Individualising Insulin Regimens: Premixed or basal plus/bolus?

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Turkey, April 2015

International Diabetes Federation

Centre of Health Professional Education

THE UNIVERSITY OF SYDNEY

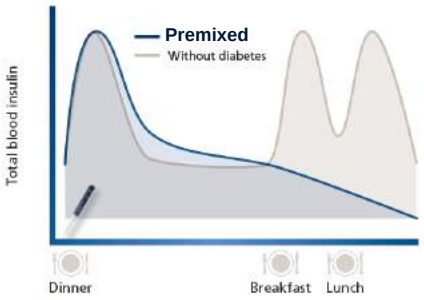
Royal Prince Alfred Hospital Diabetes Centre

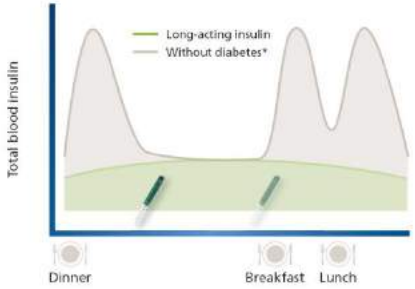
Optimising insulin therapy

Choose a progressive treatment for a progressive disease

Once-daily Premixed at dinner time

- One injection
- One insulin
- One device





Long-acting insulins

- One or two injections†
- One insulins
- One devices

Twice-daily Premixed at breakfast and dinner time

- Two injections
- One insulin
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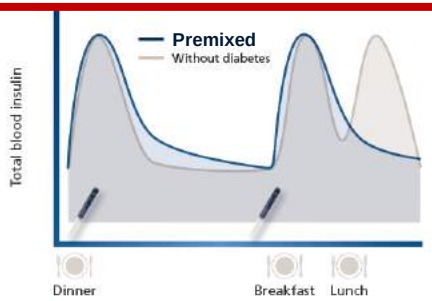

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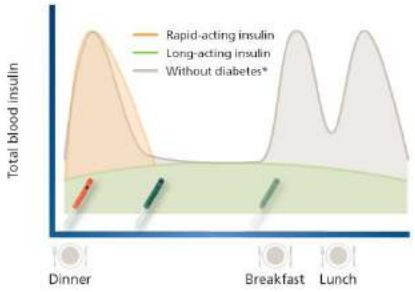

Long-acting and rapid-acting insulins

- Two or three injections†
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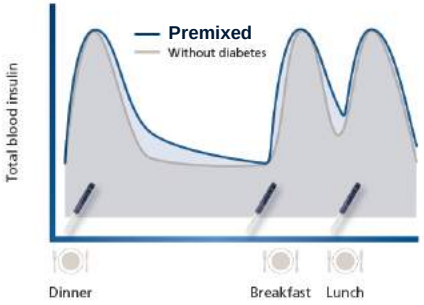
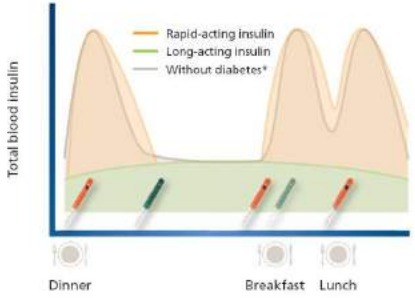
- Two devices

Thrice-daily Premixed at breakfast, lunch and dinner time

- Three injections
- One insulin
- One device





Long-acting and rapid-acting insulins

- Four or five injections†
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Ilag LL et al. (2007). Clin Ther 29: 1254-70

- Systematic review, once daily injections
- **Premixed analogues** vs **basal analogues**

	Premixed analogues	Basal analogues
HbA1c	Better vs ➔	
PPG	Better vs ➔	
"Overall control"	Better vs ➔	

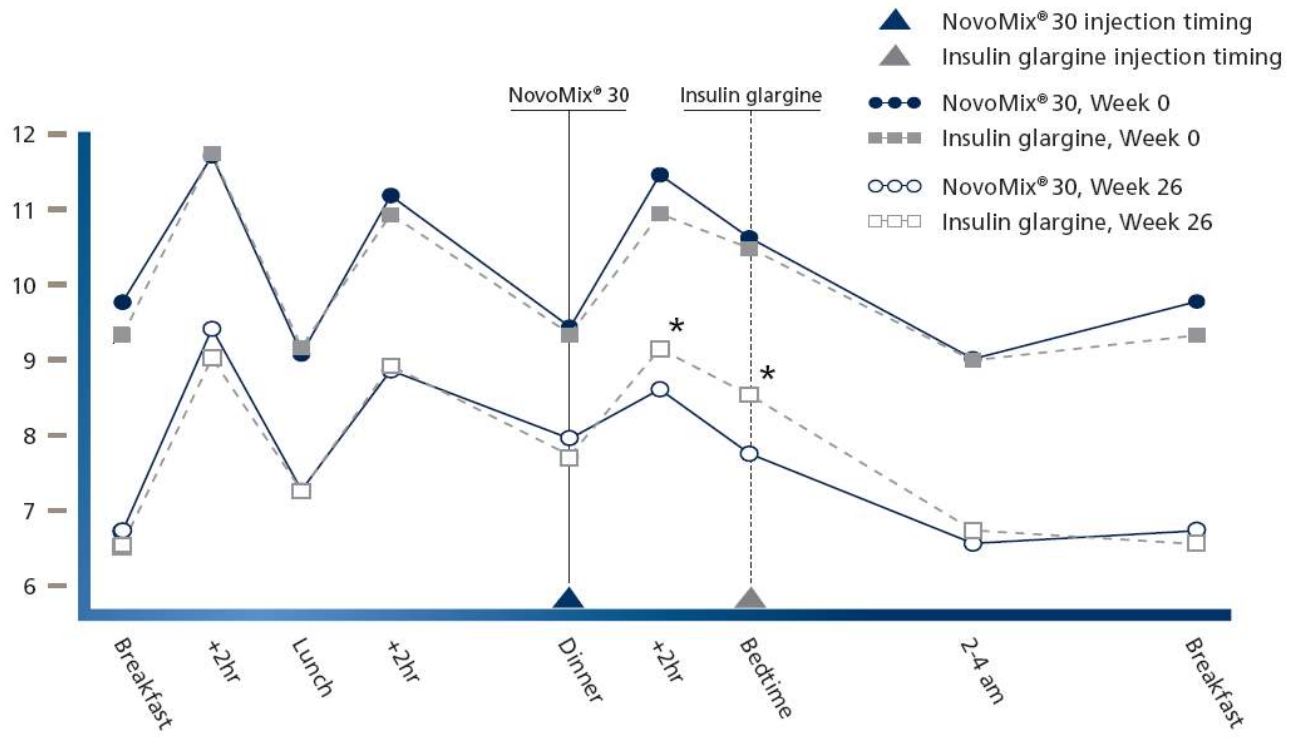
…but none of these were RCTs

OnceMix study

Strojek et al. 2009, Curr Med Res and Op. 25:2887-2894.

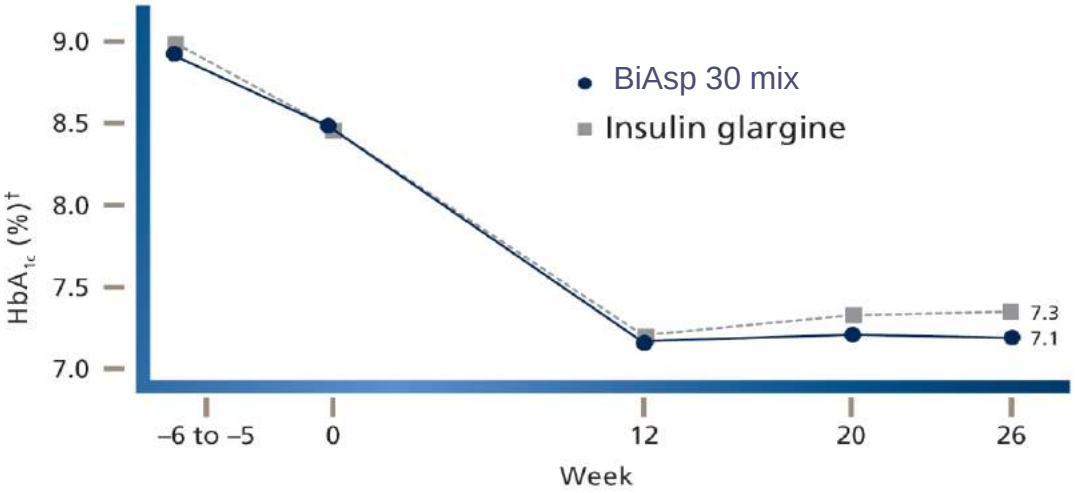
- Double blinded RCT, multi-centre
- **BIAsp30 premix** vs **glargine**
  - Poorly controlled on Metformin and SU
  - Insulin naïve
  - OHAs continued during trial
    - 26 weeks
    - n = 569

OnceMix



Estimated mean difference in favour of NovoMix® 30 was -0.52 mmol/L (95% CI [-1.02;-0.03]) post-evening meal and -0.78 mmol/L (95% CI [-1.25;-0.31]) at bedtime.

