HYPERTENSION AND DIABETES

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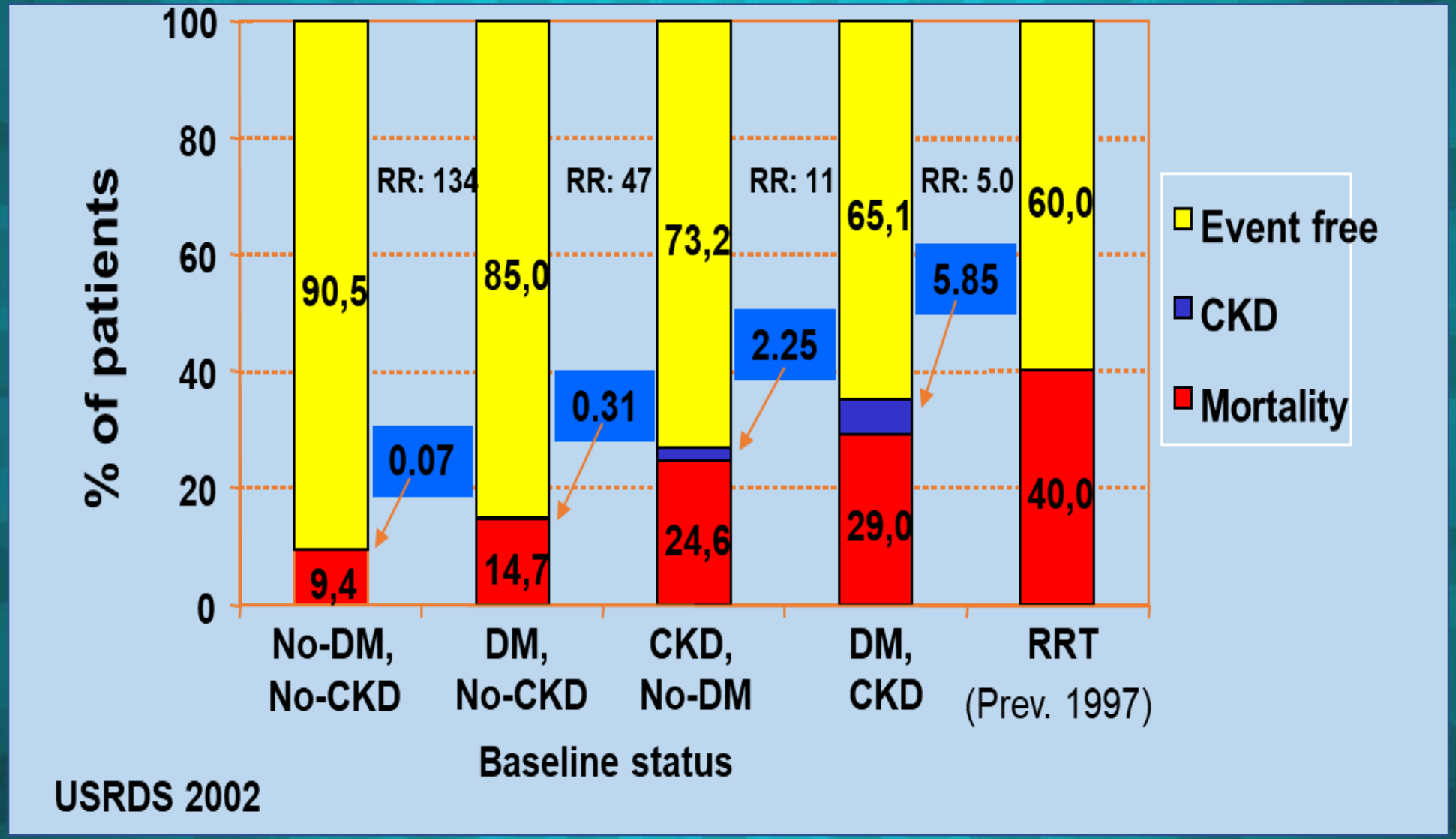
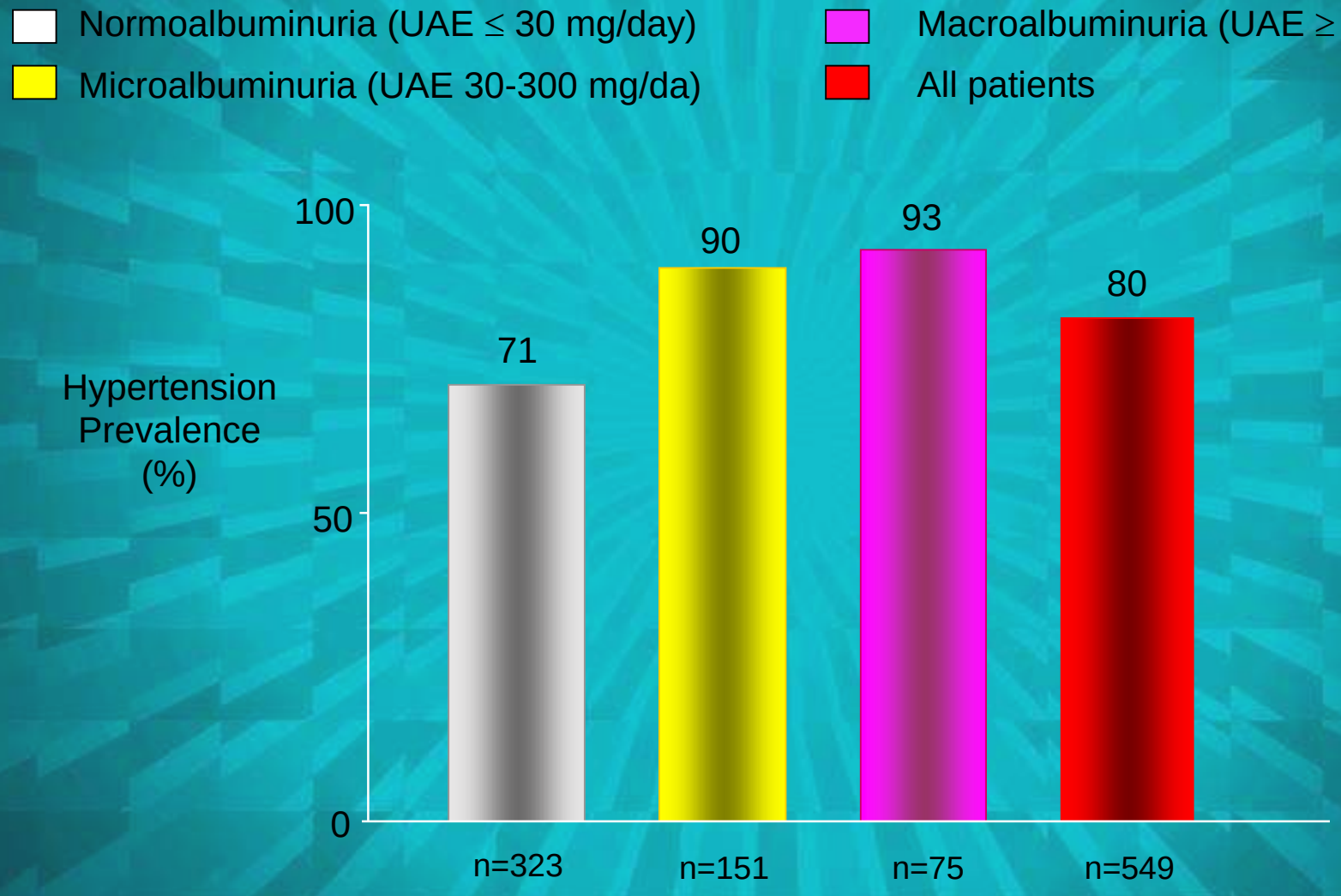
PROGRESSION TO CKD OR DEATH AND DIABETES MELLITUS

Medicare, cohort 1996-1997 (RR: Mortality vs. CKD)



HIGH BLOOD PRESSURE PREVALENCE IN DIABETES MELLITUS



Hipertensión definida como ≥140/90 mm Hg.
UAE= Urinary Albumin Excretion

Tarnow L et al. *Diabetes Care* 1994;17:1247-1251.

