Nouvelle molécule contre le diabète : indications et limites

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10.11.2016

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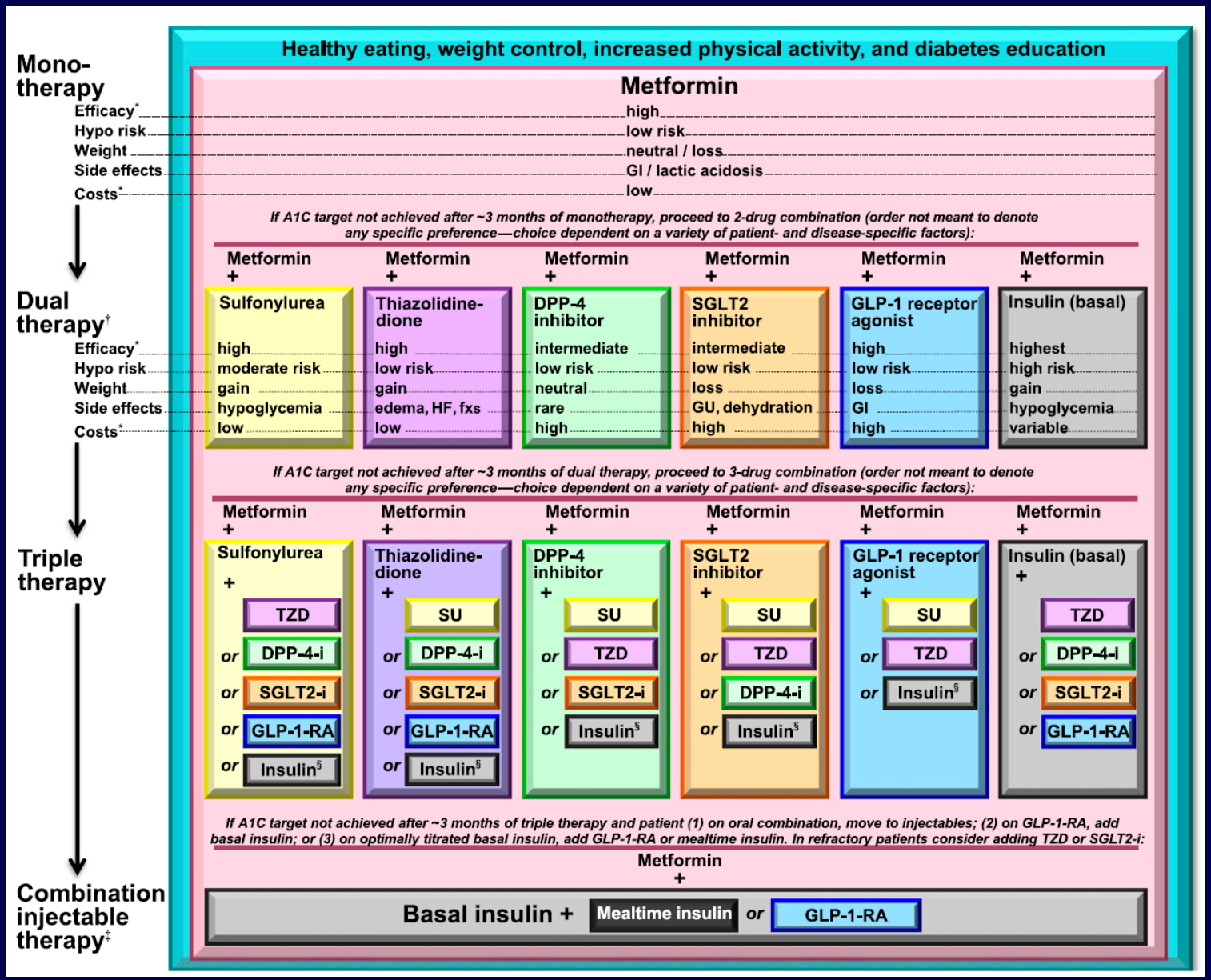
Prise en charge médicamenteuse du DM2



