

Diabetes Facts and Guidelines

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The statements in this booklet are meant to be used as guidelines only. They are based on the experience of the author and, where noted, on current recommendations from professional organizations. As in any field of medicine, proper diabetes care must take into account the clinician's personal experience, the individual requirements and capacities of the patient, and the overall success of the therapeutic program as indicated by ongoing monitoring of the patient's status. Prescribing physicians should also have complete familiarity with information provided in the package inserts of the pharmacological agents described in this booklet.

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❖ Yale Diabetes Center

Inpatient Facts & Guidelines

❖ Hospital Glycemic Management

Overview

The inpatient management of hyperglycemia has been garnering increased interest over the past several years, as evidence mounts that good glucose control in this setting may have a beneficial effect on patient outcomes. Most of the data comes to us from the critical care setting, suggesting that lowering glucose reduces mortality, complications, and hospital stay, in at least selected groups of patients. The optimal targets, however, are controversial. Whether stringent control benefits patients outside of the ICU is unknown, although improving glucose control in all patients makes general good sense. The following glucose targets in hospitalized patients are considered reasonable and achievable:

- ICU: **140–180 mg/dL** (use IV insulin)
- General medical-surgical ward: **100–140 mg/dL** (pre-meal), **100–180 mg/dL** (random)

The following algorithms provide general guidelines for managing patients in the ICU and the hospital wards. Several key questions must be considered when assessing a patient's glycemic management in the hospital:

1. What type of diabetes does the patient have? (Type 1, Type 2?)
2. What is the patient's outpatient antihyperglycemic regimen? (insulin, oral agents?)
3. How well is it controlling the patient's blood glucose (HbA1c)?
4. What is the patient's blood glucose on admission?
5. What is the patient's nutritional status? (NPO, normal diet?)

6. What is the reason for admission, and how long will the patient be hospitalized?

Physiological insulin replacement therapy will generally allow for the best control and the greatest flexibility. This typically involves 3 components:

- **Basal insulin** - to control glucose in between meals and suppress overnight hepatic glucose production; given as NPH BID, glargine QD, or detemir QD-BID.
- **Prandial insulin (sometimes referred to as "Nutritional insulin" or "Bolus insulin")** - to control post-prandial glucose spikes; given as a rapid-acting insulin analogue AC.
- **Correction insulin** - same type as and added to the prandial insulin to correct for pre-meal hyperglycemia (*for dosing recommendations, see [Sliding Scales](#), pp. 12–13*).

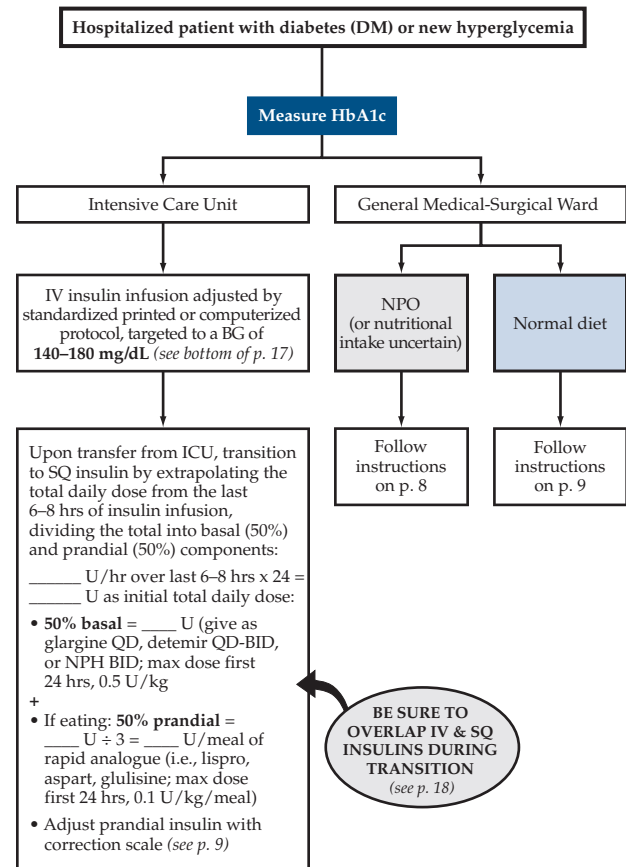
The suggested doses in the algorithms are approximations; actual doses will depend on several factors: the severity of the hyperglycemia, the patient's insulin sensitivity, calorie intake, the use of dextrose-containing IV fluids (especially TPN), glucocorticoid therapy, and the severity of the underlying illness. Careful ongoing assessment of the patient's response to therapy will best anticipate further dose adjustments, taking into account the many influences on glucose levels in the hospital. These include the frequent dyssynchrony of glucose measurement, meal consumption, and insulin administration. The clinician's aggressiveness in lowering glucose must also be guided by practical concerns, such as the trajectory of the patient's recuperation, the predicted duration of hospitalization, the nursing coverage and monitoring capacities within a specific hospital ward, the patient's ability to perceive any hypoglycemia that may result, and an overall realistic assessment of the potential benefit of stringent glucose control to a specific patient. Taking these issues into account, good glucose control in the hospital must be conducted under the guise of patient safety. An educated, trained hospital staff is the best assurance against untoward events.

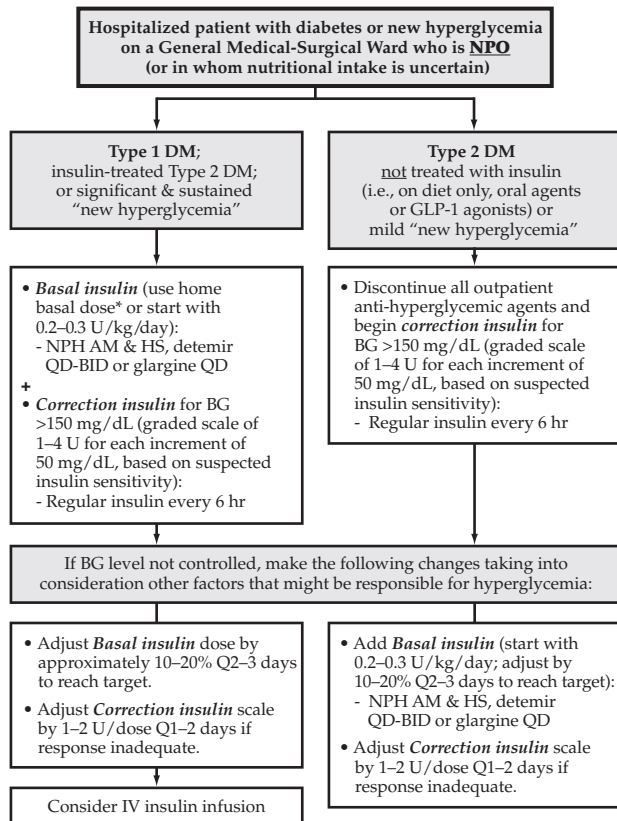
Other General Management Points

1. Avoid the temptation to “ignore” the patient’s diabetes. Although diabetes may not be the primary reason for the admission, it is frequently involved to some degree. Poor glycemic control during hospitalizations increases infectious complications, delays wound healing, and increases costs and length of stay. In addition, loss of glycemic control in a previously well-controlled patient with diabetes may undermine the doctor/hospital-patient relationship.
2. Try to distinguish true Type 1 from Type 2 patients (an older patient with diabetes may require insulin injections for glycemic control, but does not necessarily become “insulin dependent”). Type 1 patients will require at least some basal insulin at ALL times to prevent ketosis, even when they are NPO. Patients with “new hyperglycemia” should be treated as if they have diabetes since they appear to constitute an especially high-risk group.
3. Assess pre-admission diabetic medications and recent glycemic control (symptoms of hyper/hypoglycemia, home glucose monitoring results, and history of or presence of diabetic complications). Order HbA1c.
4. Influence of hospitalization on glucose levels will be difficult to predict because of effects of illness (↑), use of steroids (↑), pressors (↑), parenteral nutrition (↑), more rigid diet (↓), observed compliance with regimen (↓), inactivity (↑), etc. The tendency in most patients is for blood glucose to rise.
5. Diet should be individualized, based on body weight and other comorbidities (obesity, hyperlipidemia, hypertension, etc.); most will require a 1500, 1800, 2000, or 2400 kcal “diabetic diet” (include a bedtime snack). (*See Useful Formulas, pp. 90–91, to calculate caloric requirements.*) Obtain nutrition consultation.
6. Bedside glucose monitoring (“fingersticks”) QID in all patients with diabetes (pre-meal and HS if eating; Q6 hrs if

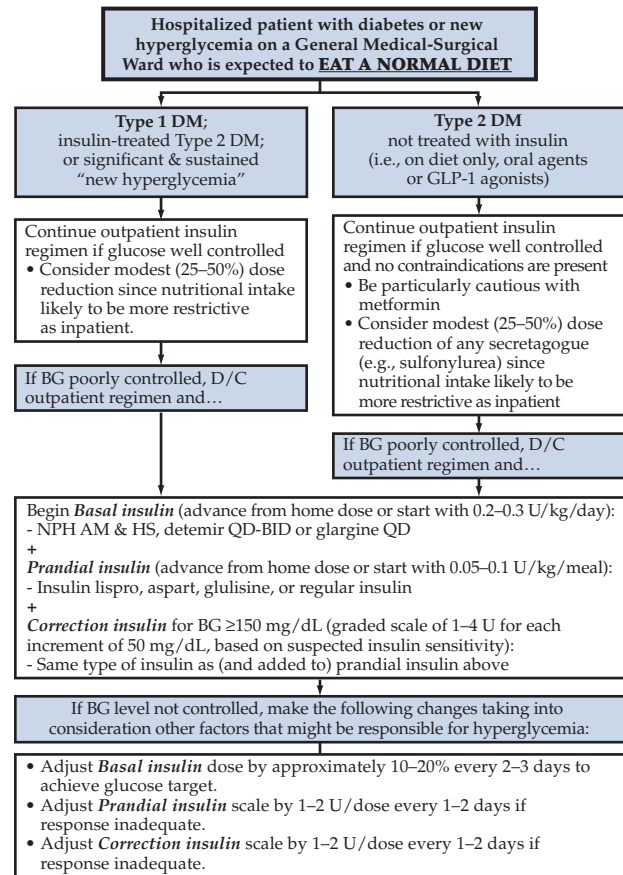
- NPO) for at least the first 48 hrs. If patient stable and under good glycemic control, and if on oral agent(s) or 1 insulin injection/day, can decrease to BID-TID.
7. The in-hospital blood glucose (BG) target in most non-ICU patients should be approximately 100–140 mg/dL before meals. Generally, post-meal checks (i.e., within 3 hours of the previous meal) should be avoided. Pregnant women may benefit from tighter control. The ADA currently endorses the following BG targets:
 - ICU patients: **140–180 mg/dL** (with goal as close to 140 as possible)
 - Non-ICU patients: **100–140 mg/dL** (pre-meal), **100–180 mg/dL** (random)
 These targets may change as new data emerge.
 8. Revise insulin regimen continuously (every 1–2 days), based on results of BG monitoring:
 - ↑ AM intermediate-acting insulin (e.g., NPH) to ↓ pre-supper BG
 - ↑ PM long/intermediate-acting insulin (e.g., glargine, detemir, NPH) to ↓ fasting BG
 - ↑ AM short/rapid-acting insulin (e.g., regular, lispro, aspart, glulisine) to ↓ pre-lunch BG
 - ↑ PM short/rapid-acting insulin (e.g., regular, lispro, aspart, glulisine) to ↓ bedtime BG
 In those patients managed with insulin infusion, adjust hourly to achieve target.
 9. Unless used for occasional “coverage” for short periods of time, do NOT leave patients on Regular Insulin Sliding Scale (RISS) as ONLY form of treatment! Adding long/intermediate-acting insulin (e.g., glargine, detemir, NPH) QD-BID, even at low doses, will significantly stabilize glycemic control, and is usually the preferred approach.

10. Try to approximate the ultimate at-home regimen as long as possible BEFORE discharge (as allowed by the patient's clinical condition). The regimen need not be perfected prior to discharge. It is rarely appropriate to extend the hospitalization to fine-tune the anti-hyperglycemic program. However, patients should also not be converted to conventional insulin regimens from RISS on the day of discharge. Patients with HbA1c <8% can usually be discharged on their pre-admission regimen. This regimen, however, should generally be advanced if the HbA1c is ≥8%.
11. Care is required when using rapid-acting insulin analogues (e.g., lispro, aspart, glulisine), due to frequent mistiming of hospital meals, as well as the common situation of a patient being summoned unexpectedly for off-ward tests/procedures. These insulins may be preferred, however, to improve post-prandial BG control.
12. Utilize the admission as a "teaching opportunity" for those patients who lack important knowledge about their diabetes or who need improvement in self-management skills. Obtain hospital diabetes nurse/educator consult; review proper BG monitoring and insulin injection technique with nursing staff; review diabetes "survival skills" (see *Diabetes Education*, p. 43). Provide brochures, videotapes, DVDs, etc.
13. Ensure that the discharge regimen is resulting in adequate glycemic control and that a follow-up visit with the primary care physician or other healthcare provider in charge of diabetes management is secured. Provide contact telephone number if problems arise. Inform patient about community resources to access further diabetes education.
14. Patients with newly discovered hyperglycemia that is mild should be reassessed as outpatients after resolution of their illness. Those with more significant hyperglycemia or with HbA1c ≥6.5% essentially have diabetes and should be so treated.





*Adjusted based on current degree of hyperglycemia; consider modest (20–25%) dose reduction if tightly controlled on admission, to be conservative.




❖ Bedside Glucose Monitoring ("Fingersticks," FSs)

- Should be done QID (ac and hs) for non-critically ill patients on most insulin injection regimens.
- For patients on oral agents alone or only 1 insulin injection per day, can be decreased to BID (pre-breakfast & pre-supper), if in good control.
- Fingersticks (FSs) should be done in correlation with Regular Insulin Sliding Scale (RISS) if written, and preferably pre-meal, if the patient is eating. Unless specific information is being sought, don't perform FS within 3 hours after a meal.
- If patient is NPO, FSs should be done Q6 hrs.
- In patients with hyperglycemia but without a prior h/o DM, check FSs BID-QID to assess status, depending on the degree of glucose elevation.
- Fingersticks should be recorded on bedside vital-sign log, along with the corresponding amount of insulin administered (all types of insulin). If possible, results should be downloaded into hospital's lab computer system for easy access to data.
- Newly diagnosed patients (or those who do not routinely perform fingersticks at home) should be educated on the technique at the time of routine hospital bedside monitoring.
- Healthcare institutions should have a written protocol for bedside BG monitoring that describes: staff training requirements, competency testing, routine meter maintenance, quality assurance, etc.

- The in-hospital BG target in most non-critically ill patients should be approximately 100–140 mg/dL (90–150 mg/dL is acceptable), with BG readings checked before meals. Generally, in this setting, post-meal checks should be avoided. Pregnant women may benefit from tighter control.

❖ Hypoglycemia Orders

- Check and record BG; treat as soon as blood obtained.
- Hypoglycemia is defined as any BG <70 mg/dL.
- Patient alert and cooperative: 15 g carbohydrates
 - 4 oz juice/soda = 15 g carbs;
 - 3 graham cracker squares = 15 g carbs.
-  **RULE OF THUMB:** 15 g carbs will ↑ BG 25–50 mg/dL.
- Non-alert patient: 25 g dextrose IV (1 amp D50) or 1 mg glucagon IM if no IV access (may repeat Q15–30 min); call MD; recheck BG after 10–15 min, depending on response.
- Goal is to achieve BG >100 mg/dL.
- If hypoglycemia severe (<40–50 mg/dL), recurrent, or related to sulfonylurea or long-acting insulin use, follow D50 with D5 or D10 drip.
- Continued follow-up is mandatory until stable, especially if hypoglycemia is due to sulfonylurea or long-acting insulin use, because of their long half-lives.
- Cause should be investigated.
- Adjust anti-hyperglycemic regimen, depending on situation.
- Document the event and its treatment.

❖ Regular Insulin “Sliding Scales” (RISS)

RISS should be discouraged as the sole anti-hyperglycemic treatment in hospitalized patients, since, in most circumstances, it does little more than respond too late to poor glycemic control during the preceding time interval. Instead, treatment of glycemia should be proactive with long/intermediate-acting insulins (e.g., glargine, detemir, NPH), in combination with fixed doses of short/rapid-acting insulins (e.g., regular, lispro, aspart, glulisine) (the latter of which can be adjusted based on results of BG monitoring). BG monitoring data are best utilized to adjust the fixed doses to be given on subsequent days. However, in certain T2DM patients who are NPO, in those in whom it is difficult to predict baseline insulin dosing requirements, or in patients with mild “new hyperglycemia” using RISS for 24–48 hrs is acceptable. Beyond that, the addition of long/intermediate-acting insulin (or beginning oral agents in stable patients) should be considered.

Short/Rapid-Acting Insulin* Dose

BG (mg/dL)	AC			HS
	Highly Insulin Sensitive	Normal Insulin Sensitivity (for most patients)	Highly Insulin Resistant	
<150	0U	0U	0U	
150–199	1U	2U	3U	
200–249	2U	4U	6U	
250–299	3U	6U	9U	0–2U
300–349	4U	8U	12U	2–4U
≥350	5U	10U	15U	4–6U

*Regular insulin is conventionally used for sliding scales. In patients who are eating, better post-prandial control is achieved with insulins lispro (Humalog®), aspart (NovoLog®), or glulisine (Apidra®).

Notes

- Prolonged use of sliding scales as the sole form of insulin coverage is strongly discouraged!
- Sliding scales, when used in patients who are eating, are preferably added to a baseline fixed dose of short/rapid-acting insulin (i.e., “correction dose”) and should always be timed with meals:
 - ① Regular insulin: 20–30 min AC [meal tray should be on ward]
 - ② Rapid-acting insulin analogues (lispro, aspart): 0–10 min AC [meal tray should be at bedside] (These analogues can even be given during or immediately after meals if amount of food to be consumed is unclear.)
- Hospitalized patients who are eating and require insulin should receive fixed mealtime doses of short/rapid-acting insulin to blunt post-prandial BG spikes. To this, “correction” doses of the same insulin type can be added to adjust for pre-meal hyperglycemia.
- In NPO patients, regular insulin should be given every 6 hours. If rapid-acting insulin analogues (e.g., lispro, aspart, glulisine) are used, dosing should be every 4 hours. Also, when patient is NPO, consider starting scale at a higher threshold (e.g., 200 mg/dL) to avoid hypoglycemia, especially in patients with Type 2 diabetes, whose BG may improve when fasting.
- In-hospital glucose target (non-ICU) = 100–140 mg/dL (pre-meal), 100–180 mg/dL (random). Try to maintain glucose values within or close to these ranges.
- Glycemic targets (and thresholds for scale initiation) should be increased for those at high risk for hypoglycemia, such as the malnourished, those with deteriorating renal function, adrenal insufficiency, gastroparesis, hypoglycemia unawareness, or a prior history of “brittle” diabetes.
- Caution is advised when using short/rapid-acting insulins when patient is scheduled for off-floor tests—i.e., if insulin is administered, meal should be consumed before patient is transported.
- Sliding scales should be adjusted every 1–2 days, based on the results of bedside BG monitoring and patient status.

