9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2020*

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American Diabetes Association

**The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes"
includes the ADA's current clinical practice recommendations and is intended to
provide the components of diabetes care, general treatment goals and guidelines, and
tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a
multidisciplinary expert committee (https://doi.org/10.2337/dc20-SPPC), are responsible
for updating the Standards of Care annually, or more frequently as warranted. For a
detailed description of ADA standards, statements, and reports, as well as the evidence-
grading system for ADA's clinical practice recommendations, please refer to the Standards
of Care Introduction (https://doi.org/10.2337/dc20-SINT). Readers who wish to com-
ment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.**

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**

9.3 Patients with type 1 diabetes should be trained to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. **C**

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β-cell function,
insulin treatment is essential for individuals with type 1 diabetes. In addition to
hyperglycemia, insulinopenia can contribute to other metabolic disturbances like
hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be
life threatening. Severe metabolic decompensation can be, and was, mostly pre-
vented with once or twice daily injections for the six or seven decades after the
discovery of insulin. However, over the past three decades, evidence has accumulated
supporting more intensive insulin replacement, using multiple daily injections of
insulin or continuous subcutaneous administration through an insulin pump, as
providing the best combination of effectiveness and safety for people with type 1
diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that
intensive therapy with multiple daily injections or continuous subcutaneous insulin
infusion (CSII) reduced A1C and was associated with improved long-term outcomes
(1–3). The study was carried out with short-acting (regular) and intermediate-acting
(NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%)
led to ~50% reductions in microvascular complications over 6 years of treatment.

However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated less macrovascular as well as less microvascular complications in the group that received intensive treatment.

Over the last 25 years, rapid-acting and long-acting insulin analogs have been developed that have distinct pharmacokinetics compared with recombinant human insulins: basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins (4–6). More recently, two new insulin formulations with enhanced rapid action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain (7), and faster-acting insulin aspart may reduce prandial excursions better than RAA (8); further investigation is needed to establish a clear place for these agents in diabetes management. In addition, new longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in patients with type 1 diabetes (9,10). Despite the advantages of insulin analogs in patients with type 1 diabetes, for some patients the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual patient to keep them safe, out of diabetic ketoacidosis, and avoid significant hypoglycemia, with every effort made to reach the patient's glycemic targets.

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. However, a recent systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (–0.30% [95% CI –0.58 to –0.02]) and for reducing severe hypoglycemia rates in children and adults (11). However, there is no consensus to guide the choice of injection or pump therapy in a given patient, and research to guide this decision-making is needed (12). The arrival of continuous glucose monitors to clinical practice has proven beneficial in specific circumstances. Reduction of nocturnal hypoglycemia in people with type 1 diabetes using insulin pumps with glucose sensors is improved by automatic suspension of insulin delivery at a preset glucose level (12–14). The U.S. Food and Drug Administration (FDA) has also approved the first hybrid closed-loop pump system. The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (15,16), and recent evidence suggests that a closed-loop system is superior to sensor-augmented pump therapy for glycemic control and reduction of hypoglycemia over 3 months of comparison in children and adults with type 1 diabetes (17). Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most patients. See Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc20-S007) for a full discussion of insulin delivery devices.

In general, patients with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in patients with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (18); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (19).

Typical multidose regimens for patients with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation, usually at night. The long-acting basal dose is titrated to regulate overnight, fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education of patients on how to adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most patients (20,21). For individuals in whom carbohydrate counting is effective, estimates of the fat and protein content of meals can be incorporated into their prandial dosing for added benefit (22).

Insulin Injection Technique

Ensuring that patients and/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the right way. Recommendations have been published elsewhere outlining best practices for insulin injection (23). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenous-delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm. Because insulin absorption from IM sites differs according to the activity of the muscle, inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose, with IM injection being associated with frequent and unexplained hypoglycemia in several reports.

Risk for IM insulin delivery is increased in younger, leaner patients when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in obese adults (24).

