SGLT2 INHIBITORS: IS IT TIME FOR NEPHROLOGISTS TO BE USING THEM FOR PATIENTS WITH DIABETIC NEPHROPATHY?

Christopher S. Wilcox
Georgetown University
KDIGO and NANFANG HOSPITAL CHINA
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SGLT INHIBITORS

1. SGLT 2i’s registered in USA and Europe:
   - dapagliflozin
   - canagliflozin
   - empagliflozin

2. Other SGLT 2i’s registered in Japan:
   - ipragliflozin
   - tofogliflozin
   - luscogliflozin

3. Combined SGLT 1 + 2i’s under development:
   - sotagliflozin
   - ertugliflozin
OVERVIEW OF SGLT2i’s

• Sites of expression and mechanisms of action
• Physiology and pathophysiology
• Effects on: BP
  CVD
  CKD
• Conclusions
PROXIMAL TUBULE GLUCOSE REABSORPTION

S2 segment

Na⁺ �ightharpoonup Na⁺

SGLT2

Glucose �ightharpoonup Glucose

NHE3

Na⁺ �ightharpoonup H⁺

GLUT2

K⁺ �ightharpoonup K⁺

Na⁺ / K⁺ ATPase

S3 segment

Na⁺ �ightharpoonup Na⁺

SGLT1

Glucose �ightharpoonup Glucose

GLUT1

Na⁺ / K⁺ ATPase

K⁺ �ightharpoonup K⁺

SGLT2: low affinity, high capacity (S2)
SGLT1: high affinity, low capacity (S3)
SGLT INHIBITORS

• There are many new anti-diabetic medications, so,
• Why is the subject important?
REDUCTION IN HbA1c, BODY WEIGHT AND SYSTOLIC BLOOD PRESSURE IN 2,250 PATIENTS WITH T2DM TREATED WITH CANAGLIFLOZIN FOR 6 MONTHS

A. HbA1c

Δ HbA1c (%)

-1.2

B. Body weight

Δ Body weight (%)

-4

C. Systolic BP

Δ SBP (%)

-6

INHIBITION OF SODIUM GLUCOSE LINKED TRANSPORTER 2 WITH DAPAGLIFLOZIN FOR 18 MONTHS IN 5,000 PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION AND WITH, OR WITHOUT, T2DM REDUCED CARDIOVASCULAR EVENTS, HOSPITALIZATION FOR HEART FAILURE, AND DEATH FROM ANY CAUSE IN THE DAPA-HF TRIAL

A. Primary end point

B. Death from CVD

C. Death from any cause

Mean values

- Placebo
- Dapagliflozin 10 mg daily

No significant differences in adverse events
No patients developed serious hypoglycemia or ketoacidosis

EMPAGLIFLOZIN SLOWS PROGRESSION OF CKD OVER FOUR YEARS IN 4,000 PATIENTS WITH TYPE 2 DIABETES

A. Nephropathy

Number with nephropathy (%)

\[ \Delta = -39\% \]

B. Scr

Doubling of serum creatinine (%)

\[ \Delta = -44\% \]

C. Progress to macroalbuminuria

Development of macroalbuminuria (%)

\[ \Delta = -38\% \]

D. RRT

Need for RRT (%)

\[ \Delta = -55\% \]

Nephropathy: • progression to macroalbuminuria, or
• doubling of serum creatinine, or
• initiation of renal replacement therapy, or
• death from renal disease

Placebo

Empagliflozin 10 or 25 mg daily

Adverse events: Empagliflozin group had more mycotic genitourinary infection but less AKI

CONCLUSION

Empagliflozin, canagliflozin and dapagliflozin for T2D:
• Reduce HbA1c
• Reduce BP and body weight
• Reduce CVD events
• Slow diabetic nephropathy
• May prolong life

Therefore, this is a hot topic!
WHAT MAY ACCOUNT FOR LOWERING OF BP WITH SGLT2 INHIBITORS?

