Targeting Aging with Metformin: Design and Rationale

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Stephen B. Kritchevsky, PhD
Sticht Center on Aging
Wake Forest School of Medicine
Contributors

- Steve Austad
- Nir Barzilai
- Morgan Canon
- Harvey Cohen
- Mark Collins
- Jill Crandall
- Mark Espeland
- Richard Faragher
- Jon Gelfond
- Tamara Harris
- Steve Kritchevsky
- George Kuchel
- Jamie Justice
- Brian Kennedy
- Jim Kirkland
- Anne Newman
- John Newman
- Michael Pollak
- Walter Rocca
- Felipe Sierra
- Stephanie Studenski
- Ella Temprosa
- Joe Verghese
- Jeannie Wei

Contributed to development
- Luigi Ferucci
- Eileen Crimmins
- Marcel Salive
- Jay Olshansky
- Caroline Blaum
- David Sinclair
- Rafa deCabo
- Sofiya Milman
- Stephanie Lederman
Evaluation Continuum

- Change in Cellular Gene Expression
- Changes In Mortality Assoc. Biomarkers
- Retard Emergence Of Age-Related Disease
- Extend Life Span
- Change in Cellular Physiology
- Slow Age-Related Physiologic Degeneration
- Lower Mortality Rate

FDA Interest

Time
Expense
Salience

Arrow indicates progression from Change in Cellular Gene Expression to Extend Life Span.
Statins and overall mortality
(BMC Med. 2005 Mar 16;3:6 Heart protection study)
Age itself is the strongest risk factor for age related diseases.
Strategies for an Aging Society: The Geroscience Hypothesis

Target a specific disease

OR

Delay aging (by targeting basic molecular processes of aging)

Delay the Targeted Disease

Delay multiple age related diseases
Multiple Morbidity Composite Outcome

• If a drug’s effect is on aging it should reduce the occurrence of multiple diseases including those that share few risk factors other than age.
• This collection is a composite endpoint of multiple age-related morbidities.
• The outcome of interest is the time until the occurrence of one of a collection of possible disease endpoints.
Metformin Facts

• Biguanide class
• Discovered in the 1920s.
• Introduced in the US in 1995.
• Most widely prescribed antidiabetic drug in the world.
• Decreases hepatic gluconeogenesis.
Targeting Aging with Metformin (TAME)

Biology of aging was targeted in cells, worms, flies, mice, rats, and primates.

1. Metformin
   - PAI-1
   - TNFα
   - IL-6
   - Insulin
   - IGF-1

2. Metformin
   - IRS-1
   - IRS-2
   - AMPK
   - mTOR
   - p70S6K
   - 4EBP1
   - ATG13
   - SIRT1
   - FOXO
   - FOXO
   - NF-kB
   - PI3K
   - AMP
   - ATP
   - NAD+
   - NADH
   - NADP+
   - NADPH
   - Resveratrol
   - Bax
   - p53
   - FOXO
   - FOXO
   - NF-kB

3. Metformin
   - Healthspan and Longevity
   - Inflammation
   - Cellular Survival
   - Stress Defense
   - Autophagy
   - Protein Synthesis
   - Healthspan and Longevity
   - Rapamycin
Why Metformin?

• It modulates critical pathways in the biology of aging so it can be used to target aging to delay or prevent disease
• It has demonstrated efficacy in preventing type 2 diabetes and cardiovascular disease in human studies
• Its use is associated with lower risk of cancer and cognitive decline
• It has been used safely for over 60 years
• It is available as a generic drug and is inexpensive
Criteria for Inclusion in the TAME Composite Outcome

Components should be:

- Age-related
- Affected by interventions targeting aging mechanism(s)
- Common in population and pose a significant health burden
- Discrete clinically apparent outcome
- Ideally - preliminary evidence to support metformin effect
Incidence of Chronic Comorbid Conditions Recommended by the US-DHHS (1-12).

Incidence of Chronic Comorbid Conditions Recommended by the US-DHHS (13-20)

Multi-morbidity Incidence: Rochester Epidemiology Project

Figure 2  Incidence rates (per 1000 person-years) of two chronic conditions (second condition in a dyad) and of three chronic conditions (third condition in a triad) in men and women separately (A and C), and stratified by ethnicity (B and D).

St Sauver JL et al. Risk of developing multimorbidity across all ages in a historical cohort study. BMJ Open 2015; 5:e006413
Long-term follow-up of the UKPDS

**D** Myocardial Infarction

- **Proportion with Event**
- **Years since Randomization**
- **P = 0.005**

**No. at Risk**
- Conventional therapy: 411, 360, 311, 213, 95, 4
- Metformin: 342, 317, 274, 214, 106, 16

**H** Death from Any Cause

- **Proportion with Event**
- **Years since Randomization**
- **P = 0.002**

**No. at Risk**
- Conventional therapy: 411, 387, 345, 246, 116, 7
- Metformin: 342, 328, 296, 239, 124, 11

**D** Myocardial Infarction

- **Hazard Ratio**
- **Years of Events**

**Hazard Ratio**
- **P = 0.01**

**No. of Events**
- Conventional therapy: 73, 83, 92, 106, 118, 126
- Metformin: 39, 45, 55, 64, 68, 81

**H** Death from Any Cause

- **Hazard Ratio**
- **Years of Events**

**Hazard Ratio**
- **P = 0.01**

**No. of Events**
- Conventional therapy: 89, 113, 136, 160, 183, 217
- Metformin: 50, 70, 86, 110, 123, 152

*NEJM 2008; 359:1577*
## Observational studies of metformin and CVD outcomes

<table>
<thead>
<tr>
<th>Observational studies</th>
<th>Population</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>Roumie (2012)</td>
<td>VA/Medicare database</td>
<td>SU</td>
<td>MACE</td>
<td>21% (HR 1.21)</td>
</tr>
<tr>
<td>Johnson (2005)</td>
<td>Canadian prescription drug database</td>
<td>SU</td>
<td>CVD hospitalization or death</td>
<td>19% (HR 0.81)</td>
</tr>
<tr>
<td>Schramm (2011)</td>
<td>Danish population database</td>
<td>SU</td>
<td>MACE</td>
<td>19-32% (HR 1.19-1.32)</td>
</tr>
<tr>
<td>Roussel (2010)</td>
<td>REACH Registry (DM w/CVD or multiple risk factors)</td>
<td>Non-use</td>
<td>mortality</td>
<td>24% RRR (HR 0.76)</td>
</tr>
<tr>
<td>Masoudi (2005)</td>
<td>Medicare database: DM hospitalized for CHF</td>
<td>Other DM meds (not sensitizers)</td>
<td>Mortality Readmission for CHF</td>
<td>13% RR (HR .87) 8% (HR 0.92)</td>
</tr>
<tr>
<td>Aguilar (2011)</td>
<td>VA patients with CHF</td>
<td>Non-use</td>
<td>Mortality</td>
<td>24% RR (HR 0.76)</td>
</tr>
</tbody>
</table>
Association between metformin and cancer incidence and cancer mortality

**A. Cancer incidence**
- Schernthaner, 2004 (QUARTET-M)
- Hanefeld, 2004 (QUARTET-C)
- Kahn, 2006 (ADOPT-G)
- Kahn, 2006 (ADOPT-R)
- Monami, 2009
- Currie, 2009
- Libby, 2009
- Home, 2010 (RECORD)
- Williams-Herman, 2010
- Yang, 2010
- Honse, 2011
- Ngwana, 2012

SRR adjusted for BMI: 0.82 (0.70–0.96)

SRR unadjusted: 0.58 (0.31–1.09)

Summary RR: 0.69 (0.52–0.90)

$I^2 = 88$

$P$ for BMI = 0.48

**B. Cancer mortality**
- UKPDS, 1998
- Landman, 2009
- Libby, 2009
- Bo, 2011
- Baur, 2011

SRR adjusted for BMI: 0.60 (0.45–0.80)

SRR unadjusted: 0.75 (0.22–2.46)

Summary RR: 0.66 (0.54–0.81)

$I^2 = 21$

$P$ for BMI = 0.002

SRR 0.69 (0.52-0.90)

SRR 0.66 (0.54-0.81)
## Cognitive decline and dementia

<table>
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<th>Effect size</th>
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<tr>
<td>Ng, et al 2014</td>
<td>Singapore Longitudinal Aging Study</td>
<td>non-use</td>
<td>MMSE &lt; 24</td>
<td>OR 0.49</td>
</tr>
<tr>
<td>Cheng, et al 2014</td>
<td>Health insurance database (Taiwan)</td>
<td>SU TZD</td>
<td>Dementia diagnosis (ICD-9)</td>
<td>HR 0.82 (SU) ns HR 0.19 (TZD)</td>
</tr>
<tr>
<td>Moore, et al 2013</td>
<td>Longitudinal studies and practice registries (Australia)</td>
<td>non-use</td>
<td>MMSE</td>
<td>OR 2.23 (worse performance with metformin)</td>
</tr>
<tr>
<td>Imfeld, et al 2012</td>
<td>UK GPRD (case/control)</td>
<td>non-use</td>
<td>Alzheimer’s diagnosis</td>
<td>Increased risk with long-term use?</td>
</tr>
<tr>
<td>Hsu, et al 2010</td>
<td>Health insurance database (Taiwan)</td>
<td>No DM meds</td>
<td>Dementia diagnosis</td>
<td>HR 0.76</td>
</tr>
</tbody>
</table>
# Cognitive decline and dementia

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Population</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo, et al 2014</td>
<td>T2DM with depression</td>
<td>placebo</td>
<td>Improved performance on cognitive battery</td>
<td>~20% (?)</td>
</tr>
<tr>
<td>Luchsinger et al (unpublished)</td>
<td>MCI (non-DM)</td>
<td>placebo</td>
<td>Improved SRT</td>
<td>NA</td>
</tr>
</tbody>
</table>
Metformin and all-cause mortality

(a)

(b)

(c)

Cumulative survival

Time to death (years)

Cumulative survival

Time to death (years)

Cumulative survival

Time to death (years)

Metformin monotherapy  Sulphonylurea monotherapy  Controls (matched with metformin)  Controls (matched with sulphonylurea)

Bannister 2014; 16:1165
### Metformin and age-related diseases: Preliminary data from trials & observational studies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Strength of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of type 2 diabetes</td>
<td>++++</td>
</tr>
<tr>
<td>Prevention of CVD</td>
<td>+++</td>
</tr>
<tr>
<td>Prevention of cancer</td>
<td>++ (largely observational)</td>
</tr>
<tr>
<td>Prevention of dementia</td>
<td>+?</td>
</tr>
<tr>
<td>Reduction in mortality</td>
<td>+++</td>
</tr>
</tbody>
</table>
TAME Design

- Double Blind Randomized Placebo Controlled Trial
- **Dose**: 850 mg 2x per day
- **18 Month Recruitment**
- **Range of Follow-up Times**: 37-54 months (median 45 months)
**Primary Prevention**
- Slow gait speed OR obesity plus hypertension and/or dyslipidemia (not CVD, Cancer, or Dementia).

**Secondary Intervention**
- 1 or 2 of CVD, Cancer, MCI present at baseline

**Inclusion Criteria**
- 3000 subjects
- 65-79 yo

**Double blind placebo control study**

**Time to clinical occurrence of composite outcome:**
- MI, Stroke, CHF, revascularization, PAD, cancer, MCI or dementia, Death.

**Primary outcome**
- Time to occurrence of composite outcome: Death, persistent severe difficulty or inability to walk ¼ mile or climb 10 steps, development of ADL limitation, MCI, or dementia transition

**Secondary outcome**
- Time to onset of 14 age-related chronic health conditions (e.g. depression, osteoporosis, osteoarthritis), rate of acute events (e.g. falls, pneumonia), change in measures of function (gait speed, etc.), and quality of life measures (pain, sleep quality, fatigue)

*Primary outcomes are incident within class*
Inclusion/Exclusion Criteria

• Inclusion
  – Age 65 – 79
  – Primary Prevention Strata [Obesity with Hypertension or dyslipidemia OR Impaired mobility function (walking speed < 1 m/s)]
  – Secondary Intervention [≤ 2 of CVD (MI, stroke, CHF, PAD, revascularization), Cancer (not non-melanoma skin cancer, not in situ), MCI (screening with MoCA then adjudication)]

• Exclusions
  – Type 2 Diabetes
  – eGFR < 60  [45]
  – Hospitalization or procedure related to CVD treatment in the past year.
  – Cancer under treatment unless excellent prognosis.
  – Dementia, Mobility disability, ADL or IADL disability, recent weight loss (>5% in the past year), limited life expectancy (<5 years)
  – Inability to provide informed consent.
Incidence rates needed for this sample size are in line with those observed from observational cohorts.

