APPENDIX 1

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APPENDIX 1A: CONFLICT OF INTEREST DECLARATIONS

In the spirit of transparency, participants reported any related activities - including expenses and/or honorariums for presentations for not-for profit organizations. No panel or scientific committee member has had a pharmaceutical industry related conflict in the past 3 years.

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
GUIDELINE PANEL									
Michel Cauchon MD, CCFP	Professor, Département de médecine familiale et d'urgence, Université Laval	No	No	No	No	No	Yes Systematic review on statins and primary prevention	No	No
Mike Cotterill MD CCFP	Assistant Professor, Division of Clinical Sciences, Northern Ontario School of Medicine University	No	No	Yes Co- applicant for a Northern Ontario Academic Medical Association grant, unrelated to cardiovascular disease	No	No	No	No	No
Norah Duggan MD CCFP FCFP	Associate Professor, Discipline of Family Medicine, Memorial University of	Yes ALARM course instructor and course director for	No	Yes Cox Award from Memorial University Faculty of Medicine for	No	No	No	No	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
	Newfoundland Faculty of Medicine	SOGC/CFPC-NL		medical education research					
Alex S Halme RPh MD FRCPC	Internist-geriatrician, CISSS Montérégie-Est (Hôpital Pierre-Boucher) and CISSS de la Gaspésie	Yes Conference for Société québécoise de gériatrie (topic was top 5 articles in the geriatric medicine literature in 2021)	No	Yes CIHR MSc grant for AI project (MSc), funding with access to Canadian longitudinal study on aging	No	No	No	Yes During rounds to residents, but not in formal context; sit on INESSS board for review of medications which include CV meds	No
Scott Klarenbach MD FRCPC MSc	Professor, Department of Medicine and Dentistry, University of Alberta	No	No	Yes Director of the Real World Evidence Consortium (Universities of Alberta and Calgary, Institute of Health Economics) that conduct investigator initiated, industry sponsored	No	No	Yes Co-author on 2 publications: Association between LDL-C and risk of myocardial infarction in CKD (2013) and Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-	Yes	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
				studies, authors retain academic freedom of publication; no current or planned studies are on individual drugs for CVD, although description of medication use in patients at CV risk (Type2 DM) is being performed			analysis (2011). Have also examined association of statin and AKI, cost-effectiveness of low / high potency statin. I did not receive industry funding for any of these.		
Michael R Kolber MD CCFP MSc	Professor, Department of Family Medicine, University of Alberta	Yes Expense reimbursement and honoraria from not for profits for presentations: CFPC, ACFP, SRPC, MEME Peterborough Health	No	Yes CIHR, PRUIS (collaborator), participant in publicly funded trials under Pragmatic Trials Collaboration (BedMed Trial)	No	Yes Founder of EMPRSS (University of Alberta spin off company that evaluates the quality of endoscopies performed)	Yes 2015 PEER lipid guideline author, various Tools for Practice	Yes Presented on CVD for primary care	No
Adrienne J Lindblad BSP ACPR PharmD	Clinical Evidence Expert Lead, College of	Yes Paid employee (CFPC 2020-	No	No	No	No	Yes Author of PEER's 2015 Simplified	Yes Various talks related to	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
	Family Physicians of Canada; Associate Clinical Professor, Dept. of Family Medicine, University of Alberta	present, ACFP 2013-2020); Speaker's honoraria (ACFP, SCFP, PEER, MEME, RxA, North of 44)					Lipid Guideline; Various Tools for Practice articles	the 2015 lipid guideline	
Raelene D Marceau BScN MN PhD	Assistant Professor, School of Nursing, University of Northern British Columbia	No	No	No	No	No	No	No	No
Tanis Poshtar	Patient	No	No	No	No	No	No	No	No
Loren D Regier BSP BA	Consultant Editor, RxFiles Academic Detailing	Yes Work for not-for-profit educational academic detailing services (RxFiles, Centre for Effective Practice)	No	No	No	No	Yes Various lipid reviews, trial summaries, and comparisons for non-profit (RxFiles Academic Detaling)	No	No
Rebecca Whitley MD	Assistant Professor,	No	No	No	No	No	No	No	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
CCFP	Department of Family Medicine, University of Manitoba								
EVIDENCE TEAM									
G Michael Allen MD CCFP	Director of Programs and Practice Support, College of Family Physicians of Canada	Yes Speaking (with travel and/or honorarium) for Diabetes Society Edmonton, ACFP family medicine summit and PEIP, SRPC, BS Medicine, NBCFP, OCFP, Peterborough Hosp Society, UBC CPD dept, Sharp HMO, WCB AB, worksafe BC, RxFiles, MEME conference, NLCFP. Nothing from drug industry	No	Yes BedMed (public funding: CIHR and PRIHS)	No	No	Yes Tools for Practice on CVD; hypertension systematic review; publications including risk assessment papers; simplified lipid guidelines	Yes Multiple talks on CVD, multiple times per year for last 10+ years.	Yes BS medicine risk calculator
Émélie Braschi	Lecturer, Department	Yes CFPC salary	No	No	No	No	No	No	Yes

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
MD CCFP PhD	of Family Medicine, University of Ottawa								CFPC Learn in the Clinic
Nicolas Dugré PharmD MSc BCACP	Pharmacist, CIUSSS du Nord-de-l'Ile-de-Montréal; Associate Professor, Faculty of Pharmacy, Université de Montréal	Yes Honoraria for articles and presentations: Fédération des médecins omnipraticiens du Québec, Ordre des pharmaciens du Québec, Uniprix, Familiprix, Jean-Coutu, College of Family Physicians of Canada, Association des pharmaciens du Saguenay-Lac-St-Jean, Société québécoise de la douleur, Fédération des pharmaciens du Québec,	No	Yes Research funded by non-industry related grants (Réseau-1 Québec and Fondation du Cercle du Doyen de la faculté de pharmacie de l'Université de Montréal)	No	No	No	Yes Presentation on hypolipemiants for the Federation des médecins omnipraticiens du Québec	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
		Pharmascope, EnsembleIQ.							
Jamie Falk BSc (Pharm) PharmD	Associate Professor, College of Pharmacy/ Department of Family Medicine, University of Manitoba	Yes Board member, conference organizer, speaker for Health Education Collaboration	No	Yes Ongoing grant to track and document opioid use and misuse in Manitoba, College of Pharmacists of Manitoba	No	No	No	Yes All of these are topics I am asked to speak on at conferences for pharmacists, physicians, and other health care professionals	No
Liesbeth S Froentjes MSc	Research Assistant, Department of Family Medicine, University of Alberta	Yes Independent contractor for CFPC	No	No	No	No	No	No	No
Scott Garrison MD CCFP PhD	Professor, Dept of Family Medicine, University of Alberta	No	No	Yes CIHR, Alberta Innovates; principal investigator for the publicly funded BedMed trial. I receive no funding from	No	No	Yes Evidence reviewer for the first Simplified Lipid Guideline	Yes CV risk reduction is often part of any talk on EBM or prevention, which I give periodically to learners or family	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
				these grants personally.				physicians at CME events	
Jessica EM Kirkwood MD CCFP (AM)	Assistant Professor, Department of Family Medicine, University of Alberta	Yes Speaker's honoraria from CFPC, ACFP and CPSS	No	No	No	No	No	No	No
Michael R Kolber MD CCFP MSc	Professor, Department of Family Medicine, University of Alberta	Yes Expense reimbursement and honoraria from not for profits for presentations: CFPC, ACFP, SRPC, MEME Peterborough Health	No	Yes CIHR, PRUIS (collaborator), participant in publicly funded trials under Pragmatic Trials Collaboration (BedMed Trial)	No	Yes Founder of EMPRSS (University of Alberta spin off company that evaluates the quality of endoscopies performed)	Yes 2015 PEER lipid guideline author, various Tools for Practice	Yes Presented on CVD for primary care	No
Christina Korownyk MD CCFP	Professor, Department of Family Medicine, University of Alberta	Yes Speaker at various conferences:	No	Yes BedMed Trial funded by CIHR, PRIHS	No	No	Yes Author on related Tools for Practice and Clinical practice guidelines have big problems: The fix is simple.	Yes Presented on primary and secondary prevention of CVD	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
Adrienne J Lindblad BSP ACPR PharmD	Clinical Evidence Expert Lead, College of Family Physicians of Canada; Associate Clinical Professor, Dept. of Family Medicine, University of Alberta	Yes CFPC; ACFP; SCFP; PEER; MEME; Alberta Pharmacists Association (RxA); North of 44 Primary Care Symposium; Paid employee (CFPC 2020-present, ACFP 2013-2020); Speaker's honararia (ACFP, SCFP, PEER, MEME, RxA, North of 44)	No	No	No	No	Yes Author of PEER's 2015 Simplified Lipid Guideline; Various Tools for Practice articles. Author: Clinical practice guidelines have big problems: The fix is simple.	Yes Various talks related to the 2015 lipid guideline	No
James P McCormack BSc (Pharm) PharmD	Professor, Faculty of Pharmaceutical Sciences, University of British Columbia	Yes Speaker at various conferences, BS Medicine Podcast, book: The Nutrition Proposition	No	No	No	No	Yes Author: Clinical practice guidelines have big problems: The fix is simple.	Yes I have given a number of talks on guidelines and lipids specifically over the last 2-3 years, all for non-	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
								profit organizations	
Samantha S Moe PharmD ACPR	Clinical Evidence Expert, College of Family Physicians of Canada	Yes ACFP, PEIP conference	No	No	No	No	No	Yes General CV topics that come up in New True Poo, Jeopardy, etc.	No
Allison Paige MD CCFP	Assistant Professor, Department of Family Medicine, University of Manitoba	Yes ACFP, speaker at the Family Medicine Summit 2022 - received an honorarium;	No	No	No	Yes Employee at the University of Manitoba Department of Family Medicine; Independent contractor at Winnipeg Regional Health Authority	Yes	No	No
Danielle Perry RN MSc	Clinical Evidence Expert, College of Family Physicians of Canada	Yes CFPC (employee), Correctional Services of Canada (employee), ACFP, PEER (PEIP + PEER North),	No	No	No	No	No	No	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
		Dalhousie CPD, Centre for Effective Practice (receipt of honoraria)							
Jen Potter MD CCFP	Assistant Professor, Department of Family Medicine, University of Manitoba	Yes	No	No	No	No	No	Yes Academic half-day sessions to family medicine residents	No
Betsy S Thomas BSc Pharm	Clinical Evidence Expert for the CFPC and Assistant Adjunct Professor in the Department of Family Medicine at the University of Alberta	Yes Honoraria received for talk at Family Medicine Summit, ACFP	No	No	No	No	Yes	Yes I have presented on various CV studies to family physicians and/or primary care providers as part of the Best Practice Support Program	No
Joey Ton PharmD	Program Manager, Programs and Practice Support Department, College of	No	No	No	No	No	Yes I have written "Tools for Practice" on PCSK-9 inhibitors	Yes I have presented on the evidence written	No

Name	Affiliation	Direct financial relationships	Advisory board or speaker's bureau	Funded grants, research, or clinical trials	Patents for a drug or device	Other investments or relationships	Written related articles	Presented on related topics	Apps, software, tools, etc.
	Family Physicians of Canada							about PCSK-9 inhibitors	
Justin Weresch MD CCFP	Assistant Professor, Department of Family Medicine, McMaster University	No	No	No	No	No	No	No	No
Jennifer Young MD CCFP (EM)	Associate Clinical Professor, Department of Family Medicine, McMaster University	Yes Speaker for OCFP; working for PEER team on pain guideline	No	No	No	No	No	Yes I have presented the Risk Calculator in a course "Practicing Wisely" and in a case of CFPC Clinic	No

ACFP = Alberta College of Family Physicians; AKI = acute kidney injury; ALARM = Advances in Labour and Risk Management; BC = British Columbia; CFPC = College of Family Physicians of Canada; CIHR = Canadian Institutes of Health Research; CISSS = Integrated Health and Social Services Centres; CIUSSS = Integrated University Health and Social Services Centre; CKD = chronic kidney disease; CME = Continuing Medical Education; CPD = Continuing Professional Development; CPSS = College of Physicians and Surgeons of Saskatchewan; CTFPHC = Canadian Task Force on Preventive Health Care; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; EBM = evidence-based medicine; INESSS = Institut National d'Excellence en Santé et Services Sociaux; LDL-C = low-density-lipoprotein-cholesterol; MEME = Making Evidence Matter for Everyone; NBCFP = New Brunswick College of Family Physicans; NLCFP = Newfoundland and Labrador College of Family Physicians; OCFP = Ontario College of Family Physicians; PCSK-9 = Proprotein convertase subtilisin/kexin type 9; PEER = Patients, Experience, Evidence, Research; PEIP = Practical Evidence for Informed Practice; PRIHS = Partnership for Research and Innovation in the Health System; RCT = randomized controlled trial; SCFP = Saskatchewan College of Family Physicians; SOGC = Society of Obstetricians and Gynaecologists of Canada; SRPC = Society of Rural Physicians of Canada; UBC CPD= University of British Columbia, Continuing Professional Development; U of A = University of Alberta; WCB AB = Workers' Compensation Board of Alberta

APPENDIX 1B: STRENGTH OF RECOMMENDATIONS SUMMARY

	RECOMMENDATION	STRENGTH
Screening and Testing		
1	In patients without CVD (primary prevention), we **suggest** lipid testing as part of global CVD risk estimation in men at age ≥ 40 y and women at age ≥50y. ● Testing can be considered earlier for patients with known traditional CVD risk factors including, but not limited to, hypertension, family history of premature CVD, chronic kidney disease, diabetes, and smoking.	Weak for
2	When reassessing cardiovascular risk in patients not taking lipid-lowering therapy, we **suggest** reassessing lipids no more than every 5 years and preferably 10, unless risk factors change.	Weak for
3	We **recommend against** fasting for lipid testing. Non-fasting lipids can be used to calculate global CVD risk.	Strong against
4	We **recommend against** risk estimation for those with pre-existing CVD as they are at high risk.	Strong against
5	We **suggest against** adding CAC scores to cardiovascular risk assessment.	Weak against
6	We **recommend against** using Lp(a) or apoB to determine a patient's cardiovascular risk.	Strong against
Interventions		
7	We **suggest** encouraging patients to participate in physical activity. The specific type, duration and intensity is likely less important than adherence.	Weak for
8	We **recommend** the Mediterranean diet to reduce cardiovascular risk.	Strong for
9	In primary prevention patients with a 10-y CVD risk of ≥ 20%, we **recommend** clinicians discuss the initiation of statins (preferably high-intensity) with patients.	Strong for
10	In primary prevention patients with a 10-y CVD risk of 10-19%, we **suggest** clinicians discuss the initiation of statins (preferably moderate-intensity statins) with patients.	Weak for
11	In primary prevention patients with a 10-y CVD risk of < 10%, we **suggest** retesting lipid levels in 5y at earliest, and preferably 10, with risk estimation.	Weak for
12	In primary prevention, we **recommend against** using non-statin lipid lowering drugs as monotherapy or in combination with statins.	Strong against
13	In secondary prevention, we **recommend** clinicians discuss the risks and benefits and encourage initiation of high-intensity statin therapy with patients.	Strong for
14	In secondary prevention, for patients desiring additional reductions in their cardiovascular risk beyond maximized statin therapy, we **recommend** a discussion of ezetimibe or PCSK-9 inhibitors. Given potential adverse effects (atrial fibrillation, bleeding), we **suggest** adding icosapent to statins only after considering ezetimibe or PCSK-9 inhibitors.	Strong for; Weak for
Considerations in Older Adults		

RECOMMENDATION		STRENGTH
15	In primary prevention patients over the age of 75, we **recommend against** lipid testing and the assessment of risk using a CVD risk calculator.	Strong against
16	We **suggest against** the routine initiation of statin therapy for primary prevention in patients over age 75. However, it may be reasonable to discuss the benefits and risks of statin therapy for primary prevention in some patients over age 75 whose overall health status is good.	Weak against
17	In patients over age 75 who have had a cardiovascular event, we **recommend** clinicians discuss the benefits and risks and encourage the initiation of statin therapy with patients.	Strong for
18	In patients already taking and tolerating a statin, we **recommend against** stopping the statin or reducing the dose just because patients have aged beyond 75y.	Strong against
19	We **recommend against** altering statin prescribing for cognitive concerns.	Strong against
Statin Intolerance		
20	In patients who do not tolerate a specific statin regimen due to non-severe muscle adverse effects, we **recommend** any statin intensity over non-statin lipid therapy. This could include different statins, doses, or alternate daily dosing, based on shared decision making.	Strong for
21	For primary prevention patients unable to tolerate any statin rechallenge, we **suggest against** use of non-statin pharmacologic therapies.	Weak against
22	For secondary prevention patients unable to tolerate any statin rechallenge, we **suggest** discussion of ezetimibe, fibrates, or PCSK-9 inhibitors. Given potential adverse events of icosapent (atrial fibrillation, bleeding), it should only be considered once other options explored.	Weak for
Follow-Up		
23	We **recommend against** the use of repeat lipid testing and cholesterol targets after a patient begins lipid-lowering therapy.	Strong against
24	We **suggest against** testing for baseline CK or ALT levels in healthy, asymptomatic individuals before starting statin therapy. Testing may be appropriate based on symptoms or other risk factors.	Weak against

ALT = alanine transaminase; apoB = apolipoprotein B; CAC = coronary artery calcium; CK = creatine kinase; CVD = cardiovascular disease; Lp(a) = lipoprotein A; PCSK-9 = proprotein convertase subtilisin/kexin type 9

APPENDIX 1C: UPDATED RECOMMENDATIONS MATRIX

*Table 1: VA/DoD recommendation categories and definitions**

Evidence Reviewed	Recommendation Category	Definition
Reviewed	New-added	New recommendation following review of the evidence

Evidence Reviewed	Recommendation Category	Definition
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation was not changed
	Amended	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment was made
	Deleted	Recommendation from previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from **The Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020** with permission from the US Department of Veterans Affairs, Department of Defense
CPG = clinical practice guideline; NICE = National Institute for Health and Care Excellence

Table 2: Updated guideline recommendations matrix

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
SCREENING			
In patients without CVD (primary prevention), we suggest lipid testing as part of global CVD risk estimation in men at age ≥ 40 y and women at age ≥ 50 y.	Not reviewed	Amended	In patients without CVD (primary prevention), we suggest lipid testing as part of global CVD risk estimation in men at age ≥ 40 y and women at age ≥ 50 y. Testing can be considered earlier for patients with known traditional CVD risk factors including, but not limited to, hypertension, family history of premature CVD, chronic kidney disease, diabetes, and smoking.

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
Testing can be considered earlier for patients with known traditional CVD risk factors including, but not limited to, hypertension, family history of premature CVD, diabetes, and smoking.	Not reviewed	Deleted	
For patients not taking lipid-lowering therapy, we suggest lipid testing as part of global CVD risk estimation, performed no more than every 5 y (moderate-level evidence). Global CVD risk estimation can be repeated sooner if other CVD risk factors develop in the interim.	Reviewed	Amended	When reassessing cardiovascular risk in patients not taking lipid-lowering therapy, we suggest reassessing lipids no more than every 5 years and preferably 10, unless risk factors change.
Patients do not need to fast for lipid testing. Nonfasting lipid levels can be used to calculate global CVD risk.	Not reviewed	Amended	We recommend against fasting for lipid testing. Nonfasting lipids can be used to calculate global CVD risk.
RISK ASSESSMENTS			
Primary prevention: We encourage risk estimation with a CVD risk calculator (e.g., Framingham) every time lipid testing is performed. Testing and risk estimation should be performed starting at age 40 y in men and 50 y in women (or earlier if indicated by other risk factors) until age 75 y.	Not reviewed	Deleted	
Primary prevention in patients with diabetes mellitus: We encourage risk estimation as above.	Not reviewed	Deleted	
Primary prevention in patients with CKD: We recommend using a CVD risk calculator (e.g., QRISK2) that includes CKD in its estimation of risk.	Not reviewed	Deleted	
We discourage risk estimation for those with pre-existing CVD, as they are automatically at high risk.	Not reviewed	Amended	We recommend against risk estimation for those with pre-existing CVD as they are at high risk.
We discourage risk estimation for those < 40 y (without additional risk factors) and those > 75 y,	Not reviewed	Deleted	

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
as risk equations are not based on patients in these age ranges.			
We discourage risk estimation for those taking lipid therapy, as calculators are not designed to adjust for changes with lipid therapy. If risk calculation is desired for patients taking lipid therapy, pre-treatment lipid levels should be used and risk should be adjusted for known benefits of statin or ASA therapy.	Not reviewed	Deleted	
We discourage the use of biomarkers as part of risk assessment until further evidence is available.	Reviewed	New-replaced	We suggest against adding CAC scores to cardiovascular risk assessment.
		New-replaced	We recommend against using Lp(a) or apoB to determine a patient's cardiovascular risk.
INTERVENTIONS			
Lifestyle interventions, including but not limited to smoking cessation, Mediterranean diet, and exercise, should be discussed with all patients.	Reviewed	New-replaced	We suggest encouraging patients to participate in physical activity. The specific type, duration, and intensity is likely less important than adherence.
		New-replaced	We recommend the Mediterranean diet to reduce cardiovascular risk.
Secondary-prevention patients: We strongly encourage clinicians to discuss the risks and benefits of high-intensity statin therapy with patients.	Reviewed	Amended	In secondary prevention, we recommend clinicians discuss the risks and benefits and encourage initiation of high-intensity statin therapy with patients.
Primary-prevention patients: We suggest clinicians discuss the risks and benefits of moderate- or high-intensity statins with their patients based on an individual’s risk of CVD.	Not reviewed	Deleted	
Primary prevention patients: For patients with a 10-y CVD risk of <10%, we suggest retesting lipid levels in 5 y with risk estimation.	Reviewed	Amended	In primary prevention patients with a 10-y CVD risk of < 10%, we suggest retesting lipid levels in 5 y at earliest, and preferably 10, with risk estimation.
Primary prevention patients: For patients with a 10-y CVD risk of 10%-19%, we suggest clinicians	Reviewed	Amended	In primary prevention patients with a 10-y CVD risk of 10-19%, we suggest clinicians discuss the

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
discuss initiation of statins (preferably moderate-intensity statins) with patients.			initiation of statins (preferably moderate-intensity statins) with patients.
Primary prevention patients: For patients with a 10-y CVD risk of ≥20%, we strongly encourage clinicians to discuss initiation of statins (preferably high-intensity) with patients.	Reviewed	Amended	In primary prevention patients with a 10-y CVD risk of ≥ 20%, we recommend clinicians discuss the initiation of statins (preferably high-intensity) with patients.
Patients who are elderly (based on frailty as much as age) or those with renal impairment can be offered lower-intensity statin therapy (low-level evidence).	Not reviewed	Deleted	
Primary prevention patients > 75 y: We discourage routinely testing lipid levels, estimating CVD risk, and prescribing statins (moderate-level evidence).	Reviewed	Amended	In primary prevention patients over the age of 75, we recommend against lipid testing and the assessment of risk using a CVD risk calculator.
Primary prevention patients > 75 y: Some patients > 75 y whose life expectancy and overall health status are good can be offered statin therapy for primary prevention, but this should be left to the clinician and patient's discretion (low-level evidence).	Not reviewed	Amended	We suggest against the routine initiation of statin therapy for primary prevention in patients over age 75. However, it may be reasonable to discuss the benefits and risks of statin therapy for primary prevention in some patients over age 75 whose overall health status is good.
Secondary prevention patients >75 y: We strongly encourage clinicians to discuss the risks and benefits of moderate-intensity statins with patients (high-level evidence).	Reviewed	Amended	In patients over age 75 who have had a cardiovascular event, we recommend clinicians discuss the benefits and risks and encourage the initiation of statin therapy with patients.
Secondary prevention patients > 75 y: Patients already taking and tolerating a statin should not have their statin stopped or reduced just because they have aged beyond 75 y (low-level evidence).	Reviewed	Amended	In patients already taking and tolerating a statin, we recommend the statin not be stopped or reduced just because they have aged beyond 75 y.
In patients ≥ 65 y, pravastatin should likely not be considered first-line therapy until uncertainty	Reviewed	Deleted	

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
surrounding cancer in this subgroup with this drug is resolved (moderate-level evidence).			
	Reviewed	New-added	We recommend against altering statin prescribing for cognitive concerns.
Patients who do not tolerate a specific statin regimen should be offered a lower-intensity regimen, with either the same or a different statin, or a short drug holiday followed by rechallenge to help clarify if statins are related to the intolerance.	Reviewed	Amended	In patients who do not tolerate a specific statin regimen due to non-severe muscle adverse effects, we recommend any statin intensity over non-statin lipid therapy. This could include different statins, doses, or alternate daily dosing, based on shared decision making.
In patients who do not tolerate a specific statin regimen, any statin intensity is preferred to non-statin lipid-lowering therapy.	Reviewed	Deleted	
In patients who do not tolerate a specific statin regimen, alternate daily dosing can be considered if a patient does not tolerate daily dosing.	Reviewed	Deleted	
	Reviewed	New-added	For primary prevention patients unable to tolerate any statin rechallenge, we suggest against use of non-statin pharmacologic therapies.
	Reviewed	New-added	For secondary prevention patients unable to tolerate any statin rechallenge, we suggest discussion of ezetimibe, fibrates, or PCSK-9 inhibitors. Given potential adverse events of icosapent (atrial fibrillation, bleeding), it should only be considered once other options explored.
In patients who have severe reactions like rhabdomyolysis, retrial might not be appropriate.	Not reviewed	Deleted	
In primary prevention, non-statin lipid-lowering drugs should not be used as first-line monotherapy or in combination with statins.	Reviewed	Amended	In primary prevention, we recommend against using non-statin lipid lowering drugs as monotherapy or in combination with statins.
In secondary prevention, ezetimibe can be considered in discussion with patients as add-on	Reviewed	New-replaced	In secondary prevention, if additional cardiovascular risk reduction is desired beyond

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
therapy to statins, but owing to the higher relative benefit of statins, statin therapy should be maximized first (to high intensity).			maximized statin therapy, we recommend a discussion of ezetimibe or PCSK-9 inhibitors. Given potential adverse effects (atrial fibrillation, bleeding), we suggest adding icosapent to statins only after considering ezetimibe or PCSK-9 inhibitors.
FOLLOW-UP			
The use of cholesterol targets for reducing CVD is not required.	Reviewed	Amended	We recommend against the use of repeat lipid testing and cholesterol targets after a patient begins lipid-lowering therapy.
We suggest that the monitoring of repeat lipid levels after a patient begins lipid-lowering therapy is not required. - Adherence to statins can be improved with patient reinforcement.	Reviewed	Deleted	
We suggest that testing for baseline CK or ALT levels in healthy individuals before starting statin therapy is generally unnecessary. The evidence against testing baseline ALT or CK levels is poor and some clinicians might prefer to test one or both.	Not reviewed	Amended	We suggest against testing for baseline CK or ALT levels in healthy, asymptomatic individuals before starting statin therapy. Testing may be appropriate based on symptoms or other risk factors.
Routine monitoring of CK and ALT levels should be reserved for those patients who are symptomatic or who are at higher risk of adverse events. Frequency should be determined at the discretion of the attending clinician.	Not reviewed	Deleted	
PRIMARY PREVENTION WITH ASA			
We discourage the use of ASA for patients without previous CVD and an estimated 10-y CVD risk < 20%.	Not reviewed	Deleted	

2015 Recommendation	Evidence Reviewed?	Recommendation Category	2023 Recommendation
We suggest ASA can be considered in primary prevention if the 10-y CVD risk is ≥ 20% and bleeding risk is low.	Not reviewed	Deleted	
Use of ASA for primary CVD prevention should be considered after statin therapy has been discussed.	Not reviewed	Deleted	
Patients offered ASA should be informed of the potential benefits and harms of ASA use.	Not reviewed	Deleted	

ALT = alanine transaminase; apoB = apolipoprotein B; ASA = acetylsalicylic acid; CAC = coronary artery calcium; CK = creatine kinase; CKD = chronic kidney disease; CVD = cardiovascular disease; Lp(a) = lipoprotein A; PCSK-9 = proprotein convertase subtilisin/kexin type 9

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APPENDIX 1D: SUPPLEMENTAL QUESTIONS

TABLE OF CONTENTS

Introduction and Methods

INTRODUCTION

This document comprises answers to various clinical questions surrounding the management of cardiovascular disease in a primary care setting. The answers explore nonpharmacological interventions for management of cardiovascular disease, the utility of screening, and treatment in an older adult population.