• Diuretic effect
• Plasma volume reduction
• Reduced vascular stiffness
• Reduced sympathetic nervous system
Renin, aldosterone generally unchanged
MODEL OF SGLT2 IN PROXIMAL TUBULE REABSORPTION

A. Normal

B. After SGLT2i

See: Layton, AT and Vallon, V. Am J Physiol 314: F643-F657, 2018
INHIBITION OF PROXIMAL FLUID REABSORPTION BY CHRONIC DAPAGLIFLOZIN ADMINISTRATION TO STREPTOZOTOXIN DIABETIC RATS

Mean ± SEM values
- Control
- Acute dapagliflozin (1mg · kg⁻¹ iv on the table)
- Chronic dapagliflozin (1 and 2mg · kg⁻¹ ig x 10-12d)

Compared to control: *, p<0.05

PROXIMAL TUBULE Na⁺ REABSORPTION”

• Na⁺ glucose reabsorption accounts for only 5 – 10%, yet
• SGLT2i’s block 27%
• What accounts for the unexpected effectiveness of SGLT2i’s?
NHE3 Na⁺/H⁺ EXCHANGE ACTIVITY MEASURED FROM BICARBONATE REABSORPTION
IN RAT PERFUSED RENAL PROXIMAL TUBULES IS INCREASED BY HEART FAILURE AND
DECREASED IN NORMAL RATS BY BLOCKING SGLT2i WITH LUMINAL PERFUSION OF PHLORIZIN (PZ)

A. Heart failure

B. SGLT2i

Mean ± SEM values
- Green: Control (before)
- Red: After heart failure or perfusion with phlorizin (2 μmol·l⁻¹)

MECHANISMS WHEREBY SGLT2 INHIBITORS MAY REDUCE PROXIMAL TUBULE REABSORPTION OF SODIUM

- SGLT2i
  - ↓ MAP17 / PDZ K1
  - ↓ Na⁺: glucose reabsorption
  - ↑ Direct interaction with NHE3
  - ↓ PT reabsorption of Na⁺ and fluid
  - ↓ NHE3 activity

      • Uthman, L et al. Diabetologia, 2 Dec, 2017
DAPAGLIFLOZIN REDUCES ESTIMATED PLASMA VOLUME IN PATIENTS WITH T2DM

Data from 4,500 patients in clinical trials
PV estimated from the Strauss formula using changes in hemoglobin and validated from measurements with $[^{125}]$ human serum albumin volume of distribution

CONCLUSION

SGLT2 inhibitors for T2D are diuretics and:
• Increase Na⁺ loss,
• Reduce body weight,
• Reduce plasma volume.
QUESTION

What are the effects of DM and SGLT2i’s on renal hemodynamics?
LOOP OF HENLE REABSORPTION INCREASES DURING SUSTAINED INHIBITION OF PROXIMAL FLUID REABSORPTION BY CHRONIC DAPAGLIFLOZIN ADMINISTRATION TO STREPTOZOTOCIN DIABETIC RATS

A. Prox reabsorption

B. Macula densa Cl⁻ delivery

Mean ± SEM values

- Control
- Acute dapagliflozin (1mg · kg⁻¹ iv on the table)
- Chronic dapagliflozin (1 and 2mg · kg⁻¹ ig x 10-12d)

Compared to control: *, p<0.05

INHIBITION OF SGLT2 WITH EMPAGLIFLOZIN IN THE EMPA-REG OUTCOME TRIAL SLOWS LOSS OF GFR IN 6,000 PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

**Graph:**
- **X-axis:** Time (weeks)
- **Y-axis:** Adjusted mean eGFR (ml/min/1.73 m²)
- **Legend:**
  - ▲ Placebo (n = 2061)
  - □ Empagliflozin 25 mg daily (similar results with 10 mg daily; n = 4170)

80% were receiving ACEI or ARB therapy
Accompanied by 14 - 38% reductions in CVD events (mainly heart failure)

