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**Валерий Шило**
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**Кафедра нефрологии ФПДО МГМСУ им. Евдокимова**

6 декабря 2015

Скандинавия, Сестрорецк

B BRAUN
SHARING EXPERTISE

# Результаты наиболее значимых клинических исследований

ORIGINAL ARTICLE

# Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

## ABSTRACT

### BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

### METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

### RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The

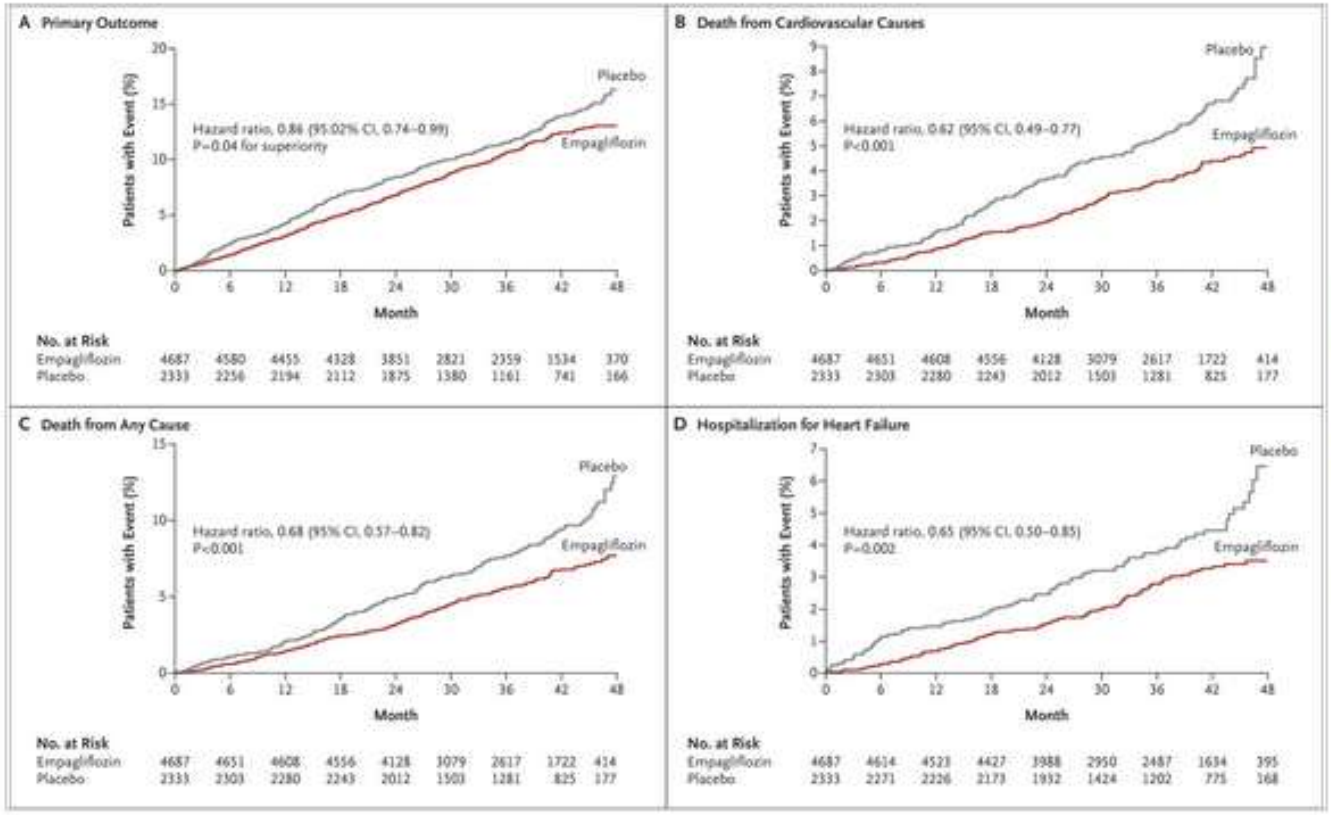



**Figure 1. Cardiovascular Outcomes and Death from Any Cause.**

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

**Table 2. Adverse Events.***

| Event | Placebo (N=2333) | Empagliflozin, 10 mg (N=2345) | Empagliflozin, 25 mg (N=2342) | Pooled Empagliflozin (N=4687) |
|---|---|---|---|---|
| | *number of patients (percent)* | | | |
| Any adverse event | 2139 (91.7) | 2112 (90.1) | 2118 (90.4) | 4230 (90.2)† |
| Severe adverse event | 592 (25.4) | 536 (22.9) | 564 (24.1) | 1100 (23.5)‡ |
| Serious adverse event | | | | |
| Any | 988 (42.3) | 876 (37.4) | 913 (39.0) | 1789 (38.2)† |
| Death | 119 (5.1) | 97 (4.1) | 79 (3.4) | 176 (3.8)§ |
| Adverse event leading to discontinuation of a study drug | 453 (19.4) | 416 (17.7) | 397 (17.0) | 813 (17.3)§ |
| Confirmed hypoglycemic adverse event¶ | | | | |
| Any | 650 (27.9) | 656 (28.0) | 647 (27.6) | 1303 (27.8) |
| Requiring assistance | 36 (1.5) | 33 (1.4) | 30 (1.3) | 63 (1.3) |
| Event consistent with urinary tract infection‖ | 423 (18.1) | 426 (18.2) | 416 (17.8) | 842 (18.0) |
| Male patients | 158 (9.4) | 180 (10.9) | 170 (10.1) | 350 (10.5) |
| Female patients | 265 (40.6) | 246 (35.5) | 246 (37.3) | 492 (36.4)‡ |
| Complicated urinary tract infection** | 41 (1.8) | 34 (1.4) | 48 (2.0) | 82 (1.7) |
| Event consistent with genital infection†† | 42 (1.8) | 153 (6.5) | 148 (6.3) | 301 (6.4)† |
| Male patients | 25 (1.5) | 89 (5.4) | 77 (4.6) | 166 (5.0)† |
| Female patients | 17 (2.6) | 64 (9.2) | 71 (10.8) | 135 (10.0)† |
| Event consistent with volume depletion‡‡ | 115 (4.9) | 115 (4.9) | 124 (5.3) | 239 (5.1) |
| Acute renal failure§§ | 155 (6.6) | 121 (5.2) | 125 (5.3) | 246 (5.2)§ |
| Acute kidney injury | 37 (1.6) | 26 (1.1) | 19 (0.8) | 45 (1.0)‡ |
| Diabetic ketoacidosis¶¶ | 1 (<0.1) | 3 (0.1) | 1 (<0.1) | 4 (0.1) |
| Thromboembolic event§§ | 20 (0.9) | 9 (0.4) | 21 (0.9) | 30 (0.6) |
| Bone fracture‖‖ | 91 (3.9) | 92 (3.9) | 87 (3.7) | 179 (3.8) |

* Data are for patients who had one or more event and who had received at least one dose of a study drug. All events occurred within 7 days after the last receipt of the study drug.
† P<0.001 for the comparison with placebo.
‡ P<0.05 for the comparison with placebo.
§ P<0.01 for the comparison with placebo.

## RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

## CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

# High Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery

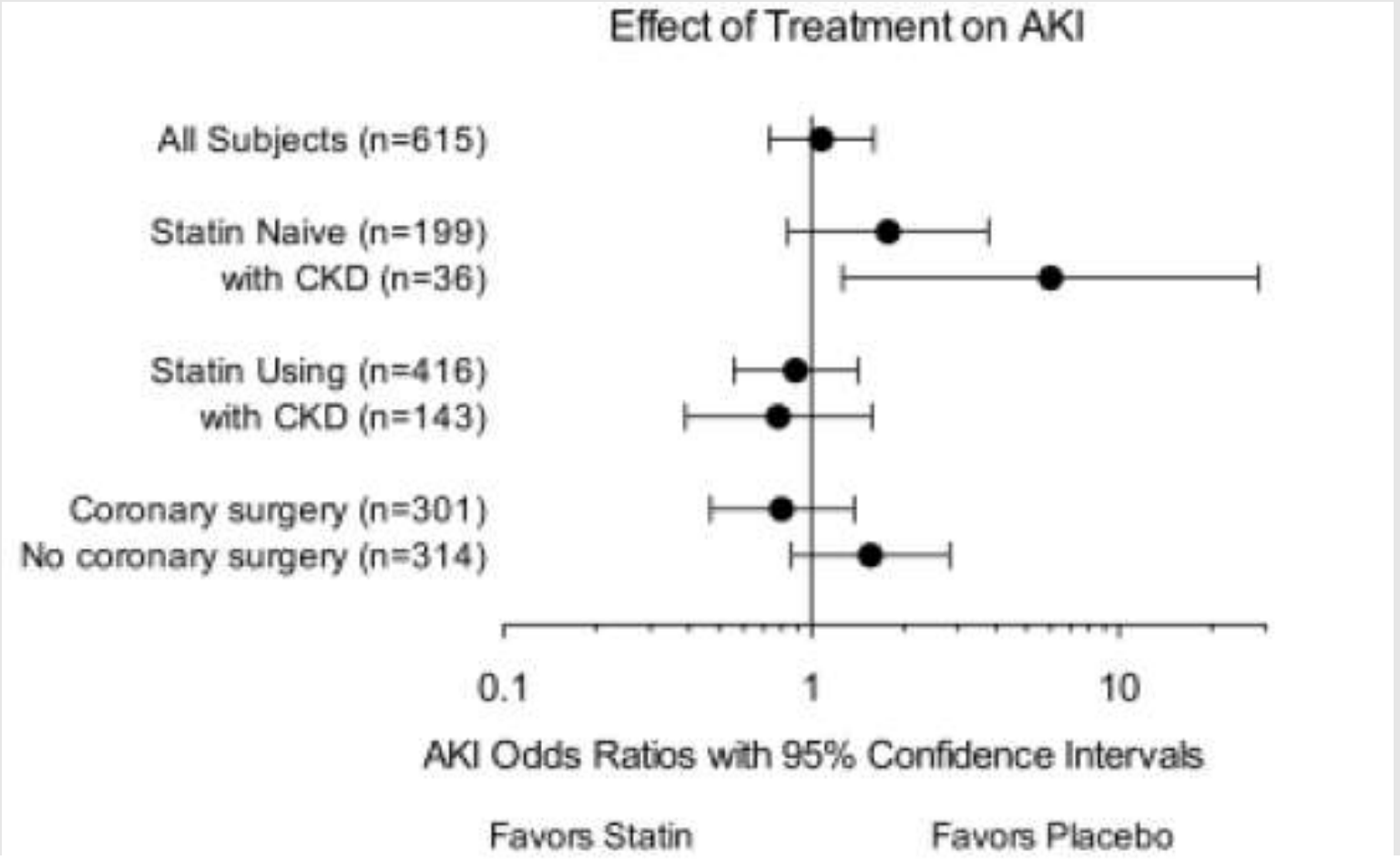
**Frederic Tremaine Billings, Chad E. Wagner, Patty Hendricks,**
Yaping Shi, Michael R. Petracek, Nancy J. Brown. *Vanderbilt Univ, Nashville, TN.*

**Background: Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins)** affect several mechanisms underlying acute kidney injury (AKI), a common and dangerous complication after cardiac surgery. We hypothesized that short-term high-dose perioperative atorvastatin would reduce AKI following cardiac surgery.

**Methods: We randomized elective cardiac surgery patients, stratified by chronic kidney** disease (CKD), to atorvastatin or matching-placebo starting the day prior to surgery until hospital discharge in pre-study statin naïve subjects or until the day after surgery in pre-study statin-using subjects. Our primary endpoint was AKI by AKIN criteria.

**Results: The study was stopped on recommendations of the DSMB after 653 of 820** subjects completed the study due to futility and an increased incidence of AKI among statinnaïve
subjects with CKD randomized to atorvastatin. AKI occurred in 20.8% of subjects randomized to atorvastatin versus 19.5% randomized to placebo (P=0.75). Among statinnaïve subjects (n=199), however, AKI occurred in 21.6 % randomized to atorvastatin versus 13.4% randomized to placebo (p=0.14), and 52.9% vs. 15.8%, P=0.03, in patients with CKD (n=36). Serum creatinine concentrations increased a median of 0.11 (-0.11 – 0.56) versus 0.05 (-0.12 – 0.33) mg/dl in statin-naïve patients randomized to atorvastatin versus placebo (P=0.007), and this effect was magnified among those with CKD, whereserum creatinine concentrations increased by 0.26 (-0.22 – 0.94) versus -0.06 mg/dl (-0.16 – 0.41), P=0.04.

**Conclusions:** High-dose perioperative atorvastatin treatment does not reduce AKI following cardiac surgery and may increase risk in patients with CKD who are naïve to statin treatment. Perioperative continuation or short-term withdrawal of statin treatment in statin-using patients does not affect AKI.



