16 EME CONGRES NATIONAL AILA

Symposium Servier

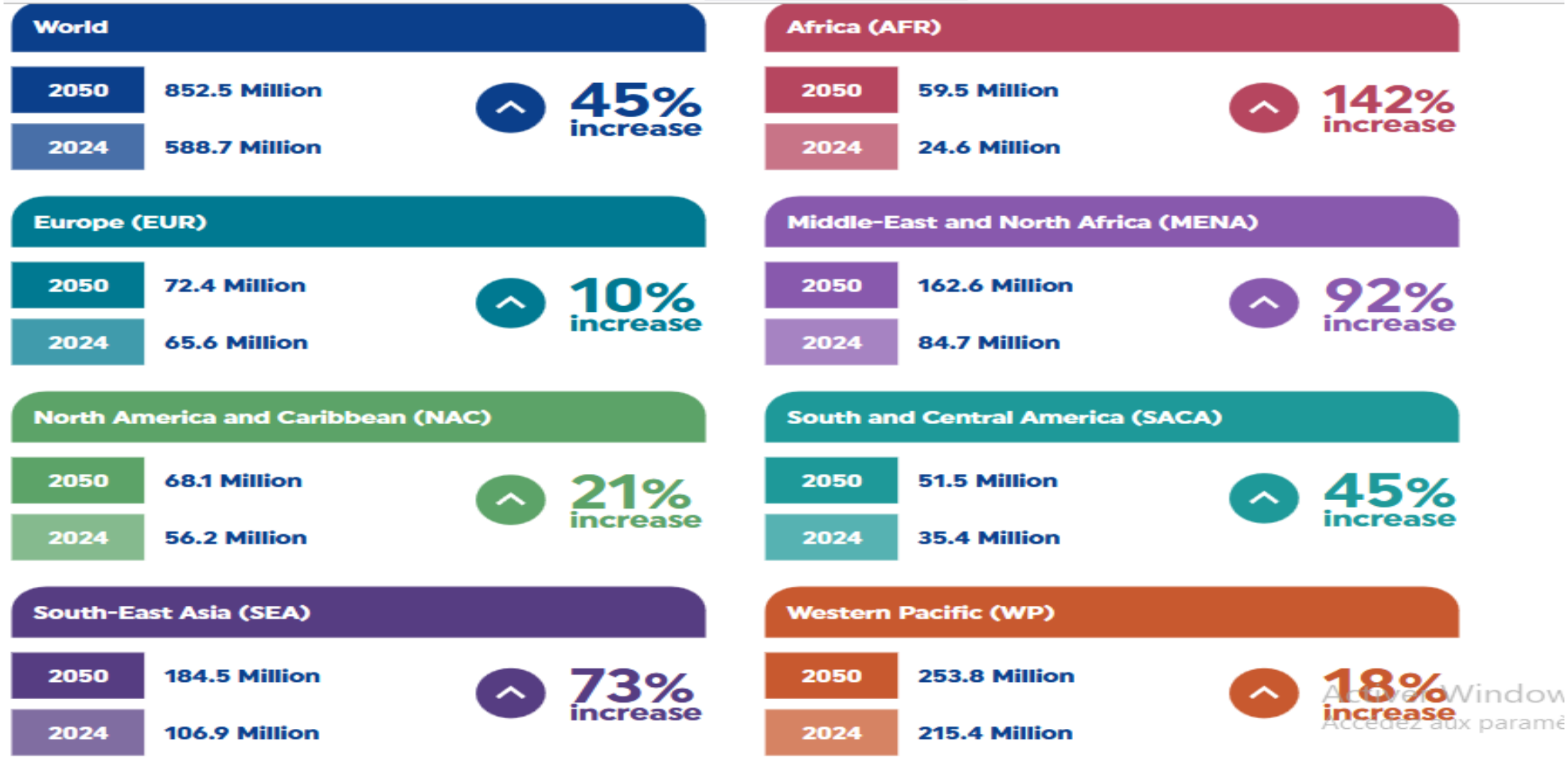
HTA et diabète: un couple dangereux!

INTRODUCTION

- Le diabète de type 2 est une maladie bipolaire qui associe quasi systématiquement un déficit de l'insulinosécrétion.

- Une certaine résistance à l'action de l'insuline.

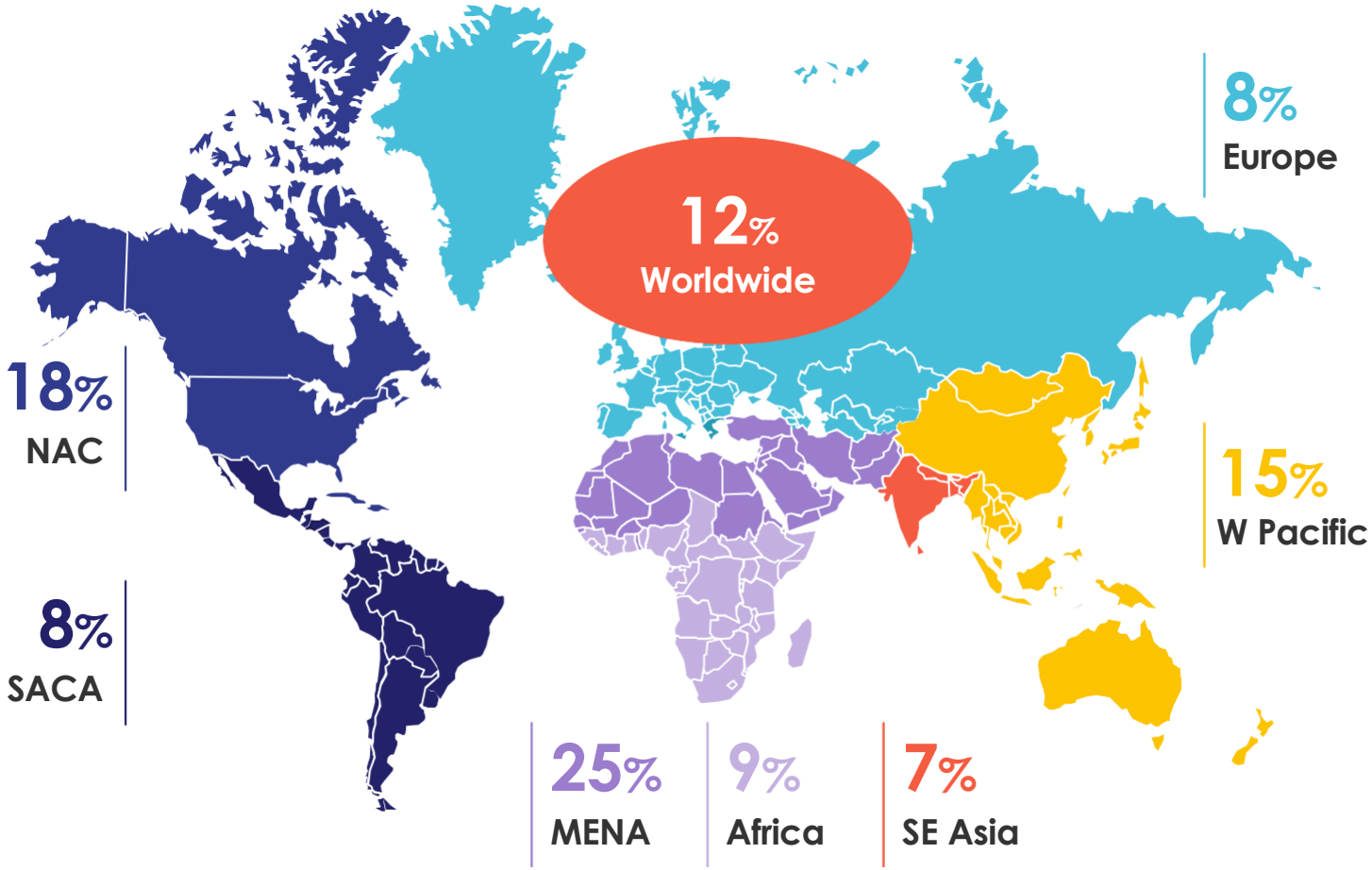
Prévalence du diabète IDF 2025



Les décès dus au diabète sont élevés dans le monde

Le diabète a été responsable de 6,7 millions de décès en 2021 (1 toutes les 5 secondes).

