Health
Northern NSW
Local Health District

Managing Diabetes & Hypertension

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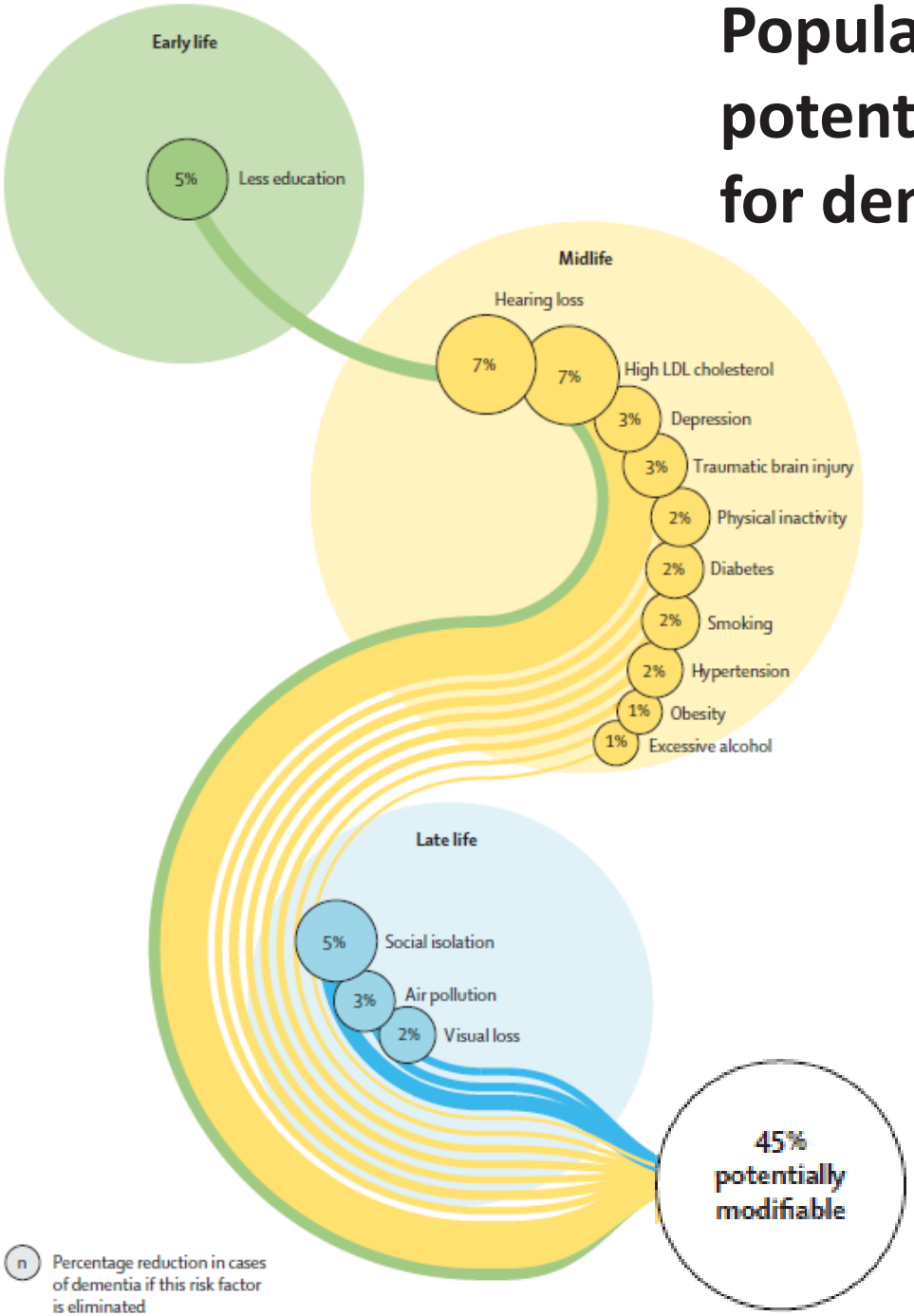
Three new modifiable risk factors for dementia

- New evidence supports adding three modifiable risk factors—excessive alcohol consumption, head injury, and air pollution—to our 2017 *Lancet* Commission on dementia prevention, intervention, and care life-course model of nine factors (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contact).

Modifying 12 risk factors might prevent or delay up to 40% of dementias.

Lancet 2020; 396: 413–46

Population attributable fraction of potentially modifiable risk factors for dementia



Lancet 2024; 404: 572–628

Diabetes

Diabetes

- Type 1
- Type 2
- Latent autoimmune diabetes of adults (LADA)
- Monogenic
- Secondary

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Diabetes - Epidemiology

Prevalence and type of known diabetes mellitus (DM) in Australia and the FDS2 study area 2007-2012.

Survey	Year	Method	Geographical area	Prevalence (%)	Numbers with DM* in FDS study area	Type 1 / Type 2 / Other or unknown type (%)
AHS	2007-08[20]	Self-reported current	Australia	4.0	6280†	10.0 / 88.2 / 1.8
AHS	2011-12[8]	Self-reported current	Australia	4.0	6739†	12.4 / 85.3 / 2.2
NDSS	17/11/2010	Registered with DM in FDS area	FDS study area	4.4	7211	11.8 / 87.8 / 0.3
NDSS	7/7/2011	Registered with DM in FDS area	FDS study area	4.6	7774	11.6 / 88.4 / 0
NDSS	9/11/2012	Registered with DM in FDS area	FDS study area	4.2	7180	11.0 / 88.6 / 0.4
FDS2	2008-11	Identified with known DM from multiple sources in FDS area	FDS study area	2.9	4639	Clinical 7.9 / 89.9 / 2.2 Laboratory testing: 7.9 / 85.8 / 6.3

*Excluding GDM;

†assuming national data apply to the FDS study area; AHS = Australian Health Survey; NDSS = National Diabetes Services Scheme

Fremantle Diabetes Study Phase II (FDS2)

Estimated prevalence of Diabetes = 4.8%, 86% T2DM

Intern Med J. 2018 Jul; 48(7): 803–809

Diabetes – Indigenous populations

Table 2 – Prevalence estimates of diabetes in terms of remoteness and ethnicity.

Reference	Population	Diabetes prevalence (%)
Remoteness		
ABS [7]	Very remote	10.0
	Remote	9.0
	Non-remote	5.0
C.E.R. [15]	Rural	13.9
	Urban	5.5
ABS [21]	Remote	16.0[a]
	Remote (crude)	7.0
	Non-remote	9.0[a]
	Non-remote (crude)	4.0
Ethnicity		
McDermott [18]	A	3.1
	TSI	4.3
McCulloch [24]	A	11.4[b]
	TSI	15.4[b]
	ATSI	7.5[b]
O'Neal [29]	A	14.8
	TSI	22.6
Rowley [28]	A	20.3
	TSI	22.3

Abbreviations: NR, not reported; A, Aboriginal; TSI, Torres Strait Islander; ATSI, both Aboriginal and TSI descent.

[a] Age standardised/adjusted prevalence.

[b] Calculated from reported data.

Diab Res Clin Pract 2011, doi:10.1016/j.diabres.2011.06.012

Diabetes – Indigenous populations

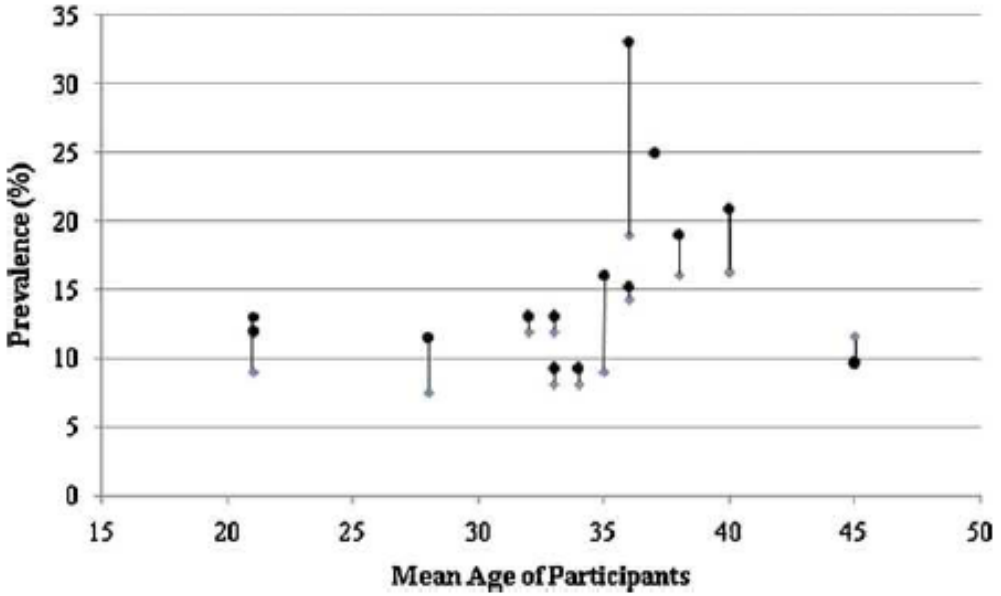


Fig. 3 – Diabetes prevalence by study and gender. *Notes:* ● Females; ◆ Males. A vertical line joins data points from the same study.

4.1 times higher among First Nations peopled compared to non-indigenous [2]

Diab Res Clin Pract 2011, doi:10.1016/j.diabres.2011.06.012
AIHW 2021, 2022

Diabetes in Australia

- 5.1% prevalence
- 19% aged 80-84 years old
- 0.7% aged <40 years
- 2.8x increase between 2000 – 2021

Journal of
Diabetes Research

Forward Series

Research Article | Open Access

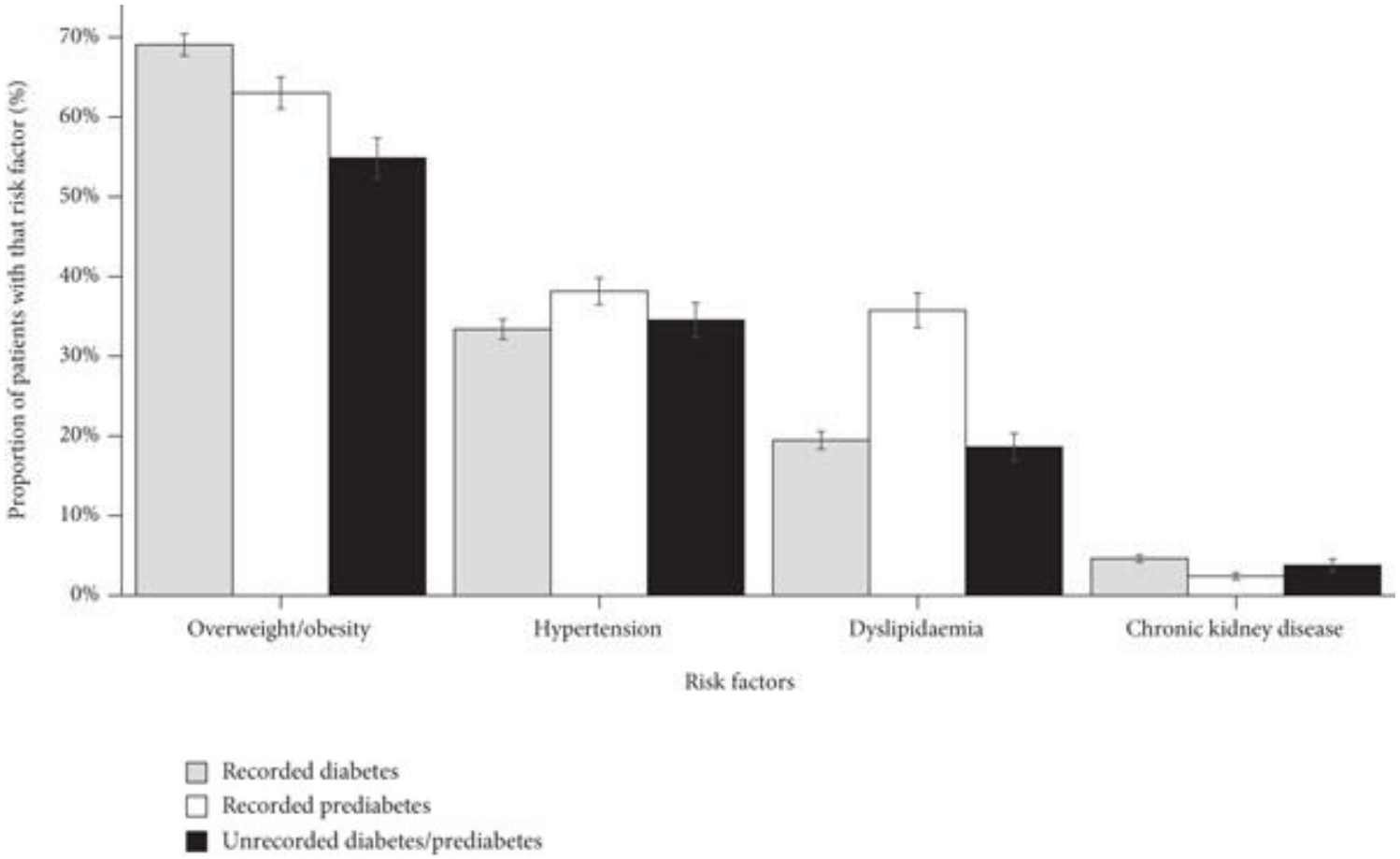
Diabetes Mellitus Diagnosis and Screening in Australian General Practice: A National Study

Mingyue Zheng, Carla De Oliveira Bernardo, Nigel Stocks, David Gonzalez-Chica

First published: 23 March 2022 | https://doi.org/10.1155/2022/1566408 | Citations: 5

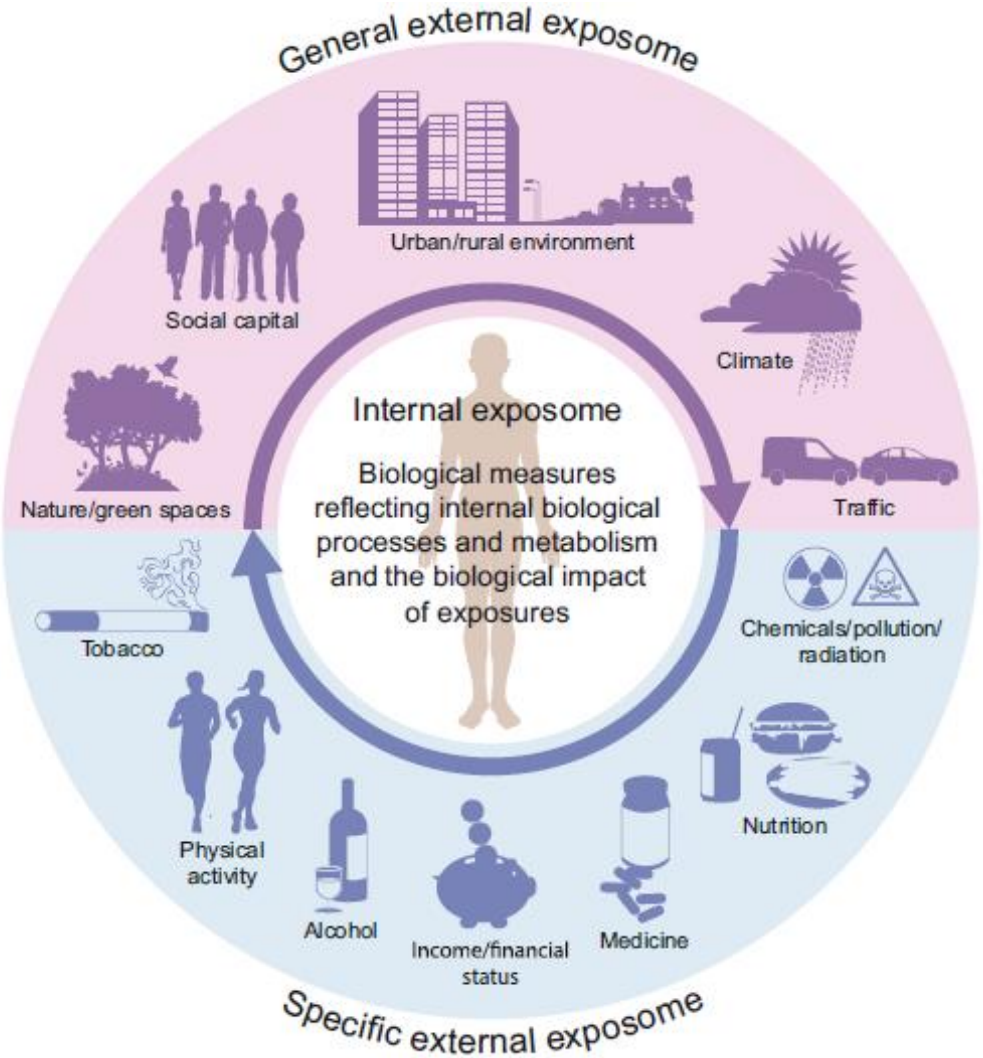
- Cross-sectional study using electronic health records; 1,522,622 patients aged 18+ years attending 544 Australian general practices
- 7.5% (95% CI 7.3, 7.8) of adults had diabetes diagnosis, 0.7% (95% CI 0.6, 0.7) prediabetes, and 0.3% (95% CI 0.3, 0.3) unrecorded diabetes/ prediabetes (elevated glucose levels without a recorded diagnosis)