❖ Peri-Op & Peri-Procedure Orders

General Rules

- Procedures should preferably be scheduled for the early morning to result in the least impact on insulin dosing. (If not practical, bring patient to hospital/procedure suite in the early a.m. for glucose monitoring, etc., until procedure.)
- BGs should be checked Q1–2 hrs before, during, and after procedure.
- Use of RISS as only insulin is discouraged because of greater likelihood of wide BG fluctuations.

Type 1 Diabetes

Need insulin at all times, even if NPO. Can become ketotic within 12–24 hrs if insulin held (even if BG <250 mg/dL).

1. Give 1/2 of intermediate-acting insulin (e.g., NPH) on the morning of procedure. Do not give rapid/short-acting insulin (e.g., regular, lispro, aspart, glulisine) unless BG >200 mg/dL, and then only in small doses (1–4 units to achieve BG <200 mg/dL). If patient on HS glargine or detemir, can give usual dose the night before, although to provide a safety margin, especially in those under tight control, a reduction in the dose of 20% is reasonable.

OR

2. Place on insulin drip (maintenance rate of 1–2 U/hr) with D5W @ 75–100 cc/hr, adjusted to maintain BG 140–180 mg/dL.

Type 2 Diabetes

When NPO, BGs tend to improve. Should not become ketotic if insulin held, although hyperglycemia may result.

- If on OHA (sulfonylurea or other insulin secretagogues), hold medication on day of procedure and resume when tolerating normal diet.
- For other agents that do not result in hypoglycemia:
 - metformin must be held for safety concerns (i.e., possible ↓ renal function peri-op). Regular metformin (Glucophage®) can be held beginning on day of procedure; the sustained-release formulation (Glucophage® XR) should be held beginning the evening before the procedure. Metformin can be resumed 48 hrs postoperatively after normal renal function is ensured.
 - α-glucosidase inhibitors, GLP-1 agonists, and DPP-4 inhibitors are mainly effective when patient is eating and therefore should be held.
 - thiazolidinediones (TZDs) can be held since missing several doses should not affect glycemic control, due to their long duration of action.
- If on insulin:
 1. Give 1/2 of intermediate-acting insulin (e.g., NPH) on the morning of procedure. Do not give rapid/short-acting insulin (e.g., regular, lispro, aspart, glulisine) unless BG >200 mg/dL, and then only in small doses (1–4 units to achieve BG <200 mg/dL). If patient on HS glargine or detemir, can give usual dose the night before, although to provide a safety margin, especially in those under tight control, a reduction in the dose of 20% is advisable.

OR

2. Place on insulin drip (maintenance rate of 1–2 U/hr; those taking large insulin doses at home may require more) with D5W @ 50–75 cc/hr, adjusted to maintain BG 140–180 mg/dL.

◆ Intravenous Insulin Infusions*

*For detailed, validated insulin infusion protocols, see Goldberg PA et al. Diabetes Care 27:461, 2004; Goldberg PA et al. Diabetes Spectrum 18:188, 2005; or Inzucchi SE. N Engl J Med 355:1903, 2006. (Note that the targets in these protocols may be tighter than advisable for routine use in all ICU patients.)

Indications

- Diabetic ketoacidosis (DKA)
- Hyperosmolar hyperglycemic state (HHS)
- Very poorly controlled diabetes despite subcutaneous insulin (i.e., blood glucose >350 mg/dL for more than 12 hours)
- Total parenteral nutrition (TPN)
- Type 1 diabetes patients who are NPO, perioperative, or in labor & delivery
- Consider in any patient with acute myocardial infarction or acute coronary syndrome and significant hyperglycemia (>180 mg/dL)
- Consider in any ICU patient with hyperglycemia (>180 mg/dL)
- Suspected poor subcutaneous absorption of insulin (rare)

Infusion Preparation

- Mix 100 units of Human Regular insulin in 100 cc of 0.9% NaCl (or 0.45% NaCl) (1 U = 1 cc).
- Run at least 20 cc through tubing before initiating infusion.

Infusion Initiation

- Start infusion at rate of 1–5 units per hour, depending on degree of hyperglycemia (rate may be higher in highly

insulin-resistant individuals, the obese, patients on steroids, and severely hyperglycemic patients).

- Alternatively, when transferring a patient from SQ to IV insulin, divide 50% of the total daily insulin dose by 24 hrs for an hourly rate (depending on patient status/condition).
- When patient is NPO, some carbohydrate calories should be provided to prevent catabolism with a D5W solution @ 75–125 cc/hr (unless patient is still very hyperglycemic—i.e., >200 mg/dL).
- A reasonable blood sugar target is 140–180 mg/dL in the ICU; higher (e.g., <200 mg/dL) targets may be considered for purposes of patient safety if IV insulin is used on a general medical-surgical ward.
- Check BG via bedside monitor Q1 hr x 4–6 hrs until stable, then Q2 hrs. For prolonged infusions, if very stable, can decrease BG checks to Q4 hrs.
- Hospitals should have policies to ensure the safe implementation of IV insulin therapy, including standardized, validated protocols used by a fully trained staff.

Infusion Adjustment

- In severely hyperglycemic patients (i.e., BG >350–400 mg/dL), insulin infusion should lower the BG by 50–75 mg/dL/hr.
- If BG is decreased by >100 mg/dL/hr, reduce drip rate by 25–50%.
- If greater BG decreases occur, hold the drip for 1 hour and restart at a rate reduced by at least 50%.
- In severely hyperglycemic patients, if BG is increasing or unchanged after 1–2 hours, increase drip rate by 50–100%.
- In patients who are hyperglycemic, but not severely so (i.e., 180–300 mg/dL), and if the blood glucose is increasing or unchanged, more modest insulin drip increases (i.e., 20–50%) are recommended to achieve target.

- If BG falls to <140 mg/dL, hold drip for 1 hour; recheck BG Q30 min. When BG >140 mg/dL, restart drip at 75% of original rate.
- If BG <80 mg/dL, treat with oral or IV carbohydrates (depending on level of consciousness); recheck BG Q30 min. When BG reaches 140 mg/dL, wait 1 hour, then restart drip at 50% of original rate.

Cautions

- When transferring a patient back to subcutaneous insulin, give short/rapid-acting insulins 1–2 hours or intermediate/long-acting insulins 2–3 hours prior to terminating the drip.
- Because of short metabolic half-life of IV insulin, there is little role for an IV bolus of insulin, unless followed by an intravenous infusion.

❖ DKA Management *(Diabetic Ketoacidosis)*

The following does not apply to DKA in children. During therapy for DKA in children, there is a greater risk of cerebral edema, so that IV fluid management is of even greater concern.

DIAGNOSTIC CRITERIA

Plasma glucose >250 mg/dL; arterial pH ≤7.30; serum HCO₃ ≤18; anion gap >10; urine/serum ketones positive; effective serum osmolality variable (*Kitabchi et al. Diabetes Care 32:1335, 2009*)

DAY 1 GOALS

- Stabilize hemodynamics.
- Replete volume.
- Correct acidosis/electrolytes.
- Search for precipitating cause.

RX

- Give R insulin 10–15 U IVB, then 5–10 U/hr IV; goal is to ↓ BG by 50–75 mg/dL/hr.
- IV NS to aggressively replete volume.
- Consider IV sodium bicarbonate if pH <6.9 and HCO₃ <5.
- Add K⁺ to IV fluids once serum K⁺ <5.5, patient NOT in renal failure, and adequate urine output documented. (FOLLOW SERUM K⁺ CLOSELY AND REplete AGGRESSIVELY.)
- Once BG reaches 200–250 mg/dL, “clamp” the BG at ~200 mg/dL with 1–2 U insulin + 5–10 g dextrose/hr (D5W–D10W @ 100 cc/hr) until anion gap is closed (≤12).
- Consider and/or rule out infection, MI, non-compliance, etc.

DAY 2 GOALS

- Begin/resume SQ insulin.
- Begin feeding (if patient able).
- Keep BG <200 mg/dL.
- Monitor electrolytes/divalents.
- Begin/reinforce patient education.

RX

- Consider Δ to SQ insulin (leave on IV if still NPO!).
- *If p.o. intake still in question*, give basal insulin plus RISS Q6 hrs. When patient is eating, switch to an eventual “at home” regimen of long/intermediate-acting insulin combined with short/rapid-acting insulin (i.e., 2–4 injections per day). If RISS is ordered alone, it is possible for a patient to receive no insulin for prolonged periods (6–12 hours), with recurrence of ketosis. Therefore, giving some basal insulin in the form of long/intermediate-acting formulations (e.g., glargine, detemir, NPH) even if at low doses is advisable.

- If patient is eating, start with a mixture of N + R as first injection, trying to time this injection to coincide with a planned meal (i.e., breakfast or supper). In patients with previously established insulin-treated diabetes, resume former regimen (depending on circumstances of decompensation).
- For Type 1 diabetes, total daily dose (TDD) of insulin is typically 0.4–0.8 U/kg; recommend starting with 0.5 U/kg.
- Insulin proportions are typically 60% in a.m. and 40% in p.m., with N:R ratio of 2:1 in a.m. and 1:1 in p.m.
 - AM dose: $TDD \times 0.4 = \text{a.m. NPH}$
 $TDD \times 0.2 = \text{a.m. Regular}$
 - PM dose: $TDD \times 0.2 = \text{p.m. NPH}$
 $TDD \times 0.2 = \text{p.m. Regular}$

Control may improve with a “basal-bolus” regimen involving a long-acting basal insulin analogue with a rapid-acting insulin analogue. If such a regimen is used, the proportions are typically 50% basal insulin (i.e., glargine QD or detemir QD-BID) and 50% bolus insulin (i.e., lispro, aspart, or glulisine), administered in divided doses TID before meals. Carbohydrate content of each meal should be kept constant.

- Basal dose: $TDD \times 0.5 = \text{QD glargine or QD-BID detemir}$
- Bolus dose: $TDD \times 0.5 \div 3 = \text{TID lispro, aspart, or glulisine}$
- Maintain IV insulin for 1–2 hours after initial injection.
- Replete K, Phos, Mg.

DAY 3 GOALS

- Keep BG <200 mg/dL.
- Monitor electrolytes/divalents.
- Continue patient education.

RX

- Try to approximate eventual home regimen (i.e., numbers and types of insulin injections).

DAY 4 GOALS

- Keep BG <200 mg/dL.
- Continue patient education.
- Consider discharge.

RX

- Adjust insulin regimen.
- Assess preparedness for discharge.
- Outpatient follow-up in 1–2 weeks.
- Phone contacts given upon discharge.
- Prescriptions for insulin, needles, meter, test strips, lancets, medical alert bracelet given upon discharge.

❖ HHS Management

(Hyperosmolar Hyperglycemic Syndrome)

DIAGNOSTIC CRITERIA

Plasma glucose >600 mg/dL; arterial pH >7.30; serum $\text{HCO}_3^- >15$; anion gap variable; urine/serum ketones absent or “small”; effective serum osmolality >320 mOsm/kg (Kitabchi et al. Diabetes Care 32:1335, 2009)

DAY 1 GOALS

- Stabilize hemodynamics.
- Replete volume.
- Correct electrolytes.
- Search for precipitating cause.

RX

- IV NS to aggressively replete volume (be cautious and monitor for CHF in elderly or those with cardiac history).
- After first liter NS is administered, give R insulin 10 U IVB, then 5–10 U/hr IV; goal is to ↓ BG by 50–75 mg/dL/hr.
- No need for “clamp” (see DKA management in previous section) since no acidosis. Leave on IV insulin until BG <200 mg/dL and ready to eat; often best to wait to begin SQ insulin until next a.m. with breakfast, for purposes of injection timing.
- Consider and/or rule out infection, MI, non-compliance, etc.

DAY 2 GOALS

- Begin/resume SQ insulin.
- Begin feeding (if patient able and glucose under control).
- Keep BG <200 mg/dL.
- Monitor electrolytes/divalents.
- Begin/reinforce patient education.

RX

- Consider Δ to SQ insulin (leave on IV if still NPO!). (Note: individual patients may be appropriate for a trial of oral agents.)
- *If p.o. intake still in question*, give basal insulin plus RISS Q6 hrs. When patient is eating, switch to an eventual “at home” regimen of long/intermediate-acting insulin combined with short/rapid-acting insulin (i.e., 2–4 injections per day). If RISS is ordered alone, it is possible for a patient to receive no insulin for prolonged periods (6–12 hours), with recurrence of hyperglycemia. Therefore, providing some basal insulin in the form of long/intermediate-acting formulations (e.g., glargine, detemir, NPH) even if at low doses is advisable. While many Type 2 patients

can be treated with oral agents or 1–2 injections of long/intermediate-acting insulin alone, the presentation with HHS indicates an advanced degree of insulin deficiency. Thus, a more complex insulin regimen, as may be used in Type 1 patients, is suggested.

- *If patient is eating*, start with a mixture of N + R as first injection, trying to time this injection to coincide with a planned meal (i.e., breakfast or supper). In patients with previously established insulin-treated diabetes, resume former regimen (depending on circumstances of decompensation).
- For Type 2 diabetes, total daily dose (TDD) of insulin is highly variable, based on body weight, the concurrent use of oral agents, endogenous insulin secretory capacity, and the degree of insulin resistance. Dose can range anywhere between 0.2–1.5 U/kg (or more). In the patient recovering from HHS, a dosing structure similar to DKA patients is recommended, i.e., starting with 0.5 U/kg.
- Insulin proportions are typically 60% in a.m. and 40% in p.m., with N:R ratio of 2:1 in a.m. and 1:1 in p.m.
 - AM dose: $TDD \times 0.4 = \text{a.m. NPH}$
 $TDD \times 0.2 = \text{a.m. Regular}$
 - PM dose: $TDD \times 0.2 = \text{p.m. NPH}$
 $TDD \times 0.2 = \text{p.m. Regular}$

Control may improve with a “basal-bolus” regimen involving a long-acting basal insulin analogue with a rapid-acting insulin analogue. If such a regimen is used, the proportions are typically 50% basal insulin (i.e., glargine QD or detemir QD-BID) and 50% bolus insulin (i.e., lispro, aspart, or glulisine), administered in divided doses TID before meals. Carbohydrate content of each meal should be kept constant.

- Basal dose: $TDD \times 0.5 = QD$ glargine or QD-BID detemir
- Bolus dose: $TDD \times 0.5 \div 3 = TID$ lispro, aspart, or glulisine
- Maintain IV insulin for 1–2 hours after initial injection.

DAY 3 GOALS

- Keep BG <200 mg/dL.
- Monitor electrolytes/divalents.
- Continue patient education.

RX

- Try to approximate eventual home regimen (i.e., number and types of insulin injections).

DAY 4 GOALS

- Keep BG <200 mg/dL.
- Continue patient education.
- Consider discharge.

RX

- Adjust insulin regimen.
- Assess preparedness for discharge.
- Outpatient follow-up in 1–2 weeks.
- Phone contacts given upon discharge.
- Prescriptions for insulin, needles, meter, test strips, lancets, medical alert bracelet given upon discharge.

❖ Yale Diabetes Center

Outpatient Facts & Guidelines

❖ Classification of Diabetes Mellitus

- **Type 1 Diabetes** (ICD-9 codes # 250.01 [controlled], 250.03 [uncontrolled]) (formerly IDDM or JODM)
(complete insulin deficiency due to β -cell destruction)
 - A: Immune-mediated
 - B: Idiopathic
- **Type 2 Diabetes** (ICD-9 codes # 250.00 [controlled], 250.02 [uncontrolled]) (formerly NIDDM or AODM)
(ranging from predominately insulin deficient to predominately insulin resistant; most affected individuals have some degree of both components; the use of insulin in a Type 2 patient does NOT reclassify that patient as a Type 1)
- **Other (“Secondary Diabetes”)**
 - Genetic defects in β -cell function*
MODY1 – hepatocyte nuclear factor-4-alpha (HNF4 α) gene mutation, chromosome 20q12-q13.1; MODY2 – glucokinase (GCK) gene mutation, chromosome 7p15-p13; MODY3 – hepatocyte nuclear factor-1alpha (HNF1A) gene mutation, chromosome 12q24.2; MODY4 – insulin promoter factor-1 (IPF1) gene mutation, chromosome 13q12.1; MODY5 – hepatic transcription factor-2 (TCF2) gene mutation, chromosome 17cen-q21.3; MODY6 – neurogenic differentiation 1 (NEUROD1) gene mutation chromosome 2q32; MODY7 – Kruppel-like factor 11 (KLF11) gene mutation, chromosome 2p25; MODY8 (or diabetes-pancreatic exocrine dysfunction syndrome) – carboxyl-ester lipase (CEL) gene mutation, chromosome 9q34; MODY9 – Paired box gene 4 (PAX4) mutation, chromosome 7q32; Mitochondrial diabetes (including

MELAS syndrome [mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome] – *mitochondrial DNA mutations (multiple genes)*

- Genetic defects in insulin action

Type A insulin resistance, leprechaunism, lipotrophic diabetes, Rabson-Mendenhall syndrome, others

- Exocrine pancreatic diseases

pancreatitis, pancreatectomy, carcinoma, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, others

- Other endocrinopathies

Cushing's, acromegaly, pheochromocytoma, glucagonoma, somatostatinoma, aldosteronoma, thyrotoxicosis, others

- Drug/chemical-induced

nicotinic acid, pentamidine, steroids, levothyroxine, diazoxide, β -blockers, thiazides, DPH, α -interferon, L-asparaginase, vacor, others

- Infections

congenital rubella, CMV, others

- Uncommon forms of immune-mediated diabetes

"Stiff-man" syndrome, anti-insulin receptor antibodies, others

- Other genetic syndromes

Down, Klinefelter's, Turner's, Prader-Willi, Laurence-Moon-Biedl, Friedreich's ataxia, Huntington's chorea, myotonic dystrophy, porphyria, others

*From: OMIM® - Online Mendelian Inheritance in Man, <http://www.ncbi.nlm.nih.gov/omim/>

- **Gestational Diabetes** (see p. 31)

From: American Diabetes Association. Diabetes Care 33:S65, 2010

❖ Type 2 DM Diagnosis

STAGE	TEST*		
	FPG*	2-HR PG DURING 75 G OGTT	HbA1c
NORMAL	<100 mg/dL	<140 mg/dL	<5.7%
PRE-DIABETES	100–125 mg/dL (IFG)	140–199 mg/dL (IGT)	5.7–6.4%
DIABETES	≥126 mg/dL	≥200 mg/dL	≥6.5%

FPG = Fasting Plasma Glucose PG = Plasma Glucose OGTT = Oral Glucose Tolerance Test IFG = Impaired Fasting Glucose IGT = Impaired Glucose Tolerance

*The diagnosis of diabetes can also be made on the basis of a causal/random PG ≥200 mg/dL if accompanied by typical hyperglycemic symptoms.

From: American Diabetes Association. Diabetes Care 33:S62, 2010

❖ Metabolic Syndrome: Diagnostic Criteria (ICD-9 Code # 277.7*)

According to the NCEP, the diagnosis of Metabolic Syndrome is established when 3 or more of the following 5 criteria are present:

1. Waist Circumference	
Men	>40 inches (102 cm)
Women	>35 inches (88 cm)
2. Triglycerides (TG)	≥150 mg/dL or drug treatment for elevated TG
3. HDL-Cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL or drug treatment for reduced HDL-C
4. Blood pressure	≥130/85 mm Hg or drug treatment for hypertension
5. Fasting plasma glucose	≥100 mg/dL

*According to the CDC, ICD-9 Code # 277.7 can be used if, in the professional opinion of the physician, Dysmetabolic Syndrome X is present. The American Association of Clinical Endocrinologists (AAACE) has developed major and minor criteria for this diagnosis:

Major criteria: include insulin resistance (hyperinsulinemia relative to glucose concentrations), or acanthosis nigricans, central obesity (see above, waist circumference), dyslipidemia (HDL-C <35, men [<45 , women] or TG >150), hypertension, impaired fasting glucose or T2DM, hyperuricemia.

Minor criteria: hypercoagulability, polycystic ovary syndrome (PCOS), vascular endothelial dysfunction, microalbuminuria, coronary heart disease (CHD).

According to the WHO, Metabolic Syndrome may be diagnosed if one of the following parameters is present: IGT, IFG, DM, or the highest 25% of HOMA-IR¹ *plus* ≥3 of the following additional diagnostic criteria: BP ≥140/90; Waist:Hip Ratio >0.9 (>0.85, women) or BMI >30 kg/m²; TGs ≥150; HDL-C <35 (<39, women); Microalbumin >30 mcg/mg Cr.

¹HOMA-IR = [FPG (mmol/L) x Fasting Plasma Insulin (uU/mL)]/22.5

NCEP Website: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>

AAACE Website: <http://www.aace.com/pub/positionstatements/>

❖ Type 2 DM Screening (for asymptomatic individuals)

- Consider in all individuals at age 45 and subsequently Q3 yrs
- Consider at earlier age/more frequently in those who are overweight (BMI >25 kg/m²) and have additional risk factor(s):
 - physical inactivity
 - 1st degree relative w/DM
 - high-risk ethnic populations (Hispanic-, Native-, African-, Asian-Americans and Pacific Islanders)
 - h/o Gestational Diabetes or if delivered baby ≥9 lbs
 - hypertensive (≥140/90)
 - HDL cholesterol ≤35 mg/dL and/or a TG ≥250 mg/dL
 - Polycystic Ovary Syndrome (PCOS) or acanthosis nigricans
 - on previous testing, had Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG)
 - h/o vascular disease

From: American Diabetes Association. Diabetes Care 33:S14, 2010

❖ Type 2 DM Prevention

Based on the results of both the Finnish Diabetes Prevention Study (DPS¹) and U.S. Diabetes Prevention Program (DPP²), lifestyle intervention (diet, weight reduction, exercise) was demonstrated to reduce the progression from impaired glucose tolerance (IGT) to T2DM by 54%, compared to control groups. The intervention utilized by the DPP consisted of:

- increasing physical activity (e.g., brisk walking) by 150 minutes/week (e.g., 30 minutes 5 days per week)
- weight reduction goal of 7% of body weight

Other studies have also shown a diabetes preventive (or delaying) effect from several drugs. These include metformin (DPP²), acarbose (STOP-NIDDM³), rosiglitazone (DREAM⁴) and pioglitazone (ACT NOW⁵) in IGT/IFG patients, and orlistat (XENDOS⁶) in obese individuals. However, none of these drugs are FDA-approved for the specific indication of diabetes prevention.

A consensus statement sponsored by the ADA and the EASD (*Nathan DM et al. Diabetes Care 30:753, 2007*) recommended that lifestyle modification (moderate intensity physical activity 30 min/day and 5–10% body weight loss) be advised for any patient with IFG or IGT. In those patients with both IFG and IGT, who constitute the highest risk for progressing to T2DM, metformin therapy should also be considered if BMI ≥ 35 kg/m² and age <60. Other factors that increase the risk of T2DM progression include family history of diabetes in a first-degree relative, elevated triglycerides, reduced HDL-cholesterol, hypertension, and HbA1c >6.0%; the presence of ≥ 1 of these factors may influence the decision to use metformin.

¹Tuomilehto et al. N Engl J Med 344:1343, 2001. ²Knowler et al. N Engl J Med 346:393, 2002. ³Chiasson et al. Lancet 359:2072, 2002. ⁴DREAM trial investigators. Lancet 368:1770, 2006. ⁵DeFronzo, et al. Actos Now for Prevention of Diabetes (ACT NOW). Presented at the 68th Scientific Sessions of the American Diabetes Association. San Francisco; June 6–10, 2008. ⁶Scheen. Rev Med Liege 57:617, 2002

❖ Gestational Diabetes (GDM)

Screening should be performed in all pregnant women. However, very low-risk patients (<25 y/o, normal body weight, no h/o abnormal glucose metabolism or poor obstetrical outcome, no family h/o DM, and not members of high-risk ethnic/racial groups: Hispanic-, Native-, African-, Asian-Americans and Pacific Islanders) may not need to be screened. High-risk patients (obese, prior h/o GDM, glycosuria, strong family h/o DM) should undergo screening at first pre-natal visit, with repeat @ 24–28 weeks. Women of average risk should have screening @ 24–28 weeks.

■ Screening 1-hr 50-g OGTT

If venous plasma glucose >140 mg/dL → proceed to 3-hr 100-g OGTT

■ Formal 3-hr 100-g OGTT

Performed in the AM, after an overnight fast (8–14 hrs), and following 3 days of unrestricted diet (≥ 150 g carbohydrates/day) & with no limit on physical activity. During OGTT, patient should remain seated and refrain from smoking.

“Carpenter/Coustan” criteria approved by 4th Int’l. Workshop-Conference on GDM, 3/97:

fasting	95 mg/dL
1 hr	180 mg/dL
2 hr	155 mg/dL
3 hr	140 mg/dL

Diagnosis of GDM = when ≥ 2 of the above plasma glucose determinations are reached or exceeded.

From: American Diabetes Association. Diabetes Care 33:S16, 2010

◆ Nutrition/Diet Therapy

The goal of nutritional therapy in diabetes is to achieve/maintain:

- 1) ideal body weight,
- 2) blood glucose levels in the target range, and
- 3) optimal blood lipids.

A meal plan, formulated with the patient by someone who has specialized training in nutritional therapy, should take into account the patient's age-based nutritive requirements, other coexisting medical conditions, and the patient's usual food preferences. Several methodologies are available to patients to keep track of their nutritional intake, such as the "exchange" system and "carbohydrate counting." Most patients simply follow general guidelines, which, in actuality, are little different from healthy diets recommended to all individuals by the U.S.D.A. and the American Heart Association.

A concurrent moderate exercise program to increase energy expenditure is additionally recommended, although this should also be individualized to patient abilities and interests. Specifically, if multiple coronary heart disease risk factors are present, consideration should be given to performing a cardiac evaluation prior to the initiation of any exercise regimen more vigorous than walking.

Calories

Caloric goals should be those that help the patient reach and maintain ideal body weight. Weight-maintaining diets for moderately active individuals include 30–35 kcal/kg/day. For purposes of weight reduction, obese patients can have their intake moderately reduced by 5–15 kcal/kg/day (i.e., down to

20–30 kcal/kg/day), particularly if they are sedentary. If usual caloric intake is reduced by 500 calories/day, gradual weight loss of 1 lb per week should occur.

Distribution of Calories

• Carbohydrates

The most recent recommendations by the American Diabetes Association do not dictate a certain percent of carbohydrate calories. Instead, the percent carbohydrate intake should vary based on the patient's intake of protein and fat, which is more precisely defined. As a result, however, most individuals will necessarily consume approximately 50–60% carbohydrates. Complex carbohydrates should be emphasized, especially fresh fruits and vegetables and whole grains. Contrary to popular belief, there is little scientific evidence that the actual mix of types of carbohydrates/sugars has substantial influence on glycemic control. Thus, no type of carbohydrate is forbidden, even sucrose. Nonetheless, many clinicians still ask their patients to curb intake of concentrated sweets, since these calories are often added to and not substituted for other carbohydrates, and since such products are also usually high in fat content. Popular "low-carbohydrate/high-protein" diets may be associated with initial weight loss and improved glycemic control, although, as in all restrictive programs, these are usually difficult to maintain for prolonged periods. In addition, the long-term effects of such diets on cardiovascular and renal endpoints are not known.

• Protein

Protein intake should be maintained at 10–20% of all calories, as is recommended to the general population. There is some evidence that restricting intake to <10% (or to 0.6–0.7 g/kg/day) may

be beneficial for individuals with overt diabetic nephropathy, although such diets are usually difficult to follow. At present, the general consensus is to restrict intake to 10%, or 0.8 g/kg/day, in patients so affected.

• Fat

As in the general population, total fat intake should be restricted to <30% of total calories, with saturated fat limited to <7% of total calories, and total cholesterol intake of <300 mg/day (National Cholesterol Education Program [NCEP] Step I Diet). Because patients with diabetes commonly have coexisting lipid abnormalities, further restrictions are usually required: saturated fats <7% of total calories and dietary cholesterol to <200 mg/day (NCEP Step II Diet).

Other Principles

A diet high in fiber should be emphasized (20–35 g/day of soluble and insoluble fiber). Modest sodium restriction to 2400–3000 mg/day. If hypertension is present, intake should be <2400 mg/day. If nephropathy is present in addition to hypertension, restrict to <2000 mg/day. Moderation of alcohol intake (≤ 2 drinks/day in men, ≤ 1 drink/day in women). Multivitamins should be considered, especially for individuals on low-calorie diets. Non-nutritive artificial sweeteners are acceptable in moderate amounts.

From: American Diabetes Association. Diabetes Care 27:S36-S46, 2004

❖ Obesity Management

The vast majority of patients with Type 2 diabetes are either overweight or obese. Obesity is associated with insulin resistance, a number of other cardiovascular disease risk factors, and increased mortality. Successful weight loss strategies include comprehensive therapeutic lifestyle changes: decrease in energy (calorie) intake, increase in energy expenditure (physical activity), nutritional counseling, behavior modification, and treatment of any underlying psychiatric condition, especially depression. Generally speaking, diets should be selected containing 1000–1200 kcal/day for most overweight women and 1200–1600 kcal/day for most overweight men. As a rule of thumb, reducing calorie intake by 500–1000 kcal/day will result in a desirable 1–2 lbs of weight loss per week. Popular low-carbohydrate diets have been shown to increase the chance of short-term weight loss, most likely due to an overall reduction in calorie intake. Carbohydrate restriction is difficult to sustain by most patients, however, and the long-term effects of these diets remain unknown.

Pharmacological Therapy of Obesity

Unfortunately, attempts at lifestyle modification and dietary restriction are frequently unsuccessful. As a result, patients commonly seek pharmacological assistance to achieve weight loss. Two such drugs are currently FDA-approved for long-term use:

- Sibutramine (*Meridia*[®]) (5, 10, 15 mg), an appetite suppressant, dosed 5–15 mg QD; side effects include hypertension and headaches.
- Orlistat (*Xenical*[®], *Alli*[®]) (120 mg, 60 mg), an intestinal fat absorption inhibitor, dosed 120 mg TID with meals; side effects include diarrhea, greasy stools, and potential malabsorption of fat-soluble vitamins (A, D, E, K).

These agents are generally limited to those patients with a BMI ≥ 30 , or those with a BMI ≥ 27 if other comorbidities are present, such as diabetes. A general rule is that, if the patient has not lost at least 2 kg after 4 weeks of therapy, it is unlikely that further benefit will be derived from the drug. Other agents, mostly amphetamine-based appetite suppressants, are marketed for short-term use only: phentermine (*Adipex-P*[®], *Fastin*[®], *Ionamin*[®]), benzphetamine (*Didrex*[®]), diethylpropion (*Tenuate*[®]), and phendimetrazine (*Bontril*[®]). They are best avoided in diabetic patients, since weight loss requires a long-term strategy and the significant risks associated with their use likely outweigh any potential benefit. All such weight-loss drugs are in general not highly effective and their role in the treatment of obese patients remains limited.

In patients with diabetes, drugs which have been associated with weight loss include exenatide, pramlintide, and metformin (*see pp. 50–57*).

Bariatric Surgery

Obesity surgery (gastric banding, gastric bypass) offers patients substantial, sometimes dramatic, and sustained weight loss. However, the procedures carry significant operative risk and long-term outcomes are not entirely clear. They should be considered options for selected, well-informed, and highly motivated patients with severe obesity (BMI ≥ 40 ; or BMI ≥ 35 with serious comorbid conditions, including diabetes), when all other options have been exhausted. Two studies, both controlled but not blinded, suggest a 24–40% reduction in mortality in

obese patients who underwent bariatric surgery vs. those who had conventional care. (*Sjostrom et al. N Engl J Med 357:741, 2007; Adams et al. N Engl J Med 357:753, 2007*)

From: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998. http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm

Classifications of Body Mass Index (BMI)

Weight Status	BMI (kg/m²)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obesity (Class 1)	30.0–34.9
Obesity (Class 2)	35.0–39.9
Extreme obesity (Class 3)	≥ 40

(*See BMI Table, p. 93.*)

Equations for calculating BMI

$$\text{Metric: BMI} = \frac{\text{weight (kg)}}{\text{height}^2 (\text{m}^2)}$$

$$\text{English: BMI} = 703 \times \frac{\text{weight (lb)}}{\text{height}^2 (\text{in}^2)}$$

❖ Mnemonic for Diabetes Office Visits*

Glycemic Control. Review glucose log; assess for hypoglycemic/hyperglycemic symptoms and optimize medical management to achieve glycemic targets. ✓ HbA_{1c} Q3–6 mo—target <7.0%. Review diet, exercise, weight control.

Lipids. Order complete lipid profile once annually or more frequently if not at target (LDL <100 mg/dL) or if receiving therapy; treat aggressively (see pp. 79–82). Statins should now be considered in all diabetic patients age >40 with at least one other CVD risk factor, unless contraindication is present.

Urine. Screen for microalbuminuria, ✓ serum Cr & UA yearly in all Type 2s; after 5 years in Type 1s. If spot albumin:Cr ratio ≥30 µg/mg, consider ACE inhibitor or ARB, even if normotensive.

Cigarettes. Assess smoking habits; counsel; consider referral, nicotine patch/gum, medications, etc.

Ophthalmological. Monitor retina status via eye care professional or with retinal photography once yearly in Type 2s; after 5 years in Type 1s.

Sex-Related Topics. *Women:* birth control in those not in good glycemic control. *Men:* inquire re: erectile dysfunction; treat/refer as indicated.

Extrémities. Inspect feet at each visit: neuropathy, vascular disease (✓ pulses), calluses, bony deformities, incipient ulcerations, nail/foot fungus. Review foot care. Refer to podiatrist as indicated. Refer to vascular surgeon if claudication or ulceration + abnormal pulses.

Blood Pressure. Measure and record at each visit; treat aggressively. Consider ACEI or ARB as first-line therapy unless contraindication. Target is <130/80 (see pp. 83–84).

Aspirin. Use aspirin for secondary prevention in any patient with established CVD, per routine guidelines. Consider aspirin (75–162 mg) for primary prevention in adults with diabetes at 10-year risk of CVD events >10% (i.e., men >age 50 and women >age 60 with at least one other major CVD risk factor (family history, hypertension, dyslipidemia, albuminuria, or smoking)).

Dental. Recommend Q6 mo dental visits for cleanings and aggressive treatment of periodontal disease.

*Office visits should be scheduled every 3–4 months in well-controlled patients. For patients who have been very stable on diet or oral agent monotherapy, office visits can be reduced to every 6 months. Suboptimally controlled patients should be seen as frequently as needed to help them attain their targets. Current financial realities make such comprehensive evaluations impractical at every visit. Thus, the co-management of patients with other healthcare professionals (CDEs, APRNs, dieticians) or frequent return visits are necessary.

❖ Self-Monitoring of Blood Glucose (SMBG)

THERAPEUTIC REGIMEN	FREQUENCY
Diet	periodically
Oral agents	1–2x/day [†]
QD insulin injections	1–2x/day [†]
BID insulin injections	2–4x/day
TID–QID insulin or insulin pump	3–6x/day

[†]Can decrease to 2–3x per week if stable.

Notes

- Results should be recorded in a log (with each column containing glucose values during the same time of day [e.g., fasting, pre-supper, etc.]), so that trends can be tracked and acted upon at each visit. Most glucose meters have download capabilities that facilitate recording and displaying glucose values, usually both in log format as well as graphically (see *Home Glucose Meters*, pp. 40–41).
- Each meter has its own specific single-use test strips, which are purchased separately. (Most containers of glucose test strips have a unique code or master strip that re-programs the meter to read that container's strips.)
- Patients will additionally require a spring-loaded lancet device and single-use lancets with which the skin can be punctured for a drop of capillary blood.
- Most meters require periodic cleaning and/or calibration.
- Capillary whole blood glucose is 8–12% lower than simultaneous venous plasma glucose. On average, therefore, plasma glucose values within the normal range are approximately 10 mg/dL

higher than whole blood glucose. While all meters read whole blood, some are pre-calibrated to report an adjusted plasma glucose value.

- In a properly functioning meter, the reported result should be within 15–20% of the blood's actual glucose content. This lack of precision should be taken into account when making clinical decisions. Meters tend to be least accurate at the extremes of the detection range.
- Meters differ, among other things, in: price, size, weight, blood volume requirement, reading range, testing time, memory capacity, averaging capability, need for calibration and cleaning, availability of software for personal computer link, and coverage under certain health insurance plans. Patients should take the time to discuss their planned meter purchase with their healthcare provider, educator, and/or pharmacist.

◆ Home Glucose Meters

LIFESCAN 800-227-8862

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NOVA BIOMEDICAL 800-681-7390

www.novabiomedical.com

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Notes: 1. Models in underlined print have software for personal computer links. 2. Models in *italics* print are approved for “alternate site testing”—i.e., testing on less sensitive areas of the body (arms, legs) than fingertips. Please note that these sites are not appropriate during times of rapid change in glucose, such as the post-prandial period. Also, results from these sites should be confirmed with a fingerstick if data seem questionable.

◆ Glucose Sensors

Office-Based Systems

The Continuous Glucose Monitoring System® (CGMS® iPro™) (*Medtronic MiniMed, Inc.*) is a Holter-style device that uses a subcutaneously inserted interstitial glucose sensor connected to a computerized pager-sized monitor. Readings are obtained every 5 minutes over a 72-hr period. During the monitoring time, the patient continues to check capillary BG, recording this information

(along with meal and exercise times) into the monitor. The monitor is returned to the physician's office, where it is connected to a communication device and linked to a personal computer. The data are downloaded and displayed in graphic form for physician review.

Home-Use Systems

Three live-read glucose sensors are now available (Guardian® REAL-Time [Medtronic MiniMed, Inc., www.minimed.com], DexCom™ Seven® Plus [DexCom, Inc., www.dexcom.com]), and Navigator [Abbott, Inc., www.abbottdiabetescare.com] for continuous or intermittent home-use by the patient. These display live glucose data with trends and alarms for hypoglycemia and severe hyperglycemia, so that the patient can incorporate this information into their treatment programs. The units consist of a disposable (every 3–7 days), subcutaneously inserted sensor which sends interstitial glucose measurement data to a connected transmitter, which, in turn, relays the data to a semi-remote receiver/display. (The Guardian® has the ability to relay this information to the Paradigm® insulin pump.) Periodic calibration with fingerstick glucose measurements is still required. Accuracy and precision of these products remain questionable, although several small studies suggest that the net effect of using a sensor is an overall modest improvement in glycemic control. At this point, they should be considered in highly motivated patients on intensive insulin regimens or in those with severe hypoglycemia awareness and multiple severe hypoglycemic episodes in whom the alarm features may provide an extra measure of safety. Importantly, insurers don't usually cover these devices and most patients cannot afford the significant investment (approximately \$800–\$1000 for the unit and \$8–\$12 per day for the sensors, which are changed every 3–7 days).

❖ Diabetes Education

Diabetes education and self-management training are integral parts of any treatment program for the patient with diabetes. A well-informed patient will have the best advantage to attain and maintain glycemic and cardiovascular risk factor control. Patients should therefore be encouraged to actively take part in locally available diabetes education programs. The Task Force to Review and Revise the National Standards for Diabetes Self-Management Education Programs has determined 10 content areas to be covered by the curricula of such programs. Specific educational needs from these topics should be determined for each individual patient (Mensing et al. Diabetes Care 23:682, 2000). For newly diagnosed patients, familiarity with so-called "Survival Skills" should be quickly secured.

• "Survival Skills"

1. How and when to take medication and/or insulin
2. How and when to monitor blood glucose
3. Basics regarding meal planning
4. How to treat hypoglycemia
5. Sick-day management
6. Date of next appointment with clinician
7. How to access further diabetes education as an outpatient
8. When to call healthcare team

• Content Areas for Diabetes Self-Management Education Programs

1. Diabetes overview: disease process and treatment options
2. Nutritional management
3. Exercise and physical activity
4. Medications
5. Blood glucose (and urine ketone) monitoring; using results to improve control
6. Preventing, detecting, and treating acute complications
7. Preventing, detecting, and treating chronic complications
8. Goal setting and problem solving
9. Psychosocial adjustment
10. Preconception care, pregnancy, and gestational diabetes

Pharmacological Therapy of Type 2 Diabetes: Comparison of Available Agents

AGENT	Efficacy (Δ HbA1c)	Mechanism of action	Benefits	Risks/Concerns
Sulfonylureas	-1 to 2%	Binds to sulfonylurea receptor on β -cells, stimulating insulin release	Extensive experience; improved microvascular outcomes in UKPDS; low cost; QD dosing	Hypoglycemia; weight gain; may impede ischemic preconditioning
Meglitinides	-1 to 1.5% (Nateglinide less potent)	Binds to sulfonylurea receptor on β -cells, stimulating insulin release	Targets post-prandial glucose; mimics physiological insulin secretion	Hypoglycemia; weight gain; no long-term experience; expensive; frequent dosing (compliance)
Biguanides	-1 to 2%	Decreases hepatic glucose production	Weight loss or weight neutrality; no hypoglycemia; extensive experience; improved macrovascular outcomes in UKPDS; QD dosing available	Diarrhea; lactic acidosis; many contraindications to consider prior to prescribing; lowers vitamin B-12 levels (but no apparent effects on hematological indices)
α -Glucosidase Inhibitors	-0.5%	Retards gut carbohydrate absorption	Targets post-prandial glucose; weight-neutral; no hypoglycemia; non-systemic	Intestinal gas, expensive; frequent dosing (compliance)
Thiazolidinediones	-1 to 1.5%	Activates PPAR- γ ; increasing peripheral insulin sensitivity	Addresses primary defect of T2DM; no hypoglycemia; lipid & other "non-glycemic" vascular benefits; potential anti-atherosclerotic properties; potential for β -cell preservation; QD dosing	Edema; heart failure in predisposed individuals; weight gain; increase in bone fractures in women; slow onset of action; expensive; liver monitoring still advised

Pharmacological Therapy of Type 2 Diabetes: Comparison of Available Agents cont.

AGENT	Efficacy (Δ HbA1c)	Mechanism of action	Benefits	Risks/Concerns
DPP-4 Inhibitors	-0.6 to 0.8%	Inhibits enzyme that deactivates endogenous incretins, GLP-1 and GIP, thereby increasing glucose-dependent insulin release and suppressing glucagon secretion	Low incidence of side effects; no hypoglycemia; QD dosing; potential β -cell preservation	Expensive; limited clinical experience; urticaria and angioedema reported
Bile Acid Sequestrants	-0.4 to 0.5%	Unknown	LDL reduction; non-systemic	Constipation; increases TCs; multiple pills per day; expensive
Dopamine-2 Agonists	-0.4 to 0.7%	Alters hypothalamic neurotransmitter tone and may reduce hepatic glucose production	No hypoglycemia; QD dosing	Orthostatic hypotension, dizziness; syncope; exacerbation of psychotic illness; nausea, vomiting; fatigue
GLP-1 Mimetics	-1%	Glucose-dependent stimulation of insulin release; suppresses glucagon; retards gastric emptying; enhances satiety	Weight loss; no hypoglycemia; potential β -cell preservation	Injectable; nausea, expensive; pancreatitis reported
Amylinomimetics	-0.4 to 0.6%	Suppresses glucagon release; retards gastric emptying; enhances satiety	Targets post-prandial glucose; weight loss	Injectable; nausea; expensive
Insulin	No "ceiling"	Increases insulin supply	Extensive experience; rapidly effective in all circumstances; no contraindications; improved microvascular outcomes in UKPDS; mortality benefits in acute settings; low cost	Hypoglycemia; weight gain; infections and more frequent glucose monitoring required; increases complexity of management; "stigma"

❖ Oral Agents

	dose sizes dose/day (mg)	dose interval	peak (hrs)	t _{1/2} (hrs)	duration (hrs)	side effects
SULFONYLUREAS (2nd generation)						
Glyburide (<i>Micronase</i> [®] <i>DiaBeta</i> [®])	2.5, 5 mg 1.25–20	QD-BID	4	10	12–24	weight gain, hypoglycemia
Micronized glyburide (<i>Glynase</i> [®])	1.5, 3, 6 mg 0.75–2	QD-BID	2	4	12–24	weight gain, hypoglycemia
Glipizide (<i>Glucotrol</i> [®])	5, 10 mg 2.5–40	QD-BID	1–3	2–4	12–24	weight gain, hypoglycemia
Glipizide-GITS (<i>Glucotrol XL</i> [®])	2.5, 5, 10 mg 2.5–20	QD	6–12	n/a	24	weight gain, hypoglycemia
Glimepiride (<i>Amaryl</i> [®])	1, 2, 4 mg 1–8	QD	2–3	9	24	weight gain, hypoglycemia
NON-SULFONYLUREA SECRETAGOGUES						
Repaglinide (<i>Prandin</i> [®])	0.5, 1, 2 mg 1.5–16	TID-QID (w/meals)	1	1	4–6	weight gain, hypoglycemia
Nateglinide (<i>Starlix</i> [®])	60, 120 mg 180–360	TID (w/meals)	0.3	1	4	weight gain, hypoglycemia
THIAZOLIDINEDIONES						
Rosiglitazone (<i>Avandia</i> [®])	2, 4, 8 mg 4–8	QD-BID	n/a	3–4	days-wks	edema, weight gain
Pioglitazone (<i>Actos</i> [®])	15, 30, 45 mg 15–45	QD	n/a	16–24	days-wks	edema, weight gain

❖ Oral Agents

BIGUANIDES

Metformin (<i>Glucophage</i> [®]) (<i>Riomet</i> [®] <i>oral solution</i>)	500, 850, 1000 mg 100 mg/mL 1000–2550	BID-TID	2–3	6	12–18	nausea, diarrhea, abd. pain, lactic acidosis
Metformin Extended Release (<i>Glucophage</i> [®] XR, <i>Fortamet</i> [®] , <i>Glumetza</i> [®])	500, 750, 1000 mg 1000–2000	QD-BID	4–8	n/a	24	nausea, diarrhea, abd. pain, lactic acidosis

α-GLUCOSIDASE INHIBITORS

Acarbose (<i>Precose</i> [®])	25, 50, 100 mg 150–300	TID (w/meals)	n/a	n/a	2–3	gas, abd. pain, diarrhea
Miglitol (<i>Glyset</i> [®])	25, 50, 100 mg 150–300	TID (w/meals)	n/a	n/a	2–3	gas, abd. pain, diarrhea

DIPEPTIDYL PEPTIDASE (DPP)-4 INHIBITORS

Sitagliptin (<i>Januvia</i> [®])	25, 50, 100 mg 100	QD	1–4	12	24+	urticaria, angioedema, ?pancreatitis
Saxagliptin (<i>Onglyza</i> [®])	2.5, 5 mg 5	QD	2	3	24	urticaria

BILE ACID SEQUESTRANTS

Colesevelam (<i>Welchol</i> [®])	625 mg 3750	QD-BID	n/a	n/a	24	constipation, TG elevation
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DOPAMINE-2 AGONISTS

Bromocriptine (<i>Cycloset</i> [®])	0.8 mg 1.6–4.8	QD	1–2	6	24	hypotension, syncope, dizziness, exacerbation of psychosis, nausea/ vomiting, fatigue
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❖ Oral Agents cont.

	dose sizes dose/day	dose interval	peak (hrs)	t _{1/2} (hrs)	duration (hrs)	side effects
FIXED COMBINATIONS						
Glyburide/ Metformin (<i>Glucovance</i> ®)	1.25/250, 2.5/500, 5/500 mg ii-iiii tabs	BID				(see individual components on pp. 46–47)
Glipizide/ Metformin (<i>Metaglip</i> ®)	2.5/250, 2.5/500, 5/500 mg i-iiii tabs	QD-BID				(see individual components on pp. 46–47)
Repaglinide/ Metformin (<i>PrandiMet</i> ®)	1/500, 2/500 mg ii-iiii tabs	BID-TID				(see individual components on pp. 46–47)
Rosiglitazone/ Metformin (<i>Avandamet</i> ®)	2/250, 2/500, 4/500, 2/1000, 4/1000 mg i-iiii tabs	QD-BID				(see individual components on pp. 46–47)
Rosiglitazone/ Glimepiride (<i>Avandaryl</i> ®)	4/1, 4/2, 4/4 mg i-ii tabs	QD-BID				(see individual components on pp. 46–47)
Pioglitazone/ Metformin (<i>Actoplus met</i> ®)	15/500, 15/850 mg ii-iii tabs	QD-BID				(see individual components on pp. 46–47)
Pioglitazone/ Glimepiride (<i>Duetact</i> ®)	30/2, 30/4 mg i tab	QD				(see individual components on pp. 46–47)
Sitagliptin/ Metformin (<i>Janumet</i> ®)	50/500, 50/1000 mg ii tabs	BID				(see individual components on pp. 46–47)

Sulfonylurea Considerations

- Generally, little benefit observed beyond doses half of “maximal” dose.
- Shorter-acting agents preferred in elderly patients.

- Should be taken 30 min AC (so that peak coincides with hyperglycemic response to meal; food also slightly ↓s absorption).
- Major risks are hypoglycemia and weight gain.
- Hepatically metabolized and renally cleared. Glyburide’s metabolites are partially active, and therefore should be avoided in patients with CKD. Glipizide (inactive metabolites) and glimepiride (substantial biliary/fecal excretion of metabolites) are preferred in this setting. All sulfonylureas should be used cautiously in patients with hepatic disease. Since most other agents are contraindicated in this setting, insulin may be the preferred agent.
- Secondary-failure rates of 5–10% per year.
- Decrease in microvascular endpoints in sulfonylurea-treated subjects in the United Kingdom Prospective Diabetes Study (UKPDS) with trend toward small decrease in macrovascular endpoints (*UKPDS Group. Lancet 352:837, 1998*). In the UKPDS long-term follow-up study (*UKPDS Group. N Engl J Med 359:1577, 2008*), both microvascular and macrovascular outcomes were reduced in the sulfonylurea group as compared to diet therapy, despite equivalent HbA1c levels after the randomized component of the trial.
- ↑ Sulfonylurea action: *NSAIDs, warfarin, salicylates, sulfonamides, allopurinol, probenecid, guanethidine, MAOIs, chloramphenicol, alcohol, β-blockers.*
- ↓ Sulfonylurea action: *steroids, diuretics, niacin, L-thyroxine, estrogens, progestins, phenytoin, diazoxide, INH, rifampin, phenothiazines, sympathomimetics.*
- First-generation sulfonylureas (chlorpropamide [*Diabinese*®], tolbutamide [*Orinase*®], tolazamide [*Tolinase*®], and acetohexamide [*Dymelor*®]) are rarely used today. At usual doses, they are equally effective as the 2nd-generation agents, but generally have more drug-drug interactions and adverse effects.

Non-sulfonylurea (SU) Insulin Secretagogue (Meglitinide) Considerations

- Predominately hepatically metabolized; metabolites have weak activity and are renally cleared. These agents should be used cautiously and dosage adjustments made carefully in patients with hepatic impairment. While their metabolism is not significantly altered in renal failure, due to decreased insulin clearance, treatment with any insulin secretagogue should be approached cautiously in patients with significant renal insufficiency.
- Stimulates insulin release through mechanism similar to that of SUs. Quicker onset and shorter duration of action than SUs improve post-prandial glucose control and decrease risk of late post-prandial hypoglycemia.
- May be preferred to SUs in those patients with erratic meal schedules or those prone to early post-prandial hyperglycemia or late post-prandial hypoglycemia.
- Should be taken 0–30 minutes AC.

Metformin Considerations

- Major risk is lactic acidosis, which is very rare (1/30,000 patient-years) and typically occurs only in patients with contraindications for its use.
- Signs/symptoms of lactic acidosis include: *malaise, somnolence, myalgias, respiratory distress, abdominal discomfort, hypothermia, hypotension, and bradycardia.*
- Cleared renally; drug levels build up significantly in renal failure patients.
- **Contraindications:** renal insufficiency (Cr ≥ 1.5 mg/dL in men, ≥ 1.4 mg/dL in women); dehydration; hemodynamic instability; metabolic acidosis; hepatic dysfunction; alcoholism; unstable CHF; advanced age (patients over age 80 should have normal Cr clearance documented prior to metformin therapy). Check LFTs, creatinine once yearly.
- For radiocontrast studies or in the perioperative setting, D/C on day of procedure or surgery and restart after 48 hrs if patient stable and eating full diet, and if renal function documented to be unimpaired.

(If sustained-release metformin [*Glucophage*® XR] is being used, it should be held beginning the evening before the procedure.)

- Recommended dosing is with meals, although food actually ↓s absorption of regular metformin. Absorption of *Glucophage*® XR is increased with food and recommended dosing is at the evening meal.
- Optimal total daily dose in most patients will be 2000 mg/day; it is uncommon to see additional benefit when dose is increased to 2550 mg/day.
- Does not lead to hypoglycemia, unless used in conjunction with insulin secretagogues or insulin.
- Preferred initial agent in the overweight Type 2 DM patient, due to lack of hypoglycemia risk, as well as non-glycemic benefits of weight loss/weight neutrality, ↓insulin resistance, improved lipid profiles, etc. In addition, ↓macrovascular events noted in overweight metformin-treated subjects in UKPDS (*UKPDS Group. Lancet 352:837, 1998*). This effect persisted in the long-term follow-up study (*UKPDS Group. N Engl J Med 359:1577, 2008*) vs diet therapy, despite equivalent HbA1c levels after the randomized component of the trial.
- When it occurs, diarrhea usually resolves after several weeks. Gradual dosing titration recommended to minimize this side effect.

α-Glucosidase Inhibitor (AGI) Considerations

- Minimal systemic absorption, but contraindicated in patients with severe hepatic or renal impairment.
- Gradual dosage titration (over 6–12 weeks) preferred to minimize GI side effects.
- Needs to be taken with carbohydrate-containing meal.
- Major effect is to decrease post-prandial glucose excursions.
- Hypoglycemia (if used with sulfonylurea or insulin) must be treated with glucose only (not sucrose or other starches).
- Compared with several other oral agent classes, the AGIs appear to have lower efficacy on HbA1c. As a result, they are not commonly used as monotherapy in the U.S., although they remain popular overseas.
- Marked reduction in myocardial infarction rates was noted with acarbose in a diabetes prevention trial (STOP-NIDDM; *Chiasson JL et al. JAMA 290:486, 2003*).

Thiazolidinedione (TZD) Considerations

- Weight gain and edema can be problematic in some patients, particularly at higher doses and when used with insulin or secretagogues. In predisposed patients, clinical heart failure can occur. Contraindicated in patients with New York Heart Association Class III-IV heart failure. Not recommended in any patient with symptomatic heart failure.
- Recent meta-analyses have suggested an increased risk of myocardial infarction in patients taking rosiglitazone (*Nissen & Wolski. N Engl J Med 356:2457, 2007; Singh et al. JAMA 298:1189, 2007*), but the data are controversial. A recent large clinical trial has not confirmed this finding, however (*RECORD; Home et al. Lancet 373:2125, 2009*).
- Of note, the concern re: myocardial infarction risk has not been extended to pioglitazone (*Lincoff et al. JAMA 298:1180, 2007*). In the only published prospective TZD clinical trial assessing cardiovascular endpoints (PROactive), pioglitazone, when added to baseline anti-hyperglycemic therapy in patients with Type 2 diabetes with established macrovascular disease, modestly reduced the secondary composite endpoint of mortality, myocardial infarction, and stroke (*Dormandy JA et al. Lancet 366:1279, 2005*). Of note, however, a significant effect from pioglitazone on the primary endpoint (a broader cardiovascular composite) was not achieved in this study.
- An increase in bone fracture rates, mainly at peripheral sites, has been observed in women with both rosiglitazone and pioglitazone.
- An earlier TZD, troglitazone (*Rezulin®*), was removed from the market because of an association with rare, idiosyncratic hepatocellular injury, sometimes leading to fulminant hepatic failure. Currently available agents have no such association. However, periodic LFT monitoring is still recommended.
- Do not use in patients with underlying hepatic dysfunction or if baseline ALT >2.5x ULN. ALT should be followed periodically per the clinical judgment of the healthcare professional; D/C if ALT ↑s to >3x ULN.
- Pioglitazone appears to have improved lipid effects compared with rosiglitazone (↓ TGs, ↑ HDL).

- Does not lead to hypoglycemia, unless used in conjunction with insulin secretagogues or insulin.
- Rosiglitazone has been shown to be a more durable therapy than glyburide and slightly more durable than metformin (“β-cell preservation”). (*Kahn SE. N Engl J Med 355:2427, 2006*)
- Delayed onset of action; may take 6–12 weeks to achieve peak effect.

DPP-4 Inhibitor Considerations

- Mechanism of action is to inhibit the enzyme which degrades endogenous incretin hormones, GLP-1 and GIP, thereby increasing their meal-stimulated levels. This results in increased glucose-dependent insulin secretion, decreased glucagon secretion, and delayed gastric emptying.
- They appear to have a good safety profile, with no major side effects reported to date. Some reports have emerged of urticaria and angioedema, although the association with sitagliptin is not clear. Reports of pancreatitis have also emerged, but, similarly, it remains unclear if related to the medication.
- They are given QD, and there is no dose titration necessary.
- Sitagliptin is renally eliminated, and it is recommended that the dose be adjusted in patients with renal insufficiency. Whereas the standard dose is 100 mg QD, this should be reduced to 50 mg QD in those with moderate renal insufficiency (GFR 30–50 mL/min), and to 25 mg QD in those with severe renal insufficiency (GFR <30 mL/min). Saxagliptin is both hepatically and renally eliminated; the usual dose of 5 mg QD should be reduced to 2.5 mg QD if the GFR is <50 mL/min. CYP3A4/5 inhibitors (simvastatin, diltiazem, ketoconazole, clarithromycin, certain HIV medications) and inducers (rifampin) will alter the pharmacokinetics of saxagliptin.
- Animal studies suggest a beneficial effect on beta-cell mass and, hypothetically, they may have a more durable effect on beta-cell function. There is no clinical trial to date that confirms this, however, in humans.

Bile Acid Sequestrant Considerations

- On the market for many years as lipid-lowering drugs.
- Colesevelam is the only member to be approved as an anti-hyperglycemic drug for Type 2 diabetes.
- Mechanism of action on glucose not well understood.
- Effect is modest — mean HbA1c reduction ~0.5%.
- Additional benefits: modest reduction in LDL-C, “non-systemic” mechanism of action, and weight neutrality.
- Frequently leads to constipation; can also increase triglyceride levels.
- Contraindicated if TG >500 mg/dL or h/o pancreatitis due to hypertriglyceridemia; h/o bowel obstruction. Avoid in those with significant h/o GI disease/symptoms.

Dopamine-2 Receptor Agonist Considerations

- Dopamine agonists used for decades for hyperprolactinemia and Parkinson disease.
- A short-acting version of bromocriptine approved as an anti-hyperglycemic drug for Type 2 diabetes.
- Mechanism of action likely involves alteration of hypothalamic neurotransmitter tone, with systemic effects on free fatty acid oxidation and hepatic glucose production.
- Weight neutral and not associated with hypoglycemia.
- Potential side effects include orthostatic hypotension, dizziness, syncope, exacerbation of underlying psychotic disorders, somnolence, fatigue, and nausea/vomiting.
- Should not be used in those taking dopamine antagonists.

❖ Non-insulin Injectables

GLP-1 Agonists

• **Exenatide (Byetta®), Liraglutide (Victoza®)**

Exenatide and liraglutide are incretin mimetics and members of the class of drugs known as GLP-1 agonists. Incretins are gut-derived peptides normally secreted in response to meals. The most widely studied incretin, glucagon-like peptide-1 (GLP-1), has several effects on glucose homeostasis: glucose-dependent stimulation of insulin, suppression of glucagon, delaying of gastric emptying, and the promotion of satiety. They are approved for use as monotherapy and in combination with sulfonylureas, metformin, or TZDs in Type 2 diabetes. (There are little data in combination with insulin.) They reduce HbA1c by approximately 1% compared with placebo; liraglutide appears to be slightly more potent especially on fasting glucose, likely due to longer activity profile. Distinct from most other diabetes drugs, the GLP-1 agonists promote weight loss. While they do not by themselves cause hypoglycemia, they may increase the risk when used with sulfonylureas.

Side effects include nausea/vomiting. Recently, reports of pancreatitis have emerged, in some cases suspected to be drug-related. In animal models, liraglutide was associated with the development of C-cell tumors and small increases in calcitonin levels were noted in human trials. Any possible effect on medullary thyroid carcinoma (MCT) in humans is not known, however. Liraglutide is contraindicated in patients with h/o MCT or MEN 2 syndrome. Exenatide is renally cleared and should not be used in patients with severe renal (GFR <30 mL/min.) Both drugs should probably be avoided in patients with significant gastrointestinal disease, especially gastroparesis.

The GLP-1 agonists are available only in injectable form and available in multi-dose pens (exenatide, 5-mcg and 10-mcg pens; liraglutide, single pen delivering 0.6–1.8 mcg/injection). To

minimize GI side effects, treatment should begin at a low dose and slowly increased. Exenatide is started at 5 mcg SQ BID, given within 1 hour of the morning and evening meals. After 1 month, the dose may be titrated up to 10 mcg BID. Liraglutide is started at 0.6 mg QD. After one week, the dose may be increased to 1.2 mg/day; this can be increased further to 1.8 mg/day if BG control remains suboptimal. A preemptive reduction in the sulfonylurea dose should be considered, especially in those patients whose BG control is near target.

In preliminary studies in animals, incretin mimetics appear to promote beta-cell growth and preserve beta-cell function. These agents may therefore be advantageous earlier in the disease course than they are typically used. There are no convincing data yet regarding durability of effectiveness in humans, no long-term safety data, and no information on micro- or macrovascular complications. Other GLP-1 mimetics injected weekly are in late stages of clinical development.

Amylin Mimetics

• Pramlintide (Symlin®)

Amylin is a natural, pancreatic islet peptide normally secreted with insulin in response to meals. It has several effects on glucose homeostasis: suppression of glucagon, delaying of gastric emptying, and the promotion of satiety. Pramlintide, a synthetic amylin analogue, is currently approved for use in patients with Type 1 diabetes and in insulin-requiring patients with Type 2 diabetes inadequately controlled on their current regimens. It is given before meals, in a separate subcutaneous injection but usually in conjunction with insulin. Its major role is to decrease post-prandial glucose excursions. In clinical trials, HbA1c reduction is very modest, ~0.5%. Pramlintide induces weight loss, which distinguishes it from insulin therapy. Side effects include nausea/vomiting, particularly at higher doses. Its frequent dosing schedule also makes it inconvenient. In Type 1 diabetes, pramlintide should be started at 15 mcg SQ TID and slowly

increased as needed to 45 mcg TID. In Type 2, the initial dose is 30 mcg TID; the dose may be increased slowly to 120 mcg TID. Pramlintide is available in vials containing 5 mL of a 600 mcg/mL solution. Injection volumes are 0.025–0.2 mL, equivalent in volume to 2.5–20 “units” in an insulin syringe. (Also available in pens: SymlinPen® 60 [delivers 15, 30, 45, or 60 mcg doses] and SymlinPen® 120 [delivers 60 or 120 mcg doses].) At this time, its niche appears to be in poorly controlled Type 1 and Type 2 patients already on intensive insulin regimens, whose glucose profile shows post-prandial hyperglycemia that cannot be adequately addressed by increasing the dose of pre-meal rapid-acting insulin. Because of its effect on satiety, it may be most attractive in overweight patients. It is contraindicated in patients with gastroparesis or hypoglycemia unawareness.

	dose sizes dose/day (mg)	dose interval	peak (hrs)	t _{1/2} (hrs)	duration (hrs)	side effects
GLP-1 MIMETICS						
Exenatide (Byetta®)	5, 10 mcg 10–20 mcg	BID	2	2–3	10	nausea, vomiting, diarrhea, ?pancreatitis
Liraglutide (Victoza®)	0.6, 1.2, 1.8 mg 1.2–1.8 mg	QD	8–12	13	24	nausea, vomiting, diarrhea, ?pancreatitis
AMYLIN MIMETICS						
Pramlintide (Symlin®)	15–120 mcg 45–360 mcg	TID	20 min	50 min	2–2.5	nausea, vomiting

❖ Insulin Types

Human Insulin & Insulin Analogues	onset*	peak*	duration*
Rapid-Acting Analogues[†]			
• Insulin lispro (<i>Humalog</i> [®])	10–15 min	1–2 hrs	3–5 hrs
• Insulin aspart (<i>NovoLog</i> [®])	10–15 min	1–2 hrs	3–5 hrs
• Insulin glulisine (<i>Apidra</i> [®])	10–15 min	1–2 hrs	3–5 hrs
Short-Acting			
• Regular	0.5–1 hr	2–4 hrs	4–8 hrs
Intermediate-Acting			
• NPH	1–3 hrs	4–10 hrs	10–18 hrs
Long-Acting Analogues			
• Insulin glargine [‡] (<i>Lantus</i> [®])	2–3 hrs	none	24+ hrs
• Insulin detemir [‡] (<i>Levemir</i> [®])	1 hr	none	Up to 24 hrs
Pre-Mixed Insulins[§]			
• 70/30 (70% NPH + 30% Regular)	0.5–1 hr	2–10 hrs	10–18 hrs
• 50/50 (50% NPH + 50% Regular)	0.5–1 hr	2–10 hrs	10–18 hrs
• Humalog Mix 75/25 (75% lispro protamine + 25% lispro)	10–15 min	1–3 hrs	10–16 hrs
• Humalog Mix 50/50 (50% lispro protamine + 50% lispro)	10–15 min	1–3 hrs	10–16 hrs
• NovoLog Mix 70/30 (70% aspart protamine, 30% aspart)	10–20 min	1–4 hrs	10–16 hrs



*Pharmacokinetics of insulins is influenced by dose, injection site, and patient-specific factors that are not well defined. Inter-individual and intra-individual differences are frequently encountered. As a result, certain patients may experience variable onsets, peaks, and durations of insulin action.

[†]Must be given no more than 15 minutes before eating. Can also be given immediately after meals.

[‡]Do not mix with any other type of insulin.

[§]Pre-mixed insulins provide convenience but do not allow for any flexibility in adjusting the dose of the short/rapid-acting component.

Notes

- All insulins available in 10 cc vials of “U-100” strength, i.e., 1 cc = 100 U (Each vial contains 1000 U).
 **RULE OF THUMB:** 1 vial will last a patient ~1 mo when used at a dose of ~30 U/day.
- Most products are available in disposable pens and some are available in cartridges for reusable pens (150 U, 300 U). Pens and cartridges are typically sold in boxes of 5.
 **RULE OF THUMB:** A 300 U pen will last a patient ~10 days when used at a dose of ~30 U/day.
- Insulins should be refrigerated for prolonged storage. May be left at room temperature for up to 1 month without loss of potency. Extremes of temperature should be avoided.
- Needleless jet injector devices are also available, although insulin absorption is erratic.
- Sites of insulin injection are an often-overlooked variable. The most reliable and quickest absorption tends to be from the subcutaneous tissue of the anterior abdomen. Thighs, buttocks, and deltoid regions are acceptable injection sites, but absorption is, at rest, slower from these areas. When a limb is exercised, however, absorption may be hastened. It is best to avoid injecting a limb if it will be exercised soon afterward. It is often helpful that a certain region of the body be used consistently for certain times of day (i.e., morning injection in abdomen; evening injection in thigh). Within a certain body region, injection sites should be rotated, so as to prevent lipohypertrophy. Absorption from lipohypertrophic areas is reduced and these areas should be avoided.

❖ Outpatient Insulin Regimens

	Breakfast	Lunch	Supper	Bedtime
1.				Glar, Det, NPH
2.	Glar, Det, NPH			
3.	Det, NPH		Det, NPH	
4.	Det, NPH			Det, NPH
5.*	Det, NPH + Reg, Lis, Asp, Glu		Det, NPH + Reg, Lis, Asp, Glu	
6.*	Det, NPH + Reg, Lis, Asp, Glu		Reg, Lis, Asp, Glu	Det, NPH
7.*	Det, NPH + Reg, Lis, Asp, Glu	Reg, Lis, Asp, Glu	Det, NPH + Reg, Lis, Asp, Glu	
8.	Reg, Lis, Asp, Glu	Reg, Lis, Asp, Glu	Reg, Lis, Asp, Glu	Glar, Det, NPH
9.	Det, NPH + Reg, Lis, Asp, Glu	Reg, Lis, Asp, Glu	Reg, Lis, Asp, Glu	Det, NPH
10.*	NPH + Lis, Asp, Glu	NPH + Lis, Asp, Glu	NPH + Lis, Asp, Glu	NPH
11.	Continuous subcutaneous insulin infusion (CSII — insulin pump) (see pp. 65–68)			

*Can use convenient but less adjustable pre-mixed insulins (70/30, 75/25, 50/50) for a portion of these regimens.

Glar = insulin glargine (basal analogue; <i>Lantus</i> [®])	Reg (or "R") = Regular human insulin (<i>Humulin</i> [®] -N, <i>Novolin</i> [®] -N)
Det = insulin detemir (basal analogue; <i>Levemir</i> [®])	Lis = insulin lispro (rapid analogue; <i>Humalog</i> [®])
NPH (or "N") = neutral protamine Hagedorn (<i>Humulin</i> [®] -N, <i>Novolin</i> [®] -N)	Asp = insulin aspart (rapid analogue; <i>NovoLog</i> [®])
	Glu = insulin glulisine (rapid analogue; <i>Apidra</i> [®])

Notes

- Any insulin regimen, as long as it results in targeted glycemic control, minimizes hypoglycemia, and is acceptable to the patient, is an appropriate regimen for that patient.
- In general, **Type 2 DM patients** can first be tried on small doses of long-/intermediate-acting insulin alone, once or twice daily (**regimens 1–4**). The most popular is regimen 1. Many patients find beginning with 0.2 U/kg at bedtime the most palatable way to initiate insulin therapy. More complex regimens are frequently necessary, particularly later in the course of disease, when endogenous insulin secretion declines further (**regimens 5–9**). Indeed, most do best with ≥ 2 injections per day of long-/intermediate + short-/rapid-acting insulins (convenient pre-mixed insulins can be used instead).
 - Optimal regimens and total daily dose (TDD) of insulin are highly variable in Type 2 DM patients, based on body weight, the concurrent use of oral agents, endogenous insulin secretory capacity, and the degree of insulin resistance. Dosing can range anywhere between 0.2–1.5 U/kg (or more). When starting a Type 2 patient with significant hyperglycemia on full insulin dosing, begin with ~ 0.5 U/kg.
 - When "split mixed" regimens are used, insulin proportions are typically 60% in a.m. and 40% in p.m., with N:R ratio of 2:1 in a.m. and 1:1 in p.m.
 - AM dose: TDD \times 0.4 = a.m. NPH
TDD \times 0.2 = a.m. Reg, Lis, Asp, Glu
 - PM dose: TDD \times 0.2 = p.m. NPH
TDD \times 0.2 = p.m. Reg, Lis, Asp, Glu

3. In general, **Type 1 DM patients** should always be treated with at least 2 injections of mixtures of short/rapid-acting and long/intermediate-acting insulin (**regimens 5–9**). The most popular mixed regimens are **8 and 9 (with glargine or detemir)**. Better control is usually achieved with “intensive” regimens, involving 3–4 injections per day or the insulin pump.

- For Type 1 diabetes, total daily dose (TDD) of insulin is typically 0.4–1.0 U/kg; recommend starting with 0.5 U/kg.
- Insulin proportions are typically 60% in a.m. and 40% in p.m., with NPH:Reg ratio of 2:1 in a.m. and 1:1 in p.m.

■ AM dose: TDD × 0.4 = a.m. NPH
 TDD × 0.2 = a.m.

■ PM dose: TDD × 0.2 = p.m. N (or L)
 TDD × 0.2 = p.m. R (or LP, A)

4. Other than an insulin pump, the “basal/bolus” regimen (**regimens 7–10**) provides insulin replacement therapy that most closely mimics endogenous insulin secretion. As a result, glycemic control is usually best with this regimen in Type 1 patients or in the more labile insulin-requiring Type 2 patients. However, implementation of basal/bolus insulin therapy requires an educated and compliant patient, frequent monitoring, and close oversight by a physician and/or diabetes educator. If glargine or detemir is used as the “basal” insulin, administer as approximately 50% of TDD, with remainder provided as Lis, Asp, or Glu, divided equally before meals (if caloric intake is equal—if not, adjust accordingly).

■ Basal dose: TDD × 0.5 = QD glargine
 QD-BID detemir

■ Bolus dose: TDD × 0.5 ÷ 3 = TID lispro, aspart,
 or glulisine

5. **Regimen 10** may be tried in extremely labile/brittle individuals who cannot achieve control with any other regimen and who refuse or cannot use an insulin pump.
6. Insulin pumps (*see pp. 65–68, Insulin Pumps*) are typically used in highly motivated patients (usually Type 1s) not achieving good control despite multiple insulin injections per day or in those who prefer this technology’s convenience, discreetness, and advanced capabilities (including the ability to communicate with a continuous glucose sensor [*see pp. 41–42, Glucose Sensors*]).
7. Use of rapid-acting insulin analogues (lispro [*Humalog*®], aspart [*NovoLog*®], glulisine [*Apidra*®]) blunts post-prandial BG excursions and decreases hypoglycemia during fasting intervals. When transferring from R insulin, no dosage change is generally required. However, in selected patients or when the R dose is especially high, it is reasonable to cut back by 10–20%. Also, when switching from R to an analogue, an increase in the patient’s dose of long-/intermediate-acting insulin may be required, due to the loss of R insulin’s “tail” of activity beyond 4 hrs from injection.
8. Changes in the insulin regimen should be made slowly and cautiously so as to avoid overtreatment and hypoglycemia. Generally, increases should be made in the long-/intermediate-acting insulin doses when BG is found to be high throughout the day or during those time periods that correspond to the major action of these insulin types. Increases in the short-/rapid-acting insulin doses should be made based on post-prandial BG readings, so as to blunt post-prandial hyperglycemia. Insulin changes should usually be made based chiefly on the results of home glucose monitoring over several days to 1–2 weeks. Changes should NOT be made too frequently, and the incessant vagaries of diet, activity level, and stress need to be taken into account

before adjusting the insulin dose. Except for severe hyper- or hypoglycemia, when more aggressive changes are necessary, increases/decreases in the insulin doses are generally made in 10–20% increments, which usually calculates to 1–5 U at a time.

9. Many diabetologists prefer pre-meal adjusted dosing of rapid-acting insulins to fixed doses, as a method of matching the patient's insulin dose to the patient's current insulin requirements. Such a program can be explained to the patient either as:
 - a classical graded **adjusted (or "sliding") scale** based on parameters of BG (e.g., "2 U for BG 100–149 mg/dL, 4 U for BG 150–199, 6 U for BG 200–249"),
OR
 - a fixed insulin dose, with modulations ("correction bolus") from that baseline, based upon the BG (e.g., "5 U + 1 extra unit for each 50 mg/dL starting at BG 150 mg/dL"). (See pp. 96–97, *Insulin Dosing Instruction Sheets*.)

More advanced patients can further adjust their pre-prandial rapid-acting insulin based on their expected carbohydrate intake (as do insulin pump patients) and/or their expected activity level during the hours after the meal. Generally, the long/intermediate-acting insulin doses are NOT changed by the patient on a day-to-day basis, unless significant changes in caloric intake or activity level are expected for that day. However, a clinical trial showed that patient-adjusted, long/intermediate-acting insulin therapy was safe and effective. (Treat-to-Target; Riddle et al. *Diabetes Care* 26:3080, 2003)
10. NPH may be mixed with short/rapid-acting insulins. Glargine and detemir may not be mixed with other insulins.
11. Proper patient education regarding proper insulin injection technique should also be stressed. Key points include: site selection, precise dose measurement, vial

"rolling" to fully resuspend insulin crystals (for insulin suspensions [i.e., "cloudy"]), mixing sequence, aseptic technique, insulin storage, etc.

❖ Insulin Pumps

An insulin pump is an electronic, pager-sized, battery-powered device that delivers insulin automatically and continuously via a plastic catheter, whose tip is inserted by the pump user into subcutaneous tissue. The catheter is changed every 2–3 days and is attached to an insulin-containing syringe that is driven by an electronic motor, controlled by the pump's computer.

Insulin is administered as one or several "**basal**" rates of rapid-acting insulin + "**boluses**" of same delivered before meals, the latter calculated based on expected carbohydrate grams to be ingested ("carb counting") (typically carb/insulin ratio = 15 g/1 U, but can range between 10/1 [more insulin] to 20/1 [less insulin] or beyond).

Indications

An insulin pump is typically chosen in Type 1 patients who cannot achieve control despite multiple daily injection (MDI) regimens, i.e., those with persistent hyperglycemia or hypoglycemia. The most common scenarios would be an individual with unpredictable "highs" or "lows" despite at least 3 injections composed of both long-acting and rapid-acting insulins, or the patient with a refractory "dawn phenomenon." Pumps are also useful in patients whose erratic work schedules/lifestyles are not compatible with the time course of action of conventional long/intermediate-acting insulins. Certain Type 2 patients may also benefit from pump therapy.

Patient Criteria

Insulin pump users are typically highly motivated individuals who have the capacity to program the pump, respond to warning alarms, monitor their BGs 4–8x per day, and calculate their pre-meal boluses based on their carbohydrate intake. Insulin pumps are NOT appropriate for patients who do not meet these criteria. An insulin pump is NOT a substitute for poor diabetes education or suboptimal self-management skills!

Calculation of “Basal Rate”¹

1. ↓ Total Daily Dose (TDD) of injected insulin by 20–25% (“safety factor”).
2. Divide this amount in half: 50% will become “basal” insulin and 50% will be divided into pre-meal boluses.
3. Divide the “basal” amount by 24 hrs to arrive at initial hourly “basal rate” (typically 0.5–1.0 U/hr). This amount will provide basal insulin requirements, chiefly to suppress hepatic glucose production and lipolysis. The basal rate can be further adjusted to provide more or less insulin during certain hours, based on BG monitoring. Changes are typically made in 0.1 U/hr increments.
4. Divide the overall “bolus” amount into 3 individual boluses, to be administered before meals. These amounts will be responsible for peripheral disposal of ingested carbohydrate calories. Alternatively, for each meal, insulin should be administered based on carbohydrate intake (*see below*).

Calculation of Mealtime “Bolus”¹

Most patients will require 1 unit of insulin to dispose of 10–15 g of ingested carbohydrates. We typically begin with a 15:1 ratio

(g carbs/U insulin), unless the patient is already taking very small (*or very large*) amounts of prandial insulin, in which case we would begin with a 20:1 (*or 10:1*) ratio. If the ratio is correct, the 2-hr post-prandial BG is close to the pre-prandial BG (increase ≤ 40 mg/dL). For example, if a patient’s ratio is 15:1, and the patient plans to eat a meal consisting of 60 g carbohydrates, the bolus insulin dose would be 4 U. If the pre-meal BG were higher (*or lower*) than target, further adjustments would be made. (*See Correction Factor next.*)

Calculation of “Correction Factor”²

To determine the expected glucose-lowering response to 1 unit of insulin: $1700 \div \text{Total Daily Dose (on pump)} = \text{_____ mg/dL}$. Pump patients can use this figure to approximate supplemental insulin requirements when their BG is out of range. Most patients’ BG will decrease between 30–50 mg/dL for each unit of insulin.

¹Bode BW, Establishing and verifying basal rates; Davidson PC, Bolus & supplemental insulin. In: Fredrickson L, ed. The Insulin Pump Therapy Book. Sylmar: MiniMed Inc., 1995

²Davidson et al. Diabetes 52(S1):A103, 2003

Insulin Types & Pump Supplies

Insulin pumps require rapid-acting insulin analogues. In addition to the pump itself, additional supplies required include: special 3-cc pump syringes, infusion catheters, adhesive dressings, and batteries. Patients must keep handy the pump manufacturer’s 24-hr toll-free emergency assistance telephone number (usually printed on the back of pump unit). Patients are also instructed to keep fresh vials of their former insulins and syringes available in rare cases of pump failure.

MANUFACTURER	WEB ADDRESS	SUPPORT LINE
Medtronic MiniMed	www.minimed.com	1-866-948-6633
Animas	www.animascorp.com	1-877-767-7373
Insulet (OmniPod)	www.MyOmniPod.com	1-800-591-3455
Roche/ Accu-Chek	www.disetronic-usa.com	1-800-280-7801
Nipro Diabetes Systems	www.niprodiabetes.com	1-888-651-7867
Sooil	www.sooil.com	1-866-747-6645
Deltec (Cozmo)*	www.cozmore.com	1-800-826-9703

*No longer manufactured, as of 2009.

◆ Targets for Glycemic Control

Criteria	Frequency	Goal
HbA1c (lab "normal" range 4–6%; desirable ≤5.6%)	Q3–6 mo	<7%
FPG/pre-prandial PG (mg/dL)	varies*	70–130
1–2 hr post-prandial PG†	varies*	<180

*See pp. 39–40, *Self-Monitoring of Blood Glucose*.

†Post-prandial glucose should be targeted if HbA1c goal is not achieved despite reaching pre-prandial target.

From: American Diabetes Association. *Diabetes Care* 33:S23, 2010

Notes

- Data from 3 large recent prospective, randomized trials (ACCORD, ADVANCE, VADT) have shown **no** benefit on CV outcomes from more stringent glycemic control, targeting HbA1c <6–6.5%. In one of these studies (ACCORD), patients assigned to more intensive therapy actually had *increased* CV mortality. Accordingly, although achieving a HbA1c <7% clearly reduces the incidence of *microvascular* disease, there remains no definitive evidence of such an effect on *macrovascular* disease risk over a period of 3–5 years of therapy. In fact, overexuberant glycemic lowering may slightly increase the risk of death in older patients with long-standing T2DM who have established CVD or several CVD risk factors. It remains unclear if this risk relates to hypoglycemia, overall polypharmacy/medication burden, or other factors. In contrast, however, secondary analyses from some of these studies suggest that patients without CVD at baseline and with shorter duration of diabetes may still benefit from a cardiovascular standpoint with more aggressive glycemic targets.
- Glucose values refer to plasma values. Subtract 10 mg/dL if using whole blood glucose or if home meter is not calibrated to plasma values (rare).
- For individual patients, less aggressive goals may be warranted: advanced complications, elderly, infirm, hypoglycemia-prone, hypoglycemia unawareness, non-compliant. For example, "fair control" = pre-meal BG <200; "loose control" = avoid hyper-/hypoglycemic symptoms only.
- Goals during pre-conception and pregnancy are more stringent than above: pre-meal BG 60–90; 1-hr post-prandial BG ≤140; 2-hr post-prandial BG ≤120.

HbA1c & Estimated Average Glucose (eAG)

HbA1c	Mean Plasma Glucose
6%	126 mg/dL (7.0 mmol/L)
7%	154 mg/dL (8.6 mmol/L)
8%	183 mg/dL (10.2 mmol/L)
9%	212 mg/dL (11.8 mmol/L)
10%	240 mg/dL (13.4 mmol/L)
11%	269 mg/dL (14.9 mmol/L)
12%	298 mg/dL (16.5 mmol/L)

From: American Diabetes Association. Diabetes Care 32:S19, 2009
(eAG calculator at <http://professional.diabetes.org/eAG>)

Notes

- In general, venous plasma glucose is approximately 15% higher than venous whole blood glucose. Laboratory glucose determinations are usually performed on plasma. Older glucose meters typically reported whole blood glucose concentrations. Newer meters are almost all “plasma standardized” — i.e., while they still obviously measure the glucose concentration in whole (capillary) blood, an internal correction is made, and the meter actually reports a higher, calculated plasma glucose.
- HbA1c measures the percentage of hemoglobin molecules that have undergone irreversible, non-enzymatic glycation, a process that is increased in a hyperglycemic milieu. HbA1c therefore indirectly reflects the average circulating glucose concentrations over the previous 2–3 months (taking into account the life span of red blood cells). The “average glucose” incorporates both fasting glucoses and the post-prandial glucoses (PPG). It is possible to have good results on fasting determinations, yet still have a high HbA1c — in these circumstances, elevated PPG is likely and

should be monitored and targeted accordingly (medication, diet). Over the past several years, there has been increasing attention paid to PPG, as it may be a better marker of increased cardiovascular disease risk than fasting glucose.

- It is possible to have a good result on HbA1c testing, yet still have suboptimal overall glucose control. Since HbA1c represents the average glucose, patients with frequent episodes of hyperglycemia and hypoglycemia may have HbA1c levels that are within the desirable range. This fact underscores the importance of home glucose monitoring for comprehensive assessment of glucose control in the diabetic patient.
- Certain patients with hemoglobin abnormalities may have unreliable HbA1c testing, depending on the specific assay used (*see www.NGSP.org for more details about various assays*). In addition, in patients with anemias associated with high bone marrow turnover (i.e., hemolytic anemia), the HbA1c will tend to be lower and also reflect BG control over a shorter period of time. HbA1c may also be reduced in patients with iron-deficiency anemia.
- ESRD patients generally have lower HbA1c than would be anticipated by their average glucose.
- Even when none of these conditions are present, HbA1c should still be considered an approximation of average glucose. It does not correlate to the same degree in all patients.
- Other blood tests to assess long-term glucose control are also available but not widely used. These reflect different durations of glycemic control and include glycated serum protein (GSP; 1–2 weeks), fructosamine (2–3 weeks), and glycated albumin (3 weeks).

◆ Type 2 DM Treatment Algorithms

Diet, exercise, and, where appropriate, weight loss remain the central components of any Type 2 diabetes (T2DM) treatment regimen. Such maneuvers may be effective by themselves and

certainly enhance the effectiveness of any pharmacological regimen. There are also additional health benefits and essentially no adverse effects. For the drug-naïve patient, which oral agent class to use first remains somewhat controversial. Choosing the best drug for an individual patient will take into account: (1) the amount and the rapidity of glucose lowering required; (2) the potential for adverse effects (toxicities, hypoglycemia, weight gain, etc.); (3) the potential for “non-glycemic benefits” (lipid lowering, insulin sensitization, etc.); (4) compliance issues; and (5) cost. All oral agents can reasonably be used as first line.

Because of the importance of insulin resistance in the pathogenesis of T2DM and its relationship to macrovascular disease, some initially favor “insulin sensitizers” (metformin, TZDs) as opposed to “insulin secretagogues.” This is particularly true for metformin in the obese patient, since weight loss frequently occurs, and this subgroup of patients enjoyed a reduction in macrovascular risk in the UKPDS. The TZDs appear to preserve β -cell function and held promise for potential anti-atherosclerotic effects. In PROactive,¹ the first TZD-CVD outcomes trial, addition of pioglitazone to pre-existing anti-hyperglycemic therapy in T2DM patients with macrovascular disease modestly reduced all-cause mortality, myocardial infarction, and stroke. There was, however, a small increase in non-adjudicated heart failure hospitalizations in active therapy patients.

Recent meta-analyses have suggested an increased risk of myocardial infarction in patients taking rosiglitazone,^{2,3} but the data are controversial. More recent clinical trials have not confirmed such a risk. However, pioglitazone is the preferred TZD by many authorities.⁴

In the ADOPT⁵ study, rosiglitazone had a more durable effect on glucose than glyburide, and slightly more than metformin. The newer DPP-4 inhibitors hold promise because of their apparently favorable adverse effect profile, at least as demonstrated in short-term clinical trials.

Importantly, when agents are combined, their efficacy is typically additive or slightly less than additive. Drug classes with different mechanisms of action can and should be combined to achieve glycemic control. Some authorities favor starting patients on combination therapy from the outset because of the dual defects of insulin resistance and insulin deficiency. On the following pages are proposed algorithms, which are pathophysiologically based, for the oral agent management of T2DM.

¹Dormandy J et al. Lancet 366:1279, 2005

²Nissen SE, Wolski K. N Engl J Med 356:2457, 2007

³Singh et al. JAMA 298:1189, 2007

⁴Nathan et al. Diabetes Care 32:193, 2009

⁵Kahn SE et al. N Engl J Med 355:23, 2006

Implications of Recent T2DM-CVD Trials

Three recent randomized clinical trials (ACCORD¹, ADVANCE², VADT³) tested the potential CV benefit of more intensive glucose control (HbA1c <6–6.5%) over a period of 3–5 years. Interestingly, all 3 trials proved negative. In ACCORD, CV mortality was actually *increased* in the intensive group, which may have reflected increased hypoglycemia or some unknown factors related to the relatively rapid reduction of glucose in this trial and/or the polypharmacy required. In one study, ADVANCE, renal outcomes (RRR=21%, $P=0.006$) were improved with the more stringent target, but not mortality nor CVD outcomes. In VADT, it was suggested that those with more recently diagnosed diabetes may indeed benefit with more intensive glycemic control, whereas this approach may actually harm those with more long-standing disease. Importantly, none of these trials addressed the question as to whether more intensive glycemic management may have benefits if applied and maintained for >5 years.

Given the concerns of hypoglycemia, the much greater efforts required to achieve near-normoglycemia, and the results of these trials, the risk of targets below the conventional <7% appears to

outweigh any potential benefit on a population level. However, more stringent targets might be considered on an individual basis. Candidates for a more aggressive approach would include younger patients with shorter diabetes duration and without established CVD, in whom the targets are easily achieved with a tolerable therapeutic program and without significant hypoglycemia. The primary goal of such an effort would be to minimize the risk of microvascular disease and, potentially, macrovascular disease—although there are no solid data to support the latter. However, in most older patients, achieving an HbA1c of $<7.0\%$ would appear to be sufficient to minimize the risk of all complications. Indeed, in those with multiple comorbidities, a more conservative goal of HbA1c $<8.0\%$ may be justifiable. Individualization is key. Importantly, blood pressure and lipid management play the primary roles in the prevention of cardiovascular events in all patients with diabetes.

Two different algorithms, both written by consensus, are also available.

1.) **ADA-EASD sponsored algorithm** (Nathan *et al.* Diabetes Care 32:193, 2009)

This protocol is generally considered more conservative and endorses insulin therapy earlier in the course of disease.

2.) **ACE-AACE official algorithm** (Rodbard *et al.* Endocrine Practice 15:540, 2009)

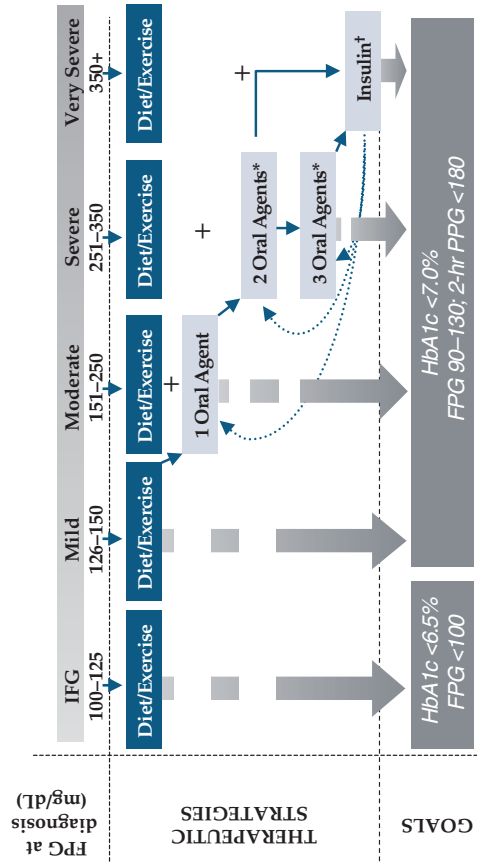
This is a more expansive and inclusive protocol. A unique feature is its different recommendations based on baseline HbA1c level.

¹ACCORD Study Group. N Engl J Med 358:2545, 2008

²ADVANCE Collaborative Group. N Engl J Med 358:2560, 2008

³Duckworth *et al.* N Engl J Med 360:129, 2009

General T2DM Therapy Algorithm Based on Degree of Hyperglycemia

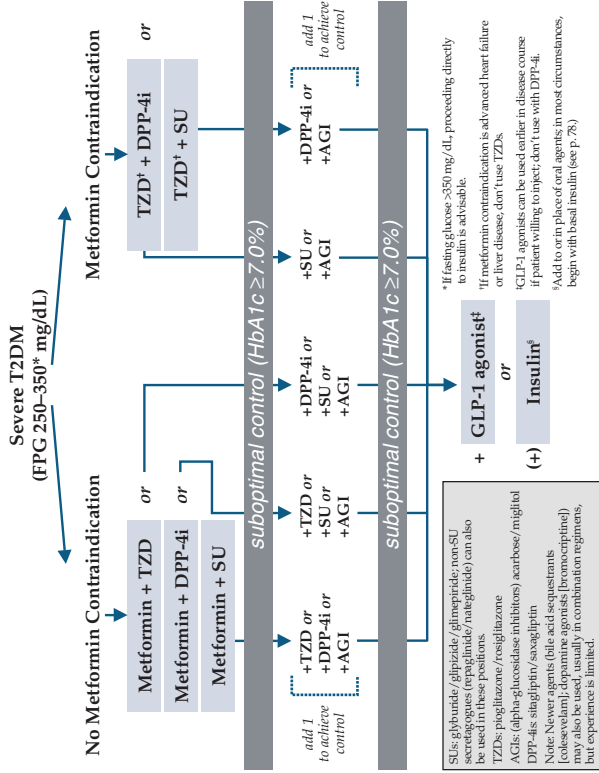
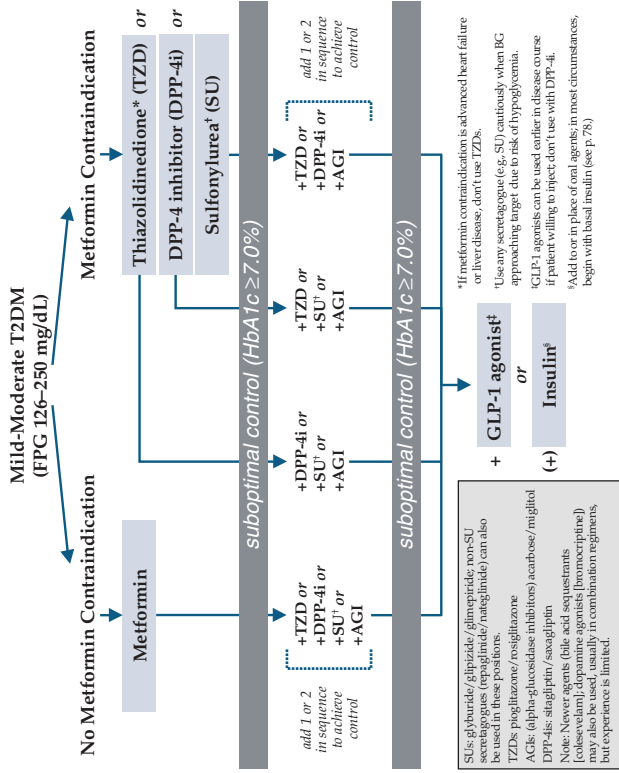


*Oral agents in combination should be chosen from classes with different mechanisms of action (i.e., metformin, thiazolidinediones, DPP-4 inhibitors, secretagogues, alpha-glucosidase inhibitors). Exenatide can be used in patients not adequately controlled by sulfonylurea and/or metformin (added to orals).

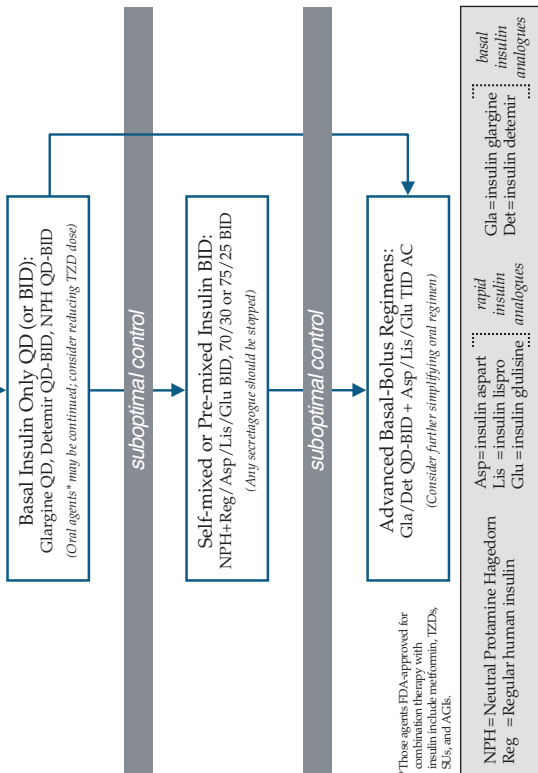
†Oral agents may be used in combination with insulin and will likely allow for better control and lower insulin doses.

Solid arrows indicate progression of therapy if glycemic goals are not achieved over a period of 2–4 months.

Dashed arrows indicate the possibility of tapering insulin therapy to oral agents in very well-controlled patients.



Suboptimal Control Despite Maximal Oral Agents +/- Exenatide



❖ Lipid Guidelines: ADA

Assessment	Frequency	Goal	Drug Rx Initiation
LDL-C			
<i>with CVD*</i>	yearly	<70 mg/dL	≥70 mg/dL
<i>no CVD*</i>	yearly	<100 mg/dL	≥100 mg/dL
HDL-C			
	yearly	>40 mg/dL (men) >50 mg/dL (women)	? ?
TG			
	yearly	<150 mg/dL	>400 mg/dL

- Order of treatment priority:
1. Lowering LDL 2. Raising HDL 3. Lowering TGs
- Optimal HDL levels: >45 mg/dL (men), >55 mg/dL (women)†
- Preferred drugs for lowering LDL are statins, followed by cholesterol absorption inhibitors, binding resins (may raise TGs), fenofibrate, or niacin.
- Preferred drugs for raising HDL are niacin or fibrates.
- Preferred drugs for lowering TGs are the fibrates, followed by high-dose statins, or niacin.

*If >40 years old with at least one additional CVD risk factor, statin therapy to achieve an LDL reduction of 30–40% regardless of baseline LDL is recommended. If <40 years old, consider statin to achieve LDL <100 mg/dL if at increased risk due to other CVD risk factors or long duration of diabetes. An optional LDL target of <70 mg/dL should be considered in those with additional CVD risk factors.

†There is no consensus on the use of drug therapy for TGs between 200–400 mg/dL, or to raise HDL-C levels. Clinical judgment should be used for individual cases.

From: American Diabetes Association. Diabetes Care 32:S29–30, 2009

❖ Lipid Guidelines: NCEP-ATP III*

1. Treatment of elevated LDL-C (>130 mg/dL)

Since diabetes is a CHD-risk equivalent (10-yr CHD risk >20%), LDL-C treatment strategies are identical to those in a patient with established CHD:

LDL-C goal <100 mg/dL
(<70 mg/dL optional goal for very high-risk patients)

LDL-C level to initiate TLC[†] ≥100 mg/dL
LDL-C level to consider drug tx (likely a statin) ≥100 mg/dL

When LDL-lowering drug therapy is used, at least a 30–40% reduction in LDL-C levels should be targeted.

2. Treatment of elevated triglycerides (>200 mg/dL)

Once LDL-C is assessed and treated, attention should turn to elevated triglycerides (TG):

TG goal <150 mg/dL OR
Non-HDL-C goal <130 mg/dL

- If TG 150–199 mg/dL: weight reduction and increased physical activity are recommended, but primary aim of therapy remains the attainment of LDL-C goal.
- If TG 200–499 mg/dL after LDL-C goal attained, consider adding additional drug tx to reach non-HDL-C goal <130 mg/dL (increase dose of LDL-C drug OR add a fibrate or nicotinic acid[§] to lower VLDL (i.e., TG).
- If TG ≥500 mg/dL, first lower TG to prevent pancreatitis by initiating a very low-fat diet (<15% total calories from fat), weight reduction and increased physical activity, fibrate or nicotinic acid.[§] Once TG <500 mg/dL, address LDL-C.

3. Treatment of low HDL-C (<40 mg/dL men, <50 mg/dL women)

Once LDL and non-HDL goals have been attained, and weight reduction and physical activity have been intensified:

- If TG <200 mg/dL (“isolated” low HDL), consider adding fibrate[‡] or nicotinic acid.[§]

*National Cholesterol Education Program — Adult Treatment Panel III. JAMA 285:2486, 2001. (update: Circulation 110:227, 2004).

[†]TLC=Therapeutic Lifestyle Changes (saturated fat intake <7% of total calories; cholesterol intake <200 mg/day; consider increased soluble fiber intake [10–25 g/day] and plant stanols/sterols [2 g/day] to enhance LDL lowering; weight reduction; increased physical activity).

[‡]Addition of a fibrate or nicotinic acid to statin therapy increases the risk of both hepatotoxicity and myositis, so caution is advised.

[§]Nicotinic acid should be used cautiously in diabetic patients, since it may increase insulin resistance and glucose levels. Intensification of glucose-lowering therapy may be required.

❖ Lipid-Lowering Agents

HMG CoA Reductase Inhibitors (“Statins”)*	Pill sizes (mg)	Dosing schedule	Daily dosing range (mg)
lovastatin (<i>Mevacor</i> ®)	10, 20, 40	QD	10–40
lovastatin, extended release (<i>Altacor</i> ®, <i>Altoprev</i> ®)	10, 20, 40, 60	QD	10–60
simvastatin (<i>Zocor</i> ®)	5, 10, 20, 40, 80	QD	5–80
pravastatin (<i>Pravachol</i> ®)	10, 20, 40, 80	QD	10–40
fluvastatin (<i>Lescol</i> ®)	20, 40	QD-BID	20–80
fluvastatin, extended release (<i>Lescol</i> ® XL)	80	QD	80
atorvastatin (<i>Lipitor</i> ®)	10, 20, 40, 80	QD	10–80
rosuvastatin (<i>Crestor</i> ®)	10, 20, 40	QD	10–40

Fibrates

gemfibrozil (<i>Lopid</i> ®)	600	BID	1200
fenofibrate	54, 67, 160, 200	QD	54–200
(<i>Tricor</i> ®)	48, 145	QD	48–145
(<i>Trilipix</i> ®)	45, 135	QD	45–135

Binding Resins (Bile Acid Sequestrants)

cholestyramine (<i>Questran</i> [®] , <i>Questran Light</i> [®])	4 g scoops, packets	QD-TID	4–24 g
colestipol (<i>Colestid</i> [®])	5 g scoops, packets, tabs	QD-TID	5–30 g
colesevelam (<i>Welchol</i> [®])	625	QD-BID	3750–4375

Cholesterol Absorption Inhibitors

ezetimibe (<i>Zetia</i> [®])	10	QD	10
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Niacin (Nicotinic Acid)

niacin	25, 50, 100, 250, 500	BID- TID	2000–3000
niacin, extended release (<i>Niaspan</i> [®])	500, 750, 1000	QD	500–2000

Omega-3 Oils

Omega-3 acid ethyl esters (<i>Lovaza</i> [®])	1 g	QD-BID	4 g
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Combination Agents

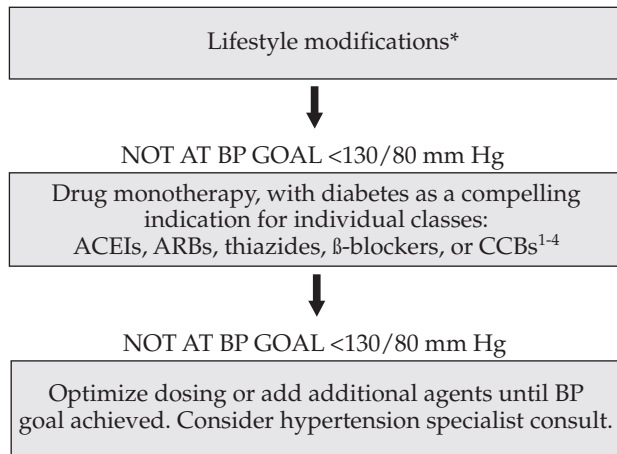
niacin, extended release/ lovastatin (<i>Advicor</i> [®])	500/20, 750/20, 1000/20	QD	i-ii tabs
atorvastatin/norvasc (<i>Caduet</i> [®])	10/5, 10/10, 20/5, 20/10, 40/5, 40/10 80/5, 80/10	QD	i tab
ezetimibe/simvastatin (<i>Vytorin</i> [®])	10/10, 10/20, 10/40, 10/80	QD	i tab

***LFT monitoring for statins**

Variable from brand to brand; most conservative and easiest to remember (after initiation of statin or after any dosage increase): 6 wk, 12 wk, 6 mo, 12 mo, then semiannually (stop statin if ↑ LFTs > 3x ULN).

❖ Hypertension Guidelines

The majority of patients with diabetes have hypertension, and control of blood pressure (BP) significantly reduces vascular complications. The current ADA and JNC-7 goals for BP control in patients with diabetes are <130/80 mm Hg. In order to achieve these levels, many or perhaps most patients will require at least 3 drugs. A target of <125/75 has also been endorsed in those with proteinuria (>1 gram/24 hrs).

JNC-7 ALGORITHM FOR THE TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETES

*Lifestyle modifications include weight reduction; a diet rich in fruits, vegetables, low-fat dairy products, and decreased total and saturated fat; Na restriction to <2.4 g/day; regular aerobic exercise; and moderation of alcohol intake.

Because of their beneficial effects on cardiovascular and microvascular risk and a variety of renal endpoints, the ADA denotes as “reasonable” the established practice of using ACE inhibitors as first-line therapy in the hypertensive diabetic patient, with ARBs used if ACEIs are not tolerated. Use of either diuretics or β -blockers as first-line is also evidence-based, but these are more commonly added to ACEIs/ARBs if additional BP reduction is necessary. Thiazide diuretics are particularly effective in this regard. In patients with microalbuminuria or established nephropathy, both ACEIs and ARBs are considered first-line to prevent renal failure progression. There are fewer data to support the use of calcium channel blockers (CCBs) routinely in diabetic patients, but these agents, particularly the non-dihydropyridines (diltiazem, verapamil), can be used safely if other drugs are not tolerated or as add-on therapies. There are few data regarding other anti-hypertensive classes, such as α -blockers or centrally acting agents, in patients with diabetes. As always, treatment decisions should be individualized, based on tolerabilities, comorbidities, personal preferences, costs, etc.

From: *Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)*. <http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm> and American Diabetes Association. *Diabetes Care* 26:580–82, 2003

¹ALLHAT Collaborative Research Group. *JAMA* 288:2981, 2002

²UKPDS Group. *BMJ* 317:713, 1998

³Lindholm et al. *Lancet* 359:1004, 2002

⁴HOPE Study Investigators. *Lancet* 355:253, 2000

◆ ACEIs & ARBs

ACE Inhibitors	Pill sizes (mg)	Dosing schedule	Daily dosing range (mg)
captopril (<i>Capoten</i> [®])	12.5, 25, 50, 100	BID-TID	12.5–450
enalapril (<i>Vasotec</i> [®])	2.5, 5, 10, 20	BID-QD	2.5–40
lisinopril (<i>Prinivil</i> [®] , <i>Zestril</i> [®])	2.5, 5, 10, 20, 30, 40	QD	2.5–80
fosinopril (<i>Monopril</i> [®])	10, 20, 40	QD	10–80
quinapril (<i>Accupril</i> [®])	5, 10, 20, 40	QD-BID	5–80
benazepril (<i>Lotensin</i> [®])	5, 10, 20, 40	QD-BID	5–80
ramipril (<i>Altace</i> [®])	1.25, 2.5, 5, 10	QD-BID	1.25–20
trandolapril (<i>Mavik</i> [®])	1, 2, 4	QD-BID	1–8
moexipril (<i>Univas</i> [®])	7.5, 15	QD-BID	7.5–30
perindopril (<i>Aceon</i> [®])	2, 4, 8	QD-BID	2–8

ACEI/Diuretic Combinations

captopril/HCTZ (<i>Capozid</i> [®])	25/15, 25/25, 50/15, 50/25	BID	ii–iii tabs
enalapril/HCTZ (<i>Vaseretic</i> [®])	5/12.5, 10/25	QD-BID	i–ii tabs
lisinopril/HCTZ (<i>Zestoretic</i> [®] , <i>Prinzide</i> [®])	10/12.5, 20/12.5, 20/25	QD	i–ii tabs
fosinopril/HCTZ (<i>Monopril-HCT</i> [®])	10/12.5, 20/12.5	QD	i–iii tabs
quinapril/HCTZ (<i>Accuretic</i> [®])	10/12.5, 20/12.5, 20/25	QD-BID	i–iii tabs
moexipril/HCTZ (<i>Uniretic</i> [®])	7.5/12.5, 15/12.5, 15/25	QD-BID	i–ii tabs
benazepril/HCTZ (<i>Lotensin HCT</i> [®])	5/6.25, 10/12.5, 20/12.5, 20/25	QD-BID	i–ii tabs

ACEI/Ca ⁺ Blocker Combinations			
enalapril/felodipine (<i>Lexxel</i> [®])	5/2.5, 5/5	QD	i–iii tabs
trandolapril/verapamil (<i>Tarka</i> [®])	2/180, 1/240, 2/240, 4/240	QD	i tab
amlodipine/benazepril (<i>Lotrel</i> [®])	2.5/10, 5/10, 5/20, 10/20	QD	i–ii tabs
enalapril/diltiazem (<i>Teczem</i> [®])	5/180	QD-BID	i–ii tabs

Angiotensin II Receptor Blockers

losartan (<i>Cozaar</i> [®])	25, 50, 100	QD-BID	25–100
valsartan (<i>Diovan</i> [®])	40, 80, 160, 320	QD	40–320
irbesartan (<i>Avalpro</i> [®])	75, 150, 300	QD	75–300
candesartan (<i>Atacand</i> [®])	4, 8, 16, 32	QD-BID	4–32
telmisartan (<i>Micardis</i> [®])	20, 40, 80	QD	40–80
eprosartan (<i>Teveten</i> [®])	400, 600	QD	400–800
olmesartan (<i>Benicar</i> [®])	5, 20, 40	QD	20–40

ARB/Diuretic Combinations

losartan/HCTZ (<i>Hyzaar</i> [®])	50/12.5, 100/12.5, 100/25	QD	i tab
valsartan/HCTZ (<i>Diovan HCT</i> [®])	80/12.5, 160/12.5, 160/25, 320/12.5, 320/25	QD	i–ii tabs
irbesartan/HCTZ (<i>Avalide</i> [®])	150/12.5, 300/12.5, 300/25	QD	i tab
candesartan/HCTZ (<i>Atacand HCT</i> [®])	16/12.5, 32/12.5	QD	i tab
telmisartan/HCTZ (<i>Micardis HCT</i> [®])	40/12.5, 80/12.5, 80/25	QD	i tab
eprosartan/HCTZ (<i>Teveten HCT</i> [®])	600/12.5, 600/25	QD	i tab
olmesartan/HCTZ (<i>Benicar HCT</i> [®])	20/12.5, 40/12.5, 40/25	QD	i tab

ARB/Ca⁺ Blocker Combinations

amlodipine/olmesartan (<i>Azor</i> [®])	5/20, 5/40, 10/20, 10/40	QD	i tab
amlodipine/valsartan (<i>Exforge</i> [®])	5/160, 5/320, 10/160, 10/320	QD	i tab
amlodipine/valsartan/HCTZ (<i>Exforge HCT</i> [®])	5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25	QD	i tab

❖ Costs of Diabetes Care Supplies/Medications

Home Glucose Monitoring	unit	retail cost*
Glucose Test Strips	Bottle of 50	\$30–70
Lancets (25, 28, 30, or 33 gauge)	Box of 100	\$5–15
Spring Lancet Device	1 device	\$20–32
Meter	1 meter	\$20–85 <small>(substantial rebates are often available)</small>
Oral Agents	1-mo supply @ max dose	retail cost*
Micronase [®] 5 mg, ii BID	120	\$153.29
DiaBeta [®] 5 mg, ii BID	120	\$145.28
Glyburide (generic) 5 mg, ii BID	120	\$26.54
Glynase [®] 6 mg BID	60	\$114.89
Micro. Glyburide (generic) 6 mg BID	60	\$33.99
Glucotrol [®] 10 mg, ii BID	120	\$144.89
Glipizide (generic) 10 mg, ii BID	120	\$25.99
Glucotrol XL [®] 10 mg, ii QD	60	\$83.97
Glipizide XL (generic) 10 mg, ii QD	60	\$39.98
Amaryl [®] 4 mg, ii QD	60	\$124.24
Glimepiride (generic) 4 mg, ii QD	60	\$29.99
Prandin [®] 2 mg, ii TID	180	\$385.04
Starlix [®] 120 mg TID	90	\$149.77
Glucophage [®] 500 mg, ii BID	120	\$139.99

Metformin (generic) 1000 mg, i BID	60	\$31.97
Riomet® 500 mg/5 mL, ii tspns BID	600 mL	\$164.76
Glucophage® XR, 500 mg, iii QD	120	\$139.98
Fortamet® 1000 mg, ii QD	60	\$325.13
Glumetza® 500 mg, iii QD	120	\$203.99
Glucovance® 5/500 mg, ii BID	120	\$184.01
Glyburide/Metformin (generic) 5/500 mg, ii BID	120	\$100.79
Metaglip® 5/500 mg, ii BID	120	\$133.30
Glipizide/Metformin (generic) 5/500 mg, ii BID	120	\$127.98
Precose® 100 mg TID	90	\$102.58
Glyset® 100 mg TID	90	\$109.99
Avandia® 4 mg BID	60	\$267.27
Actos® 45 mg QD	30	\$244.72
Avandamet® 2/500 mg, ii BID	120	\$325.38
Avandaryl® 4/4 mg BID	60	\$290.29
Actoplus met® 15/850 mg TID	90	\$337.92
Duetact® 30/4 mg QD	30	\$236.57
Januvia® 100 mg QD	30	\$193.58
Janumet® 50/1000 mg BID	60	\$195.84
Onglyza® 5 mg QD	30	\$189.98
Welchol® 625 mg, iii BID	180	\$224.84
Injectables	unit	retail cost*
Byetta® 10 mcg BID	One 10-mcg pen	\$271.45
Symlin® 60 mcg, 120 mcg TID	Two 5-mL vials Four 5-mL vials	\$379.47 \$736.00

Insulin	unit	retail cost*
Human Insulins <i>Humulin® N, R, 70/30, 50/50</i> <i>Novolin® N, R, 70/30</i>	1 vial (U-100)	\$57–61
Insulin Analogues <i>Lantus®, Levemir®</i> <i>Humalog®, NovoLog®, Apidra®</i>	1 vial (U-100)	\$102–118
Insulin Pens <i>Pens are generally available for most of the above products, either as disposables or as cartridges for permanent devices. These require disposable pen needles (28, 29, 30, or 31 gauge), in boxes of 100.</i>	Box of 5 pens or 5 cartridges (300 units per box)	~2x above prices (unit for unit)
Insulin Supplies	unit	retail cost*
Insulin Syringes	Box of 100	\$19–23
<ul style="list-style-type: none"> SPECIFY: 28, 29, 30, or 31 gauge, 1/2" or 3/8" needle length, 0.3- (30-U), 0.5- (50-U), or 1-cc (100-U) syringe volume 		
Alcohol Wipes	Box of 200	\$3–6
Glucagon IM Injection	1-mg kit	\$108.01
Glucose Tabs (4–5 gm)	Roll of 6/ bottle of 50	\$2.19/\$6.99

*Retail price from drugstore.com, accessed 1/6/10.



RULE OF THUMB: @ 30 U/d, 1 vial will last ~30 days.

Useful Formulas

Ideal Body Wt. (IBW) (see chart p. 92)

Men: 50 kg for first 5' + 2.3 kg for each 1" over 5'

Women: 45.5 kg for first 5' + 2.3 kg for every 1" over 5'

BMI (kg/m²) (see chart p. 93)

BMI = (lbs/2.2)/(inches x .0254)²

"Normal" = 20–24.9 kg/m²

"Overweight" = 25–29.9 kg/m²

"Obese" = ≥30 kg/m² (or >20% over IBW)

"Extreme Obesity" = >40 kg/m²

Nutritional Requirements

- ~25–35 kcal/kg/day* (35–45 for moderate-severe illness)
*based on activity level.
- 0.8 g protein/kg/day (1.5–2.5 for moderate-severe illness)

Basal Metabolic Rate (BMR)

Male

66.5 + (13.8 x WT [kg]) + (5.0 x HT [cm]) – (6.8 x age [yrs])

Female

655.1 + (9.6 x WT [kg]) + (1.8 x HT [cm]) – (4.7 x age [yrs])

Energy Expenditure of Activity (added to BMR)

sedentary lifestyle:	+ 400–800	kcal/day
light physical work:	+ 800–1200	kcal/day
moderate physical work:	+ 1200–1800	kcal/day
heavy labor/exercise:	+ 1800–4500	kcal/day

Nitrogen Balance Equation

daily protein intake (gm) = (24-hr urea nitrogen + 2.5 gm)
6.25

Body Fat: Calorie Relationship

1 lb body fat = 3500 kcal

Calorie Content

1 g carbohydrate = 4 kcal

1 g protein = 4 kcal

1 g fat = 9 kcal

Body Fluid Compartments

TBW (Total Body Water) = 0.6 x body WT in kg (men)
(0.5 in women)

ICF (Intracellular Fluid) = 2/3 TBW

ECF (Extracellular Fluid) = 1/3 TBW

IF (Interstitial Fluid) = 3/4 ECF

PV (Plasma Volume) = 1/4 ECF

Calculation of Anion Gap

AG = [Na⁺] – ([Cl⁻] + [HCO₃⁻])

Normal = 12 ± 4 mEq/L

Calculation of Serum Osmolality (mOsm/kg)

S_{osm} = 2[Na⁺] + [BUN]/2.8 + [glucose]/18

("Effective Serum Osmolality" = 2[Na⁺] + [glucose]/18)

Correction of Hypernatremia Due to Hyperglycemia

+1.6 mEq/L to serum [Na⁺] for every

100 mg/dL glucose above 100 mg/dL

Creatinine Clearance (CrCl)

(140 – age) x weight (in kg)*

72 x plasma Cr (mg/dL) OR $\frac{\text{urine Cr (gm/24 hrs)} \times 70}{\text{plasma Cr (mg/dL)}}$

*multiply by 0.85 for women.

Normal: 125 ± 25 mL/min in men and 95 ± 20 mL/min in women

CKD Stages:

1 (kidney damage + GFR >90 mL/min/1.73 m²); 2 (GFR 60–89); 3 (GFR 30–59);

4 (GFR 15–29); 5 (GFR <15 or dialysis)

Urinary Microalbumin:Creatinine Ratio

100 x (mg/L albumin ÷ mg/dL Cr) = µg albumin/mg Cr

normal <30; microalbuminuria = 30–300; macroalbuminuria >300

Conversion from S.I. Units

Glucose: _____ mmol/L x 18 = _____ mg/dL

Insulin: _____ pmol/L ÷ 6.0 = _____ µU/mL

C-peptide: _____ nmol/L x 3.03 = _____ ng/mL

Other Common Conversions

1 inch = 2.54 cm 1 lb = 1 kg/2.205

1 oz = 28.35 gm 1 fl oz = 29.57 cc

❖ Ideal Body Weight

Height (ft, in)	Women		Men	
	Range	Avg.	Range	Avg.
4'9"	90–118	100		
4'10"	92–121	103		
4'11"	95–124	106		
5'0"	98–127	109		
5'1"	101–130	112	105–134	117
5'2"	104–134	116	108–137	120
5'3"	107–138	120	111–141	123
5'4"	110–142	124	114–145	126
5'5"	114–146	128	117–149	129
5'6"	116–150	132	121–154	133
5'7"	122–154	136	125–159	138
5'8"	126–159	140	129–163	142
5'9"	130–164	144	133–167	146
5'10"	134–169	148	137–172	150
5'11"			141–177	155
6'0"			145–182	159
6'1"			149–187	164
6'2"			153–192	169
6'3"			157–197	174

From: *Simopoulos AP. J Am Diet Assoc 85:419, 1985*

HT (ft, in)	Body Mass Index (BMI) (kg/m ²)																												WT (lbs)			
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40									
4'8"	80	85	89	93	98	102	107	111	116	120	125	129	134	138	142	147	151	156	160	165	169	174	178									
4'9"	83	88	92	97	101	106	111	115	120	125	129	134	138	143	148	152	157	161	166	171	175	180	184									
4'10"	86	91	95	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191									
4'11"	89	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198									
5'0"	92	97	102	107	112	118	123	128	133	138	143	148	153	158	164	169	174	179	184	189	194	199	204									
5'1"	95	100	106	111	116	121	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211									
5'2"	98	104	109	115	120	125	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218									
5'3"	101	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	192	197	203	208	214	220	225									
5'4"	105	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	198	204	210	216	222	228	233									
5'5"	108	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240									
5'6"	111	117	124	130	136	142	148	155	161	167	173	179	185	192	198	204	210	216	223	229	235	241	247									
5'7"	115	121	127	134	140	147	153	159	166	172	178	185	191	198	204	210	217	223	229	236	242	248	255									
5'8"	118	125	131	138	144	151	158	164	171	177	184	190	197	203	210	217	223	230	236	243	249	256	263									
5'9"	122	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	237	243	250	257	264	270									
5'10"	125	132	139	146	153	160	167	174	181	188	195	202	209	216	223	230	236	243	250	257	264	271	278									
5'11"	129	136	143	150	157	165	172	179	186	193	200	207	215	222	229	236	243	250	258	265	272	279	286									
6'0"	132	140	147	155	162	169	177	184	191	199	206	213	221	228	235	243	250	258	265	272	280	287	294									
6'1"	136	144	151	159	166	174	182	189	197	204	212	219	227	234	242	250	257	265	272	280	288	295	303									
6'2"	140	148	155	163	171	179	187	194	202	210	218	225	233	241	249	256	264	272	280	288	295	303	311									
6'3"	144	152	160	168	176	184	192	200	208	216	224	232	240	247	255	263	271	279	287	295	303	311	319									
6'4"	148	156	164	172	180	189	197	205	213	221	230	238	246	254	262	271	279	287	295	303	312	320	328									

overweight → obese

WT (lbs)

Resources

Local

Diabetes Program or Center _____

Endocrinologist _____

Certified Diabetes Educator _____

Nutritionist _____

Ophthalmologist _____

Cardiologist _____

Vascular Surgeon _____

Podiatrist _____

ADA Chapter _____

National

American Diabetes Association (ADA) (800) DIABETES

American Association of Diabetes Educators (AADE) (800) 338-3633

AADE Diabetes Educator Access Line (800) TEAM UP-4

Medic Alert (888) 633-4298

Internet

American Academy of Family Physicians Diabetes Handouts
<http://familydoctor.org/online/famdocen/home/common/diabetes.html>

American Association of Diabetes Educators (AADE)
<http://www.diabeteseducator.org>

American Diabetes Association (ADA)
<http://www.diabetes.org>

American Heart Association
<http://www.americanheart.org>

BMI Calculator
<http://www.nhlbisupport.com/bmi>

CDC's Diabetes Public Health Resource
<http://cdc.gov/diabetes>

David Mendosa's On-line Diabetes Resources
<http://www.mendosa.com/faq.htm>

Diabetes Monitor
<http://www.diabetesmonitor.com>

Diabetes Self-Management Magazine
<http://www.diabetesselfmanagement.com>

FitDay.com (online calorie and nutrition counter)
<http://www.fitday.com>

Framingham Heart Study 10-Year CVD Risk Assessment Tool
<http://hp2010.nhlbihin.net/atp/iii/calculator.asp>

GFR Calculator
http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm

Insulin Pump Users' Web Site
<http://www.insulin-pumpers.org>

National Cholesterol Education Program
<http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>

National Diabetes Education Program
<http://www.ndep.nih.gov>

NIDDK's Health Information: Diabetes
<http://www.diabetes.niddk.nih.gov>

N.Y. Online Access to Health: Diabetes
<http://www.noah-health.org/en/endocrine/diabetes>

QD Score (Diabetes Risk Calculator)
<http://qdscore.org>

UKPDS Risk Engine (for calculation of CVD risk)
<http://www.dtu.ox.ac.uk/index.php?maindoc=/riskengine/index.php>

USDA Food & Nutrition Service
<http://www.fns.usda.gov/nutritionlink>

WebMD—Diabetes
<http://diabetes.webmd.com>

TO USE THE FOLLOWING PAGES FOR PATIENT CARE,
ENLARGE BY 200%
 ON A PLAIN PAPER COPIER OR USE SCANNER



Name _____ Date _____

Insulin Dosing Instruction Sheet**LONG-ACTING INSULIN ("BASAL INSULIN")**NPH (Humulin[®] N, Novolin[®] N)Glargex (Lantus[®])Detemir (Levemir[®])

(Don't change your long-acting insulin dose without checking with your diabetes care team.)

	Breakfast	Lunch	Supper	Bedtime
	_____ U	_____ U	_____ U	_____ U

SHORT-ACTING INSULIN ("MEAL-TIME INSULIN")Regular (Humulin[®], Novolin[®]) Lixins (Humalog[®]), Aspart (NovoLog[®]), Glulisine (Apidio[®])

(Doses of these insulin can and should be adjusted by you based on your pre-meal blood sugar reading.)

Blood Sugar Reading (mg/dL)	"SLIDING SCALE" taken before...		
	Breakfast	Lunch	Supper
<70			
70-89	_____ U	_____ U	_____ U
90-149	_____ U	_____ U	_____ U
150-199	_____ U	_____ U	_____ U
200-249	_____ U	_____ U	_____ U
250-299	_____ U	_____ U	_____ U
300-349	_____ U	_____ U	_____ U
350-399	_____ U	_____ U	_____ U
400-449	_____ U	_____ U	_____ U
450 +	_____ U	_____ U	_____ U

PRE-MIXED INSULINS (combines both basal and meal-time insulin)Humulin[®] 70/30, Novolin[®] 70/30Humalog[®] Mix 75/25, NovoLog[®] 70/30Humulin[®] 50/50, Humalog[®] Mix 50/50

	Breakfast	Lunch	Supper
	_____ U	_____ U	_____ U

USUAL BLOOD SUGAR TARGETS:

95-130 before meals, <180-180 2 hours after meals, 110-150 at bedtime

NOTE 1:

1. Some patients benefit from changing their short-acting insulin based not only on their pre-meal blood sugar, but also their reported food (especially starch) intake ("carb counting") and/or a low reported activity level during the hours after the meal. Please see your diabetes educator to learn if these more complex adjustments would be right for you.

2. If your blood sugar levels do not fall within the target ranges described to your diabetes care team (and you are having trouble understanding why), contact your team, even if it is prior to your next adjustment appointment.

3. If you have Type 1 diabetes, remember to check with diabetes educator, dietitian, or your blood sugar is persistently >250-300 and consider your diabetes care team if ketones are present in more than trace amounts.

4. The usual blood sugar targets above may not apply to you. Some patients, because of age, other medical conditions, or a tendency toward low blood sugar reactions, may require targets. Please discuss your own targets with your diabetes care team (e.g., "around 100" or "less than 200", etc.).

Name _____ Date _____

Insulin Dosing Instruction Sheet**LONG-ACTING INSULIN ("BASAL INSULIN")**NPH (Humulin[®] N, Novolin[®] N)Glargex (Lantus[®])Detemir (Levemir[®])

(Don't change your long-acting insulin dose without checking with your diabetes care team.)

	Breakfast	Lunch	Supper	Bedtime
	_____ U	_____ U	_____ U	_____ U

SHORT-ACTING INSULIN ("MEAL-TIME INSULIN")Regular (Humulin[®], Novolin[®]) Lixins (Humalog[®]), Aspart (NovoLog[®]), Glulisine (Apidio[®])

(Doses of these insulin can and should be adjusted by you based on your pre-meal blood sugar reading.)

Blood Sugar Reading (mg/dL)	"SLIDING SCALE" taken before...			USUAL DOSE
	Breakfast	Lunch	Supper	
<70				
70-89	_____ U	_____ U	_____ U	
90-149	_____ U	_____ U	_____ U	
150-199	_____ U	_____ U	_____ U	
200-249	_____ U	_____ U	_____ U	
250-299	_____ U	_____ U	_____ U	
300-349	_____ U	_____ U	_____ U	
350-399	_____ U	_____ U	_____ U	
400-449	_____ U	_____ U	_____ U	
450 +	_____ U	_____ U	_____ U	

PRE-MIXED INSULINS (combines both basal and meal-time insulin)Humulin[®] 70/30, Novolin[®] 70/30Humalog[®] Mix 75/25, NovoLog[®] 70/30Humulin[®] 50/50, Humalog[®] Mix 50/50

	Breakfast	Lunch	Supper
	_____ U	_____ U	_____ U

USUAL BLOOD SUGAR TARGETS:

95-130 before meals, <180-180 2 hours after meals, 110-150 at bedtime

NOTE 1:

1. Some patients benefit from changing their short-acting insulin based not only on their pre-meal blood sugar, but also their reported food (especially starch) intake ("carb counting") and/or a low reported activity level during the hours after the meal. Please see your diabetes educator to learn if these more complex adjustments would be right for you.

2. If your blood sugar levels do not fall within the target ranges described to your diabetes care team (and you are having trouble understanding why), contact your team, even if it is prior to your next adjustment appointment.

3. If you have Type 1 diabetes, remember to check with diabetes educator, dietitian, or your blood sugar is persistently >250-300 and consider your diabetes care team if ketones are present in more than trace amounts.

4. The usual blood sugar targets above may not apply to you. Some patients, because of age, other medical conditions, or a tendency toward low blood sugar reactions, may need higher targets. Please discuss your own targets with your diabetes care team (e.g., "around 100" or "less than 200", etc.).

Notes

This booklet was initially conceived as a practical guide for use by internal medicine housestaff at Yale-New Haven Hospital and by medical students at Yale University School of Medicine. Soon after the first edition was printed in 1998, it became popular among attending physicians and nurses at the Medical Center, as well as in residency programs at affiliated hospitals in Connecticut. It is currently in wide distribution throughout the Yale-New Haven Health System. It has been distributed nationally since 2000. Not meant as a comprehensive manual, it is instead most useful as a quick reference to assist the reader in an increasingly complex field, where new therapeutic modalities appear continuously.

For your free copy of this booklet, please call the Yale Diabetes Center at 203-737-1932 or e-mail silvio.inzucchi@yale.edu. A downloadable pdf can also be found at: <http://endocrinology.yale.edu/patient/diabetescenter.html>

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