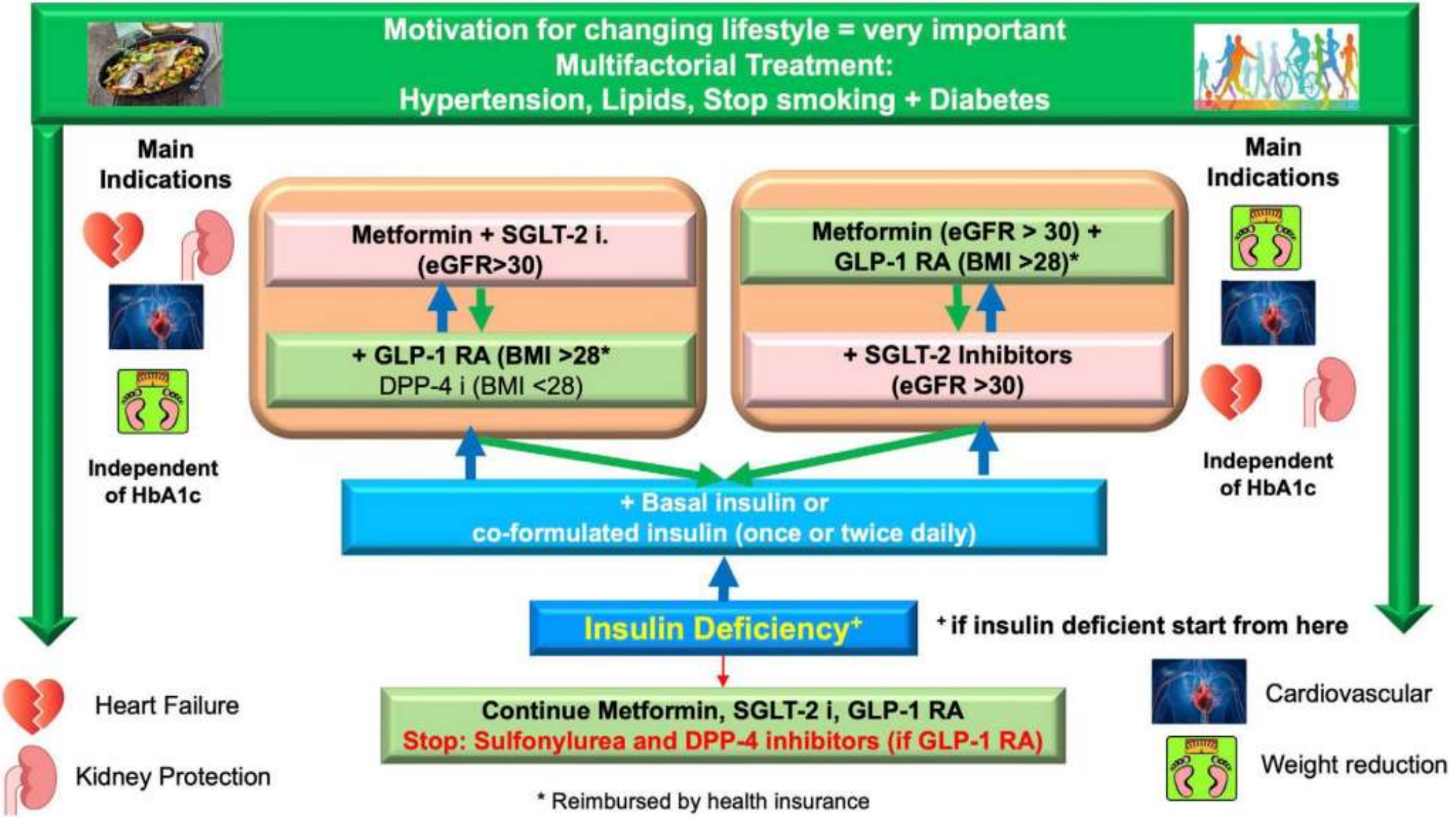
Prévention cardiovasculaire. Update : les antidiabétiques (metformine, gliflozines, analogues du GLP-1)

Prof François R. Jornayvaz
Médecin-chef de service

30.11.2023

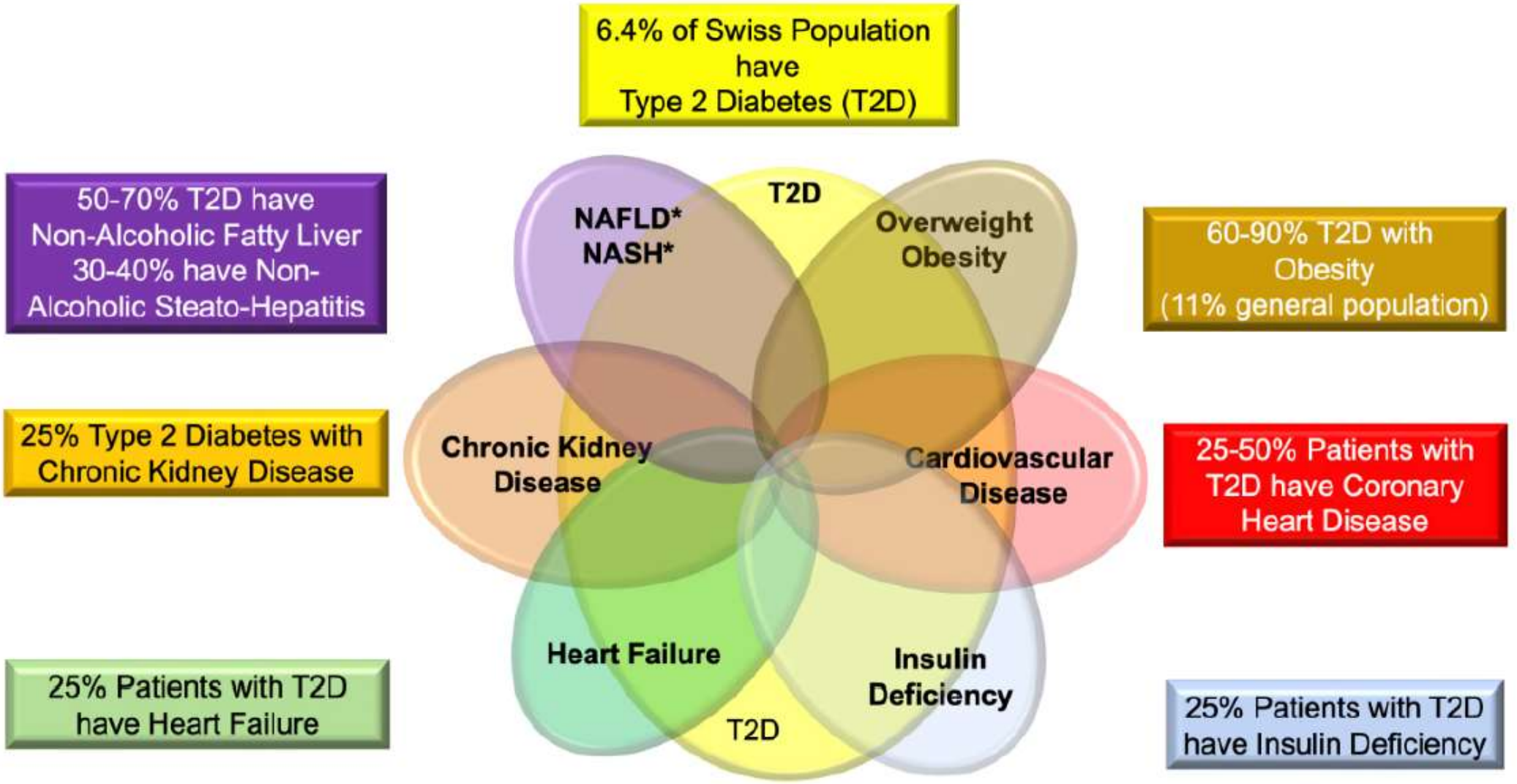
Guidelines SSED 2023



Swiss medical weekly, 2023; 153, 40060.

Comorbidités dans le diabète de type 2

Figure 4: Comorbidities in type 2 diabetes mellitus.



Swiss Med Wkly. 2023;153:40060

Metformine et 3-point MACE

Effect of metformin on all-cause mortality and major adverse cardiovascular events: An updated meta-analysis of randomized controlled trials

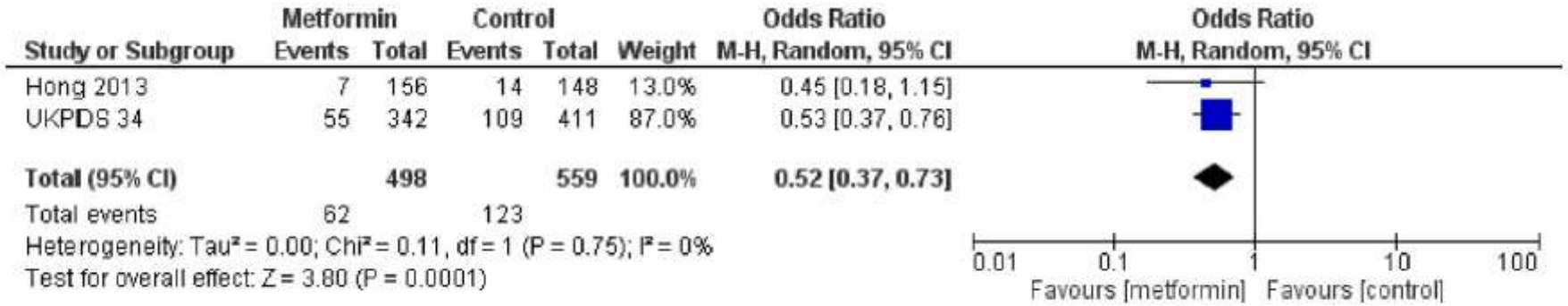


Figure 1 Risk of major adverse cardiovascular events (MACE) with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

Conclusions: This updated meta-analysis suggests that metfomin is significantly associated with lower risk of MACEs and tendentially lower all-cause mortality compared to placebo or other anti-hyperglycaemic drugs.

Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 699–704

Sulfonylurées et mortalité totale et CV

Mortality risk among sulfonylureas: a systematic review and network meta-analysis

Interpretation Gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide. Clinicians should consider possible differences in risk of mortality when selecting a sulfonylurea.

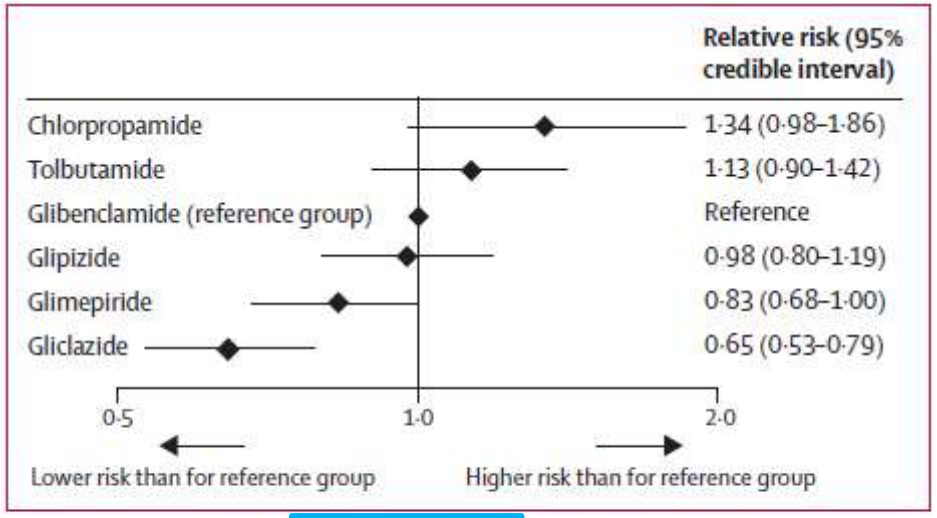


Figure 3: **Comparison of all-cause mortality between sulfonylureas using direct and indirect evidence**

Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 18 studies.[3,34-37,39,50,51,53,58,61-68]

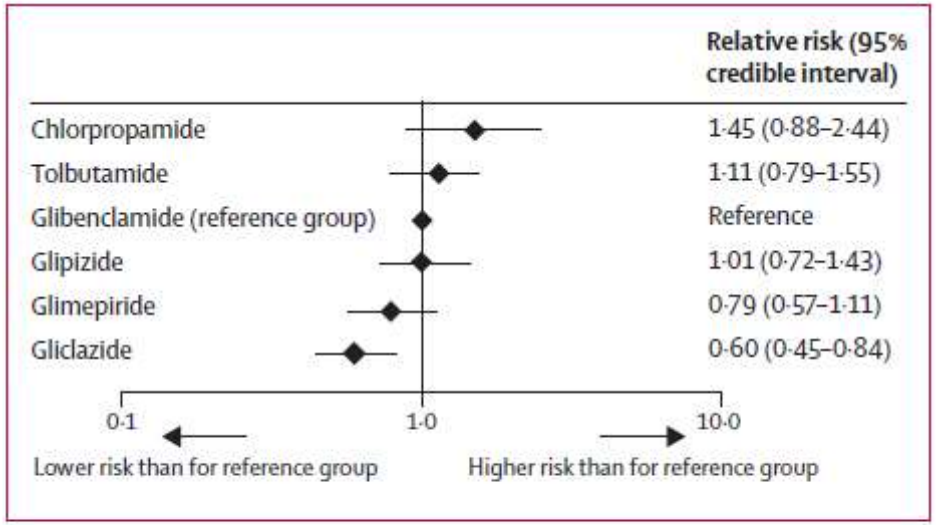


Figure 4: **Comparison of cardiovascular-related mortality between sulfonylureas using direct and indirect evidence**

Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 13 studies.[3,34,36,37,39,52,58,61,63,64,66-68]

Inhibiteurs de la DPP4 : faciles à prescrire… …mais PAS de bénéfice CV ou rénal

- **Etude SAVOR-TIMI 53 (saxagliptine) : effet neutre sur la mortalité cardiovasculaire. Augmentation significative des hospitalisations pour insuffisance cardiaque.**
- **Etude EXAMINE (alogliptine) : effet neutre sur la mortalité cardiovasculaire.**
- **Etude TECOS (sitagliptine) : effet neutre sur la mortalité cardiovasculaire.**
- **Etudes CARMELINA/CAROLINA (linagliptine) : effet neutre sur la mortalité cardiovasculaire.**
- **Vildagliptine : pas d'étude.**

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**
- **Ertugliflozine (Steglatro) : 5 mg 1x/j**

Formes combinées avec metformine, metformine XR ou inhibiteur DPP4 disponibles.

