Title

High-Quality Statin Trials Support the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines After the HOPE-3 Trial (Heart Outcomes Prevention Evaluation-3)

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High quality statin trials support the 2013 ACC/AHA cholesterol guidelines: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Importance: The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on blood cholesterol expanded primary prevention with statins by lowering the risk-based threshold for treatment. Trial evidence for this recommendation has been questioned.

Objective: To determine to what extent this recommendation is supported by evidence from randomized controlled trials (RCT) of statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD).

Design, setting, and participants: We studied MESA (Multiethnic study of atherosclerosis) participants recruited in 2000-2002 and free of ASCVD and statin use at baseline. For each individual, the 10-year risk for ASCVD was estimated using the ACC/AHA-recommended Pooled Cohort Equations (PCE), and statin eligibility was assessed based on ACC/AHA class I and IIa recommendations and evidence from 7 high-quality RCTs, including the most recent Heart Outcomes Prevention Evaluation-3 trial.

Main outcomes and measures: The proportion of ACC/AHA statin eligible individuals who had RCT evidence supporting statin efficacy.

Results: Among 4967 individuals (53% women) aged 45-75 years, 70% were statin eligible based on evidence from RCT, 50% based on ACC/AHA class I recommendations, and 13% based on the class IIa recommendation. The 10-year risk for ASCVD and the presence of RCT supporting statin therapy correlated strongly (Spearman = 1.0, $p<0.0001$). Nearly all (98%) who had a PCE risk >10% also had trial evidence documenting efficacy of statin therapy. Among individuals who qualified for statins with an ACC/AHA class I recommendation, 94% had trial evidence supporting statin use. RCT evidence for statin efficacy was also common (78%) among those who only had a class IIa recommendation (PCE risk ≥5% to <7.5%), but fell to 36% in those with a PCE risk <5%. Conversely, 23% had RCT evidence without a concomitant ACC/AHA class I recommendation for statin therapy, but the rate of ASCVD was low in such individuals (3.1 per 1000 person-years).

Conclusions and relevance: More than 9 out of 10 individuals eligible for an ACC/AHA class I recommendation for primary prevention with statins had RCT evidence supporting statin use. Thus, the

ACC/AHA recommendations seem to be a reasonable starting point for patient-physician discussions on initiation of evidence-based statin therapy.

Abbreviations and acronyms

ACC/AHA = American College of Cardiology/American Heart Association

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm

ASCVD = atherosclerotic cardiovascular disease

HOPE-3 = Heart Outcomes Prevention Evaluation-3

JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese

MESA = Multi-Ethnic Study of Atherosclerosis

PCEs = pooled cohort equations

RCT = randomized controlled trial

WOSCOPS = West of Scotland Coronary Prevention Study

Introduction

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on risk assessment and treatment of blood cholesterol represented a paradigm shift in primary prevention of atherosclerotic cardiovascular disease (ASCVD) in the United States (US) for three reasons[1-3]. First, specific low-density lipoprotein cholesterol (LDL-C) targets were abandoned. Second, a new risk calculator (pooled cohorts equations, PCEs) predicting 10-year risk of ASCVD (fatal coronary heart disease and stroke, and non-fatal myocardial infarction and stroke) was introduced. Third, risk-based indication for primary prevention with statin therapy was expanded significantly based on carefully performed risk-benefit analyses. However, ever since their introduction, the guidelines have been surrounded by controversy partly because they increase the number of individuals in the US recommended for statin therapy[3]. Although the identified 7.5% and 5% 10-year risk of ASCVD thresholds (Class I and IIa recommendations) were selected based on data from 3 randomized controlled trials (RCT) of statin therapy in primary prevention (AFCAPS/TexCAPS, MEGA and JUPITER), recent results from two population-based European cohort studies – the Copenhagen General Population Study and the Rotterdam Study – indicate that more than 30% of individuals eligible for statin therapy by class I recommendations do not have RCT data to support statin efficacy[4,5]. Further, when the US Preventive Services Task Force recently published their guidelines on primary prevention of cardiovascular disease (based on a review of trial evidence), they restricted the indication for statin therapy compared with the ACC/AHA guidelines by recommending a higher treatment threshold (PCE 10%) combined with the presence of at least one ASCVD risk factor (B recommendation)[6]. However, the evidence base for statins in primary prevention grew substantially in 2016 with publication of the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial that enrolled intermediate-risk individuals for whom statin evidence were still lacking[7].

Thus, based on a population-based and well-described US cohort representative of the US population[8], we assessed if the ACC/AHA recommendations for statin therapy are supported by currently available high-quality RCT evidence documenting efficacy of treatment.