METHODS

Each supplemental question was answered using a rapid review process and was assigned to two members of the evidence team for completion. The team drafted questions using the PICO (patient, intervention, comparator, outcome) format, and subsequently performed searches in several medical databases, including Medline, Cochrane, PubMed, and Google Scholar. Due to the varied nature of the supplemental questions, each team tailored their exact search strategy to meet the requirements of their PICO question. For example, questions examining cardiovascular screening focused on screening and diagnostic study designs. Additionally, all teams examined major cardiovascular guidelines published within the previous five years to further identify relevant evidence and examine similar recommendations (**Grundy 2019; Mach 2020; Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; Pearson 2021; US Preventive Services Task Force 2016; Visseren 2021**). Each unique search strategy is presented in each supplemental question section.

The answers are formatted to contain a bottom-line statement, the evidence and limitations concerning the included studies, the surrounding context, and more detailed methods where needed. Risk of bias assessments (**Higgins 2011; Lee 2022; Shea 2009**), and GRADE evaluations (**Balshem 2011**) for the primary outcome were also completed for each question.

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CHAPTER 1: CORONARY ARTERY CALCIUM AND CARDIOVASCULAR RISK PREDICTION

CLINICAL QUESTION

1. In patients without established cardiovascular disease, does the use of coronary artery calcium scores change cardiovascular disease risk estimation meaningfully more than standard risk estimates (e.g., age, smoking) alone?
2. In patients without established cardiovascular disease, how does risk estimation with coronary artery calcium scores compare to risk estimates using standard risk factors (e.g., age, smoking)?

BOTTOM LINE

Adding coronary artery calcium (CAC) to cardiovascular (CV) risk assessment likely leads to a small increase in c-statistics of ~0.04, with unclear clinical significance. On its own, CAC for CV risk assessment has acceptable discrimination (c-statistics ~0.77 for CV events) and is likely comparable to other CV risk assessment tools such as the Framingham risk score (FRS) based on low quality evidence. Randomized controlled trials (RCTs) are ongoing to compare the effects of screening with CAC or CV risk factor assessment on hard cardiovascular disease (CVD) endpoints.

EVIDENCE

Quality assessment and summary data of included studies can be found in *Tables 1A-C* and *Tables 2A-C*. GRADE certainty of evidence evaluation can be found in *Tables 3A-B*.

CAC added to traditional risk factors for CV risk assessment: discrimination

See *Tables 1A-C* for quality assessment and summary of systematic reviews (SRs)

- **Bell 2022**: meta-analysis of six cohort studies (N = 17,961)
    - For Framingham Risk Score, pooled cohort equation, or risk factors:
        - C-statistic range: 0.69-0.80
        - 0 out of 6 studies had c-statistic > 0.8
    - For CAC added to the above risk factor assessments:
        - C-statistic range: 0.73-0.85
        - 2 out of 5 studies had c-statistic > 0.8, one not reported
    - Pooled gain in c-statistic: 0.036 (95% confidence interval [CI] 0.020 to 0.052)
- Four SRs of 3-9 cohort studies, including one study published twice **(Peters 2012a, Peters 2012b, Lin 2018, Aparicio 2021)**:
    - Median change in c-statistic for each SR ranged from: 0.04-0.05.

CAC as a stand-alone score for CV risk assessment: discrimination

See *Tables 2A-C* for quality assessment and summary of observational studies.

- No SRs, five cohort studies identified
    - CV outcomes, 4 cohort studies (N = 1,912-66,636) **(Nakanishi 2021, Dzaye 2020, Geisel 2017, Commandeur 2020)**
        - Median area-under-the-curve (AUC): 0.77 (interquartile range 0.70-0.79)

        - Heterogeneity due to outcomes and cohort studied
    - All-cause mortality, 2 cohort studies (N = 4,915-54,678) **(Dzaye 2020, Han 2020)**
        - Median AUC: 0.68
- Three studies provided the AUC of CAC alone compared to a CV risk assessment (no statistics provided; see table below for details)

Study	Outcome	AUC for CAC	AUC for CV risk assessment
Nakanishsi 2021	10-year CVD death	0.78	ASCVD: 0.82
Geisel 2017	10-year MACE	0.70	FRS: 0.69
Commandeur 2020	15-year MI and/or cardiac death	0.77	ASCVD: 0.77

ASCVD = atherosclerotic cardiovascular disease; AUC = area under the curve; CVD = cardiovascular disease; FRS = Framingham risk score; MACE = major adverse cardiovascular events; MI = myocardial infarction

CAC with extensive screening versus standard of care: indirect RCT evidence

- DANCAVAS RCT **(Lindholt 2022)**: 46,611 men (mean age 69 years) randomized to comprehensive CV screening with treatment recommendations versus standard of care
    - Screening included assessment of CAC score to identify scores greater than sex/age median; screening for atrial fibrillation, aortic and iliac aneurysms, diabetes, and hyperlipidemia; ankle-brachial index and blood pressure measurements
    - At 5.6 years:
        - Mortality: 12.6% versus 13.1% (control) (Hazard Ratio [HR] 0.90, 95% CI 0.90 to 1.00)
        - Stroke: 7% versus 7.5% (control) (HR 0.93, 95% CI 0.86 to 0.99)
        - Acute myocardial infarction: 2.6% versus 2.8% (control) (HR 0.91, 95% CI 0.81 to 1.03)

CONTEXT

The Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM) is an example of a calculator that incorporates traditional risk factor information with CAC score to provide an individual's estimated 10-year risk of CVD events https://astrocharm.org/calculator-working/.

Discrimination

Discrimination is defined as the ability to identify individuals who will have an event, and can be assessed with AUC (which is equivalent to the c-statistic). A c-statistic value of 1.00 is perfect, 0.8 is good, 0.6-0.7 is acceptable, and 0.5 is similar to chance **(Allan 2014)**. A change in the c-statistic of ≥0.1 is large, 0.05-0.1 is moderate, 0.025-0.05 is small, and <0.025 is very small **(Lin 2018)**.

Ongoing RCTs

- **CorCal**: randomized 9,000 patients (primary prevention) to screening with CV risk factors (using Pooled Cohort Equation) or CAC, with recommendations made to the physician **(Muhlestein 2022)**. Estimated completion 2024 **(Greenland 2022)**.

- **ROBINSCA**: randomized 43,447 patients (high risk primary prevention) to screening with CV risk factors (using SCORE calculator) or CAC (with recommendations made to the physician), or care as usual (finished enrolment in 2021, only behavioural outcomes published so far) **(Denissen 2019)**. Final results expected in 2023 **(Vonder 2020)**.

Radiation and CT examination

Radiation exposure per CT examination is low: 1-2 millisievert **(Lin 2018, Nasir 2022)**. One millisievert is similar to that of bilateral mammogram or transatlantic flight **(Nasir 2022)**.

Major guideline recommendations

Recent guidelines recommendations vary from no specific recommendations to using CAC in selected intermediate- or low-risk individuals. See Appendix *Table 4* for a summary of CV guideline recommendations for CAC screening.

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METHODS

- 105 references identified from guidelines related to CAC **(Arnett 2019, Grundy 2018, Lin 2018, Mach 2020, Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020, Pearson 2021, UPSTF 2022, Visseren 2021)**.
- Duplicates removed: 91 references
- Titles and abstract +/- full text screened for RCT / Systematic Reviews (SR): 10 references
- Forward searched all 10 references with Google Scholar (used first 10 pages), restricted to trial OR "systematic review" if more than 10 pages – Sep 26, 2022: 28 references
- Searched PubMed for "Coronary Calcium Score" with filter: last 5 years, RCT and systematic review: 2 additional references Sep 28, 2022
- Searched Google scholar for "AUC" "CAC" "systematic review" – screened title / abstract +/- full text for cohort / SR – Nov 03, 2022. Identified **Tramontano 2022** (SR looking at the prognostic value of CAC)
- Backward reference searched **Tramontano 2022** to identify articles reporting AUC for CAC only using cohort > 1000 patients: 6 references
- Duplicate search done on November 30, 2022:
    - Pubmed: using terms "coronary artery calcium," "AUC," "area under the curve," "coronary calcium" and filtered to clinical study, systematic review, meta-analysis or clinical trial.
    - Google scholar: using advanced search with terms "AUC", "coronary artery calcium," "trial," "study."

Search results 27; removal of duplicates yielded two additional citations.

APPENDIX

Table 1A: Quality assessment of systematic reviews assessing discrimination of coronary artery calcium added to traditional risk factors for cardiovascular risk assessment using AMSTAR-2

Study	AMSTAR-2 rating	Critical weakness
Bell 2022	Low	No explicit mention pre-specification of protocol
Peters 2012a and b	Critically low	No explicit mention pre-specification of protocol; no comprehensive literature search
Lin 2018	Moderate	More than one non-critical weakness
Aparicio 2021	Low	No explicit mention pre-specification of protocol

AMSTAR-2 = Assessment of Multiple Systematic Reviews

Table 1B: Summary of systematic reviews characteristics assessing discrimination of coronary artery calcium added to traditional risk factors for cardiovascular risk assessment

Study	No. observational studies	No. patients	Population	Mean age (range, years)	% women	Mean follow-up (years)
Bell 2022	6	17,961 (Range: 470-5,185)	Primary prevention	50-75	38.4-59.4%	4.4-10.3
Peters 2012a and Peters 2012b	9	Range: 676-6,722	Primary prevention, no DM	52-70	10-69%	2.7-9.2
Lin 2018	18	60,486 (Range: 946-7,772)	Primary prevention	NA	NA	NA
Aparicio 2021	6	Range: 274-6,500	Primary prevention	41.7-68.9	47.8-56%	9-13

DM = diabetes mellitus; NA = not applicable

*Table 1C: Summary of systematic review results assessing discrimination of coronary artery calcium added to traditional risk factors for cardiovascular risk assessment**

Study	No. studies	Outcome	Base model description	Base model: C-statistic	Model with CAC: C-statistic	Change in C-statistic median (IQR)
Bell 2022	6	CVD and CHD	FRS, PCE, or risk factors	0.693-0.80	0.731-0.851	0.036 (0.02-0.05)
Peters 2012a (and Peters 2012b)	9	Fatal and non-fatal CHD or CVD	FRS or risk factors	0.30-0.79	0.69-0.86	0.05 (0.04-0.07)
Lin 2018	5	"Hard" CHD or "Hard" CVD	FRS	0.63-0.76	0.68-0.834	0.05 (0.04-0.07)
Aparicio 2021	3	MACE, ischemic coronary events, stroke, sudden cardiac death	FRS or risk factors	0.66-0.75	0.76-0.77	0.04 (0.01-0.05)

*When extracting data where multiple endpoints were available, we chose all participants, "major" over "any" endpoints, "hard" over "total" or "soft" endpoints, and FRS over ATP III.
ATP III = Adult Treatment Panel III; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; FRS = Framingham risk score; IQR = interquartile range; MACE = major adverse cardiovascular events; PCE = pooled cohort equation

Table 2A: Quality assessment of cohort studies assessing discrimination of coronary artery calcium alone for cardiovascular risk assessment using QUAPAS

Study	Participants	Index test	Outcome	Flow and timing	Analysis
Dzaye 2020	Low	Low	Low	Low	Unclear
Nakanishi 2021	Low	Low	Low	Low	Unclear
Geisel 2017	Low	Low	Low	Unclear	Unclear
Commandeur 2020	Low	Low	Low	High	High
Han 2020	Unclear	Low	Low	High	Unclear

QUAPAS = Quality Assessment of Prognostic Accuracy Studies

Table 2B: Summary of cohort study characteristics assessing discrimination of coronary artery calcium alone for cardiovascular risk assessment

Study	Design	No. patients	Population	Mean age (years)	% Women	Median follow-up (years)	Comparisons/comments
Dzaye 2020	Cohort (retrospective)	54,678	Primary prevention	54.2	34.4%	11.7	"CAC-Data and Reporting System" vs standard CAC scores
Nakanishi 2021	Cohort (retrospective)	66,636	Primary prevention	54	33%	10	Machine Learning vs ASCVD assessment vs CAC scores
Geisel 2017	Cohort (prospective)	4,814	Primary prevention	59.2	53%	10.3	CAC vs FRS vs FRS+CAC
Commandeur 2020	Cohort (prospective)	1,912	Primary prevention	55.8	41.6%	14.5	Machine Learning vs ASCVD risk vs CAC
Han 2020	Cohort (retrospective)	4,915	Primary prevention	54.9	33%	5.4	CAC vs FRS+CAC vs ASCVD+ CAC vs Machine Learning; used validation model

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; FRS = Framingham risk score

Table 2C: Summary of cohort study results assessing discrimination of coronary artery calcium alone for cardiovascular risk assessment

Study	**C-statistic/AUC** CVD death	**C-statistic/AUC** CHD death	**C-statistic/AUC** All-cause mortality	**C-statistic/AUC** Composite outcome	Notes
Nakanishi 2021	0.781 (ASCVD: 0.821)	0.816 (ASCVD: 0.834)	NA	NA	
Dzaye 2020	0.754	0.785	0.696	NA	

Study	**C-statistic/AUC** CVD death	**C-statistic/AUC** CHD death	**C-statistic/AUC** All-cause mortality	**C-statistic/AUC** Composite outcome	Notes
Geisel 2017	NA	NA	NA	0.703 (FRS: 0.693)	Composite outcome: incident coronary events, stroke or CV death
Commandeur 2020	NA	NA	NA	0.77 (ASCVD: 0.77)	Composite outcome: MI and/or cardiac death
Han 2020	NA	NA	0.67	NA	

ASCVD = atherosclerotic cardiovascular disease; AUC = area under the curve; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; FRS = Framingham risk score; MI = myocardial infarction; NA = not applicable

Table 3A: GRADE certainty of evidence for CAC added to risk factors to calculate risk of MACE

Prognostic factor: CAC added to risk calculator

Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient	Effect estimate (range)	Certainty
SR*	4 (274-7,772)	Not serious	Not serious	Serious Study populations and outcomes correspond to targeted population. However, various definitions of MACE used.	Not serious	Not detected	No	No	No	Median C-stat. 0.73-0.85	Moderate This outcome has one serious **(-1)** therefore **downgrade by 1 to moderate**

*SR of observational studies (primarily cohort)
†Primary prevention studies with broad eligibility criteria
CAC = coronary artery calcium; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MACE = major adverse cardiovascular events; SR = systematic review

Table 3B: GRADE certainty of evidence for use of CAC alone to calculate risk of MACE

Prognostic factor: CAC score on its own
Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient	Effect estimate (range)	Certainty
Cohort	2 (6,726)	Serious Primary prevention studies with mostly broad eligibility criteria (1 long-term FU of an RCT)	Not serious	Serious Study populations and outcomes correspond to targeted population; however, various definitions of MACE used.	Not serious	Not detected	No	No	No	C-stat. 0.703 and 0.77	Low This outcome has two serious **(-2)** therefore **downgrade by 2 to low**

*SR of observational studies (primarily cohort)
†Primary prevention studies with broad eligibility criteria
CAC = coronary artery calcium; FU = follow-up; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MACE = major adverse cardiovascular events; RCT = randomized controlled trial

Table 4: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
In patients without established CVD, does the use of CAC scores change CVD risk estimation meaningfully more than standard risk estimates (e.g., age, smoking) alone? In patients without established CVD, how does risk estimation with CAC scores compare to risk estimates using standard risk factors (e.g., age, smoking)?	"In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy. 'Intermediate-risk' patients defined as having ASCVD risk 7.5%-20%. 'Borderline risk' adults defined as 10y risk of ASCVD 5-7.5%. In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND CAC score = 0: reasonable to withhold statin therapy and reassess in 5-10	"CAC score assessment with CT may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low or moderate risk."	Suggest against the routine use of CAC testing. Suggest against the routine use of additional risk markers (including CAC) when assessing cardiovascular risk.	"We suggest that CAC screening using CT imaging might be considered for asymptomatic adults ≥40 years of age and at intermediate risk (FRS 10-19%) for whom treatment decisions are uncertain. We recommend that CAC screening using CT imaging not be undertaken for 1) high-risk individuals; 2) patients receiving statin treatment or 3) most asymptomatic, low-risk adults. We suggest that CAC screening might be considered for a subset of low-risk individuals 40 years of age or older with a family history of premature ASCVD (men ≤ 55y, women ≤ 65 years) in addition to	"CAC scoring may be considered to improve risk classification around treatment decision thresholds."	No specific recommendations.

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
	years, as long as higher risk conditions are absent (e.g. diabetes, family history of premature CHD, cigarette smoking) CAC score =1-99: reasonable to initiate statin therapy for patients ≥ 55 years old CAC score >100 (or ≥ 75th percentile), reasonable to initiate statin therapy. For adults 76-80 years of age with LDL 1.7 to 4.8mmol/L: may be reasonable to measure CAC to reclassify those with a score of zero to avoid statin therapy."			identifying known genetic causes of ASCVD such as elevated Lp(a) or FH."		

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CT = computerized tomography; CVD = cardiovascular disease; FH = familial hypercholesterolemia; FRS = Framingham risk score; LDL = low-density lipoprotein; Lp(a) = lipoprotein A

CHAPTER 2: LIPOPROTEIN A AND CARDIOVASCULAR RISK PREDICTION

CLINICAL QUESTION

In patients without established cardiovascular disease, does the addition of lipoprotein A meaningfully change cardiovascular disease risk estimation compared to standard risk estimates (e.g., age, smoking) alone?

BOTTOM LINE

Adding lipoprotein A (Lp[a]) to current cardiovascular (CV) risk calculators does not meaningfully add to cardiovascular disease (CVD) risk prediction.

EVIDENCE

Since the 2015 PEER guideline **(Allan 2015)**, there have been 2 descriptive systematic reviews (SRs) (**Forbes 2016, Kouvari 2019a)** and 11 additional observational studies published **(Agarwala 2016, Delabays 2021, Guertin 2021, Kouvari 2019b, Mehta 2020, Nomikos 2015, Pare 2019, Patel 2021, Verbeek 2017, Welsh 2022, Wilsgaard 2015).** From the 2 SRs, we identified 5 observational studies which met our inclusion criteria **(Pernod 2006, Foscolou 2018, Tunstall-Pedoe 2017, Cao 2017, Waldeyer 2017)**. We chose to report these studies individually as "meta-analysis was not possible due to heterogeneity in the CVD outcomes, populations and statistical analysis methods" **(Forbes 2016)** and not all included studies met our criteria. A summary of study characteristics and efficacy data is reported in *Tables 1A-B*. Quality assessment of included studies can be found in *Tables 2A-B*. GRADE certainty of evidence evaluation can be found in *Table 3*. All evidence statistically significant unless noted.

We found Lp(a) risk ratios (RRs)/hazard ratios (HRs)/odds ratios (ORs) to predict CVD ranged from 1.00 to 2.21. In comparison, the RR for non-traditional risk markers like leucocyte count and pro-insulin were 1.45 and 2.23, respectively. These numbers are not dissimilar to the number for Lp(a), or apolipoprotein B (apoB). In one study, **Wilsgaard 2015,** Lp(a) and three other biomarkers (ApoB/ApoA ratio, plasma kallikrein, and matrix metalloproteinase 9) were added to traditional risk factors and found the area under the receiver operator characteristic curve (ROC-AUC) to be 0.027 for 10-year incident myocardial infarction (MI), a change that is likely not clinically meaningful.

Results of 16 observational studies (N = 279-340,339).

