다양해진 당뇨병 약물 치료
Evidence-based Treatment of T2DM In Real Practice

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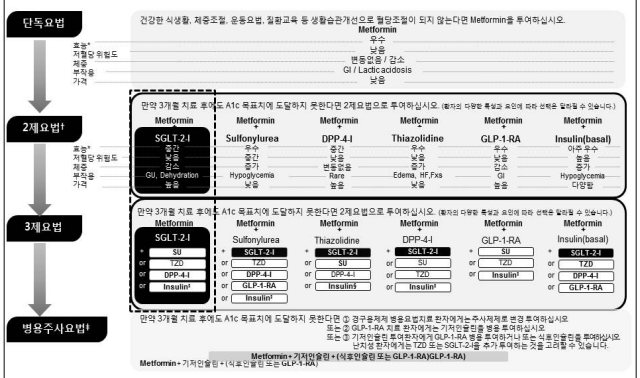
ADA/EASD Management of Hyperglycemia in T2DM, 2015: A Patient-Centered Approach



Diabetes Care 2015;38:140–149

Summary: properties of SGLT-2 inhibitors in ADA/EASD Guidelines

Class	Primary physiological action(s)	Advantages	Disadvantages
SGLT-2 inhibitors	• Blocks glucose reabsorption by the kidney, increasing Glucosuria	• No hypoglycemia • Weight reduction • BP reduction • Effective at all stages of T2DM	• Genitourinary infections • Polyuria • Volume depletion/hypotension/ dizziness • ↑ LDL-C • ↑ Creatinine (transient)

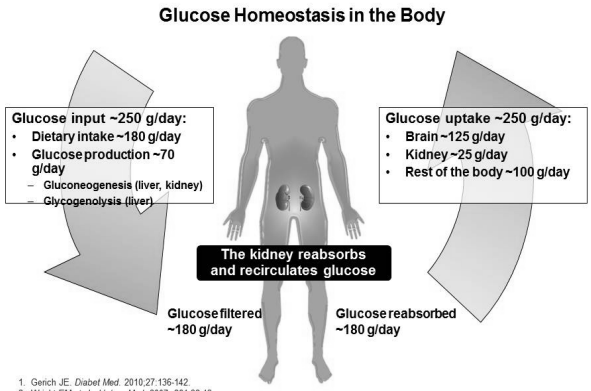
BP, Blood Pressure; LDL-C, LDL cholesterol; T2DM, Type 2 Diabetes Mellitus
Diabetes Care 2015;38:140–149

AACE 당뇨병 치료가이드라인에서는 Metformin으로 조절이 되지 않은 환자에게 DPP-4억제제보다 SGLT-2 억제제를 우선적으로 권고하였습니다.

* 약물 선호도에 따른 순서, A-GI: 알파-글루코시다제 억제제, GLP-1 RA: GLP-1 수용체 작용제
Endocr Pract 2015;21:e1-e10

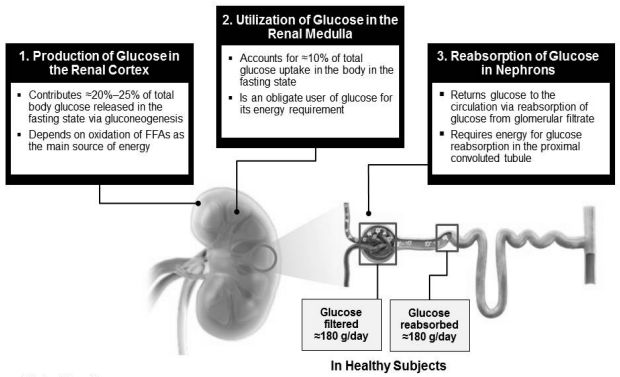
SGLT-2 inhibitors
The Role of the Kidney in Glucose Handling

The Functions of the Kidney Promote Glucose Homeostasis[1,2]



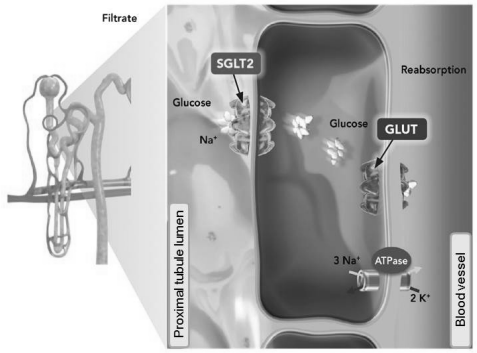
1. Gerich JE. *Diabet Med*. 2010;27:136-142.
2. Wright EM et al. *J Intern Med*. 2007; 261:32-43.

The Kidney Supports Three Key Functions in Glucose Handling



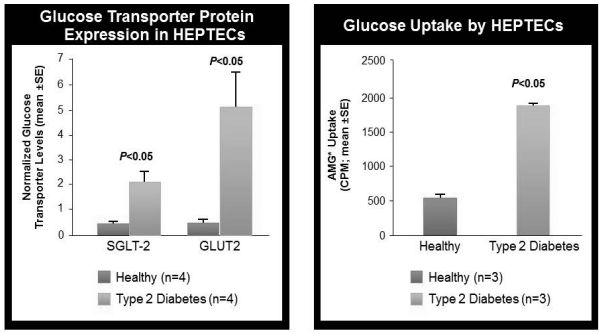
FFA=free fatty acid.
Gerich JE. *Diabet Med*. 2010;27:136-142.

Membrane Proteins Regulate Transport of Glucose Across Cellular Membranes[1,2]



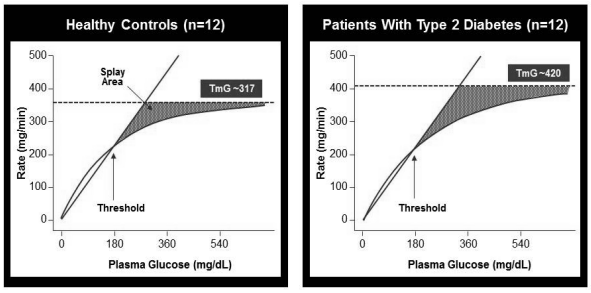
SGLT=sodium-glucose cotransporter; GLUT=facilitative glucose transporter.
1. Zhao FQ et al. *Curr Genomics*. 2007;8:113-128.
2. Asano T et al. *Curr Med Chem*. 2004;11:2717-2724.

In Type 2 Diabetes, Glucose Transporters Are Upregulated and Cellular Glucose Uptake Is Enhanced



*Uptake of AMG is Na^+ dependent and is a measure of transport by SGLTs rather than GLUTs.
HEPTEC=human exfoliated proximal tubular epithelial cells; SE=standard error; SGLT=sodium glucose cotransporter; LUT=facilitative glucose transporter; AMG=methyl-α-D-[U-14C]-glucopyranoside; CPM=counts per minute.
Rahmoune H et al. *Diabetes*. 2005;54:3427-3434. Reprinted with permission.

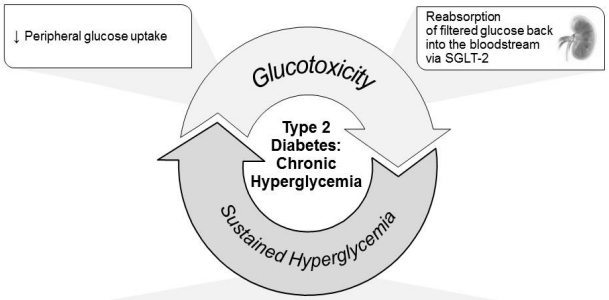
In Patients With Type 2 Diabetes, the Capacity for Glucose Reabsorption Is Increased



- TmG was 32% greater in patients with type 2 diabetes in comparison to healthy controls

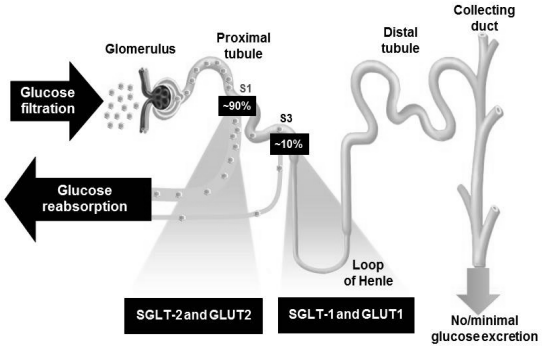
TmG=tubular maximum capacity for glucose reabsorption.
DeFronzo RA et al. *Diabetes Care*. 2013;36:3169-3176.

Continuous Glucose Reabsorption Perpetuates the Cycle of Glucotoxicity in Patients With Type 2 Diabtes[1–3]



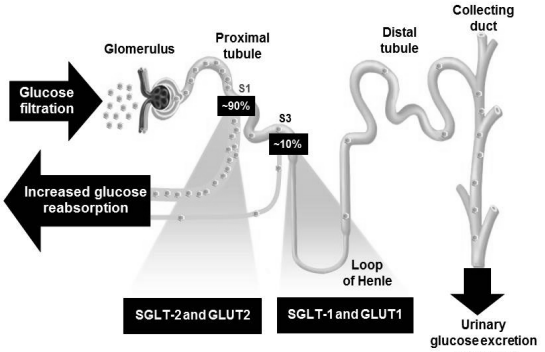
SGLT=sodium-glucose cotransporter.
1. DeFronzo RA. *Diabetes*. 2009;58:773-795.
2. Gerich JE. *Diabet Med*. 2010;27:136-142.
3. Poitout V et al. *Endocr Rev*. **2008;29:351-366**.

In normal glucose-tolerant subjects, virtually all filtered glucose is reabsorbed back into the bloodstream



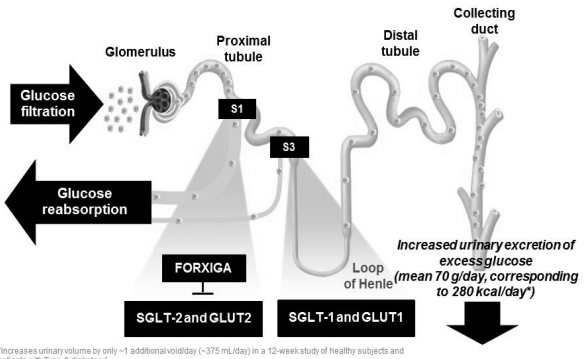
SGLT=sodium-glucose cotransporter; GLUT=facilitative glucose transporter.
1. Abdul-Ghani MA et al. *Endocr Pract*. 2008;14:782-790.
2. Bays H. *Curr Med Res Opin*. 2009;25:671-681.