Methods

Study participants and risk factor assessment

Multi-ethnic study of atherosclerosis (MESA) is a National Institutes of Health/National Heart, Lung and Blood Institute-funded study designed to describe the characteristics of subclinical atherosclerosis and to identify risk factors involved in progression of atherosclerosis to clinical ASCVD[9]. A total of 6814 men and women aged 45 to 84, free of clinical ASCVD at baseline examination, were recruited between July 2000 and September 2002. Enrollment was at 6 sites in the United States (Baltimore (Maryland), Chicago (Illinois), Forsyth County (North Carolina), Los Angeles (California), New York (New York) and St. Paul (Minnesota)). Details on the design and organization have been published previously[9].

The baseline examination in MESA has been described previously[10]. Smoking was defined as current smoking. Diabetes was defines as self-reported diabetes, a fasting glucose ≥7.0 mmol/L or use of anti-diabetic drugs.

ACC/AHA recommendations for statin therapy in primary prevention

The 2013 ACC/AHA risk assessment and cholesterol treatment guidelines recommend moderate- to high-intensity statin therapy for primary prevention to individuals aged 40-75 without clinical ASCVD or diabetes but with LDL cholesterol of 70-189 mg/dL and an estimated 10-year ASCVD risk ≥7.5%[1]. Diabetic individuals are recommended statins if they have LDL cholesterol of 70-189 mg/dL. Individuals with LDL cholesterol ≥190 mg/dL should be treated with high-intensity statin therapy, regardless of risk. These are the only three class I statin recommendations in the guideline for individuals free of ASCVD (**Supplementary Figure 1**). The guidelines further provide a class IIa recommendation for individuals aged 40-75 without clinical ASCVD or diabetes but with LDL cholesterol of 70-189 mg/dL and an estimated 10-year ASCVD risk of 5% to <7.5% (**Supplementary Figure 1**).

RCTs of statin efficacy

Evidence for statin efficacy in primary prevention is provided by data from 7 large and high-quality RCTs documenting reduction in ASCVD event rates (named in chronological order by publication year): WOSCOPS (West of Scotland Coronary Prevention Study)[11], AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)[12], ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm)[13], CARDS (Collaborative Atorvastatin Diabetes Study)[14], MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese)[15], JUPITER (Justification for the Use of Statins in prevention: An

Intervention Trial Evaluating Rosuvastatin)[16] and HOPE-3 (Heart Outcomes Prevention Evaluation-3)[7].

Enrollment criteria in these 7 RCTs are shown in **Supplementary Figure 1**.

Cardiovascular disease endpoints

Ascertainment of events has been described previously[17]

. Briefly, trained MESA personal contacted participants or family members at regular intervals to inquire about ASCVD diagnosis, including hospital admissions, outpatient diagnoses and deaths. Follow-up was completed in 92% of living participants. Medical records were obtained for approximately 98% of hospital admissions and 95% of outpatient diagnoses. A study committee, including cardiologists and neurologists, adjudicated every event.

For this study, we defined ASCVD events as coronary heart disease (myocardial infarction, resuscitated cardiac arrest and CHD death) plus fatal and nonfatal strokes. Myocardial infarction was diagnosed based on the combination of symptoms, electrocardiographic findings and levels of cardiac biomarkers. Hospital records as well as family interviews were used to determine if a death was related to CHD. Stroke was diagnosed based on a documented focal neurological deficit lasting 24 hours or until death, or if <24 hours, with imaging evidence of relevant brain lesions.

Statistical analysis

Baseline characteristics are presented as proportions for categorical variables and as medians (interquartile range) for continuous variables. We calculated the number and percentage of participants eligible for statin therapy under the ACC/AHA guidelines using both class I and IIa recommendations. Further, we determined the proportion of the MESA population with trial-based evidence of statin efficacy, that is, the proportion of individuals meeting enrollment criteria in at least one of the 7 RCTs. Then, the overlap in statin eligibility by the ACC/AHA guidelines and the 7 RCTs was determined to assess to what extent the ACC/AHA recommendations are supported by RCT evidence. Finally, the ASCVD event rate per 1000 person-years was calculated, stratified according to trial evidence and/or ACC/AHA recommendations.

Analyses were performed using Stata version 13.1 SE.

Results

This study included 4967 individuals (53% women) aged 45-75 years and free of known ASCVD or lipid-lowering medication at baseline examination (**Table 1**). The median 10-year risk for ASCVD at baseline estimated by PCE was 7.0%, higher for men (10.5%) than women (4.4%).

Statin eligibility under the ACC/AHA guidelines and trial evidence

Overall, 70% of MESA participants were statin eligible based on evidence from high-quality RCTs of statin therapy, 50% based on ACC/AHA class I recommendations, and 13% based on the class IIa recommendation (**Supplementary Figure 2 and Table 2**). There was a near-perfect relationship (spearman = 1, p<0.0001) between the 10-year risk for ASCVD and the presence of trial data supporting statin therapy (**Figure 1**). Thus, only 11% of individuals with a PCE risk <1% had trial evidence documenting efficacy of statin therapy increasing to 98% in those with a PCE risk >10%.

