Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials)

| **Study/Region/**  **Funding Source** | **Inclusion/Exclusion Criteria** | **Patient Characteristics (expressed in means unless otherwise noted)** | **Intervention/Duration** | **Study Quality** |
| --- | --- | --- | --- | --- |
| ONTARGET A  *Dual vs monotherapy (ACEI or ARB)*Tobe 201135  Multinational  Funding Source: Industry | Inclusion Criteria: aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage.  Exclusion Criteria: major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration above 265 μmol/L, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic). | 23,422 total were randomized, 5623 had a GFR <60 ml/min/1.73m2 and an additional 3310 had micro (2631) or macroalbuminuria (679) with a GFR ≥60 ml/min/ 1.73m2 (n=8933).  *Demographic data for the 8933 unless noted*.  N=8933  Age (yr): 68.2  Gender (Male %): 68  Race/Ethnicity (%): European 70, Asian 16  BMI: 28  Systolic BP (mm Hg): 144  Diastolic BP (mm Hg): 82  Albuminuria-to-creatinine ratio (ACR): 14.6 (12.2 with GFR <60; 6.7 with micro and GFR ≥60; 65.5 with macro and GFR ≥60)  Serum creatinine (mg/dL): 1.2 (1.4 GFR <60; 0.96 with micro and GFR ≥60; 0.98 with macro and GFR ≥60)  Estimated GFR (ml/min/1.73m2): 61.8 (50.2 with a GFR <60; 81.7 with micro and GFR ≥60; 81.3 with macro and GFR ≥60)  Total cholesterol (mg/dL): 192  LDL cholesterol (mg/dL): 115  Diabetes (%): 49  History of HTN (%): 77  History of CAD (%): 70  History of CHF (%): NR  History of MI (%): 45  History of Stroke (%): 20  Peripheral arterial disease (%): 17  Current smoker (%): 12 | Ramipril 10 mg/d + telmisartan 80 mg/d (n=2943)  Ramipril 10 mg/d or telmisartan 80 mg/d (n=5990)  Followup period: median 4.7 years (followup is for the entire cohort)  Study withdrawals (%): 29 (2591/8933) | Allocation Concealment: adequate  Blinding: double, endpoints adjudication committee  Intention to Treat Analysis: yes  Withdrawals/Dropouts adequately described: yes  Note: Post-hoc analysis |

| Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials) (continued) | | | | |
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| **Study/Region/**  **Funding Source** | **Inclusion/Exclusion Criteria** | **Patient Characteristics (expressed in means unless otherwise noted)** | **Intervention/Duration** | **Study Quality** |
| ONTARGET B  *Dual vs ACEI* Mann, 200818  ONTARGET  Multinational  Funding Source: Industry | Inclusion Criteria: aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage.  Exclusion Criteria: major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration above 265 μmol/L, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic). | This was a 3-arm trial of 25,620 subjects; number with CKD is not specified  Estimated GFR (ml/min/1.73m2) 51.0\*  Urine albumin creatinine ratio (mg/ mmol): 0.81\*  \*Patient characteristics not described for the different arms or for CKD subgroup | Ramipril 10 mg/d + telmisartan 80 mg/d (n=8502 overall)  Ramipril 10 mg/d (n=8576 overall)  Followup period: median 4.7 years (Followup is for the entire cohort)  Study withdrawals (%): NR | Allocation Concealment: adequate  Blinding: double  Intention to Treat Analysis: yes  Withdrawals/Dropouts adequately described: yes |
| Sengul, 200620  Turkey  Funding Source: none stated | Inclusion Criteria: microalbuminuria (AER rate 30 to 300 mg/24 hours for a minimum of three consecutive occasions); aged 40 to 65 years; previously diagnosed hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), despite receiving ACEI monotherapy for ≥6 months.  Exclusion Criteria: type 1 DM; BMI ≥ 40; secondary diabetes; alcoholism; thyroid disease; systolic BP >200 mm Hg, any nondiabetic cause of secondary HTN (including bilateral renal artery stenosis); urinary tract infection; persistent hematuria; chronic liver disease; overt carcinoma; any cardiovascular event in the previous 6 months; serum creatinine ≥150 mmol/L; serum potassium ≥5.5 mmol/L; or pregnancy. | N=219  Age (yr): 57  Gender (Male %): 37  Race/Ethnicity (%): NR  BMI: 30  Systolic BP (mm Hg): 151  Diastolic BP (mm Hg): 89  Urinary AER (mg/24 h): 260  Serum creatinine (mg/dL): 1  Estimated GFR (ml/min/1.73m2): NR  Creatinine clearance (mg/min): 97  Total cholesterol (mg/dL): 211  LDL cholesterol (mg/dL): 