Les nouveaux Antidiabetiques en 3 temps

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La physiologie en 3 temps

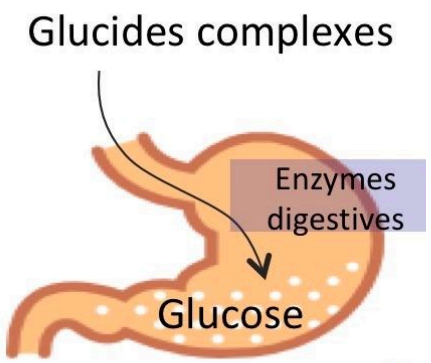
1. Quand on mange …

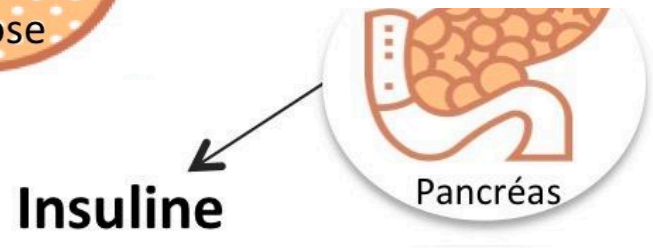
Absorption du glucose

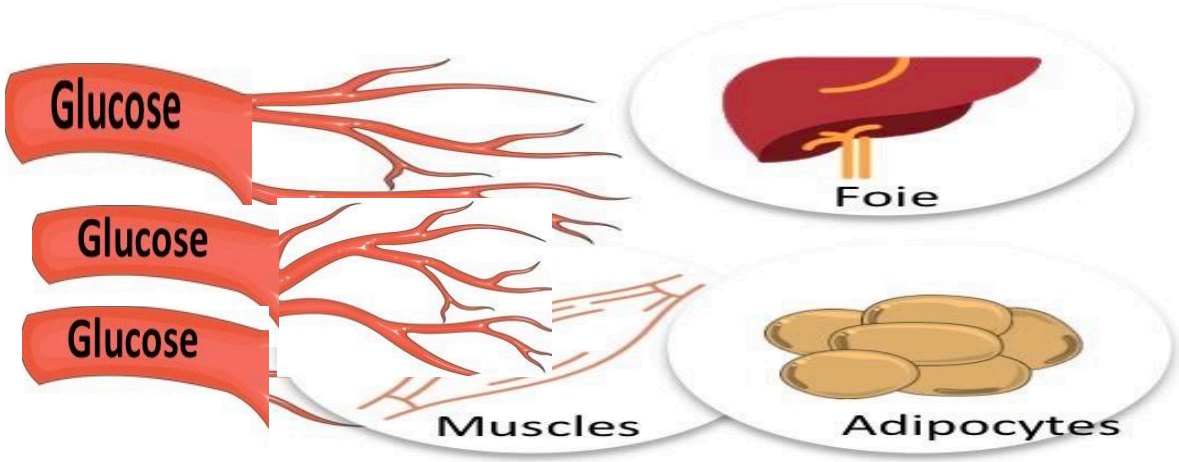
Sécrétion d'insuline

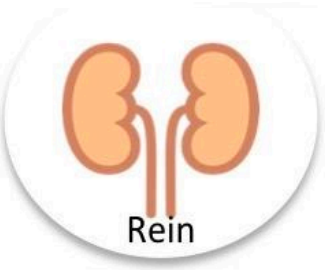
Utilisation / Stockage du Glucose

Elimination du Glucose

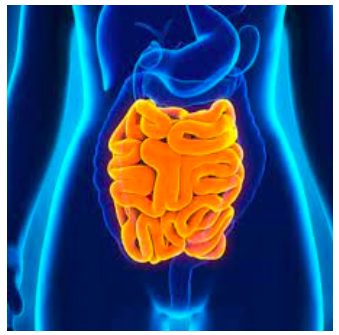






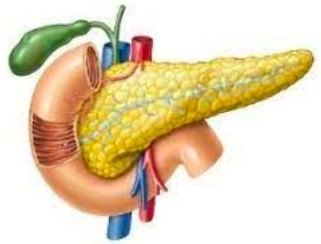


L’effet incrétine



Liberation
Incretines
GLP1

Dégradation par
l’enzyme **DPP4**



Augmentation de
l’Insuline

Diminution du
Glucagon

Régulation
Glycémie

2. Quand on mange et qu'on est diabétique…

- ↑ Absorption du glucose : c'est l'hyperglycemie post prandiale
- ↓ Sécrétion d'insuline
- ↑ Utilisation / Stockage du Glucose
- ↓ Elimination du Glucose

