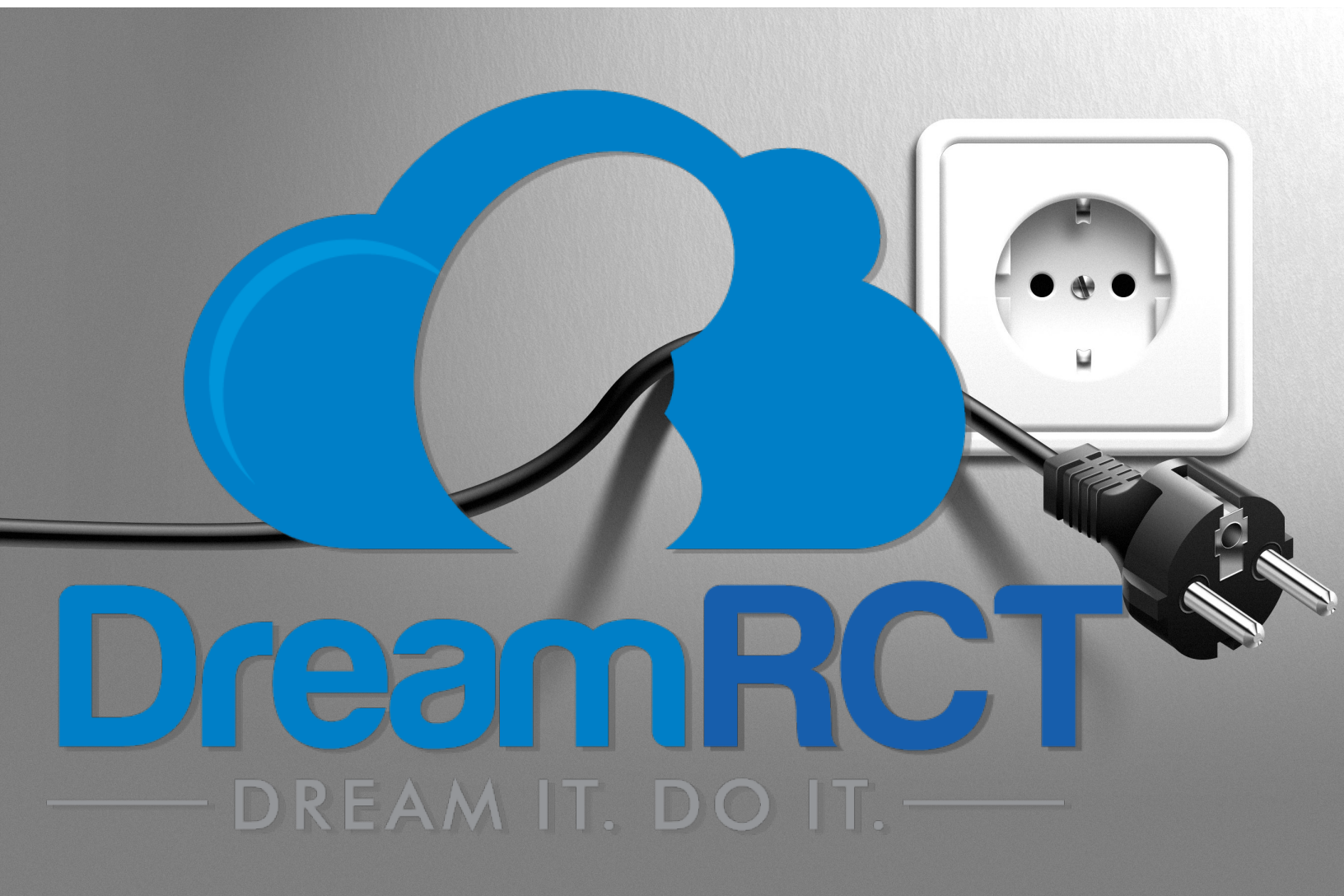


DreamRCT Unplugged

All the entries, no HTTP



The DreamRCT Collaboration:	3
The MIND Study	5
PLEX versus HCO Dialyzer	8
The Nephro-RULES AKI Study	10
Shedding Pounds Before Kidney Transplant	15
Acidosis in CKD Treatment Now Study (ACT Now)	18
The NO DUH Trial	21
Putting Oral Potassium Binders to the Test	24
CLARITY for Albuminuria's Role in T2D	28
The SONNET Trial for Social Media	31
The NoLoNaMo Trial	36
The PANIC Trial	40
How to Quash Kidney Stones	43
Do Steroids Really Alter Outcomes in AIN?	46
Single-Agent Rituxan in Lupus Nephritis	49
The AKI-REPACE Trial	51
The MAGIK Trial	58

The DreamRCT Collaboration:

Why It's Essential

<http://www.medpagetoday.com/Nephrology/DreamRCT/53854>

The most valuable assignment I received in fellowship was to write a few textbook chapters. I wrote on sodium, calcium, potassium, phosphorus, and magnesium for three different chapters. I had already developed deep knowledge of electrolytes writing "The Fluid and Electrolyte Companion," but writing these chapters forced me to look beyond how things work and dive into how we know how things work. It was a chance to peek behind the curtain to examine the data behind our proclamations of fact. The experience was a bit disorienting as this impenetrable wall of knowledge that I assumed backed up our physiologic models was more a chain-link fence. The truths that I had been memorizing were actually full of holes, unexamined suppositions, and conflicting data. The biggest lesson in writing those chapters was learning what we didn't know and how fragile our knowledge was.

As an educator now, I struggle with how to teach those lessons. One approach is the current project, DreamRCT (for dream randomized controlled trial). Nephrology, more than any other specialty in internal medicine, exists in an evidence desert. The first DreamRCT contest was conducted in early 2014 and nephrologists from across the blogosphere let their imaginations run free to come up with the most vexing issues in nephrology and designed randomized controlled trials to solve them. Here was the invitation paragraph to the first DreamRCT (along with my 2014 entry):

Okay nephrologists, we have suffered the slings and arrows of outrageous trial after trial going against us. It is time to put down those depressing journals full of non-significant P-values and stretch our imagination. It is time to design our own dream randomized controlled trial. The assignment is to target the most important question you see in nephrology today and design a trial to answer it. One question not enough for you? Design a trial to answer two questions ACCORD style. Two questions not enough, go all AASK and design a 2x3 factorial design. Money no object, forget about pesky IRBs, let your mind free and create the trial which will meaningfully push back the walls of knowledge.

We had a few dozen entries last year but something more remarkable began. People started using the nomenclature "DreamRCT" when describing an area of uncertainty that begged for

the clarity only an RCT can provide. DreamRCT evolved from a one-off contest to a general idea -- a shorthand expression to convey the idea that this was an important question, a question important enough to need a proper RCT.

DreamRCT is back for 2015 and the contest has evolved. This year we have gathered some of the top minds in the nephrology social media sphere to create DreamRCTs. Each of these will be posted at DreamRCT HQ at UKidney and will also live on MedPage Today. Readers will serve as funders and use virtual currency to vote for their favorites. Go to UKidney and register for DreamRCT and you will be given \$100,000 of virtual coin to distribute among the trials as you see fit. Any ideas speak to you as needing immediate funding, funnel your dollars their way. We will be tracking the winners and losers to see what ideas ring bells and which are just dumb bells. It's NIH meets Kickstarter. Entries should be judged on need, creativity, and feasibility.

DreamRCT also features a virtual study section. This is an all-star cast of nephrology clinical researchers. They will fund the trials with virtual currency, just like the crowd. We are intensely curious to see how the crowd and the experts agree and disagree. Additionally, the reader-funder whose contributions best match the virtual study section template will win the 2015 DreamRCT Funding Trophy!

We are proud to announce your 2015 DreamRCT virtual Study Section:

- **JAY KOYNER, MD**, is an associate professor of medicine at the University of Chicago. He is co-director of the American Society of Nephrology's Critical Care Nephrology Kidney Week Pre-course. We brought him in as our AKI sharp shooter.
- **JOHN DAUGIRDAS, MD**, has probably done more to educate generations of nephrologists than any other person with his classic text "The Handbook of Dialysis." He is the lead author of the definitive study on Kt/V, the HEMO trial.
- **ALLEN NISSENSON, MD**, is emeritus professor of medicine at the David Geffen School of Medicine at UCLA, where he served as associate dean. Dr. Nissenson is also co-chair of the Kidney Care Partners Quality Initiative. He is a former president of the Renal Physicians Association (RPA).
- **MANJULA KURELLA TAMURA, MD, MPH**, is an associate professor of Medicine at Stanford University and the Veterans Affairs Palo Alto Health Care System. She does

groundbreaking research on the quality of care for older adults with chronic kidney disease. She also won NephMadness 2015.

■ **UPTAL PATEL, MD**, is an associate professor of Medicine and Pediatrics, an investigator in the Health Services Research and Development Unit at the Durham Veterans Affairs Medical Center, and core faculty at the Duke Clinical Research Institute. His career work focuses on healthcare systems-level strategies to optimize population management for chronic diseases, with a focus on acute and chronic kidney disease.

■ **JONATHAN HIMMELFARB** is the director of the Kidney Research Institute, professor of medicine, and holds the Joseph W. Eschbach M.D. Endowed Chair in Kidney Research at the University of Washington. Dr. Himmelfarb has served on numerous study sections, grant review committees, and scientific advisory boards and is currently the president of the American Society of Nephrology.

Vote for your favorite trials at DreamRCT HQ at UKidney.

Joel Topf, MD, (@kidney_boy) is a clinical nephrologist in Detroit. He is part of the faculty at St. John Providence Medical Center where he teaches medical students, residents, and fellows. He is one of the leaders in medical social media and co-creator of DreamRCT and NephJC.

Jordan Weinstein, MD, (@Ukidney) is an assistant professor of medicine at the University of Toronto and the director and founder of UKidney. He is the co-creator of DreamRCT.

The MIND Study

Does mindfulness therapy reduce depression in ESRD patients?

<http://www.medpagetoday.com/Nephrology/DreamRCT/53863>

End-stage renal disease (ESRD) is a growing problem in the United States. There are more than a half million persons (nearly 400,000 on maintenance dialysis therapy) with ESRD and that is expected to grow to 750,000 persons by 2020.

Depression is the most common psychological problem in patients undergoing dialysis. Despite substantial resources devoted to ESRD treatment, these patients have poorer health-related quality of life (HRQoL) compared to the general population. The prevalence of depression in the maintenance hemodialysis population has been reported to be 20%-30%.

Depression and poor mental health are associated with a higher risk of hospitalization and death in this population. Depressed hemodialysis patients are more likely to have poor adherence to dietary and fluid restrictions, to withdraw from dialysis therapy, and to commit suicide.

Depression can be treated with medications and psychosocial interventions. Compared to medications, psychosocial interventions may be ideal for patients on dialysis, especially considering the polypharmacy these patients are already dealing with. The resolution of depression with psychosocial treatment may improve medical outcomes, reduce costs, and improve the quality of life of patients suffering from depression. A meta-analysis of psychosocial interventions found them to be effective at treating depression. However, clinical trials examining interventions to improve mental health in patients treated with hemodialysis are scant despite a mandate from the Centers for Medicare & Medicaid Services that dialysis facilities collect information on HRQoL.

My DreamRCT is a multi-center, randomized controlled trial to study the effect of mindfulness-based stress reduction (MBSR) on nutritional status and depression in ESRD patients on hemodialysis. It's the Mindfulness-based stress reduction Intervention for improving Nutritional status and Depression Study (the MIND Study).

Mindfulness-based stress reduction (MBSR) is a treatment for psychological distress, depression, and anxiety for people with chronic disease that is rapidly growing in popularity in the United States. Developed by Jon Kabat-Zinn, the MBSR program consists of 8–10 sessions for groups of up to 30 participants.

Mindfulness is the skill to non-judgmentally observe emotions, sensations, or cognitions. Mindfulness is moment-to-moment awareness and is trained through meditation exercises that have been adapted from Buddhist traditions. Besides these meditation skills, yoga exercises and psycho-education are also part of the program.

A number of systematic reviews and meta-analyses suggest that mindfulness-based interventions are effective in chronic pain, anxiety, and depression.

Outcome measures

- Quality of life
- Hospitalization (related primarily to depression or to a medical problem)
- Suicides or suicide attempts

- Compliance with hemodialysis treatment
- Number of withdrawals from dialysis treatment
- Number of withdrawals from the treatment intervention
- Adverse events potentially attributable to the intervention or control treatment
- All-cause mortality

Outcome tools

Beck's Depression Inventory Score (BDI-II)

The BDI-II was developed in 1996 and was derived from the BDI.

The 21-item survey is self-administered and participants score themselves 0-3 using a list of four statements arranged in increasing severity about a particular symptom of depression. Higher total scores indicate more severe depression.

Nutritional Assessment

Nutrition screening, consisting of albumin, weight, percent of ideal body weight, and subjective global assessment (SGA). SGA is a validated measure of nutritional status.

Methods

Inclusion criteria

Patients age 18- 65 years diagnosed with depression and undergoing hemodialysis for ESRD.

Exclusion criteria

Bipolar affective disorder, psychosis (not treatable with medication), social anxiety (difficulty with being in a group situation), PTSD, suicidality (previous attempts), active alcohol or drug abuse/dependence, inability to speak English, patients previously exposed to MBSR.

Scherly Leon, MD, (@SLeonMD) is a second year nephrology fellow at SUNY Downstate. She is also policy fellow for the ASN and in the inaugural class of the Nephrology Social Media Collective Internship. She is passionate about patient education, health advocacy, policy, and disparities.

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PLEX versus HCO Dialyzer

Kenar D. Jhaveri, MD, describes his ideal clinical trial for treating cast nephropathy

<http://www.medpagetoday.com/Nephrology/DreamRCT/53862>

Hypothesis: Plasmapheresis (PLEX) or use of high cut-off (HCO) dialyzer will improve recovery of renal function in patients with cast nephropathy.

Introduction: Myeloma kidney is also known as light-chain cast nephropathy and is the most common cause of kidney impairment in patients with multiple myeloma.

How do you treat cast nephropathy?

Chemotherapy is the most effective, especially bortezomib (Velcade). Increasing fluid intake is another approach.

Nephrotoxic agents should be avoided when the free light chain (FLC) burden is high.

What About the Use of PLEX?

There have been three randomized trials and the results have been [mixed](#). Two of the trials, including the [largest one](#), were [negative](#). However, serum FLC was not used as a marker of response in any of the trials and kidney biopsy was not used to confirm the diagnosis in the largest study (biggest limitation). A [Mayo Clinic report](#) found a high rate of renal recovery (86%) when PLEX was combined with a bortezomib-based therapy, but others have found nearly as high rates of recovery with bortezomib therapy alone.

What About the HCO dialyzer?

The [HCO](#) dialyzer with molecular cutoffs as high as 45 kDa have been used to remove FLC. Extended hemodialysis with the HCO 1100 dialyzer (Gambro) permits continuous and safe removal of FLC in large amounts (1.7 kg of FLC was removed from one patient over a period of 6 weeks). [Randomized trials](#) are currently being conducted with HCO dialyzers in cast nephropathy, but no studies have been done in the most recent era of better chemotherapy agents.

What Would This Trial Entail?

Design: Randomized controlled trial (three arms)

Arm 1: Standard chemotherapy only

Arm 2: Standard chemotherapy plus PLEX

Arm 3: Standard chemotherapy plus high flux dialysis (HCO dialyzer)

Outcome Measures: Independence of HD at 3 months; change in glomerular filtration rate (GFR)

Secondary Outcome Measures: Efficiency of PLEX or HCO in respect to reduced free light chain levels, duration of HD from renal recovery, hospital days, death/mortality

Study Population: Patients with biopsy- proven cast nephropathy, dialysis-dependent renal failure, and de novo multiple myeloma

Inclusion Criteria: Age ≥ 18 years, dialysis-dependent acute renal failure, criteria for the diagnosis of symptomatic de novo multiple myeloma, abnormal serum FLC ratio, and, most important, biopsy- proven cast nephropathy

Exclusion Criteria: Chronic kidney disease (CKD) IV/V at baseline, prior history of multiple myeloma on chemotherapy, other biopsy findings (light chain deposition disease, amyloidosis, cryoglobulinemia, etc.), intolerance of HD due to cardiac status, or hemodynamics hematologic contraindications to PLEX

Kenar Jhaveri, MD, (@kdjhaveri), is an associate professor of medicine at the Hofstra North Shore Long Island Jewish School of Medicine in New York City. He is an onconephrologist, nephrology education researcher, and a clinician. His interests are in chemotherapy toxicities and paraproteinemias.

The Nephro-RULES AKI Study

When is the best time for renal replacement therapy?

<http://www.medpagetoday.com/Nephrology/DreamRCT/53861>

Goal: Determine the optimal timing of renal replacement therapy in acute kidney injury.

Summary: Acute kidney injury (AKI) is the most common reason for nephrology consultation and the optimal time to start renal replacement therapy (RRT) is currently unknown. Given that dialysis has been used for AKI for over 50 years, it is time that nephrologists better understand when to apply this tool.

In this trial, it is proposed that at least 2,000 patients are enrolled (see power analysis below). The idea is for a large number of nephrologists to enroll a small number of patients. For example, 500 nephrologists could enroll 4 patients each -- or 250 nephrologists enroll 8 patients each -- or some variation on that theme. With this strategy, enrollment could be completed in about a month for a fraction of the cost of a typical RCT of this size (see -- "Why nephrologist-driven" below).

This trial is proposed to be by nephrologists, for our patients. There is no PI, we are all the PI. It is an entirely different design -- and it is clearly time for something new in clinical trials in nephrology.

This proposal is for a nephrologist-driven randomized controlled trial of RRT with a Usual, Late, or Early Start in AKI (the Nephro-RULES AKI study).

Why study RRT timing in AKI?

When to start RRT in a patient with AKI is a fundamental question that nephrologists face on a daily basis. Nephrologists have been [pondering this question](#) for well over a half century and it is widely viewed as a [top research priority](#) in the field of AKI. Since the [first published randomized controlled trial](#) (RCT) of early versus later start RRT in AKI, published in 1975, only [404 patients TOTAL](#) have been enrolled in an early versus later start RCT. Since AKI is the most common reason for inpatient nephrology consultation, and RRT is a key tool in the treatment armamentarium, knowing when to apply that tool is fundamental to the practice of nephrology.

What should be studied? The primary endpoint is mortality at 90 days in patients with AKI in the intensive care unit (ICU). Kidney function recovery is a secondary endpoint.

Rationale: Mortality is the most important endpoint for patients and their physicians and should be the primary endpoint of the study, with the hypothesis being that earlier RRT reduces mortality. Thus, survival at 90 days is the primary endpoint (as in both the [ATN](#) and [RENAL](#) studies). Although the perception has long been that earlier RRT must be beneficial, one struggles to find an explanation of why that might be the case. As early as the 1950s it was observed that despite perfect control of uremic symptoms and electrolytes, patients with AKI [died](#) of something else such as sepsis and respiratory complications. And this frustrating situation continues to this day. Whether RRT can affect any of the systemic complications of AKI that lead to mortality is unclear -- and should be an underlying theme to such a trial. Thus, data collection will include complications associated with AKI such as sepsis, mechanical ventilation duration, vasopressor use, stroke, MI, and other relevant systemic complications. Probably the leading theory now regarding the potential benefit of early RRT relates to early control of volume, and the avoidance of fluid overload -- particularly since fluid overload is consistently

associated with increased mortality -- in patients with and without AKI. Thus, cumulative fluid balance at the time of RRT initiation will be assessed.

Kidney function recovery is either a primary or secondary endpoint in almost every study of RRT in AKI, and is proposed as a secondary endpoint in this trial. It is unclear what the appropriate hypothesis regarding benefit or harm of early RRT might be. Some have argued that early RRT might accelerate kidney function recovery due to presumed removal of renal toxic mediators, while others suggest that early RRT might delay kidney function recovery due to the consequences to hemodynamic instability due to RRT. To date, the data are mixed on which might be an appropriate hypothesis. For example, a [meta-analysis](#) found that there may be a benefit to early RRT, however the [largest RCT](#) of early versus usual RRT (n=208) found that kidney recovery was delayed in the early-start group by 2 days. Whether modality has an effect on kidney function recovery is hotly debated (with many suggesting that continuous therapies have advantages over intermittent) -- to date, this question has not been adequately answered and is an important research question -- but is not the proposed primary or secondary endpoint of this trial.

For our DreamRCT, all modalities of RRT will be considered as equal. Theoretical competing effects for benefit and harm exist for all modalities. For example, IHD may theoretically delay kidney function recovery, thus increasing mortality in the IHD arm. Antibiotic and other medication dosing is much less clear and poorly attended to in CRRT (especially CVVH), and thus underdosing of medications -- especially antibiotics -- may occur in CRRT and increase mortality in that group. These effects may be worthwhile to examine, however, the fundamental question proposed here is whether removal of "usual" uremic toxins (removed by both IHD and CRRT) impacts mortality in AKI.

How many patients (i.e., power analysis)? Assuming a baseline mortality of 50% and a 15% relative reduction in mortality (to 42.5%), 1,386 patients would be required to demonstrate 80% power with a two-sided α of 0.05. To account for drop out and other study related issues, a nice round number of 2,000 patients is proposed. This level of benefit and power calculation is analogous to the Veterans Affairs/National Institutes of Health ATN (Acute Renal Failure Trial Network) [trial](#) (n = 1,124), which was powered to detect an 18% relative reduction in mortality (from 55% to 45%), and the RENAL (Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy) trial (n = 1,508), which was powered to detect a

14% relative reduction in mortality (from 60% to 52%) with intensive RRT dosing. (Both studies found no mortality benefit with intensive RRT; because the power was robust, the results were convincing and the question of dose in dialysis is essentially put to rest.)

What is early? Early will be defined as a BUN less than 60 and a creatinine less than 4. Patients who require emergent dialysis will be identified and analyzed, but excluded from the early versus later group. Nephrologists will also identify their personal opinion regarding whether the dialysis was performed early, usual (optimal), late, or emergent.

Why nephrologist driven? On World Kidney Day 2013, 598 nephrologists voluntarily filled out a survey that essentially asked about their day. Of these 598 nephrologists, 310 nephrologists reported seeing patients that day. These 310 nephrologists saw a total of 1,500 patients with AKI, 415 of whom received RRT that day. Thus, with a minority of nephrologists reporting, more patients were seen by these nephrologists ON ONE DAY than in all of the RCTs of early versus usual RCTs COMBINED (i.e., 404 patients).

According to the "[U.S. Nephrology Workforce: Development and Trends](#)" report prepared for the American Society of Nephrology, as of April 15 2014, there were 9,006 nephrologists actively practicing in adult nephrology >20 hours per week who were primarily engaged in direct patient care. Thus, if 5% of practicing nephrologists participated and enrolled 5 patients each, 2251 patients could be enrolled -- quite likely in less than a month. Or, to reduce the workload, one patient could be enrolled per month for 5 months.

Thus, rather than a few centers attempting to enroll large numbers of patients over years, a large number of nephrologists could enroll a small number of patients over a short period of time. This has many advantages, 1) trial enrollment could be completed in months, 2) center effect (better outcomes at one center versus another, thus diluting results) would be eliminated, 3) the results would be widely applicable -- real nephrologists in real centers plus academic nephrologists, versus predominantly academic nephrologists, 4) cost would be dramatically reduced (see below). Often when trials costing 10s of millions of dollars are over, the PI publishes the result and the infrastructure goes away. Nephrologists won't be going away, and once trained could be utilized repeatedly to systematically answer all of the big questions in intensive care nephrology.

What would the nephrologist have to do? The following would be required of participating nephrologists 1) getting IRB approval, 2) learning to properly consent patients and

maintain appropriate study records (for those new to clinical research), 3) complete training for IRB and HIPAA, 4) consent patients for the study, and 5) collecting data. It is anticipated that IRB and study training would take approximately 8 hours; patient-related activities (consent and data collection) would take 1 to 2 hours per patient. Thus, assuming 4 patients to be enrolled, 16 hours – or two 8 hour working days would be required.

Although we all know that nephrologists are working hard these days, I believe that we as a group are passionate about our profession and that a sufficient number of us would be willing to commit to this novel, important project that would provide essential information to our field and to our patient's benefit.

Can nephrologists do this? My view of nephrologists as a profession is that they are thoughtful, detail oriented, notably conscientious, and ethical. Completion of this trial would rest on the competence of nephrologists to collect data accurately and perform with integrity. There is no doubt that nephrologists have the skills and disposition necessary to learn and complete the tasks required. The motives are for patient betterment and the advancement of the field of nephrology -- motives that are unlikely to be susceptible to breaches of integrity.

Timeline: 18 months to train nephrologists and get IRB approval, then 6 months for patient recruitment, then 3 months for final data entry. Total time: 2 years and 3 months.

Randomization: Centralized randomization, after the patient is consented, investigators would call a toll free number where the treatment allocation would be revealed.

Who will analyze the data? After the 2,000 patient mark is met, the data will be open to anyone who wants to look at it and analyze it. Although anyone could analyze it and publish in the journal of their choosing, the hope is that multiple researchers will analyze the data and post their results on the website created for the trial. Or their own blog, or on Twitter, or send it to someone else's blog, or anywhere that can be freely accessed and openly discussed. This will be our trial -- everyone has an opportunity to participate and own the trial and its results.

Who is the PI? There is no PI. Nephrologists are the PI. All participating nephrologists will be listed on the study website. For those who analyze the data and wish to publish in conventional journals, *Nephrologists*, with a weblink to their names, must be listed as the first author.

[Sarah Faubel, MD, \(@doc_faubel\)](#) is a professor of medicine at the University of Colorado and the Denver VA, chair of the ASN AKI advisory group, and does basic research in AKI. Her overall career goal is to improve AKI care and reduce its morbidity and mortality.

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Shedding Pounds Before Kidney Transplant

Hector Madariaga, MD, describes the Weight Reduction Prior to Kidney Transplantation (WREP-KT) Trial

<http://www.medpagetoday.com/Nephrology/DreamRCT/53860>

Question: Is weight loss beneficial for obese patients undergoing kidney transplantation?

Obesity (defined as a body mass index (BMI) >30 kg/m²) is a worldwide epidemic that results in increased morbidity and mortality. It costs the U.S. approximately \$147 billion annually in healthcare expenditures.

Many transplant centers in the U.S. require kidney transplant candidates to have a BMI <35 kg/m², although some consider higher BMIs depending on muscle mass (up to 40 kg/m²). While it is well-established that obesity contributes to poor cardiovascular health in the general population, obesity has been found to increase survival in dialysis patients. Therefore, nephrologists generally do not recommend weight loss for these patients since it could adversely affect them.

Patients face many barriers in losing weight to achieve this goal. Fitness programs, diets, and bariatric surgery all pose unique problems. For instance, many patients with end-stage renal disease (ESRD) have underlying coronary artery disease (CAD), essentially excluding them from elective bariatric surgery.

Despite these rules governing transplantation in obese individuals, the available evidence is conflicting and almost entirely retrospective. The aim of this proposal is to conduct a prospective, randomized trial to assess the effect of weight loss on kidney transplant outcomes. We will test whether weight loss with a fitness program plus diet or bariatric surgery is superior to usual treatment in the **Weight Reduction Prior to Kidney Transplantation (WREP-KT) Trial**.

Methods

Inclusion Criteria

>Age 18

Pre-emptive kidney transplant candidates, related living and deceased donors

Patients that have been on hemodialysis or peritoneal dialysis for more than 6 months

Patients with AVF/AVG

Patients with BMI >40 kg/m²

Exclusion Criteria

Patients with evidence of active CAD

Patients with malignancy or life expectancy less than 1 year

Patients with tunneled hemodialysis catheters

Patients with contraindications to bariatric surgery

Patients who cannot exercise (e.g., amputation, severe osteoarthritis)

Patients with prior bariatric surgery

Uncontrolled diabetes ($A1c > 8$)

Primary endpoints

Delayed wound healing

Delayed graft function

1-year graft survival

Secondary endpoints

Perioperative complications

Allograft rejection (cellular or antibody-mediated)

Hospital length of stay

Randomization

Expected number of patients to be recruited: 500

Intervention

Patients will be randomized into three arms:

1. **Fitness Program:** Patients will be provided with an individually tailored exercise program, monitored by a fitness trainer, and attend a weekly weight loss group lead by a behavioral health psychologist and a nutritionist. The goals of this program will include changing eating patterns, eating healthy/making good choices, and identifying triggers to overeating, as well as support from group members.
2. **Bariatric surgery:** Patients that qualify and are good candidates for bariatric surgery (restrictive, malabsorptive, or combination procedures) will also be enrolled. After 10 months, post-bariatric surgery patients will be selected for kidney transplant surgery.
3. **Control Group:** Treatment as usual (patient will be provided with information about weight loss programs and plans without direct supervision).

Kidney transplant recipients will have their appropriate evaluation in transplant clinic and will be evaluated by transplant surgeons, transplant nephrologists, psychologists, dietitians, and social workers. Patients will be encouraged to lose weight for a target BMI of $< 40 \text{ kg/m}^2$. This could be achieved either by enrolling in a fitness program, bariatric surgery (which will be analyzed in a subgroup analysis), or a typical approach for weight loss.

Living related and deceased donor recipients will be included. Induction protocols will be at the discretion of the transplant center, as will as maintenance immunosuppression. Perioperative complications will be monitored such as wound dehiscence, delayed graft function, acute rejection, infection rates, etc.

Patients will be followed up with in the first year at months 1, 3, 5, 8, and 12 and then every 4 months. Surveillance protocol biopsies will be at the discretion of the transplant center, but will be recommend at month 1 and 6 after surgery.

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Acidosis in CKD Treatment Now Study (ACT Now)

Matthew Sparks, MD, describes his dream nephrology clinical trial

<http://www.medpagetoday.com/Nephrology/DreamRCT/53859>

Approximately 20% of patients with substantial chronic kidney disease (estimated glomerular filtration rate [eGFR] of 1,529) have metabolic acidosis. According to a few small trials, treating metabolic acidosis in advanced chronic kidney disease (CKD) with sodium bicarbonate improves nutritional markers and slows progression to end-stage renal disease (ESRD). This is an inexpensive therapy that could offer huge benefits to patients with CKD. One way of adding alkali to the diet is increasing consumption of fruits and vegetables. Additionally, by providing the alkali with fruits and vegetables, patients would avoid the sodium load inherent in bicarbonate or citrate therapy.

Western diets have a high ratio of acid-inducing-base-inducing proteins, the latter being mostly fruits and vegetable. Since interventions aimed at correcting acidosis are either diet-based or over-the-counter, it is unlikely that a large randomized clinical trial will ever be sponsored by pharma. However, if you review the results (see table below) of these smaller studies and imagine that the investigators were targeting a novel biologic molecule, then drug companies would be

pouring millions of dollars into a well designed clinical trial. Therefore, I propose this as my DreamRCT (Of note, there is a planned RCT in the U.K. called the BiCARB study group).

Study Author/Journal/Year	Intervention	# of patients	Outcome
de Brito-Ashurst et al JASN 2009	RCT- CKD (CrCl 15-30) oral sodium bicarb vs st. care	134	Slower progression to ESRD Improved nutrition
Phisitkul et al KI 2010	CKD Cohort with control group sodium citrate vs none	59	Slower decline of eGFR
Mahajan et al KI 2010	CKD with preserved eGFR sodium bicarb sodium chloride vs placebo	120	Slower decline of eGFR
Goraya et al KI 2012	CKD preserved eGFR/CKD reduced eGFR stand care vs sodium bicarb vs fruits and vegetables	79/120	less albuminuria in fruit and vegetable groups (similar to bicarb) vs stand care.

Primary Study Question:

Does treating mild acidosis with either sodium bicarbonate or a diet rich in fruits and vegetables impact total mortality in patients with advanced CKD (eGFR of 1,530)?

Methods

Primary Outcome:

- Total mortality
- Secondary Study Question:
- Does treating mild acidosis result in delay in initiation of renal replacement therapy (RRT) for ESRD or result in an improved quality of life (QOL)?

Secondary Outcome:

- RRT for ESRD

- Albuminuria hospitalization
- QOL score
- Cost of care analysis

Inclusion Criteria:

- >age 50
- CKD with creatinine based eGFR <30 using CKD-Epi equation documented on two visits >6 months apart
- Serum bicarbonate <22 mmol/L

Exclusion Criteria:

- Acute kidney injury
- Planned to start RRT within next 3 months
- Decompensated heart failure
- Already on sodium bicarbonate therapy
- Terminally ill
- Active treatment for malignancy
- Acute diagnosis of primary glomerular disease with active biologic therapy or
- Immunosuppressive therapy

Intervention

Randomization:

Expected number of patients to be recruited: 3,000

Patients will be randomized into three arms:

1. Sodium Bicarbonate Group: Patients will be provided with sodium bicarbonate tablets 500 mg TID to be taken throughout study.
2. Fruits and Vegetable Group: Fruits such as apples, apricots, oranges, peaches, pears, raisins, and strawberries were predominantly provided. Vegetables such as carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes, and zucchini will be provided to participants on a weekly basis. q6 month classes will be held to discuss recipes and tips for increasing consumption. q6 month food diary for all participants. Furthermore, dietary acid load will be calculated as described in this paper.
3. Placebo Group: Placebo with rescue therapy with oral sodium bicarbonate at a level of 16 mmol/L.

Potential Adverse Effects:

The data safety monitoring board would review the results of the trial every 6 months. Potential adverse effects include difficulty taking large pills (pill burden), high blood pressure, and volume overload from sodium content of sodium bicarbonate therapy. Other adverse events such as nausea, vomiting, bloating, etc., will be monitored. Potential for hyperkalemia in the fruit and vegetable group will be monitored closely. If hyperkalemia develops (>5.5 mmol/L), then diet will be altered and patient will be moved to either placebo or oral sodium bicarb group.

Matthew Sparks, MD, (@Nephro_Sarks) is an assistant professor of medicine at Duke University Medical Center and staff physician at the Durham VA Medical Center, both in Durham, N.C. He is the associate program director of the nephrology fellowship training program and director of medical student research.

The NO DUH Trial

Is loop diuretic use in ESRD really safe?

<http://www.medpagetoday.com/Nephrology/DreamRCT/53858>

Diuretics, predominantly loop diuretics such as furosemide, have been widely used in the treatment of patients with various states of fluid overload for 50 years. The ability to short circuit the ascending loop of Henle is one of the most powerful, renal-specific tools nephrologists have. The effective use of diuretics in advanced kidney disease presents a unique clinical setting. Loop diuretic efficacy in advanced chronic kidney disease (CKD) is governed by dose, continuous versus bolus administration, side effects, underlying disease state, and diuretic resistance. Patients with markedly reduced renal function require high dose diuretics.

Diuretic resistance worsens as renal function is lost and can be attributed to multiple factors including:

- Reduction in renal blood flow
- Reduced proximal tubule transport of the loop diuretic
- Increased single nephron expression of the BSC-1 transporter in the thick ascending limb of the loop of Henle
- Increased single nephron expression of the TSC transporter in the distal tubule
- Neurohormonal upregulation
- Impaired gut absorption

These and other effects require higher and higher doses to achieve the same effect.

While higher doses of loop diuretics in renal patients are readily accepted, they are not without risks. Much of the risk has been described by our cardiology colleagues, and includes neurohormonal activation, systemic vasoconstriction, electrolyte disturbances, ototoxicity, worsening renal function, and worsening mortality. A recent study by Michael Felker, the DOSE trial, examined different diuretic dosages and administrations in the treatment of patients with acute decompensated heart failure. Interestingly, the investigators did not observe a change in symptoms or length of stay regardless of dose or administration choice, however, continuous diuretic infusion showed a trend towards increased net fluid loss. This trend was also associated with worsening renal function. The study was not powered to examine rehospitalizations or mortality and many questions still remain unanswered in this population, which included patients with mild to moderate kidney disease.

But what about patients on dialysis? Within the dialysis space, the data on loop diuretics is mixed. Some researchers have described a benefit in removing excess fluid, but the central question of whether it preserves or damages residual renal function is largely unknown. An observational study by Bragg-Gresham utilizing the DOPPS database found a trend towards improved mortality in diuretic use in hemodialysis patients with preserved residual renal function. But the data is not robust. This is a question important enough that it demands the truth that only a properly done randomized controlled trial can provide.

Fluid overload is a well-known and major contributor to rehospitalization and mortality in patients with end stage renal disease (ESRD). The management of these patients presents a significant challenge due to the accumulation and re-accumulation of fluid in patients who are largely oliguric and anuric. As a result, dialysis providers have intensely focused on strategies to minimize unnecessary fluid gains such as limiting salt and fluid intake, utilizing lower sodium dialysate baths, telehealth strategies, bioimpedance devices, disease education, etc. Among these strategies, loop diuretics are frequently used despite the lack of conclusive data.

My DreamRCT, the NO DUH Trial -- No-Diuretics versus Diuretics for Euvolemia in Hemodialysis Trial -- is designed to determine if loop diuretics improve global symptoms, readmissions, length of stay, and mortality in hemodialysis patients.

Additional outcomes include drug side effects (ototoxicity), intra-dialytic weight gain, cardiac adverse events (left ventricular hypertrophy, arrhythmias), and other meaningful

secondary outcomes. We would use three arms to also answer some of the fundamental questions about loop diuretic dose and response in ESRD. Are we, by administering high dose diuretics, exposing our patients to more harm than good by only considering urine output and the treatment of edema? What about other considerations? What happens to residual renal function? Does neurohormonal upregulation have untoward consequences? Is there an opportunity to standardize such diuretic strategies and show predictable reductions in total healthcare spending? Are we truly improving outcomes such as rehospitalization and death? In my mind, this would be an intriguing and practical study on a class of medications we have long taken for granted.

The NO DUH Trial is a three-arm, double blind, placebo control, multi-center trial. All patients receive education on the importance of maintaining stable weight, minimizing fluid gain. They would all be prescribed a standard sodium dialysis bath. They would receive dietary counseling and follow-up encouraging salt fluid restrictions. Then they would be randomized to one of three groups.

1. Placebo
2. Diuretic 1: Furosemide at 80 mg twice a day but then titrated up to maximize urine output (up to 500 mg per day) without going below a doctor established "dry weight." Investigators would be encouraged to keep these patients euvolemic based on clinical judgment.
3. Diuretic 2: Furosemide at 80 mg twice a day with no adjustment for urine output or renal function.

Enrollment criteria:

- New onset hemodialysis patient
- No kidney transplants
- Patient undergoing 3 days a week in-center hemodialysis
- Urine output of at least 360 mL a day
- Consent
- No comorbidities resulting in a projected life span of less than 3 months

Patients would be randomized to the three arms at a 2:1:1 ratio so that half of the patients receive diuretics and then the two different diuretic strategies would be tested.

Outcomes:

- Time until first hospitalizations (could be surrogate for mortality)
- Number of hospitalizations and length of stay

- Quality of life
- Intradialytic weight gain
- Residual renal output
- Neurohormonal measures (Baseline, 6 months, 1 year): renin levels, aldosterone levels, endothelin-1, catecholamines
- Blood pressure
- Number of blood pressure medications
- Dose decrease or increase of blood pressure medication dose
- Echocardiogram (Baseline, 1 year)

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Putting Oral Potassium Binders to the Test

Graham Abra, MD, describes the Potassium in hemodialytic Death (PhD) Study

<http://www.medpagetoday.com/Nephrology/DreamRCT/53857>

The recent publication of trials involving two new oral potassium binders has increased attention on hyperkalemia. Although sodium polystyrene has long been part of the anti-hyperkalemia arsenal, data on its efficacy in lowering serum potassium are thin (nicely covered [here](#) by Joel Topf). In addition, data on its impact in reducing the incidence of hyperkalemia-associated arrhythmias and sudden cardiac death (SCD) are nonexistent.

In contrast, both of the novel oral potassium agents, patiromer and ZS-9, have now convincingly demonstrated they can lower serum potassium in pre-dialysis chronic kidney disease patients.

These agents do not yet have published trails detailing their use in hemodialysis patients who frequently experience hyperkalemia. As such, we are entering into a brave new era of potassium management -- a crossroads of mechanistic and evidence-based medicine.

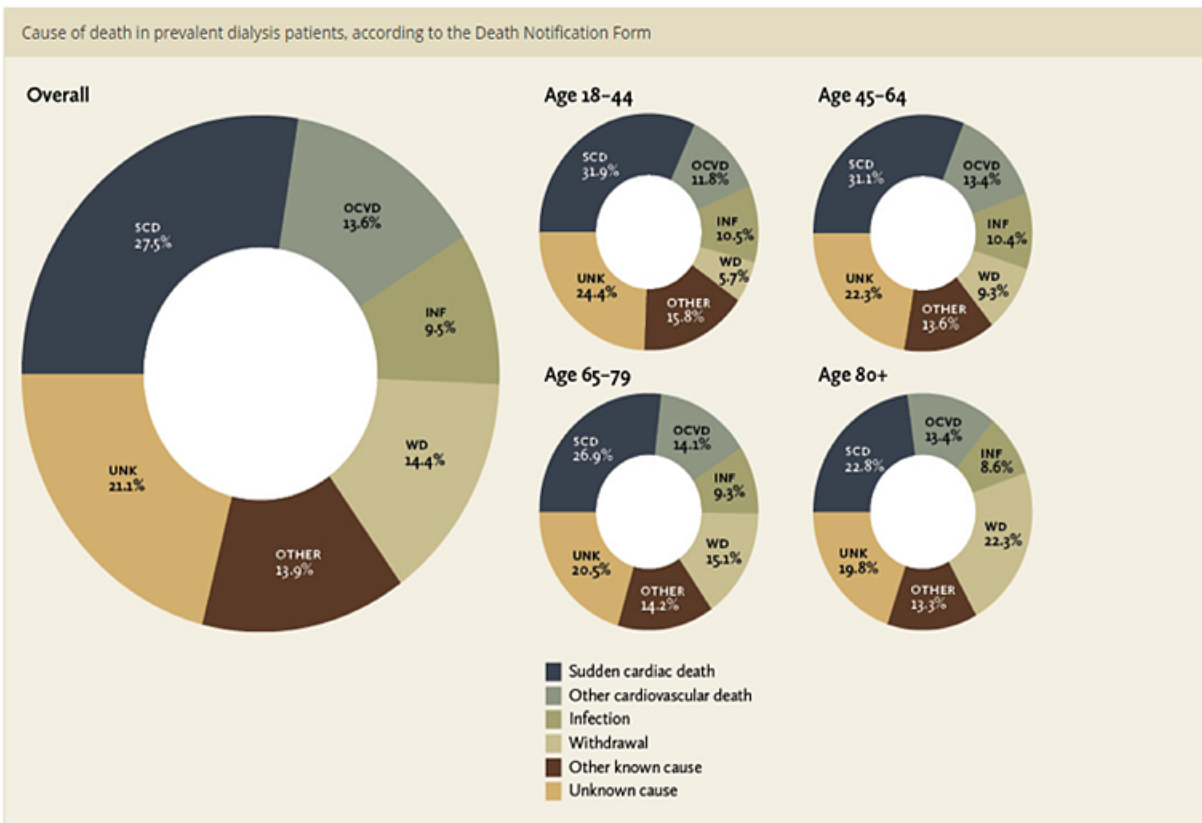
For the dialysis and nephrology communities, this represents a huge opportunity to potentially impact a risk factor for SCD. The danger is that we would allow the phosphorous binder debacle to occur once again, allowing a class of drugs that change a blood test to become standard of care without showing that they impact outcomes that are important to patients. As the opening salvo, I give you the Potassium in hemodialytic Death (PhD) Study.

Background

Cardiovascular events are the leading cause of death for patients on dialysis. Among the subtypes of cardiovascular events, SCD is the most common in both incident and prevalent patients, accounting for approximately one in every four deaths. This is nicely illustrated in the PEER data, showing the breakdown by cause of death in prevalent dialysis patients in aggregate and by age category. Regardless of age, SCD is always the leading cause of death, but accounts for larger fractions in the younger age groups.

The rate of SCD in patients on dialysis is 25- to 49-fold higher than the general population. Unfortunately, the mechanisms behind this are poorly understood. One potential contributing

factor in hemodialysis patients is hyperkalemia.

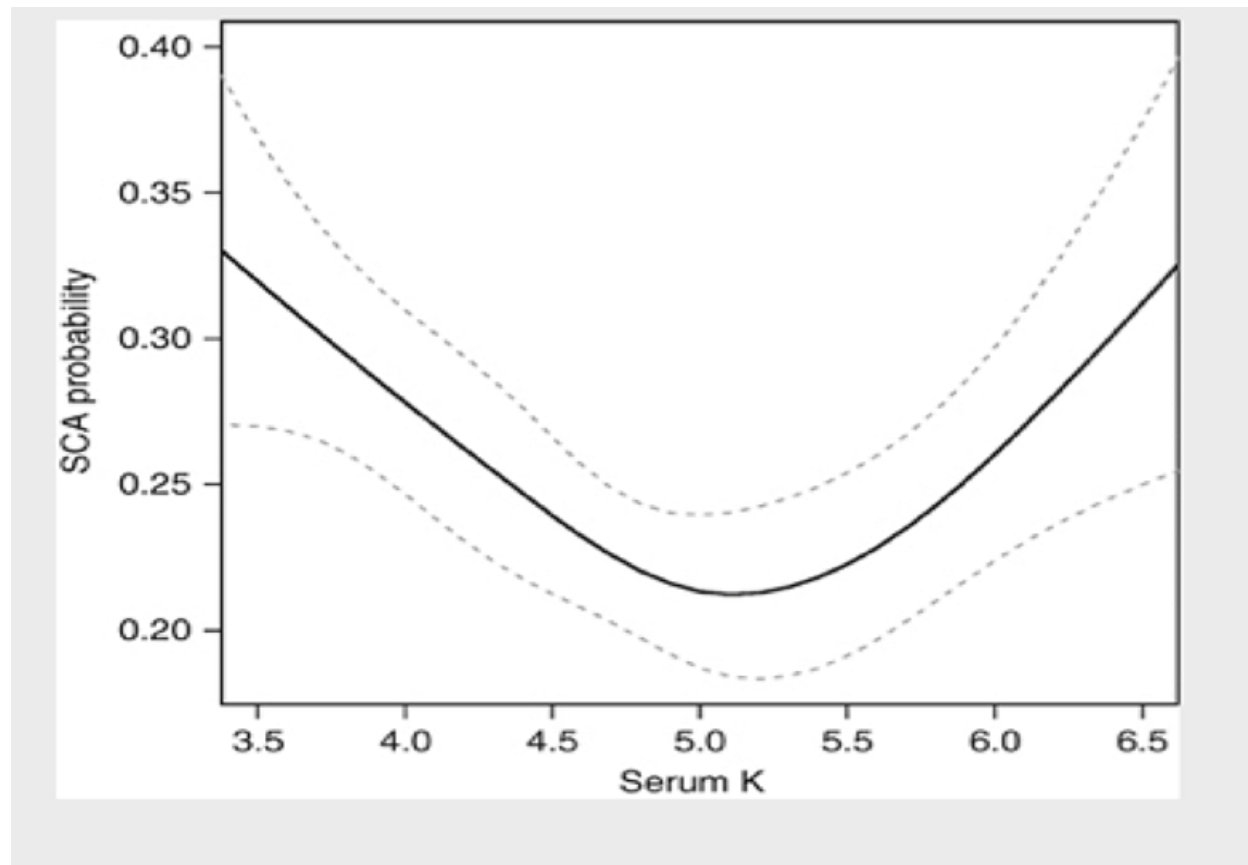


Observational data have shown that both lower and higher serum potassium are associated with mortality in hemodialysis patients. As an example, a U-shaped relationship between pre-dialysis serum potassium and witnessed sudden cardiac arrests can be seen in the data from Patrick Pun, MD, MHS, and colleagues, which examined 502 hemodialysis patients who had SCD matched against controls.

The study by Pun and colleagues additionally examined the impact of the dialysate potassium concentration on sudden cardiac arrests. They found that regardless of pre-dialysis serum potassium, the risk of sudden cardiac arrest was higher when patients were dialyzed on a <2 meq/L potassium bath, although the confidence intervals began to overlap above a pre-dialysis potassium of 5.6 meq/L. A number of other studies have also found associations between low dialysate potassium concentrations and poor outcomes.

Additionally, large associative studies have found an increased risk of SCD associated with the first treatment after the 2-day interdialytic interval and in the hours immediately preceding and after the treatment. These time-frames are ones in which hyperkalemia and subsequent rapid

serum potassium change are most likely to be present, although a number of other potentially deleterious factors are likely present as well, such as volume overload.



Given the above, reducing the pre-dialysis potassium to a more physiologic range through use of an oral potassium binder might reduce the need for low potassium dialysate, minimize large potassium swings, and could ultimately lower the rate of SCD in hemodialysis patients.

Methods

In my DreamRCT, one of the novel potassium binders would be studied in randomized, single-blinded placebo controlled fashion in prevalent hemodialysis patients with average (3 months) serum potassium levels of >5.5 meq/L. Patients would be matched based on age, sex, race, and average baseline potassium.

To make the application of results practical, study drug, dialysate prescription, and nutritional counseling would be adjusted to target a baseline serum potassium between 4.5-5.5 meq/L during a run-in period in a step-wise fashion. This would be a single-blinded study allowing investigators to adjust dose of the study drug in advance of other changes to achieve the

target baseline potassium. Subsequent modifications to the above would be at the discretion of the treating nephrologist to maintain serum potassium in the target range.

Potassium would be measured once a month or more frequently based on standard dialysis center protocol and treating nephrologist's preference. This measure would be intended as a practical replication of what typically can and does occur in practice. We want to avoid a study that uses a monitoring protocol that could never be practically achieved.

The primary outcome would be SCD as adjudicated by a study panel using predefined SCD criteria. Secondary outcomes would include hospitalization for hyperkalemia, hospitalization for arrhythmia, new arrhythmia diagnosis, and questionnaire-defined potassium intake. Changes in dialysate potassium prescription would be recorded at defined intervals throughout the study.

Cross-sectional nutritional intake surveys would be administered at defined intervals specifically designed to evaluate approximate potassium intake. Adverse medication events including GI events, hypokalemia, and hypomagnesemia would be tracked.

We need to hold the pharmaceutical companies that produce novel oral potassium binders to a high standard as these drugs enter the marketplace. Kayexalate has been on the market for decades without any data on its impact on hard clinical outcomes -- we don't want to look back in 2025 and see that we've wasted our chance to rigorously study these new agents.

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CLARITY for Albuminuria's Role in T2D

Jordan Weinstein, MD, describes his ideal clinical trial on reducing urinary albumin

<http://www.medpagetoday.com/Nephrology/DreamRCT/53856>

In nephrology -- as in life -- bias sets in gradually and insidiously over time. It must be removed by force because if bias is left unchecked, we run the risk of papering over a weak

foundation and an unproven hypothesis with flawed clinical trials and retrospective analysis that all produce conflicting results. This could set a specialty back by a decade or more.

Over the past several years, nephrologists have been called upon to engage in serious soul searching over one of its most ingrained tenets -- the importance of urinary albumin as a predictor and mediator of renal outcomes, and perhaps as a biomarker for extrarenal diseases. While it would go beyond the scope of this introduction to my proposed Dream RCT to review the database of this area in great detail, the state of proteinuria and its utility in clinical medicine can be summarized by the following:

- Proteinuria exceeding 1 g per day predicts and possibly mediates further deterioration in renal function over time, shortening renal survival. It is tempting to conclude, and likely remains sound, to purposefully reduce urinary protein with angiotensin-converting-enzyme (ACE) inhibition or angiotensin system blockade to levels below 1 g as a specific goal of care. Further reduction in urinary protein might require immunotherapy or disease-modifying treatments where applicable.
- The appearance of urinary protein as low as the microalbumin level (far below the 1 g per day threshold) in the context of cardiovascular disease, with or without diabetes, is likely associated with adverse cardiovascular outcomes, though not necessarily adverse renal outcomes. Purposeful reduction of urinary protein which begins below 1 g per day has never been associated with reversal of the adverse outcomes associated with its discovery. In other words, microalbuminuria is, at best, a predictor of cardiovascular disease, but not a mediator.

After the completion of several RCTs ([ALTITUDE](#), [VA Nephron-D](#), [ONTARGET](#), [ASCEND](#), [ROADMAP](#), [ACCOMPLISH](#)), we learned that the reduction of proteinuria -- the same proteinuria that predicted a poor cardiovascular prognosis -- was associated with no improvement in important patient outcomes. My own interpretation of these findings informs my clinical decisions today. I will aim to reduce urinary protein to levels below 1 g per day. Once that has been achieved, and assuming that patients are taking an ACE inhibitor or angiotensin II receptor blocker (ARB), but not both, and assuming blood pressure has been controlled, I stop.

But what about residual albuminuria? Do we simply acknowledge but ultimately ignore this finding? Or is there any role for further reduction and, if so, how do we do it? The answer to this question has far-reaching implications. It might allow physicians to de-escalate therapy if there is no role for further reduction of albuminuria, or it might allow a further and safe reduction in residual risk by selecting the correct strategy.

Having spoken to many colleagues in nephrology, there is palpable anxiety about leaving patients with residual albuminuria, in part because of deeply ingrained bias, but also because we are not replacing an intervention, which admittedly might not be helpful (and is possibly harmful), with anything better.

My own bias is that there is no role for purposeful reduction in urinary protein below 1 g per day once a patient is on a stable dose of an ACE inhibitor or ARB, and once adequate blood pressure (BP) control has been achieved. But to clarify this matter and hopefully exorcise bias, I propose the CLARITY trial, for ReduCtion in aLbuminuriA for the ReductIon In MortalTY.

Hypothesis: Reduction in urinary albumin by escalating dosages of an ARB or by combination therapy of ARB plus eplerenone can reduce residual renal and cardiovascular risk associated with ongoing albuminuria in patients with type 2 diabetes.

Inclusion criteria: Patients >age 18 with type 2 diabetes on either an ACE inhibitor or ARB with a PCR of 500 mg/g to 1,000 mg/g at enrollment.

Design: Patients with proteinuria between 500 mg and 1 g per day and glomerular filtration rate (GFR) 45-60 ml/min will be randomized in open-label fashion to one of two groups:

- "Usual care," using patients' enrollment with ACE inhibitor or ARB. BP is maintained <130/80 mm Hg by any means except by increasing ACE or ARB.
- Escalation of patients' enrollment with ACE or ARB by forced titration until PCR falls to 200 or less, or until it does not respond to two consecutive titrations. The physician may optionally add eplerenone to attempt further reduction in albuminuria. In order to prevent hyperkalemia as a cause for withdrawal from the study, all patients are prescribed the potassium binder, Patiromer. Additional medications other than ACE inhibitors, ARBs, or aldosterone blockers may be added to maintain BP <130/80 mm Hg.

Follow-up: Patients continue on study protocol for 5 years.

Primary Outcomes: Doubling of serum creatinine, end-stage renal disease (ESRD), or death.

Secondly Outcomes: Composite of myocardial infarction, coronary revascularization, sudden death, or stroke.

Jordan Weinstein, MD, (@UKidney) is an assistant professor of medicine at the University of Toronto and the director and founder of UKidney. He is the co-creator of DreamRCT.

The SONNET Trial for Social Media

Nikhil Shah, DO, MPH, discusses his ideal study of technology-enhanced learning

<http://www.medpagetoday.com/Nephrology/DreamRCT/53855>

The amount of medical literature published is exploding beyond any one individual's ability to keep up. This becomes especially difficult for nephrology trainees, and for that matter other subspecialty trainees, that need to both learn the fundamentals and the newest developments in their chosen field. Resources to help nephrology training include textbooks, journals, review courses, and online electronic media like *UptoDate*. New to this list of resources are social media sources such as chats, blog posts, and tweets.

Social media offers advantages such as currency, approachability, and two-way interaction. Social media excels at immediate post-publication peer review, long before letters to the editor are ever published.

There is an active nephrology social media community distributed around the world that is continuously disseminating evidence-based knowledge in the form of blogs, tweets, newsletters, online games, and organized chats.

The disadvantage of social media is similar to the problems afflicting mainstream publications -- there are innumerable sources of information and barriers to the collection, collation, and organization of this information into a cohesive format.

Some in medical education are folding social media into formal training programs. This [technology-enhanced learning \(TEL\)](#) is increasingly used in the forms of apps, simulations, and social media. But there is little data to support the idea that systematic exposure to social media will make a difference in the knowledge, enthusiasm, and competence of trainees.

One contentious issue is the term "enhanced" in TEL. Some argue that these "enhanced" tools are no better than traditional teaching.

ADVERTISEMENT

Another issue is how these techniques are assessed for their value in a [post-graduate learning](#).

Table 1 Uses of technology for learning and links to educational theory

	Use of technology		
	m-learning	Simulation	Social media
Examples	Apps (eg, medical calculators and drug reference); 'adds' (eg, monitors)	Surgical procedures; team training	Wikis (eg, Wikipedia); microblogs (eg, Twitter); content (eg, YouTube)
Settings	Workplace, close to patients (point-of-care)	'In situ' or in simulation labs	Varied locations including home and public areas
Possible educational purposes	Decision-making, problem-solving	Skills development; task performance, team work	Communication, reflection, knowledge creation
Learning	Abstract conceptualisation (Kolb ²³); reactive learning (Eraut ²⁴)	Concrete experience and active experimentation (Kolb ²³); deliberative learning (Eraut ²⁴)	Reflective observation (Kolb ²³); implicit, reactive and deliberative learning (Eraut ²⁴)

2

Bullock A, Webb K. *Postgrad Med J* 2015;0:1–5. doi:10.1136/postgradmedj-2014-132809

Table 1. A categorisation of the reviewed interventions involving technology for teaching and learning.

Nature of intervention or study	Article(s) involving this form of intervention
1. Replicating existing teaching practices (9 studies)	
a. Replicating an element of conventional teaching for delivery to students using some form of technology	Connolly et al. (2007), Delialioglu and Yildirim (2008), de Grez, Valcke, and Roozen (2009), Hui, Hu, and Clark (2007), Lorimer and Hilliard (2008), Neumann and Hood (2009), Stephenson, Brown, and Griffin (2008), Woo et al. (2008)
b. Comparing differing technologies for delivering the same material or resources to campus-based or distance learners	Griffin, Mitchell, and Thompson (2009)
2. Supplementing existing teaching practices (23 studies)	
a. Making available versions of existing course materials/resources/tools that students can access and use whenever they want	Copley (2007), Cramer et al. (2007), Dalgarno et al. (2009), Evans (2008), Fernandez, Simo, and Sallan (2009), Lonn and Teasley (2009), Swan and O'Donnell (2009), Taylor and Clark (2010), Tynan and Colbran (2006)
b. Adopting or developing additional learning resources or tools for students to use	Cubric (2007), Demetriadis et al. (2008), Elgort, Smith, and Toland (2008), Hramiak, Boulton, and Irwin (2009), Kerawalla et al. (2009), de Leng et al. (2009), McLoughlin and Mynard (2009), Murphy and Ciszewska-Carr (2007), Ng'ambi and Brown (2009), Sorensen et al. (2007), Wheeler and Wheeler (2009), Wyatt et al. (2010), Xie, Ke, and Sharma (2008), Zorko (2009)
3. Transforming the learning experience (structural changes) (15 studies)	
a. Redesigning learning activities or substantial parts of modules to provide active learning opportunities for students	Coller and Scott (2009), Cooner (2010), Dalsgaard and Godsk (2007), Hakkarainen, Saarelainen, and Ruokamo (2007), Hemmi, Bayne, and Land (2009), Herman and Kirkup (2008), Lee, McLoughlin, and Chan (2008), Torney and Henchy (2008)
b. Investigating how TEL activities could most effectively promote qualitatively richer learning among students	Bailey and Card (2009), Chen, Chen, and Tsai (2009), Downing et al. (2007), Kanuka, Rourke, and Laflamme (2007), Kirkwood (2006), Melrose and Bergeron (2007), Thorpe (2008)

Table 2. A categorisation of how *enhancement* was conceived in the accounts of technology interventions reviewed.

Conception of 'enhancement'	Article(s) exhibiting this conception
1. <i>Operational improvement</i> (6 studies)	
a. Increased flexibility (5 studies)	Copley (2007), Ng'ambi and Brown (2009), Taylor and Clark (2010), Tynan and Colbran (2006), Woo et al. (2008)
b. Improved retention (1 study)	Connolly et al. (2007)
2. <i>Quantitative change in learning</i> (32 studies)	
a. Improved engagement or time spent on learning task (10 studies)	Coller and Scott (2009), Cubric (2007), Dalsgaard and Godsk (2007), Downing et al. (2007), Kirkwood (2006), Neumann and Hood (2009), Ng'ambi and Brown (2009), Sorensen et al. (2007), Tormey and Henchy (2008), Tynan and Colbran (2006)
b. More favourable perceptions or attitudes (e.g., higher ranking of satisfaction or importance) (24 studies)	Coller and Scott (2009), Connolly et al. (2007), Cooner (2010), Copley (2007), Cramer et al. (2007), Dalgarno et al. (2009), de Grez, Valcke, and Roozen (2009), Delialioglu and Yildirim (2008), Elgort, Smith, and Toland (2008), Evans (2008), Fernandez, Simo, and Sallan (2009), Griffin, Mitchell, and Thompson (2009), Hakkarainen, Saarelainen, and Ruokamo 2007, Hui, Hu, and Clark (2007), Lonn and Teasley (2009), Sorensen et al. (2007), Stephenson, Brown, and Griffin (2008), Swan and O'Donnell (2009), Taylor and Clark (2010), Tormey and Henchy (2008), Tynan and Colbran (2006), Woo et al. (2008), Wyatt et al. (2010)
c. Improvement in test or assessment scores (14 studies)	Connolly et al. (2007), Cramer et al. (2007), Cubric (2007), Dalgarno et al. (2009), Dalsgaard and Godsk (2007), de Grez, Valcke, and Roozen (2009), Delialioglu and Yildirim (2008), Demetriadis et al. (2008), Griffin, Mitchell, and Thompson (2009), Hui, Hu, and Clark (2007), Lorimer and Hilliard (2008), Neumann and Hood (2009), Stephenson, Brown, and Griffin (2008), Swan and O'Donnell (2009)

Table 2. (Continued.)

Conception of 'enhancement'	Article(s) exhibiting this conception
3. Qualitative change in learning (28 studies)	
a. Deeper learning or understanding/ higher order thinking processes and skills (16 studies)	Coller and Scott (2009), Connolly et al. (2007), Cooner (2010), de Leng et al. (2009), Demetriadis et al. (2008), Hakkarainen, Saarelainen, and Ruokamo 2007, Hemmi, Bayne, and Land (2009), Kirkwood (2006), Lee, McLoughlin, and Chan 2008, McLoughlin and Mynard (2009), Stephenson, Brown, and Griffin (2008), Thorpe (2008), Tormey and Henchy (2008), Wheeler and Wheeler (2009), Wyatt et al. (2010), Xie, Ke, and Sharma (2008)
b. More reflection/critical awareness by students (6 studies)	Connolly et al. (2007), Cooner (2010), Herman and Kirkup (2008), Hramiak, Boulton, and Irwin (2009), Kerawalla et al. (2009), Xie, Ke, and Sharma (2008)
c. Improved student interactions in online discussion and/or collaborative activity (13 studies)	Bailey and Card (2009), Chen, Chen, and Tsai (2009), Downing et al. (2007), Elgort, Smith, and Toland (2008), Hemmi, Bayne, and Land (2009), Kanuka, Rourke, and Laflamme (2007), de Leng et al. (2009), Melrose and Bergeron (2007), Murphy and Ciszewska-Carr (2007), Neumann and Hood (2009), Thorpe (2008), Wheeler and Wheeler (2009), Zorko (2009)
d. Sharing of experiences (related to professional practices) (2 studies)	Chen, Chen, and Tsai (2009), Kerawalla et al. (2009)

Note: When multiple forms of enhancement were identified for a study, that study appears in more than one category above.

Question: In the SOcial media iN Nephrology Education and Training (SONNET) trial, we ask if systematic supplementation of local nephrology program education by a Nephrology Social Media Internship running concurrently improves the confidence and knowledge of first-year nephrology fellows versus those fellows who do not receive systematic exposure.

Inclusion criteria: All nephrology fellows joining in the first year of their nephrology training in North America.

Exclusion Criteria: Fellows who decline participation.

Randomization: 1:1 randomization to Nephrology Social Media Internship in addition to regular training versus regular training only.

Intervention:

Provisions

- Curated biweekly list of most important discussions on social media
- Regular contributions to websites/blogs ([Renal Fellow Network](#), [AJKD Blog](#))
- Exclusive access to specialized websites, such as [UKidney.com](#), which continuously curate nephrology content

All the resources available to fellows randomized to internship during the first year will be freely available to all participants in the trial at the end of first year. The change in the assessment parameters between the first and second year will then be evaluated

Assessments of Fellows/Quantitative Data

- Website traffic analysis
- Analysis of student-generated contributions online
- Analysis of quantity of online interactions
- Module assessment grades -- both groups will receive quarterly evaluations in the form of online examinations set by the trial investigator (e.g., 25 questions in American Board of Internal Medicine [ABIM] format) and an annual examination at completion of 1 and 2 years (completion of fellowship, e.g., 100 questions ABIM format)
- Attitude Scale and self-reported surveys -- Fellows self-evaluation of self-confidence and competence

All fellows will be followed up at 2 years and 5 years after graduation

Primary Outcomes: Outcomes of module assessment grades and final examinations and fellows self-reported surveys at 1 year and 2 years.

Secondary Outcomes:

- Number of research papers/abstracts, posters presented
- Survey of satisfaction and enthusiasm for nephrology

- Additional fellowships pursued (transplant, research, dialysis, hypertension, interventional nephrology)

Nikhil Shah, MBBS, DNB, (@dr_nikhilshah) is a nephrologist and Home Dialysis Fellow at the University of Alberta. He is a prolific curator and occasional creator of nephrology social media content. He is part of the inaugural class of #NSMC Interns.

The NoLoNaMo Trial

Unlocking the mysteries of altered osmolality

<http://www.medpagetoday.com/Nephrology/DreamRCT/53853>

In June of 1986, the two lead articles in the *NEJM* were on hyponatremia. The first, by [Arieff](#), reported a series of women who developed cerebral edema following acute postoperative hyponatremia. The second, by [Sterns](#), reported on the development of osmotic demyelination following rapid correction of chronic hyponatremia. Those two case series, published 30 years ago, still define the modern management of hyponatremia. How can it be that the most common electrolyte disorder's management is governed by a pair of decades-old case series?

Various studies have reported the incidence of hyponatremia. In a prospective study [Anderson and Schrier](#) found that patients had a 1% risk of developing hyponatremia ($\text{Na} < 130$ mmol/L) every day they were in the hospital. More recently, [Hoorn](#) showed that 30% of hospitalized patients had a sodium less than 136 mmol/L at least once during their hospitalization.

Combining the above epidemiology and the [CDC facts on U.S. hospital utilization](#) results in some startling numbers: using a 1% incidence, there should be 1.6 million cases of hyponatremia developing every year. Using Hoorn's prevalence, this back-of-the-envelope calculation yields 10.5 million U.S. hospitalizations complicated by hyponatremia.

Given how common hyponatremia is, one might expect our care to be based on extensive and deep use of the scientific method. Nope. The management of hyponatremia rests in an evidence wasteland with little prospective data. We are still using the lessons of those twin case series from 1986. When randomized trials have been done, like in [SALT 1 and 2](#) by Schrier, they



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Original Articles		Case Records of the Massachusetts General Hospital	
Hyponatremia, Convulsions, Respiratory Arrest, and Permanent Brain Damage after Elective Surgery in Healthy Women	1529	An 86-Year-Old Woman with Anemia, Elevation of the Erythrocyte Sedimentation Rate, and a Pelvic Mass	1564
ALLEN I. ABRER		STUART E. LIND AND DEBRA A. BELL	
Osmotic Demyelination Syndrome Following Correction of Hyponatremia		Editorial	
RICHARD H. STERN, JACK E. RUGG, AND SYDNEY S. SCOGGHEE, JR.	1535	Therapy of Hyponatremia: Does Haste Make Waste?	
ROBERT G. NARIN		1573	
Intrauterine Infection with Varicella-Zoster Virus after Maternal Varicella		Sounding Board	
SEARON G. PARVANI AND ANN M. AVAYO	1542	Selling Surgery	
CURTIS E. MARON		1575	
Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure: Results of a Veterans Administration Cooperative Study		Massachusetts Medical Society	
JAY N. COHN AND OTHERS	1547	1576	
Special Articles		Correspondence	
The Cost Implications of Academic Group Practice: A Randomized Controlled Trial		Importance of Confirmatory Tests after Strongly Positive HTLV-III Screening Tests	
DAVID I. COHEN, DANIEL BRESLAW, DAN K. PORTER, HAROLD I. GOLDBERG, NEAL V. DAVISON, CHARLES O. HERSHEY, JAK-CHEE LAY, CHRISTINE E. McCLARIN, AND NAOMI BRESLAW	1553	1577	
Protection or Peril? An Analysis of Firearm-Related Deaths in the Home		Another Whippel-like Disease in AIDS	
ARTHUR L. KULLERMAN AND DONALD T. REAY	1557	1578	
Medical Intelligence		Prevention of AIDS: Lessons from Older Risk Factors in Children and Early Atherosclerosis	
Acquisition of Genital Herpes from an Asymptomatic Sexual Partner		1579	
JAMES F. ROONEY, JAMES M. FLEISCH, JEREMY M. OUKROV, AND STEPHEN E. STRAUS	1561	1581	
Special Report		Disseminated Herpes Zoster or Varicella Following Herpes Zoster: Restriction-Endonuclease Digestion Analysis	
Adverse-Drug-Reaction Monitoring		1582	
GERALD A. FISCH		1583	
		Verapamil, Syncope, and Hypertrophic Obstructive Cardiomyopathy	
		1584	
		Bypass	
		1585	
		Affirmative Action in Medical Schools	
		1584	
		Book Reviews	
		1585	
		Notices	
		1588	

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have universally studied the endpoint of the change in the sodium concentration rather than patient oriented outcomes like falls, seizures, death, or mental status changes. The entire field has accepted the lessons of those two trials of 1986:

The only thing that matters in hyponatremia is:

How low

How fast it fell

How fast it is corrected

The last time hyponatremia was shaken up this was the number one song (U.K. charts).

A recent review by Lee et al looked at all of the RCTs done on the treatment of hyponatremia and found 21. All but three of them examined ADH

antagonists, as drug companies do the necessary studies to get their products approved. This is concerning as these drugs are used in a slim minority of cases of hyponatremia, meaning that the vast majority of hyponatremia is treated without the benefits of prospective data but simply based on dogma, animal studies, and mechanistic infernal. Adding to the lack of insight in hyponatremia is that all 21 randomized controlled trials used a change in sodium (or some related measure) as the primary outcome.

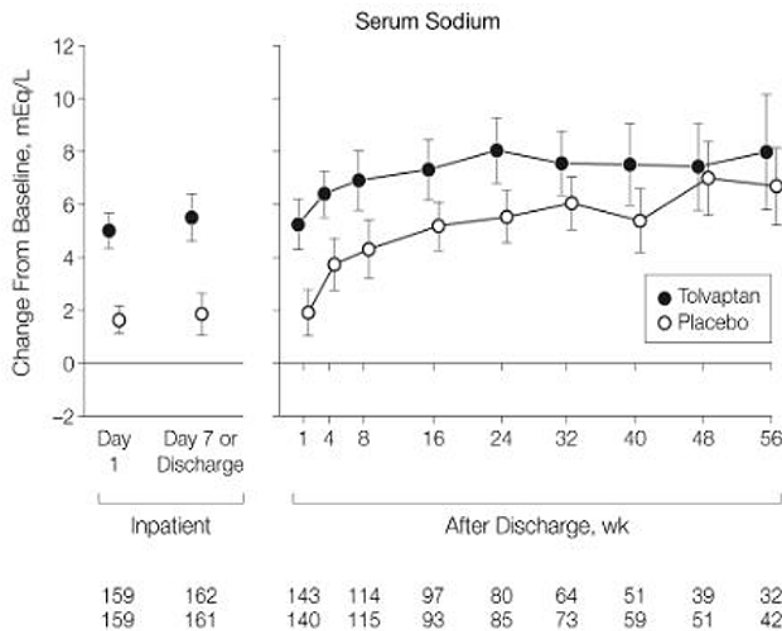
Nowhere in the realm of hyponatremia research have we demonstrated, with prospective data, that low sodium is dangerous and that correcting that dangerously low sodium improves patient well-being. Despite a lack of prospective data, there are clearly cases of acute severe hyponatremia where patients are seizing, and giving them hypertonic saline causes an immediate improvement in patient outcome. Let's dispense with this straw man immediately. No one is interested in, nor would it be ethical to consider, a placebo-controlled trial in the management of

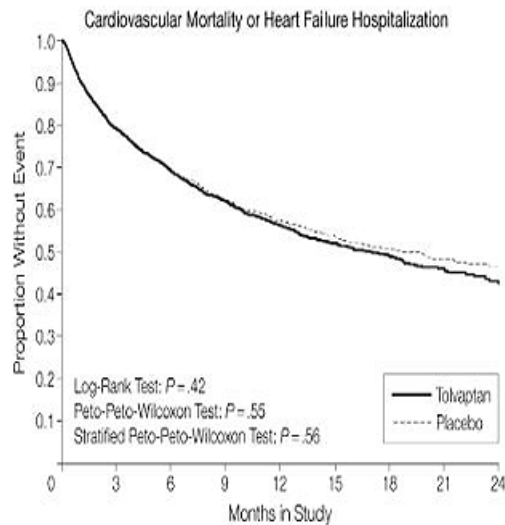
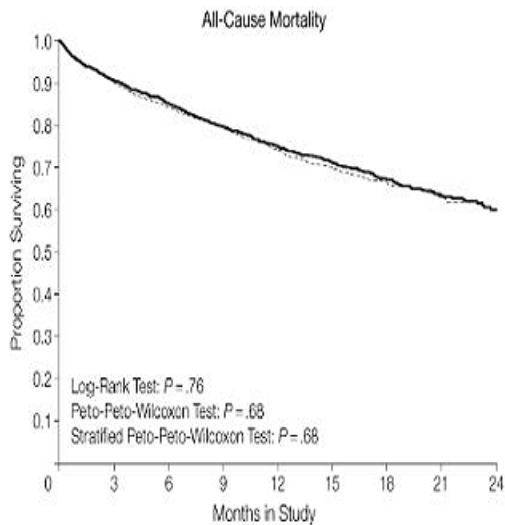
cerebral edema due to hyponatremia, especially given the highly effective therapies available. This is [the RCT and the parachute story](#). I am curious about the much larger population of apparently asymptomatic patients with mild hyponatremia.

There is extensive retrospective data that shows that this mild hyponatremia is clinically significant. It is clearly a bad prognostic marker for [heart failure](#), [cirrhosis](#), [ST-elevation MI](#), [pulmonary hypertension](#), and [pulmonary embolism](#). It is also an independent risk factor for the fascinating triad of [falls](#), [osteoporosis](#), and [fractures](#). This is not disputed. Additionally, the wizards of epidemiology have statistically shown that it is the [hyponatremia itself that is problematic](#) and the low sodium is not just a correlate. But all of the statistics in the world are unable to answer the simple and essential question.

Does fixing the sodium fix the patient?

One of the most concerning threads saying no, there is no benefit to treating this mild hyponatremia, comes from the [EVEREST trial](#). This was not a trial of hyponatremia (though 1,110 patients had a sodium less than 137), but of heart failure. In this trial patients were randomized to tolvaptan or placebo during hospitalization for acute decompensated heart failure. Patients took 30 mg of tolvaptan or placebo for a median of 8 months, and not less than 60 days. Despite having a measurable impact on the serum sodium, there was no improvement in mortality, hospitalization, or quality of life with the increased sodium.





No. at Risk	0	3	6	9	12	15	18	21	24
Tolvaptan	2072	1812	1446	1112	859	589	404	239	97
Placebo	2061	1781	1440	1109	840	580	400	233	95

This held true even for the patients who started with a baseline sodium below 137 mmol/L. Fall rates were not reported, but dizziness was actually more common in the tolvaptan group despite the higher serum sodium.

My DreamRCT

It is time to start using the most powerful tool in science to unlock some of the mysteries of one of the commonly encountered problems in medicine, altered osmolality. My randomized controlled trial: NoLoNaMo (No hyponatremia Modification).

My question is does the treatment of mild, apparently asymptomatic, hyponatremia make a snots worth of difference. To examine this we would enroll hospitalized patients with hyponatremia. They would be randomized to either active management where the goal would be essentially standard of care, i.e., interventions to bring the sodium up to 135 mmol/L prior to discharge. The experimental group would be given no specific treatment to raise their sodium. Discharge would not be protocolized and if patients in the control group were discharged at a sodium < 135 mmol/L, that would be acceptable. We would have a rescue intervention so that

patients who develop symptoms or, whose sodium drifts below 125, would be treated until the symptoms abated and the sodium rose above 125.

Because the significance of hyponatremia likely varies due to the etiology of the hyponatremia, we would block randomize patients so that CHF, cirrhosis, SIADH, and volume depletion would be equally distributed across the two groups.

The crux of the study, however, would not be the inpatient outcomes, because I suspect there would be little difference and most of the questions on the importance of mild hyponatremia occurs in the outpatient realm. After discharge, both groups would be followed up in clinic, for the patients in the control group, they would continue to get interventions to maintain a normal sodium; the placebo group, however; would followup primarily to track outcomes, but no attempt would be made to control their sodium, unless it fell below the safety threshold of 125. Bone mineral density would be performed as soon as possible after discharge and at the conclusion of the study.

The outcomes would be mortality, hospitalization, quality of life, falls, bone mineral density, and cost of care. Analysis would be by intention-to-treat, with a goal of finding non-inferiority of no treatment to treatment. This study has the potential to, if positive, dramatically reduce the cost of inpatient care by stopping the practice of correcting mild hyponatremia before discharge. If correction of hyponatremia is beneficial, we would have a new tool to help patients with a variety of problems achieve better outcomes.

This study needs to be done; we have been wandering in the uncertain depths of our internal ocean for too long.

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The PANIC Trial

Contrast nephropathy: Is it real?

<http://www.medpagetoday.com/Nephrology/DreamRCT/53866>

Contrast-induced acute kidney injury (CI-AKI) is a widely recognized phenomenon. But in recent times, there has been a question as to whether it *even truly exists* in

relation to modern IV contrast used for CT imaging. The evidence for a causal relationship is remarkably scarce and consists largely of observational studies and meta-analyses, and while this has led to ongoing debate as to the existence of CI-AKI, common clinical practice behaves as though it is a definite recognized entity.

AKI for any reason is associated with increased mortality, and while this may be a causal relationship or in certain cases more a reflection of baseline co-morbidities, we certainly want to avoid AKI wherever possible. That said, the fear of CI-AKI may cause clinicians to avoid IV contrast in situations where its use may lead to more timely diagnosis, more effective care, and ultimately decreased overall mortality -- with or without AKI. The consideration of CI-AKI impacts decisions on a daily basis in hospitals. If a patient has any renal insufficiency -- whether acute or chronic -- the tendency is to avoid contrast, either by getting a noncontrast CT (which is usually diagnostically inferior for patients in whom contrast enhanced imaging is the initial test of choice) or by avoiding CT altogether, where the presumption is that noncontrast CT would likely be too nondiagnostic to be of any management value. A clinician may even choose to delay a contrast study in order to allow time for "prehydration" or other tactics to reduce the risk of CI-AKI.

Prior studies that focused on quantifying the incidence of CI-AKI have shown conflicting results. Two more recent studies have often been cited; the first by [Davenport et al](#) looked at 20,242 CT scans and concluded that contrast administration was an independent risk factor for AKI in patients with pre-administration creatinine > 1.6 mg/dL. Their definition of AKI was an increase in serum creatinine of 50% over baseline or an increase of 0.3 mg/dL or more (KDOQI AKI Stage 1). Another study was a large meta-analysis in 2013 by [McDonald et al](#), which found no significant difference in the incidence of AKI, dialysis, and death in contrast-exposed and non-exposed groups. To date, there have been no randomized trials that link IV contrast and AKI in a causal manner. However, in the analyses of the large bodies of observational data to date, it would appear CI-AKI is a rarer phenomenon that is appreciated -- if it exists at all.

The DreamRCT I propose -- Prospective Assessment of Nephropathy due to Intravenous Contrast: a Randomized Controlled (PANIC) Trial -- would aim to describe the true incidence of contrast nephropathy. The inclusion criteria would be populations who are classically at risk for CI-AKI: those with pre-existing chronic kidney disease stage 3b-4. If CI-AKI exists, this is where

it will be found. I would enroll subjects at their baseline state of health. One would be hard pressed to randomize patients to contrast or no contrast in the acute setting where contrast is needed to make critical diagnostic and management decisions.

Subjects would be randomized to receiving IV contrast and not receiving IV contrast. No scan need be done. Serum creatinine would be measured pre-exposure and daily for up to one week post-exposure. In this setting, a rise in creatinine is also far less likely to be due to alternative explanations for AKI, which are numerous in hospitalized patients. It would be fair to continue to use the laboratory definition of AKI of >1.5-fold increase or >0.3 mg/dL increase in serum creatinine. While this can lead to greater spurious diagnosis of AKI at higher baseline creatinine levels, the effect should be comparable across both trial arms.

This trial would be a first step. It does not, however, replicate the clinical scenario where patients are getting contrast enhanced CT scans for diagnostic purposes in the setting of an acute illness, the nature of which is frequently uncertain. But if we show in a randomized controlled trial that IV contrast has no nephrotoxic potential in otherwise healthy CKD patients, then it can pave the way for more definitive, clinically convincing studies that answer tough clinical questions. Does the morbidity/mortality from possible nephropathy outweigh the morbidity/mortality that comes from delayed or missed diagnosis? Is post-contrast AKI "just a number" or does it have real implications for morbidity/mortality? Is it possible for a contrast CT to "push" an advanced CKD patient into needing dialysis? Is it possible for a contrast CT to obliterate the remaining renal function of dialysis patients who still make urine?

It's amazing that for so long we've not had an RCT answering the most basic question -- is there such a thing as contrast nephropathy? And even if the answer is yes, then the next question is, what does it all mean? Ultimately, the bottom line has to do with the safety of IV contrast, weighed against the risk of delayed or missed diagnosis. Of the two, the first is the more straightforward component to pursue; the latter is extremely variable and it would be impossible to design feasible trials without first having a better understanding of the true risk of IV contrast.

So there you have it. Contrast nephropathy... is it real, or just a #DreamRCT?

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How to Quash Kidney Stones

David Goldfarb, MD, discusses his ideal clinical trial for recurrent calcium phosphate stones

<http://www.medpagetoday.com/Nephrology/DreamRCT/53867>

Calcium phosphate stones are common, making up about 15%-20% of all calcium stones. The definition of such stones is usually a stone with at least 50% calcium phosphate or more.

Most often, calcium phosphate appears in the form of hydroxyapatite, the crystal found in bone. Other calcium phosphate crystals include brushite and carbonate apatite. The latter sometimes implies the presence of urinary tract infection, which should be sought and ruled out.

The cause of calcium phosphate stones is often obscure, but is most often related to an unexplained high urine pH level. While this high urine pH, in association with calcium stones, may be related to [incomplete renal tubular acidosis](#), that diagnosis is not often made as it requires ammonium chloride loading, a test that is not often performed in the U.S.

Such patients would often have hypocitraturia. At present, the difference between calcium oxalate and calcium phosphate stone formers appears to simply be the difference in urine pH, without convincing evidence that the difference is dietary or genetic.

In [a recent study](#), calcium phosphate stones were seen in young women in particular. Predominant calcium phosphate stones should also lead to consideration of primary hyperparathyroidism, though calcium oxalate stones are actually more common in that disorder. Carbonic anhydrase inhibitors, such as acetazolamide and topiramate (Topamax), are also [associated with increased urine pH and calcium phosphate stones](#) due to the ensuing bicarbonaturia.

Treatment of calcium phosphate stones is controversial because the use of citrate is not backed by any trials. Of course, nonspecific stone prevention regimens must be prescribed before considering the appropriateness of citrate supplementation. Increased fluid intake to 96 oz (about 3 L) is always appropriate. Dietary sodium restriction to 100 mEq (about 2.5 g) may help reduce urine calcium excretion.

When I give a talk on kidney stones, the question most often asked is whether citrate administration is associated with calcium phosphate stones and how calcium phosphate stones should be treated. This controversy about the use of alkali is long-standing.

Citrate binds calcium, forming a soluble complex, and prevents oxalate and phosphate from binding to calcium. One can think of citrate as a competitive antagonist of calcium stone formation. Citrate also prevents aggregation and agglomeration of crystals. These effects are not reflected by an effect of citrate on the urinary supersaturation of calcium salts. In addition, alkali often reduces urinary calcium excretion, an effect which is attributed to reduction of bone turnover and to stimulation of calcium absorption in the distal tubule.

However, citrate is metabolized by the liver and kidney via a process which consumes a proton, the equivalent of generating bicarbonate. The result is an increase in urine pH. As urine pH increases, monobasic phosphate (with one negative charge) in the urine has a proton titrated off, forming the dibasic phosphate with two negative charges. The two negative charges make the molecule very favorable for pairing with the divalent cation, calcium. This increase leads to an increase in the supersaturation of calcium phosphate.

In other words, while citrate in the urine may antagonize calcium stone formation, whether oxalate or phosphate, it also will lead to an increase in urine pH which might instead increase forces favoring calcium phosphate stone formation.

Background

The clinical evidence is slight. Some anecdotal studies demonstrate that renal tubular acidosis is effectively treated with alkali. In a series of patients treated for renal tubular acidosis (RTA), [Vardaman M. Buckalew Jr., MD](#), wrote that "it has long been recognized that alkali is beneficial for patients with Type I RTA." He also stated that "reluctance to use alkali therapy for renal stones was probably due to concerns over the effect of increased urine pH to increase the relative saturation ratio of brushite."

Affected patients may benefit particularly because they have a low serum bicarbonate and hypocitraturia, but the urine pH is certainly elevated to begin with. In another [nonrandomized study](#) of citrate for RTA-associated stones, the favorable effect was a 91.2% reduction in new stones from before to after treatment for 34 months (13.1 per year to 1.2 per year). Urine pH rose

from 6.5 to 7.0, urine citrate from 292 to 494 mg/day, and the relative saturation of brushite did not change.

In addition, [a study](#) of citrate administration to calcium stone formers separated patients into those whose urine pH went up to greater than 6.5 with citrate administration and those whose urine was lower than 6.5. There was no difference in the effectiveness of citrate for stone prevention in these two groups, regardless of whether urine pH went up or not. Of course these were not exclusively calcium phosphate stone formers so the result might not apply as nicely if that was the included population. However, some proportion of the study group is likely to have had calcium phosphate stones, and certainly the formation of calcium phosphate stones might have negated the effect of the citrate.

One safe way to administer potassium citrate to calcium stone formers might be to also prescribe thiazides to reduce urine calcium excretion. This regimen might allow the practitioner to feel safer about the prescription of the citrate and the concomitant increase in urine pH, as the fall in urine calcium would help reduce the increase in supersaturation resulting from the increase in urine pH.

The Trial

My dream RCT is not difficult then to imagine. Patients with recurrent calcium phosphate stones would be included. A history of at least two stones would be preferred. Patients with low serum bicarbonate at baseline would be excluded, as would patients with estimated glomerular filtration rates below 60 ml/min/1.73m².

Baseline noncontrast, low-dose CT scans would be performed in all participants. Twenty-four hour urine collections on the patients' self-selected diets would be performed.

The participants would then be randomly assigned to one of two regimens:

- Counseling regarding sodium restriction and fluid intake plus two placebo tablets twice a day (control group)
- 20 mEq of potassium citrate twice a day plus counseling regarding sodium restriction and fluid intake (active intervention group)

Twenty-four hour urine collections would be performed yearly as would repeat CT scanning. All stone episodes, including emergency room visits, urological interventions, and

spontaneous stone passage would be recorded. The patients would do a yearly stone episode questionnaire.

At the end of 3 years, the primary outcome -- the recurrence of new stones -- would be assessed, summing the results of monitoring for both asymptomatic and symptomatic stones.

David Goldfarb, MD, (@weddellite) is professor of medicine & physiology and clinical chief of nephrology at New York University Langone Medical Center in New York City. He has had three CaOx monohydrate stones.

Do Steroids Really Alter Outcomes in AIN?

Gearoid McMahon, MBBCH, describes a trial to see if steroids benefit patients with acute interstitial nephritis

<http://www.medpagetoday.com/Nephrology/DreamRCT/53868>

Much of what we do in nephrology is unfortunately not based on the best quality evidence due to a lack of randomized trials. This is particularly the case in the treatment of drug-induced interstitial nephritis, where there has been a longstanding debate about how to diagnose the disease and whether or not the patients should be treated with steroids.

Acute interstitial nephritis (AIN) is characterized by infiltration of T-cells, macrophages, and eosinophils into the interstitium with associated acute tubular injury. It presents as acute kidney injury (AKI) after exposure to an offending drug. Previously, the most common inciting drug was methicillin, but now it is more likely to see AIN associated with nonsteroidal anti-inflammatory drugs (NSAIDs) or proton-pump inhibitors.

Clinically, patients have AKI and typically will have some combination of a maculopapular rash, eosinophilia, and urine sediment with white cells, white cell casts, and occasionally eosinophiluria. Unfortunately, these findings are not consistently seen and, as a result, a renal biopsy is required to make a definitive diagnosis.

However, because the majority of patients with presumed AIN will spontaneously recover, most do not undergo a kidney biopsy. Thus, any study that includes only patients with biopsy-proven AIN will generally include patients who did not recover quickly after removal of the

offending drug. This is important to remember as it influences how you should think about the results of these studies.

Contradictory Findings

Most of the studies of steroids in AIN are in a very small number of patients and are very old. Two more recent retrospective studies provide what is probably the best evidence that we have. However, they completely contradict each other.

The first from [Michael Clarkson, MD, and colleagues](#) was a single-center, retrospective study of patients (n=60) with biopsy-proven AIN. More than half (60%) of the patients received steroids and there was no difference in outcomes between those who were treated with steroids and those who were not.

However, the median creatinine at the time of presentation was 7.6 mg/dl and 58% required acute dialysis. Clearly, this is not representative of the typical patient with AIN in the hospital setting where <10% will generally require dialysis acutely.

The second study by [Esther Gonzalez, MD, and colleagues](#) was a multicenter retrospective study of the use of steroids for AIN. In this study, 52/61 patients received steroids and the rate of long-term dialysis was lower in the patients treated with steroids relative to those who were not.

The authors additionally claimed that earlier treatment was better based on a lower final creatinine in those treated in the first 7 days after presentation.

Again, there are considerable limitations to this study. The control group was very small and there was no information given as to why they did not get treated with steroids. Second, there is a selection bias -- patients who were biopsied earlier -- and thus treated earlier -- were more likely to do better. However, it is likely that those who were biopsied late were already doing worse; they were not recovering early and were therefore biopsied for that reason.

Thus, although these findings provided support to those who claim that steroids are effective, they should be looked at with a very critical eye.

My DreamRCT

I propose a proper randomized trial of patients with drug-induced AIN to determine if steroids really alter outcomes.

All patients with AKI due to suspected AIN should undergo a renal biopsy in the absence of specific contraindications. Given the fact that the clinical criteria for AIN are not well defined currently, this would mean that many patients who did not have AIN could potentially have biopsies. This can be justified because currently, the definition of AIN is generally clinical and biopsies would provide valuable information about the accuracy of clinical AIN diagnosis, and possibly providing clinical correlates of AIN for better diagnosis in the future.

All patients would consent to retention of biological specimens including urine, blood, and DNA for potential future biomarker studies. The risk associated with kidney biopsy is low with modern ultrasound-guided techniques. The rates of major bleeding (requiring intervention or transfusion) are about 1%-3%. Rates of loss of kidney are between 1/500 to 1/1,000 while mortality is <1/5,000. Thus, kidney biopsy is relatively safe and this can be justified if there is potentially going to be some alteration in care based on the biopsy findings.

AIN would be adjudicated by two independent nephrologists. Biopsies would be scored for the percentage of the interstitium with active inflammation, the percentage interstitial fibrosis, and the prevalence of underlying disease including glomerulosclerosis and arteriosclerosis.

Patients with biopsy-proven AIN would be randomized 1:1 to steroid (1 mg/kg prednisone to a maximum of 60 mg daily) for 2 weeks followed by a taper over 2 months.

The primary outcome of this study would be dialysis dependence at 3 months. Assuming a 10% reduction in dialysis dependence (15% to 5%) and a 10% drop-out rate, the total number of patients required in each group would be 204 for a total of 408 individuals. This would clearly need to be a multicenter trial given the relatively low incidence of this disease. Secondary outcomes would include change in creatinine between peak and final (at 3 months) and the percentage of individuals with a final creatinine <2mg/dl.

Clinical Trial Criteria

There are specific criteria that a clinical trial should meet in order to be valid:

Social and clinical value: The study is designed to answer a specific question: Are steroids useful in the treatment of AIN? Even if the study is negative, it will provide valuable information.

Scientific validity: The study design of an RCT with an adequate sample size is sufficient to provide a definitive answer to the question as to whether or not steroids can be used to treat AIN.

Fair participant selection: All patients presenting with AKI >18 years will be eligible for inclusion. This will increase the generalizability of the results.

Favorable risk-benefit ratio: The major risk of this study is the routine use of kidney biopsy in individuals who would be less likely to get a biopsy under normal circumstances. However, with modern techniques, the rate of complications should be very low.

Gearoid McMahon, MB BCH, (@gearoidmm) is a nephrologist at the Brigham & Women's Hospital in Boston. His research interests include the genetics and epidemiology of chronic kidney disease. He is the editor of the [Renal Fellow Network](#).

Single-Agent Rituxan in Lupus Nephritis

Paul Sufka, MD, describes the Role of Rituximab only in Lupus Nephritis (RoRo-LuN) trial

<http://www.medpagetoday.com/Nephrology/DreamRCT/53869>

There may be fewer knowledge gaps in the intersection between nephrology and rheumatology than other areas of our specialty. The two conditions in this area that carry the highest burden are antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and lupus nephritis.

For ANCA-associated vasculitis, we are fortunate to have well-performed RCTs on the use of rituximab (Rituxan) for [induction of remission and maintenance](#), as well as [treatment of relapses](#). We have also made recent advances in our understanding of therapies for induction of lupus nephritis, with studies looking at the role of tacrolimus as [monotherapy](#) or as part of a [multitarget therapy](#) regimen along with mycophenolate mofetil (MMF).

Still, one of the biggest questions rheumatologists and nephrologists have regarding lupus nephritis is why the heck doesn't rituximab seem to work in bigger RCTs?

My entry for DreamRCT

RoRo-LuN (Role of Rituximab only in Lupus Nephritis): Previous studies looking at the role of rituximab for the treatment of lupus nephritis have been highly criticized for poor design. Initial data from the RITUXILUP group (rituximab and IV methylprednisolone on days 1 and

15 with background MMF (CellCept), but no oral steroids) have been extremely promising, but many patients cannot tolerate MMF, and the role of rituximab as monotherapy given over 6-month intervals will remain uncertain.

RoRo-LuN would randomize patients with biopsy proven class III or IV lupus nephritis to one of three arms to be followed over 2 years:

- Group 1: Rituximab without oral steroids (rituximab 1 g on weeks 0 & 2, 26 and 28, 52 and 54, 78 and 80; IV methylprednisolone 1 g on weeks 0 and 2)
- Group 2: Same as group 1, but with the addition of tapering oral steroids over 6 months
- Group 3: Standard therapy (initial pulse steroids, MMF, tapering oral prednisone)

The primary endpoint would be renal remission defined as normal creatine or return to baseline creatinine, inactive urinary sediment, and urine protein/creatinine at 0.5.

Background

Despite clinical experience by clinicians and promising reports in many smaller studies, larger RCTs have not shown effectiveness of rituximab against lupus and lupus nephritis. However, these studies have been extensively criticized for their trial design as the reason for failures.

The first of the larger RCTs evaluating the role of rituximab in lupus was the [EXPLORER trial](#), which looked at patients that did not have renal involvement. This trial randomized 257 patients with moderate-severe SLE, on one background immunosuppressive (methotrexate, azathioprine, or MMF, with 57% of patients corticosteroid dependent) to rituximab infusions or placebo at a ratio of 2:1 on days 1, 15, 168, and 182.

The primary endpoint was the effect of achieving and maintaining clinical response at week 52, assessed using the British Isles Lupus Assessment Group (BILAG) disease activity index. The primary endpoint was not met in EXPLORER trial, which was criticized for having a small number of participants, confounding background immunosuppressives, and raising questions with regard to the ability of BILAG to detect a meaningful clinical response.

The [LUNAR trial](#) looked at 144 patients with class III or IV lupus nephritis being treated with MMF and corticosteroids, and randomized them 1:1 to receive rituximab or placebo on days 1, 15, 168, and 182. The primary endpoint was a 20% superior renal response in the rituximab group at week 52. Again, the primary endpoint was not met, although overall response

rates were 56.9% in the rituximab group compared with 45.8% in placebo. Failure to meet the primary endpoint was attributed to faulty design due to background immunosuppressives confounding any benefit of rituximab. In addition, the trial was underpowered.

Interestingly, 78-week [follow-up data to the LUNAR trial](#) did suggest that rituximab had a longer term effect, with improvements in the proportion of patients who had remission of proteinuria and fewer patients who required additional immunosuppression.

In LUNAR, the exploratory data demonstrated that at week 52, the difference (10%) in the proportion of patients with 50% reduction in proteinuria favored rituximab treatment; the difference increased to 17% at week 78 ($P=0.04$). The other compelling suggestion of a benefit is the finding that significantly ($P<0.01$) fewer patients in the rituximab group required cyclophosphamide for worsening disease, and more achieved a renal domain BILAG C score that was sustained up to 78 weeks.

The ongoing [RITUXILUP trial](#) hopes to avoid oral steroids entirely in patients with class III/IV or V lupus nephritis, while determining whether rituximab is an effective therapy when added to maintenance MMF. In this regimen, patients are given two doses of rituximab (1 g) and methylprednisolone (500 mg) on days 1 and 15, and maintenance treatment with MMF, compared to standard therapy using initial IV methylprednisolone, MMF, and tapering oral steroids. This trial is powered to show superiority of the RITUXILUP trial regimen, with patients followed for at least 2 years. The estimated date for completion is in 2018.

However, [initial data from the first 50 patients treated with the regimen](#) has been extremely promising, with 90% (45/50) of patients achieving complete or partial remission by a median of 37 weeks. In addition, 72% (36/50) achieved complete remission by a median of 36 weeks, with low incidence of systemic lupus flares and infrequent adverse events.

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The AKI-REPACE Trial

Do ACE inhibitors improve survival in AKI?

<http://www.medpagetoday.com/Nephrology/DreamRCT/53876>

Acute Kidney Injury (AKI) is a **killer**. Given two hospitalized patients, identical except for the fact that one has AKI, the AKI patient is anywhere **from three to seven times as likely to die** during that hospitalization. AKI is costly in terms of life-years lost, but also in terms of hard currency -- **hospital-acquired AKI increases the average hospital bill by \$9,000**. Given that many patients with AKI will progress to require dialysis, the costs of AKI can become staggeringly high quite quickly.

It's a good thing, then, that we have such effective treatments for AKI:

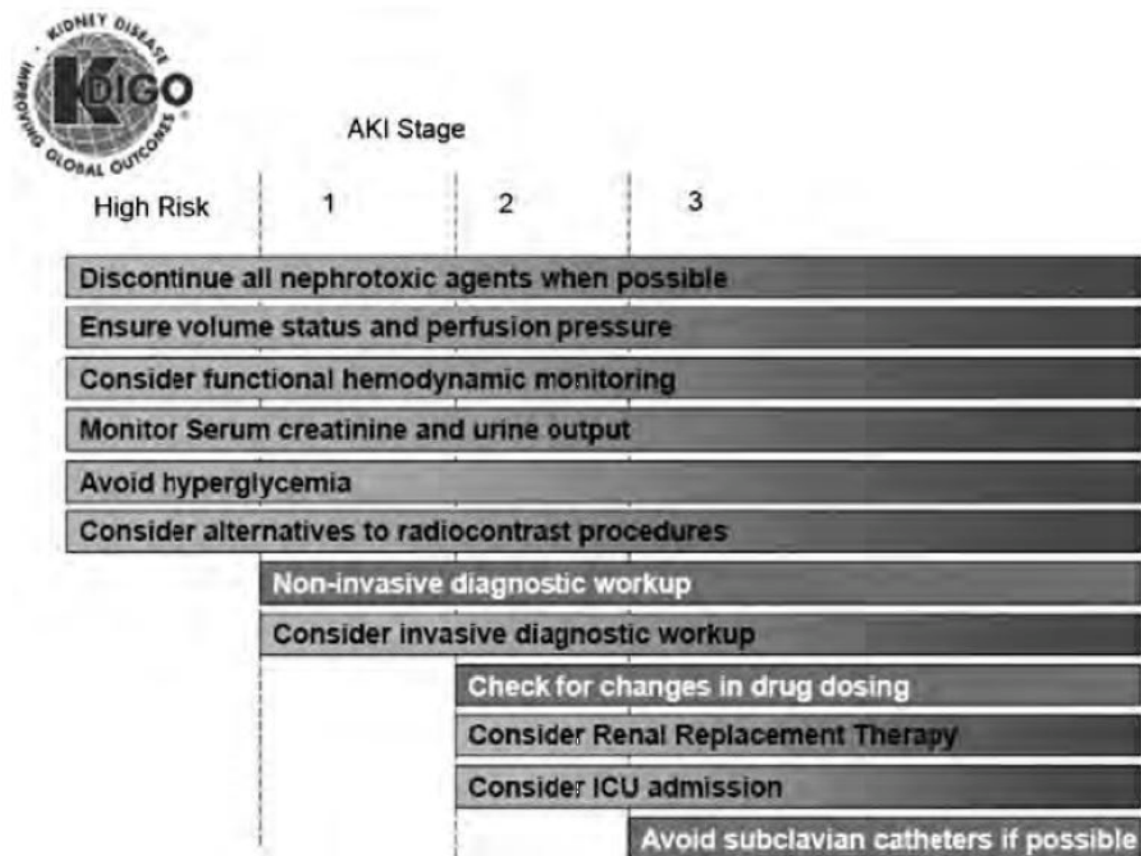


Figure 1: Kidney Disease - Improving Global Outcomes (KDIGO) management of AKI.

The reactionary paradigm of AKI treatment -- "don't make it worse" has hampered progress in this field for decades. Many trials, including **one by my team**, have failed to

demonstrate that specific interventions, targeted towards patients with early AKI, can prevent the catastrophic downstream consequences.

Maybe these trials are negative because we are ignoring a potent agent in the fight. A class of drug simultaneously loved and feared by nephrologists. A class of drug that we have decades of experience using (albeit in other venues). I present to you: angiotensin converting enzyme (ACE) inhibitors.

The physiologic effects of ACE inhibitors are well-documented. They are anti-hypertensive agents, acting to reduce the affects of angiotensin 2 on vascular smooth muscle. By preferentially reducing efferent arteriolar vasoconstriction, ACEs also decrease glomerular hydrostatic pressure (thus decreasing filtration fraction), and so *increase creatinine*.

The role of angiotensin II in maintaining adequate intraglomerular pressure

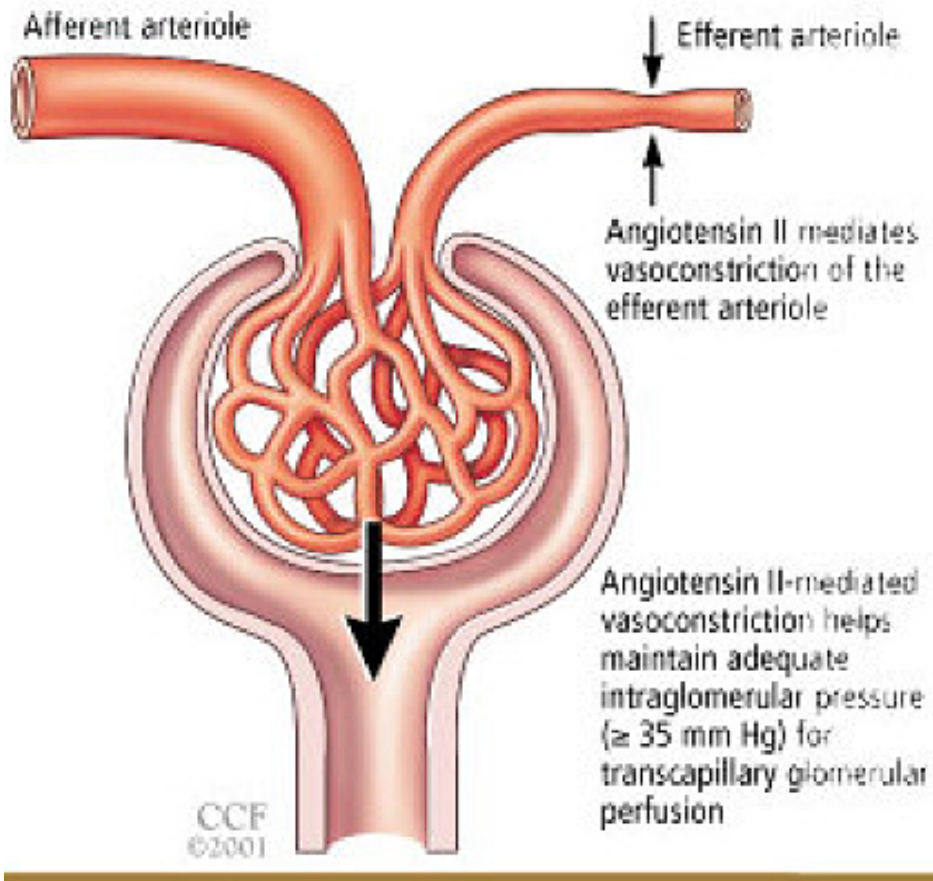


Figure 2: A reminder of what angiotensin 2 does.

It is the expected increase in creatinine that has led more pragmatic researchers to shy away from treating AKI patients with ACE inhibitors. In fact, one paper, that may or may not have been authored by me, labeled "cessation of ACE inhibitor" as a marker of "good renal care" in patients with AKI.

But there is every reason to believe that ACE inhibitors might be helpful in this population.

Acute tubular necrosis (ATN), the most common form of hospital-acquired AKI, is a disease [pathologically linked to decreased perfusion in the renal medulla](#).

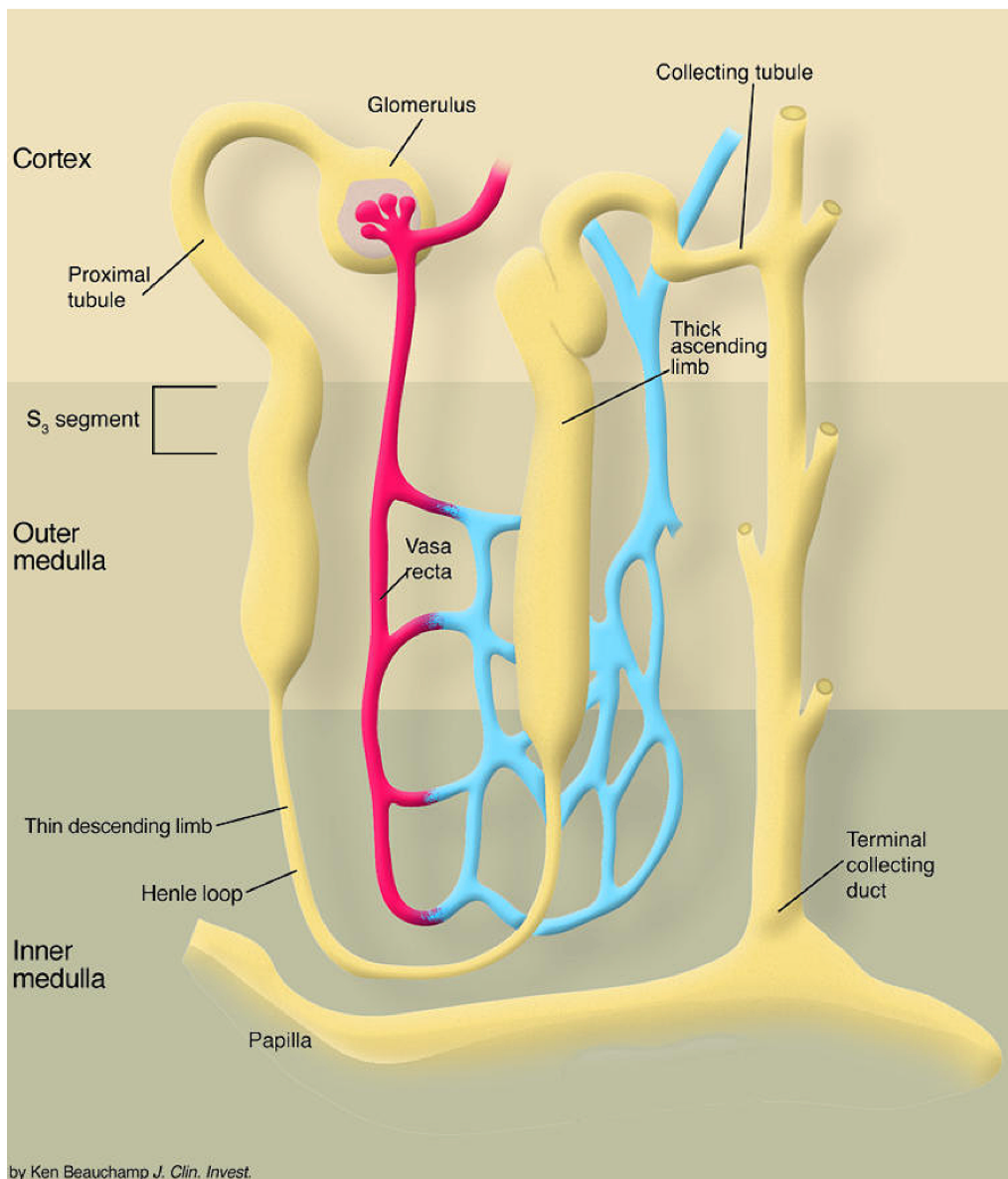


Figure 3: Note that the efferent arteriole supplies blood (and oxygen) to the chronically hypoxic renal medulla.

The renal medulla is a chronically under-perfused environment, due to the need to preserve the high osmotic gradients necessary to concentrate urine. Low blood flow in this area means that oxygen tension is low, making the cells of the renal medulla particularly susceptible to ischemic injury.

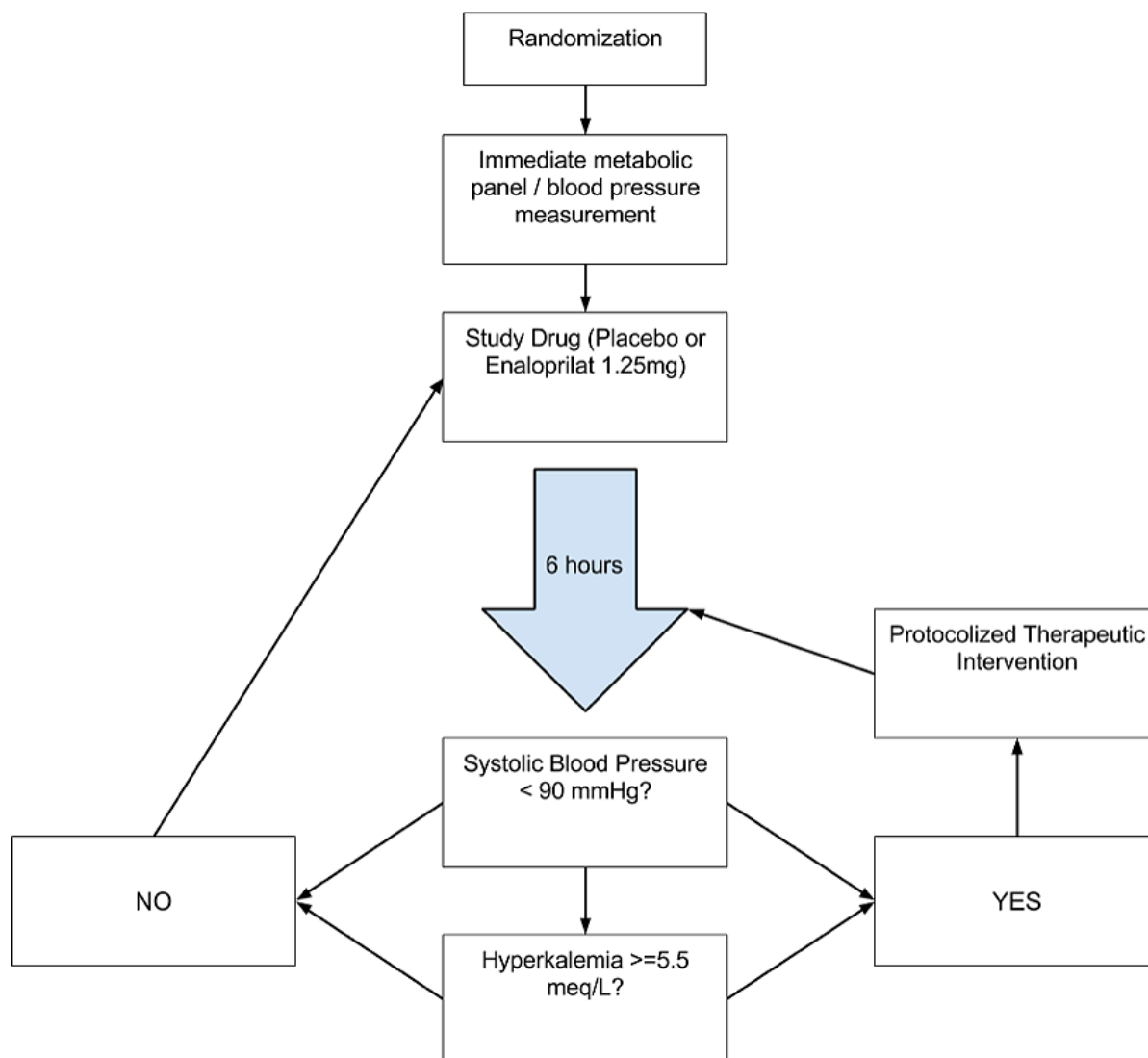
ACE inhibitors, by reducing efferent arteriolar vasoconstriction, *increase* medullary blood flow, potentially restoring adequate oxygenation to these important cells in times of kidney stress.

In the Acute Kidney Injury -- Restoring Perfusion with ACE Inhibition (AKI -- REPACE) trial, we will enroll patients with early acute kidney injury and randomize them to placebo or intravenous enalaprilat, a short-acting ACE-inhibitor. As creatinine is expected to increase more in the enalaprilat arm, the primary outcome will be all-cause mortality.

We are acutely aware that the treatment we are proposing may carry certain side effects. These include hypotension, hyperkalemia, increased BUN, and creatinine, which may result in an increased risk of dialysis in the intervention group. There is also the idiopathic risk of angioedema. Through careful trial design, we have attempted to mitigate these risks as much as possible.

Study Details

Design: We will identify patients with AKI using an electronic monitoring system. After informed consent, they will be given the first dose of study drug according to the following treatment algorithm:



We will treat with study drug every six hours (barring adverse effects). We will continue treatment until renal function recovery (as defined by a return to 10% of baseline creatinine), death, discharge from the hospital, or 7 days from randomization. Treatment will continue during dialysis.

Protocolized therapeutic intervention: Anticipating the development of hyperkalemia and hypotension in the treatment arm, we will provide a standardized treatment algorithm for all patients. Initial treatment of hyperkalemia will depend upon degree of hyperkalemia and may range from expectant management (i.e., no study drug at the next 6 hour time point, with repeat

labs) to active treatment with IV calcium, insulin, sevelamer, and/or furosemide. We will treat hypotension with intravenous fluids barring an active contraindication such as pulmonary edema or unexplained hypoxemia.

Inclusion criteria: Hospitalized patients with incident acute kidney injury as defined by a 0.3mg/dL increase in creatinine over 48 hours or a 50% increase in creatinine over 7 days.

Exclusion criteria: Allergy or previous adverse reaction to ACE inhibitor, life-expectancy (as determined by treating physician) of less than 48 hours, hypotension requiring treatment with two or more pressor agents, serum potassium ≥ 5.5 meq/L, or conditions that predispose to the rapid development of hyperkalemia (rhabdomyolysis, tumor lysis syndrome).

Sample size: We expect a control group event rate of 10% based on our prior studies. To achieve 90% power to detect a relative reduction in the risk of death of 20% (8% death rate in the intervention group) at a p-value threshold of 0.05, we will need to enroll 4,301 patients in each arm -- a total of 8,602 patients. Accounting for loss to follow-up, we will target a total enrollment of 9,000 patients.

Primary outcome: All-cause mortality during the hospitalization.

Secondary outcomes: Mortality at 30 days and 1 year. Dialysis as an inpatient, at 30 days, and at 1 year. Urinary and serum AKI biomarkers (of course). Doses of study drug received. Incidence of protocolized adverse event treatment.

Randomization: Performed in a 1:1 fashion, stratified by ICU status at the time of randomization.

Statistical methods: Mantel-Haenzsel Chi-square testing to account for stratification, with a two-sided p-value of 0.05. We will not adjust for factors that we discover are unbalanced between the treatment groups because that is just wrong.

In conclusion, the AKI-REPACE study will pave the way towards ending acute kidney injury by restoring perfusion to the renal medulla. Without high-risk, high-reward trials such as this one, we doom our patients to an overly-conservative, overly-cautious, and unambitious paradigm of AKI treatment.

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The MAGIK Trial

Investigating mortality risk in hemodialysis patients

<http://www.medpagetoday.com/Nephrology/DreamRCT/53870>

"All things are poison and nothing (is) without poison; only the dose makes the poison, not the thing."

-- Paracelsus, 1493-1541 CE

Introduction

The prevalence of ESRD requiring hemodialysis has exploded over the previous few decades but the practice has remained bogged down with minimal advancement in the same time period. Unfortunately, patient outcomes remain abysmal, with 5-year survival being worse than all major cancers, except lung and pancreatic. This is not for lack of trying -- despite [all the talk](#) of the lack of randomized trials in nephrology, hemodialysis has a bundle of major, but disappointingly negative, trials:

- Dialysis dose and high-flux versus low-flux ([HEMO](#))
- Nocturnal dialysis (from the [FHN trial network](#))
- Statins ([4D](#) and [AURORA](#))
- ACE inhibitors ([FOSIDIAL](#))
- The Anemia trials (Besarab, [CHOIR](#), [CREATE](#), [TREAT](#))
- Cinacalcet ([EVOLVE](#)) and Sevelamer ([DCOR](#))
- New drugs ([BEACON](#)/Bardoxolone)

Every nephrologist has a pet theory of how to extract the field from this quagmire it is stuck in. Some of the problems are quite obvious though. The nocturnal FHN trial failed to enroll patients as planned (notwithstanding some nifty Bayesian analysis presented in a [follow-up paper](#) to prove futility), which seems to be a recurrent problem. Lack of money is another problem -- industry has grown quite wary of dialysis after witnessing high-profile wiffs by Amgen, Genzyme, and Pfizer. CIHR and NIH funding is getting increasingly harder -- and we are not sure of the [future of PCORI](#). One issue is that the background mortality in dialysis patients is so high, an

argument can be made that it is difficult to show that any one intervention can make a difference ("too little, too late" syndrome). This long preamble hopefully sets the stage for the MAGIK trial -- Modulating MAGnesium and K(potassium) in dialysate: a cluster randomised controlled trial -- which can circumvent, solve, and preempt these hurdles.

Background

Though cardiovascular mortality is the most common cause of death in hemodialysis patients, it is not acute plaque rupture and acute myocardial infarction that account for most of this, but [sudden death](#). From [USRDS data](#), ~27% of mortality is accounted for by sudden death alone. One of the possible interventions to prevent sudden death is insertion of an implantable defibrillator (e.g., last year's DreamRCT, [Prevent DEADD](#)). However, another approach is to identify the cause of sudden death, and to re-examine dialysis factors. My DreamRCT modulates the two most important cations in the dialysate, potassium, and the hitherto overlooked magnesium, in a cluster RCT.

Hyperkalemia has long been identified as a critical risk factor for sudden death in dialysis patients. However, there is an increasing recognition that hypokalemia -- especially the large intra-dialytic drop -- and post-dialytic hypokalemia are also important risk factors. A strong association between use of low-potassium bath in dialysis and mortality has been reported in multiple observational [studies](#). (Aside: see [this](#) for an excellent discussion of potassium kinetics during dialysis). Though a [fascinating potassium profiling trial](#) was shown to reduce arrhythmias, it has never translated into a larger trial, or clinical practice.

Similarly, observational studies have also identified serum magnesium as a risk factor for mortality, and dialysate magnesium is one of the key determinants of serum magnesium. Apart from the arrhythmogenic effect of low serum magnesium and association with vascular calcification, there is also some intriguing data on its association with [intra-dialytic hypotension](#). It is indeed possible that other factors (malnutrition, serum potassium) also confound this association; hence an RCT will be the key step forward.

Methods

Study Design

This will be a cluster randomized controlled trial. Thus, individual patients will not be consented, but the dialysis centres/units they are being treated at will be the unit of randomization. The many advantages of using this trial design include:

- Avoids treatment contamination
- Administrative/logistic convenience for programming the intervention
- Increased efficiency, probability of enrolling eligible patients

The outcomes (see below) can be captured easily from existing administrative databases, and do not require interpretation, or an adjudication committee, further decreasing the administrative burden and cost of conducting this trial.

The patients and treating physicians will *not* be blinded to the assignment. However, the analysis will be done by independent investigators, who will be blinded to treatment allocation.

Population

All outpatient hemodialysis patients will be eligible for the MAGIK trial. Specifically, it would include:

- Incident and prevalent patients
- No upper age limit
- Inability to give consent not an exclusion criteria
- Diabetes, nondiabetics included
- History of cancer, poor prognosis, dementia not an exclusion

The only exclusion criteria will be:

- Patients who are not on conventional hemodialysis, i.e., 3-4 hours, 3 x week
- Patients with acute kidney injury

With respect to centre eligibility, we will include and invite:

- Academic dialysis centres
- Community dialysis units

- No geographic restriction
- For-profit/not-for-profit centres

The randomization will be stratified, however, taking into account centre characteristics:
There will be four arms, with a 2 x 2 factorial design.

	Magnesium usual care	Magnesium algorithm
Potassium usual care	Group 1	Group 2
Potassium algorithm	Group 3	Group 4

Co-Interventions

This is a pragmatic trial, trying to closely follow usual clinical care. So other co-interventions are not prohibited, e.g., dietary counselling, changing medications are all allowed and encouraged. If clinically indicated (e.g., patient has vomiting and/or diarrhea) additional laboratory tests can be drawn and the algorithm can be modified.

Algorithm details

Potassium:

Measure potassium once a month, and adjust the dialysate as follows algorithm:

Serum K in mEq/L*	Dialysate K in mEq/L*
<3	4
3.1 - 4	3
4.1- 5.5	2
5.6 – 6.5	1.5
>6.6	1

* to convert to mmol/L, multiply by 1

Magnesium:

Measure serum Mg once a month, and follow algorithm:

Serum Mg in mEq/L*	Dialysate Mg in mEq/L*
<1.6 (<0.8)	1.5
1.6 – 1.89	1.25
1.9 – 2.09	1
>2.1	0.75

* to convert to mmol/L, multiply by 0.5

Outcomes

The primary outcome will be all-cause mortality.

Secondary outcomes will include:

- Difference in cardiovascular mortality
- Difference in sudden death (within cardiovascular mortality)
- Hospitalization for any reason

Analysis

This is a superiority trial, with the alternate hypothesis being that the intervention arm is superior to the usual care arm. An intention-to-treat analysis will be undertaken. One interim analysis will be conducted when 50% of the predicted events have accrued, and the sample size will take this into account. The time taken to reach this point will be considered to expand the recruitment (centres) if necessary. An independent Data Safety and Monitoring Board will oversee the study. There will be stopping rules for considerations of safety, harm, and futility.

Discussion

Strengths

- Simple, inexpensive intervention
- Cluster RCT design makes it logistically easy to administer, conduct, and complete the trial in a meaningful manner

- A successful trial will establish a base for testing many more interventions in this population

Limitations/Threats

- A cluster RCT methodology allows doing a trial with lower cost and increased efficiency, but does require using more complex methods, since using standard methods for analysis may lead to a spurious statistical significance (type 1 error). Similarly, the power/sample size needs to take into account the cluster RCT design to avoid leading to an underpowered study (type 2 error).
- Ethical considerations: individual patients are not consented in a cluster RCT; however, this is considered ethical and is approved. There may be individual physicians who may opine that certain patients should not be included in a trial, so getting buy-in from all nephrologists will be crucial.
- Centre specific variation in practice, Hawthorne effect: There is significant variation in practice from centre to centre. Indeed, it is possible that certain centres may already be using sophisticated algorithms to guide treatment. It is also possible that centres randomized to 'usual care' may change their usual care over time.
- Patient movement: Individual patients may migrate, or move from one unit to another, and this will be a factor to consider especially if both units are participating in the trial and randomized to different arms. Since we expect that the effect of the intervention is short-lived, the effect of this transfer/migration should be minimal.

Conclusions

To quote a [recent review](#), "the true challenge in HD patients is to avoid both life-threatening pre-dialysis hyperkalemia (plasma K⁺ level >6 mmol/L) and post-dialysis relative hypokalemia (or at least a very rapid decrease in plasma K⁺ level, and the related risk of lethal arrhythmias)."

The MAGIK trial will herald a new era of providing knowledge in a fast, efficient manner and deliver potentially practice changing therapeutic strategies.

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