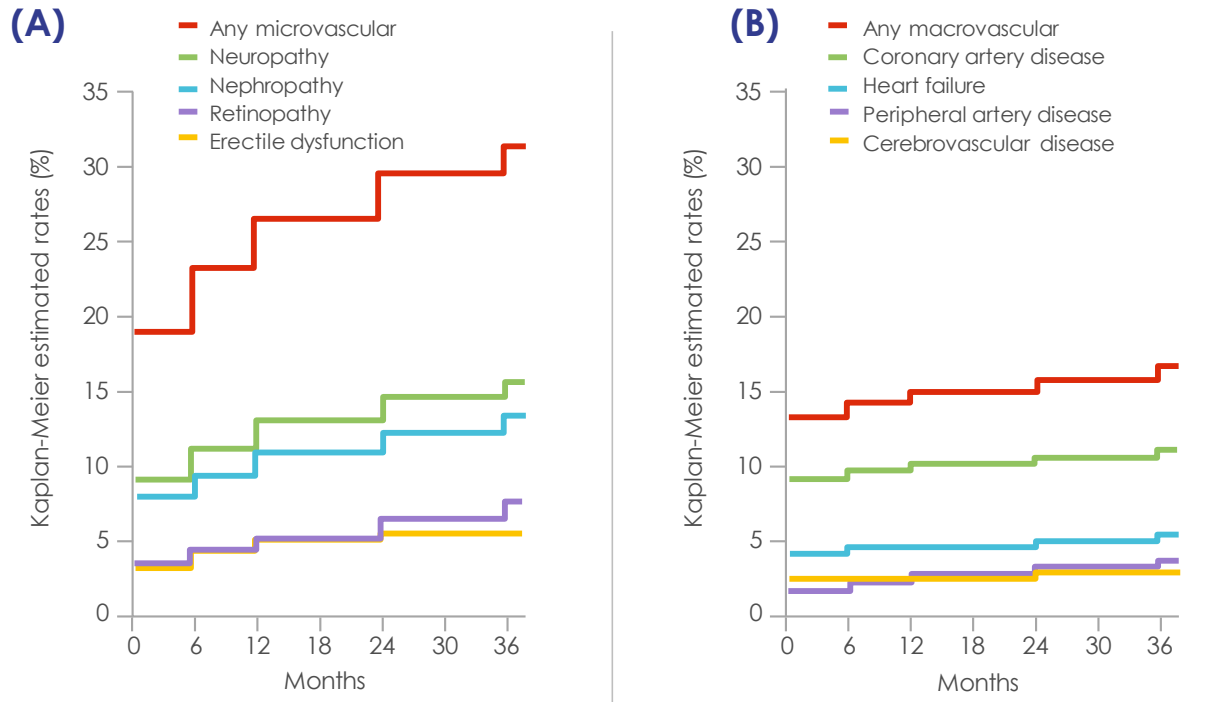
1/3 des décès dûs au diabète surviennent chez les personnes âgées de moins de 60 ans



Abbreviations: **AFR**, Africa région; **EUR**, Europe; **MENA**, Middle East and North Africa; **NAC**, North America and Carribean; **SACA**, South America and Central America; **SEA**, South- East Africa; **T2D**, type 2 diabetes; **WP**, Western Pacific. EMG, emerging markets; EST, established markets; T2D, Type 2 Diabetes; HI, High Income; MI, Middle Income; LI, Low Income IDF Region. IDF Atlas, 10th Edition, 2021; Saeedi P et al. Diabetes Res Clin Pract. 2020

Prévalence des complications microvasculaires et macrovasculaires : DISCOVER STUDY

Kaplan-Meier estimates of microvascular (A) and macrovascular (B) complication over 3 years of follow-up



	At baseline	At 3 years	3-year incidence
Microvascular complication	18.9% ▶ 31.5%		16.0%
Macrovascular complication	13.1% ▶ 16.6%		6.6%

Taux d'HbA1c élevé = ↑ risque de complications microvasculaires et macrovasculaires

DISCOVER study: multinational prospective, observational study of individuals with T20 being initiated on second-line glucose-lowering medication (either add-on or change in medication) N=11,357, 33 countries, 6 continents. Diabetes duration 5.7 years, HbA1c 8.4, 83.3% on metformin, 49.9% on SU, 43.8% on DPP4i, 11.1% on TZD, 8.3% on SGLT2i, 2.4% on GLP-1 RA Comorbidities 53.1% had hypertension, and 45.8% had hyperlipidemia with 46.0% were treated with a statin Arnold SV *et al.* https://doi.org/10.1016/j.ahj.2021.10.181

Prise en charge multidisciplinaire et évolutive

Maladie évolutive nécessitant une révision périodique des objectifs :

Une adaptation permanente du traitement

- Plan de soins personnalisé.
- Approche multidisciplinaire.
- Prise en charge des facteurs de risque.

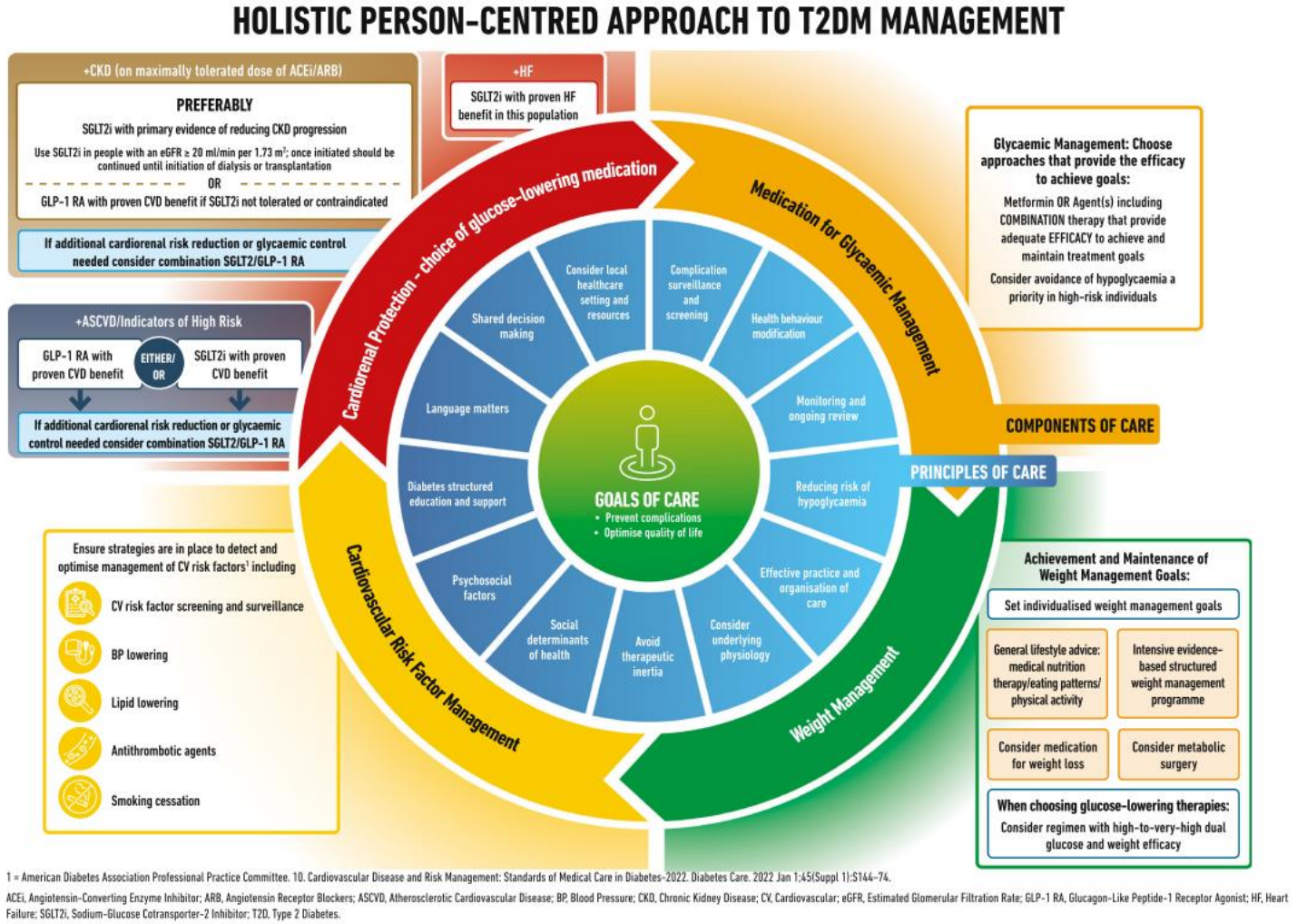
Profil patient proposé

- Homme de 55 ans Diabétique de type 2 depuis 7 ans
- HTA grade2 avec HVG
- Conducteur de camion
- BMI 36 kg/m2- FO:rhst1, pas de RD
- Sous Metformine à dose maximale

