Comparison of ACC/AHA and ESC Guideline Recommendations Following Trial Evidence for Statin Use in Primary Prevention of Cardiovascular Disease Results From the Population-Based Rotterdam Study

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**IMPORTANCE** The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) guidelines both recommend lipid-lowering treatment for primary prevention based on global risk for cardiovascular disease (CVD). However, randomized clinical trials (RCTs) for statin use have included participants with specific risk-factor profiles.

**OBJECTIVE** To evaluate the overlap between the ACC/AHA and ESC guideline recommendations and available evidence from RCTs for statin use in primary prevention of CVD.

**DESIGN, SETTING, AND PARTICIPANTS** We calculated the 10-year risk for hard atherosclerotic CVD (ASCVD) following the ACC/AHA guideline, 10-year risk of CVD mortality following the ESC guideline, and we determined eligibility for each of 10 major RCTs for primary prevention of CVD. Conducted from July 2014 to August 2015, this study included 7279 individuals free of CVD, aged 45 to 75 years, examined between 1997 and 2008 for the Rotterdam Study, a prospective population-based cohort.

**MAIN OUTCOMES AND MEASURES** Proportions of individuals qualifying for lipid-lowering treatment per guidelines, proportions of individuals eligible for any of the 10 RCTs, overlap between these groups, and corresponding ASCVD incidence rates.

**RESULTS** Of the 7279 individuals included in the study, 58.2% were women (n = 4238) and had a mean (SD) age of 61.1 (6.9) years. The ACC/AHA guidelines would recommend statin initiation in 4284 participants (58.9%), while the ESC guidelines would in 2399 participants (33.0%) (overlapping by 95.8% with ACC/AHA). A total of 3857 participants (53.0%) met eligibility criteria for at least 1 RCT. Recommendations from both guidelines and trial evidence overlapped for 1546 participants (21.2%), who were at high risk for ASCVD (21.5 per 1000 person-years). A further 1703 participants (23.4%) would be recommended for statins by the guidelines in the absence of direct trial evidence, while 1176 (16.2%) would have been eligible for at least 1 trial without being recommended statin treatment by any guideline. Finally, 1719 participants (23.6%) would not be recommended a statin, nor would qualify for any of the trials. These individuals had low incidence of ASCVD (3.3 per 1000 person-years).

**CONCLUSIONS AND RELEVANCE** Based on this European population study, ACC/AHA and ESC prevention guidelines often did not align at the individual level. However, for one-fifth of the general population, guidelines on both sides of the Atlantic recommend statin initiation, with trial data supporting the efficacy. There should be no controversy about providing optimal preventive medication to these individuals.

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Guidelines on lipid-lowering treatment for primary prevention of cardiovascular disease (CVD) are provided by the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC). The recommendations for lipid-lowering treatment initiation from both guidelines are based on evidence from randomized clinical trials (RCTs) demonstrating the efficacy of statins for primary prevention of CVD. The trial evidence was translated by recommending initiation of treatment for adults with a predicted 10-year risk for CVD exceeding a given threshold. However, global-risk algorithms were never used as an enrollment criterion for RCTs. Therefore, it has been argued that risk-based allocation of statins does not fully reflect the existing evidence. The degree of overlap and discrepancy between US and European guidelines in light of available trial evidence remains unclear.

We aimed to compare recommendations from the latest ACC/AHA and ESC prevention guidelines with the evidence from 10 major primary prevention RCTs for statins.

Methods

Study Population and Setting
The study population was derived from the Rotterdam Study, a Dutch prospective population-based cohort established in 1990. For the present analysis conducted from July 2014 to August 2015, we included 7279 participants, aged 45 to 75 years. We excluded participants with prevalent atherosclerotic CVD, defined as myocardial infarction, coronary or other arterial revascularization procedure, stroke, transient ischemic attack, or repeated prescription of nitrates (a proxy for individuals with angina pectoris).

The main outcome was incident atherosclerotic cardiovascular disease (ASCVD), composed of fatal and nonfatal myocardial infarction, myocardial revascularization, coronary heart disease mortality, and nonhemorrhagic stroke.

