Внезапная смерть на гемодиализе и не только… (навеяно конгрессом ASN Renal Week 2014)

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6. Dezember 2014

Skandinavia

B|BRAUN
SHARING EXPERTISE

ВС - определение

Неожидаемая, не травматическая смерть, возникшая менее чем через час от возникновения симптомов

- Включает смерть во сне
- Включает смерть дома без свидетелей, если человека видели живым в течение 24 часов

ВС – диализ-специфичные факторы

Электролитные сдвиги (K^+, Ca^{++})

Осмотические сдвиги

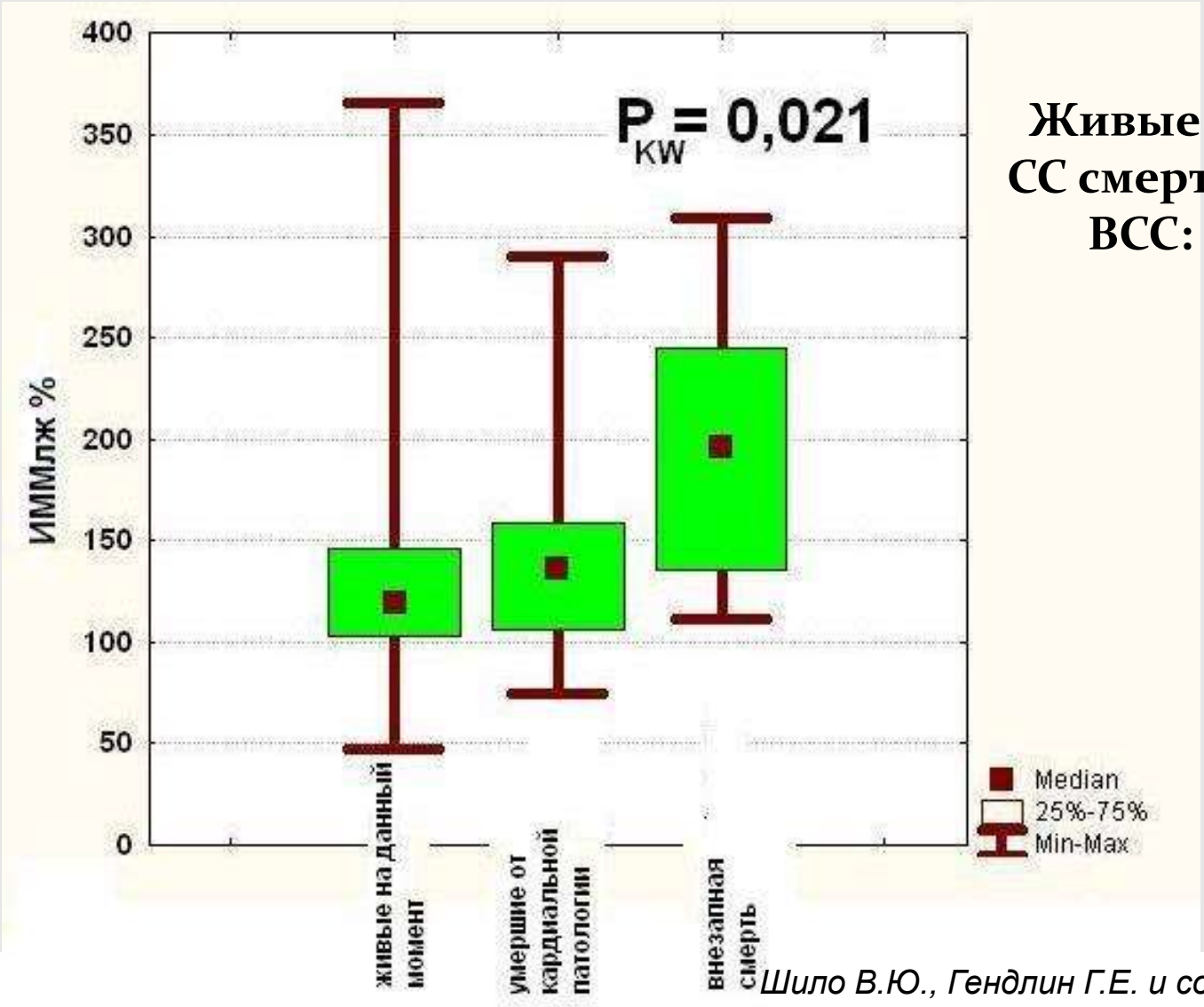
Сдвиги КЩР (метаболический алкалоз)

Большие объемные сдвиги: частая гипотензия

Три раза в неделю

- Синдром понедельника – 50% увеличение
- Частота растет в первые 12 часов после ГД, потом падает через 12-24, далее снова растет макс 60-72 часа

ИММлж (относительное значение) в зависимости от исхода



Живые: n=139
СС смерть: n=36
ВСС: n=9

Шило В.Ю., Гендлин Г.Е. и соавт 2009

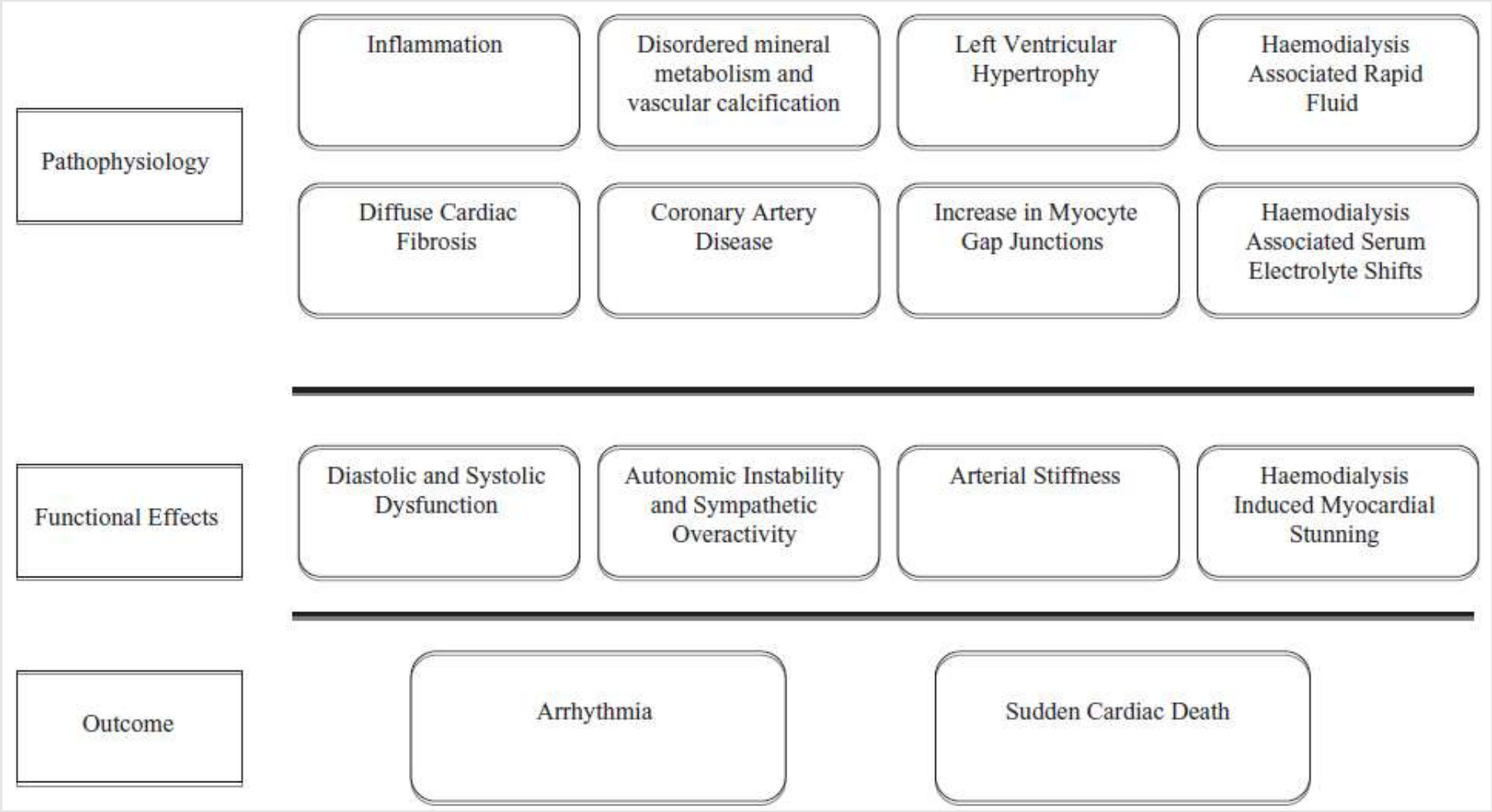
Выводы

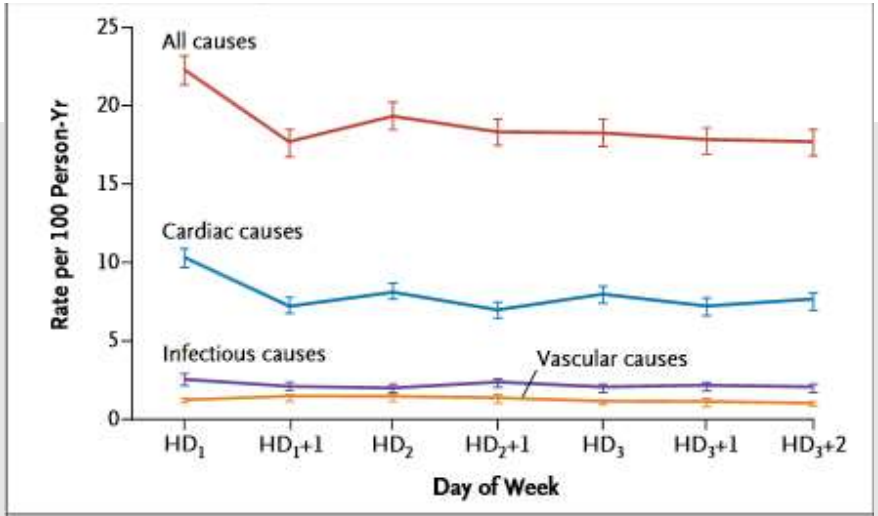
•Определение ИММлж является ценным для прогнозирования риска внезапной смерти у больных на лечении ПГД.

