Annals of Internal Medicine | Review

Lipid-Lowering Therapy in Persons With Chronic Kidney Disease

A Systematic Review and Meta-analysis

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Background: Lipid-lowering therapy is not widely used in persons with chronic kidney disease (CKD) despite a high burden of dyslipidemia and cardiovascular disease in this population.

Purpose: To synthesize evidence examining the effect of lipid-lowering therapy on clinical outcomes in persons with CKD.

Data Sources: MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from January 2000 through November 2011.

Study Selection: Randomized, controlled trials (RCTs) comparing lipid-lowering therapy with control treatment in persons with CKD, including subgroup analyses of trials in the general population.

Data Extraction: Abstracts were screened and data were extracted on study methodology, population, interventions, cardiovascular and kidney outcomes, and adverse events. Data were extracted by one author and confirmed by another. Study quality was determined by consensus. Random-effects model meta-analyses were performed.

Data Synthesis: 18 RCTs, all in adults, met the eligibility criteria. Five RCTs involved CKD populations, and 13 were CKD subgroup analyses from trials in the general population. Sixteen RCTs examined statins, and 2 examined statins plus ezetimibe. Lipid-lowering therapy does not improve kidney outcomes but decreases the risk for cardiac mortality (pooled risk ratio [RR] from 6 trials, 0.82 [95% CI, 0.74 to 0.91]; $P < 0.001$), cardiovascular events (including revascularization) (pooled RR from 9 trials, 0.78 [CI, 0.71 to 0.86]; $P < 0.001$), and myocardial infarction (pooled RR from 9 trials, 0.74 [CI, 0.67 to 0.81]; $P < 0.001$). Significant benefit was also seen for all-cause mortality but was limited by a high degree of heterogeneity. No benefit was found for other cardiovascular outcomes. Rates of adverse events were similar between intervention and comparator groups.

Limitations: Lack of data in children, heterogeneity among reviewed studies, and the possibility of selective reporting of outcomes and adverse events.

Conclusion: Lipid-lowering therapy decreases cardiac death and atherosclerosis-mediated cardiovascular events in persons with CKD.

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Patients with chronic kidney disease (CKD) have a higher burden of cardiovascular disease (CVD) than the general population (1, 2). The National Kidney Foundation Task Force on CVD recommends that CKD be considered the highest-risk category in management of CVD risk factors (3). Although dyslipidemia, a major modifiable risk factor for atherosclerotic CVD, is common in patients with CKD (4, 5), only approximately 50% of these patients who also have elevated low-density lipoprotein (LDL) cholesterol levels receive lipid-lowering therapy (6, 7). This is probably because patients with CKD are excluded from most large CVD trials, prevalence of nonatherosclerotic CVD is higher among patients with CKD, evidence is lacking that dyslipidemia imparts the same risk for CVD in the CKD population as in the general population, and patients with CKD are perceived to have higher rates of treatment-related adverse effects than those without CKD (8–10).

Several large trials and post hoc analyses examining lipid-lowering therapies and clinical outcomes in CKD have been published since the last major meta-analysis on the topic in 2008 (11). Our systematic review and meta-analysis summarizes studies that have reported on CVD outcomes, kidney outcomes, and adverse events associated with lipid-lowering therapy in persons with CKD.

Methods

We developed and followed a standard protocol for this review that builds on the evidence review conducted for the ongoing Kidney Disease: Improving Global Outcomes (KDIGO) guideline on lipid management in CKD.

Data Sources and Searches

We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from January 2000 through November 2011 for systematic reviews and randomized, controlled trials (RCTs) in any language. For earlier studies, we relied on a systematic review conducted in 2000 for the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline for managing dyslipidemia in CKD (12). **Appendix Table 1** (available at www.annals.org) shows the search strategies. We obtained additional articles from our domain expert,

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Table 1. **Randomized, Controlled Trials of Lipid-Lowering Therapy in Patients With CKD**

Study, Year (Reference)	Region	Population	Intervention	Comparator	Participants, *n*	Mean Age, *y*	Men, %
ALERT, 2003 (25, 26, 28)	Europe and Canada	Kidney transplant recipients	Fluvastatin	Placebo	I: 1050 C: 1052	I: 50 C: 50	I: 67 C: 65
4D, 2005 (39)	Germany	HD recipients	Atorvastatin	Placebo	I: 619 C: 636	I: 66 C: 66	I: 54 C: 54
UK-HARP-II, 2006 (31)	United Kingdom	Stage 3–5 CKD (HD and PD recipients)	Ezetimibe plus simvastatin	Simvastatin	I: 102 C: 101	I: 60 C: 60	I: 70 C: 69
AURORA, 2009 (24, 27)	Europe, Canada, Mexico, Brazil, Australia, and South Korea	HD recipients	Rosuvastatin	Placebo	I: 1389 C: 1384	I: 64 C: 64	I: 61 C: 63
SHARP, 2011 (21)	Europe, North America, Australia, New Zealand, China, Thailand, and Malaysia	Stage 3–5 CKD (HD and PD recipients)	Ezetimibe plus simvastatin	Placebo	I: 4650 C: 4620	I: 62 C: 62	I: 63 C: 62

4D = Die Deutsche Diabetes Dialyse Studie; ALERT = Assessment of Lescol in Renal Transplantation; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; C = comparator group; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis; I = intervention group; LDL = low-density lipoprotein; MACE = major adverse cardiac event; MI = myocardial infarction; NA = not applicable; ND = no data; PD = peritoneal dialysis; SCr = serum creatinine; SHARP = Study of Heart and Renal Protection; UK-HARP-II = Second United Kingdom Heart and Renal Protection.
* Data provided only for the entire population.

who has research expertise in lipid disorders and kidney disease, and from reference lists of pertinent studies, reviews, and editorials.

Five reviewers independently and manually screened the abstracts using the computerized screening program Abstrackr (Tufts Medical Center, Boston, Massachusetts) (13). To establish relevance and consensus among reviewers, all 5 screened and achieved consensus on an initial batch of 500 abstracts.

Study Selection

We included peer-reviewed RCTs that compared 1 or more lipid-lowering agents (statins, ezetimibe, niacin, colestipol, or cholestyramine) or lifestyle-modification strategies (weight loss, special diet, or exercise) with other lipid-lowering measures or no treatment (or placebo) in adults and children with CKD of any stage, including patients receiving dialysis and kidney transplantation patients. However, no eligible trials evaluated lifestyle-modification strategies; thus, the remainder of the systematic review pertains only to the evaluation of lipid-lowering agents.

We included analyses of CKD subgroups from trials not specifically designed to include patients with CKD. We excluded trials involving dietary supplements, phosphate binders, apheresis, stanols, or sterols. Outcomes of interest were all-cause mortality, cardiovascular mortality (both cardiac and stroke mortality), cardiac mortality, composite cardiovascular events including revascularization procedures, composite cardiovascular events excluding revascularization procedures, myocardial infarction, stroke, end-stage renal disease (ESRD), kidney graft failure, a 25% or more decrease in estimated glomerular filtration rate (eGFR) or doubling the serum creatinine level, and adverse events. Adverse events of interest were the total number of events, drug discontinuation due to adverse events, rhabdomyolysis, clinically significant liver function abnormality (alanine aminotransferase levels 3 or more times the upper limit of the normal range), and new-onset cancer.

The minimum follow-up was 6 months. Studies had to include 100 or more participants with CKD per group for adults and 25 or more per group for children.

Data Extraction and Quality Assessment

Data were extracted by one of the 5 reviewers and confirmed by another. We extracted trial-level and subgroup-level data on study design, methodology, sample characteristics, interventions, comparators, outcomes, and adverse events. We did not contact original investigators to obtain additional information.

We used a predefined 3-category grading system to denote the methodological quality of each study (**Appendix Table 2**, available at www.annals.org) (14–16). Good-quality studies have no obvious bias and largely adhere to the commonly held concepts of high quality, including a clear description of samples, setting, intervention and comparator groups, appropriate statistical and analytic methods, and transparent reporting of results. Fair-quality studies may have some deficiencies, but these are unlikely to cause major bias. Poor-quality studies fail to adequately describe samples, measures, analyses, or results of interest or have substantial flaws in reporting such that major bias cannot be excluded.

Additional criteria were used to grade CKD subgroup analyses from trials of the general population, because subgroup analyses can be subject to additional biases that may lead to overstated or misleading results (17). The methodological quality associated with the CKD subgroup results was assessed after evaluating whether the subgroup in each study was defined by measurements at baseline and prespecified before secondary analysis and whether the base-

Table 1—Continued

Mean Baseline eGFR or SCr Level, *mL/min per 1.73 m²* or *μmol/L (mg/dL)*	Baseline LDL Cholesterol Level, *mmol/L (mg/dL)*	History of Diabetes, %	History of CVD, %	Primary End Point	Major Secondary End Points	Overall Study Quality
I: Scr, 150 (1.70) C: Scr, 141 (1.60)	I: 4.09 (158) C: 4.09 (158)	I: 19 C: 19	18*	MACE-free survival	Graft loss; doubling of SCr; and combination outcomes, including mortality	Good
NA	I: 3.23 (125) C: 3.28 (127)	I: 100 C: 100	98*	Composite of CV mortality, MI, and stroke	All-cause mortality, all cardiac and cerebrovascular events combined	Good
I: eGFR, 26 C: eGFR, 29	I: 3.13 (121) C: 3.03 (117)	I: 7 C: 4	I: 14 C: 19	ND	All-cause mortality, ESRD, CV events, lipid levels	Good
NA	I: 2.59 (100) C: 2.56 (99)	I: 28 C: 25	I: 40 C: 40	Composite of CV mortality, MI, or stroke	All-cause mortality, individual cardiac and vascular events	Good
I: eGFR, 27 C: eGFR, 27	I: 2.77 (107) C: 2.78 (108)	I: 23 C: 23	I: 15 C: 15	MACE, including coronary mortality	Mortality, renal replacement therapy	Good

line characteristics by intervention and comparator were provided or potentially influenced results (**Appendix Figure 1**, available at www.annals.org). Grading of each study was done by one of the reviewers, confirmed by another, and finalized in a group meeting.

