Metformin for Prevention and Treatment of Type 2 Diabetes

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Medicines Used in Treating Type 2 Diabetes

- Metformin
- Insulin secretagogues
  - Sulfonylureas
  - Meglitinides
- Thiazolidinediones
- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- GLP-1 agonists
- SGLT2 inhibitors
- Insulin
- Weight-loss drugs
Medicines Used in Treating Type 2 Diabetes

- **Metformin**: 1st recommended drug
- Insulin secretagogues
  - Sulfonylureas
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History of Biguanides

- Goat’s rue / French lilac (guanidine) used for diabetes in medieval Europe
- Guanidine-derived compounds tried in 1920s but too toxic
- Biguanides metformin & phenformin introduced 1950s
- Phenformin withdrawn in U.S.A. in 1977 due to lactic acidosis
- Metformin approved in U.S.A. in 1995

What Does Metformin Do?

- Suppresses glucose production by the liver
- Lowers fasting glucose

American Diabetes Association: Diabetes Care 2017
Advantages and Disadvantages of Metformin

**Advantages**
- Long experience
- Rare hypoglycemia
- May lower cardiovascular disease
- Greater effect on lowering HbA1c
- Modest weight loss
- Low cost

**Disadvantages**
- Gastrointestinal side effects
- Vitamin B12 deficiency
- Not used in advanced kidney disease
- Lactic acidosis (?)

Adapted from American Diabetes Association: Diabetes Care 2017
In the 1990s We Thought Type 2 Diabetes Could Be Prevented

- Why did we think so?
- Was there a role for drugs such as metformin?
Incidence of Diabetes by BMI in Adults
GRIC Longitudinal Study

Other potentially modifiable factors:
Fasting and 2-hour plasma glucose, physical inactivity

Diabetes Prevention Program (DPP)

- Multicenter randomized clinical trial in U.S.A.
- Hypothesis: Type 2 diabetes can be prevented or delayed by treating modifiable risk factors: obesity, inactivity, insulin resistance, elevated glucose
- Nondiabetic adults at high risk of type 2 diabetes
- 1996 – 2001 with long-term follow-up

*NEJM* 346: 393-403, 2002
Diabetes Prevention Program Clinics

- 27 clinics
- 3,819 participants
DPP Study Treatment Groups

Randomize (n = 3,234)

Standard lifestyle teaching

Intensive Lifestyle (n = 1079)

Metformin 850 mg BID (n = 1073)

Placebo (n = 1082)

DPP Research Group: NEJM 346:393-403, 2002
The DPP Intensive Lifestyle Intervention

An intensive program with the following specific goals:

• ≥ 7% loss of body weight and maintenance of weight loss

• ≥ 150 minutes per week of physical activity

DPP Research Group: NEJM 346:393-403, 2002
Mean Weight Change from Baseline

- Placebo
- Metformin
- Lifestyle

DPP Research Group: *NEJM* 346:393-403, 2002
Changes in Fasting Plasma Glucose by Treatment Group

FPG (mg/dl)

Placebo

Metformin

Lifestyle

Years from Randomization

NEJM, 2002
Diabetes Incidence Rates in DPP

DPP Research Group: *NEJM* 346:393-403, 2002
DPP: Diabetes Incidence by Race/Ethnicity

DPP Research Group: *NEJM* 346:393-403, 2002
Diabetes Incidence Rates by Fasting Glucose

Fasting Plasma Glucose: mg/dl (mmol/l)

- **95-109 (5.3-6.0)** (n=2174)
- **110-125 (6.1-6.9)** (n=1060)

Cases/100 person-yr

**Lifestyle**
- **Metformin**
- **Placebo**

*NEJM, 2002*
DPP: Unanswered Questions After 3 Years

- How long will weight loss and prevention last?
- Effects on “patient-centered” outcomes: micro- and macro-vascular disease, quality of life, longevity
- Cost-effectiveness
DPPOS Protocol Changes
Mandated by Treatment Effects

- Unmask drug assignments and study results
- Discontinue placebo & continue metformin
- Group lifestyle intervention for all participants

DPP Research Group, Lancet 374: 1677-1686, 2009
DPPOS Results

Weight Loss

Change in weight (kg)

-8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5

Placebo Metformin Lifestyle

Years since DPP Randomization

DPP

DPPOS
Cumulative Incidence of Diabetes

DPP and DPPOS: All participants

Placebo  Metformin  Lifestyle

916 developed DM in first 5 years of follow-up

700 developed DM after 5 years of follow-up

Years since DPP Randomization

Cumulative Incidence (%)

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Coronary Artery Calcification Severity* in DPPOS

*Age-adjusted geometric mean severity, Agatston Units
Other Long-term Effects of Metformin in the DPPOS

- Cost saving: reduction in medical care costs outside the study were greater than the cost of the metformin intervention
- Increased rate of vitamin B12 deficiency (a known side effect)
- No effect on cognitive function (memory and thinking)
DPPOS Phase 3 (2016-2025)
Aims

• Long-term effects of metformin, started during pre-diabetes, on
  - Cardiovascular events (heart, stroke)
  - Cancer incidence

• Long-term effects of metformin or lifestyle on diabetes complications (eye, kidney, physical and cognitive function) and further diabetes
Conclusion
Metformin for Diabetes Prevention

• Although lifestyle changes (weight loss and increased physical activity) had the greatest effect on diabetes prevention, metformin was also effective, and not everyone can lose weight.

• Metformin may have other long-term benefits.

• Thank you volunteers in the DPPOS and other medical research programs for teaching us ways to improve health.
The End