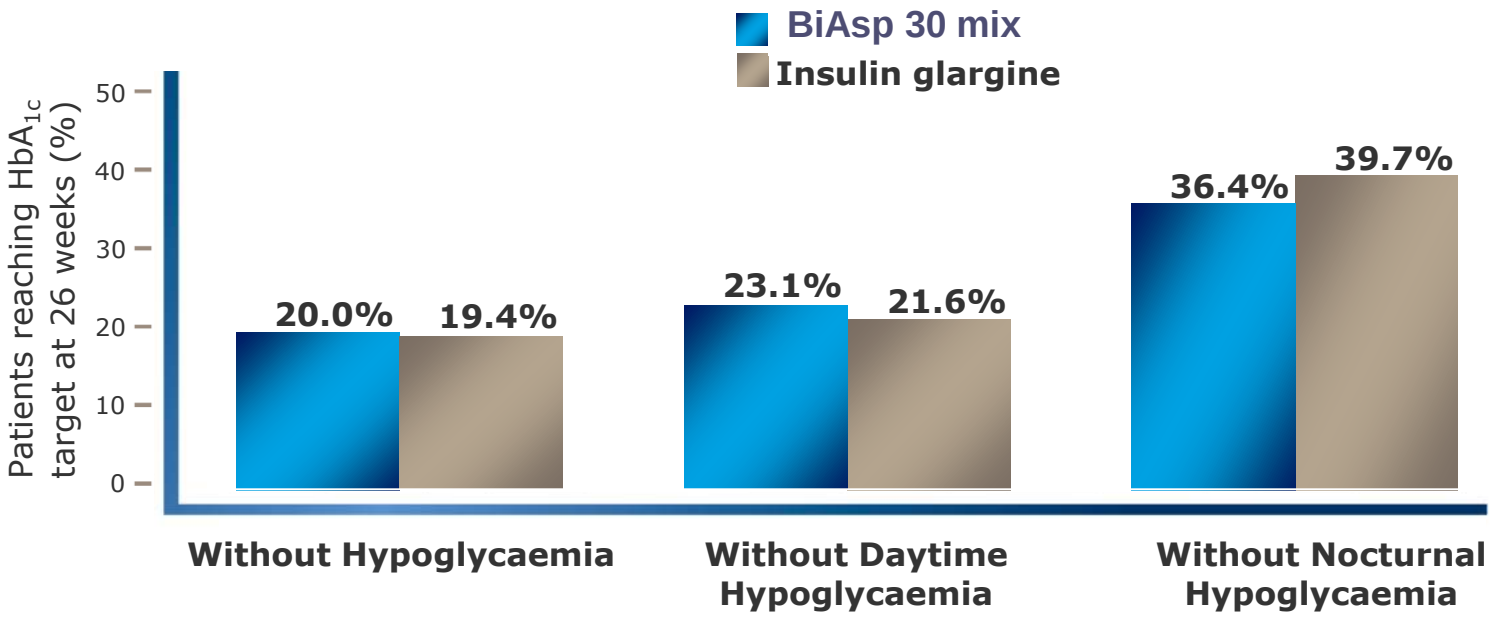
OnceMix HbA1c result



- Similar increases in mean body weight of ~1.7kg
- Mean dose was similar at 0.32 U/kg (aspart 30 mix) and 0.29 U/kg (insulin glargine)

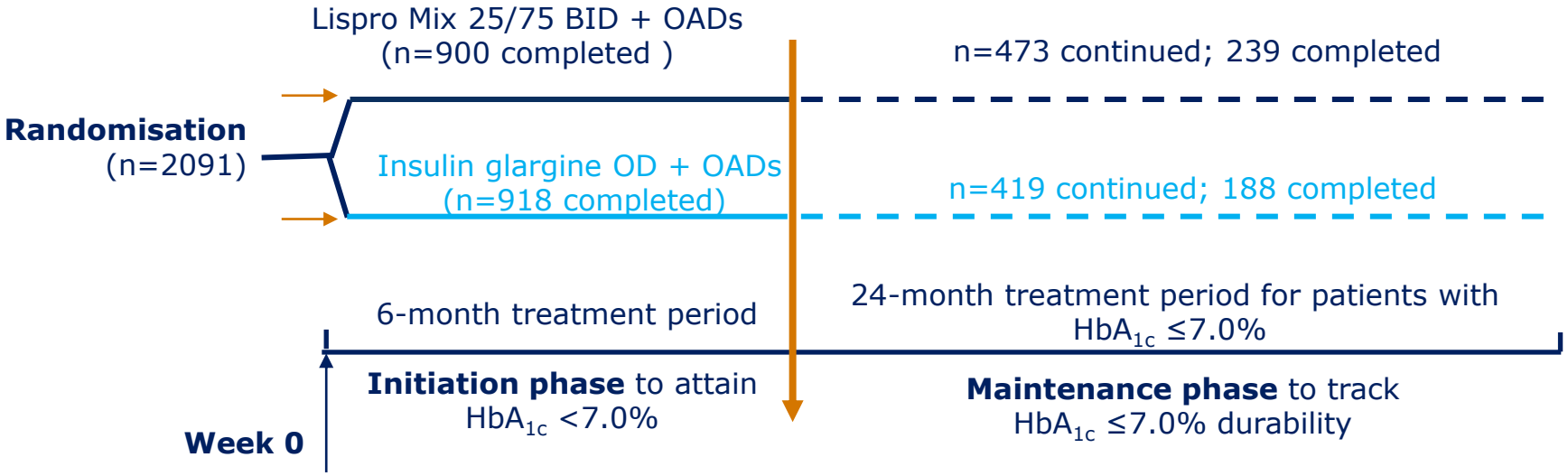
BiAsp 30 mix vs Glargine -0.16%, p=0.029

OnceMix – hypos



DURABLE: study design

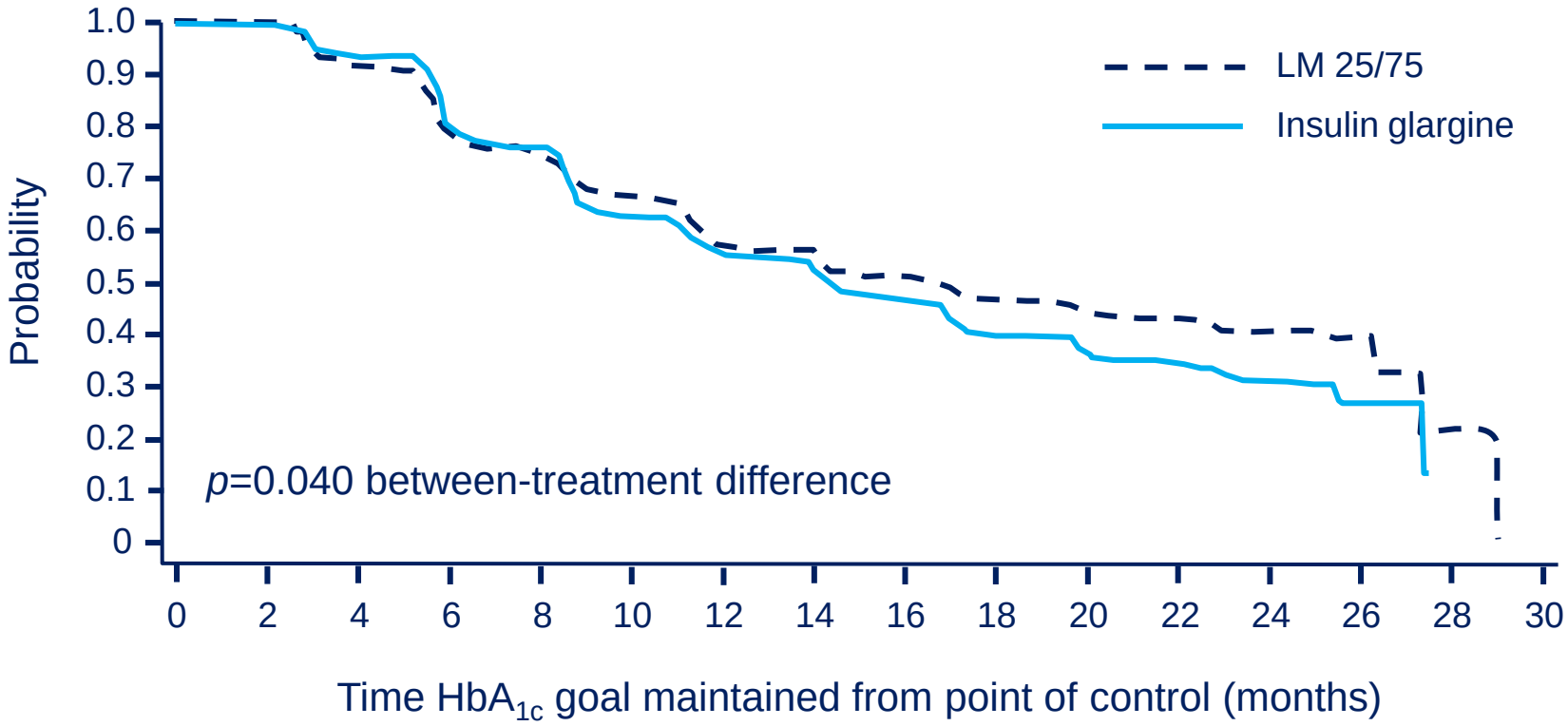
- Insulin-naïve patients with type 2 diabetes inadequately controlled with OADs
- HbA_{1c} >7.0%
- ≥2 OADs >90 days
- 30–80 years of age



LM, lispro mix; OD, once daily

Buse *et al. Diabetes Care* 2011;34(2):249–55

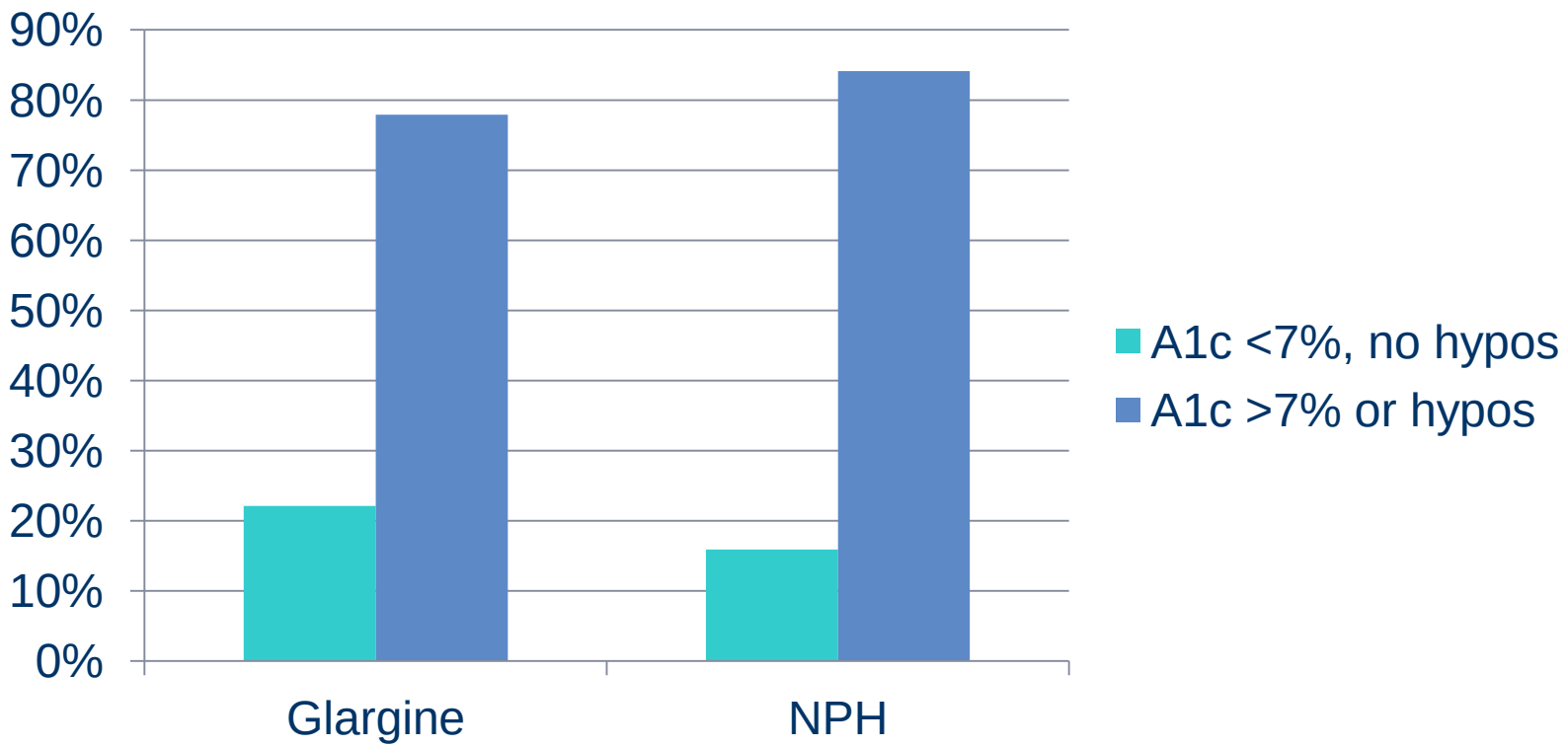
DURABLE: time to failure to maintain HbA_{1c} goal