- **Welsh 2022**: one of the largest and most relevant cohorts (N = 340,339; UK participants; median 8.9 years) as it met our population inclusion criteria (adults without CVD who were not taking statins) and included results presented in a manner that was more optimal when answering questions about the additive effect of biomarkers (e.g., C-statistics, net reclassification index).
    - *Incident CVD*: When added to classical risk factors such as age, sex, total cholesterol and high-density-lipoprotein-cholesterol (HDL-C), Lp(a) per 1-standard deviation increase (compared to reference of Lp(a)<20 nmol/L) resulted in a HR of 1.13 (95% CI 1.10 to 1.16), change in C-index of +0.0017 (95% CI 0.0008 to 0.0026), and overall net reclassification index of +0.0112% (95% CI

+0.0039 to +0.0184), all of which are considered very small changes in the c -statistic and unlikely clinically meaningful **(Welsh 2022)**

Outcomes by Lp(a) cutoffs

- *≤30 mg/dL versus >30 mg/dL*
    - In a cohort of adults aged 22-92 (N = 279), a significant increase in CVD events and CV death was found with higher Lp(a) levels, HR 1.67 (95% CI 1.04 to 2.63) **(Pernod 2006)**
- *<50 mg/dL vs ≥ 50 mg/dL*
    - In a cohort of Swiss adults aged 35-75 (N = 4,829), C-statistic difference = 0.004 between Lp(a) <50 vs ≥50 mg/dL when added to the ESC/SCORE algorithm to predict incident atherosclerotic cardiovascular disease (ASCVD), and overall net reclassification index was 3.3% (95% CI 0.8 to 5.8), both of which were not clinically meaningful **(Delabays 2021)**
    - In the EPIC-Norfolk cohort of adults aged 40-79 (N = 25,663), Lp(a) ≥50 mg/dL was associated with an increase in coronary artery disease (myocardial ischemia, MI, or other ischemic heart disease), HR 1.50 (95% CI 1.38 to 1.64) **(Guertin 2020)**
    - In the ATTICA cohort of healthy adults from Greece (mean age 46; N = 1,890), a significant increase in 10-year CVD event rate was found with Lp(a) ≥50 mg/dL when adjusting for other lipid markers and statins (HR 2.21 [95% CI 1.15 to 4.21])
        - This increase was no longer significant when the cut point was lowered to 30 mg/dL (HR 1.18 [95% CI 0.82 to 1.60]) **(Kouvari 2019b)**
    - In a case control study of the INTERHEART cohort of participants (N = 12,943), a significant increase in MI was reported with Lp(a) ≥50mg/dL, OR 1.48 (95% CI 1.32 to 1.67) **(Pare 2019)**
    - In the EPIC-Norfolk cohort of adults (N = 16,777), the net reclassification index for CVD when Lp(a) ≥50 mg/dL added to ACC/AHA (American College of Cardiology/American Heart Association) traditional risk factors was -2.27% (95% CI not reported)
        - When added to SCORE (Systematic Coronary Risk Evaluation) traditional risk factors, the net reclassification index was 0.53% (95% CI not reported)
        - When the cut point was lowered to 30 mg/dL, Lp(a) added to ACC/AHA resulted in net reclassification index of -2.76% (95% CI not reported) and when added to SCORE, the net reclassification index was 0.57% (95% CI not reported) **(Verbeek 2017)**
- *<70 mg/dL vs ≥70 mg/dL*
    - In a cohort of UK Biobank participants aged 40-69 (N = 460,506), Lp(a) ≥150 nmol/L (~70 mg/dL) was associated with a significant increase in incident ASCVD, HR 1.50 (95% CI 1.44 to 1.56) **(Patel 2021)**
- Although the results above are statistically significant, they are likely not clinically meaningful

Outcomes by increase in Lp(a) levels

- In a cohort of healthy adults in Greece (N = 3,042), a significant increase in combined incident CVD events was found with Lp(a), per 1 mg/dL increase (HR 1.02 [95% CI 1.01 to 1.04]) **(Foscolou 2018)**
- In a cohort of healthy adults in Scotland (N = 15,737), the HR was not statistically different for coronary heart disease (CHD) with Lp(a), per 3.64 mg/dL increase (HR 1.01 [95% CI 0.97 to 1.05]) **(Tunstall-Pedoe 2017)**
- In the ARIC cohort from USA communities aged 45-64 (N = 8,127), a significant increase in CHD (definite or probable MI or fatal CHD) was found with Lp(a) for 1 unit increment of the log of Lp(a) adjusted for ARIC 10-year CHD score (HR 1.09 [95% CI 1.02 to 1.16])
    - CVD (defined as CHD plus stroke) was not statistically different **(Agarwala 2016)**
- In the ATTICA cohort of adults from Greece (N = 2,583), Lp(a) per 1mg/dL increase was not statistically different for incident CVD **(Nomikos 2015)**
- In a nested case control study, a subset of participants in the 4th survey of the Tromsø study (N = 817), an increase in 10-year MI was found with Lp(a), per 1-standard deviation increase (OR 1.26 [95% CI 1.09 to 1.47]) **(Wilsgaard 2015)**

Outcomes by Lp(a) percentile

- In a cohort of adults in the USA (N = 4,629), an increase in CHD was found when comparing Lp(a) upper versus bottom 25th percentiles (≥ 39.9 vs <39.9 mg/dL) (HR 1.49 [95% CI 1.16 to 1.91]) **(Cao 2017)**
    - Similarly, an increase was found in a cohort of adults in Europe (N = 56,804) when comparing the 90th percentile (≥ 43.5 mg/dL) to the 33rd percentile (< 5.3 mg/dL) (HR 1.49 [95% CI 1.29 to 1.73]) **(Waldeyer 2017)**
- In a cohort of participants from the EPIC-Norfolk study aged 40-79 years (N = 25,663), an increase in coronary artery disease was found when comparing the highest (>69.7 mg/dL) to the lowest quintile (≤11.4 mg/dL) (HR 1.61 [95% CI 1.42 to 1.84]) **(Guertin 2020)**
- In the ARIC and DHS cohorts of participants without CVD (N = 12,149 and 2,756, respectively), an increase was found for ASCVD in the ARIC cohort when comparing quintile 5 to quintiles 1 to 4 (HR 1.25 [95% CI 1.12 to 1.40]) but no statistical difference was found in the DHS cohort (HR 1.64 [95% CI 0.96 to 2.80])
    - A significant increase was seen in CHD in the ARIC cohort with the same quintile comparison (HR 1.27 [95% CI 1.12 to 1.45]) **(Mehta 2020)**
- Although most of the results above are statistically significant, they are likely not clinically meaningful

Limitations

Limitations in evidence are profound and similar to those found in the 2015 PEER Guideline.

- Studies are heterogeneous in that:
    - Authors used multiple techniques to classify Lp(a) risk groups including various Lp(a) cut-off levels, quartiles, quintiles, and by standard deviation or mg/dL increase

    - Analysis of the Lp(a) risk groups also varied considerably including comparing highest quintiles to the lower 4 quintiles which will give smaller association effects or highest versus lowest (example 1st quartile to 4th quartile) which can give larger association effects
    - Methods of reporting the association effect size included ORs, HRs, ROC-AUC (c-statistic), and net classification index
- It is possible the apparent effect is larger than the real effect as publication bias appears to be common among CV biomarker studies **(Nissen 2013)**

CONTEXT

The argument that the measurement of Lp(a) may help identify unique individuals previously not identified as higher risk (example 5%-7.5% or 7.5%-19%) could be made for any risk factor. As noted in the 2015 PEER Simplified Lipid Guideline **(Allan 2015)**, there are scores of risk factors with statistically significant associations. Any individual test could identify unique individuals not picked by traditional assessments, but which is the preferred test or tests (Lp[a] or apoB, homocysteine, leukocyte count, pro-insulin, etc.) and what is the benefit (people identified and adverse CV events prevented) compared to the harms (cost and inconvenience of testing, overdiagnosis, harms of interventions, false reassurance, etc.)? There are too many uncertainties that add complexity to risk estimation in primary care.

Discrimination

Discrimination is defined as the ability to identify individuals who will have an event, and can be assessed with AUC (which is equivalent to the c-statistic). A c-statistic value of 1.00 is perfect, 0.8 is good, 0.6-0.7 is acceptable, and 0.5 is similar to chance **(Allan 2014)**. A change in the c-statistic of ≥0.1 is large, 0.05-0.1 is moderate, 0.025-0.05 is small, and <0.025 is very small **(Lin 2018)**.

Major guideline recommendations

The 2018 American Heart Association guideline **(Grundy 2018)** suggests an Lp(a) level ≥50 mg/dL (125 nmol/L) can be considered a "risk-enhancing" factor that favors the initiation of a statin in adults aged 40 to 75 years, without diabetes mellitus, and who have a 10-year CVD risk of 7.5% to 19.9%. They suggest the same "risk-enhancing" factor may favor statin therapy in patients at 10-year risk of 5% to 7.5%. No data is provided to quantify the increased risk attributed to a Lp(a) value ≥50 mg/dL. The 2019 European Society of Cardiology (ESC) dyslipidemia guideline **(Mach 2020)** and the 2021 Canadian Cardiovascular Society guideline **(Pearson 2021)** both recommend a single Lp(a) measurement in each adult person's lifetime to identify those with genetically high Lp(a) levels. The 2019 ESC guideline goes on to recommend Lp(a) level be considered in patients with a family history of premature CVD and for reclassification in patients who are borderline between moderate and high-risk CVD. No evidence is provided regarding the potential increase in CVD risk.

The 2020 Veteran's Affairs (VA) guideline **(Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020)** suggests against the routine use of additional markers in

assessing CVD risk, while the 2021 ESC CVD **(Visseren 2021)** prevention guideline and the 2022 United States Preventive Services Task Force **(US Preventive Services Task Force 2022)** guideline provide no recommendations on the measurement of Lp(a) levels. A summary of these guideline recommendations can be found in *Table 4*.

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METHODS

Major guidelines published in the last 5 years (2018 AHA, 2020 Veterans Affairs, 2021 CCS, 2022 USPSTF, 2019 ESC on dyslipidemia, 2021 ESC on CVD prevention) were reviewed to identify relevant recommendations and the evidence for those recommendations.

Several searches outlined below were conducted between November 17 and December 22, 2022.

- PubMed was searched using the search terms (Cardiovascular Risk Estimation OR Cardiovascular Risk Calculators OR Cardiovascular Risk Assessment) AND lipoprotein(a) [MeSH]. Results were limited to meta-analyses, systematic reviews, and to publication January 1, 2015, and later. This search returned 27 results with one systematic review meeting the inclusion criteria (**Forbes 2016)**.
- Another keyword search was performed in PubMed using the search terms Lipoprotein a AND cardiovascular risk. This search was limited to systematic reviews and to publication January 1, 2015, and later. This search returned 41 results, including the previously noted systematic review by **Forbes 2016**. One additional relevant systematic review was identified through this search (**Kouvari 2019a)**.
- A search of Google Scholar was performed using the search terms Lipoprotein a AND cardiovascular risk. Results were limited to publication January 1, 2015, and later. The first 5 pages of results were reviewed with no new relevant studies being identified.
- A search using the “similar articles” function in PubMed was performed against the relevant references that were used in the 2015 PEER Simplified Lipid Guideline. This search was limited to meta-analyses, systematic reviews, and to publication January 1, 2015, and later. In total, 103 studies were identified, many of which were duplicates of studies in the previous searches. No new relevant studies were identified in this search.

- The citation from the 2015 PEER Simplified Lipid Guideline was entered into Google Scholar and “see cited” was clicked. The results were reviewed with one additional relevant cohort study being identified (**Kouvari 2019b)**. The reference list from the 2021 CCS guidelines was reviewed with one relevant case control study identified (**Pare 2019)**.
- Given the lack of systematic reviews from the previous searches, a new keyword search was then performed in PubMed with no limits on study type for publications January 1, 2015, and later. The keywords lipoprotein a AND cardiovascular AND risk prediction were used. This search returned 240 results with 8 cohort studies and one nested case-control study identified for inclusion **(Agarwala 2016, Delabays 2021, Guertin 2020, Mehta 2020, Nomikos 2015, Patel 2021, Verbeek 2017, Welsh 2022, and Wilsgaard 2015)**.

APPENDIX

Table 1A: Summary of characteristics and efficacy data of systematic reviews

Study	Study type	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
Forbes 2016	SR of 7 high-risk primary prevention studies (1 RCT, 6 prospective cohorts), of which 1 included in analysis met our inclusion criteria	**Pernod 2006** Mixed gender adults (22-92 years) with and without type 2 diabetes	279	CVD events and CV death	Lp(a) >300 mg/L vs ≤300 mg/L	HR 1.67 (1.04 to 2.63)	Meta-analysis was not possible due to heterogeneity in CVD outcomes, populations, and statistical analysis methods; CVD events: MI, de novo angina pectoris or coronary revascularization, ischemic stroke, or PAD, CV death (due to cardiac arrhythmia, MI, or heart failure)
Kouvari 2019a	SR of 13 primary prevention studies, of which 4 included in analysis met our inclusion criteria	Varied populations (not well described in SR)	Overall: 211,087				
		Foscolou 2018 Cohort of apparently healthy adults in Greece	3,042	Combined first CVD events	Lp(a) per 1 mg/dL	HR 1.02 (1.01 to 1.04)	Adjusted for age, sex, diabetes, hypertension, hypercholesterolemia, family history of CVD, BMI, physical activity, current smoking; Median FU 8.41 years
		Tunstall-Pedoe 2017 Cohort of apparently healthy adults in Scotland	15,737	CHD	Lp(a) per 3.64 mg/dL increase	HR 1.01 (0.97 to 1.05)	Adjusted for ASSIGN score factors (i.e. age, sex, socioeconomic status, family history of CVD, diabetes, smoking, blood pressure, total cholesterol, LDL-C, HDL-C); Median FU 20 years
		Cao 2017 Cohort of apparently healthy adults in USA	4,629	CHD	Lp(a) upper vs bottom 25th percentile (≥39.9 vs	HR 1.49 (1.16 to 1.91)	Adjusted for age, sex, race/ethnicity, hypertension, smoking, education status, diabetes, LDL-C, HDL-C; Median FU 12 years

Study	Study type	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
					<39.9 mg/dL)		
		Waldeyer 2017 Cohort of apparently healthy adults in Europe	56,804	MACE	Lp(a) ≥90th vs 33rd percentile (≥43.5 mg/dL)	HR 1.49 (1.29 to 1.73)	Adjusted for age, sex, cohort, smoking status, total cholesterol, diabetes, hypertension, and BMI

BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; FU = follow-up; HR = hazard ratio; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein a; MACE = major adverse cardiovascular events; MI = myocardial infarction; PAD = peripheral artery disease; SR = systematic review

Table 1B: Summary of characteristics and efficacy data of observational studies

Study	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
Agarwala 2016	Cohort study; participants from the ARIC study from US communities; ages 45 – 64 (avg age 63); primary prevention; 59% female	8,127	CHD = definite or probable MI or fatal CHD (# of events= 620)		HR 1.08 (1.01 to 1.15)	HR for 1 unit increment of the log Lp(a) Adjusted for age at visit 4, race, and gender
					HR 1.09 (1.02 to 1.16)	HR for 1 unit increment of the log Lp(a) Adjusted for ARIC 10-year CHD risk score
			CVD = CHD + stroke (# of events= 924)		HR 1.05 (1.00 to 1.11)	HR for 1 unit increment of the log Lp(a) Adjusted for age at visit 4, race, and gender
					HR 1.06 (1.00 to 1.12)	HR for 1 unit increment of the log Lp(a) Adjusted for variables used in CHD as well as the stroke risk scores
Delabays 2021	Cohort study; Swiss adults aged 35-75 years; mean follow up of 9.9 years	4,829	Incident ASCVD	Dichotomized Lp(a) <50 vs ≥50 mg/dL added to ESC/SCORE algorithm	ESC/SCORE C-stat 0.780 (0.755 to 0.805) Adding Lp(a) C-stat 0.784 (0.759 to 0.809)	

Study	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
					Difference in C-statistic = 0.004	
					NRI 3.3% (0.80 to 5.80) (P-value=0.01)	Overall NRI
					NRI 11.4% (5.9 to 16.8)	NRI for intermediate-risk individuals only
Guertin 2020	Cohort study; Participants from the EPIC-Norfolk study; ages 40 – 79 years	25,663	CAD = myocardial ischemia, MI, or other ischemic heart disease	Lp(a) level (≤11.4 [lowest quintile] vs >69.7 mg/dL [highest quintile])	HR 1.61 (1.42 to 1.84)	Adjusted for age, sex, smoking BMI, systolic BP, diabetes, and eGFR
				Lp(a) level (<50 vs ≥50 mg/dL)	HR 1.50 (1.38 to 1.64)	
Kouvari 2019b "ATTICA"	Cohort study; Healthy volunteers residing in Greece; 1,514 men (mean age 46); 1,528 women (mean age 45)	3,042 (initial cohort); 1,890 included	10-year CVD event	Lp(a) ≥50 mg/dL versus <50 mg/dL Table 2	HR 2.21 (1.16 to 4.21) (Model 4)	CVD Event = acute MI, unstable angina, or other identified forms of ischemia; Threshold of 50 mg/dL = Lp(a) "normal"; Table 2 = Cox-regression models to evaluate the association of abnormal Lp(a) Levels (cut off point of 50 mg/dL) with 10-year CVD risk (N = 1,890); Model 4 adjusted for other lipid markers and the use of statins
				Lp(a) ≥30 mg/dL versus <30 mg/dL Table 3	HR 1.18 (0.82 to 1.60) (Model 4)	Table 3 = Cox-regression models to evaluate the association of abnormal Lp(a) Levels (cut off point of 30 mg/dL) with 10-year CVD risk (N = 1,890); Model 4 adjusted for other lipid markers and the use of statins
				Standard model adjusted for Lp(a)	Men C-index 0.769 (0.709 to 0.828) Women	Table 4: Discrimination-ability parameters of multivariate models adjusted for lipoprotein (a) over the 10-year first fatal/nonfatal CVD event;

Study	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
					C-index 0.820 (0.772 to 0.880)	Model 2- adjusted for age, BMI, current smoking, MedDietScore, hypertension, DMII, and family history of CVD
Mehta 2020	Cohort study; ARIC (Atherosclerosis Risk in Communities) and DHS (Dallas Heart Study) cohorts; participants without CVD	12,149 (ARIC) 2,756 (DHS)	ASCVD in ARIC cohort	Race-specific quintile 5 (vs quintiles 1 to 4)	HR 1.25 (1.12 to 1.40)	Adjusted for age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, and statin use at baseline
			CHD in ARIC cohort	Race-specific quintile 5 (vs quintiles 1 to 4)	HR 1.27 (1.12 to 1.45)	
			ASCVD in DHS cohort	Race-specific quintile 5 (vs quintiles 1 to 4)	HR 1.64 (0.96 to 2.80)	
Nomikos 2015	Cohort study; ATTICA cohort of adults in Greece without any chronic disease	3,042 (2,583 included)	Incident CVD	Lp(a) per 1 mg/dL	RR 1.003 (0.997 to 1.010)	All models were adjusted for age, sex, BMI, smoking habits, physical activity status, MedDietScore, history and pharmaceutical management of dyslipidemias, hypertension, and diabetes, and family history of CVD at baseline examination
		2,020	10-year CVD incidence		cNRI 6.7%	Lp(a) (per 1mg/dL) added to other predictors
Pare 2019	Case control study; INTERHEART study cohort	12,943	MI	Lp(a) <50 mg/dl vs ≥50 mg/dl	OR 1.48 (1.30 to 1.67)	Tested for associations between Lp(a) using various cut-offs of 30, 40, 60, 70 mg/dL); OR ranged from 1.33 to 1.73 (all statistically significant)
Patel 2021	Cohort study; UK Biobank participants; aged 40-69	460,506	Incident ASCVD	Lp(a) ≥150 nmol/L vs <150 nmol/L	HR 1.50 (1.44 to 1.56)	Adjusted for enrollment age, sex, and self-reported race; ASCVD = composite of coronary artery disease (MI and its acute complications, coronary artery bypass graft surgery, or percutaneous angioplasty/stent placement) and ischemic stroke (cerebral infarction due to thrombosis or cerebral atherosclerosis or cerebrovascular syndromes)

Study	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
Verbeek 2017	Cohort study; EPIC (European Prospective Investigation of Cancer)-Norfolk study participants	16,777	CVD	Lp(a) level (<30 vs ≥30 mg/dL) added to ACC/AHA	NRI -2.76%	
				Lp(a) level (<30 vs ≥30 mg/dL) added to SCORE	NRI 0.57%	
					NRI 15.88%	NRI for intermediate risk according to ACC/AHA
					NRI 16.83%	NRI for intermediate risk according to SCORE
				Lp(a) level (<50 vs ≥50 mg/dL) added to ACC/AHA	NRI -2.27%	
				Lp(a) level (<50 vs ≥50 mg/dL) added to SCORE	NRI 0.53%	
Welsh 2022	Cohort study; UK Biobank participants, aged 37-73, sub-cohort of participants without baseline CVD and not taking a statin	340,339	CVD	Lp(a) per 1-SD increase (compared to reference of <20 nmol/L)	HR 1.13 (1.10 to 1.16)	Adjusted for age, sex, total cholesterol, HDL-C, ethnicity, smoking, SBP, BP medications, and baseline diabetes;
					Change in c-index +0.0017 (0.0008 to 0.0026)	Change in C-index when added to classical risk factors; Classical risk factors: age, sex, total cholesterol, HDL-C, ethnicity, smoking, SBP, BP medications, and baseline diabetes
					Overall NRI +0.0112% (+0.0039 to +0.0184)	
Wilsgaard 2015 "TROMSO"	Nested case-control study; Subset of participants in the fourth survey of the	817 (419 cases; 398 controls)	10-year MI			Cases = all participants with no previous MI, ischemic stroke, coronary artery bypass grafting, percutaneous coronary intervention or self-reported angina at baseline AND who experienced a first-ever MI within 10 years of follow up; Controls = randomly selected from the entire group of participants completing 10-year

Study	Population	Sample size	Outcome	Cut-offs	Effect estimate (95% CI)	Notes
	Tromsø study (1994-1995) Eligible were men (aged 55-74) and women (aged 50-74) and 5-10% samples of other subjects aged 25-85. <u>Baseline Lp(a)</u> Women: Cases 160.2 ng/mL; Controls 135.2 ng/mL Men: Cases 150.6 ng/mL; Controls 101.1 ng/mL					follow-up without an event of interest and using the same inclusion criteria as the cases; Excluding subjects with DMII or who had non-fasting glucose level <u>></u>200 mg/dL or HbA1c <u>></u>6.5% at baseline
			10-year MI	Lp(a)	OR 1.26 (1.09 to 1.47)	OR (per 1 SD change of transformed concentrations calculated in control subjects); Multivariate adjustment = age, sex, age*sex, BP, BP*BP meds, total cholesterol, HDL-C, and daily smoking
			10-year MI		NRI overall 0.085 (P=0.024)	NRI comparing traditional risk factors to Lp(a) +3 other biomarkers (ApoB/ApoA ratio, kallikrein, matrix metalloproteinase 9)
			10-year MI		ROC-AUC 0.027 (P=0.002)	Lp(a) plus 3 other biomarkers compared to traditional risk factors

ACC/AHD = American College of Cardiology/American Heart Association; ApoA = apolipoprotein a; ApoB = apolipoprotein b; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; CI = confidence interval; cNRI = continuous net reclassification index; CV = cardiovascular; CVD = cardiovascular disease; DMII = type 2 diabetes mellitus; FU = follow-up; HR = hazard ratio; HDL-C = high-density lipoprotein-cholesterol; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein a; MACE = major adverse cardiovascular events; MI = myocardial infarction; NRI = net reclassification index; OR = odds ratio; PAD = peripheral artery disease; ROC-AUC = area under the receiver operating characteristic curve; RR = risk ratio; SBP = systolic blood pressure; SD = standard deviation; SR = systematic review

<u>Table 2A: Quality assessment of systematic reviews of observational studies using AMSTAR-2D</u>

Study	AMSTAR-2 Rating	Rationale
Forbes 2016	Critically low	No list of excluded studies; did not consider risk of bias when interpreting results of review
Kouvari 2019a	Critically low	No prespecified protocol; no comprehensive literature search; no list of excluded studies; did not assess risk of bias, did not consider risk of bias when interpreting results of review

AMSTAR-2D = Assessment of Multiple Systematic Reviews

Table 2B: Quality assessment of observational studies using QUAPAS

Study	Participants		Index Test		Outcome		Flow and timing		Analysis
	Could selection of participants have introduced bias?	Are there concerns that participants do not match review question?	Could the conduct or interpretation of the index test have introduced bias?	Are there concerns that the index test, its conduct, interpretation or threshold differ from review question?	Could measurements of the outcome have introduced bias?	Are there concerns that the outcome does not match the review question?	Could the study flow have introduced bias?	Are there concerns that the time horizon does not match the review question?	Could the analysis have introduced bias?
Agarwala 2016	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Delabays 2021	Unclear	Low	Low	Low	Unclear	Low	Unclear	Low	Unclear
Guertin 2020	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Kouvari 2019b	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Mehta 2020	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Nomikos 2015	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Pare 2019	High	High	Low	Low	Unclear	Low	Unclear	Unclear	Unclear
Patel 2021	Low	Low	Low	Low	Low	Low	Low	Low	Unclear
Verbeek 2017	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Welsh 2022	Low	Low	Low	Low	Low	Low	Low	Low	Unclear
Wilsgaard 2015	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear

QUAPAS = Quality Assessment of Prognostic Accuracy Studies

Table 3: GRADE certainty of evidence for addition of Lp(A) to risk calculators to predict the risk of incident CVD

Prognostic factor: Lp(A) added to risk calculator

Outcome: incident CVD

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient	Effect estimate (range)	Certainty
Prognostic obs.	2 (4,829-340,339)	Not serious	Not serious	Not serious	Not serious	Not detected	No	No	No	Change in c-stat 0.0017 to 0.004	High This outcome has no downgrades

CVD = cardiovascular disease; Lp(A) = lipoprotein A; obs. = observational

Table 4: Summary of recommendations from major guidelines published within the past 5 years

Our question	**2018 AHA**[1]	**2019 ESC Dyslipidemia**[2]	**2020 VA**[3]	**2021 CCS**[4]	**2021 ESC CVD Prevention**[5]	**2022 USPSTF**[6]
In patients without established CVD, does the use of lipoprotein A meaningfully change CVD risk estimation more than standard risk estimates (e.g., age, smoking) alone?	In adults 40 to 75 years of age without DM and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. Risk-enhancing factors include…Lp(a)>=50 mg/dL (125 nmol/L. Risk-enhancing factors may favor statin therapy in	Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterinemia (class IIa, level C). Lp(a) should be considered in selected	We suggest against the routine use of additional risk markers when assessing CV risk (weak against)	We recommend measuring Lp(a) level once in a person's lifetime as part of the initial lipid screening (strong recommendation; high-quality evidence). For all persons in the setting of primary prevention with a Lp(a) >=50 mg/dL (or >= 100 nmol/L), we recommend earlier and more intensive health behaviour	No recommendation: Lp(a) provides limited additional value in terms of reclassification potential	No recommendation

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
	patients at 10-year risk of 5-7.5% (borderline risk)	patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk (class IIa, level C)		modification counselling and management of other ASCVD risk factors (strong recommendation; expert consensus)		

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; Lp(A) = lipoprotein A

CHAPTER 3: APOLIPOPROTEIN B AND CARDIOVASCULAR RISK PREDICTION

CLINICAL QUESTION

In patients without established cardiovascular disease, does the addition of apolipoprotein B meaningfully change cardiovascular disease risk estimation compared to standard risk estimates (e.g., age, smoking) alone?

