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CKD Insight Briefing
Heaven Can Wait: Progress Against Progression in CKD

Defined Health Insight Series Webinar
11 December 2013

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Senior Consultant, Defined Health
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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
Chronic Kidney Disease, a Major Burden On Global Health
What is CKD?

♦ Chronic kidney disease (CKD) is chronic loss of kidney function with evidence of kidney damage that is defined by a persistent reduced glomerular filtration rate (eGFR/ estimated glomerular filtration rate) and/or increased urinary albumin excretion.

♦ Diabetes, hypertension and CVD are the most common risk factors for development of CKD.
CKD is Increasingly Recognized as Highly Prevalent in Both the Developing And Developed World

♦ Current estimates of global prevalence of CKD indicate approximately 10% in adults, a prevalence with a burden similar to type II diabetes. At least a third of these patients have clinically significant kidney disease. Risk of CKD increases with age.

♦ In the US, the CKD population is growing at a rate in excess of the base population growth and aging rates (NHANES shows a CAGR of >6% from the mid-1990’s).

~160 M people worldwide with clinically significant renal impairment (CKD stage 3-5).
Why Should CKD be Treated?

♦ The functions of kidney expose it to the interior milieu of body unlike any other organ and at the same time makes the body composition very sensitive to changes in kidney function.

♦ Complications of chronic kidney disease include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anemia, mineral and bone disorders, and fractures.

The Lancet 2013; 382:158-169 (DOI:10.1016/S0140-6736(13)60439-0)
Pathophysiological Interactions Between Kidney and Heart
Even in Mild CKD Contribute to Adverse CV Events

♦ Chronic kidney disease contributes to decreased cardiac function, cardiac hypertrophy and increased risk of adverse cardiovascular events.

♦ While part of the increased risk can be due to high prevalence of traditional risk factors such as hypertension and diabetes, increased inflammation, metabolic derailment, sodium overload, erythropoietin resistance and sympathetic nerve overactivity are important contributing factors.

The Lancet 2013; 382:339-352 (DOI:10.1016/S0140-6736(13)60595-4)
Key Mechanisms of CVD risk in CKD Include Hypertension, Ventricular Hypertrophy, Inflammation And Acceleration Of Atherogenesis

- **Hypertension**: Even in the early phases chronic kidney disease can cause hypertension, which is likely to increase cardiovascular risk in affected patients.

- **Left Ventricular Hypertrophy**: In patients with early or advancing chronic kidney disease, the prevalence of left-ventricular hypertrophy is strikingly increased. Apart from hypertension, renal anemia and increased vascular stiffness might have pivotal roles in development of left-ventricular hypertrophy that leads to reduced coronary reserve.
  - The high prevalence of left-ventricular hypertrophy, with its associated risk of cardiac-rhythm disturbances, could at least partly explain why the prevalence of sudden cardiac death (~5-9 times higher) is increased in people with chronic kidney disease.

- **Dyslipidemia and low-grade inflammation** are also caused by chronic kidney disease. In patients with impaired kidney function and high albuminuria, lipid profiles become atherogenic, owing partly to defective HDL cholesterol function and excessive oxidation of LDL cholesterol.
  - Mechanisms of increased systemic inflammation in chronic kidney disease are unclear, but increased production of inflammatory mediators has been attributed to raised oxidative stress and accumulation of post synthetically modified proteins and toxins that are cleared with normal renal function.

*The Lancet 2013; 382:339-352 (DOI:10.1016/S0140-6736(13)60595-4)*
The Past Decade has Led to a Growing Recognition of CKD as a Significant Burden on Global Health

*First guidelines defining chronic kidney disease were developed only a decade ago in 2002, a need stemmed from the rising incidence and prevalence of end stage renal disease, with associated high cost and poor outcomes, and concerns about late referral to nephrologists. Indeed, Independent diagnosis codes for CKD stages 1-4 in the US were developed as recently as 2005!*

- Data that is collected mainly in the US and few other countries in the developed world indicate that independent of age, sex, ethnic group, and co-morbidity, strong, graded, and consistent associations exist between poor clinical prognosis and CKD.
- Furthermore, an increasing amount of evidence suggests that the kidneys are not only target organs of many diseases but also can strikingly aggravate or start systemic pathophysiological processes through their complex functions and effects on body homoeostasis.
Enormous Increase in Global Burden of Obesity, Type II Diabetes, Hypertension and CVD Contribute to CKD Burden

♦ There are currently over 240 million people with diabetes worldwide, a number that is expected to increase to 380 million by 2025, driven by obesity and sedentary lifestyles. About 40% of people with diabetes will develop CKD which increases the risk of cardiovascular and other complications of diabetes.

