Diabetes Pharmacotherapy in the Elderly Patient

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Objectives

- Determine the appropriate goals of diabetes treatment in the elderly
- Discuss the dangers of hypoglycemia in older patients
- Review the use of oral antidiabetic agents in elderly patients
- Discuss the appropriateness of injectable antidiabetic therapies in older patients

Background

- T2DM and its complications remain major causes of morbidity and mortality
  - 26-33% of all adults age 65 and older have T2DM
- Older adults are at high risk for developing T2DM due to the combined effects of increasing insulin resistance and impaired pancreatic islet function with aging
- The number of cases of diagnosed diabetes in those aged >65 years are projected to increase by 4.5-fold (compared to 3-fold in the total population) between 2005 and 2050

T2DM in the Elderly

- Diabetes in the elderly is metabolically distinct
  - Fasting hepatic glucose production is not increased
  - Age-related loss of beta cell function leads to reduced insulin secretion and altered effectiveness of pharmacotherapy
- Lean older patients have a marked impairment in insulin secretion but relatively normal insulin action, whereas obese older patients have relatively normal insulin secretion but marked resistance to insulin

Glycemic Targets in the Elderly

- Based on the patient's overall health and projected period of survival
- A1C target in fit older adults with a life expectancy >10 years should be individualized based on health, hypoglycemia risk and adherence
  - A1C goal of <7.5% should be considered
    - Fasting and preprandial glucoses should be between 140 and 150 mg/dL

Glycemic Targets in the Elderly

- Higher A1C target in medication-treated frail older adults with medical and functional comorbidities and in those whose life expectancy is <10 years
  - A1C ≤8.0%, fasting and preprandial glucose 160 - 170 mg/dL
- Individualized goals for the very old may be even higher (A1C <8.5 %)
  - A1C of 8.5 percent equates to an estimated average glucose of 200 mg/dL

Patient characteristics/health status	Rationale	A1C goal	Fasting or preprandial glucose	Bedtime glucose
Healthy (*few coexisting chronic illnesses, intact cognitive and functional status*)	Longer remaining life expectancy	<7.5%	90–130 mg/dL	90–150 mg/dL
Complex/intermediate (*multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment*)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90–150 mg/dL	100–180 mg/dL
Very complex/poor health (*LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL dependencies*)	Limited remaining life expectancy makes benefit uncertain	<8.5%	100–180 mg/dL	110–200 mg/dL

Hypoglycemia in the Elderly

- Vulnerability to hypoglycemia is substantially increased in older adults
  - Increased risk of adverse cardiovascular events
- Older adults may have more neuroglycopenic symptoms of hypoglycemia (dizziness, weakness, delirium, confusion) compared with adrenergic manifestations (tremors, sweating)

Hypoglycemia in the Elderly

- Increased risk of severe or fatal hypoglycemia when treated with insulin or certain oral agents
  - Due to impaired secretion of counterregulatory hormones (particularly glucagon)
- Recurrent hypoglycemia is both associated with worsened cognition
- Severe hypoglycemia requiring hospitalization is associated with an increased risk of dementia
- Severe hypoglycemia linked to mortality
  - 3.4-fold increased risk of death

Changes with Aging

- Age is associated with changes in pharmacokinetics
  - Impaired elimination due to decreased renal function and phase I liver metabolism
  - Altered drug distribution due to an increase in body fat and a reduction in lean body mass
- Aging results in slow counter-regulatory hormone secretion
  - More prone to hypoglycemia when treated with insulin or insulin-releasing agents
- Pharmacodynamic changes also affect the sensitivity of older adults to drugs
  - “start low and go slow”

Cognitive Function

- The risk for vascular dementia and Alzheimer's disease increases in older people with diabetes
  - Not known if improved glycemic control or control of risk factors will reduce the risk of dementia
- Older people with diabetes also have a higher incidence of depression
  - Improved glycemic control improves affective function

Oral Therapy

Initial Treatment

- Initial treatment of T2DM is similar to younger patients
  - Nutrition, physical activity, optimizing metabolic control, and preventing complications
- Weight reduction through diet, exercise, and behavioral modification can be used to improve glycemic control, although the majority of older patients with T2DM will require medication over the course of their diabetes

Metformin

- For most older adults, metformin (in the absence of contraindications) should be initiated at the time of diabetes diagnosis

Metformin

- Decreases hepatic glucose production, increases peripheral insulin sensitivity and reduces intestinal glucose absorption
  - A1c reduction ~1.5%
- Promotes modest weight loss and improves lipids
- Potential reduction in cardiovascular events and all-cause mortality
- Main advantage for the elderly is the very low risk of hypoglycemia with monotherapy

Metformin

- eGFR>30 mL/min has been suggested as a safe level of kidney function for the use of metformin
- eGFR ≥45 mL/min: prescribe full dose
- eGFR between 30 and 45 mL/min: reduce the dose by half
  - No more than 1,000 mg per day

Metformin

- GI side effects and weight loss are most common
  - Worrisome in the frail elderly and those with poor appetite, malnutrition or low caloric intake
- B12 deficiency
- BBW for lactic acidosis
  - Older patients are at increased risk for developing conditions that reduce renal function or cause lactic acidosis
    - MI, stroke, heart failure, pneumonia

Sulfonylureas

- Insulin secretagogues stimulate insulin release from pancreatic β-cells
  - Pancreatic β-cell function decreases with aging
- A1C reduction (1%–2%)
- **Hypoglycemia**
  - High risk in the elderly

Sulfonylureas

- Glyburide has active metabolites that accumulate in renal insufficiency, causing **significant hypoglycemia**
- Glimepiride has one known active metabolite and has also been shown to cause prolonged hypoglycemia in the setting of reduced renal function
- Glipizide is metabolized to inactive metabolites, posing the least risk for hypoglycemia in the setting of reduced renal function

Dipeptidyl peptidase-4 Inhibitors

- Inhibit dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for degrading incretins (GLP1)
  - Enhanced GLP-1 activity increases insulin secretion, decreases glucagon secretion and promotes satiety
- Relatively weak agents that lower A1c by 0.7%
- Does not seem to be variation in efficacy among the different drugs available (sitagliptin, saxagliptin, vildagliptin, linagliptin and alogliptin)

