

Why dose accuracy matter?

경희의대 내분비내과 오 승 준





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주사의 정확성



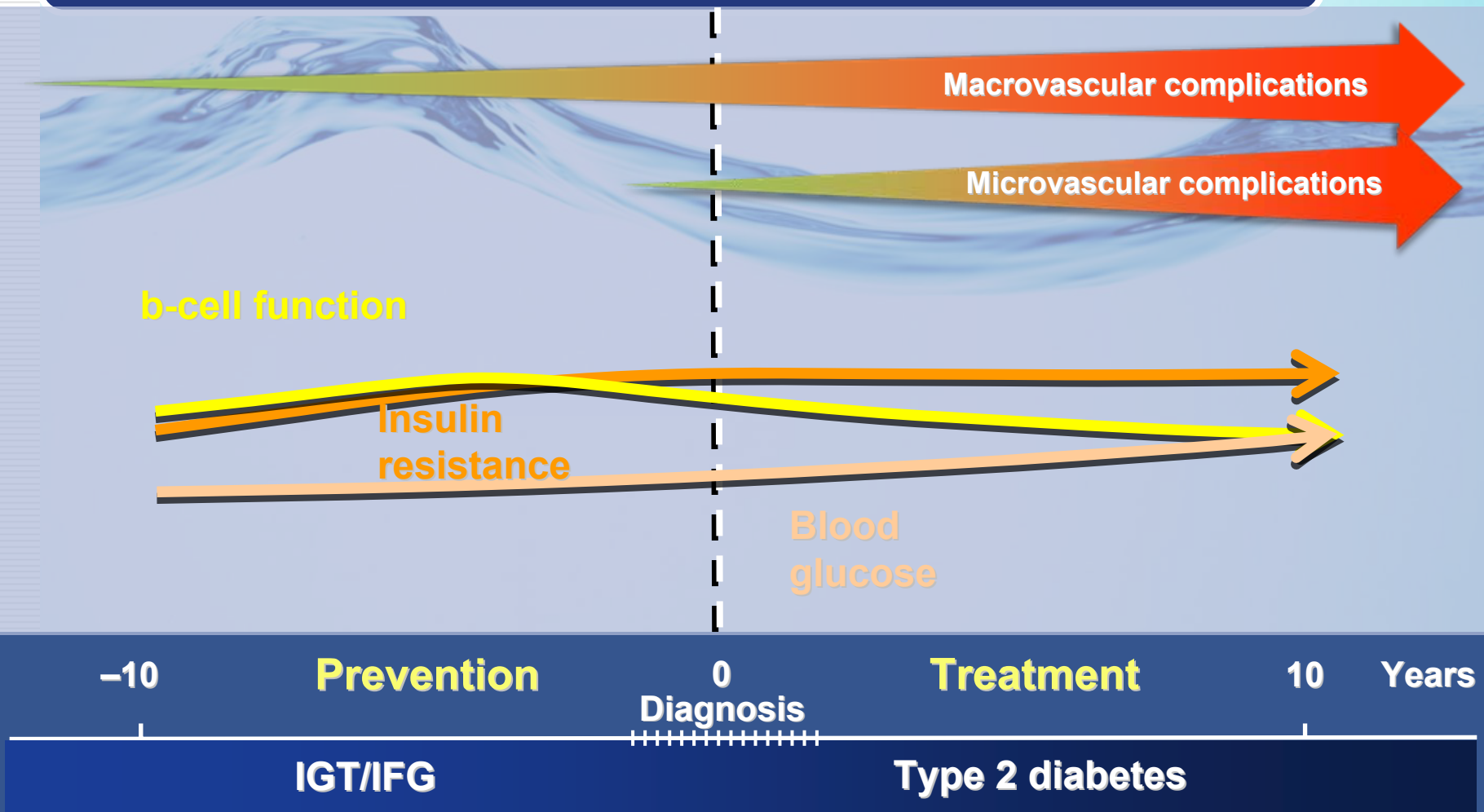
1



인슐린 치료의 어려움

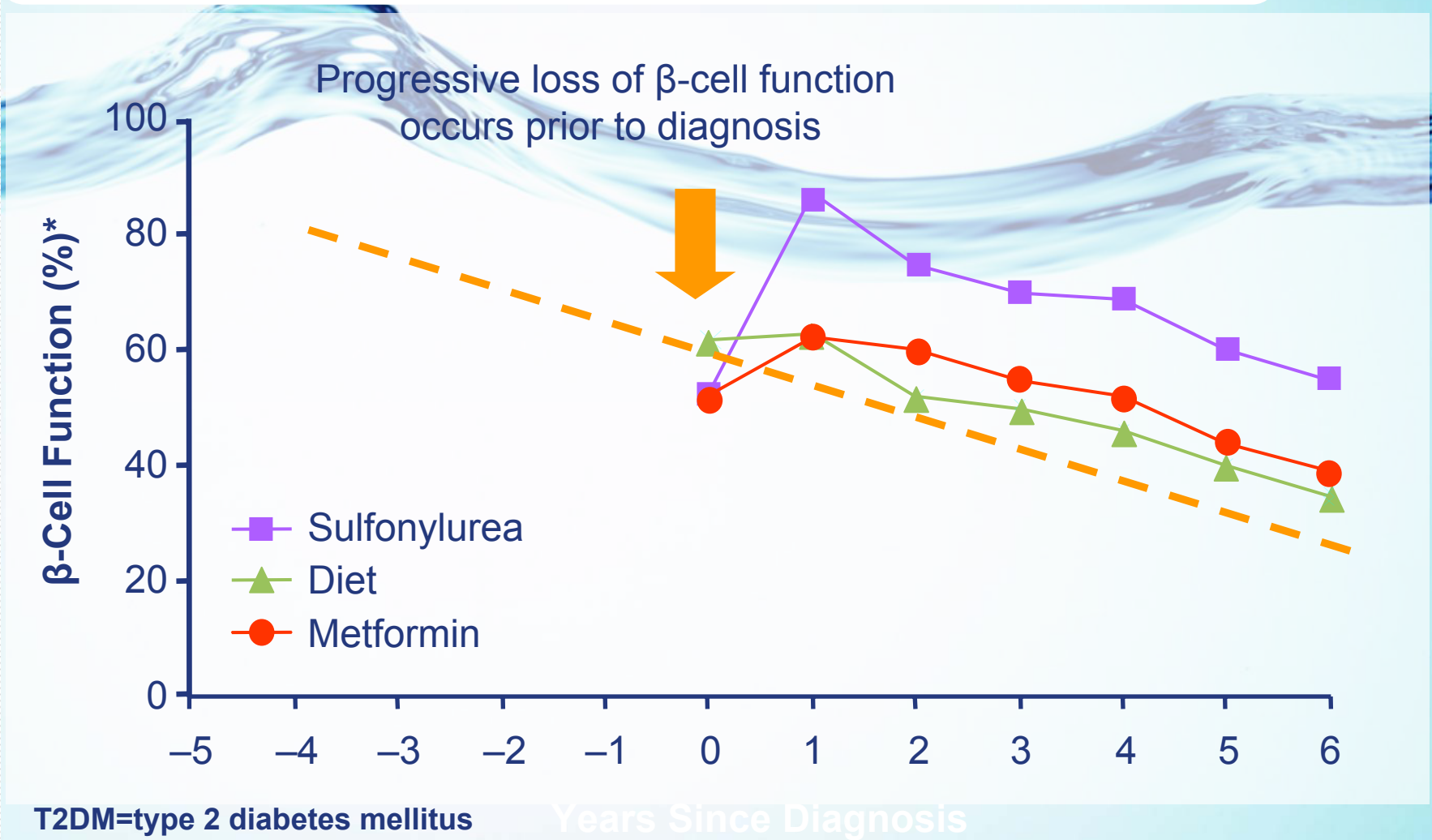


Natural history of disease progression





β -Cell Function Declines Regardless of Intervention in T2DM



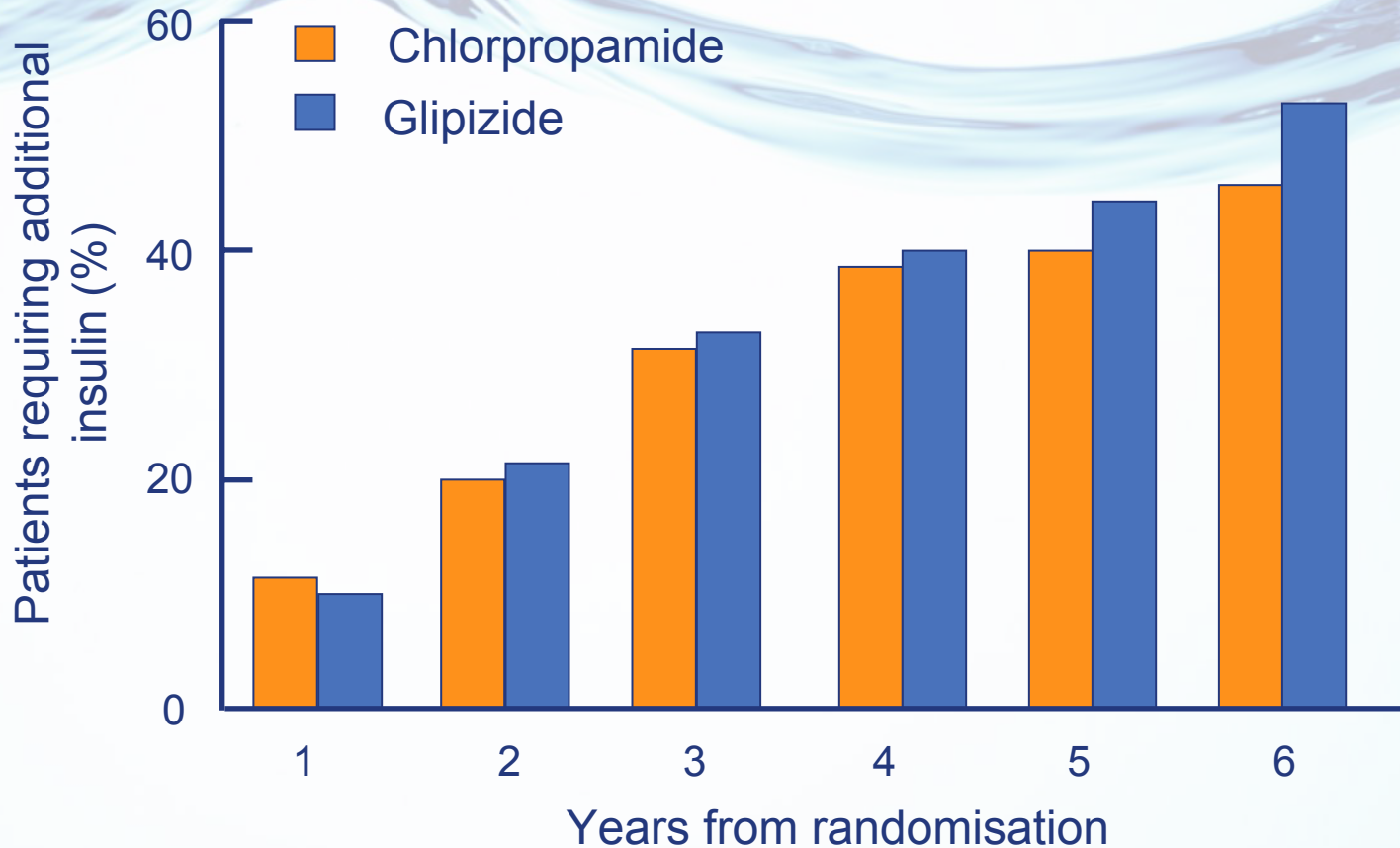
T2DM=type 2 diabetes mellitus

* β -cell function measured by HOMA

Adapted from UKPDS Group. *Diabetes*. 1995;44:1249–1258.



