INHIBITEURS DU SGLT2 ET REINS

DR LUC RADERMACHER

NEPHROLOGIE
IMMUNO-INFECTIOLOGIE
MÉDECINE INTERNE
CITADELLE
WWW.NEPHRO-LIEGE-CHR.BE
PLAN

• Effets rénaux directs et indirects des iSGLT2
• La révolution de l’étude Dapa-CKD
• Indications néphrologiques
Natriuresis effect on tubuloglomerular feedback

Afferent arteriole

Macula densa

SGLT-2

↑ Tubuloglomerular feedback leads to afferent constriction
↓ Intraglomerular hypertension
↓ Proteinuria

Na⁺/glucose cotransport inhibition with SGLT2 inhibitors

↓ Blood pressure
↓ Arterial stiffness
↓ Weight
↓ HbA1c
Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators

**DAPA-CKD:**

*Dapagliflozin in Patients With Chronic Kidney Disease*¹,²

**Objective**

To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB.

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**Key Inclusion Criteria**

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m²
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

**Key Exclusion Criteria**

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

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**Primary Outcome**

Composite of sustained ≥50% eGFR decline, ESKD³, renal or CV death

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**Secondary Outcomes**

- Composite of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

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*ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m² for at least 28 days.

ACEI = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.
Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin 10 mg (n=2152)</th>
<th>Placebo (n=2152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean</strong></td>
<td>61.8</td>
<td>61.9</td>
</tr>
<tr>
<td><strong>Gender, female, %</strong></td>
<td>32.9</td>
<td>33.3</td>
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<tr>
<td><strong>Race</strong>, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52.2</td>
<td>54.2</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>4.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Asian</td>
<td>34.8</td>
<td>33.4</td>
</tr>
<tr>
<td>Other</td>
<td>8.1</td>
<td>8.4</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>81.5</td>
<td>82.0</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>29.4</td>
<td>29.6</td>
</tr>
<tr>
<td><strong>Current smoker, %</strong></td>
<td>13.2</td>
<td>14.0</td>
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<tr>
<td><strong>Blood pressure, mmHg, mean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>136.7</td>
<td>137.4</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>77.5</td>
<td>77.5</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/L</strong></td>
<td>128.6</td>
<td>127.9</td>
</tr>
<tr>
<td><strong>Serum potassium, mEq/L</strong></td>
<td>4.6</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Race was reported by the investigators; the designation ‘other’ includes Native Hawaiian or other Pacific Islander; American Indian or Alaska Native and Other.
BL = baseline.
Diabetes Status and Investigator-reported Cause of Kidney Disease at Baseline

**Diabetes Status**
- With type 2 diabetes: 32.5%
- Without type 2 diabetes: 67.5%

**Investigator-reported Cause of Kidney Disease**
- Diabetic nephropathy: 58.3%
- Glomerulonephritides: 16.0%
- Ischemic / hypertensive nephropathy: 16.1%
- Other / unknown causes: 9.6%

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death\(^a,1\)

*ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m\(^2\) for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.\(^2\); \(^95\%\) CI, 15 to 27.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; \(^2\) NNT = number needed to treat; RRR = relative risk reduction.

2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020;
Change from Baseline in eGFR$^{1,2}$

- **PBO eGFR change from baseline to Week 2:** $-0.82 \pm 0.15 \text{ mL/min/1.73m}^2$
- **DAPA eGFR change from baseline to Week 2:** $-3.97 \pm 0.15 \text{ mL/min/1.73m}^2$
- **DAPA Chronic:** $-1.67 \pm 0.11 \text{ mL/min/1.73m}^2$/year
- **PBO Chronic:** $-3.59 \pm 0.11 \text{ mL/min/1.73m}^2$/year

**Total eGFR slope difference:** 0.93 mL/min/1.73 m$^2$/year (95% CI, 0.61, 1.25)

**Chronic eGFR slope difference:** 1.92 mL/min/1.73 m$^2$/year (95% CI, 1.61, 2.24)

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BL = baseline; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; PBO = placebo.