3. Quand on mange qu'on est diabétique et qu'on prend des Antidiabetiques

Effet Glucose / Insuline	Mec d'action	Type de médicament	Reconnaissance	Marques connues
Absorption du G	**Blocage**	Inhibiteur α glucosidase	GLUCOR	idem
Sécrétion Insuline	**Stimulation**	Sulfamides Secretagogue Analogue du GLP1 Inhibiteur de DPP4	*-gliclazide* *-glinide* *-glutide* *-gliptine*	DIAMICRON NOVONORM VYCTOZA,OZEMPIC JANUVIA
Utilisation/Stockage du G	**Stimulation**	Biguanides	METFORMINE, STAGID	idem
Elimination urinaire de G	**Stimulation**	Inhibiteurs de SGLT2	*-gliflozine*	FORXYGA JARDIANCE

M. NON

hachette

Comment en est on arriver aux nouveaux *Antidiabetiques* en 3 « NON »

Tout est glucose : NON

The lower the better : NON

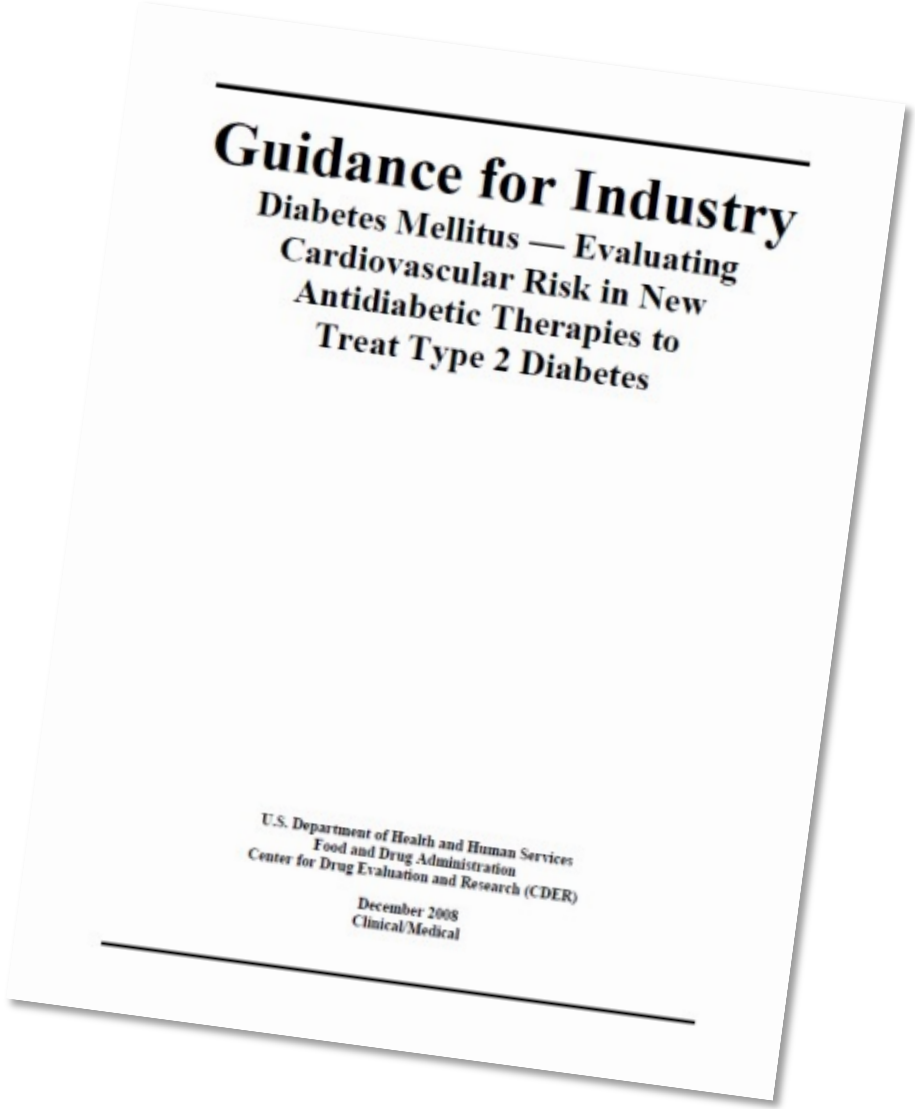
Tous les Antidiabetiques se valent : NON