Injection site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. Patients and/or caregivers should receive education about proper injection site rotation and to recognize and avoid areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. As referenced above, there are now numerous evidence-based insulin delivery recommendations that have been published. Proper insulin injection technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Results from randomized controlled studies show variable reductions of A1C (0–0.3%) and body weight (1–2 kg) with addition of pramlintide to insulin (25,26). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin to adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (27,28). The addition of the glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) liraglutide and

exenatide to insulin therapy caused small (0.2%) reductions in A1C compared with insulin alone in people with type 1 diabetes and also reduced body weight by ∼3 kg (29). Similarly, the addition of a sodium–glucose cotransporter 2 (SGLT2) inhibitor to insulin therapy has been associated with improvements in A1C and body weight when compared with insulin alone (30,31); however, SGLT2 inhibitor use in type 1 diabetes is associated with a two- to fourfold increase in ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, but only pramlintide is approved for treatment of type 1 diabetes.

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, patients receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (32). With the advent of improved continuous glucose monitors, closed-loop pump-sensor systems, and devices that offer alternative approaches for patients with hypoglycemia unawareness, the role of pancreas transplantation alone, as well as islet transplant, will need to be reconsidered.

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Recommendations

9.4 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**

9.5 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **A**

9.6 Early combination therapy can be considered in some patients

at treatment initiation to extend the time to treatment failure. **A**

9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **E**

9.8 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include cardiovascular comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (**Table 9.2** and **Figure 9.1**). **E**

9.9 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 9.1**, **Table 10.3B**, **Table 10.3C**) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors (**Figure 9.1**). **A**

9.10 In patients with type 2 diabetes who need greater glucose lowering than can be obtained with oral agents, glucagon-like peptide 1 receptor agonists are preferred to insulin when possible. **B**

9.11 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. **B**

9.12 The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.1**). **E**

The American Diabetes Association/European Association for the Study of Diabetes consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2018" and the 2019 update (33,34) recommend a patient-centered

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects — ASCVD	CV effects — HF	Cost	Oral/SQ	Renal effects — Progression of DKD	Renal effects — Dosing/use considerations*	Additional considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	Contraindicated with eGFR <30 mL/min/1.73 m²	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation **(canagliflozin)** • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide; Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors **(liraglutide, albiglutide, dulaglutide, exenatide extended release)** • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. ‡FDA-approved for heart failure indication; §FDA-approved for CKD indication. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

approach to choosing appropriate pharmacologic treatment of blood glucose (**Fig. 9.1**). This includes consideration of efficacy and key patient factors: *1*) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure (HF) (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc20-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc20-S011), *2*) hypoglycemia risk, *3*) effects on body weight, *4*) side effects, *5*) cost, and *6*) patient preferences. Lifestyle modifications that improve health (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc20-S005) should be emphasized along with any pharmacologic therapy. Section 12 "Older Adults" (https://doi.org/10.2337/dc20-S012) and Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-S013) have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively; Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc20-S010) and Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc20-S011) have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

Initial Therapy
Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for many patients this will be monotherapy in combination with lifestyle modifications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (35). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (36); there is little systematic data available for other oral agents as initial therapy of type 2 diabetes. The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration. The drug is cleared by renal filtration, and

very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be safely used in patients with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in patients with eGFR $\geq$30 mL/min/1.73 m^2 (37). A recent randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (38). This is compatible with a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (39).