•Необходимо направлять усилия на уменьшение прогрессирования ГЛЖ у пациентов на ЗПТ с целью обеспечить лучший жизненный прогноз.

•Показатели ФИ дополняют представление о функциональном состоянии сердца, позволяя построить адекватную стратегию для снижения риска общей кардиальной смертности при ПГД.

Триггеры аритмии и внезапной смерти на гемодиализе





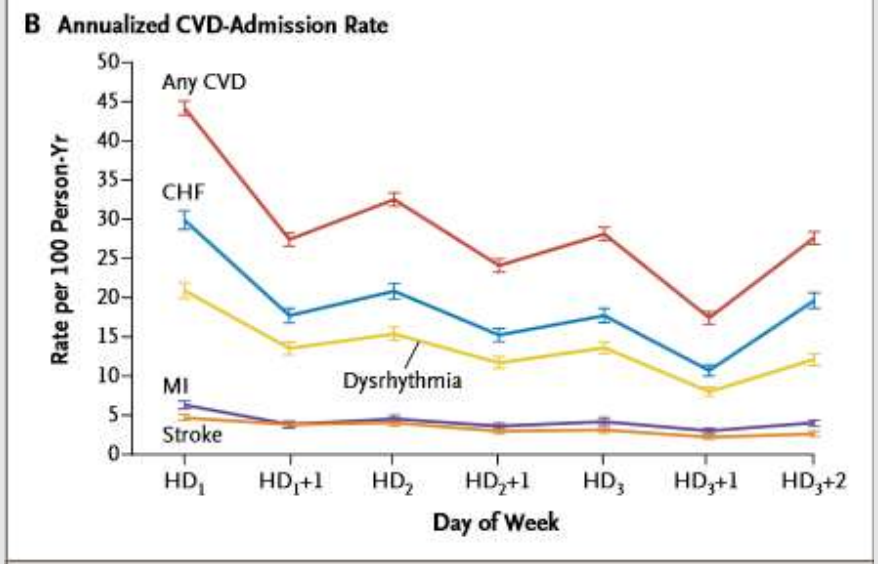


Figure 1. Annualized Mortality and Cardiovascular-Admission Rates on Different Days of the Dialysis Week.

I bars represent 95% confidence intervals. CHF denotes congestive heart failure, CVD cardiovascular disease, HD_1 the day of the first hemodialysis session of the week, HD_1+1 the day after the first session, HD_2 the day of the second hemodialysis session, HD_2+1 the day after the second session, HD_3 the day of the third hemodialysis session, HD_3+1 the day after the third session, HD_3+2 the second day after the third session, and MI myocardial infarction.

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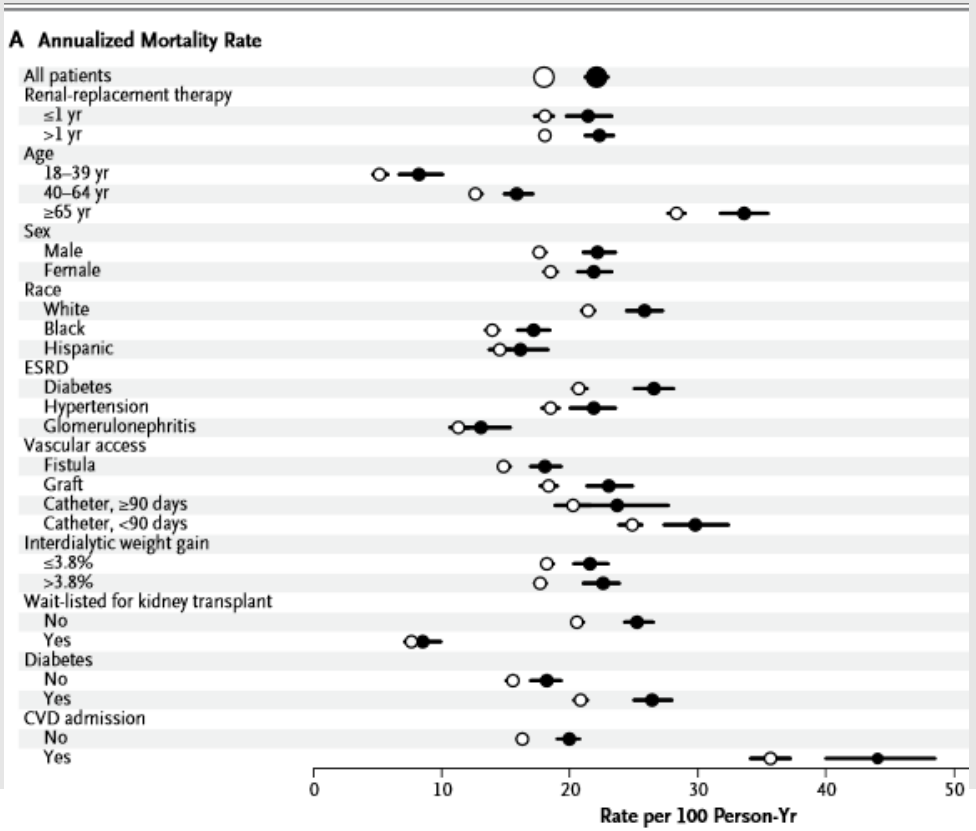
SHARING EXPERTISE

Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis

Robert N. Foley, M.B., David T. Gilbertson, Ph.D., Thomas Murray, M.S., and Allan J. Collins, M.D.

N Engl J Med 2011;365:1099-107



Модифицируемые факторы риска ВОС на ГД

Table 1 | Modifiable risk factors for prevention of sudden cardiac arrest in hemodialysis patients

Risk factor	Possible solution
Low predialysis serum potassium	Use dialysate algorithm to automatically adjust dialysate potassium bath
Low dialysate potassium concentration	Remove 0- and 1-mequiv.-per-liter-potassium dialysate baths from dialysis units
Low dialysate calcium concentration	Remove low-calcium dialysate baths below 2.0 mequiv. per liter
High serum potassium	Adjust dialysate potassium and check potassium during the run
Rapid fluid shifts during dialysis	Limit upper-range amount of fluid removal per hour or per run; consider short daily or nocturnal dialysis[22]
Hospitalization/acute events	Reevaluate serum electrolytes, dialysate potassium/calcium, and volume status after acute events[22]
Cardioprotective medications	Randomized controlled trial data needed
Automatic defibrillators, implantable defibrillators	More data needed

Reference: Ostermann.[22]

*Ostermann M . Cardiac arrests in hemodialysis patients: an ongoing challenge . Kidney Int 2008 ;**73 : 907-8.***

Стратегия предотвращения ВС на гемодиализе

Table 1. Possible strategies for SCD prevention in the high-risk patient

Strategy		Possible intervention
1.	*Reduce the progression of cardiomyopathy*	
	Systolic heart dysfunction	Assess left ventricular systolic and diastolic function within 3 months of dialysis initiation and every 3 years thereafter
	Diastolic heart dysfunction (left ventricular hypertrophy)	Use carvedilol in patients with dilated cardiomyopathy; consider frequent hemodialysis to reduce left ventricular mass
2.	*Minimize dialysis-related arrhythmic triggers*	
	Potassium shifts	Monitor potassium more frequently especially after hospitalization, and change dialysis prescription accordingly; avoid low-potassium baths (<2 meQ/l)
	Calcium shifts	Avoid low-calcium baths, especially in the context of concurrent use of QT-prolonging medications
	Rapid ultrafiltration	Encourage patient compliance with fluid restriction between treatments; avoid sodium ramping and large dialysate/serum sodium gradients; extend dialysis time to reduce ultrafiltration rate
3.	*Use ICDs*	Consider ICDs for secondary prevention; more data needed to support efficacy of prophylactic ICD implantation; consider associated vascular and infectious risks

Pun/Middleton Blood Purif 2012;33:183–189

NEPHROLOGY

Nephrology 19 (2014) 740–749

Review Article

Sudden cardiac death in haemodialysis patients: Preventative options

DIANA YUAN YNG CHIU,[1,2] SMEETA SINHA,[1,2] PHILIP A KALRA[1,2] and DARREN GREEN[1,2]