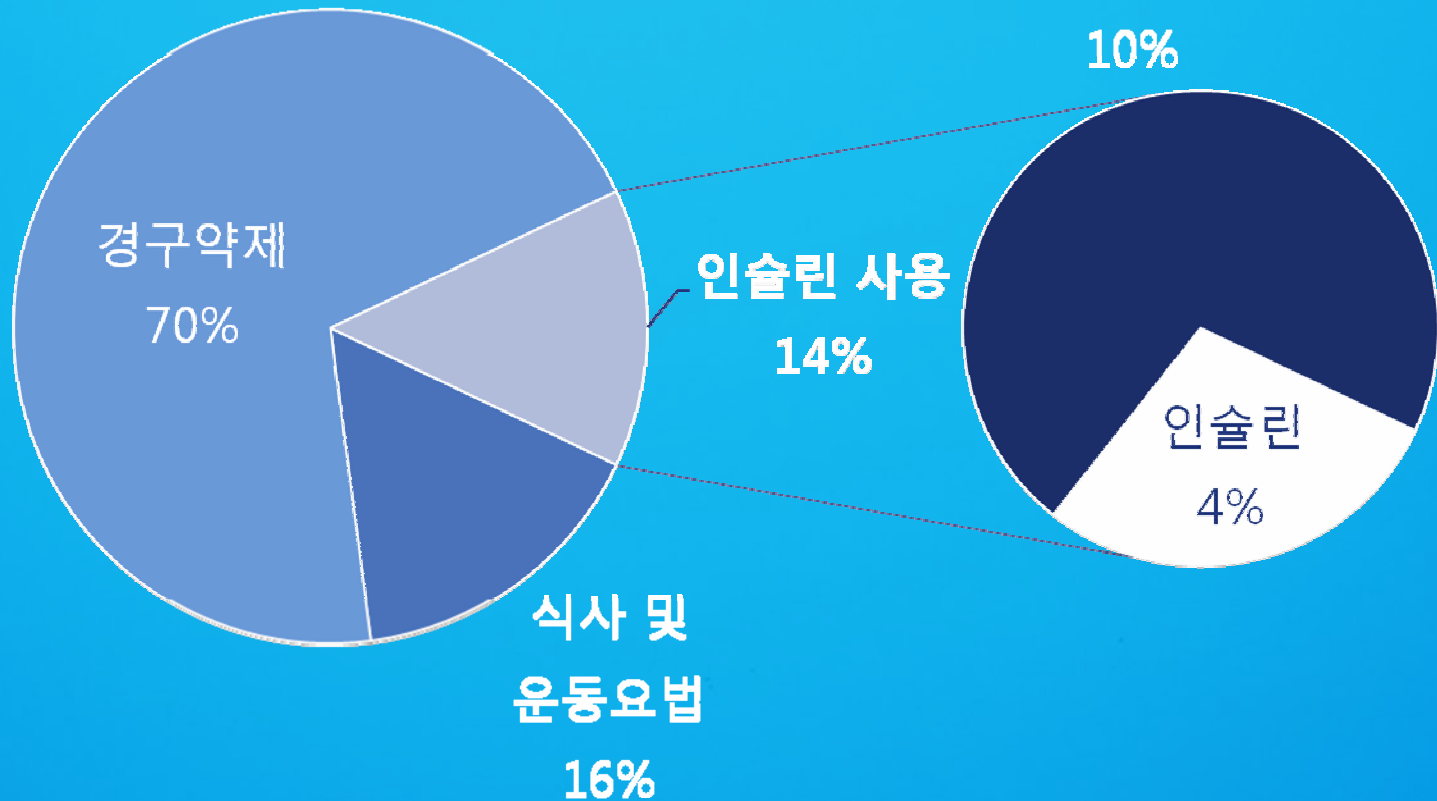
UKPDS 57: over time increasing numbers of patients required insulin





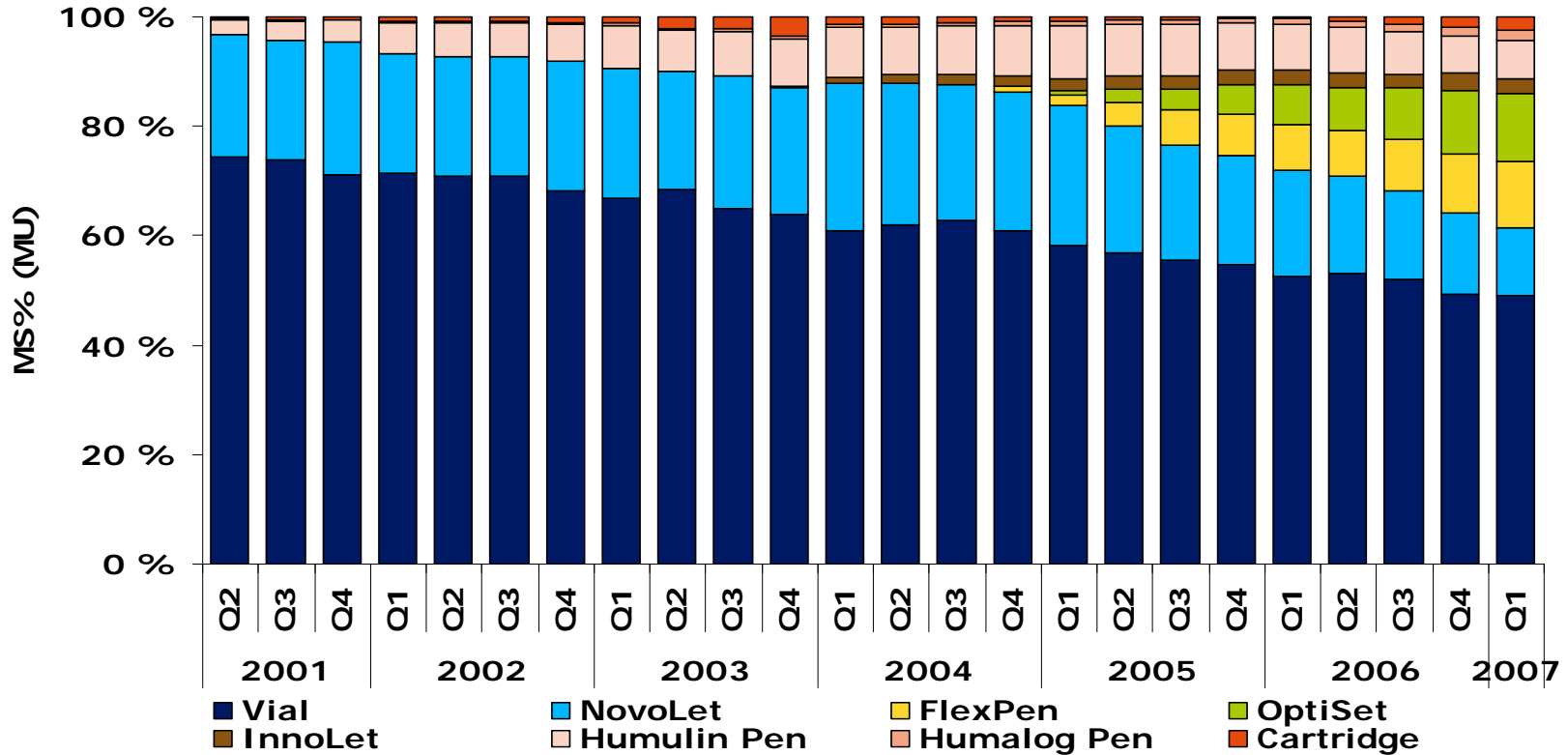
우리나라의 당뇨병 치료방법 현황

대상 2,691명





우리나라는 아직도 바이알을 대부분 사용합니다.

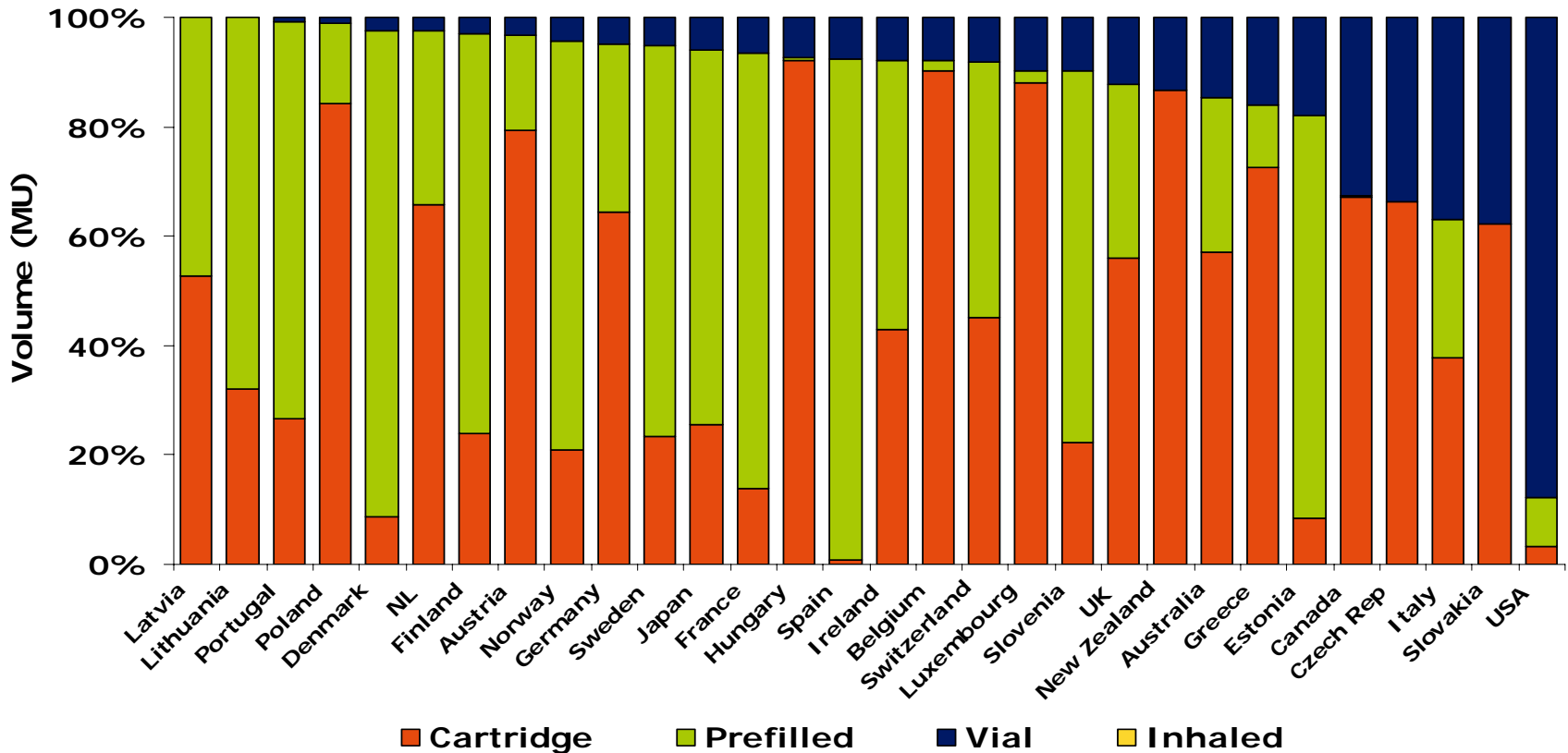


- Cartridges are basically not used at all
- FlexPen and OptiSet (Sanofi-Aventis) 12% market shares each



Different device uptake in different markets

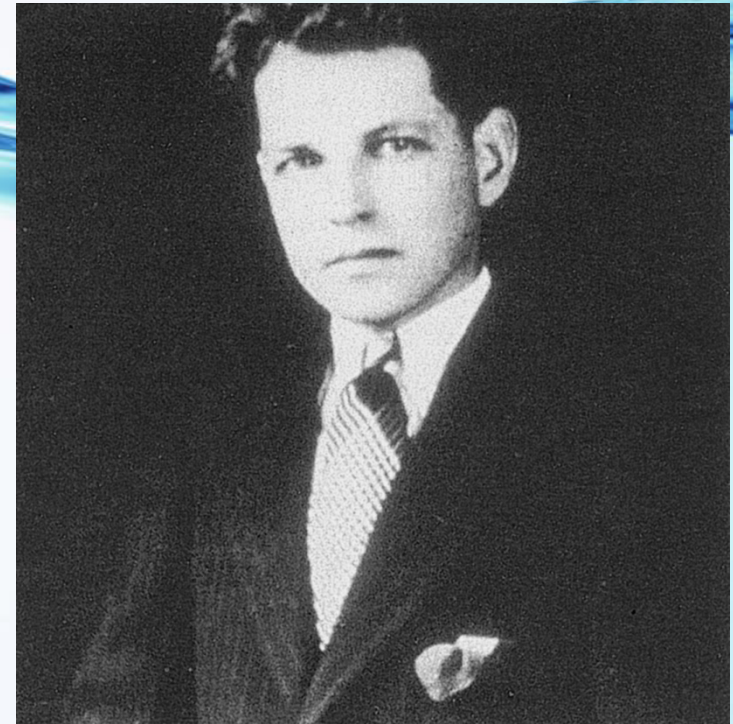
**Novo Nordisk Global: Insulin Breakdown by Delivery System
Q2 2006**



Source: IMS/BW



Discovery of Insulin



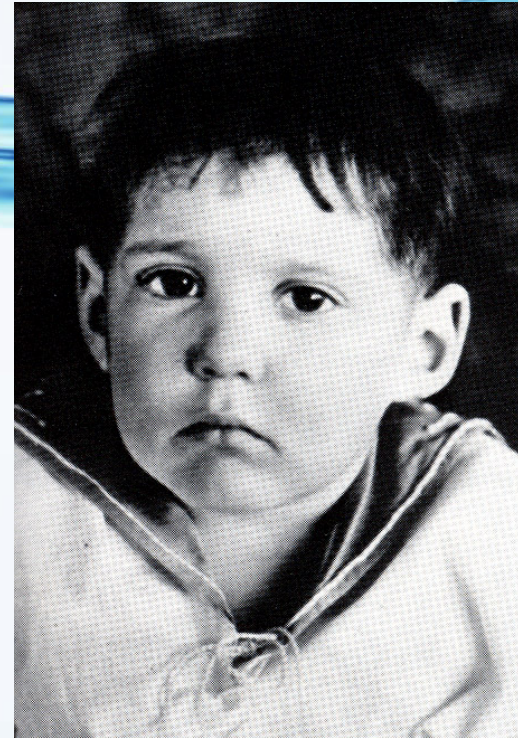
Leonard Thompson
The first patient to receive insulin
(1922)



The miracle of insulin



Patient J.L., December 15, 1922



February 15, 1923



Insulin Milestones



Paul Langerhans

Apologised to his examiners for the lack of novelty in the thesis which contained the first description of pancreatic islets. The islets were named for Langerhans in 1893 by a Frenchman called Laguesse, in a paper in which he speculated that this group of cells was responsible for an internal secretion of the pancreas.

