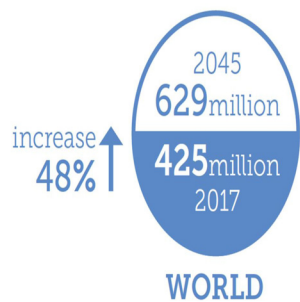


당뇨병 치료의 최신 지견 (SGLT2 억제제를 중심으로)

이 우 제
서울아산병원

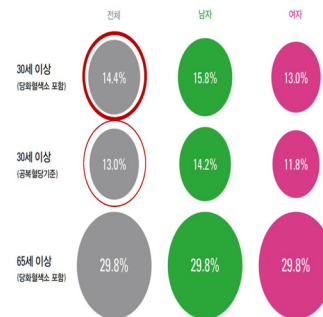
연수강좌

Number of people with diabetes worldwide (20-79 years)



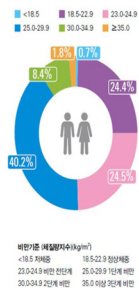
IDF Diabetes Atlas 2017

Prevalence of diabetes in Korea



Diabetes Fact Sheet in Korea 2018

Overweight/obesity in diabetes



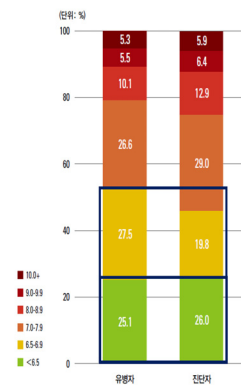
비만기준: 체질량지수(kg/m²)
<18.5 저체중
18.5-22.9 정상체중
23.0-24.9 비만 전단계
25.0-29.9 1단계 비만
30.0-34.9 2단계 비만
35.0 이상 3단계 비만

BMI ≥ 23 → 약 75%
BMI ≥ 25 → 약 50%



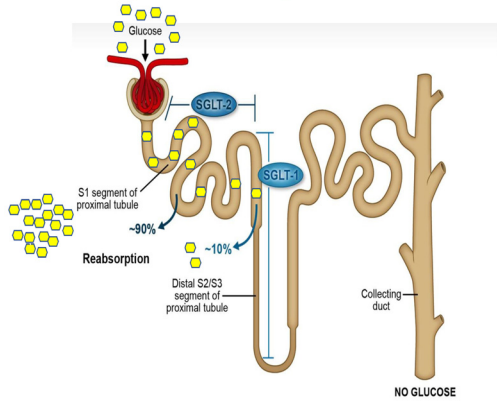
Diabetes Fact Sheet in Korea 2018

Glycemic control status in Korea

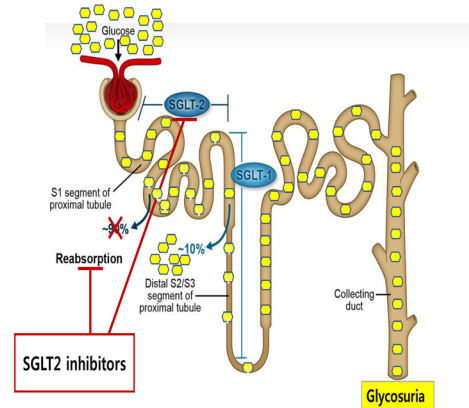


Diabetes Fact Sheet in Korea 2018

Renal glucose handling in normal condition



Mechanism of SGLT2 inhibitor in diabetes



Advantages of SGLT2 inhibitors

Glucose-lowering effect	• HbA1C: 0.5-1.0%↓ (vs. placebo)
Low Hypoglycemia	• d/t insulin-independent action • Urinary glucose excretion ↑
Weight loss	• 2~3 kg ↓ (6-12 month)
Blood pressure	• SBP : 2~4 mmHg ↓ • DBP : 1~2 mmHg ↓

Inzucchi SE, et al. Diabetologia 2015;58:429-442

Currently available SGLT-2 Inhibitors in Korea

SGLT2 Inhibitors	Product Name	Manufacturer	Dosage
Dapagliflozin	포시가	AstraZeneca	10 mg once daily
Ipragliflozin	슈글렛	Astellas	50 mg once daily
Empagliflozin	자디앙	Boehringer Ingelheim & Eli Lilly	10-25mg once daily
Ertugliflozin	스테글라트로	MSD	5mg-15mg once daily

