

New York State Medicaid Prescriber Education Program

Relative efficacy of medications
for type 2 diabetes

Treating type 2 diabetes mellitus



Key messages

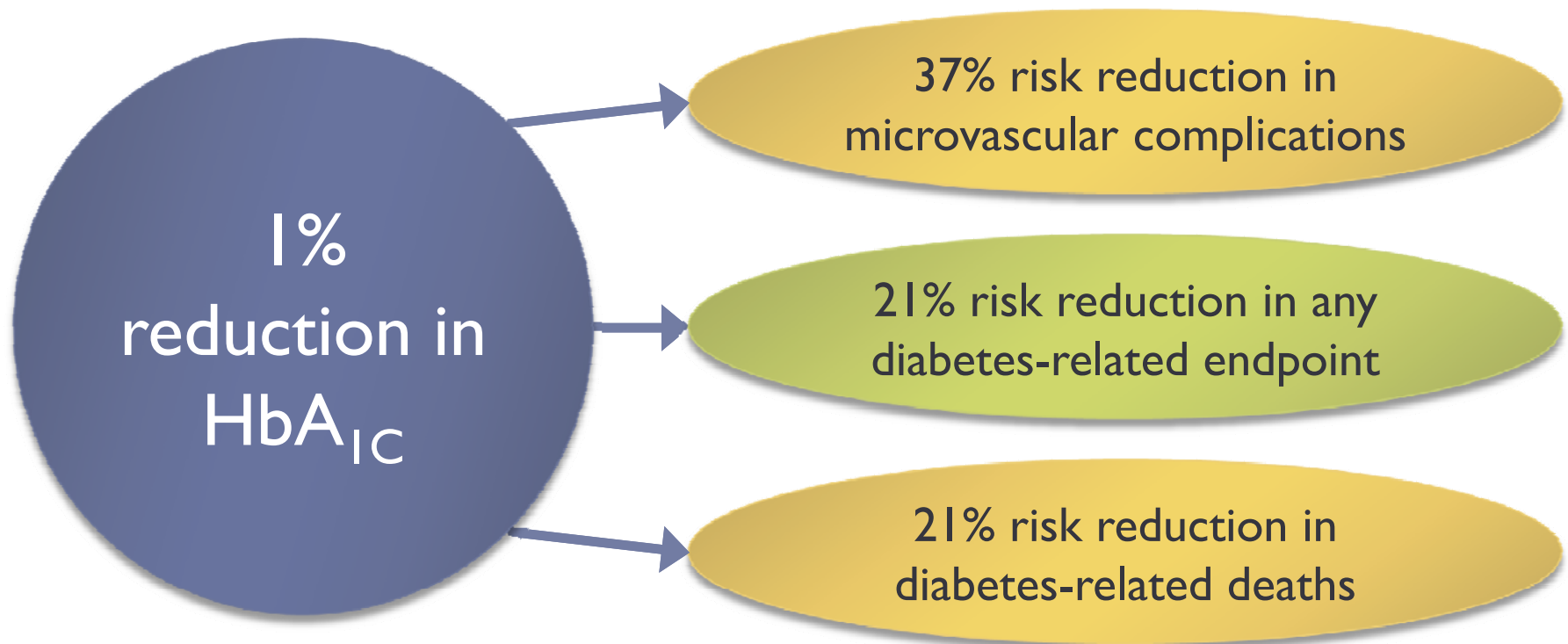
- 1) Metformin should be used as a first-line medication in almost every patient with type 2 diabetes.
 - 2) **DPP-4 inhibitors and GLP-1 agonists should not be used first-line in patients with type 2 diabetes because metformin, sulfonylureas, and insulin are more efficacious.**
 - 3) HbA1C goals should be individualized for each patient with type 2 diabetes: less than 7% for most patients and less than 8% for specific high-risk subgroups.
 - 4) Patients with type 2 diabetes should have an HbA1C test every three to six months.
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Risk reduction of diabetes-related endpoints

▶ UKPDS 35

- ▶ Objective: Collect long-term data on HbA_{1C} reduction with **sulfonylureas** and **insulin** (10-year follow-up)



- ▶ Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. Aug 12 2000;321(7258):405-12.

Metformin can lower A1C about 1-2%

Study	Results
Nathan DM et al. 2009	Metformin monotherapy will ↓ A1C levels by ~ 1.5% . Expected range with monotherapy is 1-2%
DeFronzo RA 1995	Efficacy of metformin alone was similar to that of SU alone. Metformin is equally effective when used in combination with SU. Average A1C ↓ ~ 1.3-1.7%
Garber AJ et al. 1997	Metformin lowered A1C generally in a dose-related manner. The decrease ranged from 0.6% to 2% respectively at dosages of 500 to 2,000 mg daily.
Bailey CJ et al. 1996	Efficacy of metformin in obese and non-obese patients in type 2 diabetes is similar to that achieved with a sulfonylurea.



Sulfonylureas can lower A1C about 1-2%

Study	Results
Nathan DM et al. 2009	Efficacy of SU is similar to metformin; lowers A1C by ~1.5%
Turner RC et al. 1998	UKPDS: A1C over 10yrs of treatment similar among SUs (chlorpropamide, glyburide) and insulin
Scholz GH et al. 2001	Glimepiride associated with a 1.8% reduction in A1C in newly-treated patients, 1.3% reduction among those switched from another agent
DeFronzo RA 1999	Sulfonylureas reduce A1C by 1.5%-2%



Sulfonylureas can lower A1C about 1-2%

Table 1. Comparison of Sulfonylureas, Repaglinide, Metformin, Troglitazone, and Acarbose When Used as Monotherapy*

Effect	Sulfonylureas and Repaglinide	Metformin	Troglitazone	Acarbose
Mechanism of action	Increase in insulin secretion	Decrease in hepatic glucose production; increase in muscle insulin sensitivity	Decrease in hepatic glucose production; increase in muscle insulin sensitivity	Decrease in GI absorption
Decrease in FPG level, <i>mmol/L (mg/dL)</i>	3.3–3.9 (60–70)	3.3–3.9 (60–70)	1.9–2.2 (35–40)	1.1–1.67 (20–30)
Decrease in hemoglobin A _{1c} value, <i>percentage points</i>	1.5–2.0	1.5–2.0	1.0–1.2	0.7–1.0
Triglyceride level	No effect	Decrease	Decrease	No effect
HDL cholesterol level	No effect	Slight increase	Increase	No effect
LDL cholesterol level	No effect	Decrease	Increase	No effect
Body weight	Increase	Decrease	Increase	No effect
Plasma insulin	Increase	Decrease	Decrease	No effect
Adverse events	Hypoglycemia	GI disturbances, lactic acidosis†	Anemia, hepatic toxicity‡	GI disturbances

* FPG = fasting plasma glucose, GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† Incidence of 0.03 cases per 1000 patient-years (rare).

‡ Severe, idiosyncratic, sometimes irreversible hepatic failure has been reported with troglitazone, but the precise incidence is unknown. Elevated liver enzyme levels occur in about 2% of patients.]

Insulin can lower A1C >1.5%

Study	Results
DeFronzo RA 1999	Insulin use in academic research settings can decrease A1C by ~2%
Nathan DM et al. 2009	Most effective antidiabetic agent; can decrease any A1C to target with no maximum dose ceiling effect
Fonseca V et al. 2011	Adding insulin glargine to metformin monotherapy resulted in a 2% decrease in A1C versus 1.7% reduction when added to SU monotherapy or metformin + SU combination therapy



GLP-1 agonists can lower A1C 0.5-1%

Study	Results
Nathan DM et al. 2009	Exenatide may reduce A1C by 0.5-1% . Published prior to approval of liraglutide (2010)
Kendall DM et al. 2005	Exenatide can reduce A1C by 0.6 to 0.8%
Visboll T et al. 2007	Liraglutide can reduce A1C by 0.98 to 1.45% after 14 weeks of treatment when compared to placebo.

GLP-1 agonists include exenatide (Byetta[®]) and liraglutide (Victoza[®])



DPP-4 inhibitors can lower A1C 0.5-1%

TABLE 1 A1c Change Results from Randomized Controlled Trials^a of Sitagliptin and Saxagliptin in Adult Patients with Type 2 Diabetes

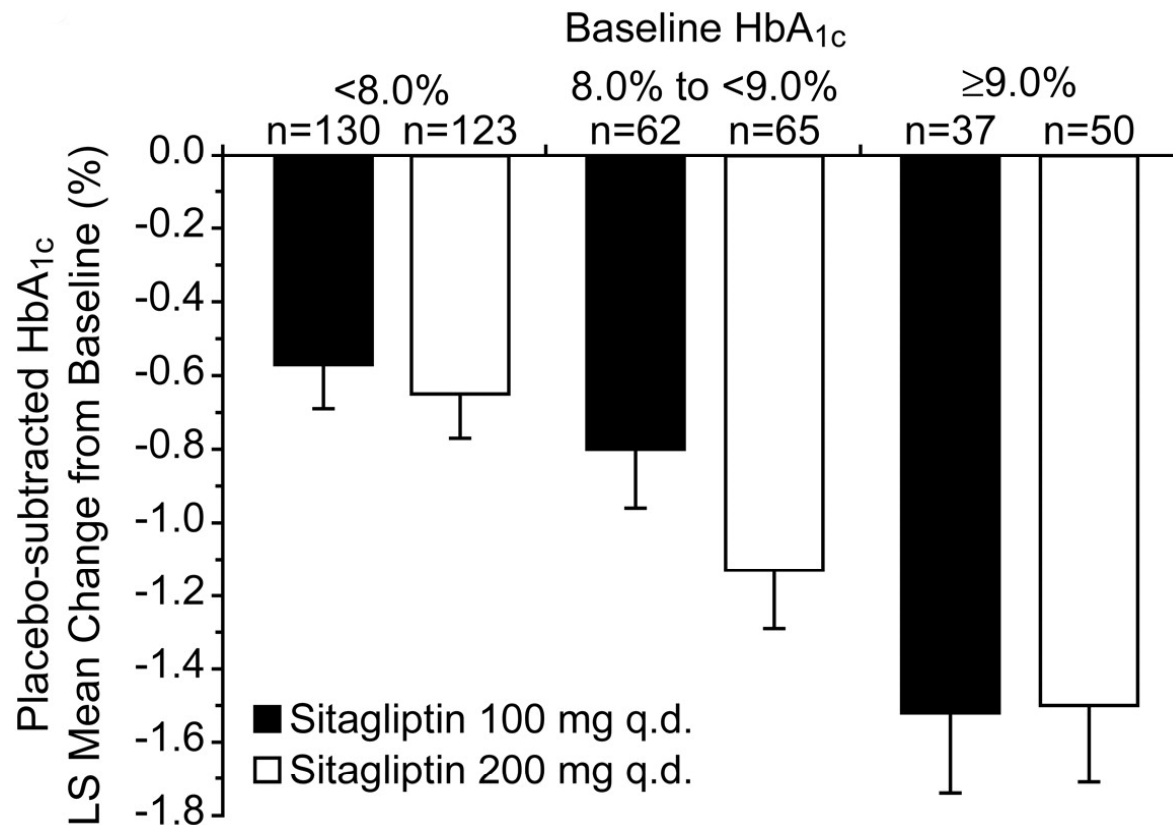
First Author and Year	Comparison	Treatment N	Control N	Length	Mean Baseline A1c		Mean Change in A1c		Mean (95% CI) Difference from Control ^b
					Treatment	Control	Treatment	Control	
Raz 2006 ²⁴	Sitagliptin 100mg monotherapy vs. placebo	193	103	18 weeks	8.0	8.1	-0.5	+0.1	-0.6 (-0.8 to -0.4)
Aschner 2006 ²⁵	Sitagliptin 100mg monotherapy vs. placebo	229	244	24 weeks	8.0	8.0	-0.6	+0.2	-0.8 (-1.0 to -0.6)
Charbonnel 2006 ²⁶	Sitagliptin 100mg + metformin vs. placebo + metformin	453	224	24 weeks	8.0	8.0	-0.7	-0.0	-0.7 (-0.8 to -0.5)
Rosenstock 2006 ²⁷	Sitagliptin 100mg + pioglitazone vs. placebo + pioglitazone	163	174	24 weeks	8.1	8.0	-0.9	-0.2	-0.7 (-0.9 to -0.5)
Hermansen 2007 ²⁸	Sitagliptin 100mg + glimepiride vs. placebo + glimepiride	102	103	24 weeks	8.4	8.5	-0.3	+0.3	-0.6 (-0.8 to -0.3)
Hermansen 2007 ²⁸	Sitagliptin 100mg + glimepiride + metformin vs. placebo + glimepiride + metformin	115	105	24 weeks	8.3	8.3	-0.6	+0.3	-0.9 (-1.1 to -0.7)
Goldstein 2007 ²⁹	Sitagliptin 100mg vs. placebo	175	165	24 weeks	8.9	8.7	-0.7	+0.2	-0.8 (-1.1 to -0.6)

DPP-4 inhibitors include sitagliptin (Januvia[®]), saxagliptin (Onglyza[®]), and linagliptin (Tradjenta[®])

▶ Fairman K, Curtiss F. Call for Comparative Effectiveness Research: Lowering A1C with Sitagliptin, Saxagliptin, or Cinnamon. JMCP. Oct 2009;15(8):696-700.

DPP-4 inhibitors can lower A1C 0.5-1%

- ▶ Aschner et al found that the largest reductions in A1C were seen in patients with a higher baseline A1C



- ▶ Aschner P, Kipnes M, Lunceford J, et al. Effect of Dipeptidyl Peptidase-4 Inhibitor Sitagliptin as Monotherapy on Glycemic Control in Patients with Type 2 Diabetes. *Diabetes Care*. Dec. 2006; 29(12):2632-2637.

DPP-4 inhibitors can lower A1C 0.5-1%

- ▶ Linagliptin approved in May 2011
 - ▶ Compared to placebo, linagliptin demonstrates similar A1C reductions compared to other DPP-4 inhibitors

Study (duration; wk)	Regimen ^b (mg)	No. of FAS pts	BL HbA _{1c} (%)	Adjusted ^c mean change in HbA _{1c} level ^d [treatment-effect] ^e (%)
Versus PL				
Del Prato et al. ^[19]	LIN 5 od	306-333	8.0	-0.44 [-0.69]**
(24)	PL	147-163	8.0	0.25
Kawamori et al. ^[299]	LIN 5 od	159	8.1 ^h	-0.49 [-0.87]**
(12)	LIN 10 od	157-160	8.0 ^h	-0.50 [-0.88]**
	PL	80	8.0 ^h	0.39

Summary of expected A1C decreases of various interventions

Intervention	Expected A1C decrease as monotherapy (%)	Advantages	Disadvantages
Lifestyle management/MNT	1.0 – 2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0 – 2.0	Weight neutral/modest weight loss	GI side effects; contraindicated with renal insufficiency
Sulfonylureas	1.0 – 2.0	Rapidly effective	Weight gain; hypoglycemia
Insulin	>1.5	No dose limit	Multiple injections; weight gain; hypoglycemia; analogs are expensive
GLP-1 agonists	0.5 – 1.0	Weight loss	Multiple daily injections (exenatide); GI side effects; expensive
Meglitinides	0.5 – 1.5	Rapidly effective	Weight gain; multiple daily dosing; expensive
AGIs	0.5 – 0.8	Weight neutral	GI side effects; multiple daily dosing; expensive
TZDs	0.5 – 1.4	Improved lipid profile	Fluid retention; CHF; weight gain; bone fractures; MI (rosiglitazone)
DPP-4 inhibitors	0.5 – 0.8	Weight neutral	Expensive



Summary

- ▶ **DPP-4 inhibitors and GLP-1 agonists should not be used first-line in patients with type 2 diabetes**
- ▶ **Metformin, sulfonylureas, and insulin are more efficacious than DPP-4 inhibitors and GLP-1 agonists in lowering HbA_{1c}**

