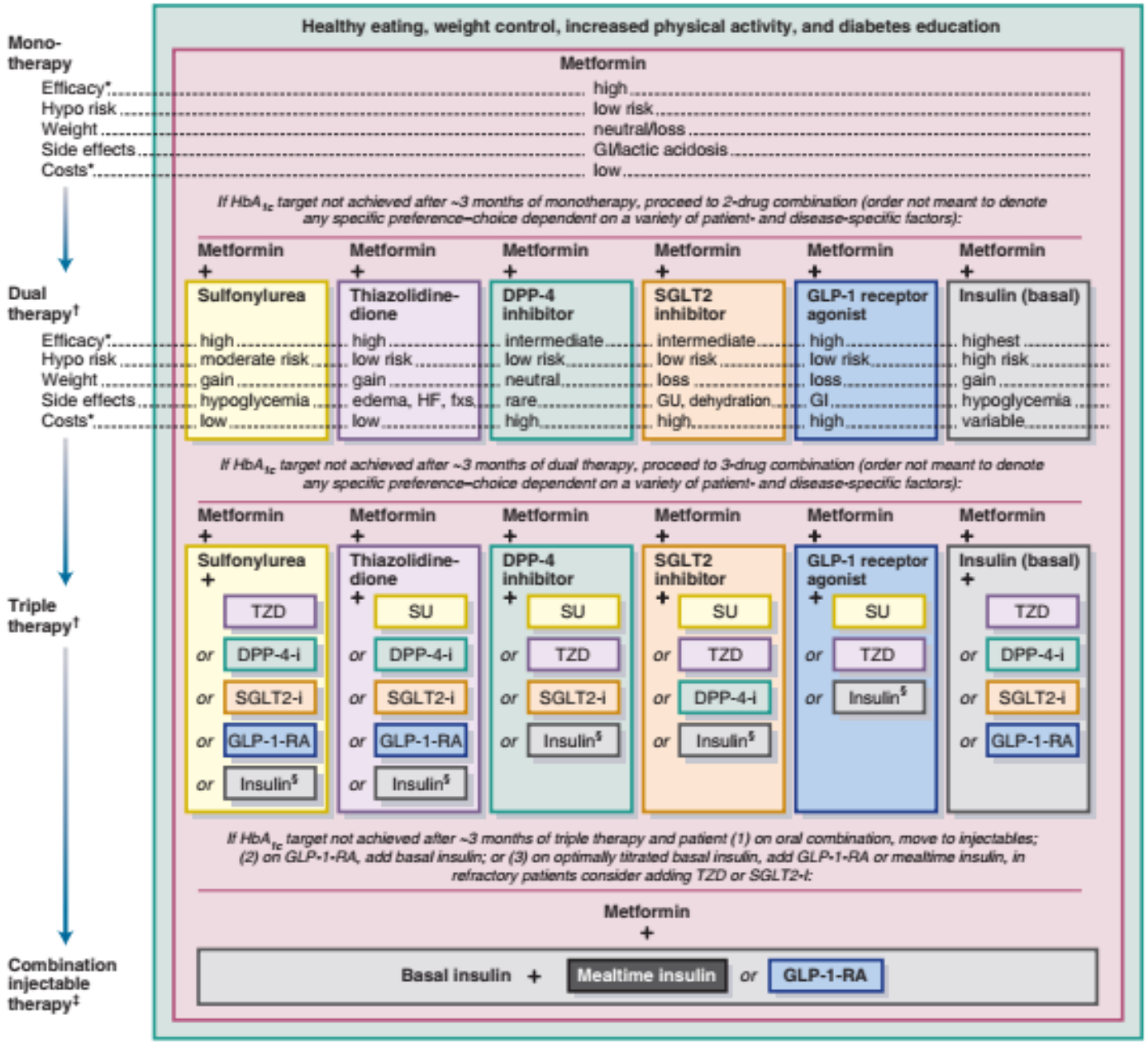