Pathophysiology of HT with DM

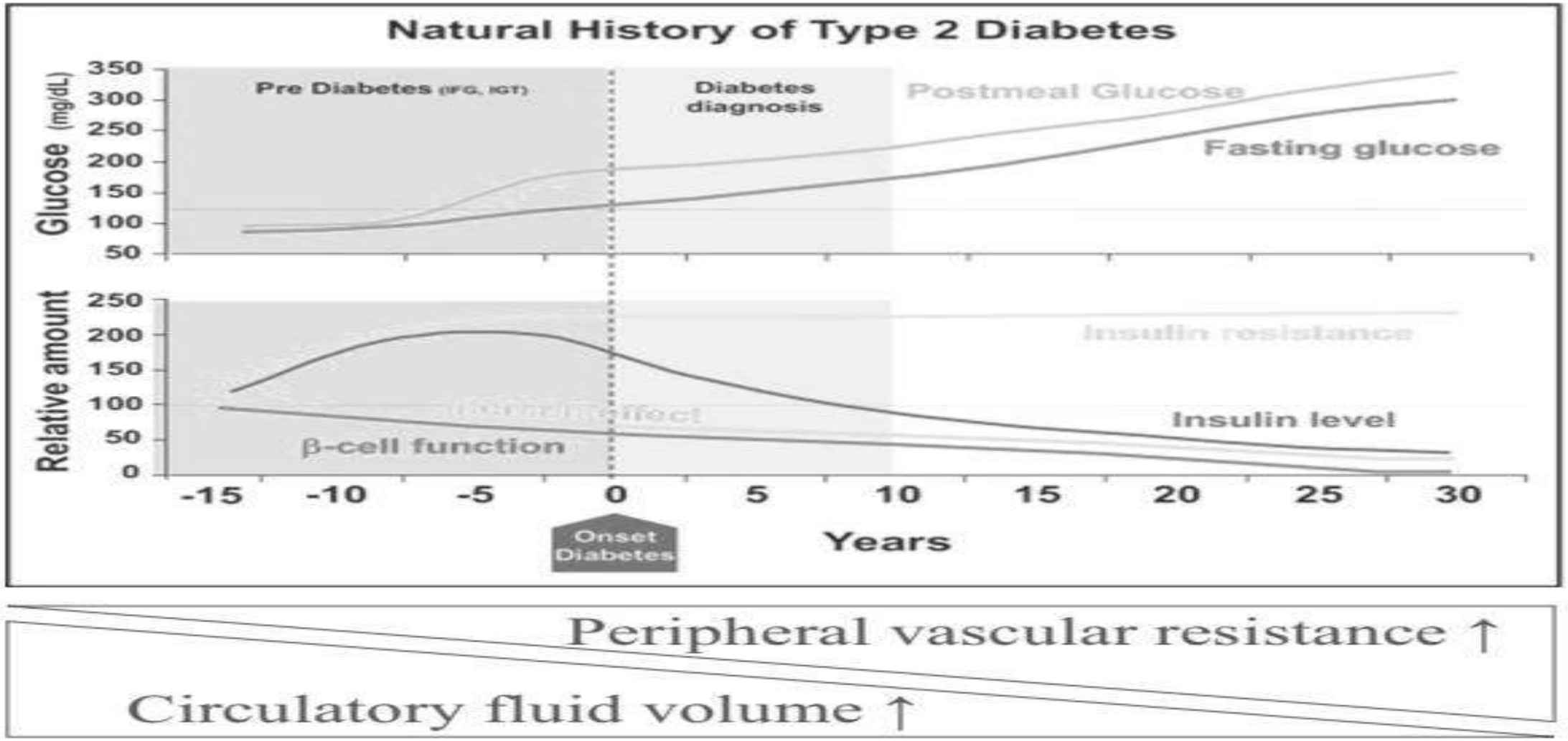
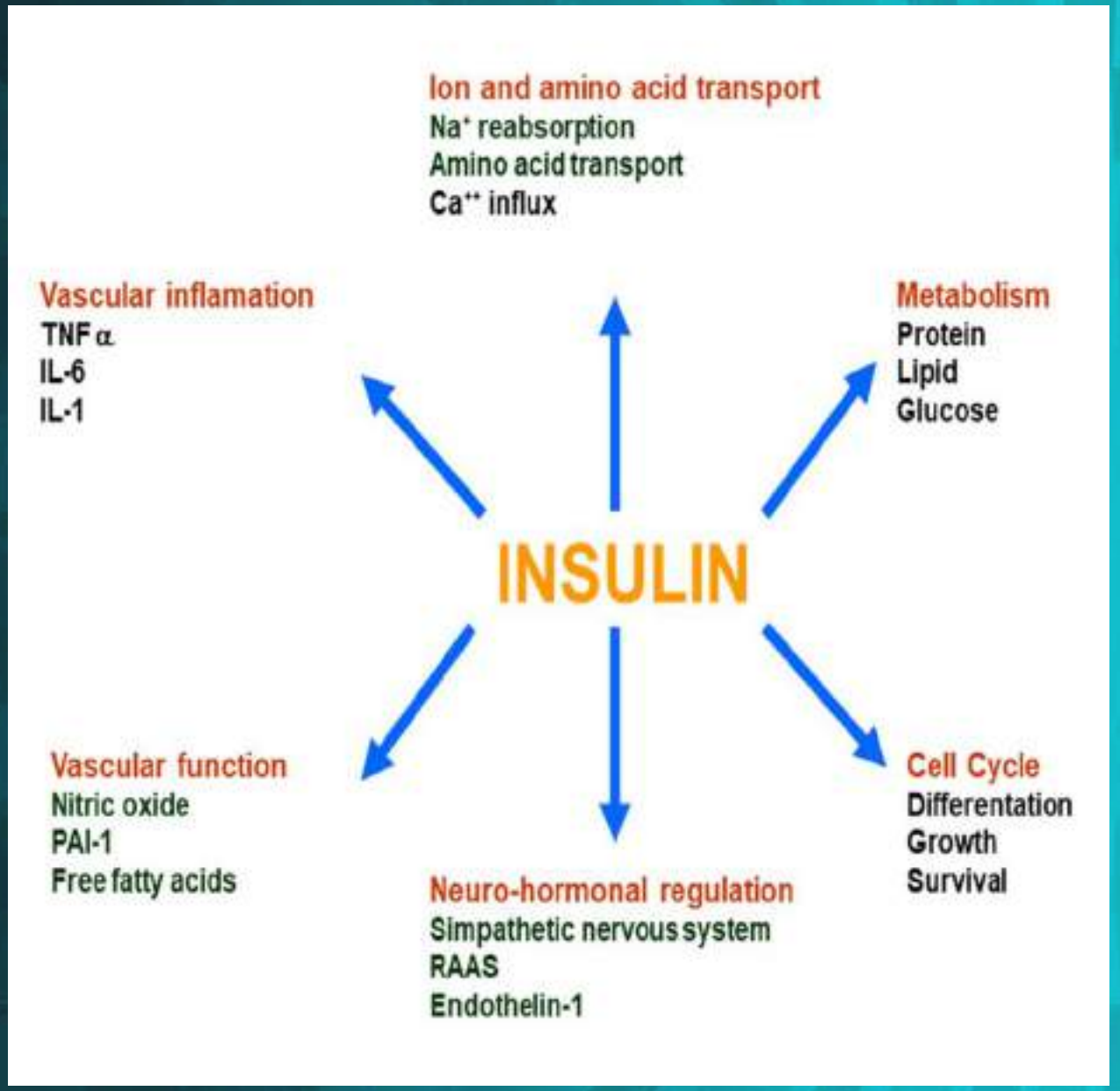
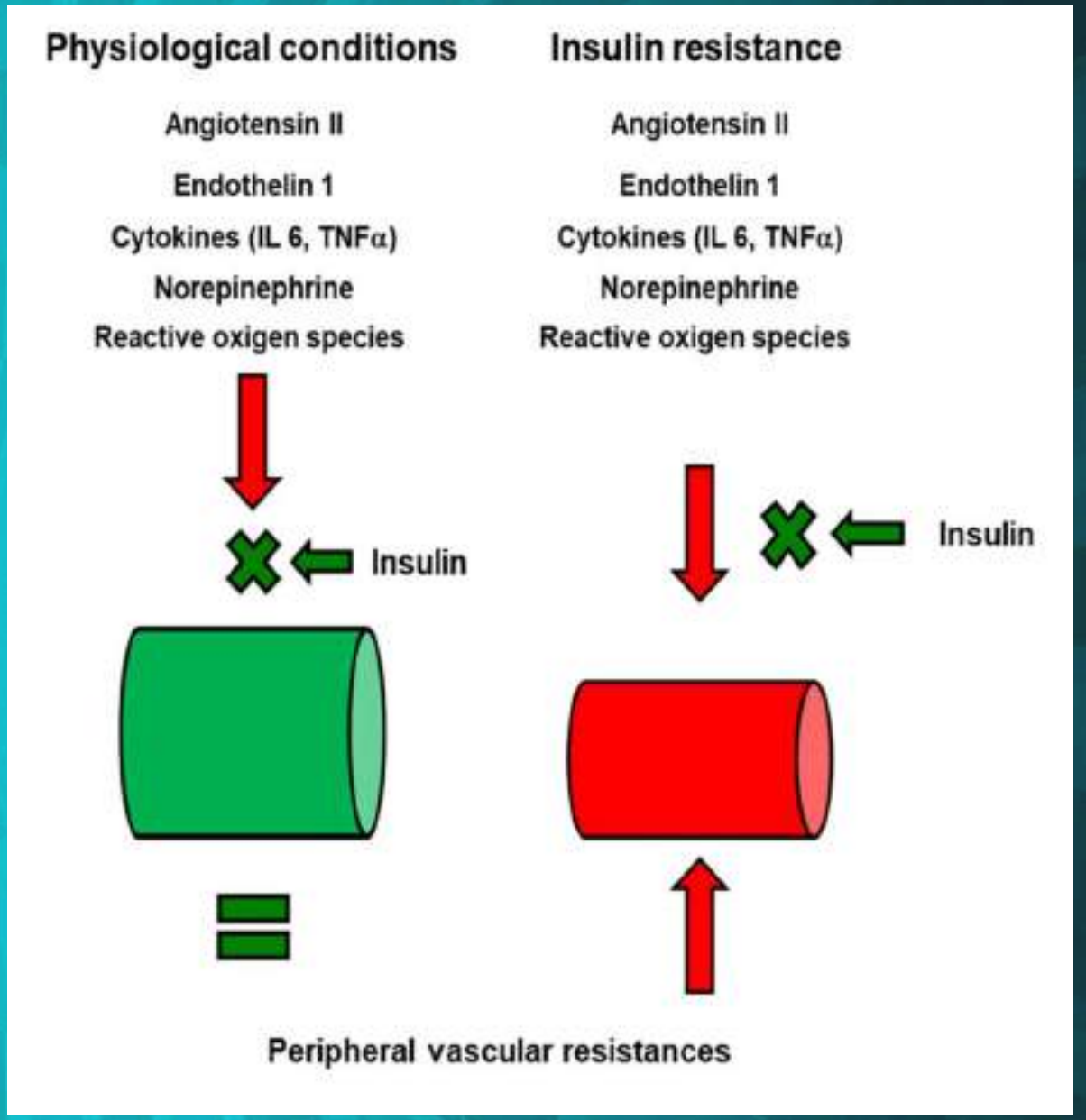


