SGLT-1 ve SGLT-2 inhibitörleri

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Endokrinoloji ve Metabolizma Hastalıkları BD

Ulusal Diyabet Kongresi-2021
Bodrum

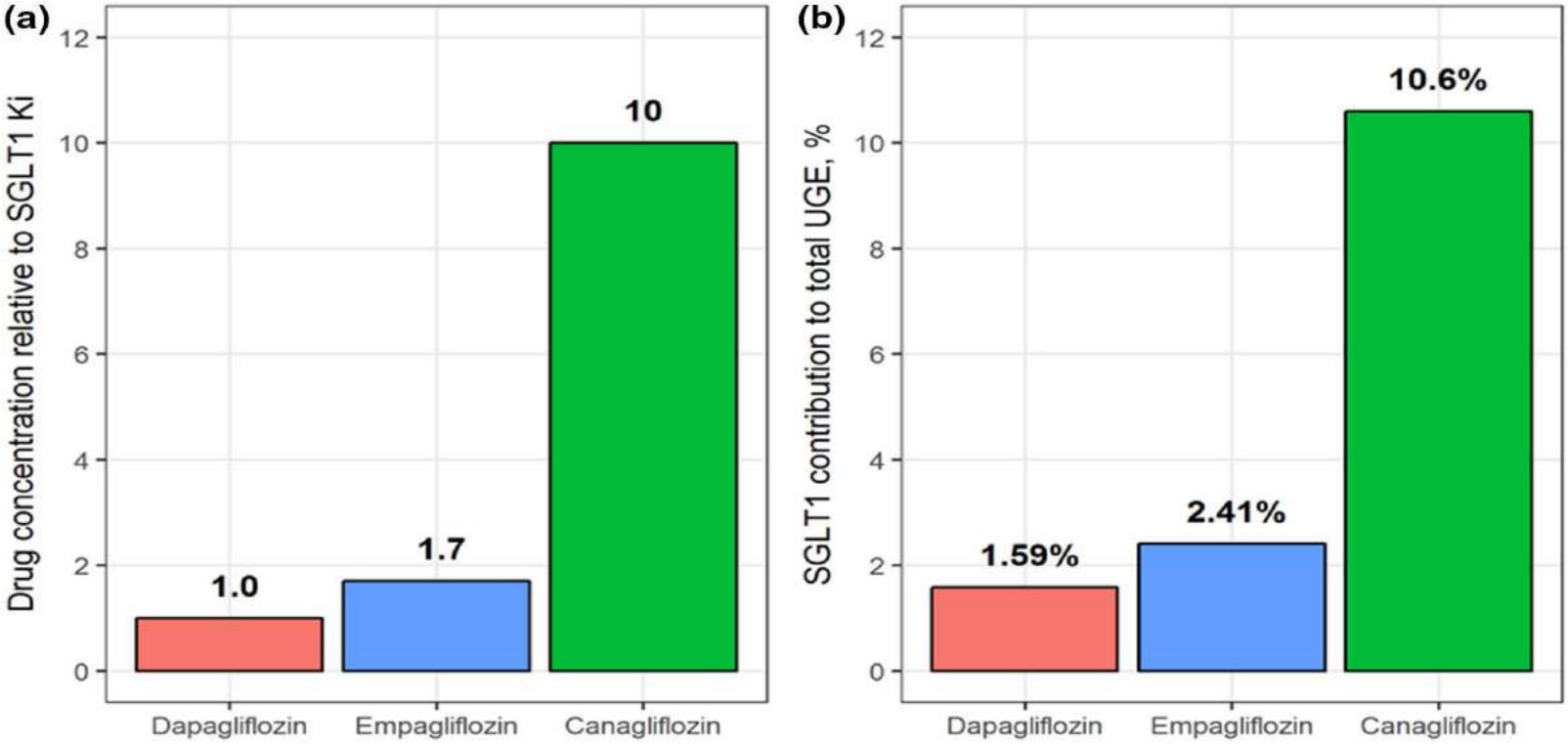
GİRİŞ

- Diyabet özellikle T2DM kronik ve kompleks bir hastalıktır
- Aynı hastada birçok hedefi gözetmeniz gerekiyor
- Tedavideki tüm olumlu gelişmelere rağmen halen bu hedeflere ulaşabilmiş değiliz
- SGLT inhibitörleri güvenilir ve etkin yeni antihiperglisemik ajanlardır
- SGLT inhibitörleri glisemik regülasyon yanında kardiyak, renal, metabolik olumlu başka etkileri ile de ön plana çıkmaktadır

SGLT ailesi

- SGLT ailesinin insanda 6 farklı izoformu tarif edilmiştir
- SGLT-1 ince barsak ve böbrekten glukoz geri emilimini sağlar. Böbrekteki geri emilim etkisi %10 kadardır
- SGLT-2 böbrekte etki gösterir. Renal glukoz geri emiliminin %90'ından sorumludur
- Ancak SGLT-2 knock-out farelerde filtre olan glukozun %30-40'ının geri emildiği gözlenmiş
- SGLT-2 inhibitörlerinin akut ve kronik kullanımında bu kompenzasyon mekanizması gösterilmiş durumdadır

SGLT-2 inhibitörlerinin SGLT-1 inhibisyonu düzeyleri

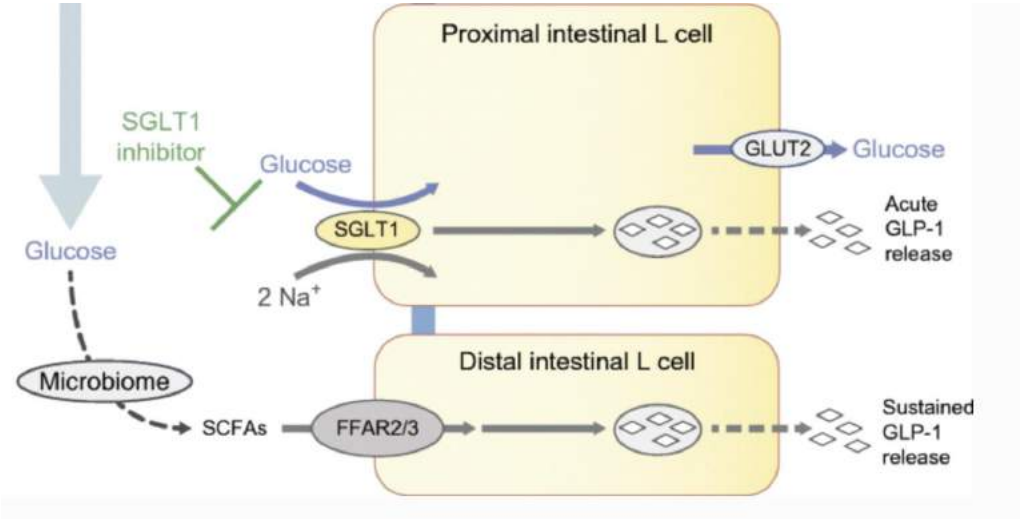


Ki: baskılama sabiti. Bağlanma afinitesini gösterir, UGE: Üriner glukoz atılımı

CPT Pharmacometrics Syst Pharmacol. 2020 Apr;9(4):222-229.

