New Perspectives in Diabetes

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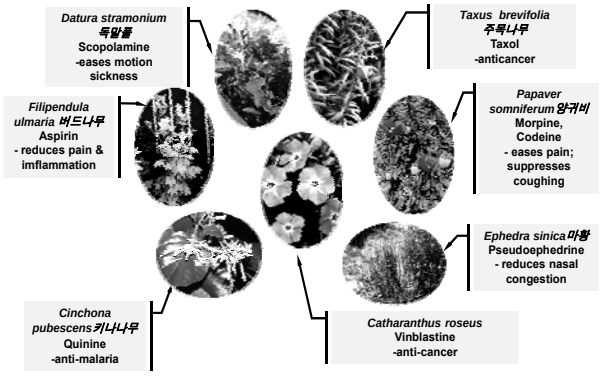
버드나무 껍질

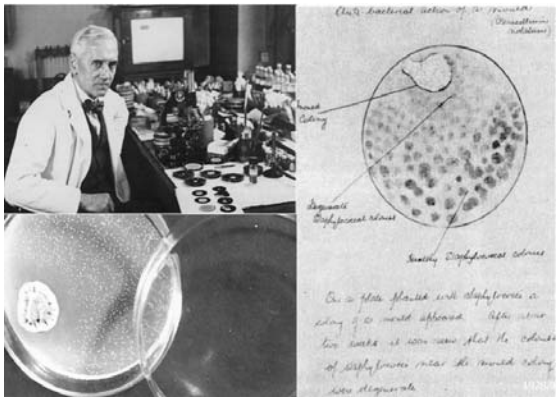
BC 5세기경, 히포크라테스는 이미 천연 아스피린을 사용

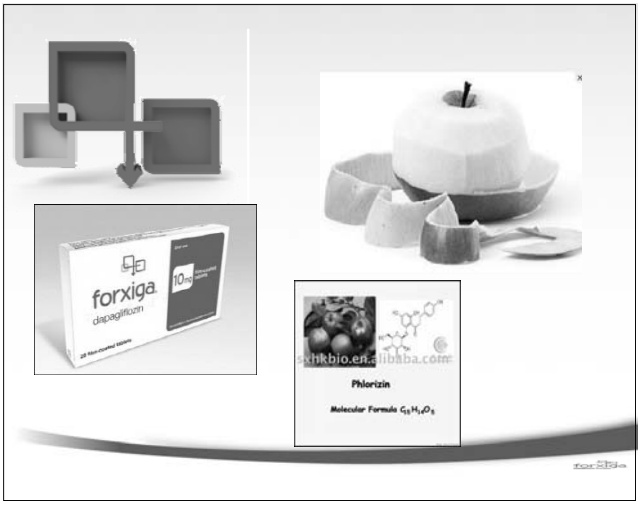
해열과 진통의 효과를 얻기 위해 살리실산이 풍부한 버드나무 껍질로부터 추출한 즙을 사용하였다고 기록되어 있다.

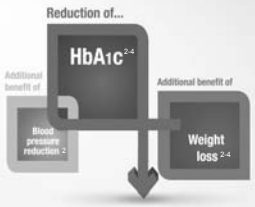
천연물로부터 개발된 의약품



알렉산더 플레밍 **1881-1955**







CURRENT CHALLENGES OF T2DM AND IMPORTANCE OF MULTI-FACTORIAL MANAGEMENT

2. FORXIGA® Prescribing Information. 3. Bailey CJ et al. Lancet 2010; 375:2223-2233. 4. Bailey CJ et al. BMC Medicine 2013; 11:43.