BOTTOM LINE

Adding apolipoprotein B (apoB) to current cardiovascular (CV) risk calculators does not meaningfully add to cardiovascular disease (CVD) risk prediction.

EVIDENCE

Since the 2015 PEER guideline **(Allan 2015)**, two new systematic reviews (SRs) **(Perera 2015, Sandhu 2016)** and 7 observational studies **(Graversen 2016, Pencina 2015, Sniderman 2016, Vasquez-Oliva 2018, Welsh 2019, Wilsgaard 2015)** were published. A summary of study characteristics and efficacy data is reported in *Table 1* Quality assessment of included studies can be found in *Tables 2A-B*. GRADE certainty of evidence evaluation can be found in *Table 3*. All evidence statistically significant unless noted.

We found apoB risk ratios (RRs)/hazard ratios (HRs)/odds ratios (ORs) to predict CVD ranged from 1.03 to 2.87. In comparison, the RR for non-traditional risk markers like leucocyte count and albumin were 1.45 and 1.55, respectively. These numbers are not dissimilar to the number for apoB.

Systematic reviews

- **Perera 2015**: SR and meta-analysis of 10 primary prevention studies (N = 200,086)
    - CV events (adjusted): HR 1.28 (95% confidence interval [CI] 1.16 to 1.42)
- **Sandhu 2016**: SR and meta-analysis of 4 studies (N = 15,854)
    - CV events (including myocardial infarction [MI], ischemic heart disease, CV death): RR 1.31 (95% CI 1.22 to 1.40)
    - Limitations include variable cut-offs, outcomes, and outcome measures reported amongst studies; two studies appear to have been reporting on the same cohort at different time-points, possibly without censoring older results, leading to double-counting of some events

Observational studies

7 observational studies (N = 756-346,686)

- The largest and most relevant cohort to our question was **Welsh 2019** (N = 346,686; median 8.9 years) as it included the population we were looking for (adults without CVD who were not taking statins) and included results presented in a manner in which was more optimal when answering questions about the additive effect of biomarkers (e.g., C-statistics, net reclassification index)

- ***Incident CVD***: when added to classical risk factors including total cholesterol and high-density-lipoprotein-cholesterol (HDL-c), apoB resulted in a change in C-index of 0.0004 (95% CI 0 to 0.0008) which is not clinically meaningful **(Welsh 2019)**
    - Net reclassification index +0.14% (95% CI -0.17 to +0.50%), not statistically different
- ***CV death***: no difference in area under receiver-operating characteristic curve (ROC-AUC) when apoB added to SCORE risk calculator (including sex, age, smoking status, systolic blood pressure, total cholesterol) **(Graversen 2016)**
- ***Coronary heart disease***: C-stat difference (based on non-HDL-c) 0.006 (95% CI 0.0003 to 0.013) between tertiles compared to the middle
    - Not clinically meaningful **(Pencina 2015)**
- ***MI***
    - OR 1.36 (95% CI 1.32 to 1.41) for each standard-deviation increase in apoB **(Sniderman 2016)**;
    - OR 1.21 (95% CI 1.01 to 1.44) for cases (1st MI) versus controls (no MI) over 10 years of follow-up **(Wilsgaard 2015)**
- ***Coronary events***: HR not different when apoB added to age, sex, smoking status, diabetes status, blood pressure, total cholesterol, HDL **(Vasquez-Oliva 2018)**

Limitations

Limitations in evidence are profound and similar to those found in the 2015 PEER Guideline **(Allan 2015)**.

- Studies are heterogeneous in that:
    - Authors used multiple techniques to classify apoB risk groups including tertiles, quintiles, deciles, and by standard deviation
    - Analysis of the apoB risk groups varied considerably including comparing highest quintiles to middle which will give smaller association effects or highest versus lowest (example 1st decile to 10th deciles) which can give larger association effects
    - Methods of reporting the association effect size included ORs, HRs, ROC-AUC, net classification index
    - Statin use was inconsistent across studies
- It is possible the apparent effect is larger than the real effect as publication bias appears to be common among CV biomarker studies **(Nissen 2013)**
- Variable approaches to analysis in individual studies may also limit comparisons or application
    - One example is **Walldius 2021** who compares apoB to low-density-lipoprotein (LDL) for ROC-AUC; however, most CV risk calculators do not include LDL and instead include HDL

- Exclusion of those with hypertriglyceridemia in one study **(Pencina 2015)** despite the 2021 CCS guideline recommending apoB testing in hypertriglyceridemic patients **(Pearson 2021)**

CONTEXT

Discrimination

Discrimination is defined as the ability to identify individuals who will have an event, and can be assessed with area under the curve (which is equivalent to the c-statistic). A c-statistic value of 1.00 is perfect, 0.8 is good, 0.6-0.7 is acceptable, and 0.5 is similar to chance **(Allan 2014)**. A change in the c-statistic of ≥0.1 is large, 0.05-0.1 is moderate, 0.025-0.05 is small, and <0.025 is very small **(Lin 2018)**.

Major guideline recommendations

Several recent guidelines have made recommendations regarding the use of apoB in primary prevention of CVD which have ranged from similar recommendations to the PEER group **(Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020)**, no recommendation **(Visseren 2021; US Preventive Services Task Force 2022)**, initiating statins in certain adults with "risk-enhancing factors" such as apoB levels ≥1.3g/L if 10-year CVD risk was 7.5-19.9% (intermediate risk) **(Grundy 2018),** and using apoB in place of LDL-cholesterol as preferred lipid parameter for screening and treatment targets for patients with elevated triglycerides greater than 1.5mmol/L **(Pearson 2021)**. A summary of guideline recommendations can be found in *Table 4*.

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METHODS

- Major guidelines published in the last 5 years (2018 AHA, 2020 Veterans Affairs, 2021 CCS, 2022 USPSTF, 2019 ESC on dyslipidemia, 2021 ESC on CVD prevention) were reviewed to identify relevant recommendations and the evidence for those recommendations. Several searches outlined below were conducted between November 17 and December 13, 2022.
- *PubMed (1)*: searched using terms [(Cardiovascular Risk Estimation OR Cardiovascular Risk Calculators OR Cardiovascular Risk Assessment) AND apolipoprotein(b)] OR [("apolipoprotein B" AND "cardiovascular risk")]. Results were limited to systematic reviews or meta-analysis, and to publication January 1, 2015 and later. This search identified two systematic reviews **(Perera 2015, Sandhu 2016)**.
    - *Similar articles search*: no additional relevant articles identified
- *Google Scholar*: search was conducted using the search terms "Apolipoprotein B and cardiovascular risk" and filtered from 2015 to present. In addition, any potentially relevant article was copied into the search bar and then clicked on "cited by" and searched for "systematic reviews" within those cited articles. This search resulted in 2 observational studies **(Pencina 2015, Sniderman 2016)** that were included for this evidence review.
    - Subsequently, another Google Scholar search was conducted using the search terms ""apolipoprotein b versus Framingham" which did not yield any additional studies.
- *PubMed (2)*: Given the lack of systematic reviews from the previous searches, a new keyword search was then performed in PubMed with no limits on study type for publications January 1, 2015, and later. The keywords "apolipoprotein B" AND "cardiovascular" AND "risk prediction" were used and resulted in 3 further studies **(Graversen 2016, Vazquez-Oliva 2018, Wilsgaard 2015)**.
    - *Similar articles search*: the most relevant systematic review citation from the 2015 PEER Simplified Lipid Guideline was entered into PubMed and "similar articles" search was completed which resulted in no new studies identified.
- *Additional searches*: two subsequent observational studies were identified as part of the apolipoprotein A search **(Walldius 2021, Welsh 2019)**.

APPENDIX

Table 1: Summary of characteristics of systematic reviews and observational studies

Study	Study type	Population	Sample size	Cut-offs	Outcome	Effect estimate* (95% CI)	Notes
Perera 2015	SR (10 studies in primary prevention)	Cohorts that had at least 12 months of follow up and a minimum of 1000 participants. This analysis looked at ApoB for primary prevention in populations not taking statins	200,086		CV events (Figure 85)	HR 1.28 (1.16 to 1.42)	HR for every 1-SD increase in ApoB
Sandhu 2016	SR (4 studies included)	Men 35+, women 45+, younger adults with CV risk factors, no previous CVD/DM, in- or out-patient settings	15,854	Varied among 4 included studies	CV events (e.g., MI, ischemic heart disease, CV death)	RR 1.31 (1.22 to 1.40)	2 studies may be same cohort at different time points; may not have been appropriate to meta-analyze outcomes due to heterogeneity (quartiles/tertiles/SD, HR/RR)
Graversen 2016	Cohort	Copenhagen City Heart Study population part 3 (1991-1994), age 21-79; excluded those with prior CVD/DM	8,476		CV death	SCORE AUC 0.837 (0.820 to 0.855); no change with apoB	SCORE risk calculator includes sex, age, smoking, systolic BP, TC
						NRI (NSS)	
						HR 2.87 (1.43 to 5.75)	ApoB adjusted for SCORE risk factors
Pencina 2015	Cohort	Framingham offspring participants who attended 4th examination cycle Excluded: previous CVD and high triglycerides	2,966	Tertiles (compared to middle)	New onset coronary heart disease	C-stat difference 0.006 (0.0003 to 0.013)	Adjusted for standard risk factors including age, sex, systolic BP, antihypertensive treatment, smoking, diabetes, HDL-C and non-HDL-C

Study	Study type	Population	Sample size	Cut-offs	Outcome	Effect estimate* (95% CI)	Notes
Sniderman 2016	Cohort	INTERHEART study cohort	20,758		OR of MI for 1-SD change in ApoB overall (all ages)	OR 1.36 (1.32 to 1.41)	
Vasquez-Oliva 2018	Case-cohort	REGICOR study cohort; age 35-74, no prior CVD	756		Coronary event	HR 1.03 (0.80 to 1.34)	Model 2 adjusted for age, sex, smoking, DM, BP, TC, HDL-C
Walldius 2021	Cohort	AMORIS cohort, consisting of individuals undergoing health examinations during 1985–1996 (baseline period); men and women (25-84 years) followed for average 17.8 years	137,100	Deciles (10th vs 1st)	MACE (for ApoB/ApoA-1 ratios)	HR 1.70	
					ApoB vs LDL (men and women combined)	ROC-AUC 0.02 (P=0.0066)	ApoB vs LDL (men and women combined)
Welsh 2019	Cohort	UK Biobank participants, aged 37-73, without CVD and not taking statins followed for median 8.9 years	346,686	Quintiles (compared to middle)	1 SD increase in ApoB and Incident CVD	HR 1.23 (1.20 to 1.26)	
					C-index on addition of ApoB to classical risk factors plus TC and HDL-C	Change in C-index 0.004 (0.0000 to 0.0008) Note: from C-index of 0.7463 (0.7406 to 0.7520)	"Adding any measure of LDL-C or ApoB alone to a model already containing TC and HDL-C offered no substantial discriminative benefit"
					NRI compared to classical risk factors plus TC and HDL-C	+0.14% (-0.17 to +0.50%)	
Wilsgaard 2015	Case control	4th survey in Tromso Study (Norway), 25-85 years with no previous CVD and experienced first MI within 10 years of follow up (cases); matched with	817		Incident MI	OR 1.21 (1.01 to 1.44)	
					Incident MI ApoB/ApoA-1 ratio plus 3 other biomarkers compared	ROC-AUC 0.027 (P=0.002)	

Study	Study type	Population	Sample size	Cut-offs	Outcome	Effect estimate* (95% CI)	Notes
		controls completing 10 year follow without event of interest; diabetics excluded			to traditional risk factors		
					NRI comparing traditional risk factors to ApoB/ApoA-1 ratio +3 other biomarkers	Overall NRI 0.085 (P=0.024)	

*Used most-adjusted numbers

ApoA = apolipoprotein A; ApoB = apolipoprotein B; BP = blood pressure; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; DM = diabetes mellitus; HR = hazard ratio; LDL-C = low-density lipoprotein-cholesterol; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; NRI = net reclassification index; NSS = not statistically significant; OR = odds ratio; ROC-AUC = area under the receiver operating characteristic curve; SD = standard deviation; SR = systematic review; RR = risk ratio; TC = total cholesterol

Table 2A: Quality assessment of systematic reviews of observational studies using AMSTAR-2D

Study	Overall confidence	AMSTAR -2: list of weaknesses
Perera 2015	Critically low	ROB, ROB interpretation, publication bias
Sandhu 2016	Critically low	A priori, literature search, excluded studies, ROB, meta-analysis methods, publication bias

AMSTAR-2D = Assessment of Multiple Systematic Reviews; ROB = risk of bias

Table 2B: Quality assessment of observational studies using QUAPAS

Study	Participants		Index Test		Outcome		Flow and timing		Analysis
	Could selection of participants have introduced bias?	Are there concerns that participants do not match review question?	Could the conduct or interpretation of the index test have introduced bias?	Are there concerns that the index test, its conduct, interpretation or threshold differ from review question?	Could measurements of the outcome have introduced bias?	Are there concerns that the outcome does not match the review question?	Could the study flow have introduced bias?	Are there concerns that the time horizon does not match the review question?	Could the analysis have introduced bias?
Graversen 2016	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear
Pencina 2015	High	High	Unclear	High	Unclear	Low	Low	Low	Unclear
Sniderman 2016	High	High	Unclear	Low	Unclear	Low	Low	Low	Unclear
Vazquez-Olivia 2018*	Low	Low	Low	Low	Low	Low	Unclear	High	Unclear
Walldius 2021*	Low	Low	Low	Low	Unclear	Low	Unclear	Low	Unclear
Welsh 2019	Low	Low	Low	Low	Unclear	Low	Unclear	Low	Unclear
Wilsgaard 2015	Low	Low	Low	Low	Low	Low	Unclear	Low	Unclear

QUAPAS = Quality Assessment of Prognostic Accuracy Studies

Table 3: GRADE certainty of evidence for addition of apo(B) to risk calculators to predict the risk of incident CVD

Prognostic factor: apo(B) added to risk calculator

Outcome: incident CVD

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient	Effect estimate (range)	Certainty
Prognostic obs.	2 (2,966-346,686)	Not serious	Not serious	Not serious	Not serious	Not detected	No	No	No	Change in c-stat 0.004 to 0.006	High This outcome has no downgrades

apo(B) = apolipoprotein B; CVD = cardiovascular disease; obs. = observational

Table 4: Summary of recommendations from major guidelines published within the past 5 years

Our question	**2018 AHA**[1]	**2019 ESC Dyslipidemia**[2]	**2020 VA**[3]	**2021 CCS**[4]	**2021 ESC CVD Prevention**[5]	**2022 USPSTF**[6]
In patients without established CVD, does the use of apolipoprotein B meaningfully change CVD risk estimation more than standard risk estimates (e.g., age, smoking) alone?	In adults 40 to 75 years of age without DM and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. Risk-enhancing factors include… apolipoprotein B ≥130 mg/dL. Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-	ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with	We suggest against the routine use of additional risk markers when assessing CV risk (weak against)	For any patient with triglycerides > 1.5mmol/L, use non-HDL-C or apoB instead of LDL-C as the preferred lipid parameter for initial screening and treatment target (< 2.6 mM for non-HDL-C or <0.8 g/L for apoB) in intermediate or high-risk individuals (Strong recommendation,	NR	No recommendation In supplementary document it states: "Apolipoprotein B directly measures the total number of atherogenic particles, though it is unclear whether it is superior to non-HDL-C as a marker of CHD risk and is more difficult and costly to measure. The USPSTF previously (last updated in 2008) recommended lipid screening

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
	7.5% (borderline risk)	high TG levels, DM, obesity, or very low LDL-C levels.		High-Quality Evidence).		with a fasting or nonfasting HDL-C, with either the total cholesterol or LDL-C."

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

ApoB = apolipoprotein B; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; NR = not reported; TG = triglyceride

CHAPTER 4: EXERCISE AND CARDIOVASCULAR DISEASE

CLINICAL QUESTION

In patients with/at risk of cardiovascular disease, does increasing physical activity (including cardiac rehabilitation) reduce the risk of cardiovascular events?

BOTTOM LINE

For patients without established cardiovascular disease (CVD), the majority of randomized controlled trial (RCT) evidence appears to show no benefit, particularly in all-cause mortality. This is based on underpowered studies that were often not designed to look at cardiovascular (CV) events or mortality.

For patients with established CVD, exercise-based cardiac rehabilitation decreases all-cause mortality by 10% and decreases myocardial infarction (MI) and CV mortality by 20-40% compared to no exercise control or usual care at >36 months. The outcome of major adverse cardiovascular events (MACE) is not consistently reported. This estimate is limited by the varied types of exercise studied, older studies, along with inconsistent intensity and duration. No evidence establishes optimal exercise duration or intensity.

EVIDENCE

We found one systematic review (SR) of Cochrane SRs, one SR of RCTs, and two RCTs looking at exercise interventions. We limited our search to SRs of RCTs between 2017 and 2022. We found 3 SRs looking specifically at exercise-based cardiac rehabilitation. *Table 1* and *Table 2* summarize characteristics and results of the SRs. *Tables 3A-B* include the quality assessment of included reviews and RCTs. GRADE certainty of evidence evaluation can be found in *Table 4*.

Primary prevention & mixed prevention

- **Garcia-Hermoso 2020**: SR
    - 90 RCTs; N = 28,523; mean age 74.2 years; duration 52-208 weeks; 39 RCTs in an "apparently healthy population"
    - Exercise intervention ≥ 1 year in patients > 65 years old versus usual care that did not include exercise. Exercise interventions were primarily multi-component exercise training, muscle strength or walking. Group based supervised training was most common.
    - Primary outcomes in 54/90 RCTs was falls/physical function and not mortality. 2/90 RCTs had a primary outcome of cardiac risk factors but not MACE.
    - All-Cause Mortality: (56 RCTs; N = 26,017)
        - RR 0.93 (95% CI 0.83 to 1.04)
        - 5.5% intervention vs 5.8% control
    - Subgroup apparently healthy though including nursing home patients (39 RCTs)
        - Mortality RR 0.96 (95% CI 0.87 to 1.06)
    - Subgroup "clinical populations" (16 RCTs) including cancer, dementia, CVD, renal, MSK or metabolic disease
        - Mortality RR 0.67 (95% CI 0.48 to 0.95)

- We reviewed four of the largest RCTs in this SR. Three were not designed to look at mortality as a primary outcome, as their primary outcomes were falls or depression, hence mortality outcomes were underpowered. The other was a cluster RCT designed to look at mortality as a primary outcome however only 26% of participants attended at least one session and the study was underpowered. In addition, it is unclear if this was primary or secondary prevention. Two RCTs reported cardiometabolic risk factor change but did not report MACE.

- **Harris 2019**: 2 RCTs combined in one publication
  - Two RCTs of a 12-week intervention with long term observational follow-up, not in the above SR (N = 1,297; age 45-75; 62% female; 82% self-report general health "very good or good")
  - Primary care practices recruiting patients into nurse supervised intervention which encouraged 3,000 steps in 30 minutes per day for 12 weeks versus usual care. Three- or 4-year follow-up using primary care data.
  - Non-fatal CV events hazard ratio (HR) 0.24 (95% CI 0.07 to 0.77)
  - Non-fatal and fatal CV events HR 0.34 (95% CI 0.12 to 0.91)

Secondary prevention

- **Dibben 2021**: Cochrane SR
  - Exercise-based cardiac rehabilitation with at least 6 months follow-up compared to a "no exercise" control
  - 85 RCTs; N = 23,340 with known coronary heart disease; mean age range 47-77 years
  - Fatal and/or nonfatal MI
    - 6 to 12 months (24 RCTs; N = 7,423)
      - RR 0.72 (95% CI 0.55 to 0.93)
      - 3.7% versus 4.8% control
    - >12 to 36 months (12 RCTs, N = 9,565)
      - RR 1.07 (95% CI 0.91 to 1.27)
      - 5.5% versus 5.0% control
    - 3 years (10 RCTs; N = 1,560)
      - RR 0.67 (95% CI 0.5 to 0.9)
      - 8.4% versus 13% control
  - CV mortality
    - 6 to 12 months (17 RCTs; N = 5,360)
      - RR 0.88 (95% CI 0.68 to 1.14)
      - 3.9% versus 4.5% control
    - >12 to 36 months (4 RCTs; N = 3,614)
      - RR 0.77 (95% CI 0.63 to 0.93)
      - 10.7% versus 13.6% control
    - 3 years (8 RCTs; N = 1,392)
      - RR 0.58 (95% CI 0.43 to 0.78)
      - 8.1% versus 14.2% control

- All-cause mortality
  - 6 to 12 months (25 RCTs; N = 8,823)
    - RR 0.87 (95% CI 0.73 to 1.04)
    - 5% versus 5.7% control
  - >12 to 36 months (16 RCTs; N = 11,073)
    - RR 0.90 (95% CI 0.80 to 1.02)
    - 8.3% versus 9.1% control
  - 3 years (11 RCTs; N = 3,828)
    - RR 0.91 (95% CI 0.75 to 1.10)
    - 25% versus 25.6% control

- **Abell 2017**: SR
  - 69 RCTs; N = 13,423 with established coronary heart disease; median duration 3 years; mean age 54; 17% female
  - Evaluating 72 exercise interventions comparing cardiac rehabilitation versus usual care
    - All interventions used aerobic training with 54% also including resistance training or calisthenic body-weight exercises, 80% group exercise, with only 18% containing sessions that were entirely unsupervised
    - Mean duration of interventions 3 months; median frequency 3 times per week; each session lasted a mean of 49 minutes (SD = 19 minutes)
  - MI (41 RCTs; N = 9,940)
    - RR 0.80 (95% CI 0.70 to 0.92)
    - 6.7% versus 8.4% usual care
  - CV mortality (31 RCTs; N = 6,926)
    - RR 0.74 (95% CI 0.65 to 0.86)
    - 8.2% versus 11.3% usual care
  - All-cause mortality (47 RCTs; N = 11,279)
    - RR 0.90 (95% CI 0.83 to 0.99)
    - 12.1% versus 13.8% usual care
  - No significant difference found in risk reduction when subgroup analyses were performed comparing groups that exercised ≥150 minutes/week versus <150 minutes/week.
- **Posadzki 2020:** SR of SRs
  - 150 Cochrane SRs; 288 RCTs; N = 485,110
  - The SRs included RCTs that evaluated only physical activity versus usual care and included both healthy patients and patients with a variety of health conditions, evaluating a variety of health outcomes
  - Age ranged from 3-85 and included children with asthma, adults with a variety of malignancies, mental health conditions, and fibromyalgia among others
  - 8 Cochrane SRs in patients with CVD were analyzed separately (166 RCTs; N = 24,275); 75% of outcomes were from a single systematic review on CV rehabilitation.
  - All-cause mortality
    - RR 0.85 (95% CI 0.76 to 0.96)

        - By frequency:
            - Up to 3 times per week RR 0.63 (95% CI 0.39 to 1.00)
            - More than 3 times per week RR 0.87 (95% CI 0.78 to 0.98)
        - By time per session (average time not reported)
            - Up to 60 min RR 0.56 (95% CI 0.35 to 0.91)
            - More than 60 min RR 0.88 (95% CI 0.79 to 0.97)
- **Long 2018**: Cochrane SR
    - Comparing exercise-based cardiac rehabilitation to usual care specifically for patients with stable angina
    - Found only 3 RCTs with outcomes on all-cause mortality and acute MI
        - 3 RCTs; N = 195-254; age 52-60; 0% females; mean duration 52 weeks
    - No statistically significant findings

Limitations

- For primary prevention, evidence is insufficient to make any recommendation
    - In the SR, RCTs did not define what "apparently healthy" meant and some of these RCTs were in a nursing home population
    - MACE was not a primary outcome in any of the RCTs.
- Most studies reported as RCTs had a short intervention period with longer term observational follow-up
- Results in meta-analyses showed wide variation in point estimates and confidence intervals
- Interventions varied in composition (for example walking, biking, swimming; aerobic versus resistance; supervised versus non-supervised), intensity (for example some specified heart rate percentage or maximal oxygen uptake [VO2max]); and duration of exposure (length of workouts and frequency of workouts)
- Risk of bias in RCTs involves inherent inability to blind the intervention though most trials blinded the outcome assessors
- Many RCTs in the SRs do not report withdrawals/non-adherence; attrition was "high" in 23% of SRs **(Posadzki 2020)**

CONTEXT

CV rehabilitation is a complex intervention that may involve a variety of therapies, including exercise, risk factor education, behaviour change, psychological support, and strategies that are aimed at targeting traditional risk factors for CV disease. Most involve weekly sessions for 6-12 weeks **(West 2012)**. Early SRs of CV rehabilitation rely on RCTs before the introduction of thrombolysis, primary angioplasty, secondary prevention with aspirin, beta-blockers, ACE-inhibitors and statins **(West 2012)**. Exercise has proven health benefits in multiple other conditions like chronic pain, osteoarthritis, mental health **(Korownyk 2022)**.

Major guideline recommendations

All major guidelines recommend physical activity to reduce CV outcomes (*Table 5*). One-hundred and fifty minutes of exercise a week is often recommended but the evidence base for this is limited.

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METHODS

- Pubmed search November 1, 2022: “cardiac rehabilitation” “mortality” “stroke” “myocardial infarction” filtered by Systematic Review 2015-2022: yielded 202 results
- Pubmed search November 1, 2022: “major adverse CV events” “exercise” “physical activity” filtered by Systematic Review: yielded 9 results
- Pubmed search on November 8, 2022: “CV disease” “exercise” filtered by Systematic Review, 2017-2022: yielded 350 results
- Cochrane search November 9, 2022 using “CV disease” AND (“cardiac rehabilitation” OR “physical activity” OR “exercise”).
- Google Scholar search November 9, 2022 using “CV disease” AND exercise AND systematic review. First 5 pages reviewed.
- “Similar article search” from retrieved systematic reviews did not reveal additional papers
- References from International Guidelines: one additional systematic review on Cardiac Rehab (Abell)
- Reference from systematic review (Patnode) relating to 2 exercise trials.
- Communication with author of systematic review (Posadski) for meta-analysis of subgroup of mortality data in patients with CVD.
- Pubmed search December 8, 2022: “primary prevention” “exercise” “CV events” “mortality” filtered by “systematic review” revealed one additional systematic review **(Garcia-Hermoso 2020)**

APPENDIX

Table 1: Systematic review baseline characteristics

Study	No. studies	Types of studies	Duration of follow-up	Mean age (years)	Intervention	Comparator	Included population	Comments
Secondary prevention								
Long 2018	7	RCTs	6-12 months	50-66	Exercise-based cardiac rehab	Usual care	Patients with stable angina	
Dibben 2021	85	RCTs	6-12 months; 12-48 months; >3 years	47-77	Exercise-based cardiac rehab	"No exercise" control	Patients with coronary heart disease (50% MI alone, 6% angina alone, 8% post-CABG, 8% post-PCI, 31% mixed population of patients with CHD)	
Abell 2017	69	RCTs	Mean 3 years	54	Cardiac rehabilitation	Usual care	A large proportion of trials (43/69; 62%) included only patients after MI; however, those published from 1990 onward often included patients diagnosed with CAD (n = 8; 12%), post-PCI (n = 5; 7%), post-CABG (n = 2; 3%) or a combination of these cardiac	

Study	No. studies	Types of studies	Duration of follow-up	Mean age (years)	Intervention	Comparator	Included population	Comments
							etiologies (n = 11; 16%).	
Posadski 2020	8	SRs	NR	NR	Any exercise	Usual care	Patients with CVD with an outcome of mortality	Overall, 130 SRs with 2,888 RCTs were reviewed but only 8 reported on mortality in patients with CVD
Primary & mixed prevention								
Garcia-Hermosa 2020	56	RCTs	52-208 weeks	74	Any exercise >1 year	Usual care	Primary care and "clinical population" including cancer, DM; however, no noted CVD population	Overall, looked at 90 RCTs, but only 56 reported on mortality, none on other CV outcomes
Harris 2019	2	RCTs	3-4 years	47-75	12-week supervised exercise	Usual care	Healthy community adults	Follow-up 4 years after 12-week intervention; using primary care data

CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SR = systematic review

Table 2: Systematic review efficacy data separated by primary/mixed prevention, secondary prevention, and RCT data

Outcome	Study	Effect estimate	SS or NSS	No. patients	Quality of evidence*	Notes for indirectness	Publication bias
Secondary prevention							
All-cause mortality	Long 2018	RR 1.01 (95% CI 0.18 to 5.67)	NSS	195	High	Indirect due to very selective search for patients with "only" stable angina which does not reflect the average patient (excluded many trials)	Not assessed
All-cause mortality	Dibben 2021 (6-12 months)	RR 0.87 (95% CI 0.73 to 1.04)	NSS	8,823	High	No major concerns	Assessed with funnel plot; no concerns
All-cause mortality	Dibben 2021 (>12-36 months)	RR 0.90 (95% CI 0.80 to 1.02)	NSS	11,073	High	No major concerns	Assessed with funnel plot; no concerns
All-cause mortality	Dibben 2021 (>36 months)	RR 0.91 (95% CI 0.75 to 1.10)	NSS	3,828	High	No major concerns	Assessed with funnel plot; no concerns
All-cause mortality	Abell 2017	RR 0.90 (95% CI 0.83 to 0.99)	SS	11,279	High	No major concerns	Assessed with funnel plot; no concerns
All-cause mortality	Posadski 2020	RR 0.85 (95% CI 0.76 to 0.96)	SS	24,275	High	Patients had CVD in the 8 SRs reviewed; authors indicate that of 114 CSRs overall, indirectness not a concern but imprecision (65%) and	"Publication bias was the least frequent reason for downgrading in 26 (17.3%)"

Outcome	Study	Effect estimate	SS or NSS	No. patients	Quality of evidence*	Notes for indirectness	Publication bias
						inconsistency (43%) were	
CV mortality	Dibben 2021 (6-12 months)	RR 0.88 (95% CI 0.68 to 1.14)	NSS	5,360	High	No major concerns	Assessed with funnel plot; no concerns
CV mortality	Dibben 2021 (>12-36 months)	RR 0.77 (95% CI 0.63 to 0.93)	SS	3,614	High	No major concerns	Assessed with funnel plot; no concerns
CV mortality	Dibben 2021 (>36 months)	RR 0.58 (95% CI 0.43 to 0.78)	SS	1,392	High	No major concerns	Assessed with funnel plot; no concerns
CV mortality	Abell 2017	RR 0.74 (95% CI 0.65 to 0.86)	SS	6,926	High	No major concerns	Assessed with funnel plot; no concerns
Fatal and/or nonfatal MI	Dibben 2021 (6-12 months)	RR 0.72 (95% CI 0.55 to 0.93)	SS	7,423	High	No major concerns	Figure 8 (MI at >12-36-month follow-up) shows some concerns
Fatal and/or nonfatal MI	Dibben 2021 (>12-36 months)	RR 1.07 (95% CI 0.91 to 1.27)	NSS	9,565	High	No major concerns	Figure 8 (MI at >12-36-month follow-up) shows some concerns
Fatal and/or nonfatal MI	Dibben 2021 (>36 months)	RR 0.67 (95% CI 0.50 to 0.90)	SS	1,560	High	No major concerns	Assessed with funnel plot; no concerns

Outcome	Study	Effect estimate	SS or NSS	No. patients	Quality of evidence*	Notes for indirectness	Publication bias
Acute MI	Long 2018	RR 0.33 (95% CI 0.07 to 1.63)	NSS	254	High	Indirect due to very selective search for patients with "only" stable angina which does not reflect the average patient (excluded many trials)	Not assessed
Acute MI	Abell 2017	RR 0.80 (95% CI 0.70 to 0.92)	SS	9,940	High	No major concerns	Assessed with funnel plot; no concerns
Primary & mixed prevention							
Mortality	Garcia-Hermosa 2020	RR 0.93 (95% CI 0.83 to 1.04)	NSS	26,017	High	Used "PEDRO" score Physiotherapy Evidence Database out of avg 6.1/11 with 40.2% failing to conceal allocation	Assessed with funnel plot; no concerns
RCTs							
Non-fatal CV events	Harris 2019	0.27 (95% CI 0.08 to 0.88)	SS	1,321	4/7	Patients were invited to participate; 80% rated general health as good or very good	
Non-fatal and fatal CV events	Harris 2019	0.34 (95% CI 0.12 to 0.91)	SS	1,321	4/7	Patients were invited to participate; 80% rated general health as good or very good	

*Used AMSTAR for SRs (*Table 3A*); used Cochrane risk of bias tool for RCTs (*Table 3B*)

AMSTAR = A Measurement Tool for Assessment of Multiple Systematic Reviews; CV = cardiovascular; CVD = cardiovascular disease; MI = myocardial infarction; NSS = not statistically significant; RCT = randomized controlled trial; RR = risk ratio; SR = systematic review; SS = statistically significant

Table 3A: Quality assessment of included systematic reviews using AMSTAR

Author, Year	Duplicate study selection and data extraction?	Comprehensive literature search performed?	Characteristics of the included studies provided?	Scientific quality of included studies assessed & documented?	Methods used to combine the findings of studies appropriate?	Was the conflict of interest stated?	Publication bias formally assessed?	Overall quality
Long 2018	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Dibben 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Abell 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Posadski 2020	1 select, 2 extract	Just Cochrane (definition)	Yes	Yes	Yes	Yes	Yes	High
Garcia-Hermosa 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

AMSTAR = Assessment of Multiple Systematic Reviews

Table 3B: Quality assessment of included randomized controlled trials using Cochrane Risk of Bias tool

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/ physicians	Blinding of outcome assessors	Loss to follow up	Selective outcome reporting	Comments
Harris 2019	Yes	Yes	NA	No	Yes	At 4 years, control 16% and intervention 18%	No	Intervention lasted 12 weeks; follow-up with primary care data at 3 or 4 years

NA = not applicable

Table 4: GRADE certainty of evidence for effect of exercise-based cardiac rehabilitation (secondary prevention) on all-cause mortality

Treatment: exercise-based cardiac rehabilitation (secondary prevention)
Outcome: all-cause mortality

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate (range)	Median (IQR)	Overall certainty
SR	3 (3,828-24,275)	Not serious	Not serious	Serious Evidence based on exercise-based cardiac rehabilitation; unclear whether this includes interventions beyond exercise.	Serious CIs included potential benefits and harms	Undetected	RR 0.85-0.91	RR 0.90 (0.85-0.91)	Low This outcome has two serious **(-2)** therefore **downgrade by two to low**

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IQR = inter-quartile range; RR = risk ratio; SR = systematic review

Table 5: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
"In patients with/at risk of CVD, does increasing physical activity (including cardiac rehab) reduce the risk of CV events?"	"… advised to engage in aerobic physical activity 3-4 sessions per week, lasting on average 40 minutes per session and involving moderate-to vigorous-intensity physical activity."	"The reduction of LDL-C levels induced by regular physical exercise is even smaller. The benefits of weight reduction and physical exercise on the CV risk profile likely impact on other risk factors, especially	"Suggest regular aerobic activity of any intensity or duration". WEAK Note Physical Activity Guideline for Americans recommends 150 min moderate, 75 min vigorous but evidence limitations. Also	"… continue to recommend that all adults should accumulate at least 150 minutes of moderate to vigorous aerobic activity per week." (STRONG, high quality)	"It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity." Class I Recommendation. "It is recommended for adults of all ages to strive for at least 150 - 300 min a week of moderate intensity or 75 - 150 min a week of	"The USPSTF has made several recommendations related to the prevention of CVD in adults… behavioral counseling to promote a healthy diet and physical activity for CVD prevention in

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
		hypertension and diabetes." "Regular physical exercise reduces plasma TG levels over and above the effect of weight reduction." "Aerobic physical activity, such as 2530 km of brisk walking per week (or any equivalent activity), may increase HDL-C levels by 0.080.15 mmol/L (3.16 mg/dL)"	evidence benefit at lower than this." "… a structured, exercise-based cardiac rehabilitation program for patients with recent occurrence of coronary heart disease" STRONG		vigorous intensity aerobic PA, or an equivalent combination thereof, to reduce all-cause mortality, CV mortality, and morbidity." Class I, Level A Recommendation "It is recommended that adults who cannot perform 150 min of moderate-intensity PA a week should stay as active as their abilities and health condition allow" Class I, Level B Recommendation "It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity." Class I, Level B Recommendation "Performing resistance exercise, in addition to aerobic activity, is recommended on 2 or more days per week to reduce all-cause mortality" Class I, Level B Recommendation	adults (with and without cardiovascular risk factors), and behavioral interventions to prevent obesity-related morbidity and mortality in adults."

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
					"Lifestyle interventions, such as group or individual education, behaviour-change techniques, telephone counseling, and use of consumer-based wearable activity trackers, should be considered to increase PA participation." Class IIa, Level B Recommendation.	

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

CV = cardiovascular; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; PA = physical activity; TG = triglycerides

CHAPTER 5: MEDITERRANEAN DIET

CLINICAL QUESTION

In patients with/at risk of cardiovascular disease, does the Mediterranean Diet reduce the risk of cardiovascular events?

BOTTOM LINE

The Mediterranean diet reduces the risk of cardiovascular (CV) events in both primary and secondary prevention. Best estimates from randomized controlled trials (RCTs) suggest a 25-30% relative risk (RR) reduction in MACE over ~5-7 years.

EVIDENCE

All evidence is statistically significant unless noted. Four systematic reviews (SRs) **(Rees 2019, Becerra-Tomas 2020, Grosso 2017, Papadaki 2020)** were found and consistently highlighted three RCTs **(Estruch 2013, de Lorgeril 1994, Singh 2002)**. Results were reported on a per-trial basis due to differences in patient populations. These four SRs found similar results overall. One recently published RCT not captured in the above SRs was found **(Delgado-Lista 2022)**. Of note is that the key RCTs had dieticians supporting the dietary interventions with individual and/or group sessions. Quality assessment of included SRs and RCTs can be found in *Tables 1A* and *1B*. GRADE certainty of evidence evaluation can be found in *Table 2*.

Primary prevention

- **PREDIMED**: trial that reported on clinical outcomes **(Estruch 2013, Estruch 2018)**
    - Three-arm study of Mediterranean diet supplemented with extra virgin olive oil (EVOO) versus Mediterranean diet supplemented with nuts versus a low-fat diet (7,447 patients at high risk of cardiovascular disease (CVD); mean age 67; 57% female; followed for 4.8 years)
    - Composite clinical events (CVD mortality, total mortality, myocardial infarction [MI], stroke)
        - Hazard ratio (HR) 0.70 (95% confidence interval [CI] 0.58 to 0.85)
    - Stroke
        - HR 0.60 (95% CI 0.45 to 0.80)
    - CV mortality, total mortality and MI were not statistically significant when analyzed separately
    - Limitations: protocol deviations in regards to randomization were identified in PREDIMED RCT at clinic sites but republished results were not significantly impacted

Secondary prevention

- **De Lorgeril 1994/Lyon Diet Heart Study**
    - Randomized, single-blinded trial of 605 patients that had previously suffered a MI; comparing Mediterranean diet to a prudent Western-type diet, followed for a mean of 46 months
    - Total mortality

        - RR 0.44 (95% CI 0.21 to 0.92)
    - CVD mortality
        - RR 0.35 (95% CI 0.15 to 0.82)
    - CVD death and non-fatal MI
        - RR 0.28 (95% CI 0.15 to 0.52)
    - Limitations
        - Statin use unknown
- **Delgado-Lista 2022**
    - RCT comparing Mediterranean diet vs. low-fat diet
    - N = 1,002 Spanish patients; mean age 59.5; 18% female; ~7 years follow up; ~87% on statin medication and 98.2% on antiplatelets or anticoagulants
    - Composite outcome (MI, revascularization, ischemic stroke, peripheral arterial disease, CV death) at ~7 years
        - 17% Mediterranean vs 22% low-fat
            - HR ~25% relative risk reduction (statistically significant)
    - Adherence
        - 9% discontinuation in Mediterranean compared to 17% in low-fat

Mixed population (secondary and primary prevention)

- **Singh 2002**
    - Randomized, single-blind trial of 1,000 patients comparing Indo-Mediterranean diet (consisting of whole grains including legumes, fruits, vegetables, nuts and mustard or soybean oil) versus control diet, followed for 2 years total
        - 48% of study population post-MI; 6-7% on statins
    - Total cardiac endpoints (non-fatal MI, fatal MI, sudden cardiac death)
        - RR 0.50 (95% CI 0.34 to 0.73)
    - Limitations
        - Two-thirds of the participants were vegetarians
        - Participants' adherence to the diet was only monitored for 3 weeks
        - Concerns raised about reliability of results after publication **(Horton 2005)**

Limitations

- Use of statin medications was inconsistent, unclear whether this impacts results

CONTEXT

The Mediterranean diet generally consists of an abundance of plant foods (including fruits, vegetables, whole grains, nuts and legumes), olive oil as a principal source of fat, cheese and yogurt consumed daily in low to moderate amounts, fish and poultry consumed in low to moderate amounts a few times per week and infrequent consumption of red meat and processed sweets **(McManus 2019)**. A visual representation of the Mediterranean diet can be found in this document:
https://memory.ucsf.edu/sites/memory.ucsf.edu/files/MediterraneanDietHandout.pdf

Major guideline recommendations

Refer to *Table 3* for recommendations pertaining to the Mediterranean diet from major guidelines published within the last 5 years.

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METHODS

Inclusion criteria were SRs that included RCTs that studied the Mediterranean diet compared to a control and reported on patient important outcomes. RCTs were included if they were published following the last SR.

- A search in PubMed was completed with the keywords “Mediterranean diet” and “cardiovascular” using filters for randomized control trials.
- In addition, a search in the MEDLINE database was completed using a search strategy that included keywords such as “mediterranean diet”, “major cardiovascular event” and “mortality” along with related terminology. A meta-analysis filter was used and the full search strategy is available upon request.
- A grey literature search was completed to find any additional randomized control trials that came out in the last 5 years.
- Full text review and data extraction was completed by two authors independently.

APPENDIX

Table 1A: Quality assessment of included systematic reviews using AMSTAR

Systematic review, year	Dual selection and extraction	Comprehensive literature search	Characteristics of included studies	Quality assessment of studies	Pooled estimates	Conflicts of interests stated	Total score
Becerra-Tomas 2020	1	1	1	1	1	1	6
Papadaki 2020	1	1	1	1	1	1	6
Rees 2019	1	1	1	1	1	1	6
Grosso 2017	1	1	1	1	1	0	5

AMSTAR = Assessment of Multiple Systematic Reviews

Table 1B: Quality assessment of included randomized control trials using the Jadad scale

Study, year	Was it randomized?	Was randomization process appropriate?	Was it double blind?	Was blinding process appropriate?	Were drop-outs described?	Deductions (for inappropriate randomization or blinding)	Total score
Delgado-Lista 2022	1	1	1	1	1	-1	4
De Lorgeril 1994	1	1	0	0	1	0	3
Singh 2002	1	1	0	0	1	-1	2
Estruch 2013/2018	1	1	0	0	1	0	3

Table 2: GRADE certainty of evidence for effect of the Mediterranean diet (primary prevention) on composite clinical events
Treatment: Mediterranean diet (primary prevention)
Outcome: composite clinical events (CVD mortality, total mortality, MI, and stroke)

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate	Certainty
SR of RCTs	1 (7,447)	Serious Original publication was retracted due to concerns re: randomization and protocol deviations and while this did not impact results, it is cause for concern	Not serious	Not serious	Not serious	Not detected	HR 0.70 (95% CI 0.58 to 0.85)	Moderate This outcome has one serious **(-1)** therefore **downgrade by one to moderate**

CVD = cardiovascular disease; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SR = systematic review

Table 3: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
In patients with/at risk of CVD, does the Mediterranean Diet reduce the risk of CV events?	"Use lifestyle counseling to recommend a heart healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids."	Dietary patterns that have been more extensively evaluated are the Dietary Approaches to Stop Hypertension (DASH) diet—particularly in relation to BP control—and the Mediterranean diet; both have	"Recommend dietitian-led Mediterranean diet for risk >12%" For primary and secondary prevention of CVD, we suggest a dietitian-led Mediterranean diet. - Weak for"	"We continue to recommend a Mediterranean dietary pattern, which has evidence of CV outcome benefit in systematic reviews and meta-analyses."	"It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD." Class I, Level A Recommendation	Did not address diet

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
		proved to be effective in reducing CV risk factors and, possibly, to contribute to ASCVD prevention.				

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease

CHAPTER 6: STATINS IN OLDER ADULTS

CLINICAL QUESTION

In patients over age 65, do statins reduce cardiovascular events compared to placebo, without significantly increasing harms?

BOTTOM LINE

Best evidence is from a large systematic review (SR) that included individualized patient data, separated by primary and secondary prevention and grouped into 5-year age categories with a median follow-up of 4.9 years. For patients 65-75 years old without cardiovascular disease (CVD) (primary prevention), statins resulted in an around 25% relative decrease in risk of major adverse cardiac events (MACE). For combined primary and secondary prevention patients, statins resulted in an around 10% decrease in cardiovascular (CV) mortality. For patients over 75 years, starting statin therapy did not significantly decrease risk of future CV events. For patients over 65 years of age (including those >75 years) with established CVD (secondary prevention), statins resulted in a 20% relative reduction in MACE.

In SRs that reported on patients >65 years of age, for secondary prevention, statins led to a relative reduction in CV mortality by 20-30% and all-cause mortality by 20%. In primary prevention, statins did not lead to a reduction in CV or all-cause mortality. Overall adverse events, adverse events resulting in medication discontinuation, and incidence of cancers were not different between statin therapy and placebo.

EVIDENCE

The focus of this review is on clinically meaningful outcomes and important harms of statin therapy in adults aged 65 years or older. Seven SRs (8-28 randomized controlled trials [RCTs]; N = 18,192-186,854; follow-up 52-588 weeks) exploring statin therapy in patients aged 65 years or older, with or without CVD were included (**Afilalo 2008, CTTC 2019, Ponce 2019, Roberts 2007, Savarese 2013, Teng 2015, Zhou 2020**). While most reviews included similar RCTs, inclusion criteria, data analysis (primary, secondary, or mixed risk populations), age categories, and outcomes reported differed. Regardless of differences, results were relatively consistent among SRs. For characteristics of the included SRs, see *Table 1*. For further explanation of the SRs including AMSTAR and GRADE see *Appendix 1*, and *Tables 2 and 3*.

Focusing on the largest SR (**CTTC 2019**), including individualized patient data comparing statins to placebo in 21 RCTs and high versus low dose statins in 5 RCTs. The review limited inclusion to trials with a minimum of 1,000 participants, followed for 2 years. 186,854 patients followed for a median 4.9 years were grouped by age at randomization (5-year categories) and by primary or secondary

prevention. Of the total population, 55% had pre-existing CVD, 79% were over the age of 55 at commencement, and 8% were over the age of 75. The primary outcome of "major vascular events" (non-fatal myocardial infarction, coronary death, coronary revascularization, or stroke) was analyzed by 5-year age categories, and by primary or secondary prevention. Further, CV and overall mortality was also reported but only analyzed by age category (not by primary or secondary prevention).

Table 1: Characteristics of included systematic reviews

Study	Trials (patients)	Duration	% Male	Mean age (years)	Population studied/ reported	Age explored, categories	Outcomes reported	Notes
Roberts 2007	18 (51,351)	Range 1-6 years	72%	NR	Primary and secondary combined (mixed)	≥60 years (also reported on patients ≥65 years	All-cause mortality, CHD mortality, fatal and nonfatal myocardial infarction, or stroke. Adverse events (LFTs, CK), discontinuation due to adverse events	
Afilalo 2008	9 (19,569)	Mean 4.9 years	NR	NR	Secondary	≥65 years	All-cause mortality, CHD mortality, non-fatal MI, revascularization, stroke	
Savarese 2013	8 (24,674)	Mean 3.5 years	57%	73	Primary	≥65 years	All-cause death, CV death, MI, stroke, and cancer	
Teng 2015	8 (25,952)	Mean 3.5	56%	73	Primary	≥65 years	MACE, mortality, 3Xs LFTs, myalgia, myopathy, rhabdomyolysis, serious AEs, diabetes, cognition	
Ponce 2019	17 (50,322)	Range 52-588 weeks	NR	NR	Primary and secondary: analyzed separately	≥65 years	CAD, CV mortality, all-cause mortality	Included non-statin trials but reported on statins alone.
CTTC 2019	28 (186,854)	Median 4.9 years	72%	63	Primary and secondary (analyzed combined and separately)	<55 years; then 5-year groupings until >75 years	Major vascular events: major coronary events, coronary revascularization, and stroke. Major coronary events: non-fatal MI or coronary death.	Analyzed with or without 4 RCTs with HF or CRF patients

Study	Trials (patients)	Duration	% Male	Mean age (years)	Population studied/ reported	Age explored, categories	Outcomes reported	Notes
							Cancers, cause-specific mortality	
Zhou 2020	11 (18,192)	Median 3 years	57%	74	Primary	≥65 years	Focus on muscle related symptoms, total and serious AEs, discontinuation for AE	Harms only

AE = adverse event; CAD = coronary artery disease; CHD = coronary heart disease; CK = creatine kinase; CRF = chronic renal failure; CV = cardiovascular; HF = heart failure; LFT = liver function test; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial

Efficacy: primary prevention

MACE

Outcomes from the largest SR are reported due to the included subgroups that analyze participants by age and CV prevention group (primary versus secondary) (**CTTC 2019**). It should be noted that overall analyses included patients under the age of 65 and results are reported per 1mmol/L of LDL reduction, which assumes a linear relationship in reduction of LDL and vascular events and may impact clinical interpretability. Another SR found that statins, on average, decrease LDL by 1.22 mmol/L, while control decreases 0.26mmol/L for an ~1mmol/L difference (**Savarese 2013**).

