2012-5-12

Insulin treatment strategies by new clinical trials

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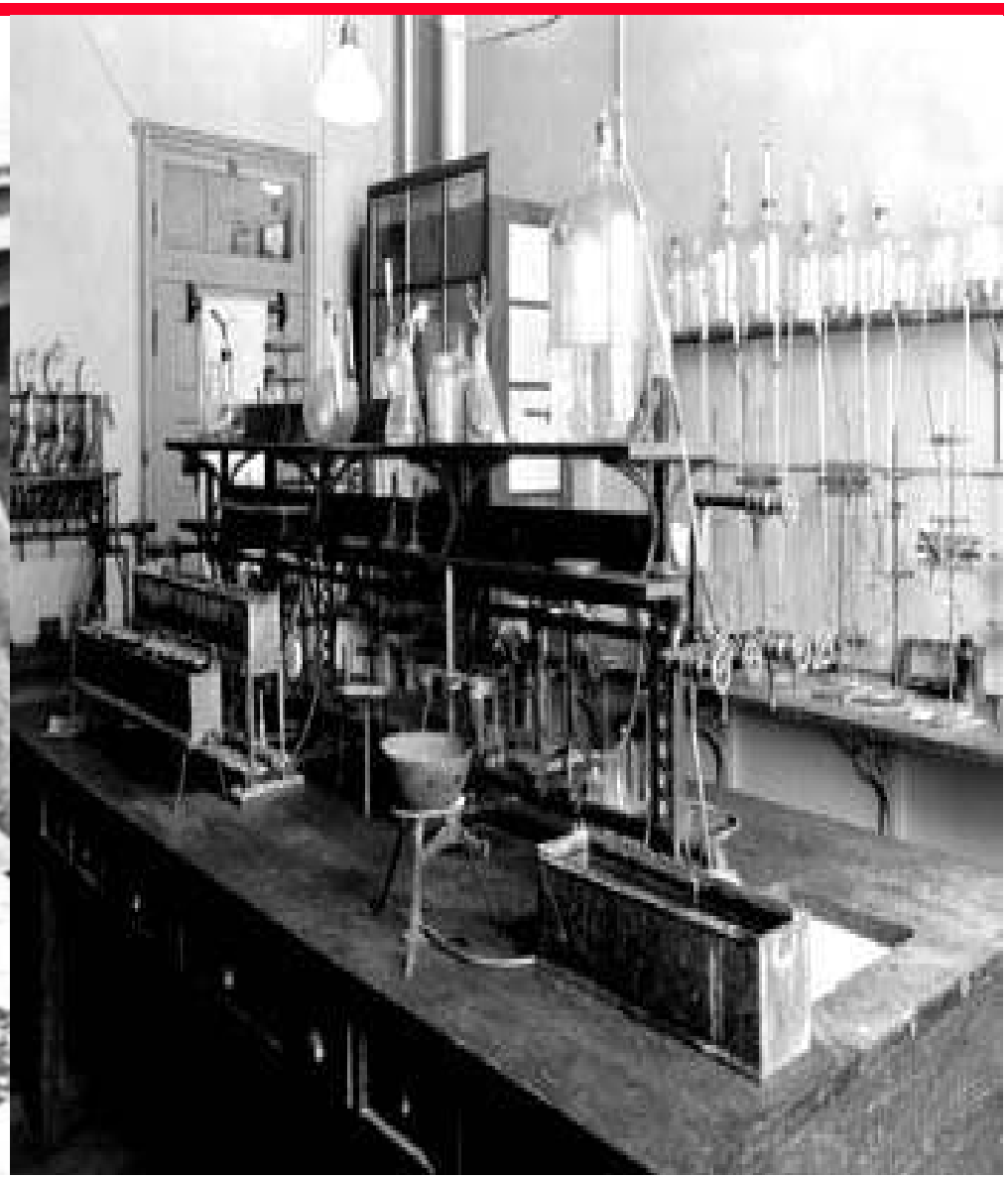
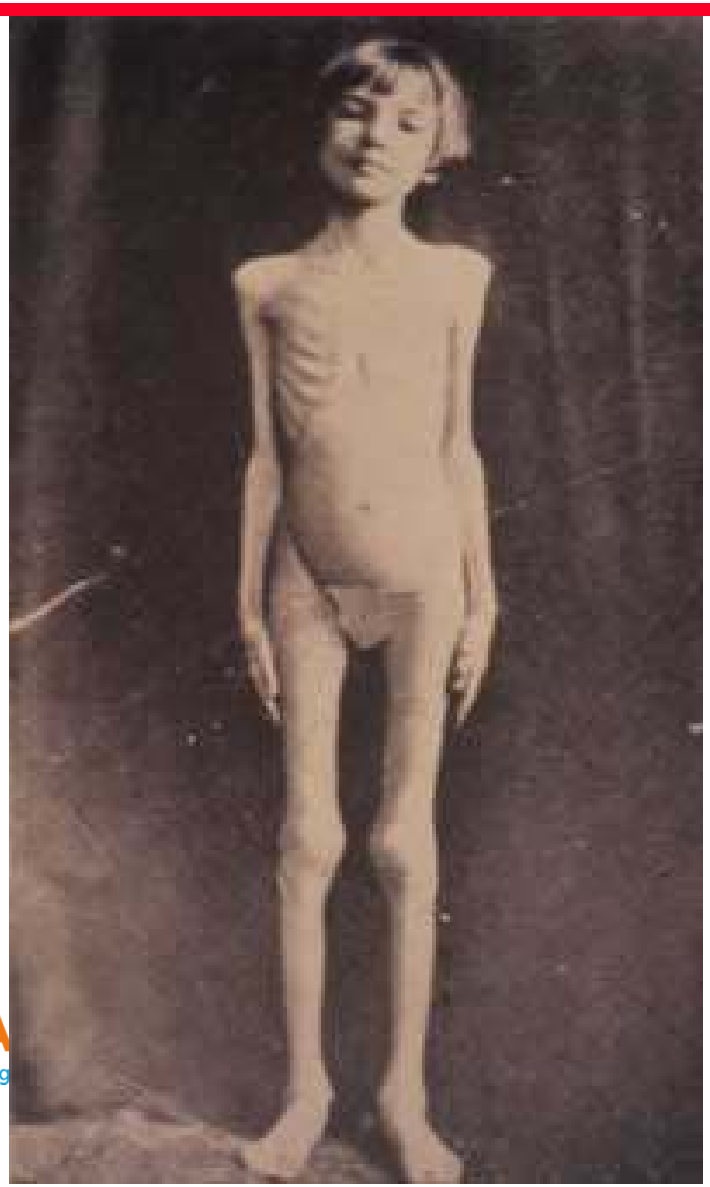
내분비-대사 내과
유 순 집

Banting & Best



One of the first diabetic patients to be treated with insulin extracted



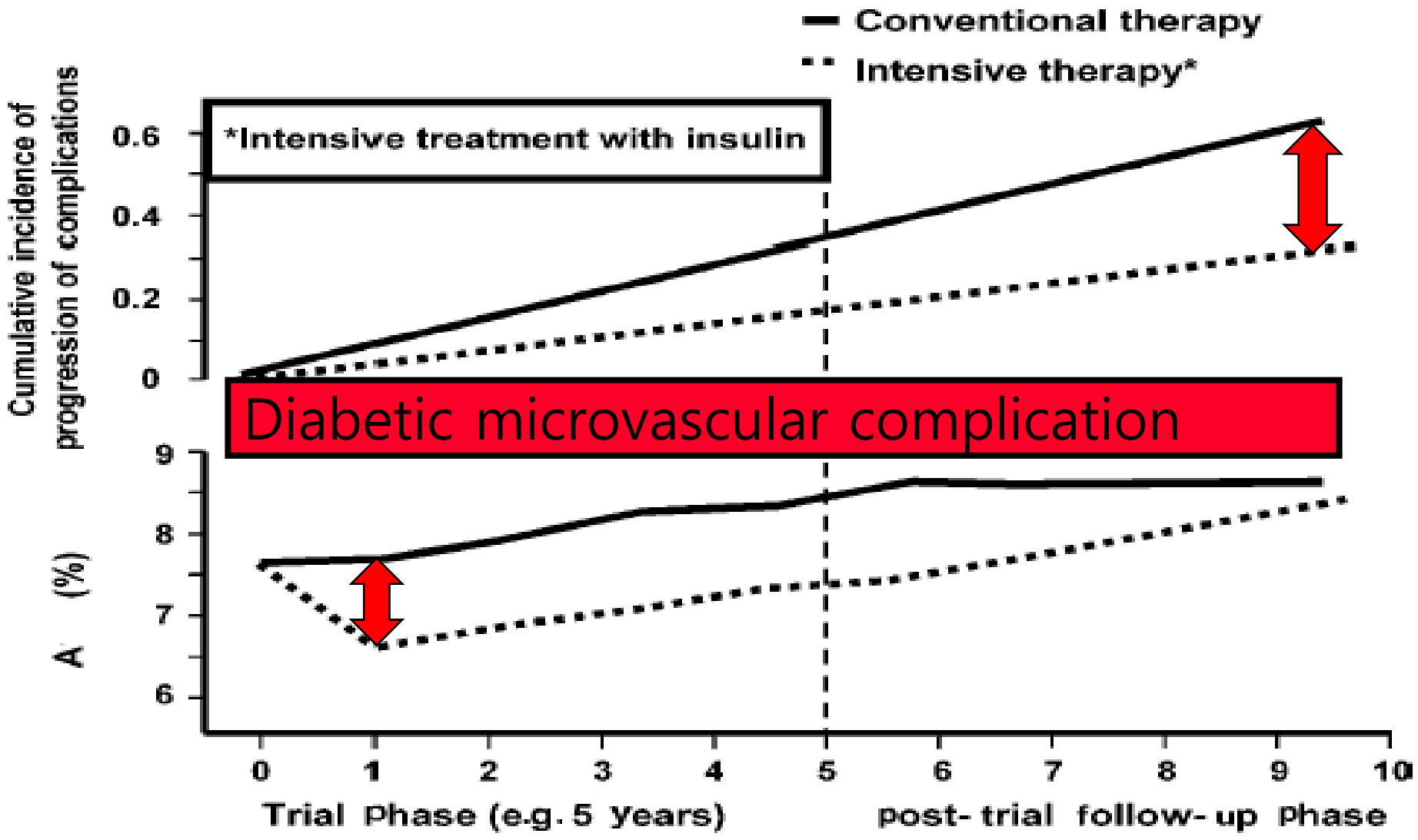
- 13세 어린 소녀
- 체중은 불과 45lbs(20.4 kg)
- Her chances of surviving for much longer are very, very poor(1921).
- 도축한 소 췌장에서 추출한 인슐린 사용

절박함에서 나온 용기

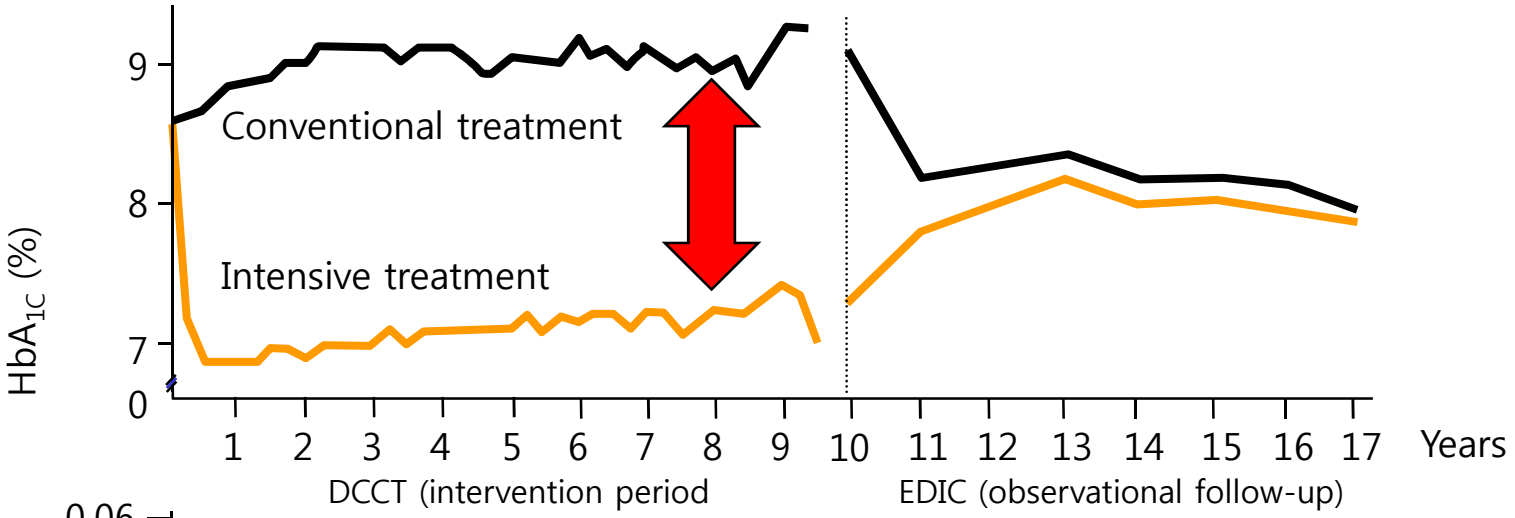
- I would have died from type 1 diabetes when I was 8 years old. However, it was already apparent at the time I was diagnosed that for too many people like me, Banting's discovery of insulin only allowed them to live just long enough to develop blindness, renal failure, and coronary disease.

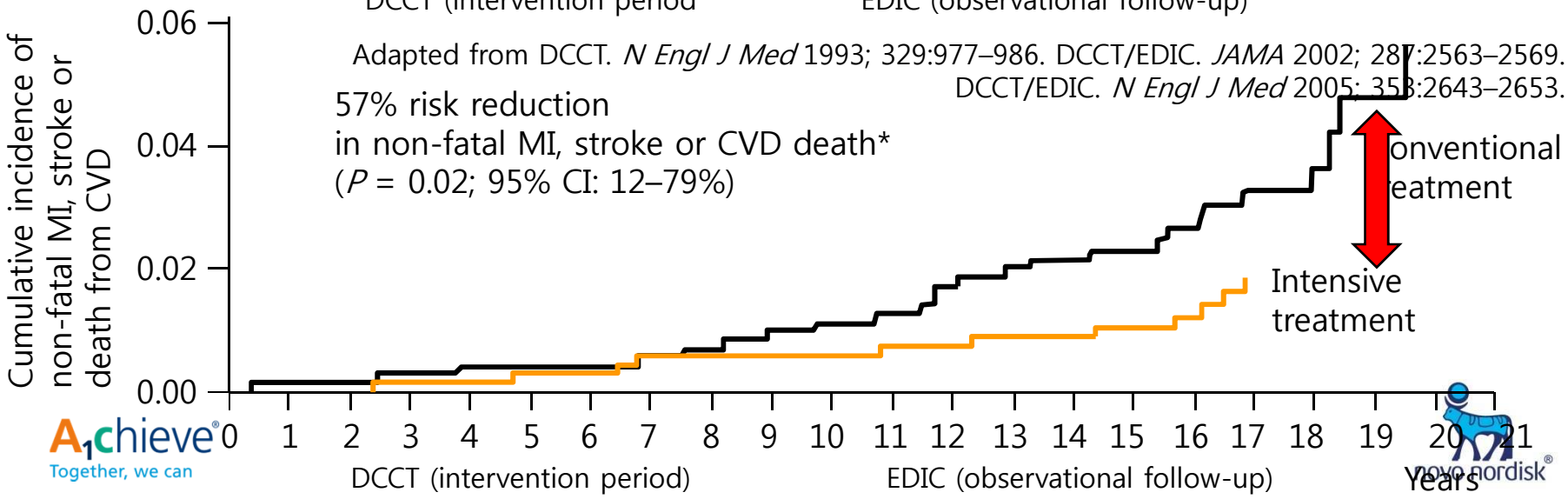
Brownlee M. 2004 ADA Baning Lecture

Initial metabolic control changes biology of diabetes



DCCT/EDIC: glycemic control reduces the risk of non-fatal MI, stroke or death from CVD in type 1 diabetes





*Intensive vs conventional treatment

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

❖20-year Interventional Trial from 1977 to 1997

- 5,102 patients with newly-diagnosed type 2 diabetes recruited between 1977 and 1991
- Median follow-up 10.0 years, range 6 to 20 years

❖ 10-year Post-Trial Monitoring from 1997 to 2007

- Annual follow-up of the survivor cohort
- Clinic-based for first five years
- Questionnaire-based for last five years

- ***Median overall follow-up 17.0 years, range 16 to 30 years***

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UKPDS-Post Trial Monitoring (PTM)

Holmann RR et al, N Engl J Med 2008;359:1577-89

Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.0099	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

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RRR = Relative Risk Reduction, P = Log Rank

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Wholistic approach in diabetic treatment
- Steno 2 study -

VBWG

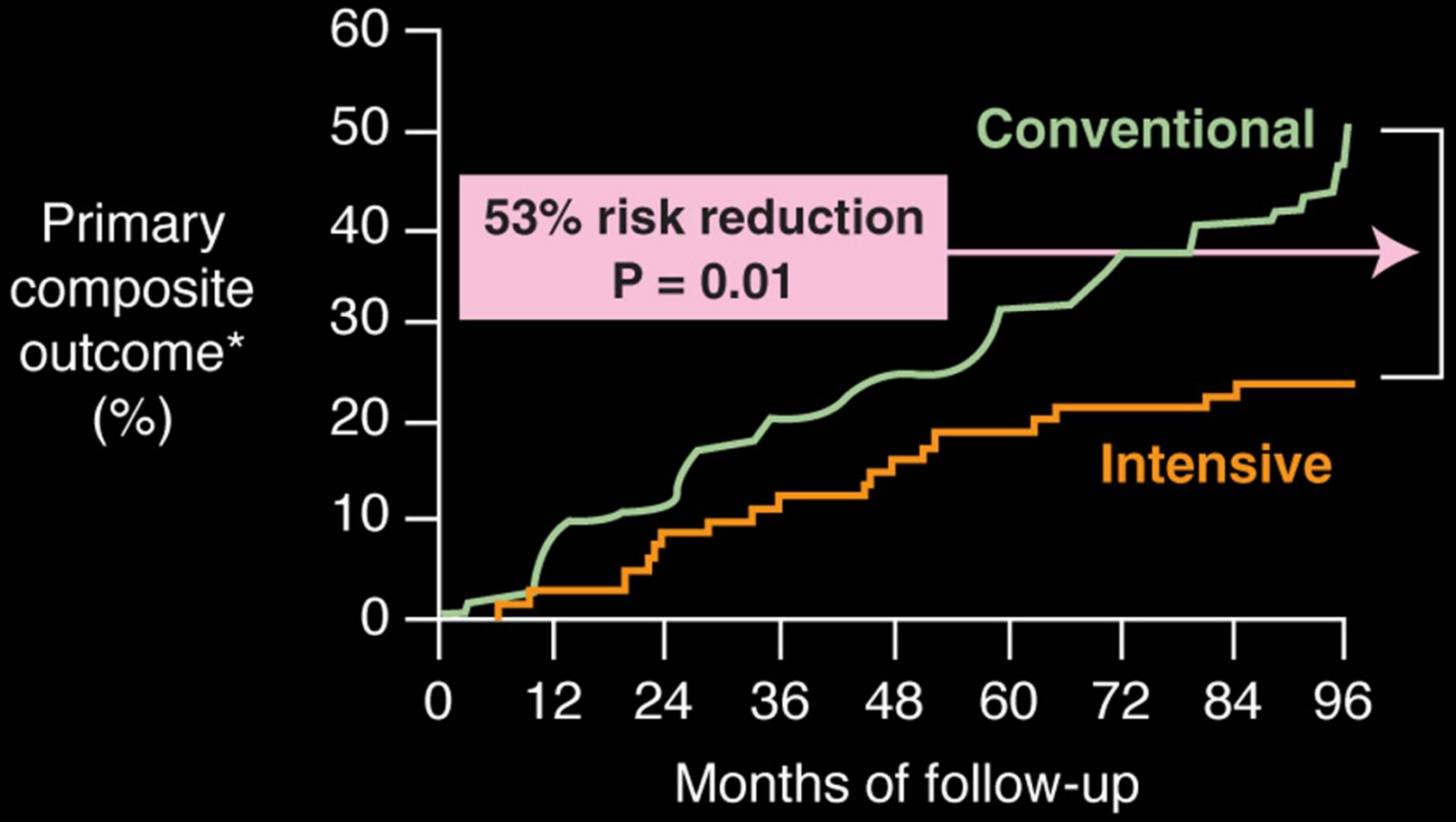
Steno-2 supports aggressive multifactorial intervention in type 2 diabetes

- Target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - Blood pressure <130/80 mm Hg
  - A_{1c} <6.5%
  - Total cholesterol <175 mg/dL
  - Triglycerides <150 mg/dL
- Produced risk reductions in CV and microvascular outcomes
  - Primary outcome (combined CV disease) 53%↓
  - Nephropathy 61%↓
  - Retinopathy 58%↓
  - Autonomic neuropathy 63%↓

Gæde P et al. *N Engl J Med.* 2000;348:383-93.

Steno-2: Effects of multifactorial intervention on CV outcomes

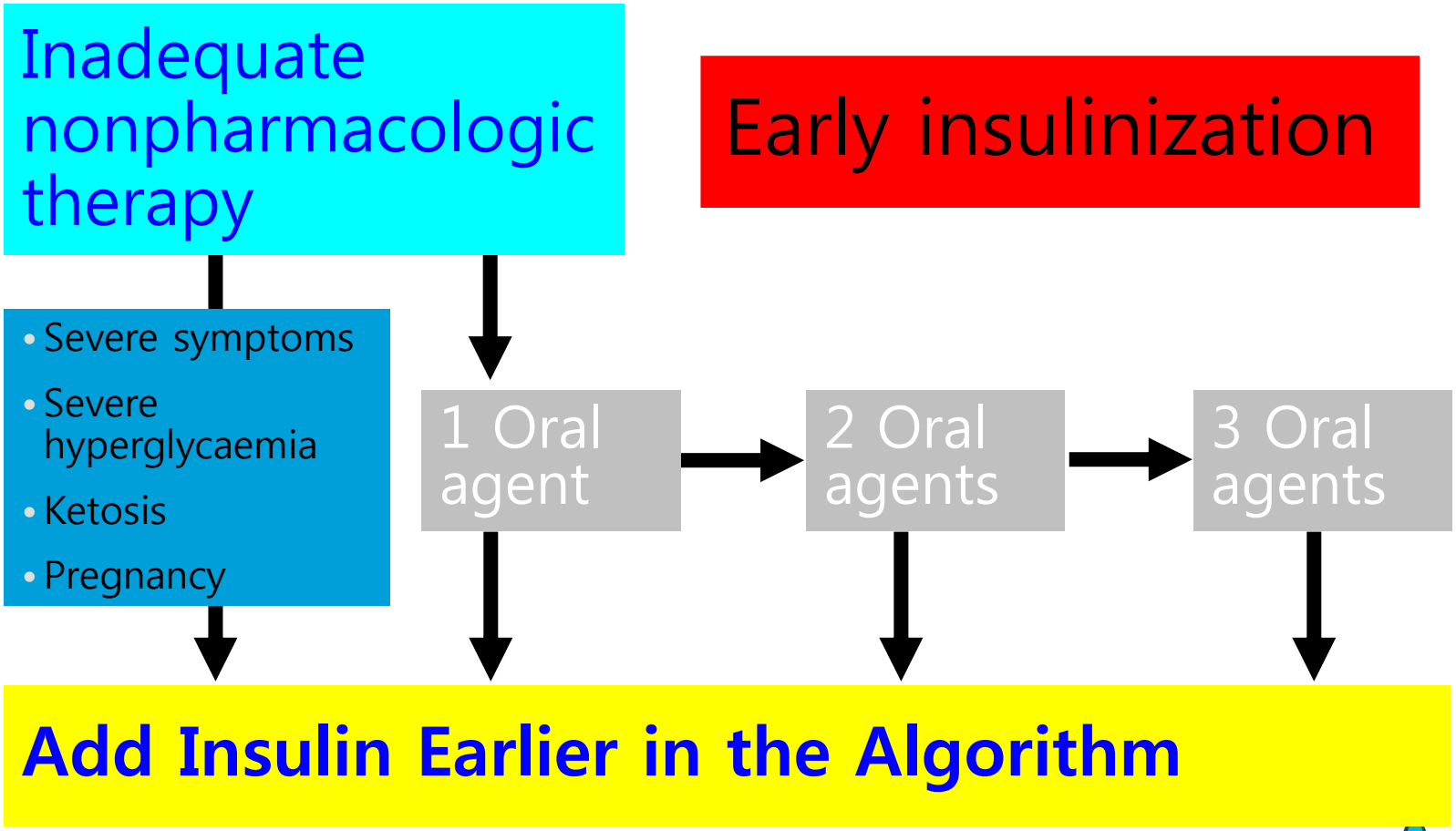
160 patients with type 2 diabetes and microalbuminuria



*CV death, MI, stroke, revascularization, amputation

Gæde P et al. *N Engl J Med*. 2003;348:383-93.

Proposed Therapeutic Algorithm for T2DM



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Barriers to intensive insulin replacement therapy in Type 2 DM

- Patients
  - fear
  - misunderstanding
  - worsening of disease
  - inconvenience
  - uncertainty
  - hypoglycemia
  - weight gain
  - edema
- Medical personal
  - hypoglycemia
  - atherosclerosis
  - edema
  - weight gain
  - sympathy

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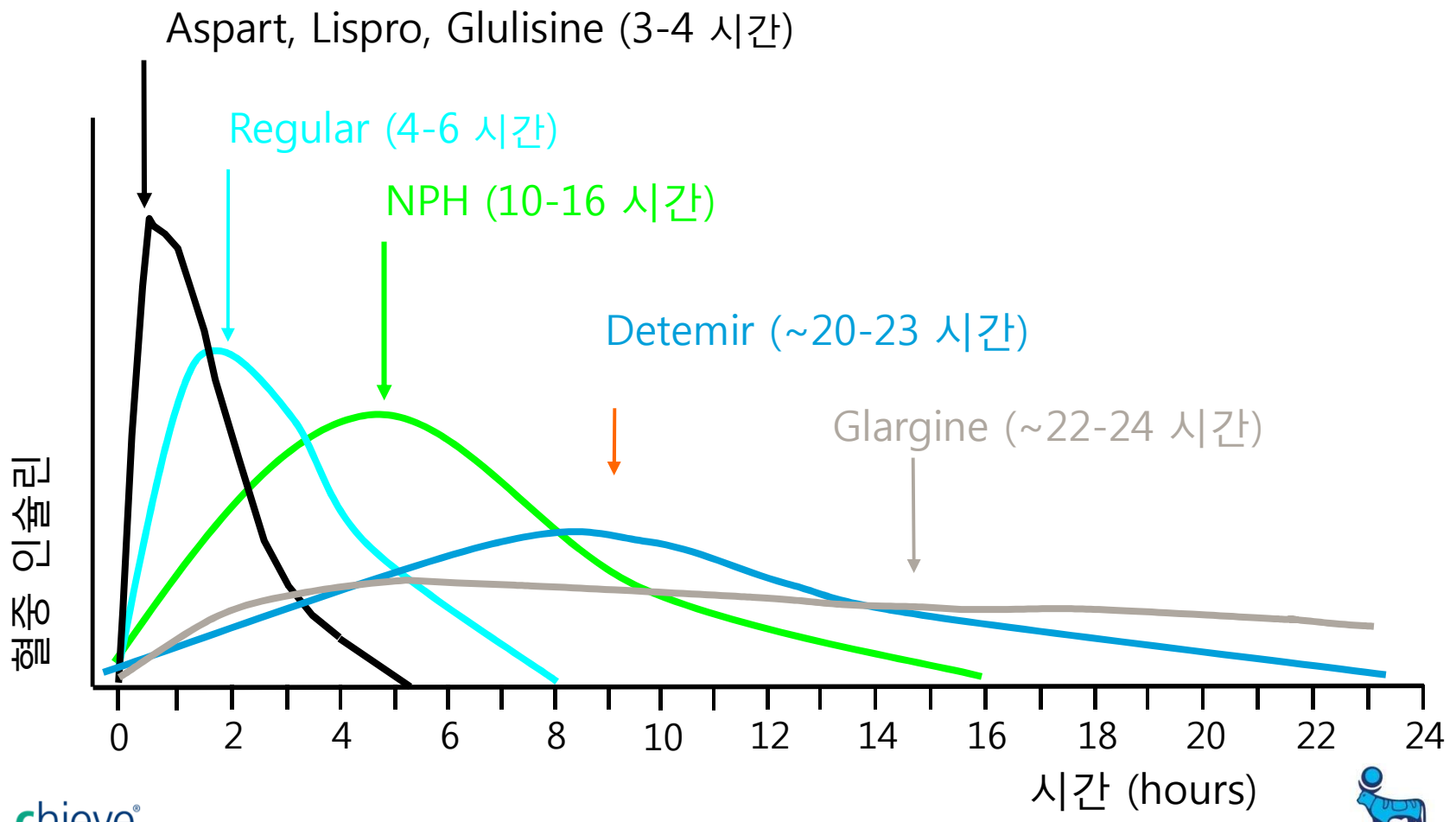
Designer's insulin



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Role of insulin analog in Diabetic Era

- Convenient
- Less Hypoglycemia
- Better Postprandial Hyperglycemia Control
- Flexibility

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What is the optimal insulin treatment in patients with inadequate glycemic control ?

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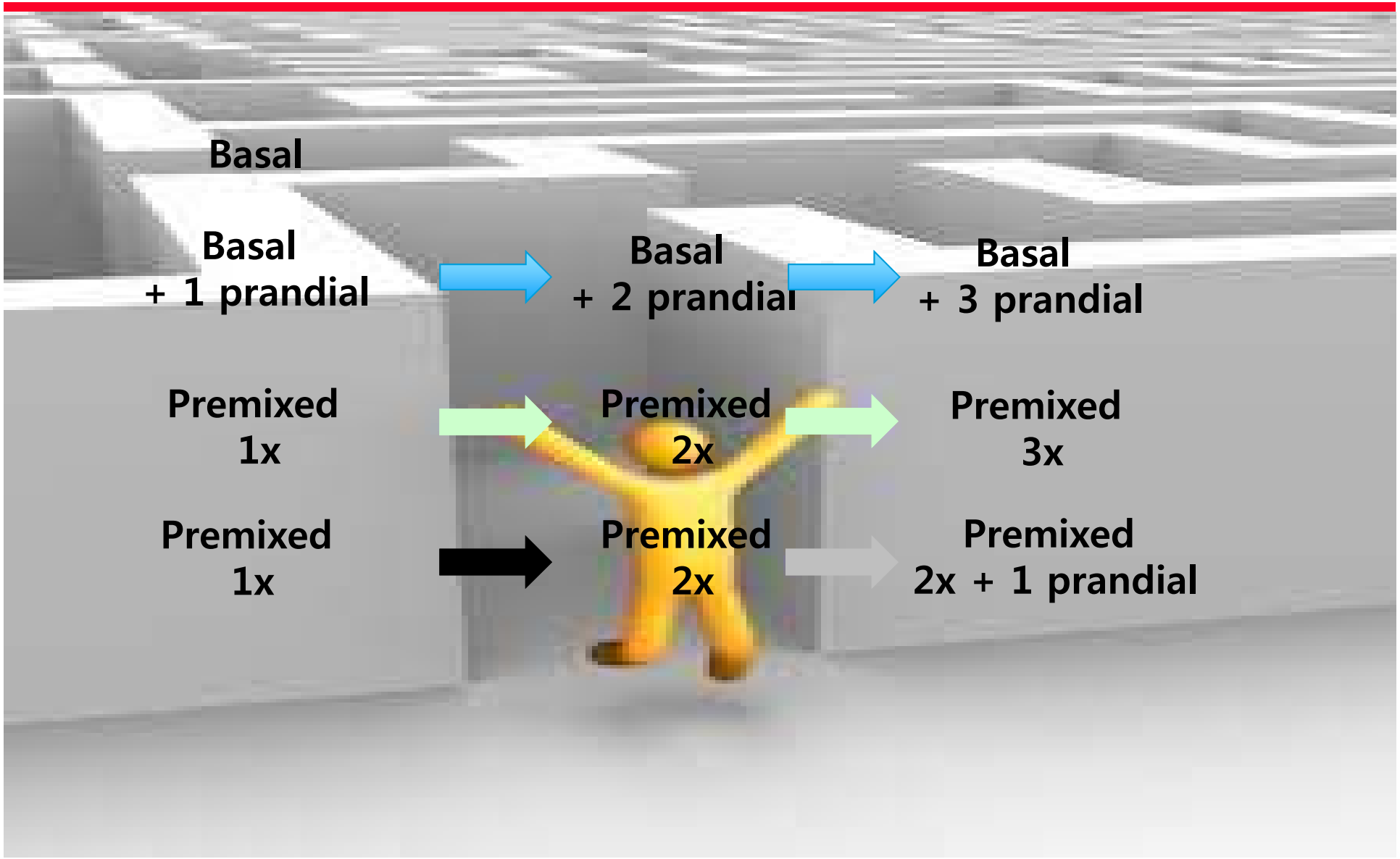
Insulin Treatment Options



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Modern Insulin analogues and 4T study

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Joanne F. Keenan, B.A., Sanjoy Paul, Ph.D., and Jonathan C. Levy, M.D., F.R.C.P., for the 4-T Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Jonathan C. Levy, M.D., F.R.C.P., Julie L. Darbyshire, M.A., M.Sc., Joanne F. Keenan, B.A., and Sanjoy K. Paul, Ph.D., for the 4-T Study Group*

Treating to Target in Type 2 diabetes (4T) Study

Rationale

- Lack of evidence based consensus for insulin **initiation** and **intensification** in patients with type 2 diabetes
- Clinically relevant protocol developed that is applicable in the primary care setting

- An independent and academic 3-year, multicentre, open-label, randomised, controlled clinical trial
- Conducted in the United Kingdom and Ireland
- Supported by Novo Nordisk and Diabetes UK

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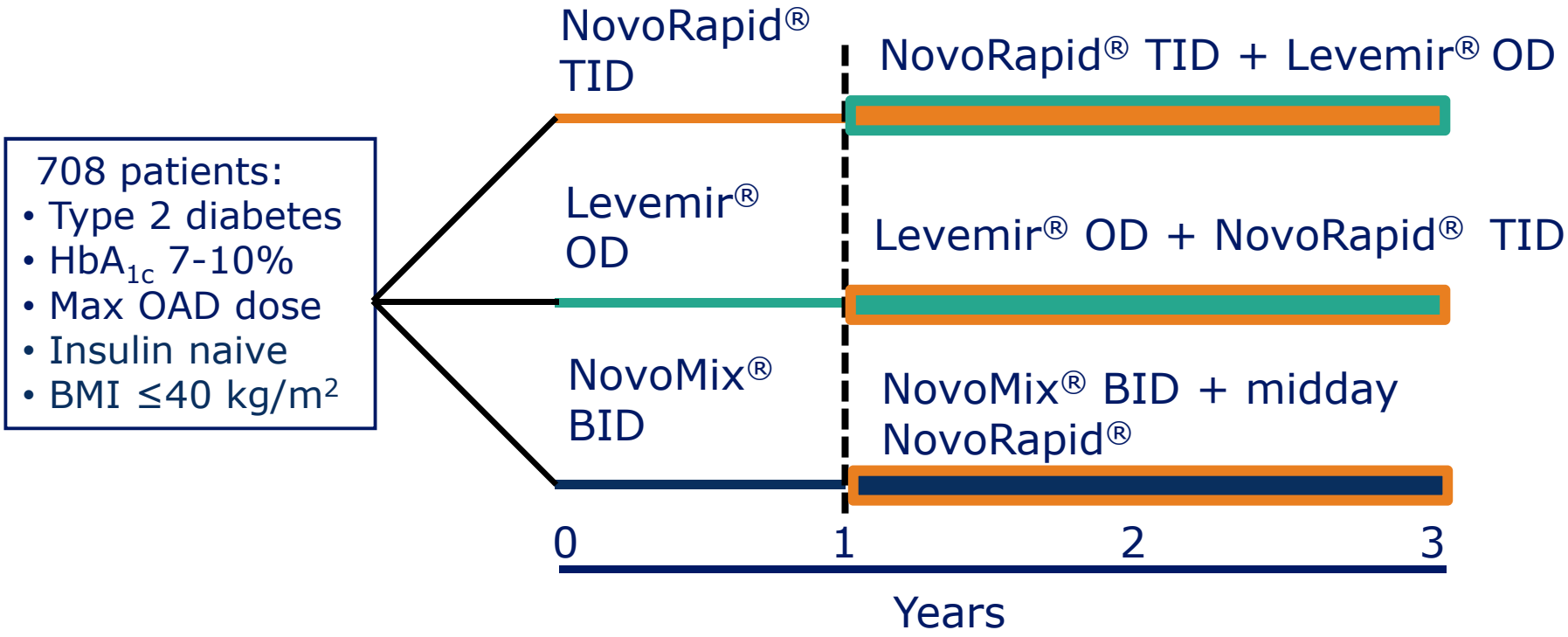
Study design to investigate insulin initiation and intensification



SU therapy replaced by second insulin in the first year if:

- HbA_{1c} ≥10% or
- HbA_{1c} ≥8% on two consecutive occasions

Or if:

- HbA_{1c} >6.5% at end of year one

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Adapted from Holman *et al. NEJM* 2009; 361:1736-47

Titrate to targets

Blood glucose targets

- Fasting and pre-meal: 4.0-5.5 mmol/l (72-99 mg/dl)
- Two-hours post meal: 5.0-7.0 mmol/l (90-126 mg/dl)

- The 4-T Online Trial Management System suggested dose adjustments using a common algorithm for all groups
- Investigators encouraged to amend suggested doses on clinical grounds and in consultation with patients
- Patients encouraged to modify doses between visits

Outcomes

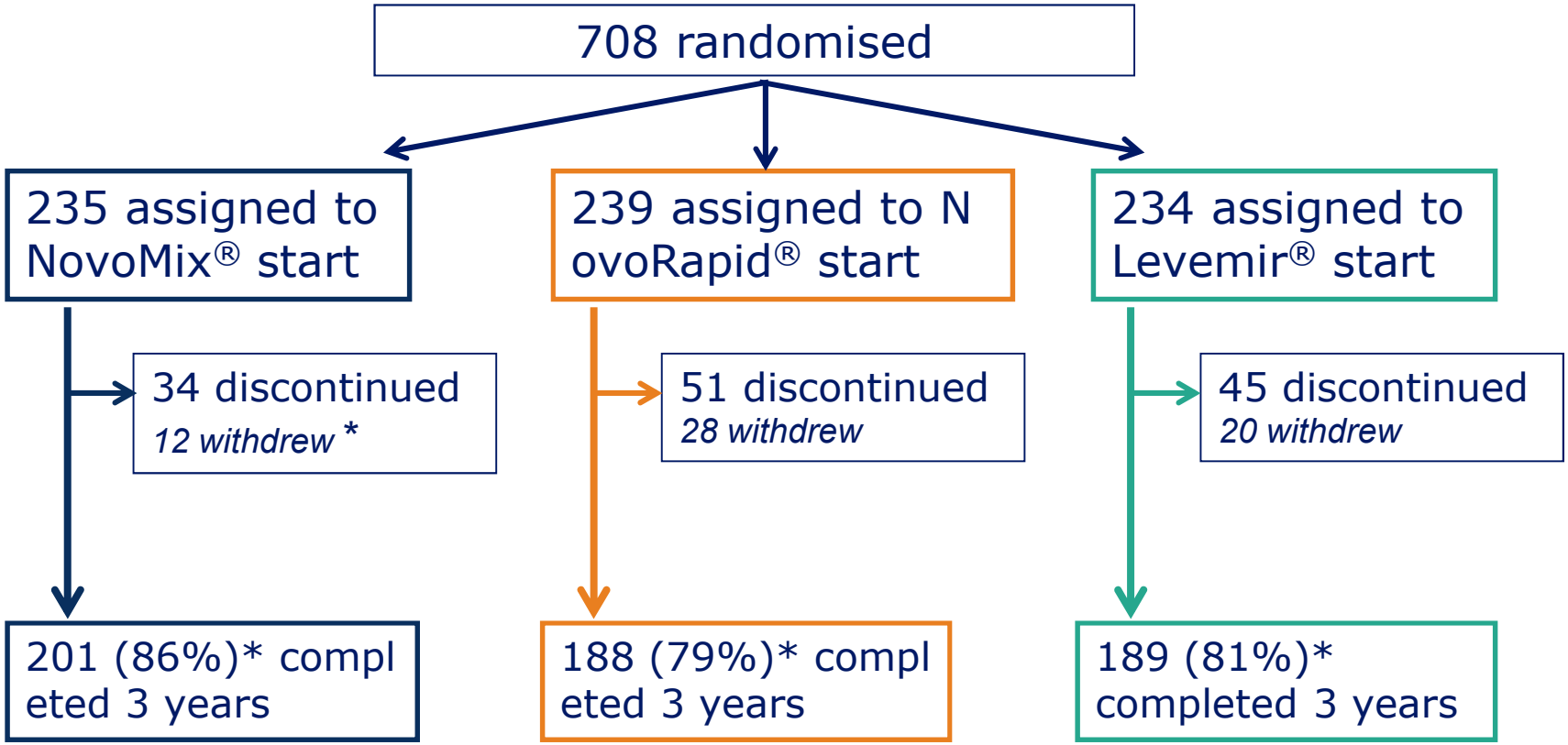
Primary outcome

- HbA_{1c} at 1 years and 3 years

Secondary HbA_{1c} outcomes

- Patients achieving HbA_{1c} ≤6.5%
- Patients achieving HbA_{1c} ≤ 6.5% without minor/major hypoglycaemia
- Weight gain

High patient retention for all insulin analogue study arms



Overall, 82% patients completed the study
*Difference between groups for number of withdrawals, p=0.04

Adapted from Holman *et al. NEJM* 2009; 361:1736-47

Well-matched baseline patient demographics

	NovoMix® start N=235	NovoRapid® start N=239	Levemir® start N=234
Age (years)	61.7±8.9	61.6±10.5	61.9±10.0
Diabetes duration (years)	9 (6-2)	9 (6-4)	9 (6-12)
Race (W/M/A/B/O) (%)	94.0/0.4/4.7/ 0.9/0	89.5/1.7/6.3/ 2.1/0.4	93.2/0.9/3.8/ 0.9/1.3
Body weight (kg)	86.9±16.8	84.9±14.4	85.5±16.3
BMI (kg/m^2)	30.2±4.8	29.6±4.5	29.7±4.6
HbA_{1c} (%)	8.6±0.8	8.6±0.8	8.4±0.8

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Race = W (White); M (Mixed); A (Asian); B (Black); O (Other)

Holman *et al. NEJM* 2007; 357:1716-30

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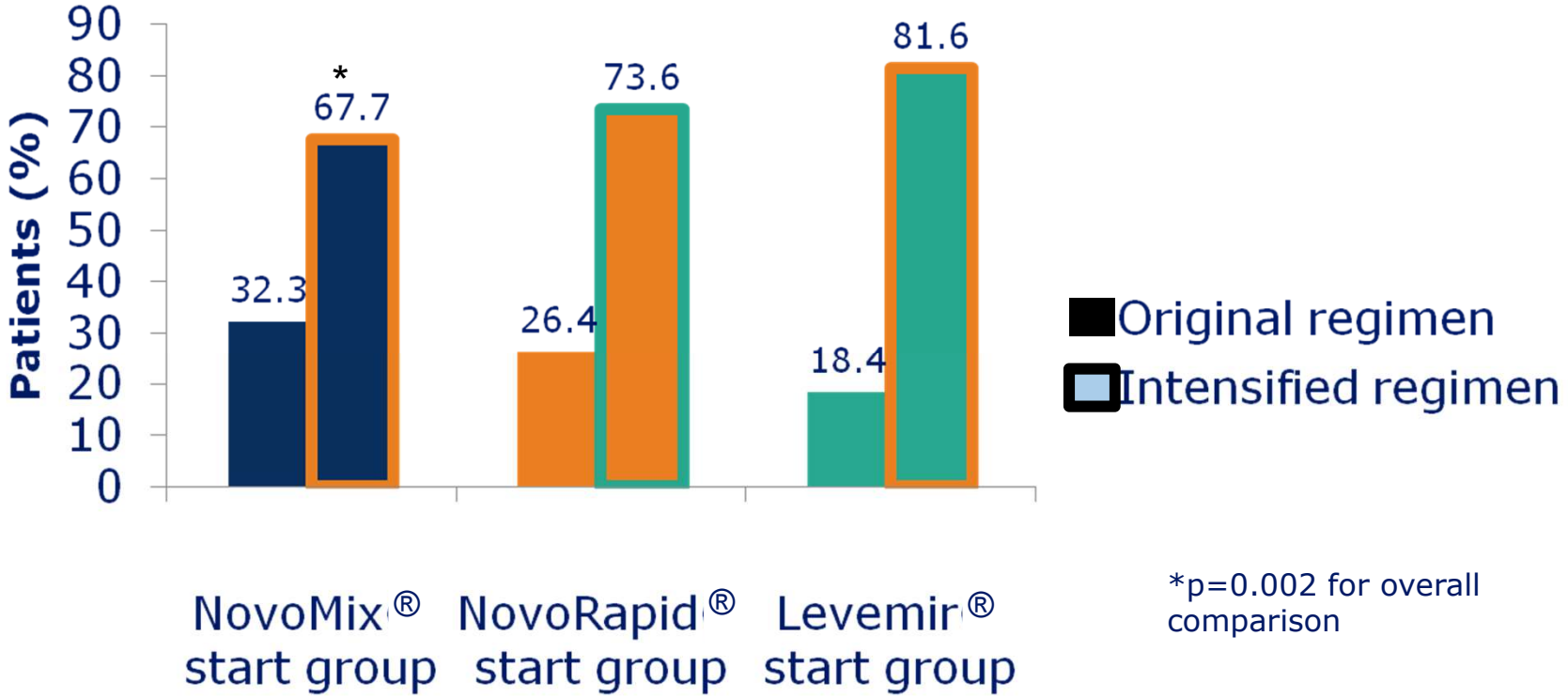
The majority of patients were intensified with a second insulin

74.3% of patients had an intensified regimen



*p=0.002 for overall comparison

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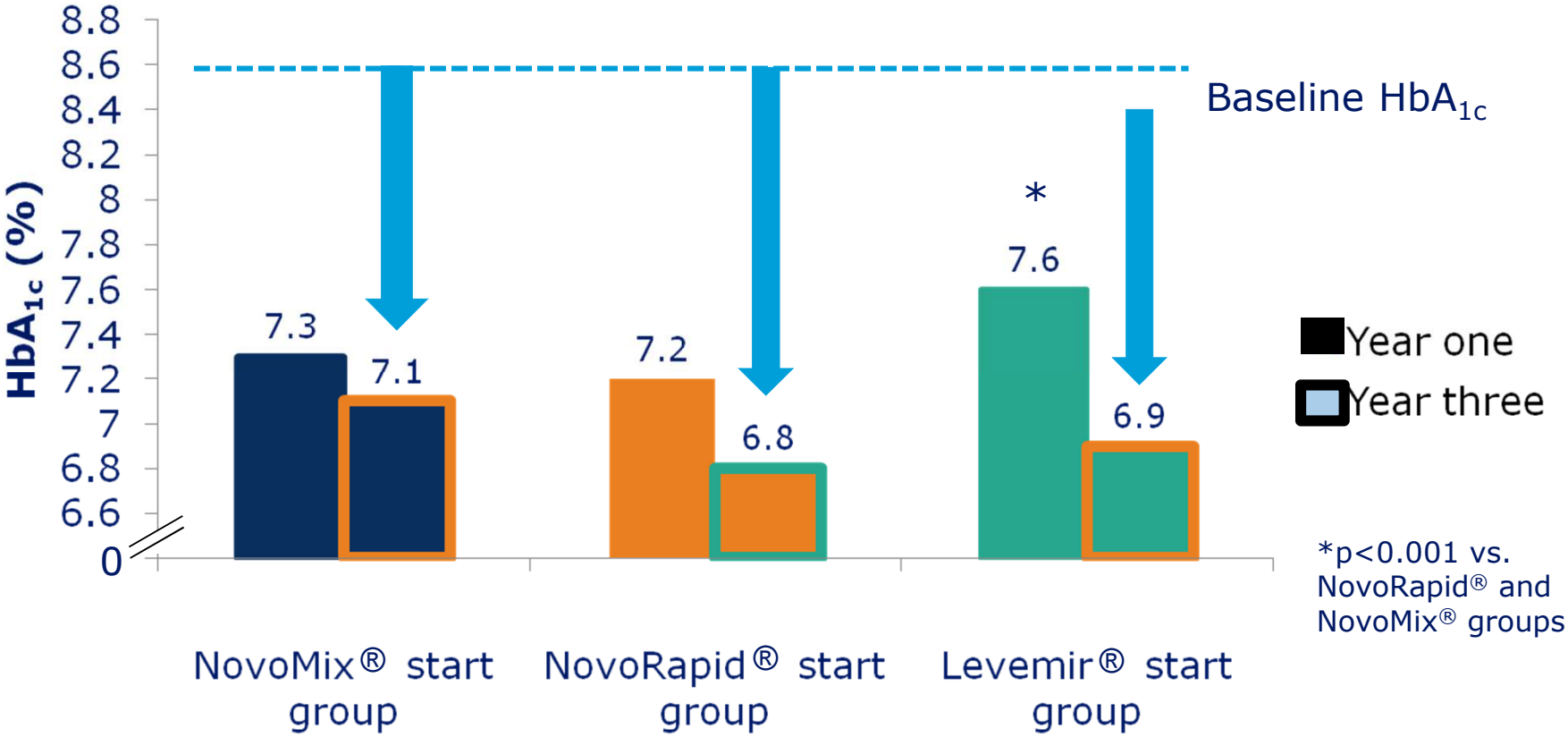
Sustainable HbA_{1c} control in all three arms



NB. Mean HbA_{1c} at 1 year; median HbA_{1c} at 3 years

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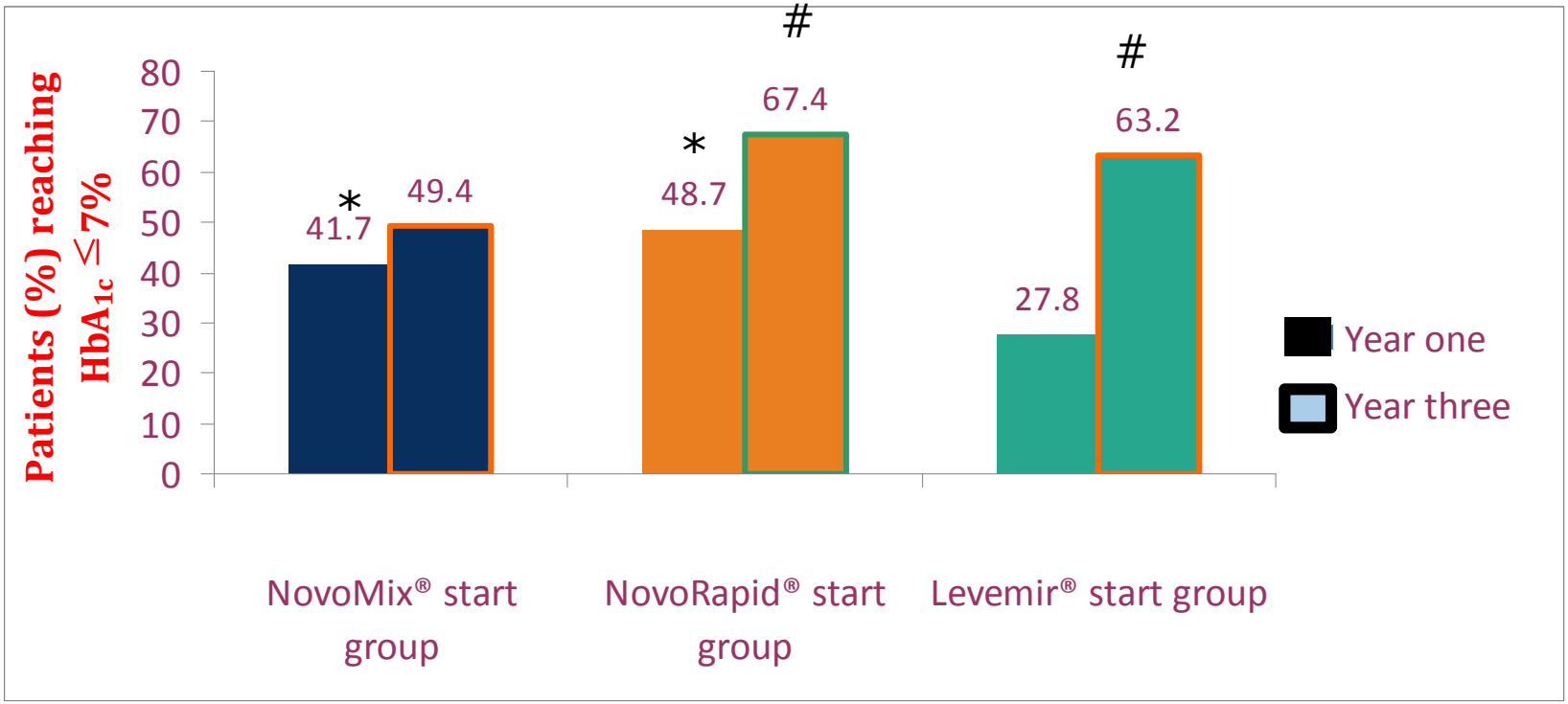
Adapted from Holman *et al. NEJM* 2007; 357:1716-30

Sustainable glycaemic control: patients with HbA_{1c} ≤7.0% at 3 years



*p<0.001 vs. Levemir® at year one
#p<0.05 vs. NovoMix® at year three

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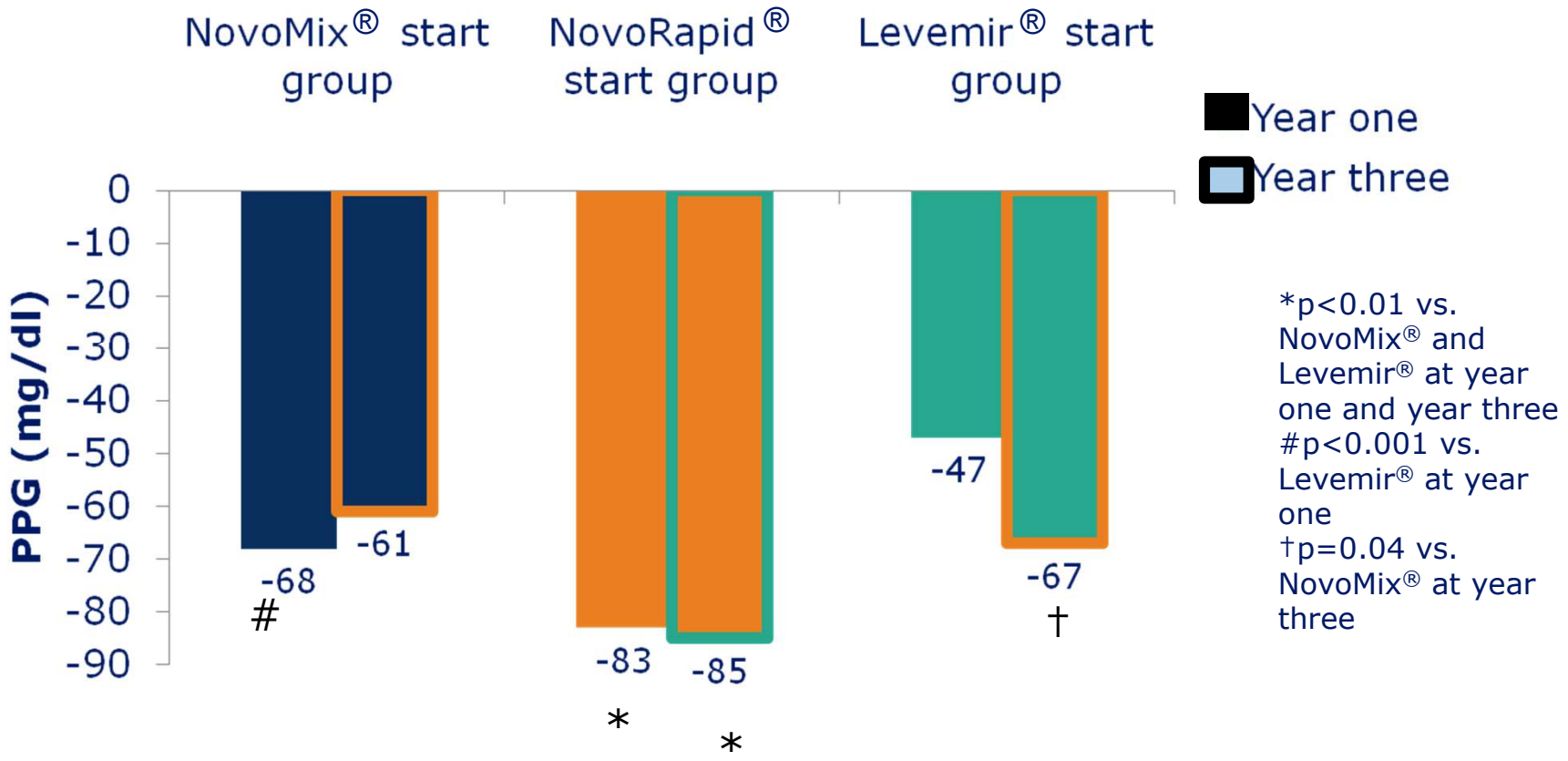
Holman *et al. NEJM* 2007; 357:1716-30

Sustainable glycaemic control: PPG reduction from baseline at 3 years



*p<0.01 vs. NovoMix® and Levemir® at year one and year three
#p<0.001 vs. Levemir® at year one
†p=0.04 vs. NovoMix® at year three

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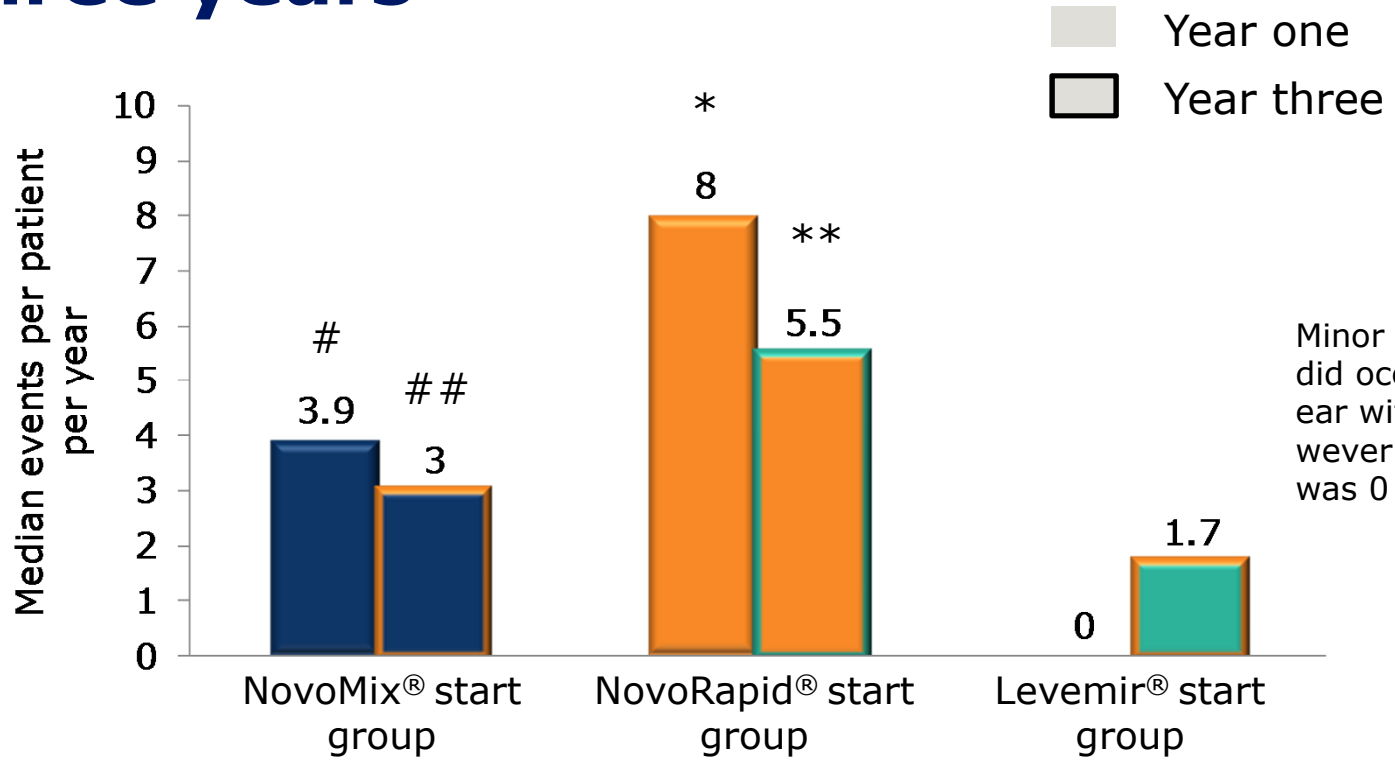
Holman *et al. NEJM* 2007; 357:1716-30

Low rates of minor hypoglycaemia at one and three years



Minor hypoglycaemia did occur in the first y ear with Levemir®, ho wever the median rate was 0

*p=0.002 and p<0.001 vs. NovoMix® and Levemir® respectively at year one
**p<0.001 vs. NovoMix® and Levemir® at year three
#p=0.01 vs. Levemir® at year one
##p<0.001 vs. Levemir® at year three

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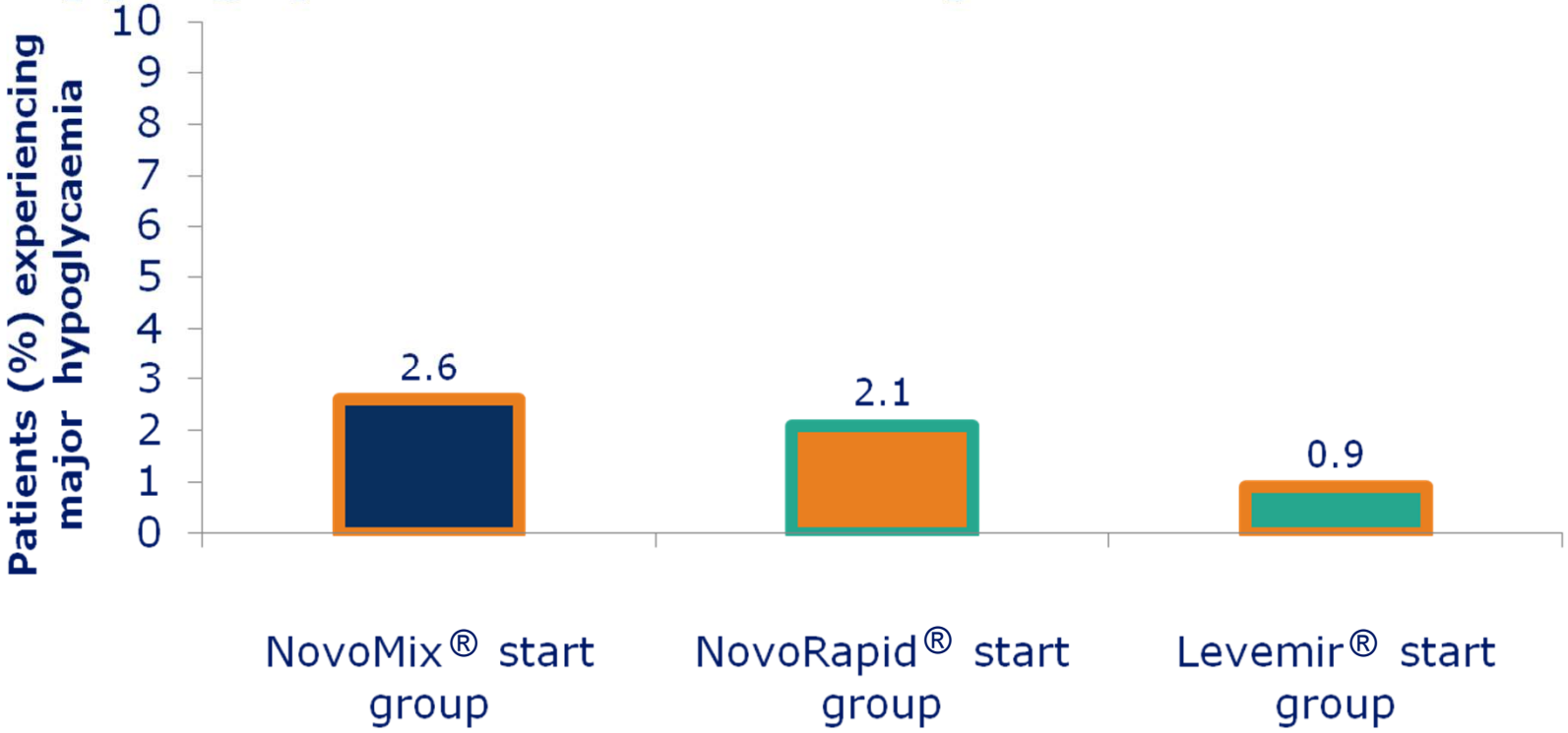
Holman et al. NEJM Oct 2009; 361:18 1736-1747

Low proportion of patients experiencing major hypoglycaemia over 3 years



No. of patients in the NovoMix® 30 start group	No. of patients in the NovoRapid® start group	No. of patients in the Levemir® start group
6	5	2

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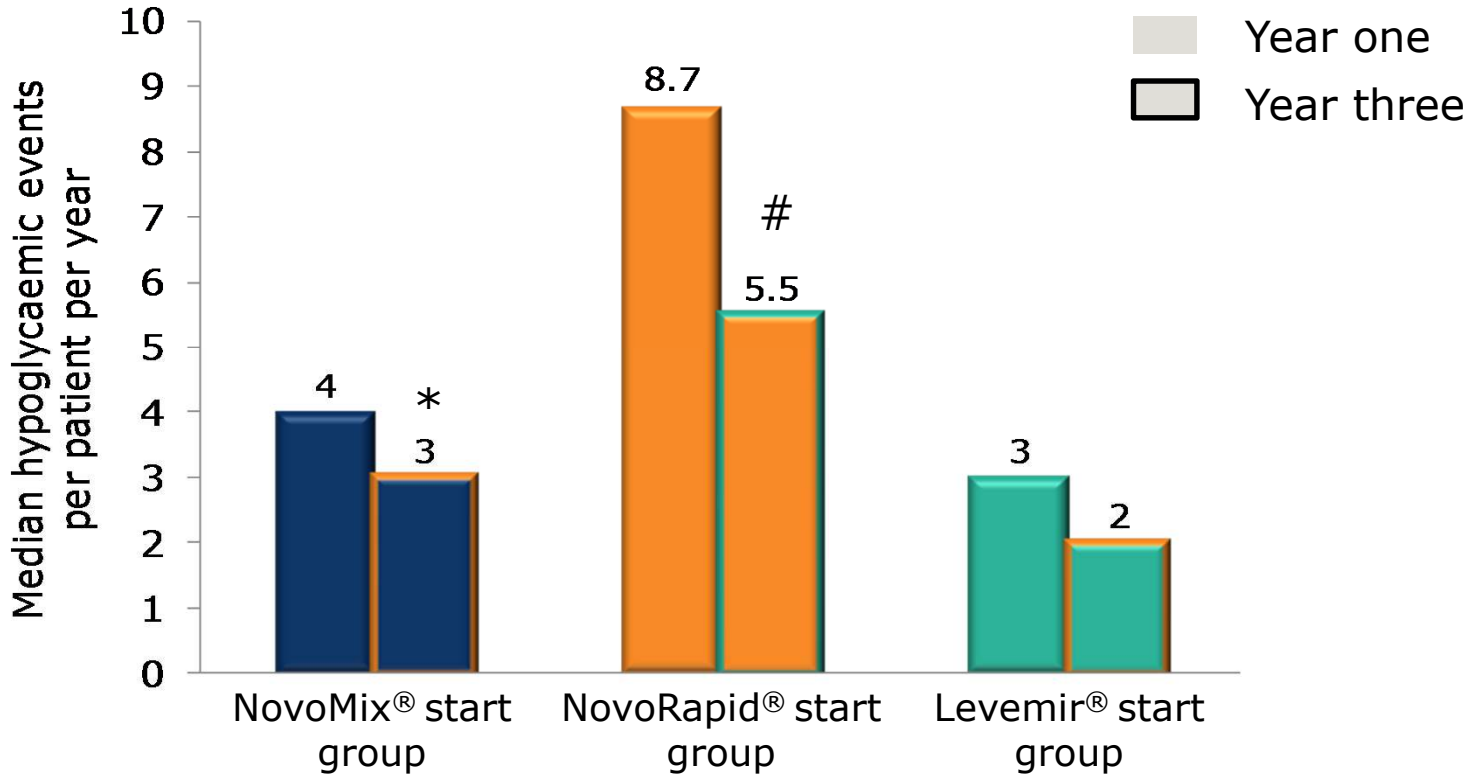
Holman *et al. NEJM* 2007; 357:1716-30

Achievement of HbA_{1c} ≤6.5% did not compromise hypoglycaemia rates



*p=0.002 vs. NovoRapid® at year three
#p<0.001 vs. Levemir® at year three

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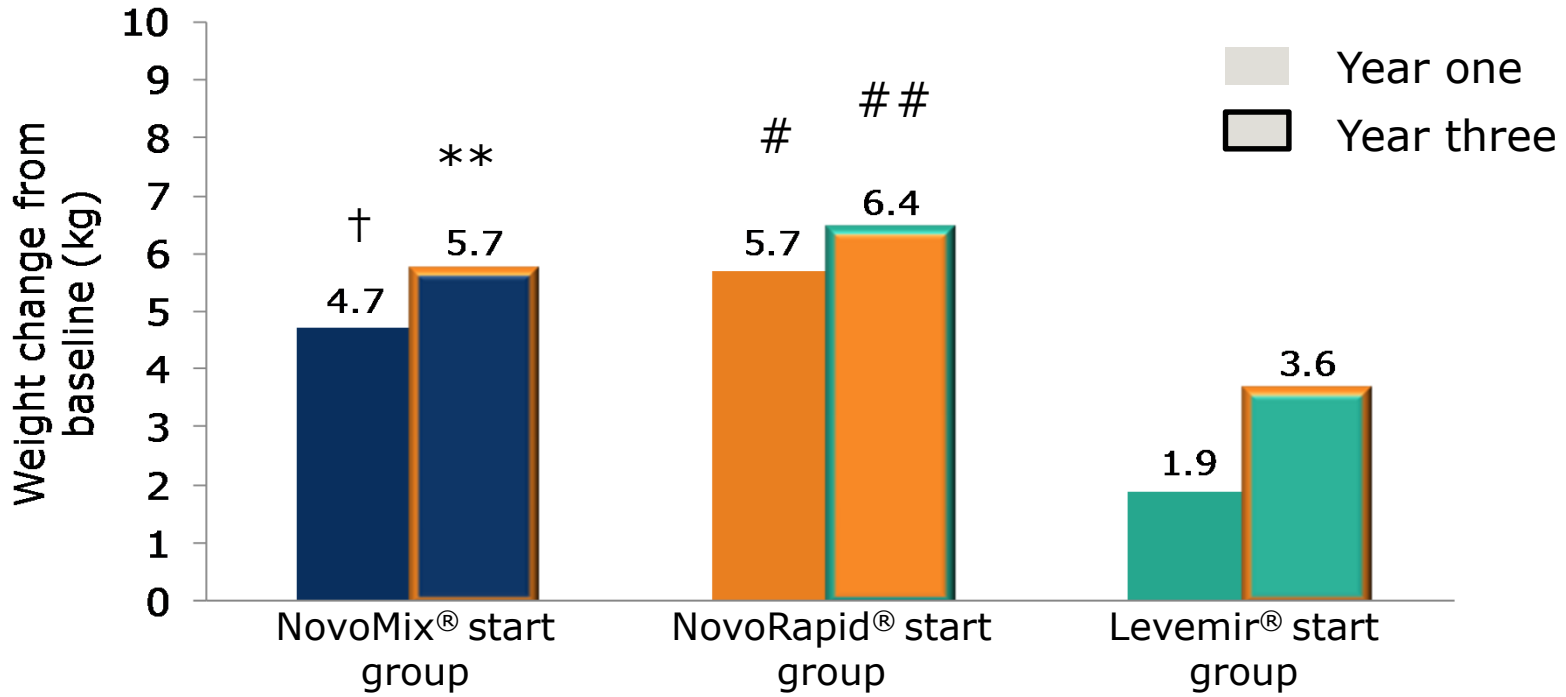
Holman et al. NEJM Oct 2009; 361:18 1736-1747

Levemir weight advantage was sustained throughout intensification



†p=0.005 vs. NovoRapid® at year one
*p<0.001 vs. Levemir® at year one
#p<0.001 vs. Levemir® at year one
**p=0.005 vs. Levemir® at year three
p<0.001 vs. Levemir® at year three

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Holman et al. NEJM Oct 2009; 361:18 1736-1747

4T: summary (1)

In the first year:

- Addition of a single analogue insulin formulation to metformin and sulfonylurea lowered HbA_{1c} by 0.8 to 1.4%
- Regimens using biphasic or prandial insulin reduced HbA_{1c} to a greater extent than basal, but were associated with greater risks of hypoglycemia and more weight gain

4T: summary (2)

After 3 years:

- Roughly three-quarters of patients had added a second insulin
  - Percentage of patients achieving HbA_{1c} ≤7.0%
    - Levemir® start: 63.2%
    - NovoMix® 30 start: 49.4%
    - NovoRapid® start: 67.4%

4T: summary (3)

After 3 years:

- Median rates of hypoglycaemia (per pt/year)
  - Levemir® start: 1.7
  - NovoMix® 30 start: 3.0
  - NovoRapid® start: 5.7
  - Hypoglycaemia rates were not significantly affected by the achievement of tight control (≤6.5% HbA_{1c})
- Mean weight gain
  - Levemir® start: 3.6 kg
  - NovoMix® 30 start: 5.7 kg
  - NovoRapid® start: 6.4 kg

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4T Conclusions

- A tight level of control was achieved and maintained over 3 years with Novo Nordisk insulin analogues.
- The overall rate of hypoglycaemia was low and no greater in patients reaching the 6.5% target.
- Due to the progressive nature of type 2 diabetes, insulin dose optimisation and intensification is required over time to maintain glycaemic control.