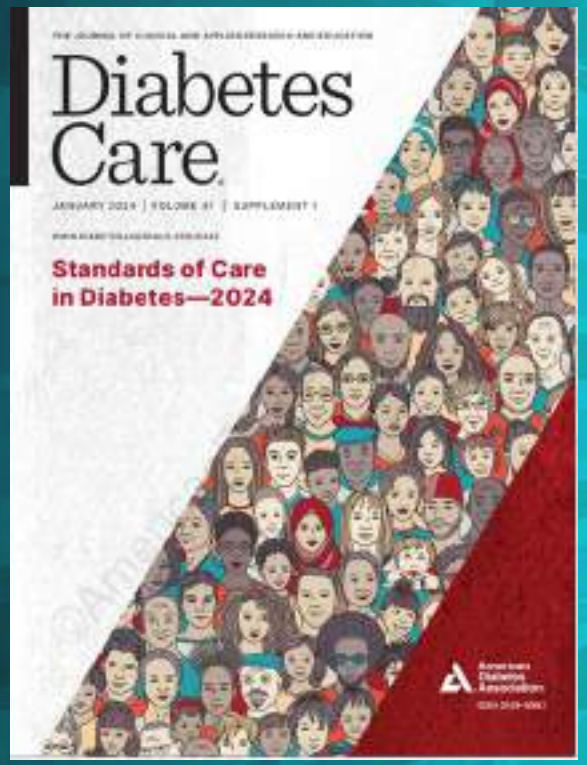
Fig. 2 Natural history of type 2 diabetes mellitus. *Source*: Ref. [18]

Ohishi M. Hypertension Research (2018) 41:389–393





Mancusi C et al. High Blood Pressure & Cardiovascular Prevention (2020) 27:515–526



