

# DIABETES AND HYPERTENSION - NEW PERSPECTIVES

# INTRODUCTION

- Hypertension is common among patients with diabetes.
- Prevalence depends on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors (1-3). Furthermore,
- hypertension is a strong risk factor for atherosclerotic cardiovascular disease (ASCVD), heart failure, and microvascular complications

# THE IMPACT OF HYPERTENSION ON DIABETES MELLITUS

- Hypertension accelerates the progression of diabetic nephropathy.
- Hypertension promotes the progression of diabetic retinopathy and neuropathy
- Hyperglycemia elevates blood pressure
- Essential hypertension patients also have insulin resistance

# CLASSIFICATION OF BLOOD PRESSURE

| Category                                    | Systolic (mmHg) |        | Diastolic (mmHg) |
|---------------------------------------------|-----------------|--------|------------------|
| Optimal                                     | <120            | and    | <80              |
| Normal                                      | 120–129         | and/or | 80–84            |
| High normal                                 | 130–139         | and/or | 85–89            |
| Grade 1 hypertension                        | 140–159         | and/or | 90–99            |
| Grade 2 hypertension                        | 160–179         | and/or | 100–109          |
| Grade 3 hypertension                        | ≥180            | and/or | ≥110             |
| Isolated systolic hypertension <sup>b</sup> | ≥140            | and    | <90              |

BP = blood pressure; SBP = systolic blood pressure.

<sup>a</sup>BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

<sup>b</sup>Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

The same classification is used for all ages from 16 years.

# RECOMMENDATIONS BY AMERICAN DIABETES ASSOCIATION

- ◉ Blood pressure should be measured at every routine clinical care visit.
- ◉ Patients found to have an elevated blood pressure (140/90 mmHg) should have blood pressure confirmed using multiple readings, measured on a separate day, to diagnose hypertension. B
- ◉ All hypertensive patients with diabetes should have home blood pressure monitored to identify white-coat hypertension. B
- ◉ Orthostatic measurement of blood pressure should be performed during initial evaluation of hypertension and periodically at follow-up, or when symptoms are present. E

# BP TARGETS RECOMMENDATIONS

- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of ,140 mmHg and a diastolic blood pressure goal of ,90 mmHg.
- A Lower systolic and diastolic blood pressure targets, such as ,130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease

# TARGETS BY DIFFERENT SOCIETIES FOR THE MANAGEMENT OF HYPERTENSION IN DIABETES

| Guideline/society | Target (mmHg) |
|-------------------|---------------|
| UK NICE           | 130/80        |
| CHEP              | 130/80        |
| WHO               | 130/80        |
| IDF               | 130/80        |
| JSH               | 130/80        |
| IGH               | 140/80        |
| ESC/ESH           | 140/85        |
| JNC-8P            | 140/90        |
| ASH/ISH           | 140/90        |
| ADA               | 140/90        |
| AHA/ACC/ASH       | 140/90        |

# TREATMENT OF HYPERTENSION IN DIABETES

| Drug line   | Drug Class                                   |
|-------------|----------------------------------------------|
| First Line  | ACE/ARB                                      |
| Second line | CCB (non-dihydropyridine)<br>Alpha1 blockers |
| Third line  | Thiazides<br>Beta blockers                   |
| Fourth line | Centrally acting drugs and<br>vasodilators   |

