Appendix Evidence Table C9. Overview of ARB monotherapy trials

| **Study/Region/**  **Funding Source** | **Inclusion/Exclusion Criteria** | **Patient Characteristics (expressed in means unless otherwise noted)** | **Intervention/Duration** | **Study Quality** |
| --- | --- | --- | --- | --- |
| ***ARB versus placebo/no treatment trials (n= 5 trials)*** | | | | |
| Tobe, 201135  TRANSCEND  Location  Multinational (40 countries)  Funding Source  Industry | Inclusion Criteria: patients intolerant to ACE inhibitors were enrolled if they had established coronary artery, peripheral vascular or CVD, or diabetes with end-organ damage. Intolerance to ACE inhibitors was defined as previous discontinuation by a physician because of intolerance, with a specific documented cause.  Exclusion Criteria: heart failure,  significant primary valvular or cardiac outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, unexplained syncope, planned cardiac surgery or cardiac revasculari- zation within the previous 3 months, systolic BP >160 mm Hg, heart transplantation, subarachnoid hemorrhage, significant renal artery stenosis, creatinine levels >265 μmol/L, proteinuria, or hepatic dysfunction. | 5926 total were randomized, 1480 had a GFR <60 ml/min/1.73m2 and an additional 511 had micro or macroalbuminuria with a GFR ≥60 ml/min/ 1.73m2 (n=1991).  *Demographic data for the 1991 unless noted*.  N=1991  Age (yr): 68.7  Gender (Male %): 51 Race/Ethnicity (%): European 59, Asian 23  BMI: 28  Systolic BP (mm Hg): 143  Diastolic BP (mm Hg): 82  Albuminuria-to-creatinine ratio (ACR): 6.8 (4.4 GFR <60; 6.8 with micro and GFR ≥60; 52.1 with macro and GFR ≥60)  Serum creatinine (mg/dL): 1.2 (1.3 GFR <60; 0.95 with micro and GFR ≥60; 0.98 with macro and GFR ≥60)  Estimated GFR (ml/min/1.73m2): 57.7 (50.1 GFR <60; 79.7 with micro and GFR ≥60; 78.8 with macro and GFR ≥60)  Total cholesterol (mg/dL): 201  LDL cholesterol (mg/dL): 120  Diabetes (%): 41  History of HTN (%): 81  History of CAD (%): 73  History of CHF (%): 0 (see exclusion criteria)  History of MI (%): 45  History of Stroke (%): 22  Peripheral arterial disease (%): 12  Current smoker (%): 8 | Telmisartan 80mg/day  (n=729 plus 226 with micro and GFR ≥60 and 37 with macro and GFR ≥60)  Placebo (n=751 plus 208 with micro and GFR ≥60 and 40 with macro and GFR ≥60)  Study duration: median  4.7 years (all subjects)  Study withdrawals (%): | Allocation Concealment : adequate (main publication)\*  Blinding: double, endpoints adjudication committee  Intention to Treat Analysis (ITT): yes (for all subjects)  Withdrawals/Dropouts adequately described: yes (for all subjects)  \* TRANSCEND, Lancet 2008;372:1174-83.36  Note: Post-hoc analysis |

| Appendix Evidence Table C9. Overview of ARB monotherapy 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** |
| Makino, 200737  Location  JapanFunding Source  NR | Inclusion Criteria: Age 30 to 74, type 2 DM and urinary albumin-to-creatinine ratio 100-300 mg/g, serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women).  