Steglatro®
(ertugliflozin)

Effets des iSGLT2 sur la sécurité cardiovasculaire dans le diabète de type 2

Réduction du risque (IC à 95%) NNT	MACE	Décès CV	Insuffisance cardiaque	Reins Critère d'évaluation comb.	Mortalité globale	Durée d'étude (années)
EMPA-REG Empagliflozine	**0.86** (0.74, 0.99) **NNT 63**	**0.62** (0.49, 0.77) **NNT 45**	**0.65** (0.50,0.85) **NNT 71**	**0.54** (0.40, 0.75) **NNT 71**	**0.68** (0.57, 0.82) **NNT 38**	3.1
CANVAS/R Canagliflozine	**0.86** (0.75, 0.97) **NNT 94**	**0.87** (0.72 1.06)	**0.67** (0.52 0.87) **NNT 86**	**0.60** (0.47, 0.77) **NNT 83**	**0.87** (0.74, 1.01)	3.4
DECLARE-TIMI Dapagliflozine	**0.93** (0.84, 1.03)	**0.98** (0.82 1.17)	**0.73** (0.61 0.88) **NNT 125**	**0.53** (0.43, 0.66) **NNT 40**	**0.93** (0.82 1.04)	4.2
VERTIS CV Ertugliflozine	**0.97** (0.85, 1.11)	**0.92** (0.77, 1.11)	**0.70** (0.54 0.90) **NNT 91**	**0.81** (0.64, 1.03)	**0.93** (0.80, 1.08)	3.5

L'efficacité des iSGLT2 sur la réduction de la glycémie (et donc de l'HbA1c) diminue lorsque l'**eGFR est <45 ml/min**.
Par contre, la **protection cardiovasculaire et rénale** persiste lorsque l'eGFR est <45 ml/min.

Acidocétose euglycémique sous iSGLT2

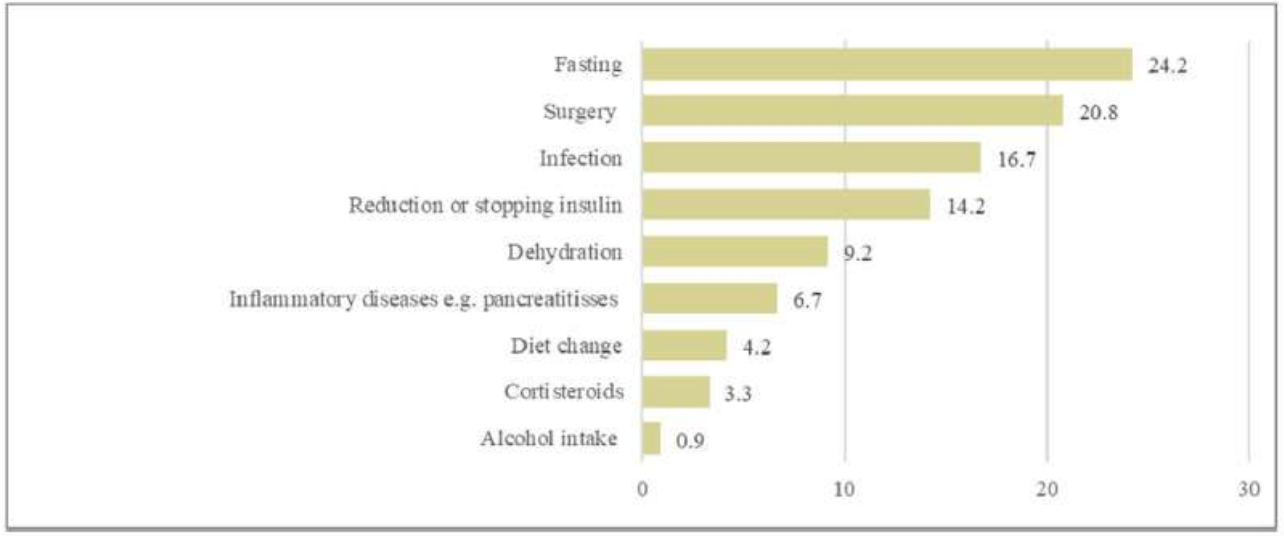


Fig. 1. Frequency (%) of conditions associated with euDKA in patients with T2DM treated with SGLT2i.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 102275

TABLEAU 3 **Situations à risque d'acidocétose euglycémique**

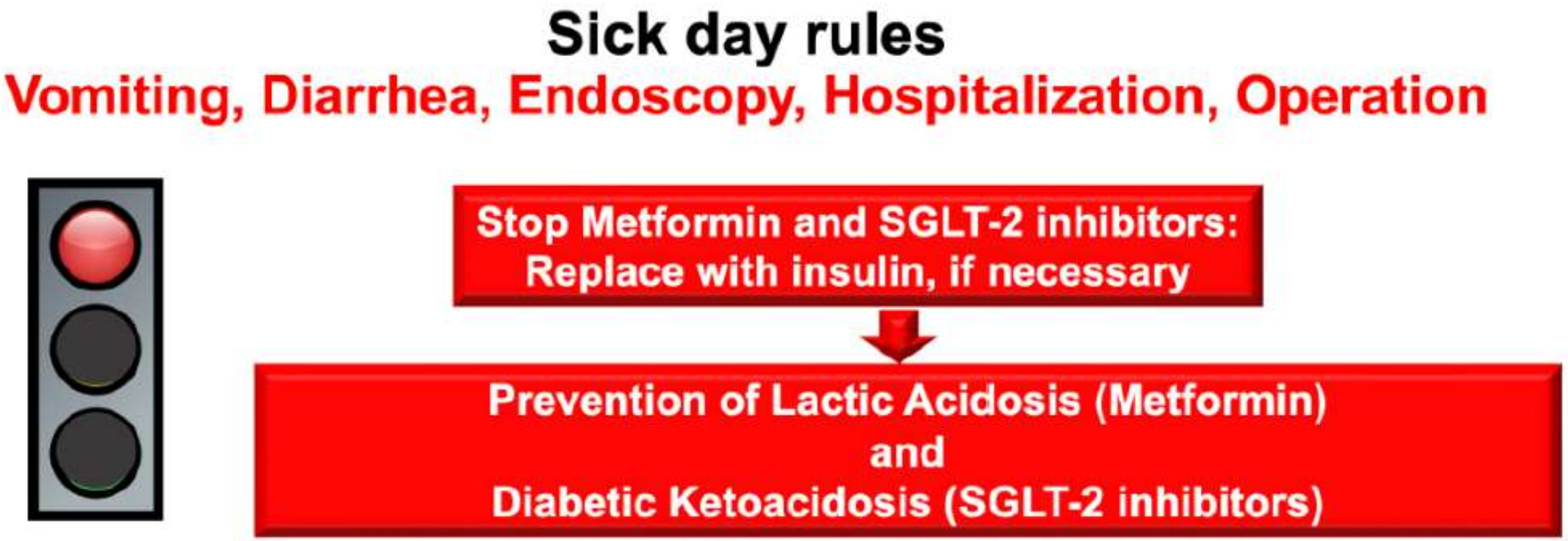
Gestion des iSGLT2 lors de situation à risque de favoriser la survenue d'une acidocétose euglycémique.
[a]Basé empiriquement sur 5 demi-vies.
iSGLT2: inhibiteurs du sodium-glucose de type 2.

