What is the evidence either supporting or refuting use of an ACE inhibitor or ARB in a normotensive patient with type 2 diabetes and microalbuminuria? How is microalbuminuria defined and determined?

Background

Albumin is a protein typically filtered out of the urine by the kidneys.[1,2] When found in the urine, it can be a sign of renal impairment. There are different methods to measure albuminuria.[3,4] A spot collection of urine can be used to measure the albumin to creatinine ratio (UACR). Urinary albumin excretion rate (UAER) can also be assessed through collection of urine over a period of time, typically 24 hours. Commonly accepted definitions of microalbuminuria are a UACR of 30 to 300 mg/g or a UAER of either 20 to 200 mcg/min or 30 to 300 mg/24 hours.[4,5] Albuminuria can occur transiently and for a number of different reasons; thus, multiple tests are recommended to confirm microalbuminuria.[2,3] The National Kidney Foundation (NKF) suggests that 3 positive tests over 3 months or more is a sign of kidney disease.[2] The American Diabetes Association (ADA) recommends confirmation with 2 positive tests out of 3 over a 3- to 6-month period.[6] The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends 2 repeat tests within 2 months if the result for an UACR is between 30 to 300 mg/g.[7] A positive result on at least 1 of these repeat tests would indicate increased albuminuria. Importantly, KDIGO advises against usage of the term 'microalbuminuria.' Per KDIGO, the term can be misleading in that it suggests the albumin level may be small or different in some way. Instead, the term 'albuminuria' with some form of quantification is encouraged.

For patients with type 2 diabetes and hypertension, albuminuria can be a predictor of poor renal and cardiovascular outcomes.[8] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are classes of medications used to treat hypertension which may be renally protective.[9] A number of studies have shown that these medications, when used in patients with hypertension and diabetes, can lower albuminuria and improve cardiovascular and renal outcomes.[10,11]

While there are many studies on use of ACE inhibitors or ARBs in type 2 diabetic patients with hypertension and microalbuminuria, there appears to be less data on use of these drugs in patients without hypertension. While the presence of albuminuria is associated with cardiovascular events, no prospective studies were identified that examine how lowering albuminuria affects cardiovascular outcomes and end stage renal disease in this population. The current ADA guidelines do not recommend the use of ACE inhibitors or ARBs for patients without hypertension for the prevention of diabetic kidney disease (DKD).[6] Per the ADA, clinical trials have not been performed in this setting. They further assert that ACE inhibitors and ARBs may not be superior to other types of antihypertensives for prevention of DKD. A study is described in which an ARB (olmesartan) was compared to placebo in patients with type 2 diabetes and normal urine albumin excretion; the development of albuminuria was reduced in patients using olmesartan, but the rate of cardiovascular events was increased.[12]

The NKF provides guidelines for the treatment of kidney disease as part of its Kidney Disease Outcomes Quality Initiative (KDOQI).[13] The current KDOQI guideline suggests that an ACE inhibitor or ARB may be used in diabetic patients with UACR ≥30 mg/g and other risk factors for DKD (e.g., hypertension). However, the NKF states that there are no long-term studies demonstrating benefits of this practice. For patients with microalbuminuria and no other risk factors, an ACE inhibitor or ARB may not be necessary. Notably, in normotensive, normoalbuminuric patients with diabetes, the NKF recommends not using an ACE inhibitor or ARB for primary prevention of DKD.

Literature evaluation

From a search of PubMed, several studies were identified which describe use of ACE inhibitors or ARBs in normotensive patients with type 2 diabetes and microalbuminuria.[14-20] Elements of these studies, including the design and outcomes are described in Table 1. Studies published prior to 2003 (≥15 years ago) are excluded from this review. Of the included studies, all except 1 were randomized controlled trials.[20] Most of these studies were placebo-controlled and utilized an

ARB. The duration of the studies ranged from 10 weeks to 72 months. All except 1 study defined microalbuminuria as UAER 20-200 mcg/min or 30-300 mg/24 hours or as UACR 30-300 mg/g. Makino et al included patients with "incipient nephropathy," defined as UACR 100-300 mg/g.[15] Most studies defined normotensive as blood pressure (BP) <140/90 mmHg. In 2 studies a definition for normotension was absent,[17,20] and in the trial by Zandbergen et al,[19] BP <160/90 mmHg was considered normotensive. However, baseline BP levels of the participants in the latter study were <140/90 mmHg. The primary endpoint or major outcome specified for most of the studies was change from baseline in urinary albumin, as measured by UAER or UACR. Many of these studies also evaluated change in BP as well as other endpoints. Results for the urinary albumin outcomes are listed in Table 1; further results from the individual studies are described below.