Diabetes Care, janvier 2016

L’octet du diabète de type 2

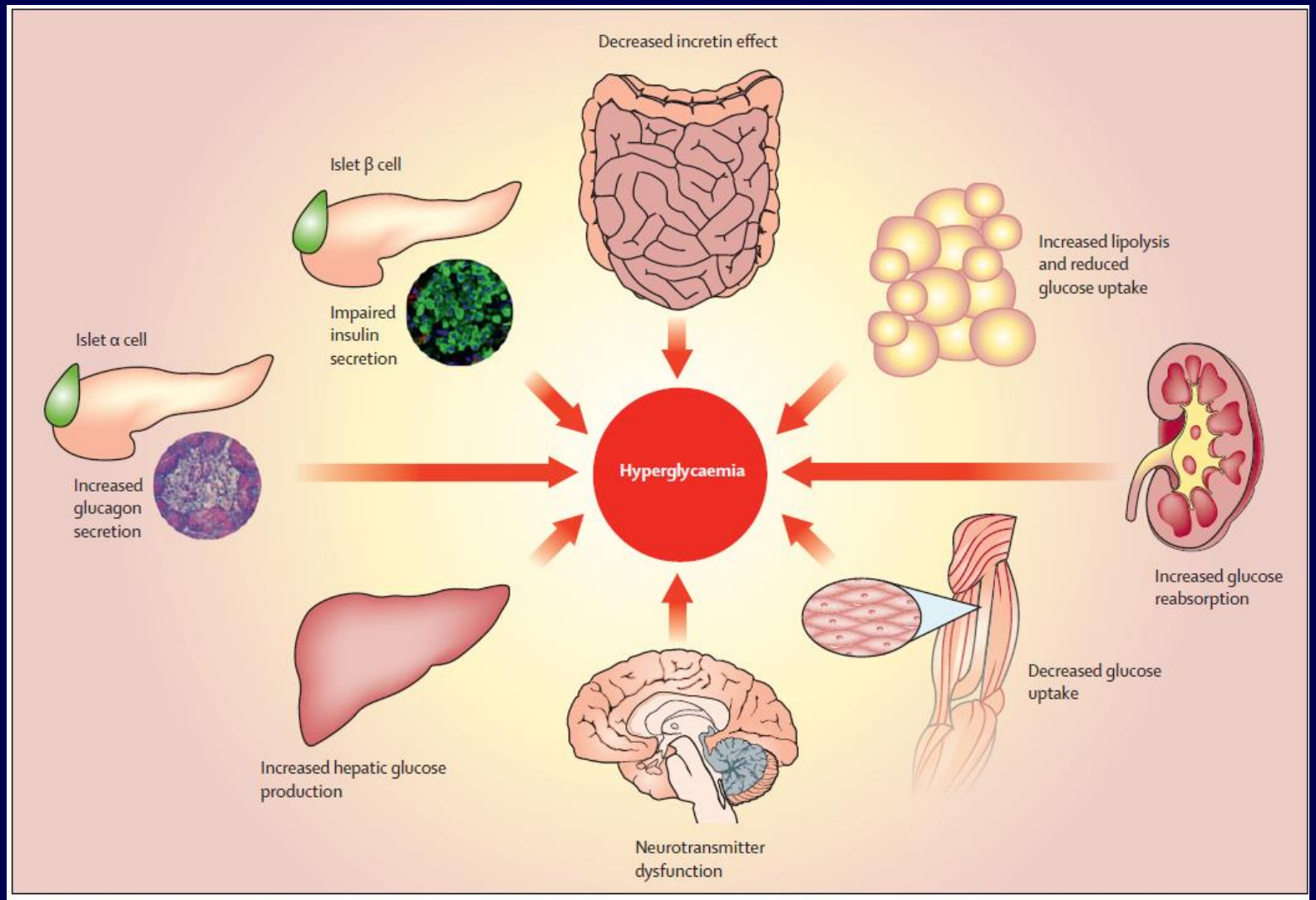


Figure 1: Typical pathogenic features of hyperglycaemia in type 2 diabetes

Tahrani AA et al, Lancet 2011

Effet des antidiabétiques sur l'HbA1c

Table 1—*Summary of glucose-lowering interventions*

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated			
TZDs	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5[a]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, expensive

[a]Repaglinide more effective in lowering A1C than nateglinide. CHF, congestive heart failure; GI, gastrointestinal; MI, myocardial infarction.

Inhibiteur SGLT2 : ~ 0.5-1.0%

Diabetes Care, 2009

Les inhibiteurs du SGLT2

- **Canagliflozine** (Invokana) : 100 mg ou 300 mg 1x/j
- **Dapagliflozine** (Forxiga) : 5 mg ou 10 mg 1x/j
- **Empagliflozine** (Jardiance) : 10 mg 1x/j

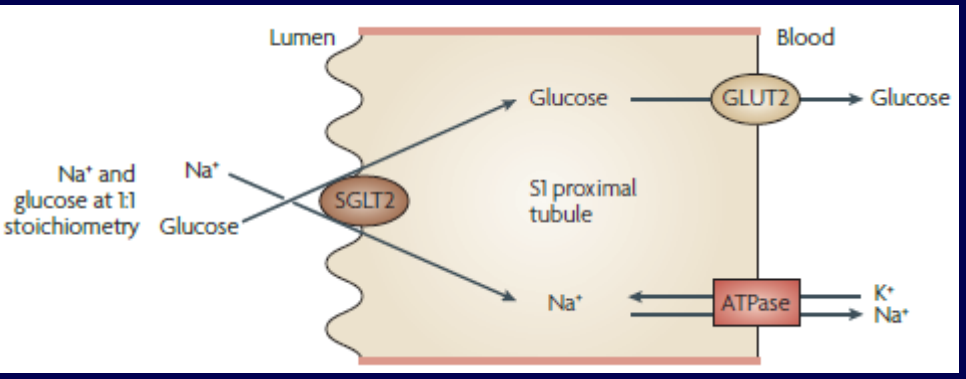
Formes combinées avec metformine ou metformine XR disponibles ou à venir

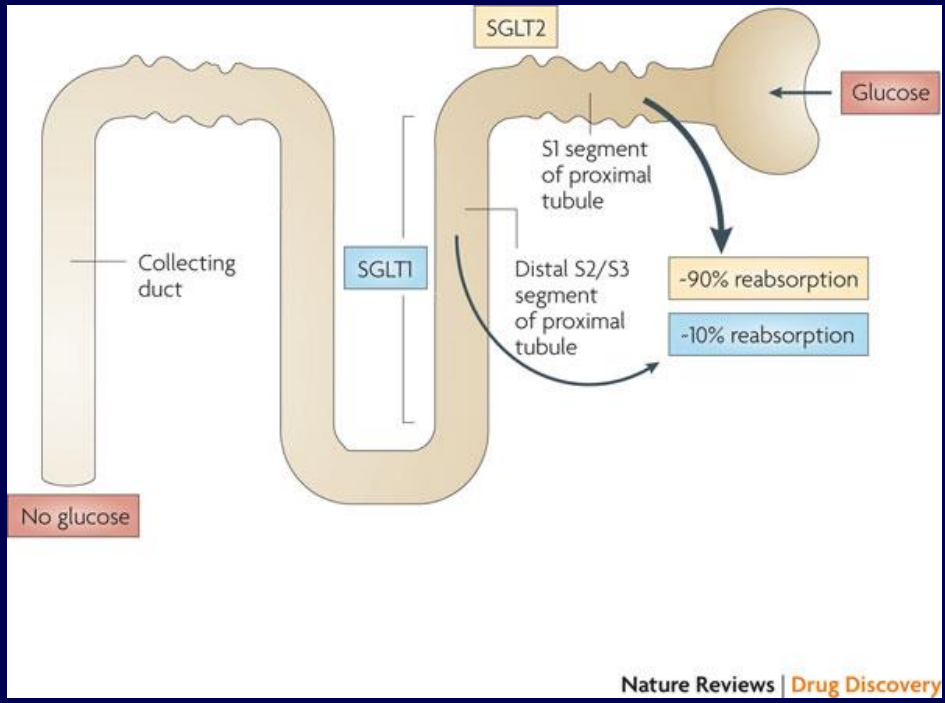
Les inhibiteurs du SGLT2 : mécanisme d'action

Table 1 | **A comparison of selected characteristics of SGLT1 and SGLT2**

	SGLT1	SGLT2
Site	Mostly small intestine, some in kidney and heart	Almost exclusively kidney
Renal location	Late proximal straight tubule (S3 segment)	Early proximal convoluted tubule (S1 segment)
Affinity for glucose	High (K_m = 0.4 mM)	Low (K_m = 2mM)
Capacity for glucose transport	Low	High
Percent of renal glucose reabsorption	~10%	~90%

SGLT, sodium–glucose co-transporter. Data from REF. 11.