Situation	Arrêt du traitement	Reprise du traitement
Chirurgie élective	3 jours avant l'intervention[a]	Dès la stabilisation du patient, reprise d'une alimentation et d'une hydratation orales
Chirurgie urgente/ hospitalisation pour affection aiguë	À l'admission	Dès la stabilisation du patient, reprise d'une alimentation et d'une hydratation orales
État fébrile	Dès le début des symptômes	Dès la résolution des symptômes
Vomissements, diarrhées, diminution de la prise alimentaire	Dès le début des symptômes	Dès la résolution des symptômes, reprise d'une alimentation et d'une hydratation orales
Exercice physique intense (par exemple, marathon)	3 jours avant l'événement[a]	24 heures après l'événement

Rev Med Suisse 2021; 17: 1072-7

Quand arrêter certains traitements?

Figure 5: Sick day rules [63-65].



Risk Factors

Ketoacidosis with SGLT2-inhibitors:

Insulin deficiency during operation, endoscopy, fasting, vomiting, diarrhea

If on insulin: continue insulin and stop SGLT-2 inhbitors immediately

Lactic Acidosis with Metformin:

Main risk factor is chronic kidney disease (eGFR < 30 ml/min) with dehydration

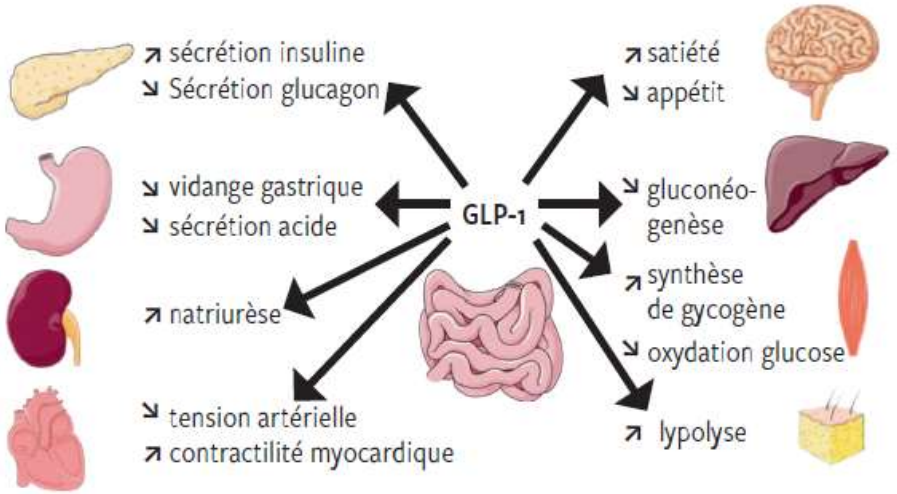
heart failure, lung disease, old age

Swiss Med Wkly. 2023;153:40004

Agonistes du récepteur du GLP-1

- **Exenatide (Byetta) : 5-10 µg 2x/j**
- **Liraglutide (Victoza) : 0.6, 1.2 ou 1.8 mg 1x/j (titration)**
- **Exenatide LAR (Bydureon) : 2 mg 1x/sem**
- **Dulaglutide (Trulicity) : 0.75 ou 1.5 mg 1x/sem**
- **Semaglutide (Ozempic) : 0.25, 0.5 (titration) puis 0.5-1.0 mg 1x/sem**
- **Semaglutide oral (Rybelsus) : 3, 7 (titration) puis 7 ou 14 mg/j**

FIG 1 Actions systémiques du GLP-1



Rev Med Suisse 2019; 15: 1117-23

Effets des analogues du GLP-1 sur la sécurité cardiovasculaire dans le diabète de type 2

Uniquement AR GLP-1 humain	MACE	Décès CV	Apoplexie	Reins Critère d'évaluation comb.	Mortalité globale	Durée d'étude (années)
LEADER Liraglutide	**0.87** (0.78, 0.99) **NNT 53**	**0.78** (0.66, 0.93) **NNT 77**	**0.86** (0.71 1.06)	**0.54** (0.67, 0.82) **NNT 67**	**0.85** (0.74, 0.97) **NNT 71**	3.8
SUSTAIN Sémaglutide	**0.74** (0.58, 0.95) **NNT 30**	**0.98** (0.65 1.48)	**0.61** (0.38 0.99) **NNT 91**	**0.64** (0.47, 0.77) **NNT 43**	**1.05** (0.74, 1.50)	2.1
REWIND Dulaglutide	**0.88** (0.79, 0.99) **NNT 71**	**0.91** (0.78 1.06)	**0.76** (0.62 0.94) **NNT 111**	**0.85** (0.77, 0.93) **NNT 40**	**0.90** (0.80 1.01)	5.4
PIONEER Sémaglutide **oral**	**0.79** (0.57, 1.11)	**0.49** (0.27, 0.92) **NNT 100**	**0.74** (0.35 1.57)	**nc**	**0.51 (0.31, 0.84) NNT 71**	1.3

Pour mémoire, les différents type d'insulines

Pharmacokinetics of commonly used insulin preparations

(A) Prandial insulin			
Insulin type	**Approximate onset of action**	**Effective peak**	**Approximate duration of action***
Lispro, lispro-aabc, aspart, faster aspart, glulisine¶	15 to 30 minutes	1 to 3 hours	4 to 6 hours
Regular	30 minutes	1.5 to 3.5 hours	8 hours
(B) Basal insulin			
Insulin type	**Half-life△**	**Effective peak**	**Approximate duration of action***
NPH	4.4 hours	4 to 6 hours	12 hours
Insulin glargine			
U-100	12 hours	No pronounced peak	20 to >24 hours
U-300	19 hours	No pronounced peak	20 to >24 hours
Insulin detemir	5 to 7 hours	3 to 9 hours	6 to 24 hours◇
Insulin degludec (U-100, U-200)	25 hours	No pronounced peak	>24 hours

* Glucose-lowering action may vary considerably in different individuals or within the same individual; the duration of action is dose dependent.