Diabetes – Associations



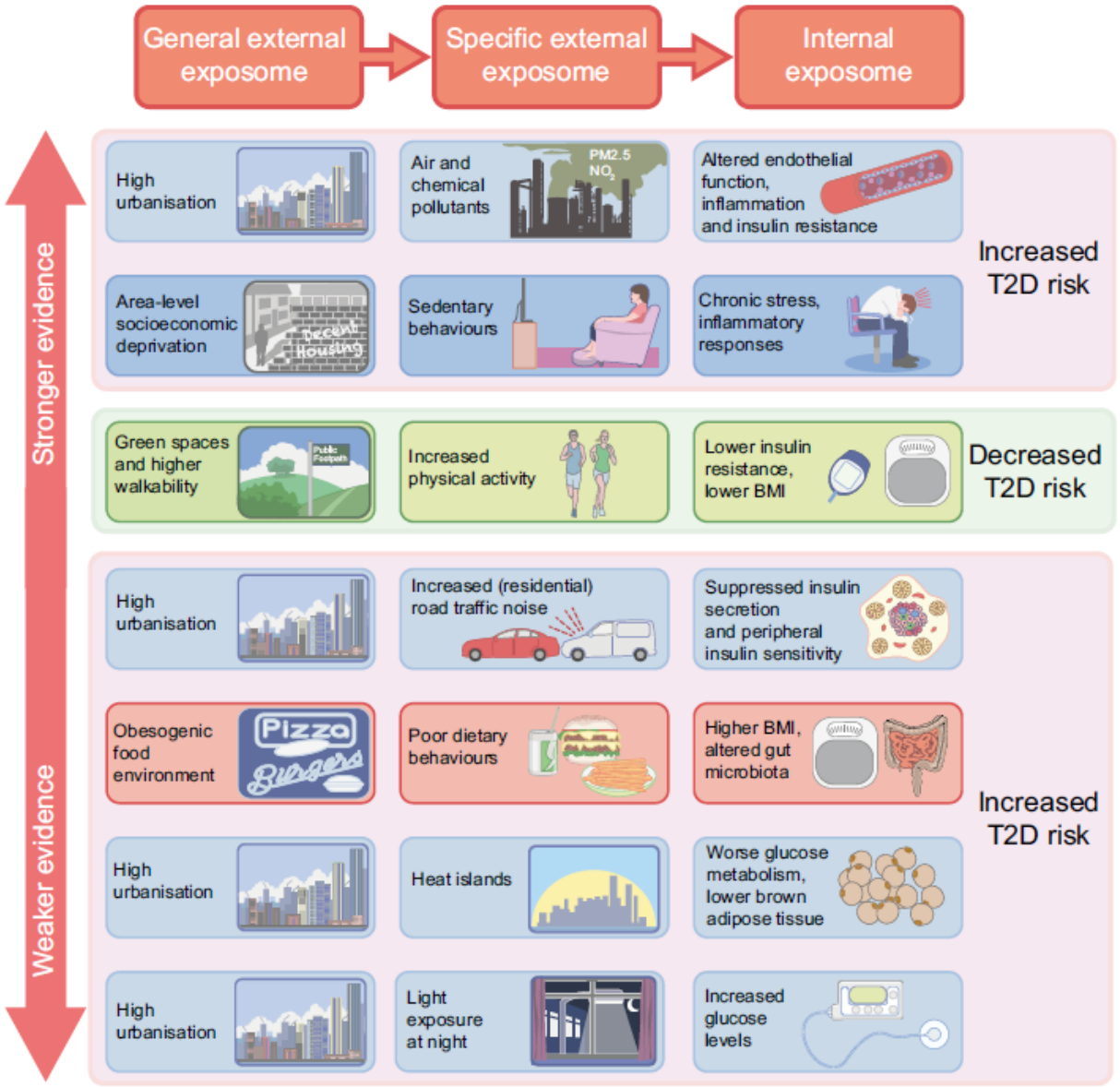
Journal of Diabetes Research, 2022, 1566408. doi.org/10.1155/2022/1566408

Diabetes & environmental risk factors



Diabetologia 2022; 65: 263-274

Diabetes & environmental risk factors



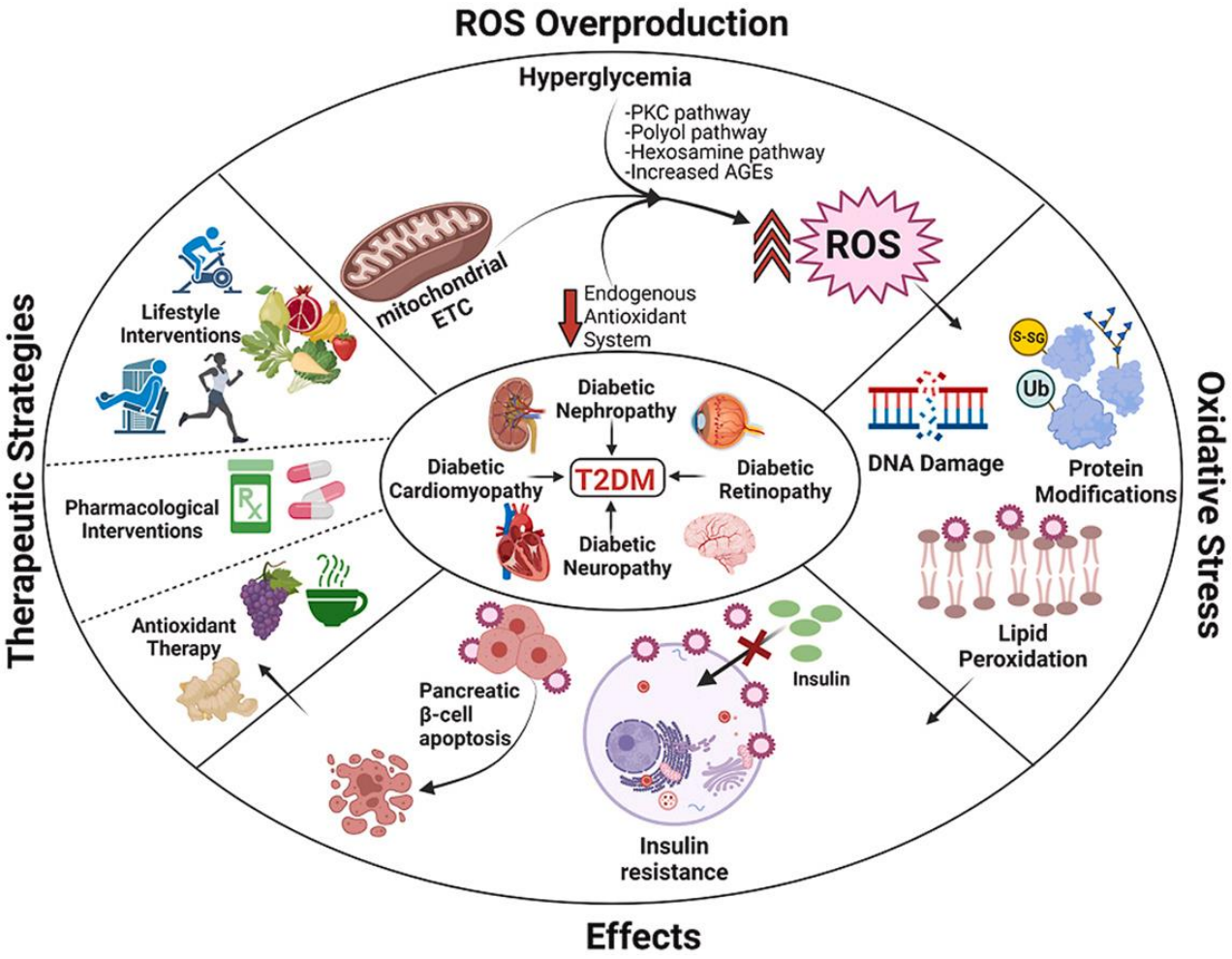
Diabetologia 2022; 65: 263-274

Diabetes & dementia

- Mechanisms:
  - Micro- & Macro-vascular changes
  - Altered brain metabolism
  - Insulin resistance & β-amyloid toxicity
  - Tau hyperphosphorylation
  - Oxidative stress & neuroinflammation
  - Etc

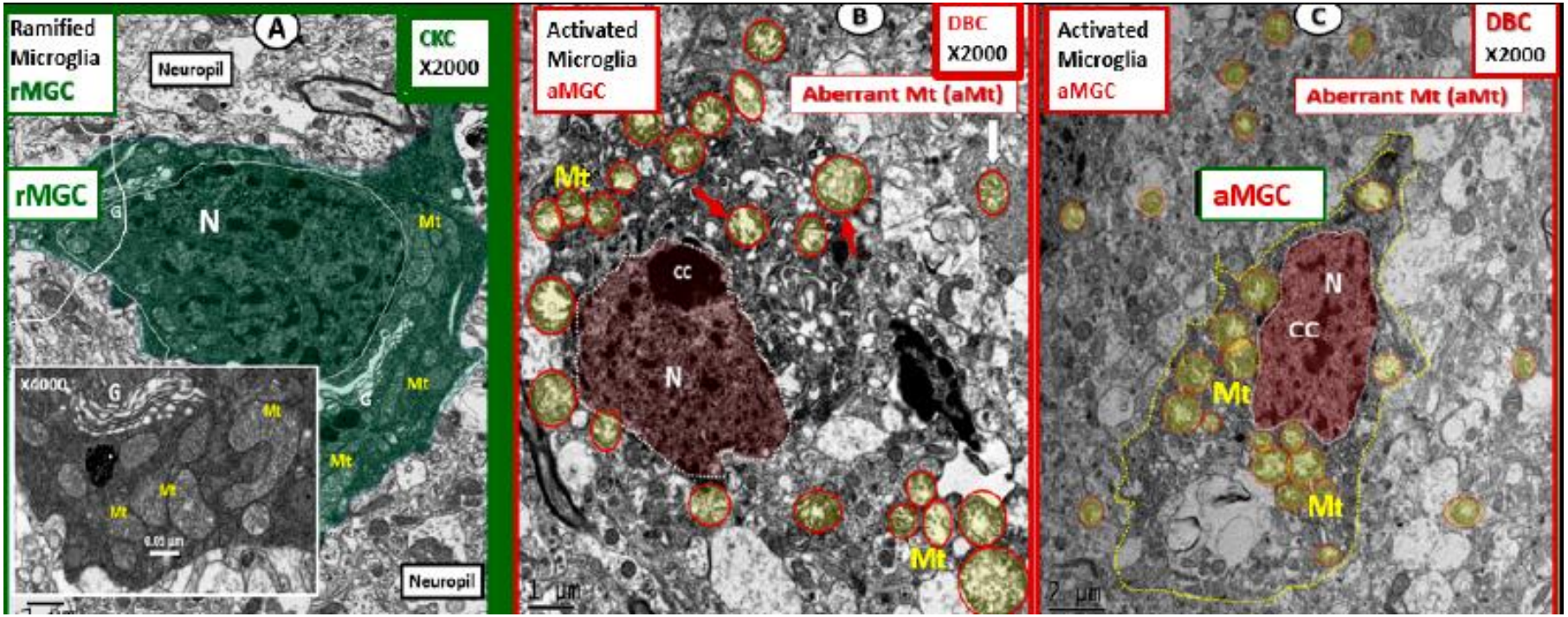
Ageing Res Rev 2019; 55: 100944
Int J Mol Sci 2022; 23: 235

Diabetes & oxidative stress



Free Radical Biology and Medicine 2022; 184: 114-134

Glycaemic status & microglia activation



Scientific Reports 2019;9: 840
Neuroglia 2018; 1: 311–326

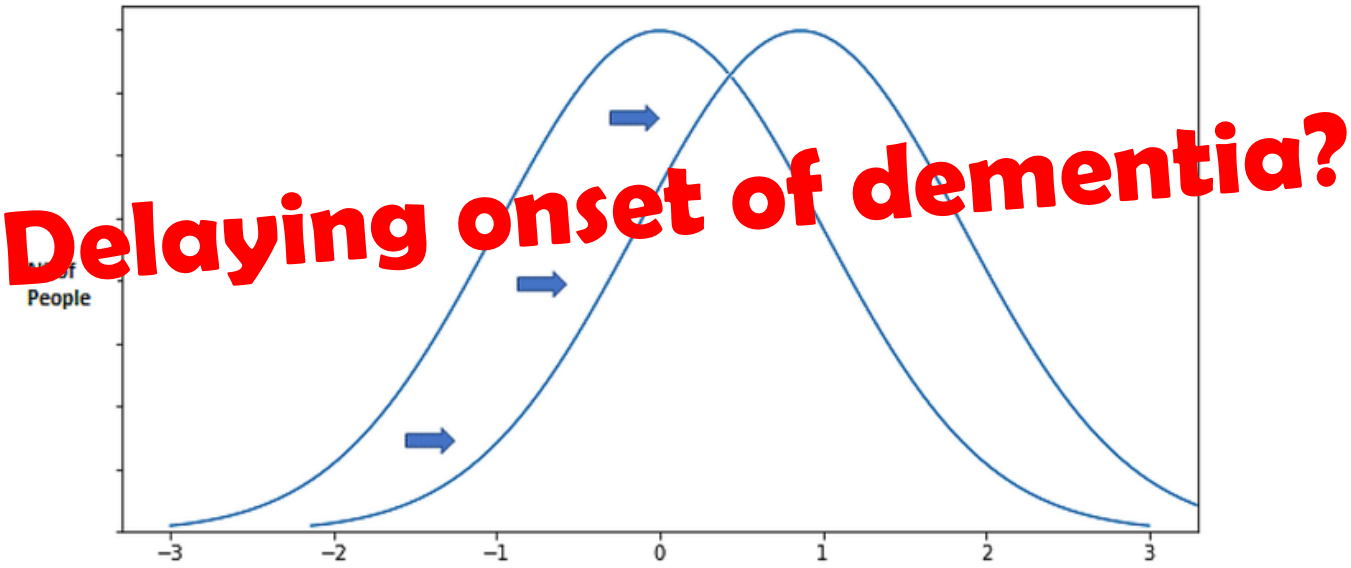
Burden of Diabetes

- Disability-adjusted life years (DALY): One DALY is equivalent to one year of healthy life lost.
- T1DM; 0.7 DALY per 1,000 population,
  0.3% total disease burden in Australia
- T2DM; 4.7 DALY per 1,000 population,
  2.2% total disease burden in Australia (11th leading specific cause)

Australian Institute of Health & Welfare, 17th June 2024

Diabetes & dementia risk

- Increase dementia risk observed for every 5-year decrease in age of type 2 diabetes onset (HR 1·24, 95% CI 1·06–1·46)



JAMA 2021; 325: 1640–49

Australian Type 2 Diabetes **Glycaemic** Management Algorithm (June 2024)

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight management. +

Determine the individual's HbA1c target – commonly ≤53 mmol/mol (7.0%) but should be appropriately individualised (refer to ADS position statement).

+ Weight loss of ≥10% will likely allow a reduction or cessation of glucose lowering medication. Consider intensive weight management options including:

- Low energy or very low energy diets with meal replacements
- Pharmacotherapy
- Bariatric surgery.

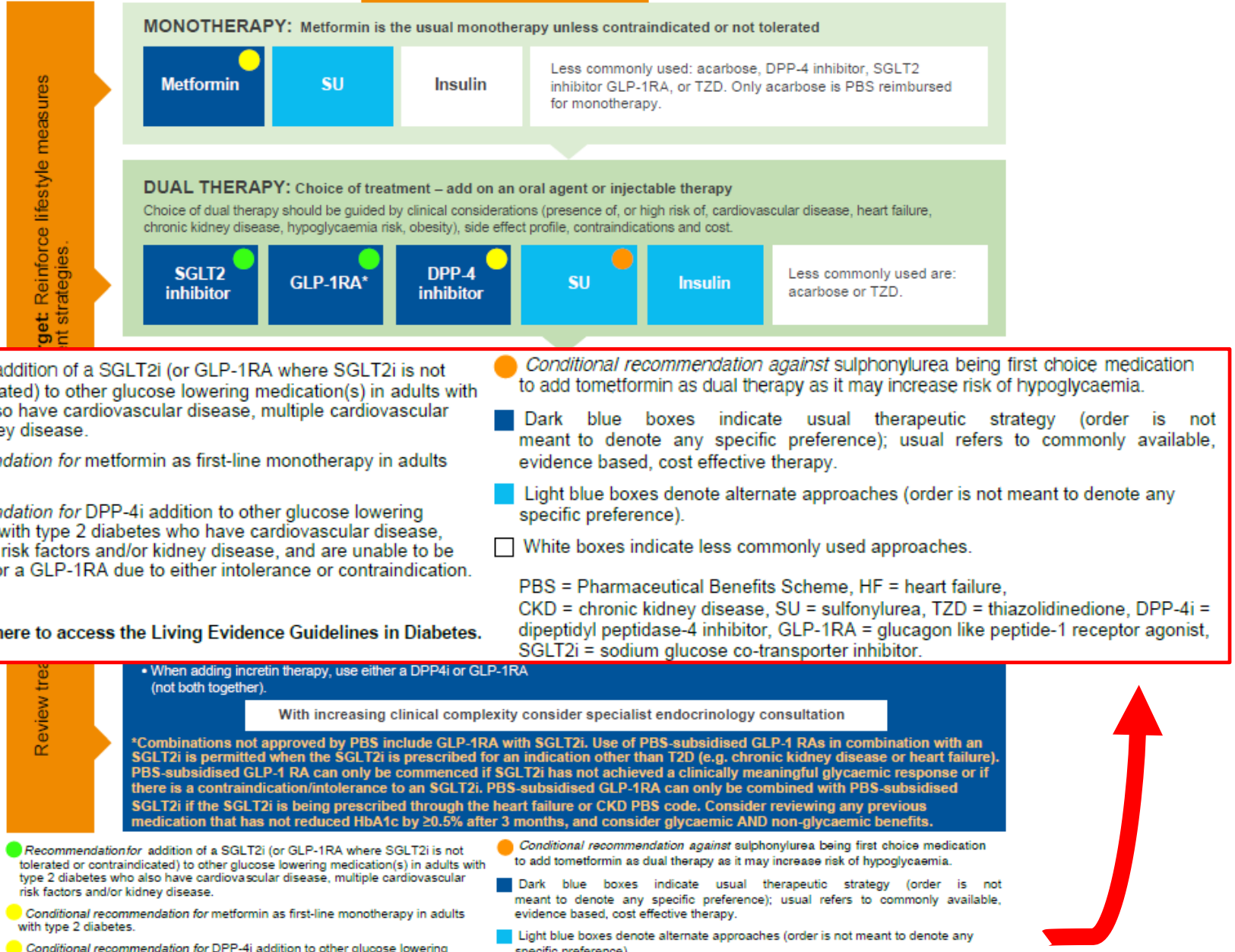
Review treatment: if not at target HbA1c or if presence of cardiovascular/chronic kidney disease –

- Check patient understanding of self-management including drug treatment
- Ensure current therapies are clinically appropriate including comorbidities/ therapies impacting glycaemic control
- Review medication adherence
- Assess tolerability, adverse effects and risk of interactions

Pharmacological management

- Sequential or Combination therapy?
  - Treatment choice based on **RISK FACTORS/ CO-MORBIDITIES**
  - Treatment choice & Dementia risk?

What's "New"?


get: Reinforce lifestyle measures
nt strategies.
MONOTHERAPY: Metformin is the usual monotherapy unless contraindicated or not tolerated
Metformin
SU
Insulin
Less commonly used: acarbose, DPP-4 inhibitor, SGLT2 inhibitor GLP-1RA, or TZD. Only acarbose is PBS reimbursed for monotherapy.
DUAL THERAPY: Choice of treatment – add on an oral agent or injectable therapy
Choice of dual therapy should be guided by clinical considerations (presence of, or high risk of, cardiovascular disease, heart failure, chronic kidney disease, hypoglycaemia risk, obesity), side effect profile, contraindications and cost.
SGLT2 inhibitor
GLP-1RA*
DPP-4 inhibitor
SU
Insulin
Less commonly used are: acarbose or TZD.
Recommendation for addition of a SGLT2i (or GLP-1RA where SGLT2i is not tolerated or contraindicated) to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.
Conditional recommendation for metformin as first-line monotherapy in adults with type 2 diabetes.
Conditional recommendation for DPP-4i addition to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT2i or a GLP-1RA due to either intolerance or contraindication.
For more details click here to access the Living Evidence Guidelines in Diabetes.
Conditional recommendation against sulphonylurea being first choice medication to add tometformin as dual therapy as it may increase risk of hypoglycaemia.
Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference); usual refers to commonly available, evidence based, cost effective therapy.
Light blue boxes denote alternate approaches (order is not meant to denote any specific preference).
White boxes indicate less commonly used approaches.
PBS = Pharmaceutical Benefits Scheme, HF = heart failure,
CKD = chronic kidney disease, SU = sulfonylurea, TZD = thiazolidinedione, DPP-4i = dipeptidyl peptidase-4 inhibitor, GLP-1RA = glucagon like peptide-1 receptor agonist, SGLT2i = sodium glucose co-transporter inhibitor.
Review trea
• When adding incretin therapy, use either a DPP4i or GLP-1RA (not both together).
With increasing clinical complexity consider specialist endocrinology consultation
*Combinations not approved by PBS include GLP-1RA with SGLT2i. Use of PBS-subsidised GLP-1 RAs in combination with an SGLT2i is permitted when the SGLT2i is prescribed for an indication other than T2D (e.g. chronic kidney disease or heart failure). PBS-subsidised GLP-1 RA can only be commenced if SGLT2i has not achieved a clinically meaningful glycaemic response or if there is a contraindication/intolerance to an SGLT2i. PBS-subsidised GLP-1RA can only be combined with PBS-subsidised SGLT2i if the SGLT2i is being prescribed through the heart failure or CKD PBS code. Consider reviewing any previous medication that has not reduced HbA1c by ≥0.5% after 3 months, and consider glycaemic AND non-glycaemic benefits.
Recommendation for addition of a SGLT2i (or GLP-1RA where SGLT2i is not tolerated or contraindicated) to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.
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Australian Type 2 Diabetes **Glycaemic** Management Algorithm

MONOTHERAPY: Metformin is the usual monotherapy unless contraindicated or not tolerated

- Metformin

DUAL THERAPY: Choice of treatment – add on an oral agent or injectable therapy

Choice of dual therapy should be guided by clinical considerations (presence of, or high risk of, cardiovascular disease, heart failure, chronic kidney disease, hypoglycaemia risk, obesity), side effect profile, contraindications and cost.

- SGLT2 inhibitor
- GLP-1RA*
- DPP-4 inhibitor
- SU
- Insulin

MULTIPLE THERAPIES: Choice of treatment : include additional oral agent or GLP-1 RA or insulin

Choice of agents should be guided by clinical considerations as above. Note: combinations not approved by PBS include GLP-1RA with SGLT2i. Consider reviewing any previous medication that has not reduced HbA1c by ≥0.5% after 3 months and take into consideration **glycaemic AND non-glycaemic benefits**.

- SGLT2 inhibitor
- GLP-1RA
- DPP-4 inhibitor
- SU
- Insulin

“Beyond Glycaemic Lowering”

- Brain & Neurovascular health
- Diabetic kidney disease & Renoprotection
- Cardiovascular risk management
- Lipid lowering strategies
- Obesity management

Treatments & dementia risk

- SGLT2 inhibitors (OR 0·41, 95% CI 0·22–0·76), GLP-1 receptor agonists (0·34, 0·14–0·85), and DPP-4 inhibitors (0·78, 0·61–0·99) associated with dementia risk reduction
- Sulfonylureas associated with increased risk (1·43, 1·11–1·82)
- Metformin not associated with a decreased or increased risk (0·71, 0·46–1·08)

[Another study found lower risk of dementia in those initiating metformin than in those not on medication for their diabetes (HR 0·88, 95% CI 0·84–0·92)]

Diabetes Metab Res Rev 2023; 39: e3673
Alzheimers Dement 2023; 19: 5681–89

Received: 11 October 2022 | Revised: 2 March 2023 | Accepted: 25 April 2023
DOI: 10.1002/dmrr.3673

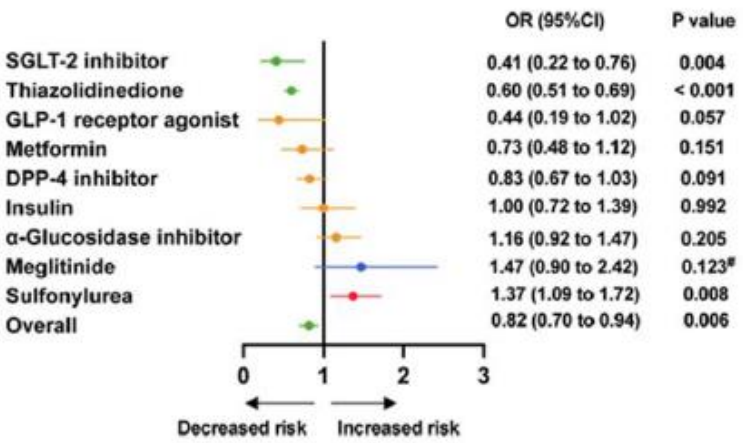
REVIEW ARTICLE

WILEY

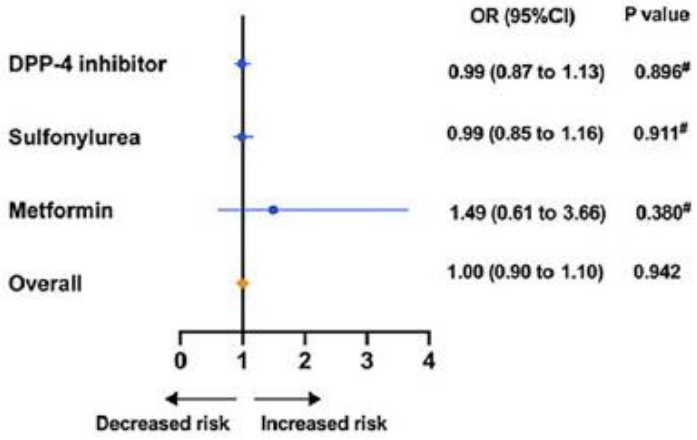
Comparison on cognitive outcomes of antidiabetic agents for type 2 diabetes: A systematic review and network meta-analysis

Sai Tian[1,2] | Jiaxuan Jiang[1,2] | Jin Wang[1,2] | Zhou Zhang[1,2] | Yingwen Miao[1,2] | Xinlu Ji[1,2] | Yan Bi[1,2]

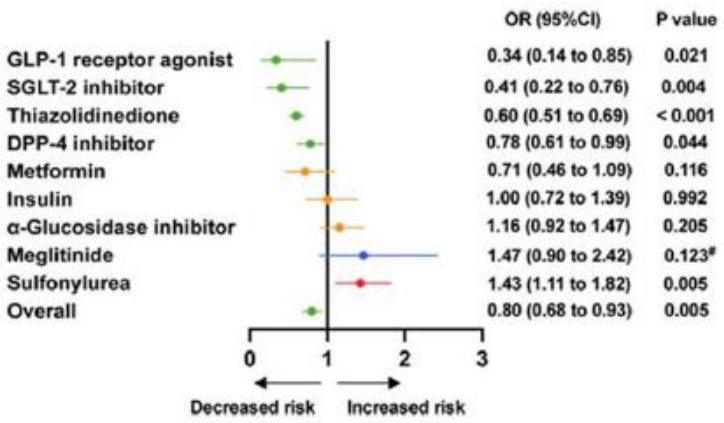
A. The relationship between hypoglycemic drugs and the risk of cognitive impairment.



B. The relationship between hypoglycemic drugs and the risk of mild cognitive impairment.



C. The relationship between hypoglycemic drugs and the risk of dementia.



? ⬇ Dementia risk:

SGLT2i
GLP-1RA
(? DPP4i)
(?? Metformin)

Diabetic kidney disease & Renoprotection

1456 THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 11, 1993

THE EFFECT OF ANGIOTENSIN-CONVERTING–ENZYME INHIBITION ON DIABETIC NEPHROPATHY

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D., AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*

- Creatinine clearance declined 23 ±25 percent per year in the captopril group vs 37 ±25 percent per year in placebo group ($p = 0.01$)
- Captopril treatment associated with 50 percent reduction in the risk of the combined end points of death, dialysis, and transplantation
- Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood-pressure control alone

Nephropathy – Potential mechanisms

Angiotensin 2 effects in diabetic nephropathy

Hemodynamic effects	Non-hemodynamic effects
Systemic hypertension	Induction of renal hypertrophy and cell proliferation
Systemic and renal vasoconstriction	Stimulation of extracellular matrix synthesis
Increased glomerular capillary pressure and permeability	Inhibition of extracellular matrix degradation
Mesangial cell contraction leading to reduction in filtration surface area	Stimulation of cytokine (e.g., TGF-β, VEGF, endothelin) production
	Stimulation of superoxide production

Kidney International, Vol. 58, Suppl. 77 (2000), pp. S-93–S-98

Albuminuria & cardiovascular disease

Cardiovascular disease	Association with albuminuria
CAD	Increased severity of CAD[10] High coronary artery calcium score[11] Predictor of silent ischemia[12] Underdeveloped collateral vessels in areas of CAD[13] Poor coronary artery bypass graft outcomes[14, 15] Risk predictor of CAD[16]
Stroke	Stroke risk predictor[17, 18]
Arterial stiffness	Predictor of arterial stiffness[19, 20, 21, 22, 23, 24]
Myocardial capillary disease	Reduced myocardial flow reserve[25, 26, 27]
Heart failure	Predictor of heart failure[28, 29] Predictor of systolic dysfunction[30] Predictor of diastolic dysfunction[31, 32, 33] Prognosis of heart failure[34, 35]
Arrhythmia	Increased prevalence and risk of atrial fibrillation[36, 37, 38] Increased percentage of time in atrial fibrillation[36] Increased prevalence of nonsustained ventricular tachycardia[36]

JAHA 2024. https://doi.org/10.1161/JAHA.123.030131

Diabetic Nephropathy

Table 1. Urine specimen results[2]

	Women	Men
Albumin creatinine ratio (mg/mmol)		
Specimen: first voided morning urine		
Normal	0–3.5	0–2.5
Microalbuminuria	3.6–35.0	2.6–25.0
Macroalbuminuria	>35.0	>25.0
Urinary albumin excretion (µg/min)		
Specimen: timed overnight urine collection		
Normal	<20	<20
Microalbuminuria	20–200	20–200
Macroalbuminuria	>200	>200

Definitions of microalbuminuria and macroalbuminuria*

	Sex	Microalbuminuria	Macroalbuminuria
UACR	Men Women	2.5 – 25mg/mmol 3.5 – 35mg/mmol	> 25mg/mmol > 35mg/mmol
24-h urinary albumin	Either	30 – 300mg/day	> 300mg/day

UACR = urinary albumin-to-creatinine ratio.

Australian Family Physician 2007; 36 (9): 713-715
Med J Aust 2012;197(4):224-225

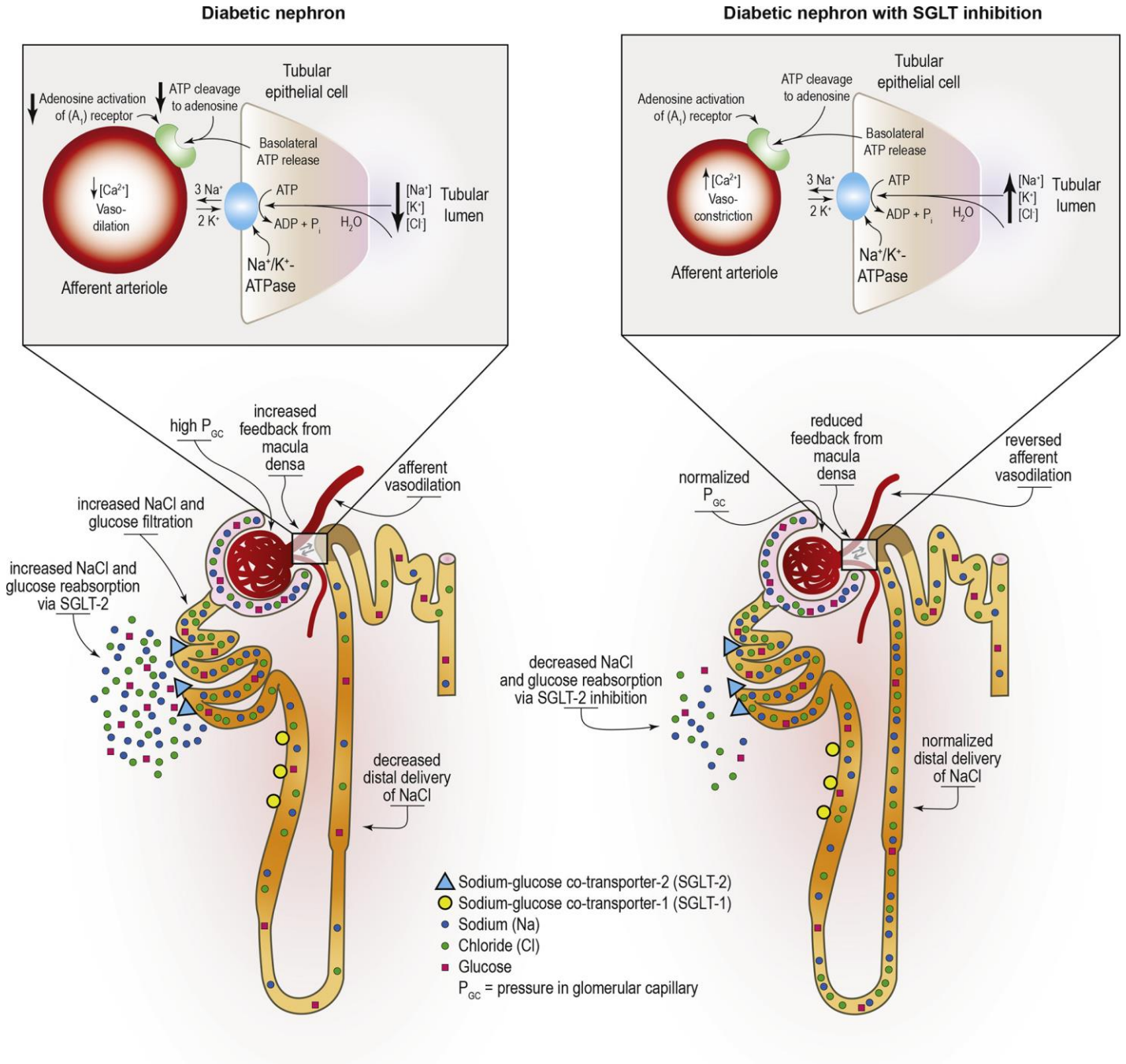
Urine Albumin: Creatinine Ratio

- Meta-analysis demonstrated extremely **low ACR testing rates in diabetes (35.1%) and hypertension (4.1%)**
- Among tested participants, **ACR ≥30 mg/g** (which defines CKD stage A2+) was common, with a median prevalence of **32.1% in diabetes and 21.9% in hypertension**
- Predicted number of undetected albumin-to-creatinine ratio ≥30 mg/g (chronic kidney disease A2+) nearly 2-fold and 20-fold of detected cases in diabetes and hypertension, respectively

Hypertension 2021;78:1042–1052

SGLT2-inhibitors

- inhibit coupled reabsorption of sodium and glucose from the proximal tubules
- increasing renal glucose and sodium excretion
- increase the delivery of sodium to the loop of Henle and can thereby activate the tubuloglomerular feedback response to reduce glomerular hyperfiltration



https://doi.org/10.1053/j.ajkd.2018.03.022

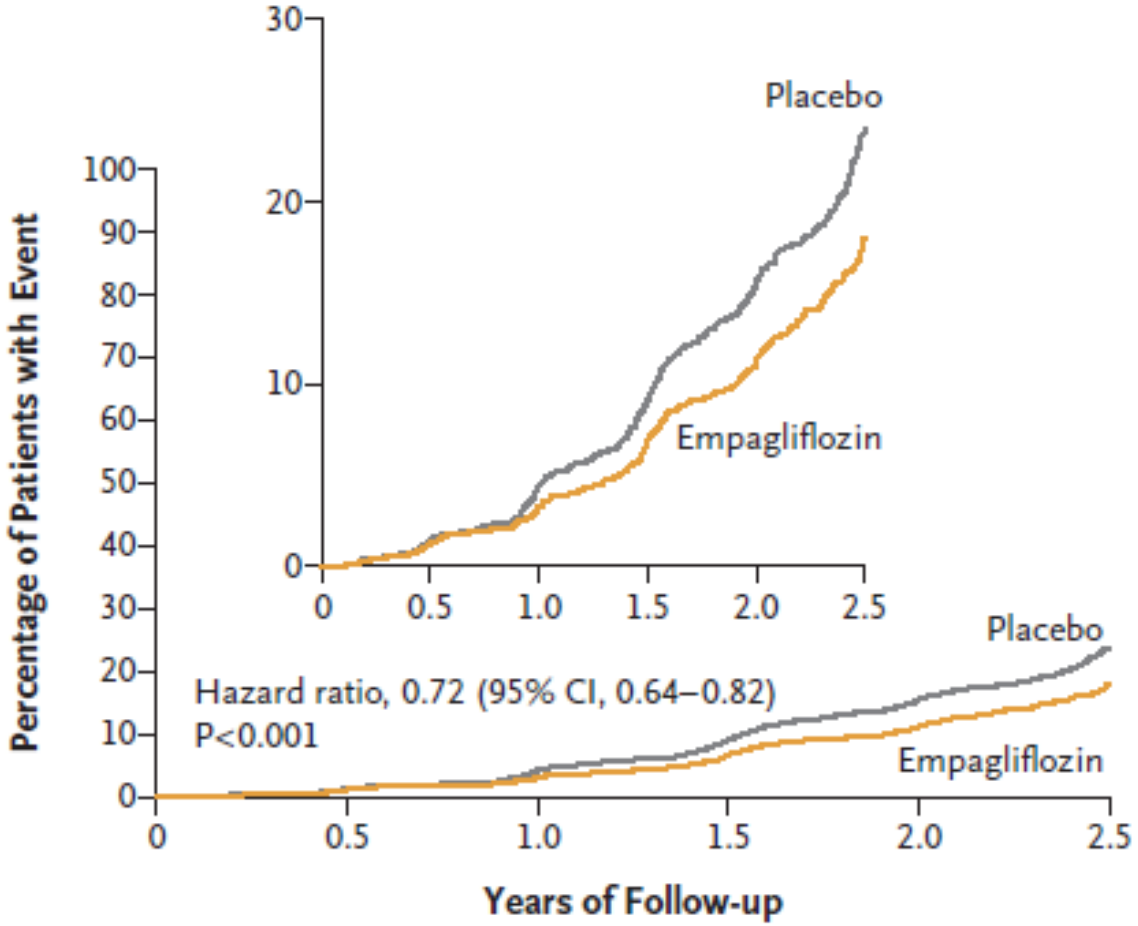
Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial

*The EMPA-KIDNEY Collaborative Group**

- 6609 participants, multicentre
- Median 2.0 years (IQR 1.5-2.4)
- Kidney disease eGFR 20-45ml/min
- 31.1% cohort Diabetic kidney disease

