Authors’ reply

We concur with David van Klaveren and colleagues that the projected treatment effect for an individual given his or her risk factors is of considerable importance since net benefit is a function of the person’s absolute risk, the projected individual benefit, as well as potential harms of therapy. We have collaborated previously using this methodology to estimate individualised benefits of statin therapy6 and in work describing the individualised number-needed-to-treat. As noted in our Comment,2 we further concur that contemporary cohorts should be used to update and recalibrate risk equations when such data are available.3 Although we recognise that methods to develop and assess prediction models from multiple studies are quite complex, and should explore and allow for heterogeneity across studies.4

Using the new American Heart Association (AHA) and American College of Cardiology (ACC) algorithms, virtually all men older than 66 years and women older than 70 years have a calculated 10-year risk greater than 7.5%, even with optimal risk factors. Nicholas Wald and Joan Morris thus suggest that screening for age alone is a simpler way to prescribe statin therapy. However, as noted in our Comment, these risk estimates are likely to be artificially high. Further, the approach of treating all individuals older than a given age exposes the largest number to therapy, including many who have never been studied in clinical trials. This approach could lead to exposure to potential hazards of statin therapy among some individuals without clear evidence of benefit, and to many others where the number-needed-to-treat to prevent one vascular event is quite large. James McCormack and colleagues present data suggesting that the new AHA/ACC risk calculator has a similar average agreement to other commonly used risk calculators. However, we respectfully believe such risk calculators cannot be directly compared because they vary greatly in terms of outcome definitions, years of follow-up, and absolute risk categories. Failure to take such major differences into account can lead to serious, but legitimate, discrepancies between estimates, as discussed in our comparison of calculators within the Women’s Health initiative.5

We believe randomised trials should provide the underlying structure for statin guidelines,6 but share William Freeman’s view that experimental data, observational studies, and genetics should inform thoughtful application of those guidelines to individual patients. We are less concerned about elimination of LDL treatment targets since the new AHA/ACC guidelines strongly emphasise the use of more intensive statins for more patients. This latter approach is consistent with available evidence and will clearly improve patient care.

PMR receives investigator-initiated research support from the National Heart, Lung, and Blood Institute, Amgen, AstraZeneca, Novartis, and Pfizer, and is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Siemens and AstraZeneca. NRC declares that she has no conflicts of interest.

*Paul M Ridker, Nancy R Cook

pridker@partners.org

Center for Cardiovascular Disease Prevention, Division of Preventive Medicine and Cardiology, Brigham and Women’s Hospital, Boston, MA 02215, USA


Statins, risk assessment, and the new American prevention guidelines

In 2008, the National Heart, Lung and Blood Institute commissioned three expert panels (on cholesterol treatment, blood pressure treatment, and obesity and overweight management) and cross-cutting and supporting work groups (focused on lifestyle and risk assessment) to create updated clinical practice guidelines for cardiovascular disease prevention. The American Heart Association and American College of Cardiology completed and published the guidelines on Nov 12, 2013.1–4 For the first time, these guideline panels and work groups took an approach that was based almost solely on systematic reviews of the medical literature and synthesis of high-quality evidence.

In their Comment,5 Paul Ridker and Nancy Cook support many of the recommendations for cardiovascular risk reduction that were made as a result of the prolonged and careful deliberations of these panels. However, they take issue with the risk assessment algorithm provided by the guidelines. For its risk calculator, the work group pooled recent data (mostly derived from the 1990s) from several long-standing, community-based US cohort studies to develop new sex-specific and race-specific equations to predict 10-year risk for atherosclerotic cardiovascular disease (ASCVD).6 These pooled cohort equations represent a major step forward for risk estimation, because, for the first time in a major guideline, they focus on estimation of risk for both heart attacks and strokes and provide estimates applicable to African American people. As a result, they are much better at representing overall, or global, cardiovascular disease risk, especially in women and African Americans, in whom risk for stroke increases earlier in life than does risk for heart attacks.