Type 2 diabetes : Glycemic and hypertension control rate in diabetes patients is still low[1]

Diabetes

Prevalence : 12.4%

GLYCEMIC CONTROL RATE (HbA_{1C})

HbA_1C < 6.5%
27.9%

HbA_1C < 7%
43.4%

- Only 27.9% of patients with diabetes have reached their target blood glucose level
- Even if the ADA recommendation of HbA1C<7% is applied, only about half are under adequate glycemic control

Hypertension

Prevalence in Diabetes : 54.6%

HYPERTENSION CONTROL RATE

Diabetes
39.5%

Non Diabetes
68.5%

Definition of hypertension
Mean SBP 140 mmHg.
DBP 90 mmHg. Or use of antihypertensive medication

Control rate of hypertension among treatment
BP < 130/80 mmHg

1. DIABETES FACT SHEET IN KOREA 2013 (Korean Diabetes Association/Korea Centers for Disease Control and Prevention)

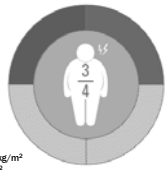
Type 2 diabetes :
Most Korean patients are overweight or obese[1]

PREVALENCE OF OBESITY IN DIABETES

당뇨병환자의 비만도

우리나라 당뇨병환자의 ¾이 과체중이거나 비만임
평균 체질량지수(BMI)는 25.2kg/m² 로 조사됨.

74.7%

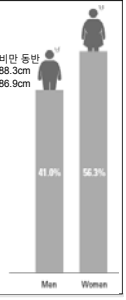


비만도 기준
과체중: **BMI 23.0-24.9kg/m²**
비만: **BMI ≥ 25.0 kg/m²**

ABDOMINAL OBESITY IN DIABETES

당뇨병환자의 복부비만율

남성 당뇨병환자의 약 40%
여성 당뇨병환자의 약 60%에서 복부비만 동반
남성 당뇨병환자의 평균 허리둘레는 88.3cm
여성 당뇨병환자의 평균 허리둘레는 86.9cm

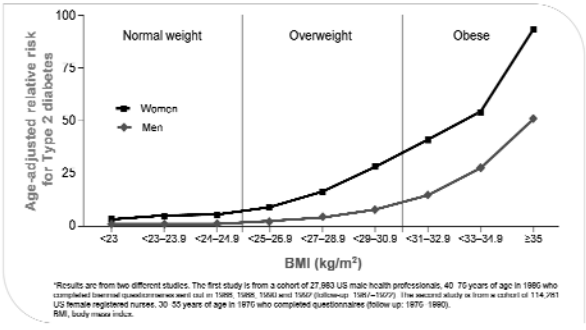


복부비만 기준
남자 허리둘레 ≥ **90cm**
여자 허리둘레 ≥ **85cm**

1. DIABETES FACT SHEET IN KOREA 2012 (Korean Diabetes Association/Korea Centers for Disease Control and Prevention)

Diabetes and obesity are closely interlinked

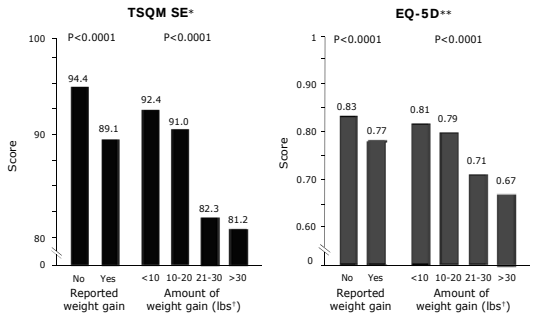
Relationship between BMI and risk of Type 2 diabetes



*Results are from two different studies. The first study is from a cohort of 27,983 US male health professionals, 40–75 years of age in 1986 who completed biennial questionnaires sent out in 1986, 1988, 1990 and 1992 (follow-up: 1986–1992). The second study is from a cohort of 114,281 US female registered nurses, 30–55 years of age in 1976 who completed questionnaires (follow up: 1976–1990).
BMI, body mass index.

Adapted from: 1. Chan J, et al. Diabetes Care 1994;17:961–9. 2. Colditz GA, et al. Ann Intern Med 1995;122:481–6.

