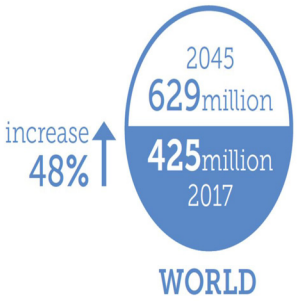
당뇨병 치료의 최신 지견 (SGLT2 억제제를 중심으로)

이 우 제
서울아산병원

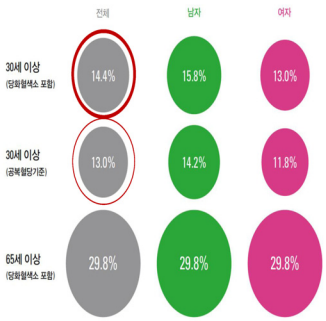
연수강좌

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



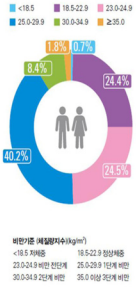
IDF Diabetes Atlas 2017

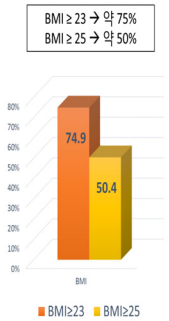
Prevalence of diabetes in Korea



Diabetes Fact Sheet in Korea 2018

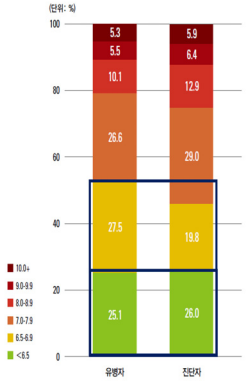
Overweight/obesity in diabetes





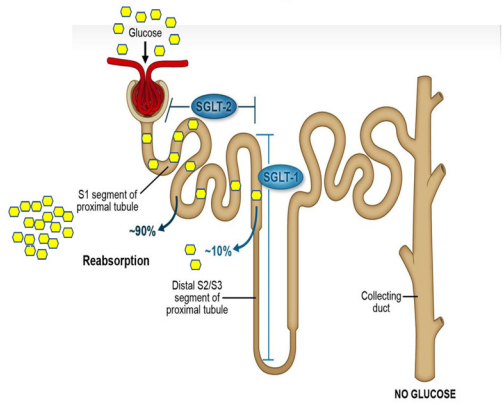
Diabetes Fact Sheet in Korea 2018

Glycemic control status in Korea

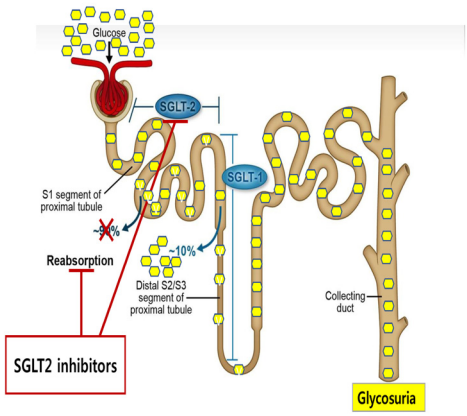


Diabetes Fact Sheet in Korea 2018

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
Empaglifolzin	자디앙	Boehringer Ingelheim & Eli Lilly	10-25mg once daily
Ertugliflozin	스테글라트로	MSD	5mg-15mg once daily

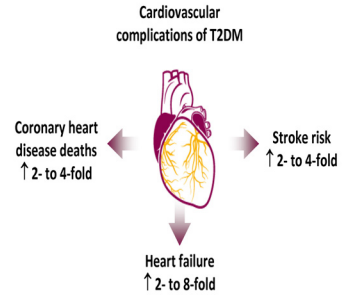
Side effects of SGLT-2 inhibitors

- **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

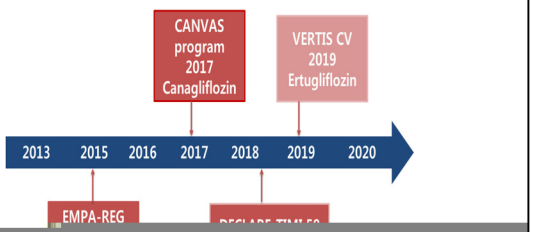
Cardiovascular complications of T2DM

~65% of deaths are due to CV disease

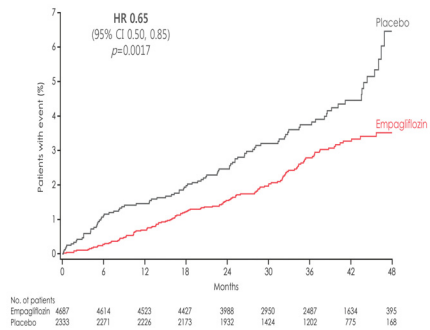


Grundy SM, et al. *Circulation*. 1999;100:1134–1146
Fox CS. Trends *Cariovasc Med*. 2010;20;90–95
Kannel WB. *Heart Fail Rev*. 2000;5:167–173

SGLT-2 inhibitor CV outcome trials

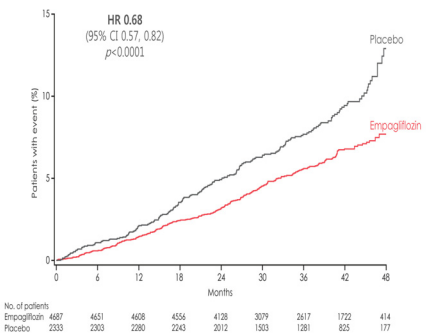


EMPA-REG: Hospitalization for heart failure



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]
↓14 %	↓38 %	↓32 %	↓35 %

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

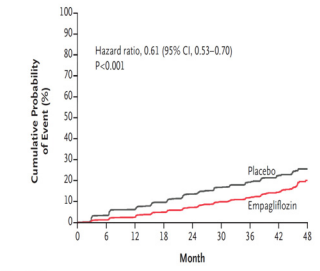
Zinman B, et al. *N Engl J Med* 2015;373:2117-28

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



No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

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

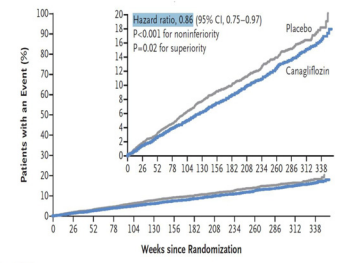
CANVAS Program

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)

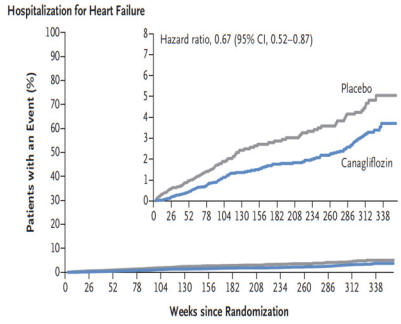


No. at Risk

Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

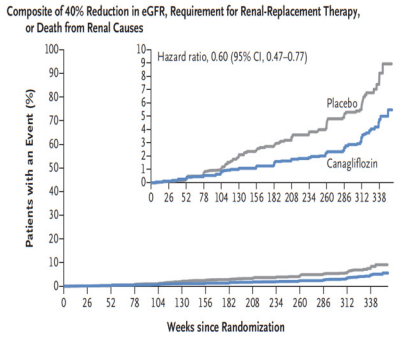
Neal B, et al. *N Engl J Med* 2017;377:644-57

CANVAS: 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

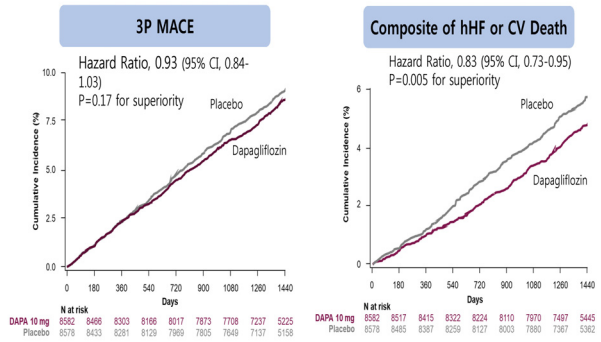
Outcomes

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 ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or new ESRD and/or renal or CV death)
- All-cause mortality

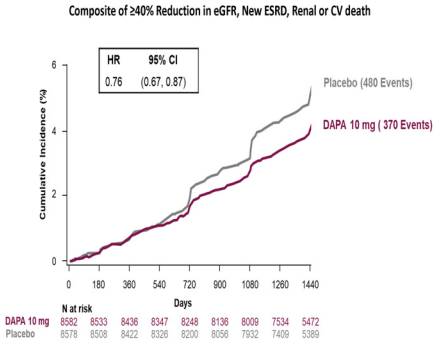
Wiviott SD, et al. *N Engl J Med* 2019;380:347-357

DECLARE-TIMI 58: Primary Outcomes



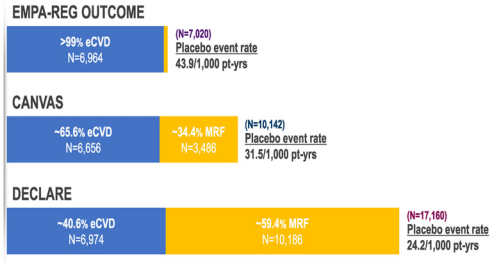
Wiviott SD, et al. *N Engl J Med* 2019;380:347-357

DECLARE-TIMI 58: Renal outcome



Wiviott SD, et al. *N Engl J Med* 2019;380:347-357

SGLT2i CVOTs: population

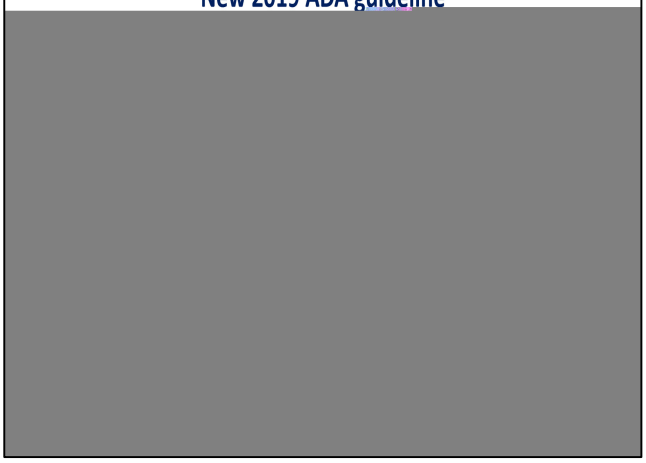


Zinman B, et al. *N Engl J Med* 2015;373:2117-28
Neal B, et al. *N Engl J Med* 2017;377:644-57
Wiviott SD, et al. *N Engl J Med* 2019;380:347-357

Summary: SGLT2i CV outcome trials

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

New 2019 ADA guideline



급여 인정 가능 2제 요법

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

*MET+SU+EMPA 3제 병용 인정