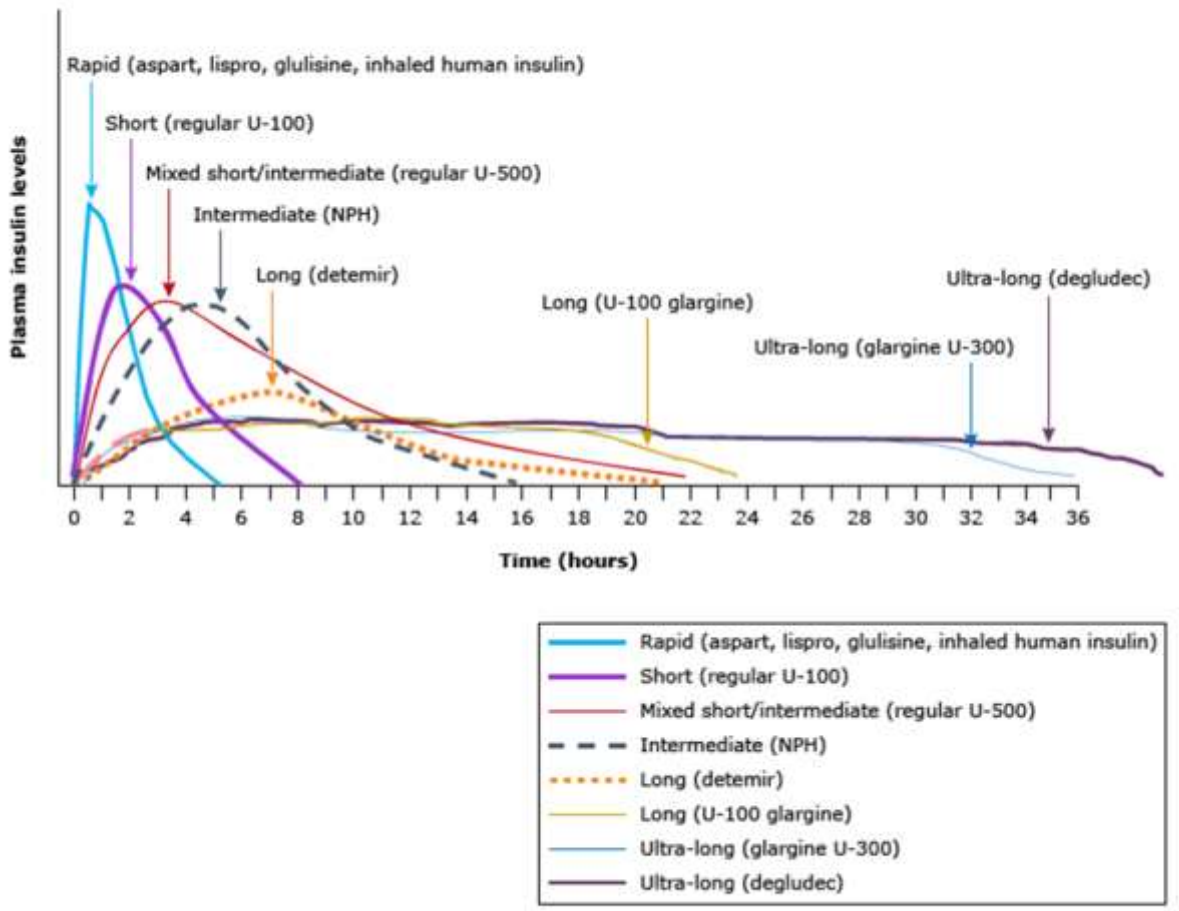
¶ Lispro-aabc and faster aspart have quicker pharmacokinetic profiles than standard lispro and aspart.

△ In general, it takes 4 half-lives to reach steady state. Dose adjustments should not be made until after steady state is achieved.

◇ At higher doses (≥0.8 units/kg), mean duration of action is longer and less variable (22 to 23 hours).

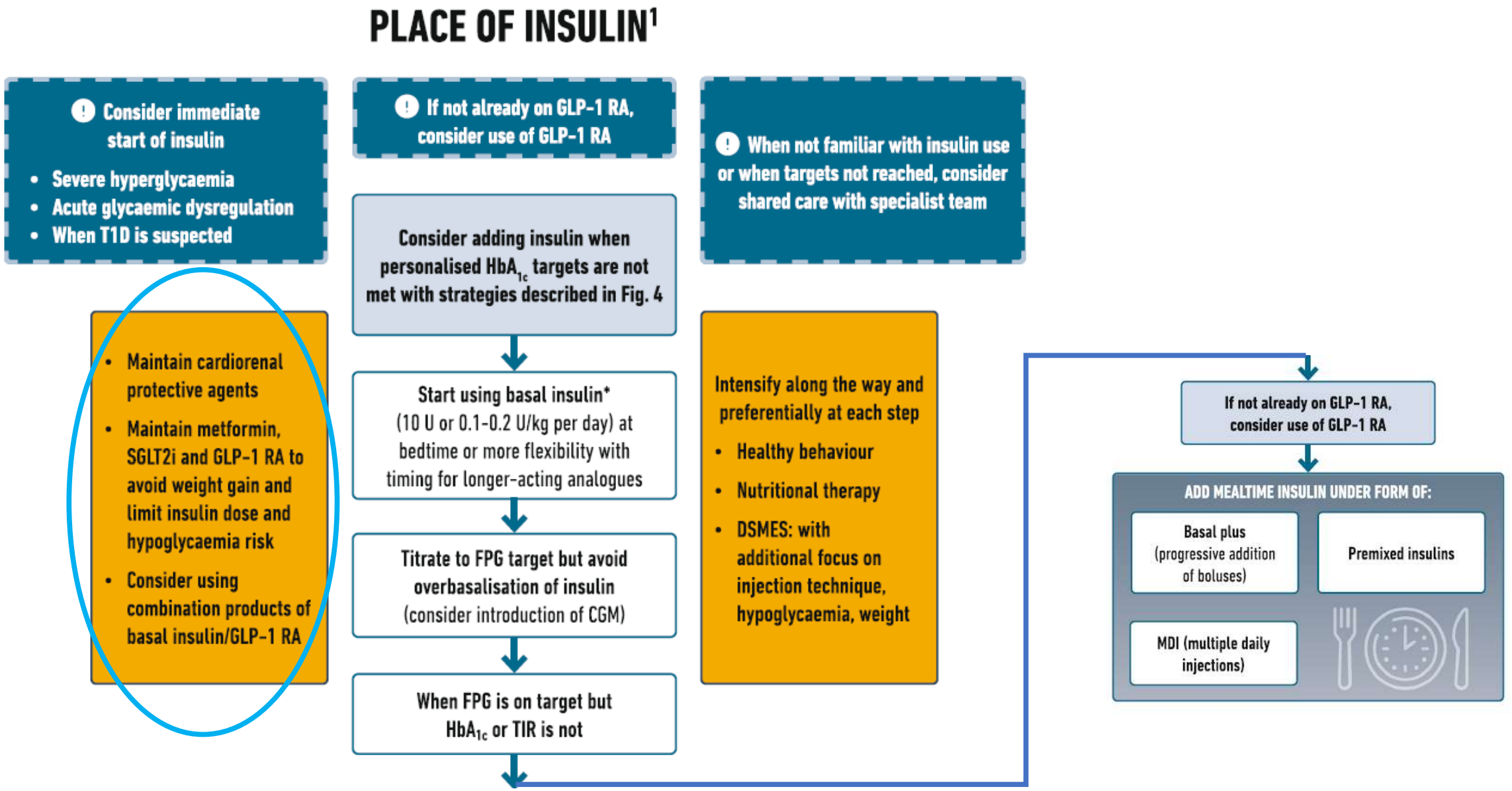
UpToDate®

Pharmacokinetic profile of currently available single insulin products



NPH: neutral protamine hagedorn.

