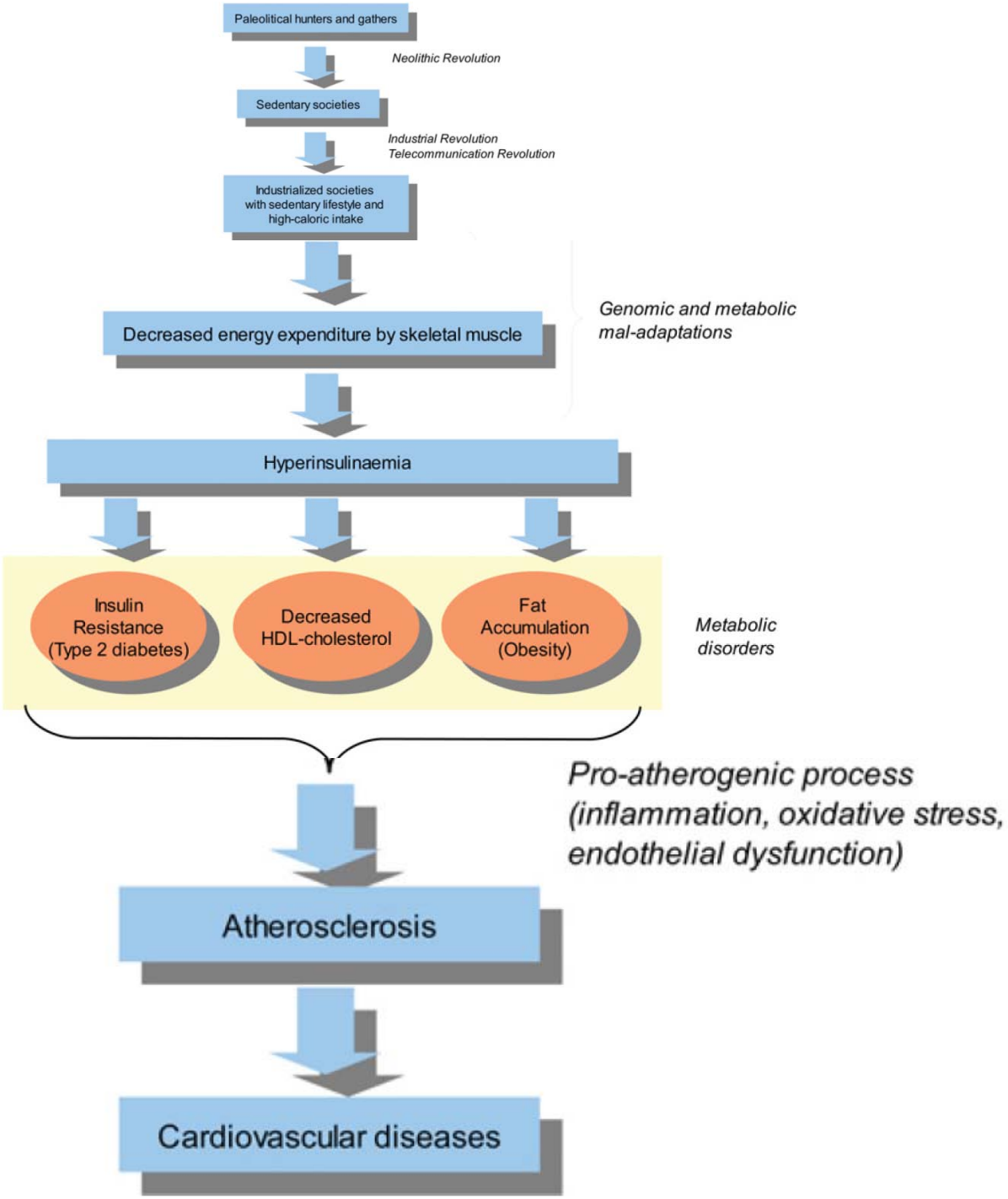
New DPP-IV inhibitor, Gemigliptin
“세계를 향한 발돋움”

Eun-Jung Rhee
Department of Endocrinology
Kangbuk Samsung Hospital
Sungkyunkwan University School of Medicine


Paleolitical hunters and gathers
Neolithic Revolution
Sedentary societies
Industrial Revolution
Telecommunication Revolution
Industrialized societies with sedentary lifestyle and high-caloric intake
Decreased energy expenditure by skeletal muscle
Genomic and metabolic mal-adaptations
Hyperinsulinaemia
Insulin Resistance (Type 2 diabetes)
Decreased HDL-cholesterol
Fat Accumulation (Obesity)
Metabolic disorders
Pro-atherogenic process (inflammation, oxidative stress, endothelial dysfunction)
Atherosclerosis
Cardiovascular diseases

당뇨병은 얼마나 많은가?

전 세계인의 문제

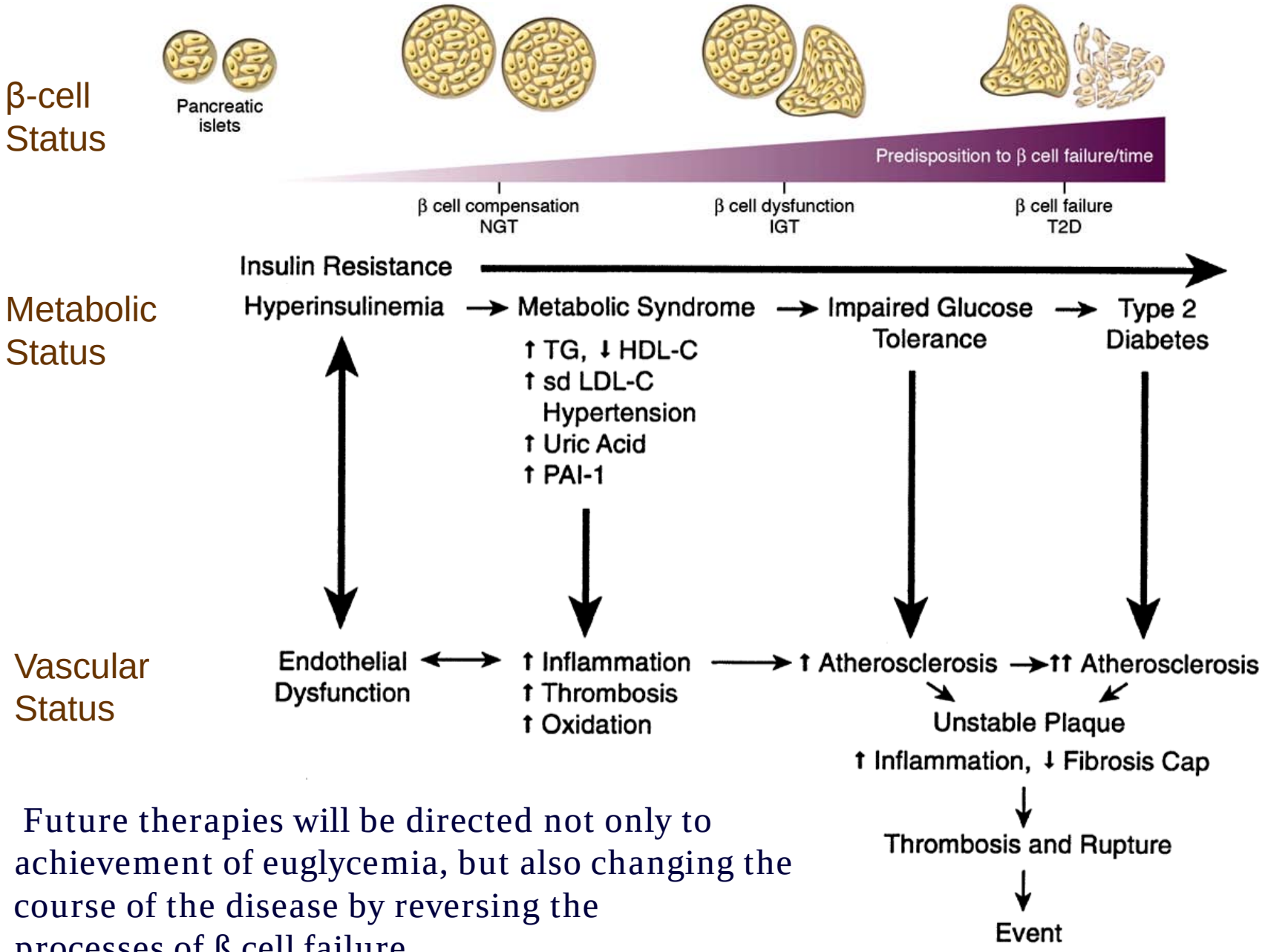
우리나라

2011년 전세계에 3억6천만명의 당뇨병 환자;
2030년에는 5억5천2백만명의 당뇨병 환자

자료 출처 : EGDM

IDF Diabetes Atlas, http://www.diabetesatlas.org/map


현재 보이는 당뇨병 환자 및
당뇨병 고위험군
진단되지 않은 당뇨병 환자,
앞으로 당뇨병이 될 위험군,
당뇨병으로 인한 합병증의 부담

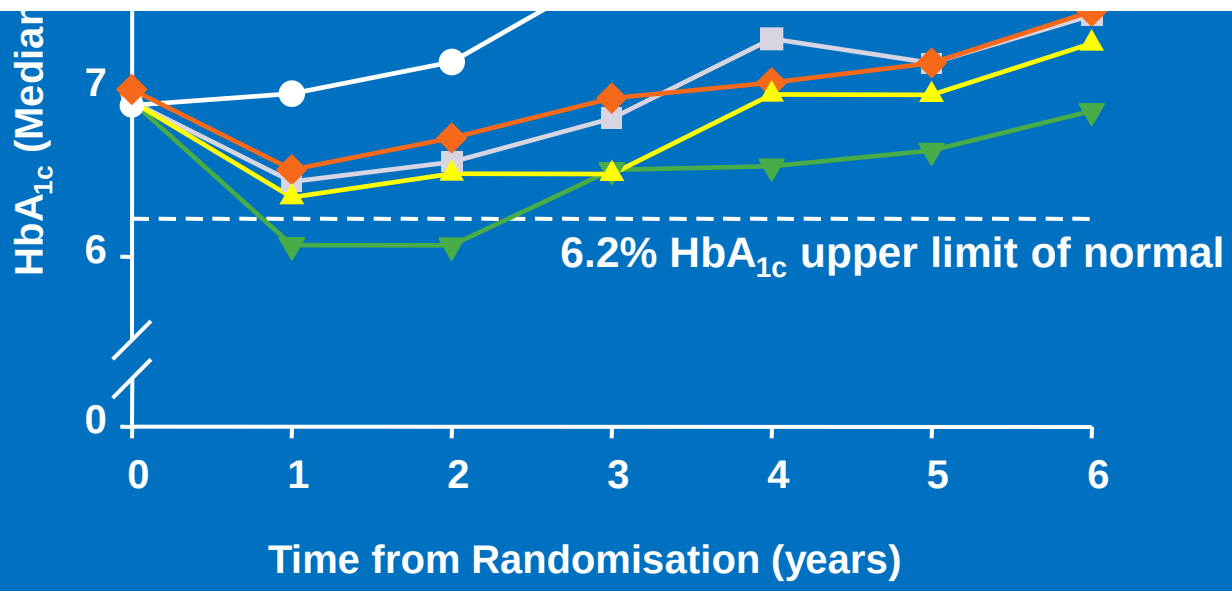


Future therapies will be directed not only to achievement of euglycemia, but also changing the course of the disease by reversing the processes of ß cell failure.

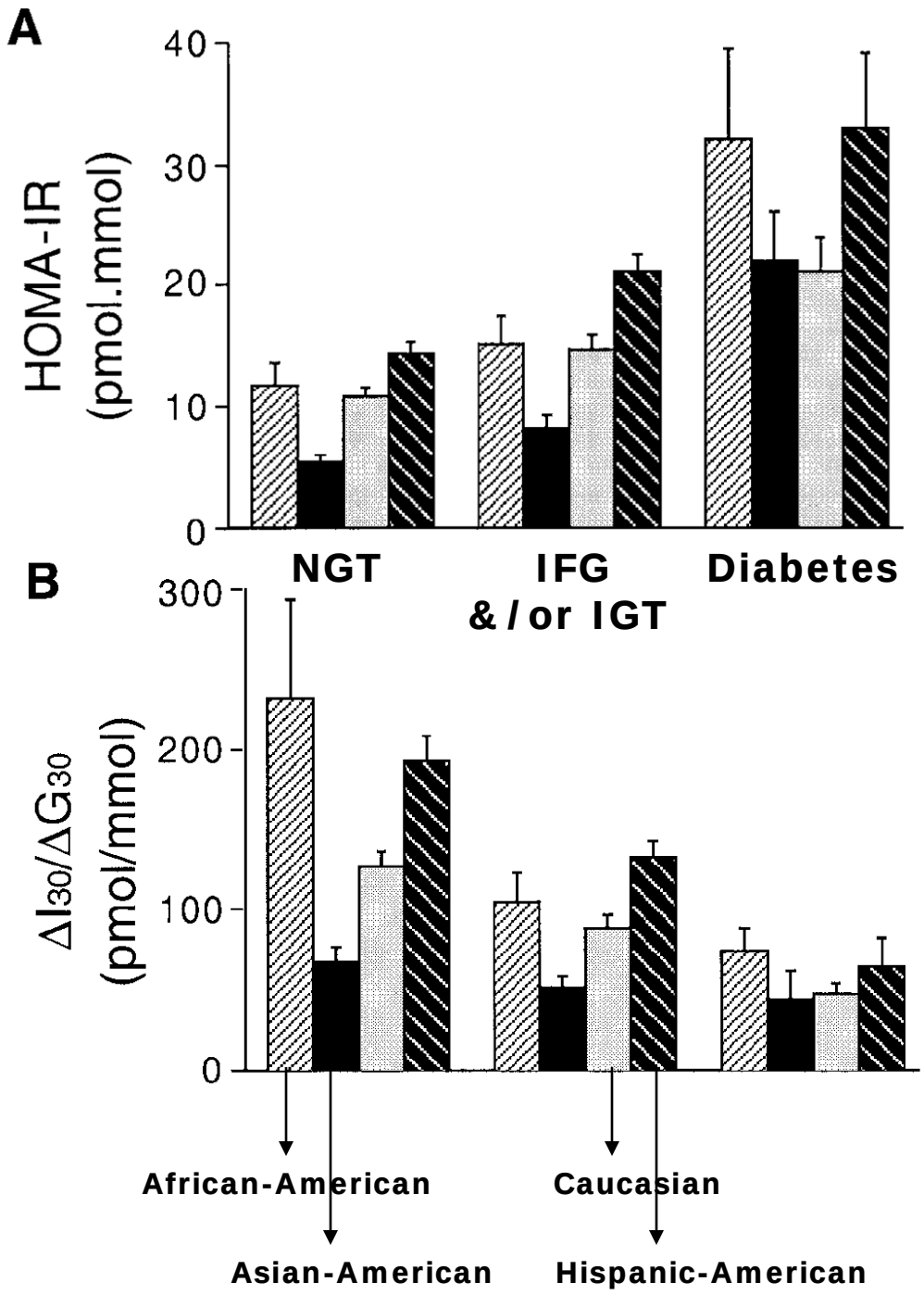
Modified from Hsueh, Am J Cardiol 92:(Supp 1) 10, 2003
and Prentki M, J Clin Invest. 2006 Jul;116(7):1802-12

제2형 당뇨병은 진행하는 질병이다
: UKPDS 6년 연구

췌장에서의 인슐린 분비능의 손상이 가장 문제가 된다...



UKPDS. *Lancet*. 1998;352:854-865.



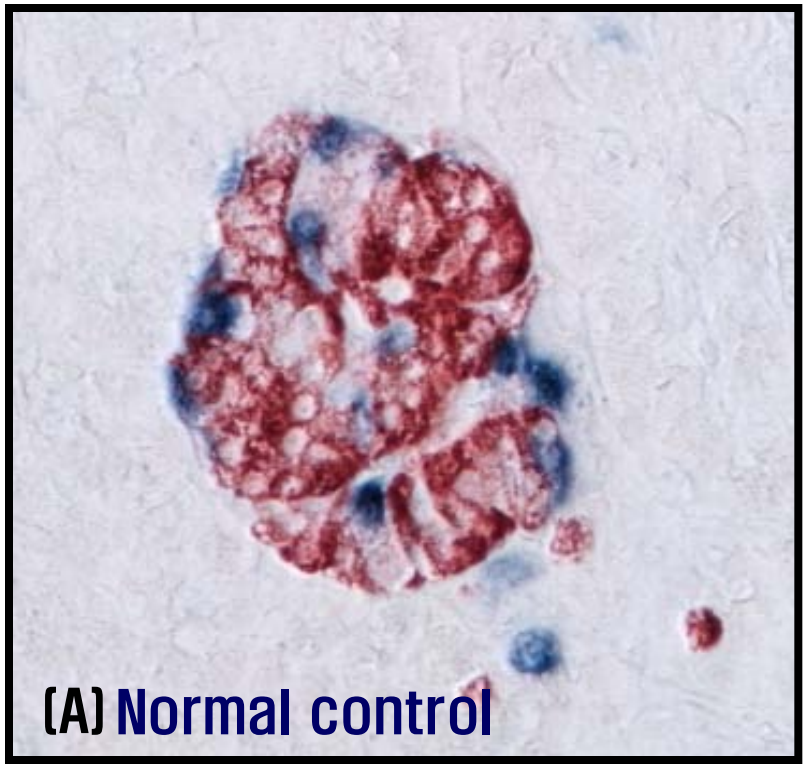
Insulin sensitivity (A) and ß-cell function (B) from an OGTT in <u>first-degree relatives of 4 different ethnic groups</u>.

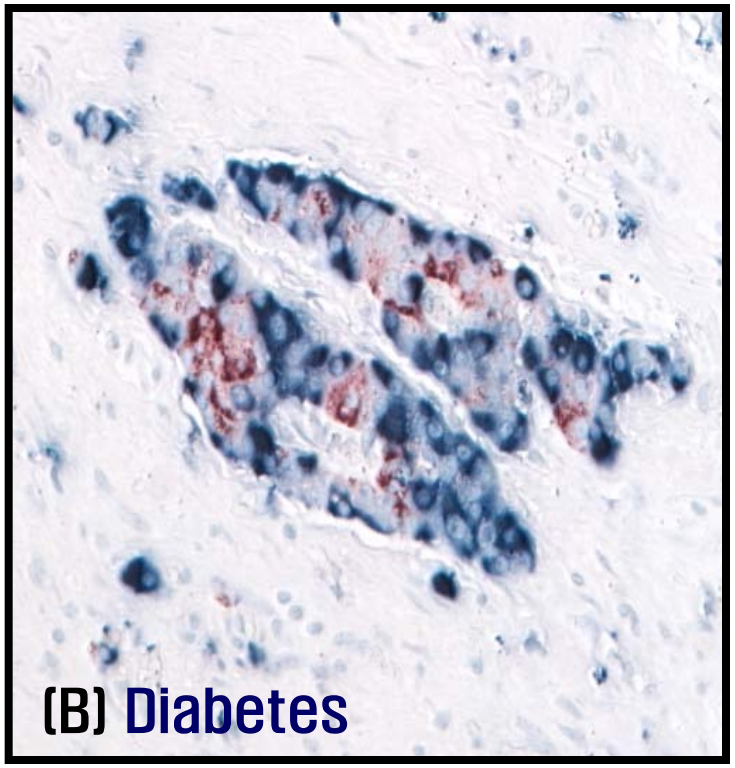
ß-cell function is a major, early determinant of dysglycemia in all ethnic group especially in Asian-American.

Jensen CC, Diabetes 2002 Jul;51(7):2170-8.

The change of Beta cell and Alpha cell mass (I)

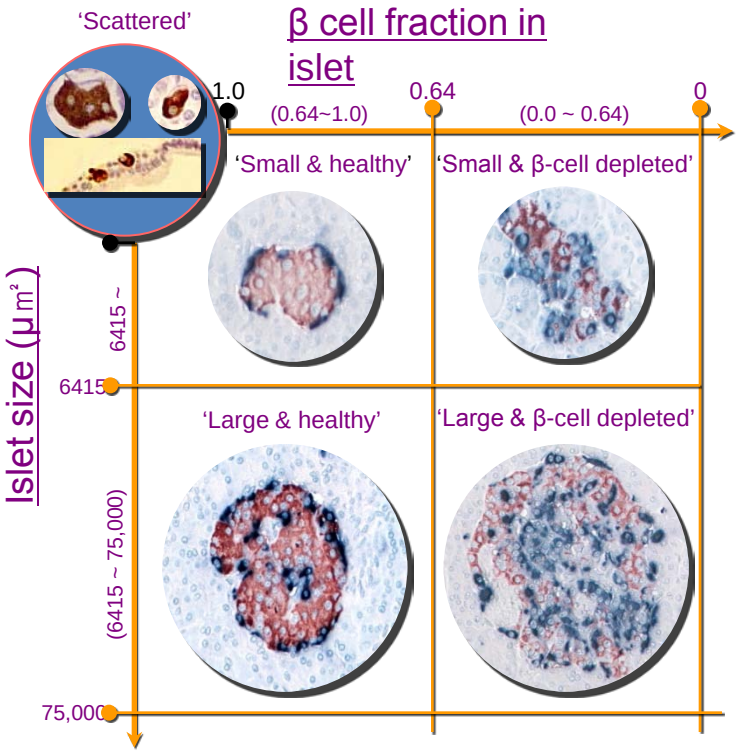
Islets stained with double immunohistochemical staining

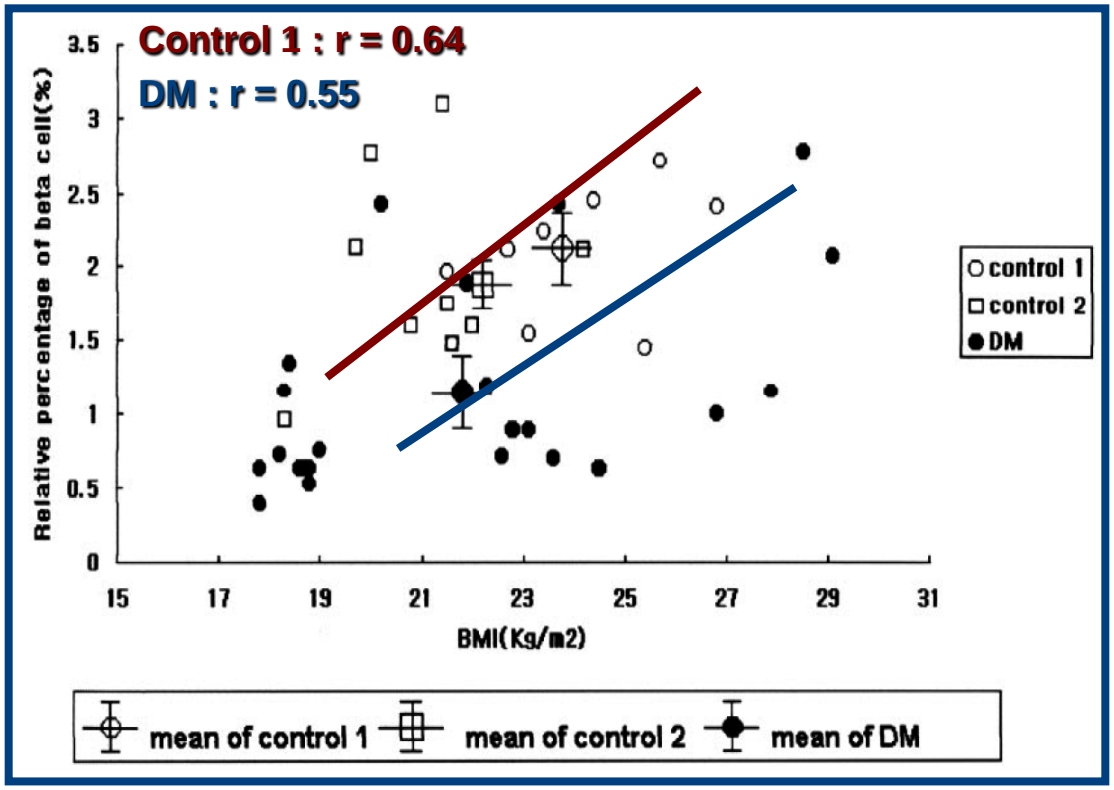




Double immunohistochemical staining. Figure A shows normal pancreatic islets. Most of cells in the islet consist of beta cells (red) and the remnants cosisting of alpha cells (blue) are positioned at the periphery of the islets. Figure B shows diabetic islets. In contrast to figure A, this shows that alpha cell mass commands overwhelming majority in the islet.