Dipeptidyl peptidase-4 Inhibitors

- Well tolerated in older adults with little effect on weight, similar efficacy as younger adults
  - Suitable for frail and debilitated elderly patients
- Can be safely used in renal insufficiency with labeled dose adjustments
- Since the insulin release mediated by GLP-1 is dependent on blood glucose concentration, the risk of hypoglycemia of GLP-1 based therapies is negligible

Dipeptidyl peptidase-4 Inhibitors

- Well tolerated in short-term studies, but long-term safety has yet to be established
- Post-marketing adverse effects include acute renal failure, allergic reactions and acute pancreatitis
  - Avoid if history of pancreatitis
- Some trials investigating the cardiovascular safety and efficacy of DPP-4 inhibitors point to an increased risk of heart failure with the use of saxagliptin and alogliptin, regardless of age
  - A 2015 review concluded that incretin-based agents do not increase major adverse cardiovascular events

Dipeptidyl peptidase-4 Inhibitors

- Ideal for monotherapy in patients who are not good candidates for metformin or a sulfonylurea or for combination therapy in older patients
- Safety profile, neutral effect on weight and once-daily dosing make these agents advantageous for use in frail and debilitated elderly patients as well as patients with cognitive dysfunction, decreased dexterity, inconsistent meal patterns or compliance issues

Dipeptidyl peptidase-4 Inhibitors

- 6-month sitagliptin therapy may be associated with improvement of cognitive function in elderly diabetic patients with and without AD
  - Experimental data have shown that DPP-4 inhibitors may delay, if not prevent, cognitive decline in Alzheimers and Parkinsons Disease
  - Recent data indicate that DDP-4 inhibitors may also have a neuroprotective effect
- High cost may be limiting

Thiazolidinediones (TZDs)

- TZDs are insulin sensitizers
  - Increase peripheral insulin sensitivity, especially of muscle and adipocytes
- Low incidence of hypoglycemia
- Lower A1C levels in older patients by 1 to 1.5%
- Serious side effects include fluid retention that can exacerbate or lead to worsening HF, weight gain, macular edema, hepatic failure and an increased risk of bladder cancer with pioglitazone
  - Contraindicated in patients with NYHA class III or IV HF

TZDs

- Increased fracture risk identified in older patients
  - Increased fractures were observed at the humerus, hand, and foot, rather than the typical osteoporotic sites
  - Mechanism is unclear
  - Use with caution in elderly
- Concern about an increased risk of CV events with rosiglitazone following the results of a large population-based study of older (>65 years) patients with T2DM that showed an increased risk of MI
  - Findings were not consistent among similar studies

TZDs

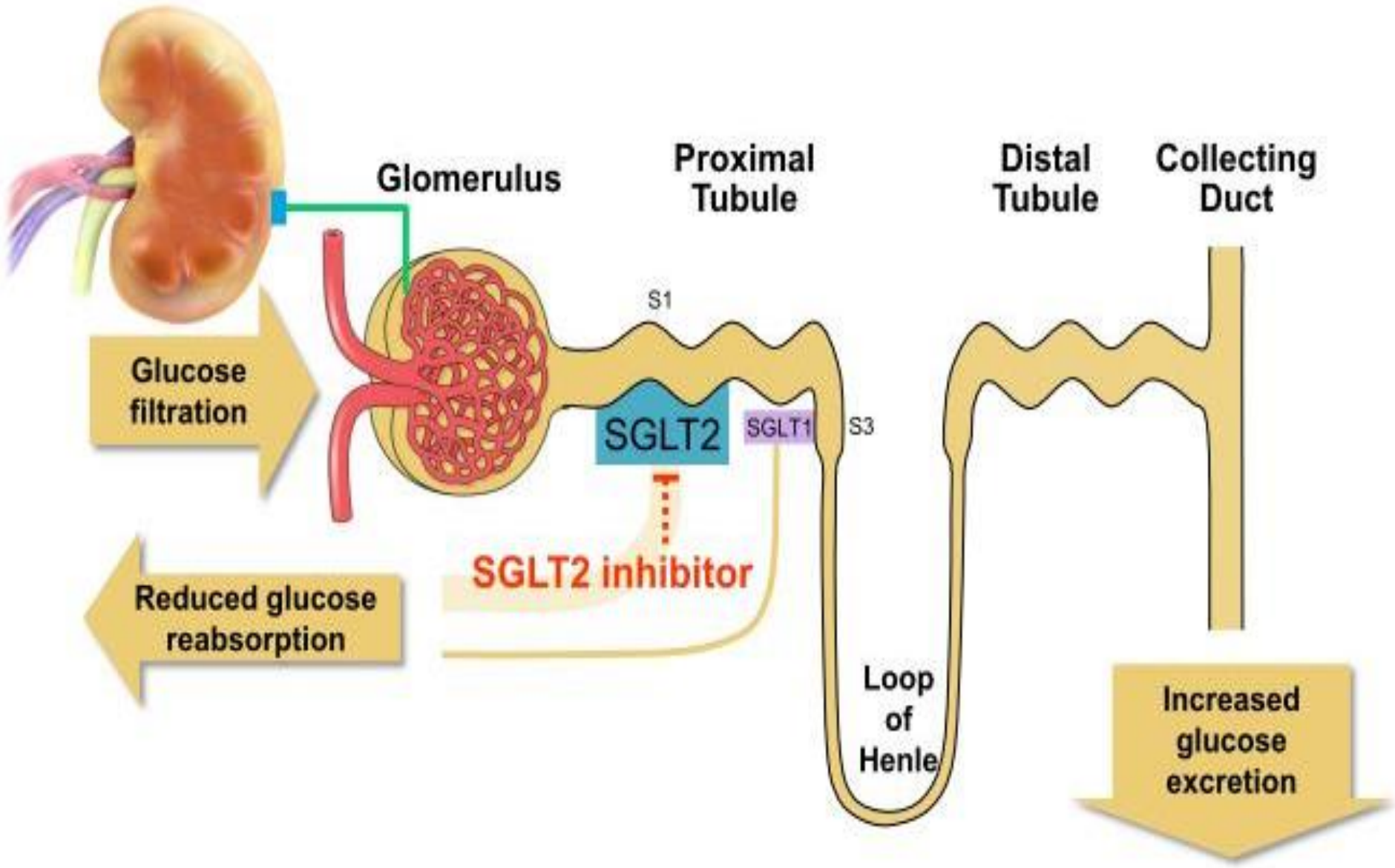
- Rosiglitazone is associated with greater decline in cognitive performance compared with insulin therapy
- Despite the current evidence against the use of rosiglitazone in Alzheimer's disease (AD), pioglitazone exhibited cognitive and functional improvement in mild AD

