KDIGO CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF BLOOD PRESSURE IN CHRONIC KIDNEY DISEASE

Supplementary Tables
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ABBREVIATIONS AND ACRONYMS FOR SUPPLEMENTAL TABLES

Δ	Change	KDOQI	Kidney Disease Outcomes Quality Initiative
↓	Decrease	kg	Kilogram
↑	Increase	L	Liter
ACEI	Angiotensin-converting enzyme inhibitors	LOCF	Last observation carried forward
ACR	Albumin-creatinine ratio	LV	Left ventricular
ARB	Angiotensin receptor blockers	µ	Micro-
β	Beta	MAP	Mean arterial pressure
BMI	Body mass index	mg	Milligram
BP	Blood pressure	MI	Myocardial infarction
CAD	Coronary artery disease	min	Minute
CCB	Calcium channel blockers	mL	Milliliter
CHD	Coronary heart disease	mmHg	Millimeters of Mercury
CHF	Chronic heart failure	mmol	Millimole
CI	Confidence interval	mo	Month
CKD	Chronic kidney disease	mol	Mole
CrCl	Creatinine clearance	nd	Not documented
CV	Cardiovascular	NS	Not significant
CVA	Cerebrovascular accident	NNT	Number needed to treat
d	day	OR	Odds ratio
DBP	Diastolic blood pressure	PCR	Protein-creatinine ratio
dL	Deciliter	PKD	Polycystic kidney disease
DM	Diabetes mellitus	pts	Patients
DRI	Direct rennin inhibitor	RCT	Randomized controlled trial
eCrCl	Estimated creatinine clearance	RR	Relative risk
eGFR	Estimated glomerular filtration rate	RRT	Renal replacement therapy
ERT	Evidence review team	SBP	Systolic blood pressure
ESRD	End stage renal disease	S_{Cr}	Serum creatinine
ESRF	End stage renal failure	SD	Standard deviation
EU	European union	UACR	Urinary albumin-creatinine ratio
g	Gram	UAE	Urinary albumin excretion
GFR	Glomerular filtration rate	UAER	Urinary albumin excretion rate
h	Hour	UK	United Kingdom
HDL	High-density lipoprotein	UPCR	Urinary protein-creatinine ratio
HR	Hazards ratio	UPE	Urinary protein excretion
HTN	Hypertension	US	United States
IQR	Interquartile range	y	year

Supplemental Table 1. General population RCTs comparing BP targets in CKD subgroups

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Mortality													
All-cause mortality	Pahor 1998 US[72]	5 y (5 y)	Active treatment [BP target: SBP<160 or ≤20 mm Hg reduction]	Placebo [No BP target]	216 (216)	177 (177)	S_{Cr} 119.4-212.2 µmol/L	nd	172/77 (172/77)	140/70 (154/75)	37 (17%) [26 (15%)]	HR 1.18 (0.72; 1.95)	NS
CV Events													
Any CV event											36 (17%) [47 (27%)]	HR 0.59 (0.38; 0.91)	nd
Stroke	Pahor 1998 US[72]	5 y (5 y)	Active treatment [BP target: SBP<160 or ≤20 mm Hg reduction]	Placebo [No BP target]	216 (216)	177 (177)	S_{Cr} 119.4-212.2 µmol/L	nd	172/77 (172/77)	140/70 (154/75)	14 (7%)[1] [22 (12%)]	HR 0.51 (0.26; 1.00)	nd
Any coronary event											16 (7%) [21 (12%)]	HR 0.62 (0.32; 1.19)	NS

[1] Primary outcome

Supplemental Table 2. Evidence profile of RCTs examining the effect of blood pressure target in patients with CKD without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	2 RCTs [1˚ in 1 RCT] (High)	1934 (972)	No limitations (0)	No important inconsistencies[2] (0)	Direct (0)	None (0)	High	No difference[3]	Critical
Mortality	3 RCTs (High)	1929 (980)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	Critical
CV mortality	2 RCTs (High)	1429 (708)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence	Critical
CV events	1 RCT (High)	1094 (540)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Insufficient evidence	Critical
ESRD	2 RCTs (High)	1927 (980)	Some limitations[4] (-1)	No important inconsistencies[5] (0)	Direct (0)	None (0)	Moderate	Possible benefit for lower target	Critical
Kidney function (categorical)	0 RCT	--	--	--	--	--	--	--	High
∆Kidney function (continuous)	3 RCTs [1˚ in 1 RCT] (High)	1674 (833)	No limitation (0)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Moderate	No difference[6]	Moderate
Proteinuria (categorical)	0 RCT	--	--	--	--	--	--	--	High
Proteinuria (continuous)	1 RCT (High)	754 (380)	No limitations (0)	NA	Uncertainty about directness (-1)	Sparse (-1)	Low	Benefit for low target	Moderate
Adverse events	1 RCT	1094 (540)						Hyperkalemia: 0% for low BP target and 1% for usual BP target (from 1 RCT)	Moderate
Total	3 RCTs	2269 (1140)							

Balance of potential benefits and harms

Possible benefit from lower target for kidney outcomes

Possibly greater benefit from lower target for kidney outcomes in higher proteinuria subgroups

Insufficient evidence for CV outcomes

Quality of overall evidence

Moderate for kidney outcomes

Moderate for CV outcomes

[2] Trial period results were not significant. Follow up of AASK was not significant. Follow-up of MDRD showed benefit of lower target.

[3] Possible benefit for individuals with proteinuria (UPCR >0.22g/g) in AASK Follow up

[4] MDRD follow-up study was considered to be "fair" quality

[5] Trial period results were not significant. Long-term follow-up of MDRD showed benefit of lower target.

[6] Benefit for proteinuria subgroups in MDRD Study 1 and 2.

Supplemental Table 3. RCTs examining the effect of blood pressure targets in patients with CKD without DM [categorical outcomes][7]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
↓GFR 50% or 25 mL/min/ 1.73 m^2, ESRD or death during the trial	AASK 2002 2006 2010[8] US[11;70;99]	4 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Mean Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	nd	Risk reduction 2% (-22; 21)[9]	NS	Good
↓GFR 50% or 25 mL/min/ 1.73 m^2 or ESRD during the trial											nd	Risk reduction -2% (-31; 20)[10]	NS	Good
ESRD or death during the trial											nd	Risk reduction 12% (-13; 32)[11]	NS	Good
First CV hospitalization and death during the trial [from post-trial follow up]					540 (540)	554 (554)					71 (13%) [78 (14%)]	HR 0.84[12] (0.61; 1.16)	NS	Fair[13]

[7] Shaded studies were included in previous KDOQI guideline
[8] Study only included African American patients
[9] Adjusted
[10] Adjusted
[11] Adjusted
[12] Adjusted
[13] From post-trial follow-up data

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
First CV hospitalization or ESRD during the trial [from post-trial follow up]		Range 8.8-12.2 y	Low BP Target in trial, then BP <130/80	Usual BP Target in trial, then BP<130/80			eGFR 48 mL/min/1.73m^2	Median UPCR 0.08		131/78 (134/78)	143 (26%) [159 (29%)]	HR 0.91[14] (0.72; 1.15)	NS	Fair[15]
Doubling of S_{Cr}, ESRD, or death both phases [from post-trial follow up]											282 (52%) [285 (51%)]	HR 0.91 (0.77; 1.08)	NS	Fair[16]
Doubling of S_{Cr} or ESRD during both phases [from post-trial follow up]											213 (39%) [209 (38%)]	HR 0.95 (0.78; 1.15)	NS	Fair[17]
ESRD or death during both phases [from post-trial follow up]											238 (44%) [256 (46%)]	HR 0.85 (0.71; 1.02)	NS (0.08)	Fair[18]
Doubling of S_{Cr}, ESRD, or death in UPCR ≤0.22 [from post-trial follow up]					357 (540)	376 (554)	eGFR 52 mL/min/1.73 m^2	Median UPCR 0.04			145 (41%) [135 (36%)]	HR 1.18 (0.93; 1.50)	NS	Fair[19]

[14] Adjusted
[15] From post-trial follow up data
[16] From post-trial follow up data
[17] From post-trial follow up data
[18] From post-trial follow up data
[19] From post-trial follow up data

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Doubling of S_{Cr} or ESRD in UPCR ≤0.22 [from post-trial follow up]											98 (27%) [83 (22%)]	HR 1.39 (1.04; 1.87)	0.03	Fair[20]
ESRD or death in UPCR ≤0.22 [from post-trial follow up]											119 (33%) [112 (30%)]	HR 1.12 (0.87; 1.45)	NS	Fair[21]
Doubling of S_{Cr}, ESRD, or death in UPCR >0.22 [from post-trial follow up]											136 (75%) [149 (85%)]	HR 0.73 (0.58; 0.93)	0.01	Fair[22]
Doubling of S_{Cr} or ESRD in UPCR >0.22 [from post-trial follow up]					181 (540)	176 (554)	eGFR 41 mL/min/1.73 m^2	Median UPCR 0.58			114 (63%) [126 (72%)]	HR 0.76 (0.58; 0.99)	0.04	Fair[23]
ESRD, or death in UPCR >0.22 [from post-trial follow up]											118 (65%) [143 (81%)]	HR 0.67 (0.52; 0.87)	0.002	Fair[24]

[20] From post-trial follow up data
[21] From post-trial follow up data
[22] From post-trial follow up data
[23] From post-trial follow up data
[24] From post-trial follow-up data

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
ESRD or death	MDRD Study 2 1994 1995[46;79]	3 y (2 y)	Lower BP [MAP ≤92 mmHg][25]	Usual BP [MAP ≤107 mmHg][26]	132 (132)	123 (123)	S_{Cr} 2.0 mg/dL GFR 19 mL/min/1.73 m^2	0.89 g/d	133/81 (133/82)	MAP 90 [126/77][27] (MAP 94 [134/81])	--	RR 0.85 (0.60; 1.22)	nd	Good
Kidney failure or all-cause mortality during the trial [from post-trial follow up]	MDRD 2005 US[86]	4 y (2 y)	Lower BP [Target MAP <92 (<125/75) or <98]	Usual BP [Target MAP <107 (<140/90) or <113]	nd	nd	GFR 33 mL/min/1.73 m^2	0.39 g/d	130/80 (131/80)	126/77 (134/81)	312 (72%)[28] [312 (76%)]	HR 0.77[29] (0.65; 0.91)	0.0024	Fair
											146 total	HR 0.77[30] (0.54; 1.11)	NS	Fair[31]
Kidney failure or all-cause mortality [from post-trial follow up]		6 y (2 y)			432 (432)	408 (408)					312 (72%)[32] [312 (76%)]	HR 0.77[33] (0.65; 0.91)	0.0024	Fair[34]
Mortality														
All cause mortality	AASK 2002[35] US[99]	4 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	2% [2%]	nd	NS	Good

[25] For patients ≥61 y, target was ≤98 mmHg
[26] For patients ≥61 y, target was ≤113 mmHg
[27] The actual mean follow-up systolic and diastolic BP in the usual group were 132.7/80.2 mmHg and in the low BP group were 125.6/76.7 mmHg (Tom Greene, PhD, personal communication, October 2009)
[28] Primary outcome
[29] Adjusted
[30] Adjusted
[31] From post-trial follow up data
[32] Primary outcome
[33] Adjusted
[34] From post-trial follow up data
[35] Study only included African American patients

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Death [from post-trial follow up]	MDRD 2005 US[86]	6 y (2 y)	Lower BP [Target MAP <92 (<125/75) or <98]	Usual BP [Target MAP <107 (<140/90) or <113]	432 (432)	408 (408)	GFR 33 mL/min/1.73 m^2	0.39 g/d	130/80 (131/80)	126/77 (134/81)	10% [6%]	nd	nd[36]	Fair[37]
Death	REIN 2 2005 Italy[85]	Median 19 mo (36 y)	Conventional BP [DBP <90]	Intensified BP [<130/80]	168 (169)	167 (169)	S_{Cr} 2.7 µmol/L GFR 34 mL/min/1.73 m^2	UPE 2.9 g/d	136/84 (137/84)	134/82 (130/80)	3 (2%) [2 (1%)]	RR 1.49[38] (0.25; 8.81)	nd	Fair
CV mortality														
CV mortality	AASK 2002 2006[39] US[70;99]	6 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	1% [1%]	nd	NS	Good
CV death		4 y (4 y)			540 (540)	554 (554)					16 (3%) [15 (3%)]	HR 0.98[40] (0.48; 2.01)	NS	Good
CV mortality	REIN 2 2005 Italy[85]	Median 19 mo (36 y)	Conventional BP [DBP <90]	Intensified BP [<130/80]	168 (169)	167 (169)	S_{Cr} 2.7 µmol/L GFR 34 mL/min/1.73 m^2	UPE 2.9 g/d	136/84 (137/84)	134/82 (130/80)	1 (1%) [1 (1%)]	RR 0.99[41] (0.06; 15.76)	nd	Fair
CV events														
CV events (composite)	AASK 2002 2006[42] US[70;99]	4 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	2% [3%]	nd	NS	Good
CV events											108 (20%) [94 (17%)]	HR 1.06[43] (0.76; 1.49)	NS	Good
Stroke events					540 (540)	554 (554)					26 (5%) [29 (5%)]	RR 0.92[44] (0.55; 1.54)	nd	Good
CHF events											27 (5%) [23 (4%)]	RR 1.20[45] (0.70; 2.07)	nd	Good

[36] Noted as statistically significant in letter to Annals by Good, 2005
[37] From post-trial follow up data
[38] Calculated by ERT
[39] Study only included African American patients
[40] Adjusted
[41] Calculated by ERT
[42] Study only included African American patients
[43] Adjusted
[44] Calculated by ERT
[45] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
CAD events											19 (4%) [23 (4%)]	RR 0.85[46] (0.47; 1.54)	nd	Good
ESRD														
ESRD during trial	AASK 2002[47] US[99]	4 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	nd	Risk reduction 6% (-29; 31)[48]	NS	Good
ESRD during the trial [from post-trial follow up]	MDRD 2005 US[86]	4 y (2 y)	Low BP [Target MAP <92 (<125/75) or <98]	Usual BP [Target MAP <107 (<140/90) or <113]	nd	nd	GFR 33 mL/min/1.73 m^2	0.39 g/d	130/80 (131/80)	126/77 (134/81)	127 total	HR 0.76 (0.52; 1.10)	NS	Fair[49]
ESRD [from post-trial follow up]		6 y (2 y)			432 (432)	408 (408)					268 (62%) [286 (70%)]	HR 0.68[50] (0.57; 0.82)	<0.001	Fair[51]
ESRD	REIN 2 2005 Italy[85]	Median 19 mo (36 mo)	Conventional BP [DBP <90]	Intensified BP [<130/80]	168 (169)	167 (169)	S_{Cr} 2.7 µmol/L GFR 34 mL/min/1.73 m^2	UPE 2.9 g/d	136/84 (137/84)	134/82 (130/80)	34 (20%) [38 (23%)]	RR 0.89[52] (0.59; 1.34)	NS	Good
ESRD in pts with proteinuria <3g/24h					106 (169)	109 (169)	S_{Cr} 2.7 µmol/L GFR 36 mL/min/1.73 m^2	UPE 1.8 g/d			--	HR 0.94 (0.45; 1.96)	NS	Fair
ESRD in pts with proteinuria ≥3g/24h					62 (169)	58 (169)	S_{Cr} 2.7 µmol/L GFR 31 mL/min/1.73 m^2	UPE 4.9 g/d			--	HR 0.92 (0.45; 1.81)	NS	Fair

[46] Calculated by ERT
[47] Study only included African American patients
[48] Adjusted
[49] From post-trial follow-up data
[50] Adjusted
[51] From post-trial follow-up data
[52] Calculated by ERT

Supplemental Table 4. RCTs examining the effect of blood pressure targets in patients with CKD without DM [continuous outcomes] [53]

Outcome (Units)	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
Acute slope: ΔGFR in first 3 mo, mL/min/1.73 m^2/y	AASK 2002[54] US[99]	4 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	46[55] (45)	Mean difference (lower vs. usual) -1.82	<0.001	Good
Chronic slope: ΔGFR after first 3 mo, mL/min/1.73 m^2/y												-2.11 (-2.32)	NS	Good
Total slope[56]: ΔGFR over 4 y, mL/min/1.73 m^2/y												-2.21 (-1.95)	NS	Good
Acute slope, ↓GFR in patients with GFR 25-55 mL/min/1.73 m^2, mL/min/4 mo	MDRD Study 1 1994 1995 US[46;79]	4 mo (2 y)	Low BP [MAP ≤92 mmHg][57]	Usual BP [MAP ≤107 mmHg][58]	285 (285)	300 (300)	S_{Cr} 2.0 mg/dL GFR 38 mL/min/1.73 m^2	1.1 g/kg/d	132/81 (132/82)	MAP 90 [126/77][59] (MAP 94 [134/81])	38 (39)	-3.4 (-1.9)	0.01	Good

[53] Shaded studies were included in previous KDOQI guideline
[54] Study only included African American patients
[55] Primary outcome
[56] The results of the blood pressure comparison differed significantly depending on the level of baseline proteinuria for the acute slope (P=0.008) and total slopes (P=0.004) but not for the chronic slope (P=0.16).
[57] For patients ≥61, target was ≤98 mmHg
[58] For patients ≥61, target was ≤113 mmHg
[59] The actual mean follow-up systolic and diastolic BP in the usual group were 132.7/80.2 mmHg and in the low BP group were 125.6/76.7 mmHg (Tom Greene, PhD, personal communication, October 2009)

Outcome (Units)	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Chronic slope, ↓GFR in patients with GFR 25-55 mL/min/1.73 m^2, mL/min/y	MDRD Study 2 1994 1995 US[46;79]	4 mo-3y (2 y)										-2.8 (-3.9)	0.006	Good
Total slope, ↓GFR in patients with GFR 25-55 mL/min/1.73 m^2, mL/min/3y		3 y (2 y)										-10.7 (-12.3)	NS	Good
Total slope, ↓GFR in subgroup of patients with GFR 25-55 and proteinuria >0.25 g/d					nd	nd	nd	nd	nd	nd	Benefit of lower BP	--	0.02[60]	Fair
Total slope, ↓GFR in patients with GFR 13-24 mL/min/1.73 m^2, mL/min/y					132 (132)	123 (123)	S_{Cr} 2.0 mg/dL GFR 19 mL/min/1.73 m^2	0.89 g/kd/d	133/81 (133/82)	MAP 90 [126/77][61] (MAP 94 [134/81])	19 (19)	-3.7 (-4.2)	NS	Good
Total slope, ↓GFR in subgroup of patients with GFR 13-24 and proteinuria >1 g/d					nd	nd	nd	nd	nd	nd	Benefit of lower BP	--	0.01[62]	Fair

[60] By interaction analysis
[61] The actual mean follow-up systolic and diastolic BP in the usual group were 132.7/80.2 mmHg and in the low BP group were 125.6/76.7 mmHg (Tom Greene, PhD, personal communication, October 2009)
[62] By interaction analysis

Outcome (Units)	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Median rate of ↓GFR, mL/min/1.73 m^2/mo	REIN 2 2005 Italy[85]	Median 19 mo (36 y)	Conventional BP [DBP <90]	Intensified BP [<130/80]	168 (169)	167 (169)	S_{Cr} 2.7 µmol/L GFR 34 mL/min/1.73 m^2	UPE 2.9 g/d	137/84 (136/84)	130/80 (134/82)	34 (36)	0.24 (IQR 0.0001; 0.56) [0.22 (IQR 0.06; 0.55)]	NS	Good
Median rate of ↓CrCl, mL/min/1.73 m^2/mo											39 (39)	0.25 (0.0001; 0.75) [0.26 (0.03; 0.53)]	NS	Good
Rate of ↓GFR in pts with proteinuria <3g/24h, mL/min/1.73 m^2/mo					106 (169)	109 (169)	S_{Cr} 2.7 µmol/L GFR 36 mL/min/1.73 m^2	UPE 1.8 g/d			36 (33)	0.21 (-0.03; 0.40) [0.18 (0.03; 0.49)]	NS	Fair
Rate of ↓GFR in pts with proteinuria ≥3g/24h, mL/min/1.73 m^2/mo					62 (62)	58 (58)	S_{Cr} 2.7 µmol/L GFR 31 mL/min/1.73 m^2	UPE 4.9 g/d			31 (42)	0.39 (0.03; 0.98) [0.51 (0.16; 1.05)]	NS	Fair
Proteinuria														
%ΔProteinuria (geometric mean UPCR)	AASK 2002[63] US[99]	4 y (4 y)	Lower BP [Target MAP 92]	Usual BP [Target MAP 102-107]	380 (540)	374 (554)	GFR 46 mL/min/1.73 m^2	Male 0.61g/24h Female 0.36 g/24h	152/96 (149/95)	128/78 (141/85)	Male 0.61; Female 0.36 (Male 0.61; Female 0.46)	-17% (+7%)	<0.001	Good

[63] Study only included African American patients

Supplemental Table 5. General population RCTs comparing ARB vs. CCB in CKD subgroups with and without DM

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Mortality													
Sudden death	CASE-J 2009 Japan[87]	3 y (3 y)	Candesartan	Amlodipine	1376 (1376)	1344 (1344)	nd	nd	163/92 (163/92)	136/77 (135/77)	8 (1%) [12 (1%)]	RR 0.65[64] (0.27; 1.59)	NS
CV Events													
Cerebrovascular events[65]	CASE-J 2009 Japan[87]	3 y (3 y)	Candesartan	Amlodipine	1376 (1376)	1344 (1344)	nd	nd	163/92 (163/92)	136/77 (135/77)	44 (3%) [40 (3%)]	RR 1.07[66] (0.70; 1.64)	NS
CV events											99 (7%) [102 (8%)]	HR 0.95 (0.73; 1.24)	NS
Cardiac events[67]											30 (2%) [32 (2%)]	RR 0.92[68] (0.56; 1.50)	NS
Cerebrovascular events[69] in patients with CKD Stage 3											32 (3%) [29 (3%)]	RR 1.09[70] (0.66; 1.79)	NS
CV events in patients with CKD Stage 3					1140 (1140)	1125 (1125)					72 (6%) [71 (6%)]	RR 1.00[71] (0.73; 1.37)	NS
Cardiac events[72] in patients with CKD Stage 3											26 (2%) [27 (2%)]	RR 0.95[73] (0.56; 1.62)	NS
Cerebrovascular events[74] in patients with CKD Stage 4					64 (64)	61 (61)					1 (2%) [4 (7%)]	RR 0.24[75] (0.03; 2.07)	NS

[64] Calculated by ERT
[65] New occurrence or reoccurrence of a stroke or transient ischemic attack
[66] Calculated by ERT
[67] New occurrence, aggravation, or reoccurrence of heart failure, angina pectoris, or acute MI
[68] Calculated by ERT
[69] New occurrence or reoccurrence of a stroke or transient ischemic attack
[70] Calculated by ERT
[71] Calculated by ERT
[72] New occurrence, aggravation, or reoccurrence of heart failure, angina pectoris, or acute MI
[73] Calculated by ERT
[74] New occurrence or reoccurrence of a stroke or transient ischemic attack
[75] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
CV events in patients with CKD Stage 4											9 (14%) [18 (30%)]	RR 0.48[76] (0.23; 0.98)	nd
Cardiac events[77] in patients with CKD Stage 4											3 (5%) [1 (2%)]	RR 2.86[78] (0.31; 26.75)	NS
Kidney Function													
Renal events[79]	CASE-J 2009 Japan[87]	3 y (3 y)	Candesartan	Amlodipine	1376 (1376)	1344 (1344)	nd	nd	163/92 (163/92)	136/77 (135/77)	19 (1%) [26 (2%)]	RR 0.71[80] (0.40; 1.28)	NS
Renal events[81] in patients with CKD Stage 3					1140 (1140)	1125 (1125)					14 (1%) [9 (1%)]	RR 1.54[82] (0.67; 3.53)	NS
Renal events[83] in patients with CKD Stage 4					64 (64)	61 (61)					3 (5%) [14 (23%)]	RR 0.20[84] (0.06; 0.68)	nd

[76] Calculated by ERT
[77] New occurrence, aggravation, or reoccurrence of heart failure, angina pectoris, or acute MI
[78] Calculated by ERT
[79] S_{Cr} ≥4.0 mg/dL, end stage renal disease, doubling of S_{Cr}
[80] Calculated by ERT
[81] S_{Cr} ≥4.0 mg/dL, end stage renal disease, doubling of S_{Cr}
[82] Calculated by ERT
[83] S_{Cr} ≥4.0 mg/dL, end stage renal disease, doubling of S_{Cr}
[84] Calculated by ERT

Supplemental Table 6. General population RCTs comparing ACEI or ARB vs. control (active or placebo) in CKD subgroups with and without DM

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Composite outcome													
Kidney failure or halving of GFR in entire subgroup with GFR <60 mL/min/1.73 m^2	ALLHAT 2006 Multi[50]	5 y (5 y)	Lisinopril	Chlorthalidone	1533 (1533)	2613 (2613)	GFR 50 mL/min/1.73 m^2	nd	nd	nd	106 (7%) [180 (7%)]	RR 1.00 (0.78; 1.29)	NS
Kidney failure or halving of GFR in DM subgroup with GFR <60 mL/min/1.73 m^2			Lisinopril		501 (501)	881 (881)	GFR 49 mL/min/1.73 m^2	nd	nd	nd	61 (12%) [96 (11%)]	RR 1.13 (0.81; 1.60)	NS
Kidney failure or halving of GFR in non-DM subgroup with GFR <60 mL/min/1.73 m^2			Lisinopril		1032 (1032)	1732 (1732)	GFR 49 mL/min/1.73 m^2	nd	nd	nd	45 (4%) [84 (5%)]	RR 0.89 (0.62; 1.30)	NS
CV death, MI or stroke in patients with S_{Cr} ≥1.4 mg/dL	HOPE 2001 Multi [58]	4 y (4 y)	Ramipril	Placebo	509 (509)	471 (471)	nd	UACR 0.73 mg/mmol	139/79 (141/79)	nd	19% [26%]	HR 0.80 (0.59; 1.09)	NS
CV death, MI or stroke in patients CrCl ≤65 mL/min					3394 (3394)						16% [21%]	HR 0.75 (0.64; 0.89)	nd
CV mortality, MI or revascularization in patients with eGFR <45 mL/min/m^2	PEACE 2006 2007 Multi[89;90]	Median 5 y (5 y)	Trandolapril	Placebo	157 (157)		S_{Cr} 1.6 mg/dL	nd	138/76	nd	25 (32%) [28 (36%)]	nd	nd
CV mortality, MI or revascularization in patients with eGFR 45-59.9 mL/min/m^2					1198 (1198)		S_{Cr} 1.3 mg/dL		135/77		153 (25%) [147 (25%)]	nd	nd

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Composite of CV death, nonfatal MI, and coronary revascularization in patients with low-medium microalbuminuria	TRANSCEND, 2009 Multi[62]	5 y (5 y)	Telmisartan	Placebo	332 (1498)	310 (1479)	S_{Cr} 1.05 mg/dL GFR 78 mL/min/m^2	UACR 25-177 µg/mg in women; 17-125 µg/mg in men	139/79		105 (32%) [86 (28%)]	RR 1.14[85] (0.90; 1.45)	NS
Composite of CV death, nonfatal MI, and coronary revascularization in patients with high microalbuminuria-macroalbuminuria					73 (1498)	75 (1479)	S_{Cr} 1.14 mg/dL GFR 75 mL/min/m^2	UACR >177 µg/mg in women; >125 µg/mg in men	147/82		23 (32%) [23 (31%)]	RR 1.03[86] (0.64; 1.66)	nd
Dialysis, or doubling of S_{Cr} in patients with UACR ≥3.4 mg/mmol					637		nd	nd	nd	nd	nd	RR 0.5[87] (0.2; 1.2)	NS
Dialysis, or doubling of S_{Cr} in patients with eGFR <60 mL/min/1.73 m^2					1629							RR 0.6[88] (0.2; 1.3)	NS
First morbid event[89] with eGFR <60 mL/min/m^2	Val-HeFT 2009 Multi[10]	2 y (2 y)	Valsartan	Placebo	2890 (2890)		GFR 47 mL/min/m^2	Serum albumin 4.0 g/dL	nd	nd	499 (34%) [549 (38%)]	HR 0.86 (0.74; 0.99)	nd
Mortality													
All death in patients with S_{Cr} ≥1.4 mg/dL	HOPE 2001 Multi [58]	4 y (4 y)	Ramipril	Placebo	509 (509)	471 (471)	nd	UACR 0.73 mg/mmol	139/79 (141/79)	nd	13% [23%]	HR 0.59 (0.42; 0.83)	nd
All death in patients CrCl ≤65 mL/min					3394 (3394)						13% [17%]	HR 0.80 (0.67; 0.96)	nd

[85] Calculated by ERT
[86] Calculated by ERT
[87] Estimated from figure
[88] Estimated from figure
[89] Death sudden death with resuscitation, hospitalization for HF, administration of IV inotropic or vasodilator drugs for ≥4 h without hospitalization

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Total mortality in patients with eGFR <45 mL/min/m^2	PEACE 2006 2007 Multi[89;90]	Median 5 y (5 y)	Trandolapril	Placebo	157 (157)		S_{Cr} 1.6 mg/dL	nd	138/76	nd	13 (17%) [20 (26%)]	nd	nd
Total mortality in patients with eGFR 45-59.9 mL/min/m^2					1198 (1198)		S_{Cr} 1.3 mg/dL		135/77		56 (9%) [72 (12%)]	nd	nd
Total mortality in patients with eGFR<60 mL/min/m^2					1355 (1355)		eGFR<60	nd	nd	nd	69 (nd) [92 (nd)]	HR 0.73[90] (0.54; 1.00)	0.05
All-cause mortality in patients with low-medium microalbuminuria					332 (1498)	310 (1479)	S_{Cr} 1.05 mg/dL GFR 78 mL/min/m^2	UACR 25-177 µg/mg in women; 17-125 µg/mg in men	139/79	nd	37 (11%) [39 (13%)]	RR 0.89[91] (0.58; 1.35)	NS
All-cause mortality in patients with high microalbuminuria-macroalbuminuria					73 (1498)	75 (1479)	S_{Cr} 1.14 mg/dL GFR 75 mL/min/m^2	UACR >177 µg/mg in women; >125 µg/mg in men	147/82		8 (11%) [13 (17%)]	RR 0.63[92] (0.28; 1.44)	NS
Death in patients with eGFR <60 mL/min/m^2	Val-HeFT 2009 Multi[10]	2 y (2 y)	Valsartan	Placebo	2890 (2890)		GFR 47 mL/min/m^2	Serum albumin 4.0 g/dL	nd	nd	362 (25%) [341 (24%)]	HR 1.01 (0.85; 1.20)	NS
CV Mortality													
CV death in patients with S_{Cr} ≥1.4 mg/dL	HOPE 2001 Multi [58]	4 y (4 y)	Ramipril	Placebo	509 (509)	471 (471)	nd	UACR 0.73 mg/mmol	139/79 (141/79)	nd	9% [15%]	HR 0.59 (0.39; 0.91)	nd
CV death in patients CrCl ≤65 mL/min					3394 (3394)						8% [11%]	HR 0.67 (0.53; 0.85)	nd
CV mortality in patients with eGFR <45 mL/min/m^2	PEACE 2006 2007 Multi[89;90]	Median 5 y (5 y)	Trandolapril	Placebo	157 (157)		S_{Cr} 1.6 mg/dL	nd	138/76	nd	11 (14%) [14 (8%)]	--	nd

[90] Adjusted
[91] Calculated by ERT
[92] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
CV mortality in patients with eGFR 45-59.9 mL/min/m^2					1198 (1198)		S_{Cr} 1.3 mg/dL		135/77		28 (5%) [36 (6%)]	--	nd
CV death in patients with low-medium microalbuminuria					332 (1498)	310 (1479)	S_{Cr} 1.05 mg/dL GFR 78 mL/min/m^2	UACR 25-177 µg/mg in women; 17-125 µg/mg in men	139/79		17 (5%) [22 (7%)]	RR 0.72[93] (0.39; 1.33)	NS
CV death in patients with high microalbuminuria-macroalbuminuria					73 (1498)	75 (1479)	S_{Cr} 1.14 mg/dL GFR 75 mL/min/m^2	UACR >177 µg/mg in women; >125 µg/mg in men	147/82		3 (4%) [8 (11%)]	RR 0.39[94] (0.11; 1.40)	NS
CV Events													
CHD in entire subgroup with GFR <60 mL/min/1.73 m^2	ALLHAT 2006 Multi[50]	5 y (5 y)	Lisinopril	Chlorthalidone	1533 (1533)	2613 (2613)	GFR 50 mL/min/1.73 m^2	nd	nd	nd	184 (12%) [318 (12%)]	RR 1.00 (0.84; 1.20)	NS
CHD in DM subgroup with GFR <60 mL/min/1.73 m^2			Lisinopril		501 (501)	881 (881)	GFR 49 mL/min/1.73 m^2	nd	nd	nd	76 (15%) [132 (15%)]	RR 1.03 (0.78; 1.37)	NS
CHD in non-DM subgroup with GFR <60 mL/min/1.73 m^2			Lisinopril		1032 (1032)	1732 (1732)	GFR 49 mL/min/1.73 m^2	nd	nd	nd	108 (11%) [186 (11%)]	RR 1.00 (0.79; 1.26)	NS
MI in patients with $S_{Cr} \geq 1.4$ mg/dL	HOPE 2001 Multi [58]	4 y (4 y)	Ramipril	Placebo	509 (509)	471 (471)	nd	UACR 0.73 mg/mmol	139/79 (141/79)	nd	14% [19%]	HR 0.78 (0.54; 1.11)	NS
MI in patients CrCl ≤65 mL/min					3394 (3394)						11% [14%]	HR 0.74 (0.61; 0.91)	nd
Stroke in patients with $S_{Cr} \geq 1.4$ mg/dL					509 (509)	471 (471)					4% [6%]	HR 0.83 (0.44; 1.56)	NS
Stroke in patients CrCl ≤65 mL/min					3394 (3394)						4% [6%]	HR 0.69 (0.49; 0.91)	nd

[93] Calculated by ERT
[94] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
CV mortality or MI in patients with eGFR <45 mL/min/m^2	PEACE 2006 2007 Multi[89;90]	Median 5 y (5 y)	Trandolapril	Placebo	157 (157)		S_{Cr} 1.6 mg/dL	nd	138/76	nd	16 (20%) [19 (24%)]	nd	nd
CV mortality or MI in patients with eGFR 45-59.9 mL/min/m^2					1198 (1198)		S_{Cr} 1.3 mg/dL		135/77		67 (11%) [68 (11%)]	nd	nd
CV events	PREVEND IT 2004 Netherlands [12]	4 y (4 y)	Fosinopril	Placebo	nd	nd	nd	Albumin >50 mg/24h	nd	nd	5% [13%]	Relative risk reduction 60%	nd
ESRD													
Kidney failure in entire subgroup with GFR <60 mL/min/1.73 m^2	ALLHAT 2006 Multi[50]	5 y (5 y)	Lisinopril	Chlorthalidone	1533 (1533)	2613 (2613)	GFR 50 mL/min/1.73 m^2	nd	nd	nd	70 (5%) [124 (5%)]	RR 0.98 (0.73; 1.31)	NS
Kidney failure in DM subgroup with GFR <60 mL/min/1.73 m^2			Lisinopril		501 (501)	881 (881)	GFR 49 mL/min/1.73 m^2	nd	nd	nd	41 (8%) [68 (8%)]	RR 1.07 (0.73; 1.58)	NS
Kidney failure in non-DM subgroup with GFR <60 mL/min/1.73 m^2			Lisinopril		1032 (1032)	1732 (1732)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	29 (3%) [56 (3%)]	RR 0.88 (0.56; 1.38)	NS
Dialysis	HOPE 2003 Multi[59]	5 y (5 y)	Ramipril	Placebo	333 (333)		SCr 1.578 mg/dL	nd	In all patients, 144/80	nd	2 (nd) [1 (nd)]	--	nd
Kidney failure													
Newly developed renal insufficiency defined as SCr ≥1.4 mg/dL	HOPE 2003 Multi[59]	5 y (5 y)	Ramipril	Placebo	3,238 (3,577)		nd	nd	nd	nd	231 (nd) [243 (nd)]	--	NS
Doubling of Scr					333 (333)		SCr 1.578 mg/dL	nd	In all patients, 144/80	nd	3 (nd) [2 (nd)]	--	nd
Dialysis											2 (nd) [3 (nd)]	--	nd

Supplemental Table 7. Evidence profile of RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	4 RCTs [1˚ in 2 RCTs] (High)	1069 (539)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	Benefit for ACEI[95]	Critical
Mortality	4 RCTs (High)	1148 (582)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence for ACEI or ARB	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	4 RCTs (High)	1148 (582)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence for ACEI or ARB	Critical
ESRD	3 RCTs (High)	483 (243)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Moderate	Possible benefit for ACEI or ARB	Critical
Kidney function (categorical)	1 RCT (High)	131 (66)	Some limitations (-1)	N/A	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence for ACEI or ARB	Critical
∆Kidney function (continuous)	5 RCTs [1˚ in 1 RCT] (High)	803 (404)	No limitations (0)	Important inconsistencies (-1)	Uncertainty about directness (-1)	None (0)	Low	Possible benefit for ACEI[96]	Moderate
Proteinuria (categorical)	1 RCTs (High)	179 (92)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Moderate	Benefit for ACEI	High
Proteinuria (continuous)	4 RCTs (High)	1069 (539)	No limitations (0)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Moderate	Benefit for ACEI and ARB	Moderate
Adverse events	6 RCTs	1458 (746)						Drug discontinuation: 1-17% for ACEI or ARB and 1-14% for placebo (from 5 RCTs) Hyperkalemia: 0-2% for ACEI or ARB and 0-1% for Placebo (from 5 RCTs) Early rise in creatinine: 0-6% in ACEI and ARB and 0-4% in Placebo (from 4 RCTs)	Moderate
Total	6 RCTs	1458 (746)							

Balance of potential benefits and harms	**Quality of overall evidence**
No benefit in individuals with no or little proteinuria from the lower target. Possible benefit from lower target in individuals with proteinuria above 0.3-1 g/d. Insufficient evidence for CV outcomes	High for no proteinuria Moderate for proteinuria 0.3-1 g/d Moderate for CV outcomes

[95] Insufficient evidence for ARB in the Li study in IgA nephropathy, but trend to benefit.
[96] Insufficient evidence for ARB in the Li study in IgA nephropathy, but trend to benefit.

Supplemental Table 8. RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD without DM [categorical outcomes] [97]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Doubling of S_{Cr} or the need for dialysis	Maschio 1996 Multi[66]	3 y (3 y)	Benazpril	Placebo	300 (300)	283 (283)	S_{Cr} 2.1 mg/dL	UPE 1.8 g/d	142/87 (144/88)	137/85 (145/87)[98]	31 (10%) [57 (20%)][99]	RR 0.51[100] (0.34; 0.77)	<0.001	Good
Doubling of S_{Cr}, ESRD, or death	Hou 2006[101] China[43]	3 y (3 y)	Benazepril (S_{Cr} 3.0-5 mg/dL)	Placebo	112 (112)	112 (112)	GFR 26 mL/min/1.73 m^2 S_{Cr} 4.0 mg/dL	UPE 1.6 g/d	153/87 (152/85)	126/75[102] (126/75)	44 (41%)[103] [65 (60%)]	RR 0.68[104] (0.51; 0.89)	0.004	Good
Doubling of S_{Cr} or ESRD	GISEN 1997 Italy[2]	3 y (3 y)	Ramipril	Placebo	78 (78)	88 (88)	GFR 40 mL/min/1.73 m^2	UPE 5.6 g/24h	150/92 (150/91)	144/88 (145/90)	18 (23%) [40 (45%)]	RR 0.51[105] (0.32; 0.81)	0.004	Good
ESRD & doubling S_{Cr}	HVKIN 2006[106] Hong Kong[53]	2 y (2 y)	Valsartan	Placebo	49 (54)	47 (55)	GFR 78 mL/min/1.73 m^2	2.3 g/d	137/83 (136/81)	MAP 92.7 (100.9)	1 (2%)[107] [4 (8%)]	RR 0.24[108] (0.03; 2.07)	NS	Good
Mortality														
Death	Maschio 1996 Multi[66]	3 y (3 y)	Benazpril	Placebo	300 (300)	283 (283)	S_{Cr} 2.1 mg/dL	UPE 1.8 g/d	142/87 (144/88)	137/85 (145/87)[109]	8 (3%) [1 (0.4%)]	RR 7.55[110] (0.95; 59.96)	nd[111]	Good

[97] Shaded studies were included in previous KDOQI guideline
[98] Estimated from graph
[99] Benefit of ramipril only statistically significant in people with 24 hour urine protein excretion ≥3g
[100] Calculated by ERT
[101] All Chinese patients
[102] Estimated from graph
[103] Primary outcome
[104] Calculated by ERT
[105] Calculated by ERT
[106] All Chinese patients
[107] Primary outcome
[108] Calculated by ERT
[109] Estimated from graph
[110] Calculated by ERT
[111] The death rates in the benazepril group and placebo groups were 1 death per 93 patient-years and 1 per 656 patient-years, respectively (P=0.04)."

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Death	Hou 2006[112] China[43]	3 y (3 y)	Benazepril (S_{Cr} 3.0-5 mg/dL)	Placebo	112 (112)	112 (112)	GFR 26 mL/min/1.73 m^2 S_{Cr} 4.0 mg/dL	UPE 1.6 g/d	153/87 (152/85)	126/75[113] (126/75)	1 (1%) [0 (0%)]	--	nd	Good
Death	Ruggenenti 1999 Italy[84]	2.5 y (2.5 y)	Ramipril	Placebo	92 (99)	83 (87)	GFR 50 mL/min/1.73 m^2	UPE 1.7 g/d	142/89 (145/90)	nd	1 (0.01%) [0 (0%)]	--	nd	Good
Death	GISEN 1997 Italy[2]	3 y (3 y)	Ramipril	Placebo	78 (78)	88 (88)	GFR 40 mL/min/1.73 m^2	UPE 5.6 g/24h	150/92 (150/91)	144/88 (145/90)	2 (3%) [1 (1%)]	RR 2.26[114] (0.21; 24.41)	nd	Good
CV events														
Non-fatal CV events (Composite)	Maschio 1996 Multi[66]	3 y (3 y)	Benazpril	Placebo	300 (300)	283 (283)	S_{Cr} 2.1 mg/dL	UPE 1.8 g/d	142/87 (144/88)	137/85 (145/87)[115]	9 (0.03%) [14 (0.05%)]	RR 0.61[116] (0.27; 1.38)	nd	Good
MI											2 (1%) [2 (1%)]	RR 0.94[117] (0.13; 6.65)	nd	Good
Stroke											2 (1%) [3 (1%)]	RR 0.63[118] (0.11; 3.74)	nd	Good
Transient ischemic attack											1 (0.3%) [1 (0.4%)]	RR 0.94[119] (0.06; 15.01)	nd	Good
Angina											1 (0.3%) [1 (0.4%)]	RR 0.94[120] (0.06; 15.01)	nd	Good
Hypertensive crisis											0 (0%) [4 (1%)]	--	nd	Good
Hypotension or dizziness											3 (1%) [3 (1%)]	RR 0.94[121] (0.19; 4.64)	nd	Good

[112] All Chinese patients
[113] Estimated from graph
[114] Calculated by ERT
[115] Estimated from graph
[116] Calculated by ERT
[117] Calculated by ERT
[118] Calculated by ERT
[119] Calculated by ERT
[120] Calculated by ERT
[121] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
MI	Hou 2006[122] China[43]	3 y (3 y)	Benazepril (S_{Cr} 3.0-5 mg/dL)	Placebo	112 (112)	112 (112)	GFR 26 mL/min/1.73 m^2 S_{Cr} 4.0 mg/dL	UPE 1.6 g/d	153/87 (152/85)	126/75[123] (126/75)	5 (4%) [8 (7%)]	RR 0.63[124] (0.21; 1.85)	nd	Good
Heart failure											3 (3%) [5 (4%)]	RR 0.60[125] (0.15; 2.45)	nd	Good
Stroke											2 (2%) [3 (3%)]	RR 0.67[126] (0.11; 3.91)	nd	Good
Atrial fibrillation	Ruggenenti 1999 Italy[84]	Median 2.5 y (2.5 y)	Ramipril	Placebo	92 (99)	83 (87)	GFR 50 mL/min/1.73 m^2	UPE 1.7 g/d	142/89 (145/90)	nd	1 (0.01%) [0 (0%)]	--	nd	Good
Heart failure											0 (0%) [2 (0.2%)]	--	nd	Good
Stroke											1 (0.01%) [0 (0%)]	--	nd	Good
Uncontrolled hypertension											0 (0%) [1 (0.01%)]	--	nd	Good
Non-fatal CV events (Composite)	GISEN 1997 Italy[2]	3 y (3 y)	Ramipril	Placebo	78 (78)	88 (88)	GFR 40 mL/min/1.73 m^2	UPE 5.6 g/24h	150/92 (150/91)	144/88 (145/90)	4 (5%) [3 (3%)]	RR 1.50[127] (0.35; 6.51)	nd	Good
MI											1 (0.1%) [1 (0.01%)]	RR 1.13[128] (0.07; 17.74)	nd	Good
Aortic aneurysm											1 (0.1%) [0 (0%)]	--	nd	Good
Uncontrolled hypertension											2 (0.03%) [2 (0.02%)]	RR 1.13[129] (0.16; 7.82)	nd	Good
ESRD														
Need for dialysis	Ruggenenti 1999 Italy[84]	Median 2.5 y (2.5 y)	Ramipril	Placebo	99 (99)	87 (87)	GFR 50 mL/min/1.73 m^2	UPE 1.7 g/d	142/89 (145/90)	nd	9 (9%) [18 (20%)]	RR 0.44[130] (0.21; 0.93)	0.01	Good

[122] All Chinese patients
[123] Estimated from graph
[124] Calculated by ERT
[125] Calculated by ERT
[126] Calculated by ERT
[127] Calculated by ERT
[128] Calculated by ERT
[129] Calculated by ERT
[130] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Need for dialysis	GISEN 1997 Italy[2]	3 y (3 y)	Ramipril	Placebo	78 (78)	88 (88)	GFR 40 mL/min/1.73 m^2	UPE 5.6 g/24h	150/92 (150/91)	144/88 (145/90)	17 (21%) [29 (33%)]	RR 0.66[131] (0.40; 1.11)	NS	Good
Need for dialysis	Cinotti 2001 Italy[26]	23 mo (24 mo)	Lisinopril	Conventional anti-HTN therapy	66 (66)	65 (65)	GFR 36 mL/min/1.73 m^2 S_{Cr} 2.27 mg/dL	UPE 0.35 mg/min	141/85 (142/86)	139/83[132] (137/82)	2 (3%) [5 (8%)]	RR 0.39[133] (0.08; 1.96)	nd	Fair
Kidney function														
Halving of GFR	Cinotti 2001 Italy[26]	23 mo (24 mo)	Lisinopril	Conventional anti-HTN therapy	66 (66)	65 (65)	GFR 36 mL/min/1.73 m^2 S_{Cr} 2.27 mg/dL	UPE 0.35 mg/min	141/85 (142/86)	139/83[134] (137/82)	3 (5%) [7 (11%)]	RR 0.42[135] (0.11; 1.56)	nd	Fair
Proteinuria														
UPE ≥3g/24h	Ruggenenti 1999 Italy[84]	Median 2.5 y (2.5 y)	Ramipril	Placebo	92 (99)	87 (87)	GFR 50 mL/min/1.73 m^2	UPE 1.7 g/d	142/89 (145/90)	nd	15 (15%) [27 (31%)]	RR 0.53[136] (0.30; 0.92)	0.005	Good

[131] Calculated by ERT
[132] Estimated from graph
[133] Calculated by ERT
[134] Estimated from graph
[135] Calculated by ERT
[136] Calculated by ERT

Supplemental Table 9. RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD without DM [continuous outcomes] [137]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
Median slope of ↓1/S_{Cr}, dL/mg/y	Hou 2006[138] China[43]	3 y (3 y)	Benazepril (S_{Cr} 3.0-5 mg/dL)	Placebo	112 (112)	112 (112)	GFR 26 mL/min/1.73m^2 S_{Cr} 4.0 mg/dL	UPE 1.6 g/d	153/87 (152/85)	126/75[139] (126/75)	4.0 (3.9)	-0.09 (-0.11)	0.02	Good
Median slope of ↓eGFR, mL/min/1.73m^2 /y											26 (26)	6.8 (8.8)	0.006	Good
↓GFR, mL/min/1.73 m^2/mo	Ruggenenti 1999 Italy[84]	2.5 y (2.5 y)	Ramipril	Placebo	99 (99)	87 (87)	GFR 50 mL/min/1.73 m^2	UPE 1.7 g/d	142/89 (145/90)	nd	50 (43)	-0.26 (-0.29)	NS	Good
Mean rate of ↓GFR, mL/min/month	GISEN 1997 Italy[2]	3 y (3 y)	Ramipril	Placebo	78 (78)	88 (88)	GFR 40 mL/min/1.73 m^2	UPE 5.6 g/24h	150/92 (150/91)	144/88 (145/90)	40 (37)	-0.53 (-0.88)	0.03	Good
GFR, Δinulin clearance, mL/min/1.73m^2	Cinotti 2001 Italy[26]	23 mo (24 mo)	Lisinopril	Conventional anti-HTN therapy	66 (66)	65 (65)	GFR 36 mL/min/1.73m^2 S_{Cr} 2.27 mg/dL	UPE 0.35 mg/min	141/85 (142/86)	139/83[140] (137/82)	36[141] (35)	-1.31 (-6.71)	<0.04	Fair
Rate of ↓GFR, mL/min/1.73m^2	HVKIN 2006[142] Hong Kong[53]	2 y (2 y)	Valsartan	Placebo	49 (54)	47 (55)	GFR 78 mL/min/1.73 m^2	2.3 g/d	137/83 (136/81)	MAP 92.7 (100.9)	78 (87)	-13.54 (-9.08)	nd	Good
Proteinuria														
%ΔUPE, g/24h	Maschio 1996 Multi[66]	3 y (3 y)	Benazpril	Placebo	300 (300)	283 (283)	S_{Cr} 2.1 mg/dL	UPE 1.8 g/d	142/87 (144/88)	137/85 (145/87)[143]	1.8 (1.8)	-29% (+9%)	nd	Good

[137] Shaded studies were included in previous KDOQI guideline
[138] All Chinese patients
[139] Estimated from graph
[140] Estimated from graph
[141] Primary outcome
[142] All Chinese patients
[143] Estimated from graph

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Rate of ↓UPE	Hou 2006[144] China[43]	3 y (3 y)	Benazepril (S_{Cr} 3.0-5 mg/dL)	Placebo	112 (112)	112 (112)	GFR 26 mL/min/1.73m^2 S_{Cr} 4.0 mg/dL	UPE 1.6 g/d	153/87 (152/85)	126/75[145] (126/75)	1.6 (1.7)	52% (20%)	<0.001	Good
UPE, g/24h	GISEN 1997 Italy[2]	3 y (3 y)	Ramipril	Placebo	78 (78)	88 (88)	GFR 40 mL/min/1.73 m^2	UPE 5.6 g/24h	150/92 (150/91)	144/88 (145/90)	5.6 (5.1)	-55% (nd)[146]	0.002	Good
ΔProteinuria, g/d	HVKIN 2006[147] Hong Kong[53]	2 y (2 y)	Valsartan	Placebo	49 (54)	47 (55)	GFR 78 mL/min/1.73 m^2	2.3 g/d	137/83 (136/81)	MAP 92.7 (100.9)	2.3 (1.8)	-0.57 (-0.38)	nd	Good
%ΔProteinuria, g/d												-34 (+15)	<0.001	Good

[144] All Chinese patients
[145] Estimated from graph
[146] Placebo value not provided but stated as not being significantly different than baseline
[147] All Chinese patients

Supplemental Table 10. Evidence profile of RCTs examining the effect of ACEI or ARB vs. CCB in patients with CKD without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	3 RCTs[148] [1˚ in 1 RCT] (High)	1059 (646)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	Benefit for ACEI	Critical
Mortality	3 RCTs (High)	908 (569)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence for ACEI vs. CCB	Critical
CV mortality	2 RCTs (High)	801 (516)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence for ACEI vs. CCB	Critical
CV events	2 RCTs (High)	801 (516)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence for ACEI vs. CCB	Critical
ESRD	1 RCT (High)	653 (436)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit for ACEI	Critical
Kidney function (categorical)	1 RCT (High)	454 (309)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit for ACEI	High
∆Kidney function (continuous)	6 RCTs [1˚ in 2 RCTs] (High)	1356 (798)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Low	No benefit for ACEI in overall slope. Possible benefit after 3 months with ACEI.[149]	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	7 RCTs (High)	1463 (851)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Low	Benefit for ACEI or ARB	Moderate
Adverse events	6 RCTs	1343 (790)						Drug discontinuation: 16-38% for ACEI or ARB and 9-40% for CCB (from 4 RCTs) Hyperkalemia: 2-5% for ACEI or ARB and 0-6% for CCB (from 3 RCTs)	Moderate
Total	7 RCTs (High)	1463 (851)							

Balance of potential benefits and harms
Benefit for ACEI for kidney outcomes
Insufficient evidence for CV outcomes

Quality of overall evidence
Moderate for kidney outcomes
Low for CV outcomes

[148] AASK study includes death in composite outcome.
[149] Decision on chronic slope primarily based on AASK results.

Supplemental Table 11. RCTs examining the effect of ACEI or ARB vs. CCB in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
↓GFR 50% or 25 mL/min/1.73 m^2, ESRD or death	AASK 2001 2006[150] US[7;70]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	87 (27%) [56 (38%)]	Risk reduction 38% (13; 56)[151]	0.005	Good
↓GFR 50% or 25 mL/min/1.73 m^2 or ESRD											70 (22%) [43 (29%)]	Risk reduction 38% (10; 58)[152]	0.01	Good
ESRD or death											65 (20%) [45 (30%)]	Risk reduction 41% (14; 60)[153]	0.007	Good
First CV hospitalization and death											61 (14%) [23 (11%)]	HR 1.27 (0.78; 2.06)	NS	Good
First CV hospitalization or ESRD											113 (26%) [65 (30%)]	HR 0.73 (0.54; 1.00)	0.05	Good
↓GFR 50% or 25 mL/min/1.73 m^2, ESRD or death in sub-group with UPCR>0.22							nd	UPCR>0.22	nd	nd	nd	Risk reduction 48% (20; 66)	0.003	Poor

[150] Study only included African American patients
[151] Adjusted
[152] Adjusted
[153] Adjusted

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
RRT, D/C due to ↓renal function, ↓50% GFR, doubling of S_{Cr}, or hospitalization for transient renal failure	AVER 2008 EU[35]	3 y (3 y)	Enalapril	Amlodipine	130 (131)	128 (132)	S_{Cr} 2.05 mg/dL GFR 45 mL/min/1.73 m^2	UPE 1249 mg/24h	165/103 (165/102)	138/85 (138/84)	15% [21%]	nd	NS	Good
Doubling S_{Cr} and/or dialysis	ESPIRAL 2001 Spain[64]	3 y (3 y)	Fosinipril	Nifedipine GITS	80 (129)	68 (112)	S_{Cr} 2.8 mg/dL	1.7 g/24h	155/96 (158/96)	135/83 (144/81)	27 (21%)[154] [40 (46%)]	OR 0.47 (0.26; 0.84)	0.01	Fair
Mortality														
Death	AASK 2001[155] US[7]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	18 (4%) [13 (6%)]	Risk reduction 31% (-41; 66) [156]	NS	Good
All cause mortality	ESPIRAL 2001 Spain[64]	3 y (3 y)	Fosinipril	Nifedipine GITS	80 (129)	68 (112)	S_{Cr} 2.8 mg/dL	1.7 g/24h	155/96 (158/96)	135/83 (144/81)	4 (3%) [6 (5%)]	RR 0.57[157] (0.17; 1.93)	nd	Poor
Death	Nephros 2001 Multi[41]	2 y (nd)	Ramipril	Felodipine	53 (53)	54 (54)	GFR 44 mL/min/1.73 m^2 S_{Cr} 149 µmol/L	UA 506 mg/24h	154/99 (159/100)	134/85 (139/88)	0 (0%) [0 (0%)]	--	nd	Fair
CV mortality														
CV death	AASK 2006[158] US[70]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	12 (3%) [7 (3%)]	HR 0.90 (0.35; 2.30)	NS	Good
CV mortality	ESPIRAL 2001 Spain[64]	3 y (3 y)	Fosinipril	Nifedipine GITS	80 (129)	68 (112)	S_{Cr} 2.8 mg/dL	1.7 g/24h	155/96 (158/96)	135/83 (144/81)	2 (2%) [3 (3%)]	RR 0.57[159] (0.10; 3.29)	nd	Poor

[154] Primary outcome
[155] Study only included African American patients
[156] Adjusted
[157] Calculated by ERT
[158] Study only included African American patients
[159] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
CV events														
CV events	AASK 2006[160] US[70]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	89 (20%) [28 (13%)]	HR 1.49 (0.90; 2.45)	NS	Good
Stroke events											23 (5%) [9 (4%)]	RR 1.27[161] (0.60; 2.70)	nd	Good
CHF events											20 (5%) [8 (4%)]	RR 1.24[162] (0.56; 1.78)	nd	Good
CAD events											19 (4%) [5 (2%)]	RR 1.89[163] (0.72; 5.00)	nd	Good
CV events	ESPIRAL 2001 Spain[64]	3 y (3 y)	Fosinipril	Nifedipine GITS	80 (129)	68 (112)	S_{Cr} 2.8 mg/dL	1.7 g/24h	155/96 (158/96)	135/83 (144/81)	1 (1%) [0 (0%)]	--	nd	Poor
ESRD														
ESRD	AASK 2001[164] US[7]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	47 (15%) [32 (21%)]	Risk reduction 44% (13; 65)[165]	0.01	Good
Kidney function														
↓GFR 50% or 25 mL/min/1.73 m^2	AASK 2001[166] US[7]	4 y (≥3y)	Ramipril	Amlodipine	309 (436)	145 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	44 (14%) [29 (18%)]	Risk reduction 41% (5; 63)[167]	0.03	Good

[160] Study only included African American patients
[161] Calculated by ERT
[162] Calculated by ERT
[163] Calculated by ERT
[164] Study only included African American patients
[165] Adjusted
[166] Study only included African American patients
[167] Adjusted

Supplemental Table 12. RCTs examining the effect of ACEI or ARB vs. CCB in patients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
Acute slope – ΔGFR in first 3 mo, mL/min/1.73 m^2/y	AASK 2001 2002[168] US[7;99]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	46[169] (46.8)	-0.16[170] (+4.03)	<0.001	Good
Chronic slope – ΔGFR after first 3 mo, mL/min/1.73 m^2/y												-2.07 (-3.22)	0.002	Good
Difference in total mean GFR slope – over 4 y, mL/min/1.73 m^2/y												0.34[171] (0.41; 1.08)	NS	Good
Chronic slope – ΔGFR after first 3 mo, mL/min/1.73 m^2/y in sub-group with UPCR≤0.22		3 y (3 y)			nd	nd	nd	nd	nd	nd	nd	-1.22 (-2.02)	0.21	Poor
Chronic slope – ΔGFR after first 3 mo, mL/min/1.73 m^2/y in sub-group with UPCR>0.22												-3.55 (-5.92)	0.003	Poor

[168] Study only included African American patients
[169] Primary outcome
[170] Significant interactions of the treatment regimen with baseline proteinuria (P=0.001) and baseline GFR (P=0.006). Acute rise in GFR with amlodipine confined to people with UPCR ≤0.22.
[171] Significant interactions of the treatment regimen with baseline proteinuria (P<0.001) and baseline GFR (P=0.003). Higher proteinuria = More beneficial effect of ramipril.

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Total mean slope over 3y in sub-group with UPCR≤0.22												-1.02 (+0.20)	0.006	Poor
Total mean slope over 3y in sub-group with UPCR>0.22												-3.60 (-5.62)	0.006	Poor
ΔGFR, mL/min/1.73 m^2	AVER 2008 EU[35]	3 y (3 y)	Enalapril	Amlodipine	130 (131)	128 (132)	S_{Cr} 2.05 mg/dL GFR 45 mL/min/1.73 m^2	UPE 1249 mg/24h	165/103 (165/102)	138/85 (138/84)	45[172] (47)	-4.44 (-2.63)	nd	Good
ΔGFR, mL/min/1.73 m^2 (LOCF)												-3.98 (-4.92)	NS	Good
ΔS_{Cr}, mg/dL											2.05 (2.00)	+0.26 (+0.25)	nd	Good
ΔS_{Cr}, mg/dL (LOCF)												+0.47 (+0.57)	NS	Good
ΔGFR in patients with proteinuria >1g/d, mL/min/1.73 m^2 (LOCF)					70 (70)		nd	nd	nd	nd	nd	-12.41 (-6.62)	NS	Poor
ΔGFR in patients with proteinuria >1g/d, mL/min/1.73 m^2					70 (70)		nd	nd	nd	nd	nd	-13.54 (-4.25)	0.04	Poor
ΔS_{Cr}, mg/dL	ESPIRAL 2001 Spain[64]	3 y (3 y)	Fosinipril	Nifedipine GITS	80 (129)	68 (112)	S_{Cr} 2.8 mg/dL	1.7 g/24h	155/96 (158/96)	135/83 (144/81)	2.8 (2.9)	+0.75 (+1.25)[173]	0.03	Fair

[172] Primary outcome
[173] ERT estimated from graph

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
ΔGFR in patients with proteinuria between 1-3g/24h, mL/min/1.73 m^2	Peng 2009[174] China[76]	1 y (1 y)	Valsartan	Benidipine	61 (61)	59 (59)	GFR 51 mL/min/1.73 m^2	1.98 g/24h	150/95 (151/95)	126/76 (126/77)	51 (51)	+16.30 (+15.5)	nd	Poor
ΔGFR in patients with proteinuria >1g/24h, mL/min/1.73 m^2					57 (57)	59 (59)	GFR 52 mL/min/1.73 m^2	0.61 g/24h	150/97 (157/96)	128/78 (127/78)	52 (50)	+16 (+17.8)	nd	Poor
ΔS_{Cr}, mg/dL	JLIGHT 2004[175] Japan[44]	12 mo (12 mo)	Losartan	Amlodipine	47 (58)	40 (59)	S_{Cr} 2.04 mg/dL	2.85 g/d	156/94 (155/93)	140/83 (134/80)	2.04 (1.97)	+0.46 (+0.33)[176]	nd	Fair
ΔCrCl, mL/min											38 (41)	-6 (-4)[177]	nd	Fair
ΔS_{Cr}, mg/dL	Del Vecchio 2004 Italy[30]	48 wks (48 wks)	Enalapril	Manidipine	44 (69)	46 (67)	S_{Cr} 1.86 mg/dL CrCl 46 mL/min	1.37 g/24h	157/100 (155/100)	134/85 (138/86)	1.86 (2.00)	+0.13 (+0.09)	NS	Poor
Slope of 1/S_{Cr}											1.064 (0.720)	--	NS	Poor
ΔCrCl, mL/min											46.3 (42.9)	-1.9 (-3.7)	NS	Poor
Slope of CrCl											-0.003 (-0.005)	--	NS	Poor
Proteinuria														
ΔUPCR, (%)	AASK 2001[178] US[7]	4 y (≥3y)	Ramipril	Amlodipine	436 (436)	217 (217)	GFR 46 mL/min/1.73 m^2	UPCR Male 0.34 Female 0.32	151/96 (150/96)	135/82 (133/81)	Male 34; Female 0.32 (Male 0.30; Female 0.30)	-20% (+0.58%)	<0.001	Good
ΔUPE, mg/24h	AVER 2008 EU[35]	3 y (3 y)	Enalapril	Amlodipine	130 (131)	128 (132)	S_{Cr} 2.05 mg/dL GFR 45 mL/min/1.73 m^2	UPE 1249 mg/24h	165/103 (165/102)	138/85 (138/84)	1249 (1296)	-246 (-149)	nd	Fair
ΔUPE. mg/24h (LOCF)												-356 (-142)	nd	Fair

[174] All Chinese patients
[175] All Japanese patients
[176] ERT estimated from graph
[177] ERT estimated from graph
[178] Study only included African American patients

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
ΔProteinuria, g/24h	ESPIRAL 2001 Spain[64]	3 y (3 y)	Fosinipril	Nifedipine GITS	80 (129)	68 (112)	S_{Cr} 2.8 mg/dL	1.7 g/24h	155/96 (158/96)	135/83 (144/81)	1.7 (1.8)	-0.65 (0)[179]	<0.05	Fair
ΔProteinuria in patients with proteinuria between 1-3g/24h, g/24h	Peng 2009[180] China[76]	1 y (1 y)	Valsartan	Benidipine	61 (61)	59 (59)	GFR 51 mL/min/1.73 m^2	1.98 g/24h	150/95 (151/95)	126/76 (126/77)	1.98 (2.01)	-1.19 (-0.82)	NS	Poor
ΔProteinuria in patients with proteinuria <1g/24h, g/24h					57 (57)	59 (59)	GFR 52 mL/min/1.73 m^2	0.61 g/24h	150/97 (157/96)	128/78 (127/78)	0.61 (0.59)	-0.43 (-0.29)	<0.01	Poor
UAE (statistical analysis of transformed values)	Nephros 2001 Multi [41]	2 y (nd)	Ramipril	Felodipine	53 (53)	54 (54)	GFR 44 mL/min/1.73 m^2 S_{Cr} 149 µmol/L	UA 506 mg/24h	154/99 (159/100)	134/85 (139/88)	506 (365)	-0.103 (+0.137)	nd	Fair
ΔProteinuria, g/24h	Del Vecchio 2004 Italy[30]	48 wks (48 wks)	Enalapril	Manidipine	44 (69)	46 (67)	S_{Cr} 1.86 mg/dL CrCl 46 mL/min	1.37 g/24h	157/100 (155/100)	134/85 (138/86)	1.37 (1.6)	-0.37 (+0.02)	<0.05	Poor
%Δ Proteinuria, g/d	JLIGHT 2004[181] Japan[44]	12 mo (12 mo)	Losartan	Amlodipine	47 (58)	40 (59)	S_{Cr} 2.04 mg/dL	2.85 g/d	156/94 (155/93)	140/83 (134/80)	2.85 (2.50)	-35.8% (+1%)[182]	nd	Fair

[179] ERT estimated from graph
[180] All Chinese patients
[181] All Japanese patients
[182] ERT estimated from graph

Supplemental Table 13. Evidence profile of RCTs examining the effect of ACEI vs. ARB in patients with CKD without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	1 RCT [1˚ in 1 RCT] (High)	343 (168)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence	Critical
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	1 RCT (High)	343 (168)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence	Critical
ESRD	1 RCT (High)	207 (101)	Some limitations (-1)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	Critical
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
∆Kidney function (continuous)	1 RCT (High)	207 (101)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Very low	No difference	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	3 RCTs [1˚ in 1 RCT] (High)	632 (309)	No limitations (0)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Moderate	No difference	Moderate
Adverse events	3 RCTs	632 (309)						Drug discontinuation: 4-9% for ACE and 3-7% for ARB (from 3 RCTs) Hyperkalemia: 2-6% for ACEI and 2-6% for ARB (from 2 RCTs) Early rise in creatinine: 2-3% in ACEI and 3% in ARB (from 1 RCT)	Moderate
Total	3 RCTs	632 (309)							

Balance of potential benefits and harms
Insufficient evidence for kidney and CV outcomes

Quality of overall evidence
Low for kidney outcomes
Low for CV outcomes

Supplemental Table 14. RCTs examining the effect of ACEI vs. ARB in patient with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Doubling of S_{Cr}, ESRD, or death	Hou 2007[183] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Losartan [200 mg/d titrated]	84 (84)	87 (87)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	150/86 (152/86)	124/76 (124/76)[184]	15 (18%)[185] [13 (16%)]	RR 1.20[186] (0.61; 2.36)	NS	Good
			Benazepril [10 mg/d fixed]	Losartan [50 mg/d fixed]	84 (84)	88 (88)	eGFR 31 mL/min/1.73 m^2	UPE 1.4 g/d	151/86 (150/86)	124/76 (124/76) [187]	26 (31%)[188] [26 (30%)]	RR 1.05[189] (0.67; 1.65)	NS	Good
CV events														
CV events	Hou 2007[190] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Losartan [200 mg/d titrated]	84 (84)	87 (87)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	150/86 (152/86)	124/76 (124/76)[191]	10 (11%) [8 (9%)]	RR 1.29[192] (0.54; 3.12)	nd	Good
			Benazepril [10 mg/d fixed]	Losartan [50 mg/d fixed]	84 (84)	88 (88)	eGFR 31 mL/min/1.73 m^2	UPE 1.4 g/d	151/86 (150/86)	124/76 (124/76) [193]	[8 (9%)] [10 (11%)]	RR 0.84[194] (0.35; 2.02)	nd	Good
ESRD														
ESRF	Woo 2009 Singapore [98]	6 y (6 y)	Enalapril 20mg/d	Losartan 200mg/d	61 (69)	63 (67)	eGFR 62 mL/min/y	UPE 2.2 g/d	134/83 (132/84)	129/83 (128/83)	19 (31%) [7 (11%)]	RR 2.08[195] (1.27; 6.19)	nd	Fair
			Enalapril 10mg/d	Losartan 200mg/d	40 (45)		eGFR 61 mL/min/y	UPE 2.3 g/d	132/86 (132/84)	130/84 (128/83)	9 (23%) [7 (11%)]	RR 2.03[196] (0.82; 5.00)	NS	Fair
			Enalapril 20mg/d	Losartan 100mg/d	61 (69)	43 (45)	eGFR 62 mL/min/y	UPE 2.2 g/d	134/83 (132/84)	129/83 (128/84)	19 (31%) [9 (20%)]	RR 1.49[197] (0.75; 42.97)	NS	Fair
			Enalapril 10mg/d	Losartan 100mg/d	40 (45)		eGFR 61 mL/min/y	UPE 2.3 g/d	132/86 (132/84)	130/84 (128/84)	9 (25%) [9 (20%)]	RR 1.08[198] (0.47; 2.43)	NS	Fair

[183] All Chinese patients
[184] Estimated from graph
[185] Primary outcome
[186] Calculated by ERT
[187] Estimated from graph
[188] Primary outcome
[189] Calculated by ERT
[190] All Chinese patients
[191] Estimated from graph
[192] Calculated by ERT
[193] Estimated from graph
[194] Calculated by ERT
[195] Calculated by ERT
[196] Calculated by ERT
[197] Calculated by ERT
[198] Calculated by ERT

Supplemental Table 15. RCTs examining the effect of ACEI vs. ARB in patient with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
ΔeGFR, mL/min/y	Woo 2009 Singapore [98]	6 y (6 y)	Enalapril 20mg/d	Losartan 200mg/d	61 (69)	63 (67)	eGFR 62 mL/min/y	UPE 2.2 g/d	134/83 (132/84)	129/83 (128/83)	62 (64)	-3.5 (-0.7)	nd	Fair
			Enalapril 10mg/d		40 (45)		eGFR 61 mL/min/y	UPE 2.3 g/d	132/86 (132/84)	130/84 (128/83)	61 (64)	-3.2 (-0.7)	nd	Fair
			Enalapril 20mg/d	Losartan 100mg/d	61 (69)	43 (45)	eGFR 62 mL/min/y	UPE 2.2 g/d	134/83 (132/84)	129/83 (128/84)	62 (61)	-3.5 (-3.5)	nd	Fair
			Enalapril 10mg/d		40 (45)		eGFR 61 mL/min/y	UPE 2.3 g/d	132/86 (132/84)	130/84 (128/84)	61 (61)	-3.2 (-3.5)	nd	Fair
Proteinuria														
%ΔProteinuria, g/d	Hou 2007[199] China [42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Losartan [200 mg/d titrated]	84 (84)	87 (87)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	150/86 (152/86)	124/76 (124/76)[200]	2.1 (2.0)	50% (53%)	NS	Good
			Benazepril [10 mg/d fixed]	Losartan [50 mg/d fixed]	84 (84)	88 (88)	eGFR 30.6 mL/min/1.73 m^2	UPE 1.4 g/d	151/86 (150/86)	124/76 (124/76) [201]	1.4 (1.6)	38% (41%)	NS	Good
ΔUPE, g/d	Woo 2009 Singapore [98]	6 y (6 y)	Enalapril 20mg/d	Losartan 200mg/d	61 (69)	63 (67)	eGFR 62 mL/min/y	UPE 2.2 g/d	134/83 (132/84)	129/83 (128/83)	2.2 (2.2)	-0.5 (-1)	nd	Fair
			Enalapril 10mg/d		40 (45)		eGFR 61 mL/min/y	UPE 2.3 g/d	132/86 (132/84)	130/84 (128/83)	2.3 (2.2)	-0.6 (-1)	nd	Fair
			Enalapril 20mg/d	Losartan 100mg/d	61 (69)	43 (45)	eGFR 62 mL/min/y	UPE 2.2 g/d	134/83 (132/84)	129/83 (128/84)	2.2 (2.0)	-0.5 (-0.4)	nd	Fair
			Enalapril 10mg/d		40 (45)		eGFR 61 mL/min/y	UPE 2.3 g/d	132/86 (132/84)	130/84 (128/84)	2.3 (2.0)	-0.6 (-0.4)	nd	Fair
↓UACR, mg/mmol	Menne 2008 Multi[67]	30 wks (30 wks)	Lisinopril	Valsartan	40 (43)	42 (43)	CrCl 105 mg/mL	UACR 9.6 mg/mmol	153/91 (153/92)	139/79 (137/81)	9.6[202] (9.1)	Geometric mean -41% (-51%)	NS	Good

[199] All Chinese patients
[200] Estimated from graph
[201] Estimated from graph
[202] Primary outcome

Supplemental Table 16. Evidence profile of RCTs examining the effect of high vs. low dose ACEI in patients with CKD without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	1 RCT [1˚ in 1 RCT] (High)	168 (84)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit for high doses of ACEI	Critical
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	1 RCT (High)	168 (84)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence	Critical
ESRD	2 RCTs (High)	269 (145)	No limitations (0)	Important inconsistencies (-1)	Direct (0)	Sparse (-1)	Low	Possible benefit	Critical
Kidney function (categorical)	1 RCT (High)	168 (84)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit for higher doses of ACEI	High
∆Kidney function (continuous)	2 RCTs (High)	269 (145)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	Sparse (-1)	Very low	Possible benefit for higher dose ACEI	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	2 RCTs (High)	269 (145)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	Sparse (-1)	Very low	Possible benefit for higher dose ACEI	Moderate
Adverse events	2 RCTs	269 (145)						Drug discontinuation: 6-7% vs. 4% for ACEI (from 2 RCTs) Hyperkalemia: 4% vs. 0% for ACEI (from 1 RCT) Early rise in creatinine: 3% vs. 2% in ACEI (from 1 RCT)	Moderate
Total	2 RCTs	269 (145)							

Balance of potential benefits and harms
Possible benefit for kidney outcomes in higher dose ACEI
Insufficient evidence for CV outcomes

Quality of overall evidence
Low for kidney outcomes
Low for CV outcomes

Supplemental Table 17. RCTs examining the effect of high dose ACEI vs. low dose ACEI in patient with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Doubling of S_{Cr}, ESRD, or death	Hou 2007[203] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Benazepril [10 mg/d fixed]	84 (84)	84 (84)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	149/86 (151/86)	124/76 (124/76)[204]	15 (18%)[205] [26 (31%)]	Risk reduction 51% (4.8; 73.3)	0.028	Good
CV events														
CV events	Hou 2007[206] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Benazepril [10 mg/d fixed]	84 (84)	84 (84)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	149/86 (151/86)	124/76 (124/76)[207]	10 (11%) [8 (9%)]	RR 1.25[208] (0.52; 3.01)	nd	Good
ESRD														
ESRD	Hou 2007[209] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Benazepril [10 mg/d fixed]	84 (84)	84 (84)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	149/86 (151/86)	124/76 (124/76)[210]	nd	Risk reduction 47% (4.2; 72.1)	0.04	Good
ESRD (CKD Stage 5, eGFR <15 mL/min)	Woo 2009[211] Singapore [98]	6 y (6 y)	Enalapril [20 mg/d]	Enalapril [10 mg/d]	61 (69)	40 (43)	eGFR 62 mL/min	UPE 2.2 g/d	134/83 (132/86)	129/83 (130/84)	19 (31%) [9 (23%)]	RR 1.38[212] (0.70; 2.75)	NS (0.09)	Fair
Kidney function														
Doubling of S_{Cr}	Hou 2007[213] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Benazepril [10 mg/d fixed]	84 (84)	84 (84)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	149/86 (151/86)	124/76 (124/76)[214]	nd	Risk reduction 49%	0.04	Good

[203] All Chinese patients
[204] Estimated from graph
[205] Primary outcome
[206] All Chinese patients
[207] Estimated from graph
[208] Calculated by ERT
[209] All Chinese patients
[210] Estimated from graph
[211] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
[212] Calculated by ERT
[213] All Chinese patients
[214] Estimated from graph

Supplemental Table 18. RCTs examining the effect of high dose ACEI vs. low dose ACEI in patient with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
%↓CrCl	Hou 2007[215] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Benazepril [10 mg/d fixed]	84 (84)	84 (84)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	149/86 (151/86)	124/76 (124/76)[216]	35 (34)	60% reduction in high vs. low dose ACE	0.02	Fair
ΔeGFR, mL/min	Woo 2009[217] Singapore [98]	6 y (6 y)	Enalapril [20 mg/d]	Enalapril [10 mg/d]	61 (69)	40 (43)	eGFR 62 mL/min	UPE 2.2 g/d	134/83 (132/86)	129/83 (130/84)	62 (61)	-3.5 (-3.2)	nd	Fair
Proteinuria														
%ΔProteinuria	Hou 2007[218] China[42]	3 y (3 y)	Benazepril [40 mg/d titrated]	Benazepril [10 mg/d fixed]	84 (84)	84 (84)	eGFR 31 mL/min/1.73 m^2	UPE 2.1 g/d	149/86 (151/86)	124/76 (124/76)[219]	2.1 (1.4)	50% [38%)	<0.05	Good
ΔUPE, g/d	Woo 2009[220] Singapore [98]	6 y (6 y)	Enalapril [20 mg/d]	Enalapril [10 mg/d]	61 (69)	40 (43)	eGFR 62 mL/min	UPE 2.2 g/d	134/83 (132/86)	129/83 (130/84)	2.2 (2.3)	-0.5 (-0.6)	nd	Fair

[215] All Chinese patients
[216] Estimated from graph
[217] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
[218] All Chinese patients
[219] Estimated from graph
[220] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)

Supplemental Table 19. Evidence profile of RCTs examining the effect of high vs. low dose ARB in patients with CKD without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	1 RCT [1˚ in 1 RCT] (High)	175 (87)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit in high doses of ARB	Critical
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	1 RCT (High)	175 (87)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence	Critical
ESRD	2 RCTs (High)	281 (150)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Moderate	Possible benefit in high doses of ARB	Critical
Kidney function (categorical)	1 RCT (High)	175 (87)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit in high doses of ARB	High
∆Kidney function (continuous)	3 RCTs (High)	608 (317)	No limitations (0)	Important inconsistencies (-1)	Uncertainty about directness (-1)	None (0)	Low	Possible benefit for higher dose ARB	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	3 RCTs [1˚ in 1 RCT] (High)	608 (317)	No limitations (0)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Moderate	Benefit for higher dose ARB	Moderate
Adverse events	3 RCTs	608 (317)						Drug discontinuation: 3-11% vs. 3-15% for ARB (from 3 RCTs) Hyperkalemia: 6% vs. 3% for ARB (from 1 RCT) Early rise in creatinine: 3% vs. 3% for ARB (from 1 RCT)	Moderate
Total	3 RCTs	608 (317)							

Balance of potential benefits and harms
Possible benefit for kidney outcomes with higher dose ARB arm
Insufficient evidence for CV outcomes

Quality of overall evidence
Moderate for kidney outcomes
Low for CV outcomes

Supplemental Table 20. RCTs examining the effect of high dose ARB vs. low dose ARB in patient with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Doubling of S_{Cr}, ESRD, or death	Hou 2007[221] China[42]	3 y (3 y)	Losartan [200 mg/d titrated]	Losartan [50 mg/d fixed]	87 (87)	88 (88)	eGFR 30 mL/min/1.73 m^2	UPE 2.0 g/d	152/86 (149/86)	124/76 (124/76)[222]	13 (16%)[223] [26 (30%)]	Risk reduction 53% (5.5; 74.1)	0.022	Good
CV events														
CV events	Hou 2007[224] China[42]	3 y (3 y)	Losartan [200 mg/d titrated]	Losartan [50 mg/d fixed]	87 (87)	88 (88)	eGFR 30 mL/min/1.73 m^2	UPE 2.0 g/d	152/86 (149/86)	124/76 (124/76)[225]	8 (9%) [10 (11%)]	RR 0.81[226] (0.34; 1.95)	nd	Good
ESRD														
ESRD	Hou 2007[227] China[42]	3 y (3 y)	Losartan [200 mg/d titrated]	Losartan [50 mg/d fixed]	87 (87)	88 (88)	eGFR 30 mL/min/1.73 m^2	UPE 2.0 g/d	152/86 (149/86)	124/76 (124/76)[228]	nd	Risk reduction 47% (3.6; 76.9)	0.05	Good
ESRD	Woo 2009[229] Singapore [98]	6 y (6 y)	Losartan [200 mg/d]	Losartan [100 mg/d]	63 (67)	43 (45)	eGFR 64 mL/min	UPE 2.2 g/d	132/84 (132/85)	128/83 (128/84)	7 (11%) [9 (20%)]	RR 0.53[230] (0.21; 1.32)	nd	Fair
Kidney function														
Doubling of S_{Cr}	Hou 2007[231] China[42]	3 y (3 y)	Losartan [200 mg/d titrated]	Losartan [50 mg/d fixed]	87 (87)	88 (88)	eGFR 30 mL/min/1.73 m^2	UPE 2.0 g/d	152/86 (149/86)	124/76 (124/76)[232]	nd	Risk reduction 50% (CI nd)	0.04	Good

[221] All Chinese patients
[222] Estimated from graph
[223] Primary outcome
[224] All Chinese patients
[225] Estimated from graph
[226] Calculated by ERT
[227] All Chinese patients
[228] Estimated from graph
[229] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
[230] Calculated by ERT
[231] All Chinese patients
[232] Estimated from graph

Supplemental Table 21. RCTs examining the effect of high dose ARB vs. low dose ARB in patient with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
%↓CrCl	Hou 2007[233] China[42]	3 y (3 y)	Losartan [200 mg/d titrated]	Losartan [50 mg/d fixed]	87 (87)	88 (88)	eGFR 30 mL/min/1.73 m^2	UPE 2.0 g/d	152/86 (149/86)	124/76 (124/76)[234]	34 (34)	55% reduction in intervention group compared to control group	0.04	Fair
%ΔeGFR, mL/min/1.73 m^2	SMART 2009 Canada[22]	30 wk (30 wk)	Candesartan [64 mg]	Candesartan [16 mg]	84 (90)	72 (90)	eGFR 55 mL/min/1.73 m^2	24h urinary protein 2.83 g/d	133/79 (133/77)	132/77 (133/75)	55 (52)	-10 (-9)	NS	Good
			Candesartan [128 mg]	Candesartan [16 mg]	75 (89)	72 (90)	eGFR 49 mL/min/1.73 m^2	24h urine protein 2.85 g/d	132/77 (133/77)	130/76 (133/75)	49 (52)	-8 (-9)	NS	Good
			Candesartan [128 mg]	Candesartan [64mg]	83 (89)	88 (90)	eGFR 49 mL/min/1.73 m^2	24h urine protein 2.85 g/d	132/77 (133/79)	130/76 (132/77)	49 (55)	-8 (-10)	nd	Fair
%ΔS_{Cr}, μmol/L			Candesartan [64 mg]	Candesartan [16 mg]	84 (90)	72 (90)	eGFR 55 mL/min/1.73 m^2	24h urinary protein 2.83 g/d	133/79 (133/77)	132/77 (133/75)	119 (127)	+9 (+8)	NS	Good
			Candesartan [128 mg]	Candesartan [16 mg]	75 (89)	72 (90)	eGFR 49 mL/min/1.73 m^2	24h urine protein 2.85 g/d	132/77 (133/77)	130/76 (133/75)	135 (127)	+7 (+8)	NS	Good
			Candesartan [128 mg]	Candesartan [64mg]	83 (89)	88 (90)	eGFR 49 mL/min/1.73 m^2	24h urine protein 2.85 g/d	132/77 (133/79)	130/76 (132/77)	135 (119)	+7 (9)	nd	Fair
ΔeGFR, mL/min/y	Woo 2009[235] Singapore [98]	6 y (6 y)	Losartan [200 mg/d]	Losartan [100 mg/d]	63 (67)	43 (45)	eGFR 64 mL/min	UPE 2.2 g/d	132/84 (132/85)	128/83 (128/84)	64 (61)	-0.7 (-3.5)	nd	Fair
Proteinuria														

[233] All Chinese patients
[234] Estimated from graph
[235] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
%ΔProteinuria , g/d	Hou 2007[236] China[42]	3 y (3 y)	Losartan [200 mg/d titrated]	Losartan [50 mg/d fixed]	87 (87)	88 (88)	eGFR 30 mL/min/1.73 m^2	UPE 2.0 g/d	152/86 (149/86)	124/76 (124/76)[237]	2.0 (1.6)	53% (41%)	<0.05	Good
Δ24h urine protein, g/d	SMART 2009 Canada[22]	30 wk (30 wk)	Candesartan [64 mg]	Candesartan [16 mg]	84 (90)	72 (90)	eGFR 55 mL/min/1.73 m^2	24h urinary protein 2.83 g/d	133/79 (133/77)	132/77 (133/75)	2.83[238] (2.80)	-22.23 (-7.49)	0.0492	Good
			Candesartan [128 mg]	Candesartan [16 mg]	75 (89)	72 (90)	eGFR 49 mL/min/1.73 m^2	24h urine protein 2.85 g/d	132/77 (133/77)	130/76 (133/75)	2.85[239] (2.80)	-36.95 (-7.49)	<0.0001	Good
			Candesartan [128 mg]	Candesartan [64mg]	83 (89)	88 (90)	eGFR 49 mL/min/1.73 m^2	24h urine protein 2.85 g/d	132/77 (133/79)	130/76 (132/77)	2.85[240] (2.83)	-36.95 (-22.23)	nd	Fair
ΔUPE, g/d	Woo 2009[241] Singapore [98]	6 y (6 y)	Losartan [200 mg/d]	Losartan [100 mg/d]	63 (67)	43 (45)	eGFR 64 mL/min	UPE 2.2 g/d	132/84 (132/85)	128/83 (128/84)	2.2 (2.0)	-1 (-0.4)	nd	Fair

[236] All Chinese patients
[237] Estimated from graph
[238] Primary outcome
[239] Primary outcome
[240] Primary outcome
[241] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)

Supplemental Table 22. RCTs examining the effect of ACEI vs. ß-blocker in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
↓GFR 50% or 25 mL/min/ 1.73 m^2, ESRD or death	AASK 2002 2006[242] US[70;99]	4 y (≥3 y)	Ramipril	Metoprolol	309 (436)	300 (441)	GFR 45 mL/min/1. 73 m^2	Male 0.61 g/24h Female 0.41 g/24h	151/96 (150/96)	135/82 (133/81)	nd	Risk reduction 22% (1; 38) [243]	0.04	Good
↓GFR 50% or 25 mL/min/ 1.73 m^2 or ESRD												Risk reduction 22% (-2; 41) [244]	NS (0.07)	Good
ESRD or death												Risk reduction 21% (-5; 40) [245]	NS	Good
First CV hospitalizati on and death					436 (436)	441 (441)					61 (14%) [65 (15%)]	HR 0.98[246] (0.69; 1.39)	NS	Good
First CV hospitalizati on or ESRD											113 (30%) [124 (28%)]	HR 0.87[247] (0.67; 1.13)	NS	Good
Mortality														
All cause mortality	AASK 2002[248] US[99]	4 y (≥3 y)	Ramipril	Metoprolol	309 (436)	300 (441)	GFR 45 mL/min/1. 73 m^2	Male 0.61 g/24h Female 0.41 g/24h	151/96 (150/96)	135/82 (135/81)	2% (2%)	nd	NS	Good
CV mortality														

[242] Study only included African American patients
[243] Adjusted
[244] Adjusted
[245] Adjusted
[246] Adjusted
[247] Adjusted
[248] Study only included African American patients

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
CV mortality	AASK 2002 2006[249] US[70;99]	4 y (≥3 y)	Ramipril	Metoprolol	309 (436)	300 (441)	GFR 45 mL/min/1.73 m^2	Male 0.61 g/24h Female 0.41 g/24h	151/96 (150/96)	135/82 (135/81)	1% (1%)	nd	NS	Good
CV death					436 (436)	441 (441)					12 (3%) [12 (3%)]	HR 1.06[250] (0.47; 2.39)	NS	Good
CV events														
CV events (composite)	AASK 2002 2006[251] US[70;99]	4 y (≥3 y)	Ramipril	Metoprolol	309 (436)	300 (441)	GFR 45 mL/min/1.73 m^2	Male 0.61 g/24h Female 0.41 g/24h	151/96 (150/96)	135/82 (135/81)	3% [3%]	nd	NS	Good
CV events					436 (436)	441 (441)					89 (20%) [85 (19%)]	HR 1.05† (0.72; 1.53)	NS	Good
Stroke events											23 (5%) [23 (5%)]	RR 1.01[252] (0.58; 1.78)	nd	Good
CHF events											20 (5%) [22 (5%)]	RR 0.92[253] (0.51; 1.66)	nd	Good
CAD events											19 (4%) [18 (4%)]	RR 1.07[254] (0.57; 2.01)	nd	Good
ESRD														
ESRD	AASK 2002[255] US[99]	4 y (≥3 y)	Ramipril	Metoprolol	309 (436)	300 (441)	GFR 45 mL/min/1.73 m^2	Male 0.61 g/24h Female 0.41 g/24h	151/96 (150/96)	135/82 (135/81)	nd	Risk reduction 22% (-10; 45)[256]	NS	Good

[249] Study only included African American patients
[250] Adjusted
[251] Study only included African American patients
[252] Calculated by ERT
[253] Calculated by ERT
[254] Calculated by ERT
[255] Study only included African American patients
[256] Adjusted

Supplemental Table 23. RCTs examining the effect of ACEI vs. ß-blocker in patients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
Acute slope –ΔGFR in first 3 months, mL/min/1.73 m^2/y	AASK 2002[257] US[99]	4 y (≥3 y)	Ramipril	Metoprolol	309 (436)	300 (441)	GFR 45 mL/min/1.73m^2	Male 0.61 g/24h Female 0.41 g/24h	151/96 (150/96)	135/82 (135/81)	46[258] (46)	-0.23 (-1.73)	0.01	Good
Chronic slope – ΔGFR after first 3 months, mL/min/1.73 m^2 /y												-1.87 (-2.12)	NS	Good
Total slope – ΔGFR over 4 y, mL/min/1.73 m^2 /y												-1.89 (-2.42)	0.007	Good

[257] Study only included African American patients
[258] Primary outcome

Supplemental Table 24. RCTs examining the effect of ACEI + CCB vs. ACEI in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Mortality														
Death	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Ramipril	51 (51)	53 (53)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/88)	0 (0%) [0 (0%)]	--	nd	Fair
Kidney function														
Regression coefficients for overall effect calculated from baseline GFR (mL/min/y)	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Ramipril	51 (51)	53 (53)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/88)	-3.2 (-6.8; 0.4) [259] [-4.7 (-8.8; -1.5)]	--	NS	Good
Regression coefficients for $1/S_{Cr}$ (1/µmol/L/y) X 10^{-3}	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Ramipril	51 (51)	53 (53)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/88)	-2.4[260] [-3.8]	--	NS	Good
Regression coefficients for long-term effect calculated from 3 month GFR (mL/min/y)	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Ramipril	51 (51)	53 (53)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/88)	-3.8 (-6.8; 0.9) [261] [-5.8 (-8.7; 0.3)]	--	NS	Good

[259] Primary outcome
[260] Primary outcome
[261] Primary outcome

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Regression coefficients for $1/S_{Cr}$ (1/µmol/L/y) X 10^{-3}											-2.8[262] [-2.1]	--	NS	Good

[262] Primary outcome

Supplemental Table 25. RCTs examining the effect of ACEI + CCB vs. ACEI in patients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Proteinuria														
UAE (statistical analysis of transformed values)	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Ramipril	51 (51)	53 (53)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/88)	530 (506)	-0.03 (-0.10)	NS	Good

Supplemental Table 26. RCTs examining the effect of ACEI + CCB vs. CCB in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Mortality														
Death	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Felodipine	51 (51)	54 (54)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/86)	0 (0%) [1 (2%)]	--	nd	Fair
Kidney function														
Regression coefficients for overall effect calculated from baseline GFR (mL/min/y)	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Felodipine	51 (51)	54 (54)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (160/99)	134/85 (139/86)	-3.2 (-6.8; -0.4) [263] [-4.8 (-8.1; -0.8)]	--	NS	Good
Regression coefficients for $1/S_{Cr}$ (1/µmol/L/y) X 10^{-3}											-2.4[264] [-7.4]	--	NS	Good
Regression coefficients for long-term effect calculated from 3 month GFR (mL/min/y)											-3.8 (-6.8; 0.9) [265] [-6.0 (-11.0; 2.3)]	--	<0.05	Good

[263] Primary outcome
[264] Primary outcome
[265] Primary outcome

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Regression coefficients for $1/S_{Cr}$ (1/µmol/L/y) X 10^{-3}											-2.8[266] [-9.0]	--	NS	Good

[266] Primary outcome

Supplemental Table 27. RCTs examining the effect of ACE + CCB vs. CCB in patients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Proteinuria														
UAE (statistical analysis of transformed values)	Nephros 2001 Multi[41]	2 y (nd)	Ramipril + felodipine	Felodipine	51 (51)	54 (54)	GFR 43 mL/min/1.73 m^2 S_{Cr} 147 mol/L	UAE 530 mg/24h	154/99 (159/100)	134/85 (139/88)	530 (365)	-0.03 (+0.14)	NS	Good

Supplemental Table 28. RCTs examining the effect of CCB vs. CCB in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Mortality														
All-cause mortality	CARTER 2007 Japan[36]	12 mo (12 mo)	Cilnidipine	Amlodipine	147 (179)	130 (160)	S_{Cr} 1.27 mg/dL	UPCR 1921 mg/g	152/87 (152/88)	133/76 (135/78)	2 (1%) [3 (2%)]	RR 0.59[267] (0.10; 3.47)	nd	Good
CV mortality														
CV mortality	CARTER 2007 Japan[36]	12 mo (12 mo)	Cilnidipine	Amlodipine	147 (179)	130 (160)	S_{Cr} 1.27 mg/dL	UPCR 1921 mg/g	152/87 (152/88)	133/76 (135/78)	0 (0%) [2 (2%)]	--	nd	Good
CV events														
CVD events-all	CARTER 2007 Japan[36]	12 mo (12 mo)	Cilnidipine	Amlodipine	147 (179)	130 (160)	S_{Cr} 1.27 mg/dL	UPCR 1921 mg/g	152/87 (152/88)	133/76 (135/78)	1 (1%) [3 (2%)]	RR 0.29[268] (0.03; 2.80)	nd	Good
Angina pectoris											1 (1%) [0 (0%)]	--	nd	Good
MI											0 (0%) [1 (1%)]	--	nd	Good
Abdominal aortic rupture											0 (0%) [1 (1%)]	--	nd	Good
Sudden death											0 (0%) [1 (1%)]	--	nd	Good
Stroke											2 (1%) [4 (3%)]	RR 0.44[269] (0.08; 2.37)	nd	Good
Stroke-cerebral infarction											2 (1%) [3 (2%)]	RR 0.59[270] (0.10; 3.47)	nd	Good
Stroke-transient ischemic attack											0 (0%) [1 (1%)]	--	nd	Good

[267] Calculated by ERT
[268] Calculated by ERT
[269] Calculated by ERT
[270] Calculated by ERT

Supplemental Table 29. RCTs examining the effect of CCB vs. CCB in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
ΔS_{Cr}, mg/dL	CARTER 2007 Japan[36]	12 mo (12 mo)	Cilnidipine	Amlodipine	147 (179)	130 (160)	S_{Cr} 1.27 mg/dL	UPCR 1921 mg/g	152/87 (152/88)	133/76 (135/78)	1.27 (1.29)	+0.1 (+0.16)	NS	Good
Proteinuria														
ΔUPCR, mg/g	CARTER 2007 Japan[36]	12 mo (12 mo)	Cilnidipine	Amlodipine	147 (179)	130 (160)	S_{Cr} 1.27 mg/dL	UPCR 1921 mg/g	152/87 (152/88)	133/76 (135/78)	1921[271] (1712)	-612 (+169)	<0.05	Good

[271] Primary outcome

Supplemental Table 30. RCTs examining the effect of ß-blocker vs. CCB in patients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
↓GFR 50% or 25 mL/min/ 1.73 m^2, ESRD or death	AASK 2002 2006[272] US[70;99]	4 y (≥3 y)	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.73 m^2	Male 0.63g/24h Female 0.44 g/24h	150/95 (150/96)	135/81 (133/81)	nd	Risk reduction 20% (-10; 41)[273]	NS	Good
↓GFR 50% or 25 mL/min/ 1.73 m^2 or ESRD											nd	Risk reduction 24% (-9; 47) [274]	NS	Good
ESRD or death											nd	Risk reduction 42% (17; 60) [275]	0.003	Good
First CV hospitalization and death					441 (441)	217 (217)					65 (15%) [23 (11%)]	HR 1.30[276] (0.81; 2.08)	NS	Good
First CV hospitalization or ESRD											124 (28%) [65 (30%)]	HR 0.85[277] (0.62; 1.14)	NS	Good
Mortality														
All cause mortality	AASK 2002[278] US[99]	4 y (≥3 y)	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.73 m^2	Male 0.63g/24h Female 0.44 g/24h	150/95 (150/96)	135/81 (133/81)	2% [2%]	nd	NS	Good
CV mortality														
CV mortality	AASK 2002 2006[279]	4 y	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.	Male 0.63g/24h	150/95 (150/96)	135/81 (133/81)	1% [1%]	nd	NS	Good

[272] Study only included African American patients
[273] Adjusted
[274] Adjusted
[275] Adjusted
[276] Adjusted
[277] Adjusted
[278] Study only included African American patients
[279] Study only included African American patients

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
CV death	US[70;99]	(≥3 y)			441 (441)	217 (217)	73 m^2	Female 0.44 g/24h			12 (3%) [7 (3%)]	HR 0.85[280] (0.33; 2.17)	NS	Good
CV events														
CV events	AASK 2002 2006[281] US[70;99]	4 y (≥3 y)	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.73 m^2	Male 0.63g/24h Female 0.44 g/24h	150/95 (150/96)	135/81 (133/81)	3% [2%]	nd	NS	Good
CV events					441 (441)	217 (217)		Male 0.57g/24h Female 0.38g/24h	150/96 (150/95)	133/81 (135/81)	85 (19%) [28 (13%)]	HR 1.41[282] (0.86; 2.32)	NS)	Good
Stroke events											23 (5%) [9 (4%)]	RR 1.26[283] (0.59; 2.67)	nd	Good
CHF events											22 (5%) [8 (4%)]	RR 1.35[284] (0.61; 2.99)	nd	Good
CAD events											18 (4%) [5 (2%)]	RR 1.77[285] (0.67; 4.71)	nd	Good
ESRD														
ESRD	AASK 2002 2006[286] US[70;99]	4 y (≥3 y)	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.73 m^2	Male 0.63g/24h Female 0.44 g/24h	150/95 (150/96)	135/81 (133/81)	nd	Risk reduction 59% (36; 74%)[287]	<0.001	Good

[280] Adjusted
[281] Study only included African American patients
[282] Adjusted
[283] Calculated by ERT
[284] Calculated by ERT
[285] Calculated by ERT
[286] Study only included African American patients
[287] Adjusted

Supplemental Table 31. RCTs examining the effect of ß-blocker vs. CCB in patients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
Acute slope – Δ GFR in first 3 months, mL/min/1.73 m^2/y	AASK 2002[288] US[99]	4 y (≥3 y)	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.73 m^2	Male 0.63g/24h Female 0.44 g/24h	150/95 (150/96)	135/81 (133/81)	46[289] (46)	-1.73 (+4.03)	<0.001	Good
Chronic slope – ΔGFR after first 3 months, mL/min/ 1.73 m^2/y												-2.33 (-3.22)	0.02	Good
Total slope – ΔGFR over 4 y, mL/min/1.73 m^2/y												-2.68 (-1.60)	0.004	Good
Proteinuria														
%ΔProteinuria (geometric mean UPCR)	AASK 2002[290] US[99]	6 mo (6 mo)	Metoprolol	Amlodipine	300 (441)	145 (217)	46 mL/min/1.73m^2	Male 0.63g/24h Female 0.44 g/24h	150/95 (150/96)	135/81 (133/81)	Male 0.61; Female 0.41 (Male 0.63; Female 0.44)	-14% (+58%)	<0.001	Good

[288] Study only included African American patients
[289] Primary outcome
[290] Study only included African American patients

Supplemental Table 32. RCTs examining the effect of central-acting agent vs. CCB in patients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Proteinuria														
Mean Δalbuminuria, g/24h	Vonend 2003 Germany & Hungary[96]	24 wk (22 wk)	Moxonidine	Nitrendipine	89 (89)	82 (82)	S_{Cr} 285 µmol/L	Albuminuria 1.3 g/24h	149/90 (150/90)	141/86[291] (137/80)	1.3 (1.9)	+0.3 (+0.2)	nd	Good

[291] Estimated from graph

Supplemental Table 33. General population RCTs comparing ACEI + diuretic vs. placebo in CKD with DM subgroups [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Composite kidney outcome													
New-onset microalbuminuria[292], new onset nephropathy[293], doubling of S_{Cr} to >200 µmol/L or ESRD in eGFR<60 mL/min/1.73 m^2	ADVANCE 2009 Multi[29]	4 y (4 y)	Perindopril-Indapamide	Placebo	1063 (1063)	1094 (1094)	nd	nd	nd	nd	300 (28%) [336 (31%)]	HR 0.87 (0.74; 1.02)	NS
Composite CV outcomes													
Composite of major macrovascular events[294] in patients with CKD 1 or 2	ADVANCE 2010 Multi[40]	4 y (4 y)	Perindopril-Indapamide	Placebo	2482		eGFR 87 mL/min/1.73 m^2	UACR ≥30	148/82	nd	128 (10%) [142 11%)]	HR 0.89 (0.70; 1.13)	NS
Composite of major macrovascular events[295] in patients with CKD 3					2033		eGFR 51 mL/min/1.73 m^2	nd	147/80	nd	126 (12%) [143 (14%)]	HR 0.87 (0.68; 1.10)	NS
Composite of major macrovascular events[296] in patients with UACR 30-150					nd		nd	UACR 30-150 mg/g	nd	nd	133 (11%) [144 (12%)]	HR 0.91 (0.72; 1.15)	NS
Composite of major macrovascular events[297] in patients with UACR ≥150							nd	UACR ≥150 mg/g			61 (14%) [77 (18%)]	HR 0.73 (0.52; 1.02)	NS
Composite of major macrovascular events[298] in patients with eGFR ≤60							eGFR ≤60 mL/min/1.73 m^2	nd			130 (12%) [163 (18%)]	HR 0.80 (0.63; 1.01)	NS
Relative risk reduction of MI, stroke or CV death	MICRO-HOPE 2000 Multi[4]	4 y (4 y)	Ramipril	Placebo	814	326	nd	UACR ≥2 mg/mmol	nd	nd	nd	RRR 0.70 (0.54; 0.90)[299]	nd

[292] UACR 30-300 µg/mg
[293] New onset macroalbuminuria defined as UACR >300µg/mg, which required confirmation by a 2nd sample
[294] CV death, non-fatal MI, or non-fatal stroke
[295] CV death, non-fatal MI, or non-fatal stroke
[296] CV death, non-fatal MI, or non-fatal stroke
[297] CV death, non-fatal MI, or non-fatal stroke
[298] CV death, non-fatal MI, or non-fatal stroke
[299] Estimated from figure

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Composite of cardiovascular death, non-fatal MI and resuscitative cardiac arrest	EUROPA 2007 Multi[19]	4 y (4 y)	Perindopril	Placebo	6295		GFR <75 mL/min/1.73 m^2	nd	140/81	nd	nd	HR 0.84 (0.72; 0.98)	0.023
Mortality													
All-cause mortality in patients with CKD 1 or 2	ADVANCE 2010 Multi[40]	4 y (4 y)	Perindopril-Indapamide	Placebo	2482		eGFR 87 mL/min/1.73 m^2	UACR ≥30	148/82	nd	114 (9%) [126 (10%)]	HR 0.90 (0.70; 1.10)	NS
All-cause mortality in patients with CKD 3					2033		eGFR 51 mL/min/1.73 m^2	nd	147/80	nd	117 (12%) [135 (13%)]	HR 0.87 (0.67; 1.10)	NS
All-cause mortality in patients with UACR 30-150					nd		nd	UACR 30-150 mg/g	nd	nd	115 (12%) [135 (14%)]	HR 0.84 (0.66; 1.08)	NS
All-cause mortality in patients with UACR ≥150							nd	UACR ≥150 mg/g			64 (12%) [69 (14%)]	HR 0.87 (0.62; 1.22)	NS
All-cause mortality in patients with eGFR ≤60							eGFR ≤60 mL/min/1.73 m^2	nd			124 (12%) [155 (14%)]	HR 0.80 (0.64; 1.03)	NS
Total death in CKD patients	PROGRESS 2007 2008 Multi[69;77]	4 y (4 y)	Perindopril-Indapamide	Placebo	1757		S_{Cr} 102 µmol/L CrCl 50 mL/min	nd	149/84	nd	153 [138]	Risk reduction -4% (-31; 17)	NS
CV mortality													
CV death in patients with CKD 1 or 2	ADVANCE 2010 Multi[40]	4 y (4 y)	Perindopril-Indapamide	Placebo	2482		eGFR 87 mL/min/1.73 m^2	UACR ≥30	148/82	nd	61 (5%) [79 (6%)]	HR 0.77 (0.55; 1.07)	NS
CV death in patients with CKD 3					2033		eGFR 51 mL/min/1.73 m^2	nd	147/80	nd	66 (7%) [82 (8%)]	HR 0.80 (0.58; 1.11)	NS
CV death in patients with UACR 30-150					nd		nd	UACR 30-150 mg/g	nd	nd	62 (5%) [78 (7%)]	HR 0.79 (0.57; 1.10)	NS
CV death in patients with UACR ≥150							nd	UACR ≥150 mg/g			40 (9%) [49 (12%)]	HR 0.76 (0.50; 1.16)	NS
CV death in patients with eGFR ≤60							eGFR ≤60 mL/min/1.73 m^2	nd			68 (6%) [94 (9%)]	HR 0.73 (0.54; 1.00)	nd

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
CV deaths in CKD patients	PROGRESS 2007 2008 Multi[69;77]	4 y (4 y)	Perindopril-Indapamide	Placebo	1757		S_{Cr} 102 µmol/L CrCl 50 mL/min	nd	149/84	nd	85 [86]	Risk reduction 7% (-24; 32)	NS
CV events													
Major coronary events in patients with CKD 1 or 2	ADVANCE 2010 Multi[40]	4 y (4 y)	Perindopril-Indapamide	Placebo	2482		eGFR 87 mL/min/1.73 m^2	UACR ≥30	148/82	nd	69 (6%) [77 (6%)]	HR 0.89 (0.64; 1.23)	NS
Major cerebrovascular events in patients with CKD 1 or 2											56 (5%) [63 (5%)]	HR 0.88 (0.61; 1.26)	NS
Major coronary events in patients with UACR 30-150					nd		nd	UACR 30-150 mg/g	nd	nd	75 (6%) [82 (7%)]	HR 0.90 (0.66; 1.24)	NS
Major cerebrovascular events in patients with UACR 30-150											58 (5%) [60 (5%)]	HR 0.96 (0.67; 1.38)	NS
Major coronary events in patients with CKD 3					2033		eGFR 51 mL/min/1.73 m^2	nd	147/80	nd	74 (7%) [86 (8%)]	HR0.85 (0.62; 1.16)	NS
Major cerebrovascular events in patients with CKD 3											51 (5%) [60 (6%)]	HR 0.84 (0.58; 1.22)	NS
Major coronary events in patients with UACR ≥150					nd		nd	UACR ≥150 mg/g	nd	nd	39 (9%) [38 (9%)]	HR 0.95 (0.61; 1.49)	NS
Major cerebrovascular events in patients with UACR ≥150											21 (5%) [36 (9%)]	HR 0.54 (0.32; 0.93)	NS
Major coronary events in patients with eGFR ≤60					nd		eGFR ≤60 mL/min/1.73 m^2	nd	nd	nd	77 (7%) [98 (9%)]	HR 0.79 (0.59; 1.07)	NS
Major cerebrovascular events in patients with eGFR ≤60											52 (5%) [65 (6%)]	HR 0.98 (0.81; 1.18)	NS
Major CV event in CKD patients	PROGRESS 2007 2008 Multi[69;77]	4 y (4 y)	Perindopril-Indapamide	Placebo	1757		S_{Cr} 102 µmol/L CrCl 50 mL/min	nd	149/84	nd	178 [222]	Risk reduction 30% (14; 42)	nd

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Stroke in CKD patients											112 [152]	Risk reduction 35% (17; 50)	nd
Major CHD event											46 [52]	Risk reduction 18% (-22; 45)	NS
Major vascular event in patients with CKD (per 100 person-y)											--	Incidence rate 6.5	nd
Relative risk reduction of major vascular event in patients with CKD											--	RRR 30% (14; 42)	nd
Major vascular event in patients with CKD over 5 y											--	ARR 8.8% (4.2; 12.5)	nd
Number needed to treat for 5 y to prevent one major vascular event in patients with CKD											NNT 11	nd	nd
Incidence rate of stroke in patients with CKD (per 100 person-y)											4.2	nd	nd
Relative risk reduction of stroke in patients with CKD											nd	RRR 35 (17; 50)	nd
Absolute risk reduction of stroke in patients with CKD over 5 y											nd	ARR 7.1 (3.5; 9.9)	nd
Number needed to treat for 5 y to prevent one stroke in patients with CKD												NNT 14	nd
Kidney Function													

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Progression of nephropathy[300] in patient with microalbuminuria	ADVANCE 2009 Multi[29]	4 y (4 y)	Perindopril-Indapamide	Placebo	1441 (1441)	1421 (1421)	nd	nd	nd	nd	89 (6%) [128 (9%)]	HR 0.69 (0.52; 0.91)	0.0074
Regression of nephropathy[301] in patients with microalbuminuria											797 (55%) [698 (49%)]	HR 1.15 (1.04; 1.27)	0.0067
Regression of nephropathy[302] in patients with macroalbuminuria					197 (197)	204 (204)					51 (26%) [47 (23%)]	HR 1.08 (0.72; 1.60)	NS
New or worsening nephropathy[303] in patients with CKD 1 or 2	ADVANCE 2010 Multi[40]	4 y (4 y)	Perindopril-Indapamide	Placebo	2482		eGFR 87 mL/min/1.73m^2	UACR ≥30	148/82	nd	75 (6%) [105 (9%)]	HR 0.69 (0.51; 0.93)	nd
New or worsening nephropathy[304] in patients with CKD 3					2033		eGFR 51 mL/min/1.73m^2	nd	147/80	nd	64 (6%) [68 (7%)]	HR 0.93 (0.66; 1.31)	NS
New or worsening nephropathy[305] in patients with UACR 30-150					nd		nd	UACR 30-150 mg/g	nd	nd	74 (6%) [97 (8%)]	HR 0.75 (0.55; 1.01)	NS
New or worsening nephropathy[306] in patients with UACR ≥150							nd	UACR ≥150 mg/g			53 (12) [64 (15%)]	HR 0.76 (0.53; 1.09)	NS
New or worsening nephropathy[307] in patients with eGFR ≤60							eGFR ≤60 mL/min/1.73m^2	nd			72 (7%) [76 (7%)]	HR 0.95 (0.69; 1.32)	NS

[300] Worsening of at least on albuminuria stage (from normoalbuminuria or either micro- or macroalbuminuria or from micro- to macroalbuminuria)
[301] Improvement of at least one albuminuria stage.
[302] Improvement of at least one albuminuria stage.
[303] Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
[304] Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
[305] Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
[306] Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
[307] Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease

Supplemental Table 34. General population RCTs comparing ACEI + diuretic vs. placebo in CKD with DM subgroups [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)	
Kidney Function													
ΔeGFR in patients with microalbuminuria, mL/min	ADVANCE 2009 Multi[29]	4 y (4 y)	Perindopril-Indapamide	Placebo	1441 (1441)	1421 (1421)	nd	nd	nd	nd	nd	1.1 (1.4)	NS
ΔeGFR in patients with macroalbuminuria, mL/min					197 (197)	204 (204)					nd	1.5 (2.7)	NS

Supplemental Table 35. General population RCTs comparing ARB or (ACE + ARB) vs. ACE in CKD subgroups with and without DM

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Composite outcomes													
Dialysis, doubling of S_{Cr} or death in patients with microalbuminuria or macroalbuminuria	ONTARGET 2008 Multi[63]	4 y (4 y)	Telmisartan	Ramipril	2673 (2673)		nd	nd	nd	nd	nd	RR 0.93[308] (0.85; 1.15)	NS
			Ramipril + Telmisartan		2648 (2648)							RR 0.99[309] (0.87; 1.8)	NS
Dialysis, doubling of S_{Cr} or death in patients with eGFR <60 mL/min/1.73 m^2			Telmisartan	Ramipril	4046 (4046)							RR 0.99 [310] (0.85; 1.7)	NS
			Ramipril + Telmisartan		3988 (3988)							RR 1.17[311] (0.97; 1.27)	NS

[308] Estimated from figure
[309] Estimated from figure
[310] Estimated from figure
[311] Estimated from figure

Supplemental Table 36. General population RCTs comparing CCB vs. active control in CKD subgroups with and without DM

Outcome	Study, Year, Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
Composite outcome													
Kidney failure or halving of GFR in entire subgroup with GFR <60 mL/min/1.73 m^2	ALLHAT 2006 Multi[50]	5 y (5y)	Amlodipine	Chlorthalidone	1516 (1516)	2613 (2613)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	90 (6%) [180 (7%)]	RR 0.85 (0.66; 1.11)	NS
Kidney failure or halving of GFR in DM subgroup with GFR <60 mL/min/1.73 m^2			Amlodipine		506 (506)	881 (881)	GFR 50 mL/min/1.73 m^2	nd	nd	nd	56 (11%) [96% (11%)]	RR 1.02 (0.72; 1.44)	NS
Kidney failure or halving of GFR in non-DM subgroup with GFR <60 mL/min/1.73 m^2			Amlodipine		1010 (1010)	1732 (1732)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	34 (3%) [84 (5%)]	RR 0.68 (0.46; 1.03)	NS
All-cause mortality and progression of CKD[312] in patients with diabetic nephropathy	ACCOMPLISH 2010 Multi[15]	3 y (3 y)	Benazepril + amlodipine	Benazepril + hydrochlorothiazide	335 (561)	309 (532)	In all CKD pts: S_{Cr} 140 mol/L eGFR 45 mL/min/1.73 m^2	In all CKD pts: UACR 28.8 mg/mmol	In all CKD patients: 145/78	nd	28 (8%) [30 (10%)]	HR 0.79 (0.47; 1.34)	NS
CV Events													
CHD in entire subgroup with GFR <60 mL/min/1.73 m^2	ALLHAT 2006 Multi[50]	5 y (5 y)	Amlodipine	Chlorthalidone	1516 (1516)	2613 (2613)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	194 (13%) [318 (12%)]	RR 1.06 (0.89; 1.27)	NS
CHD in DM subgroup with GFR <60 mL/min/1.73 m^2			Amlodipine		506 (506)	881 (881)	GFR 50 mL/min/1.73 m^2	nd	nd	nd	83 (16%) [132 (15%)]	RR 1.07 (0.81; 1.41)	NS

[312] Time to first event of doubling of serum creatinine concentration or end-stage renal disease, defined as eGFR less than 15 mL/min/1·73 m² or need for chronic dialysis.

