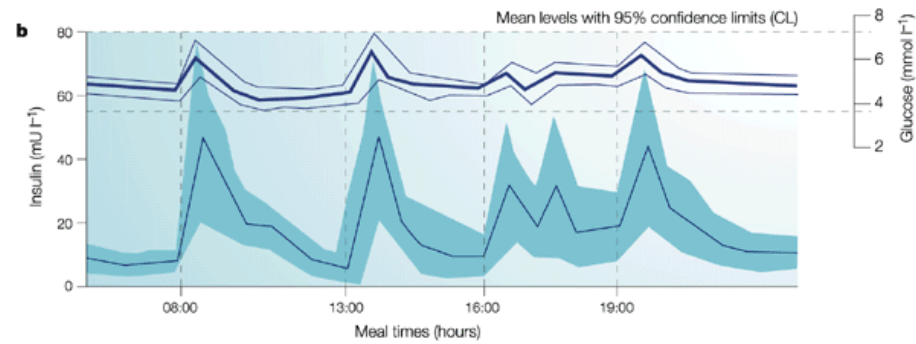
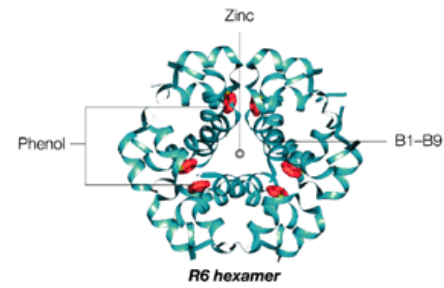
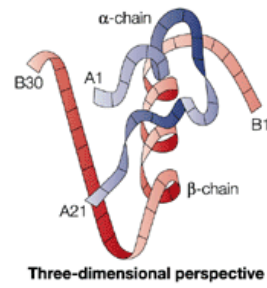
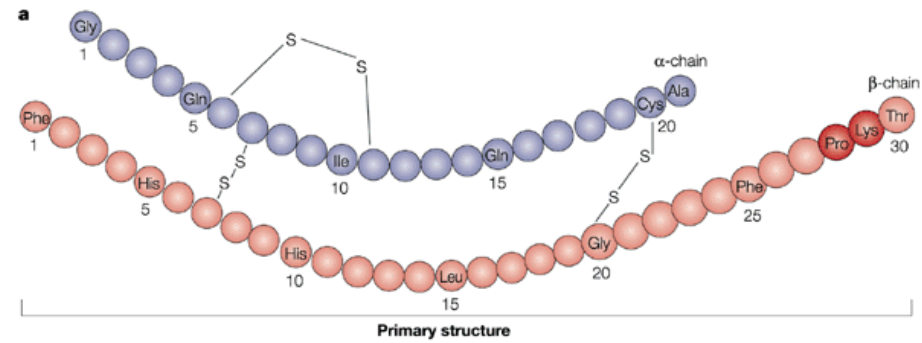


Use of Insulin in type 2 DM

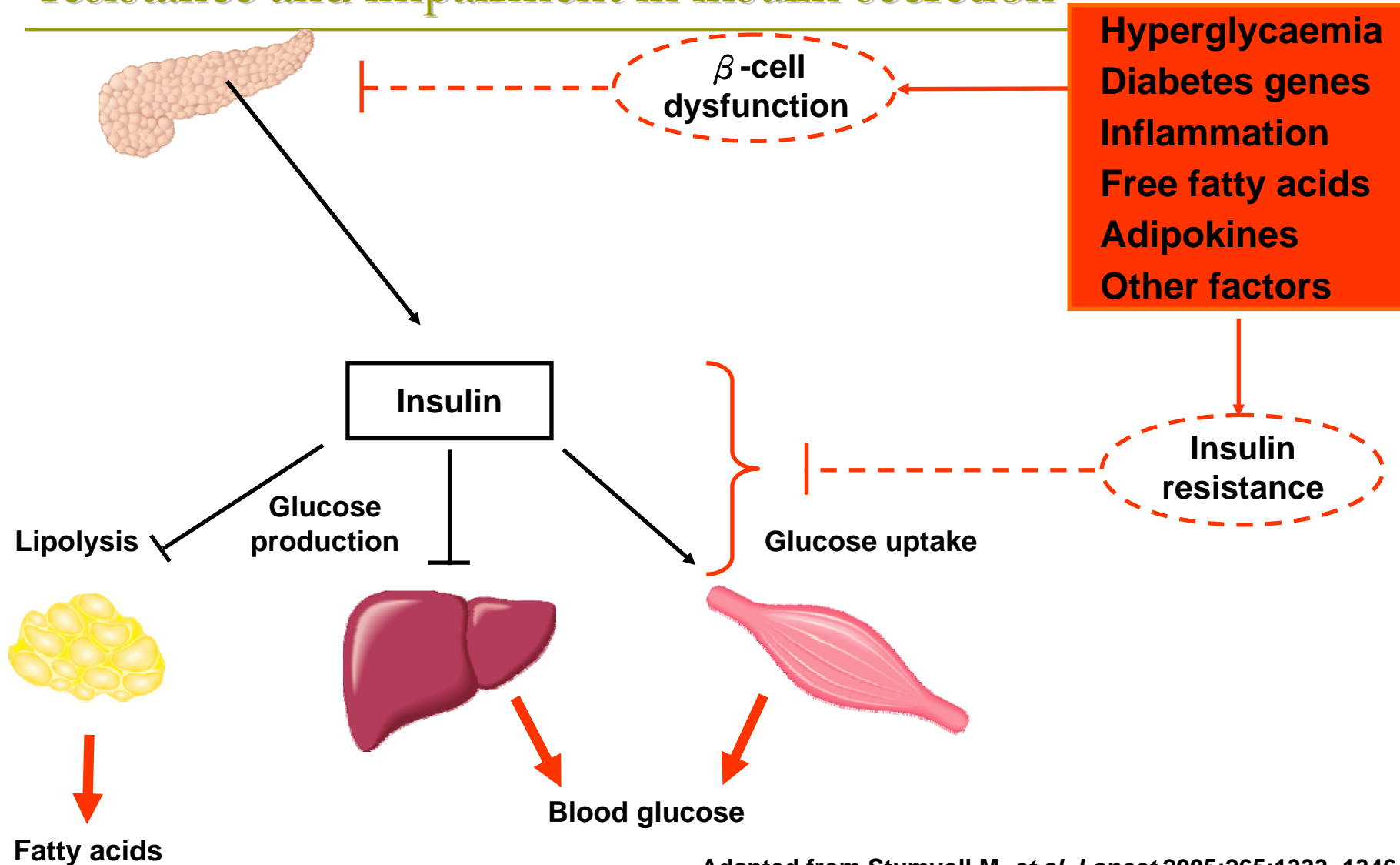
Dr. Tsang Chiu Chi
DM center
AHNH
2/2010



Insulin



Type 2 diabetes is characterised by hyperglycaemia, insulin resistance and impairment in insulin secretion



Adapted from Stumvoll M, et al. *Lancet* 2005;265:1333–1346.

Case

- M/42
- Obese Type 2 DM since 1992
- Fu GP, on metformin and gliclazide
- Seen in SOPD in 1998, HbA1c 7.8
- HT in 2000, start enalapril
- Complicated with NPDMR, microalbumiuria
- OHA maximized in 2002

