Traitement médicamenteux en 2018

Christophe Petite septembre 2018

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM

Guidance for Industry

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

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following:

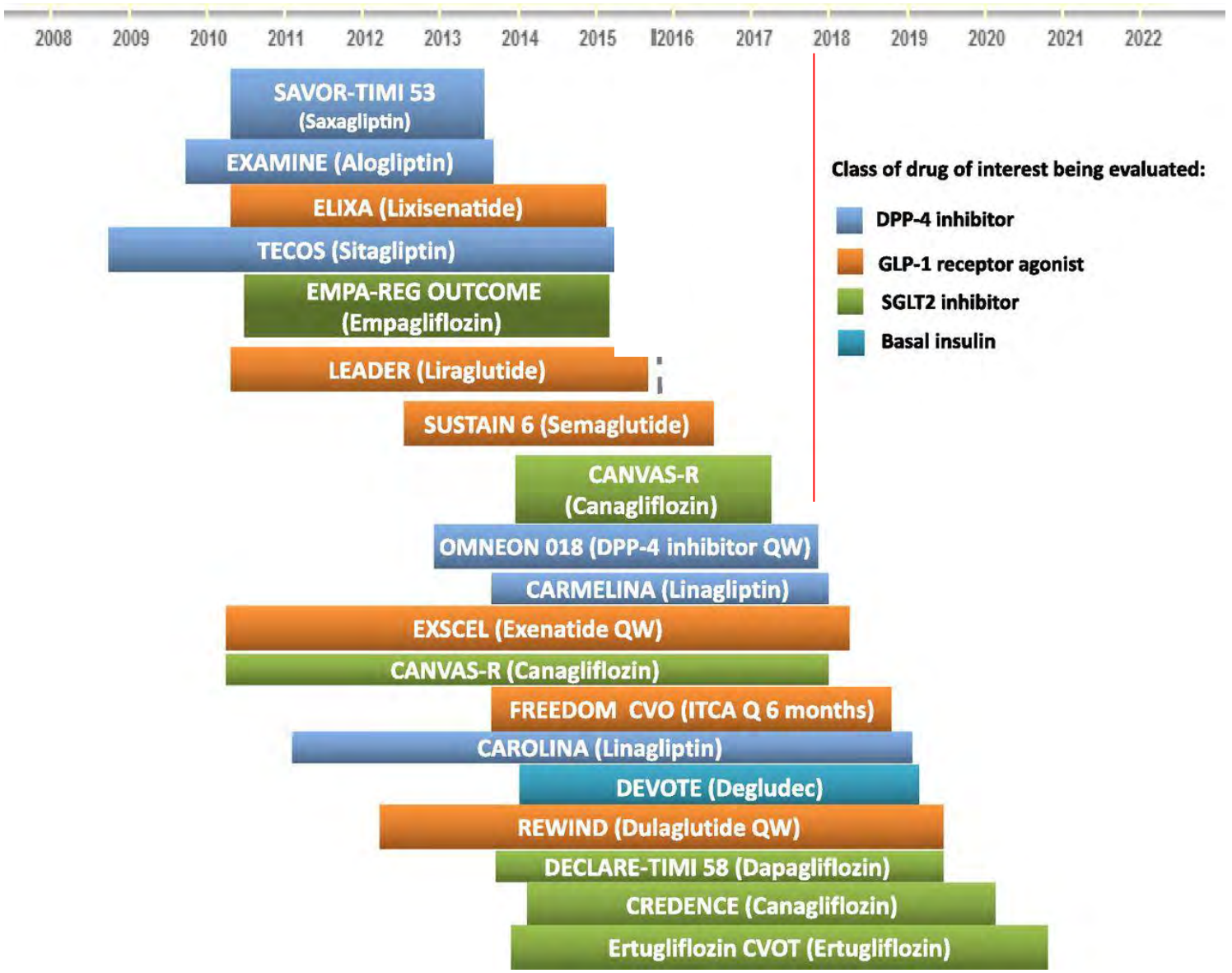
For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately examines for important study design features and pertinent study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analyses, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

FDA website. Evaluating CV risk in new T2DM therapies.


2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
SAVOR-TIMI 53 (Saxagliptin)
EXAMINE (Alogliptin)
ELIXA (Lixisenatide)
TECOS (Sitagliptin)
EMPA-REG OUTCOME (Empagliflozin)
LEADER (Liraglutide)
SUSTAIN 6 (Semaglutide)
CANVAS-R (Canagliflozin)
OMNEON 018 (DPP-4 inhibitor QW)
CARMELINA (Linagliptin)
EXSCEL (Exenatide QW)
CANVAS-R (Canagliflozin)
FREEDOM CVO (ITCA Q 6 months)
CAROLINA (Linagliptin)
DEVOTE (Degludec)
REWIND (Dulaglutide QW)
DECLARE-TIMI 58 (Dapagliflozin)
CREDENCE (Canagliflozin)
Ertugliflozin CVOT (Ertugliflozin)
Class of drug of interest being evaluated:
DPP-4 inhibitor
GLP-1 receptor agonist
SGLT2 inhibitor
Basal insulin

Les gliptines inhibiteurs de DPP4

-efficacité

-pas de prise de poids

-pas d'hypoglycémie

(utile chez âgés et IRC)

-bonne tolérance

-recul

-bon profil de sécurité

pancréatite?

-coût (± 2 frs/j)

