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Primary Prevention With Statins

ACC/AHA Risk-Based Approach Versus Trial-Based Approaches to Guide Statin Therapy

Martin B. Mortensen, MD, PhD,* Shoaib Afzal, MD, PhD,†‡ Børge G. Nordestgaard, MD, DMSc,†‡ Erling Falk, MD, DMSc*

ABSTRACT

BACKGROUND Guidelines recommend initiating primary prevention for atherosclerotic cardiovascular disease (ASCVD) with statins based on absolute ASCVD risk assessment. Recently, alternative trial-based and hybrid approaches were suggested for statin treatment eligibility.

OBJECTIVES This study compared these approaches in a direct head-to-head fashion in a contemporary population.

METHODS The study used the CGPS (Copenhagen General Population Study) with 37,892 subjects aged 40 to 75 years recruited in 2003 to 2008, all free of ASCVD, diabetes, and statin use at baseline.

RESULTS Among the population studied, 42% were eligible for statin therapy according to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) risk assessment and cholesterol treatment guidelines approach, versus 56% with the trial-based approach and 21% with the hybrid approach. Among these statin-eligible subjects, the ASCVD event rate per 1,000 person-years was 9.8, 6.8, and 11.2, respectively. The ACC/AHA-recommended absolute risk score was well calibrated around the 7.5% 10-year ASCVD risk treatment threshold and discriminated better than the trial-based or hybrid approaches. Compared with the ACC/AHA risk-based approach, the net reclassification index for eligibility for statin therapy among 40- to 75-year-old subjects from the CGPS was −0.21 for the trial-based approach and −0.13 for the hybrid approach.

CONCLUSIONS The clinical performance of the ACC/AHA risk-based approach for primary prevention of ASCVD with statins was superior to the trial-based and hybrid approaches. Our results indicate that the ACC/AHA guidelines will prevent more ASCVD events than the trial-based and hybrid approaches, while treating fewer people compared with the trial-based approach. (J Am Coll Cardiol 2015;66:2699–709) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Current guidelines on atherosclerotic cardiovascular disease (ASCVD) prevention endorse the principle of matching the intensity of risk-reducing therapy to the patient's absolute risk for new or recurrent ASCVD events (1–5). In primary prevention, multifactorial risk scores, such as Framingham risk scores, SCORE (Systematic Coronary Risk Evaluation), and QRISK, have been developed from observational cohort studies to predict the absolute risk for a first ASCVD event (6,7).

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) risk assessment and cholesterol treatment guidelines introduced a new risk calculator based on risk equations derived from carefully selected but decades-old cohort studies, the pooled cohort equations (PCEs) (1,2). Guided by risk/benefit considerations, the risk-based threshold for primary prevention with statins in subjects without diabetes was lowered to a 7.5% 10-year ASCVD risk estimated according to the PCEs

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From the *Atherosclerosis Research Unit, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; †Department of Clinical Biochemistry and the Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark; and the ‡Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
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ABBREVIATIONS AND ACRONYMS

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

ASCVD = atherosclerotic cardiovascular disease

NRI = net reclassification index

PCE = pooled cohort equation

RCT = randomized controlled trial

(Class I recommendation) (1). However, as recognized by the developers of the PCEs (2) and highlighted by others (8–12), the PCE-based risk calculator overestimates ASCVD risk systematically in many modern cohorts, which could lead to statin overuse.

SEE PAGE 2710

Given the large number of randomized controlled trials (RCTs) of statin therapy now available, the appropriateness of continued use of absolute risk prediction to guide statin allocation has been questioned (8,13). Indeed, the clinical performance of the traditional risk-based approach recommended in current guidelines (1–5) has never been formally tested. In addition, no RCT of statin therapy has ever enrolled patients based on predicted 10-year ASCVD risk, and the clinical utility of absolute risk assessment has never been evaluated in a primary prevention setting. Alternatively, a so-called "trial-based" approach has been proposed in which statins should be offered to patient populations for whom RCTs support statin efficacy, disregarding individual risk assessment and absolute risk (8,13). More recently, a combined risk- and trial-based strategy for the allocation of statin therapy in primary prevention was proposed, the so-called hybrid approach (14).

To the best of our knowledge, the clinical performance of these strategies for statin allocation in primary prevention of ASCVD has never been compared. We therefore performed a head-to-head comparison of the ACC/AHA risk-based approach (1,2) versus 2 recently proposed alternative approaches (the trial-based approach [8,13] and a hybrid approach [14]) in a large, contemporary European cohort, the CGPS (Copenhagen General Population Study).

