Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Assessment of Cardiovascular Risk Factors, Study Population, Follow-up Data Collection, and Other RCTs Inclusion and Exclusion Criteria, and Methods

Information on medication use, smoking behavior, alcohol consumption, physical activity, postmenopausal status, and medical history was collected by trained interviewers using a structured home interview. Information on prevalence and incidence of CVD (including atrial fibrillation and heart failure), and history of cancer (excluding non-melanoma skin cancer) was obtained through clinical follow-up as described in detail previously.[1-3] Anthropometric measures were obtained during a visit at the research center. Blood pressure was measured at the right brachial artery with the participant in sitting position. We used the mean of 2 consecutive measurements. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication. Unless specified by respective RCT, poorly controlled hypertension was defined as a systolic blood pressure ≥180 mmHg, diastolic blood pressure ≥100 mmHg, and untreated/uncontrolled hypertension as a systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥90 mmHg.[4,5] A 12-lead 10-second resting ECG was made and digitally processed by the Modular ECG Analysis System (MEANS).[6] Blood samples and hematological data were collected through standard laboratory techniques. Serum glucose, triglycerides, total and high-density lipoprotein cholesterol levels, were measured with standard laboratory techniques. Low-density lipoprotein cholesterol levels were estimated indirectly using the Friedewald formula.[7] C-reactive protein and thyroid-stimulating hormone were measured in participants by mass-spectrometry. Serum creatinine levels were measured using an enzymatic assay (Roche Diagnostics, Mannheim, Germany), which was calibrated by isotope dilution mass spectrometry. Unless specified by the respective RCT, end-stage renal disease (ESRD) was defined as serum creatinine ≥4 mg/dL. Estimated glomerular filtration rate was calculated using the MDRD equation.[8] Unless specified by the respective RCT, chronic liver disease was defined as the ALT levels of twice the upper limit of the local laboratory (>66 U/L). Diabetes mellitus was defined on the basis of a fasting glucose level ≥7.0 mmol/L (≥126 mg/dL), or non-fasting plasma glucose levels ≥11.1 mmol/L (≥200 mg/dL) if fasting samples were unavailable, or the use of blood glucose lowering medication. Family history of premature myocardial infarction was defined as a self-reported history of myocardial infarction before the age of 65 in a first degree family member. Global cognitive function was measured through the Mini Mental State Examination (MMSE).

Missing values (up to 4% for traditional cardiovascular risk factors) were handled separately for men and women by single imputation using predictive mean matching methods. Risk factor profiles were compared using Mann-Whitney U tests for continuous risk factors and χ^2 tests for categorical risk factors. Data were analyzed using IBM SPSS, version 21.0.

Study population

The Rotterdam Study is a prospective population-based cohort study, established in 1990 in the city of Rotterdam, the Netherlands. All inhabitants of a well-defined ZIP code area were invited. Other than a minimum age, there were no exclusion criteria. Up to 2008, a total of 14,926 participants, aged 45 years and over, were recruited in 3 phases. The participants were extensively examined at baseline and every 3-4 years during repeat examinations. For the present analysis we included participants who visited the research center for the third examination of the original cohort (RS-I-3; aged ≥61 years; 1997-1999), the baseline examination of the second cohort (RS-II-1; aged ≥55 years; 2000-2001), and the baseline examination of the third cohort (RS-III-1; aged ≥45 years; 2006-2008). In total 10,522 persons were examined in RS-I-3, RS-II-1 and RS-III-1 combined. We excluded all individuals older than75 years, and all who had the history of atherosclerotic CVD. We included a total of 7279 participants, aged 45 to 75 years in the present analysis. The Rotterdam Study rationale and design have been described in detail previously.[9]

Follow-up data collection

In this study the main outcome measure was incident atherosclerotic cardiovascular disease (ASCVD). Incident ASCVD was composed of fatal and non-fatal myocardial infarction (MI), myocardial revascularization, coronary heart disease (CHD) mortality, and non-hemorrhagic stroke. ASCVD mortality was defined as death due to CHD, non-hemorrhagic cerebrovascular disease, or other atherosclerotic

diseases. The outcome data was collected from the general practitioners and discharge reports from medical specialists, and verified by study physicians as described in detail previously.[1,3] Incident events were assessed until 01.01.2012. Out of 7279 participants included in the analysis, we had complete10-year follow-up data available for 7251 individuals, hence we present incidence rates per 1000 person-years instead of cumulative incidences.

Methods

Guideline recommendations

We calculated the 10-year risk of hard atherosclerotic CVD (ASCVD) for each participant using the recommended ACC/AHA Pooled Cohort equations and published coefficient for white individuals.[10] The sex-specific Pooled Cohort equations include age, systolic blood pressure, treatment for hypertension, total and high-density lipoprotein (HDL) cholesterol levels, current smoking, and history of diabetes mellitus. We created 4 treatment categories (eTable 1): the 3 categories detailed in the ACC/AHA guidelines, "no treatment" (<5.0% 10-year hard ASCVD risk), "treatment considered" (5.0-7.5% 10-year hard ASCVD risk), and "treatment recommended" (≥7.5% 10-year hard ASCVD risk with LDL levels ≥70 mg/dL; or history of diabetes mellitus with LDL levels ≥70 mg/dL; or (LDL) cholesterol >190 mg/dL)[11], and 1 additional category "no recommendation" since the ACC/AHA 2013 guidelines abstain from recommendations for individuals with heart failure and end-stage renal disease[12] (in this study defined as creatinine levels ≥4 mg/dL). This guideline recommends initiation of moderate to intensive statin therapy for individuals who are eligible for primary CVD prevention and have a predicted 10-year hard ASCVD risk of ≥7.5%. Furthermore, it recommends a consideration of moderate-intensity statin therapy for individuals with a 10-year hard ASCVD risk of 5.0-7.5%.

For the ESC guideline, we calculated the 10-year risk of CVD mortality for each participant, taking into account age, systolic blood pressure, total cholesterol levels, and current smoking.[12] We used the sex-specific intercepts and regression coefficients for the SCORE equations for low-risk countries.[13] We created 3 categories of treatment recommendations for the ESC guidelines: "no treatment", "treatment considered", and "treatment recommended". These were based on an individual's predicted risk, LDL cholesterol levels, history of diabetes mellitus, and renal function.

In this study, treatment recommendations were defined based on the recommendations listed as class IA or IB for both guidelines[11,12]

Trial eligibility

For the trial eligibility we identified 10 primary prevention RCTs (70,388 participants) reporting on all-cause mortality and clinical CVD events, selected in the meta-analysis by Brugts and colleagues.[14] The authors have selected RCTs that had up to 15 % of participants with a history of cardiovascular disease at baseline, and did not present data on subgroups of participants with cardiovascular disease (ALLHAT-LLT, ASCOT-LLA, WOSCOPS). For PROSPER, MRC/BHF HPS, and ASPEN, the authors have included in their meta-analysis only the data from the prevention arms of the mention RCTs.

Criteria among the clinical trials varied due to differences in design and hypothesis. Major RCT inclusion criteria included: age, sex, serum levels of cholesterol, triglycerides, C-reactive protein (CRP), history of diabetes mellitus, blood pressure, and postmenopausal status for women (eTables 2-3). Data on some of the minor exclusion criteria were not available in the Rotterdam Study, such as levels of glycated hemoglobin or creatine phosphokinase, and specific rare medical conditions.

We repeated the analysis for trial eligibility for the 18 primary prevention RCTs (56,934 participants) reported by the latest 2013 review of the Cochrane Collaboration on statins for primary prevention of CVD (eTables 2-3).[15] This meta-analysis also considered RCTs with end points such as changes in serum lipid levels and measures of subclinical atherosclerosis, and for that reason were not used in the primary, but rather in the sensitivity analysis.