Final daily insulin dose: LM 25/75: 0.45 U/kg; insulin glargine: 0.37 U/kg; $p<0.001$

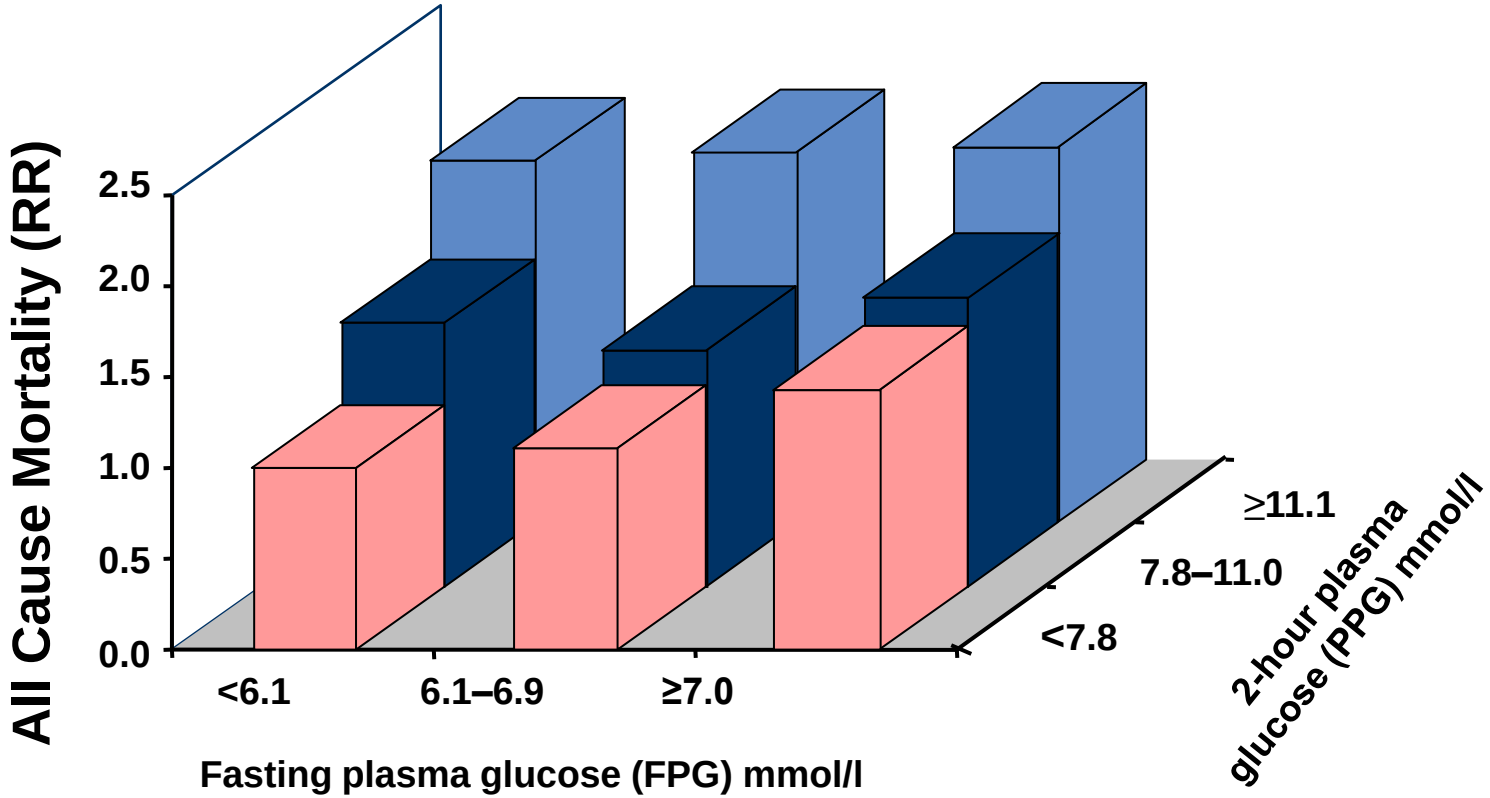
Buse *et al. Diabetes Care* 2011;34(2):249–55

“Treat-to-target” using basal insulin only



Riddle MC et al, Diab Care, 2003: 3080-86

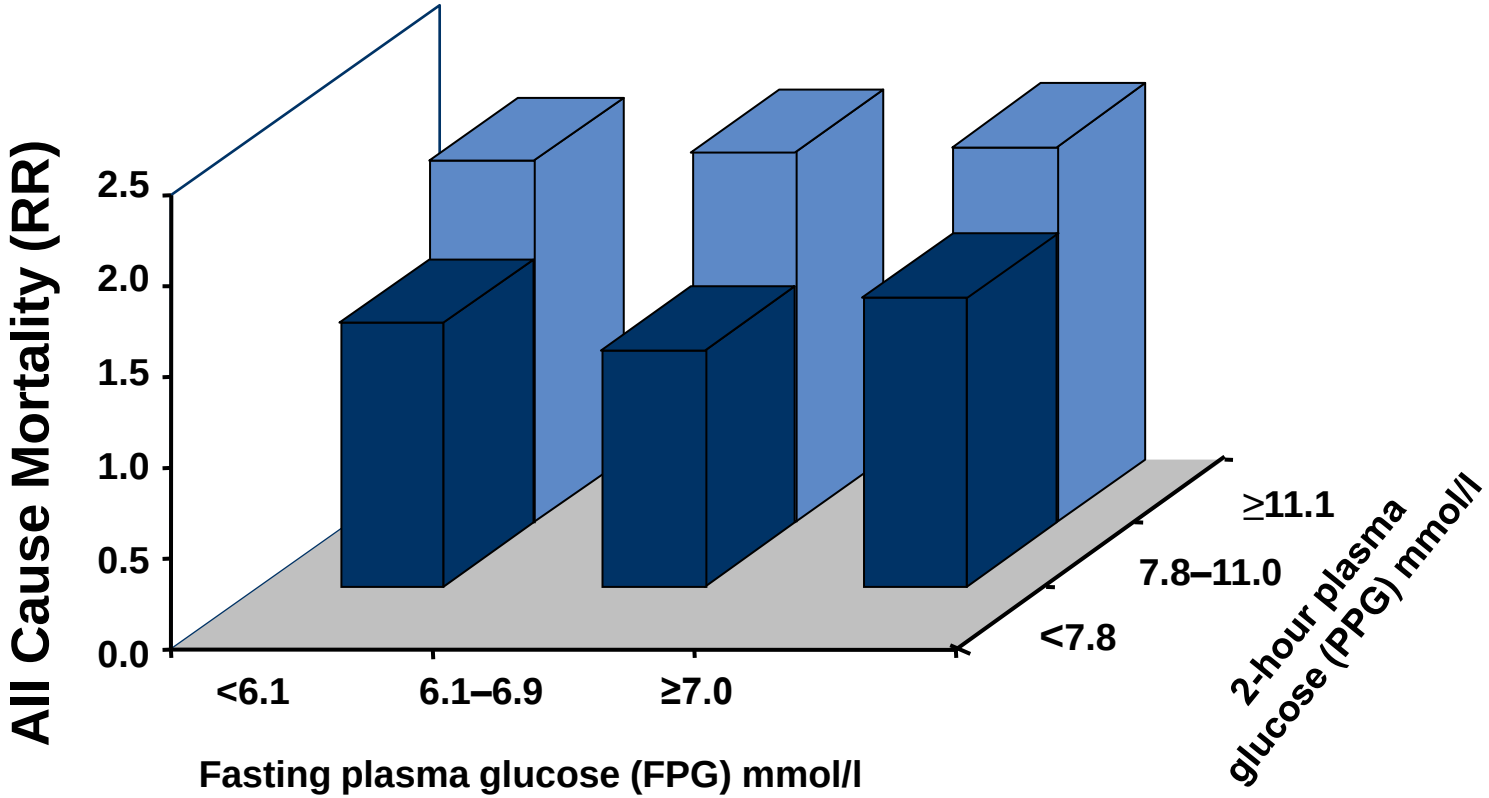
DECODE study



Mortality risk according to **2-hour glucose (PPG)** is **independent of FPG**

Lancet 1999;354:617

DECODE study



Mortality risk due to **FPG** becomes **non-significant** after **adjusting for 2-hour glucose (PPG)**

Lancet 1999;354:617

Optimising insulin therapy

Choose a progressive treatment for a progressive disease

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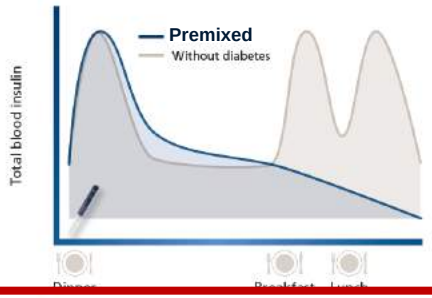

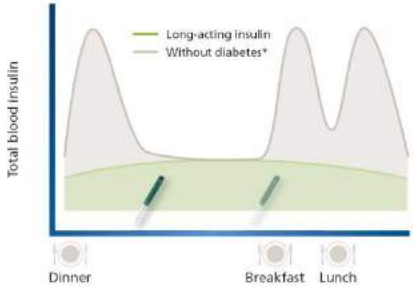

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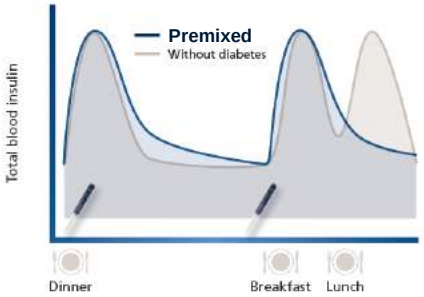