♦ Nearly one billion people worldwide have high blood pressure and that number is expected to increase to 1.56 billion by 2025. High blood pressure increases risk of CKD roughly 3 times.

In patients with diabetes, hypertension, or cardiovascular disease, the odds of a CKD diagnosis code are 2-4 times higher than in patients without these conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medicare (age 65+)</th>
<th>Adjusted odds of a CKD diagnosis code</th>
<th>Truven Health MarketScan (50-64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.1</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.7</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.4</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

National Institute of Diabetes & Digestive & Kidney Diseases, USRDS Annual Report 2013
CKD Independently Increases the Likelihood of Adverse Outcomes and High Health Care Costs of Cardiovascular Disease

♦ Despite Improvements in the management of hypertension, hyperlipidemia, hyperglycemia, and diabetes in patients with CKD over the last decade, data indicate that patients with CVD and CKD face much poorer outcomes than patients without CKD.
In the US, CKD Patients are 3-4 Times More Likely to be Hospitalized and Die than Patients Without CKD

- Hospitalization and mortality rates are further increased with disease progression.
In Addition, Rehospitalization Rates Continue to be High, Indicating a Lack of Ability to Manage Disease Progression

- CKD patients not only have higher overall hospitalization rates than those seen in the general population, but their rehospitalization rates are higher as well. The lack of improvement in rehospitalization rates over the past decade is a source of concern.
Progression to End Stage Renal Disease, although Occurring in a Small Percent of Patients, is Often Catastrophic

- End-stage renal disease (ESRD) requires costly renal replacement therapy in the form of dialysis or transplantation.
- In developed countries, ESRD is a major cost driver for health-care systems, with annual growth of dialysis programs ranging between 6% and 12% over the past two decades and continuing to grow, particularly in developing countries.
- Over 2 million people now require renal replacement therapy to sustain life worldwide, but this likely represents less than 10% of those who need it.
As a Result, Drug Costs and Fee For Service Costs are Ballooning, Especially In Medicare Patients

♦ In 2011 PartD costs for Medicare CKD patients were $5.26B.
Patients With CKD Make Up ~10% of Medicare Population But Account for ~24% of Total Medicare Expenses

The assessments below do not include ESRD patients on dialysis or with a kidney transplant, who account for another 6.4 percent of fee-for-service expenditures. The combined CKD and ESRD populations are thus associated with 24 percent of the budget, a number greater than that associated with CHF.

Costs of caring for patients with CKD in 2011

- Overall, patients with CKD account for 18% of total Medicare expenditures
- CKD patients with diabetes account for 29% of Medicare diabetes expenditures
- CKD patients with congestive heart failure account for 39% of Medicare CHF expenditures

CKD: $45.5 billion
Medicare total: $249.8 billion

CKD + diabetes: $24.6 billion
Medicare diabetes: $85.9 billion

CKD + CHF: $21.2 billion
Medicare CHF: $54.7 billion

CMS, USRDS
Last But Not Least, CKD Complicates Management of a Myriad of Other Conditions Due to Impaired Metabolism

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Adjust Dose</th>
<th>Avoid in Stages 4 and 5 of CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Beta Blockers: Acebutolol, atenolol, bisoprolol, nadolol, sotalol</td>
<td>Sotalol</td>
</tr>
<tr>
<td>A</td>
<td>ACE inhibitors /ARBs*: All ACE inhibitors</td>
<td>Olmesartan</td>
</tr>
<tr>
<td>N</td>
<td>NSAIDS**, Opioids: Codeine, morphine, oxycodone, tramadol</td>
<td>All NSAIDS, meperidine</td>
</tr>
<tr>
<td>D</td>
<td>Diuretics: Potassium sparing diuretics, thiazide diuretics</td>
<td>Potassium sparing diuretics, thiazide diuretics</td>
</tr>
<tr>
<td>D</td>
<td>Diabetic medications: Gliclazide, acarbose, insulin, gliptins</td>
<td>Glyburide, metformin, exanitide</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol medications: Pravastatin, rosvastatin; fibrates</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Antimicrobials: (Dose reductions are often delayed for 24–48 hours to allow for aggressive dosing/drug to reach steady state) <strong>Antibiotics</strong>: Most antibiotics EXCEPT cloxacillin, clindamycin, metronidazole, erythromycin, azithromycin <strong>Antifungals</strong>: fluconazole, itraconazole <strong>Antivirals</strong>: acyclovir, famciclovir, valacyclovir</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>M</td>
<td>Miscellaneous: Allopurinol, colchicine, digoxin, H₂RAs***</td>
<td>New anticoagulants</td>
</tr>
<tr>
<td>P</td>
<td>Psychotropics: Lithium; gabapentin, pregabalin, topiramate, vigabatrin; bupropion, duloxetine, paroxetine, venlafaxine</td>
<td></td>
</tr>
</tbody>
</table>

*ARBS – angiotensin II receptor blockers; **NSAIDs – nonsteroidal anti-inflammatory drugs; ***H₂RAs – Histamine-2 receptor antagonists

www.druginfo.USSK.CA
Section Summary

♦ Chronic kidney disease (CKD) is increasingly recognized as an enormous public health problem closely linked to cardiovascular disease and diabetes, the two most profound negative drivers of global human health moving forward.

♦ While significantly worsening outcomes of both these diseases, CKD independently increases the likelihood of adverse outcomes and high health care costs.

♦ Evidence indicates that even mild-moderate CKD can have detrimental effect on hypertension, dyslipidemia and CV outcomes.

♦ In order to avoid the burden on progression into later stages and CVD complications, it is important to diagnose declining renal function early in the disease course and manage risk factors for complications.
CKD Current Management and Challenges
# Current Treatments Focus on Reducing General CV Risk Factors and Managing Complications

<table>
<thead>
<tr>
<th>Treatment goal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP reduction</td>
<td>In patients with CKD, reduce BP to 140/90 mm Hg (18); if BP ≥130 mg/dL, reduce BP to &lt;125/80 mm Hg (21). BP targets and agents should be set individually according to risk of CVD progression, age, coexistent cardiovascular disease other comorbidities, presence or absence of retinopathy, and tolerance.</td>
</tr>
<tr>
<td>Inhibition of RAAS</td>
<td>Use ACE inhibitors or ARBs in patients with diabetes and ACR ≥30 mg/dL or in those with significant proteinuria and ACR ≥20 mg/dL (21). Post hoc analyses of RCTs show that treatment-induced reduction in albuminuria was associated with improved outcomes, which suggests that reductions in albuminuria might help to guide treatment. These adjustments are generally not necessary unless contraindicated by side effects (hyperkalemia or acute renal dysfunction).</td>
</tr>
<tr>
<td>Glycaemic control</td>
<td>Hemoglobin A1c &lt;7.0% of total hemoglobin (1A)</td>
</tr>
<tr>
<td>Fluid control</td>
<td>ナガレクライアットが存在するCKD患者のため、体重を基準に水の摂取と排泄を管理する。\n</td>
</tr>
<tr>
<td>Haemoglobin control</td>
<td>Consider erythropoiesis-stimulating treatment to increase haemoglobin concentrations on individual basis.</td>
</tr>
<tr>
<td>Phosphate reduction</td>
<td>Use phosphate binders and diet in patients with serum phosphate concentrations more than the normal range (2C). Evidence from observational studies suggests that serum phosphate concentrations higher than the normal range are associated with increased cardiovascular morbidity and mortality. Therefore, there is a lack of RCT data to show that lowering phosphorous concentrations positively affects cardiovascular and CKD clinical outcomes. An individualized treatment approach, therefore, seems reasonable.</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td>Create vitamin D deficiency</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Lower uric acid concentrations in serum</td>
</tr>
</tbody>
</table>

Lancet.org

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CKD Insight Briefing
However, the Absolute Risk of Adverse Outcomes in CKD Continues to be High Despite Improvements in Care

♦ Challenges that need to be addressed to improve care include
  ♦ Fragmented management of patients between specialties
  ♦ Continued lack of proper diagnosis of early stages of CKD and Identification of patients at higher risk for progression
  ♦ Lack of sensitive prognostic biomarkers to study effect of novel therapies that directly address disease progression
  ♦ Incomplete understanding of disease pathophysiology
While Diagnosis of CKD is Increasing, Continued Underreporting Indicates the Need for Increased Education

♦ In the US New stage-specific ICD-9-CM codes (585.x) were introduced in 2005, providing an opportunity to track populations with reported diagnosis codes over time.

♦ Analyses which include these codes show evidence of a growing recognition of CKD.

♦ The continued under-reporting of CKD through diagnosis codes, however, becomes clear when comparing rates obtained from the codes to those from the NHANES cohort, in which CKD is identified through biochemical data.

♦ Continued efforts of organizations such as KDIGO (kidney disease improving global outcomes) and KDOQI (Kidney Disease Outcomes Quality Initiative) are driving increasing awareness. In addition, we believe that the increasing drug development activity and increase in awareness and diagnosis of non-dialysis CKD will drive better diagnosis and collaboration between physician specialties.
Fragmented Physician Management of CKD, Second Challenge for Appropriate Care of Early CKD

♦ In the US, Medicare patients age 65 and older are twice as likely to see a cardiologist as a nephrologist following any diagnosis for CKD.

![Chart showing physician management of CKD]
Fragmented Physician Management of CKD, Second Challenge for Appropriate Care of Early CKD

♦ Among those with more advanced CKD (Stage 3 or higher), in contrast, 45–60 percent visit a nephrologist. It will be important to assess any differences in treatment among the referred and non-referred populations, and ways in which these differences might affect adverse outcomes.

♦ Collaboration across general and specialized health-care professionals is needed to fully address the challenge of diagnosis and prevention of acute and chronic kidney disease and improve outcomes.
Lack of Sensitive Prognostic Biomarkers, Another Challenge for Improving Care

- CKD is a highly heterogeneous disease with marked variations in progression and outcomes among patients.
- While proteinuria is the most sensitive marker of CKD progression in clinical practice, especially when combined with eGFR, both have their limitations.
- It is important to be able to identify those at high risk of CKD progression and its associated cardiovascular disease (CVD).
- The search for new relevant biomarkers to better stratify patients with CKD according to the risk of progression, morbidity, and mortality is current underway.
- The following section will discuss some of the emerging markers in CKD and CVD associated with CKD.
Section Summary

♦ Current treatments focus on reducing general CV risk factors such as diabetes and hypertension and managing severe complications.

♦ However, despite significant improvements in care of CKD patients, especially non-dialysis CKD patients in the last decade, the absolute risk of adverse events in this population remains high.

♦ Challenges/ unmet needs that need to be addressed in the future to improve patient care of pre-dialysis CKD include:
  ♦ Fragmented management of patients between specialists
  ♦ Continued lack of proper diagnosis of early stages of CKD and ability to identify patients at higher risk of progression
  ♦ Lack of sensitive prognostic biomarkers to study the effect of novel therapies that directly address disease progression
  ♦ Incomplete understanding of disease pathophysiology
Emerging CKD Biomarkers, in Addition to Creatinine, Albuminuria and eGFR
Biomarkers in CKD Progression

Currently used
- albuminuria
- eGFR

New and not yet validated
- NGAL
- KIM-1
- L-FABP
- Many others
A Number of Biomarkers Have Been Identified Recently Based on Current Understanding of Pathophysiology

Oxidative stress
- Oxidized low-density lipoproteins (Ox-LDL)
- Advanced oxidation protein products (AOPP)
- Thiobarbituric acid reactive substances (TBARS)
- Plasma and urinary F₂ isoprostanes
- Malondialdehyde (MDA)
- Protein reduced thiols
- Protein carbonyls
- Advanced glycation end products (AGE)
- Urinary 8-hydroxydeoxyguanosine (8-OHdG)
- 4-hydroxy-2-nonenal
- Total antioxidant status
- Antioxidant enzyme activity

Inflammation
- C-reactive protein (CRP)
- Pentraxin-3 (PTX3)
- Soluble tumor necrosis factor receptor II (sTNF-RII)
- Tumor necrosis factor alpha (TNFα)
- Interleukin-18
- Tnema cin
- Tissue inhibitor of metalloproteinases-1 (TIMP-1)
- CD14 mononuclear cells

Kidney function
- Cystatin C
- B-trace protein

Glomerular injury
- Podocin
- Nephlin
- Podocalyxin

Tubulointerstitial injury
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Kidney injury molecule-1 (KIM-1)
- Neutrophil elastase
- Lipase-type fatty acid binding protein (L-FABP)
- Tenascin and TIMP-1

Metabolic disorders
- Adiponectin
- Apolipoprotein A-I (ApoA-I)
- Fibroblast growth factor-23 (FGF-23)

Endothelial dysfunction
- Asymmetric dimethylarginine (ADMA)
- Uric acid

Fibrosis
- Fibrinogen
- Transforming growth factor-β1 (TGF-β1)

Cardiovascular dysfunction
- Atrial natriuretic peptide (ANP)
- Brain natriuretic peptide (BNP)
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- Cardiac troponin (cTnT)
- Skeletal troponin T and I
- Adrenomedullin
- Fibrinogen

Kidney International (2011) 80, 806–821
Several Sizable Studies are Underway Testing Imaging and Serum/ Urinary Markers of CKD Progression

<table>
<thead>
<tr>
<th>Name Of Study</th>
<th>Outcomes Being Measured</th>
<th>Number of Patients</th>
<th>Expected completion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CanPREDDICT - Canadian Study of Prediction of Risk and Evolution to Dialysis, Death and Interim Cardiovascular Events Over Time</td>
<td>will analyze the demographics, clinical status, medications and blood and urine samples of these patients and study the conventional biochemical, hormonal and metabolic parameters assessing which underlying biomarkers reflect the processes involved with disease progression.</td>
<td>2500 prevalent Chronic Kidney Disease (CKD) patients with Glomerular Filtration Rate (GFR) from 15-45 ml/min followed for 30 months.</td>
<td>2014</td>
<td>ADMA, IL6, CRP, ProBNP, troponin, vitamin D (25 and 1,25) and cystatin C being measured.</td>
</tr>
<tr>
<td>NEFRONA- Usefulness of imaging techniques and novel biomarkers in the prediction of cardiovascular risk in patients with CKD in Spain</td>
<td>Outcomes include CV events and mortality, carotid intima-media thickness, a composite atherosclerosis score, and biomarkers</td>
<td>2661 patients and 843 controls into a prospective observational study</td>
<td>Completed</td>
<td>DN confers a two-fold higher adjusted risk of severe silent AD as compared with patients with CKD secondary to other etiologies.</td>
</tr>
<tr>
<td>Inflammatory Markers and Adverse Outcomes in Chronic Kidney Disease (AIMtoPREVENT)</td>
<td>The goal is to determine whether and how rates of renal disease progression are affected by inflammatory markers, FGF23 levels, and genetic polymorphisms</td>
<td>2530 severe renal impairment patients</td>
<td>2016</td>
<td></td>
</tr>
</tbody>
</table>
NGAL as a Marker for CKD Progression

♦ The exact physiologic role played in the kidney by NGAL (also called lipocalin - 2 or siderocalin), a 25-kD protein, remains a mystery. It is thought to be involved in renal morphogenesis, such as induction of repair and reepithelialization.

♦ NGAL has been shown to be elevated in the plasma and urine of animal models of ischemic and nephrotoxic acute kidney injury and, considered a novel urinary biomarker for ischemic injury.

♦ Recent interest has focused on NGAL as a biomarker of CVD as well as in AKI and CKD progression. In a recent pilot study, plasma NGAL levels increased in parallel with predictive indicators of CVD, with plasma NGAL levels 4783 ng/ml correlating with CVD mortality after 2 years.
Cystatin C as a Marker for CKD Progression and CVD Risk

- Cystatin C is a 13-kD cysteine protease inhibitor that has gained popularity as an alternative to serum creatinine in the measurement of renal function of the glomerular filtration rate (GFR).
- In patients with CKD, elevated plasma levels of cystatin C are associated with all-cause mortality, cardiovascular events, and incident heart failure.

Using Cystatin C

Clinical Considerations with Varying Degrees of Kidney Function

**Early Kidney Disease**

According to early reports, cystatin C may detect mild to moderate decreases in GFR that are not evident with serum creatinine-based measurements. Some studies suggested that CysC-CFR was better than creatinine-based estimates of GFR at GFR levels >60 mL/min/1.73 m² (CKD stages 1 and 2). In addition, CysC-CFR appeared to be better correlated with microalbuminuria, while MDRD and CG creatinine estimates of GFR tend to reflect only proteinuria. Using CysC-CFR, over one-third of type 1 diabetes patients with microalbuminuria at the time of enrollment already had evidence of mild (CysC-CFR <90) or moderate (CysC-CFR <60 mL/min/1.73 m²) CKD.

**Kidney Transplantation**

Cystatin C-CFR after transplant has been used to detect allograft rejection and monitor drug nephrotoxicity, with reported diagnostic value. In kidney transplant patients, cystatin C was reported to be more sensitive than serum creatinine for detecting decreases in GFR and delayed graft function, offering an opportunity for timely intervention. Follow-up studies have found GFR was overestimated 30% when derived from plasma creatinine levels. Even though cystatin C underestimated GFR by 14%, it was still more sensitive in detecting kidney damage, with no false-negative results. Note also, though, that routine or rejection-naïve treatment with corticosteroids led to a significantly increased serum cystatin C concentration.

**Acute Kidney Injury (AKI)**

Serum cystatin C has been reported to outperform conventional biomarkers in the prediction of AKI and to have prognostic value of the need for kidney transplant and in-hospital mortality. Cystatin C has been reported to increase about one to two days earlier than serum creatinine in patients developing AKI. AKI is not rare in hospitalized patients, with a mortality rate estimated to be between 30% and 90%.
FGF-23 as a Marker for CVD Risk in CKD and Potential Therapeutic Target

♦ Elevated plasma levels of the phosphaturic hormone fibroblast growth factor 23 (FGF-23) are a hallmark of chronic kidney disease (CKD)-mineral and bone disorder.

♦ FGF-23 allows serum phosphate levels to stay within physiological limits until end-stage renal disease is reached.

♦ However, despite its seemingly beneficial role in phosphate homeostasis, several prospective studies in dialysis patients and in patients with less advanced CKD associated elevated FGF-23 with poor cardiovascular and renal outcome.

♦ Moreover, very recent evidence suggests an adverse prognostic impact of elevated FGF-23 even in subjects without manifest CKD.

♦ In vitro studies indicate a pathophysiological role of FGF-23 in the pathogenesis of myocardial injury.

Serum phosphate regulation. Black arrows indicate activating pathways; red lines indicate inhibitory pathway. Note the exact pathways by which phosphate triggers PTH and FGF-23 secretion, and the direct link between PTH and FGF-23 await further experimental studies, as indicated by dotted arrows.
Section Summary

♦ In conclusion, the search for new relevant biomarkers to better stratify patients with CKD according to the risk of progression, morbidity, and mortality is underway.

♦ Early studies indicate promise but further validation is required in larger, more diverse populations before translation into clinical practice.

♦ NGAL has promise as a biomarker of CKD progression and cystatin C as a biomarker of kidney function, CKD progression, and cardiovascular risk and FGF-23 as a marker for CVD risk.

♦ It is unlikely that a single marker will satisfy the requirement of predicting CKD progression and cardiovascular morbidity and mortality as it would be unlikely to reflect the complexities of the multiple pathophysiological processes involved in CKD progression or the underlying primary renal disease. It is more likely that a focused panel of biomarkers will be most rewarding.
Novel Drug Strategies and Pipeline Overview
Increased Pipeline Activity in Complication Management in Pre-dialysis CKD, Including Anemia

♦ With increasing evidence of the benefit of addressing complications, and guidelines defining use of agents addressing complications in pre-dialysis CKD, there is a push to expand the current multi billion dollar supportive care market for ESRD into pre-dialysis CKD.

**Table 26. Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3 and 4**

<table>
<thead>
<tr>
<th>Serum 25(OH)D (ng/mL) [nmol/L]</th>
<th>Definition</th>
<th>Ergocalciferol Dose (Vitamin D₂)</th>
<th>Duration (months)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 [12]</td>
<td>Severe vitamin D deficiency</td>
<td>50,000 IU/wk orally x 12 wks; then monthly</td>
<td>6 months</td>
<td>Measure 25(OH)D levels after 6 months</td>
</tr>
<tr>
<td>5-15 [12-37]</td>
<td>Mild vitamin D deficiency</td>
<td>500,000 IU as single I.M. dose</td>
<td>6 months</td>
<td>Assure patient adherence; measure 25(OH)D at 6 months</td>
</tr>
<tr>
<td>16-30 [40-75]</td>
<td>Vitamin D insufficiency</td>
<td>50,000 IU/wk x 4 weeks</td>
<td>6 months</td>
<td>Measure 25(OH)D levels after 6 months</td>
</tr>
</tbody>
</table>

Increasing Evidence of Benefit of Anemia Treatment in Nondialysis: Recent studies suggest that anemia care in nondialysis is far more than palliative. Gouva (2004) showed that anemia treatment in CKD slowed renal disease progression compared with no anemia treatment,¹ raising the possibility that low dose EPO is renoprotective.² In addition, according to a pharmacoeconomic study of employees with nondialysis CKD, anemia treatment was associated with increased hemoglobin levels, improved productivity, and decreased direct employer costs, ultimately saving approximately $4400 per patient per year.³ In addition, major policy organizations are lining up in favor of early therapy in CKD. One example is the UK National Institute of Clinical Excellence (NICE). NICE stated in their 2006 monograph on anemia treatment that “the patients most likely to derive the greatest long-term benefit from correction of anemia are those with chronic kidney disease who are non-dialysis. Early intervention to correct anemia has the potential to impact on the progression of chronic kidney disease and affect patient morbidity, hospitalization rates, quality of life and mortality.”

DH secondary research ; KDIQO 2012 clinical practice guidelines
Increased Pipeline Activity in Complication Management in Pre-dialysis CKD, Including Anemia

- Factors driving the growth of pipeline activity for CKD complications include:
  - **Identification of MOAs that can be targeted with orally delivered drugs.** This is particularly important since most patients receive care from PCPs in the outpatient setting. Examples include HIF-PHI (hypoxia inducible factor-prolyl hydroxylase inhibitor; Bayer, Fibrogen) and Zerenex (oral phosphate binder, Keryx Biopharmaceuticals).
  - **Improved guidelines for use of drugs addressing complications in pre-dialysis CKD.**
  - **Increasing evidence that on an individualized basis, early intervention is likely beneficial to CV outcomes.**
Roughly 30% of CKD pipeline Activity is Focused on Pre-dialysis CKD

- Increasing diagnosis and awareness of CKD Stage 3-4 (moderate to severe renal impairment), especially in diabetics, has made this large population, which is many fold larger than the end stage renal disease (ESRD) population, more attractive to drug developers.

### CKD Pipeline By Indication

- Total number of agents: 90
- Highest phase: preclinical to marketed = 90

- 39% ESRD
- 33% Pre-dialysis CKD
- 19% Undefined
- 9% Both

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ADIS R&D Insight, DH analysis
The Majority of Agents in Development for Pre-dialysis CKD Address Complication Management as the Obvious Low Hanging Fruit

Total number of agents
Highest phase: preclinical to marketed = 20

Pre-dialysis CKD

24%

Complication management

76%

Disease modifying MOA
Less Than 20% of the CKD Pipeline (Including ESRD) is Targeting ‘Disease Modification’ MOAs

- Disease modifying MOAs include endothelin receptor A antagonists, antioxidants, anti-inflammatory molecules, anti-fibrotic MOAs and Galactin-3 inhibitors.
The Majority of Disease Modifying MOAs are in Pre-POC Development and are Not Partnered

♦ The sole Phase III agent listed in the Adis R&D Insight pipeline database is AbbVie’s second generation endothelin A receptor antagonist, atrasentan.
Multiple Speed Bumps Have Slowed Down the Development of Disease Modifiers in CKD in the Last Decade

♦ In the last decade, challenges faced by drugs targeting progression of CKD and reduce CVD risk include:
  • Lack of profound understanding of the pathophysiology of chronic renal damage and associated CVD
  • Inadequate characterization of molecular mechanisms of currently approved therapies such as the renin–angiotensin–aldosterone-system (RAAS) blockade
  • Unclear biochemical property needs required for novel therapeutic approaches
  • Missing quantity and quality of clinical trials in the nephrology field
  • Most importantly, absence of prognostic renal biomarkers that reflect the severity of the structural organ damage and predict ESRD as well as CVD mortality

Going forward we hope that development of better risk stratification markers, improved trial designs and better understanding of disease off-target effects of the prior failed MOAs will accelerate drug development in CKD.
# Phase II+ Agents Addressing CKD Disease Progression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism Of Action</th>
<th>Highest Phase</th>
<th>Population</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan/thioctic acid</td>
<td>InVasc Therapeutics (Originator)</td>
<td>Angiotensin type 1 receptor antagonists, Antioxidants, Free radical scavengers</td>
<td>Phase-II</td>
<td>Pre-dialysis CKD</td>
<td>Losartan/thioctic acid</td>
</tr>
<tr>
<td>CTP 499</td>
<td>Concert Pharmaceuticals (Originator)</td>
<td>Antioxidants</td>
<td>Phase-II</td>
<td>Pre-dialysis CKD</td>
<td>CTP 499</td>
</tr>
<tr>
<td>Atrasentan</td>
<td>Abbott Laboratories (Originator)</td>
<td>Endothelin A receptor antagonists</td>
<td>Phase-III</td>
<td>Pre-dialysis CKD</td>
<td>Atrasentan</td>
</tr>
<tr>
<td>PRT 201</td>
<td>Proteon Therapeutics (Originator)</td>
<td>Extracellular matrix protein modulators</td>
<td>Phase-II</td>
<td>ESRD</td>
<td>PRT 201</td>
</tr>
<tr>
<td>GCS 100</td>
<td>Barbara Ann Karmanos Cancer Institute (Originator), Wayne State University (Originator), La Jolla Pharmaceuticals</td>
<td>Galectin 3 inhibitors</td>
<td>Phase-II</td>
<td>Pre-dialysis CKD</td>
<td>GCS 100</td>
</tr>
</tbody>
</table>
Novel MOAs in Development for CKD: Endothelin A Antagonists

♦ **MOA Rationale**: The endothelin system is chronically activated in patients with nephropathy. Binding of endothelin to the endothelin type A receptor (ETA receptor) elicits pronounced vasoconstriction, sodium retention, and promotes podocyte dysfunction leading to glomerular damage, proteinuria and renal function loss.
♦ In addition endothelin secretion promotes renal fibrosis.
♦ In contrast, endothelin type B receptor activation causes vasodilatation and sodium excretion.

♦ **Prior Failure due to lack of specificity**: Previously, avosentan, an endothelin receptor blocker, significantly reduced proteinuria in patients with type 2 diabetes and nephropathy. However, a large phase 3 trial, testing the effect of avosentan on hard renal outcomes (ASCEND), was terminated prematurely because of an excess of congestive heart failure (CHF) and mortality in the avosentan treatment arm.

AbbVie’s Atrasentan is highly specific for endothelin A receptor which could theoretically mean that adverse events related to fluid overload and edema are less likely to happen.

**Development Status**
- In May 2013, AbbVie initiated the double-blind, parallel, multicentre SONAR phase III study to evaluate the efficacy and tolerability of atrasentan in addition to standard of care for patients with diabetic nephropathies.
Novel MOAs in Development for CKD: CTP 499, Metabolite of Pentoxyfylline

♦ **MOA Rationale:** CTP-499 is an active metabolite of pentoxifylline. CTP-499 is under development based on previous studies showing anti-albuminuric effects of pentoxifylline.

