ASN 2020 Kidney Week Thoughts & Takeaways

UBC Nephrology Fellows

BC Renal Provincewide Rounds

November 20, 2020

UBC General Nephrology Fellows 2020-21

Core Fellows (Y1)

Elena Barbir

Justin Cheng

Shannon Wong

Core Fellows (Y2)

Wayne Hung

Kevin Zhang

Advanced Nephrology Trainees

Kathryn Larmour

Lachlan McMichael

Maternity Leave

Julie Ting (Y1)

Xin Bo (Justin) Cheng

- Undergrad: Chemical/Biological Engineering – UBC
- Medicine: UBC
- Internal Medicine: UBC
- PGY – 4 Nephrology Fellow
- Interests
  - CKD
  - Hemodialysis
  - Transplantation

New Era of Anemia of CKD After the Nobel Prize

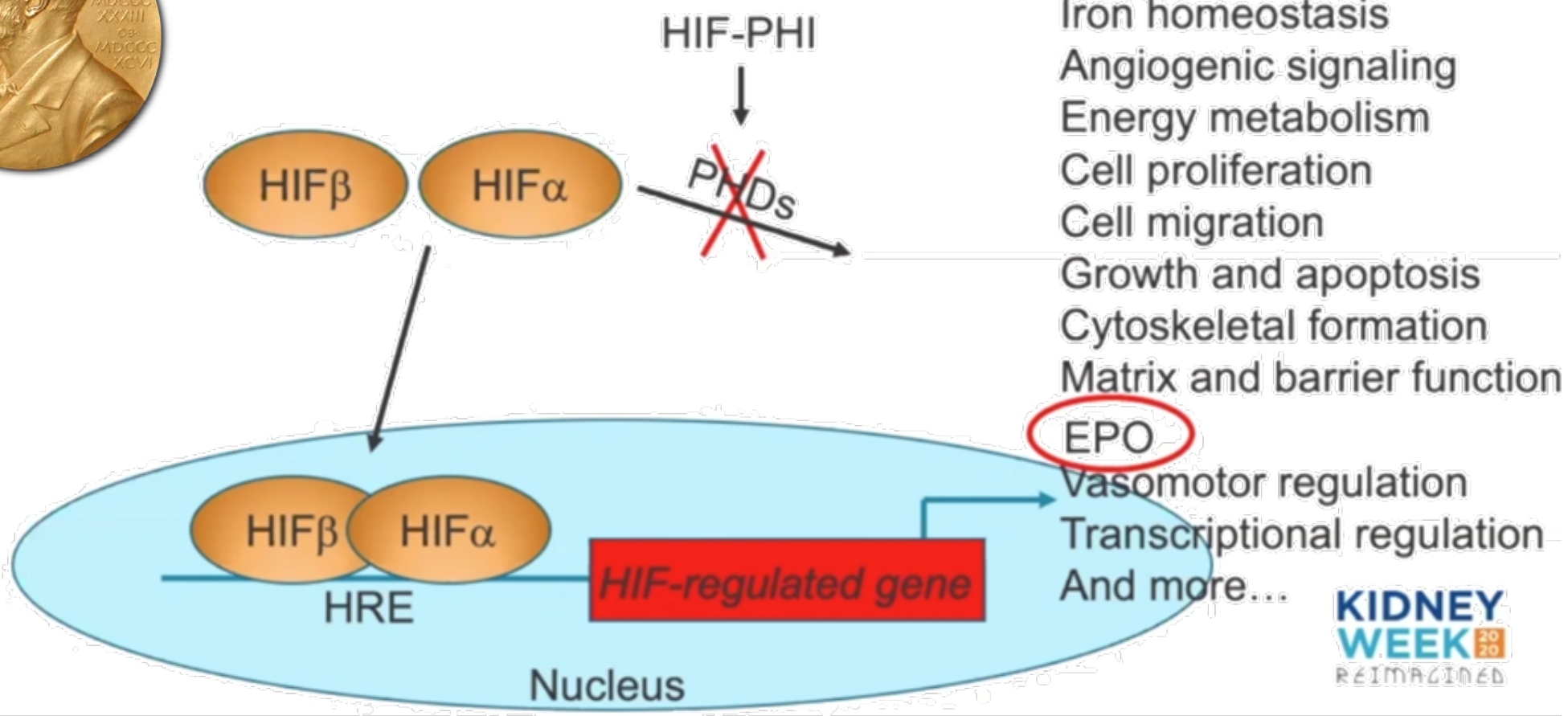
- **Jodie Babitt, MD**
  - **Massachussetts General Hospital, Harvard Medical School**
- **Volker Haase, MD, DrMed**
  - **Vanderbilt University Medical Center**
- **Masaomi Nangaku, MD, PhD**
  - **The University of Tokyo School of Medicine**

HIF: “Hypoxia induced factors” transcription factor

Gregg L. Semenza
Johns Hopkins

Sir Peter J. Ratcliffe
Oxford

William G. Kaelin, Jr.
Harvard

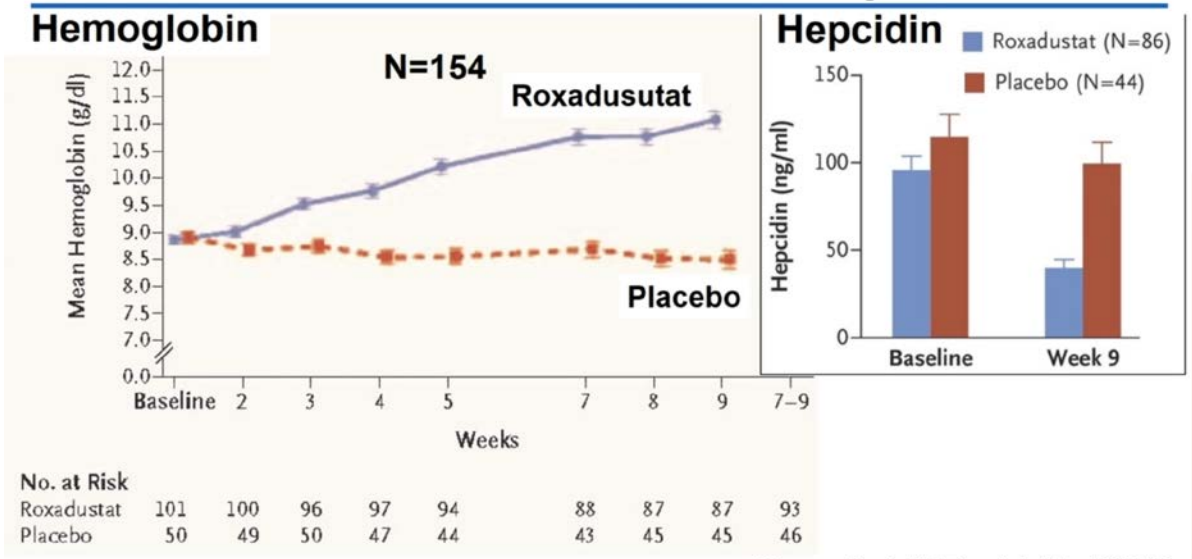


Iron homeostasis
Angiogenic signaling
Energy metabolism
Cell proliferation
Cell migration
Growth and apoptosis
Cytoskeletal formation
Matrix and barrier function
EPO
Vasomotor regulation
Transcriptional regulation
And more…

KIDNEY WEEK 2020 REIMAGINED

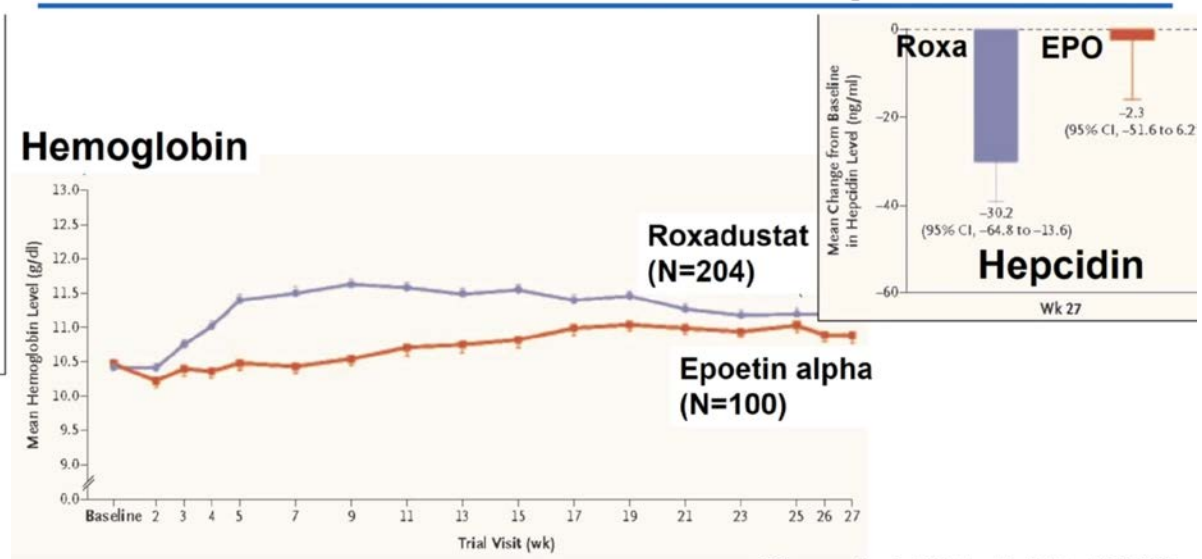
HIF Inhibitors In Action

Roxadustat in Chinese NDD patients



Chen et al. N Engl J Med 2019

Roxadustat in Chinese DD patients



Chen et al. N Engl J Med 2019

Multi-Pathway Effect: A Double Edged Sword

- Potential Advantages
  - Oral formulation
  - Effective in ESKD
  - Similar cost
  - “Physiological” EPO levels in OD dosing
  - Potential higher oral iron utilization
- Potential Disadvantages
  - Reported adverse events
    - Higher incidence of hyperkalemia
    - Higher incidence of VTE events
  - Speculated adverse events
    - HIF gene involved in angiogenesis
      - Retinal hemorrhages possible
      - Malignancy

Approved for use in China (CKD and ESKD) and Japan (ESKD only)
Roxadustat Under review by FDA

Hard-to-Control Hypertension: What to Do Next?

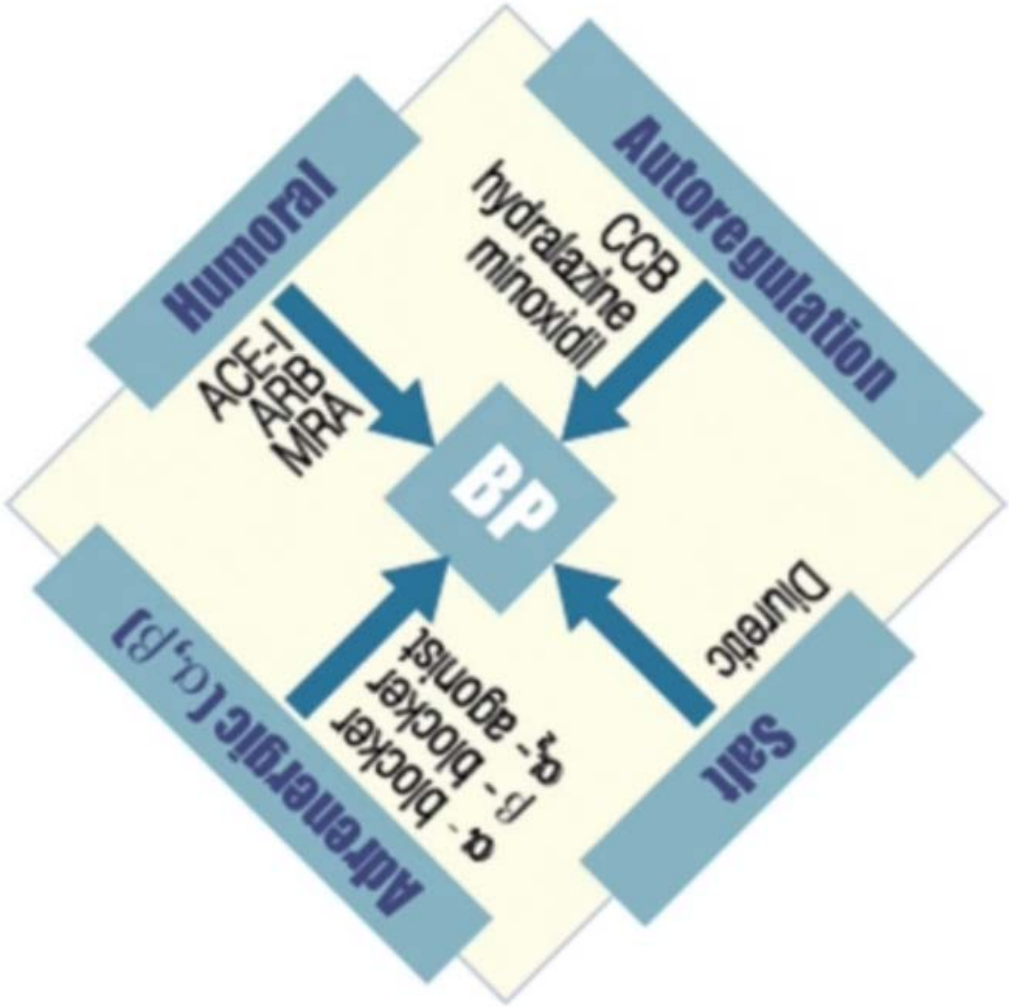
- **Dr. Tara Chang**
  - **Stanford University Medical Center**
- **Dr. John W. Funder**
  - **University of Melbourne**
- **Dr. Raymond Townsend**
  - **University of Pennsylvania**
- **Dr. Felix Mahfoud**
  - **Saarland University Hospital, Germany**