- Major vascular events (major coronary events [non-fatal myocardial infarction or coronary death] plus coronary revascularization and stroke) (**CTTC 2019**). MACE benefit with statins appears to diminish with advancing age in primary prevention, with uncertainty existing in those over 75 years (**CTTC 2019**). For example:
    - For patients >65 to ≤70 years: relative risk (RR) 0.61 (95% confidence interval [CI] 0.51 to 0.73)
    - For patients >70 to ≤75 years: RR 0.84 (95% CI 0.70 to 1.01)
    - For patients ≥75 years: RR 0.92 (95% CI 0.73 to 1.16)

Similarly, a smaller, earlier SR (8 RCTs; N = 25,952) found statins decreased MACE in patients ≥65 years old without CVD (RR 0.82 [95% Cl 0.74 to 0.92]) (**Teng 2015**).

Mortality

- CV mortality
    - Reported by two SRs; no statistically significant reduction with statin therapy (**Ponce 2019; Savarese 2013**).

- All-cause mortality
    - Reported by three SRs; no statistically significant reduction with statin therapy (**Ponce 2019; Savarese 2013; Teng 2015**).

Efficacy: secondary prevention

MACE

- Major vascular events: ~20% relative significant benefit across all ages (**CTTC 2019**)
    - Including all patients: 4.4% versus 5.4% placebo (events per annum); RR 0.80 (95% CI 0.77 to 0.82) (**CTTC 2019**)
        - For example, patients >65 to ≤70 years: 4.3% statins versus 5.5% placebo (events per annum; statistically significant)
        - For patients >75 years: 6.0% statins versus 6.8% placebo (events per annum; statistically significant)

Mortality

- CV mortality
    - Reported by two SRs, finding a 20-30% relative reduction
        - RR 0.80 (95% CI 0.73 to 0.89) (**Ponce 2019**); RR 0.70 (95% CI 0.53 to 0.83) (**Afilalo 2008**)
- All-cause mortality
    - Reported by two SRs, finding a 20% relative reduction
        - RR 0.80 (95% CI 0.73 to 0.89) (**Ponce 2019**)**;** RR 0.78 (95% CI 0.65 to 0.89) (**Afilalo 2008**)

Efficacy: primary + secondary prevention

Mortality

- Vascular death
    - Including all patients: 1.2% versus 1.4% (events per annum); RR 0.88 (95% CI 0.85 to 0.91) (**CTTC 2019**)
        - For patients >65 to ≤70: 1.4% statins versus 1.7% placebo (events per annum; statistically significant)
        - For patients >75 years: 3.7% statins versus 4.0% placebo (events per annum; not statistically significant)
    - Five SRs reporting on CV mortality found statins led to a relative reduction of 9-30%, with 4/5 results statistically significant.
- All-cause mortality
    - Including all patients: 2.2% versus 2.3% (events per annum); RR 0.91 (95% CI 0.88 to 0.93) (**CTTC 2019**)
        - For patients >65 to ≤70: 2.5% statins versus 2.8% placebo (events per annum; statistically significant)
        - For patients >75 years: 6.2% statins versus 6.6% placebo (events per annum; not statistically significant)

- Six SRs reporting on all-cause mortality found statins led to a relative reduction of 4-22%, with 4/6 results statistically significant.

Safety

Statins in a population of adults over the age of 65 were not associated with significant harms. Overall adverse events were reported by one SR in a primary prevention population (**Zhou 2020**), finding no difference between statins and placebo (RR 0.99, 95% CI 0.95 to 1.04). Serious adverse events were reported by two SRs, finding no difference between statins and placebo. Discontinuation due to adverse events was reported by two SRs, finding no difference between statins and placebo (median RR 1.08; 0/2 SRs statistically significant).

Statins and cancer

Three SRs examined the effect of statins on cancer incidence in a mixed risk population. The earliest SR (**Roberts 2007**) (based on three trials of 10,339 patients 65 years of age or older), found a borderline statistical significance increase in cancer incidence (RR 1.16, 95% CI 1.01 to 1.22). This finding was largely driven by the results of the 3-year PROSPER trial which enrolled ~5,800 older adults aged 70-82 years (mean age 75 years) with CVD and randomized to pravastatin or placebo. The 9-year follow up of the PROSPER trial did not show an increase in cancer incidence (hazard ratio [HR] 1.08, 95% CI 0.96 to 1.21) or cancer death (HR 1.12, 95% CI 0.96 to 1.30). Two subsequent and larger SRs (**CTTC 2019; Savarese 2013**) including one with individual patient data and separated by age intervals (**CTTC 2022**) did not find a difference in cancer incidence (**CTTC 2019; Savarese 2013**) or cancer death (**CTTC 2019**).

New literature

Following the completion of our search, a new SR was published, examining a population of older adults (>80 years), without CVD (primary prevention) being treated with statin therapy (**Marcellaud 2023**). This review included both RCTs and cohort studies, however did not add any new evidence to what is currently presented.

The STAREE trial (**ClinicalTrials.gov NCT02099123**) is an ongoing RCT that will determine whether taking daily statin therapy (40 mg atorvastatin) will extend the length of a disability-free life and CV outcomes in healthy participants aged 70 years and above. Estimated completion year is 2025.

CONTEXT

Major guideline recommendations

Guidelines vary in their definition of older adults and their recommended approaches. Recommendations vary from no specific recommendations, to insufficient evidence to make recommendations, to treating patients (including those >75 years) like younger patients. For a list of recommendations from recent guidelines, refer to *Table 4*.

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METHODS

Searches were conducted on December 1, 2022. In total, 380 SRs were identified through database searching and reviewed by two authors for inclusion. Seven SRs were included in this review.

- *PubMed search*: our search strategy included multiple searches. Based on previous guidelines and our broad knowledge of this topic, we chose to limit our searches to SRs. No limit was placed on year or language, to prevent missing any relevant reviews
    - (old* OR senior*) AND (cardiovascular) AND (statin*); Systematic Review Filter. Results = 16
        - Through this initial search, we did not identify any relevant SRs, therefore we broadened our search terms to include synonyms for both intervention and outcome. Based on this adjustment, the following search was conducted
    - (older adult* OR elderly) AND (statin* OR lipid*) AND (mortality OR cardiovascular) Filters: Systematic Review. Results = 364
        - This search yielded nine potentially relevant SRs, of which three were included in this review **(Teng 2015, Ponce 2019, Zhou 2020)**

- *Reference list search*: after inclusion, a reference list search was conducted on the three SRs. From this, three SRs were further identified **(Afilalo 2008, Savarese 2013, CTTC 2019)**
- *Guideline reference search*: we searched through relevant guidelines and identified one additional SR **(Roberts 2007)**

APPENDIX 1: INDIVIDUAL SYSTEMATIC REVIEWS

Roberts 2007

- This SR included 18 trials of 51,351 patients with an average age of greater than 60, followed for at least 1 year. While this review included a mixed population of CV prevention, the majority focused on a population at high risk for coronary heart disease (two in primary prevention). The search protocol for this review was narrow, searching only PubMed database. Further, this review is limited by their inclusion criteria of an average age of over 60. This means that participants under the age of 60 were likely included in this review.
- Outcomes were reported based on two groups: the overall population of the SR and a subgroup of participants ≥65 years.
- Borderline statistical significance was found in cancer incidence (RR 1.16, 95% CI 1.01 to 1.22) based on three trials of 10,339 patients 65 years of age or older.

Afilalo 2008

- This SR of secondary prevention patients included 9 trials of 19,569 patients followed for a mean 4.9 years. The authors included data from both unpublished (5/9) and published sources (4/9). One trial published in 2002 (**Heart Protection Study Group 2002**) contributed over 50% of the data, in 10,697 patients with vascular disease or diabetes. Analyses were conducted with and without this study, finding consistency in review outcomes.
- Further study details are provided below:

Author/year	Follow-up duration	Number of patients	% Male	Baseline LDL	Age range	Intervention
HPSG 2002	5.0 years	10,697	75	3.4 mmol/L	65-80 (mean/median not reported)	Simvastatin 40 mg/d

HPSG = Heart Protection Study Group; LDL = low-density lipoprotein

Savarese 2013

- This SR included 8 primary prevention trials of 24,674 patients followed for a mean 3.5 years. All included participants were ≥65 years. The authors of this review completed GRADE assessments, concluding that all reported outcomes were based on high certainty evidence.

Teng 2015

- This SR included 8 primary prevention trials of 25,952 patients followed for a mean 3.5 years. All included participants were ≥65 years. Trials were included only if they reported on at least one clinically meaningful outcome (e.g., MACE, all-cause mortality). Adverse events were reported, however there was insufficient data to conduct meta-analyses for myopathy, rhabdomyolysis and cognitive impairment.

Ponce 2019

- This SR included 17 trials in 50,322 patients, aged 65 and older, followed for a minimum of one year. Follow up in primary prevention trials ranged from 52-416 weeks and from 120-588 weeks in secondary prevention.
- A subgroup analysis was conducted, based on one primary prevention trial in 1,129 patients with diabetes. Reduction in myocardial infarction was significant (RR 0.41, 95% Cl 0.22 to 0.77).
- Coronary artery disease, CV and all-cause mortality, and stroke were not statistically significant.
- In primary prevention, two cohorts of patients were formed: ≥65-75 and >75 years of age. No statistical between group differences were found for any outcome. Based on data reporting, a cohort of patients >75 years of age could not be formed for secondary prevention trials.

CTTC 2019

- This updated meta-analysis included 28 trials in 186,854 patients with individual patient data, followed for a median 4.9 years. To be included, trials had to include at least one intervention to lower LDL cholesterol and including at least 1,000 patients followed for a minimum of two years. Twenty three of the 28 included trials compared statin therapy to placebo, while the rest included high vs lower dose statins. The included population had a 56% history of vascular disease.
- In most cases when power was sufficient, outcomes were analyzed based on six age groups: ≤55 years, 56-60 years, 61-65 years, 66-70 years, 71-75 years, >75 years. When power was low, outcomes were split into two categories: ≤75 years or >75 years. Further, four trials including patients with heart failure or on dialysis were included or excluded with sensitivity analyses being performed to determine the effect of this population on the intended outcome.
- Limitations of this SR included that the results were reported per 1mmol/L reduction in LDL and not overall for each category and that they did not publish all-cause mortality or CV mortality separated by primary or secondary prevention.

Zhou 2020

- This SR included 11 primary prevention trials in 18,192 patients, aged 65 and older, followed for a median of 3 years. This trial did not report on efficacy outcomes, however looked specifically at the harms of statin therapy in this population.
- All included trials were industry funded.
- GRADE was completed for all outcomes, concluding that most outcomes were based on moderate certainty evidence. Three outcomes (myopathy, rhabdomyolysis, and total permanent discontinuations) were based on low certainty evidence.

APPENDIX 2: TABLES

Table 2: Quality assessment of included systematic reviews using AMSTAR

Study	Duplicate study selection and data extraction	Comprehensive literature search performed	Characteristics of included studies	Scientific quality of included studies assessed	Methods to combine findings appropriate	Conflict of interest stated	Publication bias formally assessed
Afilalo 2008	Yes	Yes	Yes	Yes	Yes	Yes	No
CTTC 2019	No	Yes	Yes	No	Yes	Yes	No
Ponce 2019	Yes	Yes	Yes	Yes	Yes	Yes	No
Roberts 2007	Yes	No	Yes	No	Yes	Yes	No
Savarese 2013	Yes	Yes	Yes	Yes	No	Yes	Yes
Teng 2015	Yes	No	Yes	Yes	Yes	Yes	No
Zhou 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AMSTAR = Assessment of Multiple Systematic Reviews

Table 3A: GRADE certainty of evidence for the effect of statin therapy on MACE in primary prevention in those aged 65-75 and in secondary prevention

Treatment: statins (secondary prevention; primary prevention in patients aged 65-75)
Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Effect estimate (range)	Median (IQR)	Overall rating
SR of RCTs	2 (18,914-141,365)	Not serious	Not serious	Not serious	Not serious	Undetected	RR 0.74-0.82	RR 0.78	High This outcome has no downgrades

GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IQR = inter-quartile range; MACE = major adverse cardiovascular events; RR = risk ratio; SR = systematic review

Table 3B: GRADE certainty of evidence for the effect of statin therapy on MACE in primary prevention in those aged ≥75

Treatment: statins (primary prevention in patients aged ≥75)

Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Effect estimate	Median (IQR)	Overall rating
SR of RCTs	1 (21,926)	Not serious	Not serious	Serious CIs contain important benefit and potential harm	Not serious	Undetected	RR 0.92 (95% CI 0.73 to 1.16)	NA	Moderate This outcome has one serious **(-1)** therefore **downgrade by one to moderate**

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IQR = inter-quartile range; MACE = major adverse cardiovascular events; NA = not applicable; RR = risk ratio; SR = systematic review

Table 4: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
In patients over age 65, do statins reduce cardiovascular events compared to placebo, without significantly increasing harms?	In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. "In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences" "In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated"	"Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients" "Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years" "Initiation of statin treatment for primary prevention in older people aged >75 years may be considered, if at high-risk or above" "It is recommended that the statin is started at a low dose if there is	No specific recommendations for older adults.	No specific recommendations for older adults.	Define older adults as those aged ≥70 years. "Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients" "Initiation of statin treatment for primary prevention in older people aged ≥70 may be considered, if at high risk or above" "It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions"	"The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality in adults 75 years or older"

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
	"In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy" "In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate intensity statin may be reasonable" "In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy" "In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure coronary artery calcium (CAC) to reclassify those with a CAC score of zero to avoid statin therapy"	significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals"				

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022
ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol

CHAPTER 7: STATINS AND COGNITION

CLINICAL QUESTION

In patients on statin therapy, do statins negatively affect cognition, memory, cognitive decline, or dementia compared to no statin?

BOTTOM LINE

Based on randomized controlled trials (RCTs) and large long term observational studies, statins are not associated with an increased risk of dementia or worsening of cognition scores.

EVIDENCE

We found a total of seven systematic reviews (SRs) with meta-analysis comparing statin with placebo or no statin. Three SRs included 2-9 RCTs (N = 1,046-26,340) **(McGuinness 2016, Davis 2020, Xuan 2020)** and four SRs included 25-46 observational studies (N = 123-9,162,509) **(Chu 2018, Zhang 2018, Poly 2020, Olmastroni 2022)**. *Table 1* and *Table 2* summarize SR characteristics and results. *Tables 3A-C* include the quality assessment of included SRs. GRADE certainty of evidence evaluation can be found in *Table 4*.

Incidence of dementia

- SRs of RCTs
    - One SR (one RCT; N = 20,536; 65-80 years old) reported on the incidence of dementia **(McGuinness 2016)**
        - **Heart Protection Study Collaborative Group (2002)**: 20,536 patients with cardiovascular disease or diabetes randomized to simvastatin or placebo for 5 years. Incidence of dementia was a secondary outcome and diagnostic criteria was not described.
        - Incidence of dementia: 0.3% in each group, no difference over 5 years
- RCTs not included in above SRs
    - **Bosch 2019**: N = 2,361; mean age 74
        - 2x2 factorial design comparing candesartan/hydrochlorothiazide, rosuvastatin, or both versus placebo
        - Cognitive outcomes (example, scores on Digital Symbol Substitution Test, 12-item Montreal Cognitive Assessment test [MOCA], Trail Making Test Part 2) and functional outcomes (example Standard Assessment of Global Activities in the Elderly):
            - No statistical differences at 5.7 years
        - Number of patients who developed dementia or were institutionalized
            - 12 (rosuvastatin) versus 8 (placebo), not statistically different
    - **Hu 2020**: N = 1,244; mean age 70; baseline mini-mental state exam (MMSE) score = 29
        - 2x2 design comparing telmisartan, rosuvastatin or both versus placebo
        - Cognitive outcomes (e.g., scores on MMSE, MOCA, Mattis Dementia Rating Scale, Clinical Dementia Rating) followed annually for 7 years

        - Risk of dementia: rosuvastatin lower than control group (no event rates provided), p<0.001
        - Change in MMSE score: -1.9 rosuvastatin versus -2.6 control, difference ~0.8 over 7 years (extrapolation by PEER, no comparative statistics reported)
    - **Zhang 2019**: N = 732; mean age 70; baseline MMSE score = 26
        - 2x2 factorial design comparing telmisartan, rosuvastatin, or placebo
        - Incidence of cognitive impairment: 11% rosuvastatin versus 19% placebo, number needed to treat 12 over 5 years
- SRs of observational studies
    - These SRs show reduced risk of dementia, Alzheimer's disease, and mild cognitive impairment with statins compared to no statin exposure. Risk of vascular dementia was no different between groups.
    - Details in table below

Outcome	No. SRs	Median (IQR)	Notes
Dementia	4	RR 0.85 (0.83-0.85)[1,2,3]	One SR[4] reported odds ratio 0.80 4/4 SRs statistically significant[1,2,3,4]
Alzheimer's disease	4	RR 0.72 (0.69-0.81) [1,2,3]	One SR[4] reported odds ratio 0.68 4/4 SRs statistically significant[1,2,3,4]
Vascular dementia	2	RR 0.97[1,3]	0/2 SR statistically significant
Mild cognitive impairment	1	RR 0.74 (95% CI 0.56 to 0.98)[1]	6 studies; N = 6,808

[1]**Chu 2018**; [2]**Zhang 2018**; [3]**Poly 2020**; [4]**Olmastroni 2022**
CI = confidence interval; IQR = interquartile range; RR = risk ratio; SR = systematic review

Performance on cognitive function testing

- One SR **(McGuinness 2016)** of two RCTs **(Heart Protection Study Collaborative Group 2002; Trompet 2010)**: each RCT measured cognition using different questionnaires or tools
    - MMSE: 30-point test; lower score = worse cognition
        - Mean difference 0.06 (95% CI -0.04 to 0.16) at 3.5 years (N = 5,804)
            - Minimally clinically important difference is two points **(McGuinness 2016)**
    - Telephone interview for cognitive status questionnaire: 39-point score; scores <22 considered cognitively impaired
        - Percentage of patients classified as cognitively impaired was 24% in both groups, no difference at 5 years (N = 20,536)
    - Stroop word score: total seconds to complete
        - Mean difference 0.8 seconds (95% CI -0.4 to 2.0) at 3.5 years (N = 5,804)

Statins for treatment of existing Alzheimer's Disease

- **Xuan 2020**: one SR (9 RCTs; N = 1,489; mean age range 65-78 years) over 12-78 weeks comparing statins versus placebo
    - MMSE, ADAS-Cog, ADL: no difference
    - Neuropsychiatric Inventory Scale: one-point improvement over placebo on 36-point scale (statistically significant but not clinically meaningful)

Adverse events

- Two SRs (2 studies each; N = 1,045-26,340), comparing statins to placebo in patients with **(Davis 2020)** or without **(McGuinness 2016)** baseline dementia
    - Overall adverse effects, discontinuation due to adverse effects: no difference

Limitations

- Most RCTs evaluating the effect of statins on cognition are secondary analyses of larger cardiovascular (CV) trials (e.g., **McGuinness 2016; Bosch 2019; Hu 2020**)
- Measures used to diagnose cognitive decline/dementia varied among trials
    - Diagnostic criteria for Alzheimer's or vascular dementia not described in SRs **(Chu 2018; Zhang 2018; Zhu 2018; Poly 2020; Olmastroni 2022)** and largest RCT **(McGuinness 2016)**
    - Many cognitive tests used in RCTs are not used in clinical practice (e.g., telephone interview, Stroop-Colour-Word test)
- Low event rates (0.3%) reported in the largest RCT **(Heart Protection Study Collaborative Group 2002)**
- Results of observational studies are less reliable due to biases (e.g., 'healthy user effect' with lower risk patients more likely to use statins)
- One SR **(Zhu 2018)** had significant methodological flaws for multiple outcomes and is excluded from this summary
- One Cochrane review **(McGuinness 2016b)** searched for RCTs evaluating the effects of withdrawal or continuation of statins in people with dementia on cognitive outcomes; no RCTs were identified

CONTEXT

It is widely recognized that as people age, the risk of CV events increases and many patients will be prescribed statins. The subsequent use of statins may coincide with age-related cognitive changes.

Findings of the current review are consistent with the PEER's *Tools for Practice* article published in 2014 which states that statins do not prevent, treat, or cause cognitive impairment **(Gracias 2014)**.

The STAREE trial is an ongoing community based RCT examining the effects of statins on markers of aging, including dementia. Anticipated completion is in 2025 **(US National Library of Medicine 2014)**.

Major guideline recommendations

Recent international guidelines suggest evidence shows statins have no effects on cognition or have inconclusive effects. See Appendix *Table 5* for a summary of guideline statements.

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METHODS

- *Guideline search*
    - Reviewed six guidelines (Grundy 2018, Mach 2020, Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020, Pearson 2021, US Preventive Services Task Force 2022, Visseren 2021) and extracted references relevant to clinical question.
- *Pubmed searches*
    - **October 6, 2022**: used search terms "statin," "HMG Co A reductase inhibitor*," "cognition," "memory," "dementia," "cognitive"; filtered by meta-analysis, systematic review, 2017-2022; yielded 93 results;
    - **November 10, 2022**: used search terms "statins" "cognition" "dementia" "memory loss" filtered by systematic review, 2017-2022: yielded 26 results;

    - **December 6, 2022**: used search terms “statins” “cognition” “dementia” “memory loss” filtered by randomized controlled trial, 2017-2022; 5 potential articles reviewed; one met inclusion criteria and was added (Zhang 2019)
- *Google Scholar advanced search*
    - **November 30, 2022**: used search terms “statins,” “cognition,” “memory,” “dementia,” “cognitive”, limited to 2017-2022 (reviewed first 5 pages)- no new papers identified
- *Cochrane Database search*
    - **December 6, 2022**: used search terms “statin,” “cognition,” “memory,” “dementia,” “cognitive”: 6 results; no new papers identified
    - Included most recent Cochrane review (McGuinness 2016)
- *Reference list searches*
    - Two additional RCTs identified from discussion section of Olmastroni (Bosch et al, Hu et al)
- *Similar article search*
    - Hu and Bosch; 93 results retrieved; none relevant
- Median and interquartile calculations by PEER

APPENDIX

Table 1: Summary of characteristics of systematic reviews and randomized controlled trials

Study	No. studies	No. patients	Population	Follow-up duration	Mean age (years)	Intervention/ comparator	Other notes
Systematic reviews of observational studies							
Chu 2018	25	110-2,004,692	Cognitive dysfunction at baseline	7 years	Range 45.8-78.6	Statin vs no statin	Random effects, reported RR
Olmastroni 2021	46	123-2,004,692	Baseline status not indicated	NR	Range 45.8-80.4	Statin vs no statin	Random effects, reported OR
Poly 2020	30	9,162,509	84,101 (~1%) had dementia	1-18 years	Range 45.8-78.6	Statin vs no statin	Random effects, reported RR
Zhang 2018	31	3,332,706	Not described in paper	NR	NR	Statin vs no statin	Unclear if fixed/random effects; reported RR; reporting quality was poor (e.g., limited inclusion criteria or methods stated)
Systematic reviews of randomized controlled trials							
McGuinness 2016	2	26,340	High risk (PMH CAD, DM, HTN)	42-60 months	NR	Statin vs placebo	One RCT reported incidence of dementia; both RCTs reported other cognitive measures as secondary outcomes
Davis 2020	2	1,046	Patients with dementia	72 weeks	Range 73-75	Statin vs placebo	Assessing adverse effects
Xuan 2020	9	1,489	Patients with Alzheimer's disease	12 weeks-18 months	Range 64.5-78.2	Statin vs placebo, other meds	Evaluated the effect of statins for the treatment of Alzheimer's disease
Randomized controlled trials							
Zhang 2019	NA	732	Patients with HTN	5 years	70 years	Rosuvastatin vs placebo	2x2 factorial design with telmisartan
Bosch 2019	NA	2,361	No known CV disease	5.7 years	74 years	Rosuvastatin vs placebo	2x2 factorial design with candesartan/HCTZ
Hu 2020	NA	1,244	Patients with HTN	7 years	70 years	Rosuvastatin vs placebo	2x2 factorial design with telmisartan

CAD = coronary artery disease; CV = cardiovascular; DM = diabetes mellitus; HCTZ = hydrochlorothiazide; HTN = hypertension; NA = not applicable; NR = not reported; OR = odds ratio; PMH = past medical history; RCT = randomized controlled trial; RR = risk ratio

Table 2: Summary of systematic review results for statin effects on dementia outcomes

Study	Outcome	No. studies	Effect estimate	95% CI	SS or NSS?	No. patients	Quality of SR*	Notes for indirectness	Publication bias	Other notes
Statin effects on dementia outcomes										
Chu 2018	All cause dementia	16	RR 0.849	0.787 to 0.916	SS	2,745,149	Moderate		None	
Zhang 2018	Dementia risk	31	RR 0.85	0.80 to 0.89	SS	NR	Critically low		None	
Poly 2020	All cause dementia	30	RR 0.83	0.79 to 0.87	SS	9,162,509	Critically low		None	
Olmastroni 2022	Dementia	36	OR 0.80	0.75 to 0.86	SS	5,738,737	Critically low		Evidence of bias	
McGuinness 2016	Incident dementia	1	OR 1.00	0.61 to 1.65	NSS	20,536	High		NA	Diagnostic criteria not defined in HPS
Chu 2018	Alzheimer's	14	RR 0.719	0.576 to 0.899	SS	52,218	Moderate		Evidence of bias	
Zhang 2018	Alzheimer's	23	RR 0.81	0.73 to 0.89	SS	NR	Critically low		None	
Poly 2020	Alzheimer's	20	RR 0.69	0.60 to 0.80	SS	NR	Critically low		NA	
Olmastroni 2022	Alzheimer's	21	OR 0.68	0.56 to 0.81	SS	1,188,377	Critically low		None	
Chu 2018	MCI	6	RR 0.737	0.556 to 0.976	SS	6,808	Moderate		Evidence of bias	
Chu 2018	Vascular dementia	3	RR 1.012	0.62 to 1.652	NSS	5,987	Moderate		Evidence of bias	
Poly 2020	Vascular dementia	4	RR 0.93	0.74 to 1.16	NSS	NR	Critically low		NA	

Study	Outcome	No. studies	Effect estimate	95% CI	SS or NSS?	No. patients	Quality of SR*	Notes for indirectness	Publication bias	Other notes
Zhang 2018	Non-Alzheimer dementia	6	RR 0.81	0.73 to 0.89	SS	NR	Critically low		None	
Statins effects on cognition										
McGuinness 2016	MMSE score	1	MD 0.06	-0.04 to 0.16	NSS	5,804	High	Not serious	NA	
Xuan 2020	MMSE score	5	WMD 1.40	-0.62 to 3.43	NSS	NR	High	Not serious	None	
McGuinness 2016	Telephone interview	1	OR 0.97	0.91 to 1.04	NSS	20,536	High			
McGuinness 2016	Stroop test	1	MD 0.8 s	-0.40 to 2.00 s	NSS	5,804	High	Serious	NA	Outcome measured in seconds
Xuan 2020	ADAS-Cog	4	WMD -0.21	-4.41 to 3.98	NSS	NR	High	Not serious	None	Results including placebo are in sub-analysis
Xuan 2020	ADL	3	WMD -3.36	-8.15 to 1.43	NSS	NR	High	Not serious	None	Results including placebo are in sub-analysis
Xuan 2020	Neuropsychiatric Inventory Scale	3	WMD -1.66	-2.61 to -0.70	SS	NR	High	Not serious	None	Results including placebo are in sub-analysis
Statin adverse events										
McGuinness 2016	Discontinuation due to adverse events	2	OR 0.94	0.83 to 1.05	NSS	26,340	High	Not serious	NA	
Davis 2020	Adverse events	2	OR 1.21	0.83 to 1.77	NSS	1,045	High	Not serious	NA	

*Evaluated using AMSTAR.