Chao and Henry, Nat Rev Drug Discov 2010

SGLT = Sodium-GLucose co-Transporter

Les inhibiteurs du SGLT2 : résumé

- **Avantages :**
  - **Réduction de l'HbA1c (environ -0.50 à -1.00%).**
  - **Faible risque d'hypoglycémie.**
  - **Perte pondérale (jusqu'à -2-3 kg comparé au placebo; effet plateau).**
  - **Diminution (faible) de la pression artérielle.**

- **Désavantages :**
  - **Risque d'infection mycotique>urinaire (surtout chez femmes; moins chez hommes). Souvent peu sévère et faible risque de récidive.**
  - **Effets à long terme inconnus (études cardiovasculaires en cours).**

Inhibiteurs SGLT2 : chez qui?

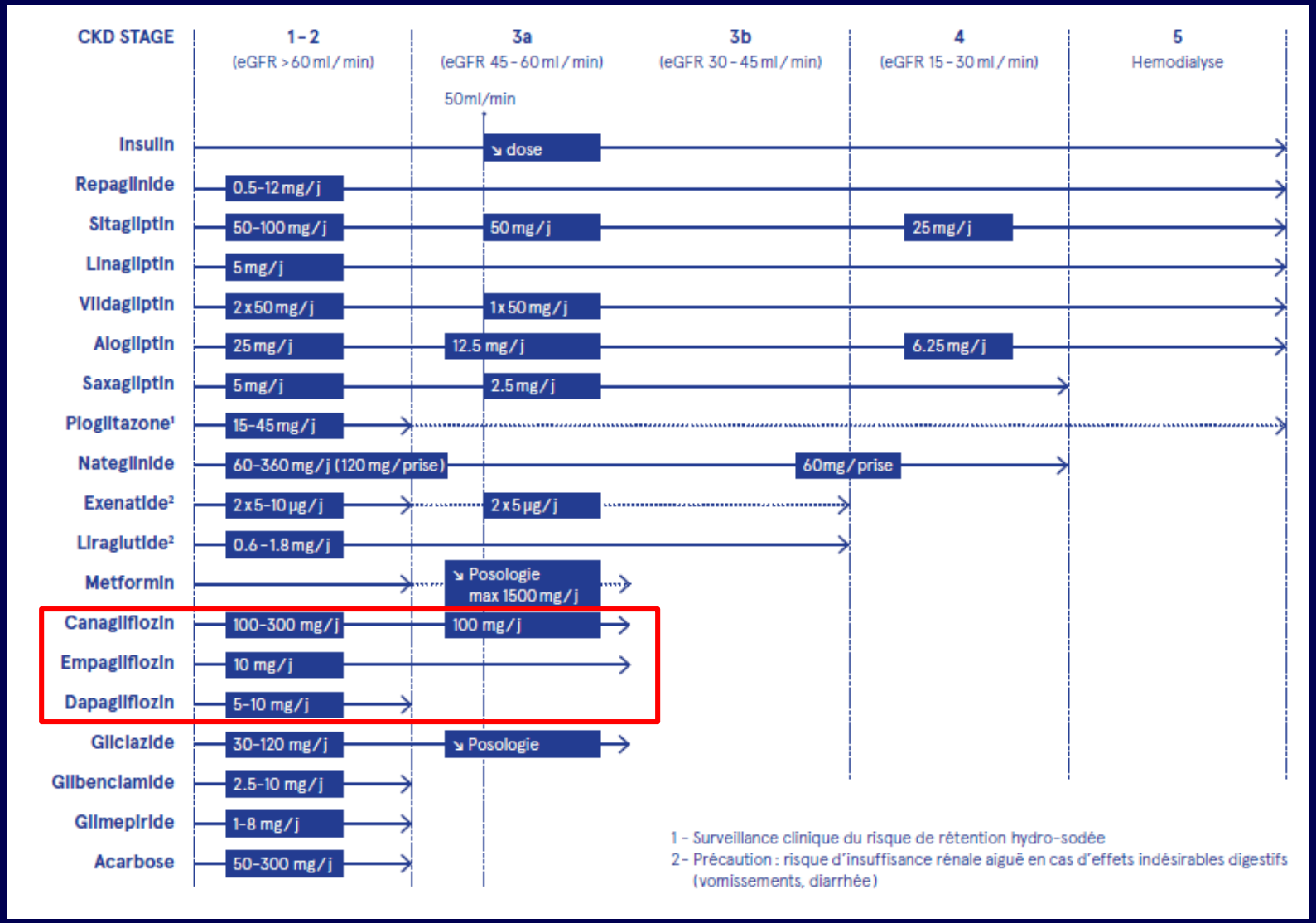
Plutôt indiqués :

- **Patient en excès pondéral ou obèse**
- **Fonction rénale conservée**
- **N'a pas d'antécédents d'infection urinaire ou génitale (dans l'idéal un homme circoncis)**
- **Patient chez lequel on souhaite éviter l'hypoglycémie**

Plutôt PAS indiqués :

- **Patient avec antécédents d'infection urinaire ou génitale**
- **Fonction rénale altérée**
- **Patient à risque de déshydratation**

Antidiabétiques oraux et insuffisance rénale



Courtesy of Anne Zanchi

EMPA-REG OUTCOME

- Randomised, double-blind, placebo-controlled CV outcomes trial.

- Objective
  To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events.

- Three groups of patients: placebo, empagliflozin 10 mg and empagliflozin 25 mg (total 7020 patients treated; Median observation time 3.1 yr).

