Diabetes Mellitus Management

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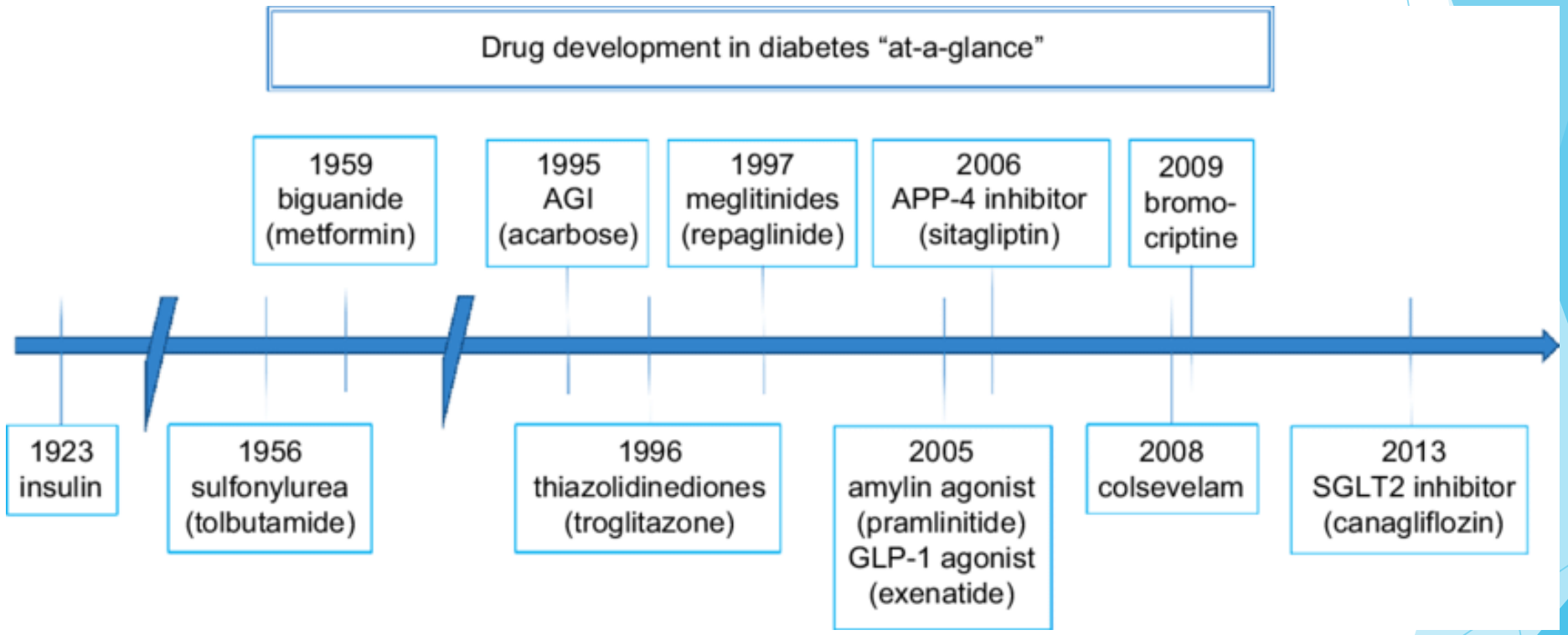
Outline

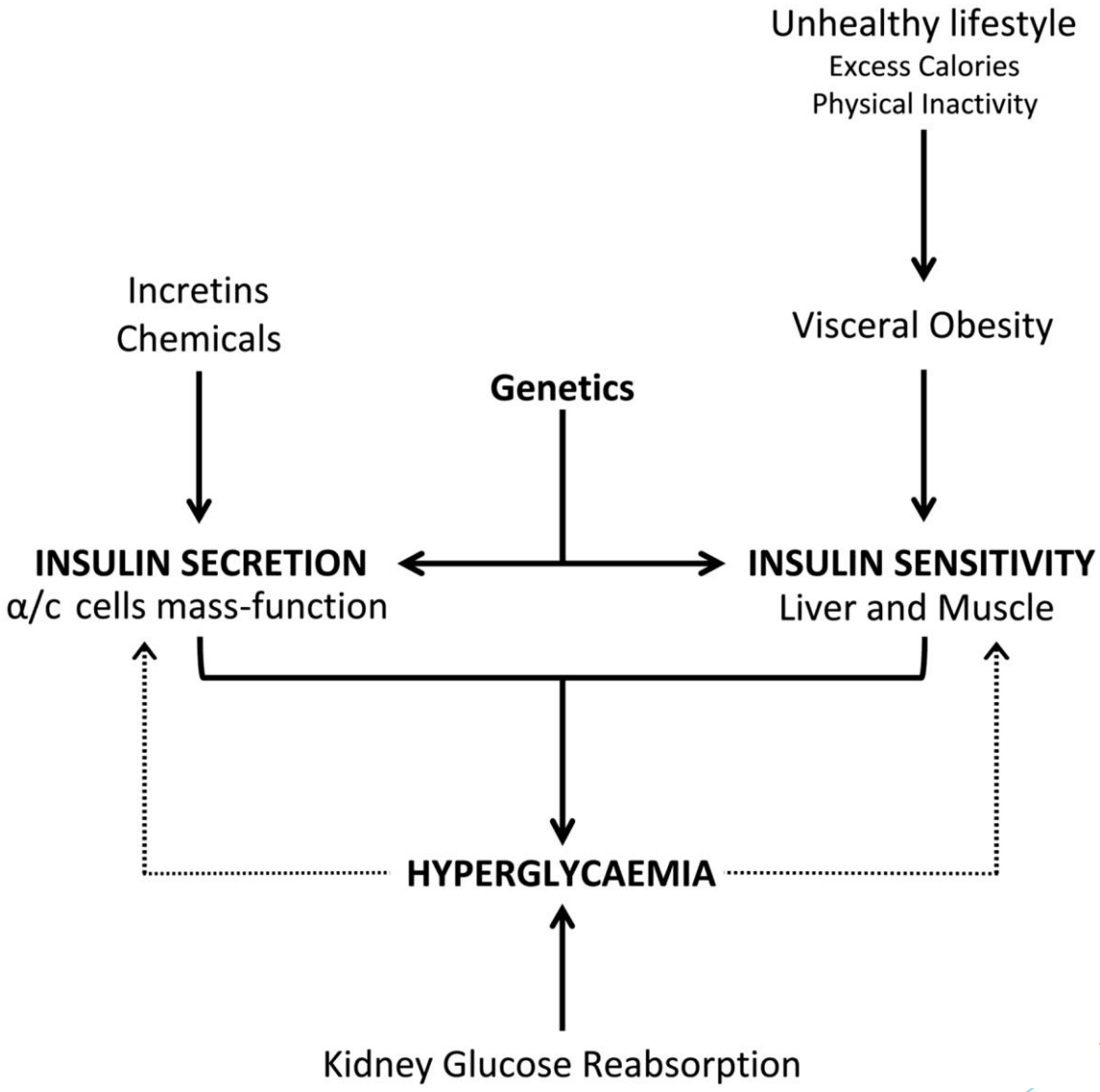
- Timeline of Diabetes drug development
- Type 2 Diabetes (T2D) Physiopathology
- Medical management of T2D
- Hypertension management in patients with Diabetes
- Hypelipidemia management in patients with Diabetes
- Medical management of Type 1 Diabetes (T1D)
- Diabetes Care in the Hospital

Timeline of treatment development



Available from: https://www.researchgate.net/figure/Timeline-for-milestones-in-the-development-of-drugs-to-manage-diabetes-Abbreviations_fig1_313849925 [accessed 1 Jan, 2019]

TYPE 2 DIABETES PATHOPHYSIOLOGY



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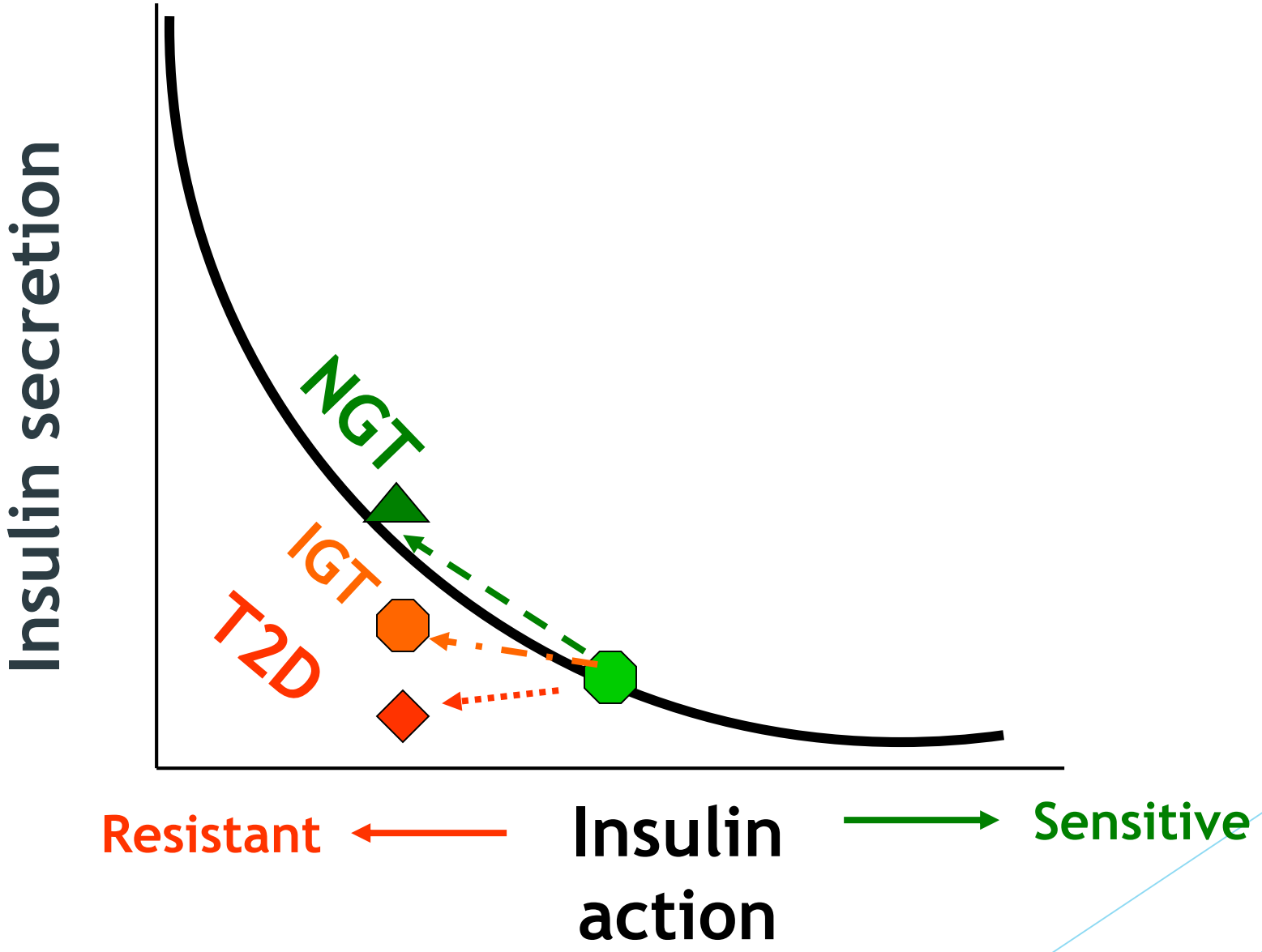
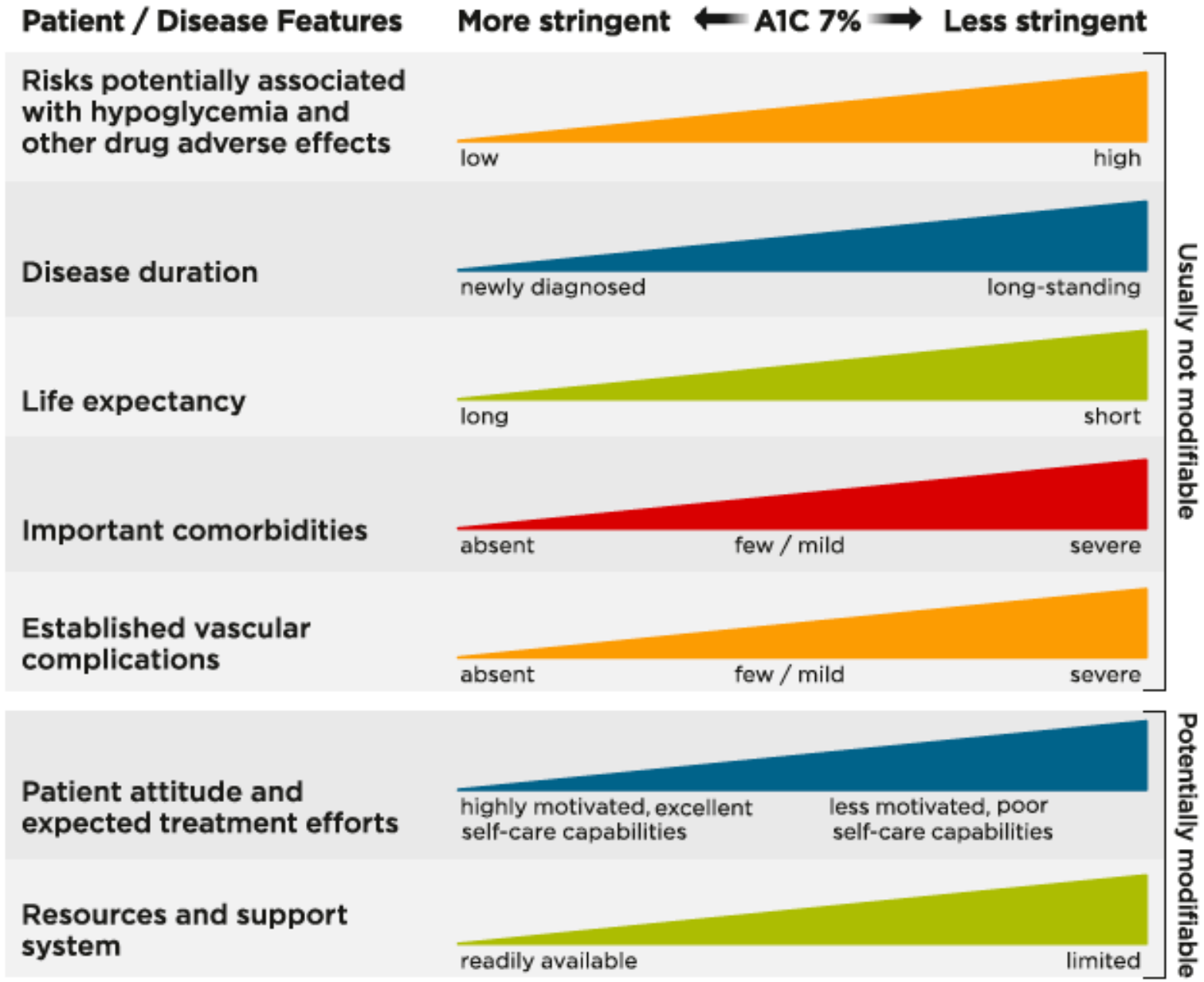
Relationship of insulin secretion with insulin action



Approach to the Management of Hyperglycemia



Parameter	Glycemic target
A1c	<7%
Pre-prandial glucose	80-130 mg/dL
Peak postprandial glucose	<180 mg/dL

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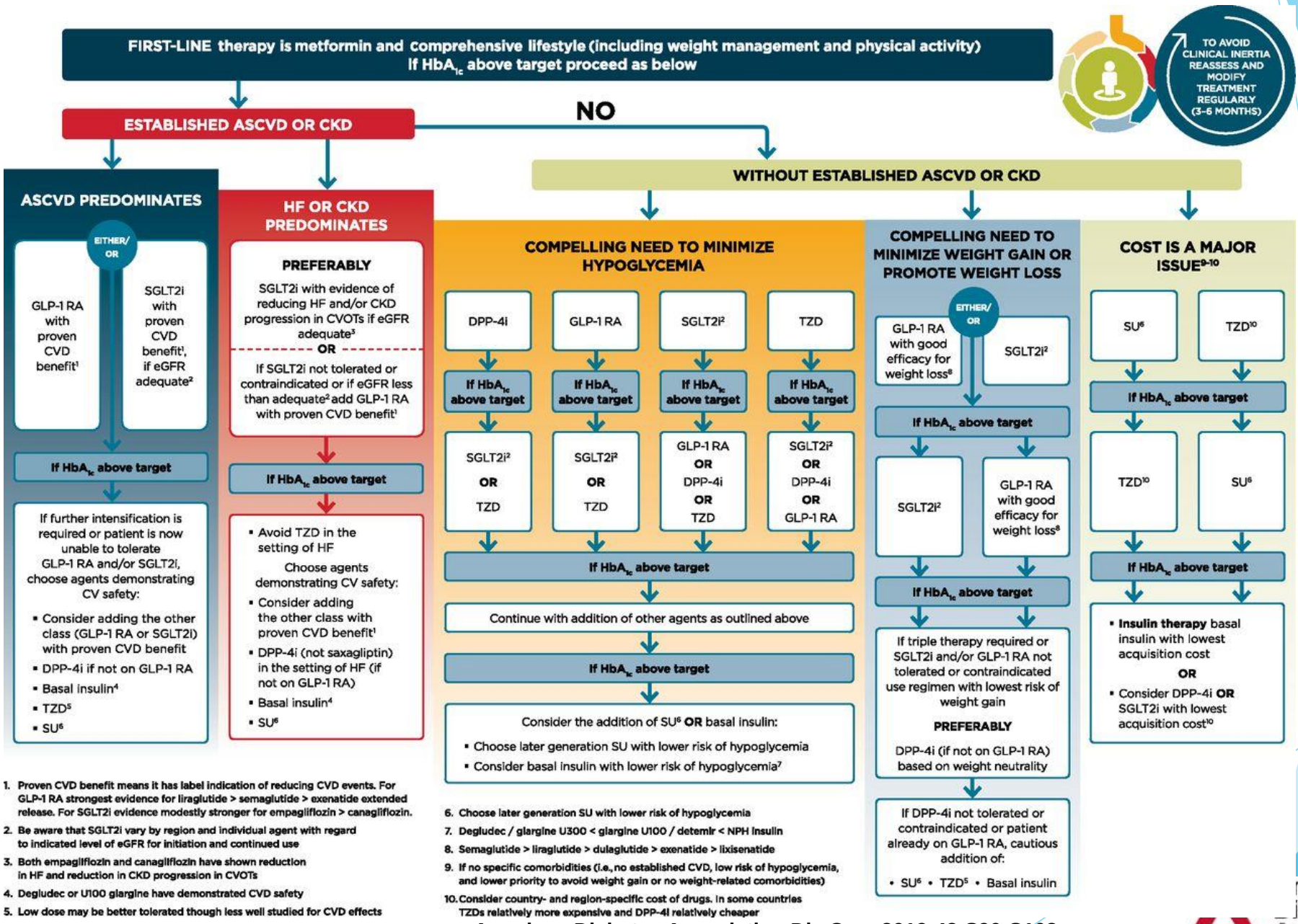
Glucose-lowering medication in type 2 diabetes: overall approach.



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
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 with lower risk of hypoglycemia
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

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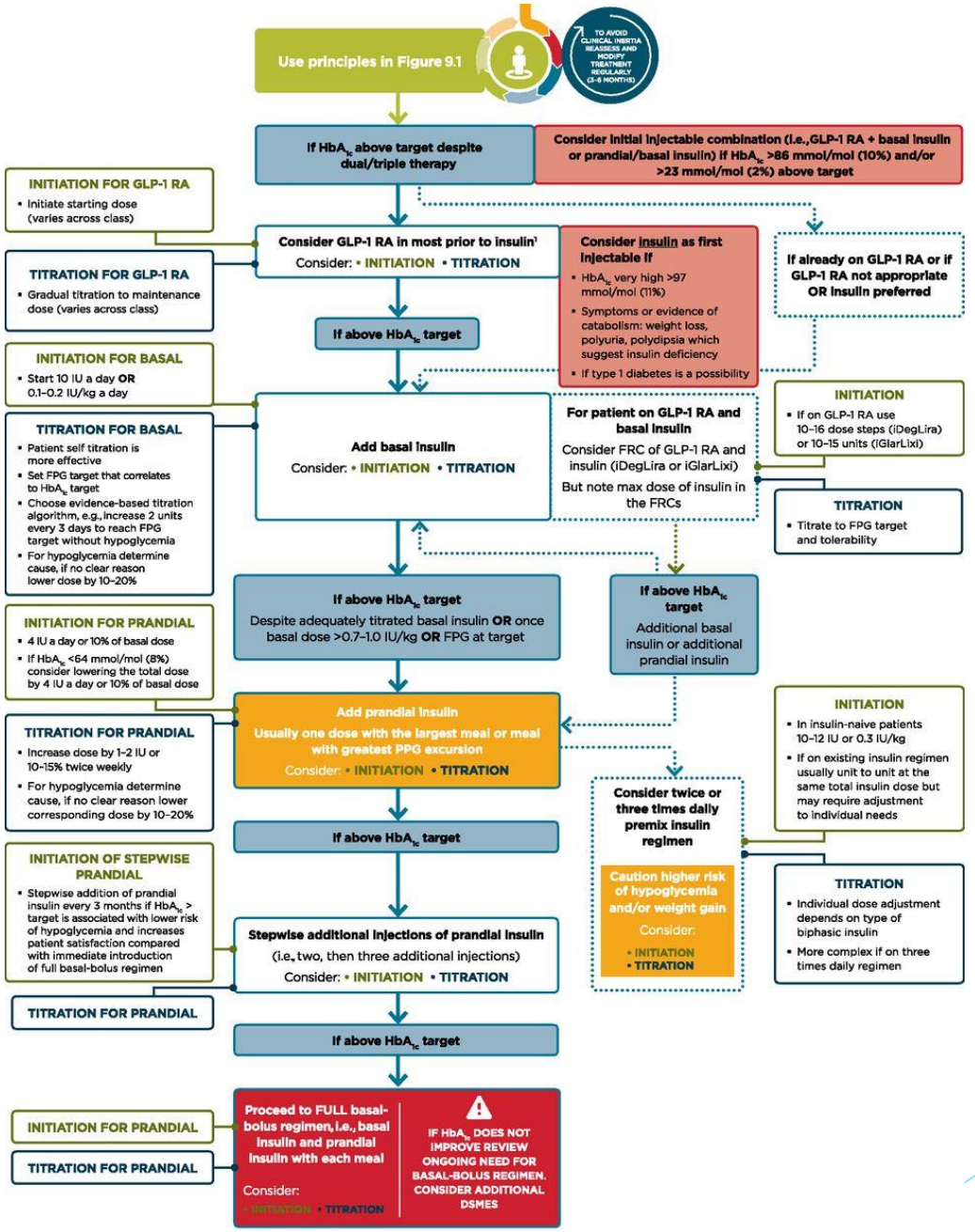
Intensifying to injectable therapies.



1. When selecting GLP-1 RA, consider: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

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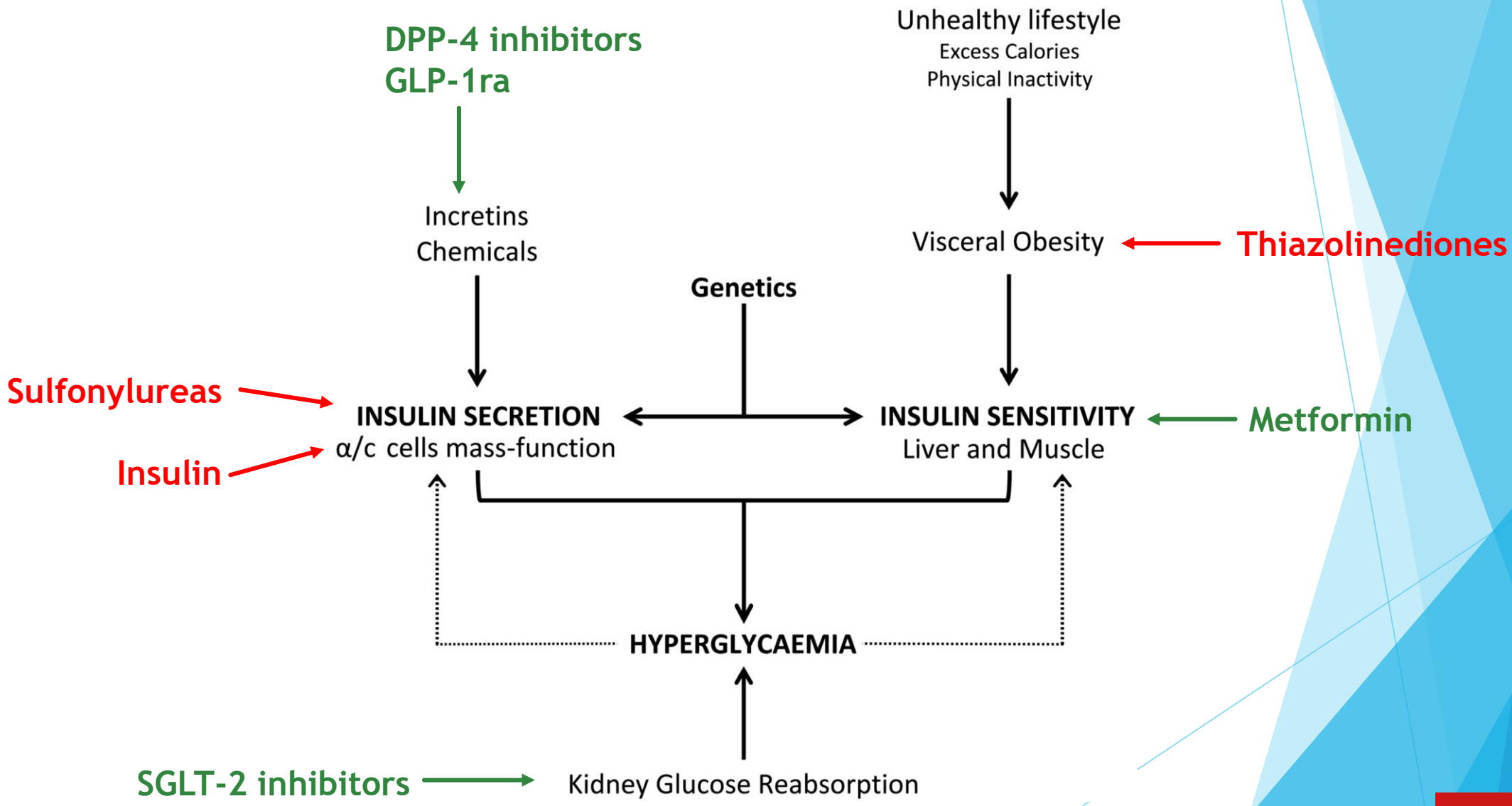
American Diabetes Association.