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eTable 1. Definitions of the Recommendation Categories for ACC/AHA 2013 and ESC 2012 Guidelines

ACC/AHA 2013	
No treatment	0-5% 10-year hard ASCVD risk based on Pooled Cohort equations
Treatment considered	5-7.5% 10-year hard ASCVD risk based on Pooled Cohort equations
Treatment recommended	≥7.5% 10-year hard ASCVD risk based on Pooled Cohort equations with LDL cholesterol level ≥70 mg/dL
	LDL cholesterol level ≥190 mg/dL
	Diabetes mellitus with LDL cholesterol level ≥70 mg/dL
No recommendation	Heart failure
	End stage renal disease
ESC 2012	
No treatment	No lipid intervention or lifestyle interventions
	0-1% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level <190 mg/dL
	1-5% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level <100 mg/dL
Treatment considered	Lifestyle intervention and consider drug
	0-1% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level ≥190 mg/dL
	1-5% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level ≥100 mg/dL
	5-10% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level <100 mg/dL
	≥10% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level <70 mg/dL
Treatment recommended	Lifestyle intervention and immediate drug intervention
	5-10% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level ≥100 mg/dL
	≥10% 10-year CVD mortality risk based on SCORE equations and LDL cholesterol level ≥70 mg/dL
	LDL cholesterol level >6 mmol/L (230 mg/dL)
	Total cholesterol >8 mmol/L (310 mg/dL)
	Diabetes mellitus with LDL cholesterol level ≥70 mg/dL
	Estimated glomerular filtration rate <60 mL/min/1.73m^2 with LDL cholesterol level ≥70 mg/dL

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ESC, European Society of Cardiology; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; SCORE, Systematic coronary risk evaluation.

eTable 2. Detailed List of the Inclusion and Exclusion Criteria per RCT (for Both Primary and Sensitivity Analysis)

Detailed list of the inclusion and exclusion criteria per trial, and information on data availability in the Rotterdam Study			
Trial selection based on meta-analysis by Brugts and colleagues, BMJ 2009			
1.	**WOSCOPS 1995[16]**		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, 45-64 y		History of MI
	Men		History of coronary revascularization
	LDL cholesterol 155-230 mg/dL		History of angina pectoris requiring hospitalization within the previous 12 months *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates[17], ever)*
			Major ECG abnormalities: evidence of prior MI or LBBB
2.	**AFCAPS/TexCAPS 1998[18]**		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, men 45-73 y, women postmenopausal 55-73 y		Uncontrolled hypertension *(in this study: SBP >160 mmHg and/or DBP >90 mmHg)*
	Men and women		History of MI
	Total cholesterol 180-264 mg/dL		History of angina pectoris *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
	LDL cholesterol 130-190 mg/dL	If LDL cholesterol is 125-129 mg/dL, then included if total cholesterol/HDL cholesterol ratio >6	History of intermittent claudication
	HDL cholesterol ≤45 mg/dL for men; ≤47 mg/dL for women		History of stroke
	Serum triglycerides ≤400 mg/dL		History of TIA
			DM type 2 managed with insulin
			DM type 1
			Body weight if 50% greater the desirable limit for height by 1983 metropolitan Life Insurance tables *(in this study: BMI >31.1 for men and 32.3 for women)*
Data not available			Secondary hyperlipidemia
			DM type 2 with a glycated hemoglobin level of at least 10% (or 20% above the upper limit of normal)
3.	**PROSPER 2002[19,20]**		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, 70-82 y *(in this study: 70-79 y)*		History of MI within the past 6 months *(in this study: ever)*
	Men and women		History of stroke within the past 6 months *(in this study: ever)*
	Total cholesterol 4-9 mmol/L		History of TIA within the past 6 months *(in this study: ever)*
	One or more of the following factors:		History of arterial surgery within the past 6 months *(in*

	current smoking; hypertension, currently receiving drug treatment; or known DM or fasting blood glucose >7.0 mmol/L	*this study: ever)*
	Physician diagnosed stable angina pectoris or intermittent claudication *(in this study: NA)*	History of amputation for vascular disease within the past 6 months *(in this study: ever)*
	History of stroke, TIA, MI, arterial surgery, or amputation for vascular disease more than 6 months before study entry *(in this study: NA)*	History of heart failure: New York Heart Association functional class III or IV *(in this study: class II, III, or IV)*
		ECG evidence of atrial fibrillation
		ECG evidence of Wolff-Parkinson-White syndrome
		Serum triglycerides ≥6 mmol/L
		TSH >20 mU/L or TSH >10 mU/L with abnormal free thyroxine *(in this study: normal range for free thyroxine is 11-25pmol/L at the Erasmus Laboratory)*
		ALT or AST >3 times the upper limit of normal *(in this study: ALT >99 U/L, 3 times the upper limit at Erasmus Laboratory)*
		Serum creatinine ≥200 µmol/L
		Plasma glucose >15 mmol/L
		Hemoglobin <11 g/dl
		Hematocrit <33%
		Platelet count <100,000/mm³
		White blood cell count <3,500/mm³ or >15,000/mm³
		Abuse of alcohol *(in this study: ≥14 glasses/week for men and ≥7 glasses/week for women)*
		Cyclosporin treatment
		Organ transplant recipients *(in this study: use of cyclosporin)*
		Use of lipid-lowering drug treatment
		Poor cognitive function (Mini Mental State Examination <24)
		Physically or mentally unable to attend the clinic for the screening visit *(in this study: all RS participants are required to visit personally the research center for the examinations)*
		History of malignancy within the past 5 years except localized basal cell carcinoma of the skin
Data not available		ECG evidence of other significant arrhythmia
		Implanted cardiac pacemakers with the capacity for ventricular pacing
		Any surgery requiring overnight hospitalization for a medical reason within the past 6 months
		Creatine kinase >3 times the upper limit of normal for the laboratory
		Abuse of drugs

4.	ALLHAT-LLT 2002[5,21]	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, ≥55 y *(in this study: 55-79 y)*	History of MI within the past 6 months *(in this study: ever)*
	Men and women	History of stroke within the past 6 months *(in this study: ever)*
	LDL cholesterol 120-189 mg/dL; For patients with history of CHD: LDL cholesterol is 100-129 mg/dL *(in this study: NA)*	History of angina pectoris within the past 6 months *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
	Serum triglycerides ≤4 mmol/L	History of heart failure
	Blood pressure: 1) If using 1 or 2 drugs for hypertension, then SBP >160 mmHg, or DBP >100 mmHg, or 2) If untreated or taking drugs less than 2 months, then SBP 140-180 mmHg, or DBP 90-110 mmHg *(in this study: untreated, ever)*	Use of more than two drugs for hypertension
	Hypertension stage 1 or 2 with at least 1 additional CHD risk factor: old (more than 6 months) or age-indeterminate myocardial infarction or stroke; history of revascularization procedure; or documented atherosclerotic cardiovascular disease *(in this study: NA)*	Use of lipid-lowering agents
	One of the following: HDL cholesterol <35 mg/dL, or current smoking, or DM type 2, or left ventricular hypertrophy on ECG or echocardiogram *(in this study: based on ECG), or* ST-T wave ECG changes indicative of ischemia *(in this study: NA)*	Use of niacin, large doses >500 mg/day *(in this study: any use of niacin)*
		Severe hepatic disease, ALT >2 times the upper limit *(in this study: ALT >66 U/L, 2 times the upper limit at Erasmus Laboratory)*
		Severe renal disease, serum creatinine >2mg/dL
		Use of immunosuppressive agents
		Untreated hypothyroidism *(in this study: TSH >1.5 times the upper limit as defined by at Erasmus Laboratory, TSH >6.9 mU/L)*
Data not available		Ejection fraction <35% if known
		Use of thiazide-like diuretics, calcium antagonists, angiotensin converting enzyme inhibitors, or alpha-blockers for reasons other than hypertension
		Nephrotic syndrome
		Use of probucol in the past year

5.	ASCOT-LLA 2003[4,22]		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, 40-79 y		History of MI
	Men and women		History of angina pectoris, currently treated *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
	Hypertension if untreated: SBP ≥160 mmHg and/or DBP ≥100 mmHg	Hypertension if treated: SBP ≥140 mmHg and/or DBP ≥90 mmHg	History of stroke within the past 3 months *(in this study: ever)*
	Total cholesterol ≤250 mg/dL		History of TIA within the past 3 months *(in this study: ever)*
	≥3 of the following risk factors: left ventricular hypertrophy, ECG abnormalities *(in this study: MI or LBBB)*, DM type 2 non-insulin dependent, peripheral arterial disease *(in this study: NA)*, previous stroke or TIA *(in this study: NA)*, male sex, age ≥55 years, microalbuminuria or proteinuria *(in this study: microalbuminuria >10 mg/L)*, smoking *(in this study: current),* ratio of plasma total cholesterol to HDL cholesterol ≥6, or premature family history of CHD		History of cerebrovascular surgery within the past 3 months *(in this study: ever)*
			History of second or third-degree AV block
			History of heart failure
			Malignant hypertension *(in this study: none of the participants had malignant hypertension)*
			Serum triglycerides > 4.5 mmol/L
			Hepatic disease, ALT levels ≥3 times the upper limit of normal *(in this study: ALT >99 U/L, 3 times the upper limit at Erasmus Laboratory)*
			Renal disease, serum creatinine ≥200 µmol/L
			Abuse of alcohol *(in this study: ≥14 glasses/week for men and ≥7 glasses/week for women)*
			Use of statins
			Use of fibrates
Data not available			History of secondary hypertension
			History of uncontrolled arrhythmias
			Abuse of drugs
			Use of diuretics, calcium channel antagonists, angiotensin converting enzyme inhibitors, alpha-blockers, or beta-blockers prescribed for reasons other than hypertension
			Clinically important hematological, gastrointestinal, or biochemical abnormalities on routine screening
			Pregnant, lactating and pre-menopausal women without appropriate contraception