## HI-OR03

# Effect of Methylprednisolone on Acute Kidney Injury in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Amit X. Garg,[1] Richard P. Whitlock.[2] *[1]Western Univ, London, Canada; [2]McMaster Univ, Hamilton, Canada and the Population Health Research Inst; for the SIRS Investigators.*

**Background:** Acute kidney injury is a common complication of the 20 million cardiac surgeries performed worldwide each year. We conducted a substudy of the Steroids In caRdiac Surgery (SIRS) trial to determine whether methylprednisolone alters the risk of acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass [substudy protocol BMJ Open 2014 Mar 5;4(3): e004842].

**Methods:** This was a randomized clinical trial of 7,286 high-risk patients undergoing cardiac surgery with cardiopulmonary bypass from 79 centres in 18 countries between June 2007 and December 2013. Patients were assigned to take intravenous methylprednisolone (250 mg at anesthetic induction and 250 mg at initiation of cardiopulmonary bypass) or placebo. Patients, care givers and outcome-assessors were blinded to allocation. Acute kidney injury was defined as ≥50% or ≥ 26.5 mmol/L (≥ 0.3 mg/dL) increase in the postoperative serum creatinine concentration from the preoperative concentration in the 14 days following surgery, or new dialysis in the 30 days following surgery.

**Results:** Methylprednisolone (n=3,647) versus placebo (n=3,639) did not alter the risk of acute kidney injury (40.9% versus 39.5%, respectively; relative risk 1.03 [95% CI, 0.96 to 1.11]). Results were consistent with multiple alternate continuous and categorical definitions of acute kidney injury, and in the subgroup with baseline chronic kidney disease.

**Conclusions:** Amongst patients undergoing cardiac surgery with cardiopulmonary bypass, the use of corticosteroids in the perioperative period did not alter the risk of acute kidney injury. Trial Registration: NCT00427388

| | Number of Events (%) | | Relative Risk (95% CI) |
|---|---|---|---|
| | Methylprednisolone n = 3647 | Placebo n = 3639 | |
| AKI | 1490 (40.9%) | 1439 (39.5%) | 1.03 (0.96 to 1.11) |
| Alternative Definitions | | | |
| AKI or death | 1513 (41.5%) | 1463 (40.2%) | 1.03 (0.96 to 1.11) |
| ≥ stage 2 AKI | 362 (9.9%) | 359 (9.9%) | 1.01 (0.87 to 1.16) |
| ≥ stage 3 AKI | 145 (4.0%) | 162 (4.5%) | 0.89 (0.71 to 1.12) |
| Acute dialysis | 95 (2.6%) | 88 (2.4%) | 1.08 (0.81 to 1.43) |

# The NEFIGAN Trial: NEFECON, a Novel Targeted Release Formulation of Budesonide, Reduces Proteinuria and Stabilizes eGFR in IgA Nephropathy Patients at Risk of ESRD

Bengt C. Fellstrom,[1] Rosanna Coppo,[2] John Feehally,[3] Jürgen Floege,[4] Johan W. De Fijter,[5] Alan G. Jardine,[6] Francesco Locatelli,[7] Bart D. Maes,[8] Alex Mercer,[9] Fernanda Ortiz,[10] Manuel Praga,[11] Søren Schwartz Sørensen,[12] Vladimir Tesar.[13] *[1]Uppsala Univ Hospital; [2]Univ Turin; [3]Univ Leicester; [4]RWTH Univ Aachen; [5]Leiden Univ Medical Center; [6]Univ Glasgow; [7]Ospedale A Manzoni, Lecco; [8]AZ Delta Roeselare; [9]Pharmalink; [10]Helsinki Univ Hospital; [11]Hospital 12 de Octubre, Madrid; [12]Rigshospitalet, Copenhagen; [13]Charles Univ, Prague.*

**Background:** IgA nephropathy (IgAN) is the most prevalent primary chronic glomerular disease. Despite RAS blockade, >25% of patients progress to ESRD within 20 years. This study evaluated a novel budesonide formulation (NEFECON) targeted for release in the distal ileum, where Peyer's patches reside, in patients at risk of ESRD despite optimized RAS blockade.

**Methods:** Double-blind, placebo-controlled study in 150 patients (62 sites, 10 EU countries) with primary IgAN, proteinuria (UPCR ³0.5 g/g OR urine protein ³0.75 g/d) and eGFR CKD-EPI ≥45 mL/min/1.73m² randomized to 8 or 16 mg/d NEFECON or placebo (1:1:1), after 6 mo run-in phase to optimize RAS blockade. Primary endpoint: reduction in UPCR at 9 mo of treatment; secondary: mean percentage change in eGFR.

**Results:** Baseline data were similar across groups; BP was 127-128/78-80 mmHg, UPCR 0.76–0.83 g/g, and eGFR 72-85 mL/min/1.73m². Primary endpoint was met at the pre-specified interim analysis. Mean UPCR decreased by 24% (NEFECON 8+16 mg/d) vs 3% increase (placebo) at 9 mo (p=0.007); reduction in the 16 mg/d group was 27% (p=0.009). At final analysis, mean change in eGFR was -4.7 mL/min/1.73m² for placebo compared with 0.32 and 1.95 mL/min/1.73m² for NEFECON 8 and 16 mg/d, respectively; difference in mean percentage change in eGFR achieved statistical significance for 8 mg/d (p=0.006) and 16 mg/d (p=0.003). Adverse event rates were higher in NEFECON groups (88–94%) than placebo (84%). Two serious adverse events were assessed as possibly related to NEFECON; deteriorated renal function (in follow-up) and deep vein thrombosis.

**Conclusions:** NEFECON reduced UPCR and maintained eGFR in patients with primary IgAN at risk of progression to ESRD despite optimized RAS blockade. Treatment was generally well-tolerated.

# Prevention of Bone Mineral Density Loss in De Novo Kidney Transplant Recipients with Twice-Yearly Denosumab: A Randomized Controlled Trial (ClinicalTrials.gov number NCT01377467)

Rudolf P. Wuthrich,[1] Diana P. Frey,[2] Jens Gunther Brockmann,[3] Thomas Fehr,[1] Thomas F. Mueller,[1] Lanja Saleh,[4] Arnold Von Eckardstein,[4] Nicole Graf,[5] Marco Bonani.[1] *[1]Div of Nephrology; [2]Div of Rheumatology; [3]Div of Visceral and Transplantation Surgery; [4]Inst of Clinical Chemistry, Univ Hospital, Zurich, Switzerland; [5]Graf Biostatistics, Winterthur, Switzerland.*

**Background:** Kidney transplantation is associated with bone loss and an increased risk of fracture. Since current therapeutic options to prevent bone loss are limited we assessed the efficacy and safety of Receptor Activator of Nuclear Factor κB Ligand (RANKL) inhibition with denosumab to improve bone mineralization in the first year after kidney transplantation.

**Methods:** We enrolled 108 kidney transplant recipients and randomized 90 patients two weeks after surgery in a 1:1 ratio to receive denosumab (subcutaneous injections of 60 mg denosumab at baseline and after 6 months) or no treatment. The primary endpoint was the percentage change in bone mineral density (BMD) measured by DXA at the lumbar spine at 12 months.

**Results:** After 12 months, the primary outcome of total lumbar spine BMD increased by 4.6% (95% CI 3.3-5.9%) in 46 patients in the denosumab group and decreased by -0.5% (95% CI -1.8-0.9%) in 44 patients in the control group (between-group difference 5.1%, 95% CI 3.1-7.0%, $p<0.0001$). Denosumab also significantly increased BMD at the total hip by 1.9% (95% CI, 0.1 to 3.7%; $p=0.035$) over that in the control group at 12 months. HR-pQCT in a subgroup of 24 patients showed that denosumab also significantly increased BMD and cortical thickness at the distal tibia and radius ($p<0.05$). Biomarkers of bone resorption (β-CTX, urine deoxypyridinoline) and bone formation (P1NP, BSAP) markedly decreased with denosumab ($p<0.0001$). Episodes of cystitis and asymptomatic hypocalcemia occurred more often with denosumab, whereas graft function, rate of rejections and incidence of opportunistic infections were similar.

**Conclusions:** Antagonizing RANKL with denosumab effectively increased BMD in *de novo* kidney transplant recipients, but was associated with more frequent episodes of urinary tract infection and decreased calcemia.

# Adverse events

| | Control (N=44) | Denosumab (N=46) |
|---|---|---|
| Urinary tract infection | 25 (9.2%) | 51 (14.6%) |
| Diarrhea | 14 (5.1%) | 32 (9.2%)* |
| Cough | 19 (7.0%) | 9 (2.6%) |
| Leg pain | 12 (4.4%) | 14 (4.0%) |
| Flu-like disease | 14 (5.1%) | 12 (3.4%) |
| Transient hypocalcemia | 1 (0.3%) | 12 (3.4%)** |
| Abdominal pain | 10 (3.7%) | 10 (2.9%) |

# Randomized, Double-Blind, Placebo-Controlled, Parallel, 3-Arm Study of Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Hemodialysis Patients with Uremic Pruritus

Vandana S. Mathur,[1] Jayant Kumar,[5] Paul W. Crawford,[3] Howard Hait,[4] Thomas Sciascia.[2]
*[1]MathurConsulting; [2]Trevi Therapeutics; [3]Research by Design; [4]Edenridge Consulting; [5]Renal Medical Associates.*

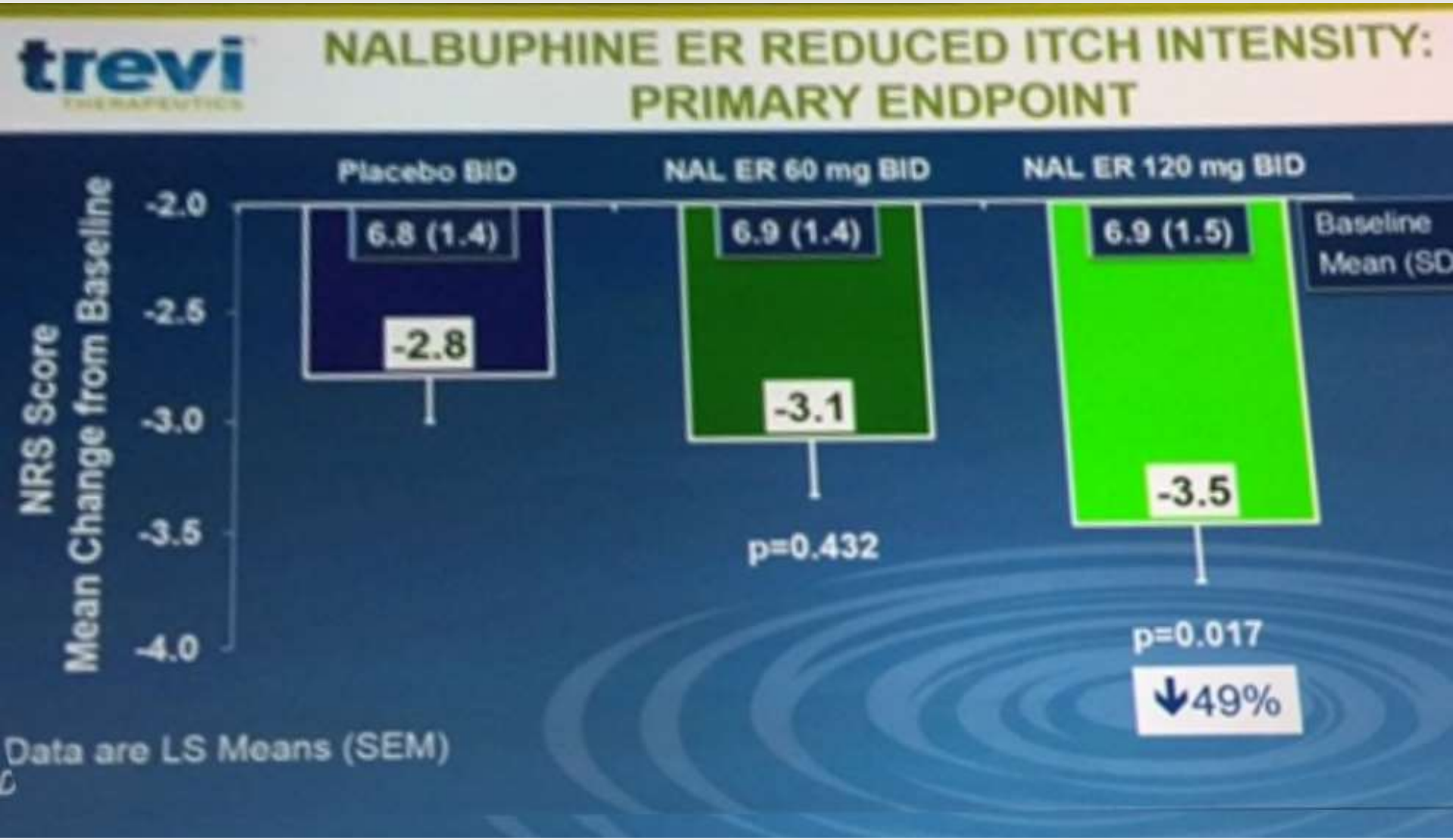
**Background:** Uremic pruritus (UP) is associated with decrements in quality of life and sleep and higher mortality. UP pathogenesis may involve endogenous κ/μ opioid ligand ratio imbalance. Nalbuphine ER tablets (NAL) are a κ-opioid agonist/μ-opioid antagonist being developed for chronic pruritic conditions.