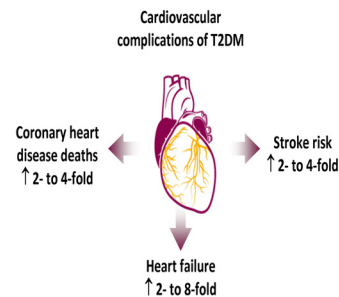
Side effects of SGLT-2 inhibitors

- Urinary tract infection & Genital infections
- Dehydration
 - ✓ Increased hematocrit, decreased blood pressure
- Use caution when initiating in the following patients:
 - ✓ Elderly, diminished renal function

Diabetes Metab Syndr Obes. 2012;5:313-327

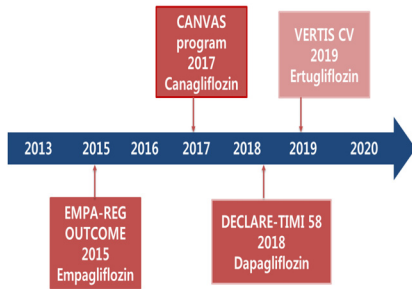
Cardiovascular complications of T2DM

~65% of deaths are due to CV disease

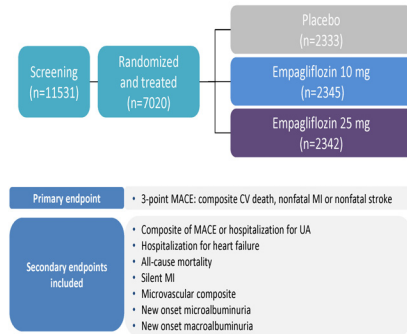


Grundey SM, et al. Circulation. 1999;100:1134-1146
Fox CS. Trends Cardiovasc Med. 2010;20:90-95
Kannel WB. Heart Fail Rev. 2006;5:167-173

SGLT-2 inhibitor CV outcome trials

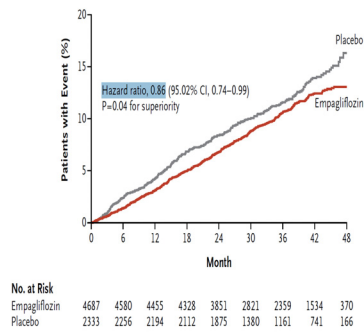


EMPA-REG OUTCOME



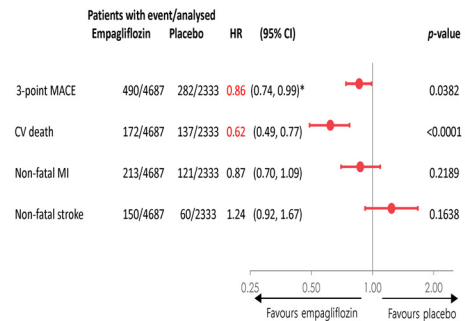
Zinman B, et al. *N Engl J Med* 2015;373:2117-28

EMPA-REG: Primary Outcome (3-point MACE)



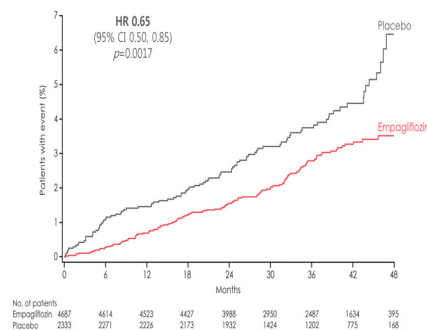
Zinman B, et al. *N Engl J Med* 2015;373:2117-28

EMPA-REG: CV death, MI and stroke



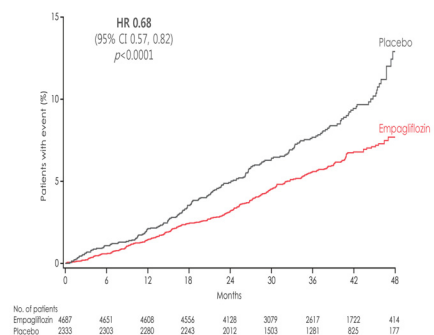
Zinman B, et al. *N Engl J Med* 2015;373:2117-28

