Metformin: Is it a cardiovascular drug?

Greg Schwartz MD PhD

Chief, Cardiology, VA Eastern Colorado Health Care System
Division of Cardiology, University of Colorado School of Medicine

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Diabetes drugs and CV drugs: The traditional view
Diabetes drugs and CV drugs: The perspective in 2018

Does metformin fit this paradigm?
The basis for a changing paradigm

• Diabetes drugs with CV benefit in patients \textit{with T2DM}:  
  – SGLT2 antagonist (empagliflozin, canagliflozin)  
  – GLP1 agonists (liraglutide, semaglutide)  
  – ?? Metformin

• Diabetes drugs with CV benefit in patients \textit{without T2DM}:  
  – Pioglitazone  
  – ?? Metformin
Metformin

• 1st line drug in T2DM; safe, generally well tolerated, cheap
• Used for 60 years; approved in US in 1994
• >100 million people with type 2 diabetes currently treated worldwide
• Third most frequently prescribed medication for chronic use in USA (following atorvastatin and amlodipine)
Is metformin a cardiovascular drug?

1. Clinical evidence for a CV benefit of metformin in patients with type 2 diabetes

2. Experimental evidence for favorable cardiovascular effects of metformin in animals without diabetes

3. Clinical evidence for/against benefit of metformin in patients without diabetes, using surrogate outcomes

4. Design of a clinical trial to test whether metformin has favorable CV effects in patients without diabetes
UKPDS

- Newly diagnosed, overweight patients with T2DM
- Patients enrolled 1977-1991
- Metformin substudy (UKPDS 34):
  - Conventional (dietary) treatment (n=411)
    - hypoglycemic meds added for FPG >270 mg/dl
  - Metformin (n=342): max dose 2550 mg/day
    - target FPG <90 mg/dl
- Average 10 year follow-up


**UKPDS 34: Key results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent Reduction (metformin vs. &quot;conventional&quot;)</th>
<th>No. of events</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td></td>
<td>258</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes-related mortality</td>
<td></td>
<td>83</td>
<td>0.02</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td>119</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td>112</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Microvascular events</td>
<td></td>
<td>62</td>
<td>NS</td>
</tr>
</tbody>
</table>

No. of events: 258
P-value: 0.002
UKPDS Caveats

- Not blinded
- Usual care allowed substantial hyperglycemia
- Small sample size; small number of CV events
- In most cases, background therapy did not include statins, aspirin, other contemporary agents
- Hypothesis generating, but nonetheless, forms the basis for current treatment guidelines
Observational data: Metformin and mortality in patients with diabetes and atherosclerosis

- REACH registry: 19,691 patients with type 2 diabetes and established atherosclerosis
- ~70% treated with aspirin and statin; 2 year follow-up (2003-2004)

Findings remained significant after multivariable and propensity score adjustments

Roussel et al., *Arch Intern Med* 2010;170:1892-1899
What is the principal mechanism of action of metformin?
Metformin: a weak inhibitor of electron transport chain Complex I

METFORMIN

Complex I

OCT1: organic cation transporter 1

How can a metabolic inhibitor afford CV protection?

1. **Steep concentration gradient of adenine nucleotides:**
   - \([\text{[ATP]} / \text{[ADP]} / \text{[AMP]} \approx 100 : 10 : 1]\)
   - A small decrease in [ATP] with metformin is amplified into larger *relative* increases in [ADP] and [AMP]

2. **Adenylate kinase reaction buffers changes in [ATP]**
   - \(\text{AK} = \text{adenylate kinase: } 2\text{ADP} \rightleftharpoons \text{ATP} + \text{AMP}\)

3. **AMPK inhibits ATP-consuming anabolic processes**

4. **Net result:** Metformin can activate AMPK without degrading ATP levels

Adapted from: Dzeja P and Terzic A. *Int J Mol Sci* 2009;10: 1729–72
Effects of AMPK activation on metabolism

Promotes a shift from anabolic (ATP-consuming) to catabolic (ATP-generating) processes

- Decreases gluconeogenesis (liver)
- Enhancement of glycolysis and glucose and fatty acid oxidation
- Decrease protein and lipoprotein synthesis

Above serve to maintain cellular energy supply [ATP] under stress.
2. Experimental evidence for favorable cardiovascular effects of metformin and/or AMPK activation in animals without diabetes
Favorable CV effects of metformin treatment and/or AMPK activation in animal models

- Anti-atherogenic
- Improves endothelial function
- Reduces infarct size
- Maintains myocardial ATP levels under stress
- Prevents ischemic arrhythmias
Metformin exerts anti-atherosclerotic effect that is dependent upon AMPK

Cai et al., Circ Res 2016;119:422-433
Metformin activates AMPK, increases eNOS phosphorylation, and reduces myocardial infarct size in rats without diabetes.

