Arteriosclerosis, Thrombosis, and Vascular Biology

AHA SCIENTIFIC STATEMENT

Aggressive LDL-C Lowering and the Brain: Impact on Risk for Dementia and Hemorrhagic Stroke: A Scientific Statement From the American Heart Association

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ABSTRACT: The objective of this scientific statement is to evaluate contemporary evidence that either supports or refutes the conclusion that aggressive low-density lipoprotein cholesterol lowering or lipid lowering exerts toxic effects on the brain, leading to cognitive impairment or dementia or hemorrhagic stroke. The writing group used literature reviews, references to published clinical and epidemiology studies, clinical and public health guidelines, authoritative statements, and expert opinion to summarize existing evidence and to identify gaps in current knowledge. Although some retrospective, case control, and prospective longitudinal studies suggest that statins and low-density lipoprotein cholesterol lowering are associated with cognitive impairment or dementia, the preponderance of observational studies and data from randomized trials do not support this conclusion. The risk of a hemorrhagic stroke associated with statin therapy in patients without a history of cerebrovascular disease is nonsignificant, and achieving very low levels of low-density lipoprotein cholesterol does not increase that risk. Data reflecting the risk of hemorrhagic stroke with lipid-lowering treatment among patients with a history of hemorrhagic stroke are not robust and require additional focused study.

Key Words: AHA Scientific Statements ■ blood-brain barrier ■ cholesterol, LDL ■ cognition ■ ezetimibe ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ PCSK9 inhibitors ■ stroke

Low-density lipoprotein (LDL) cholesterol (LDL-C) is the end product of lipoprotein metabolism. A higher plasma level of LDL-C is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) with a continuous, direct relationship (dose-response) between plasma LDL-C and ASCVD risk. Prospective randomized trials of statins without and with other lipid-lowering medications show that there is no lower limit of LDL-C reduction beneath which there is no further ASCVD risk reduction.[1–3] LDL-C targets for high- and very-high-risk patients have decreased over time.

Despite the body of evidence from basic scientific investigations, longitudinal cohorts, prospective randomized clinical trials of pharmacological interventions, and various meta-analyses, the majority of high- and very-high-risk patients remain undertreated.[4–6] More aggressive LDL-C reduction correlates with lower risk of myocardial infarction, ischemic stroke, need for coronary and peripheral revascularization, and death and lower rates of progression of atherosclerotic disease.[7,8] Given these observations, it is important to identify and ameliorate barriers to appropriate care to best serve the needs of patients at risk of ASCVD.

Dyslipidemia is epidemic throughout the world, and ASCVD remains the leading cause of death. Although debated, there is an emerging consensus that a truly physiological, nonpathogenic LDL-C level in humans is ≈25 to 60 mg/dL.[9–12] However, concern remains about potential for neurologic toxicity when LDL-C is reduced to low (<70 mg/dL) and very low (<25 mg/dL) levels. In the Multiple Risk Factor Intervention Trial, a total cholesterol of <160 mg/dL was associated with an increased

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risk for hemorrhagic stroke compared with total cholesterol that exceeded this threshold in men with diastolic hypertension.[13] Nonetheless, the number of participants with hemorrhagic stroke was small, and between-group differences were not significant. Some subsequent clinical trials with statins suggested an increased risk for hemorrhagic stroke.[14,15] In addition, some data suggested that the statins and aggressive LDL-C reduction might have a detrimental effect on cognition.[16,17]

The brain is the body's most cholesterol-rich organ, and some have questioned whether aggressive LDL-C lowering induces abnormal structural and functional changes. The objective of this scientific statement is to evaluate contemporary evidence that either supports or refutes the conclusion that aggressive LDL-C lowering or lipid lowering exerts toxic effects on the brain, leading to cognitive impairment/dementia or hemorrhagic stroke.

METHODS

The writing group used literature reviews, references to published clinical and epidemiological studies, clinical and public health guidelines, authoritative statements, and expert opinion to summarize existing evidence and to identify gaps in current knowledge. The panel reviewed the most relevant articles through computerized searches of the medical literature using MEDLINE through December 2022. The document underwent extensive American Heart Association internal peer review. The entire writing group reviewed and approved the final document. Table 1 provides a list of clinical trial abbreviations and acronyms.

IMPACT OF AGGRESSIVE LDL-C REDUCTION ON ASCVD EVENTS

Clinical Studies in Individuals With Coronary Heart Disease

Multiple prospective randomized controlled trials (RCTs) show that lowering LDL-C reduces morbidity and mortality in those at high risk for or with established ASCVD.[18–20] This information complements evidence from epidemiological and genetic studies demonstrating a log-linear relationship between serum LDL-C concentration and the development of ASCVD.[21] Previously, the benefits observed with reductions in LDL-C were limited by levels achievable with statin monotherapy. Subsequent RCTs provide robust evidence that the addition of nonstatin therapies further reduces ASCVD outcomes proportional to the absolute attained LDL-C concentration, even at very low levels of LDL-C.[1,2,22] Statin-based RCTs establish that for patients with and without manifest ASCVD, the greater the reduction in LDL-C, the greater the reduction in major adverse cardiovascular events.[23–25] The CTT (Cholesterol Treatment Trialists) Collaboration reports in a meta-analysis of 174 149 participants in 22 trials of statin versus control and in 5 trials examining the intensity of statin therapy that each 1–mmol/L (39–mg/dL) reduction in LDL-C results in a 21% reduction in risk of major adverse cardiovascular events (risk reduction, 0.79 [95% CI, 0.77–0.81]; $P<0.0001$). This relationship is consistent among patients with different comorbidities, including chronic kidney disease and diabetes, and across groups with different baseline LDL-C, age, sex, and cardiovascular risk profiles.[26] The reduction in cardiovascular risk per 1–mmoL reduction in LDL-C remains continuous at very low levels of LDL-C, achievable with the addition of nonstatin therapies.[27,28]

Ezetimibe acts to reduce LDL-C by interfering with cholesterol absorption through inhibition of the Niemann-Pick C1-like 1 protein.[29,30] Studies with ezetimibe and antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) receptors (PCSK9 inhibitors) further enhance the understanding of LDL-C biology and provide an opportunity to observe the benefits of reducing LDL-C to very low concentrations.

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated that the addition of ezetimibe to high-dose simvastatin in patients with a recent acute coronary syndrome event lowered LDL-C to a mean of 54 mg/dL with a reduction in event rates in the treatment arm at 7 years (hazard ratio [HR], 0.94 [95% CI, 0.89–0.99]; $P=0.016$).[31] The FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) demonstrated that the addition of evolocumab to maximally tolerated statin therapy among patients with stable coronary heart disease lowered LDL-C to a median concentration of 30 mg/dL with an event rate reduction at 2.2 years (HR, 0.85 [95% CI, 0.79–0.92]; $P<0.0001$).[32] Similarly, the ODYSSEY trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) found that the addition of alirocumab to maximally tolerated statin therapy among patients with a recent acute coronary syndrome event lowered LDL-C to a mean concentration of 48 mg/dL with an event rate reduction at 2.8 years (HR, 0.85 [95% CI, 0.78–0.93]; $P<0.0001$).[33] Furthermore, a prespecified analysis of the FOURIER trial included 504 patients with an achieved LDL-C of <10 mg/dL and found that their event rate was lower compared with patients at any greater LDL-C level, without an increase in serious adverse events or adverse events leading to drug discontinuation.[1]

Relevant data for the primary statin and nonstatin lipid-lowering trials are listed in Table 2, including basic trial demographic data, baseline LDL-C, on-treatment LDL-C, and treatment-related HRs.[14,15,31–55] In summary, evidence from RCTs, epidemiological studies, and genomic investigation supports the use of statins and specific nonstatin therapies to improve cardiovascular

Table 1. Clinical Trial Abbreviation Glossary

4S	Scandinavian Simvastatin Survival Study
A to Z	Aggrastat to Zocor
ACCELERATE	Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALLHAT-LLT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack–Lipid Lowering Trial
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes
ALLIANCE	Aggressive Lipid-Lowering Initiation Abates New Cardiac Events
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm
ASPEN	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events Study
CLEAR	Cholesterol Lowering via Bempedoic Acid Trial
dal-OUTCOMES	Dalcetrapib Outcomes
EBBINGHAUS	Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects
EWTOPIA 75	Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
FOURIER-OLE	FOURIER Open Label Extension
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico–Heart Failure
GISSI-P	Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico–Prevenzione
HAUSER-RCT	Trial Assessing Efficacy, Safety and Tolerability of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibition in Paediatric Subjects With Genetic Low-Density Lipoprotein (LDL) Disorders
HOPE-3	Heart Outcomes Prevention Evaluation-3
HPS	Heart Protection Study
HPS2-THRIVE	Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events
HPS3/TIMI55–REVEAL	Heart Protection Study 3/Thrombolysis in Myocardial Infarction 55–Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification
IDEAL	Incremental Decrease in Endpoints Through Aggressive Lipid Lowering
IMPROVE IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
JUPITER	Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
LEADe	Lipitor's Effect in Alzheimer's Dementia
LIPID	Long-term Intervention With Pravastatin in Ischemic Disease
LIPS	Lescol Intervention Prevention Study
MEGA	Primary Prevention of Cardiovascular Disease With Pravastatin in Japan
MS-STAT	Multiple Sclerosis Simvastatin Trial
ODYSSEY	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
PODCAST	Prevention of Decline in Cognition After Stroke Trial
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke Study
SAILS	Statins for Acutely Injured Lungs From Sepsis
SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SHARP	Study of Heart and Renal Protection
SPARCL	Stroke Prevention With Aggressive Reduction in Cholesterol Levels
SPIRE	Studies of PCSK9 Inhibition and the Reduction of Vascular Events
SPRINT	Systolic Blood Pressure Intervention Trial
STOMP	Effect of Statin Medications on Muscle Performance
STRENGTH	Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia
TST	Treat Stroke to Target
WOSCOPS	West of Scotland Prevention Study

Table 2. Statin and Nonstatin Therapies in the Treatment of LDL-C to Reduce Cardiovascular Risk

	N	Treatment, mg/d	Median follow-up, y	Mean baseline LDL-C, mmol/L	Mean treatment LDL-C, mmol/L	MACE HR (95% CI); *P* value
Placebo or standard-care controlled trials						
4S[34]	4444	S20-40 vs placebo	5.4	4.88	3.17	0.70 (0.58–0.85), *P*=0.0003
WOSCOPS[35]	6595	P40 vs placebo	4.8	4.96	3.70	0.69 (0.57–0.83), *P*<0.001
CARE[36]	4159	P40 vs placebo	5.0	3.58	2.49	0.74 (0.64–0.91), *P*=0.003
AFCAPS/TexCAPS[37]	6605	L20-40 vs placebo	5.2	3.89	2.96	0.63 (0.50–0.79), *P*<0.001
LIPID[38]	9014	P40 vs placebo	6.0	3.88	2.91	0.76 (0.65–0.88), *P*<0.001
GISSI-P[39]	4271	P20 vs no treatment	2.0	3.92	3.83	0.90 (0.71–1.15), *P*=0.41
LIPS[40]	1677	F80 vs placebo	3.9	3.42	2.50	0.78 (0.64–0.95), *P*=0.01
HPS[15]	20536	S40 vs placebo	5.4	3.38	2.38	0.87 (0.81–0.94), *P*=0.0003
PROSPER[41]	5804	P40 vs placebo	3.3	3.79	2.50	0.85 (0.74–0.97), *P*=0.014
ALLHAT-LLT[42]	10355	P40 vs usual care	4.9	3.76	2.71	0.99 (0.89–1.11), *P*=0.88
ASCOT-LLA[43]	10305	A10 vs placebo	3.3	3.44	3.34	0.64 (0.50–0.83), *P*=0.0005
CARDS[44]	2838	A10 vs placebo	4.1	3.03	2.11	0.63 (0.48–0.83), *P*=0.001
ALLIANCE[45]	2442	A10-80 vs usual care	4.7	3.80	2.50	0.83 (0.71–0.97), *P*=0.02
ASPEN[46]	2410	A10 vs placebo	4.0	2.93	2.05	0.90 (0.73–1.12), *P*=0.34
MEGA[47]	8214	P10-20 vs usual care	5.0	4.05	3.31	0.67 (0.49–0.91), *P*=0.01
JUPITER[48]	17802	R20 vs placebo	2.0	2.70	1.40	0.56 (0.46–0.69), *P*<0.00001
GISSI-HF[49]	4574	R10 vs placebo	4.2	3.06	2.15	1.00 (0.898–1.122), *P*=0.943
HOPE-3[50]	12705	R10 vs placebo	5.6	3.30	2.28	0.76 (0.64–0.91), *P*=0.002
SPARCL[14]	4731	A80 vs placebo	4.9	3.43	1.89	0.84 (0.71–0.99), *P*=0.03
Intensive vs moderate-dose therapy trials						
PROVE-IT-TIMI 22[51]	4162	A80 vs P40	2.1	2.62	1.60	0.84 (0.74–0.95), *P*=0.005
A to Z[52]	4497	S40 then S80 vs placebo then S20	2.0	2.09	1.63	0.89 (0.76–1.04), *P*=0.14
TST[53]	10001	A80 vs A10	5.0	2.52	2.00	0.78 (0.69–0.89), *P*<0.001
IDEAL[54]	8888	A40-80 vs S20-40	4.8	2.64	2.10	0.87 (0.77–0.98), *P*=0.02
SEARCH [55]	12064	S80 vs S20	7.0	2.50	2.17	0.94 (0.88–1.01), *P*=0.10
Statin with either ezetimibe or PCSK9 inhibitor						
IMPROVE-IT[31]	18144	Ezetimibe/Simva* vs placebo/Simva*	7.0	2.43	1.40	0.94 (0.89–0.99, *P*<0.0001)
FOURIER[32]	27564	Statin/evolocumab vs statin†	2.2	2.38	0.78	0.85 (0.79–0.92), *P*<0.001
ODYSSEY[33]	18924	Statin/alirocumab vs statin†	2.8	2.38	1.24	0.85 (0.78–0.93), *P*<0.001

Treatment Abbreviations: A10 indicates atorvastatin 10 mg; A80, atorvastatin 80 mg; P10–20,; L20–40, lovastatin 20–40 mg; pravastatin 10–20 mg; P20, pravastatin 20 mg; P40, pravastatin 40 mg; R10, rosuvastatin 10 mg; R20, rosuvastatin 20 mg; S20, simvastatin 20 mg; S20–40, simvastatin 20–40 mg; S40, simvastatin 40 mg; S40–80, simvastatin 40-80 mg; S80, simvastatin 80 mg; and Simva, simvastatin 40 mg.

A to Z indicates Aggrastat to Zocor; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack-Lipid Lowering Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events Study; 4S, Scandinavian Simvastatin Survival Study; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico–Heart Failure; GISSI-P, Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico–Prevenzione; HOPE-3, Heart Outcomes Prevention Evaluation-3; HPS, Heart Protection Study; HR, hazard ratio; IDEAL, Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; low-density lipoprotein cholesterol; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MACE, major adverse cardiovascular event; MEGA, Primary Prevention of Cardiovascular Disease With Pravastatin in Japan; ODYSSEY, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL, Stroke Prevention with Aggressive Reduction in Cholesterol Levels; TST, Treat Stroke to Target; and WOSCOPS, West of Scotland Prevention Study.

*Ezetimibe 10 mg and simvastatin 40 mg (Simvastatin was uptitrated to 80 mg if LDL-C remained >79 mg/dL until the Food and Drug Administration issued a safety communication restricting the use of simvastatin 80 mg).

†Maximally tolerated, high-intensity statin therapy including rosuvastatin 20 mg, rosuvastatin 40 mg, atorvastatin 40 mg, or atorvastatin 80 mg.

outcomes by aggressively lowering LDL-C with no lower threshold restriction.

Evolving Guidelines for LDL-C Lowering in Individuals With or at High Risk of ASCVD

Recommended targets for LDL-C initially reflected the effectiveness of contemporary statin therapies. With the addition of nonstatin therapies, lower LDL-C levels became achievable, and lower target levels and threshold levels, above which the addition of a nonstatin therapy would be warranted, have been endorsed. Among groups of patients with ASCVD, subsets of those with a myocardial infarction within the prior year, peripheral arterial disease, type 2 diabetes, and polyvascular disease had even greater benefits from LDL-C lowering.[30,56,57] Therefore, each iteration of national and international guidelines identified distinct highest-risk patient subgroups who would derive the greatest benefit from LDL-C lowering. The factors used to risk-stratify groups included the number of ASCVD events, metabolic profiles, age, risk calculator scores, and imaging-detected subclinical atherosclerosis.[58,59]

In 2001, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults issued a guideline for the treatment of blood cholesterol with a recommended target of LDL-C <160 mg/dL for the lowest-risk patients and LDL-C <100 mg/dL for the highest-risk group, which included a diagnosis of coronary heart disease or a coronary heart disease equivalent (including type 2 diabetes).[60] With the findings of IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), international guidelines recommended progressively lower LDL-C targets and thresholds, particularly for the highest-risk patient groups. Table 3 presents 1 historical and several contemporary guidelines and includes the definitions of their highest-risk categories corresponding to either target or threshold LDL-C values.[60–64]

The 2018 US multisociety guidelines defined a very-high-risk ASCVD category on the basis of the number of major ASCVD events and number of high-risk conditions.[61] For this category, if the LDL-C remained >70 mg/dL, the addition of ezetimibe first and then PCSK9 inhibitors was recommended.

The 2019 European Atherosclerosis Society/European Society of Cardiology guidelines defined a very-high-risk category on the basis of a diagnosis of clinical ASCVD by history, unequivocal ASCVD by imaging, and risk calculator scores (outlined in Table 3); for individuals at very high risk, an LDL-C target should be <55 mg/dL.[62] The 2020 Lipid Association of India expert consensus statement defined an extreme-risk group on the basis of ASCVD with ≥1 very-high-risk feature, recurrent acute coronary syndrome (within 1 year) despite LDL ≤50 mg/dL, or polyvascular disease with a target of ≤30 mg/dL recommended.[63] The 2022 American College of Cardiology expert consensus statement lowered the prior 2018 American College of Cardiology guideline threshold for the addition of ezetimibe or a PCSK9 monoclonal antibody to ≥55 mg/dL for patients with very-high-risk ASCVD or familial hypercholesterolemia with ASCVD.[64]

There is now evidence that, with the addition of nonstatin therapies, ASCVD risk can be reduced proportionally to the decrease in LDL-C with no lower limit. This evidence complements findings from prior statin trials and highlights the critical role of LDL-C reduction in lowering cardiovascular risk. The paradigm is now "lowest is best," and several guideline statements advocate for the achievement of very low levels of LDL-C (ie, ≤55 mg/dL) for individuals at highest risk (see Table 3).