Beta-cell loss in T2DM

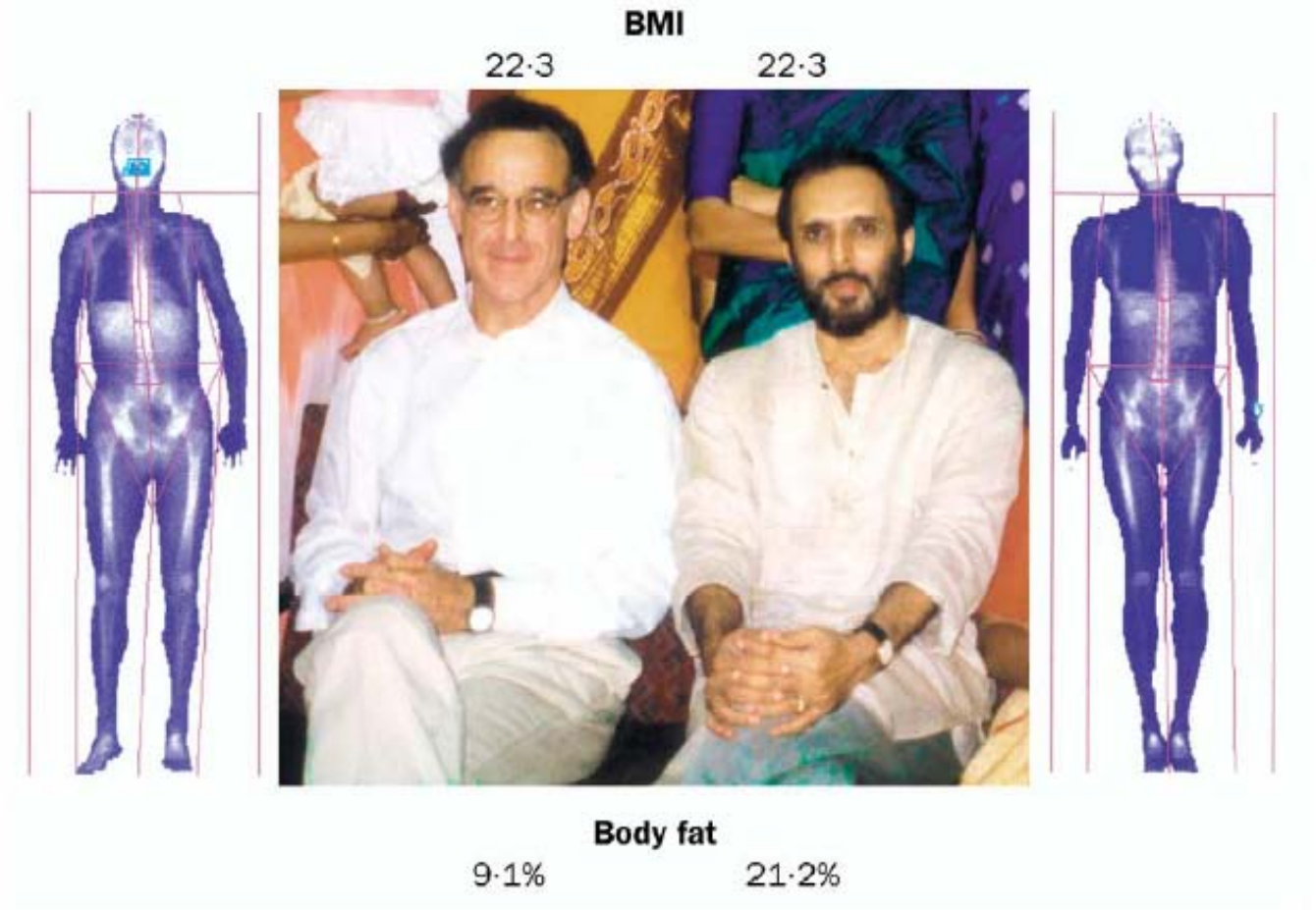




Yoon KH et al: J Clin Endocrinol & Metab 2003 May;88(5):2300-8

The Y-Y paradox

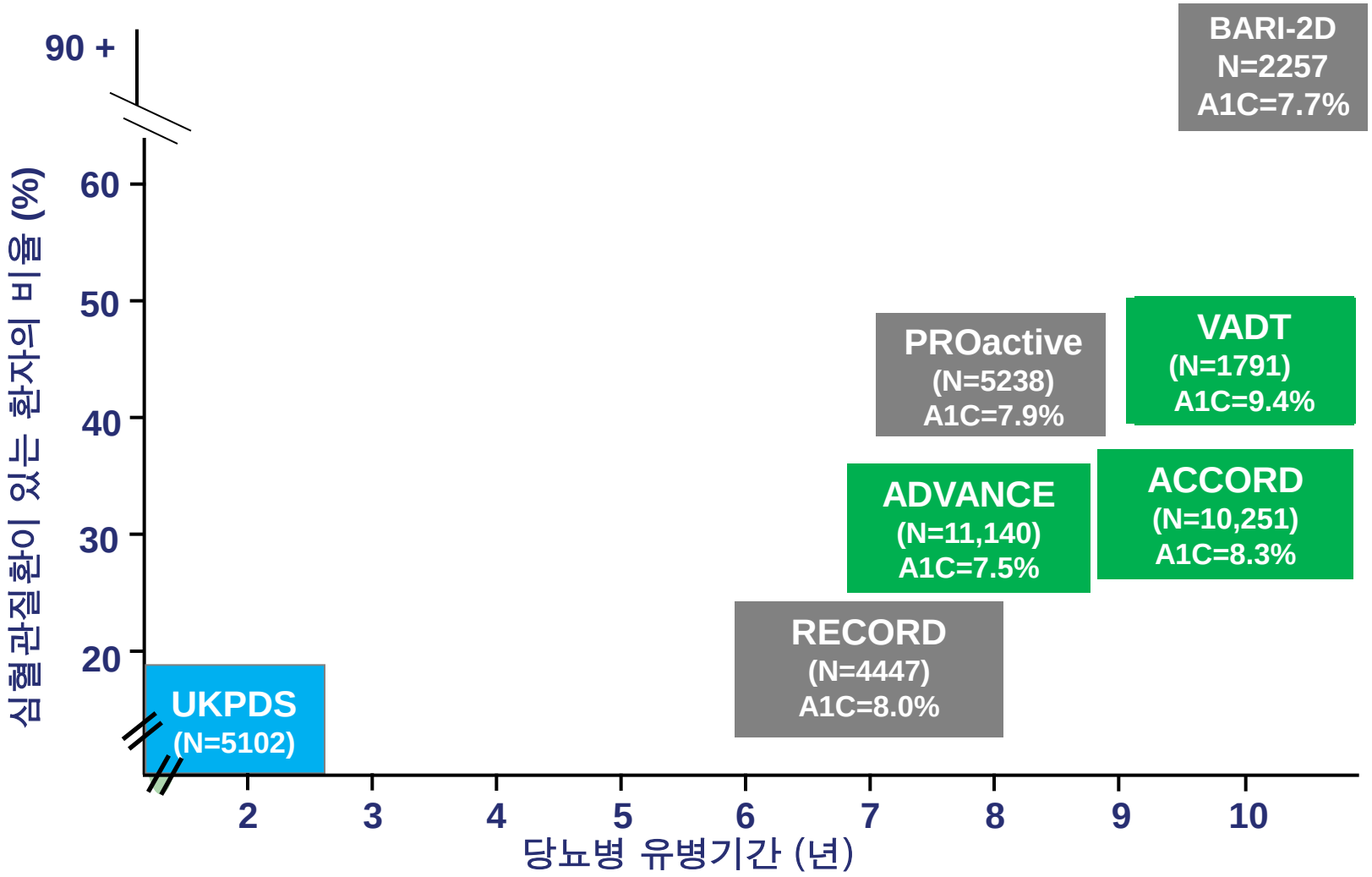
Chittaranjan S Yajnik, John S Yudkin



The two authors share a near identical BMI, but as DEXA shows the right author has substantially more body fat than the left author.
The image is a useful reminder of the limitations of BMI as a measure of adiposity across populations.

Lancet 2004; 363: 163

혈당조절에 따른 심혈관질환 예방 관련연구들



UKPDS Group. *Lancet* 1998;352:837-53; Home P *et al. N Engl J Med* 2007;357:28-8; Nissen SE, Wolski K. *N Engl J Med* 2007;356:2457-71; ACCORD study group. *N Engl J Med* 2008;358:2545-59; ADVANCE study group. *N Engl J Med*. 2008;358:2560-72; Duckworth W *et al*. *N Engl J Med* 2009;360:129-39.

Basic Characteristics of Main Trials

	ADVANCE	ACCORD	VADT	UKPDS
Number	11,140	10,251	1,791	3,869
Age (yrs)	66	62	60	53
Gender (% M/F)	58/42	62/38	97/3	61/39
DM Duration (yrs)	8	10	11.5	0
HbA1c(%)	7.5	8.1	9.4	7.1
CV Events(%)	~32	~35	~40	~2
Insulin Use(%)	~1.5	~35	~50	0
Follow-Up(yrs)	5	3.5	5.6	~10

ACCORD 연구에서의 교훈

총 10000명의 당뇨병 환자

3.5년간 추적관찰

열심히 치료군, 대강 치료군으로 나누어 관찰

조기 종료 – 열심히 치료군에서 사망률의 증가가 관찰됨
→ 혈당 조절을 열심히 하는 것이 사망률을 증가?

UKPDS (10-year follow-up)
: “Legacy Effect” of Insulin/Sulfonylurea Therapy

- After median 8.8 years post-trial follow-up

Aggregate Endpoint (Relative Risk Reduction)	1997	2007
Any diabetes related endpoint	12% (p=0.029)	9% (p=0.040)
Microvascular disease	25% (p=0.009)	24% (p=0.001)
Myocardial infarction	16% (p=0.052)	15% (p=0.014)
All-cause mortality	6% (p=0.44)	13% (p=0.007)

Legacy (유산)효과?

UKPDS 연구

대사 기억 (Metabolic memory)

발병 초기의 손상이 세포내 미토콘드리아에 기억되어 혈당 조절이 나중에 잘 되어도 원래의 손상 정도는 지속된다는 이론

초기 치료가 중요하다!!!

초기의 엄격한 치료만이 당뇨병 합병증을 예방할 수 있다.

Basic Characteristics of Main Trials

	ADVANCE	ACCORD	VADT	UKPDS
Number	11,140	10,251	1,791	3,869
Age (yrs)	66	62	60	53
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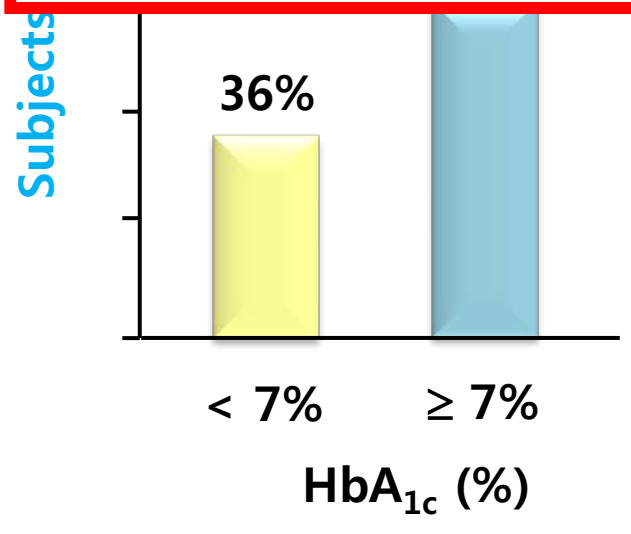
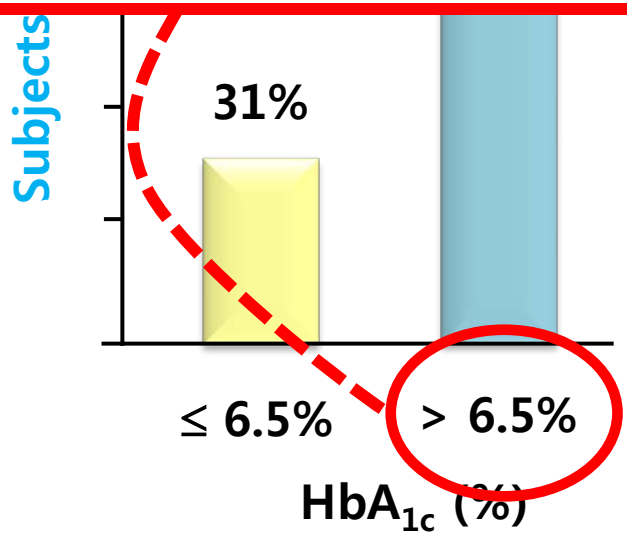
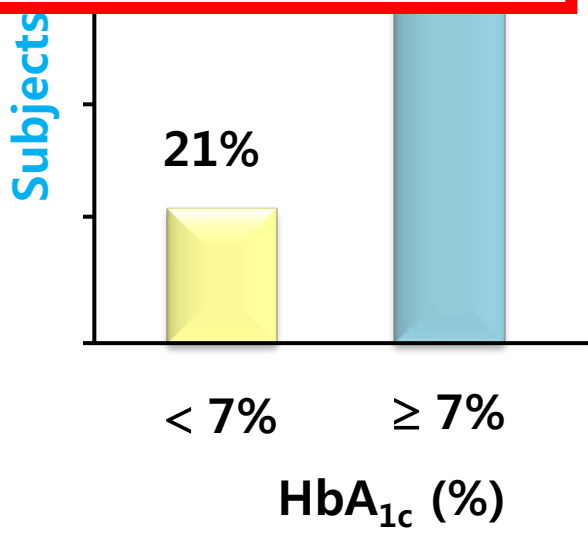
Follow-Up(yrs)	5	3.5	5.6	~10

미국, 유럽, 아시아의 당뇨병의 대부분이 혈당 조절 목표에 도달하지 못하고 있다...

꿈의 스코어...?







[1]Koro CE, *et al*. *Diabetes Care* 2004; 27:17–20. [2]Liebl A. *Diabetologia* 2002; 45:S23–S28.
Diabcare-Asia 1998 Study Group. *Diabetic Medicine* 2002; 19: 978–85.

당뇨병 치료의 현주소

우리는 어디에 있는가..?

? 흡입형 인슐린
인슐린 유도체
장 펩타이드

글루리신

아스파트

글라진

글리나이드

글리타존

리스프로

메트폴민

인간인슐린

설포닐유레아

동물 인슐린

1922 1950s 1982-85 1995 1996 2001 2003 →

Non-physiologic replacement of insulin → Physiologic replacement of insulin + insulin sensitizer + beta-cell preservation ?

제2형 당뇨병의 치료 약제

약물 종류	작용 부위	부작용
설폰요소계	췌장 베타 세포	저혈당 체중 증가
메글리티나이드계		
비구아나이드	간 근육	소화기계 이상 락토스 산혈증
알파-글루코시데이즈 억제제	소장	복부 팽만, 가스
치아졸리딘디온계	간 근육 지방	체중 증가 부종 빈혈 심혈관계 위험성 증가? 골다공증
인슐린		저혈당, 체중 증가

Moller DE. *Nature.* 2001;414:821-827.; Pickup JC, Williams G, eds. *Textbook of Diabetes 2*. Malden, MA: Blackwell;2003:45.5.

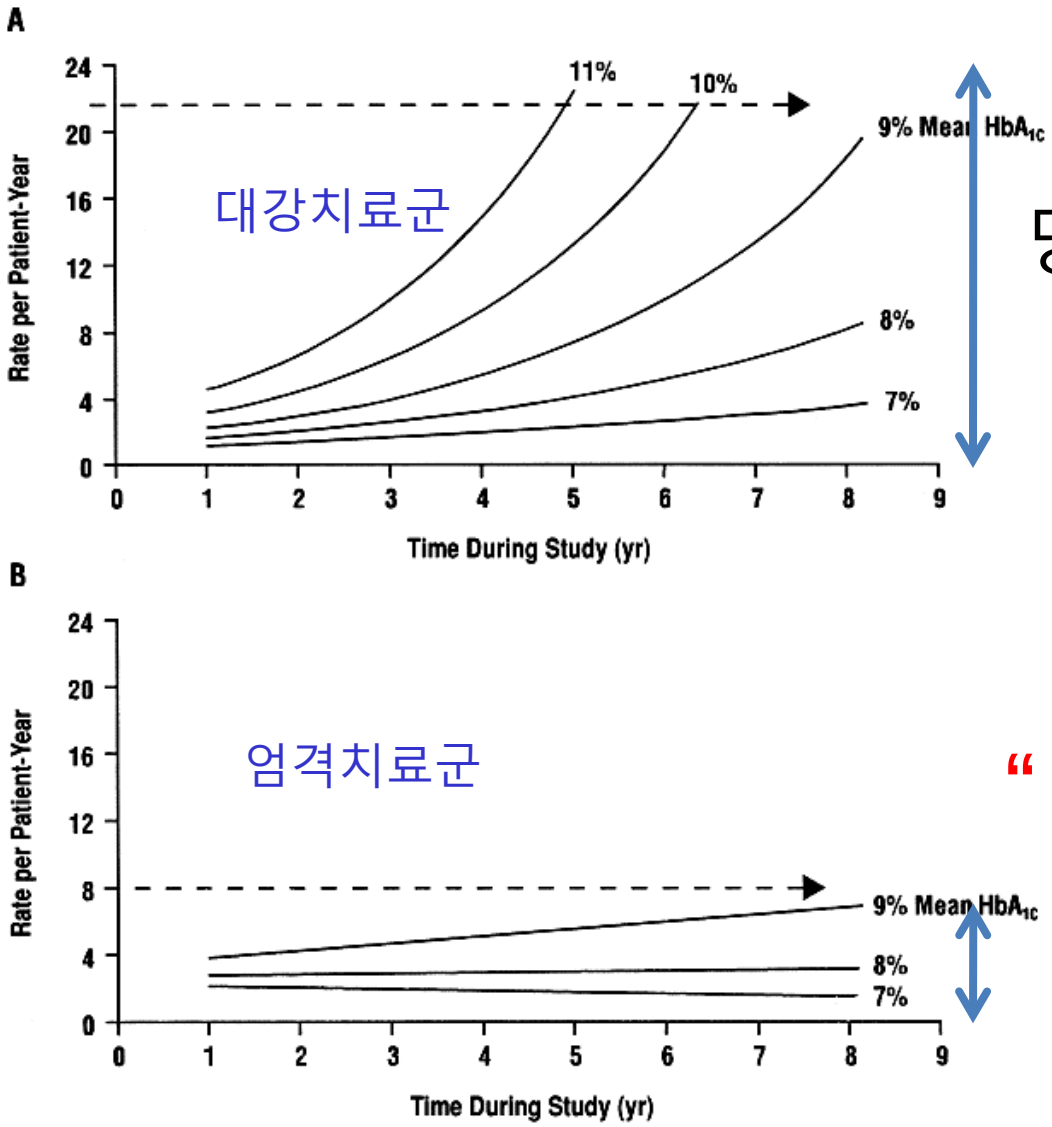
현재 당뇨병 약제의 임상적 문제점과 미래의 이상적인 당뇨병 약제

- 식후 혈당 조절의 부족
- 체중 증가
- 저혈당 위험
- 특정 군에서의 적용 불가
- 점진적인 췌장 베타 세포의 손상

현재 약제들의 문제점

미래의 이상적인 당뇨병 약제

- 감소시킬 것
  - 대혈관 합병증 위험
  - 미세혈관 합병증 위험
- 증가시킬 것
  - 인슐린 분비능과 저항성 개선능
  - 안전성
    - 낮은 저혈당 위험
    - 체중 증가의 부재
    - 다른 임상적 문제점의 부재
- 혈당 강하 효과
  - 공복 & 식후 혈당 강하 효과
  - 지속적인 혈당 강하 효과의 유지



당화혈색소의 증가는 결국 같지만, 어떤 과정으로 그 당화혈색소에 도달했는가가 중요하다

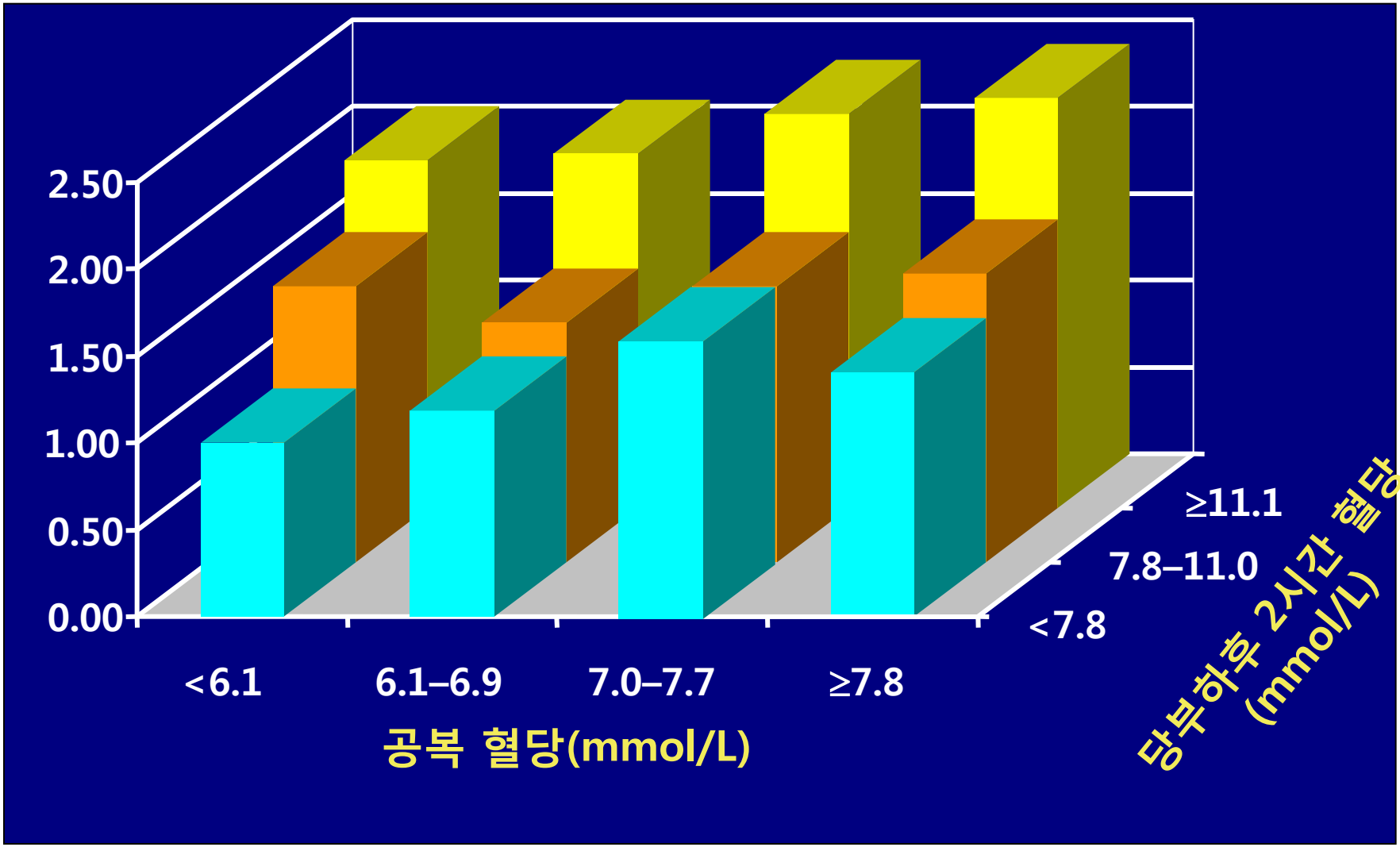
"당화혈색소의 질"

혈당의 증감의 폭이 클 경우, 혈관에 대한 스트레스는 더 크다..