METHODS

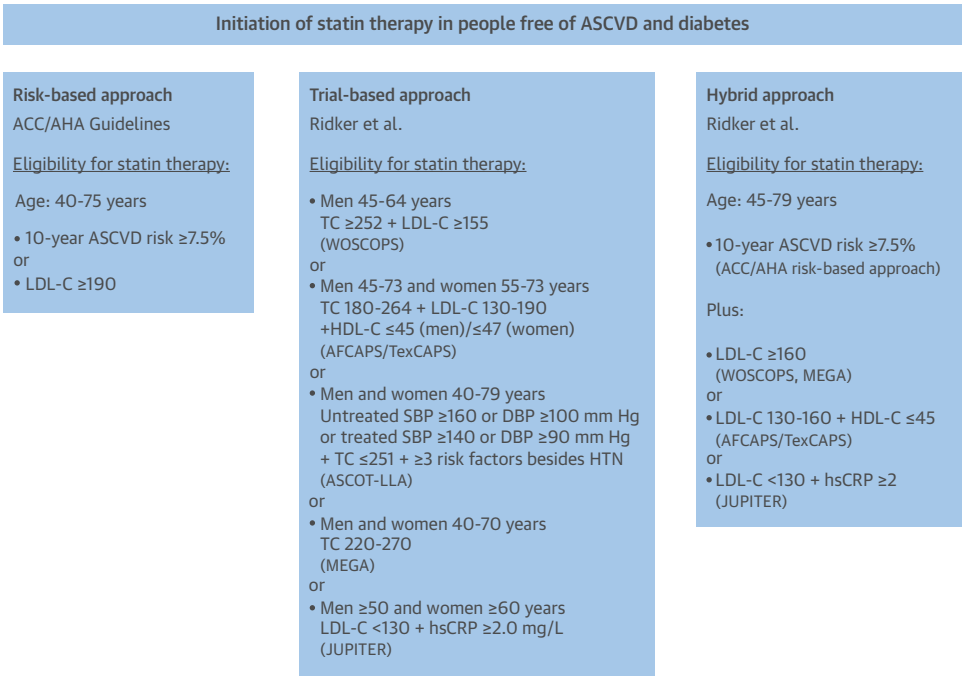
The CGPS is an ongoing prospective cohort study of the Danish general population (15–18). Enrollment began in 2003, and participants are randomly selected through the Danish Civil Registration system to reflect the Danish general population ages 20 to 100 years. All participants are white and of Danish descent. For the present study, participants enrolled between 2003 and 2008 were included. After exclusion of patients with diabetes, ASCVD, or statin use or those with missing information at baseline, 46,092 were available for analysis. As in the ACC/AHA guidelines, the age range was limited to 40 to 75 years (N = 37,892). The study was conducted in accordance with the Declaration of Helsinki and approved by Herlev and Gentofte Hospital, Copenhagen University Hospital, and a Danish ethical committee. Written informed consent was obtained from all participants. Baseline examination, ASCVD endpoints, and characteristics of individuals in the CGPS cohort are described in the Online Appendix.

The 2013 ACC/AHA risk assessment and cholesterol treatment guidelines recommend moderate- to high-intensity statin therapy for primary prevention in subjects aged 40 to 75 years without clinical ASCVD or diabetes but with low-density lipoprotein (LDL) cholesterol levels 70 to 189 mg/dl and an estimated 10-year ASCVD risk ≥7.5% (1). Adults aged >20 years with LDL cholesterol levels ≥190 mg/dl should be treated with high-intensity statin therapy, regardless of risk. These are the only 2 Class I statin recommendations in the guideline for subjects free of ASCVD and diabetes (**Figure 1**), whereas those with ASCVD and/or diabetes likewise should be prescribed statins. Identification and validation of ASCVD events for the present study (described in the Online Appendix) are identical to the approach used previously (18).

As an alternative to risk-based statin allocation, Ridker et al. (8,13) proposed a trial-based approach guided by the enrollment criteria used in the following 6 large primary prevention RCTs of statin therapy: WOSCOPS (West of Scotland Coronary Prevention Study) (19), AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) (20), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) (21), MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (22), JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) (23), and CARDS (Collaborative Atorvastatin Diabetes Study) (24). Because CARDS enrolled only patients with diabetes who, according to guidelines, should be offered statins, we disregarded CARDS in our comparison of the 2 strategies and focused on participants without diabetes. Characteristics of the 5 RCTs proposed to guide the trial-based allocation of statins in the primary prevention of ASCVD are shown in **Figure 1** and Online Table 1.

More recently, Riker et al. (14) proposed a hybrid approach in which eligibility for primary prevention with statins requires both a PCE 10-year ASCVD risk ≥7.5% (ACC/AHA Class I recommendation) and trial-based evidence of benefit. In contrast to the trial-based approach, the ASCOT trial is not used to provide trial-based evidence in the hybrid approach (14), and the trial-based inclusion criteria are not strictly met but based on a compromise and generalization beyond the age and sex limits set by some of

FIGURE 1 Eligibility Criteria for Statin Therapy



The criteria vary greatly for initiating statin therapy in subjects free of atherosclerotic cardiovascular disease (ASCVD) and diabetes as defined by the American College of Cardiology/American Heart Association (ACC/AHA) risk-based approach, the trial-based approach, and the hybrid approach. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; SBP = systolic blood pressure; TC = total cholesterol; WOSCOPS = West of Scotland Coronary Prevention Study.

the statin trials. The compromise applies to both sexes aged 45 to 79 years (Figure 1).

STATISTICAL ANALYSIS. The number and percentage of participants eligible for statin therapy were calculated based on the 3 approaches described earlier. We also created area-proportional Venn diagrams to assess agreement and disagreement in statin recommendations according to the 3 approaches. Using the aforementioned criteria for statin therapy, we then calculated the observed event rate per 1,000 person-years among statin-eligible participants.