Outcome	Study, Year, Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)	
CHD in non-DM subgroup with GFR <60 mL/min/1.73 m^2	ALLHAT 2006 Multi[50]	5 y (5 y)	Amlodipine	Chlorthalidone	1010 (1010)	1732 (1732)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	111 (11%) [186 (11%)]	RR 1.05 (0.83; 1.33)	NS
ESRD													
Kidney failure in entire subgroup with GFR <60 mL/min/1.73 m^2			Amlodipine		1516 (1516)	2613 (2613)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	65 (4%) [124 (5%)]	RR 0.92 (0.68; 1.24)	NS
Kidney failure in DM subgroup with GFR <60 mL/min/1.73 m^2			Amlodipine		506 (506)	881 (881)	GFR 50 mL/min/1.73 m^2	nd	nd	nd	44 (9%) [68 (8%)]	RR 1.11 (0.77; 1.63)	NS
Kidney failure in non-DM subgroup with GFR <60 mL/min/1.73 m^2			Amlodipine		1010 (1010)	1732 (1732)	GFR 51 mL/min/1.73 m^2	nd	nd	nd	21 (2%) [56 (3%)]	RR 0.66 (0.40; 1.09)	NS
Progression of CKD[313] in patients with diabetic nephropathy[314]	ACCOMPLISH 2010 Multi[15]	3 y (3 y)	Benazepril + amlodipine	Benazepril + hydrochlorothiazide	335 (561)	309 (532)	In all CKD pts: S_{Cr} 140 mol/L eGFR 45 mL/min/1.73 m^2	In all CKD pts: UACR 28.8 mg/mmol	In all CKD patients: 145/78	nd	16 (5%) [17 (6%)]	HR 0.78 (0.38; 1.56)	NS

[313] Time to first event of doubling of serum creatinine concentration or end-stage renal disease, defined as eGFR less than 15 mL/min/1·73 m² or need for chronic dialysis.

[314] In all CKD patients, the progression of kidney disease (doubling of S_{Cr} or ESRD) was slower in the benazepril + amlodipine group (1.6 mL/min/1.73m^2) vs. the benazepril + hydrochlorothiazide group (-2.3 mL/min/1.73m^2) [p-0.001].

Supplemental Table 37. Evidence profile of RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM

Outcome		# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings			
								Quality of evidence for outcome	Qualitative and quantitative description of effect		Importance of outcome
Composite kidney outcomes	**DM2**	2 RCTs (High) [1˚ in 2 RCTs]	2661 (1330)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	Benefit for ACEI or ARB		Critical
Mortality	**DM2**	3 RCTs (High)	3251 (1719)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference	No difference of ACEI or ARB vs. Placebo	Critical
	DM1	1 RCT (High)	405 (206)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence		
CV mortality[315]	**DM2**	3 RCTs (High)	7564 (3768)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference of ACEI or ARB vs. Placebo		Critical
CV events	**DM2**	6 RCTs (High) [1˚ in 1 RCT]	8365 (4265)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference of ACEI or ARB vs. Placebo[316]		Critical
ESRD	**DM2**	3 RCTs (High)	7573 (3773)	No limitations (0)	Important inconsistencies (-1)	Direct (0)	None (0)	Moderate	Possible benefit	Possible benefit of ACEI or ARB vs. Placebo	Critical
	DM1	1 RCT (High)	405 (206)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Possible benefit		
Kidney function (categorical)	**DM2**	3 RCTs (High)	7573 (3773)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	Benefit	Benefit of ACEI or ARB vs. Placebo	High
	DM1	1 RCT (High) [1˚ in 1 RCT]	405 (206)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit		
∆Kidney function (continuous)	**DM2**	3 RCTs (High) [1˚ in 1 RCT]	2193 (1188)	No limitations (0)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Moderate	Possible benefit of ACEI or ARB vs. Placebo		Moderate
Proteinuria (categorical)	**DM2**	2 RCT (High)	1104 (729)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit of ACEI or ARB vs. Placebo		High
Proteinuria (continuous)	**DM2**	6 RCTs (High) [1˚ in 2 RCTs]	3176 (1772)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Low	Benefit	Benefit of ACEI or ARB vs. Placebo	Moderate
	DM1	1 RCT (High) [1˚ in 1 RCT]	137 (67)	No limitations (0)	NA	Uncertainty about directness (-1)	Sparse (-1)	Low	Benefit		

[315] Includes 1 study (Brenner 2001) with a composite outcome for CVD mortality and morbidity

[316] The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.

Outcome		# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
								Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Adverse events		6 RCTs	8069 (4196)						Drug discontinuation: 8-17% for ACEI or ARB and 1-22% for placebo (from 4 RCTs) Hyperkalemia: 1-2% for ACEI or ARB and 0.5-1% for placebo (from 2 RCTs) Early rise in creatinine: 0.2-2% in ACEI and ARB and 0-2% in Placebo (from 2 RCTs)	Moderate
Total	**DM2**	7 RCTs	9240 (4795)							
	DM1	2 RCTs	542 (273)							
Balance of potential benefits and harms Possible benefit for preventing ESRD, slowing loss of kidney function and reducing proteinuria. No difference for CV outcomes[317]								**Quality of overall evidence** Moderate for kidney outcomes High for CV outcomes		

[317] The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.

Supplemental Table 38. RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM [categorical outcomes] [318]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Type 2 DM														
Overt albuminuria														
Composite of doubling of S_{Cr}, ESRD or death	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	327 (44%)[319] [359 (47%)]	Risk reduction 16% (2%; 28%)	0.02	Good
Composite of doubling of S_{Cr}, ESRD or death	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Placebo	579 (579)	569 (569)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (158/87)	140/77 (144/80)	189 (33%)[320] [222 (39%)]	RR 0.81 (0.67; 0.99)[321]	0.03	Good
Mortality														
Type 2 DM														
Overt albuminuria														
Death	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	158 (21%) [155 (20%)]	Risk reduction -2% (-27%; 19%)	NS	Good
Death	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Placebo	579 (579)	569 (569)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (158/87)	140/77 (144/80)	87 (15%) [93 (16%)]	RR 0.94 (0.70; 1.27)[322]	NS	Good
Microalbuminuria														
All-cause mortality	IRMA 2 2001 Multi[74]	24 mo (24 mo)	Irbesartan 300mg	Placebo	194 (194)	201 (201)	S_{Cr} 1.05 mg/dL	UAE 53.4 µg/min	153/91 (153/90)	141/83 (144/83)	3 (2%) [1 (1%)]	RR 3.11[323] (0.33; 29.63)	nd	Fair
			Irbesartan 150mg		195 (195)		S_{Cr} 1.0 mg/dL	UAE 58.3 µg/min	153/90 (153/90)	143/83 (144/83)	0 (0%) [1 (1%)]	RR 1.03[324] (0.02; 51.69)	nd	Fair
Type 1 DM														
Overt albuminuria														
Death	Lewis 1993 US[51]	36 mo (36 mo)	Captopril	Placebo	206 (207)	199 (202)	CrCl 84 mL/min S_{Cr} 1.3 mg/dL	UPE 2500 mg/24h	137/85 (140/86)	MAP 96 (100)	8 (4%) [14 (7%)]	RR 0.55[325] (0.24; 1.29)	nd	Good

[318] Shaded studies were included in previous KDOQI guideline
[319] Primary outcome
[320] Primary outcome
[321] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
[322] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
[323] Calculated by ERT
[324] Calculated by ERT
[325] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
CV mortality														
Type 2 DM														
Overt albuminuria														
CV-mortality	DIABHYCAR 2004 Multi[65]	47mo (47mo)	Ramipril	Placebo	2443 (2443)	2469 (2469)	S_{Cr} 89.2 µmol/L	nd	145/82 (145/82)	142/80 (142/80)	141 (6%) [133 (5%)]	RR 1.07 (0.85; 1.35)	NS	Good
CV-mortality and morbidity	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	158 (21%) [155 (20%)]	Risk reduction 10%	NS	Good
CV-mortality	IDNT 2003 Multi[18]	32 mo (≥24 mo)	Irbesartan	Placebo	574 (579)	565 (569)	S_{Cr} 1.67 mg/dL	UPE 2.9 g/d	160/87 (158/87)	140/77 (144/80)	37 (7%) [46 (8%)]	HR 0.79 (0.51; 1.22)	NS	Good
CV events														
Type 2 DM														
Overt albuminuria														
MI	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	50 (7%) [68 (9%)]	Risk reduction 28%	NS (0.08)	Good
First hospitalization for CHF											89 (12%) [127 (17%)]	Risk reduction 32%	0.005	Good
Composite of CVD	IDNT 2001 2003 Multi[18;52]	32 mo (≥24 mo)	Irbesartan	Placebo	579 (579)	569 (569)	S_{Cr} 1.7 mg/dL	UPE 2.9 g/d	160/87 (158/87)	140/77 (144/80)	138 (24%) [144 (25%)]	RR 0.91 (0.72; 1.14)[326]	NS	Good
Composite CV events											259 (in 30% of patients) [284 (in 33% of patients)]	HR 0.90 (0.74; 1.10)	NS	Good
CHF											80 (10% of patients) [113 (13% of patients)]	HR 0.72 (0.52; 1.00)	0.048	Good
Myocardial infarction											48 (8% of patients) [51 (9% of patients)]	HR 0.90 (0.60; 1.33)	NS	Good
CVA											30 (5% of patients) [28 (5% of patients)]	HR 1.01 (0.61; 1.67)	NS	Good

[326] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Cardiac revascularization											31 (5% of patients) [39 (6% of patients)]	HR 0.80 (0.49; 1.30)	NS	Good
Composite CV events	IRMA 2 2001 Multi[74]	24 mo (24 mo)	Irbesartan 300mg	Placebo	194 (194)	201 (201)	S_{Cr} 1.05 mg/dL	UAE 53.4 µg/min	153/91 (153/90)	141/83 (144/83)	9 (5%) [18 (9%)]	RR 0.52 (0.24; 1.12)	NS	Fair
			Irbesartan 150mg		195 (195)		S_{Cr} 1.0 mg/dL	UAE 58.3 µg/min	153/90 (153/90)	143/83 (144/83)	nd [18 (9%)]	nd	nd	Fair
Microalbuminuria														
Composite of combined CV events	DIABHYCAR 2004 Multi[65]	47mo (47mo)	Ramipril	Placebo	2443 (2443)	2469 (2469)	S_{Cr} 89.2 µmol/L	nd	145/82 (145/82)	142/80 (142/80)	362 (15%)[327] [377 (15%)]	RR 0.97 (0.85; 1.11)	NS	Good
MI	Trevisan 1995 Italy[92]	6 mo (6 mo)	Ramipril	Placebo	54 (60)	54 (62)	S_{Cr} 1.0 mg/dL	UPE 89.3 mg/24h	147/90 (151/91)	142/87 (149/87)	1 (2%) [1 (2%)]	RR 1.00 (0.06; 15.58]	nd	Good
Normoalbuminuria														
CV events	Ravid 1993 Israel[82]	84 mo (84 mo)	Enalapril	Placebo	49 (nd)	45 (nd)	S_{Cr} 106.5 µmol/L	UAE 11.6 mg/24h	MAP 98 (nd)	MAP 100 (102)	0 (0%) [1 (2%)	RR 0.31[328] (0.01; 7.33)	nd	Good
ESRD														
Type 2 DM														
Overt albuminuria														
ESRD	RENAAL 2001 2004 Multi[20;83]	48 mo (48 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	147 (20%) [194 (26%)]	Risk reduction 28% (11%; 42%)	0.002	Good
ESRD in highest S_{Cr} tertile (2.1-3.6 mg//dL)		41 mo (41 mo)			248 (248)	263 (263)	S_{Cr} 2.1-3.6 mg/dL CrCl 28.9 mL/min	UACR 1737	154/82 (157/83)	nd	89[329] (36%) [118 (45%)]	RR 0.80[330] (0.65; 0.99)	<0.05	Fair
ESRD in middle S_{Cr} tertile (1.6-2.0 mg//dL)					264 (264)	244 (244)	S_{Cr} 1.6-2.0 mg/dL CrCl 39.1 mL/min	UACR 1045	152/83 (153/82)		45[331] (17%) [54 (22%)]	RR 0.77[332] (0.54; 1.10)	NS	

[327] Primary outcome
[328] Calculated by ERT
[329] No of events calculated by ERT
[330] Calculated by ERT
[331] No of events calculated by ERT
[332] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
ESRD in lowest S_{Cr} tertile (0.9-1.6 mg//dL)					239 (239)	255 (255)	S_{Cr} 0.9-1.6 mg/dL CrCl 50.7 mL/min	UACR 947	149/82 (149/83)		14[333] (6%) [20 (8%)]	RR 0.75[334] (0.39; 1.44)	NS	
ESRD in CKD2					95						1[335] (3%) [6 (10%)]	Risk reduction: 82% (-64%; 98%)	NS	
ESRD in CKD3					1030		S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)		64[336] (12%) [87 (17%)]	Risk reduction: 33% (8%; 52%)	0.02	
ESRD in CKD4					387						81[337] (44%) [101 (50%)]	Risk reduction: 23% (-4%; 43%)	NS (0.08)	
ESRD	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Placebo	579 (579)	569 (569)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (158/87)	140/77 (144/80)	82 (14%) [101 (18%)]	RR 0.83 (0.62; 1.11)[338]	NS	Good
Microalbuminuria														
ESRD	DIABHYCAR 2004 Multi[65]	47mo (47mo)	Ramipril	Placebo	2443 (2443)	2469 (2469)	S_{Cr} 89.2 µmol/L	nd	145/82 (145/82)	142/80 (142/80)	4 (0.2%) [10 (0.4%)]]	RR 0.40 (0.13; 1.30)	NS	Good
Type 1 DM														
Overt albuminuria														
Dialysis or transplantation	Lewis 1993 US[51]	36 mo (36 mo)	Captopril	Placebo	206 (207)	199 (202)	CrCl 84 mL/min S_{Cr} 1.3 mg/dL	UPE 2500 mg/24h	137/85 (140/86)	MAP 96 (100)	20 (10%) [31 (15%)]	RR 0.62 (0.37; 1.06)	nd	Good
Kidney Function														
Type 2 DM														
Overt albuminuria														

[333] No of events calculated by ERT
[334] Calculated by ERT
[335] No of events calculated by ERT
[336] No of events calculated by ERT
[337] No of events calculated by ERT
[338] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Doubling of S_{Cr} mg/dL	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	162 (22%) [198 (26%)]	Risk reduction 25% (8%; 39%)	0.006	Good
Doubling of S_{Cr} mg/dL	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Placebo	579 (579)	569 (569)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (158/87)	140/77 (144/80)	98 (17%) [135 (24%)]	RR 0.71 (0.54; 0.92)[339]	0.009	Good
Microalbuminuria														
Doubling S_{Cr} mg/dL	DIABHYCAR 2004 Multi[65]	47mo (47mo)	Ramipril	Placebo	2443 (2443)	2469 (2469)	S_{Cr} 89.2 µmol/L	nd	145 /82 (145/82)	142/80 (142/80)	48 (2%) [60 (2%)]	RR 0.81 (0.56; 1.12)	NS	Good
Type 1 DM														
Overt albuminuria														
Doubling of S_{Cr}, mg/dL	Lewis 1993 US[51]	36 mo (36 mo)	Captopril	Placebo	206 (207)	199 (202)	CrCl 84 mL/min S_{Cr} 1.3 mg/dL	UPE 2500 mg/24h	137/85 (140/86)	MAP 96 (100)	25 (12%)[340] [43 (21%)]	Risk reduction 43% (6%; 65%) [341]	0.014	Good
Proteinuria														
Type 2 DM														
Microalbuminuria														
↑30% from baseline and UAE >200 µg/min	IRMA 2 2001 Multi[74]	24 mo (24 mo)	Irbesartan 300mg	Placebo	194 (194)	201 (201)	S_{Cr} 1.05 mg/dL	UAE 53.4 µg/min	153/91 (153/90)	141/83 (144/83)	10 (5%)[342] [30 (15%)]	HR 0.32 (0.15; 0.65)	<0.001	Good
			Irbesartan 150mg		195 (195)		S_{Cr} 1.0 mg/dL	UAE 58.3 µg/min	153/90 (153/90)	143/83 (144/83)	19 (10%)[343] [30 (15%)]	HR 0.56 (0.31; 0.99	0.05	Good
Transition rates from incipient to overt nephropathy (UACR >300 mg/g and ↑≥30%)	INNOVATION 2007 Japan[55]	16mo (≥12mo)	Telmisartan	Placebo	340 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	138/78 (137/77)	130/73 (132/74)	67 (20%) [87 (50%)]	RR 0.39[344] (0.30; 0.51)	<0.0001	Good
			Telmisartan 80 mg		168 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 172 mg/g	138/78 (137/77)	128/72 (132/74)	28 (17%) [87 (50%)]	RR 0.33[345] (0.23; 0.48)	<0.0001	Good
			Telmisartan 40 mg		172 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	137/78 (137/77)	132/74 (132/74)	39 (23%) [87 (50%)]	RR 0.45[346] (0.33; 0.62)	<0.0001	Good
Transition rate in			Telmisartan		109 (nd)	54 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	132/77 (128/73)	12373 (128/75)	18 (17%) [24 (44%)]	RR 0.37[347] (0.22; 0.62)	<0.01	

[339] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
[340] Primary outcome
[341] Adjustments for differences in mean arterial pressure
[342] Primary outcome
[343] Primary outcome
[344] Calculated by ERT
[345] Calculated by ERT
[346] Calculated by ERT
[347] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
normotensive patients			Telmisartan 80 mg		51 (nd)	54 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	133/78 (128/73)	123/72 (128/75)	6 (11%) [24 (44%)]	RR 0.26[348] (0.12; 0.59)	<0.01	Good
			Telmisartan 40 mg		58 (nd)	54 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	131/75 (128/73)	122/73 (128/75)	12 (21%) [24 (44%)]	RR 0.47[349] (0.26; 0.84)	<0.01	Good
			Telmisartan		340 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	138/78 (137/77)	130/73 (132/74)	58 (17%) [2 (1%)]	RR 14.84[350] (3.67; 60.05)	<0.001	Good
Micaroalbuminuria remission			Telmisartan 80 mg		168 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 172 mg/g	138/78 (137/77)	128/72 (132/74)	36 (21%) [2 (1%)]	RR 18.64[351] (4.56; 76.21)	<0.001	Good
			Telmisartan 40 mg		172 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	137/78 (137/77)	132/74 (132/74)	22 (13%) [2 (1%)]	RR 11.13[352] (2.66; 46.60)	<0.001	Good

[348] Calculated by ERT
[349] Calculated by ERT
[350] Calculated by ERT
[351] Calculated by ERT
[352] Calculated by ERT

Supplemental Table 39. RCTs examining the effect of ACEI or ARB vs. placebo in patient with CKD and DM [continuous outcomes] [353]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
Kidney Function														
Type 2 DM														
Overt albuminuria														
Median rate of ↓GFR /CrCl, ml/min/1.73 m	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	nd	-4.4 (-5.2)	0.01	Good
Change in slope of 1/Scr , dL/mg/y											nd	-0.056 (-0.069)	0.01	Good
Microalbuminuria														
ΔGFR /CrCl, ml/min/1.73 m^2	IRMA 2 2001 Multi[74]	24 mo (24 mo)	Irbesartan 300 mg	Placebo	194 (194)	201 (201)	S_{Cr} 1.05 mg/dL	UACR 53.4	153/91 (153/90)	141/83 (144/83)	108 (109)	-6[354] (-4)	NS	Fair
			Irbesartan 150 mg		195 (195)		S_{Cr} 1.0 mg/dL	UACR 58.3	153/90 (153/90)	143/83 (144/83)	110 (109)	-5[355] (-4)	NS	Fair
ΔS_{Cr}, µmol/L	Ravid 1993 Israel[82]	60 mo (60 mo)	Enalapril	Placebo	48 (nd)	42 (nd)	S_{Cr} 106.5 µmol/L	UAE 142.7 mg/24h	MAP 98 (nd)	MAP 100 (102)	106.3[356] (101.6)	2.0[357] (14.4)	nd	Good
Proteinuria														
Type 2 DM														
Overt albuminuria														
%ΔUACR	RENAAL 2001 Multi[20]	41 mo (41 mo)	Losartan	Placebo	751 (751)	762 (762)	S_{Cr} 1.9 mg/dL	UACR 1237 mg/g	152/82 (153/82)	140/74 (142/74)	1237mg/g (1261mg/g)	-35% (+20%)[21]	<0.001	Good
Microalbuminuria														
%ΔProteinuria, µg/min	IRMA 2 2001 Multi[74]	24 mo (24 mo)	Irbesartan 300 mg	Placebo	194 (194)	201 (201)	S_{Cr} 1.0 mg/dL	UAE 53.4 µg/min	153/91 (153/90)	141/83 (144/83)	53.4	-47% (+10%)[358]	<0.001	Fair
			Irbesartan 150 mg		195 (195)		S_{Cr} 1.0 mg/dL	UAE 58.3 µg/min	153/90 (153/90)	143/83 (144/83)	58.3	-9% (+10%)[359]	<0.001	Fair
↓UACR, mg/dL	Agha 2009 Pakistan[6]	6mo (6mo)	Losartan	Placebo	190 (193)	171 (190	S_{Cr} 1.2 mg/dL	UAE 102 mg/dL	134/82 (136/83)	131/79 (134/81)	102[360] (105)	54.4 (0.8)	<0.0001	Poor
ΔProteinuria, µg/min	Trevisan 1995 Italy[92]	6 mo (6 mo)	Ramipril	Placebo	54 (60)	54 (62)	S_{Cr} 1.0 mg/dL	62 µg/min	147/90 (151/91)	142/87 (149/87)	62 (65)	-9 (+18)	<0.01	Good

[353] Shaded studies were included in previous KDOQI guideline
[354] Calculated by ERT from graph
[355] Calculated by ERT from graph
[356] Primary outcome
[357] Calculated by ERT from graph
[358] Estimated from graph
[359] Estimated from graph
[360] Primary outcome

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
ΔAlbuminuria, mg/24h	Ravid 1993 Israel[82]	60 mo (60 mo)	Enalapril	Placebo	48 (nd)	42 (nd)	S_{Cr} 106.5 µmol/L	UAE 142.7 mg/24h	MAP 98 (nd)	MAP 100 (102)	142.7 (123.1)	-3.0 (+189.3) [361]	nd	Good
ΔUACR after adjustment for SBP, mg/g	INNOVATION 2007 Japan[55]	16mo (≥12mo)	Telmisartan	Placebo	340 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	138/78 (137/77)	130/73 (132/74)	172 (171)	-48.3 (+40.9)	<0.0001	Good
			Telmisartan 80 mg		168 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 172 mg/g	138/78 (137/77)	128/72 (132/74)	172 (171)	-58.8 (+40.9)	<0.0001	Good
			Telmisartan 40 mg		172 (nd)	174 (nd)	S_{Cr} 0.8 mg/dL	UACR 171 mg/g	137/78 (137/77)	132/74 (132/74)	173 (171)	-37.9 (+40.9)	<0.0001	Good
Type 1 DM														
Microalbuminuia														
%ΔProteinuria, µg/min	Laffel 1995 US[49]	24 mo (24 mo)	Captopril	Placebo	67 (70)	70 (73)	CrCl 80 mL/min S_{Cr} 1.1 mg/dL	UPE 89.3 mg/24h	MAP 92 (92)	118/78 (130/82)	62[362] (62)	-42%[363] (+14%)	≤0.05	Good

[361] Estimated from graph
[362] Primary outcome
[363] Primary outcome

Supplemental Table 40. Evidence profile of RCTs examining the effect of ACEI or ARB vs. Dihydropyridine CCB in patients with CKD and Type 2 DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	1 RCT (High) [1˚ in 1 RCT]	1146 (579)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit ACEI or ARB vs. CCB	Critical
Mortality	1 RCT (High)	1146 (579)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	No difference for ACEI or ARB vs. CCB	Critical
CV mortality	2 RCTs (High)	1229 (623)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence for ACEI or ARB vs. CCB	Critical
CV events	3 RCTs (High)	1569 (782)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference for ACEI or ARB vs. CCB[364]	Critical
ESRD	1 RCT (High)	1146 (579)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Possible benefit for ACEI or ARB vs. CCB	Critical
Kidney function (categorical)	1 RCT (High)	1146 (579)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	Benefit for ACEI or ARB vs. CCB	High
∆Kidney function (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
Proteinuria (categorical)	1 RCT (High) [1˚ in 1 RCT]	117 (53)	Serious limitations (-2)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence for ACEI or ARB vs. CCB	High
Proteinuria (continuous)	4 RCTs (High) [1˚ in 4 RCTs]	888 (449)	No limitations (0)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Moderate	Benefit for ACEI or ARB vs. CCB	Moderate
Adverse events	3 RCTs	1978 (985)						Drug discontinuation: 7-13% for ACEI (from 3 RCTs) and 6-9% in CCB (from 2 RCTs) Hyperkalemia: 2% for ACEI or ARB and 0.5% for CCB (from 1 RCT) Early rise in creatinine: 0.2% in ACEI and 0% in CCB (from 1 RCT)	Moderate
Total	7 RCTs	3466 (1739)							

Balance of potential benefits and harms

Possible benefit for ACEI or ARB in preventing ESRD, slowing loss of kidney function and reducing proteinuria

No difference for CV Events[365]

Quality of overall evidence

Moderate for kidney outcomes

Moderate for cardiovascular outcomes

[364] The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.

[365] The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.

Supplemental Table 41. RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [categorical outcomes] [366]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Overt albuminuria														
Composite of doubling of S_{Cr}, ESRD or death	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Amlodipine	579 (579)	567 (567)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (159/87)	140/77 (141/77)	189 (33%)[367] [233 (41%)]	RR 0.76 (0.63; 0.92)[368]	0.005	Good
Mortality														
Overt albuminuria														
Death	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Amlodipine	579 (579)	567 (567)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (159/87)	140/77 (141/77)	87 (15%) [83 (15%)]	RR 1.05 (0.78; 1.42) [369]	NS	Good
CV mortality														
Overt albuminuria														
CV mortality	IDNT 2003 Multi[18]	32 mo (≥24 mo)	Irbesartan	Amlodipine	574 (579)	565 (567)	S_{Cr} 1.67 mg/dL	UPE 2.9 g/d	160/87 (159/87)	140/77 (141/77)	52 (9%) [37 (7%)]	HR 1.36 (0.89; 2.07)	NS	Good
Microalbuminuria														
Death from MI	Chan 1992[370] Hong Kong[24]	12 mo (12 mo)	Enalapril	Nifedipine	49 (52)	41 (50)	CrCl 66 mL/min	UAE 64.7 mg/24h	MAP 120 (117)	MAP 99 (97)	1 (2%) [0 (0%)]	RR 2.52 (0.11; 61.12) [371]	nd	Poor
CV events														
Overt albuminuria														
Composite of CVD	IDNT 2001 2003 Multi[18;52]	32 mo (≥24 mo)	Irbesartan	Amlodipine	579 (579)	567 (567)	S_{Cr} 1.7 mg/dL	UPE 2.9 g/d	160/87 (159/87)	140/77 (141/77)	138 (24%) [128 (23%)]	RR 1.03 (0.81; 1.32) [372]	NS	Good
Composite CV events											259 in 30% of patients [278 in 28% of patients]	HR 0.90 (0.74; 1.10)	NS	Good
CHF											80 in 10% of patients [143 in16% of patients]	HR 0.65 (0.48; 0.87)	0.004	Good

[366] Shaded studies were included in previous KDOQI guideline
[367] Primary outcome
[368] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
[369] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
[370] All patients were Chinese
[371] Calculated by ERT
[372] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
MI											48 in 8% of patients [29 in 5% of patients]	HR 1.54 (0.97; 2.45)	NS (0.068)	Good
CVA											30 in 5% of patients [18 in 3% of patients]	HR 1.55 (0.84; 2.87)	NS	Good
Cardiac revascularization											31 in 5% of patients [32 in 5% of patients]	HR 0.93 (0.55; 1.55)	NS	Good
Microalbumnuria														
CV events	J-MIND 2001[373] Japan[13]	24 mo (24 mo)	Enalapril	Nifedipine retard	137 (208)	156 (228)	CrCl 102 mL/min	UAE 42 mg/d	161/90 (162/90)	145/82[374] (143/82)	8 (6%) [5 (3%)]	RR 1.82 (0.61; 5.44)[375]	NS	Poor
Composite of CV events	DIAL 2004 Italy[28]	12 mo (12 mo)	Ramipril	Lercanidipine	66 (89)	64 (91)	S_{Cr} 79.6 µmol/L	UAER 86.5 µg/min	156/93 (155/92)	140/80 (140/80)	2 (3%) [5 (8%)]	RR 0.39 (0.08; 1.93)[376]	nd	Fair
ESRD														
Overt albuminuria														
ESRD	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Amlodipine	579 (579)	567 (567)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (159/87)	140/77 (141/77)	82 (14%) [104 (18%)]	RR 0.76 (0.57; 1.02)[377]	NS (0.06)	Good
Kidney function														
Overt albuminuria														
Doubling of S_{Cr}	IDNT 2001 Multi[52]	32 mo (≥24 mo)	Irbesartan	Amlodipine	579 (579)	567 (567)	S_{Cr} 1.7 mg/dL	UAE 2900 mg/24h	160/87 (159/87)	140/77 (141/77)	98 (17%) [144 (25%)]	RR 0.61 (0.48; 0.79)[378]	<0.001	Good
Proteinuria														
Microalbuminuria														

[373] The J-MIND contains both micro- and normo-albuminuric patients
[374] Estimated from graph
[375] Calculated by ERT
[376] Calculated by ERT
[377] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
[378] Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Progression from microalbuminuria to macroalbuminuria	J-MIND 2001[379] Japan[13]	24 mo (24 mo)	Enalapril	Nifedipine retard	53 (nd)	64 (nd)	CrCl 102 mL/min	UAE 42 mg/d[380]	161/90 (162/90)	145/82[381] (143/82)	6%[382] [6%]	RR 0.91 (0.21; 3.87)[383]	NS	Poor

[379] The J-MIND contains both micro- and normo-albuminuric patients
[380] Baseline UAE is reported for all patients enrolled some of whom are normoalbuminuric.
[381] Estimated from graph
[382] Primary outcome
[383] Calculated by ERT

Supplemental Table 42. RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [continuous outcomes] [384]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Microalbuminuria														
ΔMedian UAE	Agardh 1996 UK[5]	12 mo (12 mo)	Lisinopril	Nifedipine	168 (168)	167 (167)	CrCl 101.58 mL.min S_{Cr} 94.0 µmol/L	UAE 94.3 mg/24h	163/99 (161/97)	147/88 (150/88)	65.5[385] (63)	-26.5 (-5)	0.0006	Good
ΔUAER	MARVAL 2002 UK[95]	3 mo (6 mo)	Valsartan	Amlodipine	149 (169)	144 (163)	S_{Cr} 97.3 µmol/L	UAER 57.9 µg/min	147/85 (148/86)	135/78 (136/79)	57.9 (55.4)	-16.3 (0)	nd	Good
		5 mo (6 mo)			144 (169)	142 (163)					57.9 (55.4)	-21.3 (-3.4)	nd	Good
		6 mo (6 mo)			142 (169)	136 (163)					57.9 (55.4)	-34.6 (-4.7)	nd	Good
		6 mo (6 mo) [LOCF]			163 (169)	158 (163)					57.9 (55.4)	-24.2 (-1.7)	nd	Good
%ΔUAER		6 mo (6 mo)			142 (169)	136 (163)					--[386]	56% (92%)	<0.001	Good
%↓UAER											--	44% (8%)	<0.001	Good
ΔProteinuria, µg/min	DIAL 2004 Italy[28]	12 mo (12 mo)	Ramipril	Lercanidipine	66 (89)	64 (91)	S_{Cr} 79.6 µmol/L	UAER 86.5 µg/min	156/93 (155/92)	141/80 (140/81)	66.9[387] (86.5)	-19.7 (-34.1 to 5.3) (-17.4 (-32.0 to 2.8))	<0.05	Fair
Mean albuminuria value during treatment period, mL/min	Chan 2000 [388] Hong Kong[25]	60 mo (60 mo)	Enalapril	Nifedipine	52 (52)	50 (50)	CrCl 73.7 mL/min	UAE 73.4 mg/24h	172/93 (169/93)	137/72 (132/72)	73.7[389] (76.9)	-12.2 (-11.6)	<0.01	Good

[384] Shaded studies were included in previous KDOQI guideline
[385] Primary outcome
[386] Primary outcome
[387] Primary outcome
[388] All patients were Chinese
[389] Primary outcome

Supplemental Table 43. Evidence profile of RCTs examining the effect of ACEI vs. ARB in patients with Type 2 DKD

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	0 RCTs	--	--	--	--	--	--	--	Critical
Mortality	1 RCT (High)	250 (130)	Some limitations (-1)	NA	Direct (0)	Sparse (1) Imprecision (-1)	Very low	Insufficient evidence for ACEI and ARB.	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	1 RCT (High)	250 (130)	Some limitations (-1)	NA	Direct (0)	Sparse (1) Imprecision (-1)	Very low	Insufficient evidence for ACEI and ARB.	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Kidney function (categorical)	0 RCTs	--	--	--	--	--	--	--	High
ΔKidney function (continuous)	2 RCTs (High) [1˚ in 1 RCT]	348 (179)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	Sparse (-1)	Very low	Insufficient evidence for ACEI and ARB.	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	3 RCTs (High) [1˚ in 1 RCT]	567 (289)	Serious limitations (-2)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Very low	Insufficient evidence for ACEI and ARB.	Moderate
Adverse events	1 RCT	250 (130)						Drug discontinuation: 14% for ACEI and 18% in CCB Early rise in creatinine: 0.02% in ACEI and 0.02% in CCB	Moderate
Total	3 RCTs	567 (289)							

Balance of potential benefits and harms
Insufficient evidence for CV outcomes
Insufficient evidence for kidney outcomes

Quality of overall evidence
Very low for CV outcomes
Very low for kidney outcomes

Supplemental Table 44. RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Mortality														
Death	Barnett 2004 Multi[16]	60 mo (60 mo)	Enalapril	Telmisartan	130 (130)	120 (120)	GFR 94.3 mL/min/1.73 m^2 S_{Cr} 0.99 mg/dL	Median UAE 60 µg/min	152/86 (153/85)[390]	149/79[391] (146/80)	6 (5%) [6 (5%)]	RR 0.92 (0.31; 2.78)[392]	nd	Fair
CV events														
CHF/Non-fatal MI	Barnett 2004 Multi[16]	60 mo (60 mo)	Enalapril	Telmisartan	130 (130)	120 (120)	GFR 94.3 mL/min/1.73 m^2 S_{Cr} 0.99 mg/dL	Median UAE 60 µg/min	152/86 (153/85)	149/79[393] (146/80)	13 (10%) [18 (15%)]	RR 0.67[394] (0.34; 1.30)	nd	Fair
Stroke											6 (5%) [6 (5%)]	RR 0.92 (0.31; 2.78)[395]	nd	Fair

[390] Estimated from figure
[391] Estimated from figure
[392] Calculated by ERT
[393] Estimated from figure
[394] Calculated by ERT
[395] Calculated by ERT

Supplemental Table 45. RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
Kidney function														
ΔGFR, ml/min/1.73 m^2	Barnett 2004 Multi[16]	60 mo (60 mo)	Enalapril	Telmisartan	130 (130)	120 (120)	GFR 94.3 mL/min/1.73 m^2 S_{Cr} 0.99 mg/dL	Median UAE 60 µg/min	152/86 (153/85)	149/79[396] (146/80)	94.3[397] (91.4)	-14.9 [-17.9]	nd	Fair
Difference in ΔGFR, ml/min/1.73 m^2												3.0 (+7.6; -1.6)[398]		
ΔS_{Cr}, mg/dL												0.10 [0.10]		
Difference in ΔS_{Cr}, mg/dL												0 (-0.66; 0.65)		
Geometric means of GFR, mL/min	Lacourciere 2000 Canada[48]	12 wk (52 wk)	Enalapril	Losartan	49 (52)	49 (51)	GFR 95 mL/min	UAE 73.9 µg/min	154/88 (158/90)	138/79 (144/82)	95 (97)	-2[399] (-6)	nd	Fair
		28 wk (52 wk)									95 (97)	-5[400] (-10)	nd	Fair
		52 wk (52 wk)									95 (97)	-5[401] (-9)	nd	Fair
Proteinuria														
ΔUAE rate	Barnett 2004 Multi[16]	5 y (5 y)	Enalapril	Telmisartan	130 (130)	120 (120)	GFR 94.3 mL/min/1.73 m^2 S_{Cr} 0.99 mg/dL	Median UAE 60 µg/min	152/86 (153/85)	149/79[402] (146/80)	60 (46)	0.99 [1.03]	nd	Fair
ΔUAE rate (between-group difference)												1.04 (0.71; 1.51)		
Adjusted reduction in AER, mg/24h	Sengul 2006 Turkey[88]	24 wk (24 wk)	Lisinopril	Telmisartan	110 (110)	109 (119)	CrCl 96.4 mL/min S_{Cr} 85.4 mmol/L	Median AER 264 mg/24h	151/88 (150/90)	140/82 (140/85)	264[403] (256)	-98 (-80)[404]	NS	Poor

[396] Estimated from figure
[397] Primary outcome
[398] Since upper level of 95% CI of the difference between the enalapril and telmisartan groups was greater than +10ml/min/1.73m^2, in favor of enalapril, telmisartan is not inferior to enalapril.
[399] Estimated from figure
[400] Estimated from figure
[401] Estimated from figure
[402] Estimated from figure
[403] Primary outcome
[404] Adjusted mean difference 18 (95% CI 0; 37), Adjusted for treatment, baseline value, weight and change in DBP. Adjusted mean difference 18, (0; 37.0) p=0.12

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
ΔS_{Cr}, mmol/L											85.4 (85.6)	-1.4 (+0.4)		
Geometric means of albuminuria, µg/min	Lacourciere 2000 Canada[48]	12 wk (52 wk)	Enalapril	Losartan	49 (52)	49 (51)	GFR 95 mL/min	UAE 73.9 µg/min	154/88 (158/90)	138/79 (144/82)	73.9 (64.1)	-23.2 (-9.0)	NS	Fair
		28 wk (52 wk)									73.9 (64.1)	-34.5 (-27.3)	NS	Fair
		52 wk (52 wk)									73.9 (64.1)	-40.4 (-22.6)	NS[405]	Fair

[405] There was no significant difference between groups with respect to the change from baseline in log UAE after 12 and 28 weeks of treatment. At week 52, analyses showed a significant quantitative treatment-by-center interaction characterized by a variation in the magnitude of treatment differences from center to center. The difference between groups with respect to the change from baseline in log UAE is not significant when the interaction is taken into account and significant (P = 0.026) otherwise

Supplemental Table 46. Evidence profile of RCTs examining the effect of ARB vs. ARB in patients with CKD and DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	2 RCTs (High)	1684 (835)	No limitations (0)	Important inconsistency[406] (-1)	Direct (0)	None (0)	Moderate	No difference	Critical
Mortality	2 RCTs (High)	1684 (835)	No limitations (0)	Important inconsistency (-1)	Direct (0)	Imprecision (-1)	Low	Possible benefit for Telmisartan	Critical
CV mortality and morbidity	2 RCTs (High)	1684 (835)	No limitations (0)	Important inconsistency (-1)	Direct (0)	None (0)	Moderate	Possible benefit for Telmisartan	Critical
ESRD	1 RCT (High)	857 (428)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence for Telimisartan	Critical
Kidney function (categorical)	1 RCT (High)	857 (428)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence for Telimisartan	Critical
∆Kidney function (continuous)	1 RCT (High)	857 (428)	No limitations (0)	NA	Uncertainty about directness (-1)	Sparse (-1)	Low	Possible benefit for Valsartan on measured CrCl (but not for S_{Cr} or eGFR).	Moderate
Proteinuria (categorical)	1 RCT (High)	340 (168)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	No difference	High
Proteinuria (continuous)	3 RCTs (High) [1˚ in 2 RCTs]	2024 (1003)	No limitations (0)	Important inconsistency (-1)	Uncertainty about directness (-1)	None (0)	Low	Possible benefit for Telmisartan	Moderate
Adverse events	3 RCTs	2024 (1003)						Drug discontinuation: 1.4-2% for ARB and 1.4-3% in ARB (from 2 RCTs) Hyperkalemia: 2% for ARB and 3% for ARB (from 1 RCT)	Moderate
Total	3 RCTs	2024 (1003)							

Balance of potential benefits and harms

Possible benefit for telmisartan vs. losartan for CV outcomes but no difference between telmisartan vs. valsartan.
Insufficient evidence for kidney outcomes

Quality of overall evidence

Moderate for CV outcomes
Low for kidney outcomes

[406] For mortality, the AMADEO study showed statistically significant benefit and Galle study was not statistically significant

Supplemental Table 47. RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Composite of doubling of S_{Cr}, ESRD or all-cause death	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/83)	142/79 (142/78)	22 (5%) [18 (4%)]	RR 1.23[407] (0.67; 2.25)	NS	Good
Composite of doubling of S_{Cr}, ESRD and death	AMADEO 2008 Multi[14]	12 mo (12 mo)	Telmisartan	Losartan	407 (419)	420 (441)	eGFR 49.5 mL/min/1.73 m^2 S_{Cr} 1.54 mg/dL	UPCR 1971 mg/g	144/80 (143/80)	135/77 (136/77)	3% [6%]	RR 0.5[408] (0.25; 0.97)	NS (0.08)	Good
Mortality														
All cause death	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	15 (4%) [8 (2%)]	RR 1.88[409] (0.81; 4.39)	NS	Good
All-cause mortality	AMADEO 2008 Multi[14]	12 mo (12 mo)	Telmisartan	Losartan	407 (419)	420 (441)	eGFR 49.5 mL/min/1.73 m^2 S_{Cr} 1.54 mg/dL	UPCR 1971 mg/g	144/80 (143/80)	135/77 (136/77)	2 (0.5%) [13 (3%)]	RR 0.16[410] (0.04; 0.70)	0.007	Good
CV mortality														
Death from cardiovascular cause	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	8 (2%) [6 (1%)]	RR 1.34[411] (0.47; 3.82)	nd	Good
CV mortality and morbidity														
Composite CV morbidity and mortality	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	31 (7%) [33 (8%)]	RR 0.94[412] (0.59; 1.51)	NS	Good
Myocardial infarction											4 (1%) [11 (3%)]	RR 0.36[413] (0.12; 1.14)	nd	Fair
Stroke											11 (3%) [5 (1%)]	RR 2.21[414] (0.77; 6.29)	nd	Fair

[407] Calculated by ERT
[408] Calculated by ERT
[409] Calculated by ERT
[410] Calculated by ERT
[411] Calculated by ERT
[412] Calculated by ERT
[413] Calculated by ERT
[414] Calculated by ERT

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
Cardiovascular morbidity and mortality	AMADEO 2008 Multi[14]	12 mo (12 mo)	Telmisartan	Losartan	407 (419)	420 (441)	eGFR 49.5 mL/min/1.73 m^2 S_{Cr} 1.54 mg/dL	UPCR 1971 mg/g	144/80 (143/80)	135/77 (136/77)	21 (5%) [37 (9%)]	RR 0.59[415] (0.35; 0.98)	0.04	Good
ESRD														
ESRD	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	7 (2%) [8 (2%)]	RR 0.88[416] (0.32; 2.40)	NS	Good
Kidney function														
Doubling of S_{Cr}	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	3 (1%) [3 (1%)]	RR 1.00 (0.20; 4.94)[417]	NS	Good
Proteinuria														
Transition rates from incipient to overt nephropathy (UACR >300 mg/g and ↑≥30%)	INNOVATION 2007 Japan[55]	16mo (≥12mo)	Telmisartan 80mg	Telmisartan 40mg	168 (nd)	172 (nd)	S_{Cr} 0.8 mg/dL	UACR 172 mg/g	138/78 (137/78)	128/74 (132/74)	28 (17%) [39 (23%)]	RR 1.00[418] (0.67; 1.48)	nd	Good
Transition rate in normotensive patients											6 (11%) [12 (21%)	RR 0.51[419] (0.20; 1.33)	nd	Good
Micaroalbuminuria remission											36 (21%) [22 (13%)]	RR 1.68[420] (1.03; 2.72)	nd	Good

[415] Calculated by ERT
[416] Calculated by ERT
[417] Calculated by ERT
[418] Calculated by ERT
[419] Calculated by ERT
[420] Calculated by ERT

Supplemental Table 48. RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
Kidney function														
%ΔeGFR, ml/min/1.73 m	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	48.4 (48.6)	-6% (-5%)	NS	Good
%ΔCrCl, ml/min/1.73 m^2											57.8 (59.0)	-21% (-14%)	0.001	Good
%ΔS_{Cr}, mg/24h											2750 (2890)	14% (12%)	NS	Good
Proteinuria														
%ΔUPER, mg/24h	VIVALDI 2008 Multi[37]	12 mo (12 mo)	Telmisartan	Valsartan	428 (443)	429 (442)	eGFR 56.7 ml/min/1.73 m^2	UPER 2.7 g/d	148/82 (149/82)	142/79 (142/78)	2750[421] (2890)	33% (-33%)	NS	Good
%ΔUAE, mg/24h											2750 (2890)	-39% (-36%)	NS	Good
UPCR	AMADEO 2008 Multi[14]	12 mo (12 mo)	Telmisartan	Losartan	407 (419)	420 (441)	eGFR 49.5 mL/min/1.73 m^2 S_{Cr} 1.54 mg/dL	UPCR 1971 mg/g	144/80 (143/80)	135/77 (136/77)	NA	29.8 (21.4)[422]	0.03	Good
↓UACR											1426[423] (1390)	35.5 (27.0)	0.04	Good
ΔUACR after adjustment for SBP, mg/g	INNOVATION 2007 Japan[55]	16mo (≥12mo)	Telmisartan 80mg	Telmisartan 40mg	168 (nd)	172 (nd)	S_{Cr} 0.8 mg/dL	UACR 172 mg/g	138/78 (137/78)	128/74 (132/74)	172 (173)	-58.8 (-37.9)	nd	Good

[421] Primary outcome
[422] Adjustment made for an analysis of covariance that included treatment and pooled center as class effects, with baseline as a covariate, was performed on the log-transformed data
[423] Primary outcome

Supplemental Table 49. RCTs examining the effect of DRI + ARB vs. placebo+ ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
Kidney function														
↓eGFR, ml/min/1.73 m^2	AVOID 2008 2010 Multi[75;78]	6 mo (6 mo)	Aliskiren + Losartan	Placebo + Losartan	259 (301)	265 (298)	eGFR 68.5 mL/min/1.73 m^2	UACR 513 mg/g	135/78 (134/77)	133/78 (135/79)[424]	68.5 (66.8)	2.4 (1.1; 3.7) (3.8 (2.5; 5.1))	NS (0.07)	Good
Δ eGFR in patients with GFR <60 ml/min/1.73 m^2					129 (129)	119 (119)	eGFR 47.1 mL/min/1.73 m^2	UACR 628 mg/g	136/77 (135/75)	133/76 (139/75)	47.1 (44.7)	-1.7 (+0.25)	NS	Good
Δ eGFR >60-<90 in patients with GFR 60-90 ml/min/1.73 m^2					104 (104)	122 (122)	eGFR 73.6 mL/min/1.73 m^2	UACR 410 mg/g	134/78 (133/78)	136/78 (135/80)	73.6 (72.4)	-2.7 (-4.8)	NS	Good
Δ eGFR in patients with GFR >90 ml/min/1.73 m^2					64 (64)	51 (51)	eGFR 102.5 mL/min/1.73 m^2	UACR 530 mg/g	135/80 (133/78)	134/79 (134/79)	102.5 (100.4)	-5.6 (-9.5)	NS	Good
Proteinuria														
Difference in %↓UACR, mg/g	AVOID 2008 2010 Multi[75;78]	6 mo (6 mo)	Aliskiren + Losartan	Placebo + Losartan	259 (301)	265 (298)	eGFR 68.5 mL/min/1.73 m^2	UACR 513 mg/g	135/78 (134/77)	133/78 (135/79)[425]	513[426] (553)	18% (7; 28)[427] (N/A)	0.002	Good
Difference in %↓overnight UAE rate (geometric mean)											N/A	17% (4; 29)[428] (N/A)	0.02	Good
ΔUACR at 24 wks (%) in patients with GFR <60 ml/min/1.73 m^2, mg/g					129 (129)	119 (119)	eGFR 47.1 mL/min/1.73 m^2	UACR 628 mg/g	136/77 (135/75)	133/76 (139/75)	628 (670)	-9 (+13)	0.045	Good

[424] Estimated from graph
[425] Estimated from graph
[426] Primary outcome
[427] Adjustment for the change from baseline in systolic blood pressure
[428] Adjustment for the change from baseline in systolic blood pressure

ΔUACR at 24 wks (%) in patients with GFR >60-90 ml/min/1.73 m^2, mg/g	104 (104)	122 (122)	eGFR 73.6 mL/min/1.73 m^2	UACR 410 mg/g	134/78 (133/78)	136/78 (135/80)	410 (484)	-23 (-1)	0.021	Good
ΔUACR at 24 wks (%) in patients with GFR >90 ml/min/1.73 m^2, mg/g	64 (64)	51 (51)	eGFR 102.5 mL/min/1.73 m^2	UACR 530 mg/g	135/80 (133/78)	134/79 (134/79)	530 (405)	-27 (-11)	0.202	Good
UACR reduction ≥50 (%) in patients with GFR <60 ml/min/1.73 m^2, mg/g	129 (129)	119 (119)	eGFR 47.1 mL/min/1.73 m^2	UACR 628 mg/g	136/77 (135/75)	133/76 (139/75)	628[429] (670)	25/122 (11/115)	0.019	Good
UACR reduction ≥50 (%) in patients with GFR >60 ml/min/1.73 m^2, mg/g	104 (104)	122 (122)	eGFR 73.6 mL/min/1.73 m^2	UACR 410 mg/g	134/78 (133/78)	136/78 (135/80)	410[430] (484)	28/101 (17/118)	0.012	Good
UACR reduction ≥50 (%) in patients with GFR >90 ml/min/1.73 m^2, mg/g	64 (64)	51 (51)	eGFR 102.5 mL/min/1.73 m^2	UACR 530 mg/g	135/80 (133/78)	134/79 (134/79)	530[431] (405)	18/62 (8/50)	NS	Good

[429] Primary outcome
[430] Primary outcome
[431] Primary outcome

Supplemental Table 50. RCTs examining the effect of dihydropyridine CCB vs. placebo in overtly albuminuric patients with CKD and Type 2 DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control	Events (%) Intervention [Control]	RR/OR/HR (95% CI)		
CV mortality														
CV mortality	IDNT 2003 Multi[18]	30 mo (≥24 mo)	Amlodipine	Placebo	565 (567)	565 (569)	S_{Cr} 1.65 mg/dL	UPE 2.9 g/d	159/87 (158/87)	141/77 (144/80)	37 (7%) [46 (8%)]	HR 0.79 (0.51; 1.22)	NS	Good
CV events														
Composite CV events											278 (in 28% of patients) [432] [284 (in 33% of patients)]	HR 1.00 (0.83; 1.21)	NS	Good
CHF											143 (in 16% of patients) [433] [113 (in 13% of patients)]	HR 1.11 (0.83; 1.50)	NS	Good
Myocardial infarction	IDNT 2003 Multi[18]	30 mo (≥24 mo)	Amlodipine	Placebo	565 (567)	565 (569)	S_{Cr} 1.65 mg/dL	UPE 2.9 g/d	159/87 (158/87)	141/77 (144/80)	29 (in 5% of patients) [434] [51 (in 9% of patients)]	HR 0.58 (0.37; 0.92)	0.021	Good
CVA											18 (in 3% of patients) [435] [28 (in 5% of patients)]	HR 0.65 (0.35; 1.22)	NS	Good
Cardiac revascularization											32 (in 5% of patients) [436] [39 (in 6% of patients)]	HR 0.86 (0.54; 1.38)	NS	Good

[432] Primary outcome
[433] Primary outcome
[434] Primary outcome
[435] Primary outcome
[436] Primary outcome

Supplemental Table 51. RCTs examining the effect of aldosterone antagonist + ACEI vs. placebo + ACEI in patients with CKD and Type 2 DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Overt albuminuria														
%↓UACR	Epstein 2006 Multi[33]	3 mo (3 mo)	Eplerenone 50 + Enalapril	Placebo + Enalapril	83 (91)	80 (91)	GFR 73 mL/min S_{Cr} 80µmol/L	UACR 422 mg/g	140/83 (146/88)	nd	422[437] (280)	-43 (-9)	<0.001	Good
Microalbuminuria														
%↓UACR	Epstein 2006 Multi[33]	3 mo (3 mo)	Eplerenone 100 + Enalapril	Placebo + Enalapril	77 (86)	80 (91)	GFR 75 mL/min S_{Cr} 80µmol/L	UACR 240 mg/g	140/85 (146/88)	nd	240[438] (280)	-50 (-9)	<0.001	Good

[437] Primary outcome
[438] Primary outcome

Supplemental Table 52. RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite kidney outcomes														
Death, ESRD and doubling of S_{Cr}	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	37 (8%) [41 (9%)]	RR 0.95[439] (0.62; 1.45)	nd	Fair
Mortality														
Death	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	21 (5%) [17 (4%)]	RR 1.30[440] (0.69; 2.43)	nd	Fair
CV events														
CV event	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	68 (15%) [71 (15%)]	RR 1.01[441] (0.74; 1.37)	nd	Fair
CHF											27 (6%) [29 (6%)]	RR 0.98[442] (0.59; 1.63)	nd	Fair
ESRD														
ESRD	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	20 (4%) [24 (5%)]	RR 0.88[443] (0.49; 1.56)	nd	Fair
Kidney function														
Doubling of S_{Cr}	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	2 (0.4%) [4 (1%)]	RR 0.53[444] (0.10; 2.85)	nd	Fair

[439] Calculated by ERT
[440] Calculated by ERT
[441] Calculated by ERT
[442] Calculated by ERT
[443] Calculated by ERT
[444] Calculated by ERT

Supplemental Table 53. RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention (Control)		
Kidney function														
ΔeGFR, ml/min/1.73 m^2	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	34 (33)	-3.35 (-4.08)	nd	Good
Proteinuria														
Median %ΔACR, mg/mmol	ASCEND 2010 Multi[60]	5 mo (4 mo)	Avosentan 25 mg/d	Avosentan 50 mg/d	455 (455)	478 (478)	eGFR 34 mL/min/1.73 m^2	Median ACR 160.9 mg/mmol	137/78 (137/78)	131/74 (131/73)	160.9 (166.5)	-44.30 (-49.30)	nd	Good

Supplemental Table 54. Evidence profile of RCTs examining the effect of ACEI or ARB vs. CCB in transplant recipients without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	0 RCTs	--	--	--	--	--	--	--	Critical
Mortality	1 RCT (High)	154 (76)	Some limitations (-1)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Kidney function (categorical)	1 RCT (High)	154 (76)	Some limitations (-1)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
∆Kidney function (continuous)	2 RCTs [1˚ in 1 RCT] (High)	256 (130)	Some limitations (-1)	Important inconsistencies (-1)	Uncertainty about directness (-1)	Sparse (-1)	Very low	Insufficient evidence	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	2 RCTs (High)	256 (130)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	Sparse (-1)	Very low	No difference	Moderate
Adverse events	2 RCTs	256 (130)						Drug discontinuation: 0-5% for ACEI and 11% for CCB (from 2 RCTs)	Moderate
Total	2 RCTs	256 (130)							

Balance of potential benefits and harms

Possible benefit for increase in eGFR but insufficient evidence for clinically relevant outcomes

Quality of overall evidence

Very low for kidney outcomes

Supplemental Table 55. RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM [categorical outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Mortality														
Death	Midtvedt 2001 Norway[68]	1 y (1 y)	Lisinopril	Nifedipine	76 (76)	78 (78)	S_{Cr} 146 µmol/L GFR 43 mL/min	UPE 129 mg/L	170/104 (169/104)	nd	2 (3%) [0 (0%)]	--	nd	Fair
Kidney function														
↑GFR >5 mL/min	Midtvedt 2001 Norway[68]	1 y (1 y)	Lisinopril	Nifedipine	76 (76)	78 (78)	S_{Cr} 146 µmol/L GFR 43 mL/min	UPE 129 mg/L	170/104 (169/104)	nd	18 (23%) [49 (64%)]	RR 0.38[445] (0.24; 0.58)	nd	Fair
↓GFR >5 mL/min											3 (4%) [4 (5%)]	RR 0.77[446] (0.18; 3.33)	nd	Fair

[445] Calculated by ERT
[446] Calculated by ERT

Supplemental Table 56. RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome measurement (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
ΔGFR, mL/min	Midtvedt 2001 Norway[68]	1 y (1 y)	Lisinopril	Nifedipine	76 (76)	78 (78)	S_{Cr} 146 µmol/L GFR 43 mL/min	UPE 129 mg/L	170/104 (169/104)	nd	43‡ (46)	+1 (+10)	0.0001	Fair
ΔSCr, µmol/L		1 y (1 y)									146 (137)	-2 (-12)	0.013	Fair
		2 y (1 y)										0 (-14)	NS (0.06)	Fair
ΔSCr, mg/dL	el-Agroudy 2003 Egypt[32]	12 mo (12 mo)	Losartan	Amlodipine	54 (54)	48 (54)	S_{Cr} 1.5 mg/dL	0.8 g/d	MAP 108 (108)	MAP 95 (95)	1.5 (1.4)	0.0 (+0.1)	NS	Poor
			Captopril	Amlodipine				0.9 g/d	MAP 106 (108)	MAP 94 (95)	1.5 (1.4)	0.0 (+0.1)	NS	Poor
Proteinuria														
ΔUPE, mg/L	Midtvedt 2001 Norway[68]	1 y (1 y)	Lisinopril	Nifedipine	76 (76)	78 (78)	S_{Cr} 146 µmol/L GFR 43 mL/min	UPE 129 mg/L	170/104 (169/104)	nd	129 (124)	-49 (+136)	NS	Fair
		2 y (1 y)										-24 (+76)	NS	Fair
ΔProteinuria, g/d	el-Agroudy 2003 Egypt[32]	12 mo (12 mo)	Losartan	Amlodipine	54 (54)	48 (54)	S_{Cr} 1.5 mg/dL	0.8 g/day	MAP 108 (108)	MAP 95 (95)	0.8 (0.6)	-0.4 (+0.2)	nd	Poor
			Captopril	Amlodipine				0.9 g/d	MAP 106 (108)	MAP 94 (95)	0.9 (0.6)	-0.4 (+0.8)	nd	Poor

Supplemental Table 57. Evidence profile of RCTs examining the effect of CCB vs. placebo in transplant recipients without DM

Outcome	# of studies and study design	Total N (Treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Composite kidney outcomes	0 RCTs	--	--	--	--	--	--	--	Critical
Mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV mortality	0 RCTs	--	--	--	--	--	--	--	Critical
CV events	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Kidney function (categorical)	1 RCT (High)	253 (130)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	Insufficient evidence	High
∆Kidney function (continuous)	3 RCTs (High)	581 (287)	Some limitations (-1)	No important inconsistencies (0)	Uncertainty about directness (-1)	None (0)	Low	Benefit for CCB	Moderate
Proteinuria (categorical)	0 RCTs	--	--	--	--	--	--	--	High
Proteinuria (continuous)	0 RCTs	--	--	--	--	--	--	--	Moderate
Adverse events	2 RCTs	463 (228)						Drug discontinuation: 5% for CCB and 1-2% for placebo (from 2 RCTs)	Moderate
Total	3 RCTs	581 (287)							

Balance of potential benefits and harms:
Possible benefit for kidney function outcomes

Quality of overall evidence:
Low for kidney outcomes

Supplemental Table 58. RCTs examining the effect of CCB vs. placebo in transplant recipients [categorical outcome] [447]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Kidney function														
↑S_{Cr} >22.1 µmol/L	Rahn 1999 Germany[81]	24 mo (24 mo)	Nitrendipine	Placebo	130 (130)	123 (123)	S_{Cr} 146.7 µmol/L	nd	141/88 (143/88)	138/86 (143/90)	26 (20%) [40 (33%)]	RR 0.62[448] (0.40; 0.94)	0.026	Good

[447] Shaded studies were included in previous KDOQI guideline
[448] Calculated by ERT

Supplemental Table 59. RCTs examining the effect of CCB vs. placebo in transplant recipients without DM [continuous outcome] [449]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention) [Control]		
Kidney function														
↑S_{Cr}, µmol/L	Rahn 1999 Germany[81]	24 mo (24 mo)	Nitrendipine	Placebo	130 (130)	123 (123)	S_{Cr} 146.7 µmol/L	nd	141/88 (143/88)	138/86 (143/90)	146.7 (137.0)	+1.8 (+23.4)	0.025	Good
ΔCrCl, mL/min											nd	+1.2 (-4.1)	0.014	Good
Final SCr, µmol/L	van Riemsdijk 2000 Netherlands[94]	3 mo (12 mo)	Isradipine	Placebo	98 (98)	112 (112)	nd	nd	nd	nd	nd	185 (220)	0.002	Poor
		12 mo (12 mo)									nd	141 (158)	0.021	Poor
Final CrCl, mL/min		3 mo (12 mo)									nd	56 (50)	0.026	Poor
		12 mo (12 mo)									nd	63 (58)	NS	Poor
Graft function [S_{Cr}, mg/dL]	Kuypers 2004 Multi[47]	24 mo (24 mo)	Lacidipine	Placebo	59 (66)	59 (65)	S_{Cr} 1.8 mg/dL eGFR 52 mL/min Calculated GFR 61 mL/min	nd	150/90 (150/90)[450]	138/82 (144/84) [451]	1.8 (2.0)	-0.28 (-0.24)	0.005	Poor
Graft function [eCrCl, mL/min]											52 (47)	+11.1 (+6.4)	NS (0.09)	
Graft function [calculated CrCl, mL/min]											61 (51)	+11.0 (+2.5)	0.03	
Graft function [mGFR, mL/min]					53 (66)	53 (65)					50 (47)	-0.1 (-4.7)	<0.05	

[449] Shaded studies were included in previous KDOQI guideline
[450] Estimated from graph
[451] Estimated from graph

Supplemental Table 60. RCTs examining the effect of ACE vs. ARB in hypertensive transplant recipients without DM [continuous outcomes]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline MAP Intervention (Control)	Achieved MAP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
ΔS_{Cr}, mg/dL	el-Agroudy 2003 Egypt[32]	12 mo (12 mo)	Captopril	Losartan	54 (54)	54 (54)	S_{Cr} 1.5 mg/dL	0.9 g/d	106 (108)	94 (95)	1.5 (1.5)	0.0 (0.0)	nd	Poor
Proteinuria														
ΔProteinuria, g/d	el-Agroudy 2003 Egypt[32]	12 mo (12 mo)	Captopril	Losartan	54 (54)	54 (54)	S_{Cr} 1.5 mg/dL	0.9 g/d	106 (108)	94 (95)	0.8 (0.9)	-0.4 (-0.4)	nd	Poor

Supplemental Table 61. RCTs examining the effect of ARB vs. placebo in transplant recipients [categorical outcome]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Events No (%) Intervention [Control]	RR/OR/HR (95% CI)		
Composite of kidney and CV outcomes														
Composite of all-cause mortality, CV morbidity and all-cause graft failure (CrCl<15mL/min or dialysis)	SECRET[452] 2010 EU[80]	20 mo (37 mo)	Candesartan	Placebo	255 (255)	247 (247)	nd	0.11 g/L	138/84 (138/85)	131/80 (137/83)	13 (5%)[453] [13 (5%)]	RR 0.97[454] (0.46; 2.05)	nd	Fair
Mortality														
All-cause mortality	SECRET[455] 2010 EU[80]	20 mo (37 mo)	Candesartan	Placebo	255 (255)	247 (247)	nd	0.11 g/L	138/84 (138/85)	131/80 (137/83)	3 (1%) [4 (2%)]	RR 0.73[456] (0.16; 3.21)	nd	Fair
CV mortality														
CV mortality	SECRET[457] 2010 EU[80]	20 mo (37 mo)	Candesartan	Placebo	255 (255)	247 (247)	nd	0.11 g/L	138/84 (138/85)	131/80 (137/83)	9 (4%) [5 (2%)]	RR 1.74[458] (0.59; 5.13)	nd	Fair
Proteinuria														
Nephrotic syndrome (proteinuria >3.5g/24h)	SECRET[459] 2010 EU[80]	20 mo (37 mo)	Candesartan	Placebo	255 (255)	247 (247)	nd	0.11 g/L	138/84 (138/85)	131/80 (137/83)	2 (1%) [2 (1%)]	RR 0.97[460] (0.14; 6.82)	nd	Fair

[452] A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.
[453] Primary outcome
[454] Calculated by ERT
[455] A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.
[456] Calculated by ERT
[457] A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.
[458] Calculated by ERT
[459] A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.
[460] Calculated by ERT

Supplemental Table 62. RCTs examining the effect of ARB vs. placebo in transplant recipients without DM [continuous outcome]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline SBP/DBP Intervention (Control)	Achieved SBP/DBP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention) [Control]		
Proteinuria														
ΔAlbumin concentration, mg/L	SECRET[461] 2010 EU[80]	20 mo (37 mo)	Candesartan	Placebo	255 (255)	247 (247)	nd	0.11 g/L	138/84 (138/85)	131/80 (137/83)	16.40 (16.70)	-1.80 (+1.05)	0.0001	Fair
ΔProtein concentration, g/L											0.11 (0.11)	-0.01 (0.00)	0.003	Fair
ΔUPE rate, g/24h											0.12 (0.14)	-0.01 (+0.03)	<0.0001	Fair
Relative ΔUPCR, %											0.01 (0.02)	-15.0 (+23.5)	0.0003	Fair

[461] A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.

Supplemental Table 63. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [categorical outcome]

Outcome)	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline MAP Intervention (Control)	Achieved MAP Intervention (Control)	Events No (%) Intervention [Control]	HR (95% CI)		
Composite kidney outcome														
↓50% GFR or progression to ESRD	ESCAPE 2009 EU[34]	5 y (5 y)	Intensified BP control (Target MAP <50th percentile)	Conventional BP control (Target MAP 50th-95th percentile)	182 (189)	190 (196)	GFR 46 mL/min/1.73 m^2	UPCR 1.4	90 (90)	Total cohort 82	46 (25%) [69 (36%)]	HR 0.65 (0.44; 0.94)	0.02	Good
Mortality														
Death	ESCAPE 2009 EU[34]	5 y (5 y)	Intensified BP control (Target MAP <50th percentile)	Conventional BP control (Target MAP 50th-95th percentile)	182 (189)	190 (196)	GFR 46 mL/min/1.73 m^2	UPCR 1.4	90 (90)	Total cohort 82	0 (0%) [1 (1%)]	--	nd	Fair
ESRD														
Actuarial 5-y rate of delay in the progression of renal disease[462]	ESCAPE 2009 EU[34]	5 y (5 y)	Intensified BP control (Target MAP <50th percentile)	Conventional BP control (Target MAP 50th-95th percentile)	182 (189)	190 (196)	GFR 46 mL/min/1.73 m^2	UPCR 1.4	90 (90)	Total cohort 82	70% [58%]	--	0.02	Good

[462] 50% decline in the glomerular filtration rate or progression to end-stage renal disease

Supplemental Table 64. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [continuous outcome]

Outcome	Study Year Country	Duration Outcome (Treatment)	Description		No analyzed / Enrolled		Baseline GFR or S_{Cr}	Baseline Proteinuria	Blood pressure		Results		P value	Quality
			Intervention	Control	Intervention	Control			Baseline MAP Intervention (Control)	Achieved MAP Intervention (Control)	Baseline Intervention (Control)	Δ Intervention [Control]		
Kidney function														
Annual ↓GFR rate, mL/min/1.73 m^2	ESCAPE 2009 EU[34]	5 y (5 y)	Intensified BP control (Target MAP <50th percentile)	Conventional BP control (Target MAP 50th-95th percentile)	182 (189)	190 (196)	GFR 46 mL/min/1.73 m^2	UPCR 1.4	90 (90)	Total cohort 82	46 (45)	1.1 (2.5)	NS	Good
Proteinuria														
Median UPE, g/g	ESCAPE 2009 EU[34]	6 mo (5 y)	Intensified BP control (Target MAP <50th percentile)	Conventional BP control (Target MAP 50th-95th percentile)	372 (385)		GFR 46 mL/min/1.73 m^2	UPCR 1.4	90 (90)	Total cohort 82	0.82 (IQR 0.27; 1.74)	0.36 (IQR 0.11; 0.95)	<0.0001	Fair

Supplemental Table 65. Age restriction in all RCTs for DM CKD, non-DM CKD, Transplant and CKD subgroups

Study, Year	Inclusion Criteria	Arm 1 (mean age ± SD)	Arm 2 (mean age ± SD)	Arm 3 (mean age ± SD)	Arm 4 (mean age ± SD)	Arm 5 (mean age ± SD)	Arm 6 (mean age ± SD)
DM							
Agardh 1996[5]	Males: 18-75y and Postmenopausal females: 40-75 y	Lisinopril (59 ± 9.0)	Nifedipine (58 ± 8.9)				
Agha 2009[6]	nd	Losartan (53.9 ± 11.1)	Control (54.7 ± 10.9)				
J-MIND 2001[13]	<75 y	Enalapril (59.9 ± 8.6)	Nifedipine (60.2 ± 8.9)				
AMADEO 2008[14]	21-80 y	Telmisartan (60.0 ± 9.2) 66.8% <65y	Losartan (60.5 ± 9.4) 62.1% <65 y				
Barnett 2004[16]	35-80 y	Enalapril (61.2 ± 8.5)	Telmisartan (60.0 ± 9.1)				
IDNT 2003[18]	30-70 y	Irbesartan (59.3 ± 7.1)	Amlodipine (59.1 ± 7.9)	Placebo (58.3 ± 8.2)			
RENAAL 2001[20]	31-70 y	Losartan (60 ± 7)	Placebo (60 ± 7)				
Chan 1992[24]	>18 y	Enalapril (60.1 ± 9.2)	Nifedipine (56.1 ± 9.9)				
Chan 2000[25]	nd	Enalapril (60.0 ± 9.3)	Nifedipine (56.2 ± 9.9)				
DIAL 2004[28]	40-70 y	Ramipril (60 ± 7)	Lercanidipine (58 ± 7)				
Epstein 2006[33]	nd	Eplerenone 100 mg [Median (25^{th}-75^{th} percentile)] [58 (53; 66)]	Eplerenone 50 mg [Median (25^{th}-75^{th} percentile)] [58 (52; 66)]	Placebo [Median (25^{th}-75^{th} percentile)] [60 (53; 66)]			
VIVALDI 2008[37]	30-80 y	Telmisartan (60.9 ± 9.2)	Valsartan (61.4 ± 9.1)				
Lacourciere 2000[48]	nd	Enalapril [57.8 (1.5)]	Losartan [59.2 (9.2)]				
Laffel 1995[49]	14-57 y	Enalapril (32.0 ± 8.1)	Nifedipine (33.4 ± 9.0)				
Lewis 1993[51]	18-49 y	Captopril (35 ± 7)	Placebo (34 ± 8)				
IDNT 2001[52]	30-70 y	Irbesartan (59.3 ± 7.1)	Amlodipine (59.1 ± 7.9)	Placebo (58.3 ± 8.2)			
ASCEND 2010[60]	21-80 y	Avosentan 50 mg (61.0 ± 9.1)	Avosentan 25 mg (61.2 ± 8.8)	Placebo (60.8 ± 8.9)			
DIABHYCAR 2004[65]	>50 y	Ramipril (65.2 ± 8.4)	Placebo (65.0 ± 8.3)				

Study, Year	Inclusion Criteria	Arm 1 (mean age ± SD)	Arm 2 (mean age ± SD)	Arm 3 (mean age ± SD)	Arm 4 (mean age ± SD)	Arm 5 (mean age ± SD)	Arm 6 (mean age ± SD)
IRMA 2001[74]	30-70	Irbesartan 300 mg (57.3 ± 7.9)	Irbesartan 150 mg (58.4 ± 8)	Placebo (58.3 ± 8.7)			
AVOID 2008[75]	18-85 y	Aliskiren (58.9 ± 9.6)	Placebo (61.8 ± 9.6)				
Ravid 1993[82]	nd	Enalapril or Placebo (44 ± 4) [range 34; 49 y]					
RENAAL 2004[83]	>30 y	Lowest Tertile Losartan (59.6 ± 7.4)	Lowest Tertile Placebo (60.2 ± 7.5)	Middle Tertile Losartan (60.7 ± 7.2)	Middle Tertile Placebo (60.3 ± 7.6)	Highest Tertile Losartan (59.6 ± 7.4)	Highest Tertile Placebo (60.5 ± 7.4)
Sengual 2006[88]	40-65	Lisinopril (56.7 ±8.3)	Telmisartan (56.5 ±8.2)				
Trevisan 1995[92]	18-65 y	Ramipril (56 ± 7)	Placebo (58 ± 7)				
MARVAL 2002[95]	35-75 y	Valsartan (59) [range 36; 75]	Amlodipine (57) [range 35; 75]				
Non-DM							
AASK 2001[7]	18-70 y	Ramipril (54.2 ± 10.9)	Amlodipine (54.4 ± 10.7)				
SMART 2009[22]	18-80 y	Candesartan 16mg (56.5 ± 12.2)	Candesartan 64 mg (58.4 ± 12.4)	Candesartan 128 mg (54.6 ± 12.6)			
Cinotti 2001[26]	18-70 y	Lisinopril (49.6 ± 10.8)	Control (52.1 ± 11.0)				
Del Vecchio 2004[30]	18-70 y	Enalapril (52.9 ± 10.5)	Mandipine (56.4 ± 10.0)				
ESCAPE 2009[34]	3-18 y	Intensified BP Control (11.5 ± 4.1)	Conventional BP Control (11.5 ± 4.0)				
AVER 2008[35]	18-80 y	Enalapril (58.3 ± 11.3)	Amlodipine (57.5 ± 12.9)				
CARTER 2007[36]	20-80 y	Cilnidipine (59.9 ± 13.3)	Amlodipine (59.3 ± 12.9)				
GISEN 1997[2]	nd	Ramipril (48.9 ± 13.6)	Placebo (49.7 ± 13.6)				
Nephros 2001[41]	18-74 y	Ramipril+Felodipine [Median (25^{th}-75^{th} percentile)] [52 (45; 60)]	Ramipril [Median (25^{th}-75^{th} percentile)] [53 (43; 61)]	Felodipine [Median (25^{th}-75^{th} percentile)] [54 (49; 62)]			
Hou 2006[43]	18-70 y	Benazepril (SCr 1.5-3.0 mg/dL) (45.1 ± 13.0)	Benazepril (SCr 3.1-5.0 mg/dL) (44.4 ± 16.8)	Placebo (45.0 ± 14.1)			
Hou 2007[42]	18-70	Benazepril (10 mg/d) (59.1 ± 12.6)	Benazepril (40 mg/d) (49.1 ± 14.3)	Losartan (50 mg/d) (51.5 ± 13.3)	Losartan (200 mg/d) (51.0 ± 13.5)		

Study, Year	Inclusion Criteria	Arm 1 (mean age ± SD)	Arm 2 (mean age ± SD)	Arm 3 (mean age ± SD)	Arm 4 (mean age ± SD)	Arm 5 (mean age ± SD)	Arm 6 (mean age ± SD)
J-LIGHT 2004[44]	20-74 y	Losartan (55.7 ± 13.6)	Amlodipine (57.5 ± 11.9)				
INNOVATION 2005[55]	30-74 y	Telmisartan 40 mg, Telmisartan 80 mg, or Placebo (61.7 ± 7.9)					
MDRD 1994[46]	18-70 y	No ages given					
HKVIN 2006[53]	≥18 y	Valsartan (41 ± 9)	Placebo (40 ± 10)				
ESPIRAL 2001[64]	18-75 y	Fosinopril (53 ± 14)	Nifedipine GTS (56 ± 14)				
Maschio 1996[66]	18-70 y	Benazepril (51 ± 13)	Placebo (51 ± 12)				
VALERIA 2008[67]	18-75 y	Valsartan (57.0 ± 11.4)	Lisinopril (59.7 ± 9.5)	Valsartan+Lisinopril (59.2 ± 11.4)			
AASK 2006[70]	18-70 y	Ramipril or Amlodipine or Metroprolol (55 ± 11)					
Peng 2009[76]	nd	Benidipine or Valsartan (43.2 ± 9.5)					
MDRD 1995[79]	18-70 y	Low BP goal or Usual BP goal (325 pts <55y; 260 pts ≥55y)					
Ruggenenti 1999[84]	nd	Ramipril (49.1 ± 1.3)	Control (50.3 ± 1.5)				
REIN 2005[85]	18-70 y	Intensified BP Control (54.6 ± 14.7)	Conventional BP Control (53.1 ± 15.8)				
MDRD 2005[86]	18-70 y	Low Target BP (51.5 ± 12.6)	Usual Target BP (52.0 ± 12.2)				
Vonend 2003[96]	≥18 y	Monoxidine (55.7 ± 14.0)	Nitrendipine (53.3 ± 13.4)				
Woo 2009[98]	nd	Normal dose ACE (34 ± 10)	Low dose ACE (32 ± 12)	Normal dose ARB (32 ± 10)	Low dose ARB (34 ± 11)		
AASK 2002[99]	18-70 y	Ramipril (54.4 ± 10.9)	Amlodipine (54.5 ± 10.7)	Metroprolol (54.9 ± 10.4)	Low BP target (54.5 ± 10.9)	High BP target (54.7 ± 10.4)	
Txp							
el-Agroudy 2003[32]	≥18 y	Losartan (29.9 ± 8)	Captopril (31.4 ± 8)	Amlodipine (28.6 ± 7)			
Kuypers 2004[47]	18-65 y	Lacidipine (46.5 ± 12.6)	Placebo (48.3 ± 12.6)				
Midvedt 2001[68]	≥18 y	Nifedipine (45.2 ± 8.4)	Lisinopril (43.5 ± 13.1)				
Philipp 2010[80]	30-69 y	Candesartan (50.0 ± 11.6)	Placebo (49.7 ± 10.9)				
Rahn 1999[81]	18-60 y	Nitrendipine (43 ± 1)	Placebo (42 ± 1)				

Study, Year	Inclusion Criteria	Arm 1 (mean age ± SD)	Arm 2 (mean age ± SD)	Arm 3 (mean age ± SD)	Arm 4 (mean age ± SD)	Arm 5 (mean age ± SD)	Arm 6 (mean age ± SD)
van Riemdijk 2000[94]	18-70 y	Isradipine (45) [range 21; 70]	Placebo (46) [range 25; 56]				
General Population							
ACCOMPLISH[15]	≥55 y	Benazepril + Amlodipine (≥65: 77.2%; ≥75: 35.7%)	Benazepril + Hydrochlorothalizide (≥65: 75.4%; ≥75: 28.9%)				
ADVANCE[29;40]	≥55 y	CKD Stage 1/. (65.0 ± 6.4)	CKD Stage 3 (68.3 ± 6.4)				
ALLHAT[50]	≥55 y	No ages given for CKD subgroup					
CASE-J[87]	20-85 y	No ages given					
EUROPA[19]	≥18 y	eGFR <75 (65.2)					
HOPE[57]	≥55 y	Candesartan (65.6 ± 10.3)	Amlodipine (65.3 ± 10.6)				
MICRO-HOPE[4]	≥55 y	No ages given for CKD subgroup					
ONTARGET[63]	≥55 y	No ages given					
Pahor[72]	≥60 y	Active treatment (73.9 ± 6.7)	Control (74.1 ± 7.0)				
PEACE[89;90]	≥50 y	eGFR<45: (70.2 ± 7.9) eGFR 45.0-59.9: (68.0 ± 7.7)					
PREVEND IT[12]	28-95 y	Active Fosinopril (51.1 ± 12.2)	Placebo (51.5 ± 12.2)				
PROGRESS[69]	nd	CKD Subgroup (70 ± 8)					
TRANSCEND[61]	≥55 y	No ages given for CKD subgroup					
Val-HeFT[10]	nd	CKD, No Proteinuria (66 ± 9)	CKD, Proteinuria (65 ± 10)				

Supplemental Table 66. PICO criteria for blood pressure targets in elderly studies

Study Author Year	Population	Duration	Intervention	Comparator	Achieved BP mmHg Intervention (Comparator)	Baseline GFR or SCr Intervention (Control)	Baseline Proteinuria	Outcomes
VALISH[71] Ogihara 2010 UI20530299	70-85 years, stable seated SBP of ≥160 to 199 mm Hg N=3260	Median 3 y	Strict treatment group (SBP<140 mm Hg)	Moderate treatment group (SBP maintained at ≥140 mm Hg and <150 mm Hg)	137/75 (142/77)	S_{Cr} ≤2.0 (≤2.0) mg/dL (based on exclusion criteria)	nd	Primary outcome: Composite of cardiovascular events: sudden death, fatal or non-fatal stroke, fatal or non-fatal MI, death due to heart failure, other cardiovascular death, hospitalization, and renal disorder HR 0.9 (0.6 to 1.34)
JATOS[45] Ishii 2008 UI19139601	Elderly (65-85) HTN patients SBP >160 mm Hg N=4508	2 y	Strict treatment group (SBP<140 mm Hg)	Moderate treatment group (SBP maintained at ≥140 mm Hg and <150 mm Hg)	136/75 (146/78)	S_{Cr} <1.5 (<1.5) mg/dL (based on exclusion criteria)	nd	Primary outcome: Combined incidence of cerebrovascular disease, cardiac and vascular disease and renal failure P=0.99 (P value between the 2 treatment groups did not differ significantly)
HYVET[17] Beckett 2008 UI18378519	80+years, SBP ≥160 mm Hg and <200 mm Hg sitting and ≥140 mm Hg standing with a sitting DBP of <110 mm Hg N=3845	Median 2 y	Indapamide (slow release 1.5 mg) Perindopril if needed (SBP <150 mm Hg DBP <80 mm Hg)	Placebo Matching placebo (SBP <150 mm Hg DBP <80 mm Hg)	145/79 (159/83)	S_{Cr} 88.6 (89.2) µmol/L (Excluded S_{Cr} >150 µmol/L or 1.7 mg/dL)	nd	Primary outcome: Fatal and non fatal stroke and death 51 events occurred in the active treatment group as compared with 69 events in the placebo group. RR of fatal and non fatal stroke of 30% (-1 to 51; P=0.06) RR of death from any cause of 21% (4 to 35; P=0.02)
STONE[38] Gong 1996 UI8906524	Patients 60-90 years, SBP≥160 mm Hg or DBP ≥96 mm Hg N=1632	30 mo	Nifedipine (SBP 140-159 mm Hg and DBP 90 mm Hg)	Placebo (Safety level SBP ≥200 mm Hg or DBP ≥110 mm Hg)	147/85 (156/92)	nd	nd	Primary outcome: Clinical events and risk modification. 77 events occurred in the placebo and 32 in the Nifedipine group. Significant reduction in relative risk was observed for strokes and severe arrhythmia with an overall decrease from 1.0 to 0.41 (CI 0.27 to 0.61). There was a significant decrease in RR in stages 2 and 3 HTN, which corresponded to 28.8 and 16.1% with placebo and Nifedipine.

Supplemental Table 67. Ages and BP targets in elderly studies

Trial	Year	N	Follow up (y)	Entry age (y)	Mean age (y)	Entry SBP (mm Hg)	Entry DBP (mm Hg)	Target SBP (mm Hg)	Target DBP (mm Hg)
ALLHAT Old[73]	2003	5700	4.9	>75	NA	≤180	≤110	<140	<90
ANBP2[31]	2003	6083	4.1	65-84	71.9	≥160	≥90	<160 and <140 if tolerated	<90 and <80 if tolerated
CASTEL[23]	1994	655	7.0	≥65	73.7	≥160	≥95	NS	NS
EWPHE[8]	1985	840	4.7	≥60	72	160-239	90-119	NA	<90
HEP[9]	1986	884	4.4	60-79	68.8	≥170	≥105	<170	<105
HYVET pilot[21]	2003	1283	1.1	≥80	83.8	170-219 and SBP≥140	95-119	<150	<80
HYVET[17]	2008	3845	1.8	≥80	83.6	≥160 -199 and ≥140 standing	90-110	<150	<80
JATOS[45]	2008	4418	2.0	65-85	NA	≥160	NS	<140 (strict) or <160 but, at or >140 (mild)	NS
MRC Older[93]	1992	4396	5.8	65-74	70.3	160-209	<114	If ≥180, then ≤ 160; if <180, then ≤150	NA
NISC-EH[3]	1999	414	3.9-4.5	≥60	69.8	160-220	<115	NA	NA
SCOPE[54]	2003	4969	3.7	70-89	76.4	160-179	90-99	<160	<90
SHELL[56]	2003	1882	2.7	≥60	72.4	≥160	≤95	≤160 and >20	NA
SHEP[1]	1991	4736	4.5	≥60	71.6	160-219	<90	If>180, then <160; if 160-180, then -20	NA
STONE[38]	1996	1632	3.0	60-79	66.4	≥160	>95	140-159	<90
STOP[27]	1991	1627	2.1	70-84	75.7	180-230 and DBP≥90	105-120	<160	<90
STOP 2[39]	1999	6614	5.0	70-84	76	≥180	≥105	<160	<95
SYST China[97]	1998	2394	3.0	≥60	66.5	160-219	<95	<150 and ≥20	NA
SYST Eur[91]	1997	4695	2.0	≥60	70.3	160-219 and SBP≥140	<95	<150 and ≥20	NA
VALISH[71]	2010	3079	3.07	70-84	76.1	SBP 160-199	NS	Strict SBP<140 and moderate ≥140 to <150	NS

Supplemental Table 68. PICO criteria for blood pressure agents in elderly studies

Study Author Year	Population	Duration	Intervention	Comparator	Achieved BP mmHg Intervention (Comparator)	Baseline GFR or SCr Intervention (Control)	Baseline Proteinuria	Outcomes
EWPHE[8] Amery 1958 UI2856778	60 years old +, SBP between 160 and 239 mmHg and between 90 and 119 mm Hg DBP sitting, consent N=840	12 y	HCTZ 25mg or Triamterene 50mg (titrated)	Placebo	148/85 (167/90)	nd	nd	Primary outcome: Morbidity and mortality Total cardiovascular mortality rate was significantly reduced (-38%, P=0.023) Non-fatal morbid cardiovascular study-terminating events occurred at a rate of 20/1000 patients-years in the placebo group and 8/1000 patient-years in the actively treated group. This reduction (-60%, P=0.0064) was mainly accounted for by a 63% reduction in severe CHF.
MRC[93] Tuomilheto 1992 UI1352716	Patients age 65-74, mean SBP 160-209 mm Hg and mean DBP <115 mm Hg N=4396	6 y	Diuretic 150 mm Hg	Beta-blocker 160 mm Hg	Placebo 156/77	Diuretic 153/75	Beta-blocker 165/84	nd	nd	Primary outcome: Strokes, coronary events, and death from all causes Then number of strokes (fatal and non-fatal) was significantly reduced in people randomized to receive active treatment (101 v 134 placebo, P=0.04) with RR 25% (CI 3% to 42%). Coronary events were less common in those allocated to active treatment (128 events) than in those receiving placebo (159; P=0.08) with RR of 19% (-2% to 36%). All cause mortality was similar in the treated and placebo groups (23.9 v 24.7 per patient-years).
SCOPE[54] Lithell 2003 UI12714861	Patients 70-89 years, SBP 160-179 mm Hg, DBP 90-99 mm Hg, mini mental state examination test score ≥24 N=4964	4 y	Candesartan	Placebo	145/80 (149/82)	S_{Cr} 88.0 µmol/L (89.0 µmol/L) (Excluded S_{Cr} >180 µmol/L in men and >140 µmol/L in women)	nd	Primary outcome: Major cardiovascular events, a composite of cardiovascular death, non-fatal stroke and non-fatal MI. A first major cardiovascular event occurred in 242 candesartan patients and in 268 placebo patients: RR with candesartan was 10.9% (-6.0 to 25.1, P=0.19). Candesartan treatment reduced non-fatal stroke by 27.8% (1.3 to 47.2, P=0.04) and all stroke by 23.6% (-0.7 to 42.1, P=0.056). There were no significant differences in MI and cardiovascular mortality.
SHELL[56] Malacco 2003 UI12875478	Patients ≥60 years, sitting SBP ≥160 mm Hg with a DBP ≤95 mm Hg N=1882	3 y	Prospective study with open design Lacidipine	Chlorthalidone	142/79 (143/80)	S_{Cr} >2.0 (>2.0) mg/dL (based on exclusion criteria)	nd	Primary outcome: Composite of cardiovascular and cerebrovascular events. Overall incidence of the primary endpoint was 9.3% with no significant between-group difference. Total mortality was also similar between groups.

Study Author Year	Population	Duration	Intervention	Comparator	Achieved BP mmHg Intervention (Comparator)	Baseline GFR or SCr Intervention (Control)	Baseline Proteinuria	Outcomes
SHEP[1] SHEP Cooperative Research Group 1991 UI2046107	60+ years old, SBP from 160-219 mm Hg and DBP <90 mm Hg N=4736	5 y	Chlorthalidone (step 1) Atenolol (step 2)	Placebo	144/68 (155/71	nd	nd	Primary outcome: Non fatal and fatal stroke The 5 year incidence of total stroke was 5.2 per 100 participants for active treatment and 8.2 per 100 for placebo. RR by proportional hazards regression analysis was 0.64 (P=.0003)
STONE[38] Gong 1996 UI8906524	Patients 60-90 years, SBP≥160 mm Hg or DBP ≥96 mm Hg N=1632	3 y	Nifedipine (SBP 140-159 mmHg and DBP 90 mm Hg)	Placebo (Safety level SBP ≥200 mmHg or DBP ≥110 mm Hg)	147/85 (156/92)	nd	nd	Primary outcome: Clinical events and risk modification. 77 events occurred in the placebo and 32 in the Nifedipine group. Significant reduction in relative risk was observed for strokes and severe arrhythmia with an overall decrease from 1.0 to 0.41 (CI 0.27 to 0.61). There was a significant decrease in RR in stages 2 and 3 HTN, which corresponded to 28.8 and 16.1% with placebo and Nifedipine.
STOP[27] Dahlof 1991 UI1682683	Patients 70-84 years, SBP between 180-230 mm Hg and DBP of at least 90 mm Hg or DBP between 105 and 120 mm Hg irrespective of the SBP. N=1627	5 y	Atenolol, HCTZ plus Amiloride, or Prindolol	Placebo	166/85 (193/95)	nd	nd	Primary outcome: Fatal and non fatal stroke and MI and other cardiovascular death. Active treatment significantly reduced the number of primary endpoints (94 v 58; P=0.0031) and stroke morbidity and mortality (53 v 29; P=0.0081). There was also a significant reduced number of deaths in the active treatment group (63 v 36; P=0.0079)
STOP 2[39] Hansson 1999 UI10577635	Patients 70-84 years, SBP between 180-230 mm Hg and DBP of at least 90 mmHg or DBP between 105 and 120 mm Hg irrespective of the SBP. N=6617	5 y	Conventional drugs: Atenolol, HCTZ plus Amiloride, Prindolol or Metoprolol (<160/95 mmHg)	Enalapril or Lisinopril (<160/95 mmHg) / Felodipine or Isradipine (<160/95 mmHg)	158/81 / 159/81 / 159/80	nd	nd	Primary outcome: The composite of fatal and non fatal stroke and MI and other cardiovascular disease. The primary combined endpoint occurred in 221 of 2213 patients in the conventional drugs group (19.8 events per 1000 patient-years) and in 438 of 4401 in the newer drugs group (19.8 per 1000; relative risk 0.99 (CI 0.84 to 1.16), P=0.89). The combined endpoint of fatal and non fatal stroke and MI and other cardiovascular mortality occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (CI 0.96 (0.86 to 1.08), P=0.49)

Study Author Year	Population	Duration	Intervention	Comparator	Achieved BP mmHg Intervention (Comparator)	Baseline GFR or SCr Intervention (Control)	Baseline Proteinuria	Outcomes
SYST China[97] Wang 2000 UI10647760	Patients 60+ years, sitting SBP 160-219 mm Hg and DBP <95 mm Hg N=1253	3 y	Nitrendipine	Placebo	↓20/5 (↓11/2)	S_{Cr} >2.0 mg/dL (S_{Cr} >2.0 mg/dL) (based on exclusion criteria)	nd	Primary outcome: Cardiovascular mortality, fatal and nonfatal cardiovascular events and strokes. In the placebo group diabetes raised the risk of all end points 2-to 2-fold (P≤0.05). However, active treatment reduced the excess risk associated with diabetes to a non significant level (P values ranging from .12 to 86) except for cardiovascular mortality (P=0.04). Active treatment had reduced the incidence of total mortality (P<0.01), fatal and nonfatal stroke (P<0.05), and all cardiovascular end points (P<0.01). In single and multiple regression, all end points with the exception of fatal and nonfatal stroke were positively correlated with SBP.
SYST Eur[91] Staessen 1997 UI9297994	Patients 60+years old, sitting SBP 160-219 mm Hg and DBP <95 mm Hg N=4695	2 y	Nitrendipine	Placebo	151/79 (161/84)	S_{Cr} >2.0 mg/dL (S_{Cr} >2.0 mg/dL) (based on exclusion criteria)	nd	Primary outcome: Fatal and non fatal stroke. Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patients-years (42% reduction; P=0.003). Non-fatal stroke decreased by 44% (P=0.007). In the active treatment group, all fatal and non-fatal cardiac endpoints, including sudden death, declined by 26% (P=0.03). Non fatal cardiac endpoints decreased by 33% (P=0.03) and all fatal and non fatal cardiovascular endpoints by 31% (p<0.001). Cardiovascular mortality was slightly lower on active treatment (-27%, P=0.07), but all cause mortality was not influenced (-14%; P=0.22).
ANBP2[31] Doggrell 2003 UI12740004	65-84 years old, SBP >160 mm Hg or an average DBP of >90 mm Hg N=6083	4 y	ACEI	Diuretic	141/79 (142/79)	nd	nd	Primary outcome: All CV events or death from any cause. The HR for all CV events or death from any cause among subjects in the ACEI group as compared with that of the Diuretic group was 0.89 (95% CI, 0.79 to 1.00; P=0.05).

References

1. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 265:3255-3264, 1991

2. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet 349(9069):1857-63,* 1997

3. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. *Hypertension* 34:1129-1133, 1999

4. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet 355(9200):253-9,* 2000

5. Agardh CD, Garcia-Puig J, Charbonnel B *et al.*: Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. *Journal of Human Hypertension 10(3):185-92,* 1996

6. Agha A, Amer W, Anwar E, Bashir K: Reduction of microalbuminuria by using losartan in normotensive patients with type 2 diabetes mellitus: A randomized controlled trial. *Saudi Journal of Kidney Diseases & Transplantation*429-435, 1920

7. Agodoa LY, Appel L, Bakris GL *et al.*: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA 285(21):2719-28,* 2001

8. Amery A, Birkenhager W, Brixko P *et al.*: Influence of hypotensive drug treatment in elderly hypertensives: study terminating events in the trial of the European Working Party on High Blood Pressure in the Elderly. *Journal of Hypertension - Supplement 3(3):S501-11,* 1985

9. Amery A, Birkenhager W, Brixko P *et al.*: Influence of antihypertensive drug treatment on morbidity and mortality in patients over the age of 60 years. European Working Party on High blood pressure in the Elderly (EWPHE) results: sub-group analysis on entry stratification. *Journal of Hypertension - Supplement* 4:S642-S647, 1986

10. Anand IS, Bishu K, Rector TS *et al.*: Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation 120(16):1577-84,* 2009

11. Appel LJ, Wright JT, Jr., Greene T *et al.*: Intensive blood-pressure control in hypertensive chronic kidney disease. *New England Journal of Medicine 363(10):918-29,* 2010

12. Asselbergs FW, Diercks GF, Hillege HL *et al.*: Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation 110(18):2809-16,* 2004

13. Baba S, -MIND Study Group: Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. *Diabetes Research & Clinical Practice 54(3):191-201,* 2001

14. Bakris G, Burgess E, Weir M *et al.*: Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney International 74(3):364-9,* 2008

15. Bakris GL, Sarafidis PA, Weir MR *et al.*: Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet 375(9721):1173-81,* 2010

16. Barnett AH, Bain SC, Bouter P *et al.*: Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *New England Journal of Medicine 351(19):1952-61,* 2004

17. Beckett NS, Peters R, Fletcher AE *et al.*: Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine* 358:1887-1898, 2008

18. Berl T, Hunsicker LG, Lewis JB *et al.*: Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Annals of Internal Medicine 138(7):542-9,* 2003

19. Bertrand ME, Fox KM, Remme WJ *et al.*: Angiotensin-converting enzyme inhibition with perindopril in patients with prior myocardial infarction and/or revascularization: a subgroup analysis of the EUROPA trial. *Archives of cardiovascular diseases 102(2):89-96,* 2009

20. Brenner BM, Cooper ME, de ZD *et al.*: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New England Journal of Medicine 345(12):861-9,* 2001

21. Bulpitt CJ, Beckett NS, Cooke J *et al.*: Results of the pilot study for the Hypertension in the Very Elderly Trial. *Journal of Hypertension* 21:2409-2417, 2003

22. Burgess E, Muirhead N, Rene de CP *et al.*: Supramaximal dose of candesartan in proteinuric renal disease. *Journal of the American Society of Nephrology*893-900, 1920

23. Casiglia E, Spolaore P, Mazza A *et al.*: Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly (CASTEL). *Japanese Heart Journal* 35:589-600, 1994

24. Chan JC, Cockram CS, Nicholls MG *et al.*: Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: one year analysis. *BMJ 305(6860):981-5,* 1992

25. Chan JC, Ko GT, Leung DH *et al.*: Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney International 57(2):590-600,* 2000

26. Cinotti GA, Zucchelli PC, Collaborative Study Group: Effect of Lisinopril on the progression of renal insufficiency in mild proteinuric non-diabetic nephropathies. *Nephrology Dialysis Transplantation* 16:961-966, 2001

27. Dahlof B, Lindholm LH, Hansson L *et al.*: Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 338:1281-1285, 1991

28. Dalla VM, Pozza G, Mosca A *et al.*: Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive Type 2 diabetic patients with microalbuminuria: DIAL study (diabete, ipertensione, albuminuria, lercanidipina). *Diabetes, Nutrition & Metabolism - Clinical & Experimental 17(5):259-66,* 2004

29. de Galan BE, Perkovic V, Ninomiya T *et al.*: Lowering blood pressure reduces renal events in type 2 diabetes. *Journal of the American Society of Nephrology*883-892, 2009

30. Del Vecchio L., Pozzi M, Salvetti A *et al.*: Efficacy and tolerability of manidipine in the treatment of hypertension in patients with non-diabetic chronic kidney disease without glomerular disease. Prospective, randomized, double-blind study of parallel groups in comparison with enalapril. *Journal of Nephrology 17(2):261-9,*-Apr, 2004

31. Doggrell SA: ACE inhibitors versus diuretics: ALLHAT versus ANBP2. *Expert Opin Pharmacother* 4:825-828, 2003

32. el-Agroudy AE, Hassan NA, Foda MA *et al.*: Effect of angiotensin II receptor blocker on plasma levels of TGF-beta 1 and interstitial fibrosis in hypertensive kidney transplant patients. *American Journal of Nephrology 23(5):300-6,*-Oct, 2003

33. Epstein M, Williams GH, Weinberger M *et al.*: Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clinical Journal of The American Society of Nephrology: CJASN 1(5):940-51,* 2006

34. ESCAPE Trial Group, Wuhl E, Trivelli A *et al.*: Strict blood-pressure control and progression of renal failure in children. *New England Journal of Medicine 361(17):1639-50,* 2009

35. Esnault VL, Brown EA, Apetrei E *et al.*: The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: a 3-year, randomized, multicenter, double-blind, placebo-controlled study. *Clinical Therapeutics 30(3):482-98,* 2008

36. Fujita T, Ando K, Nishimura H *et al.*: Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. *Kidney International 72(12):1543-9,* 2007

37. Galle J, Schwedhelm E, Pinnetti S *et al.*: Antiproteinuric effects of angiotensin receptor blockers: telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy. *Nephrology Dialysis Transplantation 23(10):3174-83,* 2008

38. Gong L, Zhang W, Zhu Y *et al.*: Shanghai trial of nifedipine in the elderly (STONE). *Journal of Hypertension* 14:1237-1245, 1996

39. Hansson L, Lindholm LH, Ekbom T *et al.*: Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 354:1751-1756, 1999

40. Heerspink HJ, Ninomiya T, Perkovic V *et al.*: Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. *European Heart Journal 31(23):2888-96,* 2010

41. Herlitz H, Harris K, Risler T *et al.*: The effects of an ACE inhibitor and a calcium antagonist on the progression of renal disease: the Nephros Study. *Nephrology Dialysis Transplantation 16(11):2158-65,* 2001

42. Hou FF, Xie D, Zhang X *et al.*: Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *Journal of the American Society of Nephrology 18(6):1889-98,* 2007

43. Hou FF, Zhang X, Zhang GH *et al.*: Efficacy and safety of benazepril for advanced chronic renal insufficiency. *New England Journal of Medicine 354(2):131-40,* 2006

44. Iino Y, Hayashi M, Kawamura T *et al.*: Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertension Research - Clinical & Experimental 27(1):21-30,* 2004

45. JATOS Study Group: Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertension Research - Clinical & Experimental* 31:2115-2127, 2008

46. Klahr S, Levey AS, Beck GJ *et al.*: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *New England Journal of Medicine 330(13):877-84,* 1994

47. Kuypers DR, Neumayer HH, Fritsche L *et al.*: Calcium channel blockade and preservation of renal graft function in cyclosporine-treated recipients: a prospective randomized placebo-controlled 2-year study. *Transplantation 78(8):1204-11,* 2004

48. Lacourciere Y, Belanger A, Godin C *et al.*: Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. *Kidney International 58(2):762-9,* 2000

49. Laffel LM, McGill JB, Gans DJ: The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. *American Journal of Medicine 99(5):497-504,* 1995

50. Levey AS, Uhlig K: Which antihypertensive agents in chronic kidney disease? *Annals of Internal Medicine 144(3):213-5,* 2006

51. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *New England Journal of Medicine 329(20):1456-62,* 1993

52. Lewis EJ, Hunsicker LG, Clarke WR *et al.*: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New England Journal of Medicine 345(12):851-60,* 2001

53. Li PK, Leung CB, Chow KM *et al.*: Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *American Journal of Kidney Diseases 47(5):751-60,* 2006

54. Lithell H, Hansson L, Skoog I *et al.*: The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of Hypertension* 21:875-886, 2003

55. Makino H, Haneda M, Babazono T *et al.*: Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes. *Diabetes Care 30(6):1577-8,* 2007

56. Malacco E, Mancia G, Rappelli A *et al.*: Treatment of isolated systolic hypertension: the SHELL study results. *Blood Pressure* 12:160-167, 2003

57. Mann JF, Gerstein HC, Pogue J *et al.*: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Annals of Internal Medicine 134(8):629-36,* 2001

58. Mann JF, Gerstein HC, Pogue J *et al.*: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Annals of Internal Medicine* 134:629-636, 2001

59. Mann JF, Gerstein HC, Yi QL *et al.*: Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. *American Journal of Kidney Diseases* 42:936-942, 2003

60. Mann JF, Green D, Jamerson K *et al.*: Avosentan for overt diabetic nephropathy. *Journal of the American Society of Nephrology 21(3):527-35,* 2010

61. Mann JF, Schmieder RE, Dyal L *et al.*: Effect of telmisartan on renal outcomes: a randomized trial. *Annals of Internal Medicine* 151:1-10, 2009

62. Mann JF, Schmieder RE, Dyal L *et al.*: Effect of telmisartan on renal outcomes: a randomized trial. *Annals of Internal Medicine 151(1):1-10, W1-2,* 2009

63. Mann JF, Schmieder RE, McQueen M *et al.*: Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet 372(9638):547-53,* 2008

64. Marin R, Ruilope LM, Aljama P *et al.*: A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. *Journal of Hypertension*1871-1876, 2001

65. Marre M, Lievre M, Chatellier G *et al.*: Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ 328(7438):495,* 2004

66. Maschio G, Alberti D, Janin G *et al.*: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *New England Journal of Medicine 334(15):939-45,* 1996

67. Menne J, Farsang C, Deak L *et al.*: Valsartan in combination with lisinopril versus the respective high dose monotherapies in hypertensive patients with microalbuminuria: the VALERIA trial. *Journal of Hypertension 26(9):1860-7,* 2008

68. Midtvedt K, Hartmann A, Foss A *et al.*: Sustained improvement of renal graft function for two years in hypertensive renal transplant recipients treated with nifedipine as compared to lisinopril. *Transplantation 72(11):1787-92,* 2001

69. Ninomiya T, Perkovic V, Gallagher M *et al.*: Lower blood pressure and risk of recurrent stroke in patients with chronic kidney disease: PROGRESS trial. *Kidney International 73(8):963-70,* 2008

70. Norris K, Bourgoigne J, Gassman J *et al.*: Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. *American Journal of Kidney Diseases 48(5):739-51,* 2006

71. Ogihara T, Saruta T, Rakugi H *et al.*: Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension* 56:196-202, 2010

72. Pahor M, Shorr RI, Somes GW *et al.*: Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the systolic hypertension in the elderly program. *Archives of Internal Medicine 158(12):1340-5,* 1998

73. Papademetriou V, Piller LB, Ford CE *et al.*: Characteristics and lipid distribution of a large, high-risk, hypertensive population: the lipid-lowering component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Journal of Clinical Hypertension* 5:377-384, 2003

74. Parving HH, Lehnert H, Brochner-Mortensen J *et al.*: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *New England Journal of Medicine 345(12):870-8,* 2001

75. Parving HH, Persson F, Lewis JB *et al.*: Aliskiren combined with losartan in type 2 diabetes and nephropathy. *New England Journal of Medicine 358(23):2433-46,* 2008

76. Peng T, Hu Z, Xia Q *et al.*: A comparative study of the renoprotective effects of benidipine and valsartan in primary hypertensive patients with proteinuria. *Arzneimittel-Forschung 59(12):647-50,* 2009

77. Perkovic V, Ninomiya T, Arima H *et al.*: Chronic kidney disease, cardiovascular events, and the effects of perindopril-based blood pressure lowering: data from the PROGRESS study. *Journal of the American Society of Nephrology 18(10):2766-72,* 2007

78. Persson F, Lewis JB, Lewis EJ *et al.*: Impact of baseline renal function on the efficacy and safety of aliskiren added to losartan in patients with type 2 diabetes and nephropathy. *Diabetes Care 33(11):2304-9,* 2010

79. Peterson JC, Adler S, Burkart JM *et al.*: Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Annals of Internal Medicine 123(10):754-62,* 1995

80. Philipp T, Martinez F, Geiger H *et al.*: Candesartan improves blood pressure control and reduces proteinuria in renal transplant recipients: results from SECRET. *Nephrology Dialysis Transplantation 25(3):967-76,* 2010

81. Rahn KH, Barenbrock M, Fritschka E *et al.*: Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: a randomised trial. *Lancet 354(9188):1415-20,* 1999

82. Ravid M, Lang R, Rachmani R, Lishner M: Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. *Archives of Internal Medicine 156(3):286-9,* 1996

83. Remuzzi G, Ruggenenti P, Perna A *et al.*: Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results. *Journal of the American Society of Nephrology 15(12):3117-25,* 2004

84. Ruggenenti P, Perna A, Gherardi G *et al.*: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet 354(9176):359-64,* 1999

85. Ruggenenti P, Perna A, Loriga G *et al.*: Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet 365(9463):939-46,*-18, 2005

86. Sarnak MJ, Greene T, Wang X *et al.*: The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Annals of Internal Medicine 142(5):342-51,* 2005

87. Saruta T, Hayashi K, Ogihara T *et al.*: Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: subanalysis of the CASE-J Study. *Hypertension Research - Clinical & Experimental 32(6):505-12,* 2009

88. Sengul AM, Altuntas Y, Kurklu A, Aydin L: Beneficial effect of lisinopril plus telmisartan in patients with type 2 diabetes, microalbuminuria and hypertension. *Diabetes Research & Clinical Practice 71(2):210-9,* 2006

89. Solomon SD, Lin J, Solomon CG *et al.*: Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. *Circulation 116(23):2687-93,* 2007

90. Solomon SD, Rice MM, Jablonski A *et al.*: Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. *Circulation 114(1):26-31,* 2006

91. Staessen JA, Fagard R, Thijs L *et al.*: Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 350:757-764, 1997

92. Trevisan R, Tiengo A: Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. North-East Italy Microalbuminuria Study Group. *American Journal of Hypertension 8(9):876-83,* 1995

93. Tuomilehto J: MRC trial of treating hypertension in older adults. *BMJ* 304:1631-1632, 1992

94. van R, I, Mulder PG, de Fijter JW *et al.*: Addition of isradipine (Lomir) results in a better renal function after kidney transplantation: a double-blind, randomized, placebo-controlled, multi-center study. *Transplantation 70(1):122-6,* 2000

95. Viberti G, Wheeldon NM, MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators: Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation 106(6):672-8,* 2002

96. Vonend O, Marsalek P, Russ H *et al.*: Moxonidine treatment of hypertensive patients with advanced renal failure. *Journal of Hypertension 21(9):1709-17,* 2003

97. Wang JG, Staessen JA, Gong L, Liu L: Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Archives of Internal Medicine* 160:211-220, 2000

98. Woo KT, Chan CM, Tan HK *et al.*: Beneficial effects of high-dose losartan in IgA nephritis. *Clinical Nephrology 71(6):617-24,* 2009

99. Wright JT, Jr., Bakris G, Greene T *et al.*: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA 288(19):2421-31,* 2002