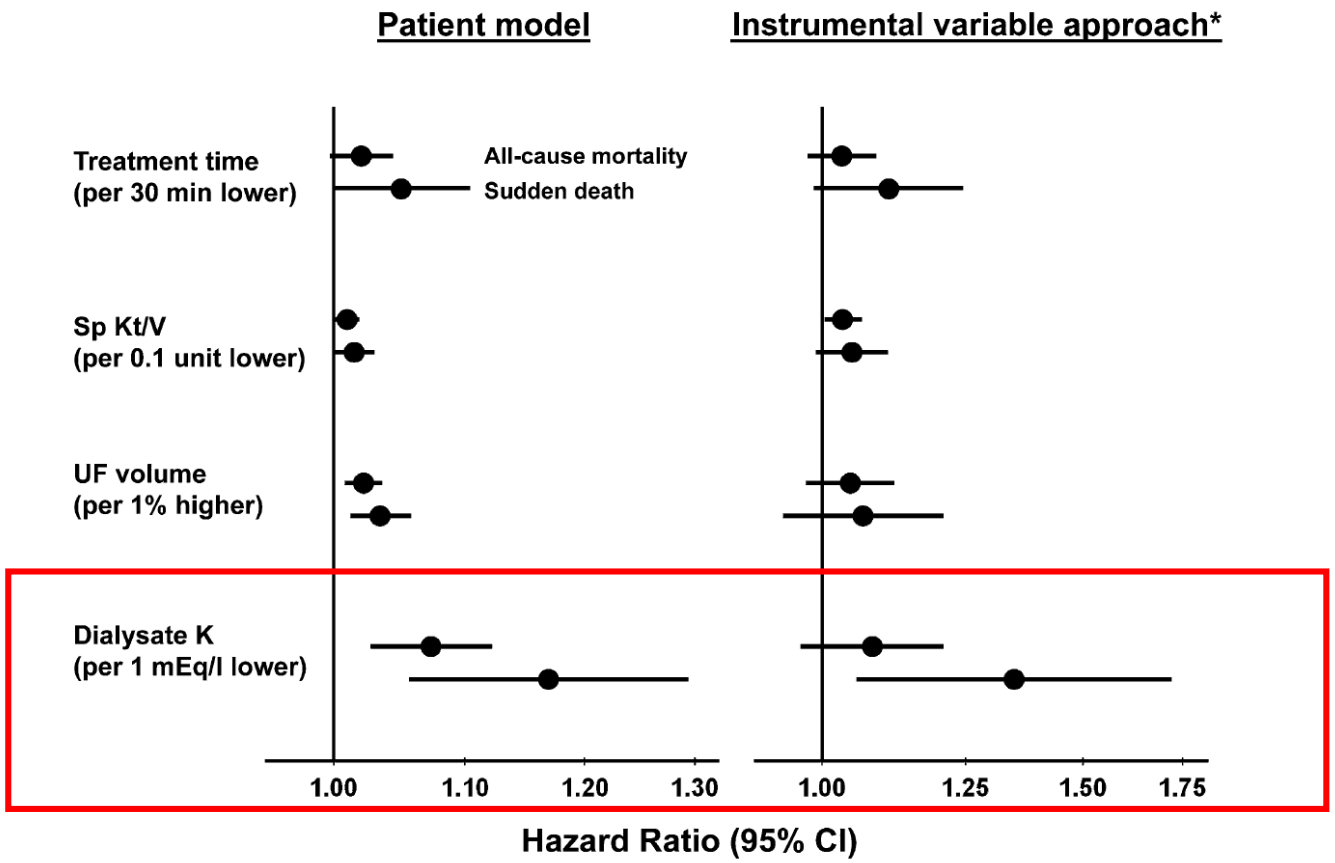
Association between dialysate potassium and clinical outcomes, according to pre-dialysis serum potassium values

Table 3. Association of K_D[a] with mortality

	Patient Level						Instrumental Variable Approach					
	K_D ≤1.5 (versus ≥3)			K_D=2–2.5 (versus ≥3)			K_D ≤1.5 (versus ≥3)			K_D=2–2.5 (versus ≥3)		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
All patients (*N*=37,741)												
all-cause mortality	1.13	(1.03–1.25)	0.01	1.08	(1.01–1.16)	0.03	1.09	(0.88–1.35)	0.43	1.23	(1.04–1.45)	0.01
sudden death	1.39	(1.12–1.74)	0.004	1.17	(1.01–1.37)	0.04	1.67	(0.99–2.81)	0.05	1.61	(1.12–2.30)	0.01
other cardiovascular death	1.14	(0.95–1.36)	0.16	1.04	(0.91–1.19)	0.54	1.11	(0.75–1.64)	0.62	1.23	(0.90–1.68)	0.19
noncardiovascular death	0.99	(0.84–1.17)	0.93	1.05	(0.94–1.16)	0.38	0.84	(0.61–1.16)	0.29	1.03	(0.83–1.29)	0.76
Among patients with serum K ≥5 (*n*=17,327)												
all-cause mortality	1.09	(0.95–1.26)	0.23	1.08	(0.97–1.20)	0.17	1.13	(0.87–1.47)	0.37	1.23	(0.99–1.52)	0.06
sudden death	1.21	(0.91–1.61)	0.18	1.11	(0.90–1.38)	0.33	1.27	(0.73–2.22)	0.40	1.30	(0.81–2.08)	0.28
other cardiovascular death	1.16	(0.88–1.52)	0.29	1.00	(0.82–1.21)	0.97	1.18	(0.74–1.88)	0.49	1.17	(0.79–1.72)	0.44
noncardiovascular death	0.97	(0.77–1.22)	0.81	1.10	(0.93–1.31)	0.27	1.02	(0.70–1.47)	0.93	1.21	(0.87–1.69)	0.25
Among patients with serum K <5 (*n*=20,414)												
all-cause mortality	1.15	(1.00–1.33)	0.04	1.06	(0.98–1.15)	0.15	1.04	(0.80–1.36)	0.76	1.23	(1.03–1.46)	0.02
sudden death	1.53	(1.10–2.13)	0.01	1.18	(0.98–1.42)	0.08	2.01	(0.96–4.24)	0.06	1.86	(1.31–2.63)	<0.001
other cardiovascular death	1.05	(0.85–1.31)	0.64	1.05	(0.88–1.24)	0.58	0.94	(0.56–1.56)	0.80	1.23	(0.86–1.76)	0.26
noncardiovascular death	1.03	(0.77–1.38)	0.83	1.00	(0.88–1.15)	0.95	0.77	(0.51–1.15)	0.20	0.95	(0.75–1.22)	0.71

Jadoul CJASN 2012

Association of treatment practices with sudden death



Jadoul CJASN 2012

Association between dialysate potassium and clinical outcomes

		All-Cause Mortality		Arrhythmia Composite[a]	
Dialysate Potassium	No. of Patients (%)	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
1.0-1.5 mEq/L	8,114 (15)	0.96 (0.90-1.03)	1.04 (0.97-1.11)	1.09 (0.95-1.24)	1.14 (1.00-1.30)
2.0-2.5 mEq/L	33,017 (61)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3.0-4.0 mEq/L	13,405 (25)	1.13 (1.07-1.18)	0.95 (0.90-1.00)	1.05 (0.96-1.15)	0.95 (0.86-1.04)

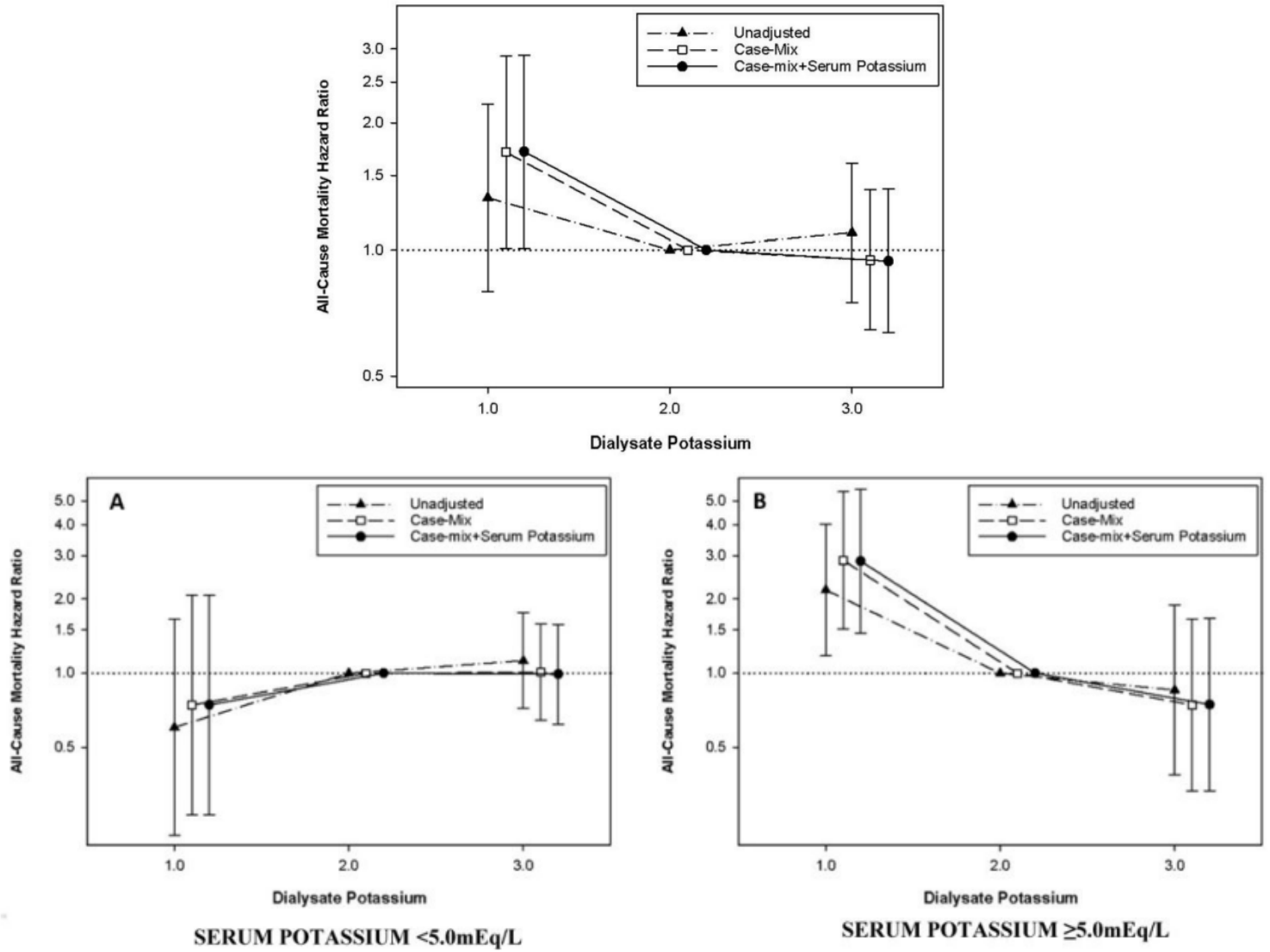
Karaboyas, AJKD 2016

Associations between predialysis serum potassium and clinical outcomes

		All-Cause Mortality		Arrhythmia Composite[a]	
Serum Potassium	No. of Patients (%)	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
<4.0 mEq/L	6,300 (11)	1.18 (1.12-1.24)	1.03 (0.97-1.09)	0.99 (0.88-1.11)	0.94 (0.83-1.05)
4.0-5.0 mEq/L	27,525 (50)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
5.1-5.5 mEq/L	10,700 (19)	0.95 (0.91-0.99)	1.02 (0.97-1.07)	0.97 (0.89-1.07)	1.00 (0.91-1.10)
5.6-6.0 mEq/L	6,259 (11)	1.02 (0.96-1.08)	1.13 (1.06-1.20)	1.05 (0.95-1.17)	1.07 (0.96-1.20)
>6.0 mEq/L	4,399 (8)	1.00 (0.93-1.07)	1.12 (1.04-1.21)	1.16 (1.02-1.32)	1.21 (1.05-1.38)