6.	MRC/BHF 2003[23,24]		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, 40-80 y *(in this study: 45-79 y)*		History of intermittent claudication
	Men and women		History of MI
	Total cholesterol >135 mg/dL		History of stroke
	DM type 2 *(in this study: fasting plasma glucose level ≥ 7.0 mmol/L, or non-fasting plasma glucose level ≥ 11.1 mmol/L , or use of blood glucose-lowering medications)*		History of peripheral arterial revascularization procedure
	Blood pressure	Individuals with drug treated hypertension, if also male and ≥65 y	History of amputation
			History of aneurism repair procedures
			History of hospital admission for angina pectoris within the previous 6 months *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
			DM type 1
			Chronic hepatic disease or abnormal hepatic function, ALT >67U/L
			Severe renal disease or substantially impaired renal function, serum creatinine >200umol/L
			Severe heart failure *(in this study: any history of heart failure)*
			Premenopausal women
			Use of concurrent treatment with cyclosporine
			Use of concurrent treatment with fibrates
			Use of high-dose niacin *(in this study: any use of niacin)*
Data not available			Inflammatory muscle disease or evidence of muscle problems
7.	**CARDS 2004[25]**		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, 40-75 y		History of MI
	Men and women		History of angina pectoris *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
	LDL ≤160 mg/dL		History of coronary vascular surgery
	Serum triglycerides ≤600 mg/dL		History of cerebrovascular accident
	DM type 2	Provided they had at least one or more: currently smoking, retinopathy, history of hypertension (taking antihypertensive therapy, or SBP ≥140 mmHg or DBP ≥90 mmHg), microalbuminuria or macroalbuminuria, albumin creatinine ratio ≥2.5 mg/mmol, albumin excretion rate ≥20 g/min	Severe peripheral vascular disease (defined as warranting surgery)
			Creatinine concentration >150 umol/L

Data not available		Glycated hemoglobin (HbA1c) >12%
8.	**ASPEN 2006[26]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, 40-75 y	History of MI
	Men and women	Episodes of unstable angina pectoris ≤3 months before screening *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
	LDL cholesterol ≤160 mg/dL	History of interventional procedure
	Serum triglycerides ≤600 mg/dL	DM type 1
	DM type 2	Active hepatic disease or hepatic dysfunction: AST or ALT levels ≥1.5 times upper limit of normal *(in this study: ALT >49.5 U/L)*
		Severe renal dysfunction *(in this study: serum creatinine ≥4mg/dL)*
		Congestive heart failure treated with digoxin
		Blood pressure ≥160/100 mmHg
		BMI ≥35 kg/m^2
		Abuse of alcohol *(in this study: ≥14 glasses/week for men and ≥7 glasses/week for women)*
		Use of immunosuppressive agents
		Use of drugs known to interact with the study or medications affecting the clinical laboratory parameters (e.g., systemic steroids or isotretinoin)
		Use other statins within 4 weeks before screening *(in this study: ever)*
		Use of lipid-altering medications 4 weeks before screening *(in this study: ever)*
		Use of drugs associated with increased risk of rhabdomiolysis with statins (e.g., cyclosporine and macrolide antibiotics)
Data not available		HbA1c >10%
		Creatine phosphokinase ≥3 × upper limit of normal
		Nephrotic syndrome
		Abuse of drugs
		Current or planned pregnancy
		Use of probucol 6 months before screening
9.	**MEGA 2006[27]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age: men 40-70 y, women postmenopausal up to 70 y	History of MI
	Men and women	History of coronary artery bypass graft
	Total cholesterol 200-270 mg/dL	History of angina pectoris *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
		History of percutaneous coronary intervention
		ECG abnormalities consistent with myocardial ischemia
		History of peripheral arterial disease
		History of stroke

		History of TIA
		History of chronic atrial fibrillation
		Current diagnosis of malignancy *(in this study: any carcinoma diagnosed within 1 year prior to the first center visit, except non melanoma skin cancer)*
		Chronic active hepatitis or cirrhosis *(in this study: ALT >66 U/L, 2 times the upper limit at Erasmus Laboratory)*
		Serum creatinine ≥4mg/dL
		Poorly controlled hypertension *(in this study: SBP >180 mmHg and/or DBP >100 mmHg)*
		DM *(in this study: fasting plasma glucose level ≥ 7.0 mmol/L, or non-fasting plasma glucose level ≥ 11.1 mmol/L , or use of anti-diabetic medications)*
		Current use of oral or parenteral corticosteroids
Data not available		Secondary hyperlipidemia
		Familial hypercholesterolemia
		History of congenital heart disease
		History of rheumatic heart disease
10.	**JUPITER 2008[28]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age: men ≥50 y, women ≥60 y *(in this study: up to 80 y)*	History of CVD
	Men and women	Previous or current use of lipid-lowering therapy
	LDL <130 mg/dL	Current use of postmenopausal hormone-replacement therapy
	Serum triglycerides <500 mg/dL	Hepatic dysfunction, ALT >2 times the upper limit *(in this study: ALT >66 U/L, 2 times the upper limit at Erasmus Laboratory)*
	C-reactive protein ≥2 mg/L	Long term use of oral glucocorticoids
		Creatinine level >2.0 mg/dL
		DM
		Hypertension (SBP >190 mm Hg and/or DBP >100 mm Hg)
		History of cancer: any carcinoma diagnosed within 5 years prior to the trial enrollment, except non melanoma skin cancer
		Uncontrolled hypothyroidism: TSH> 1.5 times the upper limit *(in this study: TSH >6.9 mU/L as defined by at Erasmus Laboratory)*
		Abuse of alcohol *(in this study: ≥14 glasses/week for men and ≥7 glasses/week for women)*
		Individuals taking immunosuppressant agents such as cyclosporine, tacrolimus, or azathioprine
Data not available		CPK levels >3 times the upper limit
		Abuse of drugs
		Inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease

Additional trials included in the analysis based on meta-analysis published by the Cochrane Collaboration, 2013

11.	**ACAPS 1994[29]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, 40-79 y	History of myocardial infarction (MI)
	Men and women	History of stroke
	LDL: 130-159 mg/dL + any coronary risk, or 160-189 mg/dL + 0 or 1 coronary risk as defined by the NCEP in 1988[30] *<u>CHD risk factors, other than LDL cholesterol, NCEP 1988:</u>* *1) Male sex* *2) Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in a parent or sibling)* *3) Cigarette smoking* *4) Hypertension* *5) HDL cholesterol <35 mg/dL* *6) Diabetes mellitus* *7) History of definite cerebrovascular or occlusive peripheral vascular disease* *8) Severe obesity* ≥30% overweight *(in this study: BMI >31.1 kg/m^2 for men and 32.3 kg/m^2 for women)*	History of angina pectoris *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
		ALT greater than 20% the upper limit for the local laboratory *(in this study: 0-33 U/L Erasmus Laboratory standardized range for ALT, with 39.6 U/L as 20% above the upper limit)*
		Serum triglycerides >400 mg/dL
	Carotid IMT, at the least 1 out of 12 maximum IMTs ≥1.5 mm in common or internal carotid arteries, or ≥1.6 mm in the bifurcation; and all IMT <3.5 mm *(in this study:1.5 ≤ IMT <3.5)*	
12.	**Bone[31]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, 40-75 y	Use of any lipid-lowering medication within 3 months before screening *(in this study: ever)*
	Women postmenopausal	History of coronary heart disease (CHD)
	LDL cholesterol 130-190 mg/dL: Women with LDL >160 mg/dL and 2 or more risk factors as by NCEP III 2001[32] were excluded; *<u>Major CHD risk factors other than LDL, NCEP 2001:</u>* *1) Cigarette smoking* *2) Hypertension (blood pressure ≥140/90 mmHg)* *3) Low HDL cholesterol (<40 mg/dL)* *4) Family history of premature CHD*	Use of other drugs affecting bone metabolism within 3 months before screening *(in this study: ever)*