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ 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: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	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, alogliptin	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	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			

TYPE 2 DIABETES PATHOPHYSIOLOGY



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Hypertension treatment in patients w/ Diabetes

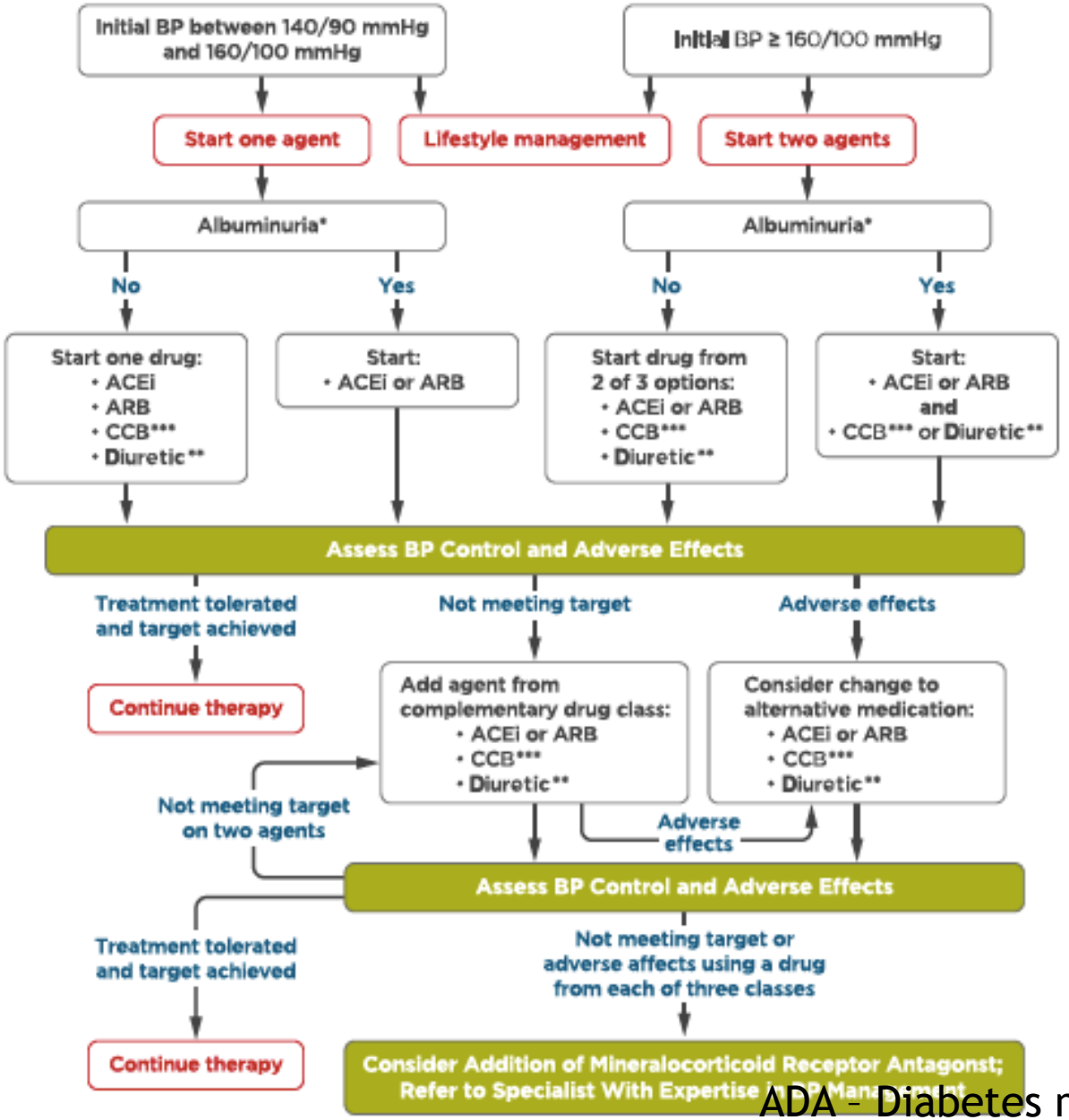

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Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Table 9.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

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Antiplatelet therapy

- Aspirin therapy (75-162mg/day) → secondary prevention strategy in those with diabetes + hx of atherosclerotic CVD
- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used.
- Dual antiplatelet therapy (low dose aspirin + P2Y12 inhibitor) → for 1 year after an ACS and may have benefits beyond this period.
- Aspirin therapy (75-162 mg/day) → primary prevention strategy in those with T1D or T2D who are at increased cardiovascular risk.
  - men and women with diabetes aged ≥50 years + one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding.