Onset rates are not very sensitive to whether on is in the Primary Prevention or Secondary Intervention stratum.
Summary Points

• TAME is the result of an 18 month process to develop an approach that provides a pathway for the FDA approval of drugs targeting aging.
• TAME is feasible and smaller than many previous prevention trials.
• It has the potential to link biomarkers and intermediate outcomes with a hard clinical endpoint paving the way for biomarker use in registration trials of future compounds.
Thank You!
Treatement of elderly now:

Aging = composites of comorbidities

Figure 13: Distribution of Medicare Fee-For-Service Beneficiaries and Medicare Spending by Number of Chronic Conditions: 2012

- 0 to 1 condition: 14%
- 2 to 3 conditions: 21%
- 4 to 5 conditions: 30%
- 6+ conditions: 34%

Percent of beneficiaries vs. Percent of Total Medicare Spending
Intervention Testing Program (NIA)

5 out of 16 compounds studied extended lifespan and healthspan in rodent models

- NDGA (Nordihydroguaiaretic acid)
- Aspirin
- Rapamycin
- Acarbose
- 17-α estradiol
Changes in Charlson Comorbidity Index Over Time: Kaiser Permanente Cohort

Conclusions

• Evidence from human studies reasonably strong for metformin effect on:
  – Diabetes (effect size ~ 40%)
  – CVD (effect size 25-35%)
  – Cancer (effect size ~30%)
  – Mortality (effect size ~ 30%)

• Effects of metformin on cognition, Alzheimer’s disease less certain

• Caveat remains that most published data are from populations with diabetes
Reported cardiovascular effects of metformin

in vivo

Improved:
• Endothelial function (increased NO availability)
• Coagulation/fibrinolysis
• Ischemic pre-conditioning/reperfusion injury
  – reduced infarct size in animal models
• Post-infarct remodeling
• Lipids (increased HDL, reduced FFA, VLDL)
• Markers of oxidative stress and inflammation
• Weight, insulin sensitivity

Mechanisms – not mediated by glucose:
• AMPK activation
• Direct effects on mitochondria (reperfusion)
• Reduced ROS production
• c/w anti-aging effects
Proposed antineoplastic mechanisms of metformin

- Energetic stress
  - ↑ AMPK
  - ↓ Gluconeogenesis
  - ↓ Glucose if elevated
  - ↓ Insulin if elevated
  - Reduced growth of the subset of cancers stimulated by the metabolic environment seen in type II diabetes and obesity

- Tumor cell sensitive to energetic stress (e.g., loss of function of AMPK, p53, or LKB1)
  - Energetic crisis
  - Cytotoxic effects

- Tumor cell capable of responding to energetic stress
  - ↑ AMPK
  - ↓ mTOR
  - ↓ FAS
  - ↓ Energy consumption
  - Cytostatic effect

Effects on host indirectly influencing target cells require:
- baseline hyperinsulinemia
- neoplasm that is insulin sensitive

Direct effects on target cells require:
- adequate drug concentration in tissue
- expression of cell surface drug transporters such as OCT1

M. Pollak Cancer Discovery 2012
Metformin effect on cognition or dementia

Potential mechanisms:
• Improved insulin sensitivity and vascular risk factors
• Reduced inflammation
• Histologic and cognitive improvement in animal models
Data Sources For Projecting Event Rates

- Diabetes Prevention Program (DPP)
- Health, Aging, and Body Composition (Health ABC) Study
- Health and Retirement Study (HRS)
- Olmsted County Study / Rochester Epidemiology Project
- Women’s Health Initiative (WHI)
Tertiary End Points

• Onset of Geriatric Syndromes
  – Incident Frailty, Mobility Disability, Anemia, Weight Loss, Falls

• Other Acute Events Disproportionately Affecting Older Adults
  – Fractures, Pneumonia

• Continuous Measures of Function
  – Gait Speed, Muscle Strength, FEV1, Body Composition (Bone Densitometry)

• Quality of Life Measures
  – Pain, Sleep Quality, Fatigue

• Blood-Based Biomarkers
  – IL-6, eGFR

• ADL & IADL Disability, Hospital Days, Disability Free Days