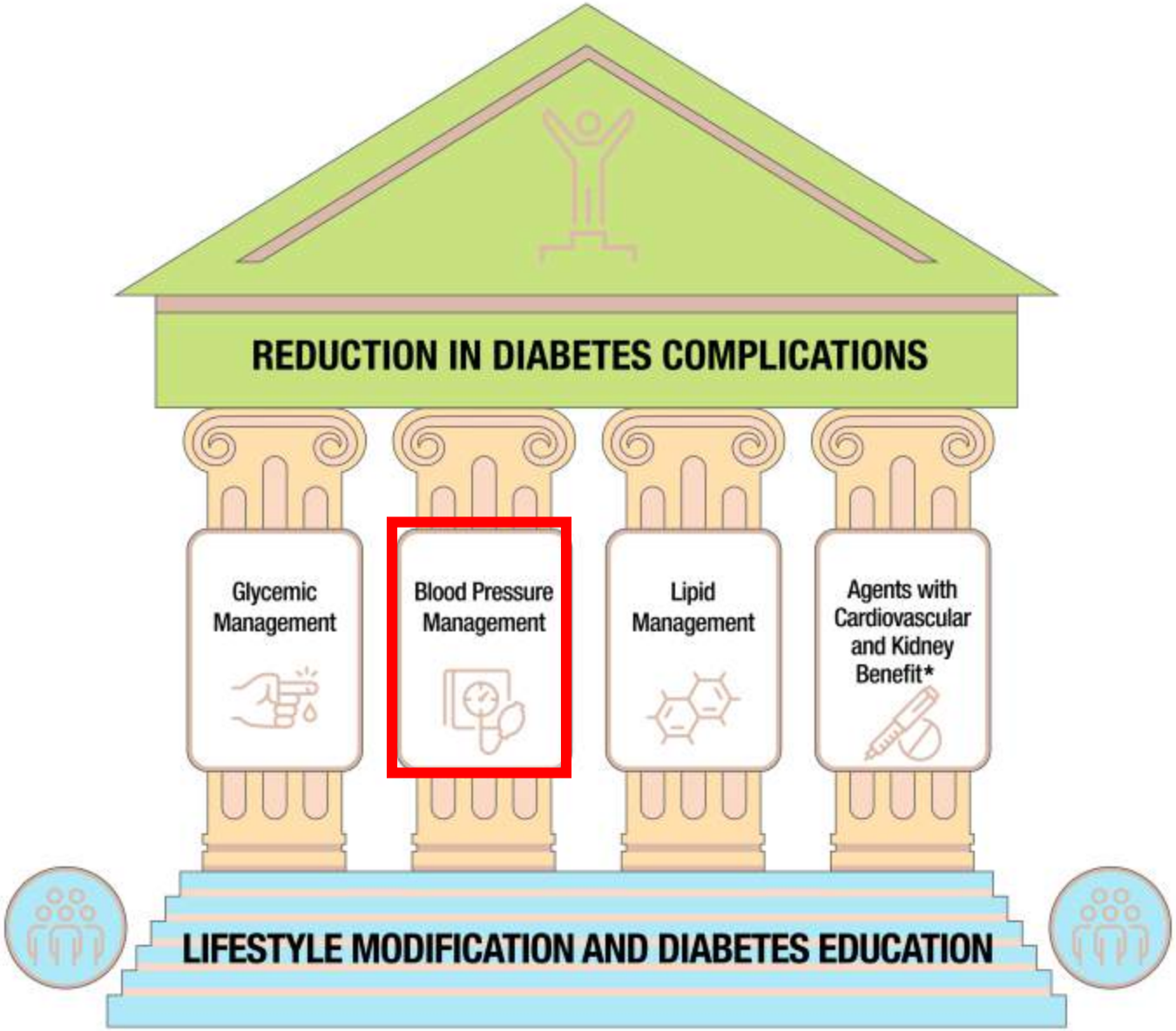


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

Initial BP ≥130/80 and <160/100 mmHg

Start one agent

Albuminuria or CAD*

No

Start one drug:
- ACEi or ARB
- CCB***
- Diuretic**

Yes

Start
- ACEi or ARB

Lifestyle management

Initial BP ≥160/100 mmHg

Start two agents

Albuminuria or CAD*

No

Start drug from 2 of 3 options:
- ACEi or ARB
- CCB***
- Diuretic**

Yes

Start:
- ACEi or ARB and
- CCB*** or Diuretic**

Assess BP Control and Adverse Effects

Treatment tolerated and target achieved

Continue therapy

Not meeting target

Add agent from complementary drug class:
- ACEi or ARB
- CCB***
- Diuretic**

Not meeting target on two agents

Adverse effects

Consider change to alternative medication:
- ACEi or ARB
- CCB***
- Diuretic**

Adverse effects

Assess BP Control and Adverse Effects

Treatment tolerated and target achieved

Continue therapy

Not meeting target or adverse effects using a drug from each of three classes

Consider Addition of Mineralocorticoid Receptor Antagonist; Refer to Specialist With Expertise in BP Management

10.9 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. A ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. A

10.10 Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs (including ARBs/neprilysin inhibitors) with direct renin inhibitors should not be used. A

10.4 The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. A

As discussed below, treatment should be individualized, and treatment should not be targeted to <120/80 mmHg, as a mean achieved blood pressure of <120/80 mmHg is associated with adverse events.

Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care

ESC/ESH HYPERTENSION GUIDELINES

Very high risk	People with any of the following: **Documented CVD, either clinical or unequivocal on imaging.** • **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm and PAD. • **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥ 50% stenosis) on angiography or ultrasound. It does not include increase in carotid intima-media thickness. • **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR < 30 mL/min/1.73 m²) • **A calculated 10-year SCORE of ≥ 10%**
High risk	People with any of the following: • **Marked elevation of a single risk factor**, particularly cholesterol > 8 mmol/L (> 310 mg/dL) e.g. familial hypercholesterolaemia, grade 3 hypertension (BP ≥ 180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, that may be moderate risk) • **Hypertensive LVH** • **Moderate CKD (eGFR 30–59 mL/min/1.73 m²)** • **A calculated 10-year SCORE of 5–10%**
Moderate risk	People with: • **A calculated 10-year SCORE of 1% to < 5%** • **Grade 2 hypertension** • **Many middle-aged people** belong to this category
Low risk	People with: • **A calculated 10-year SCORE of < 1%**

Figure 1 Categories of cardiovascular disease risk in the 2018 ESC/ESH hypertension guideline. BP indicates blood pressure;

ESC/ESH HYPERTENSION GUIDELINES

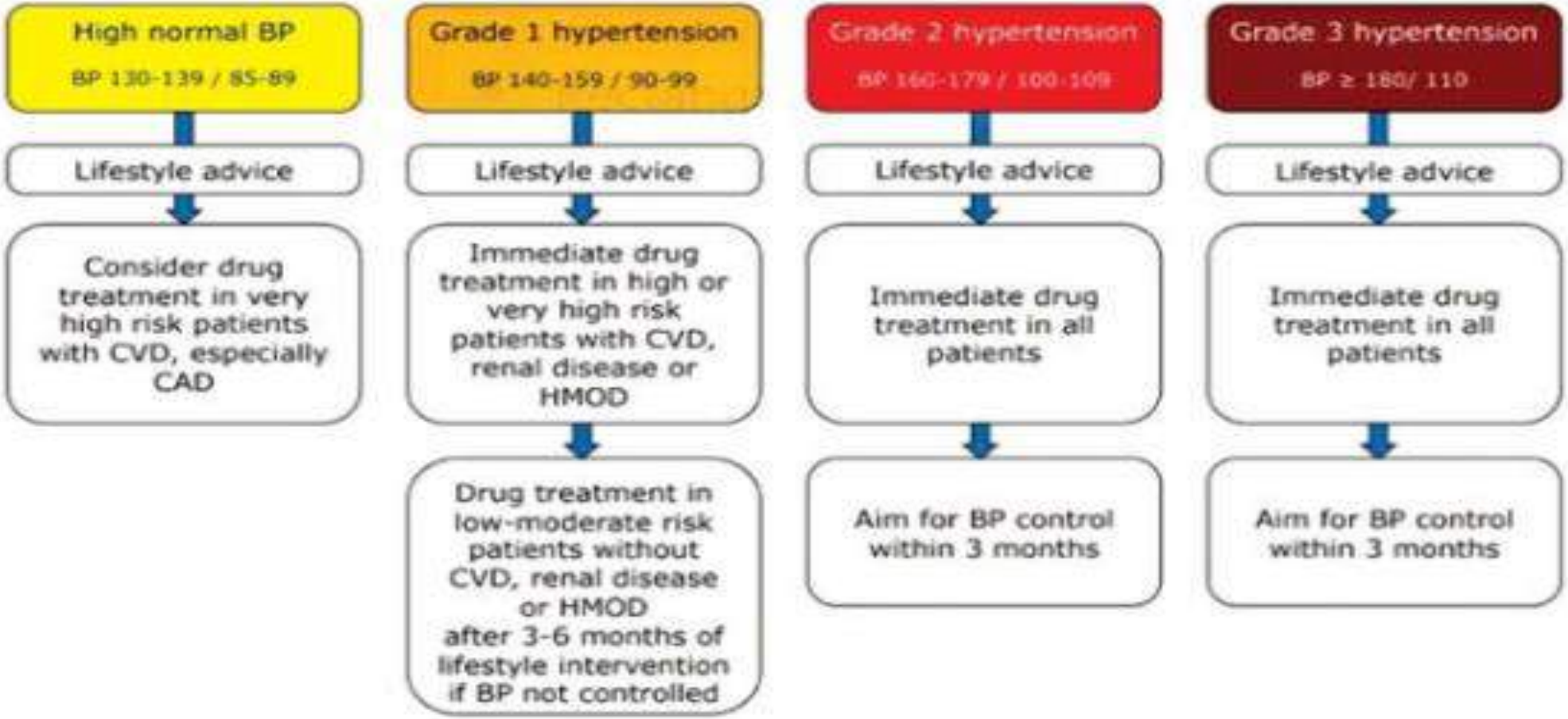


Table 19 Summary of office blood pressure thresholds for treatment

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
65 - 79 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

©ESC/ESH 2018

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

[a]Treatment may be considered in these very high-risk patients with high–normal SBP (i.e. SBP 130–140 mmHg).

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

Table 23 Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

[a]Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

[b]Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.