Data Synthesis and Analysis

We used a random-effects model to estimate pooled effects when an outcome of interest was reported by at least 3 RCTs. Analyses were done for each type of statin, across all statins, and across all lipid-lowering treatments. Because the studies reported results by using different metrics, we preferentially extracted and analyzed hazard ratios (HRs). Risk ratios (RRs) were extracted if HRs were not reported; raw data to calculate RRs were extracted if both HRs and RRs were not provided; and odds ratios were extracted if HRs, RRs, and raw data were not available. Because most studies reported RRs, we describe the summary statistic as a pooled RR.

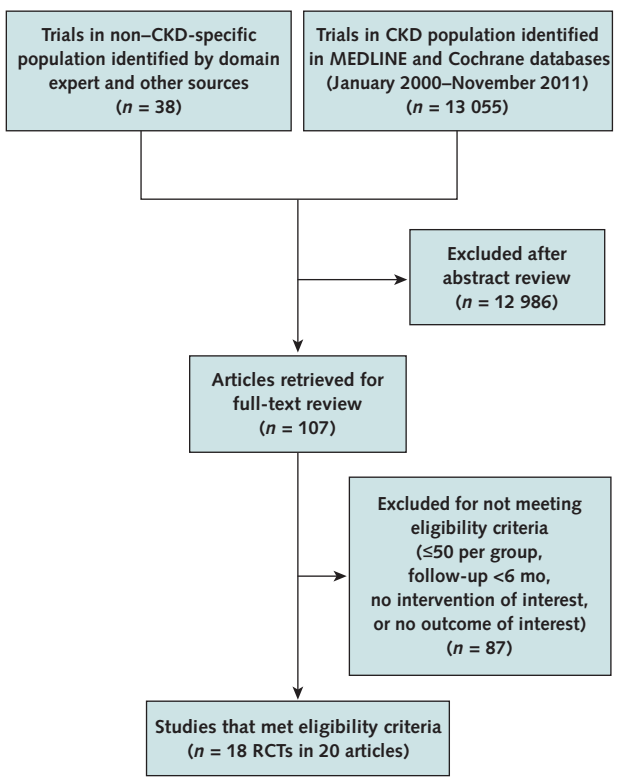
Statistical heterogeneity was assessed by using the I^2 statistic. All analyses were performed with the metan function in Stata, version 11 (StataCorp, College Station, Texas). A priori subgroup analyses were planned for diabetes mellitus and hemodialysis status. As several trials had very few participants with diabetes (≤2%), we determined that it was most logical to categorize these trials as including only participants without diabetes. We also performed post hoc metaregression analyses of the associations between baseline and net change in LDL cholesterol levels and cardiac mortality and cardiovascular events. These were performed with the metareg function in Stata.

The overall qualitative summary of the strength of the evidence was assessed by using the modified Grading of Recommendations Assessment, Development, and Evaluation approach used for KDIGO guidelines (18, 19). The strength of evidence for each outcome was rated as high, moderate, low, or very low on the basis of the methodological quality of studies, consistency of results across studies, directness or applicability to the CKD population, precision of results, and number of studies and participants contributing to the evidence base (**Appendix Figure 2**, available at www.annals.org). The overall quality for the outcome was downgraded for inconsistency if major studies contributing to the evidence base showed opposite results.

Role of the Funding Source

Kidney Disease: Improving Global Outcomes participated in formulating the study questions but did not participate in the literature search, determination of study el-

Figure 1. **Summary of evidence search and selection.**



CKD = chronic kidney disease; RCT = randomized, controlled trial.

Table 2. **General Population Lipid Trials With CKD Subgroup Results**

Study, Year (Reference)	Region	Definition	Intervention	Comparator	CKD (Total), *n (n)*	Median Follow-up, *y*	Mean Age, *y*
CARE, LIPID, WOSCOPS, 2005 (38, 40, 41)	International	Not dependent on dialysis	Pravastatin	Placebo	4676 (19 737)	5	62
LIPS, 2005 (32)	International	CrCl, <60 mL/min per 1.73 m^2	Fluvastatin	Placebo	310 (1558)	4	69
PREVEND IT, 2005 (20)	Netherlands	Microalbuminuria	Pravastatin	Placebo	864 (8592)	4	I: 52 C: 51
4S, 2007 (22)	Scandinavia	eGFR, <75 mL/min per 1.73 m^2	Simvastatin	Placebo	2314 (3842)	5	I: 61 C: 60
ALLHAT, 2008 (34)	International	eGFR, <60 mL/min per 1.73 m^2	Pravastatin	Usual care	1557 (10 355)	5	I: 71 C: 71
TNT, 2008 (36, 37)	International	eGFR, <60 mL/min per 1.73 m^2	Atorvastatin, 80 mg/d	Atorvastatin, 10 mg/d	3107 (9656)	5	I: 66 C: 66
ALLIANCE, 2009 (30)	US	eGFR, <60 mL/min per 1.73 m^2	Atorvastatin	Usual care	579 (2442)	5	I: 66 C: 65
CARDS, 2009 (23)	UK and Ireland	eGFR, <60 mL/min per 1.73 m^2	Atorvastatin	Placebo	970 (2838)	4	I: 65 C: 65
MEGA, 2009 (33)	Japan	eGFR, 30–60 mL/min per 1.73 m^2	Pravastatin plus diet modification	Diet modification	2978 (7196)	5	ND
AFCAPS/TexCAPS, 2010 (29)	US	eGFR, <60 mL/min per 1.73 m^2	Lovastatin	Placebo	304 (6604)	4	I: 62 C: 62
JUPITER, 2010 (35)	International	eGFR, 30–60 mL/min per 1.73 m^2	Rosuvastatin	Placebo	3267 (17 795)	2	70

4S = Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALLIANCE = Aggressive Lipid-Lowering to Alleviate New Cardiovascular Endpoints; C = comparator group; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; I = intervention group; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; LIPS = Lescol Intervention Prevention Study; MACE = major adverse cardiac event; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; ND = no data; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCr = serum creatinine; TNT = Treating to New Targets; UK = United Kingdom; US = United States; WOSCOPS = West of Scotland Coronary Prevention Study.
* Baseline characteristics assessed by intervention and comparator not provided for CKD subgroup.
† >20% dropout rate for the intervention group.

igibility criteria, data analysis or interpretation, preparation or review of the manuscript, or in the decision to submit the manuscript for publication.

RESULTS

Figure 1 summarizes the search yield. A total of 107 articles were retrieved for full-text review, and 20 articles from 18 RCTs were included for analysis (20–39).

Trial Characteristics

Table 1 describes 5 RCTs that examined lipid-lowering therapies in patients with CKD: ALERT (Assessment of Lescol in Renal Transplant), 4D (Die Deutsche Diabetes Dialyse Studie), UK-HARP-II (Second United Kingdom Heart and Renal Protection), AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), and SHARP (Study of Heart and Renal Protection) (21, 24–28, 31, 39). The 4D study and AURORA were conducted in patients receiving hemodialysis (24, 27, 39), the UK-HARP-II study and SHARP were conducted in patients with mild to advanced CKD (including those receiving hemodialysis or peritoneal dialysis) (21, 31), and ALERT was conducted in kidney transplant recipients (25, 26, 28). The mean age of participants ranged from 50 to 66 years, and the mean baseline LDL cholesterol level in intervention groups ranged from 2.59 mmol/L (100 mg/dL) to 4.09 mmol/L (158 mg/dL). Follow-up ranged from 6 months to 5 years, and most participants in each trial were men.

Table 2 describes 13 RCTs that were not designed specifically to include patients with CKD but provided results for a CKD subgroup (20, 22, 23, 29, 30, 32, 38, 40, 41). The CKD in most trial participants who had it was mild. The findings for patients with CKD in the CARE (Cholesterol and Recurrent Events) trial, the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) trial, and WOSCOPS (West of Scotland Coronary Prevention Study) were published together in a patient-level meta-analysis (38, 40, 41). We have com-

Table 2—Continued

Men, %	Mean Baseline eGFR or SCr Level, *mL/min per 1.73 m²* or *μmol/L (mg/dL)*	Mean Baseline LDL Cholesterol Level, *mmol/L (mg/dL)*	History of Diabetes, %	History of CVD	Primary End Point	Major Secondary End Points	Overall Study Quality
77	eGFR, 57	3.91 (151)	12	ND	CV mortality, CV event, or need for revascularization procedure	Composite of all-cause mortality, CV mortality, CV event, stroke, or need for revascularization procedure	Fair*
66	SCr, 118 (1.3)	3.39 (131)	12	ND	ND	CV mortality, CV event, need for revascularization procedure	Fair*
I: 68 C: 62	I: SCr, 90 (1.0) C: SCr, 91 (1.0)	I: 4.11 (159) C: 4.01 (155)	I: 4 C: 4	ND	CV mortality or morbidity	All-cause mortality, lipid levels	Fair†
I: 74 C: 73	I: eGFR, 65.2 C: eGFR, 65.2	I: 4.89 (189) C: 4.89 (189)	I: 5 C: 4	ND	All-cause mortality	Major first coronary event, ≥25% decrease in eGFR, lipid levels	Good
I: 45 C: 46	I: eGFR, 50.8 C: eGFR, 50.8	I: 3.80 (147) C: 3.75 (145)	I: 32 C: 30	ND	ND	ESRD, ESRD or halving of eGFR, ESRD or ≥25% decrease in eGFR, eGFR, lipid levels	Good
I: 69 C: 66	I: eGFR, 53.0 C: eGFR, 52.8	I: 2.49 (96) C: 2.50 (96)	I: 17 C: 18	ND	Major CV event	ND	Good
I: 76 C: 78	I: eGFR, 51.3 C: eGFR, 51.3	I: 3.83 (148) C: 3.78 (146)	I: 0 C: 0	ND	MACE	All-cause mortality, peripheral revascularization, hospitalization for CHF, stroke	Fair†
I: 48 C: 48	I: eGFR, 53.5 C: eGFR, 54.1	I: 3.10 (120) C: 3.10 (120)	I: 100 C: 100	ND	Cardiac events, revascularization, or stroke	All-cause mortality	Good
ND	I: eGFR, 52.6 C: eGFR, 52.5	4.0 (155)	19	ND	MACE	ND	Fair*
I: 82 C: 75	I: SCr, 124 (1.4) C: SCr, 124 (1.4)	I: 3.90 (151) C: 3.90 (151)	I: 1 C: 2	ND	First major CV event	≥25% decrease in eGFR, lipid levels	Good
35	eGFR, 56	2.82 (109)	I: 0 C: 0	ND	CV mortality, CV event, revascularizations, and stroke	All-cause mortality, doubling of SCr level, lipid levels	Good

bined the results from this meta-analysis with those from other studies to achieve the overall effect.

