

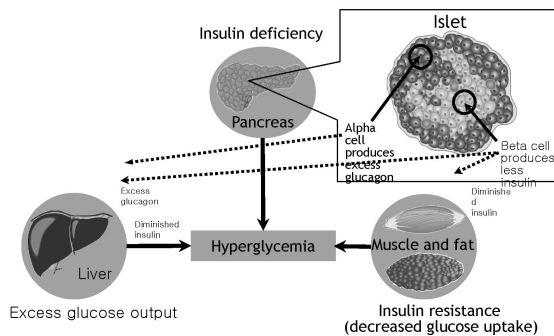


2012 대한임상건강증진학회 춘계 통합학술대회 / 심포지엄

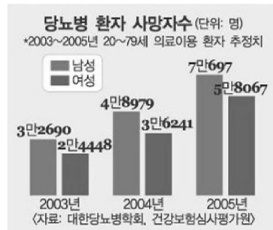
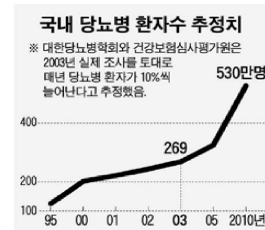
일차진료에서 당뇨병치료 및 새로운 약제 소개

분당제생병원
박영규

PATHOPHYSIOLOGY



etiology



etiology

Table 1. Diabetes Prevalence in Korea according to Various Surveys

Data source	Year	Age distribution	Methods of diagnosis	prevalence
Rural ^{ref5}	1971	> 30	UG+50g OGTT	1.5%
Rural ^{ref6}	1993	> 30	75g OGTT	6.3%
Specific employee ^{ref10}	1992	26-59	FBG	3.03%
	2000			6.29%
Rural ^{ref9}	1997	≥30	75g OGTT	6.9%
	2003			11.7%
National health insurance ^{ref8}	2003	20-79	FBG/PP2hr BG diabetes code Hx of DM med	7.7%
	1998			11.1%
	2001			8.9%
	2005			9.1%
	2007			9.1%

Epidemiology and Current Status of Diabetes in Korea Hanyang Medical Reviews Vol. 29 No. 2, 2009. Sin Gon Kim, M.D., Ph.D., Dong Seop Choi, M.D., Ph.D. Department of Internal Medicine, School of Medicine, Korea University, Seoul, Korea

etiology

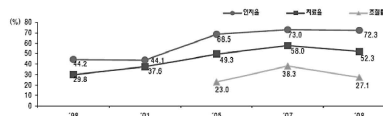


Table 3. Trends in the Awareness, Treatment, and Control of Diabetes Mellitus in Adults (more than 30 years) in the Korea

	NHANES 1998	NHANES 2001	NHANES 2005	NHANES 2007
Awareness	44.1%	44.2%	68.5%	72.2%
Treatment	29.7%	37.7%	49.2%	57.4%
Control			22.9%	37.5%

Screening tests

◎ 권고안 (2012. 대한당뇨병학회)

- 1. 당뇨병의 선별검사는 **공복혈당**, **경구당부하검사** 혹은 **당화혈색소**로 한다.
- 2. 선별검사는 **40세 이상 성인**이거나 **위험인자가 있는 30세 이상 성인**에서 매년 시행하는 것이 좋다.
- 3. 공복혈당장애 혹은 당화혈색소 수치가 아래에 해당 하는 경우 추가 검사를 시행한다.
 - 1단계 : 공복혈당 100-109 mg/dL 또는 HbA1c 5.7-6.0% 인 고위험군은 매년 공복혈당 및 당화혈색소 측정
 - 2단계 : 공복혈당 110-125 mg/dL 또는 HbA1c 6.1-6.4% 의 경우 경구당부하검사 시행

Screening tests

표 1. 제2형 당뇨병의 위험인자

- ▶ 과체중 (체질량지수 23 kg/m² 이상)
- ▶ 직계 가족 (부모, 형제지매)에 당뇨병이 있는 경우
- ▶ 공복혈당장애나 내당능장애의 과거력
- ▶ 임신성 당뇨병이나 4 kg 이상의 거대아 출산력
- ▶ 고혈압 (140/90 mm Hg 이상, 또는 약제 복용)
- ▶ HDL 콜레스테롤 35 mg/dL 미만 혹은 중성지방 250 mg/dL 이상
- ▶ 인슐린저항성 (다낭난소증후군, 흑색기저세포종 등)
- ▶ 심혈관질환 (뇌졸중, 관상동맥질환 등)

Diagnostic criteria(2012)

◎ 권고안 (2012. 대한당뇨병학회)

- 1. 정상혈당: 최소 8시간 이상 음식을 섭취하지 않은 상태에서 FPG < 100 mg/dL, 75 g 경구당부하 2시간 후 혈장 혈당 < 140 mg/dL
- 2. 공복혈당장애: FPG 100-125 mg/dL
- 3. 내당능장애: 75g OGTT 2시간 후 혈장 혈당 140-199 mg/dL
- 4. 다음 중 한 항목에 해당하면 **당뇨병**으로 진단한다.
 - 4-1. FPG ≥ 126 mg/dL: 이 기준은 명백한 고혈당이 아니라면 다른 날에 검사를 반복하여 확인해야 한다.
 - 4-2. 당뇨병의 전형적인 증상 (다뇨, 다음, 설명되지 않는 체중감소) & 임의 혈장 혈당 ≥ 200 mg/dL
 - 4-3. 75 g 경구당부하검사 후 2시간 혈장 혈당 ≥ 200 mg/dL
 - 4-4. HbA1c ≥ 6.5%
- 5. 당화혈색소 5.7-6.4%에 해당하는 경우 당뇨병 고위험군으로 진단한다.

Diagnostic criteria(2012)

표 1. 경구당부하검사 방법

1. 검사 전 적어도 3일 동안 평상시의 활동을 유지하고 하루 150 g 이상의 탄수화물을 섭취한다.
2. 검사 전날 밤부터 10시간 내지 14시간 금식 후 공복 혈당 측정을 위한 채혈을 한다.
3. 250-300 mL의 물에 희석한 우수 포도당 75 g이나 150 mL의 상용화된 포도당 용액을 5분 이내에 마신다.
4. 포도당을 마신 2시간 후에 당부하 후 혈장 혈당 측정을 위한 채혈을 한다 (포도당 용액을 마시기 시작한 시간을 0분으로 한다).
5. 필요한 경우 당부하 후 30분, 60분, 90분 혈장 혈당을 측정할 수 있다.

