BALANCING RISK AND BENEFIT IN CHRONIC KIDNEY DISEASE?
(metformin, sulfonylureas, insulin)

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Disclosure of Interests

MCT has received honoraria for educational symposia and expert panels provided on behalf of:

Astra-Zeneca, Abbott, Reata, Abvie, Sanofi Aventis, BMS, Boehringer Ingelhiem, Lilly, MSD, Servier, Janssen-Cilag, Amgen & Allergan
METFORMIN in CKD

☑ CHEAP
☑ EFFICACY
☑ ↓ HYPOGLYCAEMIA
☑ ↓ WEIGHT GAIN
☑ ↓ MORTALITY, ↑ CANCER (?)

☒ ACCUMULATION/ADJUSTMENT
☒ ↑ GASTRO-INTESTINAL TOXICITY
☒ ↑ LACTATE (ACIDOSIS?)
☒ ↓ VITAMIN B12?
**METFORMIN & MORTALITY in CKD**

*Arch Intern Med. 2010;170(21):1892-1899*

<table>
<thead>
<tr>
<th>Metformin Use</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Overall Population</td>
<td>341/7397</td>
<td>929/12 156</td>
<td>0.76 (0.65-0.89)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>243/4845</td>
<td>617/7954</td>
<td>0.82 (0.68-0.99)</td>
</tr>
<tr>
<td>Female</td>
<td>98/2548</td>
<td>312/4195</td>
<td>0.66 (0.49-0.88)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-65</td>
<td>78/2987</td>
<td>176/3859</td>
<td>0.63 (0.45-0.89)</td>
</tr>
<tr>
<td>&gt;65-80</td>
<td>191/3791</td>
<td>532/6768</td>
<td>0.77 (0.62-0.95)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>71/598</td>
<td>220/1492</td>
<td>0.92 (0.66-1.28)</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>221/6002</td>
<td>488/9120</td>
<td>0.80 (0.66-0.98)</td>
</tr>
<tr>
<td>Yes</td>
<td>116/1220</td>
<td>419/2790</td>
<td>0.69 (0.54-0.90)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30</td>
<td>14/118</td>
<td>90/455</td>
<td>1.06 (0.47-2.38)</td>
</tr>
<tr>
<td>30-60</td>
<td>86/1572</td>
<td>336/3388</td>
<td>0.64 (0.48-0.86)</td>
</tr>
<tr>
<td>≤60</td>
<td>188/4442</td>
<td>379/6326</td>
<td>0.89 (0.71-1.11)</td>
</tr>
</tbody>
</table>

* adjusted for propensity score
METFORMIN in CKD

- **CHEAP**
- **EFFICACY**
- **↓ HYPOGLYCAEMIA**
- **↓ WEIGHT GAIN**
- **↓ MORTALITY → CANCER (?)**

- **✗ ACCUMULATION/ADJUSTMENT**
- **✗ ↑ GASTRO-INTESTINAL TOXICITY**
- **✗ ↑ LACTATE (ACIDOSIS?)**
- **✗ ↓ VITAMIN B12 (~↓ 20%/3 years)**
METFORMIN pharmacokinetics


If a drug is eliminated primarily through renal excretory mechanisms, impaired renal function usually alters the drug’s PK to an extent that the dosage regimen needs to be changed from that used in patients with normal renal function.

**Single dose (850mg)**

- **AUC (µg/hr/mL)**
  - Healthy: 111
  - CKD2: 79
  - CKD3: 41

- **Cmax (µg/mL)**
  - Healthy: 4-5X
  - CKD2: 3X
  - CKD3: 3X

<table>
<thead>
<tr>
<th>ClCr</th>
<th>Healthy</th>
<th>CKD2</th>
<th>CKD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>79</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic Levels**

- **Healthy**: 3X
- **CKD2**: 3X
- **CKD3**: 3X
METFORMIN and LACTATE

Circulating lactate levels among metformin-treated patients are modestly higher compared with those taking other agents (1.32 vs 1.14 mmol/L), Elevated lactate concentrations (>2.0 mmol/L) were nearly 3 times more common in metformin-treated patients (9.2% vs 3.8%, \( P < .001 \)). Not related to dose of drug levels?
## METFORMIN in CKD