Results from the meta-analysis of the CARE and LIPID trials and WOSCOPS are counted as coming from 3 trials rather than just 1. The mean age of participants ranged from 52 to 70 years; mean baseline LDL cholesterol level in the intervention groups ranged from 2.49 mmol/L (96 mg/dL) to 4.89 mmol/L (189 mg/dL). Follow-up ranged from 2 to 5 years, and more than two thirds of participants in 9 out of 13 trials were men.

Of the 18 RCTs, 16 evaluated various statins and the remaining 2 evaluated the combination of ezetimibe and simvastatin. The TNT (Treating to New Targets) trial examined the effect of higher-dose versus lower-dose atorvastatin (36, 37). All studies were conducted in adults. We found no study that examined lipid-lowering lifestyle modifications alone (that is, without drug therapy) and clinical outcomes. **Supplements 1** to **4** and **Appendix Tables 3** to **5** (available at www.annals.org) summarize interventions, comparators, numbers analyzed, numbers enrolled, baseline characteristics, results, and quality for each study.

Mortality

Fifteen trials (not including TNT) reported the effect of lipid-lowering therapy on all-cause mortality (**Figure 2**). Overall, this therapy was found to be beneficial (RR, 0.91 [95% CI, 0.83 to 0.99]; $P = 0.031$). However, there was some uncertainty because the upper limit of the 95% CI was close to 1.0 and studies were significantly heterogeneous ($I^2 = 59\%$; $P = 0.003$) across studies. There was also important clinical heterogeneity because trials included participants with different stages of CKD and different baseline risks.

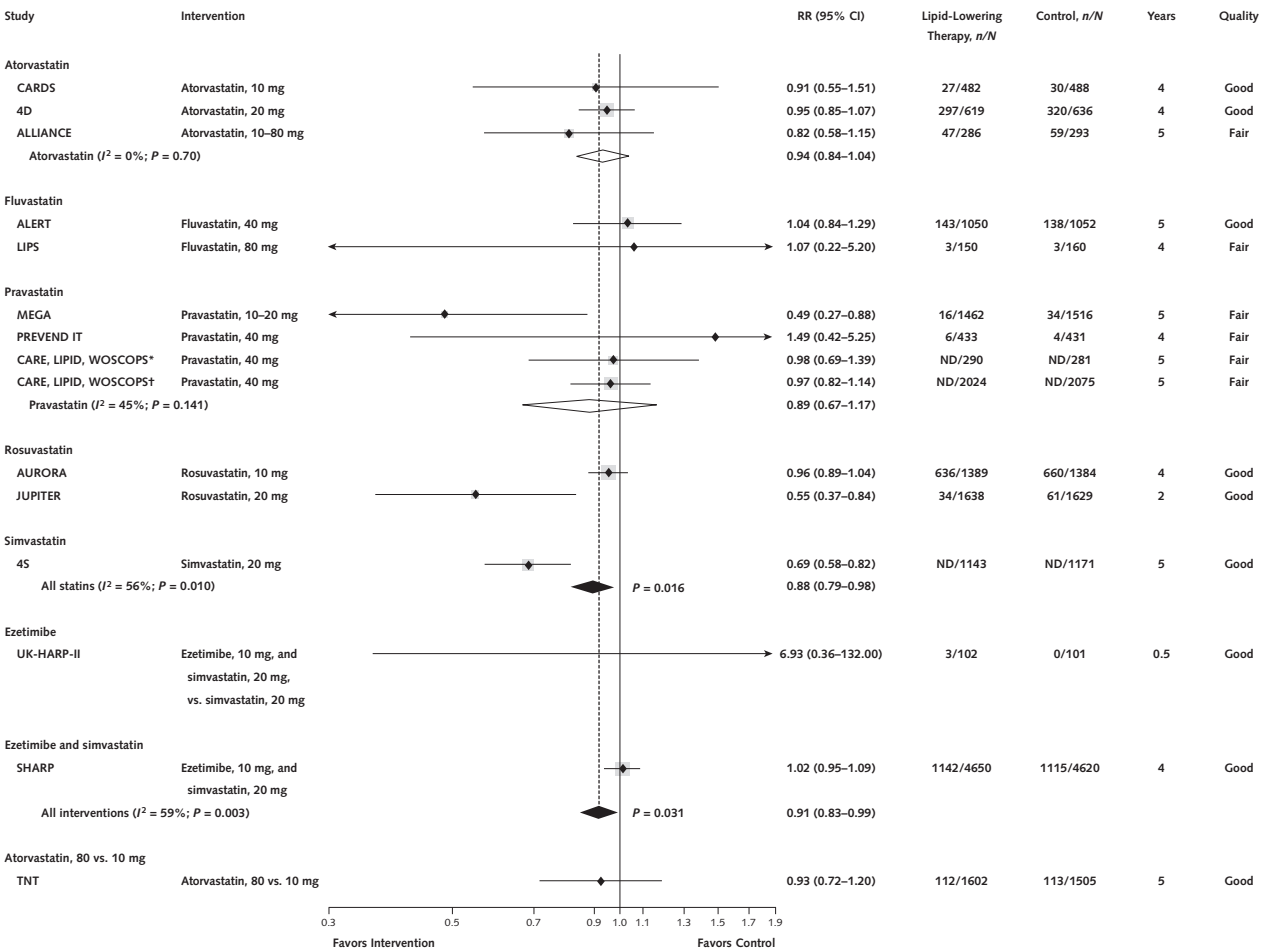
The results assessed according to diabetes and hemodialysis status showed that the RRs were less than 1.0 in all subgroups but reached statistical significance only in the subgroup of patients with CKD not receiving dialysis (**Table 3**). The quality of evidence for all-cause mortality was graded as moderate because of the inclusion of indirect evidence from unplanned subgroup analyses of outcomes for patients with CKD enrolled in large RCTs (**Table 3**).

Four trials reported on cardiovascular mortality (composite of cardiac and stroke mortality), and none found lipid-lowering therapy to be beneficial (RR, 0.96 [CI, 0.87 to 1.06]; $P = 0.41$) (**Appendix Figure 3**, available at www.annals.org). However, pooled results from 6 trials showed lipid-lowering therapy to be beneficial in preventing cardiac mortality (RR, 0.82 [CI, 0.74 to 0.91]; $P < 0.001$) (**Appendix Figure 4**, available at www.annals.org). Metaregression analyses for cardiac mortality by baseline LDL cholesterol level ($P = 0.46$) and net change of LDL cholesterol level ($P = 0.77$) did not find significant associations. The quality of evidence for both cardiovascular mortality and cardiac mortality was high (**Table 3**).

Cardiovascular Events

Nine trials reported on the composite of fatal and nonfatal cardiovascular events, including the need for re-

Figure 2. **Random-effects model meta-analyses of RR for all-cause death in patients with CKD receiving lipid-lowering interventions.**



The summary RRs centered on a combined estimate and extending to 95% CIs for all statins or all interventions versus control (*black diamonds*) and the summary RR for individual statins versus control (*white diamond*) are shown. Risk ratios (*diamonds*) and 95% CIs (*horizontal lines*) for individual studies also are shown. The size of the squares is proportional to the weight of each study in the overall meta-analysis. Within drug subgroups, studies are ordered by drug dose and sample size. 4D = Die Deutsche Diabetes Dialyse Studie; 4S = Scandinavian Simvastatin Survival Study; ALERT = Assessment of Lescol in Renal Transplantation; AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ALLIANCE = Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CARE = Cholesterol and Recurrent Events; CARDS = Collaborative Atorvastatin Diabetes Study; CKD = chronic kidney disease; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS = Lescol Intervention Prevention Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; ND = no data; PREVEND IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial; RR = risk ratio; SHARP = Study of Heart and Renal Protection; TNT = Treating to New Targets; UK-HARP-II = Second United Kingdom Heart and Renal Protection; WOSCOPS = West of Scotland Coronary Prevention Study.

* Patients with diabetes mellitus.

† Patients without diabetes mellitus.

vascularization procedures, and lipid-lowering therapy was found to be beneficial across studies (RR, 0.78 [CI, 0.71 to 0.86]; $P < 0.001$) (**Figure 3**). Studies conducted exclusively in patients receiving hemodialysis did not report this outcome. The results assessed by diabetes status were similar in persons with and without diabetes (**Table 3**). Metaregression analyses for cardiovascular events, including the need for revascularization procedures, by baseline LDL cholesterol level ($P = 0.95$) and net change of LDL cholesterol level ($P = 0.72$) did not find significant associations. The quality of evidence for cardiovascular events, including the need for revascularization procedures, was graded as moderate because of the inclusion of indirect evidence from unplanned subgroup analyses of outcomes for patients with CKD enrolled in large RCTs (**Table 3**).

