Recommendation 9-3

Should adult patients with confirmed hypertension and kidney disease be offered as initial therapy ACE inhibitor/ARB/diuretic/CCB or beta-blocker?

Critical outcomes – as per outcome table

There is high quality evidence from several meta-analyses of RCT that drugs acting on RAAS reduce the progression of nephropathy.
In a meta-analysis, the ARBs reduced proteinuria compared with placebo or calcium-channel blockers over 1 to 4 months (ratio of means, 0.57 [95% CI, 0.47 to 0.68] and 0.69 [CI, 0.62 to 0.77], respectively) and 5 to 12 months (ratio of means, 0.66 [CI, 0.63 to 0.69] and 0.62 [CI, 0.55 to 0.70], respectively). The ARBs and ACE inhibitors reduced proteinuria to a similar degree. The combination of ARBs and ACE inhibitors further reduced proteinuria more than either agent alone: The ratio of means for combination therapy versus ARBs was 0.76 (CI, 0.68 to 0.85) over 1 to 4 months and 0.75 (CI, 0.61 to 0.92) over 5 to 12 months; for combination therapy versus ACE inhibitors, the ratio of means was 0.78 (CI, 0.72 to 0.84) over 1 to 4 months and 0.82 (CI, 0.67 to 1.01) over 5 to 12 months.

All-cause mortality

ACE vs. Placebo: there was NS decrease in the risk of all-cause mortality (21 studies, N=7295). In a subgroup analysis of studies which used ACE at the maximum tolerable dose, there was a significant decrease in the risk of all-cause mortality (5 studies, N=2034 RR 0.78, 95% CI 0.61 to 0.98). This was not found in studies using half or less than half of the maximum tolerable dose of these agents (4 studies, N=5261).

ESRD

ACE vs. placebo/no treatment: there was a significant reduction in the risk of ESRD with ACE compared with placebo (10 studies, N=6819, RR 0.60, 95% CI 0.39 to 0.93).
ARB vs. placebo/no treatment: there was a significant reduction in the risk of ESRD with ARB vs. placebo/no treatment (3 studies, N=3251, RR 0.78, 0.67 to 0.91).

Doubling of serum creatinine

ACE vs. placebo/no treatment: there was NS risk in doubling of serum creatinine (9 studies, N=6780).
ARB vs. placebo/no treatment: there was a significant reduction in the risk of the doubling of serum creatinine with ARB compared with placebo/no treatment (3 studies, N=3251, RR 0.79, 0.67 to 0.93).

Dual blockade

There is evidence of harm of combining ARB with ACEI, a recent trial has reported that the combination of full doses of the ACE inhibitor ramipril and the angiotensin receptor antagonist, telmisartan, though reducing BP a few mmHg more than therapy with either ramipril or telmisartan and influencing progress of proteinuria to a slightly but significantly greater extent, was accompanied by a greater incidence of renal outcomes (mostly acute dialysis and doubling of serum creatinine) and by no further reduction of cardiovascular outcomes.

CV outcomes

ACEI/ARB also reduce the incidence of cardiovascular outcomes compared to placebo (0.84, 95% CI 0.78-0.91, P < .0001), myocardial infarction (0.78, 95% CI 0.65-0.97, P = .03), and heart failure (0.74, 95% CI 0.58-0.95, P = .02). The risk for CV outcomes was decreased with RAS blockade (0.56, 95% CI 0.47-0.67, P < .001) in nondiabetic nephropathy patients with CKD also when compared with control therapy (beta-blocker, calcium-channel blockers and other antihypertensive-based therapy).

Cough

ACE vs. placebo/no treatment: ACEI use was associated with a significant increase in the risk of cough (10 studies, N=7087, RR 3.17 95% CI 2.29 to 4.38).
ARB vs. placebo/ no treatment
There was NS difference in the risk of cough (2 studies, N=194).
ACE vs. ARB
There was NS difference in the risk of cough (2 studies, N=90).