Increased Glucose Reabsorption in Patients with Type 2 Diabetes



SGLT=sodium-glucose cotransporter; GLUT=facilitative glucose transporter.
1. Abdul-Ghani MA et al. *Endocr Pract*. 2008;14:782-790.
2. Bays H. *Curr Med Res Opin*. 2009;25:671-681.

Inhibition of SGLT-2 in the Kidney Leads to Urinary Glucose Excretion in Patients With Type 2 Diabetes



*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]

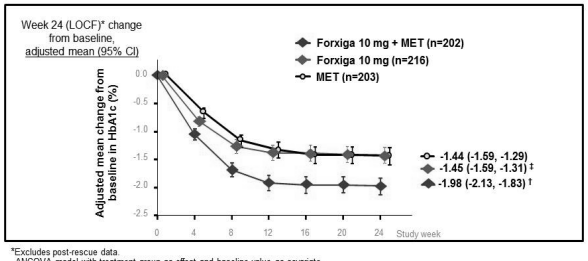
SGLT=sodium-glucose cotransporter; GLUT=facilitative glucose transporter.
1. Abdul-Ghani MA et al. *Endocr Pract*. 2008;14:782-790. 2. Bays H. *Curr Med Res Opin*. 2009;25:671-681.
3. List JF et al. *Diabetes Care* 2009;32:650-657; EU SmPC 2012; section 5.1.

Clinical application 1

✔1. Monotherapy or Initial Combination with Metformin
2. Add on to Metformin
3. Add on to Metformin and Sulfonylurea
4. Add on to DPP-4 inhibitors (Sitagliptin)
5. Add on to Insulin
6. others

Forxiga in Combination with Metformin: Change in HbA1c Over 24 Weeks

- Forxiga plus metformin demonstrated mean HbA1c reductions significantly greater than either monotherapy
- Forxiga 10 mg was non-inferior to metformin for HbA1c reduction

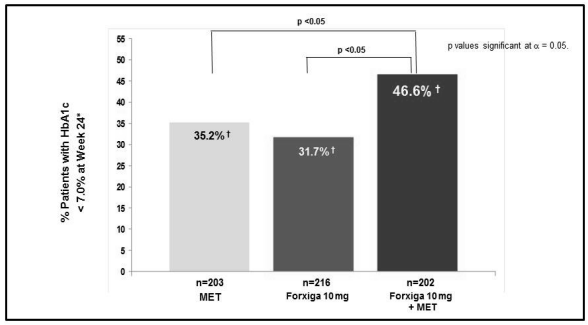


*Excludes post-rescue data.
ANCOVA model with treatment group as effect and baseline value as covariate.

† *P* value < 0.0001; ‡ Forxiga 10 mg non-inferior to MET.

LOCF, last observation carried forward.
Henry R.R. et al, Int J Clin Pract. 2012 May;66(5):446-56. doi: 10.1111/j.1742-1241.2012.02911.x. Epub 2012 Mar 13.

Forxiga in Combination with Metformin: Patients with HbA1c < 7.0% at Week 24*

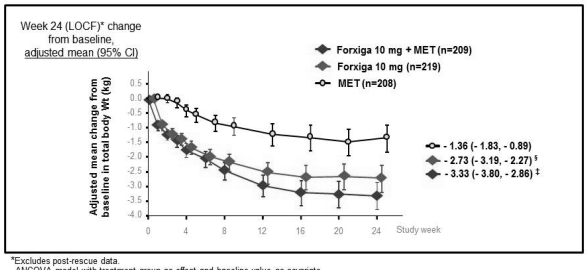


*LOCF values. Excludes post-rescue data. Baseline mean HbA1c was 9.1 – 9.2%.
†Proportion of patients at week 24 with HbA1c < 7.0% (LOCF), adjusted for baseline value.

Henry R.R. et al, Int J Clin Pract. 2012 May;66(5):446-56. doi: 10.1111/j.1742-1241.2012.02911.x. Epub 2012 Mar 13.

Forxiga in Combination with Metformin: Change in Body Weight Over 24 Weeks

Mean weight loss with combination therapy and Forxiga monotherapy was more than double the weight loss with metformin monotherapy



*Excludes post-rescue data.
ANCOVA model with treatment group as effect and baseline value as covariate.

§ *P* value < 0.0001. Forxiga 10 mg significant vs MET after sequential testing at α=0.05.
‡ *P* value < 0.0001. Forxiga + MET significant vs MET after sequential testing at α=0.05.
† *P* value < 0.0001. Forxiga + MET vs MET after sequential testing at α=0.05.

Henry R.R. et al, Int J Clin Pract. 2012 May;66(5):446-56. doi: 10.1111/j.1742-1241.2012.02911.x. Epub 2012 Mar 13.

Clinical application 1

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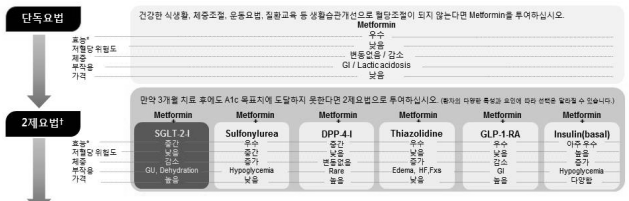
5. Add on to Insulin
6. others

2nd line: Advancing to Dual Combination, Add on to Metformin



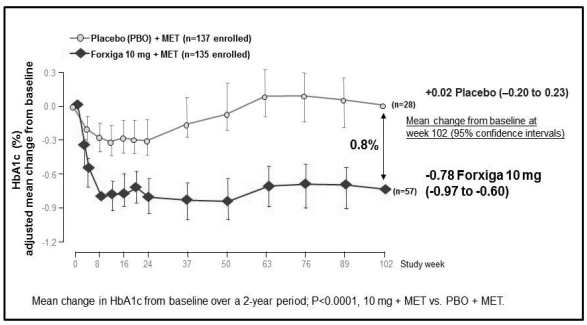
Forxiga versus Placebo

Forxiga versus SU

Forxiga versus DPP4-i

Diabetes Care 2015;38:140–149

Forxiga® (dapagliflozin) + metformin: Durable HbA1c reduction over 2 years[1,2]

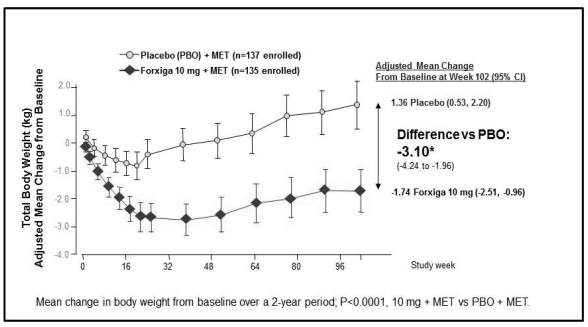


Mean change in HbA1c from baseline over a 2-year period; P<0.0001, 10 mg + MET vs. PBO + MET.

Baseline HbA1c(%)	PBO	Forxiga 10mg
	8.12 ± 0.96	7.92 ± 0.82

1. Bailey CJ, et al. *Lancet.* 2010;375:2223–33. 2. Bailey CJ, et al. *BMC Medicine.* 2013;11:43.

Forxiga® (dapagliflozin) + metformin: Durable body weight reduction over 2 years[1,2]

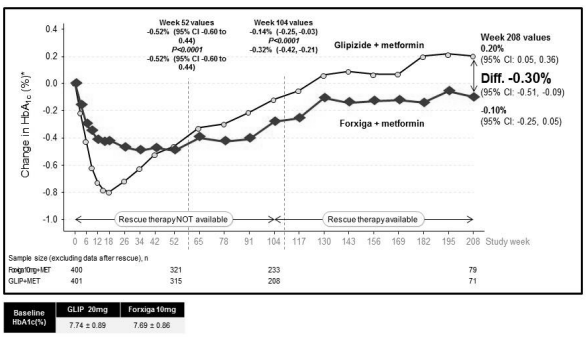


Mean change in body weight from baseline over a 2-year period; P<0.0001, 10 mg + MET vs PBO + MET.

Baseline BW (kg)	PBO	Forxiga 10mg
	87.74 ± 19.24	86.28 ± 17.53

1. Bailey CJ, et al. *Lancet.* 2010;375:2223–33.2.Bailey CJ, et al. *BMC Medicine.* 2013;11:43.

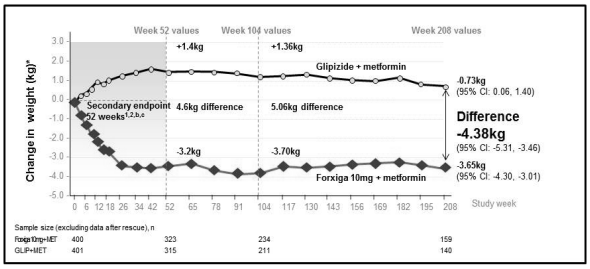
Forxiga® (dapagliflozin) + metformin, H2H study vs SU: Significant HbA1c reduction over 4 years[1-3]



Baseline HbA1c(%)	GLIP 20mg	Forxiga 10mg
	7.74 ± 0.89	7.69 ± 0.86

*Data are adjusted mean change from baseline ± 95% CI derived from a longitudinal repeated-measures mixed model
DAPA=dapagliflozin, GLIP=glipizide, MET=metformin; SBP=systolic blood pressure
1. Nauck MA, et al. *Diabetes Care.* 2011;34:2015-2022. 2. Nauck MA, et al. *ADA 71st Scientific Sessions.* June 24–28, 2011; San Diego, CA. Poster #40-LB. 3. Del Prato, et al. *ADA 73rd Scientific Sessions.* June 21-25, 2013; Chicago, IL. Abstract #62-LB.

