

CLINICAL RESEARCH

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A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis

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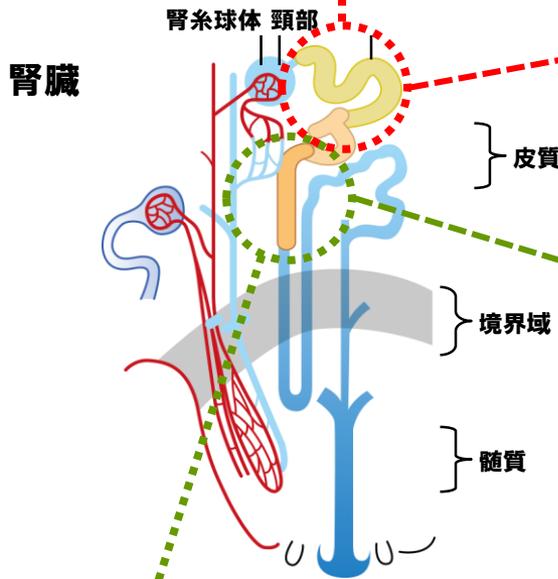
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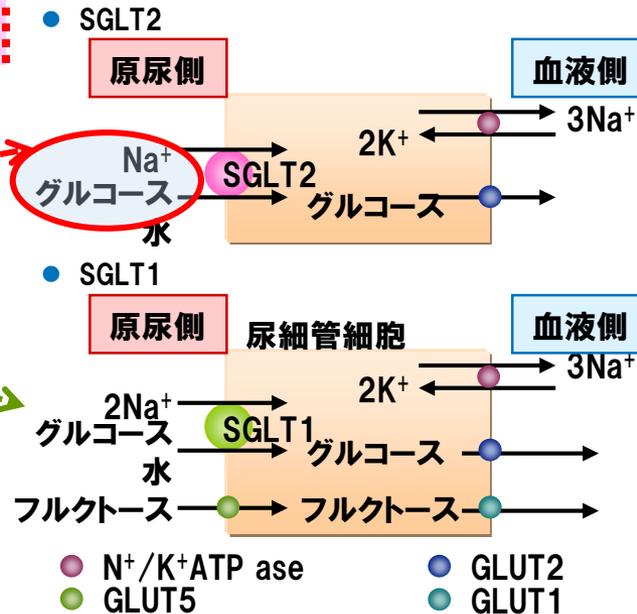
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SGLT2阻害薬は尿細管下流へのグルコース・Na排泄を促進する

近位尿細管の起始部(S1, S2セグメント)に発現するSGLT2が約90%の糖再吸収に関与する



近位尿細管の遠位側(S3セグメント)に発現するSGLT1が残り約10%の糖再吸収に関与する



輸送体	親和性	Na ⁺ :グルコース	輸送能	近位尿細管での局在	発現量
SGLT2	低い	1:1	高い	起始部	多い
SGLT1	高い	2:1	低い	遠位側	少ない

SGLT2阻害薬の作用

尿中に糖・塩・水を出す



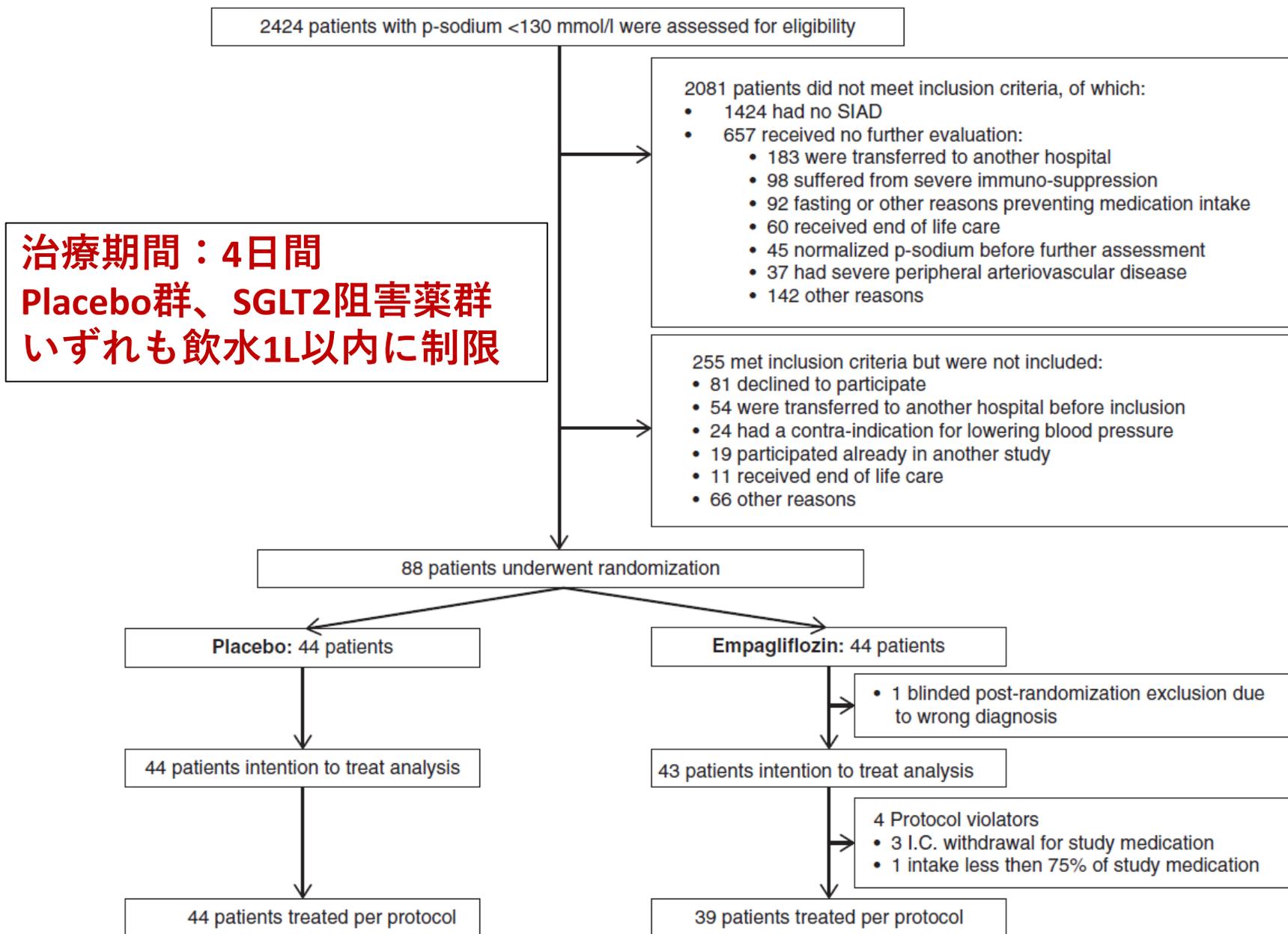


Figure 1. Study flow diagram. I.C., informed consent; p-sodium, plasma sodium; SIAD, syndrome of inappropriate antidiuresis.

投与前データ

Table 1. Baseline characteristics

	Empagliflozin, n=43	Placebo, n=44
Age, yr (SD)	74 (14)	76 (12)
Sex, women (%)	27 (63)	28 (64)
BMI, kg/m ² (SD)	24.0 (4.1)	23.1 (4.9)
Systolic BP, mm Hg (SD)	138 (17)	142 (21)
Diastolic BP, mm Hg (SD)	69 (15)	75 (14)
Heart rate, (bpm)	73 (10)	75 (16)
Comorbidities, n (%)		
Cardiovascular disease	31 (72)	33 (75)
Cerebrovascular disease	6 (14)	10 (23)
Pulmonary disease	6 (14)	9 (21)
Diabetes mellitus type 2	6 (14)	6 (14)
Psychiatric disease	9 (21)	11 (25)
Causes of SIAD, n (%)		
Central nervous system disorders	5 (12)	10 (23)
Nausea/pain	6 (14)	9 (21)
Trauma/postoperative	3 (7)	6 (14)
Drug induced (primarily antipsychotic/antiepileptic drugs)	9 (21)	5 (11)
Pulmonal disease	4 (9)	6 (14)
Infectious diseases	4 (9)	3 (7)
Malignant disease	7 (16)	1 (2)
Idiopathic	5 (12)	4 (9)

Summary statistics of patient characteristics according to the full analysis set. Categorical variables are shown as frequencies (percentage), and numerical variables are shown as mean (SD). BMI, body mass index.

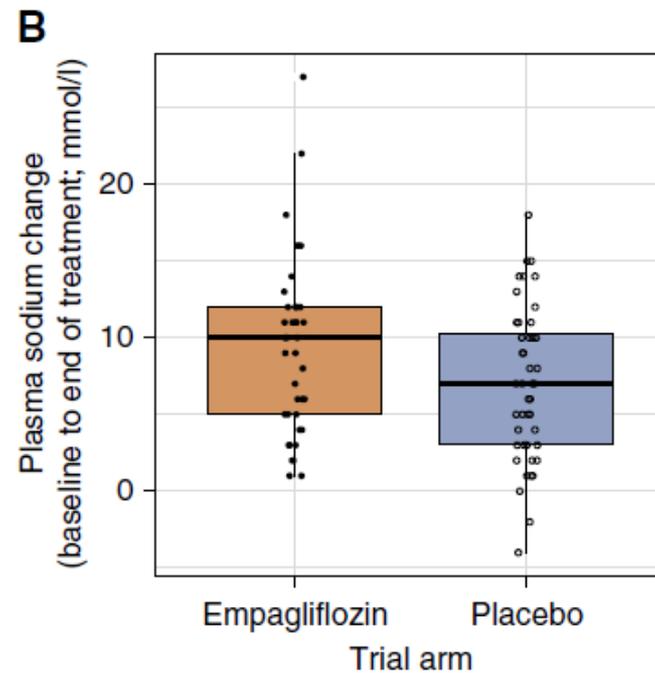
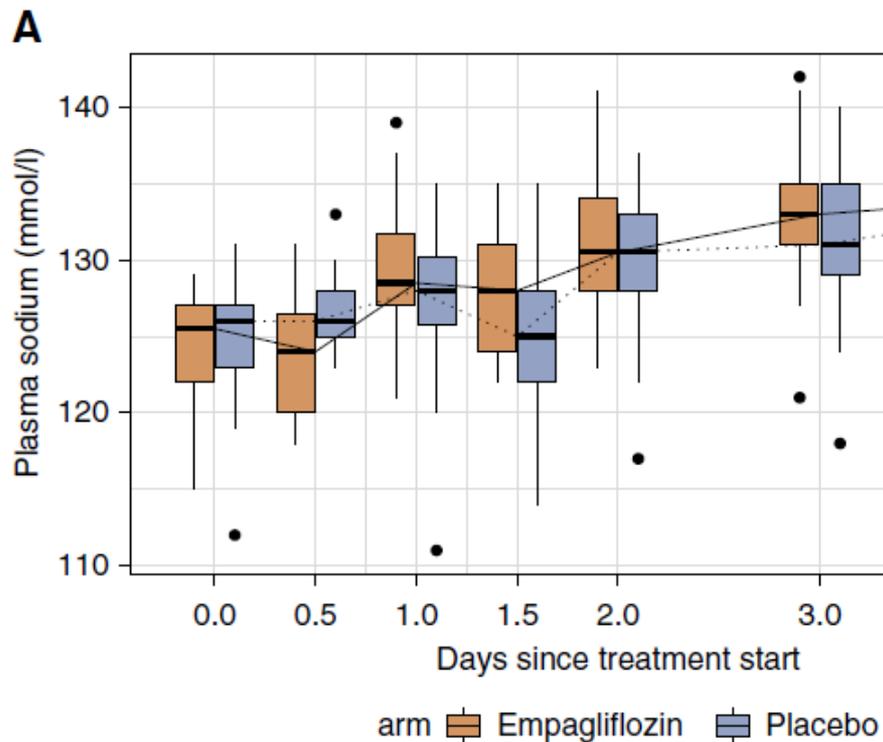
治療前後データの比較

Table 2. Study measures

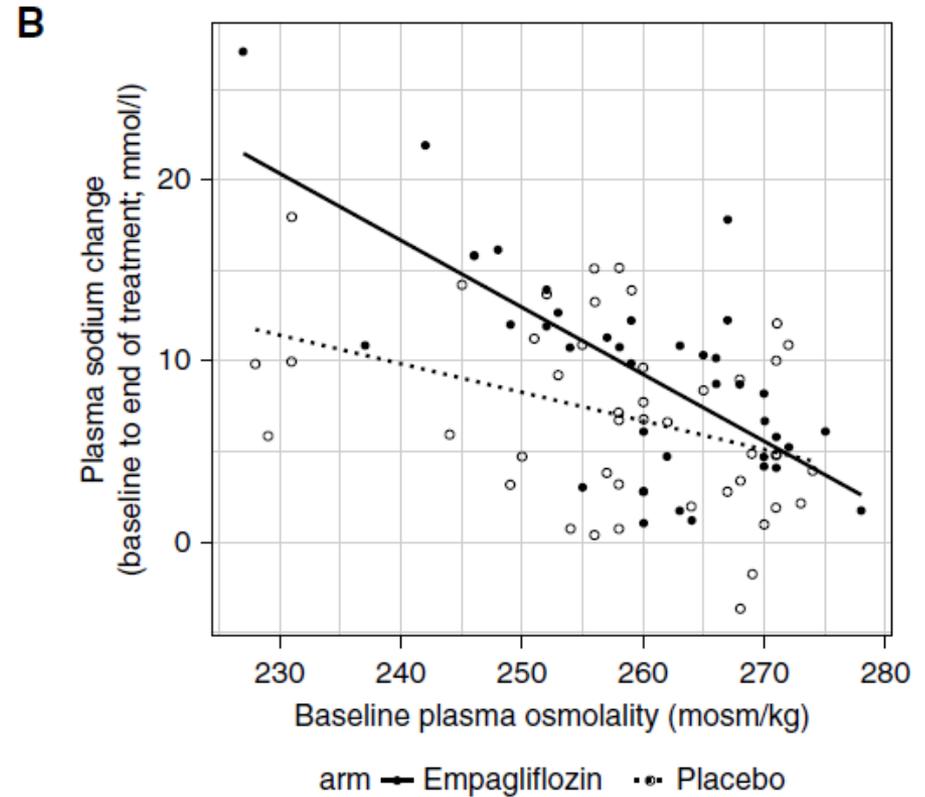
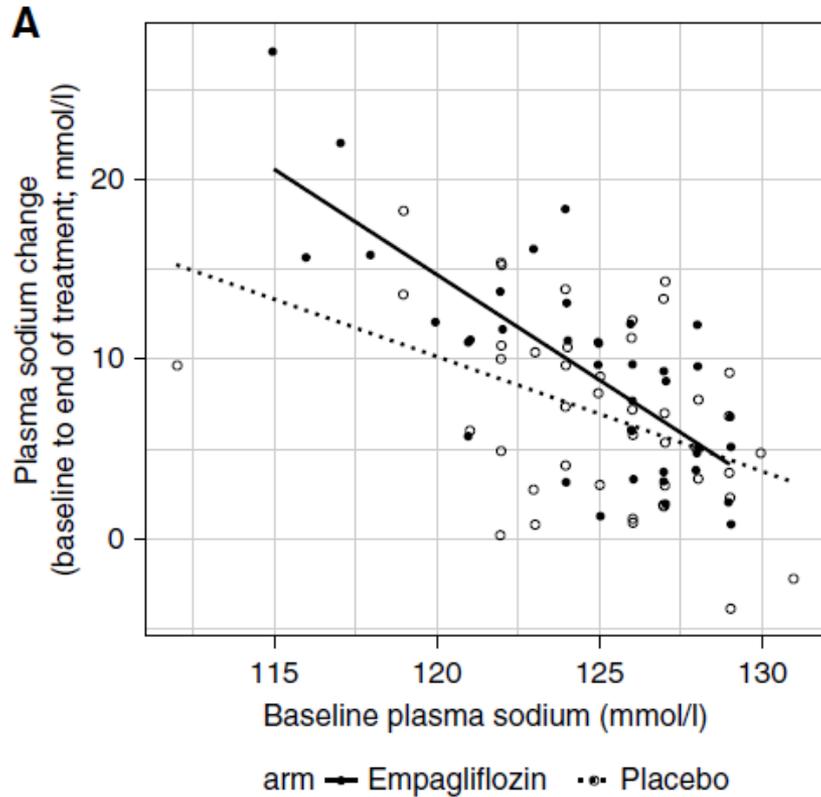
	Empagliflozin		Placebo	
	Day 0	Day 4	Day 0	Day 4
Weight, kg	68.7 (56.2–76.9)	65.5 (53.3–75.6)	59.0 (50.2–70.4)	60.1 (49.2–67.4)
P-sodium, mmol/L	125.5 (122–127)	134 (132–136)	126 (123–127)	133 (129–136)
Absolut change p-sodium levels, mmol/L		10 (5–14)		7 (3–13)
Patients achieving normonatremia, n (%)		18 (42)		13 (30)
P-potassium, mmol/L	4.0 (3.7–4.3)	4.2 (4.0–4.4)	4.0 (3.6–4.2)	4.2 (4.0–4.5)
P-glucose, mmol/L	6.3 (5.3–6.9)	5.2 (4.8–5.7)	6.2 (5.3–7.5)	5.2 (4.8–6.2)
P-urea, mmol/L	4.4 (2.9–5.5)	4.9 (3.8–6.8)	3.7 (3.1–5.2)	4.2 (3.6–5.1)
P-uric acid, mmol/L	214 (139–287)	185 (134–241)	181 (131–252)	207 (154–259)
P-osmolality, mosm/kg	260 (253–268)	281 (273–285)	259 (254–268)	274 (268–281)
U-sodium, mmol/L	68 (54–99)	81 (57–125)	71 (62–100)	81 (52–129)
U-glucose, mmol/L	0.0 (0–0)	111.2 (56–162)	0.0 (0–0)	0.3 (0.2–0.5)
U-urea, mmol/L	127 (81–169)	180 (121–247)	125 (84–171)	159 (100–216)
U-uric acid, μ mol/L	1131 (608–2350)	2126 (1501–2922)	1277 (637–1932)	1623 (1158–2719)
U-osmolality, mosm/kg	419 (297–488)	634 (490–759)	418 (291–514)	448 (357–545)
FE sodium	0.97 (0.5–1.51)	0.64 (0.43–1.34)	0.79 (0.45–1.26)	0.67 (0.40–1.19)
FE urea	46.5 (35.4–55.8)	39.6 (32.7–46.7)	42.0 (35.9–54.0)	41.8 (30.6–50.0)
FE uric acid	11.2 (8.8–14.8)	12.9 (9.2–18.2)	10.9 (5.9–13.9)	9.7 (8.0–12.6)

Summary statistics of study measures according to the full analysis set. Categorical variables are shown as frequencies (percentage), and numerical variables are shown as median (IQR). P, plasma; U, urinary; FE, fractional excretion.

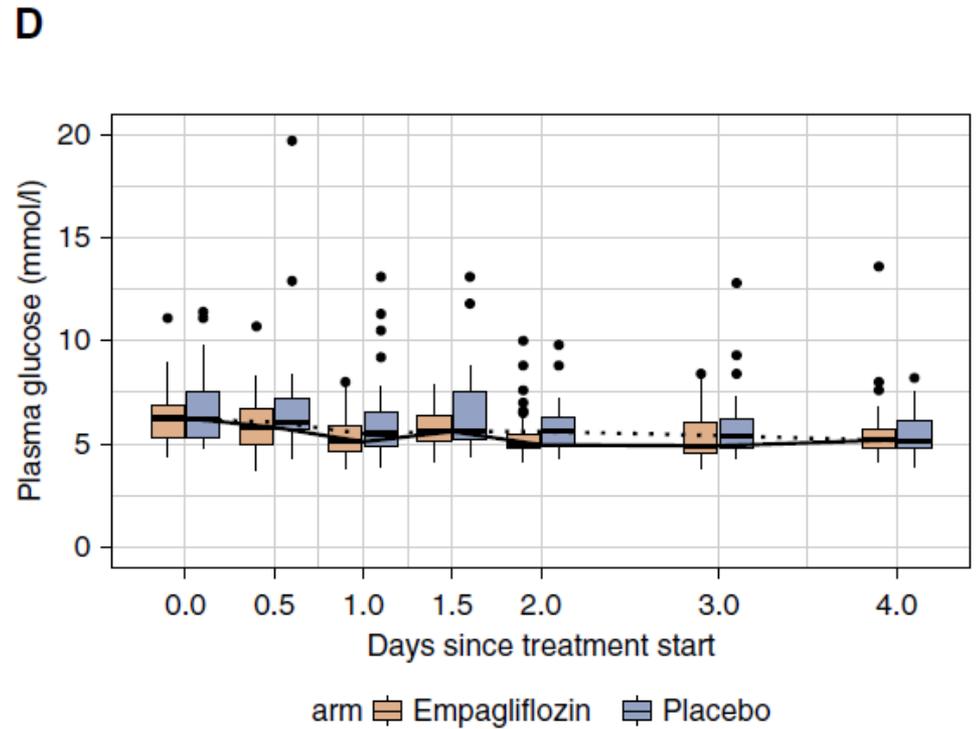
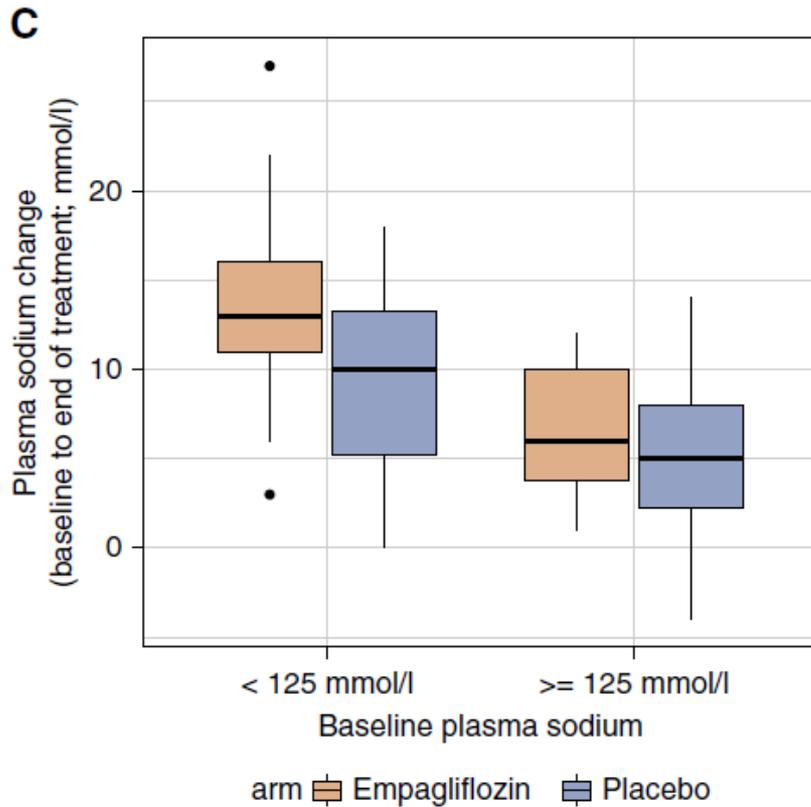
血中Na値変化の比較



投与前 血中Na値・浸透圧による Na値変化の比較



投与前血中Na値別の変化量 血糖変化の比較



結論

SGLT2阻害薬エンパグリフロジン + 飲水制限は、SIADHの新たな治療法となる。

考察

《従来のSIADH治療と課題》

飲水制限 → 効果不十分

尿素投与 → 長期効果不明, 尿素窒素上昇

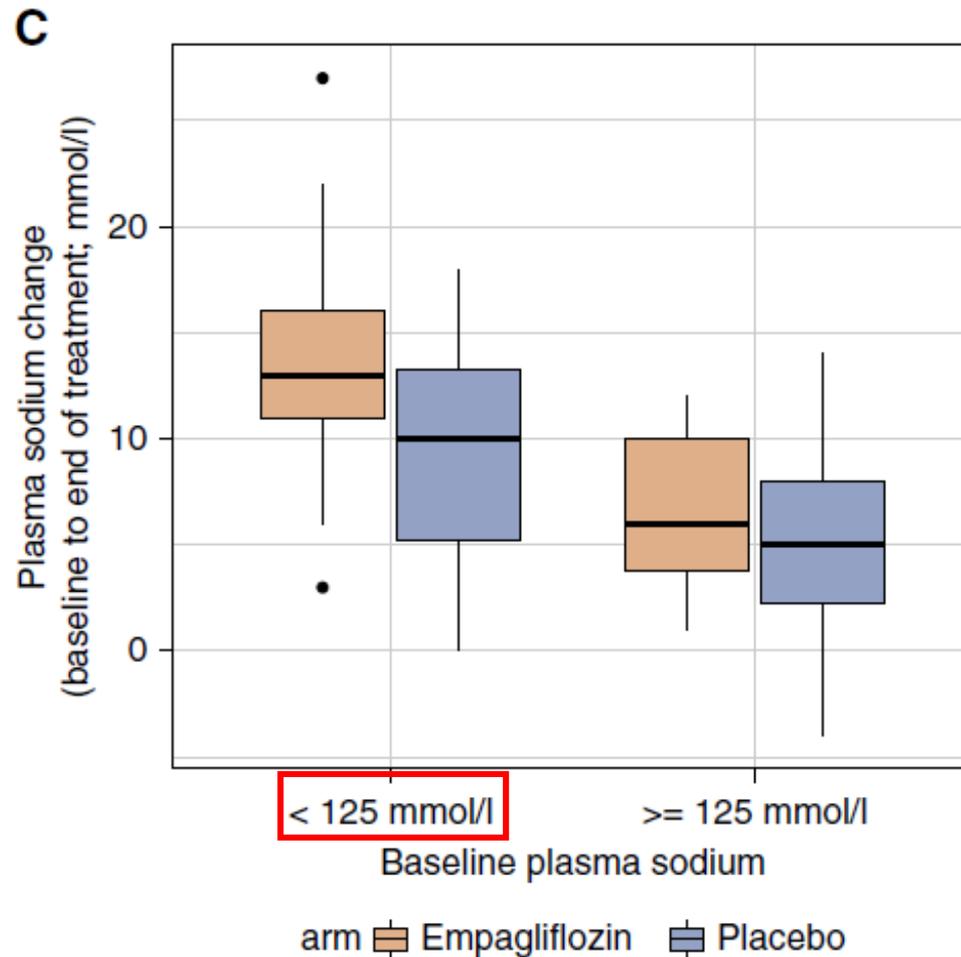
Tolvaptan → 高額、高Na血症が高頻度



SGLT2阻害薬：長期安全性データ、高Na血症少ない
高齢者での体液減少に注意

自験例を交えての考察

SGLT2阻害薬は低Na血症を改善する



SGLT2阻害薬は正常血清Na値を上昇させない

Table 1. Comparative parameters at baseline and day 7 after dapagliflozin administration

Characteristics	Baseline (n=36)	Day 7 (n=36)	<i>p</i> value
Age (years)	68.5 ± 2.1	-	-
Male gender (%)	66.7	-	-
eGFR (mL/min/1.73 m ²)	27.9 (19.2-42.0)	29.3 (17.9-39.6)	0.003
Uric acid (mg/dL)	6.6 ± 0.3	6.3 ± 0.2	0.031
<u>Serum Na⁺ (mEq/L)</u>	<u>141 (138-142)</u>	<u>141 (137-143)</u>	<u>0.402</u>
Serum K ⁺ (mEq/L)	4.4 ± 0.1	4.2 ± 0.1	0.045

Why ?

SGLT2阻害薬

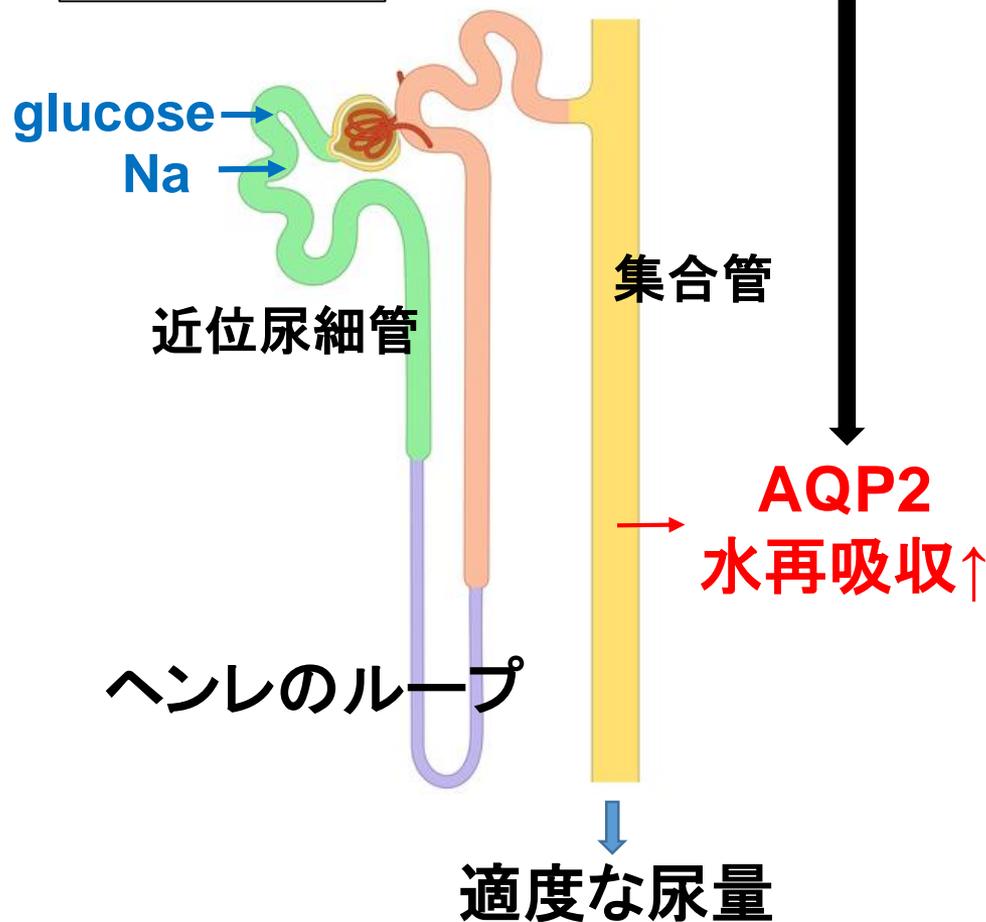
低Na血症	→	Na上昇
正常血清Na	→	Na不変



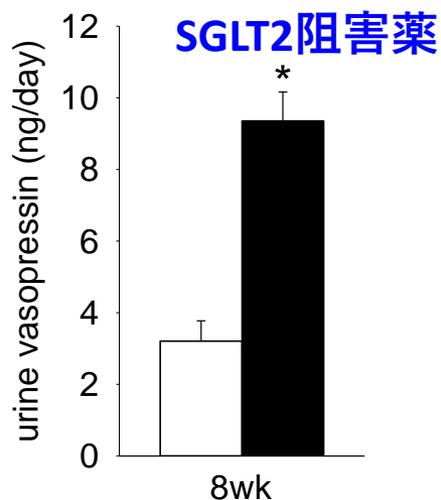
投与前の血清Na値の違いで
利尿作用（尿量）が異なる？

SGLT2阻害薬はバソプレシン分泌促進により、集合管での水再吸収を促進

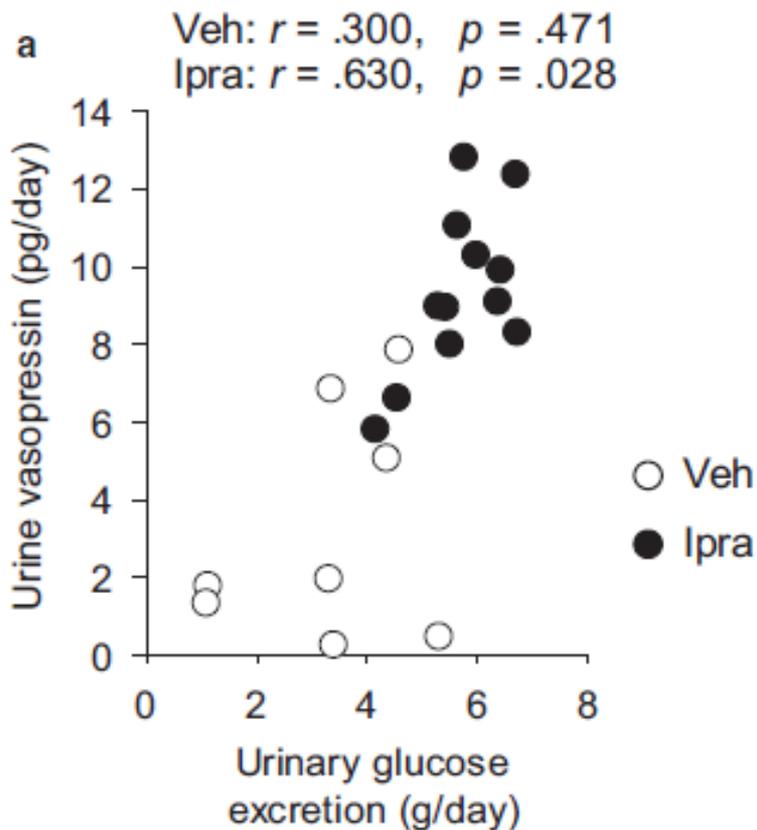
SGLT2阻害 → バソプレシン↑



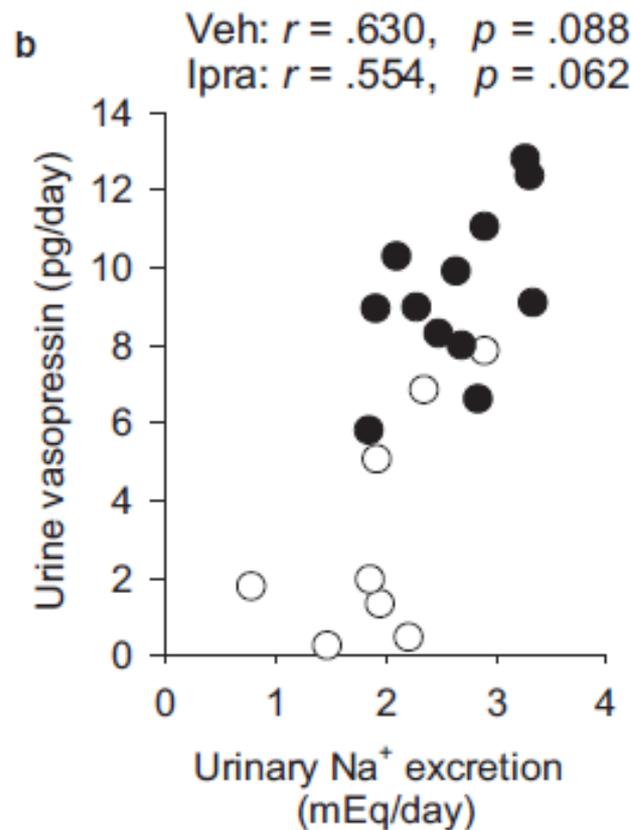
尿中バソプレシン



SGLT2阻害薬投与時のバソプレシン分泌は 尿中グルコース・Na量と正相関する