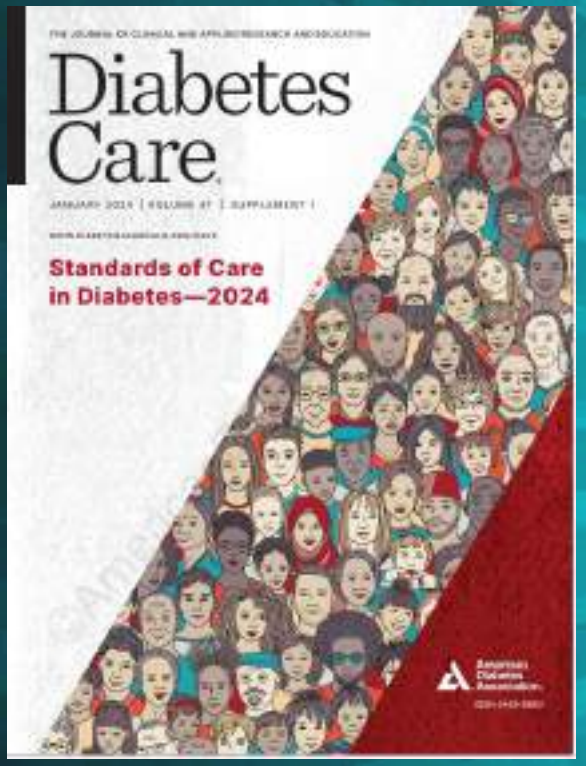


Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (34)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal 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 (35)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 5-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (310)
HOT (36)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	• 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 (33)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	• 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

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.

Influence of baseline systolic blood pressure on the relationship between intensive blood pressure control and cardiovascular outcomes in the Systolic Blood Pressure Intervention Trial (SPRINT)

Xiuting Sun[1,2] · Yue Guo[1,2] · Zhiqiang Nie[3,4] · Jing Cheng[5] · Huimin Zhou[1,2] · Xiangbin Zhong[1,2] · Shaozhan Zhang[1,2] · Zhimin Du[1,2] · Xiaodong Zhuang[1,2] · Xinxue Liao[1,2]

Clinical Research in Cardiology
https://doi.org/10.1007/s00392-018-1353-9

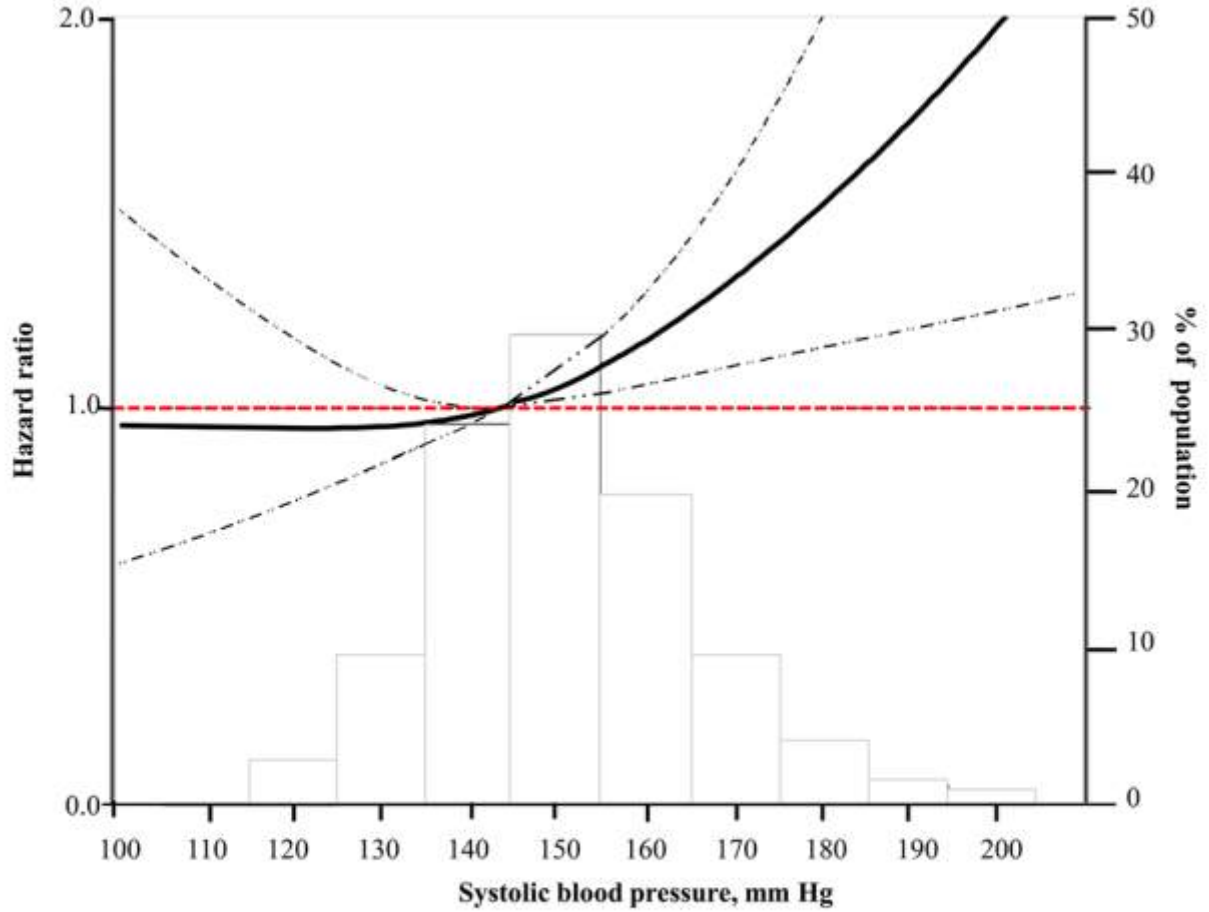
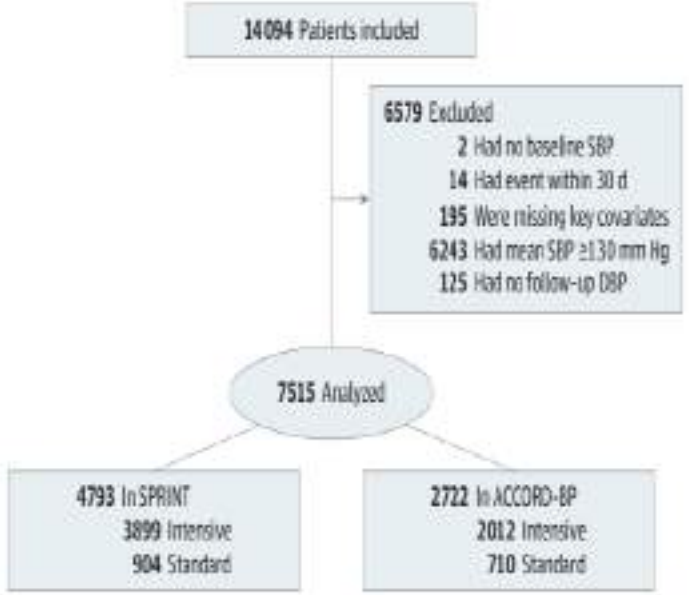


