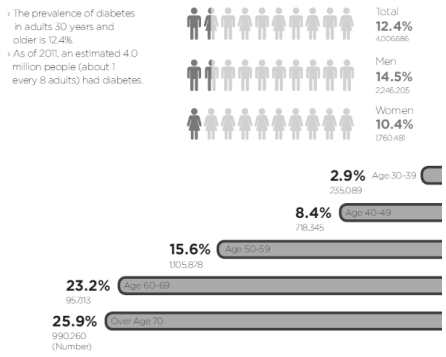
FORXIGA, The First SGLT-2 Inhibitor, How Would It Change the Landscape in Type 2 Diabetes?

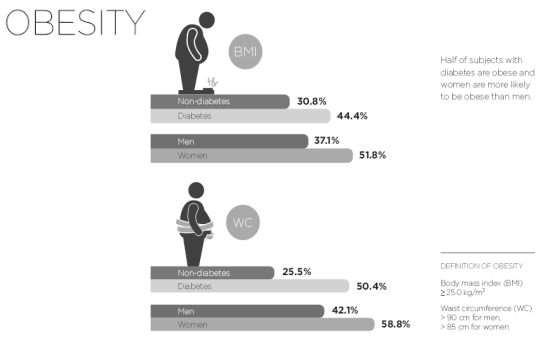
김 철 민
가톨릭의대 가정의학과

Type 2 diabetes : the prevalence of diabetes in adults 30 years and older is 12.4%



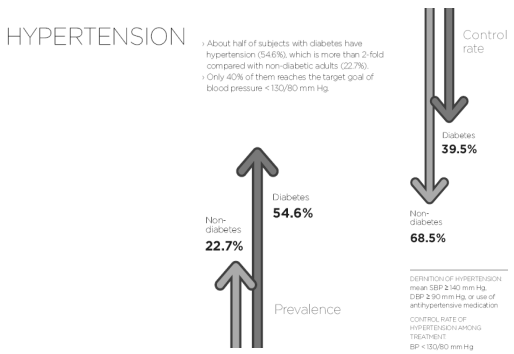
1. DIABETES FACT SHEET IN KOREA 2013 (Korean Diabetes Association/Korea Centers for Disease Control and Prevention)

Type 2 diabetes—most Korean patients are overweight[1]



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

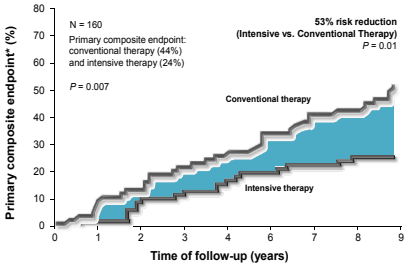
Type 2 diabetes : hypertention is uncontrolled among Korean T2DM patients[1]



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

STENO-2 : multifactorial management significantly reduces risk of cardiovascular events in type 2 DM

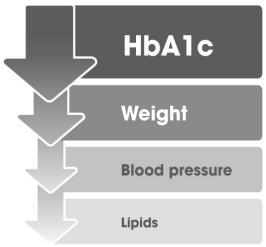
In addition to ~50% relative risk reduction in the primary composite endpoint, a sustained benefit for CV events was also observed in the intensive management group over an additional 5.5 years[2]



*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.

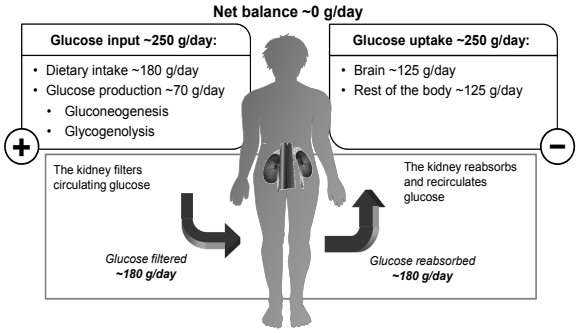
Type 2 diabetes : controlling multiple parameters is essential