SGLT2 INHIBITORS

• GFR falls ~ 5 – 10% early
• Then stabilizes over 4 years
• Consistent with sustained activation of tubuloglomerular feedback
Are there similar effects of SGLT2i’s and ACEi’s on renal hemodynamics?
REDUCTION IN GLOMERULAR PRESSURE BY SGLT2i's, ACEi's AND ARBs

SGLT2i ➔ TGF ➔ RAA

ACEi, ARB ➔ P_GC

SGLT2i, ACEi, and ARB ➔ PT R_NaCl

SGLT2i ➔ RNaCl in MD

Efferent arteriole
Afferent arteriole
Thick ascending limb of Henle
Extraglomerular mesangial cells
Distal tubule
Macula densa cells
Proximal convoluted tubule
Glomerulus
SGLT2 INHIBITOR OR ACEI FOR T1DM CORRECT HYPERFILTRATION IN HYPERFILTERING PATIENTS

A. SGLT2 INHIBITOR

- SGLT2i
  - ↑ TGF
  - ↑ Afferent arteriolar resistance
  - ↓ GFR
  - ↓ RBF

- GFR
- Inulin clearance (ml min⁻¹/1.73m²)
- PAH clearance (ml min⁻¹/1.73m²)

- ERPF

- Mean ± SEM values during euglycemic clamp in patients with baseline GFR > 135 ml min⁻¹/1.73m²:
  - Before
  - After 8 weeks of empagliflozin (25 mg daily; n = 11)
  - Before
  - After 2 weeks of enalapril (0.2 mg kg⁻¹ daily; n = 11)

B. ACE INHIBITOR

- ACEi
  - ↓ Ang II
  - ↓ Efferent arteriolar resistance
  - ↓ GFR
  - ↑ RBF

- GFR
- Inulin clearance (ml min⁻¹/1.73m²)
- PAH clearance (ml min⁻¹/1.73m²)

- ERPF

CONCLUSION

• Both SGLT2i’s and ACEi’s/ARBs correct hyperfiltration but by separate effects
• Therefore, renal protection may be additive
• Both cause a 5 - 10% rise in serum creatinine in the first weeks of therapy
HYPOTHESIS

If SGLT2i’s increase delivery and reabsorption of NaCl to the loop of Henle, then loop diuretics should become more effective.
See:  • Layton, AT and Vallon, V. Am J Physiol 314: F643-F657, 2018
       • Thompson, SC et al. Am J Physiol 302: R75-R81, 2012
       • Wilcox, CS et al. J Am Heart Assoc, Feb 10, 2018
SIX HOURLY SODIUM EXCRETIONS AFTER THE FIRST DOSE OF BUMETANIDE OR DAPA GLIFLOZIN AND AFTER ONE WEEKS EXPOSURE TO THE OTHER DRUG

A. Responses to bumetanide

B. Responses to dapagliflozin

Mean ± SEM values (n = 14 per group)
- Pink: Response to bumetanide (1mg) on day 1
- Red: Response to bumetanide on day 8 after 1 week of dapagliflozin
- Light Green: Response to dapagliflozin (10mg) on day 1
- Green: Response to dapagliflozin on day 8 after 1 week of bumetanide

After: Wilcox, CS et al. J Am Heart Assoc, 2018
POTENTIAL MECHANISMS OF MUTUAL NATRIURETIC SYNERGY BETWEEN AN SGLT2 INHIBITOR AND A LOOP DIURETIC

A. Potentiation of loop diuretic natriuresis with SGLT2i by increasing loop of Henle NaCl delivery and reabsorption by NKCC2

B. Potentiation of SGLT2i natriuresis with loop diuretic by increasing ATIR-dependent expression of SGLT2 and NHE3

After:
- Wilcox, CS et al. J Am Heart Assoc 2018, Feb 10: 7(4), e007046
QUESTION

• SGLT2i’s are not licensed for patients with a GFR < 30 – 45 ml/min.
• Is this because of increased toxicity?
THE GLYCOUSURIC EFFICACY OF THE SGLT2i CANAGLIFLOZIN DEPENDS ON THE GFR