Forxiga® (dapagliflozin) + metformin,
H2H study vs SU: Significantly greater reduction in body weight, sustained over 4 years[1-3]



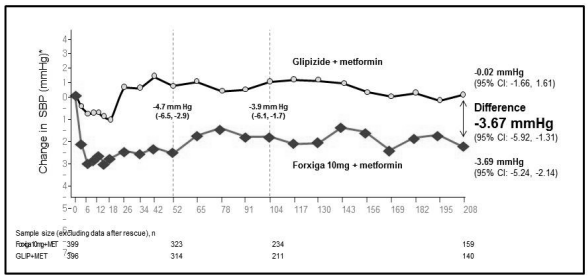
Baseline BW (kg)	GLIP 20mg	Forxiga 10mg
	87.6 ± 17.0	88.4 ± 16.3

*Data are adjusted mean change from baseline ± 95% CI derived from a longitudinal repeated-measures mixed model
* 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.

DAPA=dapagliflozin; GLIP=glipizide; MET=metformin; SU= SU

1. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 2. Nauck MA, et al. *ADA 71st Scientific Sessions*. June 24–28, 2011; San Diego, CA. Poster #40-LB. 3. Del Prato, et al. *ADA 73rd Scientific Sessions*. June 21-25, 2013; Chicago, IL. Abstract #62-LB.

Forxiga® (dapagliflozin) + metformin,
H2H study vs SU: Greater change of systolic blood pressure, sustained over 4 years[1-3*]

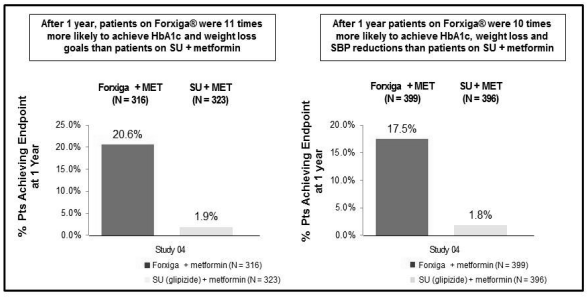


Baseline SBP (mmHg)	GLIP 20mg	Forxiga 10mg
	133.8 ± 14.7	132.8 ± 14.9

*Data are adjusted mean change from baseline ± 95% CI derived from a longitudinal repeated-measures mixed model. * 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. Note: There were no specific restrictions for changes to concomitant blood pressure medications during the study. DAPA=dapagliflozin; GLIP=glipizide; MET=metformin; SBP=systolic blood pressure

1. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 2. Nauck MA, et al. *ADA 71st Scientific Sessions*. June 24–28, 2011; San Diego, CA. Poster #40-LB. 3. Del Prato, et al. *ADA 73rd Scientific Sessions*. June 21-25, 2013; Chicago, IL. Abstract #62-LB.

Forxiga® (dapagliflozin) + metformin,
H2H study vs SU: More favourable composite endpoint data[1,2]

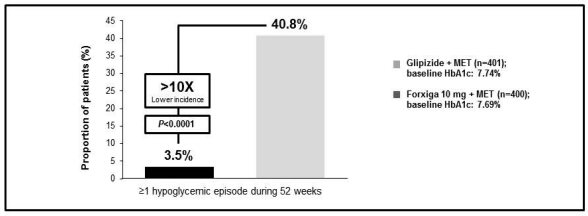


* Endpoints were no major/minor hypoglycemia and reductions of HbA1c ≥0.5%, TBW ≥3%, systolic blood pressure (SBP) ≥3 mm Hg. SU=SU. * Forxiga is indicated in patients with type 2 diabetes to improve glycemic control. It is not indicated for the management of obesity or high blood pressure, and these effects are caused by dapagliflozin's mechanism of action. A proper decision is necessary depending on patient's condition.

1. Wygant GD, et al. *Abstract 755, EASD*, Berlin. 2. Wygant GD, et al. http://www.easdvirtualmeeting.org/resources/2926.

Forxiga® (dapagliflozin) + metformin,
H2H study vs SU: Superior HbA1c reduction over 4 years[1-3]

>10X lower incidence of hypoglycemia[1,2,a–c]
Secondary endpoint at 52 weeks

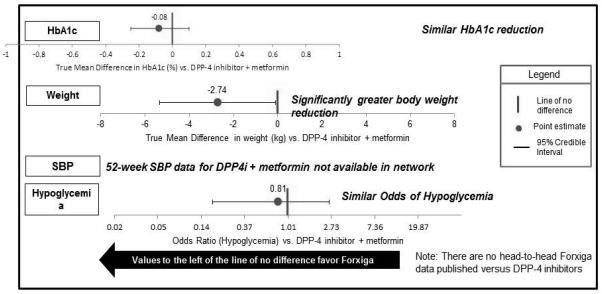


a. Phase 3, multicenter, randomized, double-blind, parallel-group, 52-week, glipizide-controlled noninferiority study to evaluate the efficacy and safety of Forxiga 10 mg + metformin (≥1,500 mg/day) vs glipizide + metformin (≥1,500 mg/day) in patients with inadequate glycemic control (HbA1c>6.5% and ≤10%) on metformin alone.[1,2]
b. Secondary endpoint: Percentage of patients experiencing ≥1 hypoglycemic event up to 52 weeks.[2]
c. The number and proportion of patients experiencing hypoglycemia were analyzed with descriptive statistics using the safety analysis set.[3]
d. The long-term, 52-week extension period allowed for one attempt at up-titration if HbA1c was >7% (only until the subject reached maximum dose), and down-titration, if medically indicated.[2]
Major hypoglycemia – symptomatic episode requiring external assistance due to severely impaired consciousness or behavior, with capillary or plasma glucose levels of 54 mg/dL (<3.0 mmol/L) and recovery after glucose or glucagon administration.[2]
Minor hypoglycemia – symptomatic episode with capillary or plasma glucose levels of 63 mg/dL (<3.5 mmol/L), irrespective of the need for external assistance.[2]

1. Forxiga® (dapagliflozin) Summary of Product Characteristics. Bristol-Myers Squibb/AstraZeneca EEIG. Middlesex, United Kingdom; 2012. 2. Nauck MA, et al. Diabetes Care. 2011;34:2011–22. 3. Nauck MA, et al. ADA 71st Scientific Sessions. June 24-28, 2011; San Diego, CA. Poster #40-LB. 4. Del Prato, et al. ADA 73rd Scientific Sessions. June 21-25, 2013; Chicago, IL. Poster #62-LB. †In a pre-specified pooled analysis of 949 subjects on Forxiga 10 mg and 1096 subjects on placebo from a placebo-controlled pool of patients.

Forxiga® (dapagliflozin) + MET:
Similar HbA1c reduction and significantly greater body weight reduction compared with DPP4i + MET[1]

The result of mixed treatment comparison/network meta-analysis over 52 weeks of treatment



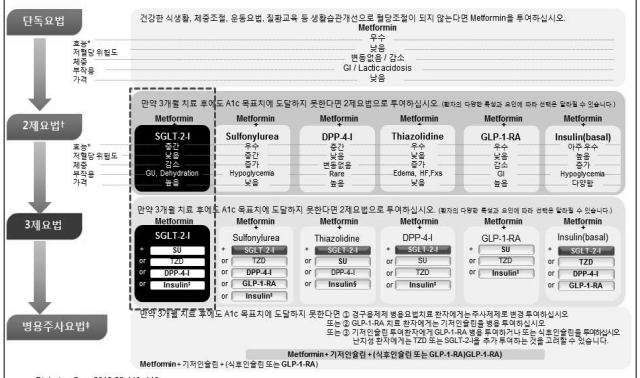
Note: There are no head-to-head Forxiga data published versus DPP-4 inhibitors

1. Goring S, et al. *Diab, Obes and Metab*, 16:433-442, 2014

Clinical application 1

1. Monotherapy or Initial Combination with Metformin
2. Add on to Metformin
3. ✔ Add on to Metformin and Sulfonylurea
4. Add on to DPP-4 inhibitors (Sitagliptin)
5. Add on to Insulin
6. others

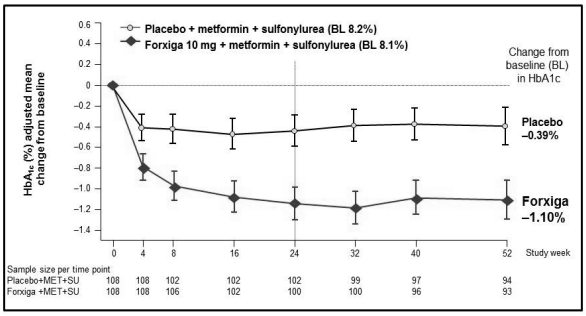
3rd line: Advancing to triple combination



Diabetes Care 2015;38:140–149

Forxiga as add-on therapy to metformin plus sulfonylurea

Sustained improvement in HbA_{1c} with Forxiga over 52 weeks

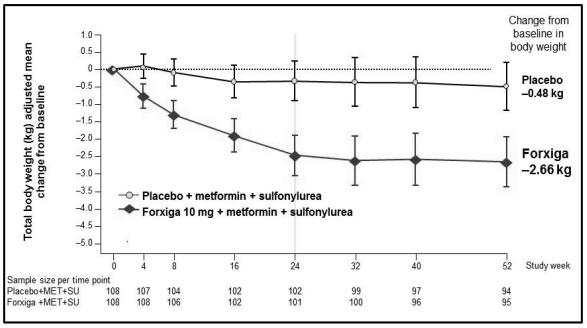


Including data after rescue; MET, metformin; SU, sulfonylurea

Matthaei S et al, Diabetes Care. 2015 Mar;38(3):365-72. doi: 10.2337/dc14-0666. Epub 2015 Jan 15.

Forxiga as add-on therapy to metformin plus sulfonylurea

Sustained reduction in body weight over 52 weeks*



Including data after rescue
*Dapagliflozin is not indicated for tretament of obesity. Weight reduction is an additional effect and was a secondary endpoint in clinical studies.