The overlap in statin eligibility based on ACC/AHA class I statin recommendations and trial evidence documenting efficacy of statin therapy is visualized in the Venn diagrams in **Figure 2**. Among individuals with an ACC/AHA class I recommendation (n=2482), 94% had trial evidence supporting statin therapy (**Figure 2 and Supplementary Figure 3**). The clinical trials providing this evidence are shown in **Figure 3**. The HOPE-3 trial provided much of the until recently missing trial-based evidence. More than 59% of ACC/AHA class I eligible individuals had evidence from 2 or more trials simultaneously (**Supplementary Figure 4**). In individuals with a 10-year ASCVD risk from 5% to <7.5% (class IIa statin recommendation), 78% had trial data supporting statin therapy falling to 36% in those with a PCE risk <5% (**Supplementary Figure 3**).

ASCVD event rates by statin eligibility

The ASCVD event rate varied greatly according to statin eligibility by ACC/AHA class I recommendations and/or trial-based evidence. As shown in **Table 2** and **Supplementary Figure 5,** the ASCVD event rate was relatively high in the 2482 individuals with an ACC/AHA class I statin indication (9.2 (95% CI 8.0-10.5) per 1000 person-years), lower in those (n=3474) with a trial-based indication (7.4 (95% CI 6.6-8.5), and even lower in those (n=1151) with a trial-based indication alone (3.1 (95% CI 2.2-4.4).

Discussion

Among MESA individuals recommended for statin therapy by 2013 ACC/AHA class I recommendations, we found that more than 9 out of 10 have evidence of statin efficacy by meeting enrollment criteria in 1 or more of 7 high quality RCTs documenting that statin treatment reduces ASCVD event rates. Even for the weaker class IIa recommendation, we found RCT evidence for more than 7 out of 10. Importantly, the results were similar for men and women separately. Taken together, these results obtained from a population-based US cohort indicate that the ACC/AHA recommendations are a reasonable starting point for patient-physician discussions on the initiation of statin therapy.

Like most other international guidelines on lipid-lowering treatment for primary prevention (i.e. NICE and ESC[18]), the 2013 ACC/AHA guidelines recommend that statin allocation should be based on absolute ASCVD risk assessment. In such a risk-based approach, treatment is targeted to individuals with a 10-year risk of ASCVD above a certain guideline-defined threshold in order to optimize the tradeoff between efficacy and safety of treatment. However, the justification and evidence base for this traditional approach for statin allocation has recently been questioned as no RCTs of statin therapy have ever enrolled participants based on 10-year ASCVD risk assessment[19-21]. Indeed, two recent reports from population-based European cohorts have shown that a substantial proportion of individuals eligible for statin therapy by ACC/AHA class I recommendations do not have RCT evidence to support statin efficacy[4,5]. Among 37892 individuals aged 40-75 years and free of ASCVD or diabetes from the Copenhagen General Population study, 32% of those eligible for statin therapy by the ACC/AHA class I recommendations did not have trial evidence to support statin efficacy as assessed by 5 high quality primary prevention RCTs documenting that statin treatment reduces ASCVD event rates[4]. A more recent analysis among 7279 individuals from the Rotterdam Study aged 45-75 years found that as many as 37% of those eligible for ACC/AHA class I statin therapy were not supported by trial evidence[5]. This analysis may even have overestimated trial evidence as it included 10 randomized statin trials, in which some did not strictly enroll primary prevention individuals, were not placebo-controlled or did not provide evidence that statin therapy reduces ASCVD event rates. Thus, as an alternative to the traditional risk-based approach to statin therapy, it has been suggested to either allocate statin therapy strictly on the basis of trial-evidence (that is what works and in whom)[19] or, alternatively, to restrict statin therapy to the subpopulation of ACC/AHA class I eligible individuals with concomitant trial-evidence of statin efficacy (the so-called hybrid approach)[22]. However, with the recent publication of the HOPE-3 trial[7], the evidence base for statin efficacy in primary prevention was expanded substantially as illustrated by our analyses. Among MESA individuals eligible for ACC/AHA class I statin therapy, evidence for statin efficacy suddenly increased from 73% to 94% (≈19 out of

20) with the HOPE-3 trial. Thus, based on currently available high quality RCTs, there is now evidence that statins reduces ASCVD event rates for nearly all individuals eligible for class I statin therapy by the 2013 ACC/AHA guidelines. With this recent development, the rationale behind a trial-based (or hybrid) approach to statin therapy may be viewed as outdated. Instead, a new question emerges: should the large group of individuals with trial-based evidence of statin efficacy but without a concomitant ACC/AHA class I recommendation be candidates for statin therapy? In MESA, such individuals (almost 1 out of 4) had much lower event-rates compared to ACC/AHA class I eligible individuals (3.1 vs. 9.2 per 1000 person-years), implying that the short term (≈ 10 year) net benefit of statin therapy is very low in these individuals.