Change in Albuminuria in the Overall Population

Mean reduction in UACR dapagliflozin vs. placebo:
29.3% (95% CI 25.2, 33.1); p<0.001

Median (IQR) baseline UACR, mg/g
Dapagliflozin: 965 (472–1903)
Placebo: 934 (482–1868)

Adjusted Mean Change in UACR, % (95% CI)

Mean reduction in UACR dapagliflozin 10 mg
42.9% reduction
Placebo 19.2% reduction

CI = confidence interval; IQR = interquartile range; UACR = urinary albumin-to-creatinine ratio
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

**DAPA-CKD population:**
- eGFR 25-75 mL/min/1.73m²
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

**Composite primary endpoint in patients with IgA nephropathy (n=270)**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Composite primary endpoint (≥50% eGFR decline/ESKD/CV or kidney death)</td>
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<tr>
<td>Patients with IgA nephropathy</td>
<td>0.29 (0.12, 0.73)</td>
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<tr>
<td>Patients with biopsy-confirmed IgA nephropathy</td>
<td>0.28 (0.11, 0.72)</td>
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<tr>
<td>Composite of kidney endpoint (≥50% eGFR decline/ESKD/kidney death)</td>
<td></td>
</tr>
<tr>
<td>Patients with IgA nephropathy</td>
<td>0.24 (0.09, 0.65)</td>
</tr>
<tr>
<td>Patients with biopsy-confirmed IgA nephropathy</td>
<td>0.23 (0.09, 0.63)</td>
</tr>
</tbody>
</table>

**CONCLUSION:**
In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression.

Wheeler et al, 2021

IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease
LS mean change in eGFR over the study in those with baseline stage 4 or stages 2/3 CKD. On the basis of the two-slope model.

Glenn M. Chertow et al. JASN 2021;32:2352-2361
A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function.

**Study design**
- eGFR 25–75 mL/min/1.73m²
- UACR 200–5000 mg/g
- With/without type 2 diabetes
- Stable, maximally-tolerated ACEi/ARB dose

**Outcomes**
- Abrupt declines in kidney function, defined as a doubling of serum creatinine between two subsequent visits (median time-interval, 100 days)
- Investigator-reported SAEs of acute kidney injury (pre-defined list)

**Results**
- Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease with increased albuminuria (Figure)
- No heterogeneity in effect of dapagliflozin versus placebo across baseline subgroups
- SAEs of acute kidney injury occurred less frequently with dapagliflozin versus placebo

**CONCLUSION:** Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease and substantial albuminuria, with and without type 2 diabetes

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eGFR=estimated glomerular filtration rate; SAE=serious adverse event; UACR=urinary albumin-to-creatinine ratio
The Risk of Morbidity and Mortality Rises Sharply as CKD Progresses

*Cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

From Proteinuria to Fibrosis: An Update on Pathophysiology and Treatment Options

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Quand utiliser un iSGLT2 en néphrologie

Le plus tôt possible pour toute IRC (Stade 2 – 4) avec protéinurie significative (> 200mg/g créat.) en ciblant surtout les pathologies à risque de progression :

- Néphropathie diabétique (type II) et hypertensive, idéalement même avant toute IR (Stade 1), si µalbuminurie.
- Syndrome métabolique (Néphropathie prédiabétique et HTA)
- Glomérulopathies (Néphropathie à IgA, GNEM, GN lésions minimes, HSF, …)
- Néphropathie tubulo-interstitielles.
- …etc…
- ADPKD, Néphropathie lupique et vascularite à ANCA ???
- Avec IEC / ARA2
  - + Spironolactone / Finerenone
  - + Patiromer / Zirconium Cyclosilicate
  - + Bicarbonate / Veverimer
Merci pour votre attention