**Methods:** 373 hemodialysis patients (HDP) with mean baseline numerical rating scale score (NRS) ≥ 4.5 for worst itching (0 [no itch] -10 [worst possible itching]) were randomized 1:1:1 to NAL 60 mg (n = 128), NAL 120 mg (n=120), or placebo (n = 125) and treated for 8 weeks.

**Results:** Demographics, dialysis adequacy and vintage, phosphorus, parathyroid hormone, pruritus duration, and antihistamine use were similar in the 3 arms at baseline. The primary efficacy endpoint was the change from Baseline to the Evaluation Period (Weeks 7 and 8) in the NRS for each dose of NAL, with pre-specified hierarchical ordering – the 120 mg vs. placebo comparison was performed first. The mean (SD) NRS in the NAL 120 mg group declined from 6.94 (1.46) to 3.51 (2.11), with an LS mean decline vs. placebo = -0.73 (0.31), p = 0.017. The mean NRS in the NAL 60 mg group declined from 6.87 (1.40) to 4.95 (2.10), with an LS mean decline vs. placebo = -0.24 (0.31), p = 0.432. A statistically significant mean reduction for NAL 120 compared to placebo was observed as early as one week following titration. The most common adverse events were nausea, vomiting, dizziness and somnolence with incidence rates of these events quickly approaching that of placebo after the first week of titration. Among subjects with NRS ≥7 (post-hoc analysis), NAL 120 reduced NRS by 4.48 (SD) vs. 3.16 (SD) vs. placebo (p=0.007) with sleep quality (Itch MOS sleep scale) improved significantly (p=0.006).

**Conclusions:** Nalbuphine ER tablets at a dose of 120 mg BID were safe and significantly reduced itching intensity.

*Funding:* Pharmaceutical Company Support - Trevi Therapeutics

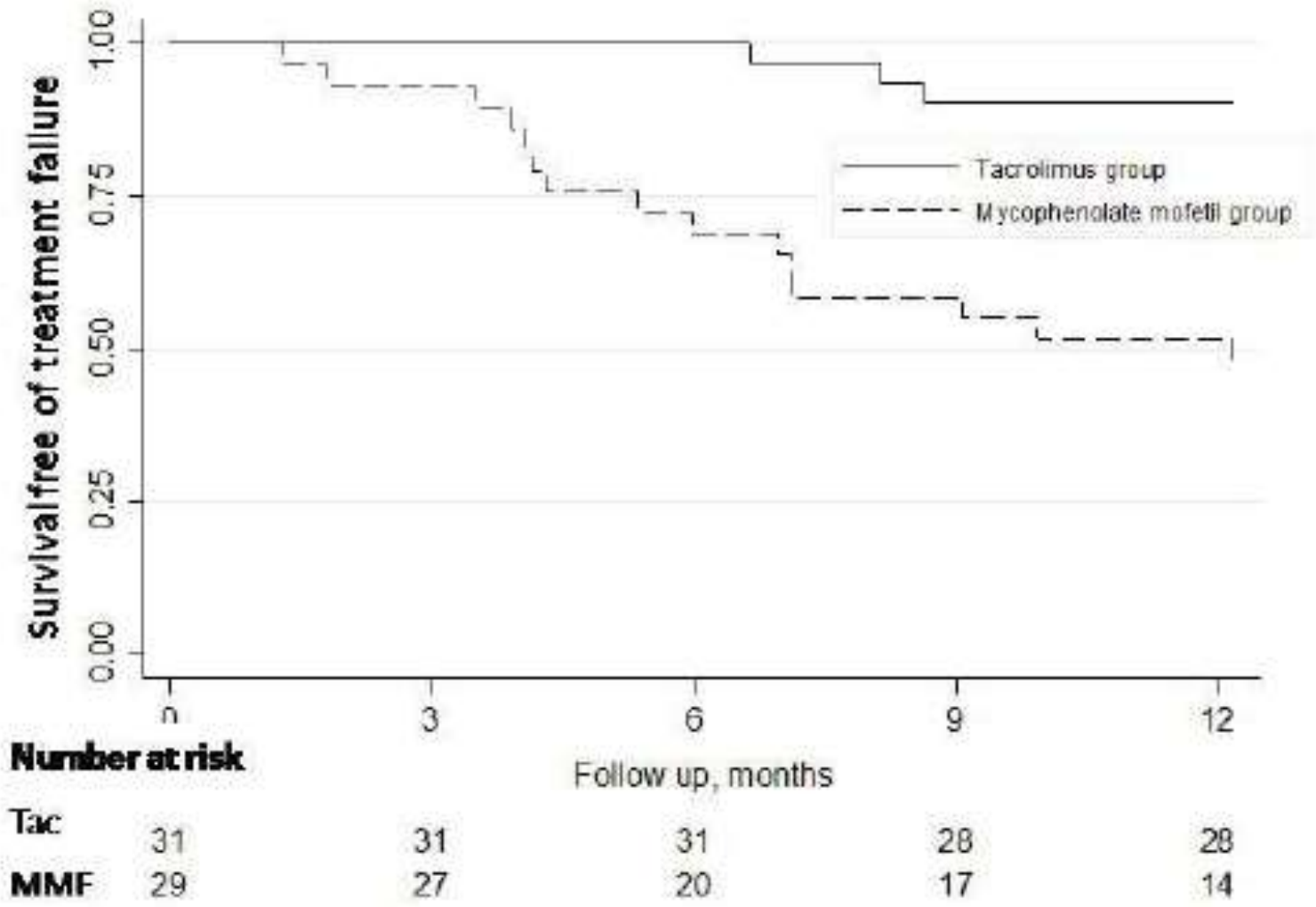

trevi
THERAPEUTICS
NALBUPHINE ER REDUCED ITCH INTENSITY:
PRIMARY ENDPOINT
Placebo BID
NAL ER 60 mg BID
NAL ER 120 mg BID
NRS Score
Mean Change from Baseline
-2.0
-2.5
-3.0
-3.5
-4.0
6.8 (1.4)
-2.8
6.9 (1.4)
-3.1
p=0.432
6.9 (1.5)
-3.5
p=0.017
↓49%
Baseline
Mean (SD
Data are LS Means (SEM)

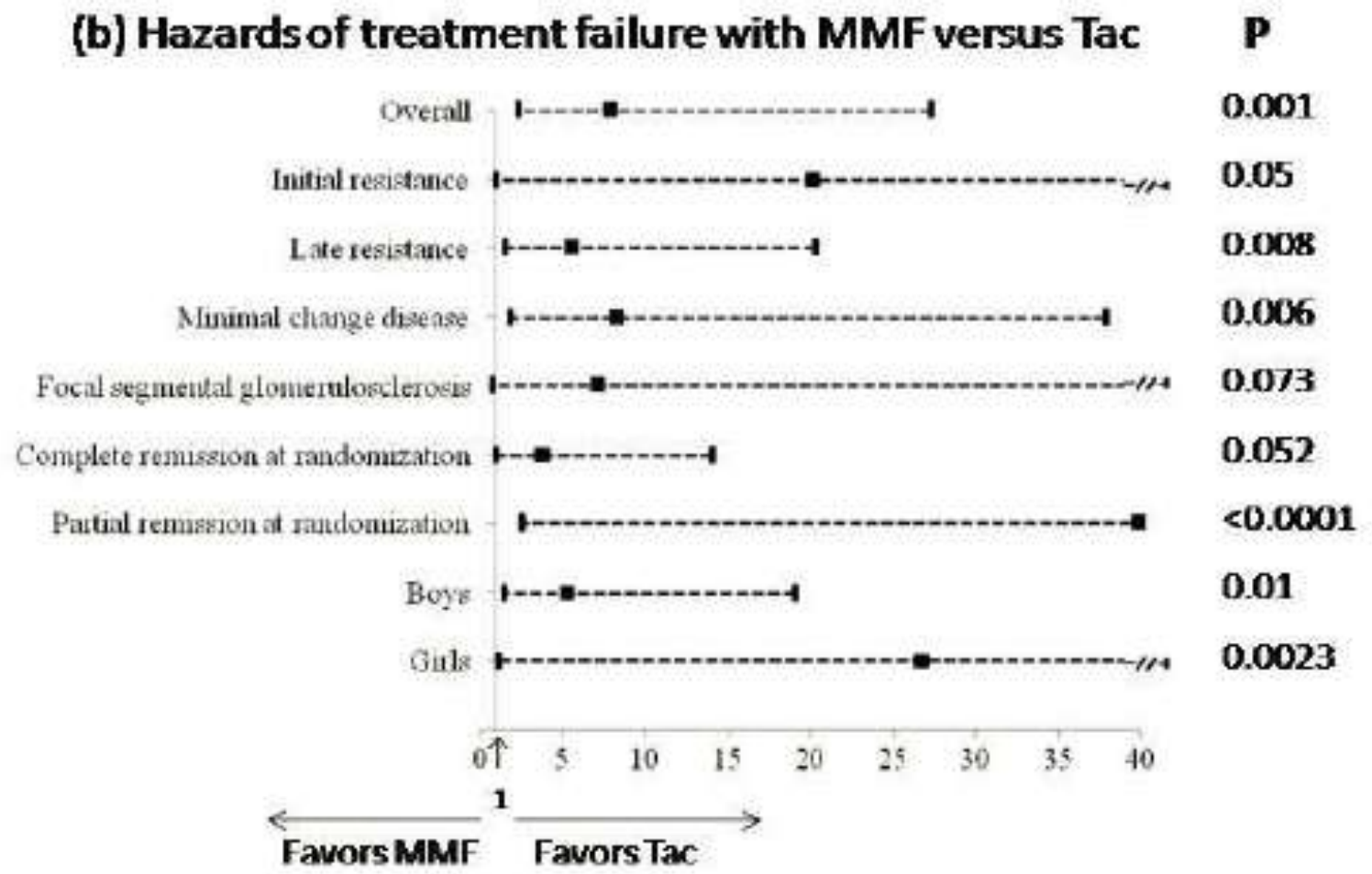
**Randomized Trial on Efficacy of Mycophenolate Mofetil versus Tacrolimus in Maintaining Remission in Children with Steroid Resistant Nephrotic Syndrome** Aditi Sinha, Arvind Bagga. *All India Inst of Medical Sciences, New Delhi, India.*

**Background:** Since prolonged therapy with tacrolimus (Tac) causes nephrotoxicity, this RCT examined non-inferiority of mycophenolate mofetil (MMF) to Tac in maintaining remission in patients with steroid resistant nephrotic syndrome (SRNS). CTRI/2012/03/00247

**Methods:** Following approvals, 84 patients with SRNS (1-18 yr; minimal change 48, FSGS 36) & eGFR >60 ml/min/1.73m$^2$ received Tac (0.15 mg/kg/d; trough 4-8 ng/ml) for 6-months. Stratifying for histology & type of response, patients with complete (Up/Uc <0.2 mg/mg) or partial remission (Up/Uc 0.2-2, albumin >2.5 g/dl) were randomized to continue Tac or receive MMF (0.75-1 g/m$^2$/d), prednisone & enalapril. Primary outcome, at 12-mo, was proportion with remission or infrequent relapses. Therapy failure was recurrent SRNS, frequent relapses or >1 SAE. Enrolment was closed after interim intention-to-treat analysis of outcome in 1/3 sample.

**Results:** Baseline features were similar. Therapy with MMF led to significantly higher treatment failure, prednisone dose & SAE; eGFR change was similar. On multivariate regression, hazards of treatment failure were high with MMF (HR 9.7, adjusted for histology, type of resistance & remission: P<0.0001).