CONSEQUENCES OF INADEQUATE LDL-C REDUCTION

Practice Gaps in Lipid Control

Despite overwhelming evidence supporting the benefit of LDL-C–lowering therapy, substantial gaps in population-level lipid control remain. Nearly 28% of US adults have an LDL-C ≥130 mg/dL, and one-third report being aware that they have high cholesterol.[65] More than 50% of adults 18 to 59 years of age presenting with a first myocardial infarction have dyslipidemia.[66] Several studies document suboptimal lipid control in routine clinical practice. In a study using US insurance claims data, most adults with established ASCVD did not meet LDL-C goals, and 38% had LDL-C levels ≥100 mg/dL.[67] A similar trend is noted internationally, with only 30% of adults with stable coronary heart disease being below an LDL-C goal of 70 mg/dL in an observational cohort including 18 countries.[68]

Underpinning these gaps in lipid control is underuse of statins and other lipid-lowering therapies. In another claims-based retrospective cohort of individuals with established ASCVD, nearly 50% were not receiving a statin, and fewer than a quarter were receiving a high-intensity statin.[69] Among those presenting with a first myocardial infarction or stroke, <30% had filled a prescription for lipid-lowering therapy before the index event.[70] Wide practice variation for the prescription of lipid-lowering therapy was noted in the American College of Cardiology National Cardiovascular Data Registry, with fewer than a third of individuals with an LDL-C ≥190 mg/dL receiving a high-intensity statin.[71] Race and ethnicity–, sex-, age-, and socioeconomics-based disparities in statin use and LDL-C control are documented. In an analysis of participants with diabetes in the REGARDS study (Reasons for Geographic and Racial Differences in Stroke Study), compared with White men, women and Black participants

Table 3. Treatment Targets and Thresholds for Highest-Risk Patients in Historical and Recent Guidelines

Guideline	Treatment target or threshold for addition of nonstatin therapy, mg/dL	Highest-risk patient population
NCEP guidelines 2001[60]	<100 (Target)	CHD or CHD equivalents Includes diabetes, AAA, PAD, and symptomatic PAD or multiple RFs that confer a 10-y Framingham risk for CHD of 20%
US multisociety guidelines 2018[61]	≥70 (Threshold)	Very-high-risk ASCVD Includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions*
ESC/EAS 2019[62]	<55 (Target)	Very high risk Includes clinical ASCVD or unequivocal ASCVD by imaging,† T2D with target-organ damage, or at least 3 major RFs, or early onset of T1D >20 y, severe CKD (eGFR<30 mL·min^{-1}·1.73^{-2}), a calculated Score ≥10% for 10-y risk of fatal CVD, or FH with ASCVD or another major RF
LAI 2020[63]	≤30 (Target)	Extreme risk Includes ASCVD with ≥1 very high-risk features,‡ recurrent ACS (within 1 y) despite LDL ≤50 mg/dL or polyvascular disease
ACC ECDP 2022[64]	≥55 (Threshold)	Very-high-risk ASCVD Includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions* or FH with ASCVD

AAA indicates abdominal aortic aneurysm; ACC, American College of Cardiology; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; ECDP, Expert Consensus Decision Pathway; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolemia; LAI, Lipid Association of India; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); PAD, peripheral arterial disease; RF, risk factor; SCORE, Systematic Coronary Risk Estimation; T1D, type 1 diabetes; and T2D, type 2 diabetes.

*For the 2018 multisociety guidelines and the 2022 ACC ECDP, major ASCVD events includes recent ACS (within the past 12 months), history of myocardial infarction, history of ischemic stroke, symptomatic PAD (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation); multiple high-risk conditions includes age ≥65 years, heterozygous FH, history of coronary artery bypass surgery or coronary intervention outside of the major ASCVD event, diabetes, hypertension, CKD (eGFR 15–59 mL·min^{-1}·1.73^{-2}), current smoking, persistently elevated LDL cholesterol >100 mg/dL despite maximally tolerated statin therapy and ezetimibe, history of congestive heart failure, need for coronary revascularization while on statin therapy, and recurrent ASCVD event while on statin treatment.

†Unequivocal ASCVD by imaging includes significant plaque on coronary angiography, carotid ultrasound, or computed tomography scan (multivessel coronary artery disease with 2 major epicardial arteries with >50% stenoses).

‡LAI very-high-risk feature includes diabetes (with ≥2 other major ASCVD risk factors or evidence of target-organ damage) or familial homozygous hypercholesterolemia.

were less likely to be treated with statins or to have an LDL-C <100 mg/dL, a finding that was not completely explained by health care use factors.[72] Extending this work, another analysis from REGARDS demonstrated that the greatest disparities in statin use were among individuals with multiple social vulnerabilities.[73]

Side Effect Concerns

Primary reasons for statin discontinuation are real or perceived side effects that occur with varying frequency according to the definition used and the population under study. The clinical implications of statin discontinuation or nonadherence are substantial; both are associated with an increased risk of cardiovascular events.[74,75] The term statin intolerance has been used to denote the clinical syndrome of adverse signs and symptoms associated with statin therapy with various definitions proposed.[76] In a meta-analysis including >4 million patients, the estimated frequency of statin intolerance ranged from 5% in randomized clinical trials to 17% in observational cohort studies.[77] Furthermore, factors such as age, race, female sex, statin dose, alcohol use, exercise, diabetes, obesity, chronic liver disease, chronic renal disease, and hypothyroidism were associated with a higher prevalence of statin intolerance.[77]

Statin-Associated Muscle Symptoms

The most common reported side effects associated with statin use are skeletal muscle symptoms; however, there have also been concerns about other potential neurological side effects. The spectrum of muscle side effects include myalgias, myopathy, and rhabdomyolysis. Typically, myalgias occur within weeks of initiation of therapy or dose escalation, occur symmetrically in large muscle groups, resolve with discontinuation of statin therapy, and are not associated with creatine kinase elevations.[78] A less frequent symptom is myopathy, defined as muscle pain or weakness, which is associated with creatine kinase elevations >10 times the upper limit of normal and is estimated to occur in 1 in 10 000 individuals.[79] Rhabdomyolysis or severe myopathy is even rarer, with an estimated frequency of 1 in 100 000.[79] A notable challenge in elucidating the prevalence of statin intolerance due to myalgias is the presence of a nocebo effect (ie, expectation of statin-related harm). In 2 n-of-1 studies (ie, masked crossover studies conducted in single participants) of patients who had discontinued statin therapy or were considering stopping therapy, similar muscle symptom scores were reported during the periods when patients were taking placebo and atorvastatin 20 mg daily.[80,81] A meta-analysis from the CTT Collaboration

leveraging individual-level trial data found that >90% of muscle symptoms reported by participants in statin trials were not attributable to statins and supports a high prevalence of a nocebo effect with statin therapy.[82] There is no association between either ezetimibe[31,83] or PCSK9 inhibitors[7,32,33] and muscle symptoms, even among those with a very low LDL-C.[1,2,22]

Other Neurological Concerns With Lipid Lowering

In addition to complaints about cognitive effects, neurological concerns such as sleep disturbances, neuropathy, depression, and aggressive behavior have been raised with statins and LDL-C lowering in anecdotal reports and observational studies. These concerns have not been supported by meta-analyses using individual participant-level data from RCTs. A systematic review of 34 studies including both observational and randomized trials concluded that the preponderance of evidence suggests no adverse effect of statins on physical function, sleep, or mood.[84] Related to mood disorders, a large population-based study in Sweden using registry data found no association between statin use and anxiety disorders or suicidality and suggested a protective relationship between statin use and depression.[85]

After initial case reports suggesting a relationship between statin use and peripheral neuropathy, several case-control and cohort studies explored the relationship with inconsistent results. For example, a small case-control study found a strong association between statin use and polyneuropathy[86]; however, a subsequent larger case-control study in the same population failed to confirm this relationship.[87] These discordant findings highlight some of the methodological limitations of these types of studies and the limitations of inferring causality.

BLOOD-BRAIN BARRIER AND LIPIDS

The presence of the blood-brain barrier (BBB) represents an important difference between the brain and other organs. Although endothelial cells in most capillaries are loosely aligned, the capillaries in the brain have tightly packed cells and form units along with pericytes, smooth muscle cells, astrocytes, microglia, and neurons.[88] In addition, the endothelial cells of brain capillaries lack fenestrae as a result of a complex tight junction system and have a continuous basement membrane.[89] This limits transport of lipid molecules into the brain through vesicular mechanisms, separating peripheral and central cholesterol metabolism.

High-density lipoprotein cholesterol, free fatty acids, and certain apolipoproteins (APO) (APO J and APO A-1) can pass across the BBB, but more important, they may activate other transport mechanisms. For example, LRP-1 (LDL receptor–related protein-1) may be activated by APO A-1 and APO E to effect transport of LDL-C across the BBB.[90] The regulation of LDL receptor is tightly linked to serum LDL-C levels to maintain a stable amount of LDL-C within the brain.[91] The scavenger receptor class B type I aids cholesterol influx between LDL-C and high-density lipoprotein cholesterol at the BBB and the possibility of transcytosis of HDL through brain vessel endothelium with involvement of caveolae-dependent endocytosis mechanism.[92] However, a low rate of vesicular transport is a property of the BBB, and its physiological relevance is uncertain.[93] Prominent pericytes in particular contribute to low transcytosis rates.[94] In addition, the *MFSD2A* gene (major facilitator super family domain containing 2a) is a BBB cell–specific gene that maintains tight junctions.[95] Of particular note, this protein product is a key element of lipid transportation for the delivery of omega-3 fatty acid docosahexaenoic acid to the brain. Mice lacking this transporter have increased transcytosis of lipids with an intact BBB.[96] The function of the gene is to inhibit vesicle formation and thus suppress transcytosis, making it an interesting target to improve BBB permeability for central nervous system drug delivery but emphasizing the important feature of suppressed lipid transport to the brain through the BBB.[97]

To summarize, the BBB markedly isolates the brain compared with other tissues through complex tight junctions, pericytes, and inhibited transcytosis of lipids. Thus, the brain does not depend on dietary or hepatic sources of cholesterol or other lipids to support structural and functional demands. Most of extracellular lipid transport inside the central nervous system is enabled by APO E-containing lipoproteins originating from the brain itself, and brain cholesterol metabolism is independent from that in plasma.

BRAIN METABOLISM OF CHOLESTEROL AND POTENTIAL EFFECT OF CHOLESTEROL-LOWERING DRUGS

The brain contains ≈25% of the body's total content of cholesterol. Cholesterol synthesis within the brain begins with 3-hydroxy-3-methylglutaryl coenzyme A reductase, similar to synthesis within the liver.[98] Astrocytes and oligodendrocytes produce the vast majority of cholesterol within the brain.[99] Cholesterol from astrocytes, in addition to assisting with neuronal stability, helps to maintain the BBB.[100] In oligodendrocytes, the majority of cholesterol production is used to produce myelin[101]; however, the cholesterol synthesis rate of the brain is low (ie, <2% of the liver's production).[93,102] Cholesterol synthesized in the brain may persist for months to years compared with days in the peripheral organs.[93] The major pathway of cholesterol metabolism within the brain is hydroxylation by cholesterol 24-hydroxylase.[103] This pathway appears

to be a brain-specific cytochrome P450 pathway that accounts for 99% of metabolism of brain cholesterol.[103] Thus, changes in 24S-hydroxycholesterol levels in serum may reflect the impact of cholesterol-lowering medications on brain metabolism.

Although 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) vary in their lipophilic properties,[104] even relatively hydrophilic statins (eg, pravastatin) can be found within the brains of animals after long-term administration.[105] It is important to note that statin treatment lowers 24S-hydroxycholesterol levels by 21.4%, suggesting an overall lower production of cholesterol within the brain.[106] These studies also demonstrated the pleiotropic effects of statin on various processes. Important to stroke risk, older nonstatin cholesterol-lowering agents (ie, excluding PCSK9 inhibitors and ezetimibe) failed to have the strong benefits of statin and statin-induced modulation of genes such as endothelial nitric oxide synthase and matrix metalloproteinases, which may explain the disparate results compared with nonstatin drugs.[107,108] Whether statins lower levels of brain cholesterol is less clear. Some studies suggest that short-term use of high-dose statins does not influence brain cholesterol metabolism.[109] Ezetimibe blocks the absorption of cholesterol from the small intestine and affects expression of adipogenic genes such as peroxisome proliferator–activated receptor-γ, which is decreased with ezetimibe treatment.[110] However, little evidence is available on its effects within the brain or crossing the BBB.

PCSK9 has a critical role in the degradation of the LDL receptor. Antibodies to PCSK9 prevent or inhibit LDL receptor degradation, leaving an increased expression of LDL receptors and increased hepatic LDL-C uptake, thereby reducing circulating cholesterol levels. PCSK9 deficiency alters brain lipid composition without affecting brain development or function.[111] Monoclonal antibodies to the catalytic domain of PCSK9 lower LDL-C by as much as 80%.[112] Antibodies, however, generally have difficulty passing the BBB. In a study of intravenous immunoglobulin therapy, <1% of systemically administered antibodies crossed the BBB.[113] One study demonstrated increased excretion of 24S-hydroxycholesterol from the brain in response to PCSK9 inhibitor therapy.[114] Whether inclisiran, an siRNA that inhibits the translation of the PCSK9 mRNA, crosses the BBB is not known.[115] PCSK9 inhibitors, through an increase in LDL receptors, could theoretically increase brain absorption of cholesterol from the periphery. Alternatively, a pleotropic effect of PCSK9 inhibitors may be an increase in the metabolism of cholesterol.

To summarize, the content of cholesterol in the brain is largely isolated from peripheral circulation levels by the BBB. Mechanisms exist for the movement of cholesterol into the brain, but the content of cholesterol in the brain is largely independent of levels in the systemic circulation. Although there are numerous gaps in our understanding of the role of cholesterol and its biosynthesis, compartmentalization, and intracellular and extracellular metabolism in the brain, there is very little mechanistic evidence supporting a possible causal effect of cholesterol-lowering medications on development of neurodegeneration.

ASCVD RISK FACTORS AND ALZHEIMER DISEASE

The most important risk factor for developing both ASCVD and Alzheimer disease (AD) is age.[116] The *APO E4* allele, a driver of hyperlipidemia, is also highly associated with AD and altered lipoprotein dynamics within the brain; in contrast, the *APO E2* allele is protective.[117] Numerous longitudinal cohorts consistently demonstrate that midlife hyperlipidemia, hypertension, obesity, metabolic syndrome, smoking, diabetes, and heightened systemic inflammatory tone (increased C-reactive protein, interleukin-6, accumulation of advanced glycation end products within the vasculature), are all associated with increased risk for AD, complicating studies aimed at evaluating associations between lipid-lowering therapies and AD.[118–120] Established ASCVD is also highly correlated with risk for AD.[121,122] SPRINT (Systolic Blood Pressure Intervention Trial) found a reduction in the combined end point of mild cognitive impairment and probable dementia among patients treated to a target systolic blood pressure of <120 mm Hg compared with those treated to a target <140 mm Hg.[123] On an ultrastructural level, ASCVD risk covariates correlate with increased risk later in life for cerebral amyloid plaques and neurofibrillary tangles, composed of β-amyloid protein and protein tau, respectively.[124,125]

Studies probing the relationship between lipid-lowering therapies or LDL-C lowering and the risk for AD typically do not adjust for other risk factors or may adjust for some but not others, making comparisons between studies and reaching conclusions about specific independent risk factors difficult. Hence, confounding may account for some of the dementia observed in unadjusted or partially adjusted analyses. Specifically with respect to lipoproteins, hyperlipidemia (typically defined as elevated LDL-C) increases the risk for AD. Some smaller studies suggested that statins and lower LDL-C may correlate with cognitive impairment. It is difficult to derive a hypothesis supporting both of these biochemical states as being causal in the pathway for AD. Data from randomized studies, however, are encouraging. Analyses from the HPS (Heart Protection Study)[15] and the PROSPER trial (Prospective Study of Pravastatin in the Elderly at Risk)[126] offer reassurance that statin therapy per se is not linked to cognitive impairment or frank AD in older patients over ≈5 years of follow-up. A comprehensive meta-analysis of 34 statin trials including cognitive assessments supports these conclusions.[127]

In the EBBINGHAUS trial (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects), no impact on cognitive function (including 5 executive domains) was shown over ≈19 months of follow-up, even when LDL-C was reduced to <25 mg/dL with the combination of a statin and evolocumab.[128] In FOURIER, the participants experienced no cognitive changes according to comprehensive self-assessment questionnaires over a median of 2.2 years, including among the 2339 patients who achieved an LDL-C <20 mg/dL.[129]

LIPID-LOWERING DRUGS AND THE RISKS OF IMPAIRED COGNITION AND DEMENTIA

Numerous studies reported the effects of lipid-lowering therapies on the risk of dementia and impaired cognition (Table 4)[2,7,127–154] and for the treatment of dementia (Table 5).[155–168] Most of the higher-quality studies explored whether LDL-C–lowering therapies affected cognition.

A systematic review and meta-analysis of 25 RCTs in 46 836 patients found no differences between statin and placebo in the incidence of adverse cognitive events or worsening cognitive test scores.[143] Similar findings showed no evidence of adverse cognitive effects associated with statin use in individuals ≥60 years of age.[130] These observations are supported by several large analyses that also included observational studies (Table 4).