EMPA-REG OUTCOME

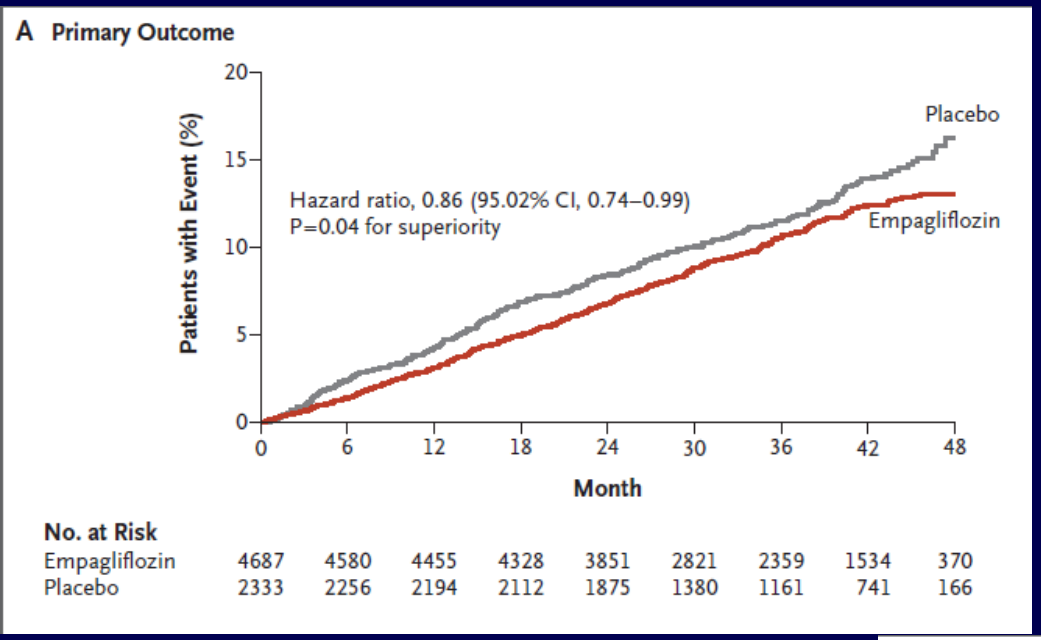
- **Key inclusion criteria**
  - **Adults with type 2 diabetes *(age ~63 yr, ~70% male, mostly long diabetes duration >10 yrs in >50% of patients)***
  - **BMI ≤45 kg/m^2 *(average ~30.6 kg/m^2)***
  - **HbA1c 7–10% *(average ~8.1%)***
  - **Established cardiovascular disease**
    - **Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease *(~75% with coronary artery disease, previous MI in ~45%; mostly patients treated for HTA, most with statin and ASA)***

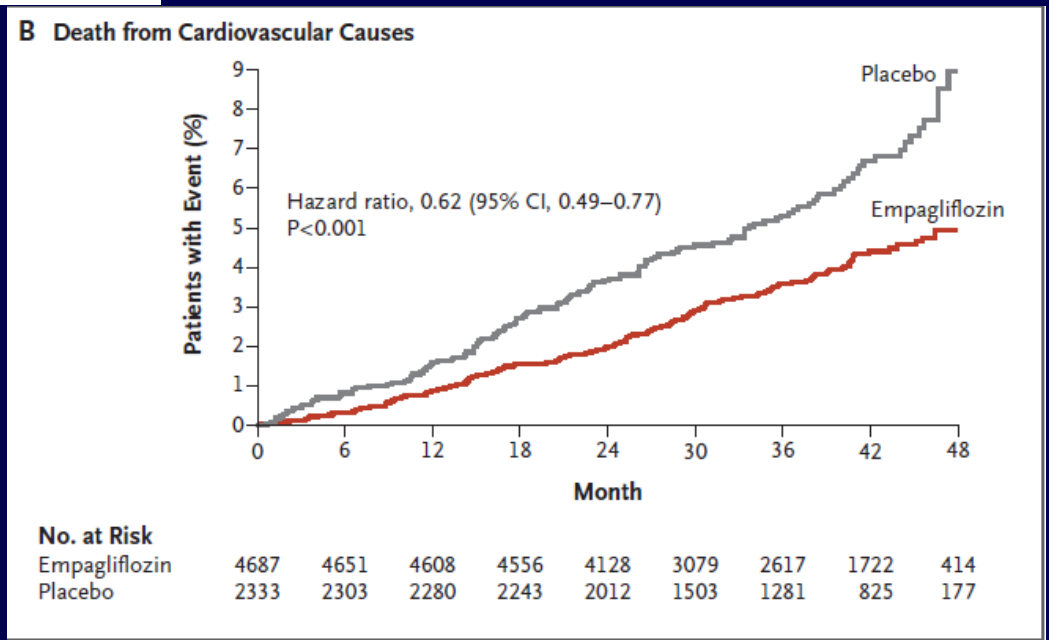
- **Key exclusion criteria**
  - **eGFR <30 mL/min/1.73m^2 (MDRD) *(~25% of patients with eGFR<60 ml/min)***

EMPA-REG OUTCOME

- **Primary outcome**
  - **3-point MACE (Major Adverse Cardiovascular Events): Time to first occurrence of CV death, non-fatal MI or non-fatal stroke**
- **Key secondary outcome**
  - **4-point MACE: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina**
- **The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event**