The risk assessment work group considered other potential approaches
to assess risk for ASCVD, including application of the complex inclusion and exclusion criteria from published clinical trials, but this approach (as suggested by Ridker and Cook) was deemed too difficult to apply routinely or appropriately in clinical practice, and can be prone to error. Most importantly, the approach does not consider the compelling data from tens of thousands of patients treated with statins in rigorous clinical trials showing that the absolute benefit of a statin is proportional to the absolute risk of a patient when based on assessment of all of their risk factor levels (including blood pressure, smoking and diabetes status, age, and sex). Thus, the higher the risk of the patient, the more likely he or she is to benefit substantially from a statin in addition to lifestyle modification as needed. But the recent data also show that benefit extends down even to patients with a roughly 5% risk for ASCVD over the next 10 years.4

Importantly, only about 31% of Americans aged 40–75 years without existing cardiovascular disease might be eligible for statin therapy under the new guidelines. This is remarkably similar to what would have occurred under the previous guidelines if the threshold for treatment were lowered modestly from 20% 10-year risk of a heart attack to 10% risk, well short of the threshold of proven benefit in recent trials. Further, many of these patients are likely already on statin therapy, and many would be recommended for treatment by either risk assessment approach.

The risk assessment document2 (and its supplement) include a detailed explanation of the sophisticated methods used to derive and validate the pooled cohort equations. These equations were subjected to more intensive validation than any other ASCVD risk equations before their publication. Few community-based cohorts have the data and length of follow-up needed to validate these equations. We examined short-term follow-up data from the Multi-Ethnic Study of Atherosclerosis (MESA) and REasons For Geographic And Racial Differences in Stroke (REGARDS) cohorts from the early 2000s. We noted some overestimation of risk by the pooled cohort equations, mainly in high-risk participants, who had fewer events than anticipated. Ironically, this observation might have been due to the very high rates of initiation of statins in high-risk participants after the baseline examinations in MESA (whose participants received their coronary artery calcium score information) and REGARDS.

Ridker and Cook provide some new data from three existing studies suggesting similar over-estimation of risk by the new pooled cohort equations. Individuals in all three cohorts were either screened for participation in, or enrolled in, clinical trials, with the very real potential for healthy volunteer effects. Indeed, event rates in the Women’s Health Initiative cohort are remarkably low, and levels of risk factors, such as smoking prevalence, are substantially lower in the Women’s Health Study (WHS) and the Physicians’ Health Study (PHS) cohorts than in the general US population addressed by the guidelines. In WHS and PHS, some risk factor levels were self-reported in ranges, rather than directly measured, leading to concerns about imprecision. Furthermore, all three cohorts might have been subject to some downstream initiation of statins. We welcome the opportunity for rigorous review of these new data to understand their implications for the risk assessment algorithm.

Because the largest magnitude of any potential overestimation is noted in patients with the highest levels of cardiovascular disease risk, it would not affect the decision to recommend that such a higher-risk patient take a statin. In patients with lower predicted risk, overestimation by the pooled cohort equations would be of greater concern. In view of this potential, the cholesterol panel did not recommend statin therapy at the threshold of 5%, at which benefit was suggested by the clinical trial data. Instead, the panel recommended a treatment threshold of 7.5%, creating a buffer against potential overestimation of risk. Importantly, the panel mandated that the patient and clinician engage in a risk discussion before prescription of a statin to understand the sources of the patient’s predicted risk, focus attention on potentially modifiable lifestyle factors that could help to mitigate that risk, and provide a balanced perspective on the potential benefits and side-effects or harms of drugs such as statins, which can only be appreciated in context with estimation of absolute risks.4

Although we all desire personalised medicine, this goal is still a long way off. No risk assessment algorithm will ever be perfect. These approaches should and will continue to be updated and improved as more data become available. However, quantitative risk assessment using the best available data from broadly representative cohorts that include African Americans, and a focus on an expanded endpoint with stroke as well as heart attack, represents our best hope to identify people at risk who could benefit from a statin.