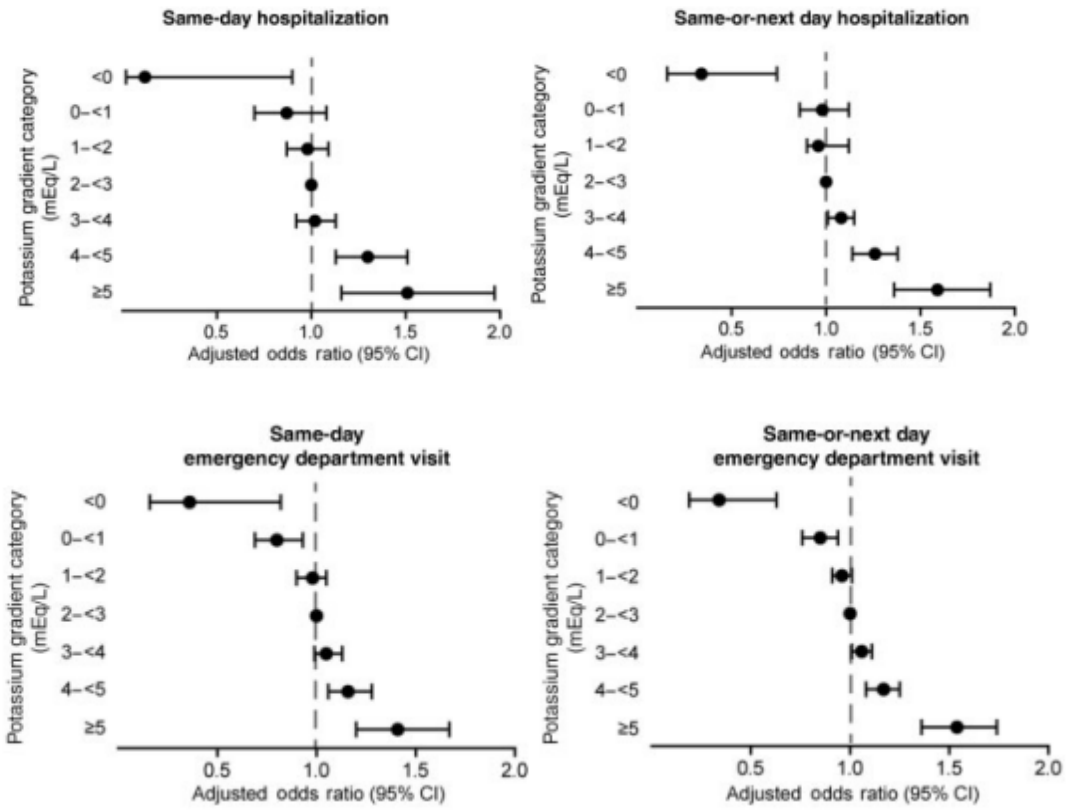
Karaboyas, AJKD 2016

Dialysate potassium and mortality in a prospective hemodialysis cohort



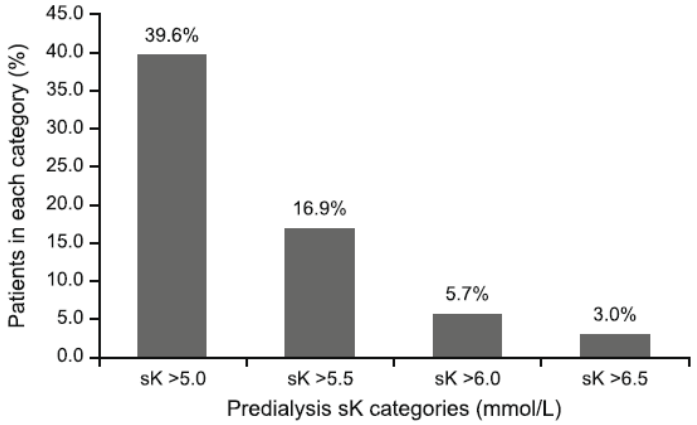
Ferrey, Am J Nephrol 2018

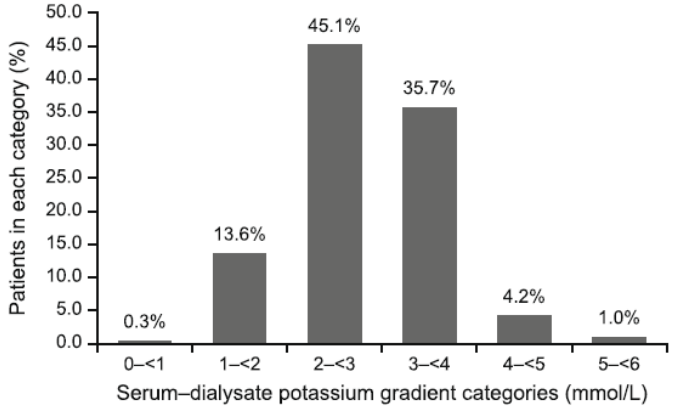
Serum-to-dialysate potassium gradient and short-term outcomes in hemodialysis patients

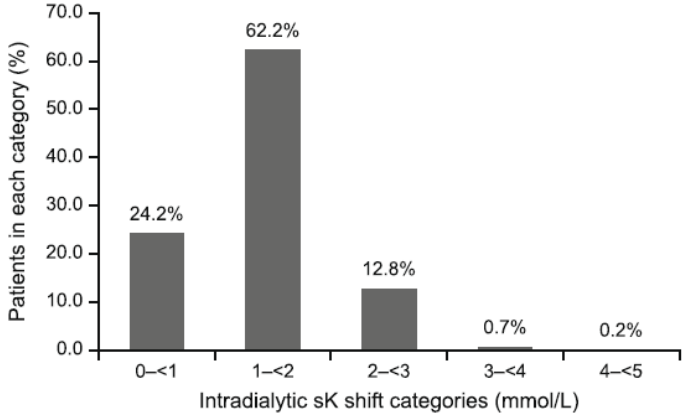


Brunelli, NDT 2018

Hyperkalaemia prevalence and dialysis patterns in Chinese patients on haemodialysis

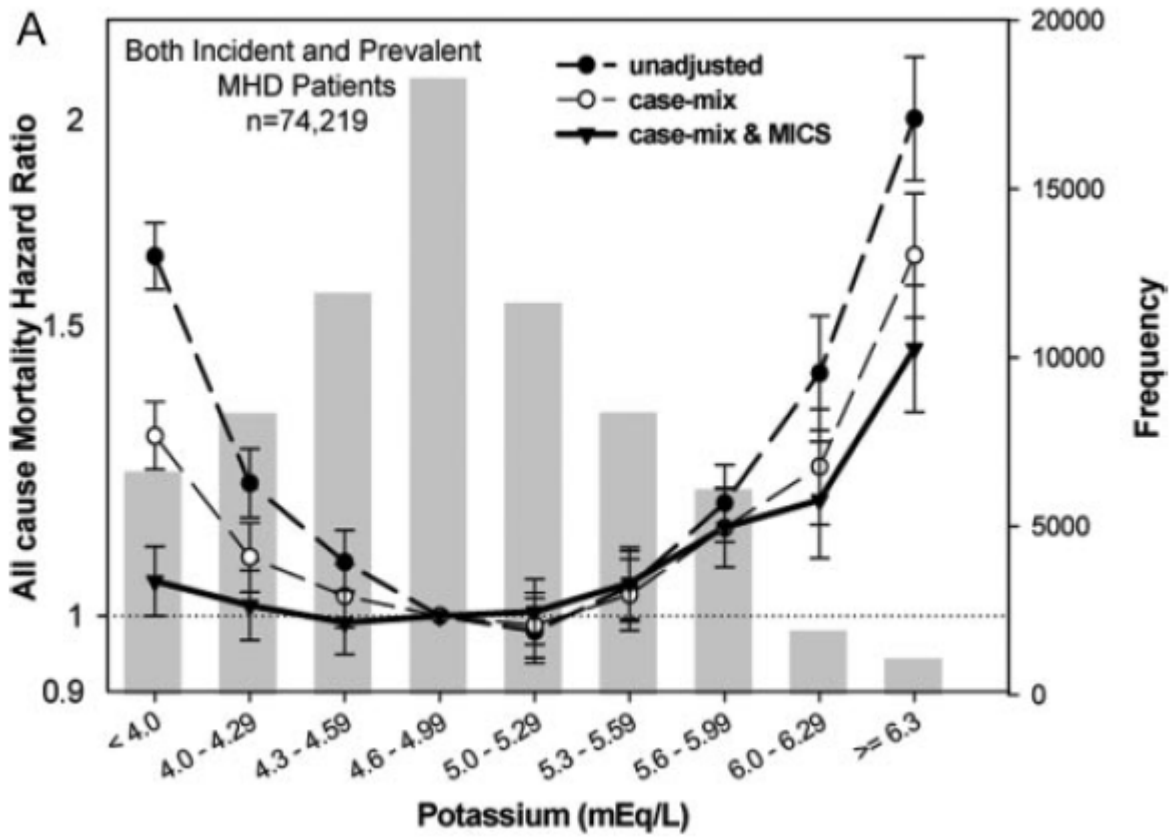






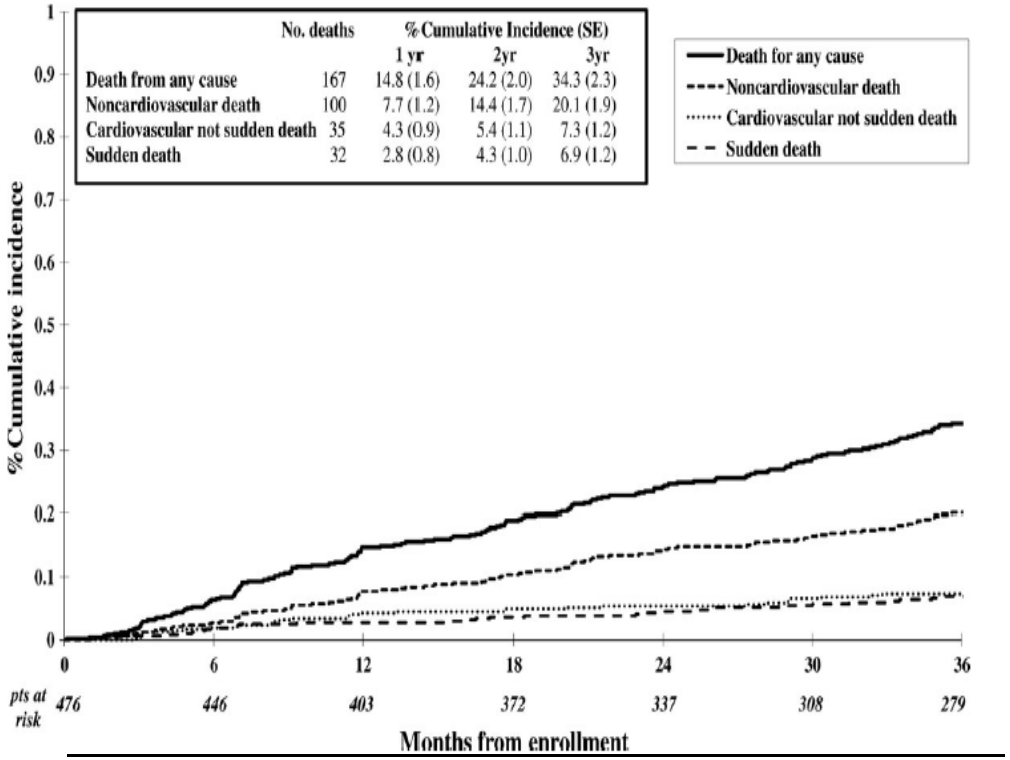
Zhaohui, BMC Nephrology 2023

Serum potassium and mortality in hemodialysis patients



Kovesdy, CJASN 2007

Sudden death and associated factors in a historical cohort of chronic haemodialysis patients



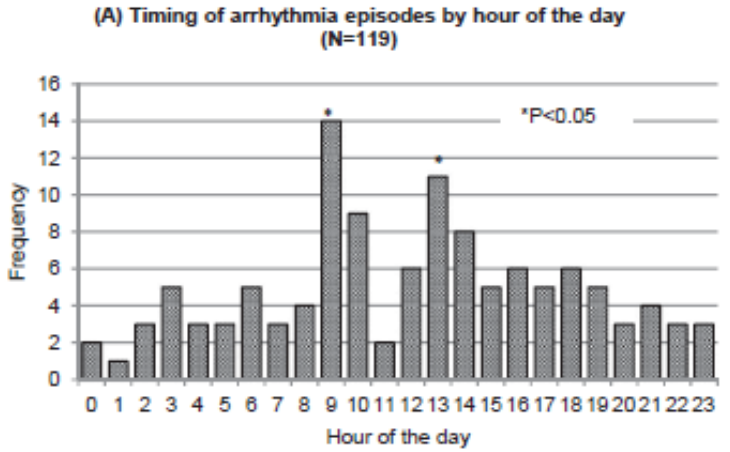
Risk factors	Hazard ratio[a] (95% confidence interval)	*P*-value
Hyperkalaemia		
No	1	
Yes	2.74 (1.28–5.85)	0.009

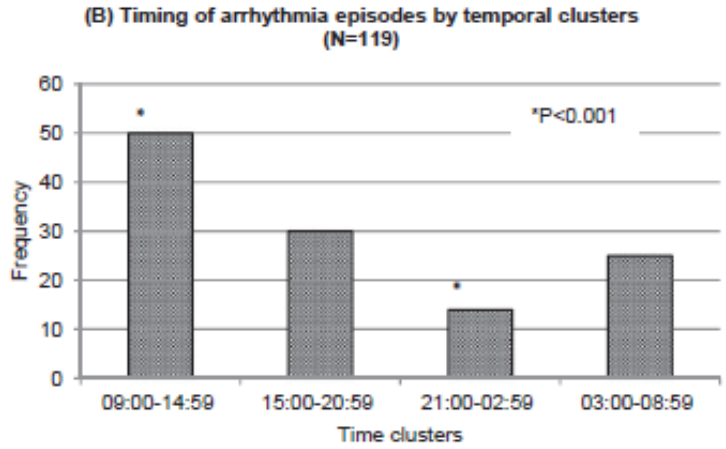
Risk of sudden death was independently associated with

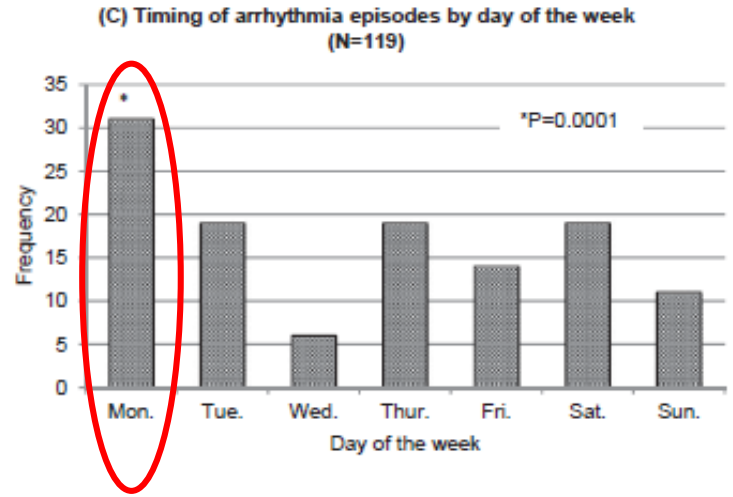
- atrial fibrillation
- diabetes mellitus
- **predialytic hyperkalemia**