Agha et al planned an initial study period of 6 months; they continued to follow up with study participants for an additional 2 months.[14] At the 2-month follow up (i.e., 8 months after study initiation), 142 of the patients in the experimental group had discontinued losartan, whereas 29 patients continued to use the drug. The mean UAER among those who discontinued losartan had increased to 91.8 mcg/min, suggesting that the effects of losartan on proteinuria were reversible upon discontinuation of the drug. Additionally, changes in BP were examined. The losartan group had a baseline mean BP of 134.3/82.3 mmHg, which decreased to 131.1/78.6 mmHg after 6 months. This difference was found to be statistically insignificant (p=not reported) and did not correlate with the reduction in albuminuria. In comparison, the mean BP changed from 136.2/82.6 mmHg at baseline to 134.1/81.3 mmHg after 6 months (p=not reported). Agha et al also stated that 15 patients taking losartan experienced mild dizziness during the first week, which resolved on its own. In all study patients, creatinine, urea, and potassium remained within normal limits.

Makino et al conducted a post-hoc analysis of the INNOVATION study, a double-blind, randomized controlled trial designed to evaluate the effects of telmisartan in both normotensive and hypertensive patients with type 2 diabetes and incipient nephropathy.[15] Patients were randomized to treatment or placebo following stratification according to baseline UACR, BP, glycosylated hemoglobin (HbA1c), gender, and age. A total of 514 patients were included in the analysis, of whom 163 were normotensive and 351 were hypertensive. Significant differences were observed in UACR from baseline to week 52 in the treatment groups vs. placebo groups for both normotensive and hypertensive patients; among the latter, 12.3% of patients receiving telmisartan 40 mg ($p<0.01$) and 21.4% of patients receiving telmisartan 80 mg ($p<0.05$) experienced normalization, compared to 0.8% of patients receiving placebo. No significant differences were observed in other renal outcomes, including serum creatinine and creatinine clearance (data not reported). Significant differences were observed in BP in both the normotensive and hypertensive groups receiving treatment vs. placebo: among normotensive patients, the mean BP at the last observation for the placebo group was 128/75 mmHg, compared to 122/73 mmHg in the telmisartan 40 mg group and 123/72 mmHg in the telmisartan 80 mg group ($p<0.05$ for both treatment groups vs. placebo). Regarding safety, no significant differences were reported in the frequency of adverse events comparing treatment to placebo in both normotensive and hypertensive patients.

The study conducted by Estacio et al was designed to select for patients without macroalbuminuria at baseline, so patients with microalbuminuria and patients without albuminuria were included in the study.[16] The study was terminated early due to lack of funding. A total of 129 patients were randomized, of whom 26 had microalbuminuria at baseline. Results for the outcomes of interest were reported for patients who had completed at least 2 years of follow-up (n=12). The investigators used a log transformation of UAER due to positive skew and variability in raw UAER. They also added 1 to baseline value to accommodate for readings of 0. In addition to albuminuria, the investigators evaluated cardiovascular outcomes and progression of retinopathy and neuropathy. Cardiovascular events were reported in 5 study participants (3 in the intensive BP control group and 2 in the moderate BP control group); this difference was not statistically significant (p=not reported). No statistically significant differences were observed between groups in percentage of participants experiencing progression or regression of retinopathy or neuropathy. One patient each from the intensive BP control group and moderate BP control group progressed by at least 1 stage of retinopathy (p=not reported); 1 patient from the intensive BP control group and 2 from the moderate BP control group regressed at least 1 stage (p=not reported). Regarding

neuropathy, 23.8% of patients in the intensive BP control group progressed versus 17.1% from the moderate BP control group (p=0.447). Importantly, baseline albuminuria status is not accounted for in these results.
Atmaca et al also evaluated changes in BP, as well as body mass index (BMI), and HbA1c.[17] They reported statistically significant reductions in systolic and diastolic BP, and BMI, comparing results at baseline and at the end of the study (p=0.001, data not reported).[18] However, no statistically significant differences were observed when comparing systolic and diastolic BP (p=0.967 and p=0.647, respectively) and BMI (p=0.647) among the treatment groups. Changes in HbA1c from baseline to the end of the study were not statistically significant (p=0.875, data not reported), nor were the differences in HbA1c among the study groups (p=0.694, data not reported).

The study by Jerums et al was designed to evaluate patients for at least 72 months, but it was terminated early.[18] Only 37 patients completed 72 months of follow-up. There were several reasons for early termination. Approximately half of the subjects in the placebo group developed hypertension, which required randomization to active treatment. Additionally, data became available reporting benefits of blockade of the renin angiotensin system in patients with type 2 diabetes and microalbuminuria. Also, there were changes to the definition of hypertension in patients with diabetes and the criteria for initiating pharmacologic therapy, leading to changes in eligibility for antihypertensive therapy in a significant portion of the placebo group. In addition to percentage changes in UAER, patients were also examined for development of macroalbuminuria or regression to normoalbuminuria. Similar rates of regression were reported, with 9% (1/11) in the perindopril group, 27% (3/11) in the nifedipine group, and 20% (3/15) in the placebo group (p=not reported). Macroalbuminuria developed in 18% (2/11) of the perindopril group, 9% (1/11) of the nifedipine group, and 47% (7/15) of the placebo group (p=0.05). Median glomerular filtration rate (GFR) gradients (in ml/min/1.73 m^2) were also assessed. No significant changes were found in the 3 groups from baseline to 12 months (p=not reported). Among the 58 patients that were followed for at least 2 years, the median GFR gradient from 12 months to last follow-up was -2.4 in the perindopril group (p<0.01), -1.3 in the nifedipine group (p=0.26), and -4.2 in the placebo group (p=0.01).

Zandbergen et al developed the protocol for their study at a time when hypertension was defined as >160/90 mmHg.[19] The inclusion criteria included BP <150/90 mmHg, but the mean baseline BP for patients in this study was <140/90 mmHg. In addition to albuminuria, creatinine clearance and BP were assessed. A relative reduction in creatinine clearance of 9.7% was observed in the losartan group from baseline to 10 weeks; creatinine clearance was unchanged for the placebo group (p=0.014 for difference between groups). With regard to BP, the losartan group experienced a reduction in mean BP from 135.9/78.8 mmHg to 131.3/75.8 mmHg over the study period; in comparison, the placebo group experienced little change in mean BP (138.3/80.3 mmHg to 138.4/79.8 mmHg; p=0.006 and 0.005 for adjusted differences in systolic BP and diastolic BP, respectively).

In the study conducted by Kubba et al, there was no control group.[20] In addition to albuminuria, autonomic function was assessed through 5 different tests: the standing to lying ratio, the 30:15 ratio, the Valsalva ratio, BP response to static exercise, and cold pressor response. Abnormal results on at least 3 out of 5 tests indicated autonomic neuropathy. Peripheral neuropathy was assessed by measuring median motor and common peroneal motor nerve conduction velocities (NCV) of the patient's dominant limbs. A patient was considered to have peripheral neuropathy if median motor NCV was <52 m/s or if common peroneal motor NCV was <41 m/s. Sixty-four percent of patients had autonomic neuropathy and 76% had peripheral neuropathy at the end of the study with no significant changes from baseline (p=not reported).