135  HbA1c (%): 7.9  Diabetes (%): 100  History of HTN (%): 100  History of CAD (%): NR  History of CHF (%): NR  History of MI (%): NR  History of Stroke (%): NR  Peripheral arterial disease (%): NR  Current smoker (%): 37 | Lisinopril 20 mg/d (n=110)  Telmisartan 80 mg/d (n=109)  After 24 weeks, half of the patients receiving lisinopril were randomized to receive telmisartan in addition. Similarly, half the patients initially treated with telmisartan received a combination of lisinopril plus telmisartan. Follow up for the combination period was 28 weeks. The remaining patients continued to be treated with monotherapy  Followup period: 1 year  Study withdrawals (%): 12 | Allocation Concealment: unclear  Blinding: open-label  Intention to Treat Analysis: no  Withdrawals/Dropouts adequately described: yes |
| Menne, 200819  VALERIA  Germany and Hungary  Funding Source: Industry | Inclusion Criteria: microalbuminuria (urine albumin creatinine ratio for women ≥3.5 mg/ mmol/L and ≤35.0 mg/mmol and men ≥2.5 mg/ mmol/L and ≤25.0 mg/mmoL); aged 18 to 75 years; essential hypertension [defined as mean sitting diastolic BP ≥85 mmHg and <110 mm Hg]. To fulfill the criteria of microalbuminuria, two of three first morning void urines needed to be positive during the screening phase.  Exclusion Criteria: primary kidney disease, renal impairment (creatinine clearance <30ml/min using the Cockroft and Gault formula; serum potassium values >5.5mmol/L; heart failure, significant arrhythmias or bradycardia; relevant valvular disease, type I DM, uncontrolled type II DM with HbA1c >8.0%; history of MI; percutaneous transluminal coronary angioplasty, bypass surgery or stroke within the last 12 months prior to study inclusion; unstable angina pectoris; renal transplantation; severe hepatic disease or hepatic failure; malignant concomitant diseases or history of malignant diseases within the last 5 years; systemic inflammatory diseases; pregnancy or breast feeding; psychiatric disease; either history of alcohol or drug abuse or both. | N=90 (in addition, there was 3rd trial arm of ARB monotherapy with n=43)  Age (yr): 58  Gender (Male %): 69  Race/Ethnicity (%): NR  BMI: 32  Systolic BP (mm Hg): 153  Diastolic BP (mm Hg): 91  Serum creatinine (mg/dL): NR  Estimated GFR (ml/min/1.73m2): NR  Creatinine clearance (mg/min): 112  Urine albumin creatinine ratio (mg/ mmol): 9.4  Total cholesterol (mg/dL): NR  LDL cholesterol (mg/dL): NR  HbA1c (%): NR  Diabetes (%): 74  History of HTN (%): 100  History of CAD “Cardiac disorders”(%): 19  History of CHF (%): NR  History of MI (%): NR  History of Stroke (%): NR  Peripheral arterial disease (%): NR  Current smoker (%): NR | Lisinopril 40 mg/d + Valsartan 320 mg/d (n=43)  Lisinopril 40 mg/d (n=47)  Followup period: 30 weeks  Study withdrawals (%): 14 | Allocation Concealment: adequate  Blinding: double plus outcome assessors and data analysts  Intention to Treat Analysis: no  Withdrawals/Dropouts adequately described: yes |
| Kanno, 200644  Japan  Funding Source: none stated | Inclusion Criteria: serum creatinine concentration of between 1.2 and 5.0 mg/dl; systolic BP (SBP) of >130 and <180 mmHg; diastolic BP (DBP) >80 and <120mmHg; and a daily urinary protein excretion of >1.0g  Exclusion Criteria: secondary hypertension, including patients who were on dialysis therapy or receiving renal transplantation; patients who had chronic renal diseases and were receiving corticosteroid hormone; patients with myocardial infarction or stroke within the previous 6 months or angina pectoris that required treatment with B blockers or calcium channel blocker; and patients with heart failure or left ventricular ejection fraction of 40% or less or with a disorder that in the treating physician’s opinion for other types of ARB | N=90  Age (yr): 60.1  Gender (Male %): 40  Race/Ethnicity (%): 100 Japanese  BMI: NR  Total BP (mm Hg): 137.5  Urinary protein excretion (g/24 h): 1.7  Serum creatinine (mg/dL): 3.01  Estimated GFR (ml/min/1.73m2): NR  Creatinine clearance (mg/min): NR  Total cholesterol (mg/dL): NR  LDL cholesterol (mg/dL): NR  HbA1c (%): NR  Diabetes (%): NR  History of HTN (%): 100  History of CAD (%): NR  History of CHF (%): NR  History of MI (%): 0  History of Stroke (%): 0  Peripheral arterial disease (%): NR  Current smoker (%): NR | ACEI + candesartan 2-12 mg/d (n=45)  ACEI (n=45)  The main ACEI used were benazepril 2.5-10 mg/d or trandolapril 2-4 mg/d  Followup period: 3.1 years  Study withdrawals (%): 5.6 | Allocation Concealment: unclear  Blinding: not blinded  Intention to Treat Analysis: no  Withdrawals/ Dropouts adequately described: yes |