		5) Age (men ≥45 y, women ≥55 y) **DM is regarded as a coronary heart disease (CHD) risk equivalent.* **HDL ≥60 mg/dL counts as a negative risk factor; its presence removes 1 risk factor from the total count.*	
	Bone mineral density: 0.772-1.047 g/cm², lumbar spine		DM *(in this study: fasting plasma glucose level ≥ 7.0 mmol/L, or non-fasting plasma glucose level ≥ 11.1 mmol/L , or use of blood glucose-lowering medications)*
	Estradiol serum levels: <110 pmol/L, *(in this study: postmenopausal status determined by interview)*		Use of bisphosphonates within 1 year before screening *(in this study: ever)*
	FSH >30 IU/L		Use of sodium fluoride within 3 months before screening *(in this study: ever)*
			Vitamin D intake >1000 IU/day within 3 months before screening *(in this study: ever)*
			Chronic systemic or inhaled glucocorticoids 3 months before screening *(in this study: ever)*
			Use of hormone therapy or selective estrogen receptor modulators within 3 months before screening *(in this study: ever)*
			Use of systemic hormone therapy within 6 months before screening *(in this study: ever)*
			Severe rheumatoid arthritis
			History of cancer within the past 5 years
Data not available			Any disease associated with metabolic bone disease, such as bone marrow disease, hereditary disorders of calcium or mineral metabolism, or untreated or inadequately treated endocrine disorders
			Use of calcitonin within 3 months before screening
13.	**CAIUS[33]**		
	Inclusion criteria		**Exclusion criteria**
Data available	Age, 45-65 y		History of coronary artery disease
	Men and women		Chronic hepatic function abnormalities *(in this study: ALT > 66 U/L, 2 times the upper limit at Erasmus Laboratory)*
	LDL cholesterol 150-250 mg/dL		Use of lipid lowering agents
	Serum triglycerides <250 mg/dL		Use of anticoagulant drugs
	Carotid IMT, 1.3-3.5 mm at the least 1 out of 12 maximum IMT *(in this study:1.3 mm ≤ IMT <3.5 mm)*		Use of calcium receptor blockers
Data not available			Absence of anatomical abnormalities (arterial coiling and kinking) and shadowing in carotid arteries

<table>
<tr><td rowspan="2">14.</td><td colspan="3">CELL A and B (2 arms)[34]</td></tr>
<tr><td colspan="2">Inclusion criteria</td><td>Exclusion criteria</td></tr>
<tr><td rowspan="5">Data available</td><td colspan="2">Age, 30-59 y</td><td>Abnormal renal function (in this study: serum creatinine ≥4mg/dL)</td></tr>
<tr><td colspan="2">Men and women</td><td>Abnormal hepatic function (in this study: ALT > 66 U/L, 2 times the upper limit at Erasmus Laboratory)</td></tr>
<tr><td>Total cholesterol ≥250mg/dL on 3 occasions, and on third ≤300 mg/dL (in this study: 250 mg/dL ≤ total cholesterol ≤300 mg/dL)</td><td rowspan="3">*Moderate hyperlipidemia (defined by total cholesterol, serum triglycerides and serum LDL/HDL ratio) and at least two other cardiovascular risk factors:
1) male gender;
2) smoker (in this study current smoking),
3) BMI ≥30 kg/m²,
4) hypertension (in this study: SBP ≥140 mmHg or DBP ≥90 mmHg)and individuals with hypertension were included if DBP <95 mmHg and controlled with ACE inhibitors, calcium channel blockers, and alfa receptor blockers;
5) personal history of cardiovascular diseases (in this study: not applicable);
6)family history of cardiovascular disease before age 60</td><td>DM type 2 (in this study: fasting plasma glucose level ≥ 7.0 mmol/L, or non-fasting plasma glucose level ≥ 11.1 mmol/L , or use of blood glucose-lowering medications)</td></tr>
<tr><td>Serum triglycerides <355mg/dL</td><td rowspan="2"></td></tr>
<tr><td>Serum LDL/HDL ratio >4.0</td></tr>
<tr><td rowspan="4">Data not available</td><td colspan="2" rowspan="4"></td><td>Secondary hyperlipidemia</td></tr>
<tr><td>Raised levels of CPK</td></tr>
<tr><td>History of drug abuse</td></tr>
<tr><td>Pancreatitis</td></tr>
<tr><td rowspan="2">15.</td><td colspan="3">CERDIA 2004[35]</td></tr>
<tr><td colspan="2">Inclusion criteria</td><td>Exclusion criteria</td></tr>
<tr><td rowspan="9">Data available</td><td colspan="2">Age, 30-80 y</td><td>History of coronary artery disease</td></tr>
<tr><td colspan="2">Men</td><td>History of ischemic stroke</td></tr>
<tr><td colspan="2">DM type 2 diagnosed for at the least 1 year (in this study: fasting plasma glucose level ≥ 7.0 mmol/L, or non-fasting plasma glucose level ≥ 11.1 mmol/L , or use of anti-diabetic medications)</td><td>History of peripheral artery bypass surgery</td></tr>
<tr><td colspan="2" rowspan="6"></td><td>History of percutaneous transluminal angioplasty</td></tr>
<tr><td>ECG criteria for a past MI</td></tr>
<tr><td>Amputation due to atherosclerotic disease</td></tr>
<tr><td>Total cholesterol ≤155 mg/dL and ≥265 mg/dL</td></tr>
<tr><td>Serum triglycerides ≥530 mg/dL</td></tr>
</table>

		ALT levels higher than 2 times the upper limit of the normal range *(in this study: ALT > 66 U/L, 2 times the upper limit at Erasmus Laboratory)*
		Creatinine clearance <30 mL/min/1.73m^2
		Any lipid-lowering therapy 8 weeks before screening
Data not available		CPK levels higher than 3 times the upper limit of the normal range
16.	**Derosa[36]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, >40 y	Use of diuretics
	Men and women	Use of beta-blockers
	Total cholesterol ≥240 mg/dL	
	BMI >30 kg/m²	
	Blood pressure, SBP <140 mmHg and DBP <90 mmHg	
	Non-smoking individuals	
	Normal thyroid function *(in this study: TSH levels 0.4-4.3 mU/L as defined by Erasmus Laboratory)*	
17.	**HYRIM[37]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, 40-74 y	Any symptomatic CVD
	Men	History of MI
	Total cholesterol 174-310 mg/dL	History of stroke
	Serum triglycerides <400 mg/dL	Congestive heart failure
	BMI 25-30 kg/m²	History of coronary interventions
	Blood pressure, individuals with drug treated hypertension	History of angina pectoris *(in this study: use of repeated nitrate prescriptions as a marker for angina pectoris nitrates [17], ever)*
	Sedentary life, or less than 1h/week of regular physical activity, and able to perform physical exercise *(in this study: less than 1 hour/week of physical activity)*	Treatment with lipid-lowering medications other than study drug
		DM type 1
		History of or suspected impaired hepatic function
		History of or known/suspected impaired renal function
		History of cancer *(in this study: any carcinoma diagnosed within 5 years prior to the first center visit, except non melanoma skin cancer)*
		Abuse of alcohol *(in this study: ≥14 glasses/week for men and ≥7 glasses/week for women)*
Data not available		Drug abuse
		Vegetarian diet
		Diet with high omega-3 fatty acid intake