Matthaei S et al, Diabetes Care. 2015 Mar;38(3):365-72. doi: 10.2337/dc14-0666. Epub 2015 Jan 15.

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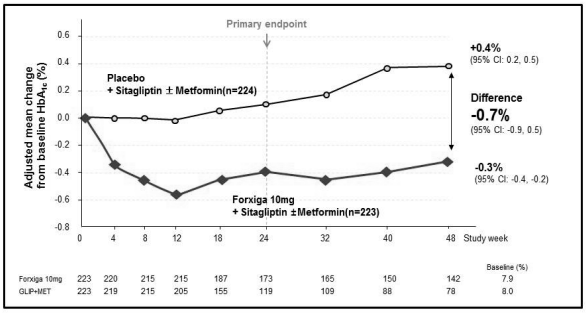
6. others

Forxiga:Significant reductions in HbA1c compared with placebo when added to DPP-4i (Sitagliptin)

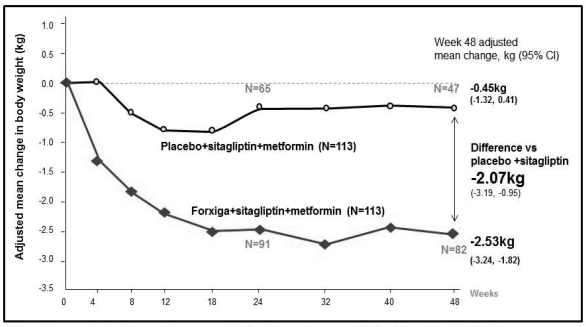
Adjusted Mean Change in HbA1c over 48 Weeks (Overall Population)



Mean values were based on the repeated measures analysis model: error bars represent 95% CIs for the adjusted mean change from baseline. CIs, confidence intervals; DAPA, dapagliflozin; HbA1c, glycated haemoglobin

Jabbour SA, et al. *ADA 2012*; poster #1071-P

Forxiga: Significant weight reduction when added to DPP-4i (Sitagliptin)



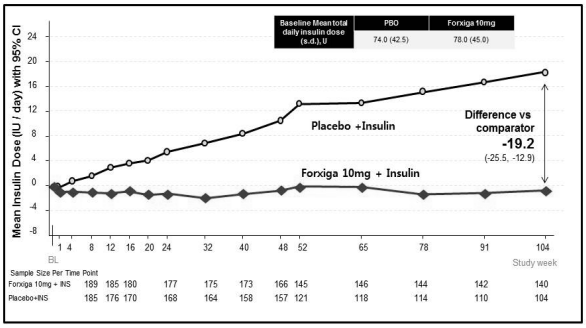
* Mean values were based on the repeated measures analysis model: error bars represent 95% confidence intervals (CIs) for the adjusted mean change from BL.
* Forxiga is indicated in patients with type 2 diabetes to improve glycemic control. It is not indicated for the management of obesity or high blood pressure, and these effects are caused by dapagliflozin's mechanism of action. A proper decision is necessary depending on patient's condition.

Jabbour SA, *et al.* ADA 2012; poster #1071-P

Clinical application 1

1. Monotherapy or Initial Combination with Metformin
2. Add on to Metformin
3. Add on to Metformin and Sulfonylurea
4. Add on to DPP-4 inhibitors (Sitagliptin)
5. ✔ Add on to Insulin
6. others

Forxiga® (dapagliflozin) + insulin: Insulin Doses Remain Stable on Forxiga Over 2 Years[1]

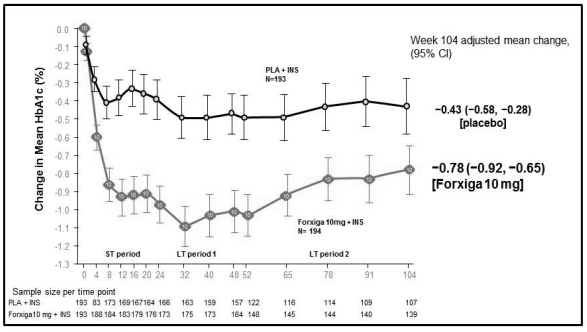


Repeated measures mixed model analysis, including data after insulin up-titration.

1.Wilding, *Diabetes, Obesity and Metabolism* 2013.

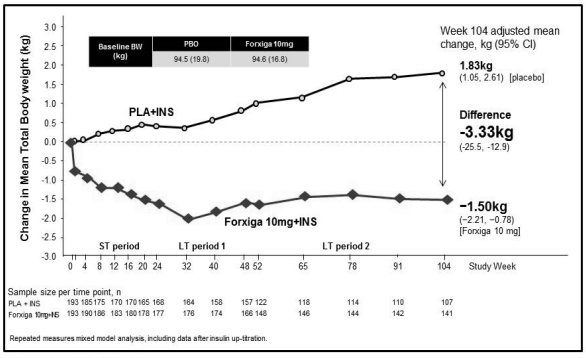
Forxiga as Add-on to Insulin: Change in HbA1c Over 104 Weeks

Forxiga added to insulin for
104 weeks enabled sustained reductions in HbA1c*



*Including data after insulin uptitration
Wilding et al. *Diabetes Obes Metab*. 2013; epub ahead of print.

Forxiga® (dapagliflozin) : Additional benefit of weight loss sustained when added to insulin over 2 years



Repeated measures mixed model analysis, including data after insulin up-titration.

*Including data after insulin uptitration
Wilding, *Diabetes, Obesity and Metabolism* 2013

Clinical application 1

1. Monotherapy or Initial Combination with Metformin
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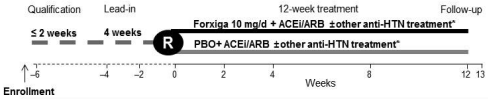
4. Add on to DPP-4 inhibitors (Sitagliptin)
5. Add on to Insulin
6. ✔ others

Forxiga® (dapagliflozin) in Patients with T2DM and Hypertension: Study Design

- Two studies: study 1 in patients with HTN inadequately controlled on ACEi/ARB; study 2 in patients inadequately controlled on ACEi/ARB and another anti-HTN treatment



Key inclusion criteria at enrollment:

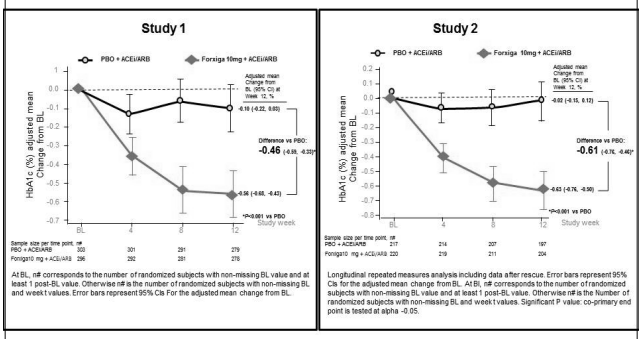
- Age 18–89 y
- T2DM (HbA1c 7%–10.5%)
- Stable antidiabetic treatment (≥ 6 weeks for OADs, ≥ 8 weeks for insulin, ≥ 12 weeks for TZDs)
- BMI ≤ 45.0 kg/m²
- SBP 140–164 mm Hg / DBP 85–104 mm Hg
- 24-h BP > 130/80 mm Hg
- Stable, effective therapeutic dose of an ACEi or ARB ≥ 4 weeks
- C-peptide value ≥ 0.8 ng/mL (0.30 nmol/L)

- Co-primary efficacy end points
  - Change from baseline at week 12 in **seated SBP and HbA1c**
- Secondary efficacy end points:
  - Change from baseline at week 12 in 24-hour mean ambulatory SBP, seated DBP, 24-hour mean ambulatory DBP, and serum uric acid

DBP, diastolic blood pressure; *Patients maintained stable dose of antidiabetic agent(s), plus their stable therapeutic dose of an ACEi or ARB, and no new antidiabetic therapy was added during the study. Open-label rescue antihypertensive therapy was available for patients with severe or sustained hypertension during the study.

Weber M, et al. *AHA 2013*; poster 2095; Weber M, et al. AHA 2013; poster 2097.

Forxiga® (dapagliflozin) in patients with T2DM and hypertension: change in HbA1c through 12 weeks

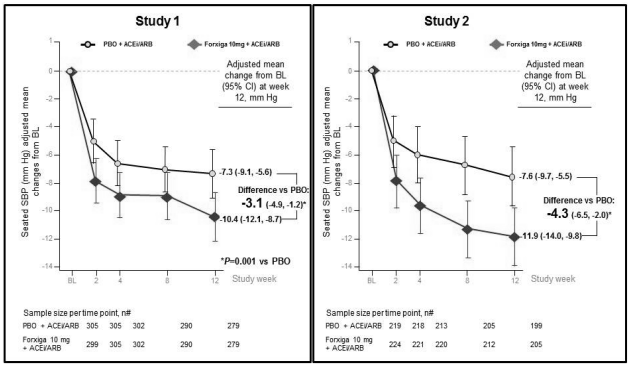


At BL, n# corresponds to the number of randomized subjects with non-missing BL value and at least 1 post-BL value. Otherwise n# is the number of randomized subjects with non-missing BL and week t values. Error bars represent 95% CIs For the adjusted mean change from BL.

Longitudinal repeated measures analysis including data after rescue. Error bars represent 95% CIs for the adjusted mean change from BL. At BL n# corresponds to the number of randomized subjects with non-missing BL value and at least 1 post-BL value. Otherwise n# is the Number of randomized subjects with non-missing BL and week t values. Significant P value: co-primary end point is tested at alpha -0.05.

Weber M, et al. *AHA 2013*; poster 2095; Weber M, et al. AHA 2013; poster 2097.

Forxiga® (dapagliflozin) in patients with T2DM and hypertension: change in seated SBP



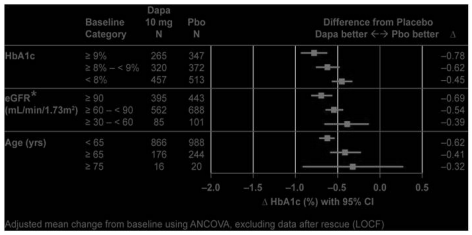
Weber M, et al. *AHA 2013*; poster 2095; Weber M, et al. AHA 2013; poster 2097.