TZDs

- A longitudinal cohort study showed that older men with diabetes using metformin or TZDs lost less lean body mass compared with those with untreated diabetes or treated with other antidiabetic agents
  - Evidence also suggests drugs that increase insulin sensitivity, such as TZDs and metformin, may attenuate the progressive loss in muscle mass that occurs in older people with diabetes and contributes to frailty
- Potentially beneficial for older adults, even in frail elderly patients, whose muscle mass is lost with aging and accelerated with impaired fasting glucose and diabetes

Sodium-glucose Co-transporter 2 Inhibitors (SGLT2)

- SGLT2 is a co-transporter that is expressed in the proximal tubule and is responsible for reabsorbing approximately 90% of the filtered glucose load
- Moderate glucose-lowering agents
  - Reduce A1c by approximately 0.5 to 1%
- Shown to be effective in patients older than 65 years


Glomerulus
Proximal Tubule
Distal Tubule
Collecting Duct
S1
Glucose filtration
SGLT2
SGLT1
S3
SGLT2 inhibitor
Reduced glucose reabsorption
Loop of Henle
Increased glucose excretion

SGLT2

- Reduce glucose levels rapidly practically as soon as the agent appears in the serum, and no other oral agent has the capability to work so fast
- Because there is a prompt lowering of glucose levels, insulin secretion is not stimulated , and the risk of hypoglycemia is low

SGLT2

- Added benefit of decreasing blood pressure and weight
- Common adverse events that occur in over 10% of patients include hypotension, hyperkalemia, increased LDL levels, acute kidney injury, genital mycotic infections and hypoglycemia when used in combination with insulin or insulin secretagogues

SGLT2

- A higher incidence of adverse effects related intravascular volume depletion have been reported in those aged 65 or older, with a more prominent increase seen in patients aged 75 or older
- Product labels recommend assessing volume status and correcting hypovolemia in elderly patients (as well as in patients with renal impairment, low BP, or patients on diuretics), and monitoring for signs and symptoms during therapy

SGLT2

- Although many adverse effects have been reported, empagliflozin was associated with significantly lower rates of all-cause and cardiovascular death and lower risk of hospitalization for heart failure in the only SGLT-2 inhibitor cardiovascular outcomes trial reported to date
- If this cardiovascular benefit is replicated in additional trials, SGLT inhibitors may become more favorable

Injectable Therapy

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

- Injectable agents that potentiate the actions of the naturally occurring incretin hormone GLP-1
- GLP-1 is a gastrointestinal hormone that stimulates glucose-dependent insulin release from pancreatic islet cells
  - Inhibits glucagon release, reduces hepatic glucose production and slows gastric emptying
- Pronounced effect on satiety
- Promote weight loss
  - Progressive and dose-dependent

GLP-1 RAs

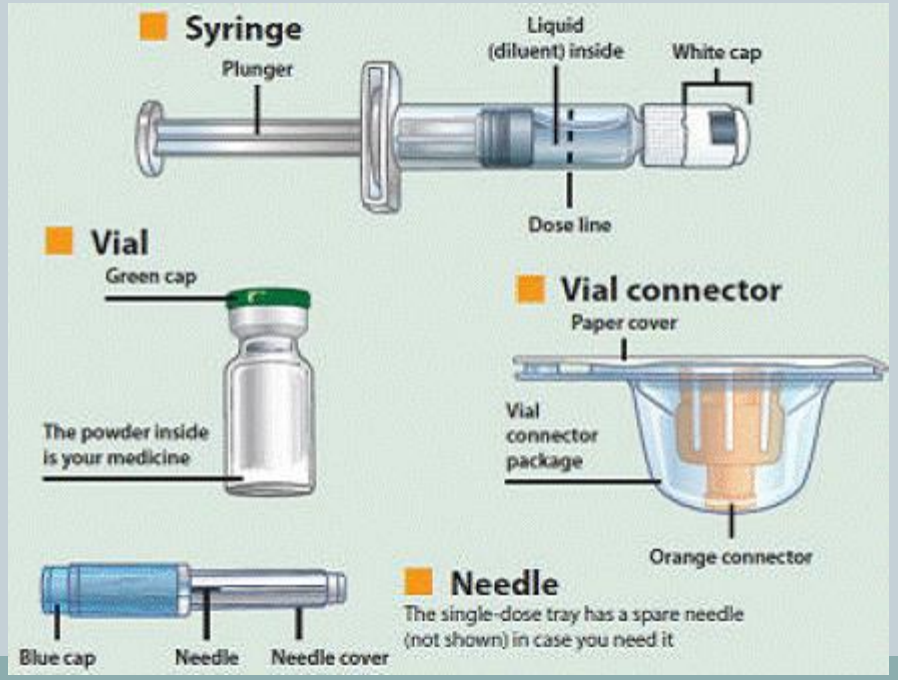
- Studies in elderly patients confirm an A1C reduction of 1 to 1.5% and a **low risk of hypoglycemia** when used alone or in combination
  - May elevate the risk of sulfonylurea induced hypoglycemia
- Common side effects: nausea, vomiting and diarrhea
  - Occur most commonly during treatment initiation and titration
  - May be avoided with dose titration and usually wane with continuation of therapy

GLP-1 RAs

- Can be used as monotherapy in older patients at risk for hypoglycemia or hypoglycemia unawareness and in combination therapy with other agents, including insulin
  - Weight loss and gastrointestinal side effects may limit use in frail or undernourished patients
- Require visual, motor and cognitive skills
- High cost

GLP-1 RAs

- Selection should be based on the frequency of administration, type of glucose control required (fasting or post-prandial) and ability to use the specific administration device