Insuline : oui, si nécessaire, mais favoriser les alternatives



Diabetologia
https://doi.org/10.1007/s00125-022-05787-2

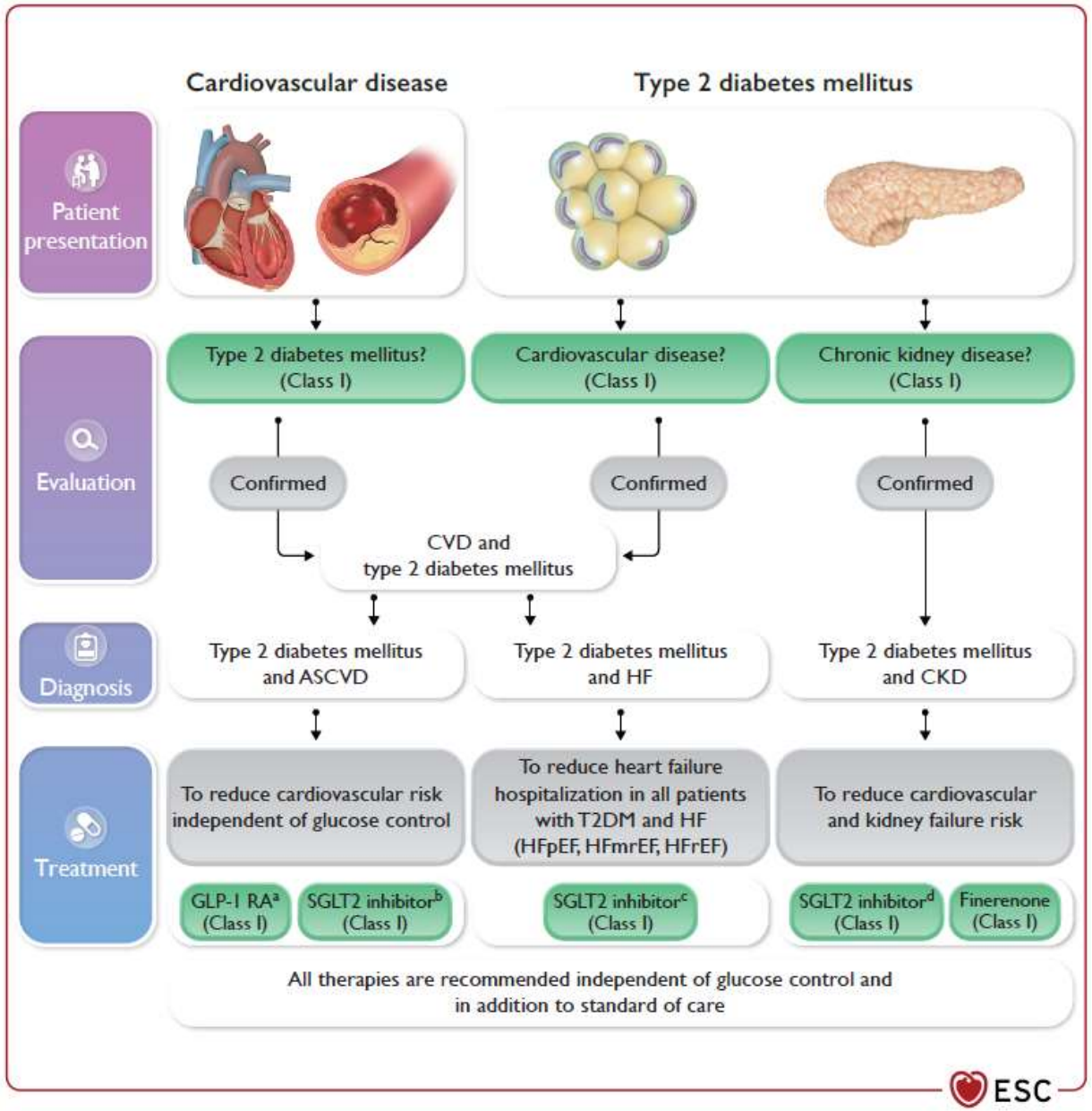
Les nouvelles recommandations 2023 de l'ESC

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

European Heart Journal (2023) **00**, 1–98
https://doi.org/10.1093/eurheartj/ehad192

Les nouvelles recommandations 2023 de l'ESC



Association GLP-1 RA et iSGLT2

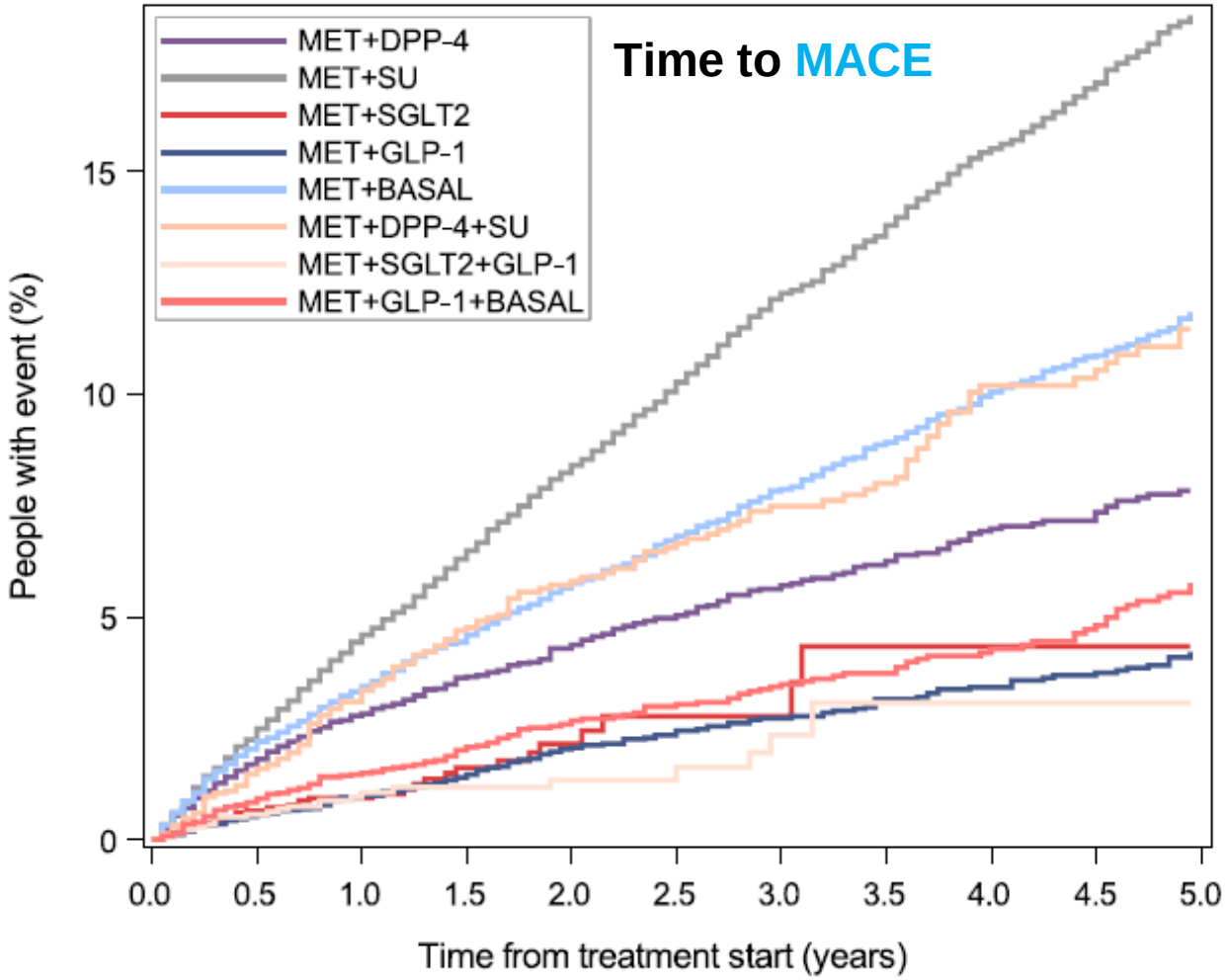
Risk of Major Adverse Cardiovascular Events, Severe Hypoglycemia, and All-Cause Mortality for Widely Used Antihyperglycemic Dual and Triple Therapies for Type 2 Diabetes Management: A Cohort Study of All Danish Users