Suite au coup de tonerre dans le ciel serein

Requirement to demonstrate that **new antidiabetes therapies to treat type 2 diabetes** *are not associated with an* ***unacceptable*** **increase in cardiovascular risk**

For completed studies prior to NDA

- Integrated meta-analysis of phase 2/3 trials to compare CV events in patients randomised to investigational drug vs control
- Demonstrate new therapy will not result in an unacceptable CV risk
  - Evaluated by MACE
  - Estimated risk ratio for upper bound of the two-sided CI for the investigational drug should be **<1.8**
  - If upper CI = **1.3–1.8**, post-marketing CV surveillance trial may be required


Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

FDA, U.S. Food and Drug Administration
FDA, 2008 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Ce que tout cardiologue interventionnel doit savoir sur les nouveaux ADO

…toujours en 3 points

3 class of new antidiabetic drugs :

DDP4 inhibitor, ***(-gliptine)***

GLP1 agonist ***(-glutide),***

SGLT2 inhibitor ***(-glifozine)***

2 class of drugs reducing CV morbidity and mortality : GLP1 agonist; SGLT2 inhibitor

1 algorithm: GLP1 agonist in patient with established CV disease; SGLT2 inhibitor in HF and CKD patient.

Davies MJ et al. *Diabetes Care* 2018. Sep; dci180033; Davies MJ et al. *Diabetologia* 2018. https://doi.org/10.1007/s00125-018-4729-5

2020

EMPEROR-REDUCED

Cardiovas
with Em

Double-blind,

Objective: To e
with chronic he
with or without

3730
patients

Inclusio
without
tional cl
fraction

empagliflozi
(N=1863)

2019

DAPA-HF TRIAL

Dapagli
Failure a

Randomized

Objective: To
cotransporte
placebo amo
reduced ejec

2020

SOLOIST-WHF TRIAL

Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?

DAPA-CKD

21 Countries
286 Centers

≥ 18 yo

eGFR ≥ 25 to ≤ 75ml/min

UACR ≥ 200 to ≤ 5000mg/g

Max tolerated dose of ACEi/ARB

With and without T2DM

Mean Age 62y, 67% ♂
eGFR 43ml/min
UACR 950mg/g
ACEi/ARB 97%
With T2DM 68%

MEAN FOLLOW-UP: 2.4 YEARS

10 mg
DAPAGLIFLOZIN
+STANDARD CARE
N=2152

N=4304

P
PLACEBO
+STANDARD CARE
N=2152

Sustained ≥ 50% decline in GFR, ESKD, Renal or CV Death	Sustained ≥ 50% decline in GFR, ESKD, Renal Death	CV Death or hHF	All-cause Mortality
HR 0.61 (95% CI 0.51-0.72) p=0.000000018 NNT=19	HR 0.56 (0.45-0.68) p=0.000000018	HR 0.71 (0.55-0.92) p=0.0089	HR 0.69 (0.53-0.88) p=0.0035