[1]Vascular Research Group, Manchester Academic Health Sciences Centre, Institute of Population Health, The University of Manchester, Manchester, and [2]Department of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, UK

Table 2 Preventative therapies for SCD in haemodialysis patients

Recommendations	Comment
Cardio-protective medications	No one drug therapy has been shown to reduce the risk of SCD in haemodialysis patients. However, in a retrospective study, β-blocker, CCB and ACEI/ARB have been associated with survival benefit after arrhythmic cardiac arrest.[12]
Revascularization for severe coronary artery disease	Current evidence suggests that revascularization does not eliminate the risk of SCD completely, and the major cause of death post-revascularization remains to be arrhythmia. The decision to revascularize should be made on an individual basis, and additional therapies may be needed to prevent SCD.
Implantable cardioverter-defibrillators	CKD-5D patients should not be excluded from receiving ICD based on the indication for device therapy from current guidelines. Results of the ICD2 trial are awaited and may shed light into whether ICDs should be inserted for primary prevention in a broader setting away from these guidelines.
Dialysis	
Avoid low or high pre-dialysis serum potassium, avoid low dialysate potassium	Low potassium dialysate and extremes of serum potassium levels have been shown to increase risk of SCD.[46]
Avoid low dialysate calcium concentration	There is an increased risk of SCD with low calcium dialysate and large serum to dialysate calcium gradients[48]
Avoid excessive ultra-filtration per session; short daily dialysis, nocturnal haemodialysis	High ultrafiltration volumes have been associated with SCD.[3] This may explain the reason for survival advantage from short daily dialysis and nocturnal haemodialysis compared with conventional haemodialysis treatment.[65,66]
Early transplant work-up	There is a longer survival in CKD-5D after renal transplant.[2]

β-blocker, beta-blocker; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CCB, calcium channel blocker; CKD-5D, end stage kidney disease; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.

Table 1 Indications for ICDs as recommended by the National Institute for Health and Clinical Excellence (NICE guidelines) (permission sought for reproduction[29])

Primary prevention of arrhythmia
– Greater than 4 weeks post myocardial infarction and *either*
LVEF <35% AND
Non-sustained ventricular tachycardia on 24 hour holter monitoring AND
Ventricular tachycardia inducible on electrophysiological testing
or
LVEF <30% AND
QRS duration ≥ 120ms
– Familial condition that predisposes to high risk of sudden cardiac death such as long QT syndrome
Secondary prevention of arrhythmia
– Previous cardiac arrest due to ventricular tachycardia or ventricular fibrillation
– Sudden unprovoked ventricular tachycardia resulting in syncope or significant haemodynamic compromise
– Sustained ventricular tachycardia without syncope or cardiac arrest and LVEF <35%.

ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction.

Table 3 Evidence for interventions for prevention of SCD or cardiac arrests

Intervention	Evidence of Benefit	Level of Evidence
Antiarrhythmics		
Beta blocker	Yes	IB
Calcium channel blocker	Yes	3B
Digoxin	No	1D
Amiodarone	Yes	1C
Other cardiac medications		
Statins	No	1C
Aspirin	No	3C
Renin-angiotensin blockers	Yes	3C
Aldosterone blockers	Yes	1B
Non-pharmacological therapies		
ICDs	Yes	1B
Coronary revascularization	No	3C
Dialysis regimen		
Type of dialysis, high flux dialysis	No	1C
Frequency of dialysis, nocturnal dialysis or short daily dialysis	No	3C
Dialysate, low potassium dialysate, low calcium dialysate, low pre-dialysis potassium	No	3D
Ultrafiltration; high volume ultrafiltration	No	3D

Note: Reference for levels of evidence from Taddio *et al*.[67] ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.

Box 1 Suggested therapies that may be implemented for prevention of SCD in haemodialysis patients

Dialysis unit

Trained staff in basic life support

Automated external cardiac defibrillation

Medications

Beta blockers

Renin-angiotensin blockers if reduced LVEF

Calcium channel blockers

Dialysis regimen

Increase frequency of dialysis – short daily dialysis or nocturnal dialysis

Avoid low potassium dialysate (<2 mmol/L or <3 mmol/L if pre-dialysis potassium is <5 mmol/L) and/or low calcium (<2 mmol/L) dialysate

Avoid low pre-dialysis potassium

Avoid high ultra-filtration volumes, hence avoid >2.5 kg inter-dialytic weight gain

Non-pharmacological interventions

ICD for secondary prevention (more data are needed for primary prevention)

ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Nephrol Dial Transplant (2014) 29: 672–681
doi: 10.1093/ndt/gft515
Advance Access publication 6 January 2014

ndt
Nephrology Dialysis Transplantation

Original Articles

Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial

Rajiv Agarwal, Arjun D. Sinha, Maria K. Pappas, Terri N. Abraham and Getachew G. Tegegne

Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans AdministrationMedical Center, Indianapolis, IN, USA

Результаты исследования атенолола и лизиноприла

Results. At baseline, 44-h ambulatory BP was similar in the atenolol (151.5/87.1 mmHg) and lisinopril groups, and improved similarly over time in both groups. However, monthly measured home BP was consistently higher in the lisinopril group despite the need for both a greater number of antihypertensive agents and a greater reduction in dry weight. An independent data safety monitoring board recommended termination because of cardiovascular safety. Serious cardiovascular events in the atenolol group occurred in 16 subjects, who had 20 events, and in the lisinopril group in 28 subjects, who had 43 events {incidence rate ratio (IRR) 2.36 [95% confidence interval (95% CI) 1.36–4.23, P = 0.001]}. **Combined serious adverse events of myocardial infarction, stroke and hospitalization for heart failure or cardiovascular death in the atenolol group occurred in 10 subjects, who had 11 events and in the lisinopril group in 17 subjects, who had 23 events (IRR 2.29, P = 0.021). Hospitalizations for heart failure were worse in the lisinopril group (IRR 3.13, P = 0.021). All-cause hospitalizations were higher in the lisinopril group [IRR 1.61 (95% CI 1.18–2.19, P = 0.002)]**. LVMI improved with time; no difference between drugs was noted.

Conclusions. Among maintenance dialysis patients with hypertension and left ventricular hypertrophy, atenolol-based antihypertensive therapy may be superior to lisinopril-based therapy in preventing cardiovascular morbidity and all-cause hospitalizations.

НОВЫЕ ФАРМАКОЛОГИЧЕСКИЕ ИНТЕРВЕНЦИИ

АНТИОКСИДАНТЫ

ОМЕГА 3 КИСЛОТЫ

АЛЛОПУРИНОЛ

РЕНАЛАЗА

see commentary on page 993

Inverse relationship between long-chain n-3 fatty acids and risk of sudden cardiac death in patients starting hemodialysis

Allon N. Friedman[1], Zhangsheng Yu[2], Rebeka Tabbey[2], Cheryl Denski[2], Hector Tamez[3], Julia Wenger[3], Ravi Thadhani[3], Yong Li[4] and Bruce A. Watkins[4]

[1]Division of Nephrology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; [2]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA; [3]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA and [4]Department of Nutritional Sciences, Lipid Chemistry & Molecular Biology Laboratory, University of Connecticut, Storrs, Connecticut, USA

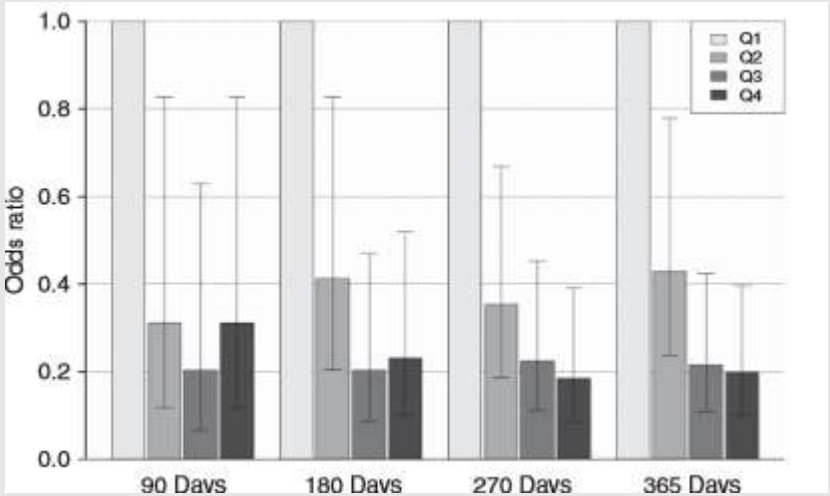
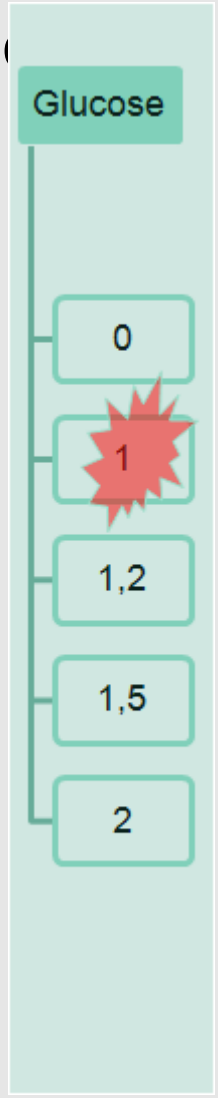


Figure 1 | Odds of sudden cardiac death for each quarter of the first year on hemodialysis by quartile of long-chain phospholipid n-3 fatty acids. At 90 days, the odds for the second, third, and fourth quartiles (compared with the first and lowest quartile) are 0.31 (95% confidence interval: 0.12–0.83), 0.20 (0.07–0.63), and 0.31 (0.12–0.83), respectively. At 180 days, the odds are 0.41 (0.21–0.83), 0.20 (0.09–0.47), and 0.23 (0.10–0.51), respectively. At 270 days, the odds are 0.35 (0.19–0.67), 0.22 (0.11–0.45), and 0.19 (0.09–0.39), respectively. At 365 days, the odds are 0.43 (0.24–0.78), 0.22 (0.11–0.42), and 0.20 (0.10–0.40), whereas the odds for the fourth quartile compared with second quartile are 0.46 (0.23–0.95).