Incremental reductions sustained over time in glycemic control (HbA1c) and other parameters can benefit the physical health of patients with type 2 diabetes[1-5]

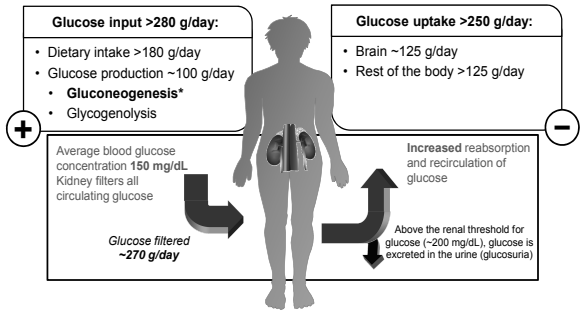
1. Stratton IM, *et al. BMJ.* 2000;321(7258):405-412. **2.** Pi-Sunyer FX. *Postgrad Med.* 2009;121(5):94-107. **3.** Williamson DF, *et al. Diabetes Care.* 2000;23(10):1499-1504. **4.** Patel A. *Lancet.* 2007;370(9590):829-840. **5.** Pyörälä K, *et al. Diabetes Care.* 1997;20(4):614-620.

Normal glucose homeostasis[1,2]



1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Gerich, JE. *Diabetes Obes Metab* 2000;**2**:345–50.

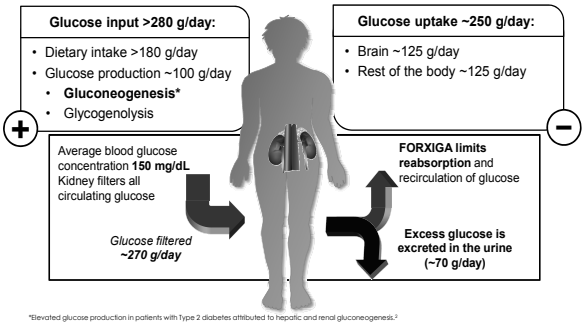
Glucose handling in Type 2 diabetes[1,2]



*Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.[2]

1. Gerich JE. *Diabet Med* 2010;**27**:136–42; 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract* 2008;**14**:782–90.

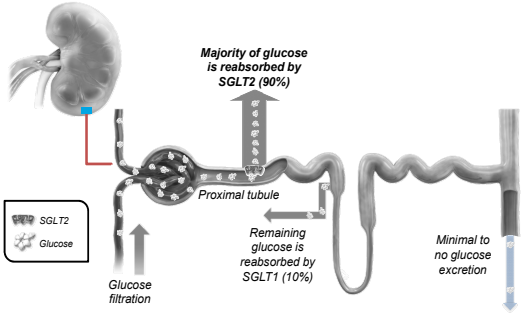
FORXIGA in patients with Type 2 diabetes[1–3]



*Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.[2]

1. Gerich JE. *Diabet Med* 2010;**27**:136–42; 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract* 2008;**14**:782–90;
3. Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

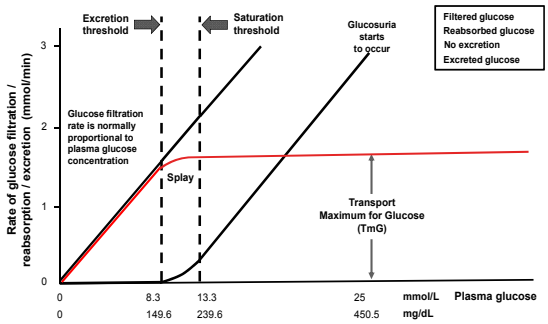
Normal renal glucose handling[1–3]



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**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21.