Diagnostic criteria(2012)

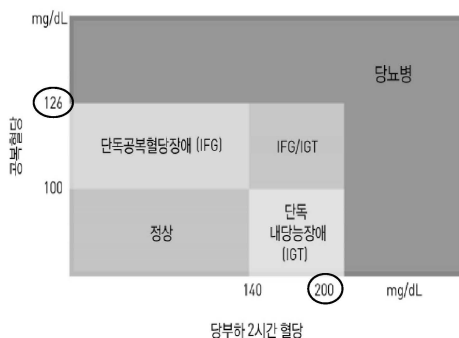
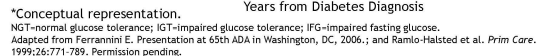


Table 7—Components of the comprehensive diabetes evaluation

- Medical history
 - Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
 - Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
 - Diabetes education history
 - Review of previous treatment regimens and response to therapy (A1C records)
 - Current treatment of diabetes, including medications and medication adherence, meal plan, physical activity patterns, and readiness for behavior change
 - Results of glucose monitoring and patient's use of data
 - DKA frequency, severity, and cause
 - Hypoglycemic episodes
 - Any severe hypoglycemia: frequency and cause
 - History of diabetes-related complications
 - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
 - Macrovascular: CHD, cerebrovascular disease, PAD
 - Other: psychosocial problems,* dental disease*
- Physical examination
 - Height, weight, BMI
 - Blood pressure determination, including orthostatic measurements when indicated
 - Fundoscopic examination*
 - Thyroid palpation
 - Skin examination (for acanthosis nigricans and insulin injection sites)
 - Comprehensive foot examination
 - Inspection
 - Palpation of dorsalis pedis and posterior tibial pulses
 - Presence/absence of patellar and Achilles reflexes
 - Determination of proprioception, vibration, and monofilament sensation
- Laboratory evaluation
 - A1C, if results not available within past 2–3 months
 - If not performed/available within past year:
 - Fasting lipid profile, including total, LDL, cholesterol and triglycerides
 - Liver function tests
 - Test for UAC with spot urine albumin-to-creatinine ratio
 - Serum creatinine and calculated GFR
 - Thyroid-stimulating hormone in type 1 diabetes, dyslipidemia, or women over age 50 years
- Referrals
 - Eye care professional for annual dilated eye exam
 - Family planning for women of reproductive age
 - Registered dietitian for MNT
 - DMSE
 - Dentist for comprehensive periodontal examination
 - Mental health professional, if needed

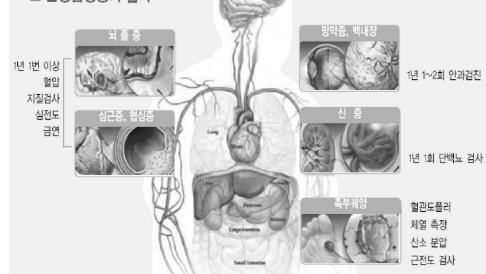
ADA 2012 criteria, VOLUME 35, SUPPLEMENT 1, JANUARY 2012

ADA 2012 criteria, VOLUME 35, SUPPLEMENT 1, JANUARY 2012



Heine RJ et al. Management of hyperglycemia in type 2 diabetes. *BMJ* 333:1200-1204, 2006

- Microvascular complication
 - Retinopathy
 - Nephropathy
 - neuropathy
- Macrovascular complication
 - Atherosclerosis: CVA, ACS...
- Etc...
 - GI/GU dysfunction
 - Infection
 - Skin lesion



최근 임상연구 요약

- 1) 당뇨병 유병 기간이 길고(ACCORD 10년, VADT 11.5년) 혈당 조절이 잘 안되었던 군(ACCORD A1c:8.3%, VADT 9.4%)에서는 뒤늦게 철저한 혈당 조절이 큰 이득이 없음
- 2) 초기부터 철저히 조절하면(UKPDS) 가장 좋은 결과를 얻을 수 있고, 유병기간이 어느 정도 되어도(ADVANCE 8년)비교적 혈당 조절이 되었다면(ADVANCE A1c:7.51%)이후 철저한 조절이 더 좋은 결과를 가져올 수 있다

treatment

goal OF GLYCEMIC CONTROL

◎ 권고안 (2012. 대한당뇨병학회)

- 1. 혈당조절의 기준: 당화혈색소, 식전 & 식후 2시간 혈당
- 2. 제2형 당뇨병에서 **미세혈관합병증 및 대혈관합병증의 발생 및 진행을 감소**시키기 위하여 **적극적인 혈당 조절**이 반드시 필요
- 3. 혈당조절의 목표: 환자의 상황에 따라 다름.
저혈당 없는 상태에서 **당화혈색소 < 6.5%**
- 4. 혈당조절의 목표 설정 시의 개별적 위험요소: 나이, 동반 질환, 당뇨병 합병증 진행 정도, 저혈당, 인지능력의 감소
위험요소가 없는 당뇨병 초기 환자의 경우 집중적인 혈당 조절을 요하나, 위험요소가 높은 환자의 경우에는 혈당조절의 목표를 개별화하고 적극적인 치료로 인한 급격한 혈당변화를 피해야 한다.
- 5. 엄격한 조절: 수술 전후, 심근경색, 임신 및 급성질환 있는 환자
혈당 조절 완화: 심한 저혈당, 짧은 여명기간, 소아 (< 13세), 노인 (> 65세) 및 타 질환이 동반된 환자

ADA 2012 criteria, VOLUME 35, SUPPLEMENT 1, JANUARY 2012

goal OF GLYCEMIC CONTROL

표 1. 미국당뇨병학회 진료지침

	당화혈색소 (%)	공복/식전 혈당 (mg/dL)	식후 2시간 혈당 (mg/dL)
정상영역	≤ 6.0	70-110	90-140
혈당조절목표	≤ 7.0	70-130	90-180

당화혈색소 목표치 개별화의 예

당화혈색소(%)	위험요소
< 6.0	40세 이하, 당뇨병 초기, 합병증 없는 경우
< 6.5	65세 이하, 당뇨병 10년 이하, 합병증이 없는 경우
7.0 -	65세 이상, 당뇨병 10년 이상, 합병증을 동반한 경우

ADA 2012 criteria, VOLUME 35, SUPPLEMENT 1, JANUARY 2012

goal OF GLYCEMIC CONTROL

Table 9—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0%*
Preprandial capillary plasma glucose	70-130 mg/dL* (3.9-7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)
* Goals should be individualized based on*	
○ duration of diabetes	
○ age/life expectancy	
○ comorbid conditions	
○ known CVD or advanced microvascular complications	
○ hypoglycemia unawareness	
○ individual patient considerations	
• More- or less-stringent glycemic goals may be appropriate for individual patients	
• Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals	

ADA 2012 criteria, VOLUME 35, SUPPLEMENT 1, JANUARY 2012

monitoring OF GLYCEMIC CONTROL

◎당화혈색소

- 혈당 조절 상태, 치료 변경 시 치료 적합성 판단
- 3개월마다, 환자 상태에 따라 기간 결정 가능

◎자가혈당 측정

- **공복 & PP2 혈당**(식사개시 후 2시간 쯤)를 포함
- 측정 횟수: 혈당 조절 정도에 따라
 - 1회 이상/일: 영양치료, 운동요법, OHA, type 2 DM insulin 2회 이내/day
 - 3회 이상/일: 다회 insulin Tx
- 환자 스스로 측정하도록 교육, 자가혈당기 오차 교정

