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Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- If glycemic targets are not achieved within 2 to 3 months of lifestyle management, antihyperglycemic pharmacotherapy should be initiated.
- Timely adjustments to, and/or additions of, antihyperglycemic agents should be made to attain target glycated hemoglobin (A1C) within 3 to 6 months.
- In patients with marked hyperglycemia (A1C ≥8.5%), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, 1 of which may be insulin.
- Unless contraindicated, metformin should be the initial agent of choice, with additional antihyperglycemic agents selected on the basis of clinically relevant issues, such as contraindication to drug, glucose lowering effectiveness, risk of hypoglycemia and effect on body weight.

Introduction

As people with type 2 diabetes form a heterogeneous group, treatment regimens and therapeutic targets should be individualized. As type 2 diabetes is characterized by insulin resistance and ongoing decline in beta cell function, glucose levels likely will worsen over time (1), and treatment must be dynamic as therapeutic requirements increase with longer duration of disease. The number of available antihyperglycemic agents is ever expanding, requiring the clinician to consider many of the following factors when choosing medications: degree of hyperglycemia, risk of hypoglycemia, medication effectiveness at reducing diabetes complications (microvascular and/or macrovascular), medication effects on body weight, medication side effects, concomitant medical conditions, ability to adhere to regimen and patient preferences. Lifestyle modification, including nutritional therapy and physical activity, should continue to be emphasized while pharmacotherapy is being used as many agent classes can cause weight gain as a side effect.

Treatment Regimens

The diagnosis of type 2 diabetes is often delayed, and 20% to 50% of people with type 2 diabetes present with microvascular and/or macrovascular complications at the time of diagnosis (2,3). When lifestyle interventions fail to control blood glucose (BG) levels adequately, pharmacological treatment becomes necessary.

In the face of more severe hyperglycemia (i.e. glycated hemoglobin [A1C] ≥8.5%), combinations of agents are usually required. The lag period before adding other antihyperglycemic agent(s) should be kept to a minimum, taking into account the characteristics of the different medications. With timely adjustments to and/or additions of antihyperglycemic agents, the target A1C level should be attainable within 3 to 6 months.

In general, A1C will decrease by about 0.5% to 1.5% with monotherapy, depending on the agent used and the baseline A1C level, with the maximum effect of oral antihyperglycemic agent monotherapy seen at 3 to 6 months (4,5). By and large, the higher the baseline A1C, the greater the A1C reduction seen for each given agent. In general, as A1C levels decrease toward target levels (<7.3%), postprandial BG control assumes greater importance for further A1C reduction (6). Several classes of antihyperglycemic agents have greater efficacy at lowering postprandial BG levels (7–20), although adopting an approach of specifically targeting postprandial BG control has not been shown to be effective at reducing macrovascular diabetes complications (21).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (22–25). Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain target BG levels (1). When combining antihyperglycemic agents with or without insulin, classes of agents that have different mechanisms of action should be used. Simultaneous use of agents within the same class and/or from different classes but with similar mechanisms of action (e.g. sulfonylureas and meglitinides or dipeptidyl peptidase [DPP]-4 inhibitors and glucagon-like peptide [GLP]-1 agonists) is currently untested, may be less effective at improving glycemia and is not recommended at this time. Table 1 identifies the mechanism of action for all classes of antihyperglycemic agents to aid the reader in avoiding the selection of agents with overlapping mechanisms.

There is debate over which antihyperglycemic agent (including insulin) should be used initially and which agents should be added subsequently. There is also debate over which agents within a given

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Table 1
Antihyperglycemic agents for use in type 2 diabetes

Class* and mechanism of action	Drug (brand name)	Expected† decrease in A1C	Relative† A1C lowering	Hypoglycemia	Other therapeutic considerations
Alpha-glucosidase inhibitor: inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase	Acarbose (Glucobay) (7,81,82)	0.6%	↓	Negligible risk as monotherapy	• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥8.5%) • Weight neutral as monotherapy • GI side effects
Combined formulations	Avandamet (metformin + rosiglitazone)	0.8%	↓↓	Negligible risk as monotherapy	• See metformin, TZDs, DPP-4 inhibitors and sulfonylureas
	Janumet (metformin + sitagliptin)	0.7%	↓↓		
	Jentadueto (metformin + linagliptin)				
	Avandaryl (glimepiride + rosiglitazone)	1.6%	↓↓↓	Moderate risk	
DPP-4 inhibitor: amplifies incretin pathway activation by inhibition of enzymatic breakdown of endogenous GLP-1 and GIP (45)	Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Trajenta)	0.7%	↓↓	Negligible risk as monotherapy	• Weight neutral • Improved postprandial control • Rare cases of pancreatitis
GLP-1 receptor agonist: activates incretin pathway by utilizing DPP-4 resistant analogue to GLP-1 (45–48)	Exenatide (Byetta) Liraglutide (Victoza)	1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	• Improved postprandial control • Significant weight loss • Nausea and vomiting • Administration parenteral • Rare cases of pancreatitis • Parafollicular cell hyperplasia • Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
Insulin: activates insulin receptors to regulate metabolism of carbohydrate, fat and protein (3,10,11,50,53,83–85)	**Bolus (prandial) insulins** *Rapid-acting analogues* Aspart (NovoRapid) Glulisine (Apidra) Lispro (Humalog) *Short-acting* Regular (Humulin-R, Novolin ge Toronto) **Basal insulins** *Intermediate-acting* NPH (Humulin-N, Novolin ge NPH) *Long-acting basal analogues* Detemir (Levemir) Glargine (Lantus) **Premixed insulins** Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix50)	0.9%—1.1%	↓↓↓	Significant risk (hypoglycemia risk highest with regular and NPH insulin)	• Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) • Allows for regimen flexibility • When initiating insulin, consider adding bedtime long-acting basal analogue or intermediate-acting NPH to daytime oral antihyperglycemic agents (although other regimens can be used) • Basal-bolus regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin

Insulin secretagogue: activates sulfonylurea receptor on beta cell to stimulate endogenous insulin secretion	**Sulfonylureas**	0.8%	↓↓		• Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Postprandial glycemia is especially reduced by meglitinides • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (94) and glimepiride is associated with less hypoglycemia than glyburide (90)
	Gliclazide (Diamicron, Diamicron MR, generic) (86,87)			Minimal/moderate risk	
	Glimepiride (Amaryl) (88–90)			Moderate risk	
	Glyburide (Diabeta, Euglucon, generic) (3)			Significant risk	
	(*Note:* Chlorpropamide and tolbutamide are still available in Canada but rarely used)				
	Meglitinides	0.7%			
	Nateglinide (Starlix) (91)		↓	Minimal/moderate risk	• Nateglinide and repaglinide are associated with less hypoglycemia than sulfonylureas due to their shorter duration of action allowing medication to be held when forgoing a meal
	Repaglinide (GlucoNorm) (92,93)		↓↓	Minimal/moderate risk	
Metformin: enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase	Glucophage, Glumetza, generic (52,95)	1.0%—1.5%	↓↓	Negligible risk as monotherapy	• Improved cardiovascular outcomes in overweight subjects • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR <60 mL/min • Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycemic agents, including insulin • B12 deficiency (96) • GI side effects
Thiazolidinedione (TZD): enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-gamma receptors (28–30,33,35,97–104)	Pioglitazone (Actos) Rosiglitazone (Avandia)	0.8%	↓↓	Negligible risk as monotherapy	• Longer duration of glycemic control with monotherapy compared to metformin or glyburide • Mild BP lowering • Between 6 and 12 weeks required to achieve full glycemic effect • Weight gain • May induce edema and/or congestive heart failure • Contraindicated in patients with known clinical heart failure or evidence of left ventricular dysfunction on echocardiogram or other heart imaging • Higher rates of heart failure when combined with insulin‡ • Rare occurrence of macular edema • Higher occurrence of fractures (29,30,33) • Possibility of increased risk of myocardial infarction with rosiglitazone (31,108) • Rare risk bladder cancer with pioglitazone (109)
Weight loss agent: inhibits lipase	Orlistat (Xenical) (105–107,110)	0.5%	↓	None	• Promote weight loss • Orlistat can cause diarrhea and other GI side effects

A1C, glycated hemoglobin; *BG*, blood glucose; *BP*, blood pressure; *CrCl*, creatinine clearance; *DPP-4*, dipeptidyl peptidase 4; *eGFR*, estimated glomerular filtration rate; *GI*, gastrointestinal; *GIP*, gastric inhibitory peptide; *GLP-1*, glucagon-like peptide 1; *AMP*, adenosine monophosphate.

Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

* Listed in alphabetical order.

† A1C percentage/relative reduction expected when agent from this class is added to metformin therapy (37,105,111) with exception of metformin where A1C percentage/relative reduction reflects expected monotherapy efficacy.

‡ Combining insulin with a TZD is not an approved indication in Canada.

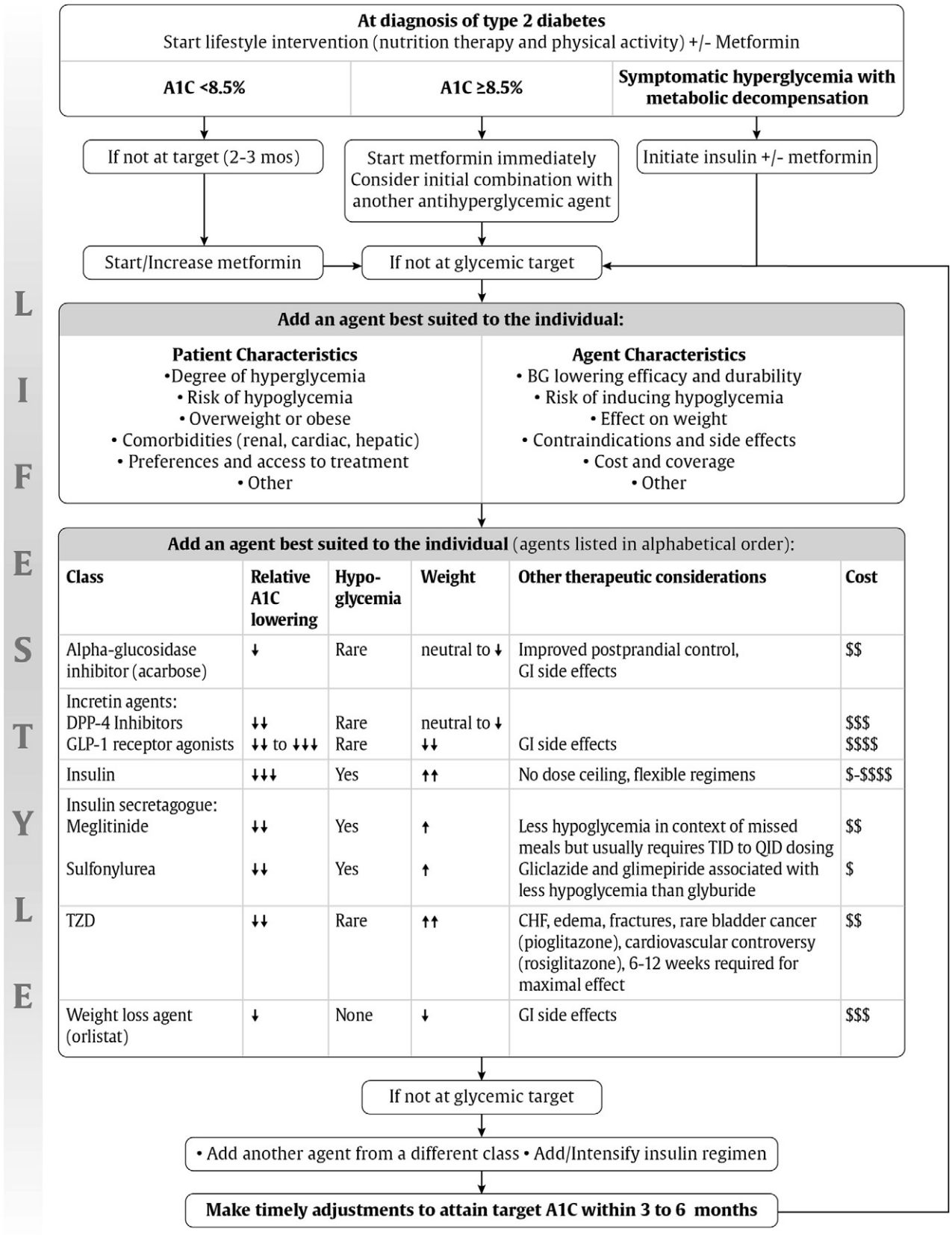

Figure 1. Management of hyperglycemia in type 2 diabetes.
Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information.
A1C, glycated hemoglobin; *CHF*, congestive heart failure; *DPP-4*, dipeptidyl peptidase 4; *GI*, gastrointestinal; *GLP-1*, glucagon-like peptide 1; *TZD*, thiazolidinedione.

class might be preferred in specific situations. Symptomatic patients with high BG and A1C levels require agents that lower BG levels substantially and quickly (e.g. insulin). However, the issue of how to reach glycemic targets may be less important than the need to achieve that target. Improved BG and A1C levels are associated with better outcomes, even if recommended glycemic targets cannot be reached (3). Each of the agents listed in Table 1 and Figure 1 has advantages and disadvantages to consider. Figure 2 illustrates the basis on which agent selection is influenced by renal function as dictated by product monograph precautions.

The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering BG, its relatively mild side effect profile, its long-term safety track record, its negligible risk of hypoglycemia and its lack of causing weight gain. The demonstrated cardiovascular benefit in overweight patients is also cited as a reason to select metformin as first-line treatment (26), but more recent evidence has been equivocal on this matter (27). While monotherapy with the thiazolidinedione (TZD) rosiglitazone produces more long-lasting glycemic control compared to metformin or glyburide therapy (28), the edema, weight gain, risk of congestive heart failure (CHF), increased risk of fractures (29,30) and inconsistent data regarding myocardial infarction (MI) risk (31–33) significantly limit the clinical utility of this drug class. Although meta-analyses of smaller, underpowered studies suggested possible risk of MI with rosiglitazone (31,32), this has not been demonstrated in a larger randomized clinical trial (33,34). Conversely, the evidence for pioglitazone suggests a possible reduced risk of cardiovascular events, although heart failure and increased fractures are still concerning side effects (35,36).

Table 1 and Figure 1 provide information to aid decision making. In deciding upon which agent to add after metformin, there must be consideration of multiple factors. First of all, the agent's effectiveness at BG lowering must be considered in terms of both the degree of baseline hyperglycemia needing correction and any heightened concerns regarding hypoglycemia (e.g. elderly patients or those with renal or hepatic dysfunction). The relative BG and A1C lowering of the various antihyperglycemic agent classes when added to metformin is shown in both Table 1 and Figure 1 and is based on network meta-analysis allowing the comparison between classes that have not yet had direct head-to-head comparison in a randomized clinical trial (37). Ideally, consideration would be made towards the selection of agents with evidence demonstrating ability to not only lower glucose levels, but also reduce the risk of diabetic microvascular and/or macrovascular complications. Unfortunately, the majority of evidence remains equivocal in this regard as most clinical trials compared varying levels of glycemic lowering as opposed to direct comparison between agents used to achieve such glycemic control (38–40). More recent studies looking at the benefits seen with select agents are of such short duration that their results are still preliminary with respect to proving clinical event reduction (41–44) and confirmation awaits the results of more definitive long-term studies.

Multiple other agent-specific advantages and disadvantages should be weighed as treatment is individualized to best suit the patient's needs and preferences. In particular, attention should be paid to the agent's effects on body weight as this is a clinically relevant issue for many people with type 2 diabetes, and some agents cause significant weight gain while others can help to promote significant weight loss. GLP-1 receptor agonists are particularly effective at promoting concomitant glycemic control and weight reduction (45–48), but long-term efficacy and safety data are currently lacking for this class.

A combination of oral antihyperglycemic agents and insulin often effectively controls glucose levels. When insulin is added to oral antihyperglycemic agent(s), a single injection of intermediate-acting (NPH) (49) or a long-acting insulin analogue

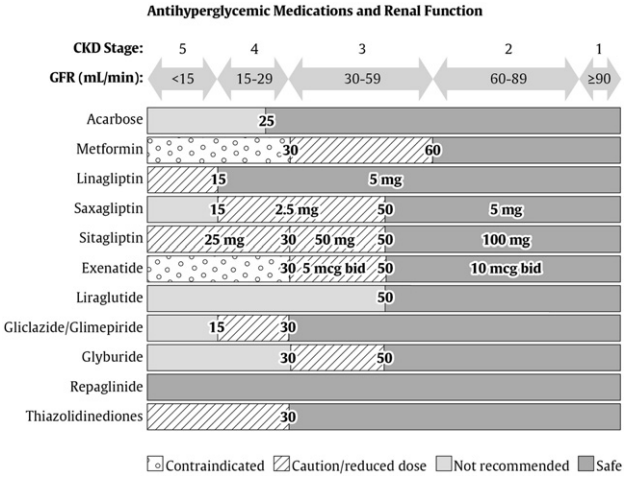

Figure 2. Antihyperglycemic medications and renal function. Based on product monograph precautions. *CKD*, chronic kidney disease; *GFR*, glomerular filtration rate; *TZD*, thiazolidinedione. Designed by and used with the permission of Jean-François Yale MD CSPQ FRCPC.

(insulin glargine or insulin detemir) (50) may be added. This approach may result in better glycemic control with a smaller dose of insulin (51), and may induce less weight gain and less hypoglycemia than that seen when oral agents are stopped and insulin is used alone (52). The addition of bedtime insulin to metformin therapy leads to less weight gain than insulin plus a sulfonylurea or twice-daily NPH insulin (53). While combining insulin with a TZD is not an approved indication in Canada, the addition of such agents to insulin in carefully selected patients improves glycemic control and reduces insulin requirements (54). Such combinations can result in increased weight, fluid retention and, in few patients, CHF. DPP-4 inhibitors and GLP-1 receptor agonists have been shown to be effective at further lowering glucose levels when combined with insulin therapy (55–58).

Insulin can be used at diagnosis in individuals with marked hyperglycemia and can also be used temporarily during illness, pregnancy, stress or for a medical procedure or surgery. There is no evidence that exogenous insulin accelerates the risk of macrovascular complications of diabetes, and its appropriate use should be encouraged (59,60). The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial studied the use of basal insulin titrated to a fasting glucose of $\leq$5.3 mmol/L in people at high cardiovascular risk with prediabetes or early type 2 diabetes over 6 years. There was a neutral effect on cardiovascular outcomes and cancer, a reduction in new-onset diabetes and a slight increase in hypoglycemia and weight. Indeed, use of insulin earlier in the course of type 2 diabetes can be an effective strategy over oral antihyperglycemic agents (60,61). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control while trying to avoid excessive hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The number of insulin injections (1 to 4 per day) and the timing of injections may vary, depending on each individual's situation (62). The reduction in A1C achieved with insulin therapy depends on the dose and number of injections per day (63). Insulin regimens based on basal or bolus insulin appear to be equally effective (21,64) and superior with respect to glycemic lowering compared to biphasic insulin-based regimens (63).

As type 2 diabetes progresses, insulin requirements will likely increase, additional doses of basal insulin (intermediate-acting or

long-acting analogues) may need to be added and bolus insulin (short-acting or rapid-acting analogues) may also be required. Generally, once bolus insulin is introduced into a treatment regimen, either as a separate meal time bolus or as part of a premixed containing regimen, insulin secretagogues, such as sulfonylureas and meglitinides, are usually discontinued. Concomitant metformin therapy, unless contraindicated, should be continued with regimens containing bolus insulin, including intensive basal-bolus regimen, to allow for improved glycemic control with less risk of weight gain and hypoglycemia (65).

Although not commonly practiced, the use of intensive insulin therapy (basal-bolus regimen or continuous subcutaneous insulin infusion pump), for a transient period of approximately 2 to 3 weeks at the time of diagnosis or early in the disease course, has been shown to induce diabetes remission, subsequently allowing adequate glycemic control with lifestyle management alone (66). This normoglycemic state is often transient, however, and such interventions have been tested only in patients early in the course of disease where the degree of residual beta cell function is relatively preserved (67).

Epidemiological evidence suggesting a possible link between insulin glargine and cancer has not been substantiated in review of clinical trial data for either glargine or detemir (60,68,69).

RECOMMENDATIONS

1. In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agent therapy should be initiated [Grade A, Level 1A (3)]. Metformin may be used at the time of diagnosis, in conjunction with lifestyle management (Grade D, Consensus).
   i. If A1C $\geq$8.5%, antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, one of which may be insulin (Grade D, Consensus).
   ii. Individuals with symptomatic hyperglycemia and metabolic decompensation should receive an initial antihyperglycemic regimen containing insulin [Grade D, Consensus].

2. Metformin should be the initial drug used [Grade A, Level 1A (26,80) for overweight patients; Grade D, Consensus for nonoverweight patients].

3. Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, Consensus], and these adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 3 to 6 months [Grade D, Consensus].

4. Choice of pharmacological treatment agents should be individualized, taking into consideration [Grade D, Consensus]:
   - Patient characteristics:
     - Degree of hyperglycemia
     - Presence of comorbidities
     - Patient preference and ability to access treatments
   - Properties of the treatment:
     - Effectiveness and durability of lowering BG
     - Risk of hypoglycemia
     - Effectiveness in reducing diabetes complications
     - Effect on body weight
     - Side effects
     - Contraindications

5. When basal insulin is added to antihyperglycemic agents, long-acting analogues (detemir or glargine) may be used instead of intermediate-acting NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (19,78,79)].

6. When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be used instead of regular insulin to improve glycemic control [Grade B, Level 2 (20)] and to reduce the risk of hypoglycemia [Grade D, Consensus)].

7. All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counseled about the prevention, recognition and treatment of drug-induced hypoglycemia [Grade D, Consensus].

Hypoglycemia

Medication-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in up to approximately 20% of patients taking insulin secretagogues (70). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin secretagogues. Few large, randomized clinical trials have compared the rates of hypoglycemia between these agents.

In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of adults with type 2 diabetes who experienced a severe hypoglycemic episode per year was significantly higher in the intensive group than in the conventional group, particularly for patients using insulin therapy (3). Although the risk of hypoglycemia was less than that seen in the patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT), each year approximately 3% of patients treated with insulin in the UKPDS experienced a severe hypoglycemic episode, and 40% had a hypoglycemic episode of any severity (3). Protocols designed to achieve normoglycemia targets (A1C $\leq$6.5%) further increase the risk of severe hypoglycemia without providing any substantial reduction in the incidence of diabetes complications (71,72).

Lower rates of hypoglycemia have been observed in some studies of patients with type 2 diabetes treated with rapid-acting insulin analogues (insulin aspart, insulin lispro, insulin glulisine) compared to those treated with short-acting (regular) insulin (19,73,74). Use of long-acting basal insulin analogues (insulin detemir, insulin glargine) reduces the risk of nocturnal hypoglycemia compared to treatment with NPH insulin (19,50,75–79).

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
Pharmacotherapy in Type 1 Diabetes, p. S56
Hypoglycemia, p. S69
Weight Management in Diabetes, p. S82
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S184

Relevant Appendix

Appendix 3: Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

References

1. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005–12.
2. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiological study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102:527–32.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.

4. Bloomgarden ZT, Dodis R, Viscoli CM, et al. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care 2006;29:2137–9.
5. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care 2010;33:1859–64.
6. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003;26:881–5.
7. Chiasson J-L, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med 1994;121:928–35.
8. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006;29:2632–7.
9. Charbonnel B, Karasik A, Liu J, et al. 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;29:2638–43.
10. Weiss SR, Cheng SL, Kourides IA, et al, Inhaled Insulin Phase II Study Group. Inhaled insulin provides improved glycemic control in patients with type 2 diabetes mellitus inadequately controlled with oral agents: a randomized controlled trial. Arch Intern Med 2003;27:2277–82.
11. Dailey G, Rosenstock J, Moses RG, et al. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care 2004;27: 2363–8.
12. Roach P, Yue L, Arora V. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 Study Group. Diabetes Care 1999;22:1258–61.
13. Boehm BO, Home PD, Behrend C, et al. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. Diabet Med 2002;19:393–9.
14. Ahren B, Gomis R, Standl E, et al. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care 2004;27:2874–80.
15. Derosa G, Mugellini A, Ciccarelli L, et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. Clin Ther 2003;25:472–84.
16. Ristic S, Collober-Maugeais C, Pecher E, et al. Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with Type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone. Diabet Med 2006;23:757–62.
17. Ross SA, Zinman B, Campos RV, et al. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. Clin Invest Med 2001;24:292–8.
18. Rosenfalck AM, Thorsby P, Kjems L, et al. Improved postprandial glycaemic control with insulin aspart in type 2 diabetic patients treated with insulin. Acta Diabetol 2000;37:41–6.
19. Sumeet R, Singh SR, Ahmad F, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180: 385–97.
20. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. Diabetes Obes Metab 2009;11:53–9.
21. Raz I, Wilson PW, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009;32:381–6.
22. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab 2002;4:201–8.
23. Rosenstock J, Goldstein BJ, Vinik AI, et al. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. Sulphonylurea Titration (RESULT) study. Diabetes Obes Metab 2006;8:49–57.
24. Rosenstock J, Rood J, Cobitz A, et al. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. Diabetes Obes Metab 2006; 8:643–9.
25. Rosenstock J, Rood J, Cobitz A, et al. Initial treatment with rosiglitazone/ metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab 2006;8:650–60.
26. 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;352:854–65.
27. Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med 2012;9:e1001204.
28. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.
29. Meymeh RH, Wooltorton E. Diabetes drug pioglitazone (Actos): risk of fracture. CMAJ 2007;177:723–4.
30. Kahn SE, Zinman B, Lachin JM, et al, A Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial. Diabetes Care 2008; 31:845–51.
31. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
32. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med 2010; 170:1191–201.
33. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009; 373:2125–35.
34. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes: an interim analysis. N Engl J Med 2007;357:28–38.
35. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.
36. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–8.
37. Liu SC, Tu YK, Chien KL. Effect of antidiabetic agents added to metformin on glycemic control, hypoglycemia, and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab 2012;14:810–20.
38. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765.
39. Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2009;151: 394.
40. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.
41. Chiasson JL, Josse RG, Gomis R, et al, STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290:486–94.
42. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010;33:1503–8.
43. Frederich R, Alexander JH, Fiedorek FT, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med 2010;122:16–27.
44. Monami M, Cremasco F, Caterina L, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. Exp Diabetes Res 2011;2011:215764.
45. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007;298:194–206.
46. Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology 2010;86:44–57.
47. Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. Eur J Endocrinol 2009;160:909–17.
48. Pinelli NR, Cha R, Brown MB, Jaber LA. Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis. Ann Pharmacother 2008;42:1541–51.
49. Yki-Järvinen H, Kauppila M, Kujansuu E, et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1992; 327:1426–33.
50. Rosenstock J, Schwartz SL, Clark Jr CM, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001;24:631–6.
51. Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A metaanalysis of the randomized placebo-controlled trials. Arch Intern Med 1996;156:259–64.
52. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998;128:165–75.
53. Yki-Järvinen H, Ryysy L, Nikkilä K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999;130:389–96.
54. Tan A, Cao Y, Xia N, et al. The addition of pioglitazone in type 2 diabetics poorly controlled on insulin therapy: a meta-analysis. Eur J Intern Med 2010; 21:398–403.
55. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2011;154:103–12.
56. Arnolds S, Dellweg S, Clair J, et al. Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: a proof-of-concept study. Diabetes Care 2010;33:1509–15.
57. Barnett AH, Charbonnel B, Donovan M, et al. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin

alone or insulin combined with metformin. Curr Med Res Opin 2012;28: 513–23.
58. Vilsboll T, Rosenstock J, Yki-Jarvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2010;12:167–77.
59. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care 1998;21:2180–4.
60. ORIGIN Trial InvestigatorsGerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–28.
61. Gerstein HC, Yale JF, Harris SB, et al. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabet Med 2006;23: 736–42.
62. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Diabetes Care 1995;18:1113–23.
63. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009;361:1736–47.
64. Bretzel RG, Nuber U, Landgraf W, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008;371:1073–84.
65. Wulffelé MG, Kooy A, Lehert P, et al. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care 2002;25:2133–40.
66. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371: 1753–60.
67. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care 2004;27:1028–32.
68. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. Diabetologia 2009;52: 2499–506.
69. Dejgaard A, Lynggaard H, Rastam J, Krogsgaard TM. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. Diabetologia 2009;52:2507–12.
70. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. Diabetes Care 1989;12: 203–8.
71. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358: 2545–59.
72. ADVANCE Collaborative GroupPatel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
73. Anderson Jr JH, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Arch Intern Med 1997;157: 1249–55.
74. Anderson Jr JH, Brunelle RL, Koivisto VA, et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Clin Ther 1997;19:62–72.
75. Yki-Järvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. Diabetes Care 2000;23:1130–6.
76. Fritsche A, Schweitzer MA, Haring HU, et al. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med 2003;138:952–9.
77. Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005;28:254–9.
78. Horvath K, Jeitler K, Berghold A, et al. A long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus (review). Cochrane Database Syst Rev 2007;2:CD005613.
79. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2008;81:184–9.
80. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
81. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, glibenclamide, or placebo in NIDDM patients. The Essen Study. Diabetes Care 1994;17:561–6.
82. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes Care 1999;22:960–4.
83. Wright A, Burden AC, Paisey RB, et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002;25:330–6.
84. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–17.
85. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab 2005;7: 56–64.
86. Harrower A. Gliclazide modified release: from once-daily administration to 24 hour blood glucose control. Metabolism 2000;49(10 suppl 2):7–11.
87. Tessier D, Dawson K, Tétrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. Diabet Med 1994;11:974–80.
88. Schade DS, Jovanovic L, Schneider J. A placebo-controlled, randomized study of glimepiride in patients with type 2 diabetes mellitus for whom diet therapy is unsuccessful. J Clin Pharmacol 1998;38:636–41.
89. Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. Horm Metab Res 1996;28: 426–9.
90. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev 2001;17:467–73.
91. Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;2:CD004654.
92. Wolffenbuttel BHR, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Diabetes Care 1999;22:463–7.
93. Damsbo P, Clauson P, Marbury TC, et al. A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. Diabetes Care 1999;22:789–94.
94. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004;34:535–42.
95. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med 1997;103:491–7.
96. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ 2010;340:c2198.
97. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. Diabetes Care 2000;23:1605–11.
98. Raskin P, Rappaport EB, Cole ST, et al. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. Diabetologia 2000;43:278–84.
99. Nolan JJ, Jones NP, Patwardhan R, et al. Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. Diabet Med 2000;17:287–94.
100. Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab 2001;86: 280–8.
101. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA 2000;283:1695–702.
102. Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Am J Med 2001;111:10–7.
103. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. Clin Ther 2000;22:1395–409.
104. Yale J-F, Valiquett TR, Ghazzi MN, et al. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001; 134:737–45.
105. Miles JM, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. Diabetes Care 2002;25: 1123–8.
106. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2002;25:1033–41.
107. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diabetes Care 1998;21:1288–94.
108. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007;298:1189–95.
109. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care 2011;34:916–22.
110. Jacob S, Rabbia M, Meier MK, Hauptman J. Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. Diabetes Obes Metab 2009;11:361–71.
111. Berne C. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. Diabet Med 2004;22:612–8.