



IMCVO

Institut des Maladies Cardio-Vasculaires de l'Ouest

# Cœur et Reins: des liens étroits

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20<sup>èmes</sup>  
**RENCONTRES  
MÉDICO  
CHIRURGICALES**  
**IMCVO**

*Palais des congrès de Versailles, le samedi 4 décembre 2021*

## **Déclaration d'intérêt**

Cette présentation a été contractualisée avec Astra Zeneca France

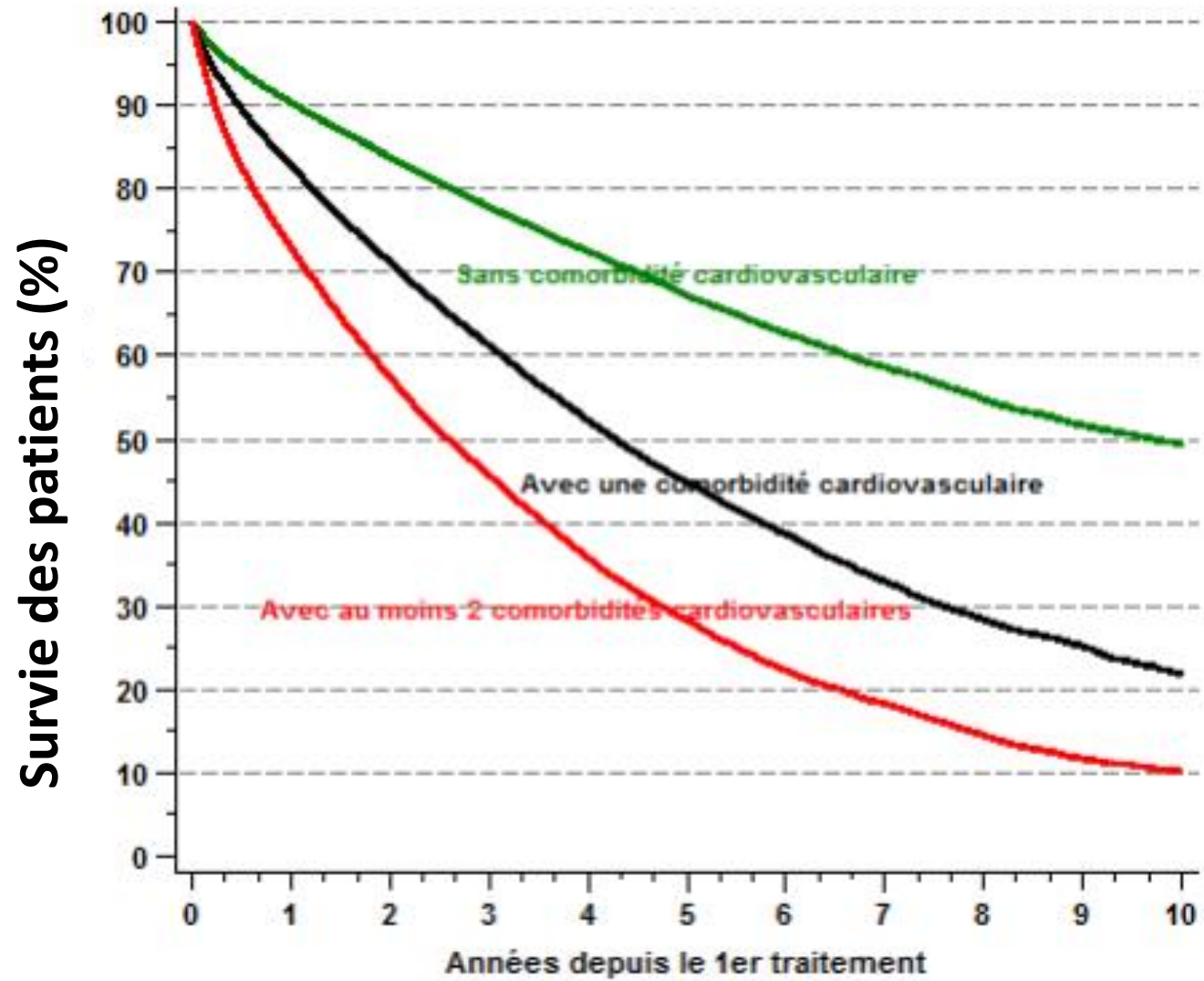
# La maladie rénale chronique en France

- Silencieuse
- Très fréquente: **7 à 10 %** de la population présente une atteinte rénale
- Morbide:
  - Prévalence de l'IRC Terminale : 1/1000 avec **89 692 malades** fin 2018
  - Augmentation constante de l'IRCT : **4 % chaque année**  
(coût annuel moyen de la dialyse: 61 296 euros/an; 4 milliards / an)
  - Énorme facteur de risque cardiovasculaire

