31 How to Use Type 2 Diabetes Treatments in Clinical Practice: Combination Therapies

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Keypoints

- Managing type 2 diabetes has become more complex as pharmacotherapy has expanded. Clinicians have more pharmaceutical agents targeted to hyperglycemia and obesity than before, but a relentlessly progressive disorder to overcome.
- Clinical trials continue to show that glycemic control is critical to reduce microvascular complications and in the long-term also cardiovascular events. Nonetheless, poor glycemic control, hypoglycemia and obesity remain stubborn barriers for clinicians.
- Few comparative data direct us in the best use of multiple drug therapies for the management of type 2 diabetes and its co-morbidities. One is guided by good clinical studies, the potential of therapeutic agents to reverse pathophysiology and ultimately the proper use of insulin which is eventually needed in most patients to replace the loss of β-cell function.

Introduction

The epidemic of type 2 diabetes mellitus (T2DM) presents the clinician as well as society with complex challenges in designing both prevention and treatment strategies for T2DM. T2DM is a worldwide epidemic with a global prevalence in 2009 of 285 million people, expected to increase to 435 million by 2030 [1]. The Centers for Disease Control and Prevention (CDC) estimates that in 2007 nearly 24 million people in the USA have diabetes [2], mostly T2DM. At least 57 million people have pre-diabetes (impaired fasting glucose or impaired glucose tolerance), providing an expanding pool of new patients with T2DM. Current prevalence represents a 90% increase in the new diagnosis of diabetes over the last decade [3] and more rapid increases in many parts of the world. This increasing prevalence of diabetes relates both to environmental and genetic factors, each of which may influence insulin sensitivity (e.g. insulin resistance) and insulin secretion capacity. Insulin resistance begins in early life and is fueled by obesity and a sedentary lifestyle which contribute to alterations in glucose homeostasis and to abnormal lipid and protein metabolism.

Relative insulin deficiency is the defining metabolic difference between obesity and the development of hyperglycemia with progression to T2DM. An inexorable progression of diabetes appears related to worsening insulin deficiency [4,5]. Most people therefore have gradually increasing needs for additional therapy. Combinations of therapy such as adopting a therapeutic lifestyle change, as well as oral and injectable medicines, are required to keep the glycemia under control. The failure to advance therapy at an early sign of therapeutic failure and, in particular, a reluctance to advance to insulin underlies the less than optimum control for many patients with diabetes.

Algorithms for management

Several approaches to the best management of T2DM have been proposed. All algorithms begin with therapeutic lifestyle change and are generally focused primarily upon controlling hyperglycemia. Consensus statements from the American Diabetes Association (ADA) have been recently revised in conjunction with the European Association for the Study of Diabetes (EASD) [6]. The most recent algorithm (Figure 31.1) moves away from the focus on glucose as the sole goal of therapy and tries to develop evidence-directed therapy to treating diabetes by normalizing hyperglycemia and minimizing cardiometabolic risk. The US Food and Drug Administration (FDA) has recently advised that new medicines for glycemic control in diabetes be routinely evaluated early for their effects upon cardiovascular disease. By doing so, they recognize atherosclerosis as the primary cause of cost and mortality in diabetes.

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

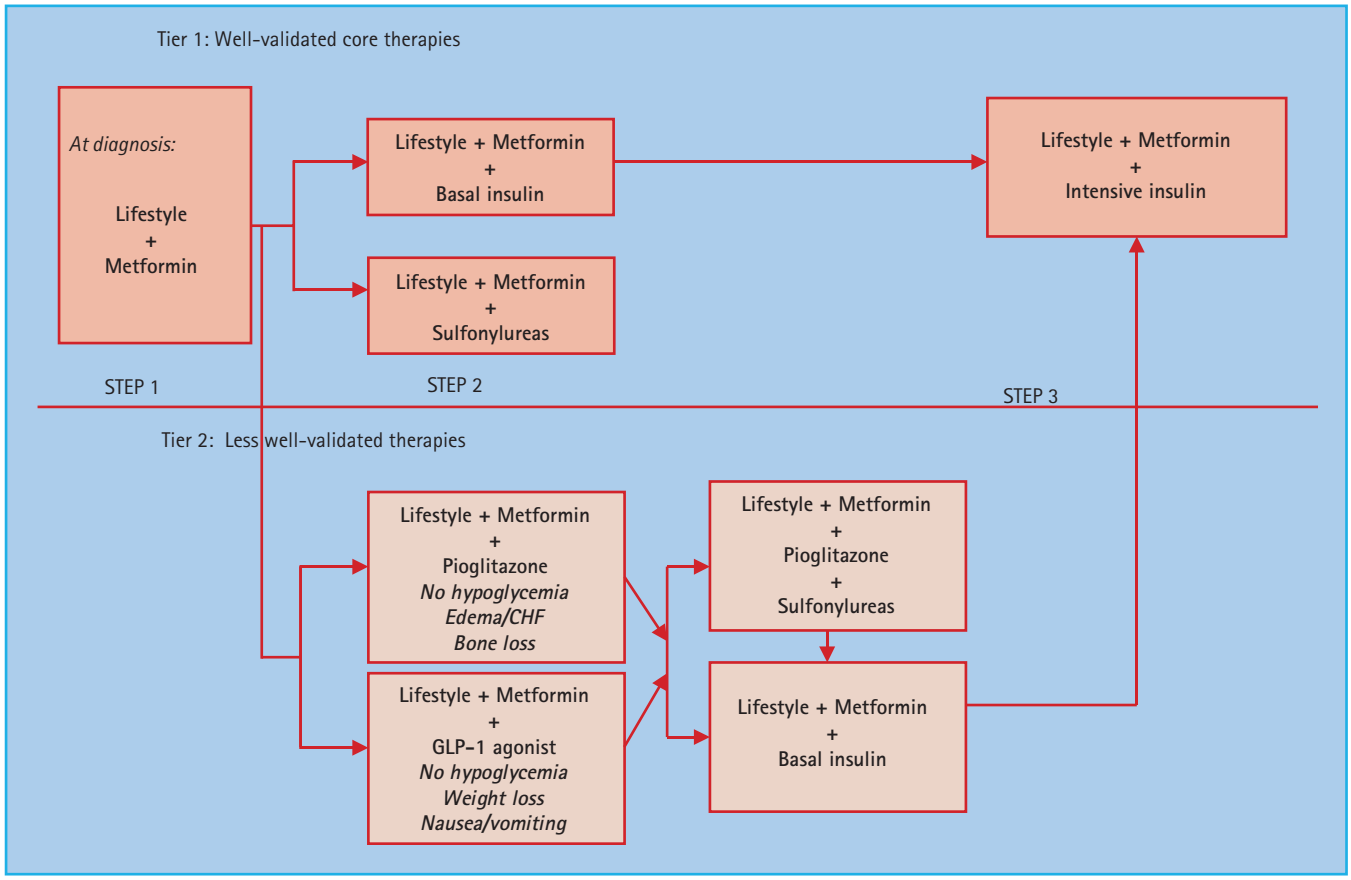

Figure 31.1 The ADA/EASD consensus statement on the recommended strategy to advance therapies to control hyperglycemia in diabetes. The top portion focuses on traditional well-validated therapies buttressed by large studies and long experience (metformin, sulfonylureas, insulin). The lower portion focuses on more recent emerging therapies that have less follow-up and validation in clinical trials (thiazolidinediones or glitazones as they are often called; e.g. pioglitazone, GLP-1 agonists such as exenatide). According to the authors, the amylin agonists, α-glucosidase inhibitors, glinides and DPP-4 inhibitors were not included in the two tiers of preferred agents in this algorithm, owing to their lower or equivalent overall glucose-lowering effectiveness compared with the first- and second-tier agents and/or to their limited clinical data or relative expense. However, they may be appropriate choices in selected patients. Similarly, colesevelam is not mentioned in this algorithm but may be appropriate for selected patients. Rosiglitazone is omitted from the algorithm because of unsettled concerns raised about cardiovascular side effects. Reproduced from the updated American Diabetes Association/European Association for the Study of Diabetes consensus statement [6].

The current consensus algorithm (Figure 31.1) moves quickly from metformin treatment failure to the addition of sulfonylurea or insulin. Newer classes of drugs (e.g. incretin mimetics, pioglitazone) are recommended later or as a secondary consideration because of the lack of compelling data to suggest their superiority compared to existing treatments and associated concerns for unintentional ill effects such as long bone fractures or increase in congestive heart failure (glitazones) or pancreatitis (exenatide). Ultimately, the treatment pathway must incorporate patient individualization, clinical acumen, and the broad experience gained from clinical trials.

Goals of treatment

Treatment goals for patients with diabetes have changed considerably over the past two decades. The Diabetes Control and Complications Trial (DCCT) [7] confirmed the concept of the relationship of glycemic control to microvascular complications in type 1 diabetes. Similar results were found for T2DM in the landmark UK Prospective Diabetes Study (UKPDS) [8,9]. Long-term analysis of subjects participating in these trials at 10 years following a period of improved glycemic control found cardiovascular risk reduction with insulin, metformin and sulfonylureas [10,11] and for T2DM also a mortality advantage.

In assigning patients to a treatment plan, consideration must be given to treatment goals. The ADA continues to recommend HbA_{1c} of <7% (<53 mmol/mol) as a general glycemic goal and individualization is recommended. For properly selected patients, either less tight control or alternatively more rigorous normalization of glycemia down to 6% (42 mmol/mol) HbA_{1c} can be recommended, if the latter can be achieved without hypoglycemia problems. Using similar data sources, the International Diabetes Federation (IDF) and American Association of Clinical Endocrinologists (AACE) suggest ≤6.5% (48 mmol/mol) as a general goal. All authorities recommend the need for individuali-

zation of goals based on co-morbidities and vulnerability to hypoglycemia among other criteria. The ACCORD trial hypothesized that close to normal glucose control (HbA_{1c} 6% or less [<42 mmol/mol]) would improve cardiovascular endpoints. Recent analysis of the ACCORD trial [12] cautions the provider against attempting to normalize glycemia in those with characteristics similar to this patient cohort (e.g. older and those with existing cardiovascular disease), as the intensively treated group had a 22% increase in mortality primarily from fatal cardiovascular events; very possibly, although unproven, this may have been as a result of hypoglycemia. This poses a dilemma to the practitioner: how best to normalize glycemia but avoid hypoglycemia. This practical consideration suggests newer therapies with a relatively low hypoglycemia risk should be considered for certain patient groups. Additionally, strategies to recognize and prevent hypoglycemia risk in patients at high risk should be adopted routinely. These include the need for self-monitored blood glucose (SMBG) tests, good communication and education about how to treat and adjust therapy should hypoglycemia become frequent or severe, especially if hypoglycemia unawareness occurs.

Ultimately, patients with T2DM require progression of therapy from combination oral therapy to combination injectable therapy (basal bolus insulin regimens, incretin insulin combinations). Initiating combination therapy early minimizes side effects while maximizing clinical effectiveness, decreasing pill counts and cost while facilitating compliance. New ACCE guidelines use all drugs and tailor their number and starting insulin to the baseline HbA_{1c} [13].

Lifestyle advice for diabetes and pre-diabetes

Lifestyle management is one of the most challenging barriers to successful diabetes control. Deriving recommendations for eating, physical activity and minimizing psychologic stressors is frequently frustrating for both the provider and patient [14]. The assumption that complex patterns of lifestyle behavior can be altered by dispensing general advice in the course of a busy medical visit is flawed, but unfortunately a reality for many providers. It should be replaced by an agreement that the patient is responsible for assisting in their disease management and is the only source of key information needed to manage their illness [15]. One strategy is to make patients more aware of their own lifestyle patterns. Developing a baseline for eating and exercise (type, frequency, duration, barriers) is as integral as obtaining initial laboratory testing in patients with T2DM to compile a treatment plan based on physiology as well as the psychology of the patient. Obtaining a narrow focus on a few behavioral objectives can increase success. Approaches we often use for patients are:

- Keep an eating behavior diary over the next week; and
- Wear a pedometer and keep track of your baseline steps for the next week.

