The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

# The New Co-formulation Insulin for Initiation and Simplifications

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# Disclosures

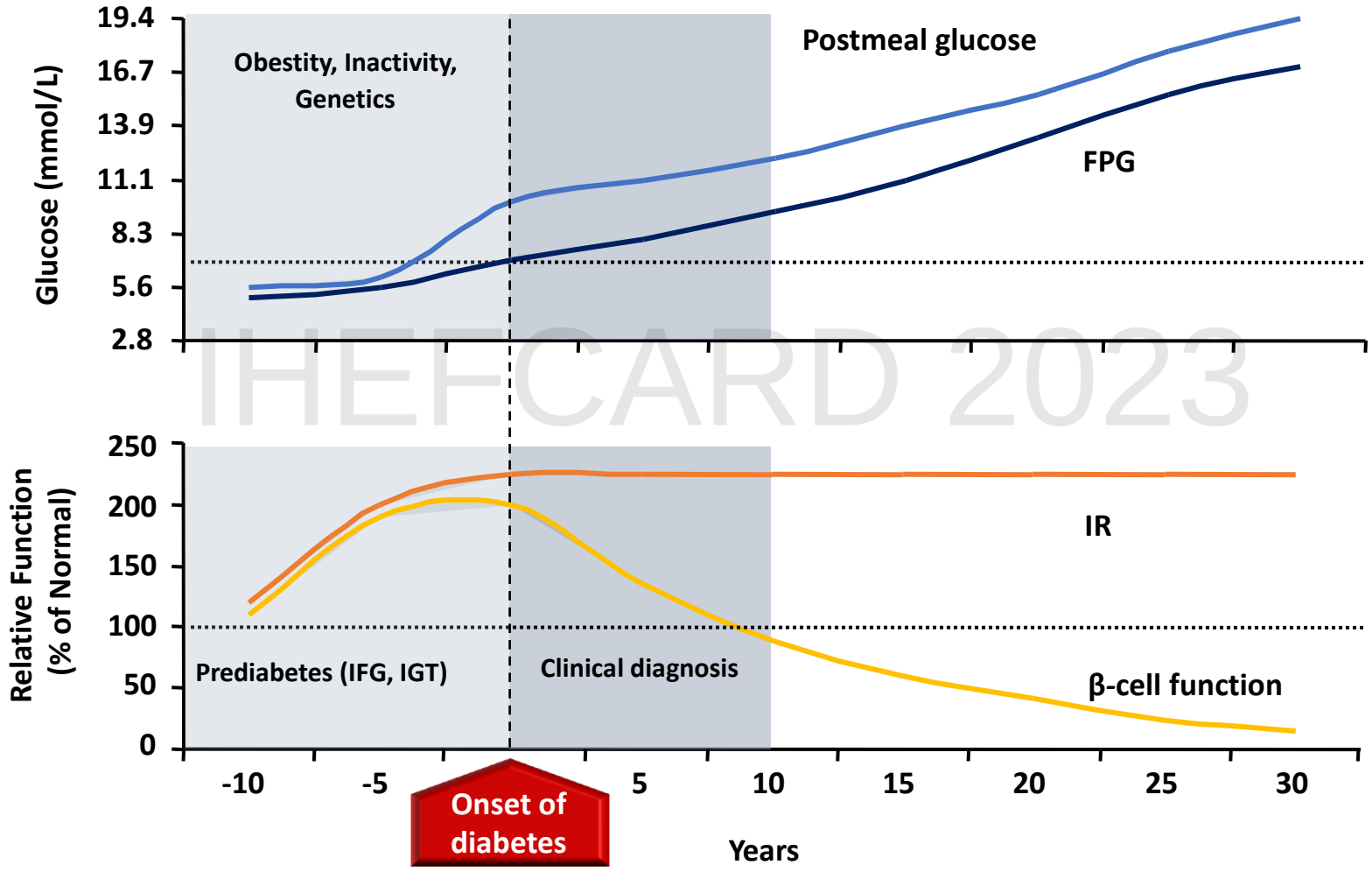
I have received honorarium as speaker/consultant, support for research/attendance at educational meetings from:

- Novo Nordisk Indonesia
- APL/ Zuellig Pharma
- MSD Indonesia
- Astra Zeneca
- Pfizer
- Sanofi Indonesia
- etc

# Outlines

- Natural history of Type 2 Diabetes and complex diabetes treatment
- Insulin preparation
  - Types of insulin
  - Pharmacokinetics of insulins
- Co-formulation insulin
  - Initiation and simplification of insulin therapy
  - Position of co-formulation insulin in Perkeni guideline
  - RCT and RWE
- Combination of co-formulation insulin and other antidiabetic drugs
- Co-formulation insulin for special populations
- Take home message

# Natural History and Progression of Type 2 Diabetes






Simonson GD, Kendall DM. *Coron Artery Dis.* 2005;16(8):465-472.

# Sasaran pengendalian diabetes



| Parameter | Sasaran |
|---|---|
| **Indeks Masa Tubuh (IMT)** | |
| • IMT (kg/m$^2$) | 18.5-22.9 |
| **Tekanan darah** | |
| • TD Sistolik (mmHg) | <140 |
| • TD Diastolik (mmHg) | <90 |
| **Kendali glikemik** | |
| • HbA1c (%) | <7 atau individual |
| • Gula darah kapiler puasa/sebelum makan (mg/dL) | 80-130 |
| • Gula darah kapiler 1-2 setelah makan (mg/dL) | <180 |
| **Lipid** | |
| • LDL-C (mg/dL) | <100, <70 jika risiko tinggi PKV |
| • Triglyceride (mg/dL) | <150 |
| • HDL-C (mg/dL) | <40 untuk laki-laki, <50 untuk perempuan |
| • Apo-B (mg/dL) | <90 |

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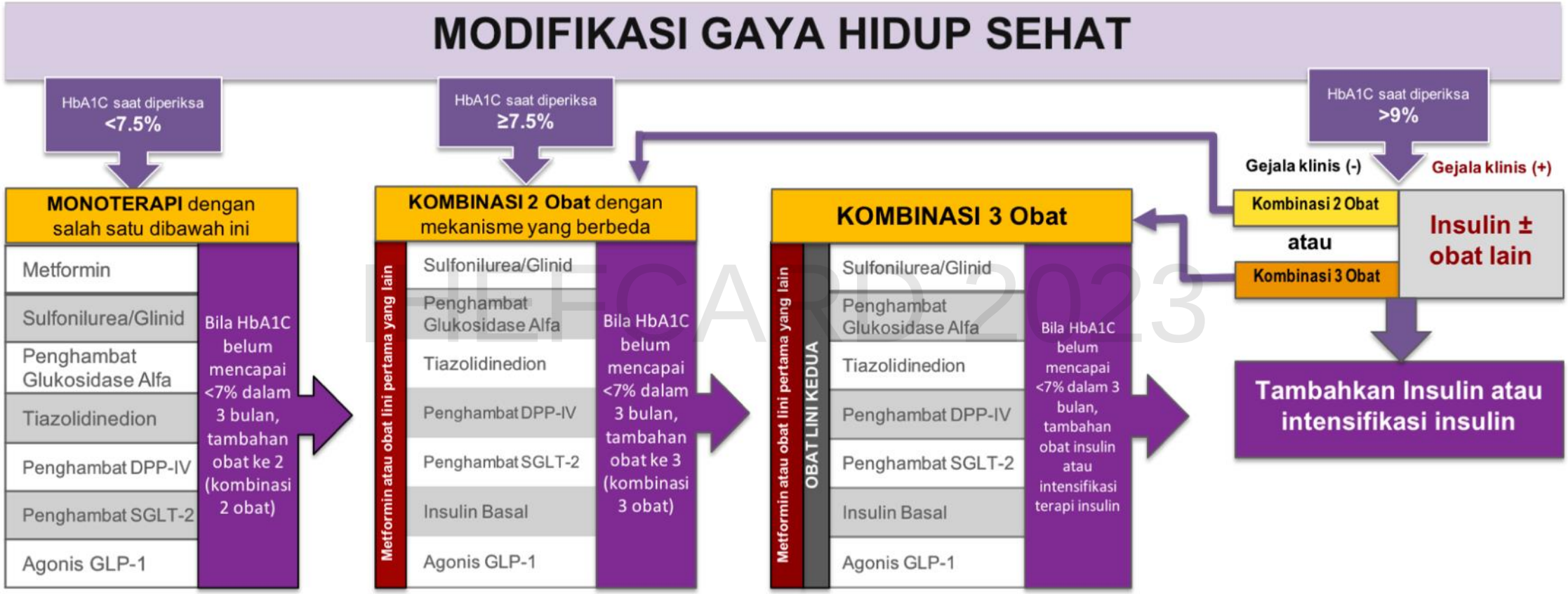
# Algoritma Pengelolaan DM Tipe 2 Tanpa Dekompensasi Metabolik