GLP-1 RAs

- Dose adjustment is required in renal impairment, with the exception of dulaglutide and liraglutide
- Caution is recommended in patients with a history of pancreatitis, and GLP-1 RAs should be stopped if pancreatitis is suspected during treatment
- GLP-1 RAs should not be used in patients with a personal or family history of thyroid-related cancers as they have been associated with medullary thyroid tumors in animals

GLP-1 RAs

- Evidence suggests GLP-1 RAs offer additional cardiovascular benefit in patients with diabetes
- In August 2017, liraglutide gained indication to reduce the risk of major adverse cardiovascular events in adults with T2DM and established CV disease
  - Based on LEADER trial liraglutide reduced major adverse CV events by 13% vs placebo and reduced CV deaths by 22%
- New indication may impact the choice of add-on therapy in CV conditions

Insulin

- Many patients will ultimately require insulin due to the progressive loss of beta cell function that occurs in advanced age or long-standing T2DM
- Initiating insulin therapy early on in the disease may restore beta cell function and reduce glucotoxicity
- Early treatment with basal insulin results in better glycemic control and less hypoglycemia than titration of oral agents in elderly patients with uncontrolled diabetes

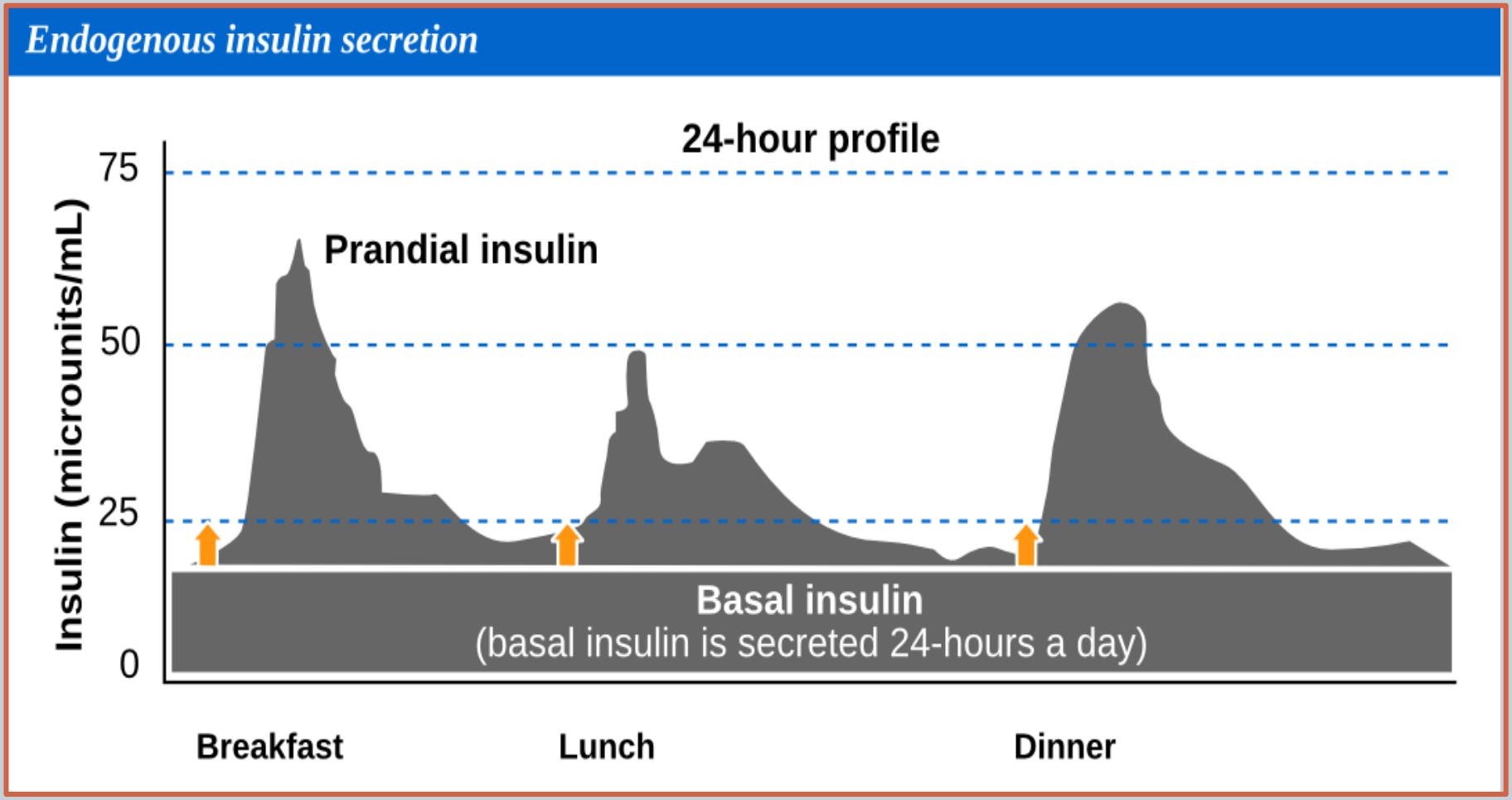
Insulin

- Despite these benefits, the use of insulin is often underutilized in the elderly due to concerns about hypoglycemia and difficulty of administration
- Safe use of insulin requires careful selection of an appropriate insulin regimen
- Insulin use has been identified as an independent predictor of severe hypoglycemia in the elderly
  - 2nd most frequent medication associated with ED visits in patients > 65 years
- Evaluate cognitive and physical ability to safely use insulin prior to initiation

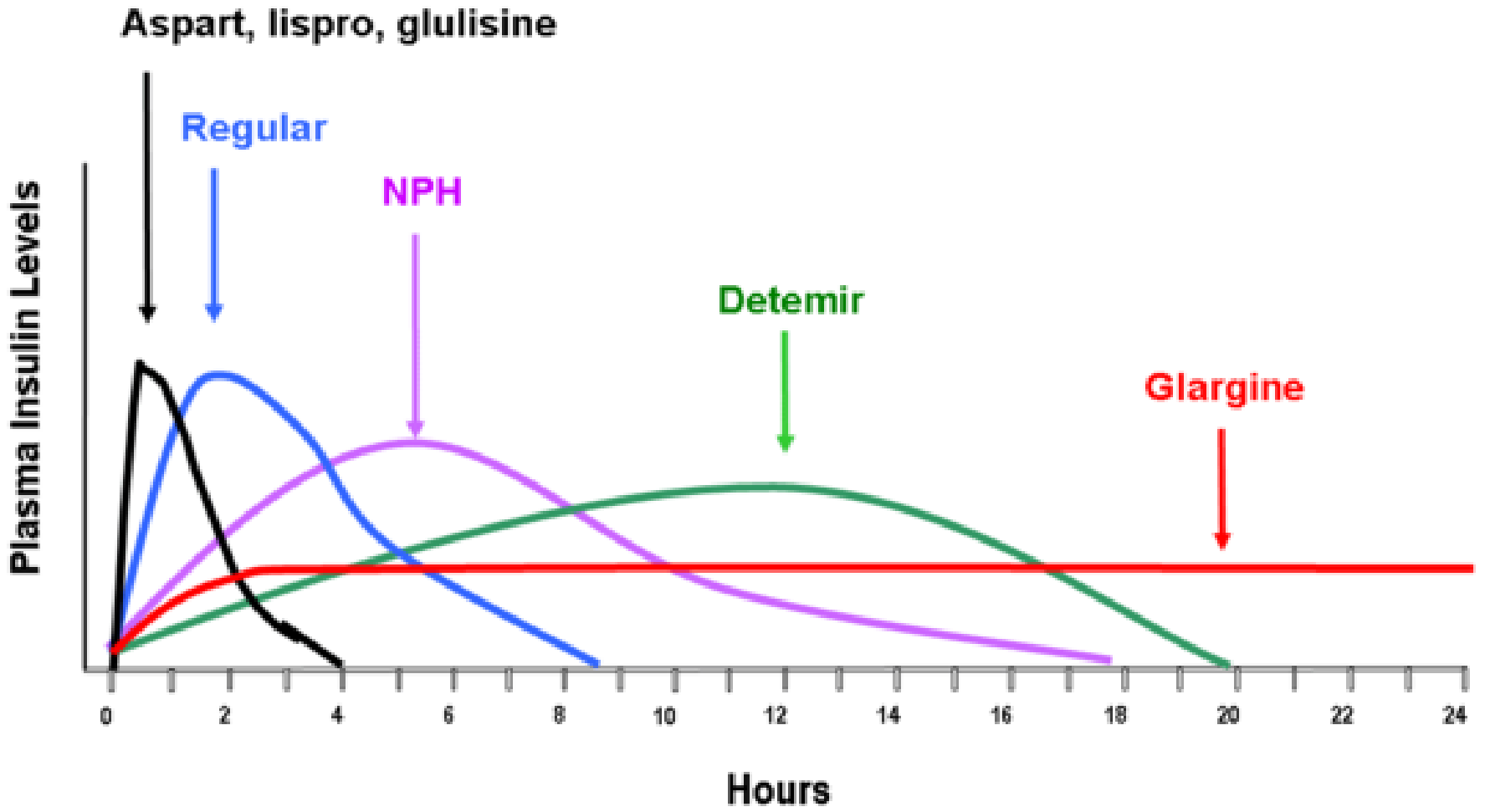
Insulin

- Multiple daily injections should be limited to use in high functioning older adults
- Regimens that mimic the normal physiologic pattern of insulin offer less risk
- Basal insulin that mimics the body's sustained basal insulin level throughout the day is associated with a lower frequency of hypoglycemia in older people with diabetes than conventional insulin regimen
- Long-acting insulins offer a lower risk of hypoglycemia, particularly nocturnal hypoglycemia which may contribute to falls

Insulin: Physiologic Secretion



Insulin


Aspart, lispro, glulisine
Regular
NPH
Detemir
Glargine
Plasma Insulin Levels
0
2
4
6
8
10
12
14
16
18
20
22
24
Hours