| Mehdi, 200945  United States, single-siteFunding Source:  Government | Inclusion Criteria:  Age 20 to 65; type 1 or 2 DM; seated systolic BP<130mmHg; proteinuria (2-24-h UACR≥300 mg/g despite treatment with ACEI or ARB for at least 3 months\*  Exclusion Criteria:  BMI>45kg/m2; serum creatinine>3.0mg/dl (females) or >4.0 mg/dl (males); known nonddiabetic kidney disease; serum potassium >5.5 mEq/L; hemoglobin A1c>11%; stroke or myocardial infarction within preceding 12 mo; heart failure; known adverse reaction to losartan or spironolactone; anticipated need for dialysis within 12 months  \*Effort was made to recruit younger patients with type 2 DM as recommended by study sponsor | Baseline characteristics based on 26 in losartan group (excluded 1 patient who withdrew prior to first dose)  N=53 Age (yr): 50.8  Gender (Male %): 47 Race/Ethnicity (%): 45% Hispanic, 34% black, 19% non-Hispanic white, 2% Native American  Weight (kg): NR BMI: 31.3 Clinic Systolic BP (mm Hg): 134.0  Clinic Diastolic BP (mm Hg): 73.0 CKD stage: NR Serum creatinine (mg/d/l): 1.6  Creatinine clearance (mL/min): 64.5 Albuminuria (μg/min): NR  Proteinuria (g/day): NR  Albumin/creatinine ratio (mg/g): 907.2  GFR (ml/min/1.73m2): NR  HbA1c (%): 7.9 Total cholesterol (mg/dl): 193.4  LDL cholesterol (mg/dl): 97.5 Diabetes (%): 100  History of HTN (%): NR Dyslipidemia (%): NR  History of CAD (%): NR  History of CHF (%): NR Peripheral arterial disease (%): NR  History of MI (%): NR  History of MI, CABG, PCTA (%): 9.4  History of Stroke (%): NR  Current smoker (%): NR History of AKI (%): NR | Losartan 50 mg/day for 1 week then 100mg/day (n=27)#  Placebo (n=27)#  Followup period: 48 weeks  Study withdrawals (%): 24.1  #All patients were taking lisinopril 80 mg/day | Allocation Concealment: Unclear  Blinding: Double blinded  Intention to Treat Analysis (ITT): No  Withdrawals/Dropouts adequately described: Yes |
| Anand, 200946  United States, Multi-siteFunding Source:  Industry | Inclusion Criteria:  Ages 18 and older; stable symptomatic heart failure (HF); receiving recommended HF therapy; left ventricular ejection fraction <40%; left ventricular internal diameters in diastole adjusted for body surface area ≥2.9 cm/m2  Exclusion Criteria:  Persistent mean standing SBP <90 mm Hg or serum creatinine >2.5 mg/dL  NOTE: results presented are from subgroup analysis of patients with CKD | N=2916 Age (yr): 65.9  Gender (Male %): 88 Race/Ethnicity (%): 91% white  Weight (kg): NR BMI: 27 Systolic BP (mm Hg):123.8  Diastolic BP (mm Hg): 74.5 CKD stage: NR Serum creatinine (mg/d/l): NR  Serum albumin (g/dL): 4.2  Creatinine clearance (mL/min): NR Albuminuria (μg/min): NR  Proteinuria (g/day): NR  Dipstick Proteinuria  Albumin/creatinine ratio (mg/g): NR  GFR (ml/min/1.73m2): 47.8  HbA1c (%): NR Total cholesterol (mg/dl): NR  LDL cholesterol (mg/dl): NR Diabetes (%): 29.1  History of HTN (%): 6.9 Dyslipidemia (%): NR  History of CAD (%): NR  History of CHF (%): 100 Peripheral arterial disease (%): NR  History of MI (%): NR  History of Stroke (%): NR  Current smoker (%): NR History of AKI (%): NR | Valsartan 40 mg twice per day; dose doubled every 2 weeks to reach target of 160 mg twice per day (n= 1477 with CKD)\*#  to Placebo (n= 1439 with CKD)#  Followup period: 23 months (mean)  Study withdrawals (%): 10% discontinued treatment (other withdrawals not reported for subgroup)  \*provided SBP ≥90 mmHg; no signs or symptoms of hypotension; serum creatinine not >150% of baseline  #91% of patients in CKD subgroup were taking an ACEI at randomization | Allocation Concealment: Adequate  Blinding: Double blind  Intention to Treat Analysis (ITT): Yes for the outcomes we are recording  Withdrawals/Dropouts adequately described: Yes |

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = [non-steroidal anti-inflammatory drug;](http://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drug) PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion