DATE: March 13, 2020

**OHSU HEALTH SYSTEM**
**OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE**
Evidence-Based Practice Summary

# Assessing and Treating Albuminuria in Patients with Type 2 Diabetes

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DATE: March 13, 2020

# ASK THE QUESTION

**Question 1a**: In patients with type 2 diabetes on angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) with either macro or micro-albuminuria, does continuing to measure patient's urine albumin excretion on a regular basis improve clinical outcomes (progression of renal disease, chronic kidney disease, end-stage renal disease, cardiovascular events, or mortality)?

**Question 1b**: In patients with type 2 diabetes and albuminuria on an ACEI or ARB, does dose adjustment change clinical outcomes if micro-albuminuria is progressing?

**Question 2**: If a patient with type 2 diabetes without documented micro-albuminuria is on an ACEI or ARB for hypertension, does checking urine microalbumin change clinical outcomes?

**Question 3**: Does starting an ACE or ARB in patients with type 2 diabetes without hypertension or micro-albuminuria change clinical outcomes?

# RECOMMENDATIONS OF OTHER GROUPS

The American Diabetes Association (ADA) released updated practice guidelines related to diabetes and chronic kidney disease in January, 2020.(1) The ADA recommends assessment of urinary albumin and estimated glomerular filtration rate (eGFR) among type 2 diabetics at least once per year. Patients with microalbuminuria (urinary albumin >30 mg/g creatinine) or impaired kidney function (eGRF <60 mL/min/1.73 $m^2$) should be monitored at least twice per year to guide treatment. The ADA strongly recommends ACEI/ARBs as first-line treatment for diabetic patients with hypertension and impaired kidney function (eGFR <60 mL/min/1.73 $m^2$ and UACR ≥300 mg/g Cr); treatment is also recommended for diabetic patients with hypertension and modestly elevated urinary albumin (UACR 30-299 mg/g Cr). The ADA also recommends periodic monitoring of serum creatinine and potassium for patients taking ACEI/ARBs. However, the ADA does not recommend ACEI/ARBs for the prevention of CKD in diabetic patients without hypertension or impaired kidney function. The ADA notes that treatment with ACEI/ARBs has been shown to reduce progression to advanced albuminuria among those with microalbuminuria but has not been shown to reduce progression to end stage renal disease. Furthermore, a renoprotective effect was not demonstrated in a trial of ACEI/ARBs among normotensive type 2 diabetic patients with or without albuminuria.(2)

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends use of ACEI/ARBs in diabetic patients with albuminuria who are at high risk of diabetic kidney disease progression, but the group recommends against use of ACEI/ARBs in normoalbuminuric and normotensive diabetic patients.(3) The group does not make a recommendation on albumin measurement intervals or dosing.

The United Kingdom's National Institute for Health and Care Excellence (NICE) does not make recommendations regarding treatment of normotensive and normoalbuminuric diabetic patients or intervals of albumin monitoring but does offer some guidance regarding dose adjustment. NICE suggests the use of serum potassium, serum creatinine, and estimated glomerular filtration rate measurements before and after commencement of ACEI/ARB treatment. Doses should only be modified if eGFR decreases from pretreatment by more than 25% or the change in serum creatinine from baseline is more than 30%; smaller changes in eGFR or serum creatinine should prompt repeat testing in 1-2 weeks.

The American Academy of Clinical Endocrinologists (AACE) recommends that diabetic patients with albuminuria be treated with the highest tolerated dose of ACEI/ARB.(4) The group does not make recommendations on treatment of normotensive and normoalbuminuric diabetic patients or on the frequency of albumin monitoring.

The International Diabetes Federation (IDF) does not produce practice guidelines but narratively summarizes guidelines of other groups.(5) The IDF notes that all guidelines recommend use of anti-hypertensive therapy with an ACEI/ARB for diabetic patients with hypertension. According to the IDF, most guidelines also recommend an ACEI/ARB in the absence of hypertension if diabetic patients have persistent microalbuminuria. The group also recommends screening for urinary albumin once per year, as well as yearly measurement of serum creatinine in patients with albuminuria or with other relevant risk factors, such as hypertension.

Other guidelines related to management of hypertension and kidney disease, including those of the European Renal Association – European Dialysis and Transplant Association(6) and Kidney Disease Improving Global Outcomes(7), do not make recommendations relevant to the key questions.

## Potentially Relevant Recommendations from Clinical Practice Guidelines

| Organization<br>Year Published | Albuminuria monitoring | Treatment | Evidence base |
|---|---|---|---|
| American Diabetes Association<br>2020 | Assess urinary albumin and estimated glomerular filtration rate (eGFR) among type 2 diabetics at least once per year (**B recommendation**). Assess patients with microalbuminuria (urinary albumin >30 mg/g creatinine) or impaired kidney function (eGRF <60 mL/min/1.73 $m^2$) at least twice per year to guide treatment (**C recommendation**). | Treat hypertensive diabetics with ACEI/ARBs, including those with microalbuminuria (**B recommendation**) and those with more advanced kidney impairment (**A recommendation**); do not use ACEI/ARBs in normotensive diabetic patients or in those without albuminuria. | Evidence and expert opinion(1) |
| National Kidney Foundation Kidney Disease Outcomes Quality Initiative<br>2012 | No recommendations regarding albumin monitoring intervals | 6.1: We recommend not using an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) for the primary prevention of CKD in normotensive normoalbuminuric patients with diabetes. (*1A*)<br>6.2: We suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g who are at high risk of DKD or its progression. (*2C*) | Systematic Review(3, 8) |
| United Kingdom National Institute for Health and Care Excellence<br>2019 | 1.6.13 If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin–angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%. **[2008]**<br><br>1.4.24 For an adult with type 2 diabetes on antihypertensive drug treatment when diabetes is diagnosed, review blood pressure control and medications used. Make changes only if there is poor control or if current drug treatment is not appropriate because of microvascular complications or metabolic problems. **[2009]** | Offer ACEI/ARBs to patients with type 2 diabetes and hypertension<br>(*No recommendations specific to Tx of normotensive/normoalbuminuric patients*) | Systematic Reviews(9) |

| | | | |
|---|---|---|---|
| American Academy of Clinical Endocrinologists 2015 | Diabetic patients with albuminuria should be treated with the highest tolerated dose of ACEI/ARB | Select antihypertensive agents on the basis of their ability to reduce blood pressure and prevent or slow the progression of nephropathy and retinopathy; angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are preferred.<br>(*No recommendations specific to Tx of normotensive/normoalbuminuric patients)* | Evidence and expert opinion(4) |
| International Diabetes Federation 2017 | Recommends screening for urinary albumin once per year, as well as yearly measurement of serum creatinine in patients with albuminuria or with other relevant risk factors, such as hypertension | Most guidelines recommend an ACEI/ARB in the absence of hypertension if diabetic patients have persistent microalbuminuria.<br>(*No recommendations specific to Tx of normotensive/normoalbuminuric patients)* | Narrative summary of other reviews(5) |
| European Renal Association – European Dialysis and Transplant Association 2015 | No recommendations regarding albumin monitoring intervals | No relevant recommendations | Systematic Review(6) |
| Kidney Disease Improving Global Outcomes 2013 | No recommendations regarding albumin monitoring intervals | No relevant recommendations | Systematic Review(7) |
| KDIGO Guideline on Diabetes in CKD 2019 | *In Press* | *In Press* | |

# CRITICALLY ANALYZE THE EVIDENCE

**Overview**

We searched MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (through February 21, 2020) for randomized trials, observational studies, systematic reviews, and published clinical practice guidelines related to use of ACEI/ARBs in patients with type 2 diabetes. We also searched the ECRI Guideline Trust and the websites of relevant professional societies and health organizations for recommendations of other groups. We screened 1,875 abstracts and identified 4 relevant systematic reviews (including a total of 12 trials comprising 17,772 patients) and 1 additional relevant trial.

## **Question 1a:** Monitoring Albuminuria in Patients Treated with an ACEI or ARB for Albuminuria

**Summary of Evidence:**

- No studies identified
- Strength of the body of evidence: **Insufficient** to draw conclusions

We found no systematic reviews or original studies on monitoring albuminuria in patients with diabetes and known albuminuria at baseline. One fair-quality systematic review(10) of screening for microalbuminuria is discussed with Question 2 below.

# **Question 1b:** Dose Adjustment in Patients with Progressive Albuminuria Treated with an ACEI or ARB

## Summary of Evidence:

- We identified 1 relevant fair-quality systematic review (4 RCTs, N= 1,051) addressing the effect of dose on albuminuria among diabetic patients treated with ACEI/ARBs.
- Higher doses of ARBs resulted in greater reduction in albumin excretion (mean difference, -18%) and likelihood of regression to normoalbuminuria than lower doses (OR 1.66; 95% CI, 1.22 to 2.27), with a marginal effect on progression to macroalbuminuria (OR 0.62; 95% CI, 0.38 to 1.02) and no significant difference in adverse events (OR 1.32; 95% CI 0.90 to 1.92).
- Strength of the body of evidence: **Moderate** for albumin excretion and regression to normoalbuminuria and **Low** for progression to macroalbuminuria and adverse events.

While we did not identify any studies of the effect of dose *adjustment* in patients with worsening microalbuminuria, we identified one systematic review evaluating dose comparisons of ACE/ARBs in diabetic patients with albuminuria (**Table 1**). The review evaluated the effect of alternate doses of ACEI/ARBs in type 2 diabetic patients with microalbuminuria and was rated fair quality for unclear dual review of data abstraction and failure to provide a list of excluded studies; studies included in the review were generally fair quality. The review updated a prior 2006 Cochrane review(11) and identified four relevant trials comprising 1,051 patients; no included study evaluated ACEIs, so all of the included evidence pertains to ARBs. Pooled results of the trials found an 18% (95% CI, 8% to 28%) greater reduction in albumin excretion with higher doses compared to lower doses (80 vs. 160 mg Valsartan, 160 vs. 320 mg Valsartan, 40 vs. 80 mg Telmirsartan, and 150 vs. 300 mg Irbesartan). Likewise, patients receiving higher doses were more likely to regress to normoalbuminuria (OR 1.66; 95% CI, 1.22 to 2.27). Progression to macroalbuminuria was also marginally lower in patients receiving higher doses (OR 0.62; 95% CI, 0.38 to 1.02). Incidence of any adverse events was numerically higher with higher-dose treatment, though the difference was not significant (OR 1.32; 95% CI 0.90 to 1.92). We identified no relevant trials published subsequent to the systematic review searches.

| Table 1: Question 1b, Dose Adjustment in Patients with Progressive Albuminuria Treated with an ACEI or ARB | | | | | | |
|---|---|---|---|---|---|---|
| **Author, Year Design, N** | **Study Quality** | **Population** | **Comparison** | **k; n** | **Outcomes included Results** | **Strength of evidence** |
| | | | | | | |
| Blacklock, 2011 Systematic Review K=4, N=1,051 | Fair; 4 included studies also fair quality | Type 2 diabetic patients with microalbuminuria | Valsartan 80 vs. 160 mg or 160 vs. 320 mg Telmirsartan 40 vs. 80 mg Irbesartan 150 vs. 300 mg | 4; 1,051 | Albumin excretion: mean difference -18%; 95% CI, -8% to -28%) | Moderate |
| | | | | 4; 989 | Regression to normoalbuminuria: OR 1.66; 95% CI 1.22 to 2.27) | Moderate |
| | | | | 4; 791 | Progression to macroalbuminuria: OR 0.62; 95% CI 0.38 to 1.02 | Low |
| | | | | 4; 668 | Adverse events: OR 1.32; 95% CI 0.90 to 1.92 | Low |

# **Question 2:** Microalbuminuria Testing in Patients Treated with an ACEI or ARB for Hypertension

## Summary of evidence:

- We identified no primary studies relevant to this question. Systematic reviews from 2001 and 2015 searching for similar studies also found none.
- Strength of the body of evidence: **Insufficient** to draw conclusions

We identified two systematic reviews relevant to Question 2 (**Table 2**). Our searches found no additional studies that met inclusion criteria for this question. The first review(12) was good-quality and broad in scope, addressing urinary dipstick screening for albumin, albumin-creatinine ratio, glucose, and other measures. Studies were excluded if tests were used to investigate patient symptoms (e.g. urinary tract infection). The review identified no studies of dipstick screening for albuminuria. An older systematic review(10) was rated fair-quality for unclear methods and limited reporting on included and excluded studies. The review focused on ambulatory patients with diabetes (type not specified) screened for microalbuminuria. Authors synthesized evidence from 31 studies reporting diagnostic performance (sensitivity and specificity), but found "no controlled trials of screening to prevent progression to nephropathy."

**Table 2: Question 2, Microalbuminuria Testing in Patients Treated with ACEI or ARB for Hypertension**

| Author, Year Design, N | Review Quality | Population | Intervention | Outcomes included | Results | Strength of evidence |
|---|---|---|---|---|---|---|
| Krogsboll, 2015(12) SR, None | Good | General and patient populations; excluded studies in patients with urinary disease | Urinary dipstick screening for albumin and other analytes | CKD, ESRD, mortality | No included studies | Insufficient |
| Scheid, 2001(10) SR, None | Fair | Diabetes, ambulatory patients | Urine screening for microalbuminuria, untimed samples, quantitative or semi-quantitative | Progression to nephropathy | No studies with clinical outcomes | Insufficient |

**Abbreviations:** CKD, chronic kidney disease; ESRD, end-stage renal disease; N, number of patients included in primary studies or number of studies in a systematic review; Obs, observational; RCT, randomized controlled trial; SR, systematic review
**Note:** table includes outcomes relevant to this rapid review; the systematic reviews included additional outcomes