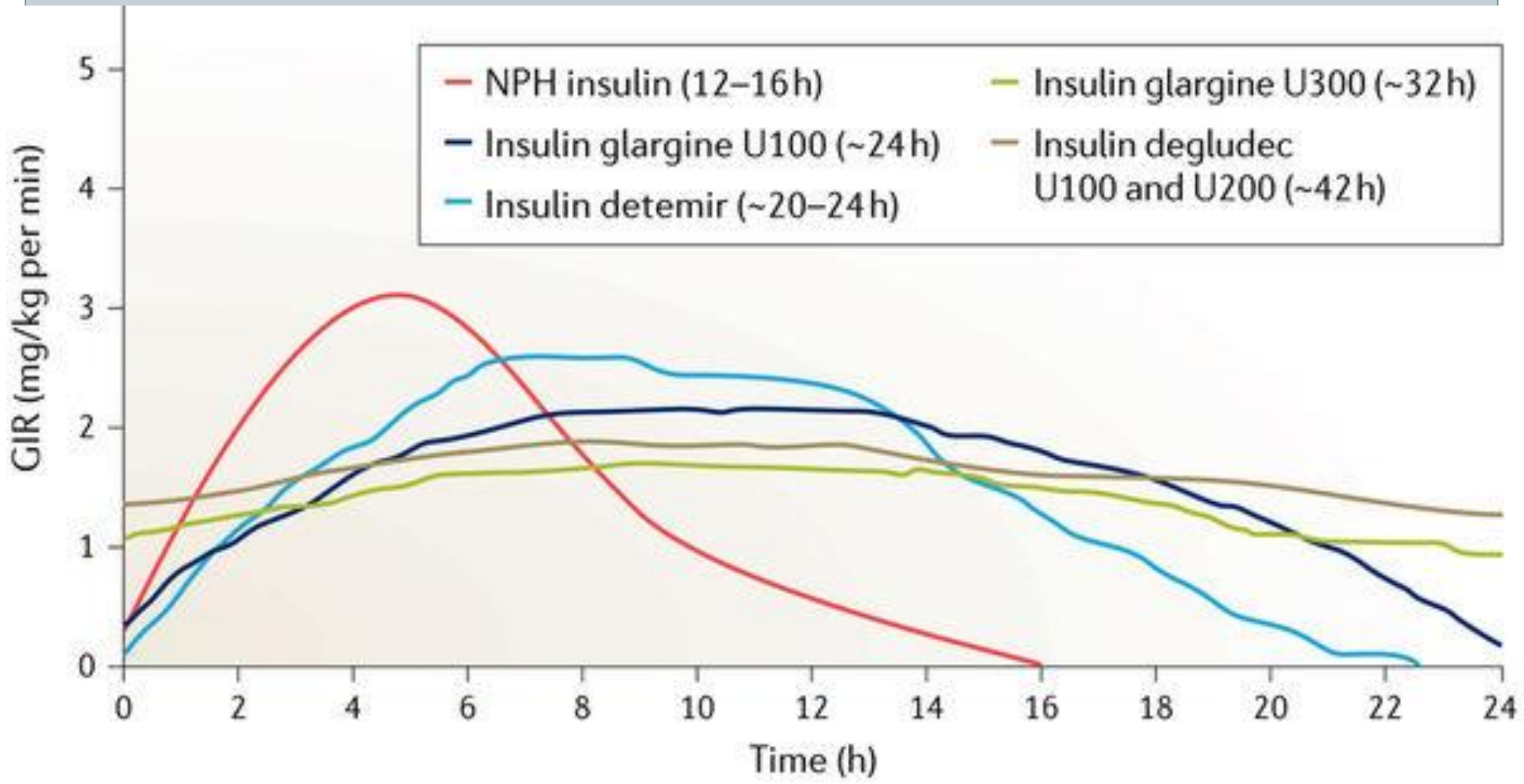
Insulin

- NPH and regular insulin are not recommended due to variable bioavailability and nonphysiological pharmacokinetics that put patients at higher risk for hypoglycemia
- Long-acting insulins are safer choices than NPH in older adults because of their lower risk of hypoglycemia, especially nocturnal hypoglycemia, which may contribute to cardiovascular morbidity and falls
- Insulin action is prolonged in renal insufficiency so the dose should be decreased when the GFR is below 50mL/min in order to avoid hypoglycemia

Insulin

- Insulin degludec may offer an advantage over insulin glargine and insulin detemir in elderly
  - Ultra-long-acting insulin with a duration of action of over 42 hours
- Elderly patients experience a lower rate of nocturnal hypoglycemia with insulin degludec than insulin glargine
  - Likely due to the stable pharmacokinetic profile and lower day-to-day variability of degludec

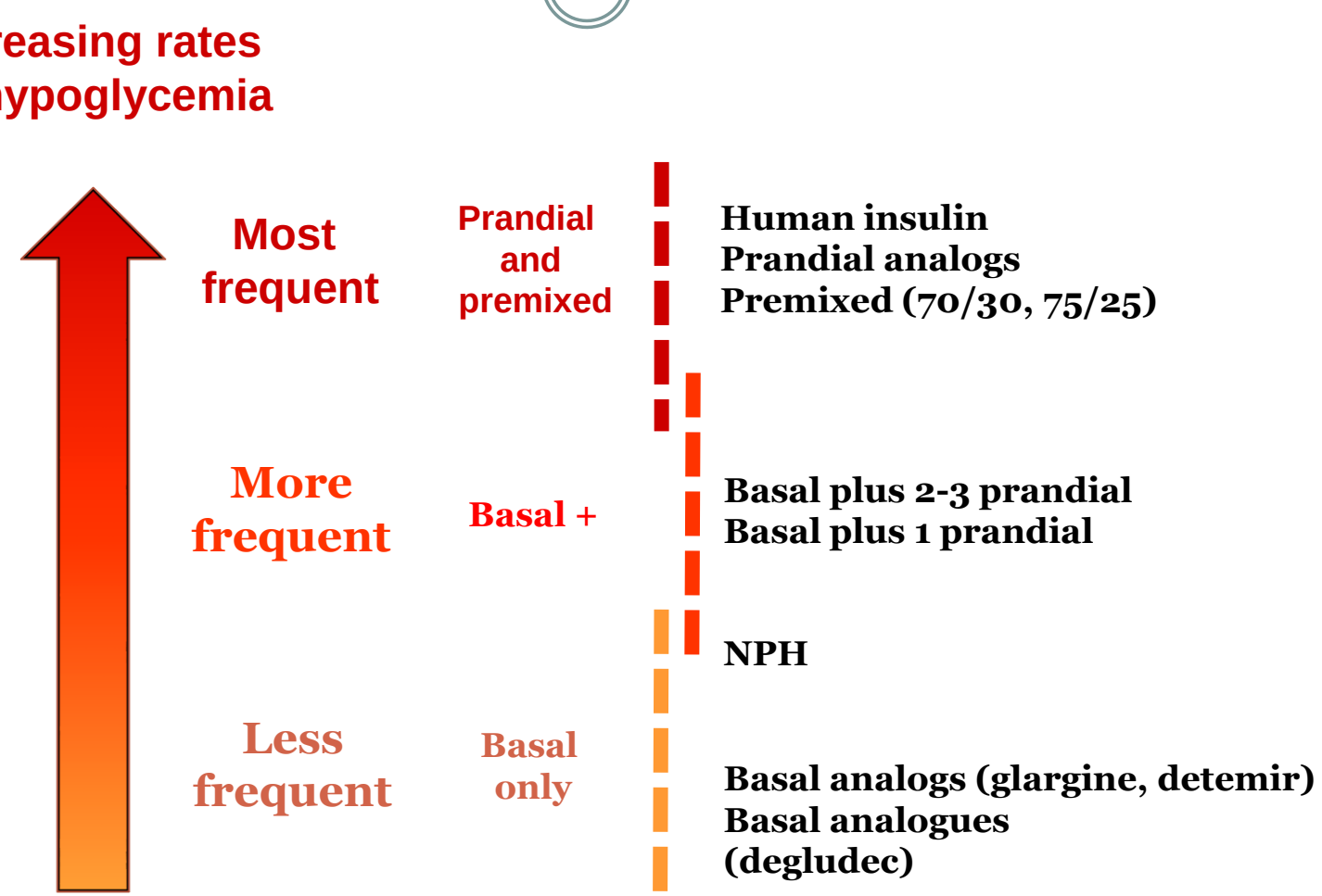
Insulin


NPH insulin (12–16 h)
Insulin glargine U100 (~24 h)
Insulin detemir (~20–24 h)
Insulin glargine U300 (~32 h)
Insulin degludec U100 and U200 (~42 h)
GIR (mg/kg per min)
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (h)