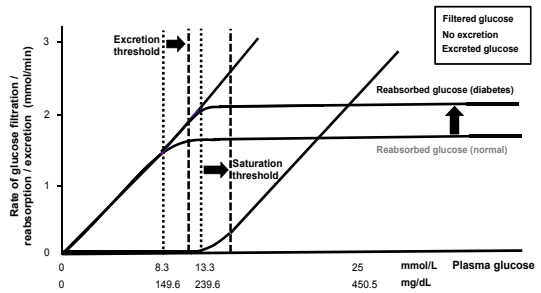
Beyond a certain plasma glucose threshold, saturation of glucose transporters results in glucosuria



Adapted from Chao EC, et al. *Nat Rev Drug Discov* 2010;9:551-559; Marsenic O. *Am J Kidney Dis* 2009;53:875-883.

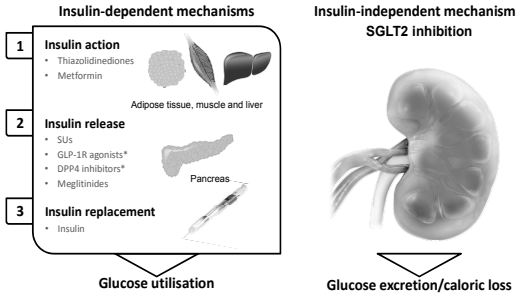
Continued glucose reabsorption even at high glucose levels induces sustained hyperglycaemia in diabetics[1,2]

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; Nairs S, et al. *J Clin Endocrinol Metab* 2010;95:34-42.

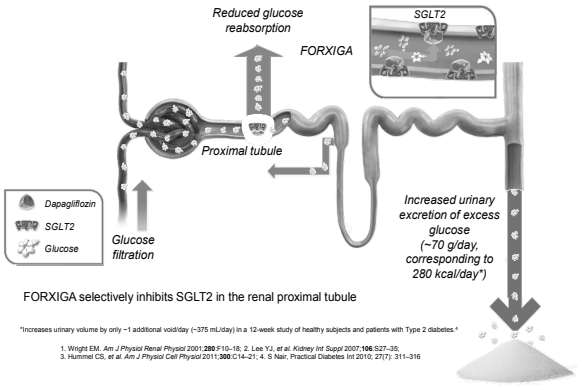
Existing and novel mechanisms to reduce hyperglycaemiain Type 2 diabetes[1–4]



*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.

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

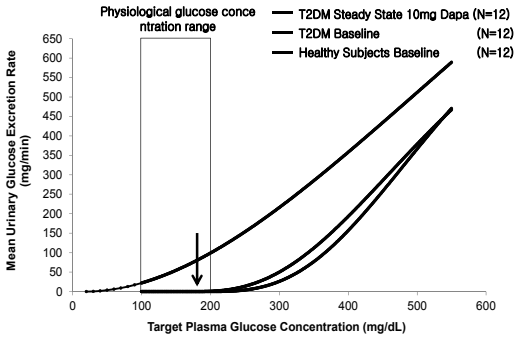


FORXIGA selectively inhibits SGLT2 in the renal proximal tubule

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.

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

FORXIGA Lowers Tubular Transport Threshold



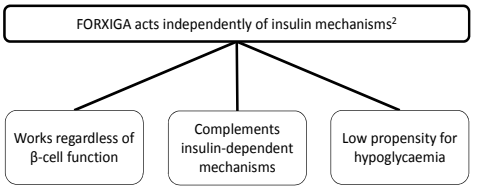
Arrows represent reduction in renal glucose threshold after dapagliflozin treatment

DeFronzo RA, et al. *Diabetes Care* 2013; 36:3169-3176.

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]

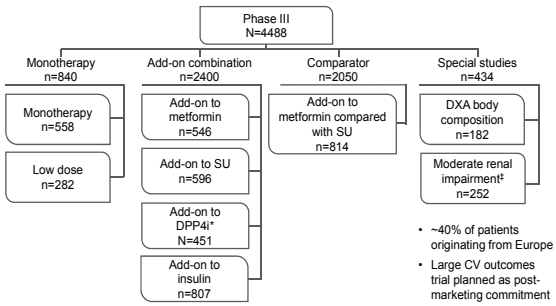
- Significant HbA_{1c} reductions[2,3]
- Additional benefits of weight loss and a reduction in blood pressure[2]



Forxiga is indicated in patients with type 2 diabetes to improve glycemic control. 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.