Taken together, our analyses add to the body of evidence supporting the ACC/AHA risk-based approach as an appropriate starting point for patient-physician discussions on prophylactic statin therapy, including risk-benefit analyses[1,2], cost-effectiveness analyses[23,24] and now also RCT evidence supporting statin efficacy.

Limitations

Our study has potential limitations. First, we were not able to consider all exclusion criteria used in the randomized statin trials. However, exclusion criteria were not mentioned in the trial-based proposal, and are most often ignored in routine clinical practices[25]. Second, as MESA only enrolled participants aged 45 to 84, we could not evaluate trial-evidence in those aged 40 to 44 that are also covered by the ACC/AHA guidelines[1]. Third, PCE has been shown to overestimate risk in MESA[26]. However, calibration of PCE is not important for assessing the trial-based evidence for statin therapy in those who qualify for treatment under the current ACC/AHA guidelines, including use of the recommended PCE risk calculator.

Strengths of our study include the high-quality assessment of risk factors at baseline (enabling assessment of enrollment criteria in the 7 RCTs) as well as adjudicated events.

Conclusion

Based on currently available trial data, there is now RCT evidence of statin efficacy for nearly all individuals qualifying for statin therapy based on ACC/AHA class I recommendations. Principally, these results provide strong trial-based evidence in support of the ACC/AHA recommendations as a starting point for a patient-physician discussion on initiation of statin therapy.

Key Words

Primary prevention; cardiovascular disease; guideline; statin; lipoproteins

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Figure 1. Relationship between 10-year ASCVD risk and presence of trial evidence supporting statin use. The 10-year risk was estimated using the Pooled Cohort Equations (PCE). The ACC/AHA class I and IIa recommendations for statin therapy and the trial data supporting statin use are specified in Supplementary Figure 1. Spearman=1.0 (p<0.0001) and r^2=0.93 (p<0.0001) for the linear regression. ASCVD = atherosclerotic cardiovascular disease.

Figure 2. Overlap in statin eligibility. Area-proportional Venn diagrams demonstrating overlap in statin eligibility based on ACC/AHA class I recommendations (green) and evidence from randomized statin trials (blue). The percentages indicate the fraction of MESA participants aged 45 to 75 years who were eligible for statin therapy, or not eligible (below diagrams).

Figure 3. Clinical trials supporting statin use in people with an ACC/AHA class I recommendation for statin therapy. Diagram illustrating the fraction of individuals with an ACC/AHA class I indication for primary prevention with statins who also meet enrollment criteria in randomized controlled statin trials. Trial criteria were applied consecutively in chronological order clockwise starting 12 o'clock, that is, first we selected individuals according to WOSCOPS criteria (1995), then we selected additional individuals according to AFCAPS/TexCAPS criteria (1998), and so on. Abbreviations as in Supplementary Figure 1.

Table 1. Baseline characteristics in MESA study population aged 45-75 years

Characteristics	Multi-Ethnic Study of Atherosclerosis		
	All	**Men**	**Women**
Participants, n	4967	2329	2638
Age, median (IQR), year	59 (52-67)	59 (52-67)	59 (52-66)
Systolic blood pressure, median (IQR), mmHg	121 (110-137)	122 (111-136)	121 (108-138)
Diastolic blood pressure, median (IQR), mmHg	72 (65-79)	75 (70-82)	69 (63-76)
Plasma cholesterol, median (IQR)			
Total cholesterol, mmol/L	5.0 (4.5-5.6)	4.9 (4.4-5.5)	5.1 (4.6-5.7)
HDL cholesterol, mmol/L	1.2 (1.0-1.5)	1.1 (1.0-1.3)	1.4 (1.2-1.7)
LDL cholesterol, mmol/L	3.1 (2.6-3.6)	3.1 (2.6-3.6)	3.1 (2.6-3.6)
Current smokers, %	15	17	13
C-reactive protein, median (IQR), mg/L	2.0 (0.8-4.4)	1.4 (0.7-3.2)	2.7 (1.1-6.1)
Diabetes, %	10	12	9
Hypertension, %	41	39	42
10-year ASCVD risk, median (IQR), %	7.0 (2.9-14.3)	10.5 (5.4-18.6)	4.4 (1.6-10.1)
10-year ASCVD events, n	254	155	99
10-year CHD events, n	158	106	52

HDL = High-density lipoprotein; LDL = Low-density lipoprotein; 10-year ASCVD risk calculated with the pooled cohort equations;

ASCVD = Atherosclerotic cardiovascular disease; CHD = Coronary heart disease; IQR = interquartile range.