SGLT'lerin Lokalizasyonu

- Vrhorac ve ark. SGLT-2'nin böbrek, SGLT-1'in böbrek, ince barsak, tükrük bezleri, karaciğer, kalp, akciğer ve beyinde lokalize olduğunu göstermiştir
- SGLT-1 ve 2 böbrekte tubullerin fırçamsı kenar membranında
- Ayrıca inkretin salgılayan K ve L hücrelerinde SGLT-1 ekspresyonu gösterilmiştir



Rieg T et al. Diabetologia. 2018 Oct;61(10):2079-2086.

SGLT-1 ve SGLT-2 transporter etki karşılaştırması

Characteristic	SGLT1	SGLT2
Capacity	Low	High
Affinity	High	Low
Function	Dietary absorption glucose and galactose (GIT) Renal reabsorption glucose	Renal reabsorption glucose
Renal location	S3 of PCT	S1 and S2 of PCT
Renal glucose reabsorption	10%	90%
Ratio Na-Glucose cotransport	2:1	1:1
Gene encoding	*SCL5A1*	*SLC5A2*

GIT: gastrointestinal tract, PCT: proximal convoluted tubule; SGLT: sodium-glucose cotransporter.

García-Ropero Á et al. Int J Mol Sci. 2019 Jul 4;20(13):3289.

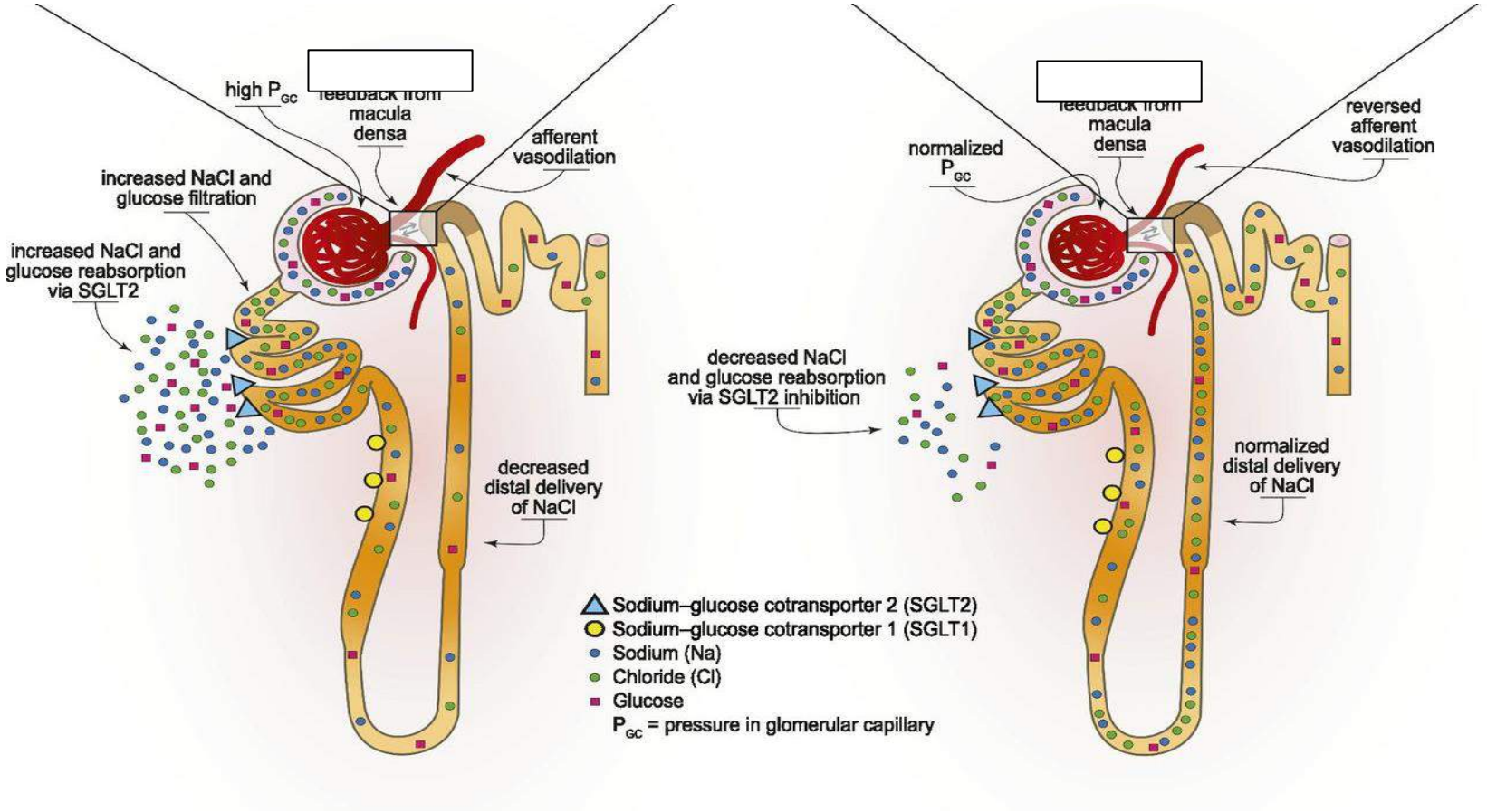
Sotagliflozin

- Oral SGLT-1 ve 2 inhibitörüdür. SGLT-2 özgüllüğü SGLT-1'e göre 20 kat fazladır. Ancak SGLT-1'i SGLT-2 inhibörlerine göre >10 kat fazla baskılar
- Sotagliflozin potent intestinal SGLT-1 inhibitörü gibi etki etmektedir
- GLUT-4 ve SGLT-1 insülin bağımlı inotropik etki gösterirler. Yani kardiyak miyositlere glukoz substratı sunarlar. Terapötik dozlarda kardiyak SGLT1 inh. gösterilmemiştir
- İskemi-reperfüzyon hasarında akut dönemde SGLT inhibisyonu olumsuz etki göstermektedir