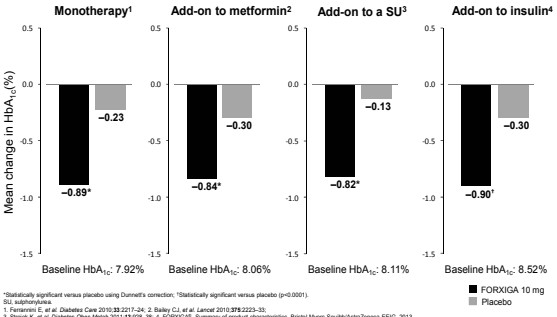
FORXIGA Phase III clinical development program



- ~40% of patients originating from Europe
- Large CV outcomes trial planned as post-marketing commitment

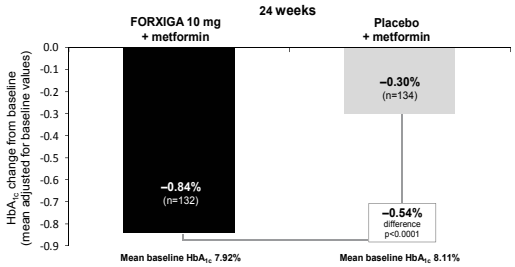
*FORXIGA is indicated for add-on to DPP-4i (sitagliptin)
‡FORXIGA should not be used in patients with moderate to severe renal impairment (CrCl <60 mL/min or eGFR <60 mL/min/1.73 m^2).
DXA, dual-energy *X*-ray absorptiometry;

FORXIGA: Consistent reduction in HbA_{1c} at Week 24 across studies



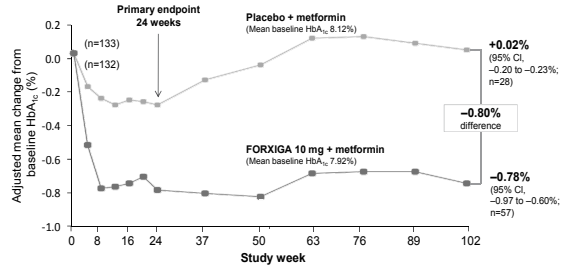
*Statistically significant versus placebo using Dunnett's correction; †Statistically significant versus placebo (p<0.0001).
SU, sulphonylurea.
1. Ferrannini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33;
3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. FORXIGA®. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2013.

FORXIGA: Significant reductions in HbA_{1c} compared with placebo at the 24-week primary endpoint



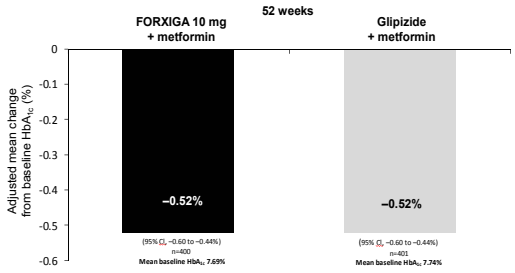
Changes reported for Week 24 are adjusted for baseline values and are based on last observation carried forward.
A Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week clinical study to evaluate the efficacy and safety of FORXIGA 10 mg + metformin (≥1500 mg/day) versus placebo + metformin (≥1500 mg/day) in adult patients with Type 2 diabetes who had inadequate glycaemic control (HbA_{1c} ≥7% and ≤10%) on metformin alone. Primary endpoint: HbA_{1c} reduction at 24 weeks.
Bailey CJ, *et al. Lancet* 2010;**375**:2223–33.