Randomized placebo-controlled studies of ezetimibe and PCSK9 inhibitor have also failed to find an association between these LDL-lowering therapies and dementia or impaired cognition, regardless of the LDL-C achieved (Table 4). Specifically designed prospective randomized placebo-controlled studies to evaluate evolocumab[128,129,136] and alirocumab[139] did not find an association between PCSK9 inhibition or lower achieved LDL-C levels and performance on formal serial cognitive assessments, self-reported change in cognition, or incidence of cognitive events (including dementia). More recent data with up to 8.4 years of treatment with evolocumab also showed no increase in cognitive adverse events,[22] even when stratified by achieved LDL-C.[22] Furthermore, a systematic review of 22 randomized trials in 117 781 patients treated with statin, ezetimibe, or PCSK9 inhibitors concluded that these treatments were not associated with cognitive impairment and that a low LDL-C level did not affect the incidence of cognitive disorders or global cognitive performance.[152]

A mendelian randomization study in participants (24 718 cases and 56 685 controls) from the International Genomics of Alzheimer's Project and Psychiatric Genomics Consortium found that variants near *PCSK9* were associated with an increased risk of AD (whereas variants near *HMGCR*, *NPC1L1*, and *APO B*, were not), supporting future pharmacovigilance among users of PCSK9 inhibitors.[167] An analysis of 13 451 patients randomized to evolocumab versus placebo who underwent *APO E* genotyping, however, did not find a relationship between PCSK9 inhibition or achieved LDL-C level and self-reported cognition or serial formal objective cognitive testing results, even among those with an *APO E4* allele, which is strongly associated with the development of Alzheimer-type dementia.[140]

Fewer smaller and lower-quality studies have evaluated treatment of dementia or other cognition disorders with lipid-lowering therapies (Table 5). A Cochrane systematic review of 4 double-blind randomized trials in 1154 patients with dementia showed no benefit of statins in the primary outcome measures of cognition assessed by Alzheimer's Disease Assessment Scale–cognitive or Mini-Mental State Examination at 26 to 78 weeks.[160] A systematic review and meta-analysis of 6 studies in 289 773 participants explored the role of statins for delirium prevention in the intensive care unit and found that statins had no benefit in decreasing the incidence of delirium in critically ill patients.[166]

REPORTS OF COGNITIVE CHANGES AFTER STATINS ARE STARTED

Prevention of strokes with statins should result in a reduction in vascular cognitive impairment and dementia. The US Food and Drug Administration warnings for statins, however, include that the class has been associated with reports of memory or cognition-related adverse events. For example, the US Food and Drug Administration labeling for atorvastatin includes the following statement:

> *There have been rare post marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1-day to years) and symptom resolution (median of 3-weeks).*[169]

Database studies raise further concerns. For example, a retrospective cohort study using data obtained from The Health Improvement Network database (1987–2013) compared acute memory loss (diagnosed within 30 days after exposure) for 482 543 statin users, all 26 484 users of nonstatin lipid-lowering drugs, and 482 543 matched nonusers of any lipid-lowering drug.[16] There was a strong association between first exposure to a statin and incident acute memory loss (adjusted odds ratio [aOR], 4.40 [95% CI, 3.01–6.42]), but the association was also present for exposure to nonstatin lipid-lowering drugs (aOR, 3.60 [95% CI, 1.34–9.70]), with no

Table 4. Studies of the Safety of Lipid-Lowering Agents in the Past Decade

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
Adhikari et al[130]	**Aim:** To examine the association between statin use and cognitive status **Study type:** Systematic review of RCTs and prospective observational studies **Size:** 3 RCTs and 21 prospective observational studies in 1 404 459 subjects	**Inclusion criteria:** Age ≥60 y RCT or prospective observational study of statin vs control **Exclusion criteria:** Age <60 y Retrospective studies, studies without comparator	**Intervention:** Statin **Comparator:** Placebo or active control **Duration:** RCTs: 3.2–5.6 y Observational studies: 3–15 y	**Primary end point:** Adverse cognitive effects **Results:** In 3 RCTS, no significant association between statin use and adverse cognitive effects (OR 1.03 [0.82–1.30]) In observational studies, 10 showed reduced incidence of dementia, 7 showed no association with incident dementia, 3 showed that decline in cognition was similar, 1 showed slower decline with statin use.	No evidence of adverse cognitive effects, including incidence of dementia, deterioration in global cognition, or specific cognitive domains associated with statin use in individuals ≥60 y of age
Bajaj et al[131]	**Aim:** To compare the rates of cognitive deficits in patients treated with and without PCSK9 **Study type:** Meta-analysis **Size:** 16 RCTs in 39 104 subjects	**Inclusion criteria:** RCTs reporting rates of ischemic stroke and cognitive deficits in patients using PCSK9 inhibitors **Exclusion criteria:** Non-RCTs, phase I trials, trials that contributed to larger phase III trials, trials reporting neither ischemic stroke nor cognitive deficits	**Intervention:** Evolocumab (6 RCTs in 33 450 patients) Alirocumab (10 RCTs in 5654 patients) **Comparator:** No PCSK9 inhibitor **Duration:** 12–114 wk	**Primary end point:** Ischemic stroke **Secondary end point:** Cognitive deficits **Results:** Significantly lower risk of ischemic stroke among those treated with vs without PCSK9 inhibitors (RR, 0.77 [95% CI, 0.64–0.93]) No difference in the risk of cognitive deficits (RR, 1.11 [95% CI, 0.93–1.32])	PCSK9 inhibitors significantly lowered the risk of ischemic stroke, without any increased risk of cognitive deficits. PCSK9 inhibitors are neuroprotective due to the decrease in ischemia-mediated neurovascular events and should be considered cognitively innocuous medications.
Bath et al[132] (PODCAST)*	**Aim:** To assess the effect of intensive blood pressure or lipid lowering on cognitive outcomes in patients with recent stroke **Study type:** RCT **Size:** 83 subjects	**Inclusion criteria:** Stroke 3–7 mo prior, age ≥70 y with MMSE score >16 or 60–70 y with MMSE score 17–20, modified Rankin Scale score 0–2, systolic BP 125–170 mm Hg, LDL-C 3–8 mmol/L **Exclusion criteria:** Dementia, need for intensive BP or lipid control, intolerance of high-intensity statins, familial stroke associated with dementia	**Intervention:** Intensive: systolic BP to <125 mm Hg or LDL-C <2.0 mmol/L (n=41) **Comparator:** Guideline: systolic BP <140 mm Hg or LDL-C <3.0 mmol/L (n=42) **Duration:** Median: 24 mo	**Primary end point:** Cognitive function as assessed by Addenbrooke's Cognitive Examination–Revised **Results:** Mean difference in primary end point between groups, 4.4 (95% CI −2.1 to 10.9), *P*=0.18	In patients with recent stroke and normal cognition, intensive BP and lipid lowering were feasible and safe but did not alter cognition over 2 y.
Chu et al[133]	**Aim:** To investigate whether statins were associated with the risk of all-cause dementia, AD, VaD, or MCI **Study type:** Systematic review of cohort studies **Size:** 25 studies: 16 studies in 2 745 149 patients with incident dementia, 14 studies in 52 218 patients with incident AD, and 3 studies in 5987 patients with VaD	**Inclusion criteria:** (1) Prospective cohort studies of statins vs nonstatins; (2) cognitively healthy at baseline without prior cognitive dysfunction; (3) outcome includes incident all-cause dementia, AD, VaD, or MCI; (4) follow-up ≥1 y; (5) peer reviewed and written in English **Exclusion criteria:** (1) Cross-sectional studies; (2) retrospective case-control studies; (3) RCTs; (4) studies that did not assess incident dementia or MCI; (5) conference abstracts and studies published in languages other than English	**Intervention:** Statins **Comparator:** Placebo or active control **Duration:** 2–20 y	**Primary end points:** All-cause dementia, AD, MCI, VaD **Results:** Statins were significantly associated with a reduced risk of all-cause dementia (adjusted RR, 0.85 [95% CI, 0.79–0.92]; *P*<0.001), AD (adjusted RR, 0.72 [95% CI, 0.58–0.90]; *P*=0.004), and MCI (adjusted RR, 0.74 [95% CI, 0.56–0.98]; *P*=0.033) but no meaningful effects on incident VaD (adjusted RR, 1.012 [95% CI, 0.62–1.65]; *P*=0.96)	Statins may reduce the risk of all-type dementia, AD, and MCI but not of incident VaD

(*Continued*)

Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
De Giorgi et al,[134] 2021*	**Aim:** To assess the 7-d effects of atorvastatin on a battery of emotional processing tasks **Study type:** RCT **Size:** 50 healthy volunteers	**Inclusion criteria:** Male or female, age 18-50 y, BMI 18–30 kg/m^2, not currently taking any regular medications (except contraceptive pill) **Exclusion criteria:** Psychiatric illness, alcohol or substance misuse, significant neurological issues	**Intervention:** Atorvastatin 20 mg (n=22) **Comparator:** Placebo (n=28) **Duration:** 7 d	**Primary end points:** Psychological questionnaires and a battery of behavioral tasks assessing emotional processing, reward learning, and verbal memory **Results:** Atorvastatin increased the recognition (*P*=0.006), discriminability (*P*=0.03), and misclassifications (*P*=0.04) of fearful facial expression	Atorvastatin increased recognition, sensitivity, and misclassifications of fearful facial expressions but not for other emotions, independently from subjective states of mood and anxiety and C-reactive protein levels
Gaba et al,[22] 2023 (FOURIER-OLE)	**Aim:** To assess the efficacy and safety of 5-y open-label treatment with evolocumab stratified by achieved LDL-C (an average of the first 2 values) **Study type:** Open-label extension of an RCT **Size:** 6559	**Inclusion criteria:** Completed FOURIER trial on study drug, enrolled in United States or selected Western European countries **Exclusion criteria:** Participating in another investigational study, not expected to complete the 5-y follow-up, or no LDL-C drawn in first 48 wk	**Intervention:** Evolocumab 140 mg every 2 wk or 420 mg every 4 wk (n=6659) Patients were stratified by achieved LDL-C (in mg/dL): <20 (n=1604), 20–<40 (n=2627), 40–<55 (n=1031), 55–<70 (n=486), and ≥70 (n=811) **Duration:** Median 5.0 y	**Primary end point:** Annualized incidence rates of investigator-reported cognitive adverse events, stratified by achieved LDL-C, adjusted for baseline characteristics **Results:** No association between achieved LDL-C and the annualized incidence of cognitive adverse events (adjusted P_{trend}=0.35; rates ranged from 0.30–0.53 per y) in patients treated with evolocumab during the 5-y open-label extension	Adjusted annualized incidence rates of cognitive adverse events were similar across achieved LDL-C values in patients treated with evolocumab during the 5-y open-label extension
Gaudet et al[136] (HAUSER-RCT)	**Aim:** To determine the effects of evolocumab on cognitive function in pediatric heterozygous FH **Study type:** RCT **Size:** 157 children	**Inclusion criteria:** Age 10–17 y with heterozygous FH on stable lipid-lowering therapy for ≥4 wk, on a low-fat diet, LDL-C ≥130 mg/dL, and triglycerides ≤400 mg/dL **Exclusion criteria:** Type 1 diabetes or poorly controlled type 2 diabetes, uncontrolled thyroid disease; CETP inhibitor within 12 mo, mipomersen or lomitapide within 5 mo; previously received evolocumab or other investigational PCSK9 inhibitor; lipid apheresis within 12 wk; homozygous FH	**Intervention:** Evolocumab 420 mg every 4 wk (n=104) **Comparator:** Placebo every 4 wk (n=53) **Duration:** 24 wk	**Primary end point:** Percent change in LDL from baseline to week 24 **Secondary end points:** Cogstate computerized test battery assessing (1) executive function by the Groton Maze Learning Test; (2) visual learning by the One-Card Learning Test; (3) visual attention by the Identification test based on the choice reaction time paradigm; (4) psychomotor function by the Detection test based on the simple reaction time paradigm **Results:** Differences between the evolocumab and placebo groups in mean test score changes for the Groton Maze Learning, One-Card Learning, Identification, and Detection tests were 0.1 (95% CI, −0.2 to 0.4), −0.1 (−0.5 to 0.4), 0.3 (0.0–0.7), and 0.3 (−0.1 to 0.8), respectively.	In pediatric patients with FH, 24-wk treatment with evolocumab did not negatively influence cognition
Gencer et al[129] (FOURIER)	**Aim:** To compare evolocumab and placebo on patient-reported cognition using a self-survey **Study type:** RCT **Size:** 22 655 subjects	**Inclusion criteria:** Patients 40–85 y of age with stable ASCVD, LDL-C ≥100, or non–HDL-C ≥130 mg/dL on moderate- or high-intensity statin **Exclusion criteria:** Did not complete ECog survey at end of study	**Intervention:** Evolocumab 140 mg every 2 wk or 420 mg every 4 wk (n=11 363) **Comparator:** Matching placebo (n=11 292) **Duration:** Median 2.2 y	**Primary end point:** Patient-reported cognition at the final visit using a 23-item questionnaire including the executive and memory domain subscales of the ECog scale **Results:** Proportion of ECog scores ≥2 for placebo vs evolocumab were as follows: total score, 3.6% vs 3.7% (*P*=0.62); for subdomains: memory, 5.8% vs 6.0%; total executive, 3.6% vs 3.7% Proportion of patients reporting a decline in total cognitive score was similar among the 2338 patients who achieved an LDL-C <20 mg/dL compared with the 3613 patients with LDL-C ≥100 mg/dL (3.8% vs 4.5%; *P*=0.57).	The addition of evolocumab to maximally tolerated statin therapy had no impact on patient-reported cognition after an average of 2.2 y of treatment, even among patients who achieved LDL-C <20 mg/dL

(*Continued*)

Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
Giugliano et al[128] (EBBING-HAUS)	**Aim:** To compare change in cognitive function with evolocumab vs placebo **Study type:** RCT **Size:** 1204 subjects	**Inclusion criteria:** Age 40–85 y Stable ASCVD, LDL ≥70 mg/dL, or non–HDL-C ≥100 mg/dL, on moderate- or high-intensity statin **Exclusion criteria:** Dementia, cognitive impairment, significant mental or neurological disorder	**Intervention:** Evolocumab 140 mg every 2 wk or 420 mg every 4 wk (n=586) **Comparator:** Matching placebo (n=618) **Duration:** Median 19 mo	**Primary end point:** Spatial working memory strategy index of executive function using CANTAB **Results:** −0.21±2.62 in the evolocumab group vs −0.29±2.81 in the placebo group (*P*<0.001 for noninferiority) **Other Results:** No significant differences in working memory, episodic memory, or psychomotor speed No associations between LDL-C levels and cognitive changes	No significant between-group differences in cognitive function between evolocumab and placebo observed over a median of 19 mo
Giugliano et al[2] (IMPROVE-IT)	**Aim:** To assess the safety and clinical efficacy of achieving a very low (<30 mg/dL) level of LDL-C at 1 mo **Study type:** RCT **Size:** 15 821 subjects	**Inclusion criteria:** Admitted for ACS ≤10 d prior LDL-C 50–100 mg/dL LDL-C measured at 1 mo **Exclusion criteria:** Event before month 1 Severe renal or liver disease Lipid therapy more potent than simvastatin 40 mg	**Intervention:** Ezetimibe 10 mg+simvastatin 40 mg daily (n=7549) **Comparator:** Placebo+simvastatin 40 mg daily (n=8272) **Duration:** Median 6 y	**Primary end point:** Cognitive adverse events **Results:** Cognitive adverse events by achieved LDL-C (in mg/dL) at month 1 for ezetimibe vs placebo: LDL<30: 2.2% vs 1.4%; *P*=0.76 LDL 30–49: 2.6% vs 2.4%; *P*=0.76 LDL 50–69: 2.4% vs 3.2%; *P*=0.073 LDL ≥70: 2.3% vs 2.%; *P*>0.99	Incidence of cognitive adverse events was similar between ezetimibe and placebo overall and when stratified by achieved LDL-C at 1 mo
Gupta et al[137] (ASCOT-LLA)	**Aim:** To assess 4 AEs of interest listed in the atorvastatin label: muscle-related side effects, erectile dysfunction, sleep disturbance, and cognitive impairment **Study type:** RCT followed by nonrandomized, nonblinded extension period **Size** 10 180 subjects	**Inclusion criteria:** Age 40–79 y with hypertension, ≥3 other cardiovascular risk factors, fasting TC ≤6.5 mmol/L, not on statin or fibrate, had no prior MI, and were not being treated for angina **Exclusion criteria:** No verifiable date for end of blinded period Death before start of open-label period	**Intervention:** Atorvastatin 10 mg daily (n=5101) **Comparator:** Matching placebo during RCT followed by 10 mg daily during extension period (n=5079) **Duration:** Median 3.3 y during RCT followed by median 2.2 y in extension phase	**Primary end point:** Multiple adverse events, including cognitive impairment **Results:** Cognitive impairment occurred in 31 (0.20% per annum) atorvastatin vs 32 (0.22% per annum) placebo followed by atorvastatin patients (HR, 0.94 [95% CI, 0.57–1.54]; *P*=0.81).	Too few cases of cognitive impairment were reported for a statistically reliable analysis
Harvey et al[138]	**Aim:** To assess the incidence of cognitive TEAEs with alirocumab vs control **Study type:** Meta-analysis of 6 phase 2 and 3 RCTs **Size:** 5234 subjects	**Inclusion criteria:** Double-blind RCTs of alirocumab vs either placebo or ezetimibe in patients with hyperlipidemia **Exclusion criteria:** Nonrandomized, open-label, and phase 1 trials of alirocumab	**Intervention:** Alirocumab 75 or 150 mg every 2 wk (n=3340) **Comparator:** Placebo (n=1276) Ezetimibe (n=618) **Duration:** 8–104 wk	**Primary end point:** Cognitive TEAEs **Results:** Alirocumab 0.9% vs placebo 0.7% (HR, 1.24 [95% CI, 0.57–2.68]) Alirocumab 1.2% vs ezetimibe 1.3% (HR 0.81 [95% CI, 0.32–2.08])	Cognitive TEAE incidences were low (≤1.2%), with no significant differences between alirocumab and controls up to 104 wk.
Janik et al[139]	**Aim:** To prospectively evaluate the risk of cognitive AEs over 96 wk of alirocumab treatment using the CANTAB scale **Study type:** Phase 4 RCT **Size:** 2176 subjects	**Inclusion criteria:** HeFH or non-FH patients at high or very high risk despite maximally tolerated statin therapy **Exclusion criteria:** AD or other dementia, schizophrenia, bipolar disorder, severe depression, cognitive impairment, or sleep disorder requiring daily pharmacological treatment; cardiovascular event ≤3 mo	**Intervention:** Alirocumab 75/150 mg every 2 wk (n=1088) **Comparator:** Matching placebo every 2 wk (n=1088) **Duration:** Median 86 wk	**Primary end point:** Least-mean-square change in CANTAB cognitive domain SWMS *z* score from baseline to week 96 **Results:** SWMS *z* score with alirocumab vs placebo least-mean-squares change −0.020 (95% CI, −0.094 to 0.055; *P*=0.61) Exploratory outcome measures, which further assessed cognitive function in the CANTAB domains, did not differ significantly over 96 wk and achieved nominal noninferiority between treatment groups.	Alirocumab showed no effect on cognitive function over 96 wk of treatment, substantially reduced LDL-C, and was generally well tolerated in patients with HeFH or non-FH at high or very high cardiovascular risk.