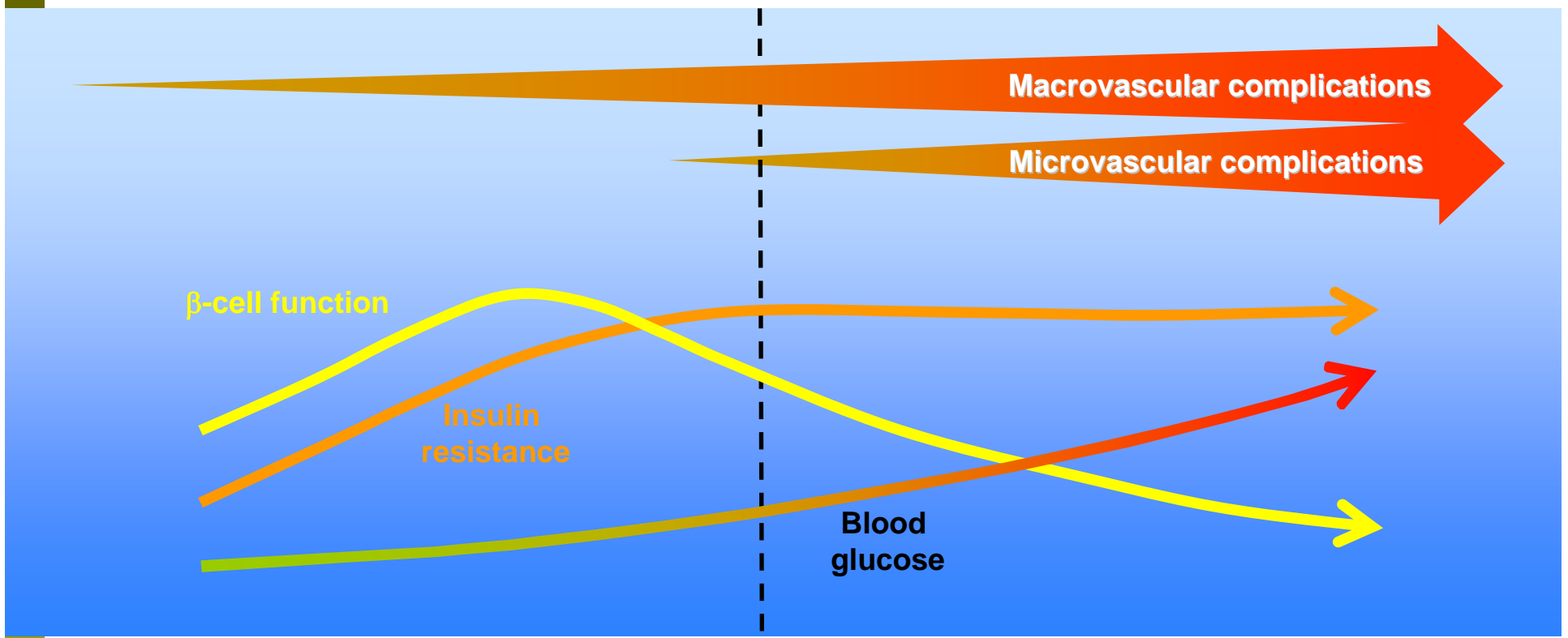
-
- Suboptimal DM control, add acarbose since 2005
 - Acarbose switched to pioglitazone in 2006
 - Glycemic control worsen, HbA1c 10.1 in 2007
 - Seen by DM nurse (injection technique, home H'stix)
 - BW 82.3kg, BMI 28
 - **Humulin N** 10u nocte started, pioglitazone stopped

-
- FBG 11.7
 - No hypoglycemic symptoms
 - Increase **Humulin N** to 20u nocte
 - HbA1c 9.6, FBG 12, Home H'stix: fasting 8-11
 - **Humulin N** 20u before breakfast, 10u before dinner
 - HbA1c 8.6, home H'stix: fasting 6-8, postprandial ~10
 - Dose of **Humulin N** adjusted

-
- HbA1c 8.2, FBG 9.6, home H'stix: 6.7-7.1 before breakfast, ~10 before bed
 - On Humulin N 26-30u om, 16-20u pm (increase dose if eating out)
 - Switch to Humulin N 26-30u om, Humulin 70/30 20-24u pm
 - HbA1c 8.9, FBG 12.9
 - Gliclazide MR stopped, insulin dose increased to Humulin N 34u om, Humulin 70/30 24u pm

-
- HbA1c 7.7, FBG 8.1, home H'stix: fasting 5.5-8.1 before breakfast, 9.2-12 before dinner
 - Humulin N 38u om, Humulin 70/30 24u pm

Type 2 diabetes is a progressive disease: early intervention is critical



Prevention

Diagnosis

Treatment

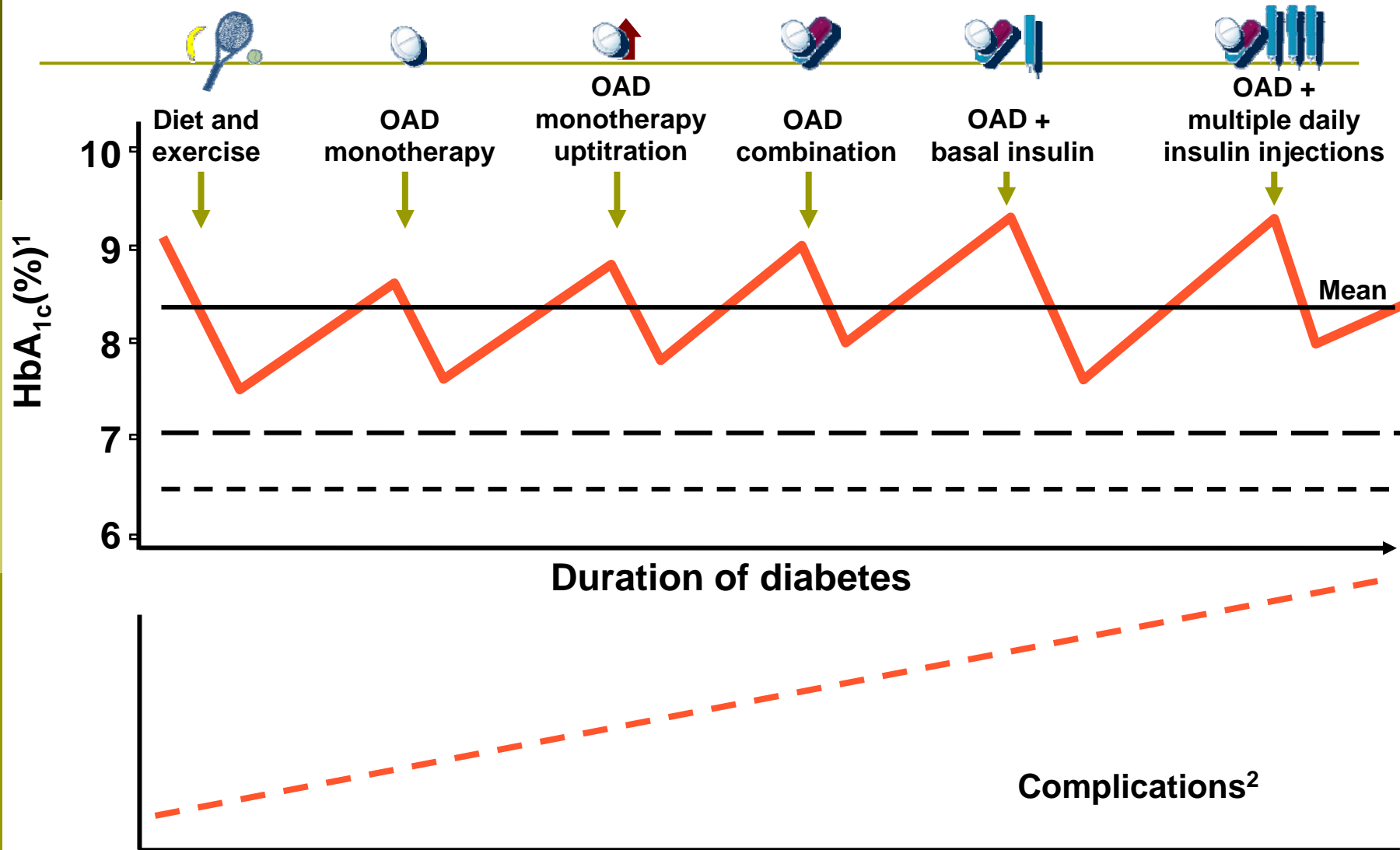
10+ Years



IFG: impaired fasting glucose
IGT: impaired glucose tolerance

Adapted from DeFronzo RA. *Med Clin N Am* 2004;88:787–835.

