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?

In patients with hypertension, the guideline panel recommends ……			
Population	Adult patients with confirmed hypertension with concomitant kidney disease		
Intervention	Initial pharmacotherapy		
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	□ Yes □ No		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).

Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	□ Yes □ No		There is clear benefit of using monotherapy with a RAAS active drug. The benefits outweigh the harms, as these are mainly related to discomfort. Hyperkalemia may cause more serious consequences.

Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	□ Yes □ No		The panel assumes that patients place more value .... and less value ....

			…… ……
Resource implications *(are the resources worth the intervention?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the less resources consumed – the more likely is a strong recommendation.	□ Yes □ No		
Overall strength of recommendation (c*onsider the extent to which one can be confident that adherence will do more good than harm)*	**Net benefits** = the intervention clearly does more good than harm. **Trade-offs** = there are important trade-offs between the benefits and harms. **Uncertain trade-offs** = it is not clear whether the intervention does more good than harm. **No net benefits** = the intervention clearly does not do more good than harm.		