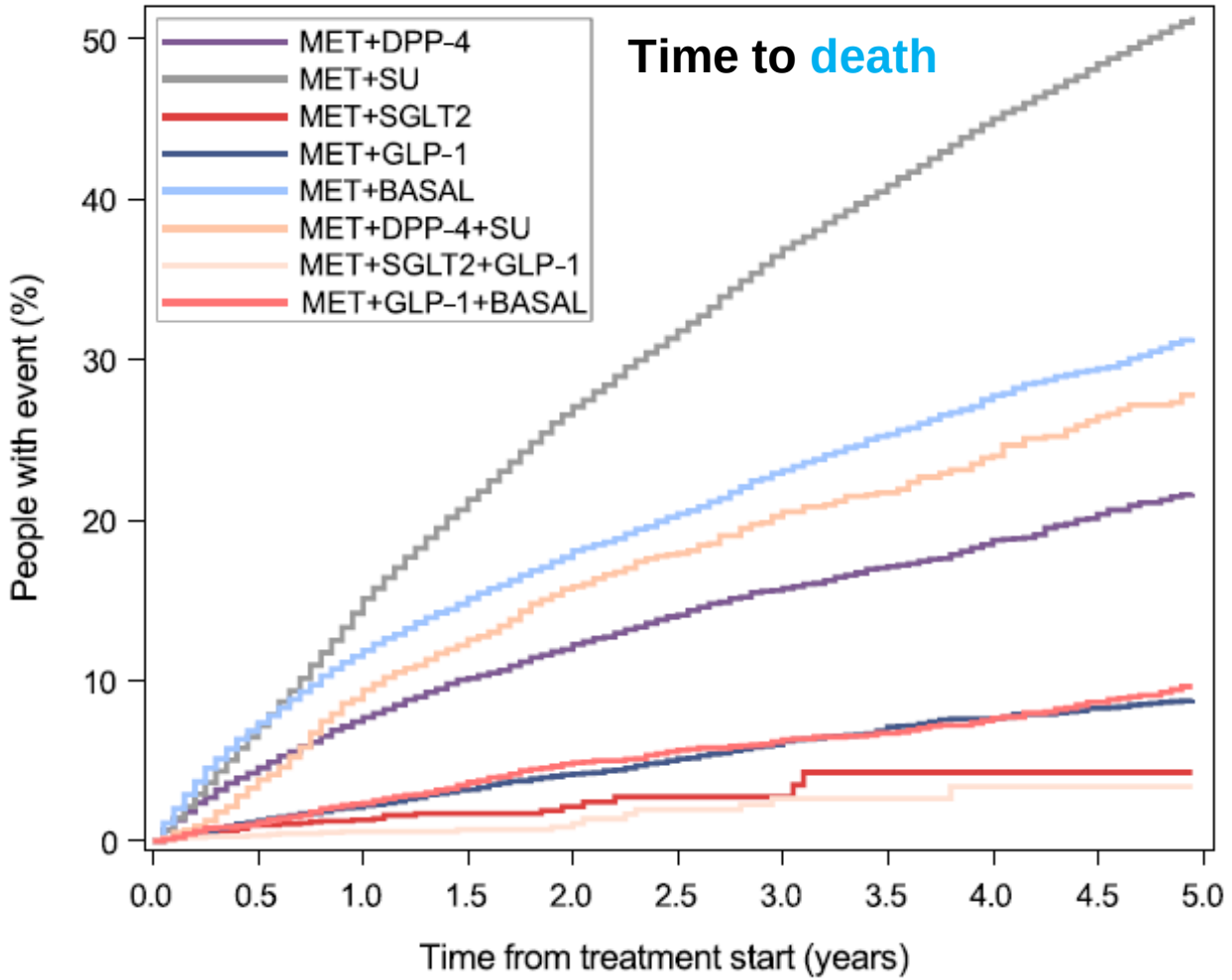
Morten Hasselstrøm Jensen,[1,2] Mads Kjolby,[3,4,5,6] Ole Hejlesen,[2] Poul Erik Jakobsen,[1,7] and Peter Vestergaard[1,7,8]