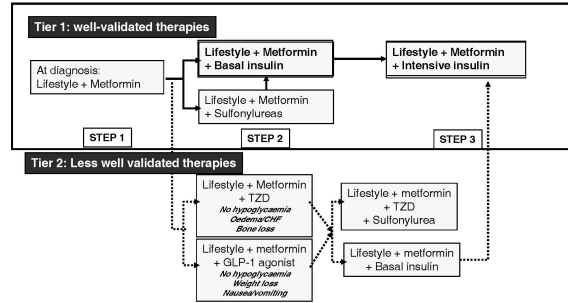
◎Fructosamine, 1,5 AG(anhydroglucitol)



Clinical management of dm

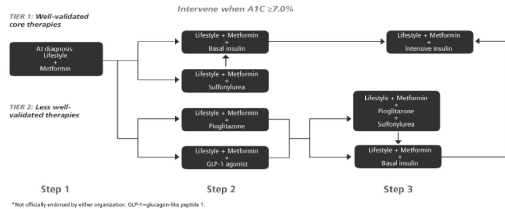
- Life style modification
 - Medical nutritional treatment
 - Exercise
 - OHA
 - Insulin Tx
-
- Evaluation & management of complications
 - Comorbidities

ADA/EASD Consensus Statement* (2009)



Nathan D, et al. Consensus algorithm. Nathan D, et al. Diabetes Care 2009;31:193-203.

DIABETES TREATMENT ALGORITHM



*Not officially endorsed by either organization. GLP-1=glucagon-like peptide 1.

Tier 1 (well-validated core therapies)	Tier 2 (less well-validated therapies)
Step 1: Begin with lifestyle changes, such as diet and exercise, along with metformin at diagnosis Step 2: If step 1 fails, another medication should be added (basal insulin or a sulfonylurea based on A1C level) Step 3: If steps 1 and 2 fail, start or intensify insulin therapy	Step 1: Begin with lifestyle changes, such as diet and exercise, along with metformin at diagnosis Step 2: If step 1 fails, pioglitazone or a GLP-1 agonist may be added based on clinical considerations and patient type. If A1C goal is still not achieved and/or therapy is not tolerated, consider adding a sulfonylurea Step 3: If steps 1 and 2 fail, proceed to step 3 of tier 1

ADA/EASD Consensus Statement* (2009)

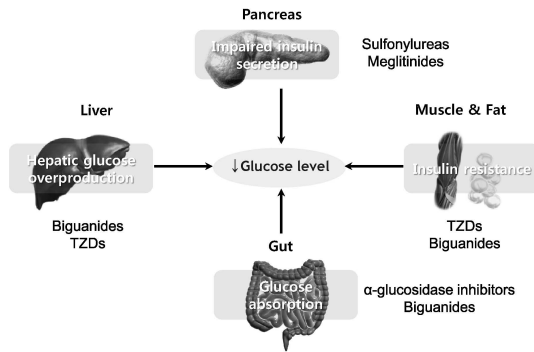
Intervention	Expected Decrease in A1C With Monotherapy (%)	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin	1.5-3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well-validated			
TZDs	0.5-1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5-1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α -Glucosidase inhibitor	0.5-0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5-1.5a	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5-1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5-0.8	Weight neutral	Long-term safety not established, expensive

ORAL HYPOGLYCEMIC AGENTS

Oral hypoglycemic agents

- Insulin secretagogues
 - Sulfonyleurea
 - Meglitinide
- Insulin sensitizer
 - Biguanide
 - Thiazolidinediones
- α -glucosidase inhibitors
- Incretine
 - DPP-IV inhibitors
 - GLP-1 receptor agonist

Major target sites of OHA



OHA (1)

Class	Compound(s)	Mechanism	Action(s)	Advantages	Disadvantages	Cost
Biguanides	Metformin	Activates AMP-kinase	- Hepatic glucose production ↓ - Intestinal glucose absorption ↓ - Insulin action ↑	- No weight gain - No hypoglycemia - Reduction in cardiovascular events and mortality (UKPDS 6)	- Gastrointestinal side effects (diarrhea, abdominal cramping) - Lactic acidosis (rare) - Vitamin B₁₂ deficiency - Contraindications: reduced kidney function	Low
Sulfonyleureas (2nd generation)	Glibenclamide, Glyburide, Glipizide, Glimepiride	Closes K ⁺ channels on β-cell plasma membranes	↑ Insulin secretion	- Generally well tolerated - Reduction in cardiovascular events and mortality (UKPDS 6)	- Relatively glucose-independent stimulation of insulin secretion - Hypoglycemia, including episodes necessitating hospital admission and causing death - Weight gain - May blunt myocardial ischemic preconditioning - Low "durability"	Low
Glucocorticoids	Diamicon, Amaryl, glimepiride	Closes K ⁺ channels on β-cell plasma membranes	Insulin secretion ↑	Accumulated effects around meal ingestion	- Hypoglycemia, weight gain, May blunt myocardial ischemic preconditioning - Dosing frequency	Medium
Novonorm	Fastic					

OHA (2)

Thiazolidinediones (Glucocorticoids)	- Glazionate - Rosiglitazone	- Activates the nuclear transcription factor PPAR-γ - As above	- Peripheral insulin sensitivity ↑ - No hypoglycemia - HDL cholesterol ↑ - Triglycerides ↓	- Weight gain - Edema - Heart failure - Bone fractures - LDL cholesterol ↑ - Weight gain - Edema - Heart failure - Bone fractures - Increased cardiovascular events (mixed evidence) - FDA warnings on cardiovascular safety - Contraindicated in patients with heart disease	High
Actos					
α-glucosidase inhibitors	- Acarbose - Miglitil	Inhibits intestinal α-glucosidase	- Intestinal carbohydrate digestion (and, consequently, absorption) slowed - Non-systemic medication - Preprandial glucose ↓	- Gastrointestinal side effects (gas, flatulence, diarrhea) - Dosing frequency	Medium
Glucobay					
Basen					

OHA (3)

Class	Compound(s)	Mechanism	Action(s)	Advantages	Disadvantages	Cost
GLP-1 receptor agonists (insulin mimetics)	- Exenatide - Liraglutide	Activates GLP-1 receptors (β-cell/endocrine pancreas; brainstem/nervous system)	- Insulin secretion ↑ (glucose-dependent) - Glucagon secretion ↓ (glucose-dependent) - Slow gastric emptying - Satiety ↑	- Weight reduction - Potential for improved β-cell mass/function	- Gastrointestinal side effects (nausea, vomiting, diarrhea) - Cases of acute pancreatitis observed - C-cell hyperplasia/medullary thyroid tumors in animals (liraglutide) - Injectable - Long-term safety unknown	High
DPP-4 inhibitors (insulin enhancers)	- Sitagliptin - Vildagliptin - Saxagliptin - Linagliptin	Inhibits DPP-4 activity, prolongs survival of endogenously released incretin hormones	- Active GLP-1 concentration ↑ - Active GIP concentration ↑ - Insulin secretion ↑ - Glucagon secretion ↓	- No hypoglycemia - Weight "neutrality"	- Occasional reports of urticaria/angioedema - Cases of pancreatitis observed - Long-term safety unknown	High
Bile acid sequestrants	Colofoleum	Bind bile acids/cholesterol	Unknown	- No hypoglycemia - LDL cholesterol ↓	- Constipation - Triglycerides ↑ - May interfere with absorption of other medications	High
Dopamine-2 agonists	Bromocriptine	Activates dopaminergic receptors	- Alters hypothalamic regulation of metabolism - Insulin sensitivity ↑	No hypoglycemia	- Dizziness/syncope - Nausea - Fatigue - Rhinitis - Long-term safety unknown	Medium