Four trials (not including TNT) reported on the composite of fatal and nonfatal cardiovascular events, excluding revascularization procedures, and lipid-lowering therapy

was not found to be beneficial (RR, 0.94 [CI, 0.86 to 1.03]; $P = 0.17$) (**Appendix Figure 5**, available at www.annals.org). The results assessed by diabetes and hemodialysis status showed an RR less than 1.0 in all subgroups but reached statistical significance in only 1 trial that examined patients with CKD who did not receive dialysis and were not diabetic (**Table 3**). However, there were uncertainties because the upper limit of the 95% CIs was close to 1.0. The quality of evidence for cardiovascular events, excluding revascularization procedures, was graded as high (**Table 3**).

Nine trials reported on myocardial infarction and found lipid-lowering therapy to be beneficial in preventing myocardial infarction (RR, 0.74 [CI, 0.67 to 0.81]; $P < 0.001$) (**Appendix Figure 6**, available at www.annals.org). Results were consistent in studies in patients receiving and not receiving hemodialysis (**Table 3**). The quality of evidence for myocardial infarction was graded as moderate because of the inclusion of indirect evidence from unplanned subgroup analyses of outcomes for patients with CKD enrolled in large RCTs (**Table 3**).

Nine trials (not including TNT) reported on the composite outcome of ischemic and hemorrhagic stroke and did not find lipid-lowering therapy to be beneficial (RR, 0.90 [CI, 0.63 to 1.27]; $P = 0.55$) (**Appendix Figure 7**, available at www.annals.org). However, the studies were statistically and clinically heterogeneous. Studies in patients not receiving dialysis suggested a nonsignificant benefit, and studies in patients receiving hemodialysis suggested significant harm with lipid-lowering treatment (**Table 3**). The quality of evidence for stroke was graded as very low because results were partially based on studies of fair methodological quality, there were important inconsistencies across studies, and indirect evidence was included from unplanned subgroup analyses of outcomes for patients with CKD enrolled in large RCTs (**Table 3**).

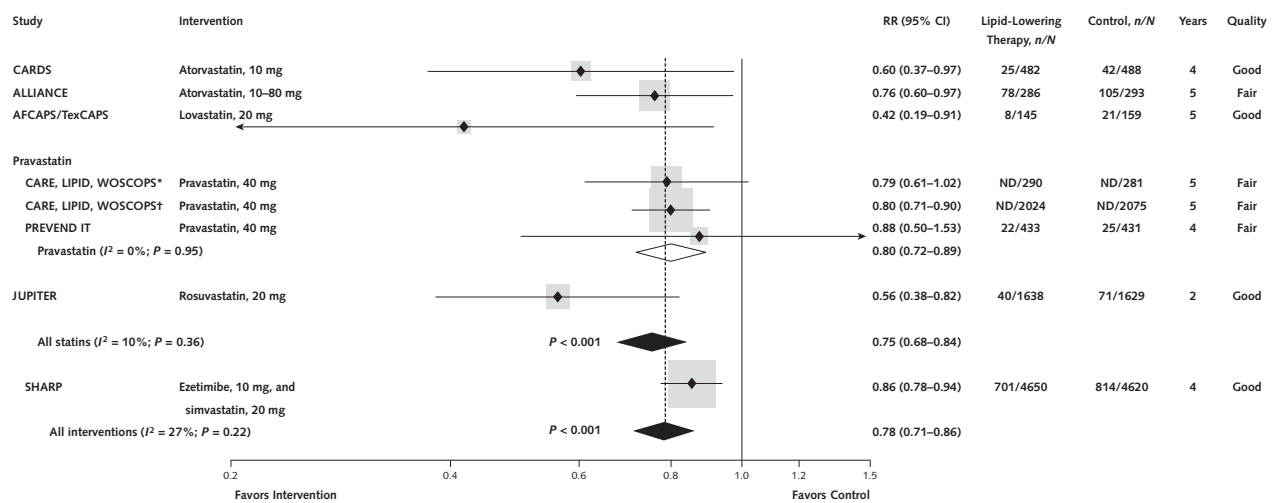
Kidney Outcomes

High-quality evidence from 3 trials did not find lipid-lowering therapy to be beneficial in preventing ESRD (RR, 0.97 [CI, 0.90 to 1.05]; $P = 0.49$) (**Appendix Figure 8**, available at www.annals.org). The results from 7 trials that analyzed the composite of ESRD, a 25% or higher decrease in the eGFR or doubling the serum creatinine level, or a 25% or higher decrease in the eGFR or doubling the serum creatinine level alone also did not find lipid-lowering therapy to be beneficial (RR, 0.91 [CI, 0.78 to 1.06]; $P = 0.21$) (**Appendix Figure 9**, available at www.annals.org). However, there was significant statistical heterogeneity ($I^2 = 60\%$; $P = 0.039$) and the quality of evidence for the composite kidney end point was graded as moderate because of the inclusion of indirect evidence from unplanned subgroup analyses of outcomes for patients with CKD enrolled in large RCTs (**Table 3**). A single study in kidney transplant recipients also showed no benefit of statin treatment for kidney graft outcomes (25, 26, 28).

Adverse Events

Table 4 summarizes the results from 14 trials that reported the total number of adverse events or at least one of the following predefined adverse events: drug discontinuation due to adverse events, rhabdomyolysis, clinically significant liver function abnormality, and new-onset cancer. The rates of adverse events were generally similar between intervention and comparator groups, and severe adverse events were rare.

Figure 3. **Random-effects model meta-analyses of RR for cardiovascular events, including revascularization, in patients with CKD receiving lipid-lowering interventions.**



See legend for **Figure 2**.

Table 3. **Summary RRs and Quality for Any Lipid-Lowering Drug Versus No Treatment, for All Studies and DM and HD Subgroups**

Outcome	Methodological Quality Across Studies	Consistency Across Studies*	Directness†	Imprecision and Sparseness
All-cause mortality	Mostly good-quality studies	No important inconsistencies	Mostly from subgroup analysis (downgrade)	No important limitations
CV mortality	Mostly good-quality studies	No important inconsistencies	Mostly from CKD trials	No important limitations
Cardiac mortality	Mostly good-quality studies	No important inconsistencies	Mostly from CKD trials	No important limitations
CV events, including revascularization	Mostly good-quality studies	No important inconsistencies	Mostly from subgroup analysis (downgrade)	No important limitations
CV events, excluding revascularization	All good-quality studies	No important inconsistencies	Mostly from CKD trials	No important limitations
Myocardial infarction	Mostly good-quality studies	No important inconsistencies	Mostly from subgroup analysis (downgrade)	No important limitations
Stroke	Some fair-quality studies (downgrade)	Important inconsistencies present (downgrade)	Mostly from subgroup analysis (downgrade)	No important limitations
ESRD	All good-quality studies	No important inconsistencies	Mostly from CKD trials	No important limitations
Worsening kidney function	Mostly good-quality studies	No important inconsistencies	Mostly from subgroup analysis (downgrade)	No important limitations

CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; ESRD = end-stage renal disease; HD = hemodialysis; RR = risk ratio.
* Downgrading the quality of evidence for inconsistency was done if the major studies contributing to the evidence base showed opposite results.
† Generalizability/applicability.
‡ Subgroup of patients receiving peritoneal dialysis not included. For peritoneal dialysis subgroup: RR, 0.71 (CI, 0.48–1.05); 1 study (n = 496).

Additional Results

Supplement 5 (available at www.annals.org) shows results for outcomes by type of statins. **Appendix Table 6** (available at www.annals.org) shows absolute risk differences between intervention and comparator groups.

DISCUSSION

We found that decreasing lipid levels with statins was safe and effective in preventing cardiac mortality and cardiovascular events, especially myocardial infarctions and revascularization procedures, in patients with CKD. The benefit was also seen for all-cause mortality, but this was limited to studies in patients with CKD not receiving dialysis and the results were highly heterogeneous. Heterogeneity among studies also limited the interpretation of stroke data. Lipid-lowering therapy was not found to be effective in preventing kidney failure, kidney graft failure, or decline in kidney function. The benefit for cardiovascular events also was not seen when the need for revascularization procedures was excluded from the composite outcome. Our findings generally agreed with those of previous meta-analyses on this topic (11, 42, 43). However, unlike earlier reports, our analyses included data from studies published in recent years, as well as data on quality, and focused exclusively on hard clinical outcomes from large RCTs.

The effect sizes in our analyses were more favorable and precise for outcomes that are closely linked with atherosclerosis, such as myocardial infarction and the composite of cardiovascular events that included revascularization procedures. Atherosclerosis is an important contributor to morbidity in patients with CKD, and our findings were consistent with the well-described effect of decreasing lipid levels on atherosclerosis (44, 45). However, nonatherosclerotic mechanisms for CVD, such as vascular calcification, high sympathetic tone, and cardiomyopathy, gain importance as CKD progresses (1); this shift in the predominant mechanism for CVD may explain why the mortality benefit from lipid-lowering therapy was limited to studies of early-stage CKD.

Stroke, also believed to be mediated by atherosclerosis, was not found to be prevented by lipid-lowering therapy in our analysis. This finding is not consistent with the results of general population studies (46–48) and must be interpreted with caution. Studies that reported on stroke were markedly heterogeneous, and negative results were mostly influenced by 2 studies of patients receiving hemodialysis (24, 27, 39). Further study is needed to better elucidate mechanisms for stroke according to the stage of CKD.

No trials testing lipid-lowering therapy in children with CKD were identified. Similarly, we did not find any trial examining lifestyle interventions for clinical outcomes in patients with CKD. The evidence base for patients receiving peritoneal dialysis also was insufficient. Although 2 trials (the UK-HARP-II study and SHARP) included patients undergoing peritoneal dialysis (21, 31), only 9% of participants in the UK-HARP-II study and 5% of participants in SHARP received peritoneal dialysis. Analyses testing interaction by dialysis status were done by classifying patients receiving hemodialysis and peritoneal dialysis as a homogeneous group. Combining peritoneal dialysis and hemodialysis may not be appropriate, and specifically ex-

Table 3—Continued

Summary of Findings					
Quality of Evidence	Summary RR (95% CI)				
	Total	DM, 100%	DM, ≤2%	HD	Non-HD
Moderate	0.91 (0.83–0.99) 15 studies (n = 31 555)	0.93 (0.86–1.01) 5 studies (n = 2796)	0.82 (0.51–1.32) 5 studies (n = 8230)	0.96 (0.90–1.02) 2 studies (n = 4028)	0.83 (0.70–0.98) 11 studies (n = 18 054)
High	0.96 (0.87–1.06) 4 studies (n = 13 211)	–	1.00 (0.25–3.95) 2 studies (n = 1168)	1.00 (0.87–1.14) 1 study (n = 2773)	1.00 (0.25–3.95) 2 studies (n = 1168)
High	0.82 (0.74–0.91) 6 studies (n = 14 247)	0.78 (0.68–0.89) 2 studies (n = 1986)	–	0.78 (0.68–0.89) 2 studies (n = 1986)	0.67 (0.48–0.94) 3 studies (n = 2991)
Moderate	0.78 (0.71–0.86) 9 studies (n = 19 924)	0.79 (0.69–0.90) 5 studies (n = 3635)	0.70 (0.54–0.91) 7 studies (n = 15 710)	0.96 (0.80–1.15) 1 study (n = 2527)‡	0.77 (0.71–0.83) 9 studies (n = 16 683)
High	0.94 (0.86–1.03) 4 studies (n = 16 565)	0.92 (0.82–1.05) 1 study (n = 1255)	0.60 (0.36–0.99) 1 study (n = 3267)	0.96 (0.88–1.05) 2 studies (n = 4028)	0.60 (0.36–0.99) 1 study (n = 3267)
Moderate	0.74 (0.67–0.81) 9 studies (n = 11 010)	0.76 (0.63–0.91) 4 studies (n = 1302)	0.75 (0.57–0.99) 4 studies (n = 4403)	0.72 (0.56–0.92) 1 study (n = 731)	0.74 (0.65–0.83) 8 studies (n = 10 279)
Very low	0.90 (0.63–1.27) 9 studies (n = 14 450)	1.16 (0.75–1.78) 6 studies (n = 3527)	0.93 (0.70–1.23) 4 studies (n = 7366)	1.47 (1.09–2.00) 2 studies (n = 1986)	0.72 (0.48–1.07) 7 studies (n = 12 464)
High	0.97 (0.90–1.05) 3 studies (n = 7956)	–	–	–	0.97 (0.90–1.05) 3 studies (n = 7956)
Moderate	0.91 (0.78–1.06) 7 studies (n = 24 323)	–	0.49 (0.11–2.05) 2 studies (n = 13 252)	–	0.91 (0.78–1.06) 7 studies (n = 24 323)

amining lipid-lowering treatments in patients receiving peritoneal dialysis would be worthwhile because this population is known to have a more atherogenic lipid profile (49).

Our review has other limitations. The reviewed studies were heterogeneous in population, interventions, and reporting of outcomes. These differences may hamper comparability across studies and limit reliable interpretation of pooled results. In addition, the results of studies comparing statin therapy and placebo in patients with CKD who are not receiving dialysis were mostly from CKD subgroups of large lipid trials of the general population. Most participants with CKD in such trials had mild CKD, and whether findings from these trials are applicable to patients not receiving dialysis with more advanced CKD is unclear. Inclusion of unplanned subgroup analyses made our review more comprehensive but also may have introduced bias. In addition, the only data for CKD subgroups of the CARE and LIPID trials and WOSCOPS were available from the patient-level meta-analysis. Combining results from this meta-analysis with those from other studies may have given the CARE, LIPID, and WOSCOPS meta-analyses more influence over the pooled estimate than if we had included data from individual trials separately, because the patient-level meta-analysis may have had smaller SEs than the results from the individual studies. Robust quantitative and qualitative assessments of intervention–comparator pairs were also limited because only a few studies tested comparisons other than statins versus placebo (21, 31, 33, 36, 37). We might have missed some pertinent data because we excluded studies with small sample sizes. However, judging by the results of previous reviews that had more liberal inclusion criteria (11, 42, 43), inclusion of small studies probably would not have substantially altered our conclusions. The reporting of adverse events was not uniform across studies, and whether the lack of information on a particular adverse event reflected its true absence or inadequate assessment was not always certain. We also were unable to collect data on cardiac variables, such as ejection fraction or use of cardioprotective medications, that could potentially affect our outcomes. Finally, we cannot exclude selective reporting of outcomes and publication bias (50).

In summary, decreasing lipid levels is safe and effective in patients with CKD, especially for prevention of atherosclerosis-mediated cardiovascular outcomes. However, because multiple mechanisms for CVD are in play in advanced CKD, further research is needed to delineate subgroups of patients in this population who are likely to benefit most from lipid-lowering treatments.

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Table 4. **Summary of Adverse Events From Lipid-Lowering Therapy in Study Participants With CKD**

Adverse Event	Studies, *n*	Participants, *n*	Summary (Reference)*	Consistency of Evidence Across Studies
Patients with CKD				
Total adverse events	4	9555	Pravastatin vs. placebo (n = 1): 10.5% vs. 11.3% (33) Rosuvastatin vs. placebo (n = 1): 315 vs. 320 events over 5 y (35) Simvastatin plus ezetimibe vs. simvastatin (n = 1): 36 vs. 25 events over 6 mo; NS (31) Atorvastatin, 80 mg vs. 10 mg (n = 1): 8.1% vs. 4.0% (36, 37)	Consistently no difference between statin and placebo
Drug discontinuation from adverse events	5	7067	Atorvastatin vs. placebo (n = 1): 21.0% vs. 18.8% (30) Pravastatin vs. placebo (n = 1): 6.2% vs. 9.7% (20) Simvastatin vs. placebo (n = 1): 6.2% vs. 6.5% (22) Simvastatin plus ezetimibe vs. simvastatin (n = 1): 8.8% vs. 7.9% (31) Atorvastatin, 80 mg vs. 10 mg (n = 1): 3.3% vs. 0.4% (36, 37)	Consistently no difference between statin and placebo
Rhabdomyolysis	9	23 517	Intervention vs. placebo: 0.0%–0.2% vs. 0.0%–0.1%; NS (21, 22, 29, 30, 35–37, 40, 41)	Consistently no difference between intervention and placebo
Clinically significant liver function abnormality†	6	18 336	Intervention vs. placebo: 0.1%–1.5% vs. 0.0%–1.5%; NS (21, 22, 29, 31, 33, 35)	Consistently no difference between intervention and placebo
Cancer	8	22 708	Statin vs. placebo (n = 6): 4.8%–8.7% vs. 4.7%–7.5% (22, 33, 35, 40, 41)‡ Simvastatin plus ezetimibe vs. simvastatin (n = 1): 4.0% vs. 0.0%; NS (31) Simvastatin plus ezetimibe vs. placebo (n = 1): 9.4% vs. 9.5% (21)	Consistently no difference between statin and placebo
Patients with CKD receiving hemodialysis				
Total adverse events	2	4028	Atorvastatin vs. placebo (n = 1): 2276 vs. 2255 events over 4 y (39) Rosuvastatin vs. placebo (n = 1): 96.3% vs. 96.7% (24)	Consistently no difference between statin and placebo
Drug discontinuation from adverse events	2	4028	Atorvastatin vs. placebo (n = 1): 73 vs. 52 events over 4 y (39) Rosuvastatin vs. placebo (n = 1): 31.5% vs. 32.1%; NS (24)	Inconsistent results for statin vs. placebo
Rhabdomyolysis	2	4028	Intervention vs. placebo: 0.0%–0.2% vs. 0.0%–0.1%; NS (24, 39)	Consistently no difference between intervention and placebo
Clinically significant liver function abnormality§	2	4028	Intervention vs. placebo: 0.4%–0.8% vs. 0.1%–0.4% (24, 39)	Consistently no difference between intervention and placebo
Cancer	2	4028	Atorvastatin vs. placebo (n = 1): 39 vs. 44 events (24) Rosuvastatin vs. placebo (n = 1): 7.7% vs. 8.6% (39)	Consistently no difference between statin and placebo
Patients with CKD and a kidney transplant				
Total adverse events	1	2102	Fluvastatin vs. placebo: 1029 vs. 1034 events over 5 y (25, 26, 28)	NA
Drug discontinuation from adverse events	1	2102	Fluvastatin vs. placebo: 0.3% vs. 0.7% over 5 y (25, 26, 28)	NA
Rhabdomyolysis§	1	2102	Fluvastatin vs. placebo: 0.3% vs. 0.1% over 5 y (25, 26, 28)	NA
Clinically significant liver function abnormality‖	1	2102	Fluvastatin vs. placebo: 1.1% vs. 1.1% over 5 y (25, 26, 28)	NA
Cancer	1	2102	Fluvastatin vs. placebo: 28.3% vs. 30.1% over 5 y (25, 26, 28)	NA

ALT = alanine aminotransferase; CARE = Cholesterol and Recurrent Events; CKD = chronic kidney disease; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; NA = not applicable (because only 1 study reported data); NS = not statistically significant; ULN = upper limit of the normal range; WOSCOPS = West of Scotland Coronary Prevention Study.
* "*n*" refers to the number of studies described in each summary statement if fewer than the total number of studies contributing data. Data are percentages of patients unless otherwise specified.
† ALT level >3 times the ULN.
‡ The rates are for nondermatologic cancer in CARE, LIPID, and WOSCOPS.
§ Creatinine kinase level ≥10 times the ULN.
‖ ALT level >4 times the ULN.

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Administrative, technical, or logistic support: A. Upadhyay, J.L. Lamont.
Collection and assembly of data: A. Upadhyay, A. Earley, J.L. Lamont, S. Haynes.