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale; ADL = activities of daily living; CI = confidence interval; MCI = mild cognitive impairment; MD = mean difference; MMSE = mini mental state examination; NA = not applicable; NR = not reported; NSS = not statistically significant; OR = odds ratio; RR = risk ratio; SR = systematic review; SS = statistically significant; WMD = weighted mean difference

Table 3a: Quality assessment of systematic reviews of randomized controlled trials using AMSTAR

Study	Duplicate study selection and data extraction?	Comprehensive literature search performed?	Characteristics of the included studies provided?	Scientific quality of included studies assessed & documented?	Methods used to combine the findings of studies appropriate?	Was the conflict of interest stated?	Publication bias formally assessed?	Total score out of 7 (1 point for yes, 0 for no)
McGuinness 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Davis 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Xuan 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7

Table 3b: Quality assessment of systematic reviews of observational studies using AMSTAR-2

Study	AMSTAR-2 rating	Rationale
Chu 2018	Moderate	Multiple non-critical flaws
Olmastroni 2022	Critically low	No prespecified protocol; no list of excluded studies
Poly 2020	Critically low	No prespecified protocol; no list of excluded studies
Zhang 2018	Critically low	No prespecified protocol; no list of excluded studies, methods not adequately described, did not consider risk of bias when interpreting results of review

AMSTAR-2 = Assessment of Multiple Systematic Reviews

Table 3c: Quality assessment of randomized controlled trials using the Cochrane Risk of Bias tool

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/ physicians	Blinding of outcome assessors	Loss to follow up	Selective outcome reporting	Comments
Bosch 2019	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Significant number of participants had undescribed “other

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/ physicians	Blinding of outcome assessors	Loss to follow up	Selective outcome reporting	Comments
								reasons" to be excluded from final analysis
Zhang 2019	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	
Hu 2020	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	

Table 4: GRADE certainty of evidence for the effect of statin treatment on incidence of dementia

Treatment: statins

Outcome: incidence of dementia

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Effect estimate	Median (IQR)	Overall rating
SR of RCTs	1	Not serious	Not serious	Serious CI includes important benefit and harm	Serious Cognitive assessments & outcomes all secondary analyses	Undetected	RR 1.00 (95% CI 0.61 to 1.65)	NA	Low This outcome has two serious **(-2)** therefore **downgrade by two to low**

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IQR = inter-quartile range; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio; SR = systematic review

Table 5: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
In patients on statin therapy, do statins negatively affect cognition,	RCTs have not shown reduced effects on cognition.	The suggested effect on Alzheimer's disease was recently	NR	NR	NR	Adverse effects on cognition have been linked with statins but not clearly established, with some studies showing no

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
memory, cognitive decline, or dementia compared to no statin?	Frequency = rare. Evidence = case report; no increase in memory/cognition problems in 3 large-scale RCTs.	reviewed in a Cochrane analysis reporting no conclusive effect from statins (McGuinness 2016a).				association. Some studies suggest statins may reduce risk of dementia. Evidence on the association between statin use… and cognitive harms was sparse but indicated no increase in risk.

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

NR = not reported; RCT = randomized controlled trial

CHAPTER 8A: STATIN INTOLERANCE – RECHALLENGING

CLINICAL QUESTION

In patients reporting muscle-related symptoms caused by statins, does rechallenging, switching statins, using a lower dose, or use of an alternate dosing strategy improve statin use?

BOTTOM LINE

Most muscle-related complaints in people taking a statin are not statin-induced, with an increase in muscle symptoms between placebo and statins in large randomized controlled trials (RCTs) being <1%. RCT evidence also shows people with a history of statin intolerance cannot differentiate whether they are taking a statin or a placebo, and most of them will tolerate a statin when rechallenged.

EVIDENCE

Results statistically significant unless indicated. GRADE certainty of evidence evaluation can be found in *Table 1*.

Risk of muscle-related adverse events associated with statins

- Systematic reviews (SRs) show the vast majority of muscle symptoms experienced by individuals using a statin are not caused by statins **(Cai 2021, Chou 2022, CTTC 2022, Davis 2021, Irwin 2018, Wang 2022, Yebyo 2019, Zhou 2020)**
    - Results from a large 2022 patient-level data SR of large randomized double-blind trials including 23 trials and 154,664 participants followed for a weighted median duration of 4.3 years **(CTTC 2022)**
        - Any muscle symptoms (e.g., pain, weakness, cramping) at any time: statins 27.1% versus placebo 26.6%
        - Any muscle symptoms within the first year: statins 14.0% versus placebo 14.8%
            - After first year: statins 14.8% versus placebo 15.0% (not statistically different)
        - Any muscle symptoms associated with less versus more intense statin treatment: more intense 36.1% versus less intense 34.8%
    - Other SRs found similar results **(Cai 2021, Chou 2022, Davis 2021, Irwin 2018, Wang 2022, Yebyo 2019, Zhou 2020)**
        - No difference by statin type **(Cai 2021)** (one network meta-analysis found conflicting results **[Wang 2022]**), lipophilic/hydrophilic statin **(Irwin 2018)**, or age **(Chou 2022, CTTC 2022, Irwin 2018)**
        - No difference in discontinuation for muscle symptoms **(Zhou 2020)**, or any adverse event **(Chou 2022, Yebyo 2019, Zhou 2020)**
    - A SR comparing blinded and open-label use of statins found a higher rate of muscle symptoms when participants are not blinded to the treatment with an estimated of 40-80% of muscle symptoms or statin discontinuation due to the drucebo effect, defined as a combination of placebo and nocebo effect **(Penson 2018)**

Management of muscle symptoms in individuals using a statin

- Re-challenging
    - **Herrett 2021, Joy 2014, Wood 2020:** three n-of-1 trials of individuals (N = 8-200) with a history of statin intolerance randomized to 3-4 cycles of ~3-8 weeks of statin or placebo, with one of the trials also including a no-treatment arm **(Wood 2020)**. At least 2 weeks between cycles or before assessing symptoms on a new cycle. Symptom scores (scale = 0-100; higher worse)
        - Statin versus placebo: not statistically different
        - Statin versus nocebo (adverse events due to placebo) **(Wood 2020)**: 16 versus 8 (nocebo)
    - **Tudor 2022**: one n-of-1 trial of 93 patients (82% were taking statins for primary prevention) who had either declined or were intolerant of statins investigated both a behavioral intervention (physician discussion around patient concerns regarding statin vs. usual care) as well as a cross-over design (randomly alternating between placebo and 20 mg of atorvastatin in both blinded and unblinded groups)
        - Patient physician discussion resulted in 45% of patients successfully restarting a statin at 6 months vs. 20% for usual care
        - Blinded vs. unblinded to medication: no difference in successfully restarting statins at 6 months
    - **Nissen 2016**: one RCT evaluating PCSK-9 inhibitors versus ezetimibe included a pre-trial phase during which atorvastatin 20mg and placebo were given for 10 weeks in a cross-over fashion to participants with a history of intolerance to at least two statins
        - 472 participants completed the run-in phase
            - 43% of participants experienced intolerable muscle symptoms with atorvastatin but not with the placebo
    - **Moriarty 2015**: one RCT randomized 314 participants with a previous intolerance to at least two statins to alirocumab, ezetimibe, or atorvastatin 20mg once a day for 24 weeks, following a 4 weeks placebo run-in phase
        - Discontinuation due to skeletal muscle-related symptoms: atorvastatin 22%, alirocumab 16% and ezetimibe 20%
    - **Taylor 2015**: one RCT evaluating the efficacy of Q10 coenzyme supplements in preventing statin-related muscle symptoms initially randomized in a cross-over fashion 120 individuals with a history of statin intolerance to simvastatin 20mg once a day or placebo for 8 weeks
        - 41 individuals (34%) developed myalgias with simvastatin but not with the placebo
    - **Kristiansen 2021**: one RCT examined rechallenging 71 patients with atorvastatin (any dose) related muscle related symptoms with a placebo crossover design (40 mg of atorvastatin for 7 weeks vs. placebo for 7 weeks with 1-week washouts in between treatment arms)

        - No difference in muscle symptom intensity overall between the two groups
- Switching to a different statin
    - **Stein 2008**: one double-blind RCT randomized 199 individuals with a history of muscle-related intolerance to a statin (other than fluvastatin) to fluvastatin 80mg, ezetimibe 10mg, or a combination of both for 12 weeks
        - Muscle related adverse event: fluvastatin 17%, ezetimibe 24%, combination 14%
        - Withdrawals due to muscle-related adverse event: fluvastatin 4%, ezetimibe 8%, combination 3%
- Using a lower dose of the same statin
    - No RCT comparing different doses of statins in individuals with a history of statin intolerance identified
    - Results from meta-analysis of RCTs looking at statins efficacy are conflicting, with some suggesting a dose-related tolerance **(CTTC 2022, Davis 2021)** and others **(Cai 2021, Wang, 2022)** not finding any difference
- Alternate dosing
    - **Awad 2017**: one SR of RCTs or quasi RCTs comparing alternate to daily dosing of statins
        - 12 RCTs (N = 37-284) and 1 quasi-RCT (N = 1023); 6-16 weeks
            - 11 RCTs compared the same dose q2d (once every 2 days) vs once a day
            - 2 RCTs compared double dosing q2d vs single dosing once a day
        - No difference (atorvastatin and rosuvastatin) on triglyceride levels
        - Total cholesterol (mean difference [MD] 12mg/L) and LDL (MD 8mg/L) improved with daily versus alternate day dosing
        - No patient-oriented outcomes reported or usable data for adverse events
    - **Muhammad 2019**: other SR with similar results, also without numbers for muscle symptoms

CONTEXT

A SR of recommendations for statin intolerance management including 26 articles found various recommendations **(Saxon 2016)**

- Most articles (88%) recommend excluding other causes for symptoms first
- Some recommend specific laboratory tests: CK (62%), ALT (12%), vitamin D (38%)
- Almost all recommend stopping the statin used (96%) but all recommend rechallenging with a statin, either a lower dose (96%), a different statin (92%) or an alternate day dosing regimen (77%)
- A wash-out period of 2 to 6 weeks before rechallenging is often recommended (50%)
- Switching to a non-statin therapy in monotherapy (58%) or adding a non-statin therapy (100%) is also recommended
- The risk associated with rechallenging statins in individuals with a history of severe muscle-related adverse event is unclear

Observational data also supports the fact that a large majority of individuals with a history of statin muscle-related intolerance can find a well-tolerated statin regimen. For example, in a large US cohort study including 6,579 individuals with a history of statin discontinuation due to adverse events, some form of statin treatment could be reinstated in 92% of them **(Zhang 2013)**.

Recent guideline recommendations

See *Table 2* for a summary of recommendations relating to statin intolerance and rechallenging from recent major guidelines.

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METHODS

- Pubmed - All time (December 2022; limited to articles in English)
    - Title: *statin* AND intolera*
        - No filter
        - 218 results
    - Title: *statin* AND adverse
        - 250 results
- Google scholar
- Uptodate
- Similar article search
- Reference search
- Help from a team working on a muscle intolerance tools for practice

APPENDIX

Table 1: GRADE certainty of evidence for tolerance for rechallenging statins in patients identified as intolerant

Treatment: Statin rechallenge

Outcome: Statin tolerance

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Effect estimate	Overall rating
RCT	8 (1,338)	Not serious	Not serious	Not serious	Not serious	Undetected	NA	High This outcome has no downgrades

GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; RCT = randomized controlled trial

Table 2: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
In patients reporting muscle-related symptoms caused by statins, does rechallenging, switching statins, using a lower dose, or use of an alternate dosing strategy	Several creatively designed randomized crossover trials in patients with SAMS[S5-3–S5-7] support a management strategy of statin discontinuation until symptoms improve, followed by rechallenge with a reduced dose, alternative agent, or alternative dosing regimen while monitoring for	While statins rarely cause serious muscle damage (myopathy, or rhabdomyolysis in the most severe cases), there is much public concern that statins may commonly cause less serious muscle symptoms. Such statin 'intolerance' is frequently encountered by practitioners and may be difficult to manage. However, placebo-controlled randomized trials have shown very	A washout period (i.e., a short-term interruption of a statin), should be implemented to evaluate whether the perceived adverse event is related to a statin. The optimal duration of the washout period was not clear in the available evidence. Based on statin half-lives, an interruption of 2 – 4 weeks is reasonable. Statin treatment then can be reinitiated with the same statin (if symptoms were deemed non-statin related), or with a different statin at recommended intensity (if	"Maximally tolerated statin dose" No mention of switching statins.	In practice, management of a patient with myalgia but without a major increase in creatine kinase is based on trial and error, and usually involves switching to a different statin or use of a very low dosage several days a week, with a gradual increase in frequency and	NR

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
improve statin use?	recurrent symptoms. If the approach of reassess, rediscuss (net clinical benefit), and rechallenge is used, a majority of patients will be able to be successfully treated with at least one or several statins.	clearly that true statin intolerance is rare, and that it is generally possible to institute some form of statin therapy (e.g., by changing the statin or reducing the dose).	symptoms resolved after discontinuation). If intolerance persists, providers could consider decreases in dosage. Also, intermittent dosing is an acceptable option in patients with continued tolerance issues. Only in the rare case of a serious adverse event (e.g., rhabdomyolysis) should statins be discontinued.		dosage. A management algorithm may help to manage these patients.	

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

NR = not reported; SAMS = statin-associated muscle symptoms

CHAPTER 8B: STATIN INTOLERANCE – OTHER DRUGS

CLINICAL QUESTION

In patients intolerant of statins, do any lipid-lowering drugs lower the risk of cardiovascular disease compared to no statin?

BOTTOM LINE

When used in monotherapy, fibrates reduce major adverse cardiovascular events (MACE) by approximately 20% but also has no effect on cardiovascular (CV) or all-cause mortality. Ezetimibe might reduce MACE but has no effect on CV or all-cause mortality and evidence is limited to one open-label trial with major limitations. When added to a statin, icosapent ethyl and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce MACE by approximately 25% and 15%, respectively, but have no effect on mortality. However, their benefit in monotherapy is unknown. Bile acid sequestrants (BAS) and niacin have not demonstrated a benefit on MACE or mortality, although the data for BAS is inconsistent. The decision to initiate non-statin lipid lowering drugs should involve informed shared decision-making.

EVIDENCE

Results statistically significant unless otherwise stated. GRADE certainty of evidence evaluation can be found in *Tables 1A-E*.

Bile acid sequestrants

- Two large double-blind randomized controlled trials (RCTs) from the pre-statin era
- **Lipid Research Clinics Coronary Primary Prevention Trial 1984**: RCT comparing 24g of cholestyramine a day versus placebo (N = 3,806; mean age 48; 100% male; mean follow-up 7.4 years)
    - Patients with primary hypercholesterolemia and at high risk for coronary heart disease (CHD)
    - Primary composite outcome of CHD death and myocardial infarction (MI)
        - Cholestyramine 8.1% versus placebo 9.8%
        - Relative risk (RR) 0.83, 95% confidence interval (CI) 0.67 to 1.01*
    - No difference on definite CHD, definite nonfatal MI, all-cause mortality, definite or suspect atherothrombotic brain infarction or transient ischemic attack
- **Dorr 1978**: RCT comparing 5g of colestipol daily to a placebo in patients with hypercholesterolemia (N = 2,278; mean age 54; 52% female; 26% CHD; 20% hypertensive; 16% type II diabetes; follow-up 1-3 years)
    - Outcomes reported by gender
    - In men, colestipol reduced death from any CV cause (2% versus 4.4% with placebo; p<0.02) and death from CHD (1.6% versus 4.0% with placebo; p<0.02)
        - No statistically significant difference in all-cause mortality, death from acute MI, or death from all vascular diseases
    - In women, only all-cause mortality and death from CHD were reported, with no difference between groups

- Two very small RCTs with 53 **(Brensike 1984)** and 143 participants **(Watts 1992)** found no difference between BAS and placebo on patient-oriented outcomes

Ezetimibe

- **Zhan 2018**: Cochrane systematic review (SR) that looked at ezetimibe, but only found RCTs with participants using a statin in the control group
- **Ouchi 2019** (Ewtopia-75 trial): open-label RCT conducted in Japan comparing ezetimibe 10mg once a day to no treatment in patients with no history of CHD and not using any lipid-lowering therapy (N = 3,796; age ≥75 years, mean ≈ 81)
    - Results at 5 years
        - Ezetimibe reduced the primary composite outcome of sudden cardiac death, MI, coronary revascularization, or stroke (5.2% versus 7.8%; hazard ratio [HR] = 0.66; number needed to treat [NNT] = 39)
        - No effect on CV or all-cause mortality
    - Limitations: open-label design, early termination, participants with no contraindication for statins, 28% of participants withdrew or were lost to follow up
- **Nissen 2016, Moriarty 2015, Stroes 2014**: 3 RCTs that compared ezetimibe to a PCSK9 inhibitor in patients intolerant to statins, but reported no patient-oriented outcomes

Fibrates

- **Keene 2014**: SR that evaluated the efficacy of fibrates without a statin (17 RCTs; N = 30,523; follow-up 2.5-7 years)
    - Reduction in non-fatal MIs in fibrates compared to placebo
        - 5.4% (fibrates) versus 7.4% (placebo)
            - RR 0.78 (95% CI 0.71 to 0.86)
    - No difference in all-cause mortality, CHD mortality, or stroke
- **Jakob 2016**: Cochrane SR that evaluated the efficacy of fibrates specifically in primary prevention patients not using a statin (4 RCTs; N = 12,153; follow-up 2-5 years)
    - Fibrates reduced MACE (composed of CV mortality, MI, and stroke)
        - 4.8% (fibrates) versus 6.0% (placebo)
            - RR 0.79 (95% CI 0.68 to 0.92)
    - No effect on all-cause mortality

Niacin

- **D'Andrea 2019**: SR looking at niacin for CV prevention in patients not using a statin (9 RCTs; N = 5,375; follow-up 2-5 years)
    - Reduction in acute coronary syndrome
        - 9.3% (niacin) versus 13,2% (placebo); RR 0.74 (95% CI 0.58 to 0.96)
    - Reduction in stroke
        - 6.5% (niacin) versus 9.8% (placebo); RR 0.75 (95% CI 0.59 to 0.94)
    - Reduction in revascularization procedures
        - 3.0% (niacin) versus 5.4% (placebo); RR 0.51 (95% CI 0.37 to 0.72)
    - No difference on MACE or CHD mortality

Icosapent ethyl

- No relevant RCT evaluating icosapent ethyl without a statin was identified
- Participants in both major trials looking at icosapent ethyl (REDUCE-IT **[Bhatt 2019]** and JELIS **[Yokoyama 2007]**) were using a statin
    - In these trials, icosapent ethyl led to a relative risk reduction (RRR) in MACE of 20-25% but had no effect on all-cause mortality

PCKS9 inhibitors

- No relevant RCT evaluating PCSK9 inhibitors and reporting CV outcomes in participants not receiving a statin was identified
- When added to a statin, PCSK9 inhibitors led to a RRR of approximately 15% but had no effect on all-cause mortality **(Dugré 2023)**

*Calculations made by PEER.

CONTEXT

Statins have the most consistent evidence for CV disease prevention and mortality reduction, both in primary and secondary prevention **(Dugré 2023)**. Statin intolerance is uncommon and should be reassessed before discussing a different lipid lowering therapy. In most cases, a statin can be restarted and tolerated **(Cholesterol Treatment Trialists' Collaboration 2022, Meza-Contreras 2022, Zhang 2013)**.

Costs vary greatly from drug to drug. A 90-day supply costs abouts $15 for ezetimibe, $25 for fibrates, $90 for icosapent ethyl, and $1500 for PCSK9 inhibitors **(McKesson Pharmaclik 2023)**.

Major guideline recommendations

See *Table 2* for a summary of recommendations pertaining to statin intolerance and other drugs from recent major guidelines.

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METHODS

- Systematic reviews included in our umbrella systematic review of systematic reviews
- Results from our search for Alternate dosage or regimen in statin intolerant individuals
- Google, UpToDate

APPENDIX

Table 1A: GRADE certainty of evidence for the use of ezetimibe as a monotherapy on MACE
Treatment: ezetimibe monotherapy
Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate	Overall certainty
RCT	1 (3,796)	Very serious Open-label; important loss to FU	Not serious	Serious Only Japanese adults aged ≥75 years	Not serious	Undetected	HR 0.66 (95% CI 0.50 to 0.86)	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**

CI = confidence interval; FU = follow-up; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; HR = hazard ratio; MACE = major adverse cardiovascular events; RCT = randomized controlled trial

Table 1B: GRADE certainty of evidence for the use of fibrates as a monotherapy on MACE
Treatment: fibrate monotherapy
Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate	Overall certainty
RCT	4 (12,153)	Not serious	Not serious	Serious Not studied in statin-intolerant subgroup	Not serious	Undetected	RR 0.79 (95% CI 0.68 to 0.92)	Moderate This outcome had one serious **(-1)** therefore

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate	Overall certainty
								downgrade by 1 to moderate.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MACE = major adverse cardiovascular events; RCT = randomized controlled trial; RR = risk ratio

Table 1C: GRADE certainty of evidence for the use of niacin as a monotherapy on MACE

Treatment: niacin monotherapy
Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate	Overall certainty
RCT	9 (5,375)	Not serious	Serious Results vary widely	Not serious	Not serious	Undetected	RR 0.81 (95% CI 0.66 to 1.00)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MACE = major adverse cardiovascular events; RCT = randomized controlled trial; RR = risk ratio

Table 1D: GRADE certainty of evidence for the use of icosapent ethyl as a monotherapy on MACE

Treatment: icosapent ethyl
Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate	Overall certainty
RCT	2 (8,179-18,645)	Serious One trial not blinded	Not serious	Very serious Treatment combined with statin and not studied in a statin-intolerant subgroup	Not serious	Undetected	HR 0.74 (95% CI 0.65 to 0.83); HR 0.81 (95% CI 0.69 to 0.95)	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; HR = hazard ratio; MACE = major adverse cardiovascular events; RCT = randomized controlled trial

Table 1E: GRADE certainty of evidence for the use of PCSK9 inhibitors as a monotherapy on MACE

Treatment: PCSK9 inhibitor monotherapy

Outcome: MACE

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect estimate (range)	Overall certainty
SR	16* (24,803-92,736)	Not serious	Not serious	Very serious Treatment combined with statin and not studied in a statin-intolerant subgroup	Not serious	Undetected	RR 0.80-0.89	Low This outcome had one very serious **(-2)** therefore **downgrade by 2 to low.**

*14 with usable data.