In patients with contraindications or intolerance to metformin, initial therapy should be based on patient factors; consider a drug from another class depicted in **Fig. 9.1**. When A1C is $\geq$1.5% (12.5 mmol/mol) above the glycemic target (see Section 6 "Glycemic Targets," https://doi.org/10.2337/dc20-S006, for selecting appropriate targets), many patients will require dual combination therapy to achieve their target A1C level (40). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for patients who present with blood glucose levels $\geq$300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmol/mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss) (**Fig. 9.2**). As glucose toxicity resolves, simplifying the regimen and/or changing to oral agents is often possible. However, there is evidence that patients with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea (41).
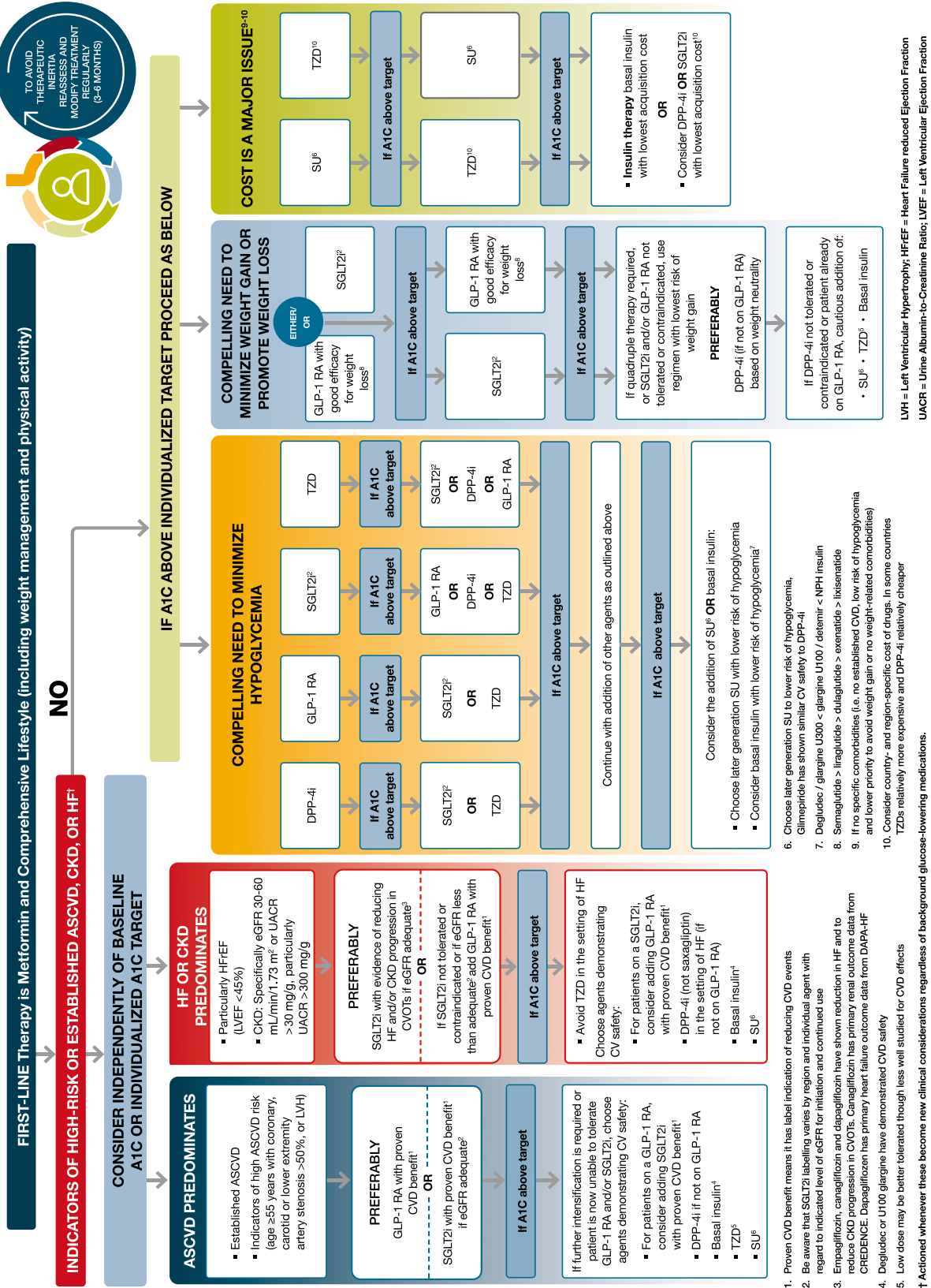
Combination Therapy
Because type 2 diabetes is a progressive disease in many patients, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which combination therapy is necessary. Current recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. This allows a clearer assessment of the

positive and negative effects of new drugs and reduces patient risk and expense (42); based on these factors, sequential addition of oral agents to metformin has been the standard of care. However, there is data to support initial combination therapy for more rapid attainment of glycemic goals (43,44), and a recent clinical trial has demonstrated that this approach is superior to sequential addition of medications for extending primary and secondary failure (45). In the VERIFY trial, participants receiving the initial combination of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin had a slower decline of glycemic control compared with metformin alone and to vildagliptin added sequentially to metformin. These results have not been generalized to oral agents other than vildagliptin, but they suggest that more intensive early treatment has some benefits and should be considered through a shared decision-making process with patients, as appropriate. Moreover, since the absolute effectiveness of most oral medications rarely exceeds 1%, initial combination therapy should be considered in patients presenting with A1C levels 1.5–2.0% above target.