Sitagliptine + metformine

Januvia®, Xelevia®

Janumet®, Janumet XR®,

Velmetia®

Vildagliptine

Galvus®

Galvumet®

Alogliptine

Vipidia®

Vipdomet®

Saxagliptine

Onglyza®

Duoglyze®, Kombiglyze XR®

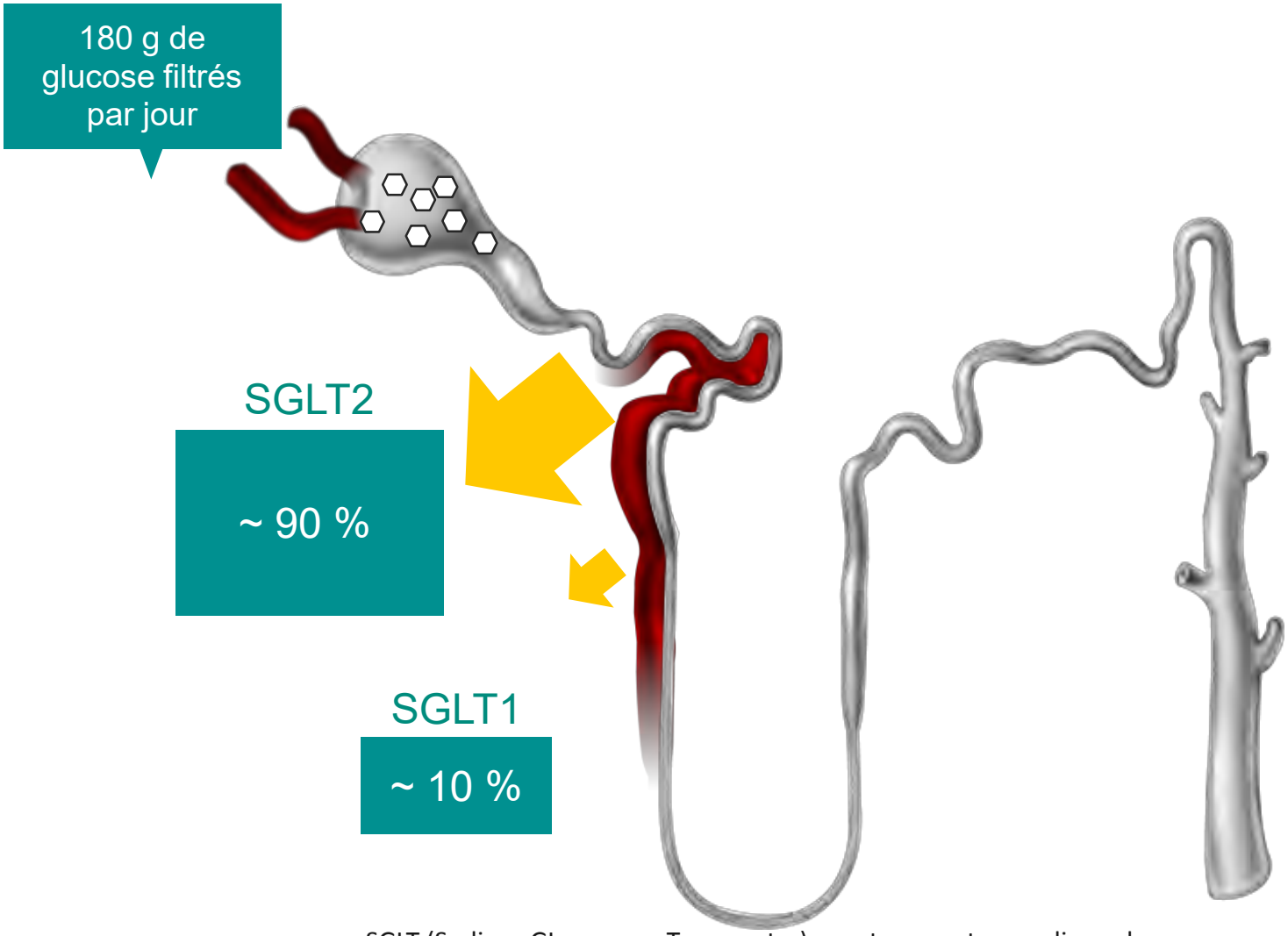
Qtern ®

Linagliptine

Trajenta®

Jentadueto®

Les gliflozines, inhibiteurs du SGLT2



SGLT (Sodium-GLucose co-Transporter) = co-transporteur sodium-glucose

Références: 1. Gerich JE: Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. *Diabet Med.* 2010;27:136–142. / 2. Bakris GL, et al.: Renal sodium–glucosetransport: role in diabetes