(*Continued*)

Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
Korthauer et al[140] (FOURIER)	**Aim:** To investigate *APO E* genotype as a moderator of the relationship between evolocumab and patient-reported cognitive impairment (assessed in the larger FOURIER cohort) and objective cognitive performance (assessed in the EBBINGHAUS subgroup) **Study type:** RCT **Size:** 13 451 subjects	**Inclusion criteria:** *APO E4* genotyping performed in the FOURIER trial (see information for FOURIER entry criteria) **Exclusion criteria:** Current or prior cognitive impairment or dementia	**Intervention:** Evolocumab 140 mg every 2 wk or 420 mg every 4 wk (n=6776) **Comparator:** Matching placebo (n=6675) **Duration:** Median 2.2 y	**Primary end point:** Patient-reported cognition at the final visit using a 23-item questionnaire including the executive and memory domain subscales of the ECog scale Spatial working memory strategy index of executive function using CANTAB **Results:** There was a dose-dependent relationship between *APO E ε4* genotype and patient-reported memory decline on the ECog in the placebo arm (*P*=0.003 for trend across genotypes; *ε4/ε4* carriers vs non-carriers (OR, 1.46 [95% CI, 1.03–2.08]) but not in the evolocumab arm (*P*=0.50; OR, 1.18 [95% CI, 0.83–1.66]). *P*=0.30 for genotype-by-treatment interaction. Genotype did not significantly modify the relationship between treatment arm and CANTAB performance after adjustment for demographic and medical covariates, (*P*>0.05).	*APO E* genotype did not significantly moderate the relationship between combination evolocumab and statin therapy and patient-reported or objective cognition.
Macedo et al[141]	**Aim:** To systematically assess unintended effects of statins from observational studies in general populations with comparison of the findings when possible with those derived from randomized trials **Study type:** Systematic review **Size:** 13 studies (8 cohort, 5 case-control) in 2 762 899 subjects	**Inclusion criteria:** Prospective studies with >1000 participants, case-control (of any size), and routine health service linkage studies of ≥1 y duration **Exclusion criteria:** Subgroup analyses, follow-up of patient case series Hospital-based cohort studies	**Intervention:** Statin **Comparator:** No statin	**Primary end point:** Dementia Cognitive impairment without dementia AD **Results:** OR (95%) CI for statin vs no stain were: Dementia: 0.70 (95% CI, 0.59–0.83) Incident AD: 0.61 (95% CI, 0.50–0.75) Dementia non-AD: 0.73 (95% CI, 0.61–0.88) Standardized mean difference in improved cognitive test scores, 0.18 (95% CI, 0.09–0.327)	Lower odds of dementia and cognitive impairment were associated with statin use.
McGuinness et al[142]	**Aim:** To evaluate the efficacy and safety of statins for the prevention of dementia in people at risk of dementia because of their age and to determine whether the efficacy and safety of statins for this purpose depend on cholesterol level, *APO E* genotype, or cognitive level **Study type:** Systematic review of RCTs of statins **Size:** 2 RCTs in 26 340 subjects	**Inclusion criteria:** RCTs of statins vs placebo that assess cognitive function History of or risk factors for vascular disease **Exclusion criteria:** Not RCT Elective use of statin Follow-up <1 y Nonstatin treatment Abnormal cognitive function at baseline	**Intervention:** Statin (simvastatin or pravastatin; n=13 160) **Comparator:** Placebo (n=13 180) **Duration:** Median 3.2 and 5.0 y	**Primary end point:** Occurrence of AD or dementia Cognitive outcomes assessed with the TICS-m Cognitive function with the MMSE, Picture-Word Learning Test, and Stroop test **Results:** Dementia occurred in 0.3% of both statin and placebo patients (OR, 1.00 [98% CI, 0.61–1.65]). Mean differences in the following: TICS-m score, 0.02 (95% CI, −0.12 to 0.16) Change in MMSE score, 0.06 (95% CI, −0.04 to 0.16) Number of correct letter digit codes, 0.01 (95% CI, −0.25 to 0.23) Number of words remembered in the Picture-Word Learning Test, 0.02 (95% CI, −0.12 to 0.16) Time needed to complete the Stroop test 0.8 s (95% CI −0.4 to 2.0)	Statins given in late life to people at risk of vascular disease have no effect in preventing cognitive decline or dementia.

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Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
O'Donoghue et al[7] (FOURIER-OLE)	**Aim:** To evaluate the long-term safety and efficacy of continued evolocumab treatment after completion of the parent FOURIER trial **Study type:** Open-label extension of an RCT **Size:** 6635	**Inclusion criteria:** Completed FOURIER trial on study drug, enrolled in United States or selected Western European countries **Exclusion criteria:** Participating in another investigational study, not expected to complete 5-y follow-up	**Intervention:** Evolocumab 140 mg every 2 wk or 420 mg every 4 wk (n=3355) **Comparator:** Placebo for 2.2 y (median) followed by open-label evolocumab 140 mg every 2 wk or 420 mg every 4 wk (n=3280) **Duration:** Median 7.1 y	**Primary end point:** Annualized incidence of investigator-reported cognitive AEs reported by investigators **Results:** No differences in the annualized incidence of cognitive events between placebo during the RCT (0.56%), evolocumab during the RCT (0.63%), and evolocumab during the open-label extension (range, 0.33%–0.98%/y over up to 8 y)	Annualized rates of cognitive AEs were similar between evolocumab and placebo during 2.2 y of double-blind RCT comparison and compared with rates during the 5-y open-label evolocumab extension period.
Olmastroni et al[127]	**Aim:** To examine the effect of statin use on the risk of AD and dementia **Study type:** Systematic review/ meta-analysis **Size:** 46 observational studies (38 cohort, 8 case-control) in 5 760 963 subjects	**Inclusion criteria:** Cohort or case-control studies; statin users compared with nonusers; and AD or dementia risk as outcome **Exclusion criteria:** Non-English publications, abstracts only, letters, comments, editorials, case reports	**Intervention:** Statin **Comparator:** No statin	**Primary end point:** Risk of dementia Risk of AD **Results:** Statins were associated with a decreased risk of dementia (OR, 0.80 [CI, 0.75–0.86]) and AD [21 studies; OR, 0.68 [CI, 0.56–0.81]).	These results confirm the absence of a cognitive risk associated with statin treatment and suggest a potential favorable role of statins.
Ott et al[143]	**Aim:** To synthesize RCT evidence on the association between statin therapy and cognitive outcomes **Study type:** Systematic review/ meta-analysis **Size:** 25 RCTs in 46 836 subjects	**Inclusion criteria:** RCTs of statins published reporting cognitive outcomes **Exclusion criteria:** Non-English reports Abstracts only Insufficient number of events to calculate effect size	**Intervention:** Statin **Comparator:** Placebo **Duration:** 2–260 wk	**Primary end point:** Adverse cognitive events Cognitive test scores **Results:** Development of dementia, confusion and other cognitive adverse events was reported in 3 of 18 RCTs; rates were low (<1%) and not different between statin and placebo. Cognitive test outcomes (all effects) SMD for statin vs placebo: Baseline normal cognition, 0.01 (95 % CI, −0.01 to 0.03; *P*=0.42) Subjects with AD, −0.05 (95% CI, −0.19 to 0.10; *P*=0.38)	Statin therapy was not associated with cognitive impairment in RCTs.
Poly et al[144]	**Aim:** To quantify the magnitude of the association between statin therapy and the risk of dementia **Study type:** Meta-analysis of observational studies **Size:** 30 observational studies in 9 162 509 subjects	**Inclusion criteria:** Observational and case-control studies in ≥500 patients with dementia, treated with statin for ≥30 d vs no statin **Exclusion criteria:** Other study designs, reviews, commentaries, follow-up <1 y	**Intervention:** Statin use ≥30 d **Comparator:** No statin use **Duration:** 1–18 y	**Primary end point:** All-cause dementia **Secondary end point:** Development of AD and VaD in the patients with statin use **Results:** Patients with statin had a lower risk of dementia (RR, 0.83 [95% CI, 0.79–0.87]; *P*<0.0001) RR, 0.69 (95% CI, 0.60–0.80; *P*< 0.0001) of AD in patients with statin use RR, 0.93 (95% CI, 0.74–1.16; *P*=0.54) of VaD with statin use	Use of statin is significantly associated with a decreased risk of dementia.

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Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
Raccah et al[145]	**Aim:** To assess cognitive safety of PCSK9 inhibitors in RCTs **Study type:** Systematic review/ meta-analysis **Size:** 21 studies in 59 733 subjects	**Inclusion criteria:** RCTs of PCSK9 inhibitors with assessment of cognitive AEs **Exclusion criteria:** Other study designs, follow-up <6 mo	**Intervention:** PCSK9 inhibitors (n=31 611) **Comparator:** Placebo (n=28 122) **Duration:** 6–34 mo	**Primary end point:** Incidence of cognitive adverse effects **Results:** RR, 1.01 (95% CI, 0.86–1.19) of cognitive AEs with PCSK9 inhibitors vs placebo Meta-regression analysis for evolocumab revealed that prolonged study duration was associated with decreased risk for cognitive adverse events (βweek=−0.0037, *P*=0.03).	Pooled results of the meta-analysis and meta-regression show that exposure to PCSK9 inhibitors is not associated with an increased risk of cognitive adverse effects.
Richardson et al[146]	**Aim:** To examine the effect of statins on cognition **Study type:** Systematic review and meta-analysis of 27 studies (3 RCTs, 16 cohort, 4 case-control, and 4 cross-sectional) **Size:** 27 studies included in the meta-analysis	**Inclusion criteria:** Studies evaluating cognitive function in adults on statin **Exclusion criteria:** Reviews, subanalyses, no cognitive end point, not applicable to general population, trials that were not randomized or placebo controlled, case reports/ series	**Intervention:** Statin **Comparator:** No statin	**Primary end point:** Incidence of dementia, AD, or MCI **Results:** Risk of dementia with statins: 1 RCT: RR, 1.00 (95% CI, 0.61–1.64); 10 cohort studies: RR, 0.87 (95% CI, 0.82–0.92); 2 case-control studies: OR, 0.25 (95% CI, 0.14–0.26); 1 cross-sectional study: OR, 0.54 (95% CI, 0.22–1.33) Risk of AD: 10 cohort studies: RR, 0.79 (95% CI, 0.63–0.99); 3 case-control studies: RR, 0.56 (95% CI, 0.41–0.78); 1 cross-sectional study: OR, 0.45 (95% CI, 0.35–0. 58) Risk of MCI: 1 RCT: RR, 0.98 (95% CI, 0.93–1.03); 4 cohort studies: RR, 0.66 (95% CI, 0.51–0.86), 1 case-control study: OR, 0.37 (95% CI, 0.16–0.84); 2 cross-sectional studies: OR, 0.97 (95% CI, 0.87–1.09)	Published data do not suggest an adverse effect of statins on cognition; however, the strength of available evidence is limited, particularly with regard to high-dose statins.
Song et al[147]	**Aim:** To investigate whether statins might be associated with a reduction on risk of dementia **Study type:** Meta-analysis **Size:** 8 studies in 59 871 subjects	**Inclusion criteria:** Prospective cohort studies with statins, reported RR with 95% CI of dementia with statin reported **Exclusion criteria:** Non-English publications, other study designs, subgroup analyses	**Intervention:** Statin **Comparator:** No statin **Duration:** 1-9 y	**Primary end point:** Dementia (VaD, AD, or unspecified) **Results:** RR, 0.62 (95% CI, 0.43–0.81) of dementia with statin	Statin use was associated with a reduced risk of dementia.
Swiger et al[148]	**Aim:** To evaluate the effect of statins on short-term cognitive function and the long-term incidence of dementia **Study type:** Systematic review/ meta-analysis **Size:** 16 studies in 24 753 subjects	**Inclusion criteria:** Adults with no history of cognitive dysfunction treated with statins from high-quality RCTs and prospective cohort studies **Exclusion criteria:** Studies that were retrospective or case-control, had high risk of bias, were nonrandomized and short term, included patients with cognitive abnormality at baseline, had incomplete reporting of methods or outcomes	**Intervention:** Statins **Comparator:** Placebo or control **Duration:** 4 wk–24.9 y	**Primary end point:** Short term: Digit Symbol Substitution Test (DSST) Long term: Incidence of dementia **Results:** Short term: No significant differences in the mean change in DSST from baseline to follow-up between the statin and placebo groups (1.65 [95% CI, −0.03 to 3.32]) Long-term: Pooled results revealed a 29% reduction in incident dementia in statin-treated patients (HR, 0.71 [95% CI, 0.61–0.82])	In patients without baseline cognitive dysfunction, short-term data are most compatible with no adverse effect of statins on cognition, and long-term data may support a beneficial role for statins in the prevention of dementia.

(*Continued*)

Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
Taylor et al[149] (STOMP)	**Aim:** To assess the effect of statins on cognition with 5 standard neuropsychological assessments and brain neural activation with fMRI on 2 tasks **Study type:** Substudy of an RCT **Size:** 150 subjects	**Inclusion criteria:** Completed the STOMP trial **Exclusion criteria:** >2 alcoholic drinks/d; illicit drug use; history of auditory or visual impairment; past traumatic brain injury; any neurological illness that could affect the brain; any form of mental illness or developmental or learning disorder; MMSE score <23	**Intervention:** Atorvastatin 80 mg daily (n=66) **Comparator:** Placebo (n=84) **Duration:** 6 mo	**Primary end point:** Cognitive testing with the HVLT-R, BVMT-R, TMT, CLOCK, WAIS-III, Stroop, LGPT, Symbol Digit, CFQ fMRI to assess neural activation during 2 in-scanner tasks (Figural Memory and Verbal Working Memory) Assessments performed at baseline and 2 mo after treatment cessation **Results:** No significant changes in neuropsychological tests with atorvastatin vs placebo (all *P*>0.56) Small but significant group-time interactions for each fMRI task were present: Participants on placebo had greater activation in the right putamen/dorsal striatum during the maintenance phase of the Sternberg task while on placebo, but the effect was reversed after drug washout (*P*<0.001) Participants on atorvastatin had greater activation in the bilateral precuneus during the encoding phase of the Figural Memory task while on drug, but the effect was reversed after drug washout (*P*<0.001)	Six months of high-dose atorvastatin therapy is not associated with measurable changes in neuropsychological test scores but did evoke transient differences in brain activation patterns.
Wong et al[150]	**Aim:** To estimate any benefit of statins in preventing dementia **Study type:** Systematic review/ meta-analysis **Size:** 20 studies (16 cohort, 2 nested case-control, 1 case-control, 1 RCT) in 4 025 454 subjects	**Inclusion criteria:** Studies of risk of dementia or AF with statin vs placebo or no statin, reporting dementia or AD **Exclusion criteria:** Non-English publications; cross-sectional studies, meta-analyses, case reports, or reviews; reporting only cognitive performance; nonhuman trials	**Intervention:** Statin **Comparator:** Placebo or no statin **Duration:** 3–25 y	**Primary end points:** Dementia AD **Results:** RR with statin vs non-statin: Dementia, 0.82 (95% CI, 0.69–0.97) AD, 0.70 (95% CI, 0.60–0.83)	Statins may provide a slight benefit in the prevention of AD and all-type dementia.
Yang et al[151]	**Aim:** To synthesize the evidence for the association of statin use with dementia and cognitive impairment among patients with stroke **Study type:** Systematic review/ meta-analysis **Size:** 4 studies in 2715 subjects with stroke	**Inclusion criteria:** Observational cohort studies or RCTs in patients with stroke **Exclusion criteria:** Studies only in patients with transient ischemic attack or subarachnoid hemorrhage Follow-up after stroke <3 mo	**Intervention:** Statin use **Comparator:** No statin use **Duration:** 3 mo–10 y	**Primary end point:** Dementia Any cognitive impairment **Results:** Pooled OR of dementia, 0.89 (95% CI, 0.65–1.21; n=1 study in 738 subjects) Pooled OR for cognitive impairment, 0.56 (95% CI, 0.46–0.69; n=3 studies in 1977 subjects)	Poststroke statin use was associated with decreased risk of cognitive impairment.
Ying et al[152]	**Aim:** To evaluate the potential association between the lowering of LDL-C with contemporary lipid-lowering medicines and cognitive function **Study type:** Systematic review/ meta-analysis **Size:** 22 RCTs in 117 781 subjects	**Inclusion criteria:** Phase 2 or 3 RCTs with >30 patients who received PCSK9 inhibitors, statins, and ezetimibe and reported cognitive outcomes **Exclusion criteria:** Lipid-lowering therapies that do not upregulate the LDL receptor, baseline cognitive impairment, studies with bococizumab (because of the generation of neutralizing antibodies	**Intervention:** Modern lipid-lowering therapies (PCSK9 inhibitors, statins, or ezetimibe): alirocumab, n=24 678; evolocumab, n=36 999; ezetimibe, n=20 595; statins, n=46 337 **Comparator:** No modern lipid-lowering therapies **Duration:** 6–260 wk	**Primary end point:** Cognitive adverse events based on treatment-emergent AE reports **Results:** RR of cognitive disorder with contemporary lipid-lowering medicines compared with control was 1.02 (95% CI, 0.90–1.16; *P*=0.696).	Contemporary lipid-lowering medicines were not associated with cognitive impairment in RCTs. A low LDL-C level did not influence the incidence of cognitive disorder or global cognitive performance.