DATE	HbA1c	DFG	LdL-Chol
03/08/2021	7,6%	> 60ml/min	136 mg/dl
09/12/2021	8,1%	55ml/min	140 mg/dl

Approche holistique centrée sur le patient

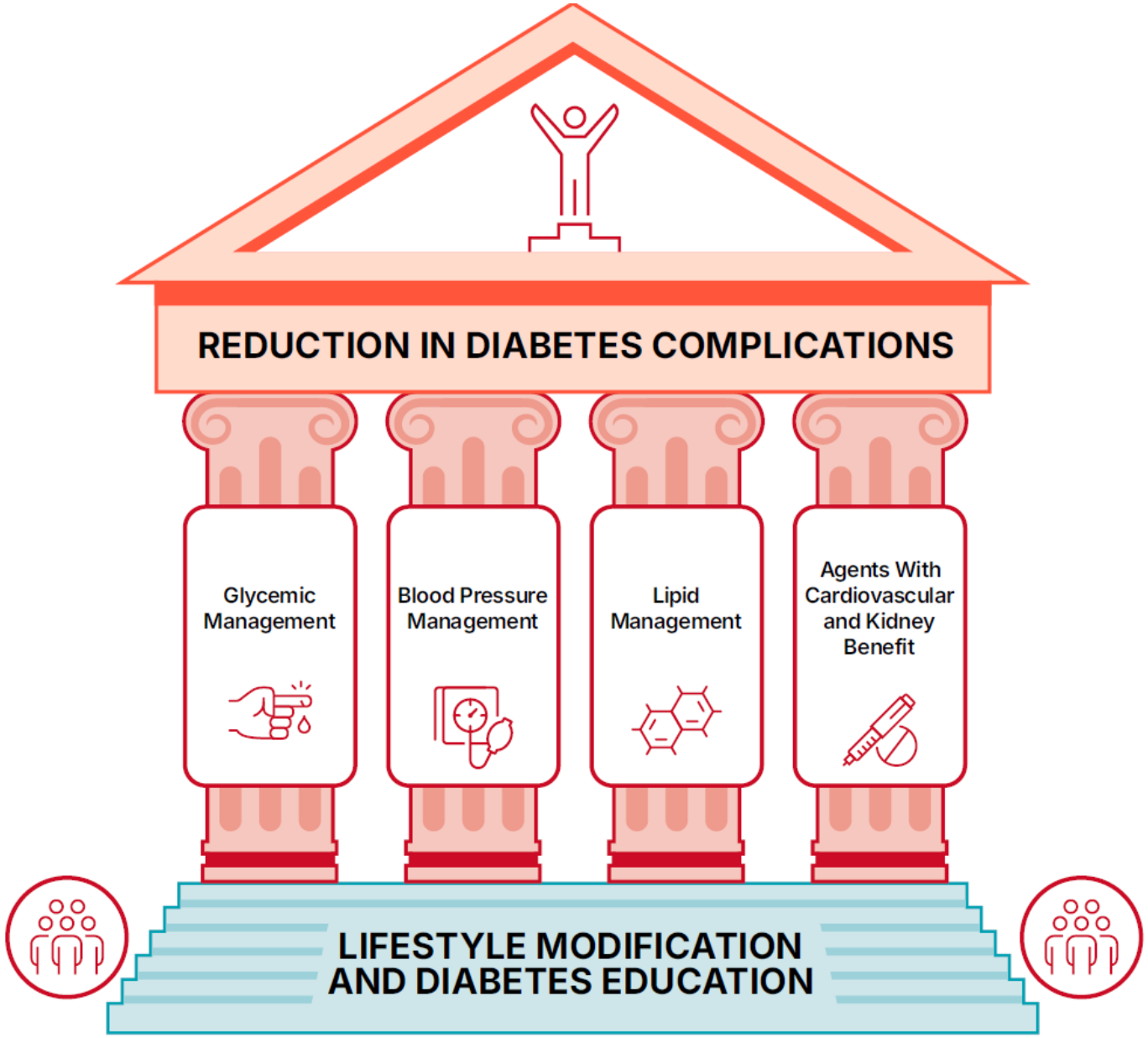
- Centré sur le patient
- Accent sur l'éducation et le soutien à l'autogestion du diabète
- Prise de décision partagée pour créer un plan de gestion avec une réévaluation régulière (tous les 3 à 6 mois)



Recommandations supplémentaires ADA 2025

Utilisation de médicaments moins coûteux pour la gestion de la glycémie (c'est-à-dire la metformine, les **sulfonylurées**, les thiazolidinediones et l'insuline humaine) en tenant compte des risques:

- Hypoglycémie.
- Prise de poids.
- Evénements cardiovasculaires et rénaux.
- Autres effets indésirables.



Cardiovascular Disease and Risk Management:
Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):S206-S238

Quelle place des Sulfamides pour réduire l'HBA1c?

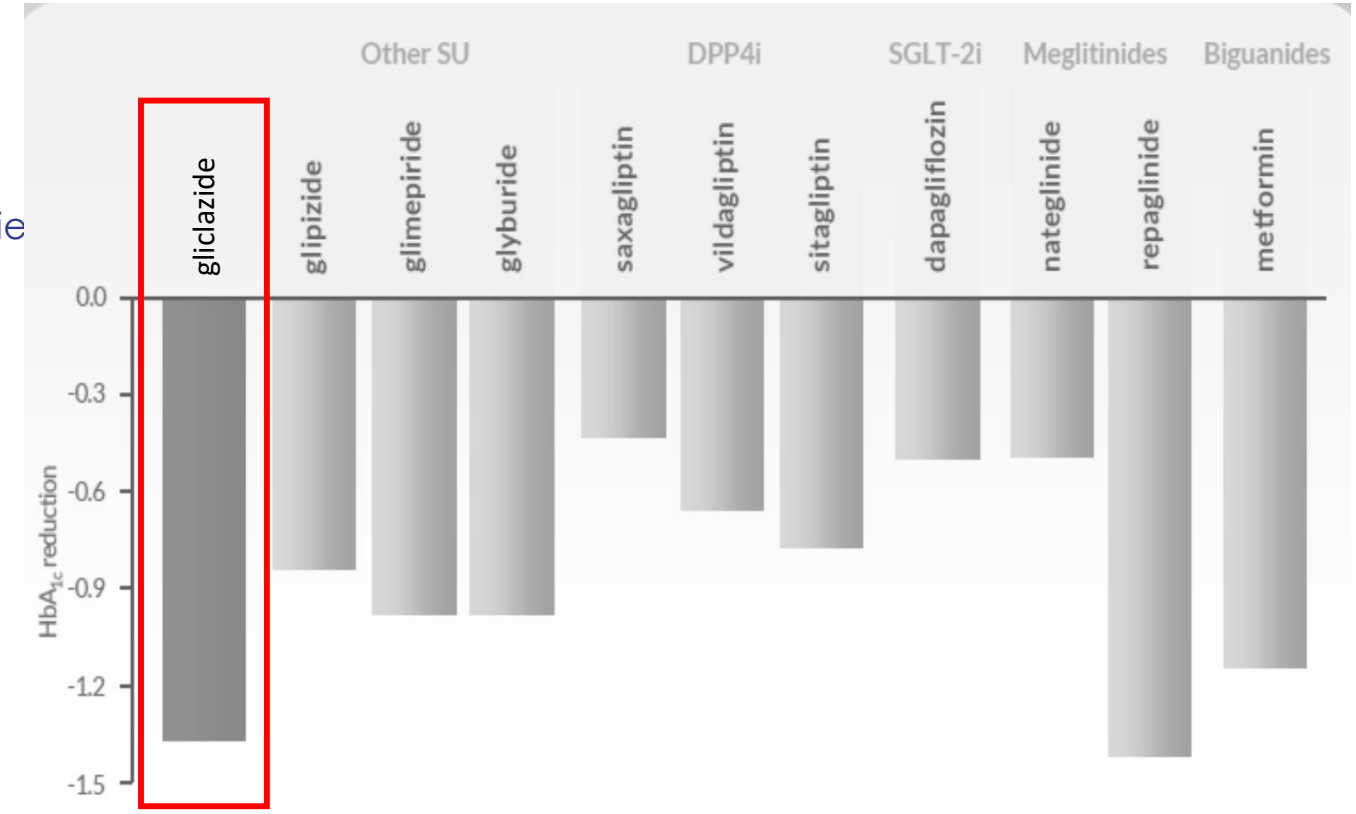
Le contrôle glycémique et Antidiabétiques oraux

Méta-analyse de JIA
Comparant l'efficacité sur la glycémie de 11 antidiabétiques oraux

- Méta-analyse en réseau
- 75 essais contrôlés, randomisés
- 33 830 patients
- 11 antidiabétiques oraux, 5 classes
- 8 pays (Arménie, Géorgie, Liban, Malaysie, Russie, Slovénie Suisse et Turquie)

- **Les antidiabétiques oraux les plus efficaces sur l'HbA1c en monothérapie sont le GLICLAZIDE, la Metformine et le Répaglinide.**

- Pas de différences significatives des résultats obtenus par sous-groups (données robustes)



Adapted from Jia Y et al. Obes Rev. 2018. doi:10.1111/obr.12753.

Proportion de patient sous Metformine et Sulfamides dans les CVOTs

La metformine et les SU étaient les traitements antidiabétiques oraux de base les plus couramment prescrits dans toutes les récentes études CVOT ainsi que les SGLT2i et les GLP1-RA..

- Essais sur les résultats cardiovasculaires (essais contrôlés randomisés d'un médicament actif par rapport à un placebo en plus des soins habituels)).

GLP-1 RA	Baseline Metformin	Baseline SU
ELIXA[1] (lixisenatide)	**77%**	**37%**
LEADER[2] (liraglutide)	**76%**	**51%**
SUSTAIN-6[3] (semaglutide)	**66%**	**33%**
EXSCEL[4] (exenatide QW)	**73%**	**29%**
HARMONY[5] (albiglutide)	**74%**	**29%**
REWIND[6] (dulaglutide)	**81%**	**46%**
PIONEER-6[7]	**~77%**	**~32%**

SGLT2i	Baseline Metformin	Baseline SU
EMPA-REG[8] (empagliflozin)	**74%**	**43%**
CANVAS Program[9] (canagliflozin)	**77%**	**44%**
DECLARE-TIMI 58[10] (dapaglifozin)	**82%**	**42%**
VERTIS-CV[11] (ertugliflozin)	**77%**	**41%**
SCORED[12] (Sotagliflozin)	**55%**	**27%**

Abbreviations: **CV**, cardiovascular; **CVOTs**, cardiovascular outcome trials; **GLP-1**, Glucagon-like peptide-1; **RCTs**, randomized controlled trials; **SU**, sulfonylurea; **T2D**, type 2 diabetes

1. Pfeffer MA et al. *N Engl J Med.* 2015;373:2247-2257
2. Marso SP et al. *N Engl J Med.* 2016;375:311-322
3. Marso SP et al. *N Engl J Med.* 2017; 376(9):891-2
4. Holman RR et al. *N Engl J Med.* 2017;377:1228-1239
5. Hernandez AF et al. *Lancet.* 2018;392:1519-1529
6. Gerstein HC et al. *Lancet.* 2019;394:121-130
7. Husain M et al. N Engl J Med. 2019; 381 (9): 841-851
8. Zinman B et al. *N Engl J Med.* 2015;373:2117-2128
9. Neal B et al. *N Engl J Med.* 2017;377:644-657
10. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357
11. Cannon CP et al. *N Engl J Med.* 2020; 383(15):1425-1435
12. Bhatt DL et al. *N Engl J Med.* 2021; 384(2):129-139

Que faire si mon patient diabétique est hypertendu ?

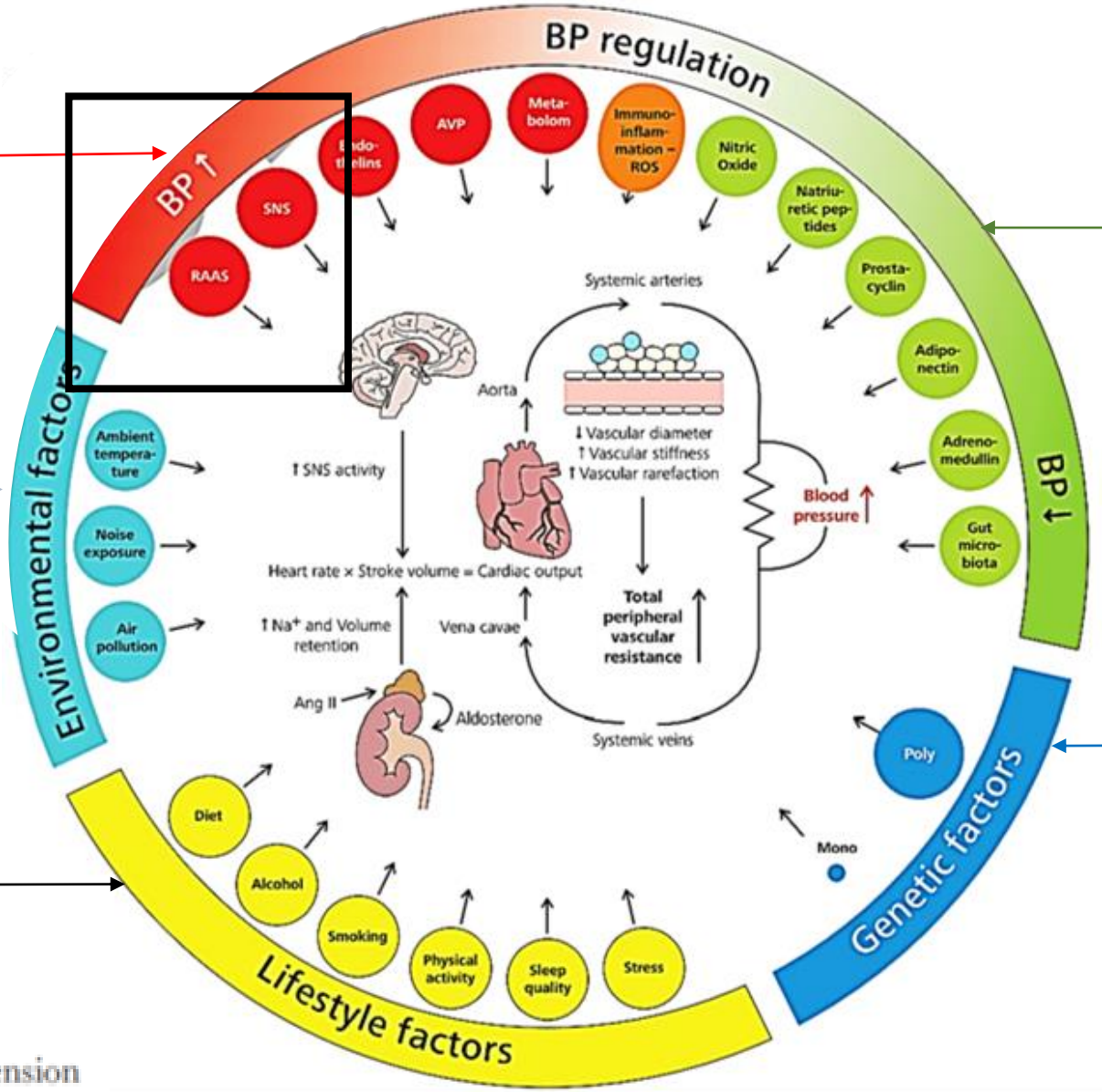
PRINCIPLES OF HYPERTENSION PATHOPHYSIOLOGY

2023 ESH Guidelines for the management of arterial hypertension

- **RAAS**
- **SNC**
- **Endothéline**

- **Température ambiante**
- **Nuisance sonore**
- **Pollution atmosphérique**

- **Diète**
- **Alcool**
- **Tabac**
- **Activité physique**
- **Qualité du sommeil**
- **Stress**



- **Inflammation**
- **NO**
- **Natriurétique péptide**
- **Prostacycline**
- **Adiponéctine**
- **Microbiote intéstinal**

- **Facteur Génétique**

Définition(s) de l'hypertension artérielle

ESH/ESC 2018 and ESH 2023

Recommendations in 2018 version	Class[a]	Level[b]
6. Definition and classification of elevated blood pressure and hype		
It is recommended that BP be classified as optimal, normal, high-normal, or grades 1–3 hypertension, according to office BP.	I	C

AHA/ACC 2017

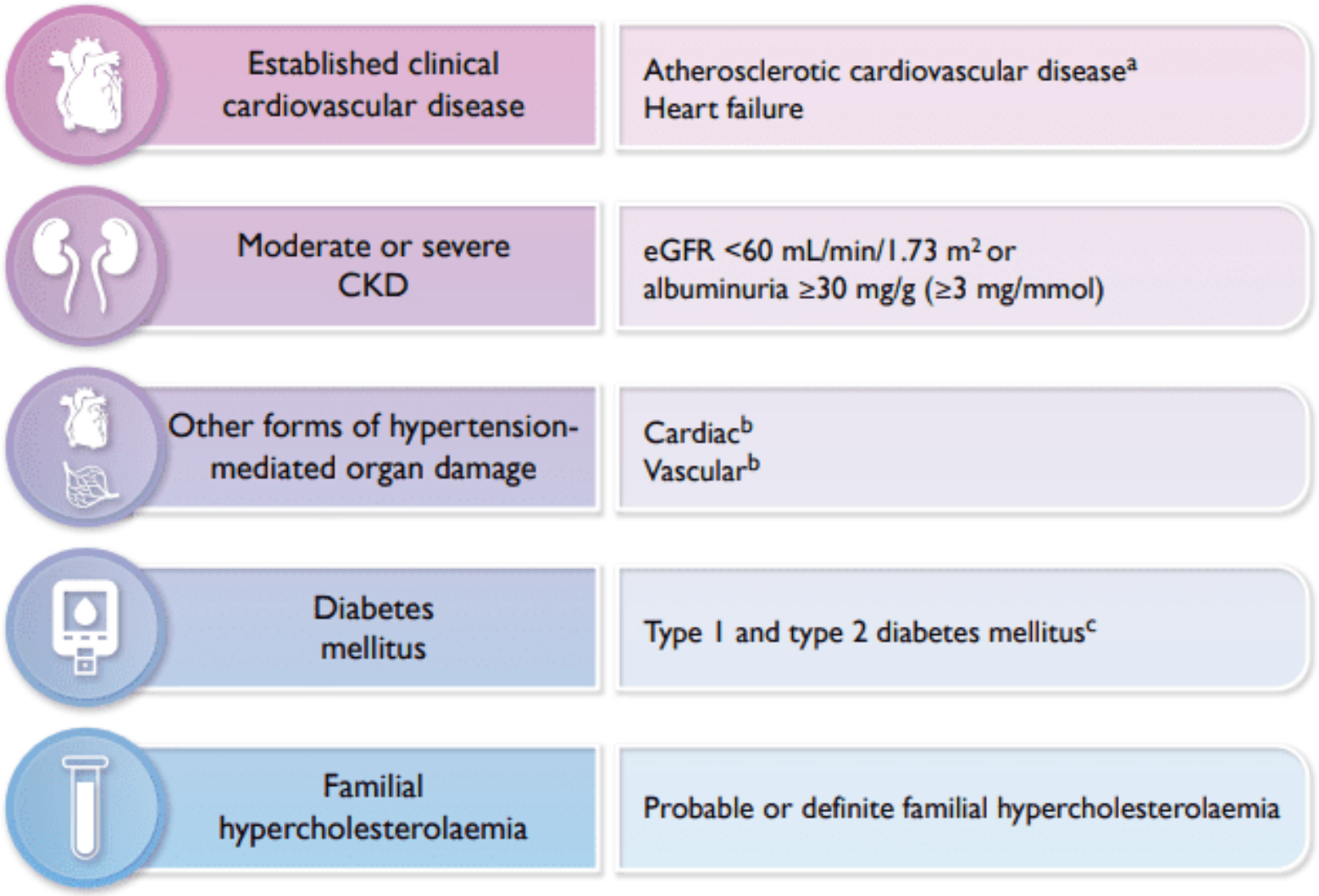
Table 6. Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

ESC 2024

Recommendations in 2024 version	Class[a]	Level[b]
ertension		
It is recommended that BP be categorized as non-elevated BP, elevated BP, and hypertension to aid treatment decisions.	I	B
SCORE2 is recommended for assessing 10-year risk of fatal and non-fatal CVD among individuals aged 40–69 years with elevated BP who are not already considered at increased risk due to moderate or severe CKD, established CVD, HMOD, diabetes mellitus, or familial hypercholesterolaemia.	I	B
SCORE2-OP is recommended for assessing the 10-year risk of fatal and non-fatal CVD among individuals aged ≥70 years with elevated BP who are not already considered at increased risk due to moderate or severe CKD, established CVD, HMOD, diabetes mellitus, or familial hypercholesterolaemia.	I	B

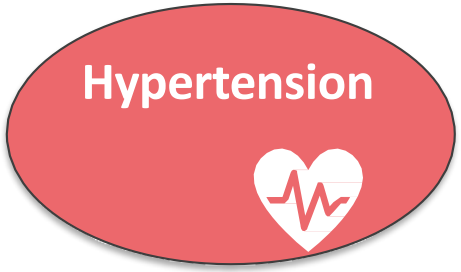
Quels sont les situations cliniques à risque selon ESC 2024 ?



75% des patients diabétiques sont hypertendus

Of people with type 2 diabetes:

- 75% have hypertension[1]
- 90% are overweight/obese[2]
- 30–60% have dyslipidemia[3]



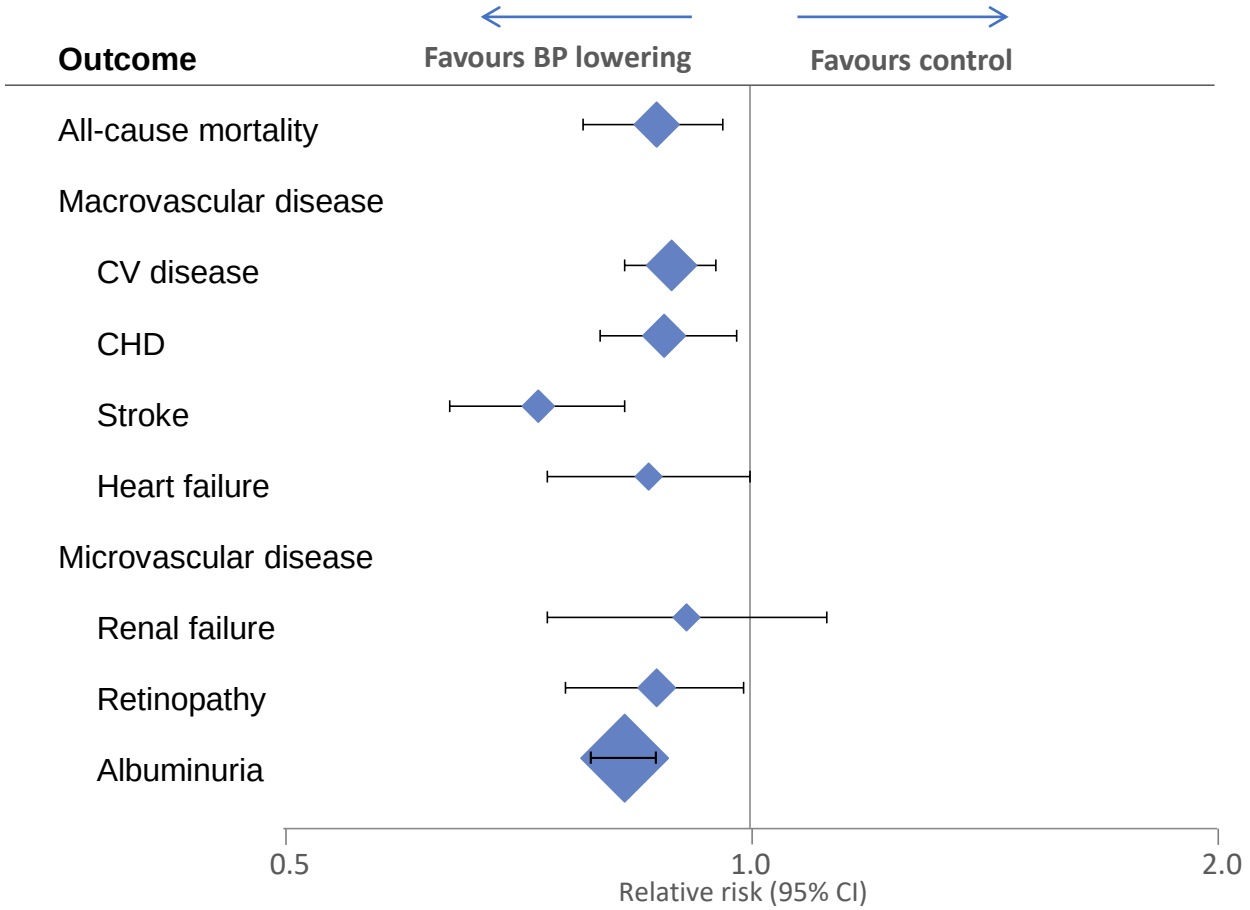
Of people with hypertension:

- 29% have type 2 diabetes[4]
- 60–70% are overweight/obese[3]
- 49% have dyslipidemia[4]
- 31% have chronic kidney disease[5]
- 47% have coronary artery disease[6]

T2DM, type 2 diabetes mellitus.

1. Nwankwo T, et al. *NCHS Data Brief.* 2013;(133):1-8; 2. Grant B, et al. *Clin Med (Lond).* 2021;21(4):e327-331; 3. Cosentino F, et al. *Eur Heart J.* 2020;41(2):255-323; 4. Thoenes M, et al. *Cardiol Res Pract.* 2012:925046; 5. Mozaffarian D, et al. *Circulation.* 2016;133(4):e38-360; 6. Lawes CMM, et al. *Lancet* 2008; 371:1513–1518.

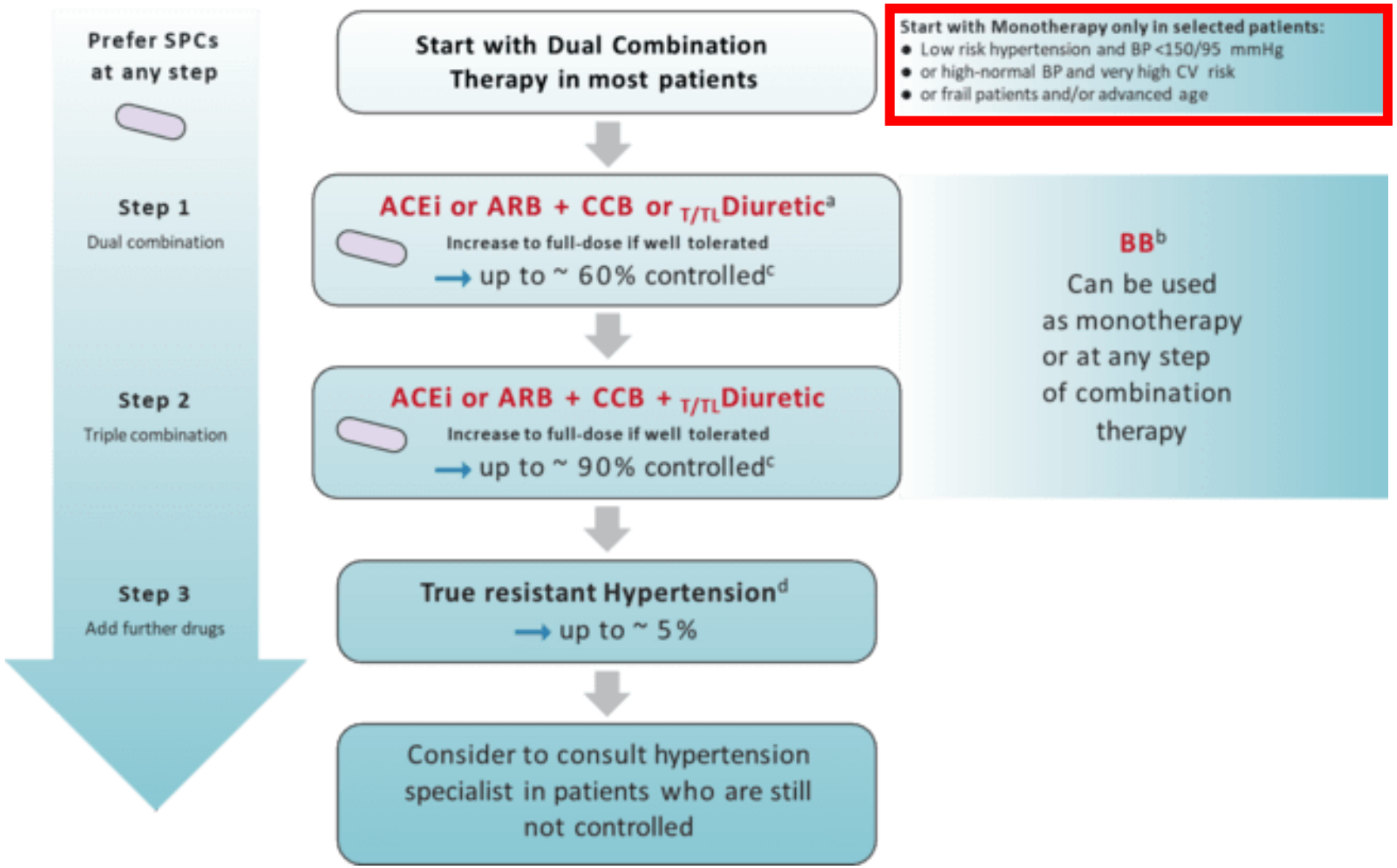
Réduire la PA de 10 mm Hg réduit le risque de mortalité toutes causes et des évènements micro et macro vasculaires chez le diabétique de type 2



Meta-analysis of 40 large scale, randomised, controlled trials of BP-lowering treatment including patients with diabetes (n=100,354 participants).

Emdin et al. JAMA 2015;313:603–15.

Stratégie générale pour le traitement des patients hypertendus: ESH



étude QUADR0 / Conclusion

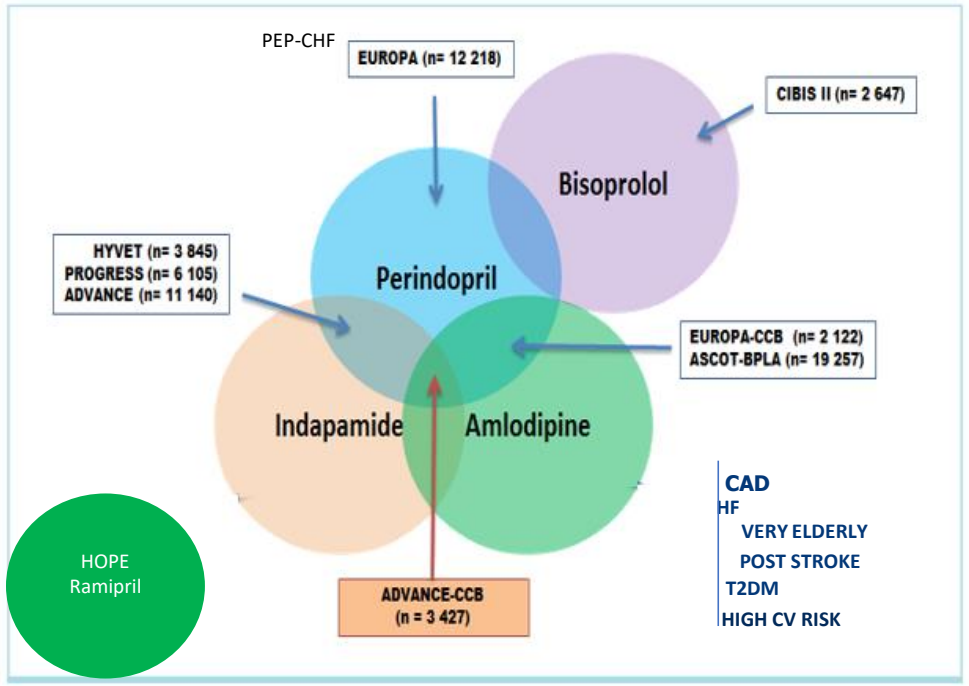
- Congrès 2024 de la Société européenne de cardiologie (ESC)

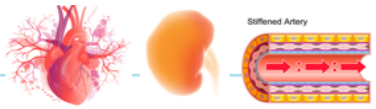
- Les résultats de l'essai QUADRO démontrent la supériorité de la combinaison en un seul comprimé de quatre molécules Antihypertensives (**périndopril, indapamide**, amlodipine et bisoprolol) par rapport à une trithérapie sans bêta-bloquant chez des patients souffrant d'HTAR.

- Cette supériorité a été observée pour la PAS et PAD, mesurée en clinique au cabinet, par MAPA, ainsi qu'en AMT. Le profil de sécurité de cette association a été jugé satisfaisant. Cette approche pourrait constituer une solution efficace pour améliorer l'adhérence au traitement et le contrôle. Une Réduction : La pression artérielle **– de 8 mmH**

PREUVES DANS LES ECRS EN FAVEUR DES IEC DANS DES PROFILS DE PATIENTS SPÉCIFIQUES

IEC SEUL OU EN ASSOCIATION





Perindopril + indapamide

- **REASON, PREMIER, PICXEL:** Properties on cardiovascular risk factors: beneficial effect on cardiac and vascular hypertrophy, endothelial function, microcirculation and microalbuminuria

Périndopril + Indapamide

Études cliniques : REASON, PREMIER, PICXEL

Mise en évidence des effets bénéfiques cardiovasculaires de l'association :

- Réduction de l'hypertrophie cardiaque et vasculaire
- Amélioration de la fonction endothéliale
- Optimisation de la microcirculation
- Diminution de la microalbuminurie
- Contribution à la réduction du risque cardiovasculaire global

Études randomisées contrôlées traitement intensif versus standard dans la prise en charge de l'HTA du diabétique

Clinical trial	Population	Outcomes
UKPDS	4801 with newly diagnosed T2DM aged 25–65	• Chaque réduction de **10 mmHg** de la PAS a été associée à une diminution de **12 %** du risque de tout critère d'évaluation lié au diabète et à une réduction de **15 %** du risque de décès lié au diabète.
ACCORD BP	4733 with T2DM aged 40–79 with prior evidence of CVD or multiple CV risk factors	• No benefit in primary endpoint: Composite of non-fatal MI, non-fatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE	11,140 with T2DM aged ≥55 with prior evidence of CVD or multiple CV risk factors	• L'intervention a permis de réduire le risque de survenue du critère d'évaluation composite principal, à savoir les maladies macrovasculaires et microvasculaires majeures. **9 %** • décès de toute cause **14 %** • et décès dû à une MCV **18 %**
HOT	18,790, including 1501 with diabetes	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
STEP	8511 aged 60–80 yrs, including 1627 with diabetes	• Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

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NEW DATA confirm the benefits of ACEIs over ARBs

B.LEVY/ JJ MOURAD

NEW 2022

REVIEW

Renin Angiotensin Blockers and Cardiac Protection: From Basis to Clinical Trials

Bernard I. Lévy[1,*] and Jean Jacques Mourad[2]

Despite a similar beneficial effect on blood pressure lowering observed with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor (AT1R) blocker (ARBs), several clinical trials and meta-analyses have reported higher cardiovascular mortality and lower protection against myocardial infarction with ARBs when compared with ACEIs. The European guidelines for the management of coronary syndromes and European guidelines on diabetes recommend using ARBs in patients who are intolerant to ACEIs. We reviewed the main pharmacological differences between ACEIs and ARBs, which could provide insights into the differences in the cardiac protection offered by these 2 drug classes. The effect of ACEIs on the tissue and plasma levels of bradykinin and on nitric oxide production and bioavailability is specific to the mechanism of action of ACEIs; it could account for the different effects of ACEIs and ARBs on endothelial function, atherogenesis, and fibrinolysis. Moreover, chronic blockade of AT1 receptors by ARBs induces a significant and permanent increase in plasma angiotensin II and an overstimulation of its still available receptors. In animal models, AT4 receptors have vasoconstrictive, proliferative, and inflammatory effects. Moreover, in models with kidney damage, atherosclerosis, and/or senescence, activation of AT2 receptors could have deleterious fibrotic, vasoconstrictive, and hypertrophic effects and seems prudent and reasonable to reserve the use of ARBs for patients who have presented intolerance to ACE inhibitors.

Keywords: ACE inhibitors; angiotensin receptors blockers; arterial hypertension; blood pressure; coronary diseases; cardiovascular risks; hypertension

https://doi.org/10.1093/ajh/hpab108

The development of captopril, the first oral active angiotensin-converting enzyme inhibitor (ACEI) in the 1970s,[1] and of losartan, the first oral active selective angiotensin II type 1 receptor (AT1R) blocker (ARB),[2] are milestones in the history of the treatment of cardiovascular diseases, especially arterial hypertension and heart failure. ACEIs and ARBs are today widely used in the treatment of arterial hypertension, heart failure, myocardial infarction (MI), and kidney diseases.[3–6]

ARBs have emerged as a leading class in the treatment of high blood pressure and have been increasingly used in type 2 diabetes. Based on their superior tolerability, this class has gradually supplanted the class of angiotensin-converting enzyme inhibitors, particularly in primary prevention.[7] Regarding assessment of cardiovascular prevention by these 2 classes, the results of morbidity/mortality studies, which evaluated the cardiac benefit of ARBs, have often been negative, unlike those dedicated to the evaluation of ACEIs. However, there is little published data on a direct comparison of these 2 therapeutic classes. For these reasons, an uncertainty remains regarding the equivalence of efficacy on hard end points between ARBs and ACEIs, fueling an abundant literature with numerous controversial publications.[8–13]

The objective of the present work is to point out the main clinical studies that have led to this debate and to propose pathophysiological hypotheses that might explain the potential differences in efficacy in terms of cardiac protection between ACE inhibitors and ARBs.

HIGHLIGHTS ON CARDIAC PROTECTION FROM MORBIDITY–MORTALITY TRIALS WITH ARBS

Several meta-analyses have shown that blood pressure (BP) lowering by all classes of antihypertensive drugs is accompanied by significant reductions of stroke and major cardiovascular events, suggesting that reduction of these events is due to BP lowering per se rather than to specific drug properties.[14,15] However, evidence of risk reduction of other events and particularly mortality was found only with some drug classes. These possible differences can be properly assessed only by head-to-head comparisons of 2 or more classes of agents. Thomopoulos *et al.* reported that treatment with ACEIs, even after adjustment for a small systolic blood pressure/diastolic blood pressure difference in favor of other drugs, was associated with a slightly but significantly higher risk of stroke (risk ratio 1.08 (1.01–1.14)) and with a slightly but significantly lower coronary disease risk (risk ratio 0.91 (0.83–0.99)). In the same meta-analysis, comparison of ARB therapy with all other drug classes did not show significantly different risk ratios for all outcomes, except for coronary events, for which a 10% higher risk was found with ARB therapy, which attained statistical significance when the fixed-effects model was used.[15]

Several studies have tested the effect of ARBs vs. placebo or active treatment on cardiovascular morbidity and mortality in a wide range of populations, in both primary and secondary prevention including normotensive subjects

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Les IEC ont un mécanisme d'action positif spécifique sur la fonction endothéliale, l'athérogenèse et la fibrinolyse.