18.	KAPS[38]	
	Inclusion criteria	**Exclusion criteria**
Data available	Age: 42, or 48, or 54, or 60 y	Use of other lipid-lowering medications
	Men	AST or ALT levels ≥1.5 times the upper limit of normal values *(in this study: ALT ≥49.5 U/L as defined at Erasmus Laboratory)*
	Total cholesterol <290 mg/dL	
	LDL cholesterol ≥155 mg/dL	
	BMI <32 kg/m²	
19.	**METEOR[39]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age: men 45-70 y, women 55-70 y	Use of lipid-lowering therapies in previous 12 months *(in this study: ever)*
	Men and women	History of clinically diagnosed coronary artery disease
	LDL cholesterol: 120-190 mg/dL + only age as a coronary risk factor; or 120-160 mg/dL + 2 or more coronary risk factors with 10-year coronary heart disease risk <10%,as defined by NCEP III 2001[32] *Major CHD risk factors other than LDL, NCEP 2001:* *1) Cigarette smoking* *2) Hypertension (SBP/DBP ≥140/90 mmHg)* *3) Low HDL cholesterol (<40 mg/dL)* *4) Family history of premature CHD* *5) Age (men ≥45 y, women ≥55 y)* **DM is regarded as a coronary heart disease (CHD) risk equivalent* **HDL ≥60mg/dL counts as a negative risk factor; its presence removes 1 risk factor from the total count*	History of peripheral atherosclerotic disease
	HDL cholesterol ≤60 mg/dL	History of prior revascularization procedures
	Serum triglycerides <500 mg/dL	10-year CHD risk of 10% or more calculated by NCEP III 2001 guidelines[32]
	Carotid IMT, 1.2-3.5 mm from 2 separate ultrasound examinations *(in this study: IMT 1.2-3.5 mm)*	DM *(in this study: fasting plasma glucose level ≥ 7.0 mmol/L, or non-fasting plasma glucose level ≥ 11.1 mmol/L , or use of blood glucose-lowering medications)*
		Uncontrolled hypertension *(in this study: SBP ≥160 mmHg, DBP ≥90 mmHg)*
		Serum creatinine concentration >2 mg/dL
Data not available		Familial hypercholesterolemia
20.	**PHYLLIS[40]**	
	Inclusion criteria	**Exclusion criteria**
Data availabl	Age, 45-70 y	History of CVD
	Men and women postmenopausal	
	LDL cholesterol 160-200 mg/dL	
	Serum triglycerides ≤300 mg/dL	

	Carotid intima-media thickness, 1.3-4.0 mm	
	Blood pressure, untreated or uncontrolled hypertension, SBP 150-210 mm Hg and DBP 95-115 mm Hg	
21.	**PREVEND IT[41]**	
	Inclusion criteria	**Exclusion criteria**
Data available	Age, 28-75 y	Use of ACE inhibitors
	Men and women	Use of angiotensin II receptor antagonists
	Total cholesterol <310 mg/dL	Creatinine clearance <60% of the normal age adjusted value *(in this study: creatinine clearance <35 mL/min/1.73m^2)*
	Microalbuminuria >10 mg/L in one early morning spot urine sample *(in this study: >10 mg/L)*	
	Blood pressure, SBP <160 mm Hg, DBP <90 mm Hg, and no use of antihypertensive medications	
	No use of lipid lowering medication	
Data not available	Microalbuminuria: 15-300 mg/24 hours in two 24-hour urine samples at least once	

To convert Total, LDL, and HDL cholesterol from mg/dL to SI (in mmol/L) multiply by 0.0259; and for triglycerides by 0.0113.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AV, atrioventricular; BMI, body mass index; BMJ, British Medical Journal; CHD, coronary heart disease; CPK, creatine phosphokinase; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; IMT, intima-media thickness; LBBB, left bundle branch block; LDL, low-density lipoprotein; MI, myocardial infarction; NA, not applicable; NCEP, National Cholesterol Education Program; SBP, Systolic blood pressure; TIA, transient ischemic attack; TSH, thyroid-stimulating hormone.
Trial abbreviations: ACAPS, Asymptomatic Carotid Artery Progression Study Research Group; AFCAPS/TexCAPS, Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT LLT, The Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT LLA, Prevention of Coronary and Stroke Events with Atorvastatin in Hypertensive Patients in the Anglo-Scandinavian Cardiac Outcomes Trial, The Lipid Lowering Arm; ASPEN, The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; Bone, Effects of Atorvastatin on Bone in Postmenopausal Women with Dyslipidemia; CAIUS, The Carotid Atherosclerosis Italian Ultrasound Study; CARDS, Collaborative Atorvastatin Diabetes Study; CELL A/CELL B, Cost Effectiveness of Lipid Lowering Study; CERDIA, Progression of Intima-Media Thickness in Patients With Type 2 Diabetes Without Manifest Cardiovascular Disease; Derosa, Comparison of the Action of Orlistat, Fluvastatin, or Both on Anthropometric Measurements, Blood Pressure, and Lipid Profile in Obese Patients with Hypercholesterolemia; HYRIM, The Hypertension High Risk Management Trial; JUPITER, Justification for the use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS, Kuopio Atherosclerosis Prevention Study; METEOR, Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low Risk Individuals With Subclinical Atherosclerosis; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; MRC/BHF, Heart Protection Study of Cholesterol Lowering with Simvastatin; PHYLLIS, The Plaque Hypertension Lipid-Lowering Italian Study; PREVEND IT, The Prevention of Renal and Vascular End Stage Disease Intervention

Trial; PROSPER, The Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS, The West of Scotland Coronary Prevention Study.

eTable 3. Overview of Selected Clinical Trials on Statin Use for Primary Prevention of CVD (for Both Primary and Sensitivity Analysis)

Trial selection based on meta-analysis by Brugts and colleagues, BMJ 2009					
Year of publication	**N**	**Sex**	**Age range, y**	**CVD outcome**	**Positive or negative findings for any CVD outcome**
WOSCOPS[a] 1995[16]	6595	Men only	45-64	Primary: Composite of non-fatal MI and CHD death. Single outcome: Total mortality, fatal CVD events, revascularizations, non-fatal MI and CHD death.	Positive +
AFCAPS/TexCAPS 1998[18]	6605	57.5% Men	Men 45-73; postmenopausal women 55-73	Primary: Composite of fatal and non-fatal MI and fatal CHD. Secondary: All-cause mortality; fatal and non-fatal CHD and stroke; and heart failure.	Positive +
PROSPER[b] 2002[19,20]	3239	48.3% Men	70-82	Primary: Composite of CHD death, non-fatal MI, and fatal or non-fatal stroke. Secondary: CHD death or non-fatal MI; fatal or non-fatal stroke, TIA, Percutaneous transluminal coronary angioplasty and coronary artery bypass graft, peripheral arterial surgery /angioplasty, all cardiovascular events, heart failure.	Positive +
ALLHAT-LLT[a] 2002[5,21]	10,355	51% Men	≥55	Primary: All-cause mortality. Secondary: Composite of non-fatal MI, fatal CHD, total incidence of stroke and heart failure.	Negative -
ASCOT-LLA[a] 2003[4,22]	10,305	81.2% Men	40-79	Primary: Composite of non-fatal MI and CHD death. Secondary: All-cause mortality; total cardiovascular events and procedures; non-fatal MI (excluding silent MI) plus fatal CHD; total coronary event; cardiovascular mortality; fatal and non-fatal stroke; fatal and non-fatal heart failure, silent MI, unstable angina, chronic stable angina, peripheral arterial disease.	Positive +
MRC/BHF Heart Protection[b]	2912	Men and	40-80	Primary: Composite of coronary and vascular	Positive +

2003[23,24]		women		events, stroke, revascularizations.	
CARDS 2004[25]	2838	68% Men	40-75	Primary: Composite of fatal and non-fatal MI, acute CHD death, and resuscitated cardiac arrest. Secondary: All-cause mortality; fatal and non-fatal MI (incl. silent) and stroke; revascularization; resuscitated cardiac arrest; and total CVD events.	Positive +
ASPEN[b] 2006[26]	1905	62.5% Men	40-75	Primary: Composite of fatal MI, stroke, sudden cardiac death, heart failure, and CVD death. Secondary: Non-fatal or silent MI and stroke; revascularization; resuscitated cardiac arrest; TIA; unstable angina; peripheral arterial disease; and ischemic heart failure.	Negative -
Adult Japanese MEGA Study 2006[27]	7832	32 % Men	Men 40-70; postmenopausal women up to 70	Primary: Composite of major CVD, sudden cardiac death, angina and revascularization. Secondary: All-cause mortality; total CVD; fatal and nonfatal MI; stroke and TIA; sudden cardiac death; angina; and revascularization.	Positive +
JUPITER 2008[28]	17,802	62% Men	Men ≥50; women ≥60	Primary: Revascularization, hospital admission for angina, MI, stroke, and CVD death. Secondary: All-cause mortality.	Positive +
Additional trials included in the analysis based on meta-analysis published by the Cochrane Collaboration, 2013					
ACAPS 1994[29]	919	52 % Men	40-79	Secondary: Fatal and non-fatal CHD; stroke.	Positive +
Bone 2007[31]	626	Women only	Postmenopausal 40-75	Non-cardiovascular end point	NA
CAIUS 1996[33]	305	53% Men	45-65	Secondary: Fatal and non-fatal MI; angina; and revascularizations.	Positive +
CELL A; and B[a] 1996[34]	455	85% Men	30-59	Non-cardiovascular end point	NA
CERDIA 2004[35]	250	Men only	30-80	Secondary: CVD events; and amputation due to atherosclerotic disease.	Positive +
Derosa 2003[36]	47	46% Men	>40	Non-cardiovascular end point	NA