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Table 4. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, or RR; and 95% CI)	Summary/ conclusion and comment(s)
Zhang et al[153]	**Aim:** To identify the potential relationship between statin use and dementia **Study type:** Systematic review/ meta-analysis **Size:** 31 studies in 3 332 706 subjects	**Inclusion criteria:** Statin studies reporting on the outcome of dementia **Exclusion criteria:** Nonhuman studies, reviews, lack of detailed information, abstract only	**Intervention:** Treatment with statin **Comparator:** No statin use	**Primary end point:** Dementia, including AD and non-AD causes **Results:** RR of statin vs no statin: Dementia, 0.85 (95% CI, 0.80–0.89; *P*<0.01) AD, 0.81 (95% CI, 0.73–0.89; *P*<0.01) Non-AD dementia, 0.81 (95% CI, 0.73–0.89; *P*<0.01)	Statin use was associated with dementia risk decrement. The potency and cumulative duration of statin used played critical roles.
Zhang et al[154]	**Aim:** To investigate the effect of low-dose statins on white matter hyperintensities and cognitive function in elderly patients undergoing antihypertensive treatment **Study type:** 2×2 RCT **Size:** 732 subjects	**Inclusion criteria:** Patients ≥60 y of age with SBP ≥140 mm Hg or DBP ≥90 mm Hg or on antihypertensive therapy **Exclusion criteria:** Secondary hypertension, hypersensitivity or contraindication to the study medications, stroke or transient ischemic attack, MMSE score ≤23, AD, Parkinson disease, claustrophobia, bipolar disorder, schizophrenia, seizures, drug or alcohol abuse, malignancy, renal failure and dialysis treatment, liver disease, inability to walk to the clinic, unable to have MRI	**Intervention:** Rosuvastatin 10 mg daily (n=366) **Comparator:** Placebo (n=366) Also second randomization to telmisartan 40 or 80 mg (n=366) vs placebo (n=366) **Duration:** 60 mo	**Primary end point:** Cognitive function assessed by Chinese versions of the MMSE and the Mattis Dementia Rating Scale Total white matter hyperintensities (periventricular and subcortical) on brain MRI as assessed by Fazekas scale, dichotomized at a score of 2 **Results:** Incidence of Fazekas scale scores ≥2 with rosuvastatin vs placebo, 12.1% vs 22.8% (*P*<0.001; HR, 0.50 [95% CI, 0.34–0.74]) Incidence of cognitive impairment with rosuvastatin vs placebo, 18.8% vs 39% (*P*=0.002; HR, 0.54 [95% CI, 0.36–0.80]). There was a significant interaction between the telmisartan and rosuvastatin arms (*P*=0.002) after adjustment for age, sex, education, smoking, and alcohol consumption.	Rosuvastatin 10 mg daily reduced brain white matter hyperintensity progression and cognitive decline in elderly patients with hypertension. There was a synergistic interaction between telmisartan and rosuvastatin.

ACS indicates acute coronary syndrome; AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–cognitive; AE, adverse event; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; BVMT-R, Brief Visuospatial Memory Test-Revised; CANTAB, Cambridge Neuropsychological Test Automated Battery; CETP, cholesterylester transfer protein; CFQ, Cognitive Failures Questionnaire; CLOCK, 18-Point Clock Test; EBBINGHAUS, Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; ECog, Everyday Cognition; FH, familial hypercholesterolemia; fMRI, functional magnetic resonance imaging; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; FOURIER-OLE, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk–Open Label Extension; HAUSER-RCT, Trial Assessing Efficacy, Safety and Tolerability of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibition in Paediatric Subjects With Genetic Low-Density Lipoprotein (LDL) Disorders; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HR, hazard ratio; HVLT–R, Hopkins Verbal Learning Test-Revised; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; LGPT, Layfayette Grooved Pegboard Test; MCI, mild cognitive impairment; MI, myocardial infarction; MMSE, Mini-Mental State Examination; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; PODCAST, Prevention of Decline in Cognition After Stroke Trial; RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; STOMP, Effect of Statin Medications on Muscle Performance; SWMS, spatial working memory strategy; Symbol Digit, Symbol Digit Modalities Test; TC, total cholesterol; TEAEs, treatment-emergent adverse events; TICS-m, Telephone Interview for Cognitive Status–Modified; TMT, Trail Making Test Parts A and B; VaD, vascular dementia; and WAIS-III, Wechsler Adult Intelligence Scale-III.

*Study judged to include lower-quality data.

difference between statin and the nonstatin drugs (aOR, 1.03 [95% CI, 0.63–1.66]). It was concluded either that all lipid-lowering drugs, regardless of class, cause acute memory loss or that the association is the result of detection bias. Another analysis using The Health Improvement Network database comparing 129 288 individuals who initiated treatment with a statin with a matched sample of 600 241 people who did not start a statin who were followed up for a median of 4.4 years, however, found a protective effect against dementia (HR, 0.80 [99% CI, 0.68–0.95]).[170] A causal relationship between statin exposure and impaired memory or cognition, however, remains uncertain.

A National Lipid Association task force assessed the relationship between statins and cognition in 2014.[171] The task force conducted a systematic literature review and formulated evidence-based recommendations to address a series of questions related to clinical care using a standardized rating and grading system. Obtaining a formal cognitive evaluation with scales such as the Mini-Mental State Examination or the Montreal Cognitive Assessment was thought to be of little value. There was a lack of evidence that statins adversely affect cognition according to case reports, case series, a dechallenge-rechallenge study, and data from 2 randomized trials (high certainty).

Table 5. Lipid-Lowering Agents in the Treatment of Dementia

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, RR, and 95% CI)	Summary/ conclusion and comment(s)
Chan et al[155] (MS-STAT)*	**Aim:** To obtain detailed longitudinal information on cognitive impairment, neuropsychiatric symptoms, and quality of life with simvastatin in patients with secondary progressive multiple sclerosis **Study type:** RCT **Size:** 140	**Inclusion criteria:** Age 18–65 y with multiple sclerosis, moderate disability, and secondary progression for ≥2 y **Exclusion criteria:** Use of disease-modifying treatment	**Intervention:** Simvastatin 80 mg daily (n=70) **Comparator:** Placebo (n=70) **Duration:** 24 mo	**Primary end point:** Cognitive and neuropsychiatric outcome measures together with health-related quality of life **Results:** At 24 mo, the Frontal Assessment Battery score was 1.2 points higher in the simvastatin-treated group than in the placebo group (95% CI, 0.2–2.3). The simvastatin group also had a 2.5-point-better mean physical component score of the 36-Item SFSI (95% CI, 0.3–4.8; *P*=0.028)	Simvastatin had a positive effect on frontal lobe function and a physical quality-of-life measure but no effect on the other outcome measures.
Davis et al[156]	**Aim:** To evaluate the evidence for the long-term effectiveness and harm of statin therapy in patients with dementia **Study type:** Systematic review/meta-analysis **Size:** 3 cohort studies in 1859 subjects	**Inclusion criteria:** Indexed publications of RCTs from developed countries between 2007 and 2019 **Exclusion criteria:** Statin treatment <6 mo Outcomes reported for <2 y	**Intervention:** Statin (n=830) prevalent use, initiation, or discontinuation within 6 mo **Comparator:** No statin (n=1029)	**Primary end point:** Major adverse cardiovascular events, dementia progression, and general health at 2 y or medication AEs at any time **Results:** 52 fewer subjects progressed from mild to moderate to severe by 2 y after diagnosis (95% CI, 13 fewer to 85 fewer)	Statins may have a small benefit in delaying progression in AD.
Geifman et al[157]*	**Aim:** To investigate the possible protective and therapeutic effect of statins in AD **Study type:** Systematic review/meta-analysis **Size:** 800 subjects across 3 patient cohorts	**Inclusion criteria:** Multiple patient cohorts of integrated clinical trial data and studies in people diagnosed with AD or *APO E ε4* carriers, observational studies, and 1 RCT of simvastatin vs placebo in AD **Exclusion criteria:** Dyslipidemia	**Intervention:** Simvastatin (n=171) **Comparator:** Pooled placebo arms (n=629)	**Primary end point:** Cognitive decline **Results:** Reanalysis of AD patient-level data from failed clinical trials suggested a trend toward slower progression of cognitive decline in patients on simvastatin, with a greater benefit in *APO E ε4* homozygotes Long-term observational studies revealed better cognitive performance in statin users, particularly among patients with AD homozygous for *APO E ε4* in 1 observational cohort study followed up for 10 y	Statins may benefit patients with AD homozygous for *APO E ε4*.
Lazashvili et al[158]*	**Aim:** To determine the efficacy and safety of statins in improving cognitive function in patients with VaD **Study Type:** RCT **Size:** 31 patients	**Inclusion criteria:** Patients with VaD **Exclusion criteria:** Heart, kidney, or liver failure	**Intervention:** Simvastatin 80 mg daily (n=20) **Comparator:** Placebo (n=11) **Duration:** 12 wk	**Primary end point:** Neuropsychological test with Mini-Mental scaling **Results:** No difference was observed between simvastatin and placebo in the change in cognitive function from baseline to week 12	No difference in cognitive function was observed at 12 wk in patients with VaD treated with simvastatin 80 mg daily vs placebo in this small (n=31), underpowered RCT.
Massardo et al[159]*	**Aim:** To evaluate the effect of statins as an addition to standard therapy on mood status, brain perfusion, and cognitive performance in patients with MDD **Study type:** RCT **Size:** 20 subjects	**Inclusion criteria:** Major depressive disorder not on medical treatment **Exclusion criteria:** Axis I mental conditions, addiction (other than smoking), head trauma, chronic medical disease	**Intervention:** Rosuvastatin 10 mg daily+sertraline (n=10) **Comparator:** Placebo+sertraline (n=10) **Duration:** 3 mo	**Primary end points:** Cognitive function assessed by HAM-D17, BDI, 6 measures of CANTAB Change in SPM 12 measured by brain single-photon emission tomography **Results:** At 3 mo: HAM-D17 improved in both groups (*P*<0.0001). BDI decreased to a greater degree after therapy with rosuvastatin (*P*<0.001) than with placebo (*P*=0.038). CANTAB assessment of attention switching task was improved with placebo (but not rosuvastatin; *P*<0.05 for 2 end points); 5 other end points showed no differences at baseline vs 3 mo. Brain perfusion differences (extension and number of significant clusters of voxels) by SPM12 were greater (*P*< 0.05) with rosuvastatin	Short-term use of low-dose statins in patients with MDD treated with sertraline results in important regional brain blood flow changes in key mood-associated areas to improvement in cognitive performance.

(*Continued*)

Table 5. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, RR, and 95% CI)	Summary/ conclusion and comment(s)
McGuinness et al[160]	**Aims:** To assess the clinical efficacy and safety of statins in the treatment of AD and VaD **Study type:** Systematic review **Size:** 4 RCTs in 1154 subjects	**Inclusion criteria:** Double-blind RCTs of statins given for at least 6 mo in people with a diagnosis of dementia **Exclusion criteria:** Low-quality studies Post hoc analyses	**Intervention:** Statin (n=574) **Comparator:** Placebo (n=579) **Duration:** 26–78 wk	**Primary end point:** Change in ADAS-Cog from baseline. **Results:** Mean difference with statin −0.26 (95% CI, −1.05 to 0.52; *P* =0.51) Mean difference in MMSE score, −0.32 (95% CI, −0.71 to 0.06; *P*=0.10) There was no significant difference in behavior, global function, or ADL in the statin and placebo groups	Statins have no benefit on the primary outcome measures of ADAS-Cog or MMSE.
Mejias-Trueba et al[161]	**Aim:** To compile the most relevant information about the efficacy of the use of statins for the treatment of patients with AD. **Study type:** Systematic review **Size:** 13 articles (6 clinical trials, 6 meta-analyses, 1 systematic review) in 855 354 subjects	**Inclusion criteria:** Clinical trials, meta-analyses, and systematic reviews that determined the efficacy of statins in AD, using parameters associated with the cause or evaluation of the pathology, in patients diagnosed with AD and ≥18 y of age **Exclusion criteria:** Other study designs, evaluation statins for the prevention of AD, articles not written in English or Spanish	**Intervention:** Statin **Comparator:** Placebo	**End point:** MMSE score ADAS-Cog score NPI total score ADCS-CGIC score Analytical variables indicating AD: levels of Aβ40 and Aβ42 in plasma and cerebrospinal fluid, total tau protein and phosphorylated tau protein levels, soluble amyloid precursor protein-β, soluble amyloid precursor protein-α, and plasma levels of 24S-hydroxycholesterol **Results:** ADAS-Cog: 8/10 articles, *P*=NS MMSE: 5/8 articles, *P*=NS CGIC: 4/5 articles, *P*=NS NPI: 4/5 articles, *P*=NS Change in biomarkers: 10/13 articles, *P*=NS	Statins have not shown an improvement in cognition and do not appear to offer significant benefits to patients with AD.
SAILS[162]	**Aim:** To test whether the pleiotropic effects of statins can reduce delirium in intensive care and decrease subsequent cognitive impairment **Study type:** RCT **Size:** 272 subjects	**Inclusion criteria:** Acute respiratory distress syndrome, receiving mechanical ventilation through an endotracheal tube, and meeting criteria for systemic inflammatory response with a known or suspected infection **Exclusion criteria:** Acute respiratory distress syndrome ≥48 h, preexisting condition adversely affecting survival or weaning from mechanical ventilation, receiving statins <48 h before randomization, and high CK, AST or ALT	**Intervention:** Rosuvastatin (40 mg load, then 20 mg daily) (N=137) **Comparator:** Placebo (N=135) **Duration:** 28 d	**Primary end point:** Daily delirium status in intensive care up to 28 d **Secondary end point:** Cognitive function at 6 and 12 mo **Results:** Mean proportion of days with rosuvastatin vs placebo with delirium was 34% vs 31% (HR, 1.14 [95% CI, 0.92–1.41]; *P*=0.22) At 6 mo, cognitive impairment was present in 36% vs 38% with rosuvastatin vs placebo (HR, 0.93 [95% CI, 0.39–2.22]; *P*=0.87) At 12 mo, cognitive impairment was present in 30% vs 28% (HR, 1.1 [95% CI, 0.5–2.6]; *P*=0.82)	No benefit of rosuvastatin in reducing delirium in intensive care or cognitive impairment was present during 12 mo of follow-up.
Padala et al[163]*	**Aim:** To evaluate the impact on cognition of statin discontinuation and rechallenge in individuals with AD on statins at baseline **Study type:** Open-label withdrawal and reinitiation study **Size:** 18 subjects	**Inclusion criteria:** Age ≥60 y, AD or stable mixed dementia with an MMSE score of ≥10 in patients taking stable doses of statins at least for 6 wk **Exclusion criteria:** MI, TIA, stroke in prior 6 mo, serious mental illness, active cancer, alcohol dependence, secondary hyperlipidemia	**Intervention:** Statin stopped for 12 wk, end points assessed, and then statin resumed after 12 wk **Comparator:** Same patients were compared after statin withdrawal and then after rechallenge **Duration:** 12 wk	**Primary end point:** Cognition measured by MMSE **Results:** Significant difference over time for MMSE score (*P*=0.018), improving with statin withdrawal and worsening after statin was resumed Paired *t* tests showed improvement in MMSE by 1.9 (*P*=0.014) with discontinuation of statins and decrease in MMSE by 1.9 (*P*=0.007) after rechallenge	This pilot study found an improvement in cognition with discontinuation of statins and worsening with rechallenge. Statins may adversely affect cognition in patients with dementia.

(*Continued*)

Table 5. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, RR, and 95% CI)	Summary/ conclusion and comment(s)
Pandey et al[164]	**Aim:** To assess the role of statins in the treatment of AD **Study type:** Meta-analysis **Size:** 5 RCTs in 6958 subjects	**Inclusion criteria:** Patients with history or at risk of AD AD measured by CGIC, MMSE, or ADAS-Cog **Exclusion criteria:** Non-RCT study designs	**Intervention:** Statin (n=3470) **Comparator:** Placebo (n=3487) **Duration:** 0.5–3.2 y	**Primary end points:** CGIC MMSE ADA-Cog **Results:** CGIC score mean difference, −0.26 (95% CI, −3.11 to 2.58; *P*>0.05) MMSE score mean difference, −0.921 (95% CI, −184 to 0.0055; *P*<0.05) ADA-CoG mean difference, −0.18 (95% CI, −1.03 to 0.66; *P*>0.05)	No significant difference in cognition with statins vs placebo in patients with AD
Sun et al[165]	**Aim:** **Study type:** Systematic review and meta-analyses of 2 RCTs **Size:** 710 subjects	**Inclusion criteria:** Age 50–90 y Probable or possible mild to moderate AD **Exclusion criteria:** Other forms of dementia, age <50 y, taking or having taken statin or treatments for AD	**Intervention:** Atorvastatin 80 mg daily (n=346) **Comparator:** Placebo (n=356) **Duration:** 50 and 80 wk	**Primary end point:** Efficacy (global function, cognitive function, daily living, and behavior) and safety (ie, incidence and severity of adverse effects) **Results:** No difference in CGIC scale (0.13 [95% CI, −0.15 to 0.40]), the ADAS-Cog subscale (1.05 [95% CI, −3.06 to 6.05]), MMSE scale (0.77 [95% CI, −0.57 to 2.10]), and the NPI (WMD, 2.07 [95% CI, −1.59 to 5.73]).	There is insufficient evidence to recommend atorvastatin for the treatment of mild to moderate AD.
Vallabhajosyula et al[166]	**Aim:** To evaluate the role of statins in delirium prevention in the intensive care unit **Study type:** Systematic review and meta-analysis **Size:** 6 studies in 289 773 subjects	**Inclusion criteria:** English language, peer-reviewed studies evaluating adult patients admitted for cardiac surgery or critical illness and ongoing statin use with comparison to a control group not receiving statin therapy reporting on delirium or confusion **Exclusion criteria:** Case reports and case series designs, pediatric and non-English literature, and studies without a control group	**Intervention:** Statins (n=22 292) **Comparator:** No statin (n=267 481) **Duration:** Duration of hospitalization	**Primary end point:** Delirium identified with the CAM-ICU, discharge diagnoses, or Intensive Care Delirium Screening Checklist **Results:** RR of delirium in statin and the nonstatin groups was 1.05 (95% CI, 0.85–1.29; P=0.56)	No benefit of statin in decreasing the incidence of delirium in critically ill patients
Williams et al[167]	**Aim:** To examine whether genetic variation affecting the expression or function of lipid-lowering drug targets is associated with AD **Study type:** Mendelian randomization **Size:** 24 718 cases and 56 685 controls	**Inclusion criteria:** Participants in the International Genomics of Alzheimer's Project and Psychiatric Genomics Consortium **Exclusion criteria:** Non-European ancestry	**Intervention:** Assessment of genes that encode the protein targets of several approved lipid-lowering drug classes: *HMGCR* (statins), *PCSK9* (PCSK9 inhibitors), *NPC1L1* (ezetimibe), and *APO B* (mipomersen) **Comparator:** Patients with wild-type genes of the above protein targets **Duration:** Not applicable	**Primary end point:** Alzheimer's dementia **Results:** Variants near *PCSK9* were associated with an increased risk of AD (OR, 1.45 [95% CI, 1.23–1.69]). Variants near *HMGCR*, *NPC1L1*, and *APO B* did not modify the risk of AD.	No genetic support for increased risk of AD was found for gene variants encoding the protein targets for statins, ezetimibe, or mipomersen. Pharmacovigilance for AD risk among users of PCSK9 inhibitors may be warranted.

