plus amlodipine or benazepril plus hydrochlorothiazide and followed them for a mean of 36 months.(168) The primary endpoint was a composite of death from CVD, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Blood pressure reduction was similar between the two groups over the course of the trial. The benazepril/amlodipine combination was superior to the benazepril/hydrochlorothiazide combination for reducing CVD events (9.6% vs. 11.8%; p<0.001), though it should be noted that heart failure was not included in the CVD composite definition. Progression of CKD was a prespecified endpoint and defined as doubling of serum creatinine concentration or need for dialysis. Progression of CKD was lower in the benazepril plus amlodipine group versus the benazepril plus hydrochlorothiazide group (2.0% vs. 3.7%; p<0.001).(169)

The Work Group found additional Moderate quality evidence for use of either ACEI or ARB with a CCB (ACEI+CCB or ARB+CCB) for lowering BP and reducing CVD events. One small RCT in the 2014 VA/DOD CKD CPG evidence base (170) showed no difference in eGFR decline among trial participants receiving a dihydropyridine CCB versus an ACEI for BP control in adults with non-diabetic CKD. However, the evidence review for the 2020 VA/DOD Hypertension CPG showed that CCB was superior to other drug classes for reducing all-cause mortality but inferior to other drug classes for preventing heart failure.(171) The current evidence review included a network meta-analysis of 16 head-to-head RCTs (172) that examined a variety of dual antihypertensive regimens versus monotherapy in adults with non-dialysis dependent CKD. Blood pressure control was better with combination ARB+CCB versus monotherapy with ACEI, ARB, or CCB. No difference in BP control was noted between ARB+CCB versus ARB+thiazide diuretic or ACEI+CCB. The combination of ARB+CCB showed lower odds of MACE versus ACEI monotherapy, combination ACEI+spironolactone, or ARB monotherapy. However, no difference in CVD events was noted between ARB+CCB combination therapy versus CCB monotherapy, CCB with a beta-blocker (BB), or CCB+thiazide diuretics. No difference in all-cause mortality was noted across drug combinations versus monotherapy with different agents in this SR.(171,172)

Another meta-analysis included in the current review examined the efficacy and safety of eplerenone, a mineralocorticoid antagonist, versus other drug classes in adults with CKD.(173) Compared to eplerenone, no difference in BP lowering was noted with ACEI/ARB or CCBs versus eplerenone, but greater BP lowering was noted with thiazide diuretics versus eplerenone.(173) At this time, evidence was insufficient to suggest the superiority of mineralocorticoid receptor antagonists (MRAs) over other drug classes for BP control or other clinical endpoints. However, data suggested a benefit with the use of finerenone, a non-steroidal MRA, on CKD progression and reduction in MACE (see Recommendation 18). There was limited data regarding the efficacy and outcomes associated with other combinations of antihypertensives, which represents an area for further research.

The Work Group systematically reviewed evidence related to this recommendation.(165-167,170,172,173) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Low. The benefits of using an ACEI or ARB in combination with a thiazide diuretic or CCB, including improved BP control and reduced risk of MACE, outweigh the potential harm of side effects, such as increased risk for gout, hypokalemia, diabetes, edema, and hyponatremia. Patient values and preferences vary because patients want to control BP to avoid complications associated with uncontrolled hypertension but may prefer