We assessed calibration of the PCEs ASCVD risk equations. Because the CGPS has not yet completed 10 years of follow-up, 5-year predicted and observed ASCVD event rates were calculated when assessing calibration of PCEs, as previously performed (25). Calibration within the risk groups was assessed by using the predicted-to-observed event ratio. The observed number of ASCVD events at 5 years was adjusted for variable follow-up time by using the Kaplan-Meier estimate. Subsequently, the area under the receiver-operating characteristic curve was calculated for discrimination between cases (those who did develop ASCVD during follow-up) and noncases for the 3 different approaches to statin therapy.

The clinical usefulness and impact on ASCVD prevention of a guideline-defined treatment threshold depend on its ability to correctly assign treatment (statins) to subjects who develop ASCVD in the future (sensitivity). However, this method should be balanced with the risk of treating those who do not need treatment (specificity). We therefore calculated the sensitivity, specificity, and the binary net reclassification index (NRI) when comparing the ACC/AHA risk-based approach with the trial-based and hybrid approaches. The binary NRI (to treat or not to treat) is the sum of Δ-sensitivity and Δ-specificity, and the theoretical range is -2 to 2.

Additional information on statistics is provided in the Online Appendix. Analyses were performed by using Stata/SE version 13.1 (StataCorp LP, College Station, Texas).

TABLE 1 Baseline Characteristics

	All	Men	Women
Participants	37,892	16,398	21,494
Age, yrs	56 (48-64)	56 (48-64)	55 (48-64)
SBP, mm Hg	139 (125-152)	140 (130-155)	135 (122-150)
DBP, mm Hg	84 (77-90)	85 (80-93)	81 (75-90)
Plasma cholesterol, mmol/l			
Total cholesterol	5.7 (5.1-6.4)	5.7 (5.1-6.4)	5.8 (5.1-6.5)
HDL cholesterol	1.6 (1.3-2.0)	1.4 (1.1-1.7)	1.8 (1.5-2.1)
LDL cholesterol	3.3 (2.8-4.0)	3.4 (2.8-4.0)	3.3 (2.7-3.9)
% current smokers	23	24	22
10-year ASCVD risk, %*	5.3 (1.9-12.3)	9.4 (4.2-17.4)	3.2 (1.1-7.8)
ASCVD events	834	467	367
Myocardial infarction	323	210	113

Values are n or median (interquartile range) unless otherwise indicated. *Based on pooled cohort equations.

ASCVD = atherosclerotic cardiovascular disease; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.

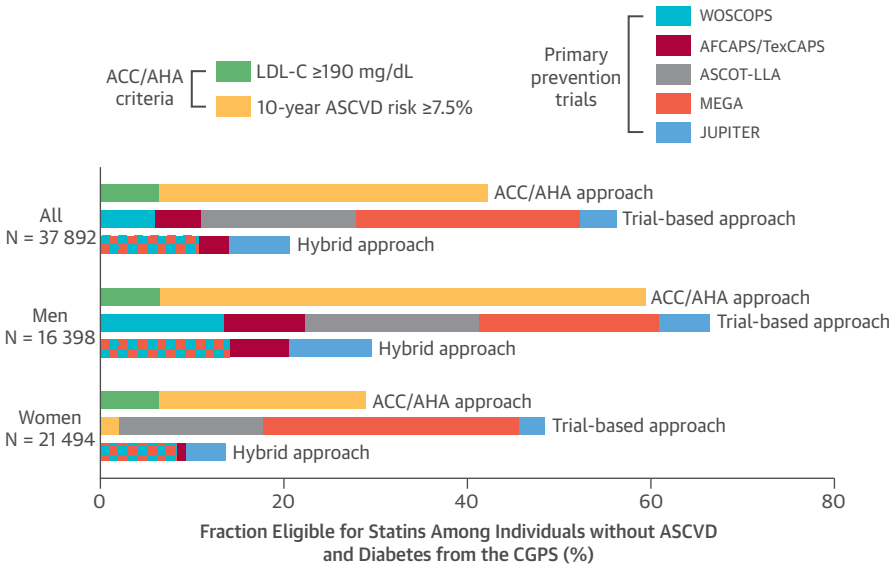
RESULTS

Baseline characteristics of the study population are shown in Table 1. All 37,892 subjects (57% women) were free of ASCVD, diabetes, and statin use at baseline. During 182,641 person-years of follow-up, 834 developed ASCVD, of which 323 were myocardial infarctions.

STATIN ELIGIBILITY. More subjects were eligible for statin therapy with the trial-based approach compared with the ACC/AHA risk-based approach (56% vs. 42%; $p < 0.0001$) (Figure 2, Central Illustration). This finding was true for women (49% vs. 29%; $p < 0.0001$) and for men (67% vs. 60%; $p < 0.0001$). By contrast, the hybrid approach substantially reduced the proportion of subjects eligible for statin therapy compared with the ACC/AHA approach (21% vs. 42%; $p < 0.0001$). With the hybrid approach, 30% of men and 14% of women qualified for statin therapy.