Insulin

- As beta-cell function declines further, prandial insulin coverage may be necessary in some patients
  - Limit to high-functioning patients
- If insulin intensification is needed after optimizing the use of basal insulin, the addition of mealtime insulin should be accomplished using a basal-bolus approach, with rapid acting insulin (insulin aspart, insulin lispro or insulin glulisine) utilized for bolus therapy

Relative Rates of Severe Hypoglycemia with Insulin



Insulin Safety

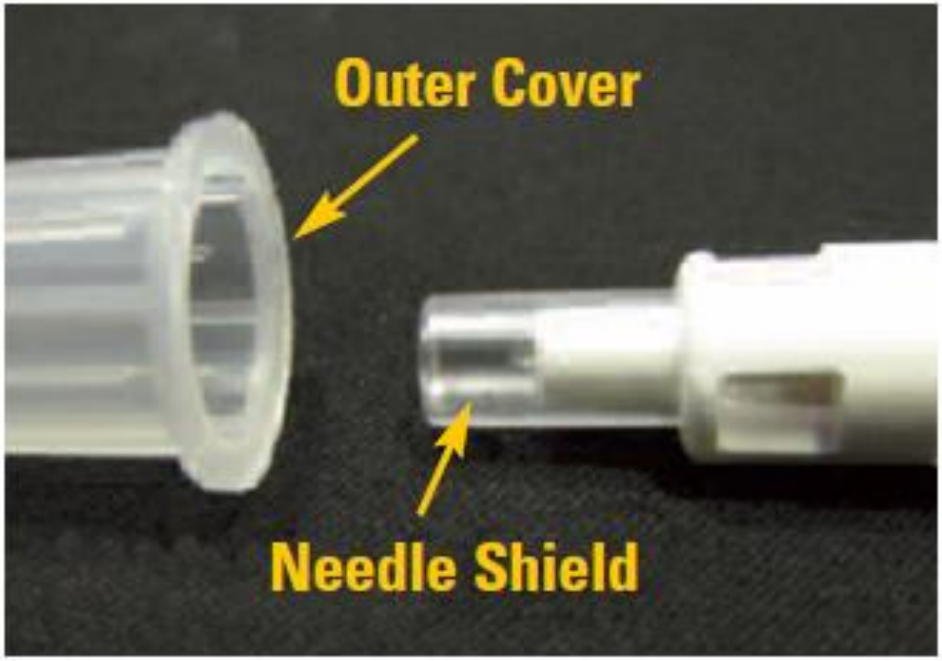
- Problems with vision or manual dexterity may be barriers to insulin therapy for some older adults
- Pen devices improve ease of use but are more costly than the use of vials and syringes
- Insulin analogs delivered through pen devices lead to improved adherence, accuracy of injection, quality of life, and decreased admissions for hypoglycemia

