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Real world data on cardiovascular morbidity and mortality from large contemporary populations as a benchmark for validating cardiovascular risk estimation equations

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In an update of lipid guidelines issued in 2013 (based on the Pooled Cohort Equation cardiovascular risk calculator), the American College of Cardiology/American Heart Association (ACC/AHA) task force recommend fixed-dose statin therapy for those at risk for atherosclerotic cardiovascular disease (ASCVD) and did not advocate non-statin lipid-lowering therapies or treatment to specific targets of low-density lipoprotein cholesterol (LDL-C) levels, thus limiting the need for repeated LDL-C testing.[1] In a recent analysis of a cohort of 1,174,545 patients, 1,129,205 (96.1%) were statin-eligible (91.2% ASCVD, 6.6% type 2 diabetes mellitus (T2DM), 0.3% off-treatment LDL-C ≥ 190 mg/dl, 1.9% estimated 10-year ASCVD risk ≥ 7.5%) and it was shown that 377,311 patients (32.4%) were not receiving statins while 259,143 (22.6%) were receiving non-statin lipid-lowering therapies.[2] During the study period, 20.8% of patients had 2 or more LDL-C assessments, and 7.0% had more than 4.[2] These data indicate that there are problems with the implementation of the 2013 ACC/AHA guidelines and one of the possible reasons might be the miscalculation of the 10-year ASCVD risk by the "Polled Cohort Equation", which is derived from data of 5 large epidemiological studies (n= 24,626) conducted in the US (Atherosclerosis Risk in Communities, Cardiovascular Health Study, Coronary Artery Risk Development in Young Adults, and the Framingham and Framingham Offspring studies) (**http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/PreventionGuidelines_UCM_457698_SubHomePage.jsp**).[3] The 2013 ACC/AHA guidelines for the treatment of dyslipidaemia were based solely on epidemiological data and not on prospective, randomised, controlled trials. This was heavily criticized because the era of defining CVD main risk factors is long gone; at present, we face difficulties in implementing previous simple treatment guidelines with specific LDL-C goals validated for optimum clinical benefit by large prospective, randomized, controlled trials.[4] This approach of the ACC/AHA risk calculator overestimated CVD risk leading to a substantial increase, even doubling, of US patients eligible for statins.[4] The 2013 ACC/AHA guidelines redefined patient populations for treatment, targeting those with confirmed ASCVD, T2DM, LDL-C levels ≥ 190 mg/dl, or 10-year CVD risk ≥ 7.5%. The new guidelines recommended a "treat to risk" strategy using fixed-dose statin medications, did not recommend use of nonstatin lipid-lowering therapies and did not recommend treatment to target LDL-C lipid levels, thus rendering repeated LDL-C on-treatment testing unnecessary. The potential impact of the new guidelines on current US cardiovascular practice is unknown. Because cardiologists typically treat patients with the highest risk for cardiac events, optimizing cholesterol management in light of the ACC/AHA guidelines would be expected to have a significant impact. Although several publications evaluated the population impact of these new guidelines[4], important questions remain unanswered. In particular, little is known about current lipid-lowering therapies (Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, ezetimibe and fibrates) and LDL-C testing patterns; this knowledge would help predict shifts in care and subsequent implications for statin use, non-statin lipid-lowering agents use, and LDL-C testing among various risk groups.

A very recent trial evaluated the accuracy of the Pooled Cohort Equation in a large contemporary, multiethnic population [registry data from 2008 to 2012 evaluated for the current practice patterns as a function of the 2013 cholesterol guidelines[5]]. Among 307,591 eligible 40-75 years-old adults without T2DM, 22,283 were black, 52,917 were Asian/Pacific Islander, and 18,745 were Hispanic.[5] During 1,515,142 person-years of follow-up, 2,061 ASCVD events were recorded.[5] In each 5-year predicted ASCVD risk category, observed actual 5-year ASCVD events was substantially lower: 0.20% for predicted risk < 2.50%; 0.65% for predicted risk 2.50% to < 3.75%; 0.90% for predicted risk 3.75% to < 5.00%; and 1.85% for predicted risk > 5.00% (C-statistic, 0.74). Similar ASCVD risk overestimation and poor calibration with moderate discrimination (C-statistic, 0.68 to 0.74) were observed in sex, racial/ethnic, and