Description of Status and Changes:

• for Glucose only one concentration will be offered: 1g/l

General information Glucose:

• high levels of glucose are correlated to increased proinflammatory processes and increases the risk of hyperglyemia in diabetic patients

• low levels of glucose are correlated to hypoglycemia, no glucose in dialysate can lead to loss of 50 – 60g glucose during one dialysis session

• use og 1g/dl glucose in dialysate leads to balanced glucose levels in dialysis patients and is recognized as safe

Nephrol Dial Transplant. 2012 Apr;27(4):1559-68

Metabolic effects of dialyzate glucose in chronic hemodialysis: results from a prospective, randomized crossover trial.

Raimann JG[1], Kruse A, Thijssen S, Kuntsevich V, Dabel P, Bachar M, Diaz-Buxo JA, Levin NW, Kotanko P.

Abstract

BACKGROUND:

There is no agreement concerning dialyzate glucose concentration in hemodialysis (HD) and 100 and 200 mg/dL (G100 and G200) are frequently used. G200 may result in diffusive glucose flux into the patient, with consequent hyperglycemia and hyperinsulinism, and electrolyte alterations, in particular potassium (K) and phosphorus (P). This trial compared metabolic effects of G100 versus G200.

RESULTS:

Fourteen diabetic and 15 non-diabetic subjects were studied. SG was significantly higher with G200 as compared to G100, both in diabetic {G200: 192.8±48.1 mg/dL; G100: 154.0±27.3 mg/dL; difference 38.8 [95% confidence interval (CI): 21.2-56.4] mg/dL; P<0.001} and non-diabetic subjects [G200: 127.0±11.2 mg/dL; G100 106.5±10.8 mg/dL; difference 20.6 (95% CI: 15.3-25.9) mg/dL; P<0.001]. SI was significantly higher with G200 in non-diabetic subjects. Frequency of hypoglycemia, P and K serum levels, interdialytic weight gain and adverse intradialytic events did not differ significantly between G100 and G200.

CONCLUSION:

G200 may exert unfavorable metabolic effects in chronic HD patients, in particular hyperglycemia and hyperinsulinism, the latter in non-diabetic subjects.

free web access! http://ndt.oxfordjournals.org/content/27/4/1559.full.pdf+html

Nephrol Dial Transplant. 2007 Apr;22(4):1184-9. Epub 2007 Feb 1.

Glucose-added dialysis fluid prevents asymptomatic hypoglycaemia in regular haemodialysis.

Burmeister JE[1], Scapini A, da Rosa Miltersteiner D, da Costa MG, Campos BM.

BACKGROUND:

Hypoglycaemia (HG) has been demonstrated during chronic haemodialysis (HD). These events may become more frequent with the current use of glucose-free bicarbonate dialysis solution, the standard formula in most dialysis facilities in the last decade. On the other hand, HG-related symptoms are unusual among patients during or just after dialysis sessions. The aim of this study was to evaluate the occurrence of HG in diabetic (DM) and non-diabetic (NDM) end-stage renal failure patients during HD using dialytic solution without and with glucose.

METHODS:

Forty-two chronic renal failure patients-21 DM and 21 NDM-randomly selected among the 97 in our dialysis unit were submitted to an HD session with glucose-free bicarbonate solution (phase 1). Serum glucose was measured at 30, 60, 150 and 240 min. In eight patients (four DM and four NDM) glucose was also measured in fluid leaving the dialyser at 30, 60 and 150 min. After a week, all procedures were repeated in the same patients, this time with a 90 mg/dl glucose-added bicarbonate solution (phase 2). We compared the glucose levels and the number of symptomatic and asymptomatic HG events in each group in phases 1 and 2, using bivariate analysis methods with confidence limit of 0.95%.

RESULTS:

Data were expressed as mean+/-SD. No patient presented any clinical evidence of HG. For all patients, the mean plasma glucose level (mg/dl) was significantly higher in phase 2 than in phase 1 (138.2+/-96.3 vs 120.7+/-75.9; P=0.0392). This occurred in DM (171.1+/-104.5 vs 132.5+/-71.0; P=0.0067), but not in NDM (101.3+/-19.4 vs 95.2+/-21.2; P=0.06). With glucose-free HD solution, 10 patients (five DM, five NDM) presented 18 measures of glycaemia under 70 mg/dl, and with glucose-added solution, only one (DM) presented two measures under 70 mg/dl-P=0.0045 (number of patients); P=0.0003 (number of HG measures). Among DM patients, values for HG measures in phase 1 (49.1+/-16.2 mg/dl) were significantly lower than in phase 2 (65.0+/-1.4 mg/dl)-P=0.0139. For all patients, glucose was lost in HD fluid leaving the dialyser at lower values in phase 2 (5.2+/-2.9 g/h) than in phase 1 (16.7+/-10.9 g/h)-P<0.0001.

CONCLUSIONS:

Asymptomatic HG was frequent during HD when **glucose-free dialysis solution was used**. Glucose was lost in dialytic fluid leaving the dialyser in significantly lower amounts when using glucose-added solution than glucose-free solution. Glucose-added dialysis solution at 90 mg/dl significantly reduced the number and severity of HG episodes and although it caused higher mean glycaemia in DM patients during HD, its use seems advisable in all patients.

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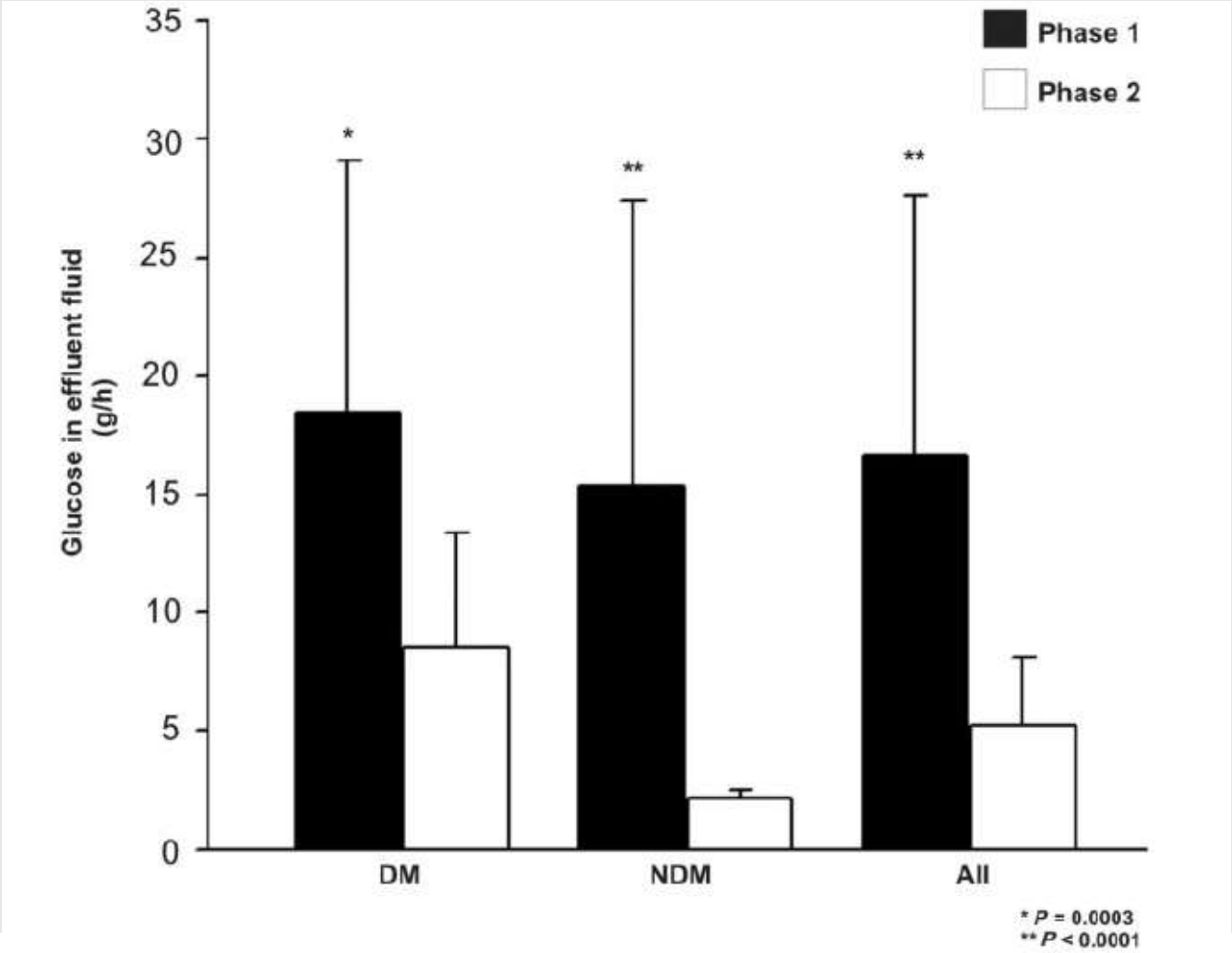
Потери глюкозы в диализат (г/час) в зависимости от наличия глюкозы в диализате



Yevzlin AS, et al "Six-month results of the RESCUE trial: Fluency Plus endovascular stent graft versus PTA for in-stent restenosis" *Kidney Week* 2014; Late-Breaking Trials.