The choice of medication added to metformin is based on the clinical characteristics of the patient and their preferences. Important clinical characteristics include the presence of established ASCVD or indicators of high ASCVD risk, other comorbidities, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. Although there are numerous trials comparing dual therapy with metformin alone, there is little evidence to support one combination over another. A comparative effectiveness meta-analysis suggests that each new class of noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (46,47). If the A1C target is not achieved after approximately 3 months, metformin can be combined with any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin; the choice of which agent to add is based on drug-specific effects and patient factors (**Fig. 9.1** and **Table 9.1**).

For patients with established ASCVD or indicators of high ASCVD risk (such as patients $\geq$55 years of age with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy), established kidney disease, or heart

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30–60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit[1]

If A1C above target
- Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i   GLP-1 RA   SGLT2i²   TZD

If A1C above target
SGLT2i² OR TZD | SGLT2i² OR TZD | SGLT2i² | SGLT2i² OR DPP-4i OR GLP-1 RA

If A1C above target
GLP-1 RA OR DPP-4i OR TZD

If A1C above target
Continue with addition of other agents as outlined above

If A1C above target
Consider the addition of SU[6] OR basal insulin:
- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[7]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[8]   EITHER/OR   SGLT2i²

If A1C above target
SGLT2i² | GLP-1 RA with good efficacy for weight loss[8]

If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU[6] • TZD[5] • Basal insulin

COST IS A MAJOR ISSUE[9-10]

SU[6]   TZD[10]

If A1C above target
TZD[10]   SU[6]

If A1C above target
- Insulin therapy basal insulin with lowest acquisition cost
OR
- Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100/ detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

If injectable therapy is needed to reduce A1C[1]

Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Gradual titration to maintenance dose (varies within class)

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above A1C target

Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to **Table 9.3** for insulin cost information.

Add basal analog or bedtime NPH insulin

INITIATION: Start 10 IU a day **OR** 0.1-0.2 IU/kg a day
TITRATION:
- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

If above A1C target
Despite adequately titrated basal analog or bedtime NPH[4]
OR once basal dose >0.5 IU/kg **OR** FPG at target

If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime
TITRATION:
- Titrate based on individualized needs

Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:	**TITRATION:**
- 4 IU a day or 10% of basal insulin dose	- Increase dose by 1-2 IU or 10-15% twice weekly
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose	- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%

If above A1C target

If above A1C target

Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)

Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)

Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
- Total NPH dose = 80% of current NPH dose
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
- Titrate each component of the regimen based on individualized needs

Consider twice daily premix insulin regimen
INITIATION:
- Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
- Titrate based on individualized needs

1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

Figure 9.2—Intensifying to injectable therapies. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (33).

failure, an SGLT-2 inhibitor or GLP-1 RA with demonstrated CVD benefit (**Table 9.1**, **Table 10.3***B*, **Table 10.3***C*) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors (**Figure 9.1**). For patients without established ASCVD, indicators of high ASCVD risk, HF, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence. Rather, drug choice is based on avoidance of side effects, particularly hypoglycemia and weight gain, cost, and patient preferences (48). Similar considerations are applied in patients who require a third agent to achieve glycemic goals; there is very little trial-based evidence to guide this choice. In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and patient burden (**Table 9.1**). In some instances, patients will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 12 "Older Adults"(https://doi.org/10.2337/dc20-S012) has a full discussion of treatment considerations in older adults, a setting where changes of glycemic goals and de-escalation of therapy is common.

Although most patients prefer oral medications to drugs that need to be injected, the eventual need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many patients. In addition, recent evidence supports the utility of GLP-1 RAs in patients not reaching glycemic targets with use of non-GLP-1 RA oral agent regimens. While most GLP-1 RA products are injectable, an oral formulation of semaglutide is now commercially available (49). In trials comparing the addition of an injectable GLP-1 RAs or insulin in patients needing further glucose lowering, the efficacy of the two treatments was similar (50–52). However, GLP-1 RAs in these trials had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support injectable GLP-1 RAs as the preferred option for patients requiring the potency of an injectable therapy for glucose control (**Fig. 9.2**). However, high costs and tolerability issues are important barriers to the use of GLP-1 RAs.