Factors affecting SGLT-2 inhibitors

Baseline eGFR & HbA1c

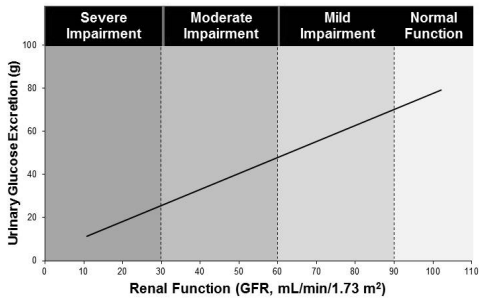
Forxiga Subgroup analysis: Change in HbA1c at Week 24

- No differential efficacy detected with gender, race, ethnicity, region, baseline BMI or duration of Type 2 diabetes
- Interactions were detected with three subgroup variables in overall population



* 고혈당 (≥ 65세)
일반적으로, 경험적 근거란 용량 조절은 정당되지 않는다. 신기능 및 체액량 감소의 위험을 고려해야 한다. 75세 이상의 환자에 대한 치료 경험이 제한적이므로, 이 약물 요법의 시작을 권장하지 않는다.
***Forxiga should not be used in patients with moderate to severe renal impairment** (patients with CrCl <60 mL/min or **eGFR <60 mL/min/1.73 m²**). **Monitoring of renal function is recommended as follows: Prior to initiation, and at least yearly thereafter; prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter; for renal function approaching moderate renal impairment, at least 2–4 times per year, if renal function falls below CrCl <60 mL/min or eGFR <60 mL/min/1.73 m², Forxiga treatment should be discontinued.**
Pooled data from nine Phase III studies, Dapa, dapagliflozin. Food & Drug Administration. Endocrinologic and Metabolic Drugs Advisory Committee: Forxiga(BMS-512148). Available at: http://tinyurl.com/7sz5j57. Last accessed October 2012.

Urinary Glucose Excretion With SGLT2 Inhibition Is Dependent on Renal Function



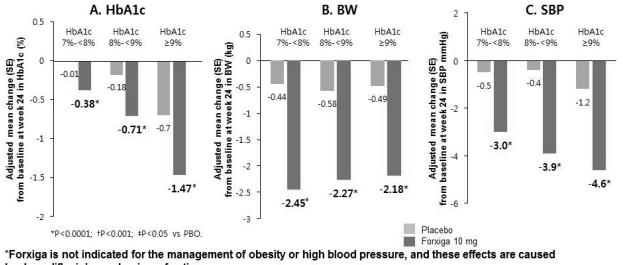
* This graph represents a model based on trends in data observed for SGLT2 inhibitors.
* Forxigashould not be used in patients with moderate to severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2, or end-stage renal disease [ESRD] or patients in dialysis according to local PI.

SGLT=sodium-glucose cotransporter; GFR=glomerular filtration rate.

1. FDA. Briefing Document. NDA 202293. 2011. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs AdvisoryCommittee/UCM262994.pdf. Accessed March 31, 2014. 2. FDA. Canagliflozin Briefing Document January 10, 2013. 3. Macha S et al. Diab Obes Metab. 2014;16:215-222.

Reductions in HbA1c, Weight, and Systolic Blood Pressure in Patients With T2DM at week 24 across HbA1c Subgroups

- Pooled data from ten 24-week placebo-controlled trials of Forxiga in patients with T2DM. (n=4,858)
- Improvements in HbA1c, BW and SBP with Forxiga were consistent across HbA1c subgroups. The greatest decrease in HbA1c was observed in patients with HbA1c ≥9% at baseline.



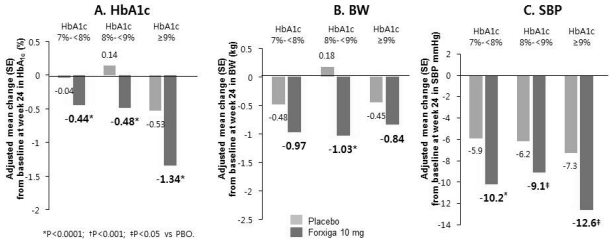
*P<0.0001; †P<0.001; ‡P<0.05 vs PBO.

***Forxiga is not indicated for the management of obesity or high blood pressure, and these effects are caused by dapagliflozin's mechanism of action.**

Jason Moran et al, 75th Scientific Sessions, American Diabetes Association 2015. Poster #1198-P

Reductions in HbA1c, Weight, and Systolic Blood Pressure in Patients With T2DM at week 12 across HbA1c Subgroups

- Separate pooled data from two 12-week placebo-controlled trials in patients with T2DM and established hypertension showed similar results to the 10-study pool. (n=1,219)
- Additional analysis found the change in SBP to significantly correlate with the change in BW (*p<0.01 in each treatment group).* However, no significant association was observed between the change in HbA1c and the change in SBP.



*P<0.0001; †P<0.001; ‡P<0.05 vs PBO.

***Forxiga is not indicated for the management of obesity or high blood pressure, and these effects are caused by dapagliflozin's mechanism of action.**

Jason Moran et al, 75th Scientific Sessions; American Diabetes Association 2015. Poster #1198-P

SGLT-2 inhibitors

Clinical Profile of Pooled data

This is only for scientific discussion to understand a class characteristic of SGLT-2 inhibitor and may include a compound which is not approved in Korea.

Forxiga is indicated in patients with type 2 diabetes to improve glycemic control. It is not indicated for the management of obesity and BP control, and these effects are caused by dapagliflozin's mechanism of action. A proper decision is necessary depending on patient's condition.

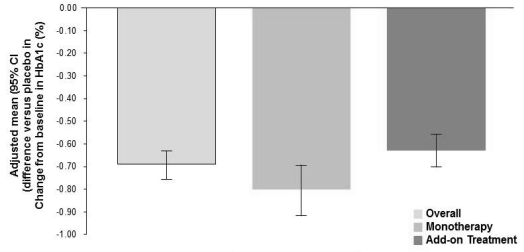
- Comprehensive literature review based on 2 meta-analyses:
  - *Vasilakou et al. Ann* Intern Med. 2013;159(4):262-274
  - Liakos et al. Diabetes Obes Metab. 2014. Oct;16(10):984-93.
  - Updated search of electronic databases through June 30, 2014

- Included studies (≥ 12 weeks duration)
  - 55 trials versus placebo (approximately 15,000 patients)
  - 15 trials versus active agents (approximately 7,000 patients)
    - 23 dapagliflozine trials
    - 12 canagliflozine trials
    - 13 empagliflozine trials
    - 7 iprgliflozine trials
    - 3 luseogliflozine trials*
    - 2 togogliflozine trials*
    - 1 ertugliflozine trials*

Results are analyses for the group allocated to the highest, most common across studies.
SGLT-2: sodium glucose cotransporter 2, EASD: European Association for the Study of Diabetes.
* Not approved in Korea

A new class of oral agents: SGLT-2 inhibitors, *Apostolos Tsapas*, Oral presentation #1358,EASD2014

Placebo-corrected change from baseline in HbA1c

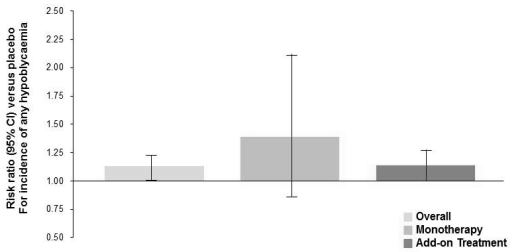


Overall	Monotherapy	Add-on Treatment
-0.69 (-0.75 to -0.63)	-0.80 (-0.91 to -0.69)	-0.63 (-0.70 to 0.56)

Pooled results for 20 studies of SGLT-2 inhibitors as monotherapy and 35 studies as add-on treatment with ≥ 12 weeks duration from published and gray literature sources through June 30, 2014 [search strategy adapted from *Vasilakou et al. Ann intern Med. 2013(4);159:262-274*]. Results are presented for the group allocated to the highest, most common dose across studies. SGLT-2: sodium glucose cotransporter 2, CI: confidence interval, HbA1c: hemoglobin A1c.

A new class of oral agents: SGLT-2 inhibitors, *Apostolos Tsapas*, Oral presentation #1358, EASD2014

Risk ratio versus placebo for incidence of any hypoglycaemia

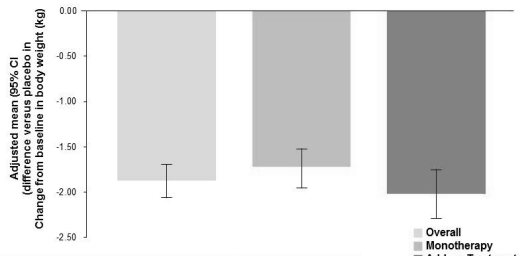


Overall	Monotherapy	Add-on Treatment
1.13 (1.03 to 1.25)	1.39 (0.87 to 2.21)	1.14 (1.02 to 1.28)

Pooled results for 20 studies of SGLT-2 inhibitors as monotherapy and 35 studies as add-on treatment with ≥ 12 weeks duration from published and gray literature sources through June 30, 2014 [search strategy adapted from *Vasilakou et al. Ann intern Med. 2013(4);159:262-274*]. Results are presented for the group allocated to the highest, most common dose across studies. SGLT-2: sodium glucose cotransporter 2, CI: confidence interval, HbA1c: hemoglobin A1c.