The graft is made of a flexible metal and lined with expanded polytetrafluoroethylene (ePTFE) plastic, and the goal is to reduce the risk of restenosis.

Yevzlin noted that an earlier study published in the *New England Journal of Medicine* in 2010 looked at this device, but only in arteriovenous grafts -- not fistulas -- and only at the location of the graft. The stent graft did show improved outcomes compared with angioplasty alone, Yevzlin said, but he and his team wanted to investigate these grafts in fistulas as well.

They enrolled 265 patients from 23 U.S. sites who had in-stent restenotic lesions in the venous outflow of their vascular access, and randomized them to angioplasty alone, or angioplasty plus the stent graft.

The primary endpoints were superiority of access circuit primary patency through 6 months and safety through 30 days, and a secondary endpoint was post-intervention lesion patency.

RESCUE trial

Ultimately 244 patients were evaluated for 30-day safety, and 220 patients were evaluated for 6-month effectiveness.

Yevzlin and colleagues found that patency of vascular access at 6 months was significantly higher in the stent graft group than in the angioplasty alone group (16.7% versus 3%, *P*<0.001).

Safety was similar: the percentage of patients free from safety events through 30 days was comparable between groups (96.6% for the stent graft group and 96.8% for the angioplasty alone group, *P*=0.007).

Post-intervention lesion patency was higher in stent graft group, they found (65.2% versus 10.4%, *P*<0.001) -- and this was true for patients whether they had a graft or a fistula:

Graft: 57.7% versus 5.2%, *P*<0.001

Fistula: 72% versus 14.7%, *P*<0.001

They also found that freedom from binary restenosis at 90 days was markedly higher in the stent graft group (81% versus 25%).

"This should change the first-line therapy for this disease state," Yevzlin told "It will reduce the frequency with which patients need to be treated for in-stent restenosis."

Jardine MJ, et al "Impact of extended weekly hemodialysis hours on quality of life and clinical outcomes: The ACTIVE dialysis multinational trial" *Kidney Week* 2014; Late-Breaking Trial.

To assess the impact of extended weekly dialysis hours on quality of life and clinical outcomes, Jardine and colleagues randomized 200 patients, mean age 52, to extended or standard dialysis for 1 year. Extended dialysis involved a target of 24 hours per week, while standard dialysis was targeted to 12 to 15 hours per week.

The primary outcome was the difference in change in quality of life betweeen baseline and 1 year using the EQ-5D questionnaire.

The mean hours achieved each week were 22.1 for the extended dialysis group compared with 14.2 hours per week in the standard care group.

Jardine reported that by the end of the trial, quality of life scores were similar between groups, and there were no differences in systolic blood pressure between groups.

Patients in the extended-hours group were, however, taking fewer blood pressure-lowering drugs than those on standard dialysis (mean difference -0.35 agents, *P*=0.01).

ACTIVE dialysis multinational trial

Doing longer dialysis was also associated with higher hemoglobin, lower potassium, and lower phosphate levels compared with standard care during follow-up (expressed as the mean difference from the standard dialysis group):

Hemoglobin: 3.51 g/L, *P*=0.037

Potassium: -0.28 mmol/L, *P*=0.0001

Phosphate: -0.17 mmol/L, *P*=0.002

Jardine said these may turn into longer-term improvements, but further research is required.

She and her team also found that the number of patients with vascular access events was similar in both groups -- a difference from previous trials, Jardine said: "We did not find evidence of excess harm. We didn't see extra infections or clotting."

They concluded that extending weekly dialysis hours for a year doesn't appear to improve quality of life, but may be a boon to some laboratory parameters and reduced blood pressure medication requriements.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.

November 21, 2014 | DOI: 10.1056/NEJMoa1411487

BACKGROUND

Hyperkalemia (serum potassium level, >5.0 mmol per liter) is associated with increased mortality among patients with heart failure, chronic kidney disease, or diabetes. We investigated whether sodium zirconium cyclosilicate (ZS-9), a novel selective cation exchanger, could lower serum potassium levels in patients with hyperkalemia.

MEDIA IN THIS ARTICLE

FIGURE 1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

ABSTRACT

BACKGROUND

Hyperkalemia increases the risk of death and limits the use of inhibitors of the renin–angiotensin–aldosterone system (RAAS) in high-risk patients. We assessed the safety and efficacy of patiromer, a nonabsorbed potassium binder, in a multicenter, prospective trial.

Исследование OPAL-HK *Funded by Relypsa*

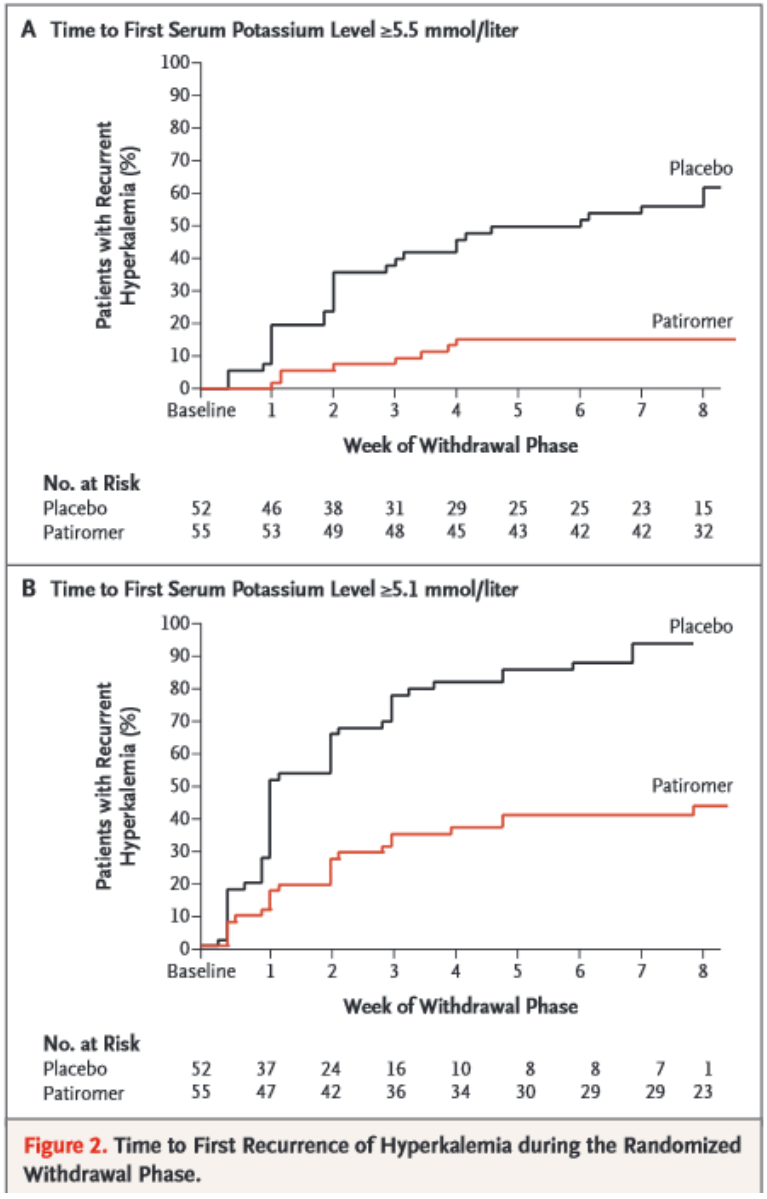


Figure 2. Time to First Recurrence of Hyperkalemia during the Randomized Withdrawal Phase.

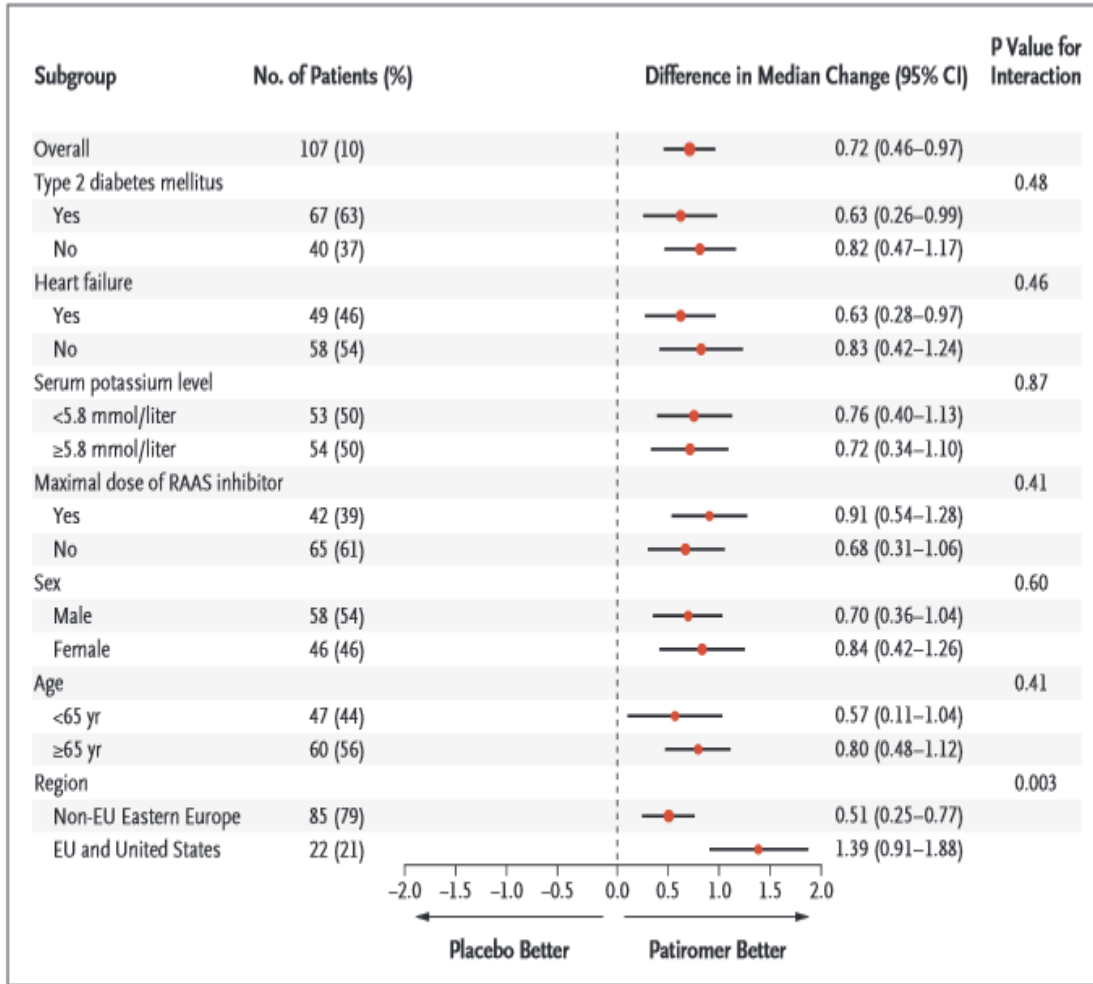


Figure 3. Primary Efficacy End Point in the Randomized Withdrawal Phase, According to Subgroup.

Shown is the difference between the placebo group and the patiromer group in the median change in serum potassium levels from the start of the randomized withdrawal phase to week 4 of that phase. The P values for interaction were calculated with the use of two-sided t-tests for the comparison of the differences between placebo and patiromer in the median change within each subgroup. EU denotes European Union.

JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Ferric Citrate Controls Phosphorus and Delivers Iron in Patients on Dialysis

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Abstract

Patients on dialysis require phosphorus binders to prevent hyperphosphatemia and are iron deficient. We studied ferric citrate as a phosphorus binder and iron source. In this sequential, randomized trial, 441 subjects on dialysis were randomized to ferric citrate or active control in a 52-week active control period followed by a 4-week placebo control period, in which subjects on ferric citrate who completed the active control period were rerandomized to ferric citrate or

Drugmaker Keryx biopharmaceuticals has filed a new drug application for Zerenex with the FDA.

B|BRAUN SHARING EXPERTISE

Patients on dialysis require phosphorus binders to prevent hyperphosphatemia and are iron deficient. We studied ferric citrate as a phosphorus binder and iron source. In this sequential, randomized trial, 441 subjects on dialysis were randomized to ferric citrate or active control in a 52-week active control period followed by a 4-week placebo control period, in which subjects on ferric citrate who completed the active control period were rerandomized to ferric citrate or placebo. The primary analysis compared the mean change in phosphorus between ferric citrate and placebo during the placebo control period. A sequential gatekeeping strategy controlled study-wise type 1 error for serum ferritin, transferrin saturation, and intravenous iron and erythropoietin-stimulating agent usage as prespecified secondary outcomes in the active control period. Ferric citrate controlled phosphorus compared with placebo, with a mean treatment difference of −2.2±0.2 mg/dl (mean±SEM) ($P<0.001$). Active control period phosphorus was similar between ferric citrate and active control, with comparable safety profiles. Subjects on ferric citrate achieved higher mean iron parameters (ferritin=899±488 ng/ml [mean±SD]; transferrin saturation=39%±17%) versus subjects on active control (ferritin=628±367 ng/ml [mean±SD]; transferrin saturation=30%±12%; $P<0.001$ for both). Subjects on ferric citrate received less intravenous elemental iron (median=12.95 mg/wk ferric citrate; 26.88 mg/wk active control; $P<0.001$) and less erythropoietin-stimulating agent (median epoetin-equivalent units per week: 5306 units/wk ferric citrate; 6951 units/wk active control; $P=0.04$). Hemoglobin levels were statistically higher on ferric citrate. Thus, ferric citrate is an efficacious and safe phosphate binder that increases iron stores and reduces intravenous iron and erythropoietin-stimulating agent use while maintaining hemoglobin.

P

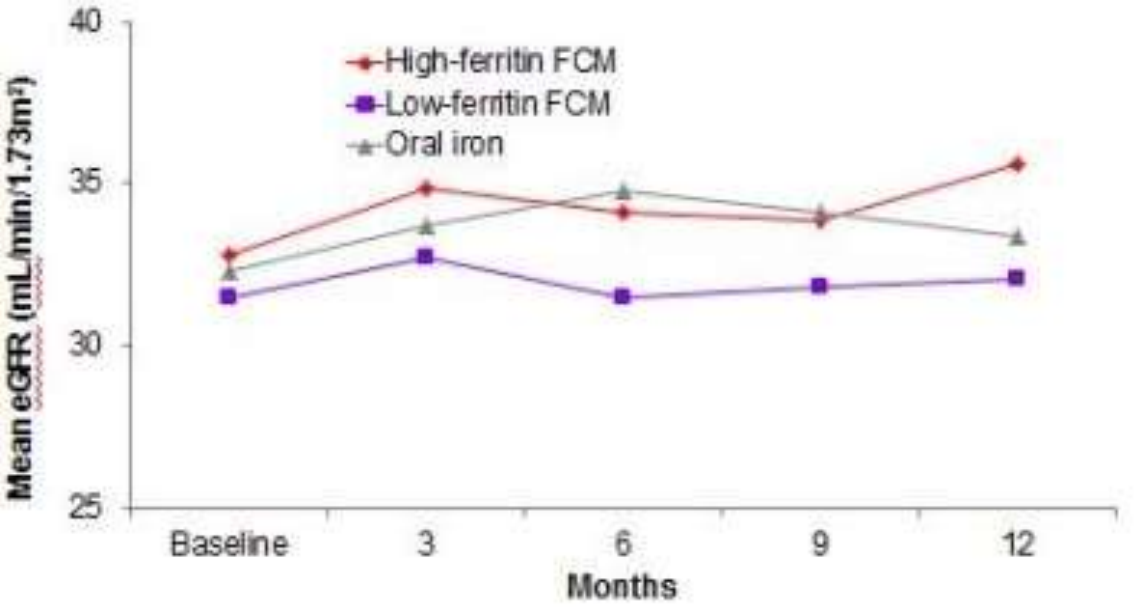
Abstract: [TH-PO829] Vitamin B6 Supplementation Increases Resistance to Erythropoiesis-Stimulating Agents in Prevalent Hemodialysis Patients: A Bicenter, Open-Label, Randomized Controlled Trial

Background: Resistance to erythropoiesis-stimulating agents (ESA) is a risk factor of cardiovascular events and death in hemodialysis patients. Vitamin B6 deficiency, which may cause sideroblastic anemia, is common in this population. We conducted this open-label, randomized controlled trial to determine whether vitamin B6 supplementation could reduce ESA resistance index (ERI). **Methods:** We screened 231 prevalent hemodialysis patients from 2 dialysis facilities in Japan. ERIs were calculated for all patients in July 2013. After excluding patients with iron deficiency, 60 prevalent patients with ERI above the median were recruited. Participants were randomly assigned to a vitamin B6 group (60 mg of intravenous pyridoxal after each thrice-weekly hemodialysis session) or a control group. The primary outcome was change in ERI between baseline and the 12th week. We employed intention-to-treat approach and last observation carried forward imputation for missing values at 12th week.This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), number UMIN000011786. **Results:** The mean baseline ERI was 9.5 (SD, 5.3) and 10.1 (SD, 5.6) IU/kg per g/dL in the control group and the vitamin B6 group, respectively. None was lost to follow-up and 53 patients completed the study. Contrary to our hypothesis, the vitamin B6 group showed significantly increased ERI at 12th week compared with the control group by 2.4 (95% CI 0.3–4.5) IU/kg per g/dL after adjustment for baseline ERI and type of ESA (p=0.028). There were no severe or moderate adverse events associated with vitamin B6 supplementation. **Conclusions:** Vitamin B6 supplementation with 60 mg of intravenous pyridoxal phosphate thrice-weekly does not improve the response to ESA in hemodialysis patients. Rather, it does increase resistance to ESA.