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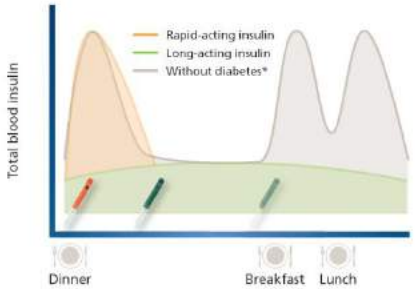

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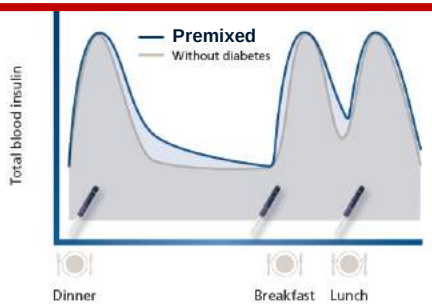

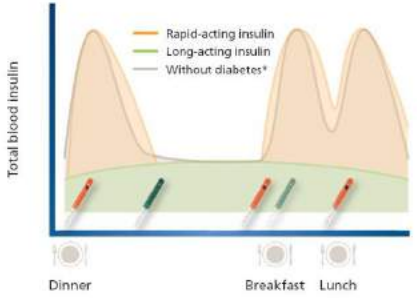

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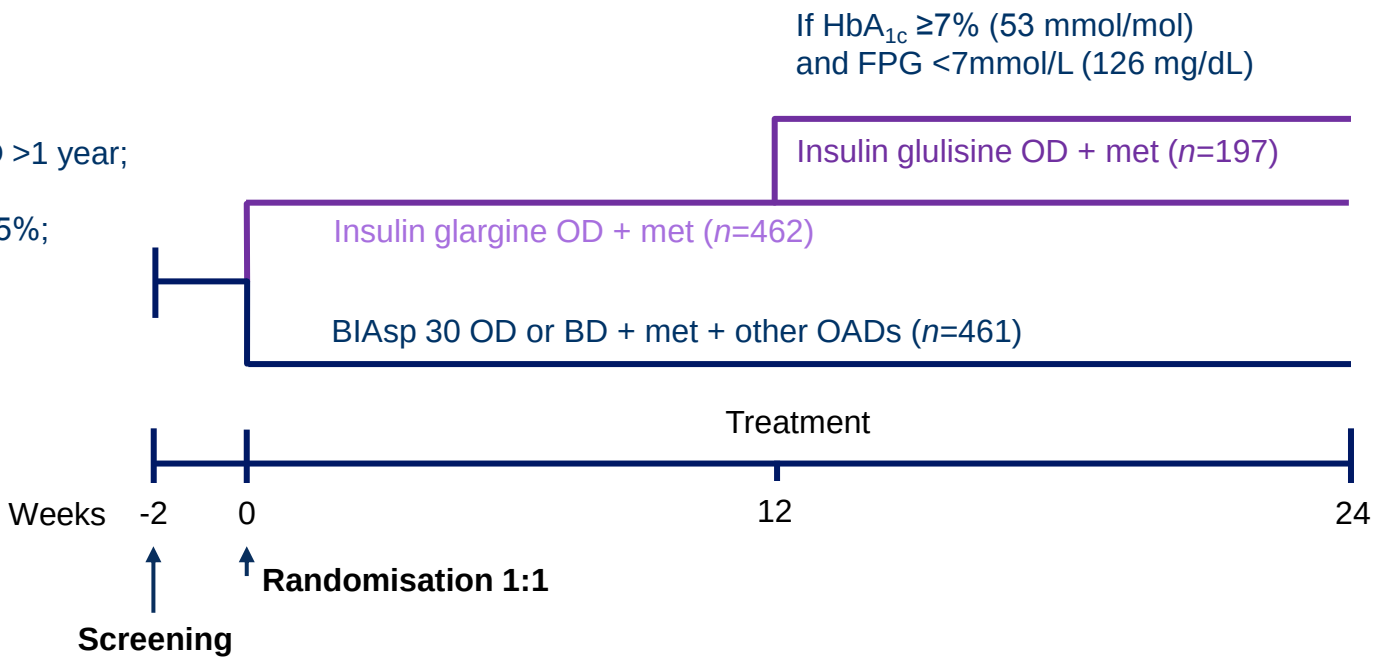
Galapagos study: Premix vs Basal / Basal-Plus

Phase 4, randomised, multi-centre, international, comparative open-label trial

n=934 patients with T2D >1 year;
Uncontrolled on OADs;
HbA_{1c} ≥7.0% and ≤10.5%;
Age ≥35 years;
BMI ≤40 kg/m^2

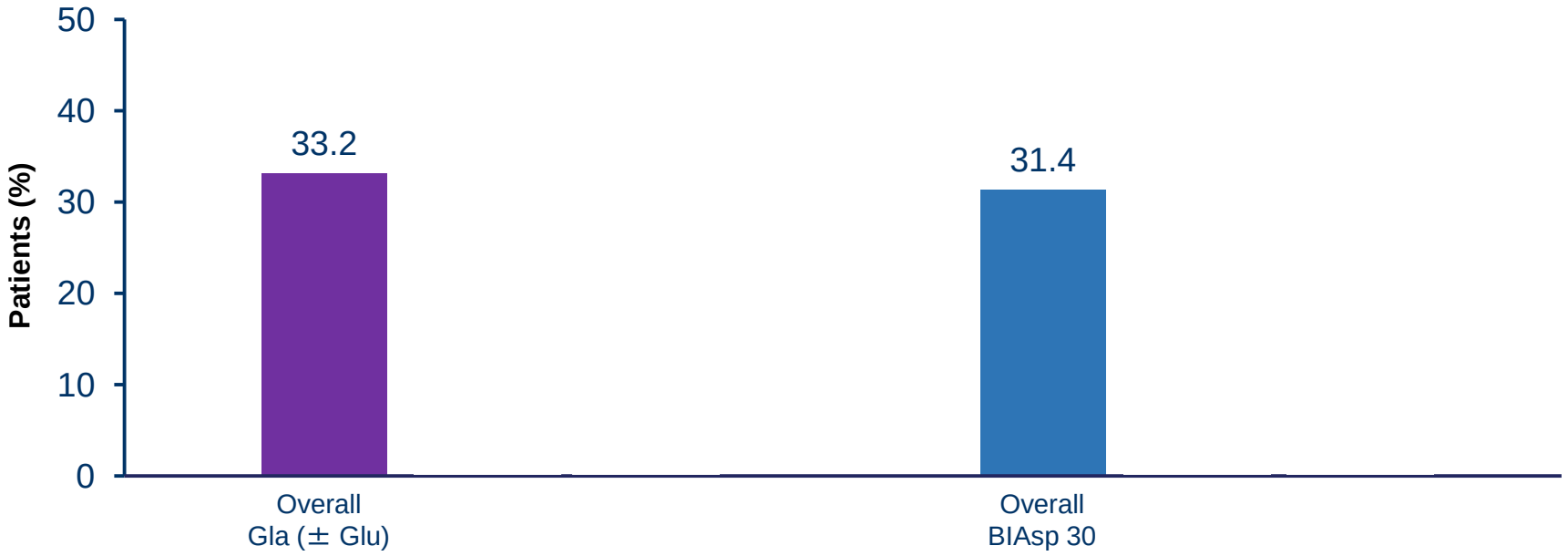


Met, metformin; SU, sulphonylurea, DPP-4, dipeptidylpeptidase-4

Aschner *et al. Diabetes* 2013;62(Suppl. 1):948-P

Galapagos study: key results

- Patients achieving HbA_{1c} <7% (53 mmol/mol) with no symptomatic hypoglycaemia at EOT, by overall treatment group and number of injections

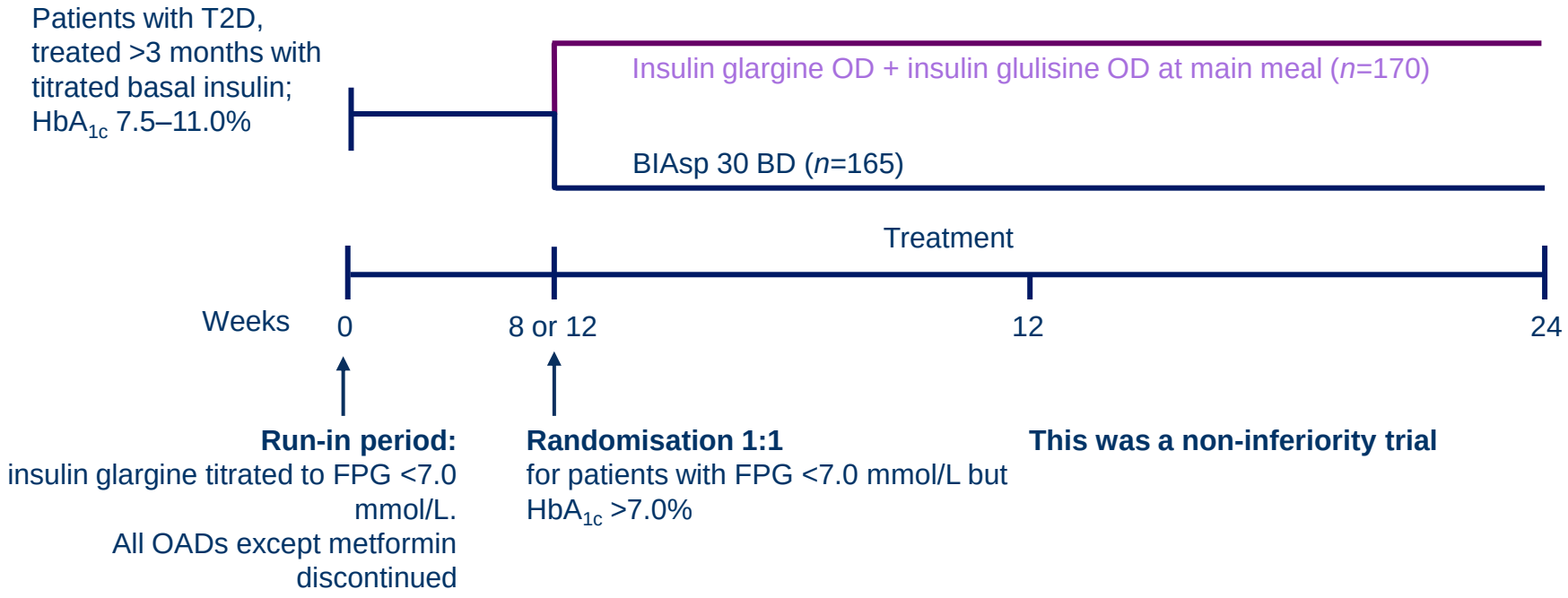


There was <u>no significant difference</u> between the two groups (overall *p*=0.56)

EOT, end of trial; Gla, insulin glargine; Glu, insulin glulisine

Aschner *et al. Diabetes* 2013;62(Suppl. 1):948-P

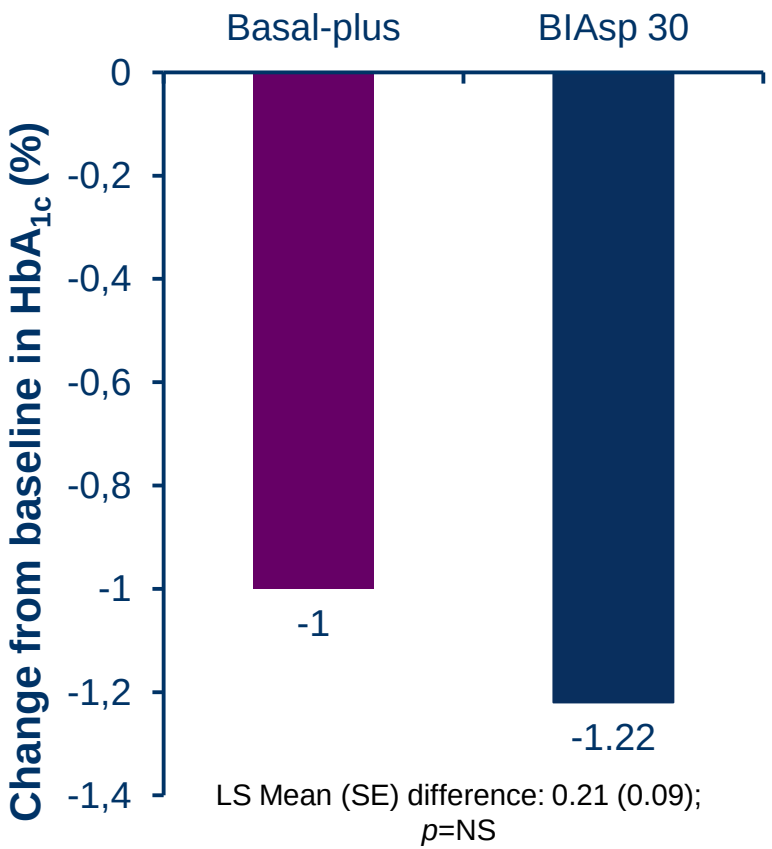
LanScape
Premix vs Basal-Plus



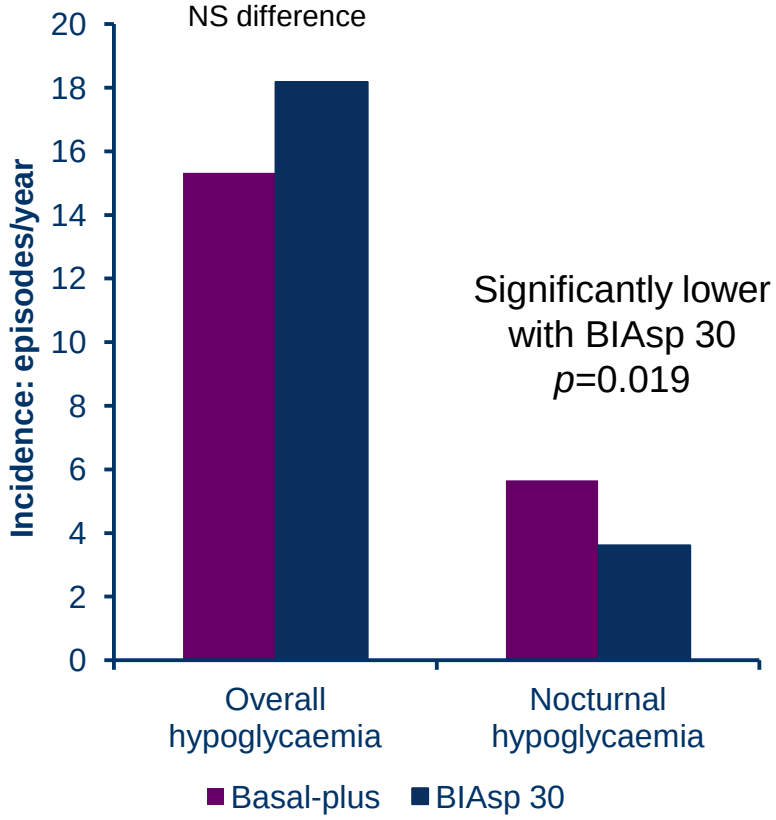
Vora *et al. Diabetes* 2013;62(Suppl. 1B):47-LB

LanScape: key results

Primary endpoint: HbA_{1c}



Hypoglycaemia



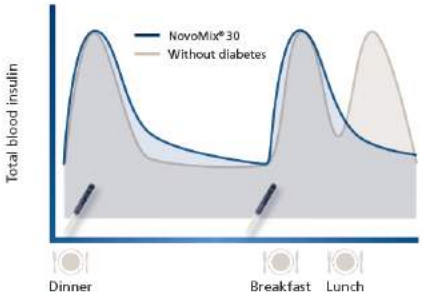
No dose data reported

Vora *et al. Diabetes* 2013;62(Suppl. 1B):47-LB

Why not just go for Basal Bolus? After all, it is “the best”, right?

Twice-daily NovoMix® 30 at breakfast and dinner time

- Two injections
  - One insulin
  - One device



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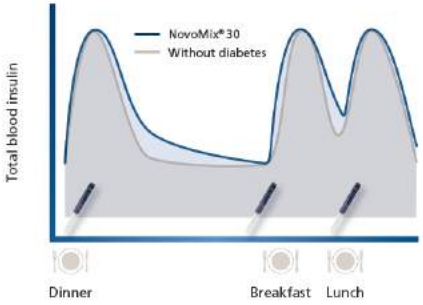

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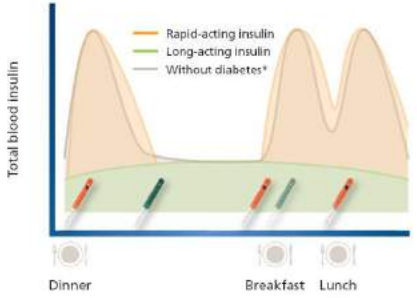

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The 1-2-3 Study Intensifying with Premixed

ORIGINAL ARTICLE

doi: 10.1111/j.1463-1326.2005.00563.x

Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study)

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[2]Endocrine Research Specialists, Ogden, UT, USA
[3]Internal Medicine Associates Research Center, Omaha, NE, USA
[4]Endocrine and Diabetes Associates, Dallas, TX, USA
[5]Novo Nordisk, Princeton, NJ, USA
[6]Milwaukee Medical Clinic, Advanced Healthcare, Milwaukee, WI, USA

Aim: This observational study in patients with type 2 diabetes failing oral agent therapy with or without basal insulin was conducted to assess whether addition and self-titration of biphasic insulin aspart 70/30 (BIAsp 30) could achieve American Association of Clinical Endocrinologists (AACE)/International Diabetes Federation (IDF) and American Diabetes Association (ADA) glycemic targets (HbA_{1c} ≤6.5 and <7%).

Methods: Enrolled patients (n = 100, HbA_{1c} ≥7.5 and ≤10%) were ≥18 years of age, had diabetes ≥12 months and had received a stable antidiabetic regimen for at least 3 months [minimum of two oral antidiabetic drugs (OADs) or at least one OAD plus once-daily basal insulin ≤60 U]. Patients discontinued prior basal insulin and added one injection of BIAsp 30 (12 U or 70–100% of prior basal insulin dose within 15 min of dinner initiation). Patients self-titrated their BIAsp 30 dose with investigator guidance every 3 or 4 days to achieve pre-breakfast fasting blood glucose (FBG) of 80–110 mg/dl. At 16 weeks, a pre-breakfast injection of 6 U of BIAsp 30 was added if week 15 HbA_{1c} exceeded 6.5%; the added dose was titrated to achieve pre-dinner BG of 80–110 mg/dl. After an additional 16 weeks, 3 U of pre-lunch BIAsp 30 was added if HbA_{1c} exceeded 6.5%. This added dose was adjusted based on 2-h post-lunch BG to achieve postprandial glucose of 100–140 mg/dl. Subjects achieving an HbA_{1c} ≤6.5% at 15 and 31 weeks completed the study at weeks 16 and 32 respectively.

Results: Addition of once-daily BIAsp 30 before dinner enabled 21% of the patients to achieve AACE and IDF targets (HbA_{1c} ≤6.5%) and 41% to achieve ADA targets (HbA_{1c} <7%). With two daily injections of BIAsp 30, these glycaemic goals were achieved by 52 and 70% of subjects. With three daily BIAsp 30 injections, 60% of patients achieved HbA_{1c} ≤6.5%, and 77% achieved HbA_{1c} <7.0%.

Conclusions: This clinical trial demonstrates that initiation of once-daily BIAsp 30 to type 2 diabetes patients poorly controlled on various OAD regimens was an effective treatment approach for achieving glycaemic goals. Additional patients safely achieved these goals by increasing the number of BIAsp 30 injections from one to two, and then, if uncontrolled, from two to three doses per day. Eventually, most patients previously uncontrolled on OADs with or without basal insulin were controlled by the addition and vigorous titration of BIAsp 30 to oral agent therapy.

Keywords: BIAsp, insulin initiation, OAD failures, premixed insulin analogue, treatment algorithm

Received 20 September 2005; returned for revision 17 October 2005; revised version accepted 17 October 2005

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E-mail:
agarber@bcm.tmc.edu

Background

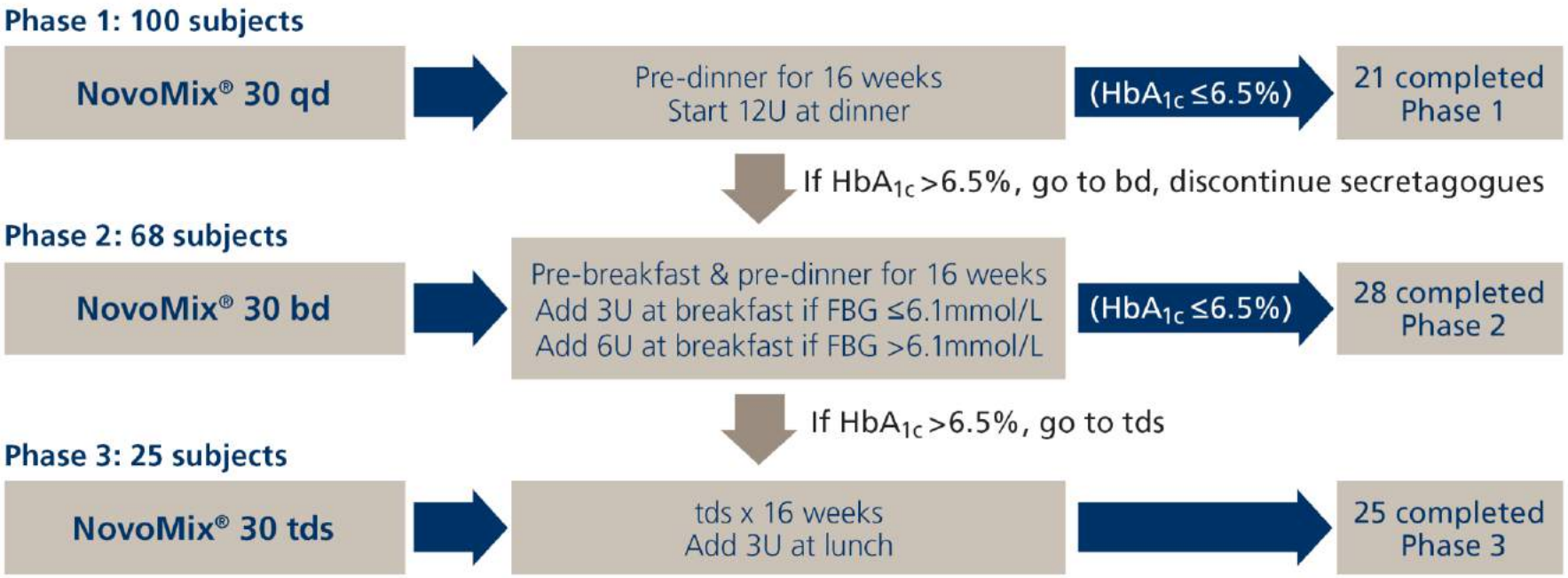
- Failing OADs or basal insulin
- Intensification of BiAsp 30 premix
  - 1x daily → 2x daily → 3x daily
- Will we get HbA_{1c} ≤6.5%?

Garber AJ *et al.* 2006, Diabetes, Obesity & Metabolism 8:58-66.

The 1-2-3 Study

Simple start and intensification to achieve glycaemic targets

Study Design

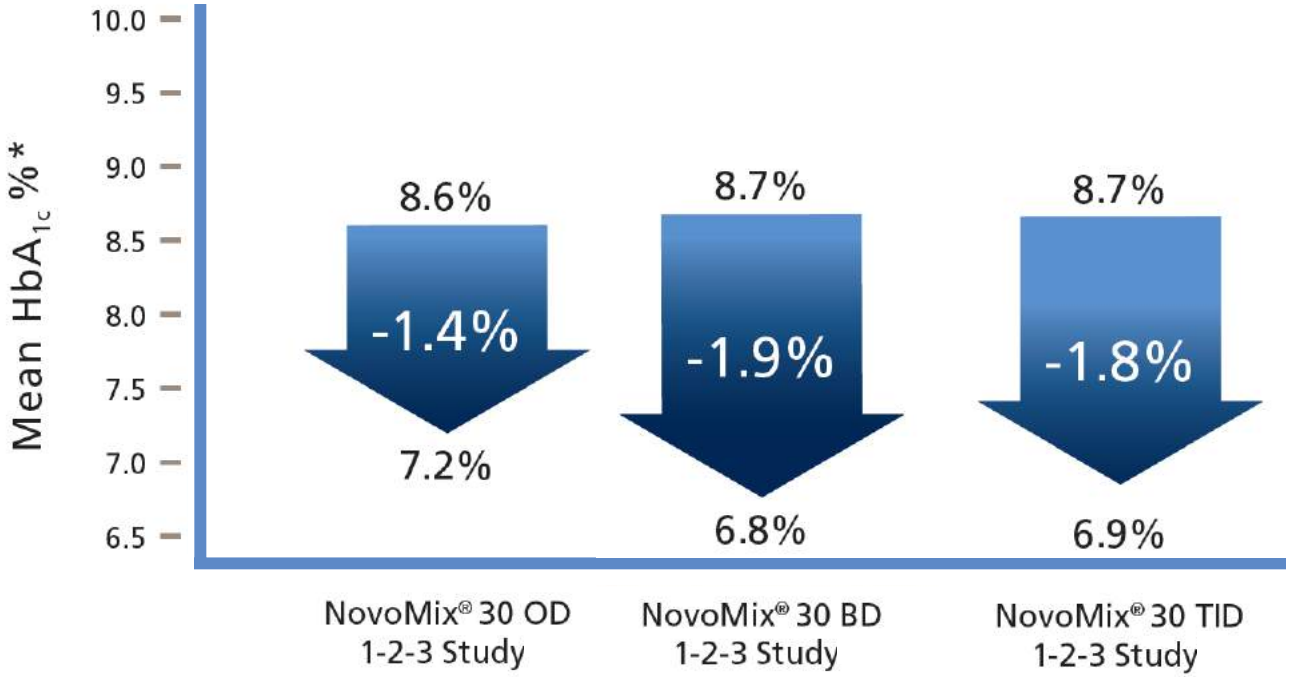


Titrate according to schedule every 3 days. Predetermined dose escalation algorithm designed for patient self–adjustment (qd = once-daily; bd = twice-daily; tds = thrice-daily).

Adapted from Garber AJ *et al*. 2006. 1-2-3 study is a 48-week, single cohort, treat-to-target study in 100 type 2 patients , mean duration of diabetes 11- 12 years.

The 1-2-3 Study

Achieve HbA_{1c} targets with BiAsp 30



		NovoMix® 30 OD 1-2-3 Study	NovoMix® 30 BD 1-2-3 Study	NovoMix® 30 TID 1-2-3 Study
% patients achieving	HbA_{1c} ≤7.0%	41%	70%	77%
	HbA_{1c} ≤6.5%	21%	52%	60%

No patients discontinued because of hypoglycaemia or weight gain at any time during the study.

1-2-3 Conclusion

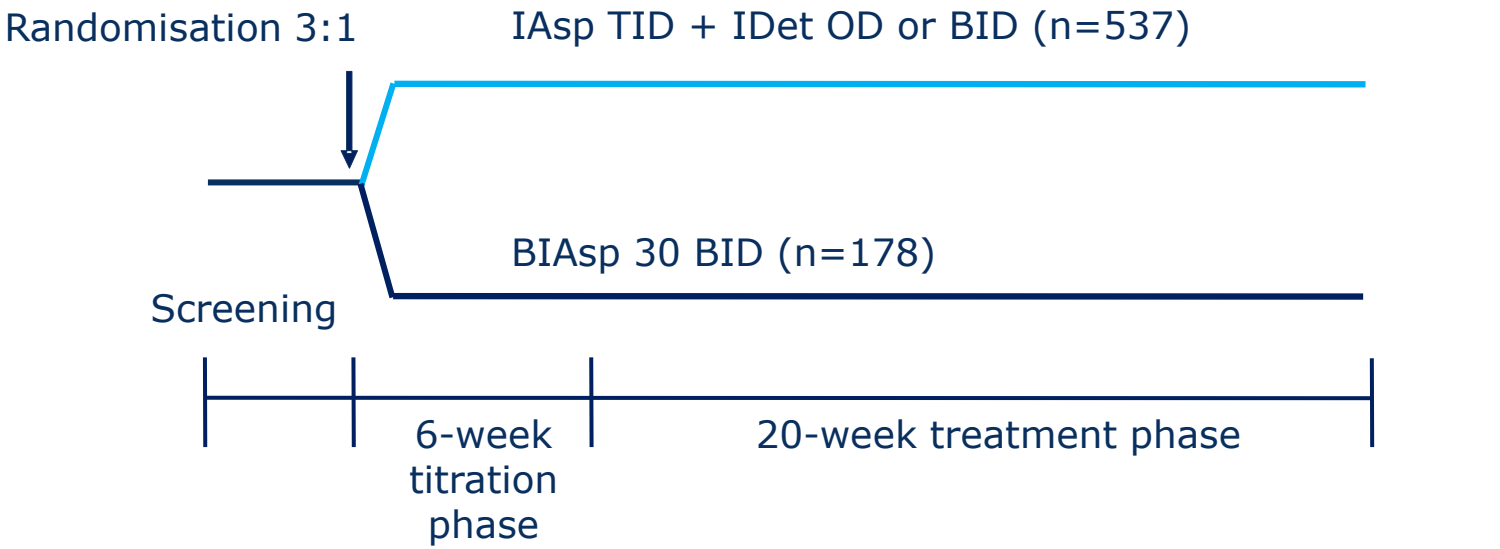
- Starting once-daily BiAsp 30 was an effective treatment approach for achieving glycaemic goals.

- Also, can safely achieved HbA1c goals by intensifying treatment
  - from 1 to 2 injections
  - and then 2 to 3 BiAsp 30 doses/day

PREFER
Premixed vs. basal–bolus

Inclusion criteria:

- One or two OADs without insulin
- One or two OADs with OD NPH/insulin glargine
- 7%≤ HbA1c ≤12%



OADs were discontinued in both arms

IAsp, insulin aspart; IDet, insulin detemir; NPH, neutral protamine Hagedorn

Liebl *et al. Diabetes Obes Metab* 2009;11:45–52

PREFER Study
Liebl A, et al (2008), Diabetes Obes Metab

	Premixed analogues	Basal bolus
HbA1c - insulin naïve	Same vs ➔	
Minor hypos	Same vs ➔	
Major hypos	0%	1%

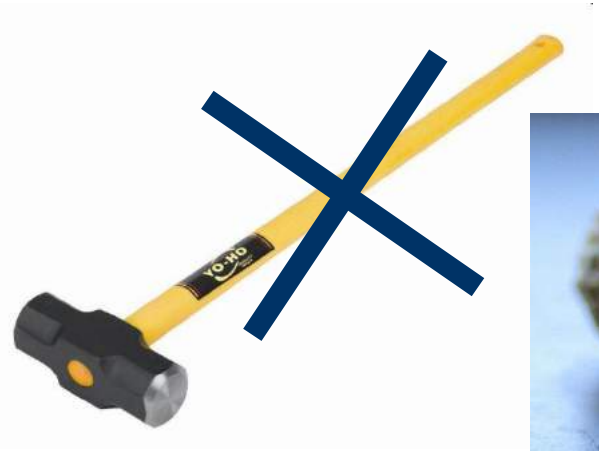
- No advantage to starting with basal-bolus in insulin naive patients

Ilag LL et al. (2007)
Clin Ther 29: 1254-70

- **Meta-analysis**
- **Premixed analogues** vs **basal bolus**

	Premixed analogues	Basal bolus
HbA1c - insulin naïve	Better vs →	
HbA1c - prior insulin Rx		← Better vs
Minor hypos	Better vs →	

Using the right tool for the job



- Basal-bolus is very effective, but very complex
- Benefits only if patient not controlled on a simpler insulin regimen
- No clear benefit to start off on basal-bolus (insulin naïve)

Premix vs Basal / Basal-plus How much difference is there?