Oskar Minkowski

Established the pancreatic origin of diabetes, and went on to show that a blood-borne secretion was responsible for preventing hyperglycaemia.



John James Rickard Macleod

A modest man who played an important role in the discovery of insulin but was glad to 'shake the dust of Toronto from his shoes'.

Hans-Christian Hagedorn

One of the great insulin pioneers, whose NPH formulation continues to benefit millions of people.



Frederick Sanger

Another modest man, who worked almost alone for years to determine the primary sequence of insulin, an achievement which led to his first Nobel Prize.

Dorothy Hodgkin

Won her Nobel Prize for the structure of vitamin B₁₂ before going on to determine the three-dimensional configuration of insulin.



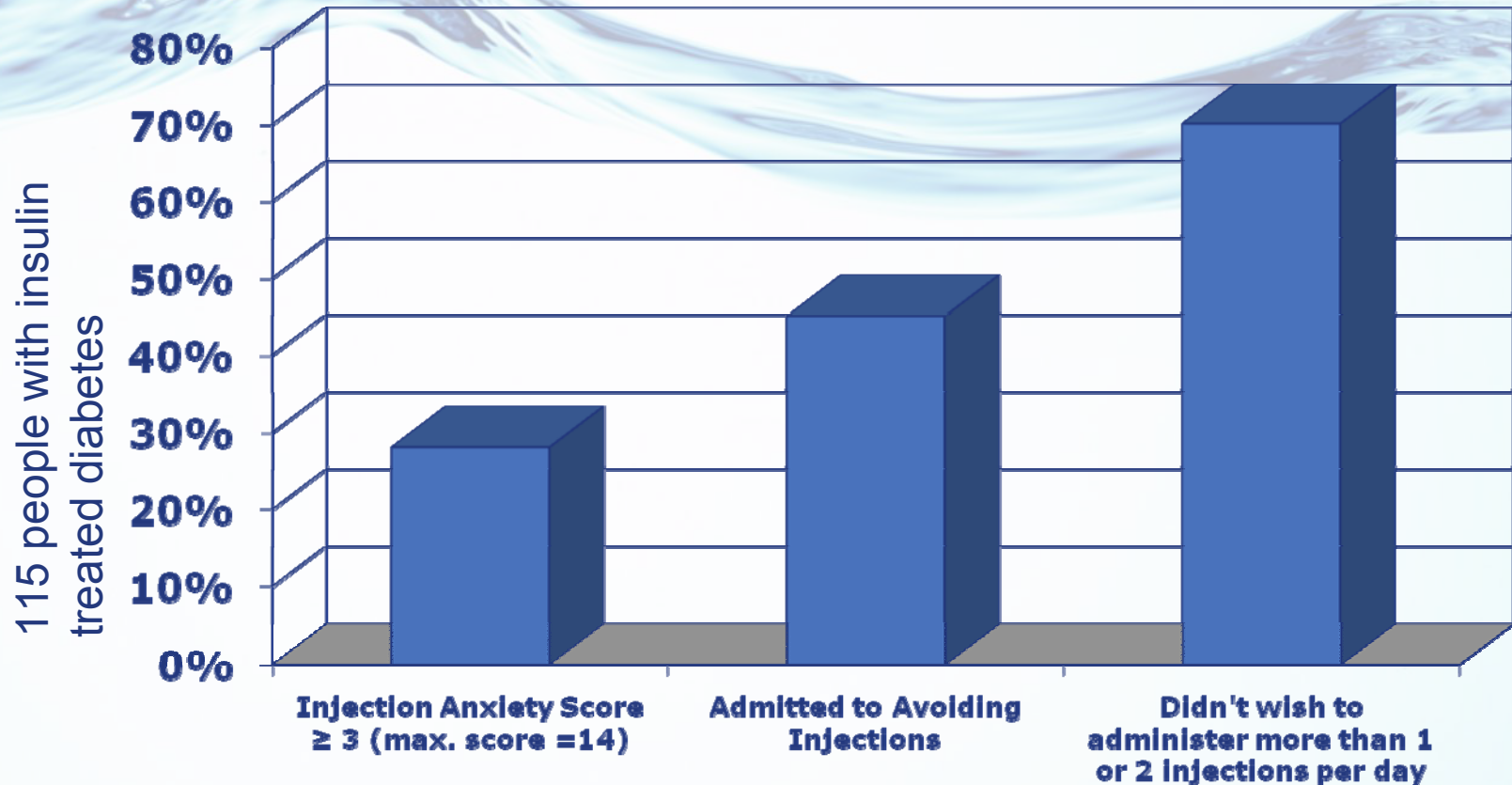


Adherence to Therapy

- ❖ Unfortunately, adherence to insulin is poor
- ❖ Patients are resistant to starting insulin
- ❖ Even they do start, patients face challenges in using insulin as recommended.



Factors Contributing to Poor Adherence: Injection Anxiety



Zambanini A, et al. Diabetes Res Clin Pract. 1999;46: 239-246.



Factors Contributing to Poor Adherence: Social Embarrassment

- ❖ Judgment of others and stigmatization as a “sick person,” a “dependent,” “or even a drug user”¹
- ❖ May prevent individuals, particularly children, from interacting socially or may result in skipped doses.²

¹Leslie CA, et al. Diabetes Spectrum. 1994; 7: 52-57.

²Grey M, et al. Diabetes Care. 1995; 18: 1330-1336.



Factors Contributing to Poor Adherence: Age-Related Difficulties

- ❖ Patients with diabetes may experience age-related difficulties in accurate self-dosing due to poor vision or impaired dexterity.

Fox C. et al. *Diabetes Res Clin Pract.* 1990; 10: 221-230.
Puxty JA, et al. *Br Med J (Clin Res Ed).* 1983; 287: 1762.



Vials and Syringes

– the only way to administer insulin before 1985





In 1985 the dream was made real

NovoPen[®] – The world's first insulin pen

150 U RI, 27G needle



1991년, 한국에는 NovoPen II가 처음 소개 되어 사용되기 시작하였습니다.



Insulin Pens Offer Expanding Choices and Features of Insulin Delivery to Aid Treatment Adherence

- Reduce insulin dosing errors verses syringe¹
- Discreet²
- Convenient³
- Promote patient compliance³

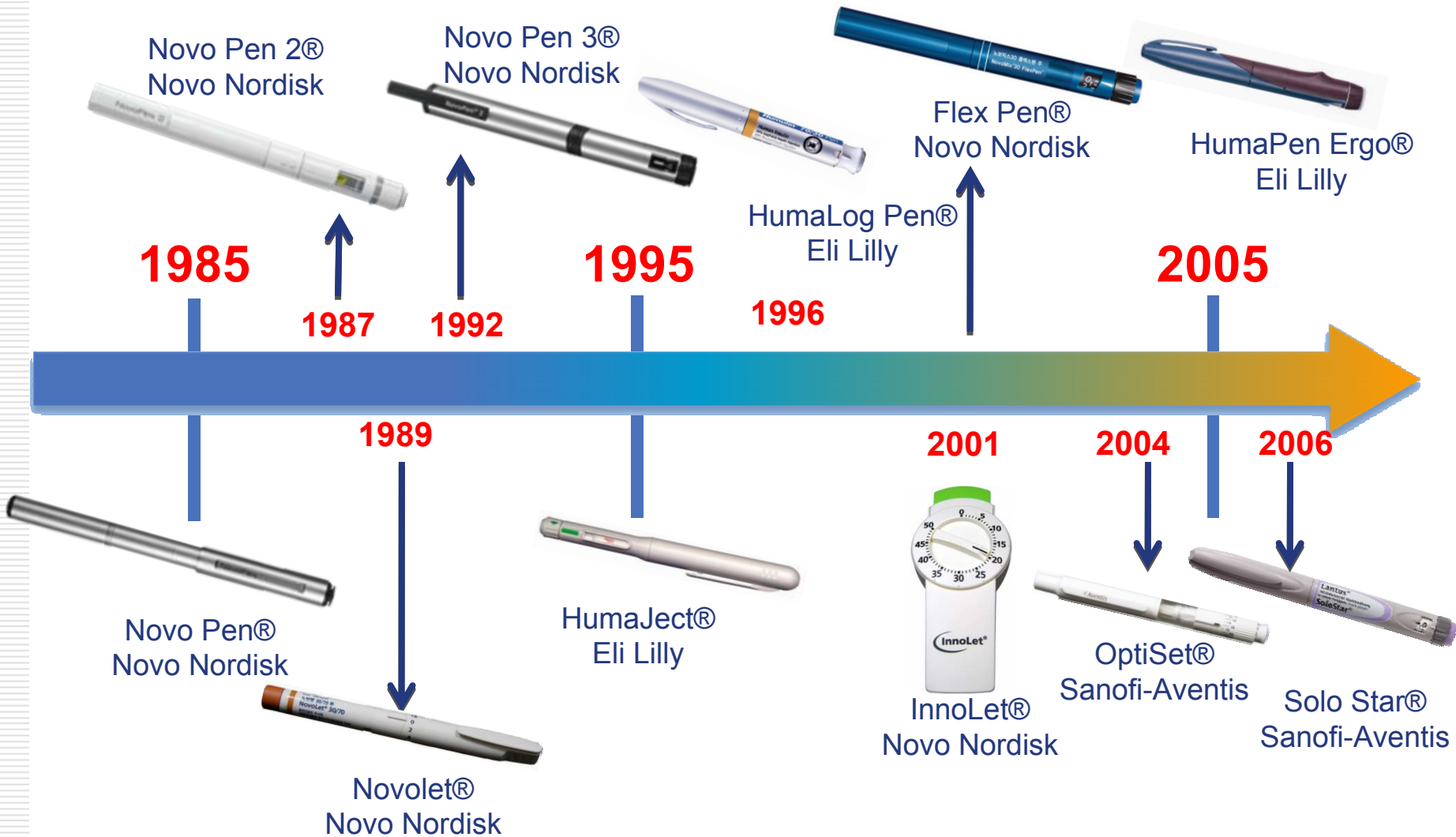
1. Lteif AN. et al. Diabetes Care. 1999;22:137-140.

2. Korykowski M, et al. Clin Ther. 2003;25:2836-2848.

3. Thurman JE. Endocr Pract. 2007;13:672-678.



Milestones in Insulin Injector

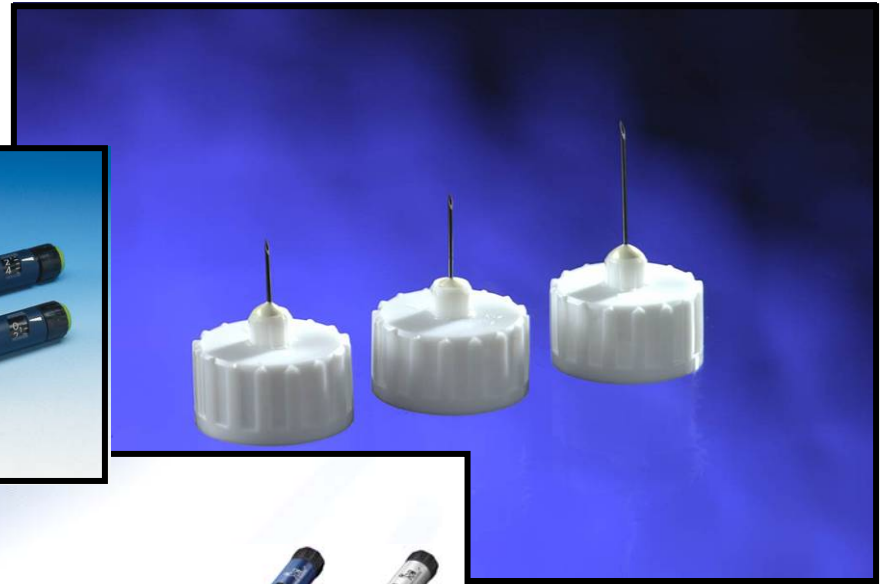




Novo Nordisk sustains improvement

27G → 28G → 30G → 31G → 32GT

NovoLet® → FlexPen®



NovoPen® 3 → NovoPen® 4



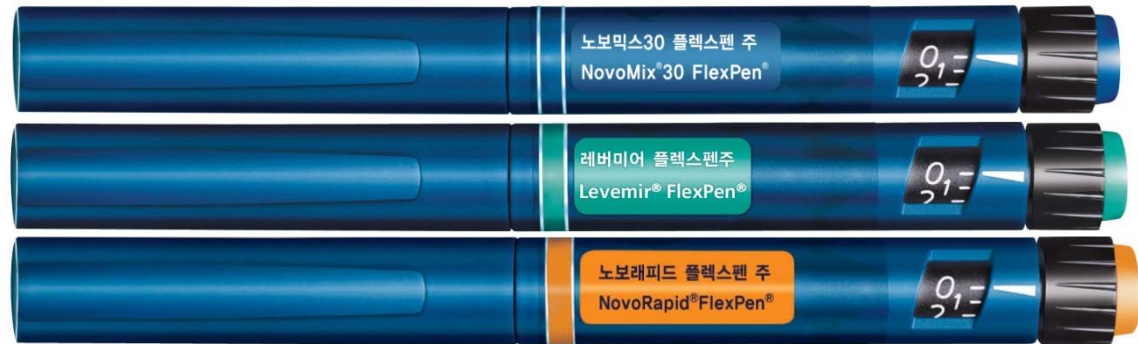
Novo Nordisk Pen type Insulin



InnoLet®



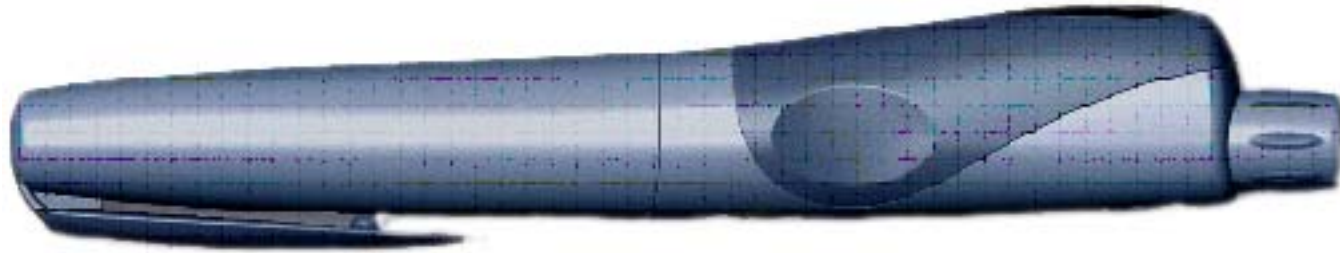
NovoLet®



FlexPen®



Sanofi-Aventis Pen type Insulin



OptiClick®



OptiSet®



SoloStar®



Eli Lilly Pen type Insulin



Humalog Pen®



HumaPen Ergo®



HumaPen Luxura®



Needle Cap의 또 다른 기능





2



사용 편의성과 치료 순응도



Patient Adherence

Adherence on average:

51%-79% patients adhere to therapy, decreasing with increased complexity of regimen.¹

Implications of low adherence:

Failure to adhere to appropriately prescribed therapeutic regimens is a major factor restricting the quality of medical care.²

Most important factors of adherence:

- Increasing convenience increases adherence³
- Increasing simplicity increases adherence³

1: Claxton et al, A systematic Review of the Associations Between Dose Regimens and Medication Compliance, Clin. Ther., Vol. 23, 2001

2: Kaplan & Simon, Compliance in medical care, Ann. Behav. Med., 12, 1990

3: Coons, Medical Compliance: The Search for Answers Continues, Clin. Ther., Vol. 23, 2001

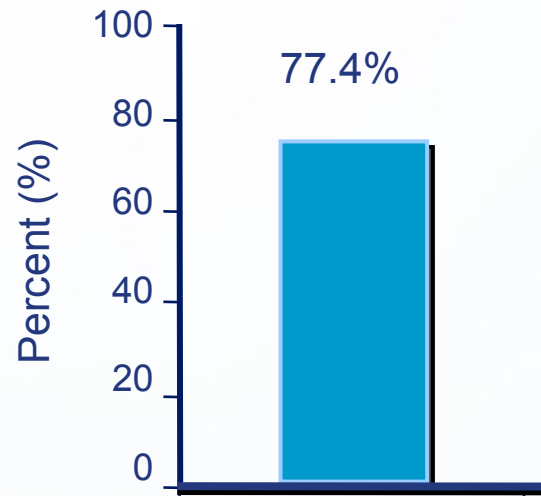


Patient adherence

Insulin adherence in type 2 patients

- Veteran Affairs database, 6,222 type 2 patients on chronic insulin therapy
- Adherence calculated by comparing prescribed insulin vs. amount of insulin received by patient (i.e. supplied by pharmacy)
- Significant correlation between adherence and A1c

Insulin adherence; mean
(US population: VA)



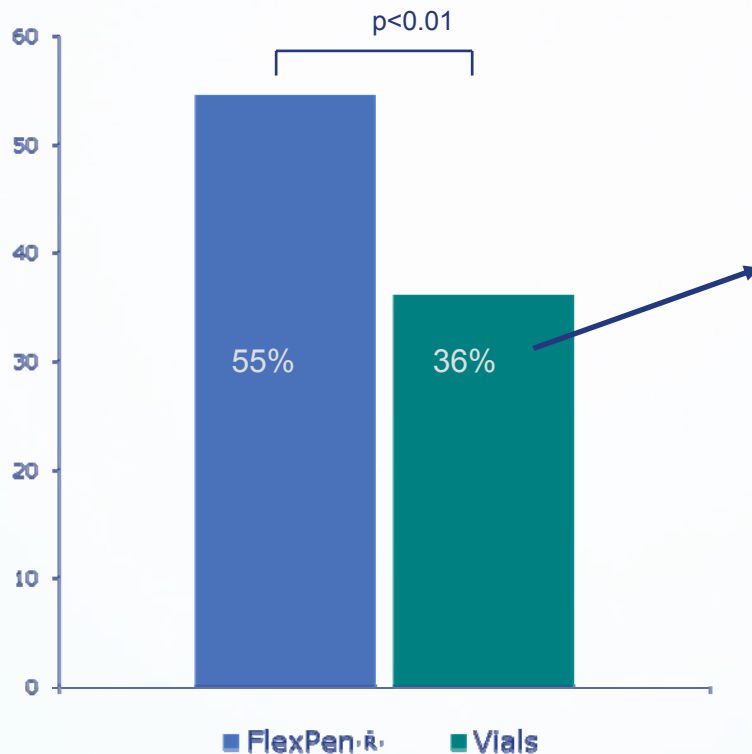


FlexPen[®] vs vial/syringe – Results

Adherence, hypoglycaemia & healthcare costs

Medication adherence improved, hypoglycaemia risk lowered and treatment cost diminished primarily because of hospitalisation cost*

Adherence (MPR>80%)*



Effect of treatment switch	Odds ratio
Hypoglycaemic events	0.50 p<0.01
Hypo-related ER visits	0.44 p<0.01
Hypo-related Dr visits	0.39 p<0.01

Mean all-cause treatment cost: -\$1.590/year



NovoMix[®] 30 FlexPen[®] vs. syringe Quality of Life

- ❖ Findings from 3-month NovoMix[®] 30 FlexPen[®] clinical experience program
- ❖ Subjects: type 2 patients treated with NovoMix[®] 30 premix insulin in vial/syringe, n=91
- ❖ Diabetes treatment satisfaction measured by Diabetes Treatment Satisfaction Questionnaire change (DTSQc). Quality of life was measured by the Quality of Life status and change questionnaire (QLsc)



NovoMix[®] 30 FlexPen[®] vs. syringe Quality of Life

Rating of FlexPen[®] in former NovoMix[®] 30 vial/syringe users

Parameter	Source	Outcome	
Convenience	DTSQc no. 4	2.19 ± 1.15	p<0.001
Flexibility	DTSQc no. 5	1.96 ± 1.22	p<0.001
Quality of life	QLsc nos. 5-12	1.06 ± 1.04	p<0.001

Data are means ± SD. Possible range of means is -3 to 3. Means greater than zero indicate that the pen device was rated higher than the previous treatment.



Types of Insulin Pens

❖ Reusable cartridge pen

- Insulin vial is replaced by inserting a new one.
- If patient requires a number of insulin types, a different reusable pen and appropriate cartridge is used for each type.

❖ Prefilled/Disposable pen

- When the insulin is gone, the entire unit is discarded.
- Factory calibrated which minimizes possibility of introducing errors during reloading of cartridges in reusable pens or using syringes.
- Each pen is prefilled and labeled separately, potential to confuse insulin formulation in a complex regimen is reduced.
- Disposable pens made from nontoxic materials and can be recycled.



Insulin Pens Reduce Needle Anxiety

- ❖ Disposable needles available with insulin pens are often shorter (8–10mm) than standard length needles (12mm) and are a larger gauge (31G/30G vs 28/27G) making them less painful to use.¹
- ❖ Needle in pen system does not puncture a stopper before injection as with the syringe/vial system. Therefore, needle retains sharpness and beveled angle, further increasing patient comfort.
- ❖ Pain perception can be reduced if the needle is unobtrusive and less visible to the patient.²
- ❖ Flexpen[®] is fitted with NovoFine[®] 30G 6–mm needles, which are short, slim, and smooth, allowing for a less painful injection.³

¹Smits JPH et al. Acta Ther. 1993;19:15-22.

²Diglas J et al. Horm Metab Res. 1998;30:A10

³Lytzen L, et al. Horm Metab. Res. 1993;25:61-67.



Social Embarrassment

- ❖ Insulin pens may help to overcome these obstacles, as they look more like a pen than a syringe and are compact in size, allowing them to be carried and used more discreetly.



Prefilled/Disposable Pen Ease of Use

❖ Modern devices such as the prefilled FlexPen[®] have features that contribute to ease of use:

- Single-unit dosing increments
- Audible click when dose is dialed
- Release button that is easy to press
- Large font dose selector
- Clear dial showing the selected dose
- After use, dose scale returns to zero





NovoMix[®] 30 FlexPen[®]

Prefilled insulin delivery system

Single-step dose setting



Dose scale



- Dose setting in 1-unit increments up to 60 units
- Impossible to dial a dose larger than remains in pen
- Large, clear dose-scale



NovoMix[®] 30 FlexPen[®]

Prefilled insulin delivery system

Dose correction



- Dial back to the correct dose without loss of insulin

Dose delivery



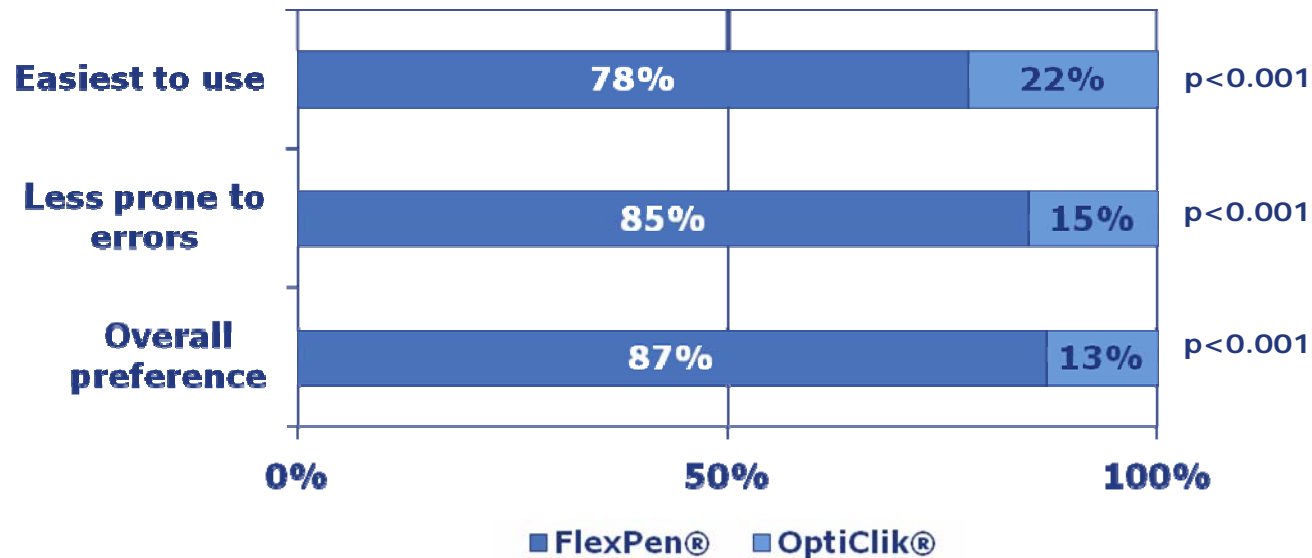
- Dose scale returns to zero during injection to allow visual confirmation of dose delivery



NovoRapid® FlexPen® vs. Lantus® OptiClik® Comparative handling study

Results:

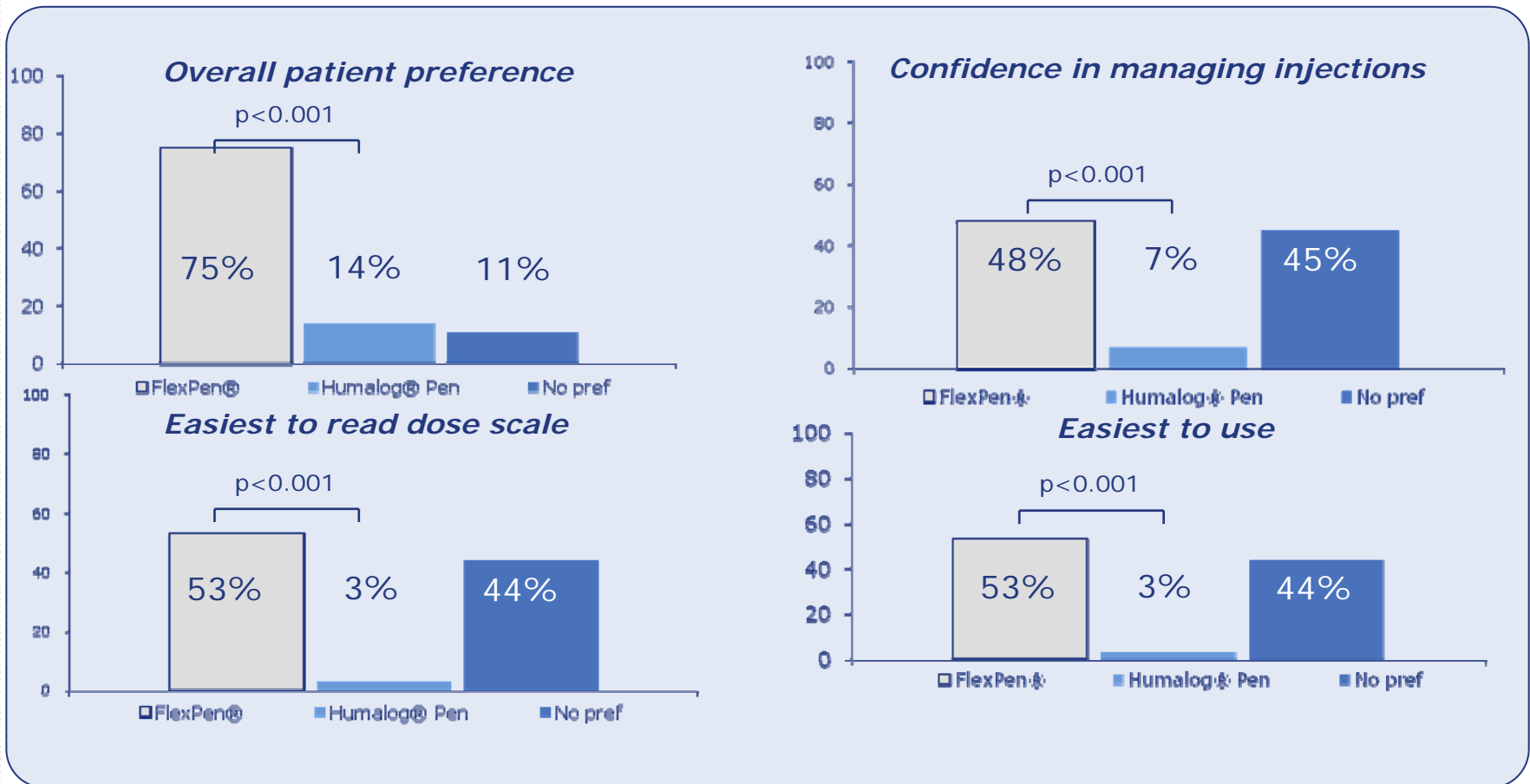
- ❖ FlexPen® was assessed as significantly better than OptiClik® regarding:
 - Intuitive usability (p<0.001)
 - Portability (p<0.001)
 - Appearance (p<0.001)





FlexPen[®] vs. Humalog[®] Pen

- ❖ Multicentre, open, randomised, 2*12 weeks cross-over trial
- ❖ Insulin treated type 2 patients, n=133



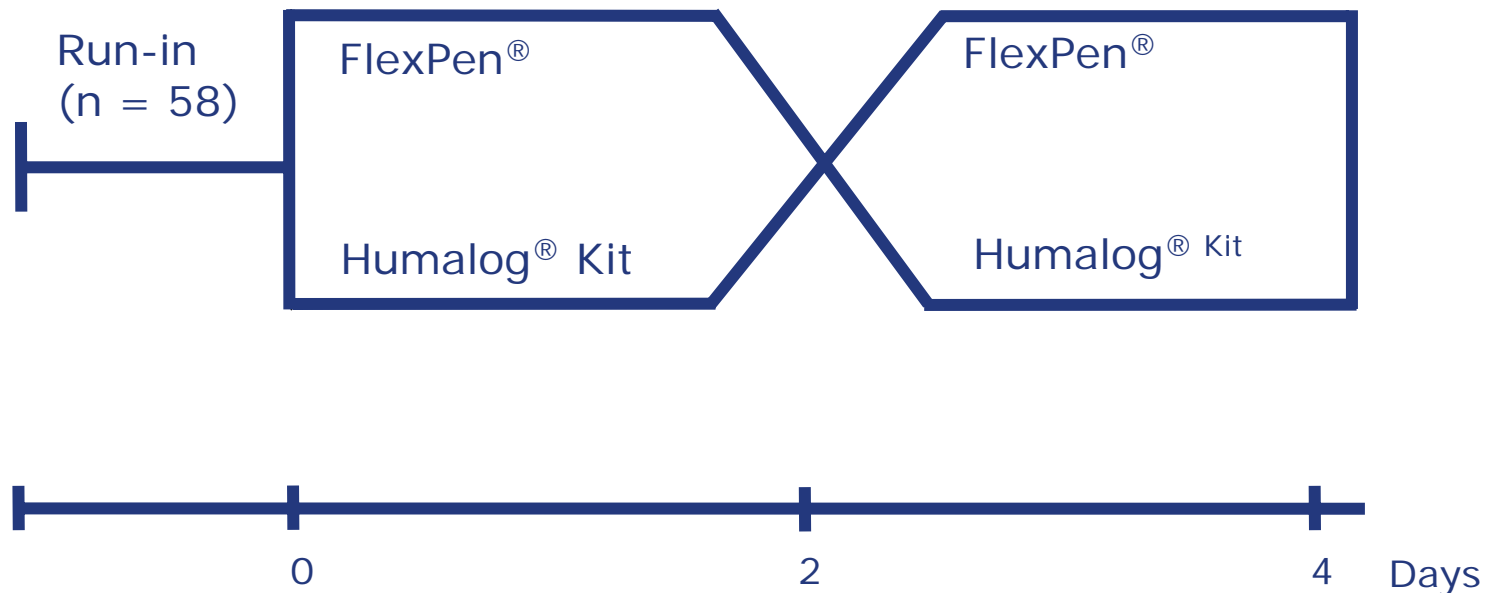


FlexPen[®] vs Humalog[®] Pen

Handling test

Study of usability and preference of FlexPen vs Humalog Kit

❖ Insulin naïve diabetes patients

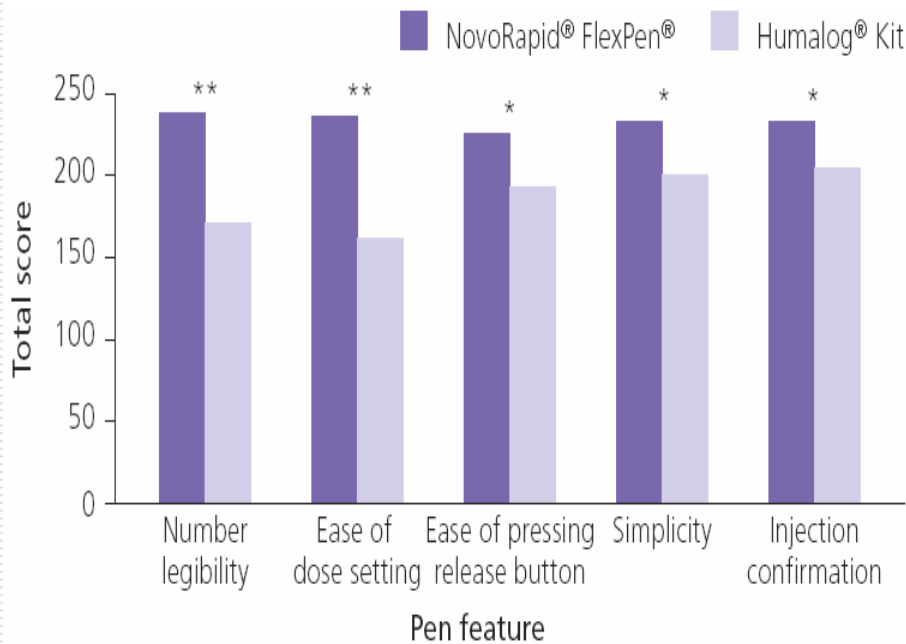


Both pens contained rapid-acting analogues, however, no insulin was injected in patients during the testing procedure

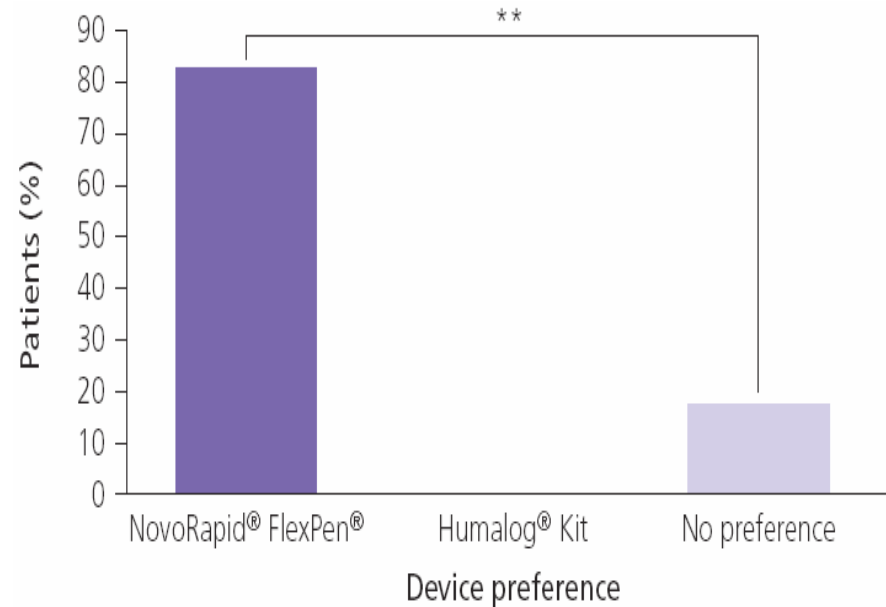


FlexPen[®] vs. Humalog[®] Pen

Usability



Preference



(**, $p < 0.001$; *, $p < 0.01$)

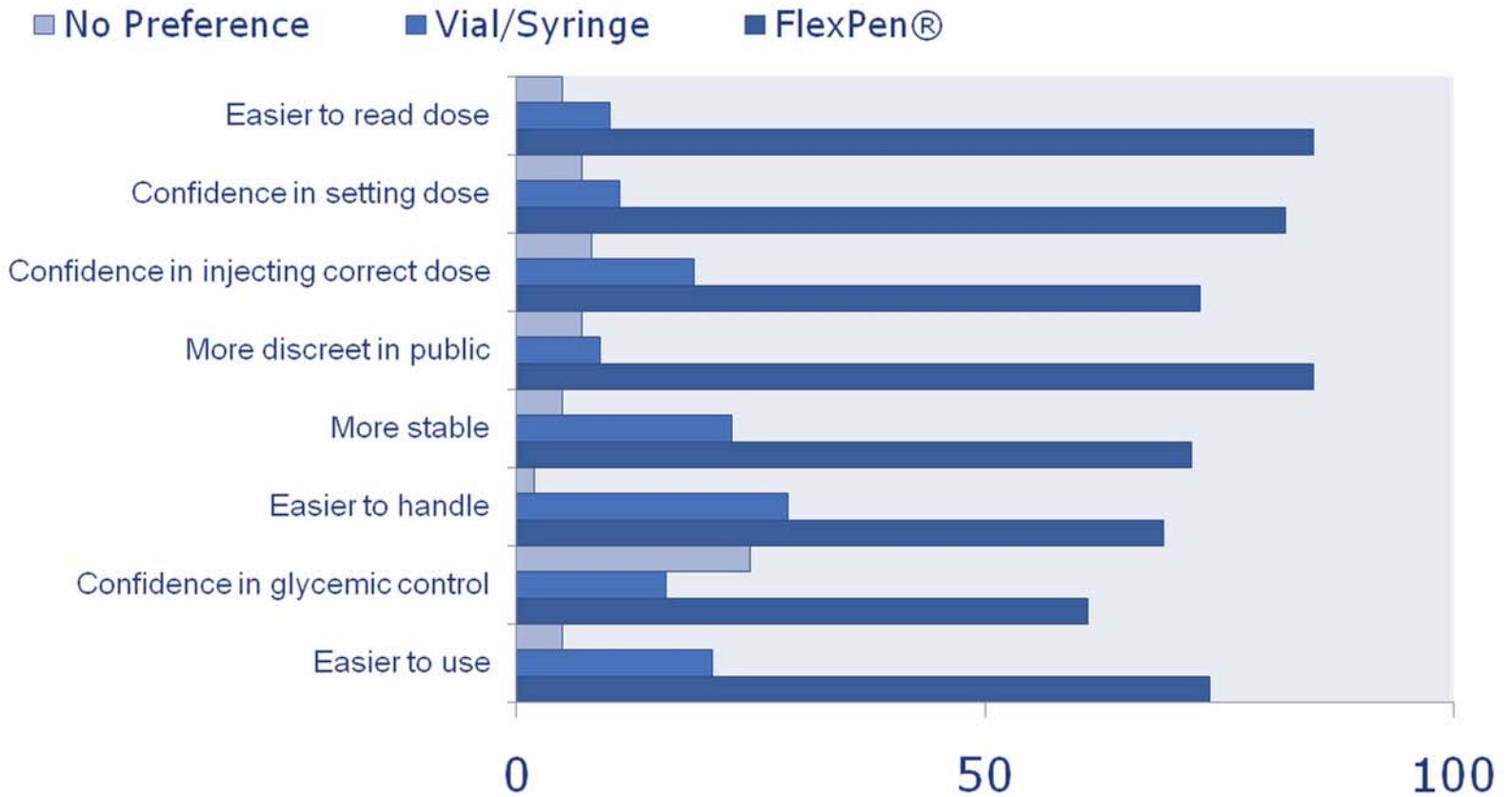


Economic Benefit of Initiating Insulin with Pen vs Syringe

	Initiating Insulin with Pen	Initiating Insulin with Syringe	p-value
Hospital Costs	\$1,195.93	\$4,965.31	P<0.05
Diabetes-Related Costs	\$7,324.37	\$13,762.21	P<0.05
Outpatient Costs	\$7,795.98	\$13,103.51	P<0.05
Total Annualized Health Care Costs	\$14,857.42	\$31,764.78	P<0.05



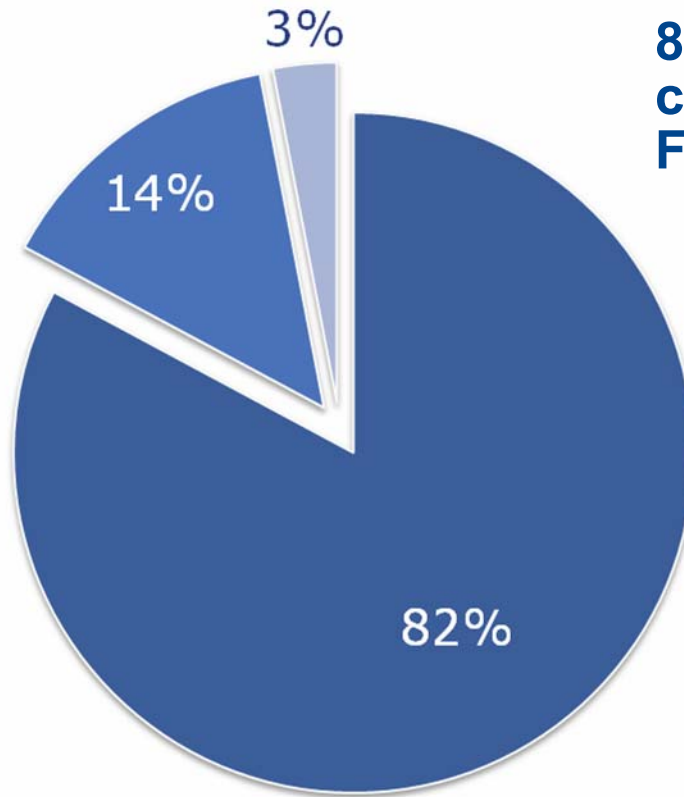
Factors Contributing to Patient Preference of FlexPen®



Korytkowski M, et al. Clin Ther. 2003;25:2836-2848.



Comparative Evaluation of FlexPen[®], a new prefilled insulin delivery system, among patients and healthcare professionals



82% of patients and health care professionals preferred FlexPen[®] (P<0.01)

- Prefer FlexPen
- Prefer Humulin pen
- Prefer Optiset



3



주사의 정확도



Dosing Accuracy

- ❖ Dosing Accuracy is measured according to EN ISO 11608-1:2000; Pen-injectors for medical use – Part 1: Pen-Injectors – Requirements and test methods
- ❖ This document defines how pens must be tested and how accuracy is to be measured. From this it can be calculated that a pen dosing at 10U must be within $\pm 1U$ and dosing accuracy at 30 units must be within $\pm 1.5U$ ($\pm 5\%$ at 30 units).
- ❖ The following studies use above accuracy limits and accuracies of devices are compared by ordinary statistical tests when pens are used according to manual.



FlexPen[®] vs. vial/syringe

Dose accuracy

- ❖ Accuracy of FlexPen[®] compared to disposable syringe by 62 healthcare professionals and 30 healthy volunteers
- ❖ Each subject delivered 10 units of insulin with each device
- ❖ Accuracy assessed utilising high precision electronic balance
- ❖ FlexPen[®] significantly more accurate than syringe in both subject groups (both; $p < 0.001$)

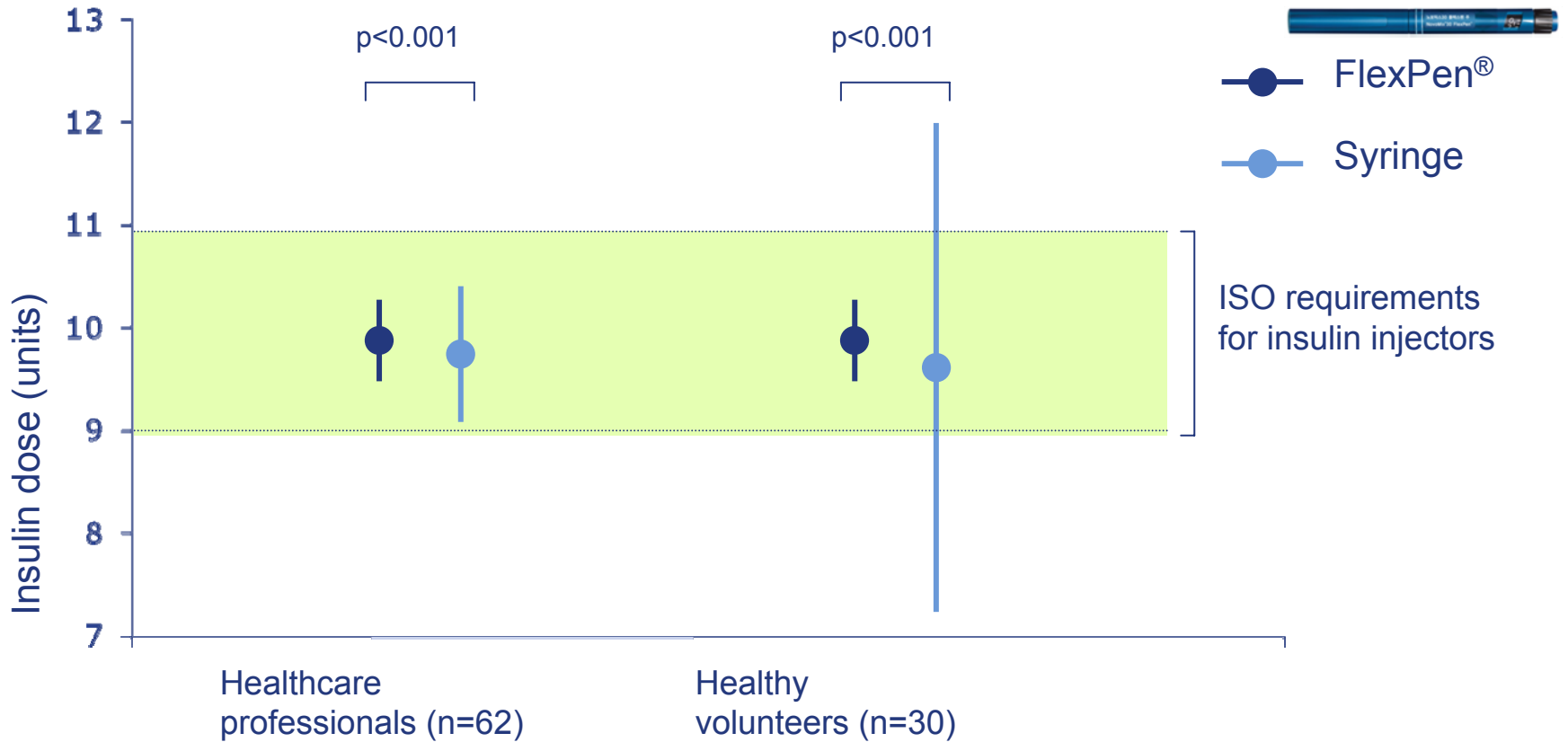




FlexPen[®] vs. vial/syringe

Dose accuracy 10 unit dose

Delivered dose (mean \pm 3sd)

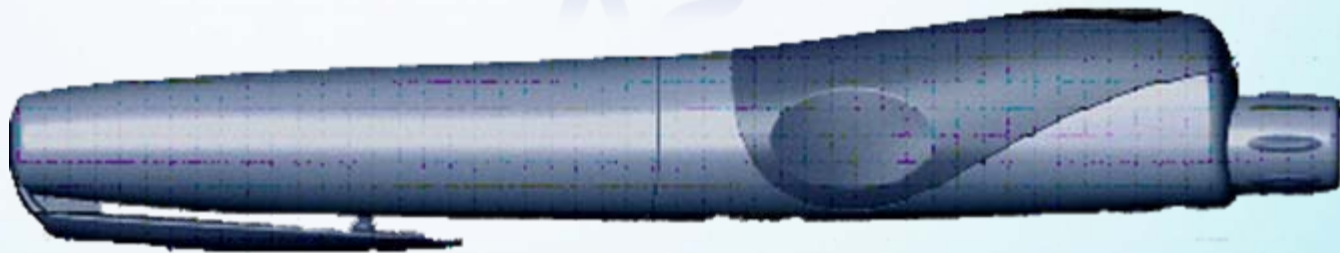




FlexPen[®] vs. OptiClick[®]



VS.

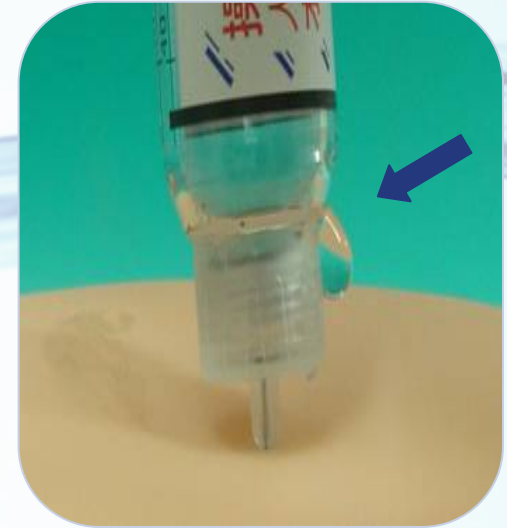




NovoRapid® FlexPen® vs. Lantus® OptiClik® Dose accuracy study

Study Rationale:

- ❖ Following launch of OptiClik® in Japan the investigator became aware of patient reports regarding insulin leakage from system during use
- ❖ Inspection revealed insulin leakage between distal pen and needle housing
- ❖ Leakage due to loss of integrity/closure of insulin cartridge septum after penetration by back-needle

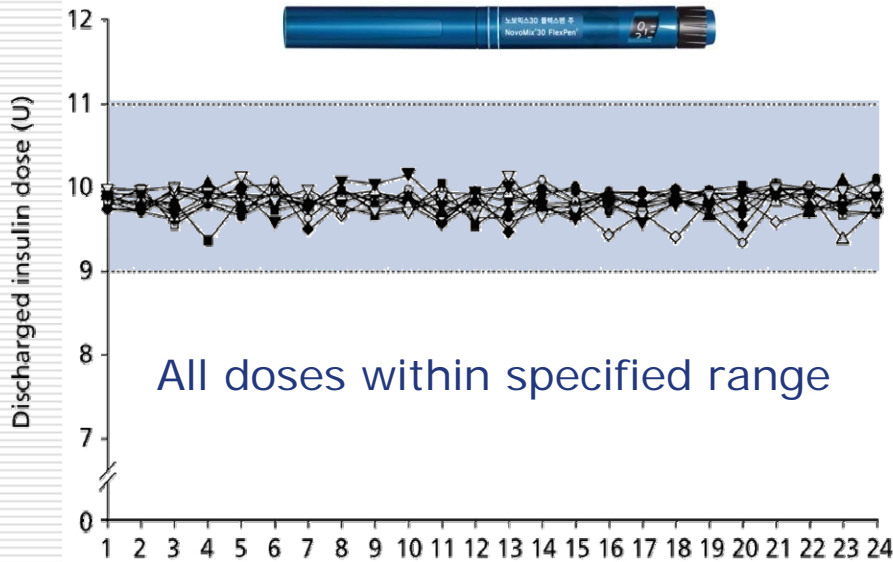


Hypothesis: Observed insulin leakage may result in clinical significant dose inaccuracy when using OptiClik®



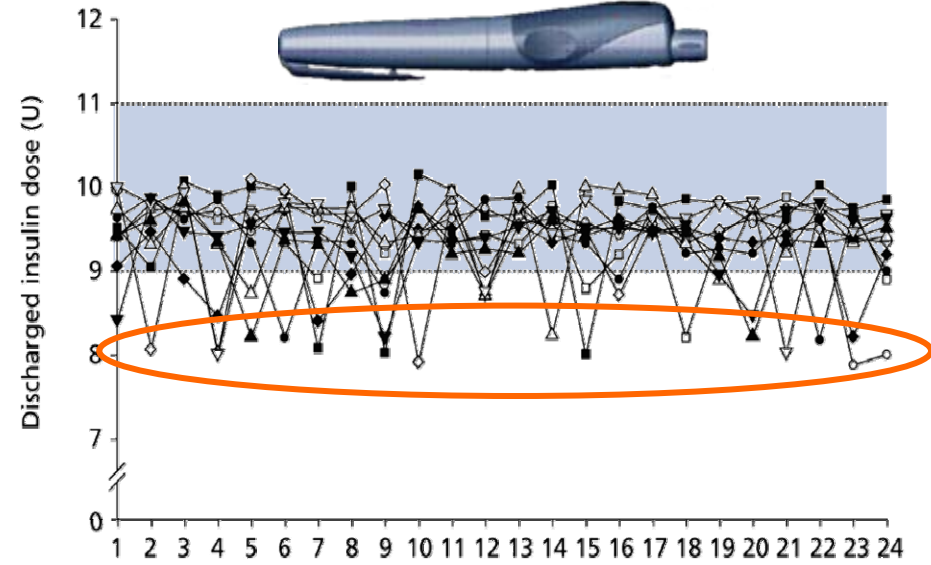
NovoRapid® FlexPen® vs. Lantus® OptiClik® Results – 10U intended dose