A new class of oral agents: SGLT-2 inhibitors, *Apostolos Tsapas*, Oral presentation #1358, EASD2014

Placebo-corrected change from baseline in body weight

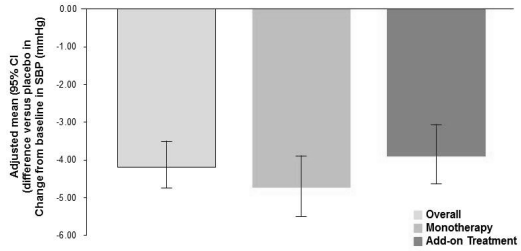


Overall	Monotherapy	Add-on Treatment
-1.87 (-2.05 to -1.70)	-1.72 (-1.92 to -1.52)	-2.02 (-2.28 to -1.75)

Pooled results for 20 studies of SGLT-2 inhibitors as monotherapy and 35 studies as add-on treatment with ≥ 12 weeks duration from published and gray literature sources through June 30, 2014 [search strategy adapted from *Vasilakou et al. Ann intern Med. 2013(4);159:262-274*]. Results are presented for the group allocated to the highest, most common dose across studies. SGLT-2: sodium glucose cotransporter 2, CI: confidence interval, HbA1c: hemoglobin A1c.

A new class of oral agents: SGLT-2 inhibitors, *Apostolos Tsapas*, Oral presentation #1358, EASD2014

Placebo-corrected change from baseline in systolic blood pressure (SBP)



Overall	Monotherapy	Add-on Treatment
-4.19 (-4.77 to -3.61)	-4.74 (-5.52 to -3.95)	-3.91 (-4.68 to -3.14)

Pooled results for 20 studies of SGLT-2 inhibitors as monotherapy and 35 studies as add-on treatment with ≥ 12 weeks duration from published and gray literature sources through June 30, 2014 [search strategy adapted from *Vasilakou et al. Ann intern Med. 2013;4):159:262-274*]. Results are presented for the group allocated to the highest, most common dose across studies. SGLT-2: sodium glucose cotransporter 2; CI: confidence interval; HbA1c: hemoglobin A1c.

A new class of oral agents: SGLT-2 inhibitors, *Apostolos Tsapas*, Oral presentation #1358, EASD2014

SGLT-2 inhibitors

Future Perspectives with 2015 ADA Updates

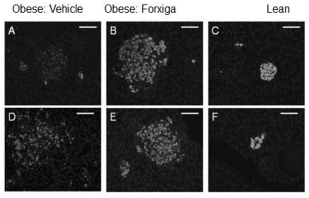
The contents herein is made for scientific discussion based on speaker's insight.
This session includes discussion points about SGLT-2 inhibitors based on up-to-date information.

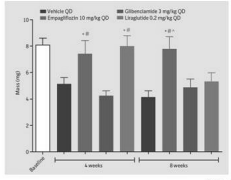
Future perspectives focusing on 2015 ADA Updates

1. Improving β-cell function and Insulin Sensitivity
2. Renal Safety
3. CV Safety

β-cell preservation with SGLT-2 inhibition: Preclinical evidence

- ZDF studies indicate increased β-cell mass and improved morphology
  - In obese, diabetic rats, Forxiga sustains pancreatic function and preserves islet morphology[1]
  - Significantly higher β-cell mass in male ZDF rats treated with a SGLT-2 inhibitor versus vehicle at Week 8[2]





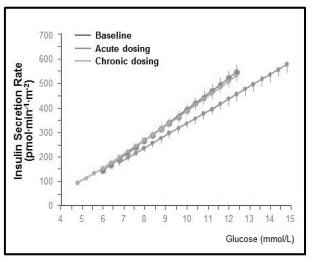
(Fig 4c)

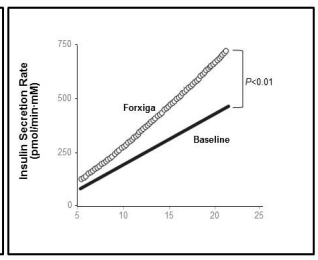
1. Macdonald FR, *et al. Diabetes, Obesity and Metabolism* 2010;**12**:1004–12; 2. Jelsing J, *et al.* J Pharmacol Exp Ther 350:657–664, September 2014

Associated with increased in β-cell glucose sensitivity

Empagliflozin Increased ß-cell function With acute and chronic dosing.

Forxiga caused a significant increase in β-cell glucose sensitivity from 23 ± 5 to 35 ± 5 pmol/min.mM (*P <0.01).*

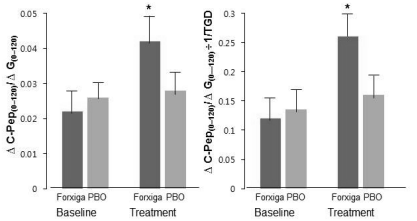




Ferrannini E et al. *J Clin Invest.* 2014;124:499-508.
Merovci A., et al. J Clin Endocrinol Metab. 2015 Feb 24:jc20143472. [Epub ahead of print]

Associated with increased in the insulin secretion/insulin resistance index

24 subjects with T2DM received Forxiga (n=16) or placebo (n=8) for 2 weeks, and a 75-gram OGTT and insulin clamp were performed before and after treatment.



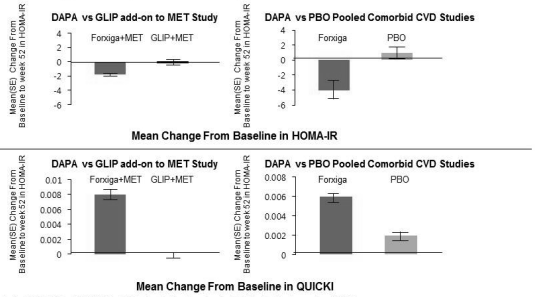
- The insulin secretion/insulin resistance index (ΔC-Pep$_{0-120}$/ Δ G$_{0-120}$÷1/TGD) increased more than two-fold in dapagliflozin-treated subjects (0.12 ± 0.04 to 0.26 ± 0.05, *P <0.01).*
- The increase in Δ C-Pep$_{0-120}$/ Δ G$_{0-120}$÷IR at 2 weeks relative to baseline in dapagliflozin-treated subjects (0.15 ± 0.03) was significantly greater (*P<0.05) than that* in placebo-treated subjects (0.03 ± 0.03).

	Forxiga		Placebo	
	Baseline	Treatment	Baseline	Treatment
FPG (mg/dl)	182 ± 8	149 ± 8	184 ± 19	171 ± 9
2h-PPG (mg/dl)	342 ± 12	269 ± 14	334 ± 16	301 ± 16

Merovci A., et al. *J Clin Endocrinol Metab.* 2015 Feb 24:jc20143472. [Epub ahead of print]

Forxiga and Insulin Resistance in Patients With Type 2 Diabetes

- Data from 3 phase 3 trials were analyzed:
  - Forxiga vs glipizide as add-on to metformin for 52 weeks (N=814)
  - 2 pooled 24-week studies of Forxiga vs placebo in patients with CVD ± hypertension (N=922 and N=964)



IR was assessed using HOMA-IR14 and QUICKI.15 HOMA-IR = fasting plasma insulin (mU/mL) x fasting glucose (mmol/L)/22.5
QUICKI = 1/[log (fasting plasma insulin, µU/mL) + log (fasting blood glucose, mg/dL)]
Arie Katz et al, 75th Scientific Sessions, American Diabetes Association 2015. Poster #1175-P

Future perspectives focusing on 2015 ADA Updates

1. Improving β-cell function and Insulin Sensitivity
2. Renal Safety
3. CV Safety

Renal Safety with Forxiga in an Asian Population

- Pooled from 8 Phase 2b/3 double-blind trials that compared Forxiga 10 mg (N=465) with placebo (N=497) for up to 24 weeks.
  - Patients were drug-naive, or receiving background therapy with oral glucose-lowering therapies (glimepiride [4 mg/day], pioglitazone [≥30 mg/day], or metformin [≥1500 mg/day])
- **Mean (SD) exposure to study drug** over 24 weeks was 149(43), 152(39) days in the placebo, Forxiga 10 mg groups, respectively.

	PBO (n=497)	Forxiga 10mg (n=465)
eGFR, mL/min/1.73m², mean (SD)	94.2 (20.3	93.7 (21.5)
eGFR, n (%)		
≥90 mL/min/1.73m²	272 (54.7)	248 (53.3)
≥60 - <90 mL/min/1.73m²	211 (42.5)	202 (43.4)
≥30 - <60 mL/min/1.73m²	14 (2.8)	15 (3.2)
Albuminuria, n (%)		
Normoalbuminuria (<30 mg/g)	366 (73.6)	356 (76.6)
Nicroalbuminuria (≥30 - <300 mg/g)	118 (23.7)	106 (22.8)
Macroalbuminuria ≥300 mg/g	13 (2.6)	3 (0.6)

* Add-on combination of Forxiga with thiazolodinedione is not an approved indication in local PI.
* Forxigashould not be used in patients with moderate to severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2, or end-stage renal disease [ESRD] or patients in dialysis according to local PI.

N is the number of treated patients in the pooled population.
MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione; XR, extended release; SD, standard deviation
Wenying Yang et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1175-P

Adverse events related to renal function in an Asian Population

- AEs related to renal function occurred in a low proportion of patients in all three treatment groups.
  - All events were mild in intensity
  - No serious AEs related to renal function occurred

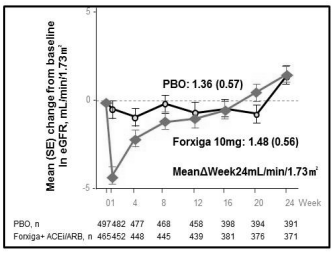
	PBO (n=497)	Forxiga 10mg (n=465)
Total number of patients with an AE related to renal function, n (%)	8 (1.6)	11 (2.4)
Renal impairment	5 (1.0)	9 (1.9)
Glomerular filtration rete decreased	0	2 (0.4)
Blood creatinine increased	2 (0.4)	0
Renal failure	1 (0.2)	0
Discontinuations due to AEs Related to renal function, n (%)	3 (0.6)	5 (1.1)

N is the number of treated patients in the intended population. Based on a predefined list of AEs of renal impairment/failure. AE, adverse event; DAPA, dapagliflozin; PBO, placebo
Wenying Yang et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1175-P

Renal function over time in an Asian Population

eGFR

- There were small reductions in mean eGFR with Forxiga at Week 1, but these returned to above baseline by Week 24.