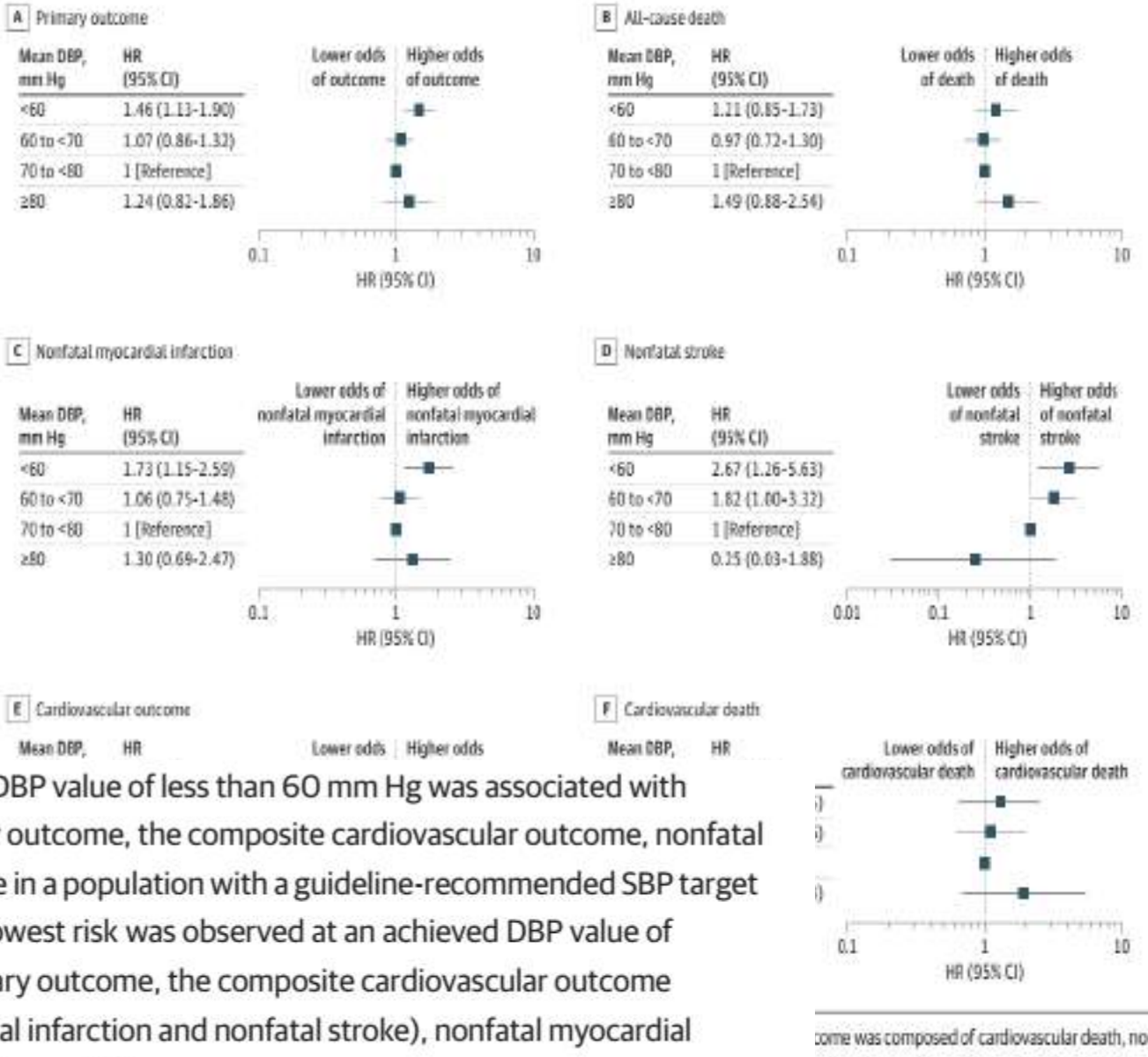
Fig. 1 Hazard ratios for sudden cardiac death by levels of baseline SBP

Figure 1. Patient Selection and Allocation Chart



JAMA Network Open. 2021;4(2):e2037554. doi:10.1001

Figure 2. Adjusted Hazard Ratios (HRs) for Achieved Diastolic Blood Pressure (DBP) and Outcomes at Achieved Systolic BP of Less Than 130 mm Hg



In this study, we found that an achieved DBP value of less than 60 mm Hg was associated with significantly increased risk of the primary outcome, the composite cardiovascular outcome, nonfatal myocardial infarction, and nonfatal stroke in a population with a guideline-recommended SBP target of less than 130 mm Hg. The nominally lowest risk was observed at an achieved DBP value of between 70 and 80 mm Hg for the primary outcome, the composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke), nonfatal myocardial infarction, and cardiovascular death in this population.

TABLE 1. Blood pressure-lowering trials reporting outcome data separately for patients with and without diabetes

Trial acronym	Treatment		Patients (n)		Baseline SBP/DBP (mmHg)		Achieved SBP/DBP (mmHg)	
	Active	Control	DM	No DM	DM	No DM	DM	No DM
Hypertension								
AASK [34]	More	Less	–	1094	–	NA	–	128/78
ABCD-H [35]	More	Less	470	–	155/88	–	132/78	–
ACCORD [36]	More	Less	4733	–	NA	–	119.2/64.7	–
ACTION [37,38]	CA	Placebo	1112	6552	NA	NA	130.3/76.2	130.3/76.2
ADVANCE [39,40]	ACEI+D	Placebo	11140	–	NA	–	134.7/74.8	–
Australian-Mild [41]	D	Placebo	–	3427	–	157.4/100.5	–	NR/88.4
BENEDICT [42]	ACEI or CA or ACEI + CA	Placebo	1204	–	NA	–	139.7/81	–
CAMELOT [43,44]	CA or ACEI	Placebo	363	1628	NA	NA	124.4/75	124.4/75
CARDIO-SIS [45]	More	Less	–	1111	–	NA	–	136/79.2
DEMAND [46]	ACEI or ACEI + CA	Placebo	380	–	NA	–	138.1/80.8	–
DIABHYCAR [47]	ACEI	Placebo	4912	–	NA	–	143.5/81.3	–
DIRECT Protect 2 [48]	ARB	Placebo	1905	–	NA	–	136/76	–
DREAM [49]	ACEI	Placebo	–	5269	–	NA	–	127.9/78.6
EUROPA [50,51]	ACEI	Placebo	1502	10716			132.8/77.4	127.4/78.1
EWPHE [52]	D	Placebo	111	729	186.8/101.2	181.8/101.0	149.5/86.4	149.5/86.4
FEVER [53,54]	CA	Placebo	1241	8470	155.3/90.2*	154.2/91.3*	139/82.3	137.9/82.7
Fogari [55]	CA + ACEI	CA or ACEI	309	–	160.3/99.3	–	132.4/82.3	–
HDFP [56,57]	D	Little treatment	772	10168	158.8/101.5	158.8/101.5	131.5/86	131.5/86
HEP [58]	BB	–	–	884	–	196.1/98.5	–	162.1/77
HOPE [59,60]	ACEI	Placebo	3577	5720	NA	NA	138.4/77.2	135.7/76.2
HOPE-3H [29]	ARB + D	Placebo	–	4240	–	154.1/ -	–	135.6/-
HOT [4,61]	More	Less	1501	17289	174.1/105.3	169.3/105.4	143.7/81	130.4/81.1
HSCG [62]	Central + D	Placebo	162	290	164/100.5	164/100.5	141/88	141/88
Hunan [63]	CA	No treatment	–	2080	–	160.5/98.5	–	140.7/85.2
IDNT [64,65]	ARB or CA	Placebo	1715	–	NA	–	140.5/77	–
I-PRESERVE [66,67]	ARB	Placebo	1134	2991	NA	NA	133.2/76.9	133.2/76.9
IRMA-2 [68]	ARB	Placebo	590	–	152/90.2	–	142/82	–
JATOS [69,70]	More	Less	521	3897	NA	NA	NR	135.9/74.8
MRC-mild [71]	D or BB	Placebo	–	17354	–	161.3/98.3	–	138.1/87
MRC-old [72]	D or BB	Placebo	–	4396	–	185/90.6	–	153/77.7
NAVIGATOR [73]	ARB	Placebo	–	9306	–	NA	–	133/78
NICOLE [74]	CA	Placebo	85	741	NA	NA	139/78	128/78
ORIENT [75]	ARB	Placebo	566	–	NA	–	132.5/73	–
OSLO [76]	D	No treatment	–	785	–	165.8/96.8	–	131/88
PEACE [77]	ACEI	Placebo	1384	6906	NA	NA	NR	129.6/74.4
PROFESS [78]	ARB	Placebo	5743	14589	NA	NA	135.4/79.2	135.4/79.2
PROGRESS [79,80]	ACEI or ACEI + D	Placebo	761	5344	NA	NA	137/78	133/79
REIN-2 [81]	More	Less	–	335	–	NA	–	129.6/79.5
RENAAL [82,83]	ARB	Placebo	1513	–	–	NA	143.5/71.7	–
ROADMAP [84]	ARB	Placebo	4447	–	–	NA	125.7/74.3	–
SANDS [85]	More	Less	499	–	–	NA	117/67	–
SCOPE [86,87]	ARB	Placebo	599	4338	166.2/90.3*	166.2/90.3*	143.5/77.6	144.1/79.2
SHEP [88,89]	D	Placebo	583	4149	170.2/75.8	170.3/76.7	146/68.5	142/68.2
SPRINT [90]	More	Less	–	9361	–	NA	–	121.5/75.4
SPS-3 [91,92]	More	Less	1106	1914	NA	NA	125.8/69	125.8/68.5
STOP [93]	D/BB or ACEI or CA	Placebo	142	1485	191.6/101	195/102.1	166.1/87.2	166/87.2
Syst-China [94,95]	CA	Placebo	98	2296	172.5/93	170.2/93	150.6/81.1	150.6/81.1
Syst-Eur [96,97]	CA	Placebo	492	4203	175.3/84.5	173.9/85.6	153.2/77.7	150.6/78.9
TOMHS [98]	Active	Placebo	–	902	–	140.4/90.6	–	124.2/78.3
TRANSCEND [99,100]	ARB	Placebo	2118	3808	NA	–	134.1/77.1	134.1/77.1
UKPDS-38 [5]	More (BB or ACEI)	Less	1148	–	160/94*	–	144/82	–
USPHS [101]	Central + D	Placebo	–	389	–	146.9/98.9	–	131.5/88.4
VAUSH [102]	More	Less	399	2861	NA	NA	136.6/74.8	136.6/74.8
Total			61038	182017				
Normal and high-normal BP								
ABCD-N [30]	More	Less	480	–	131.4/84.4	–	128/75	–
ABCD-2V [31]	More	Less	129	–	126/84	–	118/75	–
HOPE-3N [29]	ARB + D	Placebo	–	8463	–	129.9/-	–	123.7/NR
PHARAO [32]	ACEI	No treatment	135	873	135.5/84.1	134.2/83.5	127.2/78	127.2/78
Total general			61772	191353				