ACEI- Angiotensin converting enzyme inhibitor

ARB- angiotensin receptor blocker

CCB- calcium channel blocker

# SUMMARY OF BLOOD PRESSURE GOALS , INITIAL CHOICE OF ANTIHYPERTENSIVE AGENT FOR PATIENTS WITH DIABETES

**TABLE** Summary of Blood Pressure Goals and Initial Choice of Antihypertensive Agent for Patients With Diabetes Endorsed by Different Professional Societies or Expert Groups

| Recommendation (Year) | Blood Pressure Goals (mmHg) | First-Line Pharmacological Treatment                                                        |
|-----------------------|-----------------------------|---------------------------------------------------------------------------------------------|
| ADA (2018)            | <140/90 (<130/80*)          | ACEI/ARB†, thiazide-like diuretic, or dihydropyridine CCB                                   |
| ACC/AHA (2017)        | <130/80                     | No preference                                                                               |
| JNC 8 (2014)          | <140/90                     | Non-black: ACEI/ARB, thiazide-like diuretic, or CCB<br>Black: thiazide-like diuretic or CCB |
| VA/DoD (2014)         | <150/85 (140/85**)          | Thiazide-like diuretic (chlorthalidone or indapamide)                                       |
| CDA (2013)            | <130/80                     | ACEI/ARB†, thiazide-like diuretic, or dihydropyridine CCB                                   |
| ESH/ESC (2013)        | <140/85                     | ACEI/ARB†, thiazide-like diuretic, or CCB                                                   |

\*May be appropriate for individuals at high risk of CVD. \*\*Suggested for patients who can tolerate the antihypertensive medications necessary to reach this goal. †Recommended if hypertension is associated with proteinuria and suggested if hypertension is associated with microalbuminuria as the preferred first-line agent. ‡Recommended in the presence of known kidney disease, including microalbuminuria, or CVD.

# PREGNANCY RECOMMENDATIONS

- Pregnant women with diabetes and pre existing hypertension or mild gestational hypertension with BP 160/105 mmHg, and no evidence of end-organ damage do not need pharmacologic antihypertensive therapy. E
- In pregnant patients with diabetes and preexisting hypertension treated with antihypertensive therapy, blood pressure targets of 120-160/80- 105 mmHg for optimizing long-term maternal health and fetal growth

# CONTRAINDICATIONS FOR ANTIHYPERTENSIVE DRUGS

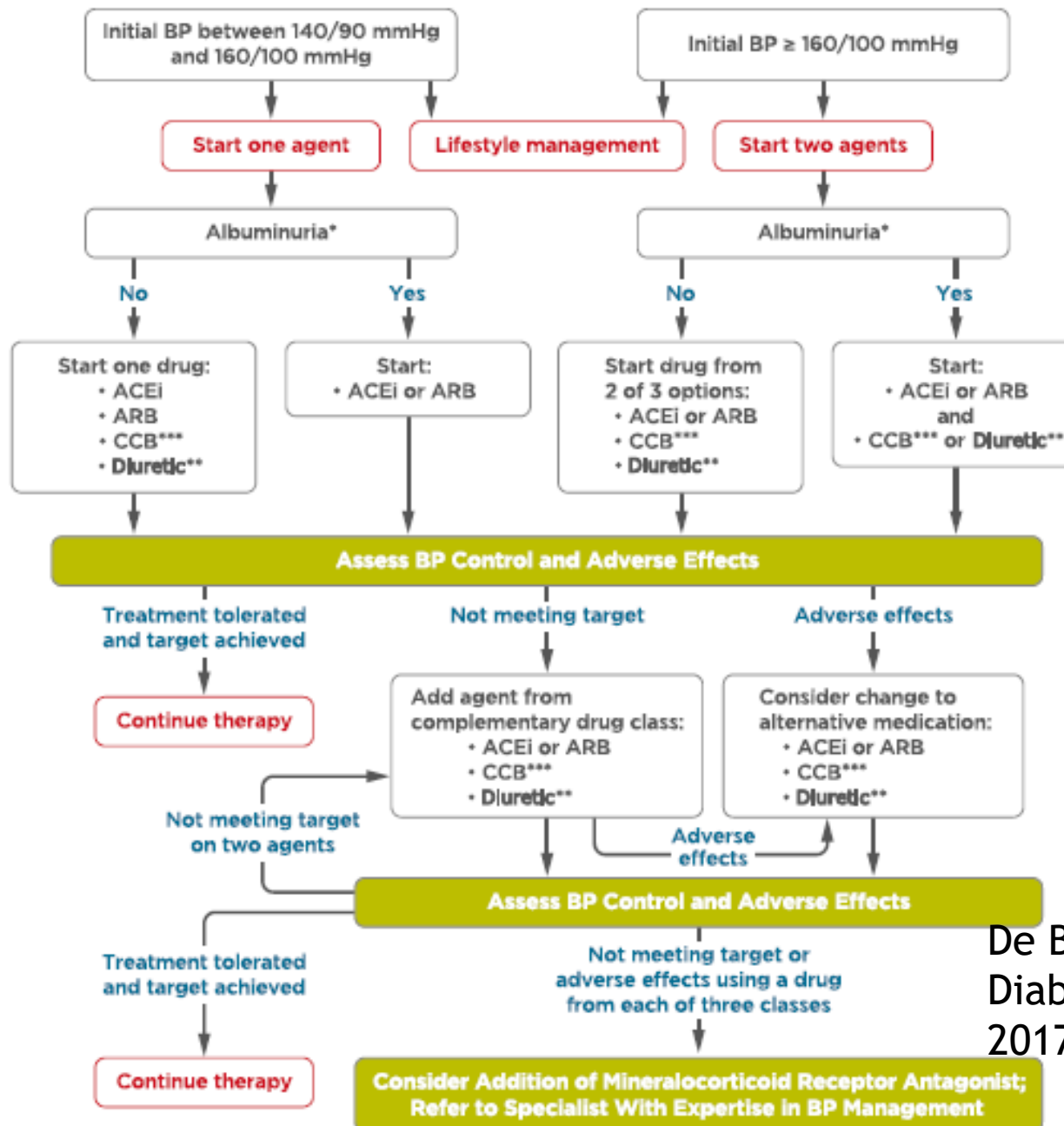
| Drug                                                                    | Contraindications                                                                                                                                                                                                                |                                                                                                                                                                              |
|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                         | Compelling                                                                                                                                                                                                                       | Possible                                                                                                                                                                     |
| Diuretics (thiazides/thiazide-like, e.g. chlorthalidone and indapamide) | <ul style="list-style-type: none"> <li>● Gout</li> </ul>                                                                                                                                                                         | <ul style="list-style-type: none"> <li>● Metabolic syndrome</li> <li>● Glucose intolerance</li> <li>● Pregnancy</li> <li>● Hypercalcaemia</li> <li>● Hypokalaemia</li> </ul> |
| Beta-blockers                                                           | <ul style="list-style-type: none"> <li>● Asthma</li> <li>● Any high-grade sinoatrial or atrioventricular block</li> <li>● Bradycardia (heart rate &lt;60 beats per min)</li> </ul>                                               | <ul style="list-style-type: none"> <li>● Metabolic syndrome</li> <li>● Glucose intolerance</li> <li>● Athletes and physically active patients</li> </ul>                     |
| Calcium antagonists (dihydropyridines)                                  |                                                                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>● Tachyarrhythmia</li> <li>● Heart failure (HFrEF, class III or IV)</li> <li>● Pre-existing severe leg oedema</li> </ul>              |
| Calcium antagonists (verapamil, diltiazem)                              | <ul style="list-style-type: none"> <li>● Any high-grade sinoatrial or atrioventricular block</li> <li>● Severe LV dysfunction (LV ejection fraction &lt;40%)</li> <li>● Bradycardia (heart rate &lt;60 beats per min)</li> </ul> | <ul style="list-style-type: none"> <li>● Constipation</li> </ul>                                                                                                             |
| ACE inhibitors                                                          | <ul style="list-style-type: none"> <li>● Pregnancy</li> <li>● Previous angioneurotic oedema</li> <li>● Hyperkalaemia (potassium &gt;5.5 mmol/L)</li> <li>● Bilateral renal artery stenosis</li> </ul>                            | <ul style="list-style-type: none"> <li>● Women of child-bearing potential without reliable contraception</li> </ul>                                                          |
| ARBs                                                                    | <ul style="list-style-type: none"> <li>● Pregnancy</li> <li>● Hyperkalaemia (potassium &gt;5.5 mmol/L)</li> <li>● Bilateral renal artery stenosis</li> </ul>                                                                     | <ul style="list-style-type: none"> <li>● Women of child-bearing potential without reliable contraception</li> </ul>                                                          |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular.