Inhibiteurs du SGLT2 ou gliflozines

Canagliflozine + metformine

Invokana®

Vokanamet®

Dapagliflozine + metformine

Forxiga®

Xigduo®

Qtern®

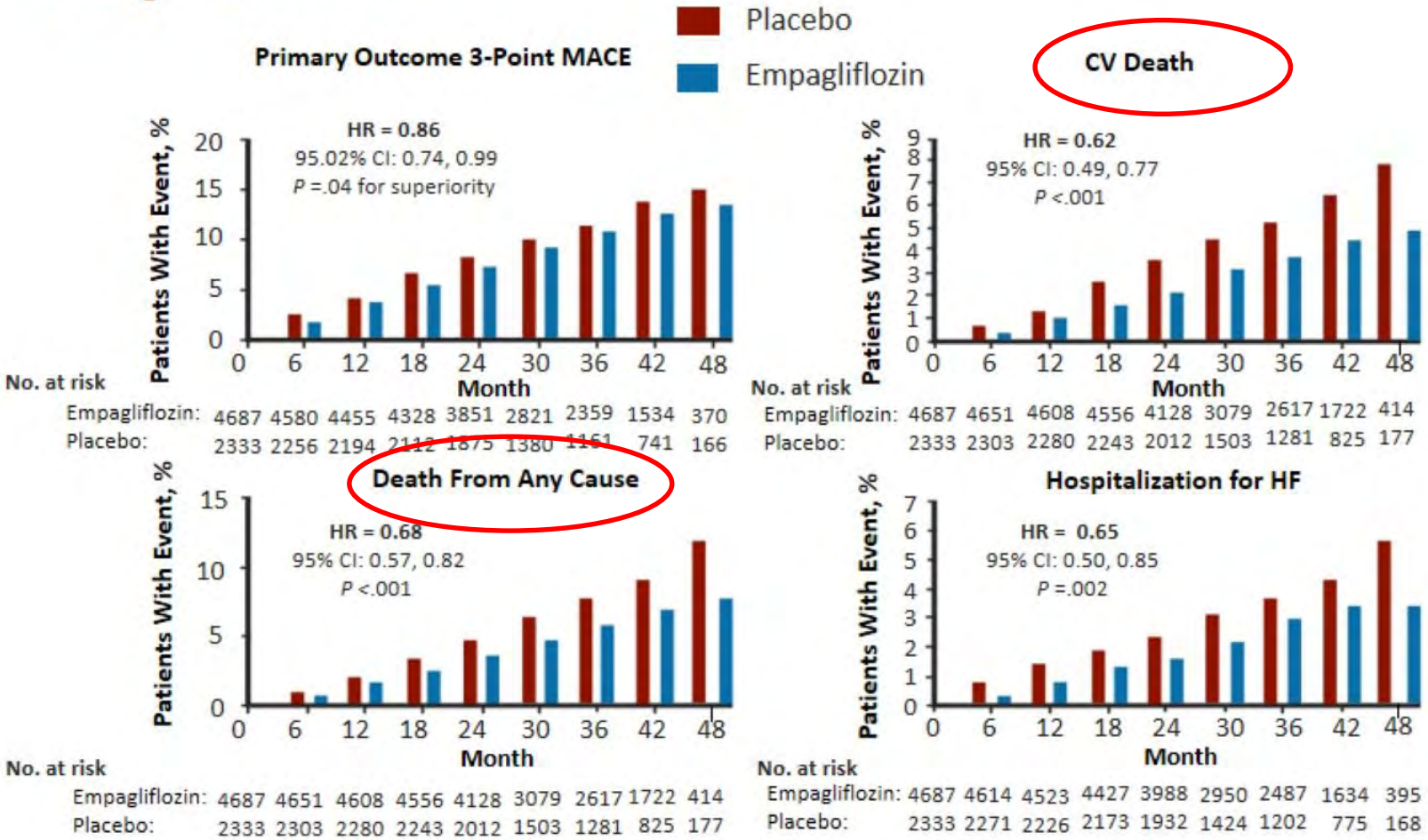
Empagliflozine + metformine

Jardiance®

Jardiance Met®

EMPA-REG OUTCOME Trial

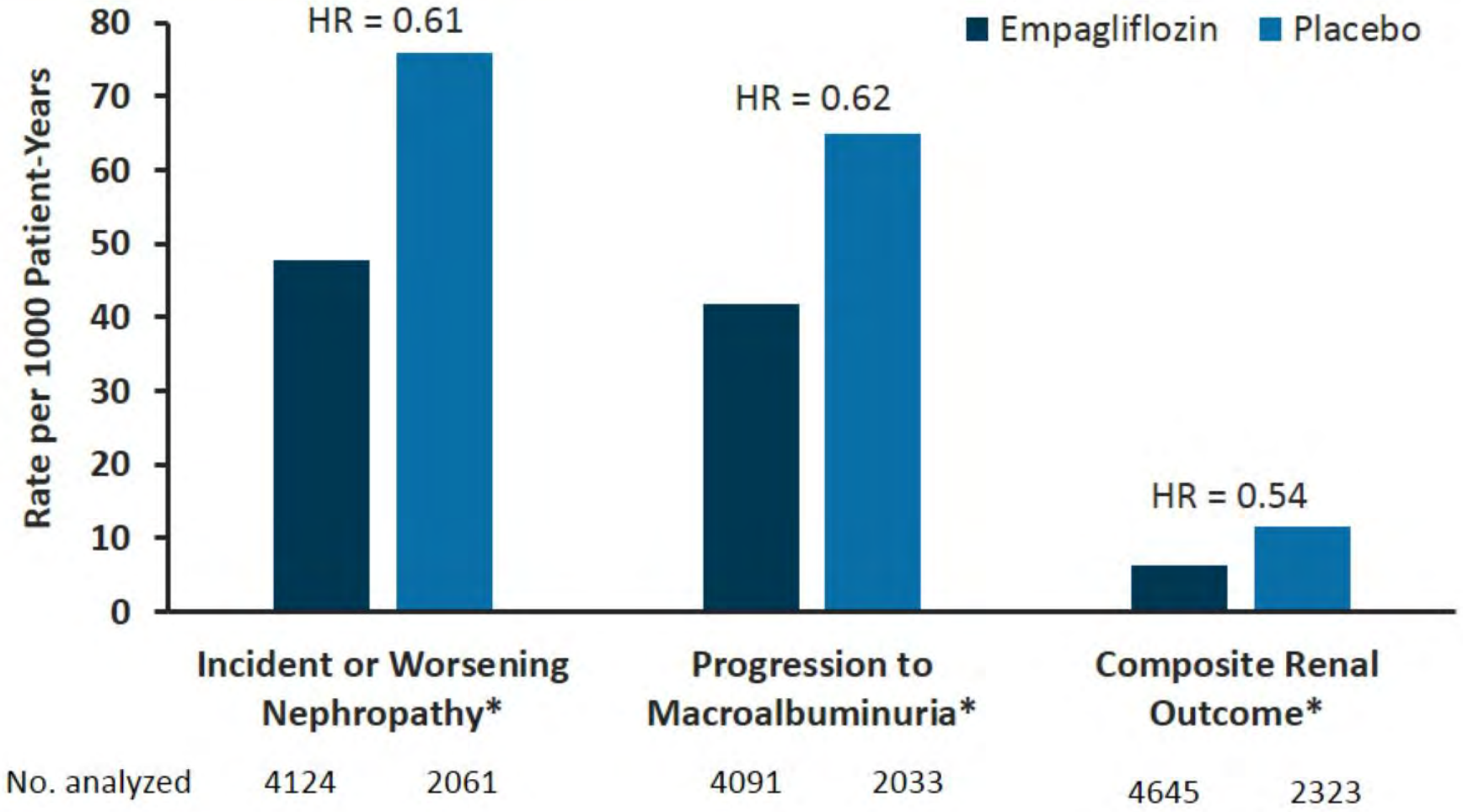
Cardiovascular Outcomes and Death From Any Cause



Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

EMPA-REG OUTCOME Trial

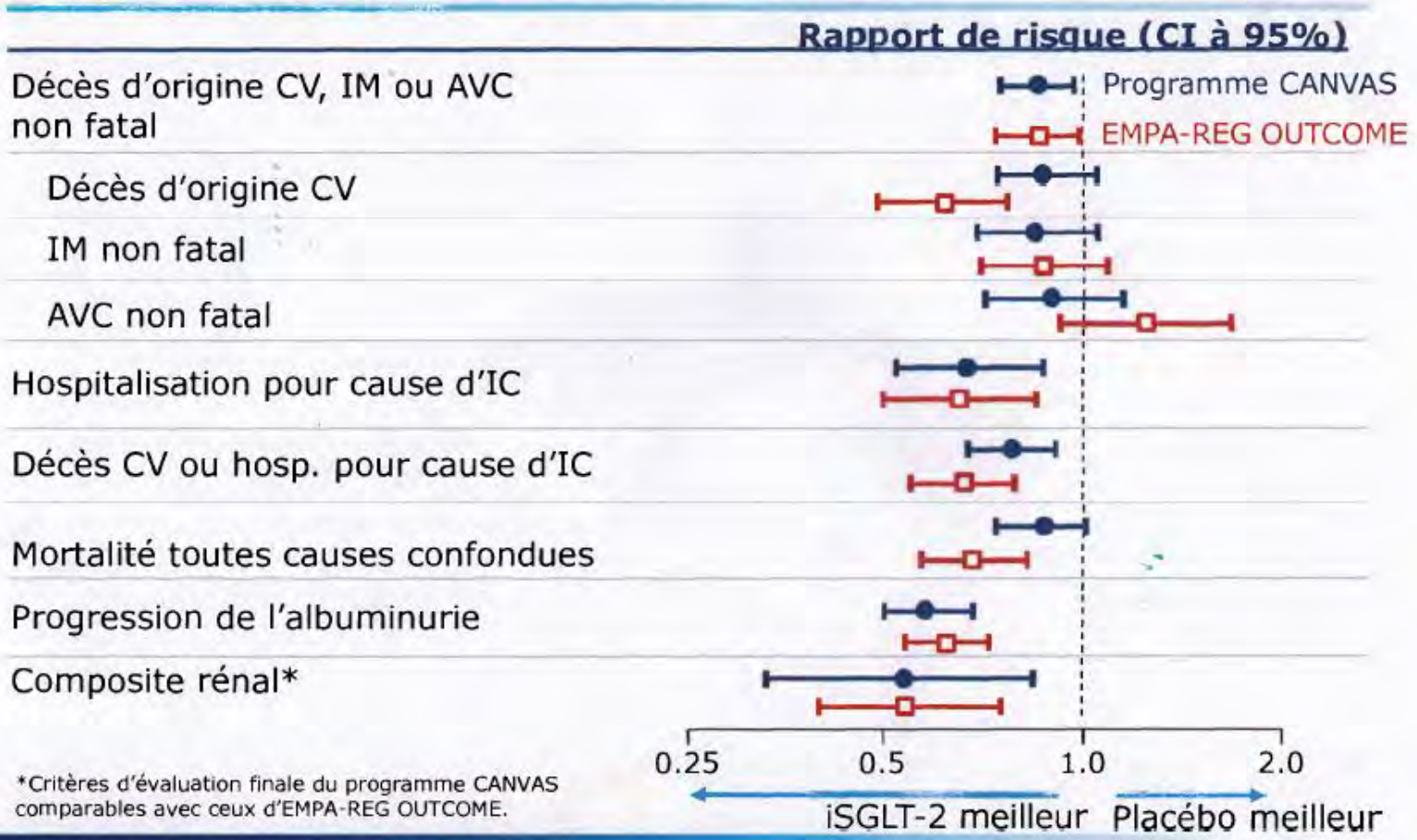
Renal Outcomes



*$P < .001$.

Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

Principaux critères d'évaluation finale dans le programme CANVAS et EMPA-REG OUTCOME



*Critères d'évaluation finale du programme CANVAS comparables avec ceux d'EMPA-REG OUTCOME.

Zinman Bet al. N Engl J Med. 2015 ;373(22):2117-2128.
Wanner K et al. N Engl J Med. 2016;375(4):323-334.

CANVAS Program

DECLARE-TIMI 2018

Mécanisme?

Effet sur TA, glycémie, lipides? Rôle mineur

Effet sur le métabolisme cardiaque, contractilité

Diminution du volume plasmatique (Ht + 3%)

Avantages

Baisse de l'HbA1c indépendante de l'insuline (-0.5-1%)

Utilisable à n'importe quel stade de diabète

Perte de poids (2-3 kg)

Baisse de la TA (TAS -2-5mmHg, TAD -1-2 mmHg)

Faible risque d'hypoglycémie

Pas d'interaction significative

Cardio- et néphro-protecteur

Effets secondaires

- mycose 10-15% (femmes), balanite 3%
- Infection urinaire (urosepsis?)
- Polyurie, polydipsie
  hypotension artérielle
  IRA
- Acidocétose diabétique euglycémique

Alarmes

- Fracture?
- Amputation distale?
- Cancer vessie?
- Sécurité à long terme?

Précautions

Contre-indications

grossesse, allaitement

diabète type 1

Prudence

diurétiques de l'anse avec hypovolémie

si IRC modérée à sévère (clearance < 60 ml/min)

cana/empa (< 45 ml/min)

patient > 75 ans

Analogues du GLP1

Exenatide LAR

Bydureon 2mg

Liraglutide

Victoza 0.6 puis 1.2 mg

Dulaglutide

Trulicity 0.75 puis 1.5 mg

Semaglutide

Ozempic 1x/semaine, per os?

Lixisénatide

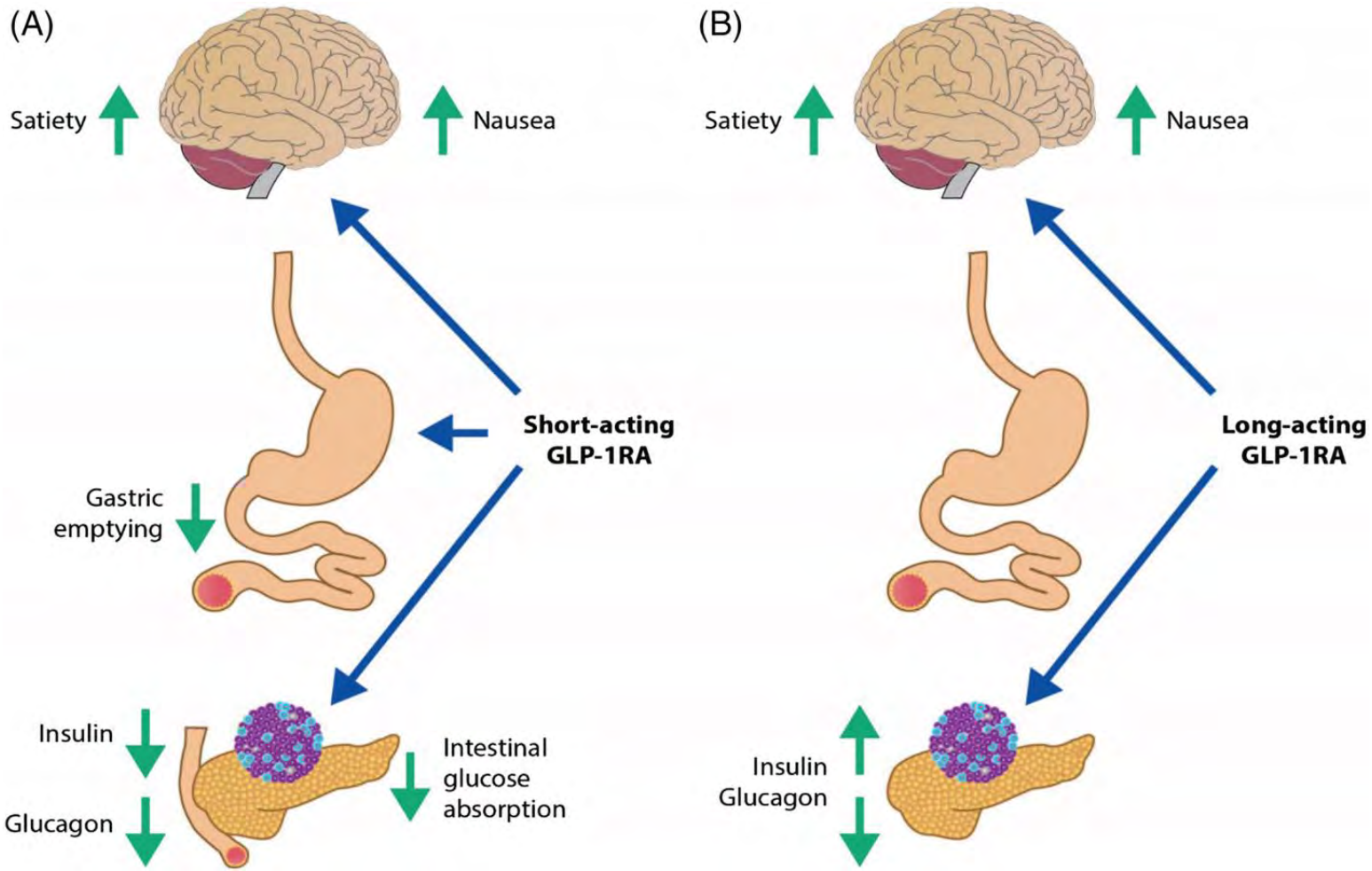
Lyxumia

Exenatide

Byetta 2x/j

Combinaison avec insuline Xultophy, Suliqua

Les GLP-1 RA ont des mécanismes d'action différents

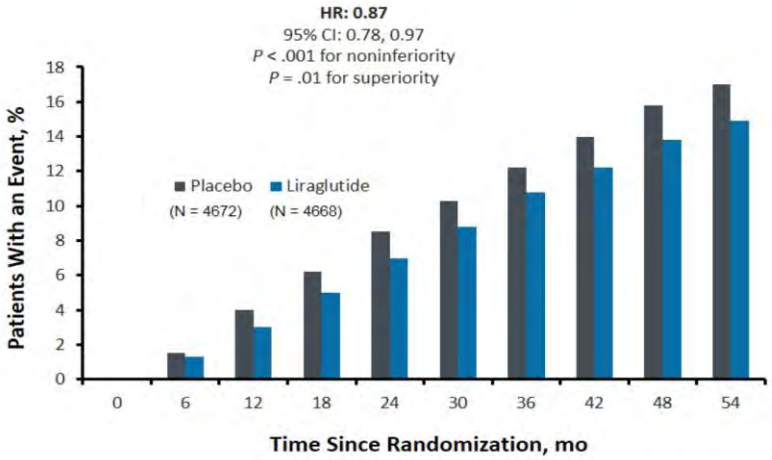


Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists, Volume: 18, Issue: 4, Pages: 317-332, First published: 29 October 2015, DOI: (10.1111/dom.12596)

Les GLP-1 RA ont des mécanismes d'action différents

	GLP-1 RA prandiaux	GLP-1 RA à longue durée d'action
Ralentissement de la vidange gastrique	+++	+
Inhibition de la sécrétion du glucagon	+++	++
Stimulation de la sécrétion d'insuline	-	++

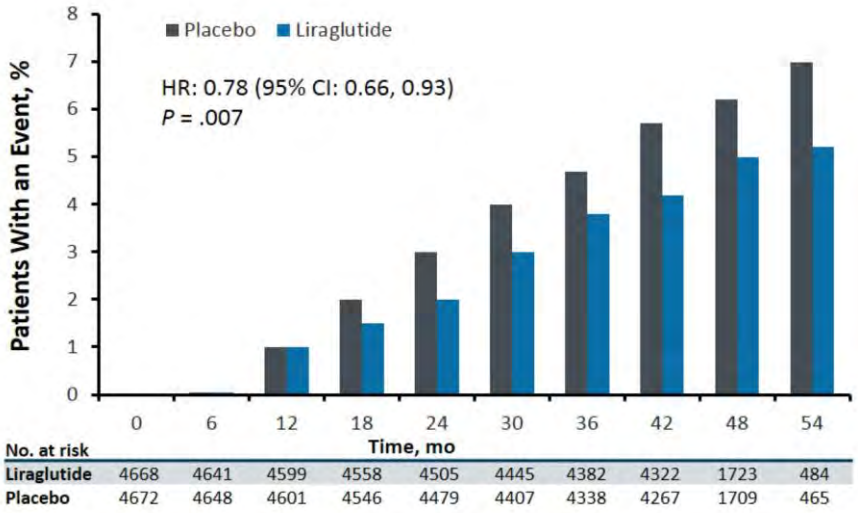
LEADER: Primary Outcome*



*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

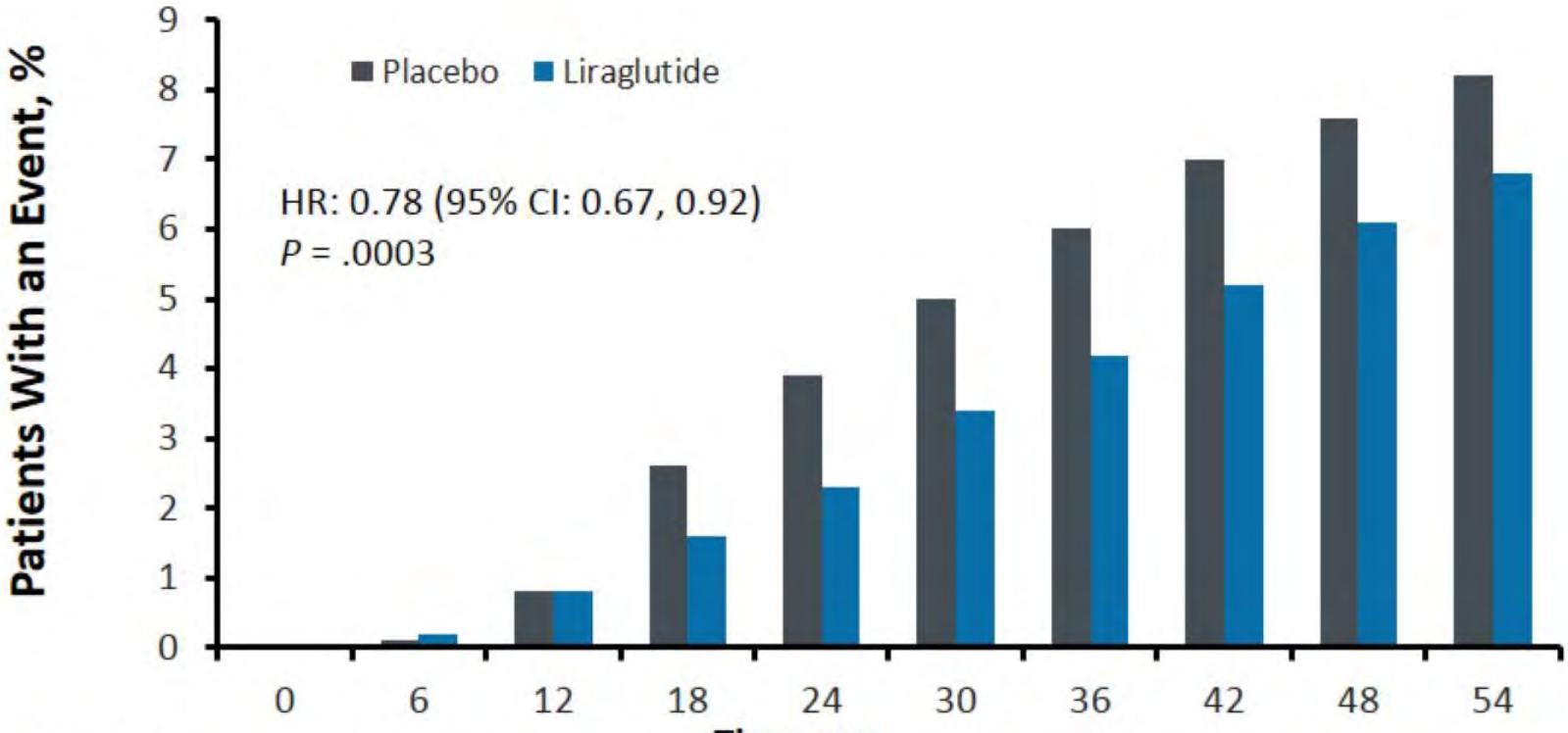
LEADER: CV Death



No. at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

LEADER: Time to First Renal Event -- Macroalbuminuria, Doubling of Serum Creatinine, ESRD, Renal Death

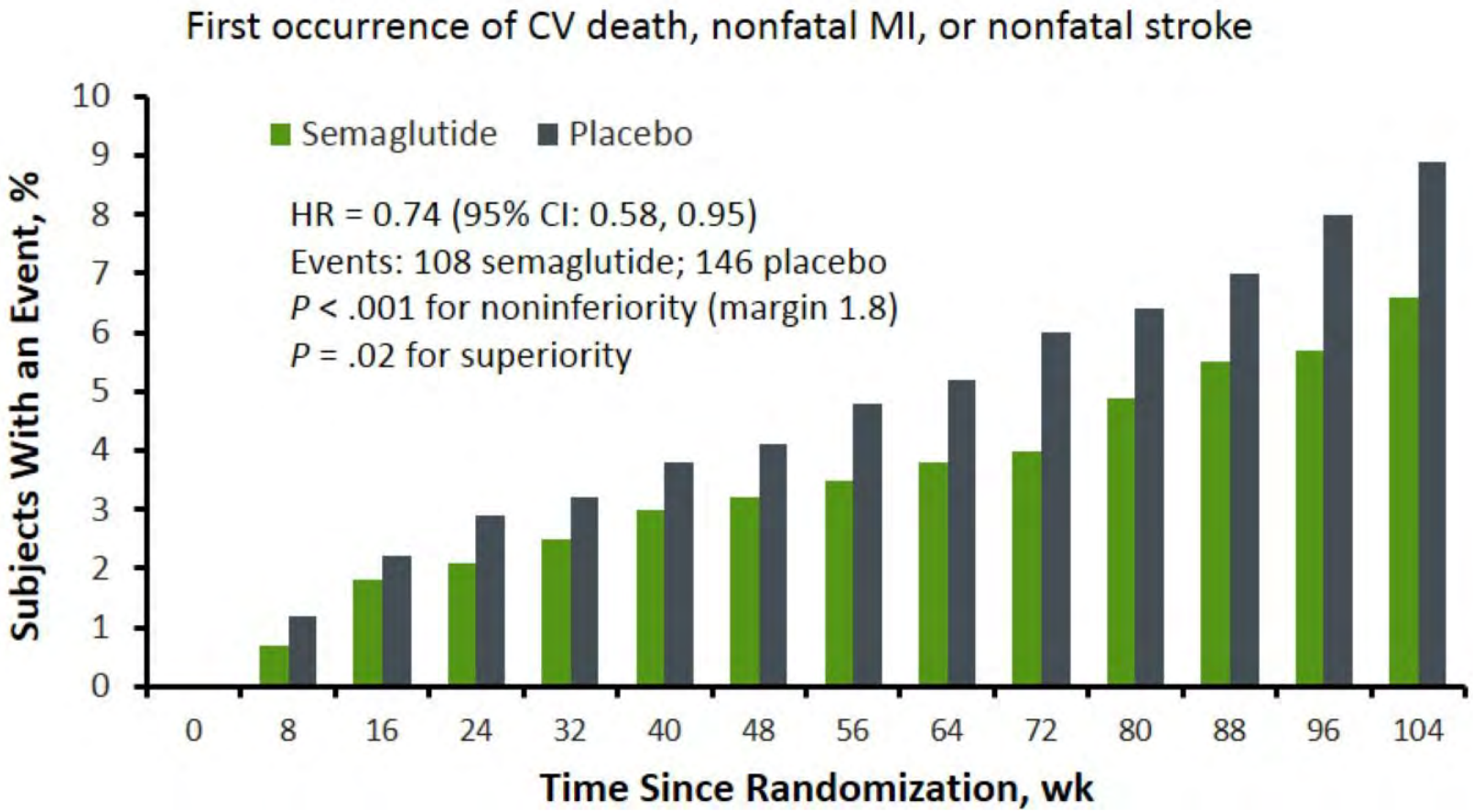


No. at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4643	4428	4316	4196	4094	3990	1613	433

The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months.

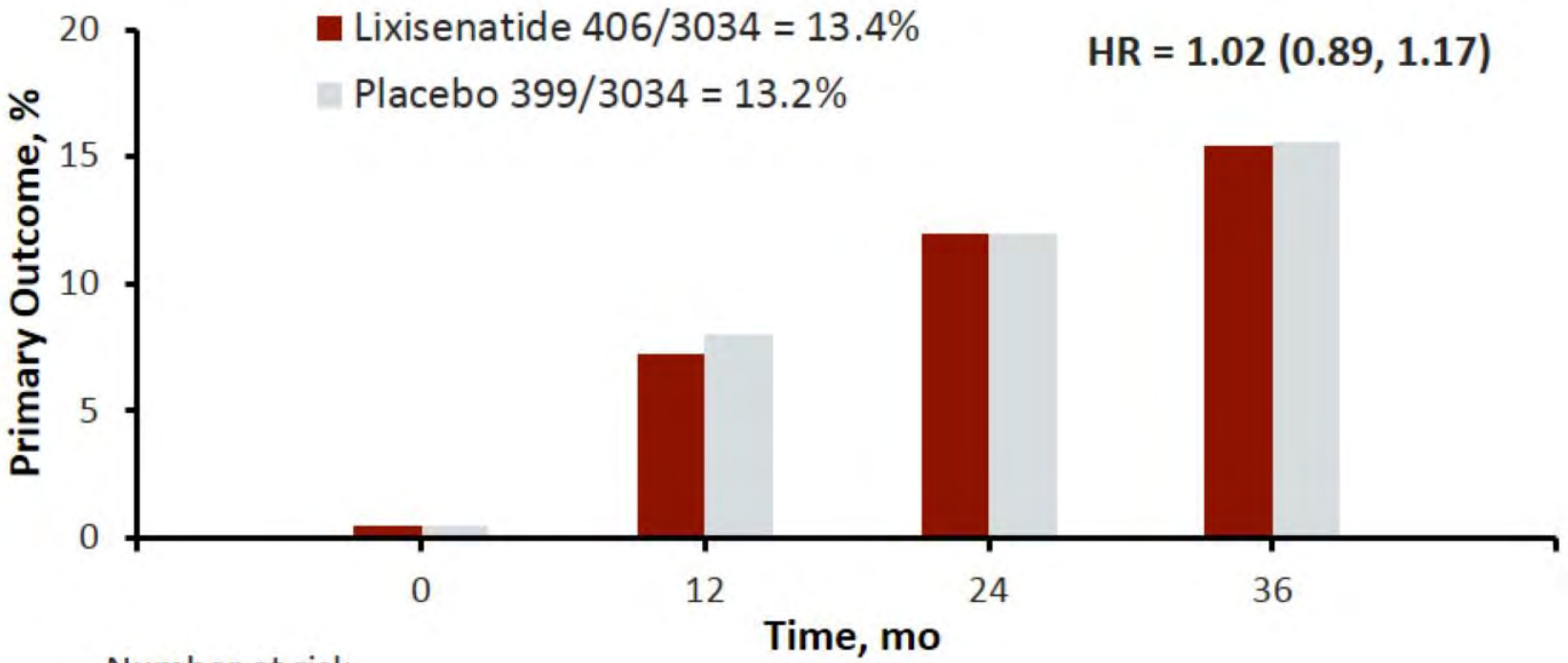
Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

SUSTAIN-6 (Semaglutide): Primary Outcome Results



Marso S, et al. *N Engl J Med*. 2016. [Epub ahead of print]

ELIXA (Lixisenatide): Primary Outcome CV Death, Nonfatal MI, Nonfatal Stroke, or Hospitalization for UA



Number at risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

- Subgroup interactions were analyzed, but none were significant
- HF occurred in 4.0% of lixisenatide patients and 4.2% of placebo patients; *P* = .63

Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

Analogues du GLP1

-BMI > 28 kg/m2

-instruction (AVSD)

-efficace HbA1c -0.5-1%

-pas d'hypoglycémie

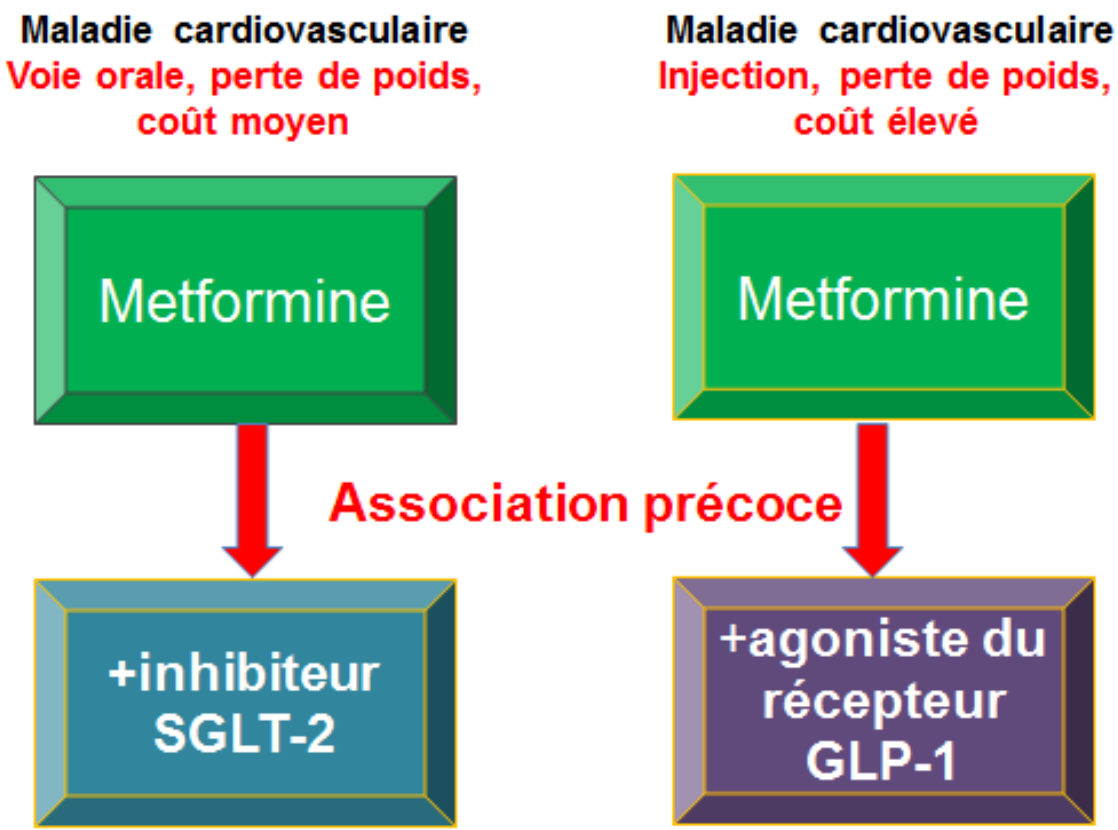
-perte de poids

-débuter à faible posologie

-avertir des effets secondaires (nausées)