HYRIM 2007[37]	287	Men only	40-74	Primary: Composite of fatal and non-fatal MI, stroke, angina, sudden CHD death, TIA, and heart failure. Secondary: MACE, composite of cardiac death, fatal and non-fatal MI and revascularization.	Positive +
KAPS[a] 1995[38]	447	Men only	42 or 48 or 54 or 60	Primary: All-cause mortality, fatal and non-fatal MI events, stroke, other cardiac death, revascularizations and heart failure.	Positive +
METEOR 2010[39]	984	59.7% Men	Men 45-70; women 55-70	Non-cardiovascular end point	NA
PHYLLIS 2004[40]	253	Men and women	45-70; postmenopausal women	Secondary: Non-fatal MI, CVD death, stroke.	Positive +
PREVEND IT[a] 2004[41]	864	64.5% Men	28-75	Primary: Composite of fatal and non-fatal CVD events.	Negative -

[a] Up to 15% of the participants had a history of cardiovascular disease at baseline.
[b] Data from the primary prevention arms of the respective RCT, persons free from cardiovascular disease at baseline.

Abbreviations: BMJ, British Medical Journal; y, years; CHD, coronary heart disease; CVD, cardiovascular disease; MACE, major adverse cardiac Events; MI, myocardial infarction; NA, not applicable; TIA, transient ischemic attack.

Trial abbreviations: ACAPS, Asymptomatic Carotid Artery Progression Study Research Group; AFCAPS/TexCAPS, Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT LLT, The Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT LLA, Prevention of Coronary and Stroke Events with Atorvastatin in Hypertensive Patients in the Anglo-Scandinavian Cardiac Outcomes Trial, The Lipid Lowering Arm; ASPEN, The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; Bone, Effects of Atorvastatin on Bone in Postmenopausal Women with Dyslipidemia; CAIUS, The Carotid Atherosclerosis Italian Ultrasound Study; CARDS, Collaborative Atorvastatin Diabetes Study; CELL A/CELL B, Cost Effectiveness of Lipid Lowering Study; CERDIA, Progression of Intima-Media Thickness in Patients With Type 2 Diabetes Without Manifest Cardiovascular Disease; Derosa, Comparison of the Action of Orlistat, Fluvastatin, or Both on Anthropometric Measurements, Blood Pressure, and Lipid Profile in Obese Patients with Hypercholesterolemia; HYRIM, The Hypertension High Risk Management Trial; JUPITER, Justification for the use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS, Kuopio Atherosclerosis Prevention Study; METEOR, Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low Risk Individuals With Subclinical Atherosclerosis; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group; MRC/BHF, Heart Protection Study of Cholesterol Lowering with Simvastatin; PHYLLIS, The Plaque Hypertension Lipid-Lowering Italian Study; PREVEND IT, The Prevention of Renal and Vascular End Stage Disease Intervention Trial; PROSPER, The Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS, The West of Scotland Coronary Prevention Study.

eTable 4. Overall Cardiovascular Risk Factor Profiles by ACC/AHA 2013, ESC 2012 Guidelines, Trial Eligibility

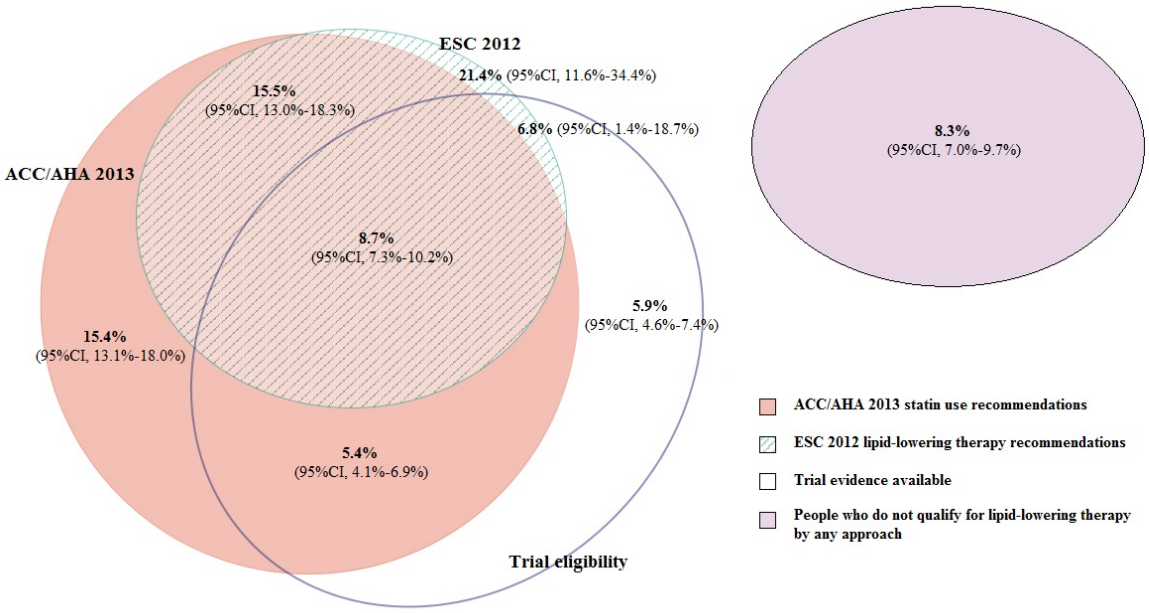
Risk factors	**Total**	**Adults eligible for statin initiation**			**Adults not eligible for statin initiation by any approach**
		ACC/AHA	**ESC**	**Trial eligible**	
	n = 7279	**n = 4284**	**n = 2339**	**n = 3857**	**n = 1719**
Male sex	3041 (41.8)	2415 (56.4)	1335 (55.6)	1858 (48.2)	353 (20.5)
Age (years)	61.1 (6.9)	64 (6.2)	66 (6.0)	62.3 (6.4)	55.5 (5.3)
Systolic blood pressure, mmHg	137 (20)	143 (21)	149 (21)	139 (20)	128 (17)
Diastolic blood pressure, mmHg	80 (11)	81 (12)	82 (12)	80 (11)	80 (11)
Body mass index, kg/m^2	27.3 (4.3)	27.5 (4.1)	27.7 (4.3)	27.5 (4.2)	27 (4.8)
Total cholesterol, mg/dL	224 (38)	230 (39)	233 (40)	230 (31)	201 (33)
LDL cholesterol, mg/dL	142 (35)	150 (36)	152 (36)	149 (29)	119 (30)
HDL cholesterol, mg/dL	55 (16)	51 (14)	52 (15)	53 (16)	60 (16)
Triglycerides, mg/dL	135 (75)	148 (77)	149 (78)	142 (71)	112 (74)
CRP, mg/L[a]	1.4 (0.6-3.2)	1.7 (0.7-3.6)	2.0 (0.9-4.0)	1.6 (0.7-3.5)	1.0 (0.4-2.3)
Estimated glomerular filtration rate, mL/min[a]	83 (74-93)	82 (73-93)	81 (70-92)	82 (73-92)	85 (75-94)
Current smoking	1798 (24.7)	1329 (31.0)	775 (32.3)	995 (25.8)	307 (17.9)
Former smoking	3254 (44.7)	1909 (44.6)	1056 (44.0)	1732 (44.9)	748 (43.5)
Blood pressure lowering medication	1746 (24.0)	1237 (28.9)	782 (32.6)	999 (25.9)	293 (17.0)
Statin treatment	674 (9.3)	448 (10.5)	266 (11.1)	265 (6.9)	142 (8.3)
History of heart failure	42 (0.6)	NA[b]	32 (1.3)	14 (0.4)	7 (0.4)
History of atrial fibrillation	178 (2.4)	122 (2.8)	86 (3.6)	57 (1.5)	37 (2.2)
Type 2 diabetes mellitus	609 (8.4)	567 (13.2)	573 (23.9)	550 (14.3)	5 (0.3)

Values are counts (percentages), means (standard deviation), or medians (25th-75th percentiles). To convert Total, LDL, and HDL cholesterol from mg/dL to SI (in mmol/L) multiply by 0.0259; and for triglycerides by 0.0113.

