

Advances in Oral Therapy

Abstract

The current Canadian Diabetes Association Guidelines recommend tight glycaemic targets in our diabetic patients, in large part based on studies such as the UKPDS which have clearly shown the benefits to be associated with improved glycaemic control. Currently available antihyperglycaemic agents, although efficacious all have limitations. Furthermore, combinations of multiple oral agents are typically required in order to meet current glycaemic targets. Thus the availability of new antidiabetic therapies is certainly welcome.

The orally administered DPP 4 inhibitors have multiple actions that are beneficial in the patient with diabetes. They slow gastric emptying; improve satiety; and increase insulin and suppress glucagon secretion thus decreasing hepatic glucose production and improving glucose uptake in fat and muscle tissue. In addition, although not yet proven in humans, they have been shown in animal models of diabetes to preserve beta cell function with increased insulin biosynthesis, promotion of β -cell differentiation and decreases in β -cell apoptosis.

Clinical trials with sitagliptin and vildagliptin have revealed that these drugs substantially improve glycaemic control (A1C, FPG, and PPG) with a greater proportion of patients achieving A1c targets. Overall they have a safety and tolerability profile similar to placebo apart from a slightly higher incidence of mild GI AEs. In general there has been a low incidence of hypoglycaemia similar to placebo, and no change in body weight relative to baseline.

References

Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006 Nov 11;368(9548):1696-705.

Drucker DJ. Enhancing incretin action for the treatment of type 2 diabetes. *Diabetes Care* 2003 Oct;26(10):2929-40.

Green BD, Flatt PR, Bailey CJ. Dipeptidyl peptidase IV (DPP IV) inhibitors: A newly emerging drug class for the treatment of type 2 diabetes. *Diab Vasc Dis Res* 2006 Dec;3(3):159-65.

Heness S, Keam SJ. Vildagliptin. *Drugs* 2006;66(15):1989-2001.

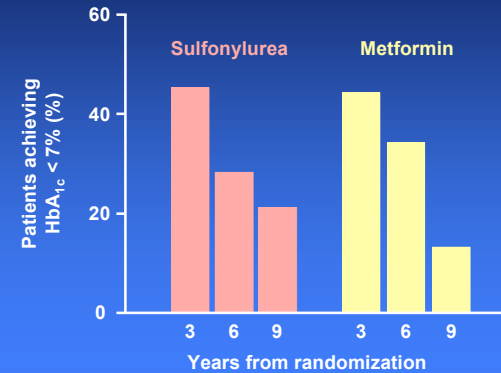
Miller S, St Onge EL. Sitagliptin: a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *Ann Pharmacother* 2006 Jul-Aug;40(7-8):1336-43.

Comparison of Anti-Hyperglycemic Agents

	Approx. drop in A _{1c} *	Effect on body weight	Hypo-glycemia	Contra-indications	Cost per month†
Metformin	1.0-1.5	Neutral or reduction	None	Renal, hepatic, cardiac failure	\$19
Insulin sensitizers	1.0-1.5	↑ 2-5 kg	None	Cardiac failure	\$100
Secretagogues	1.0-1.5	↑ 2-5 kg	10-30%		\$8-50
Insulin	1.0-3.0	↑ 2-5 kg	100%		\$30-60
Acarbose	0.5-0.8	Neutral	None		\$30

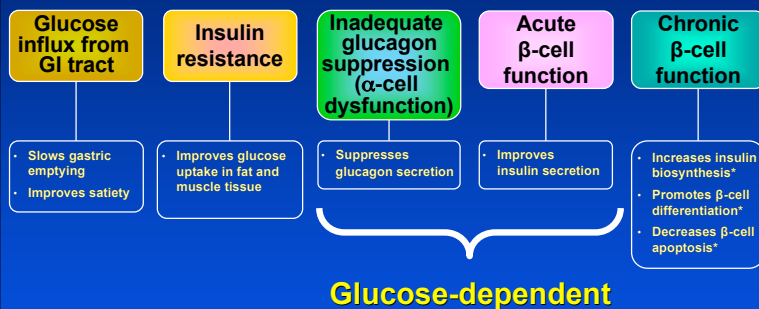
* when used as new therapy or added to existing therapy
 † estimated cost at maximum dose, Quebec formulary 2006

UKPDS: time-dependent reduction in percentage of patients achieving HbA_{1c} < 7%



UKPDS 49. JAMA 1999; 281:2005-2012.

GLP-1 Actions Address the Multiple Metabolic Defects in T2DM



GLP-1 = glucagon-like peptide-1

*Preclinical data

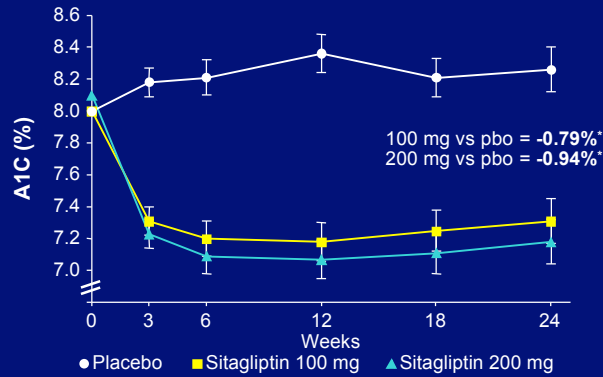
Adapted from Drucker DJ. *Diabetes Care* 2003;26:2929-2940.

Potential Strategies for Incretin-Based Therapies

- GLP-1 continuous infusion: impractical
- Agents that mimic GLP-1 action:
GLP-1 analogues
(e.g. exenatide, liraglutide)
- Agents that prevent incretin degradation:
DPP-IV inhibitors
(e.g. sitagliptin, vildagliptin, saxagliptin)

Drucker DJ et al. *Diabetes Care* 2003;26:2929-2940.
 Sinclair EM, Drucker DJ. *Physiology* 2005;20:352-365.
 Baggio LL, Drucker DJ. *Annu Rev Med* 2006;57:265-281.
 Baggio LL et al. *Diabetes* 2004;53:2492-2500.

