DOMTRU Diabetes Injectables Masterclass - 2019

Cardiovascular Outcome Trials and the ADA/EASD Diabetes Management Guidelines

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Cardiovascular Outcome Trials

- Designed to demonstrate cardiovascular safety of new diabetes drugs
- FDA recommendation following a controversial meta-analysis in 2007 demonstrating possible cardiovascular harm with Rosiglitazone
- Rosiglitazone subsequently shown to be safe in RECORD study

GLP-1 Receptor Analogue CVOTs

- LEADER – Liraglutide (Victoza)
- EXSCEL – once weekly Exenatide (Bydureon)
- REWIND – Dulaglutide (Trulicity)

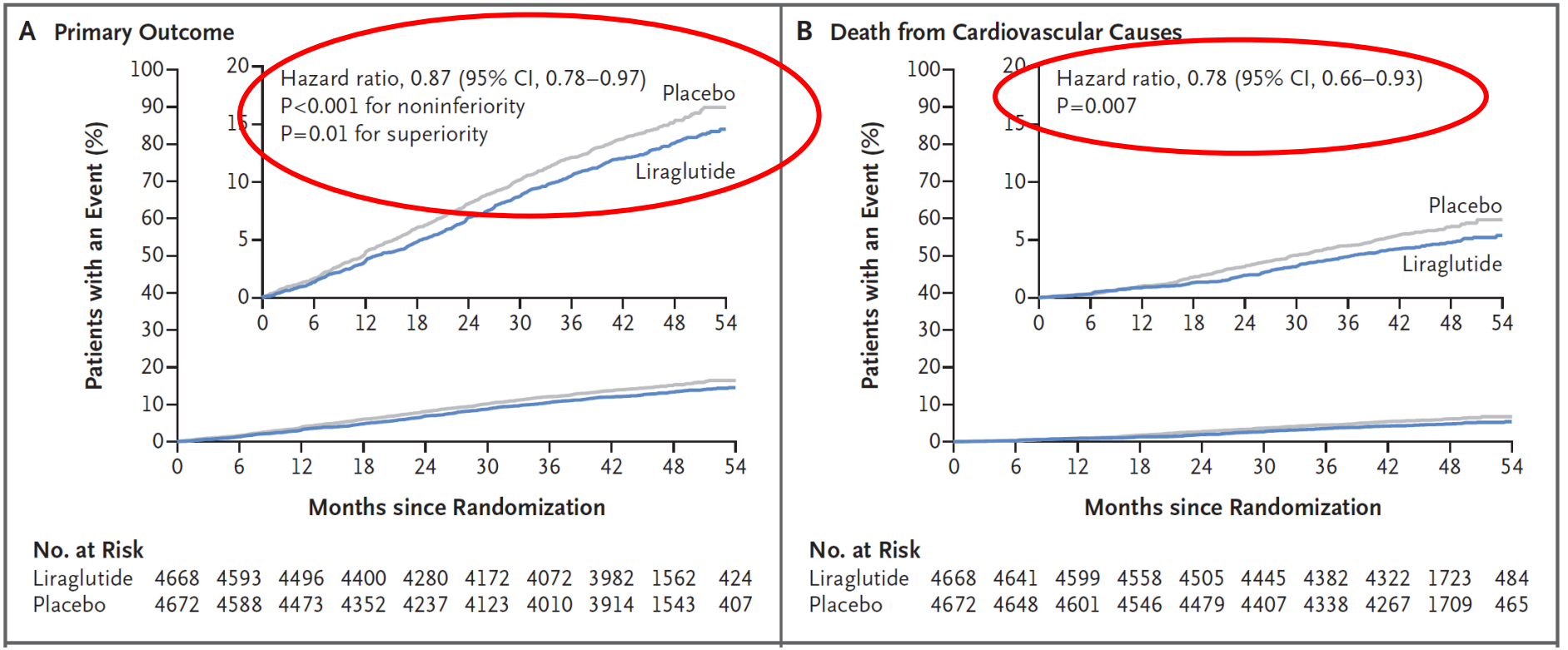
- *SUSTAIN-6 – once weekly Semaglutide*
- *ELIXA – Lixisenatide*
- *HARMONY - Albiglutide*

LEADER Trial (Liraglutide) – NEJM 2016

- 9340 patients
- 81% with established CV disease
- Diabetes duration – 12.8 years
- Mean HbA1c at enrolment – 8.7%
- 3.8 year follow-up
- Primary endpoint – 3 point MACE:
  - Death from CV causes
  - Non-fatal MI
  - Non-fatal Stroke

Marso et al, NEJM 2016: 375 ; 311-322

LEADER Trial – NEJM 2016



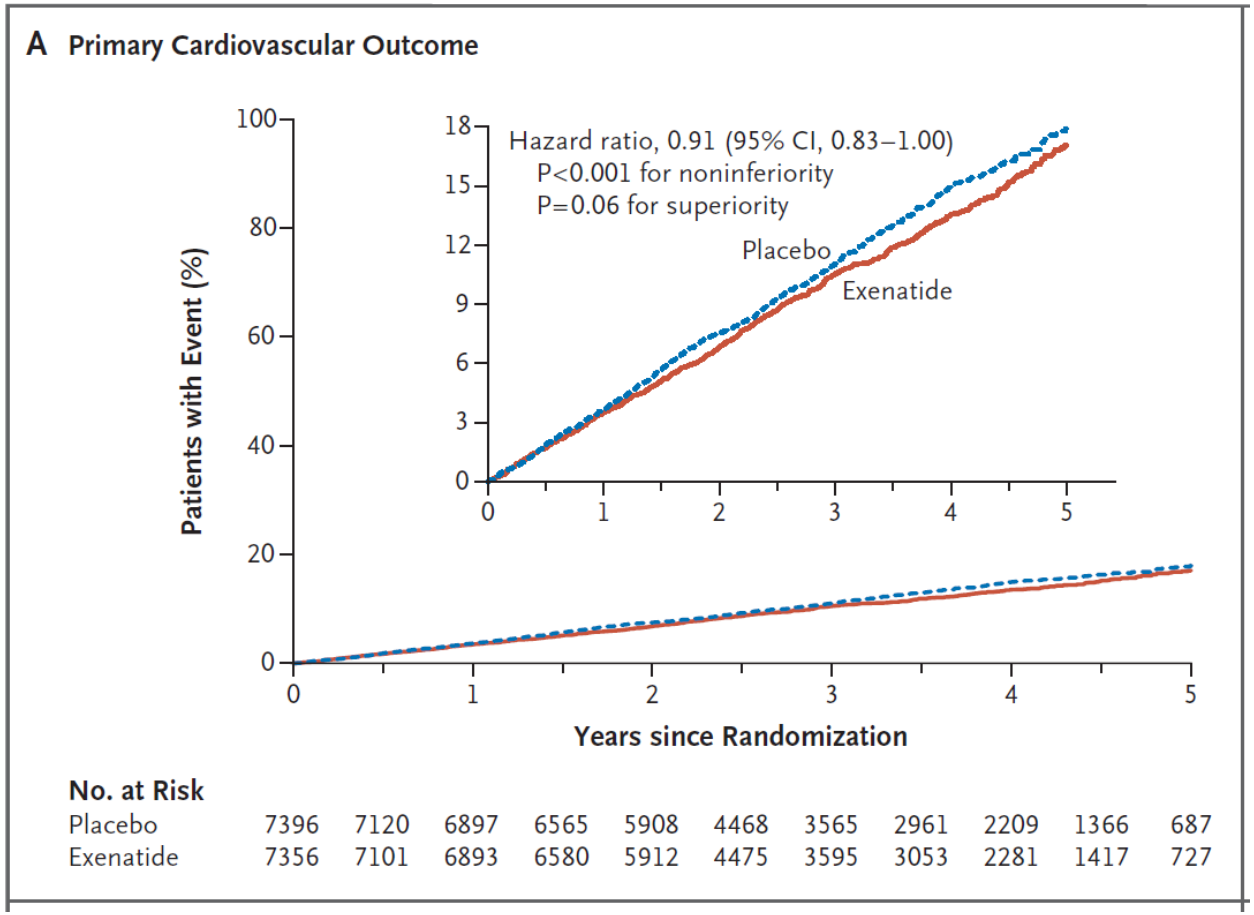
Marso et al, NEJM 2016: 375 ; 311-322

EXSCEL Trial (Bydureon) – NEJM 2017

- 14752 patients
- 73.1% with pre-existing CV disease
- Diabetes duration – 12 years
- Mean HbA1c at enrolment – 8.0%
- 3.2 year follow-up
- Primary end-point – 3 point MACE

Holman et al, NEJM 2017: 377; 1228-1239

EXSCEL Trial – NEJM 2017



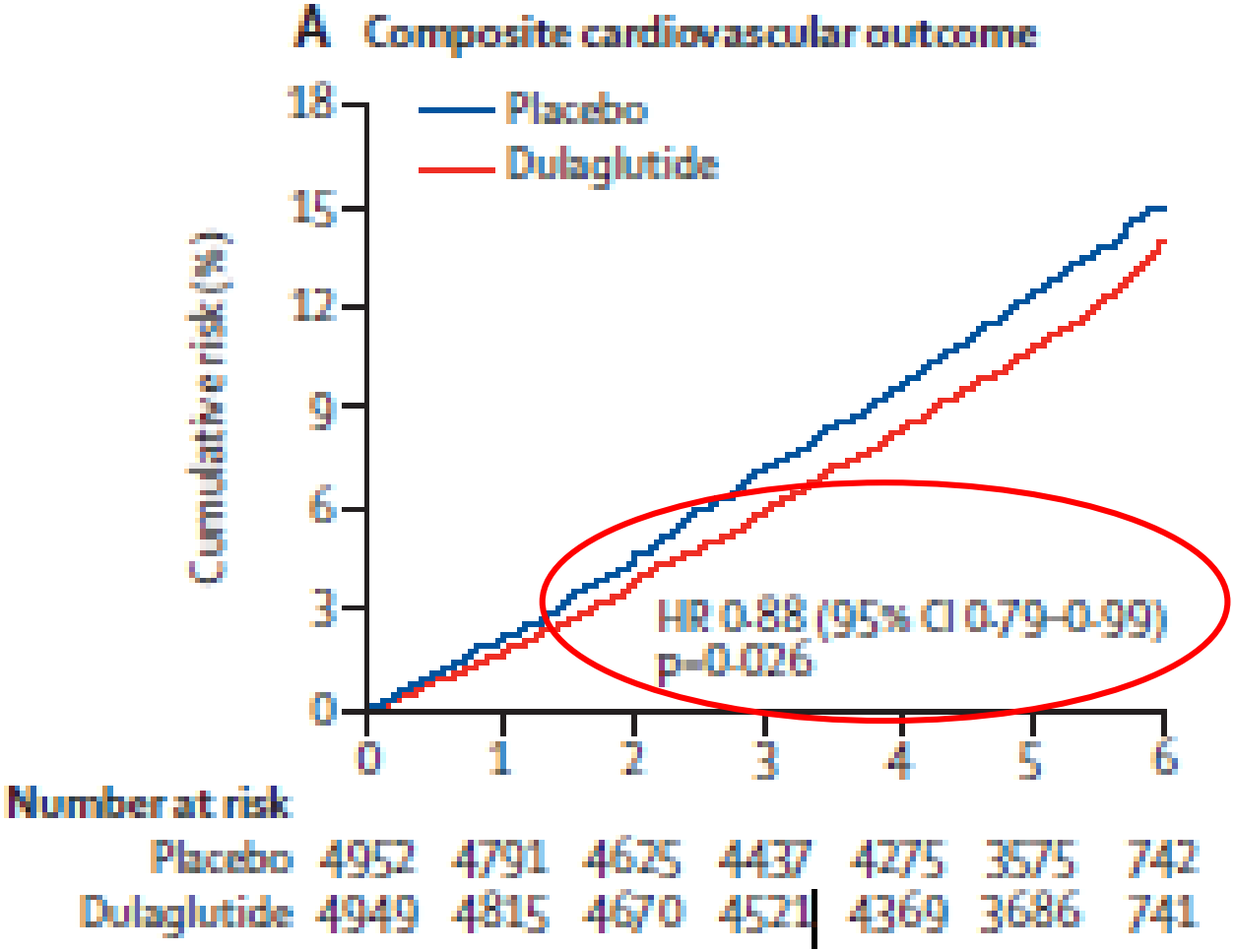
Holman et al, NEJM 2017: 377; 1228-1239

REWIND Trial (Dulaglutide) – Lancet 2019

- 9901 patients, mean age 66.2
- 31.5% with pre-existing CV disease
- Diabetes duration – 9.5 years
- Mean HbA1c at enrolment – 7.2%
- 5.4 year follow-up
- Primary end-point – 3 point MACE

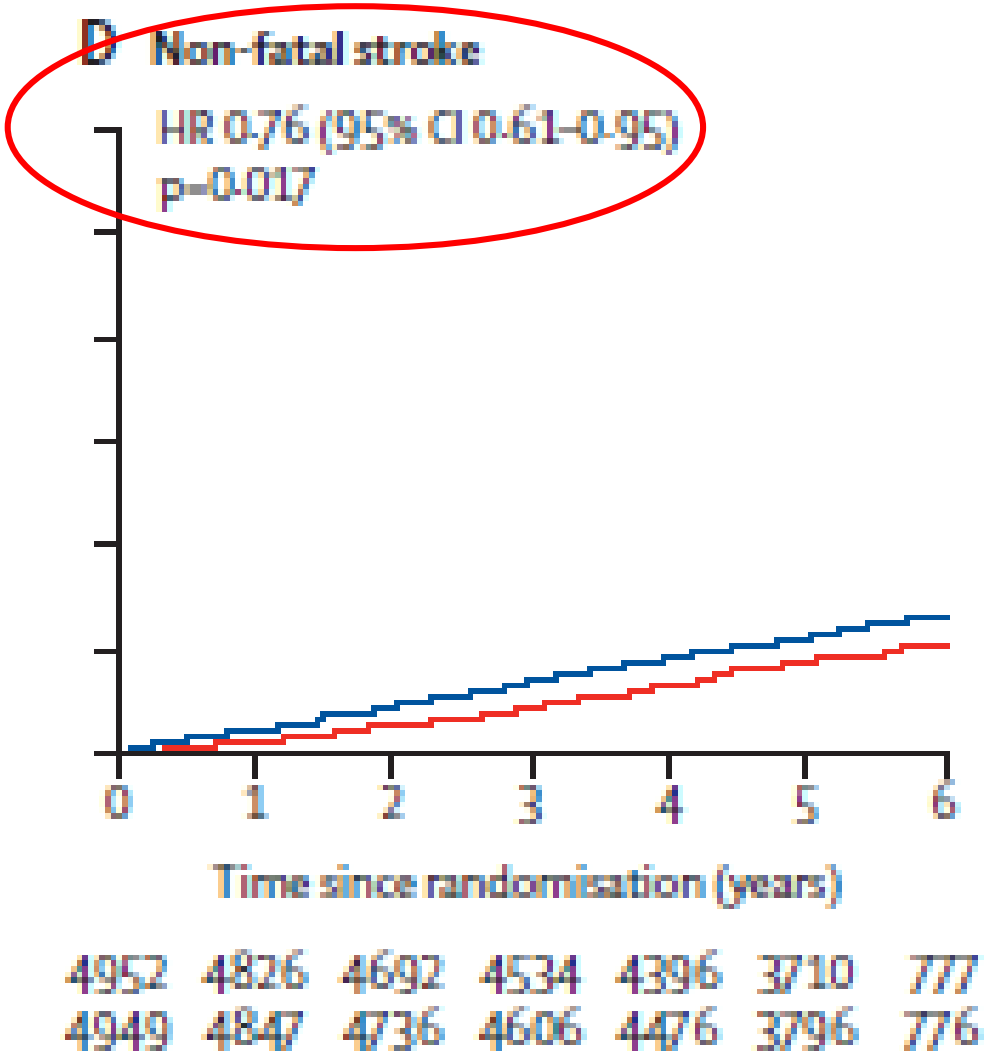
Gerstein et al, Lancet 2019: 394; 121-130

REWIND Trial (Dulaglutide) – Lancet 2019



Gerstein et al, Lancet 2019: 394; 121-130

REWIND Trial (Dulaglutide) – Lancet 2019



Gerstein et al, Lancet 2019: 394; 121-130

Summary – GLP-1RA CVOTs

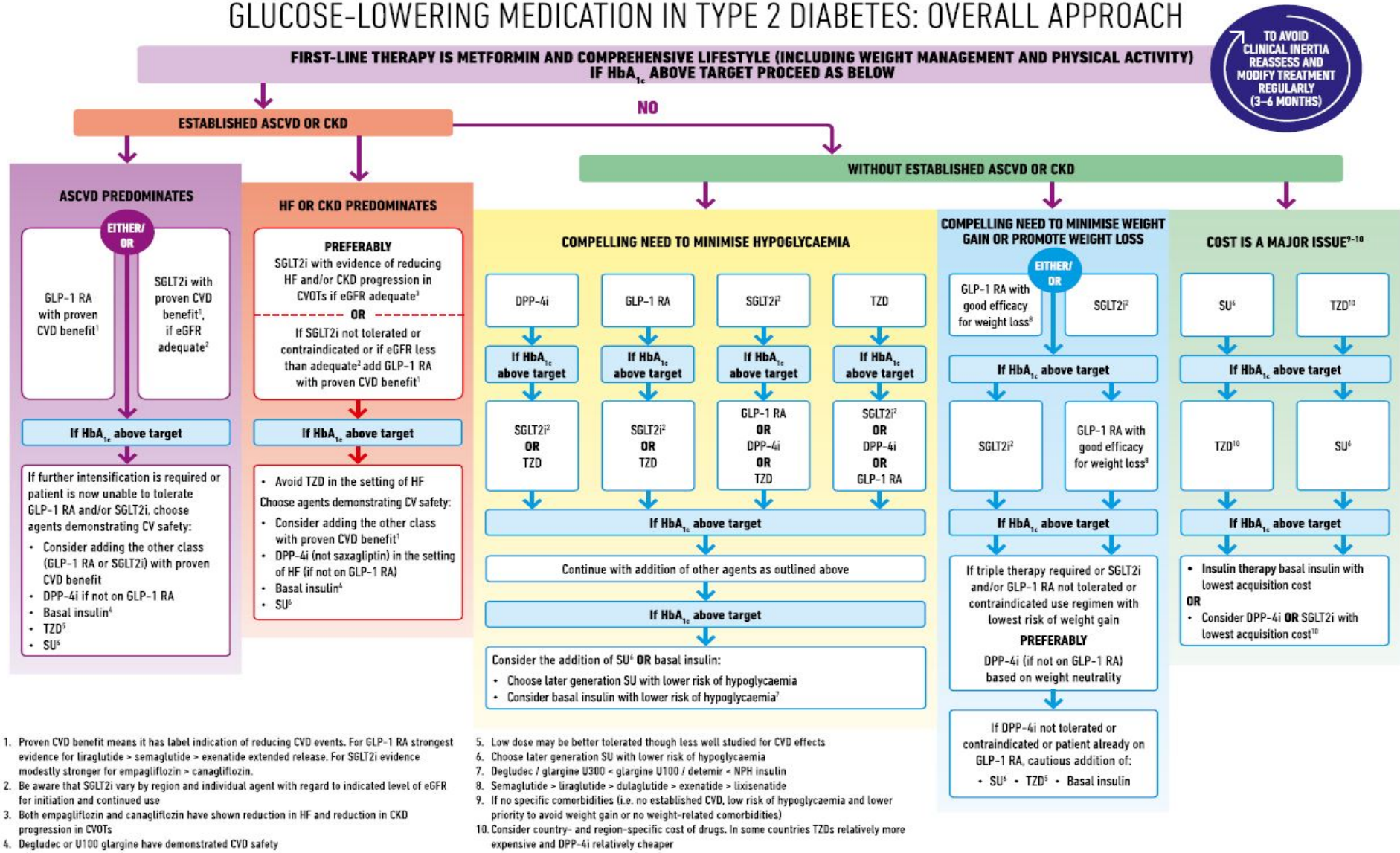
Drug:	Liraglutide	Semaglutide	Dulaglutide	Bydureon	Lixisenatide	Albiglutide
Trial:	LEADER	SUSTAIN-6	REWIND	EXSCEL	ELIXA	HARMONY
3-point MACE:	13% Benefit	26% Benefit	12% Benefit	Neutral	Neutral	22% Benefit
CV Death:	22% Benefit	Neutral	Neutral	Neutral	Neutral	Neutral
AMI:	Neutral	Neutral	Neutral	Neutral	Neutral	25% Benefit
Stroke:	Neutral	39% Benefit	24% Benefit	Neutral	Neutral	Neutral
Heart Failure:	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Renal:	Benefit	Benefit	Benefit	Benefit	Benefit	Neutral
Retinopathy:	Neutral	Harm	Neutral	-	-	Neutral

Insulin CVOTs

- ORIGIN – Glargine (Lantus)
- DEVOTE – Degludec (Tresiba/Ryzodeg 70/30)

Both trials neutral

ADA/EASD Guidelines - 2018



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 hypoglycaemia
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 hypoglycaemia 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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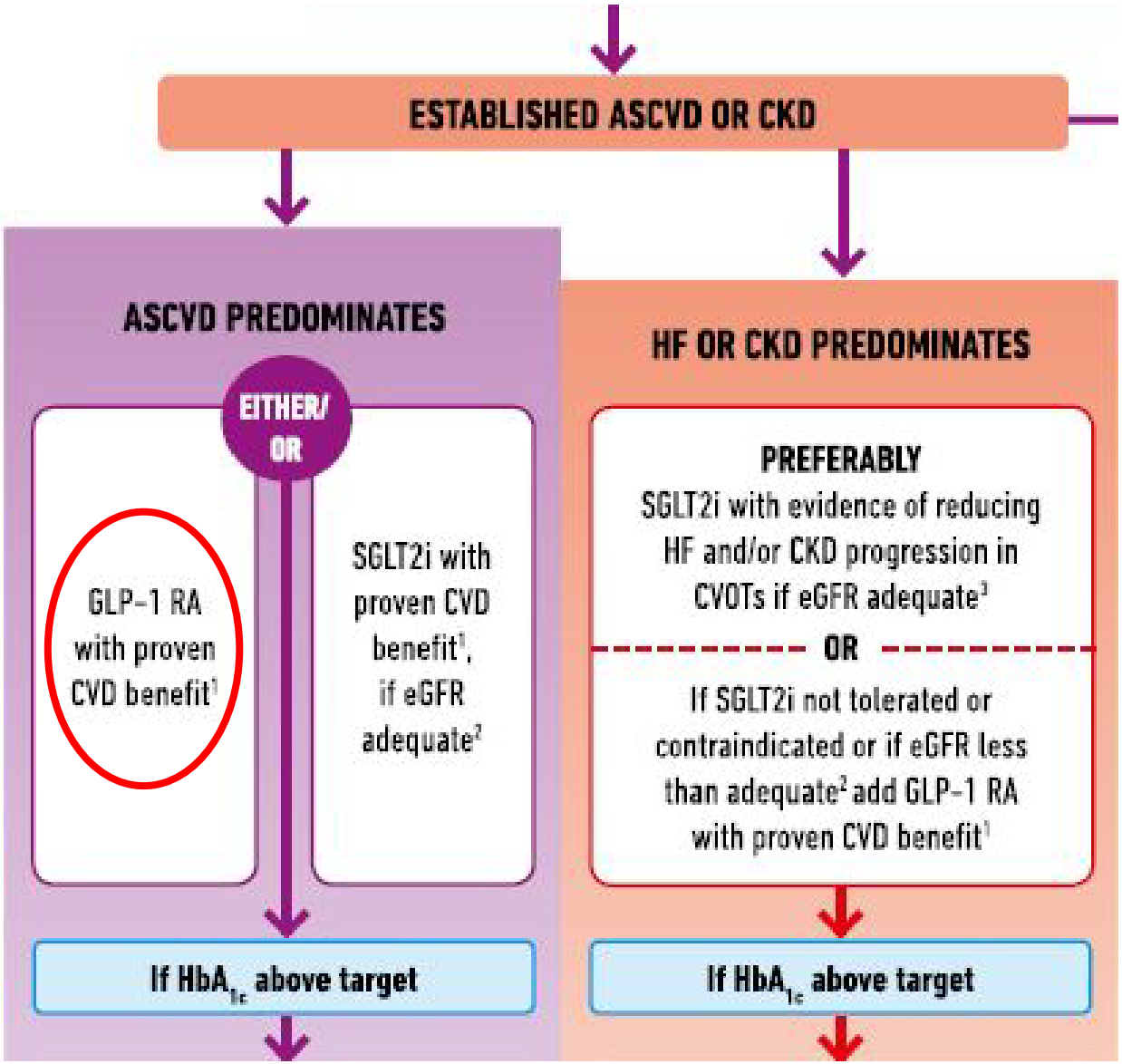

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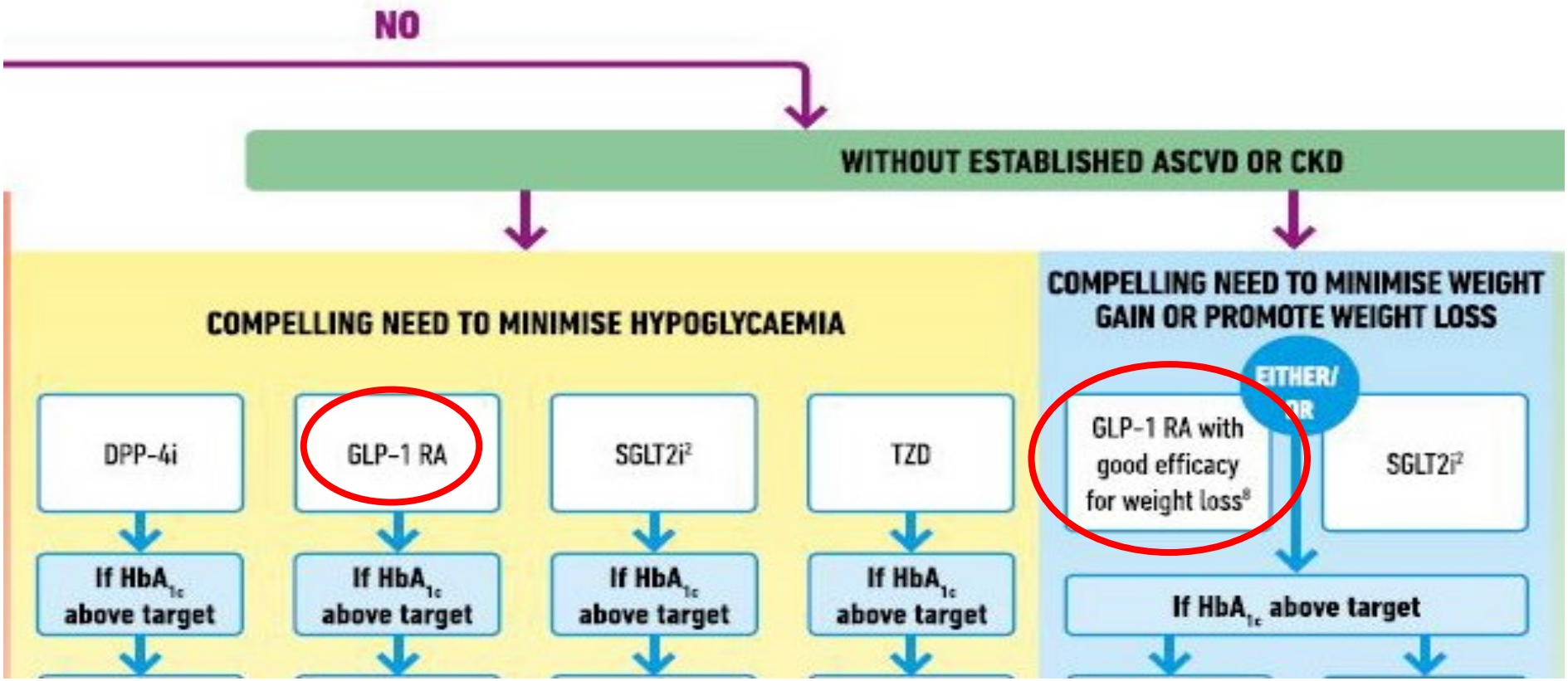

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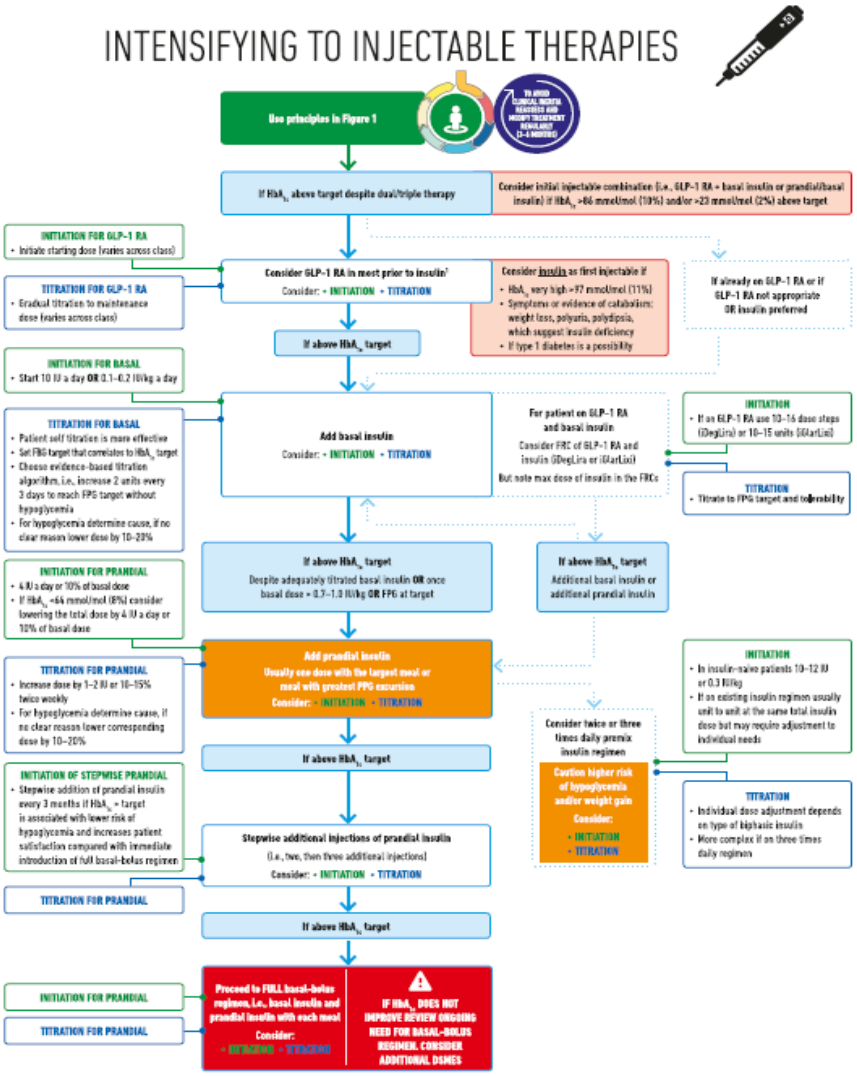

1. Consider choice of GLP-1 RA considering: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

Figure 7— Intensifying to injectable therapies. FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; FBG, fasting blood

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Consider initial injectable combination (i.e. GLP-1 RA + basal insulin or prandial/basal insulin) if HbA_{1c} > 86 mmol/mol (10%) and/or > 23 mmol/mol (2%) above target

Consider <u>insulin</u> as first injectable if

- HbA_{1c} very high > 97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
- If type 1 diabetes is a possibility

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

ADA/EASD Guidelines - 2018

Addition of injectable medications

Consensus recommendation

In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycaemia, insulin is recommended (Fig. 7).

Questions?