(a) Survival free of treatment failure (Log rank P=0.0002)
Survival free of treatment failure
0.00
0.25
0.50
0.75
1.00
Tacrolimus group
Mycophenolate mofetil group
0
3
6
9
12
Follow up, months
Number at risk
Tac 31 31 31 28 28
MMF 29 27 20 17 14



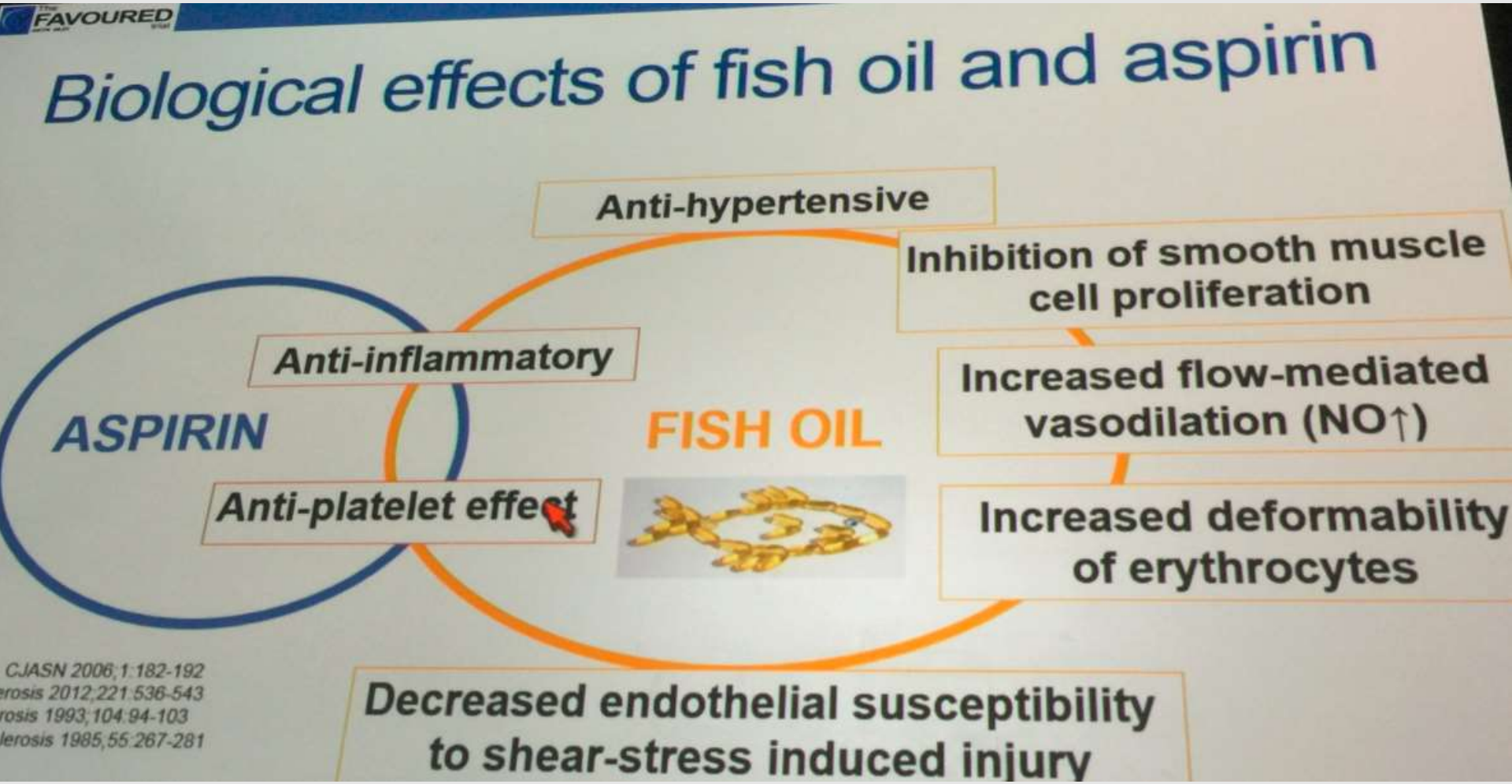

**Conclusions:** Therapy with MMF is inferior to Tac in maintaining Tac induced remission in patients with SRNS

## HI-OR08

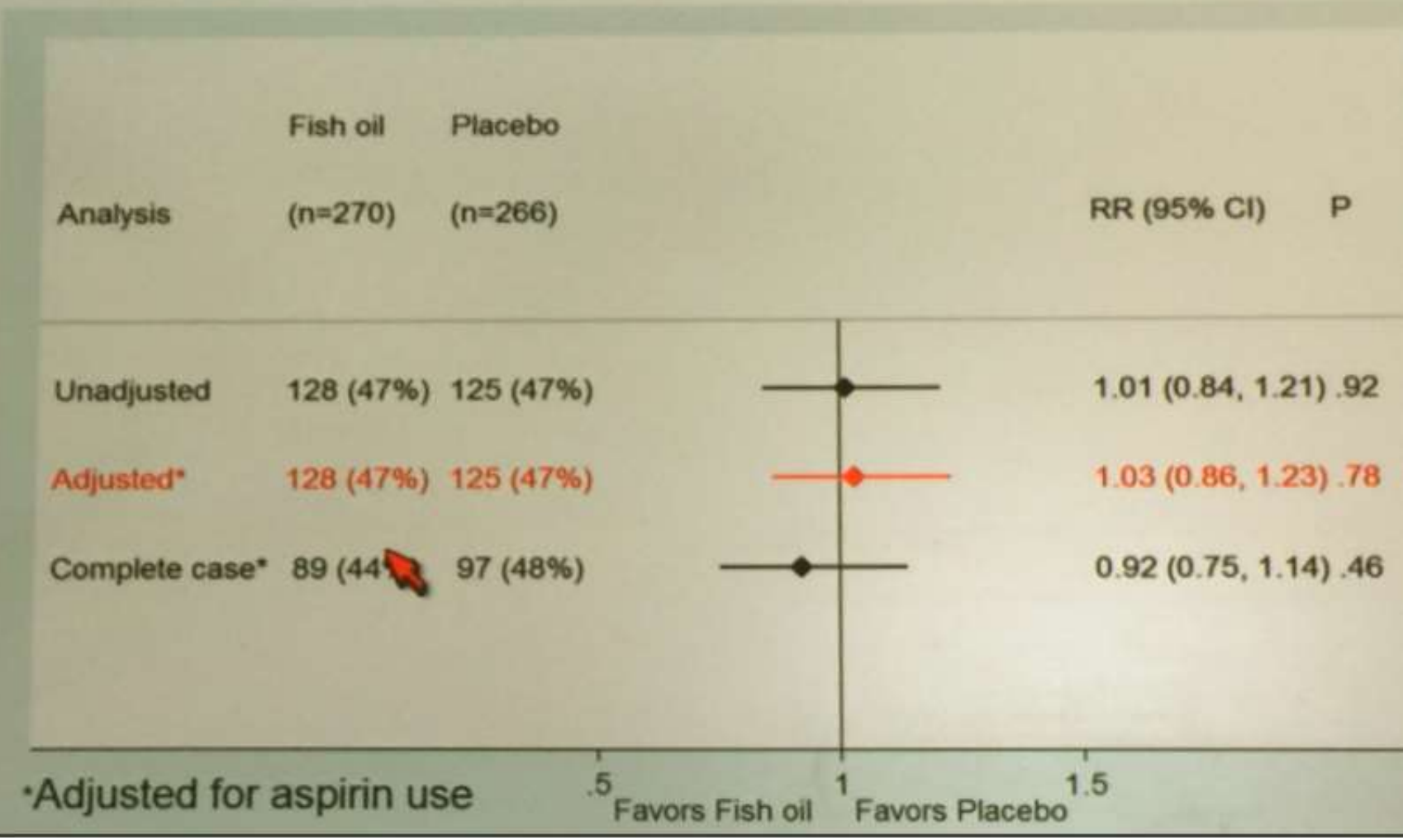
# The Omega-3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease (FAVOURED) Study: A Randomised Placebo-Controlled Trial

Ashley B. Irish.[1,2] [1]*Nephrology, Fiona Stanley Hospital, Perth, Western Australia, Australia;* [2]*Australasian Kidney Trials Network, Univ of Queensland, Brisbane, Queensland, Australia.*

**Background:** Increasing the use of arteriovenous fistulae (AVF) to improve haemodialysis access is limited by early thrombosis and maturation failure. Omega-3 polyunsaturated fatty acids (w3FA) may prevent these complications by inhibition of platelet aggregation, vasoconstriction, intimal hyperplasia and inflammation.


FAVOURED
Biological effects of fish oil and aspirin
Anti-hypertensive
Inhibition of smooth muscle cell proliferation
Anti-inflammatory
ASPIRIN
FISH OIL
Increased flow-mediated vasodilation (NO↑)
Anti-platelet effect
Increased deformability of erythrocytes
CJASN 2006;1:182-192
erosis 2012;221:536-543
rosis 1993;104:94-103
lerosis 1985;55:267-281
Decreased endothelial susceptibility to shear-stress induced injury

# Primary composite outcome



**Methods:** This international, randomised, double-blind, placebo-controlled trial examined whether 3 months therapy with w3FA (4g/day) reduced primary AVF failure at 12 months after AVF creation. AVF failure was defined as AVF thrombosis and/or abandonment and/or cannulation failure. A subset of patients received aspirin (100mg/day) or matching placebo in addition to w3FA or placebo in a factorial design (n=388).

**Results:** The 567 randomised participants had a mean age of 55 years, 63% were male and 46% diabetic. AVF failure occurred in 128/270 (47%) participants assigned to w3FA compared with 125/266 (47%) assigned to placebo (relative risk adjusted for aspirin use [RR] 1.03, 95% confidence interval [CI] 0.86-1.23, p= 0.78). Regarding each component of AVF failure, w3FA did not reduce the risk of thrombosis (22% vs 23%, RR 0.98, 95% CI 0.72-1.34, p=0.90), AVF abandonment (19% vs 22%, RR 0.87, CI 0.62-1.22, p=0.43) or cannulation failure (40% vs 39%, RR 1.03, 0.83-1.26, p=0.81). A subgroup difference was observed for diabetes mellitus (interaction p =0.038; RR 1.30 vs 0.78; diabetics vs non-diabetics) but not for age, gender, AVF site, dialysis modality and cardiovascular disease. There was no difference in any serious adverse event (AE), 9.2% vs 13.0%, p=0.14; bleeding, 8.1% vs 10.9% p=0.26, or gastrointestinal AE, 4.9% vs 5.4%, p=0.86. The risk of AVF failure was similar (45% vs 43%, RR 1.05, 95% CI 0.84-1.31) in the subset of participants randomised to aspirin or placebo-aspirin as part of the factorial design.

**Conclusions:** Three months of w3FA intake was ineffective in reducing primary AVF failure at 12 months. Aspirin may be similarly ineffective. There was no increased risk of bleeding. Neither w3FA nor aspirin increased the proportion of useable de novo AVF.

*Funding:* Other NIH Support - NHMRC Project Grant, Pharmaceutical Company Support - AMGEN Australia

# The Occurrence of Cardiac Arrhythmias in Hemodialysis Patients is Linked to the Hemodialysis Procedure and to Electrolyte Abnormalities as Recorded by Implantable Loop Recorders

Christian Combe,[1,2] Antoine Benard,[1,2] Hélène Savel,[1,2] F. Sacher.[1,2] *[1]CHU & Univ. Bordeaux, Bordeaux, France; [2]Rythmodial Study Group.*

**Background:** Sudden cardiac death (SCD) is the most common mode of death among hemodialysis (HD) patients (pts). Little is known about the terminal arrhythmic events in these pts. Our objective was to identify the mechanisms which may lead to SCD in HD pts using an implantable loop recorder (ILR, Reveal XT®, Medtronic).

**Methods:** Pts from 9 HD centers have been included in the study. Continuous monitoring of the cardiac rhythm has been performed using the remote monitoring capability of the ILR device (Carelink®). Clinical, biological, and technical HD parameters and medications have been recorded for at least 1 year. General joint frailty model for recurrent event data were used to analyze associations between these parameters and the occurrence of cardiac rythm events.

**Results:** 72 pts (65.1±8.6 yrs, 52M) have been included. Causes of ESRD were diabetes (n=32) and hypertension (n=19). 22 pts had an ischemic cardiomyopathy. In multivariate analyses, the occurrence of conduction abnormalities (n=64) was associated to high potassium (K+) concentrations (K+>5mM, RR=5.22, $p<10^{-4}$) and to body weight (bw) variation during HD (RR per %bw/h 3.22, $p<10^{-2}$). There was no association with serum calcium, hemoglobin, HD bath ions, blood pressure. Ventricular arrythmias >150/min (n=11) were associated only to high K+ levels (K+>5mM, RR=13.35, $p<0.05$), to low K+ levels (K+<4 mM, RR=24.48, $p<0.01$), and to high phosphate levels (Pi>45mg/L, RR=5.64, $p<0.04$). Atrial fibrillation was the most frequent event (n=255), with less clear associations with patient-dependent and HD-dependent variables. In 6 SCD patients, ILR tracings demonstrated progressive bradycardia followed by asystole.

**Conclusions:** Our data show that the various types of arrythmias and conduction abnormalities occurring in HD pts are linked to different pathophysiological mechanisms, with a central role of serum K+ levels, levels lower than 4 mM or higher than 5 mM being deleterious. Rapid body weight variations were linked to ventricular arrythmias. Therapeutic strategies aimed at controlling these factors can be drawn from our study.