Table 2. Baseline characteristics and observed events stratified by how statin eligibility is defined

| Characteristics | All | Statin eligibility | | | |
		Trial* evidence	ACC/AHA* class I	Trial evidence, but not* ACC/AHA class I	ACC/AHA Class IIa
Participants, n (%)	4967 (100%)	3474 (70%)	2482 (50%)	1151 (23%)	648 (13%)
Age, median (IQR), year	59 (52-67)	63 (56-69)	66 (60-70)	57 (52-62)	58 (53-64)
Systolic blood pressure, median (IQR), mmHg	121 (110-137)	126 (113-142)	132 (119-146)	115 (106-126)	119 (110-133)
Diastolic blood pressure, median (IQR), mmHg	72 (65-79)	73 (67-80)	75 (68-82)	70 (64-77)	73 (66-79)
Plasma cholesterol, median (IQR)					
Total cholesterol, mmol/L	5.0 (4.5-5.6)	5.2 (4.6-5.8)	5.1 (4.5-5.7)	5.5 (4.8-6.0)	5.1 (4.6-5.7)
HDL cholesterol, mmol/L	1.2 (1.0-1.5)	1.2 (1.0-1.5)	1.2 (1.0-1.4)	1.3 (1.1-1.6)	1.2 (1.0-1.5)
LDL cholesterol, mmol/L	3.1 (2.6-3.6)	3.2 (2.7-3.8)	3.1 (2.6-3.7)	3.4 (2.8-3.9)	3.2 (2.7-3.7)
Current smokers, %	15	14	19	6	17
C-reactive protein, median (IQR), mg/L	2.0 (0.8-4.4)	2.3 (1.0-4.6)	2.2 (1.0-4.6)	2.2 (0.9-4.7)	2.0 (0.9-4.6)
Diabetes, %	10	13	20	0	4
Hypertension, %	41	50	60	25	33
10-year ASCVD risk, median (IQR), %	7.0 (2.9-14.3)	10.5 (5.7-17.9)	14.3 (10.1-21.2)	4.6 (2.9-5.9)	6.1 (5.5-6.8)
10-year ASCVD events, n	254	233	201	34	24
ASCVD events per 1000 person-years	5.6	7.4	9.2	3.1	3.9

*For clarification, see Venn diagrams in Figure 3.

HDL = High-density lipoprotein; LDL = Low-density lipoprotein; 10-year ASCVD risk calculated with the pooled cohort equations;

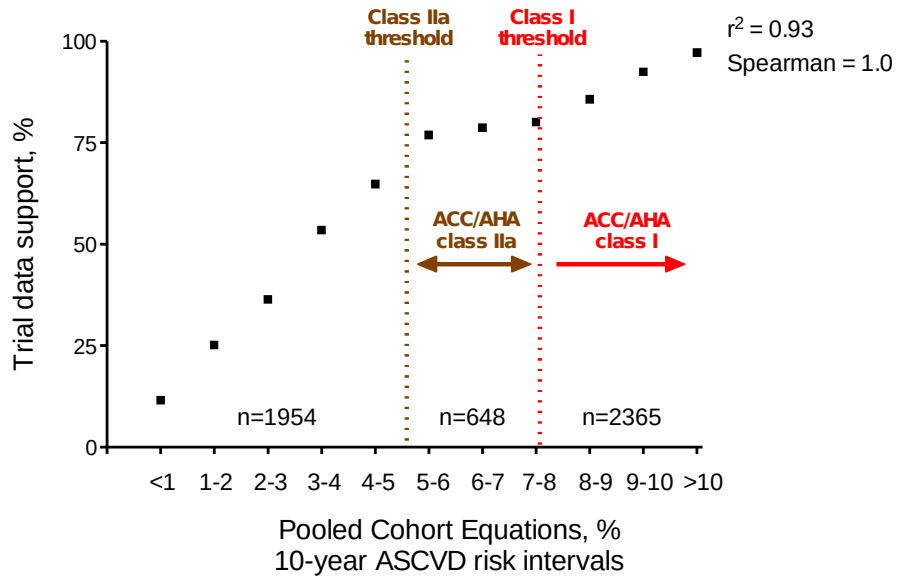ASCVD = Atherosclerotic cardiovascular disease; IQR = interquartile range.

