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## Statins: new American guidelines for prevention of cardiovascular disease

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Guidelines released on Nov 13, 2013, by the American Heart Association (AHA) and the American College of Cardiology (ACC) for the management of cholesterol are a major step in the right direction.<sup>1</sup> These new guidelines emphasise prevention of stroke as well as heart disease, focus appropriately on statin therapy rather than alternative unproven therapeutic agents, and recognise that more intensive treatment is superior to less intensive treatment for many patients. Furthermore, the new ACC/AHA guidelines show that for individuals in whom statin therapy is clearly indicated (such as those with previous vascular disease or LDL cholesterol  $\geq 4.9$  mmol/L [190 mg/dL]) the benefits on heart attack, stroke, and cardiovascular death significantly outweigh the risks for developing diabetes or myopathy. Moreover, by eliminating emphasis on LDL treatment targets and the need to measure concentrations of creatine kinase during follow-up, the new guidelines greatly simplify care for the general medicine community. These changes are substantial and will improve patient care.

It is in the realm of primary prevention that the new guidelines are likely to be more controversial. The ACC/AHA guidelines use a newly developed risk prediction algorithm based on "hard" atherosclerotic events<sup>2</sup> to recommend initiation of statin therapy in primary prevention patients with a predicted 10-year risk of greater than or equal to 7.5%, and consideration of statin therapy in patients with 10-year risks of between 5% and 7.5%. In patients with type 1 or

type 2 diabetes, the threshold of greater than or equal to 7.5% is used to select between high-intensity and moderate-intensity statin regimens, defined as daily regimens that reduce LDL cholesterol by more than 50% or between 30% and 50%. As described in the guidelines, these new criteria could result in more than 45 million middle-aged Americans who do not have cardiovascular disease being recommended for consideration of statin therapy (33 090 000 at  $\geq 7.5\%$  10-year risk; 12 766 000 at  $> 5.0$ – $7.4\%$  10-year risk); this is about one in every three American adults, many of whom are already on statin treatment under the older US guidelines.

It is reasonable to ask if any global risk prediction score is needed in 2013 to allocate statin therapy in primary prevention. Between 1995 and 2008, six major primary prevention trials, which included more than 55 000 men and women, showed statins to be effective in primary prevention for the reduction of myocardial infarction and stroke among those with raised LDL cholesterol (WOSCOPS, MEGA),<sup>3,4</sup> reduced HDL cholesterol (AFCAPS/TexCAPS),<sup>5</sup> raised concentrations of C-reactive protein (JUPITER),<sup>6</sup> diabetes (CARDS),<sup>7</sup> or hypertension (ASCOT-LLA).<sup>8</sup> Thus, trial-based guidelines that rely on randomised experiments rather than estimates from epidemiological models could instead be used to write statin guidelines.<sup>9</sup>

No trial of statin therapy has ever used a global risk prediction score as an enrolment criterion, so basing

prescription on such a metric might be difficult to defend in an evidence-based climate. In addition, trial data contradict statements that high absolute risk always predicts statin efficacy; cardiologists now understand that statins cannot be recommended simply on the basis of high risk without regard for underlying clinical conditions. As examples, the CORONA<sup>10</sup> and AURORA<sup>11</sup> trials enrolled individuals with very high vascular risk in the settings of heart failure or renal failure and found no evidence of event reduction with statin therapy despite large reductions in LDL cholesterol.

Other than age, the major drivers of high global risk are smoking and hypertension, for which the interventions of choice should be to eliminate cigarette use and to lower blood pressure, rather than to write a prescription for statin therapy. This is well acknowledged in the new guidelines that also address lifestyle factors, but can be confusing if applied without physician discretion. Consider a 55-year-old male smoker with hypertension (untreated systolic blood pressure of 145 mm Hg) with LDL cholesterol of 1.9 mmol/L (75 mg/dL) and HDL cholesterol of 1.3 mmol/L (50 mg/dL). According to the new ACC/AHA algorithm, this patient has a 10-year risk of 9.6% and thus is recommended for a statin, despite his already very low LDL cholesterol. Alternatively, consider a 60-year-old non-smoking woman with normal blood pressure (120 mm Hg) and HDL cholesterol of 1.3 mmol/L (50 mg/dL), but substantially raised LDL cholesterol of 4.7 mmol/L (180 mg/dL). According to the new risk algorithm and guideline, her 10-year risk is 3.8% and she should not be considered for statin therapy at all. Thus, as with all guidelines, context will continue to have a role in physicians' decision making. More important than absolute risk for the patient is the projected treatment effect for the individual given his or her risk factors.

Another concern for clinicians is whether the new prediction algorithm created by the ACC/AHA correctly assesses the level of vascular risk. To be useful, prediction models must not only discriminate between individuals with and without disease, but must also calibrate well so that predicted risk estimates match as closely as possible the observed risk in external populations.<sup>12</sup> We calculated predicted 10-year risks of the same atherosclerotic events using the new ACC/AHA risk

prediction algorithm and compared these estimates with observed event rates in three large-scale primary prevention cohorts, the Women's Health Study,<sup>13</sup> the Physicians' Health Study,<sup>14</sup> and the Women's Health Initiative Observational Study.<sup>15</sup>

As shown in figure 1, in all three of these primary prevention cohorts, the new ACC/AHA risk prediction algorithm systematically overestimated observed risks

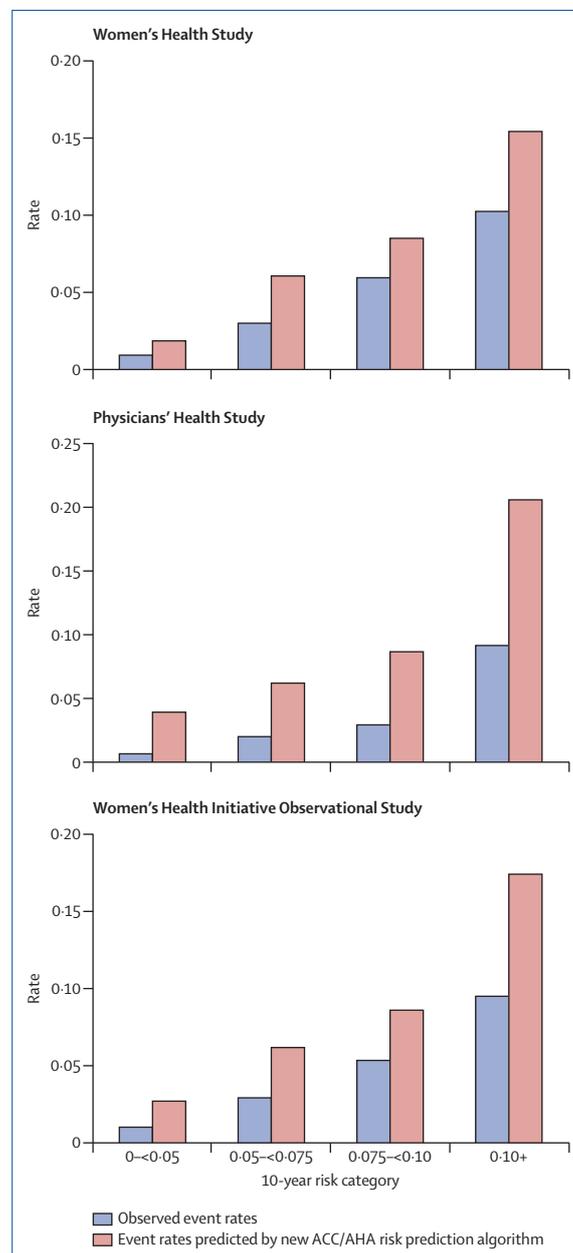
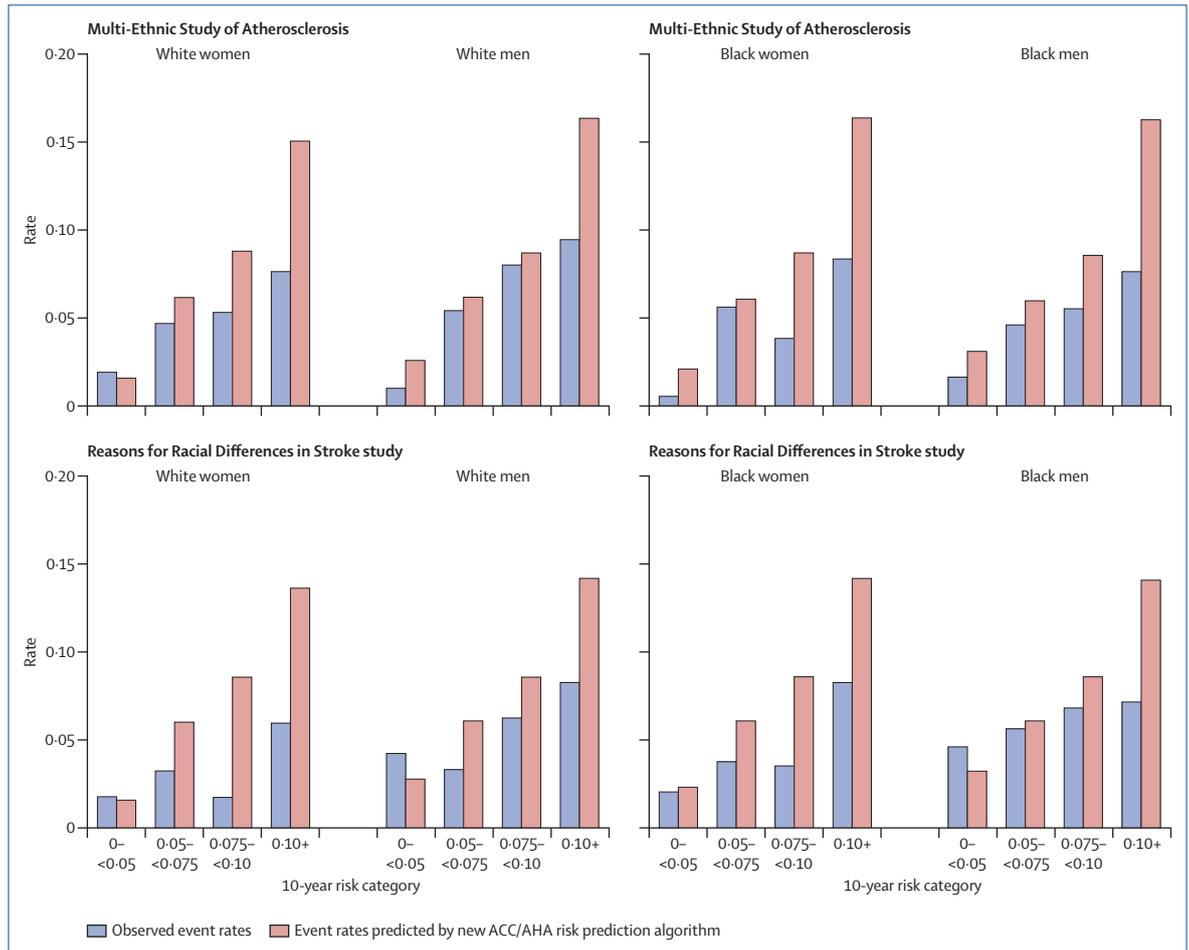


Figure 1: Comparison of observed event rates with event rates predicted by new ACC/AHA risk prediction algorithm in three external validation primary prevention cohorts: the Women's Health Study, the Physicians' Health Study, and the Women's Health Initiative Observational Study



**Figure 2:** Comparison of observed event rates with event rates predicted by new ACC/AHA risk prediction algorithm in two external validation cohorts described in the Full Work Group Report Supplement: the Multi-Ethnic Study of Atherosclerosis and the Reasons for Racial Differences in Stroke study. Data are shown stratified by gender and race.

by 75–150%, roughly doubling the actual observed risk. As shown in figure 2, similar overestimation of risk was observed in two external validation cohorts used by the guideline developers themselves, an issue readily acknowledged in the report.<sup>2</sup> Thus, on the basis of data from these five external validation cohorts, it is possible that as many as 40–50% of the 33 million middle-aged Americans targeted by the new ACC/AHA guidelines for statin therapy do not actually have risk thresholds that exceed the 7.5% threshold suggested for treatment. Miscalibration to this extent should be reconciled and addressed in additional external validation cohorts before these new prediction models are widely implemented. It is possible, for example, that the five external validation cohorts are more contemporary than the cohorts used in the risk prediction algorithm and thus reflect secular

improvements in overall health and lifestyle patterns in the USA over the past 25 years.

The recent ACC/AHA cholesterol guidelines take several major steps forward that will simplify and improve care for higher risk patients, including those with diabetes. At the same time, reliance on the new risk prediction algorithm could put many primary prevention patients on statin therapy where there is little trial evidence, while potentially denying statin therapy to other patients despite trial evidence of efficacy. In primary prevention, instead of predicting risk and presuming benefit, an alternative and simpler policy of asking “what works?” and “in whom?” based on trial evidence would reduce this problem and result in evidence-based public health recommendations for statin therapy in patient groups for whom we have hard data showing efficacy.

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## WHO's 2013 global report on tuberculosis: successes, threats, and opportunities

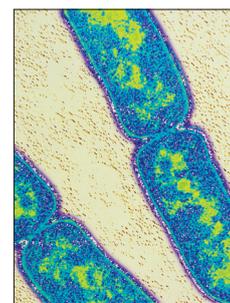


Tuberculosis has been a global public health emergency since 1993.<sup>1</sup> In 2006 WHO launched the Stop TB strategy, which was linked to the Millennium Development Goal (MDG) 6 target of reversing the spread of tuberculosis by 2015.<sup>2</sup> WHO's *Global Tuberculosis Report 2013*,<sup>3</sup> published on Oct 23, provides a comprehensive assessment of the current tuberculosis pandemic, and assesses progress in implementing tuberculosis services and control measures at country, regional, and global levels.<sup>3</sup> The report details some striking successes towards achieving MDG 6 and related 2015 targets for global tuberculosis control. It also identifies specific areas of concern for which urgent political and funder attention is required.

The report shows that the number of incident cases of tuberculosis worldwide continues to fall at a slow, steady rate of 2%; there were an estimated 8.6 million incident cases of tuberculosis in 2012, which included 2.9 million cases in women and 530 000

in children. For the first time WHO's report provides estimates of the tuberculosis burden among women disaggregated by region and HIV status, and shows that there is substantial morbidity and mortality from tuberculosis in adult women. In 2012, tuberculosis caused 1.3 million deaths, including 320 000 deaths in HIV-infected people. An estimated 170 000 deaths were from multidrug-resistant (MDR) tuberculosis, a fairly high total when compared with the estimated 450 000 global incident cases of MDR tuberculosis. In 2012, three-quarters of total tuberculosis deaths occurred in regions of Africa and southeast Asia, with South Africa and India accounting for a third of global tuberculosis deaths.

WHO's report also shows that progress has been made in reducing the burden of tuberculosis. Overall mortality rates from tuberculosis have fallen by 45% since 1990, and the global target of a 50% reduction in tuberculosis mortality by 2015 seems within reach. WHO estimates that 22 million lives were saved



*Mycobacterium tuberculosis*

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