There are several limitations to the aforementioned studies.[14-20] The studies were performed in different countries, potentially limiting the external validity of the data. Some of the studies also had small sample sizes. For example, Kubba et al included a total of 25 patients in their study,[20] and Estacio et al were only able to follow 12 patients for the planned study period.[16] When considering the time frame of these studies, many were short-term; whether the observed effects on microalbuminuria would be sustained over longer periods cannot be concluded from these data.[14,15,17,19,20] Additionally, most of these studies were designed to evaluate changes in urinary albumin measurements, whereas clinical outcomes may be of greater interest to practitioners. As alluded to previously, it is unclear whether reduction in albuminuria affects

cardiovascular outcomes and end stage renal disease in normotensive patients with type 2 diabetes. Finally, the representation of ACE inhibitors and ARBs in these data is unbalanced, with fewer studies investigating an ACE inhibitor.

In addition to these trials, a recently published network meta-analysis was identified in which Huang et al sought to compare the efficacy and safety of antihypertensive medications in diabetic patients with microalbuminuria.[21] The effects in normotensive vs. hypertensive patients within this cohort were further investigated. Included in this meta-analysis were parallel-group randomized controlled trials with a minimum follow-up period of 8 weeks, involving adults with diabetes and microalbuminuria (UAER >30 mg/day) and comparing an oral antihypertensive medication (e.g., ACE inhibitor, ARB, calcium channel blocker, beta blocker, diuretic) against a different antihypertensive medication, placebo, or control. Additionally, UAER was a required outcome and data on the hypertensive status of the population (i.e., hypertensive, normotensive, or both) were required. The primary outcome was reduction in albuminuria as measured by UAER. Standard pairwise and network meta-analyses were performed to assess the primary outcome. Surface under the cumulative ranking (SUCRA) was used to rank different treatments. Analyses were performed for all of the included trials; separate analyses were also conducted for studies with normotensive populations and studies with hypertensive populations.

A total of 38 randomized controlled trials were included in the meta-analysis; of these, 11 studies evaluated normotensive patients.[21] Four of these studies have been described previously[16-19]; the remaining studies were not discussed as they were published prior to 2003 and/or involved patients with type 1 diabetes.[22-28] The results of the standard pairwise meta-analysis showed that there was a significant reduction in albuminuria with 3 different agents in normotensive patients.[21] The 3 agents, when compared to placebo, were candesartan, captopril, and a combination of trandolapril/candesartan. The standardized mean difference in UAER for these agents vs. placebo were -2.33 (95% confidence interval [CI] -3.25 to -1.40), -2.24 (95% CI -2.76 to -1.72), and -3.41 (95% CI -4.54 to -2.29), respectively. Reductions in UAER were observed with other ACE inhibitors and ARBs when compared to placebo, but these results were not statistically significant. These agents were enalapril, lisinopril, losartan, trandolapril, ramipril, and valsartan. Based on the findings from the network meta-analysis, all of the ACE inhibitors and ARBs were associated with greater reductions in UAER compared to placebo, but none of these differences were statistically significant. Of note, 3 separately conducted sensitivity analyses revealed that type 2 diabetes status, age, and study duration had a significant impact on the findings.

This meta-analysis is not without limitations.[21] Patients with type 1 diabetes and type 2 diabetes were included, and as suggested by the sensitivity analyses, this may be a confounding factor. Similarly, though the investigators conducted separate analyses for studies involving normotensive patients and those involving hypertensive patients, there was substantial variability noted in the investigated agents and study durations. Many of the studies included for the normotensive analyses were small, of limited duration, and conducted abroad. Additionally, while the study was able to assess the effects of the drugs on UAER, the effects on clinical outcomes were not evaluated.

Conclusion

In conclusion, there are published studies that specifically evaluate the effects of ACE inhibitors and ARBs in normotensive patients with type 2 diabetes and microalbuminuria. These studies suggest that the use of an ACE inhibitor or an ARB in these patients can reduce albuminuria.[14-21] However, it is unclear whether reductions in albuminuria signify prevention or delays in progression of renal impairment. Data on clinical outcomes, such as survival, cardiovascular events, and progression to end state renal disease in this population are lacking. The limited data on progression of retinopathy and neuropathy suggest that these medications may not make a significant difference.[16,20] Many of these studies were also short-term in the range of months. The few long-term studies that followed patients over years reported substantial drop-out rates. Overall, based on the available data, an ACE inhibitor or an ARB can reduce albuminuria in normotensive patients with type 2 diabetes, but further investigation is necessary to evaluate the clinical risks and benefits of this practice.

Table 1. Selected clinical trials evaluating effects of ACE inhibitors or ARBs in normotensive patients with type 2 diabetes.

Reference	Study design and duration	Study population	Intervention	Major outcome(s)	Results		Conclusions
					Baseline mean albuminuria, BP	Major outcome(s)	
Agha 2009[14]	SB, SC, RCT 6 months	n=383 patients in Pakistan with T2DM for ≥2 years, microalbuminuria (UAER 20-200 mcg/min or 30-300 mg/24 hours), and BP <140/90 mmHg	Losartan 50 mg/d (n=193) Placebo-vitamin B12 500 mcg/d (n=190)	24-h urine albumin change from baseline to 6 months	Losartan Albumin: 101.9 mg/dL BP: 134.3/82.3 mmHg Placebo Albumin: 104.7 mg/dL BP: 136.2/82.6 mmHg	Losartan Albumin: 47.5 mg/dL Placebo Albumin: 103.9 mg/dL p<0.0001 for difference observed between groups	Losartan had significant anti-proteinuric effects in this population.
Makino 2008[15] Post-hoc analysis of INNOVATION	DB, MC, RCT Mean follow-up: 1.3 years	n=163 normotensive patients in Japan with T2DM and incipient nephropathy (UACR 100-300 mg/g)	Telmisartan 40 mg/d (n=58) Telmisartan 80 mg/d (n=51) Placebo (n=54)	Transition: progression to overt nephropathy (UACR >300 mg/g and ≥30% increase in baseline on 2 consecutive visits every 4 weeks) or Normalization: regression to normoalbuminuria (UACR <30 mg/g)	Telmisartan 40 UACR: 173 mg/g BP: 131/75 mmHg Telmisartan 80 UACR: 168 mg/g BP: 133/78 mmgHg Placebo UACR: 164 mg/g BP: 128/73 mmHg	Telmisartan 40 Transition: 7 (12.1%) Normalization: 9 (15.5%) p<0.01 vs. placebo Telmisartan 80 Transition: 5 (9.8%) Normalization: 10 (19.6%) p<0.01 vs. placebo Placebo Transition: 18 (33.3%) Normalization: 1 (1.9%)	Telmisartan prevented the progression of microalbuminuria in normotensive patients with T2DM.
Estacio 2006[16]	SC, RCT Study terminated early; reported outcomes at 2-year follow-up	n=12 patients in Colorado with T2DM, BP <140/90 mmHg, and UAER <200 mcg/min Had randomized 129 patients but had 2-year data for 12 patients.	Intensive: Valsartan 80 mg/d, target DBP 75 mmHg (n=4) Moderate: Placebo, target DBP 80-90 mmHg (n=8)	Change in log UAER from baseline	Intensive UAER: 54.2 mcg/min Moderate UAER: 70.4 mcg/min	Intensive UAER: 5.5 mcg/min (3.06 log reduction) Moderate UAER: 121.7 mcg/min p=0.09 for difference between groups	Intensive BP control with valsartan reduced progression of UAER.

Reference	Study	Study	Intervention	Major outcome(s)	Results		Conclusions
Atmaca 2006[17]	RCT 12 Months	n=26 normotensive patients in Turkey with T2DM and UAER of 30-300 mg/d	Lisinopril 10 mg/d (n=9) Losartan 50 mg/d (n=9) Lisinopril 10 mg/d plus losartan 50 mg/d (n=8)	Change from baseline in UAER	Lisinopril UAER: 70.2 mg/d BP: 120.0/77.8 mmHg Losartan UAER: 70.1 mg/d BP: 120.0/78.9 mmHg Lisinopril plus losartan UAER: 70.1 mg/d BP: 120.0/78.8 mmHg	Lisinopril UAER: 21.9 mg/d Losartan UAER: 27.8 mg/d Lisinopril plus losartan UAER: 29.6 mg/d p=0.001 for reductions for each group from baseline p=0.587 for differences between groups	Lisinopril, losartan, and a combination of each have similar effects on reducing albuminuria in this population. Combination therapy did not provide additional reduction compared to monotherapy.
Jerums 2004[18]	SB, MC, RCT 72 months	n=77 patients in Australia with T2DM for at least 1 year, microalbuminuria (UAER 20-200 mcg/min), and BP <140/90 mmHg	Perindopril 8 mg/d (n=23) Nifedipine 40 mg BID (n=27) Placebo (n=27)	Change from baseline in UAER	Perindopril UAER: 59 mcg/min BP: 139/81 mmHg Nifedipine UAER: 55 mcg/min BP: 137/81 mmHg Placebo UAER: 62 mcg/min BP: 136/81 mmHg	Median changes in UAER Perindopril -47% in first year (p=0.12); +2% per year thereafter Nifedipine +17% in first year (p=0.04); +4% per year thereafter Placebo -10% in first year; +28% per year thereafter	Long-term use of perindopril or nifedipine stabilized UAER compared to placebo.
Zandbergen 2003[19]	DB, MC, RCT 10 weeks	n=147 patients in the Netherlands with T2DM, BP <150/90 mmHg, and microalbuminuria (UAER 20-200 mcg/min)	Losartan 100 mg/d (n=74) Placebo (n=73)	Change from baseline in UAER	Losartan UAER: 78.6 mcg/min BP: 135.9/78.8 mmHg Placebo UAER: 89.4 mcg/min BP: 138.3/80.3 mmHg	Losartan UAER: 51.9 mcg/min Placebo UAER: 97.3 mcg/min p<0.001 for difference between groups	Losartan reduced UAER compared to placebo in this population.

Reference	Study	Study	Intervention	Major outcome(s)	Results		Conclusions
Kubba 2003[20]	Single-arm trial 12 weeks	n=25 normotensive patients in India with T2DM and UAER of 20-200 mcg/min	Losartan 50 mg/d	Change in urine albumin and change in autonomic and peripheral neuropathy	Urine albumin: 54 mg/L Neuropathy measures: S/L ratio: 1.025 30:15 ratio: 1.018 Valsalva ratio: 1.164 Difference in DBP on hand grip test: 12.24 Difference in SBP on CPT: 12.08 Median MNCV: 48.292 m/s Common peroneal MNCV: 41.33	Urine albumin: 32.8 mg/L (p=0.0005) Neuropathy measures: S/L ratio: 1.032 (p=0.32) 30:15 ratio: 1.028 (p=0.12) Valsalva ratio: 1.177 (p=0.14) Difference in DBP on hand grip test: 13.12 (p=0.14) Difference in SBP on CPT: 11.76 (p=0.55) Median MNCV: 48.588 m/s (p=0.35) Common peroneal MNCV: 41.723 m/s (p=0.16)	Losartan improved albuminuria in this population; a similar benefit in autonomic or peripheral neuropathy was not observed.

BID=twice daily; BP=blood pressure; CPT=cold pressor test; DBP=diastolic blood pressure; MC=multicenter; MNCV=mean normal conduction velocity; RCT=randomized controlled trial; SB=single-blind; SBP=systolic blood pressure; SC=single center; S/L=standing to lying ratio; T2DM=type 2 diabetes mellitus; UACR=albumin to creatinine ratio; UAER=albumin excretion rate

References

1. Dowling TC. Chapter e42: Evaluation of kidney function. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=134127006. Accessed August 16, 2017.
2. National Kidney Foundation. Albuminuria. Reviewed August 12, 2016. https://www.kidney.org/atoz/content/albuminuria. Accessed August 16, 2017.
3. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care*. 2014;37(10):2864-2883.
4. Triplitt CL, Repas T, Alvarez C. Chapter 74: Diabetes mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146065891. Accessed August 16, 2017.
5. Lee M. *Basic Skills in Interpreting Laboratory Data*. 5th ed. American Society of Health-System Pharmacists; 2013.
6. American Diabetes Association. Standards of medical care in diabetes – 2017. *Diabetes Care*. 2017;40(Suppl 1):S1-S135.
7. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Accessed August 16, 2017.
8. Basi S, Fesler P, Mimran A, Lewis JB. Microalbuminuria in type 2 diabetes and hypertension: a marker, treatment target, or innocent bystander? *Diabetes Care*. 2008;31(Suppl 2): S194-S201.
9. Hilal-Dandan R. Renin and angiotensin. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY*:* McGraw-Hill. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1613&sectionid=102159960. Accessed August 16, 2017.
10. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861–869.
11. Ibsen H, Olsen MH, Wachtell K, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension*. 2005;45(2):198–202.
12. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med.* 2011;364(10):907–917.
13. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.
14. Agha A, Amer W, Anwar E, Bashir K. Reduction of microalbuminuria by using losartan in normotensive patients with type 2 diabetes mellitus: a randomized controlled trial. *Saudi J Kidney Dis Transpl.* 2009;20(3):429-435.
15. Makino H, Haneda M, Babazono T, et al. Microalbuminuria reduction with telmisartan in normotensive and hypertensive Japanese patients with type 2 diabetes: a post-hoc analysis of The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study. *Hypertens Res*. 2008;31(4):657-664.
16. Estacio RO, Coll JR, Tran ZV, Schrier RW. Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes. *Am J Hypertens*. 2006;19(12):1241-1248.

17. Atmaca A, Gedik O. Effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and their combination on microalbuminuria in normotensive patients with type 2 diabetes. *Adv Ther*. 2006;23(4):615-622.
18. Jerums G, Allen TJ, Campbell DJ, et al. Long-term renoprotection by perindopril or nifedipine in non-hypertensive patients with type 2 diabetes and microalbuminuria. *Diabet Med*. 2004;21(11): 1192-1199.
19. Zandbergen AA, Baggen MG, Lamberts SW, Bootsma AH, de Zeeuw D, Ouwendijk RJ. Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus: a randomized clinical trial. *Ann Intern Med*. 2003;139(2):90–96.
20. Kubba S, Agarwal S K, Prakash A, Puri V, Babbar R, Anuradha S. Effect of losartan on albuminuria, peripheral and autonomic neuropathy in normotensive microalbuminuric type 2 diabetics. *Neurol India*. 2003;51(3):355-358.
21. Huang R, Feng Y, Wang Y, et al. Comparative efficacy and safety of antihypertensive agents for adult diabetic patients with microalbuminuric kidney disease: a network meta-analysis. *PLoS One*. 2017;12(1):e0168582.
22. Bojestig M, Karlberg BE, Lindstrom T, Nystrom FH. Reduction of ACE activity is insufficient to decrease microalbuminuria in normotensive patients with type 1 diabetes. *Diabetes Care*. 2001;24(5):919-924.
23. Nakamura T, Ushiyama C, Osada S, et al. Combination therapy of trandolapril and candesartan cilexetil reduces microalbuminuria and urinary endothelin-1 excretion in patients with type 2 diabetes. *Clin Exp Nephrol*. 2002;6(3):135-139.
24. Poulsen PL, Ebbehøj E, Mogensen CE. Lisinopril reduces albuminuria during exercise in low grade microalbuminuric type 1 diabetic patients: a double blind randomized study. *J Intern Med*. 2001;249(5):433-440.
25. Sano T, Kawamura T, Matsumae H, et al. Effects of long-term enalapril treatment on persistent microalbuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care*. 1994;17(5):420-424.
26. Schnack C, Capek M, Banyai M, Kautzky-Willer A, Prager R, Schernthaner G. Long-term treatment with nifedipine reduces urinary albumin excretion and glomerular filtration rate in normotensive type 1 diabetic patients with microalbuminuria. *Acta Diabetol*. 1994;31(1):14-18.
27. Tutuncu NB, Gurlek A, Gedik O. Efficacy of ACE inhibitors and ATII receptor blockers in patients with microalbuminuria: a prospective study. *Acta Diabetol*. 2001;38(4):157-161.
28. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. *JAMA*. 1994;271(4):275-279.