**Better the devil you know?**

### Table 2. Possible Approach to Metformin Prescribing in the Setting of CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Maximal Total Daily Dose, mg</th>
<th>Other Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60 -&lt;90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>45 -&lt;60</td>
<td>2000</td>
<td>Avoid if kidney function is or expected to become unstable. Consider more cautious follow-up of kidney function.</td>
</tr>
<tr>
<td>3B</td>
<td>30 -&lt;45</td>
<td>1000</td>
<td>Do not initiate therapy at this stage but drug may be continued. Avoid if kidney function is or expected to become unstable. Consider more cautious follow-up of kidney function.</td>
</tr>
<tr>
<td>4</td>
<td>15 -&lt;30</td>
<td>Do not use</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Do not use</td>
<td></td>
</tr>
</tbody>
</table>

METFORMIN in CKD

Some glucose lowering may be mediated through the enteroendocrine axis. Effects on microbiome? Folate/methionine metabolism

Effects on L-cells & GLP-1

Figure 1. Glucose-Lowering Effect of Metformin is not Associated with Systemic (Plasma)
Exposure: Phase 2 Randomized Placebo and Active Comparator Controlled Study LCRM105

Dissolution
Current Metformin (Met IR/XR)

Absorption
Dose:
1000 mg Met XR
Systemic (plasma) exposure:
~500 mg
Gut exposure:
~500 mg

PK*
Plasma Metformin (ng/mL)
Week 4
427
(n=31)

Efficacy*
Change in FPG (mg/dL)
Week 4
-12
(n=35)

Dose:
600 mg Met DR
Systemic (plasma) exposure:
~100 mg
Gut exposure:
~500 mg

Plasma Metformin (ng/mL)
Week 4
34
(n=33)

Change in FPG (mg/dL)
Week 4
-11
(n=35)

*Fasting plasma metformin (PK) data are median concentrations and efficacy data are the median change after 4 weeks of treatment.1

Abbreviations: Met IR = metformin immediate-release, Met XR = metformin extended-release, Met DR = metformin delayed-release, FPG = fasting plasma glucose.

- These effects of Met DR support a gut-mediated mechanism of metformin action.5
SULPHONYLUREA/INSULIN in CKD

- ✔ CHEAP
- ✔ TITATABLE EFFICACY

- ✗ ACCUMULATION/ADJUSTMENT
- ✗ INFLEXIBILITY
- ✗ ↑ HYPOGLYCAEMIA
- ✗ ↑ WEIGHT
- ✗ CARDIOVASCULAR EFFECTS?
Insulin clearance in CKD

- Most subcutaneous insulin is cleared by the liver
- But up to half may be cleared by the kidneys (60% filtered + 40% active tubular secretion)
- Insulin half-life is a "test of kidney function"
- The glucose-lowering effects of insulin and secretagogues carry over beyond post-prandial
- Despite greater insulin resistance
  - eGFR 30–45 ml/min/1.73 m²: Need ~10% less insulin
  - eGFR 15–30 ml/min/1.73 m²: Need ~25% less insulin
  - eGFR <15 ml/min/1.73 m²: Need ~50% less insulin
**SULPHONULUREAS**

Glibenclamide (= glyburide) (Daonil®; 2.5–10 mg/day) is metabolised by the liver, and is eliminated equally in bile and urine. Some of its metabolites are active and may accumulate in CKD although hepatobiliary elimination may partially compensate for the decrease in renal elimination. Glibenclamide is contraindicated in ≥3 CKD stages (eGFR <60 ml/min).

Glimepiride (Amaryl®, 1–8 mg/day) is metabolised by the liver to two main metabolites, one of which has hypoglycaemic activity. In patients with renal impairment, these metabolites can accumulate. The use of glimepiride is contraindicated in patients with a GFR of <60 ml/min.

Gliclazide (Diamicron® 80–320 mg/day; DiamicronMR® 30–120 mg/day) is metabolised by the liver to inactive metabolites, which are eliminated mainly in the urine (80%). Gliclazide poses a lower risk for severe hypoglycaemia than glibenclamide and glimepiride. But is still recommended to be stopped when GFR<40ml/min.
Sulphonylurea use in general practice

- Diamicron MR
- Daonil/Glimel
- Minidiab/Melizide
- Amaryl/Dimirel

Bar chart showing the use of sulphonylurea in general practice.
Risks for severe hypoglycemia (in the ADVANCE study)

- Increased age
- Prolonged duration of diabetes
- Renal impairment
- Albuminuria
- Lower BMI and cognitive function
- Use of multiple glucose-lowering drugs
- History of smoking

THE CHALLENGE OF CKD IN DIABETES

RIGHT RATIONALE
RIGHT TARGET/INTENSITY
RIGHT DRUG (S)
RIGHT DOSE
RIGHT MONITORING/PRECAUTIONS

TIME BETTER SPENT ELSEWHERE?