

Attaining Glycemic Targets Through Combination of Antihyperglycemic Agents

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INTRODUCTION

Despite the proven benefits of improved glycemic control, the Diabetes in Canada Evaluation (DICE) study (1) revealed that 50% of patients with type 2 diabetes in the primary care setting do not achieve the recommended A1C target of $\leq 7.0\%$. This was confirmed by another recent Canadian study (2).

In order to achieve adequate and timely glycemic control, combinations of antihyperglycemic agents are frequently needed. Combinations of different agents target different pathogenic factors, thereby achieving therapeutic goals in a more timely fashion, while reducing medication side effects because of the use of submaximal doses of drugs. Data from several studies show that combinations of 2 or more antihyperglycemic agents result in better glycemic control compared with either placebo or up-titration of a single agent (3,4). This article reviews pharmacotherapy recommendations, each class of agents and considerations regarding combination therapy in patients with type 2 diabetes.

PHARMACOTHERAPY RECOMMENDATIONS

The Canadian Diabetes Association 2008 clinical practice guidelines emphasize the importance of attaining and maintaining glycemic targets as early as possible after diagnosis (within 6 to 12 months). Lifestyle interventions are initially employed in patients presenting with an A1C level $< 9.0\%$. If glycemic targets are not met within 2 to 3 months, metformin monotherapy is recommended. If initial A1C is $\geq 9.0\%$, pharmacotherapy is initiated immediately, without waiting for effect from lifestyle intervention. Consideration should be given to adding an agent from another class to metformin (Figure 1 and Table 1) (5).

Metformin is recommended as first-line therapy in clinical practice guidelines around the world, based on its proven glycemic-lowering potency (A1C reduction of $\geq 1.0\%$), durability of glycemic control, and safety profile. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin was the only agent shown to decrease diabetes-related end-

points and myocardial infarction in overweight patients (6). Metformin works by decreasing hepatic glucose production, and also has an insulin-sensitizing action. Used as monotherapy, metformin is not associated with hypoglycemia and is weight neutral. It promotes less weight gain when combined with other antihyperglycemic agents such as insulin secretagogues and insulin (7). The drug is contraindicated in the presence of advanced kidney and liver disease, and in patients with congestive heart failure who also suffer from chronic kidney disease (CKD). Side effects are mainly gastrointestinal, and, rarely, vitamin B₁₂ malabsorption (8) and lactic acidosis (9).

Choosing a second agent

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and effective glucose-lowering effect and fewer side effects, compared with monotherapy at maximal doses. Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain blood glucose (BG) targets. In the UKPDS, the need for combination therapy to attain treatment targets was observed in 50% of subjects at 3 years into the study; this increased to 75% at 9 years (10).

The Canadian Diabetes Association 2008 clinical practice guidelines do not specify a hierarchy of second-line medications. Rather, all available medications are presented with a description of their BG-lowering efficacy, risk of hypoglycemia, and class-related pros and cons (Table 1) (5). It is therefore the practitioner's responsibility to tailor a therapeutic regimen to the individual patient after a thorough assessment of the above factors.

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Making an informed decision about which class of agent to use

Basic knowledge of the pathophysiology of type 2 diabetes and the mode of action of each antihyperglycemic agent is mandatory. The pathogenesis of type 2 diabetes includes 3 main abnormalities found in most patients: 1) insulin resistance, 2) beta cell dysfunction, and 3) increased hepatic glucose production.

Incretin agents

The discovery of reduced activity of the gastrointestinal hormone glucagon-like peptide-1 (GLP-1) in patients with type 2 diabetes has led to the addition of incretin agents to the arsenal of antihyperglycemic medications. (For a review on these agents, please see the Winter 2007 issue of *Canadian Diabetes*). In patients with type 2 diabetes, the incretin effect is reduced. Insulin secretion in response to hyperglycemia is suboptimal and glucagon levels are elevated and, secondary to decreasing GLP-1 effect, are not suppressed when BG levels rise. However, because of the very short circulating half-life of GLP-1, its use as a native hormone in the treatment of type 2 diabetes would necessitate administration via continuous intravenous infusion to attain therapeutic action. This would clearly be expensive and impractical.

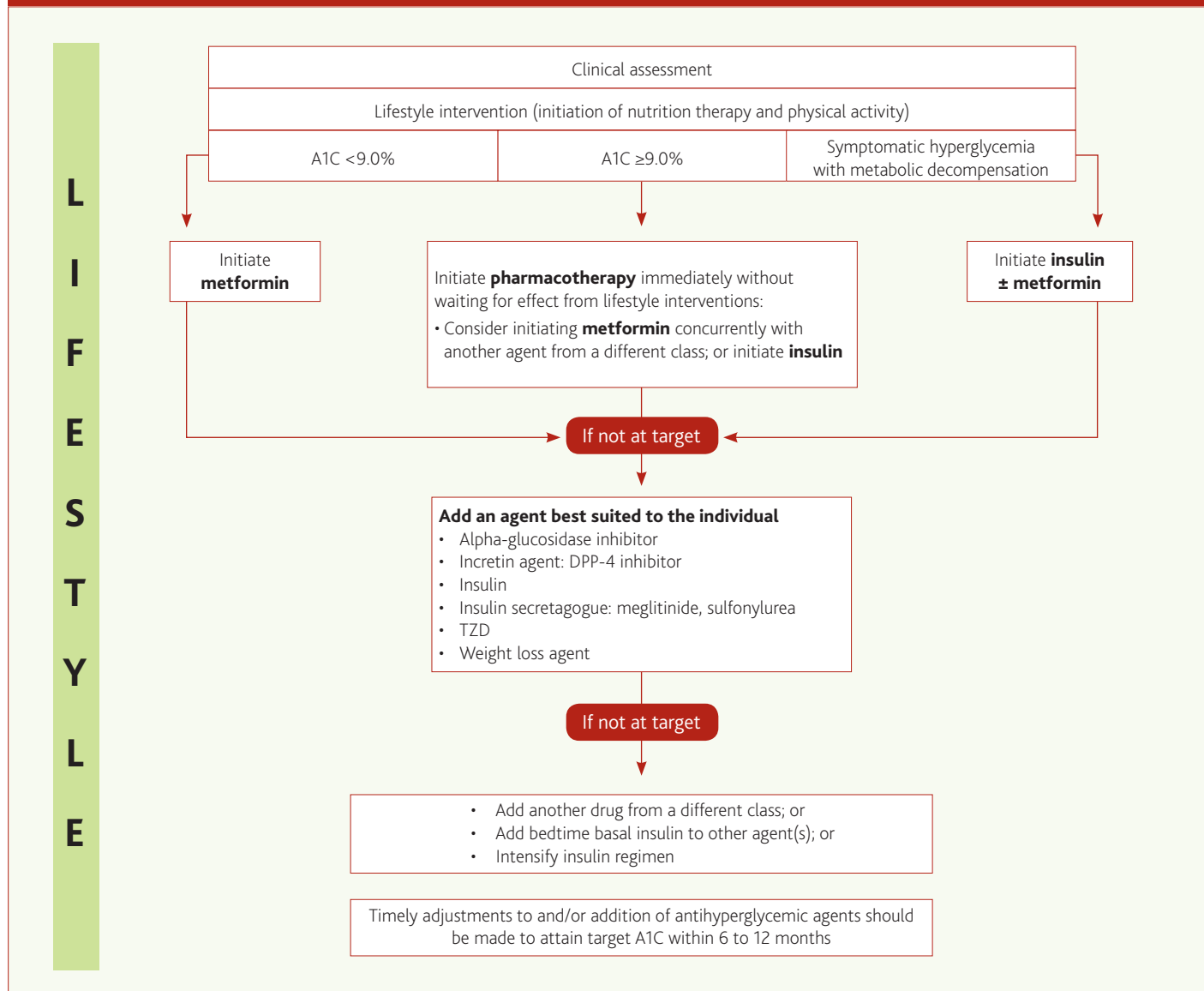
Incretin preparations in clinical practice

GLP-1 receptor agonists: The following 2 long-acting GLP-1 analogues, while not available in Canada, have been in clinical use in other parts of the world: 1) Exenatide was initially isolated from salivary gland venom of the Gila monster. It is a potent agonist of the GLP-1 receptor, and is resistant to inactivation by DPP-4. The structure of exenatide carries 50% homology with human GLP-1 (11-13); 2) Liraglutide is a modified GLP-1 molecule to which a palmitoyl fatty acid side chain has been added. This modifies its pharmacokinetics by allowing reversible albumin binding, slowing its absorption and its degradation by DPP-4 (14,15).

In clinical use, both preparations are injected subcutaneously: exenatide twice daily and liraglutide once daily. Both are associated with clinically significant reduction in A1C (liraglutide slightly more potent) and postprandial BG, as well as weight loss and decreased appetite. The most common side effects are nausea and vomiting.

DPP-4 inhibitors: DPP-4 inhibitors are oral medications that inhibit breakdown of GLP-1, thereby increasing its circulating blood levels. Sitagliptin has been in clinical use for 2 years, while saxagliptin was recently launched in Canada. In monotherapy

Figure 1: Achieving glycemic control in patients with type 2 diabetes (5)



studies, DPP-4 inhibitors show A1C reductions ranging from 0.6 to >1.0%, with greater reductions in postprandial vs. preprandial BG levels. These agents are weight neutral and well tolerated (16-17). Used in combination with metformin, either as initial combination (18) or add-on to ongoing metformin therapy (19,20), A1C levels were reduced by ≥1.8% in drug-naïve patients and by about 0.7% when added to ongoing metformin therapy. In combination with thiazolidinediones (TZDs) (pioglitazone and rosiglitazone), saxagliptin and sitagliptin showed significant A1C reductions of 0.7 to 1.0% (21,22). DPP-4 inhibitors are contraindicated in the presence of CKD (estimated glomerular filtration rate [eGFR] <50 mL/min), during pregnancy, in children and

adolescents, and in type 1 diabetes.

These agents are usually well tolerated, with a side effect profile equivalent to placebo. Nasopharyngitis and bronchitis have been noticed in few patients (23). There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions such as Stevens-Johnson syndrome (erythema multiforme major). It is not possible to reliably estimate the frequency or establish a causal relationship between these reactions and drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reactions occurring after the first dose (24).

Table 1: Options for adding another agent to metformin (alphabetical order) (5)

Class	A1C	Hypoglycemia	Other advantages	Other disadvantages
Alpha-glucosidase inhibitor	↓	Rare	Improved postprandial control Weight neutral	GI side effects
Incretin agent: DPP-4 inhibitor	↓to↓↓	Rare	Improved postprandial control Weight neutral	New agent (unknown long-term safety)
Insulin	↓↓↓	Yes	No dose ceiling Many types, flexible regimens	Weight gain
Insulin secretagogue: Meglitinide Sulfonylurea	↓to↓↓ ↓↓	Yes* Yes	Improved postprandial control Newer sulfonylureas (gliclazide, glimepiride) are associated with less hypoglycemia than glyburide	Requires TID to QID dosing Weight gain
TZD	↓↓	Rare	Durable monotherapy	Requires 12 weeks for maximal effect Weight gain Edema, rare CHF, rare fractures in females
Weight loss agent	↓	None	Weight loss	GI side effects (orlistat) Increased heart rate/BP (sibutramine)

↓ = <1.0% decrease in A1C ↓↓ = 1.0–2.0% decrease in A1C ↓↓↓ = >2.0% decrease in A1C

* Less hypoglycemia in the context of missed meals

Recently, the US Food and Drug Administration published reports of cases of acute pancreatitis in patients using sitagliptin. A causal relationship between the drug and pancreatitis has not been confirmed. In general, pancreatitis occurs more commonly in patients with type 2 diabetes, compared with the general population. Saxagliptin has been rarely associated with decreased lymphocyte count with no clinical sequelae (23).

Used as monotherapy, metformin is not associated with hypoglycemia and is weight neutral.

Other classes of antihyperglycemic agents

Alpha-glucosidase inhibitors (AGIs): Alpha-glucosidases are intestinal brush border enzymes that break down complex carbohydrates into monosaccharides, their absorbable form. AGIs delay this action, thereby decreasing postprandial BG levels. Acarbose, an AGI often used in combination with other antihyperglycemic agents, is associated with an A1C reduction of 0.5 to 0.8%. It is

weight neutral and does not cause hypoglycemia. Side effects are mainly gastrointestinal. The drug is contraindicated in chronic renal failure and with inflammatory bowel disease.

Insulin secretagogues:

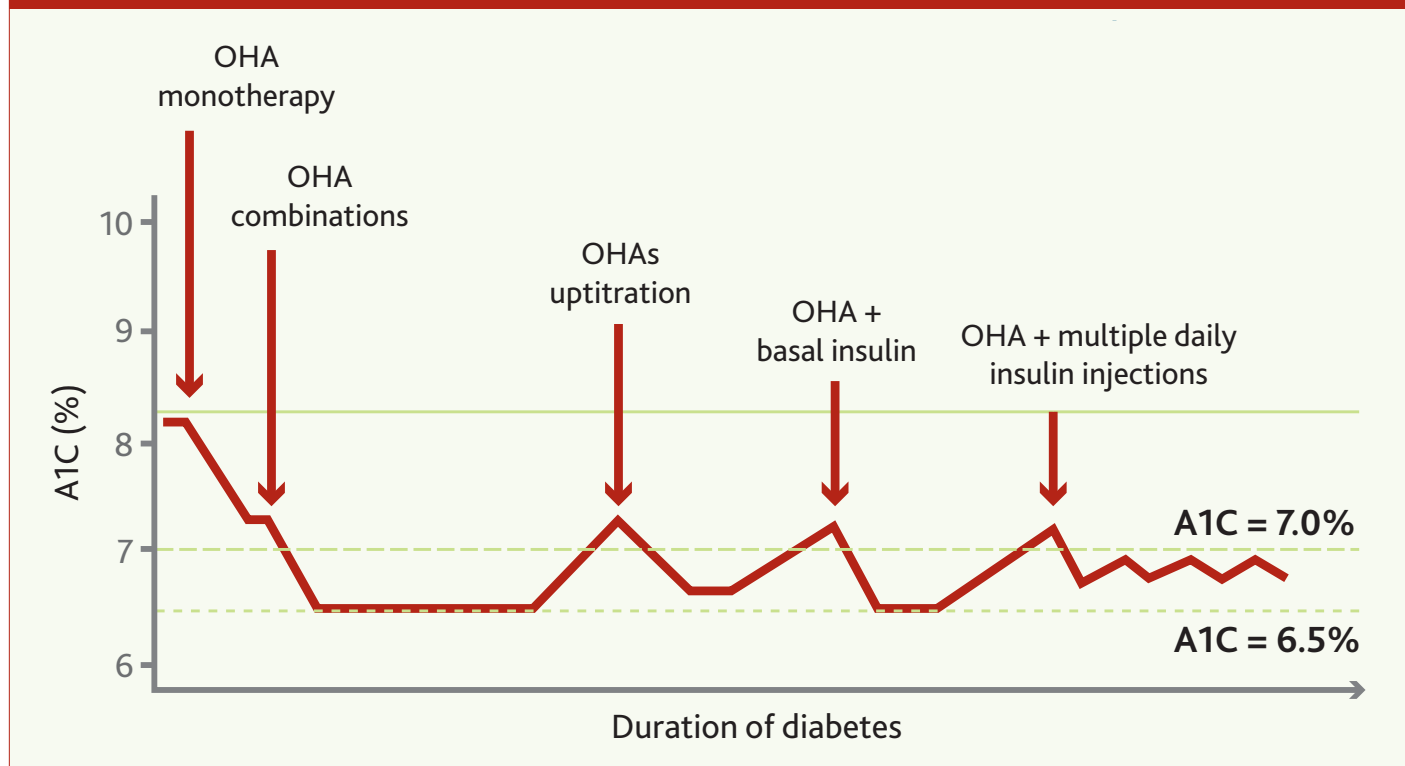
These agents stimulate insulin release from pancreatic beta cells. There are 2 classes: Sulfonylureas (including gliclazide, glimeperide, glyburide and others) and meglitinides (including repaglinide). Sulfonylurea drugs induce insulin release by binding to a specific

receptor on the beta cell membrane resulting in opening of calcium channels, which allows influx of calcium ions and, in turn, the release of insulin from the beta cells. The mechanism of action of repaglinide is similar to that of sulfonylureas.

The use of insulin secretagogues results in rapid BG lowering, with expected A1C reduction of ≥1.0%. Repaglinide, a rapid-acting secretagogue with a short duration of action, is associated with similar A1C reduction, preferential postprandial BG lowering and less hypoglycemia in the context of missed meals, compared with glyburide. Gliclazide is also associated with less hypoglycemia in the elderly. The main side effects of the class are hypoglycemia and weight gain.

Thiazolidinediones: TZDs are insulin sensitizers that reduce insulin resistance. They result in A1C reduction of about 1.0%, and do not cause hypoglycemia. They have a slow onset of action, but a more durable effect on A1C compared with glyburide or metformin. Favourable effects on vascular, inflammatory and adipokine parameters are seen with this class, but to date there are no convincing data showing decreased rates of diabetes complications. Both pioglitazone and rosiglitazone are used either as monotherapy, or in combination with metformin, insulin secretagogues or DPP-4 inhibitors. Side effects include weight gain (although waist-to-hip ratio is not increased), edema and/or heart failure, especially when combined with insulin in patients with underlying ventricular dysfunction. Both pioglitazone and rosiglitazone increase the risk of distal fractures in women (3,25).

Figure 2: Aggressive management of glycemic control: Treatment to target (26)



OHA = oral antihyperglycemic agent

Insulin: Insulin treatment can control diabetes in almost all patients with type 2 diabetes. It acts by reducing hepatic glucose production and enhancing insulin-mediated glucose uptake. There are many insulin formulations available, allowing a wide choice: basal insulins (detemir, glargine and NPH), bolus/prandial insulins (aspart, glulisine, lispro and regular insulins) and premixed insulins. Insulin use potentially provides the greatest A1C reduction of all the antihyperglycemic agents, as there is no maximum dose. When initiating insulin in patients with type 2 diabetes, consideration should be given to adding bedtime basal insulin to daytime oral agents. If the above approach fails to attain glycemic targets, more intensive insulin therapy regimens are recommended. The main side effects of insulin therapy are hypoglycemia and weight gain. Hypoglycemia occurs less frequently when basal or prandial insulin analogues are used, rather than human insulin.

Intensification of glycemic control in patients with type 2 diabetes

Figure 2 depicts a proactive approach to glycemic control—the use of early combination therapy (including insulin) to attain and

maintain target glycemic levels (26). This strategy should result in maintenance of glycemia at target levels and the prevention of vascular complications.

REFERENCES

1. Harris SB, Ekoé J-M, Zdanowicz Y, Webster-Bogaert S. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). *Diabetes Res Clin Pract.* 2005;70(1):90-97.
2. Braga M, Casanova A, Dawson K, et al. Diabetes management in Canada: evidence of an ongoing care gap [meeting abstract 1189-P]. American Diabetes Association 68th Scientific Sessions; June 6-10, 2008; San Francisco, California. Available at: http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=70078. Accessed January 6, 2010.
3. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
4. Garber AJ, Donovan DS Jr, Dandona P, Bruce S, Park JS. Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. *J Clin Endocrinol Metab.* 2003;88(8):3598-3604.

5. Harper W, Hanna A, Woo V, et al. Pharmacologic management of type 2 diabetes. In: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2008;32(suppl 1):S53-S61.
6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-865.
7. Aviles Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1999;131(3):182-188.
8. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med*. 2003;163(21):2594-2602.
9. Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS. Malabsorption of vitamin B₁₂ and intrinsic factor secretion during biguanide therapy. *Diabetologia*. 1983;24(1):16-18.
10. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA*. 1999;281(21):2005-2012.
11. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. *J Biol Chem*. 1992;267(11):7402-7405.
12. Chen YE, Drucker DJ. Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. *J Biol Chem*. 1997;272(7):4108-4115.
13. Edwards CM, Stanley SA, Davis R, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol*. 2001;281(1):E155-E161.
14. Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem*. 2000;43(9):1664-1669.
15. Degen KB, Juhl CB, Sturis J, et al. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes*. 2004;53(5):1187-1194.
16. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2006(12);29:2632-2637.
17. Rosenstock J, Aguilar-Salinas C, Klein E, et al.; CV181-011 Study Investigators. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. *Curr Med Res Opin*. 2009;25(10):2401-2411.
18. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R; CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab*. 2009;11(6):611-622.
19. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006;29(12):2638-2643.
20. DeFronzo RA, Hissa MN, Garber AJ, et al.; for the Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care*. 2009;32(9):1649-1655.
21. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2006;28(10):1556-1568.
22. Hollander P, Li J, Allen E, Chen R; CV181-013 Investigators. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. *J Clin Endocrinol Metab*. 2009;94(12):4810-4819.
23. Drug Monograph: Saxagliptin (Brand name: ONGLYZA). Health Canada website: Drugs and Health Products. Available at: <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>. Accessed January 6, 2010.
24. Drug Monograph: Sitagliptin (Brand name: JANUVIA). Health Canada website: Drugs and Health Products. Available at: <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>. Accessed January 6, 2010.
25. Meymeh RH, Wollerton E. Diabetes drug pioglitazone (Actos): risk of fracture. *CMAJ*. 2007;177(7):723-724.
26. Del Prato S, Felton AM, Munro N, Nesto R, Zimmet P, Zinman B; Global Partnership for Effective Diabetes Management. Improving glucose management: ten steps to get more patients with type 2 diabetes to glycaemic goal. *Int J Clin Pract*. 2005;59(11):1345-1355.