The 3 different approaches to statin allocation produced overlap in statin eligibility (Figure 3). By definition, those qualifying for statin therapy with the hybrid approach also did so with the ACC/AHA risk-based approach. However, 20% of participants in CGPS were eligible for statins with the ACC/AHA risk-based approach but not the hybrid approach. In contrast, substantially different groups of subjects were eligible for statin therapy according to the trial-based approach. Thus, for 41% of participants, there was a disagreement regarding statin recommendations between the trial-based approach and the

FIGURE 2 Statin Eligibility



Using the ACC/AHA, trial-based, and hybrid approaches, the fraction of statin-eligible subjects aged 40 to 75 years without clinical ASCVD, diabetes, or statin use selected from CGPS (Copenhagen General Population Study) was calculated. For the trial-based and hybrid approaches, eligible subjects were selected consecutively in chronological order from left to right; that is, subjects were first selected according to WOSCOPS criteria (1995), and additional subjects were then selected according to AFCAPS/TexCAPS criteria (1998), and so on. **Checkered bars** = combined WOSCOPS and MEGA. Abbreviations as in Figure 1.

ACC/AHA risk-based approach. Among those who qualified for statin treatment according to the trial-based approach, 68% of women and 32% of men had a 10-year ASCVD risk <7.5%, disqualifying them under the ACC/AHA approach.

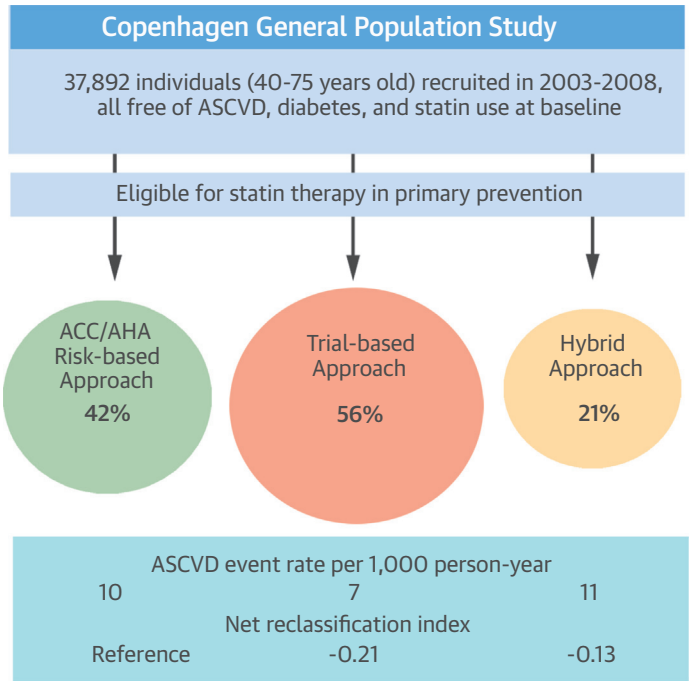
Of those eligible for statin therapy, the ASCVD event rate per 1,000 person-years was 9.8 (95% confidence interval [CI]: 9.1 to 10.6) with the ACC/AHA approach, 6.8 (95% CI: 6.3 to 7.4) with the trial-based approach, and 11.2 (95% CI: 10.1 to 12.5) with the hybrid approach (**Table 2**). Accordingly, the predicted 10-year ASCVD risk in those eligible for statin therapy was highest for the hybrid approach, lower for the ACC/AHA approach, and lowest for the trial-based approach (**Table 3**). Characteristics of participants eligible for primary prevention with statins using the 3 different approaches are presented in **Table 3**.

CALIBRATION, DISCRIMINATION, AND CLINICAL PERFORMANCE. The ACC/AHA PCE-based risk score overestimated 10-year ASCVD risk in subjects with relatively high risk (>10% 10-year ASCVD risk), but it was reasonably well calibrated around the 7.5% treatment threshold, with predicted/observed ratios ranging from 1.1 to 1.2 (**Figure 4**). The ACC/AHA Class I recommendations for statin therapy discriminated substantially better between cases (those who did develop ASCVD during follow-up) and noncases than the enrollment criteria used in statin RCTs or according to the treatment criteria defined by the hybrid approach (**Table 4**): the area under the receiver-operating characteristic curve was 0.676 for the ACC/AHA approach, 0.572 for the trial-based approach, and 0.613 for the hybrid approach ($p < 0.0001$ for all comparisons).

Compared with the risk-based approach recommended by the ACC/AHA guidelines, the 2-category NRI for eligibility for statin therapy (yes or no) among 40- to 75-year-old subjects from CGPS was -0.21 for the trial-based approach and -0.13 for the hybrid approach (**Table 4**). These values were similar for men and women separately.

Both sensitivity and specificity were higher in men with the ACC/AHA risk-based approach compared with the trial-based approach (**Table 4**). In women, only specificity was higher. The hybrid approach had a lower sensitivity but a higher specificity than the ACC/AHA risk-based approach. The shared proportions of subjects correctly identified as going to develop ASCVD (sensitivity) using statin eligibility criteria as defined by the 3 approaches are shown in Online Figure 1; their baseline characteristics are shown in Online Tables 2 to 4 and **Figure 5**. Those not eligible for statin with any approach had high lipoprotein(a) levels.

CENTRAL ILLUSTRATION Primary Prevention: Approaches to Guide Statin Therapy



Mortensen, M.B. et al. J Am Coll Cardiol. 2015; 66(24):2699–709.