Abstract: [FR-PO809] Iron Administration to Non-Dialysis CKD Patients for One Year Does not Cause Worsening of Renal Function: Results From the FIND-CKD Trial

Iain C. Macdougall, MD, Andreas H. Bock, MD, Fernando Carrera, MD, Kai-Uwe Eckardt, MD, Carlo A. Gaillard, MD, PhD, David B. Van Wyck, MD, Bernard Roubert, MD, Jacqueline G. Nolen, PharmD, Simon D. Roger, MD. King's College Hospital, UK; Kantonsspital, Switzerland; Eurodial, Portugal; Erlangen-Nuremberg, Germany; Groningen, Netherlands; Davita, US; Vifor Pharma, Switzerland; Gosford, Australia.

Background: Laboratory data suggest that intravenous (IV) iron may exacerbate oxidative stress and renal tubular toxicity but robust scientific evidence that this translates into worsening renal function in non-dialysis CKD (ND-CKD) patients is lacking. One of the secondary endpoints in the FIND-CKD study was renal function measured by eGFR and this allowed further elucidation of this controversy. **Methods:** 626 ND-CKD patients with iron deficiency anaemia (Hb 9–11g/dl; ferritin<100µg/l or <200µg/l and TSAT<20%; eGFR≤60ml/min were randomized to 1 of 3 strategies of iron administration (IV ferric carboxymaltose [FCM] aiming for a ferritin of 400–600µg/l, vs IV FCM aiming for a ferritin of 100–200µg/l, vs oral ferrous sulphate 200mg iron daily). Renal function (eGFR, MDRD-4) was measured every 3 months for 1 year. **Results:** Over the 1-year study patients received a mean total dose of 2685 and 1040mg in the high-ferritin FCM and low-ferritin FCM groups, respectively. Mean eGFR (ml/min/1.73m^2) are shown for all 3 groups.



Conclusions: This study is the longest and largest to compare oral versus IV iron in ND-CKD patients. The results demonstrate that the administration of IV FCM in doses that maintain ferritin levels of 100-200 or 400–600µg/l over 1 year do not negatively impact renal function as measured by eGFR (MDRD-4). While this study did not directly measure true GFR, assess proteinuria or tubular damage markers, it nevertheless provides reassuring data on the absence of any overt renal toxicity following IV iron administration in ND-CKD patients over the course of 1 year.

Funding: Commercial SupportVifor Pharma

Abstract: [TH-OR081] Low Predialysis Serum Sodium Modifies the Effect of Hemodialysis (HD) Frequency on Left Ventricular Mass: The Frequent Hemodialysis Network (FHN) Trial

Jochen G. Raimann, MD, Christopher T. Chan, MD, John T. Daugirdas, MD, FASN, Thomas A. Depner, MD, Frank A. Gotch, MD, Tom Greene, PhD, George A. Kaysen, MD, PhD, FASN, Alan S. Kliger, MD, Peter Kotanko, MD, Robert M. Lindsay, MD, Michael V. Rocco, MD, Glenn M. Chertow, MD, FASN, Nathan W. Levin, MD, The FHN Trial Group. Renal Research Institute; University Health Network Toronto; University of Illinois College of Medicine; University of California Davis; University of Utah; UC Davis, Nephrology; Yale New Haven Health System; London Health Sciences Centre; Wake Forest School of Medicine; Stanford University School of Medicine; NIDDK, NIH.

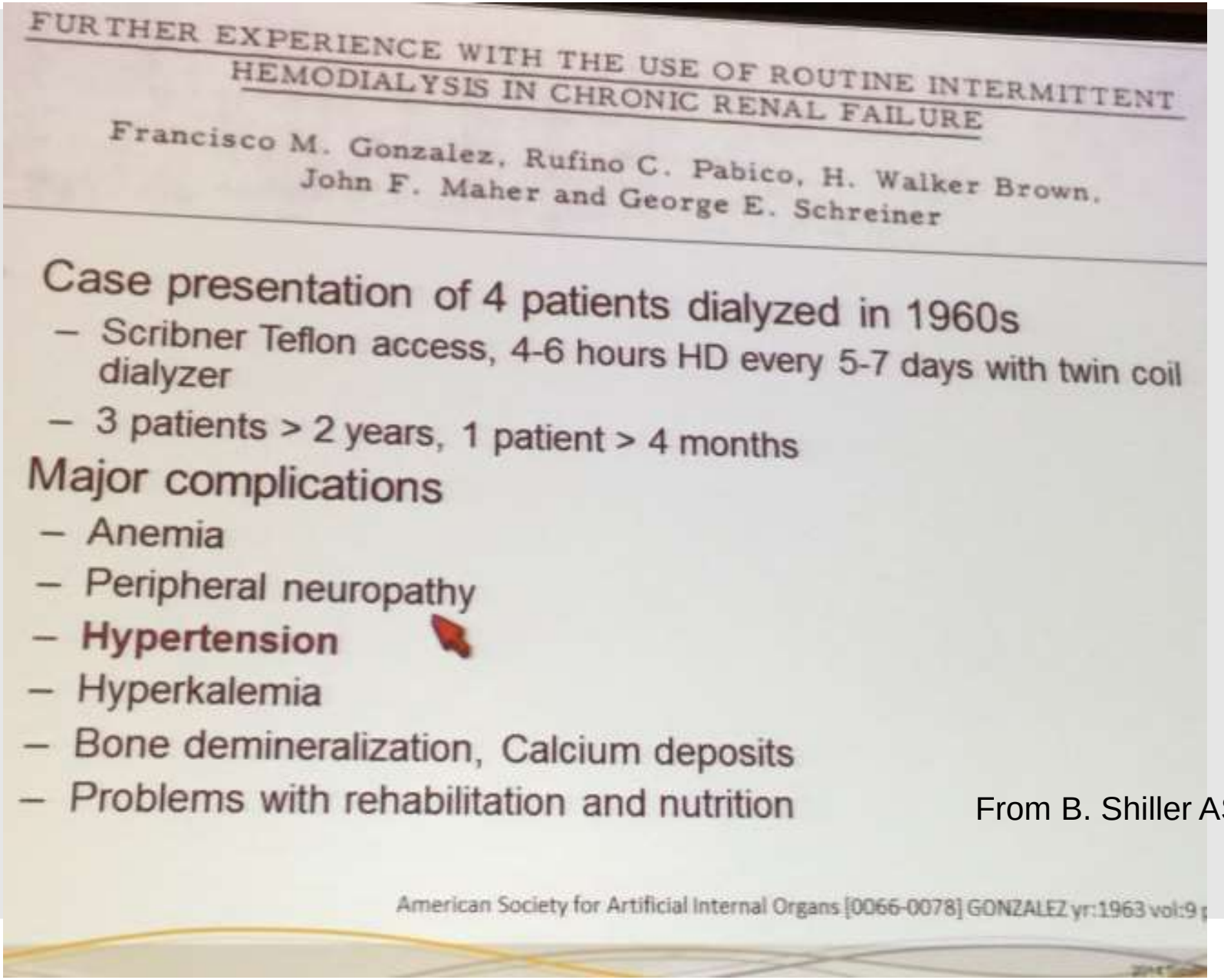
5:06 PM - 5:18 PM

Background: The FHN Trials were designed to compare HD six versus three times per week . More frequent in-center HD significantly reduced left ventricular mass (LVM), an effect that was more pronounced in subjects with low baseline urine volumes. More frequent HD also reduced measures of interdialytic extracellular fluid volume and fluid overload. Patients receiving HD with low predialysis serum sodium concentrations (SNa) are at increased risk of mortality and cardiovascular events. We hypothesized that patients with lower SNa would have a more pronounced benefit of more frequent HD on LVM compared to patients with higher SNa.

FHN Trial

Methods: The randomized treatment effect of frequency on LVM was compared in subgroups with baseline SNa≤138 vs. >138 mEq/L. The interaction of treatment effect with SNa was tested using a mixed model adjusted for age, diabetes, facility and baseline LVM. Data presented as mean and corresponding 95% CI. **Results:** In the in-center Daily Trial, the effect of frequent HD on LVM reduction was more pronounced in patients with lower baseline SNa (**Table**; Interaction P=0.03). In the at home Nocturnal Trial, change in LVM was nominally higher in patients with lower predialysis SNa, but the interaction was not statistically significant (**Table**; Interaction P=0.49). **Conclusions:** The effect of frequent HD on LVM is more pronounced in patients with lower pre-dialysis SNa.