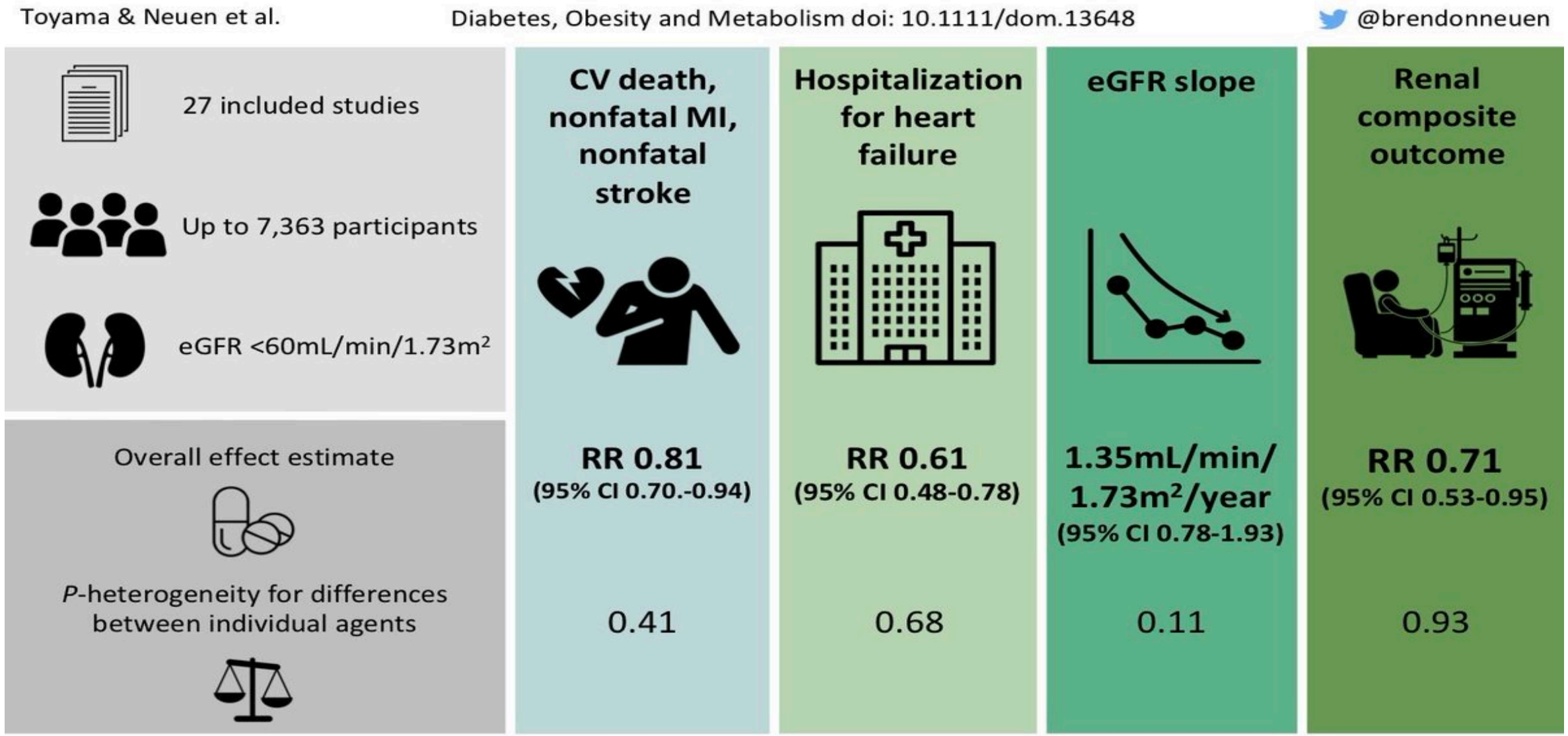
Results are consistent with patients with and without T2DM
% of patients who discontinued the drug or who experienced SAE was similar in both groups
DKA, 2 in placebo group vs none in Dapagliflozin group
No DKA or severe hypoglycemia in patients without T2DM

CONCLUSION: Dapagliflozin significantly reduces the risk of kidney failure, CV death or hospitalization for HF and all-cause mortality in patients with CKD with and without T2DM compared to placebo. Dapagliflozin was well-tolerated, in keeping with its established safety profile.