(*Continued*)

Table 5. Continued

Study	Aim, study type/ design; study size	Patient population	Study intervention, n patients/study comparator, n patients; duration	Primary end point and results (*P* value; OR, RR, and 95% CI)	Summary/ conclusion and comment(s)
Xuan et al[168]	**Aim:** To explore the effect of statins in the treatment of AD **Study type:** Systematic review/meta-analysis **Size:** 9 RCTs trials in 1489 subjects	**Inclusion criteria:** AD treated with statins, use of ≥1 AD assessment tools reporting change of scores **Exclusion criteria:** Non-RCT design, RCTs comparing statins	**Intervention:** Statin (n=742) **Comparator:** Control (no statin or non-statin US Food and Drug Administration–approved lipid therapy; n=747) **Duration:** 12–78 wk	**Primary end points:** MMSE, ADAS-Cog, NPI, ADL **Results:** Pooled statin vs control: MMSE (9 studies): WMD, 1.09 (95% CI, −0.00 to 2.18; *P*=0.05) ADAS-Cog scale (5 studies): WMD, −0.16 (95% CI, −2.67 to 2.36; *P*=0.90) NPI scale (4 studies): WMD, −1.16 (95% CI, −1.88 to −0.44; *P*=0.002) ADL scale (6 studies): WMD, −4.06 (95% CI, −6.88 to −1.24; *P*=0.005)	Statins in patients with AD had beneficial effects on the scores of MMSE scale in the short term, slowed the deterioration of neuropsychiatric status, and significantly improved ADL ability. Statins did not show an advantage in the change in ADAS-Cog scale scores.

Aβ indicates β-amyloid; AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADCS-CGIC, AD Cooperative Study–Clinical Global Impression of Change; ADL, activities of daily living; AE, adverse event; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate transaminase; BDI, Beck's Depression Inventory; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CANTAB, Cambridge Neuropsychological Test Automated Battery; CGIC, Clinical Global Impression of Change; CK, creatine kinase; HAM-D17, Hamilton Depression Score with 17 items; HR, hazard ratio; MDD, major depressive disorder; MI, myocardial infarction; MMSE, Mini-Mental State Examination; MS-STAT, Multiple Sclerosis Simvastatin Trial; NPI, Neuropsychiatric Inventory; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial; RR, relative risk; SAILS, Statins for Acutely Injured Lungs From Sepsis; SFSI, Short Form Survey Instrument; SPM12, Statistical Parametric Mapping 12; TIA, transient ischemic attack; VaD, vascular dementia; and WMD, weighted mean difference.

*Study judged to include lower-quality data.

A subsequent systematic review assessed the available evidence addressing whether midlife or long-term statin use has an impact on cognitive decline and dementia.[172] Limitations of the use of observational studies to address this question, including bias, unmeasured confounding, reverse causation, and short periods of observation, were reviewed. Three of 6 observational studies suggested a cognitive benefit associated with statin use but had methodological issues (eg, use of information in the electronic medical record to define dementia, small numbers of subjects, lack of adjustment for education and sociodemographic factors). Several small statin trials with relevant data were also identified. Trials that evaluated cognitive outcomes within 6 months of starting a statin found no strong evidence of a short-term effect of statins on cognition and provided no relevant long-term data on the effect of statins on dementia or cognition. Two larger prospective trials that included cognitive measures were identified (the PROSPER trial[41] and the HPS[15]) and provided no clear evidence of an effect of statins on cognition. Other studies using various designs were also reviewed. The overall conclusion of the review was that evidence that late-life use of statins prevents cognitive decline and dementia over the subsequent few years was lacking.

A Cochrane systematic review addressed studies assessing the use of statins to prevent dementia.[142] The review identified 2 trials with relevant data (PROSPER[41] and the HPS[15]), both of which were also cited in the systematic reviews summarized previously. These 2 trials included 26340 participants 40 to 82 years of age (11610 were ≥70 years of age). Because the 2 trials assessed cognitive function at different times with different scales, formal meta-analysis was thought inappropriate. There were no differences in cognitive outcomes between the statin and nonstatin groups.

One randomized trial evaluated the efficacy and safety of atorvastatin in patients with mild to moderate AD.[173] Participants (n=640) were 50 to 90 years of age, had mild to moderate probable AD, had LDL-C levels >95 to <195 mg/dL, and were taking donepezil at baseline. Participants were randomized to atorvastatin 80 mg/d or placebo for 72 weeks followed by double-blind atorvastatin withdrawal over 8 weeks. There was no difference in the coprimary end points (Alzheimer's Disease Assessment Scale–Cognitive Subscale) and global function (Alzheimer's Disease Cooperative Study Clinical Global Impression of Change).

Similar to a prior American Heart Association scientific statement,[79] available systematic reviews of observational studies and randomized trials and subsequent studies and analyses have found little valid evidence of cognitive harms or benefits related to statin therapy. As reflected by the National Lipid Association Statin Cognitive Safety Task Force in 2014, if a patient who is receiving a statin develops cognitive complaints, it may be reasonable to obtain cognitive testing and to evaluate the patient for other potential contributors, with treatment decisions guided by individual patient characteristics in a shared decision-making environment.[171]

LOW LDL-C AND ISCHEMIC STROKE

Ischemic stroke is a heterogeneous condition with varied subtypes, including small vessel disease, atheroembolism,

cardioembolism, or other causes. High LDL-C is an established risk factor for ischemic stroke.[174] Low LDL-C may prevent ischemic stroke primarily through mechanisms of reduced atheroembolism from lipid-laden plaques; therefore, LDL-C reduction may not uniformly reduce all stroke subtypes.[175] The consensus related to LDL-C lowering for the prevention of ischemic stroke is reflected in evidence-based guidelines, which recommend lowering LDL-C with statins or a combination of agents to <70 mg/dL in patients with stroke of atherosclerotic origin.[176]

Decades of research supports the benefits of lipid lowering for the prevention of cardiovascular disease, with the primary benefit based on lowering LDL-C.[177] Trials of statin medications in high-risk populations to prevent cardiovascular events show a consistent risk reduction for ischemic stroke,[48,50] although not all trials were powered to evaluate for an effect on stroke alone.[47,55] A meta-analysis conducted by the CTT Collaboration found a 16% (95% CI, 11%–21%) risk reduction in any stroke for each 1–mmol/L reduction in LDL-C.[19]

Later trials studied combination therapies with statins, including ezetimibe, niacin, cholesterylester transfer protein inhibitors, PCSK9 inhibitors, and omega-3 supplementation, and icosapent ethyl (Table 6).[14,22,31,33,47,48,50,53,55,178–191] The addition of ezetimibe to statin therapy may have a modest effect on stroke prevention. A large clinical trial of participants after acute coronary syndrome demonstrated that the addition of ezetimibe to statin therapy reduced the risk of stroke by 0.6% (HR, 0.86 [95% CI, 0.73–1.00]).[192] A systematic review of the benefit of ezetimibe for cardiovascular disease protection reached similar conclusions.[193] A subsequent exploratory analysis of data from the TST trial (Treat Stroke to Target) found that those in the lower–LDL-C–target group (<70 mg/dL) compared with those in the higher-target group (100±10 mg/dL) had a lower risk of cerebral infarction and urgent carotid and cerebral artery revascularization (HR, 0.57 [95% CI, 0.33–0.97]; *P*=0.037) among those who received an ezetimibe in addition to a statin compared with statin monotherapy, despite similar achieved levels of LDL-C.[178] Trials of niacin[183,184] and cholesterylester transfer protein inhibitors[185–187] did not find a benefit for cardiovascular disease protection, including ischemic stroke. When added to statins, PCSK9 inhibitors uniformly have a modest risk reduction for ischemic stroke in populations at high risk of cardiovascular disease and therefore may have a role in certain patients for LDL-C reduction.[33,188,189] Last, although omega-3 fatty acid supplementation consisting of a carboxylic acid formulation of eicosapentaenoic acid and docosahexaenoic acid did not lead to stroke prevention,[191] a highly purified formulation of icosapent ethyl (a stable ethyl ester of eicosapentaenoic acid) provided incremental stroke risk reduction in patients with cardiovascular disease (0.9% difference in outcome rate of stroke between the placebo and treatment groups).[190]

Two secondary prevention trials in patients with a history of stroke or transient ischemic attack (TIA) showed the benefits of lowering LDL-C. The SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), completed in 2006, randomized 4731 patients with noncardioembolic ischemic stroke or intracerebral hemorrhage (ICH) to atorvastatin 80 mg or placebo. Fewer patients in the atorvastatin group had recurrent stroke, leading to a 5-year absolute risk reduction of 2.2%.[14] Many years passed before another secondary stroke prevention trial addressed the question of lipid management. The TST trial, completed in 2020, assessed whether risk reduction with a low LDL target (<70 mg/dL) compared with a more modest LDL target (90–110 mg/dL) would reduce the risk of subsequent cardiovascular events.[53] The trial enrolled 2860 patients with atherosclerotic ischemic stroke or TIA and found the benefit of the lower LDL-C target for the prevention of cardiovascular events in patients with recent stroke or TIA.

LDL-C REDUCTION AND HEMORRHAGIC STROKE RISK

Epidemiological studies[194–197] found inverse relationships between cholesterol and LDL-C levels and hemorrhagic stroke (Table 7).[6,14,32,42,53,180,181,190,192,194–212] An LDL-C <70 mg/dL was associated with increased hemorrhagic stroke risks in the Women's Health Study and a prospective study in Chinese patients without stroke history.[195,196] The Asia Pacific Cohort Studies Collaboration found that each 1–mmol/L increase in total cholesterol was associated with higher risks of ischemic stroke but reduced hemorrhagic stroke risks.[197] Mendelian randomization analyses also demonstrated inverse associations between LDL-C levels and hemorrhagic stroke.[198,199]

Statins

In addition to lowering cholesterol, statins have antithrombotic and fibrinolytic properties, which might increase the propensity for hemorrhagic stroke.[213] The risk for hemorrhagic stroke with statins may vary on the basis of the patient population/comorbidities and stroke type/subtype. Statin trials do not show increased risks for hemorrhagic stroke among statin-treated patients without stroke history. A meta-analysis of 26 randomized trials found a nonsignificant excess in hemorrhagic stroke, but there was a 16% overall decrease in all strokes per 1–mmol/L LDL-C reduction, driven by reductions in ischemic stroke.[19] In patients with a history of ischemic stroke, statin use for secondary prevention has been associated with increased hemorrhagic stroke risk. In the HPS, although simvastatin was not associated with an overall increase in hemorrhagic stroke, hemorrhagic stroke risk was numerically 2-fold higher among participants with cerebrovascular disease.[200] Similarly, although

Table 6. Summary of Clinical Trials of Therapies Lowering LDL and Reported Stroke Outcomes

Trial	Study Population	Experimental group	Control group	Follow-up, y*	Primary end point	Stroke Outcome
Statins						
SPARCL[14]	4731 patients with stroke or TIA 1 to 6 mo before study entry with LDL levels 100–190 mg/dL	Atorvastatin 80 mg	Placebo	4.9	First fatal or nonfatal ischemic stroke	11.2% receiving atorvastatin and 13.1% receiving placebo had ischemic stroke at follow up; 5-y ARR, 2.2%
MEGA[47]	3966 patients with hyperlipidemia (total cholesterol, 5.69–6.98 mmol/L) and no history of CAD or stroke	Diet and pravastatin 10 or 20 mg	Diet	5.3	First occurrence of CAD	2.5% in diet and statin group had stroke, 3.0% in diet group at end of study; *P*=0.33
JUPITER[48]	17 802 healthy men and women with LDL <130mg/dL and high-sensitivity C-reactive protein levels of ≥2 mg/L	Rosuvastatin 20 mg	Placebo	1.9	Major cardiovascular events	33 patients in rosuvastatin group and 64 patients in placebo group (<0.5% of patients in each group) had any stroke on follow-up (HR, 0.52 [95% CI, 0.34–0.79])
SEARCH[55]	12 064 patients with a history of MI and an indication for statin with a total cholesterol concentration of 3.5mmol/L if on a statin or 4.5 mmol/L if not	Simvastatin 80 mg	Simvastatin 20 mg	6.7	Major vascular events	4.2% in atorvastatin group had any stroke compared with 4.6% in simvastatin group (HR, 0.91 [95% CI, 0.77–1.08])
TST[53,178]	2860 patients with ischemic stroke in past 3 mo or TIA in prior 15 d	Target LDL-C <1.8 mmol/L (70 mg/dL) vs 100±10 mg/dL with statin or statin+ezetimibe	Target LDL-C 2.3–2.8 mmol/L (90–110 mg/dL)	3.5	Major cardiovascular events	8.5% in low LDL target had cardiovascular event vs 10.9% in higher LDL target group (HR, 0.78 [95% CI, 0.61–0.98]) Exploratory analysis found lower risk of stroke among those in the lower-target group who received dual therapy despite similar levels of LDL-C.[178]
HOPE-3[50]	12 705 patients at intermediate risk of cardiovascular disease	Rosuvastatin 10 mg	Placebo	5.6	Major cardiovascular events	1.1% in rosuvastatin group and 1.6% in placebo group had stroke (HR, 0.7 [95% CI, 0.52–0.95])
Statins and ezetimibe						
SEAS[179]	1873 patients with mild to moderate asymptomatic aortic stenosis	Simvastatin 40 mg+ezetimibe 10 mg	Simvastatin 40 mg+placebo	4.4	Major cardiovascular events	3.5% in combination therapy group had nonhemorrhagic stroke vs 3.1% in simvastatin-only group (HR, 1.12 [95% CI, 0.68–1.85])
SHARP[180]	9270 patients with chronic kidney disease with no known history of MI or coronary revascularization	Simvastatin 20 mg+ezetimibe 10 mg	Simvastatin 20 mg+placebo	4.9	First major atherosclerotic event	2.8% in combination therapy group had nonhemorrhagic stroke vs 3.8% in simvastatin-only group (RR, 0.75 [95% CI, 0.6–0.94])
IMPROVE-IT[31]	18 144 patients hospitalized with acute coronary syndrome and LDL levels 50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not on lipid-lowering therapy	Simvastatin 40 mg+ezetimibe 10 mg	Simvastatin 40 mg+placebo	6	Major cardiovascular events	4.2% in combination therapy group had any stroke vs 4.8% in simvastatin-only group (HR, 0.86 [95% CI, 0.73–1.00])
EWTOPIA 75[181]	3796 participants ≥75 y of age with elevated LDL-C without history of CAD	Ezetimibe 10 mg	Placebo	4.1	Major cardiovascular events	2.7% in ezetimibe group had any stroke vs 3.5% in placebo group (HR, 0.78 [95% CI, 0.53–1.14])
Statins and other lipid-lowering therapies						
ACCORD[182]	5518 patients with type 2 diabetes	Simvastatin+fenofibrate 160 mg	Simvastatin plus placebo	4.7	Major cardiovascular events	55 stroke events in combination group and 48 in simvastatin-only group (<0.5% of patients in each group; HR, 1.05 [95% CI, 0.71–1.56])

(*Continued*)

Table 6. Continued

Trial	Study Population	Experimental group	Control group	Follow-up, y*	Primary end point	Stroke Outcome
AIM-HIGH[183]	3414 patients with established cardiovascular disease low baseline levels of HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women), elevated triglyceride levels (150–400 mg/dL), and LDL-C levels <180 mg/dL if they were not taking a statin at entry	Simvastatin±ezetimibe plus niacin 1.5–2 g	Simvastatin± ezetimibe+niacin 50 mg	3	Major cardiovascular events	1.7% in treatment group vs 1.1% in placebo group had an ischemic stroke (HR, 1.61 [95% CI, 0.89–2.90])
HPS2-THRIVE[184]	25 673 patients with vascular disease	Simvastatin±ezetimibe+niacin 2 g/laropiprant 40 mg	Simvastatin± ezetimibe+placebo	3.9	Major cardiovascular events	3.9% in both groups had any stroke (RR, 1.00 [95% CI, 0.88–1.1])
CETP inhibitors						
dal-OUTCOMES[185]	15 871 patients with recent ACS	Dalcetrapib 600 mg	Placebo	2.6	Major cardiovascular events	1.1% in treatment group and 0.9% in placebo group had stroke of atheroembolic cause (HR, 1.25 [95% CI, 0.92–1.70])
ACCELERATE[186]	12 092 patients an acute coronary syndrome within the previous 30 to 365 d, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or diabetes with CAD	Evacetrapib 130 mg	Placebo	2.3	Major cardiovascular events	1.6% in both groups had any stroke (HR, 0.96 [95% CI, 0.72–1.27])
HPS3/TIMI 55-REVEAL[187]	30 499 patients with atherosclerotic vascular disease who were receiving high-dose atorvastatin	Anacetrapib 100 mg	Placebo	1.5	Major coronary event	3.2% in both groups had presumed ischemic stroke (HR, 0.99 [95% CI, 0.87–1.12])
PSK9 inhibitors						
FOURIER[188]	27 564 patients with CAD and LDL levels of at least 70 mg/dL while on statin therapy	Evolocumab (either 140 mg every 2 wk or 420 mg monthly)	Placebo	2.2	Major cardiovascular events	1.5% in treatment group and 1.9% in placebo group had any stroke (HR, 0.79 [95% CI, 0.66-0.95])
SPIRE[189]	27 438 patients with either a prior cardiovascular event or at high cardiovascular risk who were receiving treatment with a statin	Bococizumab 150 mg every 2 wk	Placebo	0.8	Major cardiovascular events	45 patients in treatment group and 75 patients in placebo had nonfatal stroke on follow up (<0.5% of patients in each group; HR, 0.6 [95% CI, 0.41–0.86])
ODYSSEY[33]	18 924 patients with acute coronary syndrome, a low LDL-C level of at least 70 mg/dL, a non-HDL level of at least 100 mg/dL, or an APO B level of at least 80 mg/dL and were receiving statin therapy	Alirocumab 150 mg every 2 wk	Placebo	1.6	Major cardiovascular events	1.2% in treatment group and 1.6% in placebo group had any stroke (HR, 0.73 [95% CI, 0.57–0.93])
FOURIER-OLE[22]	6635 patients with atherosclerotic cardiovascular disease and LDL of at least 70 mg/dL	Evolocumab (either 140 mg every 2 wk or 420 mg monthly)	Placebo	5.0	Incidence of treatment-emergent adverse events	0.66% in treatment group and 0.63% in placebo group had any stroke (HR, 1.05 [95% CI, 0.80–1.35])
Other antilipemic medications						
REDUCE-IT[190]	8179 patients with cardiovascular disease or with diabetes and other risk factors who had been receiving statin therapy and who had a fasting triglyceride level of 135–499 mg/dL	2 g of icosapent ethyl twice daily	Placebo	4.9	Major cardiovascular events	2.4% in treatment group and 3.3% in placebo group had any stroke (HR, 0.72 [95% CI, 0.55–0.93])

(*Continued*)

Table 6. Continued

Trial	Study Population	Experimental group	Control group	Follow-up, y*	Primary end point	Stroke Outcome
STRENGTH[191]	13 078 patients with high cardiovascular risk who had been receiving statin therapy and who had elevated triglycerides and low HDL	4 g of Epanova, an omega-3, fish oil–derived mixture of free fatty acids primarily composed of eicosapentaenoic acid and docosahexaenoic acid	Corn oil (inert)	3.5	Major cardiovascular events	2.2% in treatment group and 1.9% in placebo group had nonfatal stroke (HR, 1.14 [95% CI ,0.90-1.45])

ACCELERATE indicates Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes; APO B, apolipoprotein B; ARR, adjusted risk ratio; CAD, coronary artery disease; CETP, cholesterylester transfer protein; dal-OUTCOMES, Dalcetrapib Outcomes; EWTOPIA 75, Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; FOURIER-OLE, FOURIER Open Label Extension; HDL-high-density lipoprotein; HOPE-3, Heart Outcomes Prevention Evaluation-3; HPS2-THRIVE, Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; HPS3/TIMI55–REVEAL, Heart Protection Study 3/Thrombolysis in Myocardial Infarction 55–Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification; HR, hazard ratio; IMPROVE IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MEGA, Primary Prevention of Cardiovascular Disease With Pravastatin in Japan; MI, myocardial infarction; ODYSSEY, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9, proprotein convertase subtilisin/kexin type 9; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; RR, relative risk; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; SPARCL, Stroke Prevention With Aggressive Reduction in Cholesterol Levels; SPIRE, Studies of PCSK9 Inhibition and the Reduction of Vascular Events; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia; TIA, transient ischemic attack; and TST, Treat Stroke to Target.