Devenir à 3 ans de 1,120,295 américains en fonction du DFG (*Go AS et al., N Engl J Med 2004*)

**Table 2.** Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.\*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	<i>adjusted hazard ratio (95 percent confidence interval)</i>		
≥60 ml/min/1.73 m <sup>2</sup> †	1.00	1.00	1.00
45–59 ml/min/1.73 m <sup>2</sup>	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m <sup>2</sup>	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m <sup>2</sup>	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m <sup>2</sup>	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)



**Nombre d'années en insuffisance rénale terminale**

# Néphroprotection en 2020 (retarder l'insuffisance rénale terminale)

- **Traitement de la cause de la néphropathie**
- **Pression artérielle systolique < 120 mm Hg (étude SPRINT<sup>1</sup>, KDIGO 2021<sup>2</sup>)**
- **Consultation avec un(e) diététicien(ne):**
  - ✓ **viser un index de masse corporelle < 25 kg/m<sup>2</sup>**
  - ✓ **apports protidiques < 0,8 g/kg/j**
  - ✓ **éviction de la viande rouge**
- **Eviction du tabac, des néphrotoxiques (AINS)**
- **Prise d'un inhibiteur de l'enzyme de conversion ou sartan (objectif P/C < 500 mg/g)**

1. *N Engl J Med* 2021; 384; 1921-1930

2. *Kidney Int (Suppl)* 2021; 99: S1-S87

ORIGINAL ARTICLE

# Dapagliflozin in Patients with Chronic Kidney Disease

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Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D.,  
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for the DAPA-CKD Trial Committees and Investigators\*

# DAPA-CKD: Dapagliflozin in Patients With Chronic Kidney Disease<sup>1,2</sup>



## 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

### Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m<sup>2</sup>
- 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

1:1  
Double-blind

Dapagliflozin 10 mg  
+ standard of care

Placebo  
+ standard of care

4304 Randomized  
Median follow-up 2.4 years

End Points

### Primary Outcome

Composite of sustained ≥50% eGFR decline, ESKD<sup>a</sup>, renal or CV death

### Secondary Outcomes

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

<sup>a</sup>ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m<sup>2</sup> 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.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.



# Demographics and Baseline Characteristics

	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
<b>Age, years, mean</b>	61.8	61.9
<b>Gender, female, %</b>	32.9	33.3
<b>Race<sup>a</sup>, %</b>		
White	52.2	54.2
Black or African-American	4.8	4.0
Asian	34.8	33.4
Other	8.1	8.4
<b>Weight, kg</b>	81.5	82.0
<b>Body mass index, kg/m<sup>2</sup></b>	29.4	29.6
<b>Current smoker, %</b>	13.2	14.0
<b>Blood pressure, mmHg, mean</b>		
Systolic blood pressure	136.7	137.4
Diastolic blood pressure	77.5	77.5
<b>Hemoglobin, g/L</b>	128.6	127.9
<b>Serum potassium, mEq/L</b>	4.6	4.6

<sup>a</sup>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.

Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446.

# Renal Characteristics

	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
<b>eGFR, mL/min/1.73m<sup>2</sup>, mean</b>	43.2	43.0
eGFR ≥60 mL/min/1.73m <sup>2</sup> , %	10.9	10.2
eGFR 45 to <60 mL/min/1.73m <sup>2</sup> , %	30.0	31.7
eGFR 30 to <45 mL/min/1.73m <sup>2</sup> , %	45.5	42.7
eGFR <30 mL/min/1.73m <sup>2</sup> , %	13.6	15.4
<b>UACR, mg/g, median</b>	965	934
<b>UACR &gt;1000 mg/g, %</b>	48.7	47.9

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446.