Hirsch, Am J Med 118:S1 21, 2005

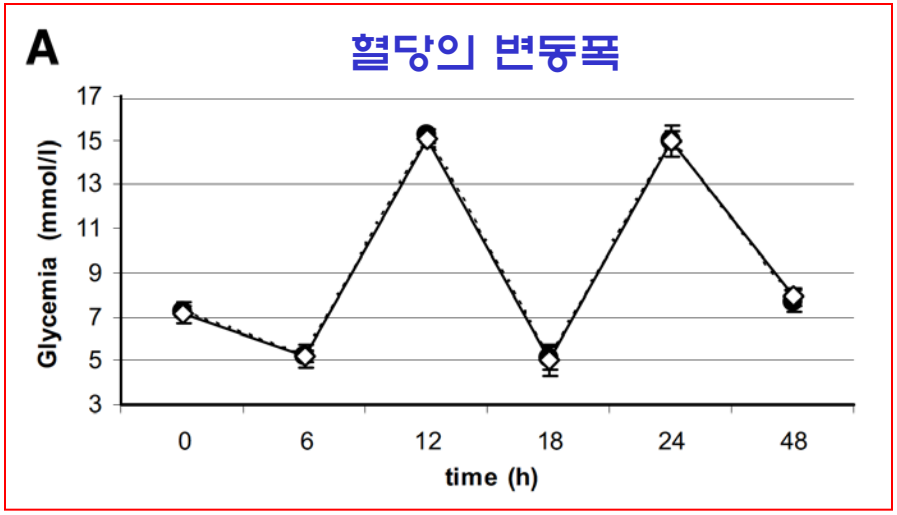
DECODE 연구

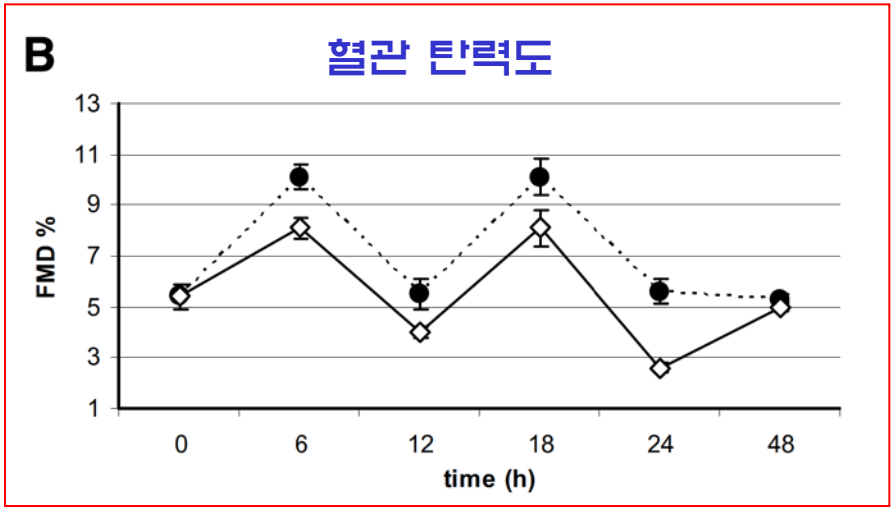
공복고혈당과 식후 고혈당이 심혈관질환에 미치는 영향



DECODE Study Group. Lancet 354:617–21, 1999

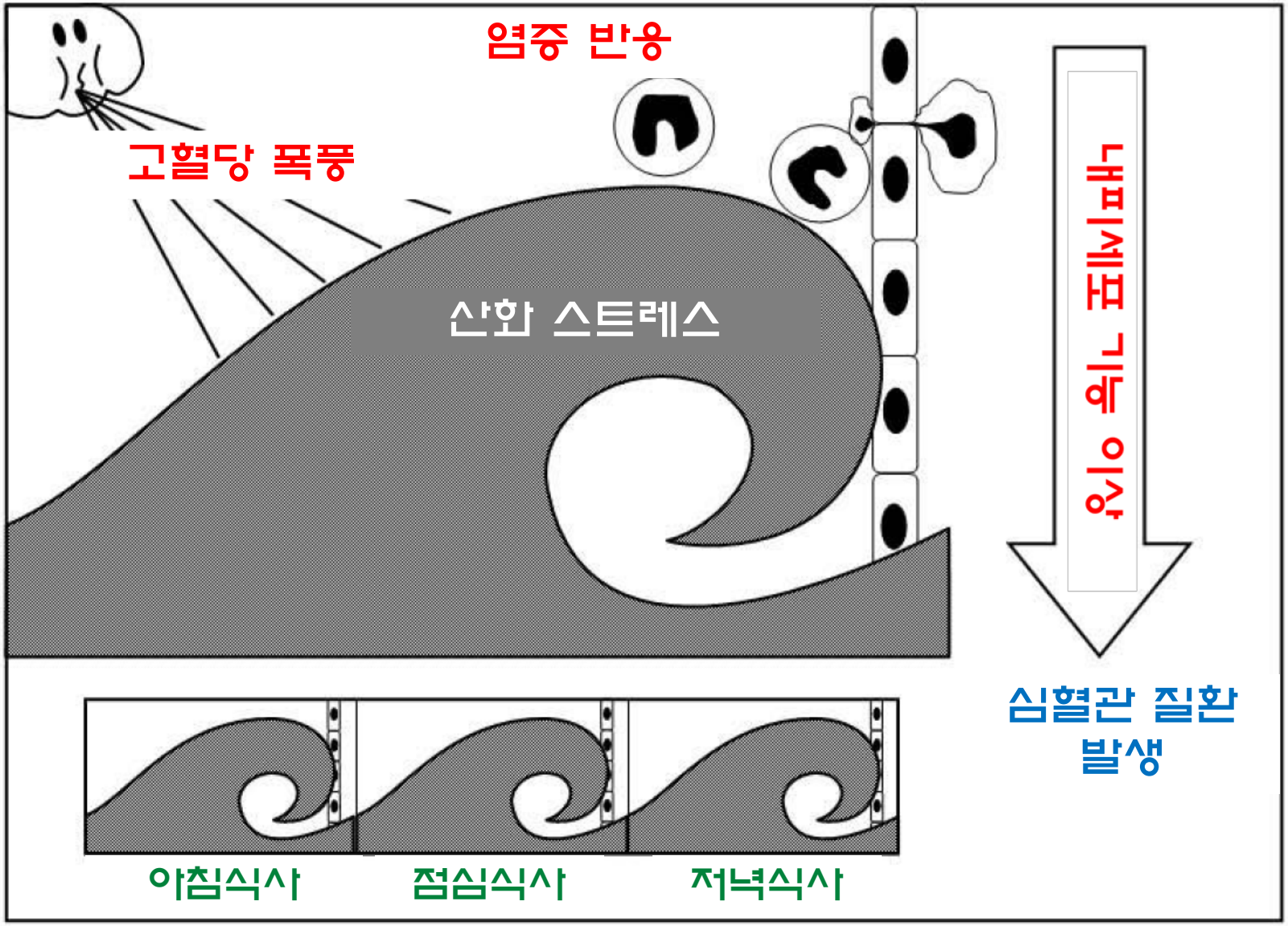
혈당의 변동폭과 혈관탄력도와의 관계





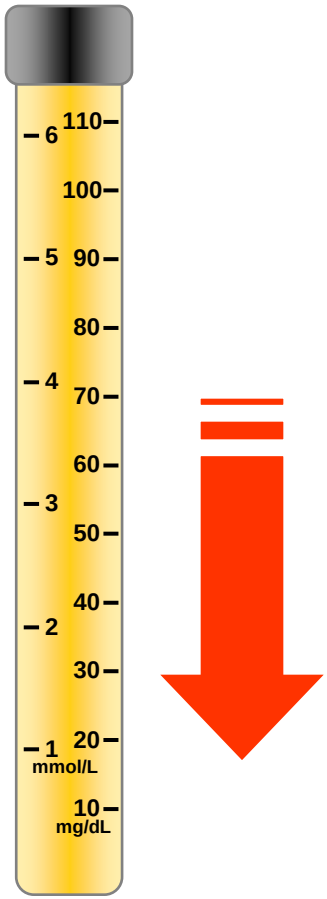
혈당이 증가함에 따라서 혈관 탄력도가 급속히 줄어든다

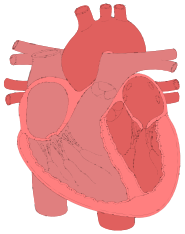
식후고혈당의 혈관에 대한 영향



Complications and Effects of Severe Hypoglycemia

Plasma glucose level





Increased Risk of Cardiac Arrhythmia[1]	Progressive Neuroglycopenia[2]
• Abnormal prolonged cardiac repolarization: ↑ QTc and QTd • Sudden death	• Cognitive impairment • Unusual behavior • Seizure • Coma • Brain death

1. Landstedt-Hallin L et al. *J Intern Med*. 1999;246:299–307.
2. Cryer PE. *J Clin Invest*. 2007;117(4):868–870.

Adverse events & Clinical measures of ACCORD

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124(2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±33.5	90.6±34.0	0.74
Blood pressure — mm Hg¶			
Systolic	126.4±16.7	127.4±17.2	0.002
Diastolic	66.9±10.5	67.7±10.6	<0.001

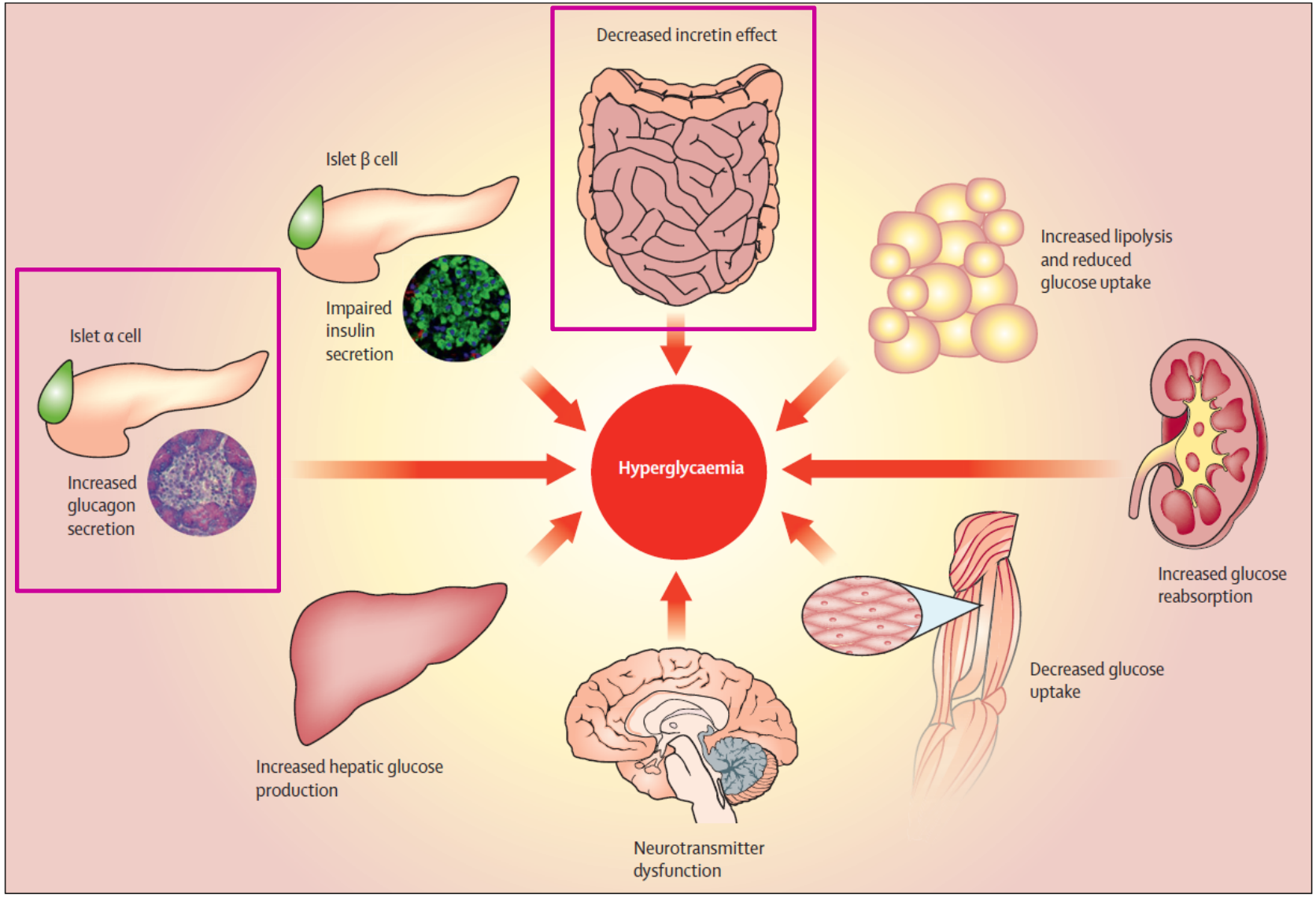
췌장의 인슐린 분비능을 유지시킬 수 있는
새로운 당뇨병 약제의 필요성

심혈관 위험도의 감소

식후 고혈당의 효율적 치료

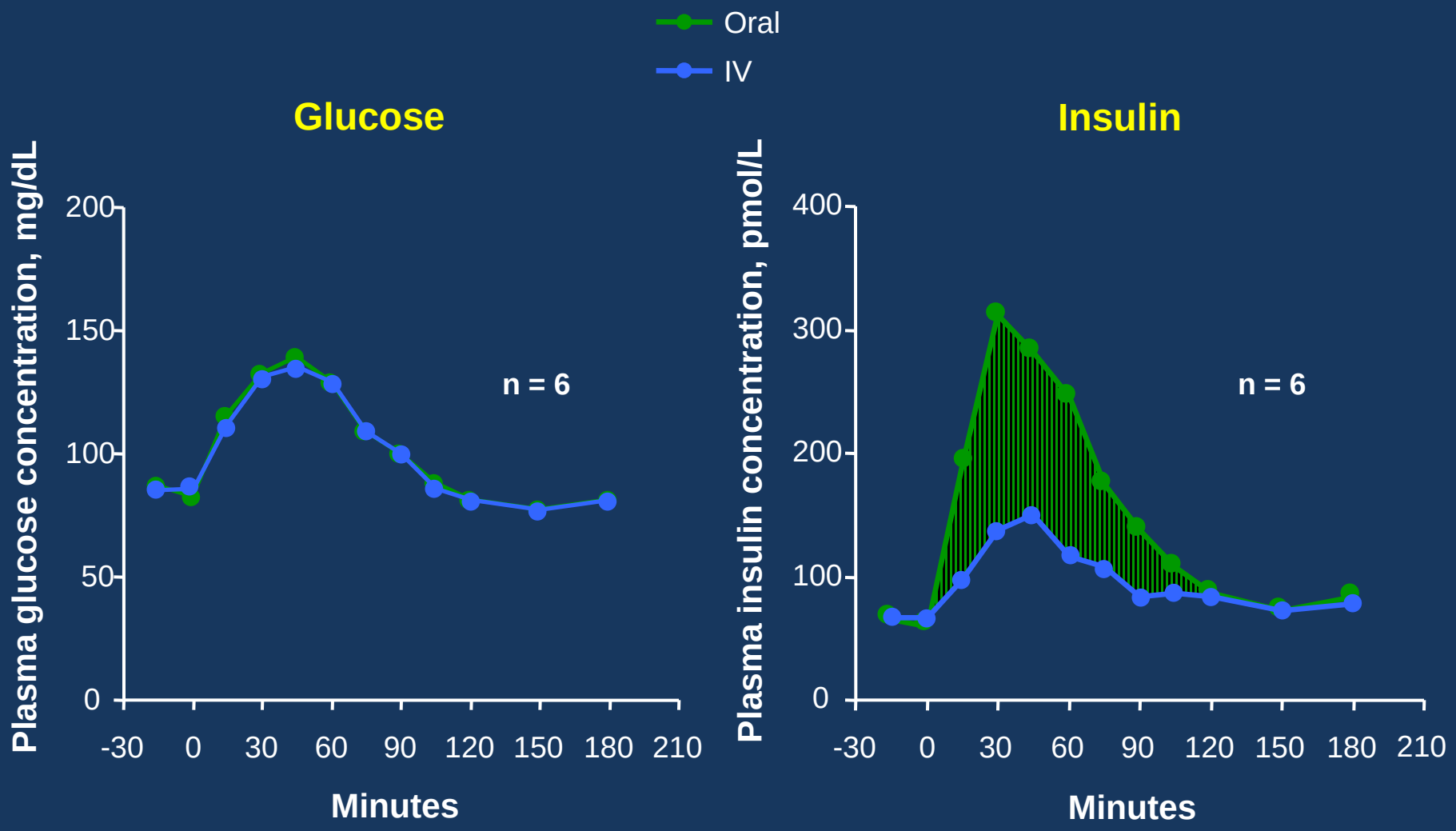
체중 증가, 저혈당 등의 부작용의 최소화

Typical pathophysiological features of hyperglycaemia in type 2 diabetes



Tahrani AA et al. Lancet 378:182-197, 2011

The Incretin Effect: Greater Insulin Response After Oral vs IV Glucose in Healthy Individuals



Nauck MA et al. *J Clin Endocrinol Metab*. 1986;63:492-498.

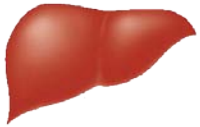
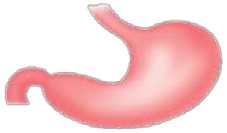
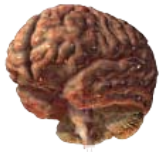
GLP-1 and GIP Are the Two Major Incretins

GLP-1	GIP
• Secreted by L-cells in the distal gut (ileum and colon)	• Secreted by K-cells in the proximal gut (duodenum)
• Stimulates glucose-dependent insulin release	• Stimulates glucose-dependent insulin release
• Inhibition of gastric emptying	• Minimal effects on gastric emptying
• Reduction of food intake and body weight	• No significant effects on satiety or body weight
• Suppresses hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner	
• Enhances beta-cell proliferation and survival in animal models and isolated human islets	• Enhances beta-cell proliferation and survival in islet cell lines

GLP-1=glucagon-like peptide 1; GIP=glucose-dependent insulinotropic polypeptide

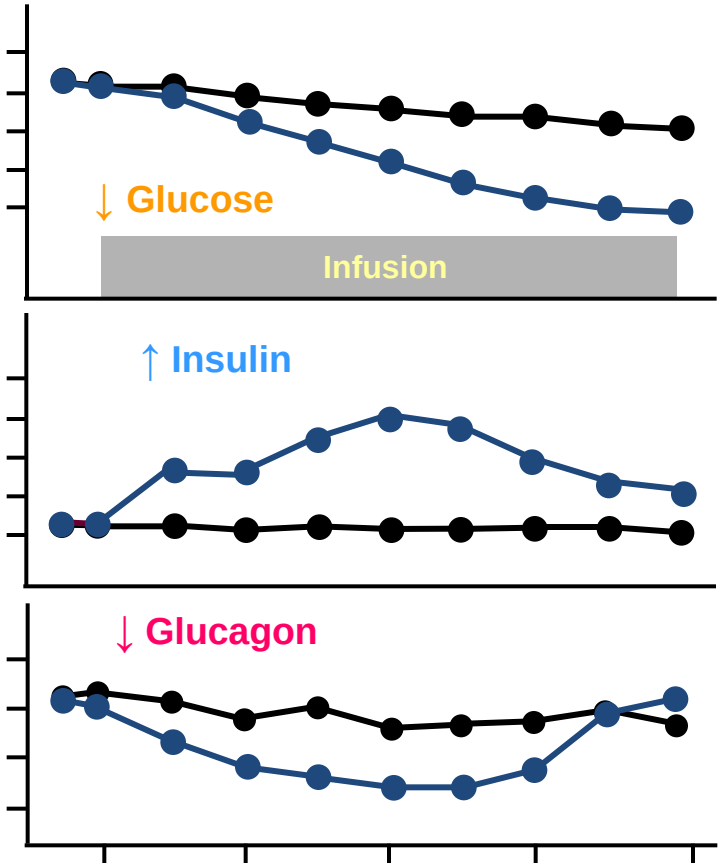
Adapted from Drucker DJ *Diabetes Care* 2003;26:2929–2940; Ahrén B *Curr Diab Rep* 2003;3:365–372; Drucker DJ *Gastroenterology* 2002;122:
531–544; Farilla L et al *Endocrinology* 2003;144:5149–5158; Trümper A et al *Mol Endocrinol* 2001;15:1559–1570; Trümper A et al *J Endocrinol* 2002;174:233–246.

Continuously Infused GLP-1 Improves th e Defects of T2D

	T2D Defects[1,3]	Continuously Infused GLP-1[1,2]
	↓ Insulin production	↑
	↓ First-phase insulin response	↑
	↑ Glucagon; ↑ glucose output	↓
	↑ Gastric emptying	↓
	↑ Food intake	↓

1. Aronoff SL, et al. *Diabetes Spectrum.* 2004;17:183-190; 2. Nielsen LL, et al. *Regul Pept.* 2004;117:77-88; 3. Drucker DJ and Nauck MA. Lancet. 2006;368:1696-1705.

Glucose-Dependent Effect of GLP-1



When glucose levels approach normal…

insulin levels return to baseline (↓), and…

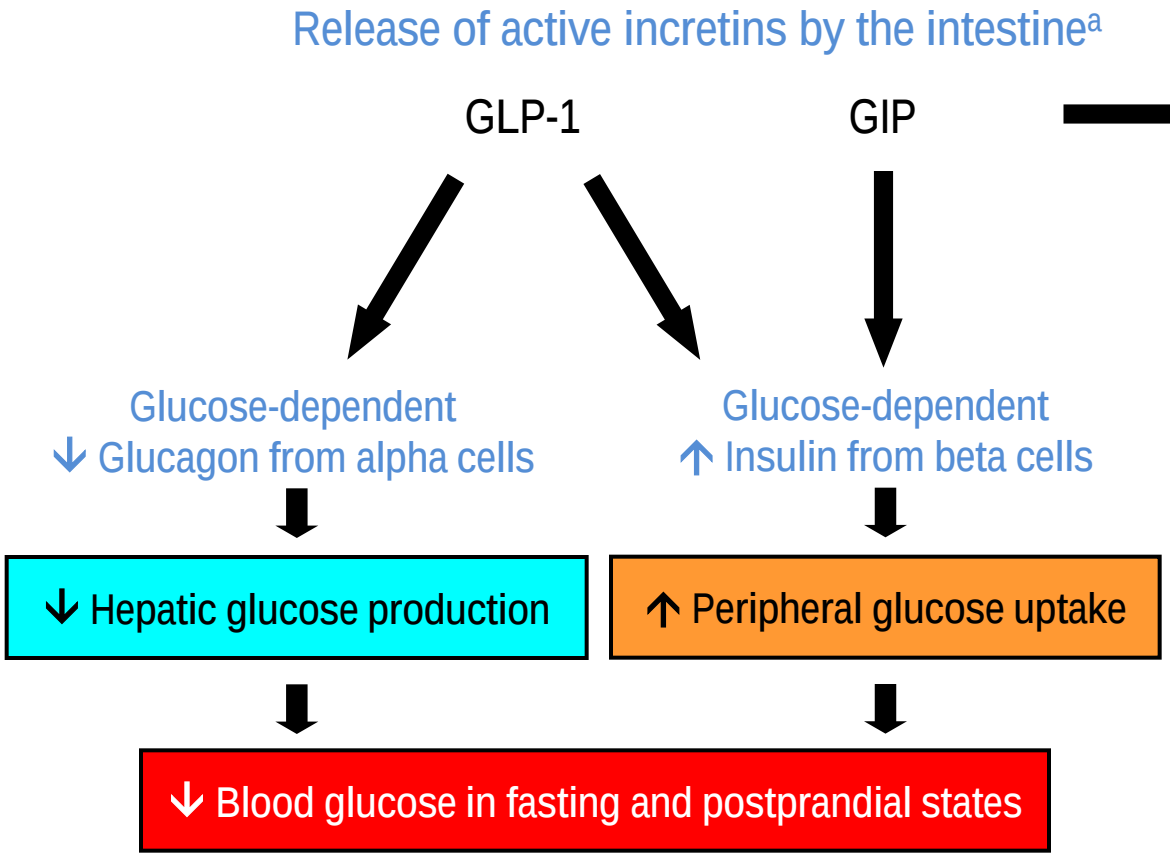
…glucagon levels rebound (↑)

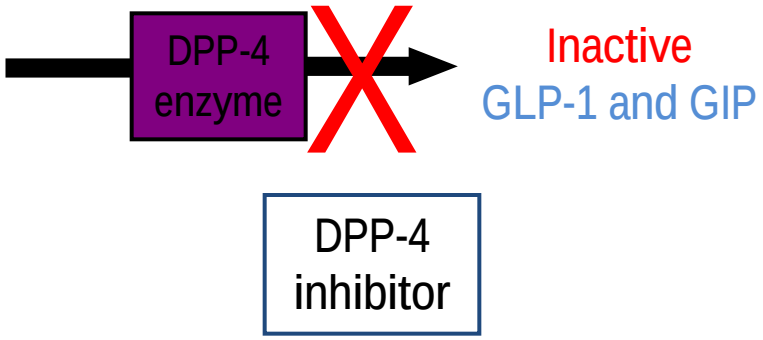
Glucose-dependent means:

Insulin 'only' when needed

<u>Less risk of:</u>
- **Hypoglycemia**
- **Weight gain**

DPP-4 Inhibition Increases Concentrations of Active Incretins[1–3]





By increasing and prolonging active incretin levels, DPP-4 inhibitors increase insulin release and decrease glucagon levels in the circulation in a glucose-dependent manner.

DPP-4=dipeptidyl peptidase-4; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.

[a]Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

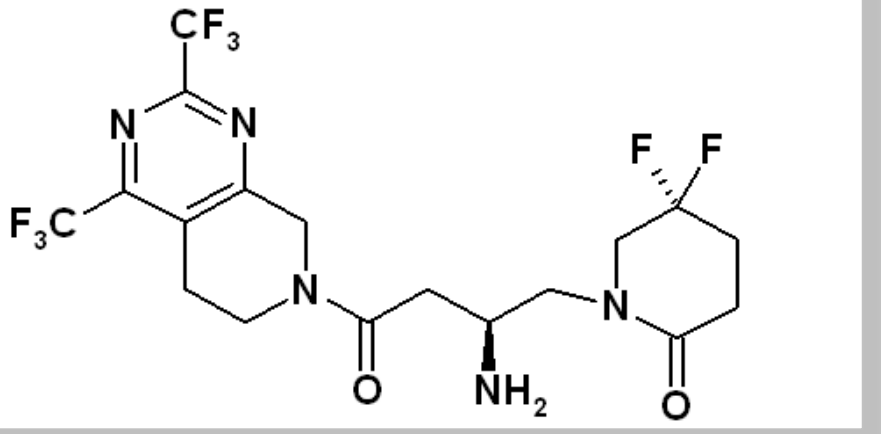
1. Kieffer TJ et al. *Endocr Rev*. 1999;20(6):876–913. 2. Drucker DJ. *Diabetes Care*. 2003;26(10):2929–2940. 3. Holst JJ. *Diabetes Metab Res Rev*. 2002;18(6):430–441.