Lancet Diabetes Endocrinol 2024; 12: 51–60

SGLT2i – EMPA-KIDNEY



Progression of kidney disease or death from cardiovascular causes occurred in 13.1% in Empagliflozin group and 16.9% in Placebo group

N Engl J Med 2023;388:117-27

EMPA-KIDNEY

	Events/participants		Hazard ratio (95% CI)	$p_{heterogeneity}$
	Empagliflozin	Placebo		
Causes of kidney disease				0·62
Diabetic kidney disease	137/1032	189/1025	0·64 (0·52–0·80)	
Hypertensive or renovascular disease	72/706	87/739	0·79 (0·58–1·08)	
Glomerular disease	115/853	139/816	0·77 (0·60–0·99)	
Other disease or unknown	60/713	89/725	0·67 (0·48–0·92)	
Types of glomerular diseases				0·25
IgA nephropathy	51/413	67/404	0·67 (0·46–0·97)	
Focal segmental glomerulosclerosis	17/98	13/97	1·35 (0·65–2·81)	
Other glomerulonephritis	47/342	59/315	0·78 (0·53–1·16)	
All participants			**0·71 (0·62–0·81)**	

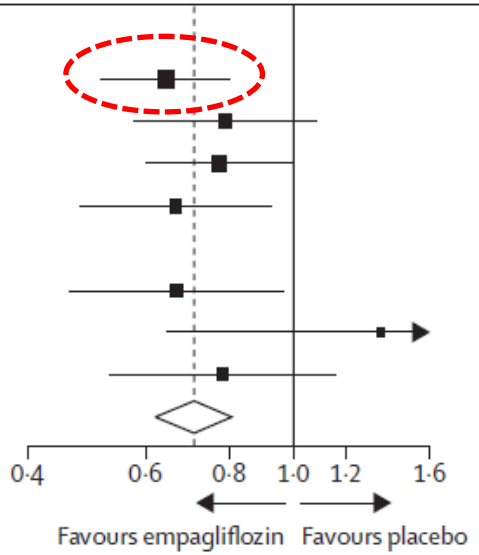


Figure 1: Kidney disease progression outcome by primary kidney disease

Lancet Diabetes Endocrinol 2024; 12: 51–60

EMPA-KIDNEY

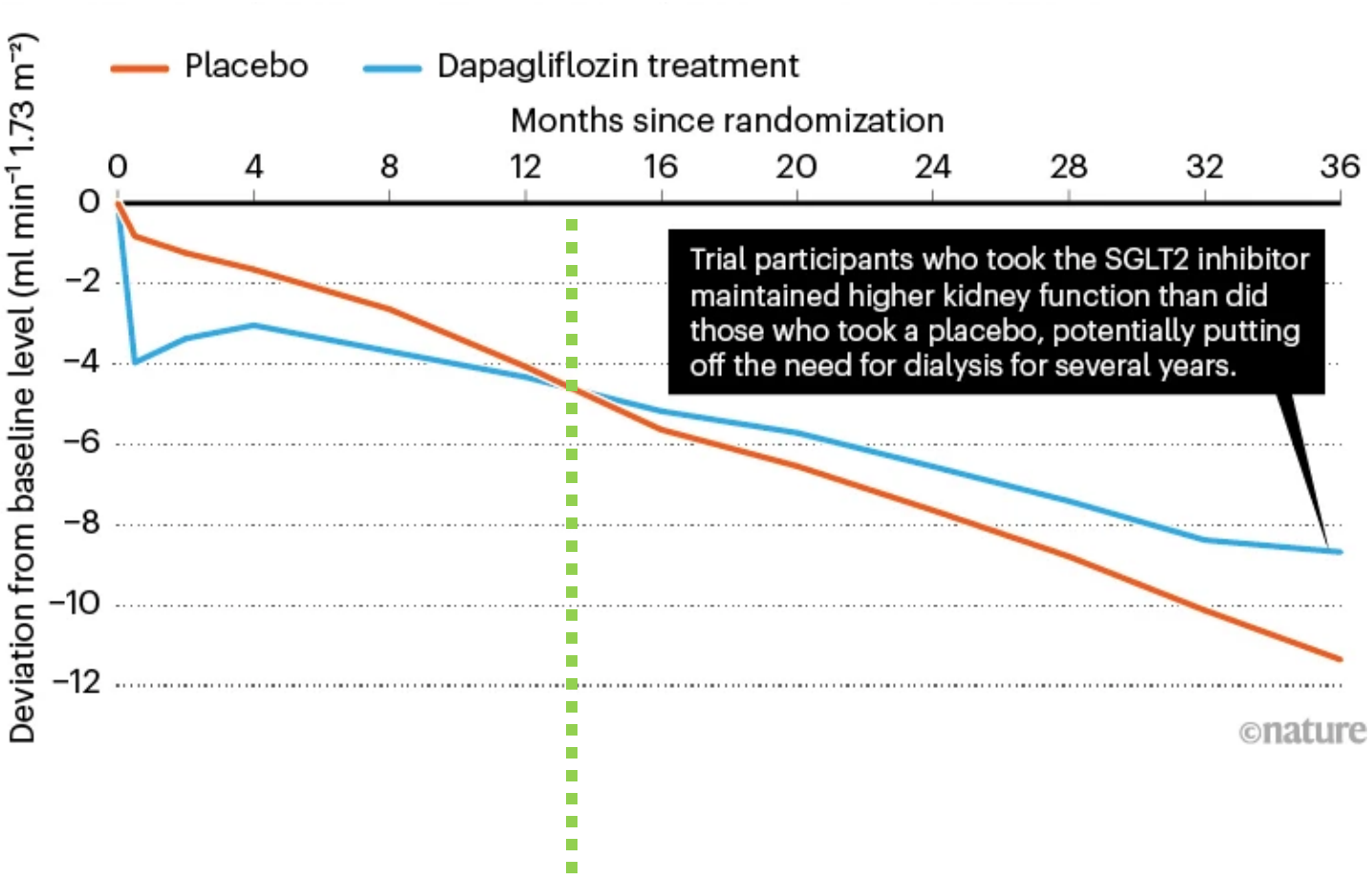
	Diabetic kidney disease (n=2057)	Hypertensive or renovascular disease (n=1445)	Glomerular disease (n=1669)	Other or unknown (n=1438)	$p_{heterogeneity}$
uACR, mg/g					
Relative difference in study average uACR compared with placebo	−28% (−34 to −21)	−16% (−25 to −7)	−15% (−24 to −6)	−14% (−23 to −4)	0·050
Blood pressure, mm Hg					
Study average difference in systolic blood pressure compared with placebo	−4·1 (−5·3 to −2·9)	−1·7 (−3·1 to −0·2)	−2·2 (−3·6 to −0·8)	−1·6 (−3·1 to −0·2)	0·023
Study average difference in diastolic blood pressure compared with placebo	−1·3 (−2·0 to −0·6)	0·2 (−0·7 to 1·1)	−0·3 (−1·1 to 0·5)	−0·2 (−1·0 to 0·7)	0·052

Data are study-average differences (95% CI) estimated using an adjusted prespecified mixed model for repeated measures approach. Analysis of effects on uACR uses central laboratory measurements at follow-up timepoints 2, 18, 24, and 30 months, with findings similar in a sensitivity analysis including a baseline quadratic term to assess the effect of the violation of the assumption of linearity for quantitative predictors. Analysis of effects on blood pressure uses measurements obtained at follow-up timepoints: 2, 6, 12, 18, 24, 30, and 36 months. Analyses required participants to have at least one follow-up measurement of the outcome variable and excluded participants with missing baseline measurements (uACR 203 [3·1%] of 6609; no missing baseline blood pressure measurements for analysed participants). uACR=urinary albumin-to-creatinine ratio.

Table 3: uACR and blood pressure assessments by primary kidney disease

Lancet Diabetes Endocrinol 2024; 12: 51–60

DAPA-CKD study



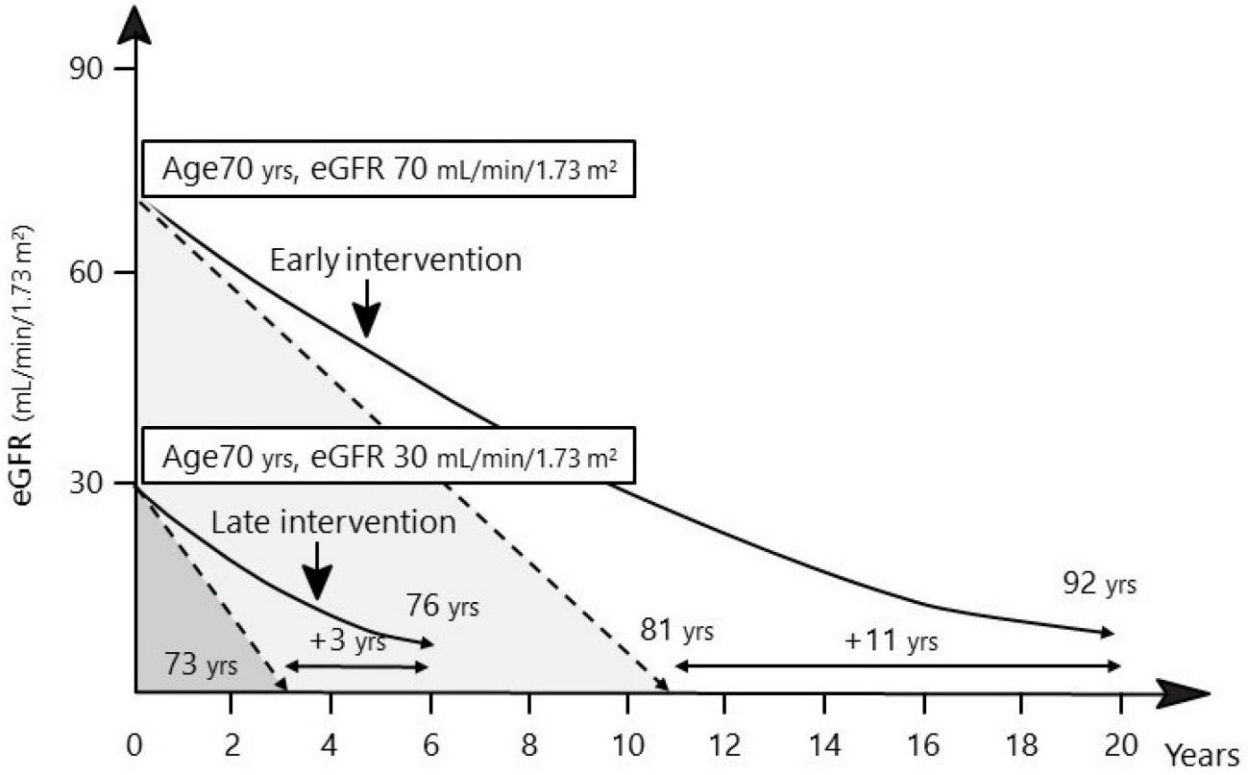
N Engl J Med 2020 Oct 8;383(15):1436-1446

Open Access Review

Sodium-Glucose Cotransporter-2 Inhibitors—Miracle Drugs for the Treatment of Chronic Kidney Disease Irrespective of the Diabetes Status: Lessons from the Dedicated Kidney Disease-Focused CREDENCE and DAPA-CKD Trials

by Tomohito Gohda * and Maki Murakoshi

Department of Nephrology, Juntendo University Faculty of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan



Int. J. Mol. Sci. 2022, 23(22), 13749

JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Retinopathy in Patients With Type 2 Diabetes

Fu-Shun Yen, MD; James Cheng-Chung Wei, PhD; Teng-Shun Yu, MS; Yu-Tung Hung, MS; Chih-Cheng Hsu, DrPH; Chii-Min Hwu, MD

Abstract

IMPORTANCE Diabetic nephropathy and diabetic retinopathy share many similarities in pathophysiological processes. Preclinical studies have shown that sodium-glucose cotransporter 2 inhibitors (SGLT2is) have a protective role in the risk of diabetic retinopathy.

OBJECTIVE To compare the risk of sight-threatening retinopathy associated with SGLT2is and other second-line glucose-lowering medications (including pioglitazone, sulfonylureas, and dipeptidyl peptidase-4 inhibitors [DPP-4is]) in patients with type 2 diabetes (T2D).

DESIGN, SETTING, AND PARTICIPANTS This cohort study in Taiwan applied a new-user and active-comparator design. Patient demographic and clinical data were obtained from the National Health Insurance Research Database. Adult patients with newly diagnosed T2D from January 1, 2009, to December 31, 2019, were recruited and followed up until December 31, 2020. Propensity score matching was used to identify pairs of patients treated with SGLT2i vs DPP-4i, SGLT2i vs pioglitazone, and SGLT2i vs sulfonylurea from January 1, 2016, to December 31, 2019. Data were analyzed between August 18, 2022, and May 5, 2023.

EXPOSURES Treatment with SGLT2i, DPP-4i, pioglitazone, and sulfonylureas starting on January 1, 2016.

MAIN OUTCOMES AND MEASURES The main outcome was sight-threatening retinopathy in participants. Cox proportional hazards regression models were used to assess relative hazards of sight-threatening retinopathy between the matched case and control groups.

Key Points

Question Could sodium-glucose cotransporter 2 inhibitors (SGLT2is) protect against the risk of sight-threatening diabetic retinopathy?

Findings In this cohort study of 3 544 383 patients with type 2 diabetes in Taiwan, SGLT2is were associated with a significantly lower risk and lower cumulative incidence of sight-threatening retinopathy than dipeptidyl peptidase-4 inhibitors, pioglitazone, and sulfonylureas.

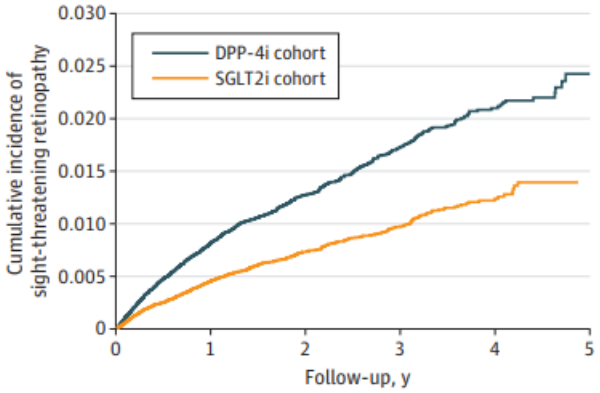
Meaning Findings from this study suggest that SGLT2is may have an association not only with reduced risk of diabetic nephropathy but also with the slow progression of diabetic retinopathy in patients with type 2 diabetes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

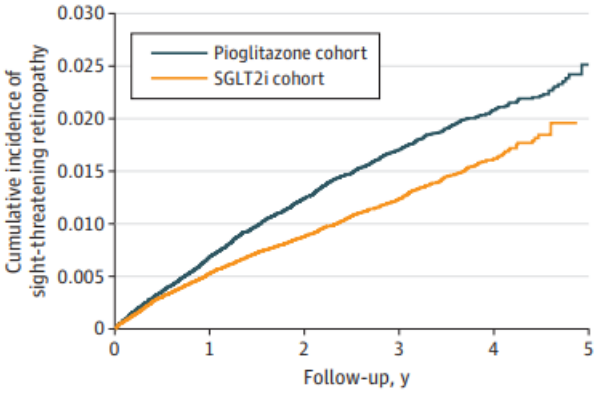
Cumulative Incidence of Sight-Threatening Retinopathy Between Medications

A DPP-4i and SGLT2i cohorts



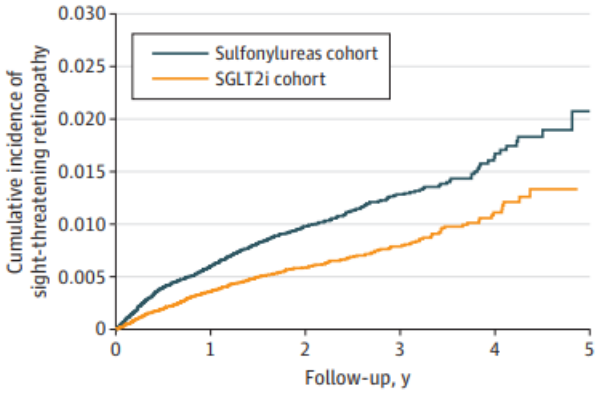
No. of patients at risk						
DPP-4i cohort	65930	63855	33666	16069	5825	0
SGLT2i cohort	65930	65004	36026	17522	5370	0

B Pioglitazone and SGLT2i cohorts



No. of patients at risk						
Pioglitazone cohort	93760	90957	58660	32606	13749	0
SGLT2i cohort	93760	92001	59938	35263	13320	0

C Sulfonylureas and SGLT2i cohorts



No. of patients at risk						
Sulfonylureas cohort	42121	40946	21532	9425	2992	0
SGLT2i cohort	42121	41584	22043	10637	3515	0

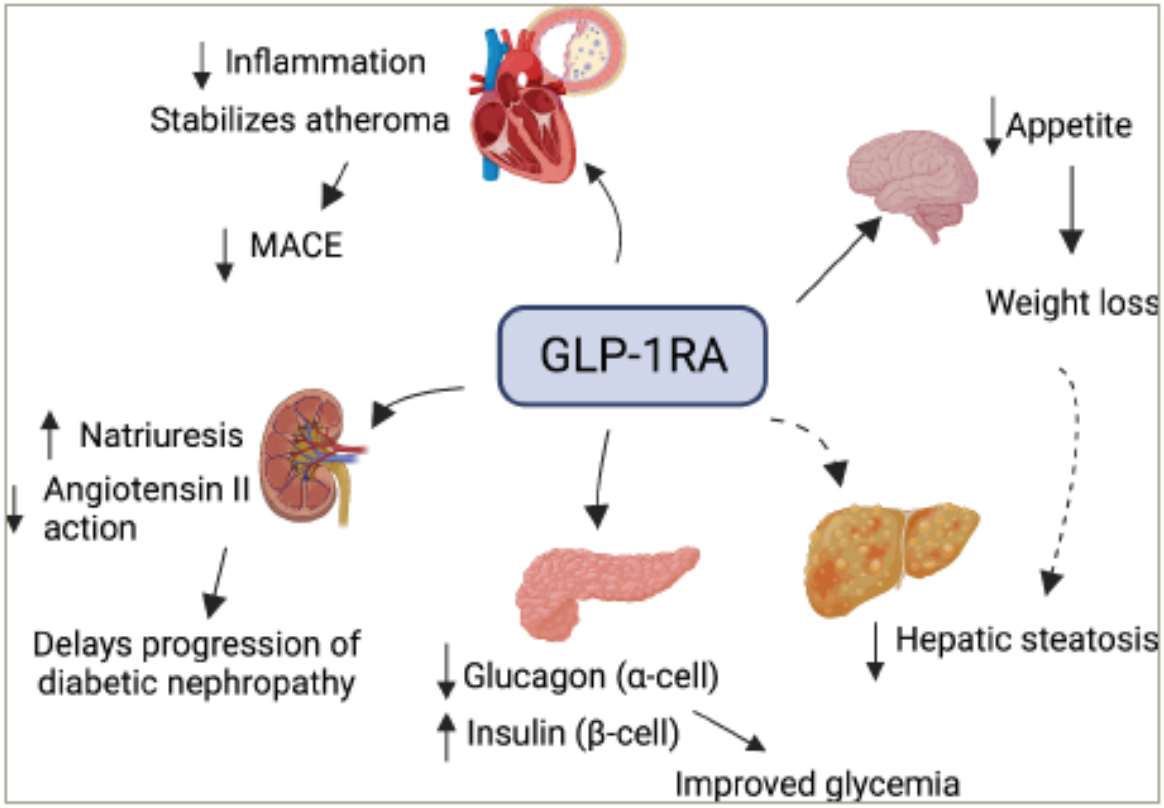
SGLT2-inhibitors

- Precautions:
  - Euglycaemic ketosis
  - Soft tissue infections
  - ? UTI
  - Major surgery/ trauma

