At present, 44% of the patients developing end stage renal disease (ESRD) in the U.S. have diabetes as its cause (1) and this number is climbing, primarily because the number of people with diabetes is increasing. However, the overall proportion of diabetic patients developing ESRD has decreased progressively and substantially since 1996 (2). This decrease is due to 3 things: (1) the markedly improved glycemic control of patients over this time; (2) better hypertension management; and (3) use of drugs that block the renin-angiotensin-aldosterone (RAAS) system. In the 1960’s, about one-third of patients developed ESRD by about 30 years duration of diabetes (3). Recently, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that the cumulative incidences of ESRD were only 1% in the prior Intensive Group and 2% in the prior Conventional Group in subjects who had mean diabetes durations of 28 years (4). Control of these factors also improves cardiovascular disease (CVD) outcomes as well and patients with diabetic CKD have a much higher risk of CVD than those without CKD (5,6).

Glycemic control, with an A1c target of ~7%, is the only modality shown to prevent/delay the onset of nephropathy as well as retard progression of established chronic kidney disease (CKD) (7). However, as CKD progresses, alterations in drug metabolism become important and the risk of hypoglycemia increases (8). Insulin doses need to be reduced. When the eGFR is < 60 ml/min/1.73m², glyburide, nateglinide, and dapagliflozin should be stopped. At 45-50 ml/min/1.73m², acarbose, miglitol, canagliflozin, and empagliflozin should be stopped and the doses reduced for metformin, sitagliptin, saxagliptin, and alogliptin. At 30 ml/min/1.73m², metformin, glimepiride and exenatide should be stopped and the doses reduced further for Sitagliptin and alogliptin. The thiazolidinediones, glipizide, liraglutide, dulaglutide, and albiglutide can be used at all stages of CKD (8).

Albuminuria and reduced eGFR independently and additively increase CVD risk, even at the earliest stage of microalbuminuria (5,6). Although glycemic control may improve mortality modestly (9), hypertension and lipid control have greater importance in reducing CVD, especially in those with type 2 DM (8,10). Hypertension develops in over 80% of diabetic patients with CKD. Hypertension control is very important as CKD progresses and the BP target should be < 140/90 mmHg (8,10). Although lower BP levels results in further CKD benefits and cerebrovascular disease, there are no further benefits in CVD and even the potential for harm (11). Often it takes multiple drugs to bring BP under control, especially as CKD advances (10). The initial antihypertensive drug should generally be an angiotensin converting enzyme (ACE) inhibitor or an aldosterone receptor blocker (ARB). Several studies have shown that these RAAS blockers may retard progression of CKD over and above their antihypertensive effects (8,10,11). Whether they should be started in the normotensive individual with only microalbuminuria is controversial, as many studies have now shown that as many individuals with microalbuminuria revert to normal albuminuria as progress to macroalbuminuria even without use of RAS blockers (12).

Lipid management is also important. The presence of microalbuminuria or a reduced GFR can be considered major CVD risk factors (probably greater than smoking) and would provide strong rationale for starting a statin. Although most of the large studies excluded patients with CKD, those that did showed that statins lower CVD outcomes as much as in patients without CKD, except for patients who have progressed to dialysis (8,10).
Thus, a multi-pronged approach is necessary for the well-being of patients with diabetes, with and without CKD, as has been shown in the Steno Study (13).

References:

2. Burrows NR, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continues to decline. Diabetes Care 2010;33;73-77.
Early Management of Diabetic Kidney Disease

63rd Annual Advanced Postgraduate Course
American Diabetes Association
San Francisco, CA
March 5, 2016

Mark E. Moltich, M.D.
Division of Endocrinology, Metabolism & Molecular Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois

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- Consulting with Pfizer, Novartis, Novo Nordisk, Lilly, Merck, Janssen

Incident counts & adjusted rates, by primary diagnosis

Incidence of Diabetic End-Stage Renal Disease per 100,000 People with Diabetes, U.S., 1980 – 2008
We are making a difference!

Risk Categories for Kidney and Mortality Outcomes

Natural History of Diabetic Nephropathy

Risk Categories for Kidney and Mortality Outcomes

Composite Ranking by Adjusted Relative Risks (KDIGO, 2009)

<table>
<thead>
<tr>
<th>Albuminuria Stage</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal and High-Normal</td>
<td>&lt;10 mg/g</td>
<td>10-29 mg/g</td>
<td>30-299 mg/g</td>
</tr>
<tr>
<td>High</td>
<td>300-1999 mg/g</td>
<td>&gt;2000 mg/g</td>
<td></td>
</tr>
</tbody>
</table>

KDIGO Level of Evidence

- G1: High and optimal
- G2: Moderate to severe
- G3: Very high and nephrosic

Albuminuria Stage

<table>
<thead>
<tr>
<th>GFR Stage</th>
<th>Description</th>
<th>Range, ml/min per 1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>High and optimal</td>
<td>90-104</td>
</tr>
<tr>
<td>G2</td>
<td>Mild</td>
<td>60-74</td>
</tr>
<tr>
<td>G3</td>
<td>Mild to moderate</td>
<td>45-59</td>
</tr>
<tr>
<td>G4</td>
<td>Moderate to severe</td>
<td>30-44</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Albuminuria Levels

- Microalbuminuria
- Albuminuria
- High albuminuria

Duration of Diabetes (years)

GFR (ml/min/1.73 m²)

Albumin (mg/24h)

Microalbuminuria

We are making a difference!

USRDS - 2008

National Diabetes Surveillance System, U.S. Renal Data System, National Health Interview Survey

Nephropathy

Primary Prevention

Secondary Intervention

DCCT Research Group

NEJM 1993;324:381

Primary & Secondary GFR Outcomes in DCCT/EDIC

<table>
<thead>
<tr>
<th>eGFR Category</th>
<th>Number of Events</th>
<th>Relative Risk Reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt; 60</td>
<td>Intensive Therapy: 46</td>
<td>Conventional Therapy: 50 (18, 69)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt; 45</td>
<td>Intensive Therapy: 39</td>
<td>Conventional Therapy: 40 (1, 64)</td>
<td>0.045</td>
</tr>
<tr>
<td>eGFR &lt; 30</td>
<td>Intensive Therapy: 23</td>
<td>Conventional Therapy: 44 (-9, 72)</td>
<td>0.088</td>
</tr>
<tr>
<td>ESRD</td>
<td>Intensive Therapy: 16</td>
<td>Conventional Therapy: 51 (-14, 79)</td>
<td>0.098</td>
</tr>
<tr>
<td>eGFR &lt;60 or death</td>
<td>Intensive Therapy: 80</td>
<td>Conventional Therapy: 37 (10, 55)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* Sustained eGFR < 60 mL/min/1.73m² (primary outcome of this study)

Risk reduction is relative difference in risk of impaired GFR (in percent) comparing intensive to conventional diabetes therapy.

Deboer et al., NEJM 2011;365:2366

Annual Transition Rates in Patients with Type 2 Diabetes in the UKDPS

No Nephropathy: 1.4%
Microalbuminuria: 4.6%
Albuminuria: 4.6%
Elevated Creatinine or Renal Replacement Rx: 19.2%

Impaired GFR = <60 mL/min/1.73m²

Afkarian M et al., JASN 2013;24:302

10-Year Excess Mortality in Type 2 Diabetes by Kidney Disease Status in NHANES III (n=15,046)

Glycemic Management in the Patient with Progressing CKD

- Common Genetic Predisposition
- Endothelial Dysfunction
- Associated Hypertension
- Insulin Resistance
- Atherogenic Dyslipidemia
- Hyperglycemia
- Volume overload

Adek et al., Kidney Intl 2003;63:225
### Sulfonylurea Use in CKD

- **Glyburide**
  - Glyburide clearance not affected but renal clearance of metabolites is reduced with CKD
  - Risk of hypoglycemia high with CKD and should not be used with eGFR < 60
- **Glimepiride**
  - Glimepiride clearance not affected but renal clearance of metabolites is reduced with CKD
  - Risk of hypoglycemia increased and should be used with caution with eGFR < 60 and avoided with eGFR < 30
- **Glipizide**
  - Less than 10% renally cleared
  - Use with caution with eGFR < 30

Rosencranz et al., Diabetologia 1996;39:1617  Ferreira et al., Diabetes Care 2012 doi:10.2337/dc12-1365/-/DC1

### Nateglinide, Repaglinide and CKD

- Nateglinide does not accumulate with CKD but metabolite M1 is metabolically active and its clearance is greatly delayed with CKD
  - Nateglinide should not be used for eGFR < 60 ml/min/1.73m²
- Repaglinide does not accumulate and no dose change is needed in CKD

Nagi et al., Dia Res Clin Pract 2003;59:191
Siman et al., Clin Nephrol 2003;60:90

### Metformin Dosing

**What to Do?**

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73m²)</th>
<th>Metformin Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>No limitation of dosing</td>
</tr>
<tr>
<td>≥ 45 - &lt;60</td>
<td>Caution with dosing Monitor eGFR every 3 – 6 mos</td>
</tr>
<tr>
<td>≥ 30 - &lt;45</td>
<td>Maximum dose 1000 mg/day Monitor eGFR every 3 – 4 mos</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Stop metformin</td>
</tr>
</tbody>
</table>

- Stop metformin in inpatients if:
  - Unstable
  - Hypotensive
  - Hypoxic
  - Septic
  - Acute worsening of renal function

Liska et al., Diabetes Care 2011;34:1430
KDIGO Controversies, In preparation

### Thiazolidinediones and CKD

- **Pioglitazone and Rosiglitazone**
  - Clearance not affected by kidney function
  - No dose reduction needed in CKD
  - Potential problems with fluid retention
  - Bone disease - ? Additive to renal osteodystrophy
  - Slight increased risk of bladder cancer (?)

Buddle et al., Br J Clin Pharmacol 2003;55:368
Colmers et al., CMAJ 2012;184:E675
Panchapakesan et al., Nephrology 2009;14:298
Betteridge, Diabetic Medicine 2011;28:759

### Incretins

- **GLP-1 receptor agonists**
  - Exenatide – discontinue for eGFR < 30
  - Liraglutide – no dose adjustments
  - Dulaglutide – no dose adjustments
  - Albiglutide – no dose adjustments
- **DPP4 Inhibitors**

<table>
<thead>
<tr>
<th>GFR</th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Alogliptin</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100 mg/d</td>
<td>5 mg/d</td>
<td>25 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>≥ 30 – &lt;50</td>
<td>50 mg/d</td>
<td>2.5 mg/d</td>
<td>12.5 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>25 mg/d</td>
<td>2.5 mg/d</td>
<td>6.25 mg/d</td>
<td>5 mg/d</td>
</tr>
</tbody>
</table>

Lipskaya et al., Br J Clin Pharmacol 2003;55:368
Panchapakesan et al., Nephrology 2009;14:298
Betteridge, Diabetic Medicine 2011;28:759

### Alpha-Glucosidase Inhibitors

- **Acarbose**
  - Minimal absorption with < 2% of drug and active metabolites appearing in urine
  - Package insert states that in patients with eGFR < 25 ml/min/1.73m², the peak concentration is increased 6x and the AUC is increased 5X but no long-term trials in patients with serum creatinine > 2 mg/dL
  - Should not be used if serum creatinine > 2 mg/dL

- **Miglitol**
  - 50-70% absorption with >95% excreted in urine
  - Package insert states that in patients with eGFR < 25 ml/min/1.73m², the peak concentration is increased 2x and no long-term trials in patients with serum creatinine > 2 mg/dL
  - Should not be used if serum creatinine > 2 mg/dL

Lipskaya et al., Br J Clin Pharmacol 2003;55:368
SGLT2 Inhibitors

- Increase urinary glucose excretion, thereby lowering blood glucose
- Less effective with eGFR < 60 ml/min/1.73m²
- Possibly more adverse effects (volume loss, hyperkalemia) with eGFR < 45 ml/min/1.73m²
  - For eGFR < 60 ml/min/1.73m², Canagliflozin should be kept at 100 mg/day and higher dose (300 mg) avoided
  - Canagliflozin and Empagliflozin currently not approved for use with eGFR < 45 ml/min/1.73m²
  - Dapagliflozin not approved for use with eGFR < 60 ml/min/1.73m²

Empa-Reg: Kidney Outcomes

- Entire study: Empagliflozin 4687 subjects
- Placebo 2333 subjects
  - Outcome of Doubling of Creatinine, ESRD, or Renal Death: HR 0.54, p=0.0002
  - Outcome of new-onset or worsening of nephropathy: HR 0.61, p=0.001

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects with eGFR &lt;60 (ml/min/1.73m²)</td>
<td>1212</td>
<td>607</td>
<td></td>
</tr>
<tr>
<td>Primary Outcome (MACE 3)</td>
<td>171 (15%)</td>
<td>99 (16%)</td>
<td>0.88</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>115 (9%)</td>
<td>72 (12%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>75 (6%)</td>
<td>48 (8%)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Glycemic Management in CKD: Summary

- eGFR < 60 ml/min/1.73m²:
  - Reduce dose of canagliflozin, stop dapagliflozin
  - Avoid glyburide
- eGFR < 45 ml/min/1.73m²:
  - Reduce doses of Insulin
  - Reduce doses of metformin, sitagliptin, saxagliptin, alogliptin
  - Restrict sulfonylureas to glipizide
  - Stop acarbose, miglitol, nateglinide, canagliflozin, & empagliflozin
- eGFR < 30 ml/min/1.73m²:
  - Stop metformin and exenatide
  - Reduce doses of sitagliptin, saxagliptin, alogliptin further

Blood Pressure
**ACCORD BP Study:**

**Primary and Secondary Outcomes**
- Patients with T2D and hypertension (N = 4733)
- Random assignment
  - Intensive therapy: target SBP < 120 mm Hg
  - Standard therapy: target SBP < 140 mm Hg
- 1° outcome: nonfatal MI, nonfatal stroke, death from CV causes
  - Mean follow-up = 4.7 y

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP after 1 year (mmHg)</td>
<td>119.3</td>
<td>133.5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1° outcome (annual rate)</td>
<td>1.87</td>
<td>2.09</td>
<td>.88</td>
<td>.20</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.28</td>
<td>1.19</td>
<td>1.07</td>
<td>.55</td>
</tr>
<tr>
<td>Stroke (annual rate)</td>
<td>0.32</td>
<td>0.53</td>
<td>0.59</td>
<td>.01</td>
</tr>
<tr>
<td>AEs (rate)</td>
<td>3.3</td>
<td>1.3</td>
<td>NR</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

INVEST Study – Secondary Analysis in Subjects with Type 2 Diabetes

- 6400 subjects with type 2 DM and CAD over age 50
- Treated with Verapamil or Trandolapril followed by an ACE inhibitor, a diuretic or both to achieve BP < 130/85
- Current analysis compared:
  - “Tight” control - SBP < 130 (n=2175)
  - “Usual” control – SBP 130-140 (n=2255)
  - “Uncontrolled” – SBP > 140 (n=1970)
- Primary Outcome: first occurrence of all-cause mortality, nonfatal MI or nonfatal stroke

Cooper-DeHoff, R. M. et al. JAMA 2010;304:61-68

INVEST: Cumulative Event Rate for Primary Outcome (first occurrence of all-cause mortality, nonfatal MI or stroke)

Cooper-DeHoff, R. M. et al. JAMA 2010;304:61-68.

INVEST: Adjusted Risk of All-Cause Mortality

ONTARGET: Relationships Between Outcome Risks and In-Trial BP

ONTARGET: Cumulative Event Rate for Primary Outcome

ADA Standards of Care BP Guidelines

- Blood Pressure Targets
  - Systolic < 140
  - Diastolic < 90
  - <130/80 mmHg may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden

- Treatment
  - Confirmed BP > 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals.

Diabetes Care 2016;39(Suppl 1):S60-S71
**Heart Protection Study**
Cardiovascular Benefits of Simvastatin in those with Normal and Abnormal Renal Function

- **% of Patients with Composite Events**
  - Placebo: 23.8
  - Simvastatin: 14.5

**Aurora Study**
2776 Patients with ESRD (19.2% with DM) assigned to Rosuvastatin 10 mg vs. Placebo, Primary Endpoint: CVD death, nonfatal MI or nonfatal stroke
43% reduction in LDL

**Summary of Lipids and CKD**
- Patients with diabetes and CKD are at very high risk of CVD
- CVD events can be significantly reduced with statins in patients with diabetes
- CVD events can be significantly reduced with statins in patients with CKD prior to dialysis
- CVD events cannot be reduced with statins in patients with diabetes undergoing dialysis
  - Reasons remain unclear - ? CVD too far progressed?
- CVD events can be reduced with statins in patients following renal transplantation
- Risks of rhabdomyolysis with statins are low - <0.1%

**SHARP: Major Atherosclerotic Events by renal status at randomization**
- Eze/simv vs. Placebo
  - Non-dialysis (n=6247)
    - Eze/simv: 296 (9.5%)
    - Placebo: 373 (11.9%)
  - Dialysis (n=3023)
    - Eze/simv: 230 (15.0%)
    - Placebo: 246 (16.5%)

**Steno-2: Multifactorial Intervention and CVD in Type 2 DM**
INTENSIVE THERAPY
- **Dietary intervention**
  - Total fat <30% calories
  - Saturated fat <10% calories
- **Exercise:** 30 min 3-5x/w
- **Smoking cessation**
- **All prescribed ACE-I/ARB**
- **Glycemic control:** Metformin/SU/insulin
- **Hypertension:** ACE-I/ARB/diuretics/CCA/BB
- **Lipid:** Statins/fibrates

**4D Study: Primary Composite End Point (Cardiac Death, Nonfatal MI & Stroke)**
Atorvastatin in Diabetic Dialysis Patients

- **Relative Risk Reduction 8%**
  - (95% CI: 0.77-1.10, P=0.37)

**Median follow-up time of 4 years**

**Cumulative incidence (%)**

<table>
<thead>
<tr>
<th>Years from Randomization</th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>636</td>
<td>619</td>
</tr>
<tr>
<td>2</td>
<td>532</td>
<td>515</td>
</tr>
<tr>
<td>3</td>
<td>383</td>
<td>378</td>
</tr>
<tr>
<td>4</td>
<td>252</td>
<td>252</td>
</tr>
<tr>
<td>5</td>
<td>136</td>
<td>136</td>
</tr>
<tr>
<td>5.5</td>
<td>51</td>
<td>58</td>
</tr>
</tbody>
</table>

Wanner et al., NEJM 2005;353:238

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**Any patient**
- Eze/simv: 526 (11.3%)
- Placebo: 619 (13.4%)

23% with Diabetes

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23% with Diabetes
Steno-2: Multifactorial Intervention and CVD in Type 2 DM

Conventional Therapy

Intensive Therapy

Follow-up (mo)

Primary composite endpoint (%)

Composite endpoint of death from CV causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation, or surgery for peripheral arterial disease.


When to Refer to the Nephrologist

- If concern about diagnosis of diabetic nephropathy
  - No retinopathy
  - No albuminuria
  - Disproportionate proteinuria
  - Active sediment
- Blood pressure difficult to control despite 3 drugs
- Rapidly falling GFR
- GFR approaching 30 ml/min/1.73m²
- Lack of comfort in dealing with problems as they are progressing
  - Secondary Hyperparathyroidism
  - Anemia
  - Blood Pressure
  - Fluid Retention
  - Hyperkalemia

What is the Role of the Diabetologist Once the Patient is Referred to the Nephrologist?

True Co-management Is Needed

- Continued glucose management
  - The nephrologist does not have our expertise in managing hyper- and hypoglycemia
- Continued management of other complications of diabetes
  - Neuropathy, peripheral and autonomic
  - Retinopathy
  - Macrovascular disease
  - Dyslipidemia
- Dialysis: Hemo- and Peritoneal
  - Nobody knows how to manage the glucose!
- Transplantation (if kidney only)
  - Worsened glucose control with immunosuppressive agents
  - Glucocorticoids
  - Tacrolimus
  - Sirolimus
  - Cyclosporine

Summary

- Prevent nephropathy with glycemic control
- Delay progression of nephropathy and CVD with glycemic, BP and lipid control and use of ACE inhibitors and ARBs
- Manage dyslipidemia and BP aggressively
- Treat 2° hyperparathyroidism and anemia
- Refer to nephrologist as disease progresses
- Continue to co-manage diabetes with nephrologist

Thank You