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CA, calcium antagonists; D, diuretics; DBP, diastolic blood pressure; DM, diabetes mellitus; NA, not available, because of background antihypertensive treatment; NR, not reported; SBP, systolic blood pressure.
*Under low-dose therapy.

Thomopoulos C, Parati G, Zanchetti A. J Hypertens 35:922–944

META-ANALYSIS CONCLUSIONS

SBP targets should be somewhat higher in presence than absence of diabetes, between 130 and 140 mmHg in patients with diabetes

In diabetes most of the cardiovascular risk reduction occurs by lowering DBP values between 80 and 90 mmHg.

For ESRD risk most of the benefit occurs at relatively high SBP values (a few mmHg above 140 mmHg), but lower values do not increase ESRD risk.

2018 ESC-ESH GUIDELINES FOR HYPERTENSION MANAGEMENT

Drug treatment strategy for hypertension

Recommendations	Class[a]	Level[b]
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.[2]	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.[233,318,327,329,341–345]	I	A
three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.[349,350]	I	A
It is recommended that if BP is not controlled[c] with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.[310]	I	B
The combination of two RAS blockers is not recommended.[291,298,299]	III	A

Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.[233,318,327,329,341–345] I A

Brian W et al. European Heart Journal (2018) 39, 3021–3104

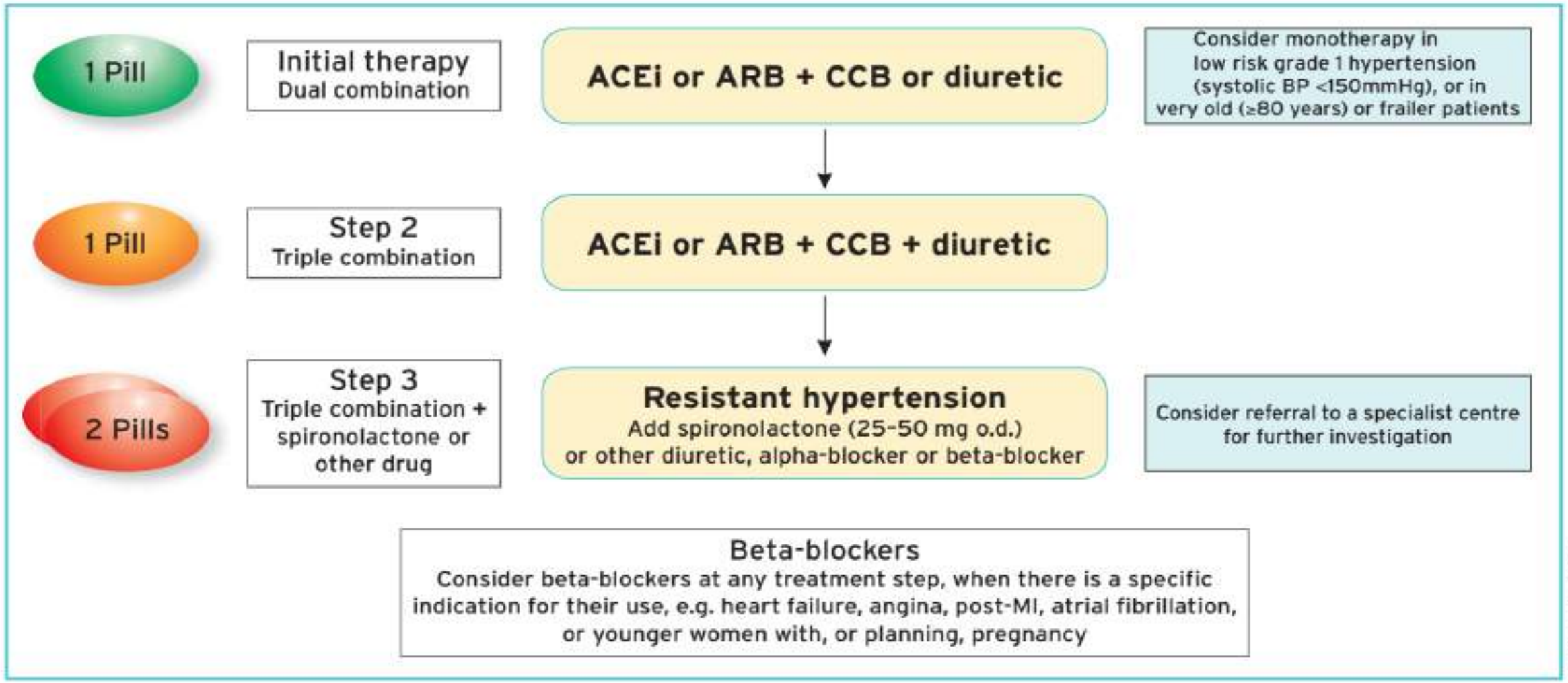
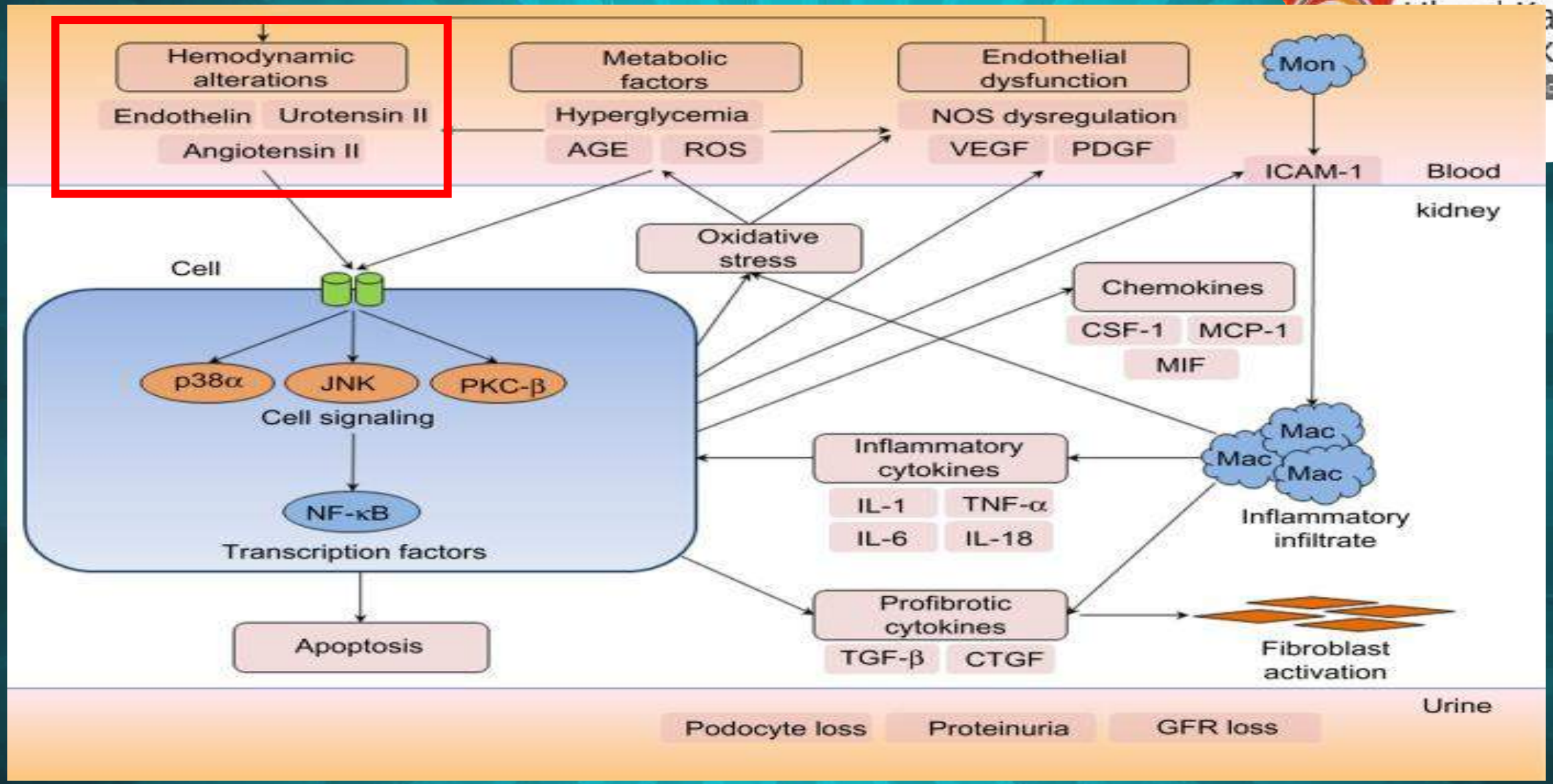