INCREASING CKD IN POOLED TRIAL DATA REDUCES THE EFFICACY OF THE SGLT2 INHIBITOR EMPAGLIFLOZIN TO LOWER HbA1c IN T2D BUT ENHANCES THE FALL IN SBP

See:  • Cherney, DZI et al. Kidney Int 93: 231-244, 2018
     • Sims, H et al. Diabet Med April 10, 2018
RENAL EFFICACY OF CANAGLIFLOZIN IN PRESERVING eGFR IN THE CANVAS TRIAL WAS PRESERVED IN PATIENTS WITH CKD DESPITE LESS EFFECT ON HbA1c

Annual mean difference between canagliflozin and placebo in eGFR slope (ml · min · 1.73m⁻²)

- All
- > 90
- 60 - 90
- 45 - 60
- < 45

P value for interaction: P = 0.21

No effect of eGFR on adverse events but lesser reduction in HbA1c by 55% in the lowest eGFR group

After: Neuren, BL et al. Circ 138: 1537-1550, 2018
CONCLUSION

In patients with CKD, SGLT2i’s lose much of their anti-diabetic effect. That is why the FDA has been reluctant to license them in this group, but

- Renal preservation is retained,
- No evidence of increased adverse effects, indeed,
- May be especially indicated in this group
QUESTION

What accounts for renal and CVD protections with SGLT2i’s?
SOME POTENTIAL MECHANISMS OF VASCULAR, CARDIAC AND RENAL PROTECTION WITH SGLT2i

SGLT2 inhibition

↑ Glycosuria

↓ Urate reabsorption  ↓ Blood glucose  ↓ Negative calorie balance  ↓ Extracellular fluid volume  ↑ TGF  ↓ Poc

↓ Plasma uric acid  ↓ ROS  ↓ Inflammation  ↓ Body weight  ↓ Blood pressure  ↓ Glomerular barotrauma

Vascular; cardiac and renal protection

• Vallon, V and Thompson, SC Diabetologia 60: 215-225, 2017
• Dekkers, CCJ et al. Curr Diabet Reports 18: 27, 2018
QUESTION

What are the adverse effects of SGLT2i’s?
ADVERSE AND BENEFICIAL METABOLIC EFFECTS
OF SGLT2 INHIBITOR THERAPY IN T2DM

SGLT2 inhibitor therapy for T2DM

↑ Renal glucose excretion

↑ Infections of:
• genitalia
• urinary tract (risk 1.7 and 3.5-fold increased)

Negative calorie balance
↓ Body fat

↓ glucagon
↓ insulin
↑ lipolysis

↑ Euglycemic ketoacidosis (risk 0 to 10-fold increased)

Weight loss

Adverse effects

After: • Feng, M et al. Medicine 96.30, 2019
QUESTION

Should nephrologists prescribe SGLT2i’s?
BALANCING BENEFITS AND PROBLEMS OF SWITCHING A PATIENT WITH T2DM TO SGLT2 INHIBITOR THERAPY

- Genital infection
- Urinary tract infection
- Euglycemic ketoacidosis
- Physician visits to adjust anti-diabetic medications

- Risk of adverse effects
- Cost of care

- ↓ HbA1c
- ↓ CVD
- ↓ Renal progression
- ↓ BP
- ↓ Body weight & fat

- ↓ Oxidative stress
- ↓ Inflammation
- ↓ Vascular stiffness
- ↓ Endothelial dysfunction
- ↓ Uric acid
- ↓ Sympathetic nervous system activity

- ↓ Disease burden
- ↓ MORTALITY
POTENTIAL FUTURE USES OF SGLT2 INHIBITORS FOR PREVENTION OF CVD, CHF AND CKD

In patients:
1. With CKD without DM
2. With CHF and diuretic resistance
THE END