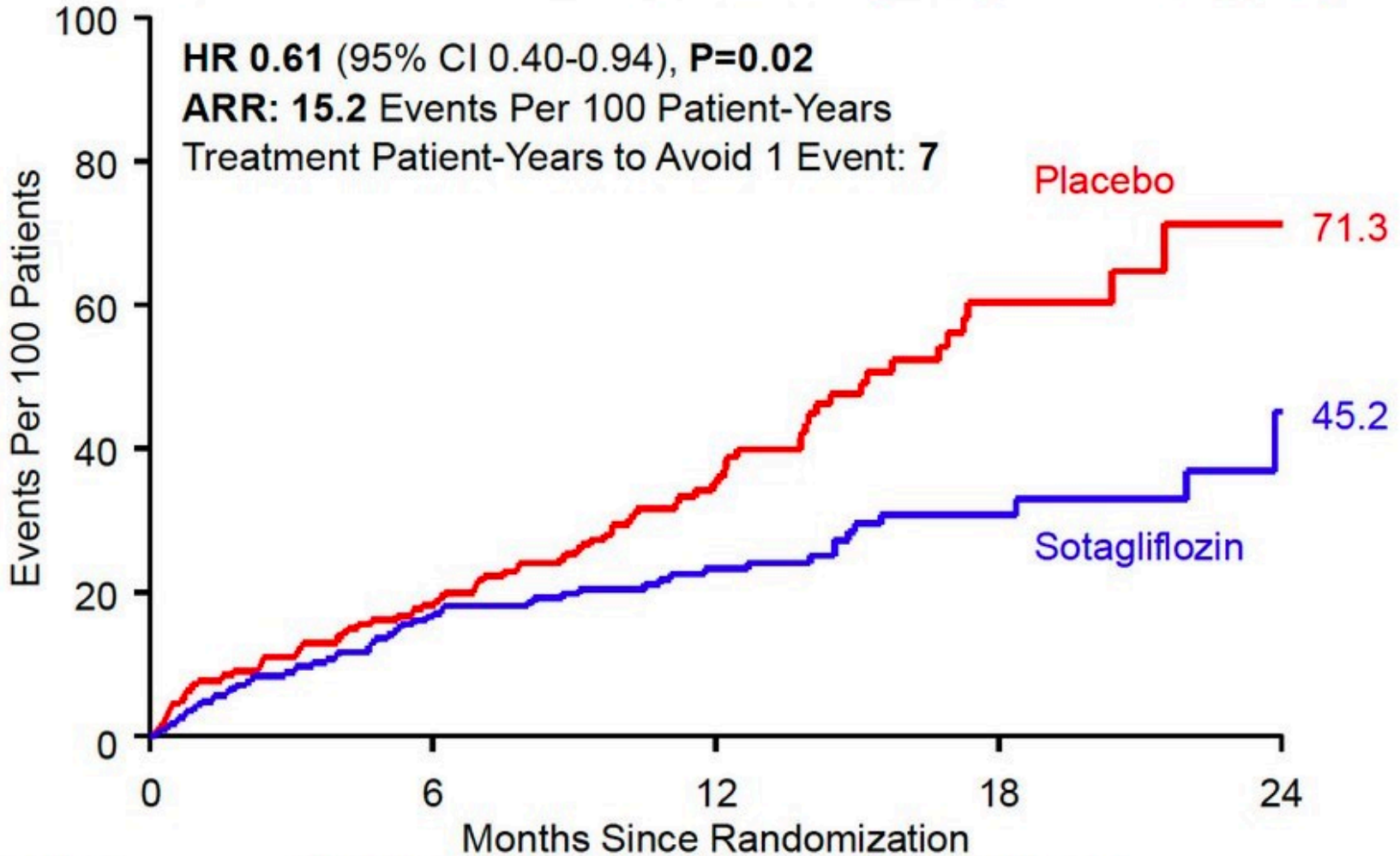
DAPA-CKD
presented by Professor Heerspink at the ESC Congress
August 30, 2020

Visual Abstract by: Ana Naidas, MD

Les SGLT2 i sont des medicaments de:
l'IC à FE altérée et de l'IRC chez le diabetique et le non diabetique
donc des Médicaments du Cardiologue



Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 456 Patients with HFmrEF (40% - <50%)*