The information almost always contains some surprises for patients but it helps them to identify personal behaviors and to focus and motivate them to take the lead in setting meaningful objectives.

The role of the physician is critical in emphasizing the importance of lifestyle change to the patient, initiating a process of working on lifestyle change, and reinforcing, and refining the education to achieve incremental obtainable objectives. Use of motivational interviewing and assessment of readiness to change are important aspects of evaluation of the patient by both the medical provider and diabetes educator. It is our practice to recommend strongly diabetes education for every patient who is willing to do so and to reinforce the recommendation for lifestyle change at any point when additional therapy needs occur. A useful acronym that we have used to help trainees remember how to assist patients in making lifestyle change is FIRM [15]. This stands for negotiating Few changes, typically 1–3 at any clinical visit; those changes should be Individualized by the patient's selection of what aspects of behavior change to embark on; the changes should be Realistic and therefore likely to succeed by setting moderate, achievable goals within a specific timeframe; and be Measureable and monitored through patient record-keeping to be shared with the provider or diabetes educator at the next visit.

Therapy for obesity as a treatment for T2DM

Because the vast majority of people with T2DM are overweight or obese, a serious consideration is the use of weight loss and increasing physical activity strategies as a useful treatment to gain control of glycemia and favorably influence multiple cardiovascular risk factors as well [16,17]. Prevention and/or treatment plans for T2DM could also legitimately consider use of pharmacotherapy for obesity. Successful weight loss of 10% or less has repeatedly been shown to improve glycemic control (HbA_{1c} reductions 0.3–0.5% [3–6 mmol/mol] and sometimes much more) as well as favorable improvements in lipids, hypertension as well as other cardiac risk factors. Currently, three drugs (phentermine, orlistat and sibutramine) are approved for management of obesity in the USA. Rimonabant was approved for use in several countries outside the USA, but recent withdrawal of support by the European Medicines Agency has ended its possibility of wider use. Other drugs of the endocannabinoid receptor blocker class have also been discontinued from clinical development. Phentermine is only approved for short-term use and is the least well-studied and is less commonly used and not generally recommended.

Orlistat is currently approved for use in the management of obesity. Orlistat functions as a gastric and pancreatic lipase inhibitor. When given at a dosage of 120 mg three times daily with meals, approximately 20–30% of ingested fat is passed into the feces. Large amounts of fat in the gastrointestinal tract result in the most difficult side effect to manage, namely anal leakage of oil to post-prandial diarrhea which may be abrupt. Attention to this expected effect as well as dietary counseling or use of daily or twice daily dosing can minimize patient's gastrointestinal accidents and may enhance patient adherence to low fat dietary regimens. No long-term malabsorption of fat-soluble vitamins

has been seen but replacement with a multivitamin including vitamin D is recommended during therapy. A lower dosage (60 mg) over-the-counter form is now available.

Orlistat has been critically studied both in the prevention [18] and in the treatment of T2DM in patients receiving metformin or insulin [19,20]. In the XENDOS trial, 3305 obese subjects at risk for T2DM were randomized to therapeutic lifestyle change or therapeutic lifestyle change plus orlistat 120 mg three times daily over a study period of 4 years. The subset of subjects with impaired glucose tolerance at entry receiving orlistat enjoyed a 37% relative risk reduction in development of T2DM at study end. Favorable lipid effects were also seen.

In obese subjects with T2DM failing metformin monotherapy [19], the addition of orlistat to the treatment plan lowered HbA_{1c} by 0.35% (4 mmol/mol) and improved lipid as well as blood pressure control. Similarly, benefits were also seen in insulin-treated patients given orlistat for 1 year [20] with improved glycemia (HbA_{1c} −0.62 ± 0.08 for orlistat-treated vs −0.27 ± 0.08% given placebo; $P < 0.002$, 7 vs 3 mmol/mol) and improved lipids despite lowered diabetes medicine doses.

Sibutramine enhances satiety and diminishes appetite primarily through central pathways, involving the inhibition of synaptic reuptake of norepinephrine, serotonin and to a lesser extent dopamine.* Doses approved for use in the management of obesity range 5–15 mg, with greatest efficacy at the cost of highest frequency of side effects seen at the 15 mg dosage. Doses up to 20 mg have been used in the clinical trial setting with a similar observation. A recent meta-analysis studied eight of 30 available clinical trials using sibutramine in the management of diabetes [21]. The authors included studies using sibutramine in combinations with sulfonylureas, metformin or a hypo-caloric diet. In general, treatment effects were associated with a 5.5-kg loss in body weight versus an approximate 1-kg weight gain in comparator groups. On average, HbA_{1c} improved 0.28% (3 mmol/mol) with variability among the different studies included. Additional positive effects were noted in reducing triglycerides and raising high density lipoprotein (HDL) without any adverse effects on blood pressure. Small increases in heart rate were noted. The presence of hypertension, especially if not ideally controlled, should be considered a contraindication to use of sibutramine, especially given how sensitive patients with diabetes are to the adverse impact of modest blood pressure changes and the effects of blood pressure upon diabetes complications.

Rimonabant, an endocannabinoid CB1 receptor blocker, has recently been removed from the European market because of concerns over exacerbating mood disorders (depression). Ongoing clinical trials using rimonabant have also been halted, raising questions over both the utility and availability of drugs acting on the endocannabinoid system. Despite its removal from studies and failure to stay widely marketed, there are studies finding a substantial antihyperglycemia effect similar to that of some approved diabetes pills. Such work validates the notion that treatment directed toward obesity have glycemic effects that are similar to some of the already approved pharmacotherapy choices for diabetes. Safety concerns regarding depression appear unlikely to allow this type of medication to be marketed in the future.

Bariatric surgery for appropriate patients (typically BMI >40 kg/m^2 or >35 kg/m^2 with co-morbidities) who have failed successful lifestyle interventions and/or pharmacotherapy for obesity is an increasingly utilized option. Improved safety and standardization combined with expanding data for the surgical management of obesity with favorable effects including long-standing remissions of T2DM in most patients make this an increasingly employed procedure [22,23]. The physiology behind such benefits remains poorly understood. Paradigms for identifying patients best suited for surgical treatment of cardiometabolic risk are evolving. Typically, many patients who are candidates for bariatric surgery are already on a combination of therapies. Following surgery, most patients who have been on insulin will be able to stop unless there is a very long history of diabetes. During the hypocaloric diet employed in preparation for such surgery, significant decreases in the need for insulin and sometimes other diabetes medications occur. For those who undergo Roux-en-Y procedures it is common to have a rapid reduction of insulin requirements within days to weeks. Decreasing insulin dosage by half or more is frequently necessary to avoid hypoglycemia.

Combination pharmacotherapy for T2DM

Therapies for T2DM can be divided into drugs facilitating supply of endogenous insulin (secretagogues, incretins) or those enhancing insulin actions (biguanides, thiazolidinediones, incretins, α-glucosidase inhibitors, amylin analogs, colesevelam). Successful treatment of T2DM combines approaches to lifestyle modification frequently in conjunction with use of pharmacologic therapy.

We conclude from data found in the UKPDS that insulin secretory loss starts on average 10 years before the formal diagnosis of T2DM, followed by insulin deficiency on average 10–12 years after diagnosis [8]. The dual aspects of T2DM, insulin resistance and insulin deficiency, are important factors in therapy selection and the subsequent response to therapy. This chapter provides an update on combinations of therapies for T2DM, presents evidence and opinions on sequences of medications, reviews new insights into diabetes and obesity treatments, and briefly describes some new medications emerging for the treatment of T2DM.

Need for combination therapy

The management of T2DM, as with any chronic illness, requires individual assessment and involvement of patient with their care

*The marketing authorization for sibutramine has recently been withdrawn in Europe following the publication of the SCOUT trial. In this trial which included 9,800 overweight or obese individuals at high risk of CVD events, treatment with sibutramine was associated with a 16% increased risk of non-fatal MI, non-fatal stroke, resuscitated cardiac arrest or CVD death. This result was driven by an increased incidence of non-fatal MI and stroke.

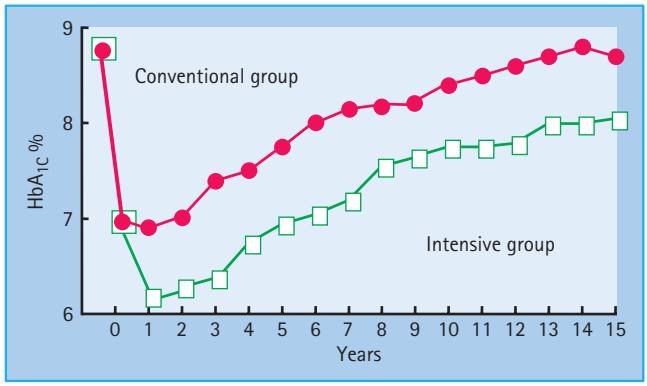

Figure 31.2 This figure, which is adapted from the UK Prospective Diabetes Study comparing conventional policy to intensive policy with sulfonylureas or insulin, shows the progressive rise of median HbA_{1c} that presumably is related to the progressive insulin secretory defect present in type 2 diabetes mellitus. A noteworthy aspect of this figure is the decline in HbA_{1c} from nearly 9% (75 mmol/mol) to around 7% (53 mmol/mol) in the first 3 months after initial evaluation. During this period, subjects in this study had visits with educators and dietitians helping them to improve lifestyle.

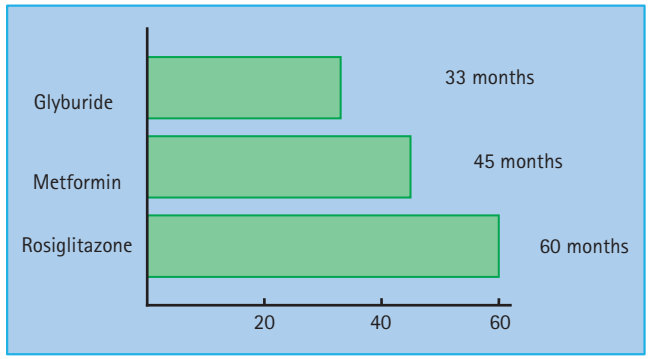

Figure 31.3 The ADOPT study examined the duration of maintenance of fasting glycemia in patients with diabetes on three monotherapies: glyburide (glibenclamide), metformin and rosiglitazone. As shown in this figure, rosiglitazone was superior to metformin which was in turn superior to glyburide in efficacy of maintenance of HbA_{1c}. Nonetheless, at 4 years most patients in each of the three groups did not maintain their HbA_{1c} goals and needed to progress to combination therapy. The analysis shown reflects time until mean HbA_{1c} within treatment group exceeds 7% (>53 mmol/mol) based on a repeated measures mixed model. Reproduced from Kahn *et al. N Engl J Med* 2006; **355**:2427–2443.

plans. Perhaps the original "combination therapy" for T2DM remains advice on flexible approaches to healthy eating styles coupled with encouragement and support to improve physical activity with consideration of the use of early pharmacologic treatment interventions in most patients. Most patients with T2DM eventually require combination pharmacologic therapy; some at the time of initial diagnosis, especially if they have a markedly elevated HbA_{1c}. Data from the UKPDS [5] showed that about 50% of patients required combination therapy within 3 years of diagnosis, and approximately 75% at 9 years after diagnosis (Figure 31.2).