MACE = major adverse cardiovascular events; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; PCSK9 = proprotein convertase subtilisin/kexin type 9; RR = risk ratio; SR = systematic review

Table 2: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
In patients intolerant of statins, do any lipid-lowering drugs lower the risk of cardiovascular disease compared to no statin?	Severe statin-associated side effects are rare, and recurrent SAMS are infrequent when a thorough reassessment and management strategy of reassess, rediscuss, and rechallenge is used. In patients at increased ASCVD risk with severe statin-associated side effects or recurrent SAMS, nonstatin therapy should be considered when there is net clinical benefit.	In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered. If the LDL-C target is not reached with the highest tolerated statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin-intolerant patients or in whom a statin is contraindicated. In patients with confirmed statin intolerance or in patients in whom a statin is contraindicated, ezetimibe should be considered.	Most discontinuation of statin therapy is attributed to presumed statin myopathy. While many patients tolerate the same statin when re-challenged, some are reluctant to resume the same or different statin they presume caused the myalgias, leaving limited evidence-based medication options for primary prevention of CVD in patients who cannot take statins. There is a need for clinical trials of alternative lipid-lowering agents for CVD risk reduction in primary prevention populations. Current medications suitable for study would be ezetimibe, PCSK9 inhibitors, bempedoic acid, and icosapent ethyl. Because of the low cost of generic ezetimibe, studies of ezetimibe monotherapy for primary prevention would offer the highest potential benefit.	Although ezetimibe or a PCSK9 inhibitor are reasonable options as monotherapy in patients with complete statin intolerance for LDL-C lowering, there is limited evidence to support either class as an alternative to statin therapy for ASCVD risk reduction.	If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.	NR

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol; NR = not reported; PCSK9 = proprotein convertase subtilisin/kexin type 9; SAMS = statin-associated muscle symptoms

CHAPTER 9: LIPID TESTING FREQUENCY

CLINICAL QUESTION

For patients without cardiovascular disease who are not taking lipid-lowering therapy, does repeating lipid testing as part of cardiovascular disease risk estimation every 5-10 years meaningfully change risk estimates compared to more frequent testing?

BOTTOM LINE

The analytic and biologic variation from a single TC (total cholesterol)/LDL (low-density lipoprotein)/HDL (high-density lipoprotein) in an individual person (10-20%) is much greater than the change in these measurements that occurs over time (<1%/year) in an individual person. Given this measurement variation in individual patients and the relatively minimal impact TC/LDL/HDL changes over time have on cardiovascular disease (CVD) risk estimates, repeat measurements add little if anything to CVD risk estimates.

EVIDENCE

GRADE certainty of evidence evaluation can be found in *Table 1*.

- As with our 2015 guideline we searched evidence specifically addressing changes in TC/LDL/HDL levels over time through citation tracking from a key 2008 paper that studied the implications of different approaches to monitoring lipid levels **(Glasziou 2008)**
- In addition, we reviewed evidence around the analytic and biologic variation of single TC/LDL/HDL measurements **(McCormack 2020)** and used a CVD risk estimation calculator to make ballpark estimates of how much a change in TC/HDL cholesterol on 10-year CVD risk estimates compared to what change occurs simply due to aging
    - We then applied that evidence to scenarios of CVD risk estimations

Measurement variation and TC/LDL/HDL changes over time

- In people over age 30, the average yearly change in TC/LDL/HDL is ≤1% **(Bakx 2000)**. So over 10 years, lipids would in most cases change <10%. The confidence interval (considering both analytic and biologic variation) around a single measurement of TC/LDL/HDL is 10-20% and 30-40% for triglycerides **(McCormack 2020)**. Certainly over 5 years, any real change in a person's lipid values over that time frame could not be reliably picked up given this measurement variability. Even at 10 years, much of any lipid change could simply be due to this variability.
- Even if we could pick up a change in lipids over time, we need to put the impact that those changes in lipids would have on absolute CVD risk estimates in context with what an increase in age does to CVD risk. The following is an example of the impact age changes and TC/HDL changes have on an intermediate (15% ten-year risk) CVD risk patient (*Figure 1*). Other specific examples are provided in the appendix at the end of this document (*Figure 2*).

Figure 1: Example of the impact of changes in TC/HDL on 10-year cardiovascular risk estimates

50 y/o male, Diabetic, Non-smoker, Systolic BP 130 mmHg, Total cholesterol 4.4 mmol/L (170 mg/dL), HDL 1 (40)

RISK FACTOR # CHANGES	Estimated 10-year risk*	Estimated absolute benefit from a statin **
Baseline at 50 y/o	15%	3.8%
⬆10 years in age	25%	6.3%
10 years + 2%/yr ⬆TC/HDL	26% 30% if just TC⬆	6.5% 7.5%

*** Framingham - cvdcalculator.com**
**** Assuming ~25% ⬇ in relative risk**

BP = blood pressure; HDL = high-density lipoprotein; TC = total cholesterol

- Over 10 years, age increases the absolute CVD risk estimate from ~15% to 25%. If TC/HDL goes up even 2%/year over that time, the impact that has on absolute CVD risk is pretty much negligible (at most 4% additional absolute risk – in most patients it is less than this) compared to the impact of age.

CONTEXT

Major guideline recommendations

Recent guidelines (2018-2022) recommend that lipids be re-measured every 5 years **(Grundy 2019; Pearson 2021; Visseren 2021)**. One guideline recommended every 10 years **(Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020)**. Two guidelines do not mention a time frame **(Mach 2020; US Preventive Services Task Force 2022)**. However, none of these guidelines provide any rationale for this time frame nor discuss measurement variation issues associated with serial lipid measurements. A summary of recommendations published by major guidelines in the past 5 years can be found in *Table 2*.

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METHODS

- Identified two key papers:
    - As with our 2015 guideline we searched evidence specifically addressing changes in TC/LDL/HDL levels over time through citation tracking from a key 2008 paper that studied the implications of different approaches to monitoring lipid levels **(Glasziou 2008)**
    - Identified key paper addressing evidence around the analytic and biologic variation of single TC/LDL/HDL measurements **(McCormack 2020)**
- Similar article searches using the 2 key articles (**Glasziou 2008; McCormack 2020**) on PubMed database
    - No additional articles found

APPENDIX

Figure 2: Impact of changes in cholesterol on 10-year cardiovascular risk estimates

ACC/AHA	Baseline 10-year risk (%)	Fatal and non-fatal heart attacks/stroke	After 5 years (%) latest (TC/HDL)	After 10 years (%) latest (TC/HDL)
FEMALE 50 y/o, non smoker, SBP 130, baseline TC 4, HDL 1	1.4	Age but no change in cholesterol	2.1 (4/1)	3.5 (4/1)
		Cholesterol 1%/year⬆	2.1 (4.2/1.1)	3.6 (4.4/1.1)
		Cholesterol 2%/year⬆	2.2 (4.4/1.1)	3.6 (4.8/1.2)
MALE 50 y/o, non smoker, SBP 130, baseline TC 4, HDL 1	3.2	Age but no change in cholesterol	5.3 (4/1)	8.3 (4/1)
		Cholesterol 1%/year⬆	5.3 (4.2/1.1)	8.6 (4.4/1.1)
		Cholesterol 2%/year⬆	5.6 (4.4/1.1)	8.7 (4.8/1.2)
MALE DIABETIC 50 y/o male, non smoker, SBP 130, baseline TC 4, HDL 1	6.1	Age but no change in cholesterol	10.0 (4/1)	15.5 (4/1)
		Cholesterol 1%/year⬆	9.9 (4.2/1.1)	16.0 (4.4/1.1)
		Cholesterol 2%/year⬆	10.4 (4.4/1.1)	16.2 (4.8/1.2)
		Cholesterol 4%/year⬆	10.6 (4.8/1.2)	16.6 (5.6/1.4)

Framingham	Baseline 10-year risk (%)	Fatal and non-fatal heart attacks/ stroke, heart failure, angina, intermittent	After 5 years (%) latest (TC/HDL)	After 10 years (%) latest (TC/HDL)
FEMALE 50 y/o, non smoker, SBP 130, baseline TC 4, HDL 1	4.3	Age but no change in cholesterol	5.4 (4/1)	6.5 (4/1)
		Cholesterol 1%/year⬆	5.7 (4.2/1.1)	7.0 (4.4/1.1)
		Cholesterol 2%/year⬆	5.9 (4.4/1.1)	7.2 (4.8/1.2)
MALE 50 y/o, non smoker, SBP 130, baseline TC 4, HDL 1	7.9	Age but no change in cholesterol	10.4 (4/1)	13.4 (4/1)
		Cholesterol 1%/year⬆	10.3 (4.2/1.1)	13.9 (4.4/1.1)
		Cholesterol 2%/year⬆	10.9 (4.4/1.1)	14.1 (4.8/1.2)
MALE DIABETIC 50 y/o male, non smoker, SBP 130, baseline TC 4, HDL 1	13.6	Age but no change in cholesterol	17.8 (4/1)	22.6 (4/1)
		Cholesterol 1%/year⬆	17.6 (4.2/1.1)	23.4 (4.4/1.1)
		Cholesterol 2%/year⬆	18.5 (4.4/1.1)	23.6 (4.8/1.2)
		Cholesterol 4%/year⬆	18.6 (4.8/1.2)	24.1 (5.6/1.4)

This table shows the changes in risk that accompany changes in TC/HDL over time.
ACC = American College of Cardiology; AHA = American Heart Association; HDL = high-density lipoprotein; SBP = systolic blood pressure; TC = total cholesterol

Table 1: GRADE certainty of evidence for lipid variability over years

Outcome: cholesterol variability over years

Study design	No. studies (no. patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient	Effect estimate	Certainty
Cohort	1 (2,325)	Not serious	Not serious	Not serious	Not serious	Not detected	No*	No	No	Change in cholesterol of ~10-15% or <1% per year	High This outcome has no downgrades

*The question can't be answered with relative risks. Total cholesterol changed over an 18-year period between 0% and 20% depending on age and sex. The mean effect was a change in cholesterol of ~10-15% or <1% per year.
GRADE = Grading of Recommendations, Assessment, Development, and Evaluations

Table 2: Summary of recommendations from major guidelines published within the past 5 years

Our question	2018 AHA[1]	2019 ESC Dyslipidemia[2]	2020 VA[3]	2021 CCS[4]	2021 ESC CVD Prevention[5]	2022 USPSTF[6]
For patients without CVD who are not taking lipid-lowering therapy, does repeating lipid testing as part of CVD risk estimation every 5-10 years meaningfully change risk estimates compared to more frequent testing?	Retest lipids every 4-6 years	NR	Retest lipids no more than every 10 years	Retest lipids every 5 years	Retest lipids after 5 years (or sooner if risk was close to treatment thresholds)	NR

[1]Grundy 2018; [2]Mach 2020; [3]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [4]Pearson 2021; [5]Visseren 2021; [6]US Preventive Services Task Force 2022
CVD = cardiovascular disease; NR = not reported

CHAPTER 10: LIPID TARGETS

CLINICAL QUESTION

In patients with/at risk of cardiovascular disease, does attainment of specific low-density lipoprotein, apolipoprotein B, or non-high-density lipoprotein levels decrease the risk of cardiovascular disease compared to use of statins without achieving specific targets?

BOTTOM LINE

At present, the best available evidence does not, and may never be able to, definitively prove whether targeting treatment to low-density lipoprotein (LDL) or simply using/adding medications that have been shown to reduce the risk of cardiovascular disease (CVD) is best. Most clinical trials have used fixed dose (mostly moderate intensity) statins based on CVD risk and find benefit occurs irrespective of LDL levels achieved. In addition, lipid measurement variation (analytic and biologic) of 10-20% with repeated measurements in individual patients makes it difficult to assess if changes seen are due to the treatment or simply due to measurement variation. Other downsides of repeat measurements include the costs of testing, the inconvenience to the patient, and the frustration of patients as many will not reach proposed LDL targets.

In the absence of clear evidence that one approach is better than the other and the additional limitations to clinical application, our suggested approach is to not use routine monitoring of lipid levels to guide future therapy in patients taking statins. Rather, a more rational and simplified approach is to have clinicians focus on the discussion of the benefits and harms of proven therapies for individual patients. As in the case of the initial decision to initiate a statin, the decision of whether to intensify therapy or add additional agents should involve informed shared decision-making through the discussion of individual estimates of potential benefits and harms and link this with patient preferences and values.

EVIDENCE

Treat to Stroke Target RCT ***(Amarenco 2020)***

- The only RCT that directly compares lower versus higher LDL targets
    - LDL target approach
    - Patients with previous strokes were randomized to an LDL of <1.8 mmol/L or 2.3-2.8 mmol/L
        - Major adverse cardiovascular events (MACE) 2.4% lower (22% relative) over the 3.5 years of follow-up in the lower target arm
    - This trial has been used to support treating to a target LDL of <1.8 in secondary prevention (in this case, post-stroke)
- *Limitations*
    - Trial methodology does not really answer the question of whether a target LDL approach leads to better cardiovascular (CV) outcomes than treatment with a fixed-dose strategy; rather, it answers the question: does adding medications that have been shown to reduce CVD outcomes lead to a reduction in CVD outcomes?

- The trial design led to a greater number of people (53% versus 14%) in the lower LDL target group receiving higher statin doses or the addition of ezetimibe
    - Medication intensification (higher doses or additional agents) in the majority of RCT and meta-analysis evidence of statin and non-statin agents without LDL target goals have found that the use of higher intensity statins or the addition of ezetimibe (i.e., treatment intensification) adds an additional ~5-15% relative reduction in CV events (*Table 1*) **(Management of Dyslipidemia 2020)**
    - This suggests a similar difference in outcomes could have been achieved by simply adding proven treatments rather than targeting a specific LDL target goal
- Absolute risk reduction (ARR) seen for the MACE outcome of 0.69% per year in favor of the lower vs the higher LDL target in this RCT is similar to that seen in a secondary prevention meta-analysis (0.5% per year for more- vs less-intensive statins irrespective of targets) **(Koskinas 2018)**
- Ultimately, while this RCT was designed as a trial of LDL target comparisons, it really presents as a trial of intensification of treatment with similar ARR findings to those of the previous meta-analyses of comparative medication intensification

*Table 1: Lipid lowering and CVD reduction by intensification approach**

Intensification approach	Comparison†	LDL lowering (%)	MACE RRR (%)
Low-medium dose statin	Statin 10-20mg vs. placebo	35-40%	25%
Increased statin dose	Statin 10-20mg vs. statin 80mg	15-20%	12%
Add ezetimibe	Statin 20mg + ezetimibe vs. statin 20mg alone	15-20%	6%
Add PCSK9i (alirocumab or evolocumab)	Statin >20-40mg + PCSK9i vs. statin >20-40mg alone	55-70%	15%

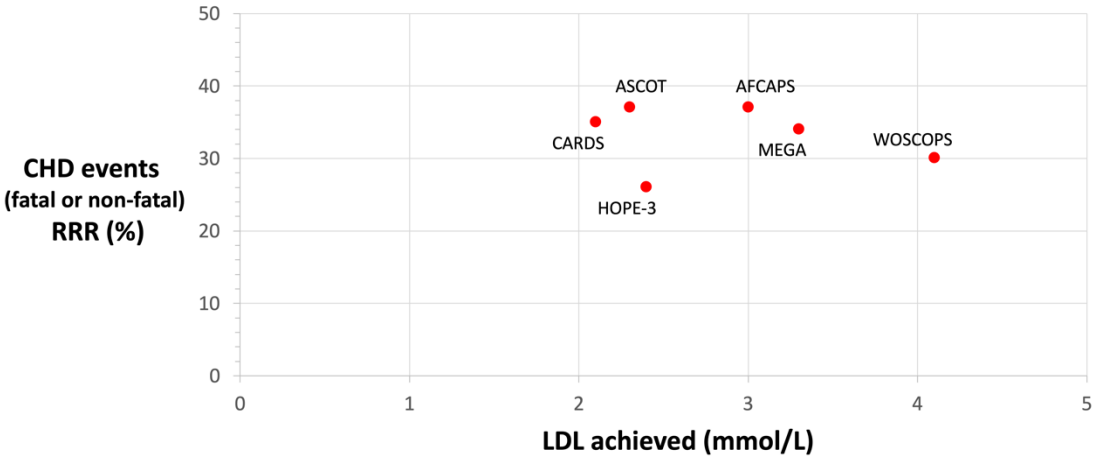
*Afilalo 2007; Cannon 2006; Cannon 2015; Taylor 2013; Koskinas 2018; Sabatine 2017; Schwartz 2018; Zhan 2018
†Statin dose is approximate atorvastatin equivalent
LDL = low-density lipoprotein; MACE = major adverse cardiovascular events; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; RRR = relative risk reduction

Primary prevention

- In primary prevention, large RCTs have been performed typically using moderate intensity statins without intensification **(Colhoun 2004; Downs 1998; Nakamura 2006; Sever 2003; Shepherd 1995; Yusuf 2016)**
- Although LDL targets were not the comparison in question in these RCTs, it is difficult to discern any clear pattern of greater risk reduction with lower end-of-trial LDL levels when plotting coronary heart disease (CHD) risk reduction against achieved LDL (*Figure 1*)

- Overall, primary prevention RCTs showed an ~25-35% relative reduction in CHD events regardless of LDL level.

Figure 1: Primary prevention RCTs using moderate intensity statins (equivalent to ~10mg atorvastatin)



CHD = coronary heart disease; LDL = low-density lipoprotein; RCT = randomized controlled trial; RRR = relative risk reduction

Variability in individual lipid measurement

- Another important factor that is often overlooked when it comes to measuring lipids in individual patients is the consideration of lipid lab measurement variation (analytical and biological) when attempting to assess an individual person's lipid level response to medications
    - A 10-20mg dose of a high potency statin (e.g., atorvastatin or rosuvastatin) reduces LDL by ~35-40% and increasing the dose to 40-80mg adds another ~15% reduction in LDL **(Law 2003)**
    - Similarly, the addition of ezetimibe would also reduce LDL by ~15%
    - Unfortunately, the measurement variation for cholesterol values is in the ballpark of 10-20% **(McCormack 2020)**
- When measurement variation is as much if not more than the expected change, serial lipid measurements in individual patients cannot reliably identify whether or not a change in lipid levels has occurred
    - Even if one could somehow identify that a lipid level had gone down, with this amount of measurement variation, one can't know the magnitude of the change with any certainty
    - This is true even if one does multiple measurements before and after an intervention

Downsides to serial lipid measurement

- Costs of testing
- Inconvenience to the patient

- High likelihood of not reaching proposed LDL targets leading to frustration for both the clinician and patient
    - The ability to achieve lower LDL targets (e.g., LDL <1.8) has been shown to be challenging for nearly half of clinical trial patients
        - A meta-analysis by Boekholdt, et al **(Boekholdt 2014)** found >40% were not able to reach the target of <1.8 mmol/L, similar to the Treat to Stroke Target findings of 47% of the lower target group being above the 1.8 mmol/L target
        - In several earlier meta-analyses, less than 50% of patients achieved an LDL of <2 mmol/L **(Cholesterol Treatment Trialists' Collaboration 2010; Josan 2008)**
- Paradoxically, if a patient is identified as having reached a target LDL, they then may not be offered the addition of other medications or doses that have been shown to lower CVD
- Focusing on lipid targets may distract from the ultimate goal of getting people to eat healthier food, be more active and if interested, being on medications that have been shown to reduce CVD risk

Conclusions

- At present, the best available evidence does not, and may never be able to, definitively prove whether targeting treatment to LDL or simply using/adding medications that have been shown to reduce the risk of CVD is best.
    - What has been established with much greater certainty, however, is the incremental reduction in CV risk seen with the incremental addition of either higher doses of statins or of different therapies (ezetimibe/PCSK9 inhibitors) that have been shown to reduce risk in varying degrees in clinical trials, primarily in secondary prevention
- Lower LDL levels have been associated with a lower CV risk **(Cholesterol Treatment Trialists' Collaboration 2019)**
    - However, the lack of evidence that this reduction in CV risk can be directly attributed to an LDL target over simply intensification of therapy suggests that we should focus on the discussion of the benefits and harms of proven therapies for individual patients as a more rational and simplified approach
- Our suggested approach, therefore, is to not use ongoing monitoring of lipid levels to guide future therapy in patients taking statins
    - Rather, as in the case of the initial decision to initiate a statin, the decision to intensify therapy should necessarily involve shared decision-making through the discussion of individual estimates of potential benefit and harm of intensification along with patient preferences and values

CONTEXT

Major guideline recommendations

While several recent guidelines recommend treating to a target lipid goal, our review of the available data leads to a similar perspective and conclusion as that taken by the DVA/DoD

(Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020). And, while the USPSTF **(US Preventive Services Task Force 2022)** does not provide a formal recommendation on this question, the absence of a recommendation, their statement that moderate-intensity statins are reasonable for most primary prevention patients, and their acknowledgement of this as a research gap is in keeping with the uncertainty we have presented in our synopsis. In the absence of direct evidence that use of defined LDL targets result in unique CVD benefit for patients, utilizing the simplest approach to care is necessary for individual patients, clinicians, and the healthcare system.

Organizations internationally present two different approaches around the decision to intensify medications for lipidemia management for CVD risk reduction (*Table 2*):

1. Treating to a target goal (either to a specified level or by % reduction) for a defined marker (e.g., LDL), or;
2. Not having a target goal for a defined marker but simply discussing/recommending the use of medications that have been shown in clinical trials to reduce CVD outcomes.

Table 2: Current guideline recommendations

Guideline	Recommendation	Recommend treat to target approach?
CCS 2021[1] (Dyslipidemia)	● Primary prevention: If LDL ≥2 or ApoB ≥0.8 or non-HDL >2.6 on maximally tolerated statin dose, discuss add-on therapy (Fig 1) **(No formal graded recommendation)** ● Secondary prevention: Recommend intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy for all secondary prevention CVD patients in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose. **(Strong Recommendation; High-Quality Evidence)**	Yes
ACC/AHA 2018[2] (Dyslipidemia)	● Adherence to changes in lifestyle and effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety. **(Class I, LOE A)** ● Intermediate risk: Reduce LDL-C by 30-49% for **(Class I, no LOE)** ● High risk: Reduce LDL-C by ≥50% for **(Class I, no LOE)**	Yes
ESC/EAS 2019[3] (Dyslipidemia)	● See Table 3, p120 ("New/revised concepts") and p132 for the many varied LDL level and % LDL reduction targets depending on risk level **(range of Class and LOE grades depending on recommendation)**	Yes
ESC 2021[4] (CVD prevention)	● Lipid goals are the same as in the 2019 ESC/EAS dyslipidemia guidelines (above) **(range of Class and LOE grades depending on recommendation)**	Yes

Guideline	Recommendation	Recommend treat to target approach?
DVA/DoD 2020[5] (Dyslipidemia)	● Suggest against the routine monitoring of lipid levels in patients taking statins. No target recommendation. **(Weak Against)**	No
USPSTF 2022[6] (Statins in primary prevention)	● **No target recommendation** ("Research Needs and Gaps: *Trials that directly compare statin therapy titrated to target lipid levels vs fixed-dose therapy to inform optimal dosing strategies")* ● Use of moderate-intensity statin therapy stated as reasonable for the primary prevention of CVD in most persons	No

[1]Pearson 2021; [2]Grundy 2018; [3]Mach 2020; [4]Visseren 2021; [5]Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group 2020; [6]US Preventive Services Task Force 2022
ApoB = apolipoprotein B; CVD = cardiovascular disease; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein-cholesterol; LOE; PCSK9 = proprotein convertase subtilisin/kexin type 9

Guidelines that recommend specific LDL/apolipoprotein B (ApoB)/non-HDL (high-density lipoprotein) targets typically suggest these recommendations are Strong or Class 1; however, no randomized controlled trials (RCTs) have directly compared treatment with statins titrated, or non-statins added, to attain target cholesterol levels versus other (e.g., fixed-dose or fixed treatment) treatment strategies **(US Preventive Services Task Force 2022)**. Of note, despite the recommendation to use a targeted biomarker approach, the CCS states "no clear target to which LDL-C or non HDL-C or ApoB levels should be lowered is clearly identified in RCTs" **(Pearson 2021)** and the ESC/EAS 2019 states "the Task Force is aware of the limitations of some of the sources of evidence and accepts that RCTs have not examined different LDL-C goals systematically, but felt that it was appropriate to look at the totality of the evidence" **(Mach 2020)**.

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METHODS

- Since the US DVA/DoD guidelines performed a complete and thorough systematic review to answer this question in 2019 **(Management of Dyslipidemia 2020)**, we reviewed their data without an additional, independent literature search
- Other major guidelines and statements (Canadian Cardiovascular Society, AHA/ACC, European Dyslipidemia, European CVD Prevention, and USPSTF) were reviewed for the evidence they used to support or avoid the use of lipid targets

    - References utilized by the above guidelines pertaining to lipid targets were then reviewed
- Reviewed evidence around the analytic and biologic variation of cholesterol