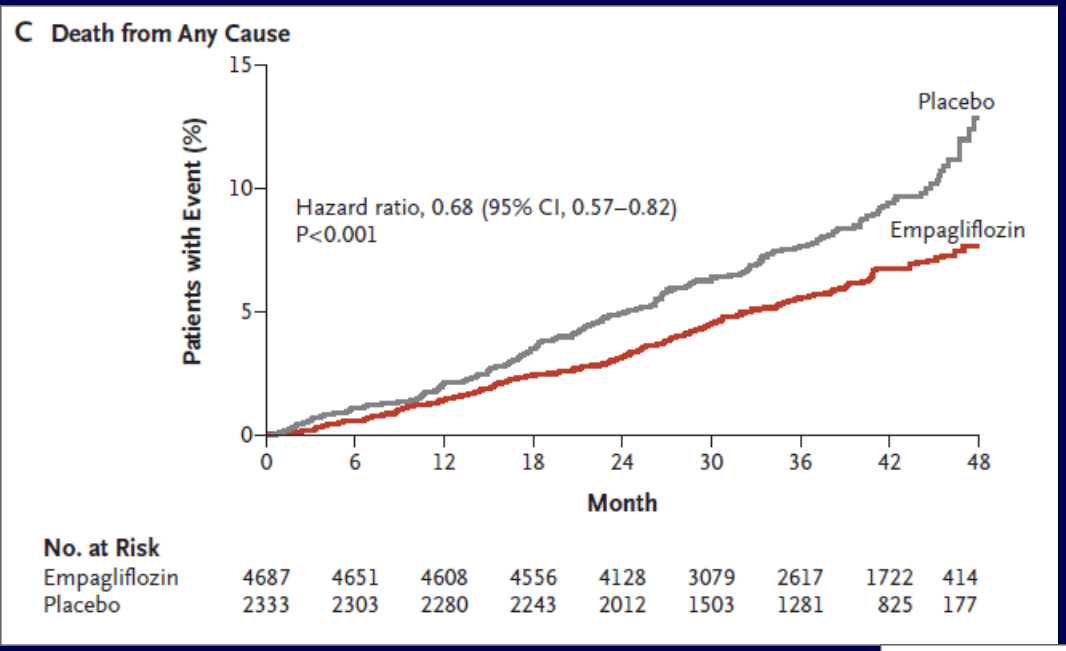
EMPA-REG OUTCOME RESULTS

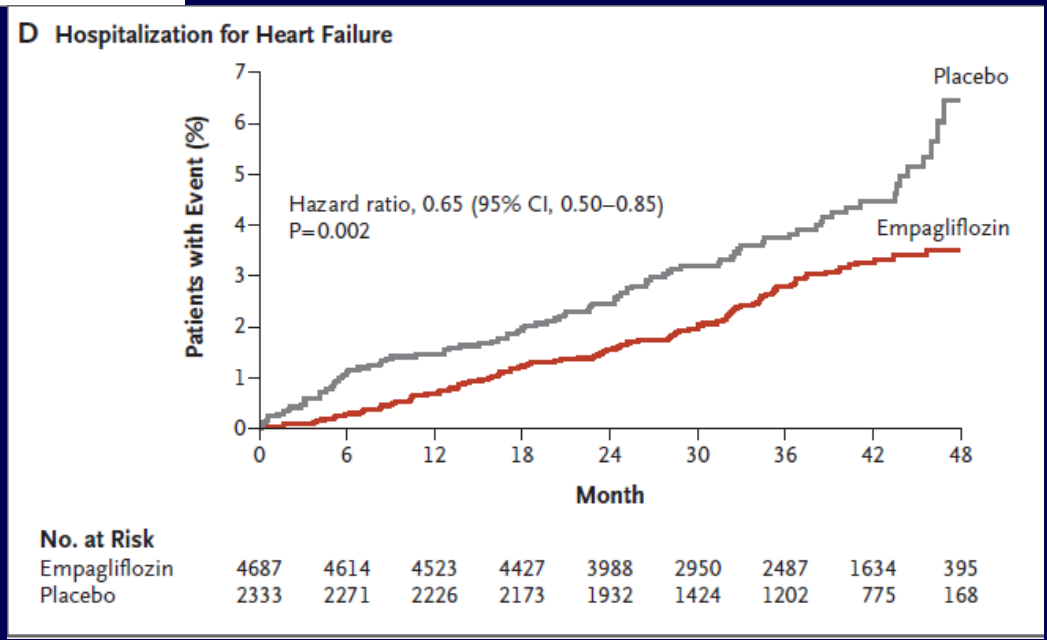




N Engl J Med 2015;373:2117-28.
DOI: 10.1056/NEJMoa1504720

EMPA-REG OUTCOME RESULTS





N Engl J Med 2015;373:2117-28.
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Nombre de sujets à traiter pour prévenir un décès chez les patients présentant un risque cardiovasculaire élevé : « Essais cliniques clés » de grande envergure

Simvastatine[1] pendant ***5,4*** ans

30

Risque cardiovasculaire élevé
5 % diabète, 26 % hypertension artérielle

Ramipril [2] pendant ***5*** ans

56

Risque cardiovasculaire élevé
38 % diabète, 46 % hypertension artérielle

Empagliflozine [3] pendant ***5*** ans

25

Diabète de type 2 associé à un risque cardiovasculaire élevé
92 % hypertension artérielle

Avant l'ère des statines

Avant l'ère des IECA/ARA

< 29 % statines

>80% IECA/ARA

> 75 % statines

1994 **2000** **2015**

4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. Yusuf S. et al. N Engl J Med 2000; 342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm
3. Zinman B, et al. New England Journal of Medicine Sep 2015, DOI: 10.1056/NEJMoa1504720

Méta-analyse sur les effets CV des inhibiteurs SGLT2

Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis

Jason H Y Wu, Celine Foote*, Juuso Blomster, Tadashi Toyama, Vlado Perkovic, Johan Sundström, Bruce Neal*

En résumé, ces données suggèrent un potentiel effet classe en terme de bénéfice CV pour les inhibiteurs SGLT2, mais il faut attendre les études dédiées en cours pour la dapagliflozine et la canagliflozine (à venir en 2018).