Cost for diabetes medicine has increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (53). **Table 9.2** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (54) and National Average Drug Acquisition Costs (NADAC) (55), separate measures to allow for a comparison of drug prices but do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. Medication costs can be a major source of stress for patients with diabetes and contribute to worse adherence with medications (56); cost-reducing strategies may improve adherence in some cases (57).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with an SGLT2 inhibitor (empagliflozin, canagliflozin, dapagliflozin) or GLP-1 RA (liraglutide, semaglutide, dulaglutide); see Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc20-S010) for details. The subjects enrolled in the cardiovascular outcome trials using empagliflozin, canagliflozin, liraglutide, and semaglutide had A1C ≥7%, and more than 70% were taking metformin at baseline. Thus, a practical extension of these results to clinical practice is to use these drugs preferentially in patients with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these patients, incorporating one of the SGLT2 inhibitors or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (**Table 9.1**). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD. See Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc20-S011) for a detailed discussion on how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.2**). See the section INSULIN INJECTION TECHNIQUE above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients, and providers should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized. Educating and involving patients in insulin management is beneficial. For example, instruction of patients in self-titration of insulin doses based on self-monitoring of blood glucose improves glycemic control in patients with type 2 diabetes initiating insulin (58). Comprehensive education regarding self-monitoring of blood glucose, diet, and the avoidance and appropriate treatment of hypoglycemia are critically important in any patient using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen and can be added to metformin and other oral agents. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (59,60). Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin (61–66), although these advantages are modest and may not persist (67). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (68–74). Despite evidence for reduced hypoglycemia with newer, longer-acting basal insulin analogs in clinical trial settings, in practice these effects may be modest compared with NPH insulin (75).

The cost of insulin has been rising steadily over the past two decades, at

Table 9.2—Median monthly (30-day) cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($4, $85)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($87, $7,412)	$5 ($5, $988)	2,000 mg
		750 mg (ER)	$74 ($65, $74)	$4	1,500 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$224 ($224, $910)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$4	8 mg
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$5	40 mg (IR)
		10 mg (XL)	$48	$15	20 mg (XL)
	• Glyburide	6 mg (micronized)	$50 ($48, $71)	$4	12 mg (micronized)
		5 mg	$93 ($63, $103)	$11	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$4	45 mg
	• Rosiglitazone	4 mg	$407	$330	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$23	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$39	360 mg
	• Repaglinide	2 mg	$878 ($162, $897)	$39	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$168	25 mg
	• Saxagliptin	5 mg	$505	$403	5 mg
	• Linagliptin	5 mg	$523	$419	5 mg
	• Sitagliptin	100 mg	$541	$433	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$338	$271	15 mg
	• Dapagliflozin	10 mg	$591	$473	10 mg
	• Empagliflozin	25 mg	$591	$473	25 mg
	• Canagliflozin	300 mg	$593	$475	300 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$840	$672	2 mg**
	• Exenatide	10 μg pen	$876	$730	20 μg
	• Dulaglutide	1.5/0.5 mL pen	$911	$730	1.5 mg**
	• Semaglutide	1 mg pen	$927	$745	1 mg**
		14 mg (tablet)	$927	N/A	14 mg
	• Liraglutide	18 mg/3 mL pen	$1,106	$886	1.8 mg
	• Lixisenatide	300 μg/3 mL pen	$744	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$712 ($674, $712)	$177	3.75 g
		3.75 g suspension	$675	$415	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$906	$729	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,623	$2,097	120 μg/injection†††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [54] or NADAC [55] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. †††AWP and NADAC calculated based on 120 μg three times daily.

a pace several fold that of other medical expenditures (76). This expense contributes significant burden to patients as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct patient costs contribute to treatment nonadherence (76). Therefore, consideration of cost is an important component of effective management. For many patients with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (75). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.3** at select pharmacies.

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets. A dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on patient needs (see **Figure 9.2**). People with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (77). Titration can be based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in patients with type 2 diabetes have not reported important differences in A1C or hypoglycemia (78,79).

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (54) and NADAC (55) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$126
		U-100 prefilled pen	$202	$162
	• Lispro	U-100 vial	$330	$264
		U-100 3 mL cartridges	$408	$327
		U-100 prefilled pen; U-200 prefilled pen	$424	$340
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$353
	• Aspart	U-100 vial	$347†	$278†
		U-100 3 mL cartridges	$430	$345
		U-100 prefilled pen	$447†	$358†
	• Inhaled insulin	Inhalation cartridges	$924	$606
Short-acting	• human regular	U-100 vial	$165 ($165, $178)††	$134 ($134, $146)††
Intermediate-acting	• human NPH	U-100 vial	$165 ($165, $178)††	$135 ($135, $146)††
		U-100 prefilled pen	$377	$304
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$144
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$261	$210
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		U-300 prefilled pen	$346	$280
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165 ($165, $178)	$134 ($134, $145)
		U-100 prefilled pen	$377	$303
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial	$360	$289
		U-100 prefilled pen	$447	$358
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$565	$454
	• Degludec/Liraglutide	100/3.6 prefilled pen	$832	$668

