Management of Type 2 Diabetes: Should We Change Our Algorithm? Drugs for Type 2 Diabetes

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3. ANTI-HYPERGLYCEMIC THERAPY

- Glycemic targets
  - HbA1c < 7.0% (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - Individualization is key:
    ➢ Tighter targets (6.0 - 6.5%) - younger, healthier
    ➢ Looser targets (7.5 - 8.0%*) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

Approach to the management of hyperglycemia

- More stringent
- Less stringent

- HbA1c 7%

- Disease duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude and expected treatment efforts
- Resources and support system

- Usually non-modifiable
- Potentially modifiable


Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442

The Y Takes On Diabetes

CDC Funding
- The American Association for Diabetes Educators
- America’s Health Insurance Plans
- Black Women’s Health Imperative
- National Association of Chronic Disease Directors
- YMCA of the USA

Medicare Funding!
- Begins 1/1/2018
- 12 month intervention
  - At least 16 weekly core 1 hour sessions
  - Medicare Part B
  - BMI >24 (Asian >22)
  - HbA1c 5.7 to 6.4 or FBS 110-125
  - No dx of type 1 or type 2 DM (can have hx gestational DM)
  - No ESRD
- Payment structure - TBD
- Must be recognized CDC Diabetes Prevention Recognition Program

More stringent
Less stringent
Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians

Recommendation 1:
ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control.

(Grade: strong recommendation; moderate-quality evidence)


Metformin and Lactic Acidosis
• “Metformin may provoke lactic Acidosis which is most likely to occur in patients with renal impairment. It should not be used with even mild renal impairment” 1
• Metformin probably not as unsafe as previously thought.
  – 25% users have relative contraindication 2
  – Patient’s with lactic acidosis usually have acute renal failure 3


Metformin: The Safest Hypoglycaemic Agent in Chronic Kidney Disease?
• There is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other oral hypoglycaemic treatments.

Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes.
Nephron Clin Pract 2011;118:c385-c393

FDA and Metformin: 2016
• Eliminated the heart failure warning in response to 2 large observational studies that suggested that metformin is safe and may be beneficial in patients with compensated heart failure.
• As a result of 2 citizen petitions, Metformin allowed in patients with:
  – mild to moderate kidney dysfunction, defined as an estimated glomerular filtration rate (eGFR) of 30 to 60 mL/min/1.73 m²,
  – but not in those with severe kidney dysfunction (eGFR <30 mL/min/1.73 m²).
The Effect of Intravenous Contrast on Renal Function in Diabetic Patients on Metformin

SF VA - - retrospective
- 130 patients
- precontrast renal function did not predict a decline in postcontrast renal function
- patients with precontrast eGFR >60 mL/min/1.73 m² did not have any deterioration in renal function.
- no significant deterioration in renal function in patients with a precontrast eGFR >60 mL/min/1.73 m².

UCSF - - Prospective
- 40 patients
- no significant change in serum creatinine was observed (baseline range from 0.7 to 1.2 mg/dL). Notably, an additional 15 patients were recruited, but they did not obtain a postcontrast creatinine measurement despite receiving reminders.

2015 American College of Radiology Manual on Contrast Media

Iodinated Contrast

Category I. (eGFR ≥30 mL/min/1.73 m²)
In patients with no evidence of AKI and with eGFR ≥30 mL/min/1.73 m², there is no need to discontinue metformin either prior to or following the intravenous administration of iodinated contrast media, nor is there an obligatory need to reassess the patient’s renal function following the test or procedure.

Category II. (eGFR <30 mL/min/1.73 m²)
In patients taking metformin who are known to have acute kidney injury or severe chronic kidney disease (stage IV or stage V; i.e., eGFR <30 mL/min/1.73 m²), or are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reintroduced only after renal function has been re-evaluated and found to be normal.

Gadolinium-based contrast material
It is not necessary to discontinue metformin prior to contrast medium administration when the amount of gadolinium-based contrast material administered is in the usual dose range of 0.1 to 0.3 mmol per kg of body weight.
Long-term Metformin Therapy and Monitoring for Vitamin B12 Deficiency Among Older Veterans

- Veterans 50 years or older with either type 2 diabetes and long-term metformin therapy (n = 3,687) or without diabetes and no prescription for metformin (n = 13,258)
- 37% of older adults with diabetes receiving metformin were tested for vitamin B12 status
- Mean B12 concentration was significantly lower in the metformin-exposed group (439.2 pg/dL) compared to those without diabetes (522.4 pg/dL) (P = .0015).
- About 7% of persons with diabetes receiving metformin were vitamin B12 deficient (<170 pg/dL) compared to 3% of persons without diabetes or metformin use (P = .0001)


Metformin and B12

- Anemia may be minimal to severe
- May present only as a peripheral neuropathy, possibly being misdiagnosed as diabetic neuropathy.

1. Parenteral vitamin B12 treatment  (9 to 10 loading injections of 1000 µg each, followed by monthly 1000 µg injections)
2. High-dose oral vitamin B12 treatment (1000 to 2000 µg daily)
3. Effective vitamin replacement will correct blood counts in 2 months and correct or improve neurological signs and symptoms within 6 months.

Va longitudinal study (Wian et al - ADA 2016)

- Metformin exposure longer than 2 years
- Significant reduction in neurodegenerative disease (reduced cognitive decline, Parkinson’s, Alzheimer’s)
- Metformin may be neuroprotective

Targeting Aging with Metformin (TAME) study

- Demonstrated to slow the aging process in certain microbes and mammals
- The researchers will give Metformin to about 3,000 elderly people, who either suffer from or have a high risk of developing diseases like cancer, heart disease, or cognitive problems.

Cancer

- Studies on lung cancer, head and neck cancers, esophageal cancer
- Affect multiple key processes related to cell growth, proliferation, and survival, both metabolic and intracellular-signaling activity. Downregulation of the Ras/Raf/MEK/ERK and PI3K/AKT/mTOR signaling pathways. One or both of these pathways are often activated in many types of cancer cells.
Asymptomatic Episodes of Hypoglycemia May Go Unreported

- Hypoglycemia: glucose <60 mg/dl
- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by 3 day continuous glucose monitoring
- HbA1c 8 (T1) 7.4 (T2)

Patients Are Worried About the Risk of Hypoglycemia: The Diabcare–Asia 2003 Study

- Survey of 15,549 patients with diabetes
- 96% had type 2 diabetes and 4% of patients had type 1 diabetes
- 54% of respondents were anxious about the risk of hypoglycemia all or most of the time

Cardiac Effects of Sulfonylurea Related Hypoglycemia

- 30 type 2 DM patients on sulfonylureas
- Mean HbA1c 6.9
- 48 hour CGM
- Hypoglycemia (<63 mg/dl for >20 minutes) was detected in 9 of 30 subjects
- Episodes were typically nocturnal (67%) and asymptomatic (73%).
- Hypoglycemia associated QTc prolongation was seen in 5 subjects with a large variation in individual response.
- Higher QT dynamicity, a poor prognostic factor in cardiac disease, was seen in subjects who experienced hypoglycemia compared with subjects who did not (0.193 vs. 0.159 for the nocturnal period; P = 0.01). This finding persisted after the hypoglycemic event.
- The rates of ventricular and supraventricular ectopy demonstrated a nonsignificant trend toward an increase during hypoglycemia
Positive Side to TZDs
- Reduction in glucose
- Reduces BP
- Reduces albuminuria
- Reduces CRP
- Possible DM prevention
- Reduces NASH
- Reduces LFT

- Reduces IMT
- Reduces stent failure
- Reduces death after CHF
- Increases adiponectin
- Increases HDL

Current TZD Side Effects
- Weight Gain: 5-12 lbs in 1 year
  - Blunted with metformin
  - Worse with insulin
- Edema: 4-30%
  - Unresponsive to diuretics
- BUT:
  - Increased Cardiac Index
  - Increased Stroke volume
  - Decreased systemic resistance
  - Decreased Blood Pressure

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack
- Multicenter, double-blind trial
- 3876 patients who had had a recent ischemic stroke or TIA
- No diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index
- Received either pioglitazone (target dose, 45 mg daily) or placebo.

- Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).

- Pioglitazone can help prevent recurrence of stroke and progression into diabetes in those patients with insulin resistance and recent cardiovascular events.

- Bone mineral density should be closely monitored in patients taking pioglitazone due to high rates of bone fracture, hospitalizations, and surgeries.

**Pioglitazone Bladder Cancer**

2013 Meta Analysis (1):
- Hazard ratio higher in patients using pioglitazone (hazard ratio 1.22; 95% CI 1.08-1.39)

2012 Meta Analysis (2):
- Hazard ratio higher in patients using pioglitazone (pooled RR 1.22, 95% CI 1.07-1.38)

2016 Population study:
- 145,608 patients over 14 years
- Compared with other antidiabetic drugs, pioglitazone was associated with an increased risk of bladder cancer (121.0 v 88.9 per 100,000 person years; hazard ratio 1.63, 95% confidence interval 1.22 to 2.19). Conversely, rosiglitazone was not associated with an increased risk of bladder cancer (86.2 v 88.9 per 100,000 person years; 1.10, 0.83 to 1.47). Duration-response and dose-response relations were observed for pioglitazone but not for rosiglitazone.

2016 FDA:
- After updating its review of published research, which had gone back and forth on the issue.
- Concluded pioglitazone may still pose an increased risk for bladder cancer.

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**Negative Side to TZDs**

- Weight Gain
- Edema
- Bone loss
- Bladder Cancer

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**INCRETINS**

- Gut factors that promote insulin secretion in response to nutrients

- Major incretins: GLP-1, CCK, GIP

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**Plasma Insulin Responses to Oral and Intravenous Glucose**

<table>
<thead>
<tr>
<th>Non-Diabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>90</td>
</tr>
<tr>
<td>Intravenous</td>
<td>60</td>
</tr>
</tbody>
</table>

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(2)  CMAJ, 2012 Sep 4;184(12):E675-83.
(3)  BMJ 2016;352:i1541.

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Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon Levels in Patients With Type 2 Diabetes

When glucose levels approach normal values, glucagon levels rebound.

When glucose levels approach normal values, insulin levels decreases.

*P < 0.05

Patients with type 2 diabetes (N=10)

Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With Type 2 Diabetes

Glycemic outcome. Change from baseline in hemoglobin A1c level.

Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With Type 2 Diabetes

Changes in body weight and glucose levels over 30 weeks.

Data are least-squares means estimated from a mixed model, in which the postbaseline response variable = treatment + pooled investigator + visit + baseline + baseline hemoglobin A1c stratum (≤8.0% or >8.0%) + (treatment × visit), and the participant is treated as a random effect with an unstructured covariance matrix.
Incretin Agents: Safety Concerns

- Thyroid Cancer and Neoplasia:
  - Thyroid C-cell tumors in rodent models
  - Not recommended for use in patients with a personal or family history of MTC or MEN 2A or 2B

- Pancreatitis

- Pancreatic Cancer

Incretin Drugs: Pancreatitis

- Patients without Diabetes
  - General Population in US
    - 0.33-0.44 events per 1000 adults per year (1)
    - Severe disease in 15-20% of these cases (2)
    - Death in 2-4% of cases (2)

- Type 2 Diabetes Patients
  - Epidemiology study shows 3 times risk compared to subjects without diabetes (3)


Acute Pancreatitis in Type 2 Diabetes Treated With Exenatide or Sitagliptin
A retrospective observational pharmacy claims analysis

Diabetes Care 33:2349–2354, 2010
Risks of Pancreatitis and Pancreatic Cancer with Incretin therapies

- FDA and EMA independent reviews of patient data and animal studies have identified no evidence for causal relationship but maintain that the **risks should be disclosed and further investigated** (Egan et al NEJM 2014; EMA Report 2013).
- No prospective studies have identified a causal relationship thus far
- Represents an area of ongoing investigation

DPP-4 Inhibitor–Related Pancreatitis: Rare but Real!

- Large-scale CVOTs have now been reported for three DPP-4 inhibitors: saxagliptin, alogliptin, and sitagliptin.
- There were clear numerical imbalances, with more cases of acute pancreatitis occurring with each of the three DPP-4 inhibitors than in the control groups, which failed to reach statistical significance in each of the individual trials.
- The estimated odds ratio for an increased risk of acute pancreatitis with DPP-4 inhibitors was 1.79 with an absolute increased risk of 0.13%.
- Translates to one to two additional cases of acute pancreatitis for every 1,000 patients treated for 2 years.
- Translated to 1 million users in the U.S., a very conservative estimate, this would result in ~750 additional cases of acute pancreatitis per year.

Incretins (dpp-4): CVD

**SAVOR-TIMI 53:** Saxagliptin
- unexpected excess rate of hospitalization for heart failure in the saxagliptin group (hazard ratio, 1.27; 95% CI, 1.07 to 1.51)

**EXAMINE:** Alogliptin
- nonsignificant numerical imbalance in hospitalization for heart failure in the alogliptin group as compared with placebo (hazard ratio, 1.19; 95% CI, 0.90 to 1.58)

**TECOS:** Sitagliptin
- rates of hospitalization for heart failure was no different from placebo

Retrospective (Diabetes Care 2016):
- In patients with type 2 diabetes, there was no association between HF, or other selected cardiovascular outcomes, and treatment with a DPP-4i relative to SU or treatment with saxagliptin relative to sitagliptin.

Meta-analysis of the cardiovascular outcome trials reporting the risk of HF with DPP-4 inhibitors.

- **Kristian B. Filion, and Samy Suissa** Diabetes Care 2016;39:735-737 ©2016 by American Diabetes Association
Incretins (GLP-1): CVD

**ELIXA:** Lixisenatide (N Engl J Med 2015; 373: 2247-2257)
- Neutral effect on heart failure and other cardiovascular problems

- Rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

Renal Glucose Reabsorption in Type 2 Diabetes

- Sodium-glucose cotransporter 2 (SGLT2) plays a role in renal glucose reabsorption in proximal tubule
- Renal glucose reabsorption is increased in type 2 diabetes
- Selective inhibition of SGLT2 increases urinary glucose excretion, reducing blood glucose

Rationale for SGLT2 Inhibitors

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- This therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes are likely to respond

SGLT2 Inhibitors

- **Potential Advantages**
  - Weight loss
  - Low risk of hypoglycemia
  - Possible BP lowering effect
  - Effect independent of insulin
- **Concerns**
  - Polyuria
  - Electrolyte disturbances
  - Bacterial UTIs
  - Fungal genital infections
  - Euglycemic DKA
### Canagliflozin added to metformin lowers HbA1C with minimal hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Glimperide 100mg</th>
<th>Canagliflozin 100mg</th>
<th>Canagliflozin 300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg LS mean (SE) change</td>
<td>0.70 (0.2)</td>
<td>-3.7 (0.2)</td>
<td>-4.0 (0.2)</td>
</tr>
<tr>
<td>Systolic BP LS mean (SE) change</td>
<td>0.2 (0.6)</td>
<td>-3.3 (0.6)</td>
<td>-4.6 (0.6)</td>
</tr>
<tr>
<td>Hypoglycemia (n, %)</td>
<td>164 (34%)</td>
<td>27 (6%)</td>
<td>24 (5%)</td>
</tr>
</tbody>
</table>

### Dapagliflozin added to metformin enables sustained A1C and weight lowering

### Canagliflozin: Genitourinary and Renal side effects

<table>
<thead>
<tr>
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<th>Glimperide 100mg</th>
<th>Canagliflozin 100mg</th>
<th>Canagliflozin 300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital urinary</td>
<td>20(2%)</td>
<td>17(2%)</td>
<td>26(4%)</td>
</tr>
<tr>
<td>Related adverse events</td>
<td>20(2%)</td>
<td>12(3%)</td>
<td>12(2%)</td>
</tr>
<tr>
<td>Urine tract infection</td>
<td>20(2%)</td>
<td>12(3%)</td>
<td>12(2%)</td>
</tr>
<tr>
<td>Genitourinary adverse events</td>
<td>20(2%)</td>
<td>12(3%)</td>
<td>12(2%)</td>
</tr>
<tr>
<td>Vescourethral</td>
<td>20(2%)</td>
<td>17(2%)</td>
<td>26(4%)</td>
</tr>
<tr>
<td>Valvular related adverse events</td>
<td>20(2%)</td>
<td>17(2%)</td>
<td>26(4%)</td>
</tr>
</tbody>
</table>

### Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Primary outcome: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
Possible mechanisms that could contribute to the reduction of CV mortality by empagliflozin in the EMPA-REG OUTCOME study

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Unlikely</th>
<th>Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowered plasma glucose concentration</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td>Increased renal sodium excretion</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td>Increased plasma uric acid concentration</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td>Increased plasma glucose concentration</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td>Increased 24-hour ambulatory activity</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
</tbody>
</table>

| Antihypertensive actions                       | Unlikely | Likely |
| Decrease in blood pressure                    | Unlikely | Likely |
| Diabetic effect and decrease in extracellular fluid volume | Unlikely | Likely |
| Regional arterial stiffness                    | Possible | Possible |
| Decreased sympathetic tone                    | Possible | Possible |

| Rate of amputations per every 1000 patients   |          |        |
| 100 mg/day: 7                                |          |        |
| 300 mg/day: 5                                |          |        |
| Placebo: 3                                   |          |        |

SGLT2 Inhibitors

- Bone Loss
  - 714 elderly patients with type 2 diabetes (mean age, 64 years; range, 55 - 80 years).
  - At 2 years,
    - Decreases in total hip BMD were seen with canagliflozin 100 and 300 mg versus placebo (-1.7%, -2.1%, -0.8%; differences of -0.9% and -1.2%)
    - No bone loss at other sites, (normal age-related bone loss, ~0.5-1.0%/year).
  - Fractures tended to occur as early as 12 weeks after initiating treatment and were primarily located in the distal parts of the upper and lower extremities.
  - Why?
    - SGLT2 inhibitors increase concentrations of phosphate in serum, probably via increased tubular reabsorption, which has the potential to adversely affect bone.
    - SGLT2 inhibitors increase concentrations of parathyroid hormone (PTH).
    - Sustained increase in PTH concentration enhance bone resorption and increase the risk for bone fractures.

SGLT2 Inhibitors Amputations

- Increased risk for lower-limb amputations (toes)
  - Limited data
  - 3.4 year interim analysis of CANVAS

<table>
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<tr>
<td>300 mg/day: 5</td>
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<tr>
<td>Placebo: 3</td>
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</table>
1. Patient-Centered Approach

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”

- Gauge patient’s preferred level of involvement.
- Explore, where possible, therapeutic choices. Consider using decision aids.
- Shared Decision Making – a collaborative process between patient and clinician, using best available evidence and taking into account the patient’s preferences and values
- Final decisions regarding lifestyle choices ultimately lie with the patient.


204 studies analyzed
50 spanned several continents, while others were conducted across Europe, Asia and the United States.
Most of the studies were short term, with only 22 mostly observational studies lasting more than two years

Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis

204 studies analyzed
50 spanned several continents, while others were conducted across Europe, Asia and the United States.
Most of the studies were short term, with only 22 mostly observational studies lasting more than two years

Pooled between-group differences in the change in HbA1c for comparisons of monotherapies and metformin-based combination therapies.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Studies, p</th>
<th>Participants, p</th>
<th>Data Characteristics</th>
<th>Effect Size (95% CI)</th>
<th>Summary Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU vs. TZD</td>
<td>23</td>
<td>1721</td>
<td></td>
<td>-0.54 (-1.11 to 0.03)</td>
<td>High</td>
</tr>
<tr>
<td>SU vs. DPP-4</td>
<td>6</td>
<td>1873</td>
<td></td>
<td>-0.53 (-0.85 to -0.21)</td>
<td>High</td>
</tr>
<tr>
<td>SU vs. GLP-1</td>
<td>10</td>
<td>3086</td>
<td></td>
<td>-0.50 (-0.76 to -0.25)</td>
<td>High</td>
</tr>
<tr>
<td>DPP-4 vs. GLP-1</td>
<td>2</td>
<td>1751</td>
<td></td>
<td>-0.21 (-0.52 to 0.09)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Pooled between-group differences in the change in weight for comparisons of monotherapies and metformin-based combination therapies.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Studies, p</th>
<th>Participants, p</th>
<th>Data Characteristics</th>
<th>Effect Size (95% CI)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU vs. TZD</td>
<td>6</td>
<td>3774</td>
<td></td>
<td>-0.53 (-1.00 to -0.07)</td>
<td>High</td>
</tr>
<tr>
<td>SU vs. DPP-4</td>
<td>7</td>
<td>264</td>
<td></td>
<td>-0.54 (-0.74 to -0.34)</td>
<td>High</td>
</tr>
<tr>
<td>SU vs. GLP-1</td>
<td>5</td>
<td>1915</td>
<td></td>
<td>-0.50 (-0.77 to -0.23)</td>
<td>High</td>
</tr>
</tbody>
</table>


Pooled odds ratios for mild and moderate hypoglycemia for comparisons of monotherapies and metformin-based combination therapies.

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians

**Recommendation 2:**
ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered.

(Grade: weak recommendation; moderate-quality evidence.)
ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.
Clinical Inertia in People with Type 2 Diabetess

- 81,000 people with Type 2 DM
- Followed from 2004-2011
- Median time to add another drug

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>On 1 drug</th>
<th>On 2 drugs</th>
<th>Adding insulin if on 1-3 oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;7</td>
<td>2.9</td>
<td>7.2</td>
<td>8.7</td>
</tr>
<tr>
<td>&gt;7.5</td>
<td>1.9</td>
<td>7.2</td>
<td>9.1</td>
</tr>
<tr>
<td>&gt;8</td>
<td>1.6</td>
<td>6.9</td>
<td>9.7</td>
</tr>
</tbody>
</table>