Lancet Diabetes Endocrinol 2016

Published Online
March 18, 2016

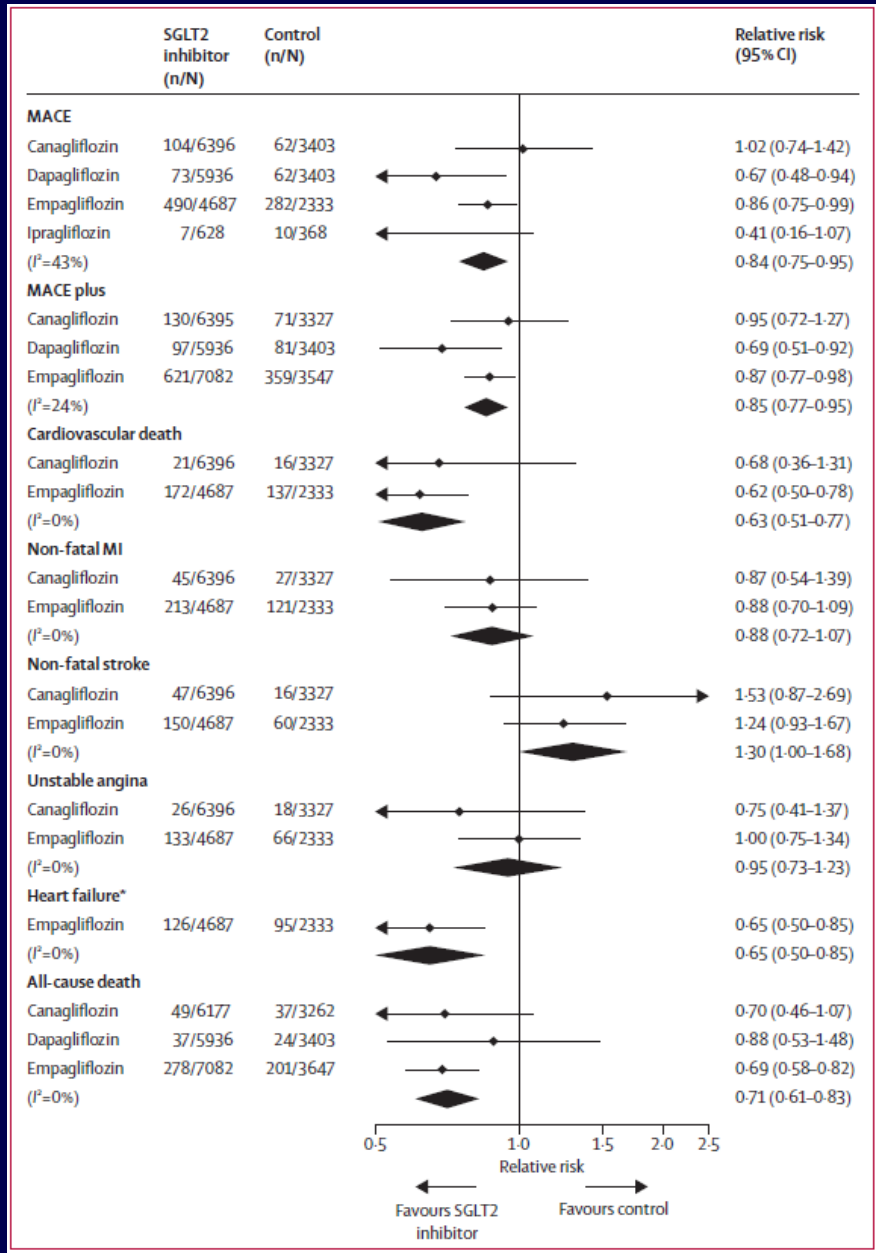
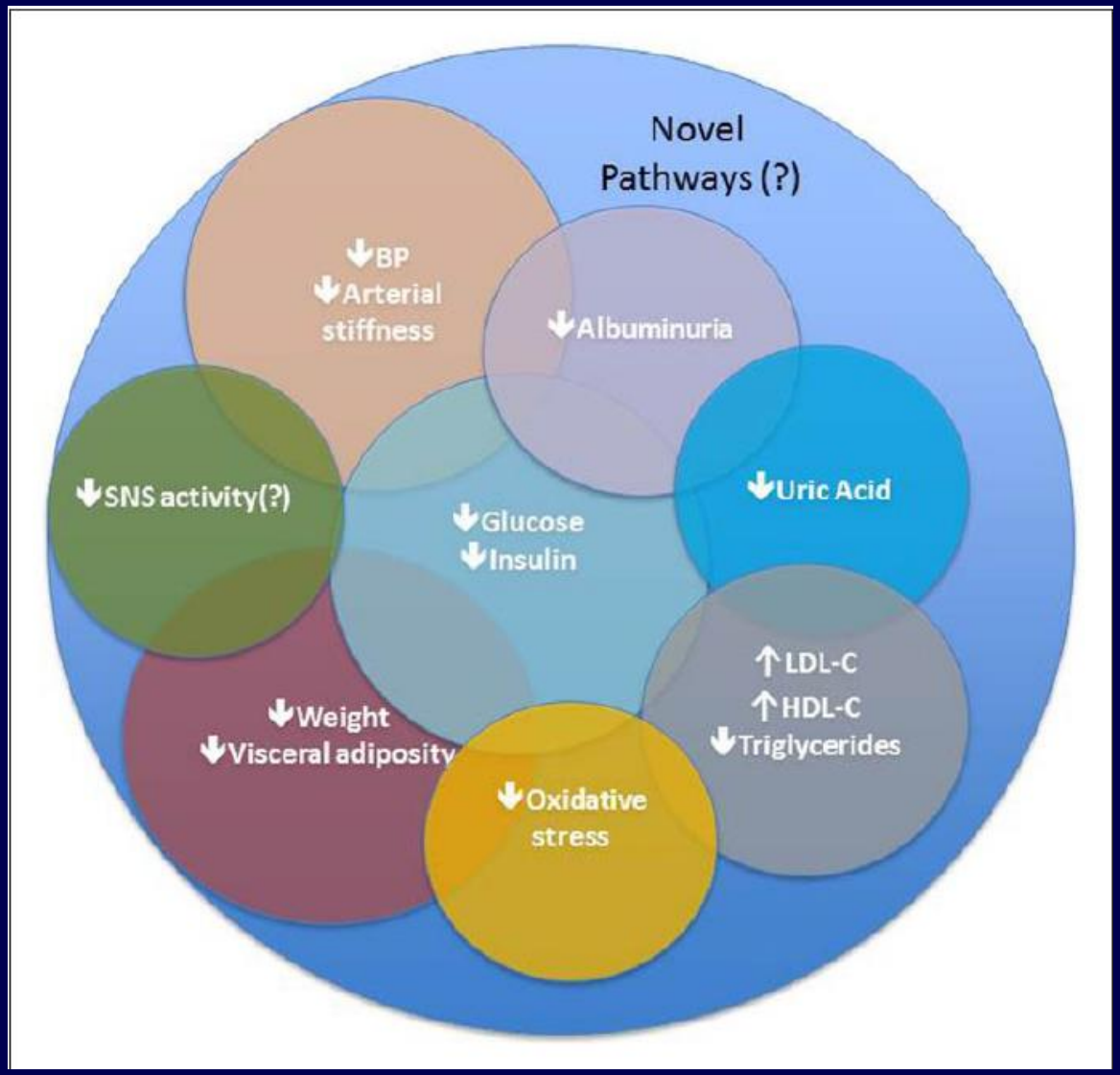