# LIFESTYLE RECCOMENDATIONS

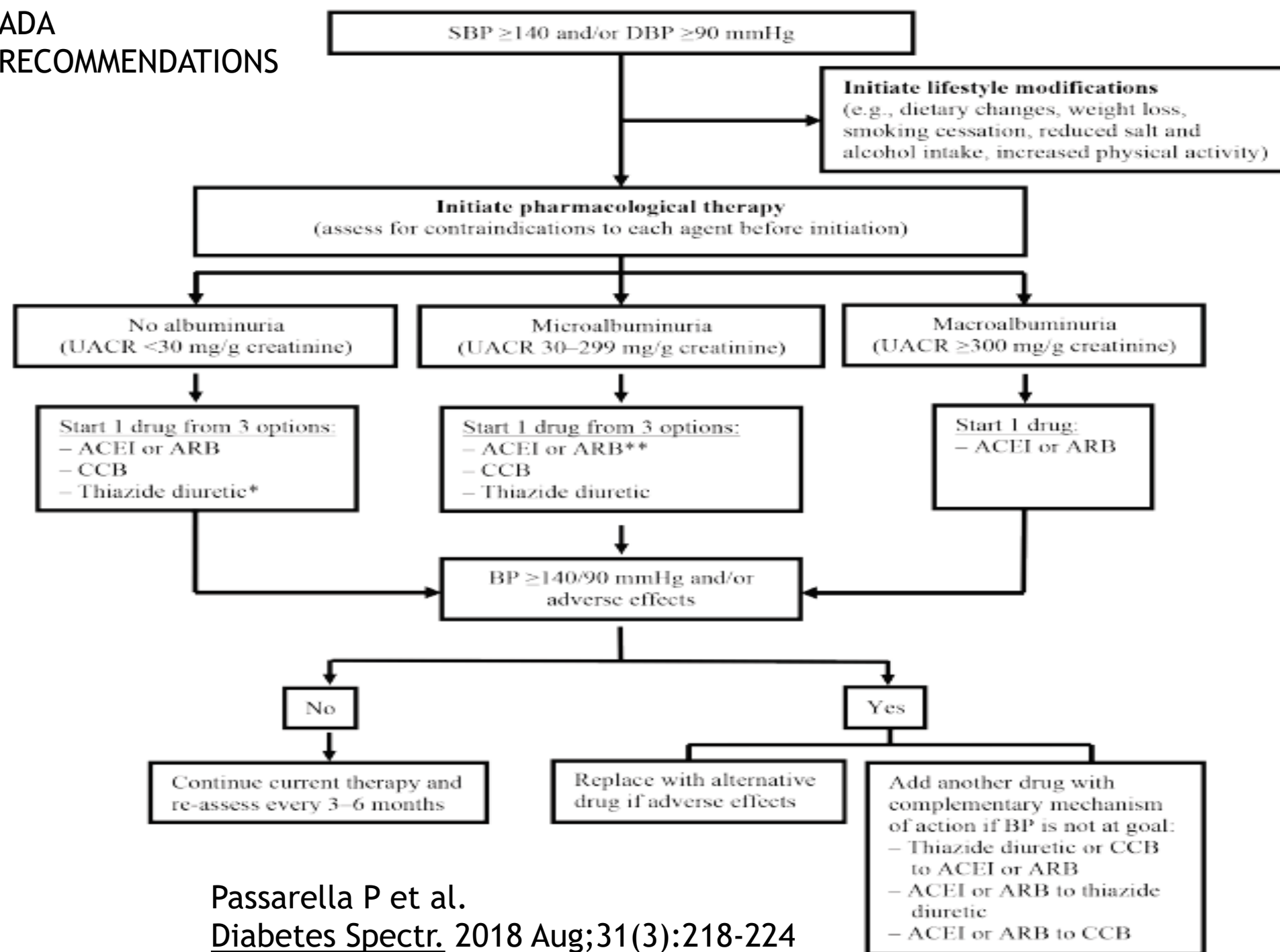
- ◉ Weight loss if overweight or obese
- ◉ Dietary Approaches to Stop Hypertension include
  1. Reduced sodium
  2. Increased potassium intake
  3. Increased fruit and vegetable consumption.
  4. Moderation of alcohol intake
  5. Increased physical activity.

## Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



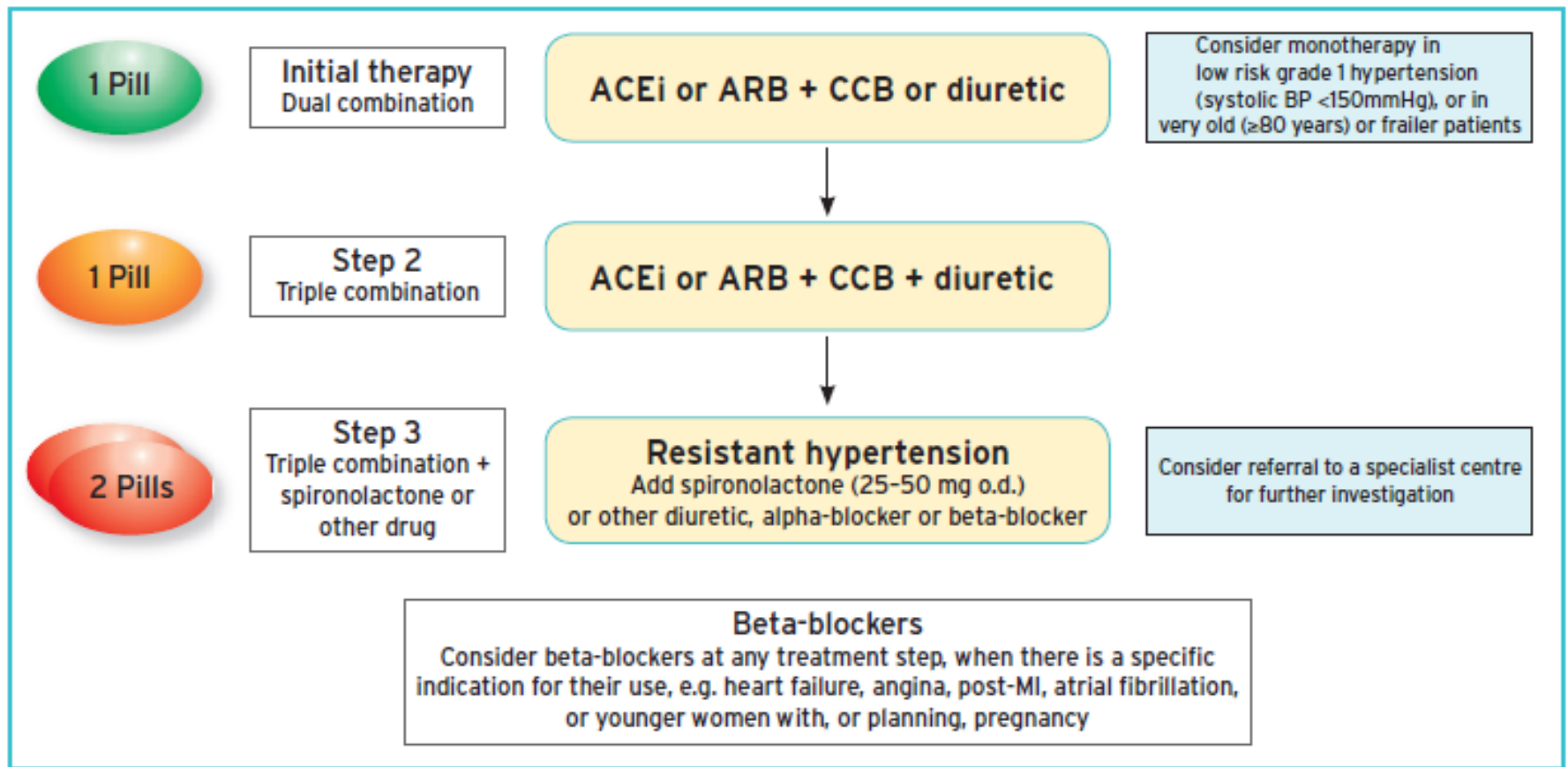
De Boir IH et al.  
Diabetes Care  
2017;40:1273-1284

# ADA RECOMMENDATIONS



Passarella P et al.  
Diabetes Spectr. 2018 Aug;31(3):218-224

# TREATMENT STRATEGY FOR UNCOMPLICATED HYPERTENSION



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**Figure** 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.

# ESC/ESH ARTERIAL HYPERTENSION GUIDELINES

| 2013                                                                                                                                                                                                                                                                                                                                                                                                          | 2018                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Diagnosis</b>                                                                                                                                                                                                                                                                                                                                                                                              | <b>Diagnosis</b>                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Office BP is recommended for screening and diagnosis of hypertension.                                                                                                                                                                                                                                                                                                                                         | It is recommended to base the diagnosis of hypertension on: <ul style="list-style-type: none"> <li>• Repeated office BP measurements; or</li> <li>• Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible.</li> </ul>                                                                                                                                                                             |
| <b>Treatment thresholds</b><br><b>High normal BP (130–139/85–89 mmHg):</b> Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high-normal BP.                                                                                                                                                                                                      | <b>Treatment thresholds</b><br><b>High normal BP (130–139/85–89 mmHg):</b> Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD.                                                                                                                                                                                                                                                            |
| <b>Treatment thresholds</b><br><b>Treatment of low-risk grade 1 hypertension:</b><br>Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low-moderate-risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures. | <b>Treatment thresholds</b><br><b>Treatment of low-risk grade 1 hypertension:</b><br>In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.                                                                                                                                    |
| <b>Treatment thresholds</b><br><b>Older patients</b><br>Antihypertensive drug treatment may be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.                                                                                                                                             | <b>Treatment thresholds</b><br><b>Older patients</b><br>BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.                                                                                                                                                             |
| <b>BP treatment targets</b>                                                                                                                                                                                                                                                                                                                                                                                   | <b>BP treatment targets</b>                                                                                                                                                                                                                                                                                                                                                                                                              |
| An SBP goal of <140 mmHg is recommended.                                                                                                                                                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>• It is recommended that the first objective of treatment should be to lower BP to &lt;140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.</li> <li>• In patients &lt;65 years it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.</li> </ul> |

# ESC/ESH ARTERIAL HYPERTENSION GUIDELINES

| BP treatment targets in older patients (65–80 years)                                                                                                                                      | BP treatment targets in older patients (65–80 years)                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| An SBP target of between 140–150 mmHg is recommended for older patients (65–80 years).                                                                                                    | In older patients ( $\geq 65$ years), it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.                                                                                                                                                                                                                            |
| BP treatment targets in patients aged over 80 years                                                                                                                                       | BP treatment targets in patients aged over 80 years                                                                                                                                                                                                                                                                                           |
| An SBP target between 140–150 mmHg should be considered in people older than 80 years, with an initial SBP $\geq 160$ mmHg, provided that they are in good physical and mental condition. | An SBP target range of 130–139 mmHg is recommended for people older than 80 years, if tolerated.                                                                                                                                                                                                                                              |
| DBP targets                                                                                                                                                                               | DBP targets                                                                                                                                                                                                                                                                                                                                   |
| A DBP target of $<90$ mmHg is always recommended, except in patients with diabetes, in whom values $<85$ mmHg are recommended.                                                            | A DBP target of $<80$ mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities.                                                                                                                                                                                                            |
| Initiation of drug treatment                                                                                                                                                              | Initiation of drug treatment                                                                                                                                                                                                                                                                                                                  |
| Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.                                       | It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. The exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is $<150$ mmHg).                                                                                               |
| Resistant hypertension                                                                                                                                                                    | Resistant hypertension                                                                                                                                                                                                                                                                                                                        |
| Mineralocorticoid receptor antagonists, amiloride, and the $\alpha$ -1 blocker doxazosin should be considered if no contraindication exists.                                              | Recommended treatment of resistant hypertension is the addition of low-dose spironolactone to existing treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin. |
| Device-based therapy for hypertension                                                                                                                                                     | Device-based therapy for hypertension                                                                                                                                                                                                                                                                                                         |
| In case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered.                                               | Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.                                                                                                                 |

# CLASSIFICATION OF HYPERTENSION STAGES

| Hypertension disease staging      | Other risk factors, HMOD, or disease                                         | BP (mmHg) grading                       |                                     |                                       |                                                |
|-----------------------------------|------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------|---------------------------------------|------------------------------------------------|
|                                   |                                                                              | High normal<br>SBP 130-139<br>DBP 85-89 | Grade 1<br>SBP 140-159<br>DBP 90-99 | Grade 2<br>SBP 160-179<br>DBP 100-109 | Grade 3<br>SBP $\geq 180$<br>or DBP $\geq 110$ |
| Stage 1<br>(uncomplicated)        | No other risk factors                                                        | Low risk                                | Low risk                            | Moderate risk                         | High risk                                      |
|                                   | 1 or 2 risk factors                                                          | Low risk                                | Moderate risk                       | Moderate to high risk                 | High risk                                      |
|                                   | $\geq 3$ risk factors                                                        | Low to Moderate risk                    | Moderate to high risk               | High Risk                             | High risk                                      |
| Stage 2<br>(asymptomatic disease) | HMOD, CKD grade 3, or diabetes mellitus without organ damage                 | Moderate to high risk                   | High risk                           | High risk                             | High to very high risk                         |
| Stage 3<br>(established disease)  | Established CVD, CKD grade $\geq 4$ , or diabetes mellitus with organ damage | Very high risk                          | Very high risk                      | Very high risk                        | Very high risk                                 |

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**Figure** Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities. CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

# PHARMACOLOGIC ANTIHYPERTENSIVE TREATMENT

- Patients with confirmed office based blood pressure 140/90 mmHg should, in addition to lifestyle therapy, have timely titration of pharmacologic therapy to achieve blood pressure goals. A
- Patients with confirmed office based blood pressure 160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. A
- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes:
- ACE inhibitors, angiotensin receptor blockers (ARBs), thiazide-like diuretics, or dihydropyridine calcium channel blockers.
- Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and ARBs). A

# PHARMACOLOGIC ANTIHYPERTENSIVE TREATMENT

- ◉ An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended
- ◉ first-line treatment for hypertension in patients with diabetes and urine albumin-to creatinine ratio  $\geq 300$  mg/g creatinine (A) or 30-299 mg/g creatinine (B).
- ◉ If one class is not tolerated, the other should be substituted. B
- ◉ For patients treated with an ACE inhibitor, ARB, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. B

# HYPERTENSION MANAGEMENT IN TYPE 1 DIABETES

- ◉ In patients with type 1 diabetes and normoalbuminuria, threshold for blood pressure therapy of a upright (sitting or standing) blood pressure that is greater than or equal to 140/80 mmHg (Grade 2D).
- ◉ Persistent microalbuminuria or macroalbuminuria, ACEI therapy should be considered irrespective of blood pressure, and that the target upright blood pressure should be less than or equal to 130/80 mmHg. dose of ACEI should be titrated to the maximum tolerated.
- ◉ In children and adolescents with type 1 diabetes, hypertension is defined as average systolic blood pressure and/or diastolic blood pressure greater than the 95th percentile for the patient's gender, age and height on more than three occasions (Grade 1B).