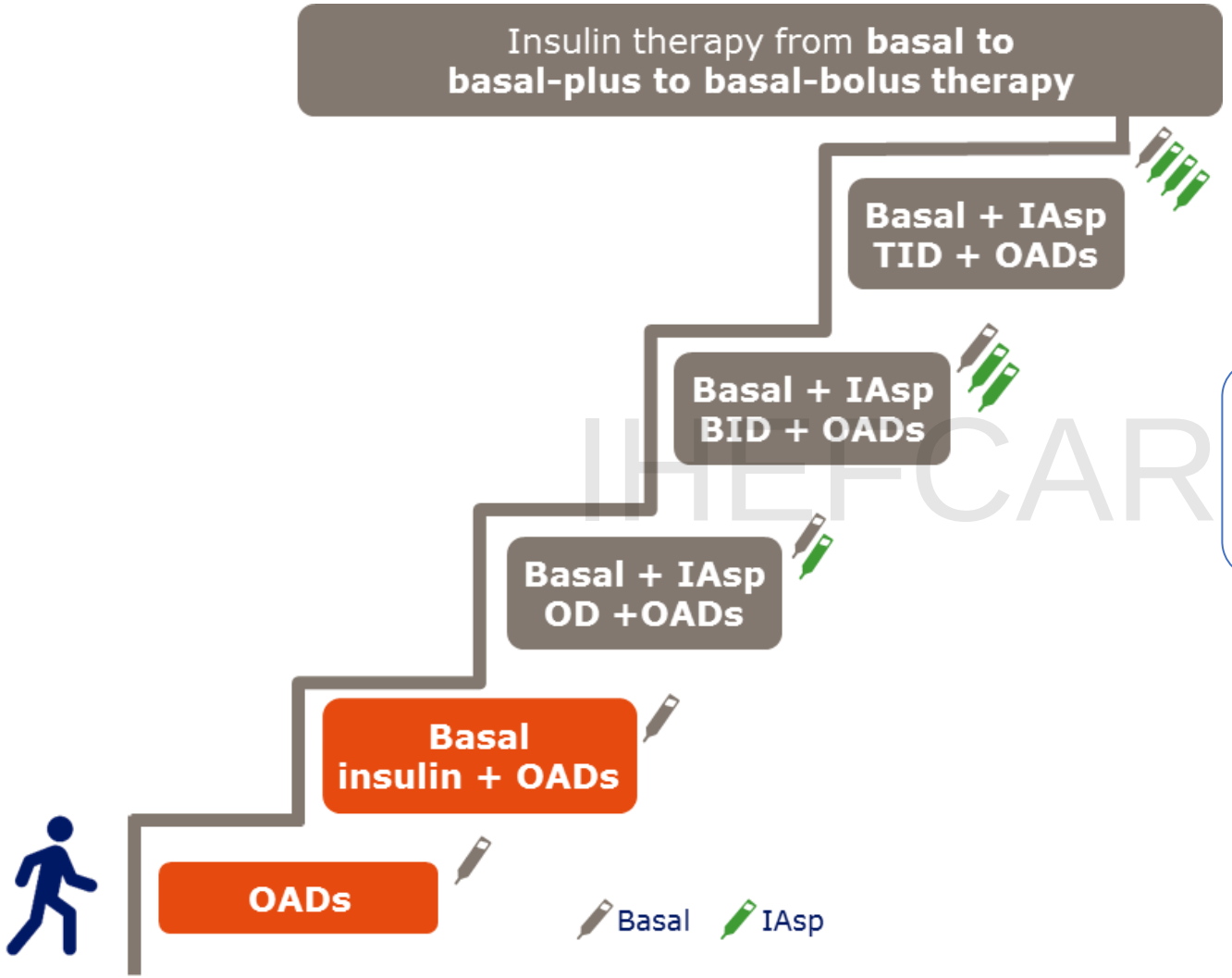
## Sasaran kendali glukosa darah: HbA1c <7% (individualisasi)






1. **Pemilihan dan penggunaan obat mempertimbangkan faktor pembiayaan, ketersediaan obat, efektivitas, manfaat kardiorenal, efek samping, efek terhadap berat badan, serta pilihan pasien**
2. **Pengelolaan bukan hanya meliputi gula darah, tetapi juga penanganan faktor risiko kardiorenal yang lain secara terintegrasi.**
3. **Obat agonis GLP-1 dan penghambat SGLT2 tertentu menunjukkan manfaat untuk pasien dengan koorbid penyakit kardiorenal aterosklerosis, gagal jantung dan gagal ginjal. Kedua golongan obat ini disarankan menjadi pilihan untuk pasien dengan komorbid/komplikasi penyakittersebut**
4. **Bila HbA1c tidak bisa diperiksa maka sebagai pedoman dipakai glukosa darah rerata yang dikonversikan ke HbA1c (poin 7 penjelasan algoritma)**

# Insulin therapy from basal to basal-bolus is complex[1]



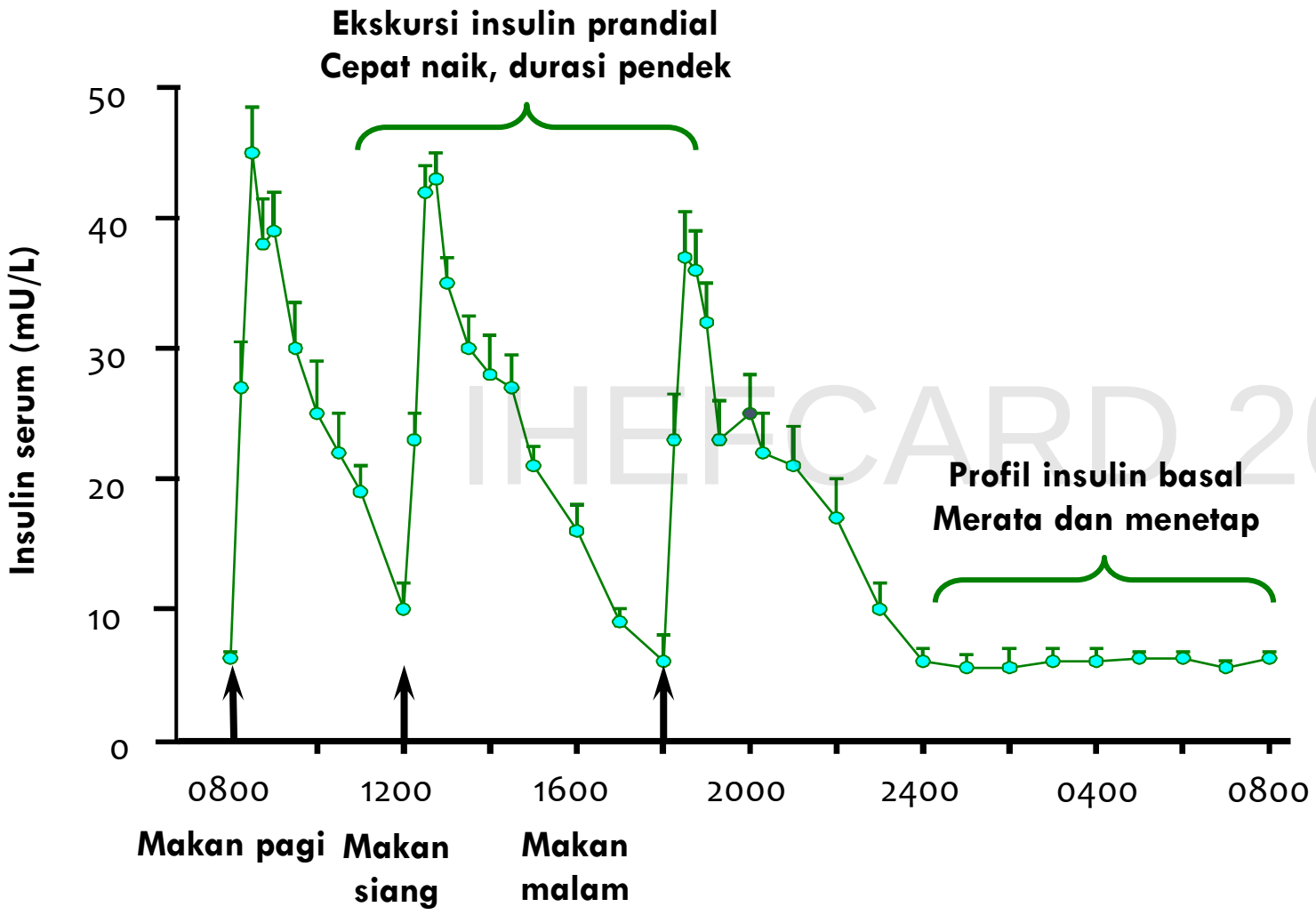



Additional bolus insulin pens/injections:

- Need more education, monitoring
- Lead to confusion, lower adherence[2,3]

BID, twice daily; OAD, oral antidiabetic drug; OD, once daily; IAsp, insulin aspart; TID, thrice daily

1. Adapted from *American Diabetes Association. Diabetes Care* 2017;40(Suppl.1):S64–S74 | 2. Peyrot et al. Diabet Med. 2012;29: 682–9
3. Jarab et al. Int J Clin Pharm. 2014;36(4):725-33






# Profil fisiologi insulin

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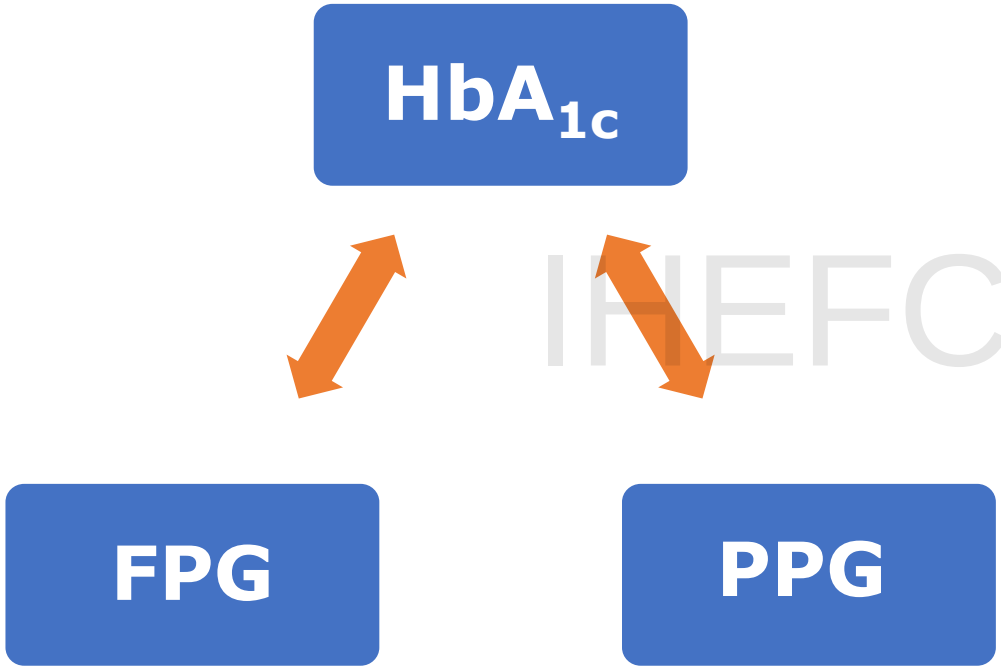
# Glycaemic control requires attention to both FPG and PPG[1]




PPG is the predominant contributor in patients with satisfactory to good control of diabetes, contribution of FPG increases with worsening diabetes[2]

PPG and FPG increase with HbA1c[3]

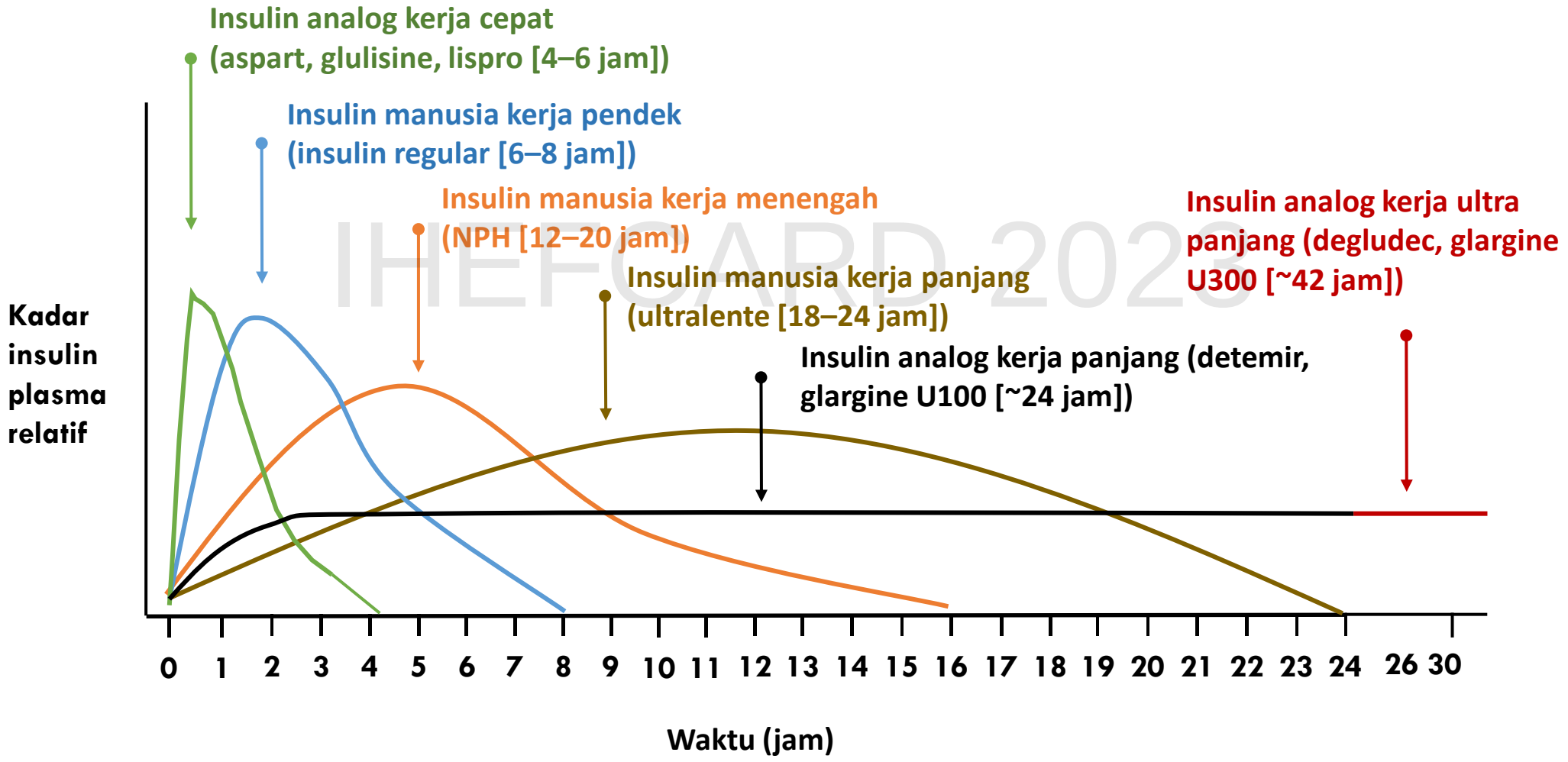
PPG has a stronger correlation with HbA1c than FPG[4]



FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose

1. Riddle M, et al. Diabetes Care 34:2508–2514, 2011 | 2. Monnier *et al. Endocr Pract.* 2006;12:S1:42–6
3. Monnier *et al. Diabetes Care*. 2007;30:263–9 | 4. Ketema *et al. Arch Public Health.* 2015;73:43.