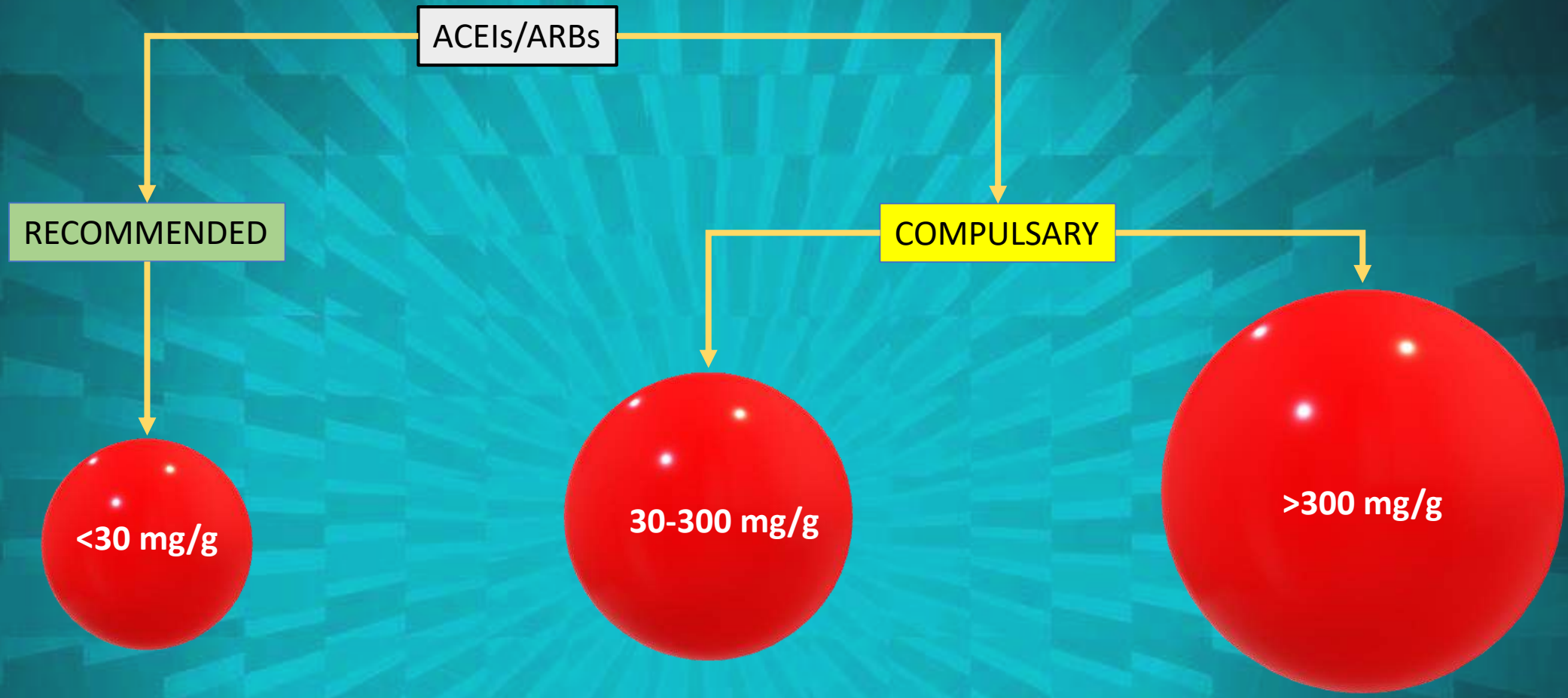
Figure 4 Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.

Treatment strategies in people with diabetes

Recommendations	Class[a]	Level[b]
Antihypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.[1,226,235,482]	I	A
In people with diabetes receiving BP-lowering drugs it is recommended:		
• To target SBP to 130 mmHg and <130mmHg if tolerated, but not <120 mmHg.[1,231,235]	I	A
• In older people (aged ≥65 years aged), to target to an SBP range of 130–139 mmHg.[1,205,235]	I	A
• To target the DBP to <80 mmHg, but not <70 mmHg.	I	C
It is recommended to initiate treatment with a combination of a RAS blocker with a CCB or thiazide/thiazide-like diuretic.[c] [1,175,205]	I	A
Simultaneous administration of two RAS blockers, e.g. an ACE inhibitor and ARB, is not indicated.[291,298,299]	III	A

DIABETIC NEPHROPATHY FISIOPATOLOGY





11.4c An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in people with diabetes who have normal blood pressure, normal urinary albumin-to creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. A

TAKE HOME HOSPITAL MESSAGES

- High blood pressure is very frequent in diabetic patients.
- It is not clear that a straighter blood pressure target should be used for patients with diabetes mellitus.
- Most of patients could need drugs combinations.
- ACEis or ARBs are compulsory, specially when increased albuminuria is present.

ÇOX SAĞ OL

1. Blood-pressure-lowering treatment is indicated to reduce risk of cardiovascular disease in hypertensive patients both in presence and in absence of diabetes.

2. Systolic BP targets should be somewhat higher in presence than absence of diabetes, between 130 and 140 mmHg in patients with diabetes and below 130 mmHg in patients without diabetes, as in presence of diabetes bringing SBP a few mmHg below 130 mmHg does not add further benefit (though apparently it does not increase cardiovascular risk).

3. Diastolic BP targets below 80 mmHg can be recommended both in presence and absence of diabetes, but in diabetes most of the cardiovascular risk reduction occurs by lowering DBP values between 80 and 90 mmHg.

4. Blood-pressure-lowering treatment can be recommended in patients with diabetes also to reduce risk of renal insufficiency: for ESRD risk most of the benefit occurs at relatively high SBP values (a few mmHg above 140 mmHg), but lower values do not increase ESRD risk.

Thomopoulos C, Parati G, Zanchetti A. J Hypertens 35:922–944