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REVIEW TOPIC OF THE WEEK

A Proposal to Incorporate Trial Data Into a Hybrid ACC/AHA Algorithm for the Allocation of Statin Therapy in Primary Prevention

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ABSTRACT

Current algorithms for statin allocation in primary prevention use epidemiologic estimates of absolute risk. However, a global risk prediction score has not been used as an enrollment criterion in any randomized trial of statin therapy. Moreover, completed statin trials show greater relative risk reductions for those patients at lower levels of absolute risk. Thus, risk calculators that rely solely on epidemiologic modeling do not ensure that those who will benefit are selected for treatment. We propose a hybrid approach to statin prescription for apparently healthy men and women that strongly endorses pharmacologic treatment for those who have estimated 10-year risks ≥7.5% *and* for whom trial-based evidence supports statin efficacy in primary prevention. Although individuals could still be treated on the basis of absolute risk alone, the hybrid approach is evidence-based, is easily applied in clinical practice, and may increase the transparency of physician–patient interactions concerning prescription of statin therapy in primary prevention. (J Am Coll Cardiol 2015;65:942–8) © 2015 by the American College of Cardiology Foundation.

Despite extensive randomized trial data demonstrating the efficacy of statin therapy in primary prevention, there is controversy about how best to allocate these agents among apparently healthy men and women to prevent first heart attacks and strokes. Current U.S. guidelines for statin prescription are on the basis of epidemiologic estimates of 10-year risk and make the implicit assumption that the greatest absolute risk reductions will occur among those at the greatest absolute risk. For example, utilizing an epidemiologic risk-based algorithm for the prediction of atherosclerotic events (1), the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend initiating a discussion regarding statin therapy among primary prevention patients with a predicted 10-year risk of ≥7.5% and an optional consideration of statin therapy among those with 10-year risks between 5% and 7.5% (2).

There are substantial limitations to this traditional absolute risk-based approach to statin allocation. First, as cardiovascular event rates have fallen over the past 30 years, risk calculators on the basis of old data may overestimate contemporary risk (3). This latter problem can be addressed by recalibrating the ACC/AHA prediction model, as we have previously advocated (4).

Recalibration alone, however, does not address the remaining limitations of an absolute risk-based approach to statin allocation on the basis of

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epidemiologic modeling. This is because no trial of statin therapy has ever used a global risk prediction score as an enrollment criterion. Worse, completed statin trials contradict the premise that high absolute risk always predicts greatest efficacy; this issue is already recognized in the ACC/AHA guidelines, where it is correctly noted that 4 placebo-controlled trials enrolled individuals with high absolute risk in the settings of heart failure or renal failure, but found little evidence of event reduction with statin therapy despite large reductions in low-density lipoprotein (LDL) cholesterol (5–8). Conversely, meta-analyses of completed statin trials show statistically significant greater relative risk reductions for those at lower levels of absolute risk than for those at higher risk levels (9) (**Figure 1**). In addition, other than age, the major determinants of high global risk are smoking and hypertension, where the initial interventions should be smoking cessation and blood pressure reduction. Last, risk calculators that rely on epidemiologic modeling in general populations, rather than in those actually enrolled in clinical trials, do not ensure that those selected for treatment are, in fact, those who benefit (3,10).

In an attempt to address these limitations, alternative approaches to statin allocation have been proposed. One alternative eliminates the measurement of risk factors, instead relying on thresholds of age alone for statin prescription, a concept underlying the "polypill" approach to prevention (11). A second alternative seeks to address the core clinical questions of "what works?" and "in whom?" on the basis of completed randomized trials (12,13). As opposed to the traditional risk-based approach using epidemiologic modeling, this trial-based approach seeks to match statin prescription in primary prevention as closely as possible to those individuals actually enrolled into the extensive database of available clinical trials.

To date, estimates of the number of Americans who might be treated using these alternative methods for statin allocation have not been readily available. We addressed this issue using data from the 2007 to 2010 National Health and Nutrition Examination Survey (14) to derive estimates of the number of middle-aged Americans who would be recommended for statin therapy using the ACC/AHA approach of drug prescription on the basis of calculated 10-year risks for hard atherosclerotic events. We then derived similar estimates for the alternative approaches. For the trial-based approach, we developed a statin allocation algorithm on the basis of results of the 5 randomized, double-blind, placebo-controlled trials of statin therapy that were reported between 1995 and 2008, and which together comprise most of the formal evidence base documenting the effectiveness of statin therapy in primary prevention (15–19) (**Central Illustration**, top). Details and methods underlying these analyses are provided in Online Table 1.

Our analyses suggest that 47.9 million of an estimated 97.8 million American men and nonpregnant women age 40 to 79 years and free of cardiovascular disease would be recommended for consideration of statin therapy on the basis of the "polypill" approach of having diabetes or simply being ≥55 years of age. A smaller number, 42.0 million, would be recommended for consideration of statin therapy on the basis of having diabetes or meeting the core entry

ABBREVIATIONS AND ACRONYMS

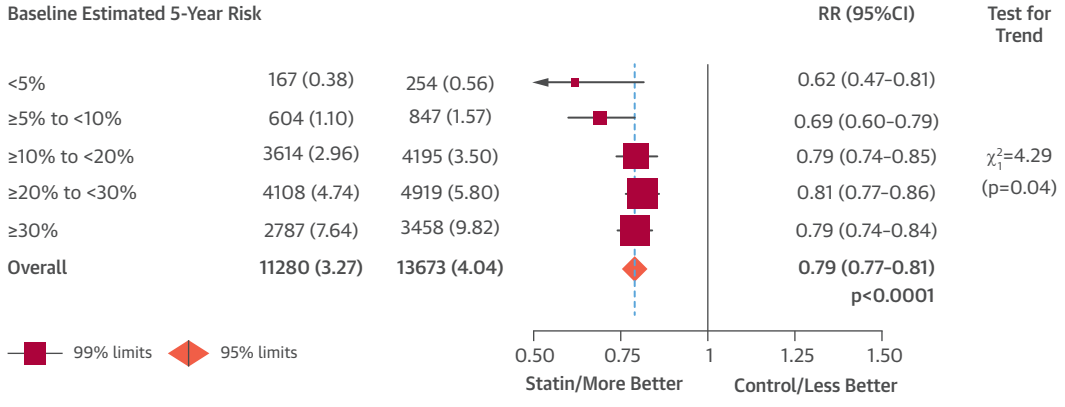
ACC = American College of Cardiology

AHA = American Heart Association

hsCRP = high-sensitivity C-reactive protein

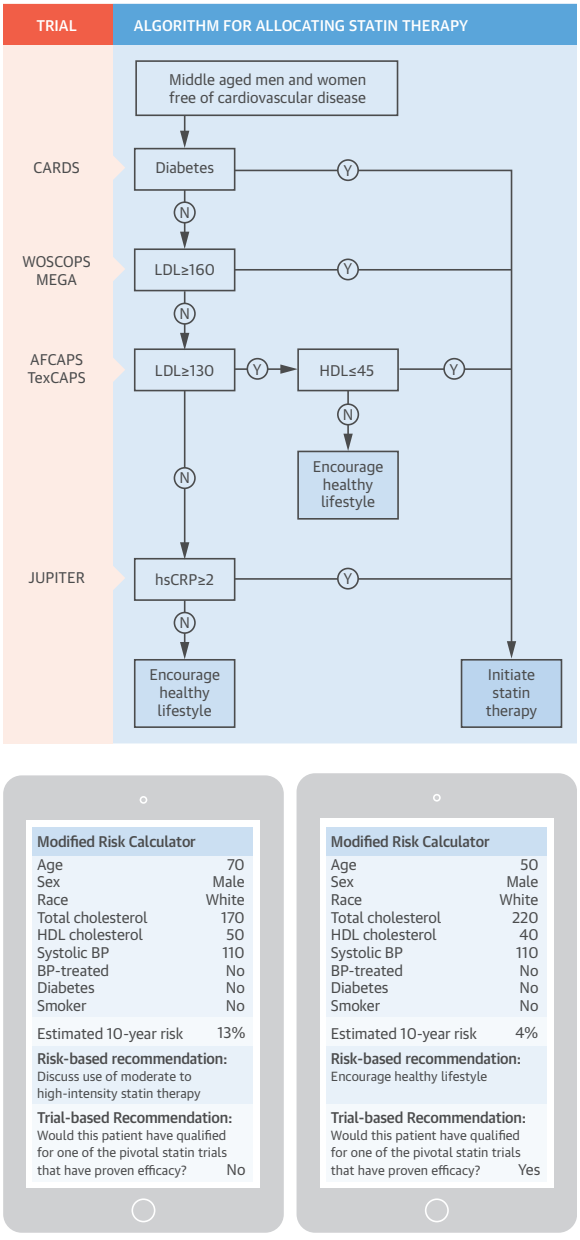
LDL = low-density lipoprotein cholesterol

FIGURE 1 Relative Risk Reductions per 1 mmol/l Reduction in LDL Cholesterol With Statin Therapy Compared With Control Patients



Reductions are significantly greater with statin therapy for patients at low levels of absolute vascular risk than for those at higher levels (p = 0.04 for trend test for heterogeneity). Data from Ridker (24). CI = confidence interval; LDL = low-density lipoprotein; RR = relative risk.

CENTRAL ILLUSTRATION **Incorporating Trial Data Into a Hybrid Statin Algorithm for Primary Prevention**



Ridker, P.M. et al. J Am Coll Cardiol. 2015; 65(9):942–8.

(Top) A trial-based algorithm for allocating statin therapy in primary prevention. Using a trial-based approach, statins would be allocated to those meeting the fundamental entry criteria of the CARDS (Collaborative Atorvastatin Diabetes Study), WOSCOPS (West of Scotland Coronary Prevention Study), MEGA (Management of Elevated cholesterol in the primary prevention Group of Adult Japanese study), AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), and JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Thus, a trial-based approach guarantees that those prescribed statin therapy meet the inclusion criterion of at least 1 of the pivotal trials demonstrating that statin therapy in primary prevention reduces rates of myocardial infarction, stroke, and cardiovascular revascularization procedures (see Online Appendix for details). **(Bottom)** A modified American College of Cardiology (ACC)/American Heart Association (AHA) risk calculator. The proposed modified ACC/AHA risk calculator provides an estimate of 10-year risk and an indication as to whether or not trial data exist for the participant of interest (see text for details). BP = blood pressure; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein (hsCRP); LDL = low-density lipoprotein.

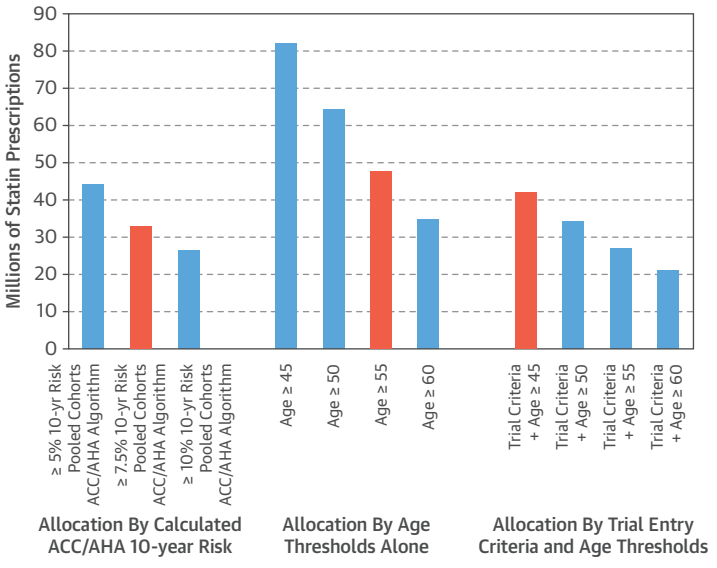
criteria for at least 1 of the randomized trials that have demonstrated statin efficacy. In contrast, using current ACC/AHA algorithms, 32.6 million Americans would be recommended for consideration of statin therapy on the basis of having diabetes or a calculated 10-year risk estimate of ≥7.5%. The number of individuals potentially eligible for statin therapy ranged widely when we varied age thresholds for treatment or varied levels of 10-year risk (**Figure 2**).

Unfortunately, our analyses also demonstrate that reliance on any 1 of these approaches results either in recommendations to consider treatment for individuals where trial data are lacking, recommendations to consider treatment for individuals at low absolute risk, or both. As shown in the Venn diagram (**Figure 3**), the traditional 10-year risk approach and the formal evidence-based approach using trial data identified substantially different groups of individuals for whom treatment would be considered.

For example, 11.1 million (34%) of those who would be recommended to consider treatment using the ACC/AHA 10-year risk cutpoint of ≥7.5% would not have qualified for any of the major statin trials that demonstrate efficacy. This group includes many individuals with high absolute risk driven by hypertension and smoking, conditions where first-line interventions should be smoking cessation and blood pressure reduction; calculated risk for such individuals would be substantially lower if these interventions were successful. Furthermore, 28.5% of this group (3.2 million) had no major modifiable risk factors, and yet had 10-year risk estimates calling for statin therapy simply due to older age. Conversely, 20.6 million (49%) of those who would be recommended to consider treatment using the trial-based approach had estimated 10-year risks below 7.5%. This group tended to include younger individuals, women, and those with isolated elevations of high-sensitivity C-reactive protein (hsCRP) or LDL (Online Table 2). The proportion treated according to the 3 strategies was also very different by age (**Figure 4**). The risk-based approach would initiate a discussion of statin therapy for all individuals older than 70 years of age (66 years of age for men), whereas the age-based approach would treat everyone above 55 years of age. The trial-based approach is less age-dependent because it is on the basis of individual risk factors.

We believe a hybrid approach that minimizes these limitations merits serious consideration by the ACC and AHA as these organizations develop new treatment guidelines. A hybrid approach represents a statin allocation strategy that conservatively combines aspects of the risk- and trial-based approaches

FIGURE 2 Individuals Recommended for Statin Therapy

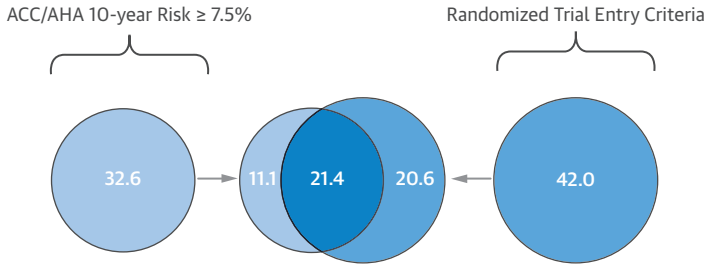


Each **bar** represents the number of Americans 40 to 79 years of age and currently free of cardiovascular disease who would be recommended for treatment with statin therapy in sensitivity analyses using the American College of Cardiology (ACC)/American Heart Association (AHA) 10-year absolute risk approach **(left)**, the age-alone approach as suggested for the "polypill" **(middle)**, and the trial entry criteria approach **(right)**. Diabetic subjects are included in all allocation schemes, and a range of age cutpoints from ≥45 through ≥60 years is shown. **Salmon bars** indicate the base case for each allocation scheme (see Online Appendix for details).

to define a population who clearly *should* be treated. Specifically, the hybrid approach would strongly endorse statin therapy in primary prevention for those in the intersection of the Venn diagram in **Figure 3**, that is, the 21.4 million middle-aged Americans who have estimated 10-year risks ≥7.5% *and* for whom there is clear trial-based evidence of statin efficacy in primary prevention.

There are potential advantages to this proposal. Most importantly, the hybrid approach provides transparency and avoids the pitfalls inherent in the current absolute-risk system used to allocate statin therapy that result in recommendations both to consider treating some individuals where trial data are lacking and to withhold treatment from others where trials have demonstrated efficacy. For example, the current 10-year risk approach results in recommendations to consider treatment for a substantive number of individuals (3.2 million) with no modifiable risk factors, yet who are calculated to be at high absolute risk due to older age alone. In part to avoid this problem, the ACC/AHA guidelines suggest the use of secondary criteria such as family history,

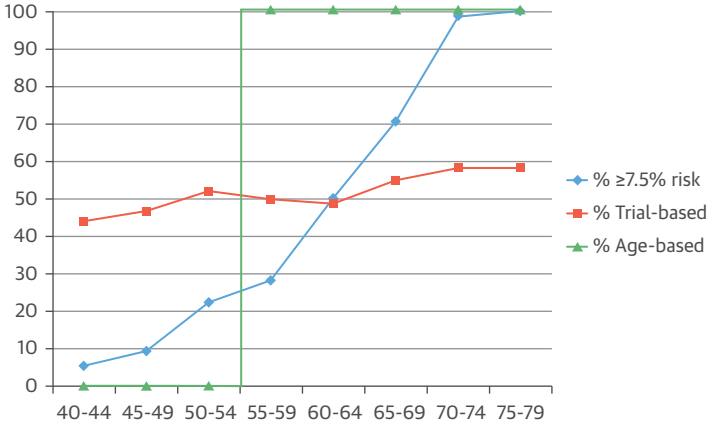
FIGURE 3 Venn Diagrams Illustrating the Hybrid Approach to Statin Allocation: Base Case



Venn diagram comparing the 10-year absolute risk approach with the trial entry criteria approach for allocation of statin therapy in primary prevention. As shown, 32.6 million Americans would be recommended for statin treatment using the ACC/AHA 10-year risk criteria of >7.5% **(light blue circle, left),** whereas 42.0 million Americans would be recommended for statin therapy using the base case randomized trial entry criteria **(medium blue circle, right)**. The intersection of these 2 approaches indicates that 21.4 million individuals have both a calculated 10-year risk >7.5% and would have qualified for at least 1 of the major statin trials demonstrating efficacy **(dark blue, middle)**. Abbreviations as in Figure 2.

coronary artery calcium, hsCRP, or the ankle-brachial index in these settings (1,2). However, in contrast to the JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial data for hsCRP (19), there are no prospective, randomized trial data to support the use of coronary artery calcification, family history, or ankle-brachial index as a method to allocate statin therapy.

FIGURE 4 Effect of Age on Treatment Decisions



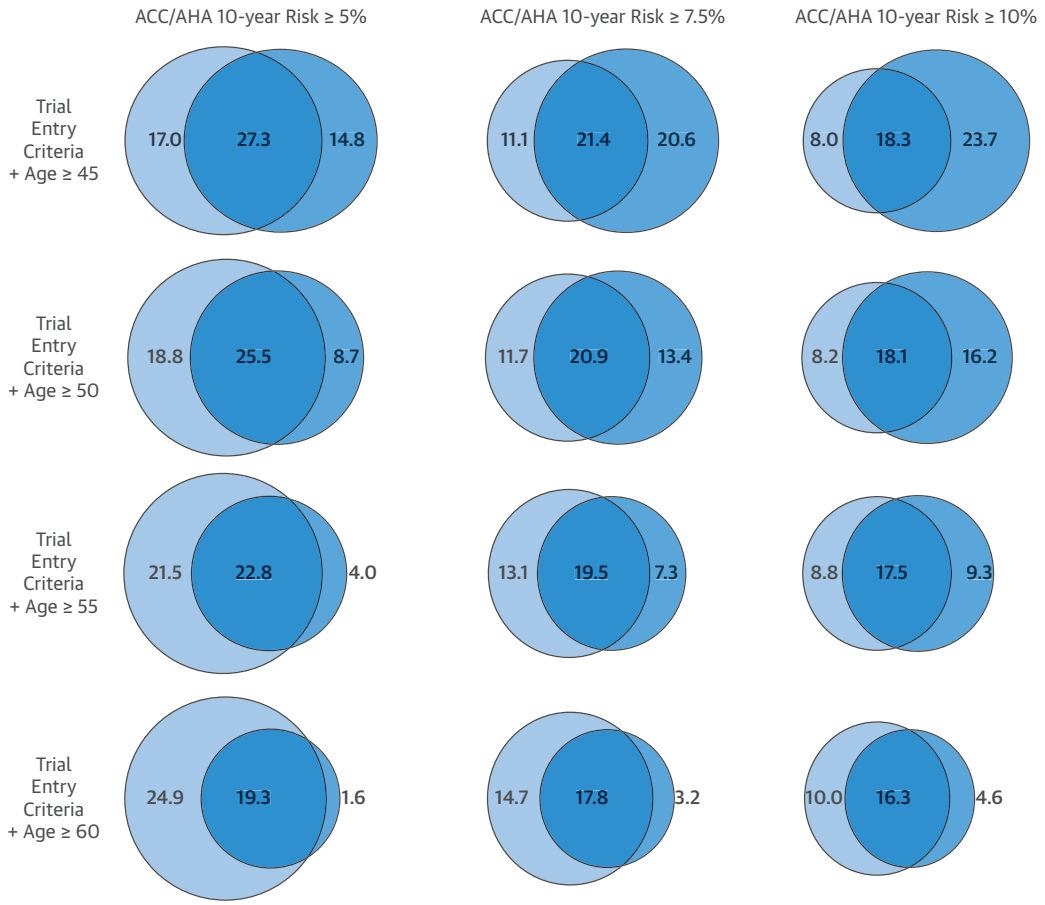
Estimated proportions of the National Health and Nutrition Examination Survey population fulfilling the risk-, trial-, and age-based criteria. Data are presented across a full range of ages from 40 to 79 years.

An additional advantage of our proposed hybrid approach might be increased utilization of statins among those physicians who have voiced concern about the net benefit to risk ratio of statin therapy in primary prevention, a clinically-relevant issue given the small, but statistically significant, increases in rates of muscle injury and diabetes in this setting (20,21). For such physicians, the combined approach outlined here avoids the perception of recommending statin therapy in settings such as heart failure or renal failure, where absolute risk is high, yet statin therapy has not proven effective at lowering event rates despite substantial LDL reduction (4–7). This approach is consistent with current ACC/AHA recommendations, but the current risk calculator does not make this explicit. The hybrid approach further avoids the problem faced in 10-year risk approaches, where statin allocation is inadvertently driven by hypertension and cigarette consumption, for which the initial interventions are blood pressure reduction and smoking cessation, respectively. The combined approach also avoids inadvertent recommendations to treat those at high risk simply due to older age. Of interest, because it takes into account both the patient's individual absolute risk and evidence-based treatment effects for patient groups found to have a benefit, the combined approach comes close to that of using individualized treatment effects (22).

Critics may argue that a hybrid approach is too complicated to implement. We strongly disagree. All that is required to bring this hybrid approach into clinical practice is the addition of a single new output on the current ACC/AHA website for risk prediction stating whether or not the patient of interest would have qualified for 1 of the pivotal statin trials demonstrating efficacy in primary prevention. A simple yes or no answer, using the flow diagram in the **Central Illustration**, would let the responsible physician know immediately if there is hard trial evidence to support prescription for the patient under consideration.

We note that a change in the 10-year risk threshold (for the absolute risk approach) or a change in the age threshold (for the trial-based approach) will not effectively substitute for the hybrid approach proposed here. **Figure 5** presents Venn diagrams for sensitivity analyses comparing the 10-year risk approach to the randomized trial approach. As shown, in all instances, the 10-year absolute risk approach to statin allocation continued to result in recommendations to consider treatment for many individuals for whom trial data are lacking. Similarly, in all instances, the clinical trial criteria approach continued to result in recommendations to

FIGURE 5 Sensitivity Analyses for the Hybrid Approach



Venn diagrams for sensitivity analysis comparing the current ACC/AHA 10-year risk approach for various levels of risk **(light blue)** with the trial entry criteria approach for various age thresholds **(medium blue)**, as well as the intersection inclusive of both approaches **(dark blue)**. As shown, regardless of the scenario chosen, the number recommended for statin therapy using the hybrid approach (at the intersections of the Venn diagrams) does not vary widely. Abbreviations as in Figure 2.

consider treatment for many individuals because the absolute risk was low. This trend toward potential under-treatment of those where trial data indicate efficacy and potential overtreatment of those where trial data are lacking (using the 10-year risk-based approach), or potential overtreatment where absolute risk was low (using the trial-based approach), is a consistent finding that cannot be eliminated by increasing or decreasing the 10-year thresholds of risk. However, as also shown in the Venn diagrams of Figure 5, the number of individuals in the intersections (reflecting the proposed hybrid allocation approach) does not vary widely. For example, in sensitivity analyses for the 10-year risk threshold of ≥7.5%, the number of individuals in the intersection who additionally fulfilled trial-based criteria varied between 17.8 million and 21.4 million.

The bottom of the Central Illustration presents examples of how the hybrid proposal would work in daily practice using a modified ACC/AHA risk calculator as a smartphone application. As shown on the left, a healthy, white, 70-year-old male with "optimal" risk factors (total cholesterol 170 mg/dl, high-density lipoprotein cholesterol 50 mg/dl, untreated systolic blood pressure 110 mm Hg, nonsmoker, no diabetes) is nonetheless found to have a 10-year estimated risk of 13% according to the current ACC/AHA prediction algorithm. However, this man would not have qualified for randomization into any of the clinical trials that demonstrate statin efficacy in primary prevention, a fact made fully

transparent by the modified ACC/AHA calculator. In contrast, as shown on the right, a hyperlipidemic, white, 50-year-old male would have qualified for multiple pivotal statin trials, but is found to have an ACC/AHA estimated 10-year risk of only 4%.

We are hopeful that the ACC/AHA will recalibrate the existing pooled risk calculator to avoid overestimation of 10-year risk and consider adding the simple "yes/no" question concerning trial eligibility. It is not our intent to suggest that following the hybrid approach is necessarily the best way to prescribe statin therapy in primary prevention, and we recognize that this approach has not been subject to randomization. Furthermore, as recently described (23), randomized trials also have substantive limitations and may not accurately address all patient needs in the community. We do believe, however, that a risk calculator providing both a 10-year risk estimate and a statement related to trial eligibility has the potential to improve care by increasing the transparency of physician-patient interactions concerning the prescription of statin therapy in primary prevention.

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KEY WORDS algorithms, hydroxymethylglutaryl CoA reductase inhibitors, myocardial infarction, primary prevention, risk factors, stroke

APPENDIX For supplemental methods, tables, and figures, please see the online version of this article.