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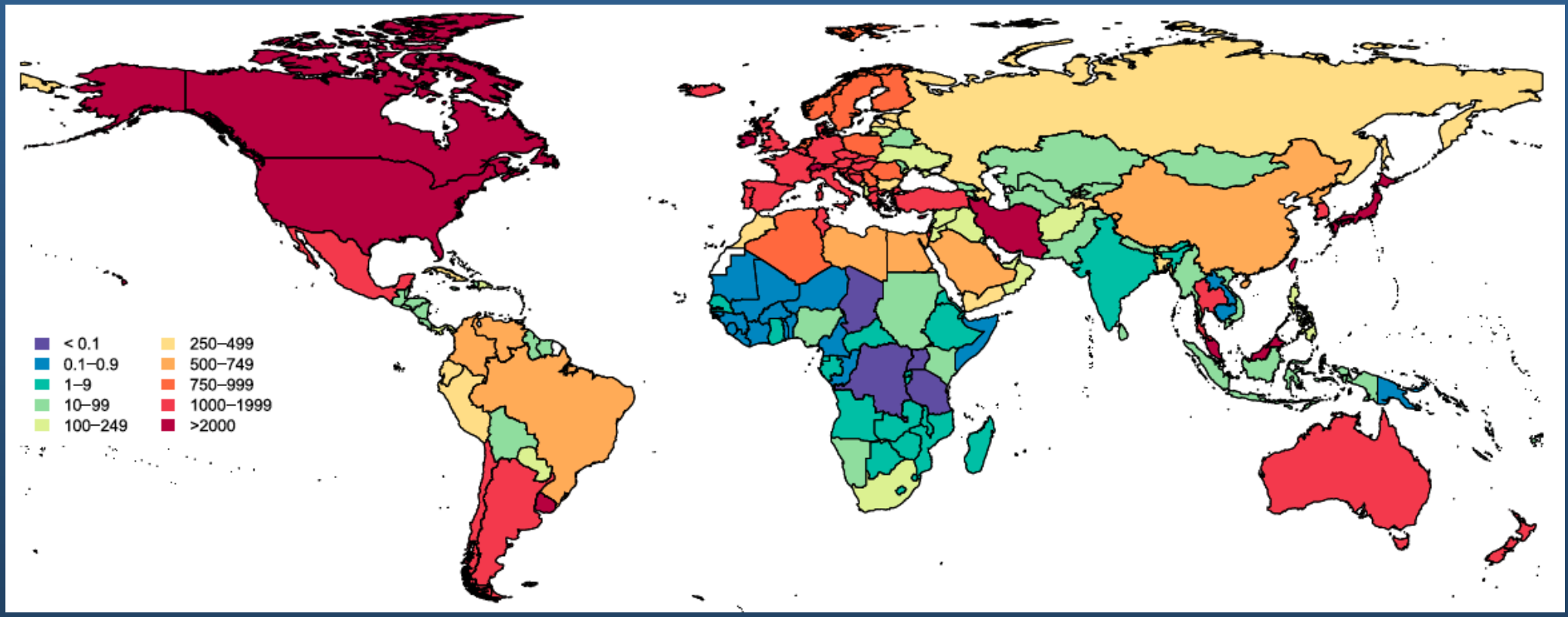
Wearable Artificial Kidney
Back to the future?

Presentation Outline

- RRT: needs and wants
- The challenge of a WAK
- History of WAK
- Current market situation
- Actual perspective and future direction
- Wearable to implantable?
- Conclusions

The epidemic of CKD



Costs: more than $30 billion/year in the US

Mortality rate of CKD patients

= metastatic carcinoma of breast, colon or prostate

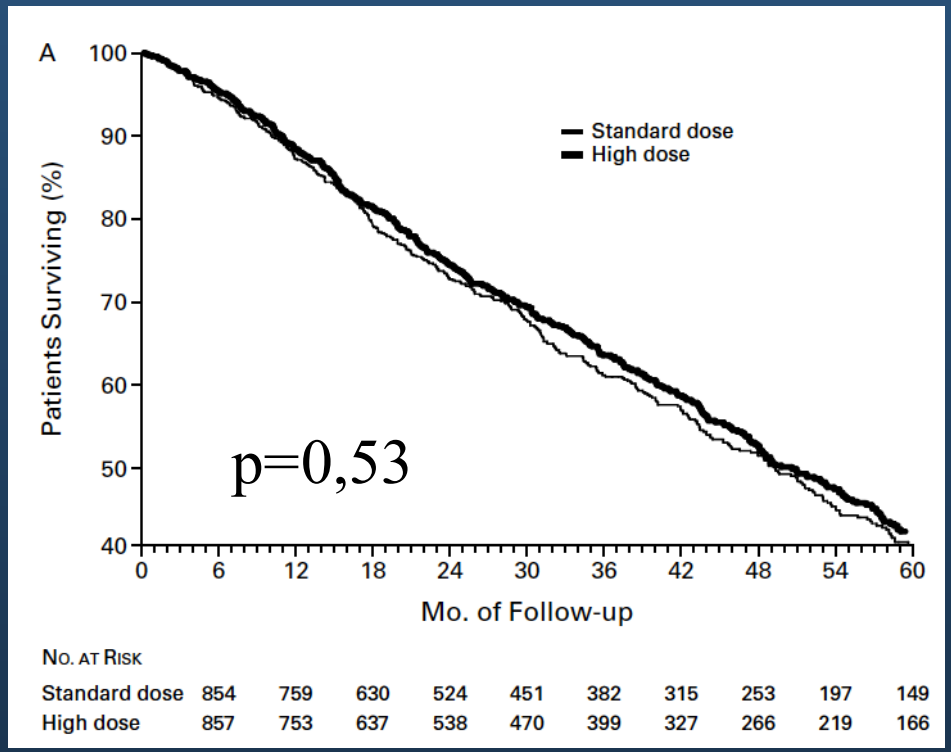
B. Thomas et al, "Maintenance Dialysis throughout the World in Years 1990 and 2010," J. Am. Soc. Nephrol. JASN, vol. 26, no. 11, pp.2621–2633, Nov. 2015.

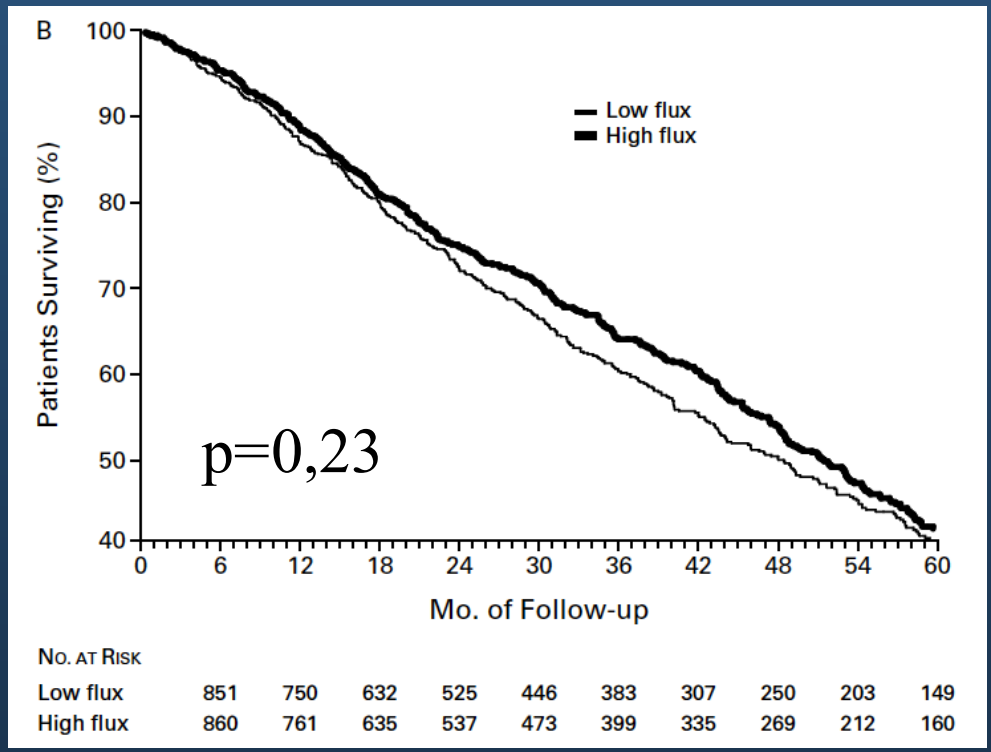
C. Ronco et al, "A wearable artificial kidney: dream or reality?" Nat Clin Pract Nephrol. 2008 Nov;4(11):604-5

Better patient tolerance, but stagnant outcomes despite improvement in techniques

Current RRT: high-flux HD

HEMO study, 2002



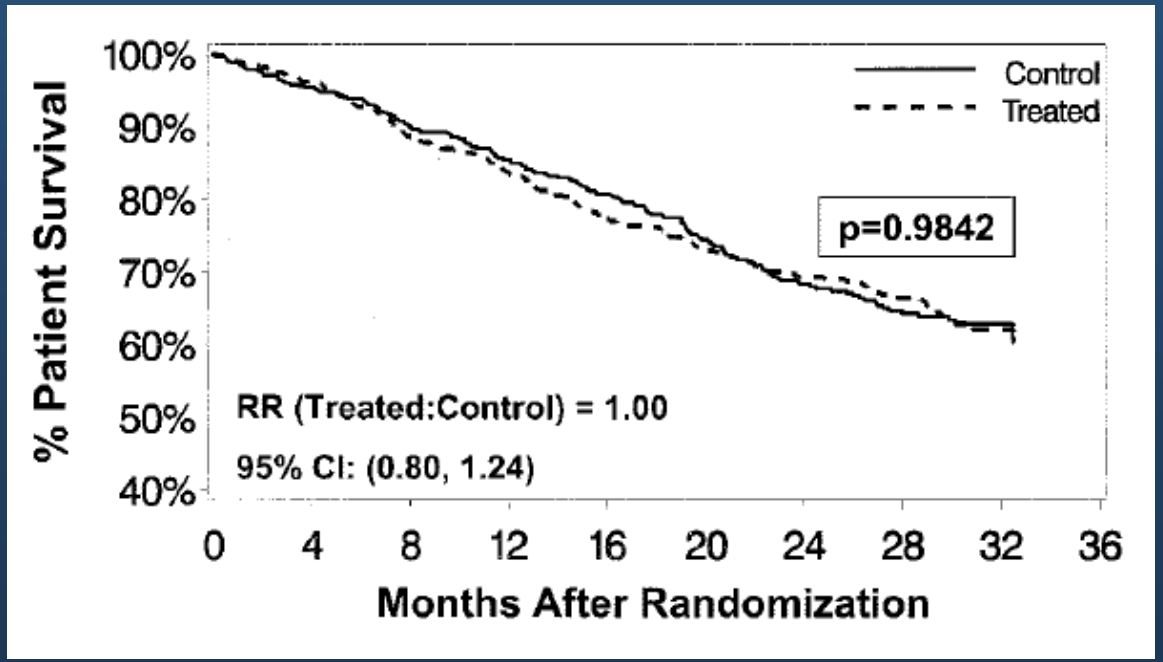


G. Eknoyan et al, "Effect of dialysis dose and membrane flux in maintenace hemodialysis", N Engl J Med 2002 Dec 19; 347(25):2010-9

Better patient tolerance, but stagnant outcomes despite improvement in techniques

Current RRT: high efficiency PD

ADEMEX study, 2002

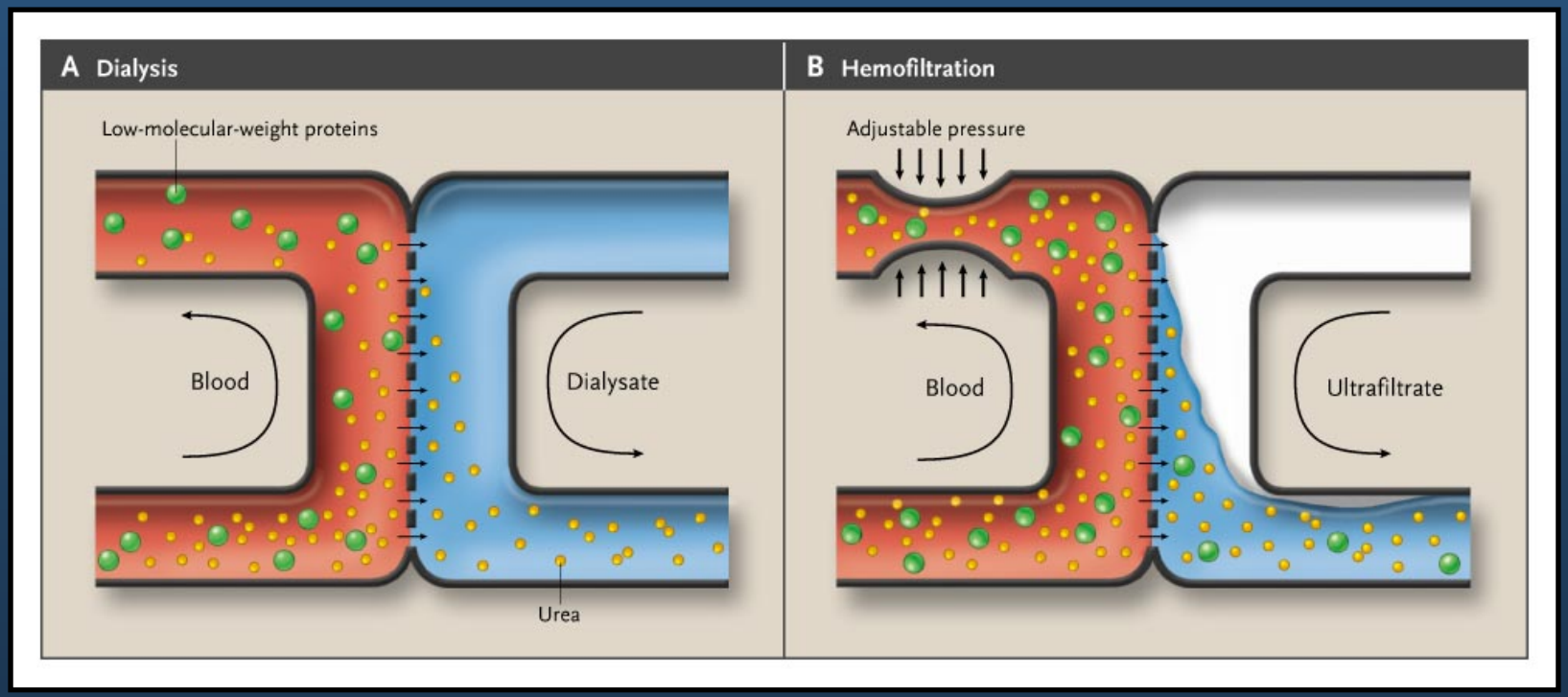


R. Paniagua et al, "Effects of Increased Peritoneal Clearances on Mortality Rates in Peritoneal Dialysis: ADEMEX, a Prospective, Randomized, Controlled Trial", J Am Soc Nephrol 2002 May; 13(5)1307-20

"Modern" treatments eventually not superior to traditional ones?

A move towards convection

Current RRT: HDF



Meyer T & Hostetter T: N Engl J Med 357:1316-1325, 2007

Current RRT: HDF

DOPPS study, 2006

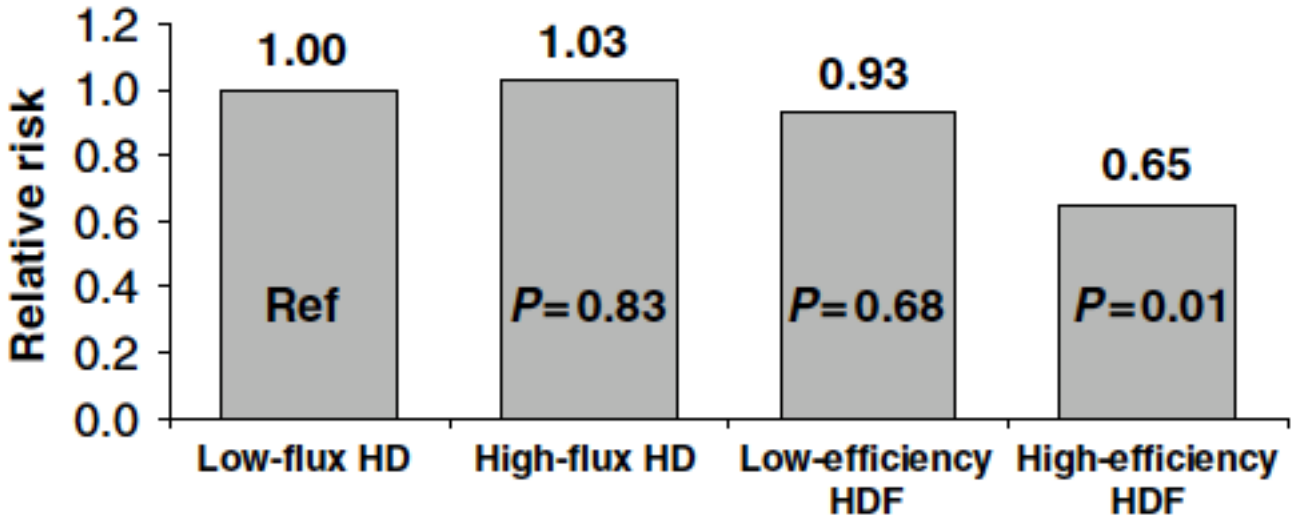
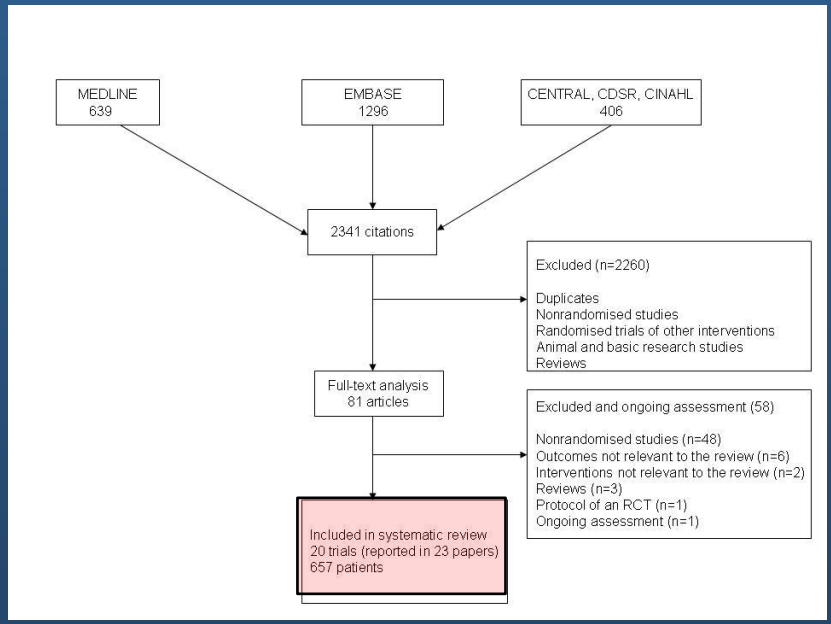


Figure 1 | Relative risk of mortality by dialysis type. (Adjusted for age, sex, time on dialysis, 14 summary comorbid conditions, weight, catheter use, hemoglobin, albumin, normalized protein catabolic rate, cholesterol, triglycerides, Kt/V, erythropoietin, MCS, and PCS.)

Canaud B et al, Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS **Kidney Int 69:2087–2093, 2006**

Current RRT: HDF

Meta-Analysis of Convective vs. Diffuse Therapies for ESRD



Authors' conclusions

"We were unable to demonstrate whether convective modalities have significant advantages over HD with regard to clinically important outcomes of mortality, dialysis-related hypotension and hospitalization. More adequately-powered good quality RCTs assessing clinically important outcomes (mortality, hospitalization, quality of life) are needed."

Rabindranath KS et al: *Cochrane Database of Systematic Reviews* 2008, Issue 1

Current RRT: HDF

Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials

HDF Pooling Project

Sanne A.E. Peters[1,2], Michiel L. Bots[2], Bernard Canaud[3,4], Andrew Davenport[5], Muriel P.C. Grooteman[6], Fatih Kircelli[7], Francesco Locatelli[8], Francisco Maduell[9], Marion Morena[4,10,11], Menso J. Nubé[6], Ercan Ok[7], Ferran Torres[12,13], Mark Woodward[1,14,15] and Peter J. Blankestijn[16] on behalf of the HDF Pooling Project Investigators

ndt Nephrology Dialysis Transplantation
Advance Access
October 22, 2015

follow-up 2.5 years (1.9-3)	HD	Events/	HDF	Events/	HR (95% CI) for
Causes of mortality	*n*	100 PY	*n*	100 PY	HDF versus HD
All-causes	1369	12.10	1367	10.45	0.86 (0.75; 0.99)
Cardiovascular disease	1302	4.84	1289	3.73	0.77 (0.61; 0.97)
Infections	1302	2.27	1289	2.13	0.94 (0.68; 1.30)
Sudden death	1302	1.65	1289	1.63	0.99 (0.68; 1.43)

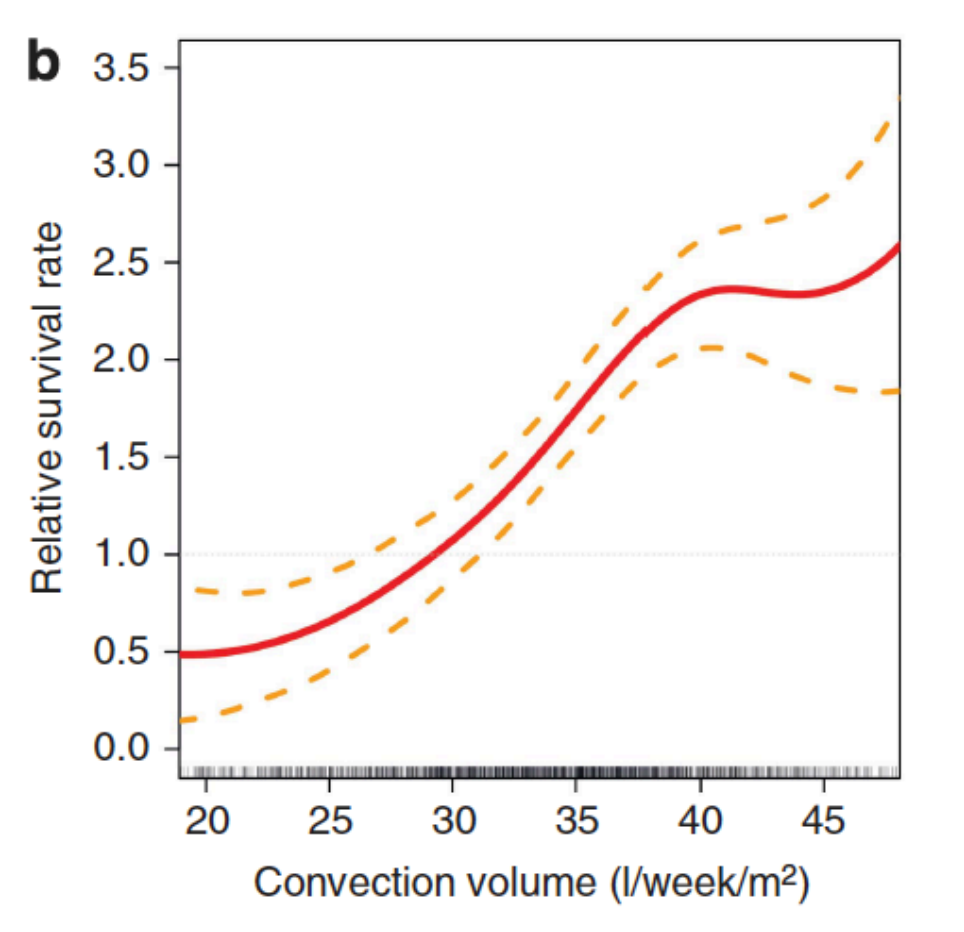
Cause	Online HDF: BSA-adjusted convection volume (L/session)		
	<19	19–23	>23
	HR (95% CI)		
All-causes			
Unadjusted	0.91 (0.74; 1.13)	0.88 (0.72; 1.09)	0.73 (0.59; 0.91)
* Adjusted	0.83 (0.66; 1.03)	0.93 (0.75; 1.16)	0.78 (0.62; 0.98)
Cardiovascular			
Unadjusted	1.00 (0.71; 1.40)	0.71 (0.50; 1.01)	0.69 (0.48; 0.98)
Adjusted	0.92 (0.65; 1.30)	0.71 (0.49; 1.03)	0.69 (0.47; 1.00)

Dysomogeneous sample, different study design and inclusion criteria
→ "Observational" data

Current RRT: HDF

Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration

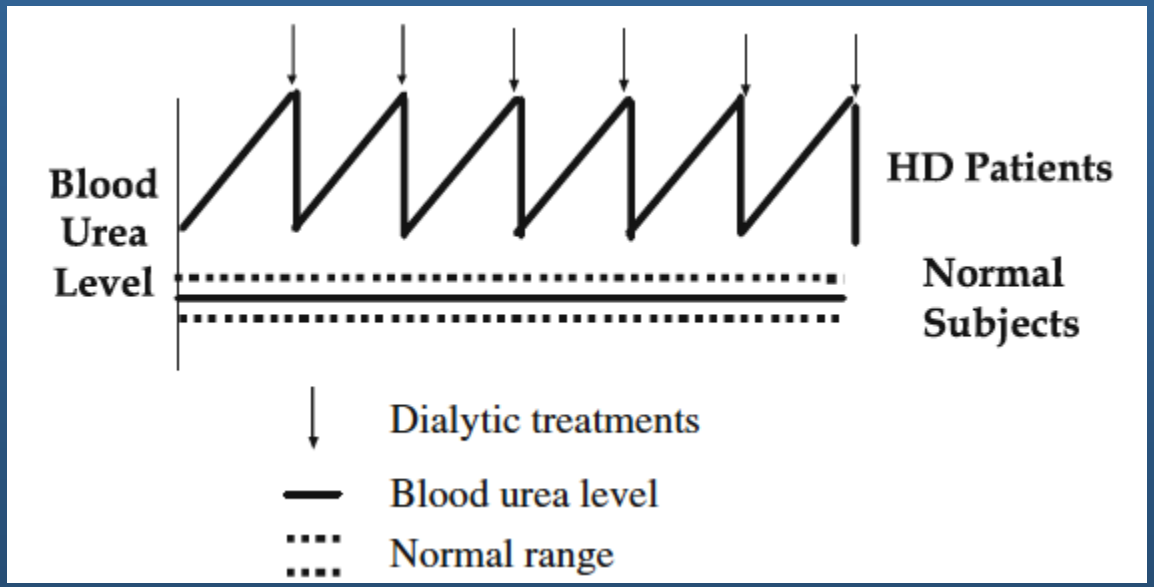
Bernard Canaud[1,2], Carlo Barbieri[2], Daniele Marcelli[2,3], Francesco Bellocchio[2], Sudhir Bowry[2], Flavio Mari[2], Claudia Amato[2] and Emanuele Gatti[2,3]



Higher convective volumes improve survival

wouldn't it be only a matter of dialysis time?

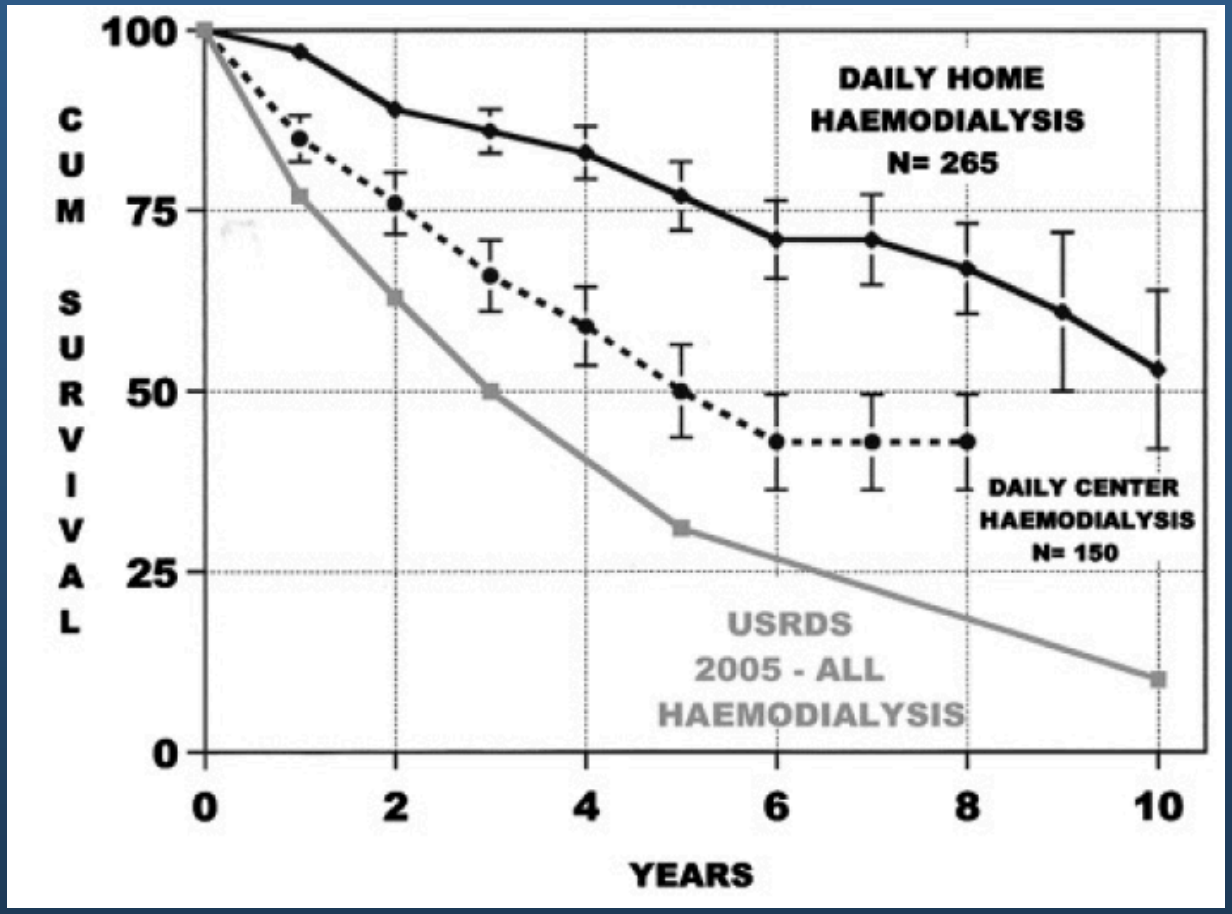
Canaud B et al, Optimal convection volume for improving patient outcomes in an international incident dialysis cohort Treated with online hemodiafiltration, KIDNEY INT. 2015 NOV;88(5):110-16



- **Continuous, round-the-clock** metabolic and fluid regulation
- Excretion of water soluble, middle molecular weight and protein-bound toxins, in addition to small molecular weight toxins
- **Function automatically, imposing no restriction** to the individual's life

Lee et al, "A peritoneal-based automated wearable artificial kidney". Clin Exp Nephrol. 2008 Jun;12(3):171-80

Current RRT: daily dialysis



Kjellstrand et al, " Short daily haemodialysis: survival in 415 patients treated for 1006 patient-years ", Nephrol Dial Transplant (2008) 23: 3283–3289

Current RRT: daily dialysis

Frequent Hemodialysis Network Daily Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 9, 2010 VOL. 363 NO. 24