## **Question 3:** Starting Treatment with ACEI or ARB in Patients without Hypertension or Albuminuria

### Summary of Evidence:

- In patients with normal albumin and type 1 or 2 diabetes with or without hypertension, treatment with an ACEI compared with no treatment is associated with decreased all-cause mortality and progression to albuminuria (Strength of Evidence: **High**)
- In patients with normal albumin and type 1 or 2 diabetes with or without hypertension, treatment with an ARB compared with no treatment is not associated with changes in all-cause mortality or progression to albuminuria (Strength of Evidence: **Moderate** and **Low**, respectively)
- Evidence suggests reduced rates of progression to albuminuria in patients with type 2 diabetes treated with an ARB, and in those without hypertension treated with an ACEI. (Strength of Evidence: **Unclear**)

One good-quality Cochrane systematic review(13) assessed treatment with an ACEI or ARB in patients with type 1 or type 2 diabetes with or without hypertension. The review included the large ADVANCE, DIRECT, HOPE, RASS, ROADMAP, and TRANSCEND trials; follow-up ranged from two to seven years. Analyses focused on patients with normal urine albumin at baseline (review authors contacted trial authors for this information when trials also included patients with albuminuria.) Patients with type 2 diabetes and without hypertension (populations relevant to Question 3) were presented independently as subgroups for the outcome progression to albuminuria, but the review did not provide information necessary to assess strength of evidence for these analyses. **Table 3** summarizes information for the full trial population and for the relevant subgroups.

For the broader population (including both types of diabetes and any hypertension status), the review found lower rates of all-cause mortality and of progression to micro- or macroalbuminuria in patients treated with an ACEI than in those given placebo or not treated. The strength of this evidence across eight included trials was high. The review did not find statistically significant effects on mortality or progression to albuminuria for patients treated with an ARB. Strength of evidence for these ARB results was low to moderate, with imprecise findings and some inconsistency in

results across studies. Few patients treated with either drug class developed end-stage renal disease (21 among 16,721 patients), and evidence was insufficient to assess effects of treatment on this outcome.

**Table 3: Question 3, Systematic Review of ACEI or ARB in Patients without Albuminuria(13)**

| Population | Intervention (vs Placebo) | Outcome | N; n | Results Risk Ratio (95% CI) | Strength of Evidence |
|---|---|---|---|---|---|
| Adults with Type 1 or Type 2 diabetes, normoalbuminuric, with or without hypertension | ACEI | Mortality | 6; 11,350 | **0.84 (0.73 to 0.97)** | High |
| | | ESRD | 3; 10.504 | 1.94 (0.66 to 5.70) | Insufficient |
| | | New Albuminuria | 8; 11,906 | **0.71 (0.56 to 0.89)** | High |
| | ARB | Mortality | 5; 7,653 | 1.12 (0.88 to 1.41) | Moderate |
| | | ESRD | 3; 6,217 | 0.50 (0.09 to 2.71) | Insufficient |
| | | New Albuminuria | 5; 7,653 | 0.90 (0.68 to 1.19) | Low |
| Adults with **Type 2** diabetes, normoalbuminuric, ± hypertension (Subgroup analysis) | ACEI | New Albuminuria | 3; NR | 0.67 (0.43 to 1.04) | Not assessed |
| | ARB | | 3; NR | **0.83 (0.73 to 0.94)** | |
| Adults with Type 1 or 2 diabetes, normoalbuminuric and **normotensive** (Subgrop analysis) | ACEI | | 5; NR | **0.82 (0.73 to 0.92)** | |
| | ARB | | 5; NR | 1.06 (0.67 to 1.69) | |

**Abbreviations:** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; N, number of studies in a systematic review; n, number of patients included in primary studies

For patients with type 2 diabetes and any hypertension status, ARB treatment was associated with less progression to albuminuria, but the effect of ACEI treatment on progression was not statistically significant. For normotensive patients with either type 1 or 2 diabetes, the reverse was true; ACEI treatment was associated with lower progression rates, while ARB treatment had no effect.

We identified one new study published since the 2013 Cochrane review relevant to Question 3 (**Table 4**),(2) assessing losartan (an ARB) treatment in American Indian patients with type 2 diabetes. The study included patients both with and without baseline albuminuria, but results were

presented separately for normoalbuminuric patients; among these, 95% were also normotensive. Median follow-up was 5.9 years. The study included 91 patients with normal albumin, far fewer than the large trials included in the Cochrane review, and alone provided insufficient evidence of the effects of treatment on outcomes. For the outcome of progression to macroalbuminuria, the study suggested *higher* rates of progression with treatment, but statistical significance was borderline and the confidence interval was wide.

**Table 4: Question 3, Trial of an ARB in Patients without Hypertension or Albuminuria(2)**

| Author, Year Design, N | Study Quality | Population | Comparison | Outcomes included Results | Strength of evidence |
|---|---|---|---|---|---|
| Weil, 2013 RCT, 91[a] | Fair | American Indians with Type 2 diabetes and normoalbuminuria; 95% normotensive[x] | 100 mg losartan daily vs placebo | Decline in GFR to ≤60 mL/min or to half the baseline value: RR 1.02 (95% CI 0.15 to 6.95)<br>First appearance of elevated albuminuria (ACR≥30 mg/g): HR 0.65 (95% CI 0.23 to 1.82)<br>Progression to macroalbuminuria (ACR ≥300 mg/g): **HR 8.12 (95% CI 1.02 to 64.98**) | Insufficient |

[a]Trial also included 78 patients with microalbuminuria, but results reported separately and only normoalbuminuric patients included here.
**Abbreviations:** ACR, albumin to creatinine ratio; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; HR, hazard ratio; n, number of patients included in primary studies; RR, relative risk

# Summary

- **Key Question 1a.** We identified no studies assessing the effect of monitoring albuminuria on patient outcomes in diabetic patients on ACEI/ARBs with albuminuria.

- **Key Question 1b.** We identified 1 relevant fair-quality systematic review addressing the effect of dose on albuminuria among diabetic patients treated with ACEI/ARBs. Higher doses of ARBs resulted in greater reduction in albumin excretion and likelihood of regression to normoalbuminuria than lower doses, with a marginal effect on progression to macroalbuminuria and no significant difference in adverse events.

- **Key Question 2.** We identified no primary studies assessing the effect of urinary albumin monitoring on outcomes among diabetic patients on ACEI/ARBs without documented albuminuria. Systematic reviews from 2001 and 2015 searching for similar studies also found none.

- **Key Question 3.** In patients with normal albumin and type 1 or 2 diabetes with or without hypertension, treatment with an ACEI compared with no treatment is associated with decreased all-cause mortality and progression to albuminuria. In patients with normal albumin and type 1 or 2 diabetes with or without hypertension, treatment with an ARB compared with no treatment is not associated with changes in all-cause mortality or progression to albuminuria. Evidence suggests reduced rates of progression to albuminuria in patients with type 2 diabetes treated with an ARB, and in those without hypertension treated with an ACEI.

# REFERENCES


1. American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes−2020. Diabetes Care. 2020;43(Supplement 1):S135-S51.
2. Weil EJ, Fufaa G, Jones LI, Lovato T, Lemley KV, Hanson RL, et al. Effect of Losartan on Prevention and Progression of Early Diabetic Nephropathy in American Indians With Type 2 Diabetes. Diabetes. 2013;62(9):3224-31.
3. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850-86.
4. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American association of clinical endocrinologists and american college of endocrinology – clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2015. Endocr Pract. 2015;21(Supplement 1):1-87.
5. Aschner P. New IDF clinical practice recommendations for managing type 2 diabetes in primary care. Diabetes Res Clin Pract. 2017;132:169-70.
6. Bilo H, Coentrão L, Couchoud C, Covic A, De Sutter J, et al. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant. 2015;30(suppl_2):ii1-ii142.
7. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco ALM, De Jong PE, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2013;3(1):1-150.
8. Slinin Y, Ishani A, Rector T, Fitzgerald P, MacDonald R, Tacklind J, et al. Management of Hyperglycemia, Dyslipidemia, and Albuminuria in Patients With Diabetes and CKD: A Systematic Review for a KDOQI Clinical Practice Guideline. Am J Kidney Dis. 2012;60(5):747-69.
9. United Kingdom National Institute for Health and Care Excellence. NG136. Hypertension in adults: diagnosis and management 2019 [Available from: https://www.nice.org.uk/guidance/ng136/chapter/Recommendations#treating-and-monitoring-hypertension.
10. Scheid DC, McCarthy LH, Lawler FH, Hamm RM, Reilly KE. Screening for microalbuminuria to prevent nephropathy in patients with diabetes: a systematic review of the evidence. Journal of Family Practice. 2001;50(8):661-8.
11. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006(4):CD006257.
12. Krogsboll LT, Jorgensen JK, Gotzsche PC. Screening with urinary dipsticks for reducing morbidity and mortality. Cochrane Database Syst Rev. 2015(1).
13. Lv J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli FMG. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2013(8).