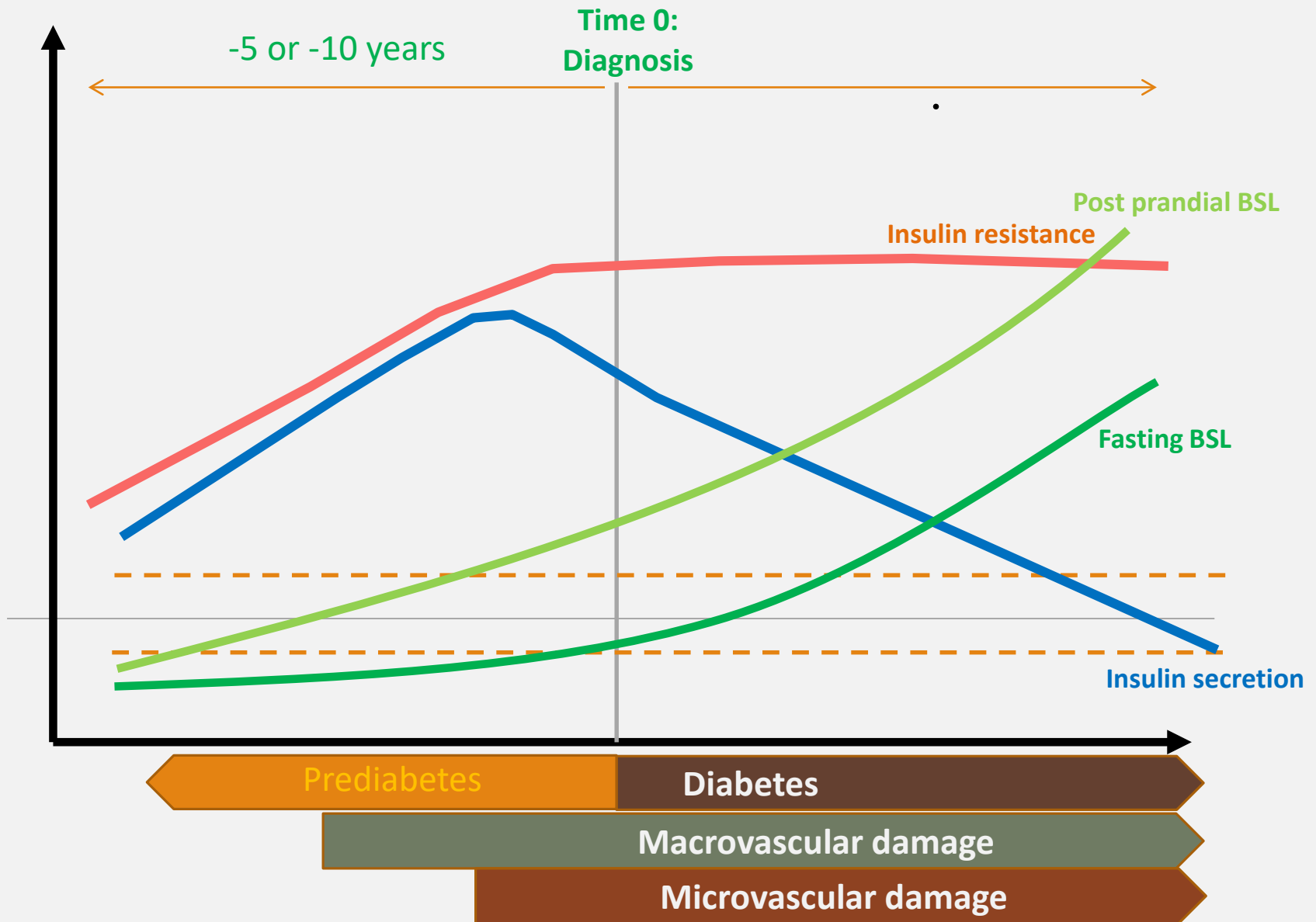


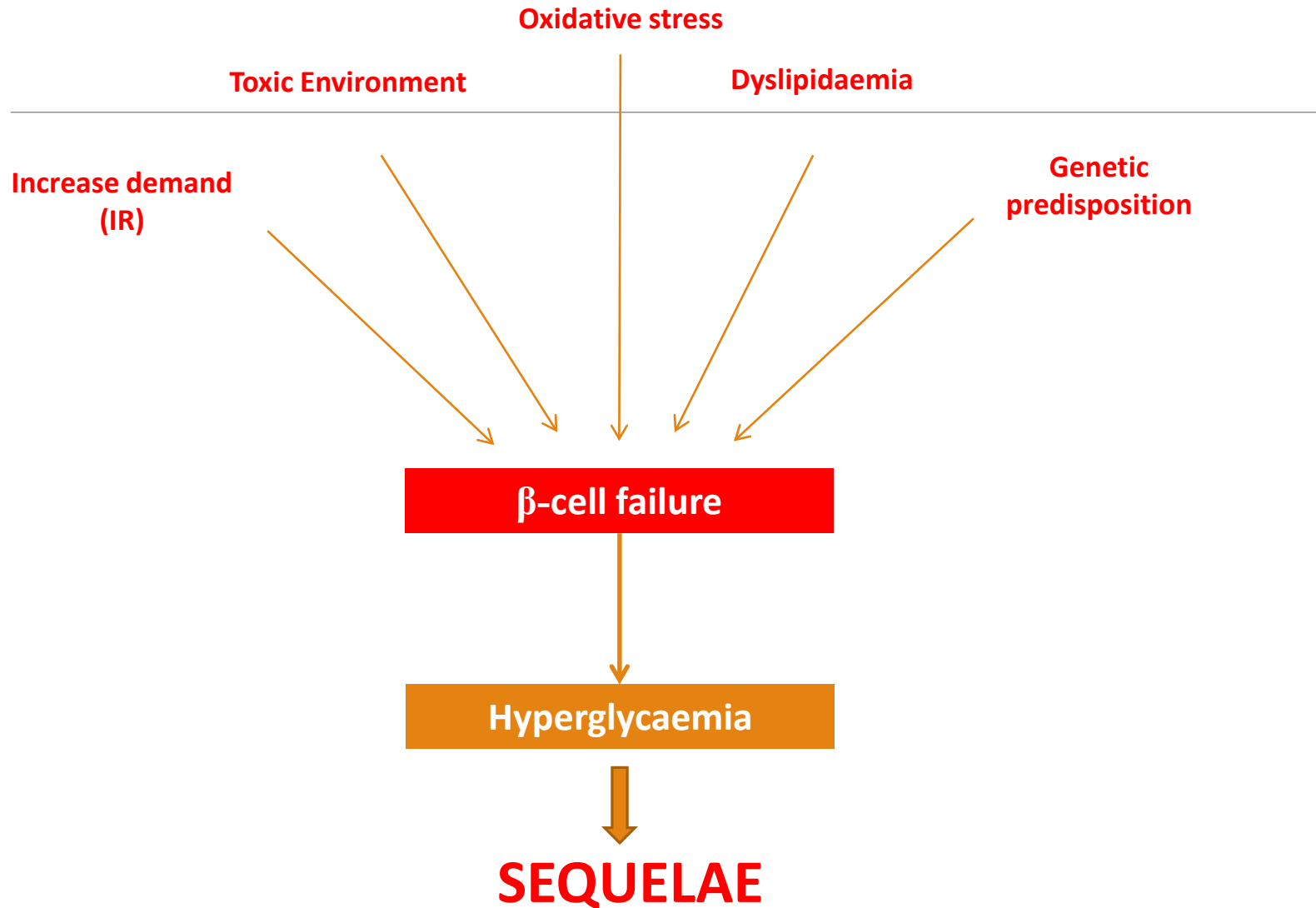
THE ROLE OF  
INJECTABLES

# Pathophysiology in type 2 diabetes

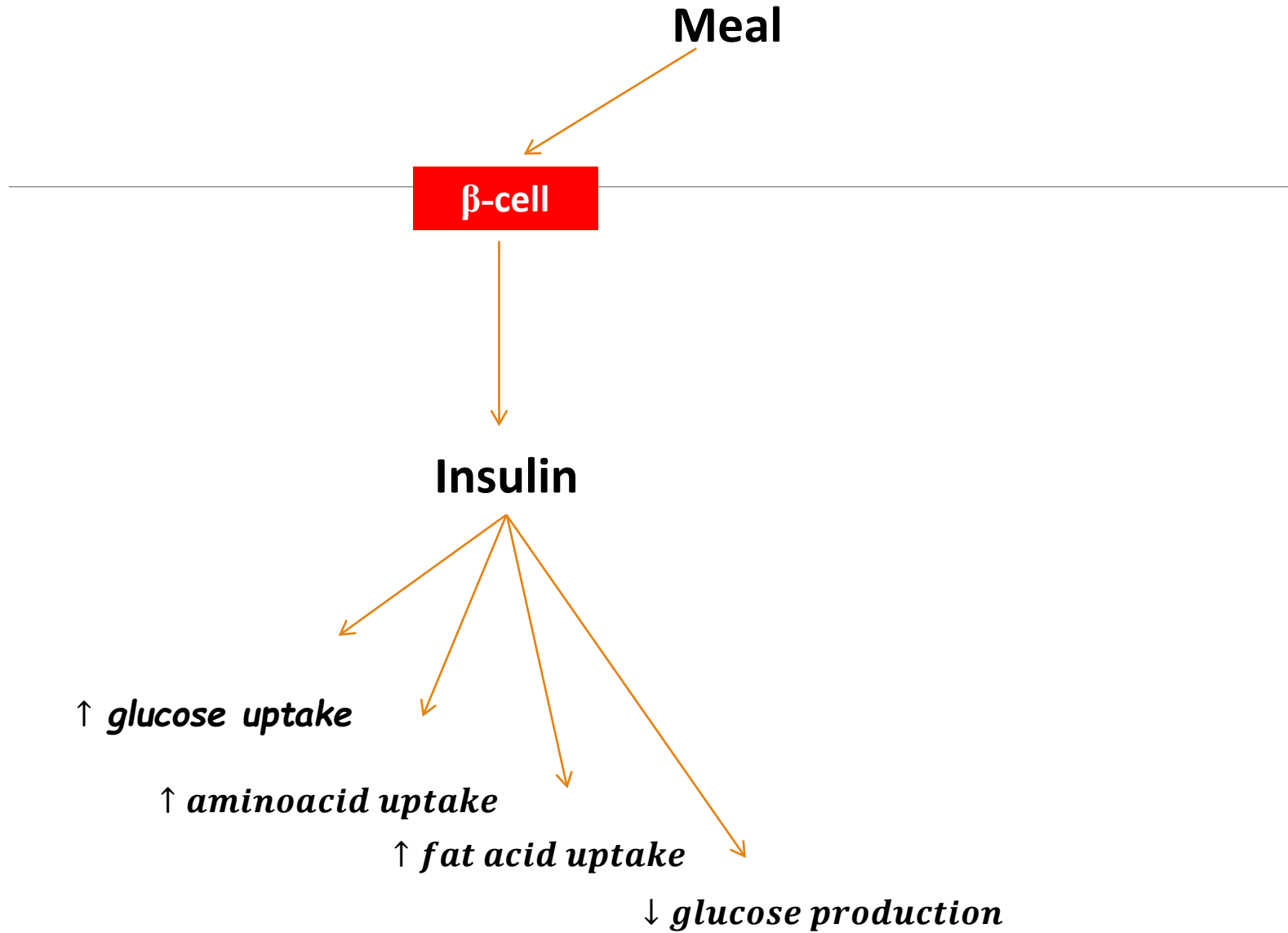
# The progression of T2D



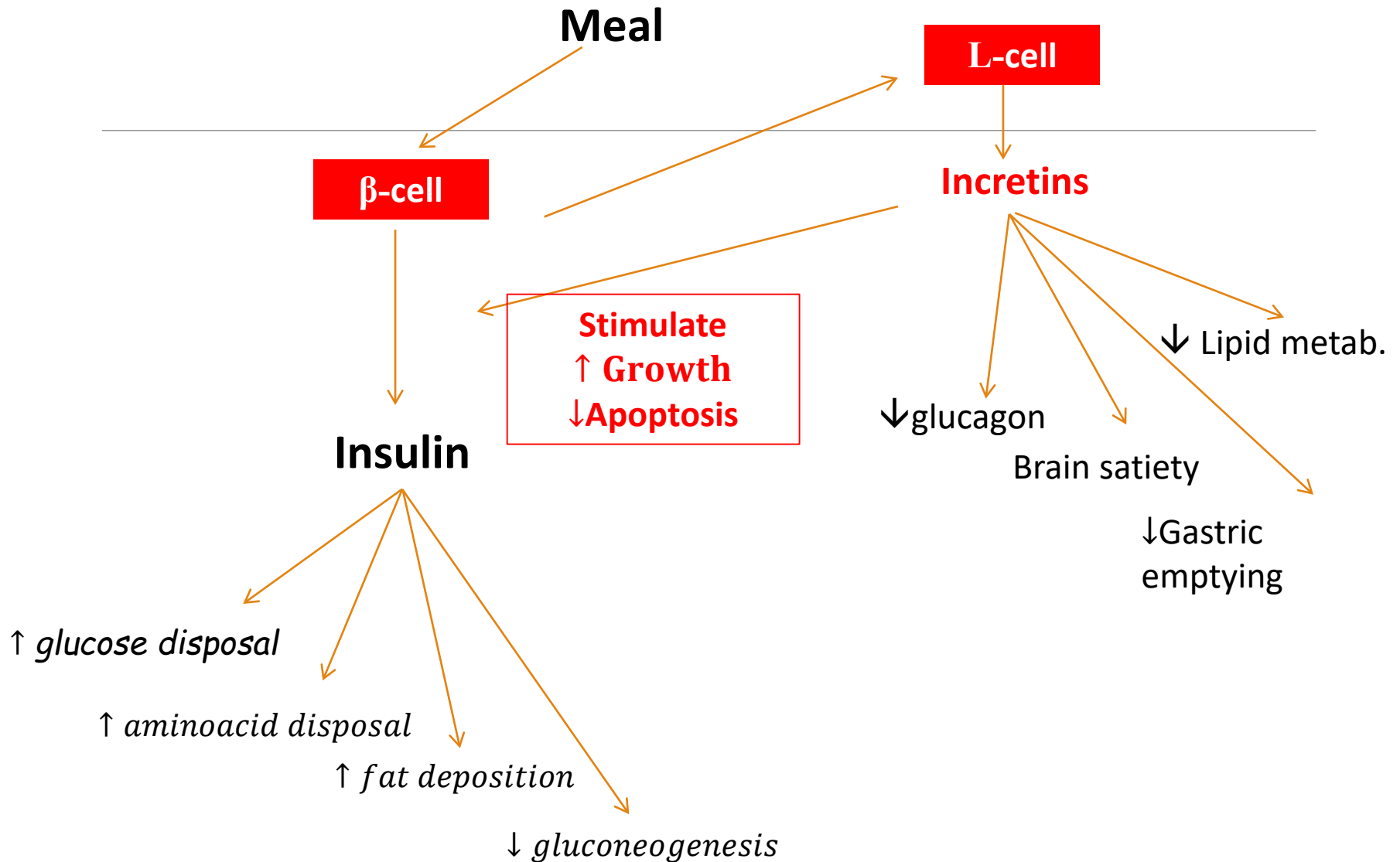
# Life used to be simple...



*In other words...*



Now...



## The defects in T2D



Decreased beta cell function –  
reduced insulin secretion



Increased alpha cell activity –  
increased glucagon secretion



Reduced incretin effects  
(GLP1, GIP)



Impaired brain  
neurotransmitter function

# What do incretins do?

- Mechanism of action



Stimulate beta cell secretion of insulin



Reduce glucagon secretion



Reduce gastric emptying



Induce brain satiety



Increase lipolysis (fat breakdown)

# What can insulin do?

## - Mechanisms of action of insulin

### Glucose

Reduce glucose levels:

- Increase peripheral glucose uptake:
- Reduce gluconeogenesis:

### Protein

Increase protein synthesis & Inhibit proteolysis

### Fats

Increase lipogenesis and inhibits lipolysis



# Why GLP1-RA?



GLP1 RA lowers glucose levels without hypos



GLP1 RA reduce appetite, assist in weight loss



Stepping stone to insulin therapy



Some GLP1 RA may have cardiovascular benefits



Convenience – daily or weekly injection



Protective effect on beta cells?

# GLP1-RAs: The differences



Pharmacodynamics



Effect on fasting and post prandial glucose



Efficacy



Devices



**Cardiovascular outcomes?**



PBS Rebate

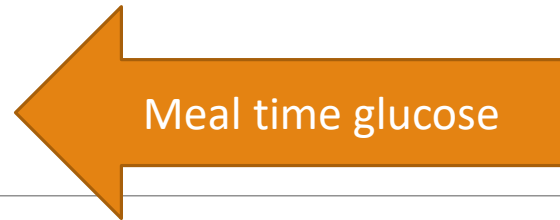


PBS Authority

# The Agents

## Short Acting (twice daily)

- Exenatide (Byetta<sup>®</sup>)



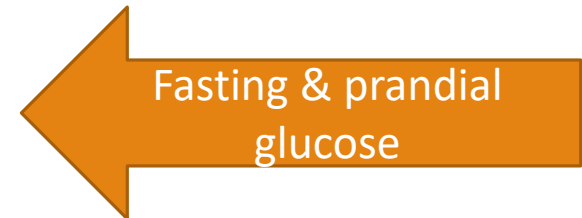
## Long Acting (once daily)

- Liraglutide (Victoza<sup>®</sup>, Saxenda<sup>®</sup>)



## Longer Acting (weekly)

- Exenatide XR (Bydureon<sup>®</sup>)
- Dulaglutide (Trulicity<sup>®</sup>)
- **Albiglutide (Tanzeum<sup>®</sup>)**
- **Lixisenatide (Lyxumia<sup>®</sup>)**
- **Semiglutide (injectable or oral)**



# GLP1 -RAs in Australia

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## DAILY

Once daily – liraglutide (Victoza®)  
Twice daily – Exenatide (Byetta®)

## WEEKLY

Exenatide Weekly (Bydureon®)  
Dulaglutide (Trulicity®)

When is  
insulin  
commonly  
necessary?



Type 1 diabetes



Secondary diabetes – e.g. post severe pancreatitis



Diabetes in pregnancy



Symptomatic or severe hyperglycaemia



Peri-operative care



Sick day including sepsis



Patients on corticosteroids

# Why insulin therapy



Reduce hyperglycaemia

↓hepatic gluconeogenesis,  
↑glucose uptake



Reduce hypertriglyceridaemia

↓Lipolysis,  
↑lipogenesis



Increase protein synthesis

↑Amino-acid uptake



Clean up toxic environment

## Advantages of insulin

- When oral or non-insulin injectable fails
- Unlimited potency
- Works even in extreme hyperglycaemia
- Can be used at any stage of diabetes disease
- Cost effective
- Can be combined with any oral agents
- Can be used even in severe renal or hepatic impairment
- Modern insulin have low hypoglycaemia rates

# Insulins

```
graph TD; Insulins --> Mealttime[Mealttime insulins]; Insulins --> LongActing[Long Acting Basal]; Insulins --> Mixed[Mixed/Co-Formulation]; Mealttime --> Prandial[Prandial]; Mealttime --> Rapid[Rapid]; LongActing --> Lantus[Lantus]; LongActing --> Toujeo[Toujeo]; LongActing --> Levemir[Levemir]; LongActing --> Tresiba[Tresiba]; LongActing --> Others[Others]; Mixed --> Humalog[Humalog Mix 25/75]; Mixed --> Novomix[Novomix 30/70]; Mixed --> Ryzodeg[Ryzodeg 70/30]; Mixed --> Older[Older]; Mixed --> Mixtard[Mixtard]; Mixed --> Humulin[Humulin 30/70];
```

## Mealttime insulins

Prandial

Rapid

Humalog<sup>®</sup>  
NovoRapid<sup>®</sup>  
Apidra<sup>®</sup>  
Fiasp<sup>®</sup>

Older:  
Actrapid  
Humulin R

## Long Acting Basal

Lantus<sup>®</sup>

**Toujeo<sup>®</sup>**

Levemir<sup>®</sup>

Tresiba<sup>®</sup>

Others  
NPH  
Humulin

## Mixed/Co-Formulation

Humalog Mix 25/75<sup>®</sup>

Novomix 30/70<sup>®</sup>

**Ryzodeg 70/30<sup>®</sup>**

Older  
Mixtard

Humulin 30/70



# Insulins

30 mins – 6 hrs

## Short Acting

Actrapid®  
Humulin R®

## Rapid acting

Lispro (Humalog®)  
Aspart (NovoRapid®)  
Glulisine (Apidra®)

15 mins – 4.5 hrs

## Faster acting lasp (FIASP)

10 mins – 4 hrs

## Intermediate acting

NPH  
Determir  
Levemir®

1-2 hrs – 12-16 hrs

## Long Acting

Glargine U100  
• Lantus®

1-2 hrs – 14-24 hrs

## Ultra Long Acting

Toujeo®  
“Degludec”

1-2 hrs – 26 hrs

Toujeo® = insulin glargine 300 units/mL  
Lantus® = insulin glargine 100 units/mL

# The Mixed/Co-formulation Insulins

## Intermediate + **Short Acting**

Mixtard 30/70<sup>®</sup>

HumulinMix 30/70<sup>®</sup>

Mixtard 50<sup>®</sup>

Start: 30 mins  
Peak: 2-5 hour  
Last 12-16 hours

## Intermediate + **Rapid Acting**

Novomix 30/70<sup>®</sup>

Humalog Mix 25/75<sup>®</sup>

Ryzodeg 70/30<sup>®</sup>

Start: 5-15 mins  
Peak: 1 hour  
Last 12-16 hours  
Last 26 hours

**Ultra-long acting**

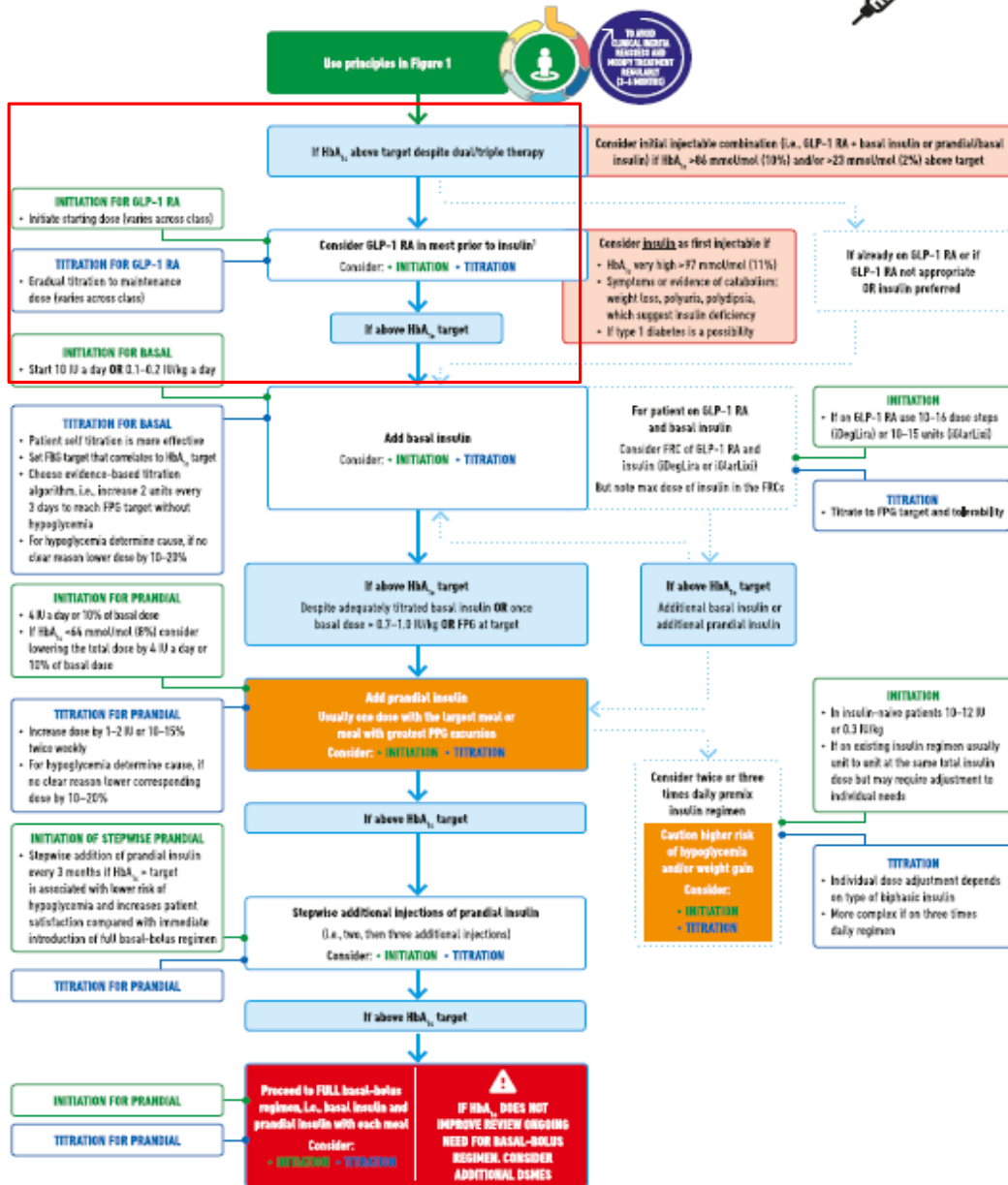
# Guidelines

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EASD/ADA 2018



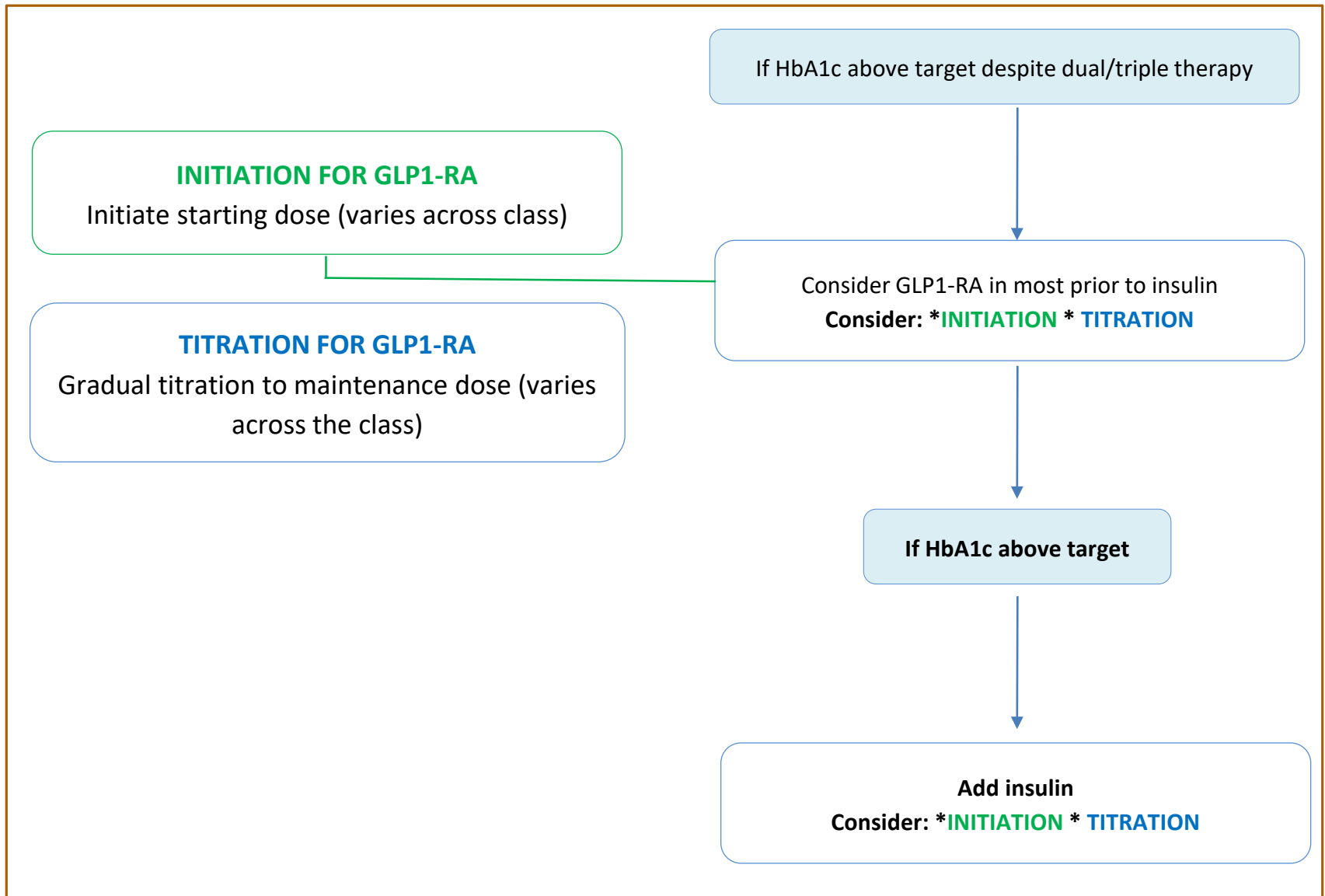
# INTENSIFYING TO INJECTABLE THERAPIES



ADA/EASD Guidelines Oct 2018

1. Consider choice of GLP-1 RA considering: patient preference, HbA<sub>1c</sub> 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; FPG, fasting blood



# PBS Algorithm (oral)

Diet + Exercise + Metformin



Sulphonylureas (if appropriate)



**Only one of the following**

**DPP4i**

**SGLT2i**

**GLP1-RA**

**TZD**

**INSULIN**

**ACARBOSE**

# PBS Algorithm (insulin)

**INSULIN**

+

**One of the following**

**DPP4i**

**SGLT2i**

**Byetta**

**TZD**

Factors to  
consider in  
escalating  
treatment

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Individualised glycaemic targets

---

Cardiovascular benefits

---

Renal benefits

---

Glucose lowering potency

---

Weight loss potential

---

Hypoglycaemia risk

---

Adherence

---

Needle load

---

Age

---

Costs



## In summary

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There are many defects in type 2 diabetes

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There is a relative deficiency in insulin secretion

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There is also a relative deficiency in incretins

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Insulin therapy address some (but not all) the defects

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Incretin therapy address some (but not all) the defects

---

Guidelines suggest initiating GLP1-RA before insulin if HbA1c not on target

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Insulin therapy is sometimes necessary before GLP1-RA

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There are PBS restrictions when combining injectables/orals



# What else helps us decide which agent?

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DR ROHIT RAJAGOPAL