Choice of initial therapy

No therapy has rigorously been proven to alter the natural history of progressive β-cell decline and the ultimate need for combination treatment. Nonetheless, randomization to rosiglitazone in the ADOPT trial [24] was associated with longer monotherapy success for a new diagnosis of T2DM (60 months) versus metformin (45 months) or glyburide (glibenclamide) (33 months). The data from this study (Figure 31.3) found that at the 4-year evaluation, 40% of the 1456 patients in the rosiglitazone group had a glycated hemoglobin level of less than 7% (<53 mmol/mol), compared with 36% of the 1454 patients in the metformin group ($P = 0.03$) and 26% of the 1441 patients in the glyburide group ($P < 0.001$). Thus, even with some superior durability of treatment-related glycemic response, it is clear that most patients with T2DM will require combination therapy within the first 3–6 years after medication is begun.

Rationale for combination therapy

In the context of at least two major physiologic defects in T2DM, insulin resistance and progressive insulin secretory failure, combining treatments with complementary actions can be a logical approach. Several distinct advantages of combining agents can be distinguished.

Efficacy

The first rationale for combination therapy (either with oral agents alone, with oral agents and insulin or oral agents with other injectable medicine such as incretin mimetics) is its superior efficacy. One principle that emerges from randomized controlled trials of antidiabetic therapies is that switching from one medication to another does not work as well as adding on or combining therapies. Figure 31.4 shows a classic study of combination oral agent therapy that illustrates this point [25]. Patients with inadequate glycemic control on maximal doses of glyburide were randomized to continuation of that monotherapy, to metformin monotherapy gradually titrated to maximal doses (850 mg orally three times a day), or to a combination of glyburide and metformin. Neither monotherapy resulted in any significant improvement in fasting plasma glucose (FPG), but combination therapy with an insulin secretagogue and metformin showed a dramatic improvement. Similarly, studies with other combination therapies showed no benefit of switching to a new agent class, but greater glucose-lowering efficacy through combining it with an agent with a different mechanism. A final benefit of combination treatment may add efficacy by using some agents that treat preprandial hyperglycemia and others that treat post-prandial hyperglycemia. As with basal and bolus insulin, it may be important to use both approaches in balance.

Tolerability and convenience

Most side effects of glycemic medications are dose-related. For example, hypoglycemia is a side effect of insulin or insulin secretagogues, gastrointestinal side effects are common with met-

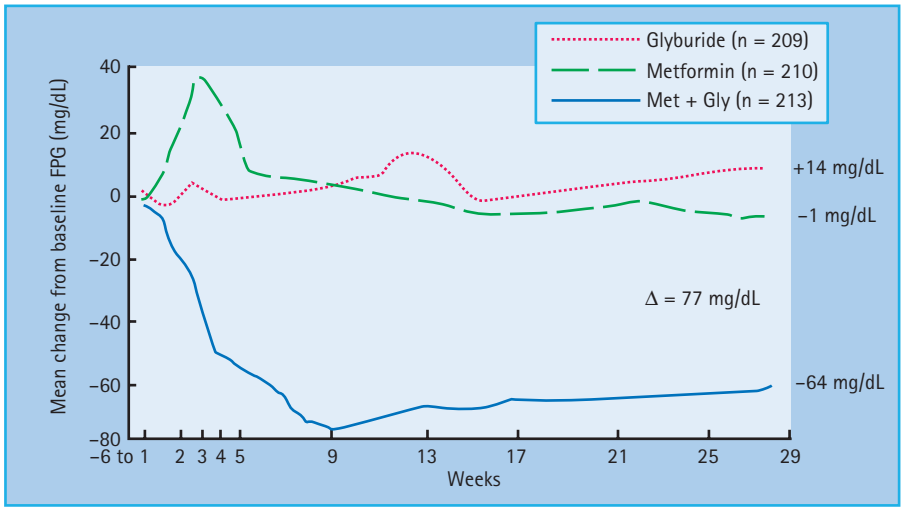

Figure 31.4 As shown by DeFronzo *et al.* [25] in subjects failing maximal dose glyburide (dotted line), continuation of the "failing" secretagogue led to gradually worse hyperglycemia. Likewise, a switch from glyburide to metformin (dashed line) showed little glycemic improvement. A worsening of hyperglycemia with increased fasting plasma glucose (FPG) was seen in the metformin group after glyburide had been stopped and before full dose titration of metformin had occurred. This study exemplifies the general principle that switching makes little sense as the combination of therapy (solid line) substantially improves FPG which is not observed with either monotherapy.

formin, incretin mimetics and α-glucosidase inhibitors, and fluid retention or weight gain may occur with the thiazolidinediones. In contrast to some of the adverse effects of diabetes agents noted above, the efficacy of oral agents in glucose lowering is often not linear with increasing dose. Thus, with dose escalation one may increase undesirable side effects while gaining little in efficacy. One option is to utilize lower doses of two complementary medications, which can minimize side effects while achieving equal or better glycemic control. This principle has been tested directly for the combination of glyburide and metformin [25].

Using combinations of oral agents may seem more complex than monotherapy, but in some cases their convenience can be enhanced. Combining a single dose of a long-acting sulfonylurea, such as glimepiride, with one or two tablets of metformin, may have greater benefit than three or four tablets of metformin alone. Metformin–secretagogue (metformin–glyburide, metformin–glipizide, metformin–repaglinide) combination pills, have been introduced. Similarly, metformin–thiazolidinedione (metformin–rosiglitazone, metformin–pioglitazone) combination pills are also available. Recently, thiazolidinediones–secretagogue (rosiglitazone–glimepiride, pioglitazone–glimepiride) combination pills have become available. Some newer agents such as sitagliptin have been approved for use when combined with metformin and are also available as a combination pill.

The trend to use combination pills will likely increase in the future. Formulations of two agents in a single pill with dual actions may appeal to many patients and practitioners. While separate titration of agents may be desirable for many patients, for others a case can be made for combination preparations. Side effects are often characteristic of a particular agent (e.g. sulfonylureas with hypoglycemia, metformin with gastrointestinal side effects, glitazones with fluid retention) and thus can be commonly attributed correctly to the specific agent in a combination pill. Occasionally, rarer or idiosyncratic side effects could be less readily attributed to the specific agent. This tactic may prove especially attractive for patients who must take not only two or more agents for glycemic control, but also other medications for manage blood pressure, lipid abnormalities, heart disease and other problems.

Secretagogues

Whether rapid or longer-acting, secretagogues work well with both metformin [25] and thiazolidinediones [26]. Their use with basal insulin therapy, such as evening NPH or glargine [27] is also evidence-based. Use of secretagogues with a mixture of evening basal plus mealtime insulin reduces insulin requirements and prevents interim hyperglycemia during insulin dose titration [28], however, their use with two or more mealtime insulin doses is considered superfluous, and might increase the risk of hypoglycemia. Insulin secretagogues work by binding to sulfonylurea receptors (SUR), which in the pancreas are of the SUR1A subtype. SUR are linked to potassium inward rectifier (Kir 6.2) channels. When Kir channels are closed by secretagogue binding to SUR, calcium channels are opened and insulin is released. The Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction 1 (DIGAMI-1) study [29] showed that, compared with usual care, insulin treatment reduced mortality from acute myocardial infarction in diabetes mellitus; thus, it seems reasonable to avoid secretagogues, particularly glyburide, in patients with active ischemic heart disease (acute coronary syndromes or the presence of stable angina). DIGAMI-2 [30] did not confirm the mortality differential found in DIGAMI-1. The DIGAMI-2 study was

limited by the inability to achieve targeted glycemic goals (5–7 mmol/L) and a small separation of glycemic control between treatment groups. Nevertheless, the investigators confirmed the epidemiologic relationship between hyperglycemia and cardiac mortality. Taken together, this information suggests cardiac ischemia with hyperglycemia may still be best managed with insulin.

The primary side effect of secretagogues, used alone or in combination, is hypoglycemia. Avoidance of hypoglycemia, particularly in older patients or patients with cardiovascular disease as recently highlighted by the ACCORD trial [12], restricts overuse of this class. For a few patients hypoglycemia occurs overnight. Chlorpropamide and glyburide are the secretagogues most likely to cause hypoglycemia although it may occur with any of the sulfonylureas. Nonetheless, daytime hypoglycemia, most commonly in the mid afternoon, with once daily morning dosing is a more common timing of hypoglycemia. It should lead to advice not to skip or delay lunch and may occasionally require a snack when patients are physically active in the middle of the day.

Loss of early prandial insulin release is thought to be an early event in the development of T2DM [31]. Epidemiologic studies suggest that post-prandial hyperglycemia or impaired glucose tolerance independently predicts risk for cardiovascular disease in patients with diabetes mellitus and normal fasting glycemia [32,33]. Several antidiabetes agents specifically target post-prandial hyperglycemia. These agents include the rapid-acting insulin analogs aspart, lispro and glulisine; α-glucosidase inhibitors; rapid-acting insulin secretagogues and incretins. Table 31.1 lists commonly used medication, their efficacy and their preprandial and post-prandial effects and side effects of different agents.

Rapid-acting secretagogues (glinides)

The meglitinide repaglinide and the phenylalanine derivative nateglinide have theoretical advantages, with rapid prandial insulin release potentially mimicking normal physiology. Some facilitation of prandial insulin release, however, does occur with long-acting secretagogues. The differential effect on early insulin secretion with rapid-acting secretagogues compared to sulfonylureas has not been consistently seen in all studies. Carroll *et al.* [34] failed to identify a substantial and consistent prandial glycemic benefit of rapid-acting secretagogues in comparison to extended- or immediate-release glipizide. Rapid-acting secretagogues are considered most appropriate for sulfonylurea-intolerant patients, patients with erratic food intake and patients in whom there is a demonstrated individual benefit. The absence of data showing improved clinical outcome, greater cost, more frequent dosing and no superiority in HbA_{1c} reduction limits enthusiasm for their wider use. Moreover, the rapid kinetics of nateglinide may explain its somewhat reduced overall antihyperglycemic efficacy. Secretagogues will retain their role in restoring insulin secretory deficits, especially in leaner patients, alone and in combination.

Biguanides

The antihyperglycemic effect of metformin is largely brought about by suppression of hepatic glucose release, thus reducing insulin resistance in the liver. Metformin may accomplish this by activation of the enzyme adenosine 5′-monophosphate-activated protein kinase (AMPK), which acts as a "fuel sensor." Although not approved by the FDA for the treatment of the metabolic syndrome or intermediate hyperglycemia, some clinicians have taken advantage of the insights from the Diabetes Prevention Program (DPP) [35]; in patients with impaired glucose tolerance, there was a delay in the onset of T2DM through the use of intensive lifestyle modification (58% reduction), metformin (31% reduction) and troglitazone (early DPP data suggest a benefit, but this study arm was discontinued because of the

Table 31.1 Diabetes drugs with efficacy, preprandial and post-prandial effects and side effects.

Drug type	HbA_{1c} lowering	Pre-prandial effect	Post-prandial effect	Actions	Side effects
Sulfonylureas and non-SU rapid secretagogues	1.0–2.0%	++	+	Direct/indirect secretagogue	Hypoglycemia, wt gain
Biguanides	1.0–2.0%	+++	–	↓ Hepatic glucose output	GI, lactic acidosis, wt neutral
Thiazolidinediones	0.5–1.6%	+++	–	↑ Muscle insulin sensitivity	Edema, CHF
Incretin agonists	0.9–1.1%	+	++	Strong GLP-1 effects ↑ insulin ↓ glucagon	Nausea, vomiting, wt loss
DPP-4 inhibitors	0.6–0.8%	+	++	Moderate GLP-1 effects ↑ Insulin ↓ glucagon	Nausea, wt neutral
Insulin Basal (NPH, glargine and detemir)	1.5–2.5%	+++	– Depends upon type	↓ Hepatic glucose output, ↑ muscle glucose disposal	Hypoglycemia, wt gain
Insulin Meal (analog and regular)	1.0–2.0%	–/+	++ Depends upon type	↓ Hepatic glucose output, ↑ muscle glucose disposal	Hypoglycemia, wt gain
Pramlintide	0.5–0.7%	–/+	++	↑ Insulin ↓ glucagon	Nausea, vomiting

CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like receptor 1; SU, sulfonylurea; wt, weight. HbA_{1c} 1%=11 mmol/mol.

hepatotoxicity observed). Thus, in patients with pre-diabetes or the metabolic syndrome, metformin is sometimes used in combination with intensive lifestyle modification for prevention of T2DM.

Metformin is usually the preferred initial treatment selection in most T2DM. Data, again from the UKPDS, demonstrate that metformin as monotherapy in overweight patients reduced mortality, myocardial infarction and weight gain [9]. Long-term follow-up from the UKPDS suggests this cardiovascular and mortality benefit persists [11]. The use of metformin in combination with secretagogues in T2DM is very common and two combination pills are available. One formulation combines metformin with glyburide, and the other combines metformin with glipizide. Combination medications are also available for metformin with thiazolidinediones, repaglinide and sitagliptin. The combination medications do not include the extended-release versions of metformin, and this may limit gastrointestinal tolerance for a few patients.

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin-sensitizing agents that act as ligands of the nuclear transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ) [36]. In so doing, they improve not only glycemia but may ameliorate dyslipidemia, inflammation and hypercoagulability associated with insulin resistance [37]. As a result, there is particular interest in their potential cardiovascular benefits in T2DM. The pleiotropic effects of TZDs beyond glycemic control lie in the role of their ligand, PPAR-γ, on lipid metabolism and inflammatory pathways. PPARs are members of a nuclear receptor superfamily that regulates gene expression in response to ligand binding. There are three known PPARs: α, δ (sometimes called β) and γ. PPAR-α is found in the liver, the heart, muscle and vascular walls, and binds fibrates, with subsequent free fatty acid oxidation, reduced triglycerides, improved high-density lipoprotein (HDL) cholesterol and a decrease in inflammation [37]. PPAR-γ is most abundant in adipose tissue, but also is in β-cells of pancreatic islets, vascular endothelium and macrophages. It regulates gene expression, influencing adipocyte differentiation, fatty acid uptake and storage, and glucose uptake [36,37].

Rosiglitazone and pioglitazone are both FDA approved for monotherapy and in combination with metformin and sulfonylureas [38–41]. Because of concerns about cardiovascular risk, rosiglitazone is no longer recommended with insulin or nitrate therapy. Pioglitazone is approved for use with insulin. A TZD predecessor, troglitazone, was FDA approved in 1997 but withdrawn in 2000 because of reports of fatal hepatotoxicity, which is not seen with current TZDs. In a meta-analysis of 13 randomized clinical trials, less than 0.3% of patients on pioglitazone or rosiglitazone had alanine aminotransferase (ALT) levels greater than three times the upper limit of normal, compared to nearly 2% of patients on troglitazone [42]. Nonetheless, it is recommended that liver function tests be performed prior to initiation of therapy and periodically thereafter. Of interest, recent reports suggest that TZD therapy may improve elevated transaminase values and even liver histology in patients with T2DM and non-alcoholic fatty liver disease or non-alcoholic steatohepatitis [43].

Both pioglitazone and rosiglitazone effectively lower HbA_{1c}, up to about 1–1.5% (11–16 mmol/mol), with maximum doses in monotherapy [44] but less on average. Glycemic control is improved on average more than with nateglinide or α-glucosidase inhibitors, but less than with sulfonylureas or metformin in unselected patients, partly because of a heterogeneous response; some patients have a small response, but others have a robust response. When TZDs are added to sulfonylureas, metformin or insulin, an additional 0.8–1.5% (9–16 mmol/mol) HbA_{1c} decline can generally be achieved [45]. A combination form of metformin and rosiglitazone is currently available. A combination pill of pioglitazone and metformin is now marketed. As with the sulfonylurea combination pills, the immediate-release form of metformin is used in these formulations. For very insulin-resistant patients (usually with high BMI, marked central obesity and hypertriglyceridemia) with preserved insulin secretion (shorter duration of diabetes), use of metformin with a TZD can be very effective. These same characteristics probably identify good TZD monotherapy responders. Combination pills of metformin and rosiglitazone or pioglitazone may be preferable for some patients because there are fewer pills to take or there is lower co-payment from insurance in some countries. TZD–secretagogue combinations are effective in insulin-resistant patients with moderate insulin secretory reserve. Combination pills are available, both for pioglitazone (with glimepiride) and rosiglitazone (with glimepiride).

As described above, the ADOPT (A Diabetes Outcome Progression Trial) trial (Figure 31.3) [24] assessed the durability of glycemic efficacy of glyburide, metformin and rosiglitazone as a monotherapy. It used as a primary endpoint the ability to maintain fasting plasma glucose less than 180 mg/dL. Secondary outcomes included time from randomization to FPG >140 mg/dL. Other prespecified outcomes included levels of FPG and glycated hemoglobin, weight and measures of insulin sensitivity and β-cell function as determined by homeostasis model assessment using the HOMA 2 method (Figure 31.5). The primary study endpoint, the proportion of those who failed to keep the FPG less than 180 mg/dL was achieved by 143 patients on rosiglitazone (2.9 per 100 patient-years), 207 on metformin (4.3 per 100 patient-years) and 311 on glyburide (7.5 per 100 patient-years). The percentages of patients HbA_{1c} achieving <7.0% (<53 mmol/mol) while on assigned therapy at study end were 26% for glyburide, 36% for metformin and 40% for rosiglitazone. Weight gain was greater with rosiglitazone than glyburide (2.5 kg) and greater still than metformin (6.9 kg) while hypoglycemia was more common with glyburide and gastrointestinal side effects with metformin as would be expected. Cardiovascular events were reduced with glyburide but not with the other two therapies.

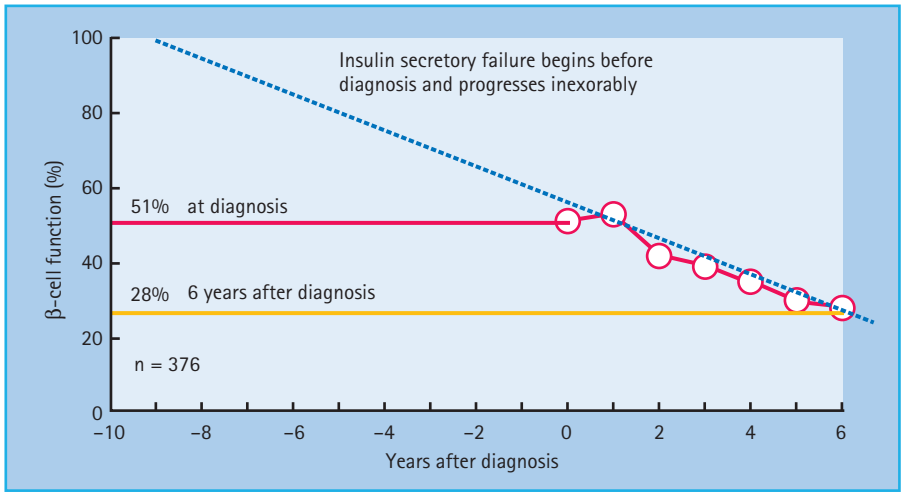

Figure 31.5 Based upon a homeostasis (HOMA) model, residual maximal insulin secretory reserve is depicted at the time of diagnosis and yearly for 6 years in subjects receiving diet only in the UK Prospective Diabetes Study. This figure illustrates that nearly half of insulin secretion is lost at diagnosis. It also shows the progressive loss of insulin secretory reserve, which predicts essentially complete insulin deficiency in about a dozen years if further loss were linear.

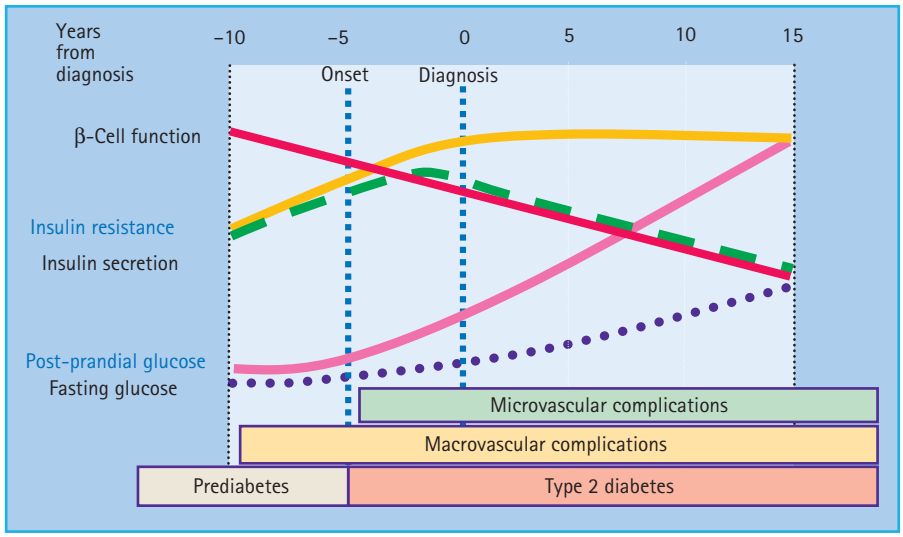

Figure 31.6 The natural history of type 2 diabetes mellitus. Long before diagnosis β-cell function begins a gradual and inexorable decline (solid red line at top of figure). Insulin resistance (solid orange line) begins to increase during early adulthood in conjunction with cardiovascular risks. The dashed green line depicts the initial compensatory increase in insulin secretion in response to increasing insulin resistance, which initially maintains euglycemia but which eventually fails and causes progression from euglycemia to prediabetes to diabetes. At the bottom of the figure post-prandial glucose levels rise (solid pink line) initially as insulin secretion fails to keep pace with insulin resistance. Later (dotted purple line) fasting glucose will also begin to rise progressively as insulin secretion wanes further. Progressive insulin deficiency requires progressive therapy combinations. After about 10 years of diagnosed diabetes frank insulin deficiency leads to the need for basal and then basal and meal insulin treatment in most people with type 2 diabetes. Microvascular complications occur only after several years of hyperglycemia. Macrovascular complications may precede or arrive simultaneously with diagnosis of diabetes because of the long prodrome of insulin resistance-related cardiovascular risks. Adapted from Holman RR. *Diabetes Res Clin Pract* 1998; **40**(suppl):S21–S25; Ramlo-Halsted BA, Edelman SV. *Prim Care* 1999; **26**:771–789; Nathan DM. *N Engl J Med* 2002; **347**:1342–1349; UKPDS Group. *Diabetes* 1995; **44**:1249–1258.

Overall, most editorialists have concluded that glitazones remain in the balance less attractive as initial therapy than metformin [46].

TZDs also stimulate the production and circulation of adiponectin [47], a fat-cell-derived hormone (or adipokine) that increases AMPK activity in the liver, adipose tissue and skeletal muscle. Low adiponectin levels are seen in patients with T2DM and are thought to contribute to insulin resistance and subsequent hyperglycemia [48]. The stimulation of adiponectin production, in addition to direct activation of AMPK, may explain some of the beneficial lipid effects of TZDs as well as their ability to increase insulin sensitivity [48]. Low adiponectin levels may predict a therapeutic response to TZDs, and polymorphisms in the PPAR-γ gene could potentially help to explain the variability of therapeutic response to TZDs and progression of diabetes (see Chapter 12) [48].