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Type 1 Diabetes (T1D)

Pharmacologic Approaches T1D

- Multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion.
- Recommend use rapid-acting insulin analogs to reduce hypoglycemia risk
- Education on matching prandial insulin doses to:
  - carbohydrate intake
  - premeal blood glucose levels
  - anticipated physical activity
- Successful use of continuous subcutaneous insulin infusion → continued access to this therapy after they turn 65 years of age

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Type 1 DM

- Insulin → starting dose: 0.4 to 1.0 units/kg/day
  - Long acting
    - Glargine U100 (Lantus) and U300 (Degludec)
  - Short acting
    - Aspart
    - Lispro
    - Inhaled insulin
- Pramlintide
- Experimental drugs
  - Metformin
  - Incretin-based (GLP1 agonist and DPP4 inhibitors)
  - SGLT2 inhibitors
- Surgical approach → pancreas and islet cells transplantation

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Diabetes Care in the hospital

- A1C on all patients with diabetes or hyperglycemia (BG>140 mg/dL) if not performed in the prior 3 months.
- Insulin therapy (validated written or computerized protocols)
  - For treatment of persistent hyperglycemia ≥180 mg/dL.
  - Target glucose range of 140-180 mg/dL
  - More stringent goals, such as 110–140 mg/dL may be appropriate for selected patients, if this can be achieved without significant hypoglycemia.
- BG monitoring
  - Patient who is eating meals → to be be performed before meals
  - Patient who is not eating → every 4-6 h
  - Patient on intravenous insulin → More frequent testing (from Q30min to Q2 h)

Diabetes Care in the hospital

- Preferred treatment for noncritically ill patients
  - A basal + bolus correction insulin regimen, with the addition of nutritional insulin in patients who have good nutritional intake
- Preferred treatment for noncritically ill patients with poor oral intake or those who are taking nothing by mouth (NPO)
  - Basal insulin or a basal plus bolus correction insulin
- To correct hyperglycemia
  - The use of subcutaneous rapid- or short-acting insulin before meals or every 4-6 h if no meals are given or if the patient is receiving continuous enteral/parenteral nutrition is indicated
- Sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged.

Diabetes Care in the hospital

- Transitioning from IV to SC insulin
  - Patients should receive SC basal insulin 2-4 h before the IV insulin is discontinued
  - Converting to basal insulin at 60-80% of the daily infusion dose
- A few recent randomized pilot trials in general medicine and surgery patients reported that a dipeptidyl peptidase 4 inhibitor alone or in combination with basal insulin was well tolerated and resulted in similar glucose control and frequency of hypoglycemia compared with a basal-bolus regimen
- Hypoglycemia management protocol
  - Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked.
  - The treatment regimen should be reviewed and changed as necessary to prevent further hypoglycemia when a blood glucose value is ≤70 mg/dL

Table 14.1—Insulin dosing for enteral/parenteral feedings

Situation	Basal/nutritional	Correctional
Continuous enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine/degludec daily Nutritional: regular insulin every 6 h or rapid-acting insulin every 4 h, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia
Bolus enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine/degludec daily Nutritional: give regular insulin or rapid-acting insulin SQ before each feeding, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia
Parenteral feedings	Add regular insulin to TPN IV solution, starting with 1 unit per 10 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia

IV, intravenous; SQ, subcutaneous; TDD, total daily dose; TPN, total parenteral nutrition.

Diabetes Care in the hospital

- Patients using Glucocorticoids
  - Short-acting→ intermediate-acting (NPH) insulin may be sufficient
  - Long-acting → long-acting insulin may be used
- Pre-operative care
  - Target glucose range for the perioperative period should be 80–180 mg/dL.
  - Preoperative risk assessment for patients at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure
  - Withhold metformin the day of surgery
  - Withhold any other oral hypoglycemic agents the morning of surgery or procedure and give half of NPH dose or 60–80% doses of a long-acting analog or pump basal insulin
  - Monitor blood glucose at least every 4–6 h while NPO and dose with short acting insulin as needed.

Questions?

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