https://doi.org/10.2337/dc19-2535

Diabetes Care Publish Ahead of Print, published online April 1, 2020

Association GLP-1 RA et iSGLT2





En résumé

Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events

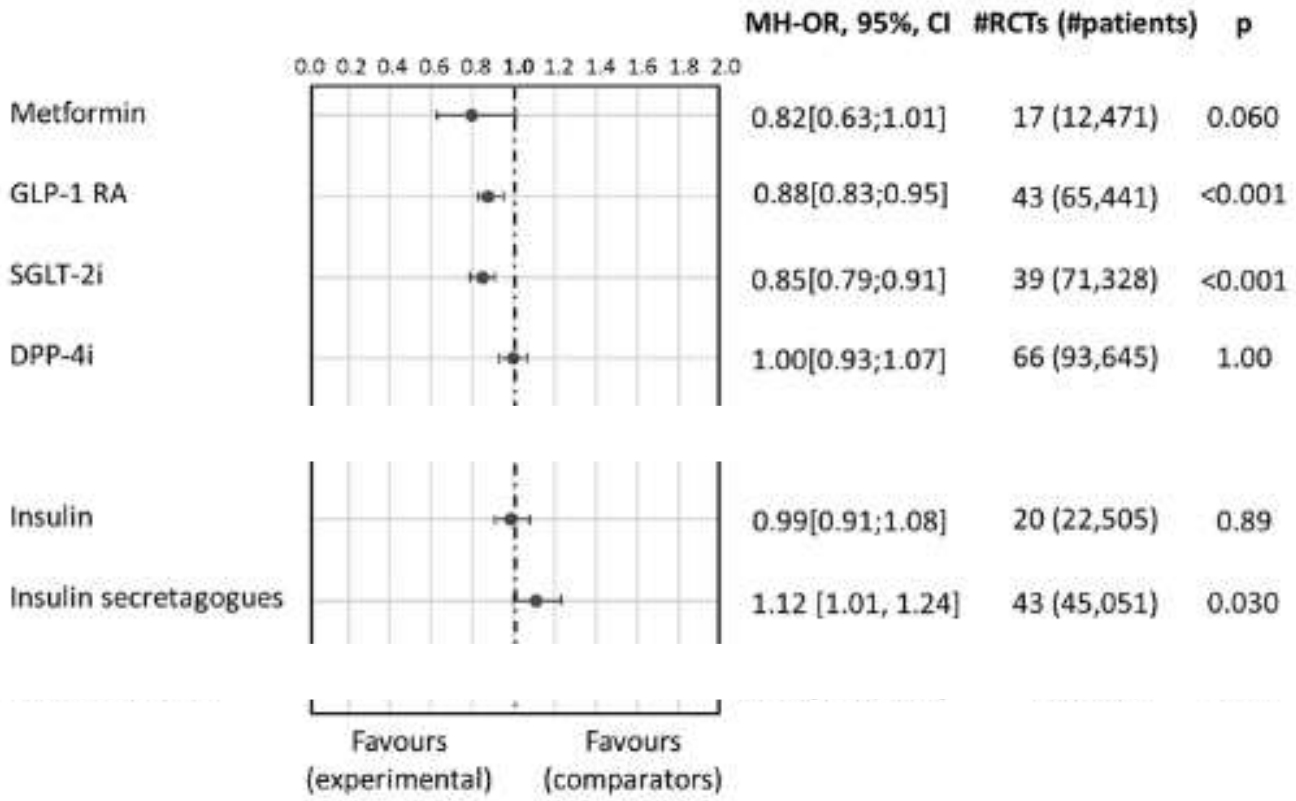


FIGURE 1 Effects of different classes of drugs on the risk of all-cause mortality (MH-OR, 95% CI: Mantel-Haenszel odds ratio with 95% confidence intervals). DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonists; RCT, randomized controlled trials; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Diabetes Obes Metab. 2023;25:444–453.

En résumé

Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events

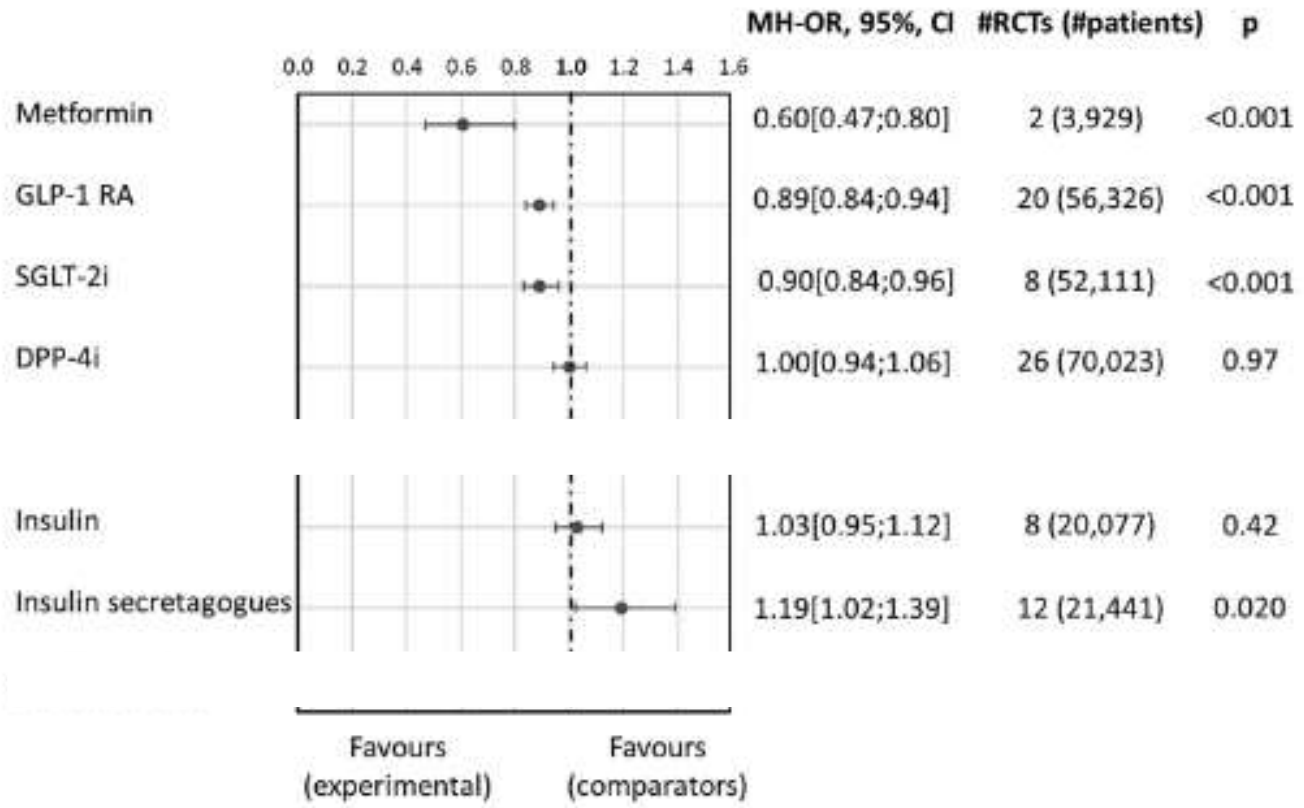


FIGURE 2 Effects of different classes of drugs on the risk of 3-point major adverse cardiovascular events (MH-OR, 95% CI: Mantel-Haenszel odds ratio with 95% confidence intervals). DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonists; RCT, randomized controlled trials; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Diabetes Obes Metab. 2023;25:444–453.

En résumé

Table 2—Considerations for selecting glucose-lowering agents in patients with T2D and CKD (2,17)

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

[a]Benefit supported by primary and secondary outcome data. [b]Benefit supported by secondary outcome data. [c]Benefit or risk is agent specific. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

Diabetes Care 2022;45:3075–3090

En conclusion

- **Les analogues du GLP-1 (à initier seulement en cas d'IMC ≥ 28 kg/m^2) et inhibiteurs du SGLT2 présentent un avantage en cas de maladie cardiovasculaire avérée, d'insuffisance cardiaque et/ou d'atteinte rénale et représentent dès lors des médicaments de 2ème ligne après la metformine.**

- **La combinaison analogues du GLP-1/inhibiteurs du SGLT2 ne peut pas se faire, en principe, sans demande préalable à l'assurance maladie. Cependant, cette combinaison représente le futur de la prise en charge de nos patients diabétiques.**

- **La prise en charge actuelle du diabète s'intéresse à la prévention complications et n'est plus uniquement glucocentrique.**

Merci de votre attention!

Montée à la Jungfrau (4158 m), 10.09.2023

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