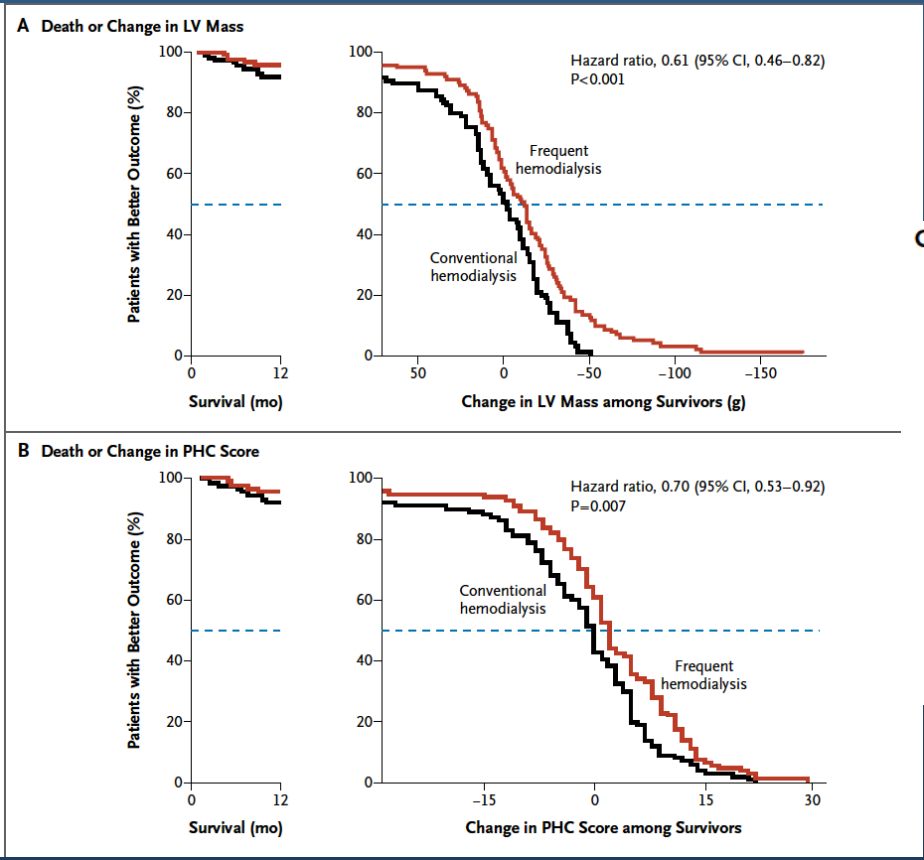
In-Center Hemodialysis Six Times per Week versus Three Times per Week

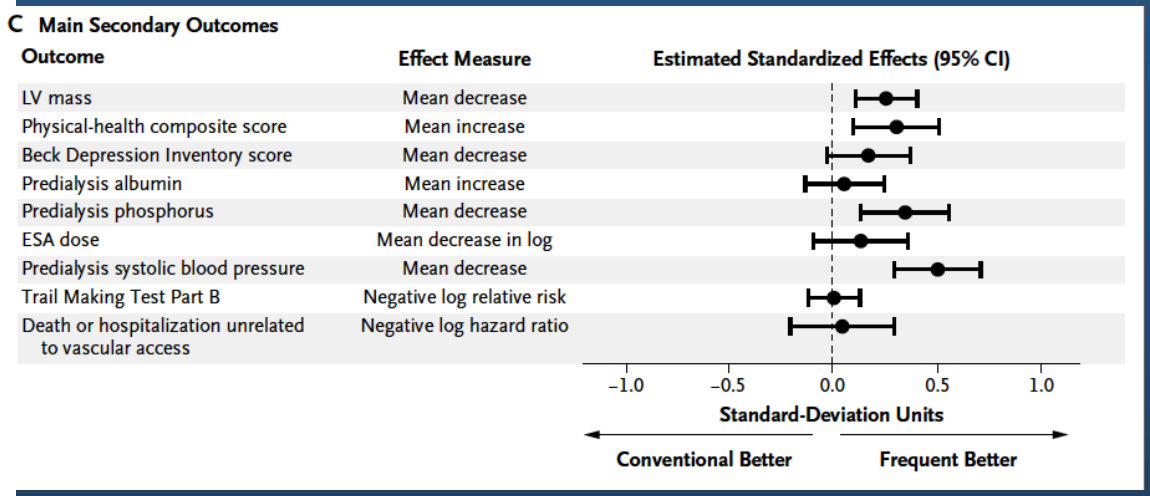
The FHN Trial Group*

Chertow et al, "In-center hemodialysis six times per week versus three times per week", N Engl J Med. 2010 Dec 9;363(24):2287-300

Current RRT: daily dialysis

Frequent Hemodialysis Network Daily Trial





Chertow et al, "In-center hemodialysis six times per week versus three times per week", N Engl J Med. 2010 Dec 9;363(24):2287-300

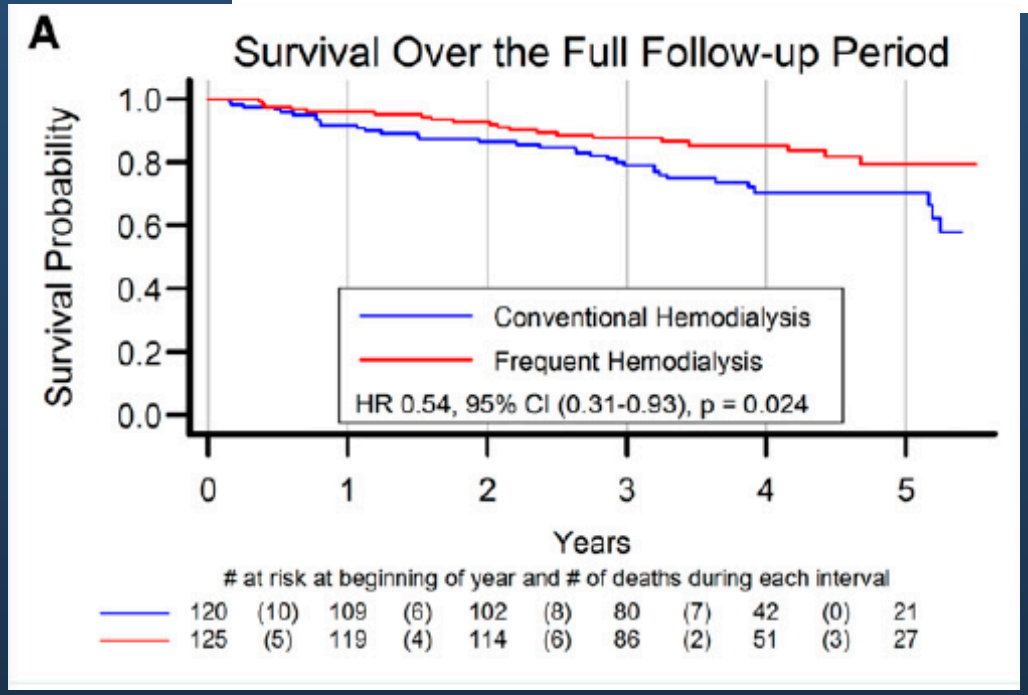
Current RRT: daily dialysis

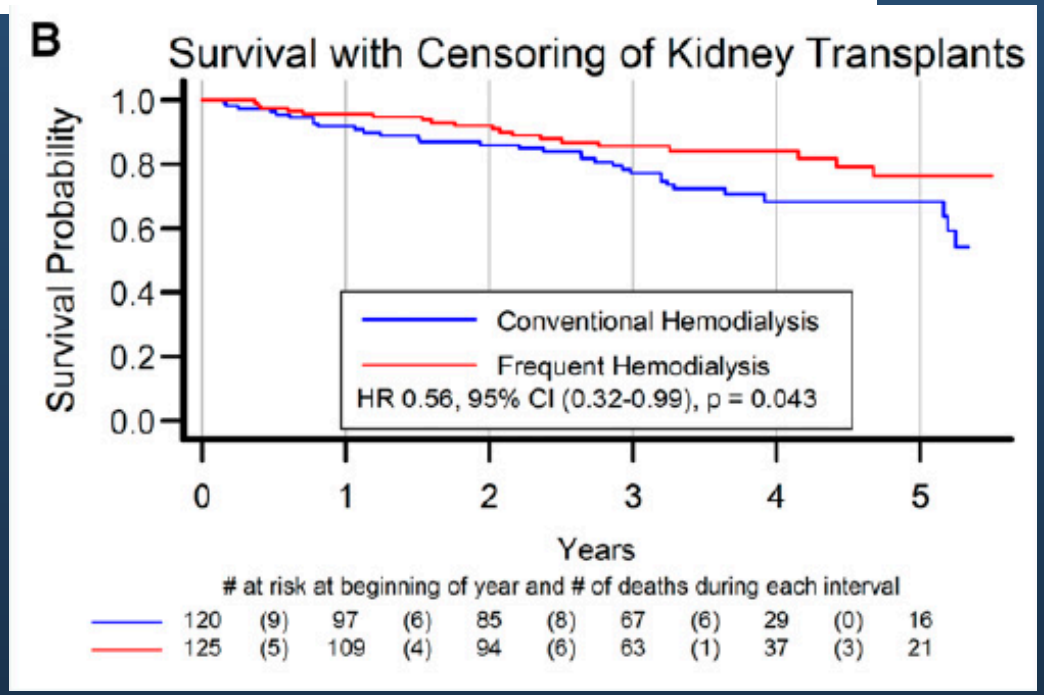
Frequent Hemodialysis Network Daily Trial

Long-Term Effects of Frequent In–Center Hemodialysis

Glenn M. Chertow,* Nathan W. Levin,† Gerald J. Beck,‡ John T. Daugirdas,§
Paul W. Eggers,‖ Alan S. Kliger,¶ Brett Larive,‡ Michael V. Rocco,** and Tom Greene,‡††
for the Frequent Hemodialysis Network (FHN) Trials Group

J Am Soc Nephrol 27: ●●●–●●●, 2015. doi: 10.1681/ASN.2015040426

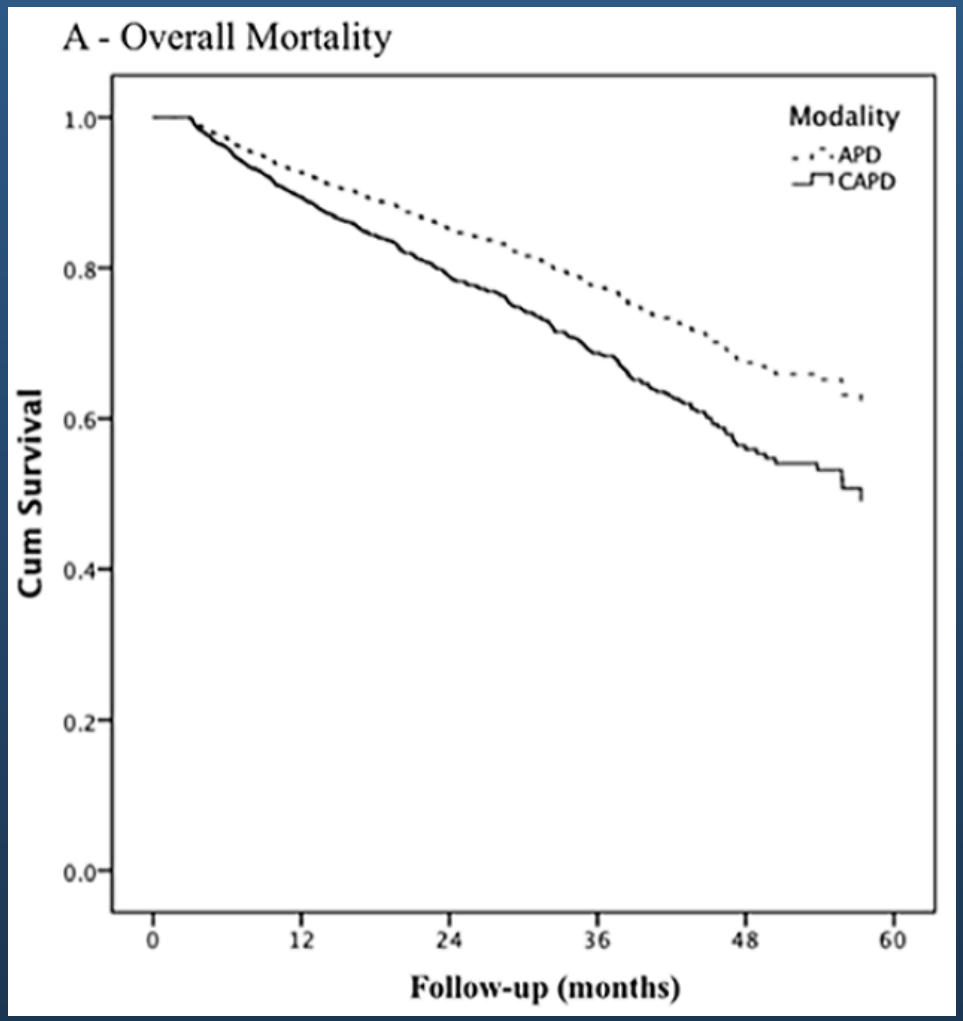




Chertow et al, "Long-term effects of frequent in-center hemodialysis", J Am Soc Nepèhrol 27, 2015

Current RRT: PD

Comparing PD modalities



G. de C. Beduschi, et al, "Automated Peritoneal Dialysis Is Associated with Better Survival RatesCompared to Continuous Ambulatory Peritoneal Dialysis: A Propensity Score Matching Analysis," PloS One, vol.10, no. 7, p. e0134047, 2015.

Dialysis: the longer the treatment, the better?

Longer and more frequent dialysis is infeasible for most patients:

- Nowhere to do it
- Nobody to do it
- Who pays?
- **Patients want freedom**

The challenge for a WAK

3 reason for developing a WAK:

- **Clinical**: better outcomes and quality of life for daily dialysis
- **Technical**: take advantage of technological progress
- **Socio-economics**: costs of current RRT modalities, unacceptable mortality rates for CKD patients

Ronco, Davenport and Gura, A wearable artificial Kidney: dream or reality? Nature clinical practice nephrology, 2008

The challenge for a WAK

"It seems like one factor the nephrology community was never able to fully identify and modify is **dialysis time**..."

The WAK is intended to be used for CRRT 24h a day 7 days a week

Must be able to deliver proposed CrCl of 30 ml/min and UF 30 ml/min

Light weight, ergonomic, energy independent, safe; no risk of clotting, infection, toxicity

C Ronco et al, Critical Care Nephrology, 2° edition, Elsevier

The challenge for a WAK

Technical requirements for a WAK

Dialysate regeneration

Power sources

Vascular Access

Dialysis membranes

Pumping system

Monitoring system

P Armignacco et al, "Wearable devices for blood purification: principles, miniaturization and technical challenges", Semin Dial. 2015 Mar-Apr(2):125-30
C Ronco et al, "The future of Artificial Kidney: moving towards wearable and miniaturized devices", Nefrologia 2011;31(1)9-16

“whoever wishes to foresee the future must consult the past; for human events ever resemble those of preceding times”

N. Machiavelli

Discourses on the First Ten Books of Titus Livius,
Chapter XLIII
1513 b.c.

WAK: first attempts (1976)

Proc Eur Dial Transplant Assoc. 1976;12:511-8.

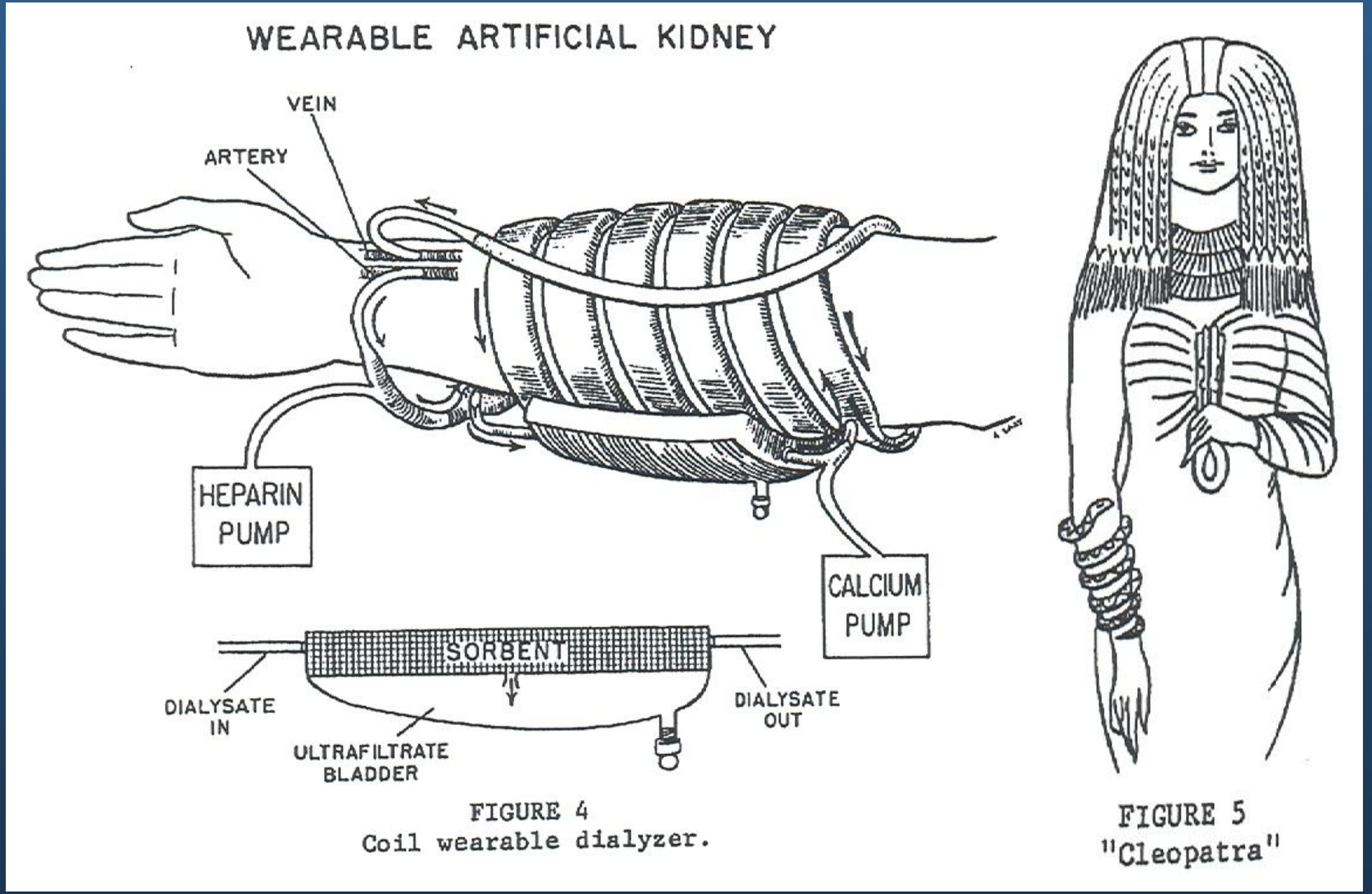
Portable/wearable artificial kidney (WAK) - initial evaluation.

Stephens RL, Jacobsen SC, Atkin-thor E, Kolff W.

Abstract

This report discusses the modus operandi and results achieved using this new mode of haemodialysis. An insulated 20 L dialysate bath acts as a carrying case for the system. When empty the case is large enough to hold the wearable module and complete supplies for one week's operation. The total weight is 17 kg. The wearable unit consists of a combined blood and dialysate pump (1.2 kg), rechargeable batteries, tubing, Dow dialyser and charcoal regeneration module with a total weight of 3.5kg. Ideally the patient dialyses using a single needle some 3 hours/day, 6 days/week. It is necessary for the wearable module to be connected to the 20 L dialysate bath for an average of 90 minutes to achieve adequate urea and 5+ removal. One patient was dialysed on 35 consecutive days and 4 others were dialysed intermittently. Routine laboratory tests and mass balance studies were performed on all patients. Ultrafiltration rates reached 700 ml/hour, routine serum chemistries remained stable and mass balance studies demonstrated a daily removal of urea 14-20 G, creatinine 1500-2000 mg, uric acid 500-900 mg and K+ 30-55 mEq. It is concluded that dialy dialysis with WAK is biochemically adequate and also permits the patient a much less restricted esistence.

WAK: hypothesis (1977)



Landè, "In search of a 24 hours per day artificial kidney", Journal of dialysis 1977

REDY or not? (1979)

Adsorption

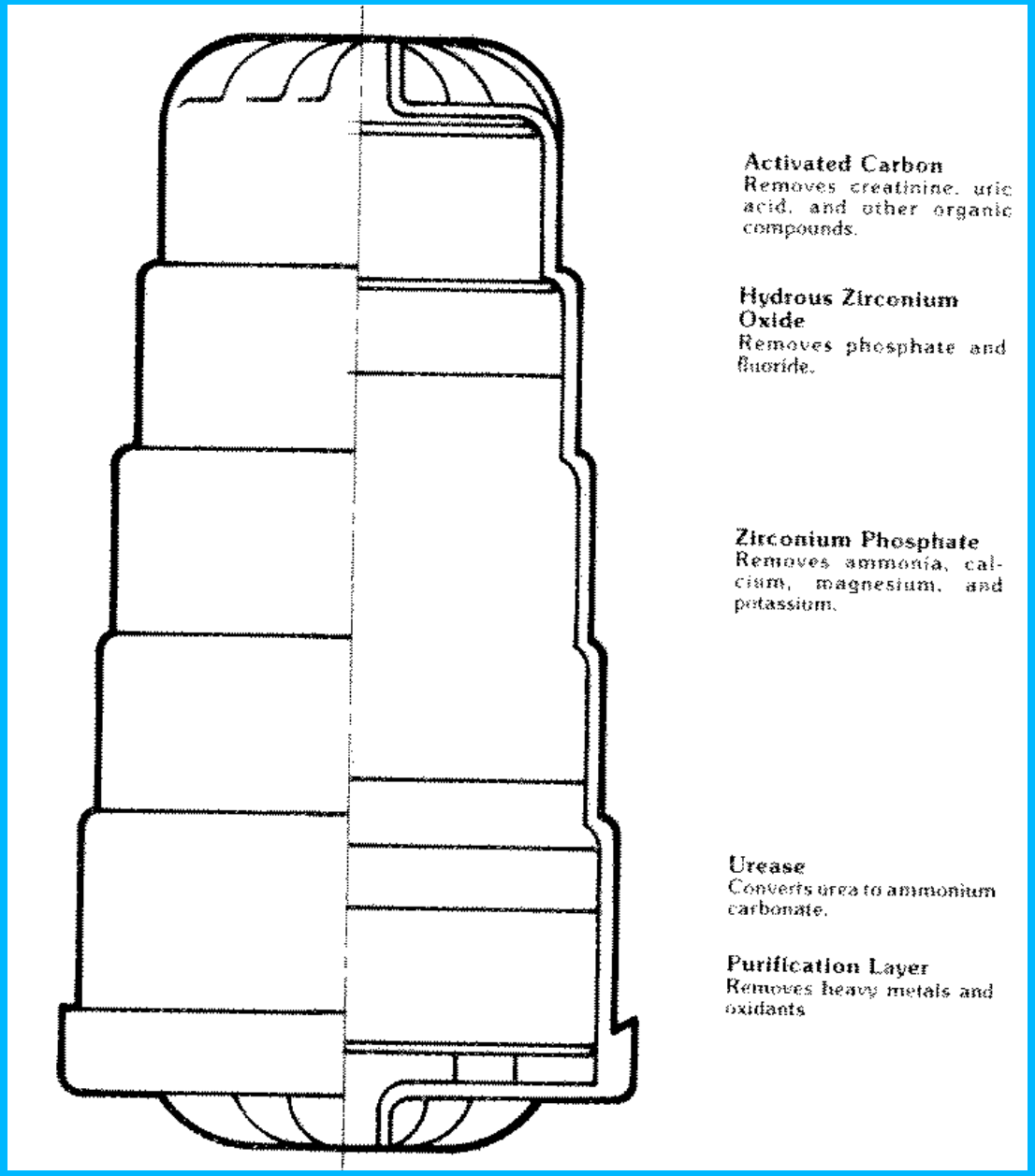
separation of a solute from its solvent by a solid agent

REDY System (Recirculating DialYsis)

Sorbent dialysis, suitable for HD and PD

Blumenkrantz, Application of the Redy sorbent system to HD and PD, Artificial Organs, 1979

REDY or not? (1979)



Blumenkrantz, Application of the Redy sorbent system to HD and PD, Artificial Organs, 1979

WAK: REDY or not? (1979)

Drawbacks:

- Cartridge **weight**, **cost**, and **unregenerability**
- **Na+ and H+ load** (in exchange for NH_4^+ produced by urea breakdown by urease)
- **Aluminium release**

Standard REDY cartridge: 3,3 kg of active compounds, suitable for 3 HD sessions (removal of 50 g urea)

Blumenkrantz, Application of the Redy sorbent system to HD and PD, Artificial Organs, 1979

REDY: first clinical application

Long-term Experience of Home Dialysis with Sorbent Regeneration of Dialysate

M A MANSELL, A J WING
St Thomas's Hospital, London, England

11 patients, thrice/weekly dialysis 6-7 hours, 3 REDY cartridge per week, independent for water supply and drainage

Slight elevation of creatinine and urea

Mansell MA, Wing AJ, long-term experience of home dialysis with sorbent regeneration of dialysate, Proc Eur Dial Transplant Assoc 13:275, 1977

REDY: first clinical application

TABLE II. Comparison of Pre-dialysis Biochemistry and pH in Single-pass System (SPS) Patients and Sorbent Regeneration Dialysate (SRD) Patients

	Single-pass system (SPS)	Sorbent Regeneration of Dialysate (SRD) Acetate prime	SRD (1) 31 mmol/L	SRD (2) 42 mmol/L	SRD (3) 55 mmol/L
Blood Urea (mmol/L) ± SEM	22 ± 0.8		25 ± 0.6	26 ± 1.2	25.4 ± 1.0
Plasma Creatinine (mmol/L) ± SEM	970 ± 40		1100 ± 30	1083 ± 27	1067 ± 37
Plasma Sodium (mmol/L) ± SEM	139 ± 0.9		140 ± 0.5	141 ± 0.5	140.7 ± 0.4
Plasma Potassium (mmol/L) ± SEM	4.9 ± 0.1		4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1
Plasma Bicarbonate (mmol/L) ± SEM	24 ± 0.5		15 ± 0.5	17.4 ± 0.6	19.5 ± 0.5
pH ± SEM	7.40 ± 0.03		7.33 ± 0.05	7.37 ± 0.04	7.38 ± 0.06
Leucocyte Potassium (mmol/kg cells dry weight) ± SEM	424 ± 19		364 ± 17	400 ± 24	–
Plasma Calcium (mmol/L) ± SEM	2.52 ± 0.02		2.37 ± 0.02	2.60 ± 0.03	2.49 ± 0.03
Plasma Phosphate (mmol/L) ± SEM	1.75 ± 0.05		1.95 ± 0.1	1.80 ± 0.1	2.06 ± 0.1

Wearable hemofiltration (1980)

CONTINUOUS AMBULATORY HEMOFILTRATION

S. Shaldon, M. C. Beau, G. Deschodt, M. J. Lysaght*,
P. Ramperez, and C. Mion

2 ESRD patients in HD
inter-dialytic UF through a polysulphone minifilter (femoral AV shunt)
0,6 ml/min UF (average 800 ml/day)
Anticoagulation through injected salycilate

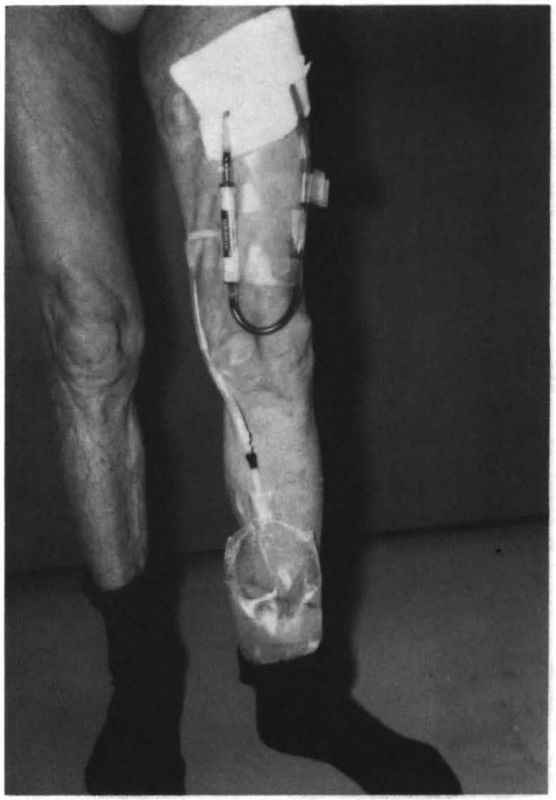


Figure 3. Minifilter + collection sac strapped to lower leg.

Shaldon et al, Continuous ambulatory hemofiltration, Trans Am Soc Artif Intern Organs, 1980

Continuous wearable hemofiltration (1986)

Continuous Arterio-venous Hemofiltration in a Wearable Device to Treat End-stage Renal Disease

A. Murisasco, J. P. Reynier, A. Ragon, Y. Boobes, M. Baz, C. Durand, P. Bertocchio, C. Agenet, and M. El Mehdi

A-V Schribner shunt
2 patients treated daily for 1 and 3 months
3-4 minicartridges per day

Problems:
- Maintaing access patency
- Risk of long term Al toxicity

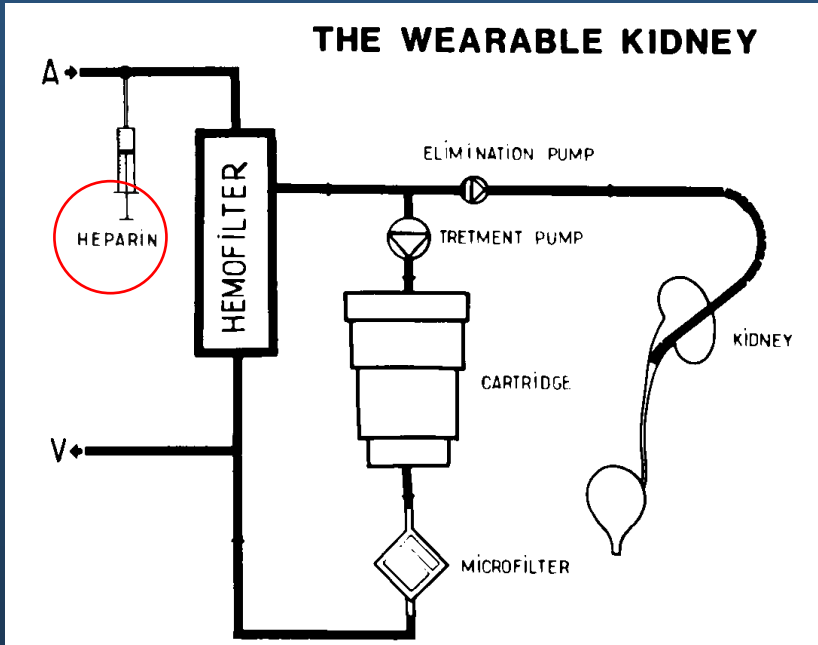


Figure 2. The "wearable kidney."

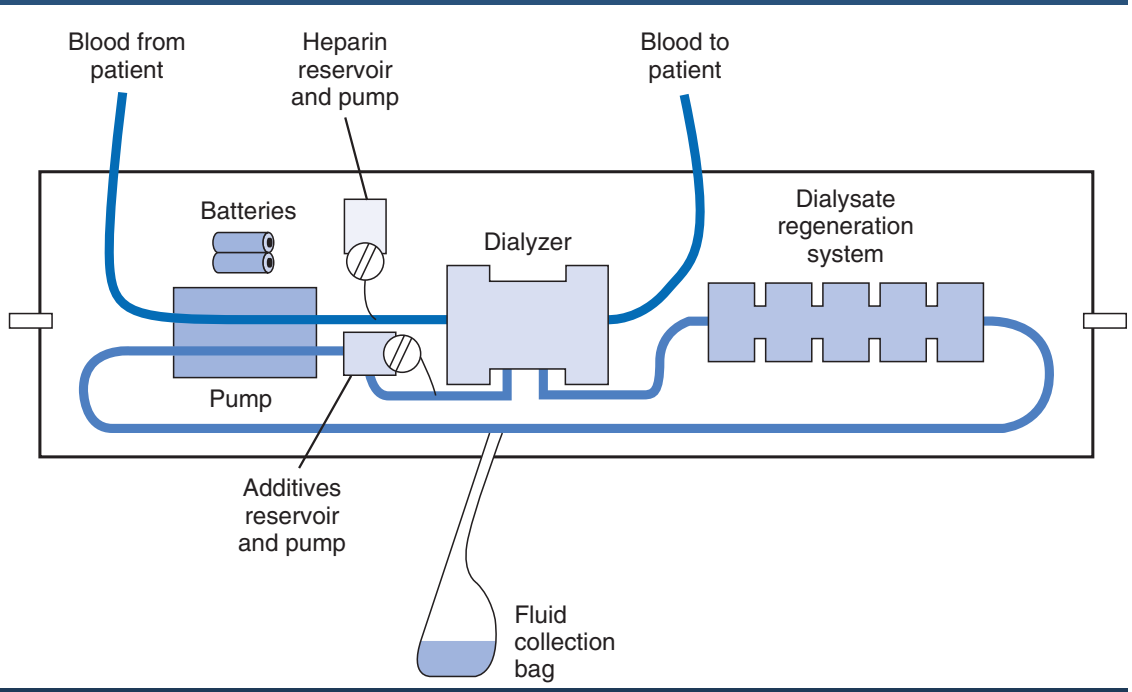
Murisasco et al, Continuous arterio-venous hemofiltration in a wearable device to treat end-stage renal disease, Trans Am Soc Artif Intern Organs, 1986

WAK: modern times (2005)

Contrib Nephrol. 2005;149:325-33.