- "**No single insulin or regimen was best on all endpoints**. Furthermore, while the differences may have reached statistical significance, they were **often of limited clinical relevance**."[1]
- "The authors of this **study found inconclusive evidence**...GPs know their patients well and are in a good position to **select the appropriate regimen for their patients**"[2]

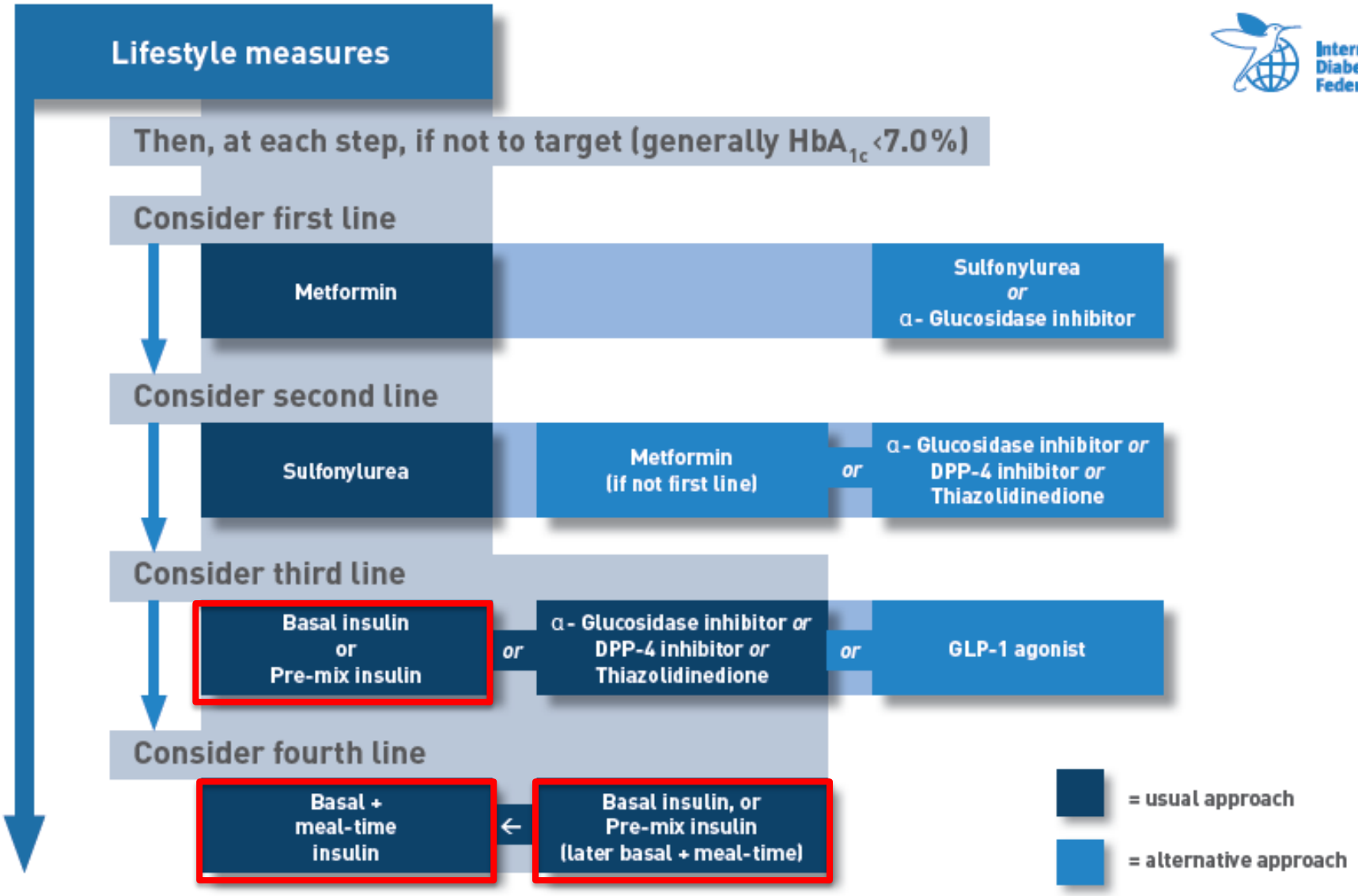
1. Wu T, et al. IDF WPR, Singapore Nov 2014
2. Mosenzon O, Raz I. *Diabetes Care* 2013;36 Suppl 2:S212–8

Better Glucose Control

The most important thing is to take the first step:

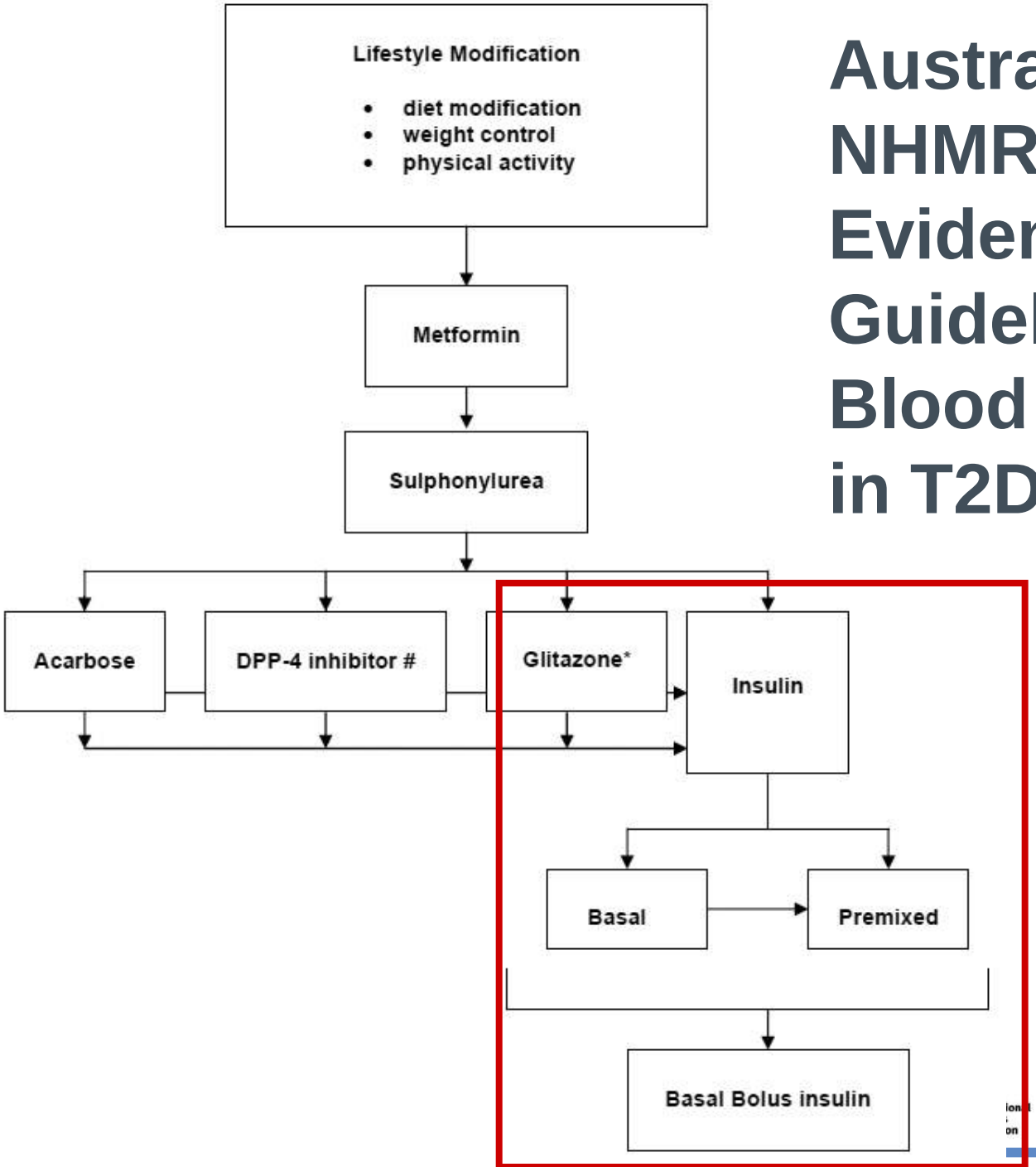
Start insulin

IDF Treatment Algorithm for People with Type 2 Diabetes

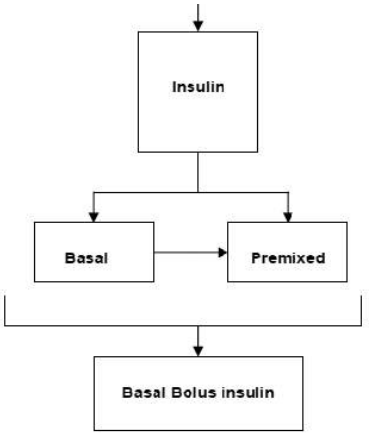


IDF Global Guideline for Type 2 Diabetes. http://www.idf.org/global-guideline-type-2-diabetes-2012

Australian NHMRC, National Evidence Based Guideline for Blood Glc Control in T2DM, 2012