Details on the design of the Rotterdam Study, assessment of cardiovascular risk factors, and outcomes are available in the eAppendix in the Supplement. The Rotterdam Study complies with the Declaration of Helsinki and has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study), executed by the Ministry of Health, Welfare, and Sports of the Netherlands. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Guideline Recommendations
For each participant, we calculated the 10-year risk for hard ASCVD following ACC/AHA guidelines and the 10-year risk for CVD mortality following ESC guidelines. As recommended by ACC/AHA, we used sex-specific pooled cohort equations for white individuals, and for ESC guidelines, we used sex-specific Systematic Coronary Risk Evaluation (SCORE) equations for low-risk countries. Next, we created 3 categories following the ACC/AHA and ESC recommendations based on predicted risk thresholds (eTable 1 in the Supplement): no treatment, treatment considered, and treatment recommended. Additionally, for ACC/AHA only, we created an extra category of no recommendation, as US guidelines abstain from recommendations for individuals with heart failure and end-stage renal disease.

Trial Eligibility
For the statin trial eligibility, we identified 10 primary prevention RCTs, reporting on all-cause mortality and CVD events, selected in the meta-analysis by Brugts and colleagues (eTable 2 and eTable 3 in the Supplement). Every participant was checked for eligibility criteria in each of the 10 RCTs (see the eAppendix in the Supplement for details).

The 10 randomized clinical trials included 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 LLT (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); CARDS (Collaborative Atorvastatin Diabetes Study); 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 Study Group); MRC/BHF (Heart Protection Study of Cholesterol Lowering With Simvastatin); PROSPER (The Prospective Study of Pravastatin in the Elderly at Risk); and WOSCOPS (The West of Scotland Coronary Prevention Study).

Statistical Analysis
We determined the proportions of the study population who would qualify for statin treatment under the ACC/AHA and ESC guidelines, and these were compared with trial eligibility. Further, we compared cardiovascular risk factor profiles of groups with discrepant guideline recommendations.
Observed ASCVD incidence rates (IRs) are expressed per 1000 person-years over up to 10 years of follow-up.

Sensitivity analyses are provided in the Supplement, including (1) results based on 18 RCTs (including 8 trials that did not assess clinical CVD event rates) selected in the 2013 Cochrane Collaboration review on statins for primary prevention of CVD (eFigure 2), (2) results based on the study population free of diabetes (eFigure 3), and (3) results based on the study population not using statins at baseline (eFigure 4).

Results

The mean (SD) age of the participants was 61.1 (6.9) years, and 58.2% were women (n = 4238). Among all participants, 24.7% were current smokers (n = 1798) and 8.4% had type 2 diabetes (n = 609) (Table 1). A total of 674 participants (9.3%) used statins at baseline (eFigure 1 in the Supplement).

For the treatment-recommended category, 4284 (58.9%) and 2399 (33.0%) of the entire study population qualified for lipid-lowering therapy based on the ACC/AHA 2013 and ESC 2012 guidelines, respectively. Based on the eligibility criteria, 3857 of all participants (53.0%) would have been eligible for at least 1 of 10 RCTs (Table 2). Among all 3857 trial eligible participants, 1 in 3 did not immediately qualify for lipid-lowering treatment under the US guidelines, and more than half did not qualify under the European guidelines. A total of 95.8% of 2399 participants qualifying for lipid-lowering treatment by the ESC also qualified under the ACC/AHA recommendations (Figure).

<p>| Table 1. Cardiovascular Risk Factor Profiles by ACC/AHA 2013 Guideline Recommendations, ESC 2012 Guideline Recommendations, and Statin Trial Eligibility* |</p>
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All Adults (N = 7279)</th>
<th>Discrepancies, No. (%)</th>
<th>ACC/AHA and ESC Guidelines</th>
<th>ACC/AHA and Trial Eligibility</th>
<th>ESC and Trial Eligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA Recommended, But Not by ESC (n = 1985)</td>
<td>1101 (55.5)</td>
<td>21 (21.0)b</td>
<td>818 (49.7)</td>
<td>261 (21.4)g</td>
<td>393 (48.6)</td>
</tr>
<tr>
<td>ESC Recommended, Not by ACC/AHA (n = 100)</td>
<td>63.0 (7.0)</td>
<td>63.9 (6.2)</td>
<td>58.5 (5.0)n</td>
<td>66.3 (5.9)</td>
<td>59.8 (5.5)n</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
<td>ACC/AHA Recommended, But Not by ESC (n = 1985)</td>
<td>ESC Recommended, Not by ACC/AHA (n = 100)</td>
<td>ACC/AHA and Trial Eligible (n = 1647)</td>
<td>ESC and Trial Eligible (n = 809)</td>
<td>ACC/AHA and Trial Eligibility (n = 1220)</td>
</tr>
<tr>
<td>ACC/AHA Recommended, Not Trial Eligible (n = 2399)</td>
<td>142 (22)</td>
<td>129 (16)b</td>
<td>149 (24)</td>
<td>132 (16)b</td>
<td></td>
</tr>
<tr>
<td>ESC Recommended, Not Trial Eligible (n = 809)</td>
<td>81 (12)</td>
<td>78 (10)b</td>
<td>82 (13)</td>
<td>79 (10)b</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA Recommended, Not Trial Eligible (n = 1220)</td>
<td>393 (48.6)</td>
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<td>59.8 (5.5)n</td>
<td></td>
</tr>
</tbody>
</table>

**Significant P values for comparison between discrepant groups (ACC/AHA and ESC guidelines, ACC/AHA and trial eligibility, and ESC and trial eligibility) are indicated in the table.**

* Significant P values for comparison between discrepant groups (ACC/AHA and ESC guidelines, ACC/AHA and trial eligibility, and ESC and trial eligibility) are indicated in the table.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.

St conversion factors: to convert cholesterol to millimoles per liter, multiply by 0.0259; and CRP to nanomoles per liter, multiply by 9.524.

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Although cardiovascular risk-factor profiles of treatment-recommended participants were similar for both guidelines, adults eligible by the ESC but not ACC/AHA guideline were more likely to be older, women, and have a considerably lower estimated glomerular filtration rate. Trial-eligible individuals, not qualifying for statin treatment under the US or European guidelines, were predominantly younger women, with more favorable lipid profiles when compared with the trial-ineligible individuals qualifying for statin treatment only under the US or European guidelines (Table 1; eTable 4 in the Supplement).

The Venn diagram demonstrates the overlap of treatment recommendations for ACC/AHA and ESC prevention guidelines, as well as the trial eligibility for any of 10 randomized clinical trials studying the efficacy of statins in primary prevention of cardiovascular disease in the general population. For each subgroup, atherosclerotic cardiovascular disease incidence rates (IRs) per 1000 person-years over up to 10 years of follow-up are presented in the figure.

Although cardiovascular risk-factor profiles of treatment-recommended participants were similar for both guidelines, adults eligible by the ESC but not ACC/AHA guideline were more likely to be older, women, and have a considerably lower estimated glomerular filtration rate. Trial-eligible individuals, not qualifying for statin treatment under the US or European guidelines, were predominantly younger women, with more favorable lipid profiles when compared with the trial-ineligible individuals qualifying for statin treatment only under the US or European guidelines (Table 1; eTable 4 in the Supplement).

The ASCVD IRs for each subgroup are presented in the Figure. A high rate (21.5 per 1000 person-years) was observed among those recommended treatment by both guidelines supported by trial data, while a low rate (3.7 per 1000

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### Table 2. Treatment Recommendations Based on the ACC/AHA 2013 or ESC 2012 Guidelines and Trial Eligibility

<table>
<thead>
<tr>
<th>Guideline Recommendations</th>
<th>Total Population (N = 7279)</th>
<th>Men (n = 3041)</th>
<th>Women (n = 4238)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eligible</td>
<td>Not Eligible</td>
<td>Total</td>
</tr>
<tr>
<td>ACC/AHA 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>704 (9.7)</td>
<td>1274 (17.5)</td>
<td>1978 (27.2)</td>
</tr>
<tr>
<td>Treatment considered</td>
<td>502 (6.9)</td>
<td>471 (6.5)</td>
<td>973 (13.4)</td>
</tr>
<tr>
<td>Treatment recommended</td>
<td>2637 (36.2)</td>
<td>1647 (22.6)</td>
<td>4284 (58.9)</td>
</tr>
<tr>
<td>No recommendation</td>
<td>14 (0.2)</td>
<td>30 (0.4)</td>
<td>44 (0.6)</td>
</tr>
<tr>
<td>ESC 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>415 (5.7)</td>
<td>1183 (16.3)</td>
<td>1598 (22.0)</td>
</tr>
<tr>
<td>Treatment considered</td>
<td>1852 (25.4)</td>
<td>1430 (19.6)</td>
<td>3282 (45.1)</td>
</tr>
<tr>
<td>Treatment recommended</td>
<td>1590 (21.8)</td>
<td>809 (11.1)</td>
<td>2399 (33.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ESC, European Society of Cardiology; LDL, low-density lipoprotein.

SI conversion factors: to convert cholesterol to millimoles per liter, multiply by 0.0259; and CRP to nanomoles per liter, multiply by 9.524.

* In summary, ACC/AHA treatment recommendations combined a 10-year cardiovascular disease mortality risk with different LDL cholesterol levels, LDL cholesterol levels greater than 230 mg/dL, total cholesterol levels greater than 310 mg/dL, diabetes, and estimated glomerular filtration rate less than 60 mL/min/1.73 m². Detailed definitions of the treatment categories for both ACC/AHA 2013 and ESC 2012 guidelines are provided in eTable 1 in the Supplement.
Discussion

In this European population-based study of adults aged 45 to 75 years free of CVD, we observed that ESC 2012 guideline recommendations were highly (95.8%) overlapping with the ACC/AHA 2013 guidelines, yet the US guidelines recommended substantially more persons for lipid-lowering treatment (58.9%) as compared with the ESC (33.0%), which is mostly explained by the lowered treatment threshold in the US guidelines. These estimates are very much in line with results from several observational studies in this field.17-21 Overall, 21.2% of adults were recommended to initiate a statin based on both guidelines supported by trial data. However, in individuals without direct RCT evidence, we noted discrepancies between the guidelines: a small group (0.8%) at very high risk (IR, 27.0 per 1000 person-years) was eligible by the ECS but not ACC/AHA guidelines (Figure). These individuals were significantly more likely to have chronic kidney disease and heart failure, which can be explained by ACC/AHA abstaining from the recommendations for individuals with heart failure and end-stage renal disease.2 On the other hand, 12.3% of the population at high risk (IR, 9.2 per 1000 person-years) was eligible by the ACC/AHA but not ESC guidelines (Figure). These discrepancies between the guidelines contribute to the ongoing discussion regarding selection of high-risk individuals and the translation of the available trial evidence into clinical practice guidelines for lipid-lowering treatment for primary prevention of CVD. For future iterations of prevention guidelines, participating experts from the ACC, AHA, ESC, and other global organizations might consider working in unison to create a homogeneous set of recommendations as has been done before in other cardiology subspecialties.22,23

Although 16.2% of the studied population (n = 1176) would not be recommended for statin treatment by either ACC/AHA or ESC guidelines despite the availability of conclusive trial data in these individuals, we observed that such individuals had a low short-term risk for CVD (Figure). However, given that these individuals have high-risk features that qualified them for these trials, they may likely have an increased lifetime risk for CVD.24,25 Several US-based research groups have demonstrated that lowering ASCVD risk thresholds for initiating statin treatment even further would still be cost-effective, while preventing additional CVD events.26,27 Early identification and treatment of persons with elevated CVD risk factors could be considered even more cost-effective in the long run as compared with waiting to initiate treatment until absolute short-term risk is elevated.

This study had several limitations. First, 95% of the Rotterdam Study population is of European ancestry; therefore, our findings should be cautiously extrapolated to other ethnicities. Second, 9.3% of the studied population used statins; therefore, calculated ASCVD incidence rates might be disproportionately underestimated, especially in the higher-risk subgroups where statin use was most frequent (eFigure 1 in the Supplement). Finally, all population-based cohorts involving active participation are subject to the healthy volunteer effect,28 thus leading to underestimation of the proportions of individuals qualifying for lipid-lowering therapy.

Conclusions

We found that discrepancies existed between current CVD prevention guidelines on both sides of the Atlantic and available trial evidence. Yet, for 1 of 5 adults aged 45 to 75 years, the ACC/AHA 2013 guidelines, ESC 2012 guidelines, and presence of RCT evidence support statin treatment for primary prevention of CVD. Because improved patient outcomes have been demonstrated for these individuals, it should be an imperative to ensure that they are identified and are offered optimal evidence-based treatment to reduce the burden of CVD.
Comparison of ACC/AHA vs ESC Guidelines for Primary Prevention Statin Therapy

Brief Report  Research

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REFERENCES