*Funding:* Pharmaceutical Company Support - Medtronic, Government Support - Non-U.S.

## Cardiac Investigations - Implantable Loop Recorder (ILR, Reveal device)

If a patient has very troublesome but *infrequent* symptoms, for example feeling faint, severe palpitations or loss of consciousness, it is highly likely that short-term monitoring will fail to pick up the underlying abnormality. In these circumstances it may be appropriate to use an implantable loop recorder (ILR) such as the Reveal™ device, which has been available for a number of years. The ILR is a compact but highly sophisticated device, smaller than a pack of chewing gum, which is implanted under the skin on the front of the chest; this is performed as a day case procedure, taking 30 to 40 minutes, and requiring only a local anaesthetic.

The ILR continuously monitors the heart beat and ECG for the lifetime of the battery, approximately three years in the latest models. Sudden changes in heart rate are automatically recorded by the device and can be subsequently downloaded using a programmer, which looks like a laptop computer. The patient, or a family member or friend, can also activate the ILR to store information on the heart beat at the time of symptoms or upon recovery, whichever is most practical. The ILR is activated using a small hand-held device which is placed on the skin overlying the ILR; pressing the button on the activator stores the ECG for a set period of time before, during and immediately after the activation. The activator should be carried by the patient at all times. By looking at automatically stored and patient stored ECGs it is possible to determine whether or not a patient's symptoms are due to significant changes in the heart rate and rhythm. Once a diagnosis has been made, or if it becomes clear that there is *not* an underlying heart abnormality, the ILR is removed under local anaesthetic. If it has been shown that the symptoms are due to inappropriate slowing of the heart a permanent pacemaker can be inserted at the same time.

# Randomised Controlled Trial to Determine the Appropriate Time to Initiate Pertioneal Dialysis after Insertion of Catheter to Minimise Complications

Helen G. Healy,[1] George T. John,[1] Edward Yeoh,[1] Nicola Williams,[1] Thin M. Han,[2] Lakshmanan Jeyaseelan,[3] Kavitha Ramanathan,[3] Dwarakanathan Ranganathan.[1] *[1]Renal Dept, Royal Brisbane & Women's Hospital, Brisbane, Queensland, Australia; [2]Renal Dept, Rockhampton Hospital, Rockhampton, Queensland, Australia; [3]Dept of Statistics, Christian Medical College, Vellore, India.*

**Background:** The optimal time for the commencement of peritoneal dialysis (PD) after PD catheter insertion is not well known. If dialysis is started too soon after insertion, dialysate leaks and infection may occur. However by starting PD earlier, morbidity and costs can be reduced through less need for haemodialysis. This is the first randomised controlled trial to determine the safest and shortest interval to commence PD after catheter insertion.

**Methods:** All consecutive patients undergoing PD catheter insertion at the Royal Brisbane and Women's Hospital and Rockhampton Hospital from 1st March 2008 to 31st May 2013, and who met the inclusion and exclusion criteria were invited to participate in the study. Participants were randomised to one of three groups. Group 1 ($G_1$) commenced PD at one week, group 2 ($G_2$) at two weeks and group 3 ($G_3$) at four weeks after Tenckhoff catheter insertion. The groups were stratified by hospital and the presence of diabetes. Primary outcomes were the incidence of peritoneal fluid leaks or PD related infection during the 4 weeks after commencement of PD.

**Results:** 122 participants were recruited, with 39, 42 and 41 randomised to groups $G_1$, $G_2$ and $G_3$ respectively. The primary outcome of either catheter leaks or infection was significantly different in both intention to treat (ITT) and per protocol (PP) analyses (p=0.016 and 0.006 respectively). Multiple pairwise comparison showed a significant difference between G1 and G3 in PP analysis (p-value=0.010) but not in the ITT analysis.

**Conclusions:** Overall complications were higher in patients commencing PD one week after catheter insertion compared with the other two groups.

*Funding:* Pharmaceutical Company Support - Baxter Medical

P

# Eculizumab in Prevention of Acute Antibody-Mediated Rejection in Sensitized Deceased-Donor Kidney Transplant Recipients: Updated 12-Month Outcomes

D. Glotz,[1] G. Russ,[3] Lionel Rostaing,[3] Christophe M. Legendre,[3] Steven J. Chadban,[3] J. Grinyo,[3] Nizam Mamode,[3] Gunnar Tufveson,[3] Lionel Couzi,[3] P. Riggoti,[3] Y. Lebranchu,[3] S. Sandrini,[3] W. Marks.[2] *[1]Hôpital Saint-Louis, Paris, France, Metropolitan; [2]Alexion Pharmaceuticals, Inc., Cheshire, CT; [3]The International Eculizumab Transplant Study Group.*

**Background:** Complement activation by preformed DSA is the major mechanism of acute antibody-mediated rejection (aAMR) in sensitized, kidney transplant recipients (SKTR). In a previous interim study report, the C5 inhibitor eculizumab (Ec) appeared effective in preventing aAMR in deceased donor (DD) SKTR compared to historical controls. We now report 12-mo efficacy and safety data from a Sept 2015 update of this ongoing, open-label, single-arm trial.

**Methods:** SKTR defined as current DSA >3000MFI detected by SAB; or B- or T-cell flow cytometric crossmatch ³300 and ≤500 mean channel shift; or historical positive complement-dependent cytotoxicity crossmatch to donor HLA. All recipients received Ec 1200mg postoperative day (POD) 0 prior to reperfusion, 900mg on POD 1, 7, 14, and 28, and 1200mg at wks 5, 7, and 9. Recipients received Rabbit ATG for induction and corticosteroids, tacrolimus, and mycophenolate for maintenance immunosuppression. Plasmapheresis was not allowed through Post-transplant week 9. The primary composite endpoint was clinically significant, biopsy (bx)-proven aAMR grade II/III (Banff 2007, based on centrally read bx), graft loss, death, or loss to follow-up at 9wks. Graft and patient (pt) survival were estimated by K-M.

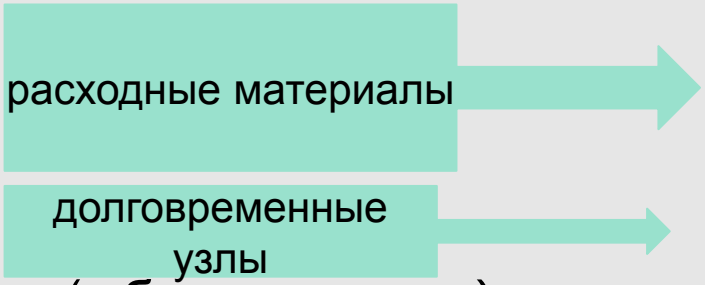
**Results:** 80 pts were transplanted (48 F, 32 M); median age 52y (range, 24–70). 7 of 80 SKTR had aAMR (8.8%) compared to 30% expected for historical controls. 11/80 SKTR met the 9wk composite primary endpoint based on local bx (13.8% [95% CI 7.1–23.3]). Graft survival at 6 and 12mo was 93.7% and 88.7%, respectively; pt survival at 6 and 12mo was 97.4%. SCr levels (mg/dL) at baseline, 1 and 12mo were 7.43 (±2.51), n=79; 1.86 (±1.07), n=74; and 1.63 (±0.76), n=69. No new safety concerns were identified.

**Conclusions:** Ec appeared to be effective in reducing aAMR in SKTR. Pt and graft survival and kidney function at 12mo were similar to those expected for non-sensitized KTR. Ec was well tolerated.

*Funding:* Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

# Протез почки: миф или реальность

1. Портативные аппараты
2. Носимая почка на основе ГД
3. Носимая почка на основе ПД
4. Имплантируемая почка
5. Имплантируемая гибридная почка (с биореактором)
6. Биологический протез почки
    1. Полученная из стволовых клеток
    2. Ксенотрансплантация специально подготовленного протеза



# Вильям Кольф 1977

Exponential growth of future artificial organs.
Artif. Organs 1977 1, 8-18

- WAK wearable artificial kidney
- IFAC (Filtrating)
- PAK (Peritoneal)
- IHAK (Hemoperfusion)

# Первый аппарат Мини-1 для домашнего ГД 1964

Milton-Roy Model A—First Machine Used for Nocturnal Home Hemo: 1964

This Model A machine was built from a prototype "Mini-1" machine designed by Albert "Les" Babb for his best friend's daughter, Caroline Helm. It was called the Mini-1 because Dr. Babb had built a much larger one—"The Monster"—for the University of Washington before this smaller home version.

The Model A was built by the Milton Roy Company in St. Petersburg, Florida in 1964. It was designed to perform nocturnal home HD. The wooden veneer was used to give it a furniture look for home use. The Model A had automatic hot water (90° C) disinfection, automatic alarms, solid-state (diode) logic, and acoustic tile inside to reduce noise.

# Мини II аппарат для домашнего ГД
# Mini II Hemodialysis Machine (mid 1960s)

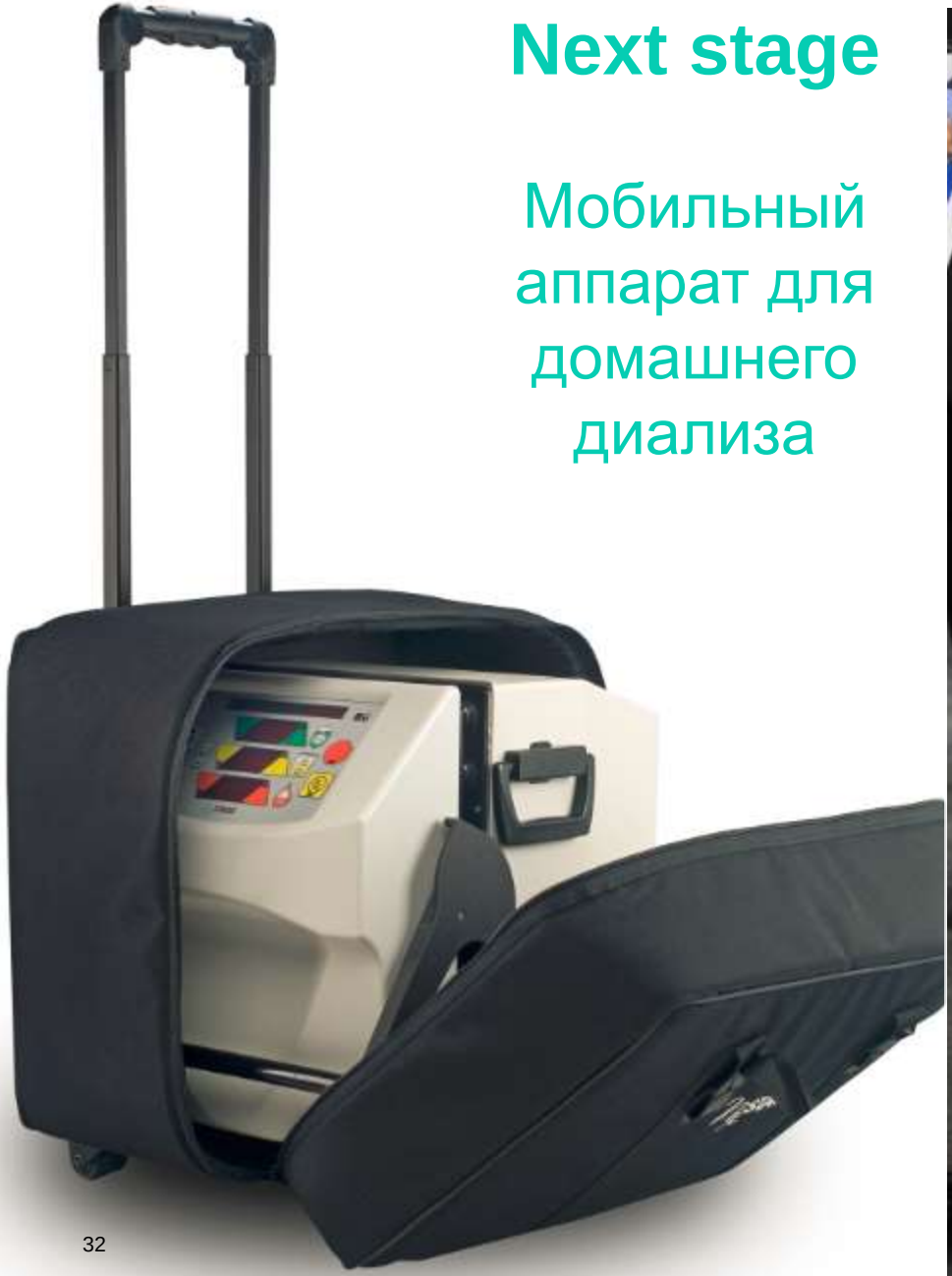
On an airplane flight from Seattle to an East Coast conference in 1965, four innovators refined the design of the first home dialysis machine, which they had created a few months before. Dr. Scribner, Professor Babb, Lars Grimsrud, a grad student of Babb's, and Jack Cole, the first dialysis engineer, met around a coffee table in the back of the plane. They came up with the new design in about 4 hours. The Milton Roy Company in Florida made five of these new Mini-II machines for home dialysis trials. The mini-II proved successful and became the first commercial home dialysis machine.