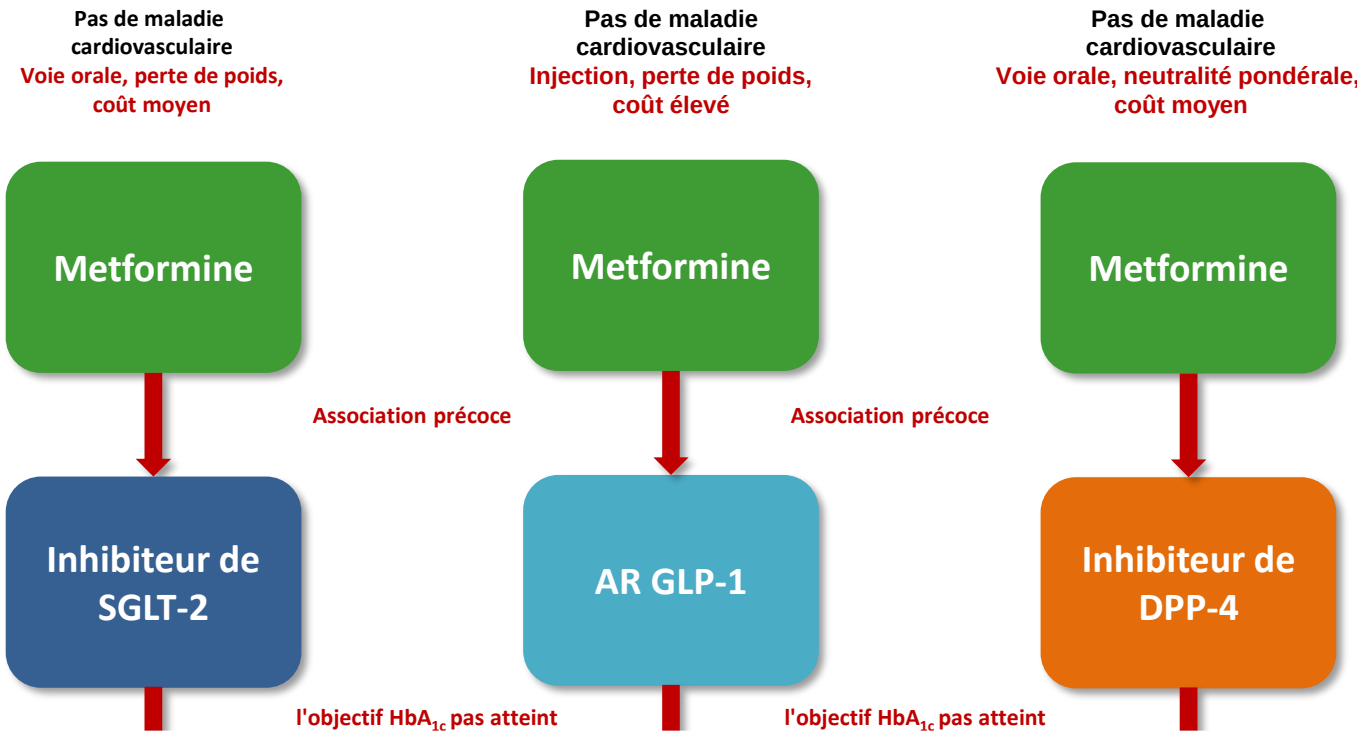
-contre-indications
pancréatite, eGFR < 30 ml/min

-précautions
risque IRA, hypoglycémie si insuline ou SU

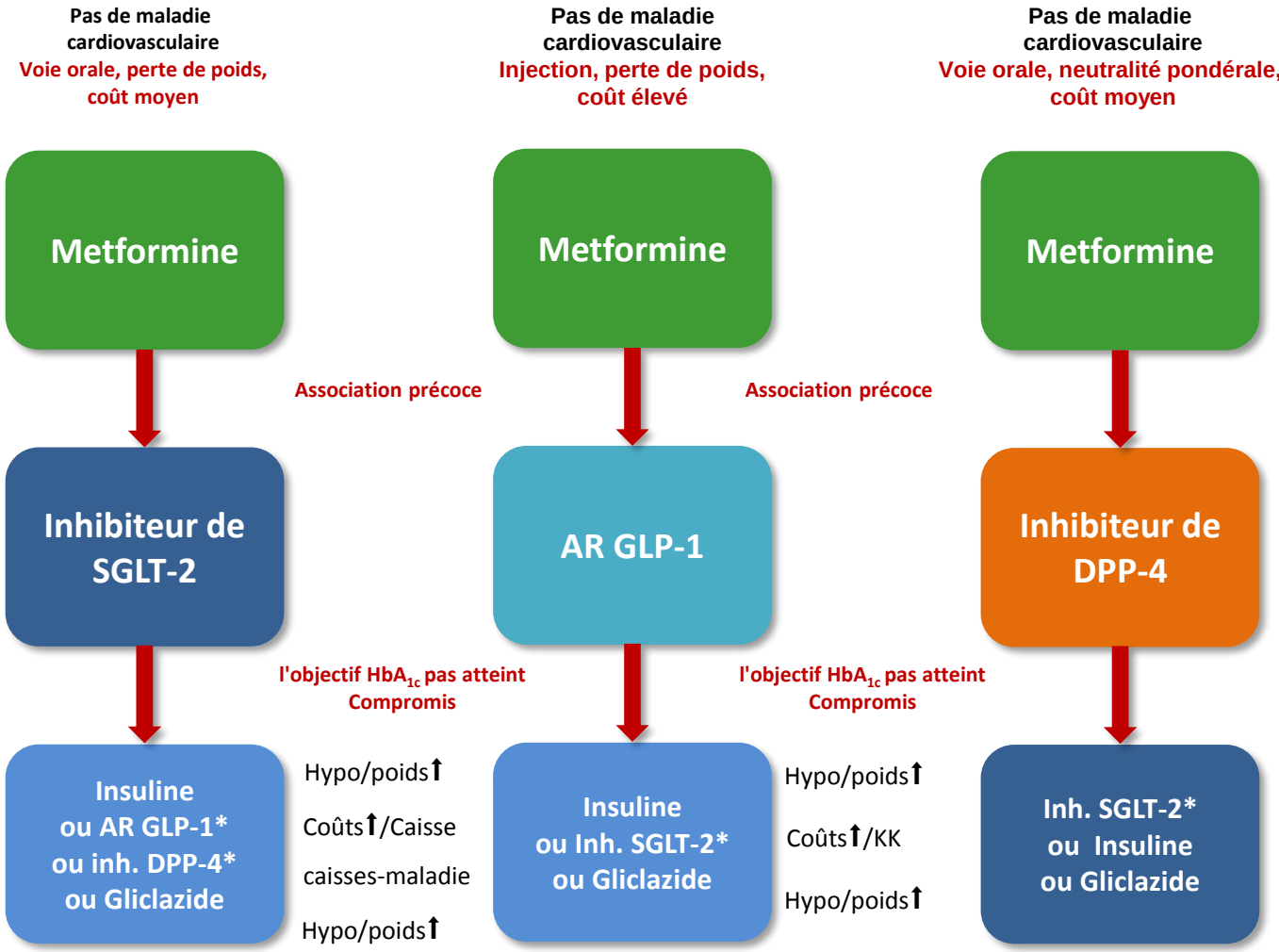


Validé par le comité SSED/SGED sur demande du groupe de travail de la SSED/SGED lors de sa séance du 24 août 2016.