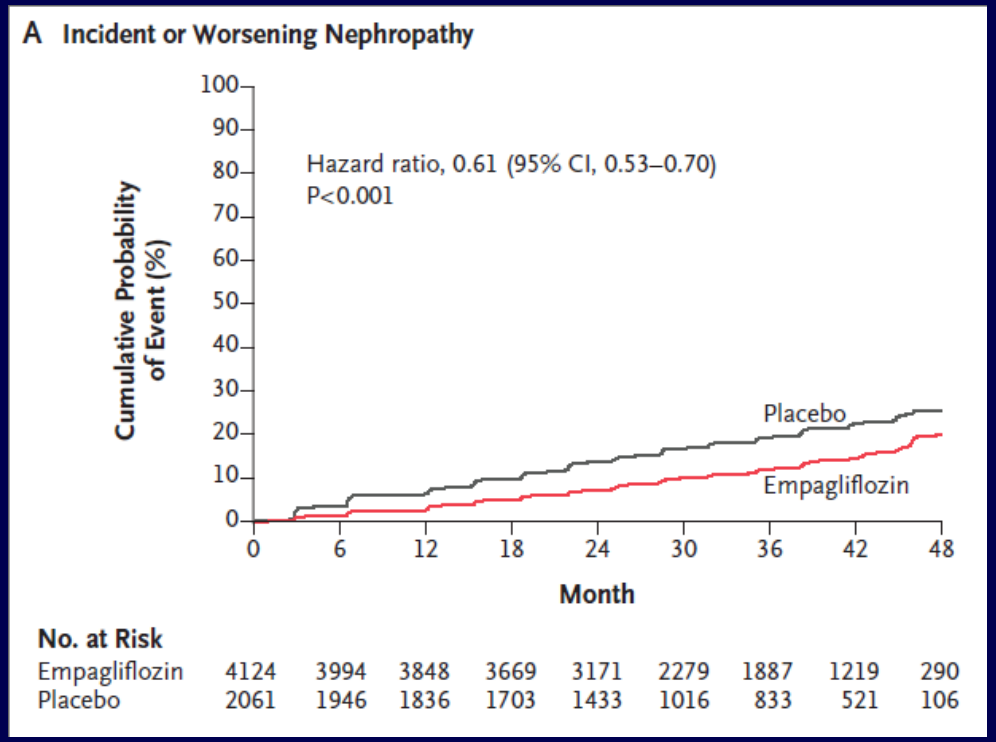
Figure 2: Effects of SGLT2 inhibitors on vascular outcomes, overall and for each drug

Mécanismes potentiels des effets CV des inhibiteurs SGLT2



Inzucchi SE, et al. Diabetes and vascular disease research. 2015; 12:90-1000

EMPA-REG RENAL OUTCOME



« Incident or worsening of nephropathy » = progression vers la macroalbuminurie; doublement de la créatinine sérique; initiation de la dialyse; ou mortalité de cause rénale.

Il n'y a pas eu de réduction d'incidence de la microalbuminurie.

N Engl J Med 2016;375:323-34.

Décompensation acido-cétosique euglycémique sous inhibiteurs SGLT2

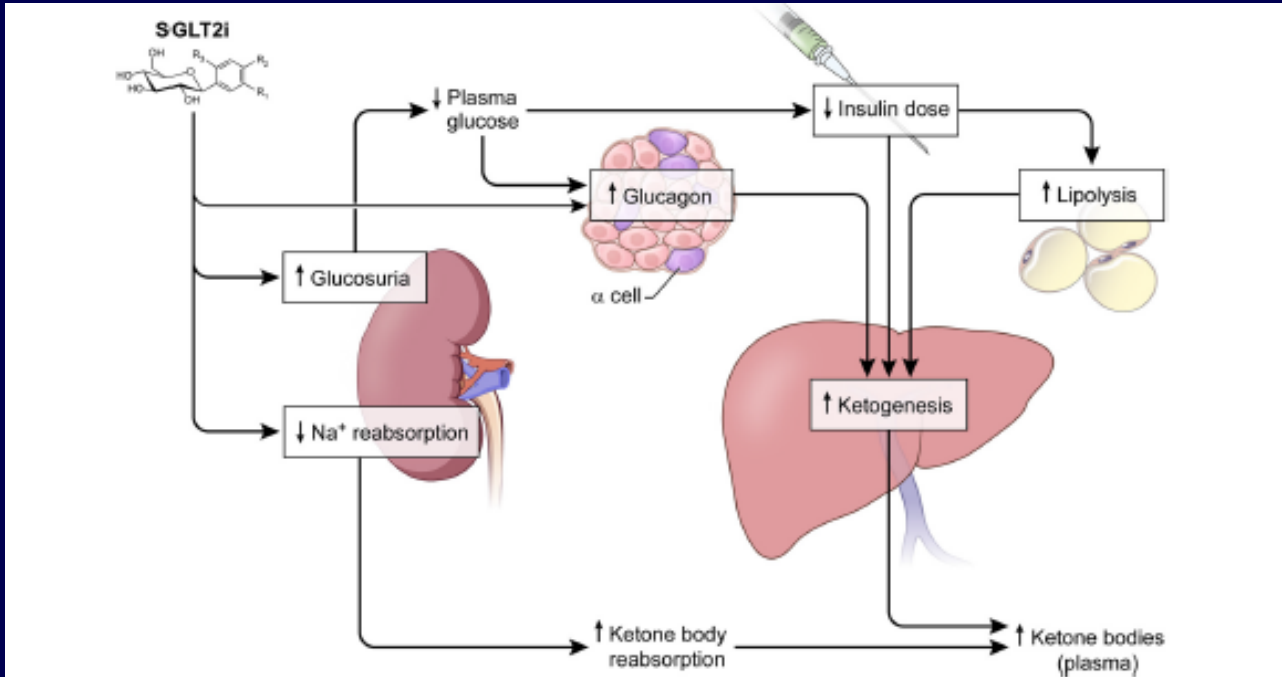


Figure 1. Potential mechanisms whereby adjunctive therapy with SGLT2 inhibitors may promote ketosis and increase the risk of ketoacidosis in T1D patients. SGLT2 inhibitors (SGLT2i) decrease glucose by an insulin-independent mechanism. To minimize the risk of hypoglycemia, T1D patients may need to decrease their insulin dose, which is predicted to increase the rate of adipose tissue lipolysis and hepatic ketogenesis. In addition, SGLT2 inhibitors have been demonstrated to increase plasma glucagon levels in T2D patients (12, 13), possibly to compensate for increased urinary excretion of glucose. In addition, it has recently been reported that SGLT2 inhibitors increase preproglucagon gene expression by acting directly upon pancreatic α-cells (14). Furthermore, phlorizin (a nonselective inhibitor of SGLT1 and SGLT2) has been demonstrated to increase renal tubular reabsorption of acetoacetate (9). If selective SGLT2 inhibitors mimic this action of phlorizin, it is possible that they could also decrease renal clearance of ketone bodies.

Recommandations : éviter de donner des inhibiteurs SGLT2 chez les patients avec néoglucogenèse réduite (alcooliques chroniques…) ou avec diète pauvre en hydrates de carbone. Ne pas donner chez les diabétiques de type 1. Suspendre le médicament avant une intervention chirurgicale élective.