T2DM'lilerde SGLT-2 inhibisyonun nefron hemodinamisi üzerine etkileri

Diyabetik nefron

SGLT-2 inhibisyonu sonrası diyabetik nefron

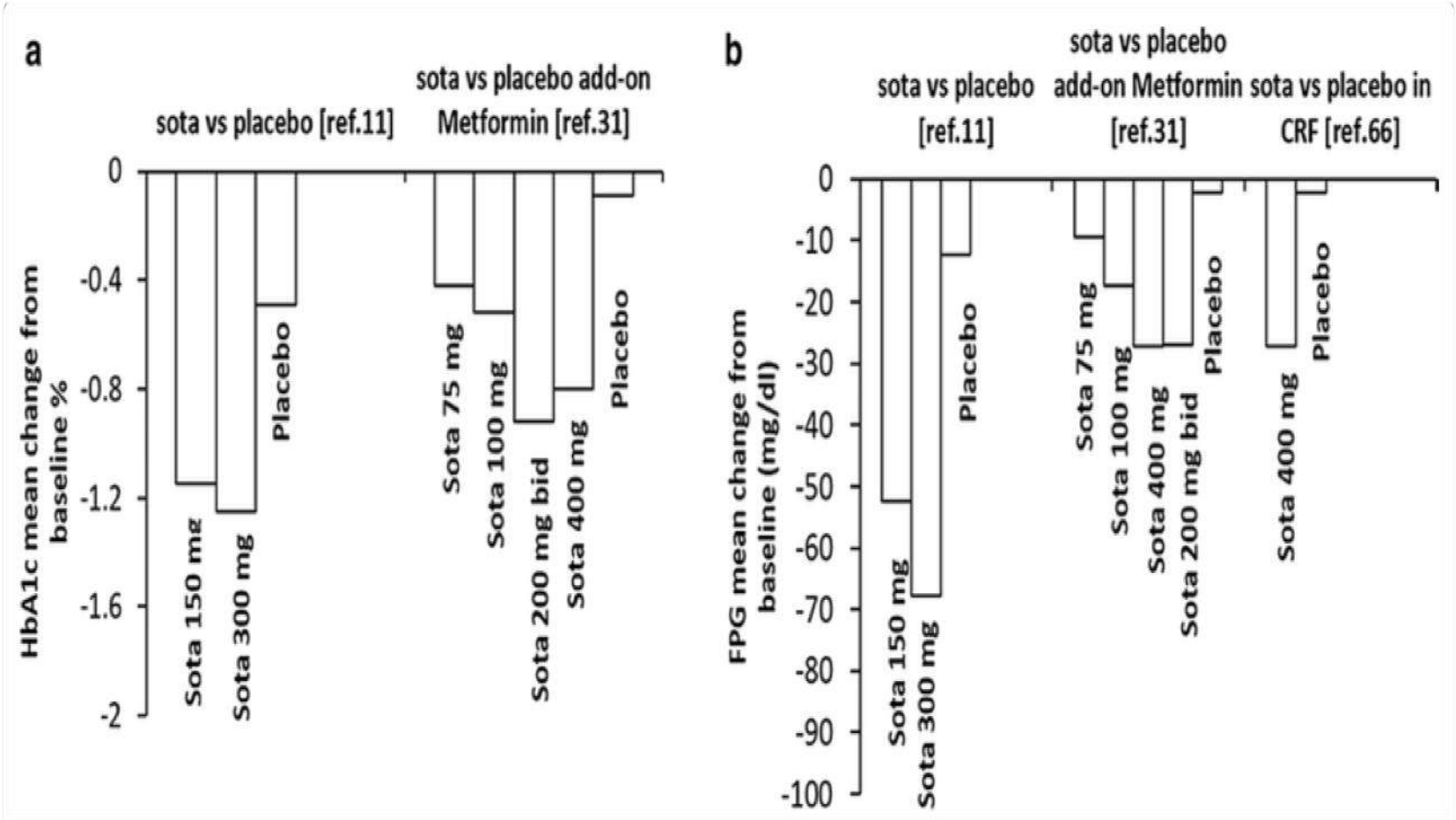


Radica Z. Alicic, et al. Diabetes 2019;68:248-257

SGLT inhibitörlerinin glukoz reabsorbsiyonu üzerine etkileri

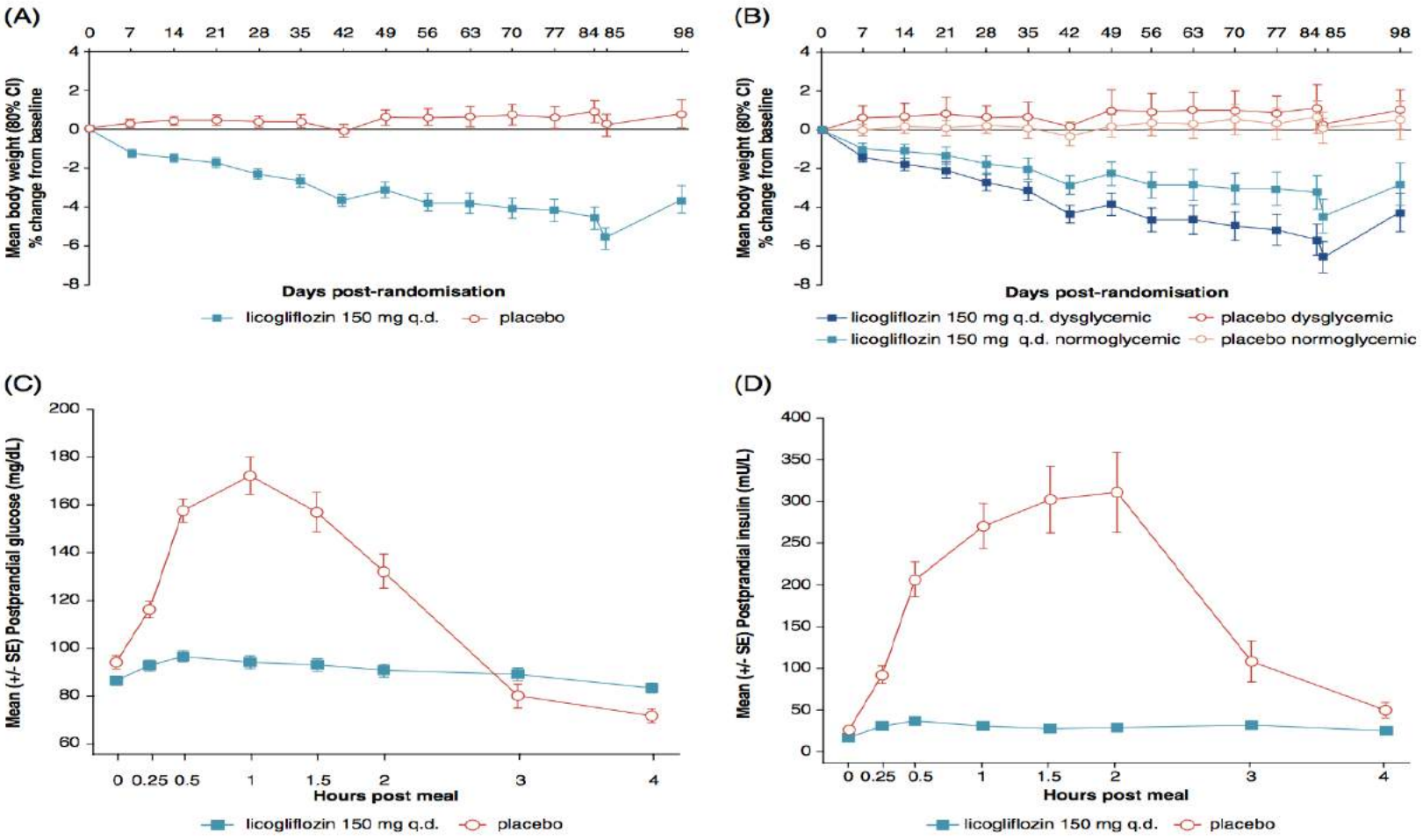
Drug dosage	Filtered glucose (g/24 h) (eGFRx mean glucose mg/mL)	UGE (g/24 h)	Absorbed glucose (g/24 h)	Inhibition of glucose reabsorption (%)
Sotagliflozin 150 mg	256	36	220	14.1
Sotagliflozin 300 mg	287.5	47	240	16.5
Sotagliflozin 200 mg, 200 mg bid, 400 mg	–	~60	–	–