Weight gain is associated with low patient-reported antidiabetic treatment **satisfaction and HRQoL**



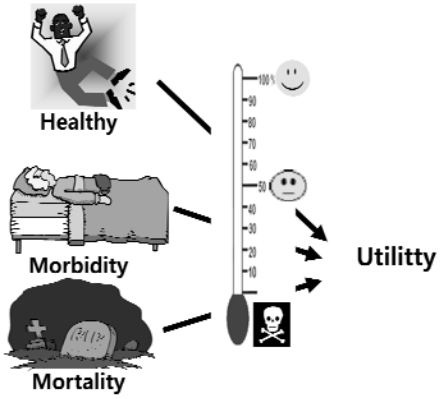
*TSQM: Treatment Satisfaction Questionnaire for Medication v.1.4; SE, side effects
TSQM score range: 0-100 (greatest satisfaction)

**EQ-5D, EuroQol-5D: (Measuring quality of life)
EQ-5D score range: −0.038 to 1.0
(US preference-weighted index score)

†1 kg= 2.204 lbs

Marrett E, et al. Diabetes Obes Metab. 2009;11:1138-44.

EQ-5D

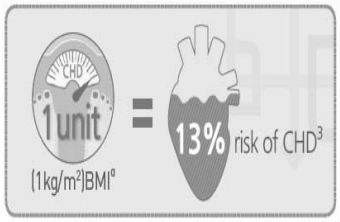


EQ-5D

- Five dimensions:
  - Mobility
  - Self care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression
- Each with three levels
- PLUS thermometer (VAS)

Increase of visceral fat is related to the increase of **insulin resistance and CV risk** in DM patients

내장지방의 증가는 제2형 당뇨병 환자의 인슐린 저항성을 높이고 심혈관계 질환의 위험을 높이는 것으로 나타났습니다[1-3]



1. Carr DB, et al. Diabetes. 2004;53(8):2087-2094. 2. Eeg-Olofsson K, et al. Diabetologia. 2009;52(1):65-73. 3. Pi-Sunyer FX. The Impact of Weight Gain on Motivation, Compliance, and Metabolic Control in Patients with Type 2 Diabetes Mellitus. Postgrad Med. 2009;121:94-107.

5-10% **weight loss** can provide many **clinical benefits** to DM patients

* ~ 50% visceral adipose tissue loss (diet, physical activity, pharmacotherapy)
**Coronary heart disease
Despres JP, et al. BMJ 2001;322:716-20

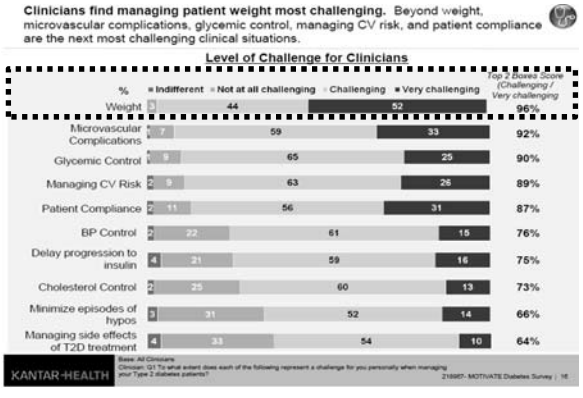
KDA highlights the importance of **glycemic control and weight loss** in overweight DM patients

2013 당뇨병학회 진료지침

- 제2형 당뇨병환자에서 미세혈관합병증 및 대혈관 합병증의 발생위험을 감소시키기 위해서 적극적인 혈당조절이 필요하다.
- **과체중이거나 비만한 제2형 당뇨병환자에서는 섭취 에너지를 제한하여, 중등도 (체중의 7%)로 체중을 감량하면 혈당과 인슐린감수성을 개선시킨다.**
- 신체 활동 및 행동 교정은 체중 감량 프로그램의 주요 요소이며, 감량된 체중을 유지하는 데에도 도움이 된다.

2013 당뇨병학회 진료지침

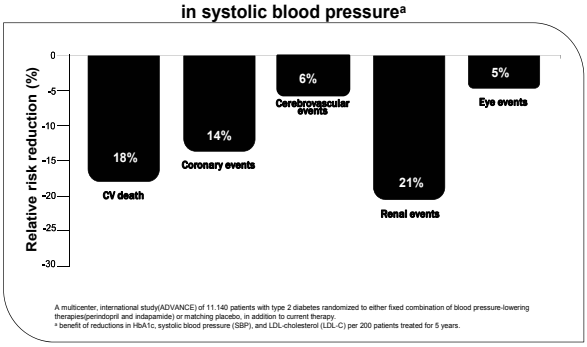
Clinicians find **managing patient weight** is the most challenging thing



KANTAR HEALTH 2011년 MOTIVATE Global Survey 연구결과

Type 2 diabetes : decreasing blood pressure reduces risk of complications

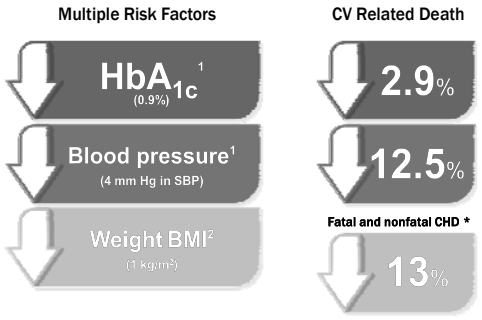
Decrease in risk with a mean 6 mm Hg reduction in systolic blood pressure[a]



A multicenter, international study(ADVANCE) of 11,140 patients with type 2 diabetes randomized to either fixed combination of blood pressure-lowering therapies(perindopril and indapamide) or matching placebo, in addition to current therapy.
[a] benefit of reductions in HbA1c, systolic blood pressure (SBP), and LDL-cholesterol (LDL-C) per 200 patients treated for 5 years.

Patel A. *Lancet*. 2007;370(9590):829-840.

Multiple risk factors reduction plays important roles to manage type 2 diabetes



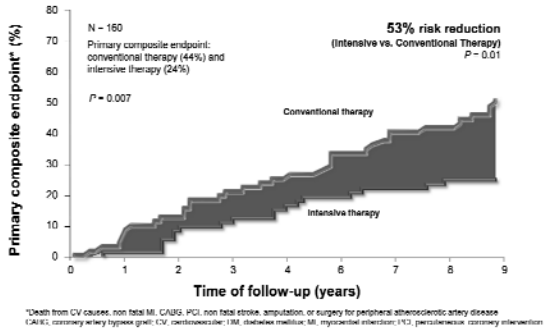
*CHD: coronary heart disease

1- Adapted from: Schernthaner G. Wien Med Wochenschr. 2010: 160(1-2): 8-19.

2- Pi-Sunyer FX. Postgrad Med 2009;121:94–107

STENO-2 : multifactorial management significantly reduces risk of cardiovascular events in type 2 DM[1–2]

In addition to ~50% relative risk reduction in the primary composite endpoint, a sustained benefit for CV events was also observed in the intensive management group over an additional 5.5 years[2]



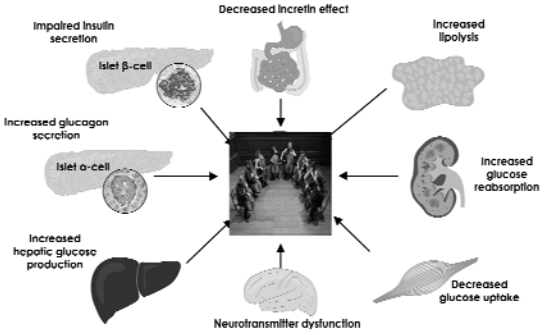
*Death from CV causes, non fatal MI, CABG, PCI, non fatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease (CABG, coronary artery bypass graft; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention

1. Gaede P, et al. N Engl J Med 2003;348:383–93. 2. Gaede P, et al. N Engl J Med 2008;358:580–91.

THE NEED FOR A NEW INSULIN-INDEPENDENT APPROACH IN T2DM AND THE ROLE OF SGLT-2 INHIBITORS

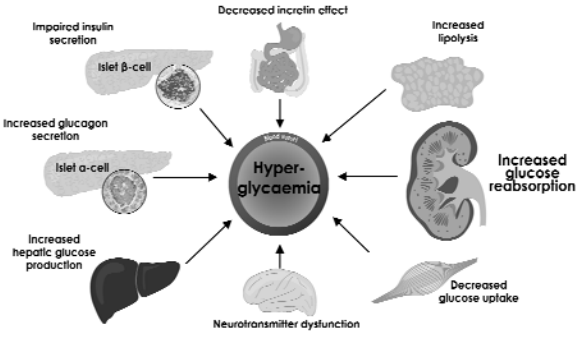
2. FORXIGA® Prescribing Information. 3. Bailey CJ et al. Lancet 2010; 375:2223-2233, 4. Bailey CJ et al. BMC Medicine 2013; 11:43.

Multiple pathophysiological failures contribute to hyperglycaemia - **The "Ominous Octet"**



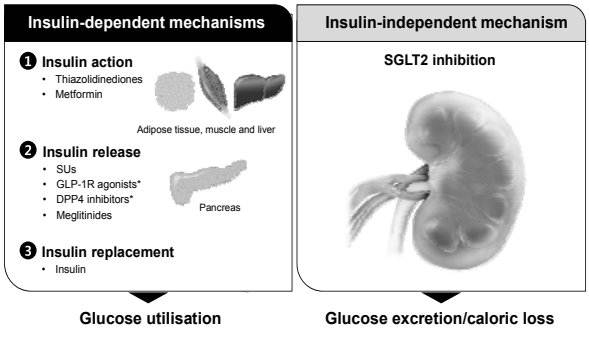
Adapted from: DeFronzo RA. Diabetes 2009;58:773–95. ©Wolters Kluwer Health

Multiple pathophysiological failures contribute to hyperglycaemia - **The "Ominous Octet"**



Adapted from: DeFronzo RA. Diabetes 2009;58:773–95. ©Wolters Kluwer Health

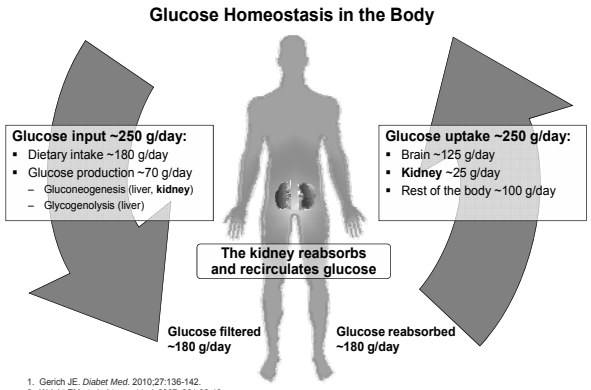
Existing and novel mechanisms to reduce hyperglycaemia in Type 2 diabetes[1–4]



*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1R agonists and DPP4 inhibitors also act to decrease glucagon secretion. DPP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; SUs, sulphonylureas.

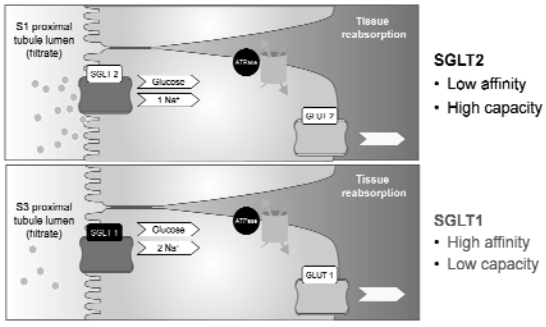
1. Washburn WN. *J Med Chem* 2009;**52**:1785–94; 2. Bailey CJ. *Curr Diab Rep* 2009;**9**:360–7; 3. Srinivasan BT, *et al. Postgrad Med J* 2008;**84**:524–31; 4. Rajesh R, *et al. Int J Pharma Sci Res* 2010;**1**:139–47.

The role of the kidney promote glucose homeostasis[1,2]



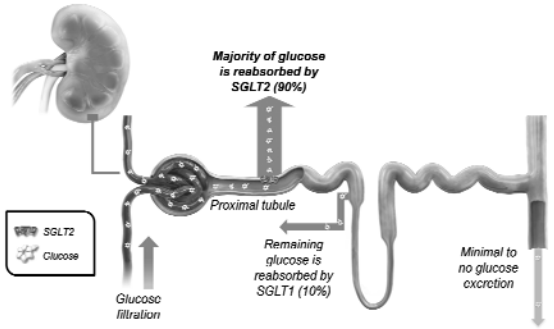
1. Gerich JE. *Diabet Med*. 2010;27:136-142.
2. Wright EM et al. *J Intern Med*. 2007; 261:32-43.

Mechanism of glucose reabsorption in the proximal tubule by SGLT2 and SGLT1



GLUT, glucose transporter; SGLT, sodium-glucose co-transporter
Adapted from: Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18

Normal renal glucose handling[1–3]

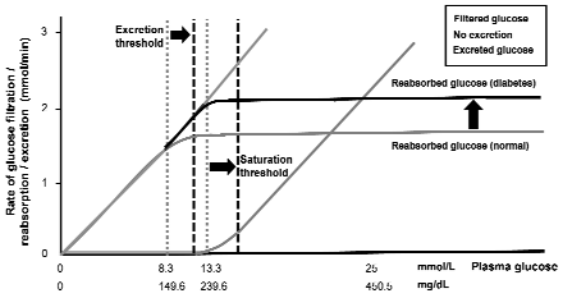


SGLT, sodium glucose co-transporter

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–30;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21

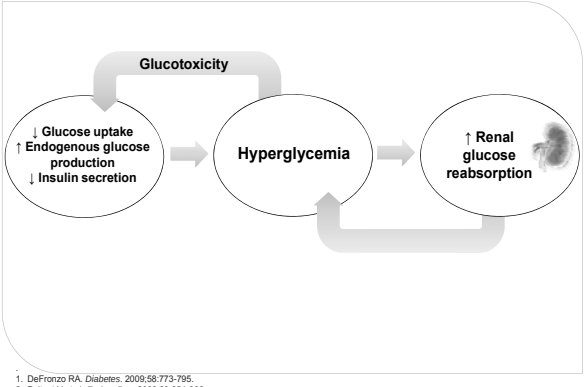
Continued glucose reabsorption even at high glucose levels induces sustained hyperglycaemia in T2DM[1,2]

Paradoxically, SGLT2 reabsorbs glucose through an insulin-independent pathway, even in the presence of hyperglycaemia



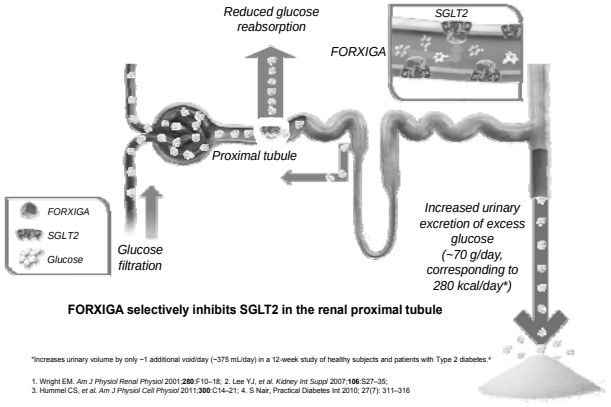
Adapted from Chao EC, *et al. Nat Rev Drug Discov* 2010;9:551–559; Marsenic O. *Am J Kidney Dis* 2009;53:875–883; Nair S, *et al. J Clin Endocrinol Metab* 2010;95:34–42

Continuous glucose reabsorption perpetuates the cycle of glucotoxicity in patients with T2DM[1-2]



1. DeFronzo RA. *Diabetes*. 2009;58:773-795.
2. Poitout V et al. *Endocr Rev*. 2008;29:351-366.

FORXIGA: A novel insulin-independent approach to remove excess glucose[1–3]



FORXIGA selectively inhibits SGLT2 in the renal proximal tubule

*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. S Nair, Practical Diabetes Int 2010; 27(7): 311–316

The Benefits of FORXIGA's Unique MoA (Mechanism of Action)

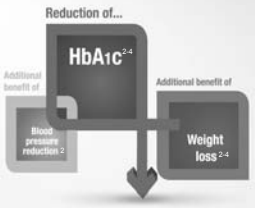
FORXIGA's inhibition of SGLT2 results in daily urinary excretion of excess glucose ~70 g providing:[1]

- Significant HbA_{1c} reductions[2,3]
- Additional benefits of weight loss and a reduction in blood pressure[2]

FORXIGA acts **independently of insulin** mechanisms[2]

- Works regardless of β-cell function
- Complements insulin-dependent mechanisms
- Low propensity for hypoglycaemia

Forxiga is indicated in patients with type 2 diabetes to improve glycemic control(10mg, once a day).
It is not indicated for the management of obesity or high blood pressure, and these effects are caused by dapagliflozin's mechanism of action.
A proper decision is necessary depending on patient's condition.
SGLT2, sodium-glucose co-transporter-2.
1. List JF, *et al. Diabetes Care* 2009;**32**:650–7; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Bailey CJ, *et al.* ADA 2011: Poster 988-P.



INDICATION AND REIMBURSEMENT GUIDANCE

2. FORXIGA® Prescribing Information. 3. Bailey CJ et al. Lancet 2010; 375:2223-2233. 4. Bailey CJ et al. BMC Medicine 2013; 11:43.

FORXIGA can be used with various anti-diabetic agents due to '**insulin independent'** mode of action

Insulin-dependent	Insulin action : TZDs / Metformin	Insulin release : Sus / GLP-1 / DDP-4 / Meglitinides	Insulin replacement : Insulin
Insulin-Independent	Removal of glucose in kidney : SGLT2 inhibitor "**forxiga**"		

Forxiga Prescribing Information

FORXIGA has proven efficacy and safety through abundant clinical trials and real life experience

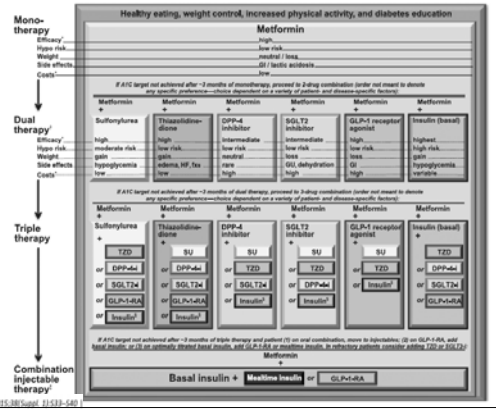
>20,000 patients in ongoing trials[1,2]

4-year data already available[3]

>193,000 patients treated worldwide*[4,5]

*This information is an estimate derived from the use of information under licence from the following IMS Health information service: NPA Market Dynamics for period February – April 2014. IMS expressly reserves the rights of copying, distribution and republication.
1. EMDAC background document. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf. Last accessed September 2014; 2. ClinicalTrials.gov. Identifier: NCT01730534. Available online at: ClinicalTrials.gov (updated 30 September 2014); 3. Del Prato S, *et al.* Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA, 21–25 June 2013. Abstract 62-LB;
4. Data on file (Cegedim Strategic Data, Longitudinal Patient Databases, October 2014); 5. Data on file (IMS NPA Market Dynamics).

2015 ADA/EASD diabetes treatment algorithm recommend **SGLT-2 inhibitors** as dual or triple therapy



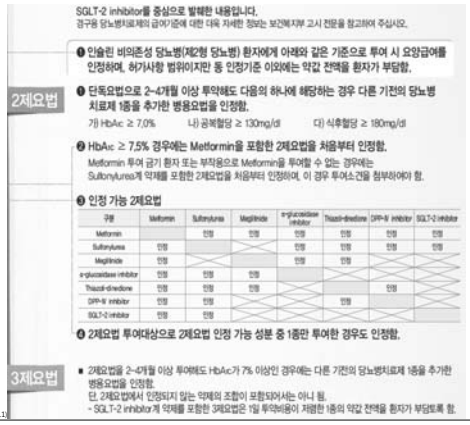
FORXIGA can be used with various anti-diabetic agents based on its indication

이 약은 **단독요법**으로 투여한다.

이 약은 다음의 경우 **병용요법**으로 투여한다.

- 이전 당뇨병 약물치료를 받은 경험이 없으며 단독요법으로 충분한 혈당조절이 어려운 경우 메트포르민과 병용투여
- 메트포르민 또는 설포닐우레아 단독요법으로 충분한 혈당조절을 할 수 없는 경우
- 인슐린 (인슐린 단독 혹은 메트포르민 병용) 요법으로 충분한 혈당조절을 할 수 없는 경우
- 디펩티딜 펩티다제-4(DPP-4) 저해제인 시다글립틴 (시다글립틴 단독 혹은 메트포르민 병용) 요법으로 충분한 혈당조절을 할 수 없는 경우
- 메트포르민과 설포닐우레아 병용요법으로 충분한 혈당조절을 할 수 없는 경우

당뇨병용제 급여기준 일반원칙*세부인정기준 및 방법 – 2014년 9월 1일 시행



SGLT-2 inhibitor를 중심으로 발췌한 내용입니다.
경구용 당뇨병치료제의 급여기준에 대한 더욱 자세한 정보는 보건복지부 고시 전문을 참고하여 주십시오.

❶ 인슐린 비의존성 당뇨병(제2형 당뇨병) 환자에게 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 허가사항 범위이지만 동 인정기준 이외에는 약값 전액을 환자가 부담함.

2제요법

❶ 단독요법으로 2~4개월 이상 투약해도 다음의 하나에 해당하는 경우 다른 기전의 당뇨병 치료제 1종을 추가한 병용요법을 인정함.

가) HbA1c ≥ 7.0%　　나) 공복혈당 ≥ 130mg/dl　　다) 식후혈당 ≥ 180mg/dl

❷ HbA1c ≥ 7.5% 경우에는 Metformin을 포함한 2제요법을 처음부터 인정함.

Metformin 투여 금기 환자 또는 부작용으로 Metformin을 투여할 수 없는 경우에는 Sulfonylurea계 약제를 포함한 2제요법을 처음부터 인정하며, 이 경우 투여소견을 첨부하여야 함.

❸ 인정 가능 2제요법

구분	Metformin	Sulfonylurea	Meglitinide	α-glucosidase inhibitor	Thiazolidinedione	DPP-IV inhibitor	SGLT-2 inhibitor
Metformin		인정	인정	인정	인정	인정	인정
Sulfonylurea	인정			인정	인정	인정	인정
Meglitinide	인정			인정	인정		
α-glucosidase inhibitor	인정	인정	인정				
Thiazolidinedione	인정	인정	인정			인정	
DPP-IV inhibitor	인정	인정			인정		
SGLT-2 inhibitor	인정	인정					

❹ 2제요법 투여대상으로 2제요법 인정 가능 성분 중 1종만 투여한 경우도 인정함.

3제요법

▪ 2제요법을 2~4개월 이상 투여해도 HbA1c가 7% 이상인 경우에는 다른 기전의 당뇨병치료제 1종을 추가한 병용요법을 인정함.
단, 2제요법에서 인정되지 않는 약제의 조합이 포함되어서는 아니 됨.
- SGLT-2 inhibitor계 약제를 포함한 3제요법은 1일 투약비용이 처method한 1종의 약값 전액을 환자가 부담토록 함.

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