AWP, average wholesale price; GLP-1, glucagon-like peptide 1; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**. †Inclusive of both the original and "faster-acting" products. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. Regular U-500 has distinct pharmacokinetics with delayed onset and longer duration of action, has characteristics more like an intermediate-acting (NPH) insulin, and can be used as two or three daily injections (80). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations, and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (81,82). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200

units/mL). These concentrated preparations may be more convenient and comfortable for patients to inject and may improve adherence in those with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials (a dedicated syringe was approved in July 2016), other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Inhaled Insulin

Inhaled insulin is available for prandial use with a limited dosing range; studies in people with type 1 diabetes suggest rapid pharmacokinetics (7). A pilot study found evidence that compared with injectable rapid-acting insulin, supplemental doses of inhaled insulin taken based on postprandial glucose levels may improve blood glucose management without additional

hypoglycemia or weight gain (83), although results from a larger study are needed for confirmation. Inhaled insulin is contraindicated in patients with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in patients who smoke or who recently stopped smoking. All patients require spirometry (FEV$_1$) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day) and A1C remains above target, consider advancing to combination injectable therapy (**Fig. 9.2**). This approach can use a GLP-1 RA added to basal insulin or multiple doses of insulin. The combination of basal insulin

and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (84–86). Two different once-daily fixed-dual combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide and insulin degludec plus liraglutide.

Intensification of insulin treatment can be done by adding doses of prandial to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a regimen with multiple prandial doses if necessary (87). Alternatively, in a patient on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal/prandial regimens offer greater flexibility for patients who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.2** outlines these options, as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating combination injectable therapy, metformin therapy should be maintained while sulfonylureas and DPP-4 inhibitors are typically discontinued. In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once a basal/bolus insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 12 "Older Adults," https://doi.org/10.2337/dc20-S012).

References

1. Cleary PA, Orchard TJ, Genuth S, et al.; DCCT/EDIC Research Group. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes 2006;55:3556–3565
2. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
3. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383
4. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ 2014;349:g5459
5. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442–449
6. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254–2264
7. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 2015;38:2266–2273
8. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care 2017;40:943–950
9. Lane W, Bailey TS, Gerety G, et al.; Group Information; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA 2017;318:33–44
10. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care 2015;38:2217–2225
11. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336–347
12. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. J Diabetes Sci Technol 2013;7:1567–1574
13. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
14. Buckingham BA, Raghinaru D, Cameron F, et al.; In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. Diabetes Care 2015;38:1197–1204

15. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408
16. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163
17. Tauschmann M, Thabit H, Bally L, et al.; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 2018;392:1321–1329
18. Peters A, Laffel L (Eds.). *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook.* Alexandria, VA, American Diabetes Association, 2013
19. Chiang JL, Kirkman MS, Laffel LMB, Peters AL; *Type 1 Diabetes Sourcebook* Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2034–2054
20. Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2014;2:133–140
21. Vaz EC, Porfírio GJM, Nunes HRC, Nunes-Nogueira VDS. Effectiveness and safety of carbohydrate counting in the management of adult patients with type 1 diabetes mellitus: a systematic review and meta-analysis. Arch Endocrinol Metab 2018;62:337–345
22. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015;38:1008–1015
23. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. Mayo Clin Proc 2016;91:1231–1255
24. Bergenstal RM, Strock ES, Peremislov D, Gibney MA, Parvu V, Hirsch LJ. Safety and efficacy of insulin therapy delivered via a 4mm pen needle in obese patients with diabetes. Mayo Clin Proc 2015;90:329–338
25. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004;21:1204–1212
26. Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care 2006;29:2189–2195
27. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2018;34:e2983
28. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597–609
29. Wang W, Liu H, Xiao S, Liu S, Li X, Yu P. Effects of insulin plus glucagon-like peptide-1 receptor agonists (GLP-1RAs) in treating type 1 diabetes

mellitus: a systematic review and meta-analysis. Diabetes Ther 2017;8:727–738

30. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:864–876

31. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care 2018;41:2560–2569

32. Dean PG, Kukla A, Stegall MD, Kudva Y. Pancreas transplantation. BMJ 2017;357:j1321

33. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701

34. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 19 December 2019 [Epub ahead of print].DOI: 10.2337/dci19-0066

35. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589

36. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751

37. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Accessed 1 November 2019. Available from http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm

38. Out M, Kooy A, Lehert P, Schalkwijk CA, Stehouwer CDA. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3year trial. J Diabetes Complications 2018;32:171–178

39. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101:1754–1761

40. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;66:446–456

41. Babu A, Mehta A, Guerrero P, et al. Safe and simple emergency department discharge therapy for patients with type 2 diabetes mellitus and severe hyperglycemia. Endocr Pract 2009;15:696–704

42. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care 2016;39(Suppl. 2):S137–S145

43. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab 2015;17:268–275

44. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 2014;16:410–417

45. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Prato SD; VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394:1519–1529

46. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613

47. Maloney A, Rosenstock J, Fonseca V. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. Clin Pharmacol Ther 2019;105:1213–1223

48. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174:1227–1234

49. Pratley R, Amod A, Hoff ST, et al.; PIONEER 4 investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:39–50

50. Singh S, Wright EE Jr, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2017;19:228–238

51. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. Diabetes Metab Syndr Obes 2017;10:123–139

52. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. Diabetes Obes Metab 2017;19:216–227

53. Riddle MC, Herman WH. The cost of diabetes care-an elephant in the room. Diabetes Care 2018;41:929–932

54. Truven Health Analytics. Micromedex 2.0 Introduction to RED BOOK Online, 2018. Accessed 1 November 2019. Available from http://www.micromedexsolutions.com/micromedex2/4.34.0/WebHelp/RED_BOOK/Introduction_to_REDB_BOOK_Online.htm

55. Centers for Medicare & Medicaid Services. NADAC (national average drug acquisition cost), drug pricing and payment. Accessed 1 November 2019. Available from https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d.

56. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. Diabetes Res Clin Pract 2018;143:24–33

57. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. Med Care 2016;54:796–803

58. Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. Diabetes Obes Metab 2009;11:623–631

59. Porcellati F, Lucidi P, Cioli P, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. Diabetes Care 2015;38:503–512

60. Wang Z, Hedrington MS, Gogitidze Joy N, et al. Dose-response effects of insulin glargine in type 2 diabetes. Diabetes Care 2010;33:1555–1560

61. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180:385–397

62. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007 (2):CD005613

63. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2008;81:184–189

64. Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. Diabetes Res Clin Pract 2017;124(Supplement C):57–65

65. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086

66. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29:1269–1274

67. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49:442–451

68. Bolli GB, Riddle MC, Bergenstal RM, et al.; on behalf of the EDITION 3 study investigators. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015;17:386–394

69. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a

randomized controlled trial (EDITION JP 2). Diabetes Obes Metab 2016;18:366–374

70. Yki-Järvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. Diabetes Obes Metab 2015;17: 1142–1149

71. Marso SP, McGuire DK, Zinman B, et al.; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723–732

72. Rodbard HW, Cariou B, Zinman B, et al.; BEGIN Once Long trial investigators. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabet Med 2013;30:1298–1304

73. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA 2017; 318:45–56

74. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012;35:2464–2471

75. Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine Hagedorn insulin with hypoglycemia-related emergency

department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. JAMA 2018;320:53–62

76. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Conclusions and recommendations. Diabetes Care 2018;41:1299–1311

77. McCall AL. Insulin therapy and hypoglycemia. Endocrinol Metab Clin North Am 2012;41:57–87

78. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. Diabetes Obes Metab 2009;11:53–59

79. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. J Diabetes 2013;5:482–491

80. Wysham C, Hood RC, Warren ML, Wang T, Morwick TM, Jackson JA. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular U500 insulin in severely insulin-resistant patients with type 2 diabetes. Endocr Pract 2016;22:653–665

81. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab 2015;17:835–842

82. Yki-Järvinen H, Bergenstal R, Ziemen M, et al.; EDITION 2 Study Investigators. New insulin glargine 300 units/mL versus glargine 100

units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care 2014;37:3235–3243

83. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. Diabetes Technol Ther 2018;20:639–647

84. Diamant M, Nauck MA, Shaginian R, et al.; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014; 37:2763–2773

85. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 2014;384: 2228–2234

86. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care 2017;40:614–624

87. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2: 30–37