LG생명과학

Gemigliptin




Chemistry

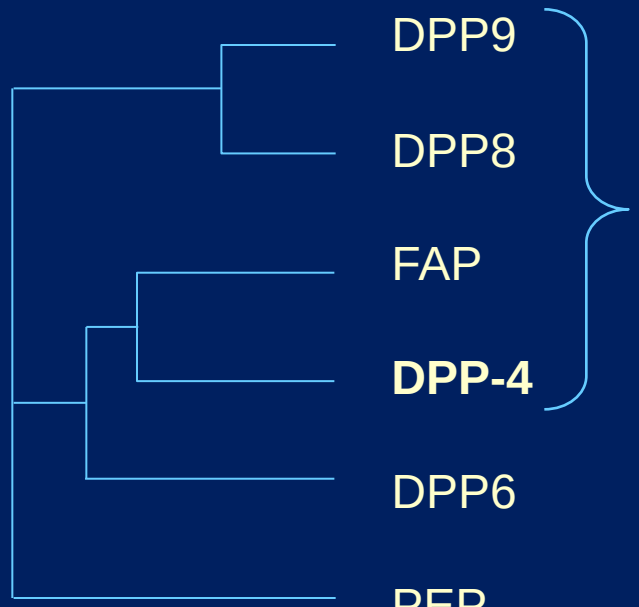


Gemigliptin

1- [2- amino- 4- (2, 4-bis-trifluoromethyl- 5, 8- dihydro- 6H-pyrido [3, 4-d] pyrimidin-7-yl)-4-oxo-butyl]-5, 5-difluoro-piperidin-2-one tartrate sesquihydrate

Compound	Chemistry	Binding Kinetics
Gemigliptin (LG)	Pyrimidinopiperidine based, Substrate like	Competitive, reversible inhibitor (Non-covalent interaction)
Sitagliptiin (Merck)	Triazolopiperazine based, Substrate like	Competitive, reversible inhibitor (Non-covalent interaction)
Vildagliptin (Novartis)	Cyanopyrrolidine based, Substrate like	Slow-tight binding inhibitor (Covalent interaction)
Saxagliptin (BMS)	Cyanopyrrolidine based, Substrate like	Slow-tight binding inhibitor (Covalent interaction)
Linagliptin (Boehringer Ingelheim)	Fused imidazole based, nonsubstrate-like	Competitive, reversible inhibitor (Non-covalent interaction)

Potential Issue: Toxicities due to Non-Selective Inhibition: The DPP-4 Protease Family



DPP-4 Gene Family

Other Proline Specific Peptidases

	Specificity	Function
DPP9		unknown
DPP8		unknown
FAP	NH_2-Xaa-Pro~Yaa--	unknown
DPP-4		GLP-1 / GIP cleavage
DPP6	catalytically inactive	unknown
PEP	--Xaa-Pro~Yaa--	unknown
QPP/DPPII	NH_2-Xaa-Pro~Yaa--	unknown
APP	NH_2-Xaa~Pro-Yaa----	unknown
prolidase	NH_2-Xaa~Pro-COOH	unknown

Enzyme Selectivity

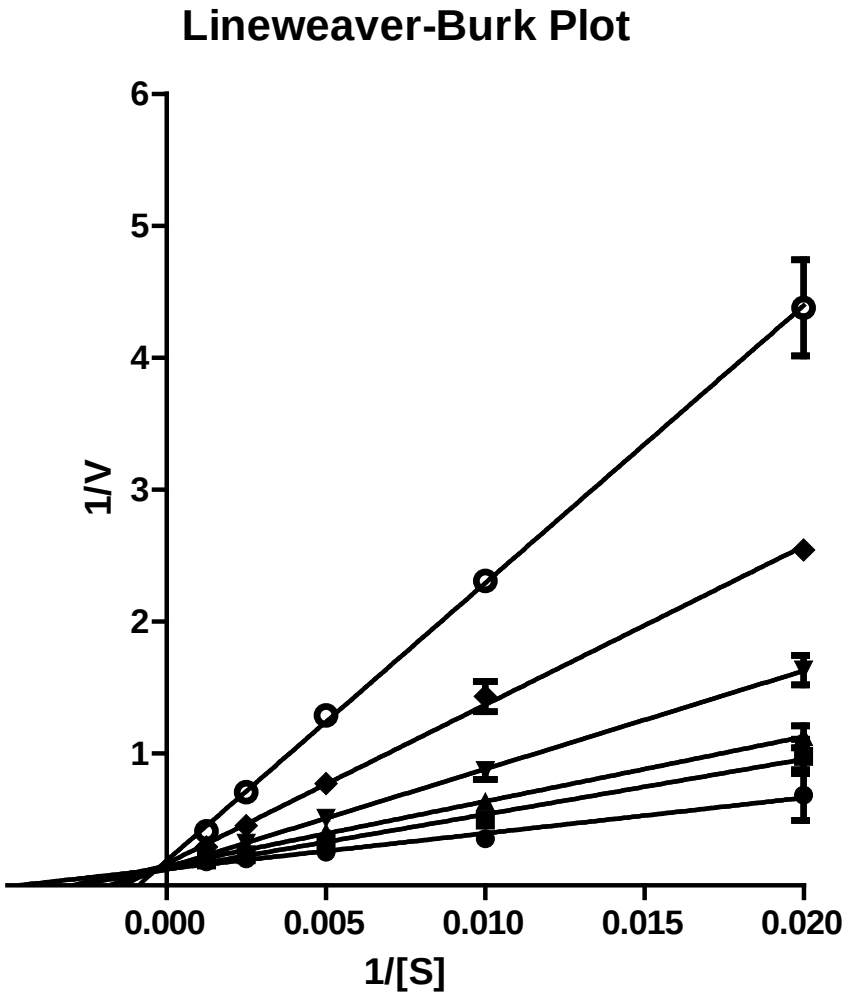
Gemigliptin is a selective DPP IV inhibitor

Compound	Fold Selectivity vs. DPP 8, 9 or FAP	DPP 8 (fold)	DPP 9 (fold)	FAP (fold)
Gemigliptin (LG)	High	9565	3412	22,458
Sitagliptiin# (Merck)	High	>2,600	>5,500	>5,500
Vildagliptin# (Novartis)	Moderate	270	32	285
Saxagliptin# (BMS)	Moderate	390	77	>4,000
Linagliptin# (Boehringer Ingelheim)	Moderate	40,000	>10,000	89

#Diabetes, Obesity and Metabolism 13: 7–18, 2011
Fold: vs. DPP IV activity

Enzyme Kinetics

Gemigliptin is a potent and competitive DPP IV inhibitor

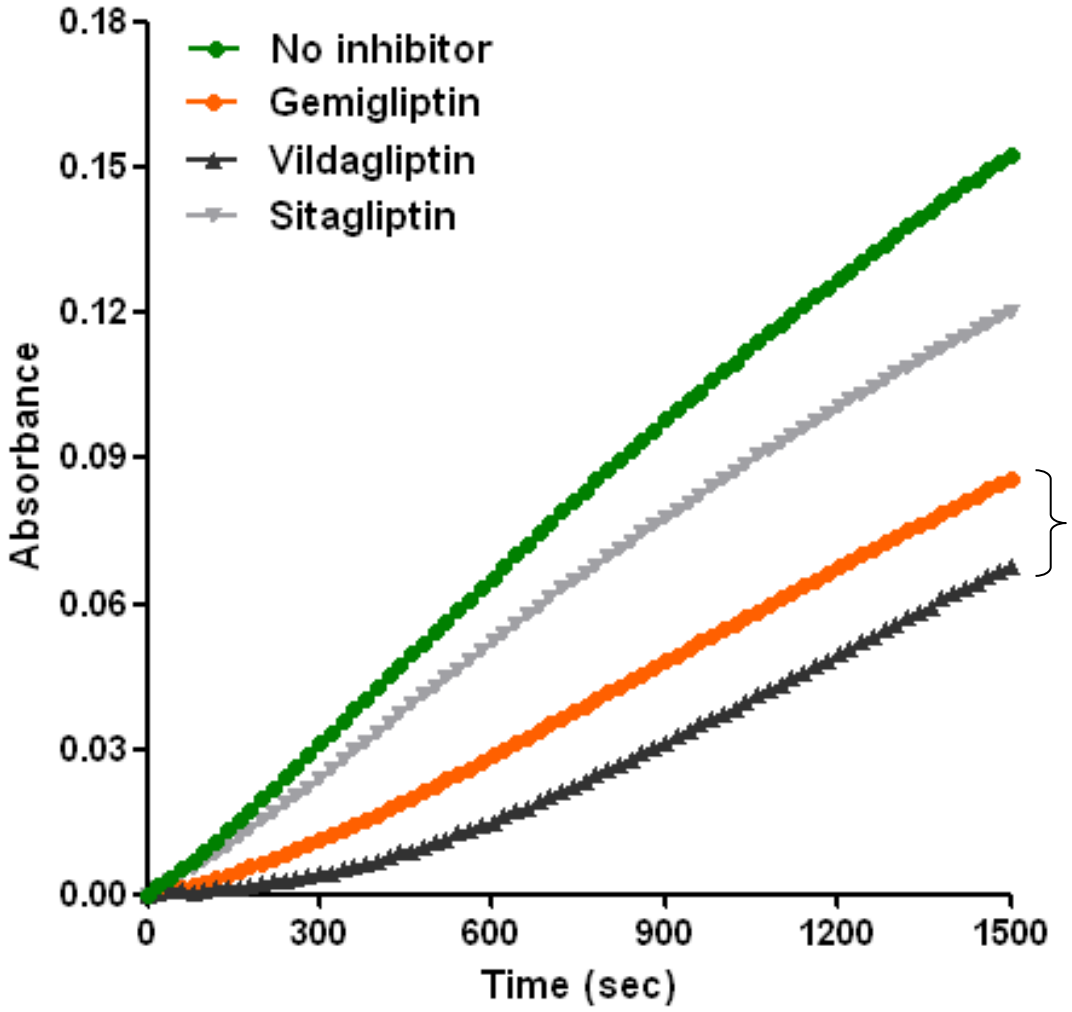


Ki of Gemigliptin: 9.04 ± 0.55 nM

Lineweaver-Burk Plot of Recombinant Human DPP IV Activity Measured in the Presence of Varied Concentrations of Gemigliptin & Substrate (Gly-Pro-pNA)

Enzyme Kinetics

Gemigliptin is a slowly reversible inhibitor



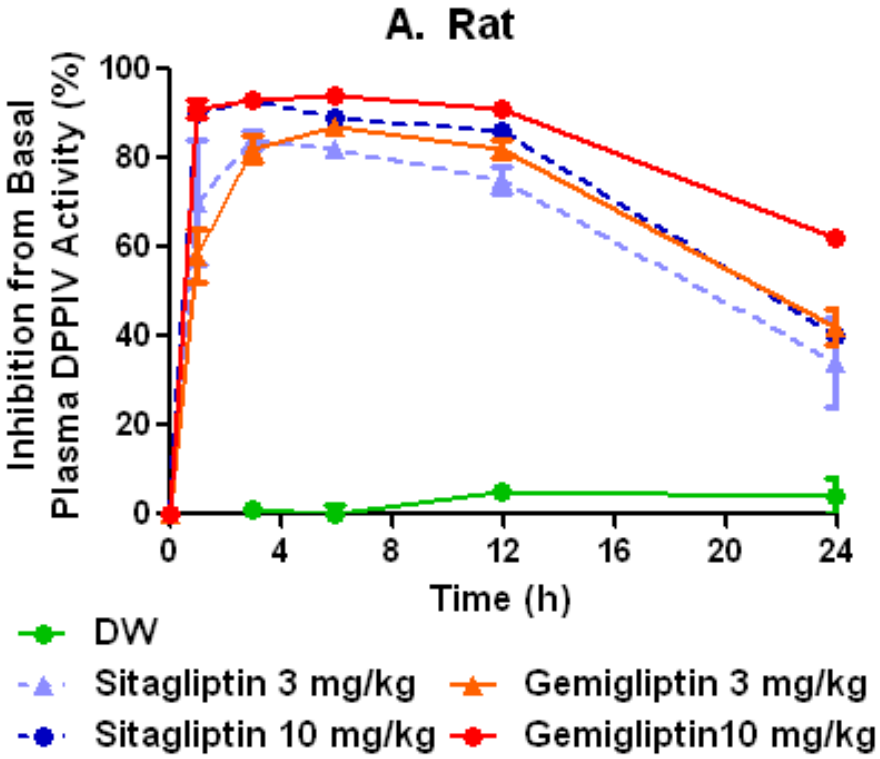
Rapidly reversible

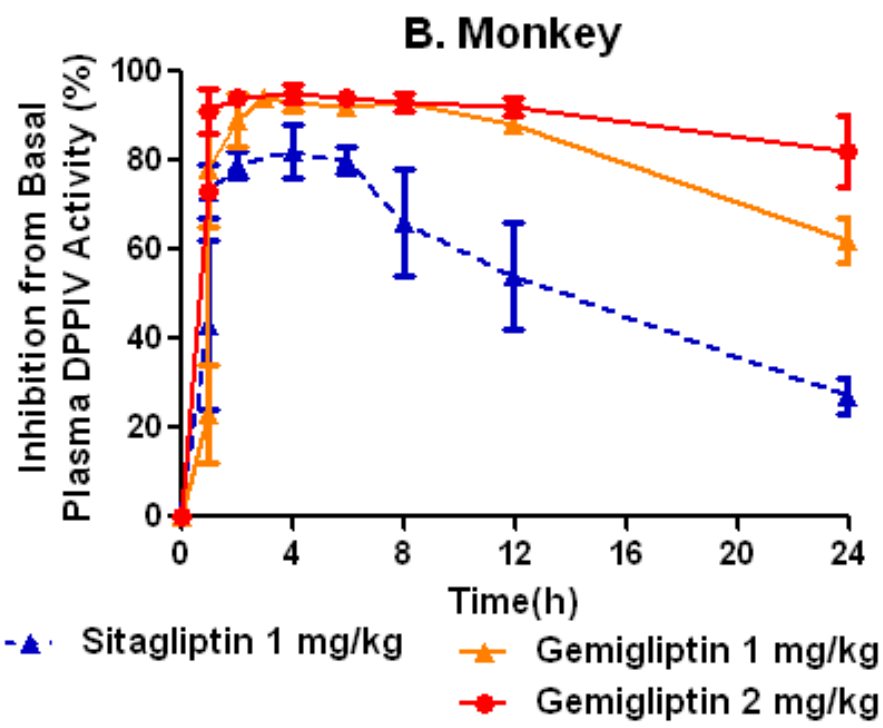
Slowly reversible

Dissociation of the Inhibitors-enzyme complex following dilution into substrate.

Efficacy | *in vivo* DPP IV inhibition

Higher DPP IV inhibition rate & longer duration of Gemigliptin





2006 ADA Poster No.502

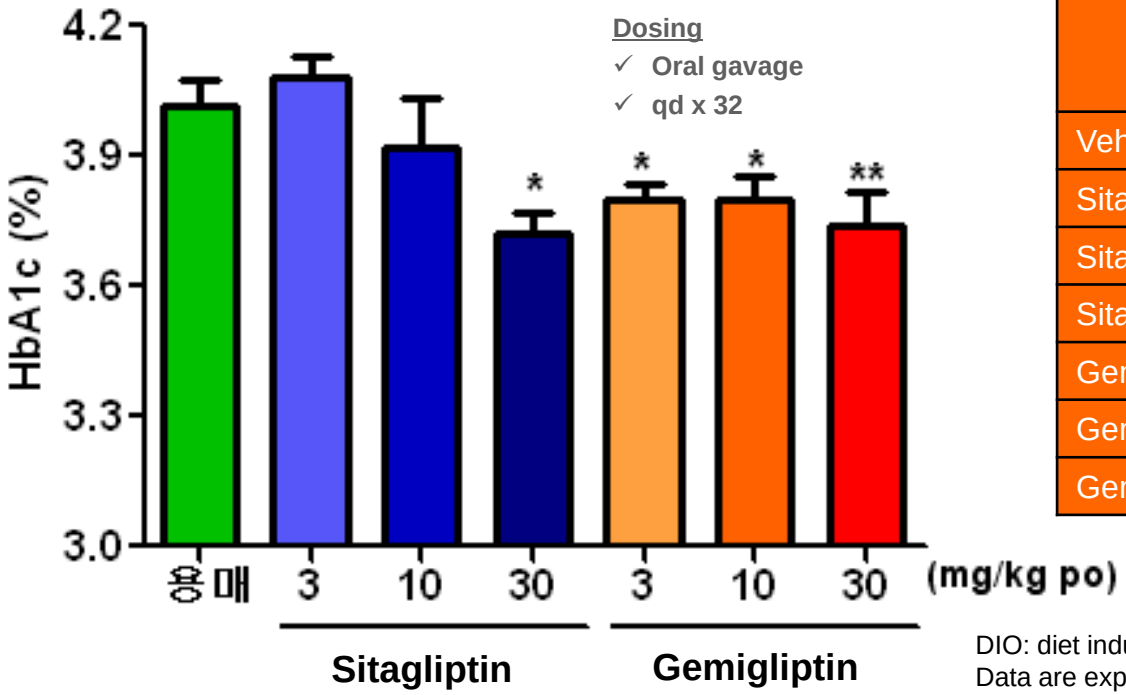
Efficacy | HbA1c

Gemigliptin was superior to sitagliptin for reduction of HbA1c

Animals
- ✓ male DIO C57BL/6 mice
- ✓ 28 weeks old
- ✓ N = 6

Diet
- ✓ 60 kcal% fat diet

Dosing
- ✓ Oral gavage
- ✓ qd x 32



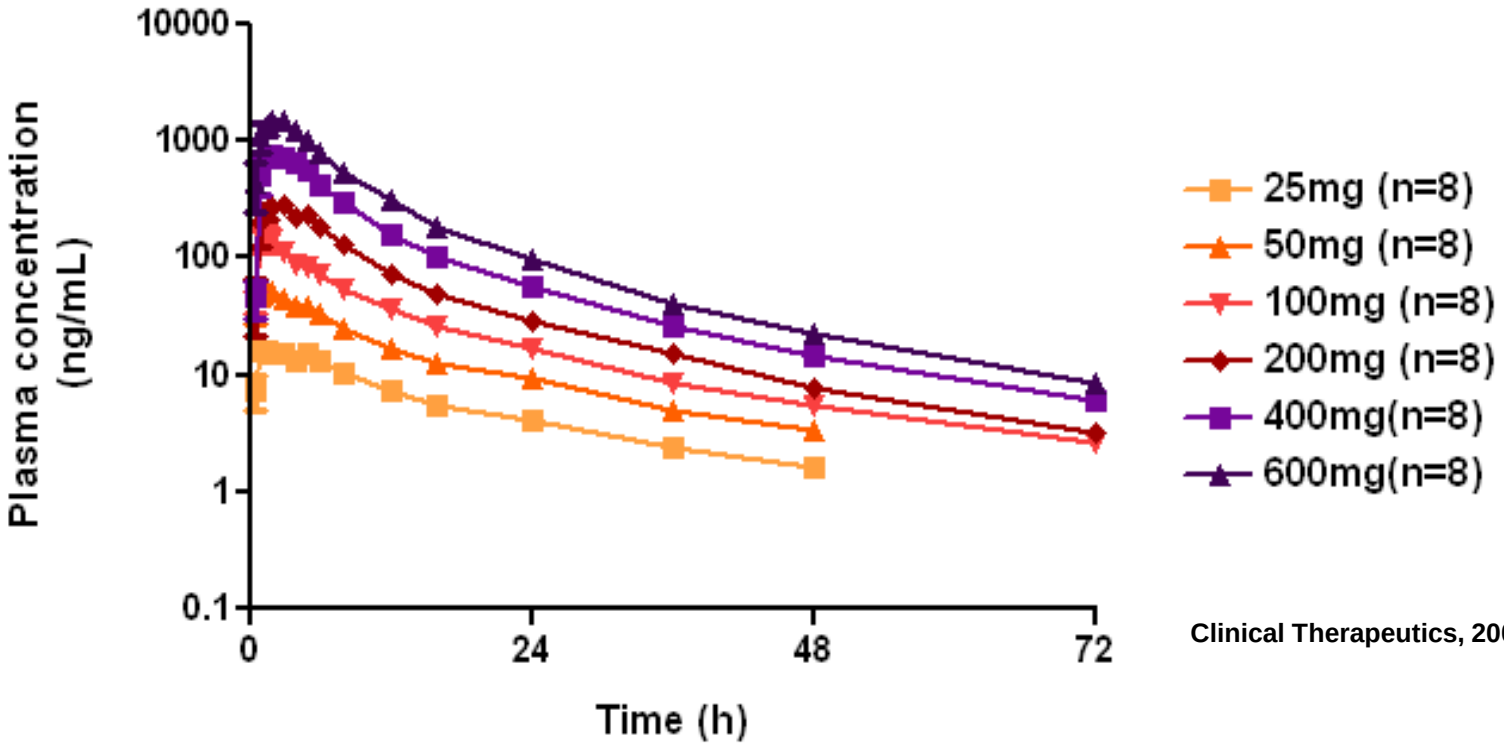
Compound	22 Hours after the 32nd Dosing
	DPP IV Activity (%)*
Vehicle Control	100.0 ± 8.7
Sitagliptin, 3 mg/kg	68.9 ± 4.2
Sitagliptin, 10 mg/kg	43.4 ± 7.6
Sitagliptin, 30 mg/kg	31.5 ± 8.5
Gemigliptin, 3 mg/kg	18.8 ± 1.9
Gemigliptin, 10 mg/kg	8.4 ± 0.3
Gemigliptin, 30 mg/kg	6.4 ± 0.5

DIO: diet induced obese mice
Data are expressed as the mean ± SE
* p<0.05, **p<0.01 vs Control (Dunnett's Test)

2006 ADA Poster No.502

Pharmacokinetics | Half- life

Gemigliptin exhibited linear pharmacokinetics properties



Clinical Therapeutics, 2008; 30: 1817~1830

	Gemigliptin	Sitagliptin#	Vildagliptin#	Saxagliptin#	Linagliptin#
Half-life (hr)	17~21	8~14	2~3	2.5 (3.1)	120

#Drug, 2011;71(11):1441~1467

LG생명과학

Gemigliptin

Clinical Trial Results of Gemigliptin

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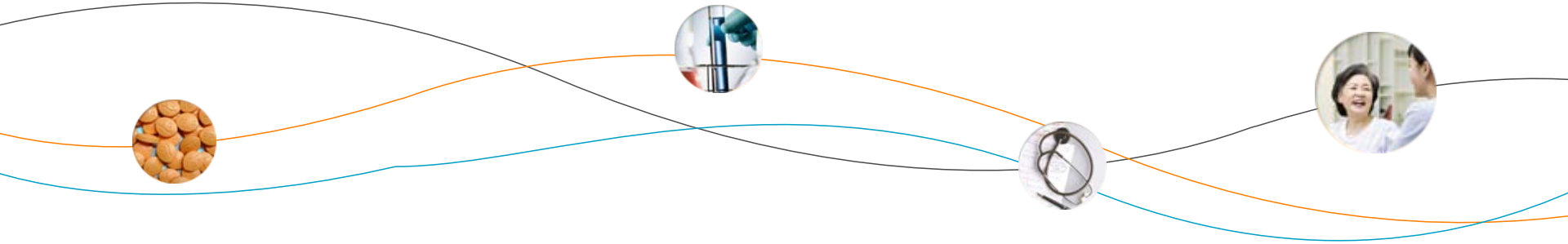
Gemigliptin Phase III Results

LG-DPCL005, LG-DPCL006

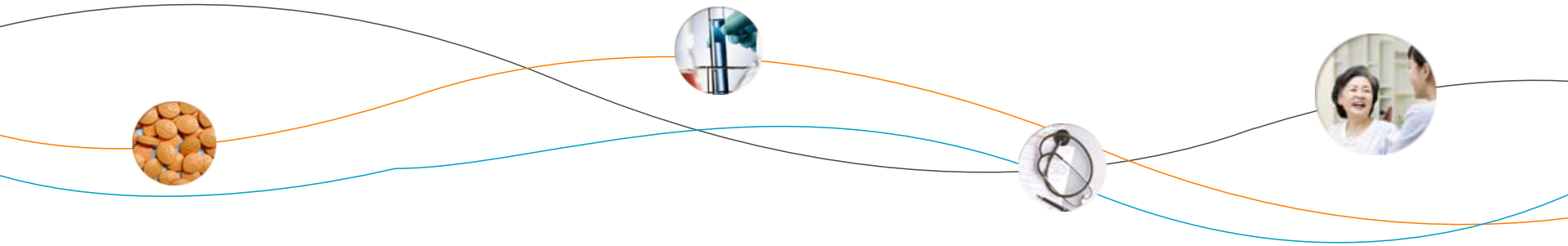


LG생명과학

LG-DPCL005

Monotherapy

A multicenter, multinational, randomized, placebo-controlled, parallel group, double-blind, Phase 3 trial to evaluate the efficacy and safety of LC15-0444 in patients with type 2 diabetes