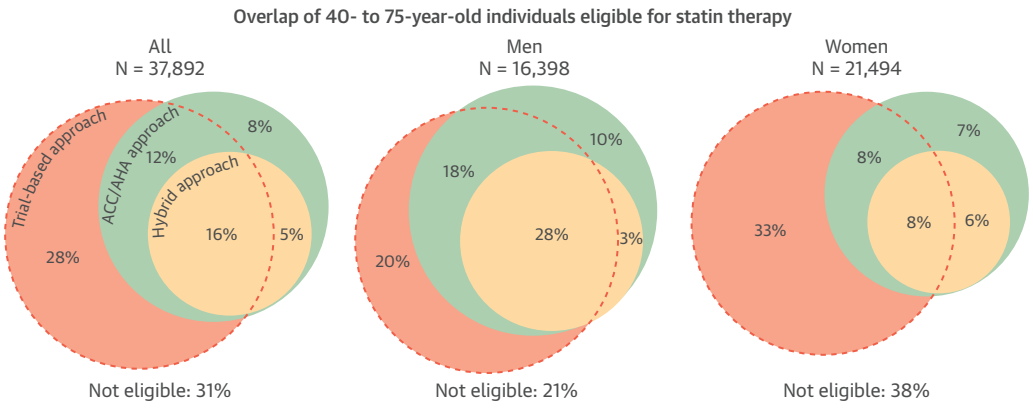
With the trial-based approach, more people were eligible for statin therapy; of those selected for treatment, there was a lower atherosclerotic cardiovascular disease (ASCVD) event rate compared with the American College of Cardiology/American Heart Association (ACC/AHA) risk-based approach or the hybrid approach. As assessed by using the net reclassification index, the clinical performance of the ACC/AHA approach was superior to the other approaches and prevented more ASCVD events than the trial-based approach by treating fewer people.

DISCUSSION

In a contemporary European cohort, the clinical performance of the ACC/AHA risk-based approach for ASCVD primary prevention with statins was superior to the trial-based and hybrid approaches (**Central Illustration**). Our results indicate that the ACC/AHA guidelines will prevent more ASCVD events than the trial-based and hybrid approaches; compared with the trial-based approach, it will prevent more ASCVD events by treating fewer people.

Based on enrollment criteria used in 5 primary prevention RCTs, more subjects were eligible for statin therapy with the trial-based approach recommended by Ridker et al. (8,13) than with the risk-based approach recommended by the ACC/AHA guidelines. Even more people might have been eligible for

FIGURE 3 Overlap in Statin Eligibility



Area-proportional Venn diagrams demonstrate overlap in statin eligibility with the ACC/AHA risk-based approach **(light green)**, the trial-based approach **(red)**, and the hybrid approach **(peach)**. The percentages indicate the fraction of all subjects in CGPS aged 40 to 75 years who were eligible for statin therapy. Abbreviations as in Figures 1 and 2.

statin therapy with the trial-based approach by applying wider enrollment criteria; that is, by covering >5 of the 18 primary prevention RCTs included in a recent Cochrane review (26). Thus, allocation of statins based on a trial-based approach endorsing the principle of "What works and in whom?" significantly increases the number of subjects recommended for statin therapy compared with the ACC/AHA guideline. This finding is not unexpected because the ACC/AHA guidelines aim to offer statins to those who will likely benefit the most, whereas enrollment criteria in RCTs are decided by using many other criteria, including regulatory approval and commercial interests. By contrast, we observed that substantially fewer subjects were eligible for statin therapy with the hybrid approach (14). This approach, among those eligible for statin therapy according to the ACC/AHA guidelines, only selects those with evidence from trials of a clinical benefit.

TABLE 2 Observed ASCVD Event Rate in Statin-Eligible Subjects

	All	Men	Women
Observed ASCVD event rate per 1,000 person-years (95% CI)			
ACC/AHA approach	9.8 (9.1–10.6)	10.3 (9.3–11.3)	9.0 (7.9–10.3)
Trial-based approach	6.8 (6.3–7.4)	8.0 (7.2–8.3)	5.6 (4.9–6.3)
Hybrid approach	11.2 (10.1–12.5)	11.7 (10.2–13.3)	10.5 (8.8–12.5)
Observed no. of ASCVD events			
ACC/AHA approach	639	411	228
Trial-based approach	586	355	231
Hybrid approach	357	231	126
5-year KM-adjusted observed events (95% CI)			
ACC/AHA approach	788 (723–855)	509 (459–565)	278 (242–319)
Trial-based approach	733 (671–801)	435 (389–486)	295 (256–340)
Hybrid approach	444 (397–495)	287 (250–326)	156 (130–188)

Statin-eligible subjects were selected as shown in Figures 1 and 2.

ACC/AHA = American College of Cardiology/American Heart Association; CI = confidence intervals; KM = Kaplan-Meier; other abbreviation as in Table 1.

RCT EVIDENCE USE. The evidence behind the 3 strategies originates exclusively from RCTs of statin therapy, but the evidence is used differently. In the risk-based approach (1,2), results from RCTs are used to show that the relative risk reduction by statin therapy is dose dependent and similar in all tested subgroups (except for patients with congestive heart failure or undergoing hemodialysis), regardless of sex and enrollment criteria. Thus, in primary prevention, global risk assessment and absolute ASCVD risk can be used to balance expected benefit of treatment against risk of harm. By contrast, global risk assessment is irrelevant in the trial-based approach in which RCTs are used to identify those subjects in whom efficacy of statin therapy has been documented (8,13).

In a risk-based strategy, the risk score used must be well calibrated to the target population to treat subjects as intended. In the CGPS, the ACC/AHA-recommended PCEs were reasonably well calibrated around the 7.5% treatment threshold. However, calibration depends on the target population and may change over the course of time, requiring regular

TABLE 3 Baseline Characteristics: Statin Therapy Eligibility Stratified According to Approach

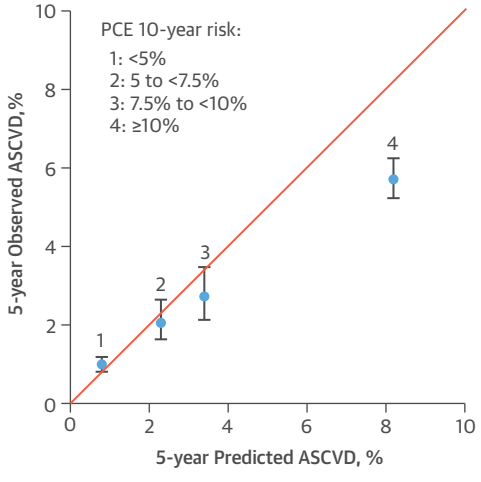
	Men			Women		
	ACC/AHA Eligible	Trial-Based Eligible	Hybrid Eligible	ACC/AHA Eligible	Trial-Based Eligible	Hybrid Eligible
Participants	9,754	10,902	4,870	6,228	10,419	2,963
Age, yrs	62 (56–68)	57 (50–64)	61 (56–67)	67 (62–71)	59 (52–65)	67 (63–71)
SBP, mm Hg	147 (135–160)	145 (132–160)	148 (135–160)	150 (136–165)	141 (128–160)	152 (140–167)
DBP, mm Hg	88 (80–95)	88 (80–96)	88 (80–96)	85 (80–92)	85 (78–92)	86 (80–94)
Plasma cholesterol, mmol/l						
Total cholesterol	5.9 (5.3–6.6)	6.0 (5.5–6.5)	6.2 (5.4–7.0)	6.4 (5.7–7.2)	6.0 (5.7–6.4)	6.7 (5.7–7.4)
HDL cholesterol	1.4 (1.1–1.7)	1.4 (1.1–1.7)	1.2 (1.0–1.5)	1.7 (1.4–2.1)	1.8 (1.5–2.2)	1.6 (1.2–2.0)
LDL cholesterol	3.6 (3.0–4.2)	3.7 (3.1–4.2)	4.1 (3.2–4.6)	3.9 (3.2–4.7)	3.5 (3.0–3.9)	4.3 (3.2–4.8)
% current smokers	34	26	37	33	22	38
10-year ASCVD risk, %	15.5 (10.8–22.8)	11.5 (6.0–19.1)	16.9 (11.9–24.4)	12.0 (8.8–17.5)	4.5 (2.0–9.1)	13.3 (9.8–18.7)

Values are n or median (interquartile range) unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

assessment and recalibration. This goal is challenging, exemplified by miscalibration of PCEs in certain modern U.S. cohorts (8,9,11) (although these cohorts may not all be representative of the entire U.S. population) and by suboptimal guidance to ethnic groups other than non-Hispanic white and African-American subjects in the 2013 ACC/AHA guidelines (1,2). However, it is reasonable to suggest that the present calibration results based on the CGPS may resemble what could be expected for large parts of the U.S. population of white European descent: Denmark, as with the United States, has experienced a major drop in ASCVD rates over the last decades that coincides with major decreases in smoking rates and increases in statin use.

The trial-based strategy does not rely on a risk score, but the generalizability and durability of results obtained in randomized statin trials enrolling selected populations up to decades ago may also be questioned with respect to applicability to the

FIGURE 4 Observed ASCVD Events Versus Predicted Risk



10-year predicted ASCVD risk	Events in 5 years: Kaplan-Meier adjusted observed, %	Predicted, %	P/O ratio
<5%	1.0 (0.8-1.2)	0.8	0.8
5% to <7.5%	2.1 (1.6-2.7)	2.3	1.1
7.5% to <10%	2.7 (2.1-3.5)	3.4	1.2
≥10%	5.7 (5.2-6.3)	8.2	1.4

The pooled cohort equations (PCE) in the ACC/AHA guidelines overestimated risk in subjects at highest risk for ASCVD but were well calibrated around the 7.5% 10-year ASCVD risk threshold for statin therapy. Because CGPS has not yet completed 10 years of follow-up, the calibration assessment is based on 5-year Kaplan-Meier adjusted observed events and predicted events previously calculated according to the 5-year PCE (25). **Orange line** = perfect calibration (i.e., predicted events = observed events). **Error bars** = 95% confidence intervals. ASCVD = atherosclerotic cardiovascular disease; P/O = predicted/observed.

