Dernières recommandations pour le traitement du diabète:

Quelles nouveautés pour la personne âgée?

Prof Anne Wojtusciszyn
Médecin Adjoint, Service EDM, CHUV

Diabètes du sujet âgé

- ¼ des patients de plus de 65 ans ont un diabète et la moitié sont pré-diabétiques

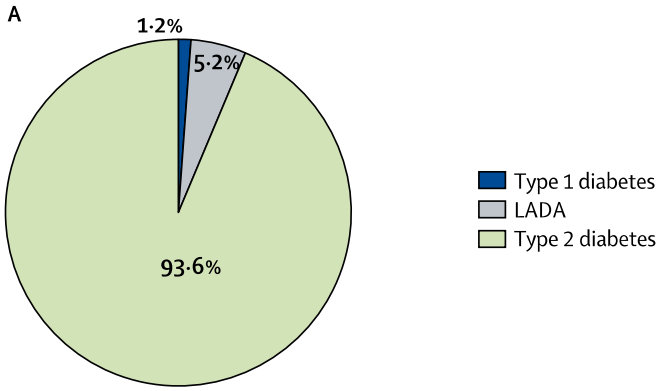
- Formes très différentes de diabètes
  - Diabète récent, non compliqué
  - Diabète de découverte récente, déjà compliqué
  - Diabète ancien, insulinorequérant, compliqué
  - Diabète de type 1 … ancien et insulino**dépendant**

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

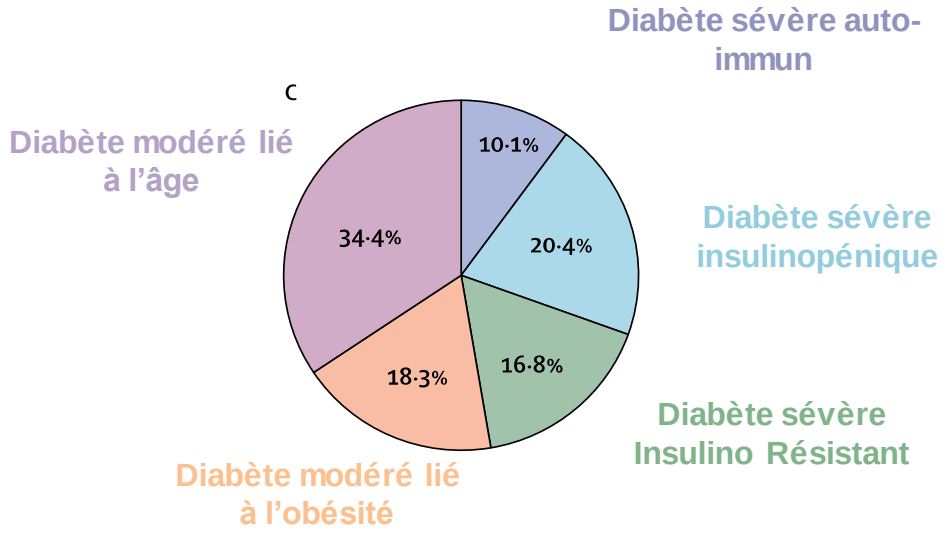
Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*

Lancet Diabetes Endocrinol 2018; 6: 361–69

Vision habituelle de la classification des diabètes

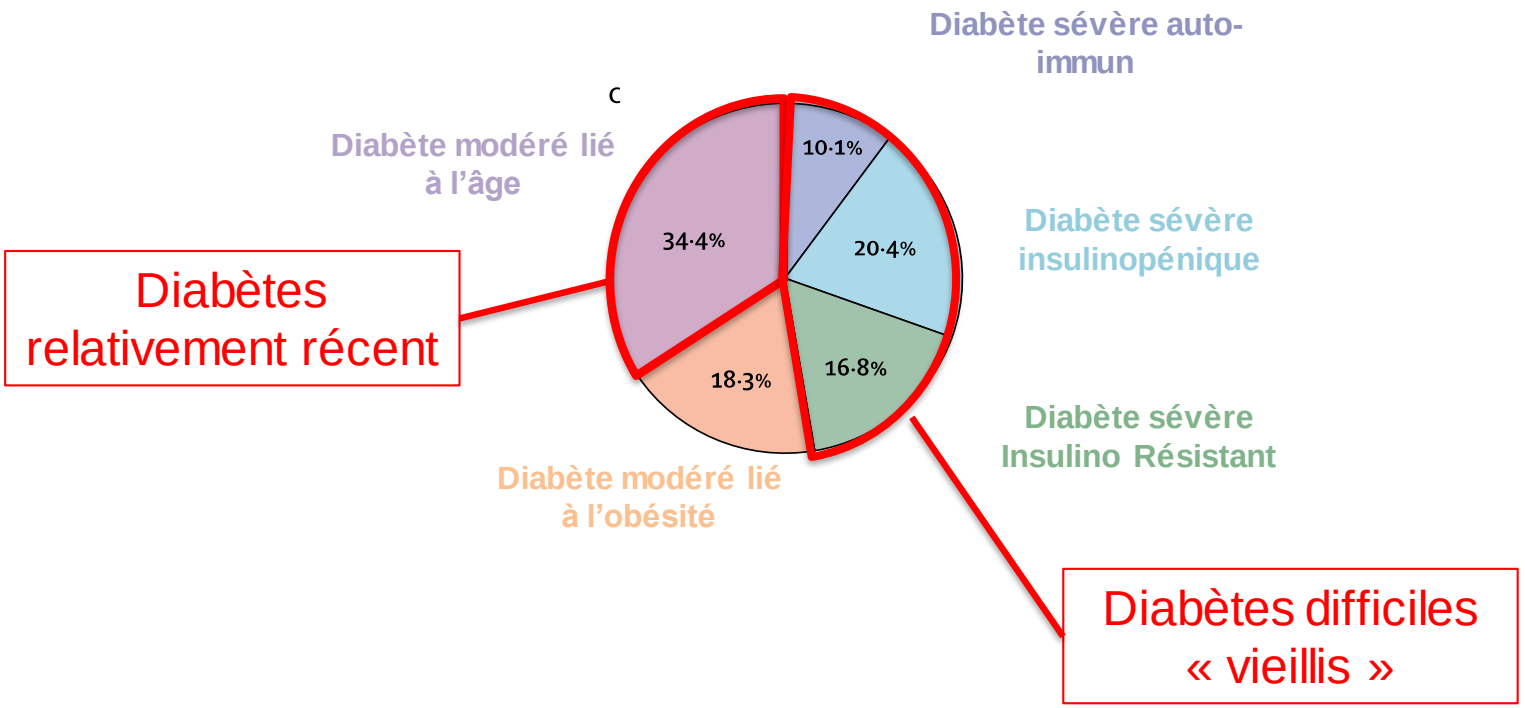


Vision récente de la classification des diabètes



- Environ 30% de diabètes insulino-prives → insulinothérapie personnifiée
- Environ 20% de diabètes insulino-résistants → Pas d'insulinothérapie si possible et risque de complication secondaires CV élevées
- Le diabète lié au vieillissement est le plus fréquent. Il est plus facile à traiter. Cependant, mal traité il expose au même risque de complications

Diabètes du sujet âgé



Diabètes du sujet âgé

- ¼ des patients de plus de 65 ans ont un diabète et la moitié sont pré-diabétiques

- Formes très différentes de diabètes
  - Diabète récent, non compliqué
  - Diabète de découverte récente, déjà compliqué
  - Diabète ancien, insulinorequérant, compliqué
  - Diabète de type 1 … ancien et insulino**dépendant**

- Présentation très différentes de nos séniors:
  - De l'hyperactif indépendant → la personne dépendante ou en fin de vie…

Particularités de la prise en charge

- **Attention particulière**
  - Aux ATCD d'hypoglycémie: très haut risque de récidive
  - Aux pieds → mobilité
  - Au déclin cognitif→ évaluation annuelle
  - Au statut nutritionnel
  - Aux personnes ressources
  - Aux autres FDR CV: LDL, tabac, HTA…

- **Pour le choix thérapeutique**
  - Hypos
  - Poids
  - Cardiovasculaire
  - Rein

… mais aussi
- **état de santé/ espérance de vie**
- **comorbidité**
- antécédents
- choix du patient

L'échelle clinique de fragilité

1. Very fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. Managing well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5. Mildly frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and

6. Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7. Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

Impact du diabète chez la personne âgée

- Le diabète augmente le risque de …

… mort prématurée
… déficit fonctionnel, perte musculaire, fractures
… AVC, HTA, maladie coronarienne
… déficit cognitif
… dépression
… douleur chronique
… infections

et fragilise une personne potentiellement déjà fragile

Effet du contrôle glycémique sur les complications micro et macrovasculaires

Aggregate Endpoint		**1997**	**2007**
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction

Holman. N Eng J Med 2008; 359

Objectifs d'HbA1c chez la personne âgée

- Pour les personnes âgées, la cible d'HbA1c est plus large

Patients > 65 ans en bonne santé
- Peu de comorbidités
- Fonction cognitives intactes
- Esp vie > 15 ans

Objectifs < 7,5%

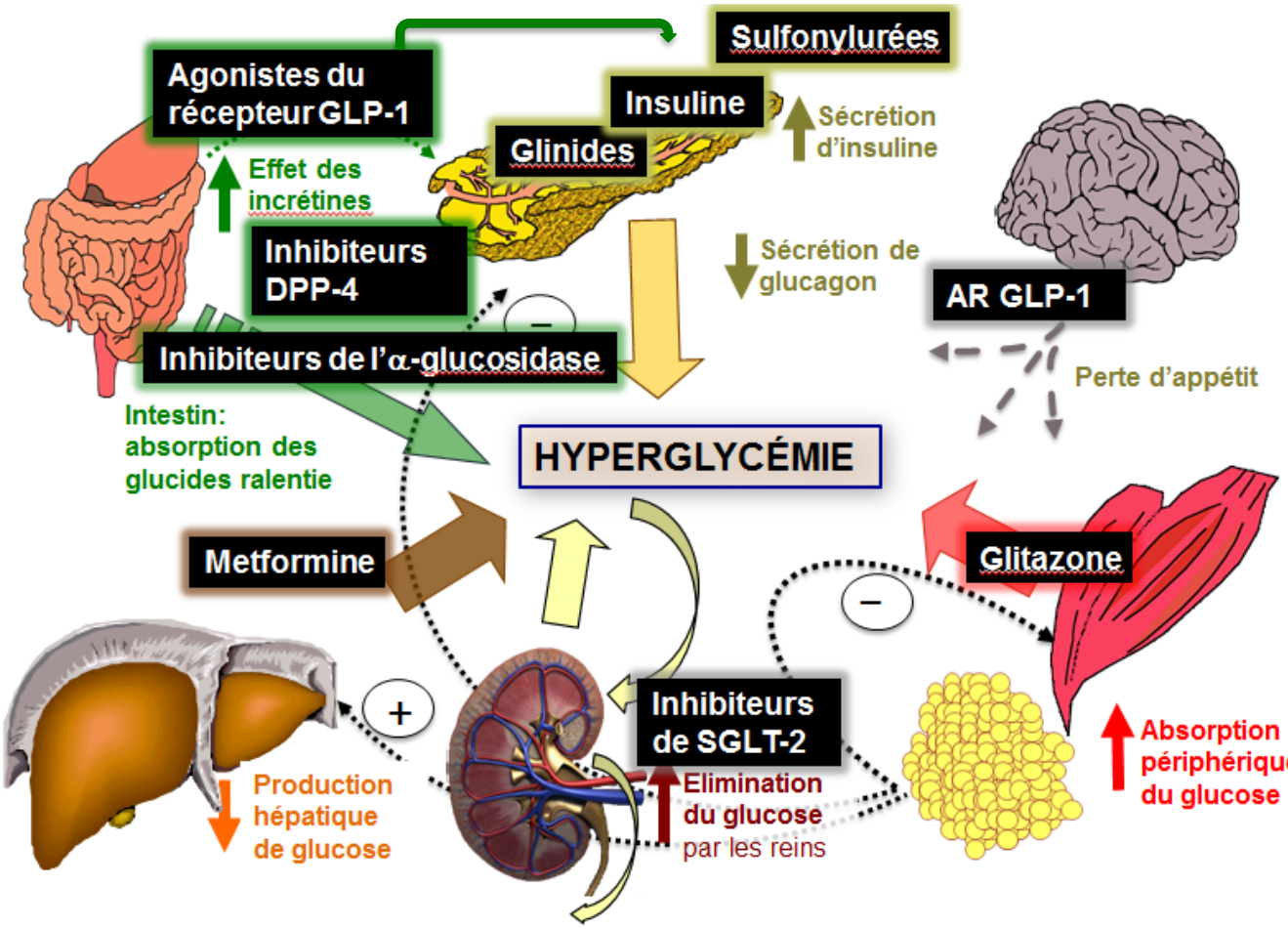
Patients âgés plus complexe
- Comorbidités plus nombreuses
- Fonction cognitives légèrement atteintes
- Esp vie 5-10 ans