Figure 1. Relationship between 10-year ASCVD risk and presence of trial evidence supporting statin use.
The 10-year risk was estimated using the Pooled Cohort Equations (PCE). The ACC/AHA class I and IIa recommendations for statin therapy and the trial data supporting statin use are specified in Supplementary Figure 1. Spearman=1.0 (p<0.0001) and r^2=0.93 (p<0.0001) for the linear regression. ASCVD = atherosclerotic cardiovascular disease.
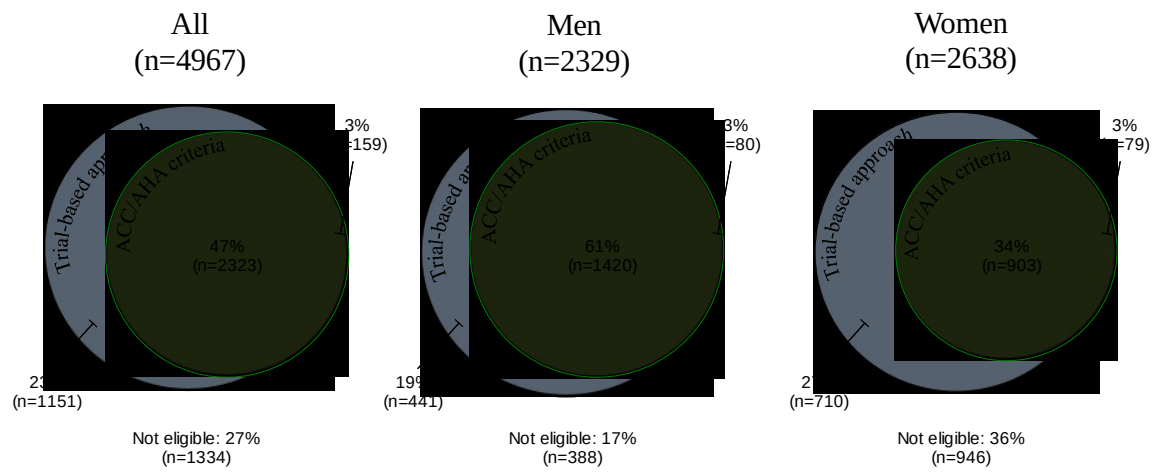
All
(n=4967)

Men
(n=2329)

Women
(n=2638)

Trial-based approach

ACC/AHA criteria

3%
(n=159)

47%
(n=2323)

23%
(n=1151)

Trial-based approach

ACC/AHA criteria

3%
(n=80)

61%
(n=1420)

19%
(n=441)

Trial-based approach

ACC/AHA criteria

3%
(n=79)

34%
(n=903)

27%
(n=710)

Not eligible: 27%
(n=1334)

Not eligible: 17%
(n=388)

Not eligible: 36%
(n=946)

Figure 2. Overlap in statin eligibility. Area-proportional Venn diagrams demonstrating overlap in statin eligibility based on ACC/AHA class I recommendations (green) and evidence from randomized statin trials (blue). The percentages indicate the fraction of MESA participants aged 45 to 75 years who were eligible for statin therapy, or not eligible (below diagrams).

Figure 3. Clinical trials supporting statin use in people with an ACC/AHA class I recommendation for statin therapy. Diagram illustrating the fraction of individuals with an ACC/AHA class I indication for primary prevention with statins who also meet enrollment criteria in randomized controlled statin trials. Trial criteria were applied consecutively in chronological order clockwise starting 12 o'clock, that is, first we selected individuals according to WOSCOPS criteria (1995), then we selected additional individuals according to AFCAPS/TexCAPS criteria (1998), and so on. Abbreviations as in Supplementary Figure 1.

Eligibility for statin therapy

ACC/AHA recommendations	RCT entry criteria

Class I
• LDL-C ≥190 mg/dL (4.9 mmol/L)
 	
or
 	
• LDL-C 70-189 mg/dL (1.8-4.9 mmol/L)
  PCE ≥7.5%
  Age 40-75 years
 	
or
 	
• LDL-C 70-189 mg/dL (1.8-4.9 mmol/L)
  Diabetes
  Age 40-75 years
 	
Class IIa
• LDL-C 70-189 mg/dL (1.8-4.9 mmol/L)
  PCE ≥5.0%
  Age 40-75 years
	WOSCOP
	• Men 45-64 years
	  TC ≥252 + LDL-C ≥155
	
	AFCAPS/TexCAPS
	• Men 45-73 and women 55-73 years
	  TC 180-264 + LDL-C 130-190
	  + HDL-C ≤45 (men)/≤47 (women)
	
	ASCOT-LLA
	• Men and women 40-79 years
	  Untreated SBP ≥160 or DBP ≥100 mmHg
	  or treated SBP ≥140 or DBP ≥90 mmHg
	  + TC ≤251 + ≥3 risk factors besides HTN
	
	CARDS
	• Men and women 40-75 years
	  Diabetes + LDL-C ≤159 + TG ≤600
	  + HTN and/or albuminuria and/or smoking
	
	MEGA
	• Men and women 40-70 years
	  TC 220-270
	
	JUPITER
	• Men ≥50 and women ≥60 years
	  LDL-C <130 + hsCRP ≥2.0 mg/L
	
	HOPE-3
	• Men ≥55 and women ≥65 (or ≥60*) years
	  + ≥1 additional risk factor**: High waist/hip ratio,
	  smoking, low HDL-C, dysglycemia, renal
	  dysfunction and/or family history

Supplementary Figure 1. Statin eligibility based on ACC/AHA recommendations and enrollment criteria used in statin trials. The figure summarizes ACC/AHA class I and IIa recommendations for primary prevention with statins (risk-based approach) and enrollment criteria used in randomized statin trials in people free of ASCVD (trial-based approach).

ASCVD=atherosclerotic cardiovascular disease; WOSCOPS=West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; CARDS= Collaborative Atorvastatin Diabetes Study; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; HOPE-3= Heart Outcomes Prevention Evaluation-3.

TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; SBP=systolic blood pressure; DBP=diastolic blood pressure; HTN=hypertension; hsCRP=high-sensitivity C-reactive protein; Cholesterol concentrations are shown in mg/dL (to convert to mmol/L, divide by 38.6).

*Women 60-65 years of age were eligible for statins with HOPE-3 trial if they had at least two additional risk factors.

**High waist/hip ratio, ≥0.90 in men and ≥0.85 in women; Low HDL-cholesterol, < 1.0 mmol/L in men and <1.3 mmol/L in women; Dysglycemia, impaired fasting glucose, impaired glucose tolerance or uncomplicated diabetes treated with diet only; Renal dysfunction, microalbuminuria, eGFR<60 ml/min/1.73m^2 or creatinine >124 µmol/L.
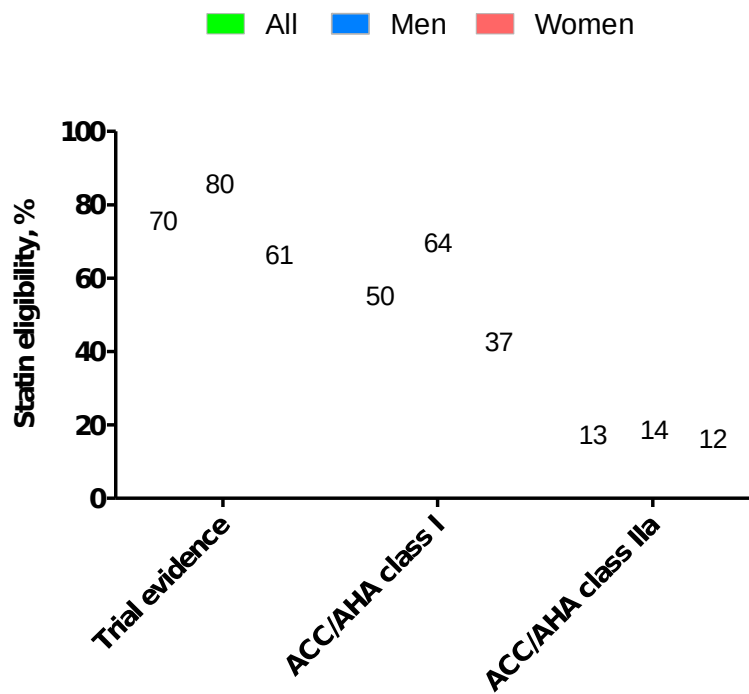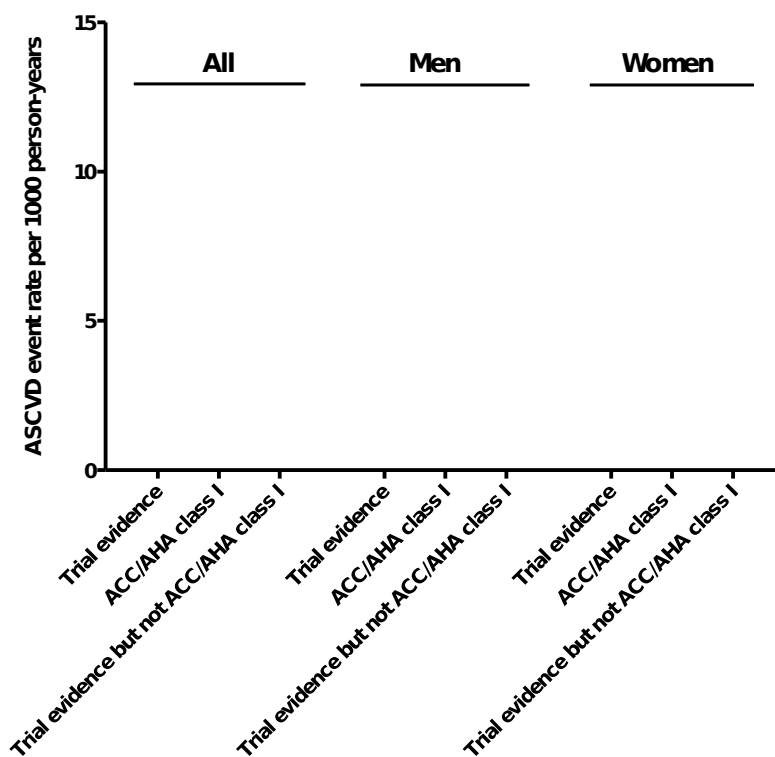