Continuous renal replacement therapy for end-stage renal disease. The wearable artificial kidney (WAK).

Gura V[1], Beizai M, Ezon C, Polaschegg HD.



BIOCHEMICAL INDEX	Finding GROUP I	GROUP II
Effective urea clearance (mL/min)	24.3 ± 1.4	23.9 ± 3.5
Effective creatinine clearance (mL/min)	25.5 ± 1.4	24.7 ± 3.2
Total urea removal (g)	12.7 ± 2.8	12.0 ± 2.9
Total creatinine removal (g)	0.9 ± 0.2	1.0 ± 0.1
Total phosphorus removal (g)	0.8 ± 0.2	0.84 ± 0.4
Total potassium removal (mmol)	71.9 ± 13.3	89.1 ± 25.7
Extrapolated standard Kt/V (urea)	5.4 ± 2.4	8.4 ± 1.5

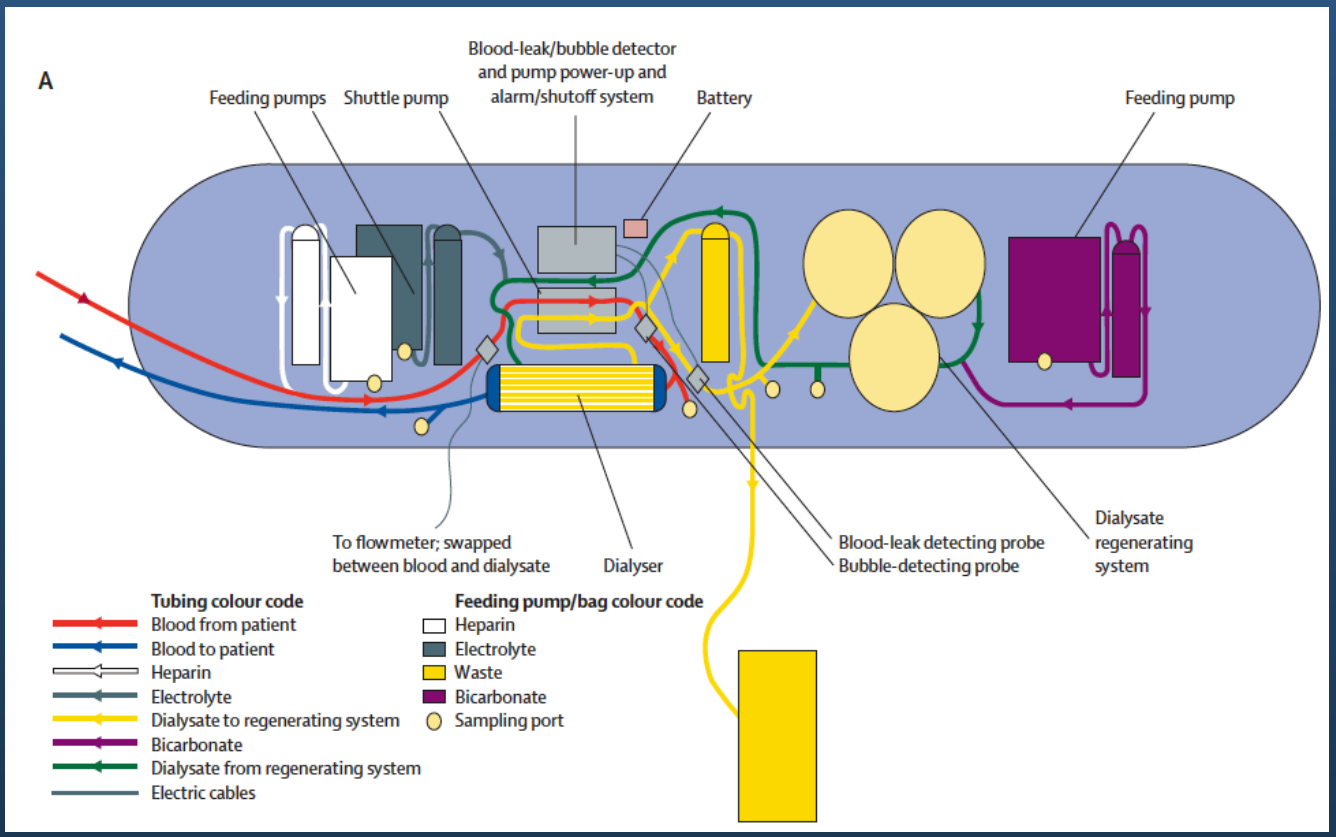
*In uremic pigs. In Group I, a blood flow rate of 44 mL/minute was used; in Group II, blood flow rate was 75 mL/minute. Values are means ± SD. Data from Gura V, Beizai M, Ezon C, Polaschegg HD: Continuous renal replacement therapy for end-stage renal disease: The wearable artificial kidney (WAK). In Ronco C, Brendolan A, Levin NW (eds): Cardiovascular Disorders in Hemodialysis. Basel, Karger, Contrib Nephrol 2005;149:325-333.

Dialysate continuously regenerated through a sorbent unit (tot dialysate 375 ml)

WAK: modern times (2007)

A wearable haemodialysis device for patients with end-stage renal failure: a pilot study

Andrew Davenport, Victor Gura, Claudio Ronco, Masoud Beizai, Carlos Ezon, Edmond Rambod



A. Davenport et al, " A wearable haemodialysis device for patients with end stage renal failure: a pilot study". Lancet. 2007 Dec 15;370(9604):2005-10

WAK: modern times (2007)

Mean treatment time 6,4 h
Mean blood flow 58,6 ml/min
Mean dialysate flow 47,1 ml/min

	Treatment time (h)	Weight (kg)		Extracellular fluid/total body fluid		Urea removed (mmol)	Creatinine removed (mmol)	Plasma urea clearance (mL/min)	Plasma creatinine clearance (mL/min)	Standard hourly urea clearance (Kt/V)
		Before treatment	After treatment	Before treatment	After treatment					
Patient 1	4	81·6	80·7	0·342	0·339	6·2	5·4	15·2	12·6	0·02
Patient 2	4	59·7	59·3	0·343	0·337	9·1	5·4	31·6	28·0	0·05
Patient 3	4	56·4	55·5	0·345	0·342	5·7	3·6	22·8	18·0	0·03
Patient 4	7	62·6	62·3	0·324	0·319	7·0	5·4	19·5	19·9	0·03
Patient 5	8	56·5	56·9	0·344	0·343	14·0	15·2	26·8	25·9	0·04
Patient 6	8	88·5	86·7	0·327	0·320	15·5	8·9	25·4	24·1	0·05
Patient 7	8	117·3	115·8	0·352	0·350	18·0	13·4	21·3	20·1	0·02
Patient 8	8	48·0	46·6	0·337	0·335	6·7	4·5	18·4	16·9	0·04
Mean (SD)	6·4 (2·0)	71·3 (23)	70·5 (22·6)	0·339 (0·009)	0·335 (0·010)	10·3 (4·8)	7·7 (4·4)	22·7 (5·2)	20·7 (4·8)	0·035 (0·01)

No hemolysis, stable electrolytes and pH, no alteration in BP or HR

A. Davenport et al, " A wearable haemodialysis device for patients with end stage renal failure: a pilot study". Lancet. 2007 Dec 15;370(9604):2005-10

WAK: modern times (2007)

Problems:

Release of bubbles of carbon dioxide (decomposition of urea by urease)

- One patient had clotting of the CVC
- One patient had clotting of the circuit
- One patient suffered fistula needle dislodgement and temporary disconnection

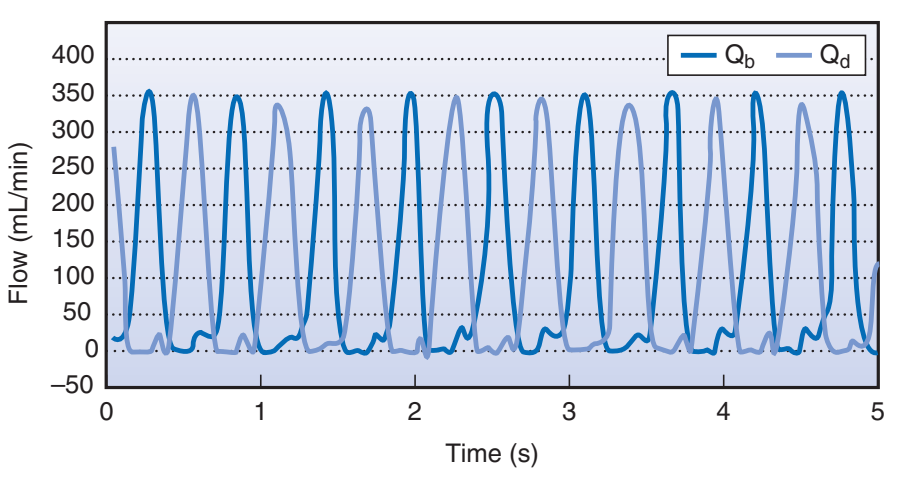
A. Davenport et al, " A wearable haemodialysis device for patients with end stage renal failure: a pilot study". Lancet. 2007 Dec 15;370(9604):2005-10

WAK: modern times (2009)

Technical Breakthroughs in the Wearable Artificial Kidney (WAK)

Victor Gura,*† Alexandra S. Macy,‡ Masoud Beizai,‡ Carlos Ezon,‡ and Thomas A. Golper§

Reverse flow is not permitted by the pump valves → push-pull flow



Fresh dialysate back filters into the blood compartment in the distal portion of the hollow fiber → sort of post-dilution → "pulsatile push-pull HDF"

V. Gura et al, "Technical breakthroughs in the wearable artificial kidney (WAK)", Clin J Am Soc Nephrol. 2009 Sep;4(9):1441-8

WAK: modern times (2009)

β_2-Microglobulin and Phosphate Clearances Using a Wearable Artificial Kidney: A Pilot Study

Victor Gura, MD,[1,2] Andrew Davenport, MD,[3] Masoud Beizai, PhD,[2] Carlos Ezon, MD,[2] and Claudio Ronco, MD[4]

Average β2-microglobulin and phosphate clearances were about respectively 50% and 95% of creatinine clearance

Table 1. Total Amounts and Clearances of Phosphate and β_2-Microglobulin Removed During Treatment With the Wearable Artificial Kidney

Patient No.	Time (h)	Inorganic Phosphate Removed (mg)	β_2-Microglobulin Removed (mg)	Inorganic Phosphate Clearance (mL/min)	β_2-Microglobulin Clearance (mL/min)
1	4	252.1	28.7	19.2	10.0
2	4	331.4	79.7	23.1	12.1
3	4	317.1	62.7	23.9	12.1
4	7	1,105.8	183.5	25.0	12.1
5	8	590	123.5	24.2	10.9
6	8	151.3	12.9	27.1	7.1
7	8	662.0	146.8	16.9	15.2
8	8	151.6	160.7	14.0	11.0
Mean ± SD	6.4 ± 2.0	445.2 ± 325.9	99.8 ± 63.1	21.7 ± 4.5	11.3 ± 2.3

Will longer treatment time saturate sorbents? Is β2-microglobulin representative of the clearance with WAK of potential middle-sized uremic toxins?

Cheung et al, "Serum β2-microglobulin predict mortality in dialysis patients: results of the HEMO study", J Am Soc Nephrol 2006

V Gura et al, "β2-Microglobulin and Phosphate Clearances Using a Wearable Artificial Kidney: A Pilot Study", Am J Kid Disease 2009

WAK: modern times (2006)

Continuous Renal Replacement Therapy for Congestive Heart Failure: The Wearable Continuous Ultrafiltration System

VICTOR GURA,* MASOUD BEIZAI,† CARLOS EZON,† AND EDMOND RAMBOD*

9 pigs with urether ligation; UF for 8 hours

Table 1. Average Blood Flow (Qb) and Cumulative and Average Ultrafiltration Rate (UF, in millititers) from Each Animal

Pig No.	1	2	3	4	5	6	7	8	9	Average
Qb, ml/min	38.6	44.2	54.2	69.5	62.2	81.7	78.2	79.1	75.4	64.8
UF, 1 h	100	150	180	160	390	50	190	90	225	170.5
UF, 2 h	200	220	200	370	500	85	370	190	260	266.1
UF, 3 h	300	380	350	560	540	95	440	360	355	375.6
UF, 4 h	500	500	700	725	540	95	545	520	390	501.7
UF, 5 h	800	600	700	810	540	160	545	520	435	568.9
UF, 6 h	1000	680	1400	880	600	445	545	520	525	732.8
UF, 7 h	1100	700	1400	960	640	625	620	580	615	804.4
UF, 8 h	1150	800	1400	1000	645	685	645	640	680	849.4
UF, average	144	100	175	125	81	87	81	80	85	106

V Gura et al, "Continuous renal replacement therapy for congestive heart failure: the wearable continuous ultrafiltration system". ASAIO J. 2006 Jan-Feb;52(1):59-61

WAK: modern times (2009)

A wearable hemofilter for continuous ambulatory ultrafiltration

V Gura[1], C Ronco[2], F Nalesso[2], A Brendolan[2], M Beizai[3], C Ezon[3], A Davenport[4] and E Rambod[5]

6 volume overloaded patients (in HD)
UF for 6 hours

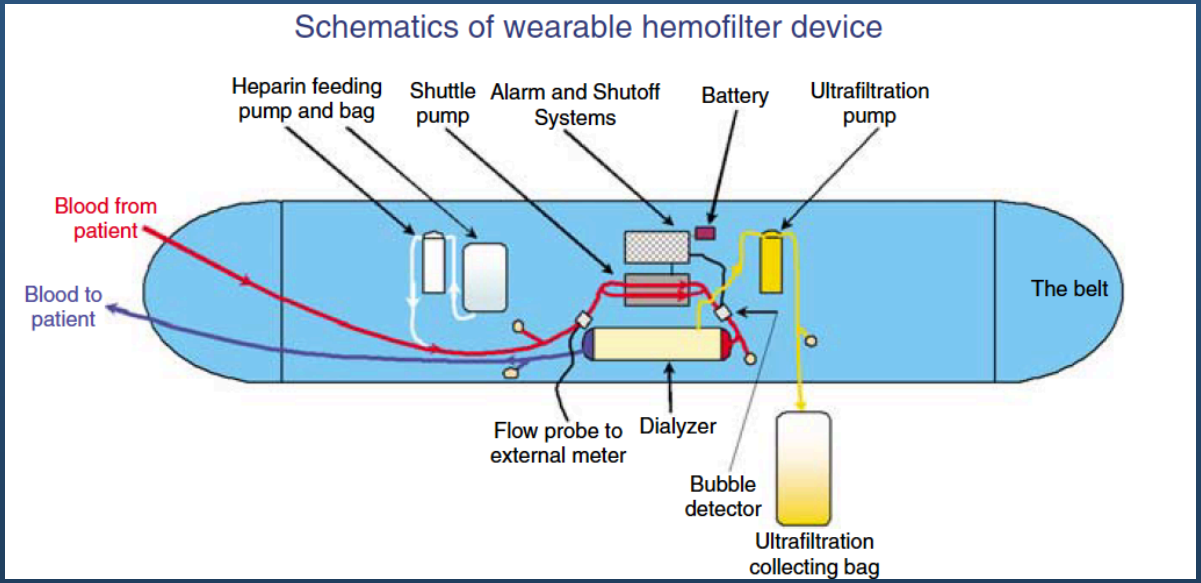


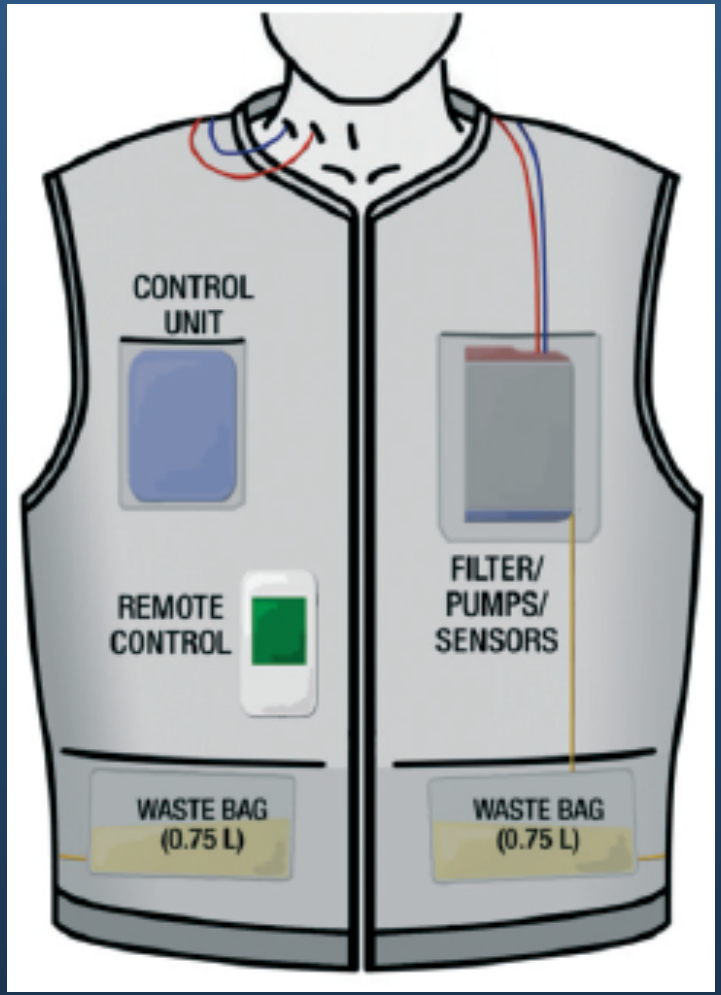
Table 3 | Patient parameters during treatment with the wearable hemofiltration device

Patient no.	1	2	3	4	5	6	Mean ± s.d.	*P*-value
MAP mm Hg pre-UF	119.0	111.0	90.3	88.3	138.0	109.7	109.4 ± 18.5	
MAP mm Hg post-UF	87.3	111.0	98.7	76.7	120.0	117.0	101.8 ± 17.3	0.03
Total UF (ml)	770	984	708	1610	1233	1201	1084.3 ± 335.4	
Na_{UF} (mmol)	107.8	132.8	97.0	223.8	172.6	171.7	150.0 ± 47.6	

Shows mean arterial pressure (MAP), volume ultrafiltered (UF), and sodium removed in ultrafiltrate (Na_{UF}). Data expressed as mean ± s.d.

WAK: modern times (2009)

Evolution of the concept: **WAKMAN**



C Ronco et al, "The future of Artificial Kidney: moving towards wearable and miniaturized devices", Nefrologia 2011;31(1)9-16

WAK: the problem of extracorporeal circulation

- Continuous anticoagulation and a complex monitoring system → **risk of clotting** despite aggressive heparinization (Neff, Murisasco, and lastly Davenport)
- Risk of **occult bleeding** or **disruption** of the blood circuit or **disconnection**
- Will continuous extracorporeal circulation affect the **longevity of the vascular access**?

Is peritoneal dialysis the solution for a WAK?

→ **continuous flow peritoneal dialysis** → potentially more efficient than the conventional inflow/outflow PD

Amerling et al, "Continuous flow peritoneal dialysis: principles and applications". Semin Dial. 2003 Jul-Aug;16(4):335-40

Lee et al, "A peritoneal-based automated wearable artificial kidney". Clin Exp Nephrol. 2008 Jun;12(3):171-80

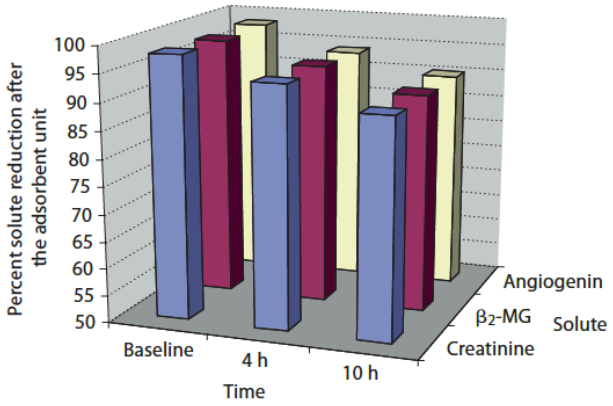
The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD)

WAK for PD

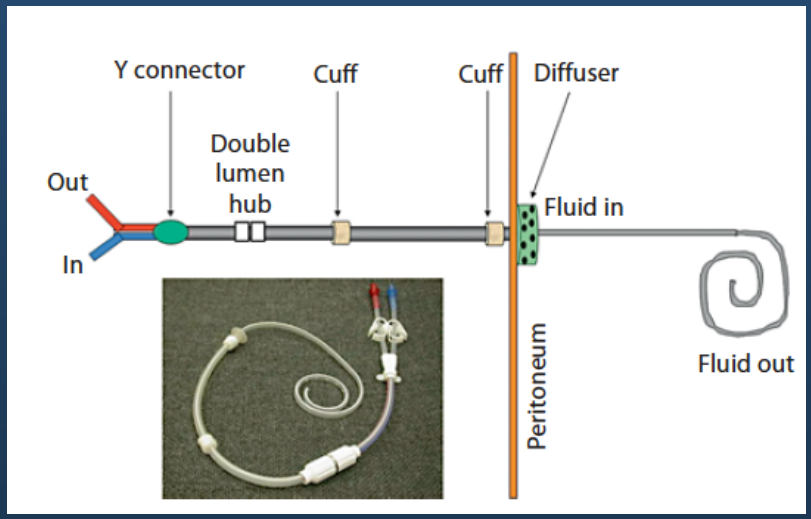
Claudio Ronco[a] Luciano Fecondini[b]

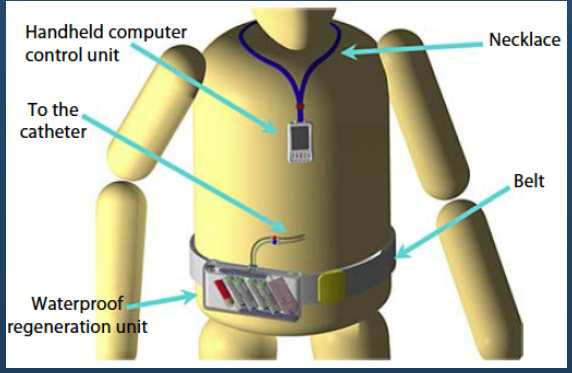
In vitro test and design/miniaturization

Spent dialysate filtered through a small polysulphone filter (to remove fibrin) and then circulated through 4 cartridges containing activated charcoal (removes creatinine) and polystyrenic resins (remove middle-molecules)



	Baseline	4 h	10 h
Creatinine	98.13 ± 1.21	94.20 ± 3.13	90.10 ± 2.59
β_2-MG	97.88 ± 1.11	99.00 ± 2.88	92.00 ± 2.59
Angiogenin	98.31 ± 1.00	93.88 ± 2.76	90.35 ± 2.20





C Ronco et al, "The Vicenza wearable artificial kidney for peritoneal dialysis (ViWAK PD)". Blood Purif 2007;25(4):383-8

WAK for PD

Proposed treatment schedule:
peritoneum filled in the morning with 2 l of fresh PD solution, after 2 h (50% plasma/dialysate equilibration) recirculation is activated for 10 h at 20 ml/min. Glucose may be added to achieve UF if needed through a line connected to a small reservoir. Icodextrin exchange overnight for further UF.

Considering an in vitro net clearance of 11,2 l/day for creatinine (and adding 4-5 l clearance for overnight exchange and equilibration) → weekly clearance > 100 l

C Ronco et al, "The Vicenza wearable artificial kidney for peritoneal dialysis (ViWAK PD)". Blood Purif 2007;25(4):383-8

WAK for PD

A peritoneal-based automated wearable artificial kidney

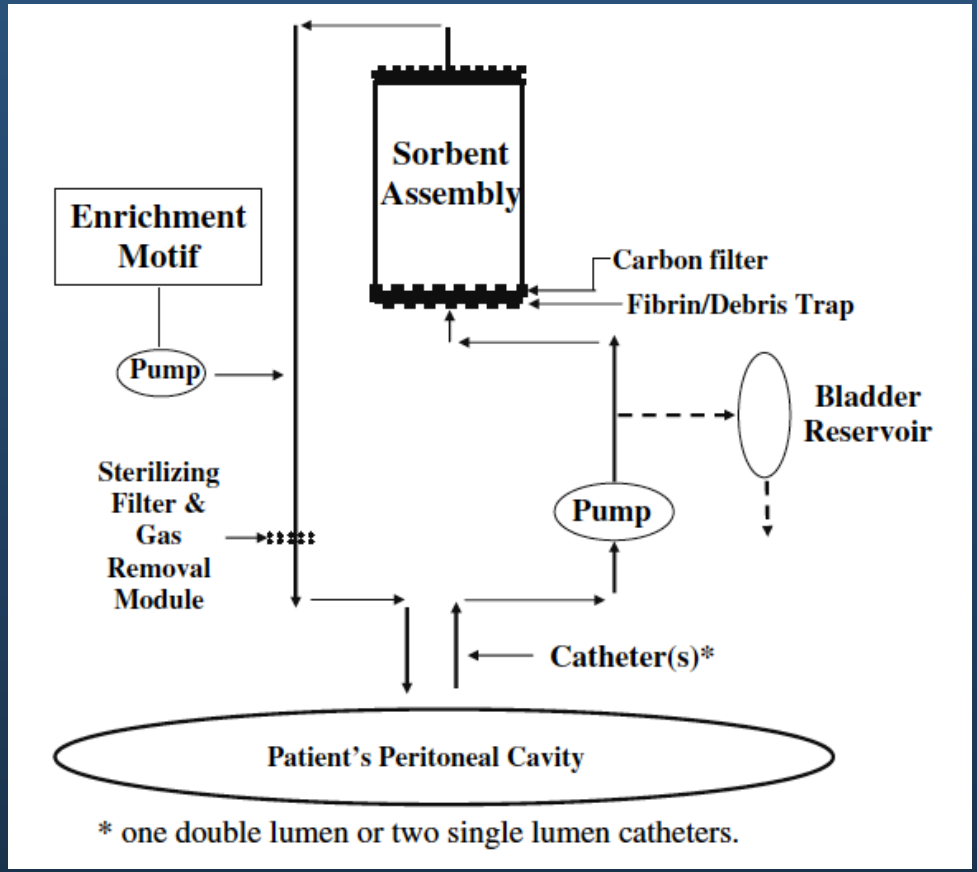
David B. N. Lee · Martin Roberts

AWAK

Clin Exp Nephrol (2008) 12:171–180
DOI 10.1007/s10157-008-0050-9

Double catheter or single-catether tidal PD

Fibrin-debris trap



Lee et al, "A peritoneal-based automated wearable artificial kidney". Clin Exp Nephrol. 2008 Jun;12(3):171-80

WAK for PD

Regeneration of proteins in spent dialysate
→ autologous protein containing dialysate, reducing risk of protein loss and enhancing protein-bound toxins (aluminium, drugs as salicylate) clearance, and glucose sparing effect for UF

Expected flow rate 96 l/day (8-12 fold increase over the current dialysate use of 8-12 l per 24h)

The sorbent cartridge needs to be replaced every 4-8 hours!!

Lee et al, "A peritoneal-based automated wearable artificial kidney". Clin Exp Nephrol. 2008 Jun;12(3):171-80

The smallest "portable" HD device

NxSTAGE® Invent. Improve. Inspire.

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The System One

Chronic therapy at home or on the road

The NxStage System One helps makes home therapy more accessible. It is the only truly portable hemodialysis system cleared for home use during the day or overnight. The System One was designed to provide simplicity, flexibility and portability to make home hemodialysis a practical reality, without compromising safety.

Due to NxStage's continuous innovation, patients now have the opportunity to enjoy the clinical and lifestyle benefits of more frequent home hemodialysis.

The System One Difference

Making Dialysis Accessible
The simple interface is easy to learn and use.

Our 24/7 technical support gives you peace of mind while dialyzing, no matter when or where.

Designed for the Home
Simple plumbing connections and standard electrical plug minimize the impact on your home.

Integrated dialysate mixing conserves water usage and fits your lifestyle.

THE NxStage System One

Specifications at a glance

Therapy Options
Hemodialysis with or without ultrafiltration

Flow Rates
Blood: Up to 600 mL/min
Fluid Exchange: Up to 18 L/hr
Fluid Removal: Up to 2.4 L/hr

System One Cycler Size
Dimensions: (in) 15 x 15 x 18
Weight: About 75 pounds

For nocturnal specific therapy please see our required and recommended ancillary devices.

PureFlow SL Size

Current Market Situation

Acquisitions

www.prnewswire.com/news-releases/renal-solutions-inc-announces-acquisition-by-fresenius-medical-care-59896662.html

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Renal Solutions, Inc. Announces Acquisition by Fresenius Medical Care

Nov 29, 2007, 00:00 ET from Renal Solutions, Inc.

Xcorporeal Announces Signing Agreement for the Sale of Substantially All of Its Assets

December 18, 2009 04:30 PM Eastern Standard Time

LOS ANGELES--(BUSINESS WIRE)--Xcorporeal, Inc. (Pink Sheets:XCRP) (the "Company" or "Xcorporeal") announced today that on December 14, 2009 it signed an asset purchase agreement (the "Purchase Agreement") with National Quality Care, Inc. ("NQCI", and together with the Company, the "Sellers"), and Fresenius USA, Inc. (the "Purchaser"), a Massachusetts corporation and a wholly owned subsidiary of Fresenius Medical Care Holdings, Inc., to sell substantially all of the assets of the Sellers to the Purchaser for an aggregate cash purchase price of $8,000,000 (the "Purchase Price") and certain additional royalty payment rights. The Purchase Price will be payable to the Sellers in three installments. The Company's board of directors has unanimously approved the Purchase Agreement. The sale represents the conclusion of a process to sell substantially all of the Company's assets. The closing is scheduled to occur on or before February 28, 2010.

In addition, the Purchaser will pay royalties to the Sellers during the life of the patents included in the HD WAK Technology being transferred to the Purchaser, as well as royalties to the Sellers during the life of the patents included in the supersorbent technology being transferred to the Purchaser.

XCORPOREAL, INC.
NQB:XCRP

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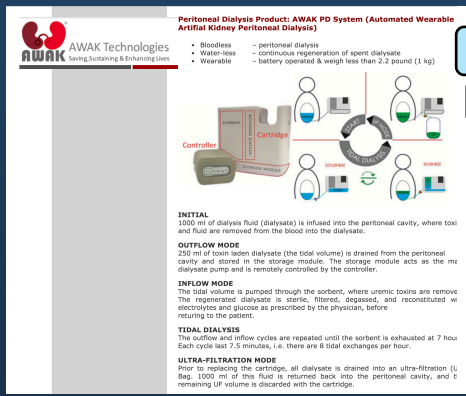
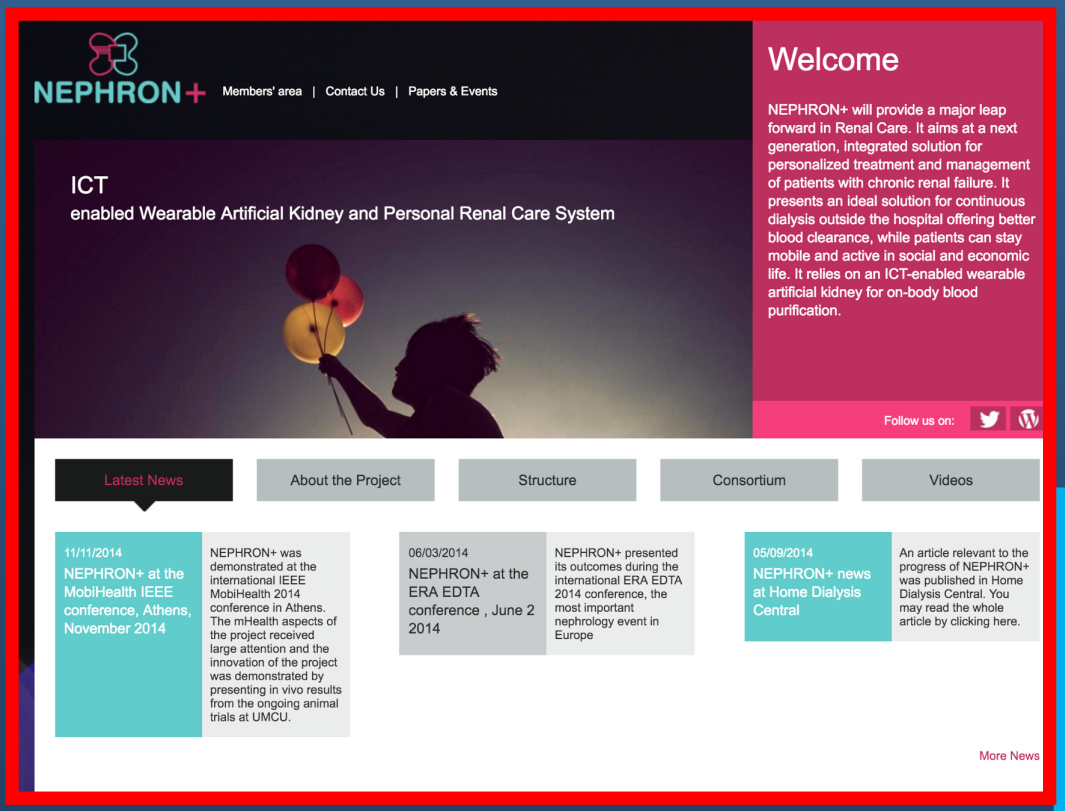


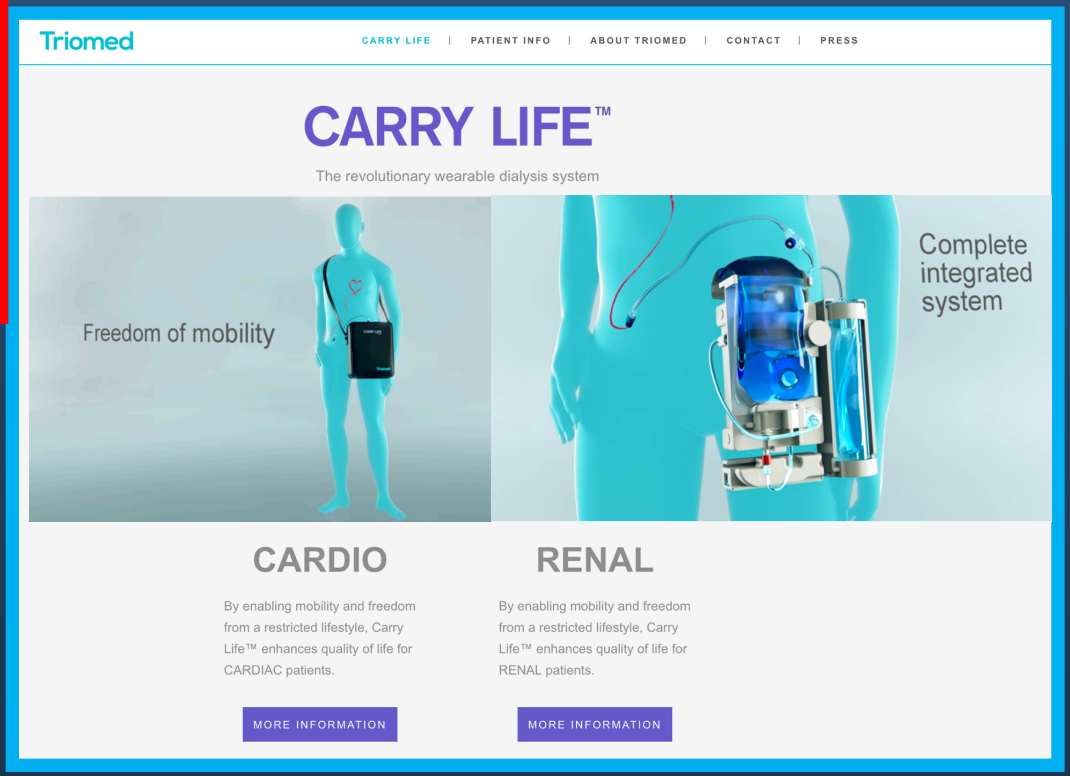
AWAK TECHNOLOGIES ENTERS INTO AN EXCLUSIVE AGREEMENT WITH BAXTER INTERNATIONAL FOR THE DEVELOPMENT OF WEARABLE DIALYSIS TECHNOLOGY

Singapore – 7 Jan, 2013: AWAK Technologies announced today it has entered into an exclusive agreement with Baxter International, Inc. for the development of innovative wearable dialysis technology. The agreement enables AWAK to continue the development of its investigational peritoneal dialysis-based automated wearable artificial kidney.

Current Market Situation

Solutions under development





Regenerability

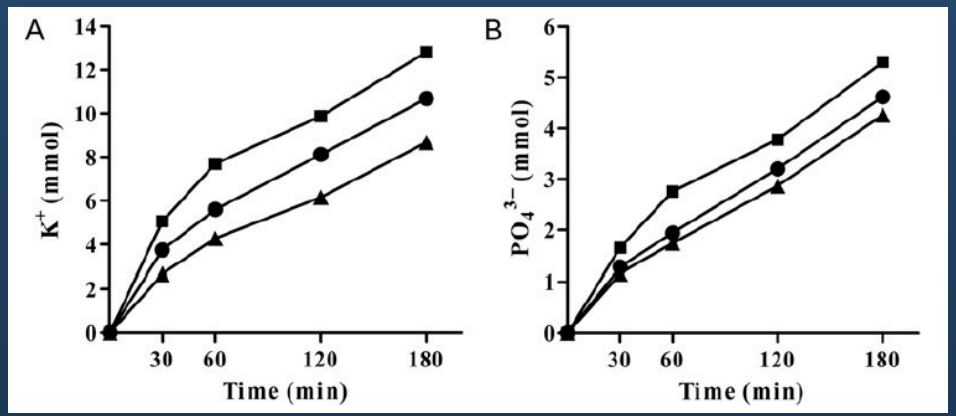
A regenerable potassium and phosphate sorbent system to enhance dialysis efficacy and device portability: an *in vitro* study

Maarten Wester[1], Frank Simonis[2], Karin G. Gerritsen[1], Walther H. Boer[1], Will K. Wodzig[3], Jeroen P. Kooman[4] and Jaap A. Joles[1]

[1]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Nanodialysis BV, Oirschot, The Netherlands, [3]Department of Clinical Chemistry, Maastricht University Medical Center, Maastricht, The Netherlands and [4]Department of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands

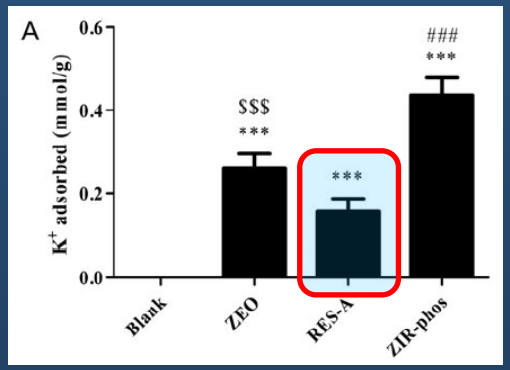
Nephrol Dial Transplant (2013) 28: 2364–2371
doi: 10.1093/ndt/gft205
Advance Access publication 3 July 2013

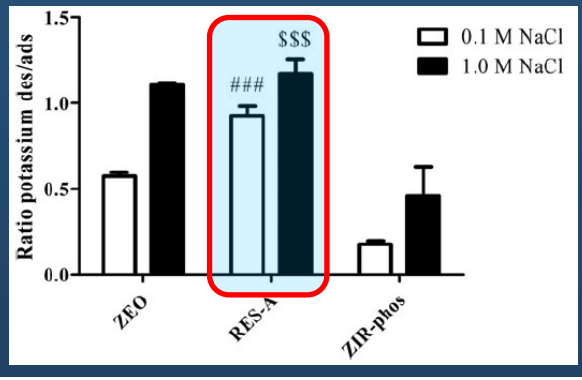
Dynamic tests with sorbent beads [RES-A and FeOOH]

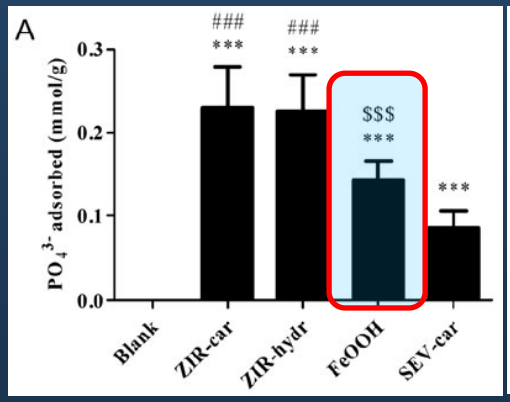


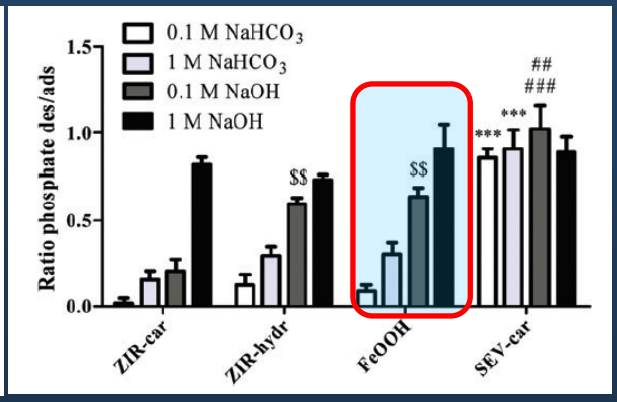
in 3h 10 and 5 mEq of K and PO4 removed

Batch tests and **regenerability**









Wester et al, "A regenerable potassium and phosphate sorbent system to enhance dialysis efficacy and device portability: an in vitro study".Nephrol Dial Transplant 2013(28):2364-2371

Regenerability

All sorbents adsorbed some Ca and Mg → solvent preloading → no need for post- cartridge supplementation

Conclusion:

Adequate potassium and phosphate adsorption from dialysate can be achieved by the use of **modest amounts of RES-A and FeOOH**. RES-A shows excellent and FeOOH acceptable regenerability under mild conditions. Use of ZIR-car and ZIR-hydr may further increase phosphate adsorption but may compromise sorbent regenerability. Use of polymeric amines for phosphate adsorption may enhance sorbent regenerability.

Wester et al, "A regenerable potassium and phosphate sorbent system to enhance dialysis efficacy and device portability: an in vitro study".Nephrol Dial Transplant 2013(28):2364-2371

Urea removal

Hydrolysis of urea by urease (REDY)
large amount of cation exchange material
(Zirconium Phosphate) to remove NH_4^+
NH_4^+ is partly exchanged for Na^+ with consequent
Na^+ release

Removal of Urea in a Wearable Dialysis Device: A Reappraisal of Electro-Oxidation

Artificial Organs 2014, 38(12):998–1006

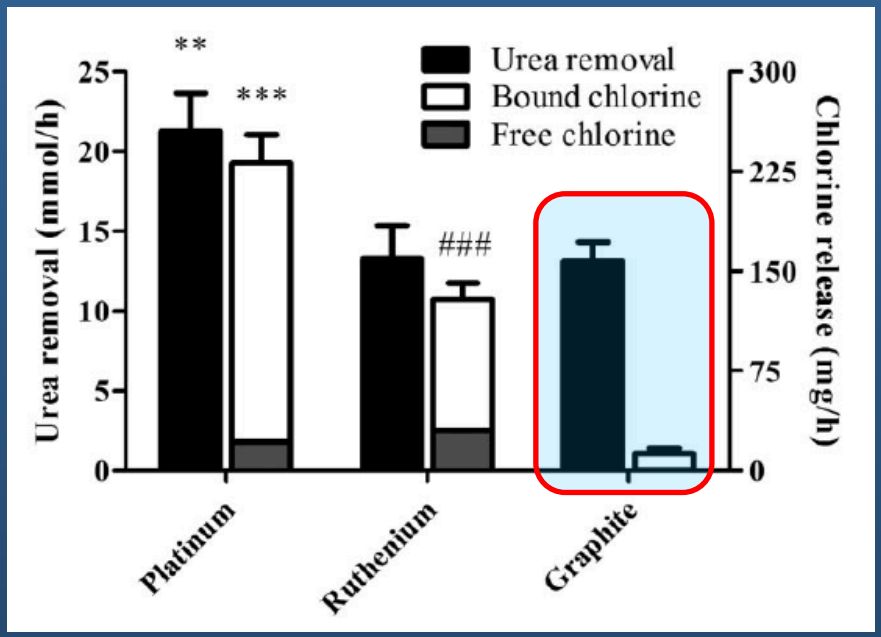
*Maarten Wester, †Frank Simonis, *‡Nadia Lachkar, §Will K. Wodzig, **Frank J. Meuwissen, ††Jeroen P. Kooman, *Walther H. Boer, *Jaap A. Joles, and *Karin G. Gerritsen

*Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht; †Nanodialysis BV, Oirschot; ‡MIRA, Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede; and Departments of §Clinical Chemistry, **Medical Instrumental Services, and ††Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands

can be miniaturized, needs no regeneration, is inexpensive.

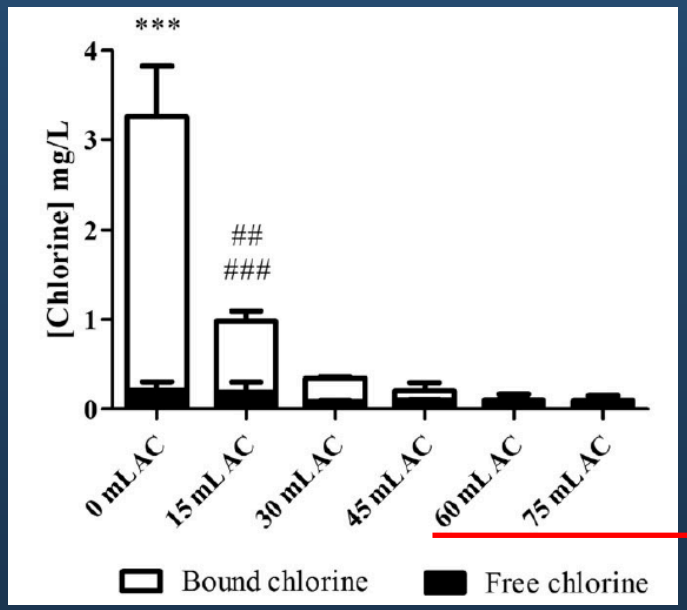
Wester et al, "Removal of urea in a wearable dialysis device: a reappraisal of electro-oxidation", Artificial Organs 2014, 38(12):998-1006

Urea removal



Graphite electrodes: less chlorine release

Higher current led to higher urea removal, but higher chlorine release

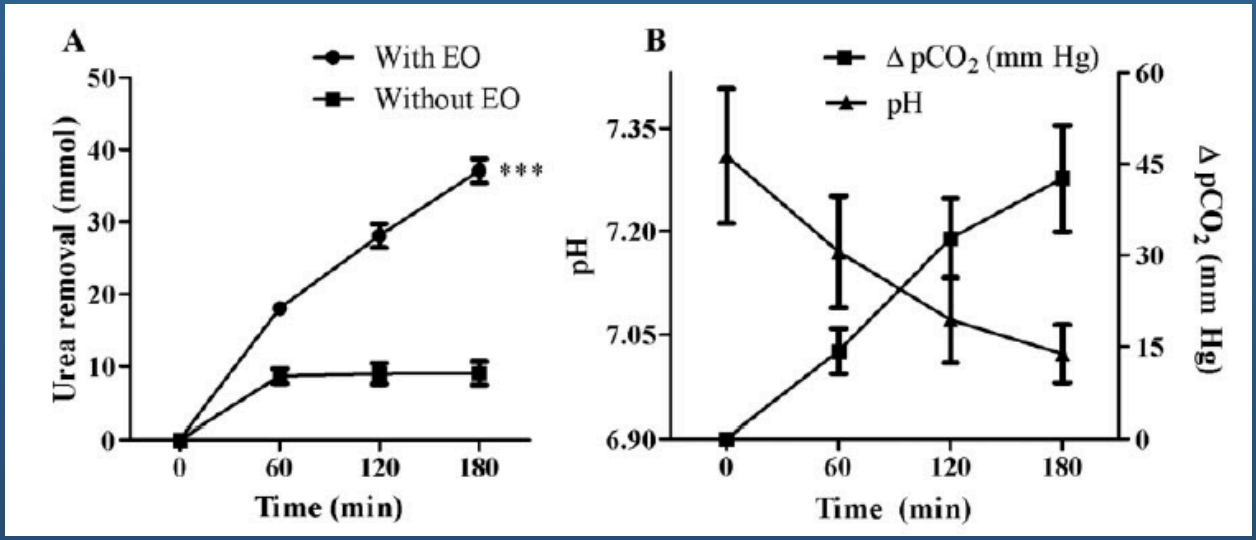


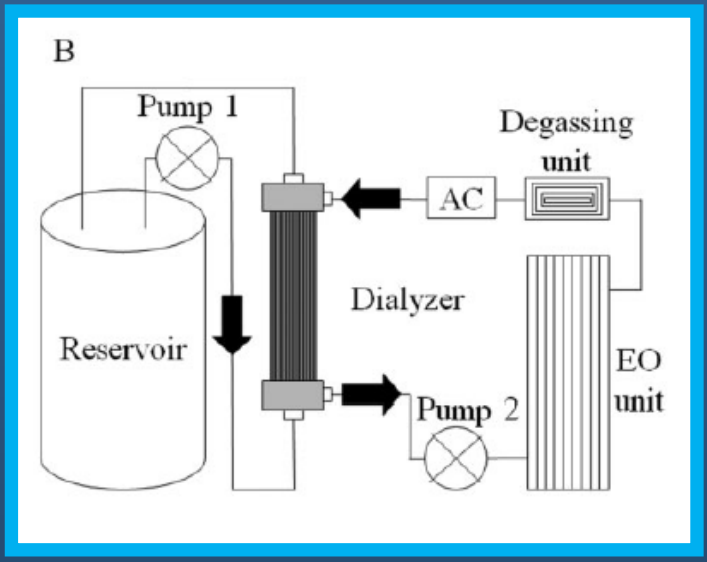
Removal of chlorine with activated carbon downstream

60 ml (30 g) of AC resulted in chlorine levels below recommended limits with inlet urea concentratio 20 mM (56 mg/dl)

Wester et al, "Removal of urea in a wearable dialysis device: a reappraisal of electro-oxidation", Artificial Organs 2014, 38(12):998-1006

Urea removal





CO2 (400 mmol daily) and N2 generation → **degassing system** should be included

Potential disadvantage of EO: generation of large quantities of oxidative by-products that could negative affect REDOX state (→ however downstream AC oxigen reduction potential was low)

Can EO be safely applied in vivo??