FORXIGA: Reductions in HbA_{1c} were sustained over time[1,2]



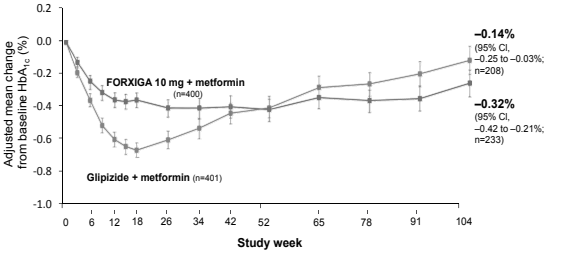
Data are mean change from baseline after adjustment for baseline value. Data after rescue are excluded. Analyses were obtained by longitudinal repeated measures analyses.
CI, confidence interval.
1. Bailey CJ, *et al. BMC Med* 2013;**11**:43; 2. FORXIGA®. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2013.

FORXIGA: Comparable HbA_{1c} reduction to a SU at the 52-week primary endpoint



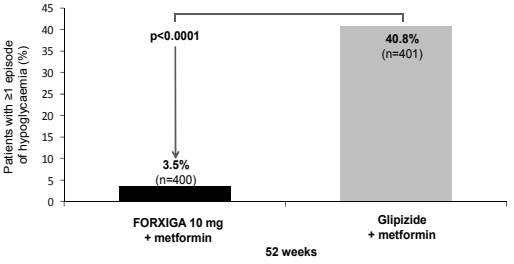
Data are adjusted mean change from baseline and 95% CI derived from analysis of covariance using the full analysis set and last observation carried forward values.
A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study to evaluate the efficacy and safety of FORXIGA 10 mg + metformin (≥1500 mg/day) versus glipizide + metformin (≥1500 mg/day) in patients with inadequate glycaemic control (HbA_{1c} >6.5% and ≤10%) on metformin alone.
CI, confidence interval; SU, sulphonylurea.
Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22.

FORXIGA: Reductions in HbA_{1c} were sustained over 104 weeks



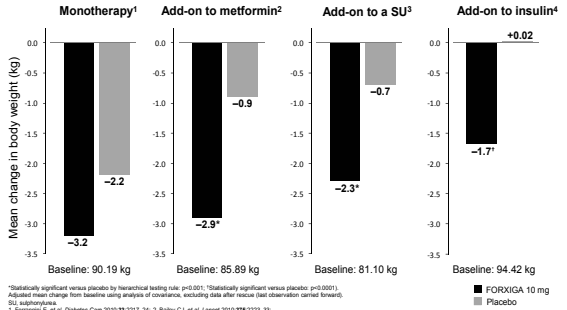
Data are adjusted mean change from baseline and 95% CI derived from a repeated measures mixed model.
CI, confidence interval.
1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22; 2. Nauck MA, *et al. Diabetes* 2011;**60**(Suppl. 1):Poster 40-LB.

Lower incidence of hypoglycaemia with FORXIGA compared with a SU



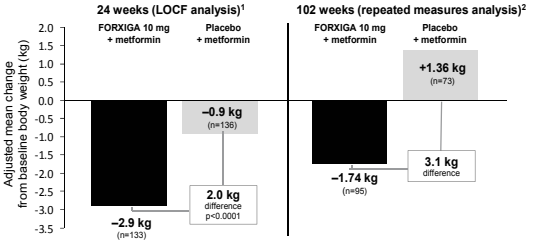
SU, sulphonylurea.
Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22.

FORXIGA, additional benefit of weight loss: Change in body weight at Week 24



*Statistically significant versus placebo by hierarchical testing rule: p<0.001; †Statistically significant versus placebo: p<0.0001).
Adjusted mean change from baseline using analysis of covariance, excluding data after rescue (last observation carried forward).
SU, sulphonylurea.
1. Fantasmini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33;
3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. FORXIGA®. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2013.