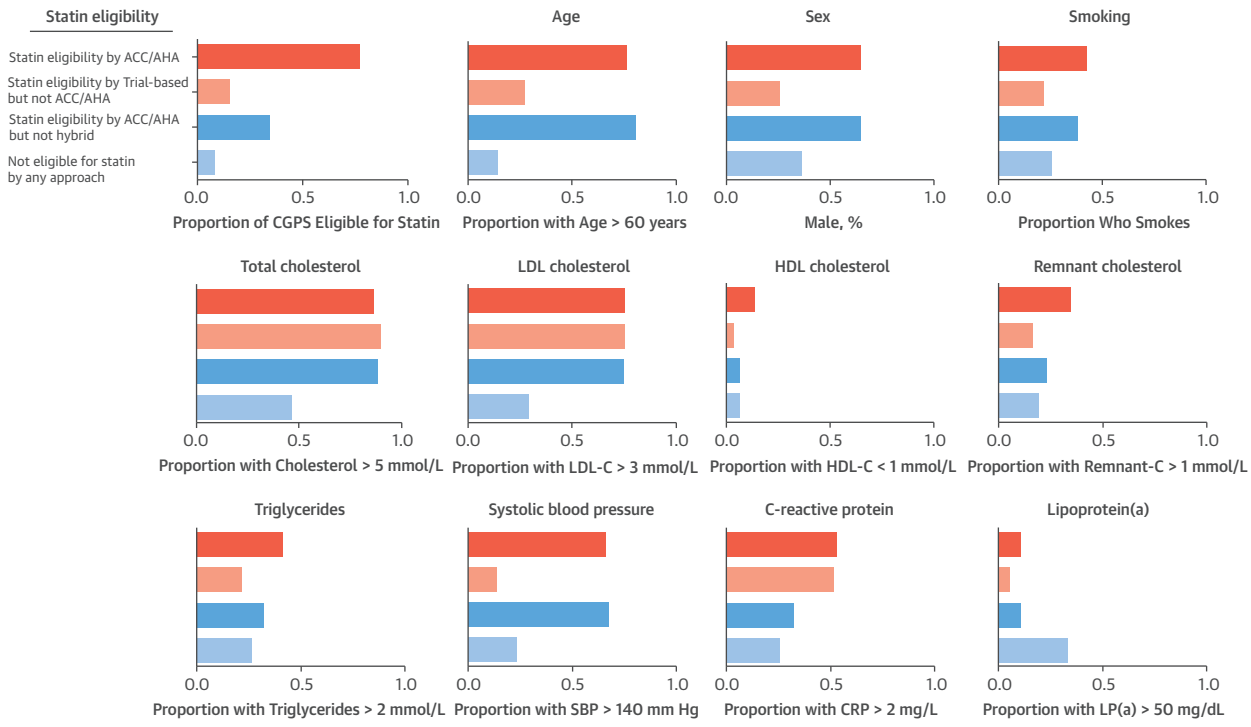
TABLE 4 Clinical Performance: ASCVD Event Identification

	NRI	ΔSensitivity (%)	ΔSpecificity (%)	Sensitivity (%)	Specificity (%)	AUC
All						
ACC/AHA	Ref	Ref	Ref	77	59	0.676 (Ref)
Trial-based	−0.21 ($p < 0.0001$)	−7 ($p = 0.002$)	−13 ($p < 0.0001$)	70	45	0.572 ($p < 0.0001$)
Hybrid	−0.13 ($p < 0.0001$)	−34 ($p < 0.0001$)	21 ($p < 0.0001$)	42	80	0.613 ($p < 0.0001$)
Men						
ACC/AHA	Ref	Ref	Ref	88	41	0.647 (Ref)
Trial-based	−0.21 ($p < 0.0001$)	−14 ($p < 0.0001$)	−8 ($p < 0.0001$)	76	33	0.549 ($p < 0.0001$)
Hybrid	−0.12 ($p = 0.001$)	−42 ($p < 0.0001$)	30 ($p < 0.0001$)	49	71	0.602 ($p < 0.0001$)
Women						
ACC/AHA	Ref	Ref	Ref	62	72	0.669 (Ref)
Trial-based	−0.19 ($p < 0.0001$)	1 ($p = 0.83$)	−20 ($p < 0.0001$)	63	52	0.574 ($p < 0.0001$)
Hybrid	−0.13 ($p < 0.0001$)	−28 ($p < 0.001$)	15 ($p < 0.0001$)	34	87	0.605 ($p < 0.0001$)

AUC = area under the curve; NRI = net reclassification index (Δsensitivity + Δspecificity); other abbreviations as in Table 2.

entire general population (27). Indeed, clinical endpoints differed (19–23) and >10 exclusion criteria (23,28,29) were common in such trials. One trial ended up enrolling only 4% of those invited to be screened (19); another randomized only 6% of those who attended pre-trial cholesterol screening (20). It is thus uncertain how well these study participants, who were enrolled in trials to assess efficacy and safety in selected populations, represent individuals in real-world clinical practice (27). Finally, many high-risk subjects were excluded from these RCTs and will, in principle, remain

FIGURE 5 Baseline Characteristics of Individuals Who Developed an ASCVD Event Stratified According to Statin Eligibility Approach



Individual baseline characteristics of participants who developed an ASCVD event were stratified according to statin eligibility with the ACC/AHA risk-based approach alone and with combined approaches. CRP = C-reactive protein; Lp(a) = lipoprotein(a); remnant-C = remnant cholesterol; other abbreviations as in Figures 1 and 2.

ineligible for statin therapy with the trial-based approach, including those with familial hypercholesterolemia (30).