LG생명과학

Gemigliptin

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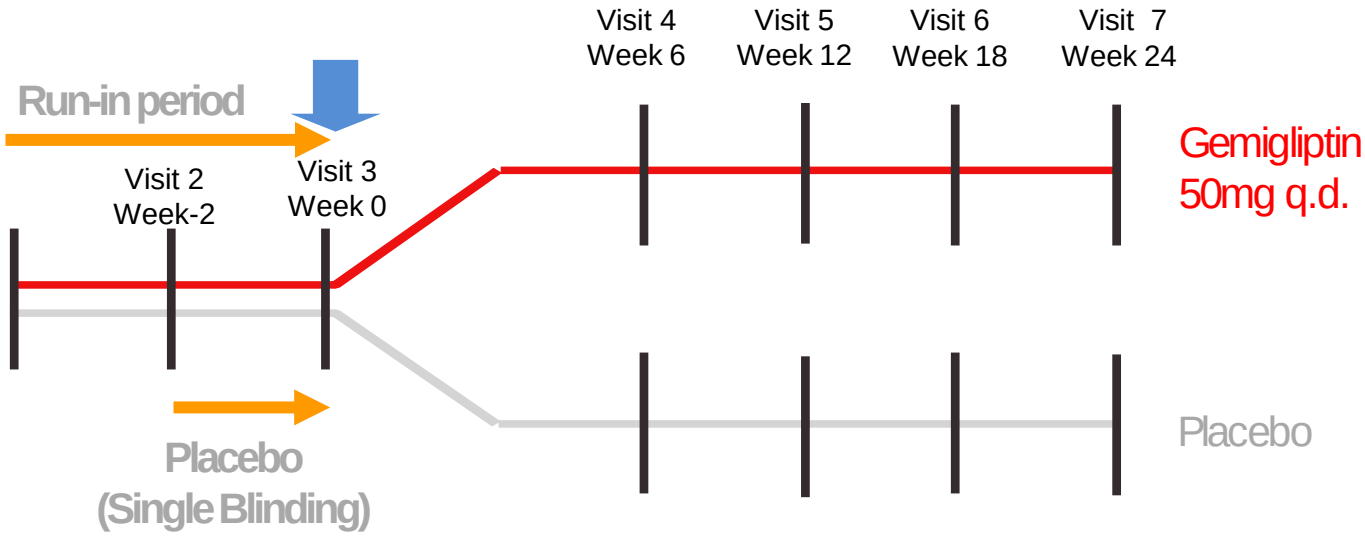
Study Design

- Objective | Evaluate the efficacy & safety in T2DM.
- Patients | Naïve (no anti- diabetes for 3 months prior to study), HbA_{1c} 7~ 11%
  No. = 180 (90/group, included 20% attrition)
- Dose | Gemigliptin 50mg q.d. or placebo
- Treatment | 24 weeks (extension to 52 weeks)
- Primary endpoint | HbA_{1c} change from baseline
- Study sites | 5 sites in Korea and 9 sites in India



Study End Points

Efficacy |

[Primary endpoint]

- HbA_{1c} change from baseline (W24)

[Secondary endpoint]

- HbA_{1c} responder rate (at Week 24: HbA_{1c} <7 %, <6.5 %)
- HbA_{1c} change from baseline (W18)
- Fasting plasma glucose (W18, W24)
- Fasting serum insulin (W24)
- Fasting serum proinsulin (W24)
- Fasting serum C-peptide (W24)
- HOMA-β (W24)
- HOMA-IR (W24)

[Tertiary endpoint]

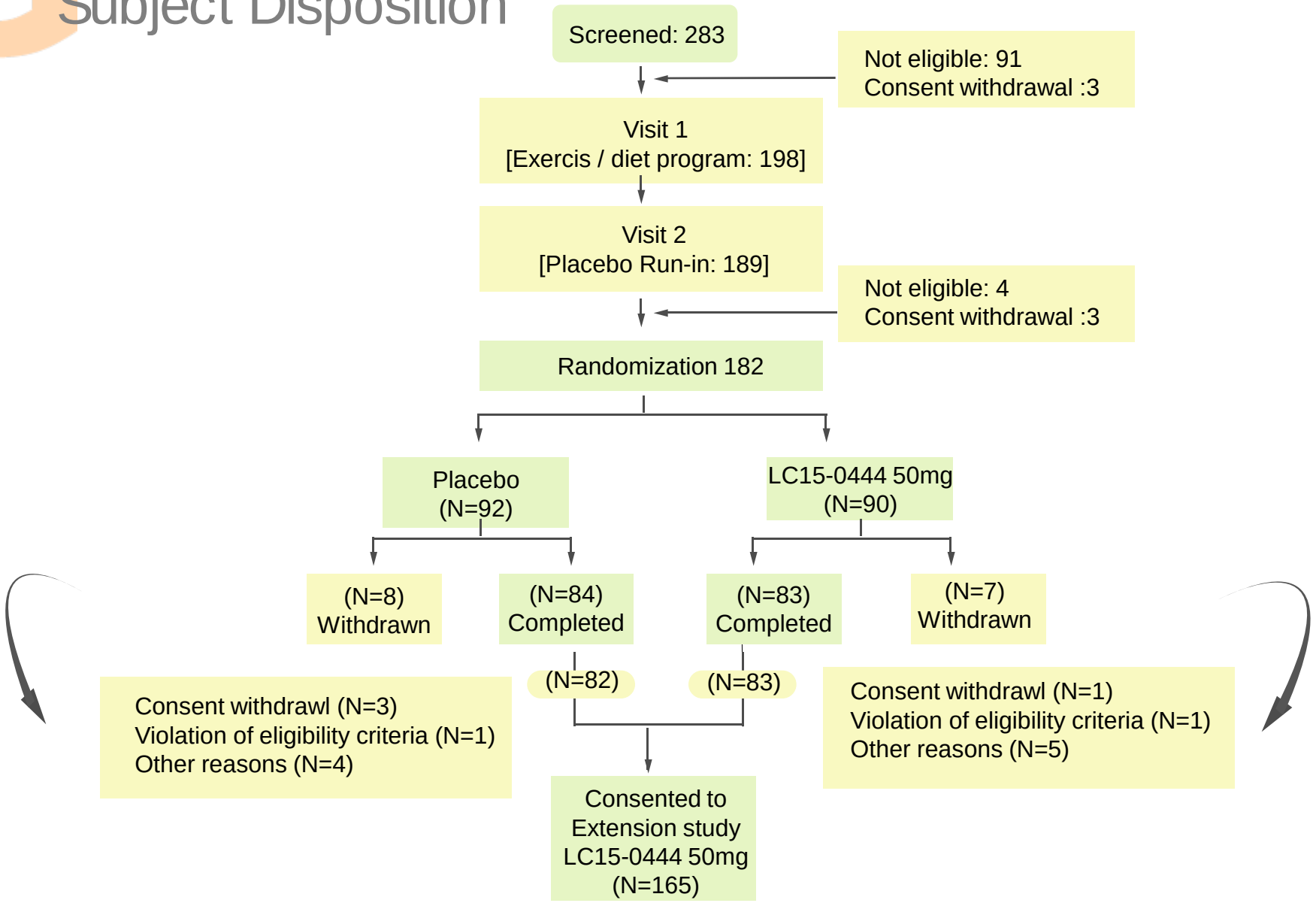
- OGTT parameters : 2-h PPG, 2-h Insulin, 2-h C-peptide, 각 $AUC_{0\text{-}2h}$
- GLP-1
- Insulinogenic index
- Proinsulin/Insulin ratio
- DPP IV activity
- Fasting lipid parameter : TC, LDL, HDL, Triglyceride
- Body weight
- Waist circumference

Safety |

- Adverse events
- Vital signs
- Laboratory tests

**W24 : Change from baseline at Week 24*
**W18 : Change from baseline at Week 18*

Subject Disposition



Analysis | FAS : Placebo (n=87) / Gemigliptin (n=87)

FAS : The Full Analysis Set (FAS) consisted of all the patients who observed ITT principle, received the investigational drug at least once and had the efficacy variables after randomization. The FAS was the primary population for the analysis of efficacy evaluation.

Demographics

□□□□□ □□□ □□ □□ □□.

Safety Set		Placebo (N=92)	Gemigliptin 50mg (N=90)	P-value
Sex	Male (%)	48 (52.17)	58 (64.44)	0.0933 ‡
	Female (%)	44 (47.83)	32 (35.56)	
Nationality	Indian (%)	56 (60.87)	52 (57.78)	0.6712 ‡
	Korean (%)	36 (39.13)	38 (42.22)	
Age (yrs)	Mean (±SD)	52.21 (9.4)	52.49 (8.92)	0.5560 #
Height (cm)	Mean (±SD)	159.04 (9.48)	161.05 (8.6)	0.1188 #
BMI (kg/m^2)	Mean (±SD)	27.02 (3.72)	26.34 (4.25)	0.1105 #

✓ N=Number; SD=Standard Deviation
p-value obtained from Wilcoxon's rank test
‡ p-value obtained from Chi-square test

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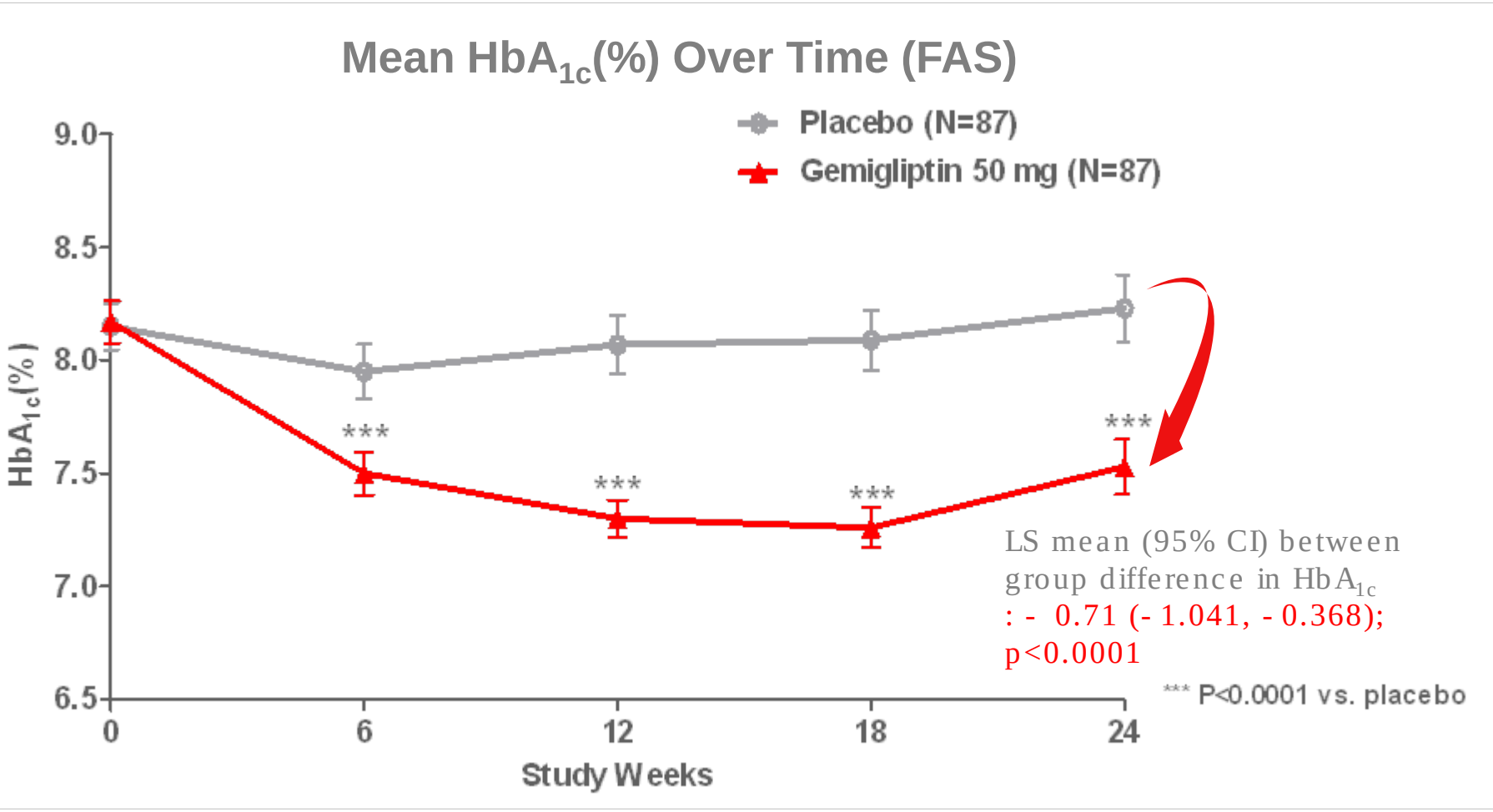
Efficacy | HbA1c

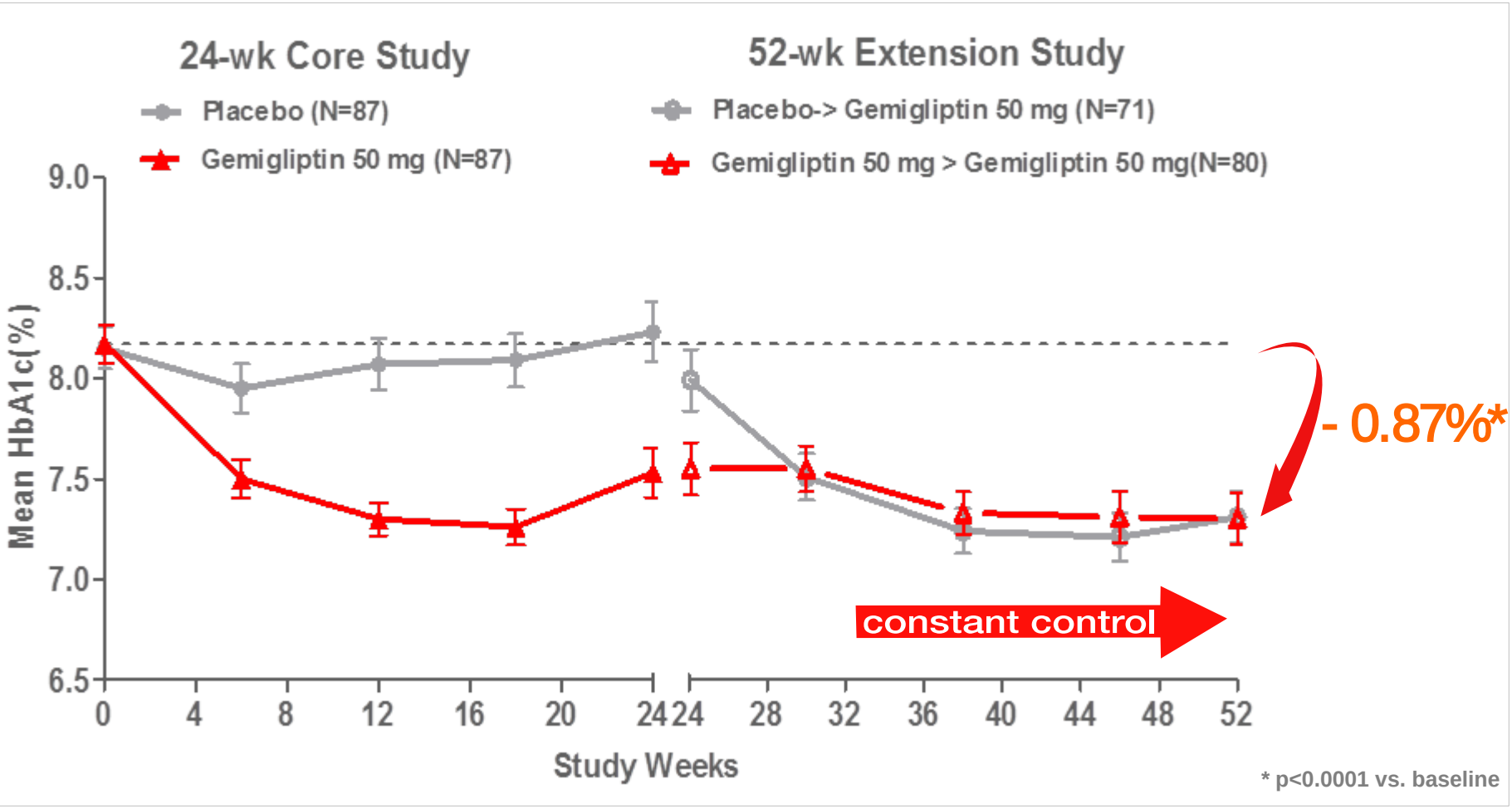
제미글립틴 50mg



50mg군과 위약군간의 보정된 평균의 차이는 -0.71% [95% CI -1.041 to -0.368]으로,
양측 95% 신뢰구간의 상한치가 -0.368로 0보다 작아 위약 대비 50mg의 우월성을 성공적으로 입증함.

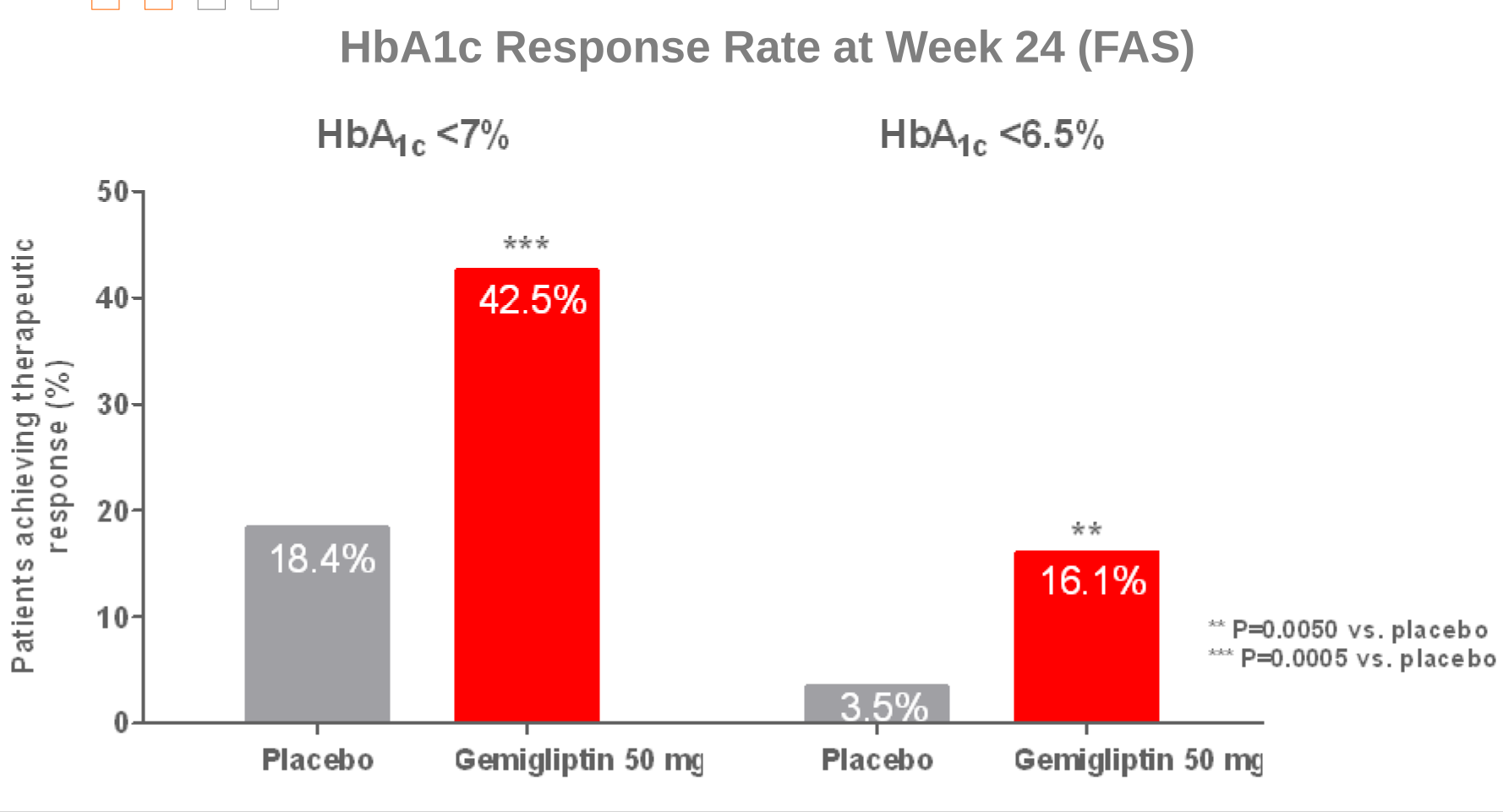
Efficacy | Long Term (52week)

50mg 52



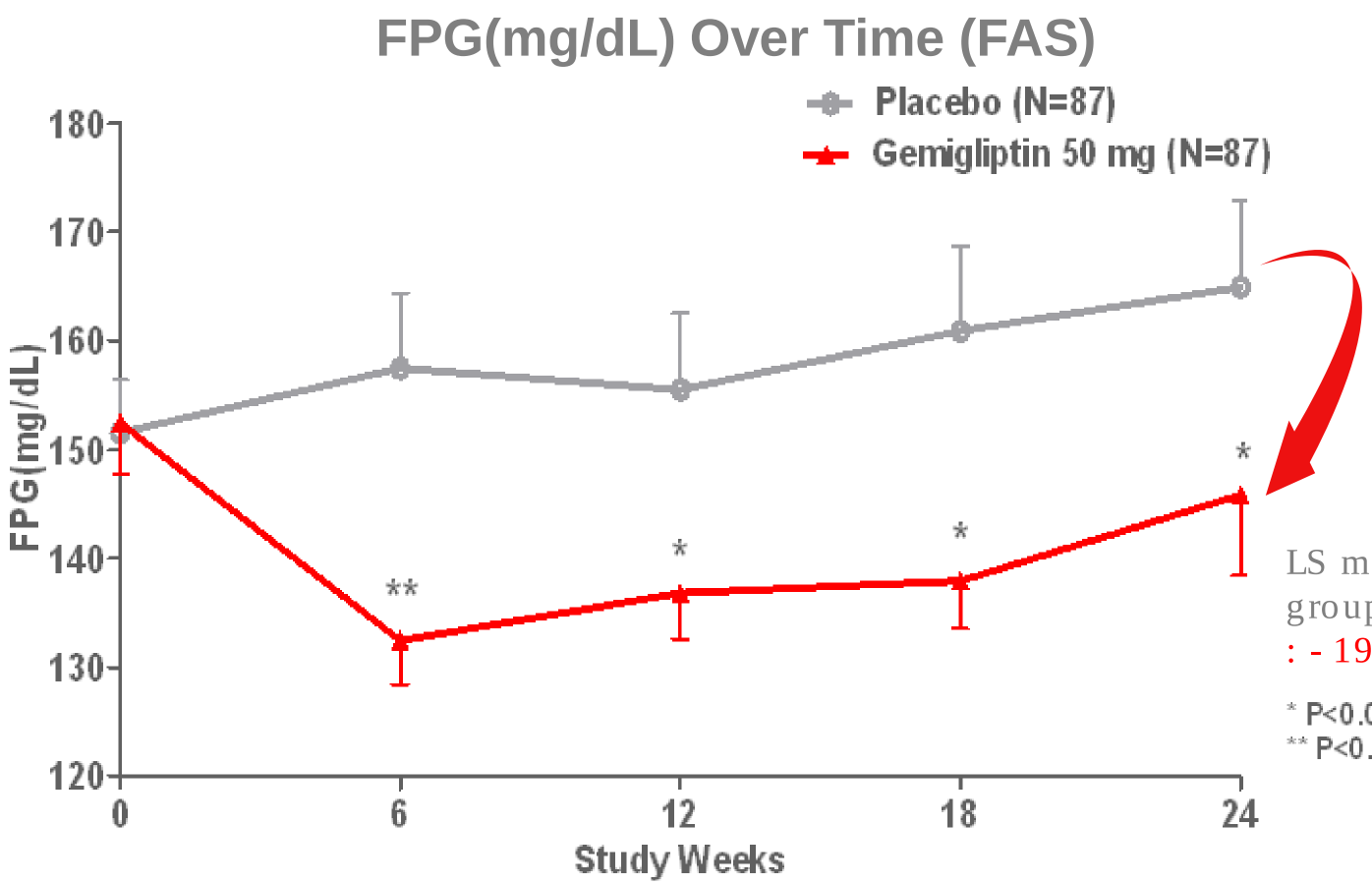
Efficacy | Response Rate

제미글립틴 50mg 은 위약대비 목표혈당 도달율 을 유의하게



Efficacy | FPG

제미글립틴 50mg 은 기저치 및 위약대비 FPG 를 유의하게 감소 시킴



LS mean between group difference in FPG : - 19.79mg/dL

* P<0.01 vs. placebo
** P<0.001 vs. placebo

LG생명과학

Gemigliptin

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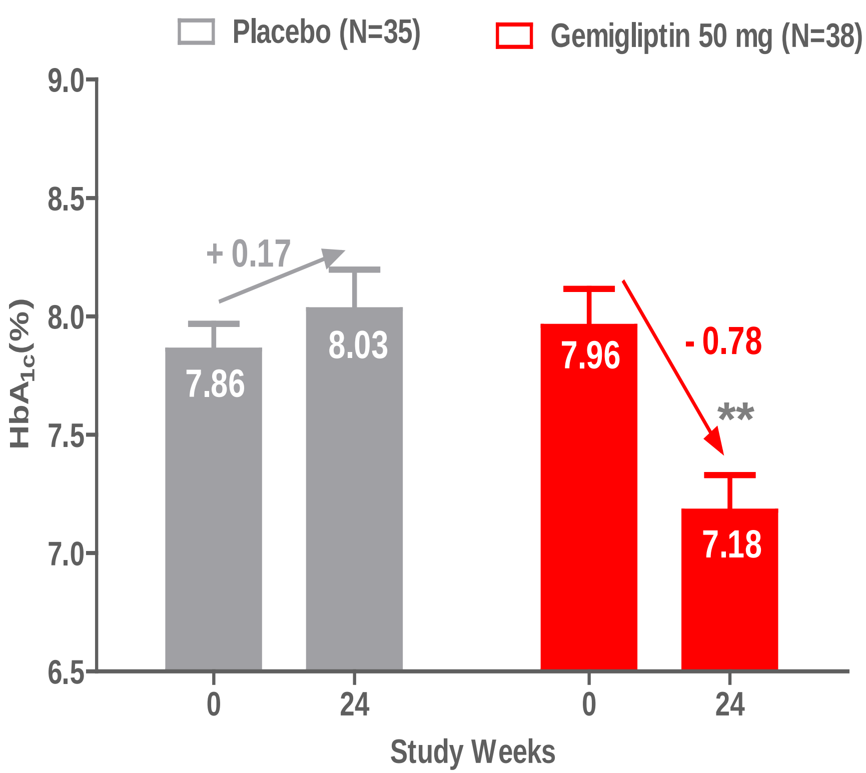
Subgroup | Country