American Journal of Hypertension, hpab108, https://doi.org/10.1093/ajh/hpab108

Protection rénale et cardiovasculaire des antihypertenseurs chez les patients diabétiques

Trial	Treatment	BP baseline, mmHg	SBP difference vs control, mmHg	Reduction in renal outcomes	Reduction in mortality CV	Reduction in mortality Total
IDNT (N = 1,148)	Irbesartan vs placebo	159/87	-3.3	-20% (p = 0.02) Secondary prevention	No	No
RENAAL (N = 1,513)	Losartan vs placebo	153/82	-2	-16% (p = 0.02) Secondary prevention	-	No
DIRECT (N = 5,231)	Candesartan vs placebo	118/73	-3.3	-5.5% (p = 0.024) Secondary prevention	-	No
ROADMAP (N = 4,447)	Olmesartan vs placebo	136/81	-3	Yes Primary prevention	No	No
TRANSCEND (N = 5,927)	Telmisartan vs placebo	141/82	-4	No	No	No
ONTARGET (N = 17,118)	Telmisartan vs ramipril	142/82	-2.4	No	No	No
ADVANCE (N = 11,140)	Perindopril/indapamide vs placebo	145/81	-5.6	-21% (p < 0.0001) Primary and secondary prevention	-18% (p = 0.025)	-14% (p = 0.027)
ACCOMPLISH (N = 11,506)	Benazepril/amlodipine vs benazepril/HCTZ	145/80	-1.1	-48% (p < 0.0001) Secondary prevention	No	No
ACCORD N = 4,733)	Intensive vs standard	139/76	-14.2	Yes Secondary prevention	No	No

Efficacité et Tolérance : Perindopril 10mg/Indapamide 2,5mg

Un meilleur taux de contrôle tensionnel avec le Périndopril 10 mg / Indapamide 2,5 mg chez les patients diabétiques hypertendus.

Perindopril 5 mg/ Indapamide 1,25 mg

Perindopril 10 mg/ Indapamide 2,5 mg

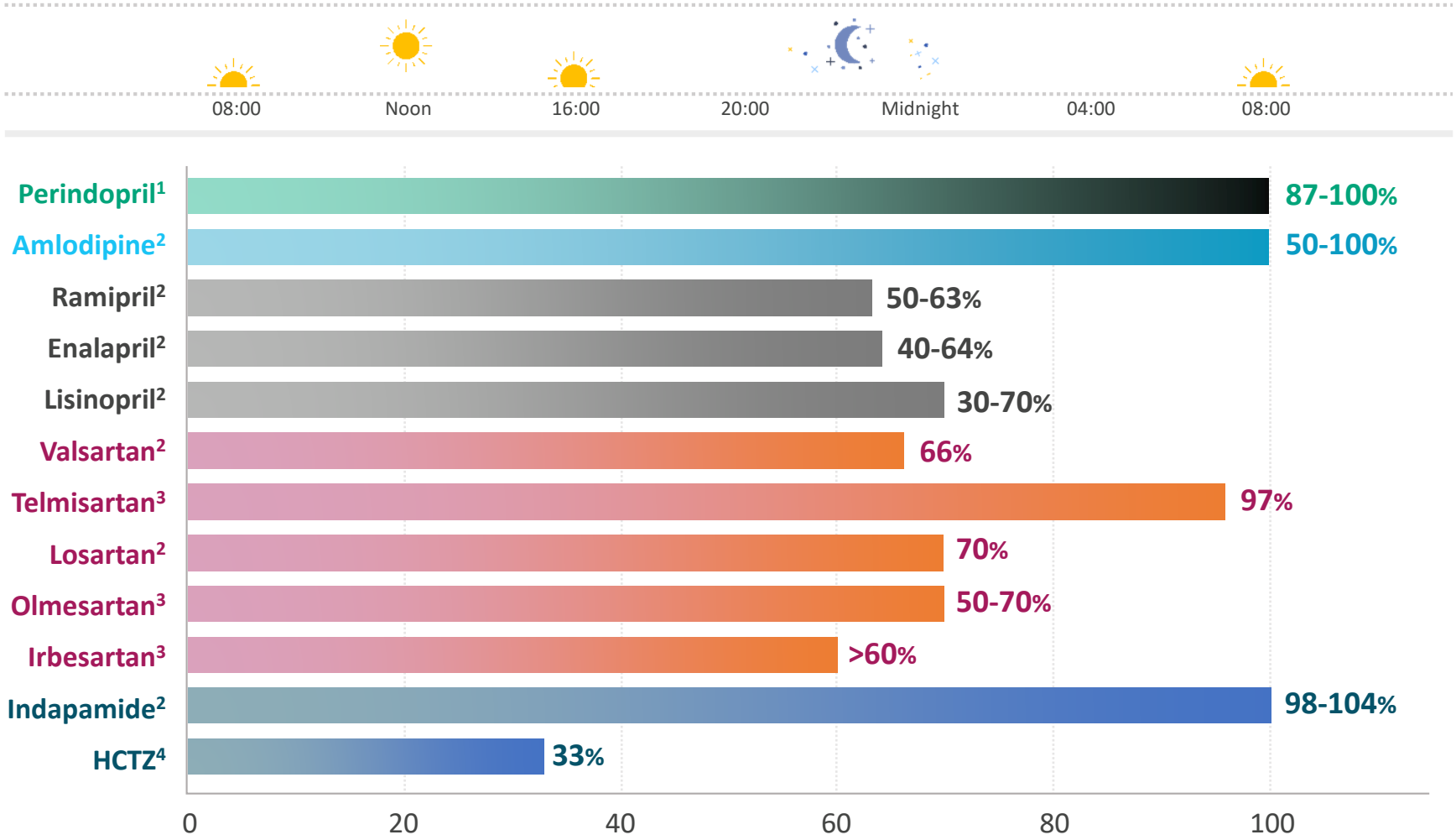
n= 397 hypertensive patients with diabetes

Number of patients with blood pressure controlled BP<140/90 mm Hg

Number of patients with blood pressure uncontrolled BP≥140/90 mm Hg

Netchessova TA et al. *High Blood Press Cardiovasc Prev*. 2013;21:63-69.

Perindopril & indapamid provide sustained BP control over 24-hour



HCTZ: hydrochlorothiazide.

1. Coveryl SmPC. **2.** Flack JM, Nasser SA. *Vasc Health Risk Manag.* 2011;7:777-787. **3.** Song JC, White CM. *Formulary.* 2001;36:487-499.
4. Lacourcière Y et al. *Am J Hypertens*. 1995;8:1154-1159.
In EU, Perindopril / Amlodipine SPC is indicated as substitution therapy in patients already controlled with perindopril and amlodipine.

En conclusion

- Les sulfamides hypoglycémiants restent avec la metformine le traitement de référence du diabète de type 2 reconnu par les dernières recommandations internationales

- Les insulinosécréteurs ne constituent pas une classe homogène : ils différent par leur structure, leur activité, leur tolérance et leur niveau de preuves

- Gliclazide 60 mg LM est le seul sulfamide basé sur les preuves d'une stratégie de contrôle glycémique validée par une grande étude de morbimortalité dans le diabète de type 2, l'étude ADVANCE et son suivi ADVANCE ON

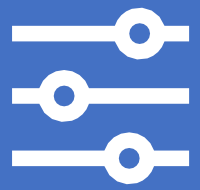
Sulfamide de référence des dernières recommandations

Key take-home points

Des mécanismes communs, tels que la régulation du SRAA, le stress oxydatif, l'inflammation et l'activation du système immunitaire expliquent la relation étroite entre le diabète et l'hypertension.

Un contrôle intensif de la pression artérielle chez les patients diabétiques de type 2 permet une réduction des complications micro et macrovasculaires et de la mortalité.

le contrôle glycémique est aussi important que la réduction du risque cardiorénal dans la prise en charge du diabète de type 2 et doit être pris en compte dans le choix thérapeutique.



Les choix de cibles et des traitement doit être individualisé et tenir compte de l'âge, la durée de la maladie, les comorbidités, la gravité des complications diabétiques, l'espérance de vie, les ressources et les préférences des patients

CV, cardiovascular; RAAS, renin-angiotensin aldosterone system; T2DM, type 2 diabetes mellitus.

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