Diabetes mellitus and renal disease

Pathophysiology, clinical management, therapy prescription, complications

M.M. Couttenye
September 2016
Outline of the lecture

1. Introduction
2. Pathology
3. Clinical presentation
4. Microalbuminuria
5. Epidemiology
6. Pathophysiology
7. Clinical management
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Mogensen CE. How to protect the kidney in diabetic patients: with special reference to IDDM. Diabetes 1997; 46 Suppl 2: S104-11
The effect of the administration of placebo or captopril to patients with type 1 diabetes with overt proteinuria and a plasma creatinine concentration equal to or greater than 1.5 mg/dL (132 µmol/L). The likelihood of a doubling of the plasma creatinine concentration (Pcr) was reduced by more than 50 percent in the captopril group.

Proof of concept?

Anno 2016: new insights

PS: diabetes = t1 + t2 unless specified
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Definition

- Glomerulopathy with typical features
  - Thickening GBM
  - Mesangial matrix expansion
  - Glomerular sclerosis
    - segmental/global --- nodular ("Kimmelstiel-Wilson")
  ± Hyaline deposits
    - arteriolar
    - fibrin cap (capillary wall)
    - capsular drop (Bowman’s capsula)
Normal glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

*Courtesy of Helmut G Rennke, MD.*
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis.

*Courtesy of Helmut Rennke, MD.*
Advanced diabetic glomerulosclerosis

Light micrograph in advanced diabetic nephropathy shows diffuse and nodular mesangial expansion and characteristic hyaline thickening of the arteriole at the glomerular hilum (arrow). Although not shown, diabetes typically affects both afferent and efferent arterioles; in comparison, only the afferent arteriole is usually involved with hypertensive injury.

Courtesy of Helmut Rennke, MD.
Fibrin cap (capillary wall)
Capsular drop
Basement membrane thickening in diabetic nephropathy

Electron micrograph in diabetic nephropathy shows a 2 to 3 fold increase in the thickness of the glomerular basement membrane (GBM). Although not seen, the mesangium is also expanded by basement membrane-like material, a process that contributes to nodule formation and glomerulosclerosis. Mes: mesangium; Ep: epithelial cell.

Courtesy of Helmut Rennke, MD.
## Classifications (predictive value?)

<table>
<thead>
<tr>
<th>Diabetic kidney disease class</th>
<th>Pathologic criteria on light microscopy</th>
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<tbody>
<tr>
<td>I</td>
<td>Isolated glomerular basement membrane thickening</td>
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<tr>
<td>II (a)</td>
<td>Mesangial expansion (mild) in &gt; 25% of glomeruli</td>
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<tr>
<td>(b)</td>
<td>Mesangial expansion (severe) in &gt; 25% of glomeruli</td>
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<tr>
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<td>Without nodular sclerosis</td>
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<td>III</td>
<td>With nodular sclerosis (Kimmelstiel–Wilson)</td>
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<td>&lt; 1 glomerulus with nodular increase in mesangial matrix</td>
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<td>IV</td>
<td>Global glomerulosclerosis &gt; 50% of glomeruli lesions from classes I to III</td>
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Nodular glomerulosclerosis: differential diagnosis

- Dysproteinemia, amyloidosis
- Non-amyloid fibrillar depositions (e.g. immunotactoid glomerulonephritis)
- Chronic hypoxic / ischemic conditions
- Chronic membranoproliferative glomerulonephritis
- "Idiopathic", associated with smoking, hypertension and metabolic syndrome without overt diabetes
Recently more attention to:

- podocyte lesions: ~ proteinuria, GFR decline (see figure)
- interstitial and tubular fibrosis (IFTA) ~ GFR decline
- vascular lesions

Glomerular basement membrane (GBM) denudation due to detachment of foot processes (FP) of podocytes (PC). (A) No detachment, (B) incipient detachment and (C) complete detachment of podocytes from GBM.