Wester et al, "Removal of urea in a wearable dialysis device: a reappraisal of electro-oxidation", Artificial Organs 2014, 38(12):998-1006

Nanomaterials

Nanoporous biomaterials for uremic toxin adsorption in artificial kidney systems: A review

Wee-Keat Cheah,[1] Kunio Ishikawa,[2] Radzali Othman,[1,3] Fei-Yee Yeoh[1]

[1]School of Materials and Mineral Resources Engineering, Universiti Sains Malaysia Engineering Campus, 14300 Nibong Tebal, Penang, Malaysia

[2]Department of Biomaterials, Kyushu University, Fukuoka, Nishi Ward, Japan

[3]Faculty of Manufacturing Engineering, Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100n, Durian Tunggal, Malacca, Malaysia

Considering scarce urea adsorption with activated charcoal (REDY and others) there is plenty of room for improvement in terms of nanoporous materials for adsorption

Zeolite → high capacity of removing uremic toxins, but tend dissolve partially in the dialysate fluid (amphoteric nature).

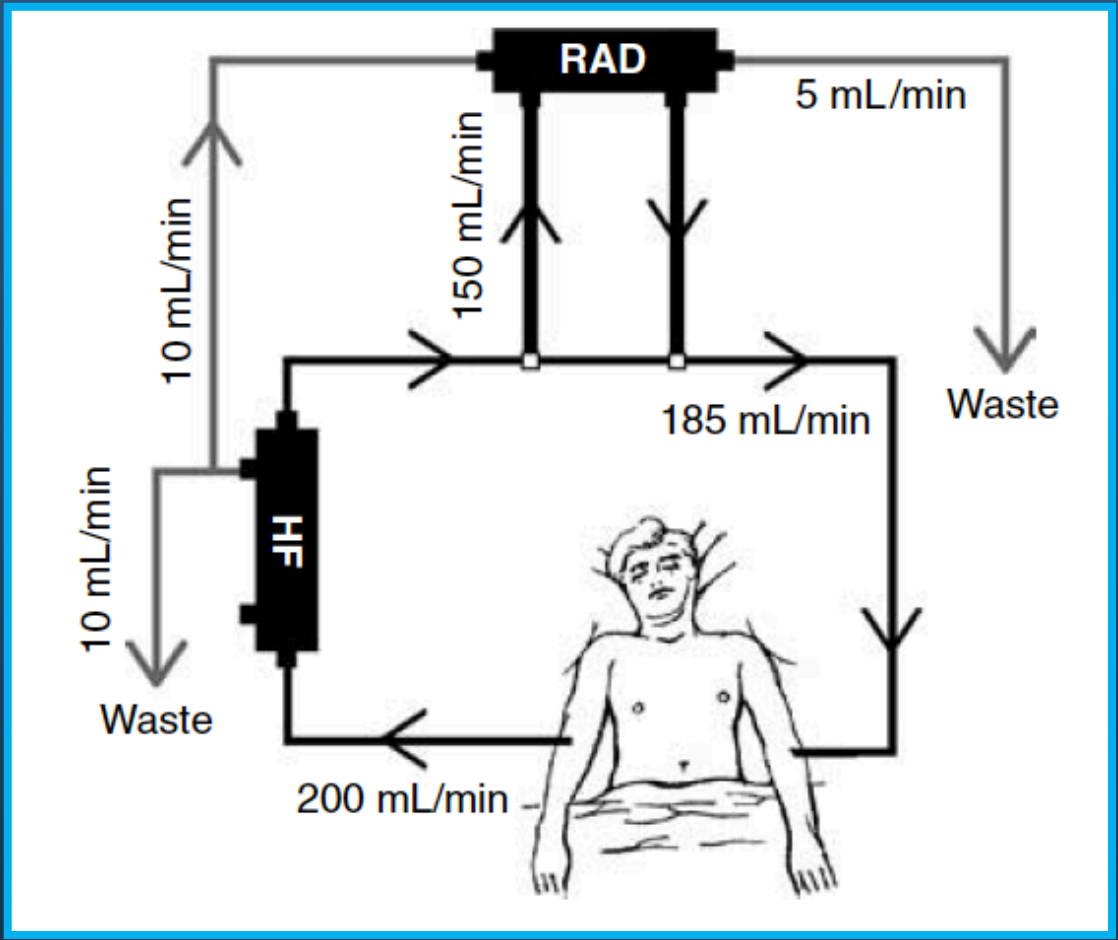
Chean et al, "Nanoporous biomaterials for uremic toxin adsorption in artificial kidney systems: a review". J Biomed Mater Res B Appl Biomater 2016 feb 23. Epub ahead of print

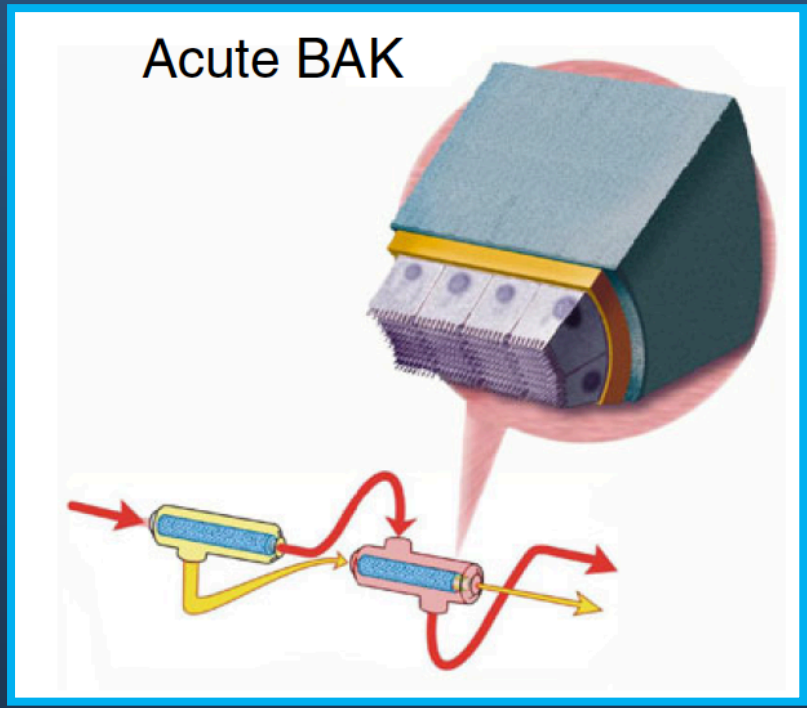
Wearable to implantable

Renal Tubule Assist Device

Cell theraphy?

RAD: a combination of livin tubular cells supported on polymeric substrata acting as a scaffold for the cells





Renal Tubule Assist Device

Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure

H. David Humes, William F. Weitzel, Robert H. Bartlett, Fresca C. Swaniker, Emil P. Paganini, Jack R. Luderer, and Joseph Sobota

Kidney International, Vol. 66 (2004), pp. 1578–1588

58 patients receiving CVVH for ARF and multiple organ failure → 40 received RAD therapy

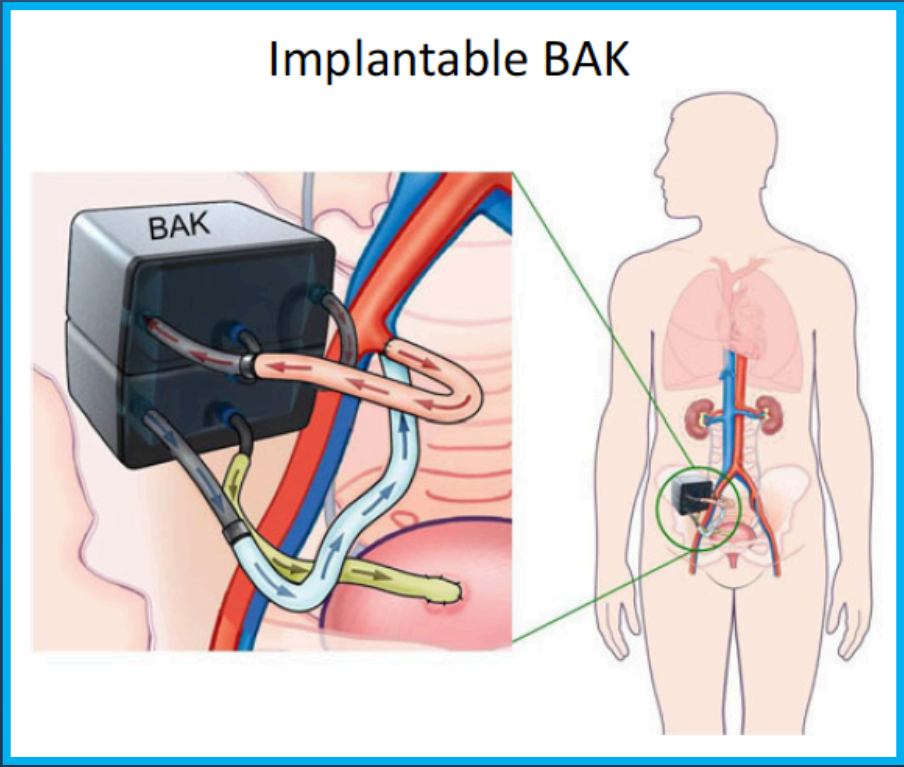
Renal cell therapy improved the 28-day mortality rate from 61% (control group only CVVH) to 34% (RAD + CVVH group)

Renal Tubule Assist Device

Bioartificial kidney (BAK)

=

conventional synthetic hemofilter + **RAD**



Problems with implantable BAK:

- Pump size must be reduced
- Dialytic water volume
- biocompatibility of silicon membranes
- Necessity for long-term anticoagulation
- Vascular perfusion of the BAK

Humes et al, "the bioartificial kidney: current status and future promise", Pediatr Nephrol (2014) 29:343-351

Human Nephron Filter

HNF: application of atomically precise nanotechnology to RRT

Two membranes operating in series simulating glomerular and tubular function

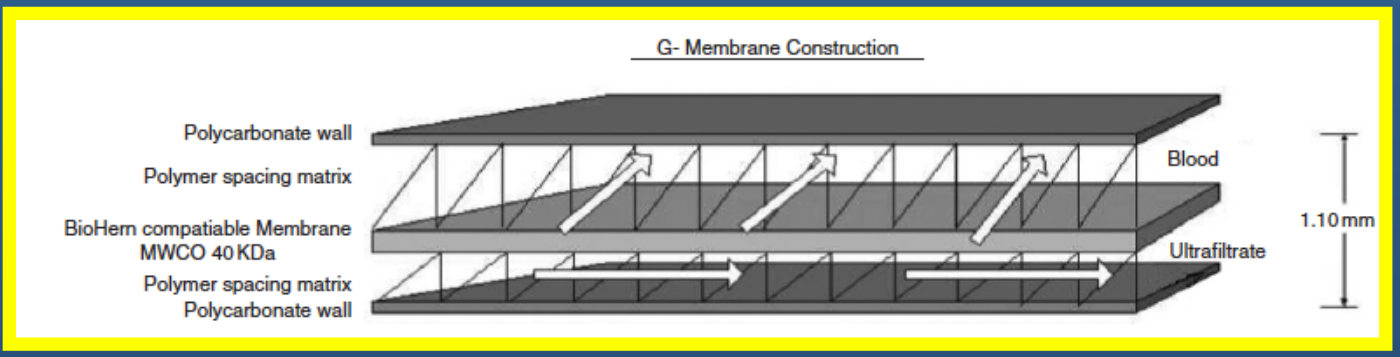
NO dialysate, operates all by CONVECTION

Could provide 30 ml/min of GFR operating 12 hours per day (**computer modeling**)

Nissenson et al, Continuously functioning artificial nephron system: the promise of nanotechnology, Hemodialysis international 2005; 9:210-217

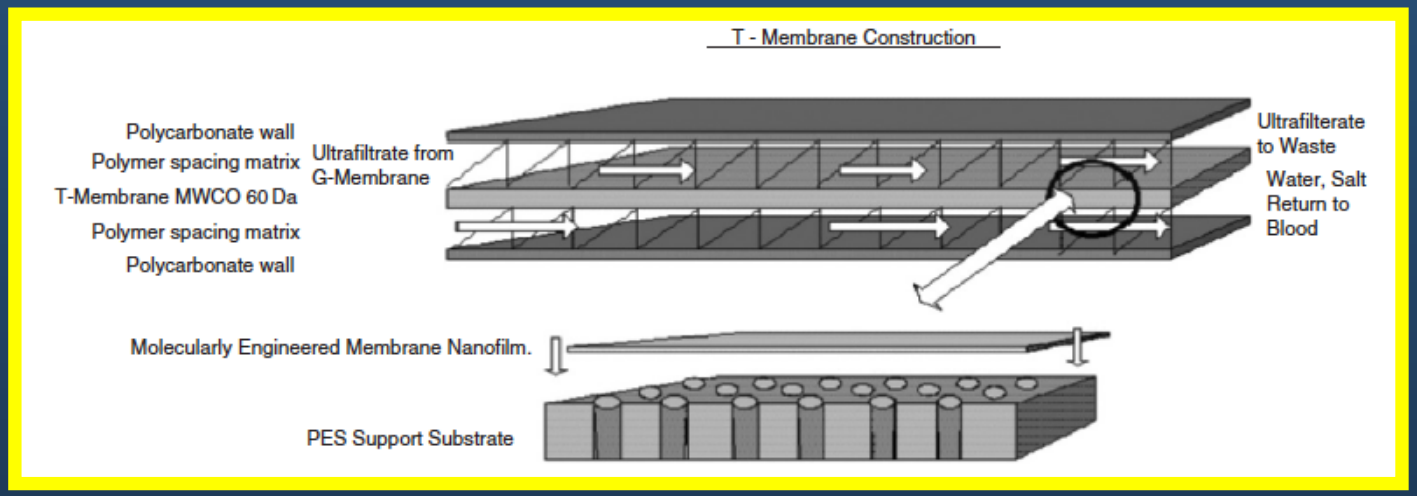
Wearable to implantable

Human Nephron Filter



G membrane: mimics glomerulus using convective transport to generate a plasma UF

T membrane: mimics renal tubule selectively reclaiming solutes by convection



Nissenson et al, Continuously functioning artificial nephron system: the promise of nanotechnology, Hemodialysis international 2005; 9:210-217

Conclusions

Vascular access is a big issue

may PD be the solution?

Urgent need for **LONG-TERM information**:

- Assess long-term biocompatibility of devices
- Human clinical trials to evaluate efficacy in comparison to standard treatments

Will the WAK improve outcomes in ESRD?

Can the WAK be worn by humans over prolonged and continuous periods of time?