FlexPen®
(n=10; 24 doses per pen)



Consecutive doses from each of 10 pens
■ □ ● ○ ◆ ◇ ▼ ▽ ▲ △ Pens 1 to 10

OptiClik®
(n=10; 24 doses per pen)



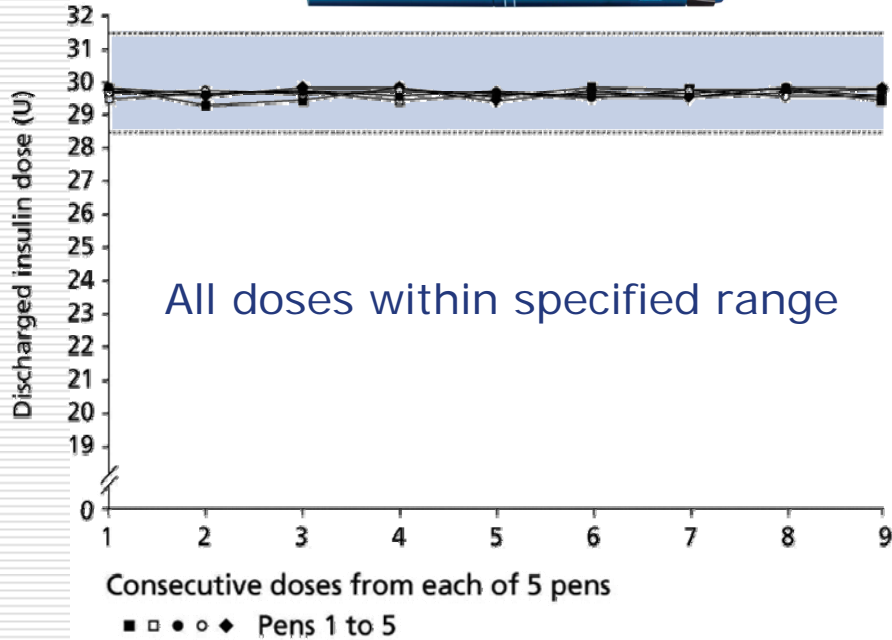
Consecutive doses from each of 10 pens
■ □ ● ○ ◆ ◇ ▼ ▽ ▲ △ Pens 1 to 10

..... Investigator specified dose accuracy range
(± 1U; based on ISO standards)

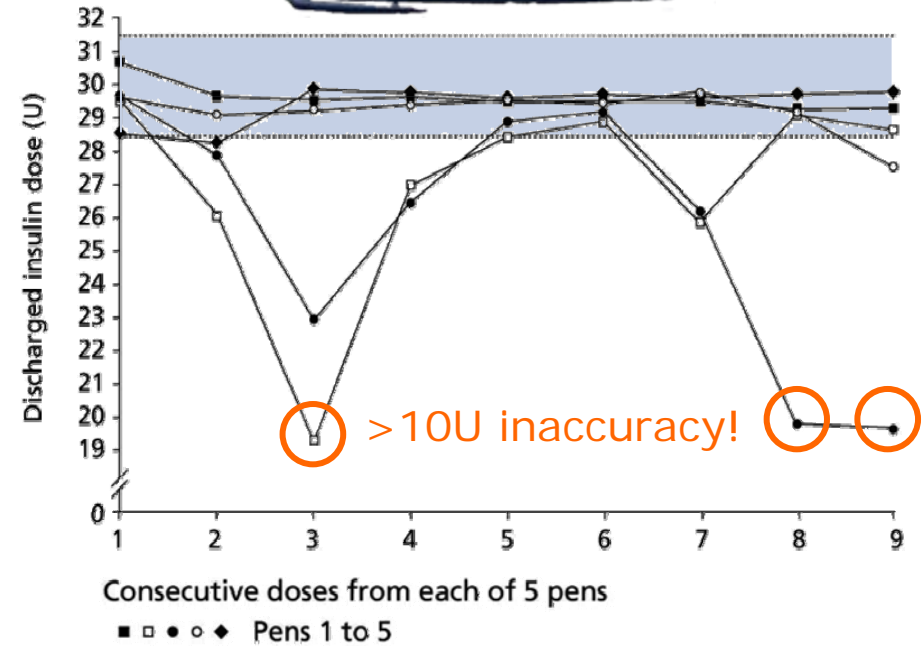


NovoRapid® FlexPen® vs. Lantus® OptiClik® Results – 30U intended dose

FlexPen® (n=5; 9 doses per pen)



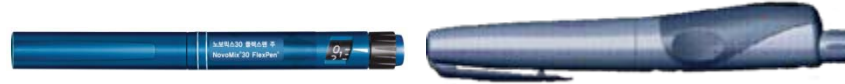
OptiClik® (n=5; 9 doses per pen)



Investigator specified dose accuracy range
(± 1.5 U; based on ISO standards)



NovoRapid[®] FlexPen[®] vs. Lantus[®] OptiClik[®] Results – number of doses outside limits



	FlexPen [®]	OptiClik [®]	
10U dose*	0%	17.1%	p<0.0001
30U dose†	0%	28.9%	p<0.0001

Investigator specified dose accuracy range based on ISO standards
(*10U ± 1U, †30U ± 1.5U)

Conclusion: FlexPen[®] delivered 100% of doses in compliance within specifications utilised in study



NovoRapid[®] FlexPen[®] vs. Lantus[®] OptiClik[®]

Results – average deviations from intended dose

	Median absolute difference		Median relative difference		
	FlexPen [®]	OptiClik [®]	FlexPen [®]	OptiClik [®]	
10U dose	0.159U	0.528U	1.6%	5.3%	p<0.0001
30U dose	0.338U	0.737U	1.1%	2.5%	p<0.0001

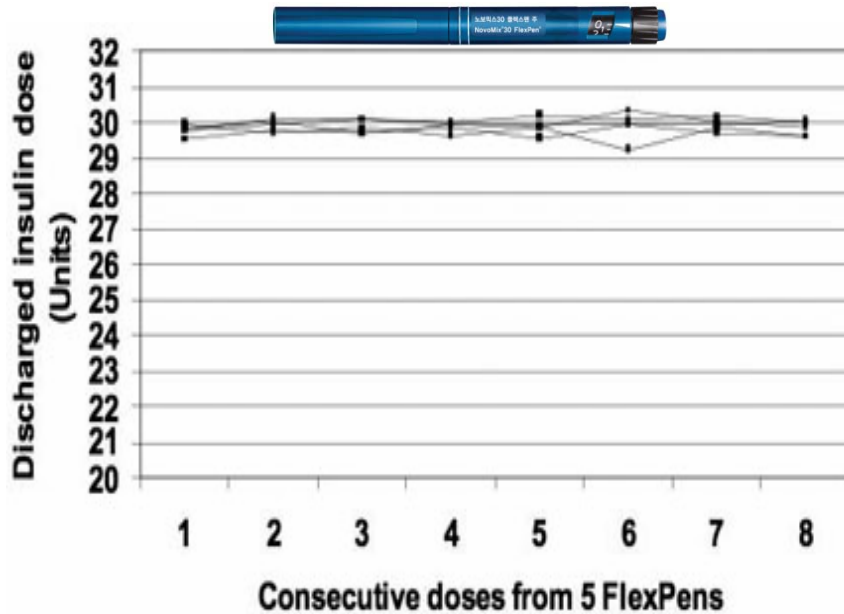
Conclusion: FlexPen[®] was significantly more accurate than OptiClik[®]



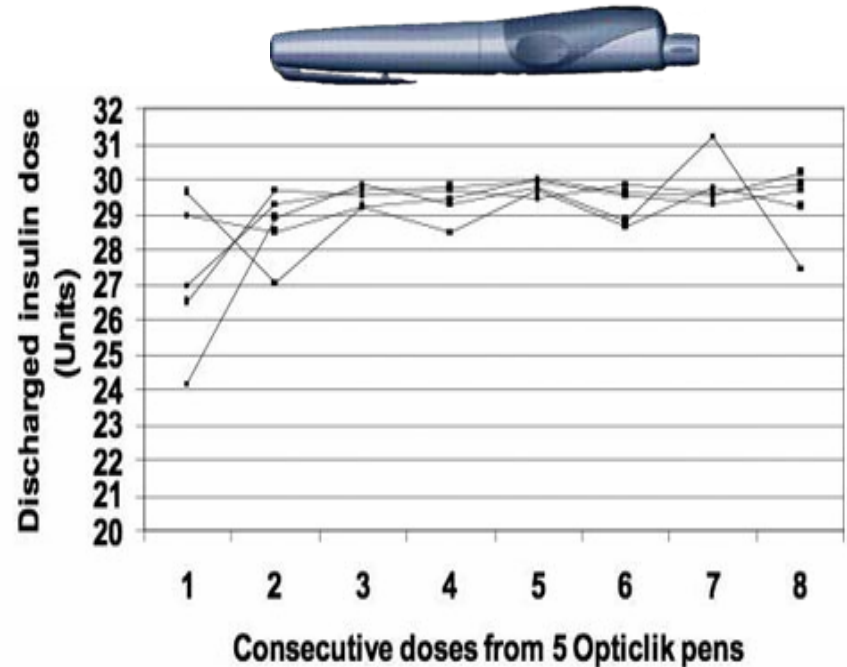
Levemir® FlexPen® vs. Lantus® OptiClik® Dose accuracy study (USA 2006)

Test if dose accuracy are within limits, when used according to user manual on pens available in USA.

FlexPen®



OptiClik®



Conclusion: The FlexPen® insulin pen is more accurate than the OptiClik® pen in delivering specified doses of insulin at 10 units and 30 units



Dosing Accuracy: NovoLog® FlexPen® vs. Lantus® OptiClik® in Germany

Number of doses outside limits

	FlexPen®	OptiClik®
10U dose*	0%	8.3%
30U dose†	0%	16.7%

Investigator-specified dose accuracy range based on ISO standards
n (10U) = 192 dosings (two different lots); n (30U) = 72 dosings (two different lots)
All tested OptiClik® pens underdosed at least once. *10U ±1U, †30U ±1.5U



FlexPen[®] vs. SoloStar[®]



VS.



SoloSTAR® delivers doses both in the laboratory and patients injection environment with 100% accuracy¹

Study Design

1. Subject: 60 diabetes patients
(49 patients type 2 and 11 patients type 1)
2. Method : Delivering 6 different doses
 - Lantus®SoloStar® (10, 40, 80)
 - Apidra®SoloStar® (5, 15, 30)

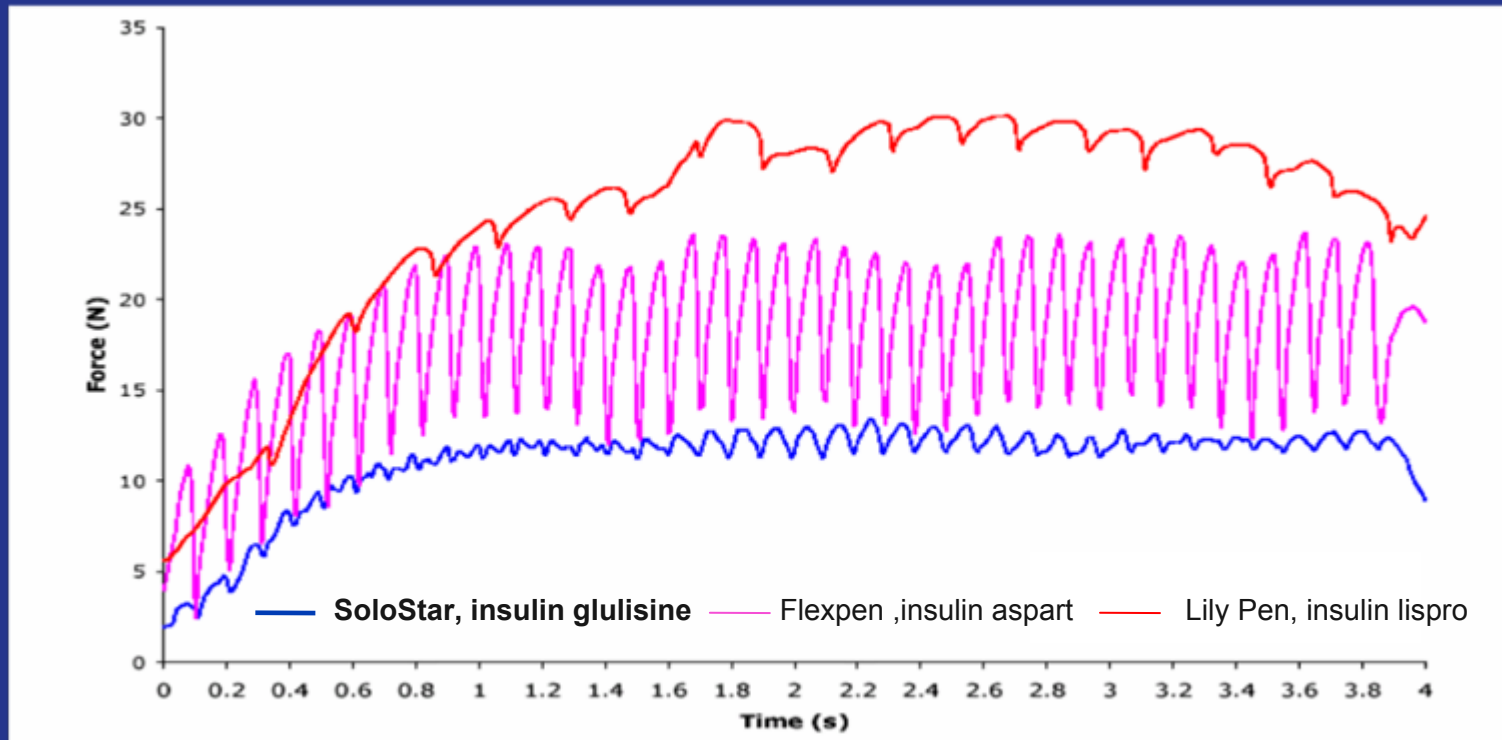
Result

Lantus®	%of delivered doses within ISO standard	Passes ISO Standard
60 x 10U	100%	✓
60 x 40U	100%	✓
60 x 80U	100%	✓