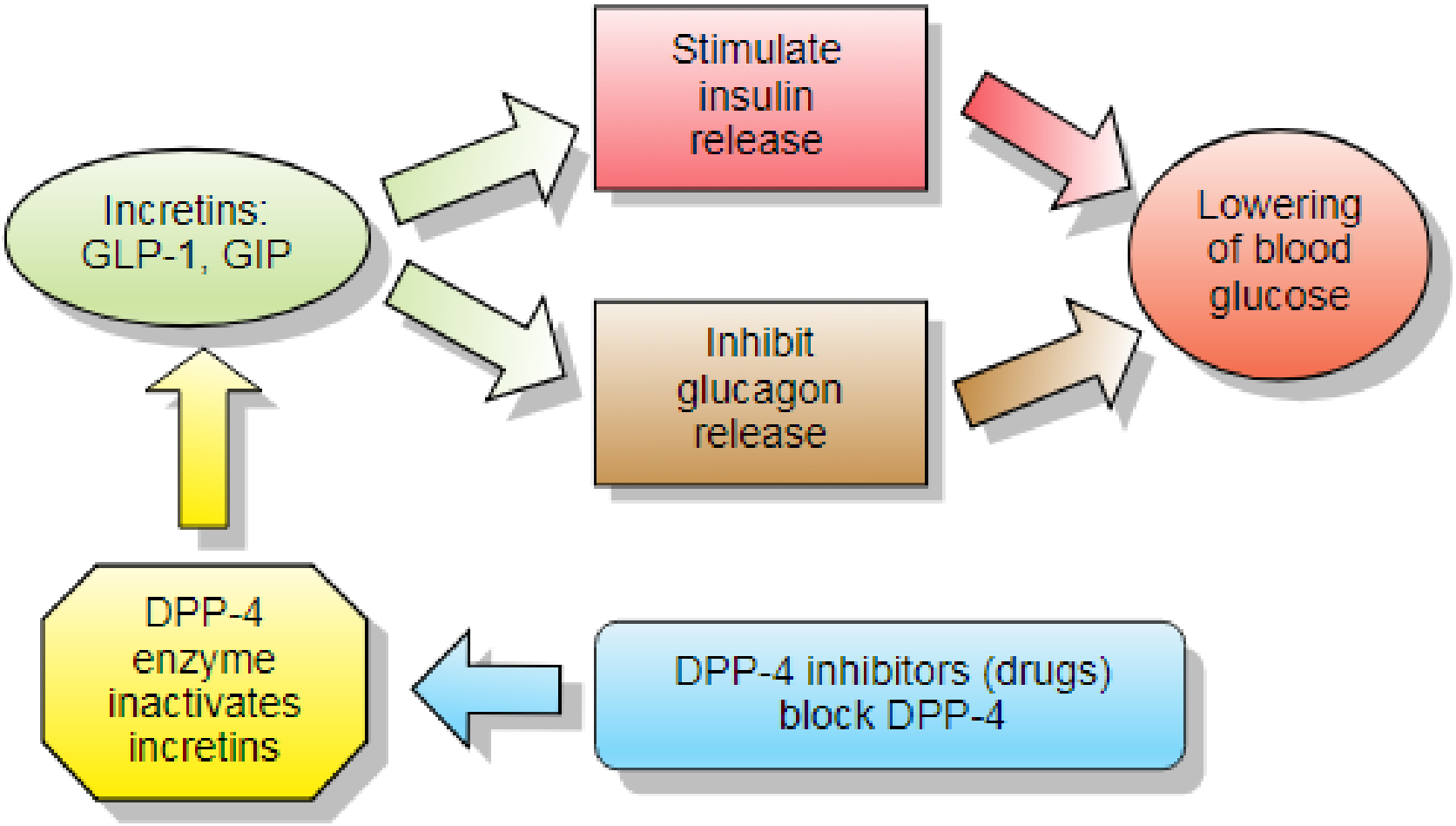

بسم الله الرحمن الرحیم

VICTOSA and Renal impairment

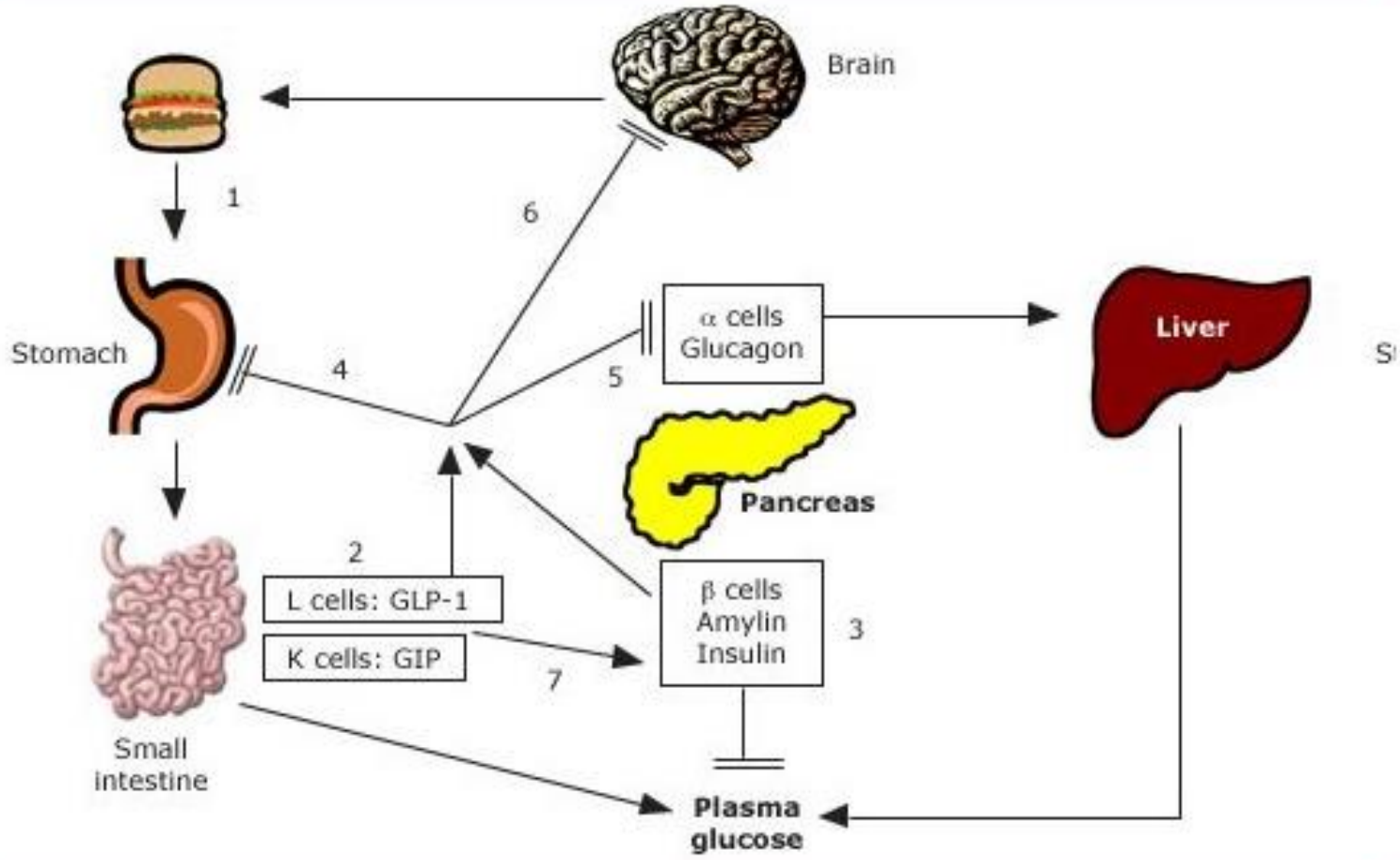
DR.R.S.SAJAD

February 2019


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral/loss
Side effects GI/lactic acidosis
Costs* low
If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference–choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference–choice dependent on a variety of patient- and disease-specific factors):
Triple therapy†
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin, in refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA


Stimulate insulin release
Incretins: GLP-1, GIP
Lowering of blood glucose
Inhibit glucagon release
DPP-4 enzyme inactivates incretins
DPP-4 inhibitors (drugs) block DPP-4

Multihormonal regulation of glucose



In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

- **Main effect of GLP-1 is :**
- Stimulating glucose dependent insulin release from the pancreatic islets.
- Slow gastric emptying
- Inhibit inappropriate post meal glucagon release
- Reduce food intake and due to side effects of nausea and vomiting is associated with weight loss.

GLP-1 Recepor agonists:

Short –acting: Exenatide , lixisenatide

Long- acting: Liraglutide , Exenatide OW

GLP-1 Receptor Agonists

- Exenatide is the first GLP-1-based therapeutic agent to be approved for human use.

- When injected subcutaneously, it produces the effects listed earlier and has a peak of action and half-life of approximately 2 hours.

- With twice-daily injection within 1 hour before a meal, it produces a reduction of approximately 1% in HbA1c, driven largely by a reduction in postprandial glucose along with modest weight loss (average= 5 to 10 lb/year).

- With prolonged use, weight loss has been associated with expected improvements in blood pressure and lipids.

- The most common adverse effect is nausea, which occurs in 40% to 50% of patients, usually early in the course of therapy

- longer-acting agents are associated with greater HbA1c-lowering efficacy owing to more predominant effects on FPG than exenatide in the twice daily formulation.

- They are also associated with fewer gastrointestinal adverse effects, probably because they seem to produce little or no gastric emptying effects.

- Hypoglycemia is not a direct effect of GLP-1 receptor agonists, but they can amplify the hypoglycemic effects of other agents.

- Therefore, for coadministration with secretagogues or insulin, it is recommended that the minimum dose of secretagogue be used when initiating GLP-1 receptor agonist therapy, uptitrating the secretagogue later if necessary.

- A 20% insulin dose reduction is prudent when initiating GLP-1 receptor agonists in insulin-treated patients with T2DM and HbA1c less than 8%.
- A concern that emerged from postmarketing reports is pancreatitis.

- A causal link has not been proved, nor has a mechanism been established.

- Nevertheless, it is recommended that incretin-based therapy be avoided in those with a history of pancreatitis.

- Exenatide is renally cleared and is contraindicated in the setting of advanced kidney disease (eGFR <30 mL/minute per 1.73 m2).

- The other GLP-1 receptor agonists do not share this feature with exenatide.

- cases of acute renal failure have been reported in association with GLP-1 receptor agonist therapy, usually in patients with chronic renal insuffciency who develop superimposed prerenal azotemia in the context of prolonged nausea, anorexia, and vomiting.

- To mitigate the risk of pancreatitis and renal failure, it is prudent to instruct patients treated with GLP-1 receptor agonists to hold their medication if they develop nausea, vomiting, or abdominal pain of more than a few hours' duration and to seek medical attention if they are unable to keep down fluids after 4 hours.

- A new safety concern that arose in preclinical testing with these long-acting agents is medullary thyroid cancer.

- No signal exists for this problem with GLP-1–based therapy in humans, but there is a clear increase in the incidence of these tumors in rodents, although not in other animal models.

- GLP-1 plays a role in regulation of C cells in the rodent but apparently not in the human.

- Nevertheless, it is suggested that these agents be avoided in those with a personal or family history of medullary thyroid cancer.

- Long-acting GLP-1 agents :

- Liraglutide is a once daily injectable GLP-1 analog available for use in the United States, Europe, and in Japan.

- Liraglutide is a GLP-1 analog that has been modified to non-covalently bind to serum albumin through a lipid side chain, resulting in slower degradation and allowing for once-daily subcutaneous dosing.

- Liraglutide is available in prefilled pens. The initial dose is 0.6 mg once daily for one week to reduce gastrointestinal side effects.

- After one week, the dose should be increased to 1.2 mg once daily for one week.

- If blood glucoses remain above the goal range, the dose can be increased to 1.8 mg once daily.

- Adverse effects — The most common adverse events are nausea, vomiting, and diarrhea, occurring in the above trials at rates of 10 to 40 percent.

Adverse Reactions Significant

- >10%: Gastrointestinal: Nausea (28%), diarrhea (17%), vomiting (11%)

1% to 10%:

- Central nervous system: Headache (9%)
- Gastrointestinal: Constipation (10%)
- Local: Injection site reactions

- Protein binding: >98%
- Metabolism: Endogenously metabolized by dipeptidyl peptidase IV (DPP-IV) and endogenous endopeptidases ; metabolism occurs slower than that seen with native GLP-1
- Bioavailability: ~55%
- Half-life, elimination: ~13 hours
- Time to peak, plasma: 8-12 hours
- Excretion: Urine (6%, as metabolites); feces (5%, as metabolites

- Liraglutide is metabolised in a similar manner to large proteins, and no specific organ is responsible for its elimination. Intact liraglutide is recovered neither in the urine nor in the feces.

- Unlike exenatide, liraglutide shows no increase in half-life and hence no reduced clearance in patients with mild, moderate, or even severe renal impairment.

- Therefore, the kidney is not a major site of liraglutide elimination or breakdown.
- Patients with mild renal impairment require no dose adjustment.

- Experience with liraglutide is however very limited in patients with moderate renal impairment and nonexistent in those with severe renal impairment. Therefore, this treatment is contraindicated in these settings.

BJCP British Journal of Clinical Pharmacology
BRITISH PHARMACOLOGICAL SOCIETY

Br J Clin Pharmacol. 2009 Dec; 68(6): 898–905.
doi: 10.1111/j.1365-2125.2009.03536.x

PMCID: PMC2810801
PMID: 20002084

Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide

Lisbeth V Jacobsen, Charlotte Hindsberger, Richard Robson,[1] and Milan Zdravkovic

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Renal dyafunction was not found to increase exposure of liraglutide and patients with type 2 DM and renal impairment should use standard treatment regimens of liraglutide

ORIGINAL ARTICLE

Liraglutide and Renal Outcomes in Type 2 Diabetes

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D., Kirstine Brown-Frandsen, M.D., Steven P. Marso, M.D., Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D., Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D. for the LEADER Steering Committee and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

- Renal outcom: new –onset persistent macroalbuminuria ;persistent doubling of serum creatinine ;renal replacement therapy ;death due to renal disease

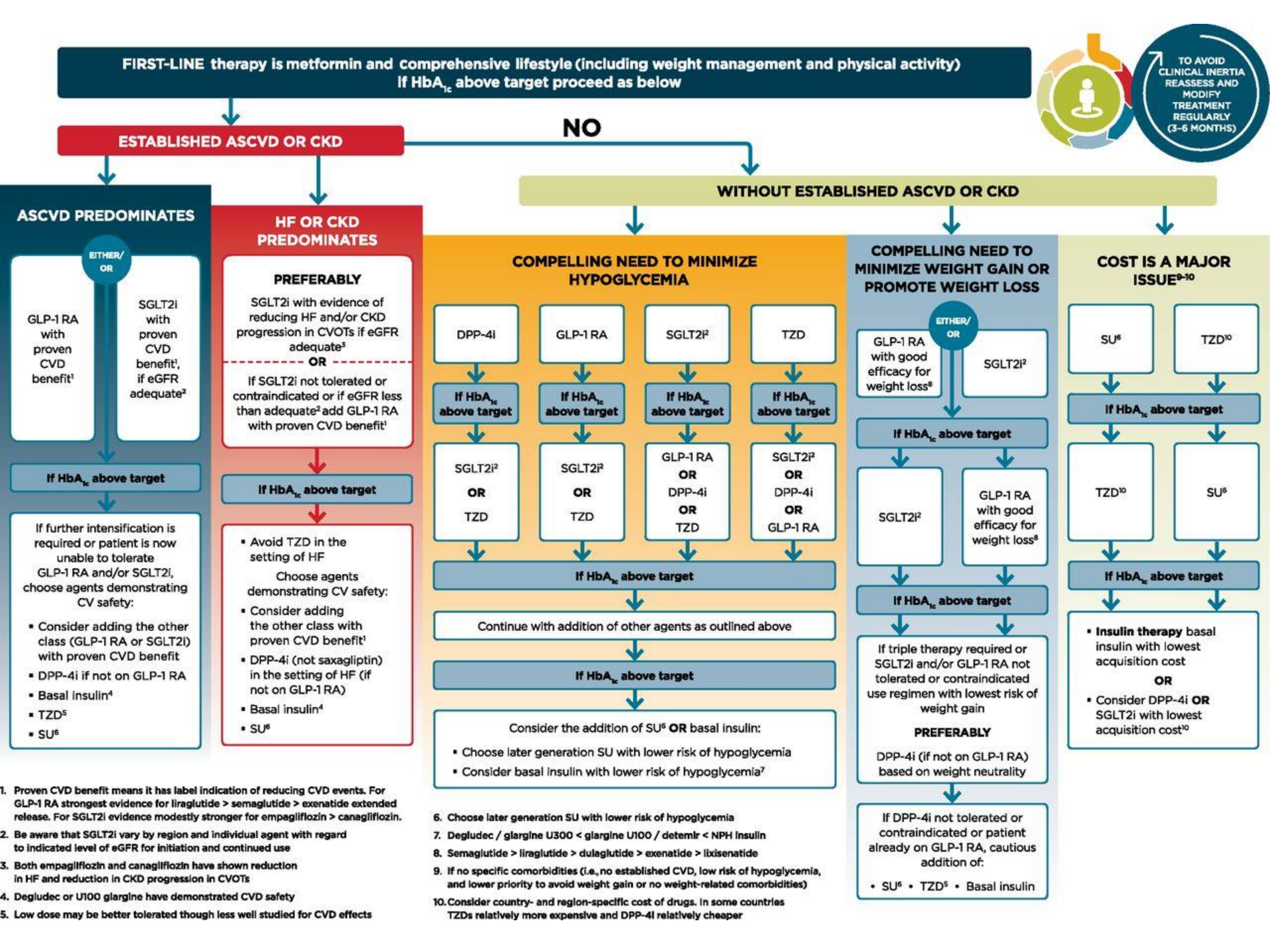
conclusions:liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo.

Dosing: Renal Impairment

- *U.S. labeling:*
- Mild-to-severe impairment: No dosage adjustment provided in manufacturer's labeling; however, use with caution, due to limited experience and reports of acute renal failure and exacerbation of chronic renal failure

- *Canadian labeling:*
- Mild impairment: No dosage adjustment necessary.
- Moderate-to-severe impairment: Use is not recommended.

- For patients in whom ASCVD, HF, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated cardiovascular risk reduction, after consideration of drug-specific and patient factors.



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