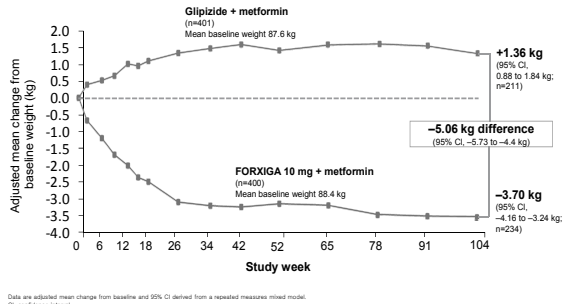
FORXIGA also had the additional benefit of weight loss over time[1–3]



- Weight loss at 6 months was associated with body-fat mass reduction[1]
- In a separate dedicated weight loss study, weight loss in patients treated with FORXIGA came from fat mass reduction[3]

Data are mean change from baseline after adjustment for baseline value (**mean baseline weight**: FORXIGA 86.3 kg, placebo 87.7 kg).
24–week data are based on *LOCF* analysis excluding data after rescue: 102–week data are based on longitudinal repeated measures analysis and include data after rescue.
LOCF, last observation carried forward.
1. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 2. Bailey CJ, *et al. BMC Med* 2013;**11**:43; 3. Bolinder J, *et al. J Clin Endocrinol Metab* 2012;**97**:1020–31.

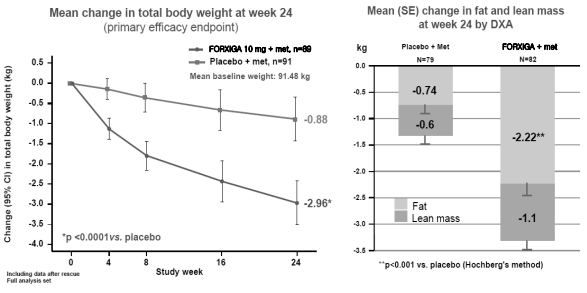
FORXIGA: Additional benefit of weight loss sustained over time



Data are adjusted mean change from baseline and 95% CI derived from a repeated measures mixed model.
CI, confidence interval.
1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22; 2. Nauck MA, *et al. Diabetes* 2011;**60**(Suppl. 1):Poster 40-LB.

FORXIGA reduces total body weight and fat mass at week 24

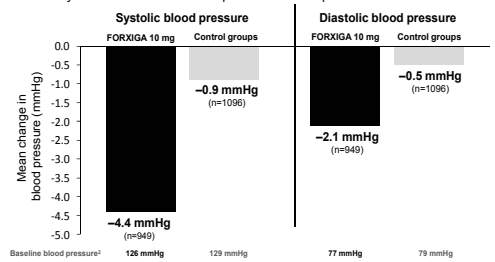
DXA: dual X-ray absorptiometry



J Clin Endocrinol Metab, March 2012, 97(3)

FORXIGA: Reduction in blood pressure

In a prespecified pooled analysis of 12 placebo-controlled studies, FORXIGA 10 mg reduced systolic and diastolic blood pressure versus placebo at Week 24[1]



FORXIGA is not indicated for the management of high blood pressure. Mean seated systolic and diastolic blood pressure were based on a placebo–controlled, pooled analysis from the 24–week, short–term, double–blind treatment period, including data after rescue. N is the number of subjects with non–missing baseline and Week 24 (last observation carried forward) values in the randomised full analysis set. Change in blood pressure was primarily assessed as safety or exploratory efficacy endpoints in the Phase III clinical programme; therefore, the background antihypertensive medications were not controlled.
1. FORXIGA. Summary of product characteristics. Bristol–Myers Squibb/AstraZeneca EEIG, 2012;2. BMS/AZ data on file.

Safety and tolerability from a comprehensive clinical programme

The overall incidence of adverse events (short-term treatment) in subjects treated with FORXIGA 10 mg was similar to placebo

Adverse reactions in placebo-controlled studies of FORXIGA (24-week data regardless of glycaemic rescue)

System organ class	Very common (≥10%)	Common* (≥1% to <10%)	Uncommon† (≥0.1% to <1%)
Infections and infestations		Vulvovaginitis, balanitis and related GIs UTIs	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglycaemia (when used with a SU or insulin)		Volume depletion Thirst
Gastrointestinal disorders			Constipation
Skin and subcutaneous tissue disorders			Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	
Renal and urinary disorders		Dysuria Polyuria	Nocturia
Investigations		Dyslipidaemia Haematocrit increased	Blood creatinine increased Blood urea increased

GI, genital infection; SU, sulphonylurea; UTI, urinary tract infection.
FORXIGA®. Prescribing Information

Urinary tract infections (UTIs) and genital infections (GIs)*

- Type 2 diabetes is associated with an increased incidence/prevalence of GIs and UTIs[1]
- FORXIGA works by eliminating excess glucose through the kidney and is associated with a higher incidence of GIs and UTIs[2]
- Most GIs† and UTIs were mild to moderate, responded to initial course of standard therapy, and rarely led to discontinuation of FORXIGA[2]
- Events of GI (vulvovaginitis, balanitis and related GIs) and UTIs with FORXIGA 10 mg versus placebo:[2]

	FORXIGA (24 weeks)	Placebo (24 weeks)
UTIs	4.3%	3.7%
GIs	4.8%	0.9%

- Pyelonephritis was uncommon and occurred at a similar frequency to control[1]

GI, genital infection; UTI, urinary tract infection.
*In a prespecified pooled analysis of 12 placebo-controlled studies; †GI includes the preferred terms, listed in order of frequency reported: Vulvovaginal mycotic infection, vaginal infection, balanitis, GI fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, GI, GI male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.
1. Sexual and Urologic Problems of Diabetes. National Diabetes Information Clearinghouse. Available at http://diabetes.niddk.nih.gov/dm/pubs/sup/.
2. FORXIGA®. Prescribing Information

Events of volume depletion similar to control at 24 weeks

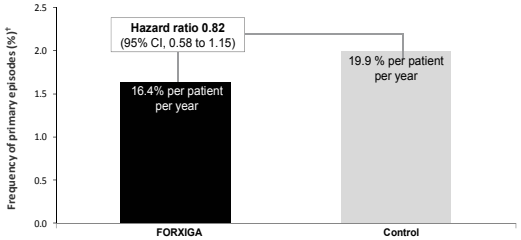
Frequency of reactions related to volume depletion*	All events
FORXIGA 10 mg	0.8%
Control	0.4%

- Serious events occurred in <0.2% of patients and were comparable between groups

*Including dehydration, hypovolaemia or hypotension.
FORXIGA is not recommended for initiation of therapy in patients who are volume depleted.
Temporary interruption of FORXIGA is recommended for patients who develop volume depletion until the depletion is corrected.
FORXIGA®. Prescribing Information

Cardiovascular safety

FORXIGA is not associated with an increase in cardiovascular risk*



†In a meta-analysis of cardiovascular events in 12 double-blind clinical studies of FORXIGA 2.5–10 mg adjudicated by an independent committee.
*Cardiovascular death, stroke, myocardial infarction or hospitalisation for unstable angina.
CI, confidence interval.
Plaszynska et al. Postgraduate Medicine. Vol 125. 2013

FORXIGA: Indication

- 이 약은 **<u>단독요법</u>**으로 투여한다.

- 이 약은 다음의 경우 **<u>병용요법</u>**으로 투여한다.
  - 메트포르민 또는 설포닐우레아 단독요법으로 충분한 혈당조절을 할 수 없는 경우 이 약을 병용투여
  - 인슐린 (인슐린 단독 혹은 메트포르민 병용) 요법으로 충분한 혈당조절을 할 수 없는 경우 이 약을 병용투여
  - 디펩티딜 펩티다제-4(DPP-4) 저해제인 시타글립틴 (시타글립틴 단독 혹은 메트포르민 병용) 요법으로 충분한 혈당 조절을 할 수 없는 경우 이 약을 병용투여

식약처 허가사항

FORXIGA: Dosing and Administration

- 이 약의 권장 용량은 단독 요법 및 인슐린 등 다른 혈당 강하제와의 추가 병용 요법에 대하여 **<u>1일 1회 10mg</u>**이다. 이 약을 인슐린 또는 설포닐우레아와 같은 인슐린 분비 촉진제와 병용하여 사용하는 경우, 저혈당의 위험을 줄이기 위해 더 낮은 용량의 인슐린 또는 인슐린 분비 촉진제를 고려할 수 있다.

- 이 약은 **<u>음식 섭취와 관계없이, 1일 1회 하루 중 언제라도 경구 투여</u>**할 수 있다. 정제는 통째로 삼켜야 한다.

식약처 허가사항

FORXIGA: Dosing and Administration

- ***신장애***
  이 약의 유효성은 신기능에 따라 다르며, 중등증의 신장애 환자에서 유효성이 감소하며, 중증의 신장애 환자의 경우, 유효성이 없을 수도 있다. 이 약은 중등증 내지 중증의 신부전 환자에게 (크레아티닌 클리어런스 [CrCl] < 60 ml/min이거나, 평가된 사구체 여과율[estimated glomerular filtration rate (eGFR)] < 60 ml/min/1.73 m^2인 환자) 사용이 권장되지 않는다.
  경증의 신장애 환자에 대한 용량 조절은 필요하지 않다.

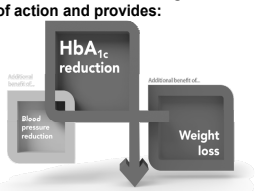
- ***간장애***
  경증 또는 중등증의 간장애 환자에 대한 용량 조절은 필요하지 않다. 중증의 간장애 환자에 대하여, 시작 용량으로 5 mg이 권장된다. 내약성이 양호한 경우, 이 용량은 10mg으로 증가시킬 수 있다.

- ***고령자 (≥ 65세)***
  일반적으로, 연령에 근거한 용량 조절은 권장되지 않는다. 신기능 및 체액량 감소의 위험을 고려해야 한다. 75세 이상의 환자에 대한 치료 경험이 제한적이므로, 이 약물 요법의 시작을 권장하지 않는다.

식약처 허가사항

Summary

- **FORXIGA is a first-in-class SGLT2 inhibitor in Asia and Korea MFDS**
- **FORXIGA is a highly selective SGLT2 inhibitor, removes excess glucose via an insulin-independent mechanism of action and provides:**
  - Significant and sustained HbA_{1c} reductions[1–5]
  - Additional benefits of weight loss[1–5] and a reduction in blood pressure*[1,5]
  - Low incidence of hypoglycaemia[1,5]
  - In one 10 mg tablet a day[5]



"Add-on for patients uncontrolled on metfor... ...additional benefit of weight loss and have normal or only mildly impaired renal function"

*FORXIGA is not indicated for the management of obesity or high blood pressure. Weight change was a secondary endpoint and blood pressure change was primarily assessed as a safety or exploratory efficacy endpoint in clinical trials.[4]
FORXIGA can be used in patients with normal or mildly impaired renal function (eGFR >60 mL/min/1.73 m²).FORXIGA should not be used in patients with moderate or severe renal impairment (creatinine clearance <60 mL/min or eGFR <60 mL/min/1.73 m²) in patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased up to 10 mg.
eGFR, estimated filtration rate; SGLT2, sodium-glucose co-transporter-2.
1. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 2. Bailey CJ, *et al. BMC Med* 2013;**11**:43; 3. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22; 4. Nauck MA, *et al. Diabetes* 2011;**60**(Suppl. 1):Poster 40-LB; 5. FORXIGA®. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2013.