EMPA-REG: Hospitalization for heart failure



Zinman B, et al. *N Engl J Med* 2015;373:2117-28

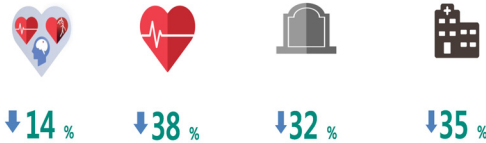
EMPA-REG: All-cause mortality



Zinman B, et al. *N Engl J Med* 2015;373:2117-28

Empagliflozin reduces cardiovascular outcomes

[3P-MACE] [CV death] [All-cause mortality] [Hospitalization for HF]



Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in patients with T2D at high CV risk

Zinman B, et al. *N Engl J Med* 2015;373:2117-28

EMPA-REG: Renal outcome

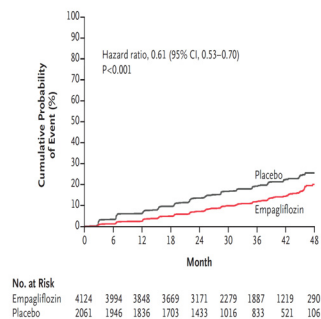
Incident or worsening nephropathy

- Progression to macroalbuminuria
- Doubling of the serum creatinine level
- Initiation of renal-replacement therapy
- Death from renal disease

Incident albuminuria

Wanner C, et al. *N Engl J Med* 2016;375:323-34

EMPA-REG: Incident or Worsening Nephropathy



Wanner C, et al. *N Engl J Med* 2016;375:323-34

CANVAS Program Outcomes

Primary endpoint

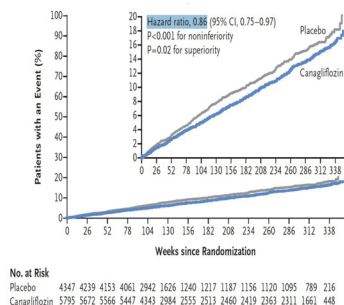
- 3-point MACE: CV death, nonfatal MI or nonfatal stroke

Secondary endpoints

- All-cause mortality
- CV death
- Albuminuria progression (>30% increase in albuminuria and change in category)
- Composite of CV mortality or hHF

Neal B, et al. *N Engl J Med* 2017;377:644-57

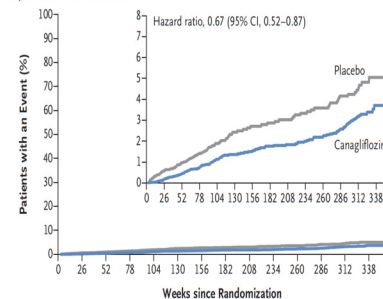
CANVAS: Primary Outcome (3-point MACE)



Neal B, et al. *N Engl J Med* 2017;377:644-57

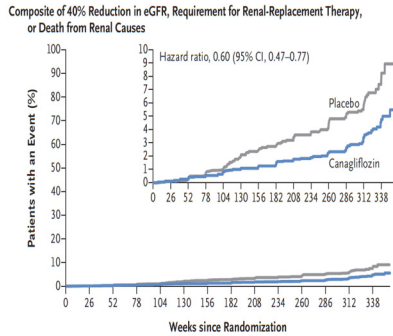
CANVAS: Hospitalization for heart failure

Hospitalization for Heart Failure



Neal B, et al. *N Engl J Med* 2017;377:644-57

CANVAS: Renal outcome



Neal B, et al. *N Engl J Med* 2017;377:644-57

DECLARE-TIMI 58

Outcomes

Primary endpoints

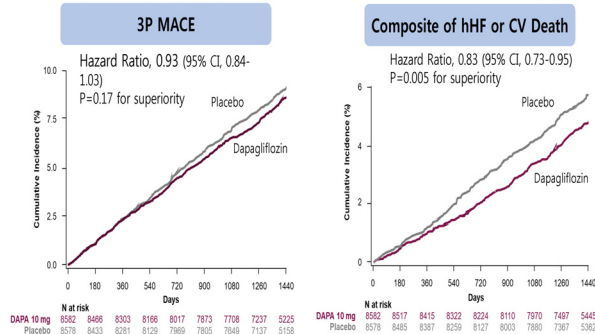
- Primary safety endpoint: 3-point MACE
- Primary efficacy endpoints:
 - 3-point MACE
 - Composite of CV death or hHF