Sadly, although many people in the USA are asymptomatic for cardiovascular disease, they are hardly healthy; these same individuals who are at risk based on multiple well-defined causal but modifiable risk factors would, in fact, benefit from statin therapy. If left untreated, they will be the individuals who become the statistics that make cardiovascular disease the leading cause of death, disability, lost quality of life, and medical costs in the USA. At present, more than 70 million Americans are regarded as candidates for blood pressure lowering drugs to reduce risk for heart disease and stroke. According to these new guidelines, just more than 30 million people without existing cardiovascular disease might be candidates for statin therapy. These numbers are cause for a call to action to first focus on the prevention of cardiovascular risk factors such as high cholesterol and high blood pressure.
Until we get serious about personal lifestyle modification and national policies to promote environmental and behavioural change, we will need blood pressure lowering medications and statins to contain the epidemic of cardiovascular disease.

NJS was Chair of the Cholesterol Guidelines Panel, and DML-J and DG were co-Chairs of the Risk Assessment Work Group.

*Donald M Lloyd-Jones, David Goff, Neil J Stone

dlj@northwestern.edu

Northwestern University Feinberg School of Medicine, Chicago 60611, IL, USA (DML-J, NJS); and Colorado School of Public Health, Aurora, CO, USA (DG)


Late effects of breast radiotherapy

We welcome the publication of the 10-year results of the START trials, but we have concerns about the reporting of late tissue effects. We note that the categories used in the latest report differ from those in the 5-year quality of life study, and find this problematic.

For instance, in Hopwood and colleagues’ 5-year follow-up report, up to a third of women reported moderate or marked pain in the arm or shoulder over 5 years, while the 10-year follow-up report by Haviland and colleagues makes no mention of pain, merely of shoulder stiffness. Because our personal experience of late effects is that they are progressive, we find this odd. It is also confusing from the point of view of comparison to have different descriptions of adverse events, using different vocabulary (eg, induration vs hardness, and telangiectasia vs skin problems). We find too that some post-radiotherapy effects that we ourselves have experienced are still not mentioned, notably bone necrosis (not necessarily leading to fractures, though these do occur). However, it is a step forward to have 10-year results, and since follow-up data are still being collected, and follow-up was still short for cardiac events, we hope that these data and other late effects will continue to be monitored.

The publication of this Article offers an opportunity to reassess the role of radiotherapy in the overall treatment of breast cancer. It prompts the observation that timing is crucial, especially for fast-growing tumours, and we note that the time from surgery to randomisation in these trials was remarkably long (8–9 weeks from surgery to randomisation in these trials was remarkably long (8–9 weeks in START A and more than 7 weeks in START B). Also, randomisation did not allow for grade of tumour.

Patients now expect fully informed consent to treatment, and if they so wish are given details of their pathology. Surely a one-size-fits-all approach is inappropriate for radiotherapy. Fast-growing tumours might well need swift decisions and a different fractionation regimen from the slow-growing tumours. It has been convincingly suggested that differing protocols should be applied to different tumours. Now may be the time to take stock: perhaps weekend working should be considered, and NICE might yet need to revise their guidance.

We declare that we have no conflicts of interest.

*Heather Goodare, Jan Millington, Pam Pond, Christina Rogers, David Bainbridge

hm.goodare@virgin.net

RAGE (Radiotherapy Action Group Exposure), Southborough TN4, UK


Department of Error

Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraprostatic radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014; 383: 603–13—In table 3 of this Article (published online Nov 11, 2013), in the Postpathology section of the Absolute difference column, the 90% CI for All patients should have been 0 to 2, 6, the 90% CI for Mature cohort should have been 0 to 3, and the difference for Earliest cohort should have been 1.8%. In the Postpathology section of the Z score column, the score for Mature cohort should have been 0.409. These corrections have been made to the online version as of Feb 14, 2014, and to the printed Article.

Krum H, Schlaich MP, Böhm M, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet 2014; 383: 622–29—In this Article (published online Nov 7, 2013), Paul Sobotta should have been listed as an author. This correction has been made to the online version as of Feb 14, 2014, and to the printed Article.