*Mean or median follow-up reported, depending on trial report.

atorvastatin was associated with decreased overall and ischemic stroke in the SPARCL trial, post hoc exploratory analysis found that hemorrhagic stroke risk was increased.[14] A SPARCL/HPS meta-analysis showed a reduction in overall stroke despite an increase in hemorrhagic stroke with statins.[201] A subsequent secondary analysis of SPARCL data found that hemorrhagic stroke risk was highest in statin-treated patients with cerebral small vessel disease or whose qualifying stroke was a hemorrhagic stroke.[202]

A Danish population-based study included 16 235 cases with ICH and 640 943 controls.[207] Current statin use (cases, 25.9% versus controls, 24.5%; aOR, 0.74 [95% CI, 0.71–0.78]) and a longer duration of current statin use (<1 year: aOR, 0.86 [95% CI, 0.81–0.92]; ≥1–<5 years: aOR, 0.72 [95% CI, 0.68–0.76]; ≥5–<10 years: aOR, 0.65 [95% CI, 0.60–0.71]; ≥10 years: aOR, 0.53 [95% CI, 0.45–0.62]; P_{trend}<0.001) were associated with a lower risk of ICH.

PCSK9 Inhibitors

A meta-analysis of statin and PCSK9 inhibitor trials reported increased hemorrhagic stroke risk with statins but not with the addition of PCSK9 inhibitors.[203] In ODYSSEY OUTCOMES, alirocumab reduced ischemic stroke without increasing hemorrhagic stroke among participants with a history of ischemic stroke, regardless of LDL-C levels.[204] Similar results were reported in FOURIER, in which aggressive reductions in LDL-C levels with evolocumab were not associated with increased risk for hemorrhagic stroke among study participants, of whom 19% had a history of ischemic stroke.[188]

Other Lipid-Lowering Therapies

Data on the risk of hemorrhagic stroke with other lipid-lowering therapies, particularly in patients with a history of hemorrhagic stroke, are limited. The available data do not suggest that ezetimibe monotherapy increases the risk for hemorrhagic stroke. In the EWTOPIA 75 trial (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older), hemorrhagic stroke occurred in 0.5% of participants treated with ezetimibe versus 0.6% treated with placebo.[181] In the TST trial in patients with a history of ischemic stroke or TIA, the frequency of hemorrhagic stroke was 1.3% with an aggressive reduction of LDL-C to <70 mg/dL with ezetimibe, a statin, or both compared with 0.9% among those with a higher LDL-C (HR, 1.38 [95% CI, 0.68–2.82]).[53] The rate of major cardiovascular events, however, was lower in the lower-target group (8.5% versus 10.9%; HR, 0.78 [95% CI, 0.61–0.98]). In IMPROVE-IT, in which 3.8% of patients had a history of stroke, there was a nonsignificant increase in the rate of hemorrhagic stroke with ezetimibe plus simvastatin compared with placebo plus simvastatin (0.8% versus 0.6%; HR, 1.38 [95% CI, 0.93–2.04]; P=0.11), whereas the addition of ezetimibe to simvastatin reduced the frequency of ischemic stroke (3.4% versus 4.1%; HR, 0.79 [95% CI, 0.67–0.94]; P=0.008).[31] There was no difference in the primary composite end point (death resulting from cardiovascular causes, myocardial infarction, or stroke) among those with versus without a prior stroke ($P_{interaction}$=0.11).[192] Similar results were found in REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial), in which the frequency of hemorrhagic stroke was 0.3% with icosapent ethyl versus 0.2% with placebo in

Table 7. Effect of Statins and Other Lipid-Lowering Agents on the Risk of Hemorrhagic Stroke

Study	Population and No. of participants	Design	Drugs used	Duration of follow-up	Main results
Pezzini et al[194]	3492 patients with ICH and 3492 age- and sex-matched stroke-free control subjects enrolled in the setting of MUCH-ITALY	A case-control analysis comparing consecutive patients with ICH with age- and sex-matched stroke-free controls to test for the presence of interaction effects between total serum cholesterol levels and statins on the risk of ICH	Various statin drugs and doses	NA	Increasing levels of total cholesterol were associated with a decreased risk of ICH within statin strata (OR, 0.87 [95% CI, 0.86–0.88) for every increase of 0.26 mmol/l of total cholesterol concentrations. There was an interaction between total cholesterol levels and statin use for the risk of ICH (interaction OR, 1.09 [95% CI, 1.05–1.12]). Statin use was associated with an increased risk of ICH (OR, 1.54 [95% CI, 1.31–1.81]) The protective effect of serum cholesterol against ICH was reduced by statins in strictly lobar more than in nonlobar locations.
Rist et al[195]	27 937 women enrolled in the Women's Health Study	Retrospective analysis of observational data to examine the association between lipid levels and HS risk The Women's Health Study started as a randomized trial of low-dose aspirin and vitamin E supplementation for the primary prevention of cardiovascular disease and cancer in initially healthy female health professionals ≥45 y of age. The randomized trial has ended, and the study has evolved into an observational study.	Low-dose aspirin and vitamin E	Mean, 19.3 y	Subjects with LDL-C levels <70 mg/dL had 2.17 times the risk (95% CI, 1.05–4.48) of experiencing a HS compared with those with LDL-C levels of 100–129.9 mg/dL. Women in the lowest quartile of triglycerides had a significantly increased risk of HS compared with women in the top quartile (adjusted RR, 2.00 [95% CI, 1.18–3.39]).
Ma et al[196]	96 043 subjects without history of stroke, myocardial infarction, and cancer at baseline	Prospective population-based cohort study examining the association between LDL-C and ICH risk. LDL-C levels were assessed at baseline (2006), 2008, 2010, and 2012. Cumulative average LDL-C was calculated.	NA	9 y	Participants with LDL-C <70 mg/dL had a higher risk of developing ICH than those with LDL-C of 70–99 mg/dL; adjusted HR, 1.65 (95% CI, 1.32–2.05) for LDL-C 50–69 mg/dL vs 2.69 (95% CI, 2.03–3.57) for LDL-C <50 mg/dL. A restricted cubic spline model identified a cutoff point of LDL-C at 75.7 mg/dL (HR, 1.24 [95% CI, 1.00–1.54]) at which the association between lower LDL-C and higher risk of ICH became significant.
Zhang et al[197]	352033 participants in 29 Asia Pacific prospective cohort studies	Individual-participant data meta-analysis of prospective studies from the Asia-Pacific region to examine the associations between total cholesterol and major cardiovascular diseases.	NA	2 million person-years	Each 1–mmol/l higher level of total cholesterol was associated with 35% (95% CI, 26%–44%) increased risk of coronary death, 25% (95% CI, 13%–40%) increased risk of fatal or nonfatal IS, and 20% (95% CI, 8%–30%) decreased risk of fatal HS.
Sun et al[198]	16 541 participants in the China Kadoorie Biobank (5475 IS cases, 4776 ICH cases, and 6290 healthy controls)	Nested case-control study using observational and genetic (genetic risk score comprising 46 SNPs most strongly associated with plasma LDL-C concentration) analyses to examine the association of blood lipids with incident stroke in Chinese adults.	NA	Median=9 y	Plasma concentrations of LDL-C were positively associated with risk of IS and inversely associated with risk of ICH. Throughout the range examined (1.7–3.2 mmol/L), each 1–mmol/L higher LDL-C was associated with a 17% (adjusted RR, 1.17 [95% CI, 1.10–1.25]) higher risk of IS and a 14% (RR, 0.86 [95% CI, 0.80–0.92]) lower risk of ICH, which translated into an RR of 0.85 (95% CI, 0.80-0.91) for IS and 1.16 (95% CI, 1.08–1.25) for ICH, for each 1–mmol/L lower LDL-C. Each 1–mmol/L lower genetically instrumented LDL-C was associated with RRs of 0.75 (95% CI, 0.60–0.95) for IS and 1.13 (95% CI, 0.91–1.40) for ICH. In a meta-analysis of the worldwide randomized trials of LDL-C–lowering drug treatment, each 1–mmol/L lower LDL-C was associated with RRs of 0.80 (95% CI, 0.76–0.84) for IS and 1.17 (95% CI, 1.03–1.32) for ICH.

(*Continued*)

Table 7. Continued

Study	Population and No. of participants	Design	Drugs used	Duration of follow-up	Main results
Falcone et al[199]	316 428 participants in the UK Biobank, and 1286 patients with ICH and 1270 controls who participated in GOCHA, ISGC ICH, and GERFHS	Case-control study using PRS per lipid trait (total cholesterol, LDL, HDL, and triglycerides) to estimate the effect of each PRS on ICH risk to conduct mendelian randomization analyses	NA	NA	Genetically elevated LDL levels were associated with lower risk of ICH. A 1-SD increase in the PRSs for total cholesterol (OR 0.92, 95%CI 0.85–0.99; *P*=0.03) and LDL-C (OR 0.88; 95%CI, 0.81–0.95; *P*=0.002) were inversely associated with ICH risk. Mendelian Randomization analyses indicated that 1 mmol/L (38.67 mg/dL) increase of genetically instrumented total and LDL-C were associated with 23% (OR 0.77; 95%CI 0.65–0.98; *P*=0.03) and 41% lower risks of ICH (OR 0.59; 95%CI 0.42–0.82; *P*=0.002), respectively.
Baigent et al[180]	39 612 participants in 5 randomized trials of more vs less intensive statin regimen and 129 526 participants from 21 trials of statin vs control	Meta-analysis of individual participant data	Various statin drugs and doses	Median, 4.8–5.1 y	In the 5 trials of more vs less intensive statin therapy, the incidence of first stroke of any type was 0.6%/y vs 0.7%/y, with a risk reduction of 14% (95% CI, 4%–23%; *P*=0.009). There was a 16% (99% CI, 1%–29%) reduction in the risk of IS (RR, 0.84 [99% CI, 0.71–0.99]; *P*=0.005) and a nonsignificant excess of HS (RR, 1.21 [99% CI, 0.76–1.91]; *P*=0.3). Taking all 26 trials together, the stroke risk reduction was 16% (95% CI, 11%–21%; *P*<0.0001) per 1.0–mmol/L LDL-C reduction. RR in IS was 0.79 (95% CI, 0.74–0.85; *P*<0.0001). There was a nonsignificant excess of HS (RR, 1.12; 95% CI, 0.93–1.35; *P*=0.2).
Collins et al[200]	20 536 adults (40–80 y of age) with coronary disease, other occlusive arterial disease, or diabetes (including 3280 with cerebrovascular disease) who participated in the HPS	Subgroup analyses of the HPS (a randomized, placebo-controlled trial)	Simvastatin (40 mg)	4.8 y	Overall, treatment with simvastatin resulted in a significant 20% reduction in composite major vascular events (myocardial infarction, coronary death, stroke, and revascularization procedures) among patients with history of cerebrovascular disease. There was no reduction in the incidence of stroke among patients with preexisting cerebrovascular disease; 6.1% in simvastatin-treated patients vs 7.5% in patients treated with placebo (RR, 0.98 [95% CI, 0.79–1.22]). In patients with cerebrovascular disease, the incidence of HS was 1.3% with simvastatin vs 0.7% with placebo compared with 0.3% vs 0.5%, respectively, in patients without cerebrovascular disease.
Amarenco et al[14]	4731 patients who had a noncardioembolic stroke or TIA within the previous 6 mo	Randomized, placebo-controlled trial.	Atorvastatin (80 mg)	Median, 4.9 y	Mean LDL-C level during the trial was 73 mg /dL (1.9 mmol/L) among patients receiving atorvastatin. A total of 11.2% of atorvastatin-treated patients and 13.1% of patients receiving placebo had a fatal or nonfatal stroke (5-y absolute reduction in risk, 2.2%; adjusted HR, 0.84 [95% CI, 0.71–0.99]; *P*=0.03). Although the odds of IS were reduced by 22% with atorvastatin, the odds of HS were significantly increased by 66%; 88 patients had HS: 55 in the atorvastatin group vs 33 in the placebo group. Post hoc analyses indicated significant differences in the treatment effect (HRs) based on the type of stroke occurring during the trial. The cause-specific adjusted HRs in the atorvastatin group vs placebo were 0.78 (95% CI, 0.66–0.94) for IS and 1.66 (95% CI, 1.08–2.55) for HS.
Mankelow et al[201]	10 000 patients >18 y of age with a history of IS or HS or TIA who participated in 8 randomized, placebo-controlled trials, including LIPID, CARE, HPS, VACSA, SPARCL, and FASTER	Cochrane systematic review and meta-analysis of 8 RCTs of lipid-lowering interventions	Lipid-lowering intervention, including drugs (pravastatin, atorvastatin, simvastatin, clofibrate, and conjugated estrogen) and diet (fiber)	Variable (4 mo–6.2 y)	There was a reduction in subsequent vascular events in patients with a history of stroke or TIA with lipid-lowering therapy (OR, 0.77 [95% CI, 0.70–0.84]; *P*<0.0001). Fixed-effect analysis showed no overall effect on stroke recurrence, but statin therapy alone had a borderline benefit (OR, 0.88 [95% CI, 0.77–1.00]). Analysis by type of subsequent stroke (2 showed a protective effect of statins for IS (OR, 0.78 [95% CI, 0.67–0.92]) but increased risk of HS (OR, 1.72 [95% CI, 1.20–2.46]).

(*Continued*)

Table 7. Continued

Study	Population and No. of participants	Design	Drugs used	Duration of follow-up	Main results
Goldstein et al[202]	4713 patients who participated in SPARCL trial, including 93 who had HS as the entry event	Post hoc analysis of SPARCL trial	Atorvastatin (80 mg)	Median, 4.9 y	HS risk was higher with atorvastatin treatment (HR, 1.68 [95% CI, 1.09–2.59]; *P*=0.02), among patients who had a HS as the entry event (HR, 5.65 [95% CI, 2.82–11.30]; *P*<0.001), in men (HR, 1.79 [95% CI, 1.13–2.84]; *P*=0.01), with age (10-y increments; HR, 1.42 [95% CI, 1.16–1.74]; *P*=0.001), and in patients with hypertension at the last study visit before a HS (HR, 6.19 [95% CI, 1.47–26.11]; *P*=0.01). There was no effect of most recent LDL-C level in those treated with atorvastatin.
Sanz-Cuesta et al[203]	204 918 participants in 36 statin randomized trials and 76 140 participants in PCSK9 inhibitors trials	A systematic meta-analysis assessing HS rates across all completed statin and PCSK9 inhibitors randomized clinical trials with treatment >3 mo	Various statins and PCSK9 inhibitors	>3 mo–7 y	Statins were associated with increased HS risk across all patient types and all medication doses/potencies (RR, 1.15; *P*=0.04). Higher-dose/potency statins were associated with magnified HS risk (RR, 1.53; *P*=0.002). Prior IS/TIA was associated with increased risk of HS (RR, 1.43; *P*=0.04), and index ICH was associated with an extremely high effect estimate of risk of recurrent HS (HR, 4.06). PCSK9 inhibitors were not associated with HS risk.
Jukema et al[204]	18 924 patients with recent acute coronary syndrome and dyslipidemia who participated in the ODYSSEY OUTCOMES trial, including 944 (5%) patients with history of cerebrovascular disease, of whom 611 had a history of IS Patients with HS were excluded.	Double-blind, randomized, placebo-controlled trial	Alirocumab	Median, 2.8 y	Alirocumab reduced the risk of any stroke (HR, 0.72 [95% CI, 0.57–0.91]) and IS (HR, 0.73 [95% CI, 0.57–0.93]) without increasing hemorrhagic stroke (HR 0.83; 95% CI 0.42–1.65). The effect of alirocumab on was similar in patients with a history of previous cerebrovascular disease and those without a history of cerebrovascular disease ($P_{interaction}$ = 0.37). There was no apparent adverse relation between lower achieved LDL-C and incidence of HS.
Sabatine et al[32]	27 564 patients with atherosclerotic cardiovascular disease and LDL-C ≥70 mg/dL who were receiving statin therapy; 19% of study participants had a history of IS Patients with HS were excluded.	Double-blind, randomized, placebo-controlled trial.	Evolocumab	Mean, 2.2 y	Evolocumab reduced the risk of the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (9.8% vs 11.3%; HR, 0.85 [95% CI, 0.79–0.92]; *P*<0.001) The rate of IS during follow-up was 1.2% with evolocumab vs 1.6% with placebo (HR, 0.75 [95% CI, 0.62–0.92]). The rate of HS was 0.21% vs 0.18%, respectively (HR, 1.16 [95% CI, 0.68–1.98]).
Ouchi et al[181]	1716 patients ≥75 y of age with elevated LDL-C and without history of coronary disease randomly assigned to ezetimibe vs usual care	Multicenter, prospective, randomized, open-label, blinded–end point evaluation study	Ezetimibe (10 mg once daily)	Median, 4.1 y	Ezetimibe reduced the incidence of the primary outcome (cardiac death, myocardial infarction, coronary revascularization, or stroke; HR, 0.66 [95% CI, 0.50-0.86]; *P*=0.002). There was no difference in the incidence of IS in ezetimibe-treated vs control patients (2.7% vs 3.5%; HR, 0.78 [95% CI, 0.53–1.14]; *P*=0.20). There was no difference in the incidence of HS in ezetimibe-treated vs control patients (0.5% vs 0.6%; HR, 0.73 [95% CI, 0.29–1.81]; *P*=0.49).
Amarenco et al[53]	2860 patients with history of IS in the previous 3 mo or a TIA within the previous 15 d randomly assigned to a target LDL-C level <70 mg/dL (lower-target group) or to a target range of 90–110 mg/dL (higher-target group) The trial was stopped for administrative reasons after 277 of an anticipated 385 end-point events had occurred.	Randomized, parallel-group, event-driven, multicenter trial	Statin, ezetimibe, or both	Median, 3.5 y	The composite of IS, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularization, or death resulting from cardiovascular causes occurred in 8.5% of patients in the lower-target group and 10.9% in the higher- target group (adjusted HR, 0.78 [95% CI, 0.61–0.98]; *P*=0.04). IS or TIA occurred in 8.4% of patients in the lower-target group and 9.7% in the higher-target group (HR, 0.87 [95% CI, 0.68–1.11]). Intracranial hemorrhage occurred in 1.3% of patients in the lower-target group vs 0.9% in the higher-target group (HR, 1.38 [95% CI, 0.68–2.82]).