A recent meta-analysis raised the question of cardiac safety with rosiglitazone with findings of a 43% relative increased risk

in ischemic heart disease events [49]. Some studies using the same data have confirmed this increase in risk while others have failed to do so. Further analysis, including interim safety analysis of the RECORD trial, failed to show increased rates of major adverse cardiac events (see below) [50]. Results from recently published prospective randomized controlled clinical trails (VADT, ADVANCE, ACCORD) [12,51,52] which had high rates of TZD usage failed to show reduction in major adverse cardiovascular events (MACE) with tighter glycemic control and did not suggest increases in MACE associated with TZD use. Nevertheless, the ADA/EASD algorithm has taken a conservative stance and has not included rosiglitazone in its standard alternative recommendations.

What does become clear in review of the available safety data for this class is their propensity for promoting fluid retention in some patients, who may be difficult to predict in advance. Close tracking of patient weight and reviewing medication dose or diuretic use may need to be performed when patients gain more than 5–7 lb (3 kg). This has lead to a re-emphasis on their potential for exacerbation of congestive heart failure particularly in patients with class III or IV heart failure [53].

Subsequent analysis of clinical trial data, both old and new, with an emphasis on analysis of those patients at risk for MACE lead to significant changes in the labeling for use of TZDs. In particular, concomitant usage of insulin or nitrates was associated with increased risk for congestive heart failure and other cardiovascular events, and combination therapy of insulin and/or nitrates with rosiglitazone is no longer indicated. Currently, neither pioglitazone nor rosiglitazone are indicated in patients with class III or IV heart failure.

The link between TZD usage and possible adverse cardiovascular events or potential cardiovascular risk reduction remains unanswered. Rosiglitazone was used in large numbers of patients in both the ACCORD [12] and VADT trial [52] without a clear MACE signal, suggesting the drug does not promote cardiovascular events. Pioglitazone was studied in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) to examine its effects on morbidity and cardiovascular mortality and the secondary cardiovascular endpoints of myocardial infarction, death and stroke were favorably affected [54]. This study of 2600 actively treated patients showed no increase in mortality or MACE. Future studies may assist the practitioner to reach a clearer answer to this important but unresolved question.

Two recent studies tend to affirm the cardiovascular safety of rosiglitazone. They are the RECORD trial [55] and the BARI 2D trial [56]. These studies compared the cardiovascular benefits of rosiglitazone to other monotherapy (RECORD) in a non-inferiority analysis, while an insulin sensitizing approach was compared with an insulin providing approach in the BARI 2D trial. In the BARI 2D trial [56], 2368 patients with both T2DM and heart disease were randomly assigned to either prompt revascularization with intensive medical therapy or intensive medical therapy alone. They were also assigned to either insulin-sensitization or insulin-provision therapy, with either insulin or secretagogues. The primary endpoints were the rate of death and a composite of death, myocardial infarction or stroke (major cardiovascular events). At 5 years, survival rates were similar with revascularization (88.3%) and medical therapy (87.8%; $P = 0.97$) or with insulin-sensitization (88.2%) and insulin-provision (87.9%; $P = 0.89$). Similarly, freedom from major cardiovascular events did not differ significantly among the groups: 77.2% with revascularization and 75.9% with medical treatment ($P = 0.70$) and 77.7% with insulin-sensitization and 75.4% with insulin-provision group ($P = 0.13$). Severe hypoglycemia was more common with insulin provision (9.2%) than with an insulin-sensitization strategy (5.9%; $P = 0.003$).

In the RECORD study [55], 4447 patients with T2DM on metformin or sulfonylurea monotherapy with mean HbA_{1c} of 7.9% (63 mmol/mol) were randomly assigned to added rosiglitazone (n = 2220) or to metformin and sulfonylurea (n = 2227). The primary endpoint was cardiovascular hospitalization or cardiovascular death, with a hazard ratio (HR) non-inferiority margin of 1 : 20; 321 people offered added rosiglitazone and 323 in the control group experienced the primary outcome during 5.5-year follow-up, meeting the criterion of non-inferiority (HR 0.99; 95% CI 0.85–1.16). HR was 0.84 (0.59–1.18) for cardiovascular death, 1.14 (0.80–1.63) for myocardial infarction, and 0.72 (0.49–1.06) for stroke. Although these cardiovascular endpoints did not differ significantly, heart failure leading to hospitalization or death occurred in 61 people with rosiglitazone and 29 in the control group (HR 2.10, 1.35–3.27). Limb fracture rates were increased (about double), mainly in women randomly assigned to rosiglitazone. Mean HbA_{1c} was lower (approximately 0.25% [3 mmol/mol]) in the rosiglitazone group than in the control group at 5 years. Although the preponderance of this evidence now appears to exculpate rosiglitazone from the concern regarding ischemic heart disease, it does not indicate a clear benefit in this regard either.

Lastly, an unanticipated complication seen with both TZDs is an increase in observed long bone fractures in woman participating in PROactive [54] and rosiglitazone trials (ADOPT) [24]. In both cases, the fracture rates were approximately double (5.1% vs 2.5%: PROactive) that of comparator groups, were seen early and were unrelated to diabetic control. A potential mechanism may relate to PPAR involvement in osteoblast cell differentiation [57], but this remains incompletely understood. Consideration should be given to screening for fracture risk including at the wrist to assess cortical bone in patients on TZD therapy at initiation and periodically thereafter until further information regarding the mechanism of the increased fracture rate associated with TZD usage is provided.

Taken together, the adverse event profile for the rosiglitazone without compelling evidence for specific cardiovascular benefit suggests use of this agent be reserved for patients unable to tolerate alternative drug regimens. This is in concordance with the current ADA/EASD recommendations. It should be acknowledged that this recommendation is controversial and we may see revision of this in due course.

Incretin therapy combinations

The recent availability of incretin mimetics, either glucagon-like peptide 1 (GLP-1) receptor agonists, such as exenatide and liraglutide, or dipeptidyl peptidase 4 (DPP-4) inhibitors, such as sitagliptin, saxagliptin, alogliptin and vildagliptin, has opened up new possibilities in combination therapy [58]. Exenatide is an injectable synthetic analog of the Gila monster (*Heloderma suspectum*) salivary protein exendin 4. This compound has substantial homology with GLP-1 and tightly binds to GLP-1 receptors and thereby mimics the actions of native GLP-1 when given in doses of 5 or 10 μg twice daily. Three registration trials of similar design show the use of exenatide in 30-week long studies in patients with oral agent failure with sulfonylureas [59], metformin [60] or both [61]. After a 4-week placebo run in, subjects were randomized to blinded placebo versus exenatide 5 μg twice daily for 1 month and then continued this dose or increased to 10 μg twice daily. All subjects continued their prior oral agents.

When exenatide versus placebo was added to metformin, 272 patients completed the study [60]. They were middle-aged (53 ± 10 years), obese (34.2 ± 5.9 kg/m^2 BMI) and with inadequate glycemic control (HbA_{1c} 8.2 ± 1.1% [66 mmol/mol]). At 30 weeks, the HbA_{1c} change from baseline was −0.78 ± 0.1% (10 μg), −0.4 ± 0.11% (5 μg) and 0.08 ± 0.1% for placebo; $P < 0.002$, (8, 4 and 1 mmol/mol, respectively). Exenatide was associated with weight loss: −2.8 ± 0.5 kg (10 μg), −1.6 ± 0.4 kg (5 μg); $P < 0.001$ versus placebo. Gastrointestinal side effects including nausea, vomiting and diarrhea were more common with exenatide but lessened toward the end of the trial. In the 5 and 10 μg groups, exenatide resulted in a placebo subtracted percentage for nausea of 11% and 22%, for vomiting 7% and 8%, and for diarrhea 4% and 8% overall during the study.

In the sulfonylurea failure study [59], the study population was similar with obese middle-aged subjects with slightly higher baseline glycemia (HbA_{1c} 8.6 ± 1.2% [70 mmol/mol]). The change from baseline HbA_{1c} at 30 weeks was −0.86 ± 0.11 (10 μg), −0.46 ± 0.12 (5 μg) and 0.12 ± 0.09% (placebo); $P < 0.001$, (9, 5 and 1 mmol/mol, respectively). Weight loss was somewhat less with 10 μg than in the metformin alone study (−1.6 kg). The third trial was for patients inadequately controlled on the combination of effective doses of sulfonylurea and metformin. Similar subjects were studied with middle-aged, obese, poorly controlled subjects (baseline HbA_{1c} 8.5 ± 1.0% [69 mmol/mol]). The change from baseline HbA_{1c} occurred at 30 weeks was −0.8 ± 0.1% (10 μg), −0.6 ± 0.1% (5 μg) and 0.2 ± 0.1% (placebo); $P < 0.0001$, (9, 7 and 2 mmol/mol, respectively). Weight loss in this study averaged 1.6 kg for the 10 μg dose group and was similar to the sulfonylurea alone study.

A similar study has been conducted showing comparable glycemic benefit in patients in a thiazolidinedione alone or with metformin to which 5 and then 10 μg doses of exenatide were added for 16 weeks [62]. Again, approximately 1% (11 mmol/mol) reduction in HbA_{1c} occurred from a baseline of 7.9% (63 mmol/mol) in comparison to placebo controls and approximately a 30 mg/dL (1.7 mmol/L) decline in fasting glucose occurred with a greater weight loss in the exenatide group (~1.5 kg). Nausea was more common with exenatide (40 vs 15% for placebo) and the drop-out rate was also higher.

Is it reasonable to choose exenatide as an alternative to basal insulin therapy? Perhaps if patients are not very far from glycemic goal the answer may be yes. Heine *et al.* [63] reported a study of 551 subjects with T2DM who were inadequately controlled. They were randomized to either insulin glargine once a day at bedtime or 5 μg for 1 month then 10 μg exenatide for the duration of this 26-week long trial. Baseline HbA_{1c} was 8.2% (66 mmol/mol) for patients receiving exenatide and 8.3% for those on insulin glargine. By study end, exenatide and insulin glargine therapies resulted in equal reduction of HbA_{1c} levels by 1.11% (12 mmol/mol). Exenatide reduced post-prandial plasma glucose levels more than insulin glargine, while insulin glargine reduced FPG levels more than exenatide. This is well illustrated in the seven-point self-monitored glucose levels before and after meals and at 3 AM performed at study beginning and end. Body weight decreased 2.3 kg with exenatide and increased 1.8 kg with insulin glargine. Rates of symptomatic hypoglycemia were similar, but nocturnal hypoglycemia occurred less frequently with exenatide (0.9 vs 2.4 events/patient-year). Gastrointestinal symptoms were more common in the exenatide group than in the insulin glargine group, including nausea (57.1% vs 8.6%), vomiting (17.4% vs 3.7%) and diarrhea (8.5% vs 3.0%). Despite similar lowering of HbA_{1c}, there were marked differences in prandial versus preprandial control, suggesting these interventions had different patterns of benefit.

In all of the studies of exenatide in which sulfonylureas were used, an increased risk of hypoglycemia occurred that sometimes required a reduction in sulfonylurea dose to reduce the risk of hypoglycemia symptoms. In patients on sulfonylureas treated with exenatide (and likely also with DPP-4 inhibitors), it may be appropriate to pre-emptively reduce sulfonylurea doses by half if patients' lowest blood sugars are less than 100 mg/dL because the glucose-dependent insulin secretion with this combination is lost as a result of the sulfonylurea. Taken together, these studies suggest that exenatide may represent a desirable alternative for overweight patients for whom lifestyle intervention alone is insufficient in improving weight and who also need improved glycemia control but are reluctant to use insulin.

One study by Nauck *et al.* [64] studied exenatide twice daily (n = 253) vs biphasic insulin aspart (70/30, n = 248) in patients poorly controlled on metformin and sulfonylureas in a non-inferiority analysis. Exenatide was found to be non-inferior with a mean ± SEM decrease in HbA_{1c} from baseline of −1.04 ± 0.07% (11 mmol/mol), and for biphasic insulin aspart it was −0.89 ± 0.06% (10 mmol/mol); the difference was −0.15% ((5% CI −0.32 to 0.01%). Exenatide-treated patients lost weight and had nausea in 35%, while patients treated with biphasic insulin aspart gained weight (between-group difference −5.4 kg; 95% CI −5.9 to 5.0 kg). Both treatments reduced fasting glucose (exenatide −1.8 ± 0.2 mmol/L, $P < 0.001$; biphasic insulin aspart −1.7 ± 0.2 mmol/L, $P < 0.001$). Greater reductions in post-

prandial glucose excursions at all meals were observed with exenatide. The withdrawal rate was 21.3% (54/253) for exenatide and 10.1% (25/248) for biphasic insulin aspart.

In a second study which compared 70/30 insulin aspart analog mixture, as alternatives for patients failing oral agent therapy, Bergenstal *et al.* [65] found that more patients responded to the biphasic insulin than to exenatide. The higher baseline HbA_{1c} (10.2% [88 mmol/mol]) was thought to reflect more advanced disease and thus would be associated with less β-cell function, which is a requirement for full clinical response to exenatide.

Although not approved for use together, exenatide with insulin therapy is reportedly used in patients with T2DM. The rationale is based upon the potential insulin sparing effects of exenatide presumably through its multiple effects to augment insulin and reduce glucagon at meals as well as its effects upon gastric emptying, appetite and weight loss. Sheffield *et al.* [66] described a series of 134 patients initiating exenatide in combination with insulin in private endocrine practice with a 1-year follow-up. Exenatide use resulted in a 0.87% (9 mmol/mol) reduction of HbA_{1c}, despite a 45% discontinuation of premeal insulin, reduction in insulin injection number and discontinuation of sulfonylureas. Its use resulted in reduced weight slightly over 5 kg, although some weight loss was observed in 72% of patients. Slightly over one-third of patients (36%) discontinued the exenatide primarily because of gastrointestinal side effects, while 10% of patients had hypoglycemia. The authors have some experience with the use of exenatide with a basal insulin as an alternative for selected patients who have difficulty with accurate dosing of meal insulin in combination with basal insulin, which mirrors the experience reported in this case series.

Liraglutide is a GLP-1 analog with 97% homology to human GLP-1 which has now had several clinical trials, and has now been approved by the US FDA and European Medicines Agency. Phase 3 trials have included monotherapy and trials in combination with either metformin, with sulfonylureas or the combination of the two oral agents. In a 52-week study [67], doses of 1.2 and 1.8 mg were given once daily to 746 patients with early T2DM. The subjects in this study were randomly assigned to once daily liraglutide (1.2 mg [n = 251] or 1.8 mg [n = 247]) or glimepiride 8 mg (n = 248). The primary outcome was change in HbA_{1c} from baseline. The analysis was by intention-to-treat. At 52 weeks, the HbA_{1c} was decreased by 0.51% (SD 1.20%) with glimepiride, compared with 0.84% (1.23%) with liraglutide 1.2 mg (difference –0.33%; 95% CI –0.53 to –0.13; $P = 0.0014$) and 1.14% (1.24%) with liraglutide 1.8 mg (–0.62; –0.83 to –0.42; $P < 0.0001$). Five patients in the 1.2 mg liraglutide, and one in 1.8 mg groups discontinued the treatment because of vomiting, but none in the glimepiride group did so. The frequently self-monitored blood glucose profiles appear to show very good fasting glucose control, although interestingly a bit less marked blunting of post meal glucose than in some of the exenatide studies. There is no direct comparison with exenatide in this study.

In a multiple-arm study [68] of 1041 adults with T2DM with an average age of 56 ± 10 years (mean ± SD) over 26 weeks, liraglutide (0.6, 1.2 or 1.8 mg/day) or rosiglitazone (4 mg/day) or placebo was added to glimepiride monotherapy. Liraglutide (1.2 or 1.8 mg) reduced HbA_{1c} from baseline more (–1.1% [12 mmol/mol]; baseline 8.5% [69 mmol/mol]) when compared with placebo (+0.2% [2 mmol/mol]; $P < 0.0001$; baseline 8.4% [68 mmol/mol]) or rosiglitazone (–0.4% [4 mmol/mol]; $P < 0.0001$; baseline 8.4% [68 mmol/mol]). A lower dose of liraglutide was less effective and only reduced HbA_{1c} by 0.6% (7 mmol/mol). Fasting plasma glucose decreased by week 2, with a 1.6 mmol/L decrease from baseline at 26 weeks with liraglutide 1.2 mg (baseline 9.8 mmol/L) or 1.8 mg (baseline 9.7 mmol/L) compared with a 0.9 mmol/L increase with placebo ($P < 0.0001$; baseline 9.5 mmol/L) or 1.0 mmol/L decrease with rosiglitazone ($P < 0.006$; baseline 9.9 mmol/L). Post-prandial plasma glucose decreased more from baseline with liraglutide 1.2 or 1.8 mg (–2.5 to –2.7 mmol/L [baseline 12.9 mmol/L for both]) compared with placebo (–0.4 mmol/L; $P < 0.0001$; baseline 12.7 mmol/L) or rosiglitazone (–1.8 mmol/L; $P < 0.05$; baseline 13.0 mmol/L). Changes in body weight with liraglutide 1.8 mg (–0.2 kg; baseline 83.0 kg), 1.2 mg (+0.3 kg; baseline 80.0 kg) or placebo (–0.1 kg; baseline 81.9 kg) were less than with rosiglitazone (+2.1 kg; $P < 0.0001$; baseline 80.6 kg). The adverse events for all treatments were minor hypoglycemia (<10%), nausea (<11%), vomiting (<5%) and diarrhea (<8%).

A recently published article studied the addition of liraglutide [69] in 533 patients with diabetes failing on oral agents, randomizing them in a 1:1:1 ratio to liraglutide 1.2 or 1.8 mg daily or placebo in addition to rosiglitazone 4 mg twice daily and metformin 1 g twice daily for 26 weeks. HbA_{1c} values decreased significantly more in the liraglutide groups vs placebo (1.5 ± 0.1% for both liraglutide 1.2 and 1.8 mg and –0.5 ± 0.1% for placebo [mean ± SE]). FPG decreased by 40, 44 and 8 mg/dL for liraglutide 1.2, 1.8 and placebo, respectively, and 90 minutes post meal post-prandial plasma glucose (PPG) decreased by 47, 49 and 14 mg/dL, respectively ($P < 0.001$ for all liraglutide groups vs placebo). Dose-dependent weight loss occurred with liraglutide 1.2 and 1.8 mg (1.0 ± 0.3 and 2.0 ± 0.3 kg, respectively; $P < 0.0001$) as compared to weight gain with placebo (0.6 ± 0.3 kg). Interestingly systolic blood pressure decreased by 6.7, 5.6 and 1.1 mmHg with liraglutide 1.2, 1.8 mg, and placebo, respectively. These data, dissimilar to some with exenatide, suggest a greater effect on fasting glucose control and a more commensurate change in fasting with post-prandial control. A 26-week head-to-head comparison of exenatide 10 μg twice daily with liraglutide 1.8 mg daily showed a 0.3% (3 mmol/mol) greater reduction in HbA_{1c} with liraglutide in a population of adults with inadequately controlled T2DM on maximally tolerated doses of metformin, sulphonylurea, or both [70]. Furthermore, more patients receiving liraglutide achieved an HbA_{1c} of less than 7% (54%vs 43%). Liraglutide also reduced mean fasting plasma glucose more than did exenatide. Both drugs promoted similar weight losses but nausea was less persistent and minor hypoglycaemia was less frequent with liraglutide.

Drucker *et al.* [71] have compared exenatide with a longer acting preparation given once weekly of the same agent. This randomized non-inferiority study compared long-acting release

exenatide 2 mg once weekly with 10 µg exenatide administered twice daily, in 295 patients with T2DM (HbA_{1c} 8.3% ± 1.0 SD [67 mmol/mol]), mean fasting glucose 9 ± 2 mmol/L, weight 102 ± 20 kg and diabetes duration of 6.7 ± 5.0 years. The patients were either naive to drug therapy or on one or more oral antidiabetic agents. The primary endpoint was change in HbA_{1c} at 30 weeks. At study endpoint the patients given exenatide once a week had lower HbA_{1c} than those on exenatide twice daily (−1.9 ± 0.1%; SE vs −1.5 ± 0.1%; (95% CI −0.54% to −0.12%; $P = 0.0023$). More patients receiving treatment once weekly vs twice daily achieved HbA_{1c} levels of 7.0% (53 mmol/mol) or less (77% vs 61%; $P = 0.0039$). Again, in this trial as in the liraglutide studies there appears to be more effect upon fasting glycemic control than with twice daily exenatide. It is a little difficult to know if in this study differences were to be attributed mostly to kinetics differences or changes in the achieved levels of the incretin mimetic in the blood at the end of the study. However, the ability to lower fasting control to a greater degree than currently available with exenatide seems an important observation and may relate to overall antihyperglycemic efficacy.

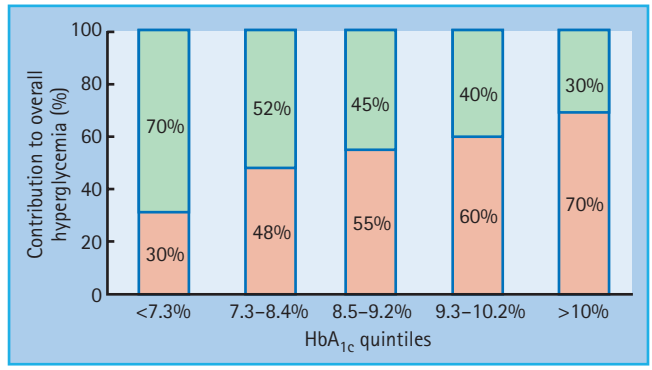

Figure 31.7 The relative contribution of fasting plasma glucose (FPG; shown in the open bars) and the post-prandial plasma glucose (PPG; shown in the shaded bars) to overall hyperglycemia. An area-under-the-curve analysis suggests that as HbA_{1c} approaches the ADA goal for minimum desirable glycemic control (<7.0% [53 mmol/mol]), the PPG makes a greater contribution to overall hyperglycemia. Conversely, as the HbA_{1c} rises far from goal, the contribution of FPG to overall hyperglycemia is greater. For patients with poor hyperglycemia a focus on the fasting glucose thus becomes an important priority. As patient approach targeted glycemic goals a greater attention should be directed to post-prandial hyperglycemia. The equivalent IFCC units for the quintiles are: <56 mmol/mol, 56–58 mmol/mol, 69–77 mmol/mol, 78–88 mmol/mol, >88 mmol/mol,

DPP-4 inhibitors

Incretin action can also be provided by inhibiting the rapid degradation of GLP-1 and glucose-dependent insulinotropic peptide (GIP). Although with DPP-4 inhibition the level of circulating GLP-1 agonist activity probably does not rise to a degree similar to that seen with receptor agonists such as exenatide and liraglutide, the glycemic lowering efficacy of sitagliptin and vildagliptin is close to that seen with injectable receptor agonists. Vildagliptin 50 mg once daily added to patients inadequately controlled on metformin (baseline HbA_{1c} 7.7% [61 mmol/mol]) resulted in a placebo subtracted difference in HbA_{1c} at 52 weeks of −1.0 ± 0.2% (11 mmol/mol, $P < 0.001$) [72].

Vildagliptin combined with a sulfonylurea or a thiazolidinedione also improved glycemia in patients with T2DM in trials of 24–52 weeks. In patients inadequately controlled with metformin, added vildagliptin 100 mg/day was non-inferior to add on therapy with pioglitazone; each treatment reducing HbA_{1c} an additional 1% (11 mmol/mol) [73]. Vildagliptin is also available as a fixed-dose formulation with metformin. Vildagliptin has also been studied by Fonseca *et al.* [74] added to insulin treatment and has a small additional effect (approximately 0.3% [3 mmol/mol] HbA_{1c} lowering) when compared with placebo. In an interested recent physiologic study, Ahren *et al.* [75] have found that glucagon responsiveness is not only suppressed with a glucose challenge with vildagliptin, but there is also a slight improvement in glucagon increment to insulin hypoglycemia.

DPP-4 inhibitors do not cause nausea and vomiting and are weight neutral, lacking the weight-reduction effects of the GLP-1 agonists observed at 1 year. This is likely because of lower levels of GLP-1 activity. Sitagliptin has been studied as monotherapy [76,77] and as additional treatment for those not meeting glycemic goals on either metformin [78] or a thiazolidinedione [79]. In doses of 100 mg for patients with normal renal function in two monotherapy studies of 18 and 24 weeks' duration, sitagliptin reduced HbA_{1c} by 0.6% (7 mmol/mol) and 0.8% (9 mmol/mol), respectively. Added to either metformin or pioglitazone, it further reduced HbA_{1c} by 0.7% (8 mmol/mol) in 24-week duration studies. DPP-4 inhibitors are weight neutral, probably because of an appetite effect of raising endogenous GLP-1 levels. Their glycemic effects on peak prandial control appear superior to effects on preprandial control. This should complement the primarily preprandial effects of metformin or thiazolidinediones. Incretin drugs appear especially favorable for prandial glycemic control and may be favored also because of positive effects of weight loss or minimal weight gain. Prandial control has been observed by Monnier *et al.* [80,81] to be important particularly as HbA_{1c} nears goal (Figure 31.7). Also, if prandial euglycemia contributes to decreased cardiovascular risk through reducing oxidative stress then incretins could have an additional favorable action.

Colesevelam

After a pilot trial of 12 weeks' duration, 65 subjects with T2DM showed that the addition of the bile acid sequestrant colesevelam reduced HbA_{1c} by 0.5% (5 mmol/mol, $P < 0.007$) as well as the expected lipid benefit [82]. Further studies have examined combination therapy in several different groups. Bays *et al.* [83] looked at its effects in doses of 3.75 g/day (n = 159) compared with matched placebo (n = 157) in subjects with T2DM on met-

formin and other diabetes oral agents, confirming the early pilot with a reduction of HbA_{1c} of 0.54% (6 mmol/mol, $P < 0.001$). Those on metformin alone were reduced by 0.47% compared with placebo; those on combined therapy (mostly sulfonylureas, or glitazones and a few other agents) were reduced by 0.62% (7 mmol/mol). Goldberg *et al.* [84] found that patients who were on insulin therapy but not adequately controlled also show the similar level of glycemic benefit after 16 weeks when compared with placebo (−0.41% HbA_{1c} for colesevelam vs +0.09% for the placebo group; $P < 0.001$). Fonseca *et al.* [85] found that patients on sulfonylureas given colesevelam 3.75 g/day for 26 weeks showed a placebo corrected difference of −0.54% (6 mmol/mol) HbA_{1c}. Overall, these data suggest a modest consistent benefit of colesevelam, on average of 0.5% (6 mmol/mol) reduction in HbA_{1c}, in people with T2DM on a variety of combination regimens. The drug is well known and may certainly cause hypertriglyceridemia in those who have pre-existing high levels of triglycerides (usually >250 mg/dL would be high risk). In addition, like other bile acid sequestrants it may cause constipation. With absent high triglycerides at baseline, it is both safe and likely in patients on statins to reduce low density lipoprotein (LDL) cholesterol significantly and contribute to achieving cardiovascular risk reduction.

Transition to insulin

Current consensus guidelines endorse early adoption of insulin therapy. In general, insulin is an underutilized therapy as a result of both patient and provider hesitance to adopt an injectable therapy associated with weight gain and potential severe life-threatening hypoglycemia. Attention to patient reluctance and provider barriers can maximize successful initiation of insulin therapy. Providing simple patient titration schemes enhance practitioner and patient acceptance [86]. Combination insulin (parenteral) and sulfonylurea (oral) therapy has been widely studied and provides a basis for many later basal insulin studies. Twice daily (bedtime insulin, daytime sulfonylurea) therapy [87–90] was shown to be an effective therapy prior to the widespread use of metformin in the USA. The use of bedtime insulin suppressed hepatic glucose output and facilitated the use of sulfonylurea for prandial insulin support.

Initiation of insulin therapy can be performed safely and efficiently with the addition of a basal insulin (NPH, glargine, detemir) with titration of dosage to desired target blood glucose. Several studies and reviews support the safety and effectiveness of this approach [6,91–95].

An alternative to a single dose of basal insulin, which has similar overall efficacy but a different pattern of control, is prandial dosing. The APOLLO trial (Figure 31.8) [93] examined basal once daily insulin glargine in comparison to three times a day insulin lispro at meals in 418 subjects with inadequate glycemic control while on oral diabetes agents. In this study, which was 44 weeks in duration, the HbA_{1c} drop was similar (−1.7% [19 mmol/mol] for glargine −8.7% [72 mmol/mol] to 7% [53 mmol/mol], −1.9% [21 mmol/mol] for lispro – from 8.7% [72 mmol/mol] to 6.8% [51 mmol/mol]), and as might be expected from the kinetics and timing of the insulin preparations showed superior fasting glycemic control with insulin glargine (−4.3 vs −1.8 mmol/L; 77 vs 32 mg/dL) and better nocturnal control but less effective daytime control (each by about 0.5 or 10 mg/dL). Not surprisingly in this open label study, patients found it preferable to use once daily injection. Subjects taking glargine had fewer hypoglycemia episodes than those on lispro. This study suggests that either meal insulin or basal can be used to achieve improved control although patient preference suggests a basal insulin strategy.

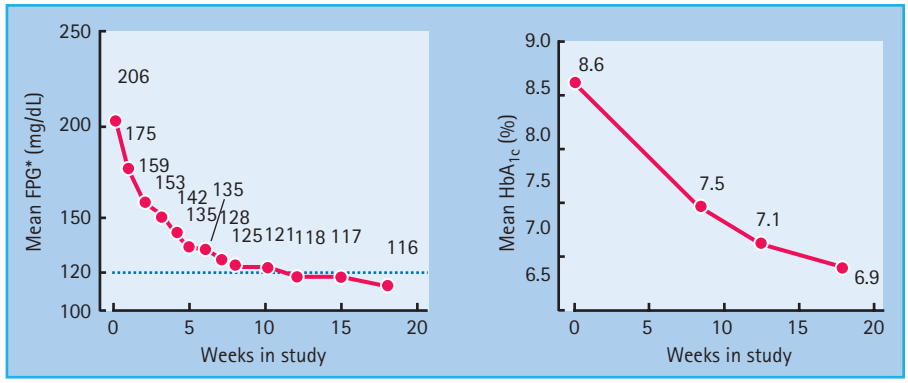

Figure 31.8 From the APOLLO study, nine-point self-monitored blood glucose profiles in the APOLLO trial. This open labeled study compared the effects of once daily insulin glargine in comparison to lispro three times daily at meals. Average glycemia and HbA_{1c} were similar, although hypoglycemia was increased with lispro while weight gain was similar in the two groups. The pattern of glycemia reveals that fasting glucose control improved to a greater degree with glargine and that as one would expect prandial control is better with lispro. These two strategies are complementary in the glycemic patterns suggesting that using basal insulin and some meal analog insulin may be a useful strategy for many patients. The highest increase in prandial glycemia occurred at breakfast and dinner [94].

Combining insulin and oral agent therapy

Insulin therapy is eventually needed for most patients with T2DM. An evening insulin strategy is a simple way to begin insulin therapy that will achieve glycemic goals and is easily understood by patients. The rationale for evening insulin has previously been reviewed [86,91,92]. In brief, an evening injection of intermediate- or long-acting insulin addresses a fundamental need in management of T2DM by suppressing overnight endogenous glucose production and thereby preventing hyperglycemia prior to the first meal of the day. This approach is useful for most patients with T2DM, with the notable exception of patients taking morning glucocorticoid therapy.

There are several versions of this strategy, including the use of intermediate-acting insulin at bedtime, intermediate and quick-acting insulin mixed in a single injection at dinnertime, and insulin glargine or insulin detemir at bedtime. For some patients, an alternate timing of glargine may be used earlier in the day; for those using large doses (0.8 units/kg) of detemir use early in the day may also be possible. Most of the evidence for these regimens comes from trials of insulin combined with oral agents, such as a sulfonylurea alone or with metformin, with the oral agents continued while the insulin dosage is gradually increased until control is re-established.

NPH at bedtime

Addition of an injection of NPH insulin within an hour of bedtime is usually able to restore adequate fasting glycemic control for patients who are no longer well-controlled with one or more oral agents alone. This tactic may be best employed in patients who do not eat a very large meal toward the end of the day and thus do not need short-acting insulin at suppertime. A multicenter trial has shown bedtime NPH insulin plus daytime oral agents achieves glycemic control as effectively as insulin taken in the morning with oral agents, or mixed intermediate and regular insulin twice daily without oral agents; however, there is less weight gain with evening NPH [89]. Other trials show better glycemic control with bedtime NPH plus a sulfonylurea than with a single injection of insulin alone [87,88]. Evening NPH insulin also reduces free fatty acids to a greater degree than use of daytime insulin. Patients can begin with a low dose of NPH insulin, usually about 10 units. They are instructed to self-titrate the dose up by 2–4 units every 3–7 days based upon the stability of their fasting glycemic response [86]. Stable patients may titrate more quickly, based upon the pattern of response, but there is little reason to hurry because glucose control will steadily improve at any rate of titration so long as the oral agents are continued. The insulin dosage required is frequently in the range of 30–50 units daily [91], or about 0.4–0.5 units/kg body weight. The target for fasting glucose should be individualized and adjusted when hypoglycemia occurs, but often can be ADA recommended 90–130 mg/dL (5–7.2 mmol/L) value in plasma-referenced home glucose-monitoring systems. Patients need to wake at a reasonably consistent time and eat breakfast consistently. Oral agents are continued, although sulfonylureas are usually given only with the first meal of the day. A randomized trial has examined the choice of daytime therapy accompanying bedtime NPH insulin [89]. This study compared four different regimens in a prospective 1-year randomized controlled trial. The four regimens included bedtime insulin combined with morning insulin, glyburide alone, metformin alone or glyburide combined with metformin. The least weight gain occurred when metformin was the only oral agent, and hypoglycemia was a limiting factor when glyburide was used.

Pre-mixed insulin with the evening meal

A second form of evening insulin that appears to work better for more obese patients (BMI >30 kg/m^2) is the combination of morning sulfonylureas and suppertime mixed insulin, the latter commonly offered as 70/30 (70% NPH with 30% Regular) insulin. In a multicenter study using the long-acting sulfonylurea glimepiride [90], patients achieved a more rapid restoration of glycemic control with self-titration of 70/30 insulin while continuing the oral agent, rather than with insulin alone. Insulin was started at 10 units and titrated weekly, seeking FPG equivalent to 140 mg/dL (7.8 mmol/L, plasma-referenced). Nearly all subjects using the combination regimen reached the titration target rapidly, but 15% of the subjects in the placebo plus insulin group dropped out, mainly because of hyperglycemia during the transition to insulin. The mean HbA_{1c} declined from almost 10% (86 mmol/mol) to 7.6% (60 mmol/mol) for subjects completing the trial in both groups. The mean dose in the insulin alone group was 78 units and for the glimepiride plus insulin combination was 49 units. More subjects in this study who were on insulin alone needed doses higher than 100 units daily, and so had to take more than one injection. A smaller study with a more aggressive titration scheme found better glycemic control using 70/30 insulin with the evening meal plus glyburide once daily than with evening insulin alone [83]. Premixed rapid analog mixes [e.g. lispro–neutral protamine lispro (25/75%) and aspart–neutral protamine aspart (30/70%)] similarly may achieve control with somewhat more convenient meal timing of insulin. It is critical for safety that patients understand the appropriate timing of meals and do not skip meals. Garber *et al.* [96] have reported a small observational study using either once, twice or three times daily administration at meal time of the 70/30 aspart mixture in patients inadequately controlled or oral agents with or without basal insulin treatment. In this study, once daily administration at dinner of 70/30 reduced HbA_{1c} by 1.4% (15 mmol/mol), twice daily at breakfast and supper by 1.9% (21 mmol/mol) and thrice daily with an added lunch dose by 1.8% (20 mmol/mol). Use of insulin pens at meal times is often desirable especially for those who eat outside the home frequently. Pre-mixed insulins are commonly given twice a day, sometimes more or less frequently. When given more frequently they may become somewhat non-intuitive as to which dose to adjust and this may confuse some patients.

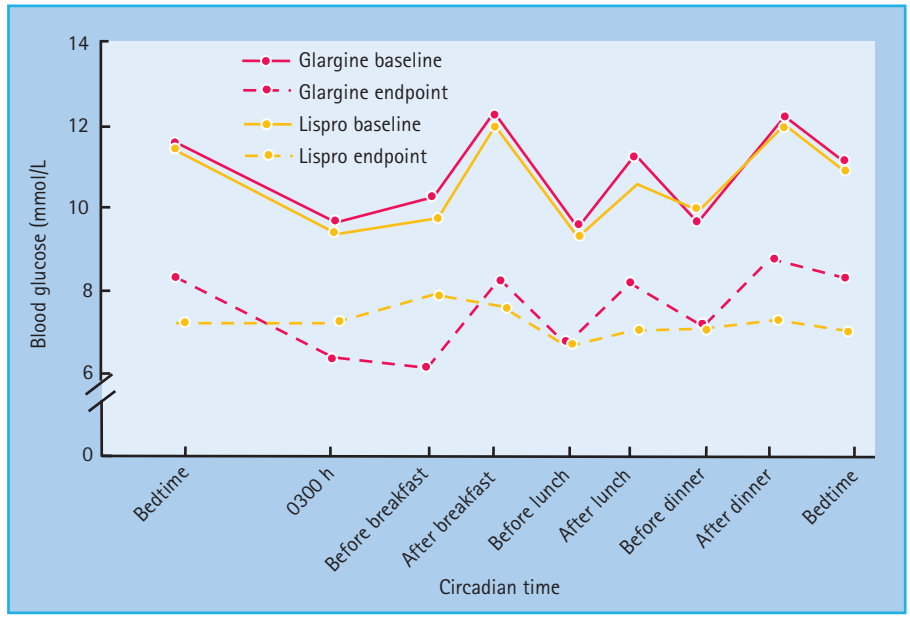

Figure 31.9 Improved metabolic control with patient titration of insulin. Metabolic control (FPG and HbA_{1c}) improved in all insulin-treated patients in the treat to target study. Based upon a forced titration strategy of increases between 2 and 8 units each week based upon average fasting plasma glucose (FPG; an average of 2 days) after starting with 10 units, the course of FPG (solid line) and HbA_{1c} (dotted line) are depicted on the left and right of the above figure. By week 18, FPG decreased from 206 mg/dL to 116 mg/dL ($P = 0.0001$) and HbA_{1c} decreased from 8.6% to 6.9%. To convert to mmol/L divide FPG values by 18. DCCT result (%) = (0.0915 × IFCC result in mmol/mol) + 2.15.

Insulin glargine at bedtime

A study using insulin glargine [97] suggested this agent offers another option for starting insulin with an evening injection. In this 1-year European study, 426 subjects were randomly assigned to either insulin glargine or NPH insulin at bedtime, while continuing previous oral therapy. The therapeutic target was a fasting blood glucose <120 mg/dL (6.7 mmol/L), using a method that was probably not plasma-referenced. The insulin dosages used (23 units for glargine and 21 for NPH) and HbA_{1c} values achieved (8.3% and 8.2%, 67 mmol/mol and 66 mmol/mol) were similar with the two insulins, but the rates of hypoglycemia were significantly less for the group using glargine (33% vs 51% for all symptomatic hypoglycemia), despite similar average insulin doses. Nocturnal hypoglycemia occurred in less than half as many subjects using glargine (13% vs 28%). Moreover, glucose control was better in the afternoon and evening with glargine, presumably because of its longer duration of action than NPH.

The Treat to Target Trial (Figure 31.9) [91], also compared insulin glargine with NPH insulin at bedtime. Subjects in this study averaged a baseline HbA_{1c} of 8.6% (70 mmol/mol). Both NPH and glargine study groups were instructed to initiate doses of 10 units of insulin at bedtime and each week the dose was raised between 0 and 8 units based upon how close the subjects were to the glycemic goal (<5.5 mmol/L; 100 mg/dL). This forced weekly titration of dose based upon fasting glucose concentration with patient self-adjustment according to the pattern of therapy response was a key concept in reaching the targeted goal of HbA_{1c} <7% (<53 mmol/mol) in about 60% of patients in this study on both NPH and glargine insulin. Subjects in this study did not need to achieve the targeted FPG because hypoglycemia would have been too frequent. Hypoglycemia overnight was more common with NPH insulin as might be expected based upon the differences in kinetics of NPH versus glargine with the former having a greater peak effect usually within the first 4–8 hours after subcutaneous administration.

Insulin detemir

Insulin detemir is a newer formulation of intermediate- to long-acting insulin with a duration of effect in type 1 diabetes single-dose studies that is dose-dependent. Based upon a common dosage of 0.4 units/kg, an average duration of action of about 20 hours is predicted. With higher doses a longer duration approaching 24 hours is achieved [98]. In one study [99], twice daily insulin therapy with NPH versus detemir was compared in subjects with T2DM inadequately controlled (HbA_{1c} 8.5% [69 mmol/mol] and 8.6% [70 mmol/mol] for NPH and detemir, respectively) on therapy (mostly metformin plus secretagogues with some use of α-glucosidase inhibitors and about 30% of subjects not on oral agents when insulin was used). A total of 475 subjects were randomized to participate in a 24-week study comparing twice daily administration of these two insulins at breakfast and bedtime. Starting with 10 units per injection subjects were instructed to titrate doses every 3 days based upon pre-dinner and pre-breakfast self-monitored glucose averages from 2 up to 10 units per injection. At 24 weeks, subjects with insulin detemir decreased HbA_{1c} by 1.8% (20 mmol/mol) to an average value of 6.8% (51 mmol/mol), while subjects on NPH decreased the HbA_{1c} by 1.9% (21 mmol/mol) to an average value of 6.6% (49 mmol/mol). Most subjects (about 70%) achieved HbA_{1c} less than 7% (<53 mmol/mol) but more subjects on detemir achieved the goal without hypoglycemia. Overall hypoglycemia was significantly less on detemir, which by non-inferiority analysis was comparable in overall glycemic lowering efficacy to NPH. Doses of insulin were a bit higher than might have been expected (36.1 units in the morning and 29.5 units in the afternoon for detemir; and 25.3 units in the morning and 19.7 units in the afternoon for

NPH) given that the average BMI of these patients was a little over 29 kg/m^2. Detemir can be administered once in the evening or twice daily. Its desirable features include a lower rate of hypoglycemia, somewhat greater consistency in glycemic response from day to day, and possibly a reduced tendency for weight gain.

Optimal manner of initiating insulin and progressive insulin treatment

Recent studies have tried to readdress the issue of whether there is a best way to initiate insulin treatment. The strategy of basal insulin only vs the alternative of basal and prandial insulin combined continues to be addressed. The 4-T Study, which is a multicenter multiyear trial of insulin therapy carried out in an open-label manner is one such study [100]. In this study, 708 patients with HbA_{1c} of 7–10% (53–86 mmol/mol) while on maximally tolerated doses of metformin and sulfonylureas were randomized to receive biphasic insulin aspart (70/30) twice daily at breakfast and supper, prandial insulin aspart three times daily, or basal insulin detemir once daily or twice if required. The outcomes of this study included mean glycated hemoglobin level, the proportion of patients with a glycated hemoglobin level of 6.5% or less (<48 mmol/mol), the rate of hypoglycemia, and weight gain. At 1 year, mean HbA_{1c} levels were similar in the biphasic group (7.3%, 56 mmol/mol) and the prandial group (7.2% [55 mmol/mol]; $P = 0.08$) but higher in the basal group (7.6% [60 mmol/mol]; $P < 0.001$) for both comparisons. The proportions of patients with HbA_{1c} level of 6.5% or less were 17.0%, 23.9% and 8.1% in mixed insulin, prandial insulin and basal insulin, respectively. The average of hypoglycemic events per patient-year was 5.7, 12.0 and 2.3, respectively. The mean weight gains were 4.7, 5.7 and 1.9 kg, respectively. Rates of adverse events were similar among the three groups. After 3-years of treatment, the median HbA_{1c} ranged from 6.8–7.1% (51–54 mmol/mol) and did not differ between groups [101]; however, there were important differences between the regimens. Fewer participants receiving biphasic insulin reached a target of either of 6.5% (48 mmol/mol) or 7.0% (53 mmol/mol) than the other groups. Hypoglycemia rates were lowest in those who began with basal insulin while weight gain was highest in those who began with prandial insulin. The authors concluded that this study provides evidence to support the addition of basal insulin to oral therapy with subsequent intensification to a basal-bolus regimen as the preferred method of insulin initiation in people with type 2 diabetes. A subsequent editorial, however, felt that while it was clear that insulin initiation with basal insulin is preferred to prandial insulin, biphasic insulin may still provide an effective means of obtaining glycemia control for patients and clinicians wanting a less intensive insulin regimen [102].

In general, the authors' practice is to begin patients on either a weight-based dose (e.g. 0.2 unit/kg) or an arbitrary starting dose and titrate basal insulin weekly or every 3 days if quite stable with the dose, increase by 2–4 units if on low doses or by 10–20% of basal dose if higher insulin doses are needed or if the patient is poorly controlled. Patient self-titration is clearly more effective than waiting until the next physician visit and involves the patient in their own care.

When patients no longer can continue adequate glycemic control despite fasting glycemia in a desirable range or if erratic fasting control exists, the authors often add meal insulin at dinner or at the largest meal of the day based on weight (0.1 units/kg) or an arbitrary low dose and titrate upward by assessing 2-hour post-prandial glucose levels [93]. The overuse of basal insulin alone can lead to serious hypoglycemia overnight. When there is a history of overnight or early morning hypoglycemia, testing of post-prandial control is very important. Commonly, one needs to make at least a unit for unit trade-off between meal insulin and basal insulin; as the former increases, an equal decrease in basal insulin helps to minimize nocturnal hypoglycemia.

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