Genovesi, NDT 2009

Sudden Cardiac Arrest in Hemodialysis Patients with Wearable Cardioverter Defibrillator

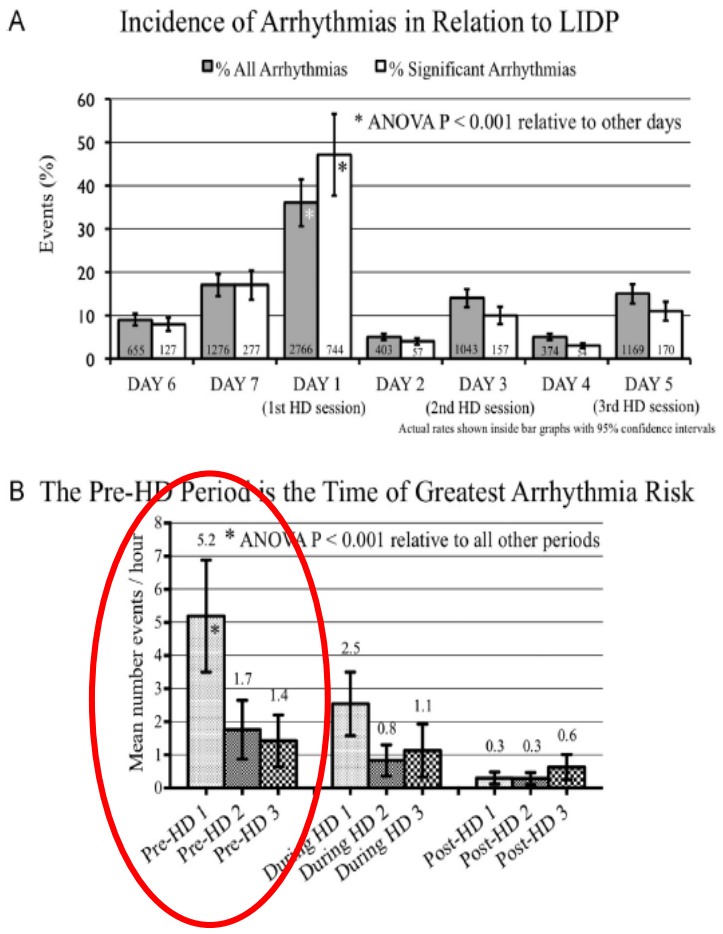




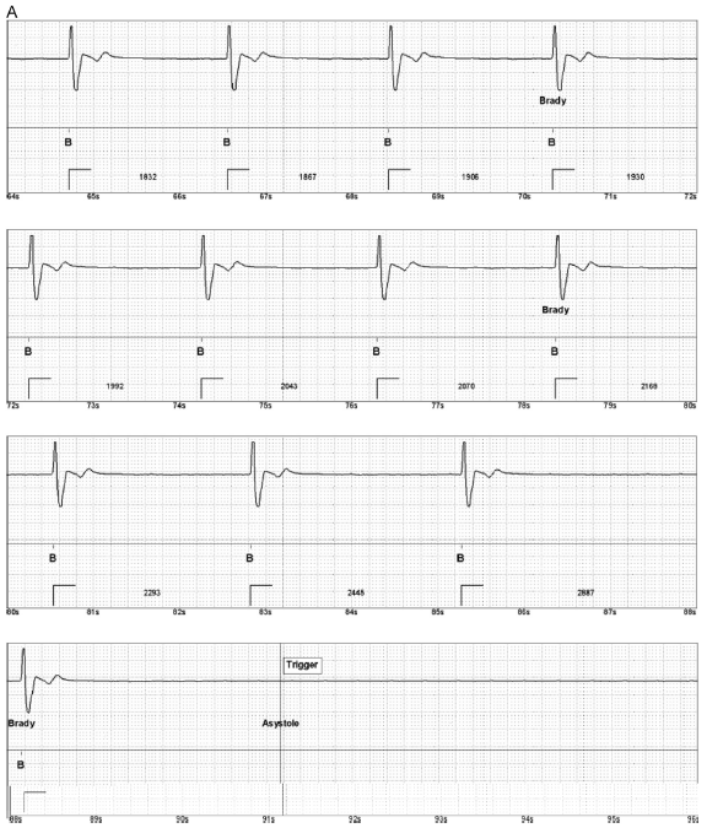


Wan ANE 2014

Temporal distribution of arrhythmic events in chronic kidney disease: Highest incidence in the long interdialytic period



Wong, Heart Rhythm 2016



First short interdialytic interval

Long interdialytic interval

Wan, ANE 2014

Wong, Heart Rhythm 2016

Implantable loop recorder and arrhythmias in hemodialysis patients

Four SDs occurred, with progressive bradycardia followed by asystole.

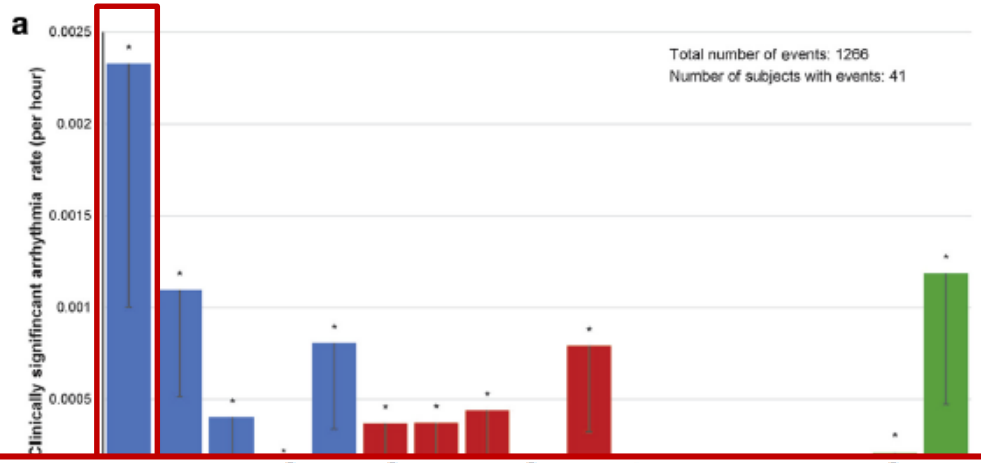
A higher risk for conduction disorder was associated with plasma potassium >5.0 mmol/l and the longer interdialytic period

A higher risk for ventricular arrhythmia was associated with potassium <4.0 mmol/l

Sacher, JACC Electrophysiol 2017

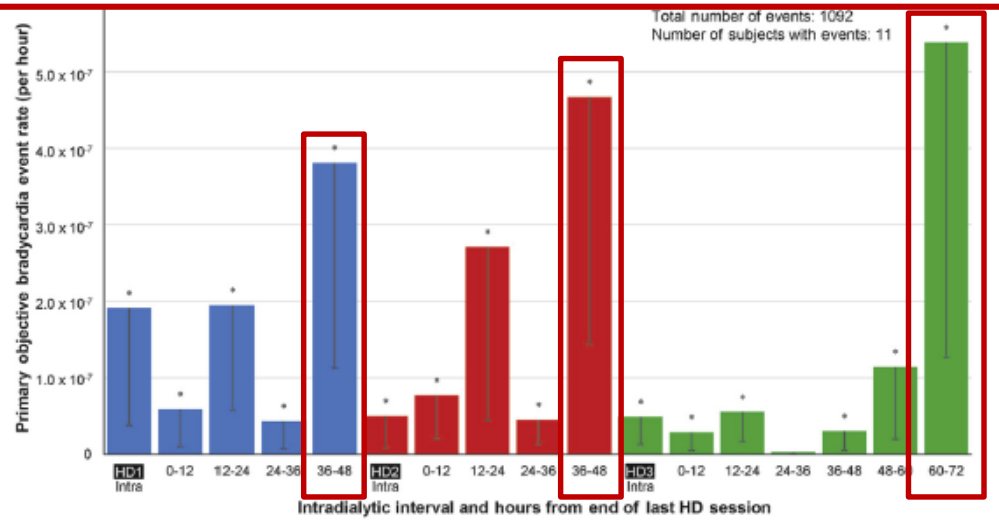
Loop recorders in hemodialysis patients

All arrhythmias



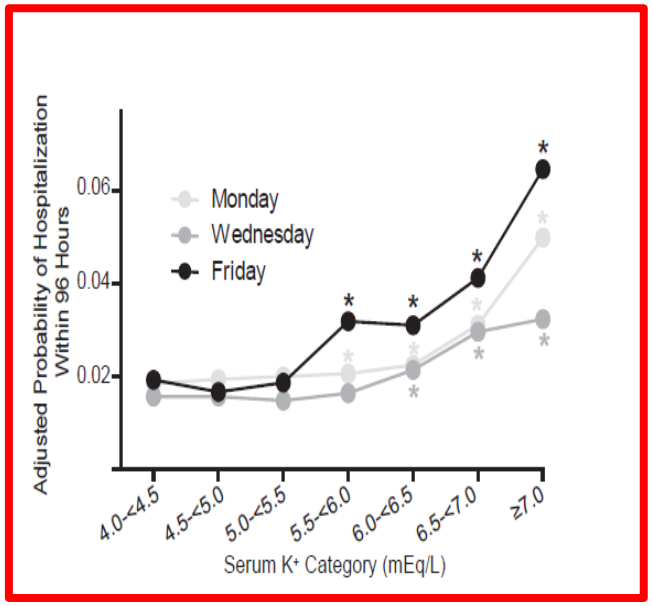
The majority were bradycardias (1461), with 14 episodes of asystole and only one of sustained ventricular tachycardia.

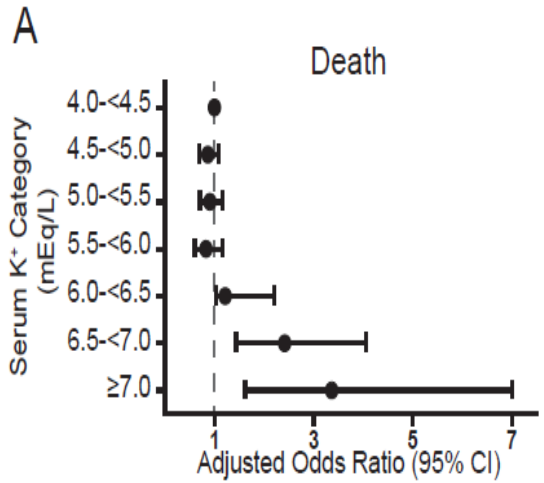
Bradyarrhythmias

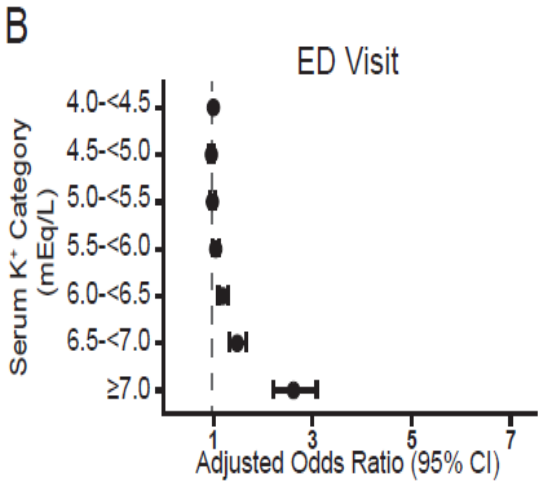


Roy-Chaudury, KI 2018

Serum potassium and clinical outcomes among hemodialysis patients: impact of the long interval