Empagliflozin 2.5 mg	–	–	–	39
Empagliflozin 10 mg	–	–	–	46
Empagliflozin 25 mg	–	–	–	58
Empagliflozin 100 mg	–	–	–	64
Dapagliflozin 2.5 mg	191.16	52	139.16	27.2
Dapagliflozin 5 mg	207.6	64	143.6	55.7
Dapagliflozin 10 mg	206.1	68	138.1	54.5
Dapagliflozin 20 mg	196.9	85	111.9	51.7
Dapagliflozin 50 mg	191.3	82	109.3	53.1

Sotagliflozin HbA1c'de %0.9-1.4, AKŞ'de 30-68 mg/dL azalma sağlıyor



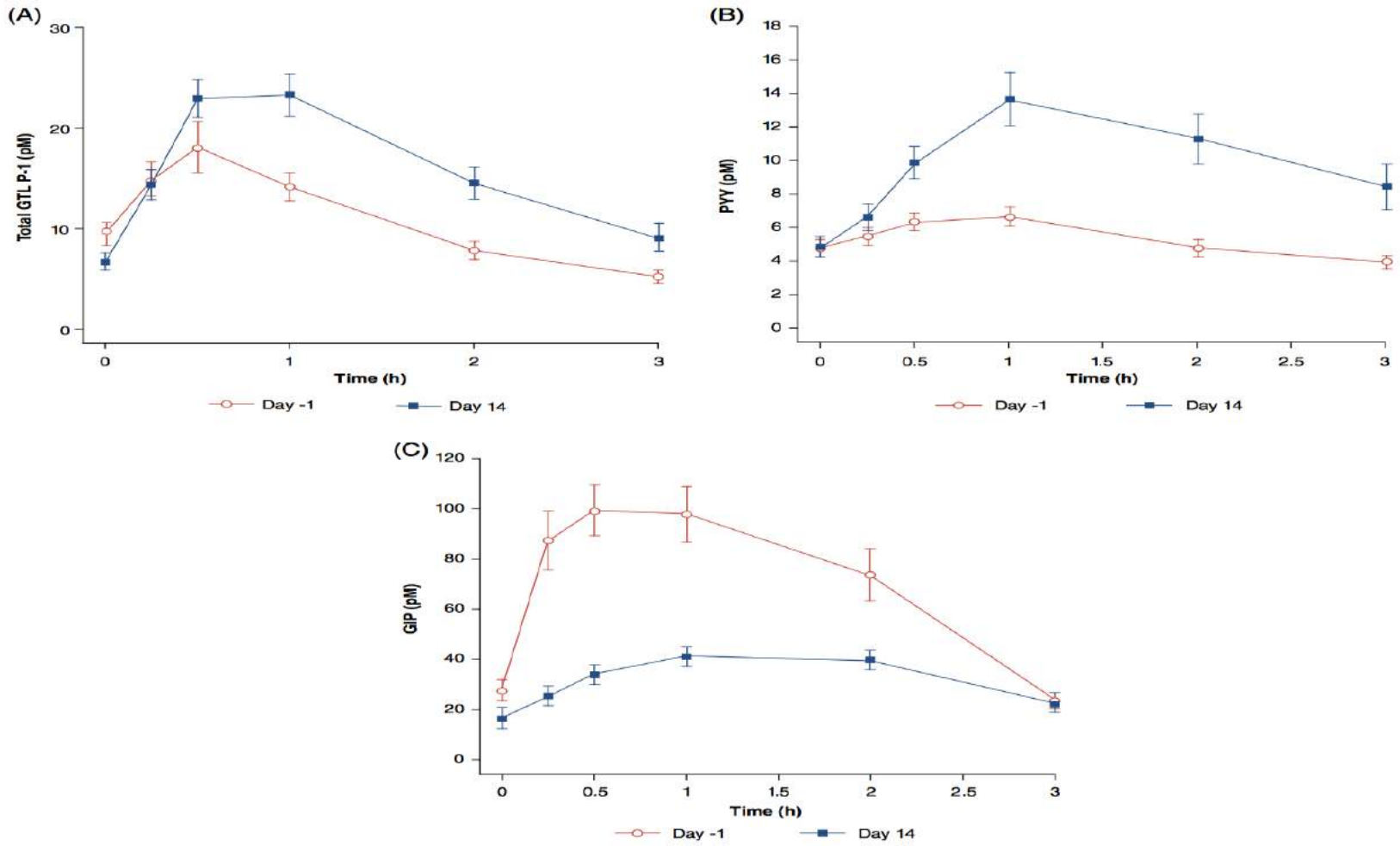
Cefalo et al. Cardiovasc Diabetol (2019) 18:20

Obez hastalarda 3 aylık Licogliflozin kullanımı **ile vücut ağırlığı ve metabolik parametrelerdeki değişim**



He Y et al. Diabetes Obes Metab. 2019;21:1311–1321

T2DM'de 14 günlük Licogliflozin tedavisi sonrası OGTT'de inkretin hormon düzeyleri



He Y et al. Diabetes Obes Metab. 2019;21:1311–1321

Licogliflozin **kullanan Obez grupta görülen ek yan etkileri**

	Licogliflozin 150 mg q.d. N = 44 n (%)	Placebo q.d. N = 44 n (%)
Participants with AEs	43 (97.7)	39 (88.6)
Diarrhea	40 (90.9)	11 (25.0)
Headache	9 (20.5)	16 (36.4)
Flatulence	19 (43.2)	4 (9.1)
Abdominal pain	12 (27.3)	5 (11.4)
Abdominal distension	11 (25.0)	4 (9.1)
Nausea	8 (18.2)	3 (6.8)
Dyspepsia	6 (13.6)	4 (9.1)
Oropharyngeal pain	3 (6.8)	6 (13.6)

Sotagliflozinin hem bazal-bolus hem de SC insülin inf. pompası kullanan T1DM'de etkinlik ve güvenlilik çalışmaları yapılmış

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

Satish K. Garg, M.D., Robert R. Henry, M.D., Phillip Banks, M.S., John B. Buse, M.D., Ph.D., Melanie J. Davies, M.D., Gregory R. Fulcher, M.D., Paolo Pozzilli, M.D., Diane Gesty-Palmer, M.D., Ph.D., Pablo Lapuerta, M.D., Rafael Simó, M.D., Ph.D., Thomas Danne, M.D., Darren K. McGuire, M.D., M.H.Sc., Jake A. Kushner, M.D., Anne Peters, M.D., and Paul Strumph, M.D.

ABSTRACT

BACKGROUND
In most patients with type 1 diabetes, adequate glycemic control is not achieved with insulin therapy alone. We evaluated the safety and efficacy of sotagliflozin, an oral inhibitor of sodium–glucose cotransporters 1 and 2, in combination with insulin treatment in patients with type 1 diabetes.

METHODS
In this phase 3, double-blind trial, which was conducted at 133 centers worldwide, we randomly assigned 1402 patients with type 1 diabetes who were receiving treatment with any insulin therapy (pump or injections) to receive sotagliflozin (400 mg per day) or placebo for 24 weeks. The primary end point was a glycated hemoglobin level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. Secondary end points included the change from baseline in glycated hemoglobin level, weight, systolic blood pressure, and mean daily bolus dose of insulin.

RESULTS
A significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved the primary end point (200 of 699 patients [28.6%] vs. 107 of 703 [15.2%], P<0.001). The least-squares mean change from baseline was significantly greater in the sotagliflozin group than in the placebo group for glycated hemoglobin (difference, −0.46 percentage points), weight (−2.98 kg), systolic blood pressure (−3.5 mm Hg), and mean daily bolus dose of insulin (−2.8 units per day) (P≤0.002 for all comparisons). The rate of severe hypoglycemia was similar in the sotagliflozin group and the placebo group (3.0% [21 patients] and 2.4% [17], respectively). The rate of documented hypoglycemia with a blood glucose level of 55 mg per deciliter (3.1 mmol per liter) or below was significantly lower in the sotagliflozin group than in the placebo group. The rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% [21 patients] and 0.6% [4], respectively).

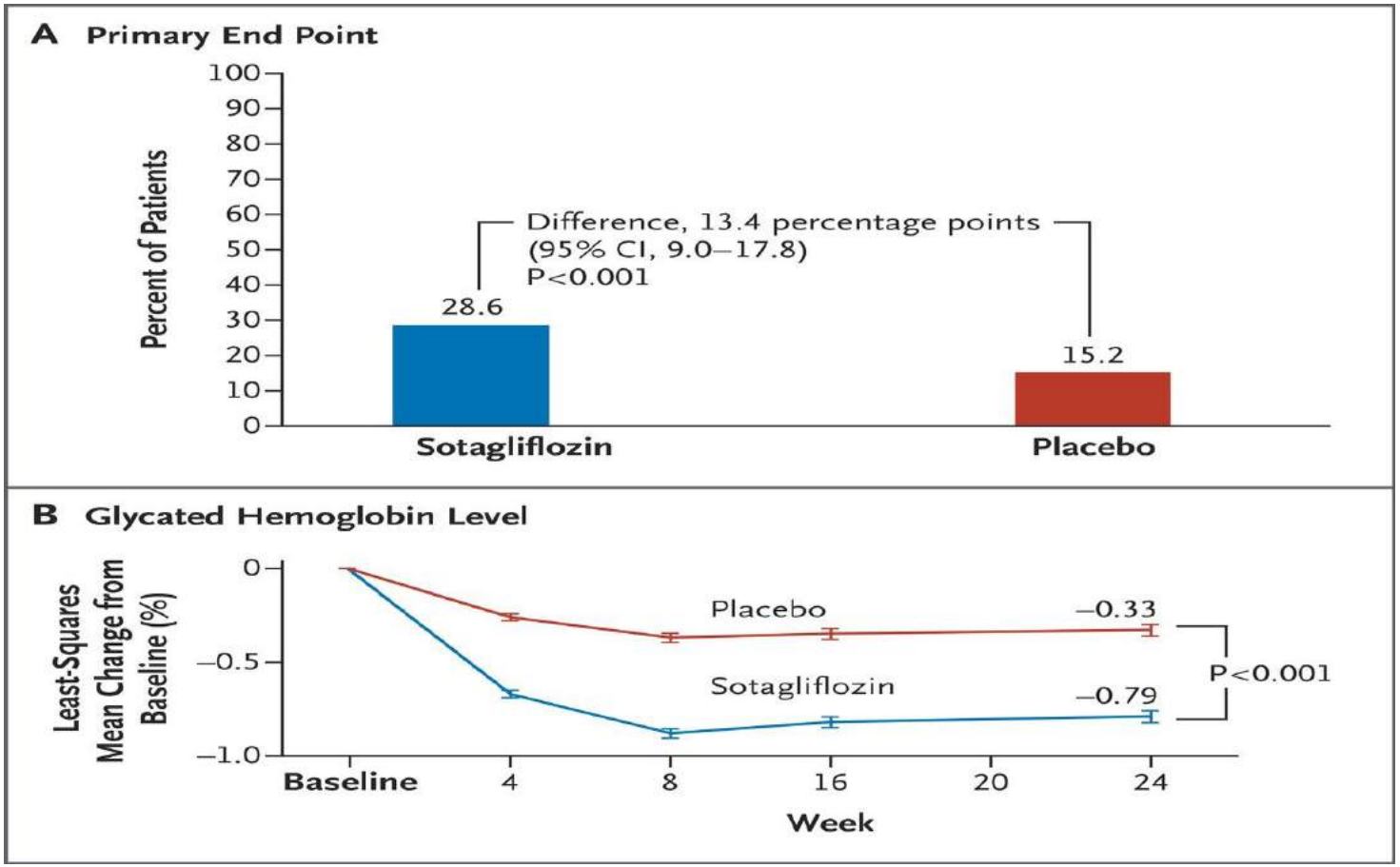
CONCLUSIONS
Among patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a glycated hemoglobin level lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group. However, the rate of diabetic ketoacidosis was higher in the sotagliflozin group. (Funded by Lexicon Pharmaceuticals; inTandem3 ClinicalTrials.gov number, NCT02531035.)

Çalışma glisemik regülasyon sağlanamayan uzun süreli T1DM'lilerde gerçekleştirilmiş

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sotagliflozin (N = 699)	Placebo (N = 703)
Age — yr	43.3±14.2	42.4±14.0
Female sex — no. (%)	341 (48.8)	364 (51.8)
Race or ethnic group — no. (%)†		
White	619 (88.6)	621 (88.3)
Black	24 (3.4)	22 (3.1)
Asian	7 (1.0)	5 (0.7)
Hispanic	49 (7.0)	47 (6.7)
Native American or Alaska Native	1 (0.1)	5 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0
Other	47 (6.7)	50 (7.1)
Duration of diabetes — yr	20.5±12.4	19.6±12.1
Glycated hemoglobin — %	8.26±0.96	8.21±0.92
Fasting plasma glucose — mg/dl	165.1±71.6	163.4±69.1
Weight — kg	82.40±17.13	81.55±17.03
BMI‡	28.29±5.13	28.10±5.18
BMI ≥25 — no. (%)‡	495 (70.8)	497 (70.7)
Systolic blood pressure — mm Hg	122.0±15.3	121.8±14.8
Diastolic blood pressure — mm Hg	76.4±8.8	76.7±9.1
Systolic blood pressure ≥130 mm Hg — no. (%)	203 (29.0)	203 (28.9)
Daily total dose of insulin — IU/kg	0.69±0.28	0.71±0.29
Insulin dose — IU/day		
Total	56.88±27.60	58.35±29.09
Basal	29.54±16.29	29.63±15.54
Bolus and corrections	27.34±16.97	28.72±19.04
Type of insulin therapy — no. (%)§		
Subcutaneous injections	424 (60.7)	423 (60.2)
Pump	275 (39.3)	280 (39.8)

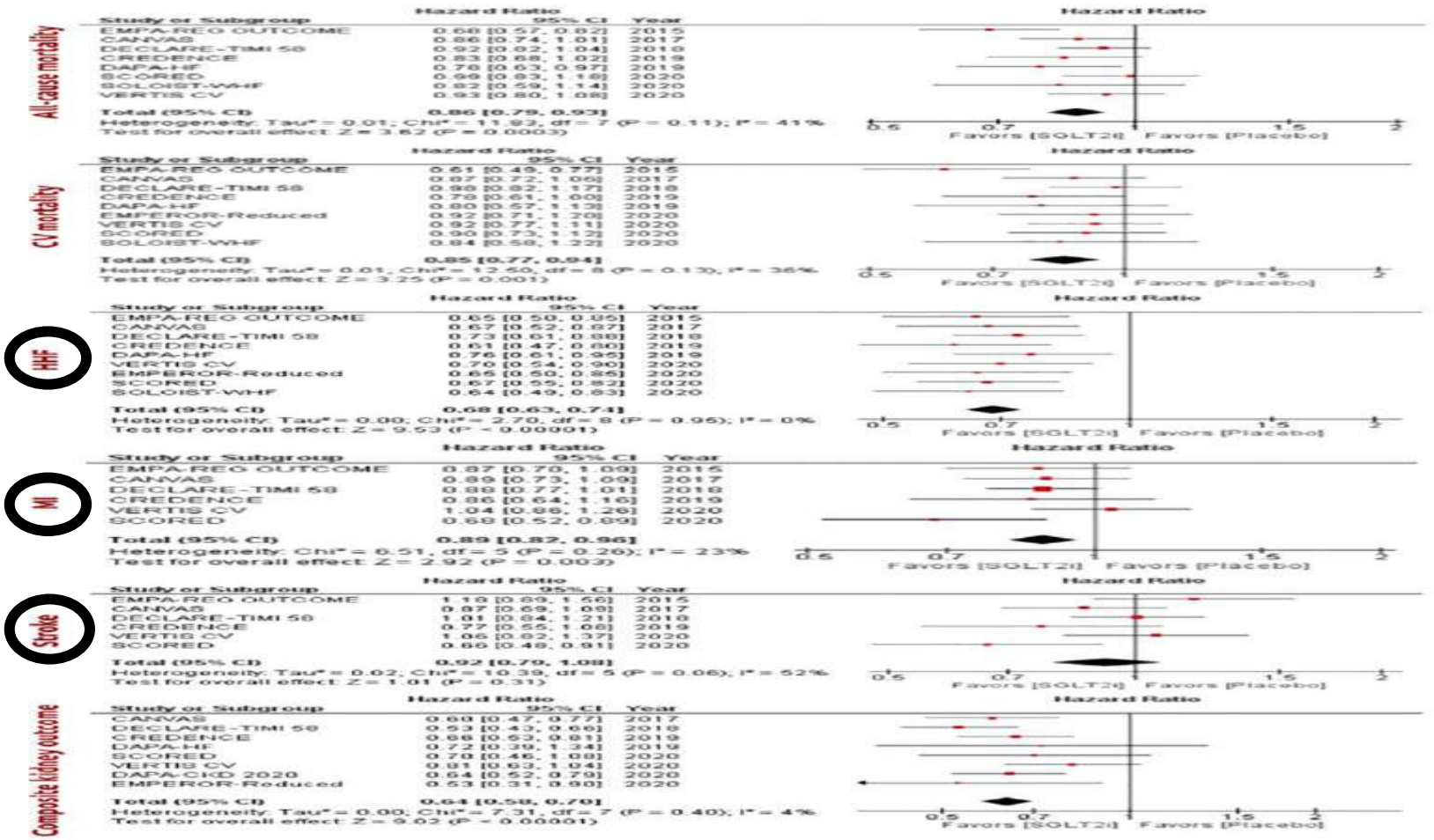
Sotagliflozin ile primer sonlanım noktasına ulaşan hasta oranı %13.4 ile daha yüksektir. %0.46 ek HbA1c düşüşü sağlamıştır



Sotagliflozin grubunda genital mikotik enfeksiyonlar, şiddetli olmayan hipoglisemi, diyare ve az oranda DKA görülmüş

End Point	Sotagliflozin (N=699)	Placebo (N=703)	Difference (95% CI)	P Value
	no./total no. (%)		*percentage points*	
Patients with glycated hemoglobin <7.0% and no severe hypoglycemia or diabetic ketoacidosis				
All patients	200/699 (28.6)	107/703 (15.2)	13.4 (9.0 to 17.8)	<0.001
Patients who used insulin pump	88/275 (32.0)	45/280 (16.1)	15.9 (8.6 to 23.3)	<0.001
Patients who did not use insulin pump	112/424 (26.4)	62/423 (14.7)	11.8 (6.1 to 17.4)	<0.001
Patients with glycated hemoglobin ≥7.0% and ≥1 episode of severe hypoglycemia*	16/699 (2.3)	13/703 (1.8)	0.4 (−1.0 to 1.9)	0.56
Patients with glycated hemoglobin ≥7.0% and ≥1 episode of diabetic ketoacidosis*	18/699 (2.6)	4/703 (0.6)	2.0 (0.7 to 3.3)	0.003

SGLT1 ve SGLT2 inhibitörlerinin T2DM genel etkinliği



Salah HM et al. Am Heart J. 2021 Mar;233:86-91

Sotagliflozin **DM+ KY olan grupta hKY azaltıyor**

Abstract

Background: Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure or death from cardiovascular causes among patients with stable heart failure. However, the safety and efficacy of SGLT2 inhibitors when initiated soon after an episode of decompensated heart failure are unknown.

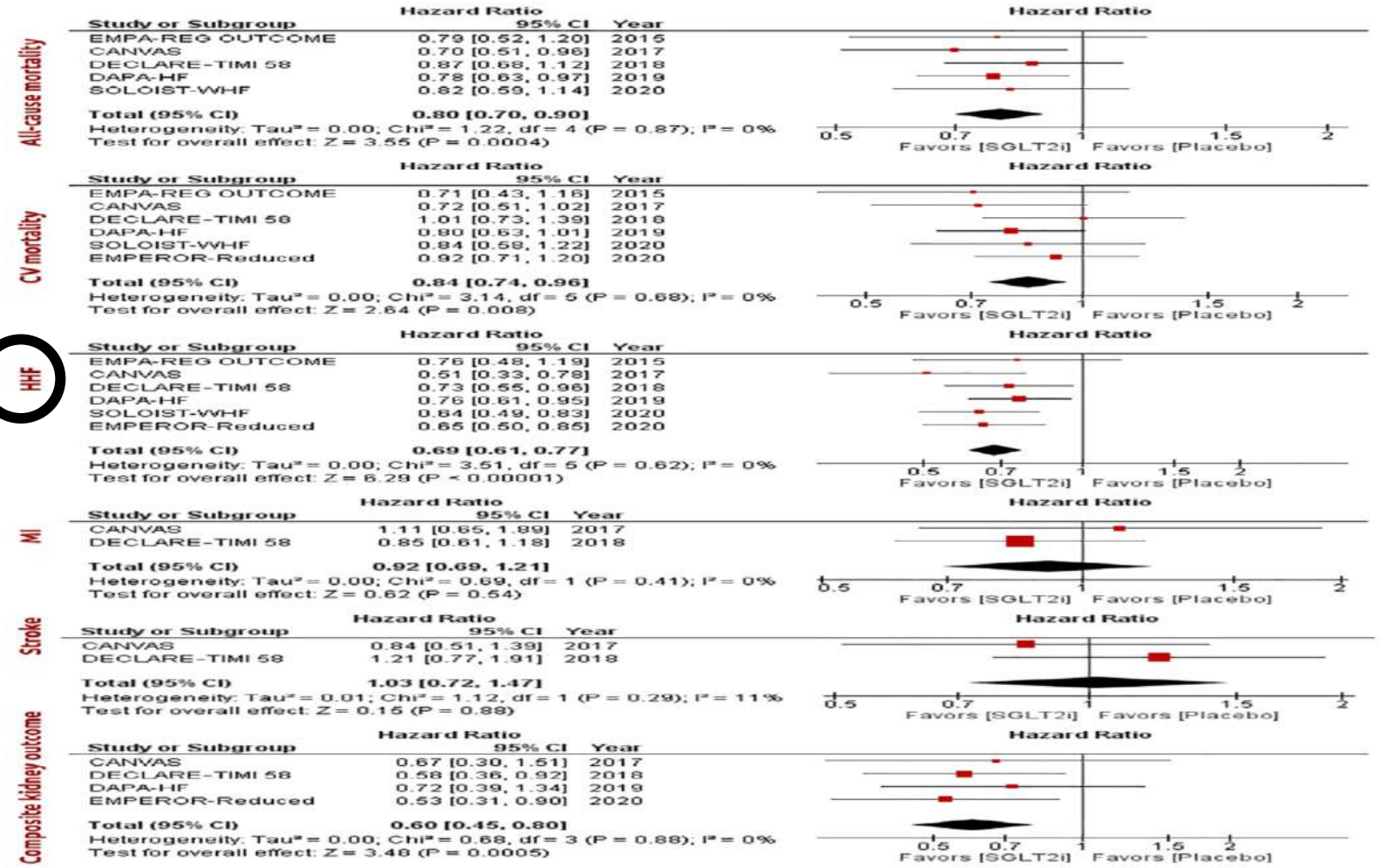
Methods: We performed a multicenter, double-blind trial in which patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure were randomly assigned to receive sotagliflozin or placebo. The primary end point was the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events). The trial ended early because of loss of funding from the sponsor.

Results: A total of 1222 patients underwent randomization (608 to the sotagliflozin group and 614 to the placebo group) and were followed for a median of 9.0 months; the first dose of sotagliflozin or placebo was administered before discharge in 48.8% and a median of 2 days after discharge in 51.2%. Among these patients, 600 primary end-point events occurred (245 in the sotagliflozin group and 355 in the placebo group). The rate (the number of events per 100 patient-years) of primary end-point events was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.85; P<0.001). The rate of death from cardiovascular causes was 10.6 in the sotagliflozin group and 12.5 in the placebo group (hazard ratio, 0.84; 95% CI, 0.58 to 1.22); the rate of death from any cause was 13.5 in the sotagliflozin group and 16.3 in the placebo group (hazard ratio, 0.82; 95% CI, 0.59 to 1.14). Diarrhea was more common with sotagliflozin than with placebo (6.1% vs. 3.4%), as was severe hypoglycemia (1.5% vs. 0.3%). The percentage of patients with hypotension was similar in the sotagliflozin group and the placebo group (6.0% and 4.6%, respectively), as was the percentage with acute kidney injury (4.1% and 4.4%, respectively). The benefits of sotagliflozin were consistent in the prespecified subgroups of patients stratified according to the timing of the first dose.

Conclusions: In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.

Voors AA et al, SOLOIST-WHF Trial N Engl J Med. 2021 Jan 14;384(2):117-128.

SGLT1 ve SGLT2 inhibitörlerinin DM + KY hasta grubunda etkinliği



Salah HM et al. Am Heart J. 2021 Mar;233:86-91

Sotagliflozin **DM+ KBH olan grupta Mİ, inme ve hKY riskini azaltıyor**

Abstract

Background: The efficacy and safety of sodium–glucose cotransporter 2 inhibitors such as sotagliflozin in preventing cardiovascular events in patients with diabetes with chronic kidney disease with or without albuminuria have not been well studied.

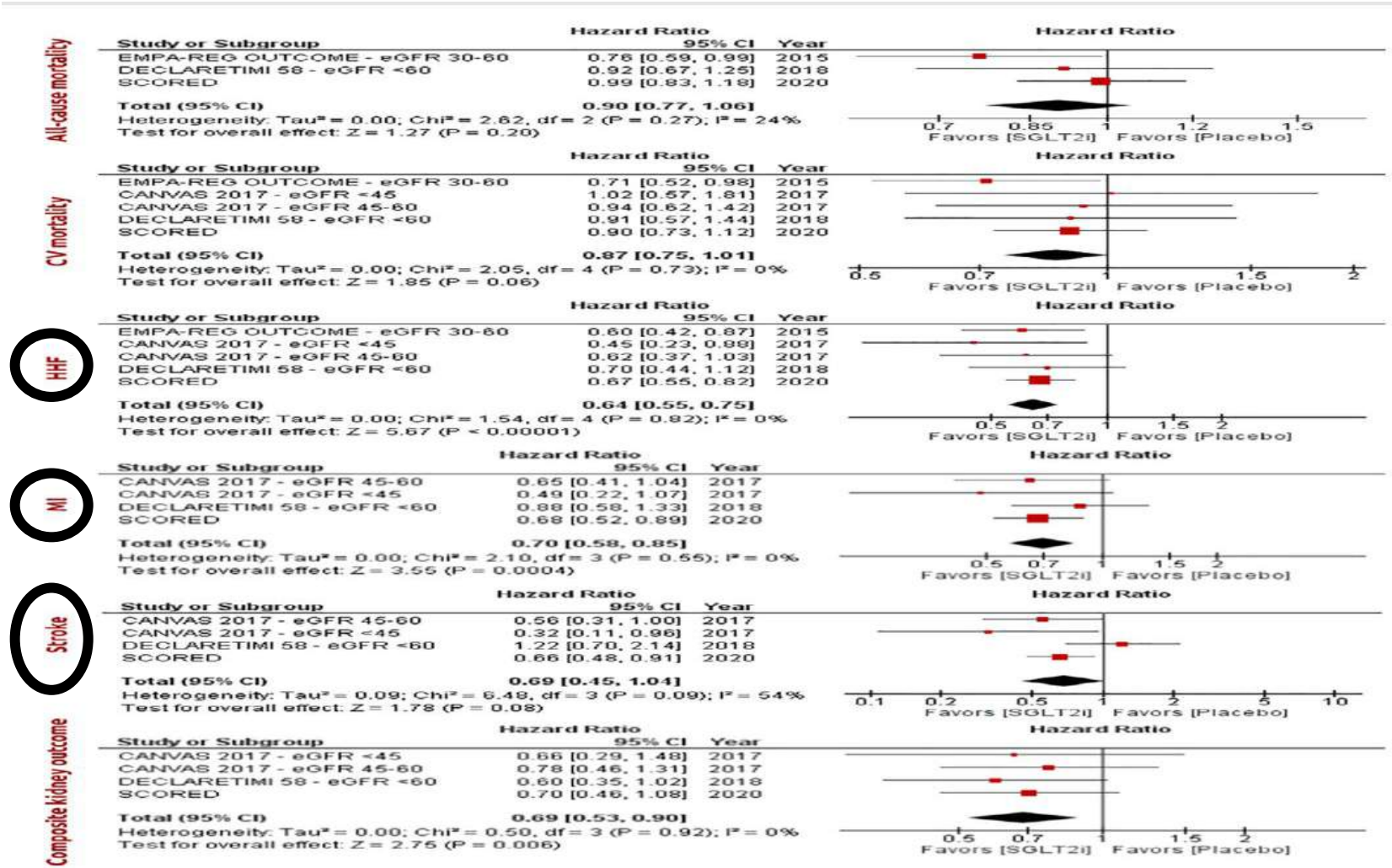
Methods: We conducted a multicenter, double-blind trial in which patients with type 2 diabetes mellitus (glycated hemoglobin level, ≥7%), chronic kidney disease (estimated glomerular filtration rate, 25 to 60 ml per minute per 1.73 m^2 of body-surface area), and risks for cardiovascular disease were randomly assigned in a 1:1 ratio to receive sotagliflozin or placebo. The primary end point was changed during the trial to the composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. The trial ended early owing to loss of funding.

Results: Of 19,188 patients screened, 10,584 were enrolled, with 5292 assigned to the sotagliflozin group and 5292 assigned to the placebo group, and followed for a median of 16 months. The rate of primary end-point events was 5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.63 to 0.88; P<0.001). The rate of deaths from cardiovascular causes per 100 patient-years was 2.2 with sotagliflozin and 2.4 with placebo (hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P = 0.35). For the original coprimary end point of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, the hazard ratio was 0.84 (95% CI, 0.72 to 0.99); for the original coprimary end point of the first occurrence of death from cardiovascular causes or hospitalization for heart failure, the hazard ratio was 0.77 (95% CI, 0.66 to 0.91). Diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than with placebo.

Conclusions: In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events. (Funded by Sanofi and Lexicon Pharmaceuticals; SCORED ClinicalTrials.gov number, NCT03315143.).

Bhatt DL, SCORED TRİAL. N Engl J Med. 2021 Jan 14;384(2):129-139.

SGLT1 ve SGLT2 inhibitörlerinin DM + KBH hasta grubunda etkinliği



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