Secondary endpoints

- Renal composite endpoint (sustained $\geq 40\%$ decrease in eGFR to eGFR < 60 mL/min/1.73 m² and/or new ESRD and/or renal or CV death)
- All-cause mortality

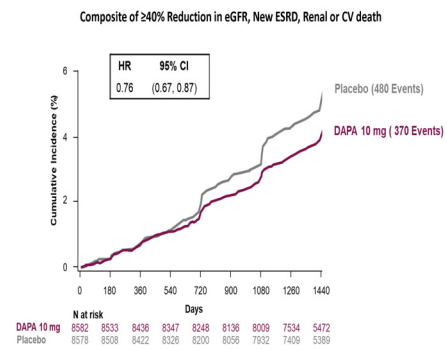
Wiviott SD, et al. *N Engl J Med* 2019;380:347-57

DECLARE-TIMI 58: Primary Outcomes



Wiviott SD, et al. *N Engl J Med* 2019;380:347-57

DECLARE-TIMI 58: Renal outcome



Wiviott SD, et al. *N Engl J Med* 2019;380:347-57

SGLT2i CVOTs: population

EMPA-REG OUTCOME

>99% eCVD
N=6,964
(N=7,020)
Placebo event rate
43.9/1,000 pt-yrs

CANVAS

~65.6% eCVD
N=6,666
~34.4% MRF
N=3,486
(N=10,142)
Placebo event rate
31.5/1,000 pt-yrs

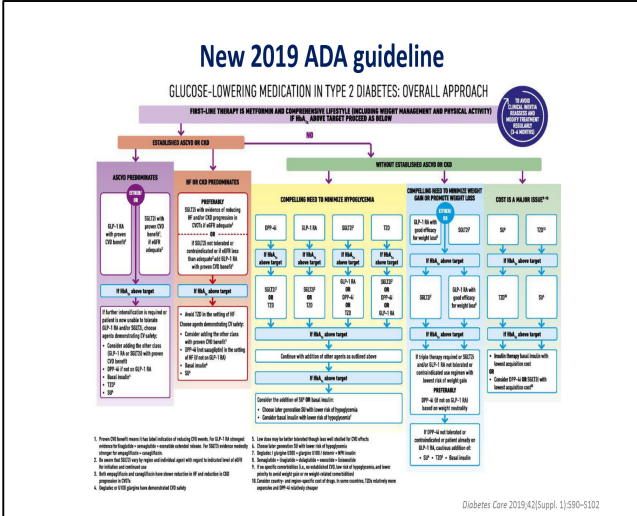
DECLARE

~40.6% eCVD
N=6,974
~59.4% MRF
N=10,186
(N=17,160)
Placebo event rate
24.2/1,000 pt-yrs

Zinman B, et al. *N Engl J Med* 2015;373:2117-26
Neal B, et al. *N Engl J Med* 2017;377:644-57
Wiviott SD, et al. *N Engl J Med* 2019;380:347-57

Summary: SGLT2i CV outcome trials

	EMPA-REG	CANVAS	DECLARE
3P MACE	↓	↓	↔
CV Death	↓↓	↔	↔
MI	↔	↔	↔
Stroke	↔	↔	↔
HHF	↓↓	↓↓	↓
All-cause mortality	↓↓	↔	↔
Renal outcome	↓↓	↓↓	↓↓



급여 인정 가능 2제 요법

구 분		Metformin	SU	Meglitinide	α-GI	TZD	DPP-IV inhibitor	SGLT-2 inhibitor			
								dapagliflozin	ipragliflozin	empagliflozin	ertugliflozin
SGLT-2 inhibitor	Metformin		인정	인정	인정	인정	인정	인정	인정	인정	
	SU	인정			인정	인정	인정	인정		*3제 인정	
	Meglitinide	인정			인정	인정					
	α-GI	인정	인정	인정							
	TZD	인정	인정	인정			인정			비급여	
	DPP-IV inhibitor	인정	인정			인정		비급여		비급여	
	dapagliflozin	인정	인정				비급여				
	ipragliflozin	인정									
	empagliflozin	인정	*3제 인정				비급여	비급여			
	ertugliflozin	인정									

*MET+SU+EMPA 3제 병용 인정