Insulin Safety

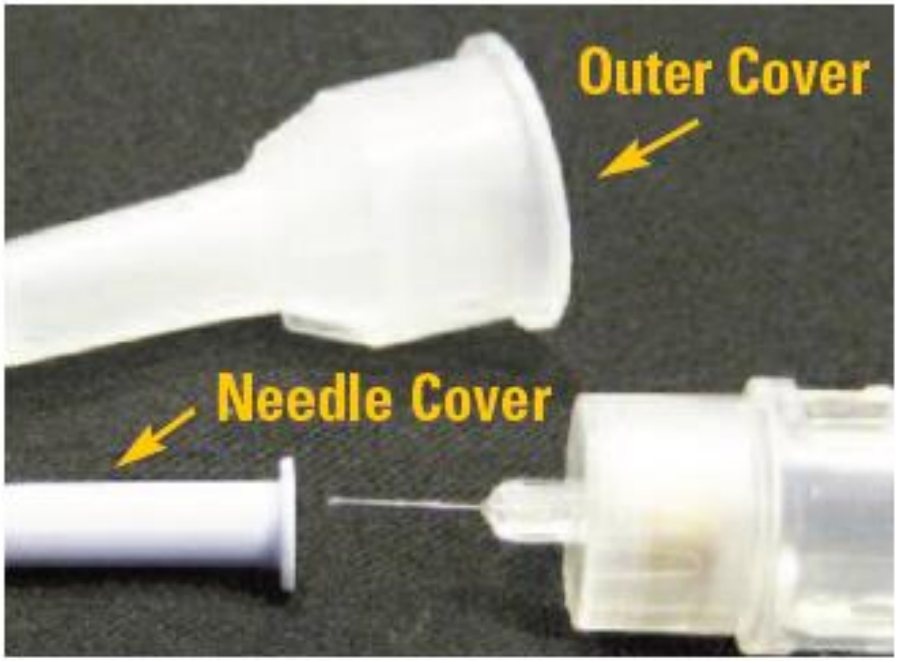
October 12, 2017

Severe hyperglycemia in patients incorrectly using insulin pens at home

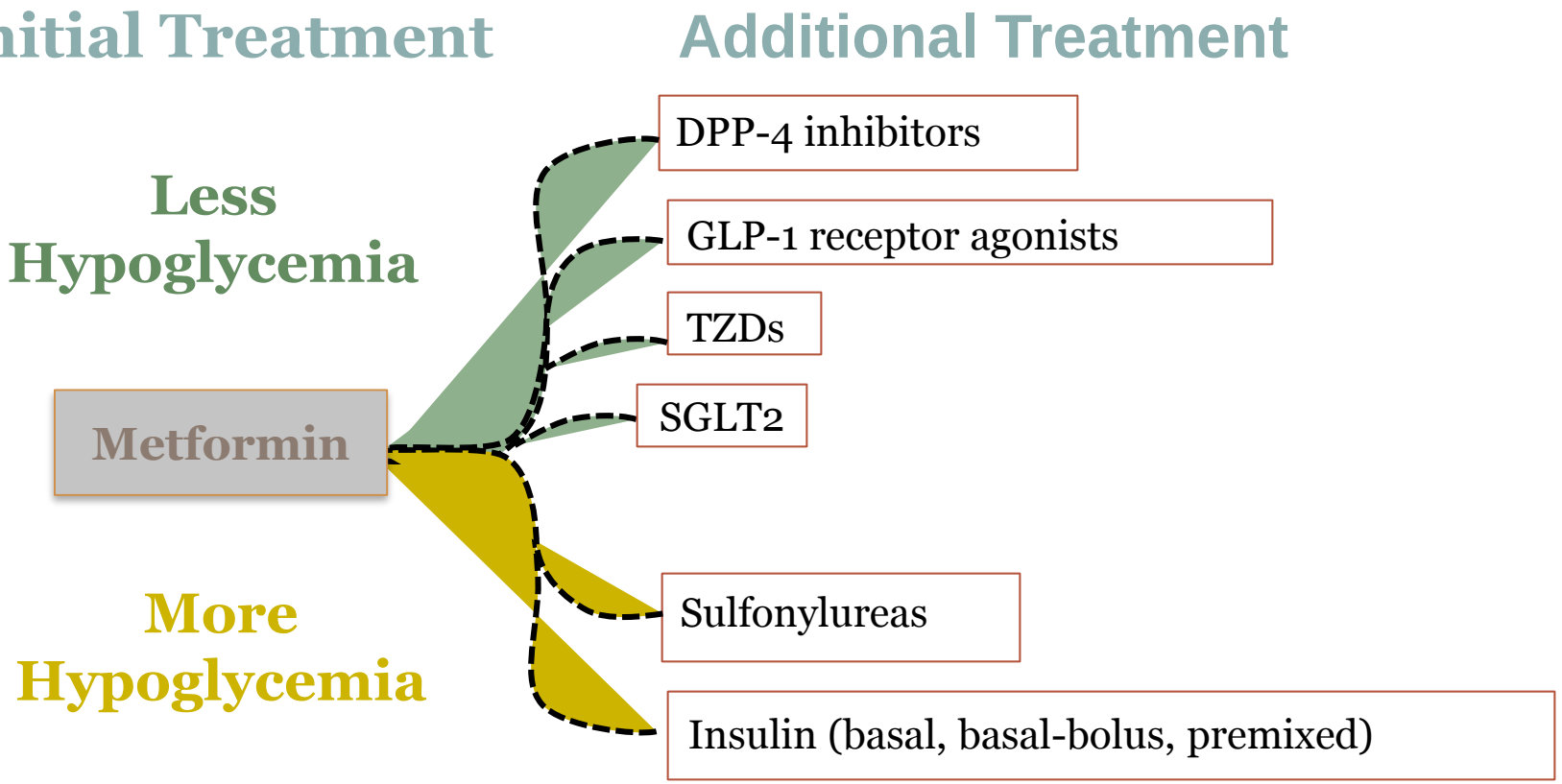
Safety Pen Needle



Standard Pen Needle

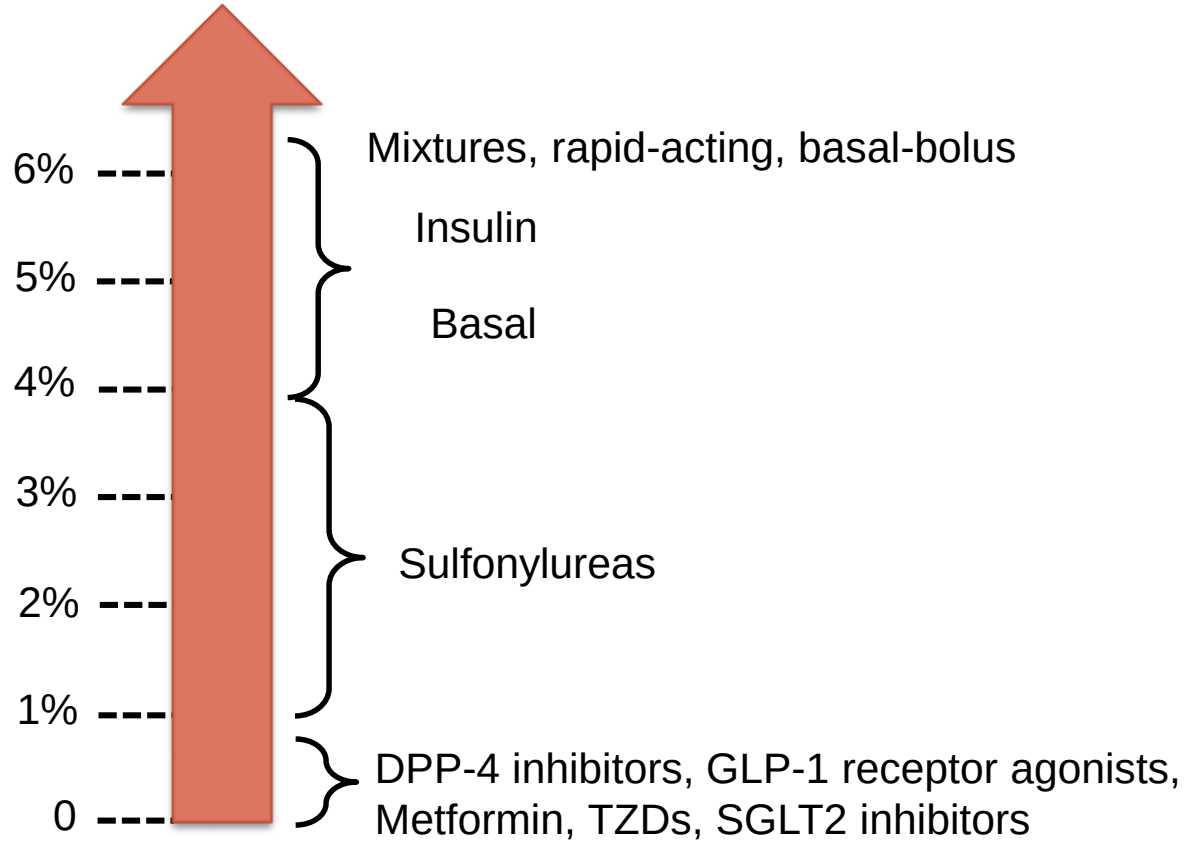


Hypoglycemia Risk With Antihyperglycemic Agents Added to Metformin



Frequency of Severe Hypoglycemia With Antihyperglycemic Agents

Percentage of Patients Treated in 1 Year



Questions