제 2형 당뇨병에서 경구용 약제의 선택기준

LFT, serum Cr 측정

Cr > 2.0 mg/dL

Yes

LFT 정상 ; TZD
Repaglinide
LFT 이상 ; Insulin

Cr 1.4-2 mg/dl

Yes

LFT 정상 ; SU, TZD, α-GI
LFT 이상 ; Insulin

Cr < 1.4 mg/dL

Yes

LFT 정상 ; SU, TZD, α-GI
Metformin
LFT 이상 ; Insulin

IN·CRE·TIN

INTESTIN

SECRETION

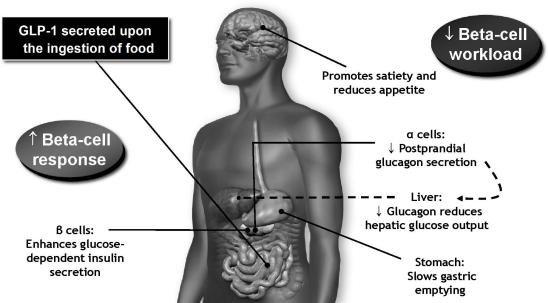
INSULIN



Incretin hormones – GLP-1 and GIP

- Two incretins are primarily responsible for the incretin effect:
 - Glucagon-like peptide 1 (GLP-1)**
 - Synthesized and released: ileum and colon
 - Multiple sites of action: pancreatic β and α cells, GI tracts, CNS and heart
 - Secretion is impaired in T2DM
 - Glucose-dependent insulintropic polypeptide (GIP)**
 - Synthesized and released: duodenum and jejunum
 - Sites of action: predominantly pancreatic β cells, also adipocytes, osteoblasts
 - T2DM: normal levels of GIP or even slightly increased, but its action is minimal

GLP-1 effects in human



Incretin hormones – GLP-1 and GIP

- GLP-1 analogues
 - Mimic the effect of GLP-1 but are resistant to degradation by DPP-4
 - Exenatide (Byetta)**
 - Liraglutide (Victoza)**
- DPP-4 inhibitors
 - Potentiate incretin hormones by inhibiting the enzyme responsible for their degradation
 - Increase the half life of endogenous GLP-1
 - Sitagliptin (Januvia)**
 - Vildagliptin (Galvus)**
 - Saxagliptin (Onglyza)**

OHA (3)

Class	Compound(s)	Mechanism	Action(s)	Advantages	Disadvantages	Cost
GLP-1 receptor agonists (incretin mimetics)	• Exenatide • Liraglutide	Activates GLP-1 receptors (β -cell/endocrine pancreas; brain/stomach/nervous system)	• Stimulates insulin secretion (glucose-dependent) • Glucagon secretion ↓ (glucose-dependent) • Satiety ↑ • Nausea	• Weight reduction • Potential for improved β -cell mass/function	• Gastrointestinal side effects (nausea, vomiting, diarrhea) • Cases of acute pancreatitis observed • C-cell hyperplasia/medullary thyroid cancer in animals (liraglutide) • Injectable • Long-term safety unknown	High
DPP-4 inhibitors (incretin enhancers)	• Sitagliptin • Vildagliptin • Saxagliptin • Liraglutide	Inhibits DPP-4 activity, prolongs survival of endogenously released incretin hormones	• Active GLP-1 concentration ↑ • Active GIP concentration ↑ • Insulin secretion ↑ • Glucagon secretion ↓	• No hypoglycemia • Weight "neutrality"	• Occasional reports of urticaria/angioedema • Cases of pancreatitis observed • Long-term safety unknown	High
Biguanides	• Metformin	Inhibits hepatic glucose production	• Unknown	• No hypoglycemia • LDL cholesterol ↓	• Constipation • Trigonitrides ↑ • May interfere with absorption of other medications	High
Dopamine-2 agonists	• Bromocriptine	Activates dopaminergic receptors	• Alters hypothalamic regulation of metabolism • Insulin sensitivity ↑	No hypoglycemia	• Dizziness/syncope • Nausea • Fatigue • Headache • Long-term safety unknown	Medium

	적용기전과 용법	A1c 감소 (단독요법)	부작용	주의점
Sulfonylurea (gliclazide, glibenclamide, glibenclamide)	체중 증가, 저혈당 위험 증가	1.0~2.0%	저혈당, 체중 증가, 관상동맥 질환, 기원저항	간장애 (정상치의 3배, 신장환 Cr > 2.0 mg/dL)
Biguanide (Metformin)	간 당생성 감소, 인슐린감수성 개선, 식욕과 함께 복통, 소화불량	1.0~2.0%	체중증가와 저혈당 없음, 소화기 장애 (식욕감퇴/오심/구토/설사), 위산증	< GFR 30 mL/min 고령, 간장애, 심부전, 간부전, 방사선요도 조영제를 장기간 투여하는 검사 환자
α -glucosidase inhibitor (acarbose, voglibose, miglitol)	상부위장관에서 다당류 흡수를 억제하여 식후 고혈당 감소, 하루 3회 식전 복용	0.5~0.8%	체중 증가 및 저혈당 없음, 소화 장애	신장환 (Cr > 2.0 mg/dL), 간장애, 염증성 장 질환
Thiazolidinedione (pioglitazone)	근육, 간, 지방의 인슐린감수성 개선	0.5~1.4%	체중 증가, 부종, 혈액소 감소, 골관절염, 심부전	중증 심부전 또는 기원저항 (NYHA 분류 3, 4), 간장애, 종양 신장장애
Meglitinide (repaglinide, nateglinide)	인슐린분비 증가, 식후 고혈당 개선, 하루 3회 식전복용	0.5~1.5%	체중 증가, 저혈당, 변비, 심기도 장애, 부비염	간기능 이상 시 용량조정
DPP-4 inhibitor (sitagliptin, vildagliptin)	Incretin (GLP-1, GIP) 분해 억제, 포도당 의존 인슐린분비, 식후 글루카곤분비 억제, 포도당 의존 인슐린분비, 식후 글루카곤분비 억제, 위배출 억제	0.5~0.8%	체중 증가 및 저혈당 없음	신장환 장기사용 시 안전성 미확보
GLP-1 receptor agonist (exenatide)	인슐린분비 증가, 식후 고혈당 개선, 하루 3회 식전복용	0.5~1.0%	저혈당 위험, 체중 감소, 위장장애	장기사용 시 안전성 미확보