Hyperkalaemia

ACE vs. placebo/no treatment: There was NS difference in the risk of hyperkalaemia (2 studies, N=1219).
ARB vs. placebo/ no treatment: There was a significant increase in the risk of hyperkalaemia with ARB compared with placebo (2 studies, N=2287 RR 5.41, 95% CI 1.87 to 15.65).

Guidelines

Several of the guidelines provide recommendations.
Canada 2010: in patients with proteinuric nondiabetic chronic kidney disease, ACE inhibitors or ARBs (if intolerant to ACE inhibitors) are recommended; and in patients with diabetes mellitus, ACE inhibitors or ARBs (or, in patients without albuminuria, thiazides or dihydropyridine CCBs) are appropriate first-line therapies.
ESC2007: In several studies blockade of the renin-angiotensin system has been shown to be superior in delaying end stage renal disease and increase of serum creatinine, and in reducing proteinuria and microalbuminuria. Admittedly, this has not been found in other studies, e.g. in ALLHAT, but reaching a very low blood pressure goal usually requires combination therapy, and therefore it appears reasonable to suggest that any combination should include either an ACE inhibitor or an angiotensin receptor antagonist and that in the few cases in which a single agent can be used, this should be ablocker of the renin-angiotensin system. If the blood pressure goal is achieved, but proteinuria remains .1.0 g/ day (or .1 g/g creatinine) therapy should be further intensified. In this regard, there are promising data by the use of ACE inhibitors and angiotensin receptor antagonists in combination or of high doses of angiotensin receptor antagonists,451,452 provided careful attention is paid to possible rises in serum creatinine and potassium.
ESC2009: in the last 2 years, further evidence has accumulated in favor of targeting reduction of microalbuminuria and proteinuria, mostly through blockers of the renin–angiotensin system, in order to reduce end-stage renal disease and cardiovascular events.
NICE 2008: start treatment with an ACE inhibitor first then move to an ARB if the ACE inhibitor is not tolerated. When using ACE inhibitors/ARBs titrate them to the maximum tolerated therapeutic dose before adding a second-line agent. In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACE inhibitor/ARB therapy. Repeat these measurements between 1 and 2 weeks after starting ACE inhibitor/ARB therapy and after each dose increase. ACE inhibitor/ARB therapy should not normally be started if the pretreatment serum potassium concentration is significantly above the normal reference range (typically more than 5.0 mmol/litre).

References

We evaluated the benefits and harms of adding selective and nonselective AA in CKD patients already on RAS. DESIGN: MEDLINE, EMBASE, and Renal Health Library were searched for relevant randomized clinical trials in adult CKD patients. Results were summarized using the random-effects model. Eleven trials (991 patients) were included. In comparison to angiotensin- converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) plus placebo, nonselective AA along with ACEi and/or ARB significantly reduced 24 h proteinuria (seven trials, 372 patients, weighted mean difference [WMD] -0.80 g, 95% CI -1.27, -0.33) and BP. This did not translate into an improvement in GFR (WMD -0.70 ml/min/1.73m(2), 95% CI -4.73, 3.34). There was a significant increase in the risk of hyperkalemia with the addition of nonselective AA to ACEi and/or ARB (relative risk 3.06, 95% CI 1.26, 7.41). In two trials, addition of selective AA to ACEi resulted in an additional reduction in 24 h proteinuria, without any impact on BP and renal function. Data on cardiovascular outcomes, long-term renal outcomes and mortality were not available in any of the trials. CONCLUSIONS: Aldosterone antagonists reduce proteinuria in CKD patients already on ACEis and ARBs but increase the risk of hyperkalemia. Long-term effects of these agents on renal outcomes, mortality, and safety need to be established.	Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009 Mar;4(3):542-51.

Recent data questioned the ability of renin-angiotensin-aldosterone system (RAAS) blockers to delay progression of diabetic nephropathy. This study evaluated the effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients with diabetic nephropathy. METHODS: A systematic literature search of MEDLINE/PubMed and EMBASE databases was performed to identify randomized trials published up to June 2007 comparing the effects of ACEIs or ARBs with placebo and/or a regimen not including a RAAS blocker on the incidence of end-stage renal disease (ESRD), doubling of serum creatinine (DSC), or death from any cause in patients with diabetic nephropathy. Treatment effects were summarized as relative risks (RRs) using the Mantel-Haenszel fixed-effects model. RESULTS: Of the 1,028 originally identified studies, 24 fulfilled the inclusion criteria (20 using ACEIs and 4 using ARBs). Use of ACEIs was associated with a trend toward reduction of ESRD incidence (RR 0.70; 95% confidence interval (CI) 0.46-1.05) and use of ARBs with significant reduction of ESRD risk (RR 0.78; 95% CI 0.67-0.91). Both drug classes were associated with reduction in the risk of DSC (RR 0.71; 95% CI 0.56-0.91 for ACEIs and RR 0.79; 95% CI 0.68-0.91 for ARBs) but none affected all-cause mortality (RR 0.96; 95% CI 0.85-1.09 for ACEIs and RR 0.99; 95% CI 0.85-1.16 for ARBs). CONCLUSION: Treatment of patients with diabetic nephropathy with a RAAS blocker reduces the risks of ESRD and DSC, but does not affect all-cause mortality. These findings are added to the evidence of a renoprotective role of RAAS blockers in such patients.	Sarafidis PA, Stafylas PC, Kanaki AI, Lasaridis AN. Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis. Am J Hypertens. 2008 Aug;21(8):922-9.
The role of renin angiotensin system (RAS) blockade in controlling hypertension and the positive impact on cardiovascular (CV) outcomes is well known. However, the role of RAS blockade in improving CV outcomes in patients with chronic kidney disease (CKD) is still unclear. METHODS: Randomized controlled trials that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) were included in our study. The relative risk across all study groups was computed using Mantel-Hanszel random effects model. Results were calculated with 95% CI and was considered statistically significant if 2-sided alpha error was <.05. Renin angiotensin system blockade-based therapy was compared with placebo and control (beta-blocker, calcium-channel blockers and other antihypertensive-based therapy) therapy in the study. RESULTS: Twenty-five trials (N = 45758) were used for analysis. Renin angiotensin system blockade decreased the risk for heart failure in patients with diabetic nephropathy when compared with placebo 0.78 (95% CI 0.66-0.92, P = .003) and control therapy (0.63, 95% CI 0.47-0.86, P = .003). The risk for CV outcomes was decreased with RAS blockade (0.56, 95% CI 0.47-0.67, P < .001) in nondiabetic nephropathy patients with CKD when compared with control therapy. There was also a significant reduction of CV outcomes (0.84, 95% CI 0.78-0.91, P < .0001), myocardial infarction (0.78, 95% CI 0.65-0.97, P = .03), and heart failure (0.74, 95% CI 0.58-0.95, P = .02) when we pooled all the patients with	Balamuthusamy S, Srinivasan L, Verma M, Adigopula S, Jalandhara N, Hathiwala S, Smith E. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. Am Heart J. 2008 May;155(5):791-805.

CKD and compared RAS blockade to placebo. CONCLUSIONS: A pooled analysis of all causes of CKD revealed a reduction in the risk for myocardial infarction, heart failure, and total CV outcomes when RAS blockade was compared with placebo. RAS blockade decreases the risk for CV outcomes and heart failure when compared with control therapy in patients with proteinuria. There were also benefits with RAS blockade in reducing the risk of CV outcomes and heart failure in patients with diabetic nephropathy when compared with placebo.	
Angiotensin-converting enzyme (ACE) inhibitors reduce blood pressure and urine protein excretion and slow the progression of chronic kidney disease. PURPOSE: To determine the levels of blood pressure and urine protein excretion associated with the lowest risk for progression of chronic kidney disease during antihypertensive therapy with and without ACE inhibitors. DATA SOURCES: 11 randomized, controlled trials comparing the efficacy of antihypertensive regimens with or without ACE inhibitors for patients with predominantly nondiabetic kidney disease. STUDY SELECTION: MEDLINE database search for English-language studies published between 1977 and 1999. DATA EXTRACTION: Data on 1860 nondiabetic patients were pooled in a patient-level meta-analysis. Progression of kidney disease was defined as a doubling of baseline serum creatinine level or onset of kidney failure. Multivariable regression analysis was performed to assess the association of systolic and diastolic blood pressure and urine protein excretion with kidney disease progression at 22 610 patient visits. DATA SYNTHESIS: Mean duration of follow-up was 2.2 years. Kidney disease progression was documented in 311 patients. Systolic blood pressure of 110 to 129 mm Hg and urine protein excretion less than 2.0 g/d were associated with the lowest risk for kidney disease progression. Angiotensin-converting enzyme inhibitors remained beneficial after adjustment for blood pressure and urine protein excretion (relative risk, 0.67 [95% CI, 0.53 to 0.84]). The increased risk for kidney progression at higher systolic blood pressure levels was greater in patients with urine protein excretion greater than 1.0 g/d ($P < 0.006$). CONCLUSION: Although reverse causation cannot be excluded with certainty, a systolic blood pressure goal between 110 and 129 mm Hg may be beneficial in patients with urine protein excretion greater than 1.0 g/d. Systolic blood pressure less than 110 mm Hg may be associated with a higher risk for kidney disease progression.	Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD Study Group. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003 Aug 19;139(4):244-52.
Reduction of proteinuria is associated with delayed progression of chronic kidney disease. Reports suggest that angiotensin-receptor blockers (ARBs) reduce proteinuria, but results are variable. The relative effect of ARBs and angiotensin-converting enzyme (ACE) inhibitors, and their combined administration, remains uncertain. PURPOSE: To establish the effect of ARBs versus placebo and alternative treatments, and the effect of combined treatment with ARBs and ACE inhibitors, on proteinuria. DATA SOURCES: English-language studies in MEDLINE	Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008 Jan 1;148(1):30-48.

and the Cochrane Library Central Register of Controlled Trials (January 1990 to September 2006), reference lists, and expert contacts. STUDY SELECTION: Randomized trials of ARBs versus placebo, ACE inhibitors, calcium-channel blockers, or the combination of ARBs and ACE inhibitors in patients with or without diabetes and with microalbuminuria or proteinuria for whom data were available on urinary protein excretion at baseline and at 1 to 12 months. DATA EXTRACTION: Two investigators independently searched and abstracted studies. DATA SYNTHESIS: Forty-nine studies involving 6181 participants reported results of 72 comparisons with 1 to 4 months of follow-up and 38 comparisons with 5 to 12 months of follow-up. The ARBs reduced proteinuria compared with placebo or calcium-channel blockers over 1 to 4 months (ratio of means, 0.57 [95% CI, 0.47 to 0.68] and 0.69 [CI, 0.62 to 0.77], respectively) and 5 to 12 months (ratio of means, 0.66 [CI, 0.63 to 0.69] and 0.62 [CI, 0.55 to 0.70], respectively). The ARBs and ACE inhibitors reduced proteinuria to a similar degree. The combination of ARBs and ACE inhibitors further reduced proteinuria more than either agent alone: The ratio of means for combination therapy versus ARBs was 0.76 (CI, 0.68 to 0.85) over 1 to 4 months and 0.75 (CI, 0.61 to 0.92) over 5 to 12 months; for combination therapy versus ACE inhibitors, the ratio of means was 0.78 (CI, 0.72 to 0.84) over 1 to 4 months and 0.82 (CI, 0.67 to 1.01) over 5 to 12 months. The antiproteinuric effect was consistent across subgroups. LIMITATIONS: Most studies were small, varied in quality, and did not provide reliable data on adverse drug reactions. Proteinuria reduction is only a surrogate for important progression of renal failure. CONCLUSION: The ARBs reduce proteinuria, independent of the degree of proteinuria and of underlying disease. The magnitude of effect is similar regardless of whether the comparator is placebo or calcium-channel blocker. Reduction in proteinuria from ARBs and ACE inhibitors is similar, but their combination is more effective than either drug alone. Uncertainty concerning adverse effects and outcomes that are important to patients limits applicability of findings to clinical practice.	
A consensus has emerged that angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) have specific renoprotective effects. Guidelines specify that these are the drugs of choice for the treatment of hypertension in patients with renal disease. We sought to determine to what extent this consensus is supported by the available evidence. METHODS: Electronic databases were searched up to January, 2005, for randomised trials assessing antihypertensive drugs and progression of renal disease. Effects on primary discrete endpoints (doubling of creatinine and end-stage renal disease) and secondary continuous markers of renal outcomes (creatinine, albuminuria, and glomerular filtration rate) were calculated with random-effect models. The effects of ACE inhibitors or ARBs in placebo-controlled trials were compared with the effects seen in trials that used an active comparator drug. FINDINGS: Comparisons of ACE inhibitors or ARBs with	Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet. 2005 Dec 10;366(9502):2026-33.

other antihypertensive drugs yielded a relative risk of 0.71 (95% CI 0.49-1.04) for doubling of creatinine and a small benefit on end-stage renal disease (relative risk 0.87, 0.75-0.99). Analyses of the results by study size showed a smaller benefit in large studies. In patients with diabetic nephropathy, no benefit was seen in comparative trials of ACE inhibitors or ARBs on the doubling of creatinine (1.09, 0.55-2.15), end-stage renal disease (0.89, 0.74-1.07), glomerular filtration rate, or creatinine amounts. Placebo-controlled trials of ACE inhibitors or ARBs showed greater benefits than comparative trials on all renal outcomes, but were accompanied by substantial reductions in blood pressure in favour of ACE inhibitors or ARBs. INTERPRETATION: The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably result from a blood-pressure-lowering effect. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.	
Angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors are known to reduce proteinuria. Their combination might be more effective than either treatment alone, but long-term data for comparative changes in renal function are not available. We investigated the renal effects of ramipril (an ACE inhibitor), telmisartan (an ARB), and their combination in patients aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage. METHODS: The trial ran from 2001 to 2007. After a 3-week run-in period, 25 620 participants were randomly assigned to ramipril 10 mg a day (n=8576), telmisartan 80 mg a day (n=8542), or to a combination of both drugs (n=8502; median follow-up was 56 months), and renal function and proteinuria were measured. The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00153101. FINDINGS: 784 patients permanently discontinued randomised therapy during the trial because of hypotensive symptoms (406 on combination therapy, 149 on ramipril, and 229 on telmisartan). The number of events for the composite primary outcome was similar for telmisartan (n=1147 [13.4%]) and ramipril (1150 [13.5%]; hazard ratio [HR] 1.00, 95% CI 0.92-1.09), but was increased with combination therapy (1233 [14.5%]; HR 1.09, 1.01-1.18, p=0.037). The secondary renal outcome, dialysis or doubling of serum creatinine, was similar with telmisartan (189 [2.21%]) and ramipril (174 [2.03%]; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212 [2.49%]: HR 1.24, 1.01-1.51, p=0.038). Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (-2.82 [SD 17.2] mL/min/1.73 m(2)vs -4.12 [17.4], p<0.0001) or combination therapy (-6.11 [17.9], p<0.0001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) or with combination therapy	Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsärinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008 Aug 16;372(9638):547-53.

(p=0.001) than with ramipril. INTERPRETATION: In people at high vascular risk, telmisartan's effects on major renal outcomes are similar to ramipril. Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes.	