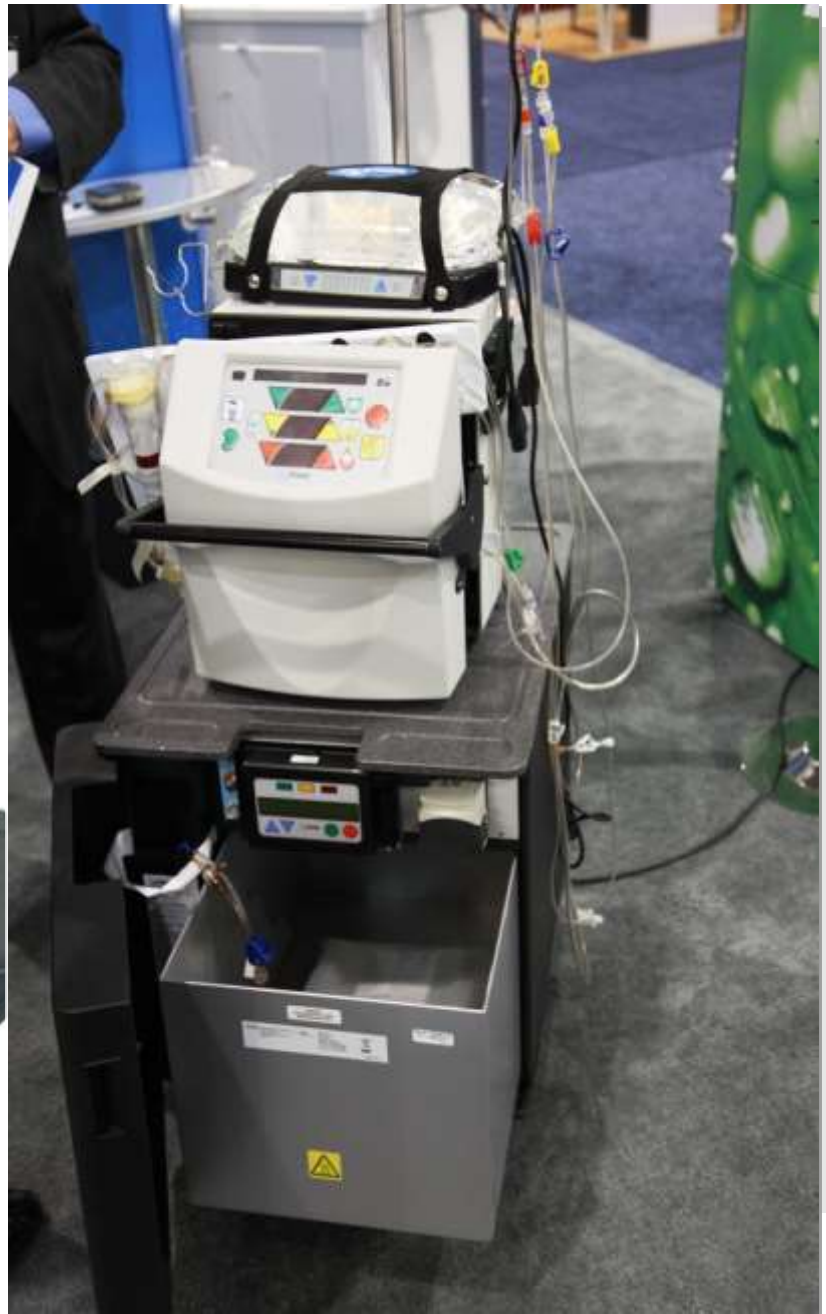
# Аппарат для домашнего диализа “Next Stage”

B BRAUN
SHARING EXPERTISE

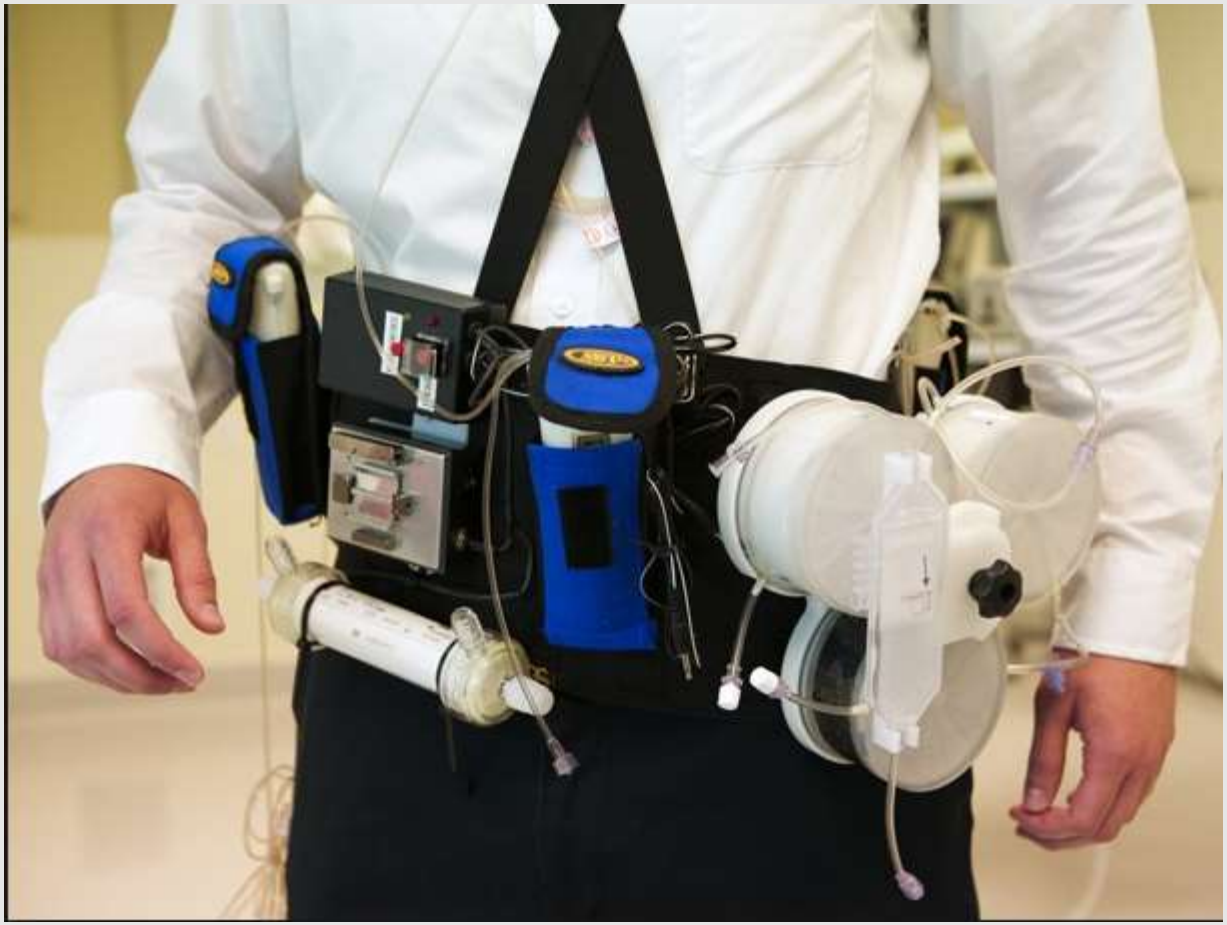
# Next stage

Мобильный аппарат для домашнего диализа

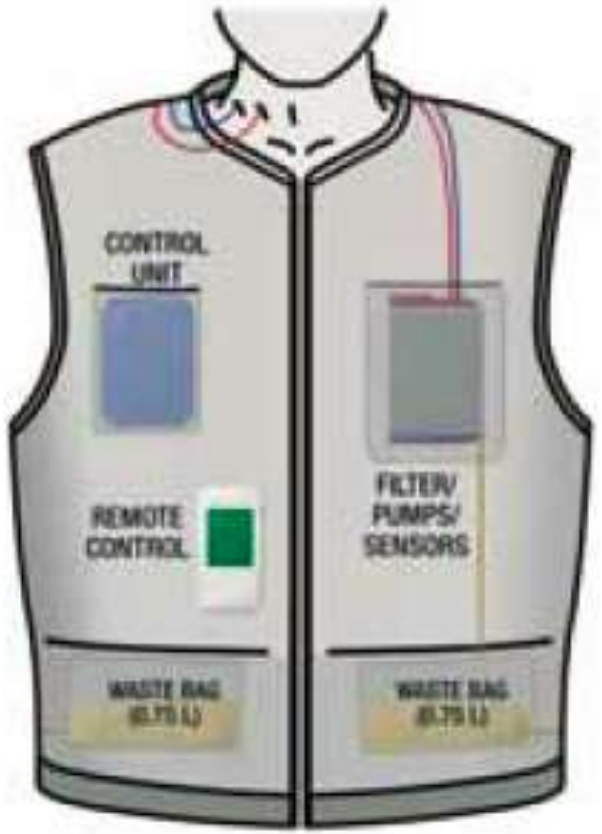




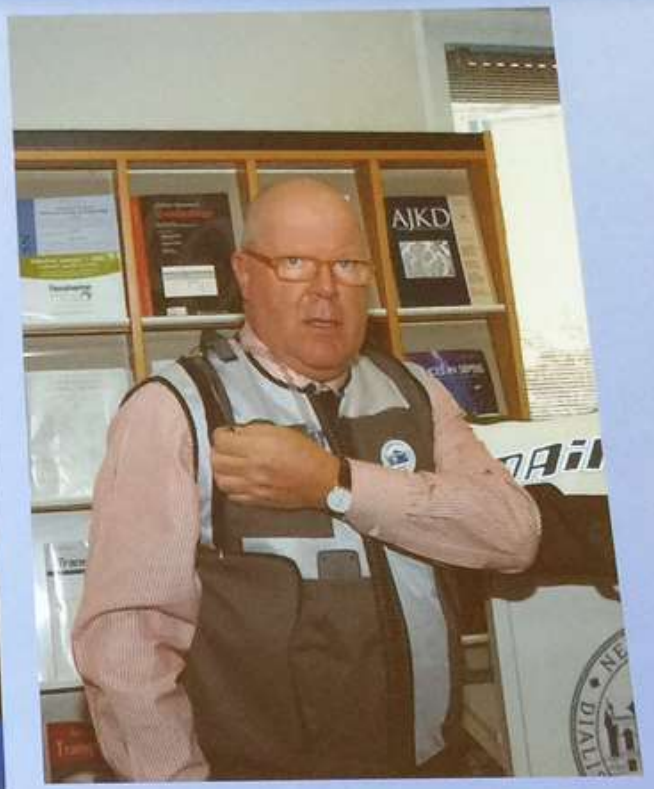
# Первое устройство, прошедшее клинические исследования