# HYPERTENSION MANAGEMENT IN TYPE 1 DIABETES

- ◉ Angiotensin converting-enzyme inhibitor (ACEI) therapy should be used as a first-line agent for blood pressure lowering
- ◉ If ACEI therapy is contraindicated or not tolerated, angiotensin receptor blockers (ARBs) should be considered.
- ◉ There is no current evidence to support a role for ACEI therapy for blood pressure control or renal protection in patients with type 1 diabetes who are normotensive and normoalbuminuric.

# HYPERTENSION MANAGEMENT IN TYPE 1 DIABETES

- Little evidence that candesartan to prevent the development or progression of retinopathy in patients with type 1 diabetes who are normotensive and normoalbuminuric (Grade 1C).
- Women of childbearing age should be encouraged to stop RAAS-blocking drugs prior to actively considering pregnancy (Grade 1B).
- Patients with type 1 diabetes with significant renal function impairment (estimated glomerular filtration rate (eGFR)  $<45$  ml/min/1.73 m<sup>2</sup>) should be advised to withhold RAAS-blocking drugs during periods of acute illness.

# METABOLIC PROFILES OF DIFFERENT ANTIHYPERTENSIVE DRUGS

| Drug class     | Effect on glucose | Effect on lipids       | Comments                                  |
|----------------|-------------------|------------------------|-------------------------------------------|
| Thiazides      | Raise             | Raise LDL<br>Lower HDL | –                                         |
| Beta blockers  | (Raise) glucose   | Raise TG               | Decrease awareness of hypoglycemia        |
| CCB            | Neutral           | Neutral                | Dihydropyridines may increase proteinuria |
| ACE            | Neutral           | Neutral                | Specific renoprotective effect            |
| Alpha blockers | Neutral           | Raise HDL<br>Lower LDL | ├                                         |

Shaik A et al.  
Diabetes Ther  
(2017) 8:981-989

# ANTI DIABETICS IN HYPERTENSION

- GLP-1 Agonists- Exenatide and Liraglutide significantly reduced SBP and DBP by 1-5 mmHg in a meta-analysis of 16 RCTs compared with antidiabetic drugs including insulin, glimepiride, and placebo for patients with T2DM.

# ANTI DIABETICS IN HYPERTENSION

- Sitagliptin has shown SBP reduction of 1-3 mmHg , while in other studies it reduced BP significantly ( $p < 0.01$ ) without reducing body mass index and also reduced office as well as home BP.

Mistry GC et al. . J Clin Pharmacol. 2008;48(5):592-8.  
Ogawa S et al. Tohoku J Exp Med. 2011;223:133-5.  
Yuasa S et al. J Clin Med Res. 2017 Mar; 9(3): 188-192.

# ANTI DIABETICS IN HYPERTENSION

- All three have been reported to significantly decrease systolic and diastolic BP by 3-5/2-3 mmHg .
- A meta-analysis published in 2014 reported that SGLT2 inhibitors decrease systolic and diastolic BP by 4 and 1.6 mmHg compared with placebo.

# SUMMARY

- Hypertension is a strong, modifiable risk factor for the macrovascular and microvascular complications of diabetes
- Strong evidence from clinical trials and meta-analyses supports targeting blood pressure reduction to at least ,140/90 mmHg in most adults with diabetes
- Treatment should be individualized to the specific patient based on their comorbidities;