TO TREAT OR NOT TO TREAT WITH STATINS. The ACC/AHA guidelines recommend the new 7.5% risk threshold based on risk/benefit considerations (1,2). A commensurate risk threshold was more recently recommended by the National Institute for Health and Care Excellence in the United Kingdom based on cost-effectiveness considerations (4,5). Importantly, such a cutoff can be modified by those who disagree with the underlying assumptions (31), and it can be changed over time as, for example, ASCVD rates and statin availability changes and as new cholesterol-lowering drugs become available. By contrast, in the trial-based approach, and partly in the hybrid approach, the "cutoff" is given a priori by the enrollment criteria in the undertaken RCTs, producing poorer discrimination to statin allocation between cases and noncases than the ACC/AHA risk-based approach. Importantly, using the trial-based approach instead of the risk-based approach was detrimental to all clinical performance parameters. Noteworthy, because age dominates among risk predictors, the risk-based approach inevitably will favor statin treatment of older people, disregarding younger people with a high lifetime ASCVD risk (32,33). However, the ACC/AHA guidelines recommend statin therapy initiation only within the context of a clinician-patient discussion to determine benefits, harms, and patient preferences, allowing for more lenient initiation of preventive measures in older subjects with favorable risk factors.

Unless specific contraindications exist, all who have similar absolute risk are treated equally in the risk-based approach, regardless of sex and ethnicity (1,2). The number-needed-to-treat is constant for a given absolute risk, and women will, in general, qualify for statin therapy approximately 10 years later in life than men because their absolute risk is lower than in men of the same age. In the trial-based approach, women at lower absolute risk may qualify equally for statin therapy as high-risk men of similar age if "positive" RCT data are available. Thus, the number-needed-to-treat will be higher in low-risk women than in high-risk men (34), and the same will apply to all low-risk subjects who were enrolled in RCTs.

In CGPS, a larger proportion of participants, especially women, would qualify for statin therapy with the trial-based approach compared with the ACC/AHA risk-based approach, meaning that statin treatment should be initiated at a much earlier age in women at low risk. This finding may be surprising, considering that data from WHS (Women's Health Study) were used to express concern about potential overuse of statins based on the new ACC/AHA guidelines, and the trial-based approach was recommended to avoid overtreatment (8). Recent data (9) indicate that only 12% of women in WHS would qualify for ACC/AHA risk-based statin therapy (PCE risk ≥7.5%). By contrast, with a mean cholesterol level of 212 mg/dl and a median C-reactive protein level ≥2.0 mg/l in WHS (35), substantially more women would qualify for statin therapy based on the enrollment criteria used in AFCAPS/TexCAPS, MEGA, and JUPITER, as illustrated in the present study based on CGPS.

STUDY LIMITATIONS. A potential limitation of the application of trial-based and hybrid approaches to statin allocation in our study is the limited ability to consider all the exclusion criteria used in the RCTs of statins. However, potential exclusion criteria were not mentioned in the alternative proposals (8,13,14), and trial exclusion criteria are often ignored in routine clinical practices (27). Another limitation is that we only studied white subjects, and our results therefore do not necessarily apply to other ethnicities. Because follow-up in CGPS was <10 years, we assessed PCE calibration by using a 5-year model (25), assuming that the correlation of 5- to 10-year ASCVD events in CGPS is similar to that observed in the PCE cohorts. Finally, although use of preventive medications was limited during follow-up (18), preferential prescription of such medications to those at highest risk might have contributed to the observed overestimation of risk in subjects with PCE >10%.

Our study possesses several strengths. Our results originate from a contemporary, population-based, large cohort with complete follow-up. In addition, predicted outcomes were appropriately identified and adjudicated, which is essential to assess calibration of a risk score. Finally, and just as importantly, the ACC/AHA PCE-based 10-year ASCVD risk score in the CGPS cohort was reasonably well calibrated around the 7.5% Class I recommendation for statin therapy in the primary prevention of ASCVD.

CONCLUSIONS

In CGPS, the ACC/AHA risk-based approach to primary prevention of ASCVD with statins was superior to the trial-based approach assessed by discrimination, sensitivity, specificity, and binary NRI, indicating that more ASCVD events will be prevented by treating fewer subjects. The recently proposed hybrid

approach substantially decreased the number of subjects eligible for statin therapy in the general population, but the balance between sensitivity and specificity still favored the ACC/AHA risk-based approach.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Børge G. Nordestgaard, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. E-mail: boerge.nordestgaard@regionh.dk.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The decision to initiate preventive statin therapy should be based on ASCVD risk assessment rather than on criteria used to include patients in RCTs.

TRANSLATIONAL OUTLOOK: Future research should be directed toward developing more accurate cardiovascular risk prediction tools.

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KEY WORDS atherosclerotic, cardiovascular disease, lipoproteins, pooled cohort equations

APPENDIX For an expanded Methods section and supplemental Tables and Figure, please see the online version of this article.