# Жилет WAKMAN



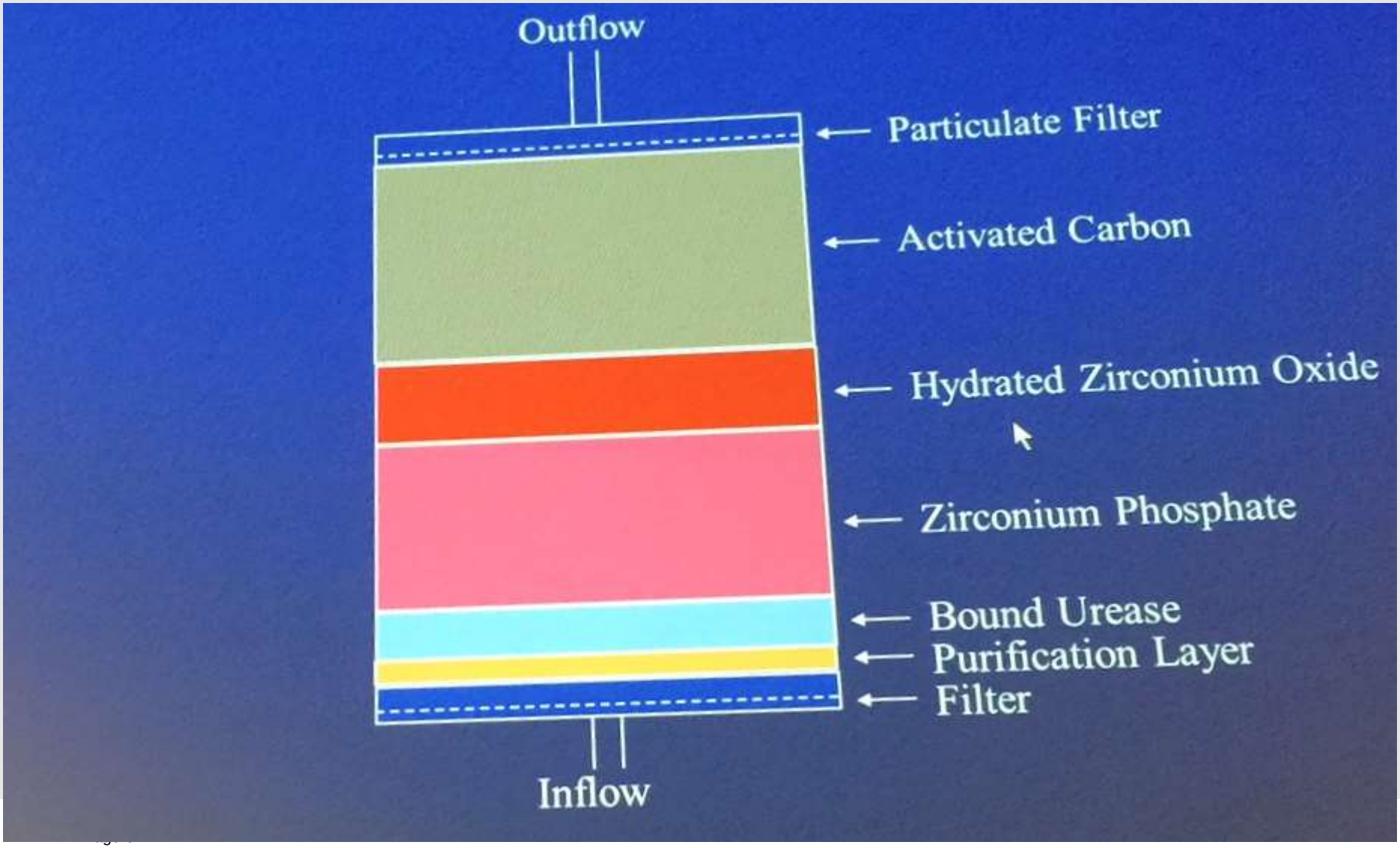
# Wakman: The Circuitry


RAND

IRRIV
International
Renal Research
Institute Vicenza

# Многокомпонентный регенерирующий сорбент




Dialysate regeneration for water-less treatment
Enable miniaturization for existing dialysis machines
AWAK TECHNOLOGIES
AWAK TECHNOLOGIES
HOW IT WORKS
SORBENT DIALYSIS
AWAK PD OPERATION MODES
AWAK

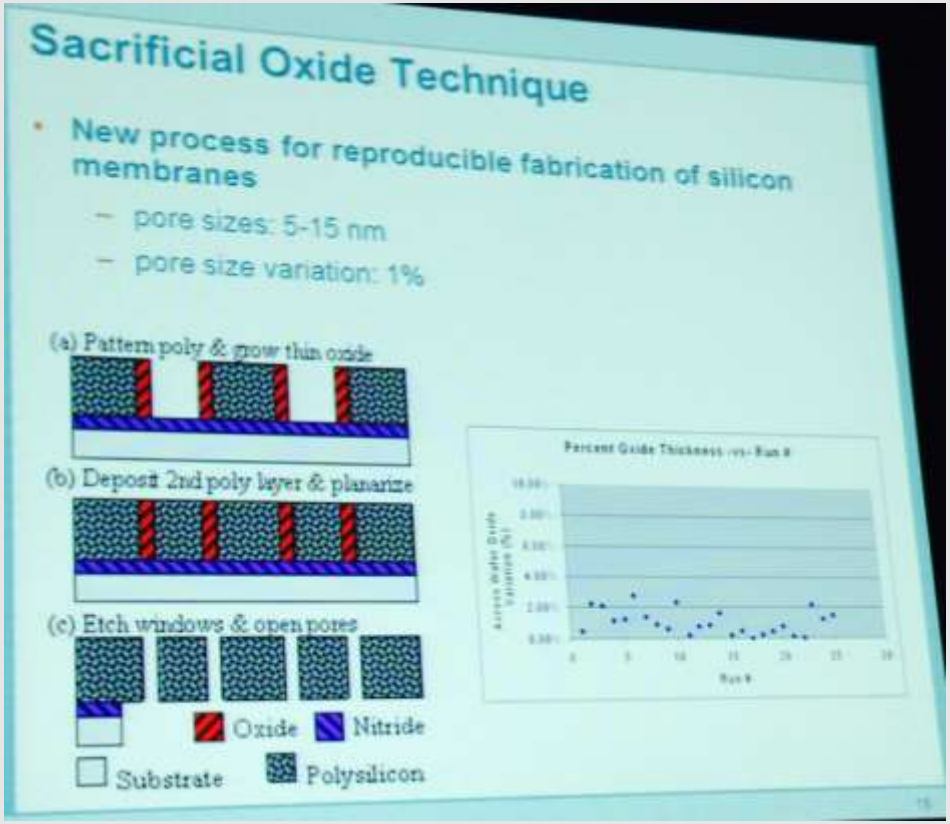

We are the solution for a portable dialysis system.
Design flexibility for custom
Dialysate regeneration for wate
Enable miniaturization for existing
AWAK
Your Pa

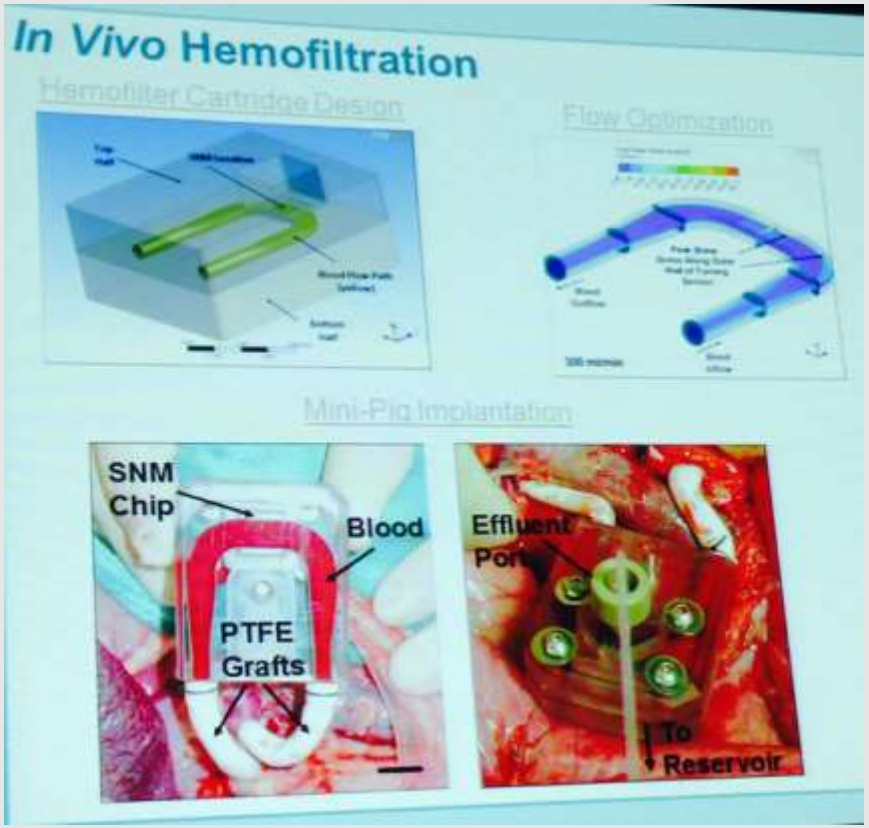
# Major step towards portable artificial kidney

## Debiotech, AWAK and Neokidney Development sign partnership to bring compact home haemodialysis machine to first patients by 2017

***Lausanne, May 23rd 2014 –*** *Today three international innovators join forces to develop and deliver to patients the world's first portable artificial kidney. Debiotech of Switzerland, AWAK of Singapore and Neokidney Development, an initiative of the Dutch Kidney Foundation, have signed a joint venture agreement to complete a functional model in 2015. Clinical trails are planned for 2017. The portable artificial kidney will enable the frequent and longer home haemodialysis that significantly improves and extends patients' lives.*