- Considerations:
  - Co-morbidities; Heart failure (vs *cor pulmonale*), severe COPD (& other risk factors of acidosis)

GLP-1RA

- Glucagon-like peptide-1 receptor agonists



Reviews in Endocrinology 2023;19(1): 38-45

GLP1-RA

Table 2. Baseline Characteristics and Use of Glucose-Lowering Agents Across Trials

	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN 6 (n=3297)	EXSCEL (n=14 752)	HARMONY OUTCOMES (n=9463)	REWIND (n=9903)	PIONEER-6 (n=3183)	AMPLITUDE-O (n=4076)
Drug	**Lixisenatide**	**Liraglutide**	**Semaglutide**	**Exenatide**	**Albiglutide**	**Dulaglutide**	**Semaglutide**	**Efpeglenatide**
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Subcutaneous
Target dose	10 µg/d or 20 µg/d	1.8 mg/d	0.5 mg/wk or 1 mg/wk	2 mg/wk	30 mg/wk or 50 mg/wk	1.5 mg/wk	14 mg/d	4 mg/wk or 6 mg/d
Age, y	60±10	64±7	65±7	62±9	64±7	66±7	66±7	65±8
Sex								
Female	31%	36%	39%	38%	31%	46%	32%	33%
Male	69%	64%	61%	62%	69%	54%	68%	67%
BMI kg/m²	30.1±5.6	32.5±6.3	32.8±6.2	32.7±6.4	32.3±5.9	32.3±5.7	32.3±6.5	32.7±6.2
Diabetes duration, y	9.2±8.2	12.8±8.0	13.9±8.1	13.1±8.3	14.2±8.8	10.5±7.2	14.9±8.5	15.4±8.8
HbA1c %	7.7±1.3	8.7±1.6	8.7±1.5	8.1±1.0	8.7±1.5	7.3±1.1	8.2±1.6	8.9±1.5
Established cardiovascular disease	100%	81%	83%	73%	100%	31%	85%	90%
History of heart failure	22%	18%	24%	16%	20%	9%	12%	18%
Systolic blood pressure (mm Hg)	129±17	136±18	136±17	135±17	135±17	137±17	136±18	135±16
eGFR, mL/min per 1.73 m²*	78±21	80 (NR)	80 (61–92)	77 (61–92)	79±25	77±23	74±21	72±22

Circulation 2022;146:1882–1894

GLP1-RA

	Main analysis with all 8 CVOTs (HR; I^2)	Sensitivity analyses minus ELIXA (HR; I^2)
MACE	0.86 (0.80 to 0.93) 45%	0.85 (0.80 to 0.90) 15%
CV death	0.87 (0.80 to 0.94) 13%	0.85 (0.78 to 0.93) 12%
MI	0.90 (0.83 to 0.98) 27%	0.88 (0.81 to 0.96) 16%
All-cause mortality	0.88 (0.82 to 0.94) 10%	0.87 (0.81 to 0.94) 17%
Incident HHF	0.89 (0.82 to 0.98) 3%	0.88 (0.79 to 0.98) 12%
Kidney composite (+ albuminuria)	0.79 (0.73 to 0.87) 48%	0.78 (0.71 to 0.87) 57%
Worsening kidney function (eGFR)	0.86 (0.72 to 1.02) 43%	0.82 (0.69 to 0.98) 40%

CV indicates cardiovascular; CVOTs, cardiovascular outcome trials; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE001; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

Circulation 2022;146:1882–1894

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GLP1-RA

RESEARCH Open Access

Time-dependent effect of GLP-1 receptor agonists on cardiovascular benefits: a real-world study

Sara Piccini[1,2], Giuseppe Favacchio[2], Cristina Panico[1,3], Emanuela Morenghi[4], Franco Folli[5], Gherardo Mazziotti[1,2], Andrea Gerardo Lania[1,2] and Marco Mirani[2*]

Abstract

Background Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown cardiovascular benefits in cardiovascular outcome trials in type 2 diabetes mellitus. However, the most convincing evidence was obtained in subjects with established cardiovascular (CV) disease. We analyzed the determinants of GLP-1 RA-mediated CV protection in a real-world population of persons with type 2 diabetes with and without a history of CV events with long-term follow-up.

Methods Retrospective cohort study of 550 individuals with type 2 diabetes (395 in primary CV prevention, 155 in secondary CV prevention), followed at a single center after the first prescription of a GLP-1 RA between 2009 and 2019. CV and metabolic outcomes were assessed.

Results Median duration of follow-up was 5.0 years (0.25–10.8) in primary prevention and 3.6 years (0–10.3) in secondary prevention, with a median duration of treatment of 3.2 years (0–10.8) and 2.5 years (0–10.3) respectively. In the multivariable Cox regression model considering GLP-1 RA treatment as a time-dependent covariate, in the primary prevention group, changes in BMI and glycated hemoglobin did not have an impact on MACE risk, while age at the time of GLP-1 initiation (HR 1.08, 95% CI 1.03–1.14, $p = 0.001$) and GLP-1 RA cessation by time (HR 3.40, 95% CI 1.82–6.32, $p < 0.001$) increased the risk of MACE. Regarding the secondary prevention group, only GLP-1 RA cessation by time (HR 2.71, 95% CI 1.46–5.01, $p = 0.002$) increased the risk of MACE. With respect to those who withdrew treatment, subjects who continued the GLP-1 RA had significantly greater weight loss and lower glycated hemoglobin levels during follow-up.

Conclusions In this real-world type 2 diabetes population, discontinuation of GLP-1 RA treatment was associated to a higher risk of major cardiovascular events, in both subjects with and without a history of CV events.

Keywords Diabetes, GLP-1 receptor agonists, Cardiovascular events, Real-world

Cardiovasc Diabetol 2023;22: 69. doi.org/10.1186/s12933-023-01800-z

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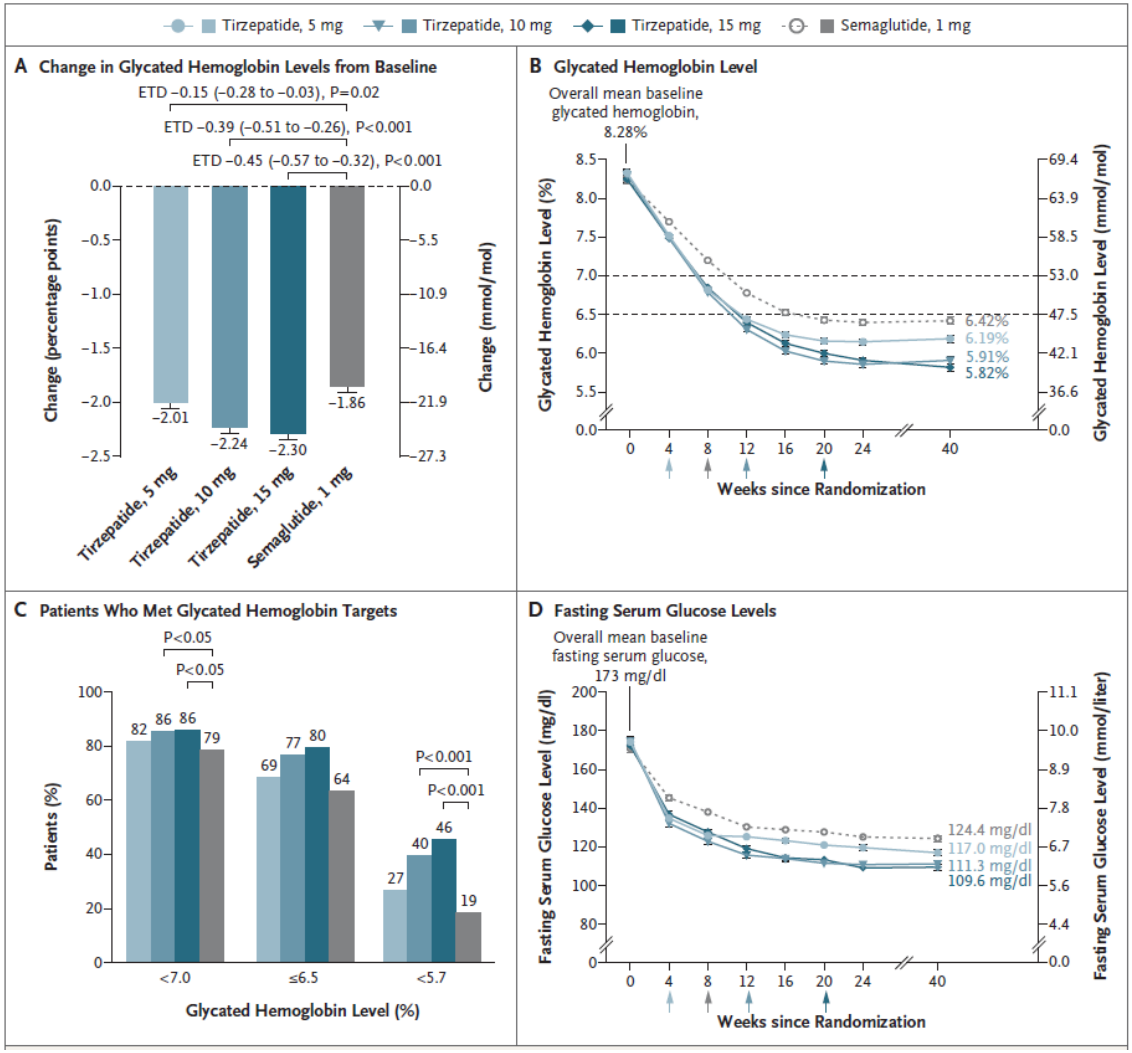
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

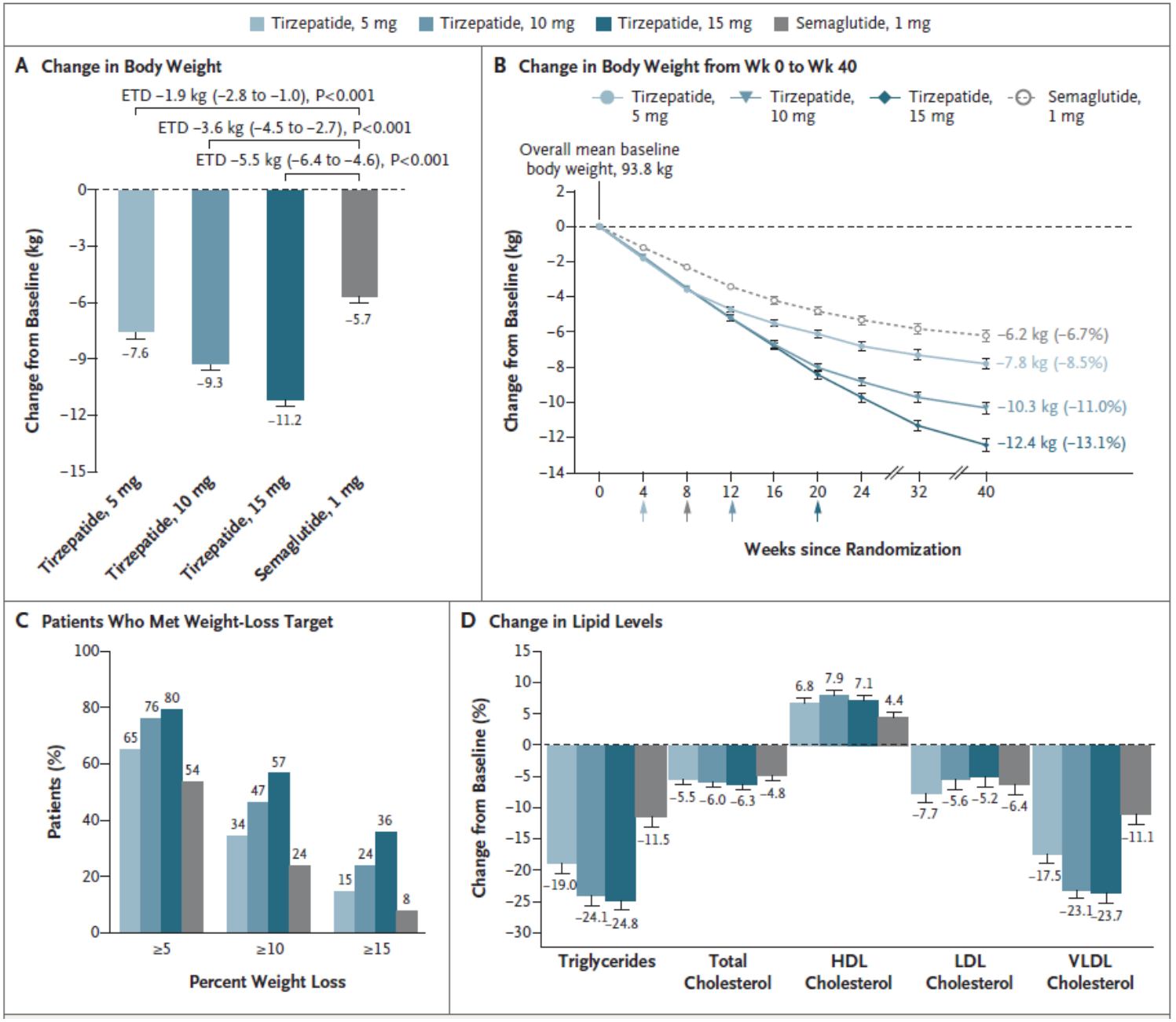
GLP1-RA/ GIP

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*



N Engl J Med 2021;385:503-15



N Engl J Med 2021;385:503-15

Hypertension

- What's new?

ESH GUIDELINES

2023 ESH Guidelines for the management of arterial hypertension *The Task Force for the management of arterial hypertension of the European Society of Hypertension*

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

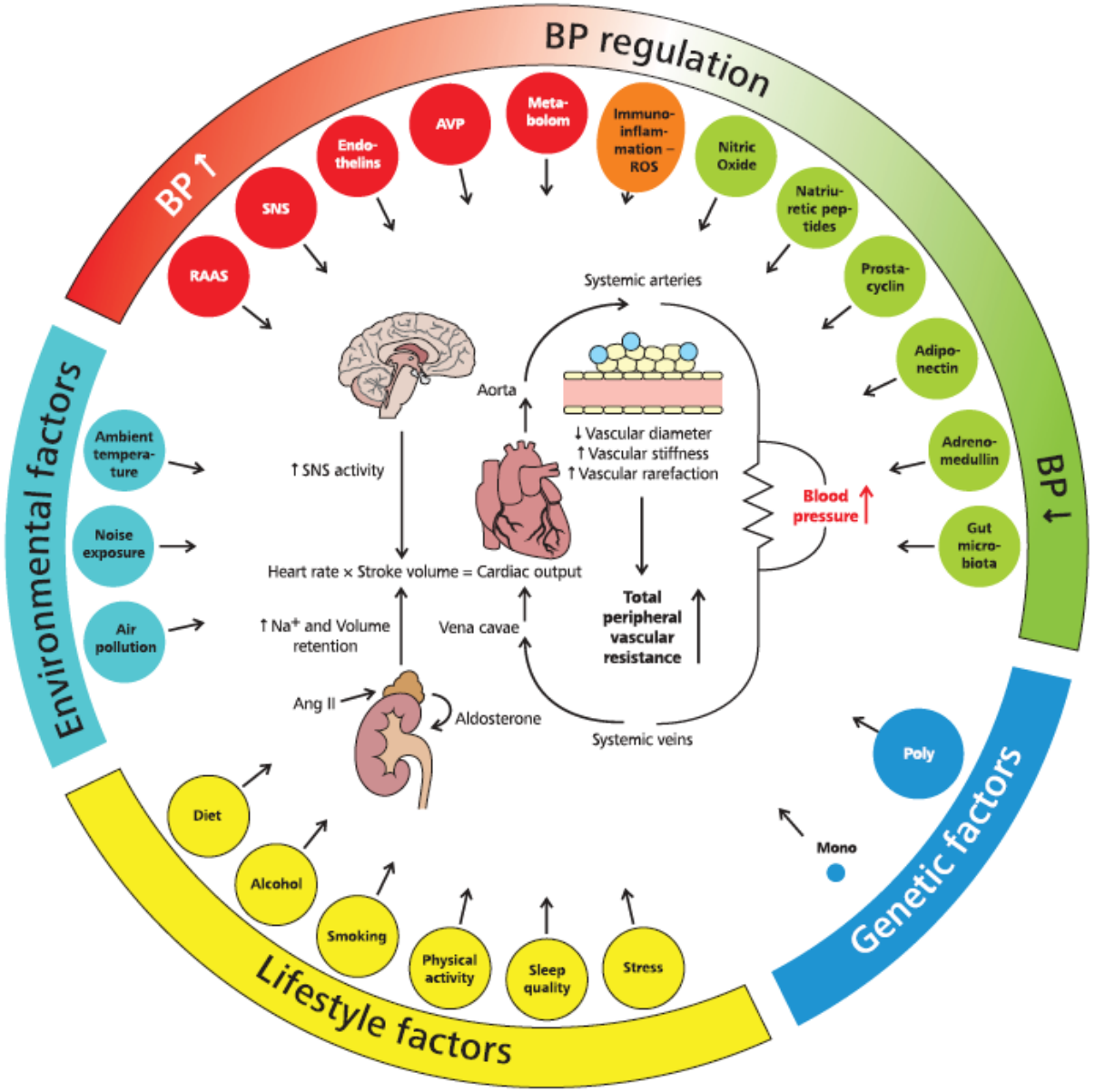
ESC European Society of Cardiology

European Heart Journal (2024) **45**, 3912–4018
https://doi.org/10.1093/eurheartj/ehae178

ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

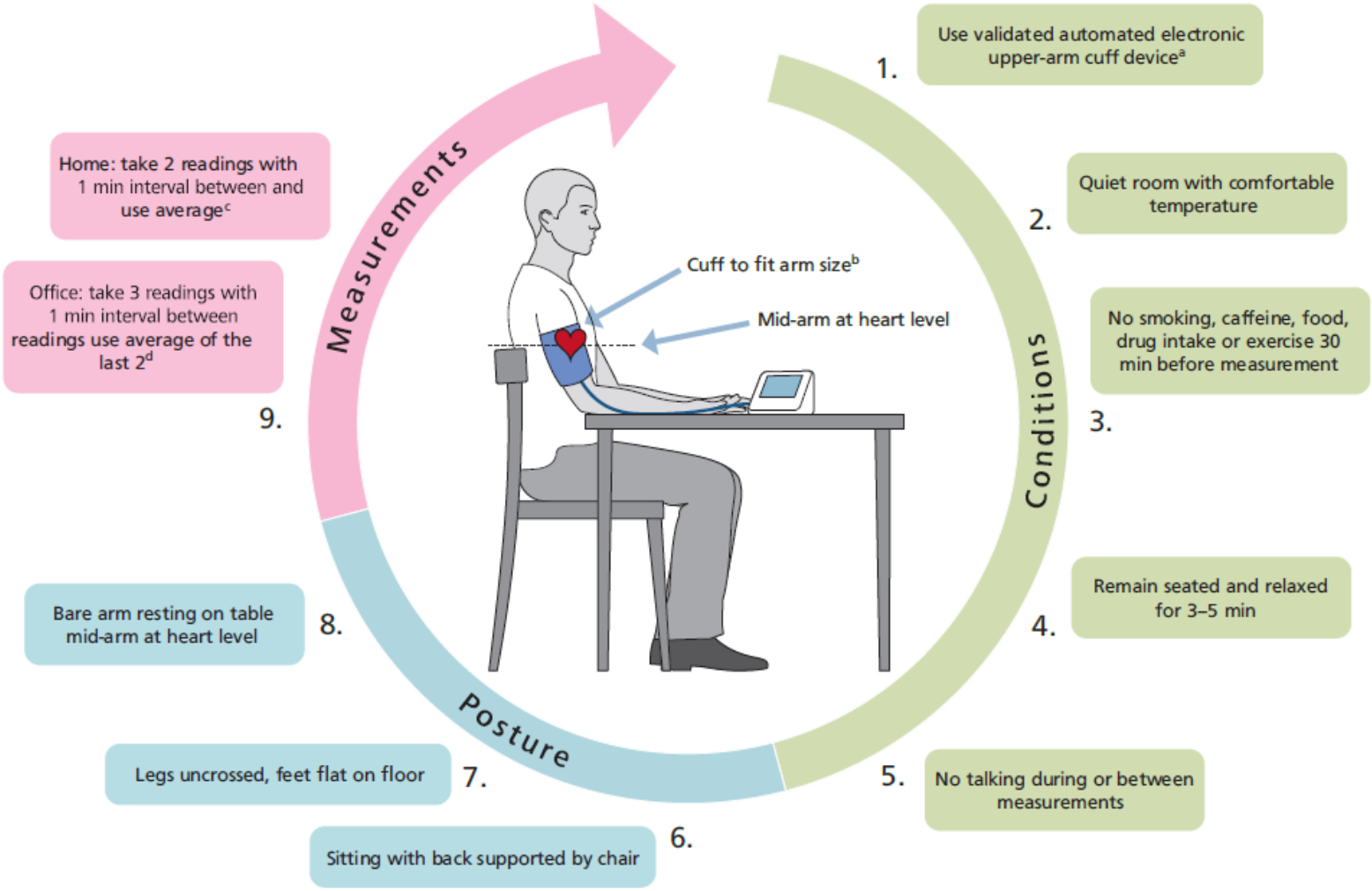
Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and *endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)*



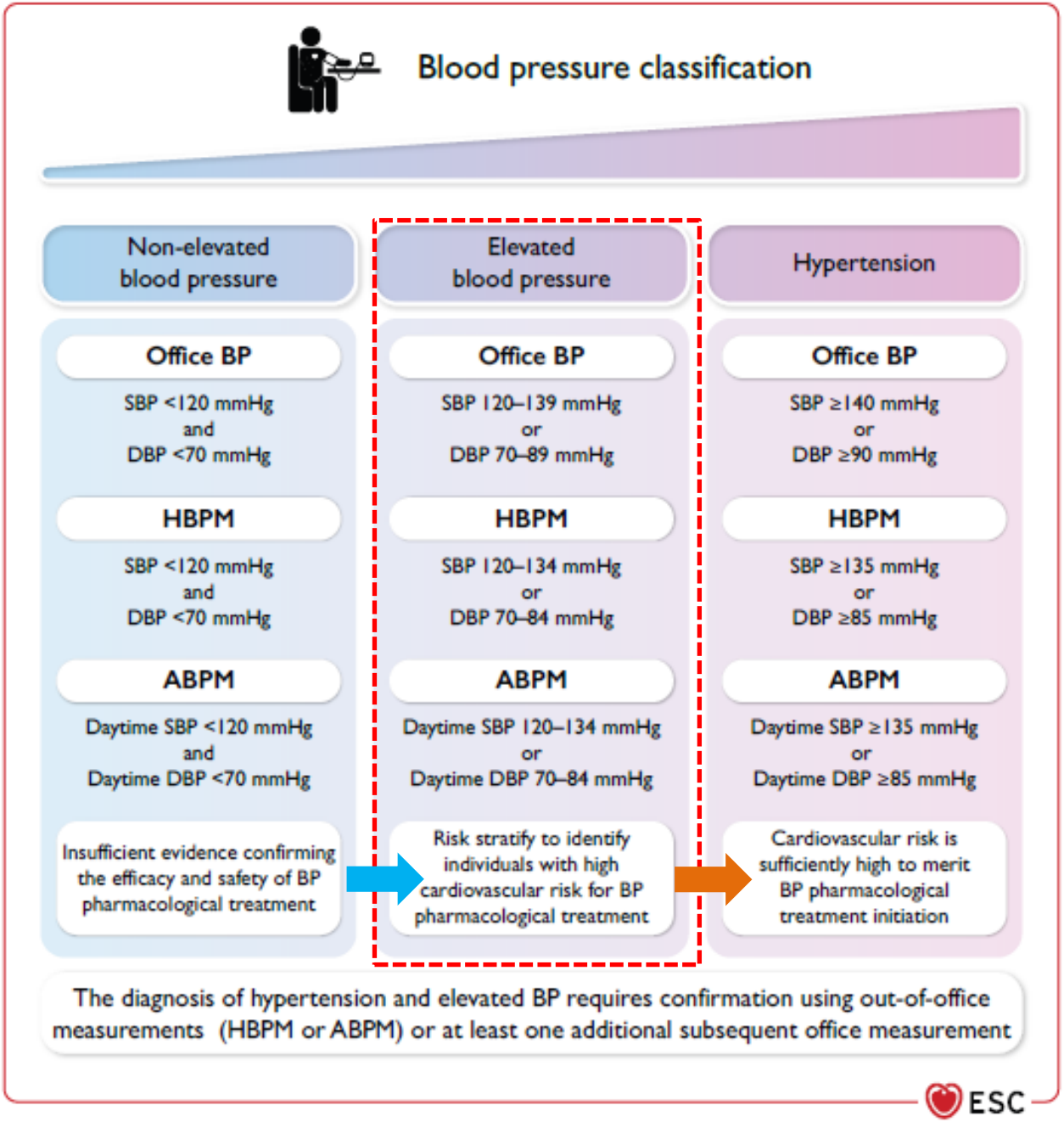
Mechanisms involved in BP regulation and the pathophysiology of hypertension.

Journal of Hypertension 2023 41:1874–2071

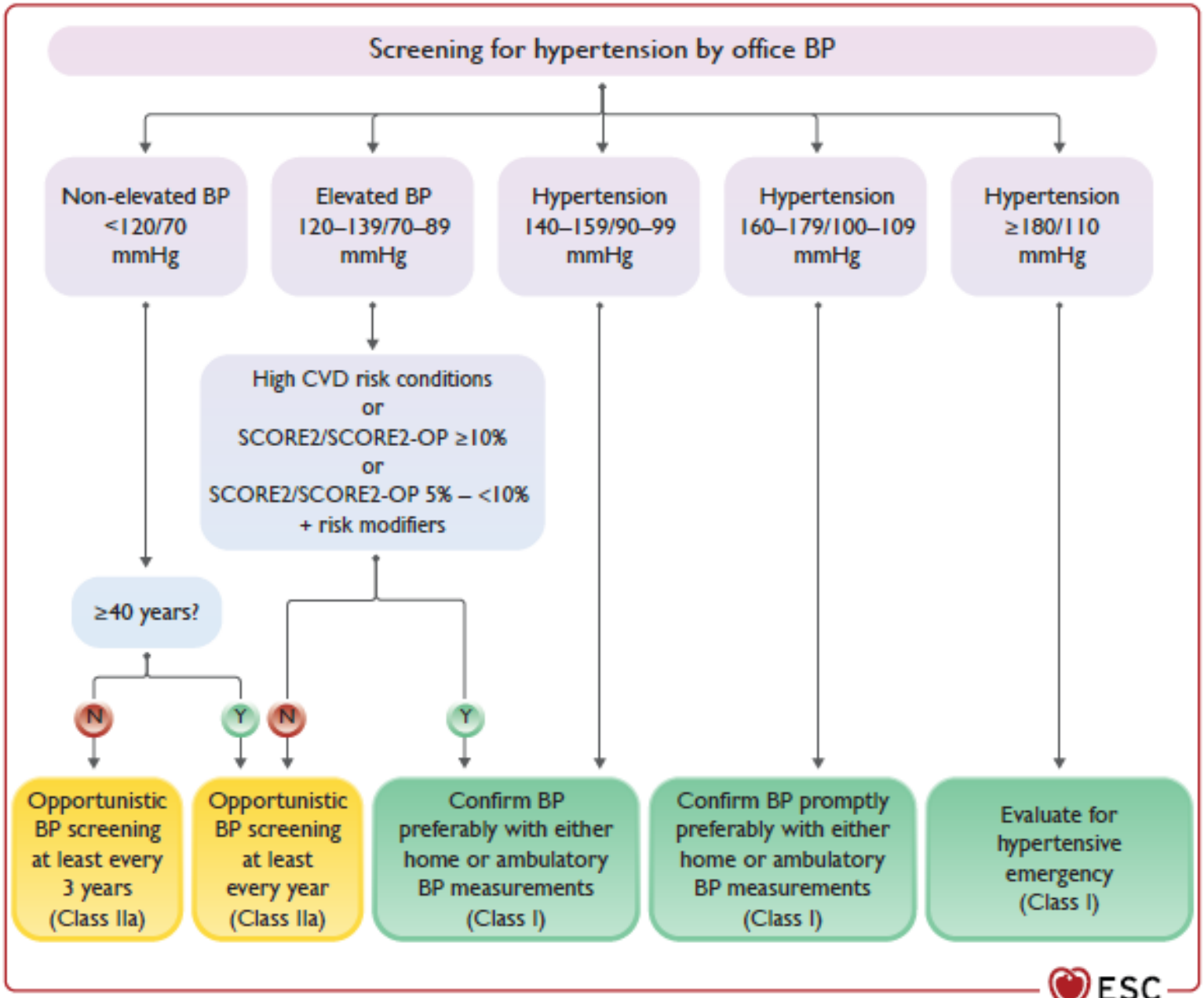
Recommendations for BP measurements in the office and at home



Journal of Hypertension 2023 41:1874–2071



European Heart Journal 2024; 45: 3912–4018



European Heart Journal 2024; 45: 3912–4018

Cardiovascular risk: Stage & Grade

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

Journal of Hypertension 2023 41:1874–2071

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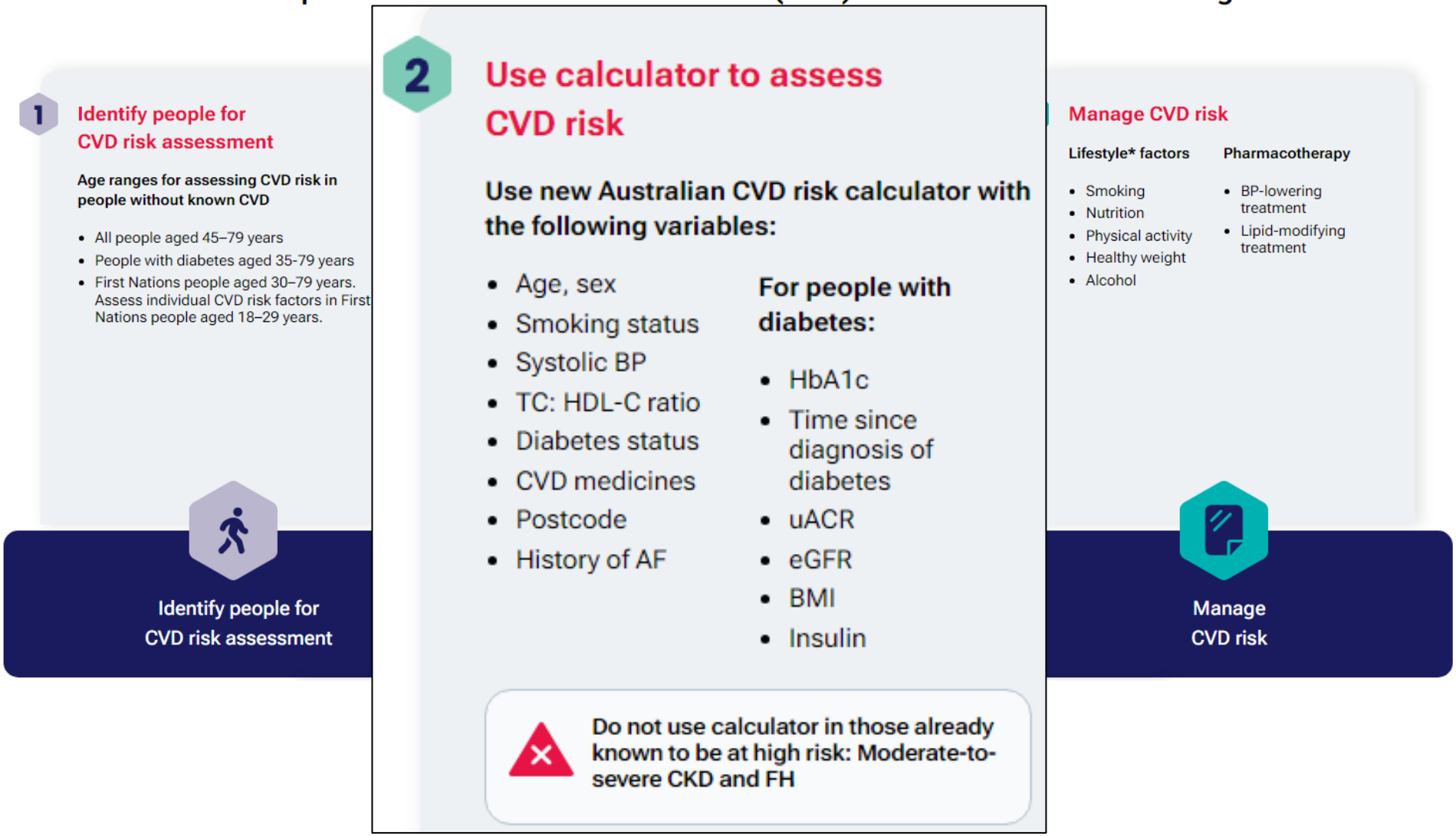
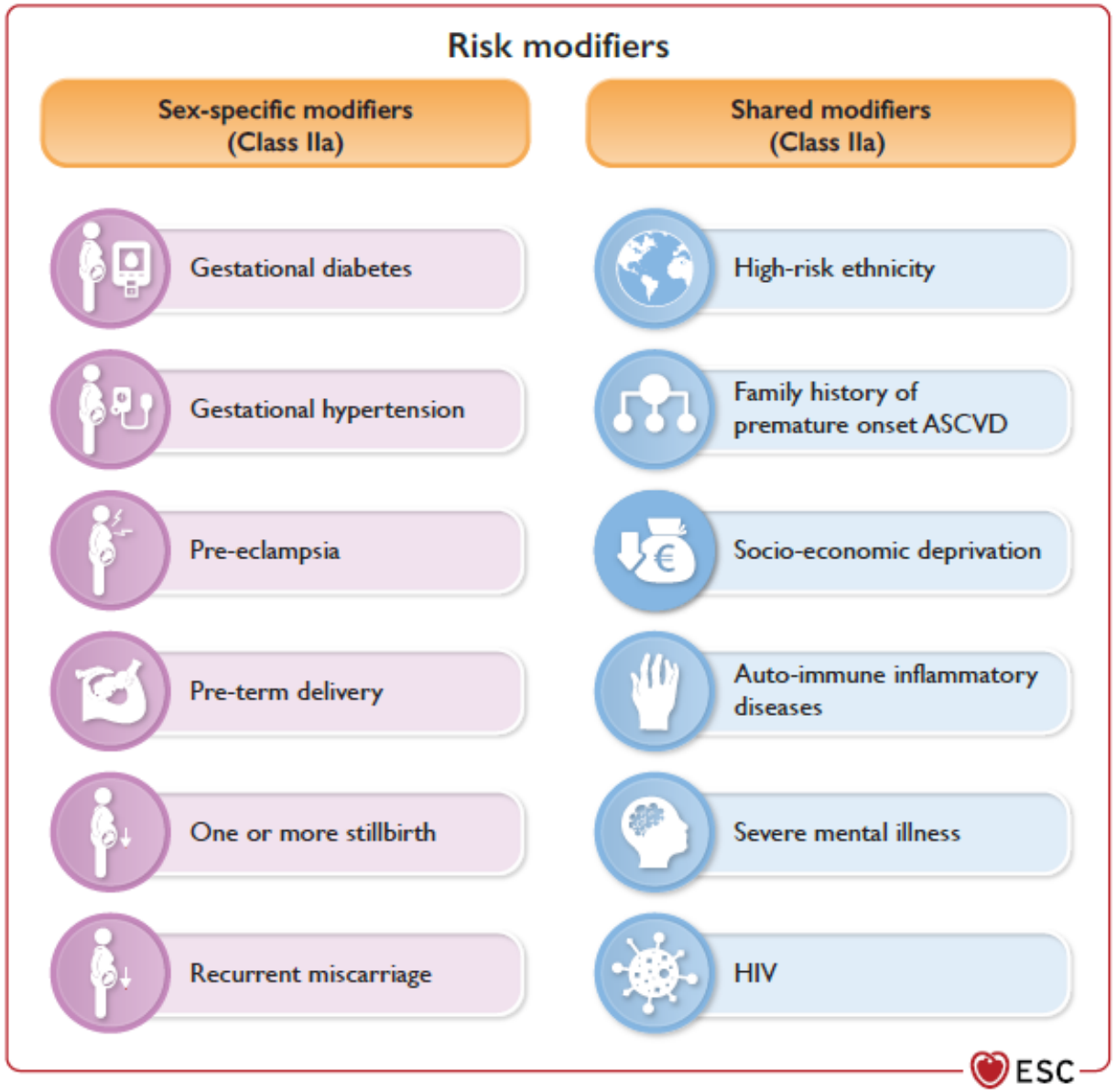
Coronary risk evaluation