Inhibiteurs du SGLT2 et os

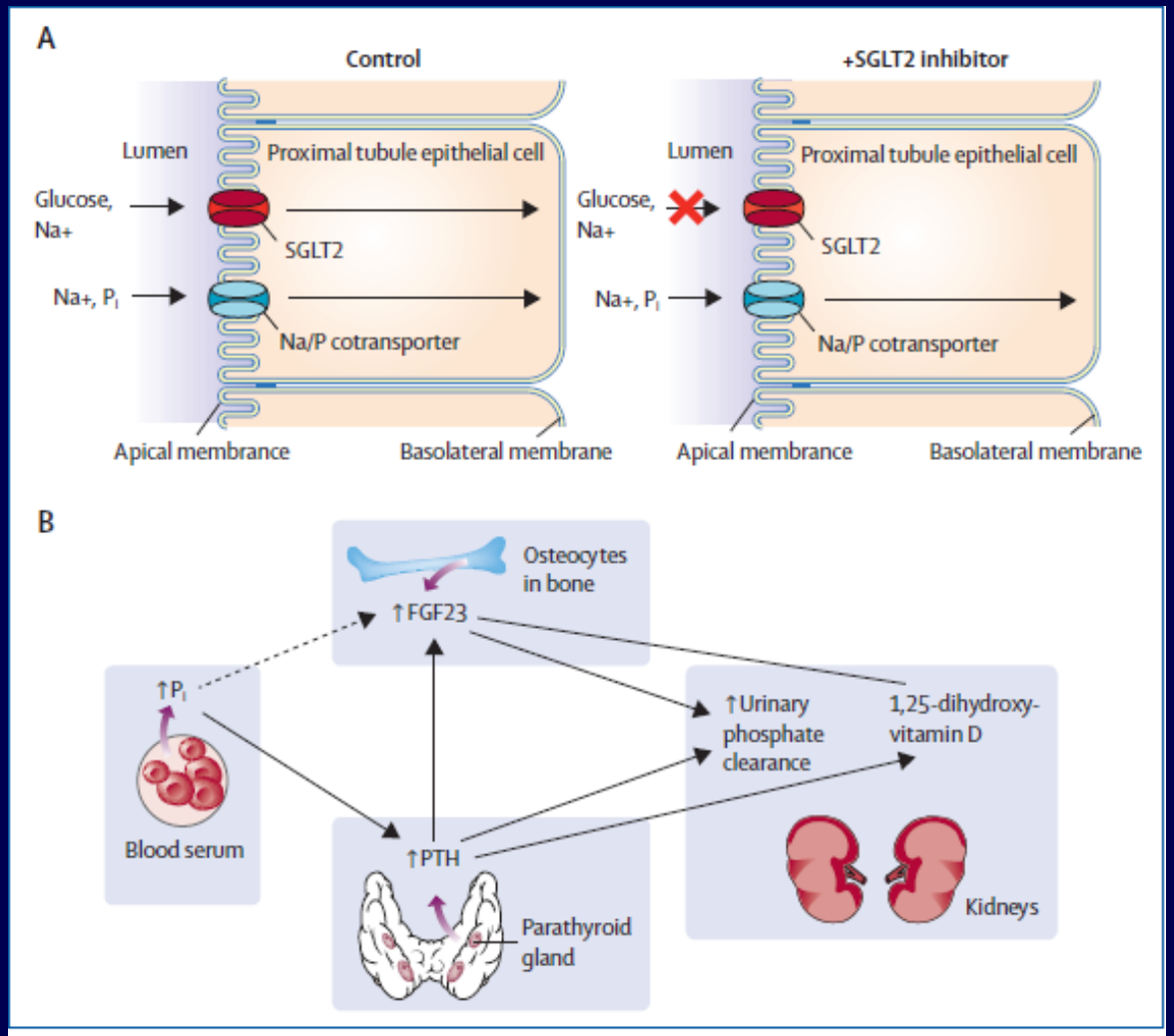


Figure: **Proposed mechanisms whereby SGTL2 inhibitors exert adverse effects on bone**
(A) SGLT2 inhibitors reduce Na^+ transport, which increases availability of Na^+ to drive cotransport of phosphate and Na^+. (B) Increased serum phosphate is predicted to increase secretion of PTH by the parathyroid gland and has the potential to increase secretion of FGF23 by osteocytes.[7-9] SGLT2–sodium glucose cotransporter 2. P_i–inorganic phosphate.

- **FDA warning :**

risque augmenté de fracture osseuse et de réduction de la densité minérale osseuse sous canagliflozine.

Taylor SI et al,
Lancet Diabetol Endocrinol 2015

Prix des traitements journaliers

MEDICAMENT	DOSAGE	PRIX PAR JOUR
Metfin	1 g 2x/j	0.48 CHF
Diamicron MR	60 mg 1x/j	0.92 CHF
Bydureon	2 mg/sem	5.31 CHF
Trulicity	0.75 ou 1.5 mg 1x/sem	6.19 CHF
Januvia/Xelevia	100 mg 1x/j	2.57 CHF
Victoza	1,8 mg 1x/j	7.53 CHF
Onglyza	5 mg 1x/j	2.38 CHF
Trajenta	5 mg 1x/j	2.32 CHF
Invokana	100 mg 1x/j 300 mg 1x/j	2.53 CHF 3.44 CHF
Forxiga	5 ou 10 mg 1x/j	2.66 CHF
Jardiance	10 mg 1x/j	2.54 CHF

Source : Compendium Suisse des Médicaments, septembre 2016

CONCLUSIONS

- La majorité des antidiabétiques a un effet neutre ou inconnu sur la mortalité cardiovasculaire, sauf l'empagliflozine et le liraglutide qui ont un effet bénéfique.

- L'empagliflozine (un inhibiteur SGLT2) est un antidiabétique oral qui a démontré un effet favorable sur la mortalité cardiovasculaire et totale, sur les hospitalisations pour insuffisance cardiaque et sur la progression de l'atteinte rénale. Les raisons de ces bénéfices restent à élucider. Il reste aussi à savoir s'il s'agit d'un effet classe ou molécule.

- La place de l'empagliflozine est indiquée après la metformine chez les patients diabétiques de type 2 en prévention secondaire, les nouvelles recommandations suisses favorisent cette approche.

Merci de votre attention!

EMPA-REG OUTCOME RESULTS

Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
		number of patients (percent)		
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

NEJM, September 2015