Should angiotensin-converting enzyme inhibitors (ACE-I) be used for diabetic patients with hypertension only if there is also proteinuria?

Current guidelines for the treatment of hypertension in patients with diabetes with or without microalbuminuria (excretion of 30 mg to < 300 mg/24 hours albumin in the urine[1]) or macroalbuminuria (excretion of >300 mg/24 hours albumin in the urine[1]) were reviewed. Guidelines were included from the American Diabetes Association (ADA), American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), Eighth Joint National Committee (JNC8), and the National Kidney Foundation. See the table below for selected relevant recommendations from these guidelines. The cited guidelines were published between 2007 and 2016, with the guidelines from the ADA being most recent. In summary:

- Recommendations from ADA[2] and AACE/ACE[3] state that initial pharmacological therapy for hypertension in patients with diabetes should include either an ACE-I or an angiotensin II receptor blocker (ARB). These recommendations did not include any reference to the presence or absence of microalbuminuria, macroalbuminuria, or proteinuria.
- The JNC8[4] included ACE-Is or ARBs for initial treatment for nonblack people with diabetes, but also included thiazide diuretics or calcium channel blockers (CCB) as other options. In the general black population, initial treatment should include a thiazide diuretic or a CCB. If a patient has chronic kidney disease (CKD), with or without diabetes, an ACE-I or ARB should be used.
- Recommendations from the National Kidney Foundation were included in 3 different publications.[1,5,6] (See Table). By definition, these guidelines cover those patients who have CKD, although these patients do not necessarily have microalbuminuria. Recommendations for specific antihypertensive medications were not provided for patients with CKD and urine albumin excretions of <30 mg/24 hour period.

It is apparent from this review that various recommendations exist for the initial treatment of hypertension in patients with diabetes without micro-or macro-albuminuria. The guidelines from the ADA and AACE/ACE are the most recent of those reviewed, and both of these guidelines include recommendations for ACE-Is or ARBs for treatment of hypertension. JNC8 includes an ACE-I or ARB as an option for initial treatment for nonblack patients, but not for black patients. Guidelines from the Nation Kidney Foundation include recommendations only for patients with CKD.

Table

Guideline	Selected Recommendations / Comments
Guidelines from Diabetes Organizations	
American Diabetes Association.[2]	• Treatment regimens for patients with both DM and HTN should include either an ACE-I or an ARB, but not both. If one class is not tolerated, the other should be tried. • An ACE-I or ARB is recommended for the treatment of patients (nonpregnant) with DM and albuminuria of 30-299 mg/day and is strongly recommended for patients with albuminuria of ≥300 mg/day and/or eGFR <60 mL/min/1.73 m^2. • An ACE-I or an ARB is not recommended for the primary prevention of DKD in patients with DM who have normal BP, normal urinary albumin–to–creatinine ratio (<30 mg/g), and normal eGFR.
Handelsman et al.[3]	• ACE-I or ARBS are preferred for the treatment of HTN in patients with DM. **Table 13** **Suggested Priority of Initiating Blood Pressure-Lowering Agents** **Therapy** / **Reference (evidence level and study design)** Evidence based RAAS blockers (ACE inhibitor or ARB) — (198 [EL 1; RCT]; 199 [EL 1; RCT]) Thiazide diuretic — (194 [EL 4; review NE]) β-Adrenergic blocker — (199 [EL 1; RCT]) Individualized therapy Calcium channel blockers — (214 [EL 1; RCT, posthoc analysis]) Aldosterone receptor blockers — (202 [EL 4; CPG NE]) Direct renin inhibitor Selective α_1-adrenergic blockers Central α_2 agonists Direct vasodilators Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; RAAS = renin-angiotensin-aldosterone system. [pg 34]

Guidelines from JNC8	
James et al.[4]	• In the general nonblack population, including those with DM, initial treatment for HTN should include a thiazide-type diuretic, CCB, ACE-I, or ARB. • In the general black population, including those with DM, initial treatment for HTN should include a thiazide-type diuretic or CCB. • In the population ≥18 years of age with CKD and hypertension, initial (or add-on) treatment for HTN should include an ACE-I or ARB to improve kidney outcomes. This applies to all patients with CKD and HTN regardless of race or DM status.
Guidelines from the National Kidney Foundation	
National Kidney Foundation[1] 2007	• Patients with DM and CKD stages 1-4 who have HTN should be treated with an ACE-I or an ARB, usually along with a diuretic. The target BP in DM and CKD stages 1-4 should be < 130/80 mm Hg.
National Kidney Foundation[5] 2012	• It is recommended not to use an ACE-I or ARB for the primary prevention of DKD in patients with DM who do not have HTN or albuminuria. • It is suggested that an ACE-I or an ARB be used in normotensive patients with DM and albuminuria levels > 30 mg/g who are at high risk of DKD or its progression.
Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group[6] 2012	"Chapter 4: BP management in CKD ND patients with DM 4.1: We recommend that adults with DM and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B) 4.2: We suggest that adults with DM and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (2D) 4.3: We suggest that an ARB or ACE-I be used in adults with DM and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). (2D) 4.4: We recommend that an ARB or ACE-I be used in adults with DM and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). (1B) *Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/ creatinine ratio, and protein reagent strip results—are given in Table 1, Chapter 1." [pg 342] "Recommendation 4.1 applies to diabetic patients with CKD, defined as a GFR <60 ml/min/1.73 m^2, and normal albumin excretion (normoalbuminuria) prior to the use of BP-lowering drugs such as ACE-Is or ARBs. …" [pg 364]

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; CKD ND = non-dialysis-dependent CKD of any stage; DKD = diabetic kidney disease; DM = diabetes mellitus; EL = evidence level; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial

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