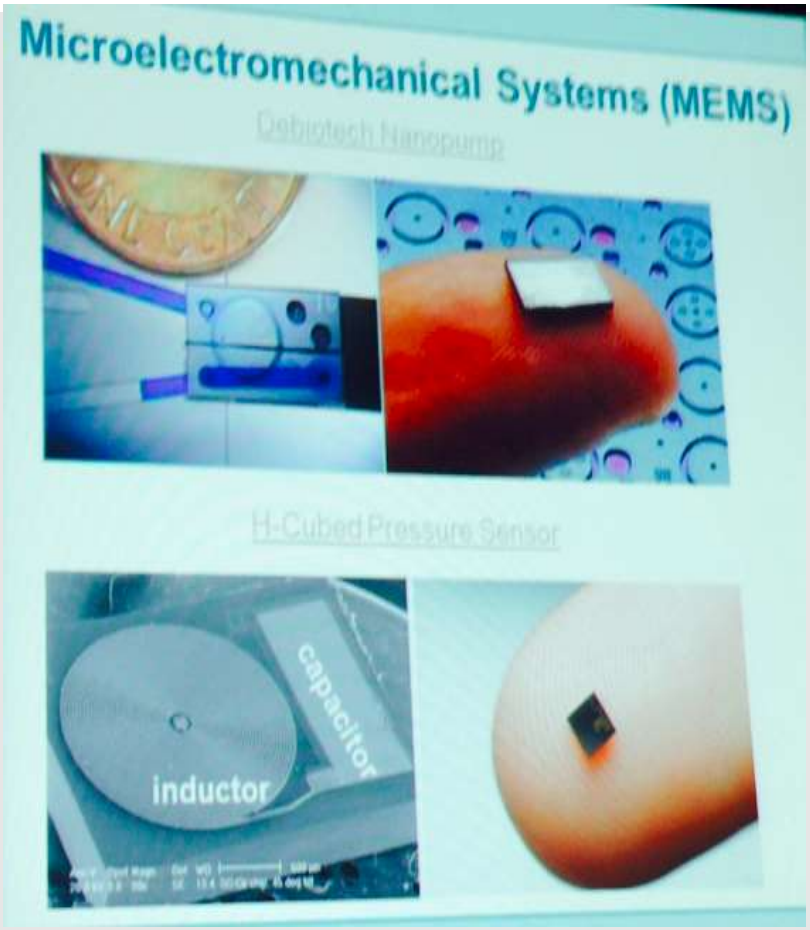
# МЕМБРАНЫ БУДУЩЕГО

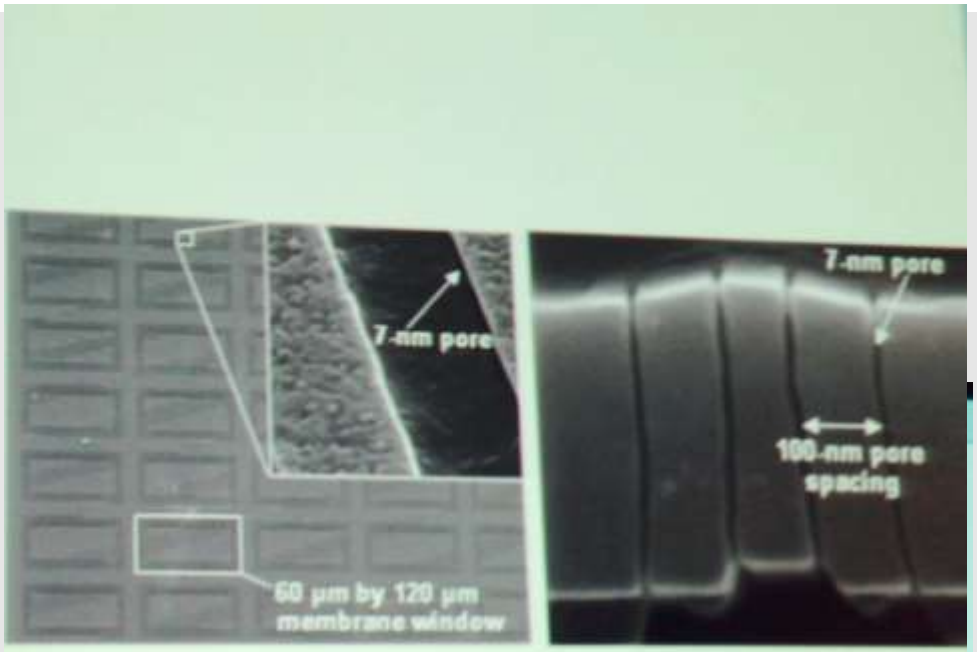


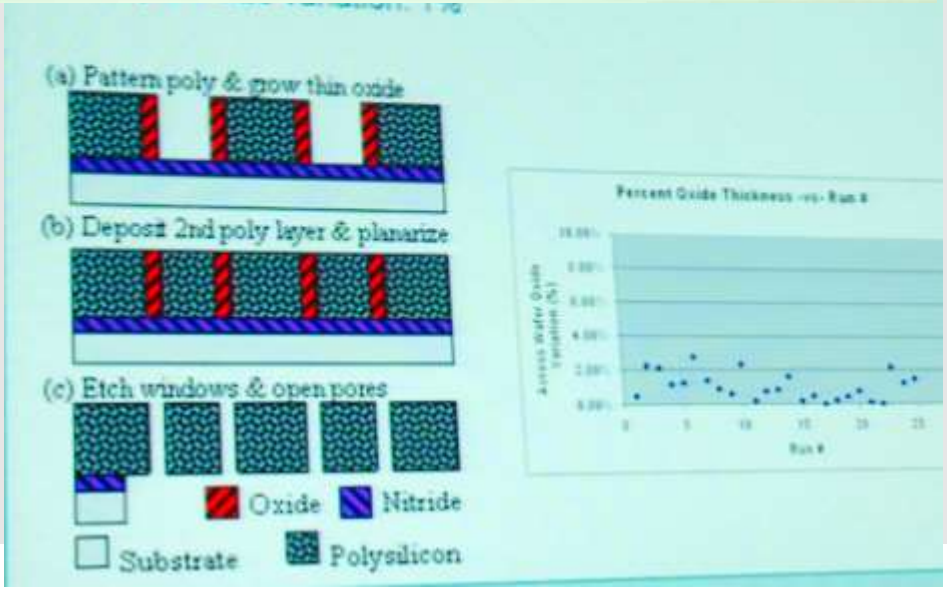





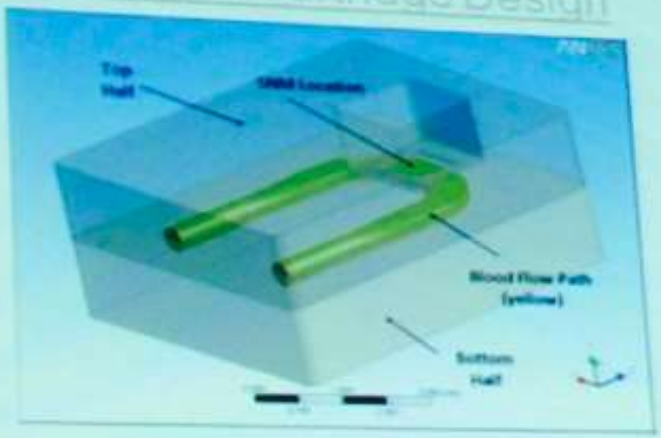
Shulvo Roy UCSF 2013


Microelectromechanical Systems (MEMS)
Debiotech Nanopump
H-Cubed Pressure Sensor
capacitor
inductor

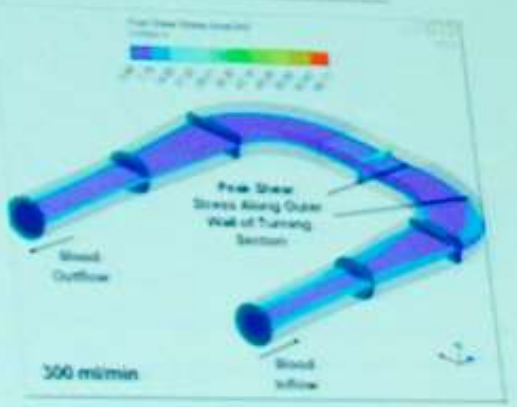

7-nm pore
60 μm by 120 μm membrane window
7-nm pore
100-nm pore spacing


(a) Pattern poly & grow thin oxide
(b) Deposit 2nd poly layer & planarize
(c) Etch windows & open pores
Oxide
Nitride
Substrate
Polysilicon
Percent Oxide Thickness

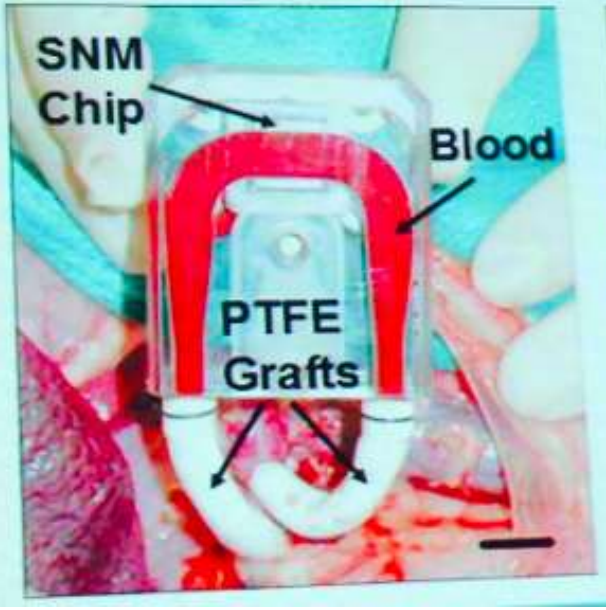
## Hemofilter Cartridge Design

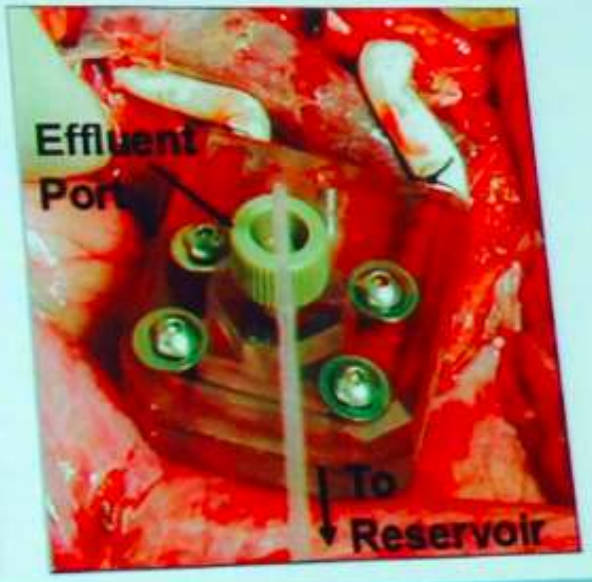


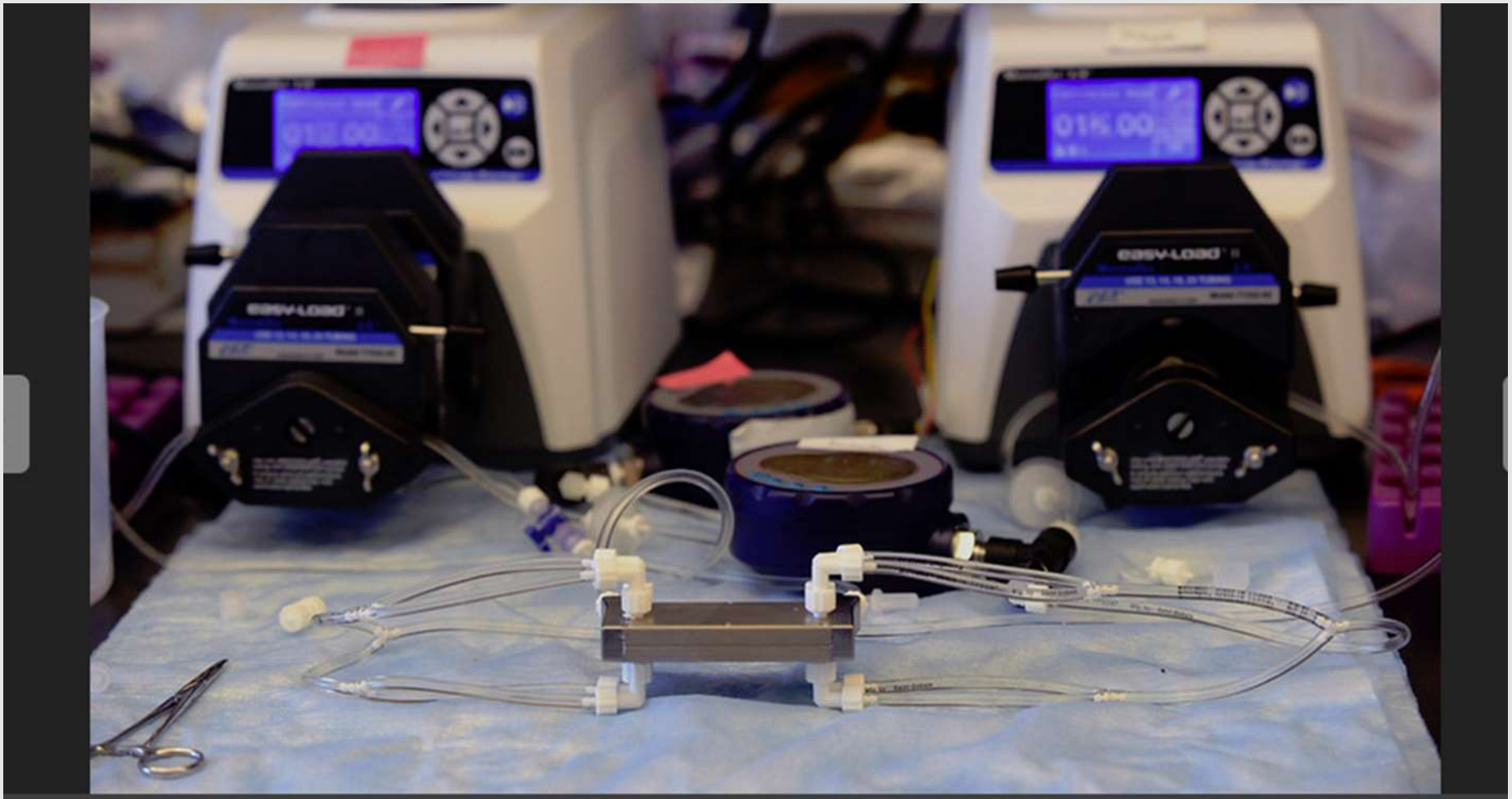

## Flow Optimization




## Mini-Pig Implantation

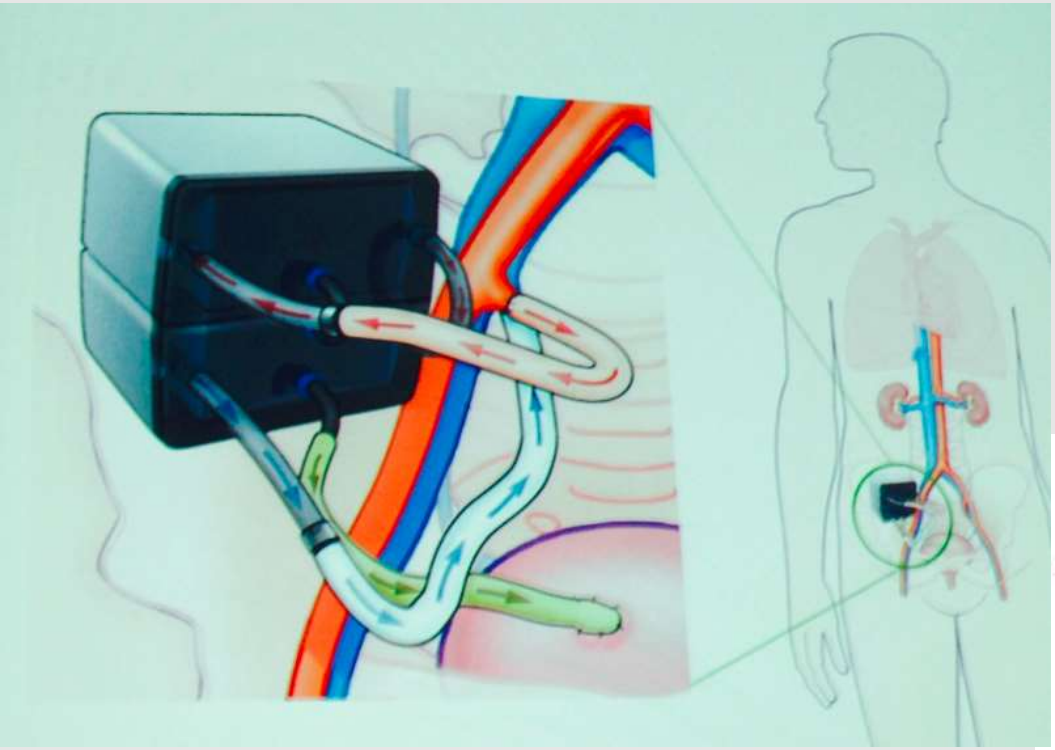




Silicon filters within the small metal case are being tested for efficiency at QB3/Byers Hall on the campus of UCSF in San Francisco, Calif. on Friday, April 12, 2013. UCSF is leading a team of researchers from around the country who are attempting to create an implantable ...

# Цель – имплантируемая почка



*Implantable Artificial Kidney – Shown without filters or cover plates installed*


# An implantable, artificial kidney

University of California

Подписаться 2 891

35 779