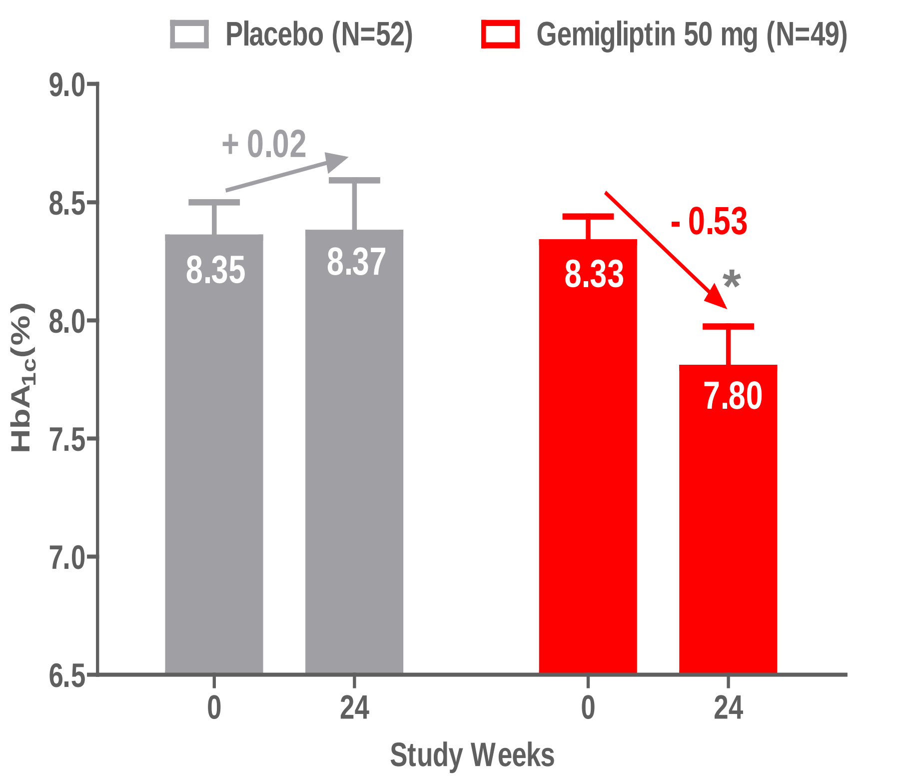
□ □ □ □ □ 50mg□ □ □ □ □ □ □, □ □ □ □ □ □ □ □ □ □ □ □ □.

Korea



** P<= 0.0001 vs. baseline
LS mean (95% CI) between group difference -0.935(-1.356, -0.515)

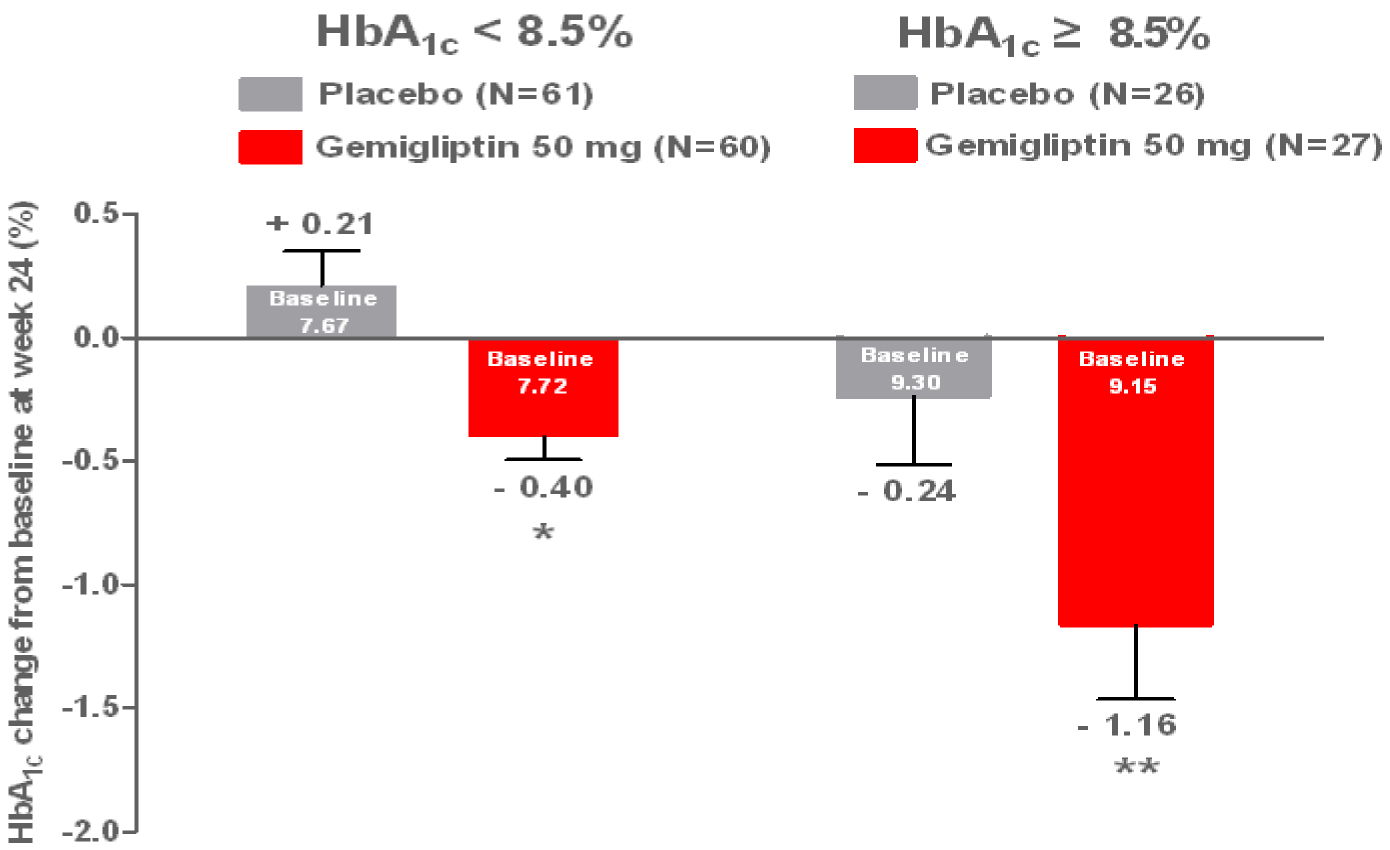
India



* p<= 0.0030 vs.baseline
LS mean (95% CI) between group difference -0.553(-1.064, -0.042)

Subgroup | Baseline HbA_{1C}

제미글립틴 50mg 은 기저 HbA_{1C} 가 높은 경우 더 우수한 효과를 보임

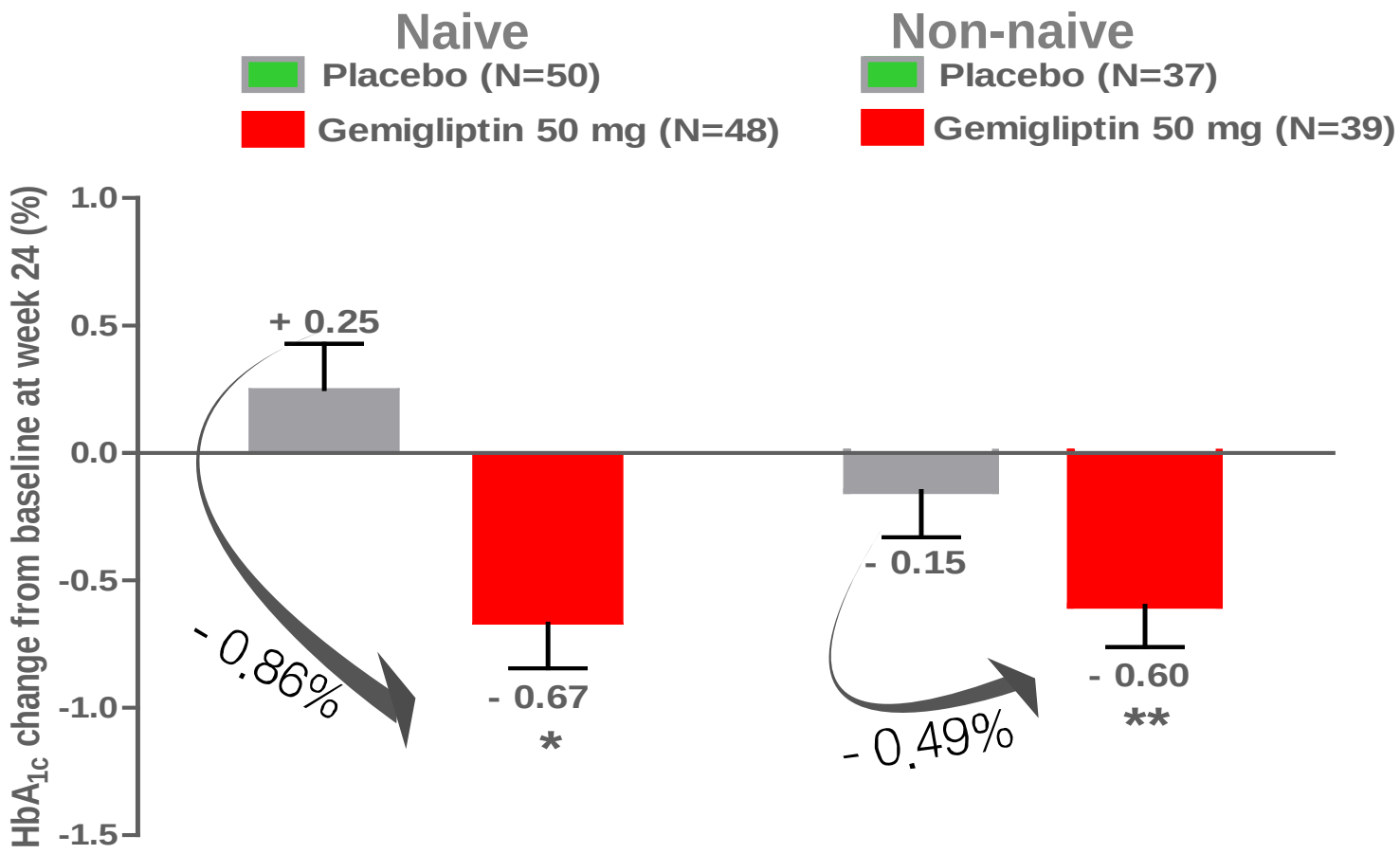


*P< 0.0001 vs. baseline
LS mean (95% CI) between group difference -0.595(-0.939, -0.252)

** P< 0.0008 vs. baseline
LS mean (95% CI) between group difference -0.994(-1.803, -0.185)

Subgroup | Naïve, Non- naïve

□ □ □ □ □ 50mg□ □ □ □ □ □ □, □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □



*P<=0.0004 vs. baseline
LS mean (95% CI) between group difference -0.862%(-1.351, -0.372)

** P< 0.0001 vs. baseline
LS mean (95% CI) between group difference -0.493%(-0.933, -0.052)

LG생명과학

Gemigliptin

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LG생명과학

Safety | Summary of AEs

□□□□□ □□□□ □□□ □□□.

Adverse Events Summary	Placebo	Gemigliptin 50mg
Number of patients	92	90
Number of patients experienced an AE	38 (41.30)	39 (43.33)
Number of patients dropped out due to AE	0 (0)	0 (0)
Number of patients experienced a SAE	2 (2.17)	3 (3.33)
Number of AEs	73	77
Number of SAEs	2 (2.74)	3 (3.90)

Safety | Most Common AEs (≥2.5%)

Preferred Term	Placebo (N=92)	Gemigliptin 50mg (N=90)
Eosinophilia	3 (3.26)	2 (2.22)
Pyrexia	5 (5.43)	1 (1.11)
Nasopharyngitis	4 (4.35)	4 (4.44)
Upper respiratory tract infection	3 (3.26)	1 (1.11)
Alanine aminotransferase increased	3 (3.26)	0 (0.00)
Blood creatine phosphokinase increased	5 (5.43)	2 (2.22)
Hypercholesterolaemia	3 (3.26)	1 (1.11)
Arthralgia	0 (0.00)	5 (5.56)

Safety | ADRs

System Organ Class/ Preferred Term	Placebo (N=92)	Gemigliptin 50mg (N=90)
Gastrointestinal disorders	3 (3.26)	1 (1.11)
Constipation	0 (0.00)	1 (1.11)*
Flatulence	1 (1.09)	0 (0.00)
Gastritis	1 (1.09)	0 (0.00)
Nausea	1 (1.09)	0 (0.00)
Infections and infestations	0 (0.00)	2 (2.22)
Nasopharyngitis	0 (0.00)	1 (1.11)
Upper respiratory tract infection	0 (0.00)	1 (1.11)
Investigations	0 (0.00)	1 (1.11)
Blood creatine phosphokinase increased	0 (0.00)	1 (1.11)
Metabolism and nutrition disorders	0 (0.00)	2 (2.22)
Hypoglycaemia	0 (0.00)	2 (2.22)
Skin and subcutaneous tissue disorders	0 (0.00)	1 (1.11)
Rash	0 (0.00)	1 (1.11)

* Reported in Korean patients. All the other ADRs were experienced by Indian patients.

Safety | Others

No clinically meaningful abnormalities were found in the laboratory tests, urinalysis, ECG, or vital signs.

LG생명과학

Gemigliptin

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Conclusion

유효성 결과

1. 제미글립틴 50mg 은 기저치 및 위약대비 HbA_{1c} & FPG 를 유의하게 감소 □ □ .

2. 제미글립틴 50mg 은 위약대비 목표혈당 도달 환자수를 유의하게 증가시킴 .

안정성 결과

제미글립틴 50mg 은 우수한 내약성을 가지고 , 위약과 유사한 이상반응 발현율을 □ □ .

LG생명과학

LG-DPCL006

Metformin Add-on Theraphy

A multicenter, multinational, randomized, active-controlled, parallel group, double-blind, Phase III trial to evaluate the efficacy and safety of LC15-0444 compared with Sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone

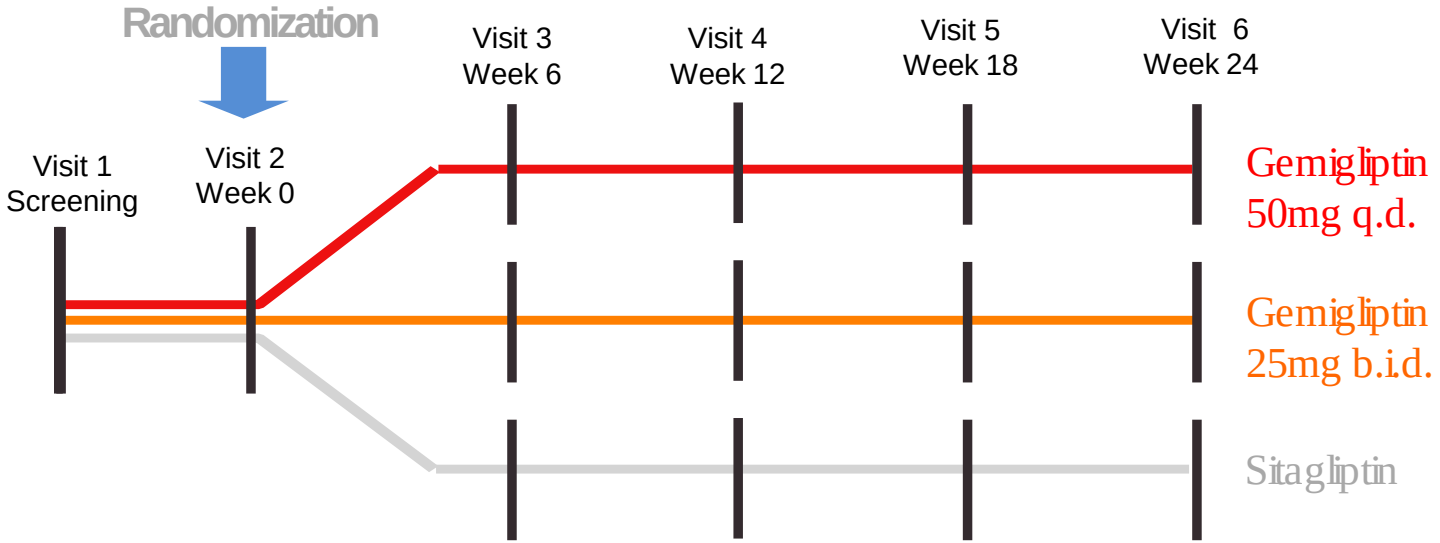
LG생명과학

Gemigliptin

Table of Contents

Study Overview

- Objective | Evaluate the efficacy and safety compared with Sitagliptin added to metformin therapy in T2DM.
- Patients | Inadequate glycemic control while taking metformin monotherapy
  HbA_{1c} 7~11% No. = 426 (142/group, including 30% attrition)
- Dose | Gemigliptin 50mg q.d., Gemigliptin 25mg b.i.d., or Sitagliptin 100mg q.d.
- Treatment | 24 weeks (extension to 52 weeks)
- Primary endpoint | HbA_{1c} change from baseline
- Study sites | 28 sites in Korea and 10 sites in India



Study End Points

Efficacy |

[Primary endpoint]

HbA_{1c} change from baseline (W24)

[Secondary endpoint]

HbA_{1c} responder rate (at Week 24: HbA_{1c} <7 %, <6.5 %)
HbA_{1c} change from baseline (W18)
Fasting plasma glucose (W18, W24)
Fasting serum insulin (W24)
Fasting serum proinsulin (W24)
Fasting serum C-peptide (W24)
HOMA-β (W24)
HOMA-IR (W24)

[Tertiary endpoint]

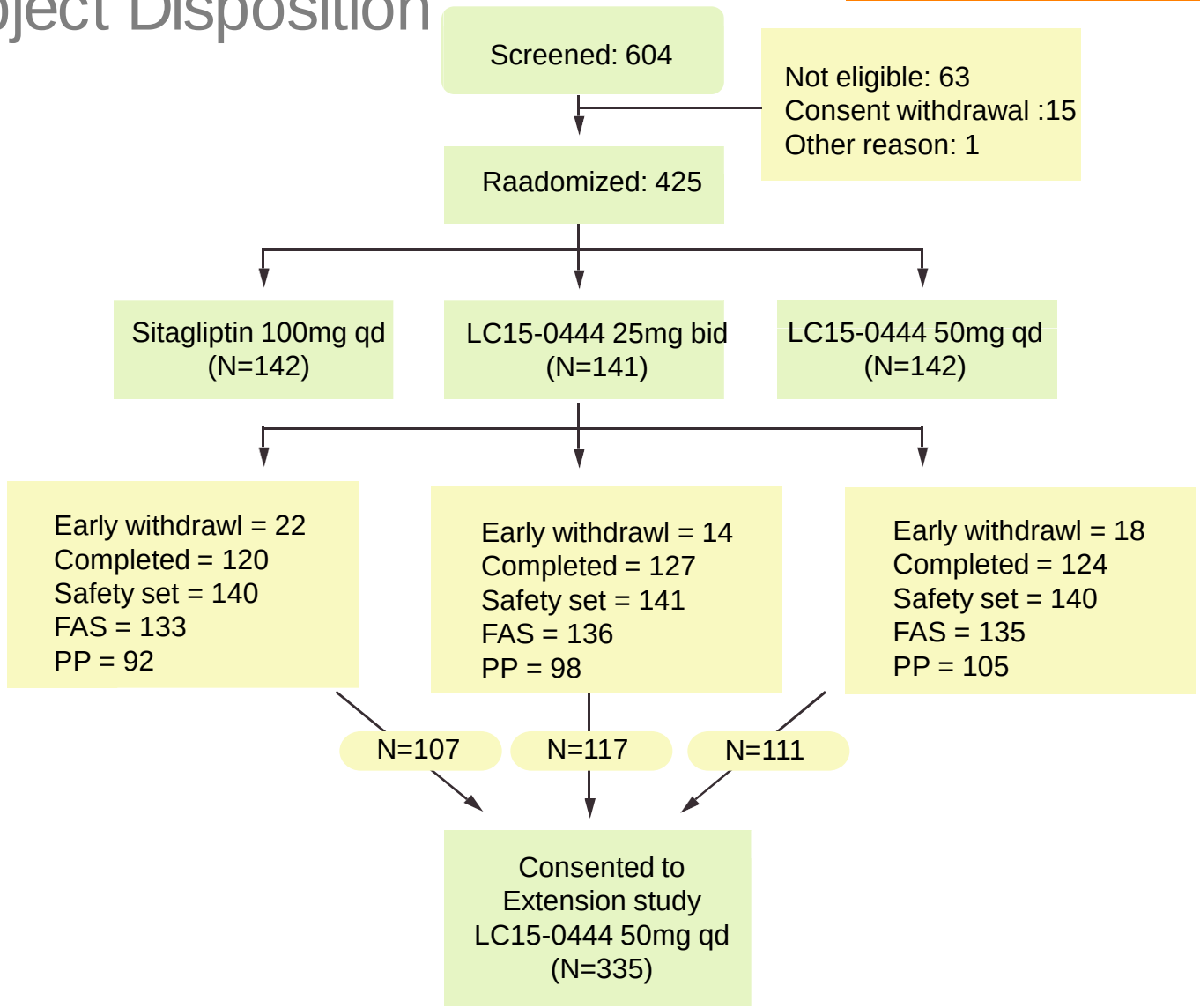
OGTT parameters : 2-h PPG, 2-h Insulin, 2-h C-peptide, 각 $AUC_{0\text{-}2h}$
GLP-1
Insulinogenic index
Proinsulin/Insulin ratio
DPP IV activity
Fasting lipid parameter : TC, LDL, HDL, Triglyceride
Body weight
Waist circumference

Safety |

Adverse events
Vital signs
Laboratory tests

**W24 : Change from baseline at Week 24*
**W18 : Change from baseline at Week 18*

Subject Disposition



Analysis | FAS : The Full Analysis Set (FAS) consisted of all the patients who observed ITT principle, received the investigational drug at least once and had the efficacy variables after randomization. The FAS was the primary population for the analysis of efficacy evaluation.

Demographics

□□□□□ □□□ □□ □□ □□.