socioeconomic status subgroups, and in sensitivity analyses among patients receiving statins for primary prevention. Calibration among 4,242 eligible adults with T2DM was better, but discrimination was worse (C-statistic, 0.64). Thus, under contemporary "real world" settings the ACC/AHA Pooled Cohort Equation substantially overestimated actual 5-year risk in adults without T2DM, in all patient categories and across all socio-demographic subgroups.[5] Moreover, in US cardiovascular practices, 32.4% of statin-eligible patients, as defined by the 2013 ACC/AHA cholesterol guidelines, were not currently receiving statins. In addition, 23% were receiving non-statin lipid-lowering therapies and 21% underwent repeated LDL-C testing.[5] Thus, the risk calculator overestimates the CVD risk and physicians do not implement the 2013 ACC/AHA statin guidelines.

An even more recent study reported that, 2 years after the ACC/AHA guidelines publication, only 11.5% of 8,762 Medicare beneficiaries with an acute cardiovascular event received a prescription for a high-intensity statin at hospital discharge and within 1 year after hospital discharge.[6]

Moreover, analysis of 10-year clinical event rate data from the Multi-Ethnic Study of Atherosclerosis (MESA[7]) suggests that substituting the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) cholesterol guidelines (first published in 2001 and updated in 2004) with the 2013 ACC/AHA cholesterol guidelines in MESA will more than double the number of participants eligible for statin therapy.[7] Assuming 10 years of high-intensity statin therapy, according to 2013 ACC/AHA guidelines, the corresponding estimates for reductions in ASCVD and increases in new-onset diabetes (NOD) were as follows: ASCVD 2.70% (number needed to treat (NNT), 37.5) and NOD 2.60% (number needed to harm (NNH), 38.6).[7] This brings to surface the major issue of NOD. As shown above, the NNT to avoid one ASCVD event is equal to the NNH for one event of NOD. This suggests that any overestimation of CVD risk by the Polled Cohort Equation that might lead to unnecessary statin treatment and might result in an increased incidence of NOD without substantial CVD benefit; therefore, the benefit/risk ratio might be disadvantageous. The result of overestimating CVD risk leading to overtreatment with statins of an "obese" nation like US might turn out to be catastrophic.

Mortality from ASCVD in the US has decreased substantially in recent decades.[8] From 1980 through 2000, the age-adjusted death rate from coronary heart disease (CHD) was halved, from 543 to 267 deaths per 100,000 men and from 263 to 134 deaths per 100,000 women, resulting in 341,745 fewer deaths from CHD in 2000 as compared to 1980.[8] This substantial reduction was attributed to life-style changes and medical interventions.[8] This reduction was partly offset by increases in CHD deaths in obese people and in patients with T2DM, diseases that became more prevalent during these two decades; these increased accounted for an higher number of deaths (8% from obesity and 10% from T2DM).[8] This means that it is not wise to double the number of patients on "diabetogenic" statin treatment in US increasing substantially the incidence of NOD, given that T2DM is one of the two causes for increasing CHD mortality at a time that ASCHD mortality is decreasing sharply and steadily (the objective is to help or at least to do no harm-Hippocrates, 460-370 BC).

Recommendations by the US National Lipid Association (NLA) suggested besides lifestyle therapies, focus on groups with special considerations, including children and adolescents, women, older patients, certain ethnic and racial groups, patients with chronic kidney disease (CKD), patients infected with human immunodeficiency virus, patients with rheumatoid arthritis, and patients with residual cardiovascular risk despite statin therapy (e.g. those with mixed (atherogenic) dyslipidaemia); as well as strategies to improve patient outcomes by increasing adherence and using team-based collaborative care.[9] These very important issues were not incorporated in the Pooled Cohort Equation and were not taken into consideration in the 2013 ACC/AHA statin guidelines.