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Final Results

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Agenda

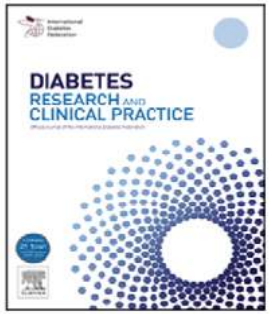
- Study Design

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



The A_1chieve study: a 60 000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice

Siddharth N. Shah[a], *León Litwak*[b], *Jihad Haddad*[c], *Praful N. Chakkarwar*[d,*], *Issam Hajjaji*[e]

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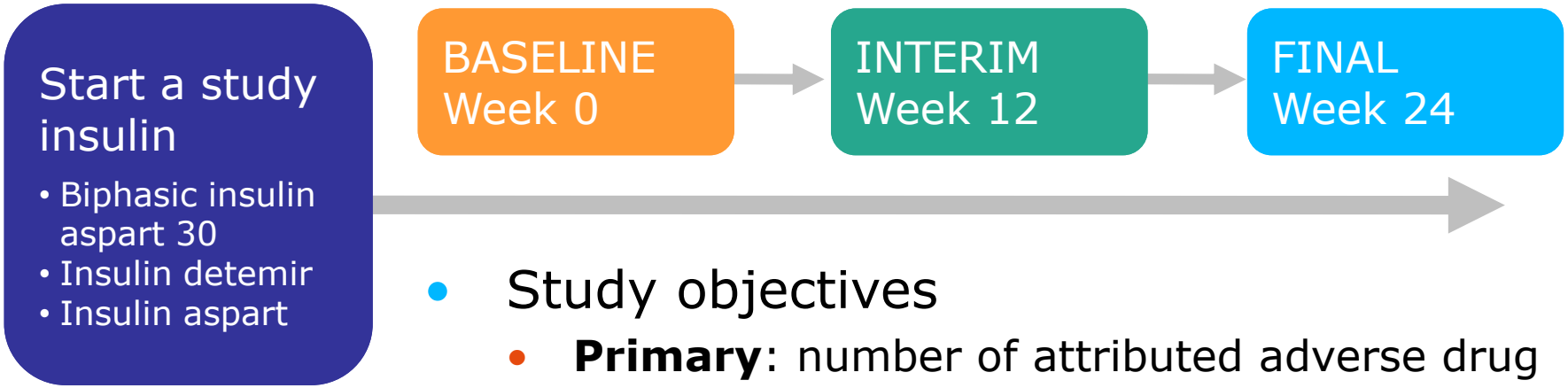
Shah SN at al, Diabetes Res Clin Pract. 88:S11-6, 2010

A_1chieve study overview and design

- Observational study of people with T2DM in routine clinical practice



- Study objectives
  - **Primary**: number of attributed adverse drug reactions (includes major hypoglycaemia)
  - **Secondary**: other safety and effectiveness measures

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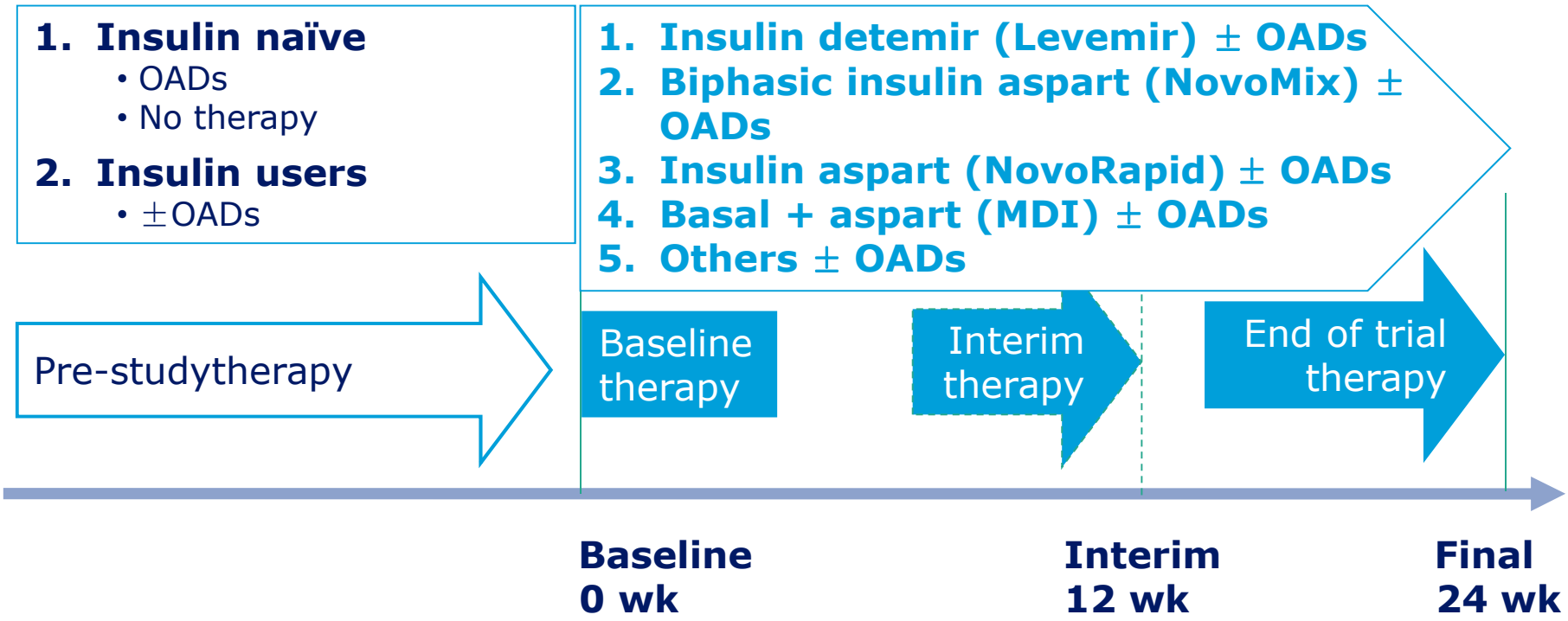
Treatment before and during the study



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Regions and countries

China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
China	Bangladesh	Indonesia	Algeria	Bahrain	Argentina	Russia
	India	Korea	Libya	Egypt	Mexico	
	Pakistan	Malaysia	Morocco	Iran		
		Philippines	Tunisia	Jordan		
		Singapore		Kuwait		
		Taiwan		Oman		
				Qatar		
				Saudi Arabia		
				Turkey		
				UAE		
				Yemen		

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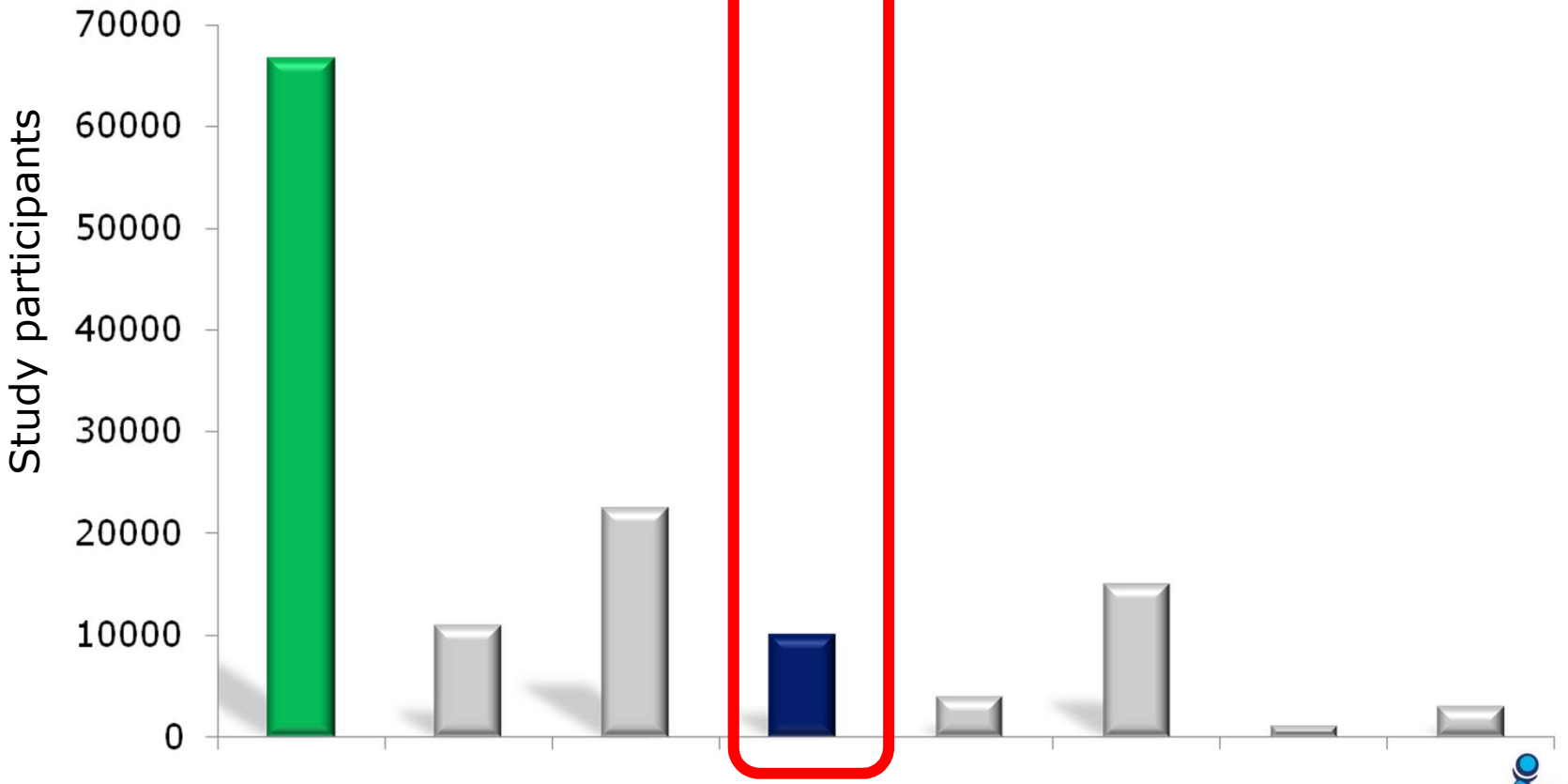
Participant enrolment per region

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
n	66726	11020	22447	10032	4039	14976	1138	3074



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Overview of baseline characteristics by pre-study therapy: global

	Total	No therapy	OAD alone	Insulin± OAD
N	66726	6010	38862	21854
Percent of total	-	9	58	33
Sex M/F (%)	55.6/44.4	60.9/39.1	56.8/43.2	51.9/48.1
Age (years)	54.0 (12.0)	51.8 (14.4)	53.5 (11.1)	55.6 (12.5)
Weight (kg)	72.9 (15.0)	67.3 (12.7)	72.4 (14.6)	75.3 (15.9)
BMI (kg/m^2)	27.1 (5.0)	25.2 (4.2)	26.9 (4.7)	27.9 (5.5)
Diabetes duration (yr)	8.0 (6.2)	2.6 (4.9)	7.2 (5.2)	10.8 (6.8)
HbA_{1c} (%)	9.5 (1.8)	10.2 (2.3)	9.5 (1.7)	9.4 (1.8)

Mean (SD), number or percent; OGLD, oral glucose-lowering drug

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Overview of baseline characteristics by pre-study therapy: Korea

	Total	No therapy	OAD alone	Insulin± OAD
N	4058	493	1824	1741
% of total	-	12.1	44.9	42.9
Gender M/F (%)	53.6/46.4	60.4/39.6	52.1/47.9	53.3/46.7
Age (years)	57.1 (13.0)	51.9 (14.1)	58.2 (12.3)	57.4 (13.0)
Weight (kg)	63.9 (11.6)	65.0 (12.4)	63.6 (11.4)	63.8 (11.6)
BMI (kg/m^2)	24.2 (3.6)	24.1 (3.7)	24.2 (3.6)	24.3 (3.7)
Diabetes duration (yrs)	10.1 (7.8)	4.8 (6.7)	9.9 (7.1)	11.8 (8.1)
HbA_{1c} (%)	9.8 (2.0)	10.6 (2.4)	9.7 (1.9)	9.7 (2.0)

All data are mean (SD)

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OGLD, oral glucose-lowering drug

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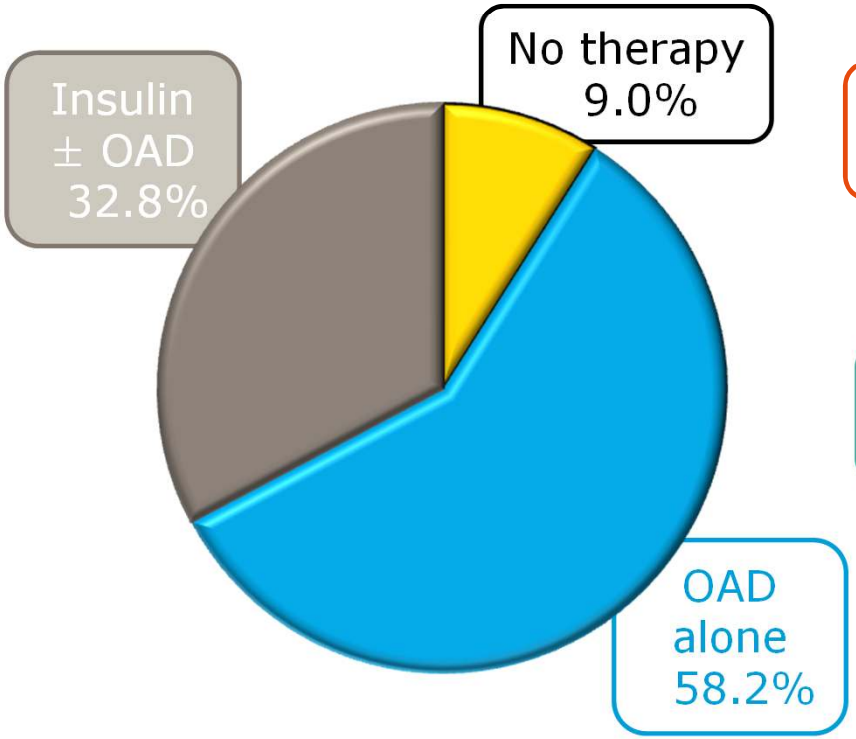
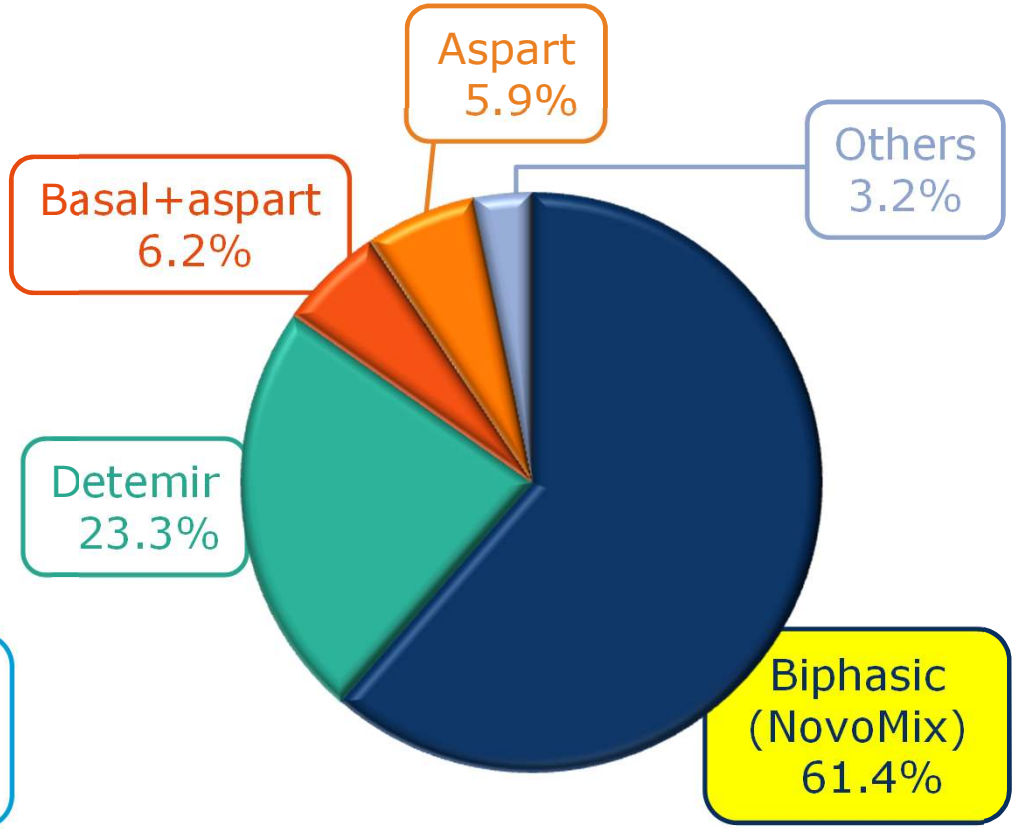
Participant distribution by pre-study therapy and allocated insulin: Global

Pre-study therapy
(n=66726)



Study therapy
(n=66726)



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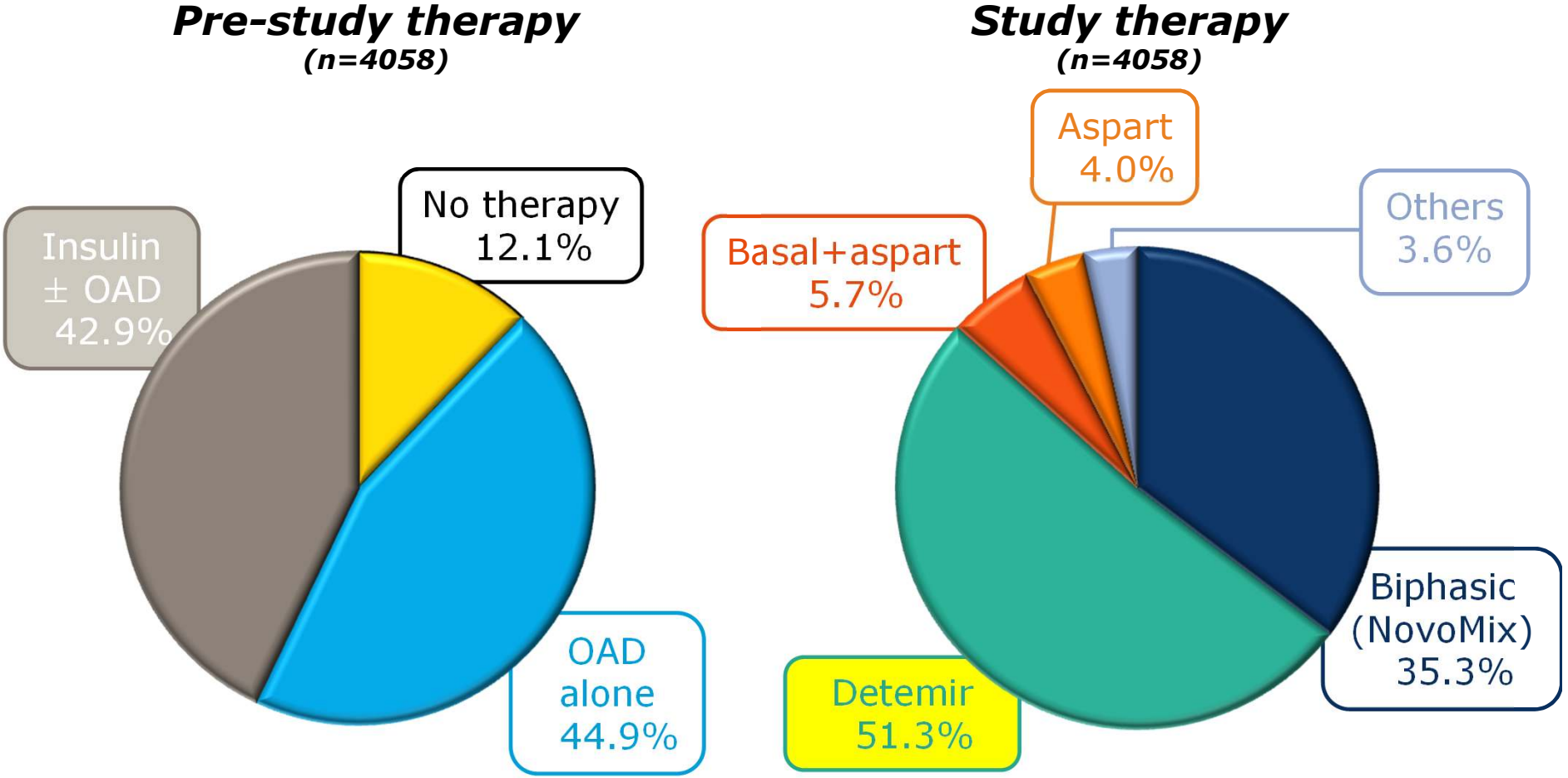
Participant distribution by pre-study therapy and allocated insulin: Korea



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Prevalence of macro- and micro-vascular complications by previous therapy at baseline

Complications	Total n=4058	No therapy n=493	OAD alone n=1824	Insulin± OAD n=1741
Cardiovascular (%)	23.7	14.6	24.2	25.6
Neuropathy (%)	33.5	17.4	32.1	39.4
Renal (%)	27.0	18.1	24.4	32.3
Eye (%)	25.4	14.6	22.6	31.4
Foot ulcer (%)	2.5	2.6	1.5	3.6

A patient can have multiple complications

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Agenda

- Study Design
- Korea Final Result Review

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International Diabetes Federation

An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The A$_1$chieve study☆,☆☆

Philip Home[a,*], *Nabil El Naggar*[b], *Mohammed Khamseh*[c], *Guillermo Gonzalez-Galvez*[d], *Chunduo Shen*[e], *Praful Chakkarwar*[e], *Wenying Yang*[f]

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Home P at al, Diabetes Res Clin Pract. 94:352-63, 2011

ABSTRACT

Aim: The aim of A_1chieve was to remedy the deficit of data on the efficacy and safety of insulin analogues in routine clinical care in less well-resourced/newly developed countries.

Methods: A non-interventional, 6-month, observational study of 66,726 people with type 2 diabetes, both insulin users and non-insulin users, started on insulin detemir, insulin aspart or biphasic insulin aspart in 28 countries across four continents.

Results: Baseline HbA_{1c} (±SD) was poor: 9.5 ± 1.8%. At 6 months, improvement was −2.1 ± 1.7% in the entire cohort, and −2.2 ± 1.7% and −1.8 ± 1.7% for prior non-insulin users and insulin users. All three analogue therapies gave similar results, again independently of prior insulin use, but also from seven pre-specified country groupings. Overall, hypoglycaemia did not increase in those new to insulin, and fell in those switching insulins. There was no change in body weight (−0.1 ± 3.7 kg), while lipid profile and systolic blood pressure (−6.3 ± 17.1 mmHg) were improved.

Conclusions: Beginning insulin analogue therapy in people with type 2 diabetes and poor blood glucose control is associated with marked improvements in diverse aspects of vascular risk factor profile without evidence of clinically significant safety or tolerability problems.

Glycaemic Control

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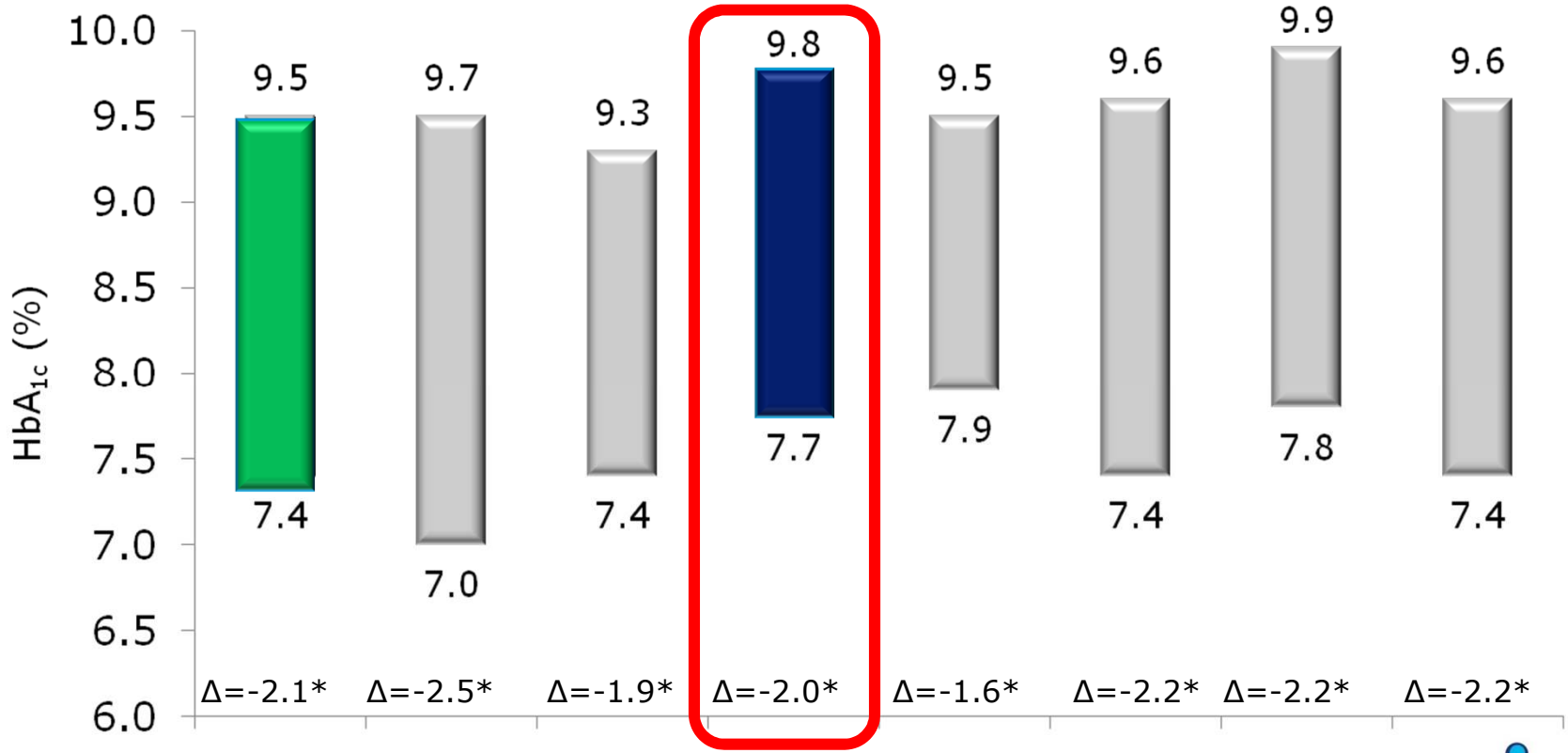
Change in HbA_{1c} across all regions

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
n	44661	5784	17111	4167	2601	11618	573	2807



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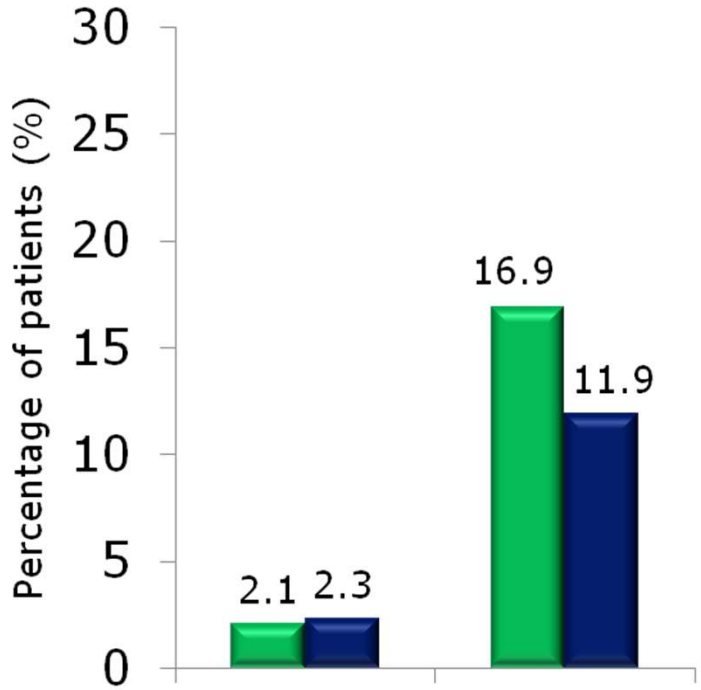
*p<0.001

Achievement of HbA_{1c} targets

Global
Korea

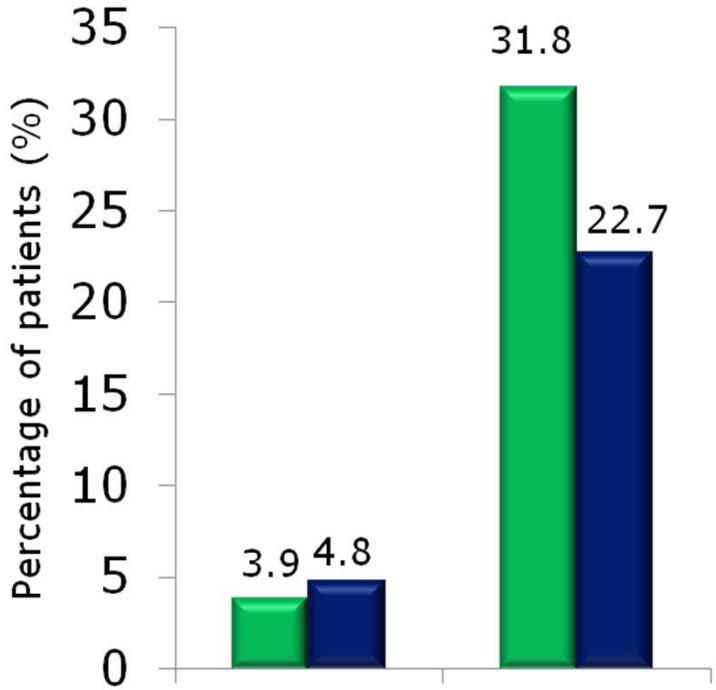
HbA_{1c} ≤6.5%

	Baseline		24 Weeks	
n	57250	3074	49102	2022



HbA_{1c} <7.0%

Baseline		24 Weeks	
57250	3074	49102	2022



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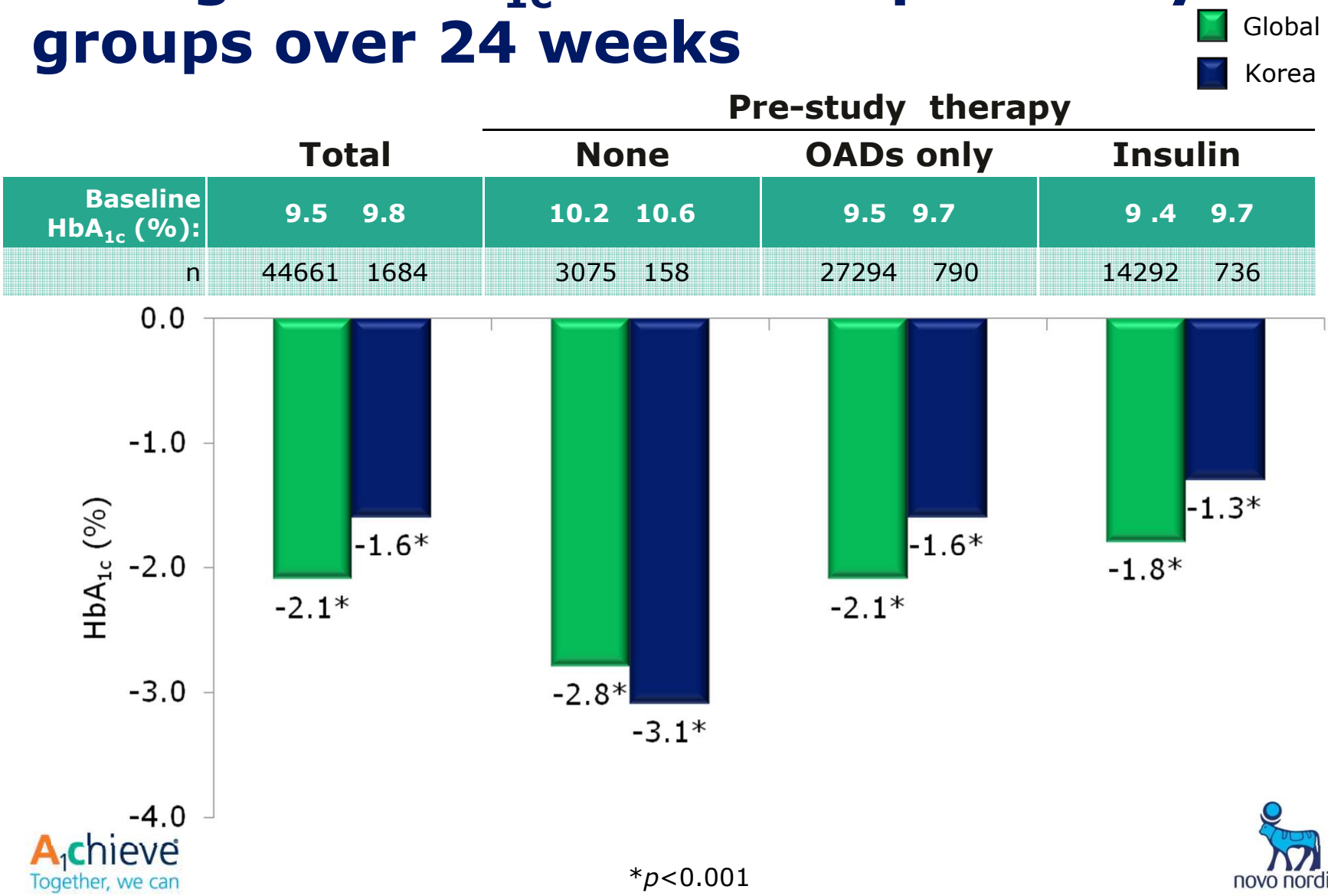
Change in HbA_{1c} across all pre-study groups over 24 weeks



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*$p<0.001$

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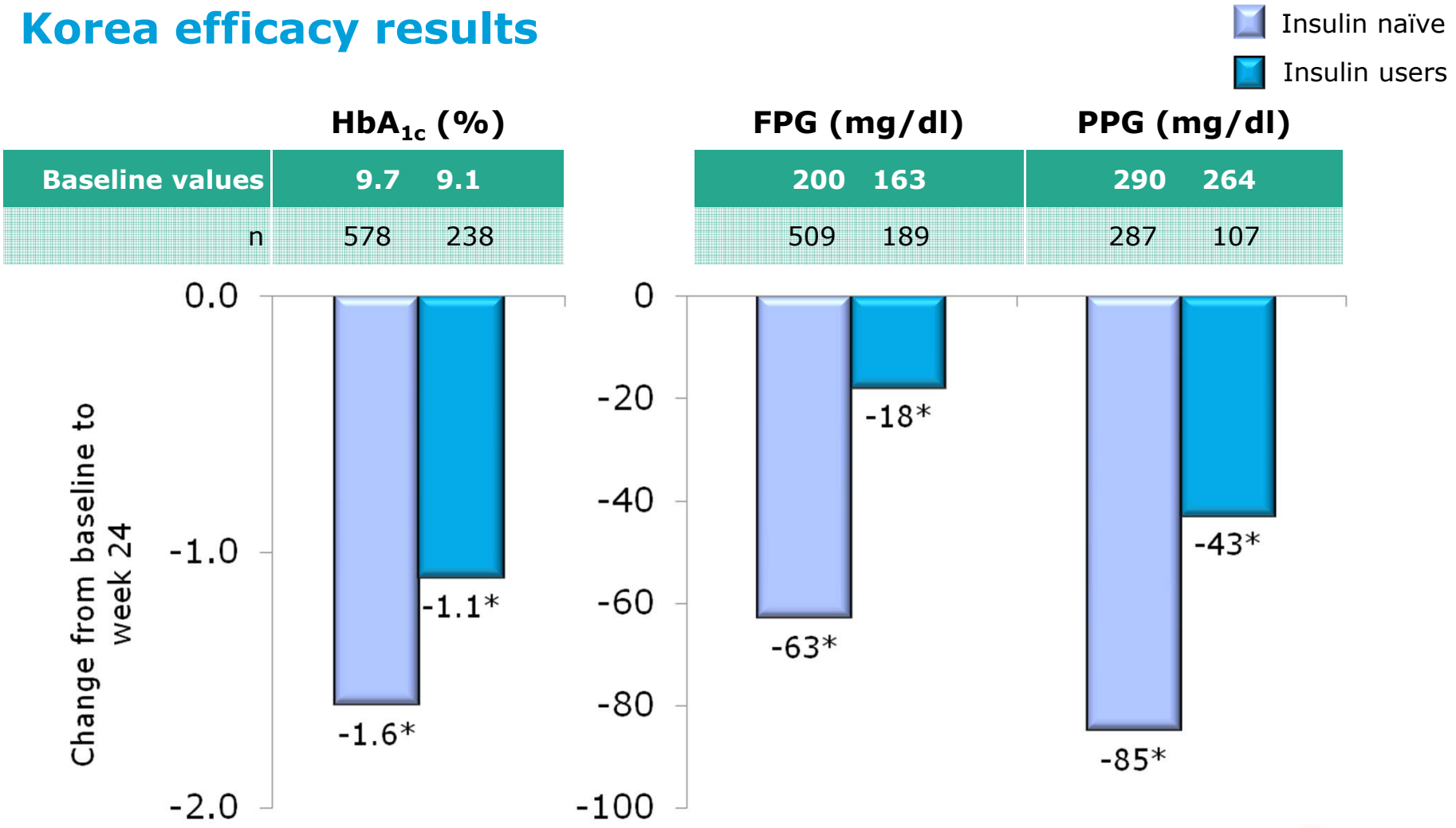
Levemir ± OAD:

Korea efficacy results



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*$p<0.001$

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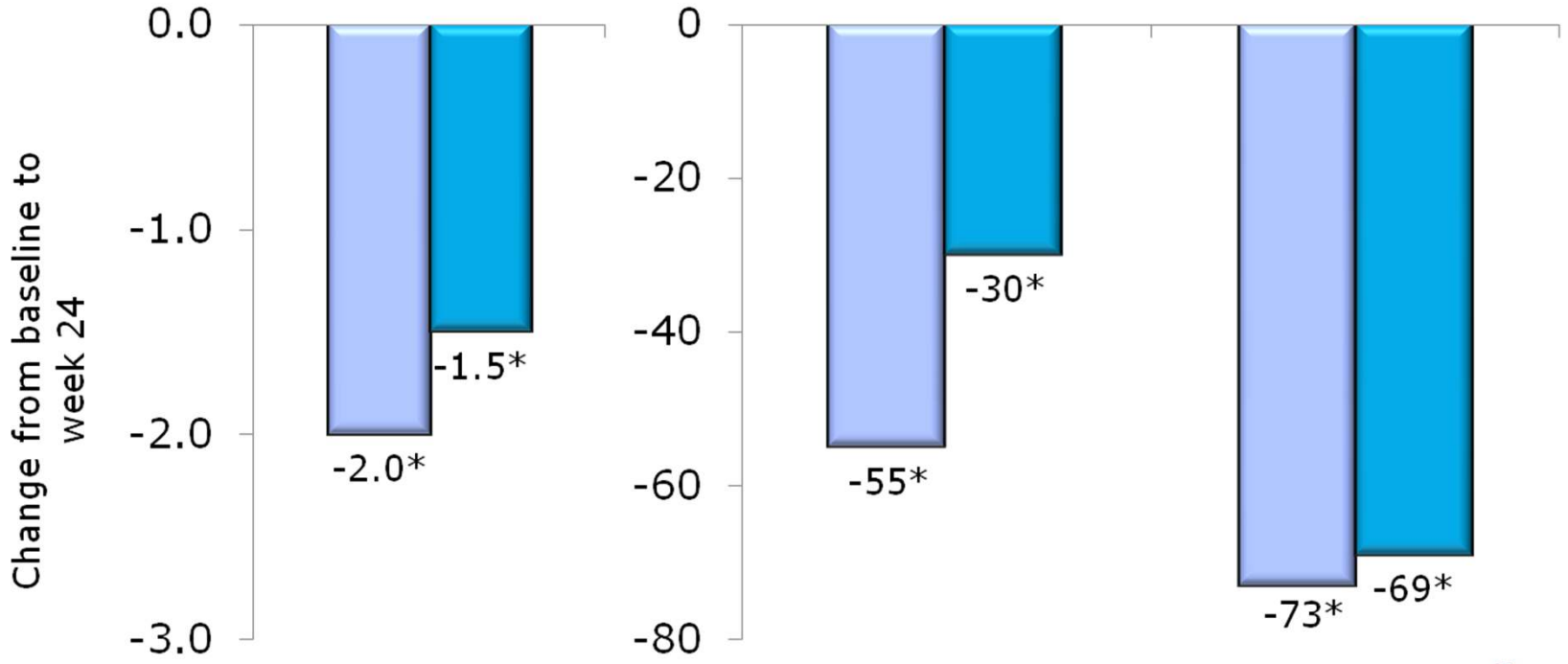
NovoMix ± OAD:
Korea efficacy results

Insulin naïve
Insulin users

	HbA_{1c} (%)		FPG (mg/dl)		PPG (mg/dl)	
Baseline values	**10.2**	**10.1**	**203**	**183**	**282**	**278**
n	270	357	225	309	132	171



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*p<0.001

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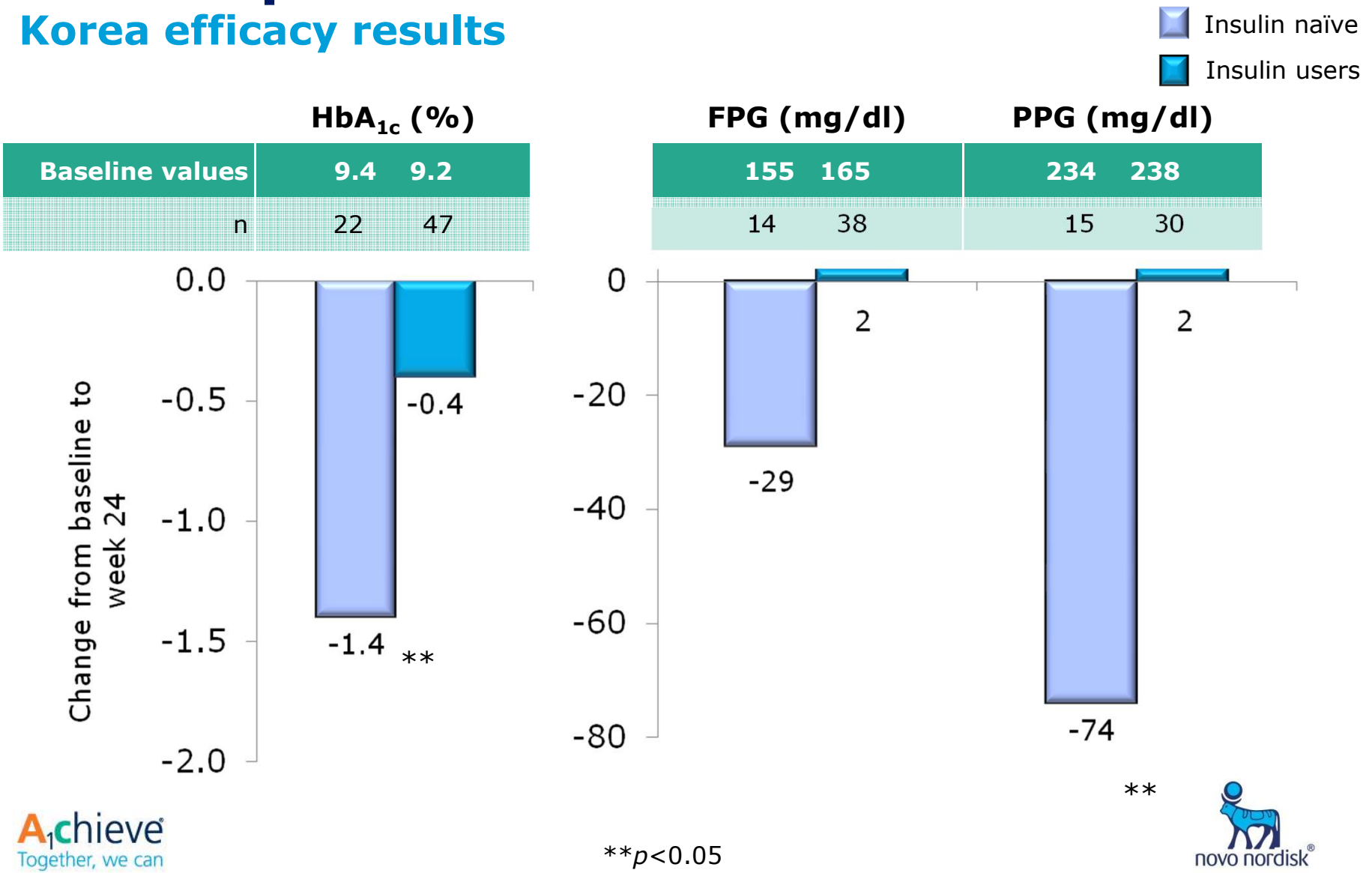
NovoRapid ± OAD:

Korea efficacy results



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**$p<0.05$

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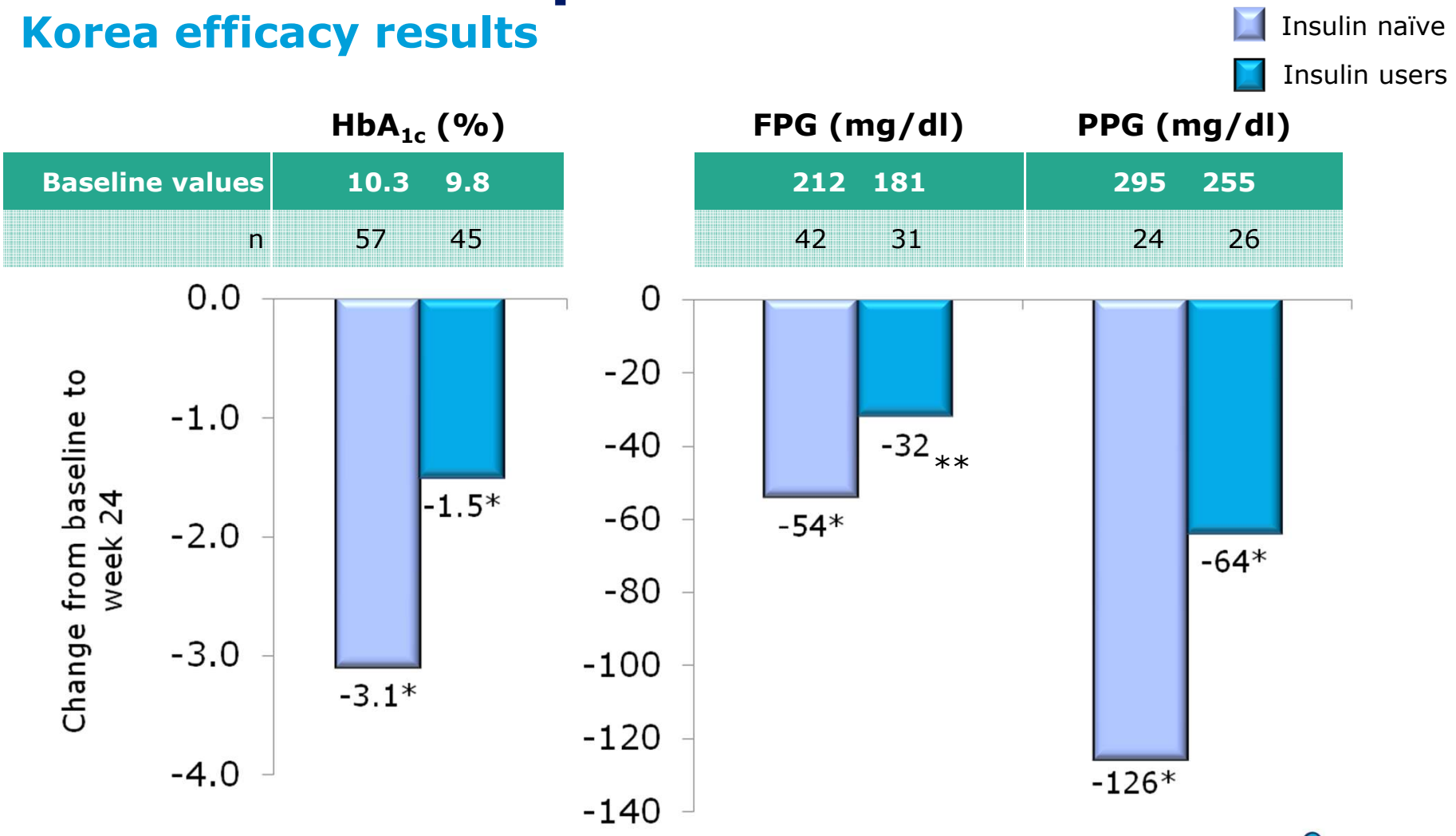
Basal + NovoRapid ± OAD:

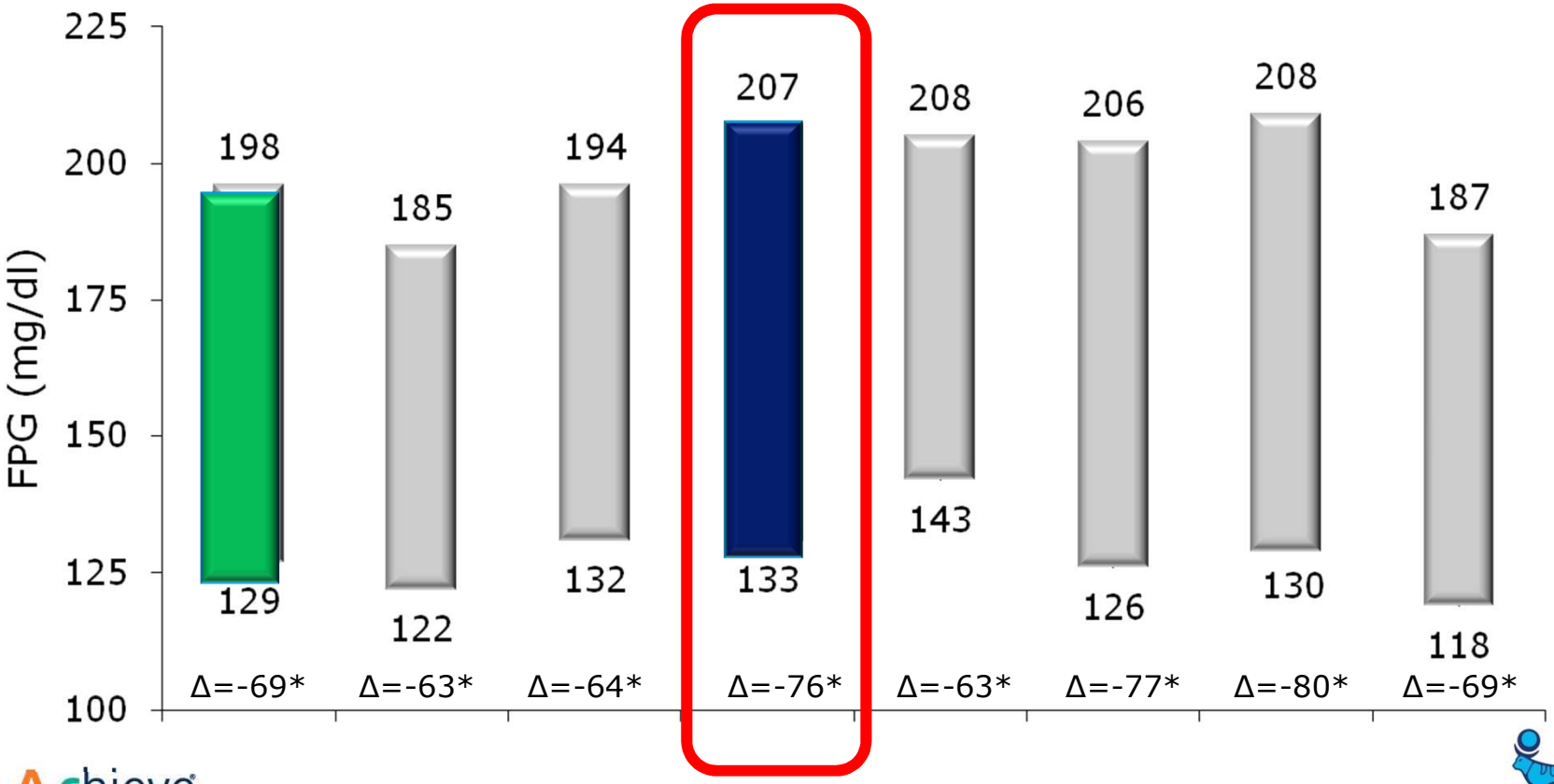
Korea efficacy results



*p<0.001
**p<0.05

Change in FPG (before breakfast) across all regions

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
n	48191	8281	17287	5225	2904	10737	738	3019



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*p<0.001

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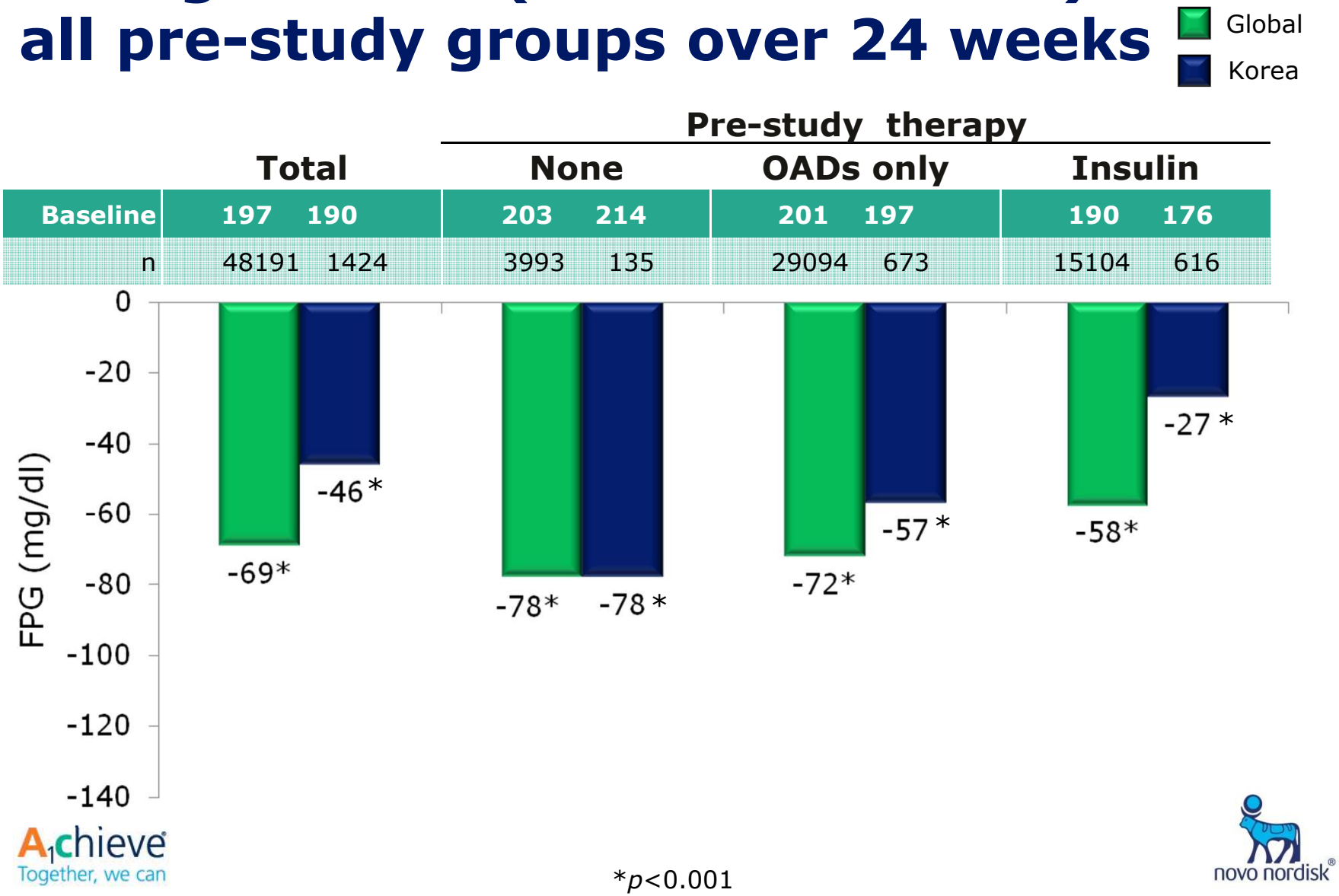
Change in FPG (before breakfast) across all pre-study groups over 24 weeks



*p<0.001

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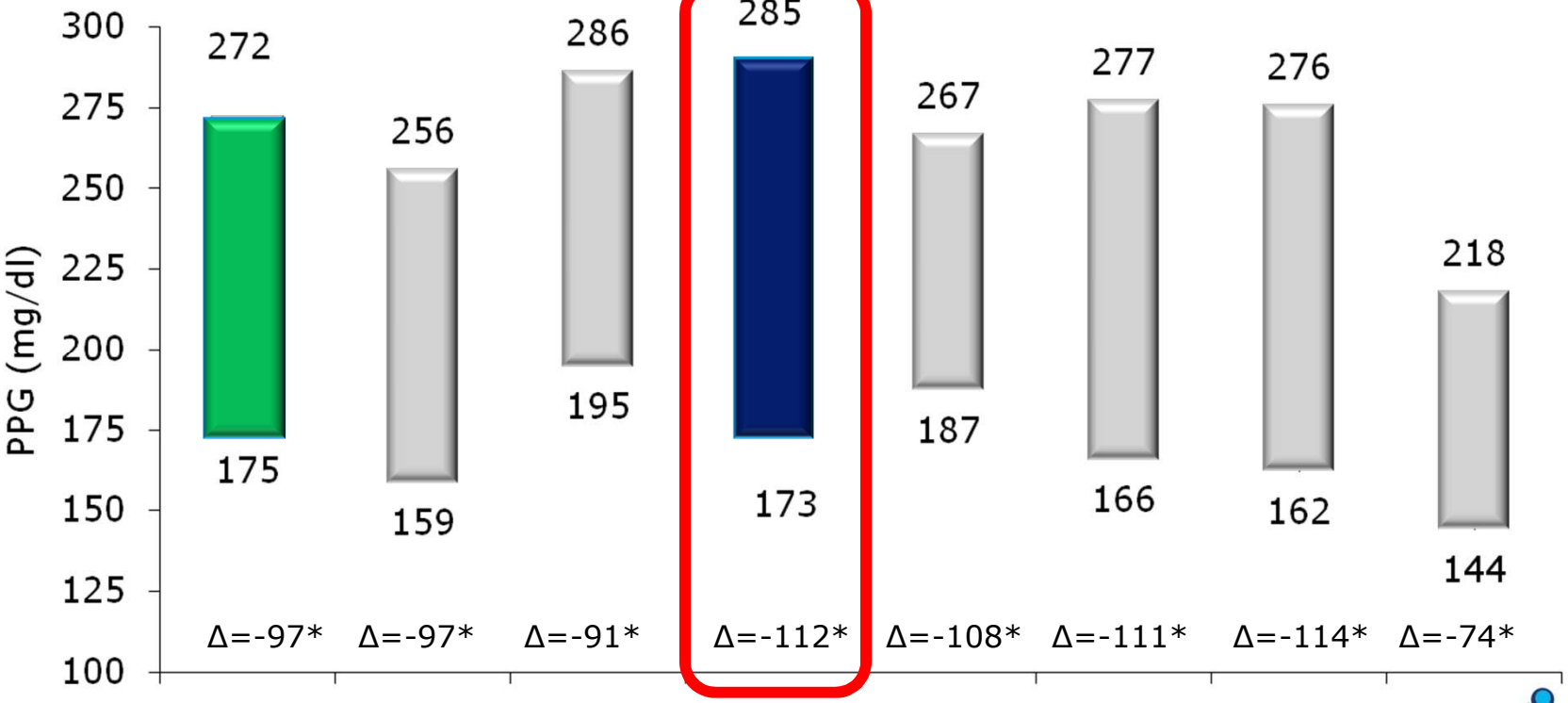
Change in PPG (after breakfast) across all regions

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
n	33742	6251	12570	2987	1683	7588	146	2517



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*p<0.001

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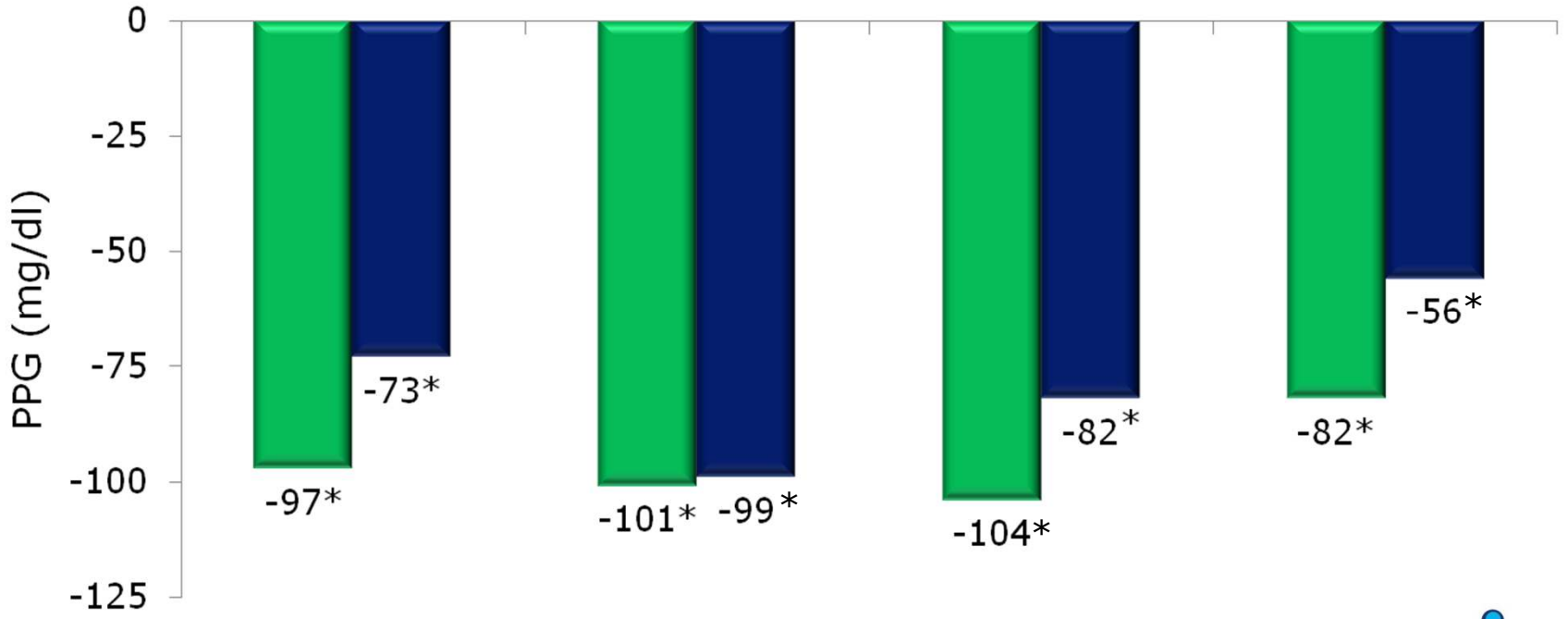
Change in PPG (post breakfast) across all pre-study groups over 24 weeks

Global
Korea

		Pre-study therapy		
	Total	None	OADs only	Insulin
Baseline (mg/dl)	274 280	288 299	280 283	258 270
n	33742 827	2960 96	20734 373	10408 358



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*p<0.001

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Summary

- Significant HbA_{1c}, FPG and PPG reductions were achieved on insulin therapy:
  - Improvements in all regions and in all pre-study therapy groups
- Levemir, NovoMix and NovoRapid were all shown to be effective at:
  - Reducing HbA_{1c}

	Insulin	
	naive	user
1. Insulin detemir ± OADs	1.6	1.1
2. Biphasic insulin aspart ± OADs	2.0	1.5
3. Basal + aspart ± OADs	1.4	0.4
4. Insulin aspart ± OADs	3.1	1.5

  - Reducing FPG
  - Reducing PPG

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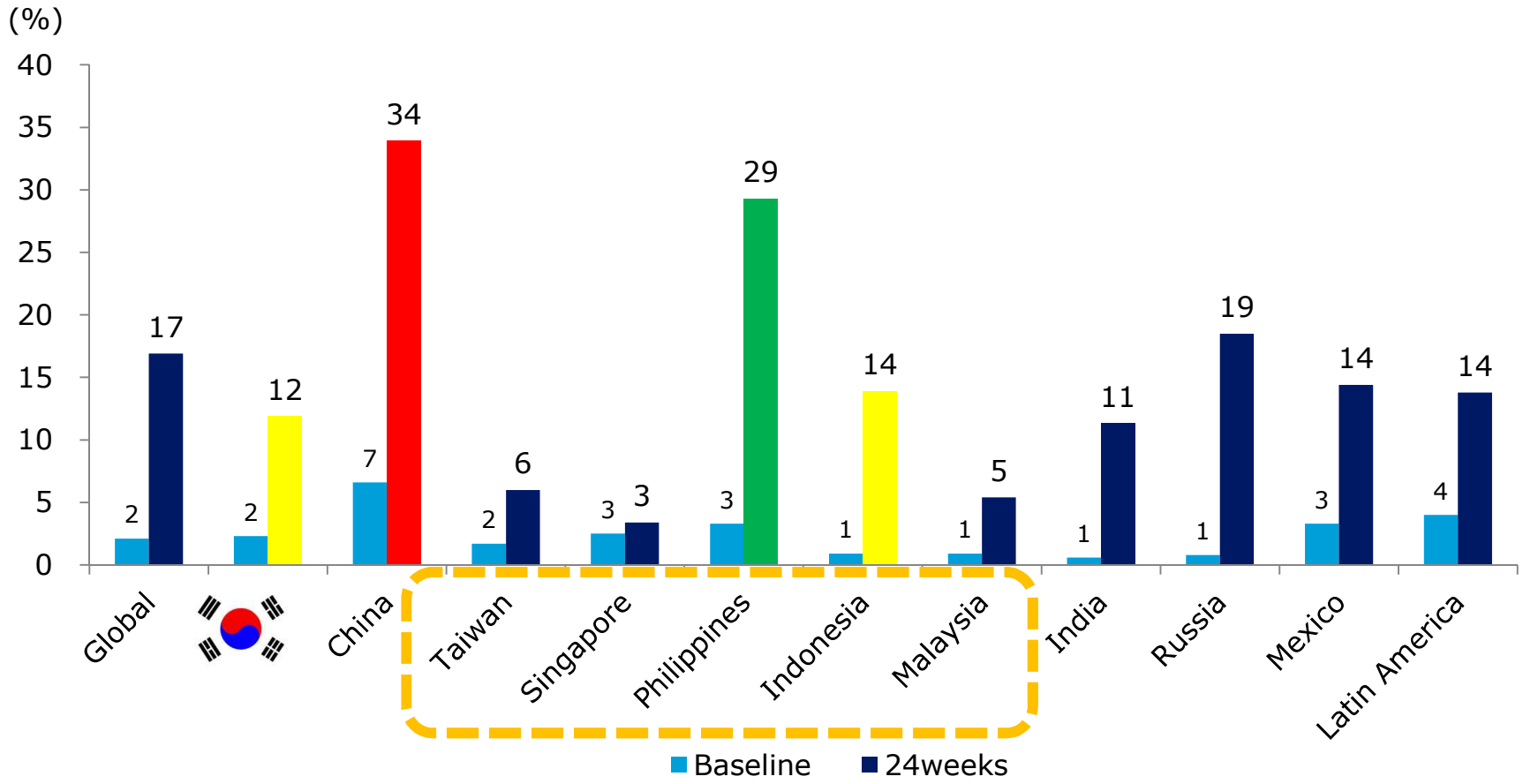
Proportion of patients achieved HbAc1 ≤ 6.5



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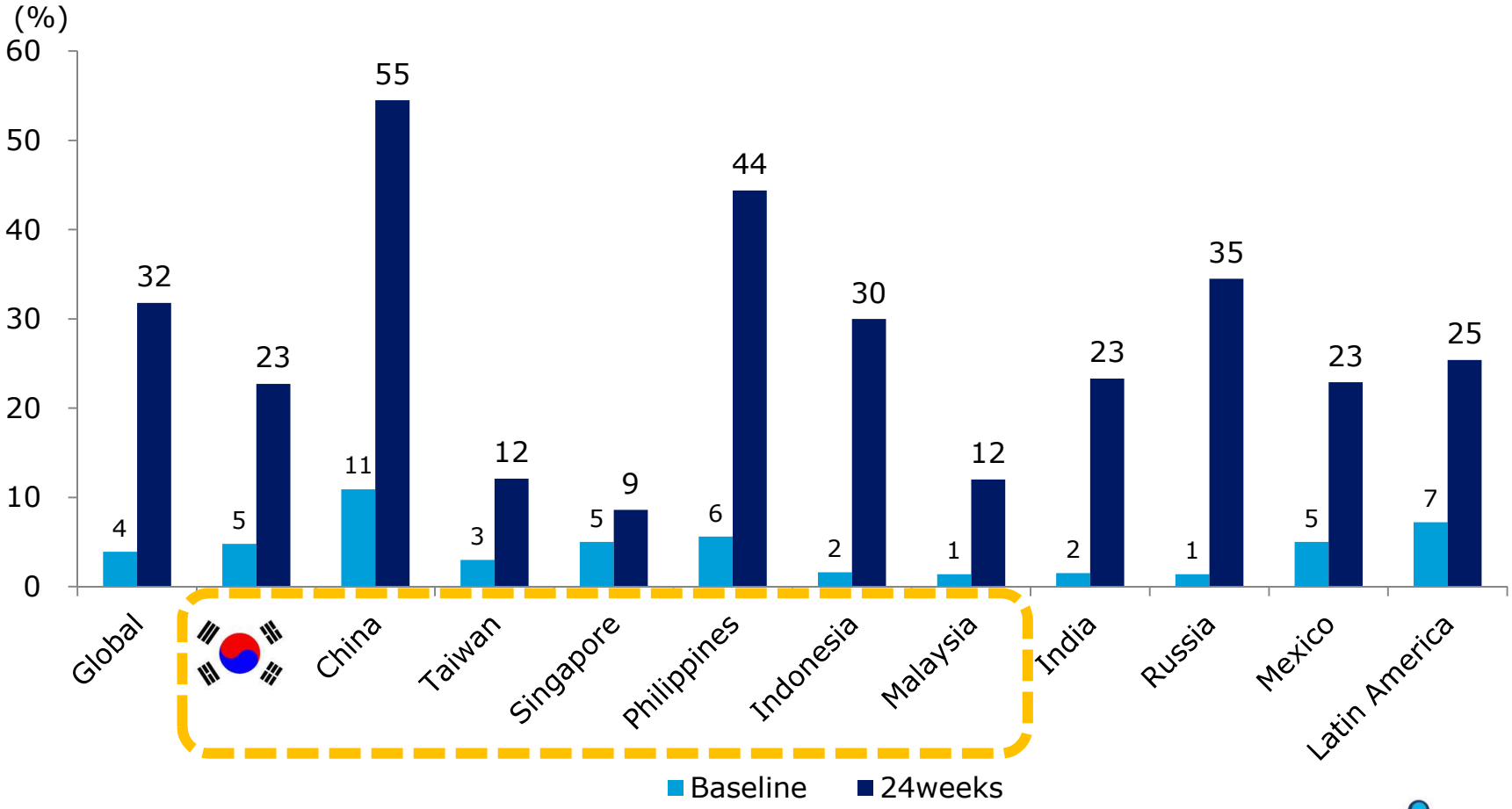
Proportion of patients achieved HbAc1 ≤ 7.0



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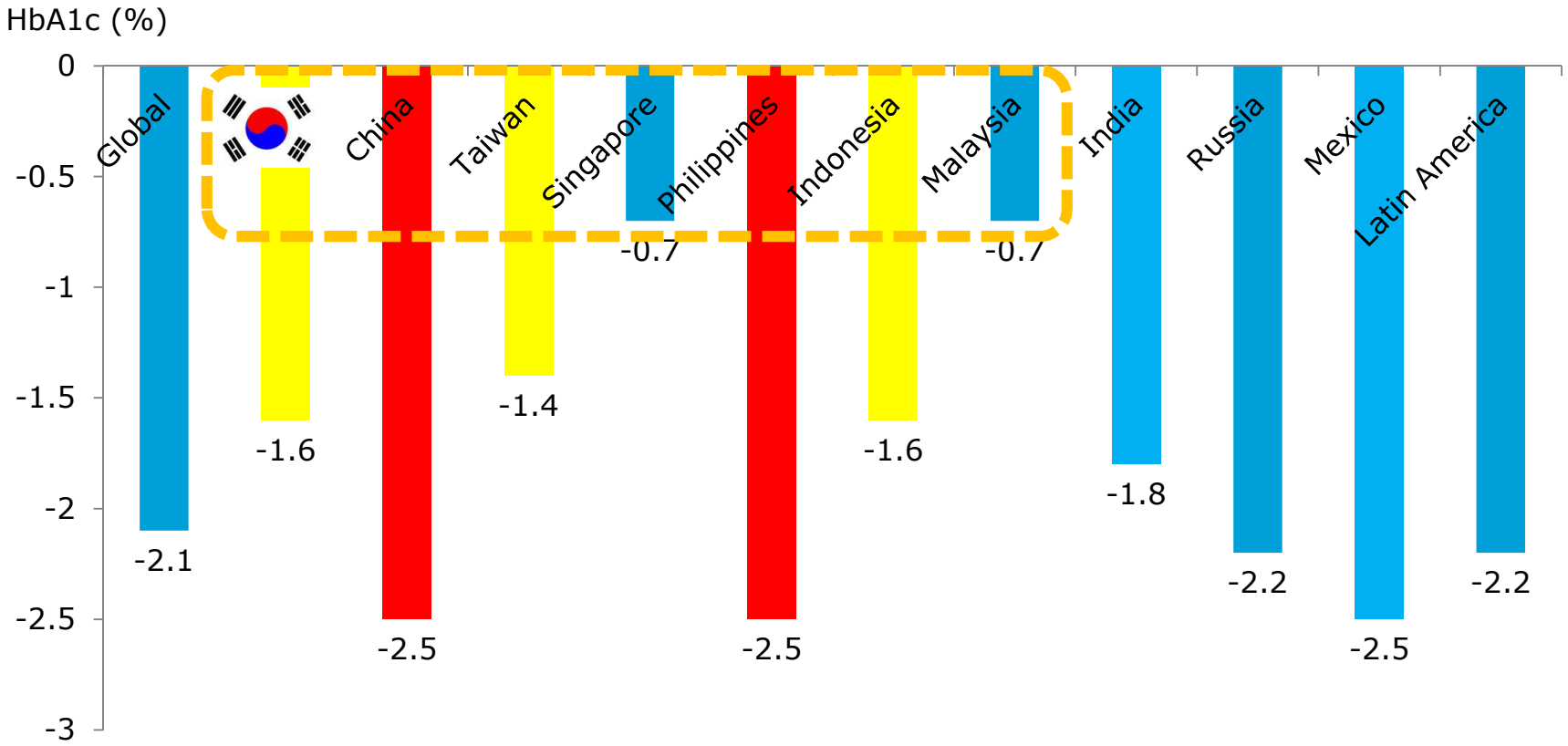
HbA1c changes at 24 weeks



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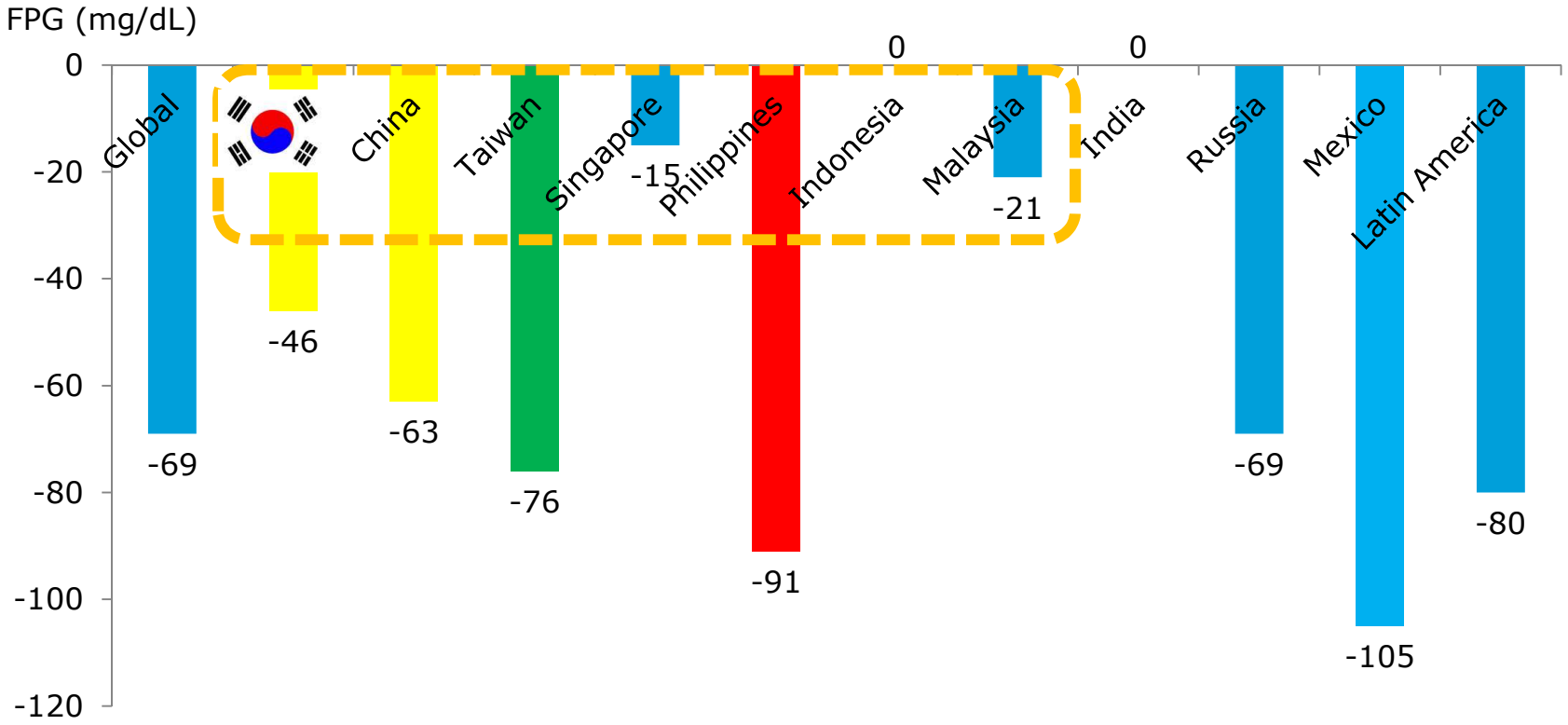
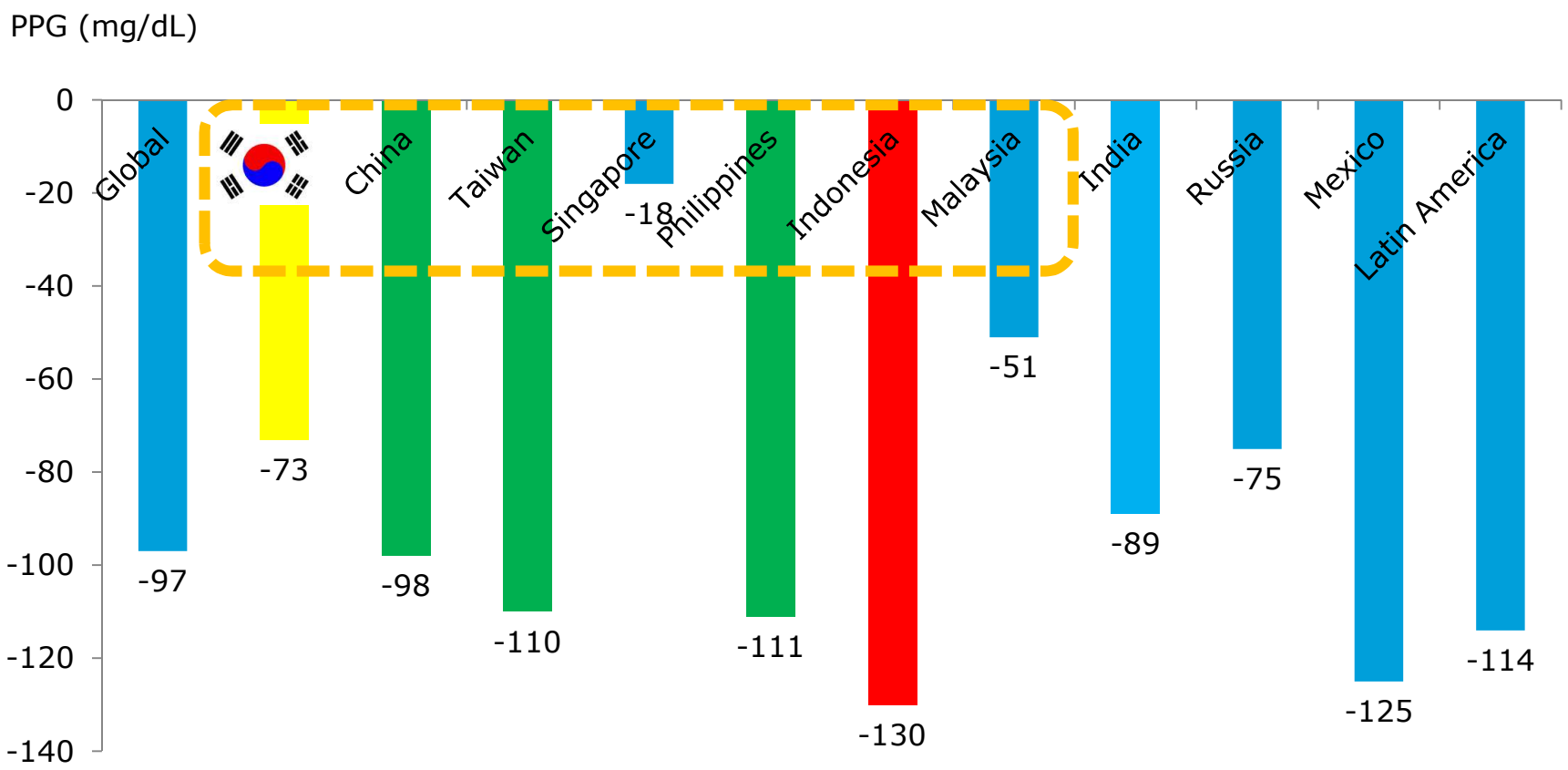
FPG changes at 24 Weeks



PPG changes at 24 weeks



Overview of baseline characteristics by pre-study therapy: China

	Total	No therapy	OAD alone	Insulin±OAD
N	11020	3251	4955	2814
% of total	-	**29.5**	45.0	25.5
Gender M/F (%)	57.2/42.8	62.9/37.1	54.6/45.4	55.2/44.8
Age (years)	54.9 (14.7)	51.0 (14.8)	56.3 (13.9)	56.7 (15.3)
Weight (kg)	68.2 (11.8)	68.3 (12.4)	68.2 (11.5)	68.1 (11.7)
BMI (kg/m^2)	24.7 (3.4)	24.5 (3.4)	24.7 (3.3)	24.8 (3.4)
Diabetes duration (yrs)	6.3 (6.3)	2.3 (4.3)	6.9 (5.5)	9.7 (7.0)
HbA_{1c} (%)	9.5 (2.3)	10.2 (2.4)	9.4 (2.2)	9.0 (2.3)

平均值(标准差), 数量或百分比

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OGLD, 口服降糖药

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Overview of baseline characteristics by pre-study therapy : Philippines

	Total	No therapy	OGLD alone	Insulin± OGLD
N	2468	203	1775	490
% of total	-	8.2	**71.9**	19.9
Gender M/F (%)	45.3/54.7	53.2/46.8	45.3/54.7	42.0/58.0
Age (years)	56.0 (12.0)	51.7 (13.5)	56.1 (11.3)	57.6 (13.6)
Weight (kg)	65.9 (14.6)	65.1 (16.4)	66.1 (14.3)	65.4 (15.0)
BMI (kg/m^2)	25.7 (5.3)	25.7 (6.0)	25.7 (5.0)	25.7 (5.8)
Diabetes duration (yrs)	7.1 (5.6)	3.2 (5.1)	7.0 (5.0)	9.2 (6.5)
HbA_{1c} (%)	9.6 (2.1)	10.2 (2.4)	9.6 (2.0)	9.4 (2.1)

All data are mean (SD)

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OGLD, oral glucose-lowering drug

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Hypoglycaemia

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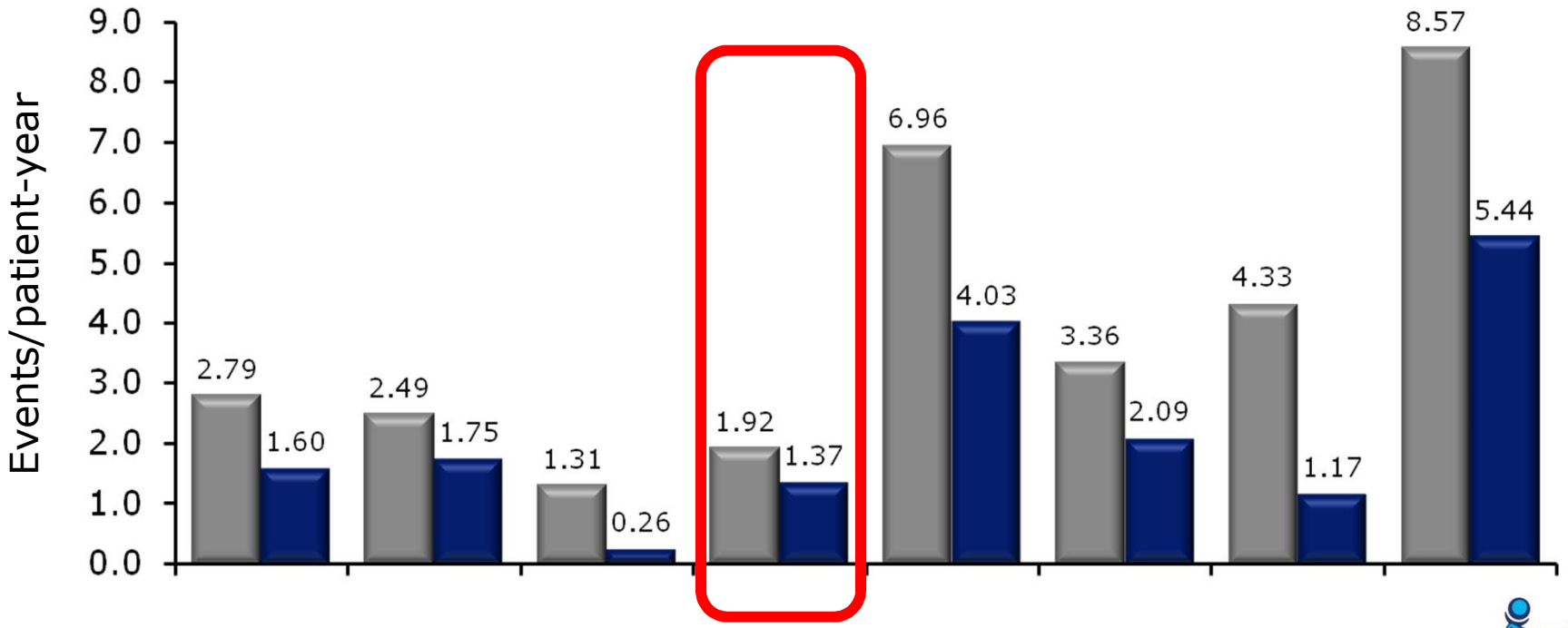
Rate of all minor hypoglycaemia by region

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
No. of pt w/hypo	5645 3358	877 693	1407 274	614 410	729 462	1425 1003	124 51	469 465



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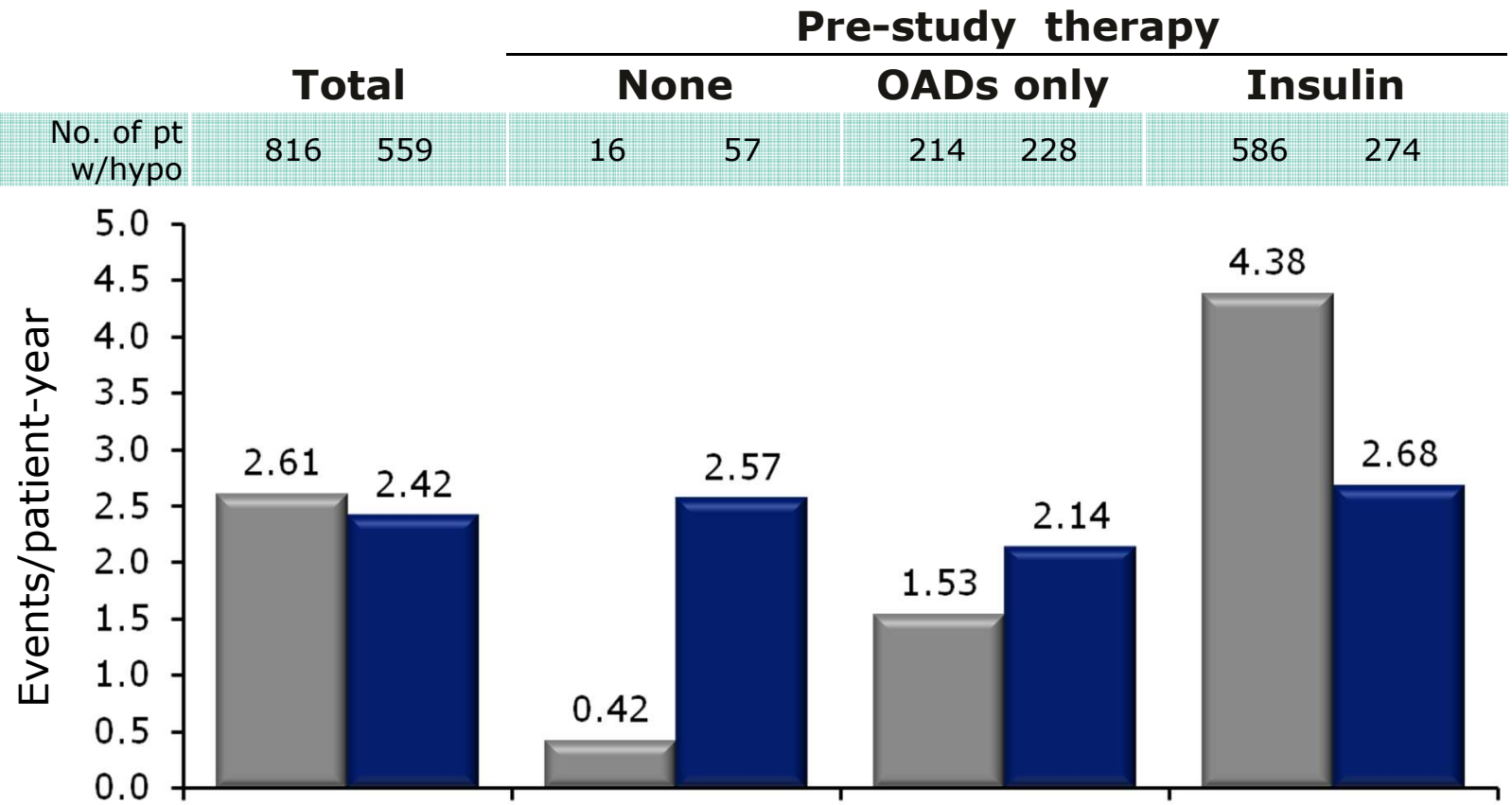
Rate of all minor hypoglycaemia by pre-study therapy: Korea



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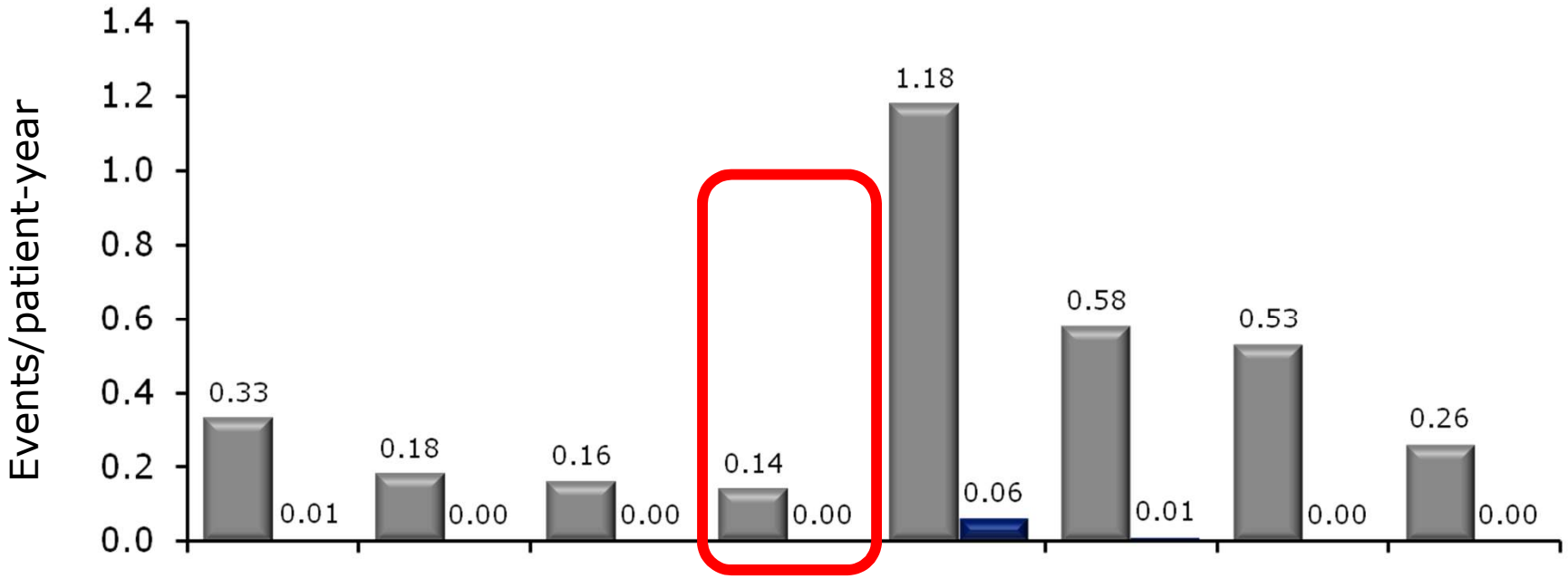
Rate of all major hypoglycaemia by region

Baseline
24 weeks

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
No. of pt w/hypo	1006 18	97 0	215 0	64 1	213 7	368 10	19 0	30 0



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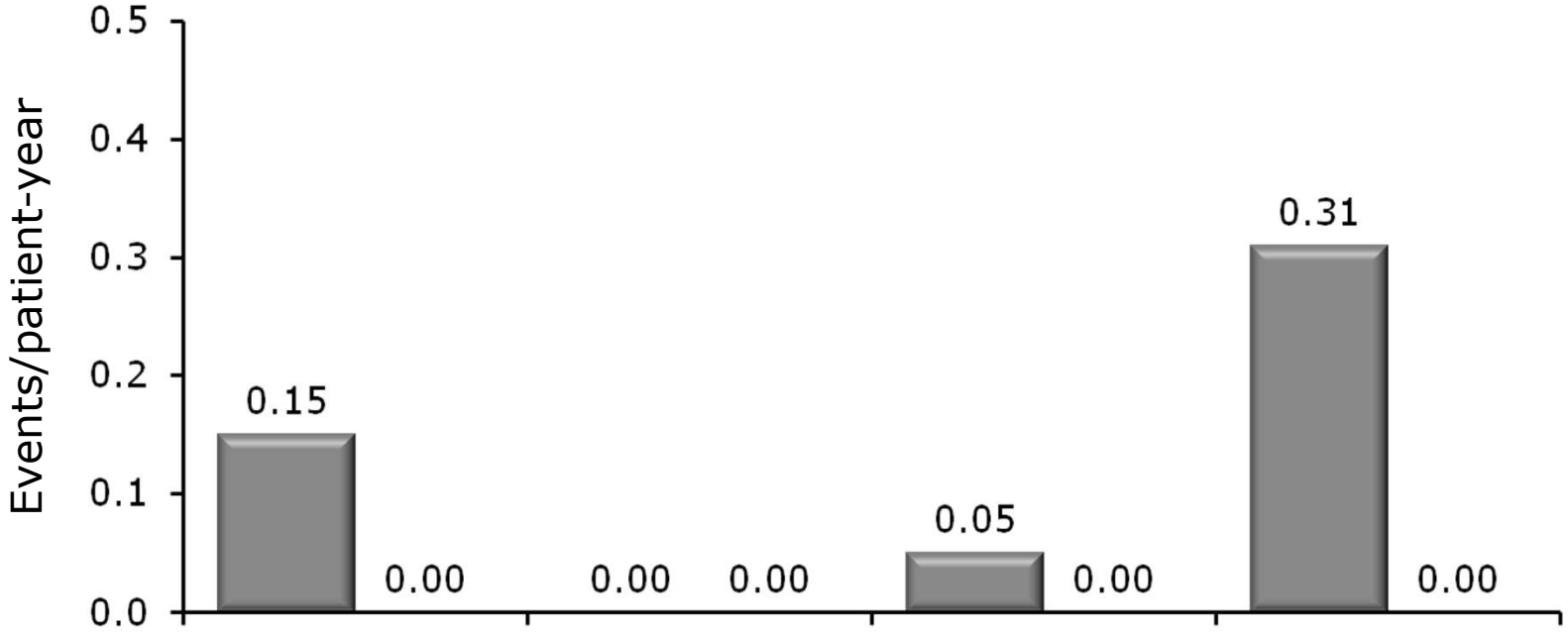
Rate of all major hypoglycaemia by pre-study therapy: Korea

Baseline
24 weeks

	Total		Pre-study therapy: None		OADs only		Insulin	
No. of pt w/hypo	48	0	0	0	7	0	41	0



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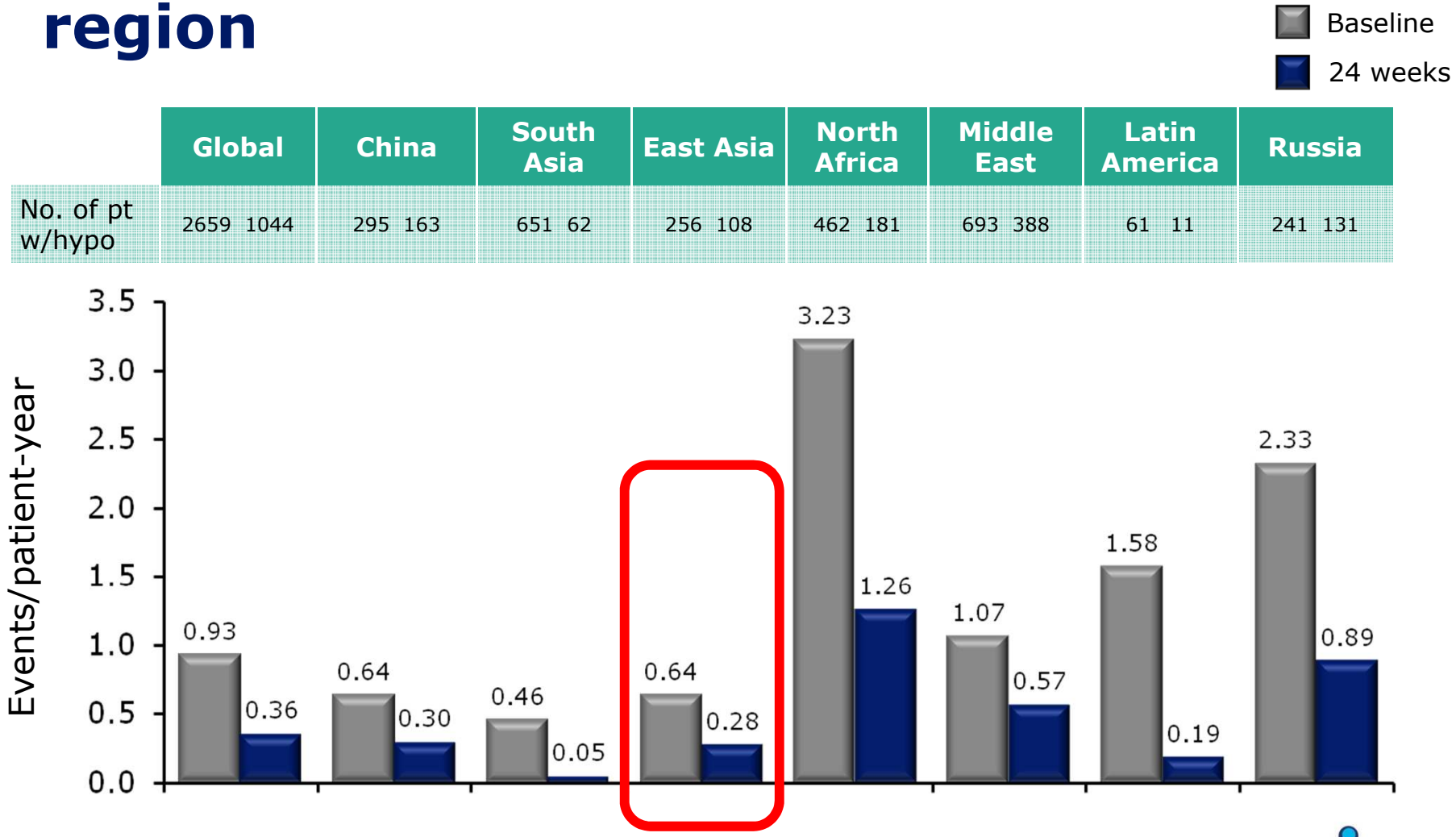
Rate of all nocturnal hypoglycaemia by region



	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
No. of pt w/hypo	2659 1044	295 163	651 62	256 108	462 181	693 388	61 11	241 131

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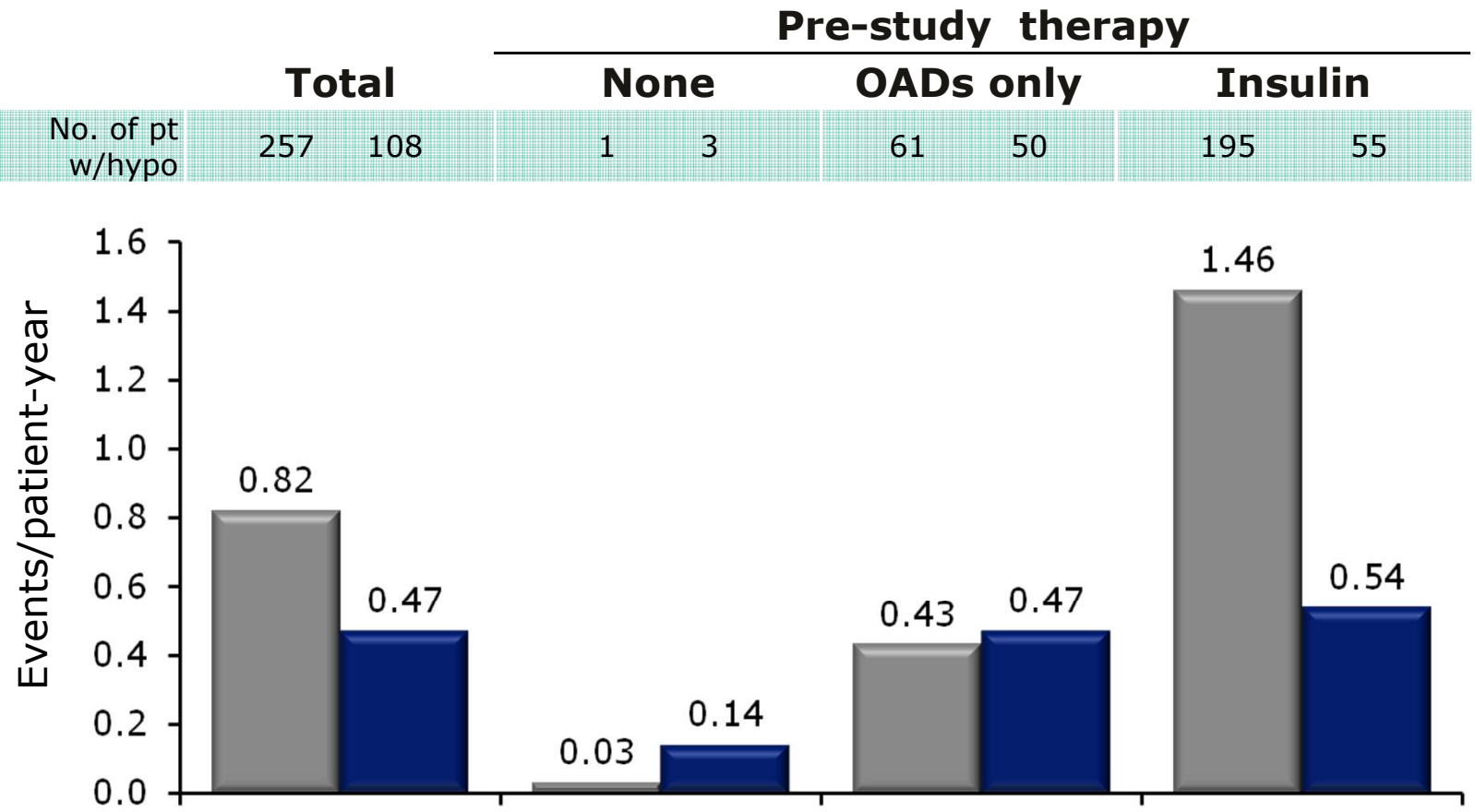
Rate of all nocturnal hypoglycaemia by pre-study therapy: Korea



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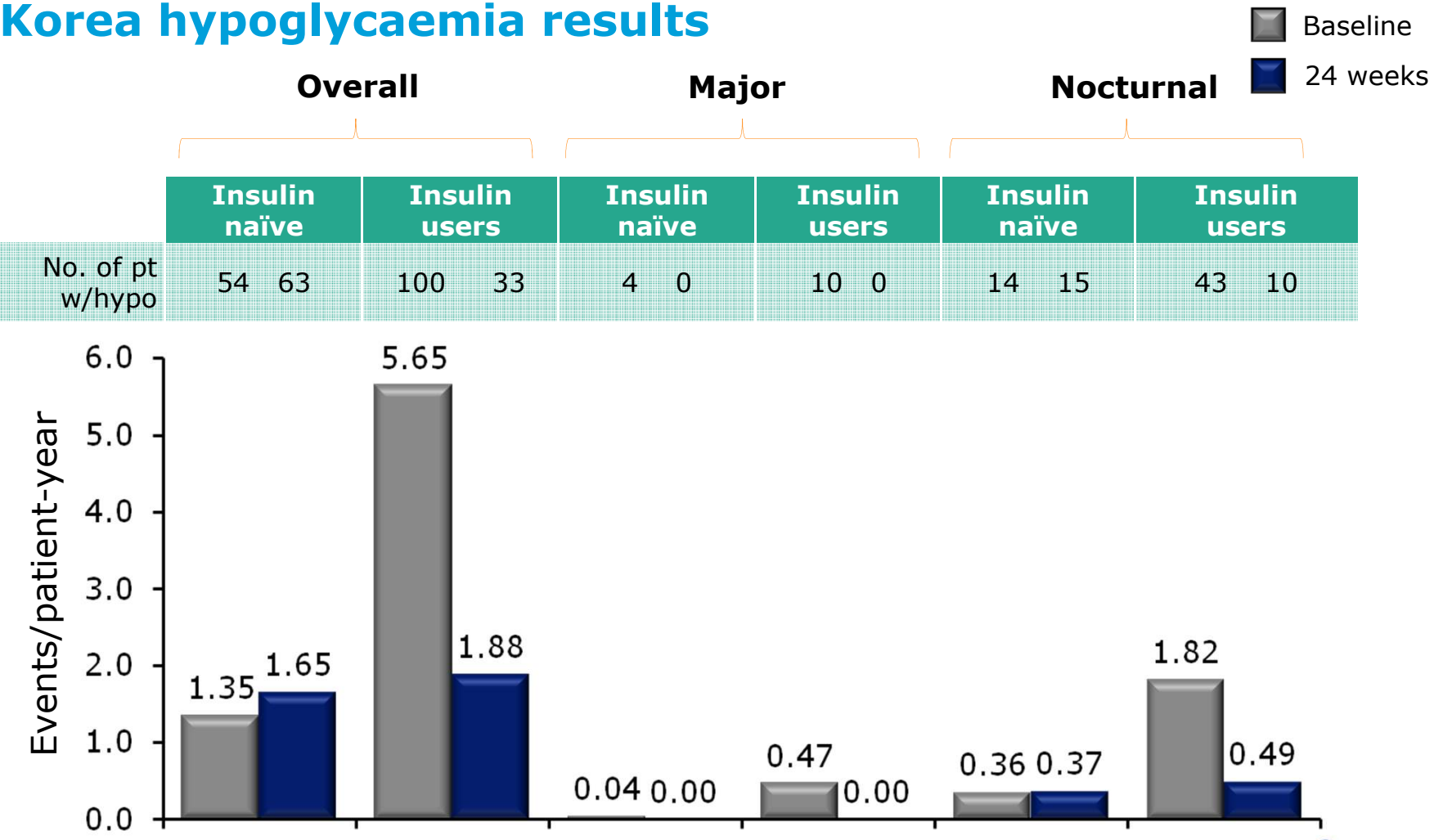
Levemir ± OAD:

Korea hypoglycaemia results



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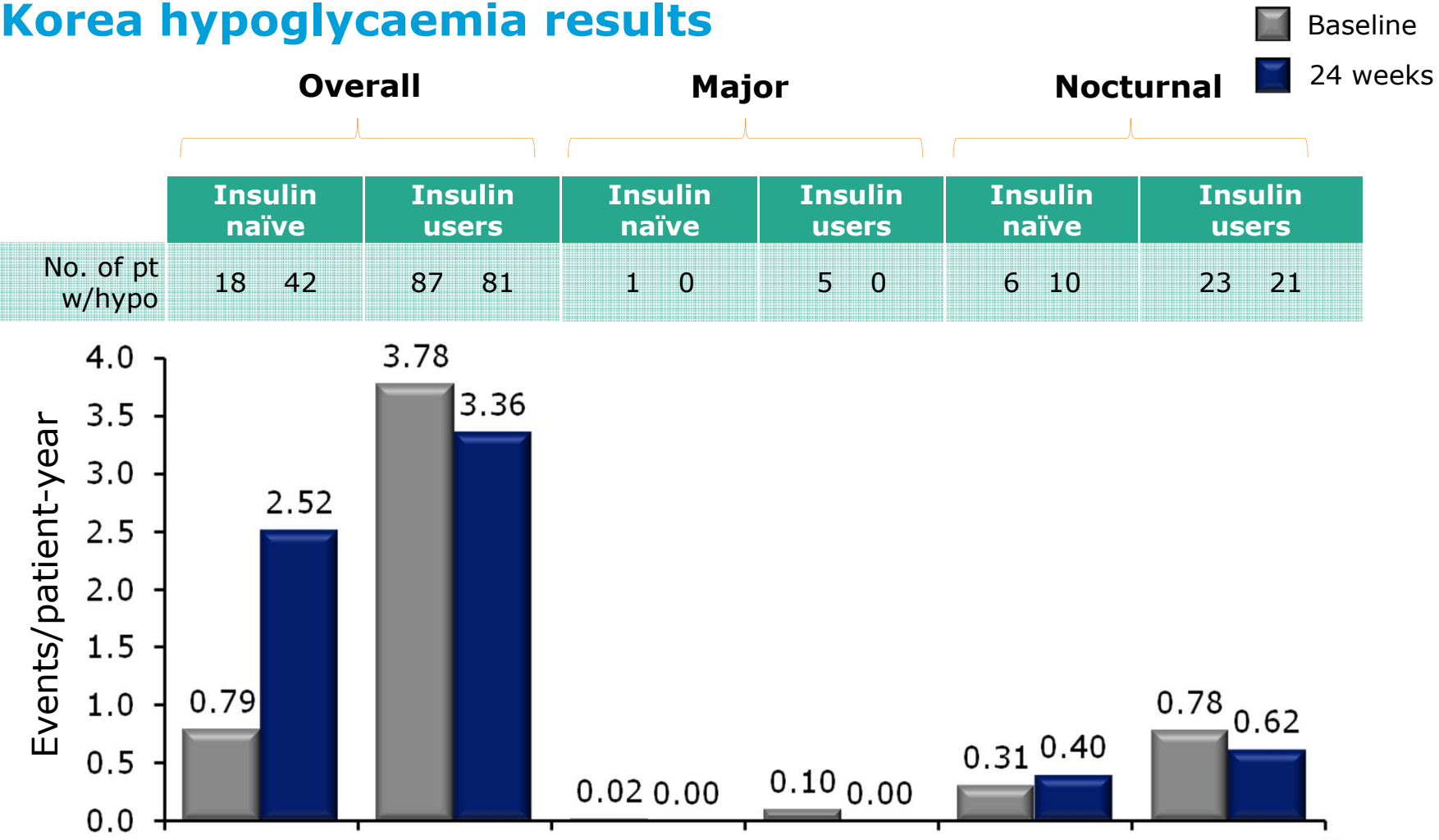
NovoMix ± OAD:

Korea hypoglycaemia results



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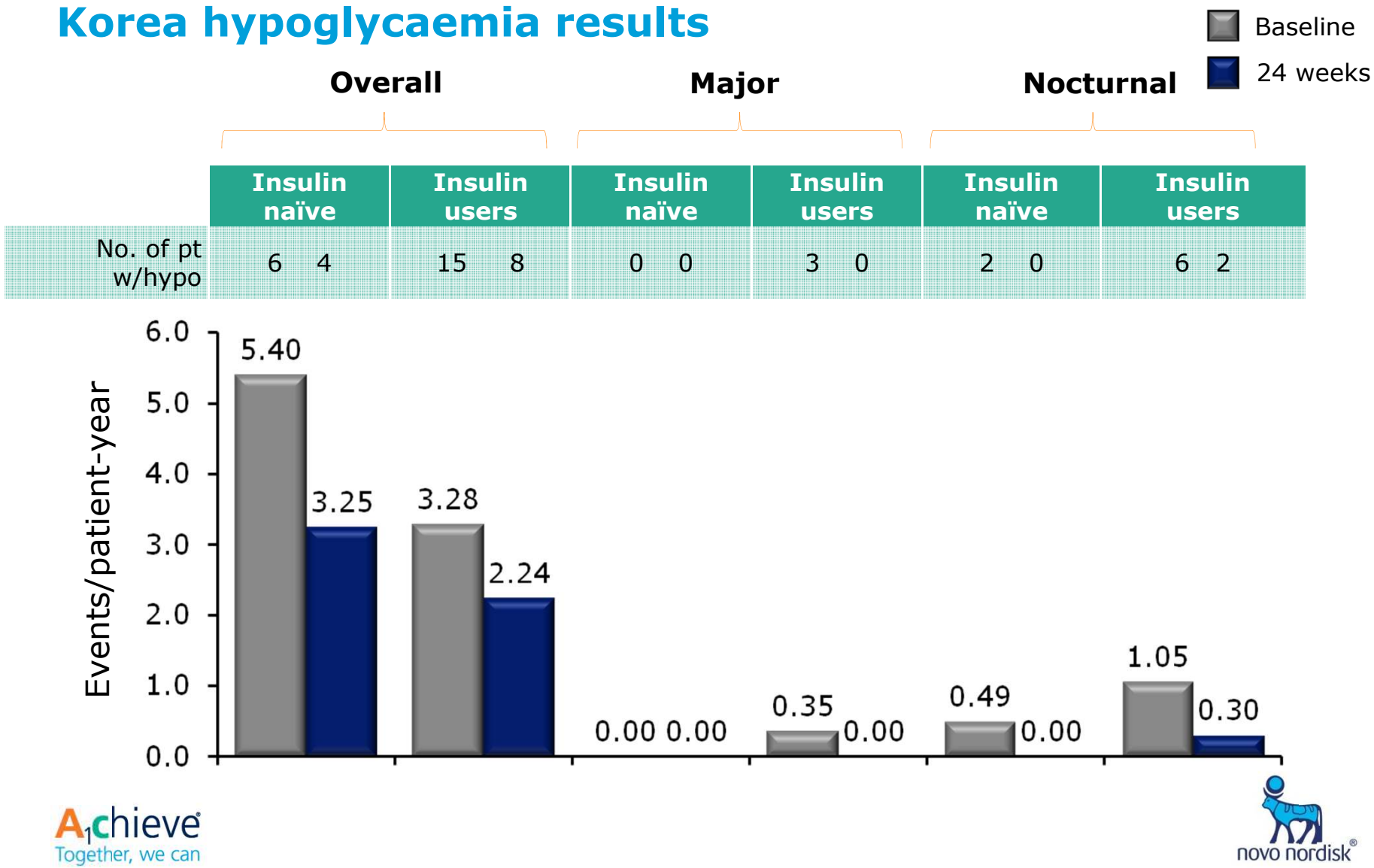
NovoRapid ± OAD:

Korea hypoglycaemia results



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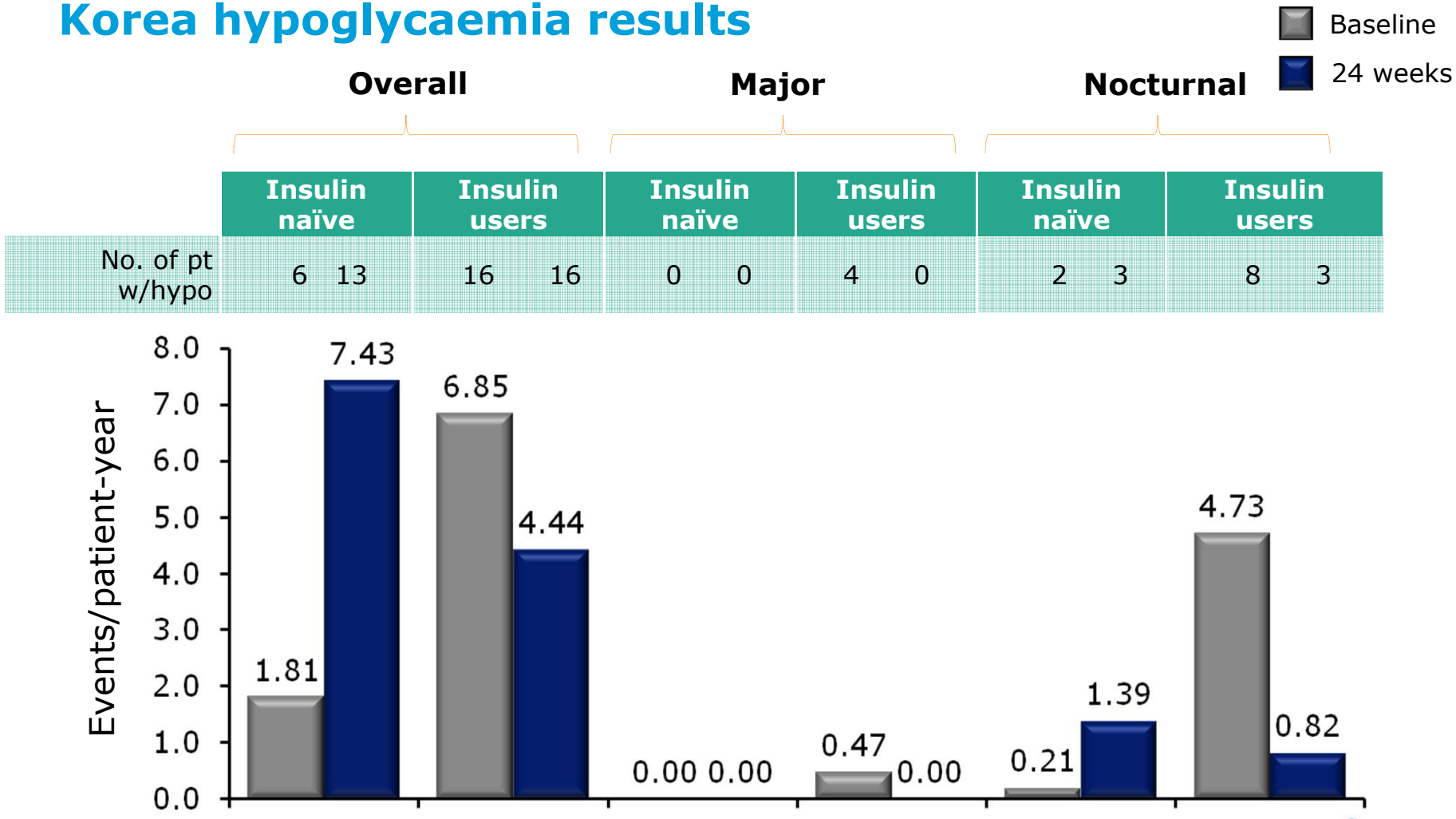
Basal + NovoRapid ± OAD:

Korea hypoglycaemia results



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Summary

- Korean patients reported low rates of hypoglycaemia at 24 weeks, regardless of pre-study therapy
  - Minor
  - Major
  - Nocturnal

	Overall		Nocturnal	
Grouping according to treatment	**naive**	**user**	**naive**	**user**
1. Insulin detemir ± OADs	**1.65**	**1.88**	**0.37**	**0.49**
2. Biphasic insulin aspart ± OADs	**2.52**	**3.36**	**0.4**	**0.62**
3. Insulin aspart ± OADs	**3.25**	**2.24**	**0**	**0.3**
4. Basal + aspart ± OADs	**7.43**	**4.44**	**1.39**	**0.82**

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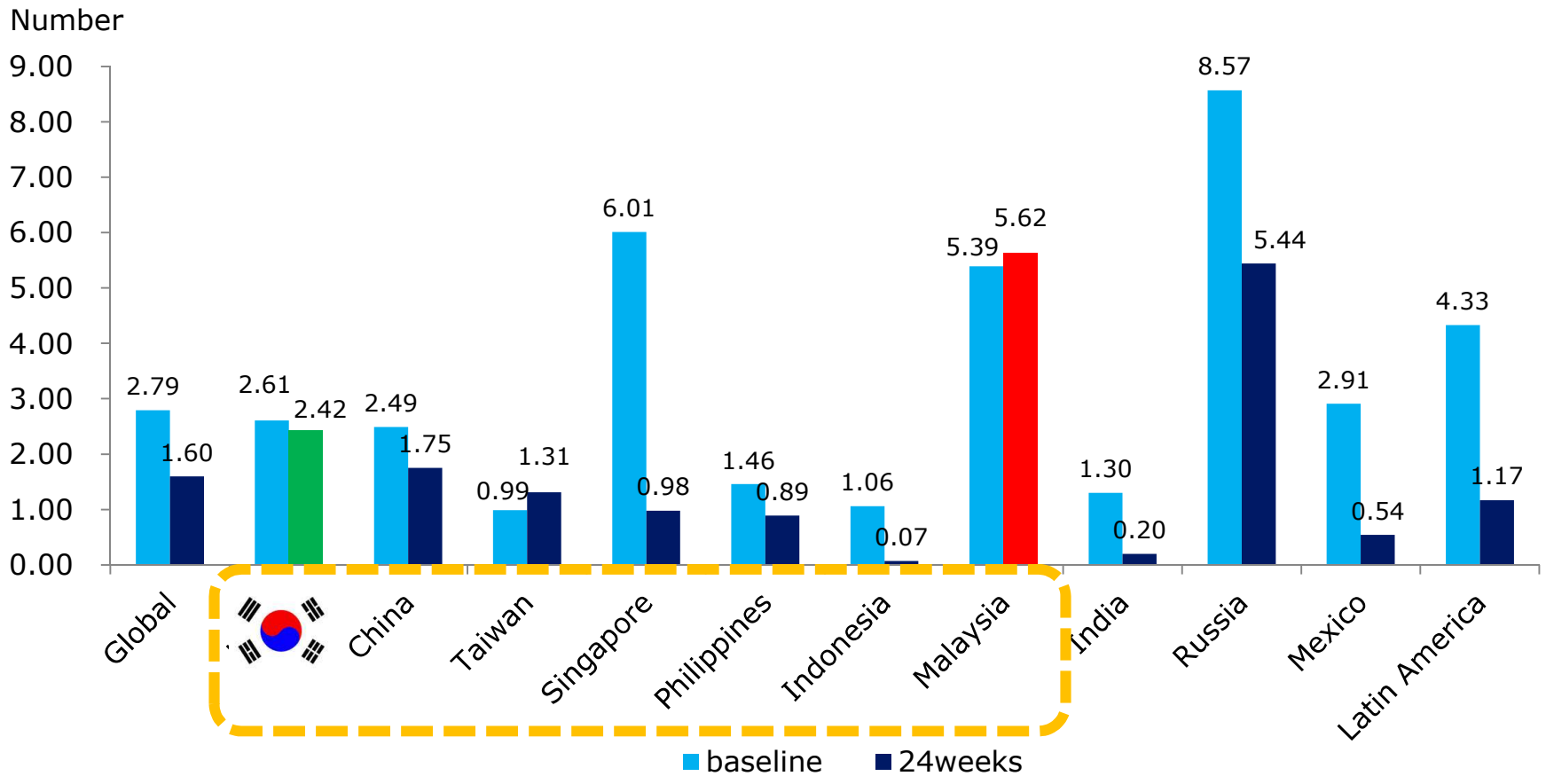
Minor Hypoglycemia



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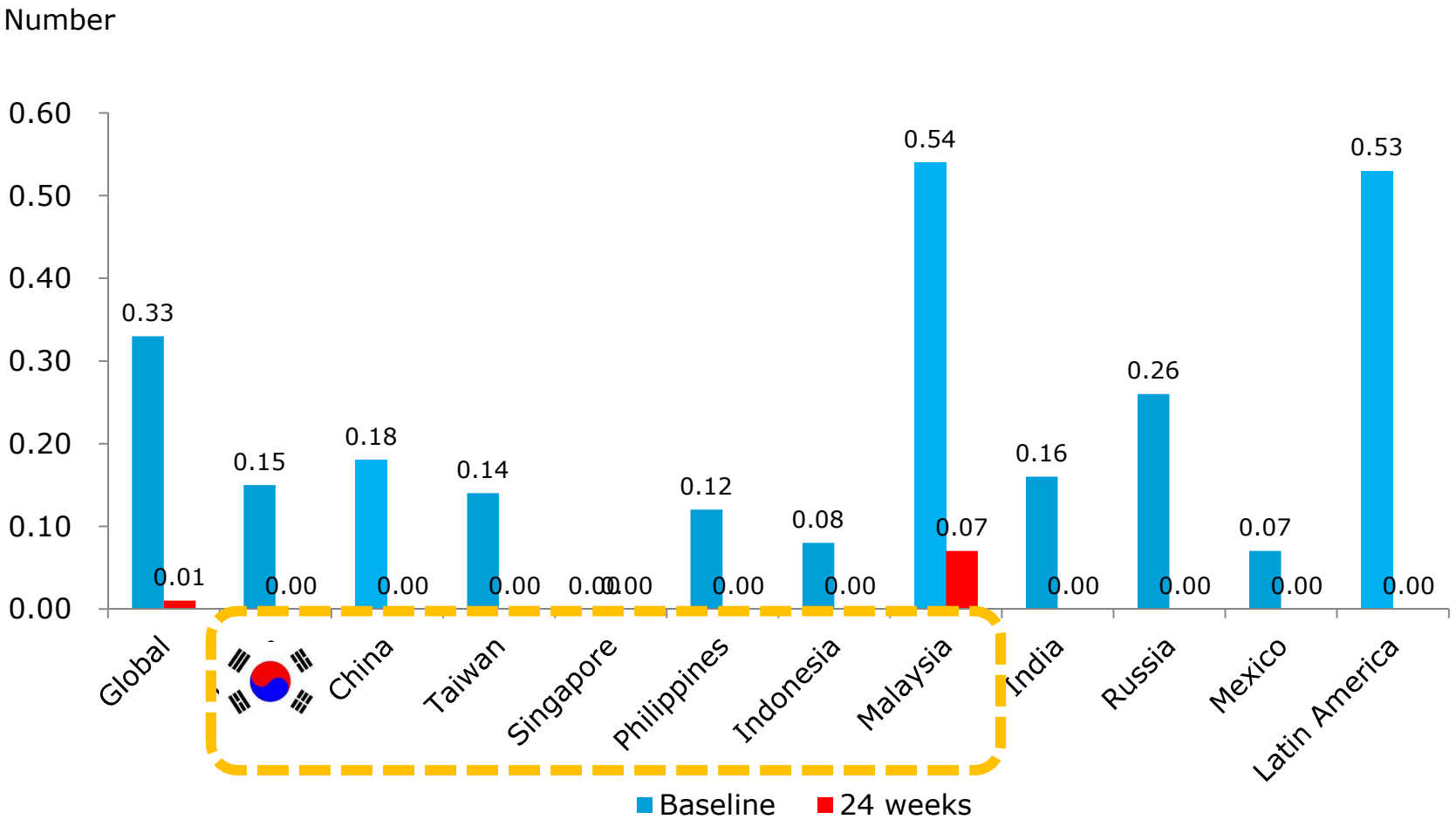
Major Hypoglycemia



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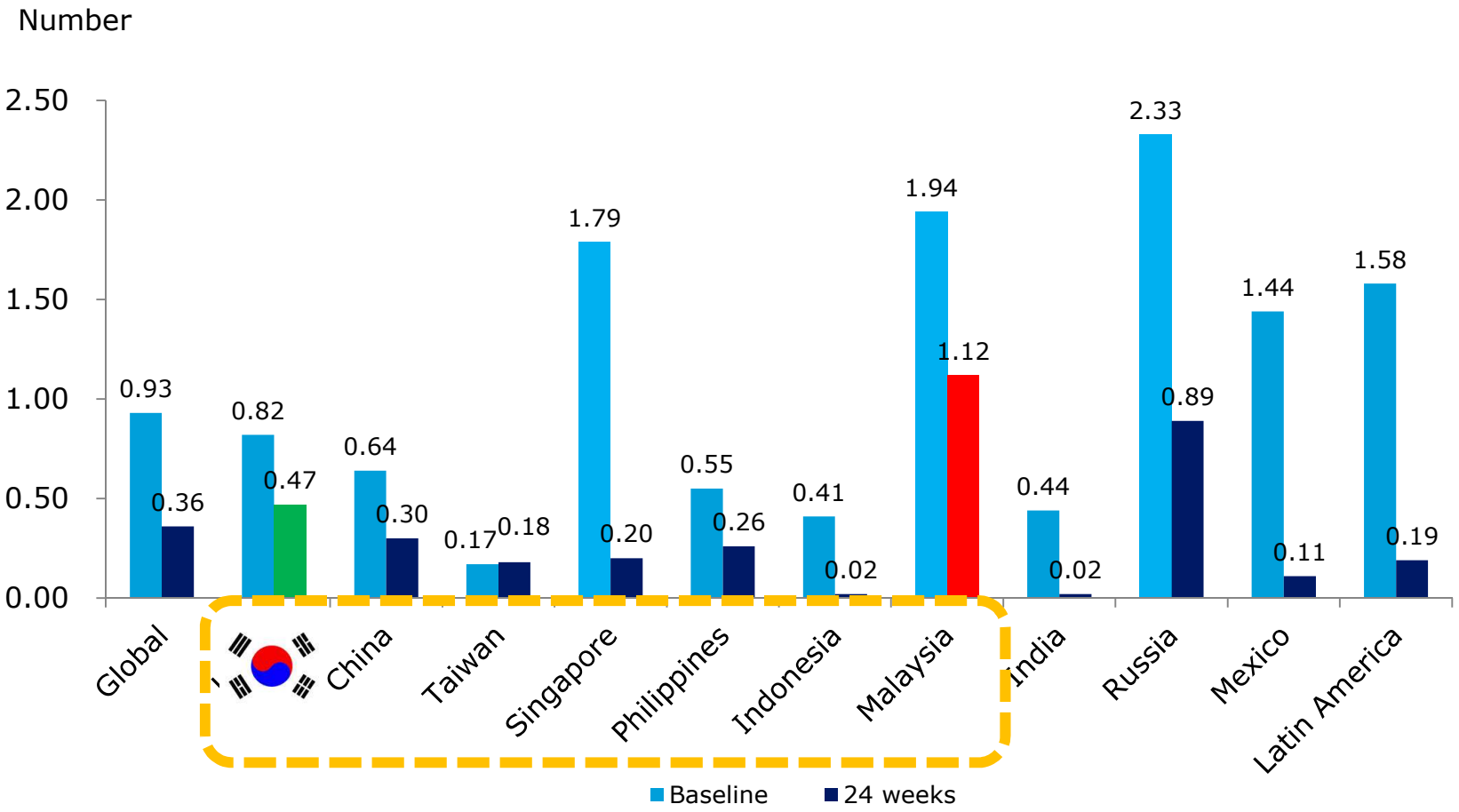
Nocturnal Hypoglycemia



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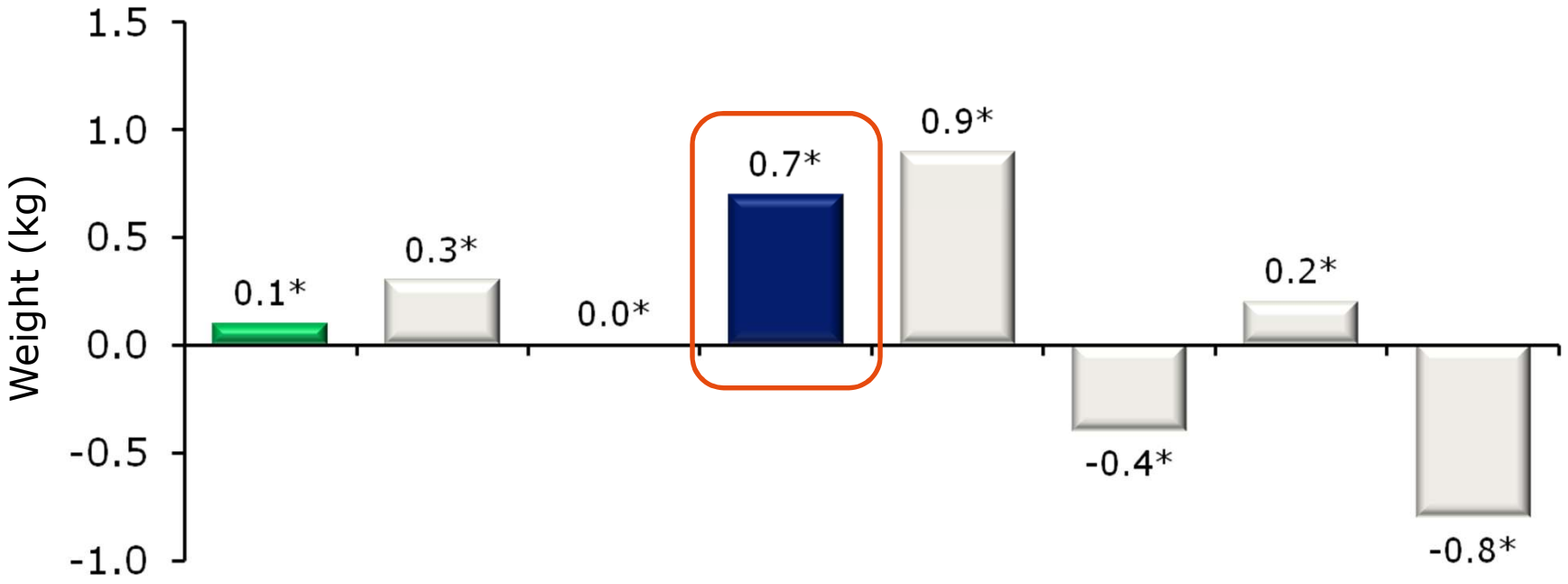
Weight Gain

Change in weight across all regions

	Global	China	South Asia	East Asia	North Africa	Middle East	Latin America	Russia
Baseline (kg)	**73.3**	**68.6**	**68.9**	**64.0**	**75.4**	**84.4**	**77.9**	**85.2**
n	50059	7815	16869	6831	3202	11357	964	3201



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*$p<0.001$

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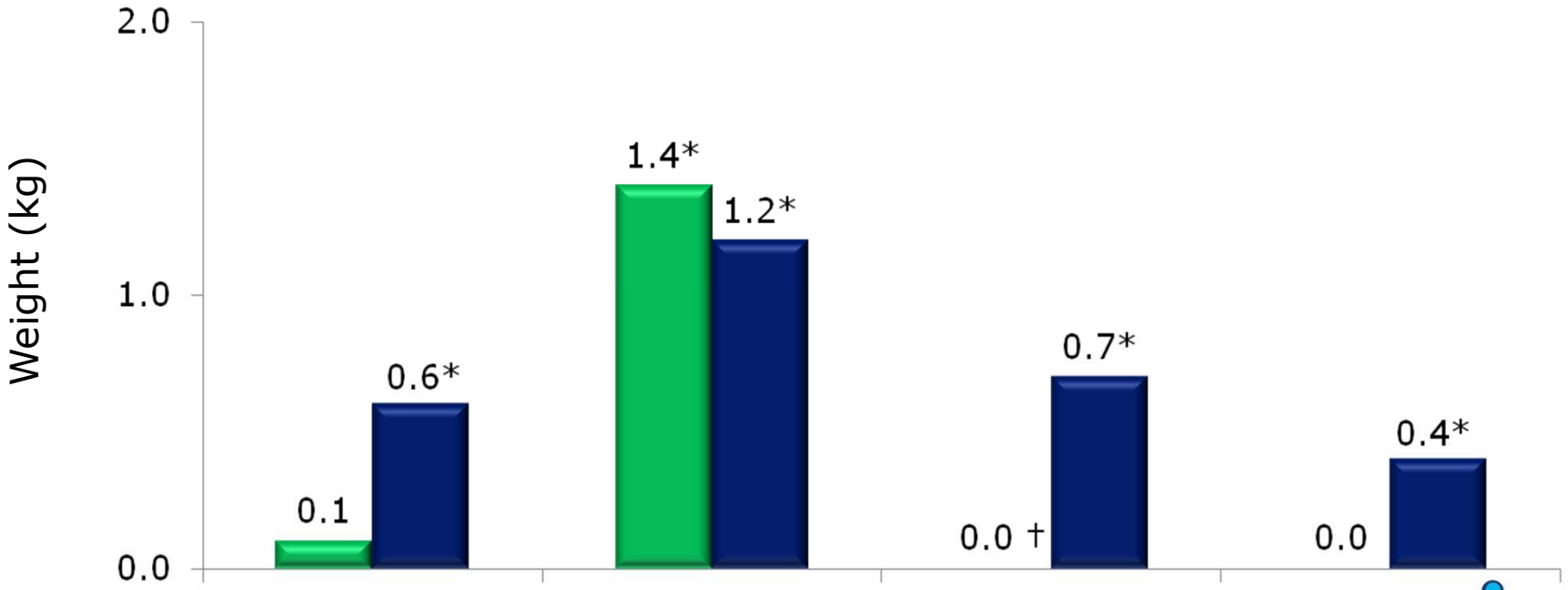
Change in weight across all pre-study groups over 24 weeks

Global
Korea

	Total	Pre-study therapy		
		None	OADs only	Insulin
Baseline (kg)	73.3 63.7	67.3 65.0	72.4 63.6	75.3 63.8
n	50059 2160	4029 198	29687 990	16343 972



*p<0.001
†p=0.029

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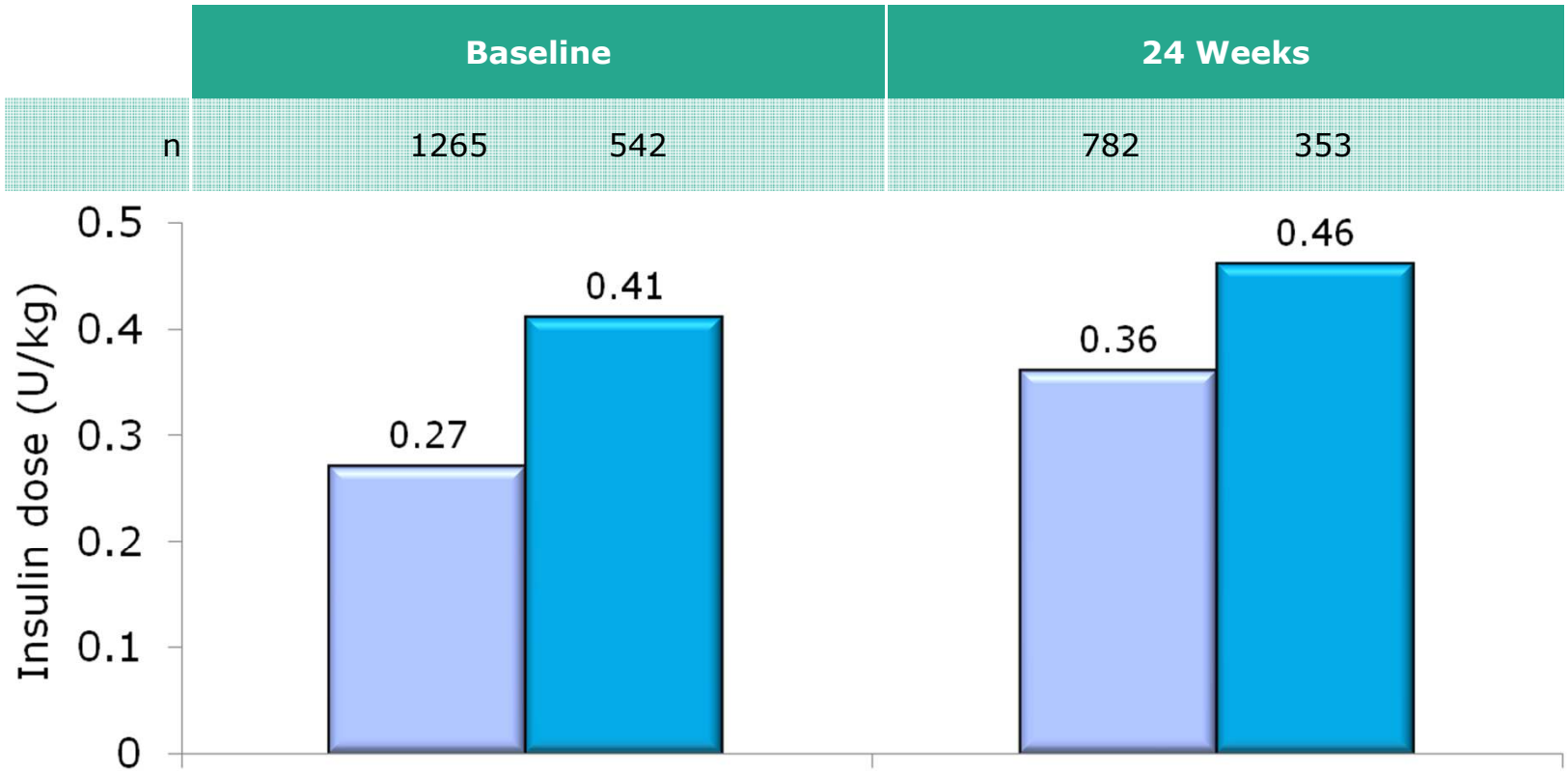
Levemir ± OAD:

Korea insulin dose results



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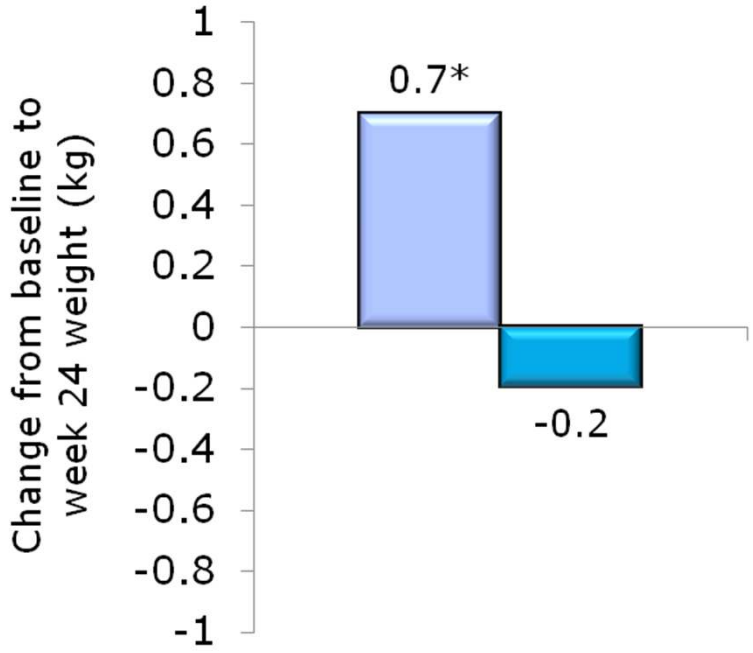
Levemir ± OAD:

Korea weight results

Insulin naïve

Insulin users

Baseline Weight (kg)	63.8	63.3
n	767	348



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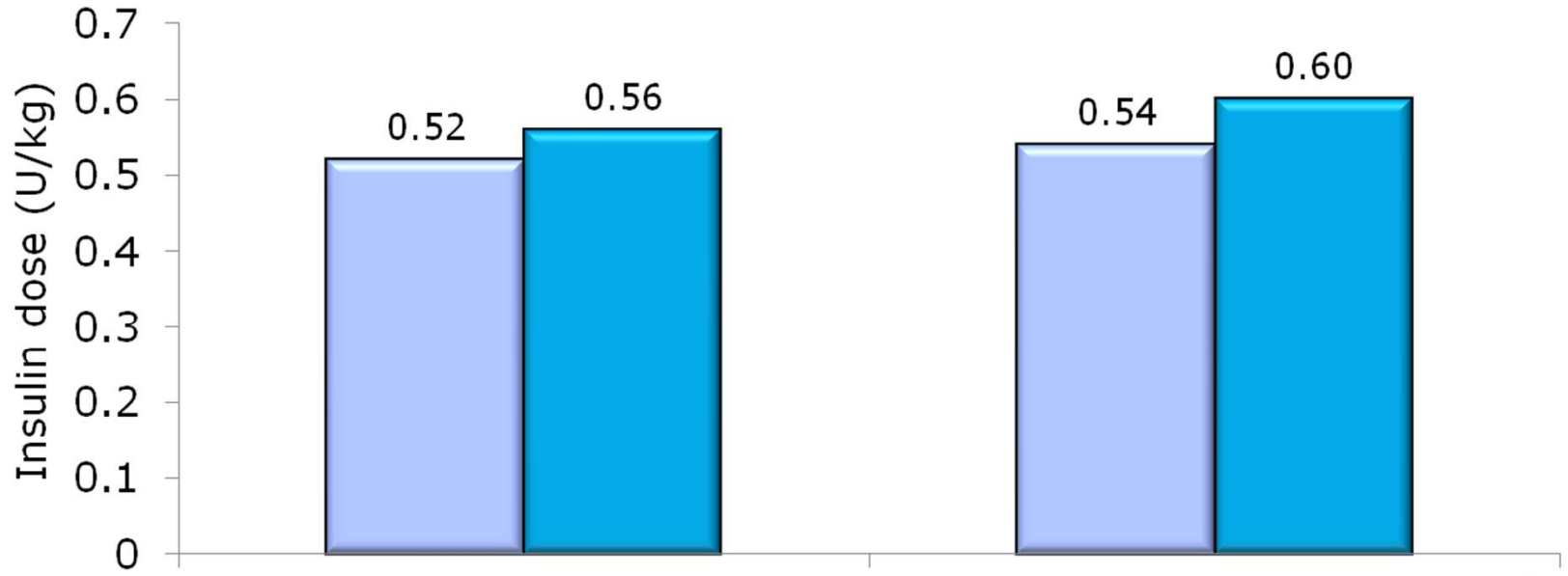
NovoMix ± OAD:

Korea insulin dose results

Insulin naïve

Insulin users

	Baseline		24 Weeks	
n	551	751	323	457



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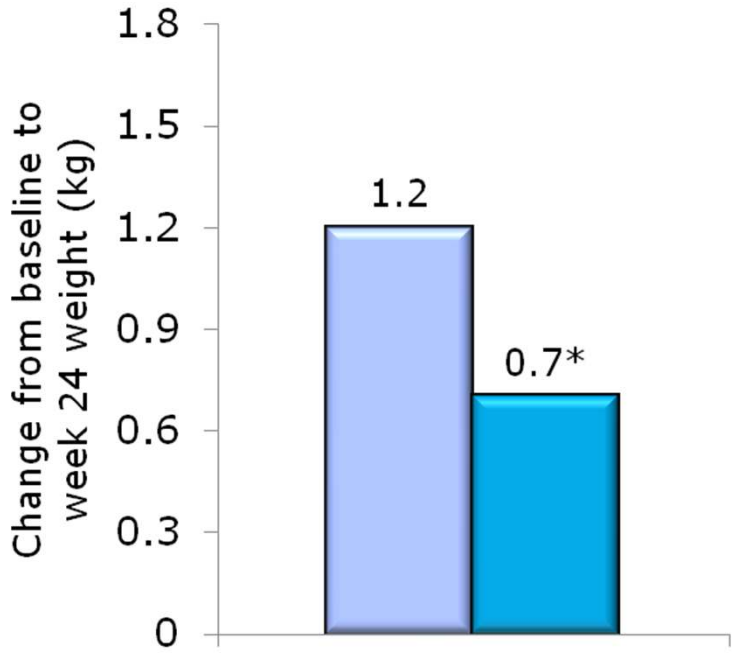
NovoMix ± OAD:
Korea weight results

Insulin naïve
Insulin users

Baseline Weight (kg)	63.5	64.1
n	315	447



*p<0.001

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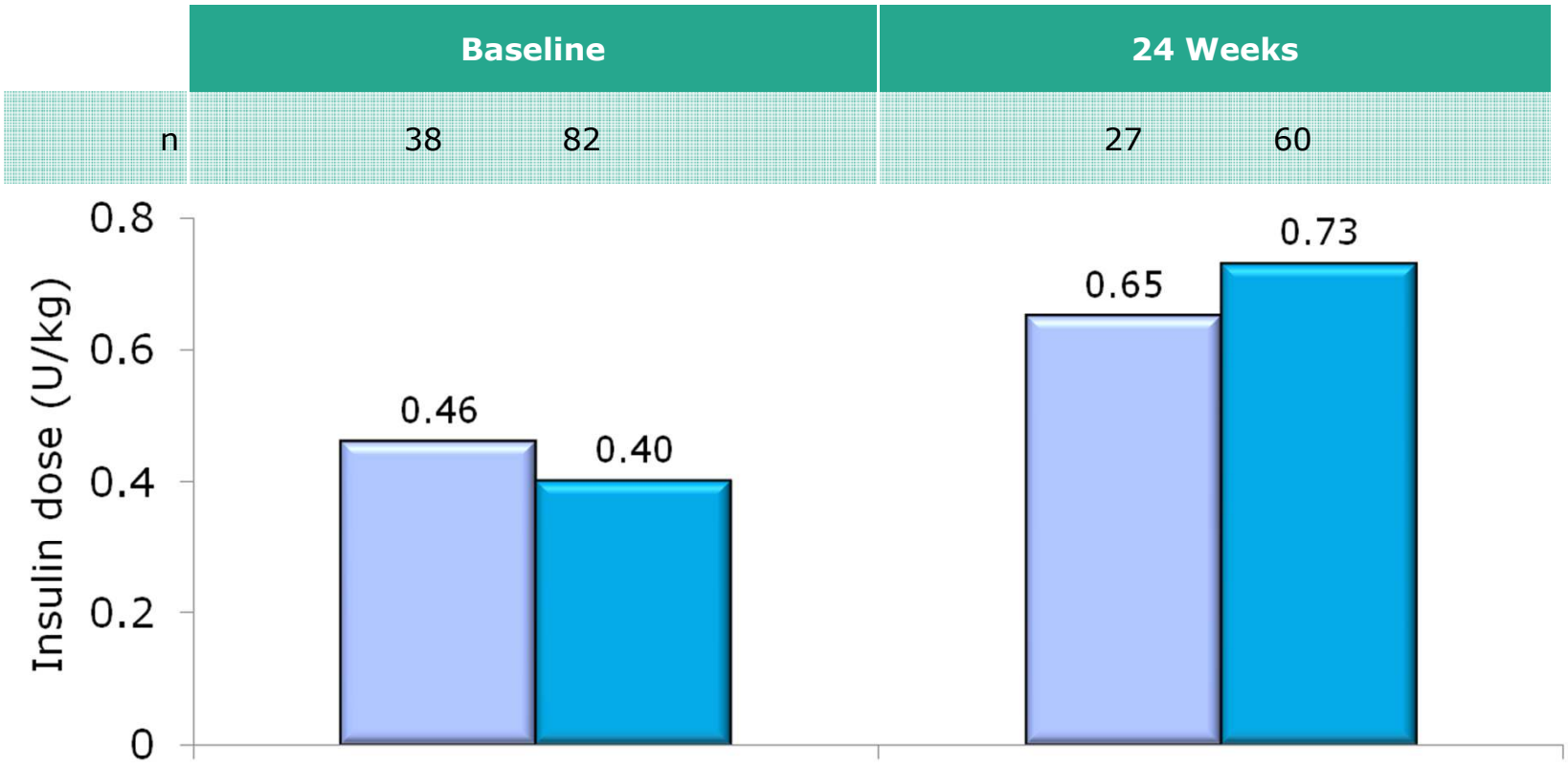
NovoRapid ± OAD:

Korea insulin dose results



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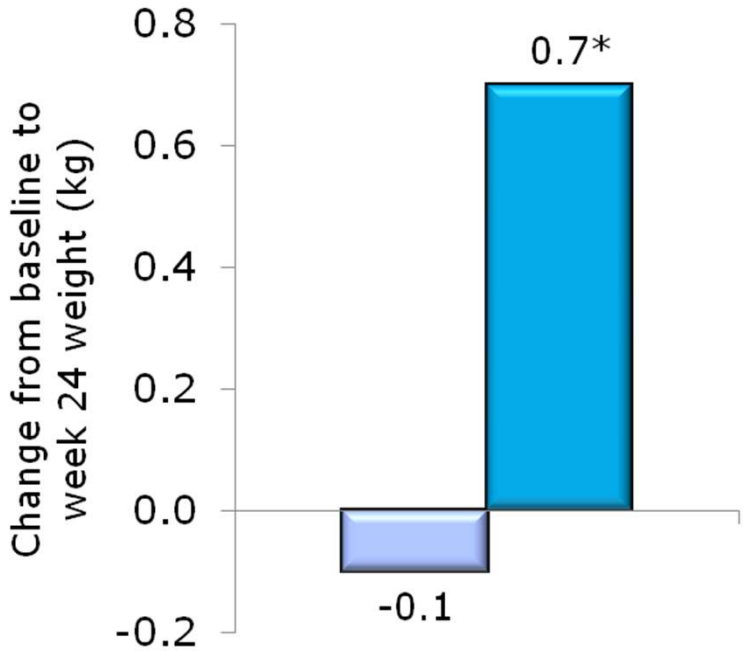
NovoRapid ± OAD:

Korea weight results

Insulin naïve

Insulin users

Baseline Weight (kg)	66.3	66.9
n	23	57



*p<0.001

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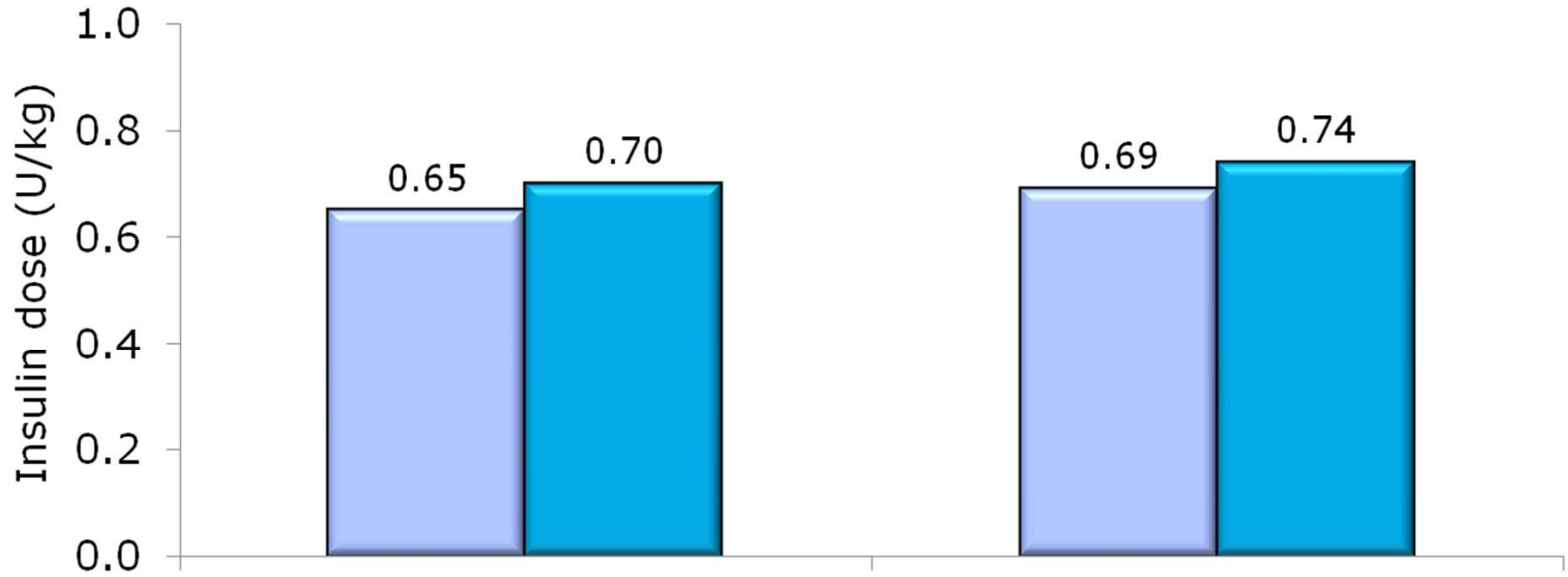
Basal + NovoRapid ± OAD:

Korea insulin dose results

Insulin naïve

Insulin users

	Baseline		24 Weeks	
n	114	98	64	63



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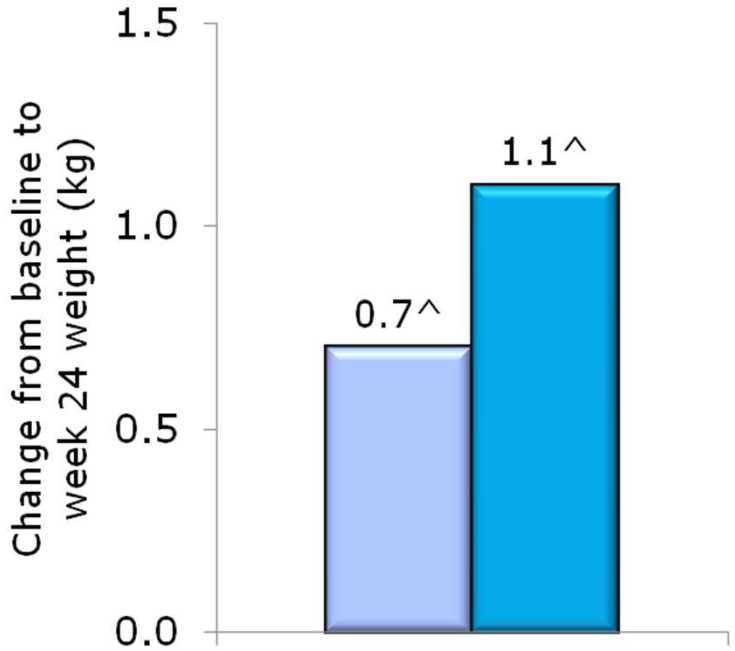
Basal + NovoRapid ± OAD:

Korea weight results

Insulin naïve

Insulin users

Baseline Weight (kg)	64.6	62.8
n	61	60



^p<0.01

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Summary

- There was a moderate weight gain on all study insulins
- Should we be more aggressive with insulin dose titration in our patients?

	Ins. 24 wk		Wt. gain	
	naive	user	naive	user
1. Insulin detemir ± OADs	0.36	0.46	0.7	-0.2
2. Biphasic insulin aspart ± OADs	0.54	0.60	1.2	0.7
3. Insulin aspart ± OADs	0.65	0.73	-0.1	0.7
4. Basal + aspart ± OADs	0.69	0.74	0.7	1.1

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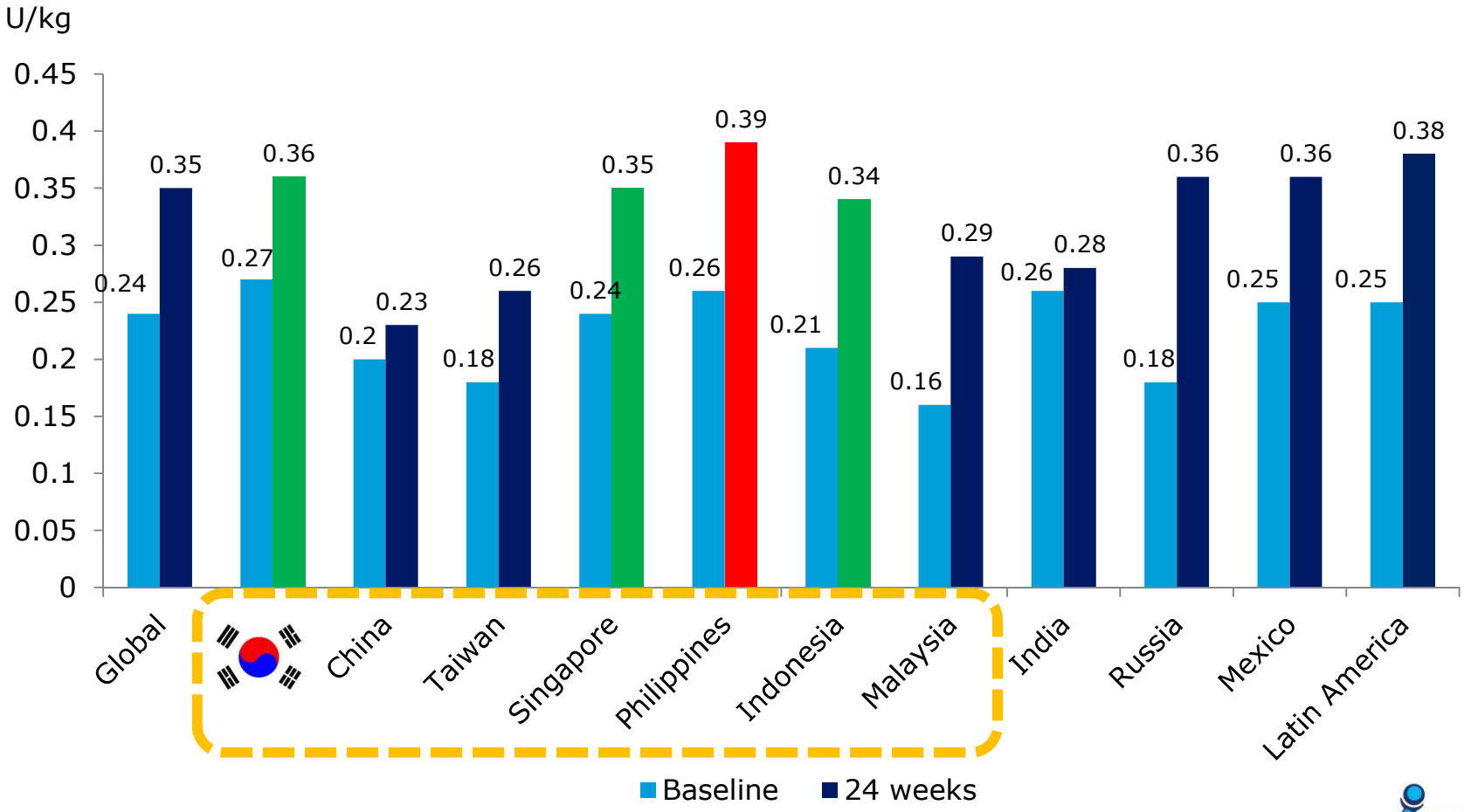
Insulin dose in insulin naïve patients : Levemir ± OAD



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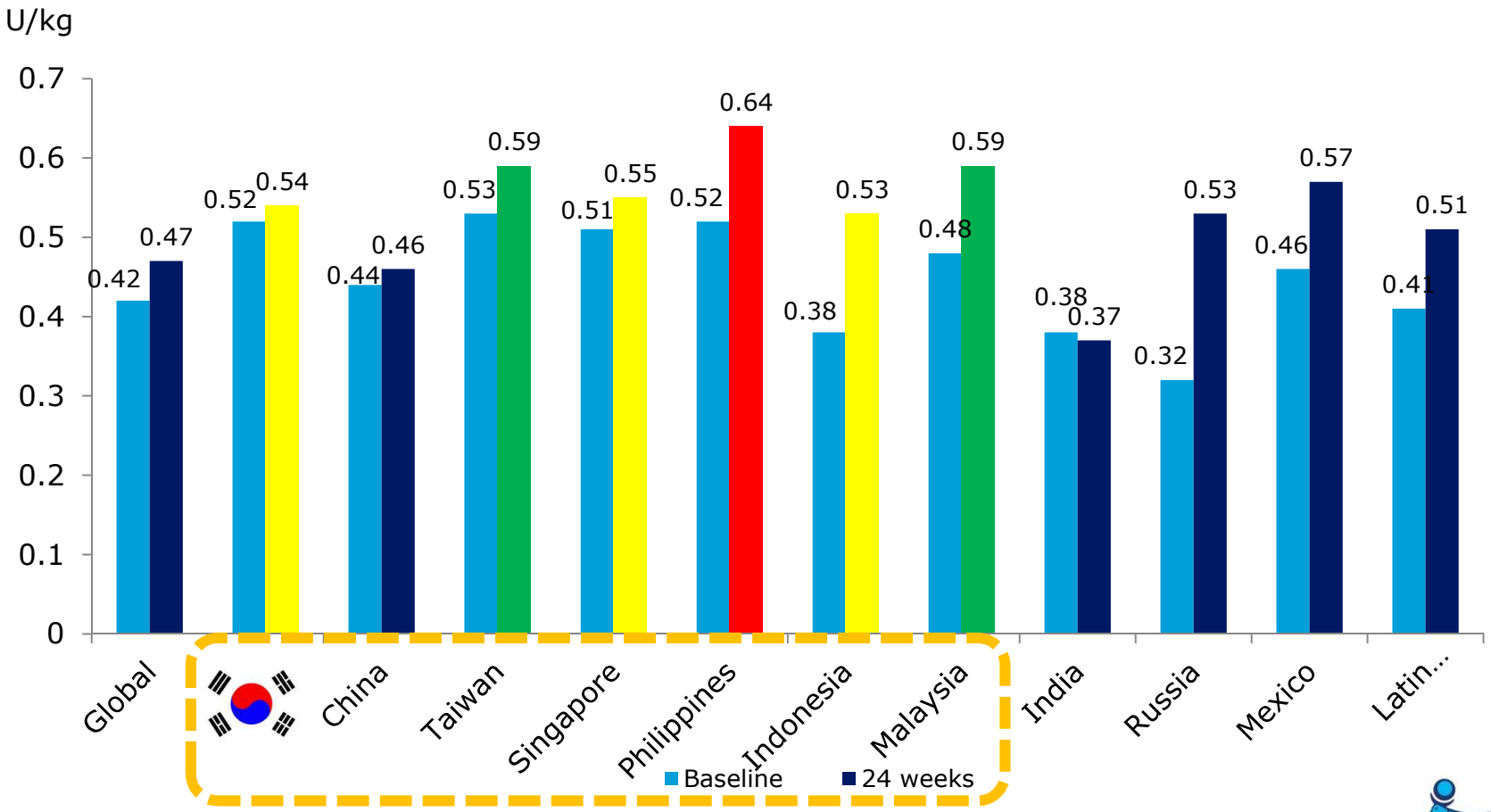
Insulin dose in insulin naïve patients : NovoMix30 ± OAD



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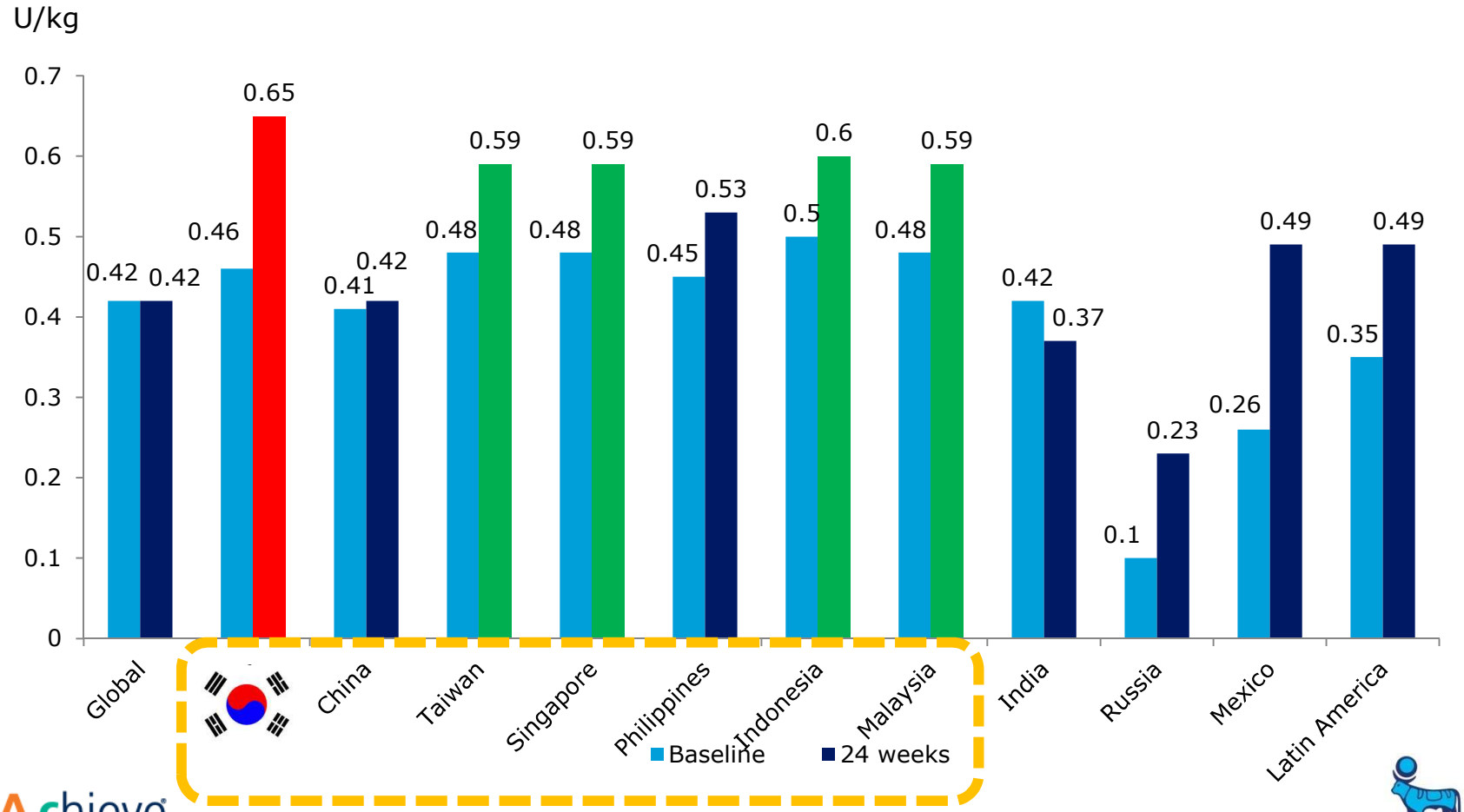
Insulin dose in insulin naïve patients : NovoRapid ± OAD



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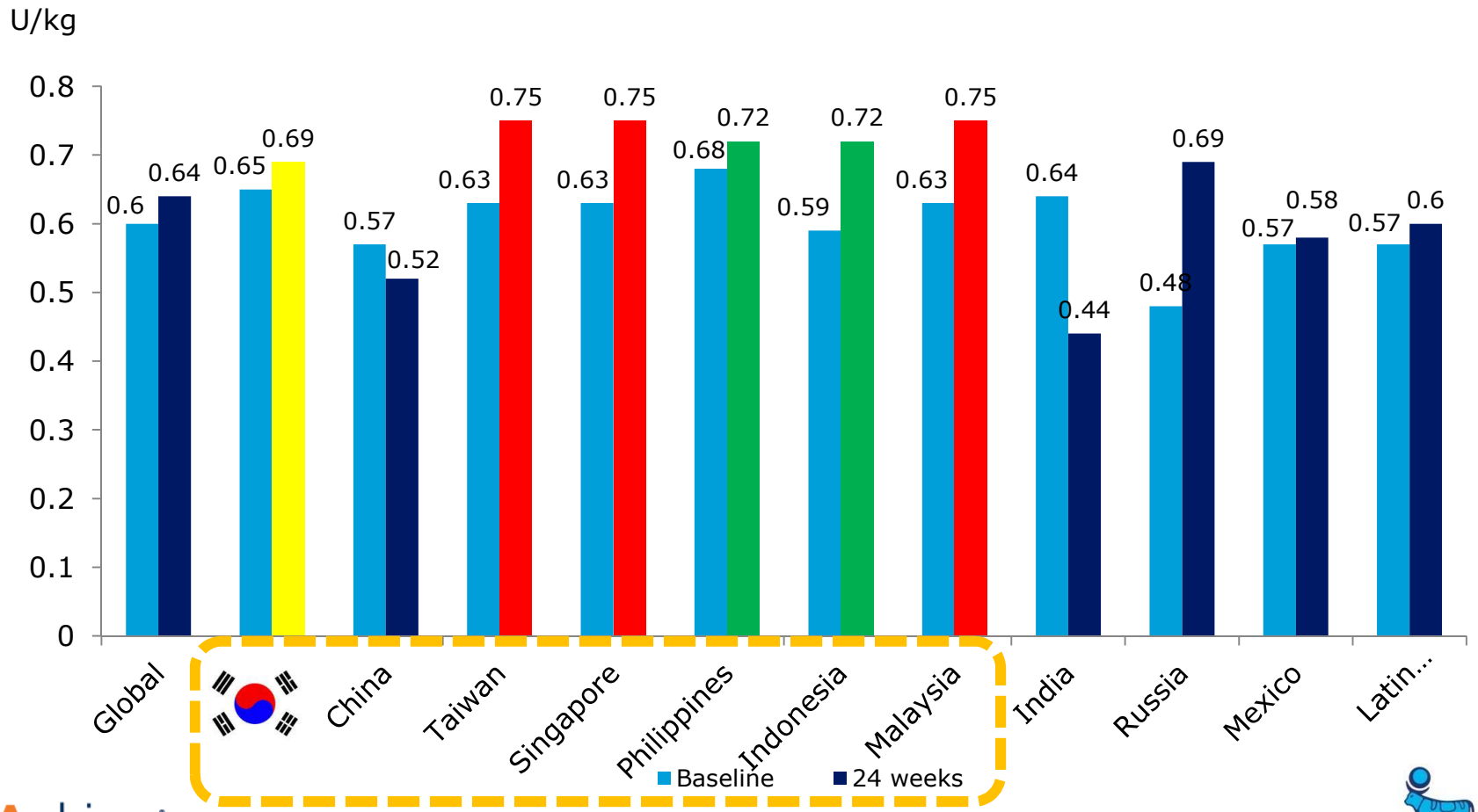
Insulin dose in insulin naïve patients : Basal+NovoRapid ± OAD



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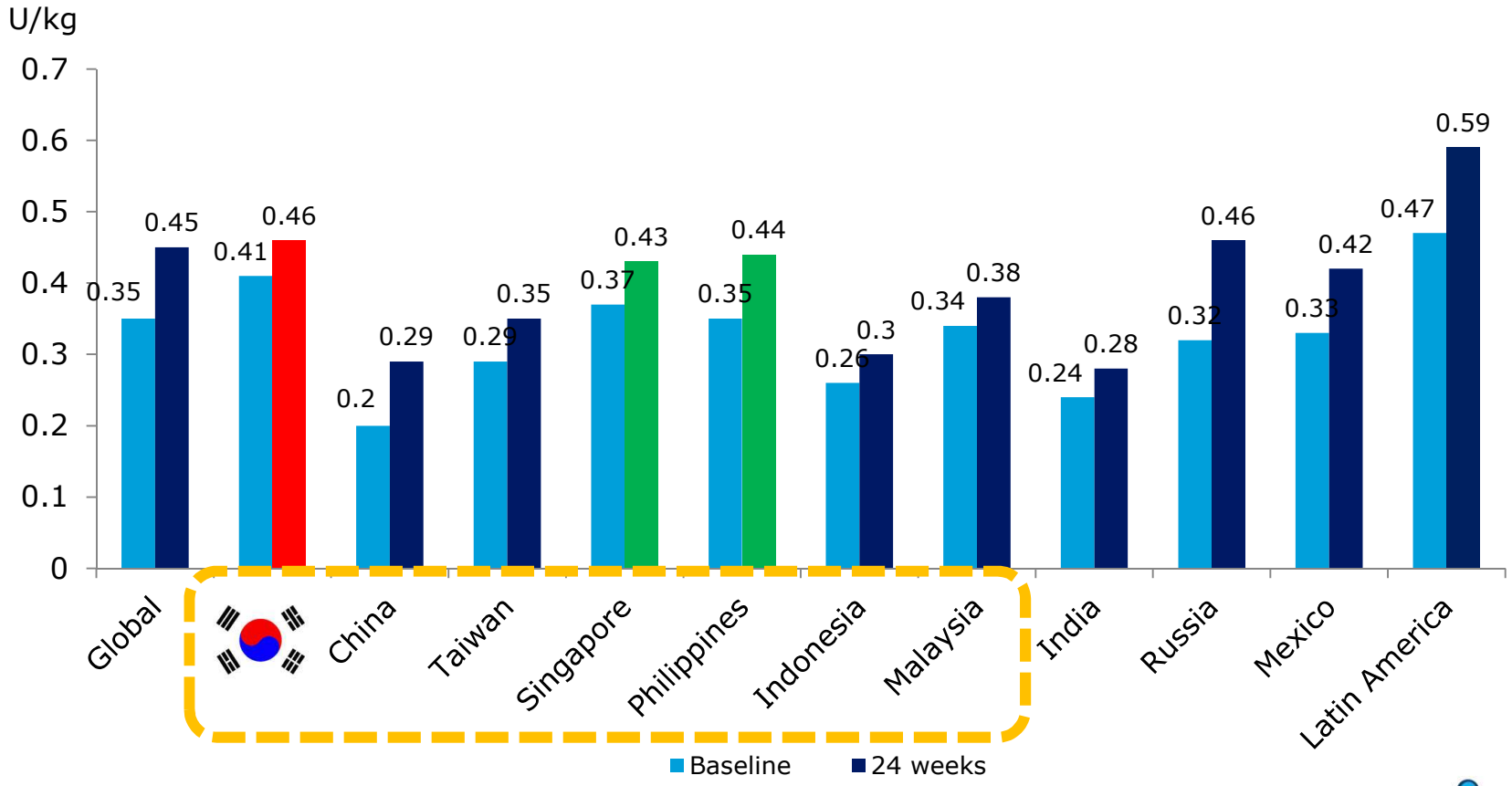
Insulin dose in insulin user : Levemir ± OAD



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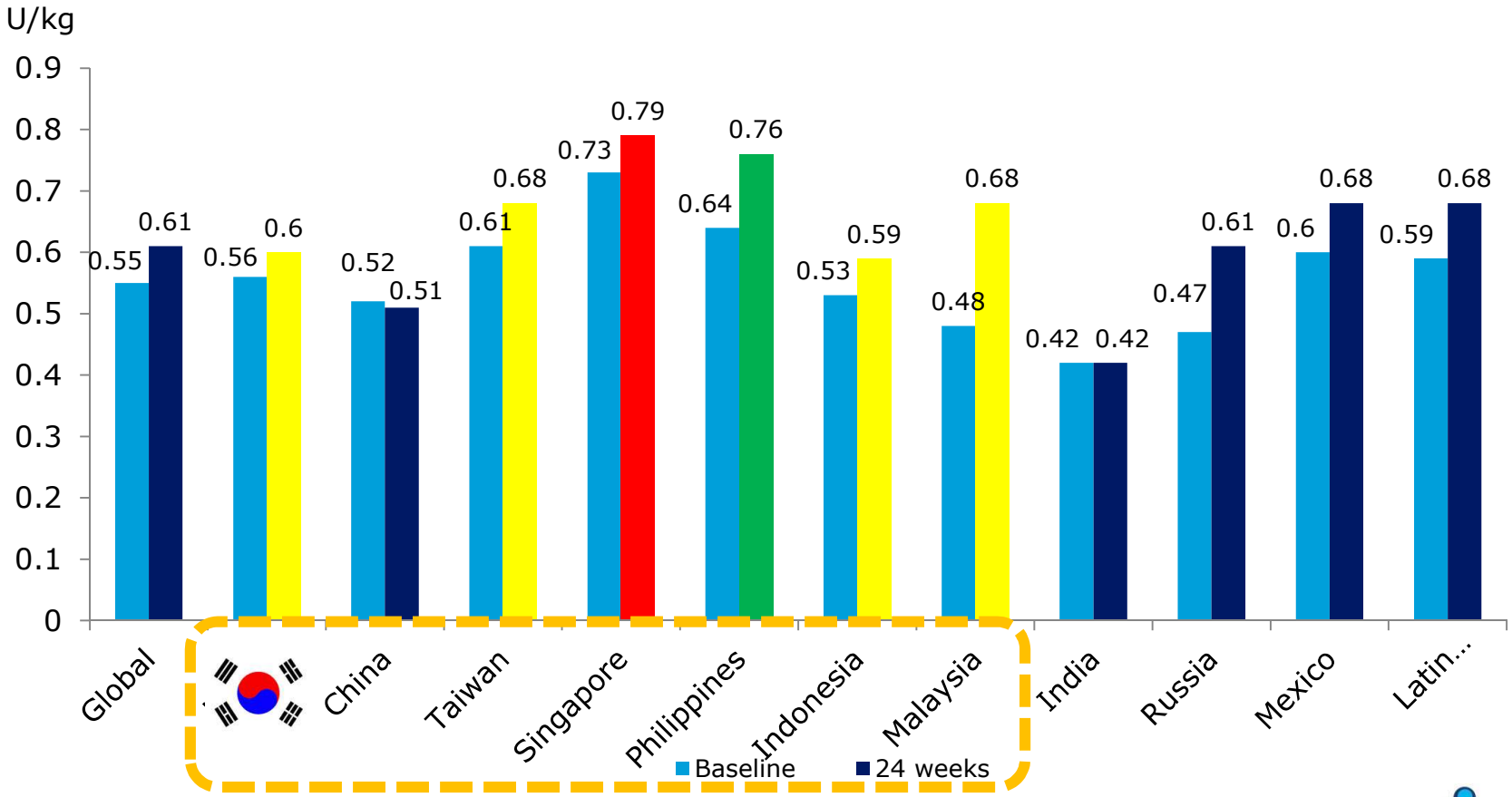
Insulin dose in insulin user : NovoMix ± OAD



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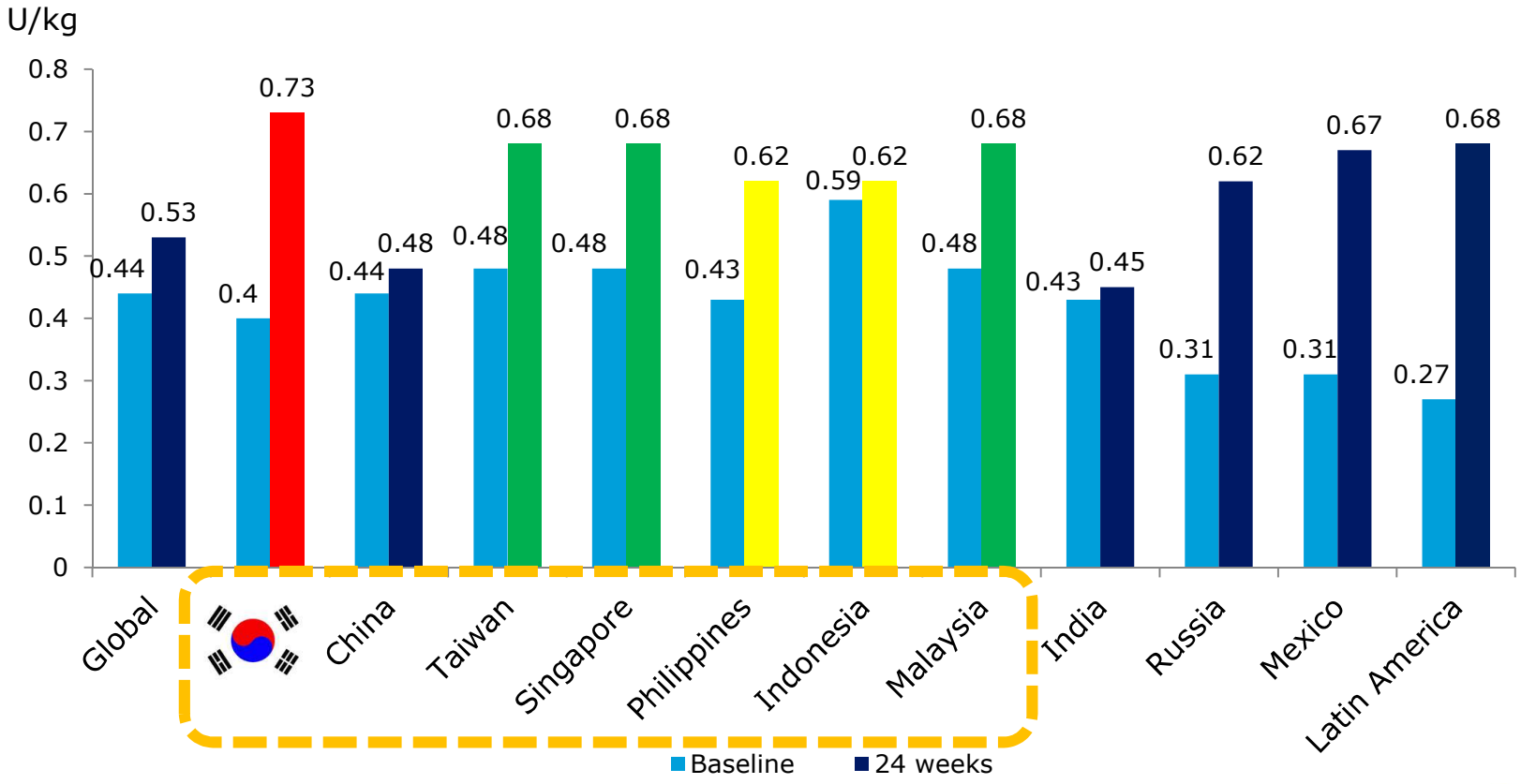
Insulin dose in insulin user : NovoRapid ± OAD



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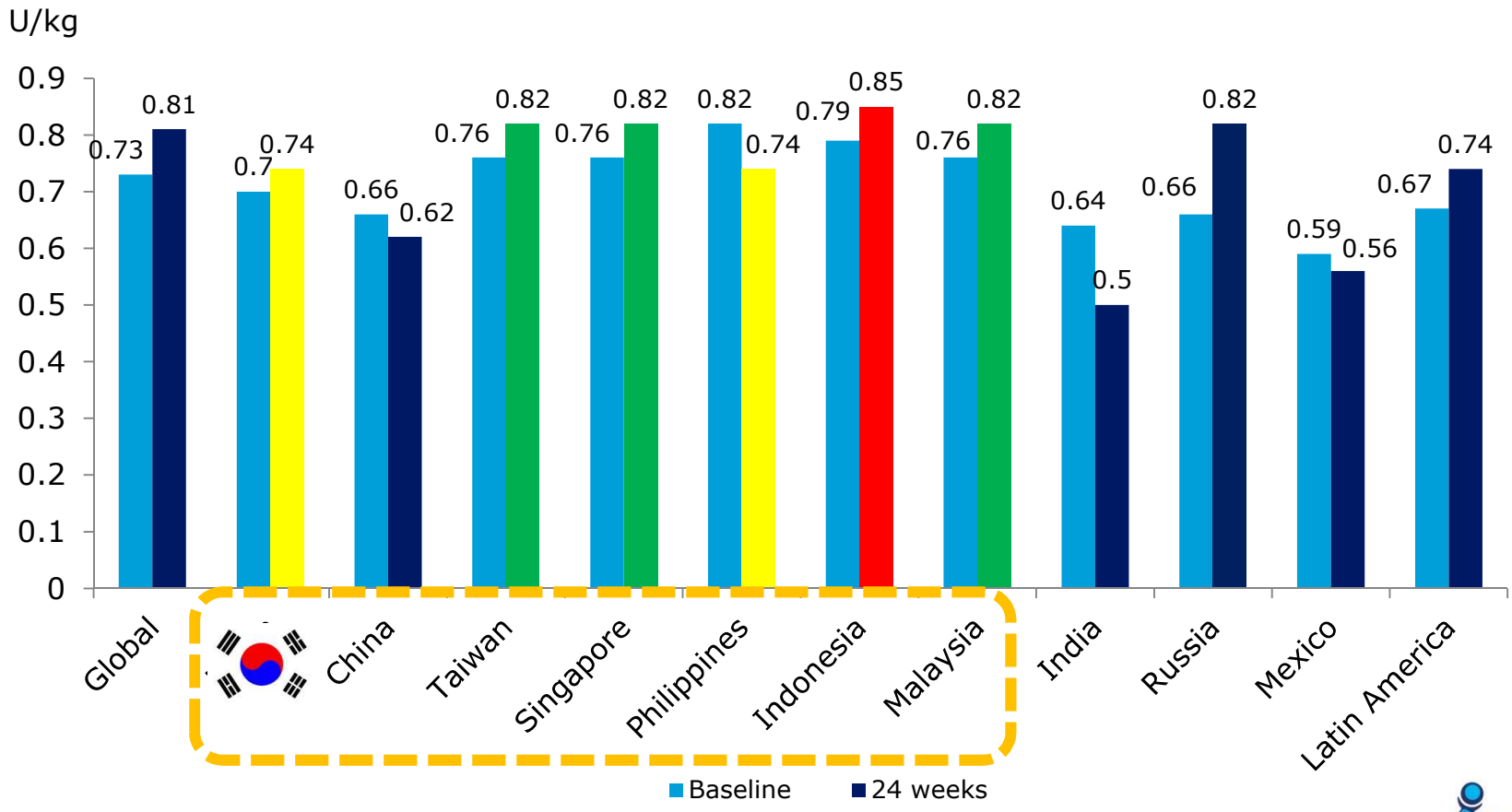
Insulin dose in insulin user : Basal+ NovoRapid ± OAD



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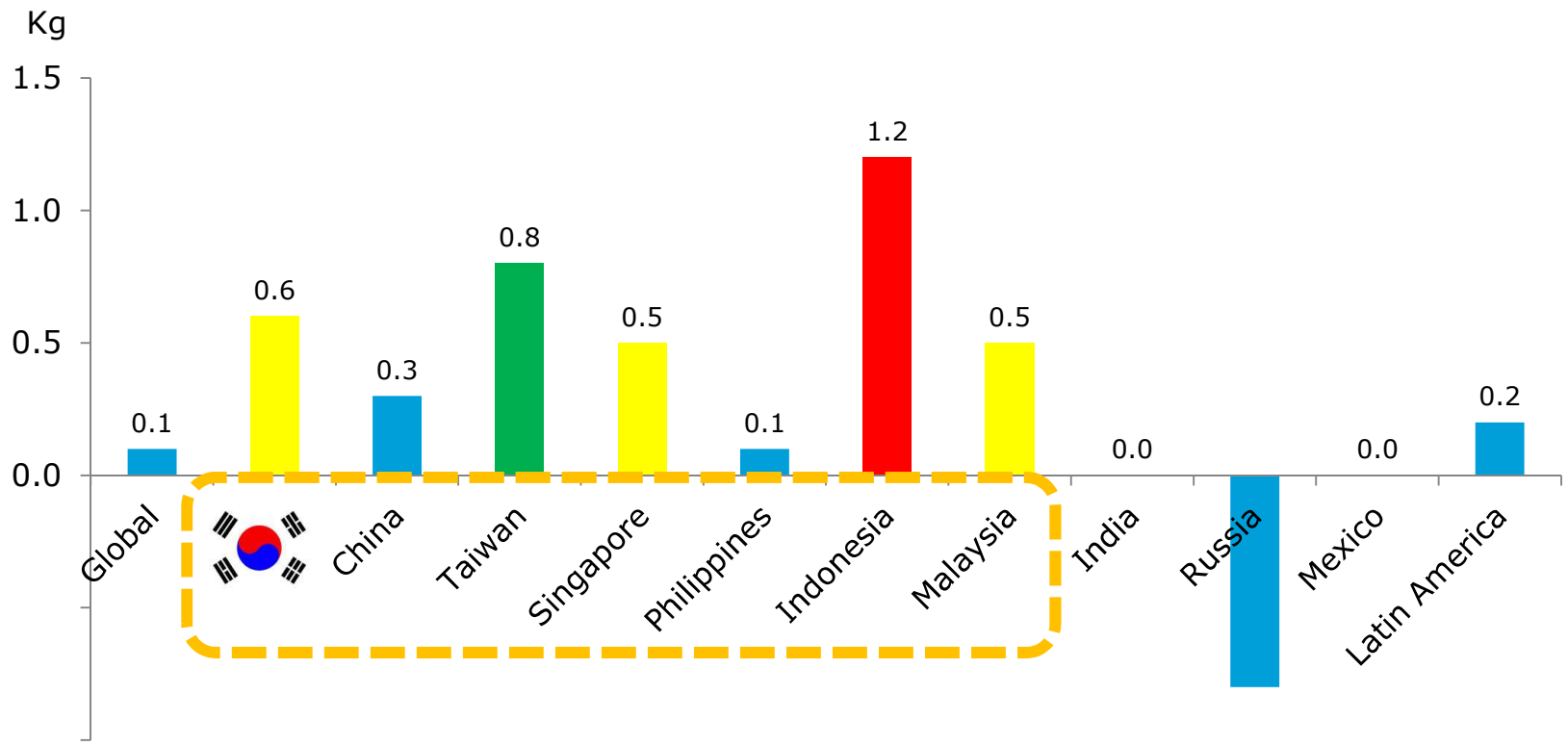
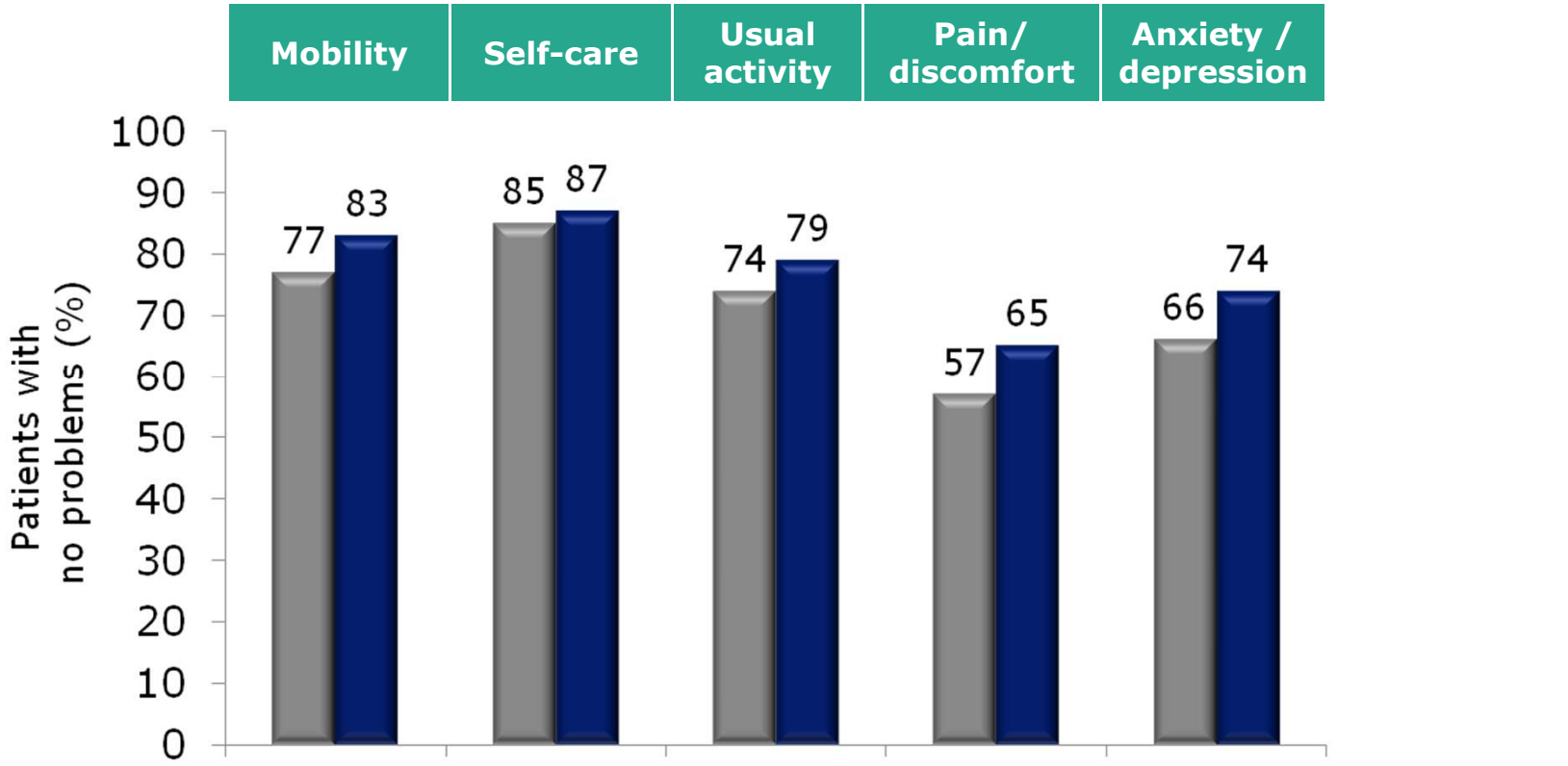
Weight changes



Levemir ± OAD:

Self-rated health in insulin naïve patients



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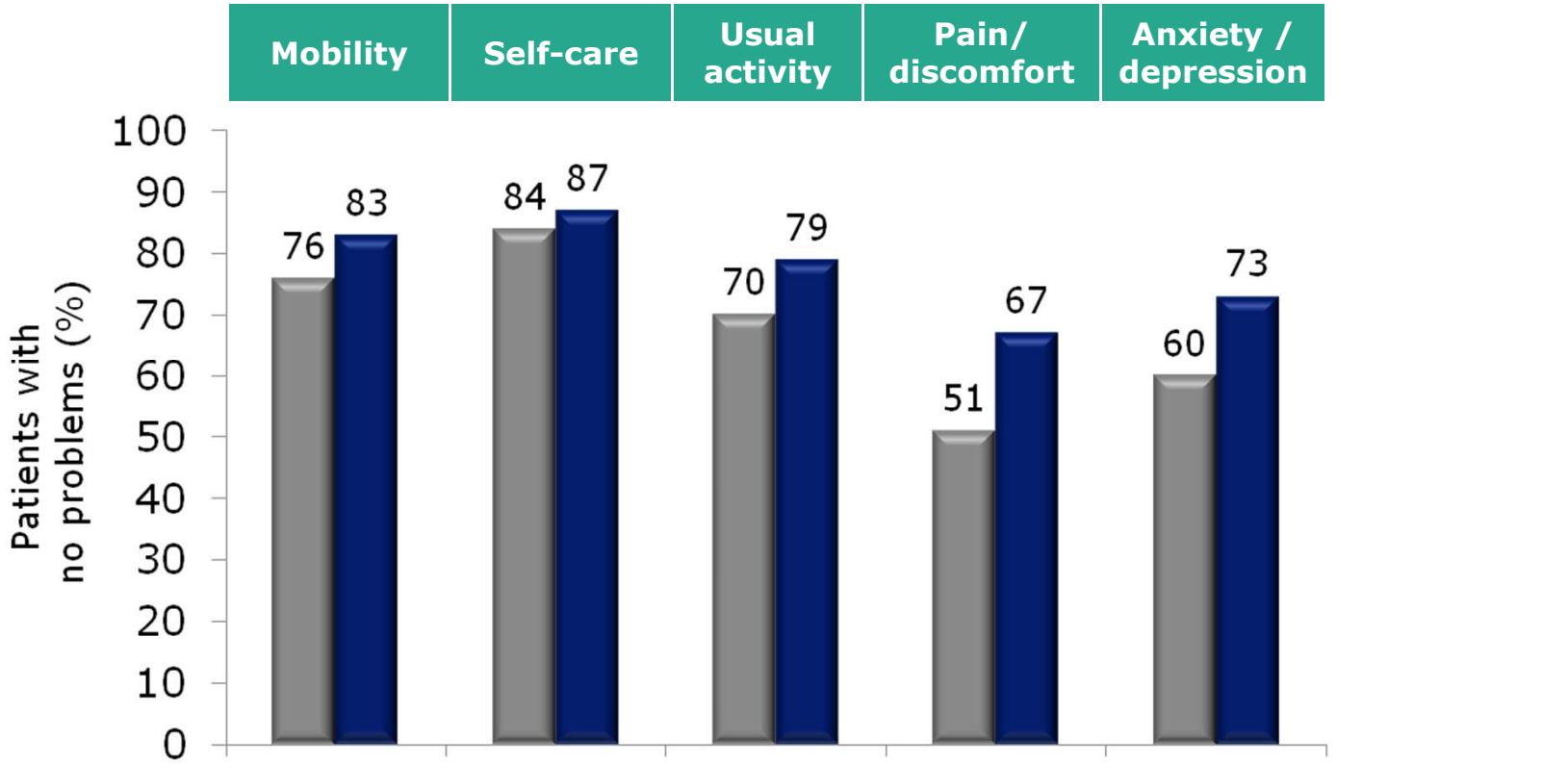
Levemir ± OAD:

Self-rated health in insulin users



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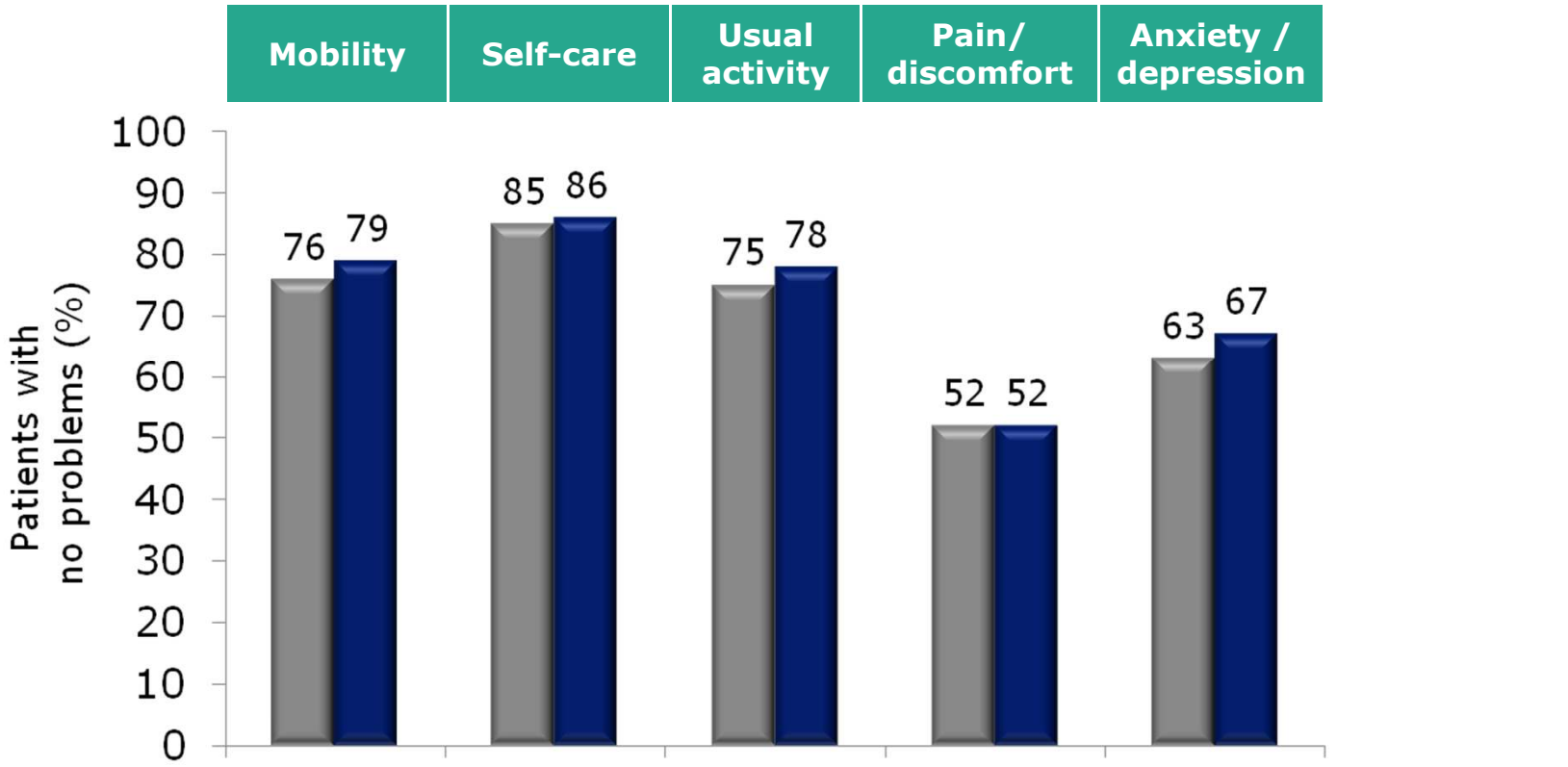
NovoMix ± OAD:

Self-rated health in insulin naïve patients



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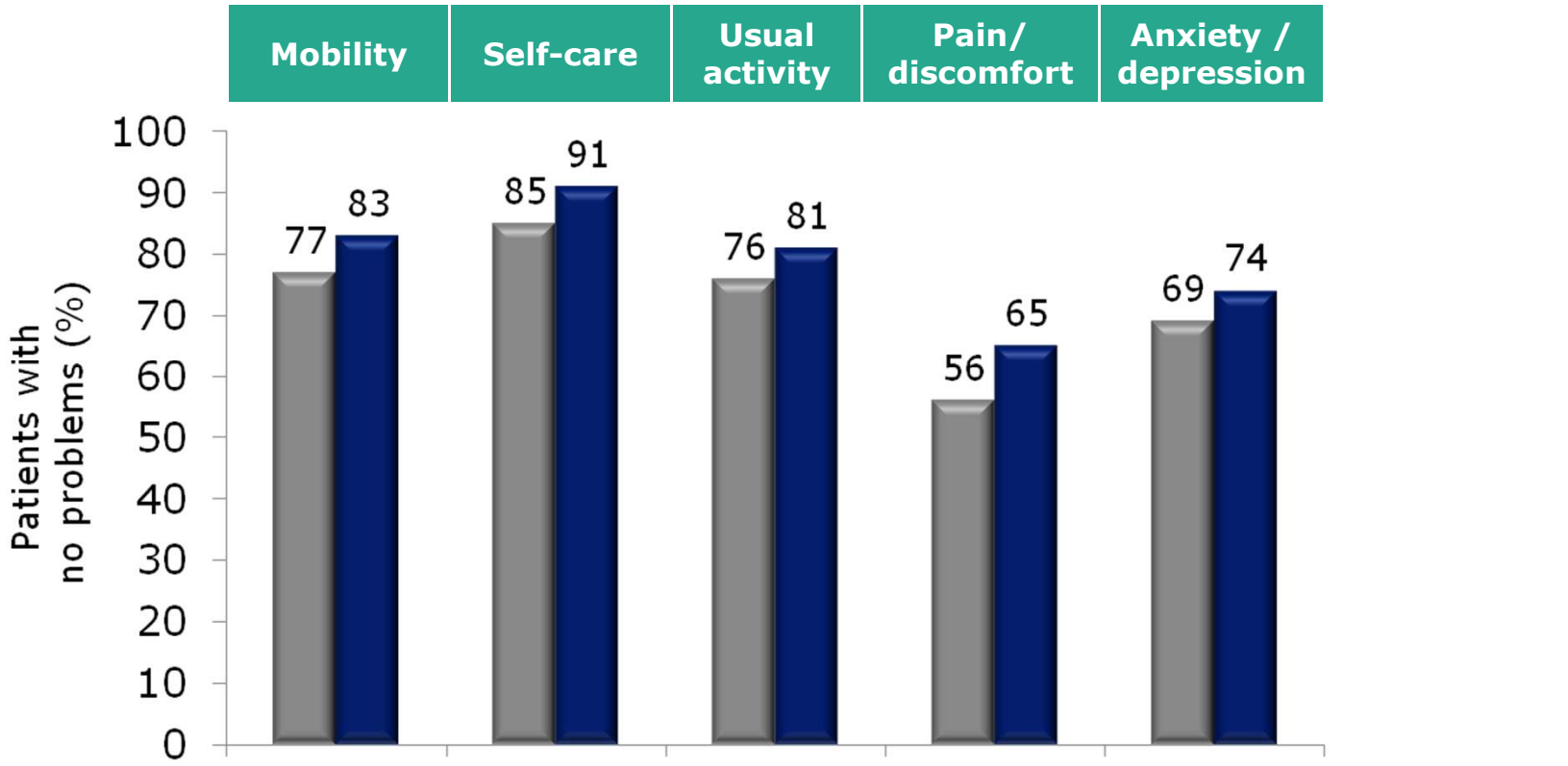
NovoMix ± OAD:

Self-rated health in insulin users



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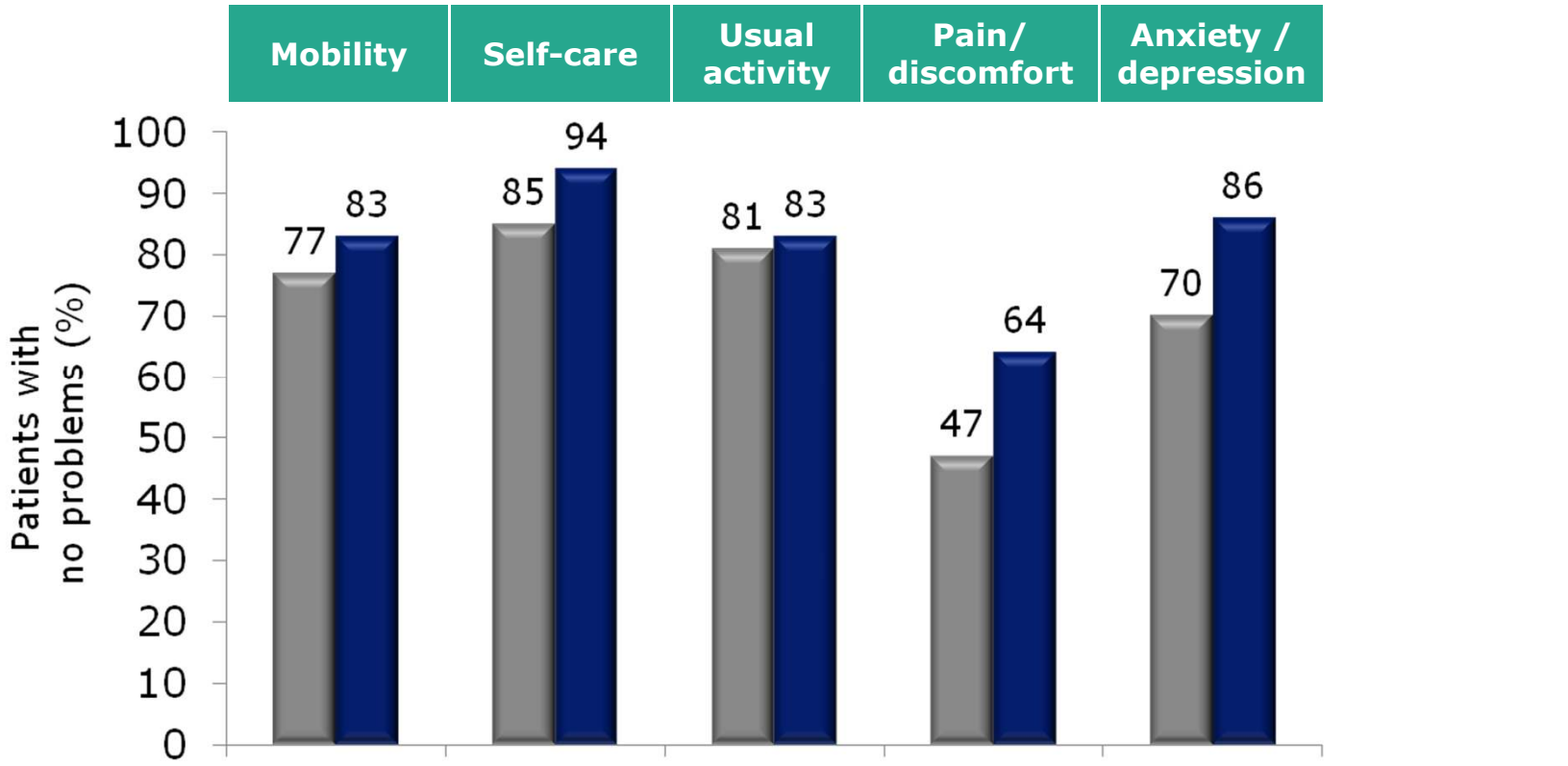
NovoRapid ± OAD:

Self-rated health in insulin naïve patients



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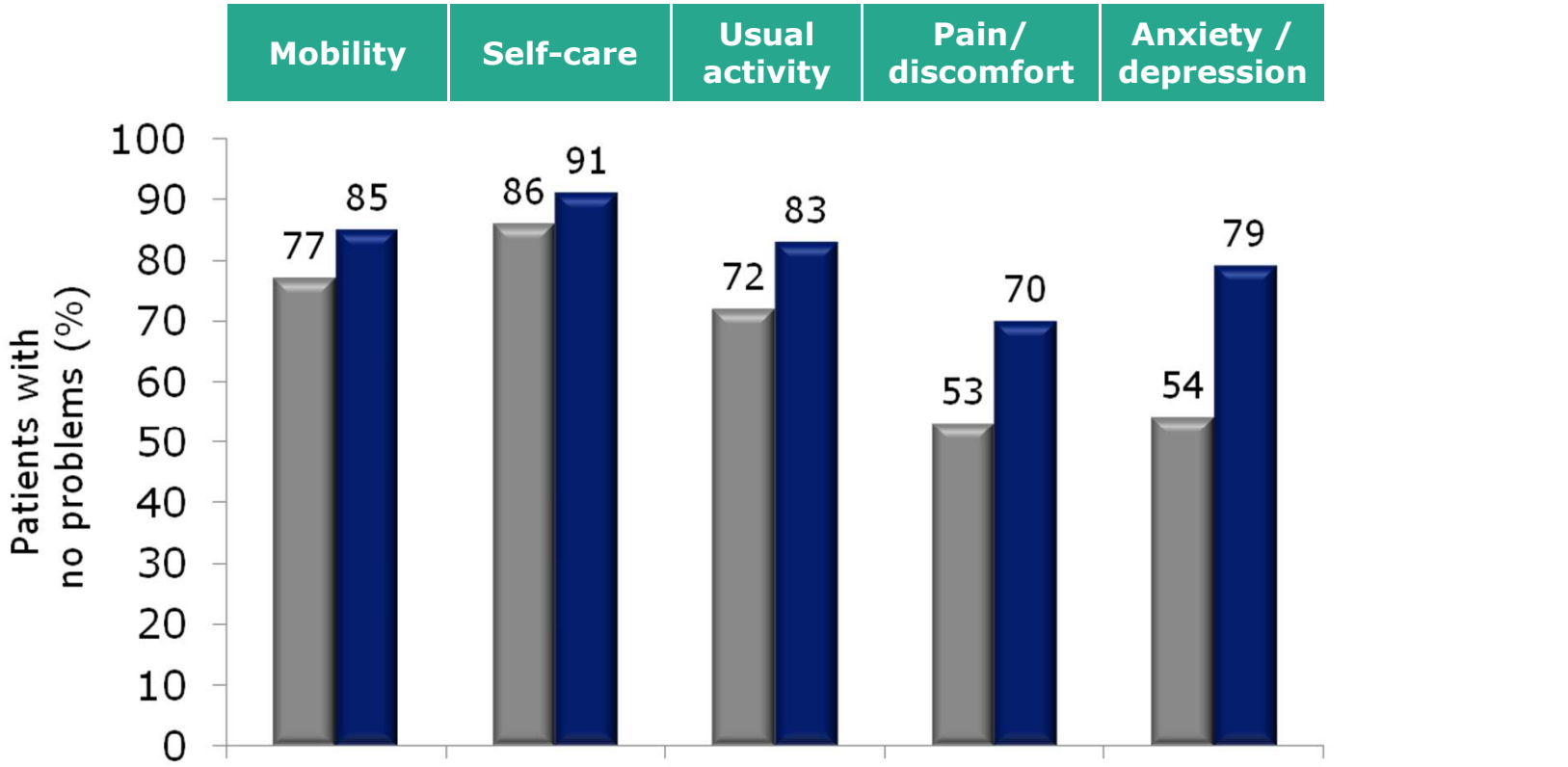
NovoRapid ± OAD:

Self-rated health in insulin users



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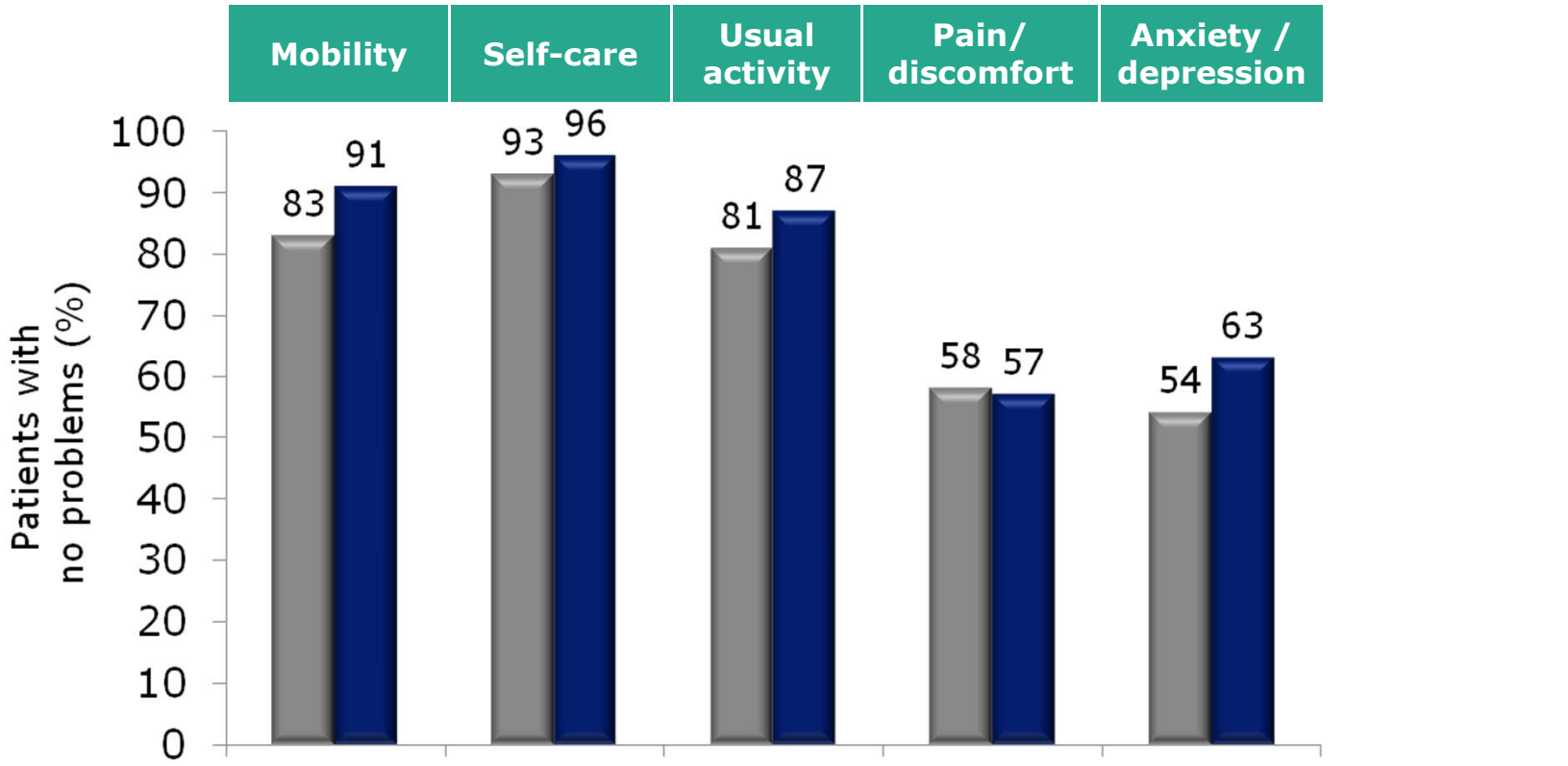
Basal + NovoRapid ± OAD:

Self-rated health in insulin naïve patients



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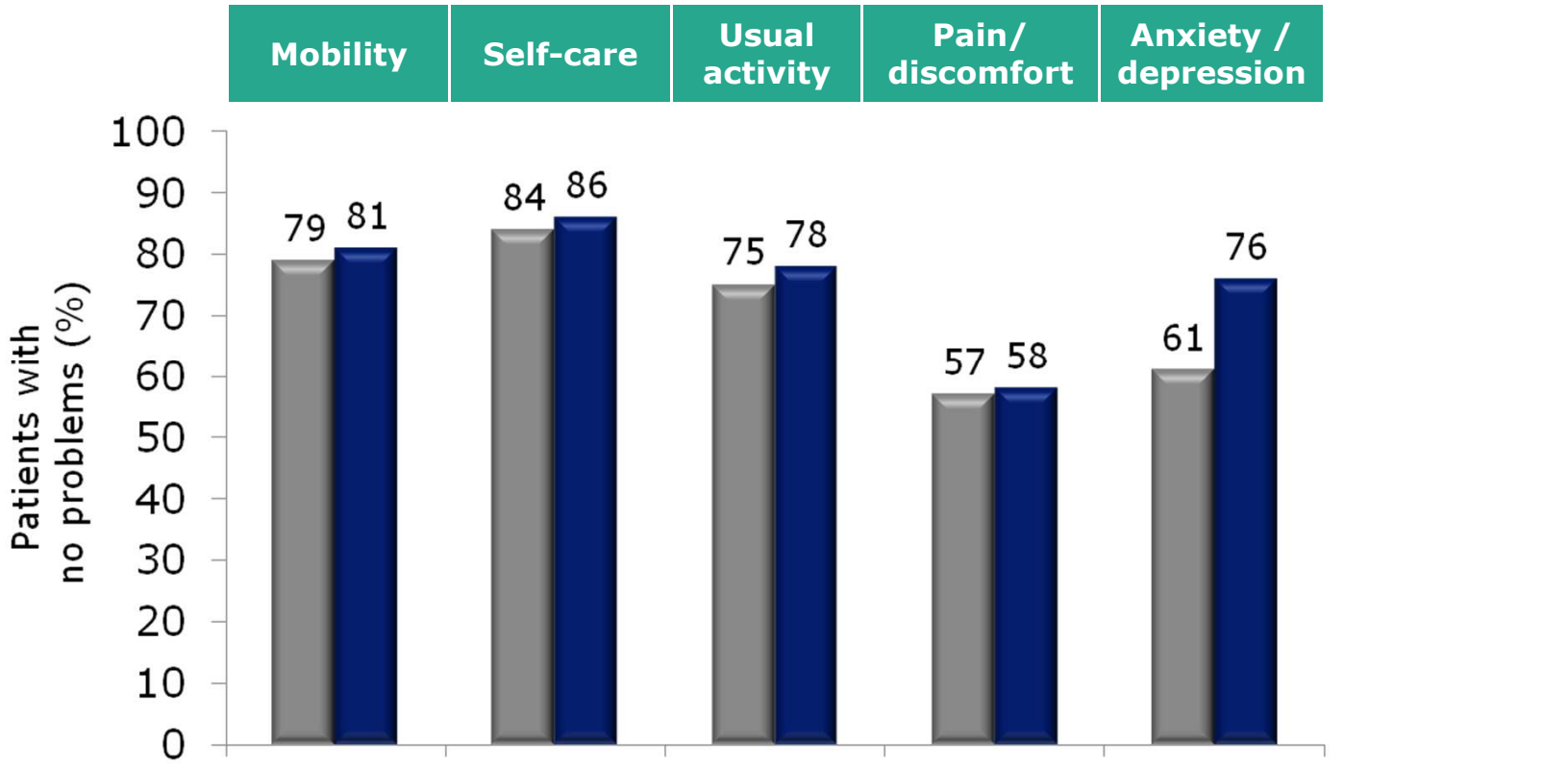
Basal + NovoRapid ± OAD:

Self-rated health in insulin users



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ABSTRACT

Aims: To determine the effects on quality of life after starting insulin with, or switching to, insulin analogue therapies in the 24-week, prospective, non-interventional, observational A_1chieve study conducted across four continents in people with type 2 diabetes.

Methods: Health-related quality of life (HRQoL) was assessed at baseline and at 24 weeks by the validated EQ-5D questionnaire (visual analogue score [VAS] and five dimensions) in 66,726 people who had started using basal insulin detemir, mealtime insulin aspart (with or without a basal insulin) or biphasic insulin aspart 30.

Results: For the overall cohort, reported HRQoL increased significantly by 13.8 points from 63.4 points at baseline to 77.2 points at 24 weeks ($p < 0.001$) (scale 1–100, 100 = best health imaginable). Beginning or changing insulin was associated with a significant increase in HRQoL score (+15.0 points and +11.1 points, respectively), resulting in a similar score at 24 weeks in the two populations (77.8 and 75.9 points). Reported HRQoL also increased statistically significantly in people administering any insulin analogue regimen and across all regions, although there were some marked regional differences in reported HRQoL at baseline.

Conclusion: Compared with baseline scores, beginning insulin with, or switching to, insulin analogue therapies are associated with increased HRQoL.

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Shah S at al, Diabetes Res Clin Pract. 94:364-70, 2011

Summary

- All insulin therapies used during the study scored highly in terms of self-rated health (EQ5D) after week 24
  - Levemir, NovoMix, NovoRapid and Basal + NovoRapid received similar ratings amongst insulin naïve patients and insulin users

Agenda

- Study Design
- Korea Final Result Review
- Overall Summary and Q&A session

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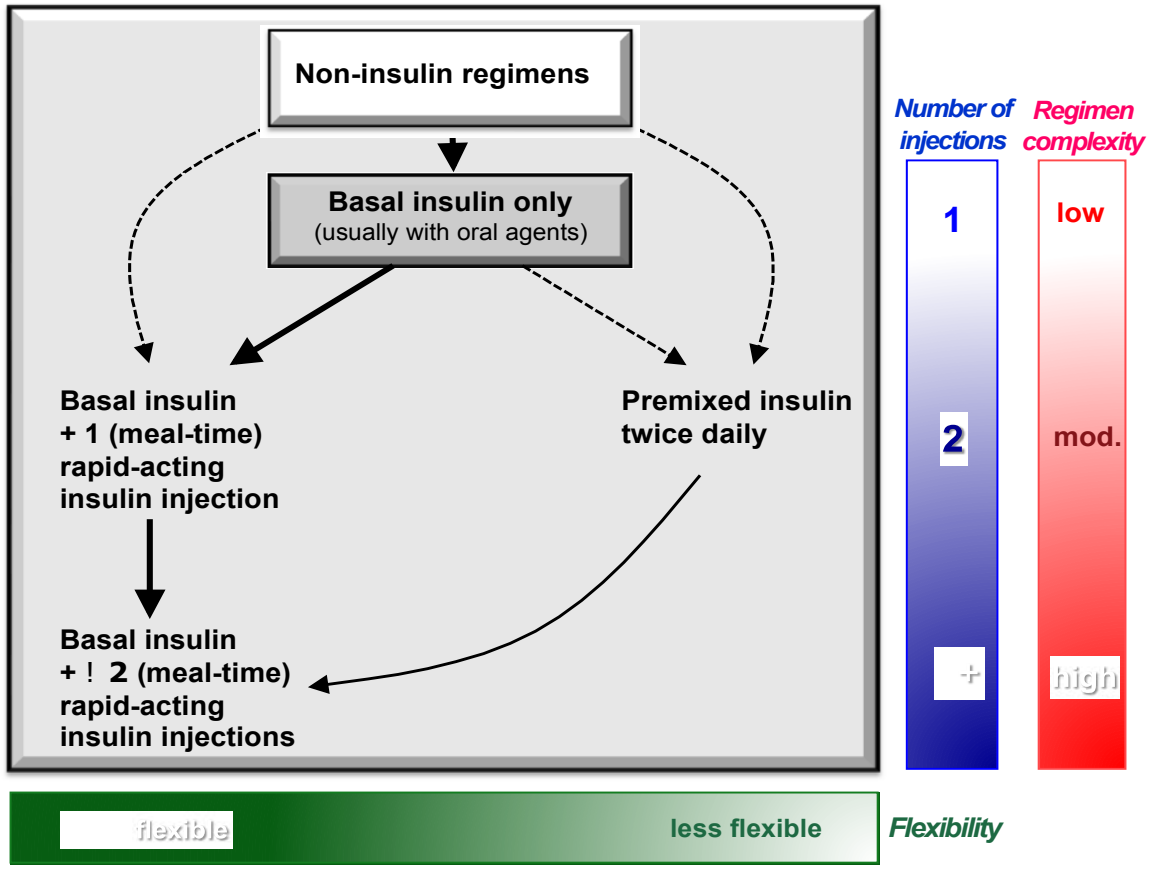
Overall summary

- Significant HbA_{1c} reductions on all study insulins
    - 22.7% of Korean patients achieved HbA_{1c} <7.0%
- Low rates of hypoglycaemia on all study insulins with minimal weight gain observed in all treatment groups
- Self-rated health was greater across all study insulins after 24 weeks of treatment

Sequential Insulin Strategies in T2DM



Inzucchi F et al., Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

Key Messages on Insulin in Type 2 Diabetes (Position Statement of the ADA and EASD)

- Any insulin will lower glucose and HbA1c
- All insulins are associated with some weight gain and some risk of hypoglycemia
- The larger the doses and the more aggressive the titration, the lower the HbA1c, but often with a greater likelihood of adverse effects
- Generally, long-acting insulin analogs reduce the incidence of overnight hypoglycemia, and rapid-acting insulin analogs reduce postprandial glucose excursions as compared with corresponding human insulins (NPH, Regular), but they generally do not result in clinically significantly lower HbA1c

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Inzucchi SR et al., Diabetes Care 2012, published online April 19, 2012

Insulin regimen choice should be an individualised approach based on many factors including lifestyle, social, economic, desired glycaemic targets, age, duration of diabetes, co-morbidity and hypoglycaemia risk

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Thank you for your attention

현재 당뇨병 치료의 중요한 개념

- Early intensive glycemic control
- Wholistic approach
- Early insulinization and Beta cell protection
- Aggressive complicaton evaluation and management
- Maintaining Healthy Body Composition
  - Fat mass and skeletal muscle

EQ-5D quality of life scores at 3 years

Winzorized mean ± 95% confidence interval

Biphasic:	0.76 (0.71 to 0.80)	p=0.73	p=0.86
Prandial:	0.77 (0.73 to 0.81)	p=0.86	
Basal:	0.80 (0.77 to 0.83)		

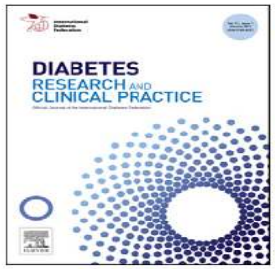
Treatment Satisfaction

Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Improvements in quality of life associated with insulin analogue therapies in people with type 2 diabetes: Results from the A$_1$chieve observational study☆,☆☆

Siddharth Shah[a,*], *Alexey Zilov*[b], *Rachid Malek*[c], *Pradana Soewondo*[d], *Ole Bech*[e], *Leon Litwak*[f]

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Shah S at al, Diabetes Res Clin Pract. 94:364-70, 2011

- Having T2DM has a negative impact on quality of life (QoL).
- Having to deal with lifestyle change, complex treatment regimens, potentially having to manage self-injection, and sometimes fear of hypoglycemia and weight gain can contribute to poor QoL and adverse perceptions of diabetes therapies.
- Consequently, people with T2DM and their physicians often delay starting or optimizing insulin therapy, despite the current burdens of poor glycemic control [4–7].
- Alongside effective glycaemic control, maintaining or improving QoL is an integral part of the successful management of diabetes. Indeed, it is known that measured QoL improves with better glycemic control.

EQ5D: Self-rated health rating scale

1. Mobility
2. Self-care
3. Usual activities
4. Pain / discomfort
5. Anxiety / depression

1. No problem
2. Moderate problem
3. Extreme problem

5-digit code e.g.
12221

This code relates to a 'utility' value between 0 and 1

The EQ VAS records the respondent's self-rated health on a vertical scale

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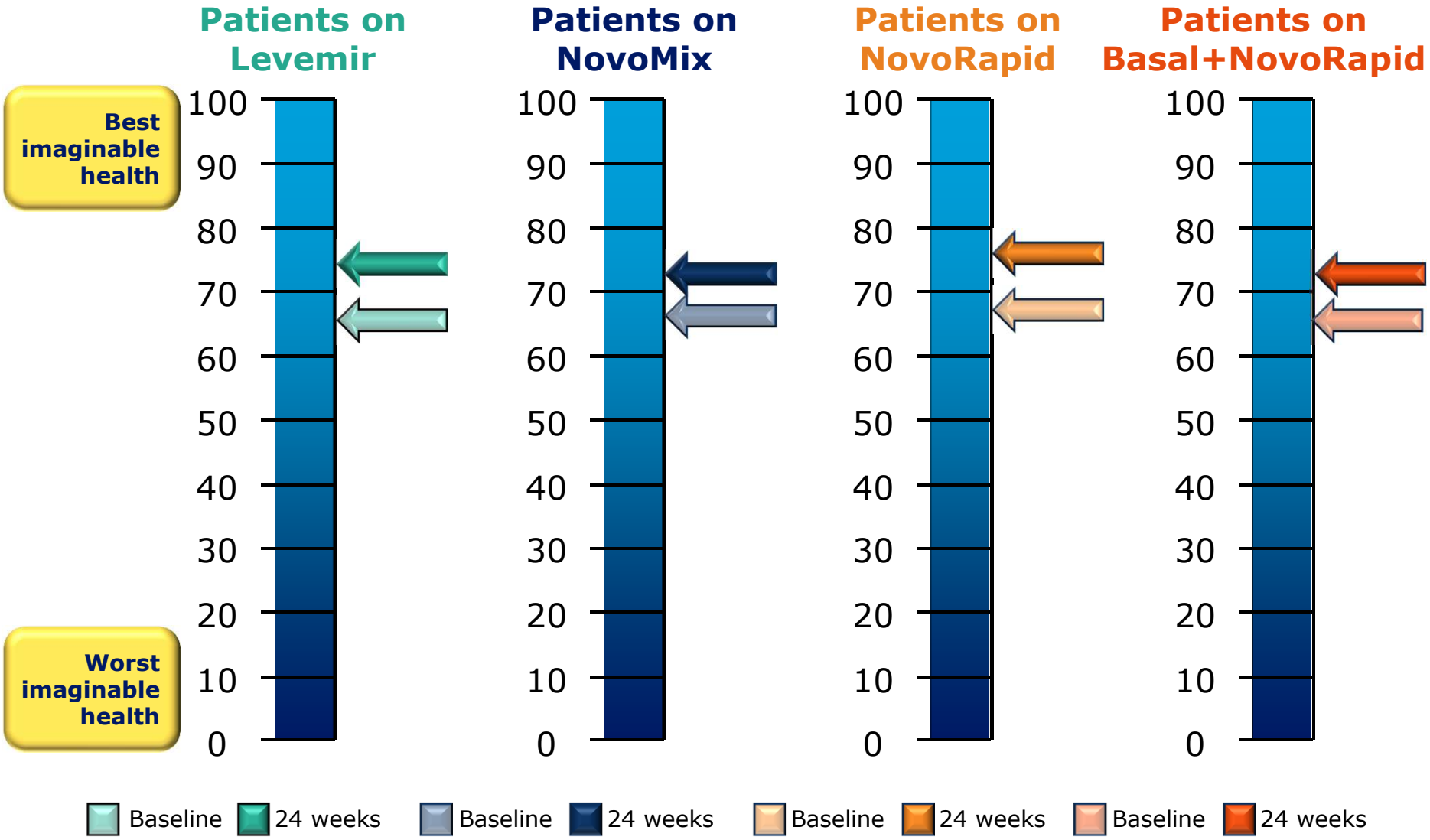
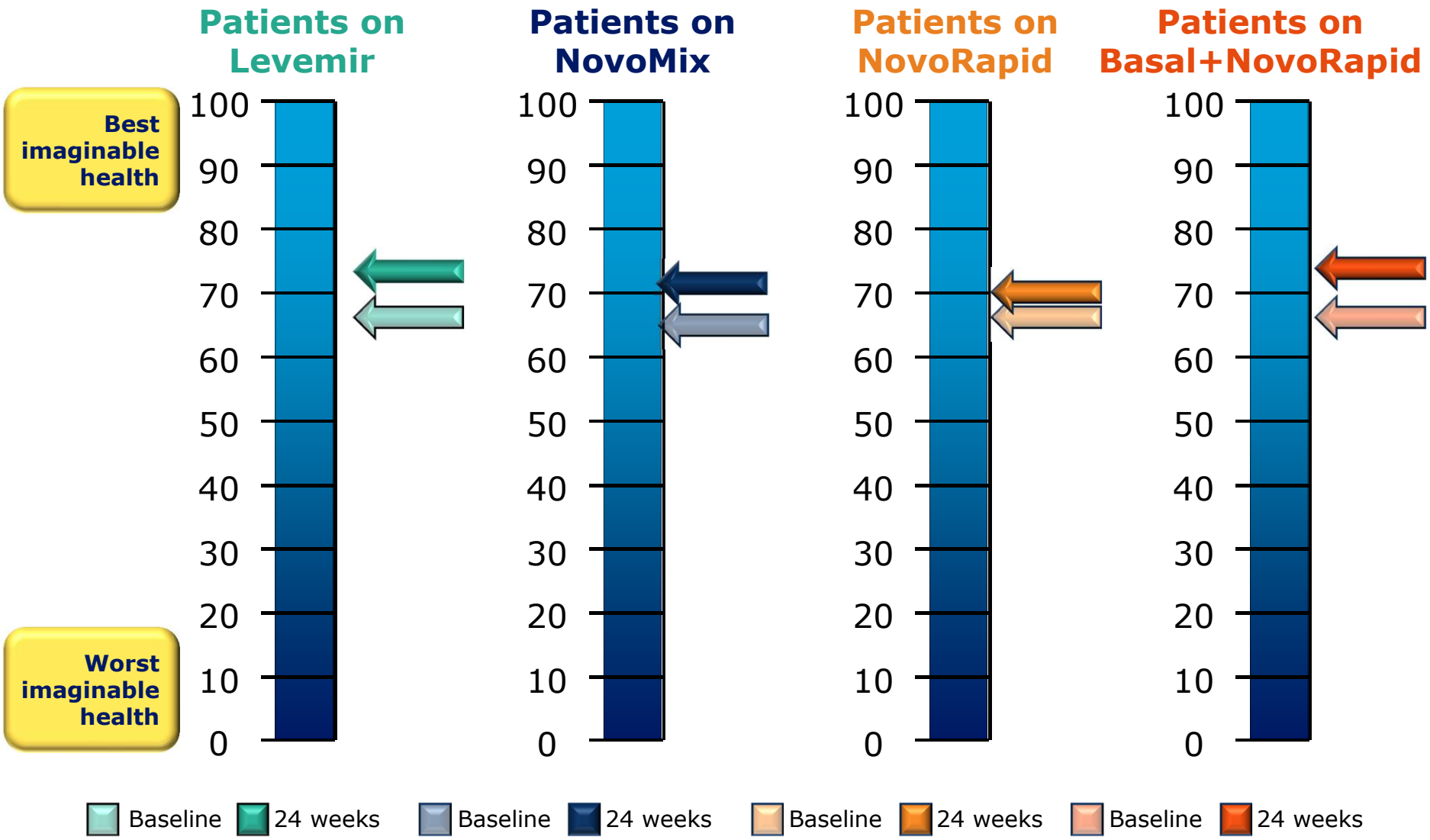
Self-rated health in insulin naïve patients



Self-rated health in insulin users



Insulin treatment in Type 2 Diabetes

- Naive type2 diabetes
- Oral hypoglycemic agents failure
- Intensifying insulin treatment regimen

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Key deciding factors

- Metabolic parameters – initial glucose levels, osmotic symptoms, glucose profile
- Individual preference – number of injections
- Lifestyle – variable versus predictable
- Occupation
- Presence of physical or cognitive disability
- Social circumstances – living alone, leisure activities, etc.
- Willingness to frequent self monitor
- Insurance coverage and cost
- Compliance

Noncompliance independent associated with increased all-cause mortality in patients with type 2 diabetes

Data were extracted from U.K. general practice records and included patients (*N* = 15,984) with type 2 diabetes

1. **C**linic nonattenders were more likely to be smokers, younger, have higher HbA_{1c}, and have more prior primary care contacts and greater morbidity ($P < 0.001$).

2. Medication noncompliers were more likely to be women ($P = 0.001$), smokers ($P = 0.014$), and have higher HbA_{1c}, more prior primary care contacts, and greater morbidity (all $P < 0.001$)

3. After adjustment for confounding factors:

   A. Medication noncompliance (HR 1.579 [95% CI 1.167–2.135])
   B. Clinic nonattendance of:
      I. 1 or 2 missed appointments (HR 1.163 [1.042–1.299])

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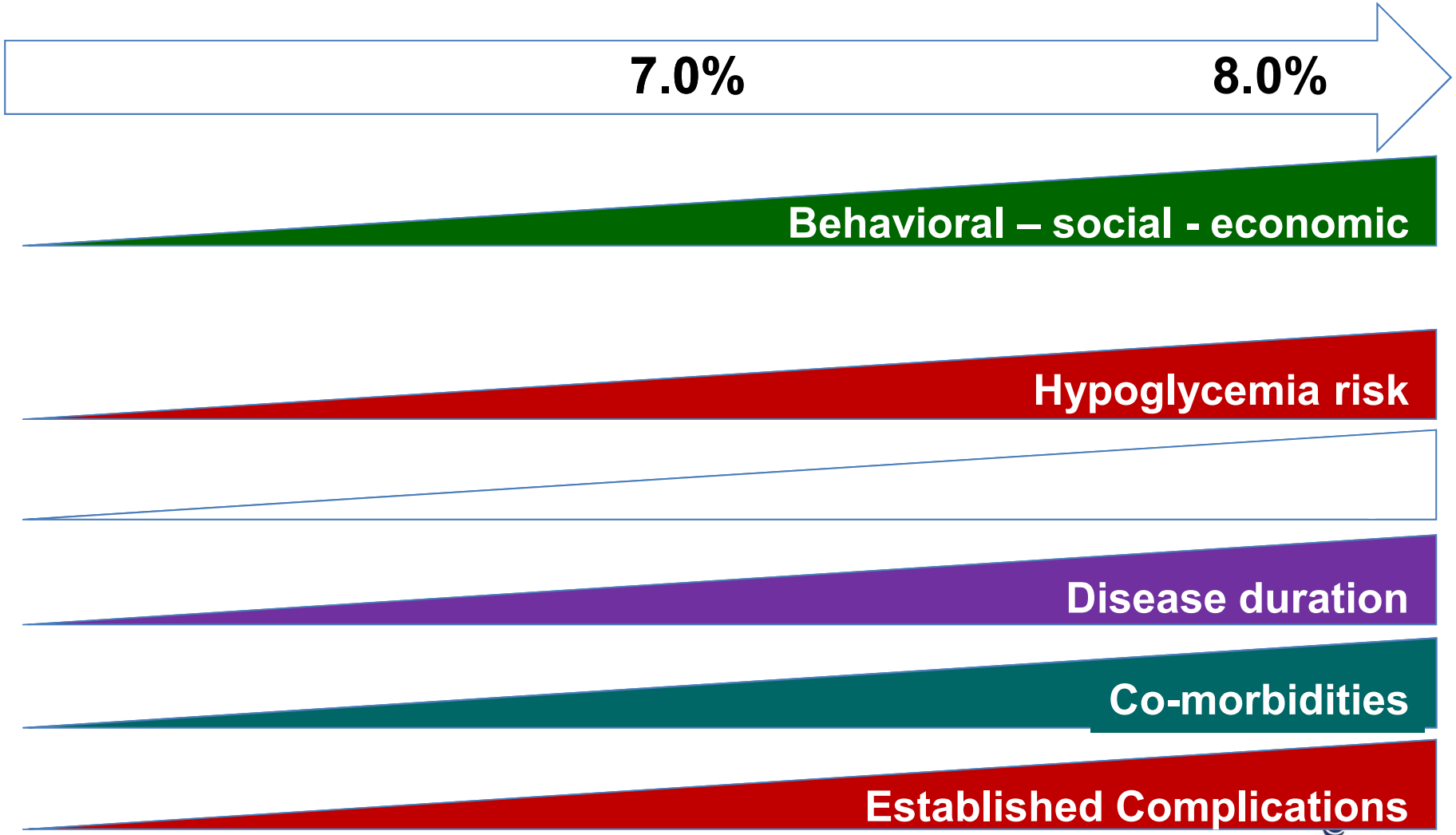
Currie CJ et al., Diabetes Care 2012 published online April 1

Individualizing Treatment Targets in Diabetes



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