Appendix Table 1. Search Strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. Random Allocation/
5. Double-blind Method/
6. Single-Blind Method/
7. clinical trial.pt.
8. Clinical Trials.mp. or exp Clinical Trials/
9. (clinic$ adj25 trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
11. Placebos/
12. placebo$.tw.
13. random$.tw.
14. trial$.tw.
15. (randomized control trial or clinical control trial).sd.
16. (latin adj square).tw.
17. Comparative Study.tw. or Comparative Study.pt.
18. exp Evaluation studies/
19. Follow-Up Studies/
20. Prospective Studies/
21. (control$ or prospectiv$ or volunteer$).tw.
22. Cross-Over Studies/
23. or/1-22
24. exp kidney glomerulus/
25. exp kidney disease/
26. exp kidney function tests/
27. exp renal replacement therapy/
28. exp kidney transplantation/
29. exp kidney, artificial/
30. exp ultrafiltration/
31. exp sorption, detoxification/
32. renal.af. or renal.tw.
33. nephro$.af. or nephro$.tw.
34. kidney.af. or kidney.tw.
35. ur?emia.af. or ur?emia.tw.
36. h?emodialysis.af. or h?emodialysis.tw.
37. (hemofiltr$ or haemofiltr$).af. or (hemofiltr$ or haemofiltr$).tw.
38. or/24-37
39. Animals/ not humans.mp.
40. 38 not 39
41. exp lipid/ or exp triacylglycerol/ or exp lipoprotein/
42. exp apoprotein/
43. exp lipids/
44. exp cholesterol/
45. (ldl or vldl or hdl or triglyceride$ or cholesterol or lipoprotein$ or chylomicron$ or apoprotein$ or apolipoprotein$).tw.
46. (dyslipid$ or hypolipid$ or hyperlipid$).tw.
47. atorvastatin.tw. or 110862-48-1.rn.
48. Fluvastatin.tw. or 93957-54-1.rn.
49. lovastatin.tw. or 75330-75-5.rn.
50. pitavastatin.tw. or 147511-69-1.rn.
51. pravastatin.tw. or 81093-37-0.rn.
52. rosuvastatin.tw. or 287714-41-4.rn.
53. simvastatin.tw. or 79902-63-9.rn.
54. fenofibrate.tw. or 49562-28-9.rn.
55. gemfibrozil.tw. or 25812-30-0.rn.
56. clofibrate.tw. or 637-07-0.rn.
57. ciprofibrate.tw. or 52214-84-3.rn.
58. benzafibrate.tw.
59. cholestyramine.tw. or 11041-12-6.rn.
60. colesevelam.tw. or 182815-44-7.rn.
61. colestipol.tw. or 50925-79-6.rn.
62. ezetimibe.tw. or 163222-33-1.rn.
63. niacin.tw. or 59-67-6.rn.
64. nicotinic acid.tw.
65. or/41-64

Continued

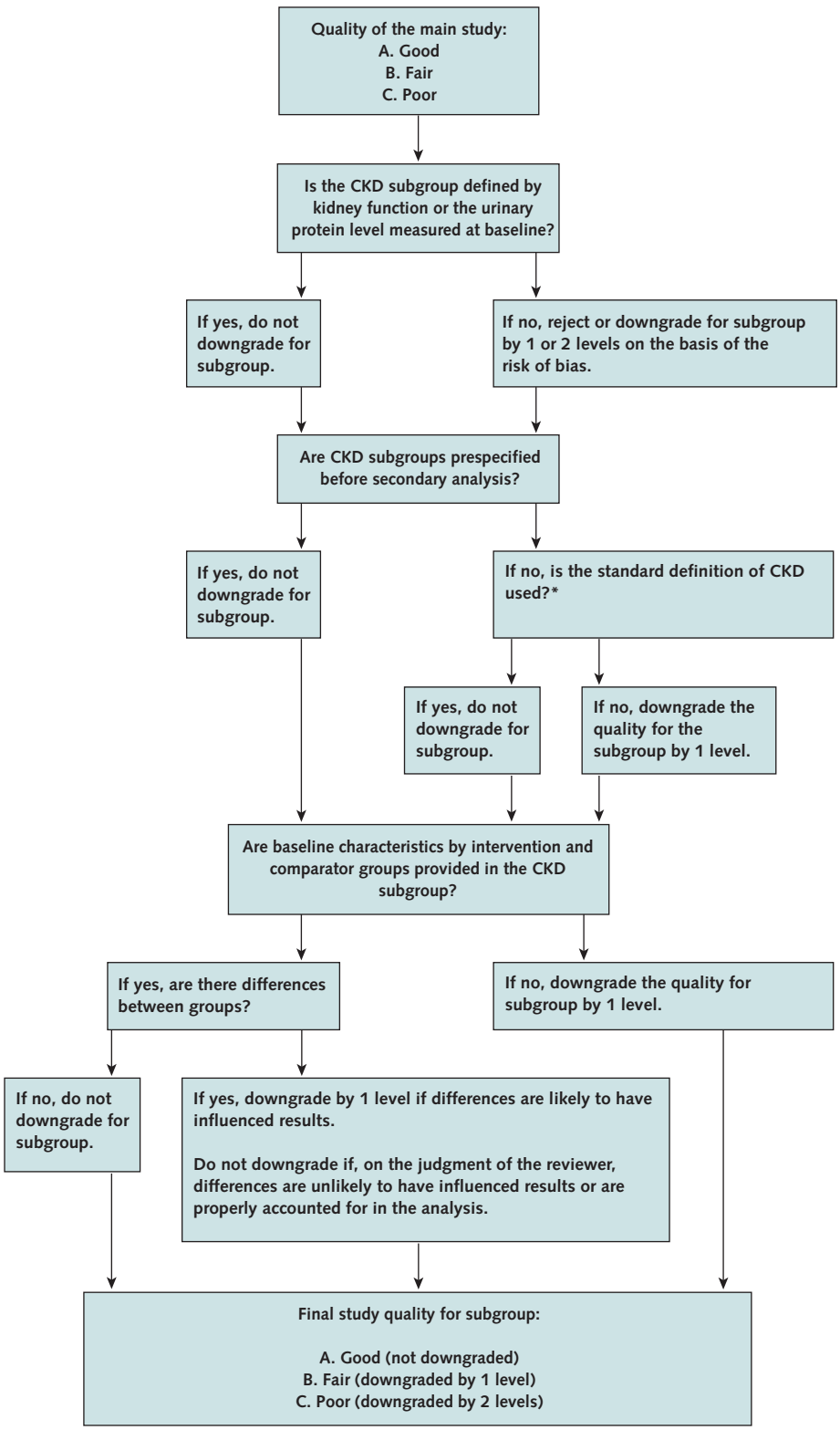
Appendix Table 1—Continued

66. obesity.mp. or exp ANTI-OBESITY AGENTS/ or anti-obesity agents.mp. or exp OBESITY, MORBID/
67. weight loss.mp. or exp Weight Loss/
68. body mass index.mp. or exp Body Mass Index/ or exp Body Mass/ or body mass.mp. or exp body weight/ or body weight.mp.
69. exp DIET/ or exp Diet, REDUCING/ or exp DIET FADS/ or exp DIET THERAPY/ or dietary.mp.
70. exercise.mp. or exp EXERCISE/ or exp EXERCISE THERAPY/
71. exp BEHAVIOR THERAPY/ or behavior therapy.mp. or exp lifestyle/ or lifestyle.mp.
72. bariatric surgery.mp. or exp Bariatric Surgery/
73. low-protein diet.mp. or exp Diet, Protein-Restricted/ or Protein-free diet.mp. or diet therapy/ or diet, protein-restricted/ or diet/
74. feeding behavior/ or food habits/
75. or/66-74
76. 23 and 40
77. 76 and 65
78. limit 77 to yr="2000-2011"
79. 76 and 75
80. limit 79 to yr="2000-2011"

Appendix Table 2. Grading Study Quality

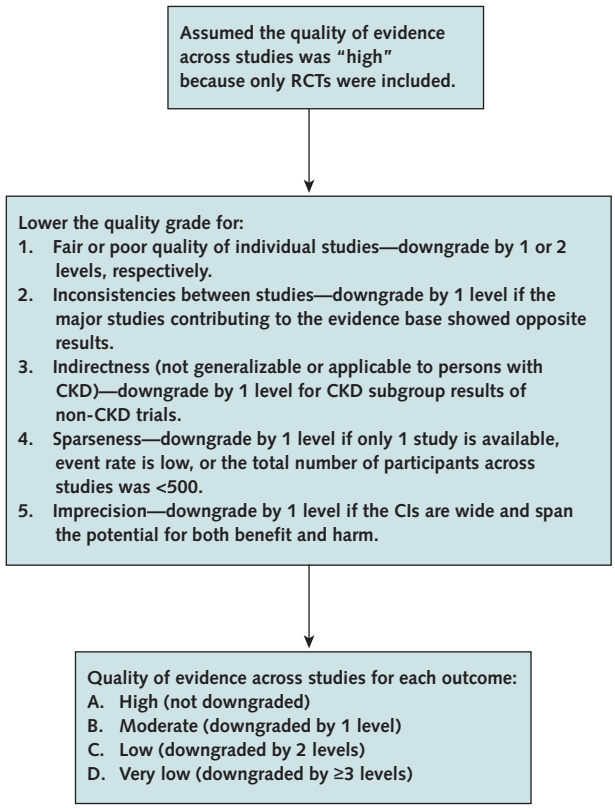
Study Quality	Explanation
Good	Studies with low risk of bias that mostly adhere to the following commonly held concepts of high quality: a formal randomized, controlled design; clear description of samples, setting, intervention, and comparator groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; <20% dropout rate; clear reporting of dropouts; and no obvious bias.
Fair	Studies susceptible to some bias that is not sufficient to invalidate the results. They do not meet all the criteria of a "good" study. The studies may be missing information, making it difficult to assess limitations and potential problems.
Poor	Studies with substantial bias that may invalidate the results: serious errors in design, analysis, or reporting; large amounts of missing information or discrepancies in reporting.

Appendix Figure 1. **Grading the quality of CKD subgroups of non-CKD trials.**



CKD = chronic kidney disease.
* Estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

Appendix Figure 2. **Grading the quality of evidence across studies.**



CKD = chronic kidney disease; RCT = randomized, controlled trial.

Appendix Table 3. **Summary Table of the UK-HARP-II Study Examining Statin Plus Ezetemibe Versus Statin Plus Placebo in Patients With CKD**

Variable	Outcome	
	Death	ESRD
Duration of outcome measurement (duration of treatment), *mo*		6 (6)
Description		I: Simvastatin, 20 mg/d, plus ezetimibe, 10 mg/d C: Simvastatin, 20 mg/d
Participants analyzed (participants enrolled), *n*		I: 102 (102) C: 101 (101)
DM, *%*		I: 12 C: 10
Mean baseline values		
eGFR, *mL/min per 1.73 m²*		I: 26.1 C: 29.7
Cholesterol, *mmol/L (mg/dL)*		
TC		I: 5.13 (198) C: 5.05 (195)
LDL-C		I: 3.13 (121) C: 3.03 (117)
HDL-C		I: 1.04 (40) C: 1.04 (40)
TG, *mmol/L (mg/dL)*		I: 1.9 (167) C: 2.1 (188)
Results		
Events, *n (%)*	I: 3 (2) C: 0 (0)	I: 14 (14) C: 14 (14)
RR (95% CI)	ND	RR, 0.99 (0.50–1.97)*
P value	ND	NS
Quality	Good	Good

C = comparator group; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HDL-C = high-density lipoprotein cholesterol; I = intervention group; LDL-C = low-density lipoprotein cholesterol; ND = no data; NS = not significant; RR = risk ratio; TC = total cholesterol; TG = triglycerides; UK-HARP-II= Second United Kingdom Heart and Renal Protection.
* Calculated by the authors.

Appendix Table 4. **Summary of TNT Trial Examining the Effect of Dose of Atorvastatin in Patients With CKD**

Study (Reference)	Median Duration of Outcome Measurement (Duration of Treatment), *y*	Description	Participants Analyzed (Participants Enrolled), *n*	Mean Baseline Values					
				eGFR, *mL/min per 1.73 m²*	DM, *%*	Cholesterol Level, *mmol/L (mg/dL)*			TG Level, *mmol/L (mg/dL)*
						TC	LDL-C	HDL-C	
TNT (36)	5 (5)	I: Atorvastatin, 80 mg C: Atorvastatin, 10 mg	I: 273 (273) C: 273 (273)	I: 51.5 C: 50.7	I: 100 C: 100	I: 4.56 (176.1) C: 4.61 (178.0)	I: 2.47 (95.5) C: 2.51 (97.0)	I: 1.16 (44.9) C: 1.16 (45.2)	I: 2.0 (181.6) C: 2.0 (180.2)
TNT (37)	5 (5)	I: Atorvastatin, 80 mg C: Atorvastatin, 10 mg	I: 1602(1602) C: 1505 (1505)	I: 53.0 C: 52.8	I: 17 C: 18	I: 4.66 (175.9) C: 4.66 (175.9)	I: 2.49 (96.3) C: 2.49 (96.5)	I: 1.24 (48.0) C: 1.24 (47.6)	I: 1.8 (159.2) C: 1.8 (159.8)

C = comparator group; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; I = intervention group; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; TNT = Treating to New Targets.

Appendix Table 5. **Results of TNT Trial Examining the Effect of Dose of Atorvastatin in Patients With CKD**

Outcome	Results		*P* Value*	Quality
	Events, *n* (%)	RR or HR (95% CI)*		
All-cause mortality				
TNT (36)	I: 33 (12) C: 32 (12)	RR, 1.03 (0.65–1.63)	NS	Good
TNT (37)	I: 112 (7) C: 113 (8)	HR, 0.95 (0.70–1.2)†	NS	Good
CV events				
TNT (36)				
Major CV event (primary)‡	I: 38 (14) C: 57 (21)	HR, 0.65 (0.43–0.98)	0.04	Good
Any CV event	I: 120 (44) C: 140 (51)	RR, 0.86 (0.72–1.02)	NS (0.08)	Good
Major coronary event§	I: 28 (10) C: 43 (16)	RR, 0.65 (0.42–1.02)	NS (0.06)	Good
Any coronary event	I: 80 (29) C: 97 (36)	RR, 0.82 (0.65–1.05)	NS	Good
Cerebrovascular event	I: 24 (9) C: 36 (13)	RR, 0.67 (0.41–1.09)	NS	Good
Stroke	I: 13 (5) C: 20 (7)	RR, 0.65 (0.33–1.28)	NS	Good
CHF with hospitalization	I: 25 (9) C: 34 (13)	RR, 0.74 (0.45–1.20)	NS	Good
Peripheral artery disease	I: 35 (13) C: 30 (11)	RR, 1.17 (0.74–1.84)	NS	Good
TNT (37)				
Major CV event (primary)‡	I: 149 (9) C: 202 (13)	HR, 0.68 (0.55–0.84)	0.0003	Good
Any CV event	I: 489 (31) C: 574 (38)	HR, 0.76 (0.67–0.86)	ND	Good
Major coronary event§	I: 110 (7) C: 157 (10)	HR, 0.65 (0.51–0.83)	ND	Good
Any coronary event	I: 356 (22) C: 431 (29)	HR, 0.75 (0.65–0.86)	ND	Good
Cerebrovascular event	I: 74 (5) C: 104 (7)	HR, 0.66 (0.49–0.89)	ND	Good
Stroke	I: 49 (3%) C: 84 (6%)	HR, 0.54 (0.38–0.77)	ND	Good
CHF with hospitalization	I: 121 (8) C: 112 (7)	HR, 1.0 (0.8–1.4)†	ND	Good
Peripheral artery disease	I: 149 (9) C: 202 (13)	HR, 0.68 (0.55–0.84)	0.0003	Good

C = comparator group; CHF = congestive heart failure; CV = cardiovascular; HR = hazard ratio; I = intervention group; ND = no data; NS = not statistically significant; RR = relative risk; TNT = Treating to New Targets.

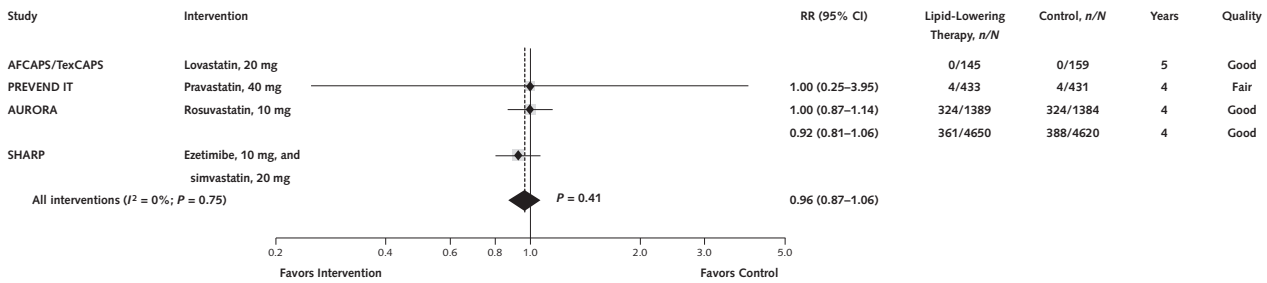
* Calculated by the authors for all outcomes other than primary outcome of major CV event.

† Estimated from Figure 3 in reference 37.

‡ Death from coronary heart disease, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

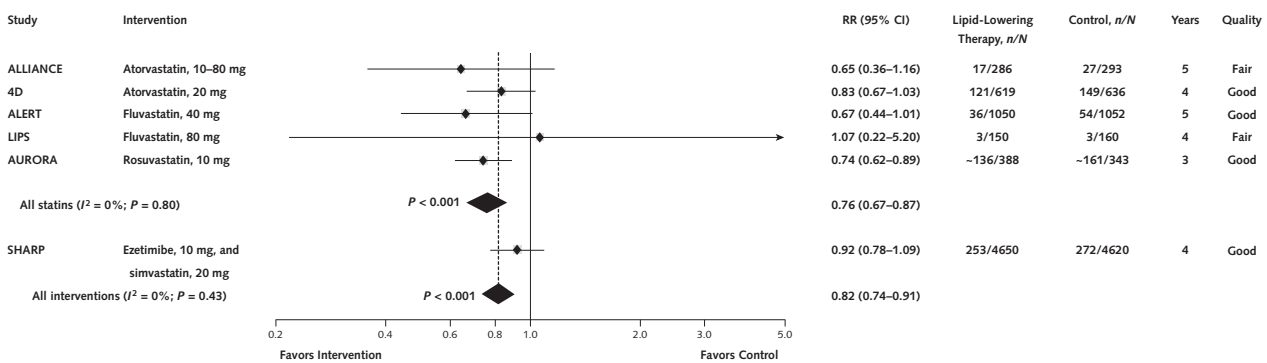
§ Death from coronary heart disease, nonfatal non–procedure-related myocardial infarction, or resuscitation after cardiac arrest.