Stepwise strategy can delay patients achieving goals and increase complications

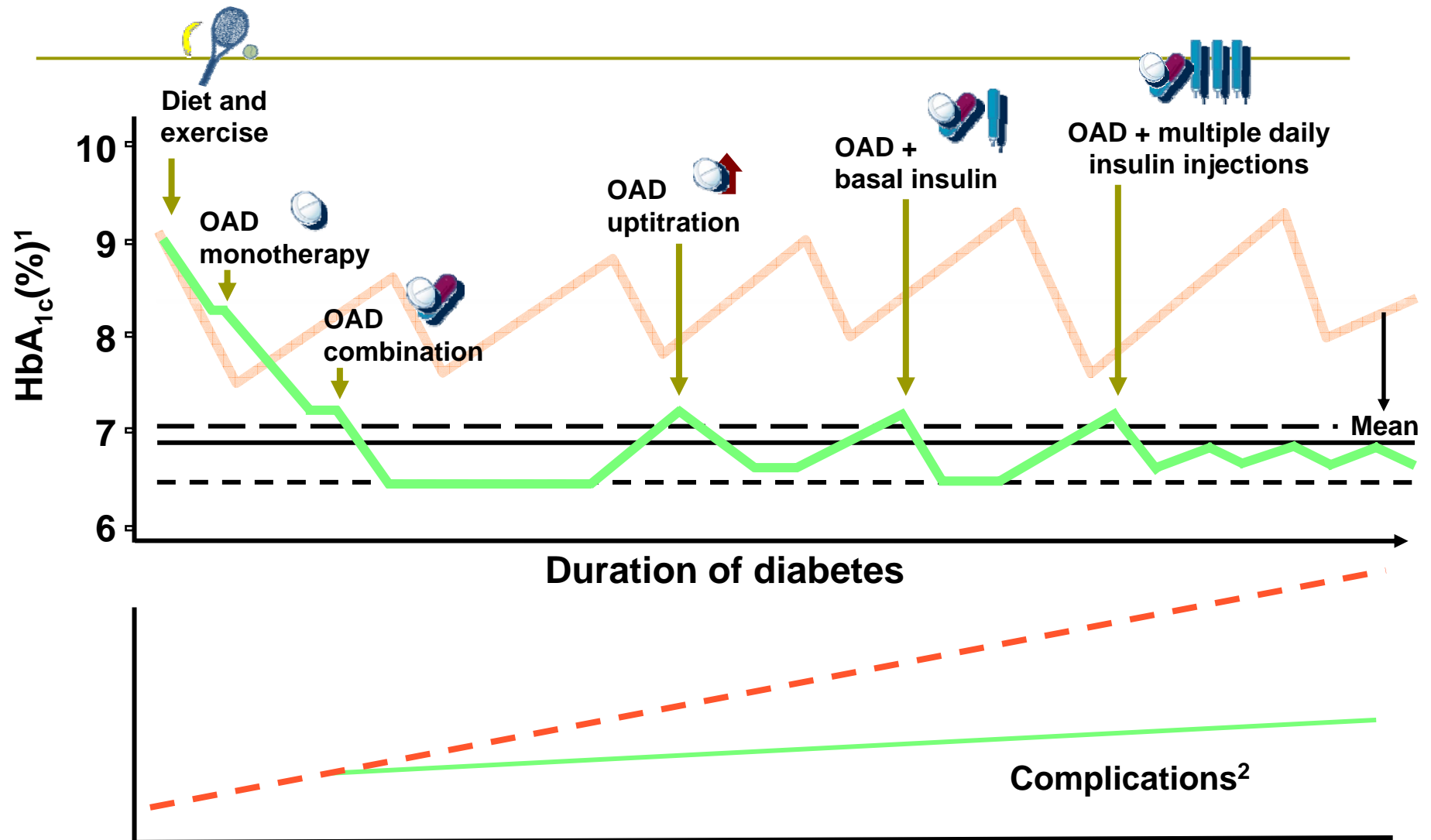


OAD = oral anti-diabetic

¹Adapted from Campbell IW. *Br J Cardiol* 2000;7:625–631.

²Stratton IM, et al. *BMJ* 2000;321:405–412.

The case for early combination therapy: reaching and maintaining glycaemic goals

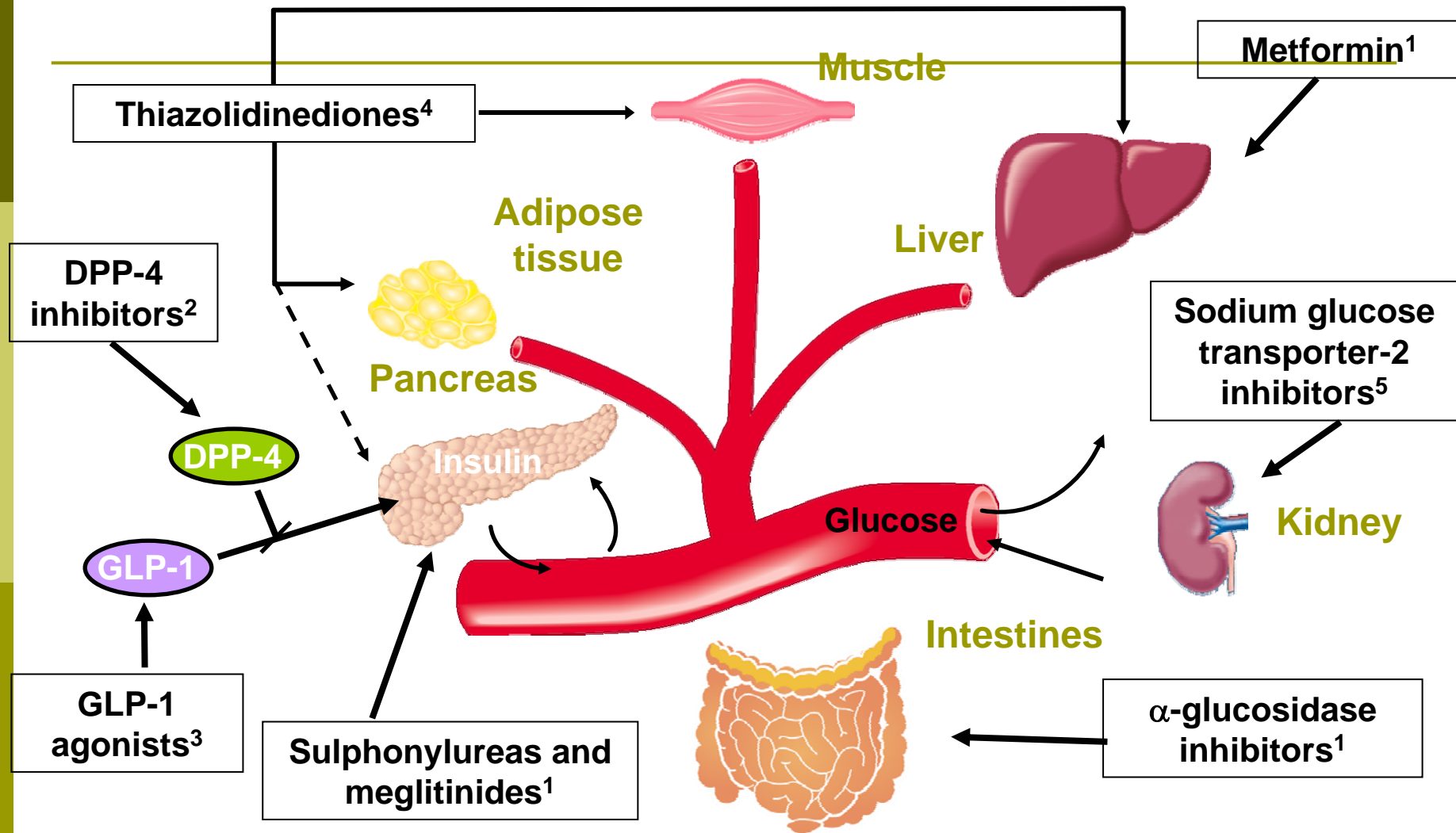


OAD = oral anti-diabetic

¹Adapted from Del Prato S, et al. *Int J Clin Pract* 2005;59:1345–1355.

²Stratton IM, et al. *BMJ* 2000;321:405–412.

Primary sites of action of anti-diabetic agents



¹Adapted from Krentz A and Bailey C. *Drugs* 2005;65:358–411. ²Ahren B. *Expert Opin Emerg Drugs* 2008;3:593–607.

³Todd JF, et al. *Diabet Med* 2007;24:223–232. ⁴Natras M, et al. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999;13:309–329. ⁵Jabbour S and Goldstein B. *Int J Clin Pract* 2008;62:1279–1284.

Current and new antidiabetic medications: benefits and risks

Intervention	Advantages	Disadvantages
Metformin ¹	<ul style="list-style-type: none"> • Weight neutral • May improve lipid profile 	<ul style="list-style-type: none"> • GI side effects • Lactic acidosis (rare)
Sulphonylureas ¹	<ul style="list-style-type: none"> • Well established 	<ul style="list-style-type: none"> • Weight gain • Hypoglycaemia
Thiazolidinediones ¹	<ul style="list-style-type: none"> • Durable glycaemic control 	<ul style="list-style-type: none"> • Fluid retention, congestive heart failure • Weight gain, bone fractures
Meglitinides ¹	<ul style="list-style-type: none"> • Short duration 	<ul style="list-style-type: none"> • Weight gain • Frequent dosing
Insulin ²	<ul style="list-style-type: none"> • No dose limit • Improves lipid profile 	<ul style="list-style-type: none"> • Injections • Weight gain • Hypoglycaemia
α -Glucosidase inhibitors ¹	<ul style="list-style-type: none"> • Weight neutral • Do not cause hypoglycaemia 	<ul style="list-style-type: none"> • Frequent GI side effects • Dosing 3 times/day
Amylin analogues ³	<ul style="list-style-type: none"> • Weight loss 	<ul style="list-style-type: none"> • Injections, frequent GI side effects • Limited experience
DPP-4 inhibitors ⁴	<ul style="list-style-type: none"> • Weight neutral 	<ul style="list-style-type: none"> • Limited experience
GLP-1 agonists ⁴	<ul style="list-style-type: none"> • Weight loss 	<ul style="list-style-type: none"> • Injections, frequent GI side effects • Limited experience

¹Krentz A and Bailey C. *Drugs* 2005;65:385–411. ²Carver C. *Diabetes Educ* 2006;32:910–917.
³Krentz A, et al. *Drugs* 2008;68:2131–2162. ⁴Bosi E, et al. *Diabetes Res Clin Pract* 2008;82:S102–S107.

Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy

-Diabetologia, 2009 January;52(1)

- The consensus algorithm developed on behalf of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Algorithm for the metabolic management of type 2 diabetes

Initiating Insulin

- ◆ Bedtime intermediate / long acting insulin, dosage start at ~15% of BW, max ~50% of BW
- ◆ On average, start at 8-10u nocte, split the dose when reaching 20-30u

STEP 1

STEP 2

STEP 3

Tier 2: Less well validated the

Step to step, consider:

- Diet and drug compliance
- Insufficient physical activity
- Increase in BW
- Onset of another illness, e.g. Cushing's syndrome

Lifestyle + meformin
+
Basal insulin

Lifestyle + meformin
+
Sulfonylurea

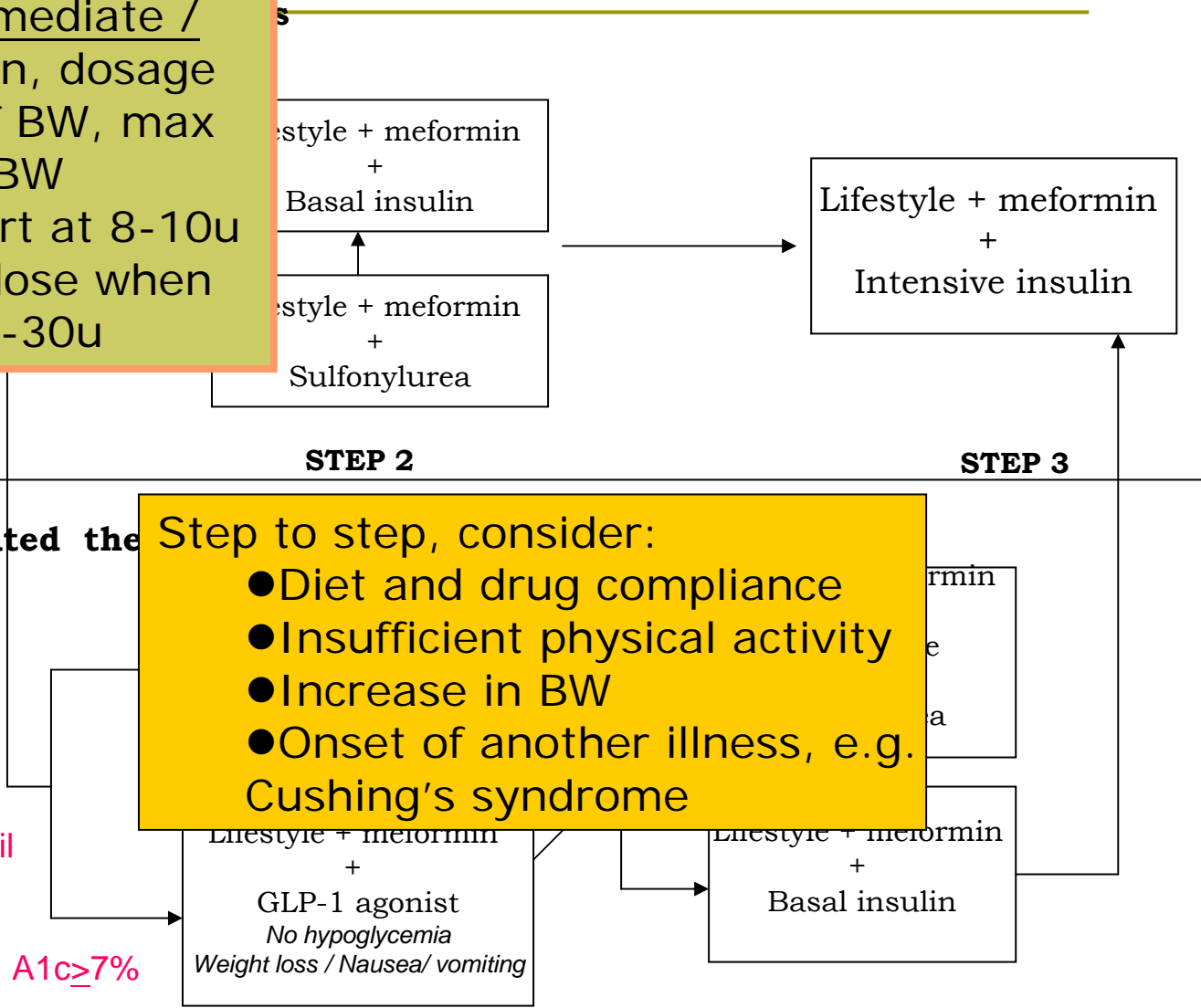
Lifestyle + meformin
+
Intensive insulin

Lifestyle + meformin
+
GLP-1 agonist
*No hypoglycemia
Weight loss / Nausea/ vomiting*

Lifestyle + meformin
+
Basal insulin

* Check HbA1c every 3 months until <7%, then at least every 6 months

* Intervention should be changed if A1c ≥ 7%



Syringe and vials Reusable device (loadable cartridges)

Actrapid Vial & Penfill



Protaphane Vial & Penfill



Mixtard 30 Vial & Penfill



NovoRapid Penfill



Humalog Penfill



Prefilled multidose disposable device

Glargine pen



Detemir pen

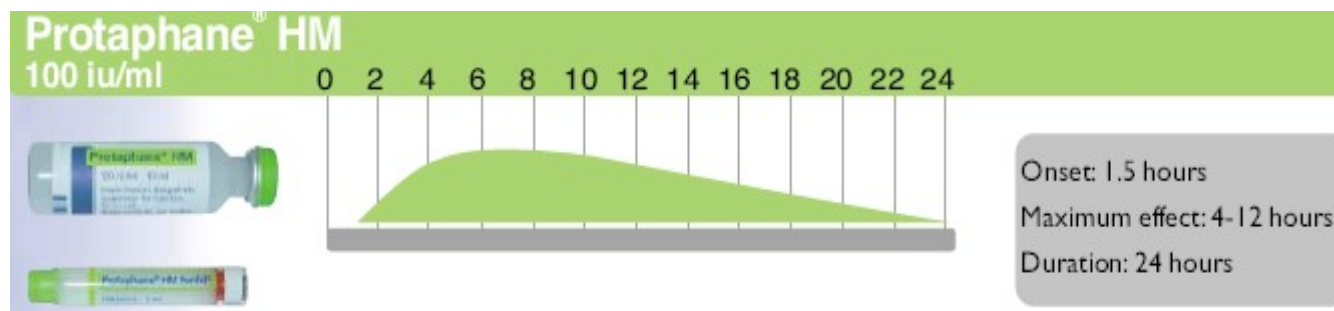
瑞和密爾 諾易筆®



NPH insulin

NPH (Neutral Protamine Hagedorn) / isophane insulin

- Intermediate acting insulin, cloudy (re-suspension uniformly before use), act as basal insulin
- Protaphane (Novolin N, 諾和靈N)
- Humulin N (Humulin NPH, 优泌林中效)



Combination therapy of insulin and OAD

Supplementary insulin treatment

- in HK Chinese type 2 DM patients with secondary OAD failure
- low dose supplementary insulin treatment (intermediate acting insulin)
(mean dose: 14 u/day) (after 6m)
 - 2% reduction in HbA_{1c}
 - weight gain of 2kg
- compared with patients treated with full-dose insulin replacement regimen (mean dose: 57 u/day)
 - similar glycaemic control but weight gain of 5kg

Chow et al. Diabetes Care 1997

Combination therapy of insulin and OAD

Supplementary insulin treatment

- as an “interim” regimen & allows smoother transition before switched over to a full insulin regimen.
- reduce peripheral hyperinsulinaemia (weight gain & BP)
- 0.1-0.2 u/kg of intermediate or long acting insulin (given at bedtime and increase at 3-4 daily interval)
- If glycaemia fails to improve with 0.5 u/kg of insulin or more: full insulin replacement

Lilly Insulin Range For Your Patient's Treatment Needs

Lilly Brand Name	Type of Insulin (Generic name)	Product Description	Presentation	Schematic Action Profile*1,2,3
Humulin® R	Insulin neutral (Soluble)	SHORT-ACTING	Humulin® R 10 mL vials and 3 mL [†] cartridges	<p>Onset: 30 mins Peak: 2-4 hours Duration: 6-8 hours</p>
Humulin® N	Insipine (NPH)	INTERMEDIATE ACTING	Humulin® N 10 mL vials and 3 mL [†] cartridges	<p>Onset: 1 hour Peak: 4-10 hours Duration: 24 hours</p>
Humulin® 70/30	30% Insulin neutral, 70% Insipine (NPH)	PREMIXED INSULIN	Humulin® 70/30 10 mL vials and 3 mL [†] cartridges	<p>Onset: 30 mins Peak: 2-12 hours Duration: 24 hours</p>
Humalog^{mix} 25	30% Insulin lispro, 70% Insulin lispro protamine suspension	PREMIXED INSULIN LISPRO	Humalog ^{mix} 25 3 mL [†] cartridges	<p>Onset: 0-15 mins Peak: 1 hour Duration: 24 hours</p>
Humalog	Insulin lispro	RAPID-ACTING	Humalog [®] 10 mL vials and 3 mL [†] cartridges	<p>Onset: 0-10 mins Peak: 1 hour Duration: 2-5 hours</p>

*Duration of action may vary from patient to patient. †For use in the HumaPen® 3 mL reusable pen. Before prescribing, please review Approved Product Information.



Eli Lilly Asia, Inc.
 Sulfax 2501-9, 25/F, Shell Tower, Times Square, 1 Matheson Street, Causeway Bay, Hong Kong
 Tel: (852) 2572 0160 Fax: (852) 2572 7993
www.lilly.com.hk

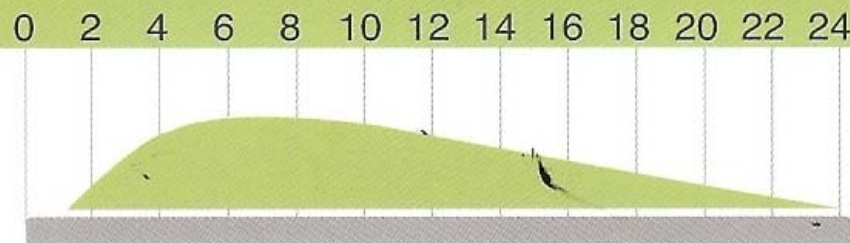
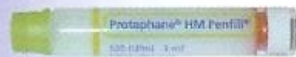
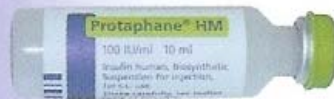
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Actrapid[®] HM 100 IU/ml



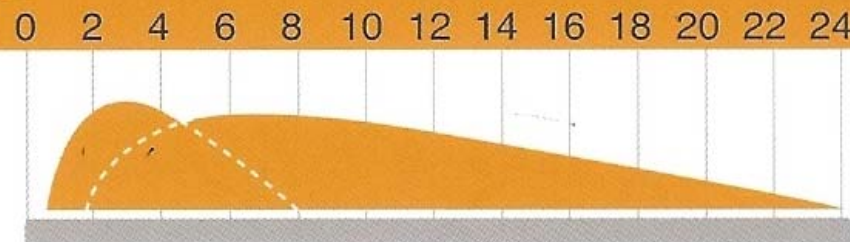
Onset: 0.5 hour
Maximum effect: 1.5-3.5 hours
Duration: 8 hours

Protaphane[®] HM 100 IU/ml



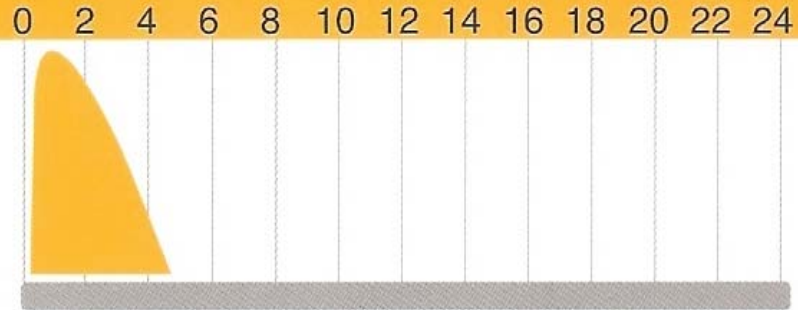
Onset: 1.5 hours
Maximum effect: 4-12 hours
Duration: 24 hours

Mixtard[®] 30 HM 100 IU/ml



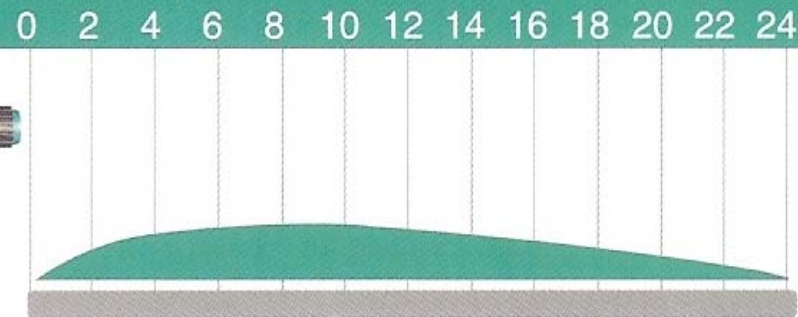
Onset: 0.5 hour
Maximum effect: 2-8 hours
Duration: 24 hours

NovoRapid[®] 100 U/ml



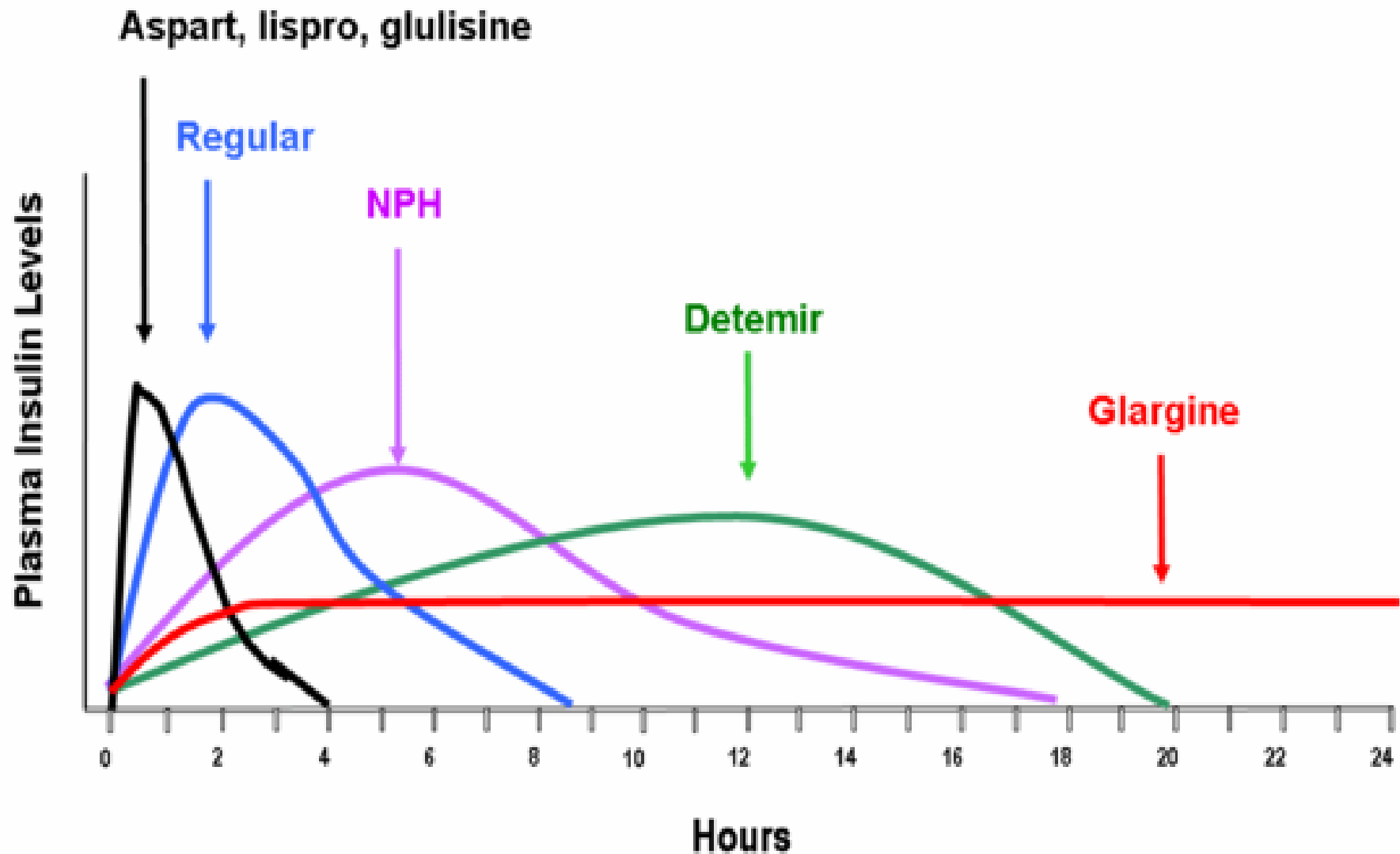
Onset: 10-20 minutes
Maximum effect: 1-3 hours
Duration: 3-5 hours

Levemir[®] FlexPen[®] 100 U/ml



Maximum effect: 3-14 hours
Duration: Up to 24 hours

Action profile of insulin



Titration of insulin

- Home H'stix monitoring
- Target at:
 - Fasting glucose (before breakfast) → evening glucose (before dinner) → post-prandial glucose (2-hr after meal)
- Monitor hypoglycemia

Newer insulin analogues

Human Insulin



Glargine



Glargine

← glycine

← arginine

Detemir



Lispro

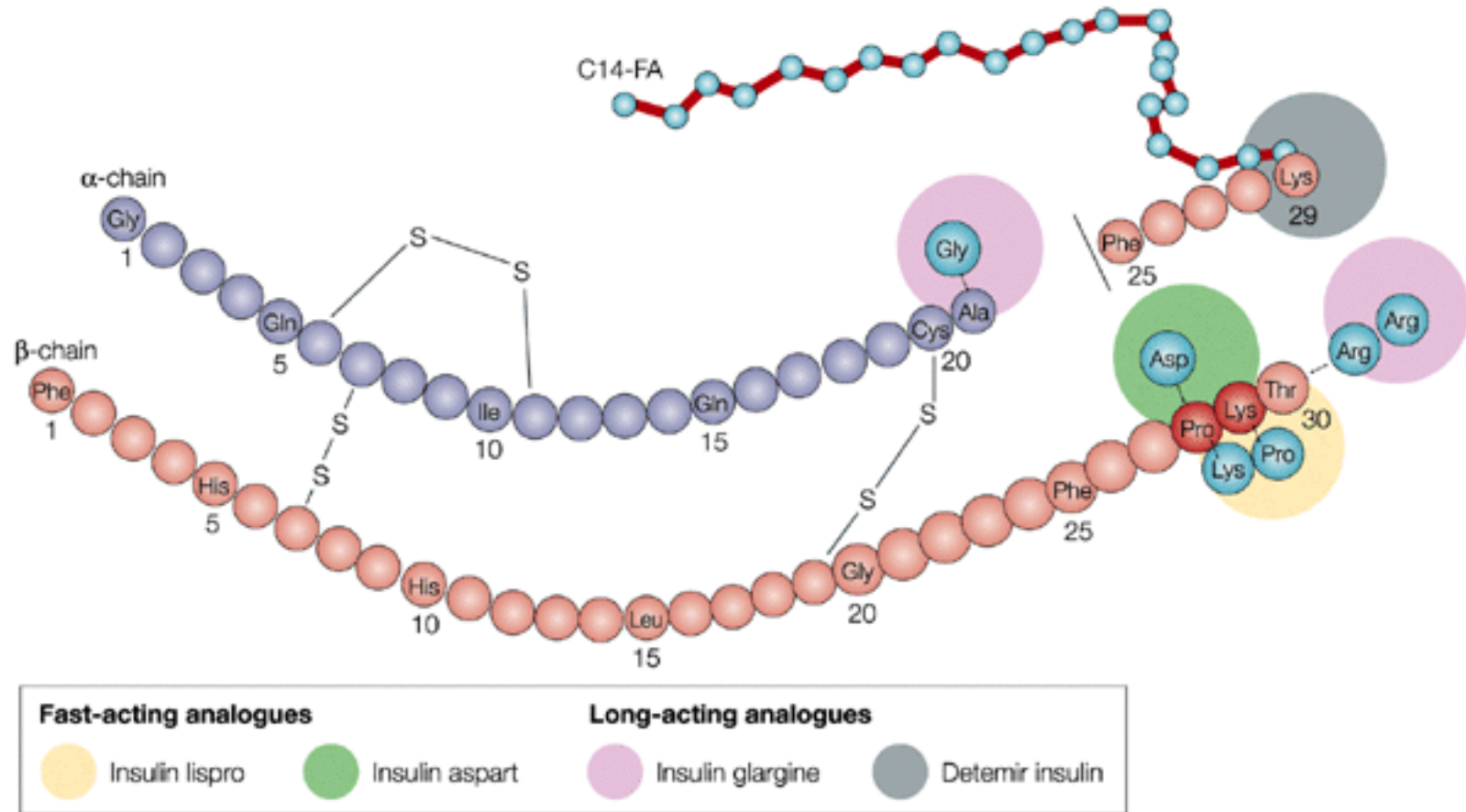


← Lysine / proline lispro

Aspart



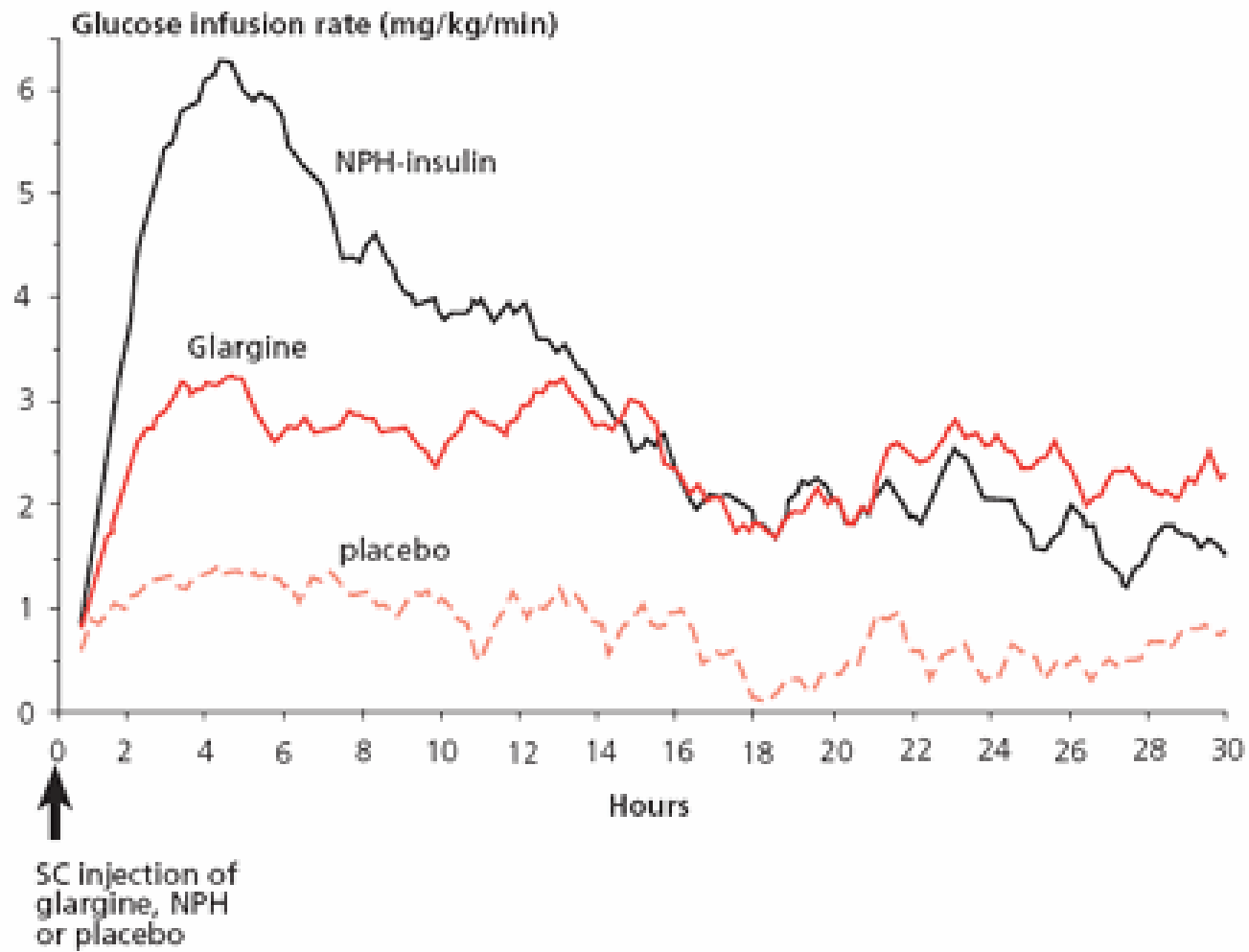
Newer insulin analogues



Example: Insulin Glargine

- Clear solution in pH of 4
 - Not require mixing before use
- Precipitate in interstitial fluid and dissociate gradually and provide peakless basal insulin supply to the circulation
 - Can be given once daily at any time of the day

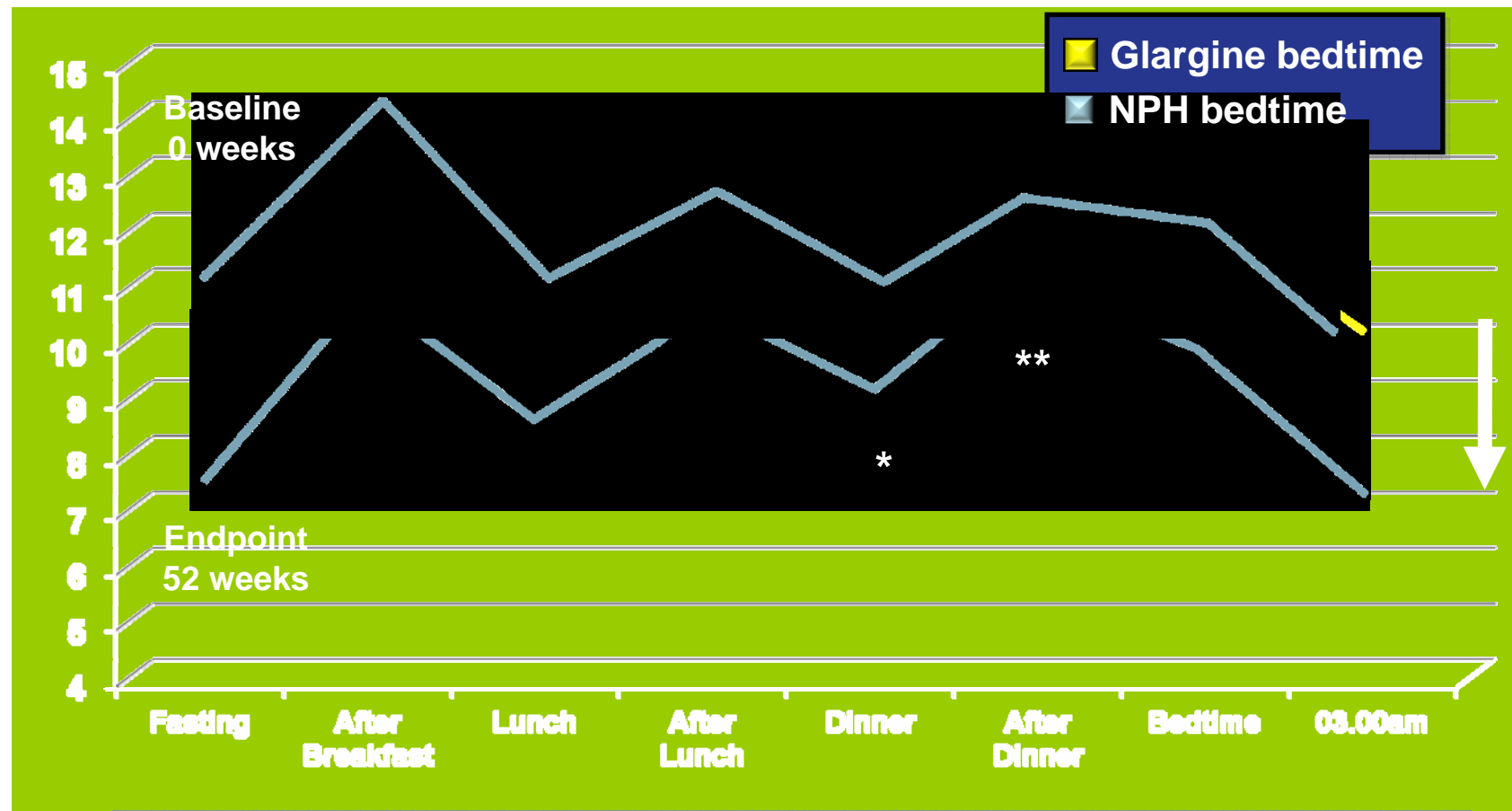
<i>Insulin</i>	<i>onset</i>	<i>peak</i>	<i>duration</i>
NPH	1-4 hrs	8-12 hrs	12-20 hrs
Glargine	1-4 hrs	none	24 hrs



Diabetologia 1999;42:(suppl 1); Abstract 880

Insulin glargine effectively lowers 24-hour blood glucose compared with NPH

Lower pre- and post-dinner glucose levels with a lower risk of nocturnal hypoglycemia

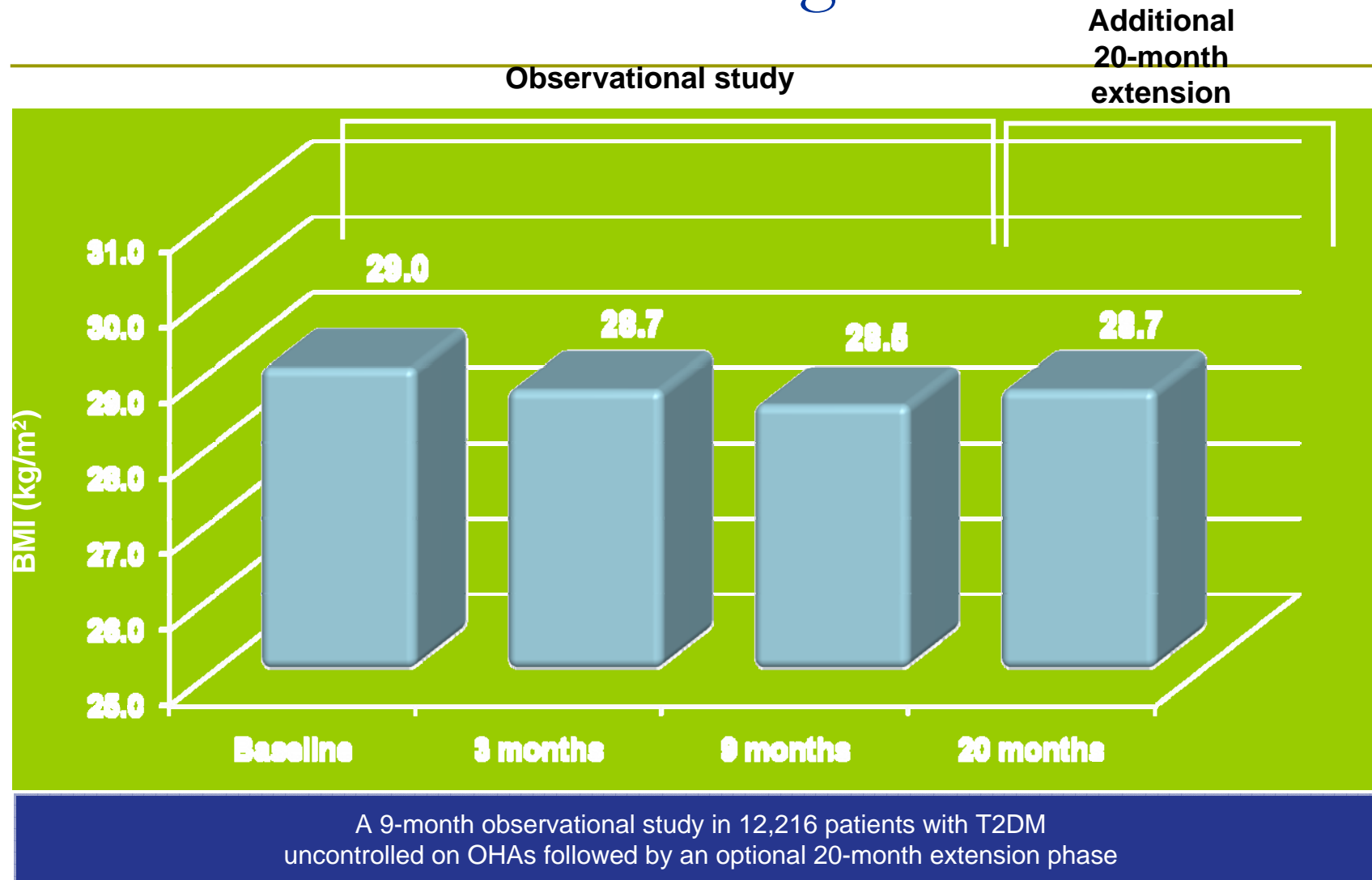


52-week study comparing insulin glargine with NPH in 426 insulin-naïve patients with T2DM

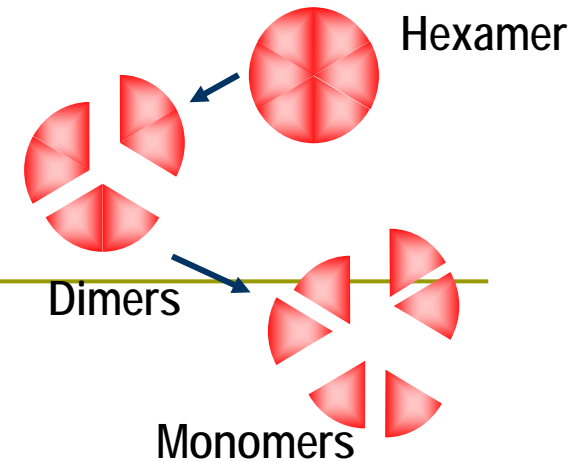
* $p < 0.035$ and ** $p = 0.0094$ between treatments

1. Yki-Jarvinen H *et al. Diabetes Care* 2000;23:1130–1136

Insulin glargine treatment for 2.5 years has a neutral effect on weight

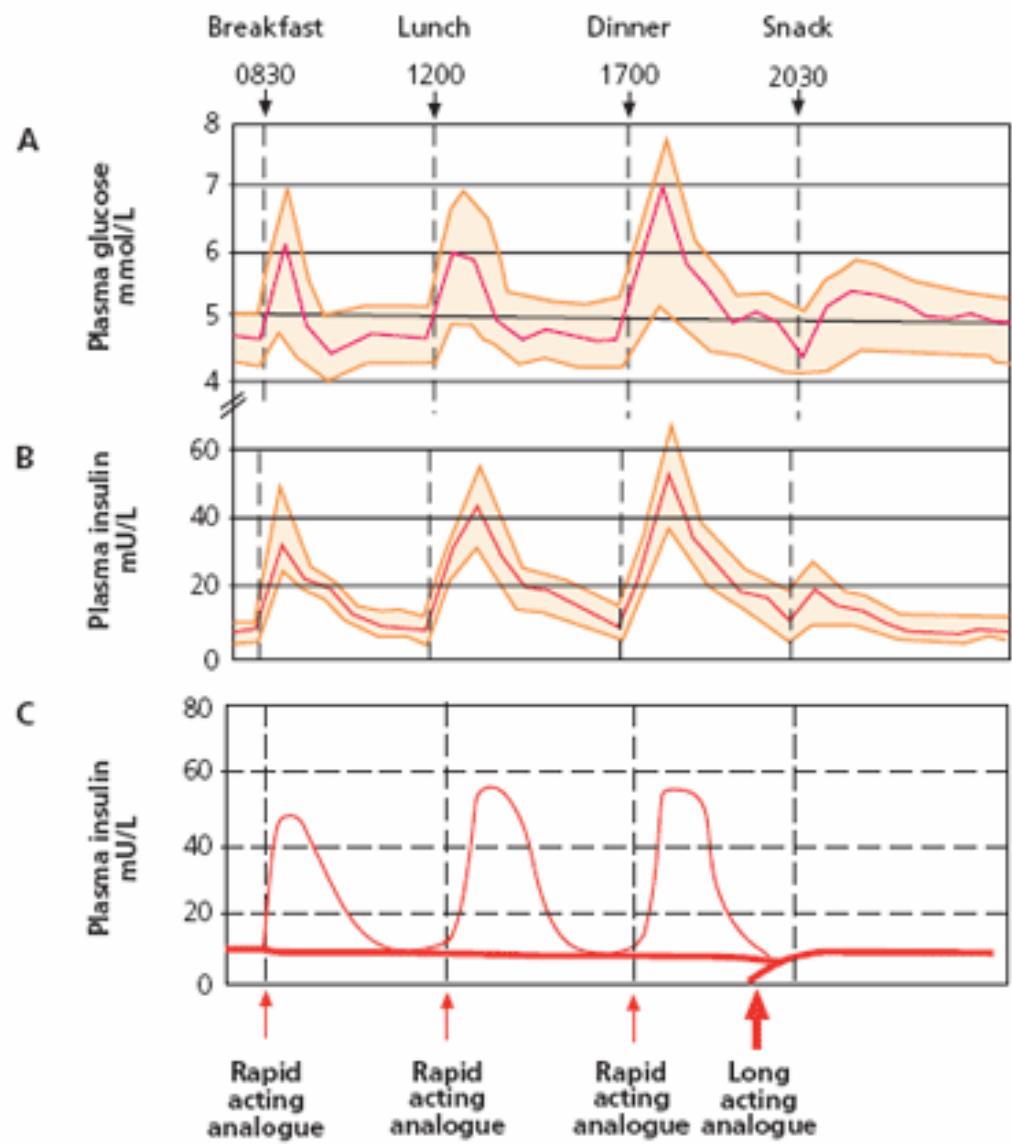


Example: Insulin Lispro



- Amino acid alternation prevent the formation of insulin hexamer seen with regular insulin
- Rapid absorption from subcutaneous sites
 - Can be given before, during or after the meal to target postprandial hyperglycemia
 - Potential more severe hypoglycemia

<i>Insulin</i>	<i>onset</i>	<i>peak</i>	<i>duration</i>
Regular	30-60 mins	2-4 hrs	6-8 hrs
Lispro	5-15 mins	1-2 hrs	3.5-5 hrs



Summary

- Intervention of type 2 DM should be early and intensive
- Combination of OHA and basal insulin is a well-validated therapy
- Insulin therapy should fit patient's lifestyle
- Newer insulin analogues and delivery systems may provide effective and user-friendly treatment
- Side effects of insulin
 - Weight gain
 - Hypoglycemia (*home H'stix monitoring, patient information*)

FAQ: Why does patient refuse insulin injection?

- [我個病係唔係好嚴重 ?]
 - Emphasize the natural progression rather than treatment / patient failure
 - More complications is more serious than insulin injection
- [我好怕痛呀 !]
 - Pain usually less than expected
- [打針好唔方便。]
 - Simple regimen in elderly
 - Penfill
- [我唔識打過啲。]
 - DM nurse / insulin clinic