Calvert et al., Diabetes 2008;57:696-705
Metformin restores balance of NO to peroxynitrite release from endothelium

- Obese Zucker rats on high-fat diet
- Metformin 300 mg/kg/day or vehicle x 4 weeks
- No difference in fasting blood glucose
- NO and peroxynitrite release from aortic rings in vitro under CaI stimulation

Metformin maintains myocardial ATP during ischemia in non-diabetic rat heart: $^{31}$P NMR

Kawabata et al., *Hypertens Res* 2003;26:107-110
Metformin modifies response to myocardial ischemia in metabolically normal pigs

- Juvenile domestic farm pigs, 25-30 kg
- Metformin 30 mg/kg/day for 2-3 weeks, vs untreated controls
- Low flow myocardial ischemia (50% LAD flow reduction for 90 min, followed by 45 min reperfusion)
Instrumentation of heart
(under anesthetized, open-chest conditions)

- Drill biopsy sites
- Infusion catheter in LAD
- Hydraulic occluder
- Ultrasonic flow probe
- Anterior interventricular vein catheter
- Left anterior descending coronary artery
- Anterior LV crystal array
- Ischemic region
- LA catheter
- LV micromanometer catheter
- Drill biopsy sites
Metformin increases survival free of ischemic VF in metabolically normal pigs

Lu et al., *Diabetologia* 2017; 60:1550-1558
Monophasic action potential technique

- Surrogate for single cell action potential
- Duration of MAP reflects duration of single-cell action potential
- Responds to ischemia and pharmacologic interventions similar to direct action potential recording

Franz M, Prog Cardiovasc Dis 1991;33:347
Anti-fibrillatory effect of metformin is due to stabilization of action potential during ischemia

The abrogation of action potential shortening in ischemia by metformin implies that metformin prevents $K_{ATP}$ opening during ischemia

Lu et al., *Diabetologia* 2017; 60:1550-1558
Metformin reduces heterogeneity of repolarization between ischemic and non-ischemic regions, thereby ameliorating the conditions for arrhythmia.

* p<0.001 vs untreated
Anti-fibrillatory effect of metformin is associated with activation of AMPK and preservation of ATP

Lu et al., Diabetologia 2017; 60:1550-1558
Ischemia

↓ energy charge,
↓ [ATP]

K\textsubscript{ATP} channels open

Action potential shortens in ischemic myocardium

Dispersion of refractoriness between ischemic and non-ischemic regions

Ventricular fibrillation

Metformin

AMPK activation ± other cellular actions

Lu et al., Diabetologia 2017; 60:1550-1558
3. Clinical evidence for/against a benefit of metformin in patients without diabetes, based on surrogate outcomes
Metformin in patients without diabetes: Is there evidence of benefit?

<table>
<thead>
<tr>
<th>Measurement or marker</th>
<th>Benefit shown?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>Yes, average 3 kg reduction</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Yes, increased</td>
</tr>
<tr>
<td>Vascular endothelial function</td>
<td>Yes, improved</td>
</tr>
<tr>
<td>Markers of thrombogenic tendency</td>
<td>Yes, improved</td>
</tr>
<tr>
<td>Progression from pre-diabetes to diabetes</td>
<td>Yes, delayed (DPP)</td>
</tr>
<tr>
<td>Progression of coronary calcification</td>
<td>Yes, attenuated</td>
</tr>
<tr>
<td>Carotid IMT</td>
<td>No, null effect</td>
</tr>
<tr>
<td>LV function after STEMI</td>
<td>No, null effect</td>
</tr>
</tbody>
</table>
Metformin prevents or retards progression from pre-diabetes to diabetes: DPP

- 3234 patients with pre-diabetes, no other serious illness
- Assigned to placebo, intensive lifestyle modification, or metformin
- Very few cardiovascular events

P<0.001 for:
- MET vs placebo
- LIFESTYLE vs placebo

Metformin retards progression of coronary calcification in patients with pre-diabetes

- 2029 participants with pre-diabetes in DPP assigned to metformin, placebo, or intensive lifestyle modification
- **Change in coronary artery calcium score** from baseline to mean 14 yrs’ follow-up

Goldberg RG et al., *Circulation* 2017;136:52-64.
No effect of metformin on carotid IMT in patients without diabetes

- 158 patients with established CAD, treated with statin, and not diabetic
- No lower limit on HbA1c (mean ± SD = 5.6 ± 0.3)
- Metformin (850-1700 mg/d) versus placebo

No effect of metformin on LVEF after STEMI in patients without diabetes

- 379 patients with STEMI
- Metformin 1000 mg/d or placebo for 4 months
- LVEF at 4 months by cMRI

<table>
<thead>
<tr>
<th>Table 2. Outcomes at 4 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Primary end point, % (95% CI)</td>
</tr>
<tr>
<td>LVEF</td>
</tr>
</tbody>
</table>
4. Can metformin provide CV benefit in patients without T2DM?