Objectifs < 8%

Patients âgés dépendant
- En institution
- Espérance de vie limitée

Objectifs glycémiques: [5,5-11,1 mmol/L]

Mode d'action des antidiabétiques



Particularités de la prise en charge chez les plus fragiles

- **Attention à la tolérance des traitements:**
  - GLP-1 et vomissement/ perte de poids
  - SGLT2-I et deshydratation/ hypotension/ infection/ jeûne
    - Risque d'acido-cétose euglycémique
    - Risque d'amputation?
  - TZD et risque de fracture
  - Insuline (rapide) et risque d'hypoglycémies
  - NPH et risque d'hypoglycémies
  - Insuline ultra-lente (>30h de ½ vie) et accumulation IR

  ➢ **Favoriser**
    - ➢ **les drogues non hypoglycémiantes,**
    - ➢ **les insulines « plates », durée 24h max ou plus courtes, données le matin**
    - ➢ **Mais l'association basale/ DPPIV i n'a-t-elle pas fait long feu?**

Table 4—Advantages, disadvantages, and caveats in using glucose-lowering agents in LTC population

	Advantages	Disadvantages	Caveats in LTC population
Biguanides	• Low hypoglycemia risk	• Many contraindications in population with high comorbidity burden	• Can be used until estimated glomerular filtration rate is <30 mL/min/1.73 m^2
Metformin	• Low cost • Known side effects • Established safety record	• May cause weight loss or gastrointestinal upset in frail patients	• Extended release formulation has lower complexity and fewer gastrointestinal side effects • Assess for vitamin B_{12} deficiency
Sulfonylureas	• Low cost	• High risk of hypoglycemia • Glyburide has the highest risk of hypoglycemia and should be avoided	• Avoid if inconsistent eating pattern • Careful glucose monitoring during acute illness or weight loss • Consider discontinuing if already on substantial insulin dose (e.g., >40 units/day)
Meglitinides	• Short duration of action	• Can be held if patient refuses to eat	• Some risk of hypoglycemia • Increased regimen complexity due to multiple daily mealtime doses
TZDs	• Low hypoglycemia risk • Low cost • Can be used in renal impairment	• Many contraindications in population with high comorbidity burden	• Less concern for bladder cancer if shorter life expectancy
DPP-4 inhibitors	• Low hypoglycemia risk • Once-daily oral medication	• High cost • Lower efficacy	• Can be combined with basal insulin for a low complexity regimen
SGLT2 inhibitors	• Low hypoglycemia risk	• High cost • Limited evidence in LTC population	• Watch for increased urinary frequency, incontinence, lower blood pressure, genital infections, and dehydration
GLP-1 agonists	• Low hypoglycemia risk • Once-daily and once-weekly formulation	• High cost • Injection	• Monitor for anorexia and weight loss
Insulin	• No ceiling effect • Many different types can be used to target hyperglycemia at different times of the day	• High risk of hypoglycemia • Matching carbohydrate content with prandial insulin if variable appetite	• Basal insulin combined with oral agents may lower postprandial glucose while reducing hypoglycemia risk and regimen complexity • Continue basal–bolus regimen in patients with type 1 or insulin-deficient type 2 diabetes

Diabetes Care 2019;42(Suppl. 1):S90–S102 | https://doi.org/10.2337/dc19-S009

Les recommandations récentes

Annals of Internal Medicine CLINICAL GUIDELINE

Pharmacologic Approaches to Glycemic Treatment of Type 2 Diabetes: Synopsis of the 2020 American Diabetes Association's Standards of Medical Care in Diabetes Clinical Guideline

Kacie Doyle-Delgado, DNP, APRN; James J. Chamberlain, MD; Jay H. Shubrook, DO; Neil Skolnik, MD; and Jennifer Trujillo, PharmD, CDCES, BC-ADM

Schweizerische Gesellschaft für Endokrinologie und Diabetologie
Société Suisse d'Endocrinologie et de Diabétologie
Società Svizzera d'Endocrinologia e da Diabetologia
Societad Svizra d'Endocrinologia e Diabetologia

Swiss Recommendations of the Society for Endocrinology and Diabetes (SGED/SSED) for the Treatment of Type 2 Diabetes Mellitus (2020)

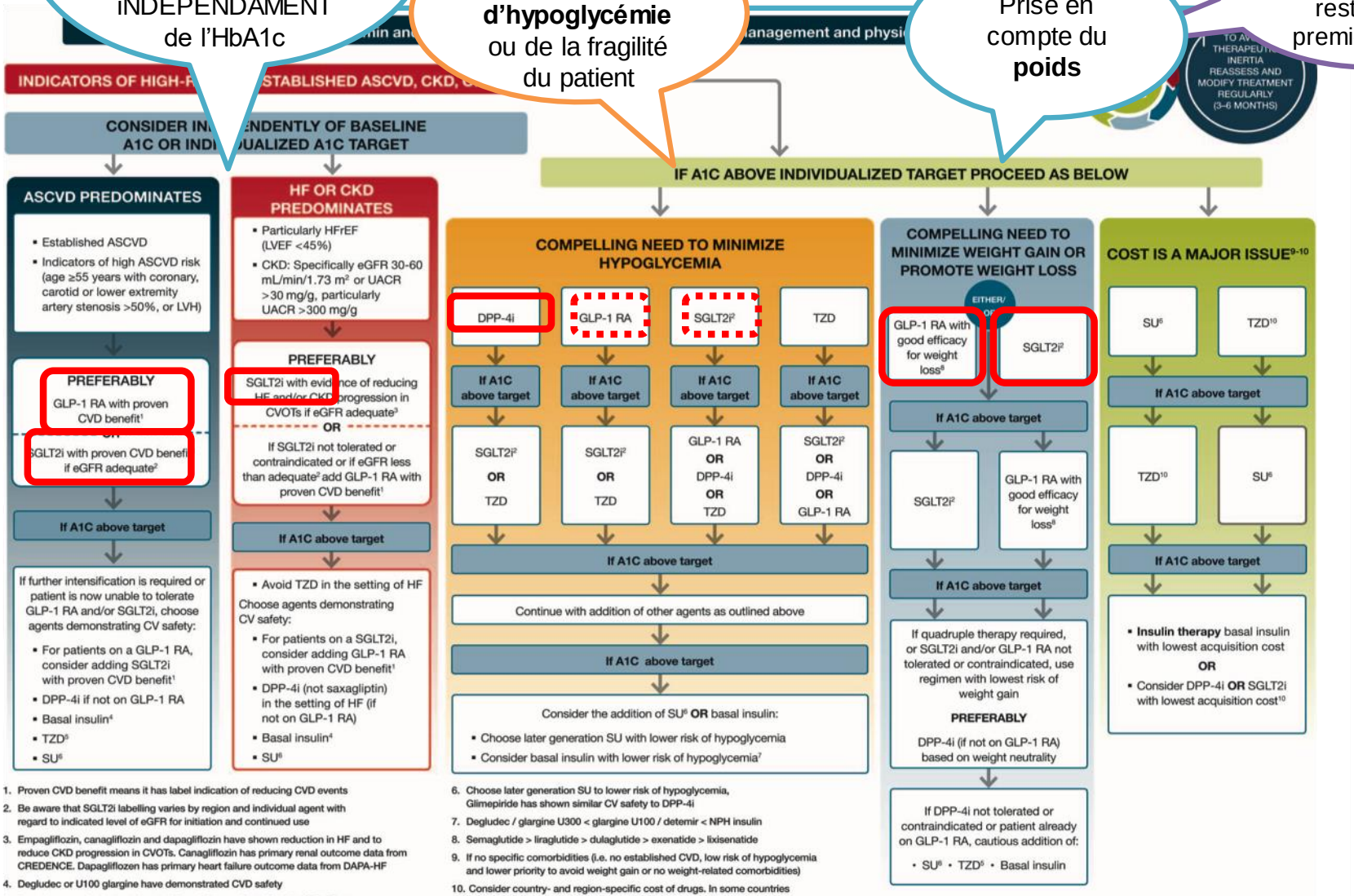
Les nouvelles recommandations internationales 2020-2021

La notion de **complications pré-existantes CV et rénales i**nfluence la PEC iNDEPENDAMENT de l'HbA1c

Prise en compte du **risque d'hypoglycémie** ou de la fragilité du patient

Prise en compte du **poids**

Les modifications du mode de vie et la metformine restent en première ligne

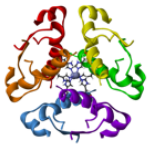


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries

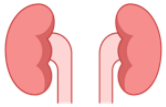
Les recos suisses

Important characteristics of Type 2 Diabetes
3 Questions

Insulin Deficiency?



Kidney function (e-GFR)?



Treatment or prevention of heart failure?

Motivation for Lifestyle Changes = very important
Multifactorial Treatment:
Hypertension, Lipids, Smoking cessation + Diabetes

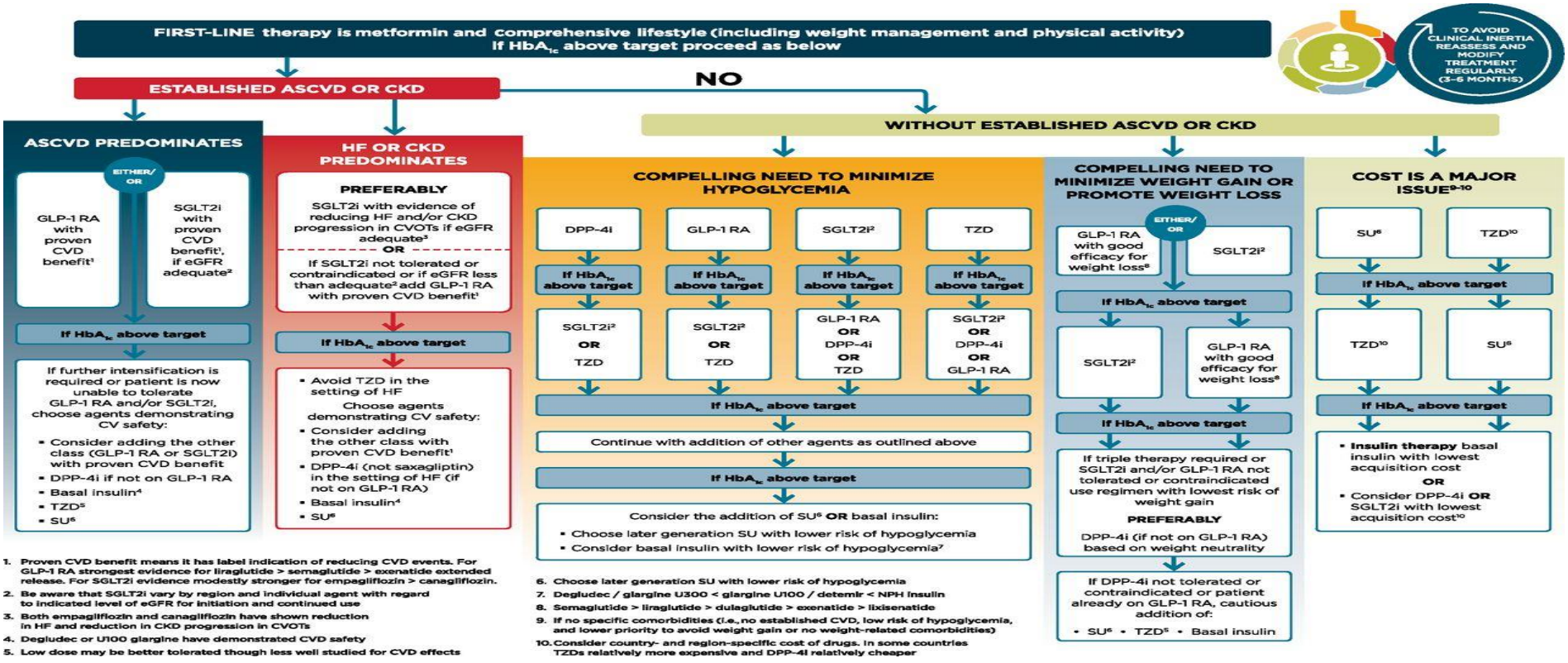
Metformin + SGLT-2 i.* → **+ GLP-1 RA/DPP-4 i.** → **+ Basal Insulin or Sulfonylurea (Gliclazide)**

Metformin + GLP-1 RA* → **+ SGLT-2 i.** → **+ Basal Insulin or Sulfonylurea (Gliclazide)**

Basal-Bolus Insulin or Premixed Insulin
continue with: Metformin, SGLT-2 i., GLP-1 RA
Stop: Sulfonylurea and DPP-4 inhibitor

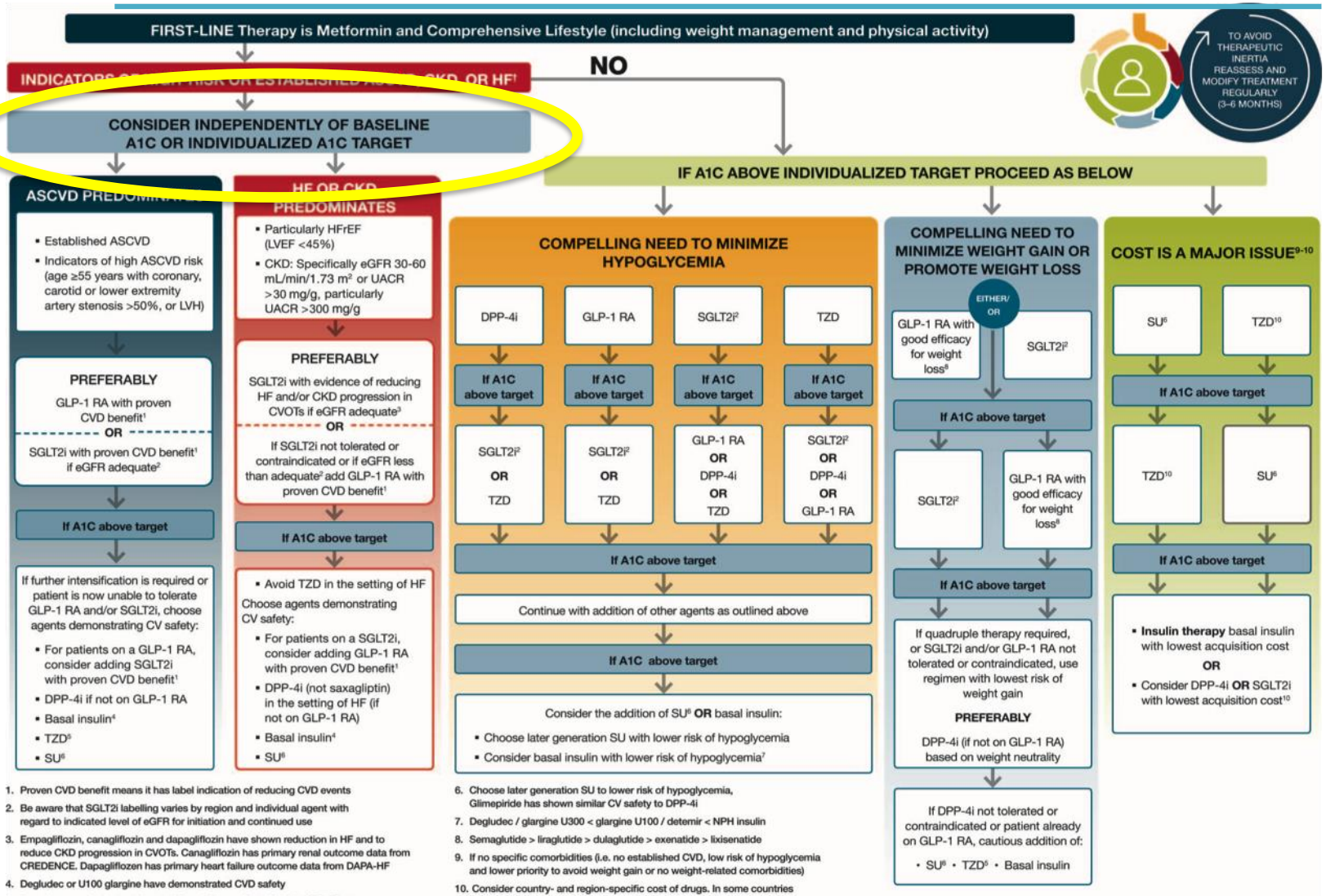
*In patients with low to moderate cardiovascular or no risk factors, you might consider the use of DPP-4 inhibitors or sulfonylureas (gliclazide preferred)

Les nouvelles recommandations internationales 2018-2019



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Les nouvelles recommandations internationales 2020-2021



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries

Objectifs thérapeutiques personnalisés

1. Very fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. Managing well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

- Prévenir les complications à long terme car longue espérance de vie
  - ➢ Suivi des recos selon profil

- Cibles
  - ➢ préprandiales: 5- 7,2mmol/L
  - ➢ au coucher: 5-8,3 mmol/L
  - ➢ TA: <140/90
  - ➢ statines: Oui

- Considérer une décroissance thérapeutique en cas d'hypoglycémie ou de dégradation des fonctions cognitives/ motrices

Objectifs thérapeutiques personnalisés

5. Mildly frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6. Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

- Prévenir les complications aigues, les chutes et les surinfections
  - ➢ Suivi des recos « risque d'hypos »

- Cibles
  - ➢ préprandiales: 5-8,3 mmol/L
  - ➢ au coucher: 5,6-10 mmol/L
  - ➢ TA: <140/90
  - ➢ Statines : oui en prévention secondaire, à discuter sinon

- Considérer une simplification thérapeutique si dégradation de l'état général, perte d'un aidant, difficulté à gérer une polymédication

Objectifs thérapeutiques personnalisés

7. Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

- Prévenir la déshydratation due à l'hyperglycémie majeure et les hypoglycémies/Hors reco

- Cibles
  - préprandiales: 5,6-10 mmol/L
  - au coucher: 6,1-11,1 mmol/L
  - TA: <150/90
  - Statines : non

- Considérer une <u>simplification thérapeutique,</u> reprise des schémas antérieurs à une hospitalisation, alléger la gestion des médicaments par ordre de priorité

Illustrations cliniques

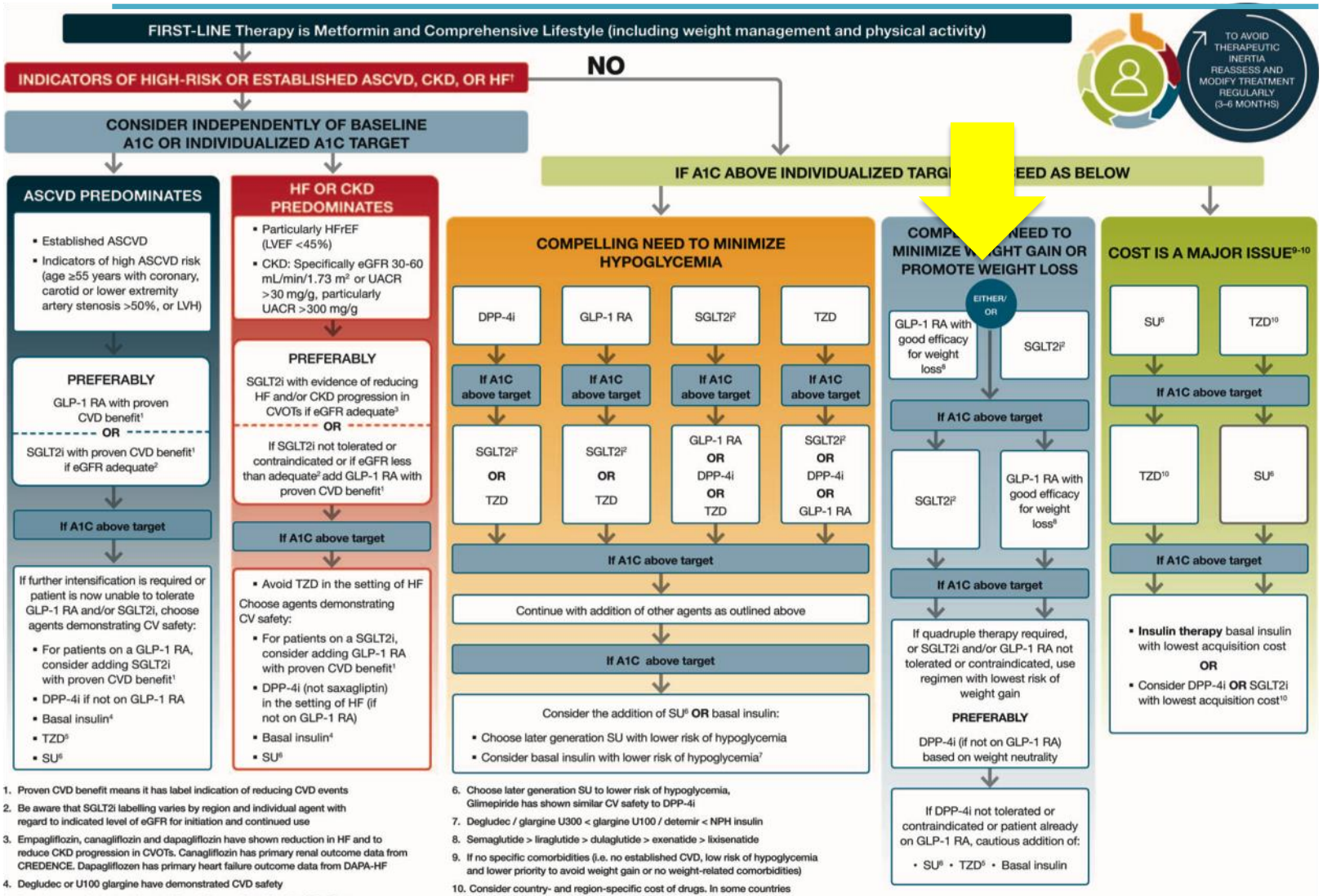
Illustration clinique n°1

Jean Daniel D. , 75 ans, bon vivant

- **Obésité** (Poids: 105, Taille 1,75, IMC 34,3kg/m2)

- Dépistage glycémie à jeun 8,35 mmol/L, HbA1c 8,6%, instauration de mesures hygiéno-diététiques et metformine il y a 4 mois
- **HbA1c actuelle 8,2 %**. Glycémies à jeun> 6mmol/L
- Pas d'antécédent médical notoire hormis **antécédent de balanite** lors de la découverte du diabète

Les nouvelles recommandations internationales 2020-2021



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries

Illustration clinique n°1

Jean Daniel D. , 75 ans, bon vivant

- **Obésité** (Poids: 105, Taille 1,75, IMC 34,3kg/m2)
- Dépistage glycémie à jeun 8,35 mmol/L, HbA1c 8,6%, instauration de mesures hygiéno-diététiques et metformine il y a 4 mois
- **HbA1c actuelle 8,2 %**. Glycémies à jeun> 6mmol/L
- Pas d'antécédent médical notoire hormis **antécédent de balanite** lors de la découverte du diabète

RHD+METFORMINE

+

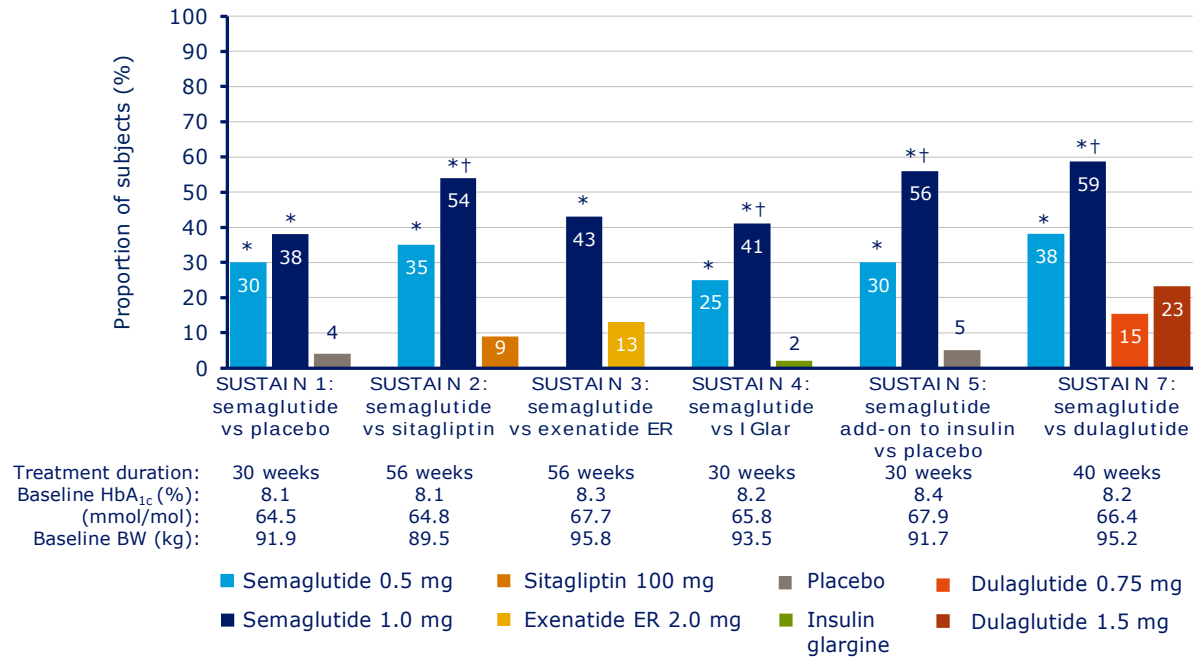
GLP1-RA

+

Insuline basale | SU courte durée d'action

Efficacité sur le poids des différents antidiabétiques

Figure 3. Proportion of subjects achieving the clinically meaningful outcome of HbA_{1c} reduction ≥ 1.0% and weight loss ≥ 5.0% (SUSTAIN 1–5 and 7)



*p<0.0001 vs comparator; †p<0.0001 vs semaglutide 0.5 mg. SUSTAIN 7 results based on an exploratory analysis. BW, body weight; exenatide ER, exenatide extended release

Semaglutide> liraglutide> dulaglutide > exenatide> lisixenatide

Rodbard H., Endocrine Pract 2019

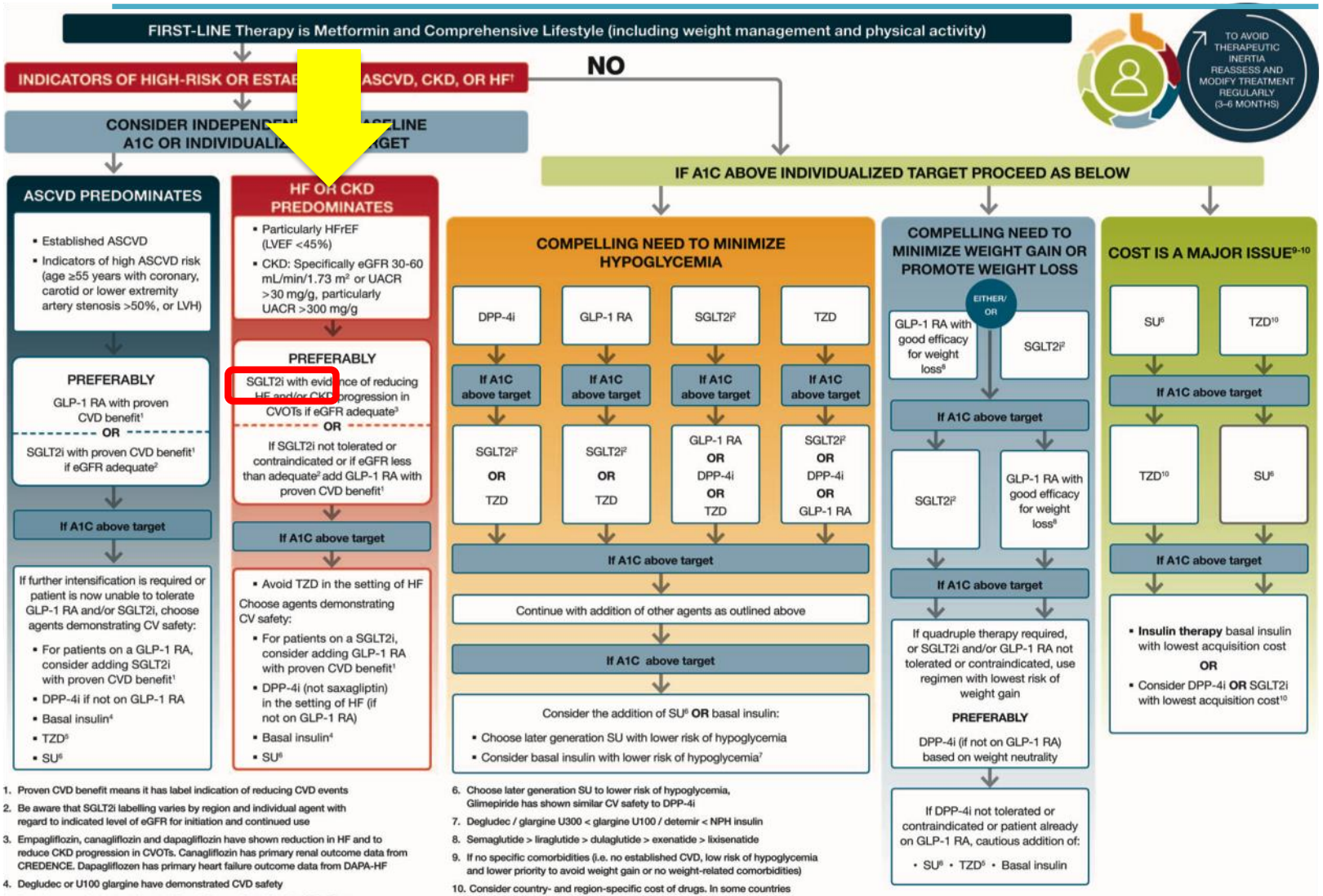
Illustration clinique n°2’

Diego M. , 73 ans

- Surpoids, IMC 26kg/m2
- Dépistage glycémie à jeun 9,35 mmol/L, HbA1c **8,8**%,
- Instauration de mesures hygiéno-diététiques et metformine il y a 3 mois
- HbA1c actuelle à **7,2**%
- Antécédents d’insuffisance rénale avec DFG à 59 ml/min avec **macroalbuminurie**

RHD+METFORMINE 1/2

Les nouvelles recommandations internationales 2020-2021



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries

Illustration clinique n°2’

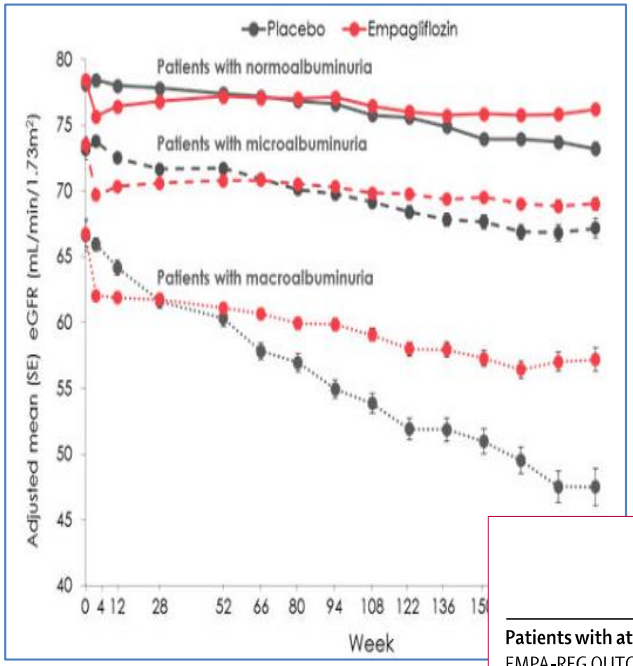
Diego M. , 73 ans

- Surpoids, IMC 26kg/m2
- Dépistage glycémie à jeun 9,35 mmol/L, HbA1c **8,8**%,
- Instauration de mesures hygiéno-diététiques et metformine il y a 3 mois
- HbA1c actuelle à **7,2**%
- Antécédents d’insuffisance rénale avec DFG à 59 ml/min avec **macroalbuminurie**

RHD+METFORMINE 1/2 + SGLT2-I + DPP-4I ou GLP1 RA

SGLT-2 I: rôle sur la fonction glomérulaire?

EMPA



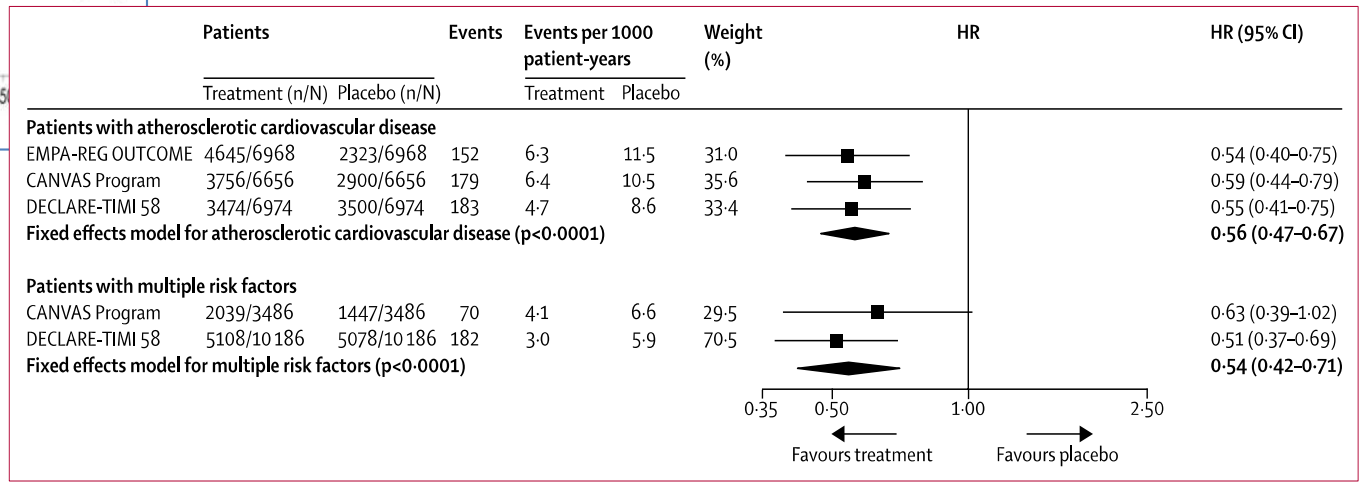


Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease

Cherney et al. Lancet Diab Endo 2017; Zelniker TheLancet , 2018

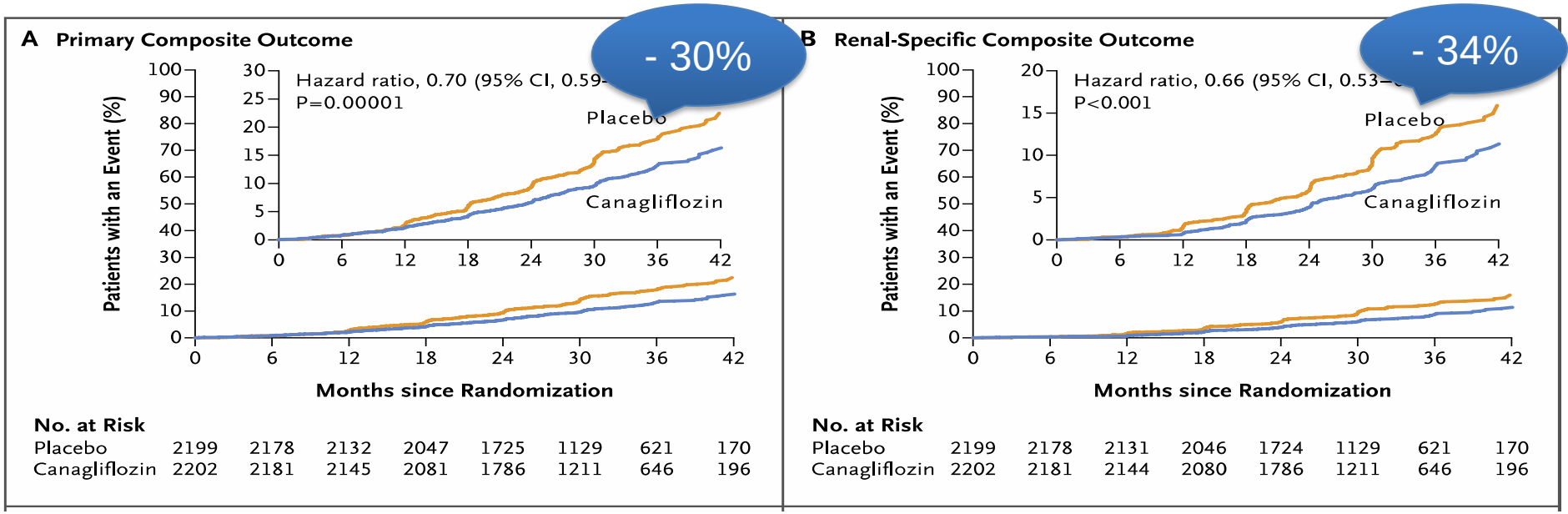
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

NEW

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*



Etude chez des patients DT2, avec DFG< 90ml/min (60% < 60) et RAC > 300 mg/g

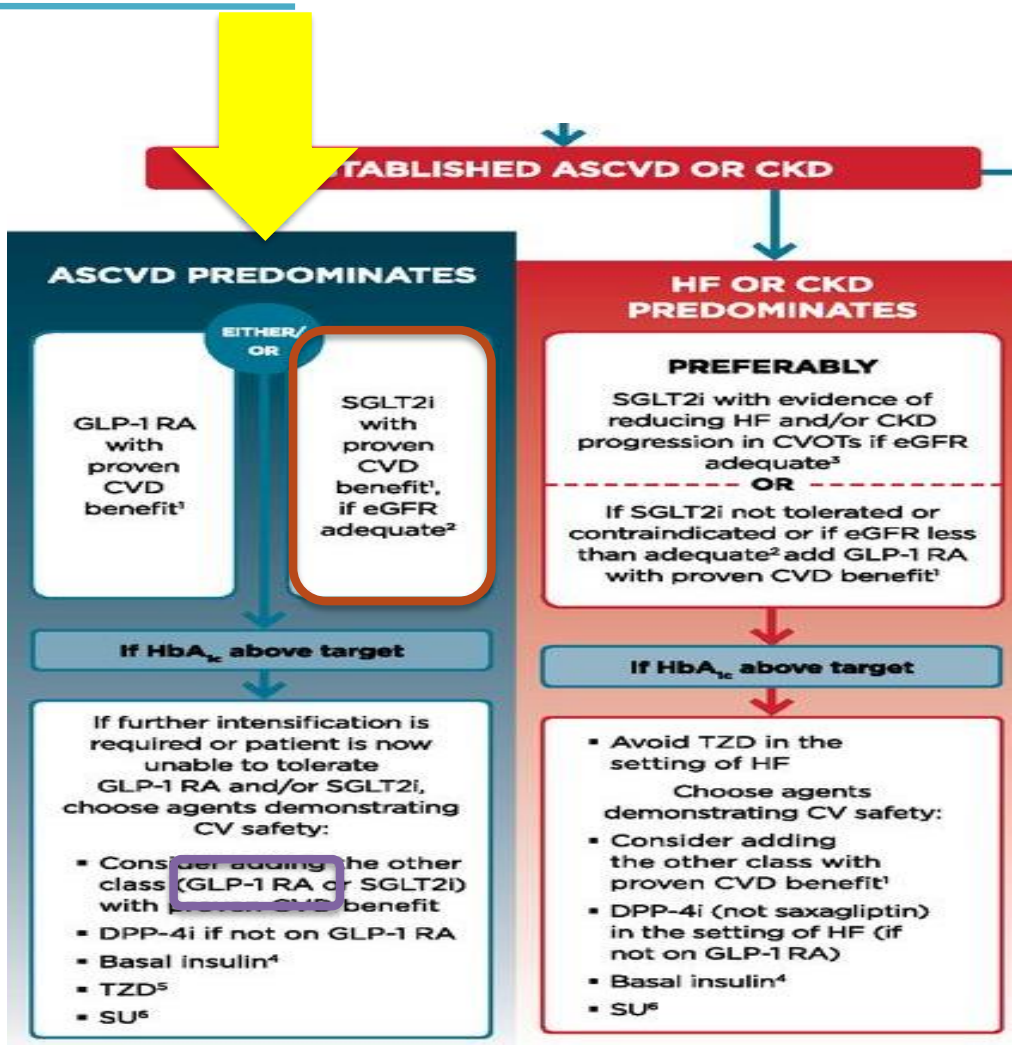
Illustration clinique n°3

Yves B. , 66 ans

- Surpoids (Poids: 94, Taille 1,82, IMC 28kg/m2)
- Diabète depuis 6 ans
- **infarctus du myocarde** il y a 3 mois.

- HbA1c 8,9%, **pas d'insuffisance cardiaque.**

- Sous mesures hygiéno-diététiques et metformine à l'hôpital : amélioration mais maintien de valeurs post prandiales >11 mmol/L et HbA1c à **8,1%**



RHD+METFORMINE + SGLT2I + GLP1-RA

Effets des SGLT2-I sur les complications macrovasculaires

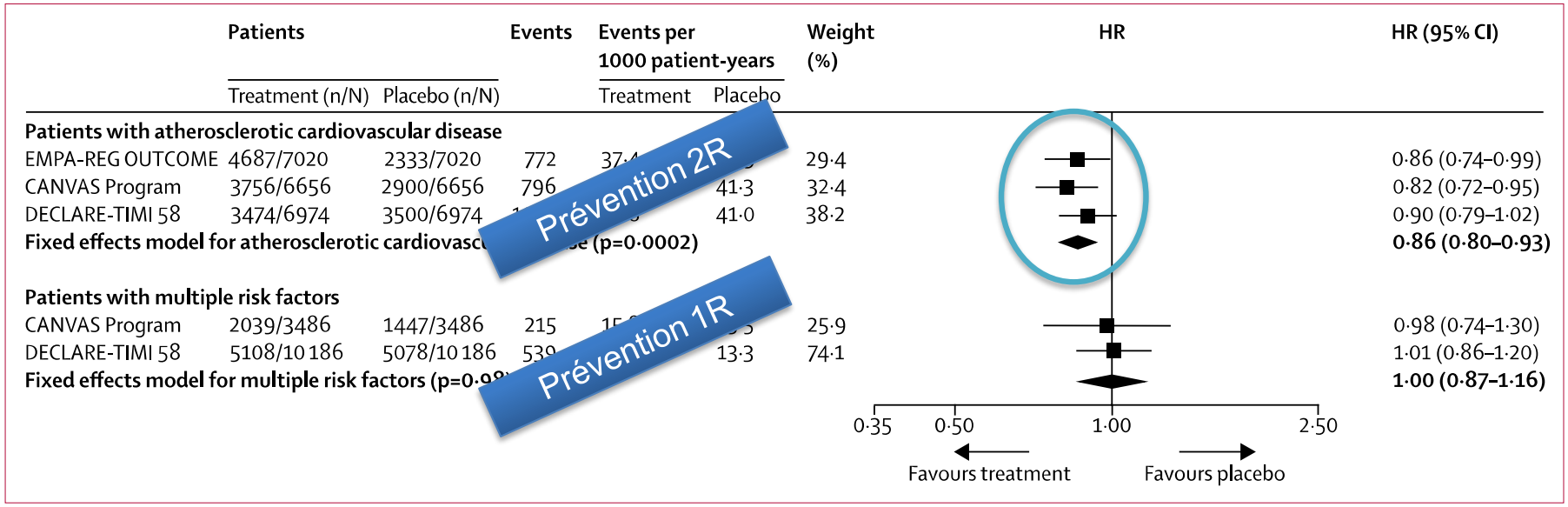
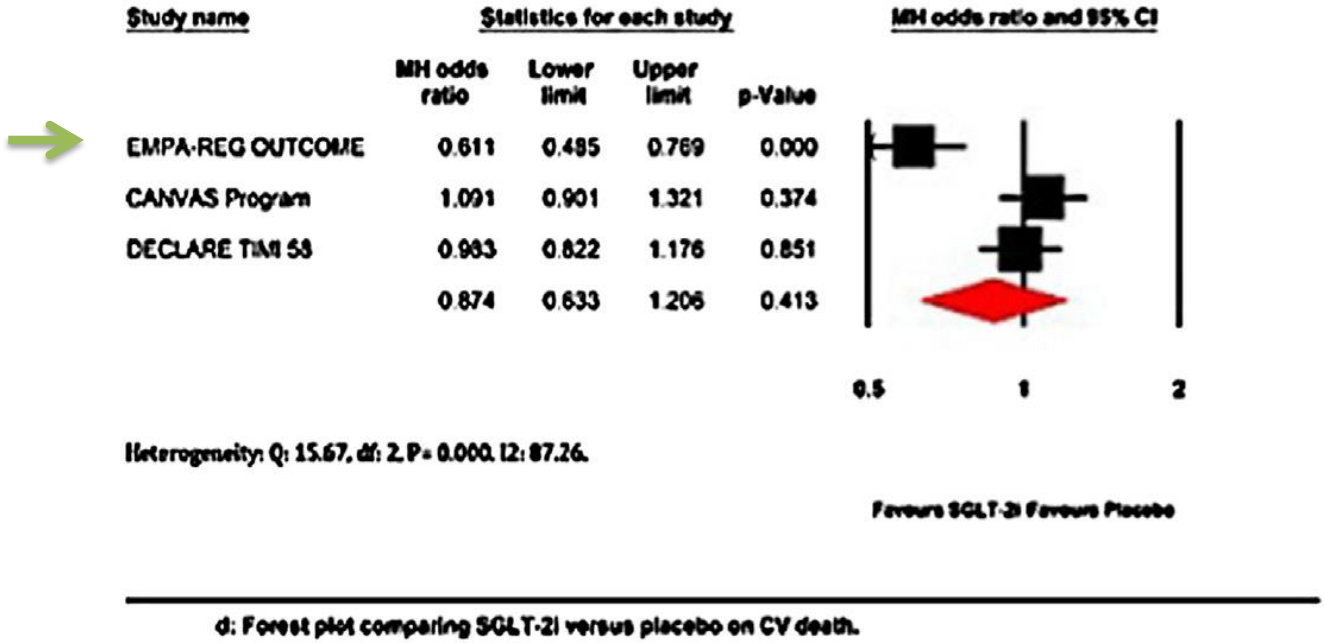


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

Zelniker TheLancet , 2018

Effets des SGLT2-I sur les complications macrovasculaires

Sur Mortalité CV



d: Forest plot comparing SGLT-2i versus placebo on CV death.

Sinha B, Diab Res & Clin Pract, 2019

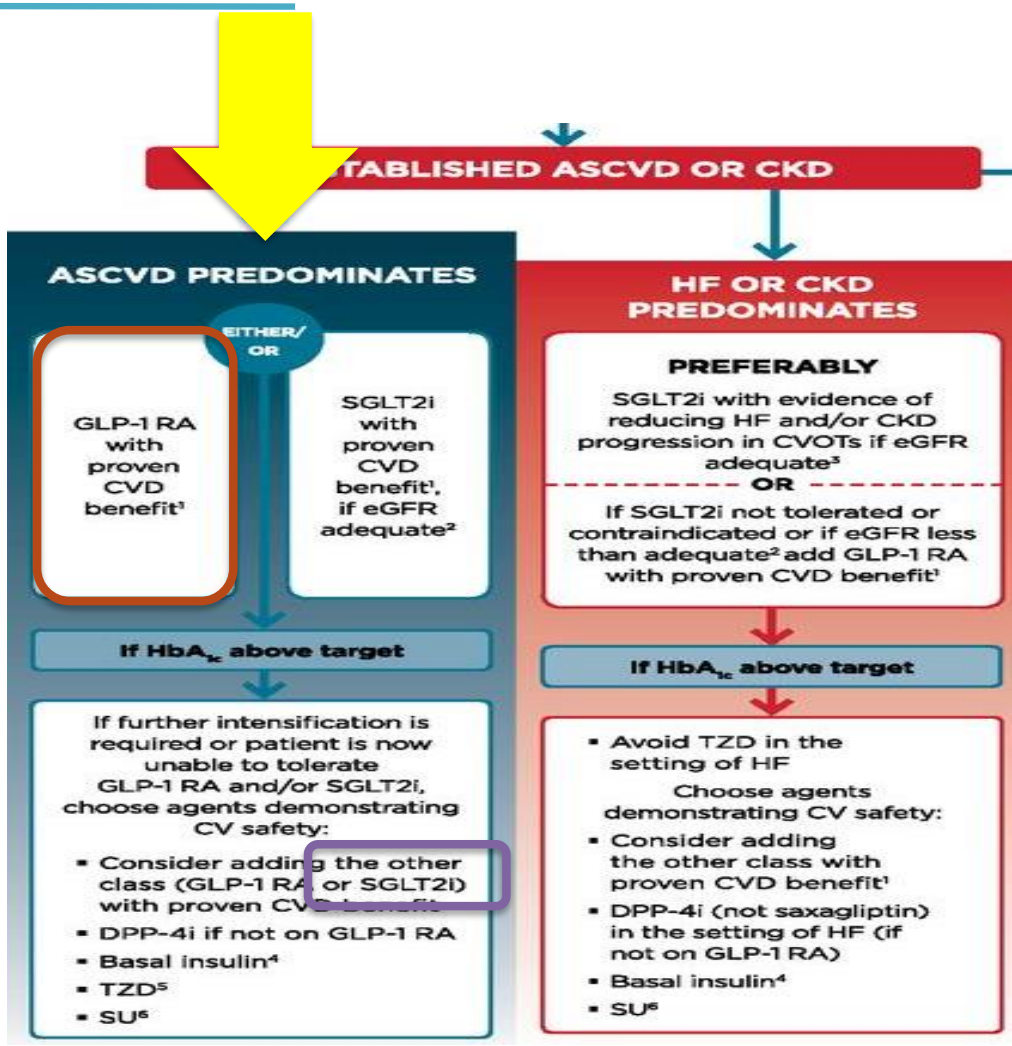
Illustration clinique n°3

Yves B. , 66 ans

- Surpoids (Poids: 94, Taille 1,82, IMC 28kg/m2)
- Diabète depuis 6 ans
- **infarctus du myocarde** il y a 3 mois.

- HbA1c 8,9%, **pas d'insuffisance cardiaque.**

- Sous mesures hygiéno-diététiques et metformine à l'hôpital : amélioration mais maintien de valeurs post prandiales >11 mmol/L et HbA1c à **8,1%**

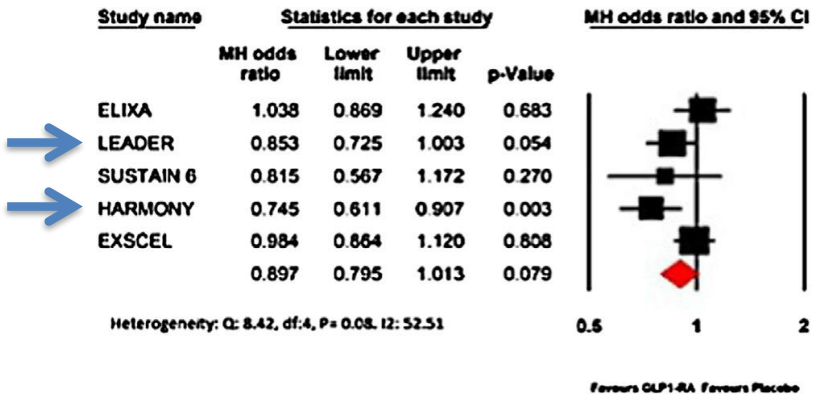


RHD+METFORMINE + GLP1-RA + SGLT2I

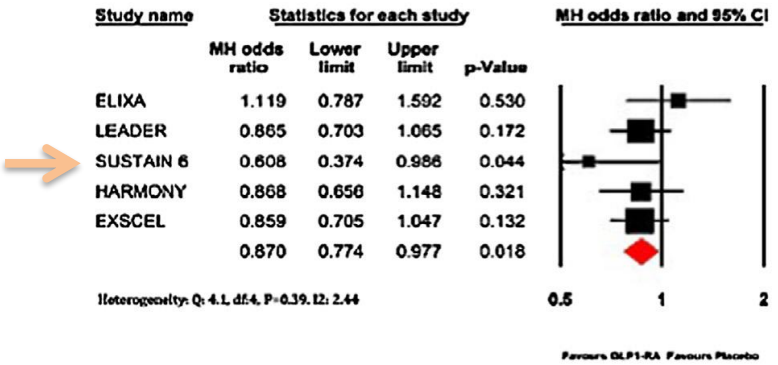
Effets des GLP1-RA sur les complications macrovasculaires

GLP-1RA	
Lixisenatide	ELIXA
Liraglutide	LEADER
Semaglutide+	SUSTAIN-6
Exenatide-LAR	EXSCEL
Albiglutide	HARMONY

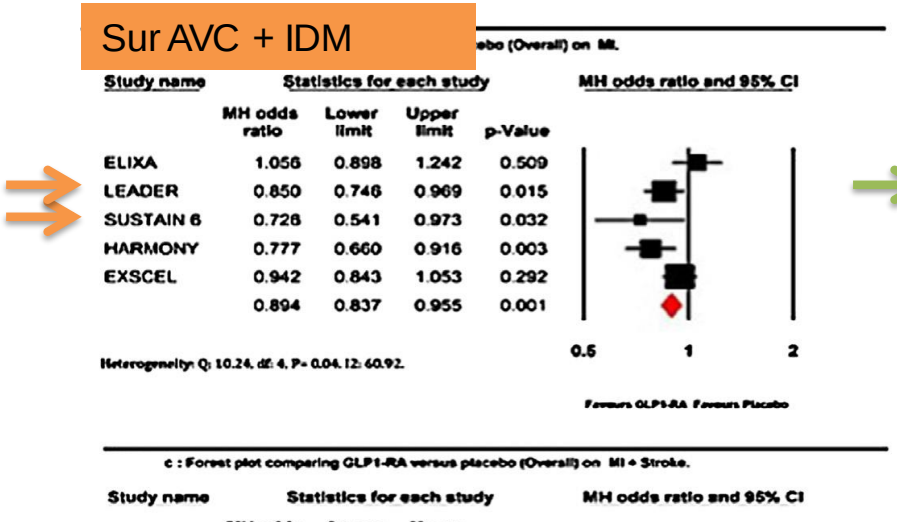
Sur infactus du myocarde (P° 2R)



Sur AVC



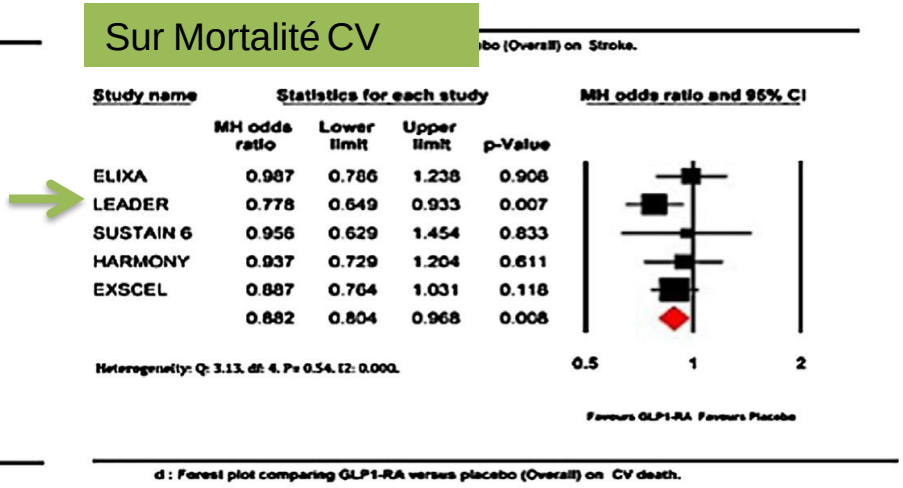
Sur AVC + IDM



c : Forest plot comparing GLP1-RA versus placebo (Overall) on MI + Stroke.

Study name Statistics for each study MH odds ratio and 95% CI

Sur Mortalité CV



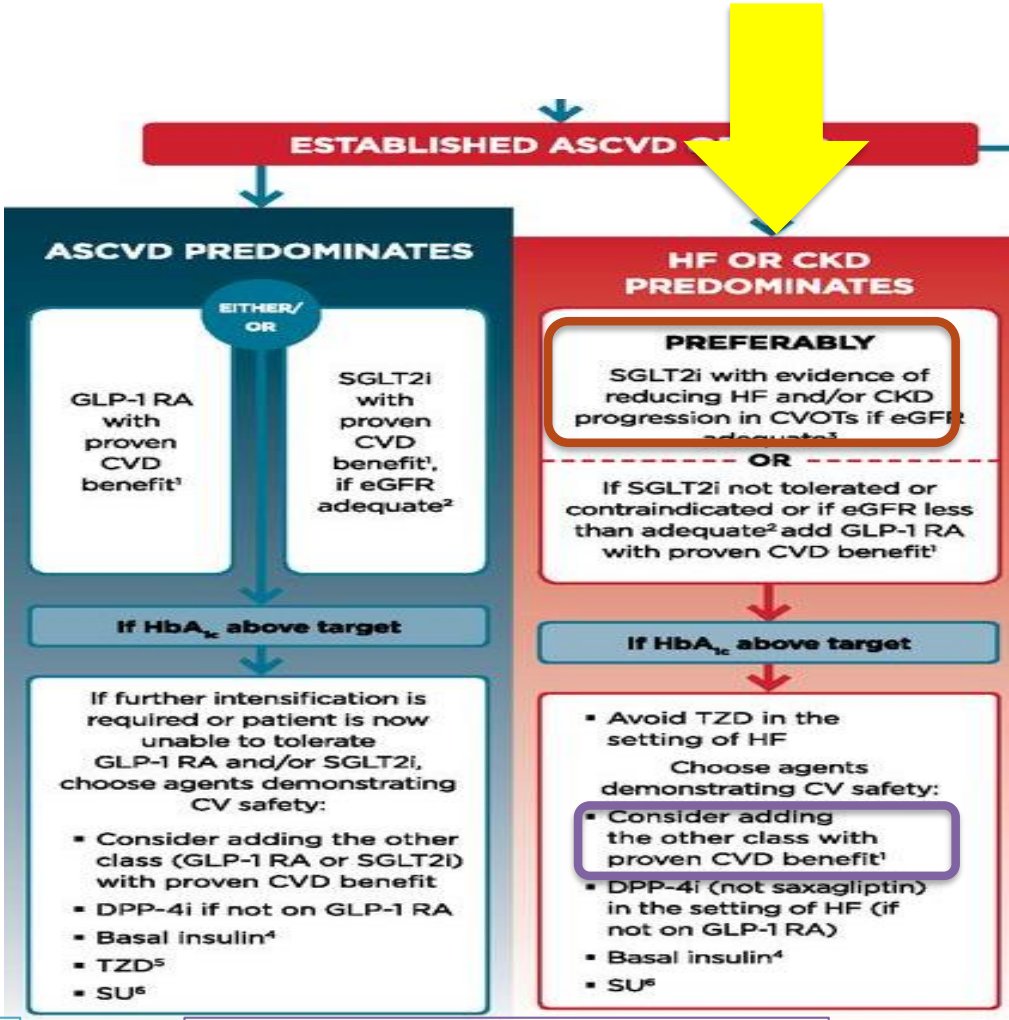
d : Forest plot comparing GLP1-RA versus placebo (Overall) on CV death.

Sinha B, Diab Res & Clin Pract, 2019

Illustration clinique n°3’

Yves B. , 66 ans

- Surpoids (Poids: 94, Taille 1,82, IMC 28kg/m2)
- **infarctus du myocarde** il y a 3 mois.
- Glycémie à l’entrée 12,1 mmol/L, HbA1c 8,9%,
- **insuffisance cardiaque avec FEVG 35%**
- Sous met +RHD amélioration mais maintien de valeurs post prandiales >11 mmol/L et HbA1c à **8,1%**



RHD+METFORMINE + SGLT2I + GLP-1RA ou DPPIVI?

Effets des SGLT2 I sur l'insuffisance cardiaque

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1			0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·			0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	·6·4			0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8			0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·			0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**

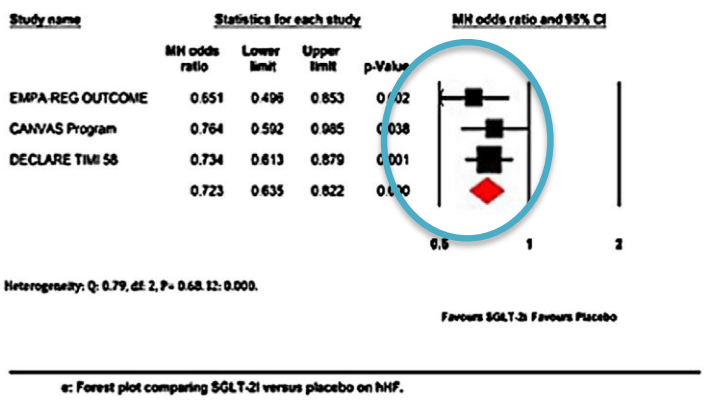
Prévention 2R

Prévention 1R

0·35 0·50 1·00 2·50

Favours treatment Favours placebo

Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**



e: Forest plot comparing SGLT-2i versus placebo on hHF.

Zelniker TheLancet , 2018

Sinha B, Diab Res & Clin Pract, 2019

Les SGLT-2I dans l'insuffisance cardiaque sans le diabète

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Liungman, P. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. S… C. Held, D.L. DeMets, K.F. Docherty, P.S. J… and A.-M. Langkilde, for the DAPA-HF Tri…

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

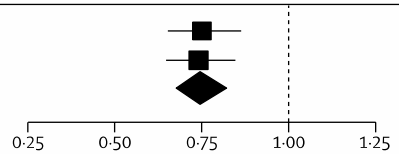
M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.P. Gonzalez-Juanatey, S. Kaul, H.-P. Brunner-La Rocca, …l. Pina, P. Ponikowski, N. Sattar, M. Senni, …, S. Taddei, C. Wanner, and F. Zannad, …educed Trial Investigators*

> 50% des patients inclus ne sont pas diabétiques

C First hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
DAPA-HF	386/2373 (16·3%)	502/2371 (21·2%)	0·74 (0·65–0·85)
Total			**0·74 (0·68–0·82)**

Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·89



Zannad, the Lancet 2020

Les SGLT-2I dans l'insuffisance cardiaque sans le diabète

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, P. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. S… C. Held, D.L. DeMets, K.F. Docherty, P.S. J… and A.-M. Langkilde, for the DAPA-HF Tri…

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

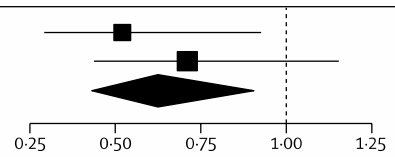
M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.P. Gonzalez-Juanatey, S. Kaul, H.-P. Brunner-La Rocca, … I. Pina, P. Ponikowski, N. Sattar, M. Senni, …, S. Taddei, C. Wanner, and F. Zannad, …educed Trial Investigators*

> 50% des patients inclus ne sont pas diabétiques

E First kidney outcome composite

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			**0·62 (0·43–0·90)**

Test for overall treatment effect p=0·013
Test for heterogeneity of effect p=0·42



Zannad, the Lancet 2020

Les SGLT-2I dans l'insuffisance cardiaque sans le diabète

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, P. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. S… C. Held, D.L. DeMets, K.F. Docherty, P.S. J… and A.-M. Langkilde, for the DAPA-HF Tri…

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

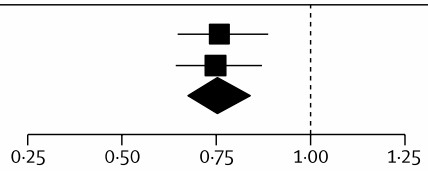
M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.P. Gonzalez-Juanatey, S. Kaul, H.-P. Brunner-La Rocca, …l. Pina, P. Ponikowski, N. Sattar, M. Senni, …, S. Taddei, C. Wanner, and F. Zannad, …educed Trial Investigators*

> 50% des patients inclus ne sont pas diabétiques

F **All (first and recurrent) hospitalisation for heart failure or cardiovascular death**

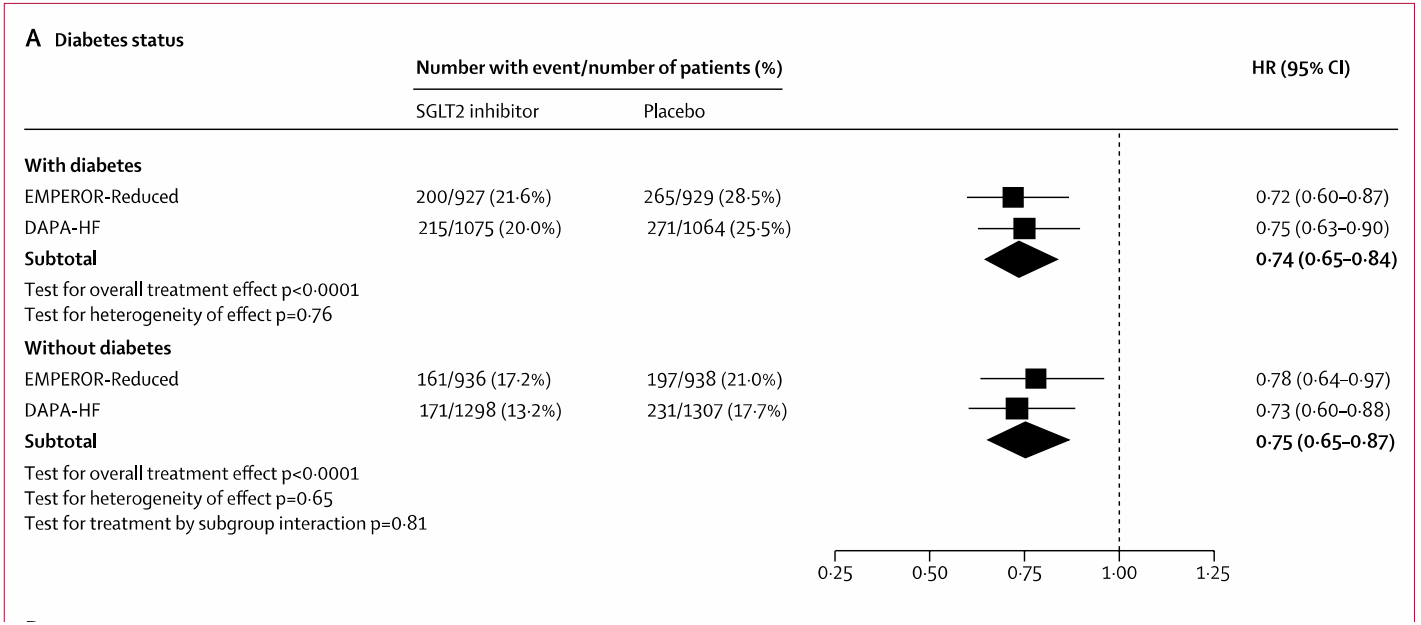
	Number with event/number of patients (%)		RR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	575/1863 (30·9%)	753/1867 (40·3%)	0·76 (0·65–0·89)
DAPA-HF	567/2373 (23·9%)	742/2371 (31·3%)	0·75 (0·65–0·88)
Total			**0·75 (0·68–0·84)**

Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·91



Zannad, the Lancet 2020

Les SGLT-2I dans l'insuffisance cardiaque sans le diabète



A Diabetes status

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
With diabetes			
EMPEROR-Reduced	200/927 (21·6%)	265/929 (28·5%)	0·72 (0·60–0·87)
DAPA-HF	215/1075 (20·0%)	271/1064 (25·5%)	0·75 (0·63–0·90)
Subtotal			**0·74 (0·65–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·76			
Without diabetes			
EMPEROR-Reduced	161/936 (17·2%)	197/938 (21·0%)	0·78 (0·64–0·97)
DAPA-HF	171/1298 (13·2%)	231/1307 (17·7%)	0·73 (0·60–0·88)
Subtotal			**0·75 (0·65–0·87)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·65			
Test for treatment by subgroup interaction p=0·81			

0·25 0·50 0·75 1·00 1·25

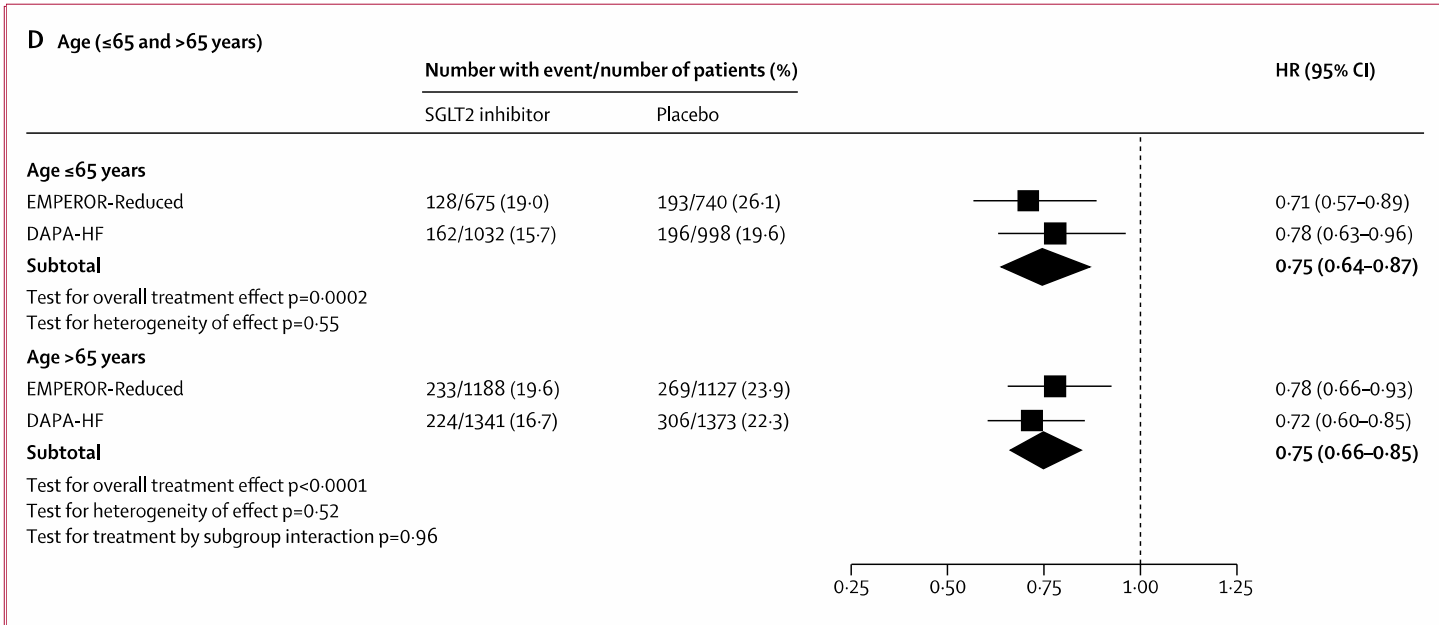
F All (first and recurrent) hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		RR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	575/1863 (30·9%)	753/1867 (40·3%)	0·76 (0·65–0·89)
DAPA-HF	567/2373 (23·9%)	742/2371 (31·3%)	0·75 (0·65–0·88)
Total			**0·75 (0·68–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·91			

0·25 0·50 0·75 1·00 1·25

Zannad, the Lancet 2020

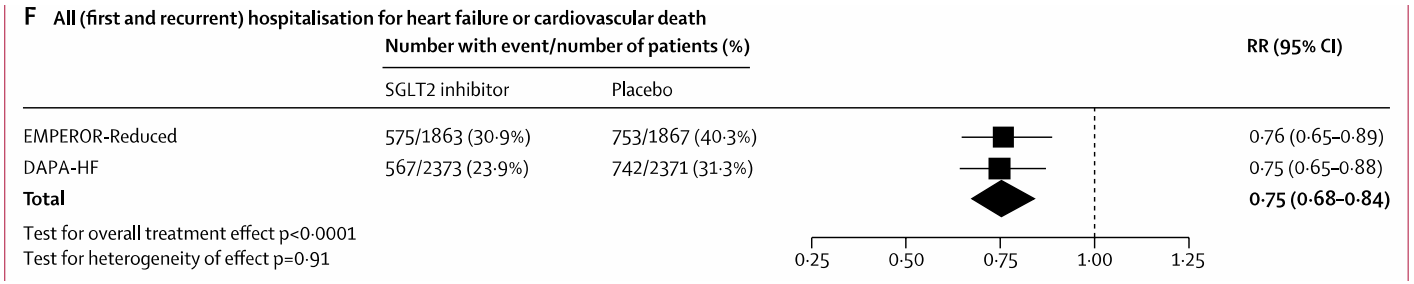
Les SGLT-2I dans l'insuffisance cardiaque sans le diabète et quelque soit l'âge



D Age (≤65 and >65 years)

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
Age ≤65 years			
EMPEROR-Reduced	128/675 (19·0)	193/740 (26·1)	0·71 (0·57–0·89)
DAPA-HF	162/1032 (15·7)	196/998 (19·6)	0·78 (0·63–0·96)
Subtotal			**0·75 (0·64–0·87)**
Test for overall treatment effect p=0·0002			
Test for heterogeneity of effect p=0·55			
Age >65 years			
EMPEROR-Reduced	233/1188 (19·6)	269/1127 (23·9)	0·78 (0·66–0·93)
DAPA-HF	224/1341 (16·7)	306/1373 (22·3)	0·72 (0·60–0·85)
Subtotal			**0·75 (0·66–0·85)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·52			
Test for treatment by subgroup interaction p=0·96			

0·25 0·50 0·75 1·00 1·25



F All (first and recurrent) hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		RR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	575/1863 (30·9%)	753/1867 (40·3%)	0·76 (0·65–0·89)
DAPA-HF	567/2373 (23·9%)	742/2371 (31·3%)	0·75 (0·65–0·88)
Total			**0·75 (0·68–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·91			

0·25 0·50 0·75 1·00 1·25

Zannad, the Lancet 2020

Illustration clinique n°4

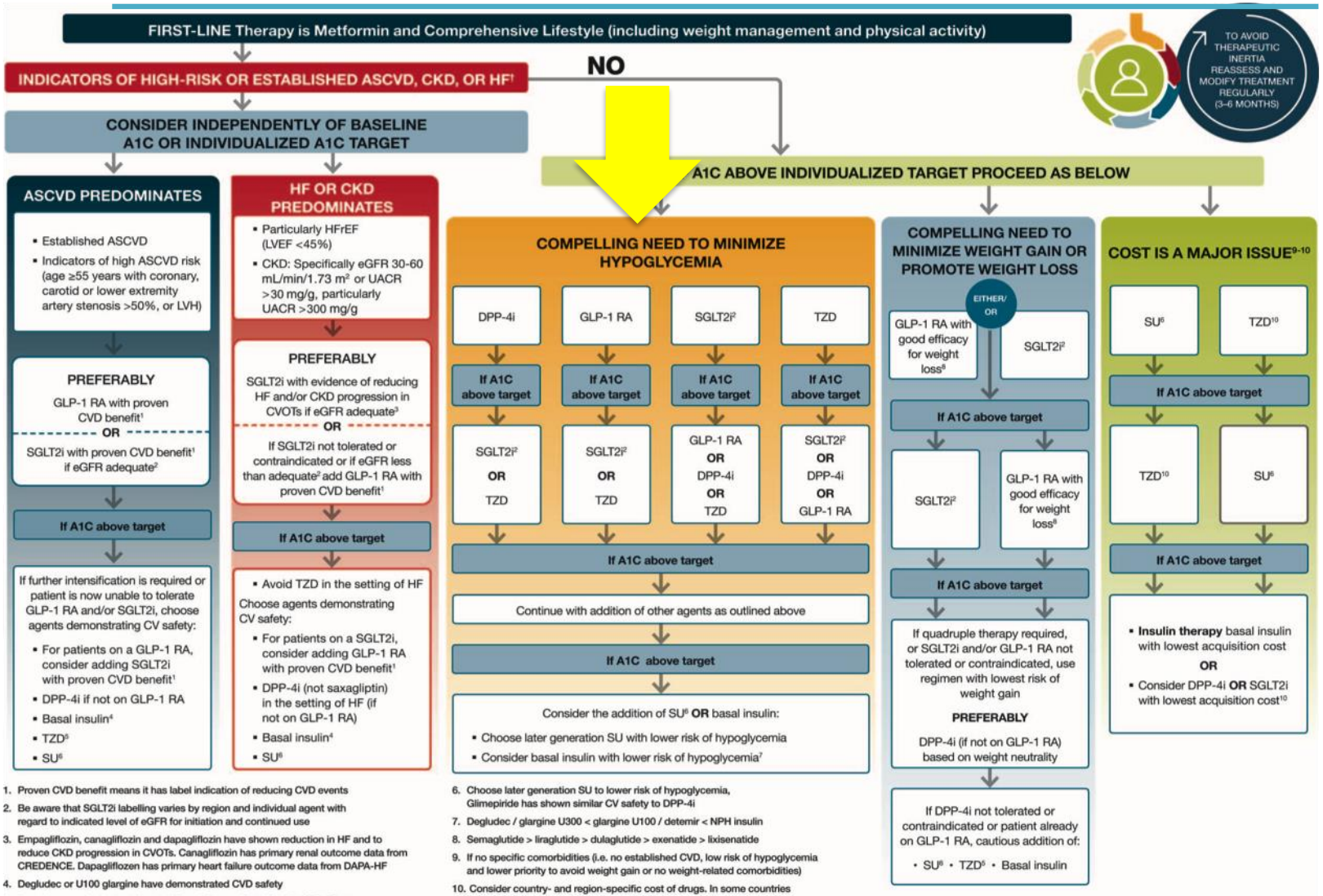
Elena, 82 ans

- Poids normal
- Diabète depuis 16 ans
- **ATCD: infarctus du myocarde** il y a 3 ans, AVC avec séquelles motrices il y a 10 ans, cancer du sein traité il y a 7 ans
- Clairance 52 ml/min

- HbA1c 9,2%, **glycémie à jeun à 10, 2 mmol/L**

- Sous gliclazide 120, metformine 500 X 2, ajout récent d'un SGLT-2 inhibiteur

Les nouvelles recommandations internationales 2020-2021



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries

Illustration clinique n°4

Elena, 82 ans

- Poids normal
- Diabète depuis 16 ans
- **ATCD: infarctus du myocarde** il y a 3 ans, AVC avec séquelles motrices il y a 10 ans, cancer du sein traité il y a 7 ans
- Clairance 52 ml/min

- HbA1c 9,2%, **glycémie à jeun à 10, 2 mmol/L**

- Sous gliclazide 120, metformine 500 X 2, ajout récent d'un SGLT-2 inhibiteur

Les risques liés à son traitement

- Déshydratation, hypotension, majoration IR , chute sous SGLT2-I
- Hypo sous sulfamides

Que feriez-vous?

- Arrêt SGLT-2
- Arrêt SH
- Une insuline lente le matin (**Laquelle?**)
- DPPIV-I? Repaglinide?

Les différentes basales

- Faible coût
- Reproductibilité intra sujet faible
- Risque d'hypoglycémie ++ nocturne si bed time

- Bonne reproductibilité intra sujet
- Risque d'hypoglycémie plus faible que NPH
- Durées d'action entre 14 et 24 h (individuel Levemir® < Lantus®)

- Faible variabilité intra et inter-sujet
- Profil plat
- Indifférence de l'horaire d'injection
- Moins d'hypo que Lantus
- Titration sans danger d'hypo
- Durée Trésiba® > Toujeo®

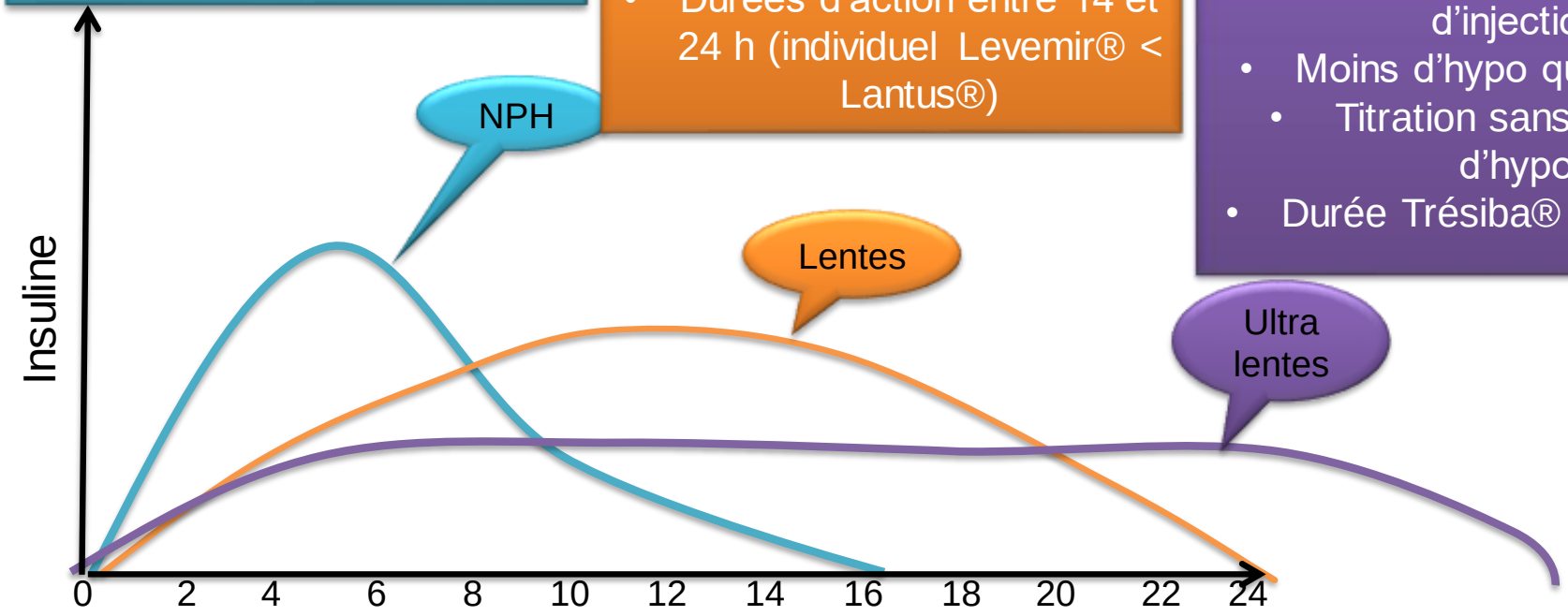


Illustration N°5

Raymond, 80 ans,

- Poids normal
- Sous Lantus 32, NR aux repas
- Diabète de type 1 depuis l'âge de 25 ans
- Décrit des hypoglycémies pré-prandiales non ressenties sur son ASG
- ATCD: troubles mnésiques débutants, rétinopathie diabètique, IR avec eGFR 52 ml/min

- HbA1c 9,2%, sous basal-bolus

Que feriez-vous?

- Une éducation CGMS et une pose de CGMs

- Une pose de CGM diagnostique pour 1 à 2 semaines si refus pose en continu

La mesure continue du glucose

Freestyle Libre

Dexcom,5 et 6

Guardian connect

Eversense

AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019–10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

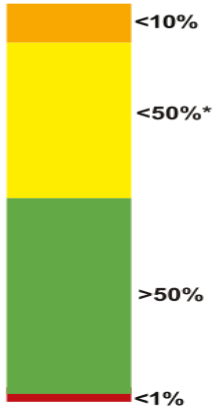
Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

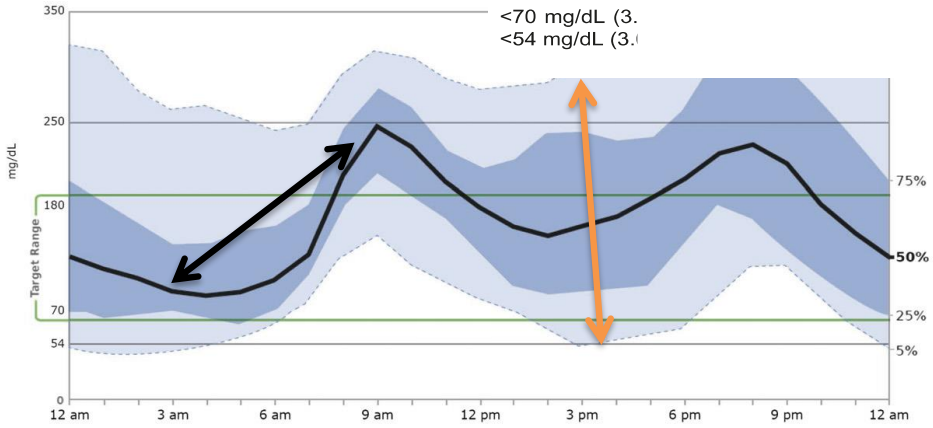
Defined as percent coefficient of variation (%CV); target ≤36%

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%)

Chez le DT1 et DT2 plus âgés ou à risque





DAILY GLUCOSE PROFILES

Battelino, Diabetes Care,2019

Preuve chez le sujet âgé

- Diamond study/ amélioration HbA1c 100 patients 67+/-5 ans
- Wisdm study: 203 patients de plus de 60 ans, 30% > 70 ans
- Test SGM vs CGMS pendant 6 mois

→ Améliorqtion HbA1c
→ Moins de temps passé en hypo
→ Moins d'hypos sévères
→ Moins de fractures? (p=0,08)

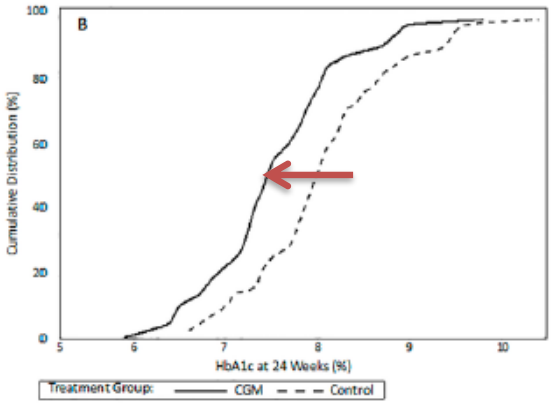
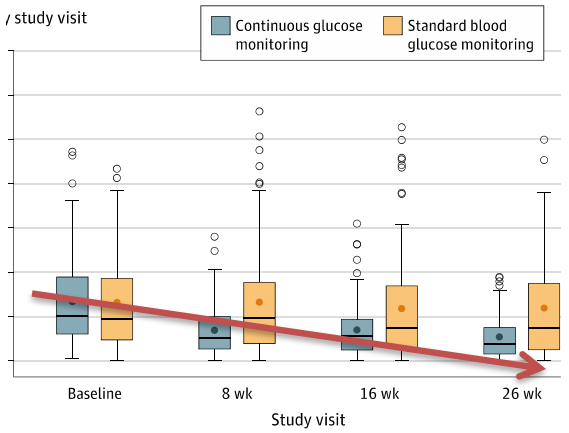
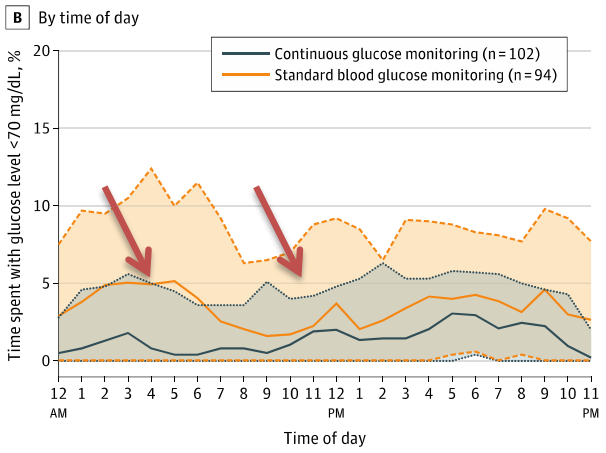


Figure 2. Percentage of Time Spent With Less Than 70 mg/dL by Study Visit and Time of Day





Ruedy K. J et al. , J Diabetes Sci; Technol, 2017, 11(6); 1138.

Pratley E.R et al. JAMA 2020, 323(23); 2397.

Illustration N°5

Raymond, 80 ans,

- Poids normal
- Diabète de type 1 depuis l'âge de 25 ans
- ATCD: troubles mnesiques débutants, rétinopathie diabètique, IR avec eGFR 32 ml/min
- Cancer du rein métastatique
- Soins palliatifs

- HbA1c 8,2%, sous basal-bolus

Que feriez-vous?

- Décroissance thérapeutique sur les doses de bolus principalement/ simplifier les schémas de bolus
  - Si > 11 : 2 UI
  - Si > 14: 3 UI
  - Si > 16: 4 UI

- En phase terminale: **maintien de la lente seule**

Conclusion

- Des nouvelles **directives internationales proches des recos suisses**
- Mise en avant de la personnalisation des traitements: **+++ chez la personne agée.**
- **Les études avec SGLT2i ou RA GLP-1/** courtes et…positives chez des patients avec co-morbidités
- Mise en avant des **SGLT-2I et des GLP1 RA** qui montrent à la fois des résultats probants sur
  - L'HbA1c
  - Le poids
  - Le risque cardiovasculaire
  - La prévention rénale
  - ➢ Abandon de la cible d'HbA1c dans ces indications car effet indépendant de la glycémie

    … mais aussi un profil d'effets secondaires plus complexes à gérer
- Chez les personnes fragiles:
  - Simplifier, simplifier , simplifier…
  - Basale matin ou Ultra lente +/- gliptine= bon compromis