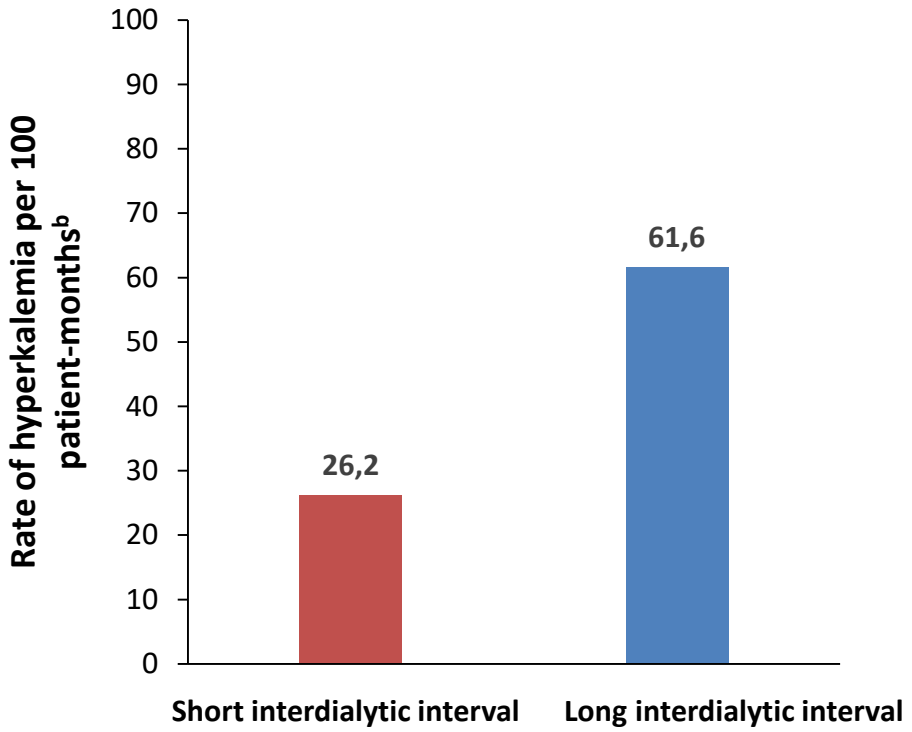






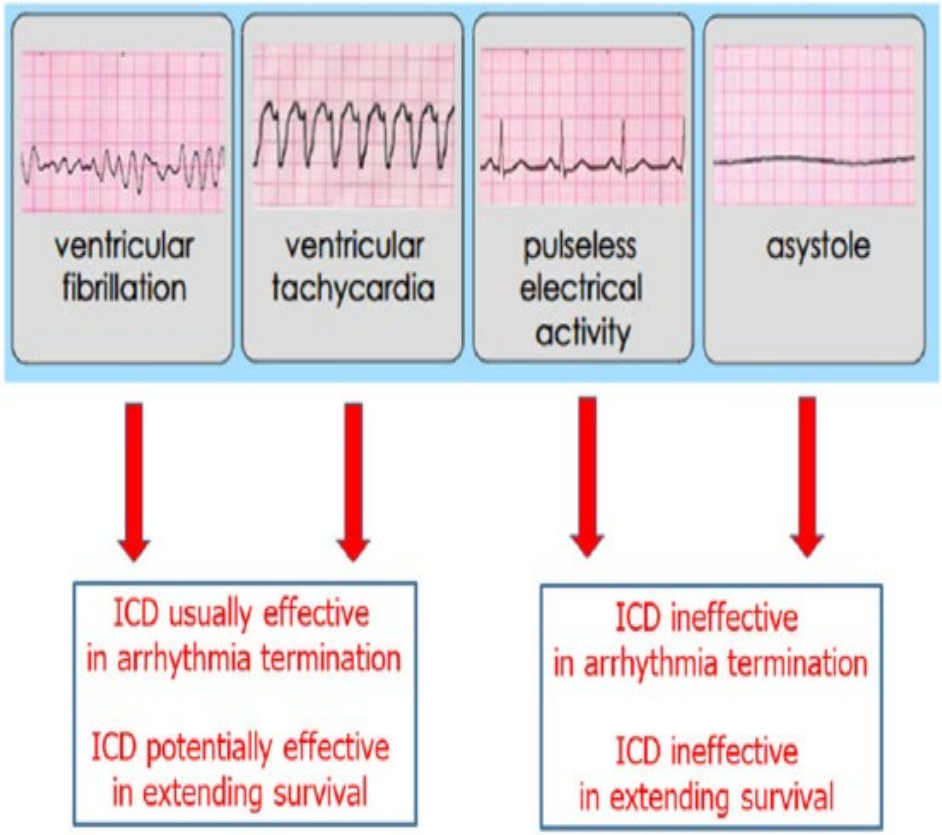
Brunelli, AJKD 2017

Prevalence of hyperkalemia is higher after the long interdialytic interval

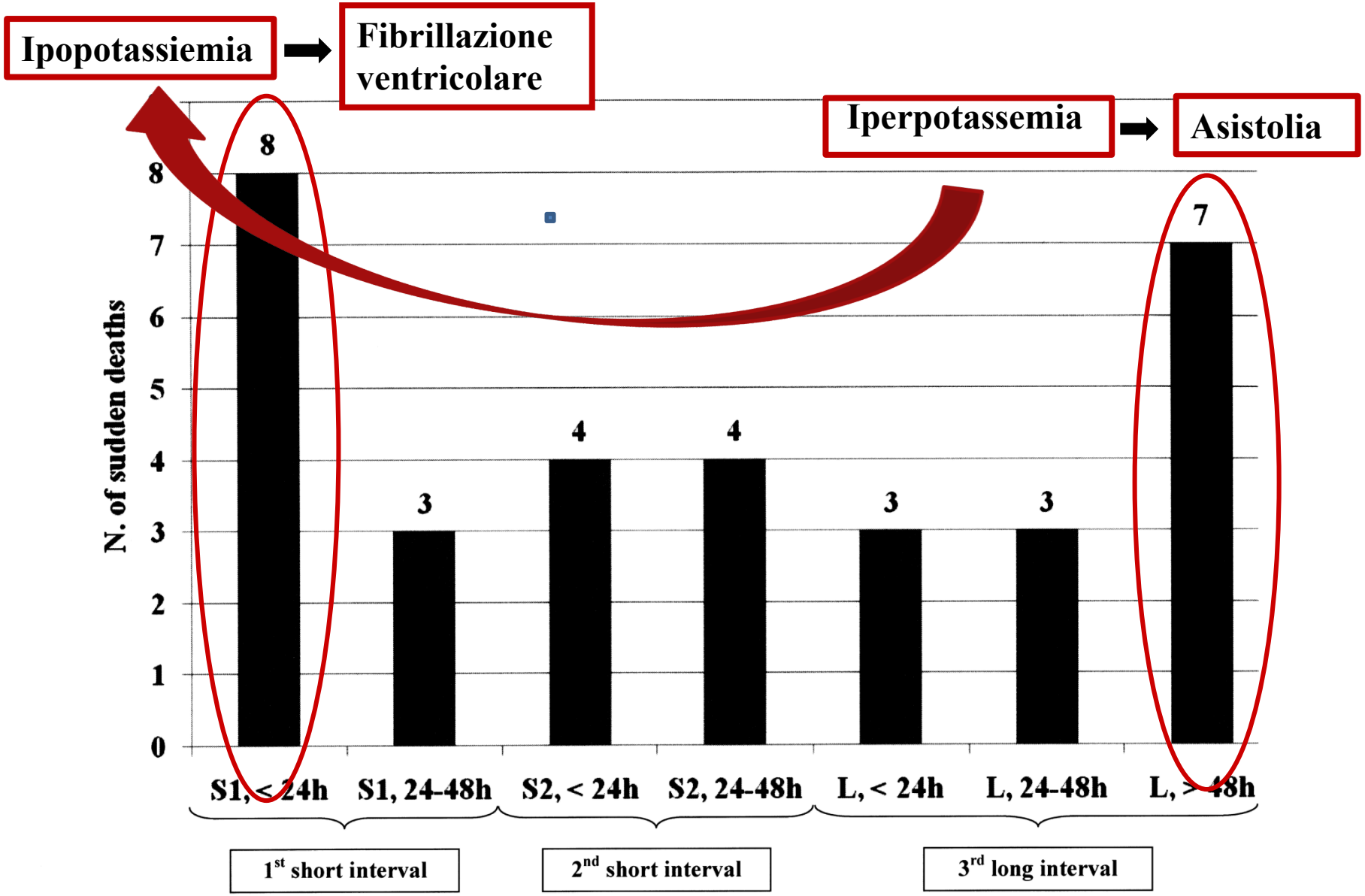


Yusuf Am J Nephrol 2016

Sudden cardiac death in ESRD patients: causes and management strategies:
EUDIAL position paper

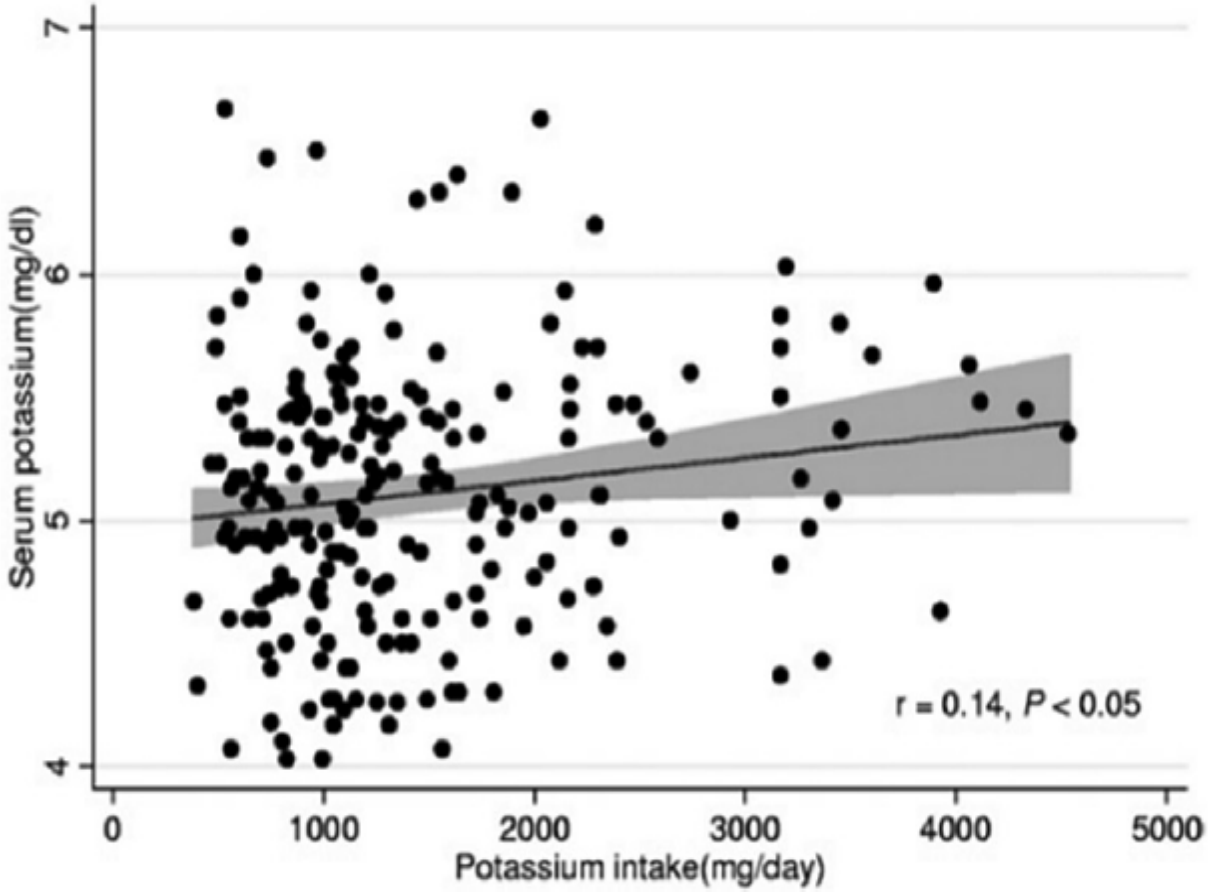


Genovesi, Nephrology Dialysis Transplantation 2021



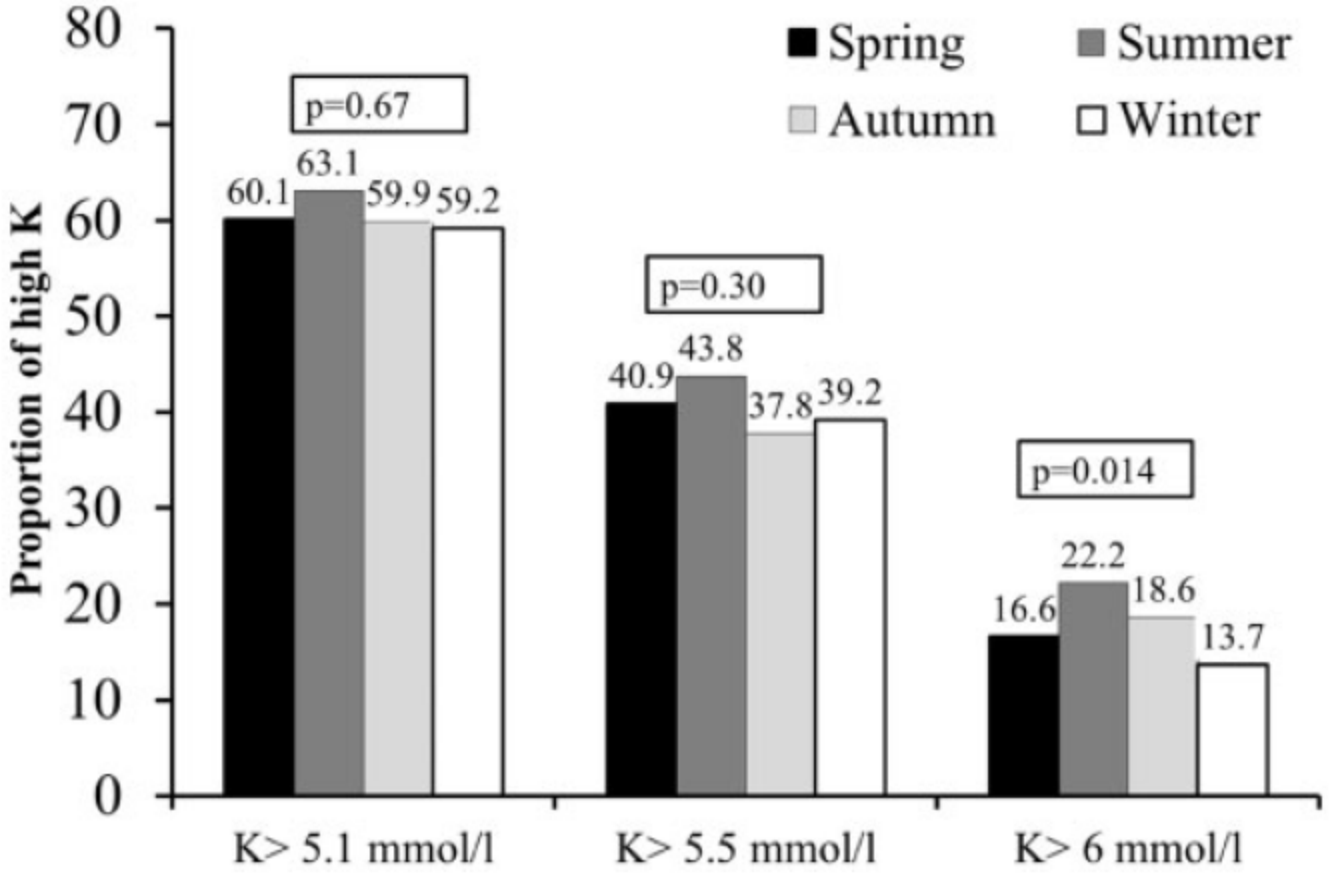
Genovesi Nephr Dial Transp 2009

Associations of reported dietary potassium intake and serum potassium in hemodialysis patients



Noori AJKD 2010

Hyperkalemia and seasonality in HD patients



Rossignol NDT 2017

Potassium-lowering drugs

Pharmacologic property	Sodium polystyrene sulfonate (SPS)[11]	Patiromer calcium sorbitex[20–22]	Sodium zirconium cyclosilicate[18,23–25]
Brand name	Kayexalate	Veltassa	Lokelma
Mechanism of action	Exchange K/Na	Exchange K/Ca	Exchange K/Na and H
	tract and facilitates excretion in the feces	feces	feces
Selectivity for potassium ion	Nonselective; also binds calcium and magnesium	Selective; also binds magnesium	Highly selective; nine times the potassium-binding capacity compared to SPS; also binds ammonium
Sodium content	1,500 mg sodium per 15 g dose	No sodium content	Approximately 1,000 mg sodium per 10 g dose
Sorbitol content	20 g sorbitol per 15 g dose	4 g sorbitol per 8.4 g dose	No sorbitol content
Onset of effect	Variable; 2–6 hours	7–48 hours	1–6 hours
Duration of effect	Variable; 6–24 hours	12–24 hours	Unclear; appears to be 4–12 hours based on trial data

Risk of hospedalization for gastrointestinal events associated with SPS use

Figure. 30-Day Probability of Gastrointestinal (GI) Injury Requiring Hospitalization or Emergency Department Visit Associated With Sodium Polystyrene Sulfonate Use Compared With Nonuse

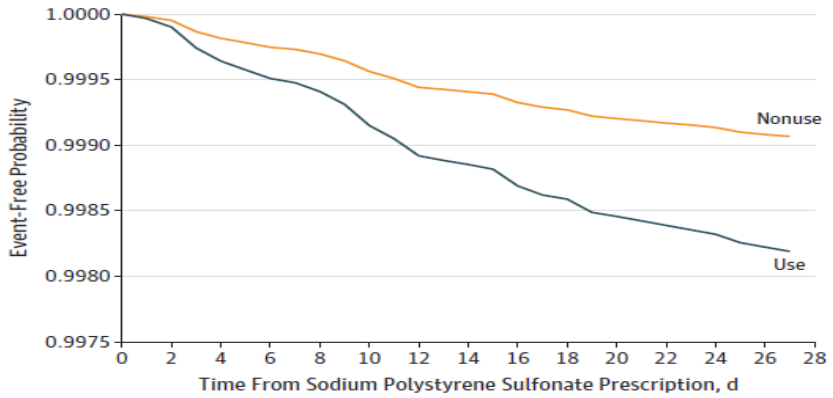


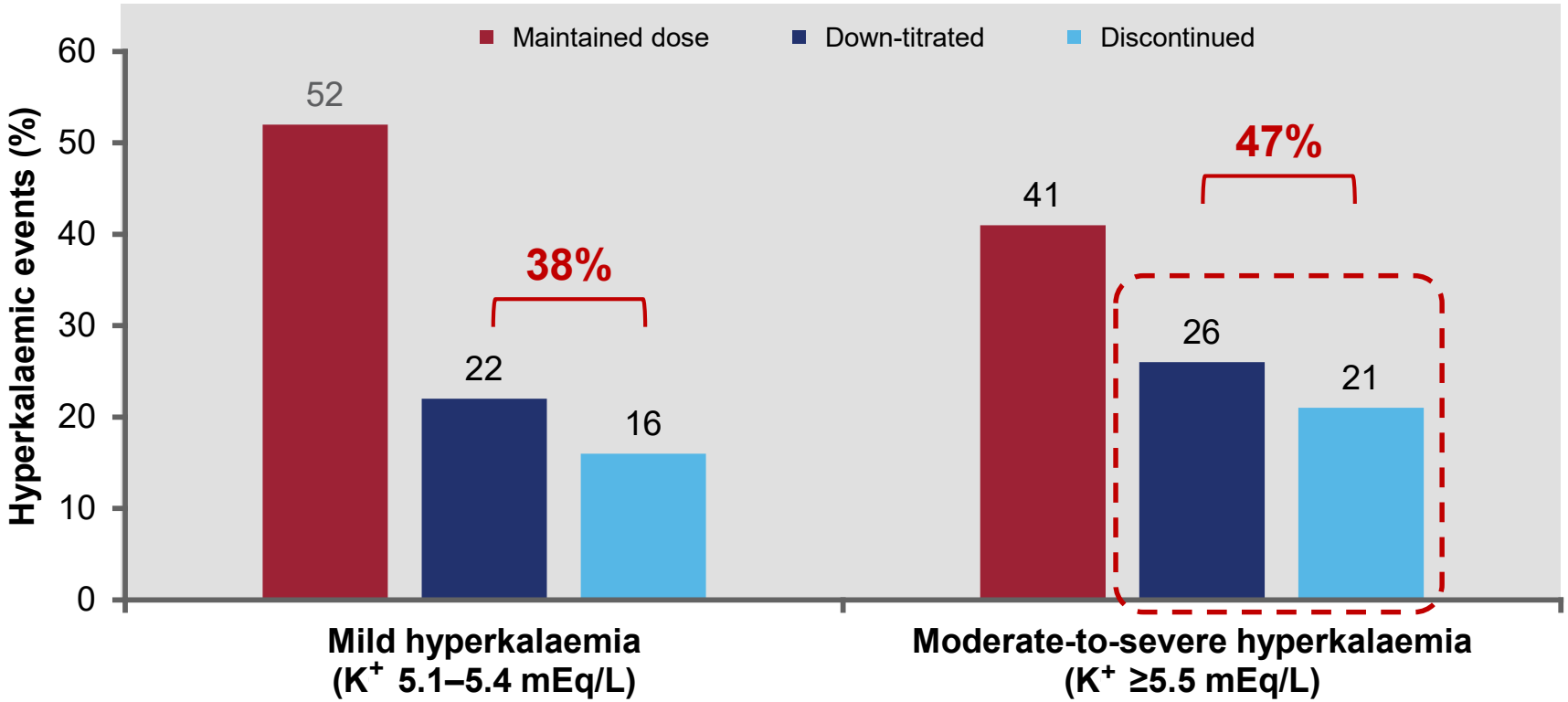
Table 3. Association of Sodium Polystyrene Sulfonate Use vs Nonuse With Hospitalization or Emergency Department Visit by Type of Gastrointestinal (GI) Event Within 30 Days[a]

	Use		Nonuse		
Variable	No. of Events (% Total)[b]	Incidence Rate (95% CI) per 1000 Person-Years	No. of Events (% Total)	Incidence Rate (95% CI) per 1000 Person-Years	HR (95% CI)
Intestinal ischemia/thrombosis	11 (0.1)	6.82 (3.78-12.32)	<5[c]	1.22 (0.31-4.89)	4.92 (1.09-22.25)
GI ulceration/perforation	13 (0.1)	8.07 (4.68-13.89)	7 (0)	4.28 (2.04-8.98)	1.75 (0.70-4.41)
Resection/ostomy	14	8.69 (5.15-14.67)	10 (0.1)	6.11 (3.29-11.36)	1.34 (0.59-3.02)

	Use		Nonuse		
Variable	No. of Events (%)	Incidence Rate (95% CI) per 1000 Person-Years	No. of Events (%)	Incidence Rate (95% CI) per 1000 Person-Years	HR (95% CI)[a]
Chronic Dialysis					
Yes	NR	NA	NR	NA	NA
No	37 (0.2)	NA	17 (0.1)	NA	2.05 (1.15-3.65)

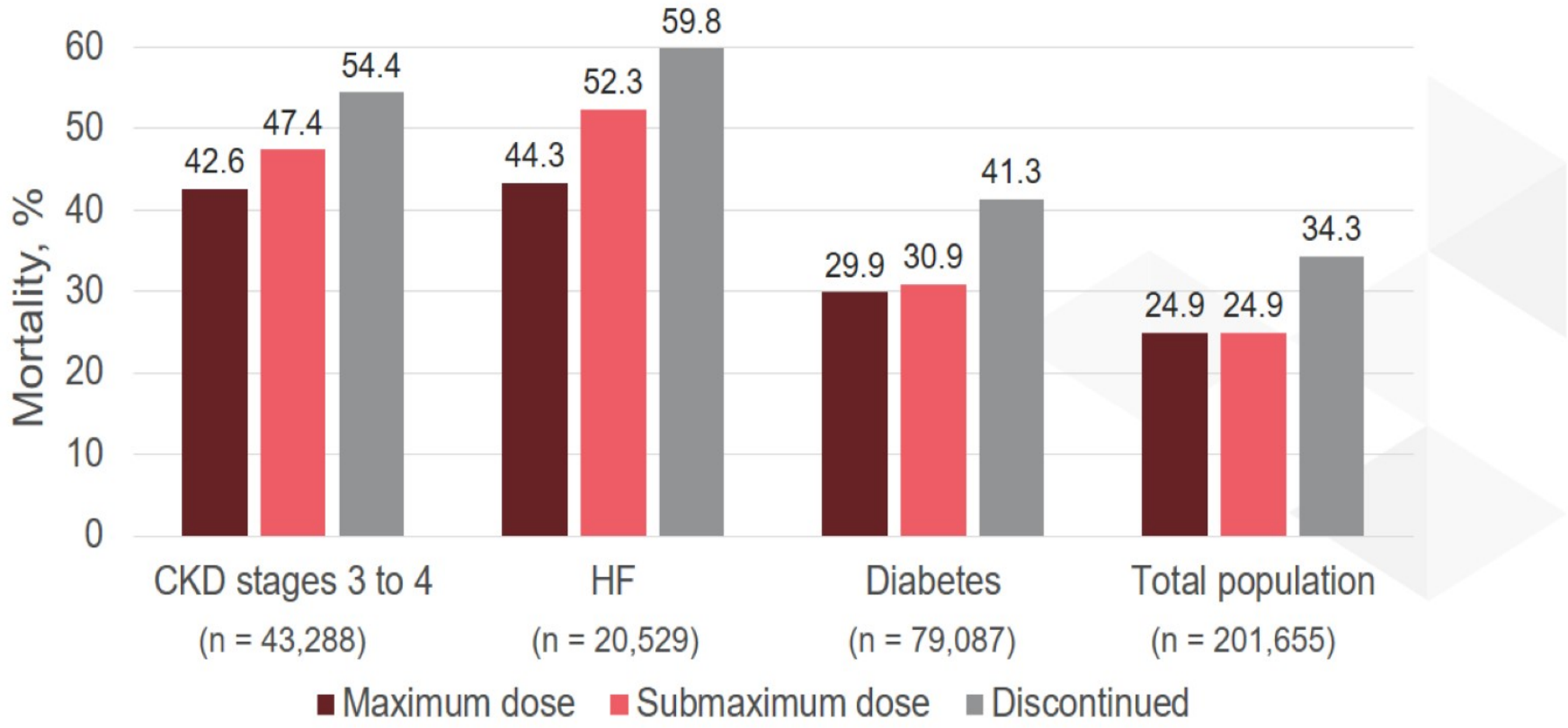
Noel JAMA Int Med 2019

Elevated K^+ is associated with dose reduction or discontinuation of RAASi



Epstein M, *Am J Manag Care.* 2015

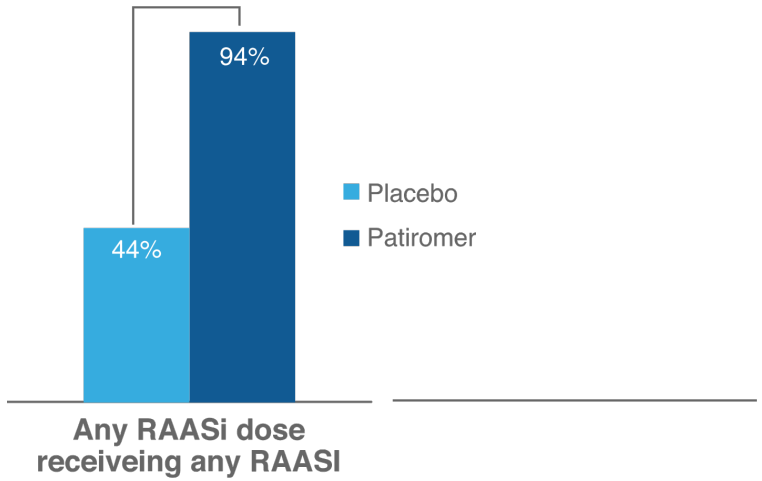
Using Maximum vs Submaximum Doses of RAAS Inhibitors Is Associated With Reductions in Mortality



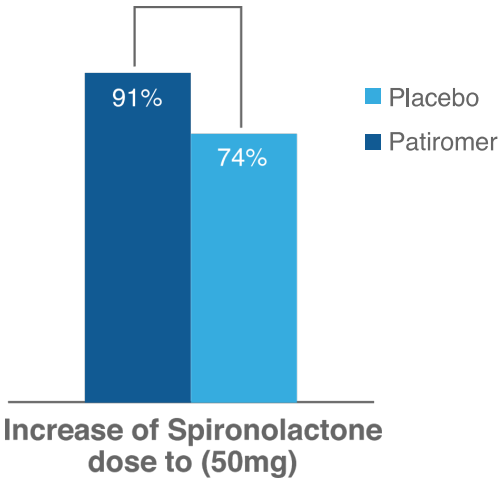
Epstein M, et al. *Am J Manag Care*. 2015;21:S212-S220.

Evidence about Patiromer enabling RAASi

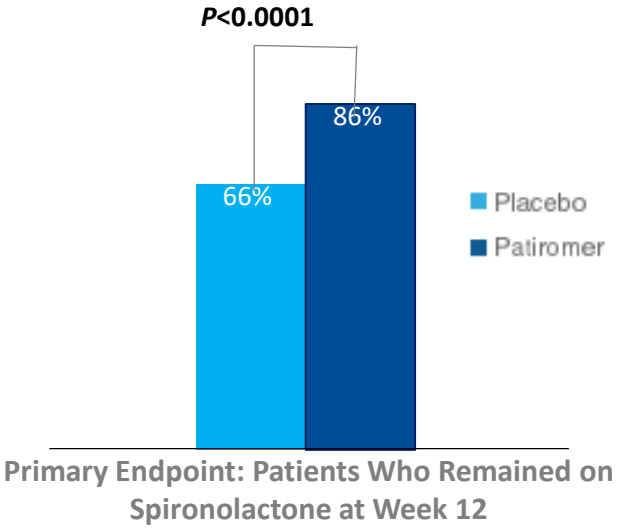
- **OPAL Weir NEJM 2015[2]**
  GFR 15-59; K^+ 5.1-6.4; RAASi; 42-49% HF
  8w randomized withdrawal → 60% v 15% recurrence



- **PEARL-HF EHJ 2011; n=105[3]**
  HF + ([K^+ requiring d/c RAASi] or [eGFR<60])
  4w □ normoK in 24% v 7%; prevent recurrence



- **AMBER LANCET 2019; n=295[4]**
  rHTN; eGFR 25-45 mL/min/1.73 m^2; sK^+ 4.3-5.1 mEq/L



SZC provided rapid K^+ reduction within 48 hours and sustained K^+ control for up to 1 year

ZS-004 (HARMONIZE)[1] | **ZS-004E (11-MONTH EXTENSION)[3]**

Open-label CP (48 hours)[1]
SZC 10 g TID (n=258)

Randomized, Double-blind MP (Days 1-29)[1,b]
Placebo (n=82) | SZC 5 g[c] (n=45) | SZC 10 g[c] (n=50) | SZC 15 g[c] (n=54)

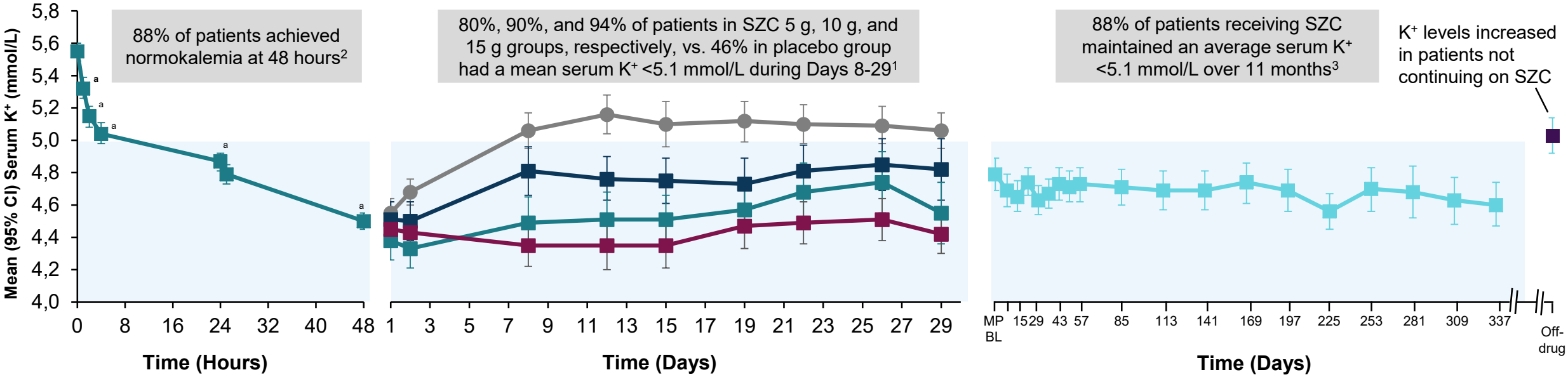
Open-label MP (Days 1-337)[3,d]
SZC titrated dose[e] (N=123)

88% of patients achieved normokalemia at 48 hours[2]

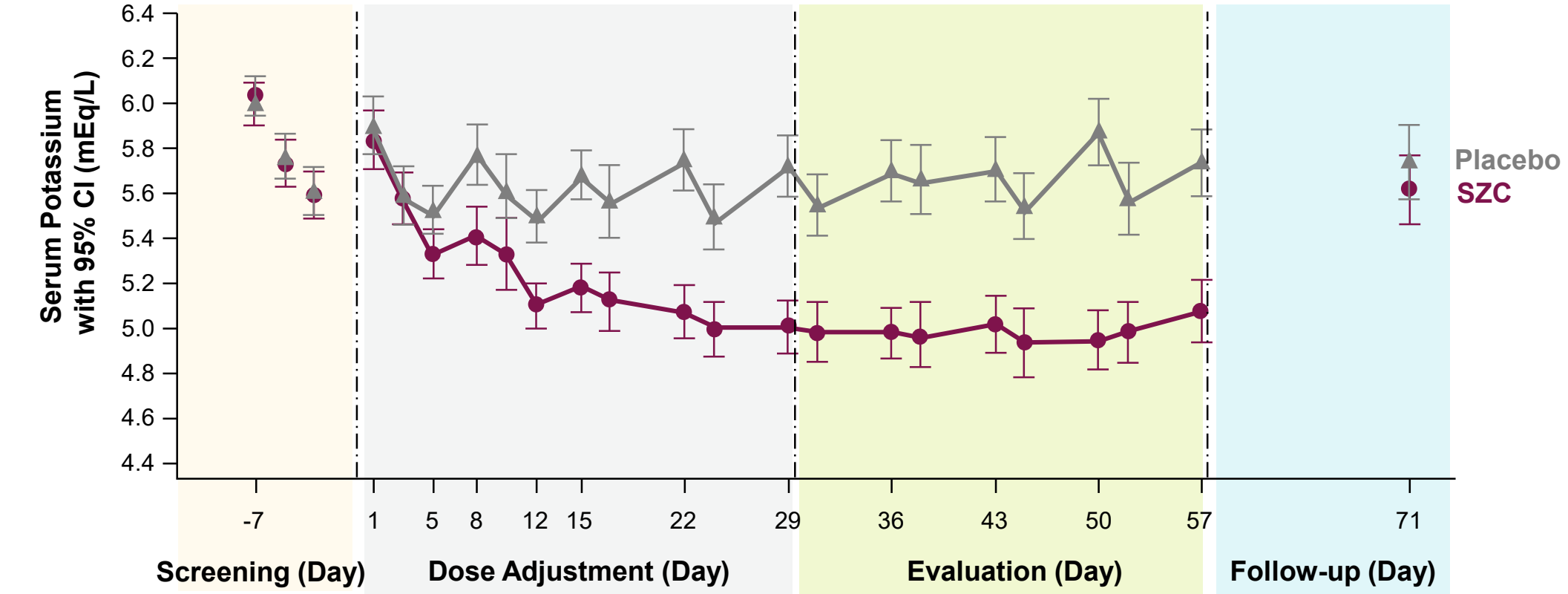
80%, 90%, and 94% of patients in SZC 5 g, 10 g, and 15 g groups, respectively, vs. 46% in placebo group had a mean serum K^+ <5.1 mmol/L during Days 8-29[1]

88% of patients receiving SZC maintained an average serum K^+ <5.1 mmol/L over 11 months[3]

K^+ levels increased in patients not continuing on SZC

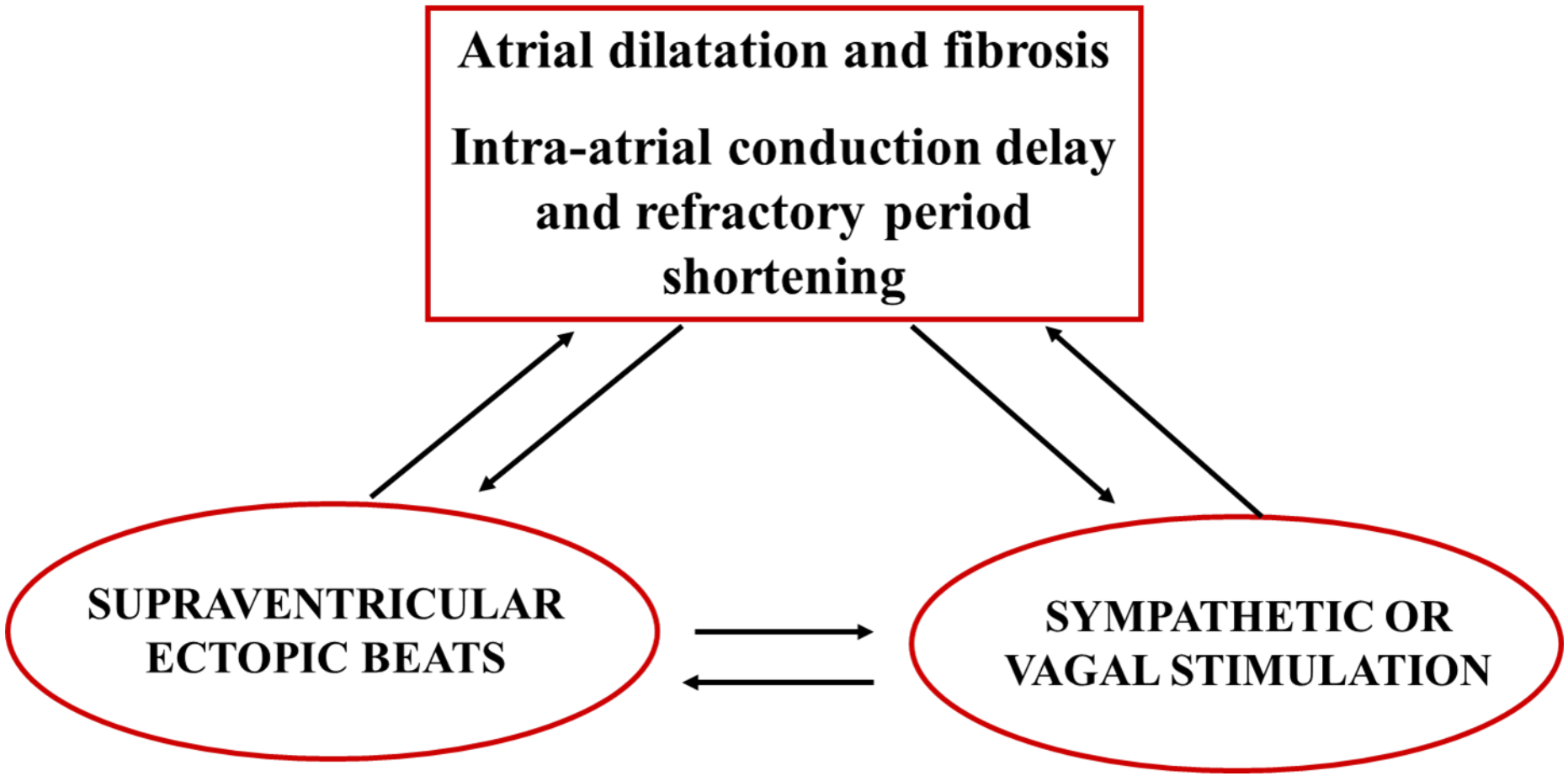


DIALIZE Trial

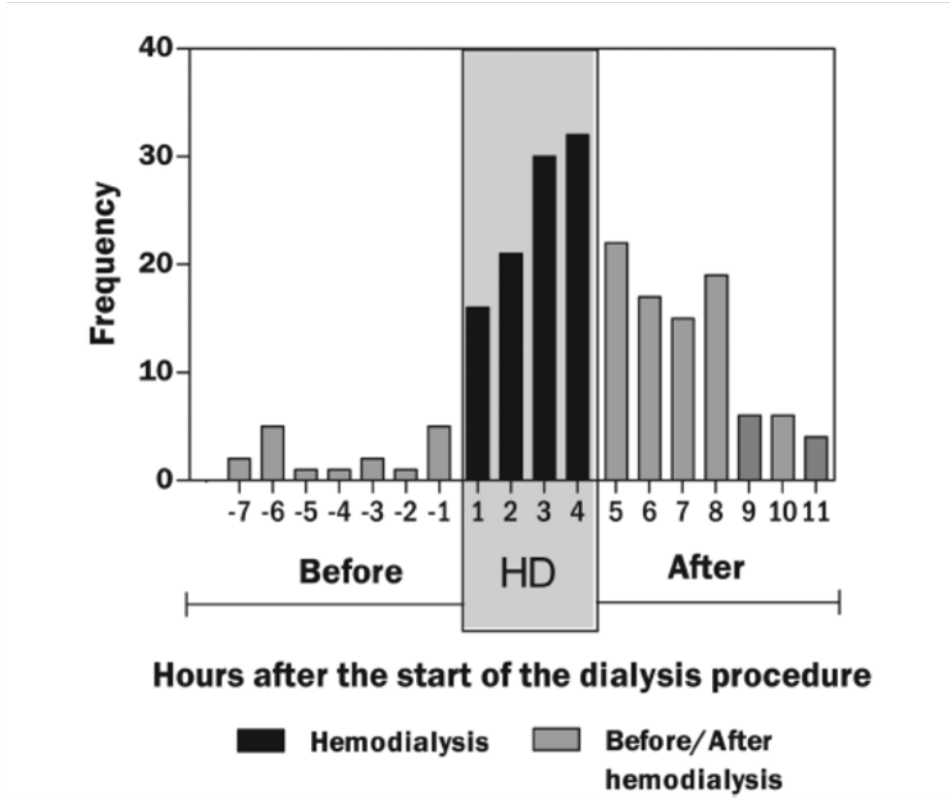


Subjects (n)												
SZC	95	81	90	89	92	90	93	92	88	90	90	82	87
Placebo	99	86	89	86	94	87	89	88	86	88	90	90	91

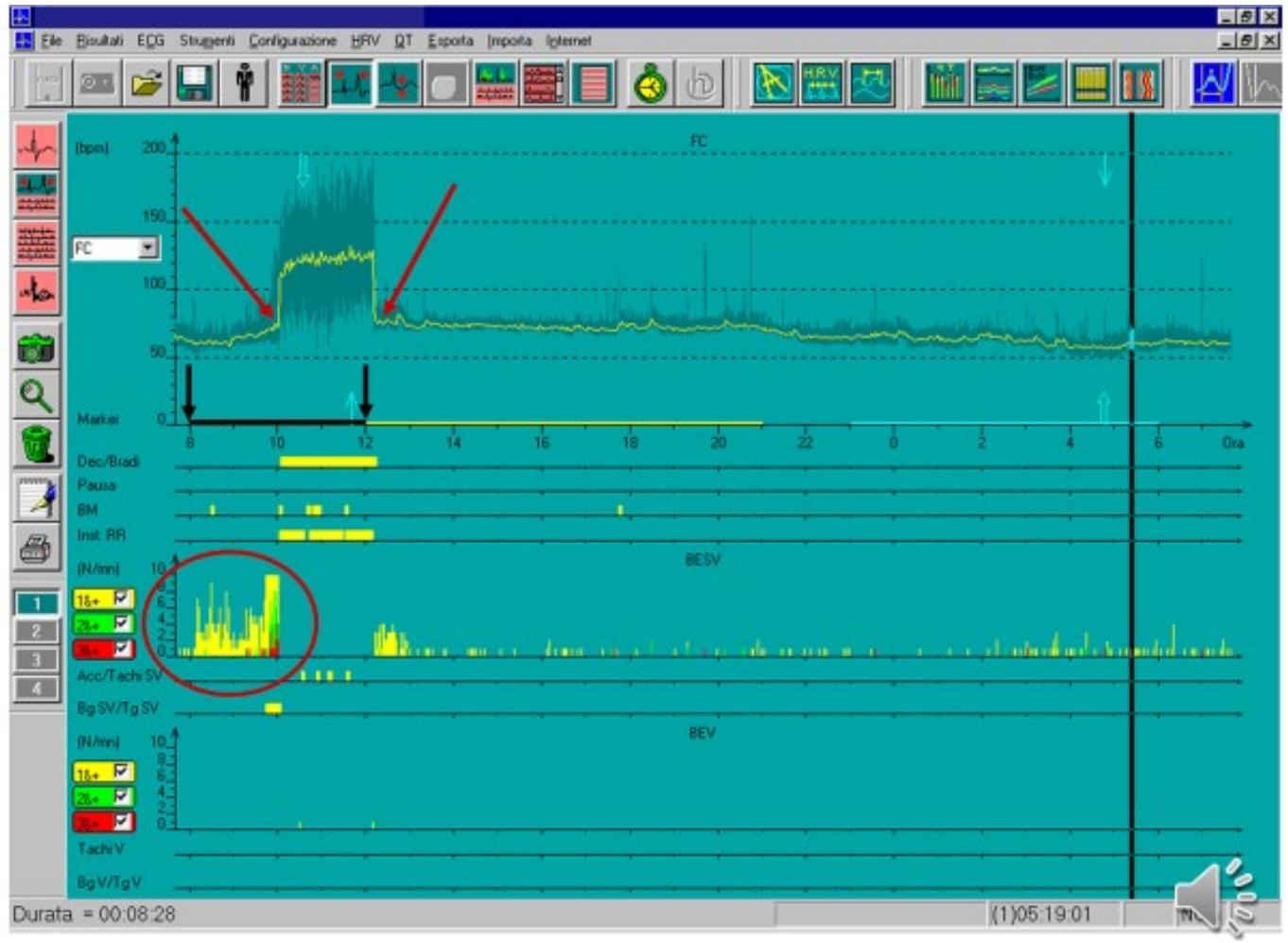
Atrial fibrillation

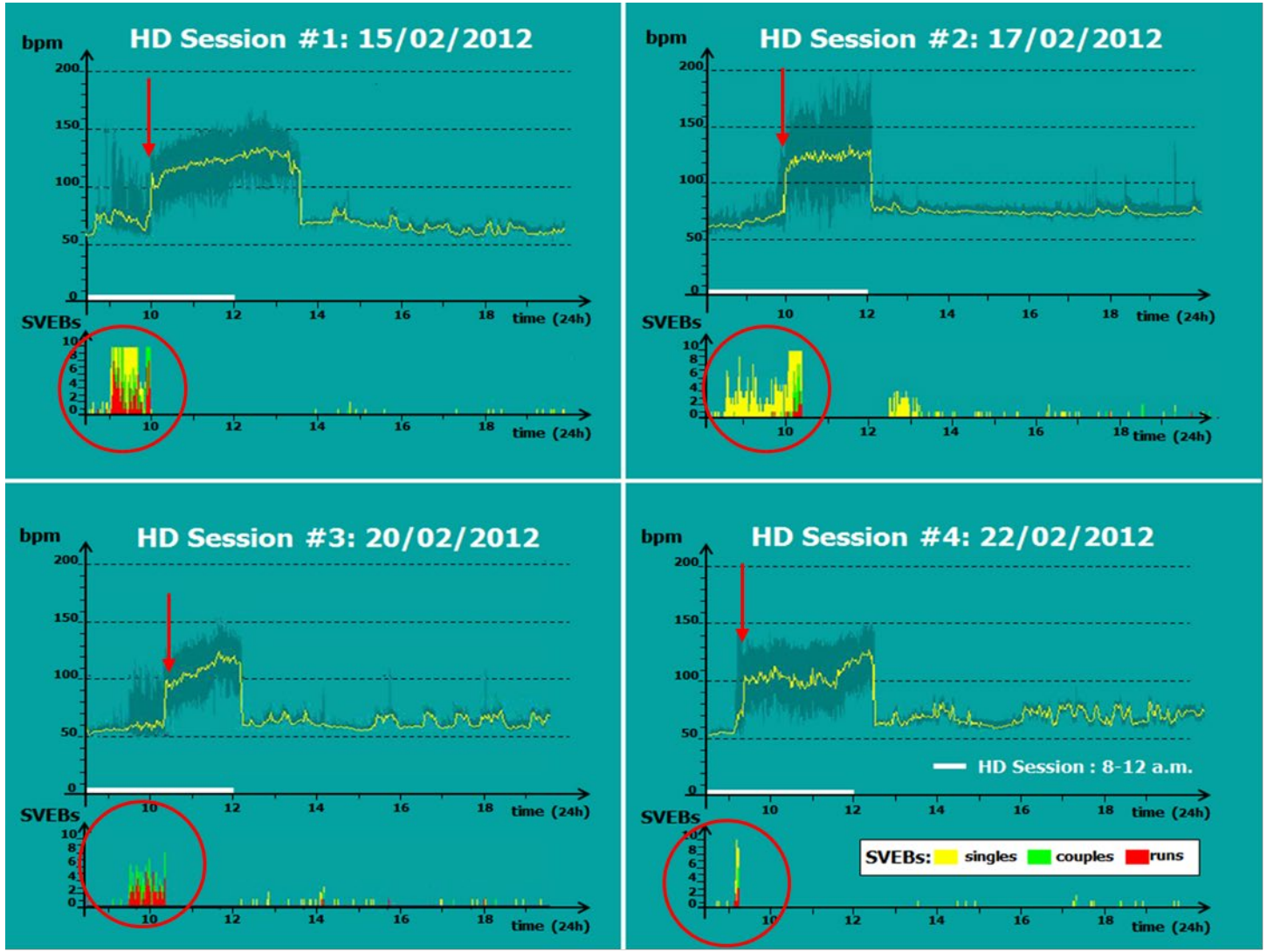


Onset of atrial fibrillation episodes in relation to start of the dialysis procedure



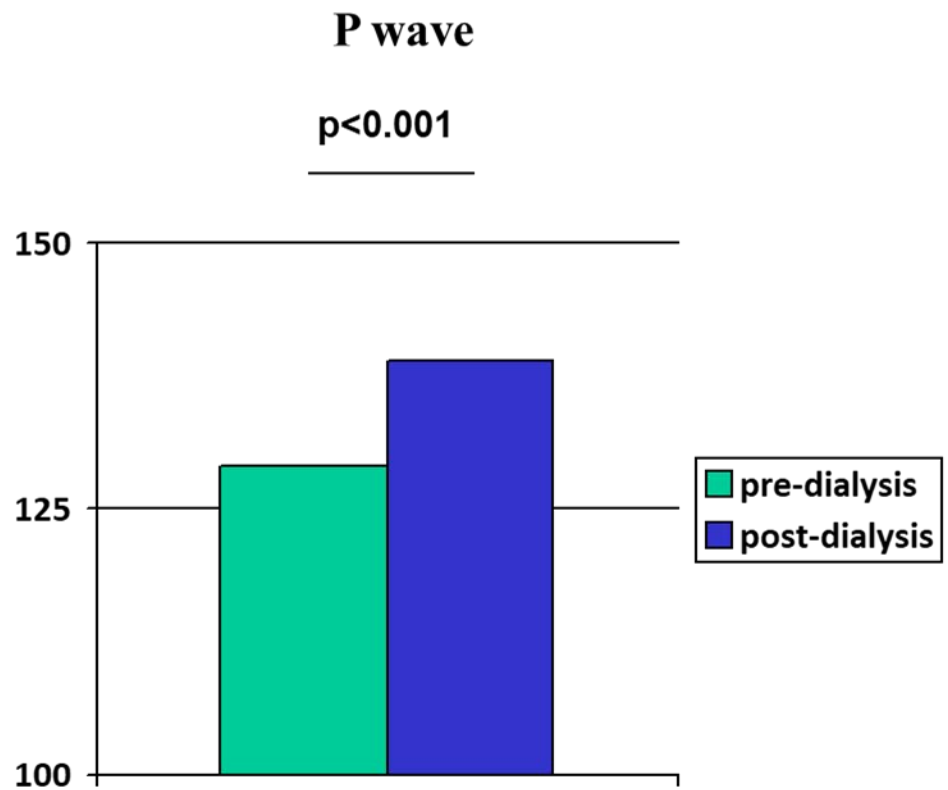
Buiten, Heart 2014

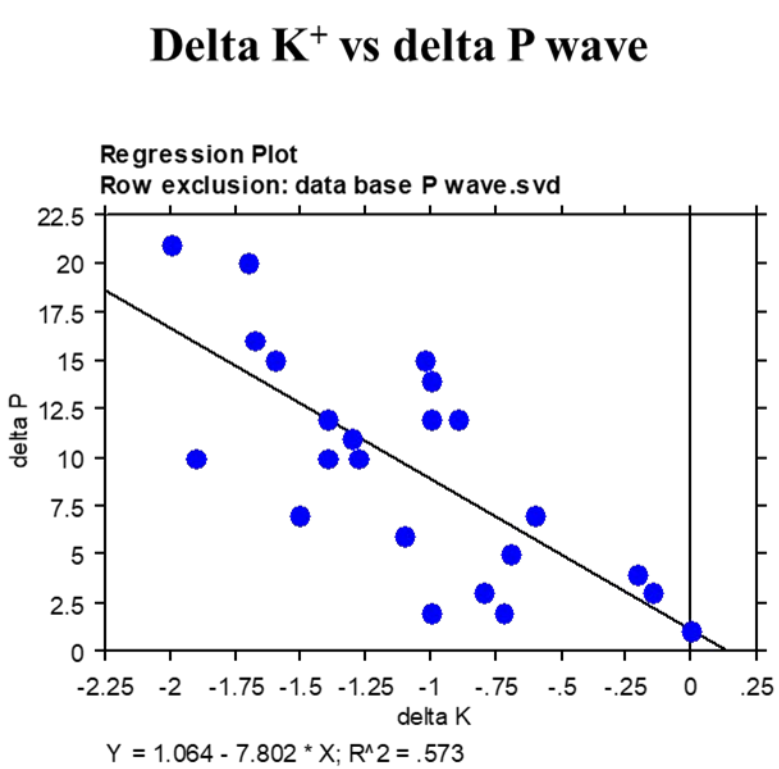

File Risultati ECG Strumenti Configurazione HRV QT Esporta Importa Internet
(bpm)
200
150
100
50
0
FC
Marker
8
10
12
14
16
18
20
22
0
2
4
6
Ora
Dec/Bradi
Pausa
BM
Inst. RR
(N/mn)
BESV
Acc/Tachi SV
Bg SV/Tg SV
BEV
Tachi V
Bg V/Tg V
Durata = 00:08:28
(1)05:19:01



Vincenti, Severi e Genovesi, Europace 2015

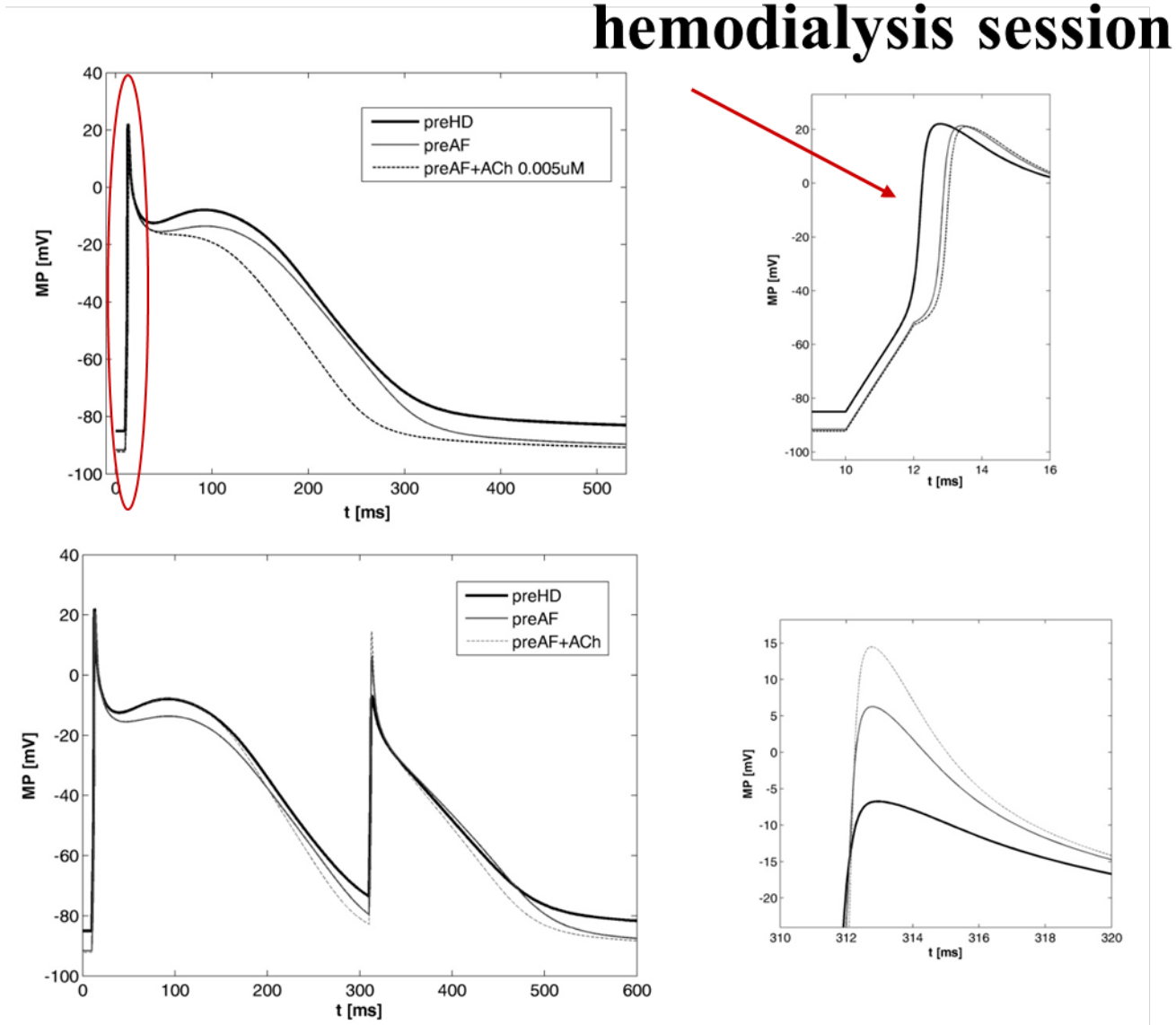
Effects of hemodialysis session on intra-atrial conduction velocity (P wave of ECG)





Genovesi, Europace 2010

Atrial action potential modifications during hemodialysis session



Depolarization time (P wave)

↓

Prolongation

Effective refractory period

↓

Shortening

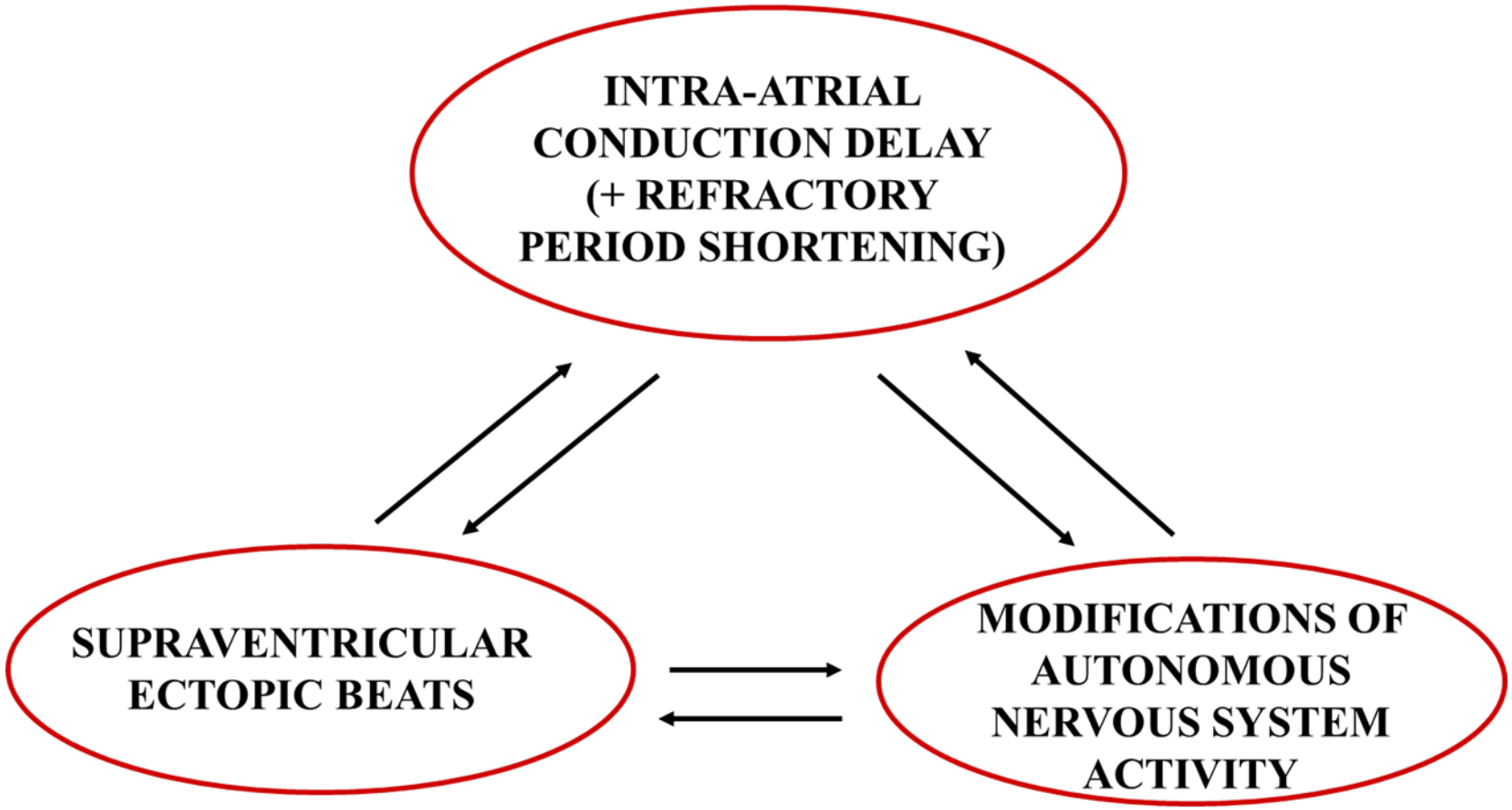
Severi and Genovesi, Europace 2010

HD session	SUPRAVENTRICULAR ECTOPIC BEATS					
	Isolated		Couples		Runs	
	Basal	Pre-AF	Basal	Pre-AF	Basal	Pre-AF
#1	2.3	227.0	0.1	86.0	0.3	76.0
#2	11.3	261.0	0.6	45.0	0.2	20.0
#3	1.5	82	0.2	21	0.15	35
#4	1.3	72.0	0.1	32.0	0.08	41.0
mean ± SD	4.1 ± 4.8	160.5 ± 97.5*	0.2 ± 0.2	46.0 ± 28.4*	0.2 ± 0.1	43.0 ± 23.7*

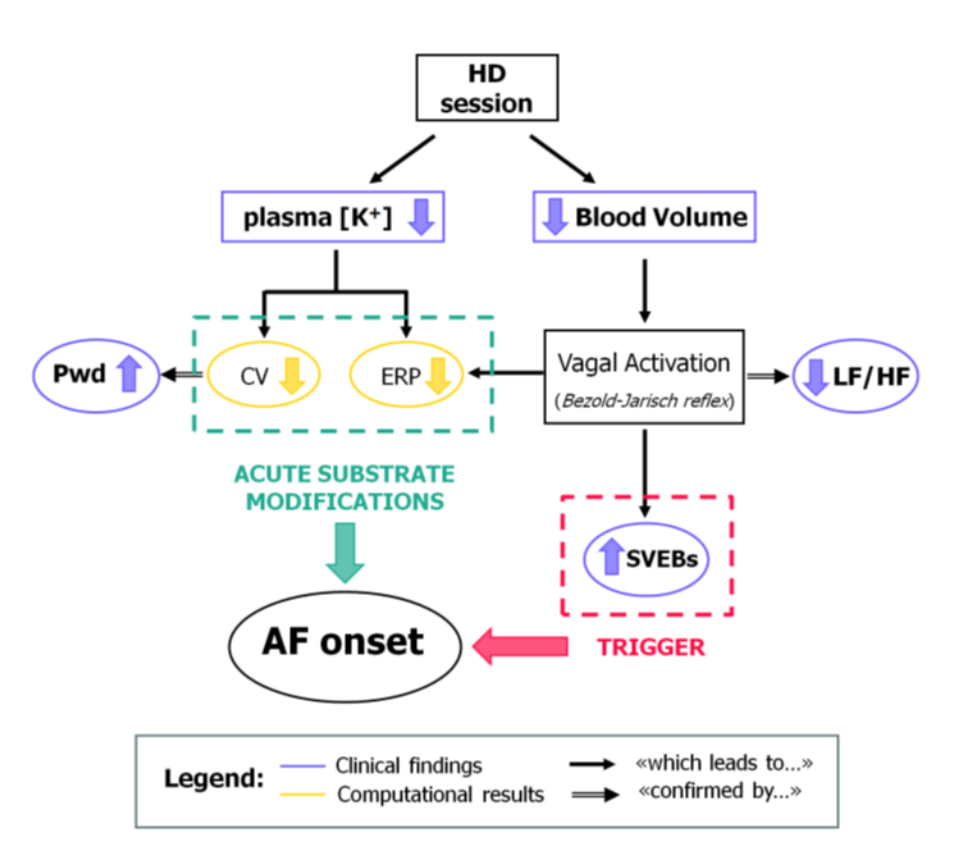
HD session	LF (nu)			HF (nu)			LF/HF		
	-30	-20	-10	-30	-20	-10	-30	-20	-10
#1	26.1	17.7	10.7	67.0	49.8	52.2	0.39	0.36	0.20
#2	52.7	41.6	36.7	36.1	46.1	48.9	1.46	0.90	0.75
#3	43.5	28.9	19.8	49.9	58.3	58.0	0.87	0.51	0.36
#4	23.6	18.6	17.9	55.8	64.4	63.4	0.42	0.29	0.25
mean ± SD	36.5 ± 14	26.7 ± 11.2*	21.3 ± 11**	52.2 ± 12.9	54.7 ± 8.3	55.6 ± 6.4	0.79 ± 0.5	0.51 ± 0.3	0.39 ± 0.2*

Vincenti, Severi e Genovesi, Europace 2015

Hemodialysis session



In presence of dilated and fibrotic atria



Vincenti, Severi e Genovesi, Europace 2015

Associations of serum and dialysate potassium concentrations with incident atrial fibrillation in hemodialysis patients

Models	Dialysate [K^+] (mEq/l)	Hazard ratio (95% CI)
Model 1	1	1.08 (0.90–1.26)
	2	–
	3	0.96 (0.84–1.03)
	4	1.15 (0.77–1.52)
Model 2	1	1.08 (0.90–1.25)
	2	–
	3	0.89 (0.80–0.99)
	4	1.08 (0.70–1.46)
Model 3	1	1.07 (0.90–1.25)
	2	–
	3	0.87 (0.78–0.96)
	4	1.06 (0.66–1.45)

Hu, KI Reports 2023