Improvement in A1C over 24 weeks with Sitagliptin Monotherapy

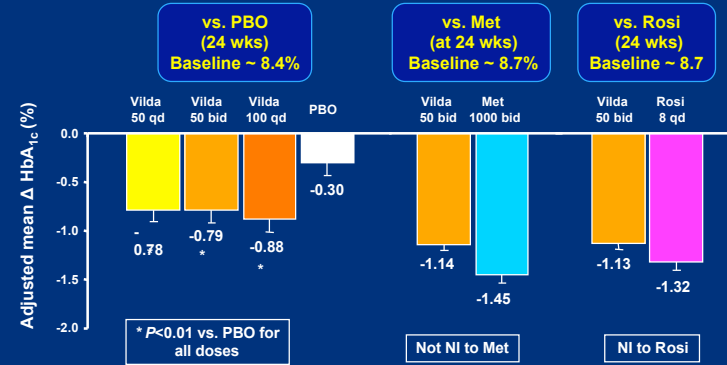


*Difference in LS mean change from baseline vs. placebo at Week 24; $p < 0.001$

Protocol 021.

Aschner P et al Diabetes Care 2006; 29(12):2632-2637

Vildagliptin Shows Consistent Lowering of HbA_{1c} in Monotherapy

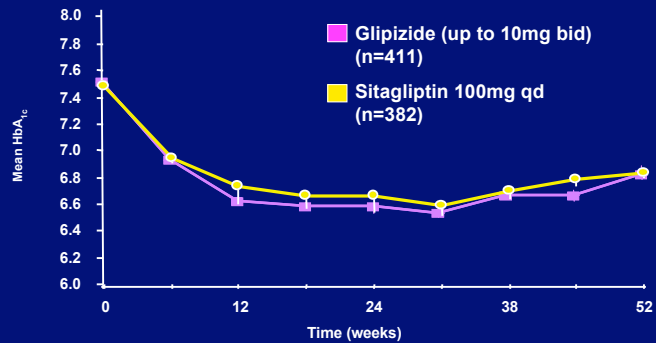


Primary efficacy ITT population
Diabetes 2006;55(S1):A557
Diabetes 2006;55(S1):A120
Data on file, Novartis

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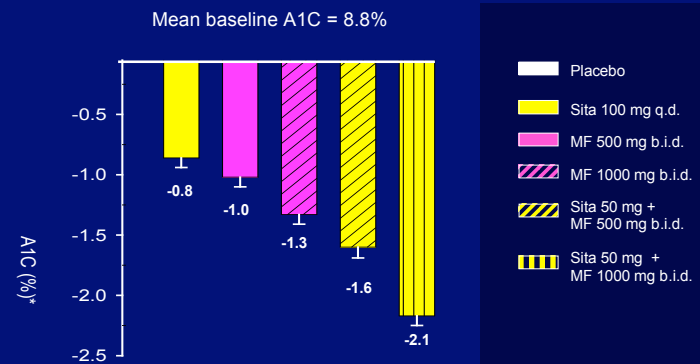
Sitagliptin shows Comparable Glycemic Efficacy to Glipizide when added to Metformin (52 weeks)

Achieved primary hypothesis of non-inferiority to Glipizide



Presented at ADA 2006

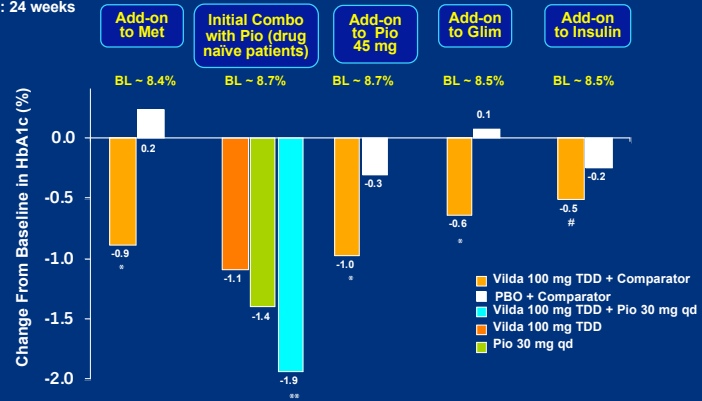
Improvements in A1C with Initial Co-administration of Sitagliptin and Metformin



*Placebo-subtracted LS mean change from baseline at Week 24

Vildagliptin: Clinically Relevant Efficacy

Duration: 24 weeks



Vilda=vildagliptin, Met=metformin, SU=sulfonylurea, Pio=Pioglitazone PBO=placebo; Primary efficacy ITT population
 * P<0.001, # P=0.022 (vs PBO), ** P<0.001 vs Pio 30 mg qd
 Dose regimen in 2355 is 100 mg qd, and 50 mg bid in 2303, 2304, 2305, 2311
 Diabetes 2006;55(S1):A121:A467. Nathwani A. Late-Breaking Trials 66th Scientific Sessions ADA 2006

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Summary of clinical trials with gliptins

Gliptin monotherapy:

- Substantially improved glycemic control A_{1c}, FPG, and PPG
 - Greater proportion achieved A_{1c} targets
 - Greater A_{1c} reductions with higher baseline A_{1c}
 - Improved B-cell function
- Demonstrated overall safety and tolerability similar to placebo
 - Slightly higher incidence of mild GI AEs
 - Low incidence of hypoglycemia, similar to placebo
 - No change in body weight relative to baseline