Equipoise

\[\rightarrow\]

Need for a randomized, placebo-controlled CV outcomes trial
VA Cooperative Study #2002: clinicaltrials.gov NCT02915198

**VA-IMPACT**

*Investigation of Metformin in Pre-Diabetes on Atherosclerotic CV Outcomes*

- **Hypothesis**: Metformin reduces major adverse CV events in patients with pre-diabetes and established ASCVD

- **Rationale**:  
  - Placebo-controlled trial not feasible in established T2DM  
  - Patients with pre-diabetes and ASCVD comprise a high-risk population that might benefit from treatment
VA-IMPACT: design

• **Inclusion criteria**
  – Established coronary, cerebrovascular, or peripheral artery disease
  – Prediabetes (based upon HbA1c, FBG, or OGTT)
  – eGFR ≥45 mL/min/1.7m²

• **Randomized treatment assignment**
  – Metformin ER, titrated to target dose 2000 mg/d  OR matching placebo
VA-IMPACT: design

• **Primary Outcome measure:**
  – Time to first occurrence of death, non-fatal MI, stroke, unstable angina, or ischemia-driven coronary revascularization

• **Anticipated event rate** in placebo group: 4.85% per year
  – Benchmarked to contemporary studies in similar populations

• **Projected HR** metformin/placebo 0.85

• **Sample size** ~7860 patients followed to 1360 primary endpoints to provide 85% power
  – Expected median f/u 4 years
VA-IMPACT: design

• 37 VA sites

• “Large, simple trial”:
  – Use of national VA electronic health record to identify patients
  – Telephone follow-up after randomization
  – Centralized, direct-to-patient drug dispensing
  – No blinded labs
  – Limited reporting of non-serious adverse events

• Projected completion 2025
Is metformin a CV drug?

stay tuned...
Collaborators

• Swine lab:
  – Li Lu MD PhD
  – Cliff Greyson MD
  – Rebecca Scalzo PhD
  – Leslie Knaub MS
  – Jane Reusch MD

• VA Cooperative Studies Program
  – Lee Anne Mandich RN
  – Bob Edson MA
  – Marcel Bizien PharmD
  – Jennifer Lee, MD PhD
  – Mei-Chiung Shih PhD
Anti-cancer effect of metformin

• 4085 Scottish patients with T2DM who were new users of metformin; 4085 matched controls (T2DM and no metformin use)
• Followed for new diagnosis of cancer

Postulated due to activation of tumor suppressor kinase LKB1

Libby et al., *Diabetes Care* 2009;32:1620-5
CSP Facts

- Multi-center clinical trials within VHA and in conjunction with NIH
- Studies involve 80+ VA medical centers
- Study duration: 3 – 15 years
- Study participants: 25 – 50,000
- History of landmark trials
CSP History

1946
VA Streptomycin Trial for TB

1960
A Double Blind Control Study of Antihypertensive Agents

1983
Aspirin after MI

2001
Shingles Vaccine

2009
Diabetes: VADT

2015
Blood Pressure Targets: SPRINT
No effect of metformin on contractile function or oxygen consumption during ischemia

**Contractile function**

- **Untreated CTL (N=8)**
  - Stroke Work Index (Pa)
  
- **Chronic Metformin MET (n=8)**
  - Stroke Work Index (Pa)
  
  NS

**Oxygen consumption**

- **Baseline**
  - CTL (N=8)
  - MET (n=8)

  NS

- **Isc 15 min**
  - CTL (N=8)
  - MET (n=8)
Upregulation of mitochondrial respiratory capacity in response to chronic metformin treatment

State 3 Respiration:
Complex I substrates

\[ P = 0.002 \]

\[ \text{O}_2 \text{ consumption (pmol/(s*mg))} \]

\[ 0 \text{mM MET} \quad 0.1\text{mM MET} \quad 1\text{mM MET} \]

\[ P < 0.0001 \]
Untreated

Metformin

0.00

0.05

0.10

0.15

Metformin (mM)

0.00

0.05

0.10

0.15

Untreated

Metformin