Apidra®	%of delivered doses within ISO standard	Passes ISO Standard
60 x 5U	100%	✓
60 x 15U	100%	✓
60 x 30U	100%	✓

SoloSTAR® significantly reduced the injection force¹

Patients with varying hand strength or dexterity can use SoloSTAR® comfortably because of its shorter dial extension than some other insulin pens



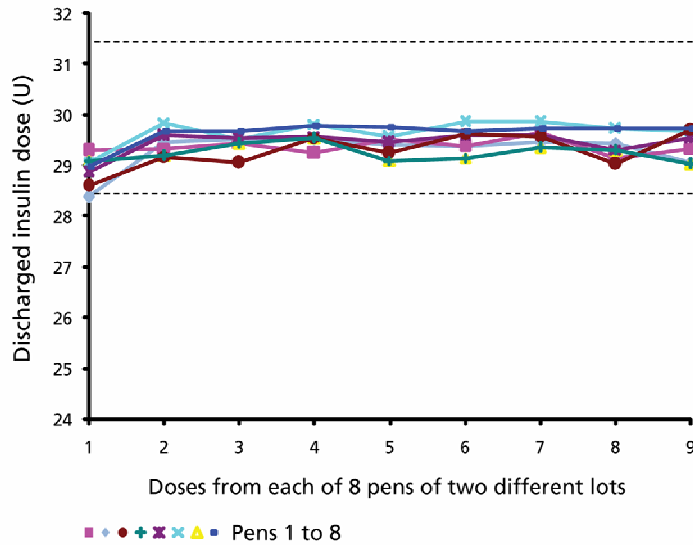
**The injection force to deliver 40 units of insulin in 4 seconds
With SoloStar(insulin glulisine), FlexPen(insulin aspart), Lily Pen(insulin lispro)**



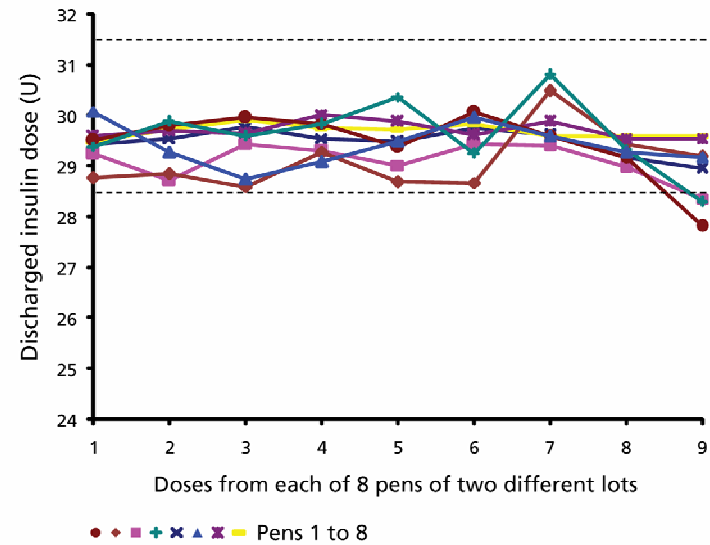
Levemir® FlexPen® vs. Lantus® SoloSTAR® Dose Accuracy Study



Levemir® FlexPen® dosing accuracy at 30U



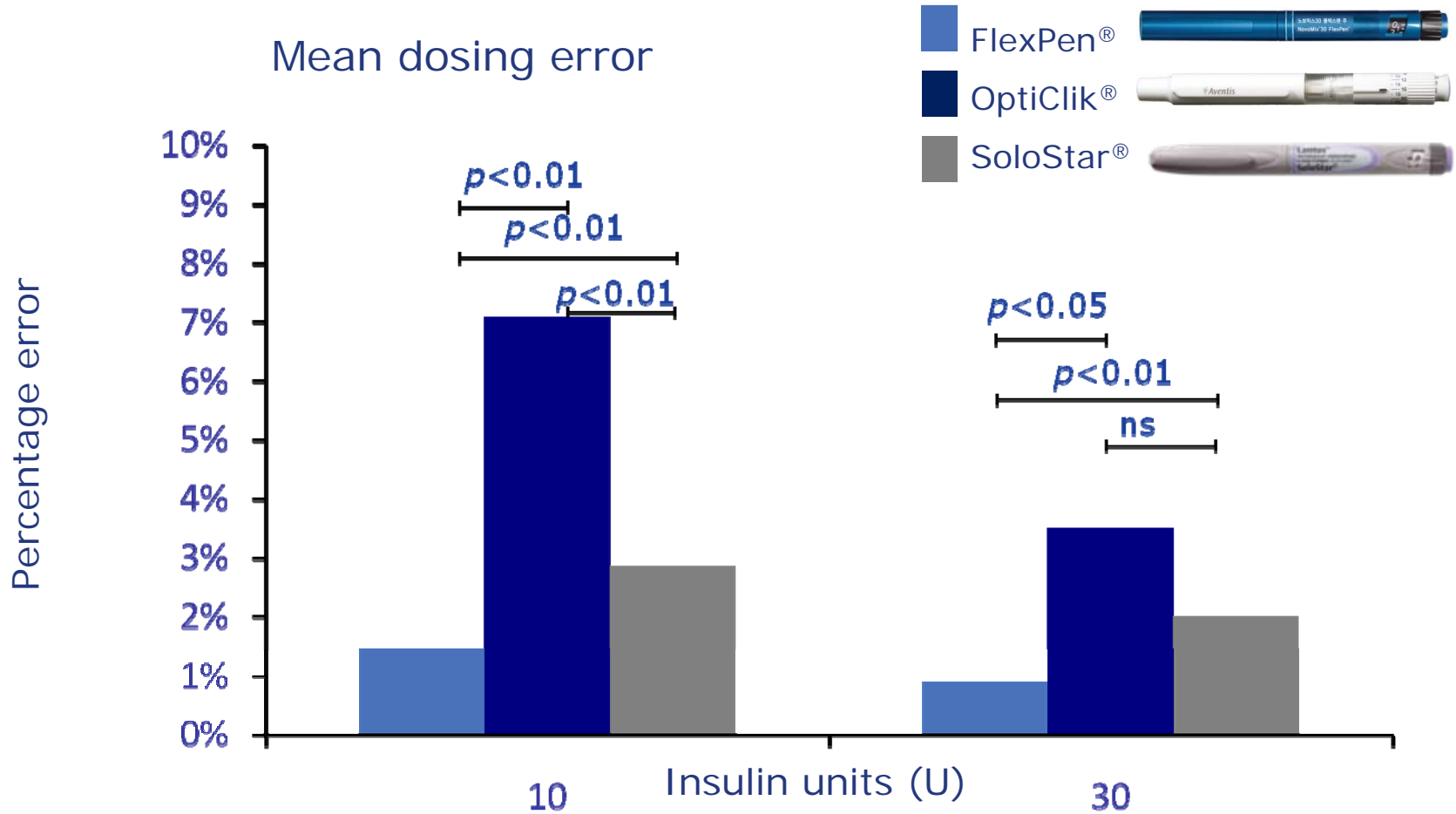
Lantus® Solostar® dosing accuracy at 30U



Investigator-specified dose accuracy range
($\pm 1.5U$; based on ISO standards)



Levemir® FlexPen® vs. Lantus® OptiClik® vs. Lantus® SoloStar®



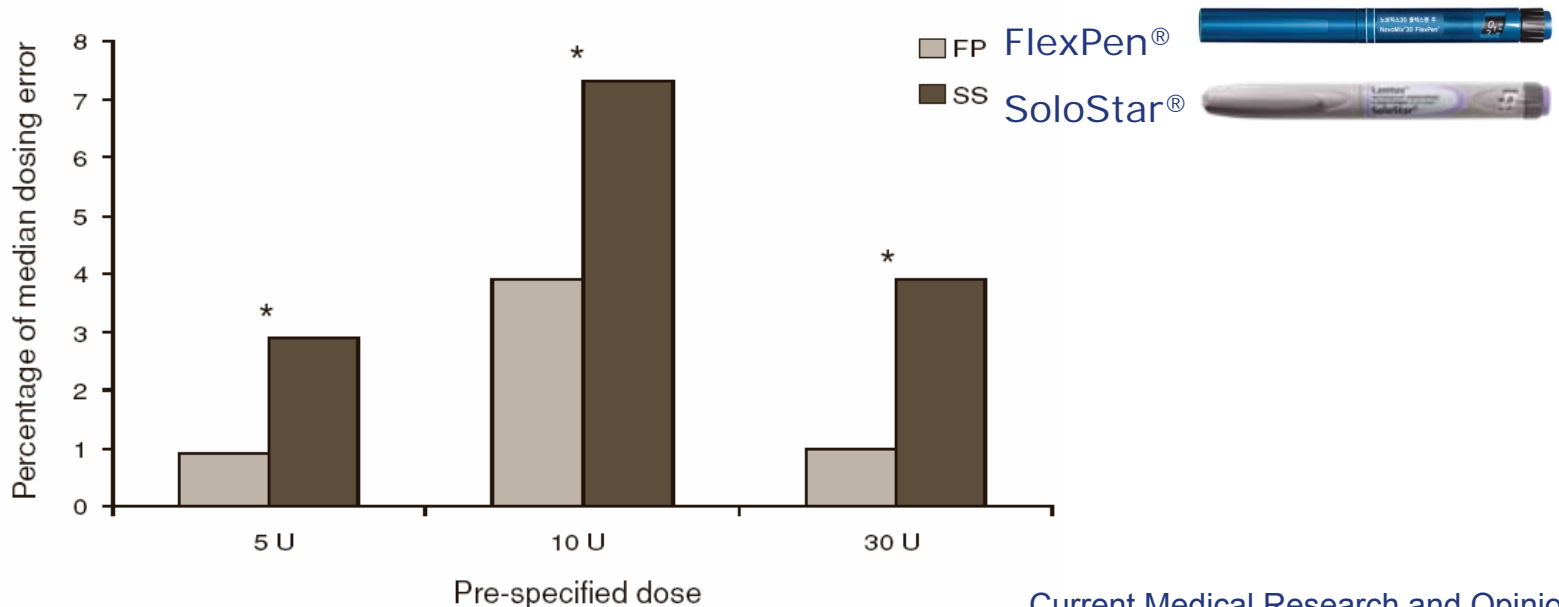
Conclusion: The FlexPen® is more accurate than SoloStar® and OptiClik® pens in delivering insulin



Difference between delivered dose and prespecified dose (FlexPen[®] vs. SoloStar[®])

Intended dose (U)	Mean delivered dose (SD) ± 95% CI	
	FP	SS
5	4.95 (0.19) ± 0.06	4.86 (0.39) ± 0.12*
10	9.61 (0.27) ± 0.11	9.27 (0.52) ± 0.20**
30	29.70 (0.34) ± 0.22	28.73 (0.47) ± 0.31**

Difference between pens: * $p < 0.05$; ** $p < 0.001$; FP = FlexPen; SS = SoloStar



* $p < 0.001$; FP = FlexPen; SS = SoloStar



Flex Pen® vs. Solo Star®





Summary

- ❖ Insulin is the best agent to improve glycemic control.
- ❖ Unfortunately, patients are resistant to starting insulin and even when they do start, there is poor adherence to prescribed insulin regimens.
- ❖ Insulin Pens (compared with vial/syringe) address a number of factors driving poor adherence because they are easy for patients to learn and use, are discreet and offers patients convenience and flexibility.
- ❖ These features can give patients confidence to overcome needle anxiety and social embarrassment associated with self injection.
- ❖ FlexPen® has repeatedly been shown to be more accurate in delivering insulin than OptiClik® and SoloSTAR®
- ❖ Improved adherence to dosing schedules leads to improved disease management and quality of life.



Thank you for
attention.