Safety Set		Gemigliptin 25mg bid (N=141)	Gemigliptin 50mg qd (N=140)	Sitagliptin 100mg qd (N=140)	P- value
Sex	Male (%)	70 (49.65)	83 (59.29)	74 (52.86)	0.2563 §
	Female (%)	71 (50.35)	57 (40.71)	66 (47.14)	
Nationality	Indian (%)	43 (30.50)	43 (30.71)	43 (30.71)	0.9990 §
	Korean (%)	98 (69.50)	97 (69.29)	97 (69.29)	
Age (yrs)	Mean (±SD)	51.96 (10.57)	53.68 (8.88)	53.01 (10.61)	0.3551 #
Height (cm)	Mean (±SD)	161.57 (8.85)	162.07 (8.42)	161.6 (9.93)	0.8497 ##
BMI (kg/m^2)	Mean (±SD)	26.04 (3.58)	25.6 (3.38)	26.32 (3.58)	0.1868 ##

✓ N=Number; SD=Standard Deviation
p-value obtained from Wilcoxon's rank test
‡ p-value obtained from Chi-square test

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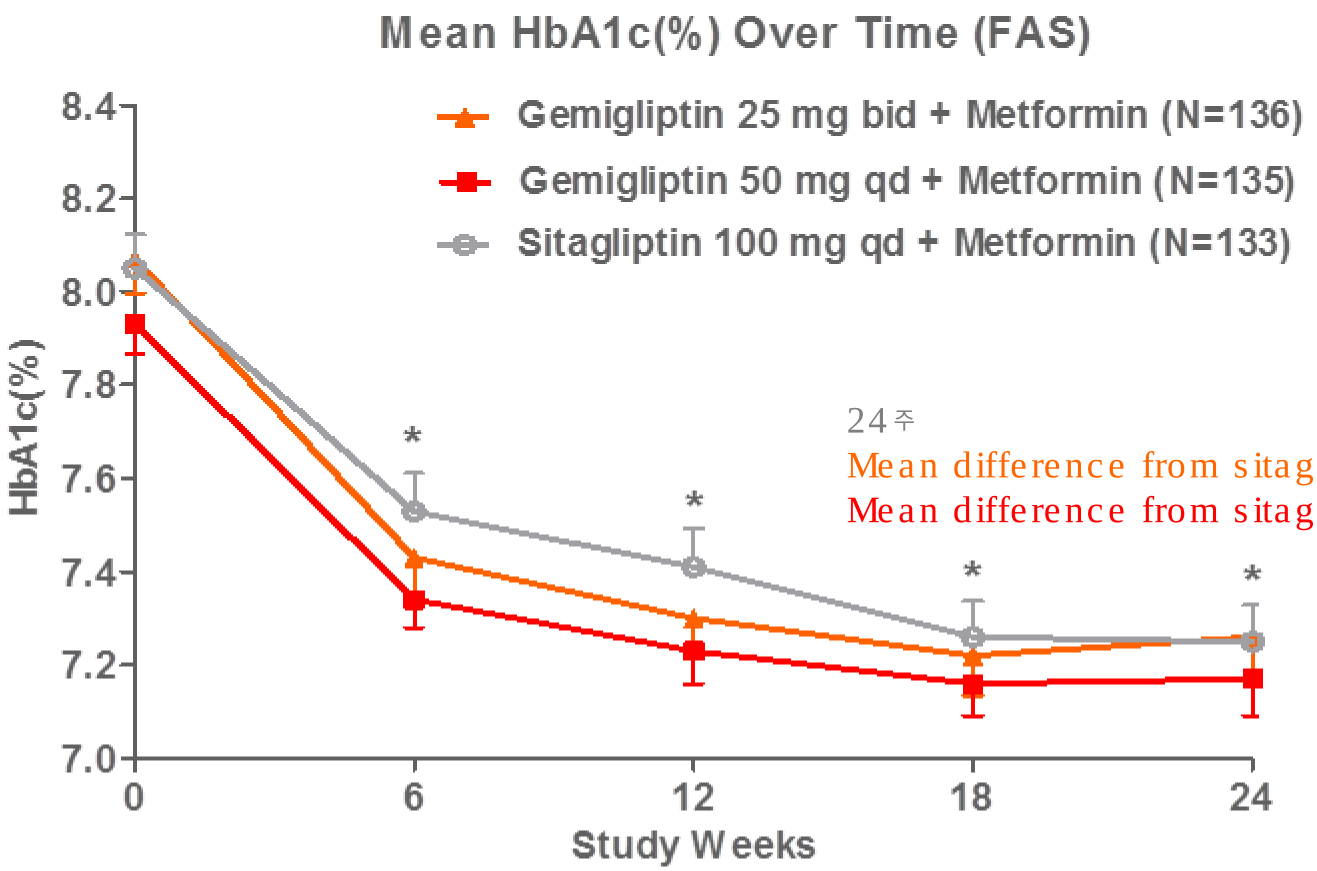
Efficacy | HbA1c

제미글립틴의 임상적 유효성 이 시타글립틴 대비 비열등함을 입증함



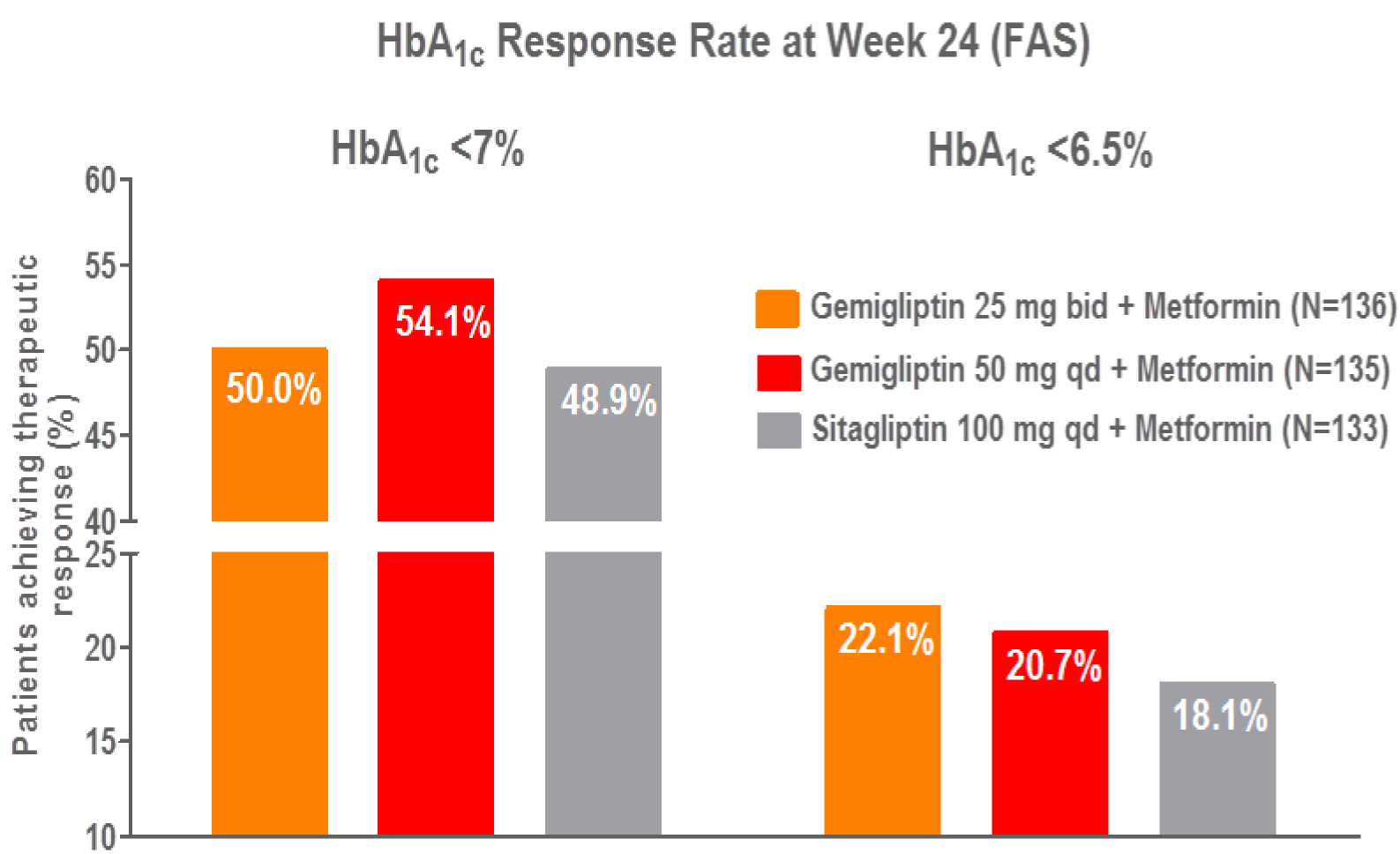
24주
Mean difference from sitagliptin : - 0.011% (- 0.181, 0.16)
Mean difference from sitagliptin : 0.004% (- 0.15, 0.157)

* P<0.0001 vs. baseline

제미글립틴군과 시타글립틴군간의 보정된 평균의 차이 : 50mg qd군은 0.004% [90% CI -0.15 to 0.157]
25mg bid군은 -0.011% [90% CI -0.181 to 0.16]
모든 제미글립틴군에서 양측 90% 신뢰구간의 상한치가 0.4보다 작아 Sitagliptin 대비 비열등성을 성공적으로 입증.

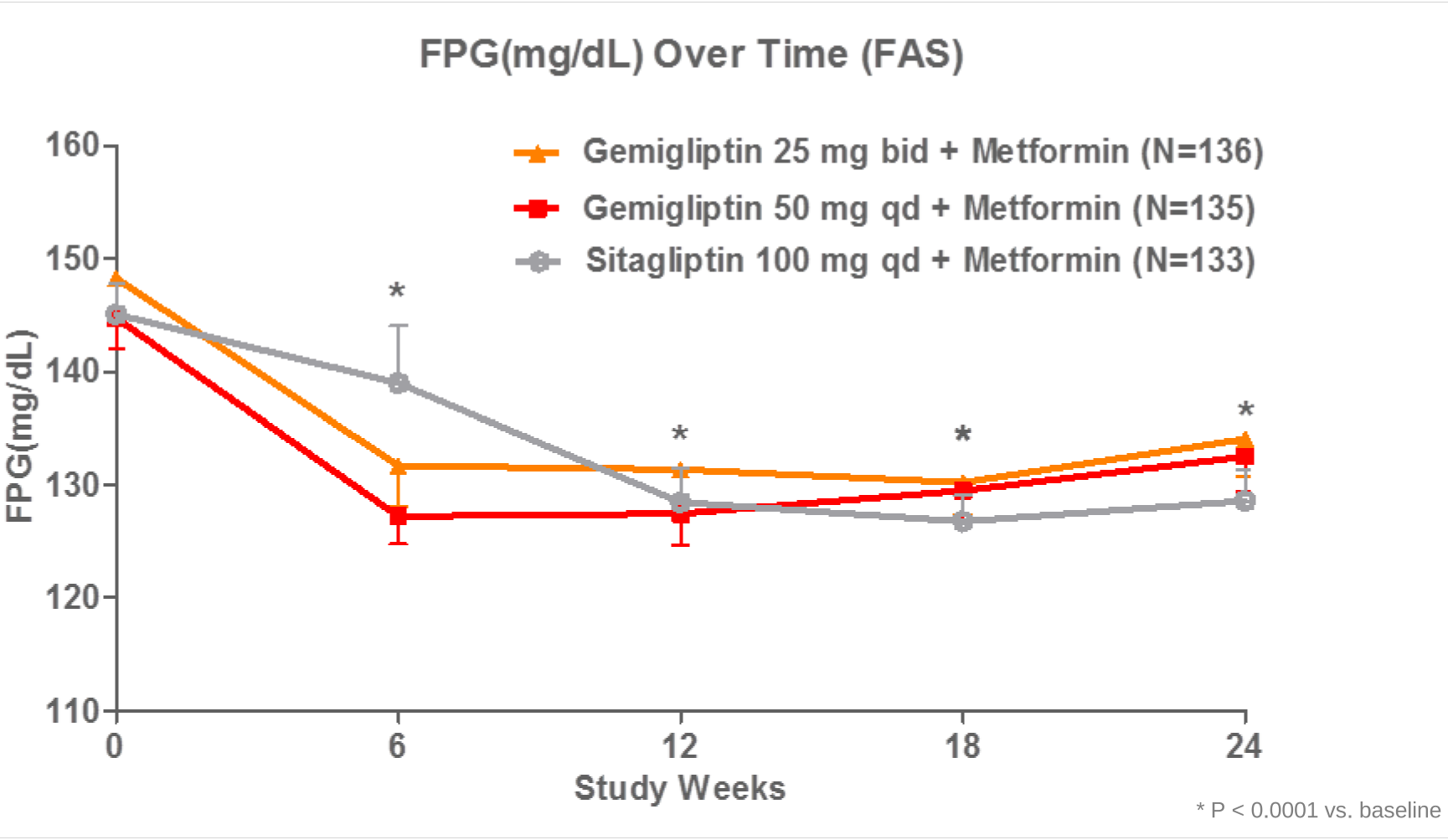
Efficacy | Response Rate

제미글립틴 50mg qd 에서 목표혈당 도달률 이 우수 함 .



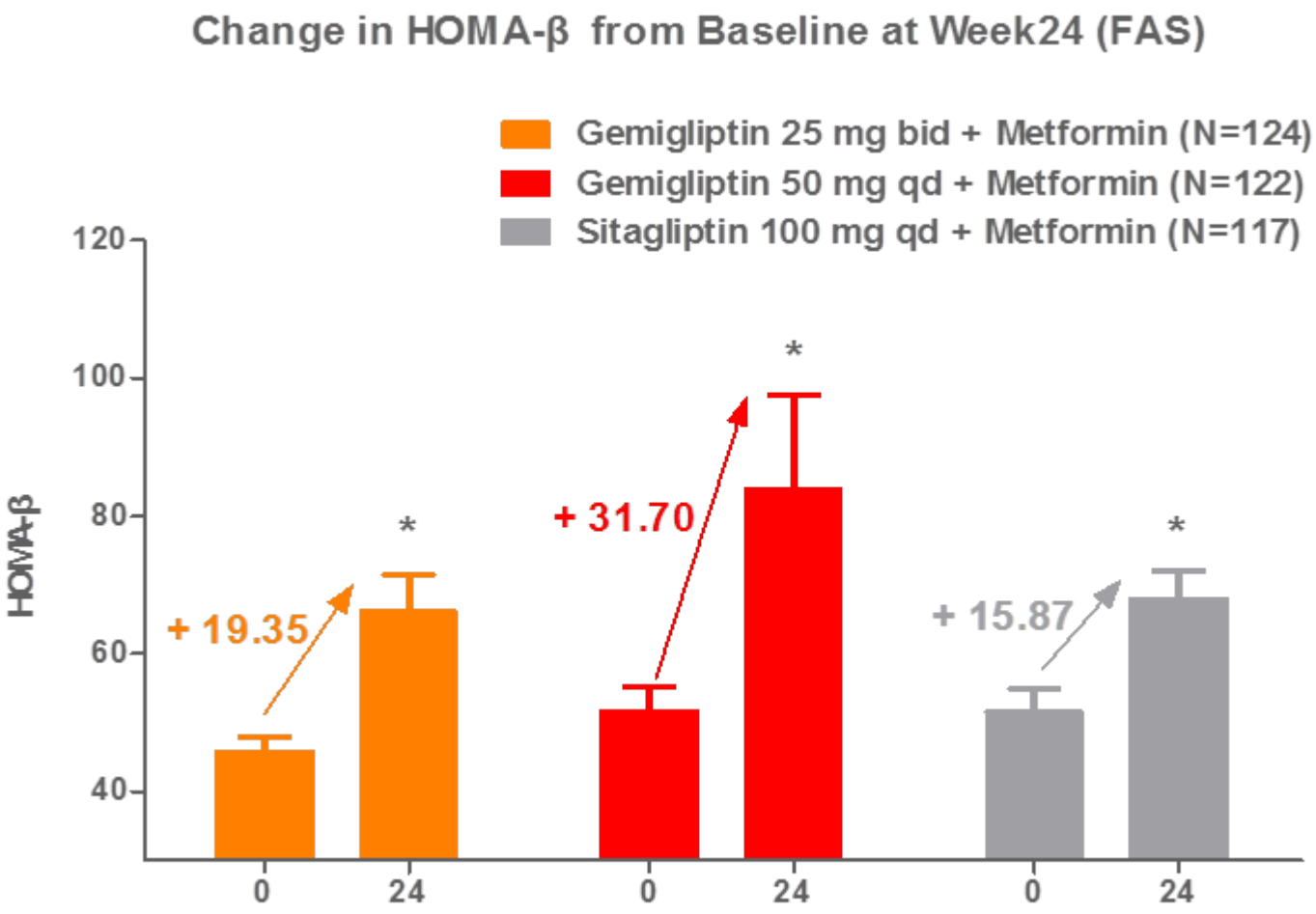
Efficacy | FPG

세군 모두 기저치 대비 FPG를 유의하게 감소 시킴 .



Efficacy | HOMA- β

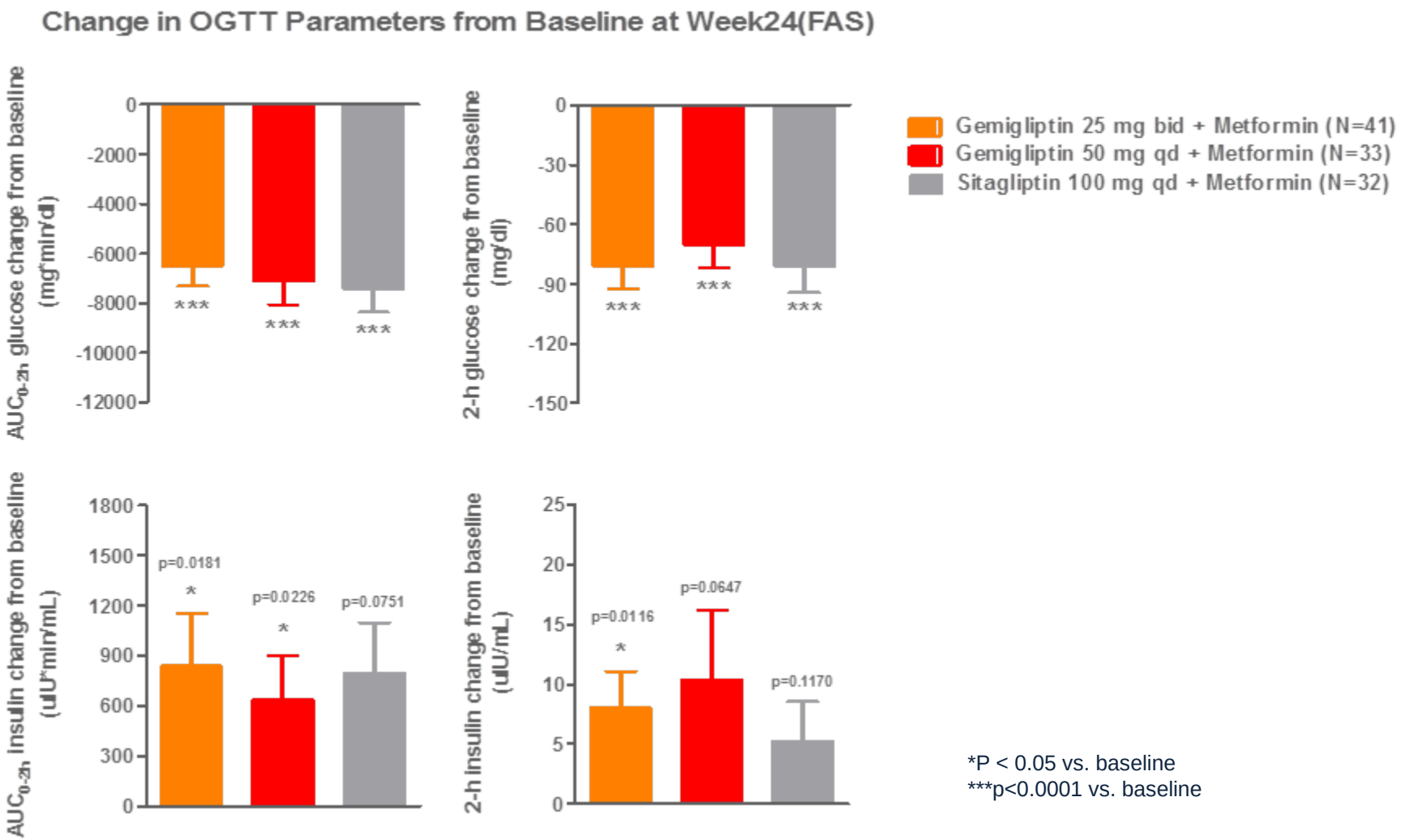
□ □ □ □ □ 50mg qd□ □ HOMA- β□ □ □ □ □ □ □.



* P < 0.0001 vs. baseline

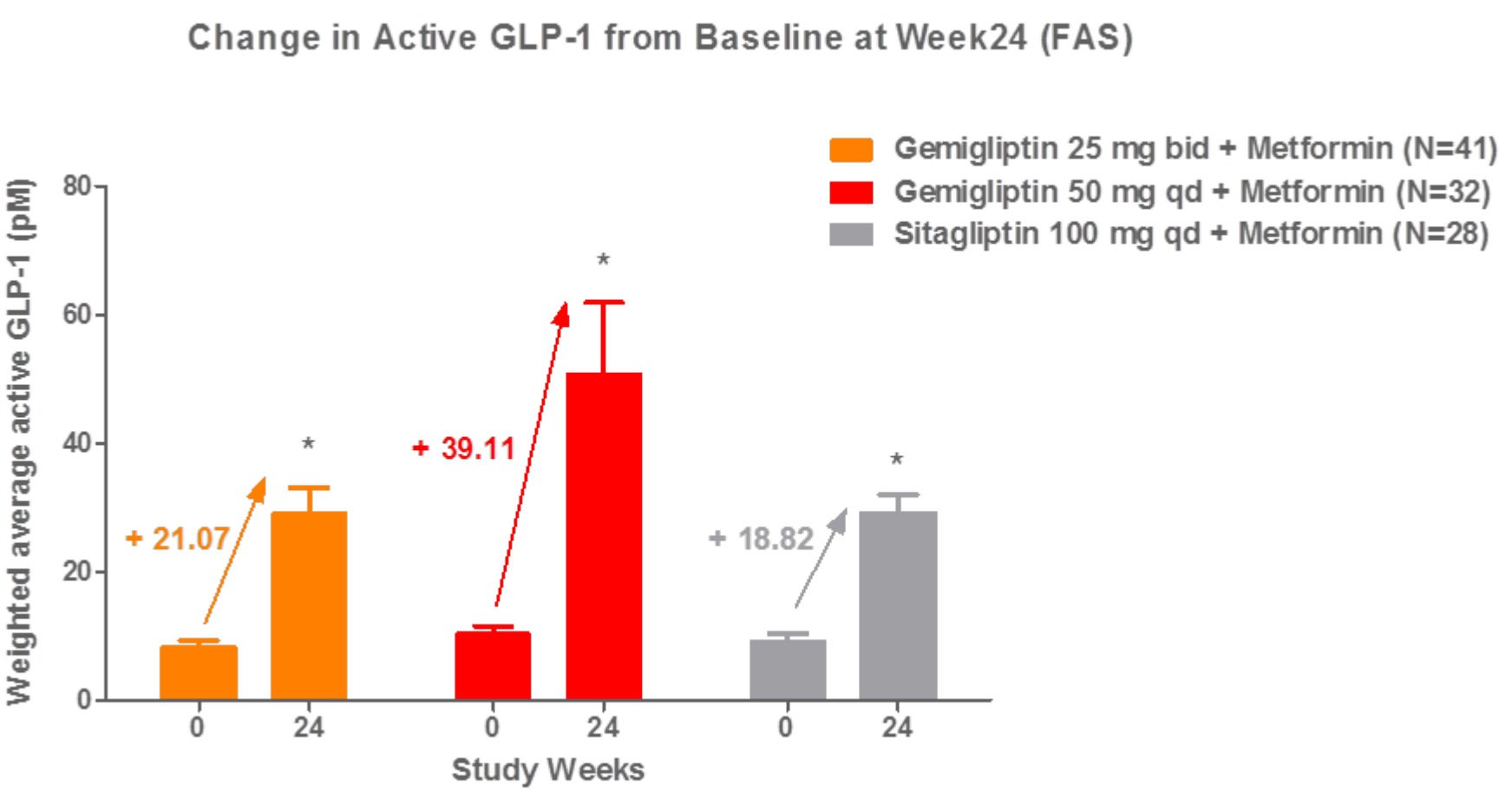
Efficacy | Postprandial Glucose, Insulin

제미글립틴은 □□ □□□ □□□ □□□ □□ .



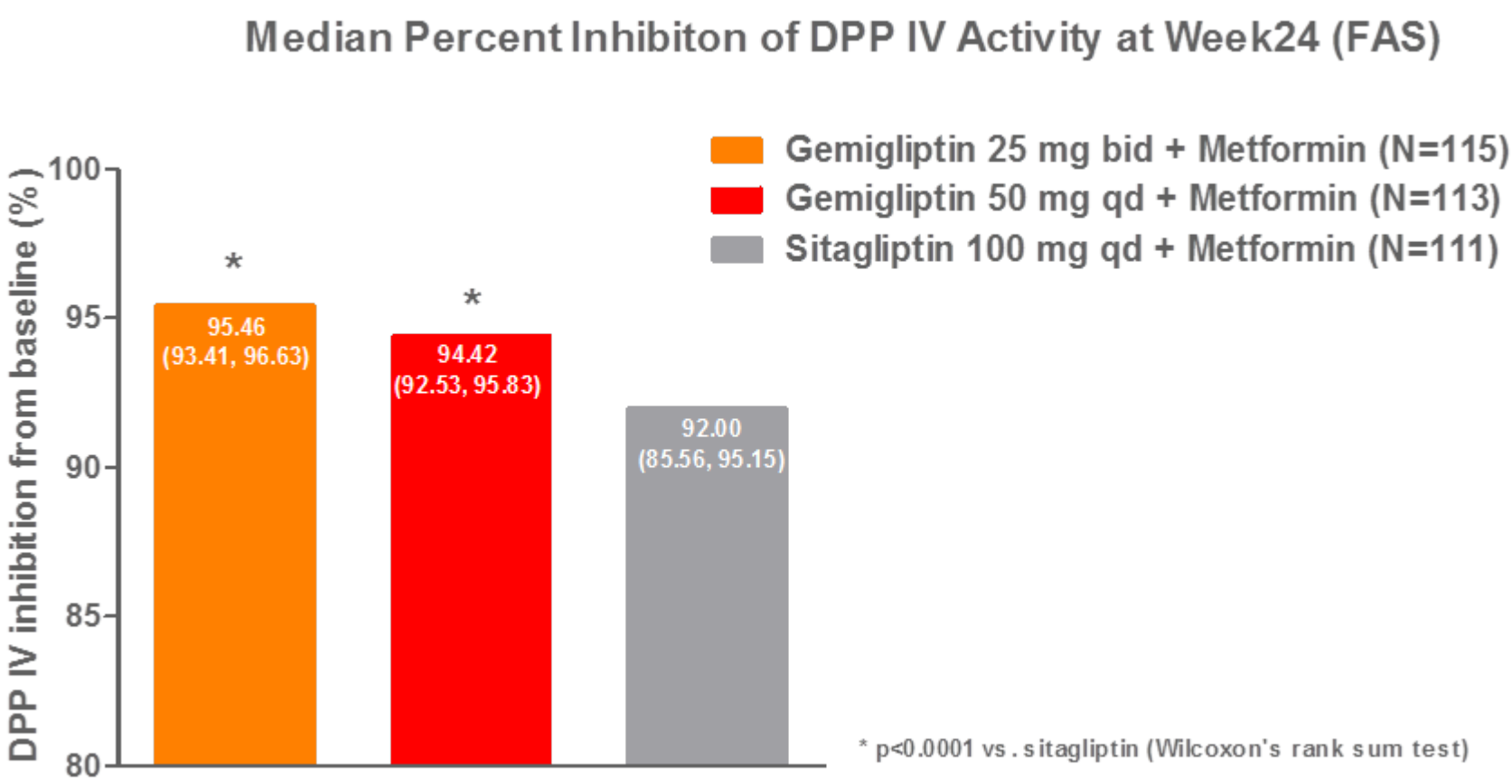
Efficacy | Active GLP- 1

제미글립틴 50mg qd □□ active GLP- 1 □□□ □ □□□.