Exclusion Criteria: DM type 1, age of diabetes onset <30 years, seated systolic blood pressure (SBP)/diastolic blood pressure (DBP) >180/100 mmHg, and definable chronic kidney disease other than diabetic nephropathy | | N=527Age (yr): 61.7  Gender (Male %): NR Race/Ethnicity (%): NR  BMI: NRSystolic BP (mm Hg): 137  Diastolic BP (mm Hg): 77Albuminuria: NR, see Inc. criteria  Serum creatinine (mg/dL): NR, see Inc. criteria Estimated GFR (ml/min/1.73m2): NRTotal cholesterol (mg/dL): NR  LDL cholesterol (mg/dL): NRDiabetes (%): 100  History of HTN (%): NR History of CAD (%): NR  History of CHF (%): NR  History of MI (%): NR  History of Stroke (%): NR  Peripheral arterial disease (%): NR  Current smoker (%): NR | n= 168 to Telmisartan 80mg/day  n= 172 to Telmisartan 40mg/day  n= 174 to placebo period: median  1.3 +/- 0.5 years  Study withdrawals (%):  2.4 % excluded from primary analysis due to suspected type 1 DM or for missing UACR measurements | Allocation Concealment Unclear  Blinding: Double blinded  Intention to Treat Analysis (ITT): No  Withdrawals/Dropouts adequately described: Yes |
| Brenner, 200138  RENAAL  LocationMultinational Funding Source  Industry | Inclusion Criteria: Age 31 to 70 years with type 2 DM and nephropathy defined as 2 occasions of urinary albumin/creatinine ratio >300 mg/g (or urinary protein excretion >0.5 g/day) and serum creatinine 1.3 – 3.0 mg/dL with lower limit of 1.5 mg/dL for male patients weighing >60kg.  Exclusion Criteria: Type 1 DM or nondiabetic renal disease including renal-artery stenosis. MI or CABG within the previous month, PCI within the previous six months, CVA or TIA within the previous year. History of CHF. Patients on ACEI or ARB prior to study had these medications stopped. | | N=1513Age (yr): 60  Gender (Male %): 63.2 Race/Ethnicity (%): Asian: 16.7, Black: 15.2, White: 48.6, Hispanic: 18.2, Other: 1.3  BMI: 29Systolic BP (mm Hg): 153  Diastolic BP (mm Hg): 82Albuminuria: Median Urine Alb/Cr: 1250 mg/g  Serum creatinine (mg/dL): 1.9Estimated GFR (ml/min/1.73m2): NRTotal cholesterol (mg/dL): 228  LDL cholesterol (mg/dL): 142Diabetes (%): 100  History of HTN (%): 93.5 History of CAD (%): 0.1 (not all CAD as only refers to history of coronary revascularization procedure)  History of CHF (%): 0  History of MI (%): 11.2  History of Stroke (%): 0.1  Peripheral arterial disease (%): NR  Current smoker (%): 18.3 | n= 751 for 50-100mg/day Losartan (71% reached 100 mg/day)  n= 762 PlaceboAll patients also given “standard antihypertensive therapy” (CCB, Diuretics, Alpha blockers, Beta-blockers and centrally acting agents) to maintain BP<140/90.  Followup period: median  3.4 years  Study withdrawals (%): 7.8  46.5 Losartan | Allocation Concealment Adequate  Blinding: Double blind  Intention to Treat Analysis (ITT): Yes  Withdrawals/Dropouts adequately described: Yes |
| Parving, 200139  IRMA-2  Location:96 centers worldwideFunding Source  Industry | Inclusion Criteria: HTN, age 30 to 70, type 2 DM, persistent microalbuminuria (UAER 20 to 200 μg/min in 2 of 3 consecutive, sterile, overnight samples), serum creatinine <1.5 mg/dl for men and <1.1 mg/dl for women.  Exclusion Criteria: Nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within two years, and an indication for ACEI or ARBs. | | N=590Age (yr): 58  Gender (Male %): 68.5Race/Ethnicity (%): White: 97.3, Non-White: 2.7  BMI: 30Systolic BP (mm Hg): 153  Diastolic BP (mm Hg): 90Albuminuria: 55.5 μg/min  Serum creatinine (mg/dL): 1.18Estimated GFR (ml/min/1.73m2):NRTotal cholesterol (mg/dL): 224  LDL cholesterol (mg/dL): 140Diabetes (%): 100  History of HTN (%): 100 History of CAD (%): 4.5  History of CHF (%): NR  History of MI (%): 3.0  History of Stroke (%): 3.1  Peripheral arterial disease (%): 5.2  Current smoker (%): 18.6 | n= 201 placebo  n= 195 Irbesartan 150mg  n= 194 Irbesartan 300mg  Followup period: median  2 years  Study withdrawals (%): 13 | Allocation Concealment: Not defined  Blinding: Double blind  Intention to Treat Analysis (ITT): Yes  Withdrawals/Dropouts adequately described: Yes |
| Lewis, 200140  IDNT  LocationUSAFunding Source:  Industry | Inclusion Criteria: Age 30 - 70, documented diagnosis of type 2 DM, HTN (SBP>135 mm Hg, DBP>85 mm Hg, or documented treatment with antihypertensive agents), proteinuria (urinary protein excretion > 900 mg per 24 hours), serum creatinine 1.0 - 3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men  Exclusion Criteria: NR | | N=1,148Age (yr): 59  Gender (Male %): 68  Race/Ethnicity (%): White 74.3 Hispanic 4.7  Black 12.3 Asian 4.4 Other 4.3  BMI: 30.7Systolic BP (mm Hg): 159  Diastolic BP (mm Hg): 87Albuminuria: NR  Median Urine Protein Excretion 2.9 g/24hr  Median Urine Albumin Excretion 1.9 g/24hr  Serum creatinine (mg/dL): 1.68Estimated GFR (ml/min/1.73m2): NRTotal cholesterol (mg/dL): NR  LDL cholesterol (mg/dL): NRDiabetes (%): 100%  History of HTN (%): 100%History of CAD (%): 28.0 with history of “cardiovascular disease”  History of CHF (%): NR  History of MI (%): NR  History of Stroke (%): NR  Peripheral arterial disease (%): NR  Current smoker (%): NR | n= 579 Irbesartan 300  n= 569 PlaceboAdditional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85.  Followup period:  median 2.6 years  Study withdrawals (%): 0.8 | Allocation Concealment : Adequate  Blinding: Patients, investigators, and assessors  Intention to Treat Analysis (ITT): Yes  Withdrawals/Dropouts adequately described: yes |
| ***ARB versus CCB trials (n=4 trials)*** | | | | | |
| Saruta, 200941  CASE-J  Location Japan  Funding Source  Industry and Government | | Inclusion Criteria: For main study, inclusion criteria were: SBP >180mmHg or DBP >110mmHg, type II diabetes, history of stroke or transient ischemic attack, left-ventricular hypertrophy, angina pectoris or a history of myocardial infarction, proteinuria or a serum creatinine >1.3mg/dL, or arteriosclerotic peripheral artery obstruction. For this post-hoc analysis, CKD defined as proteinuria (positive urine dipstick) and/or decreased GFR (<60ml/min/1.73m2).  Exclusion Criteria: SBP ≥200 mmHg or DBP ≥120 mmHg, Type I DM, MI or CVA <6 months before screening, PTCA or CABG <6 months before screening or currently scheduled, current treatment for CHF (New York Heart Association functional class II-IV) or ejection fraction <40%, CAD requiring beta blocker or calcium channel blocker, atrial fibrillation or atrial flutter, serum creatinine ≥3 mg/dL, AST and/or ALT ≥100 IU/L, malignancy <5 years before enrollment, suspected contraindication for candesartan or amlodipine, pregnancy, possible pregnancy, or plan to conceive a child within 5 years of enrollment, not suited to the clinical trial as judged by a collaborating physician, inability to give informed consent. | N= 2720 (subset with GFR <60ml/min/1.73m2 from among larger study cohort of 4728)  Age (yr): 65  Gender (Male %): 51.8 Race/Ethnicity (%): NR  BMI: 24.5 Systolic BP (mm Hg): 163  Diastolic BP (mm Hg): 91 Albuminuria: NR  Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): NR  LDL cholesterol (mg/dL):NR Diabetes (%): 42.4  History of HTN (%): 100  History of CAD (%): NR  History of CHF (%): NR  History of MI (%): 4.8  History of Stroke (%): 11.8  Peripheral arterial disease (%): 1.2  Current smoker (%): NR | n=1376 Candesartan 4 to 12mg daily titrated to target BP  n=1344 Amlodipine 2.5 to 10mg daily titrated to target BP  Doses titrated to goal BP <130/85 for ages <60 years  <140/90 for ages 60-69  <150/90 for ages 70-79  <160/90 for ages >80  Followup period: Total 36 months  Study withdrawals (%):No data were reported | Allocation Concealment: Not defined  Blinding: Assessor  Intention to Treat Analysis (ITT): Yes  Withdrawals/Dropouts adequately described: Inadequate |
| Ogawa, 200742  Location  Japan  Funding Source  NR | | Inclusion/Exclusion Criteria:  Type 2 DM outpatients who previously had untreated moderate hypertension (130/80 – 200/110 mmHg); microalbuminuria with repeat x 3 urinary albumin-to-creatinine ratio (ACR) of 100-300 mg/g; glycated hemoglobin Alc (HbAlc)<8.0%; no changes in medications or hospitalization during past 3 years; body mass index (BMI)<30 kg/m2; serum creatinine < 1.2 mg/dl; no other renal diseases; no severe cerebral or cardiovascular diseases or liver dysfunction; and no active retinopathy. | N=58 Age (yr): 62.7  Gender (Male %): 46.6 Race/Ethnicity (%): NR  BMI: 23.6 Systolic BP (mm Hg): 152  Diastolic BP (mm Hg): 90 Albuminuria: 100%  Mean urine Alb/Cr ratio: 237  Serum creatinine (mg/dL): 0.74 Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): 199.6  LDL cholesterol (mg/dL): NR Diabetes (%): 100%  History of HTN (%): 100%  Peripheral arterial disease (%): NR  Current smoker (%): NR  History of CHF (%): NR  History of CAD (%): NR  History of MI (%): NR  History of Stroke (%): NR | n=40 Candesartan 4 - 8mg/d  n=18 Nifedipine 20 - 40mg/d  Followup period: median 56 weeks  Study withdrawals (%): 2/58 (3.4)  Candesartan and Nifedipine doses were 4 mg and 20mg daily, respectively, for first 48 weeks, then doses increased to 8mg and 40 mg daily, respectively. | Allocation Concealment: Not defined  Blinding: Patient only  Intention to Treat Analysis (ITT): Unclear  Withdrawals/Dropouts adequately described: Yes |
| Viberti, 200243  MARVAL  Location 31 centers in the United Kingdom  Funding Source  Industry | | Inclusion Criteria: 35 to 75 years of age, type 2 diabetes mellitus, persistent microalbuminuria (median UAER of 3 nonconsecutive timed overnight urine collections 20 to 200 g/min during 5 week period before entry), normal serum creatinine, BP <180/105 mm Hg.  Exclusion Criteria: Type 1 DM (onset at <35 years of age and requiring insulin within the first year), use of ACEIs, alpha 2 blockers, or CCB <5 weeks before random assignment; child-bearing potential for women; heart failure within preceding 6 months requiring ACE inhibitor therapy; MI, PTCA or CVA within the preceding 3 months; severe diabetic neuropathy; history of hypertensive or hepatic encephalopathy; hepatic disease. | N=332 Age (yr): 58  Gender (Male %): 79.8 Race/Ethnicity (%): White: 86.5 Asian: 10  BMI: 30.8 Systolic BP (mm Hg): 148  Diastolic BP (mm Hg): 86 Albuminuria: 100%  Baseline UAER: 56.7 μg/min  Serum creatinine (mg/dL): 1.08 Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): 198.5  LDL cholesterol (mg/dL): NR Diabetes (%): 100  History of HTN (%): 65  History of CAD (%): NR  History of CHF (%): NR  History of MI (%): 0  History of Stroke (%): NR  Peripheral arterial disease (%): NR  Current smoker (%): NR | n= 169 valsartan initiated at 80 mg/d, could be titrated to 160 mg/d to reach target BP 135/85 mm Hg  n= 163 amlodipine initiated at 5 mg/d, could be titrated to 10 mg/d to reach target BP 135/85 mm Hg  Mean daily doses at end of study were 122 mg valsartan and 8 mg amlodipine.  If BP target not reached with maximum study drug dose, 2.5 mg/d bendrofluazide could be added.  Followup period: median 12 weeks, total 24 weeks  Study withdrawals (%): 12.3 | Allocation Concealment: Yes  Blinding: Patients, investigators  Intention to Treat Analysis (ITT): Yes  Withdrawals/Dropouts adequately described: Yes |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | Lewis, 200140  IDNT  LocationUSAFunding Source  Industry | Inclusion Criteria:  Age 30 - 70, documented diagnosis of DMII, htn, (SBP>135 mm Hg while sitting, DBP>85 mm Hg while sitting, or documented treatment with antihypertensive agents), and proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum Cr 1.0 - 3.0 mg per deciliter (88 and 265 μmol per liter) in women and 1.2 - 3.0 mg per deciliter (106 and 265 μmol per liter) in menExclusion Criteria:  NR  \*\* Other antihypertensives (besides Ace, Arb or CCB) where permitted to maintain target BP (SBP<135mmHg, or 10mmHg lower than SBP at screening if SBP>145, and DBP<85), including diuretics, BB, a1 blockers and a2 agonists.  Placbo required av 3.3 nonstudy drugs, 3.0 for ARB and CCB groups | N=1148Age (yr): 59  Gender (Male %): 68Race/Ethnicity (%): White 74.3 Hispanic 4.7  Black 12.3 Asian 4.4 Other 4.3  BMI: 30.7Systolic BP (mm Hg): 159  Diastolic BP (mm Hg): 87Albuminuria:  -Median Urine Protein Excretion 2.9 g/24hr  -Median Urine Albumin Excretion 1.9 g/24hr  Serum creatinine (mg/dL): 1.68Estimated GFR (ml/min/1.73m2): NRTotal cholesterol (mg/dL): NR  LDL cholesterol (mg/dL): NRDiabetes (%): 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 (%): NR  “History of Cardiovascular Disease”: 28.0 | n= 579 Irbesartan 300  n= 569 PlaceboFollow-up period: median 2.6 years  Study withdrawals (%):23.7 | Allocation Concealment : Y  Blinding: P,I,A  Intention to Treat Analysis (ITT): Y  Withdrawals/Dropouts adequately described: A | | | Inclusion Criteria: Age 30 – 70 yrs, type 2 DM, HTN (SBP >135 or DBP >85 mm Hg, or treatment with antihypertensive agents), proteinuria (urinary protein excretion >900 mg per 24 hours), serum creatinine 1.0 - 3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men  Exclusion Criteria: NR | N=1,146Age (yr): 59  Gender (Male %): 64.3Race/Ethnicity (%): White 72.1 Hispanic 5.0  Black 13.0 Asian 5.1 Other 4.7  BMI: 30.9Systolic BP (mm Hg): 160  Diastolic BP (mm Hg): 87Albuminuria: NR  Median Urine Protein Excretion: 2.9 g/24hr  Median Urine Albumin Excretion: 1.9 g/24hr  Serum creatinine (mg/dL): 1.66Estimated GFR (ml/min/1.73m2): NRTotal cholesterol (mg/dL): NR  LDL cholesterol (mg/dL): NRDiabetes (%): 100%  History of HTN (%): 100%History of CAD (%): 28.7 with history of “cardiovascular disease”  History of CHF (%): NR  History of MI (%): NR  History of Stroke (%): NR  Peripheral arterial disease (%): NR  Current smoker (%): NR | n=579 Irbesartan 300 mg daily  n= 567 Amlodipine 10mg daily  Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85.  Followup period: 2.6 years  Study withdrawals (%): 0.6 | Allocation Concealment : Yes  Blinding: Patients, investigators, assessors  Intention to Treat Analysis (ITT): Yes  Withdrawals/Dropouts adequately described: Adequate |

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ALT = alanine aminotransferase; ARB = angiotensin II receptor blocker; AST = aspartate aminotransferase; BB = bete blocker; BMI = body mass index; BP = blood pressure; DBP=diastolic blood pressure; CABG= coronary artery bypass grafting; 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) PTCA= percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP=systolic blood pressure; TIA = transient ischemic attack; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin