Objectives:
1. To discuss the current state of CKD, AKI, and dialysis clinical trials in Canada
2. To discuss the current and future role of the CANN-NET Clinical Trials Committee
3. To initiate the development of a collaborative Canadian Nephrology Clinical Trials Network, through meeting of investigators, identification of barriers, and discussion of solutions

Agenda:

1. Introduction
   a) Welcome and Housekeeping Issues
   b) Purpose of the Meeting in context of CANN-NET
   c) Self-Introductions

2. Current state of CKD, AKI and dialysis trials in Canada:
   a) CANN-NET Clinical Trials review process
   b) Ongoing and planned trials in Canada
   c) Patient priorities survey
   d) Discussion:
      I. What did you hope to gain by coming to this meeting?
      II. What concrete deliverables do you think that the Clinical Trials Committee should work towards providing for you?
      III. What should the specific goals of this network be?
           e.g. To have infrastructure and money to give people such as small planning grants ($15K each), access to a national research coordinator, etc., OR to be a loose network providing knowledge of what is going on and access to people.
      IV. Should future Canadian nephrology trials focus on patient-identified priorities, and if so, how can we facilitate this?

3. Development of a Canadian Nephrology Clinical Trials Network
   a) Examples of successful networks:
      • Australian Kidney Trials Network
      • Canadian Kidney Transplant Network
      • Other - UK EUVAS, CCTG
      • Pediatric Networks
   b) Discussion
      I. What are the barriers and potential solutions to participating in nephrology trials in Canada?
      II. What specific steps can this committee and network take to implement solutions

4. Wrap Up, Discussion of Next Steps:

Date: April 24, 2014
Breakfast 7:00-8:00 am
Meeting: 8:00 am – 11:30 am Location: Renaissance Hotel-Ballroom
1133 West Hastings Street Vancouver, BC V6E 3T3
Attachment for Agenda Item 3b:

Assuming you feel the topic is worthwhile and will provide important information, for the two problems below, please discuss the specific barriers and potential solutions with respect to conducting trials in dialysis and chronic kidney disease at your centre.

**Problem 1:**

Dr. Smith is conducting a randomized trial of blood pressure lowering algorithm strategies in hemodialysis patients, including pharmacotherapy, and reduction of target weight. The follow-up is 2 years. He has invited you to enroll and randomize 25 patients over 1 year. Do you agree to participate? Why or why not?

**Problem 2:**

Dr. LeBlanc is conducting a randomized trial of a pre-dialysis education strategy to increase uptake of arteriovenous fistulae and home dialysis. She has invited you to participate and enroll 50 patients over 1 year. Do you agree to participate? Why or why not?

**Guiding Questions:**

1. From an investigator standpoint: What are the barriers to recruiting additional centers?
2. From a participating site standpoint: What are the specific barriers to participating in clinical trials at your center? (consider logistical, financial, time, knowledge, or other)

Try to divide these into easily surmountable, surmountable with some effort or money, likely insurmountable

3. Are there potential specific solutions that could be implemented at your center?

Try to divide these into local solutions, solutions that would potentially be solved through having a national Clinical Trials Committee infrastructure

**Examples:**

**Barrier:**
- We have no research coordinator.
- Surmountable with some effort and money.

**Solution:**
- Hire a nurse with dialysis experience part-time.
- Solution would be facilitated by CANN-NET Clinical Trials Committee infrastructure if specific training of the nurse could be provided by them.
# CANN-Net Clinical Trials Committee Members

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Nadia Zalunardo</td>
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<td>Sarah Gil (KT assistant)</td>
<td>University of Calgary</td>
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<td>Braden Manns (CANN-NET Chair)</td>
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<td>Susan Samuel</td>
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<td>Claudio Rigatto</td>
<td>University of Manitoba</td>
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<td>Irene Aguzzi</td>
<td>Kidney Foundation of Canada</td>
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# National Participants

## British Columbia

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<td>Sean Barbour</td>
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<td>Michael Copland</td>
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<td>Daniel Schwartz</td>
<td>Fraser Health Renal Program</td>
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<td>Brian Forzley</td>
<td>Penticton Regional Hospital</td>
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<td>Roop Dhillon</td>
<td>Royal Inland Hospital</td>
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<td>Michael Schachter</td>
<td>Vancouver Island Health Authority’s Renal Program</td>
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## Alberta

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<tr>
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<td>Neesh Pannu</td>
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<td>Louis Girard</td>
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<td>Rob Quinn</td>
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<td>Aijaz Ahmed</td>
<td>Medicine Hat Regional Hospital</td>
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## Saskatchewan

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<td>Joanne Kappel</td>
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<td>Paul Komenda</td>
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<td>Swapnil Hiremath</td>
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<td>Humber River Regional Hospital</td>
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<td>Andrew Steele</td>
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<td>Leo Lam</td>
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<td>Scarborough Hospital</td>
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<td>Arturo Wadgymar</td>
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<td>Karthik Tennankore</td>
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A web-based referral and consultation support system for optimal care delivery among remote-dwellers with heavy proteinuria: a pilot cluster randomized trial

Aminu Bello

**Context:** A significant proportion of remote-dwellers with heavy proteinuria do not receive standard guideline-recommended care due to systems and provider barriers resulting in adverse consequences of renal and cardiovascular (CV) outcomes. The current model of referral for specialist kidney care appears uncoordinated and sub-optimal. We propose to investigate how to overcome these barriers using a web-based CKD referral and consultation support system. *This model (being piloted in Edmonton for implementation) involves a family doctor communicating to a kidney specialist via a secured website exchanging patient information for kidney care delivery.* We hypothesize that this new care structure will improve process of care leading to better clinical outcomes.

**Methods:** A pilot cluster randomized controlled trial (RCT) to compare the effectiveness of the new care model (intervention) versus the usual care. Four primary care group practices in rural Alberta (two for each arm of the study) will be randomized. The unit of observation for the outcome measures will be at the level of individual patients (eligible if proteinuria at the point of referral>1g), and identified from the provincial laboratory database with 250 patients per practice cluster (N=1000). The practice enrolment and patients’ accrual will occur over a 6-month period, and a follow up period of 6 months will be allowed to assess study outcomes. The primary outcomes are: (1) improvements in the process of care (proteinuria, BP, glycemia, and use of medications – statins, ACEi/ARBs and ASA), and (2) proportion of patients that received appropriate specialist care. Other factors such as improved accessibility (reduction in wait times), time savings for nephrologist (reduction in unnecessary referrals), provider and patient satisfaction will be used as secondary outcomes.

**Discussion:** Our findings will determine the utility of this initiative in improving the process of care for patients with proteinuric CKD living in rural/remote places. The findings will have implications on optimal care organization and delivery for this group of high risk population for adverse renal and CV outcomes.
Context: The current model of specialist-primary care interactions appears uncoordinated and sub-optimal in delivering high quality care for CKD patients living in remote/rural communities of Alberta.

Objective: To assess the effectiveness of a web-based referral and consultation support system in comparison to the usual care (traditional paper-based approach) in improving process of care for patients with proteinuric CKD in rural Alberta using a cluster randomized trial.

Design:

**A pilot cluster RCT:**
Level of randomization (PCPs)
Level of observation (patients)

**Intervention:**
Use of a secured web-based system for referrals/consultations to kidney specialist

**Comparator:**
Usual care (traditional referral/consultation system)

**Outcomes**

Primary: Improved process of care
- Optimization of risk factors for CKD progression and CVD risk
- Increased specialist input to care

Secondary:
- Accessibility
- Efficiency (time savings + reduced wait times)
- Satisfaction (patient and provider)

Discussion: The findings will determine the utility of the new model in improving the process of care for patients with proteinuric CKD living in rural/remote areas, with significant implications on how care is organized and delivered for this high risk population group.
GFR Measurement in Canada

Christine White

Novel interventions to reduce the progression of CKD are urgently required. One of the challenges in trial design in Nephrology is the selection of outcome measures. Hard clinical endpoints (need for dialysis or graft loss) are impractical and costly. Surrogate endpoints such as kidney function are therefore far more commonly used instead. Most trials utilize serum creatinine or estimates of glomerular filtration rate (GFR). These are inaccurate, imprecise and insensitive at detecting changes in GFR and it has been repeatedly recommended that GFR be measured in clinical trials. Direct GFR measurement involves administration of exogenous tracers and determination of either plasma or urinary tracer clearance. In Canada, plasma clearance of $^{99m}$TcDTPA using 4 hour sampling is the most common method of GFR assessment. However there is now a crisis in supply of medical radioisotopes. Evidence also suggests that a final time point of 4 hours overestimates GFR in patients with advanced CKD. The accuracy of plasma clearance in patients with advanced edema is also unclear. Inulin, the gold standard GFR tracer is difficult to obtain and assay and is excessively expensive. Iohexol is safe, widely available and inexpensive. We have developed an iohexol assay that is precise and accurate. We are also developing plasma clearance protocols using very low dose iohexol that are simple to perform, inexpensive and have similar accuracy to the gold standard urinary inulin clearance across a range of kidney function, kidney diseases and edematous stages. The protocols and assay will be made available to investigators and clinicians wishing to accurately and inexpensively measure GFR in Canada.
GFR Measurement in Canada

• Novel interventions urgently needed in CKD and Tx to improve outcomes.

• GFR measurement essential if kidney function is important endpoint

• Iohexol is cheap, safe and easily available alternative to inulin

• Iohexol assay using HPLC-Mass Spectroscopy now developed at Queen’s

• Protocols using low dose iohexol to measure GFR across CKD stage and edematous states under development

• Goal: Provide Canadian investigators with accurate iohexol-based GFR measurement protocols appropriate for particular study group and access to inexpensive assay.
The Prevention of Acute Kidney Injury following Contrast-Enhanced Computed Tomography: A Trial of Oral Fluid versus Intravenous Saline

Swapnil Hiremath

Background: Intravenous saline is the accepted prophylactic measure for prevention of contrast-induced acute kidney injury. However, most trials for contrast nephropathy prevention have been in the setting of arterial contrast, such as with cardiac catheterization, and not with venous contrast, such as computed tomography (CT). There is insufficient data on effective prophylactic strategies to prevent acute kidney injury following contrast-enhanced CT scans. We hypothesize that oral salt and water loading, which is much more convenient for the patient, simpler logistically and less expensive, will prevent AKI as effectively as intravenous saline.

Objective: Is volume expansion by oral salt and water loading as effective as intravenous saline in preventing AKI after contrast-enhanced CT?

Design: A randomized open-label controlled trial with two parallel arms, non-inferiority design.

Study Population: 1030 patients with chronic kidney disease (eGFR < 30 mL/min/1.73m2) who are undergoing an outpatient contrast-enhanced CT scan.

Intervention: Random allocation to either intravenous saline or oral salt and water loading, based on body weight.

Outcomes: Primary outcome measure: Incidence of AKI (≥25% or ≥44 µmol/L rise in serum creatinine from baseline to 48 hours).

Relevance: The standard IV regimen requires significant health care resources as it requires a same-day hospital stay, nursing time as well as patient inconvenience. If the results of this study show that oral salt loading is effective as the standard intravenous saline, it would result in a significant reduction in the use of these resources.
**Baseline creatinine**

**Intravenous saline pre and post CT scan**

48 hours* → 7 days → 28 days

**Creatinine*, Safety outcomes**

**Control Arm**

**Intervention Arm**

**Screening, Consent and randomization**

**Baseline creatinine**

**Intravenous saline pre and post CT scan**

48 hours* → 7 days → 28 days

**Creatinine*, Safety outcomes**

---

*If creatinine elevated >25% or 44 µmol/L then repeat creatinine every 48 hours until return to baseline or patient starts acute dialysis

**Self reported symptoms such as nausea, vomiting with oral salt/water or discomfort with venipuncture
First Nation Community Based Screening to Improve Kidney Health and Prevent Dialysis 2 (FINISHED 2)

Paul Komenda

Lead Investigators: Paul Komenda, Barry Lavallee, Navdeep Tangri, Claudio Rigatto

BACKGROUND: The province of Manitoba has some of the highest incidence and prevalence of Kidney Failure in Canada, driven by a disproportionate burden of CKD in First Nations communities. Preventative health care screening and delivery presents a unique challenge in that First Nations people often reside in remote communities, although health disparities persist regardless of location. Our group has done extensive work in the area of mass primary point of care screening, risk prediction, on site counselling and direct referral to nephrology specialists based on the risk of CKD progression. We have screened over 1200 patients in 6 communities to date achieving 30% screening rates. Despite our success at screening, active screening for CKD cannot yet be recommended as the standard of care for all First Nations communities. We need to demonstrate that such a strategy improves disease identification, treatment, and outcomes compared to a more conservative strategy of community engagement and education.

We propose a cluster randomized trial of 30 First Nations communities in Manitoba over 5 years. We are requesting $2,000,000 to screen 4,600 individuals in this definitive study on the effectiveness of primary screening for diabetes, hypertension and CKD in First Nations Communities.

Primary Objective: To evaluate the risks and benefits of a nurse led, point-of-care, active screening strategy vs. a strategy of community engagement and education alone.

Hypothesis: The addition of coordinated, nurse led, point-of-care, mass screening for Diabetes, Hypertension and Chronic Kidney Disease in First Nations Communities will improve case finding, disease treatment, and disease outcomes, compared to a strategy of ongoing community engagement and education alone.

Primary outcome: Number of incident cases of diabetes, hypertension and CKD identified in each arm over the period of the study. If the intervention is effective, we will observe a significantly higher incidence of the index disease in the active screening arm.

Ascertainment: Incident diabetes and hypertension will be ascertained using linkages to administrative data at Manitoba Health using validated case definitions. CKD will be ascertained using linkages to a laboratory information system (Diagnostic Services of Manitoba).
First Nation Community Based Screening to Improve Kidney Health and Prevent Dialysis 2 (FINISHED 2)  

**CKD is common and harmful, but preventable**

*Most patients with CKD will never need dialysis*

*We need to treat high risk patients aggressively and low risk patients cautiously*

**Mobile Mass Screening/Risk Prediction Feasible**

**POC Mobile Mass Screening**
- CKD/RISK of KF
- HTN
- DM2

**Outcomes**
**Incident:**
- HTN
- DM2
- CKD
- Kidney Failure
- C/E
- Qualitative Acceptance

**RCT**

**Community Capacity Building**
- Media Campaign
- Local primary care infrastructure
- “Lay” workers to raise awareness and encourage screening

**CKD/KF Rates**
High in MB First Nations Communities

kidneyhealth.ca

CANADIAN NEPHROLOGY CLINICAL TRIAL NETWORK @csn2014
The iPACK-HD Study

Rachel Holden

There is animal model evidence and newly emerging clinical data to support a role for vitamin K in the prevention of vascular calcification (VC) in the setting of CKD. Ultimately, we aim to explore whether vitamin K supplementation in this population reduces morbidity and mortality. Before moving directly to a large scale, expensive, Phase III trial powered to examine the treatment effect on mortality, we think it prudent to conduct a Phase II study demonstrating that vitamin K has a favorable effect on coronary artery calcification (CAC), a validated surrogate marker for vascular events. This is a multicenter randomized, placebo-controlled clinical trial in six academic health science centers in Canada and one in the United States. We will enroll 410 patients (≥18 years old) with end stage kidney disease who have received hemodialysis treatments for less than 6 months and who have a baseline CAC score of ≥30 Agatston Units. Patients will be randomized to receive 10 mg of phylloquinone or matching placebo to be administered orally following their hemodialysis treatment three times per week. The total treatment duration is 12 months. The primary outcome will be the progression of CAC score at 12 months as defined by an increase of 15% or more from baseline. A simple nutrient strategy that modifies VC and bone health, such as we propose, could reduce morbidity and save lives. The multicenter nature of this study will enhance the generalizability of the study findings.
The iPACK-HD Study

• **Hypothesis:** The provision of vitamin K to patients with ESKD will prevent the progression of coronary artery calcification

• **Design:** multicenter, randomized, placebo-controlled clinical trial

• **Setting:** 6 academic centers in Canada and the US

• **Study population:** 410 patients with ESKD within the first 6 months of RRT with CAC score $\geq 30$ AUs

• **Intervention:** 10 mg phylloquinone 3x/wk vs placebo

• **Outcomes:**
  – **Primary outcome:** Progression of CAC defined as an increase of $\geq 15\%$ from baseline
  – **Secondary outcomes:** vertebral #, clinical outcomes, feasibility outcomes relevant to the design of a Phase III study in the future, vit K biomarkers

• **Significance:** There are no guidelines for vitamin K intake in HD patients. A simple nutrient strategy that modifies arterial calcification and bone health could reduce morbidity and save lives
RosIE, A pilot study to evaluate the feasibility and safety of performing a double blind, placebo-controlled, randomized controlled trial of The Routine use of SSRI’s at the Initiation of End-stage Renal Disease Treatment

Vanita Jassal

Over 120,000 people with kidney disease start chronic dialysis therapy across North America each year. Mortality rates on dialysis are more than 5-fold that of the general population, particularly early in the treatment history. Cross-sectional studies of dialysis patients suggest that in addition to multiple comorbidities, there is a high prevalence of non-specific symptoms including fatigue, depression and pain (estimated at >70%, 15-43%, and >60% respectively). While both pharmacological and non-pharmacological treatments are effective in treating depression, no trials have studied the impact on quality of life, hospitalization or mortality. Our data suggest that the success of a screening program would be limited by patient-specific barriers, while others have shown that fewer than 25% of patients on dialysis who screen positive for depression are treated or referred for further assessment, suggesting MD and system barriers.

Newer antidepressants, such as SSRIs, have a favorable safety profile, and have been used widely in people with chronic diseases for depression for other indications such as pain management, fatigue and hot flashes. In patients with strokes, SSRIs improve cognitive and functional recovery. Serious adverse events are uncommon and, in clinical trials, withdrawal rates and adverse events occur equally in both treatment and placebo groups. Several small uncontrolled studies have used SSRIs for the management of depression in the dialysis population. However none, to date, have studied the impact on non-specific symptoms, hospitalization or mortality.

We believe the high baseline mortality rate seen in the dialysis population, the prevalence and burden of non-specific depressive symptoms, and the association between depressive symptoms and risk of death mean that a high proportion of patients starting dialysis stand to gain from the routine administration of an antidepressant. We hypothesize that the routine administration of an SSRI at the time of starting dialysis may be effective in improving the overall outcomes of patients starting dialysis. Data on the feasibility of recruitment and retention and the practicality of application of secondary outcome methods in this population are lacking. We propose a pilot study, in 60 patients, across 3 centres in Ontario. Patients will be randomized to either escitalopram or placebo using a double-blind, placebo-controlled parallel study design. We will use the results to inform a definitive study aimed at determining if routine administration of escitalopram, compared with placebo, improves quality of life (primary outcome) and increases the number of hospital-free days over a 12-month period (secondary outcome).

Primary objective
1. To determine the proportion of consecutive incident dialysis patients that are eligible, the proportion of eligible patients that will consent to randomization, and of those randomized, the proportion that comply with their group assignment.

Secondary Objectives
2. To determine the safety profile in dialysis patients with escitalopram
3. To determine the feasibility of administering the planned secondary outcome measures: quality of life score (KDQOL), cognitive function (measured by the SF-36 MHC), depression (PHQ-9 questionnaire) and physical function (measured using 2-minute walk & handgrip test).

Study Design: Multicentre, double blind, placebo controlled, parallel group RCT
Study Population: Patients initiated onto chronic dialysis therapy within a 12 weeks window around the first dialysis treatment (1 weeks prior to, to 11 weeks after)
Active Intervention: Escitalopram 5mg daily x 2 wks ⇒ 10mg daily x 22wks ⇒5mg daily x 2 wks.
WISHED (Web-based IHCA for Successful HomE Dialysis)

Scott Brimble

**Background:** Home-based dialysis offers many advantages over facility-based therapies, including improvement in quality of life and decreased overall healthcare costs. Numerous barriers to initiation of home-based therapies have been identified, including: lack of confidence in performing the therapy, perceived burden on family members and fear of a catastrophic event. Disease-specific web-based Interactive Health Communication Applications (IHCAs) provide health information and offer some form of support involving either social, decision or behavioral change support.

**Objectives:** To determine if utilization of a web-based IHCA will increase the proportion of patients who initiate home dialysis over facility-based HD.

**Design:** The multi-centered randomized controlled trial is being conducted at several Canadian centres in adult patients with an eGFR $\leq 20$ ml/min/1.73m$^2$, who have received modality education, and have personal access to a home computer with internet access.

**Intervention:** This study will randomize patients to either access to a secure web-based IHCA which promotes home-based dialysis (website [www.independentdialysis.ca](http://www.independentdialysis.ca)) or usual care. Follow-up will be a minimum of one-year and recruitment will continue until it is estimated that 152 events will have occurred by study completion.

**Outcomes:** The primary outcome is the difference between groups in proportion of patients starting home-based dialysis. Secondary outcomes will include difference between groups in: (i) proportion of patients intending to perform home-based dialysis; (ii) dialysis knowledge; (iii) decision conflict; (iv) sense of social support.

**Conclusion:** This study will assess whether a web-based IHCA can increase the proportion of patients who initiate a home-based dialysis therapy.
**WISHED (WEB-BASED IHCA FOR SUCCESSFUL HOME DIALYSIS)**

**Intervention:**
- Secure website requiring login that promotes home dialysis therapies through education (video, pictures, narratives and posts) and decision and social support (videos, patient blogs, posts, ask the expert, chat room)

**Baseline info:**
- Demographics
- Distance to HD unit
- Social supports
- Economic status
- Education level
- Frailty
- Cognition (MOCA)
- Health literacy

- Adult CKD patients
- eGFR < 20 ml/min/1.73m²
- Received ESRD education
- Personal internet access

**Usual care**

**Web-site access**

**Outcomes (152 primary events)**
- **Primary:** Difference in proportion who start home-based dialysis
- **Secondary:** Difference in:
  1. Proportion of patients intending to start home-based dialysis
  2. Dialysis knowledge
  3. Decision conflict
  4. Sense of social support
Protection of the Heart with Aldosterone antagonism in End-stage renal disease (PHASE2) trial

Michael Walsh

Background: Cardiovascular disease, particularly heart failure and sudden cardiac death, is a major health problem for dialysis patients. Aldosterone is implicated as a mediator of progressive cardiac disease. Aldosterone antagonism with drugs like spironolactone are effective in non-dialysis patients and may be effective in dialysis patients.

Objectives: to determine the effect of spironolactone 25 mg daily on cardiovascular death and heart failure hospitalizations in patients that require chronic dialysis.

Methods: Eligible, prevalent dialysis patients will undergo a 4-week active run-in period with spironolactone 25 mg daily. Participants that tolerate this dose and are compliant will be randomly allocated to receive either spironolactone 25 mg daily or matching placebo. Participants will be followed for a mean of 4 years. The primary outcome will be cardiovascular death or hospitalization for heart failure.

Progress: In-kind active drug will be supplied by Teva pharmaceuticals. A CIHR grant is submitted and there is broad buy in nationally and by international partners.

Conclusions: PHASE-2 is planned as a large, international, placebo controlled trial that has the potential to improve outcomes for patients with dialysis.
**PISCES:** Protection against **Incidence of** Serious **Cardiovascular Events** Study with Daily Fish Oil Supplementation in Dialysis Patients

Charmaine E. Lok

**Background:** Dialysis patients are at high risk for cardiovascular (CV) morbidity and mortality and their CV risk factors differ from non-dialysis patients. Hemodialysis patients also have low serum levels of omega-3 polyunsaturated fatty acids (n-3 PUFA) due to reduced intake, uremic malabsorption and dialysate losses; studies have shown an inverse relationship between n-3 PUFA levels and CV death. We hypothesize that low n-3 PUFA serum levels are a non-traditional risk factor for CV events in hemodialysis patients that can be improved with n-3 PUFA dietary supplementation.

**Primary objective:** To compare the rate of serious CV event in hemodialysis patients who are randomized to daily n-3 PUFA supplementation (4 g/day) versus matching placebo supplementation. Serious CV events are CV-related death and non-fatal CV events.

**Design:** Multicentre triple-blinded, RCT. The study n-3 PUFA supplement and placebo capsules will be steam deodorized and flavoured. The study placebo does not contain n-3 PUFA and will be identical in size, shape, colour, consistency, odour and taste. Participants will receive either 4x1 gram capsules a day of n-3 PUFA or placebo. They will be followed for a minimum of three years. Prior to randomization, participants will be stratified by study site and by whether they have had a prior CV event.

**Progress:** Six hemodialysis centers across Canada have started recruiting. There has been support from the Heart and Stroke Foundation, local grant funding support (Peter Munk Cardiac Care Innovation Fund and Lawson Health Research Institute), in-kind contribution of the study capsules from Ocean Nutrition Canada (DSM) and private funding.

**Conclusions:** If n-3 PUFA is found to be beneficial in reducing CV events, it will represent an easily accessible, inexpensive, safe and novel nutrition-based therapy to improve outcomes in the high risk hemodialysis population.
Robert Quinn

Background: Chronic kidney disease affects 13% of the adult population in North America and is a spectrum of disease that ranges from mild kidney impairment to kidney failure requiring renal replacement therapy. People with kidney failure suffer significant morbidity, have poor quality of life, and a high risk of mortality. As a consequence, they are responsible for up to 7% of health care expenditures in developed countries. Over 80% of people with kidney failure are treated with hemodialysis, thus requiring access to the bloodstream, and while vascular access (“access”) is a lifeline, it is also a key driver of morbidity, mortality, and cost.

Nearly 98% of Canadian hemodialysis patients use either an arteriovenous fistula (“fistula”) or a central venous catheter (“catheter”) for access. Fistulas are preferred by providers, endorsed by national guidelines worldwide, and are actively promoted. Canadian, American, and European guideline statements cite evidence from observational studies that fistulas are associated with the best patient survival, the lowest risk of complications, and are the least expensive form of access to create and maintain. Further, the proportion of individuals treated with fistulas is considered a proxy for the quality of care in hemodialysis programs and has prompted initiatives to increase fistula use including the Ontario Dialysis Access Initiative, the Canadian Society of Nephrology Vascular Access Working Group, and the National “Fistula First Breakthrough Initiative” in the U.S..

However, there has never been a randomized comparison of fistulas to catheters and the observational literature on which the claimed superiority of fistulas is based has important limitations and may have exaggerated their benefits. Further, while catheters are typically placed and maintained by interventional radiologists or nephrologists and are available in a timely manner, fistulas require an organized, multidisciplinary approach that requires the coordination of several disciplines including nephrologists, surgeons, and radiologists. The majority of dialysis programs have committed significant resources to hiring dedicated vascular access nurses and creating the infrastructure required to increase the numbers of patients successfully treated with fistulas based on low quality evidence. As a consequence, this is an important health services question.

Primary Objectives: We seek funding for a pilot study to test the feasibility and safety of a large randomized controlled trial (RCT) comparing the two most common strategies for establishing access to the bloodstream in hemodialysis patients: an attempt at fistula creation or use of a catheter. Feasibility will be defined as the ability to recruit 100 participants over 12 months and >80% protocol adherence, while safety will be assessed using conventional endpoints. The large RCT will compare a fistula strategy to a catheter strategy and will be powered to detect a difference of 20% in all-cause mortality. It will require approximately 1000 participants followed for a minimum of 2 years (see Appendix 1).

Feasibility and Significance: We have completed a systematic review of the vascular access literature, secured CIHR funding to study this question, have a strong track-record in vascular access research, and demonstrated that Canadian nephrologists are willing to participate in a RCT comparing fistulas to catheters in a recent survey. Guideline committees and patients have identified vascular access as a priority research area. An RCT is needed to determine the relative efficacy of these two strategies for vascular access, to ensure that previous studies have not overstated the benefits of fistulas, and that efforts to increase fistula utilization do not have unintended consequences for patients or the health care system. As a preliminary step, we will conduct a pilot trial to establish the feasibility of recruiting patients for a large RCT, and to test the ability of sites to adhere to study protocol. The large RCT will have important implications for practice and the way that end-stage renal disease care is structured, delivered, and resourced.
Membranous Nephropathy Trial of Rituximab (MENTOR Trial)

Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in Caucasian adults with approximately 40% of affected patients eventually developing end stage renal disease (ESRD). To date, the best-proven therapy for patients with MN consists of the combined use of corticosteroids and cyclophosphamide (CYC). However, the majority of academic centers consider this treatment too toxic. Since the mechanism of action of CYC includes suppression of various stages of the B cell cycle including B cell activation, proliferation, and differentiation as well as inhibition of immunoglobulin secretion, it lends credence to the hypothesis that B cell abnormalities are involved in the pathogenesis of MN. This has been further supported by the recent finding of anti-PLA2R antibodies in ~70% of patients with primary MN. It is therefore reasonable to postulate that suppression of antibody production by depleting B cells may improve or even resolve the glomerular pathology and be reflected by a reduction in proteinuria. As such, patients (n=120) will be randomized to receive treatment with rituximab or cyclosporine for 12 months. The primary objectives of this study are: a) to determine whether or not the B cell targeting with rituximab is more effective than cyclosporine in inducing long term remission of proteinuria; b) to assess the association between serial measurements of anti-PLA2R and clinical response; and c) to compare the quality of life and adverse events profile between the two treatments.
Mentor Study

Inclusion Criteria
• Idiopathic MN with diagnostic biopsy
• ACEI and/or ARB, for >3 months prior to randomization and adequate blood pressure
• Proteinuria >5g/24h on two 24-hour urine collection collected within 14 days of each other
• Estimated GFR ≥40 ml/min/1.73m2 while taking ACEI/ARB therapy

Exclusion Criteria
• Presence of active infection or a secondary cause of MN
• Type 1 or 2 diabetes mellitus
• History of resistance to CSA or RTX. Patients who previously responded to CSA/CNI after 3 months or relapsed off RTX after 6 months are eligible.
Membranous Nephropathy

**Rituximab**
- 1 g Day 1 & 15
- NR (<30% in proteinuria) → PR → CR
- Failure → Retreat at 6 months
- Exit → Treatment stops at 12 months
- Observation for 12 months

**CsA**
- 3.5 mg/kg/day
  - Trough 125 to 175 ng/ml
- NR (<30%) → PR → CR
- Failure → Continue Rx
- Exit → Treatment stops at 12 months
- Observation for 12 months

Taper over 3 months
TESTING Trial: Steroids to Reduce Renal Outcomes in IgA Nephropathy

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis in Canada and the most frequent cause of end-stage renal disease (ESRD) in younger patients. Accumulating data suggests that therapy with a short course of corticosteroids may reduce the risk of ESRD in IgAN, but to date this has not been tested in an appropriately powered, randomized, controlled trial. As a result, steroid use for the treatment of IgAN varies considerably across Canada and the world. The Therapeutic Evaluation of STeroids in IgA Nephropathy Global (TESTING) study, which aims to recruit 1300 patients, is a large international, multi-center, double-blind, placebo controlled trial that will provide clear and definitive evidence regarding the potential benefit of a 6 month course of corticosteroids in preventing clinically relevant renal outcomes in patients with IgAN. Patients at high risk for progression will be randomized to oral methylprednisolone or matching placebo, and followed for up to 6 years for key outcomes: risk of ESRD, a 50% reduction in renal function or death due to kidney disease. The CIHR has provided funding to support the recruitment and follow-up of 120 patients from 10 centers across Canada.
Testing Study—IgA Nephropathy

**Inclusion Criteria:**
- IgA nephropathy proven on renal biopsy
- Proteinuria: >1.0g/day while receiving maximum tolerated dose of RAS blockade
- eGFR: 20 to 70ml/min per 1.73m²

**Exclusion Criteria:**
- Indication for immunosuppressive therapy with corticosteroids, such as: MCD with IgA deposits or Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.
- Contraindication to immunosuppressive therapy with corticosteroids
- Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (ie. squamous or basal cell carcinoma)
- Current or planned pregnancy or breastfeeding
- Systemic immunosuppressive therapy in the previous year.
- Malignant/uncontrolled hypertension (>160 systolic or 110mmHg diastolic)
- Unstable kidney function for other reasons
- Secondary IgA nephropathy: e.g. due to lupus, liver cirrhosis, HSP

**Canadian Goal = 120/1300 patients**
10 Canadian Sites funded by the CIHR
Testng Study – IgA Nephropathy

• Oral methylprednisolone or placebo 0.8mg/kg/day with a maximum 48mg/day x 2 months, taper by 8mg/day every month to stop within 6---8 months. All the patients will also receive optimal blood pressure control and full dose of ACE inhibitors or ARBs as recommended by guidelines throughout the trial.

• Follow-up 5---6 years