Efficacy | DPP- IV Inhibition

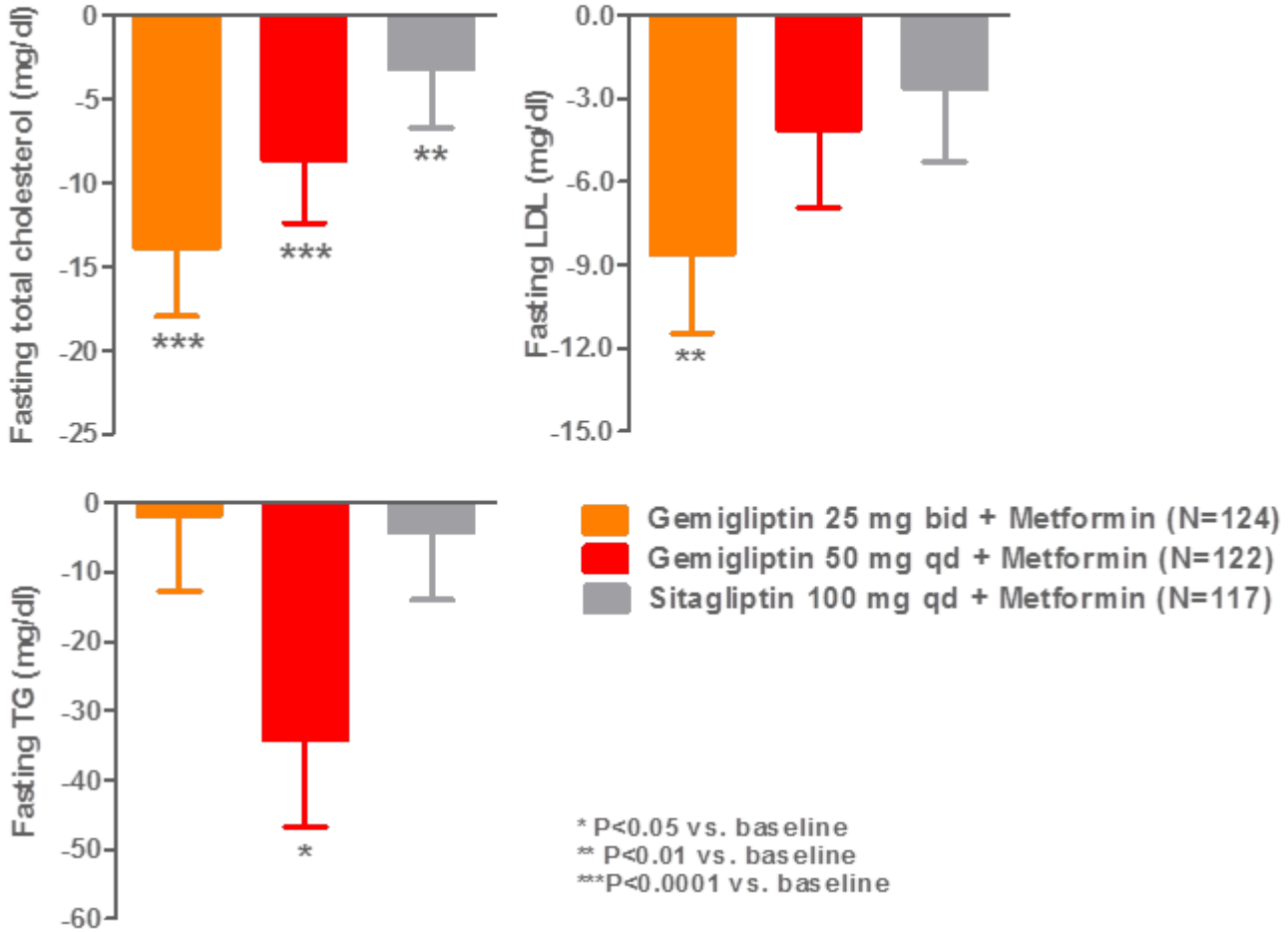
제미글립틴은 □ □ □ □ □ □ □ □ □ □ □ □ □ □ DPP IV □ □ □ □ □ □



✓ Median(Q1,Q3) : (Q1,Q3) is interquartile range, Q1=first quartile, Q3=third quartile

Efficacy | Lipid Profile

세군 □ □ □ □ Total cholestrol□ □ □ □ □ □ □ □ □ □ .



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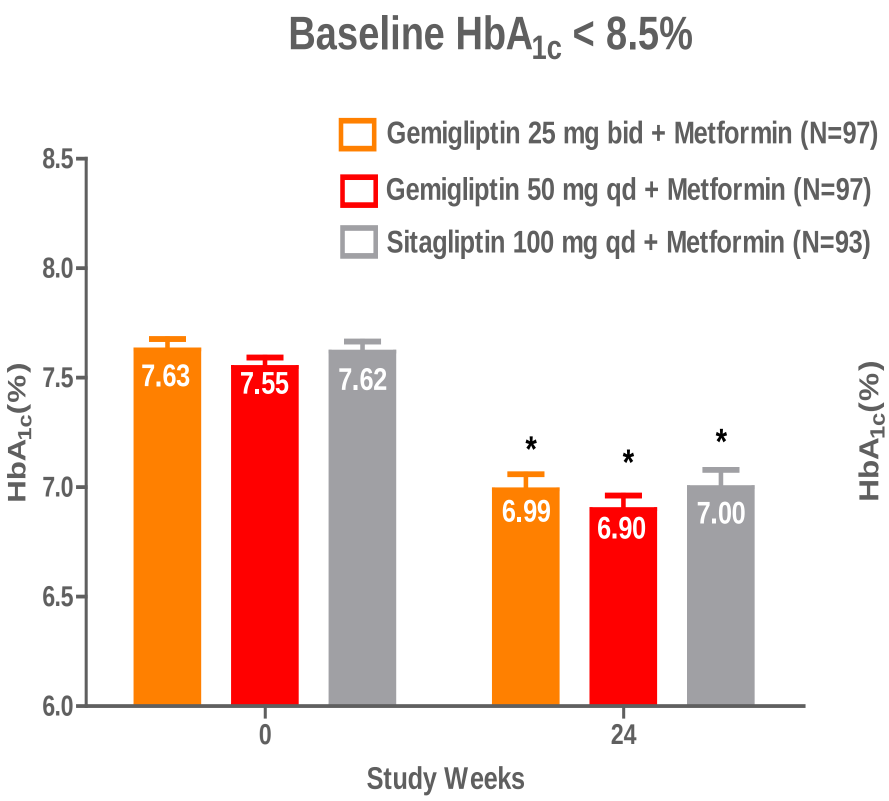
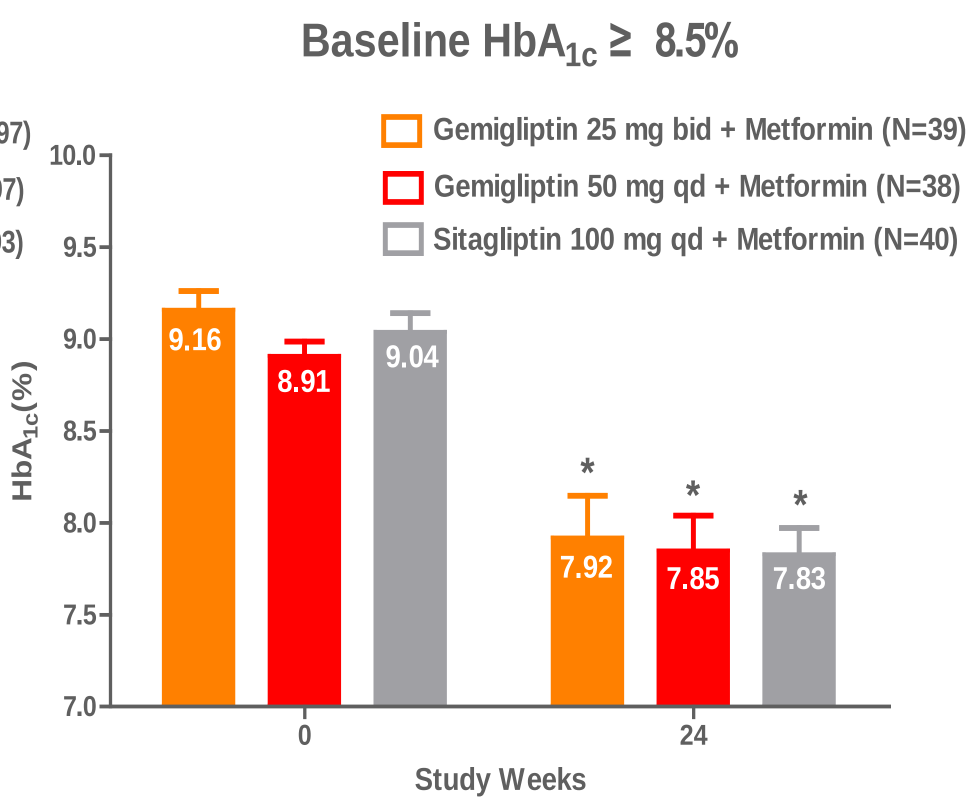
Subgroup | Baseline HbA_{1C}

세군 모두에서 기저 HbA_{1C}가 높은 경우 더 높은 HbA_{1C} 강하효과 를 보임 .

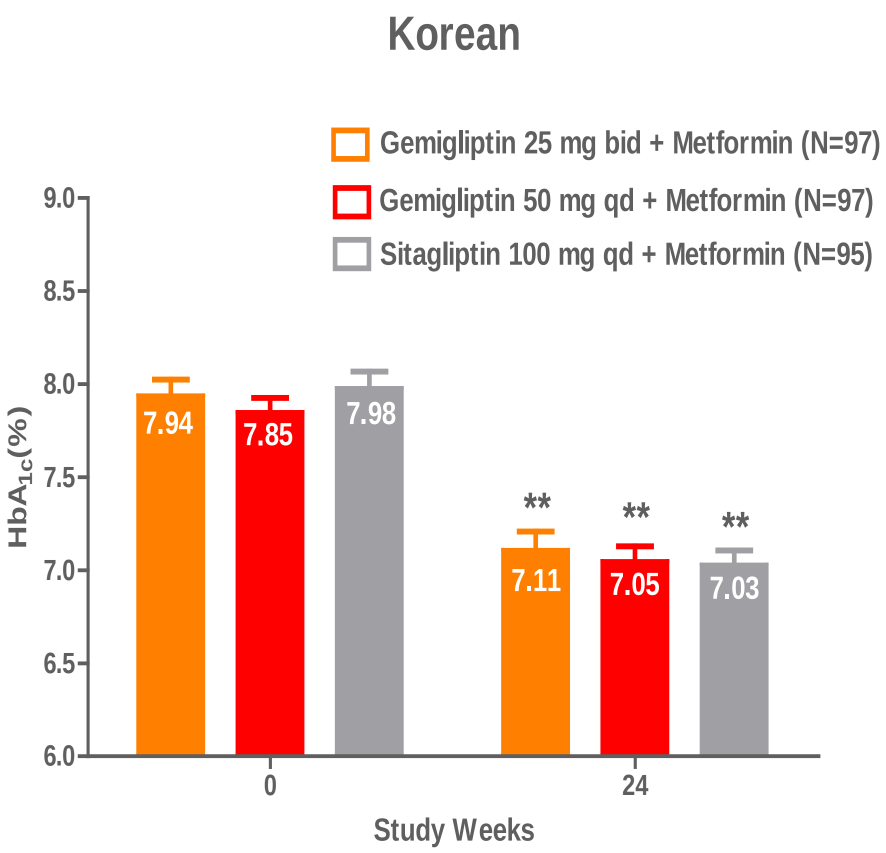


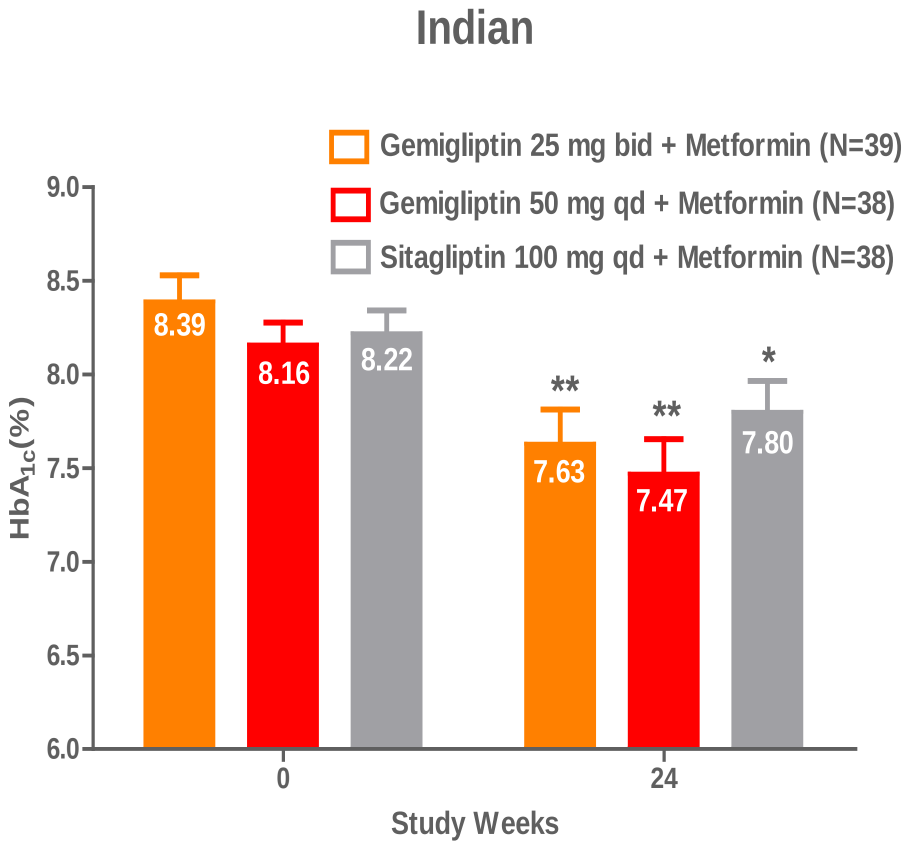


* P < 0.0001 vs. baseline

Subgroup | Country

세군 모두에서 한국과 인도 모두 유의한 효과 를 보임





* p < 0.0043 vs. baseline
** p < 0.0001 vs. baseline

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Safety | Summary of AEs

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Adverse Events Summary	Gemigliptin 25mg bid	Gemigliptin 50mg qd	Sitagliptin 100mg qd
Number of patients	141 (100)	140 (100)	140 (100)
Number of patients experienced an AE	69 (48.94)	63 (45)	58 (41.43)
Number of patients dropped out due to AE	0 (0)	0 (0)	0 (0)
Number of patients experienced a SAE	4 (2.84)	5 (3.57)	8 (5.71)
Number of AEs	160 (100)	134 (100)	105 (100)
Number of SAEs	4 (2.5)	5 (3.73)	9 (8.57)

Safety | Most common AEs (≥2.5%)

Preferred Term	Gemigliptin 25mg bid (N=141)	Gemigliptin 50mg qd (N=140)	Sitagliptin 100mg qd (N=140)
No. of patients with AE	69	63	58
Total No. of AEs	160 (100)	134 (100)	105 (100)
Constipation	3 (1.88)	1 (0.75)	3 (2.86)
Dyspepsia	2 (1.25)	2 (1.49)	3 (2.86)
Pyrexia	6 (3.75)	3 (2.24)	3 (2.86)
Nasopharyngitis	13 (8.13)	9 (6.72)	4 (3.81)
Upper respiratory tract infection	7 (4.38)	8 (5.97)	7 (6.67)
ALT increased	4 (2.5)	0 (0.00)	0 (0.00)
Lipase increased	7 (4.38)	6 (4.48)	4 (3.81)
Arthralgia	2 (1.25)	2 (1.49)	4 (3.81)
Back pain	4 (2.5)	3 (2.24)	0 (0.00)
Urticaria	4 (2.5)	0 (0.00)	0 (0.00)

Safety | ADRs 1/2

System Organ Class	Preferred Term	Gemigliptin 25mg bid (N=141)	Gemigliptin 50mg qd (N=140)	Sitagliptin 100mg qd (N=140)
Investigations		5 (3.55)	6 (4.29)	1 (0.71)
Investigations	Alanine aminotransferase abnormal	0 (0.00)	1 (0.71)	0 (0.00)
Investigations	Alanine aminotransferase increased	1 (0.71)	0 (0.00)	0 (0.00)
Investigations	Blood amylase increased	0 (0.00)	2 (1.43)	1 (0.71)
Investigations	Blood creatine phosphokinase increased	0 (0.00)	1 (0.71)	0 (0.00)
Investigations	Hepatic enzyme increased	1 (0.71)	0 (0.00)	0 (0.00)
Investigations	Lipase increased	4 (2.84)	3 (2.14)	1 (0.71)
Investigations	Weight decreased	0 (0.00)	1 (0.71)	0 (0.00)
Respiratory, thoracic and mediastinal disorders		1 (0.71)	0 (0.00)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (0.71)	0 (0.00)	0 (0.00)
Skin and subcutaneous tissue disorders		2 (1.42)	0 (0.00)	1 (0.71)
Skin and subcutaneous tissue disorders	Alopecia	0 (0.00)	0 (0.00)	1 (0.71)
Skin and subcutaneous tissue disorders	Photosensitivity reaction	1 (0.71)	0 (0.00)	0 (0.00)
Skin and subcutaneous tissue disorders	Pruritus	1 (0.71)	0 (0.00)	0 (0.00)
Skin and subcutaneous tissue disorders	Pruritus generalised	1 (0.71)	0 (0.00)	0 (0.00)
Skin and subcutaneous tissue disorders	Urticaria	1 (0.71)	0 (0.00)	0 (0.00)

Safety | ADRs 2/2

System Organ Class	Preferred Term	Gemigliptin 25mg bid (N=141)	Gemigliptin 50mg qd (N=140)	Sitagliptin 100mg qd (N=140)
Gastrointestinal disorders		1 (0.71)	2 (1.43)	2 (1.43)
Gastrointestinal disorders	Abdominal pain	0 (0.00)	0 (0.00)	1 (0.71)
Gastrointestinal disorders	Constipation	0 (0.00)	0 (0.00)	1 (0.71)
Gastrointestinal disorders	Dyspepsia	0 (0.00)	1 (0.71)	1 (0.71)
Gastrointestinal disorders	Gastrointestinal disorder	1 (0.71)	0 (0.00)	0 (0.00)
Gastrointestinal disorders	Nausea	0 (0.00)	1 (0.71)	0 (0.00)
General disorders and administration site conditions		1 (0.71)	0 (0.00)	0 (0.00)
General disorders and administration site conditions	Swelling	1 (0.71)	0 (0.00)	0 (0.00)
Infections and infestations		2 (1.42)	2 (1.43)	2 (1.43)
Infections and infestations	Asymptomatic bacteriuria	2 (1.42)	1 (0.71)	2 (1.43)
Infections and infestations	Nasopharyngitis	0 (0.00)	1 (0.71)	0 (0.00)
Metabolism and nutrition disorders		0 (0.00)	1 (0.71)	2 (1.43)
Metabolism and nutrition disorders	Hypoglycaemia	0 (0.00)	1 (0.71)	2 (1.43)
Nervous system disorders		0 (0.00)	1 (0.71)	1 (0.71)
Nervous system disorders	Dizziness	0 (0.00)	1 (0.71)	0 (0.00)
Nervous system disorders	Headache	0 (0.00)	0 (0.00)	1 (0.71)
Psychiatric disorders		0 (0.00)	1 (0.71)	0 (0.00)
Psychiatric disorders	Insomnia	0 (0.00)	1 (0.71)	0 (0.00)

Safety | Others

No clinically meaningful abnormalities were found in the laboratory tests, urinalysis, ECG, or vital signs.

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Conclusion

유효성 결과

1. 세군 모두 기저치 대비 HbA1C & FPG를 유의하게 감소시킴 .
2. □□□□□ 50mg □□ □□□□ □□□□ □□ □□□.
3. □□□□□ 50mg □□ HOMA-β & active GLP-1 □□□□ □□ □□□.
4. 제미글립틴은 기저 및 시타글립틴 대비 DPP Ⅳ를 유의하게 저해함 .

안정성 결과

□□□□□□ □□□ □□□□ □□□, □□□□□□ □□□ □□□□ □□□□ □□.

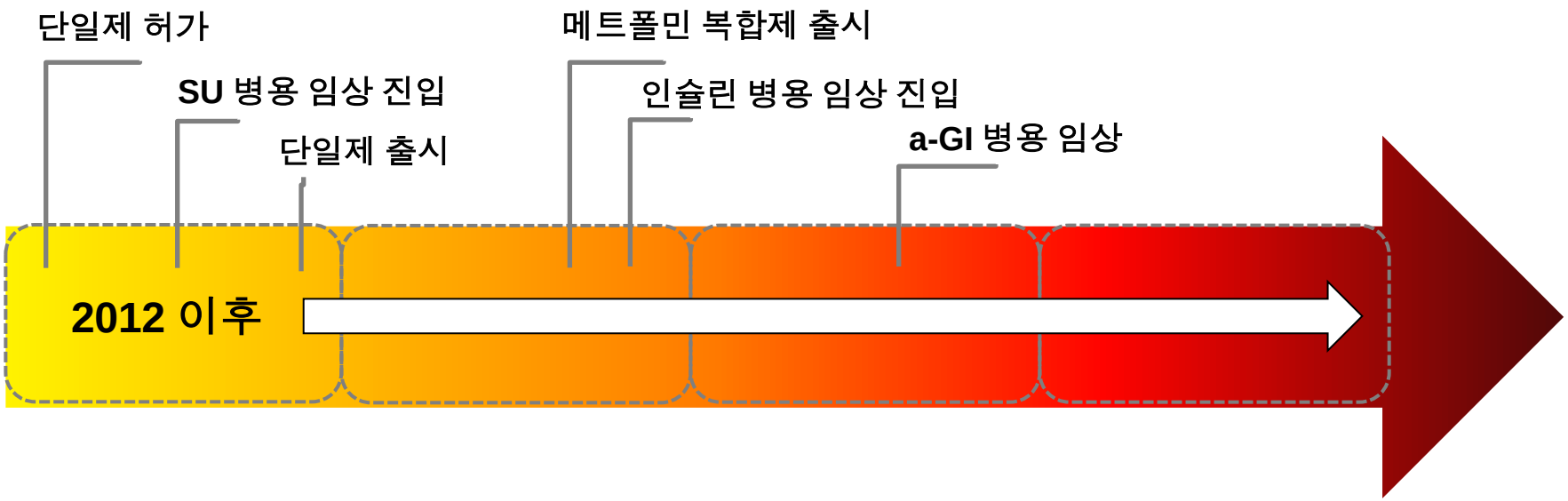
Conclusion

유효성 결과

1. Monotherapy, metformin에 add 한 연구에서 혈당강하효과가 우수함
2. □□□□□ 50mg □□ □□□□ □□□□ □□ □□□.
3. □□□□□ 50mg □□ HOMA-β &active GLP-1 □□□□ □□ □□□.
4. 제미글립틴은 기저 및 시타글립틴 대비 DPP Ⅳ를 유의하게 저해함 .

안정성 결과

□□□□□□ □□□ □□□□ □□□, □□□□□□ □□□ □□□□ □□□□ □□.


단일제 허가
SU 병용 임상 진입
단일제 출시
메트폴민 복합제 출시
인슐린 병용 임상 진입
a-GI 병용 임상
2012 이후


Thank you for your attention!!!