♦ Pentoxifylline is a methyl xanthine derivative that acts *in vivo* as a phosphodiesterase inhibitor.

♦ A number of clinical studies have shown the antialbuminuric properties of pentoxifylline and a combined meta-analysis of these trials documented that oral pentoxifylline reduced albuminuria by nearly 300 mg day−1 vs. control therapy.

♦ Effect on hard renal progression outcomes has not been established for this MOA.

CTP-499 is thought to have an improved metabolic profile. Specifically, a pre-clinical study has shown that CTP-499 possesses anti-inflammatory, antifibrotic and anti-oxidant properties.

**Development Status**

- A 24-week phase 2 randomized placebo controlled trial is currently ongoing to assess whether CTP-499 exerts anti-albuminuric effects in 170 patients with type 2 diabetes and nephropathy (NCT01487109).

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Adis R&D Insight, DH analysis

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Novel MOAs in Development for CKD: A Galectin3 Inhibitor

MOA Rationale: Preclinical studies have shown a direct, causal role of galectin-3 in tissue fibrosis leading to kidney failure, and increased circulating levels of galectin-3 have been linked to poorer outcomes in patients with kidney and heart failure.

GCS 100 is a first-in-class, polysaccharide molecule that is being developed by La Jolla Pharmaceutical Company for the treatment of chronic kidney disease (renal insufficiency/renal failure) and cancer. The compound sequesters galectin-3.

Development Status
• A Phase IIa trial is ongoing. Approximately 117 patients with chronic kidney disease will be enrolled in the trial, in the US. Patients will be randomized 1:1:1 to receive either a low dose of GCS 100, a high dose of the agent or placebo.
• The primary endpoint is effect on eGFR after 8 weeks in severe renal impairment patients.
Emerging Drug Targets in CKD- Diabetic Nephropathy

Interaction of metabolic and hemodynamic pathways in the pathogenesis of diabetic nephropathy and potential new therapeutic strategies.

AGE advanced glycation end product, RAGE AGE receptor, PKC protein kinase C, ROCK rho-associated kinase, RAAS renin-angiotensin-aldosterone system.
Novel MOAs, Supportive Care for CKD: HIF-PHI

**Novelty**
- Small molecule indirect stimulants of erythropoiesis. Hypoxia inducible factor- prolyl hydroxylase inhibitors stabilize levels of the transcription factor HIF via inhibition of the prolyl hydroxylase inhibitor.
- HIF, the key regulatory protein that coordinates all elements of erythropoiesis necessary for proper formation of mature red blood cells.
- Advantages over ESA include oral delivery and completely different MOA that might carry less safety risk since erythropoietin levels are not artificially increased.

**Estimated launch**
- First agent in phase III; 2-4 years.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Highest Phase</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS 1093</td>
<td>Daiichi Sankyo Company (Originator)</td>
<td>Phase-I</td>
<td>Undefined</td>
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<tr>
<td>Molidustat</td>
<td>Bayer Schering Pharma (Originator)</td>
<td>Phase-II</td>
<td>Pre-dialysis CKD</td>
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<tr>
<td>AKB 6548</td>
<td>Procter &amp; Gamble (Originator, Akebia Therapeutics (Licensee))</td>
<td>Phase-II</td>
<td>ESRD</td>
</tr>
<tr>
<td>FG 2216</td>
<td>FibroGen (Originator) Astellas Pharma (Licensee)</td>
<td>Phase-II</td>
<td>ESRD</td>
</tr>
<tr>
<td>Roxadustat</td>
<td>FibroGen (Originator) Astellas Pharma (Licensee)</td>
<td>Phase-III</td>
<td>Both</td>
</tr>
</tbody>
</table>
Conclusions

♦ The non-dialysis CKD patient population represents a large and growing patient population with significant unmet needs.

♦ It is only in the last few years that the various stages of progression have been laid out and guidelines developed internationally which has led to increased awareness among clinical community and some improvements in patient care.

♦ Drug development in non-dialysis CKD is in its nascence due to various challenges including lack of sensitive risk stratification methods and endpoints to measure benefit in preclinical and clinical studies.

♦ Going forward, we believe there is tremendous opportunity for early movers to this pharma “white space,” not only due to the large patient population, but also since there is increased recognition worldwide of the need to better manage non-dialysis CKD to decrease the costs of morbidity later on.

♦ The lowest hanging fruit based on current understanding of disease progression and availability of patients for treatment would be targeting the pre-dialysis, Stage 3 and 4 CKD patients. The most immediate opportunities are for mechanisms that can address anemia, hyperphosphatemia and other complications in CKD, particularly those that can be addressed with an oral, easily administrable, affordable drug.
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CKD Insight Briefing