尿中グルコース



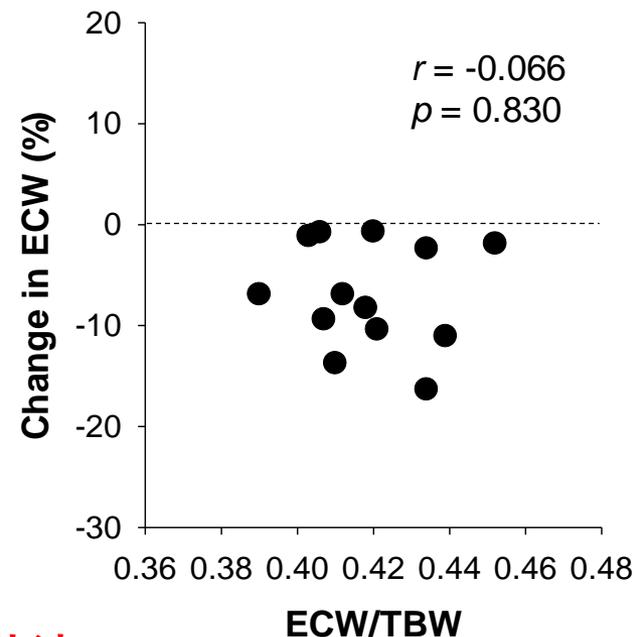
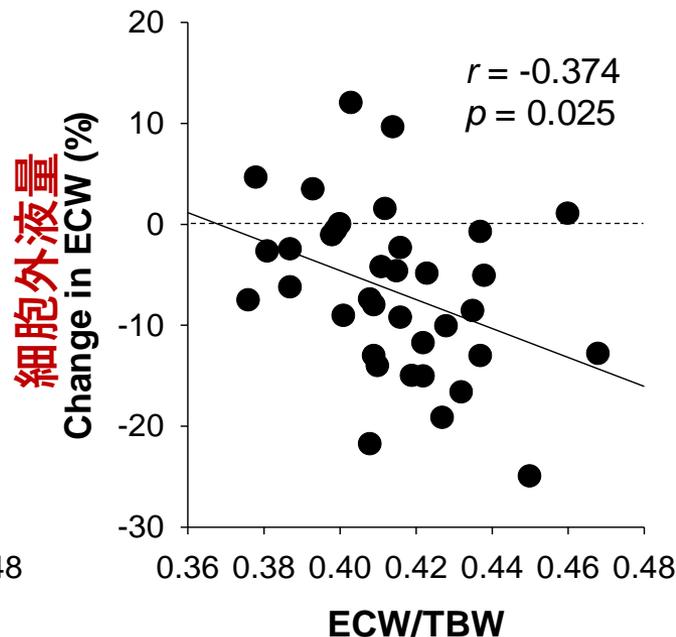
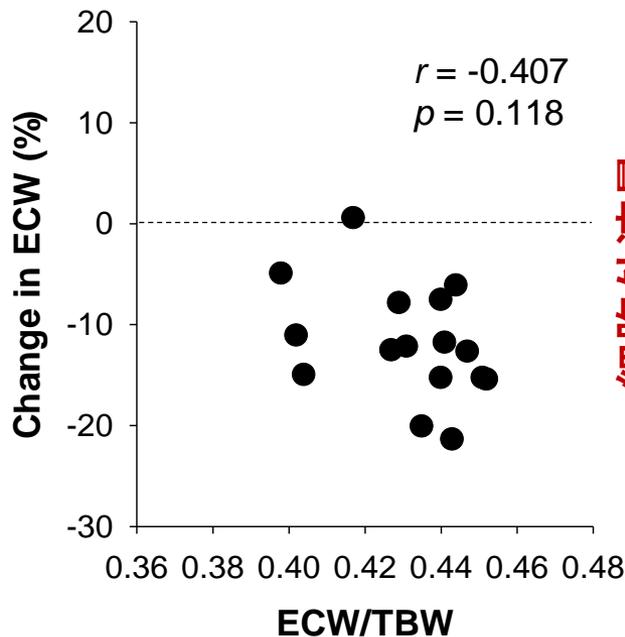
尿中Na

SGLT2阻害薬は投与前の体液量により 投与後の体液量変化率が異なる

ループ利尿薬
フロセミド

SGLT2阻害薬
ダパグリフロジ

バソプレシンV2
受容体拮抗薬
トルバプタン



体液過小
(脱水)



体液
過剰

ECW: 細胞外水分量、TBW: 総水分量

まとめ

SGLT2阻害薬

血清Na
体液量

正常化及び維持作用



体内状態で変化するバソプレシン分泌を介した尿量調節機能の関与が推定