(*Continued*)

Table 7. Continued

Study	Population and No. of participants	Design	Drugs used	Duration of follow-up	Main results
Bohula et al[192]	15 281 patients with an acute coronary syndrome who participated in IMPROVE-IT; 15.5% of participants had a history of stroke before randomization.	Post hoc analysis of a multicenter, double-blind, randomized, placebo-controlled trial to investigate the efficacy of the addition of ezetimibe to statin/simvastatin for prevention of first and subsequent stroke and other cardiovascular events, with a particular focus on patients with a history of stroke	Ezetimibe+ simvastatin or placebo+ simvastatin	Median, 6 y	3.5% of participants had a stroke during follow up; 82% were ischemic and 16% were hemorrhagic. There was a nonsignificant reduction in the first event of stroke of any cause (4.2% vs 4.8%; HR, 0.86 [95% CI, 0.73–1.00]; P=0.052) with ezetimibe/simvastatin vs placebo/simvastatin, driven by a significant 21% reduction in IS (HR, 0.79 [95% CI, 0.67–0.94]) and a nonsignificant increase in HS (0.8% vs 0.6%; HR, 1.38 [95% CI, 0.93–2.04]). History of stroke was the most important independent predictor of recurrent stroke of any cause (HR, 3.06 [95% CI, 2.40–3.92]; P<0.001).
Bhatt et al[190]	8179 participants in REDUCE-IT trial with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy, and who had a fasting triglyceride level of 135–499 mg/dL and LDL-C of 41–100 mg/dL	Post hoc analysis of a multicenter, randomized, double-blind, placebo-controlled trial to investigate stroke end points	Icosapent ethyl	Median, 4.9 y	Event rates for any stroke were 2.4% with icosapent ethyl vs 3.3% with placebo (HR, 0.72 [95% CI, 0.55–0.93]). Rates for HS were 0.3% with icosapent vs 0.2% with placebo (HR, 1.28 [95% CI, 0.56–2.93]).
Ribe et al[205]	55 692 patients initiating statin treatment after a first-time stroke diagnosis (n=2728 ICHs and 52 964 ISs), and 65 640 statin nonusers included as references	Propensity score–matched cohort study using information from Danish nationwide registers	Various statins	Up to 10 y	Among those with prior ICH, the adjusted HR for recurrent HS was 0.90 (95% CI, 0.72–1.12) compared with an adjusted HR of 0.53 (95% CI, 0.45–0.62) with prior IS. Among those with prior ICH, the risk of recurrent ICH was similar for statin users and nonusers. Among those with prior IS, the risk of ICH was 42%–66% lower for statin users compared with nonusers.
Lin et al[206]	8927 patients with ICH and dyslipidemia from the National Health Insurance Research Database in Taiwan (1613 received statins; 7314 were not taking statins)	Retrospective observational study using propensity score matching	Various statin drugs and doses	5 y	Statin-treated patients had lower risks of all-cause mortality (HR, 0.54 [95% CI, 0.45–0.65]), cardiovascular death (HR, 0.54 [95% CI, 0.39–0.75]), and recurrent ICH (HR, 0.62 [95% CI, 0.46–0.83]) compared with those who did not receive statins.
Rudolph et al[207]	16 235 patients with first-ever ICH and 640 943 matched controls from the Danish Stroke Registry	Retrospective observational study	Various statin drugs and doses	10–13 y	Current statin use (aOR, 0.74 [95% CI, 0.71–0.78]) and a longer duration of statin use (<1 y: aOR, 0.86 [95% CI, 0.81–0.92]; ≥1–<5 y: aOR, 0.72 [95% CI, 0.68–0.76]; ≥5–<10 y: aOR, 0.65 [95% CI, 0.60–0.71]; ≥10 y: aOR, 0.53 [95% CI, 0.45–0.62]; P<0.001) were associated with a lower risk of ICH.
Ziff et al[208]	317 291 patients from 43 observational and randomized studies comparing statin therapy with control (placebo or no treatment) in patients with a previous hemorrhagic or IS	Systematic literature review and meta-analysis	Various statin drugs	Weighted average, 1.8 (range, 0.1–7 y)	In patients with previous ICH: Statins had no impact on the pooled RR for recurrent ICH (1.04 [95% CI, 0.86–1.25]). Statins were associated with reduced mortality (RR, 0.49 [95% CI, 0.36–0.67]) and poor functional outcome (RR, 0.71 [95% CI, 0.67–0.75]). In patients with previous IS, statins were associated with a nonsignificant increase in ICH (RR, 1.36 [95% CI, 0.96–1.91]) but significantly lower risks of recurrent IS (RR, 0.74 [95% CI, 0.66–0.83]), any stroke (RR, 0.82 [95% CI, 0.67–0.99]), mortality (RR, 0.68 [95% CI, 0.50–0.92]), and poor functional outcome (RR, 0.83 [95% CI, 0.76–0.91]).

(*Continued*)

Table 7. Continued

Study	Population and No. of participants	Design	Drugs used	Duration of follow-up	Main results
Teoh et al[209]	11 576 subjects with previous IS or HS or TIA who participated in 17 randomized trials	Meta-analysis followed by a trial sequential analysis to assess the reliability and conclusiveness of available evidence in the meta-analysis	Various statin drugs	7 d–4.9 y	Statin therapy increased the risk of HS (RR, 1.42 [95% CI ,1.07–1.87]) but reduced the risk of IS (RR, 0.85 [95% CI, 0.75–0.95]). For the net composite end points (IS, HS, TIA, myocardial infarction, and cardiovascular mortality), statin therapy was associated with a 17% risk reduction (95% CI, 12%–21%). At a control event rate of 2% and an RR increase of 40%, the trial sequential analysis–adjusted RR for HS was 1.42 (95% CI, 1.04–1.93), suggesting a conclusive signal of an increased risk of HS with statin use.
Sprügel et al[210]	1275 patients with ICH (277 taking statin on admission) from the prospective UKER-ICH study	Observational study utilizing multivariable regression modeling and propensity score matching	Various statin agents and doses	Up to 12 mo.	Statin treatment on hospital admission was associated with higher rates of lobar vs nonlobar ICH (OR, 1.57 [95% CI ,1.03–2.40]; *P*=0.038). Patients on statins had fewer cardiovascular adverse events and more frequently had functional recovery after 12 mo (OR, 1.67 [95% CI, 1.09–2.56]; *P*=0.019).
Woo et al[211]	558 patients with ICH and 1444 controls who participated in the GERFHS; and 1020 ICH cases and 382 controls from the GOCHA study	Genetic study test whether hyperlipidemia and *APO E* polymorphisms affect the risk of ICH by statin use. The discovery cohort was from the GERFHS study, a case-control study of HS that used prospective, population-based case ascertainment, and the replication cohort was from GOCHA.	Various statin agents and doses	NA	Statin users with *APO E4/E4* genotype had a high risk of lobar ICH in the discovery (OR, 4.5 [95%CI, 1.3–16.0]; *P*=0.02) and replication (OR, 12 [95% CI, 2.5–54]; *P*<0.0001) cohorts. Similarly, *APO E2/E4* statin-treated patients had a higher risk for lobar ICH (OR, 11.3 [95% CI, 2.0–64]; *P*=0.005) than the controls (OR, 2.0 [95% CI, 0.8–5.2]; *P*=0.18) in the discovery cohort and the replication cohort (OR, 7.4 [95% CI, 1.5–3.7], *P*=0.008 vs OR, 3.7 [95% CI, 1.3–11], *P*=0.01).
Nissen et al[212]	Trial of bempedoic acid in 13 970 statin intolerant patients who had or were at high risk of cardiovascular disease (CLEAR)	Secondary subgroup analysis	Bempedoic acid 180 mg daily or placebo	Median, 40.6 mo	Although underpowered for subgroup analyses, there was no effect on fatal or nonfatal stroke (HR, 0.85 [95% CI, 0.67–1.07]; *P*=0.16) with a reduction in IS (HR, 0.78 [95% CI, 0.61–0.99]) but an increase in HS (HR, 2.21 [95% CI, 1.01–4.85]).

aOR indicates adjusted odds ratio; CARE, Cholesterol and Recurrent Events Study; CLEAR, Cholesterol Lowering via Bempedoic Acid Trial; FASTER, Fast Assessment of Stroke and Transient ischemic attack to Prevent Early Recurrence; GERFHS, Genetic and Environmental Risk Factors for Hemorrhagic Stroke; GOCHA, Genetic Risks for Medication-Related Hemorrhagic Stroke; HDL, high-density lipoprotein; HPS, Heart Protection Study; HS, hemorrhagic stroke; ICH, intracerebral hemorrhage; IMPROVE IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; IS, ischemic stroke; ISGC ICH, International Stroke Genetics Consortium Intracerebral Hemorrhage; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; MUCH-Italy, Multicenter Study on Cerebral Hemorrhage in Italy; NA, not applicable; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; PRS, polygenic risk score; RCT, randomized controlled trial; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; SPARCL, Stroke Prevention With Aggressive Reduction in Cholesterol Levels; TIA, transient ischemic attack; and UKER-ICH, Universitätsklinikum Erlangen Cohort of Patients With Spontaneous Intracerebral Hemorrhage; VACSA, Veterans Administration Cooperative Study of Atherosclerosis.

statin-treated patients with elevated triglycerides and atherosclerosis (*P*=0.55).[6,190] A trial of bempedoic acid in statin-intolerant patients who had or were at high risk of cardiovascular disease found a reduction in the primary end point (composite death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization; 11.7% versus 13.3%; HR, 0.87 [95% CI, 0.79–0.96]; *P*=0.004).[212] Although the study was underpowered for subgroup analyses, there was no effect on fatal or nonfatal stroke (HR, 0.85 [95% CI, 0.67–1.07]; *P*=0.16), with a reduction in ischemic stroke (HR, 0.78 [95% CI, 0.61–0.99]) but an increase in hemorrhagic stroke (HR, 2.21 [95% CI, 1.01–4.85]).

Overall, aggregate randomized data do not show an increased risk for hemorrhagic stroke with statins or other lipid-lowering therapies in patients without a history of stroke. Some suggest a tendency for a small increased risk in some patient groups, particularly those with prior ischemic stroke, but this is offset by the benefits of reducing overall stroke and other major cardiovascular events.

LDL-C REDUCTION AFTER HEMORRHAGIC STROKE

There is paucity of prospective and randomized data on statin effects in patients who have had a hemorrhagic stroke. Interpretation of studies has been controversial because very few patients with hemorrhagic stroke were included in statin trials and most studies are retrospective, nonrandomized, observational, and prone to

confounding. Several observational studies found no or even negative association between statins and hemorrhagic stroke,[205–207] and results of meta-analyses have been inconsistent.[208,209] Some studies suggest that hemorrhagic stroke in lobar locations, which is often attributed to cerebral amyloid angiopathy, occurs more frequently among statin users than nonusers[194,210] and that statins attenuate the protective effect of hyperlipidemia against hemorrhagic stroke in lobar regions[210] and confer higher risks for lobar ICH in *APO E4/E4* and *E2/E4* carriers.[211] Other analyses suggest no clear benefits from statins in patients with hemorrhagic stroke.[200–202] A meta-analysis of statins and PCSK9 inhibitor trials found that high-dose statins and index hemorrhagic stroke were associated with an increased risk of recurrent hemorrhagic stroke with no effect of the addition of PCSK9 inhibitors. (Patients with a history of hemorrhagic stroke and uncontrolled hypertension were excluded from these trials; therefore, the risks and benefits of PCSK9 inhibitors are unknown in patients with ICH.)[203]

Some studies suggest that patients with cerebral angiopathies such as cerebral amyloid angiopathy or CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) may constitute groups susceptible to bleeding from statins or LDL-C lowering.[214] There is an association between statin use and the presence and extent of cortico-subcortical cerebral microbleeds (more frequent in the setting of cerebral amyloid angiopathy) but not other microbleeds in patients with an ICH.[215]

Regardless of stroke risk, there might be value in treating patients with hemorrhagic stroke with a statin. Statin therapy in such patients is associated with reduced influx of inflammatory white cells into the infarct zone, more rapid resolution of cerebral edema, increased angiogenesis, and better potential for survival and functional recovery.[216] In a Kaiser Permanente study including 3481 participants with hemorrhagic stroke, inpatient statin therapy was associated with a greater likelihood of being alive 30 days after presentation (odds ratio [OR], 4.25 [95% CI, 3.46–5.23]; $P<0.001$) and were more likely than untreated patients to be discharged home or to a rehabilitation facility (OR, 2.57 [95% CI, 2.16–3.06]; $P<0.001$). Participants whose statin therapy was discontinued were less likely to survive to 30 days compared with patients whose statin therapy was continued (OR, 0.16 [95% CI, 0.12–0.21]; $P<0.001$) and were less likely than statin users to be discharged home or to a rehabilitation facility (OR, 0.26 [95% CI, 0.20–0.35]; $P<0.001$).[217]

In a study from Taiwan, among propensity score–matched hemorrhagic stroke survivors, compared with no statin treatment, statin therapy was associated with lower all-cause mortality (32 versus 42%) and ischemic stroke and no difference in hemorrhagic stroke recurrence over 10 years.[218] A population-based study conducted in Denmark found that statin use within 1 year of ICH (OR, 0.92 [95% CI, 0.60–1.4]), last use between 8 days and 1 year (OR, 1.81 [95% CI, 0.99–3.28]), and statin use at the time of ICH (OR, 0.77 [95% CI, 0.49–1.21]) were not associated with the overall ICH risk among 157 patients with ICH and 884 controls with a history of ischemic stroke/TIA.[219] In another population-based study conducted in Denmark, the risk of hemorrhagic stroke was similar over 10 years for those who were and those who were not treated with a statin after a hemorrhagic stroke, and the risk of ICH was reduced by ≈42% to 66% in those with a history of ischemic stroke.[205]

Studies of the effects of statin continuation/discontinuation on neurological recovery and early mortality have several limitations such as prescriber bias, lack of information based on ICH location/cause, and lack of data on the exact cause of death.[220] In patients who have sustained a hemorrhagic stroke, statins have an unclear effect on the risk of recurrent ICH but may be associated with reduced risks of ischemic stroke and ASCVD events. Effects of statins on perihematomal edema remain unsettled.[210] Overall, available data on the risks and benefits of statin therapy on ICH outcomes and recurrence relative to overall prevention of cardiovascular events are unclear with data from prospective clinical trials lacking.

CONCLUSIONS

1. The available data consistently show that lowering LDL-C reduces the risk of adverse ASCD-related events in high-risk populations.
2. Although some older retrospective, case-control, and prospective longitudinal studies suggest that statins and LDL-C lowering are associated with cognitive impairment or dementia, the preponderance of observational studies and data from randomized trials do not support this conclusion, at least over the course of the trials that varied from a median of 1.6 to 6.0 years of follow-up. Additional studies are needed to ensure cognitive safety over longer periods of time. In the interim, contemporary guidelines recommending the risk-stratified attainment of lipid-lowering goals are reasonable.
3. The risk of a hemorrhagic stroke associated with statin therapy in patients without a history of cerebrovascular disease is small and consistently nonsignificant. There is no evidence that PCSK9 inhibitors or ezetimibe increases bleeding risk. There is no indication from either randomized studies or mendelian inheritance studies evaluating patients or populations with lifelong low LDL-C that they have enhanced vulnerability to hemorrhagic stroke, and there is little evidence that achieving very low levels of LDL-C increases that risk. It is clear, however, that lower LDL-C correlates with lower risk of overall stroke and stroke recurrence,

mostly related to a reduction in ischemic stroke. Concern about hemorrhagic stroke risk should not deter a clinician from treating LDL-C to guideline-recommended risk-stratified targets.

4. Data reflecting the risk of hemorrhagic stroke with statin treatment among patients with a history of hemorrhagic stroke are not robust. PCSK9 inhibitors have not been adequately tested in patients with prior ICH. Lipid lowering in this populations requires more focused study.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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†Significant.

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