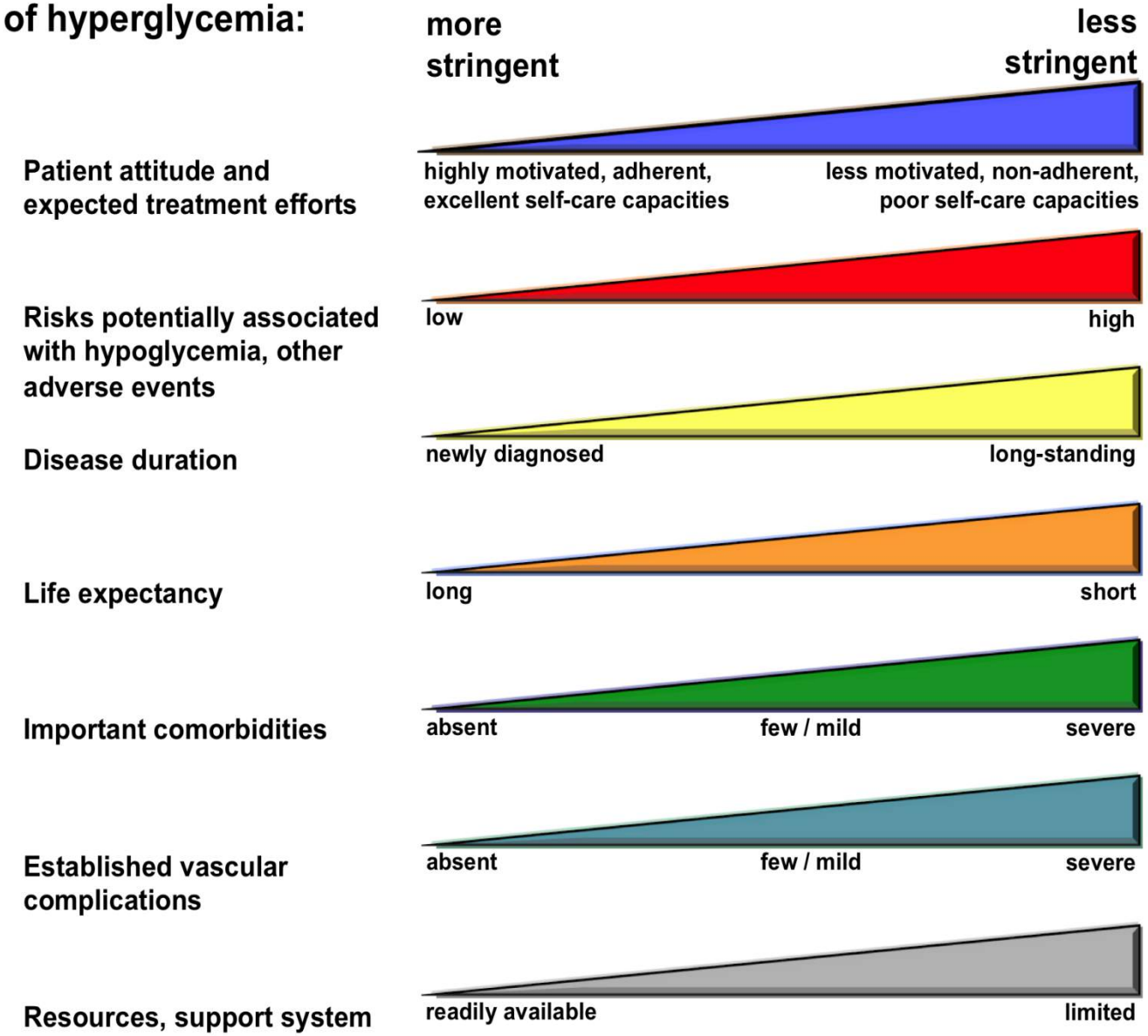
NHMRC guideline, 2012



- **Premixed insulin** and **basal insulin** are **equal first line option** for starting insulin in T2DM (level 1 evidence)
  - Premixed insulin is an intensification option if not controlled on basal insulin + OHA

- If equal first line, which one to choose?
  - Individualise
  - High FPG only → Add daily glargine
  - **High PPG → Add daily premixed**

Approach to management of hyperglycemia:



Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

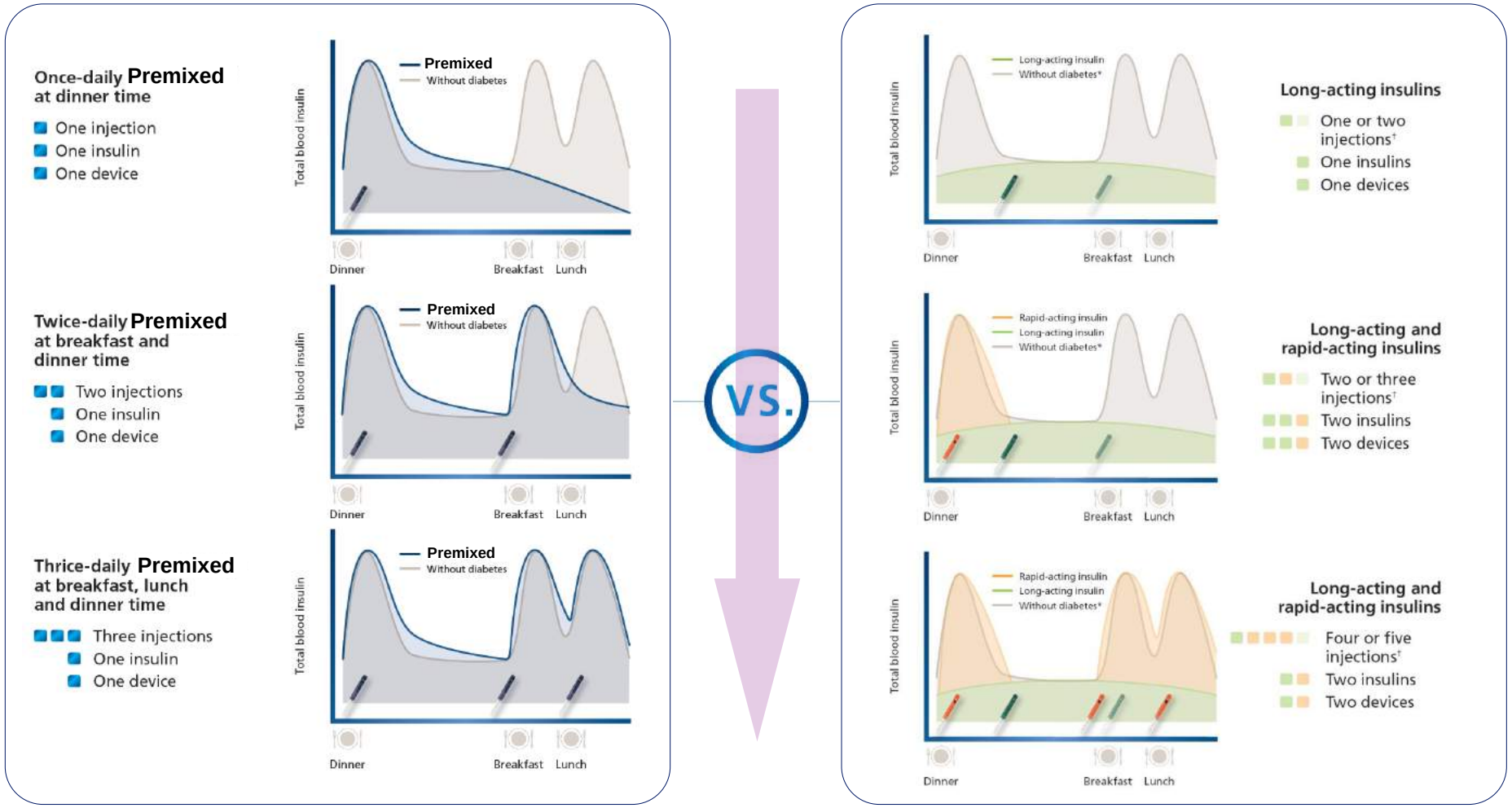
“Practical guidance on the use of premix insulin analogues in initiating, intensifying or switching insulin regimens in T2DM”

- **Ted Wu**, Bryan Betty, Michelle Downie, Manish Khanolkar, Gary Kilov, Brandon Orr-Walker, Gordon Senator, Gregory Fulcher

- Expert panel convened in February 2014
- First published, IDF Western Pacific Forum
  - Singapore, November 2014
- Gives guidance on individualising insulin regimens

Favours basal/ basal-bolus		Favours premix
<1 mmol	What is the post-prandial increment?	**>3 mmol**
Yes	Will the patient likely manage basal-bolus therapy when intensification is needed?	**No**
No	I there a large carbohydrate intake at one or 2 meals?	**Yes**
No	Is the patient's lifestyle predictable (eating pattern, working hours etc)?	**Yes**
OK with more injections	Patient preference regarding number of injections	**Prefers fewer injections**
OK with more frequent	Patient preference regarding SMBG	**Prefers less frequent**
Good	Patient ability to inject (cognitive ability, manual dexterity, need for carer etc)	**Poor**
Favours basal/ basal-bolus		**Favours premix**

Wu T, et al. IDF WPR, Singapore Nov 2014



“Begin as you mean to go on”

Think about which regimen is most suitable for your patient, and start on that regimen

Hospital patients are mostly on Basal-Bolus

- RPA Hospital at forefront of intensive Basal-Bolus insulin for all inpatients needing insulin
- “Triple-B” (basal-bolus-booster) subcutaneous insulin regimen: a pragmatic approach to managing hospital inpatient hyperglycaemia
- **But what happens when the patient is discharged?**

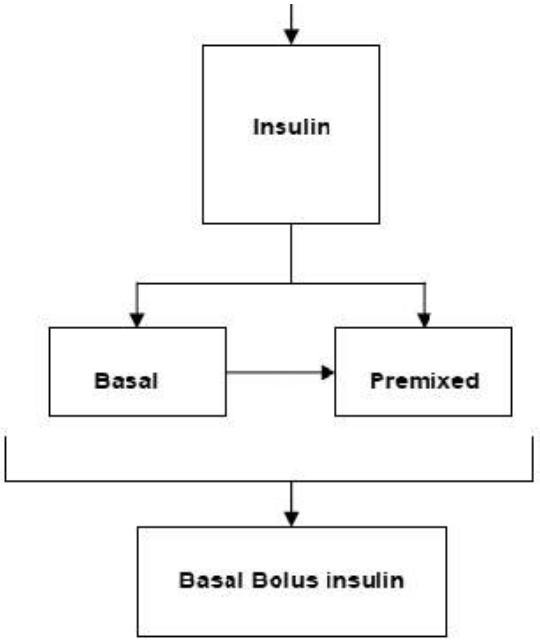
NJ Perera, AJ Harding, MI Constantino, L Molyneaux, M McGill, EL Chua, SM Twigg, GP Ross and DK Yue. Practical Diabetes International 2011 (28): 266–269

Switching from basal-bolus back to premix insulin analogue

- Reduce total daily dose of all insulin by 20–30%
- Then split this to give you the starting dose of premix insulin analogue at breakfast and evening meal
  - 50% AM, 50% PM
  - Unusual meal patterns may lead you to reconsider the initial dose ratio
- Titrate the dose. Adjust the evening meal dose first, followed by the breakfast dose.

Summary

- Modern insulin analogs → **excellent results from both** Premixed and Basal / Basal-Plus regimens



- The key in **individualisation**
  - We **individualise regimens** just as we do HbA_{1c} targets
  - **New guidance** is available to help with individualising

Favours basal/ basal-bolus		Favours premix
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Favours basal/ basal-bolus		Favours premix

Individualising Insulin Regimens: Premixed or basal plus/bolus?

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Turkey, April 2015

International Diabetes Federation

Centre of Health Professional Education

THE UNIVERSITY OF SYDNEY

Royal Prince Alfred Hospital Diabetes Centre