# Medical History and Baseline Medications

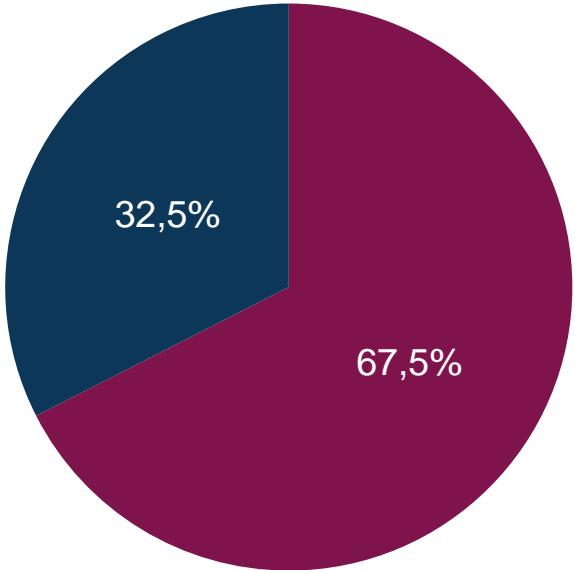
	Dapagliflozin 10 mg (n=2152)	Placebo (n=2152)
Type 2 diabetes, %	67.6	67.4
CV disease, %	37.8	37.0
Heart failure, %	10.9	10.8
<b>Prior medication, %</b>		
ACEi	31.3	31.6
ARB	67.1	66.3
Diuretic	43.1	44.3
Statin	64.8	65.0

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BL = baseline; CKD = chronic kidney disease; CV = cardiovascular.

Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446.

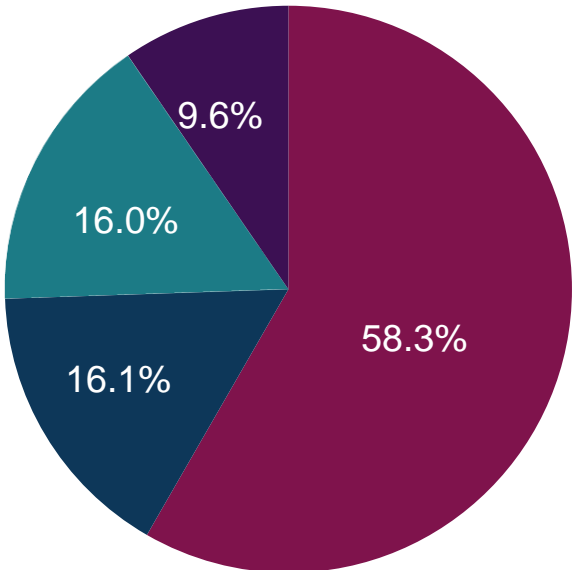
# Diabetes Status and Investigator-reported Cause of Kidney Disease at Baseline

### Diabetes Status



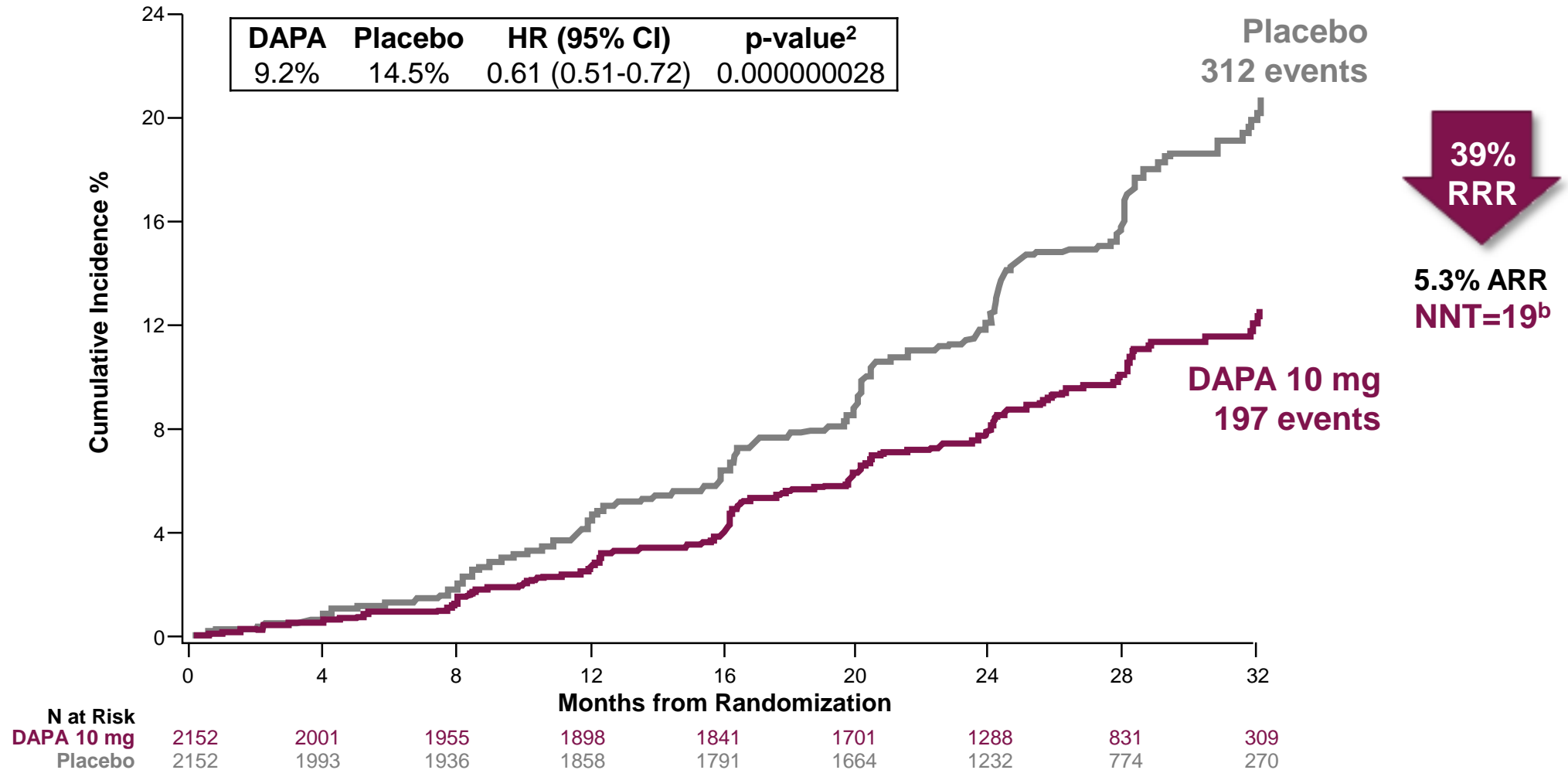
- With type 2 diabetes
- Without type 2 diabetes

### Investigator-reported Cause of Kidney Disease



- Diabetic nephropathy
- Glomerulonephritides
- Ischemic / hypertensive nephropathy
- Other / unknown causes

# Primary Composite Outcome: Sustained $\geq 50\%$ eGFR Decline, ESKD, Renal or CV Death<sup>a,1</sup>



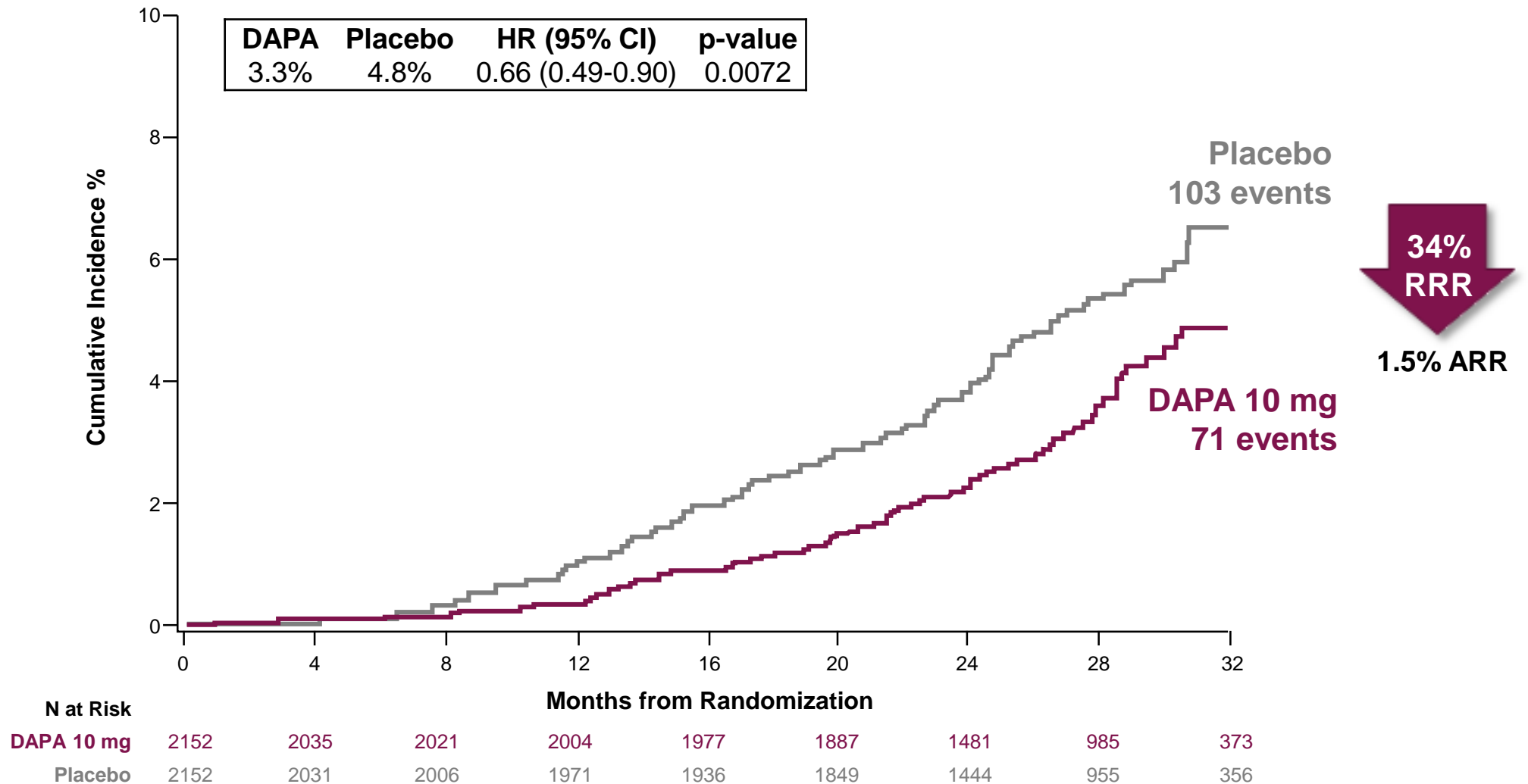
<sup>a</sup>ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m<sup>2</sup> for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.<sup>3</sup>; <sup>b</sup>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; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020;

3. Heerspink HJL et al. *Nephrol Dial Transplant.* 2020;35:274–282.

# Exploratory Composite Outcome: Chronic Dialysis, Kidney Transplantation, or Renal Death<sup>1,2</sup>



ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

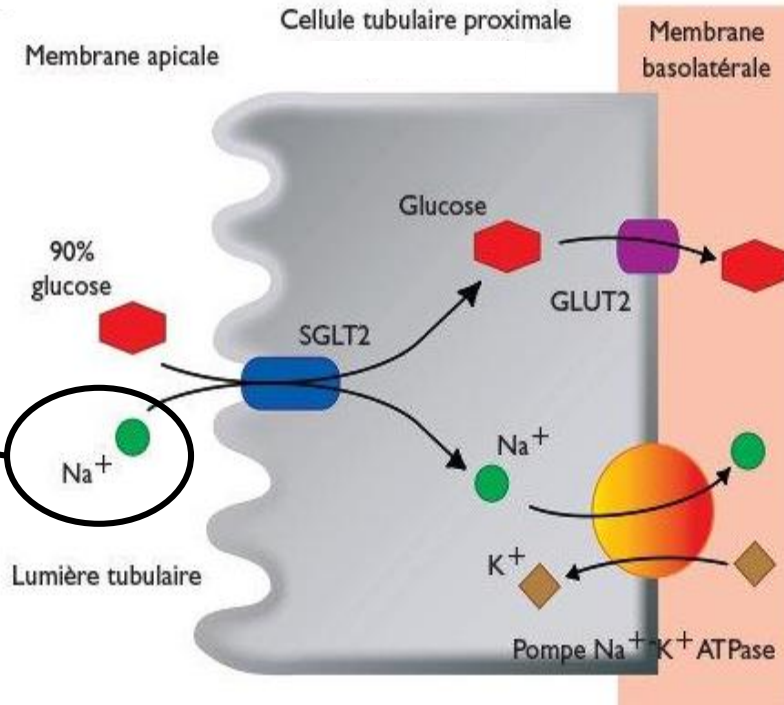
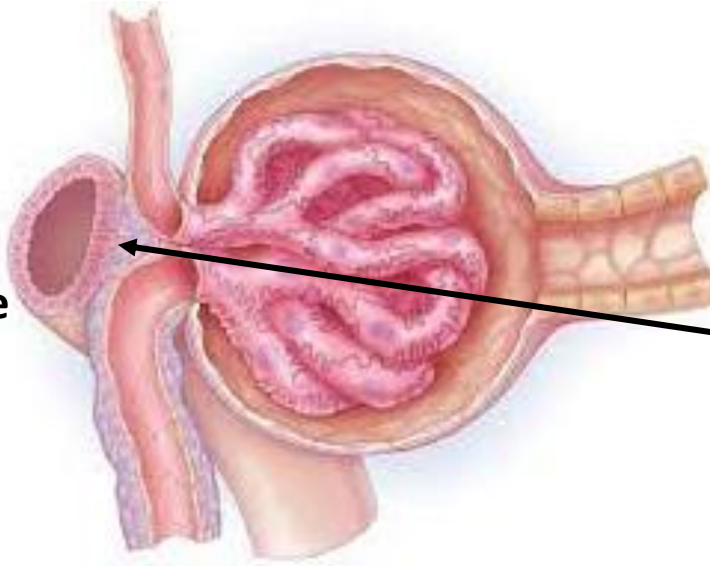
1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.



# Comment ça marche ?

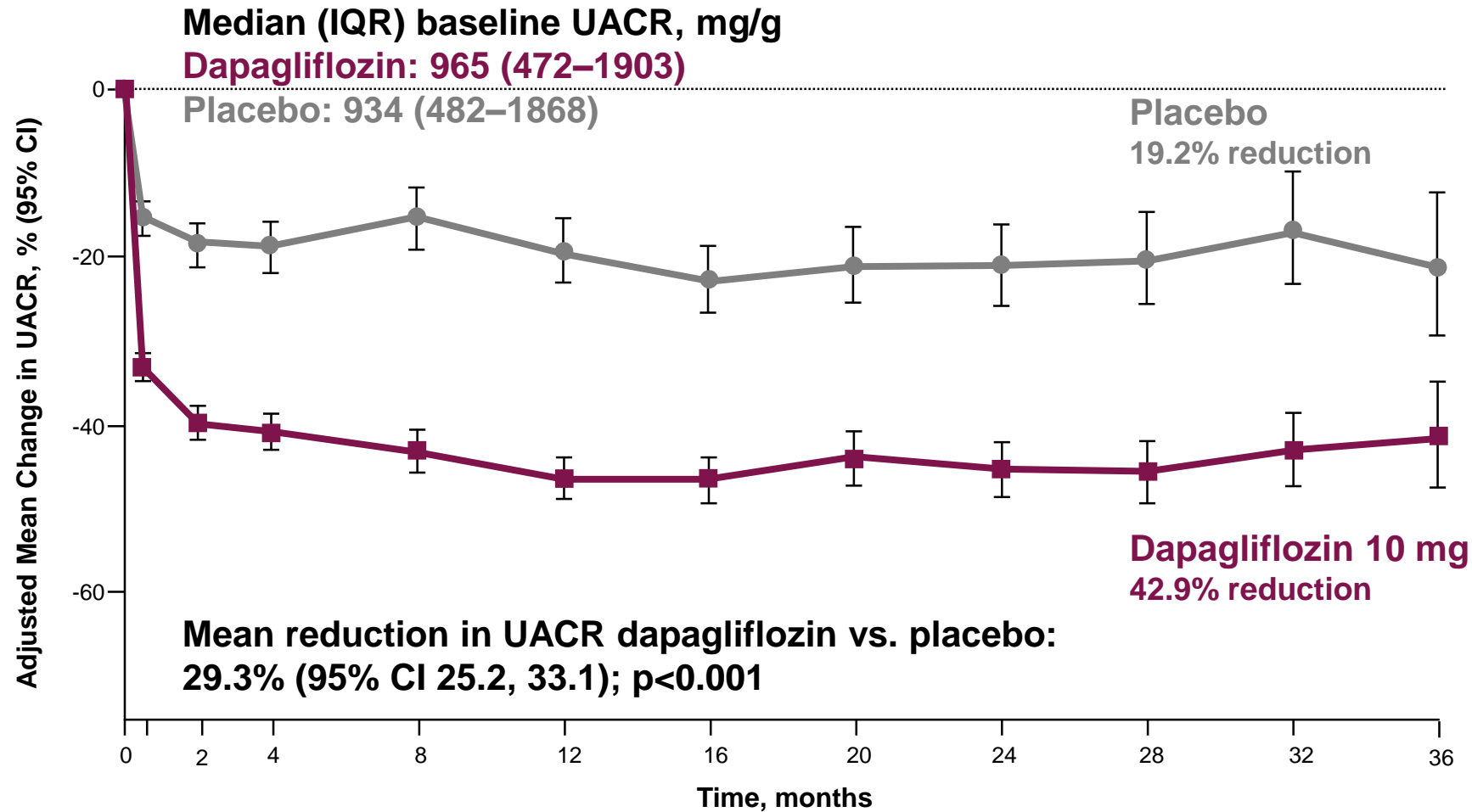
V/C artériole afférente  
Diminution P glom