Abbreviation: ACC/AHA, American College of Cardiology/American Heart Association; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[b] NA, not applicable since ACC/AHA 2013 guidelines do not provide recommendations for individuals with heart failure.

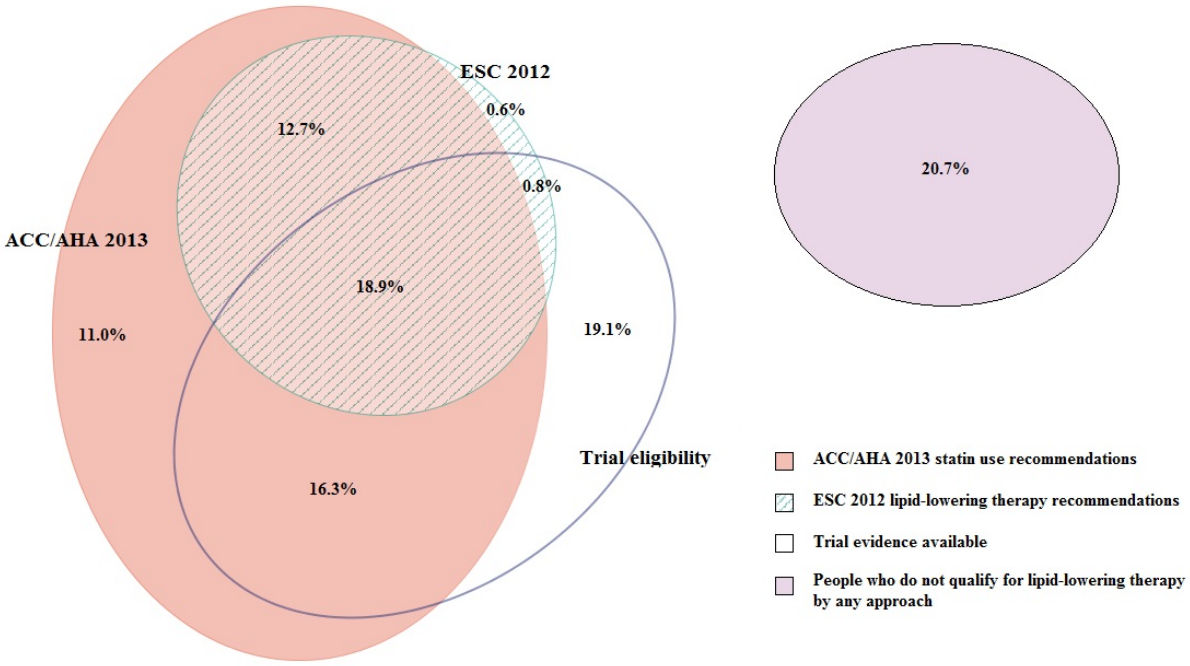
eFigure 1. Statin Use at Baseline Within Subgroups of ACC/AHA 2013, ESC 2012 Guidelines, and Trial Eligibility



Within each subgroup presented in the main Figure 1 we have determined the percentage of statin use at baseline. This figure should be interpreted with caution, as it represents statin use at the time when none of the assessed guidelines, nor some of the evaluated RCTs were published (1997-2008). This figure provides information on the distribution of statin use at baseline, it will most likely underestimate contemporary rates of statin use in general population.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ESC, European Society of Cardiology, RCT, randomized clinical trial.

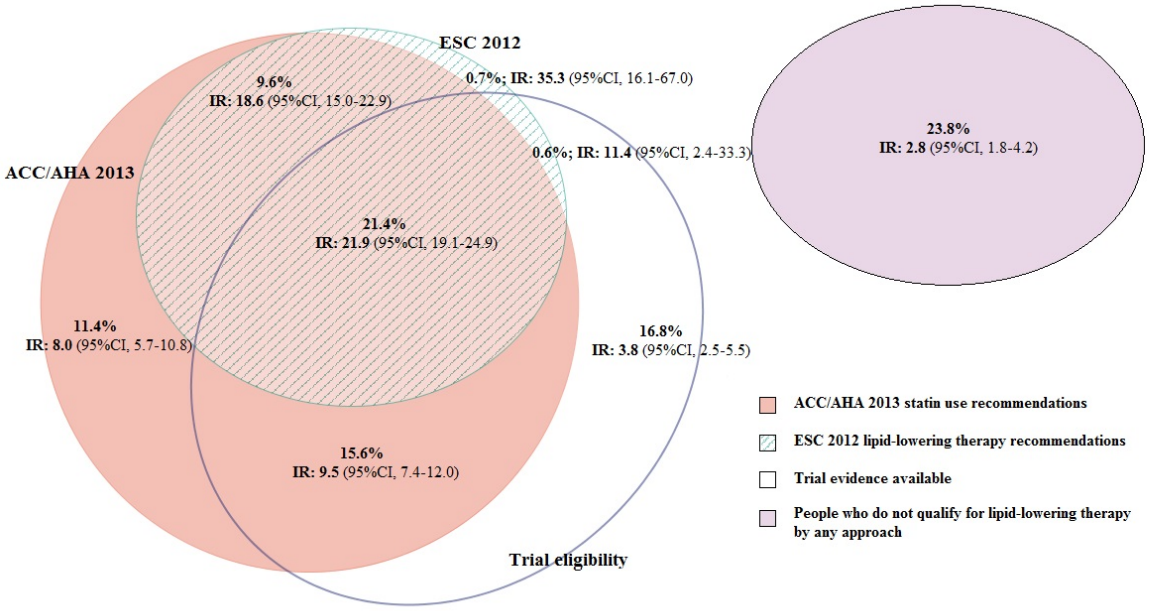
eFigure 2. Venn Diagram Comparing the ACC/AHA 2013, ESC 2012 Recommendations and Eligibility for 18 Statin Trials Selected in the 2013 Review by the Cochrane Collaboration on Statins for Primary Prevention of Cardiovascular Disease



This figure is identical in design as compared to Figure 1 of the main manuscript with the use of 18 trials instead of 10 trials on statin use in primary prevention of cardiovascular disease. ACC/AHA 2013 recommended statin treatment to 4284 (58.9%) of the CVD free Rotterdam Study population. ESC 2012 guideline recommends statin treatment to 2399 (33.0%). Overall, trial eligible were 4007 (55.0%) participants free of CVD. A total of 1504 (20.7%) participants were neither recommended treatment by any of the guidelines, nor were they eligible for any of the trials. From the Venn diagram overlap among these groups can be observed.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; CVD, cardiovascular disease; ESC, European Society of Cardiology.

eFigure 3. Venn Diagram Comparing the ACC/AHA 2013 and ESC 2012 Guideline Recommendations and Eligibility for 10 Statin Trials for Primary Prevention of Cardiovascular Disease, Excluding Statin Users at Baseline