In a prospective European study, the Rotterdam Study (n= 4,854 participants), the risk engines of 3 different set of guidelines were compared and

the proportions of individuals eligible for statins according to the ACC/AHA, NCEP-ATP-III and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines and relations of predicted and actual ASCVD events were evaluated.[10] The ACC/AHA guidelines recommended statins to nearly all men (96.4% (95% confidence interval (CI), 95.4%-97.1%); n=1,825) and two thirds of the women 65.8% (95% CI, 63.8%-67.7%); n=1,523).[10] With the ACC/AHA Pooled Cohort Equation, the average predicted risk vs the actual observed cumulative incidence of ASCVD events was 21.5% (95% CI, 20.9%-22.1%) *vs* 12.7% (95% CI, 11.1%-14.5%) for men (192 events) and 11.6% (95% CI, 11.2%-12.0%) *vs* 7.9% (95% CI, 6.7%-9.2%) for women (151 events).[10] At the other end of the world, in a large Korean cohort (19,920 participants), more subjects would have qualified for statin treatment according to the new ACC/AHA guidelines compared with the proportion recommended for statin treatment by the NCEP ATP III guidelines (47 *vs* 34%, p<0.01).[11] Japan developed its own cardiovascular risk estimation equation based on a prospective study (n=15,672).[11] Moreover, the Pooled Cohort Equation provided poor calibration and moderate discrimination in Hong Kong Chinese subjects, whereas the Framingham CVD risk equation can be applied to the Chinese population but requires recalibration in men.[13] Australia adopted the SCORE (Systematic Coronary Risk Evaluation) risk chart based on Australian national mortality data and average major CVD risk factor levels and did not change it after the 2013 ACC/AHA guidelines.[14] Finally, a large Israeli cohort, the Maccabi Healthcare Services (MHS) included 725,784 subjects older than 40 years of age; 30% were on statins at baseline. The adoption of the Pooled Cohort Equation would increase the proportion of statin-treated members to 48% (a 60% increase, mainly in primary prevention). The calculated incremental annual cost for medications in Israel would be US $13.5 million and the cost per ASCVD event prevented would be US $20,500.[15]

Overall, the Pooled Cohort Equation appears to substantially overestimate the risk for ASCVD in populations all over the world, even in the US. This leads to unnecessary statin treatment and to related adverse effects (for example NOD). The risk benefit ratio trends to diminish with this ASCVD risk prediction equation.

The 2013 ACC/AHA guidelines had two major issues. One was the overestimation of risk by the Pooled Cohort Equation that has to be changed in the next version of the guidelines and the other was the abandonment of specific LDL-C level treatment targets. The latter was also a major problem because guidelines did not provide any LDL-C levels after statin treatment at which non-statin lipid-lowering therapies (PCSK9 antibodies, ezetimibe) could be implemented for maximum reduction of LDL-C and for concomitant maximum clinical benefit. A very recently published Consensus from ACC on non-statin lipid-lowering drug use[16,17] suggests, besides the original > 50% reduction in LDL-C targets, consideration of attaining LDL-C < 70 mg/dL or non-high-density lipoprotein cholesterol (HDL-C) < 100 mg/dL targets in high ASCVD risk patients and LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL in intermediate ASCVD risk patients, reinstating the previous specific LDL-C goals, which were very helpful to clinicians.[16,17] One of the two issues of the 2013 ACC/AHA guidelines has been fixed.[16,17] If another ASCVD risk engine that better estimates ASCVD risk is used in the next ACC/AHA guidelines, it would be ideal. For example the Reynolds Risk Engine has been shown in a large modern multiethnic cohort (MESA study[7,18]) to be the closest to the real life settings of nearly all available risk engines. This risk engine overestimated ASCVD risk by only 9% in men and underestimated ASCVD risk by 21% in women.[18] Clinicians ask: Tell me and I will listen, convince me and I will implement. Let's do that.

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