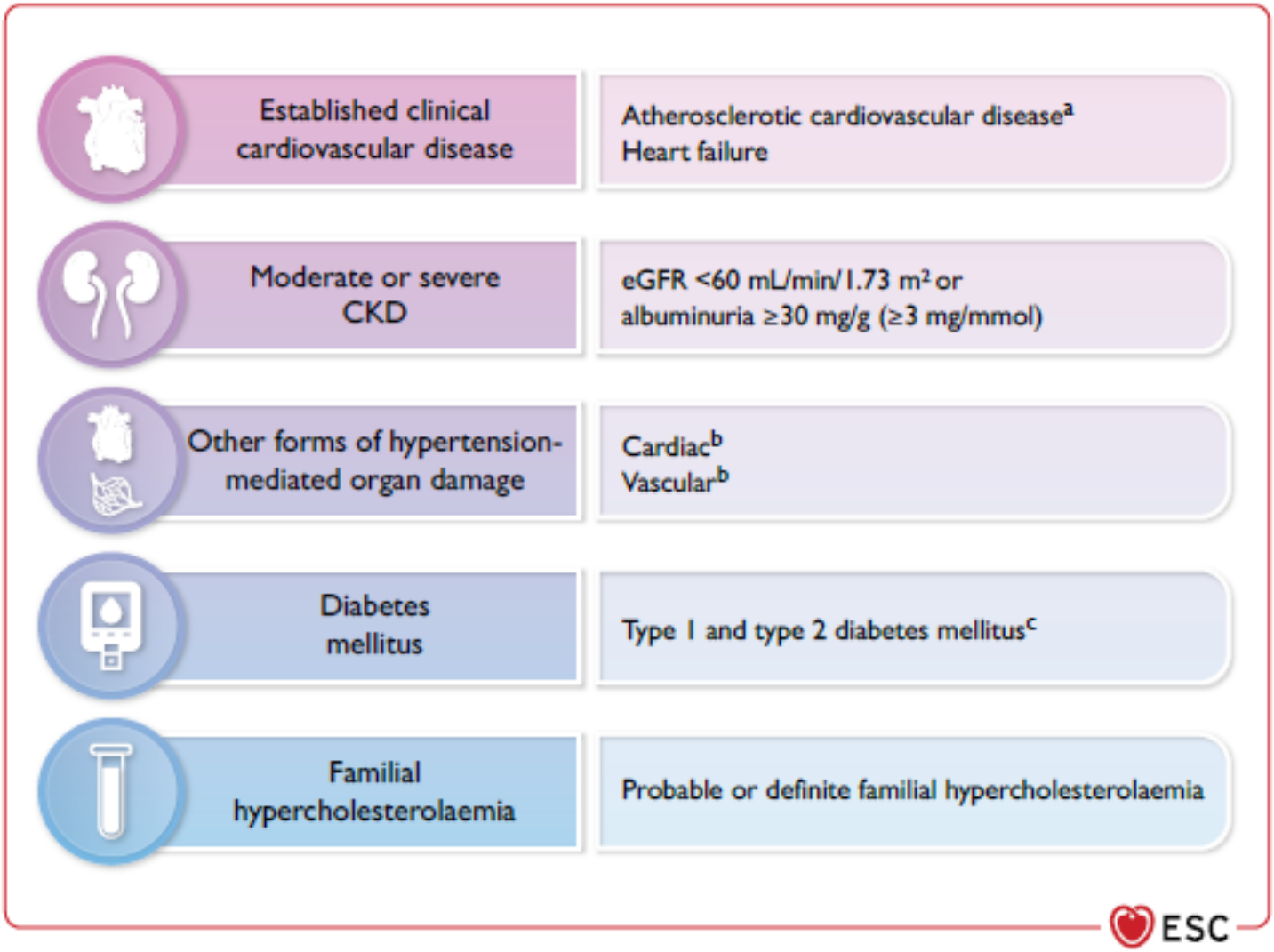
Overview of process for cardiovascular disease (CVD) risk assessment and management



European Heart Journal 2021; 42: 2439–2454

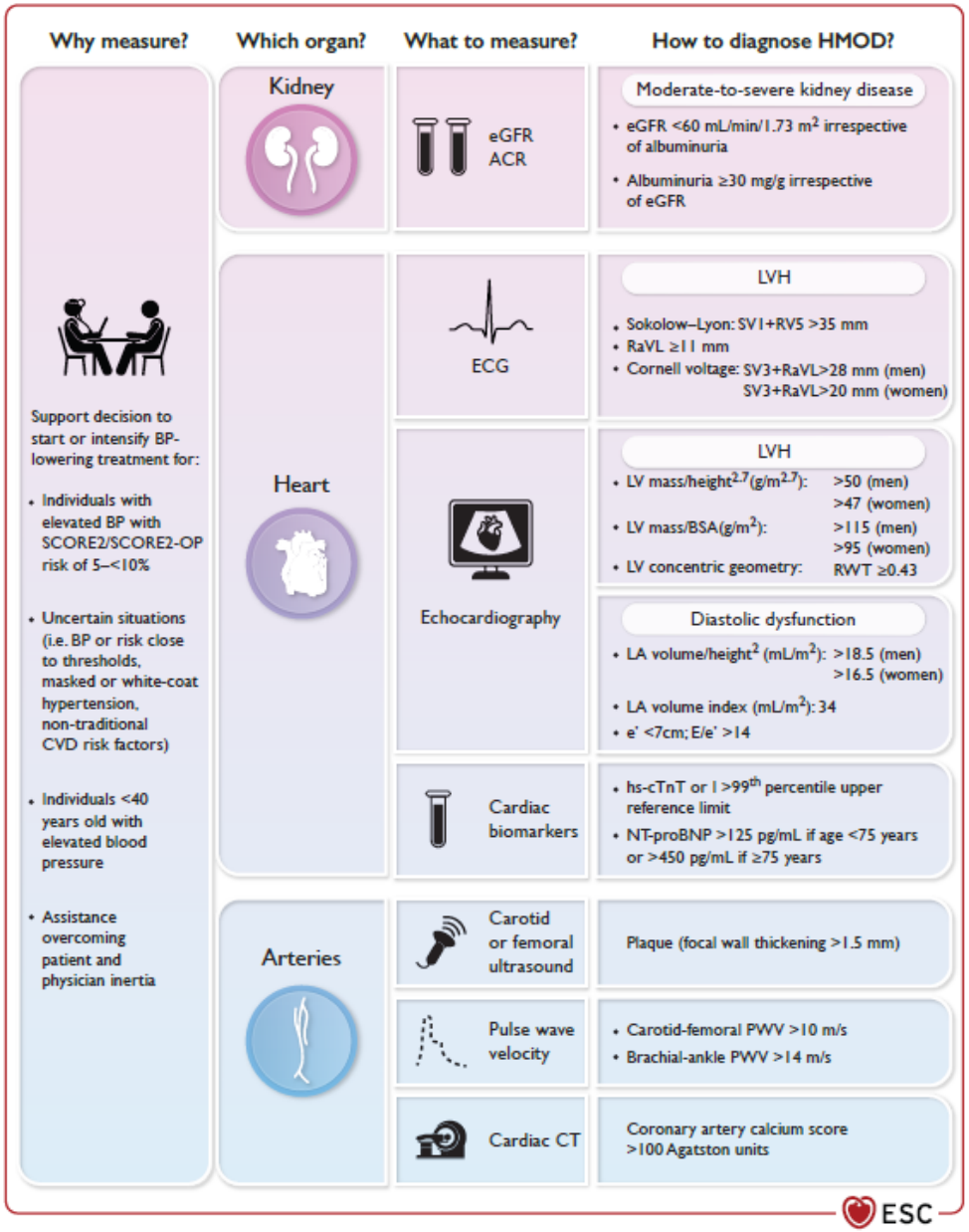


European Heart Journal 2024; 45: 3912–4018



European Heart Journal 2024; 45: 3912–4018

Hypertension-mediated organ damage



European Heart Journal 2024; 45: 3912–4018

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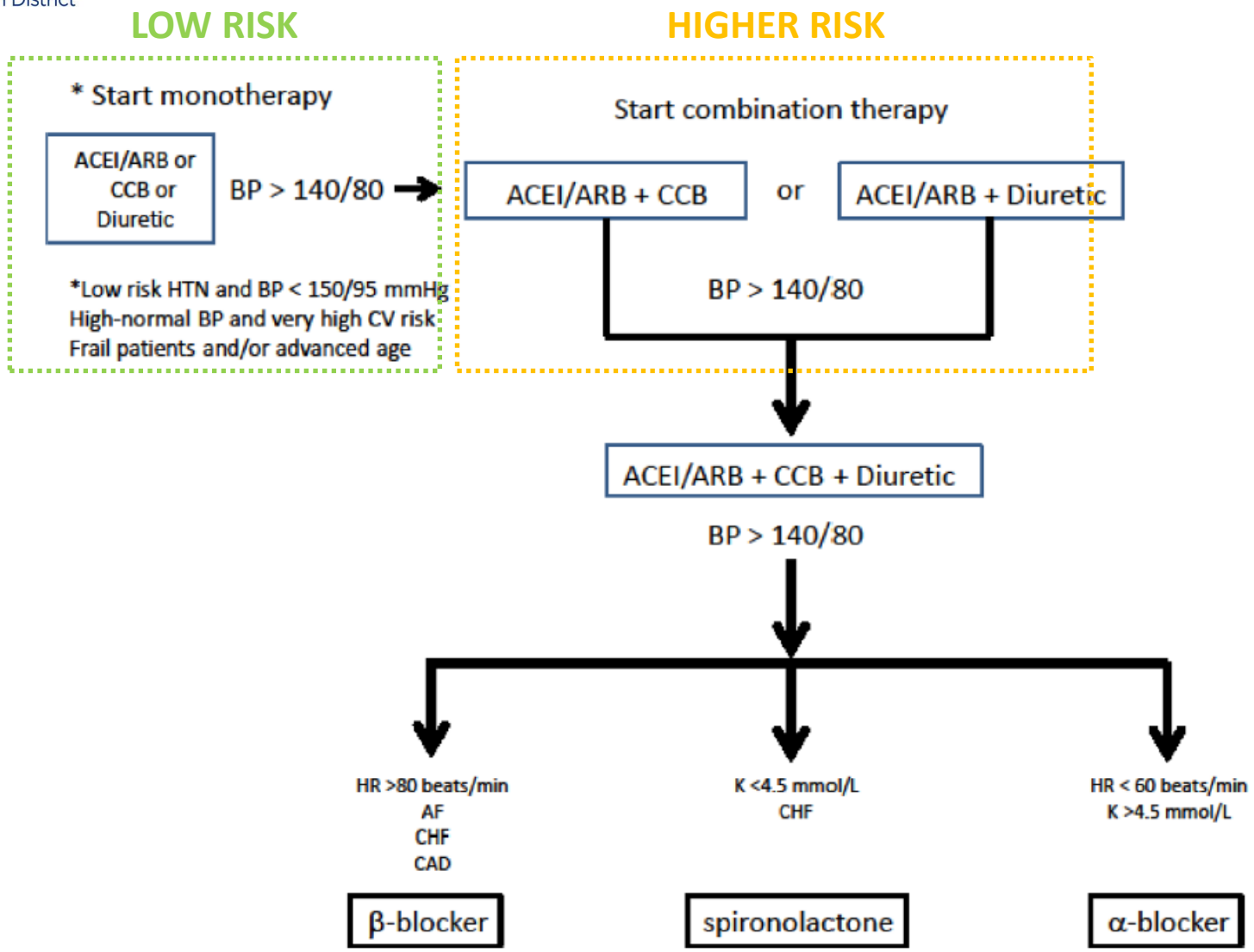
TREATMENT INITIATION



Based on European Journal of Internal Medicine 2023; 116: 1–7

True Resistant hypertension

Defined by all the following (I C):

1) SBP≥140 or DBP ≥90 mmHg despite 3-drug combination at maximum recommended and tolerated doses,
2) elevated BP confirmed by ABPM,
3) Causes of pseudo-resistant hypertension (i.e., poor adherence, drugs, secondary hypertension, etc) excluded.

Home BP to confirm resistant hypertension if ABPM unavailable (II C)

Manage resistant hypertension as a high-risk condition (I C)

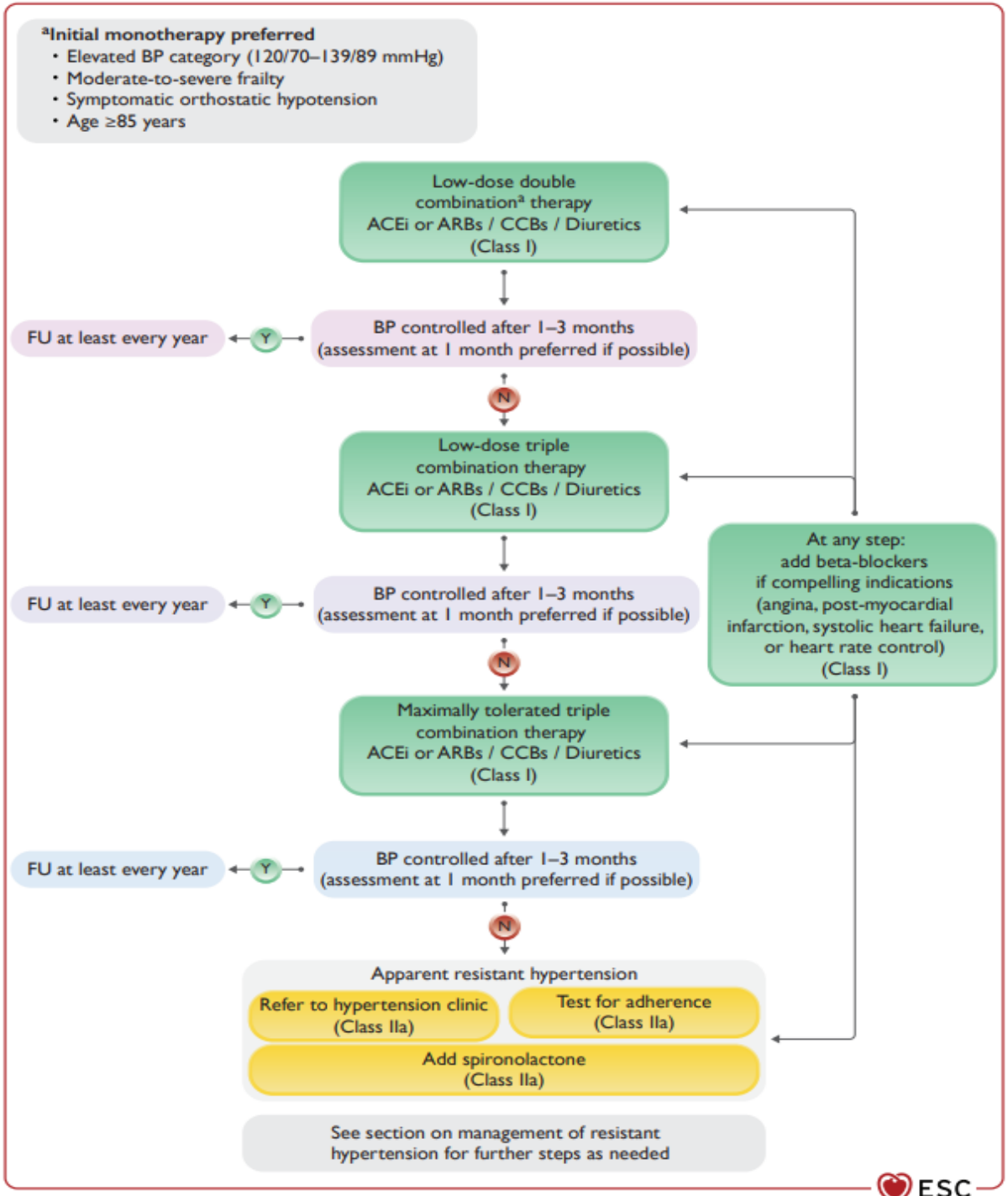
Reduce BP to <140/90 mmHg, and to <130/80 mmHg if well tolerated (I B)

Reinforce life-style measures (I B)

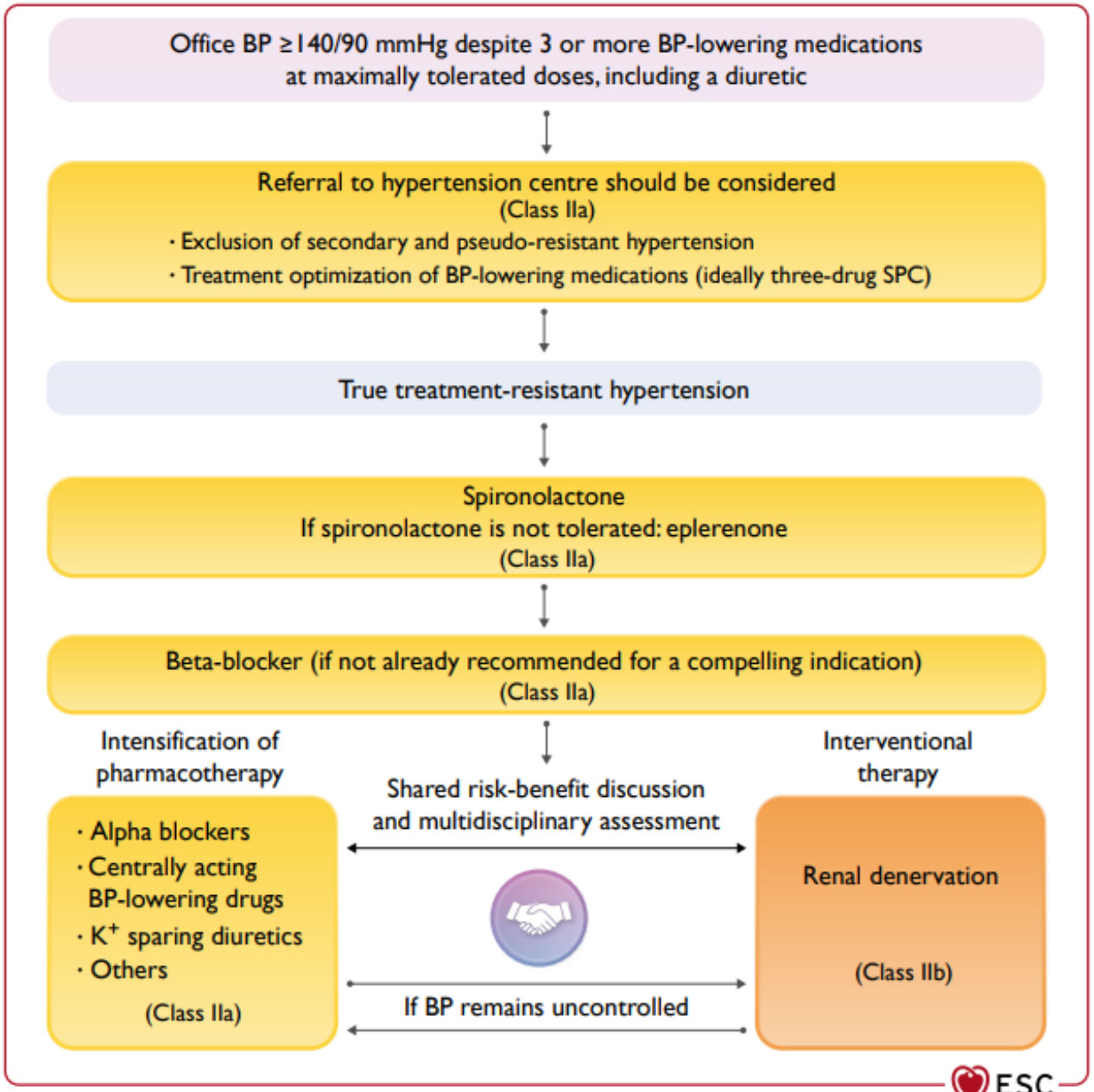
Consider the following additional treatment:

- ✓ **Spironolactone** (or other mineralcorticoid receptor antagonists) (II B)
- ✓ **β-blockers** (II B)
- ✓ **Alpha-1 blockers** (II B)
- ✓ **Centrally acting drugs** (clonidine) (II B)
- ✓ **Amiloride** (II B)
- ✓ **Thiazide/Thiazide-like diuretics** if eGFR≥30 ml/min/1.73 m2. (I B)
- ✓ **Loop diuretics** if eGFR<45 ml/min/1.73 m2 and if eGFR falls <30 ml/min/1.73 m2. (I B)
- ✓ **Chlorthalidone** (12.5 or 25 mg/day) with or without a loop diuretic if eGFR<20 ml/min/1.73 m2 (II B)
- ✓ **Renal denervation** as an option if eGFR>40 ml/min/1.73 m2 (II B)
- ✓ **Close follow-up of patients** (ABPM, home BP assessment of organ damage, kidney function, serum K) (I C)

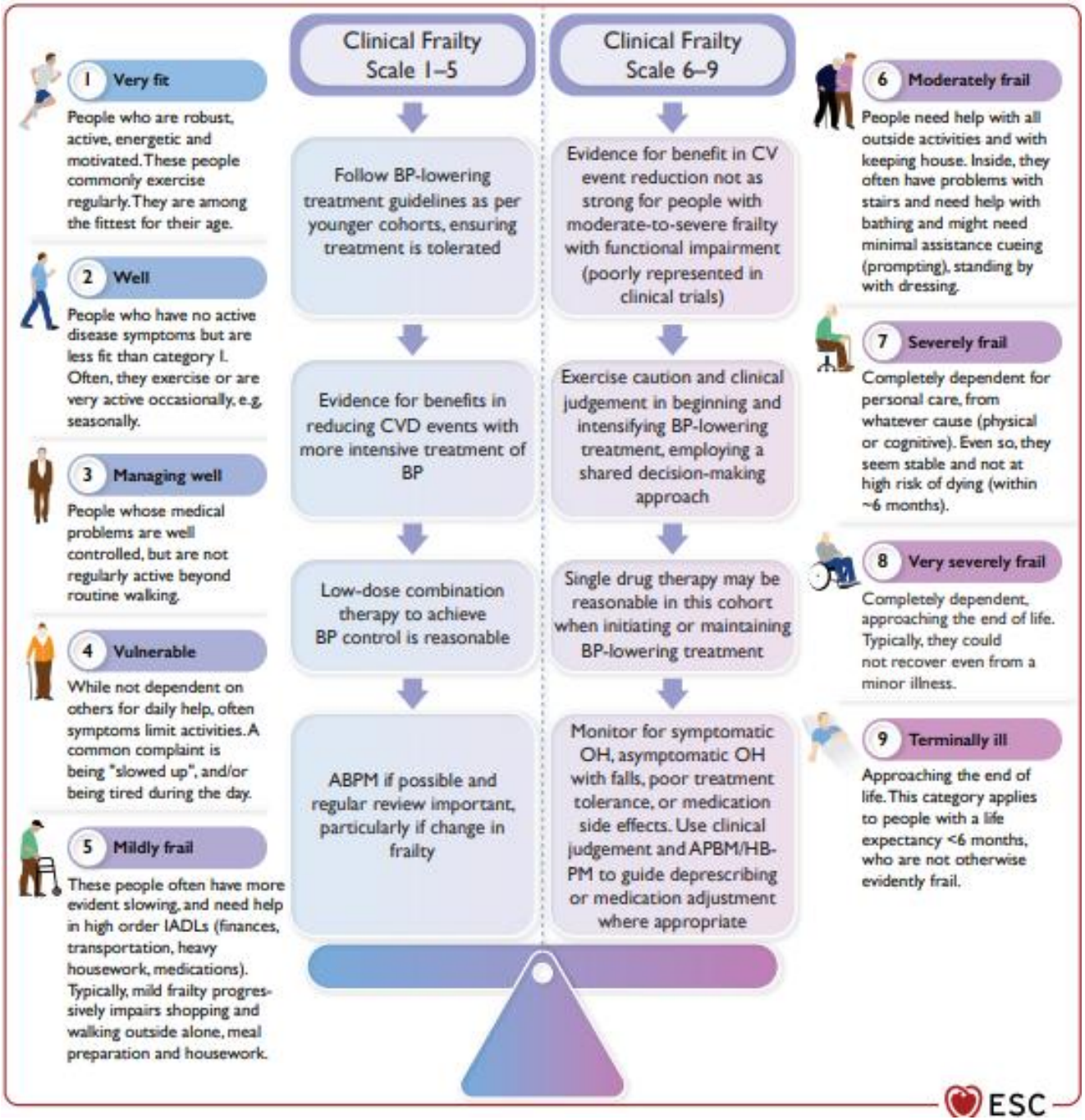
European Journal of Internal Medicine 2023; 116: 1–7


[a]Initial monotherapy preferred
• Elevated BP category (120/70–139/89 mmHg)
• Moderate-to-severe frailty
• Symptomatic orthostatic hypotension
• Age ≥85 years
Low-dose double combination[a] therapy ACEi or ARBs / CCBs / Diuretics (Class I)
BP controlled after 1–3 months (assessment at 1 month preferred if possible)
Y
FU at least every year
N
Low-dose triple combination therapy ACEi or ARBs / CCBs / Diuretics (Class I)
BP controlled after 1–3 months (assessment at 1 month preferred if possible)
Y
FU at least every year
N
Maximally tolerated triple combination therapy ACEi or ARBs / CCBs / Diuretics (Class I)
BP controlled after 1–3 months (assessment at 1 month preferred if possible)
Y
FU at least every year
N
Apparent resistant hypertension
Refer to hypertension clinic (Class IIa)
Test for adherence (Class IIa)
Add spironolactone (Class IIa)
See section on management of resistant hypertension for further steps as needed
At any step: add beta-blockers if compelling indications (angina, post-myocardial infarction, systolic heart failure, or heart rate control) (Class I)
ESC

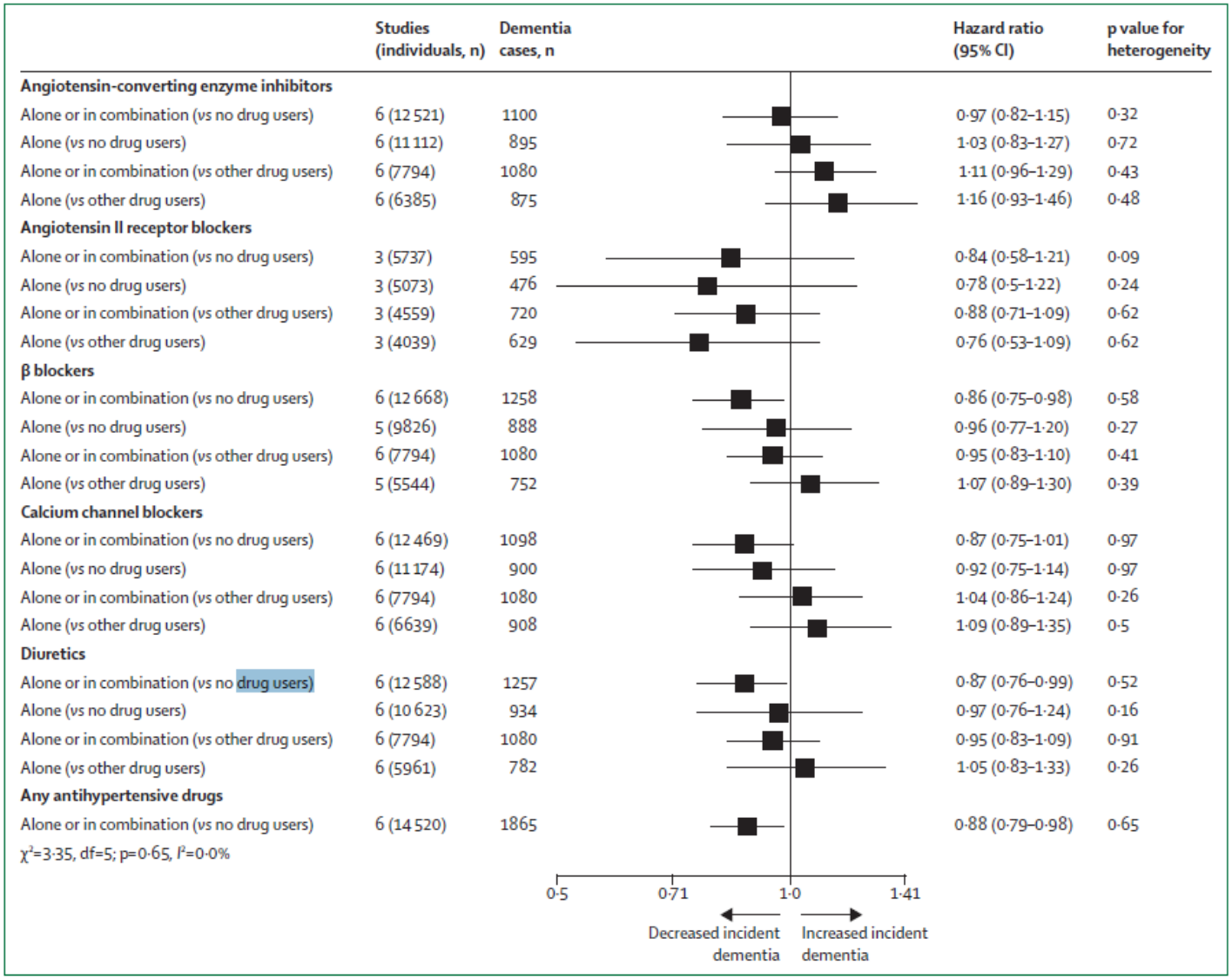
Management of Resistant Hypertension



European Heart Journal 2024; 45: 3912–4018


Clinical Frailty Scale 1–5
Clinical Frailty Scale 6–9
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 housework.
Follow BP-lowering treatment guidelines as per younger cohorts, ensuring treatment is tolerated
Evidence for benefits in reducing CVD events with more intensive treatment of BP
Low-dose combination therapy to achieve BP control is reasonable
ABPM if possible and regular review important, particularly if change in frailty
Evidence for benefit in CV event reduction not as strong for people with moderate-to-severe frailty with functional impairment (poorly represented in clinical trials)
Exercise caution and clinical judgement in beginning and intensifying BP-lowering treatment, employing a shared decision-making approach
Single drug therapy may be reasonable in this cohort when initiating or maintaining BP-lowering treatment
Monitor for symptomatic OH, asymptomatic OH with falls, poor treatment tolerance, or medication side effects. Use clinical judgement and APBM/HBPM to guide deprescribing or medication adjustment where appropriate
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 cueing (prompting), standing by 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.
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.
ESC

Antihypertensive treatment choice



	Studies (individuals, n)	Dementia cases, n	Hazard ratio (95% CI)	p value for heterogeneity
Angiotensin-converting enzyme inhibitors				
Alone or in combination (*vs* no drug users)	6 (12 521)	1100	0·97 (0·82–1·15)	0·32
Alone (*vs* no drug users)	6 (11 112)	895	1·03 (0·83–1·27)	0·72
Alone or in combination (*vs* other drug users)	6 (7794)	1080	1·11 (0·96–1·29)	0·43
Alone (*vs* other drug users)	6 (6385)	875	1·16 (0·93–1·46)	0·48
Angiotensin II receptor blockers				
Alone or in combination (*vs* no drug users)	3 (5737)	595	0·84 (0·58–1·21)	0·09
Alone (*vs* no drug users)	3 (5073)	476	0·78 (0·5–1·22)	0·24
Alone or in combination (*vs* other drug users)	3 (4559)	720	0·88 (0·71–1·09)	0·62
Alone (*vs* other drug users)	3 (4039)	629	0·76 (0·53–1·09)	0·62
β blockers				
Alone or in combination (*vs* no drug users)	6 (12 668)	1258	0·86 (0·75–0·98)	0·58
Alone (*vs* no drug users)	5 (9826)	888	0·96 (0·77–1·20)	0·27
Alone or in combination (*vs* other drug users)	6 (7794)	1080	0·95 (0·83–1·10)	0·41
Alone (*vs* other drug users)	5 (5544)	752	1·07 (0·89–1·30)	0·39
Calcium channel blockers				
Alone or in combination (*vs* no drug users)	6 (12 469)	1098	0·87 (0·75–1·01)	0·97
Alone (*vs* no drug users)	6 (11 174)	900	0·92 (0·75–1·14)	0·97
Alone or in combination (*vs* other drug users)	6 (7794)	1080	1·04 (0·86–1·24)	0·26
Alone (*vs* other drug users)	6 (6639)	908	1·09 (0·89–1·35)	0·5
Diuretics				
Alone or in combination (*vs* no drug users)	6 (12 588)	1257	0·87 (0·76–0·99)	0·52
Alone (*vs* no drug users)	6 (10 623)	934	0·97 (0·76–1·24)	0·16
Alone or in combination (*vs* other drug users)	6 (7794)	1080	0·95 (0·83–1·09)	0·91
Alone (*vs* other drug users)	6 (5961)	782	1·05 (0·83–1·33)	0·26
Any antihypertensive drugs				
Alone or in combination (*vs* no drug users)	6 (14 520)	1865	0·88 (0·79–0·98)	0·65

χ^2=3·35, df=5; p=0·65, I^2=0·0%

Lancet 2020; 396: 413–46

Specific actions for risk factors across the life course

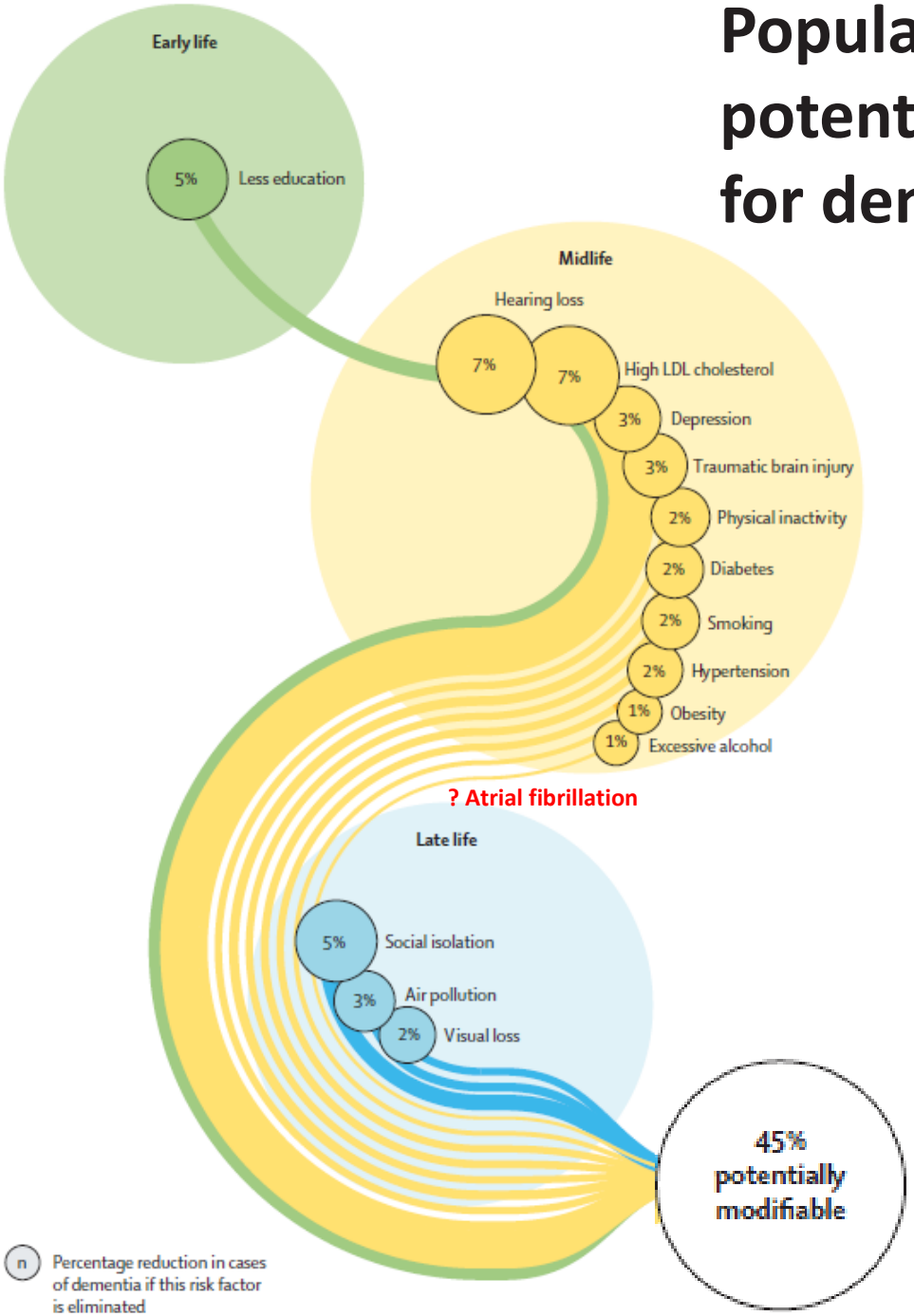
- Aim to maintain systolic BP of 130 mm Hg or less in midlife from around age 40 years (antihypertensive treatment for hypertension is the only known effective preventive medication for dementia).

? 'Old news'

→ We may have more refined risk stratification & therapeutic considerations now

Lancet 2020; 396: 413–46

Population attributable fraction of potentially modifiable risk factors for dementia



Lancet 2024; 404: 572–628

Summary:

- Optimal screening for diabetes
- Role of Urine ACR in both, diabetes & hypertension
- Utilise latest diabetes glycaemic Rx guidelines
- Think 'Beyond Glycaemic Lowering (BGL)'

- Prompt diagnosis & treatment of hypertension
- Review and follow-up is essential
- Think beyond hypertension in the cardiovascular system. E.g. dysrhythmias, hyperlipidaemia, etc

Kairos (Ancient Greek: καιρός), ancient Greek - 'the right or critical moment'

Thank you!

Questions?

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