# Pola Farmakokinetik Berbagai Jenis Insulin



# Key Challenges for type 2 diabetes patient needing insulin treatment

**42%**

Patients with T2DM had **$HbA_{1c}$ >9%[1]** before they start insulin

Asian populations generally shown a high-carbohydrate consumption, it leads to **high insulin resistance** and **PPG levels.** [2]

**Our Realities**

**70%**

patients on basal insulin **FAILED** to achieved HbA1C target[3]

Intensification from basal to basal plus/bolus is **COMPLEX.**[4]

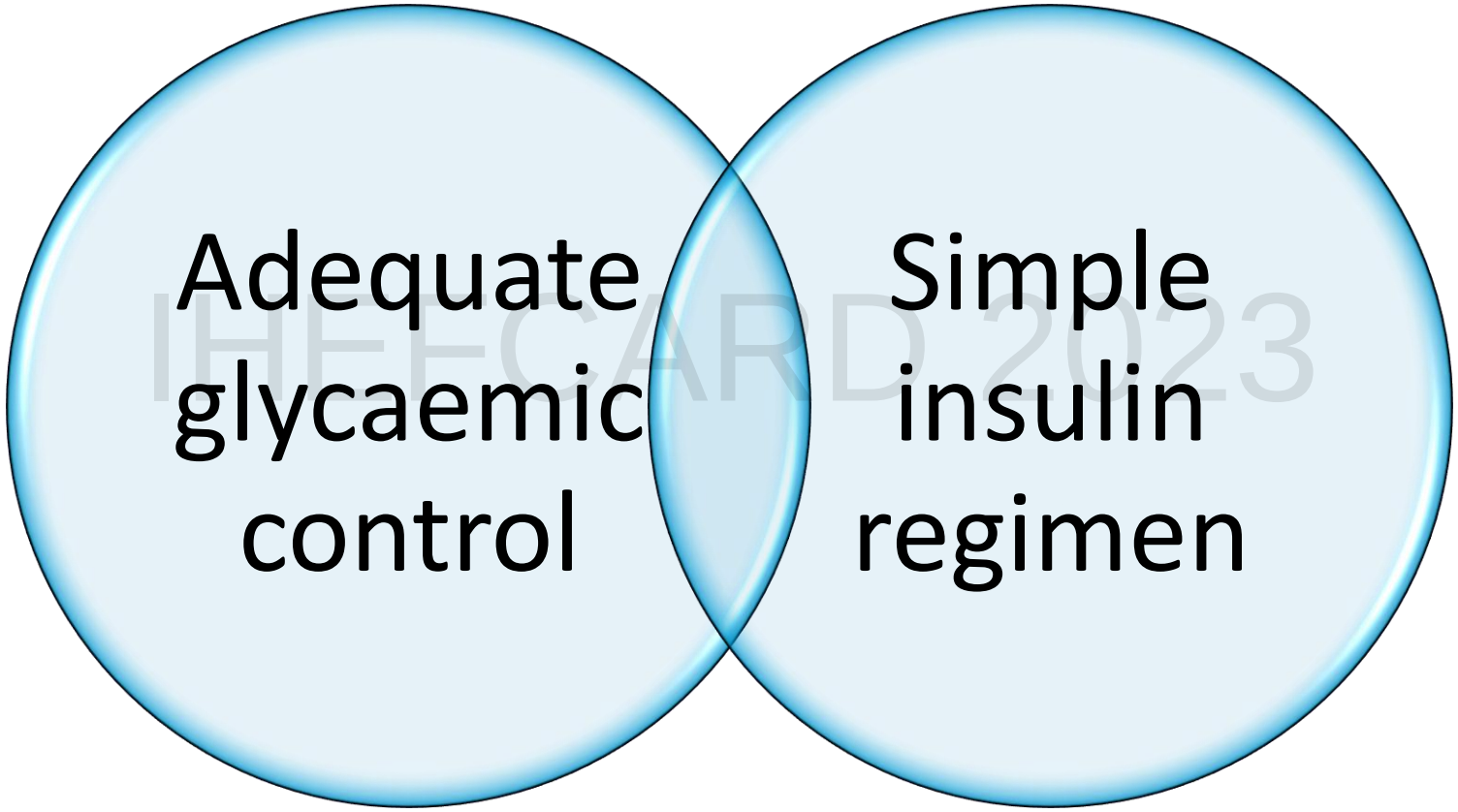
**3-4**

injections



**References: 1.** Khunti et al. Diabetes, obesity and metabolism 14:654-661, 2012. **2.** Kumar, et al. J Diabetol 2020;11:148-57 3. Mauricio D, et al. Diabetes Obes Metab. 2017 Aug;19(8):1155-1164 4. Adapted from American Diabetes Association. Diabetes Care 2017;40(Suppl.1):S64–S74

# Can a co-formulation address the major unmet needs with current insulin therapy?



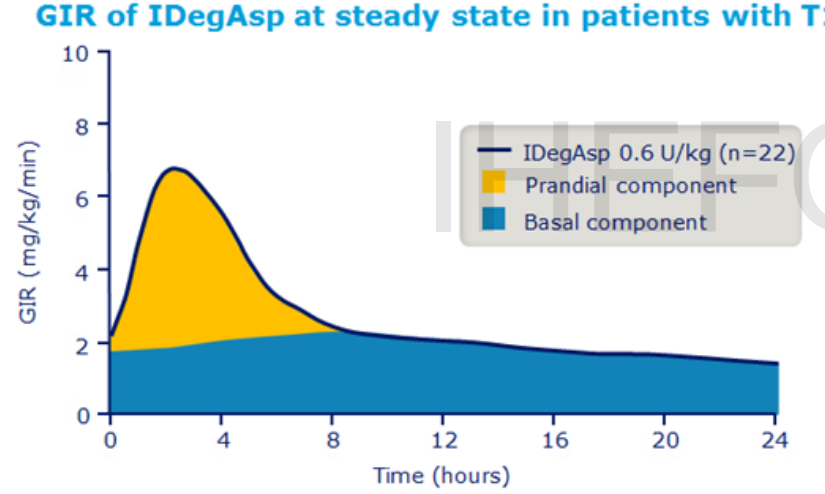



**FPG, PPG, HbA1c**

**OD/BID, flexible**

# Properties of IDeg and IAsp are retained in IDegAsp at steady state

## Distinct prandial and basal glucose-lowering effects of IDegAsp at steady state






## Delivered in FlexTouch®

**30%** **Insulin aspart**
Mealtime insulin analogue with over a decade of clinical experience

**70%** **Insulin degludec**
First basal insulin analogue that can be combined in a soluble solution with a mealtime insulin

## IDegAsp is fully soluble with no need for re-suspension[1-3]

BID; twice daily, IAsp; insulin aspart, IDeg; insulin degludec. IDeg/Asp: Insulin Degludec/Insulin Aspart

**1.** Jonassen I, et al *Pharm Res* 2012;29:2104-2114. **2.** Heise T, et al *Diabetes Ther* 2014;5(1):225–265. **3.** Niskanen L, et al *Eur J Endocrinol* 2012;167:287–294.

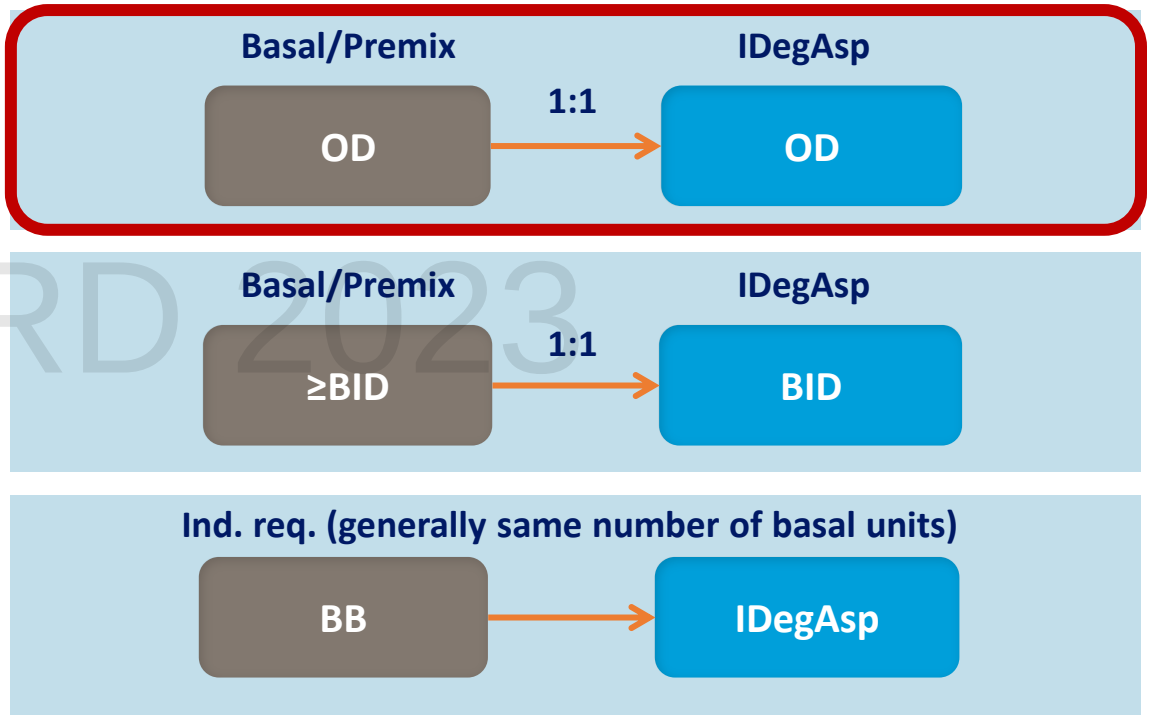
# Dosing of IDegAsp in T2D

## INITIATION

- ✓ Administer OD or BID with the main meal(s)
- ✓ Administer:
  - alone or
  - in combination with OADs or bolus insulin
- ✓ Recommended (total) daily starting dose 10 U
- ✓ Requires subsequent individual dosage adjustments



## SWITCHING



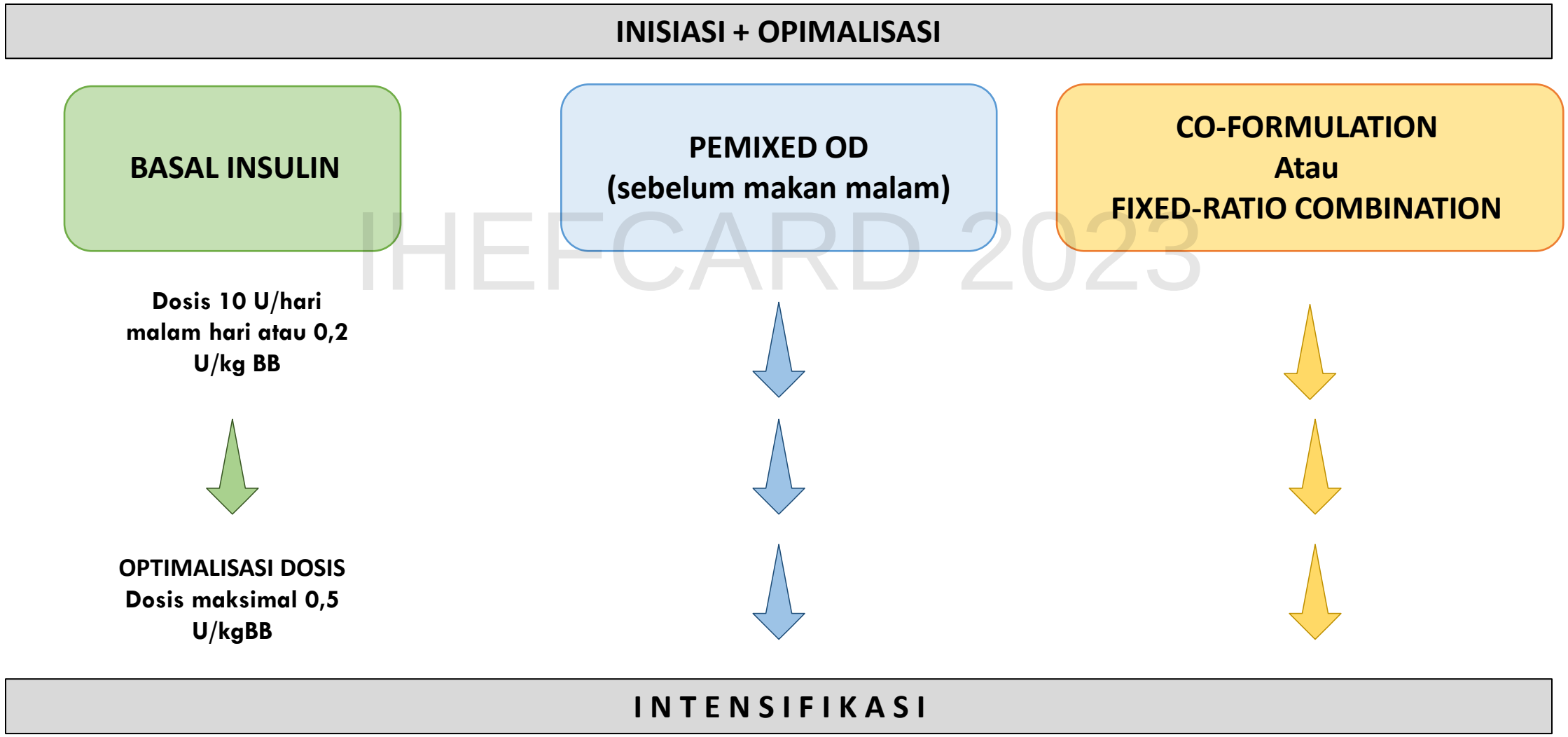

Recommend using close glucose monitoring for first few weeks

BB, basal–bolus; BID, twice daily; IDegAsp, insulin degludec/insulin aspart; Ind. req., individual requirements; OAD, oral antidiabetic drug; OD, once daily; T2D, type 2 diabetes; U, units

Ryzodeg® Prescribing Information Indonesia

# Algoritma terapi insulin:

## Pasien DM Tipe 2 + OHO (mono/dual/tripel) dengan HbA1c ≥7,5%



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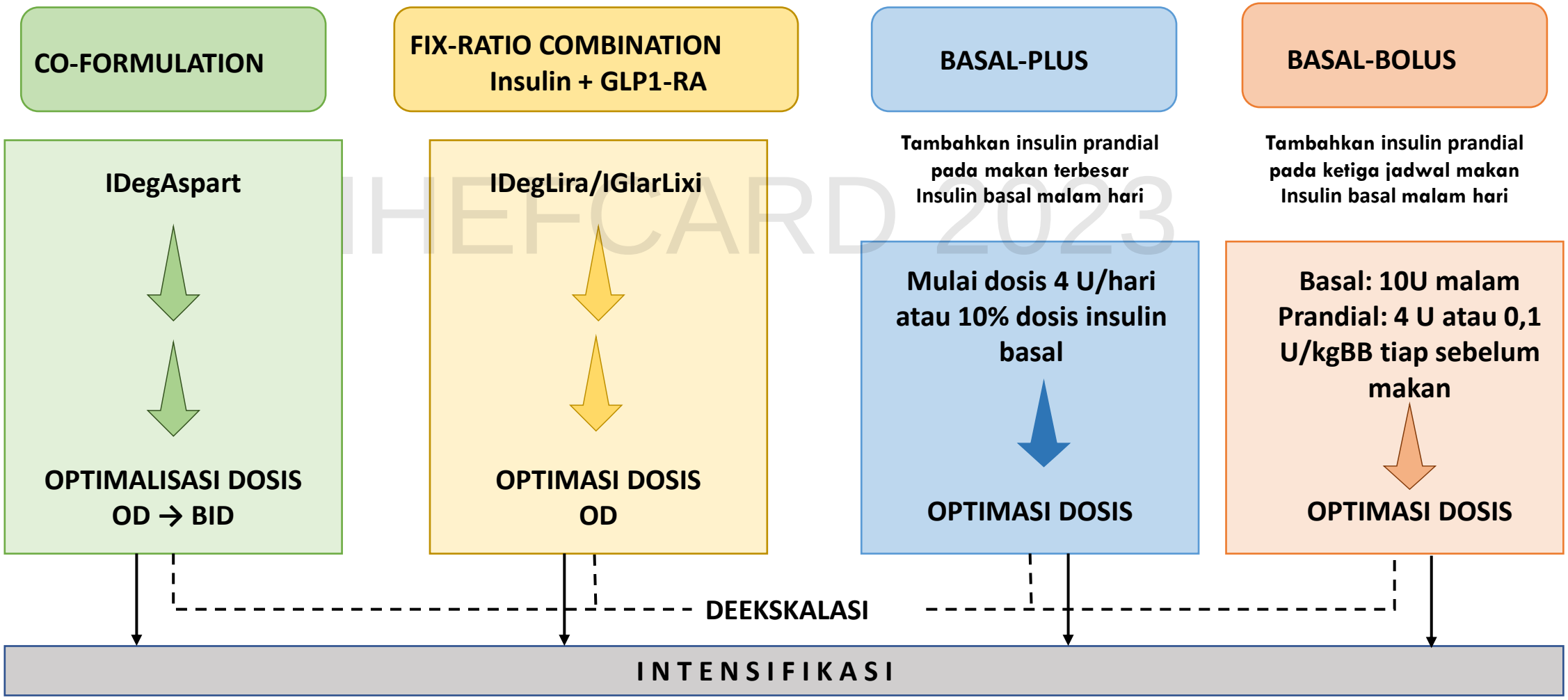
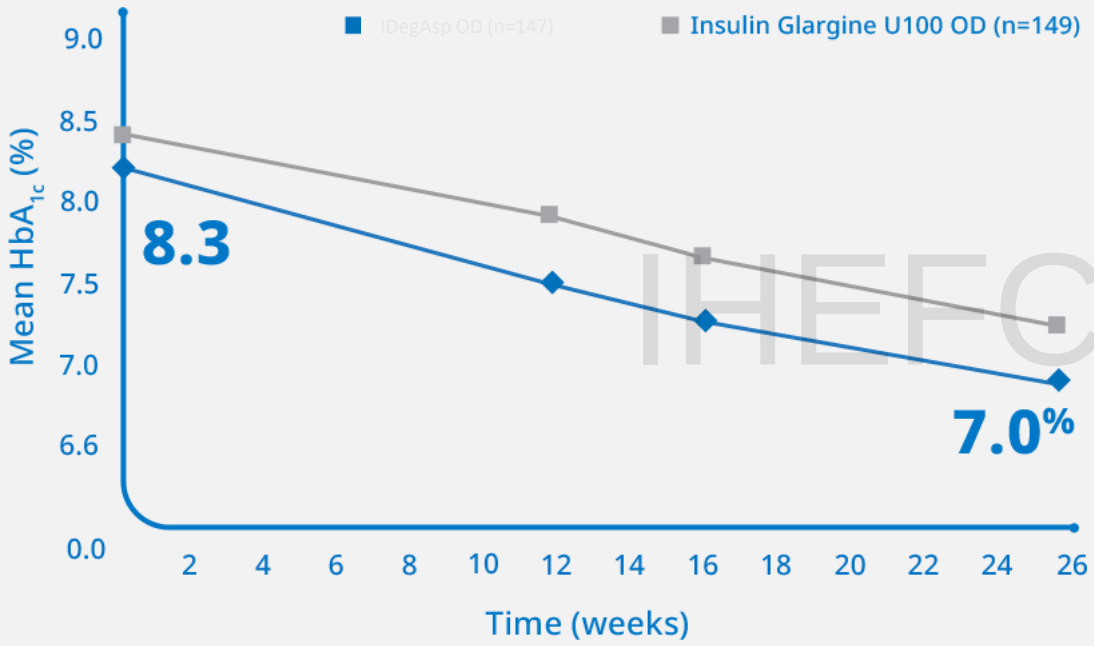
# Algoritma terapi insulin:

## Pasien DM Tipe 2 baru + HbA1c ≥9% atau GDP ≥250 mg/dL atau GDS ≥300 mg/dL, diserta gejala dekompensasi metabolic*



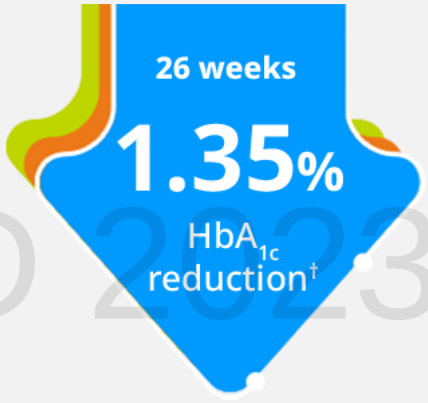
# RCT's: ONISHI

## Mean $HbA_{1c}$ vs insulin glargine U100

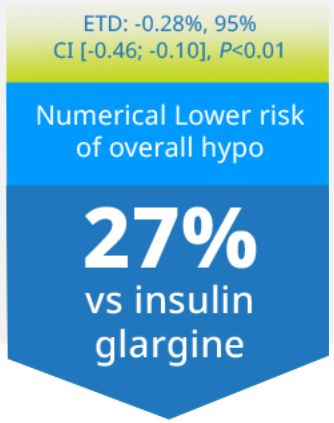


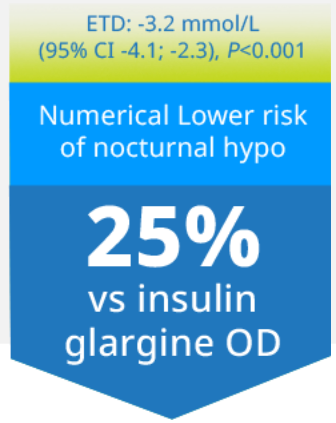

Estimated treatment difference: -0.28% (95% CI-0.46, -0.10); ρ<0.01 Superiority confirmed, "vs insulin glargine U100 mean reduction from baseline

## Significantly reduced HbA1c and better PPG control after dinner with IDegAsp OD





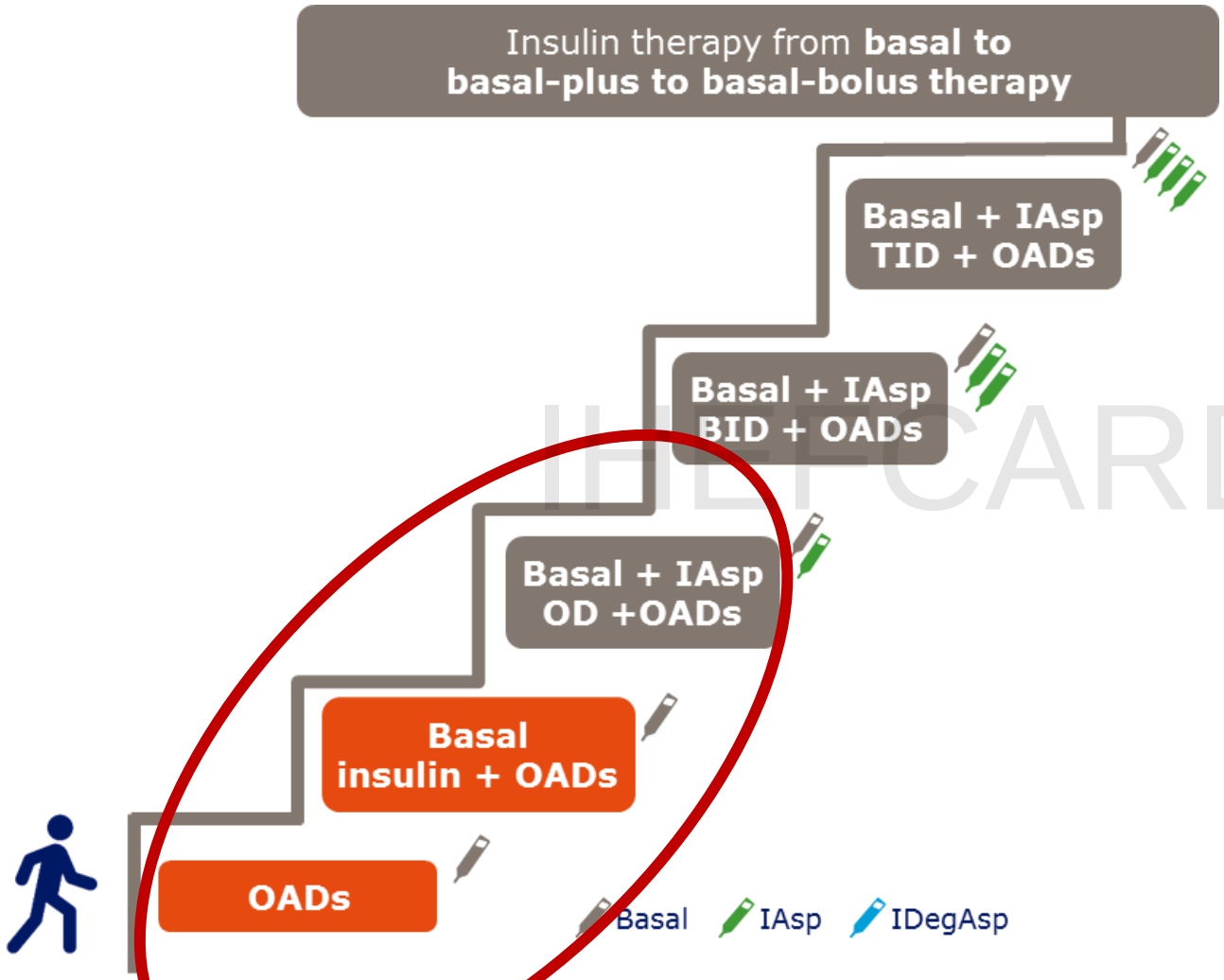


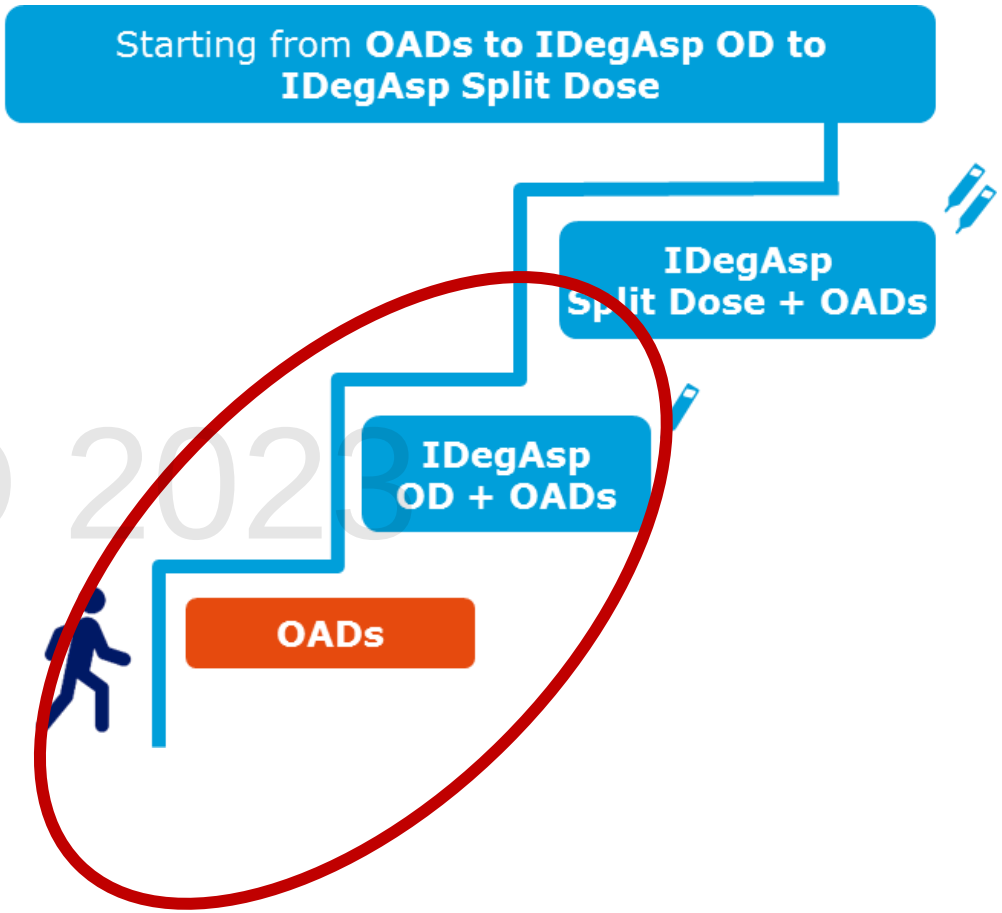






IDegAsp Offers Flexibility in the Timing of Insulin Administration[1]

# After OAD failure, starting once-daily IDegAsp simplifies insulin therapy with better glycaemic control and similar safety versus IGlar U100





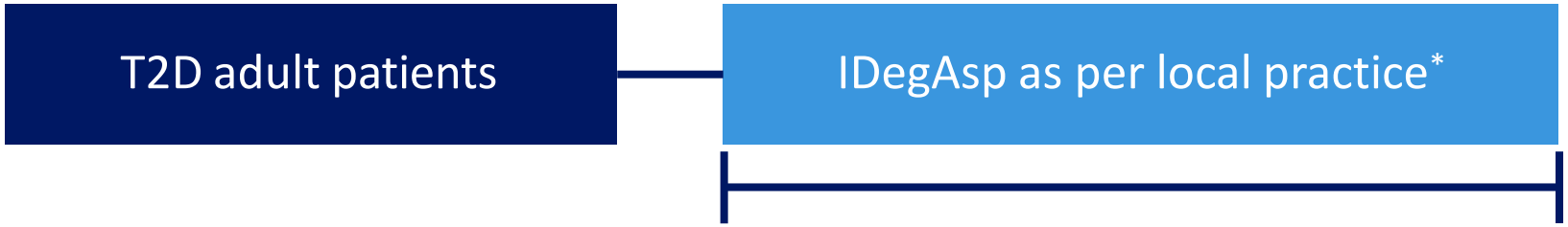

Basal IAsp IDegAsp

BID, twice daily; OAD, oral antidiabetic drug; OD, once daily; IAsp, insulin aspart; TID, thrice daily

Adapted from *American Diabetes Association. Diabetes Care* 2017;40(Suppl.1):S64–S74

# ARISE Study

## RWE data of IDegAsp in patients with T2D






### Study information

- Non-interventional
- Multi-centre
- Prospective, primary data collection
- Visit frequency according to the local standard of care

### Key inclusion criteria

- Physician's decision to initiate treatment with IDegAsp
- Age ≥18 years
- Diagnosed with T2D and treated with any anti-hyperglycaemic medication(s) other than IDegAsp
- Available $HbA_{1c}$ value ≤12 weeks

### Countries

- Australia
- India
- Malaysia
- Philippines
- Saudi Arabia
- South Africa

**Visit 1 (treatment initiation visit) and visit 3 (end of study visit) were mandatory for all patients. Visit 2 was intermediary and only warranted as per clinical practice*

*Fulcher G, Akhtar S, Al-Jaser S, et al. Improved glycaemic control in people with type 2 diabetes initiating or switching to IDegAsp from any anti-hyperglycaemic treatment in a real-world setting across six countries. Abstract and oral presentation at Australasian Diabetes Congress, August 13, 2021..*

# Baseline characteristics

| | Overall (N=1102) |
|---|---|
| Body weight (kg), mean (SD) | 79.5 (19.56) |
| Duration of diabetes (years), mean (SD) | 13.3 (8.33) |
| BMI (kg/m$^2$), mean (SD) | 29.2 (5.86) |
| FPG (mmol/L), mean (SD) | 11.0 (4.22) |
| $HbA_{1C}$, mean (SD) | 9.8 (1.99) |
| Previous Antidiabetic Treatment | |
| • OAD Only | 371 (35.1) |
| • Basal Insulin (± OADs) | 230 (21.8) |
| • GLP-1 RA ± insulin (± OADs) | 87 (8.2) |
| • Basal bolus (± OADs) | 137 (13.0) |
| • Premix/self-mixed insulin ± bolus (± OADs) | 232 (21.9) |



*BMI, body mass index; FPG, fasting plasma glucose; $HbA_{1c}$; glycated haemoglobin; N, total number of patients in full analysis set; SD, standard deviation.*

*Presented at the Australasian Diabetes Congress (ADC) virtual meeting, 11–13 August 2021*

# ARISE summary

**Initiation with or switch to IDegAsp, led to**

**STATISTICALLY REDUCTIONs**
in $HbA_{1c}$

1.4%

**STATISTICALLY SIGNIFICANT REDUCTIONs**
in overall FPG

48.6 mg/dl

**LOWER**
daily basal but higher prandial insulin dose for previous insulin users

2.3 unit

**NUMERICAL REDUCTION**
in hypoglycemic events (expect GLP-1RA prior user) and no unexpected safety findings

77%
Nocturnal hypoglycaemia



*FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonists; IDegAsp, insulin degludec/insulin aspart*

# Recommended starting dose for initiations

## Starting dose

**10** Unit/OD

With largest meals

## Severe Hyperglycemia

HbA1c >10% (86 mmol/mol)*

**>10** Unit/OD

With largest meals



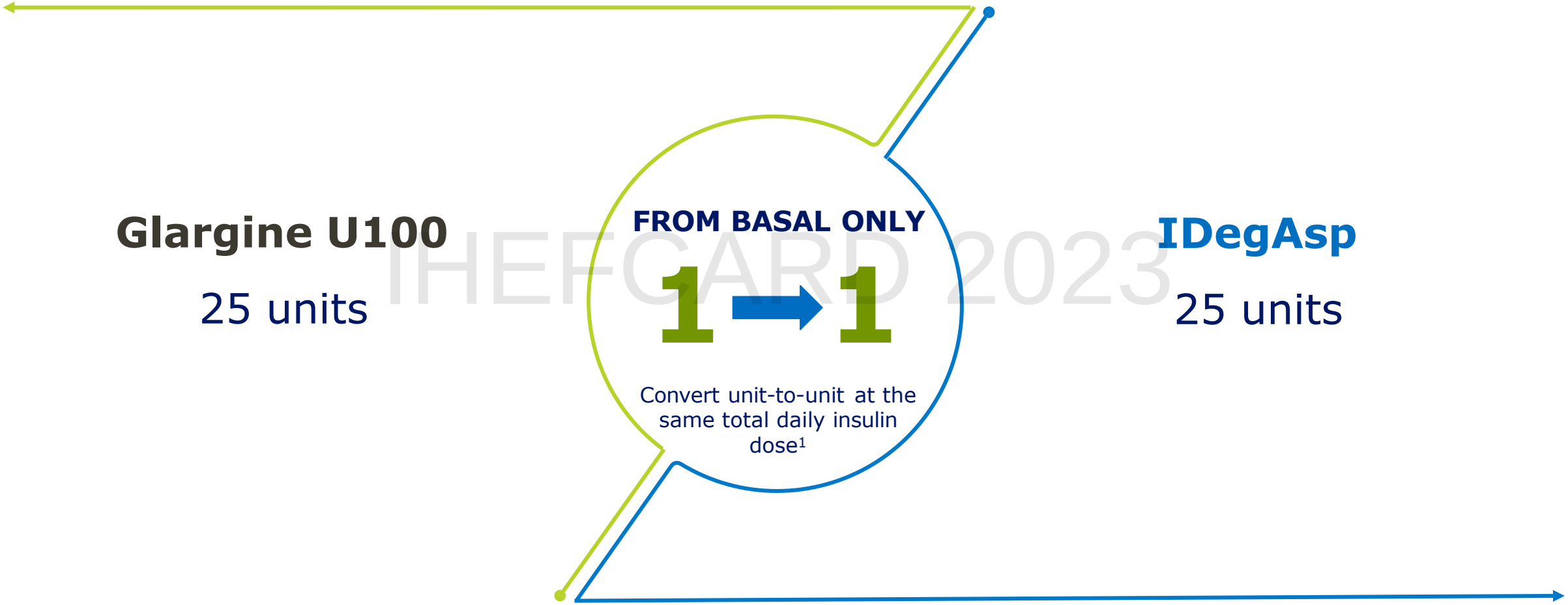
Followed by subsequent **INDIVIDUAL** dosage **weekly** adjustment until the desired **FPG** reached

*This posology is based on expert recommendations from Sarah G et al.

**References: 1.** Sarah Galtras et al. J Clin Med 2020. 2. Roopa M et al. Diabetes Obes Metab. 2020;1-15 3. Ryzodeg®. Indonesia Prescribing Information. 2021

# Recommended to switch to IDegAsp[1-3] if

## glycaemic management is suboptimal with basal insulin






1. Glastras SJ, et al. J Clin Med. 2020;9:1091. 2. Mehta R, et al. Diabetes Obes Metab. 2020;10.1111/dom.14128., 3. Ryzodeg® Indonesia Prescribing Information 2021.

# Suggested once-weekly titration schedule for IDegAsp in T2D

Sasaran kontrol glikemik (PERKENI, 2021)

| | |
|---|---|
| **HbA1C** | 7 % |
| **Glukosa darah puasa**/pre-prandial capillary plasma glucose | 80-130 Mg/dL |
| **Glukosa darah 1-2 jam PP** | <180 Mg/dL |



| | Target FPG | Dosis IDegAsp |
|---|---|---|
| + | >130 mg/dL | **+2** |
| | 80 - 130 mg/dL | **Pertahankan dosis** |
| − | <80 mg/dL | **-2** |

1. Fulcher *et al. Diabetes Care* 2014;37:2084–90; 2. Gerety *et al. Endocr Pract* 2016;22:546–54; 3. Konsensus Perkeni 2021

| | |
|---|---|
| **SGLT- 2** | • If SGLT-2 added to IDegASp: **decrease dose 10-20%**<br>• & titrated weekly to reduce the risk of side effects |
| **SUs** | • Caution when combining IDegAsp with (SUs) Sulphonylureas.<br>• For IDegAsp **OD**, SUs may need to be **discontinued** or **dose reduced**<br>• For IDegAsp **BID**, SUs should be **discontinued** |
| **Pioglitazone** | • The long-term effect still **uncertain.** The combination has been associated with the development of heart failure & heart disease or stroke. |
| **Metformin**<br>**Acarbose**<br>**DPP4-inh** | • No additional consideration are required. |
| **GLP-1** | • Add IDegAsp to GLP-1RA, **no decrease** in insulin dose. Daily dose 10 u is recommended.<br>• If GLP-1RA added to IDegAsp, insulin dose **may be decreased**, depending on HbA1C level |



**References: 1.** Sarah Galtras et al. J Clin Med 2020. 2. Roopa M et al. Diabetes Obes Metab. 2020;1-15

# IDegAsp® in special populations[1-3]

| | | STRONGEST EVIDENCE |
|---|---|---|
| **Elderly people**<br>May be useful in elderly people due to flexible dosing and low injection burden | ✓ | *Post-hoc* analysis of two phase 3 trials[4] |
| **Intermittent fasting**<br>May be useful in individuals with variable eating regimens | ✓ | Randomised treat-to-target trial[5] |
| **Hepatic or renal impairment**<br>Intensive glucose monitoring needed in chronic renal or hepatic illness* | ✓ | Similar PK profiles of IDeg[6,7] and IAsp[8] with or without renal or hepatic impairment |
| **Hospitalised individuals**<br>Prescribers must be aware of the long half-life of insulin degludec in the hospital setting |  | No evidence available[1,2] |
| **Pregnancy**<br>Not recommended for use | ✗ | No evidence available[1,2,3] |



***Examples of chronic illness include end-stage kidney disease and liver cirrhosis.**

**IAsp,** insulin aspart; **IDeg,** insulin degludec; **IDegAsp,** insulin degludec/insulin aspart co-formulation; **PK,** pharmacokinetic.

1. Glastras SJ, *et al. J Clin Med.* 2020;9:1091; 2. Mehta R, et al. Diabetes Obes Metab. 2020;10.1111/dom.14128., 3. Ryzodeg® 70/30 Australian Product Information (March 2020); 4. Fulcher G, *et al. Diabetes Ther.* 2019;10:107–18; 5. Hassanein M, *et al. Diabetes Res Clin Pract.* 2018;135:218–26; 6. Kiss I, *et al. Clin Pharmacokinet.* 2014;53:175–83; 6. Kupcova V, *et al. Clin Drug Investig.* 2014;34:127–33; 8. Holmes G, *et al. Br J Clin Pharmacol.* 2005;60:469–76.

# Take home message

- Diabetes is a progressive disease and need complex regimen therapy at advance stage
- Co-formulation insulin consist of basal and prandial insulin in one pen
- Ideg Asp can be initiated among T2DM naïve insulin tx or switched from basal/premixed/basal bolus insulin regimen who can't tolerate complexity of the regimen or need to reduce hypoglycemia risk.
- For initiation, co-formulation insulin showed superority in reducing HbA1c compare to basal insulin
- For intensification, co-formulation insulin offers less hypoglycemia risk and regimen simplification

# Thank you