	Serum Sodium Concentration (SNa^+) [mEq/L]	LVM reduction (Month 12 – Baseline value)
Daily	≤ 138 mEq/L	**-27.98 (-40.54 to -15.41)**
	> 138 mEq/L	-1.97 (-15.45 to 11.50)
Nocturnal	≤ 138 mEq/L	-14.70 (-32.92 to 3.52)
	> 138 mEq/L	-7.54 (-24.77 to 9.68)



FURTHER EXPERIENCE WITH THE USE OF ROUTINE INTERMITTENT HEMODIALYSIS IN CHRONIC RENAL FAILURE

Francisco M. Gonzalez, Rufino C. Pabico, H. Walker Brown, John F. Maher and George E. Schreiner

Case presentation of 4 patients dialyzed in 1960s

- Scribner Teflon access, 4-6 hours HD every 5-7 days with twin coil dialyzer
- 3 patients > 2 years, 1 patient > 4 months

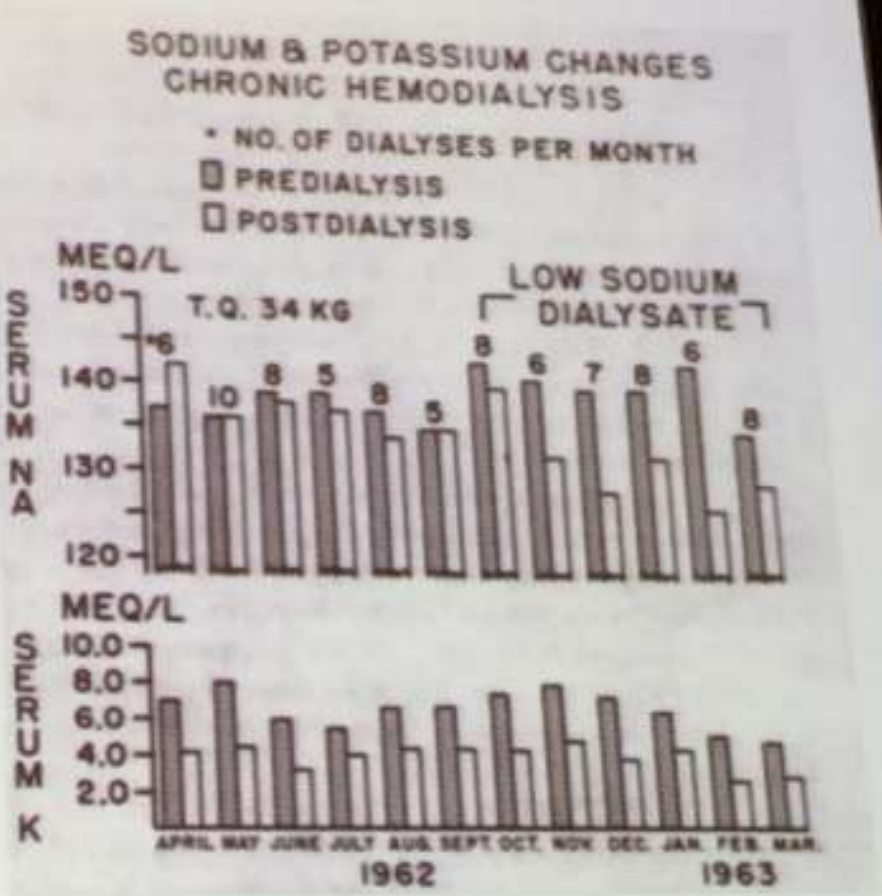
Major complications

- Anemia
- Peripheral neuropathy
- **Hypertension**
- Hyperkalemia
- Bone demineralization, Calcium deposits
- Problems with rehabilitation and nutrition

American Society for Artificial Internal Organs [0066-0078] GONZALEZ yr:1963 vol:9

From B. Shiller ASN 2014

Na_d and Hypertension



From B. Shiller ASN 2014

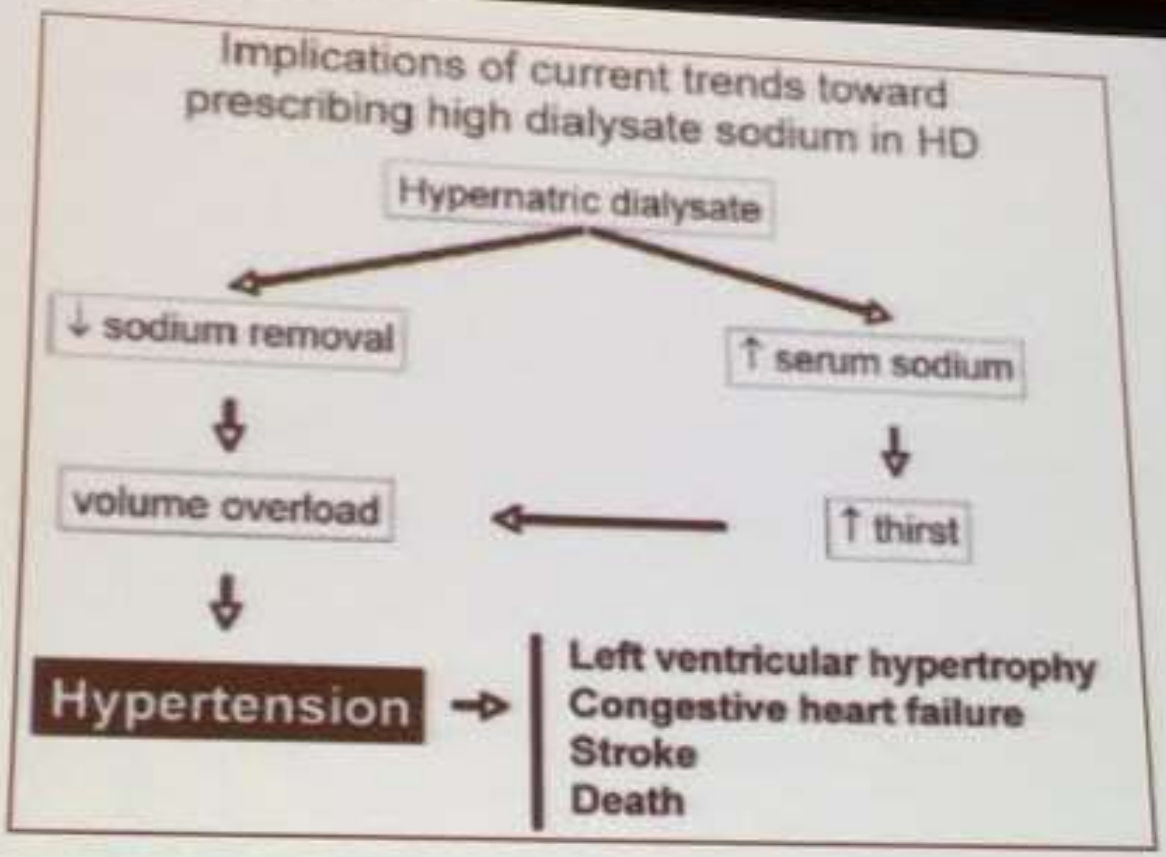
The control of hypertension has been extremely difficult in all of our patients in spite f drug therapy, moderate dietary salt restrictions and ultrafiltration during dialysis. Rigid odium restriction controlled the blood pressure, but was poorly tolerated. A low sodium ialysate (Na 120-125 mEq./L.) accomplished dialytic removal of sodium and has controlled e blood pressure on a moderate sodium intake.

Early Clinical Observation

the blood pressure again began to rise. The use of a low-sodium dialysate (120-125 mEq./L.) was then begun in order to deplete body sodium and the blood pressure gradually returned to near normal limits even though the patient remained on a regular diet. The use of a low sodium bath was occasionally accompanied by periods of disorientation and even convulsions, when the bath sodium was under 120 mEq./L. These usually occurred towards the end of the dialysis when sodium depletion was maximal. There seemed to be no immediate response to the infusion of isotonic saline solution. Hypertonic saline infusion was not attempted. After a post-ictal period lasting several hours, the patient's mental status returned to normal and he was able to carry on normal activities on the following day. When a low sodium dialysate was employed excess glucose was added to the bath to maintain isosmolarity. We have continued to use a low sodium bath, but keeping the levels above 120 mEq./L., where substantial sodium removal can still be achieved without disturbing mentation.

DR. SCHREINER: In reply to Dr. Epstein's comment: when we let our patient stay hypertensive for a couple of months, he did develop actual cardiovascular disease with measurable cardiomegaly and a ventricular diastolic gallop, and on correction of his hypertension, his heart size has gone back to normal and his gallop has disappeared. Perhaps a short term hypertension is not significant but a sustained hypertension probably does have pathologic significance.

From B. Shiller ASN 2014



Revisiting the Dialysate Sodium Prescription as a Tool for Better Blood Pressure and Interdialytic Weight Gain Management in Hemodialysis Patients

Sergio F. F. Santos and Aldo J. Peixoto

Clin J Am Soc Nephrol 3: 522–530, 2008.

Associations of a Facility Level Decrease in Na_d Concentration with BP and IDWG

- 52 patients
- Decreasing dialysate sodium from 141 to 138 mEq/L for 8 months
  - Statistically significant reduction in pre- and post-dialysis systolic and diastolic blood pressure were found
  - Without increasing adverse events

Thein H, Halcob I, Marshall MR, *Nephrol Dial Transplant* 2007;22:2630-2639

From B. Shiller ASN 2014