Supplementary Figure 2. Statin eligibility based on clinical trials and guidelines. Overall, 70% of 4967 MESA participants were statin eligible based on evidence from randomized statin trials (n=3474), 50% based on ACC/AHA class I recommendations (n=2482), and 12% based on the class IIA recommendation (n=648). The specific statin eligibility criteria are shown in Supplementary Figure 1.
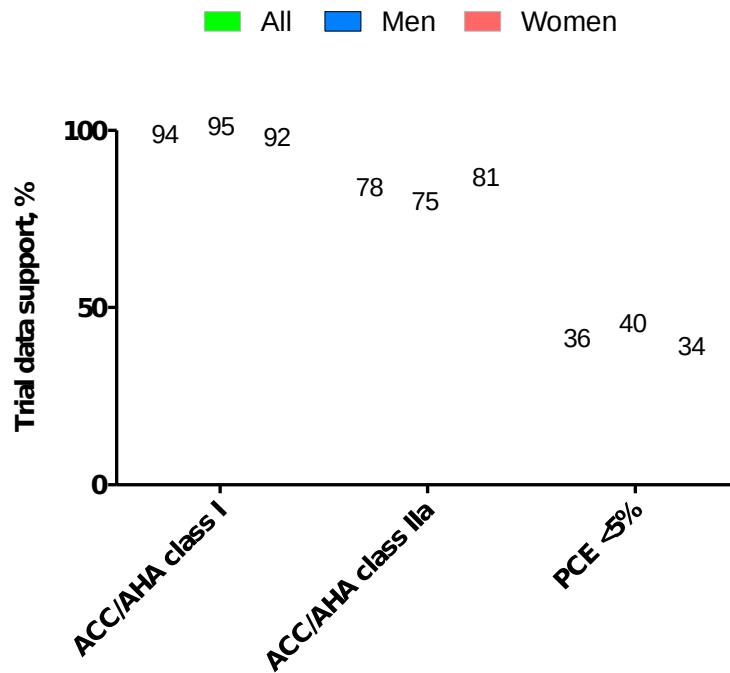
Supplementary Figure 3. Trial evidence for statin therapy stratified by ACC/AHA-defined eligibility.
Evidence from clinical trials supports use of statins in 94% of MESA participants with ACC/AHA class I indications and 78% with a class IIa indication for statin therapy. As many as 36% of those without an ACC/AHA class I or IIa indication for statin therapy (PCE risk <5%) had trial evidence for efficacy of this treatment. PCE = Pooled Cohort Equations.
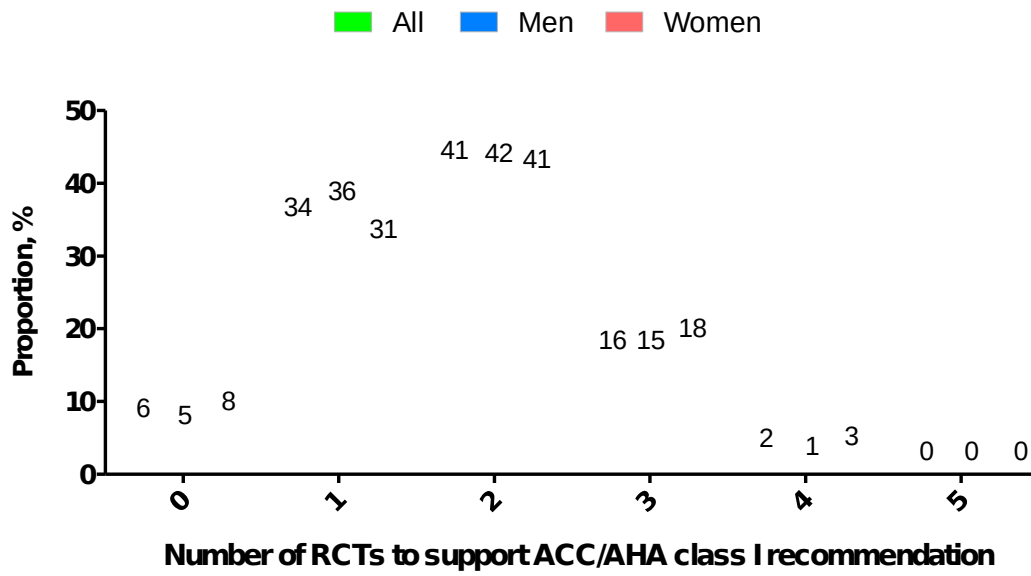
Supplementary Figure 4: Number of RCTs supporting statin efficacy in individuals eligible for statins with ACC/AHA class I recommendations.

Supplementary Figure 5: ASCVD event rates per 1000 person-years stratified by statin eligibility according to trial evidence and/or ACC/AHA class I recommendation. Error bars indicate 95% confidence intervals.