Diagnosis of Resistant Hypertension

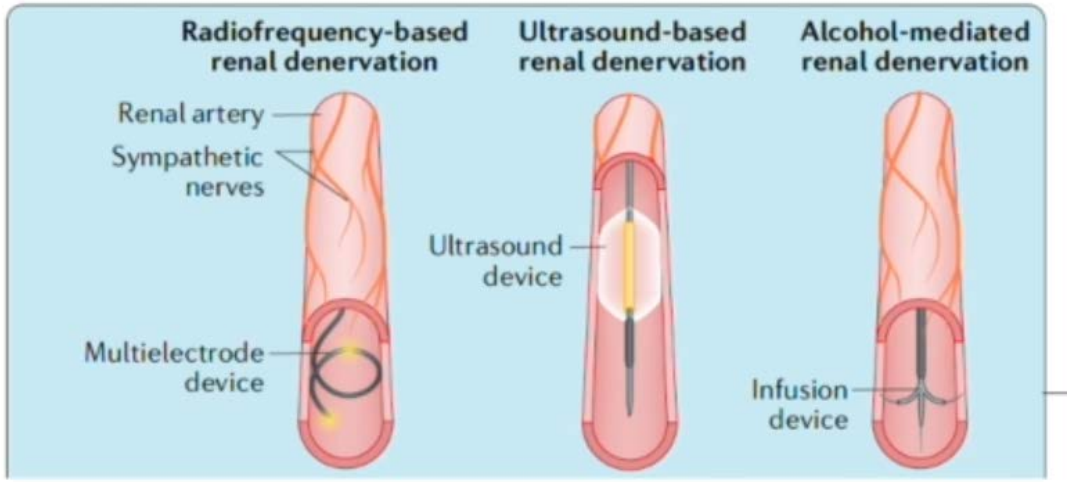
- Accurate measurement
- Ambulatory BP measurement
  - Agarwal et al. showed 56% normotensive in office had masked HTN on 24 hr ambulatory BP measurement
- Assess patient adherence
  - Berra et al. showed 17% of resistant HTN pts took no meds; 44% of resistant HTN pts took meds incorrectly
- Consider secondary HTN, especially primary hyperaldosteronism
  - Brown et al. showed that there is under-recognition of significant primary hyperaldosteronism and that 24 hour urine aldosterone excretion is more sensitive than renin-aldosterone ratio
  - John Funder (University of Melbourne) advocates for utilizing urine aldosterone excretion for hyperaldosteronism diagnosis and management

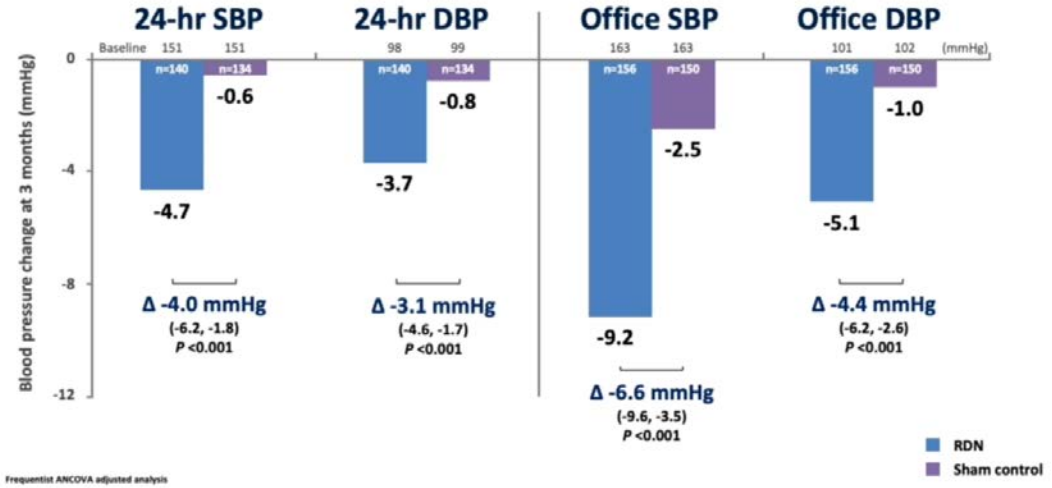
Treatment of Resistant Hypertension – Dr. R. Townsend

- Diuretics
  - Thiazide-like diuretic first
  - Assess renin/aldosterone ratio
    - Low renin and moderate or high aldosterone
      - Spironolactone
    - Low renin and low aldosterone
      - Amiloride (query ENaC problem)



Experimental therapy – Renal Denervation





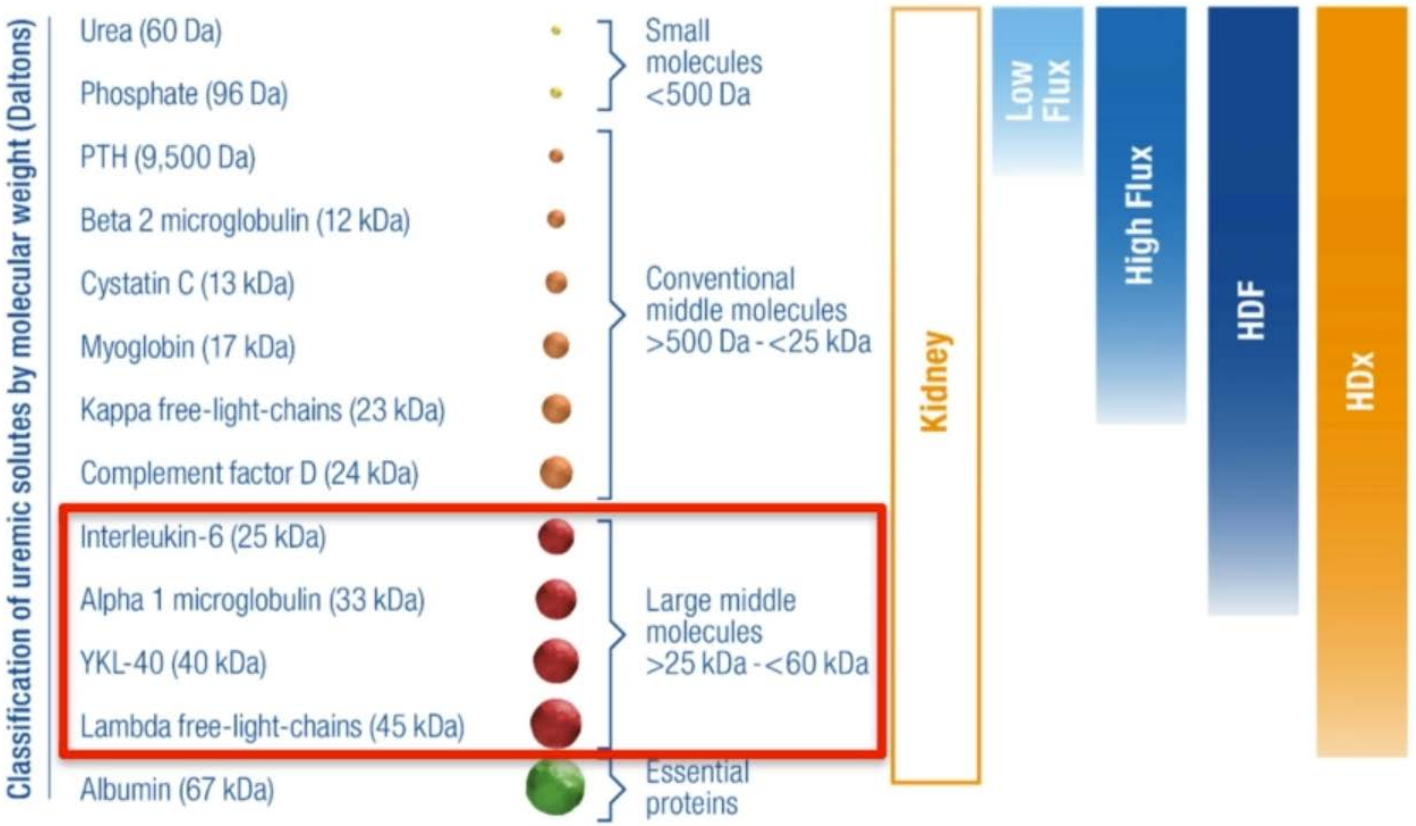
- SPYRAL HTN – Off Med
  - Low risk HTN: no medical tx (n = 330)
  - RFA vs. sham procedure at 3 months: SBP - 4.7 mmHg vs. -0.6 mmHg (P < 0.001)
  - SPYRAL HTN – On Med in progress
- RADIANCE-HTN Solo
  - RFA vs. sham procedure
  - Titrate antihypertensives for 6 months to reach target BP
  - 0.9 +/- 0.9 vs. 1.3 +/- 0.9 antihypertensive drugs (p = 0.01)

Removal of Large Middle Molecular Uremic Toxins: Room for Innovation

- **Dr. Peter Stenvinkel**- Professor of Renal Medicine at Karolinska University Hospital, Karloniska Institutet, Stockholm, Sweden, *"Biology and Clinical Significance of Large Middle Molecular Uremic Toxins in ESKD"*

- **Dr. Colin Hutchinson**- District Health Board in Hawke's Bay New Zealand, *"Dialysis Modalities and Technologies to Remove Large Middle Molecules"*

Middle Molecule Clearance and HD Modality

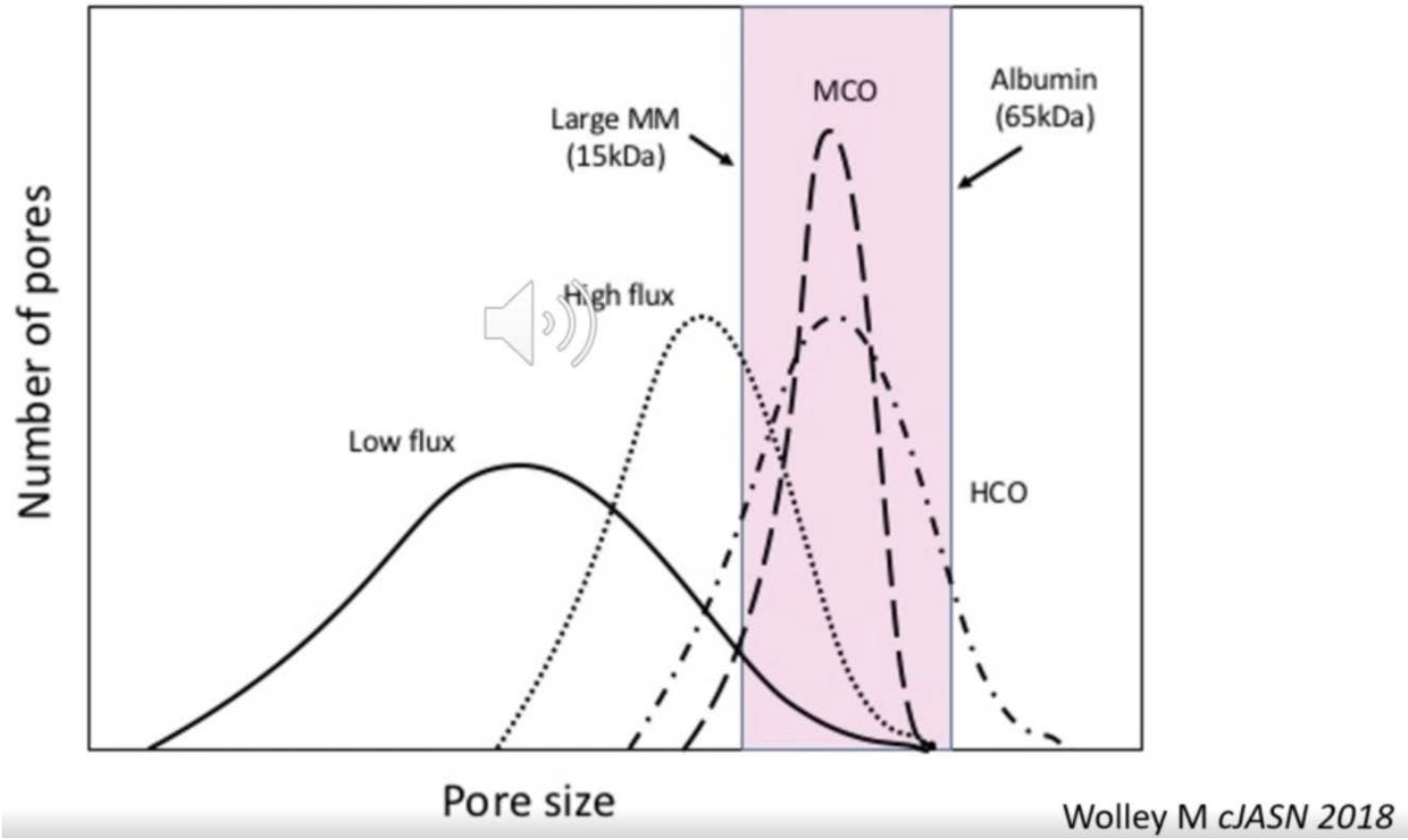


1. Adapted from Azar AT, Canaud B. Chapter 8: Hemodialysis system. In: Azar T, ed. Modelling and Control of Dialysis Systems. SCI 404. Berlin: Springer-Verlag, 2013

- Middle molecule toxins associated with poor outcomes
  - B2-microglobulin associated with cardiovascular disease
  - IL-6 associated with mortality in hemodialysis patients

HDx and Medium Cut-off (MCO) Membranes

- HDx: Expanded Hemodialysis
  - RRT using innovative membranes with improved selectivity and permeability that achieve toxin removal without replacement fluid
  - “MCO” Membranes



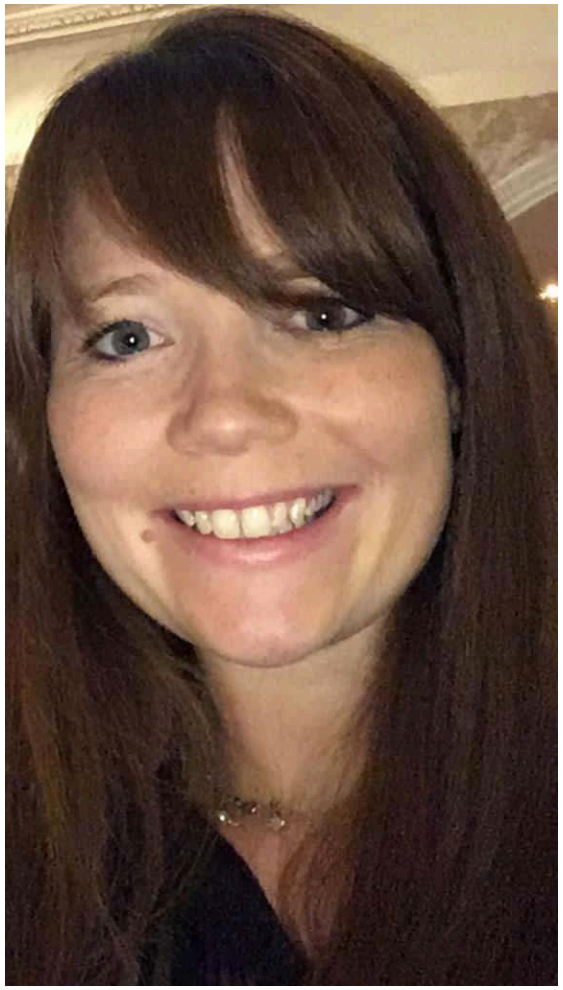
MCO Outcomes and Future Work

- Removal-HD (n=89 Cohort study)
  - 1 mo wash-in with High flux HD then 6 mo MCO dialyzer followed by 1 month High flux HD washout
  - No significant albumin loss, INR/PTT change
  - Reduction in both kappa and lambda FLCs (surrogate marker for large middle molecules)
    - Relative reduction ratio ~5-20% compared to
- Columbia Study on QoL with MCO dialyzer
  - 11.9% ARR in restless leg syndrome

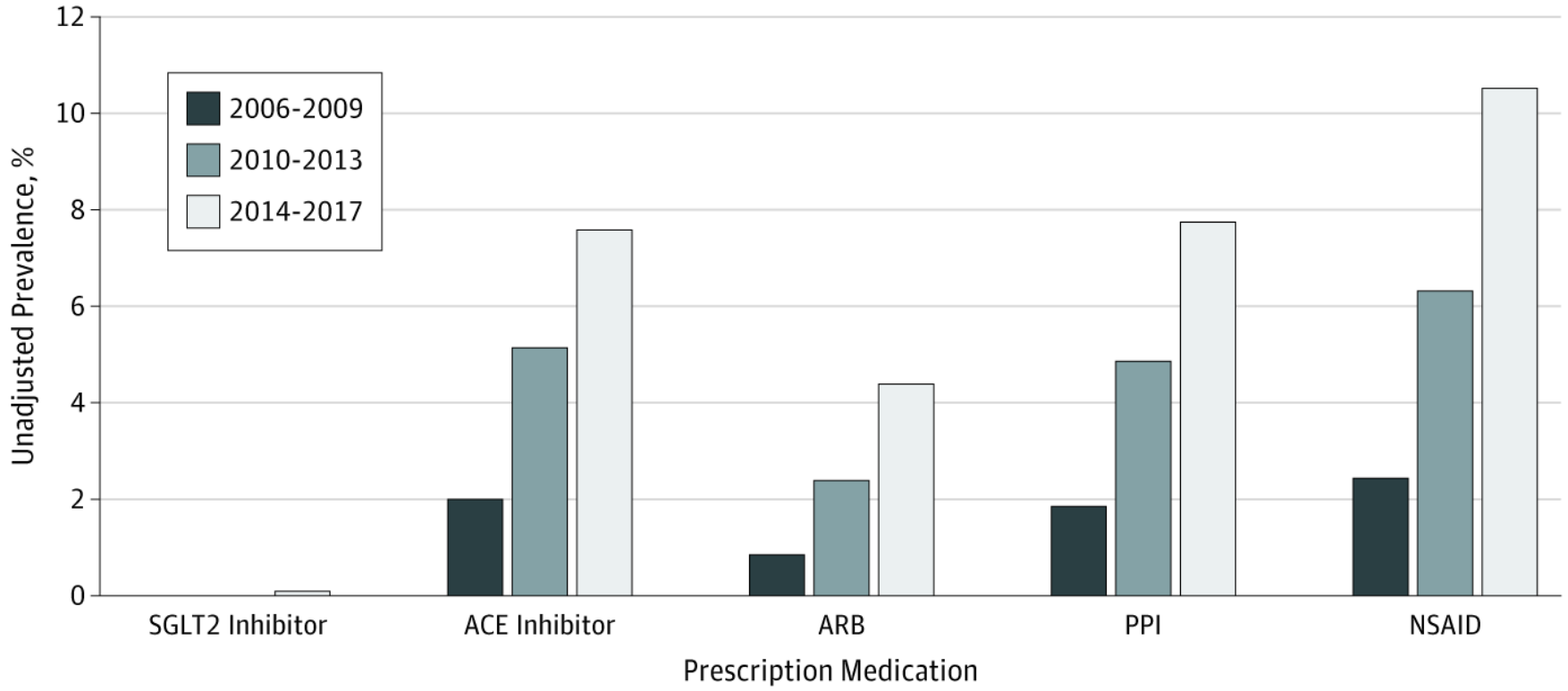
	Average change from week 0 to week 6 (95% CI)	p value
lambda FLCs	-7.48 (-14.40, -0.56)	0.03
kappa FLCs	-4.72 (-9.75,0.32)	0.07
	Average change from week 28 to week 32 (95% CI)	**p value**
lambda FLCs	7.85(0.82, 14.87)	0.03
kappa FLCs	8.18(1.28, 15.08)	0.02

Kathryn Larmour

- Queen's University Belfast, Northern Ireland
- Renal/ General internal medicine Registrar
- Advanced Training in Nephrology Clinical Fellowship since January 2020



- Low rates of CKD awareness and detection in current era
- Medication use in CKD stages 3-5 in 2 large US health care systems
  - Use of ACE/ ARB low < NSAID/ PPI use
  - DM with CKD and HTN: ACE/ ARB use in 25%



Tuttle, KR et at. JAMA Netw Open. 2019;2(12):e1918169. doi:10.1001/jamanetworkopen.2019.18169

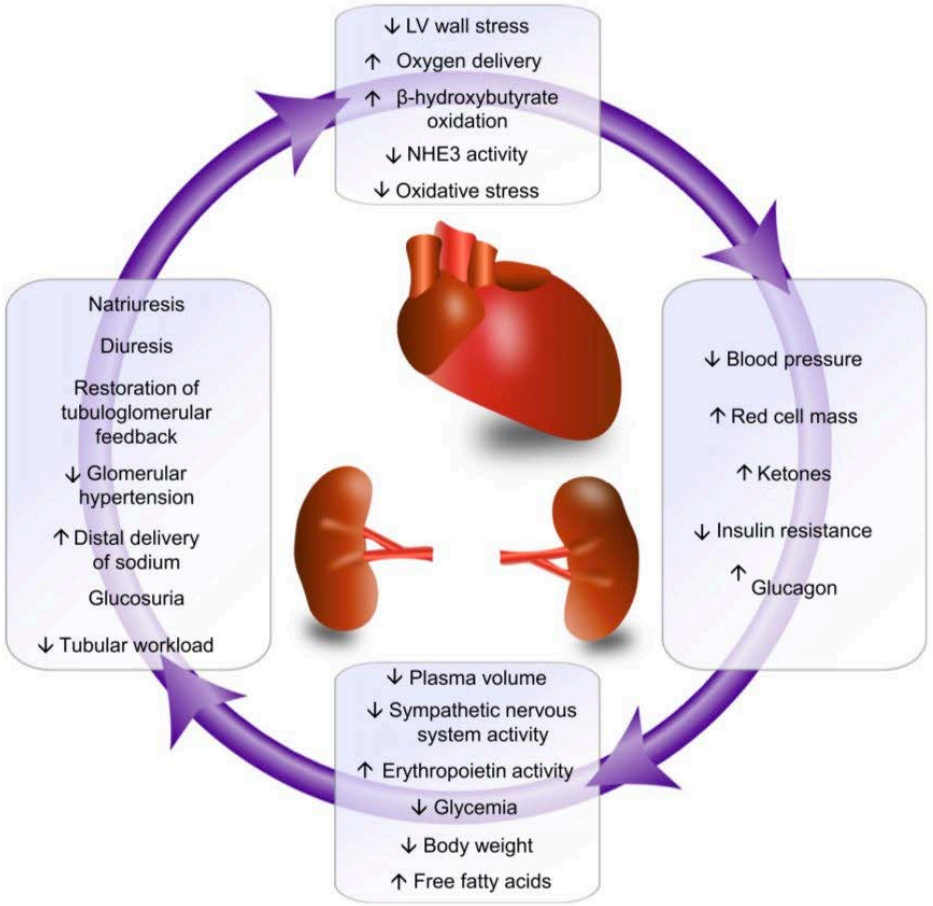
The Heart

Natriuresis- intravascular AND interstitial

Inhibition of SGLT2 AND NH3

Increased hematocrit

Improved myocardial energetics resulting in decreased LV remodelling



The kidney

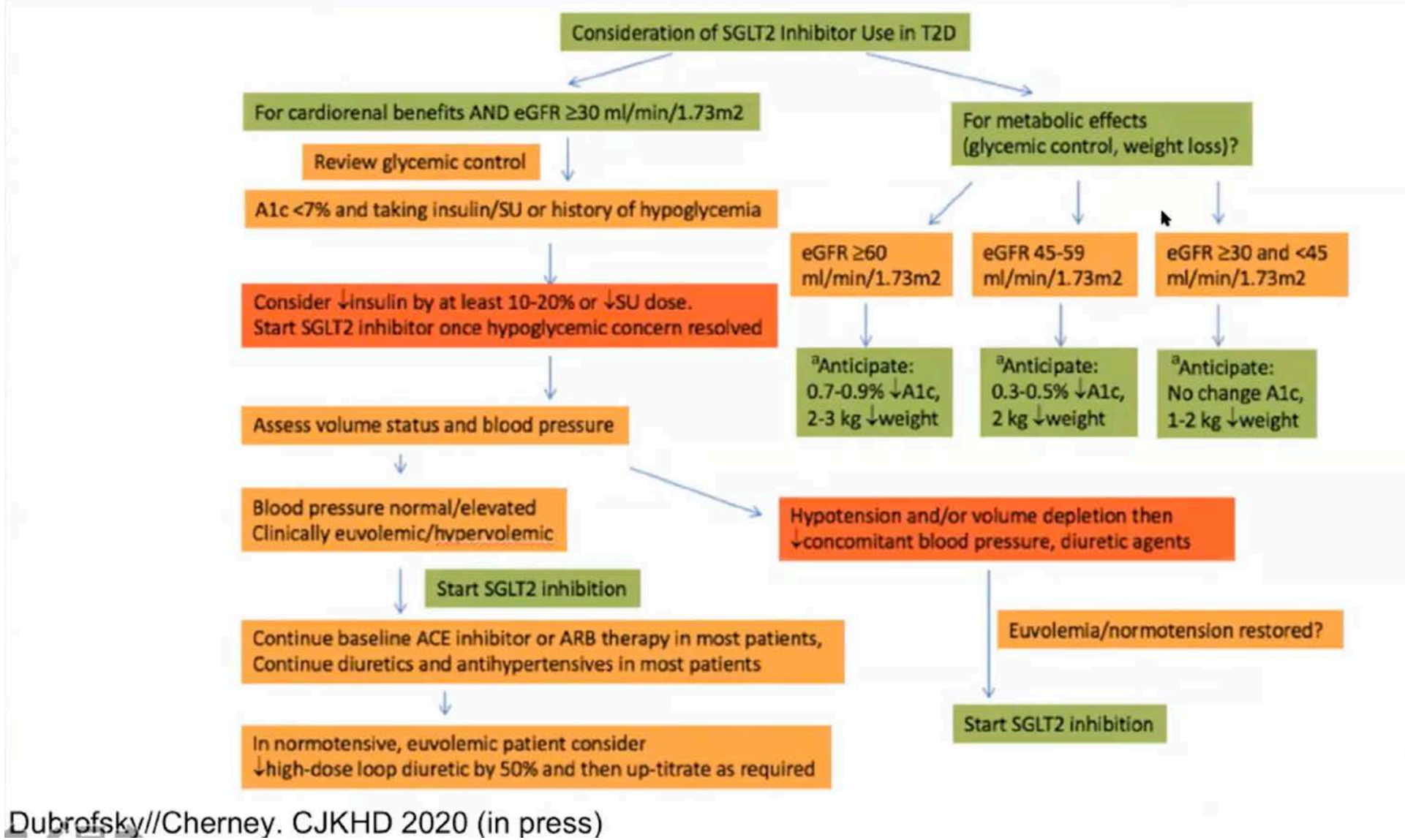
Reduced intraglomerular pressure

Decreased cortical hypoxia and mitochondrial dysfunction

Increased myocardial output

Decreased inflammation and fibrosis

JACC 2019; 73(15): 1931-1944
AJKD in press; Diabetes in press

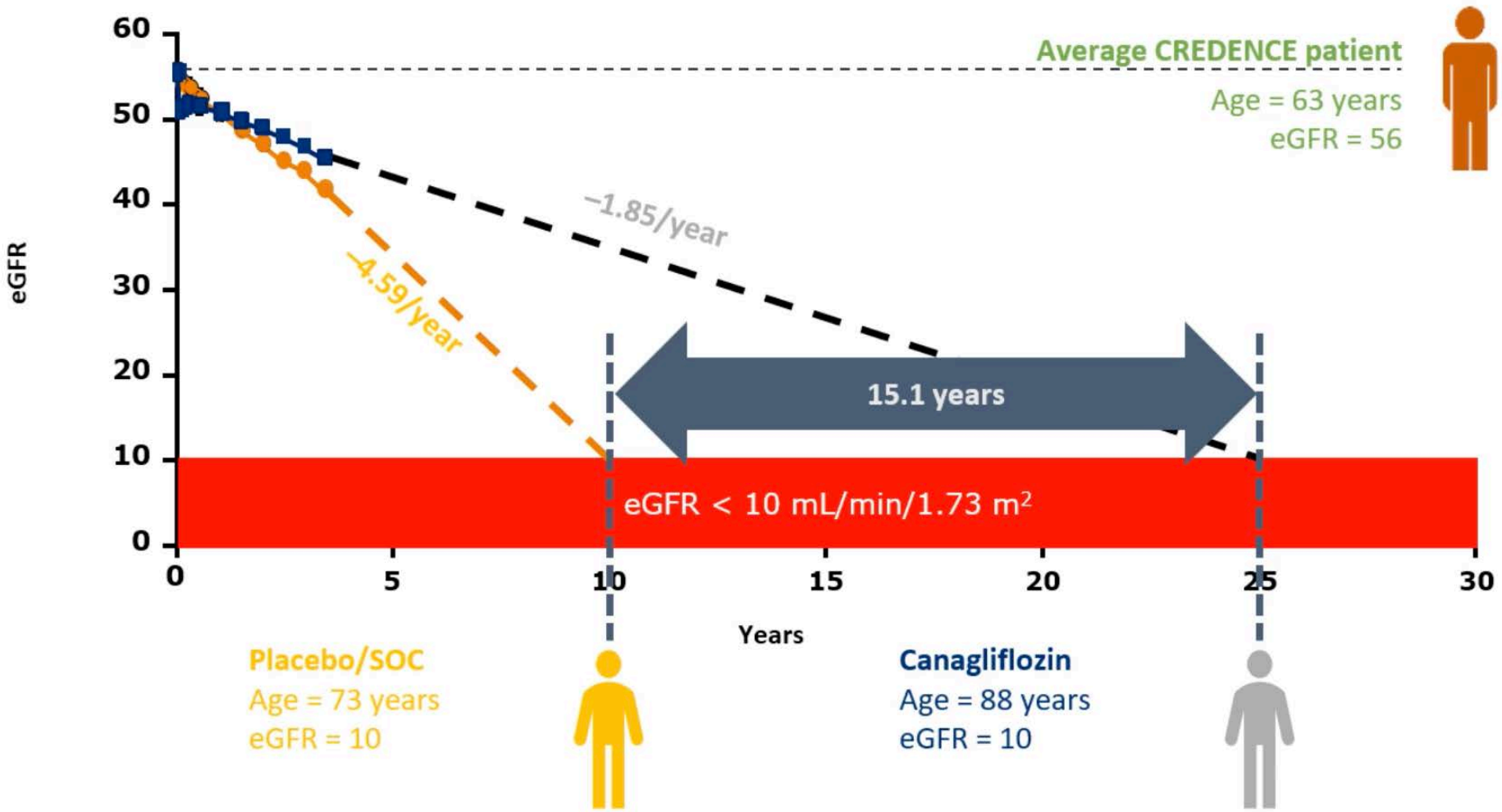


Dubrofsky//Cherney. CJKHD 2020 (in press)

How to avoid clinical inertia. . .

- AKI safety
  - GFR dip is reversible and not a sign of injury
  - May reduce AKI
- Significant volume depletion/ hypotension rare
- BP lowering effects modest
- Glucose management
  - Effects of SGLT2 inhibitors on glycemia decline as GFR declines
  - Benefits are independent of glucose
- DKA/ genital tract infections
- Who should not get SGLT-2 inhibitor?
- Advice for patients
- Review

Projected effects on eGFR



Prof A Levin

Elena-Bianca Barbir, PGY4

Education background:
B.Sc. + B.A. Physics/English
MD – Queen's Alumni

<u>Interests:</u>

hemodialysis/
extracorporeal therapies

Nephrocritical care (if it were a thing!)

onconephrology

Renal Toxicities of Immune checkpoint inhibitor therapy

- Shift from traditional cytotoxic therapies to targeted agents and immunotherapies
- Challenges:
  - Balance implications for kidney disease vs cancer outcomes: what is the right time for therapy cessation, re-challenge, and when does pre-existing renal disease constitute a barrier to pursuing CA therapy?
  - Is the AKI a result of the therapy or the natural history of the disease?

Risk factors for ICI AKI

- Concurrent use of drugs known to cause AIN, i.e. PPI, NSAID's, Abx's (observational study showing that 70% of pts diagnosed with checkpoint nephritis were on an "AIN med" at baseline).
- Patients receiving combination therapy (CTLA-4 agent, and PD-1 inhibitor use)
- Unclear if baseline CKD is a risk factor; conflicting low quality evidence to date
- ICI AKI recurs in ~23% of patients being re-challenged (Cortazar and Leaf. JASN 2020), but most responded to therapy

Diagnosis of ICI AKI

- Incidence of AKI after ICI: 15-20%, of which 1-4% will be immune mediated AKI
- ATN, Pre-Renal, Obstruction more common causes of AKI
- Most common lesion: AIN (**Cortazar and Leaf. JASN 2020**), sometimes associated with granulomatous features.
- Typical Presentation:
  - On average, occurs 3-4 months after Tx initiation, but can be as early as 1 month
  - 50% have other immune related adverse events

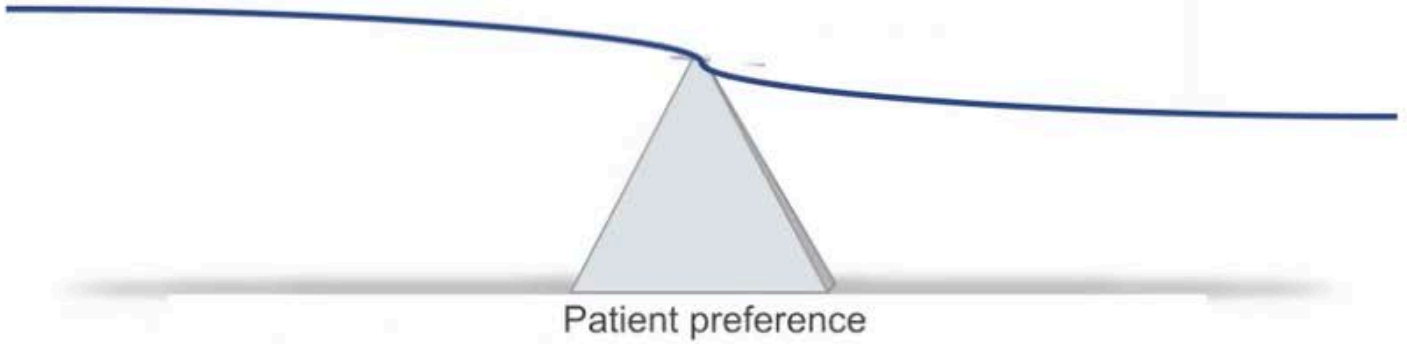
ICI AKI – WHO TO BIOPSY?

Factors favoring kidney biopsy

- Proteinuria > 1 gram, +serologic testing
- Clinical syndrome suggests a possible alternative cause
- Receiving other nephrotoxic chemotherapies
- Newly starting therapy, melanoma

Factors favoring empiric treatment

- No significant proteinuria
- Taking other AIN meds
- No other hemodynamic disturbances
- High risk biopsy (anticoagulation, single kidney)
- Patient frailty, patient preference



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Sise, ASN 2020

Management

- Hold ICI
- Stop all other meds that can provoke AIN
  - Change PPI to H2 blocker, change Abx, no NSAID's
- High dose steroids, 1 mg/kg per day pred equivalent; start taper when Cr < 1.5 times baseline
- Second line: Infliximab, Tocilizumab, MMF (not much evidence to guide this), but rarely steroid refractory
- **Giving steroids may affect overall cancer survival (Faje. Cancer. 2018), important to try and minimize steroids
- Can re-challenge while still on initial steroid taper (< 10 mg pred/day)

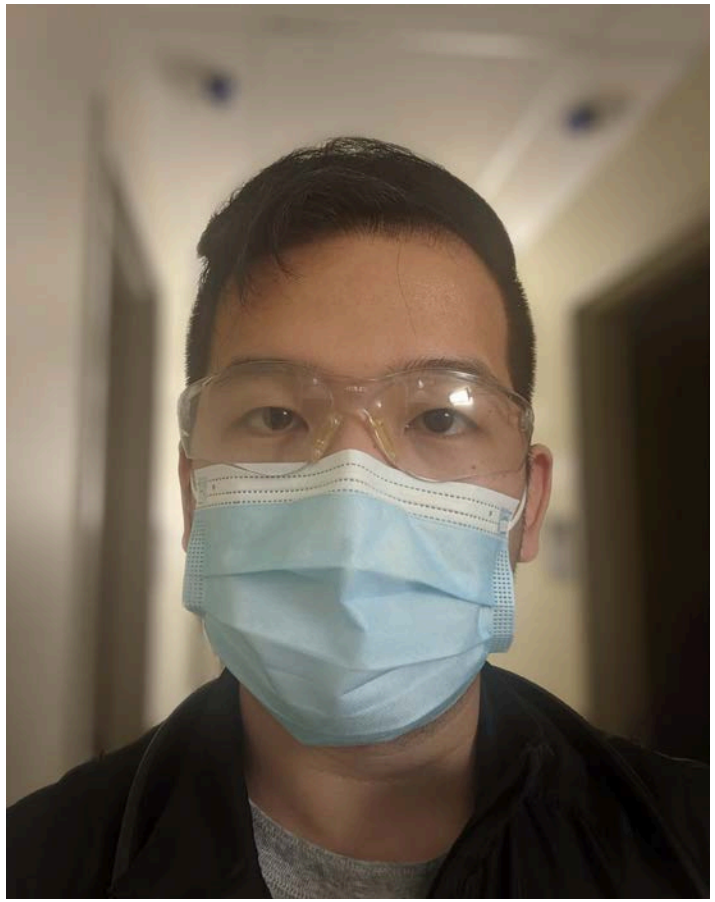
Less common renal lesions associated with ICI in biopsy series

- Less data on how to treat these (case report/case series territory); they can occur concomitantly with AIN
- First line is still ICI cessation + glucocorticoids with complete remission in nearly half of patients; and partial remission in ~40%
- Podocytopathies (MCD, FSGS) – Re-challenge has been documented to result in relapse of Nephrotic Syndrome.
- Proliferative Glomerular Lesions (Pauciimmune GN, Immune Complex Mediated GN's)
- Vascular Lesions (TMA)

Wayne Hung

- PGY-5 Nephrology
- UBC Internal Medicine

- Additional interests:
  - Geriatric nephrology
  - Hemodialysis
  - Medical education
  - Quality improvement



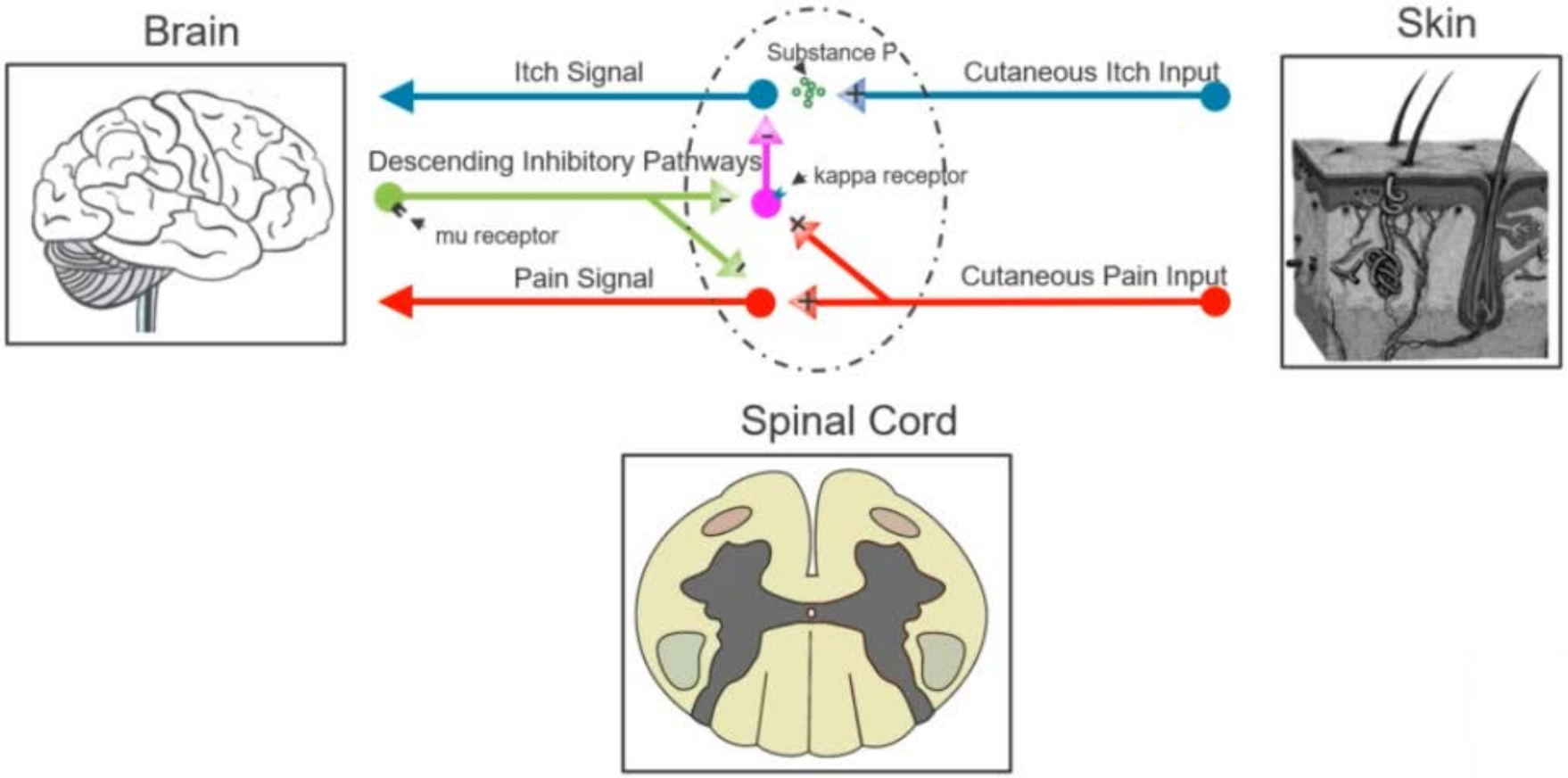
Sessions of note

- Causes & Treatments of CKD-Associated Pruritus
  - Sara Combs, Peter Juergensen
- Future of Dialysis: Bioengineering Tools to Improve Kidney Therapies
  - Shuvo Roy, David Cooper, Lauren Woodard, Joris Rotmans
- Facilitating Change with Patient-Centred Interventions in Hemodialysis
  - Martin Wilkie, Connie Rhee, Carmel Hawley

Causes & Treatments of CKD-Associated Pruritus

- CKD-AP markedly affects patient QoL
- Diagnosis of exclusion
- Current available treatments are not very effective
- New understanding of pathophysiology of CKD-AP
- Studies underway examining use of opioid receptor

Causes & Treatments of CKD-Associated Pruritus



Combs, ASN 2020

Causes & Treatments of CKD-Associated Pruritus

Future Approach for CKD-aP Treatment

Newer potential treatments

a. Nalfurafine, a kappa opioid receptor agonist
(nalfurafine is currently approved for use in Japan, crosses blood brain barrier)

b. Nalbuphine, a muopioid receptor antagonist and kappa-opioid receptor agonist

c. Difelikefalin, a peripheral kappa opioid receptor agonist (does not cross blood brain barrier)

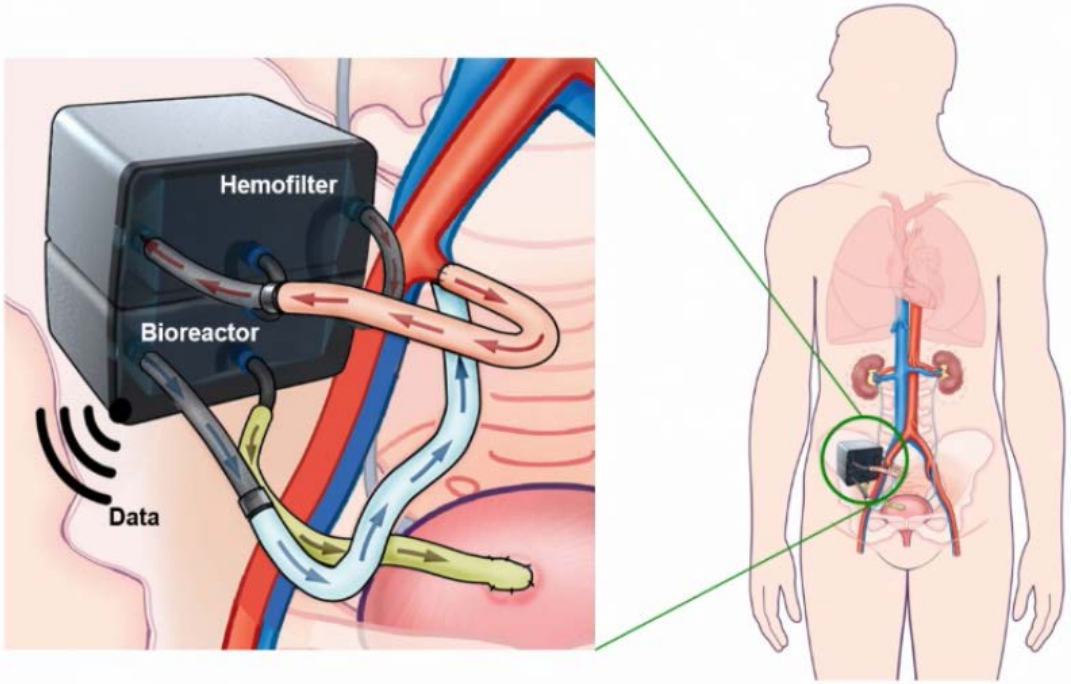
All showed positive results in large, double-blind RCTs.

Combs, ASN 2020

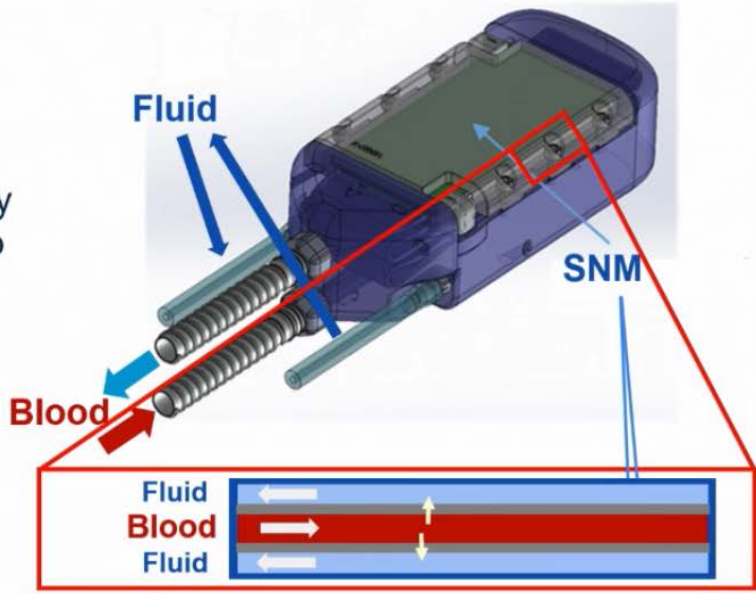
Future of Dialysis: Bioengineering Tools to Improve Kidney Therapies

- Xenotransplantation using genetically-engineered pig kidneys to bridge gap between long waitlist and insufficient donors
- Stem cell therapy to regrow and repair kidneys
- Tissue engineered AV grafts to customize vascular access
- Kidney Project - mechanical UF unit + bioreactor (kidney epithelial therapy unit) to provide tubular function

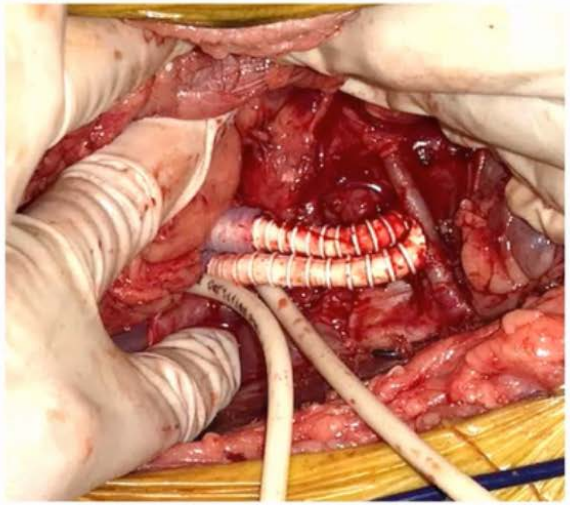
SNM Hemofilter: Device Refinement

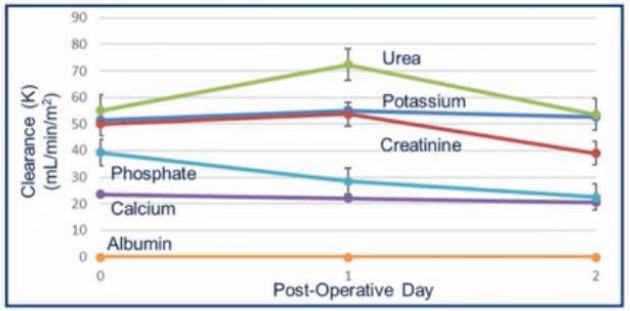


- Parallel SNM configuration
  - Low blood flow resistance
  - Eliminates blood pumps
  - Perfusion-pressure blood flow
- Refinement of implantation strategy in swine offers >90% patency up to 30 days
  - Subcutaneous or retroperitoneal
  - Silicone-reinforced ePTFE grafts
  - Anti-platelets agents only



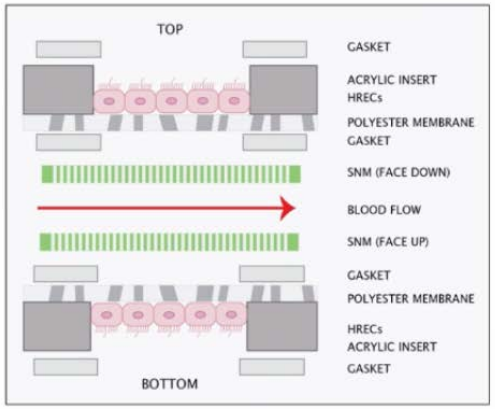
SNM Hemofilter: 3 Day Implanted Dialysis



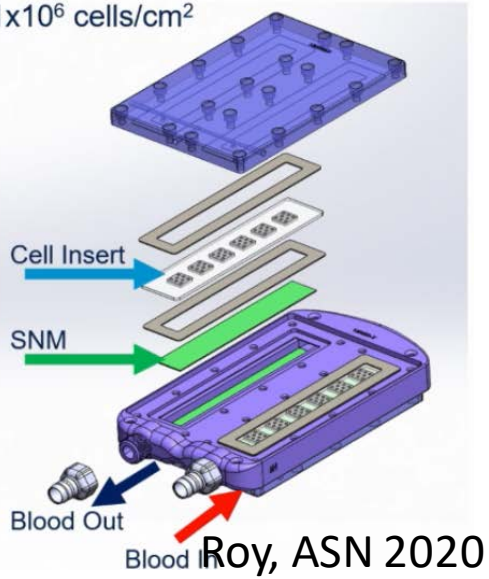


SNM Bioreactor: Device Construction

- Analogous to hemofilter
  - SNM for immunoprotection
  - Primary human renal tubule cells



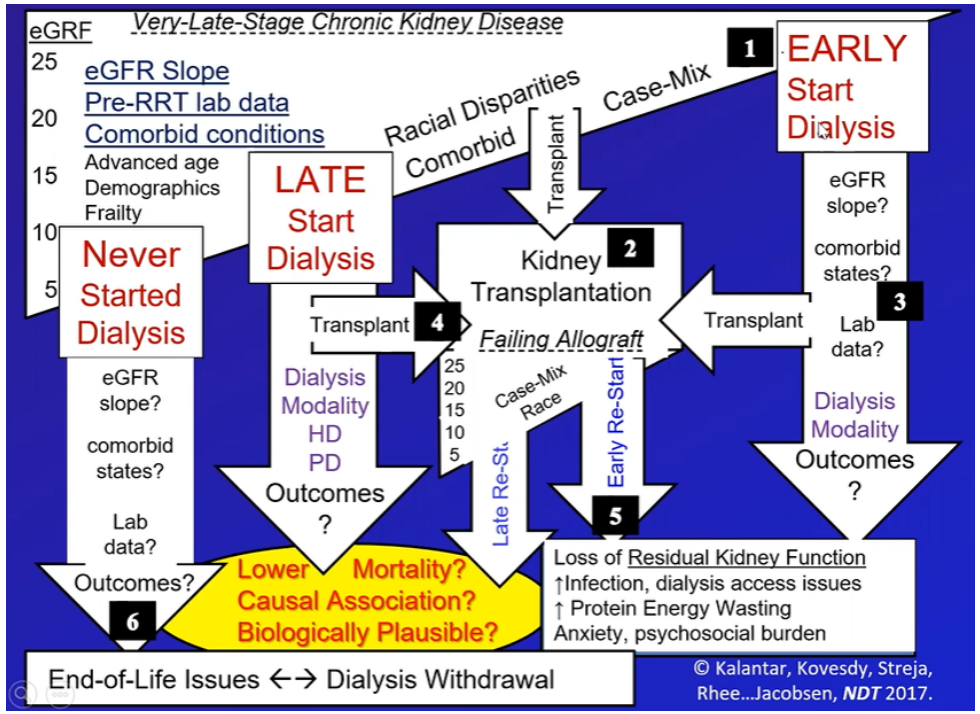
$1x10^6$ cells/cm²

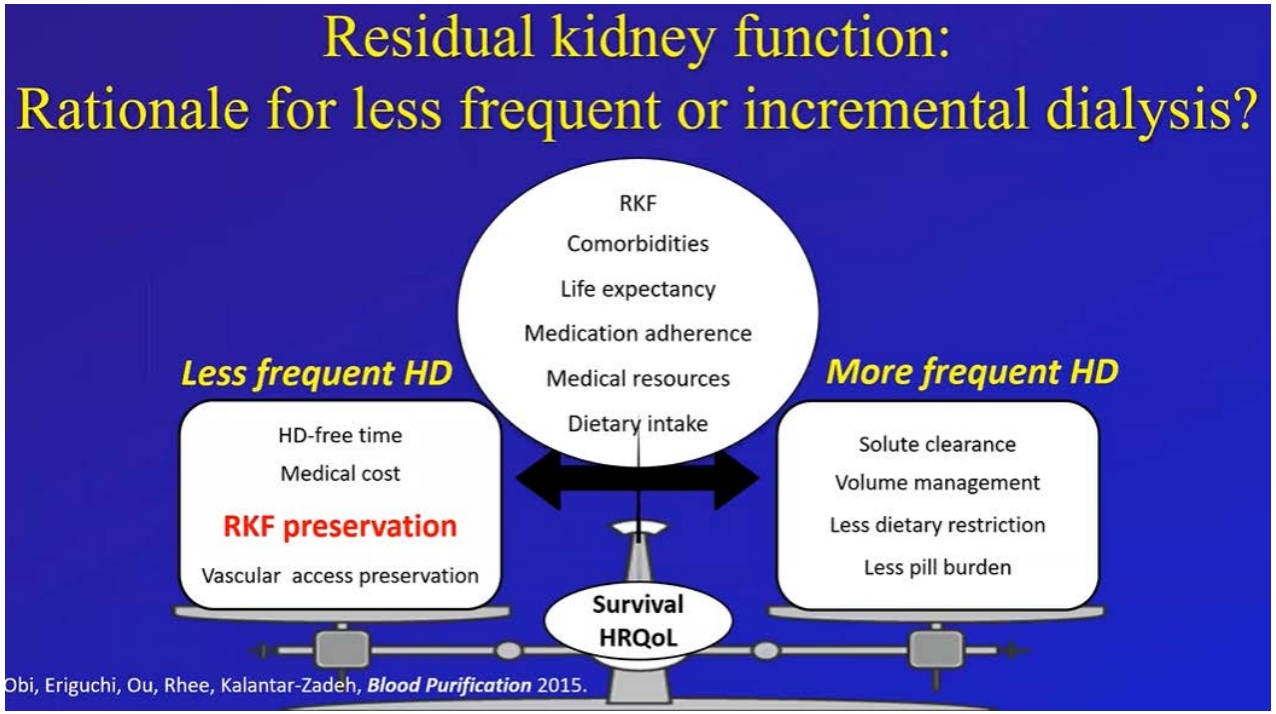


Roy, ASN 2020

Facilitating Change with Patient-Centred Interventions in Hemodialysis

- Shared-care improves patient engagement and outcomes
- Alternatives to usual dialysis schedules – transitional dialysis models
- Multi-faceted approach to overcome hurdles in improving uptake of home dialysis therapies



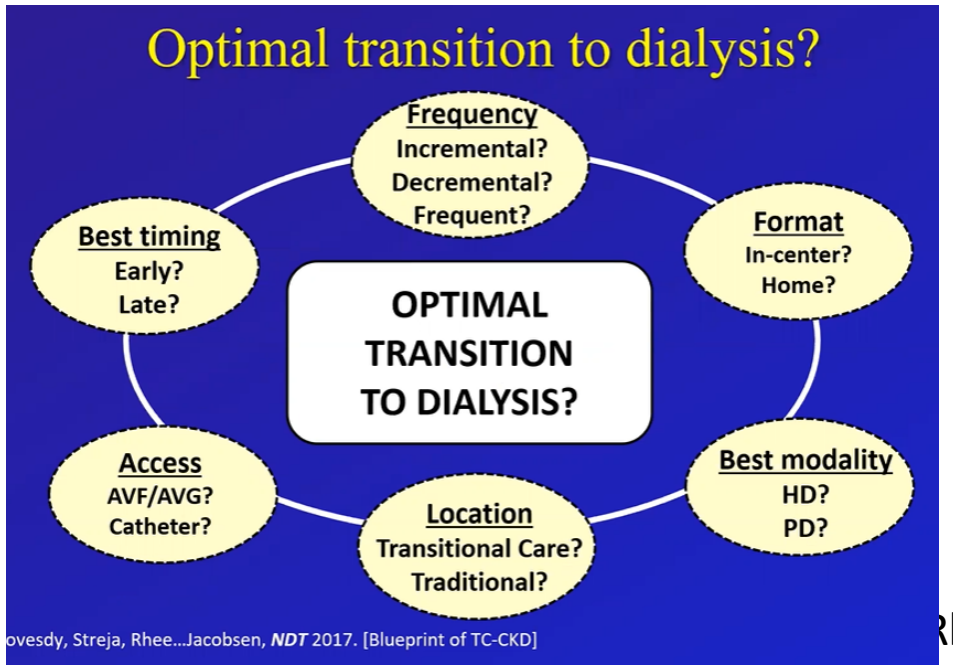


Suboptimal, crash & unplanned dialysis starts

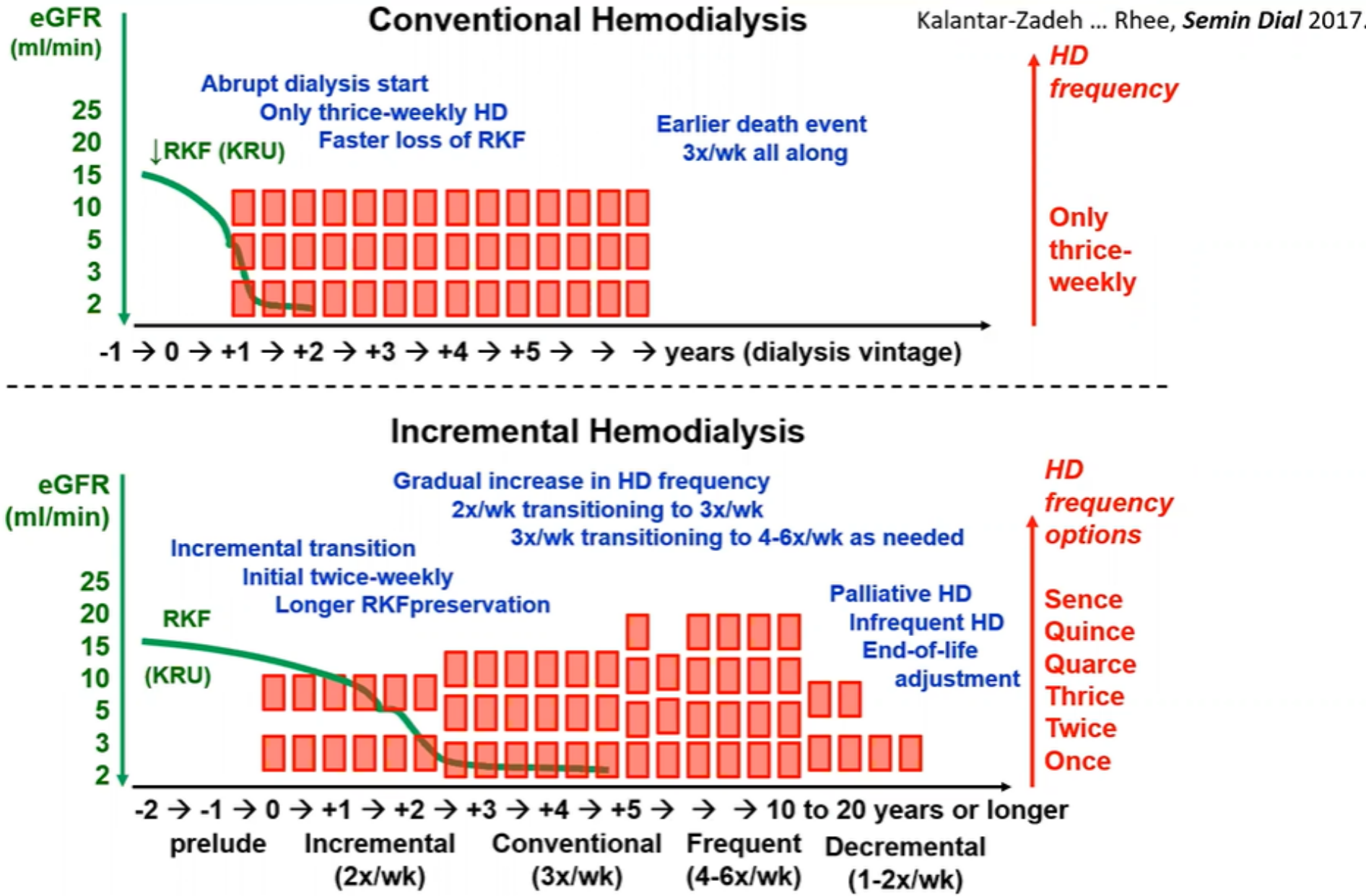
SUBOPTIMAL DIALYSIS	CRASH DIALYSIS	UNPLANNED DIALYSIS
Definition: • 1st dialysis treatment in a hospital setting, and/or • Initiating dialysis with a CVC.	**Definition:** • Referred late to nephrologist, • Little to no nephrology care prior to dialysis	**Definition:** • Does not start dialysis using his/her chosen modality, • Starts dialysis in-hospital, or • Starts dialysis with CVC

- *~21% of patients lack pre-ESRD care*
- *~23-38% of patients crash into dialysis*
- *~33-63% of patients initiate dialysis in an unplanned fashion.*

USRDS ADR 2019.
Soohoo...Rhee...Kalantar, *Mayo Clin Proc* 2018.
Molnar et al, *Syst Reviews* 2016.
Bowman et al, *AJKD* 2018.
Bowman, *CJASN* 2019.



Rhee, ASN 2020



Rhee, ASN 2020

Lachlan McMichael

- Educational Background
  - Advanced Nephrology Trainee, University of British Columbia
  - Prior nephrology training in Adelaide, Australia
    - Final year trainee with Royal Australian College of Physicians
  - Candidate - Masters of Medicine (Clinical Epidemiology)
  - MBBS, University of Adelaide, Australia

- Research Interests
  - Access to transplantation
  - Quality & safety in healthcare

Obesity & Transplantation

- Issue
  - High & increasing rates of obesity worldwide
  - Obesity associated with faster progression of CKD and higher numbers of patients presenting for assessment for renal transplantation
  - Potential barrier to access transplantation

- ASN Presentation Commentary
  - Difficulties in assessing obesity in patients presenting for transplant assessment
  - BMI is insufficient to assess obesity
  - No streamlined pathway for management of patients with obesity presenting for transplantation
  - Need to consider the whole patient including genetics, body habitus, muscle mass & social determinants of health
  - Need to be aware of our own biases towards patients with obesity

Timing is of the essence – Pregnancy in end-stage kidney disease

- Issue
  - Management and timing of pregnancy in patients with ESKD (CKD, dialysis, transplantation)

- ASN Discussion
  - Pregnancy in dialysis patients is more common than generally expected (17.8 pregnancies per 1000 person years)
  - Limited focus on discussion regarding family planning & contraception in dialysis & transplant patients
  - Need for comprehensive multi-disciplinary care for patients anticipating and planning pregnancy who are CKD, dialysis or transplant recipients

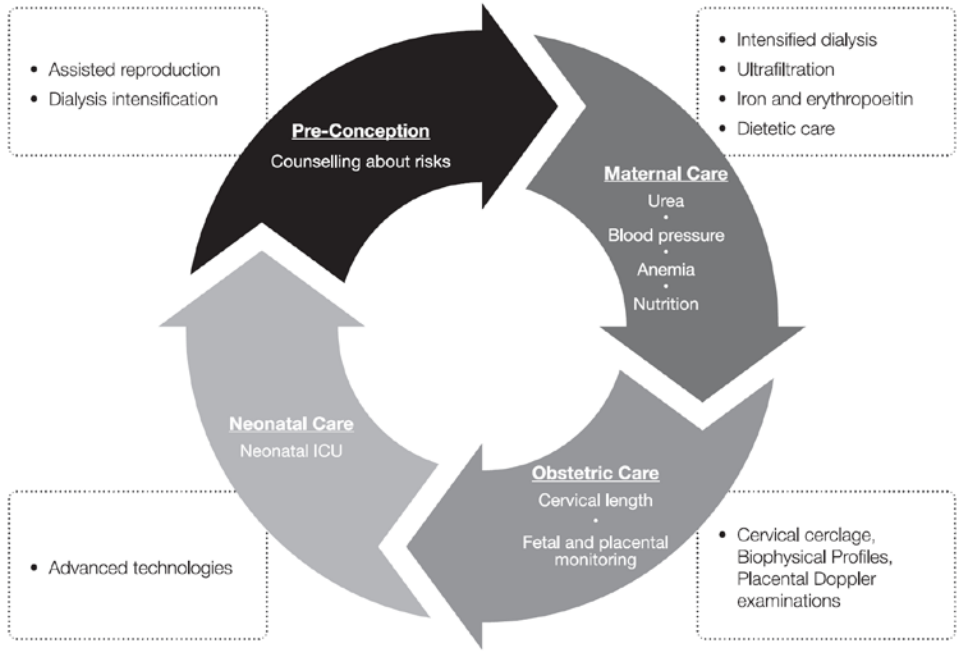
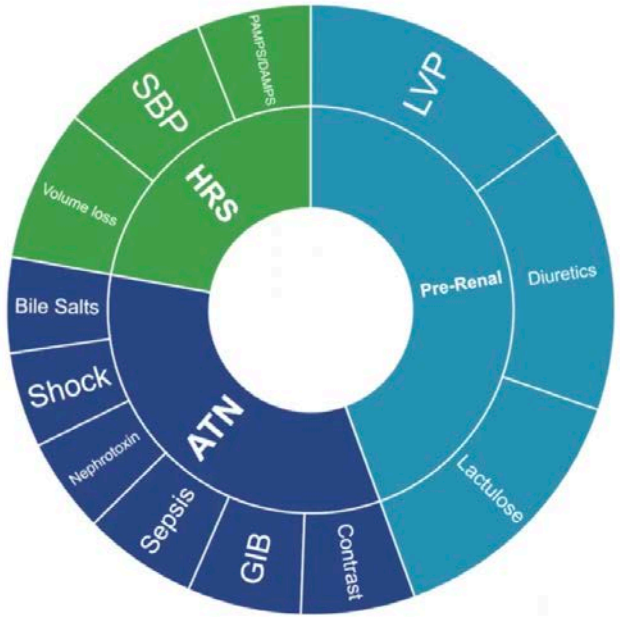


Figure 3. Multidisciplinary care of women on intensive hemodialysis. BPP, _____.

Hepatorenal syndrome type 1 – diagnosis, methods and management

- Issue
  - Common clinical encounter in acute inpatient nephrology
  - Difficult to manage and assess
- ASN Discussion
  - Reinforced for all clinicians that AKI in patients with cirrhosis is extremely challenging to assess, particularly differentiating ATN from HRS
  - The distinction between HRS and ATN is rarely pure
  - Limited effective treatments for established HRS however some progress towards the possibility of terlipressin in North America
  - Reinforced focus on conservative pathways for patients with HRS who are not transplant candidates



Precipitants are not specific to diagnoses

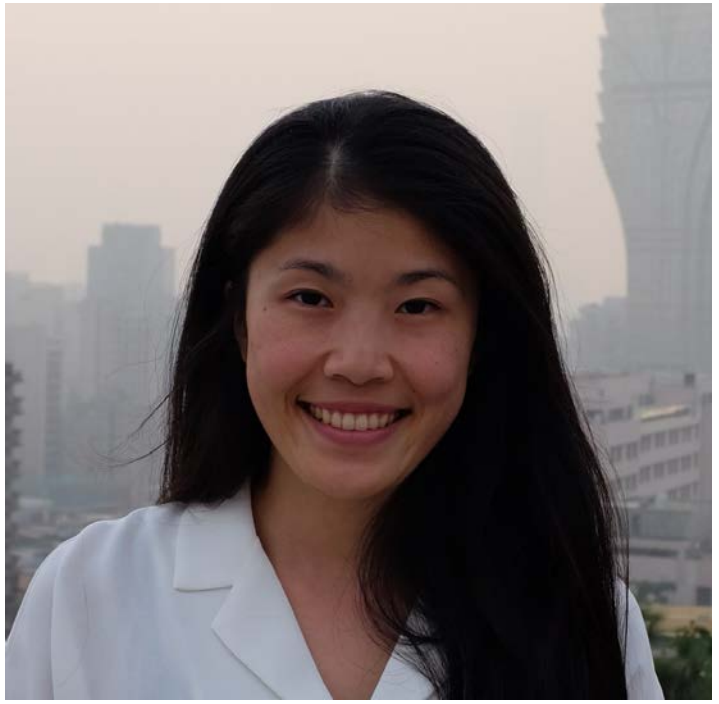
KIDNEY WEEK REIMAGINED

Shannon Wong

- Level of training: PGY4

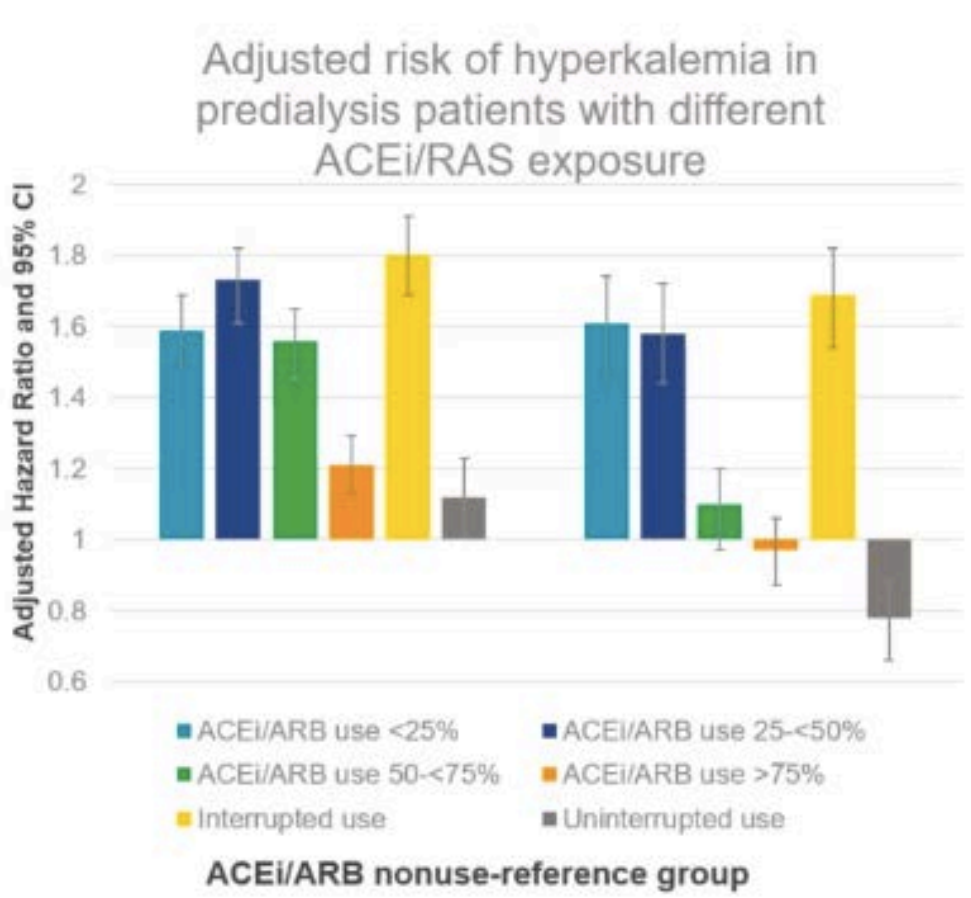
- Education background:
  - Bachelor of Science
  - UBC Medical School
  - UBC Internal Medicine

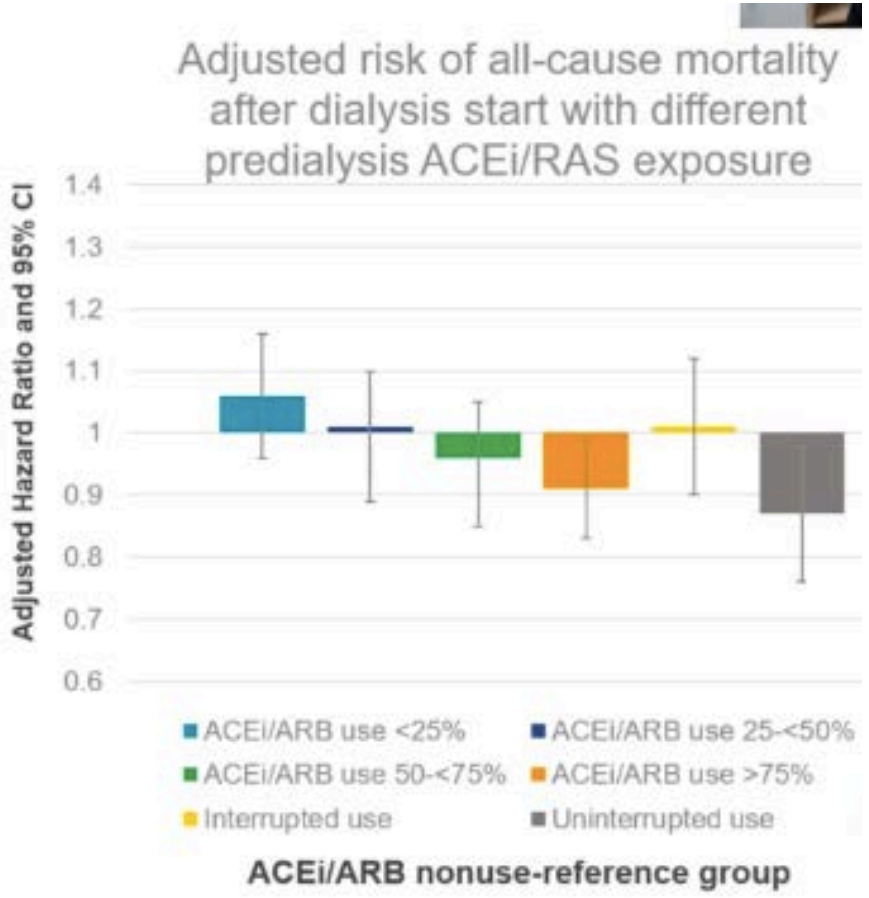
- Specific interests:
  - Integration of palliative care and home therapies
  - Feedback in medical education



Novel therapeutic options in hyperkalemia

STOP-ACEi Trial





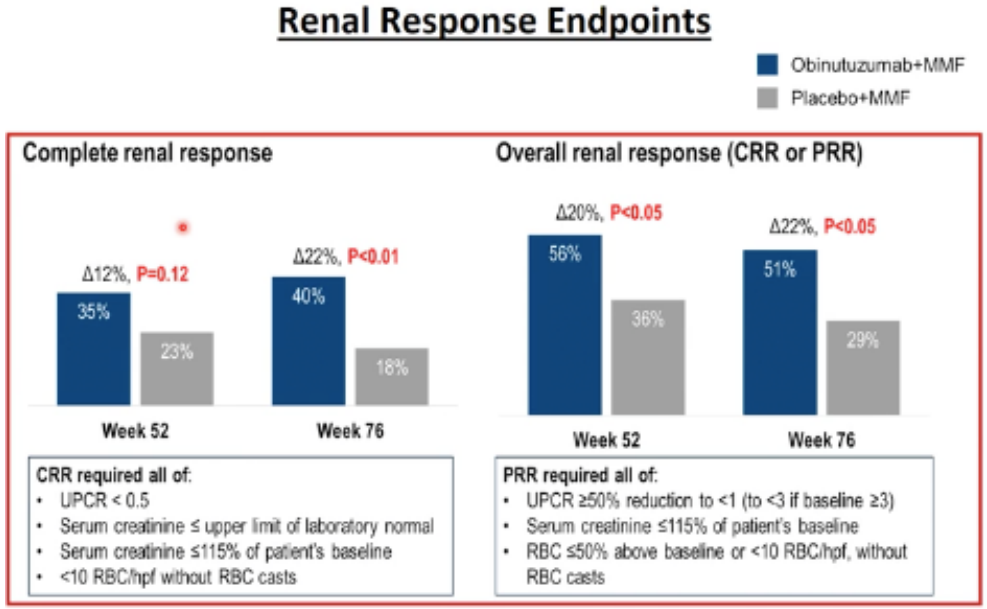
Management of Hyperkalemia

	Sodium Polystyrene Sulfonate	Patiromer	Sodium – Zirconium Cyclosilicate
Approval date	1958	2015	2018
Exchangeable ion	Nonspecific	Ca^{++}	Na^{+}, H^{+}
Initial effect	Variable	7 hrs	1 hr
Initial dose	15g	8.4g	10g Q8H x 48H
Maintenance dose	15g Q6H	8.4g QD	5-15g QD
Longest Duration studied	7 days	1 year	1 year
Storage	Room temp	Refrigerate	Room temp
Electrolytes	K, Ca, Mg	K, Ca, Mg	K
GI Symptoms	++	++	No
Colonic necrosis	+Colonic necrosis	No	No
Edema	+	No	++
Timing of Medications	Do not take other medications withing ~2-3 hours before/after any of these agents		

KIDNEY WEEK

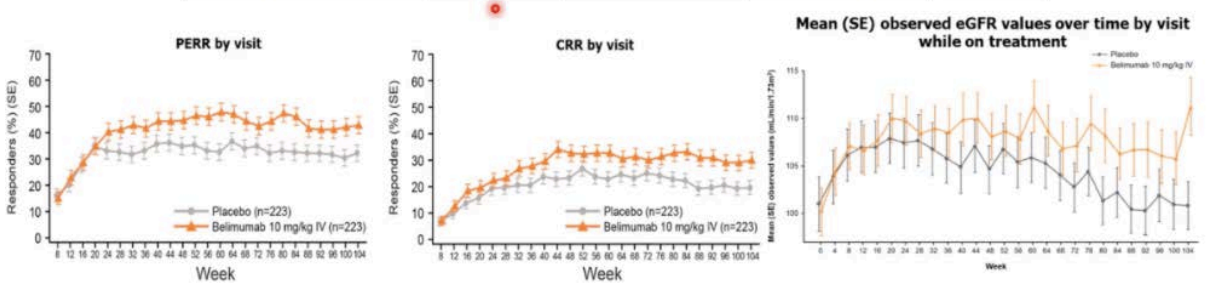
Lupus nephritis: Emerging Therapies

- Obinutuzumab (anti-CD20 monoclonal Ab)
  - NOBILITY trial
    - Proliferative LN, ethnically diverse population
    - All patients received MMF + methylpred and a prednisone taper
    - Significant difference in renal response in obi compared to placebo

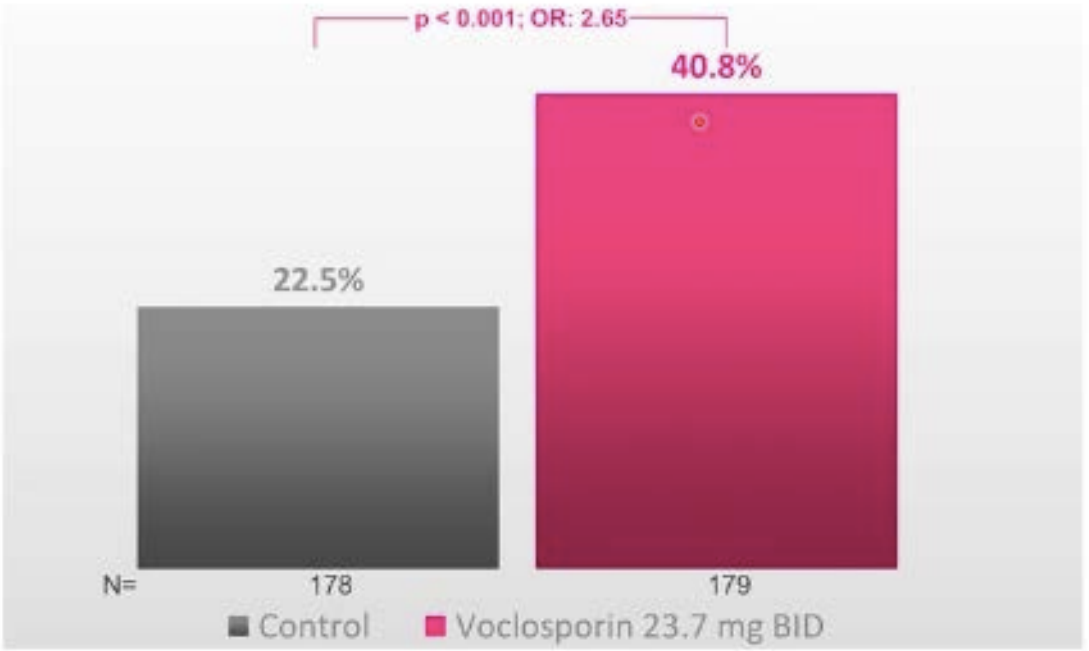


- Belimumab (monoclonal Ab against BLyS)
  - BLISS LN Trial
    - Proliferative and membranous LN
    - Randomized to induction with MMF + steroids vs. CYC + steroids
    - Addition of belimumab to SOC therapy showed significant difference in renal response

	Patients (%)		OR (95% CI)	p-value
	Placebo n=223	Belimumab 10 mg/kg IV n=223		
PERR at Week 104	72 (32.3)	96 (43.0)	1.55 (1.04, 2.32)	0.0311
CRR at Week 104	44 (19.7)	67 (30.0)	1.74 (1.11, 2.74)	0.0167



- Voclosporin (small molecule CNi)
  - AURORA trial
    - Proliferative LN
    - All patients received induction with MMF + methylpred and steroid taper
    - Significant increase in CRR in voclosporin compared to placebo

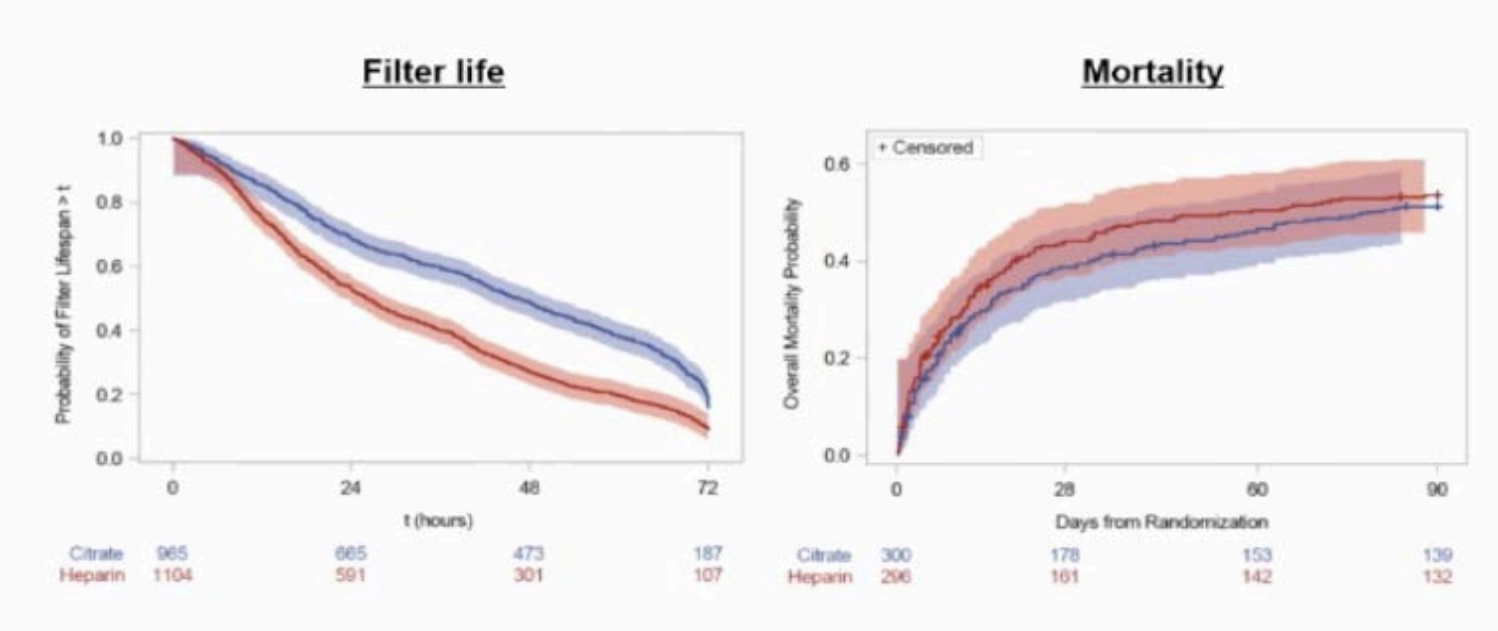


- When to consider these new drugs
  - Voclosporin
    - Consider in patients with evidence of significant podocyte injury, well-preserved renal function with minimal chronic changes on biopsy, or in whom steroid use must be minimized
  - B cell therapies
    - Consider in patients with impaired renal function and modest chronic changes on biopsy
    - Add on to modest dose MMF + modest dose steroids
    - Continue for at least 2 years, then B cell therapy alone

High Impact Clinical Trials

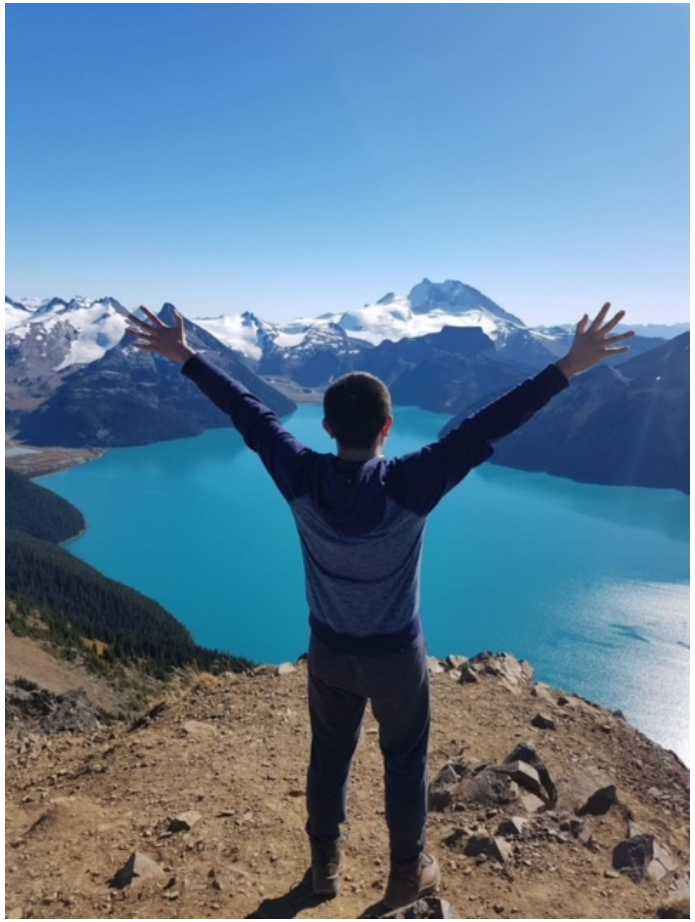
RICH Trial

- Hypothesis: citrate AC for CRRT increases filter life and decreases mortality in critically ill patients with AKI, compared to use of systemic heparin AC for CRRT
- Outcomes: filter life and 90-day all-cause mortality



- Conclusion: use of citrate AC leads to significantly longer dialysis filter lifespan, but no difference on mortality rate in critically ill patients with AKI compared to heparin

Introduction



Kevin Zhang PGY-5

Personalizing Care in Dialysis Vascular Access

- KDOQI 2019 Guidelines
- Shift in focus from ***fistula first, catheter last → ESRD Life-Plan***

- ***"Right patient, Right access, Right time and Right reasons"***

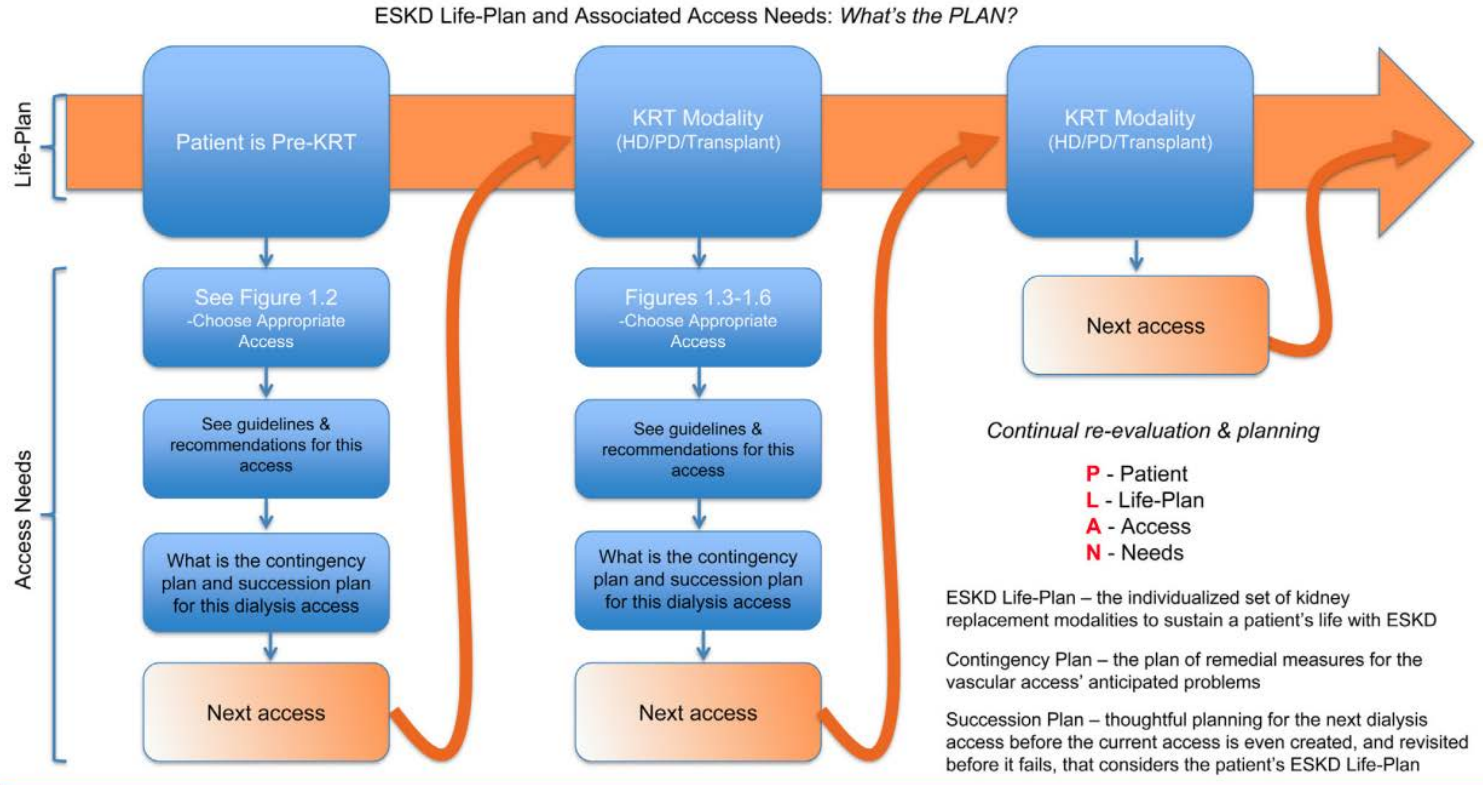


Figure 1.1. ESKD and Dialysis Access Life Plan: *What's the P-L-A-N?* Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; KRT, kidney replacement therapy.

Personalizing Care in Dialysis Vascular Access

- Monitoring *(physical exam and symptoms)*

  VERSUS

- Surveillance *(pressure/flow measures, imaging)*

- Reflect on local practice of access flow monitoring and use of IR angioplasty

Surveillance to Facilitate Patency

13.4 **There is inadequate evidence for KDOQI to make a recommendation on routine AVF surveillance by measuring access blood flow, pressure monitoring, or imaging for stenosis, that is additional to routine clinical monitoring, to improve access patency.**

Note: In other words, monitoring of vascular access is primary, while surveillance findings are supplementary, and action should not be based solely on surveillance findings.

13.5 **KDOQI does not suggest routine AVG surveillance by measuring access blood flow, pressure monitoring, or imaging for stenosis, that is additional to regular clinical monitoring, to improve AVG patency. (Conditional Recommendation, Low Quality of Evidence)**

Note: In other words, monitoring of vascular access is primary, while surveillance findings are supplementary, and action should not be based solely on surveillance findings.

Endovascular Intervention to Improve Patency

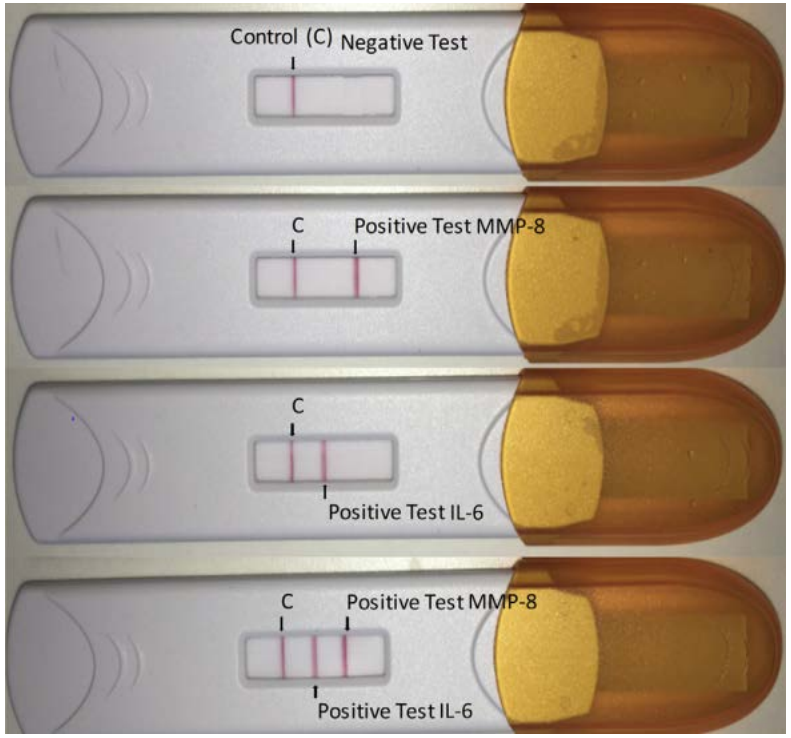
13.6 **KDOQI does not recommend pre-emptive angioplasty of AVFs with stenosis, not associated with clinical indicators, to improve access patency. (Conditional Recommendation, Moderate Quality of Evidence)**

Improving Peritoneal Dialysis Outcomes to Increase Its Use

- Shifting focus from Kt/V to patient centred goals and quality of life

The aim is to establish realistic care goals that (1) maintain quality of life for the person doing PD as much as possible by enabling them to meet their life goals, (2) minimize symptoms and treatment burden while (3) ensuring high-quality care is provided.

- Improving PD Peritonitis
  - Overall rate of PD peritonitis decreased over last two decades
  - Novel methods for identification of PD peritonitis with potential implications for practice are on the horizon



Improving Peritoneal Dialysis Outcomes to Increase Its Use

- SONG-PD initiative
  - Establishing meaningful and relevant outcomes
  - IE. Exercise program to reduce fatigue in patients receiving dialysis

- PD in the elderly
  - Aim to improve well-being while minimizing treatment burden
  - Focus on patient goals as opposed to clearance targets
  - Assisted PD programs in Japan as a representative example

THANK YOU!

ASN 2020 Kidney Week Thoughts & Takeaways

UBC Nephrology Fellows

BC Renal Provincewide Rounds

November 20, 2020