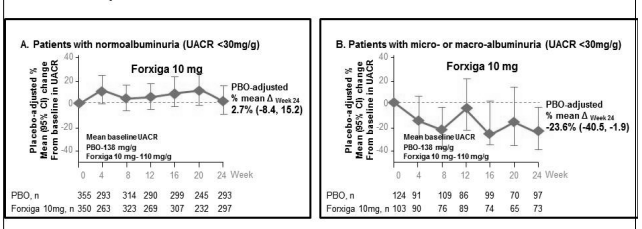
Laboratory parameters

- Most renal laboratory parameters showed no clinically relevant mean changes over 24 weeks
  - Small increases in **phosphorus** and reductions in **uric acid** were noted in dapagliflozin-treated patients
  - For **potassium**, there was a numerical increase in the proportion of patients with levels ≥6 mEq/Lin the Forxigagroups but not in the placebo group, however, frequency was low (≤1.2%) in all groups.

DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; PBO, placebo; SE, standard error.
Wenying Yang et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1175-P

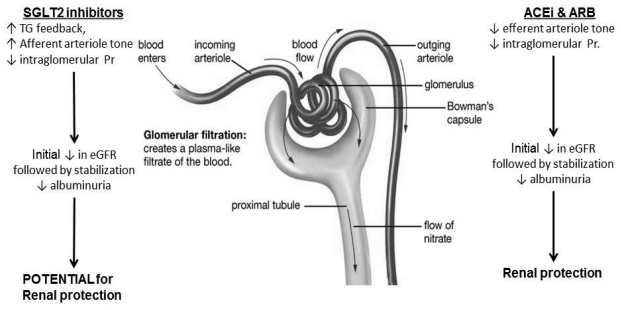
Urinary albumin-to-creatinine ratio in an Asian Population

- For patients with normoalbuminuria at baseline, there were small, clinically insignificant changes in UACR at Week 24.
- For patients with micro- or macro-albuminuria at baseline there was a tendency for UACR to be reduced over time.



Values are adjusted percent mean change in log-transformed UACR. Longitudinal repeated-measures mixed model analysis including data after rescue for inadequate glycemic control.
CI, confidence interval; DAPA, dapagliflozin; PBO, placebo; UACR, urinary albumin-to-creatinine ratio.
Wenying Yang et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1175-P

Hypotheses Regarding the Effect of SGLT2-inhibitors on the Progression of DM Nephropathy



Ther Adv Endocrinol Metab 2014, Vol. 5(3) 53–61
Inquiry into Biology (Whitby, ON: McGraw-Hill Ryerson, 2007), 311, fig. 9.4.

Forxiga Reduces Albuminuria in Hypertensive Diabetic Patients Using Renin-Angiotensin Blockers

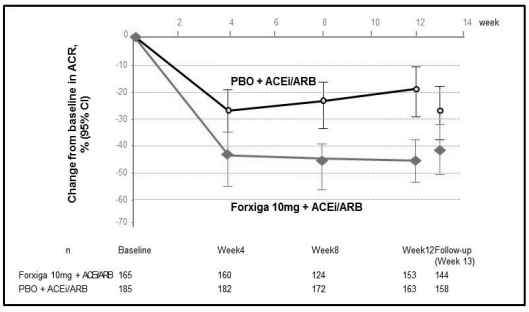
- Pooled from 2 phase 3 trials (T2DM+HTN patients) of 12 weeks' treatment duration evaluated the safety and efficacy of Forxiga in patients with:
  - Inadequately controlled T2DM (HbA1c, 7% to 10.5%).
  - Uncontrolled hypertension (SBP, 140 to 165 mm Hg; DBP, 85 to 105 mm Hg).
  - A stable dose of ACEi or an ARB therapy for ≥ 4 weeks.
  - Background anti-diabetes treatment consisting of oral as well as insulin-based therapies.
- For this post hoc analysis, patients with either micro- or macro albuminuria at baseline (defined as ACR ≥ 30 mg/g) were selected.
- **Effect on blood pressure and HbA1c**
  - At week 12, patients receiving Forxiga 10 mg had PBO-corrected changes in HbA1c of –0.5% (95% CI, –0.7 to –0.3), and PBO-corrected changes in blood pressure of –3.5 mm Hg (95% CI, –5.9 to –1.0).

H.J. Lambers Heerspink et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1176-P

Effect on renal function parameters in Hypertensive Diabetic Patients Using Renin-Angiotensin Blockers

- **Albuminuria**

Forxiga 10 mg caused a PBO-corrected reduction in ACR at week 12 of –33.2% (95% CI, –45.4 to –18.2).



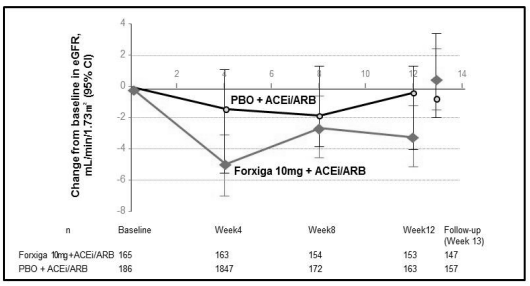
n	Baseline	Week4	Week8	Week12	Follow-up (Week 13)
Forxiga 10mg + ACEi/ARB	165	160	124	153	144
PBO + ACEi/ARB	185	182	172	163	158

H.J. Lambers Heerspink et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1176-P

Effect on renal function parameters in Hypertensive Diabetic Patients Using Renin-Angiotensin Blockers

- **eGFR**

An initial decrease in eGFR was observed in the Forxiga groups from baseline. However, the reduction in eGFR was completely reversible after treatment discontinuation.



n	Baseline	Week4	Week8	Week12	Follow-up (Week 13)
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PBO + ACEi/ARB	186	1847	172	163	157

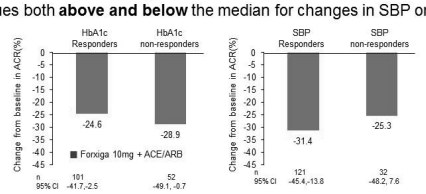
H.J. Lambers Heerspink et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1176-P

Albuminuria-lowering effect independent of changes in HbA1c, SBP, or eGFR

- **Albuminuria-lowering effect does not depend only on changes in HbA1c, SBP or eGFR.**

	ANCOVA including covariates For ΔHbA1c, ΔSBP, and ΔeGFR	ANCOVA not including covariates For ΔHbA1c, ΔSBP, and ΔeGFR
	Forxiga 10mg (n=227)	Forxiga 10mg (n=153)
Differences vs PBO	-26.8	-33.2
95% CI	-40.3, -10.4	-45.4, -18.2

- The albuminuria-lowering effect was also present in patients with 12-week values both **above and below** the median for changes in SBP or HbA1c.



H.J. Lambers Heerspink et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1176-P

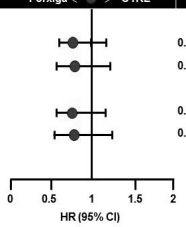
Future perspectives focusing on 2015 ADA Updates

1. Improving β-cell function and Insulin Sensitivity
2. Renal Safety
3. CV Safety

Composite Adjudicated CV Endpoint Analyses

- The overall HR for the prespecified primary endpoint of MACE plus UA between Dapa and control cohorts was 0.79
- The overall HR for MACE between Forxiga and control cohorts was 0.77
- No increased risk in patients with prior CV disease

Subgroup	Favors Forxiga ← → CTRL	HR (95% CI)
Primary CV endpoint		
All phase 2b and 3 pool (n=176)		0.79 (0.58, 1.07)
Patients with prior CV disease (n=128)		0.81 (0.56, 1.16)
MACE		
All phase 2b and 3 pool (n=134)		0.77 (0.54, 1.10)
Patients with prior CV disease (n=95)		0.80 (0.53, 1.22)



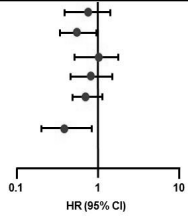
CI, confidence interval

EMDAC Background Document :
http://www.fda.gov/downloads/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

Individual Components of CV Endpoints

- The estimated HRs for individual components contributing to the composite endpoints of MACE and MACE plus UA, as well as other CV events, were ≤1.0

Event	Patients with events		Favors Forxiga ← → CTRL	HR (95% CI)
	Forxiga N=5936	CTRL N=3403		
CV death	20/3825	18/2200		0.70 (0.36, 1.36)
MI	30/5244	33/3014		0.57 (0.34, 0.95)
Stroke	25/4227	18/2412		1.00 (0.54, 1.86)
UA	26/4592	20/2697		0.87 (0.48, 1.59)
Unplanned coronary revascularisation	58/5525	55/3153		0.73 (0.50, 1.07)
Hospitalization for heart failure	10/2576	16/1780		0.36 (0.16, 0.84)



EMDAC Background Document :
http://www.fda.gov/downloads/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

Efficacy and Safety of Forxiga in Patients with T2DM and Concomitant HF: Safety Outcomes

- Pooled data were analyzed from five clinical trials of up to 52 weeks in duration that selected patients with a documented history of HF randomized to Forxiga 10mg (N=171) or placebo(N=149)

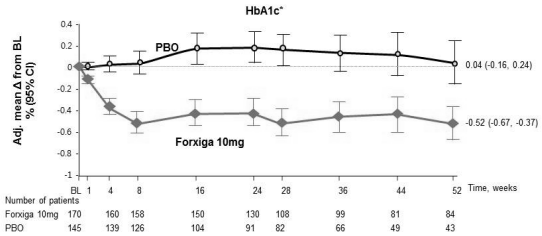
- ***Safety outcomes***
  - Primary CV composite endpoint: CV death, MI, stroke and hospitalization for unstable angina
  - Secondary CV composite endpoint: CV death, MI, stroke, hospitalization for UA + unplanned coronary revascularization and hHF

	Forxiga 10mg, n=171 n (%)	Placebo, n=149 n (%)	HR* Forxiga vs placebo (95% CI)
Primary CV composite endpoint†	9 (5.3)	9 (6.0)	0.87 (0.34, 2.23)
Secondary CV Composite endpoint‡	12 (7.0)	16 (10.7)	0.67 (0.32, 1.44)
MACE§	7 (4.1)	7 (4.7)	0.87 (0.30, 2.53)
Hospitalization for HF	1 (0.6)	7 (4.7)	0.14 (0.02, 1.15)