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• “Classical” picture
  1. Albuminuria
  2. Progressive loss of renal function

• ! “non classical” presentation:
  → non-diabetic renal disease ?
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<th><strong>Inclusion</strong></th>
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<td>Pre-existing diabetes*, impaired glucose</td>
<td>Other systemic disease process</td>
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<td>Persistent albuminuria, proteinuria</td>
<td>Rapid increase in proteinuria, nephrotic syndrome</td>
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<td>Elevated creatinine, decreased GFR</td>
<td>Rapid decrease in GFR</td>
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<td>Normal to large kidneys on ultrasonography</td>
<td>Presence of active urinary sediment</td>
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<td>Diabetic retinopathy(\text{□}) or neuropathy</td>
<td>Refractory hypertension</td>
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*Not within 5 years after diagnosis of t1 !  
\(\text{□}\)Retinopathy can be absent in t2  
\(^\Delta\)Think of nephrosclerosis or renal artery stenosis

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Definitions

• MICRO (or “moderately increased” or “high”):
  ▪ 30 – 300 mg/day
  or
  ▪ 30 – 300 mg/g creatinine (in random sample)

• MACRO (or “very high” or “overt nephropathy”):
  ▪ > 300 mg/day
  or
  ▪ > 300 mg/g creatinine
Measurement of microalbuminuria

- **Golden standard:** 24h urine collection
- **Dipstick:** Micral® (only morning specimens)
- **Albumin/creatinine ratio on random single void specimen:** highest sensitivity
- **!!! False positives**
  - vigorous exercise
  - Cachexia (muscle mass)
  - temporarily dysregulated glycemia
  - non-diabetic disease: fever, heart failure, urinary tract infection
Recommendations

• **Definite diagnosis:**
  – albumin/creatinine ratio of 30 – 300 mg/g creatinine in 2 or 3 samples taken at random over a 3-6 month period

• **When to start screening?**
  – t1: 5 years after diagnosis
  – t2: at time of diagnosis
Prognostic significance

- Classical evolution

  micro → macro → GFR ↓ → ESRD
  → t1: retinopathy, neuropathy
  → t1 + t2: all cause and CV mortality
Prognostic significance

- Non-classical evolution
  - progressive disease without albuminuria
    - Joslin Kidney Study (Perkins et al. Kidney Int 210; 7: 57)
    - N=79:
      - 12 year follow-up after onset microalbuminuria
      - 11/79: despite regression or stable microalbuminuria develop GFR ↓ (albeit at lower rate)
    - Reason(s) unclear
Prognostic significance

• Non-classical evolution
  – Regression to normo-albuminuria and ↓ risk for GFR decline
  – In ± 50% of patients with either t1 or t2
    → independent risk factors:
      • shorter duration of microalbuminuria
      • better glycemic control
      • lower blood pressure
      • lower serum lipids
      • less hyperfiltration
Prevention and treatment

1. Tight glycemic control → prevention or delay of (micro)albuminuria, both in t1 (DCCT) and t2 (UKPDS)

PS: “Metabolic memory” (DCCT-EDIC)
Prevention and treatment

2. RAAS inhibition: degree of evidence

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<th>µA/BP</th>
<th>t1</th>
<th>t2</th>
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<td>O / nl</td>
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<td>O / ↑</td>
<td>1B (ACEI)</td>
<td>1B (ACEI/ARB)</td>
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<td>+ / nl</td>
<td>2C (ACEI)</td>
<td>2C (ACEI/ARB)</td>
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<tr>
<td>+ / ↑</td>
<td>1B (ACEI)</td>
<td>1B (ACEI/ARP)</td>
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Prevention and treatment

• Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes Treatments that produce a lasting decrease in urinary albumin excretion may slow the progression of DKD even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension. Assessment of albuminuria is addressed in Guideline 1. Management of hypertension is addressed in Guideline 3 and the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD.

  ▪ 6.1: We recommend not using an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) for the primary prevention of DKD in normotensive normoalbuminuric patients with diabetes. (1A)

  ▪ 6.2: We suggest using an ACE- or an ARB in normotensive patients with diabetes and albuminuria levels > 30 mg/g who are at high risk of DKD or its progression. (2C)
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Epidemiologic data
(“Bias” of treatment)

• Type 1
  – era before intensive treatment:
    • 25-45% → overt nephropathy
    • at 30 years after diagnosis: 46% ESRD
  – recent data:
    • at 15 years from diagnosis: 20-30% microalbuminuria
      → 15% resolves
      → 15% → macroalbuminuria
    • at 30 years from diagnosis: 7.8% ESRD
    • at 20 years from diagnosis: if no albuminuria → no risk of renal disease
Epidemiologic data
(“Bias” of treatment)

• Type 2
  – Less data (Pima Indians):
    • equivalent risk for renal disease as t1
    • regression of microalbuminuria also described
Prevalence of ESRD in Flanders

Number of incident cases of ESRD attributable to diabetes according to calendar time increases in 40- to 49-year-olds and decreases in 20- to 39-year-olds. Total number of incident cases among 20- to 49-year-olds in 1990 was 3359; in 1995, it was 3972; in 2000, it was 4287; and in 2006, it was 4600. We obtained from the U.S. Renal Data System (http://www.usrds.org/) the number of incident cases of ESRD attributed to diabetes between 1990 and 2006 that occurred in the white U.S. population. In these patients, T1DM is the predominant diabetes type and almost the exclusive type in those with sufficient diabetes duration to develop diabetes associated ESRD. Rosolowsky ET et al. J Am Soc Nephrol 2011; 22(3): 545-53.
Conclusions from epidemiological data

1. Intensive treatment (glucose/BP/ACEI)
   → improvement of renal prognosis
   – BUT: no complete prevention of ESRD!

2. Intriguing observation: microalbuminuria can regress or remain stable

• ? Other risk factors or pathophysiological factors besides:
  – hyperfiltration
  – (intraglomerular) hypertension
  – hyperglycemia
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New proposed mechanisms

• Hyperglycemia
  → mesangial matrix production
  → glycation of matrix proteins
  → mesangial cell expansion
  → effect of GBM electronegativity (heparanase)

• Ischemic injury due to macrovascular disease

• Regulation of matrix proteins via microRNAs (new target ?)
New proposed mechanisms

- AGE’s → accumulation in mesangial matrix
- In t2: hyperinsulinism
  → atherogenic effect
  → growth promoting effect
- Profibrotic effect of ATII ? (role of vitamin D as anti-RAAS without effect on blood pressure)
New proposed mechanisms

- **AMPK** (AMP-activated kinase = energy sensor, implicated in protein synthesis)
  - ↓ in diabetic nephropathy
  - ↑ by metformin (new therapy ?)

- **Podocyte disease**
  - nephrin expression ↓
  - mTOR activation in podocyte in diabetic nephropathy (role for rapamycin ?)
New proposed mechanisms

• Notch-1: a cell membrane receptor on podocyte that leads to apoptosis after its activation (new target ?)
• VEGF ↑ → anti-VEGF in experiments, but side effects in humans !
• Prorenin ↑ → MAPK (mitogen-activated kinases) activity ↑ (role for pro-renine receptor blockade ?)
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- **Aims**
  a) renal protection
  b) ↓cardiovascular risks

- **Methods**
  a) glycemic control
  b) RAAS blockade
  c) lipid lowering
  d) SGLT-2 inhibitors
  e) others
1. Tight glycemic control

• reduces risk for
  → Microvascular complications: both in t1 (DCCT) and t2 (UKPDS)
    !!! nephropathy: evidence mainly on (micro)albuminuria, by extrapolation on GFR
  → Cardiovascular disease: only demonstrated in t1
Intensive insulin therapy in diabetes type 1: effect on development and progression of complications (DCCT)

- 1441 normotensive patients with type 1
- Intensive therapy (> 3 insulin injections/day) versus conventional therapy (1 or 2 injections/day)
- Follow-up: 3 to 9 years (average: 6.5 years)
- Intensive insulin therapy reduced by:
  - 76% the development of retinopathy
  - 60% clinical neuropathy
  - 39% the occurrence of microalbuminuria
  - 54% the occurrence of clinical albuminuria (UAE ≥ 300 mg/day)

UKPDS: Microvascular endpoints

renal failure or death, vitreous haemorrhage or photocoagulation 346 of 3867 patients (9%)

- Conventional
- Intensive

Risk reduction 25% (95% CI: 7% to 40%)

p=0.0099

Years from randomisation

% of patients with an event

UKPDS: Microvascular endpoints

Introduction
Pathology
Clinical presentation
Microalbuminuria
Epidemiology
Pathophysiology
Clinical management

Lancet 1998; 352; 837-53
UKPDS: Myocardial infarction

fatal or non fatal myocardial infarction, sudden death 573 of 3867 patients (15%)

% of patients with an event

Risk reduction 16%
(95% CI: 0% to 29%)

Years from randomisation

Lancet 1998; 352; 837-53
UKPDS: Glucose control summary

The intensive glucose control policy maintained a lower HbA1c by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

- 12% for any diabetes related endpoint  \( p=0.029 \)
- 25% for microvascular endpoints  \( p=0.0099 \)
- 16% for myocardial infaction  \( p=0.052 \)
- 24% for cataract extraction  \( p=0.046 \)
- 21% for retinopathy at twelve years  \( p=0.015 \)
- 33% for albuminuria at twelve years  \( p=0.000054 \)

Lancet 1998; 352; 837-53
1. Tight glycemic control

- reduces risk for
  - Microvascular complications: both in t1 (DCCT) and t2 (UKPDS)
    - Nephropathy: evidence mainly on (micro)albuminuria, by extrapolation on GFR
  - Cardiovascular disease: only demonstrated in t1

!!! Balancing for hypoglycemia
1. Tight glycemic control: how tight?

- ACCORD – ADVANCE – VADT: no decrease of major cardiovascular outcomes in intensively treated t2 patients, but increased risk for hypoglycemia
- ACCORD: increased all cause mortality in intensively treated t2 patients
- TARGET HgA1c ???
HgA₁C in renal failure

• Sources of error?
  1. Analytical interference of ureum → false high HgA₁C
  2. HgA₁C level depends on life span RBC
     • thus: low turnover → false ↑ HgA₁C (e.g. Fe-deficiency)
     • High turnover → false ↓ HgA₁C (e.g. hemolysis (hemodialysis), treatment with ESA’s)
Recommendation

• HgA$_1$C remains the best clinical marker of long-term glycemic control, particularly if combined with self-monitoring of blood glucose, in patients with diabetes and CKD.
Risk of hypoglycemia in diabetics with CKD

- Kidneys: important contribution to gluconeogenesis!
  → reduced kidney mass increases risk for hypoglycemia

- Decreased clearance of insulin and some oral anti-diabetic agents.
### Dose recommendation in CKD

<table>
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<th>Medication</th>
<th>CKD-1</th>
<th>CKD-2</th>
<th>CKD-3</th>
<th>CKD-4</th>
<th>CKD-5ND</th>
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<td>Metformin</td>
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<td>500 mg/day**</td>
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Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min) Nephrol Dial Transplant 2015; 30 (suppl 2): ii1-ii142.
Assessment of risk for hypoglycaemia

- Metformin
- Alpha glucosidase inhibitor
- DPP-IV inhibitors
- Incretin mimetics
- TZD’s
- SGLT-2 inhibitors

- Short-acting SU derivate or SU derivate with inactive metabolites
- Meglitinides

- Drug-drug interactions
- Hepatic failure
- CKD stage 5
- Gastroparesis

- Insulin
- Long-acting SU derivate with active metabolites

Hypoglycaemia risk

Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min) Nephrol Dial Transplant 2015; 30 (suppl 2): ii1-ii142.
Management of Hyperglycemia and General Diabetes Care in CKD

- Guidelines 2: Hyperglycemia, the defining feature of diabetes, is a fundamental cause of vascular target organ complications, including diabetic kidney disease (DKD). Intensive treatment of hyperglycemia prevents elevated albuminuria or delays its progression, but patients treated by approaches designed to achieve near normal glycemia may be at increased risk of severe hypoglycemia. Evidence that intensive treatment has an effect on loss of glomerular filtration rate (GFR) is sparse.

  - 2.1: We recommend a target hemoglobin A1c (HbA1c) of 7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD. (1A)
  - 2.2: We recommend not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia. (1B)
  - 2.3: We suggest that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia. (2C)

2. RAAS blockade (renal protection)

a) Effect on reducing proteinuria and slowing rate of progression

→ ACEI: Lewis (t1)
→ ARB: Renaal (t2)
2. RAAS blockade (renal protection)

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2. RAAS blockade (renal protection)

Combination therapy?

→ ACEI + ARB? Effective BUT NOT RECOMMENDED: risk for AKI, hyperkalemia and hypotension (ONTARGET)

→ RAAS blockade + alliskiren? No effect on renal outcome, risk for hyperkalemia (ALTITUDE)
2. RAAS blockade (renal protection)

• Therapeutic goals
  → Proteinuria

  • Despite good correlation between degree of proteinuria and decline of GFR: decline in proteinuria as surrogate maker is **not recommended**

2. RAAS blockade (renal protection)

- In clinical practice, changes in eGFR and albuminuria are suggested to be used together to monitor kidney status, even in the absence of conclusive evidence that they predict precisely long-term reduction in risk of actual health outcomes such as ESRD.
2. RAAS blockade (renal protection)

- Therapeutic goals
  → Bloodpressure?

  **recommendation** in clinical practice
  
  BP: < 140/90 in all patients
  
  < 130/80 if proteinuria > 500 mg/d

  Beware!
  
  not < 120 in t2 patients + cardiovascular disease (CVD) or 2 risk factors for CVD in view of finding of additional side effects for only little benefit (only stroke) (ACCORD)
2. RAAS blockade (cardiovascular protection)

- Cardiovascular death rate and number of risk factors (cholesterol, blood pressure, smoking), age adjusted (per 10,000 person years)

2. RAAS blockade (cardiovascular protection)

Hypertension (DBP >90 mm Hg)  
Smoking  
Serum total cholesterol level (>240 mg/dL)

2. RAAS blockade (cardiovascular protection)

• Tayside
## 2. RAAS blockade (cardiovascular protection)

### Complications of diabetes per 1000 patients per year

<table>
<thead>
<tr>
<th>Complication</th>
<th>DM type 1</th>
<th>DM type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blindness</td>
<td>1.06</td>
<td>3.84</td>
</tr>
<tr>
<td>ESRD</td>
<td>3.19</td>
<td>0.41</td>
</tr>
<tr>
<td>Amputation</td>
<td>2.13</td>
<td>2.33</td>
</tr>
<tr>
<td>Periferal vascular disease</td>
<td>4.26</td>
<td>10.30</td>
</tr>
<tr>
<td>Angina</td>
<td>6.39</td>
<td>15.93</td>
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<tr>
<td>Hypertension</td>
<td>17.04</td>
<td>24.98</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4.26</td>
<td>8.78</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.26</td>
<td>10.30</td>
</tr>
</tbody>
</table>
## 2. RAAS blockade (cardiovascular protection)

<table>
<thead>
<tr>
<th>Condition</th>
<th>DM type 1</th>
<th>DM type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blindness</td>
<td>0.33</td>
<td>9.37</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.66</td>
<td>5.68</td>
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<tr>
<td>Periferal vascular disease</td>
<td>1.34</td>
<td>25.12</td>
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<tr>
<td>Angina</td>
<td>2.00</td>
<td>38.85</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.34</td>
<td>60.93</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.34</td>
<td>21.41</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.34</td>
<td>25.12</td>
</tr>
</tbody>
</table>
2. RAAS blockade (cardiovascular protection)

• Thus:
  – In CKD 3-5: (cv) death is a more likely outcome than progression to ESRD
  – Diabetes: multiplies this risk
  ⇒ Need for protection: RAAS blockade?
  ⇒ Trade off: earlier in dialysis?
2. RAAS blockade (cardiovascular protection)

- Effect on CV outcomes: ACE I

**T2DM-microHOPE-studie**

2. RAAS blockade (cardiovascular protection)

- Effect on CV outcomes: ARB

T2DM-IDNT-studie

ERBP statement

**Statements**

3.2.1 We recommend that adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m² or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) be treated with an ACE-I at maximally tolerated dose (1B).

3.2.2 We suggest there is insufficient evidence to justify the start of an angiotensin-receptor blocker (ARB) in adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m² or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) but intolerance for ACE-I (2B).

3.2.3 We recommend not combining different classes of renin angiotensin-blocking agents (ACE-I, ARBs or direct renin inhibitors) (1A).
3. Lipid lowering

a) Reducing proteinuria and slowing rate of progression
   – No unequivocal data
   – Fibrates (via PPAR - ligand ?)
3. Lipid lowering

a) Reducing proteinuria and slowing rate of renal progression

<table>
<thead>
<tr>
<th>Study</th>
<th># treated/# with DM and CKD</th>
<th>Randomized fibrate</th>
<th>CVD Outcome</th>
<th>Regression from micro- to normoalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA-HIT – Tonelli⁶⁶</td>
<td>136/297</td>
<td>Gemfibrozil, 600 mg BID</td>
<td>Composite outcome 26.5% (36/136) in the gemfibrozil treated group vs. 41.0% (66/161) in the placebo</td>
<td>Not reported</td>
</tr>
<tr>
<td>FIELD – Keech⁶⁵,⁶⁷</td>
<td>4895/9795</td>
<td>Fenofibrate, 200 mg/day (mean dose)</td>
<td>Not reported</td>
<td>47.0% (462/983) in the fenofibrate group vs. 39.3% (400/1017) in the placebo group</td>
</tr>
<tr>
<td>DAIS – Ansquer⁶⁴</td>
<td>155/314</td>
<td>Fenofibrate, 200 mg/day</td>
<td>Not reported</td>
<td>37.7% (20/53) in the fenofibrate group vs. 34.1% (15/44) in the placebo group</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice a day; DAIS, Diabetes Atherosclerosis Intervention Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; VA-HIT, Veterans Affairs High-density lipoprotein Intervention Trial.
3. Lipid lowering

b) Cardiovascular disease

- Guideline 4: Management of Dyslipidemia in Diabetes and CKD

Dyslipidemia is common in people with diabetes and CKD. Cardiovascular events are a frequent cause of morbidity and mortality in this population. Lowering low-density lipoprotein cholesterol (LDL-C) with statin-based therapies reduces risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD including those with diabetes.

  • 4.1: We recommend using LDL-C lowering medicines, such as statins or statin/ezetimibe combination, to reduce risk of major atherosclerotic events in patients with diabetes and CKD, including those who have received a kidney transplant. (1B)

  • 4.2: We recommend not initiating statin therapy in patients with diabetes who are treated by dialysis. (1B)
4. SGLT-2 inhibitor

- Effect beyond glucose lowering?
- Renoprotective

Canagliflozin slows progression of renal function decline independently of glycemic effects.

4. SGLT-2 inhibitor

- Effect Beyond glucose lowering?
- Renoprotective

Empagliflozin and progression of kidney disease in type 2 diabetes.

4. SGLT-2 inhibitor

- Effect beyond glucose lowering?
- Renoprotective
- Cardiovascular protection!

Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes

5. Others

- Bardoxolone Methyl: oral anti-oxidant inflammation modulator (activator of a transcription factor)
  - BEAM: t2 – eGFR 20-40 ml/min

Effects of Bardoxolone Methyl on the Estimated Glomerular Filtration Rate (GFR).

5. Others

- **Bardoxolone Methyl**
  - BEAM (2011): t2 – eGFR 20-40 ml/min
    - increase in eGFR
    - but albuminuria ↑ and many events → dropout
  - BEACON (2013): t2 – eGFR 15-30 ml/min
    - terminated because of higher rate of cardiovascular events


4. Others

- Protein restriction
  - not proven
  - but: compliance?
    - risk of protein malnutrition in insulin-penic state ↑

- Salt restriction (< 100 meq/d)
  - reinforce RAAS blockade
TAKE HOME MESSAGES

• Diabetic nephropathy: not always “classical picture”
• Microalbuminuria: evaluation, marker of?
• New insights fysiopathological mechanisms, future new therapeutics ?
• ΔΔ diabetes – non-diabetic nephropathy in diabetics
• Different therapeutic targets (renal – non renal)
• Cost-benefit of therapy !