Traitement combiné précoce pour les patients ne souffrant pas d'une maladie cardiovasculaire



Traitement combiné précoce pour les patients ne souffrant pas d'une maladie cardiovasculaire



http://www.sgedssed.ch; *Pour le moment, pas d'indication ni de remboursement pour l'association des inhibiteurs du SGLT2 avec des AR du GLP-1 ainsi que pour les inhibiteurs du SGLT2 avec la plupart des inhibiteurs de la DPP-4 (exception: dapagliflozine). Pour d'autres détails sur les produits: www.swissmedicinfo.ch

Love Affair With Metformin: Still Strong, or Time to Move On?

Lisa Nainggolan

June 23, 2018

Metformine en premier?

Pour

Efficace

Diminution complications micro

Coût

Sécurité

Nouveaux médicaments

(long terme?, nombreuses alarmes ?

études seulement chez diabétiques à haut risque vasculaire)

Metformine en premier?

Contre

Protection CV pas aussi efficace

Pas de perte de poids, de baisse de la TA

Pas d’effet néphroprotecteur

Metformine

Si intolérance

-prendre avec nourriture

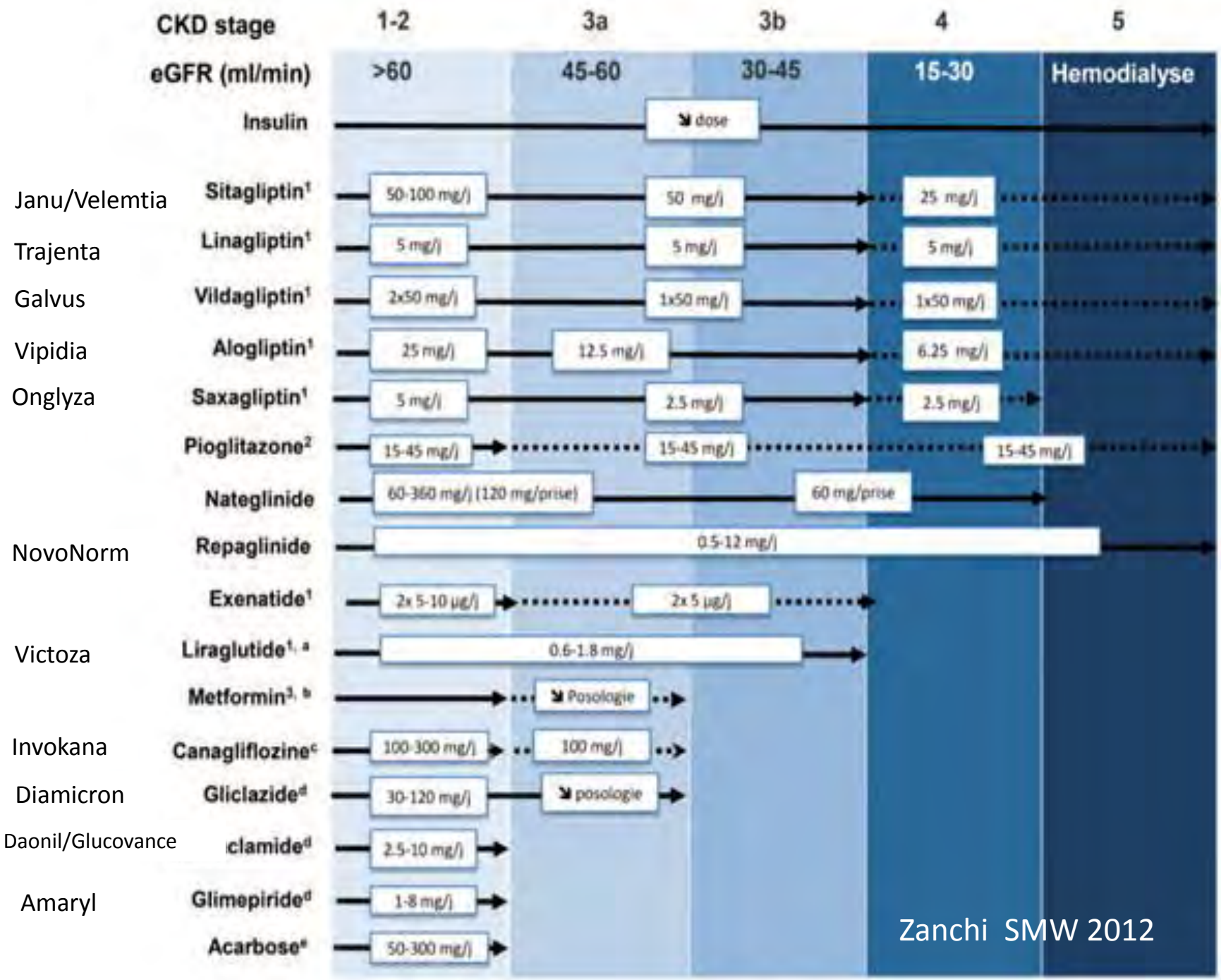
-titration lente

-long-acting metformine

CAVE: acidose lactique

carence en B12

Cl < 60 ad diminution dose, Cl < 45 ou 30 ? stop


CKD stage
1-2
3a
3b
4
5
eGFR (ml/min)
>60
45-60
30-45
15-30
Hemodialyse
Insulin
dose
Janu/Velemtia
Sitagliptin¹
50-100 mg/j
50 mg/j
25 mg/j
Trajenta
Linagliptin¹
5 mg/j
5 mg/j
5 mg/j
Galvus
Vildagliptin¹
2x50 mg/j
1x50 mg/j
1x50 mg/j
Vipidia
Alogliptin¹
25 mg/j
12.5 mg/j
6.25 mg/j
Onglyza
Saxagliptin¹
5 mg/j
2.5 mg/j
2.5 mg/j
Pioglitazone²
15-45 mg/j
15-45 mg/j
15-45 mg/j
Nateglinide
60-360 mg/j (120 mg/prise)
60 mg/prise
NovoNorm
Repaglinide
0.5-12 mg/j
Exenatide¹
2x 5-10 µg/j
2x 5 µg/j
Victoza
Liraglutide¹, ª
0.6-1.8 mg/j
Metformin³, ᵇ
Posologie
Invokana
Canagliflozine°
100-300 mg/j
100 mg/j
Diamicron
Gliclazide⁴
30-120 mg/j
posologie
Daonil/Glucovance
clamide⁴
2.5-10 mg/j
Amaryl
Glimepiride⁴
1-8 mg/j
Acarbose°
50-300 mg/j
Zanchi SMW 2012

Les «barrières» du patient

- Complexité
- Coût
- Ne pas se sentir malade
- Manque de compréhension
- Dépression
- Croyances
- Effets secondaires
- …

Conclusions

- Combinaisons de médicaments «sur mesure»
- Fixer cibles glycémiques et HbA1c
- Amélioration du mode de vie
- Combattre l’inertie thérapeutique
- Observance médicamenteuse