Appendix Figure 3. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for cardiovascular mortality.**



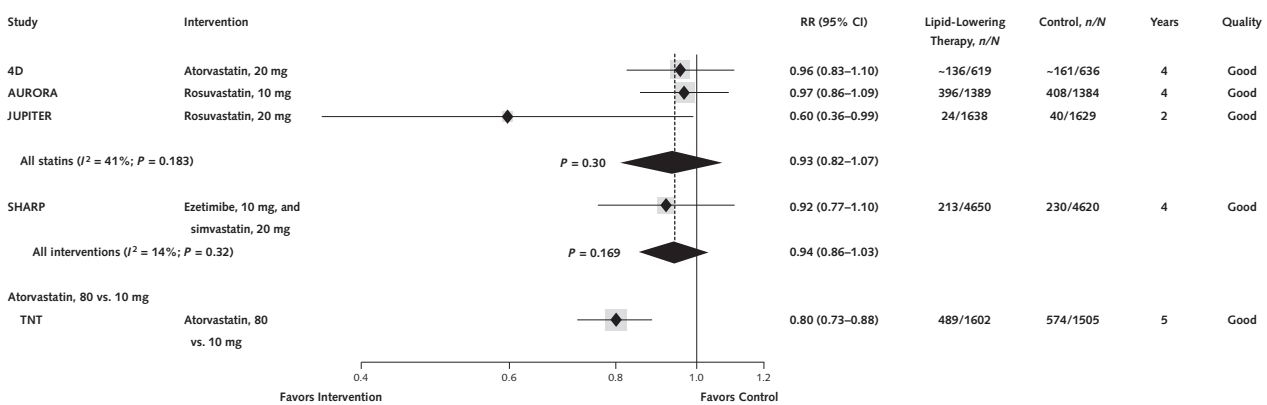
See legend for **Figure 2**.

Appendix Figure 4. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for cardiac mortality.**



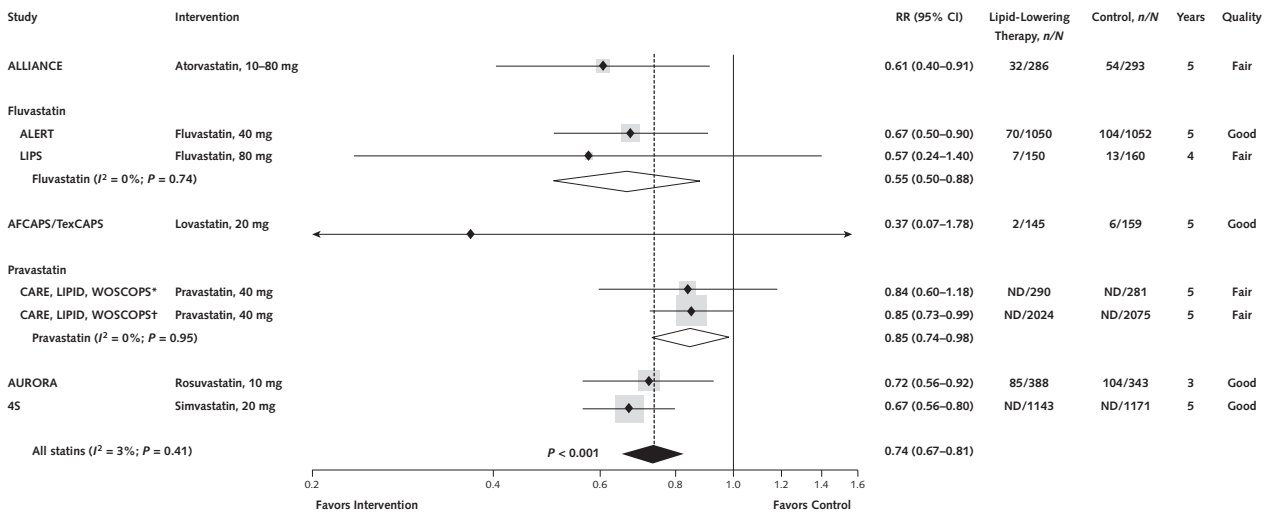
See legend for **Figure 2**.

Appendix Figure 5. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for cardiovascular events, excluding revascularization.**



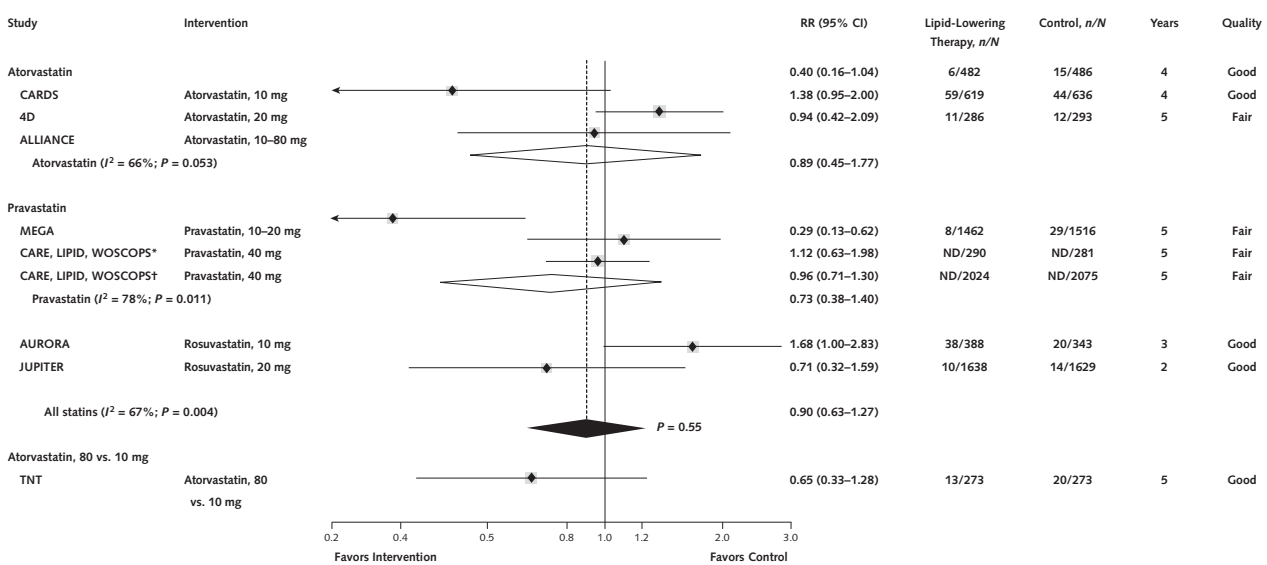
See legend for **Figure 2**.

Appendix Figure 6. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for myocardial infarction.**



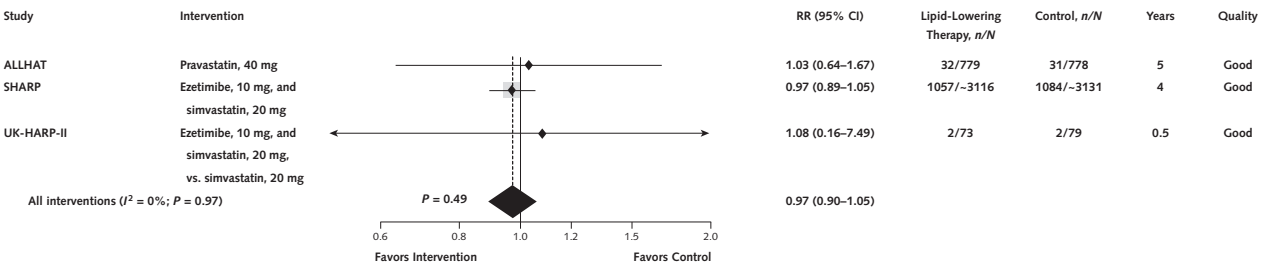
See legend for **Figure 2**.

Appendix Figure 7. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for stroke.**



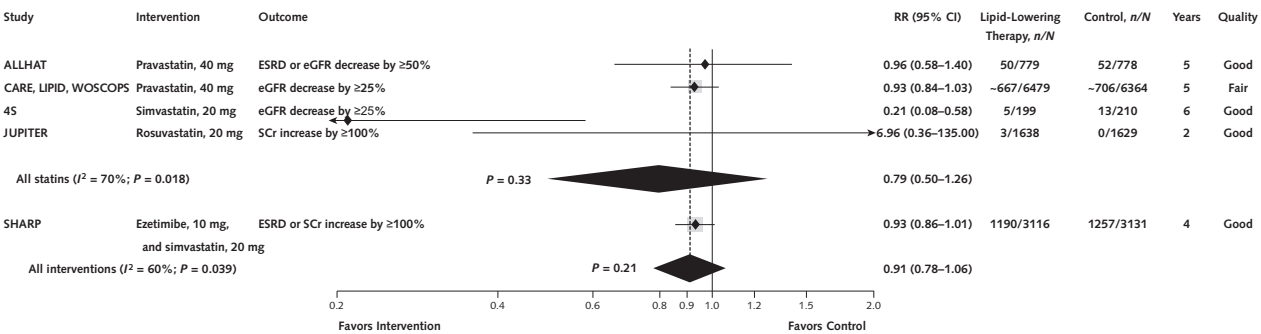
See legend for **Figure 2**.

Appendix Figure 8. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for end-stage renal disease.**



See legend for **Figure 2**.

Appendix Figure 9. **Random-effects model meta-analyses of RR in patients with CKD with lipid-lowering interventions for end-stage renal disease or worsening kidney function.**



See legend for **Figure 2**. eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; SCr = serum creatinine.

Appendix Table 6. **Risk Difference Between Intervention (Treated) and Comparator (Untreated) Groups**

Outcome	Pooled CR Estimate		Low CR Estimate*		High CR Estimate†	
	CR per 1000	Risk Difference (95% CI) Fewer per 1000	CR per 1000	Risk Difference (95% CI) Fewer per 1000	CR per 1000	Risk Difference (95% CI) Fewer per 1000
All-cause mortality	112	10 (1–19)	38	3 (0.4–7)	217	19 (2–37)
CV mortality		NS				
Cardiac mortality	59	11 (5–15)	21	4 (2–5)	115	21 (10–30)
CV events (including revascularization)	127	28 (18–37)	61	13 (9–18)	214	47 (30–62)
CV events (excluding revascularization)		NS				
Myocardial infarction	129	34 (25–43)	59	15 (11–19)	222	58 (42–73)
Stroke		NS				
ESRD		NS				
Worsening kidney function		NS				

CR = control rate (from a random-effects model of the arcsin transformed event rates in the control groups); CV = cardiovascular; ESRD = end-stage renal disease; NS = not statistically significant.
* Based on the lower bound of the 95% CI of the pooled CR.
† Based on the upper bound of the 95% CI of the pooled CR.