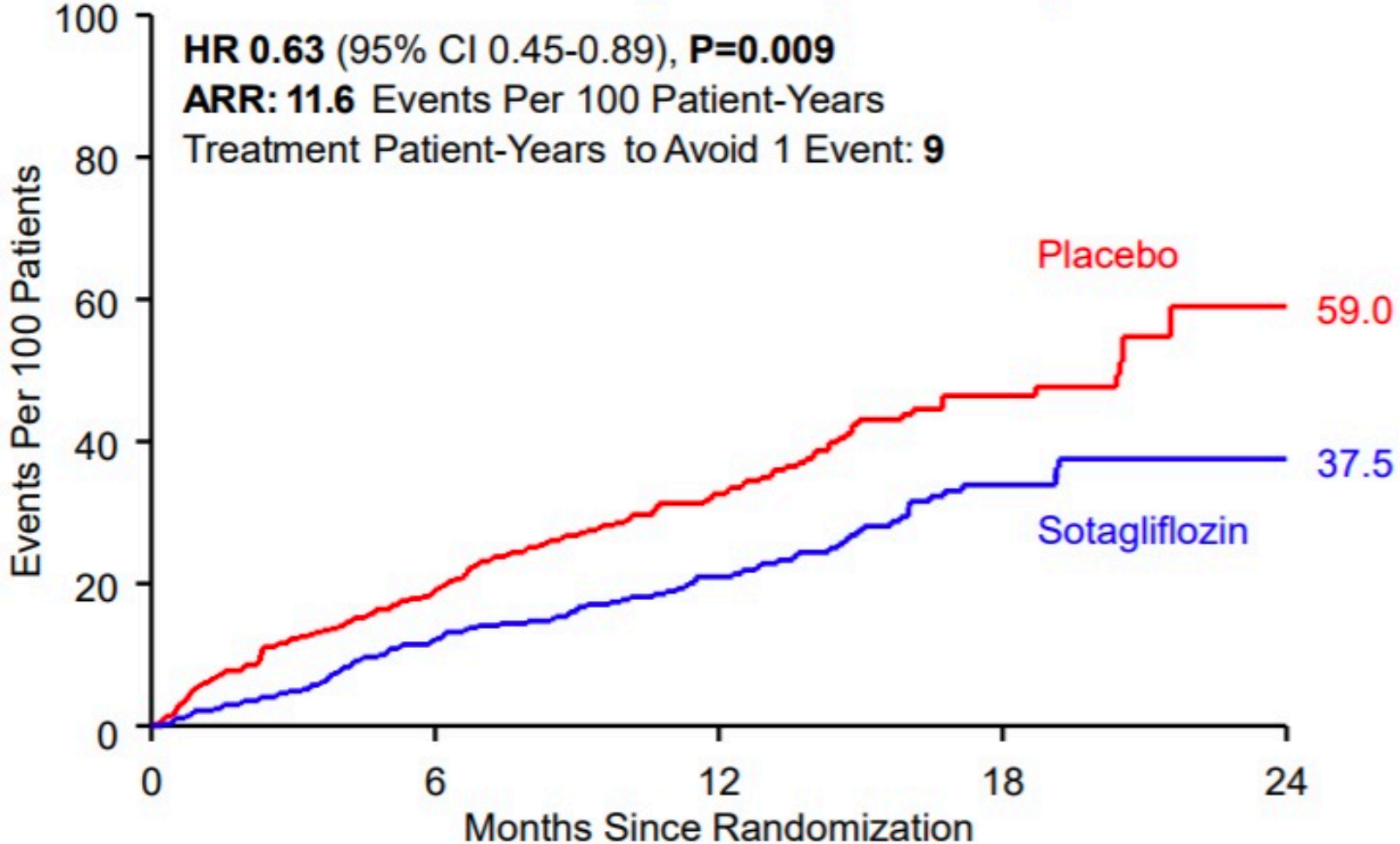
t DL. ACC 2021, virtual.

For this analysis, patients from SCORED needed to have a history of HF within 2 years.

*post hoc

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 739 Patients with HFpEF (≥50%)

SOLOIST
SCORED



For this analysis, patients from SCORED needed to have a history of HF within 2 years.

Bhatt DL. ACC 2021, virtual.

Practical message for Interventional Cardiologist

No emergency to start

Refer patients to Diabetologist (i.e. CAD, CHF patient)

GLP1 agonist increase

nausea/ vomiting at initiation : avoid in ICU or if drugs fluctuations increase CV risk (APA and stent thrombosis, OAC and thrombosis in A Fib patient).

HR (3-5 bpm) good association with b blockers in patient with CAD

SGLT2 inhibitors are diuretics and lower BP :

NO need to stop before coronary angio, adapt ACEi, Diuretics if eGFR< 30 ml/min

Reduces BP (caution Hypertension, Heart Failure, Valvular Heart Disease)

Improves Heart Failure

Vademecum

Pour le cardiologue tout n'est pas glucose mais tout est reduction de la MM CV.

Certains ADO reduisent la MM CV chez le diabétique .

Le contrôle de l'HbA1c est nécessaire pour prévenir les complications microvasculaires.

Certains ADO reduisent de la MM chez l'IC ou l'IR (diabétique ou non)

Patient diabétique cardio renal : a t'il un inhibiteur de SGLT2 ?
Patient diabétique athérosclerotique : a t'il un analogue du GLP1 ?

Ces médicaments sont les IEC ou Statines de demain