Feed back  
tubulo-  
glomérulaire



**300 gr de glucose réabsorbés quotidiennement par les néphrons (qui restent !)**

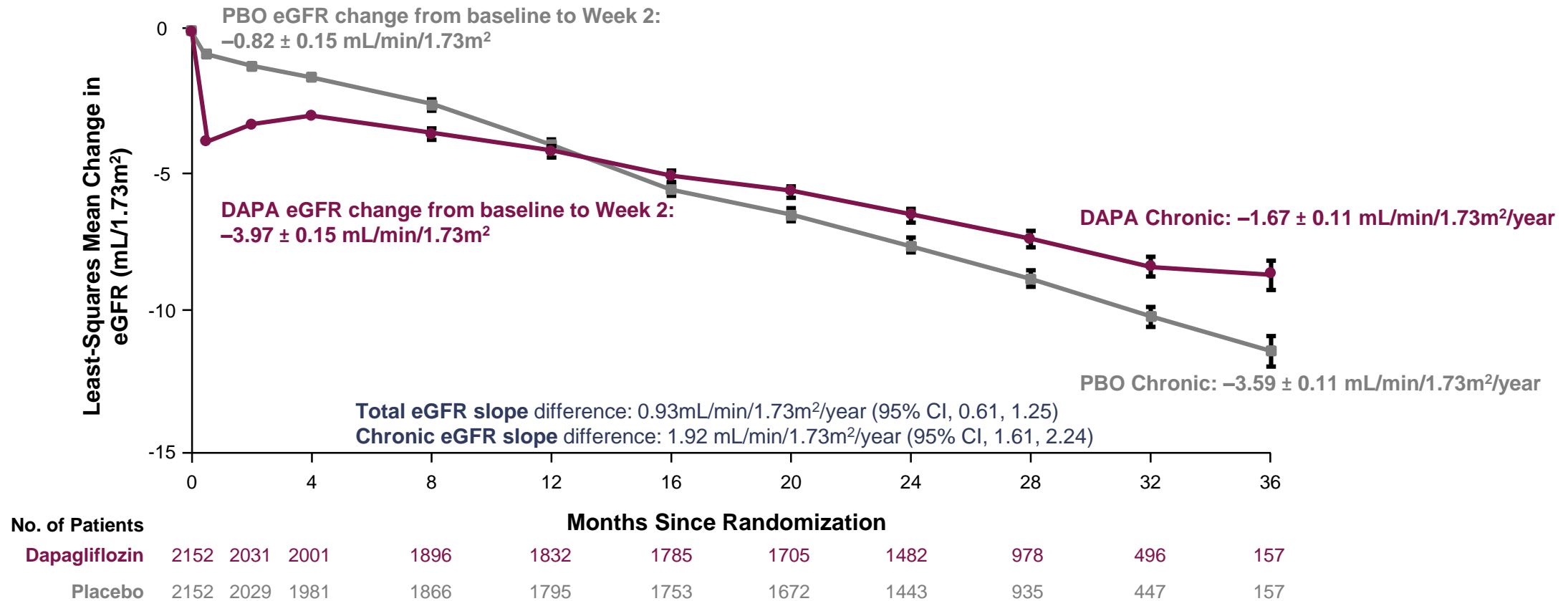
# Change in Albuminuria in the Overall Population



<b>Dapagliflozin</b>	2152	2085	2047	2048	1943	1884	1843	1778	1631	1172	692	233
<b>Placebo</b>	2152	2090	2054	2033	1909	1854	1818	1748	1581	1135	640	229



# Change from Baseline in eGFR<sup>1,2</sup>



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

1. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 2. Toto R. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

# Safety Outcomes<sup>1</sup>

Safety Outcomes <sup>a</sup> , n (%)	Dapagliflozin 10 mg (n=2149)	Placebo (n=2149)	p-value
<b>Discontinuation of study drug</b>	274 (12.7)	309 (14.4)	NA
<b>Discontinuation due to adverse event</b>	118 (5.5)	123 (5.7)	0.79
<b>Any serious adverse event</b>	633 (29.5)	729 (33.9)	0.002
<b>Adverse events of interest</b>			
Amputation <sup>b</sup>	35 (1.6)	39 (1.8)	0.73
Any definite or probable diabetic ketoacidosis	0	2 (0.1)	0.50
Fracture <sup>c</sup>	85 (4.0)	69 (3.2)	0.22
Renal-related adverse event <sup>c</sup>	155 (7.2)	188 (8.7)	0.07
Major hypoglycemia <sup>d</sup>	14 (0.7)	28 (1.3)	0.04
Volume depletion <sup>c</sup>	127 (5.9)	90 (4.2)	0.01
Serious adverse events of volume depletion <sup>2</sup>	22 (1.0)	18 (0.8)	NA
<b>Fournier's Gangrene</b>	0	1(<0.1)	NA

<sup>a</sup>Safety outcomes reported in participants on and off treatment; <sup>b</sup>Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma;

<sup>c</sup>Based on pre-defined list of preferred terms; <sup>d</sup>Adverse events with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention.

1. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

# Néphroprotection en 2021 (retarder l'insuffisance rénale terminale)

- Traitement de la cause de la néphropathie
- Pression artérielle systolique < 120 mm Hg (étude SPRINT<sup>1</sup>, KDIGO 2021<sup>2</sup>)
- Consultation avec un(e) diététicien(ne):
  - ✓ index de masse corporelle < 25 kg/m<sup>2</sup>
  - ✓ apports protidiques < 0,8 g/kg/j
  - ✓ éviction de la viande rouge
- Eviction du tabac, des néphrotoxiques (AINS)
- Prise d'un inhibiteur de l'enzyme de conversion ou sartan (objectif P/C < 500 mg/g)
- Prise de dapagliflozine, 10 mg/j<sup>3</sup>

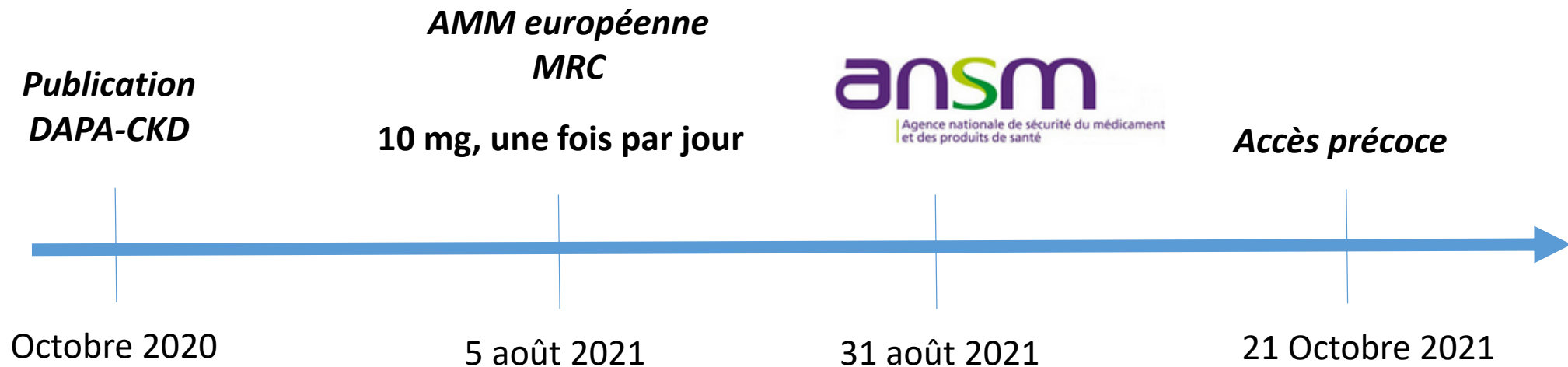
1. *N Engl J Med* 2021; 384; 1921-1930

2. *Kidney Int (Suppl)* 2021; 99: S1-S87

3. *N Engl J Med* 2020; 383: 1436-1446

# DAPAGLIFLOZINE

## Aspects réglementaires en néphrologie (patient MRC, DFG > 25 ml/min)



- En association à un traitement standard optimisé (inhibiteur de l'enzyme de conversion (IEC) ou antagoniste du récepteur de l'Angiotensine II (sartans), sauf si contre-indication)
- Avec un débit de filtration glomérulaire (DFG) compris entre 25 et 75 mL/min/1,73m<sup>2</sup> et un rapport albumine / créatinine urinaire compris entre 200 et 5 000 mg/g
- Insuffisamment contrôlée malgré des thérapeutiques médicamenteuses bien conduites : IEC ou sartans.



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