Oral hypoglycemic agents

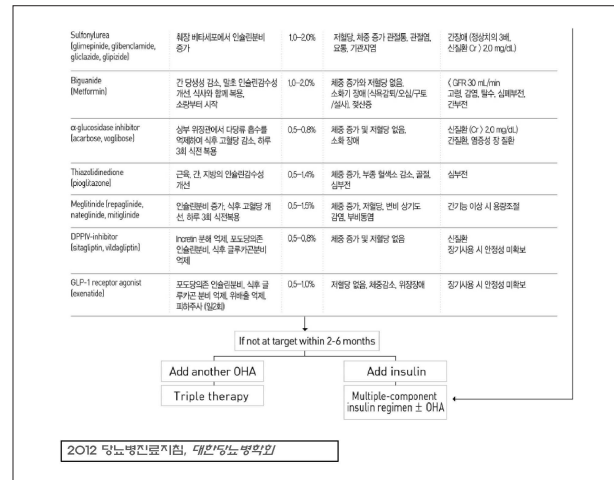
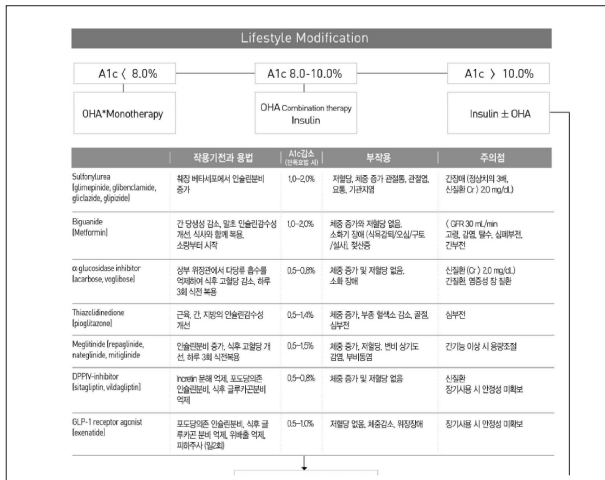
◎ 권고안 (2012. 대한당뇨병학회)

■ 초기 치료 원칙

- 당뇨병 합병증의 예방을 위하여: 초기부터 적극적인 생활습관개선 + 적극적인 약제 투여가 필요
- 혈당조절 목표: **당화혈색소 6.5% 이하** cf ADA: HbA1c < 7%
- 생활습관개선 **2-3개월** 내에 혈당조절의 목표 도달 실패 시 약제투여를 시작
- 심한 고혈당: 생활습관개선 + **약제(metformin)** 진단 시부터 투여
- 약제 선택: 환자의 임상적 특성, 약제의 작용기전 및 효능, 비용 및 안전성을 고려
- OHA 단독요법의 실패: 생활습관의 개선 + 최대 용량으로 **3-6개월** 이내에 당화혈색소의 목표치에 도달하지 못한 경우 → **적극적인 병합요법을 시작!!**

■ 약물 병합 요법

- 단독 요법 실패 시: 용량 증량 or 병합 요법 시작
- 환자의 혈당 조절 상태에 따라 초기 혹은 초기 병합 요법 고려
- 병합 요법 실패 시: **insulin Tx** or **3제 병합 요법** 고려



INSULIN

- ## Indication of Insulin
- Type 1 DM
 - Gestational DM
 - Type 2 DM
 - MNT와 OHA로 혈당 조절이 안 되는 경우
 - 조절 되지 않는 체중 감소 시
 - Type 1 DM과 감별이 되지 않을 시
 - 진행된 만성 신질환이나 간질환 동반 시
 - OHA에 과민 반응 시
 - MI, CVA, 급성 질환 동반 시
 - 공복 혈당이 250 mg/dl 이상 (glucose toxicity)
 - 임신 및 수유
 - 급성대사합병증 (DKA, NKHC)
 - 심한 감염증, 대수술 등 stressful condition

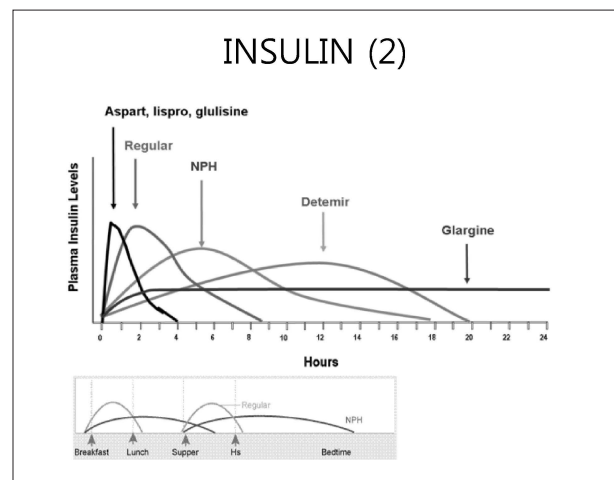
INSULIN (1)

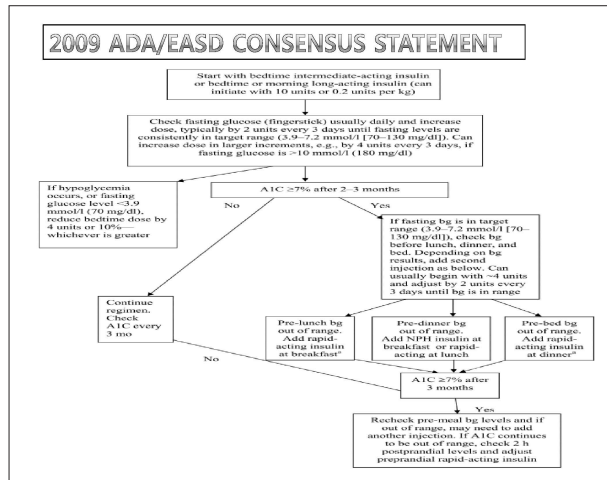
표 1. 국내에서 유통 중인 인슐린의 종류와 인슐린별 특성

인슐린 종류 (상품명)	작용시작	최고작용	작용시간
식사 시 인슐린			
속효성인슐린유도체 (투명) - 초속효성			
인슐린아스파르트 (NovoRapid)	10-15분	1-1.5시간	3-5시간
인슐린리소프로 (Humalog)	10-15분	1-2시간	3.5-4.75시간
인슐린글루린 (Apidra)	10-15분	1-1.5시간	3-5시간
속효성인슐린 (투명)			
휴물린 R	30분	2-3시간	6.5시간
기저 인슐린			
중간형인슐린 (혼탁)			
휴물린 N	1-3시간	5-8시간	18시간까지
장시간형 기저인슐린 유도체 (투명)			
인슐린 디테미어 (Levermir)	90분	없음	24시간까지 (글루린 24시간, 디테미어 16-24시간)
인슐린 글라르진 (Lantus)			
혼합형 인슐린			
혼합형 속효성 인슐린 + NPH (혼탁)			
- 휴물린 30/70			
- 이노벡 30/70			
혼합형 인슐린 유도체 (혼탁)			
- 노보믹스 30, 50			
- 휴미로그 믹스 25, 50			

비이형 또는 펌핑 인슐린 안에 고정 비율의 인슐린이 섞여 있는 형태 (속효성 인슐린 또는 속효성 인슐린 유도체와 중간형 인슐린)

2012 당뇨병 진료지침, 대한당뇨병학회





Insulin TREATMENT

● 리고안 (2012 당뇨병진료지침, *대한당뇨병학회*)

- 경구혈당강하제에 반응이 없을 경우 인슐린 치료방법의 선택
 - 1. 메트포르민과 인슐린의 병합요법: 인슐린 단독 투여보다 혈당조절이 항상, 인슐린 용량의 감량 및 저혈당 위험이 감소 / 체중 증가가 적다
 - 2. A1c < 8.5%: 기저 인슐린요법 고려, 식후 고혈당을 조절위해 OHA or 식전 인슐린요법을 병용
 - 3. A1c > 8.5%: 1일 2-3회의 혼합형 인슐린, 식전 인슐린, 다요소 인슐린요법(multiple-component insulin regimen)을 시행할 수 있다.
 - 4. A1c < 8.5%: 고혈당 증상의 개선 및 신속한 혈당 감소를 위해 혼합형 인슐린, 식전 인슐린 또는 다회인슐린주사법 또는 인슐린 펌프
- 강화인슐린요법
 - 1. OHA와 기저인슐린요법 병용으로 혈당 목표 도달 실패 시: 식전 속효성인슐린유사제 투여 또는 1일 2회 이상의 혼합형인슐린 투여법으로 전환
 - 2. 2회 이상의 혼합형인슐린 투여로 목표 혈당 도달 실패 시: 다요소인슐린요법 또는 인슐린 펌프 치료로 전환하는 것을 고려

Insulin TREATMENT

표 2. 경구혈당강하제 실패 시 고려할 수 있는 인슐린 요법의 비교

	기저 인슐린요법	혼합형 인슐린 유사제 투여법	식전 인슐린요법
장점	저혈당 발생 및 체중 증가 면에서 유리	비교적 높은 당화혈색소 (> 8.5%)를 보이는 경우 효과적	식후 고혈당조절 및 당화혈색소 감소에 효과적
단점	비교적 당화혈색소 (> 8.5%)가 높은 경우 기저 인슐린요법만으로 목표 당화혈색소에 도달하기 어려움	기저 인슐린요법에 비해 저혈당 발생 빈도가 높고 체중 증가가 많으며 인슐린 용량이 많음	기저 인슐린요법에 비해, 잦은 주사의 번거로움, 잦은 혈당 측정, 빈번한 저혈당 발생
기타	식후 혈당을 조절하기 위한 경구혈당강하제 병용 고려	치료 만족도 및 삶의 질 평가에는 이점이 있음	삶의 질 평가에는 이점이 있음

지속적 환자관리

Tests	Interval
SMBG	Individualized frequency
A1c	2-4 times/yr
DM education	Annual
MNT education	Annual
Eye exam., AER	Annual
Foot exam.	1-2 times/yr by Dr., daily by Pt.
Lipid profile	Annual
Influenza/pneumococcal immunizations	Annual
Blood pressure	4 times/yr

TYPE 2 DIABETES-THE WAY
FORWARD

Onglyza® (Saxagliptin) Clinical Data

Bristol-Myers Squibb

OGZ-45L-0312 AstraZeneca

Contents

- The incretin effect and role of incretins in glucose homeostasis
- Saxagliptin clinical profile
 - Efficacy
 - Safety
 - Use in special populations

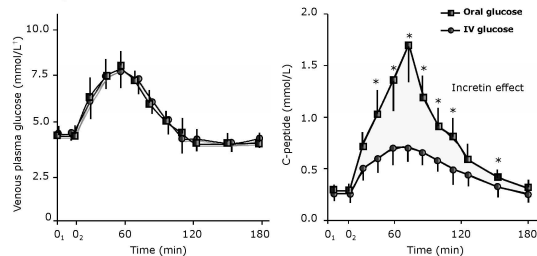
TYPE 2 DIABETES-THE WAY
FORWARD

The incretin effect and role of incretins in glucose homeostasis

Bristol-Myers Squibb AstraZeneca

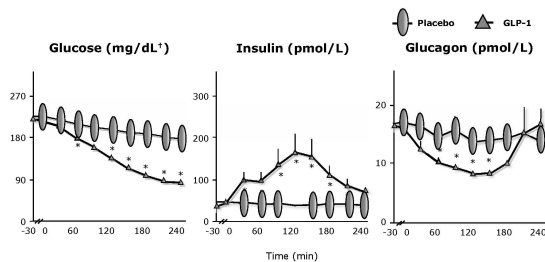
The incretin effect increases β -cell response to oral vs IV glucose

- The incretin effect is demonstrated by increased C-peptide levels after oral glucose load

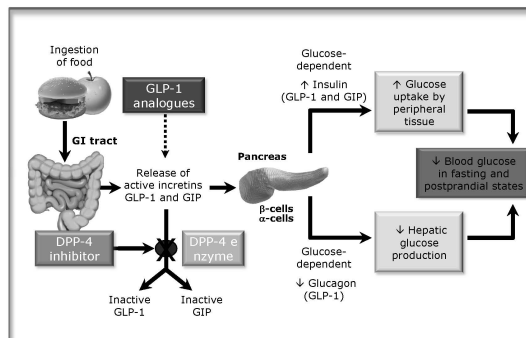


Glucagon-like peptide-1 (GLP-1) increases insulin secretion in a glucose-dependent manner

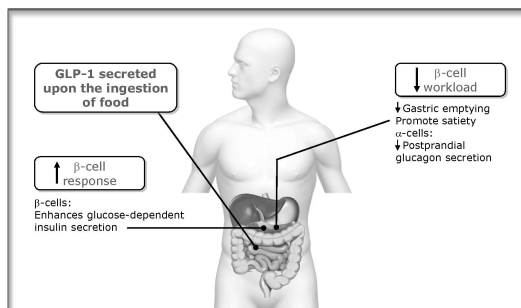
Responses to IV administration of GLP-1 in patients with type 2 diabetes (n=10)



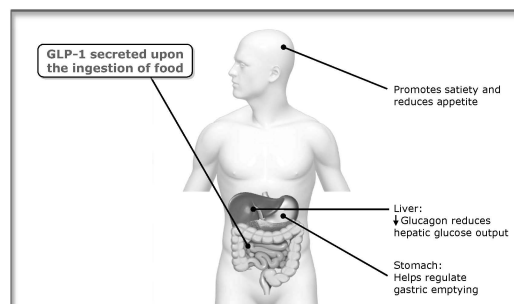
Role of the incretin system in glucose homeostasis



The actions of GLP-1: pancreatic effects



The actions of GLP-1: extrapancreatic effects



GLP-1 actions in peripheral tissues

May act directly on the endocrine pancreas, heart, stomach and brain, whereas the actions on liver and muscle are indirect

Drucker DJ. Cell Metab. 2006;3:153-65.

Saxagliptin clinical development programme

 Bristol-Myers SquibbAstraZeneca

1. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-55. 2. Chacra AR, et al. *Int J Clin Pract*. 2009;63:1395-406. 3. Hollander P, et al. *J Clin Endocrinol Metab*. 2009;94(12):4810-9.

- FPG: Fasting Plasma Glucose; PPG: Postprandial Plasma Glucose

1. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-55. 2. Chacra AR, et al. *Int J Clin Pract*. 2009;63:1395-406. 3. Hollander P, et al. *J Clin Endocrinol Metab*. 2009;94(12):4810-9.

Saxagliptin clinical efficacy

 Bristol-Myers SquibbAstraZeneca 

Short-term Period		SAXA 5 mg (n)	Control (n)	Difference from Control (95% CI)
Monotherapy	(-011)	105	92	-14.7
	(-038)	71	71	-14.0
Add-on therapy	to MET (-014)	187	176	-23.3
	to SU (-040)	252	265	-10.3
	to TZD (-013)	185	181	-14.5
		SAXA 5 mg + MET (n)	MET (n)	
Initial Comb with MET	(-039)	315	320	-12.5

-30 -25 -20 -15 -10 -5 0 5

Difference in FPG (mg/dL)

Comb: Combination; FPG: Fasting plasma glucose; LOCF: Last observation carried forward; MET: Metformin; SAXA: Saxagliptin; SU: Sulphonylureas; TZD: Thiazolidinediones.

1. Saxagliptin, FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting; NDA 22-350. Available at: <http://www.fda.gov/CHRM/S/DOCKETS/ec/09/briefing/2009-4422b1-02-Bristol.pdf>. Accessed: 5 May 2011.

Adjusted mean change from baseline in 120-minute PPG for saxagliptin vs placebo¹

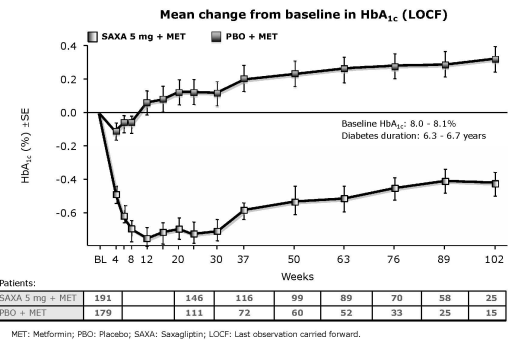
Short-term Period		SAXA 5 mg (n)	Control (n)	Difference from Control (95% CI)
Monotherapy	(-011)	84	71	-37.30
	(-038)	47	47	-30.50
Add-on therapy	to MET (-014)	155	135	-46.30
	to SU (-040)	202	206	-41.70
	to TZD (-013)	134	127	-50.00
		SAXA 5 mg + MET (n)	MET (n)	
Initial Comb with MET	(-039)	146	141	-41.10

-70 -60 -50 -40 -30 -20 -10 0 1
Difference in 120-min PPG Conc (mg/dL)

Comb: Combination; LOCF: Last Observation Carried Forward; MET: Metformin; PPG: Postprandial Plasma Glucose; SAXA: Saxagliptin; SU: Sulphonylureas; TZD: Thiazolidinediones

1. Saxagliptin, FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting: NDA 22-350. Available at: <http://www.fda.gov/OHRMS/DOCKETS/ac/09/briefing/2009-4422b1-02-Bristol.pdf>. Accessed: 5 May 2011.

Saxagliptin provides sustained glycaemic benefits when added to metformin over 102 weeks¹

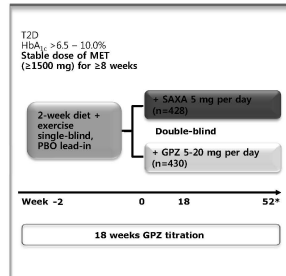


1. Ravichandran S, et al. *Diabetologia* 2009; 52(Suppl. 1):S60 [Abstract 132]. Presented as an Oral Presentation at the European Association for the Study of Diabetes Congress, Vienna, Austria, September 2009 [Presentation no. 132].

Saxagliptin vs SU as add-on to metformin¹

Study design

- 52-week*, randomised, parallel-group, active-controlled, double-blind, international, multicentre trial (N=858)
- Primary endpoint
 - Change from baseline in HbA_{1c} (non-inferiority[†])
- Saxagliptin 5 mg added to metformin vs glipizide 5-20 mg (upitrated as needed)

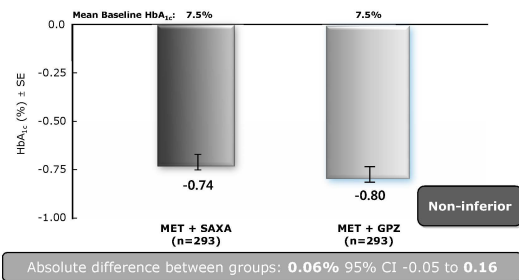


*Followed by another 52-week, long-term period (ongoing)
 †The tested hypothesis: MET+SAXA is non-inferior to MET+GPZ if upper confidence limit of difference in adjusted HbA_{1c} change from baseline to week 52 is <0.35%
 GPZ: glipizide; MET: metformin; PBO: placebo; SAXA: saxagliptin; T2D: type 2 diabetes.

1. Gökçe B, et al. *Int J Clin Pract*. 2010;64(12):1619-31.

Saxagliptin is non-inferior to SU in lowering HbA_{1c} as an add-on to metformin at 52 weeks¹

Adjusted mean change in HbA_{1c} from baseline (PP analysis set)

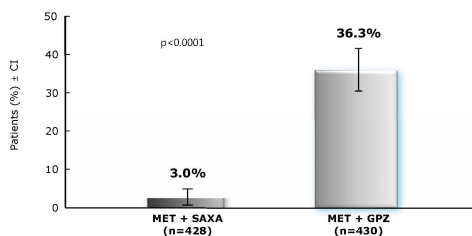


MET+SAXA was considered non-inferior to MET+GPZ if upper confidence limit of difference in adjusted HbA_{1c} change from baseline to week 52 was <0.35%;
PP: per protocol; GPZ: glipizide; PBO: placebo; MET: metformin; SAXA: saxagliptin.

1. Göke B, et al. *Int J Clin Pract*. 2010;64(12):1619-31

Significantly fewer patients experience hypoglycaemia with saxagliptin vs SU as add-on to metformin¹

Proportion of patients with ≥ 1 hypoglycaemic episode at Week 52 (safety analysis set)

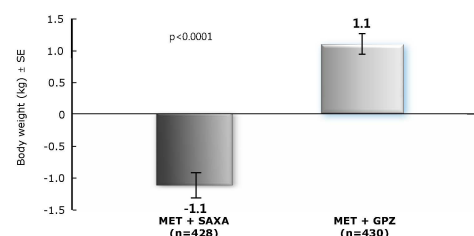


CI: confidence interval; GPZ: glipizide; MET: metformin; SAXA: saxagliptin

1. Göke B. et al. *Int J Clin Pract*. 2010;64(12):1619-31.

Difference in weight change was significant between saxagliptin vs SU as add-on to metformin¹

Adjusted mean change in body weight from baseline to Week 52 (safety analysis set)



GPZ: glipizide; MET: metformin; SAXA: saxagliptin

1. Göke B. et al. *Int J Clin Pract*. 2010;64(12):1619-31.



Summary of efficacy¹⁻⁵

- Saxagliptin 5 mg, when added to metformin, sulphonylurea or thiazolidinedione, provides **comprehensive glycaemic control** through consistent, clinically meaningful and significant reductions in:
 - HbA_{1c}
 - PPG
 - FPG
- The **risk of hypoglycaemia** with saxagliptin 5 mg is **similar to placebo** with **no or minimal impact on weight**
- As add-on to metformin saxagliptin 5 mg is non-inferior to SU in lowering HbA_{1c} with **significantly less hypoglycaemia** and a **beneficial effect on weight**
- The addition of saxagliptin 5 mg to metformin provides **sustained glycaemic benefits over 102 weeks**
- Saxagliptin 5 mg also provides significant blood glucose-lowering efficacy in initial combination with metformin over 76 weeks

1. DeFronzo RA, et al. Diabetes Care. 2009;32:1649-55. 2. Chacra AR, et al. Int J Clin Pract. 2009;63:1395-406. 3. Hollander P, et al. J Clin Endocrinol Metab. 2009;94(12):4810-9. 4. Göke B, et al. Int J Clin Pract. 2010;64(12):1619-31. 5. Ravichandran et al. Diabetologia 2009; 52(Suppl. 1):S60.

TYPE 2 DIABETES-THE WAY
FORWARD

Saxagliptin clinical safety

Bristol-Myers Squibb AstraZeneca

Overall summary of adverse events

Placebo-controlled pooled population
(short-term period including rescue therapy)

	Percentage of subjects			
	SAXA 2.5 mg (n=882)	SAXA 5 mg (n=882)	SAXA 10 mg (n=279)	All SAXA (n=2043)
At least one AE	72.0	72.2	76.7	72.7
Deaths	0.2	0	0	<0.1
At least one SAE	3.5	3.4	2.5	3.3
Discontinuations due to AEs	2.2	3.3	3.9	2.9
				PBO (n=799)
				70.6
				0.3
				3.4
				1.8

AE: Adverse event; PBO: Placebo; SAE: Serious adverse event; SAXA: Saxagliptin;

Saxagliptin, FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting: NDA 22-350. Available at: <http://www.fda.gov/CDRMS/DOCKETS/ac/09/briefing/2009-442201-02-Bristol.pdf>. Accessed: 5 May 2011.

General safety and tolerability profile

- Saxagliptin was well-tolerated at all doses studied in Phase 3 trials over 24 weeks and in addition to metformin over 102 weeks
- The risk of hypoglycaemia with saxagliptin 5 mg was similar to placebo
- Saxagliptin had a neutral impact on weight
- There were no changes in lipid parameters, blood pressure or heart rate
- No hepatic, pancreatic, skeletal myopathy, or renal safety signals have been identified
- No evidence of clinically meaningful effects on haematological or blood chemistry parameters was detected

Saxagliptin, FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting: NDA 22-350. Available at: <http://www.fda.gov/CDRMS/DOCKETS/ac/09/briefing/2009-442201-02-Bristol.pdf>. Accessed: 5 May 2011.

FDA guidance on CV safety

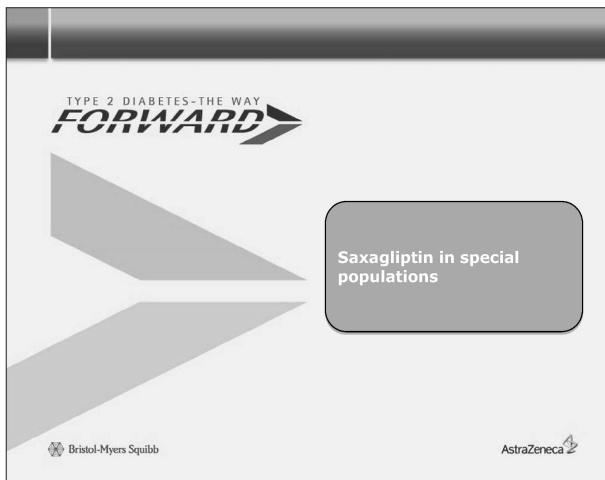
- In **December 2008**, the FDA recommended that new drugs for type 2 diabetes must generate data demonstrating they are not associated with an unacceptable increase in **CV risk**
- Phase 2 and 3 studies need to be designed to allow reliable **meta-analysis of CV events**
 - Independent blinded adjudication committee for CV events which should include **cardiovascular mortality, myocardial infarction, and stroke**, and can include hospitalization for acute coronary syndrome urgent revascularisation procedures, and possibly other endpoints
 - Include **high-risk patients**

FDA, Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available at: <http://www.fda.gov/downloads/CDRMS/DOCKETS/09/09/09-442201-02-Bristol.pdf>. Accessed: 12 Nov 2010.

Summary of efficacy and safety

Saxagliptin 5 mg:

- Provides **comprehensive glycaemic control** through consistent, clinically meaningful and statistically significant reductions in HbA_{1c}, PPG and FPG
- Provides a favourable safety and tolerability profile with a **low risk of hypoglycaemia** and **no or minimal differences in weight change**
- Provides reassurance on cardiovascular safety with **no CV safety signal** identified in the retrospective analysis of a large Phase 2b/3 clinical trial population
- Offers a **treatment option with a favourable benefit/risk profile** for people with type 2 diabetes who are not at glycaemic goal



Saxagliptin in renal impairment

- Dosing in patients with type 2 diabetes and renal impairment:¹
 - Mild renal impairment (CrCl >50 to ≤80 ml/min): 5 mg/day
 - Moderate renal impairment (CrCl ≥30 to ≤50 ml/min): 2.5 mg/day
 - Severe renal impairment (CrCl <30 ml/min): 2.5 mg/day
- In this patient population saxagliptin is generally well tolerated with a safety profile comparable to placebo²
- No meaningful changes in renal function parameters have been observed²

1. Saxagliptin. Summary of Product Characteristics. 2. Nowicki M, et al. Diabetes Obes Metab. 2011;13(6):523-32.

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- American Diabetes Association: *Standards of Medical Care in Diabetes 2012*
- 대한당뇨병학회: 2012 당뇨병진료지침
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- Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy, A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes: Volume 27, Number 1, 2009 • Clinical Diabetes

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- Effects of Exenatide on measures of b-cell function after 3 years in metformin-treated patients with type 2 diabetes: Vol. 34, september 2011, Diabetes Care