ORGANOPROTECTION EN DIABETOLOGIE

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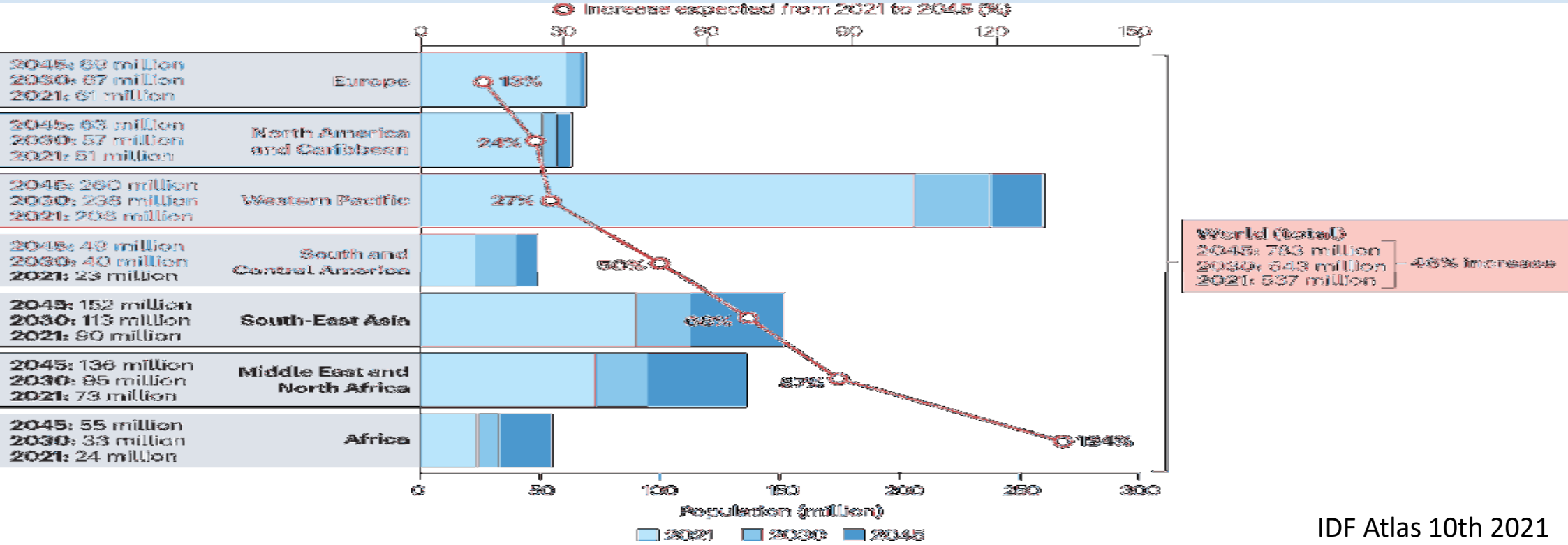
Plan

- Introduction
- Epidémiologie
- Mécanismes des complications du diabète
- Complications du diabète
- Stratégies d'organoprotection
  - Dépistage précoce
  - Traiter pour prévenir
- Equilibre du diabète et FRCV: résultats des études
- Diabète et atteinte hépatique
- Conclusion

Introduction

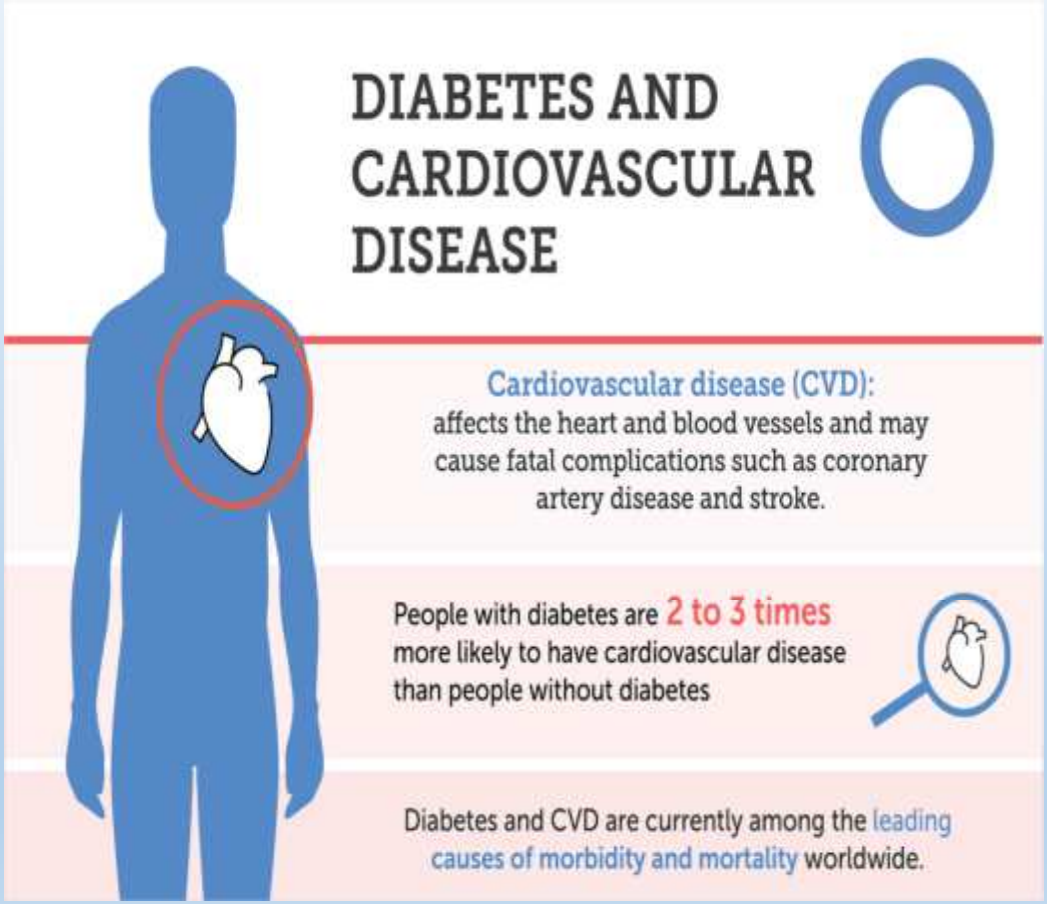
- Diabète sucré(DS): pandémie mondiale en progression perpétuelle
- Evolution: complications micro et macrovasculaires
- Association aux FRCV: augmentation de la morbi-mortalité
- Prévention de complications: PEC multidisciplinaire et efficace



IDF Atlas 10th 2021

Epidémiologie

- Diabetes: leading causes of chronic kidney diseases (CKD)
  - 30 to 40% of people living with diabetes developing CKD.
- Type 2 diabetes: largest contributor to the burden of CKD.
- MRC: augmente le risque CV avec progression vers une IR et le décès.



IDF Atlas 10th 2021

Epidémiologie

Figure Number of deaths due to diabetes in adults (20–79 years), by age and sex in 2021

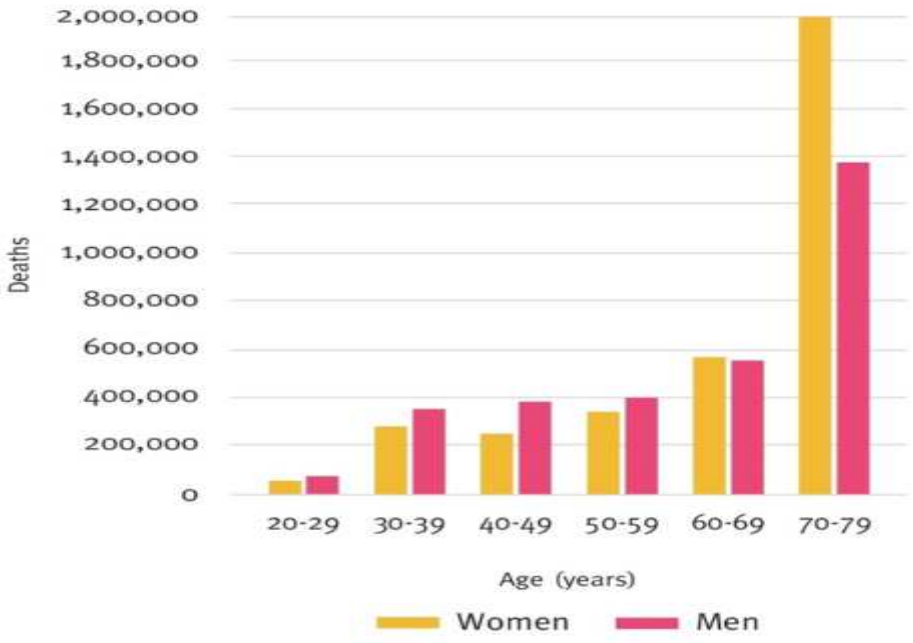


Table Proportion and number of adults who died from diabetes before the age of 60 years in 2021, globally and by IDF Region, ranked by the proportion of deaths due to diabetes

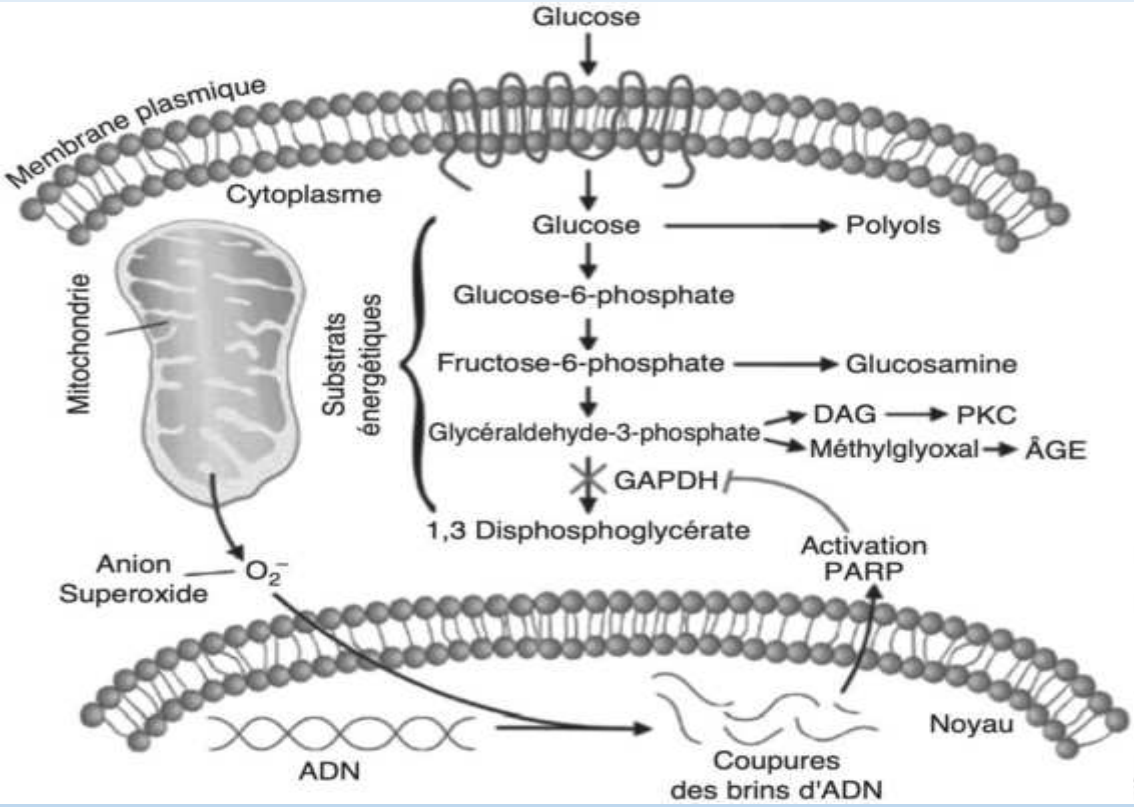
IDF region	Number of deaths due to diabetes before the age of 60 years (thousands)	Proportion of total deaths due to diabetes before the age of 60 years (%)
World	**2,184.4**	**11.8**
MENA	428.6	24.5
NAC	199.9	18.4
WP	717.4	15.0
AFR	306.0	8.9
SACA	86.7	8.0
EUR	144.7	7.7
SEA	301.2	6.9

- 2021: 6,7 millions de décès liés au diabète

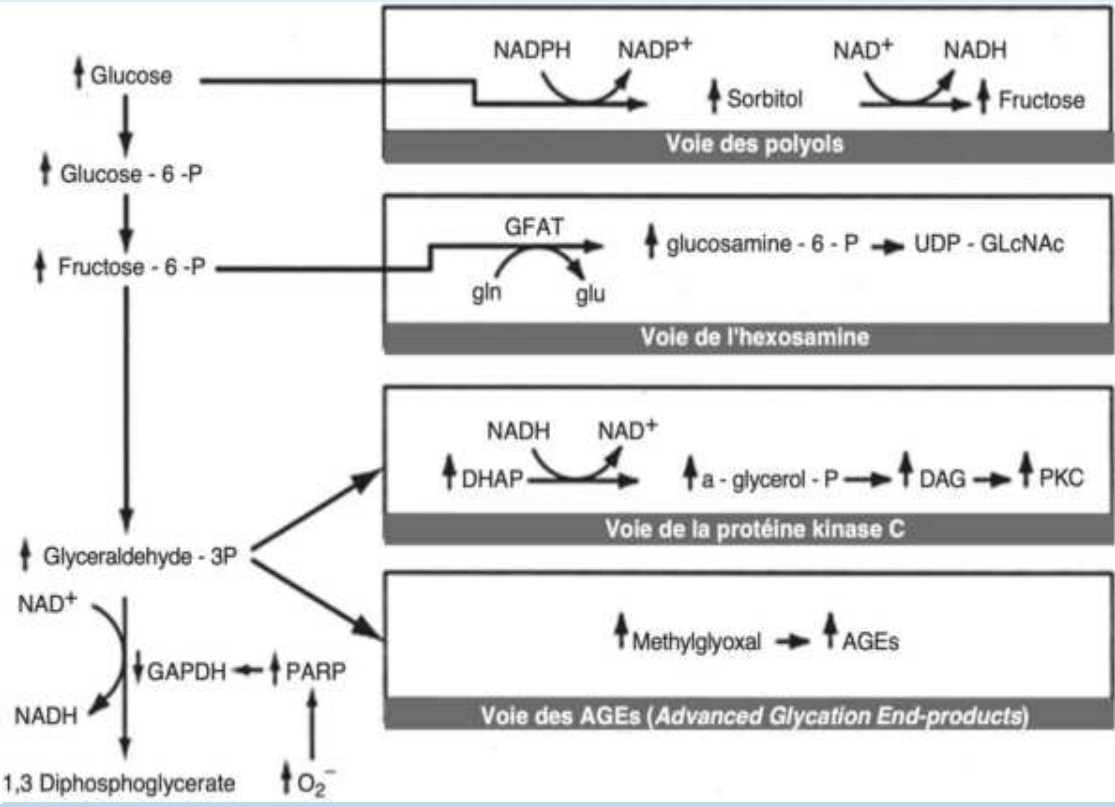
IDF Atlas 10th 2021

Mécanismes des complications

- Mécanismes cellulaires de défense ou de réparation

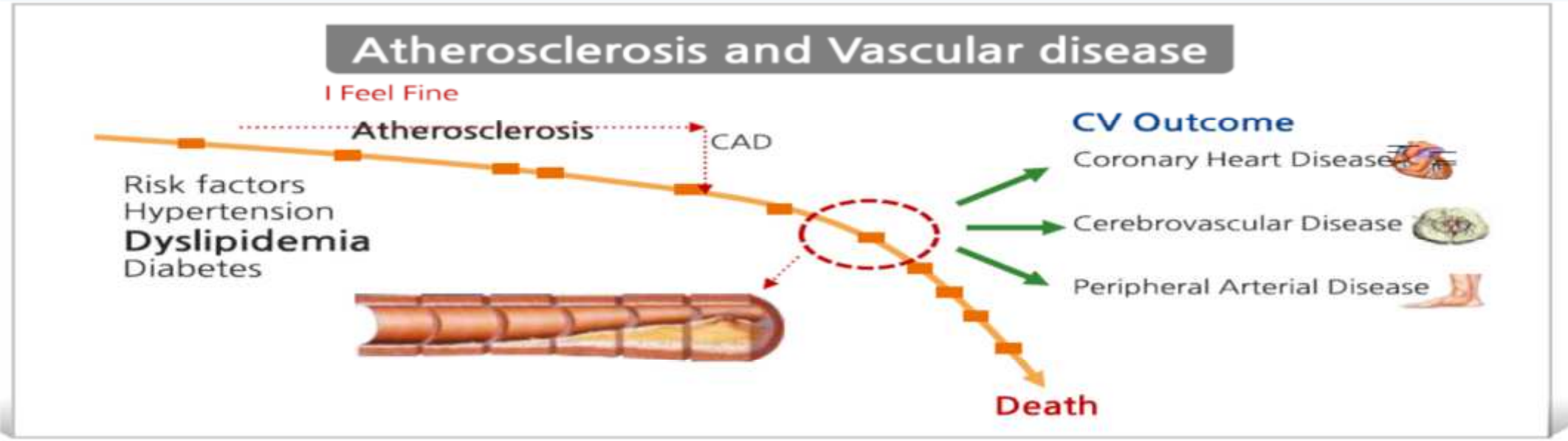


- Voies métaboliques de toxicité cellulaire



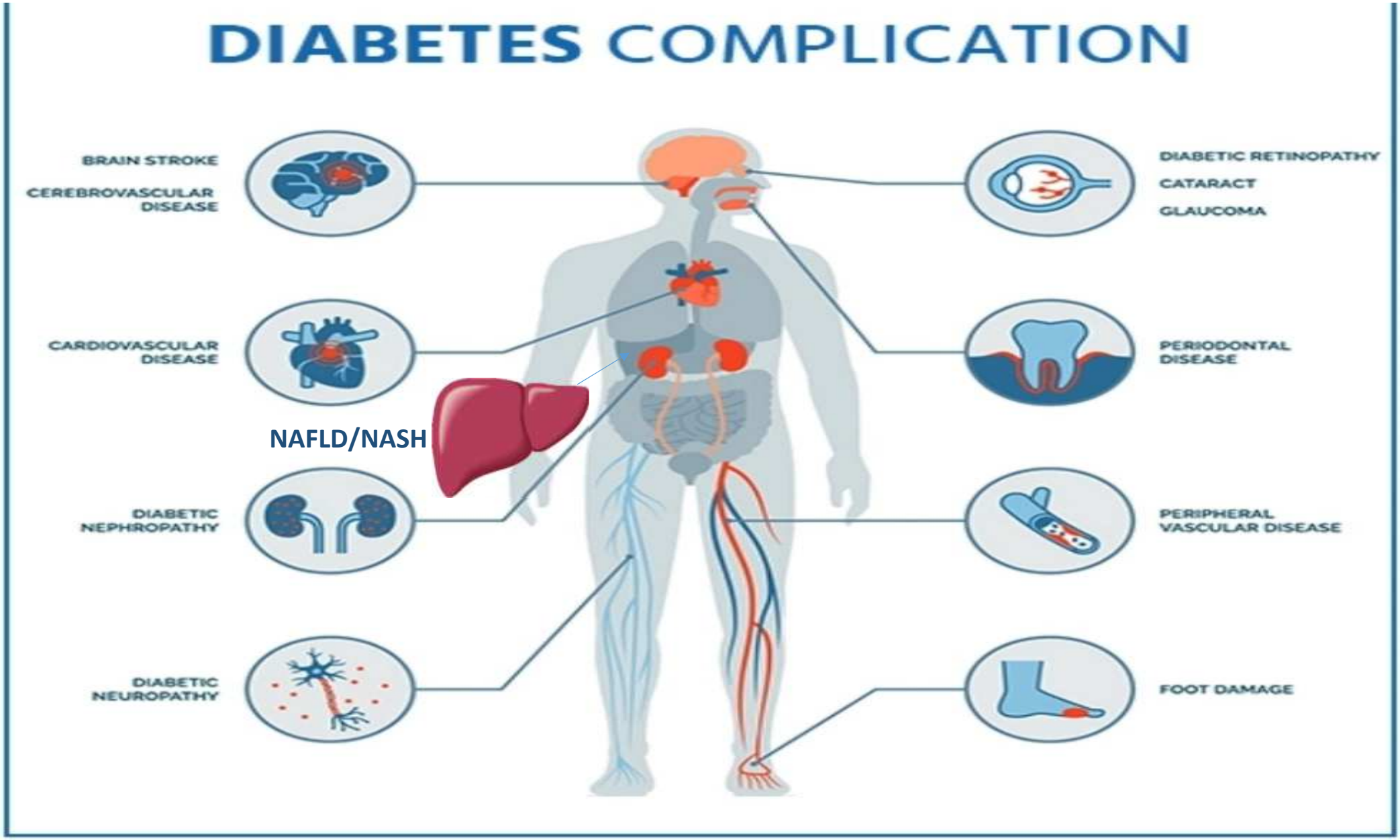
CEEDMM, 2021
Diabetes, 2005 ; 54 : 1615–25

Mécanismes des complications: DT2 et FRCV



Risk factors	Atherosclerosis	Vascular disease
☑ Dyslipidemia	☑ Carotid artery	☑ Atherosclerotic Stroke
☑ DM	☑ Coronary artery	☑ Ischemic heart disease
☑ Hypertension	☑ Aorta	☑ Peripheral artery disease

Journal of ASC, 2017 ; 6 9 (22); 2 7 5 9 – 6 8

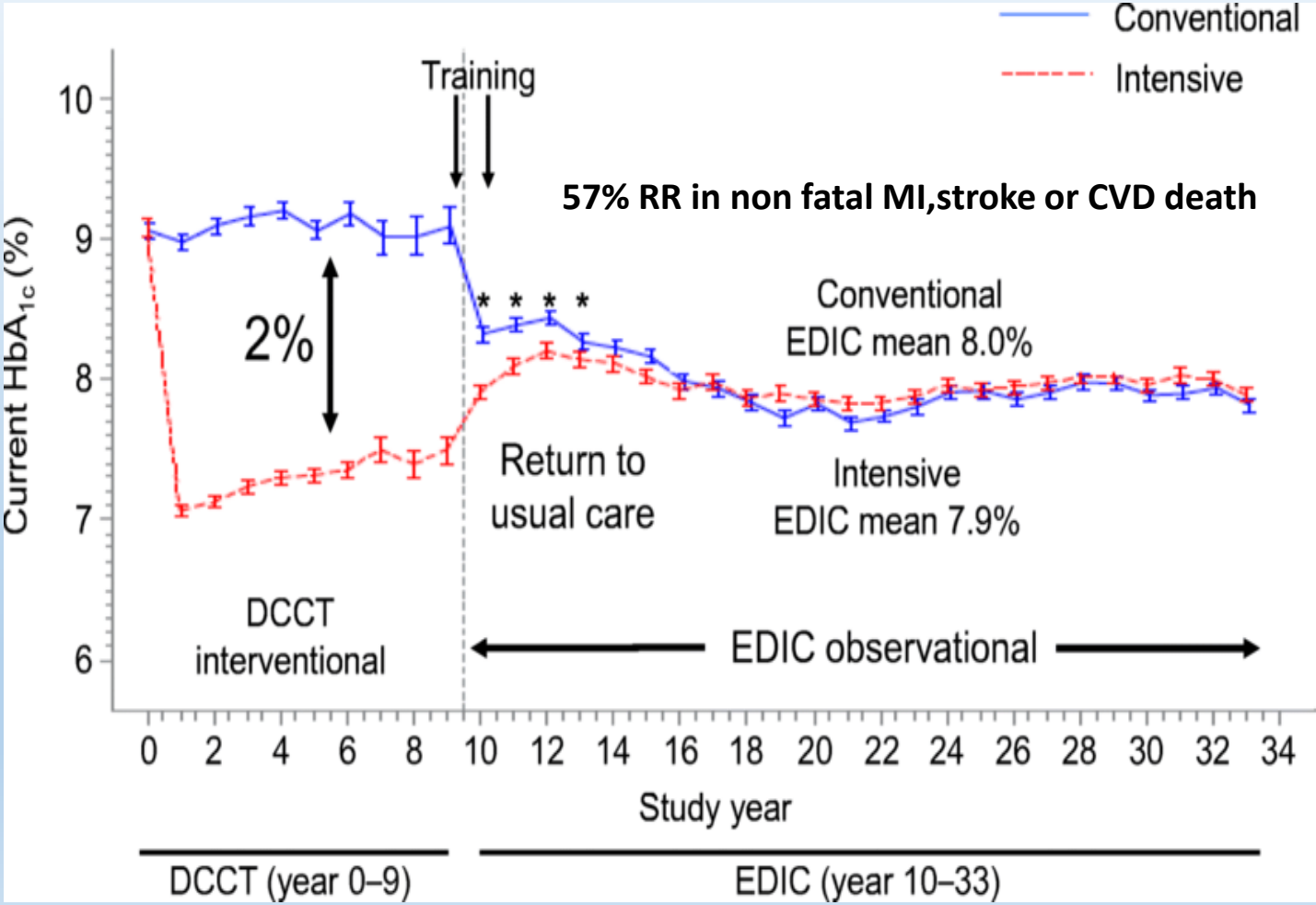

DIABETES COMPLICATION
BRAIN STROKE
CEREBROVASCULAR DISEASE
CARDIOVASCULAR DISEASE
NAFLD/NASH
DIABETIC NEPHROPATHY
DIABETIC NEUROPATHY
DIABETIC RETINOPATHY
CATARACT
GLAUCOMA
PERIODONTAL DISEASE
PERIPHERAL VASCULAR DISEASE
FOOT DAMAGE

Stratégies d’organoprotection

- Dépistage précoce: (DT2 dès le diagnostic, DT1 après 5 ans)
- Treat to target
  - Recommandations
  - Individualisation des objectifs
- Evaluation du risque cardiovasculaire
- PEC Multifactorielle
- Utilisation rationnelle des molécules aux bénéfices CV prouvés

Equilibre du DT1: DCCT et EDIC

- **DCCT: Intensif vs conventionnel**
  - Meilleur équilibre
  - Moins de complications
- **EDIC**
  - Bénéfice du meilleur équilibre: legacy effect
  - Risque mortalité réduit



DCCT: NEJM 1993

Equilibre du DT1: The Medalist study

- 1948: living with diabetes for 25 years
  - Proper self-management : minimizing long-term complications.
- 1970: 50-Year Medal
- 1996 75-Year Medal
- 2013: 1st 80-Year Lifetime Achievement

G.King et al. The medalist (Diabetes care 2007)

Equilibre du DT1: The Medalist study

- Since 1970: more than 5,000 50-Year Medals.
- from 1996: > 90 Medals 75-Year.
- **The Medalist Study:** over 1,000 people with type 1 diabetes
  - Existence of protective factors to prevent the development of severe complications?
  - 35 % of patients do not have significant complications
  - Hyperglycemia condition for 50 years.

G.King et al. The medalist (Diabetes care 2007)

Bénéfices de l'équilibre du diabète: DT2

Bénéfices du contrôle glycémique optimal dans le diabète de type 2

Etude	Complications microvasculaires		Evénements cardiovasculaires		Mortalité	
UKPDS (7,0 vs 7,9%)	↓	↓	↔	↓	↔	↓
ACCORD (ION) (6,4% vs 7,5%)	↓	?	↔	↔	↑	↑ CV
ADVANCE (ON) (6,3% vs 7,0%)	↓	↓	↔	↔	↔	↔
VADT (6,9 vs 8,4%)	↓	?	↔	↓	↔	↔

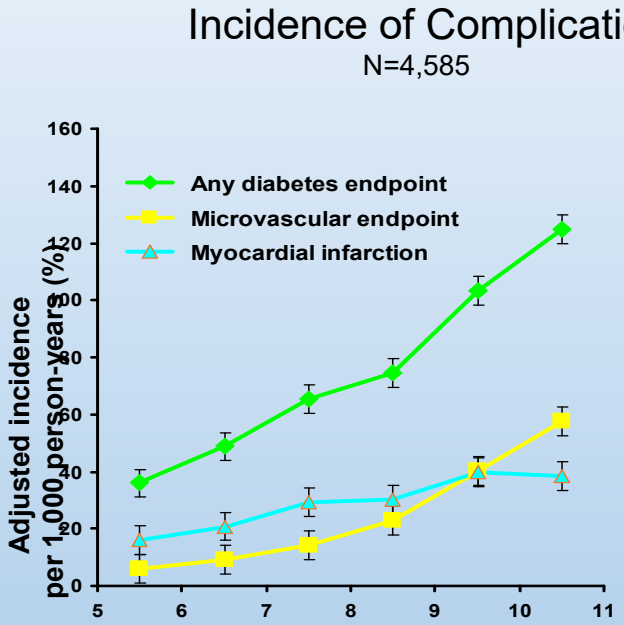
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med.* 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med.* 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:25. 60.
Duckworth W et al. N Engl J Med 2009;360:129 (erratum Moritz T. N Engl J Med 2009;361:1024).
Zougas S et al. N Engl J Med 2014;371:1392. Hayward RA et al. N Engl J Med 2015;372:2197. DCCT/EDIC Study Research Group. Diabetes Care 2016, on line. ACCORD investigators. Diabetes Care 2016; 39:701-708

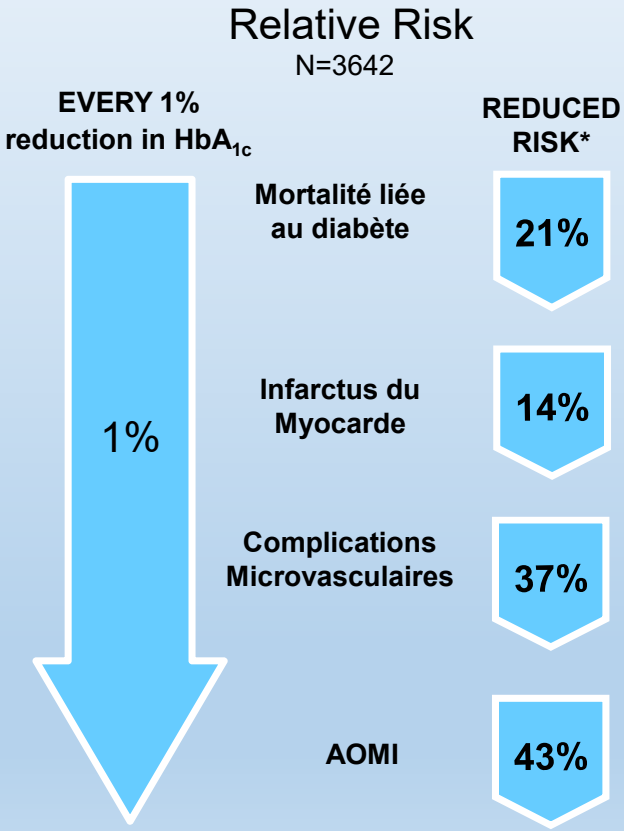
A la fin de l'essai

Suivi à long terme

Société francophone du diabète

UKPDS: équilibre et complications





UKPDS

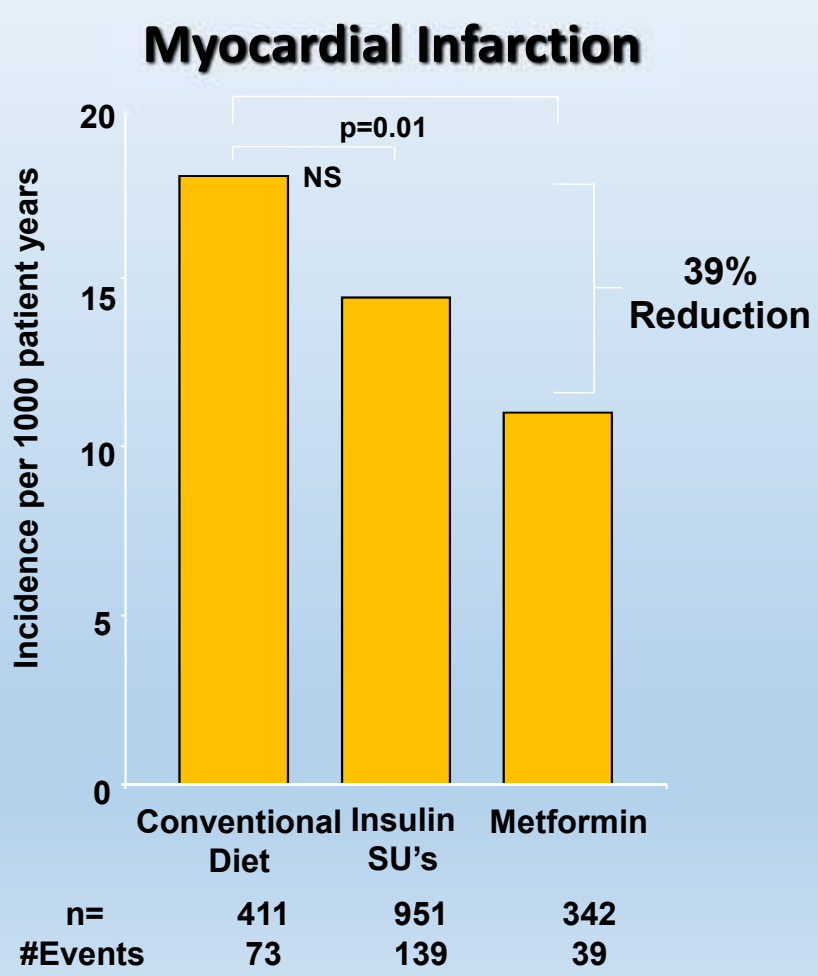
- Randomisée, multicentrique
- 4209 D2 récent, âge moyen 54 ans
- Evaluer les effets du contrôle glycémique optimisé sur complications micro et macrovasculaires
- Traitement optimal vs conventionnel du DT2

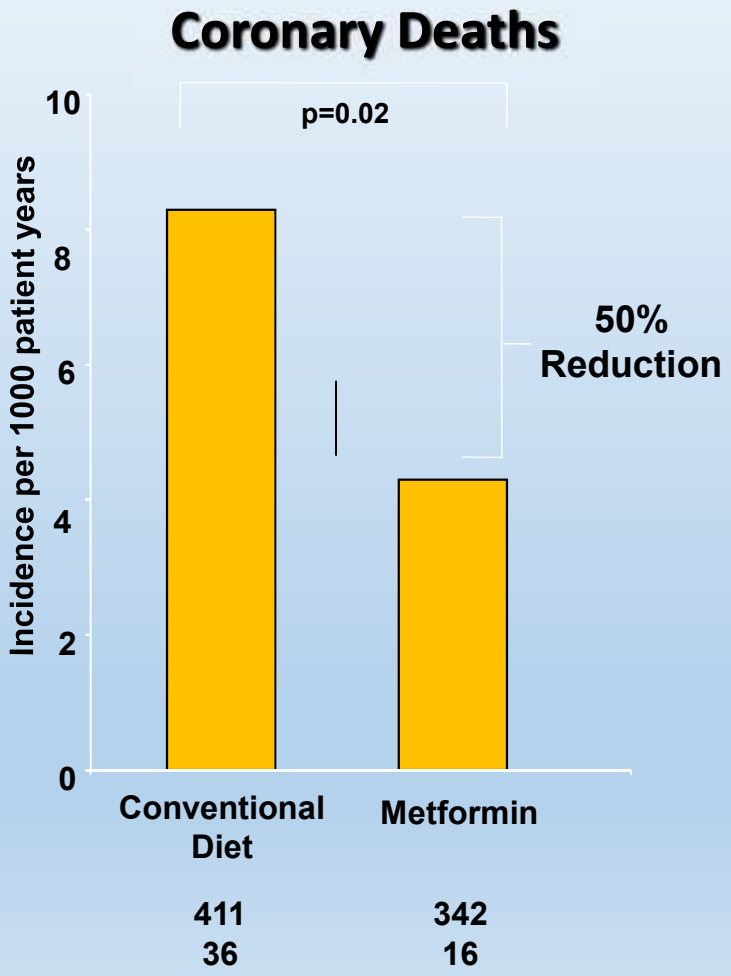
Observational study of participants from the UKPDS trial of intensive control of blood glucose after diagnosis of type 2 diabetes.
*p<0.0001.

Stratton IM et al. *BMJ* 2000;321:405–412.

THE LANCET

UKPDS Metformin Sub-Study: CHD Events

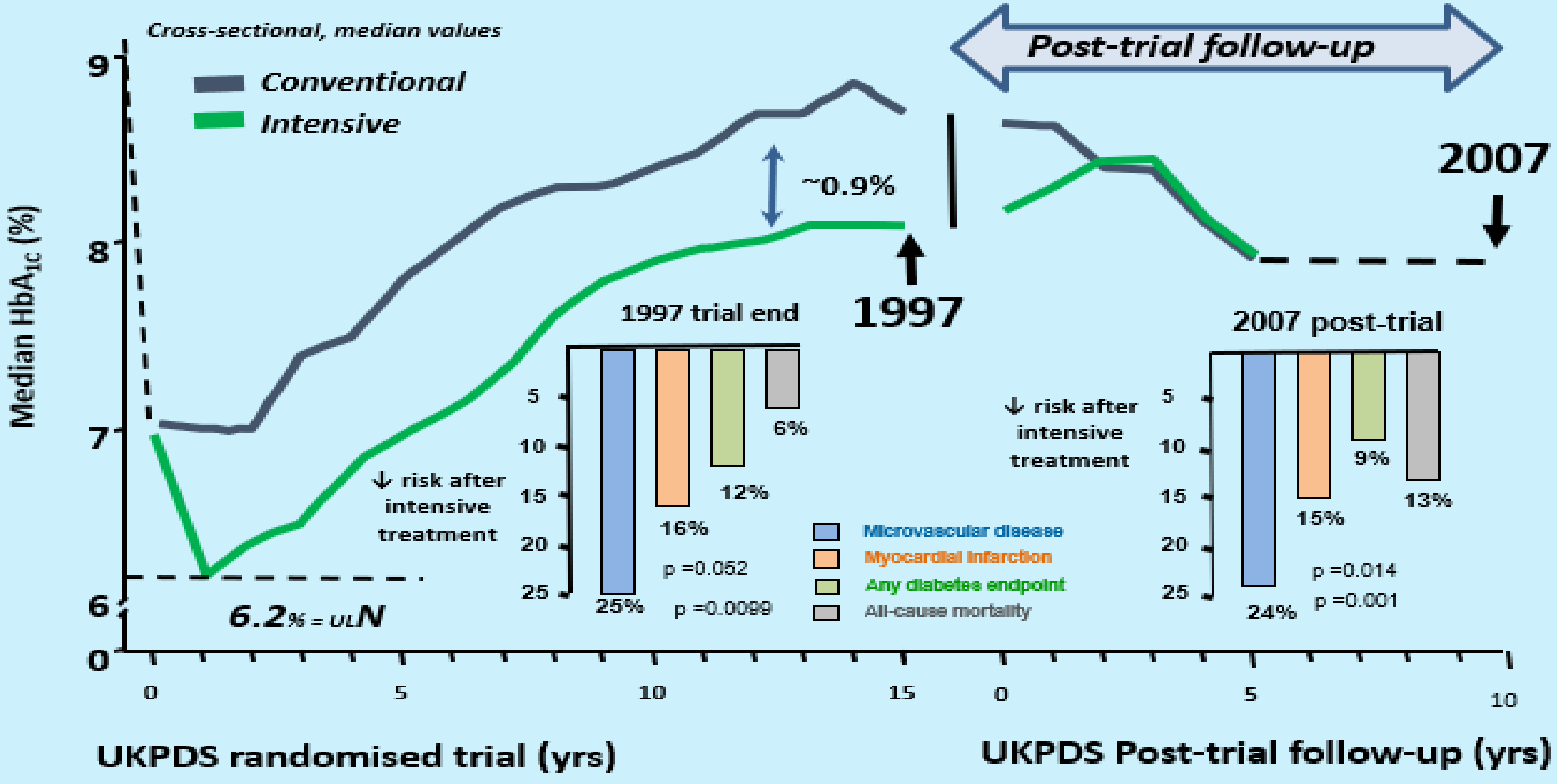




UKPDS 34, Lancet 352: 854, 1998

UKPDS: Legacy 'benefits' of early control

Benefits of early intensive glycaemic control



Prise en charge multifactorielle: STENO2

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2003 VOL. 348 NO. 5

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

CONCLUSIONS

A target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50 percent.

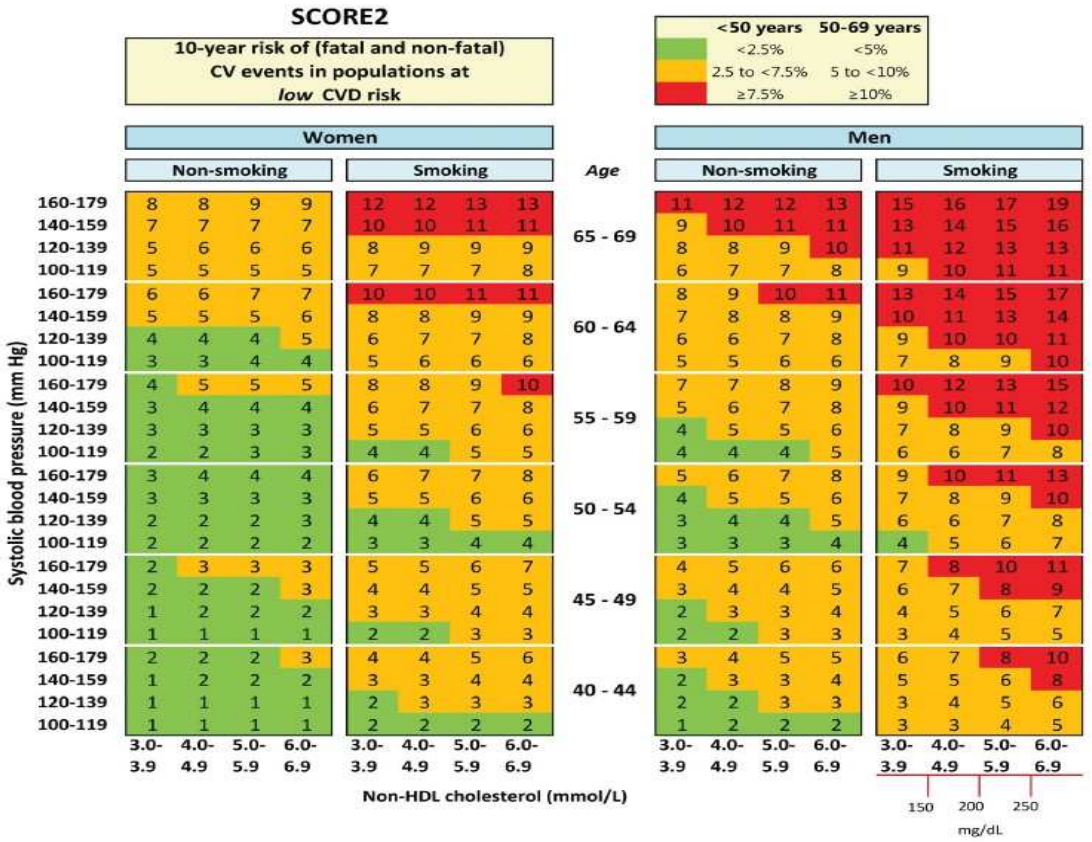
Evaluation du risque cardiovasculaire

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors[a]	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Moderate to high risk	High risk	High risk	Very high risk
Stage 3	Established CVD or CKD grade ≥4	Very high risk	Very high risk	Very high risk	Very high risk

	<50 years	60–69 years	≥70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

Complementary risk estimation in Stage 1 with SCORE2/SCOR2-OP

ESC 2023



Légende des couleurs
Vert : risque CV faible à modéré ; Orange : risque CV élevé; Rouge : risque CV très élevé. Reproduit de la référence 10 avec permission

Eur Heart J. 2021;42:2439-54

Prévention MCV: objectifs LDLc

ÉVALUATION DES RISQUES	TRÈS HAUT RISQUE	HAUT RISQUE	RISQUE MODÉRÉ	RISQUE FAIBLE
Historique cardio-vasculaire	MCVA (clinique/imagerie)	-	-	-
Diabète	• Atteinte d'organe (microalbuminurie, rétinopathie ou neuropathie) • ≥ 3 facteurs de risque majeurs • DT1 depuis > 20 ans	Sans atteinte d'organe mais avec • ≥ 1 facteur de risque ou • Depuis ≥ 10 ans (DT1 ou DT2)	Patients jeunes • DT1 < 35 ans • DT2 < 50 ans avec durée du diabète de moins de 10 ans sans autre facteur de risque	-
Fonction rénale	eGFR < 30 mL/min/1,73m²	eGFR 30 – 59 mL/min/1,73m²	-	-
Facteur hérité	HF & MCVA ou un autre facteur de risque majeur	HF sans autre facteur de risque majeur	-	-
Facteur de risque isolé	-	• PA > 180/110 mmHg • CT > 310 mg/dL • LDL-C > 190 mg/dL	-	-
SCORE	≥ 10 %	≥ 5 % et < 10 %	≥ 1 % et < 5 %	< 1 %
1re CIBLE **LDL-C**	< 40 mg/dL** Classe IIb < 55 mg/dL ET ≥ 50 % réduction* Classe I	< 70 mg/dL ET ≥ 50 % réduction* Classe I	< 100 mg/dL Classe IIa	< 116 mg/dL Classe IIb
2e CIBLE Non-HDL-C OU ApoB	< 85 mg/dL < 65 mg/dL	< 100 mg/dL < 80 mg/dL	< 130 mg/dL < 100 mg/dL	
Intervention	1. Changement de mode de vie ET statine de haute intensité 2. ÉZETIMIBE 3. Inhibiteur PCSK9 Les taux de lipides doivent être réévalués 4 à 6 semaines après le SCA.	1. Changement de mode de vie 2. Statine de haute intensité 3. EZETIMIBE	1. Changement de mode de vie 2. Statine	Conseils sur le mode de vie

MCVA: Maladie Cardiovasculaire Athérosclérotique/* par rapport à la valeur non traitée/ PA: Pression Artérielle/CT: Cholestérol Total/ DT1: Diabète de Type I/DT2: Diabète de Type 2/ HF: Hypercholestérolémie Familiale/ SCA : Syndrome Coronarien Aigu; **: voir texte

Etude ACCORD: augmentation du RCV

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

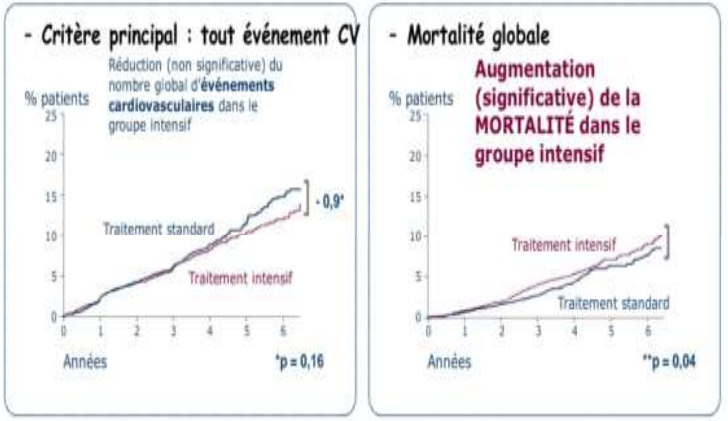
Critères d'inclusion:DT2, HbA1c> 7.5%
âge entre 40 -79 ans et atcd CV âge 55-79 ans et athérome clinique, microalb, HVG ou 2 FDR CV

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

Résultat du traitement intensif : augmentation significative de la mortalité globale

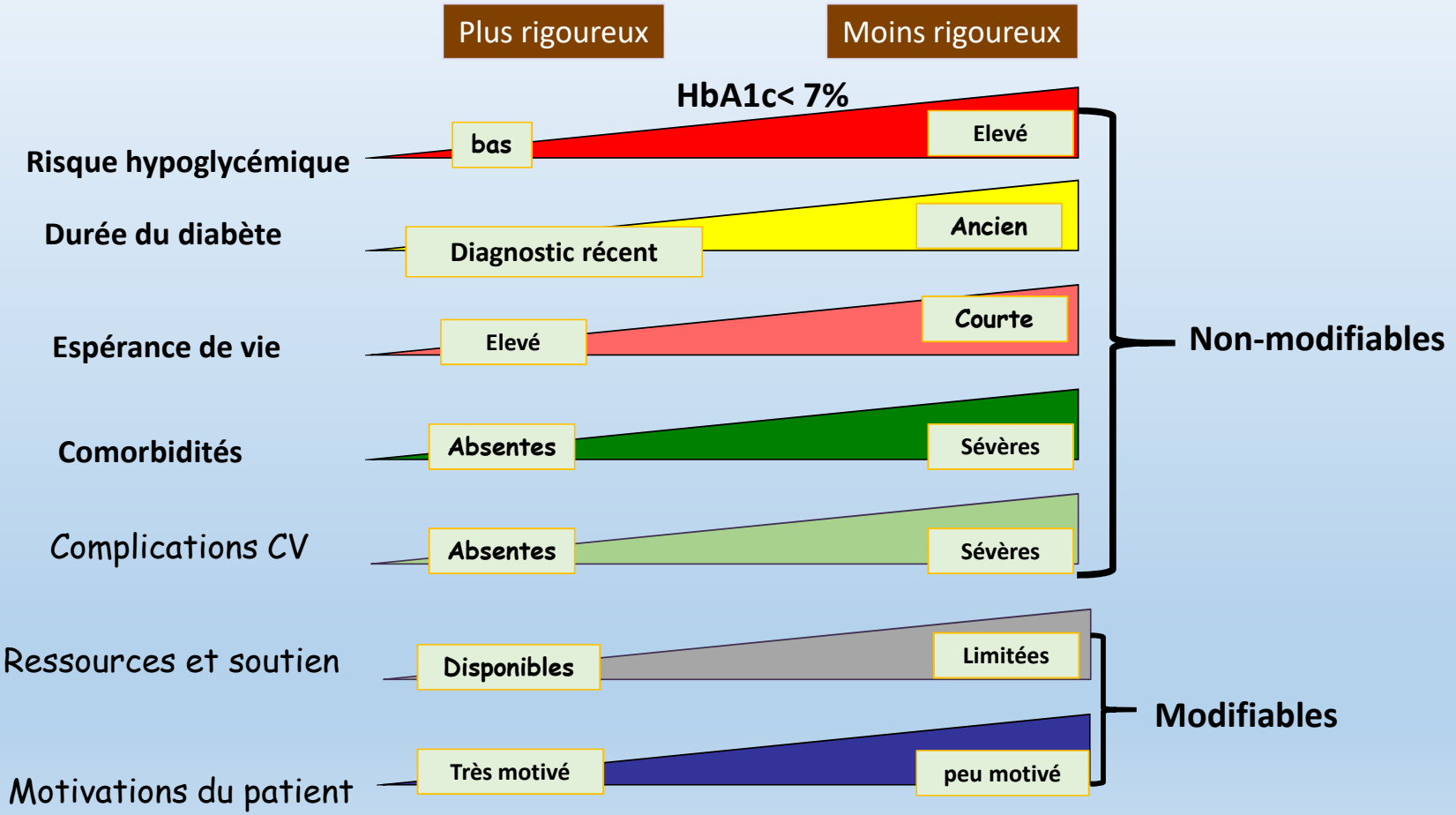
ACCORD



Arrêt du bras intensif en février 2008 (3,5 ans)
Surmortalité **non observée** dans VADT et ADVANCE
- hypothèses: hypoglycémies majeures et prise de poids importante

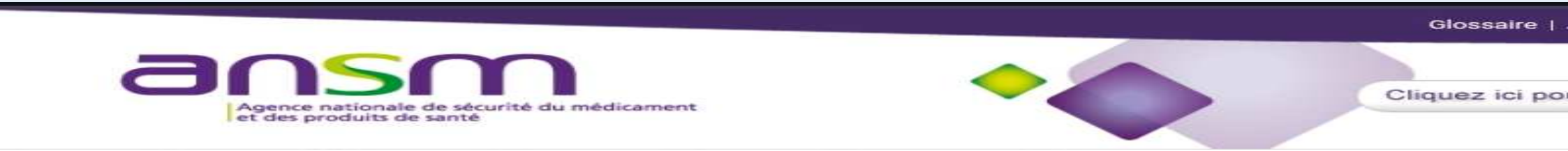
The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose in type 2 diabetes: June 12, 2008: N Engl J Med. 358: 2545-59.

Individualisation des objectifs



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

Rosiglitazone: augmentation du RCV



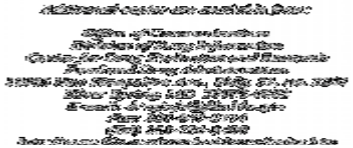
- EMA: Suspension des AMM de la Rosiglitazone
- CHMP: Rapport bénéfice/risques défavorable
- Augmentation du risque CV: IDM,AVC

EMA: Agence Européenne du Médicament
CHMP: Comité Européen d'évaluation des médicaments à usage humain

Nouvelles règles d'approbation par la FDA

Guidance for Industry

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



GUIDANCE DOCUMENT

Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry

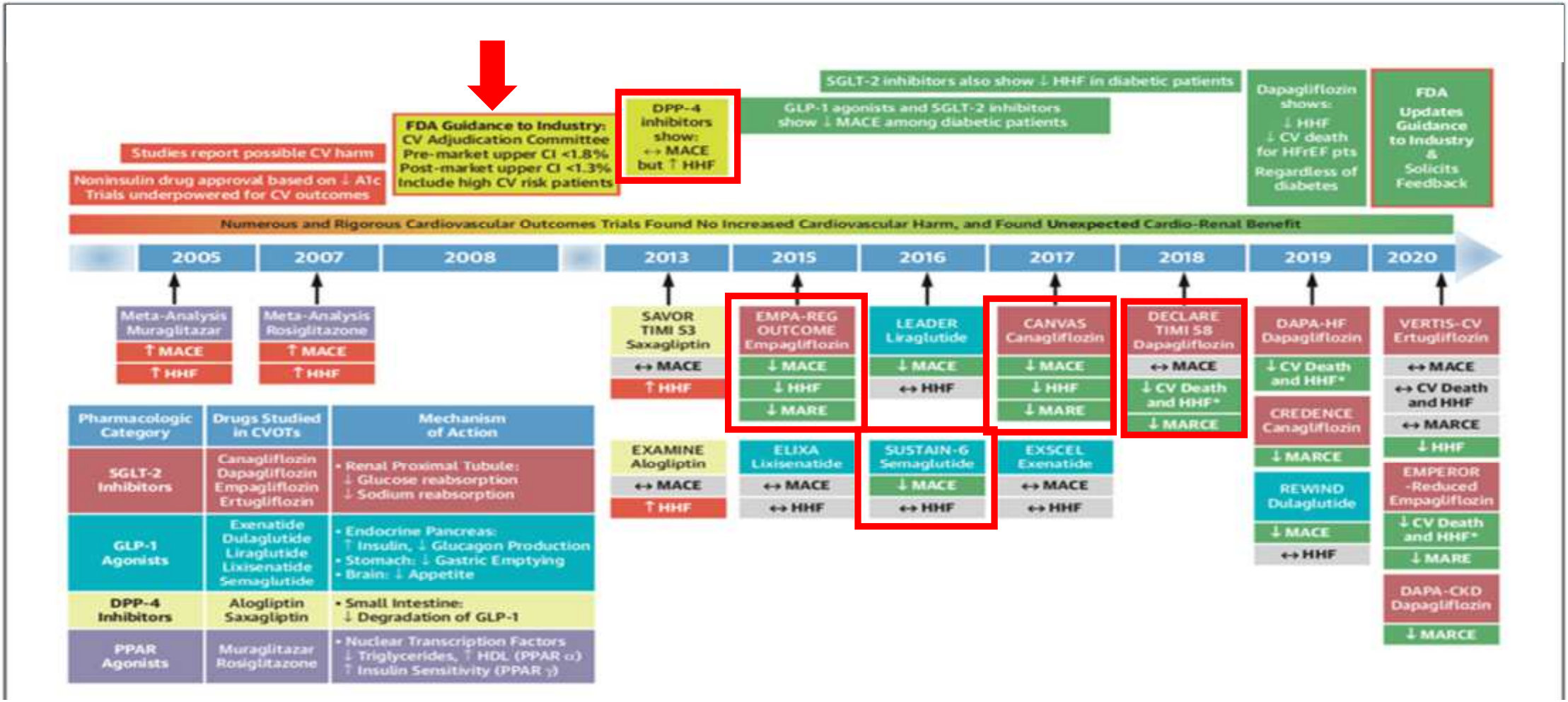
MARCH 2020

www.fda.gov/cder/guidance/index.htm

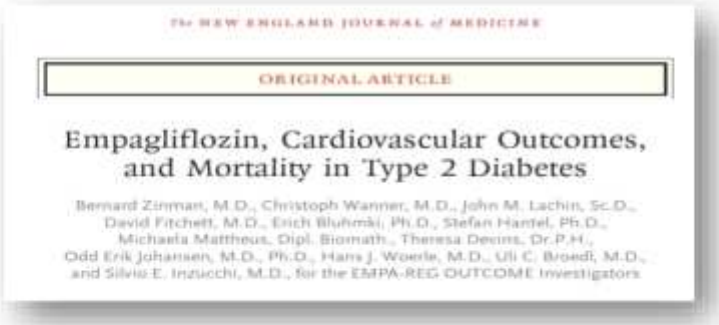
III. RECOMMENDATIONS

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.

Traitement du diabète type 2 et risque cardio-rénal



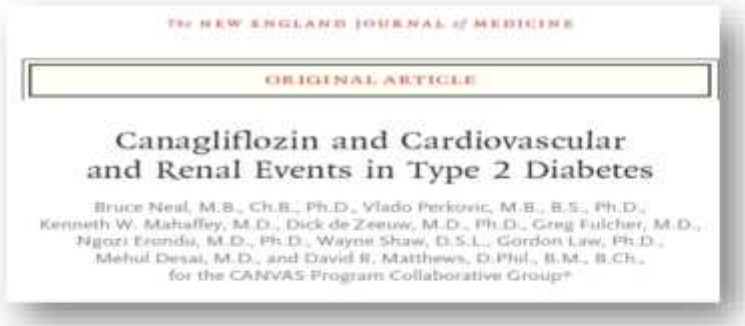
Critère primaire : MACE - 3P
(décès CV, Infarctus du myocarde ou AVC)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

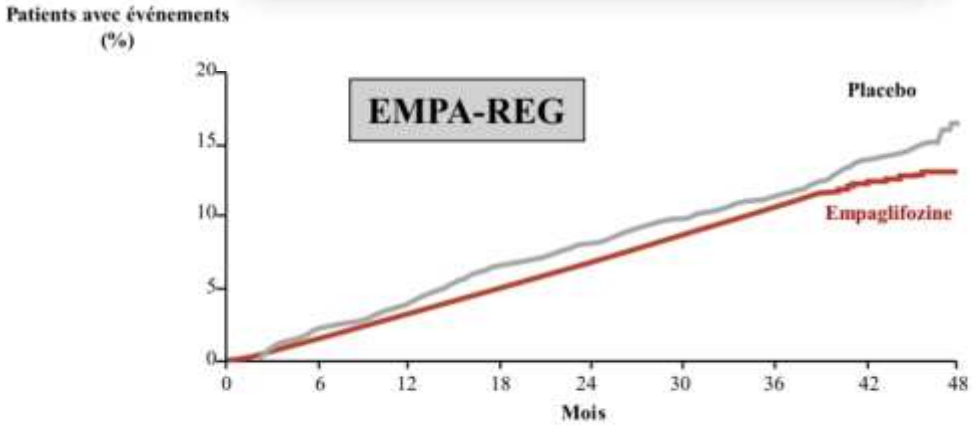
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

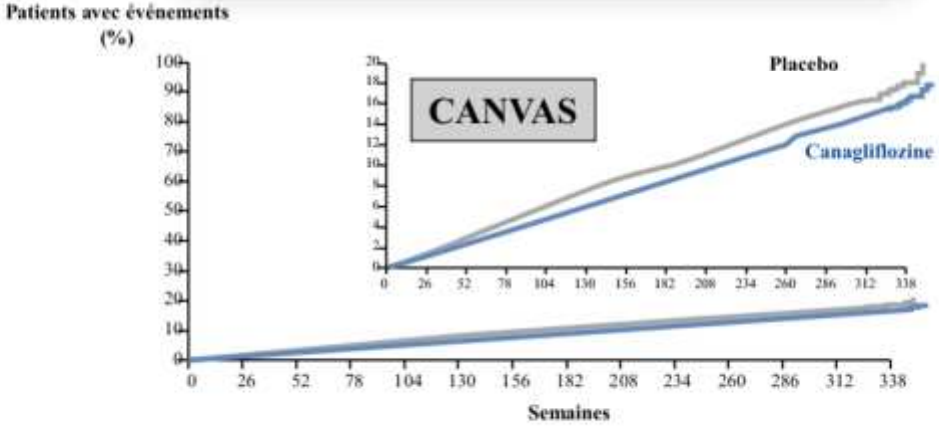

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*





HR = 0,86 (0,74 – 0,99)

p = 0,04 (supériorité)

HR = 0,86 (0,75 – 0,97)

p = 0,02 (supériorité)

Zinman B et al. N Engl J Med 2015; 373: 2117-28

Neal B et al. N Engl J Med. 2017; 377: 644-57

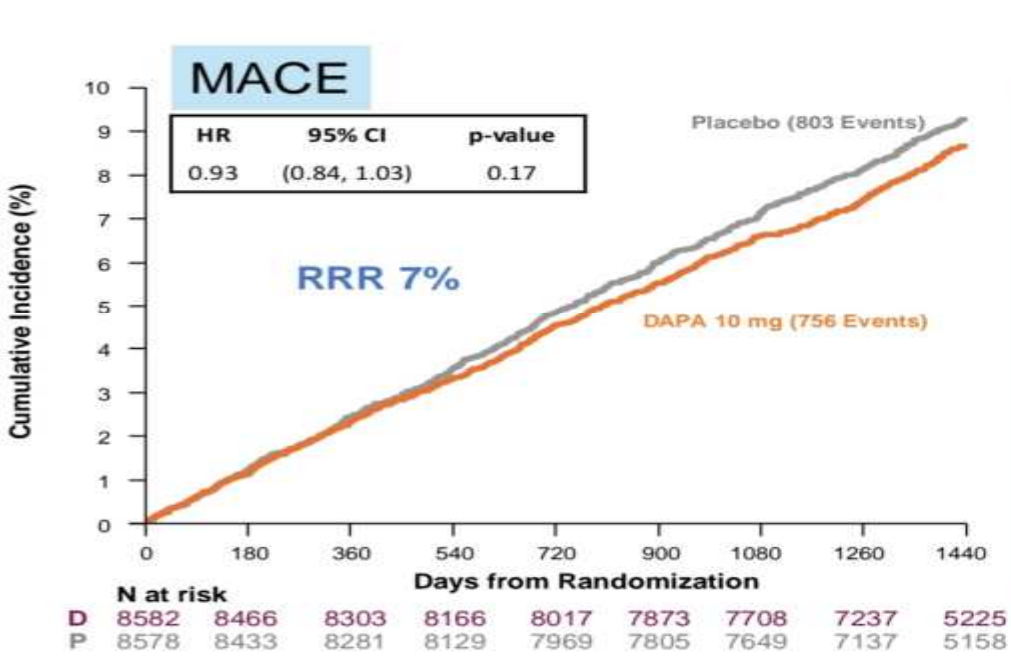
The NEW ENGLAND JOURNAL of MEDICINE

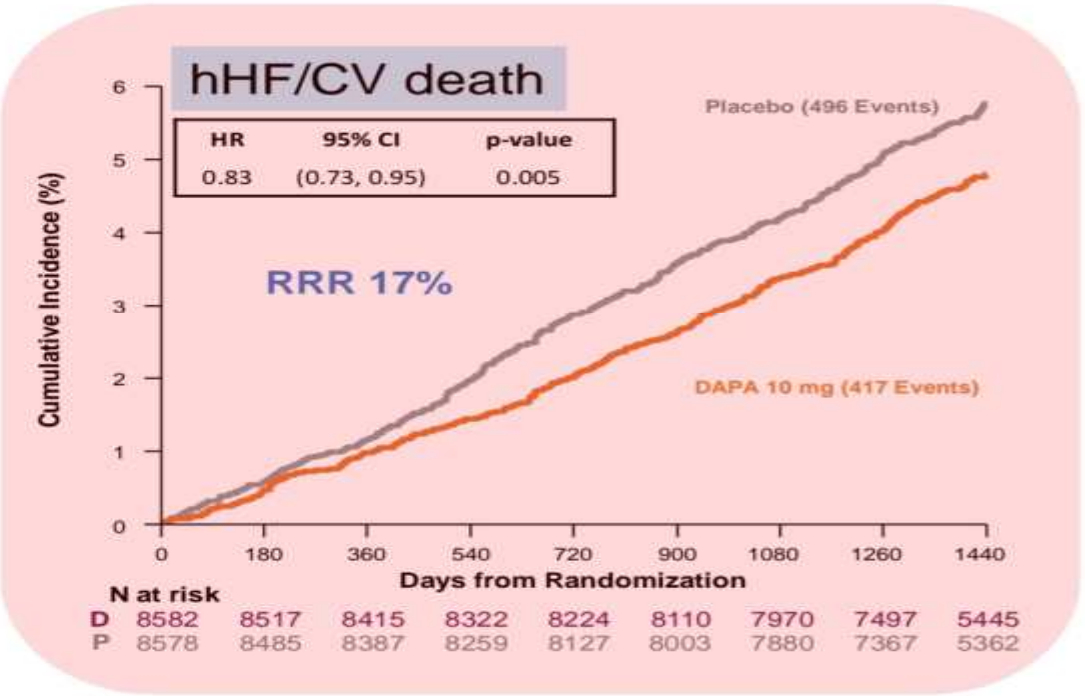
ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

N Engl J Med. 2019;380:347-357





N at risk is the number of subjects at risk at the beginning of the period. 2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.
CV = cardiovascular; CVD = cardiovascular disease; DAPA = dapagliflozin; hHF = hospitalization for heart failure; MACE = major adverse cardiac event
Wiviott SD et al. *N Engl J Med*. 2019;380:347-357

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

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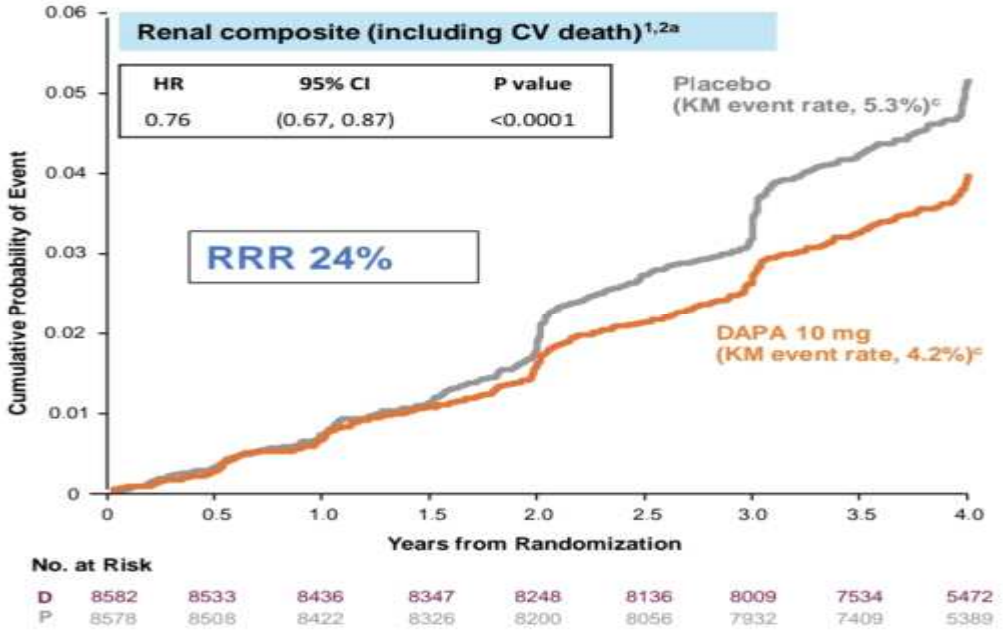
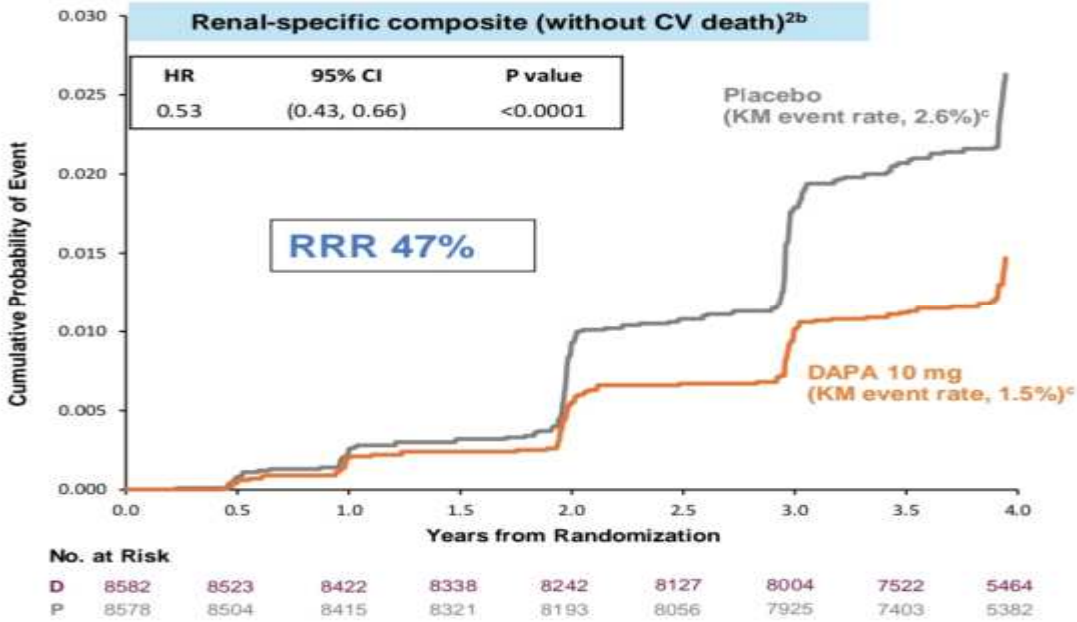
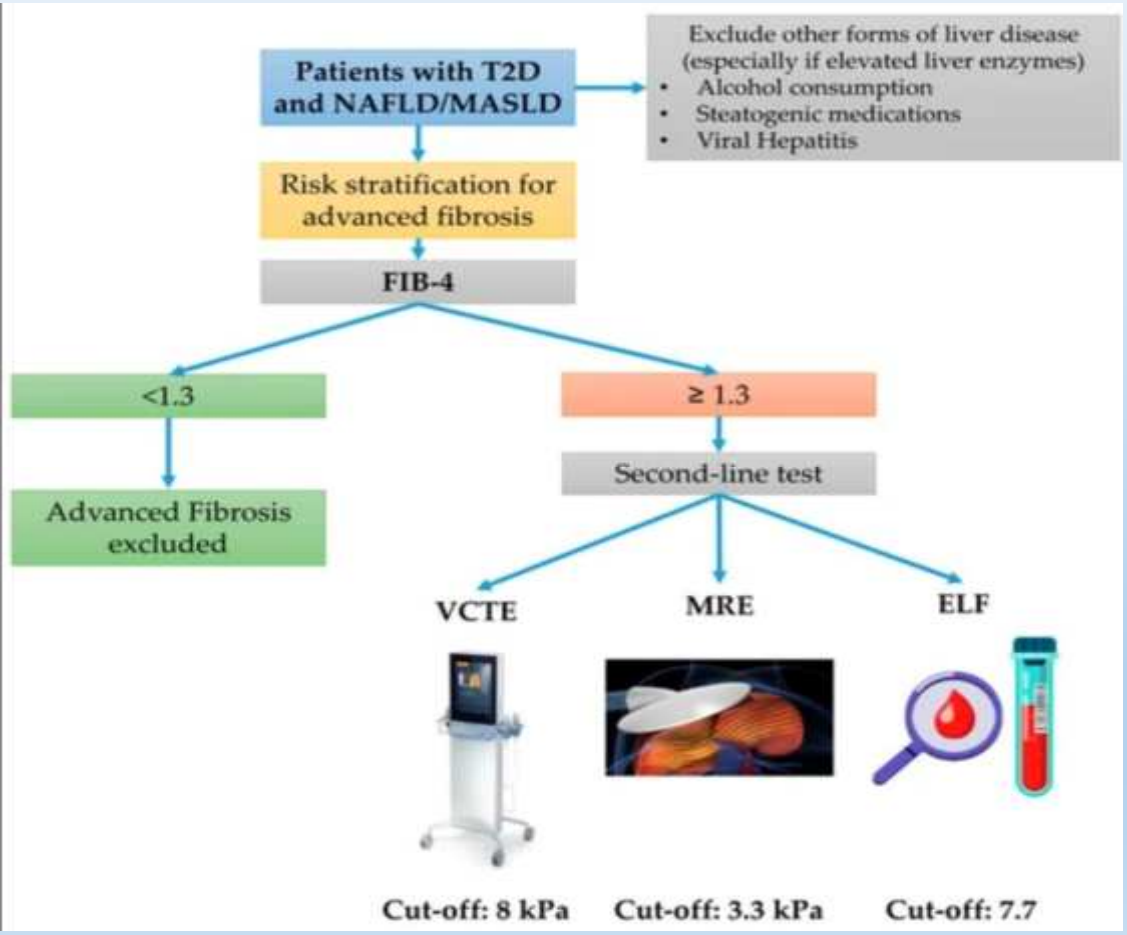
N Engl J Med. 2019;380:347-357

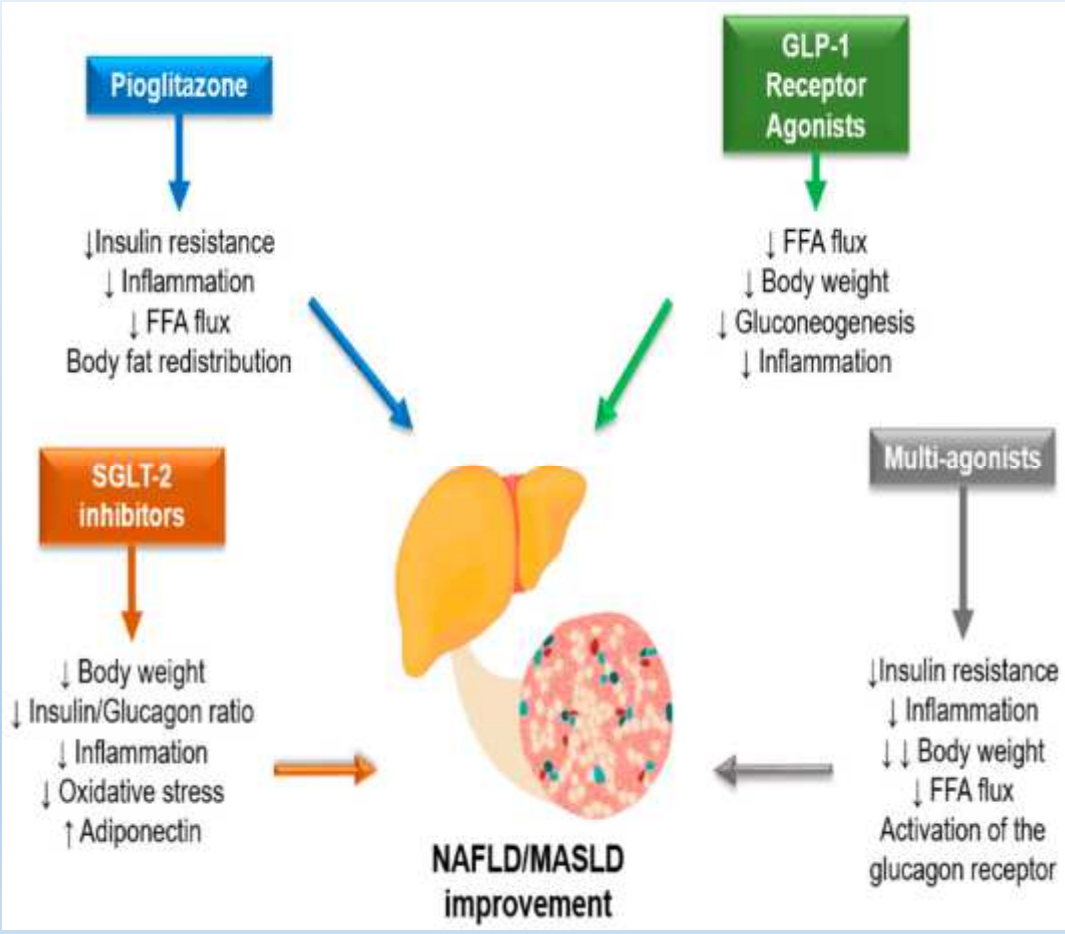




[a]Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 ml/min/1.73m² using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 ml/min/1.73m²) and/or renal or CV death (prespecified secondary outcome); [b]Renal composite endpoint without CV death (prespecified endpoint); [c]KM event rate is at 4 years. CV = cardiovascular; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; KM = Kaplan Meier; T2D = type 2 diabetes. 1. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357; 2. Mosenzon O et al. Online ahead of print. *Lancet Diabetes Endocrinol.* 2019.

Diabète et atteinte hépatique: NAFLD





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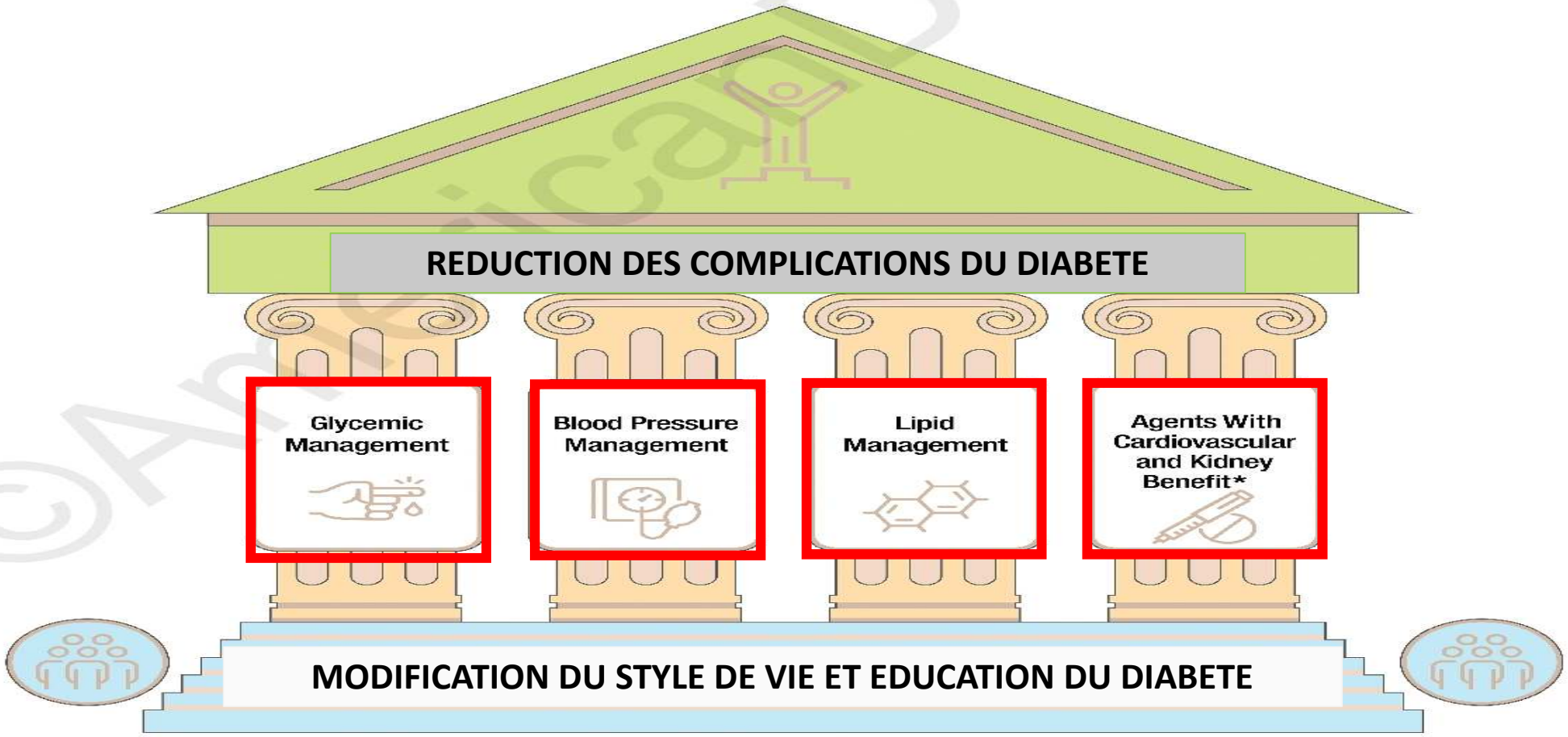
En résumé: Approche multidisciplinaire



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Conclusion

- Organoprotection en diabétologie est associée:
  - Equilibre du diabète
  - Traitement des FRCV associés
  - Objectifs individualisés
- Choix thérapeutiques: sécurité CV+++
- Amélioration de la qualité de vie
- Réduction de la morbi-mortalité liée au diabète et FRCV.

Merci