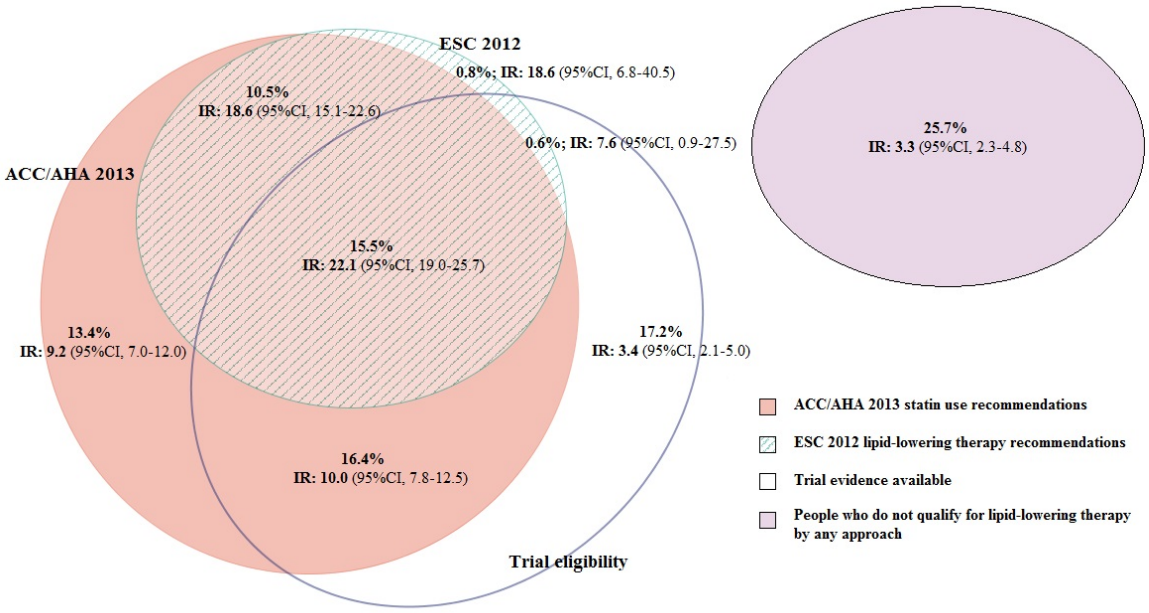


This figure is identical in design as compared to Figure 1 of the main manuscript with the exclusion of statin users at baseline. When all statin users are excluded, the ACC/AHA 2013 guideline recommends statin treatment to 3824 (58.1%) of the Rotterdam Study population. The ESC 2012 guideline recommends lipid-lowering treatment to 2129 (32.3%) of the population. Overall, 3583 (54.4%) Rotterdam Study participants would be eligible for at least one out of 10 trials. A total of 1570 (23.8%) participants were neither recommended treatment by any of the guidelines, nor were they eligible for any of the trials. From the Venn diagram overlap among these groups can be observed.

For the population free of statin users at baseline, the ASCVD incidence rates per 1000 person-years with 95% confidence intervals over up to 10 years of follow-up are presented in the figure.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; CI; confidence interval; ESC, European Society of Cardiology; IR, Incidence rate.

eFigure 4. Venn Diagram Comparing the ACC/AHA 2013 and ESC 2012 Guideline Recommendations and Eligibility for 10 Statin Trials for Primary Prevention Of Cardiovascular Disease, Excluding Individuals With Type 2 Diabetes at Baseline

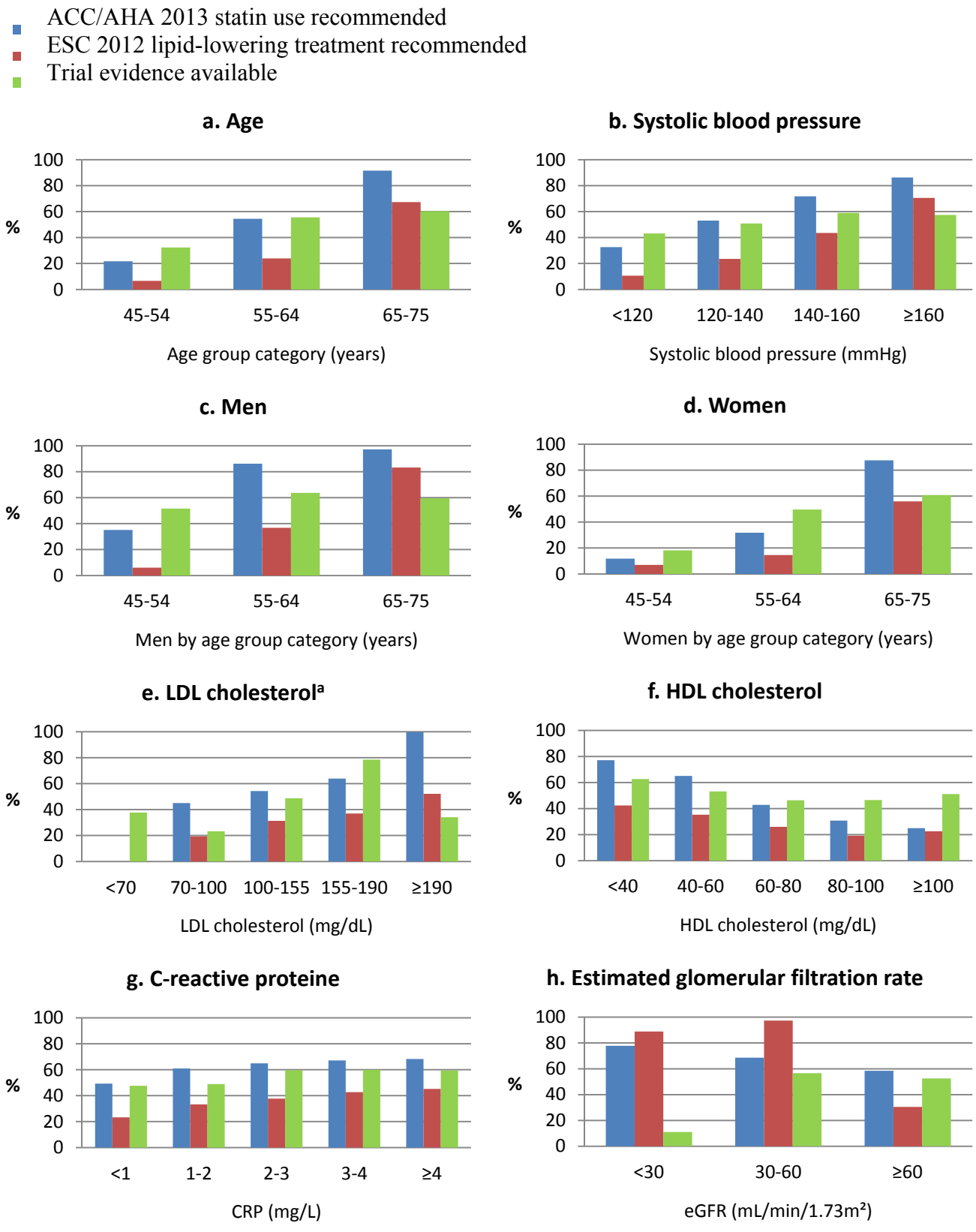


This figure is identical in design as compared to Figure 1 of the main manuscript with the exclusion of individuals with type 2 diabetes mellitus at baseline. When all individuals with diabetes mellitus are excluded, the ACC/AHA 2013 guideline recommends statin treatment to 3700 (55.7%) of the Rotterdam Study population. The ESC 2012 guideline recommends lipid-lowering treatment to 1818 (27.4%) of the population. Overall, 3297 (49.7%) Rotterdam Study participants would be eligible for at least one out of 10 trials. A total of 1705 (25.7%) participants were neither recommended treatment by any of the guidelines, nor were they eligible for any of the trials. From the Venn diagram overlap among these groups can be observed.

For the population free of diabetes mellitus at baseline, the ASCVD incidence rates per 1000 person-years with 95% confidence intervals over up to 10 years of follow-up are presented in the figure.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; CI; confidence interval; ESC, European Society of Cardiology; IR, Incidence rate.

eFigure 5. ACC/AHA 2013 and ESC 2012 Guideline Recommendations and Trial Eligibility by Clinical Characteristics



To convert Total, LDL, and HDL cholesterol from mg/dL to SI (in mmol/L) multiply by 0.0259; and for triglycerides by 0.0113.

Graphs: A. Age, percentage of population in each age group with statin indication based on guidelines recommendations and trial eligibility; B. Systolic blood pressure, percentage of population with indication for statin initiation by systolic blood pressure levels; C. Men, percentage of men with indication for statin initiation by age; D. Women, percentage of women with indication for statin initiation by age; E. LDL cholesterol, percentage of population with indication for statin initiation by LDL cholesterol levels; F. HDL cholesterol, percentage of population with indication for statin initiation by HDL cholesterol levels; G. C-reactive protein, percentage of population with indication for statin initiation by CRP levels; H. Estimated glomerular filtration rate, percentage of population with indication for statin initiation by estimated glomerular filtration rate.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]ACC/AHA and ESC for LDL cholesterol levels <70 mg/dL deem additional criteria for the assessment of the treatment recommendations for primary prevention of CVD apart from the estimated 10-year risk. In this study, we have followed the treatment recommendations listed as class I for both guidelines[11,12], therefore in graph E. it appears that guidelines do not identify anyone for treatment recommendations. In our study sample overall 130 (1.8%) of the population had LDL cholesterol levels <70 mg/dL. In addition, trials in subgroups of individuals with very high cholesterol levels (e.g. familial hypercholesterolemia) were explicitly not covered by the meta-analyses which we based the trial selection upon, an apparent discrepancy appears between guideline recommendations and available trial evidence in those with very high LDL levels.