CV, Cardiovascular; MI, Myocardiac infacrtion; UA, unstable angina; hHF, hospitalization for Heart Failure; MACE, Major adverse cardiac event
심부전 환자 중 NYHA class I-II에서의 경험은 제한적이므로, 이들 환자에서는 신중히 사용하여야 한다.
NYHA class III-IV에 대한 이 약의 임상시험 경험이 없기 때문에 이 약의 사용이 권장되지 않는다.
Mikhail Kosiborod et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1211-P

Efficacy and Safety of Forxiga in Patients with T2DM and Concomitant HF: Efficacy Outcomes

- HbA1c and body weight reductions were consistently and substantially greater with Forxiga 10 mg than with placebo throughout the 52-week treatment period



Number of patients

	BL	1	4	8	16	24	28	36	44	52
Forxiga 10mg	170		160	158	150	130	108	99	81	84
PBO	145		139	126	104	91	82	66	49	43

*Pooled data from five studies ≤52 weeks (NCT00663260, NCT00680745, NCT00673231, NCT01031680, NCT01042977); †Pooled data from two studies ≤52 weeks (NCT01031680, NCT01042977). Data based on longitudinal repeated-measures models, excluding data after rescue therapy for inadequate glycemic control (HbA1c, body weight) or change in medication affecting blood pressure (SBP). Adj, adjusted; BL, baseline; CI, confidence interval; DAPA, dapagliflozin; SBP, systolic blood pressure
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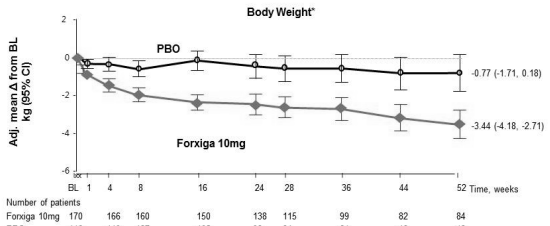

Number of patients

	BL	1	4	8	16	24	28	36	44	52
Forxiga 10mg	170		166	160	150	138	115	99	82	84
PBO	146		140	127	105	93	81	64	48	43

*Pooled data from five studies ≤52 weeks (NCT00663260, NCT00680745, NCT00673231, NCT01031680, NCT01042977); †Pooled data from two studies ≤52 weeks (NCT01031680, NCT01042977). Data based on longitudinal repeated-measures models, excluding data after rescue therapy for inadequate glycemic control (HbA1c, body weight) or change in medication affecting blood pressure (SBP). Adj, adjusted; BL, baseline; CI, confidence interval; DAPA, dapagliflozin; SBP, systolic blood pressure
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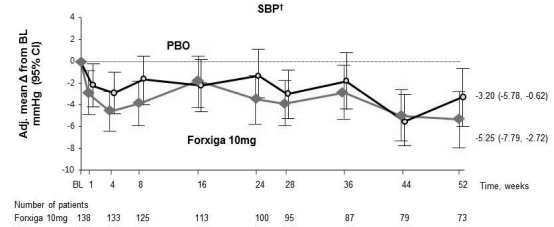
Mikhail Kosiborod et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1211-P

Efficacy and Safety of Forxiga in Patients with T2DM and Concomitant HF: Efficacy Outcomes

- Reduction in SBP varied over time in both groups, but was numerically greater with Forxiga 10 mg versus placebo for most time points



Number of patients

	BL	1	4	8	16	24	28	36	44	52
Forxiga 10mg	138		133	125	113	100	95	87	79	73
PBO	127		124	118	109	95	89	83	77	70

*Pooled data from five studies ≤52 weeks (NCT00663260, NCT00680745, NCT00673231, NCT01031680, NCT01042977); †Pooled data from two studies ≤52 weeks (NCT01031680, NCT01042977). Data based on longitudinal repeated-measures models, excluding data after rescue therapy for inadequate glycemic control (HbA1c, body weight) or change in medication affecting blood pressure (SBP). Adj, adjusted; BL, baseline; CI, confidence interval; DAPA, dapagliflozin; SBP, systolic blood pressure
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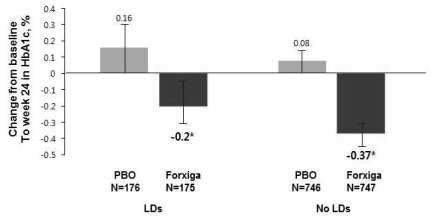
Mikhail Kosiborod et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1211-P

Safety and Efficacy of Forxigain Patients With T2DM and Cardiovascular Disease Receiving Loop Diuretics

- Pooled from 2 published phase 3 studies designed to evaluate efficacy and safety in patients with T2DM and prior CVD.

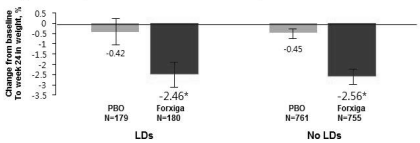


- HbA1c was reduced from baseline to 24 weeks with Forxiga compared with placebo to a similar degree in patients with or without loop diuretics.

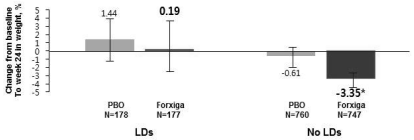
T2DM, Type 2 Diabetes Mellitus; CVD, cardiovascular disease; LD, loop diuretics
Error bars represent 95% CIs. P versus placebo. †P<0.0001; ††P=0.0010.
Dapagliflozin은 루프계 이뇨제를 투여하고 있거나 위장관 질병과 같은 급성 질병 등으로 체액량이 감소된 환자에게는 사용이 권장되지 않는다.
William T. Cefalu et al. 75th Scientific Sessions, American Diabetes Association 2015. Poster #1216-P

Safety and Efficacy of Forxigain Patients With T2DM and Cardiovascular Disease Receiving Loop Diuretics

- Reductions from baseline to week 24 in total body weight were observed with Forxiga versus placebo and were similar in patients with or without LDs



- SBP was lower at week 24 in patients without LDs receiving Forxigacompared with placebo but no difference was observed between the treatment groups for patients with LDs



T2DM, Type 2 Diabetes Mellitus; CVD, cardiovascular disease; LD, loop diuretics; SBP. Systolic blood pressure
Error bars represent 95% CIs. P versus placebo. †P<0.0001; ††P=0.0010.
Dapagliflozin은 루프계 이뇨제를 투여하고 있거나 위장관 질병과 같은 급성 질병 등으로 체액량이 감소된 환자에게는 사용이 권장되지 않는다.
William T. Cefalu et al. 75th Scientific Sessions, American Diabetes Association 2015. Poster #1216-P

Safety and Efficacy of Forxigain Patients With T2DM and Cardiovascular Disease Receiving Loop Diuretics

- AEs and SAEs were more commonly reported over 24 weeks in patients with LDs and were generally balanced between Forxigaand PBO treatment groups.

	Loop diuretics		No loop diuretics	
Safety over 24 weeks, n (%)	PBO (n=182)	Forxiga 10mg (n=182)	PBO (n=763)	Forxiga 10mg (n=760)
≥ 1 AE	110 (60.4%)	112 (61.5%)	421 (55.2%)	434 (57.1%)
≥ 1 SAE	19 (10.4%)	17 (9.3%)	53 (6.9%)	51 (6.7%)
≥ 1 incidence of hypoglycemia[a]	33 (18.1%)	45 (24.7%)	135 (17.7%)	145 (19.1%)
Major episode	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Minor episode	32 (17.6%)	44 (24.2%)	128 (16.8%)	136 (17.9%)
Other	4 (2.2%)	4 (2.2%)	14 (1.8%)	19 (2.5%)
Renal impairment/failure[b]	10 (5.5%)	18 (9.9%)	19 (2.5%)	37 (4.9%)
Decrease in creatinine clearance	3 (1.6%)	7 (3.8%)	11 (1.4%)	13 (1.7%)
Renal impairment	4 (2.2%)	6 (3.3%)	5 (0.7%)	11 (1.4%)
Increase blood creatinine	2 (1.1%)	4 (2.2%)	3 (0.4%)	2 (0.3%)
Volume depletion	3 (1.6%)	3 (1.6%)	8 (1.0%)	12 (1.6%)
Hypotension	1 (0.5%)	2 (1.1%)	2 (0.3%)	6 (0.8%)
Genital infection	0 (0%)	10 (5.5%)	4 (0.6%)	42 (5.5%)
Urinary tract infection	11 (6.0%)	7 (3.8%)	26 (3.4%)	41 (5.4%)

AE, adverse events; SAE, serious adverse events; LD, loop diuretics; PBO, placebo
a One patient without LDs discontinued treatment with Forxigadue to a hypoglycemic event.
b Based on a predefined list of events.
William T. Cefalu et al. 75th Scientific Sessions, American Diabetes Association 2015. Poster #1216-P

Summary

SGLT-2 inhibitors have established anti-hyperglycemic efficacy without increasing risk for hypoglycemia and are associated with weight loss and mild reduction of blood pressure.

Their anti-hyperglycemic efficacy is related to eGFR and baseline HbA1c by mode of action

Reduction of the plasma glucose concentration by inducing glucosuria in T2DM individuals significantly improved beta cell function. Improvement in hyperglycemia with dapagliflozin also improved insulin sensitivity.

Following the current knowledge regarding of renal or cardiovascular safety, more research is needed to explain the apparent puzzle and some of their clinical implications.

1. Komoroski B, et al. *Clin Pharmacol Ther.* 2009;85(5):520-526. 2. Brooks AM, et al. *Ann Pharmacother.* 2009;43(7):1286-1293. 3. Turner RC, et al. *JAMA.* 1999;281(21):2005-2012 4. Merovci A., et al. *J Clin Endocrinol Metab.* 2015 Feb 24:jc20143472. [Epub ahead of print] 5. Arie Katz et al, *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1179-P 6. Wenying Yang et al. *75th Scientific Sessions, American Diabetes Association 2015.* Poster #1175-P