JACC Vol. 54, No. 6, 2009
August 4, 2009:573–6

Don't Throw the Baby Out With the Bath Water

Budoff et al. (1) have presented important information from the MESA (Multi-Ethnic Study of Atherosclerosis) trial about the interpretation of coronary artery calcium (CAC) scores. There has been some controversy as to how to interpret what constitutes a high-risk score. Is the age/sex/ethnicity adjusted percentile score or the absolute total score best? To me it seems to depend on what is your question about high risk. In the Budoff et al. (1) article, clearly the authors are interpreting high risk as the risk for a cardiac event in the short term (46 months). However, to the clinician and patient, it is of great importance to determine which individuals are at high risk in the longer term (i.e., decades).

The authors cite an example of a 50-year-old Hispanic woman who has a CAC score of 25, which places her in the 95th percentile for age/sex/ethnicity compared with an 83-year-old white man with a CAC of 1,572, which places him in the 72nd percentile for his age/sex/ethnicity. The main point of the article is that although the man has a lower percentile than the woman, he is at much greater risk for a short-term cardiac event. No argument, the greater the atherosclerotic burden the greater the short-term risk. However, I think it is important to recognize that the percentile score has clinically useful information that the absolute score does not. The fact that the 50-year-old woman's score places her in the 95th percentile for age/sex/ethnicity means she will reach the high-risk score of 400 at a much earlier age, probably within 15 years (2), compared with many of her peers, who had the more likely score of 0 and will take 35 years or longer to achieve a high-risk score. I believe this is very useful information for the physician and the patient and will significantly impact decision-making about diet, lifestyle, and medications. In other words, I think we and our patients are interested in both the short- and long-term risk. If I am a 39-year-old white man with a score of 50, I certainly would want to know that I am likely to have a high-risk score within 10 years (3).

Knowing both short- and long-term risk is useful. The percentile score predicts the long-term risk and tells us how soon, untreated, we will reach a high-risk score. The absolute score represents the atherosclerotic burden currently present and therefore best predicts the short-term risk.

However, the Budoff et al. (1) article and the accompanying editorial seem to downplay the importance and value of the percentile score in their enthusiasm to identify the most powerful predictor of short-term risk. The data presented support their enthusiasm, but please don't throw the baby out with the bath water.

***Bruce H. Brundage, MD**

*Medical Director
Heard Institute of the Cascades
2500 N.E. Neff Road
Bend, Oregon 97701
E-mail: Bhbrundage@cascadehealthcare.org

doi:10.1016/j.jacc.2009.02.083

REFERENCES

1. Budoff MJ, Nasir K, McClelland RL, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2009;53:345–52.
2. McClelland RL, Chung H, Detrano R, Post W, Kronmal. Distribution of coronary artery calcium by race, gender and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006;113: 30–7.
3. Hoff JA, Chomka EV, Kranik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87:1335–9.

Reply

We completely agree with Dr. Brundage's supposition that a more important marker for treatment targets may be lifetime risk. Data suggest that 67% of men and 50% of women over 40 years of age will develop chronic heart disease (1). The concept of lifetime risk was highlighted in the National Cholesterol Education Program Adult Treatment Panel III guidelines (2) and is especially important for individuals who are young to middle-aged.

However, most data with risk factors, C-reactive protein, and coronary artery calcium (CAC) have shorter-term follow-up and enable clinicians to match intensity of therapy to intensity of risk for near-term events. Lifetime lipid treatment or other antiatherosclerotic therapies may start shifting cost benefits and possibly even risk benefits away from treatment strategies.

Dr. Brundage correctly points out that while absolute scores are better short-term predictors, we cannot completely forgo percentile scores. From our standpoint, presence of "any" CAC, irrespective of percentile, especially in younger individuals is an indicator of significant intermediate-term and lifelong risk. The issues with using "only" percentiles for risk assessment pose problems at 2 levels. First, at each age group, women presenting with the same level of CAC scores as men are less likely to be considered as high risk and, thus, to be treated. Second, another risk of using the percentile scores is underestimation of risk, and, thus, there is potential for undertreatment of those persons with higher scores. Persons with scores as high as 1,500 may be deemed "normal" by age and sex cutpoints, but clearly have at least a 20-fold increased risk of future cardiovascular events (3). As participants with baseline calcium scores are followed up to 12 years, risk continues to diverge based upon baseline score, supporting the concept that CAC is a good predictor of lifetime risk (4).

One limitation of the MESA (Multi-Ethnic Study of Atherosclerosis) study is that there were no persons under age 45 years, so really assessing younger patients with advanced atherosclerosis is outside the scope of our study. Younger patients especially need to rely more heavily on percentile scores, as they rarely achieve scores >100, yet may be at increased risk. Taylor et al. (5) prospectively followed 2,000 persons (mean age 43 years) for 3 years, and the presence of any plaque was associated with an 11.8-fold increased risk of a cardiovascular event (5). Using a percentile to give patients a relative place compared with their age, sex, and ethnic/racial peers allows physicians to treat patients who are "ahead of the curve" with increased vascular age. By emphasizing both absolute and percentile scores, we can identify those at higher risk of lifelong cardiovascular disease by acknowledging presence of any CAC as a marker of subclinical disease.

***Matthew J. Budoff, MD**
Khurram Nasir, MD, MPH

*Los Angeles Biomedical Research Institute at Harbor
University of California, Los Angeles
1124 West Carson Street, RB2
Torrance, California 90502
E-mail: Budoff@ucla.edu

doi:10.1016/j.jacc.2009.04.046

Please note: This research was supported by R01 HL071739 and contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics. Dallas, TX: American Heart Association, 2008.
2. National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
3. Budoff MJ, Nasir K, McClelland RL, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2009;53:345–52.
4. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.
5. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors. J Am Coll Cardiol 2005;46:807–14.

Clinical Significance of Iodine-123 Metaiodobenzylguanidine Cardiac Imaging

In a recent issue of the *Journal*, Tamaki et al. (1) found that in their study sample of 106 consecutive patients with stable congestive heart failure (CHF), those experiencing a sudden cardiac death (SCD) had on average a higher washout rate of iodine-123 metaiodobenzylguanidine (MIBG WR) compared with those who survived. Statistically, the cardiac MIBG WR was a powerful predictor of SCD in patients with mild-to-moderate CHF. But how can this best be applied clinically?

The mean (X1) washout rate in those with SCD was 39.9% with a standard deviation (SD1) of 15.2%. For those without SCD, the mean (X2) washout rate was 27.6% with a standard deviation (SD2) of 14.2%. Using this data, we can determine the crossover point below which a patient is more likely than not to fall into the low-risk group (no SCD) and above which a patient is more likely than not to fall into the high-risk group (SCD) (2).

The crossover point (CP) = $(SD1 \cdot X2 + SD2 \cdot X1)/(SD1 + SD2) = 33.5\%$. This CP falls 0.42 SDs above X2 and 0.42 SDs below X1 (i.e., $X2 + 0.42 \cdot SD2 = X1 - 0.42 \cdot SD1$). In normally distributed data, using a *z*-score table, we find that, at best, 34% of the patients will be miscategorized when using the MIBG WR if a fixed threshold value is utilized. If we use a threshold of 27%, as proposed by Ogita et al. (3), then over 50% of the low-risk patients will be miscategorized. Threshold values either above or below the CP will only lead to a miscategorization rate >34%.

In clinical practice, fixed threshold values for continuous data such as the MIBG WR are not rigidly followed. Patients are frequently categorized as "borderline normal" or "borderline abnormal." Are there better ways to make sense of the data so it can be more clinically useful? Simply reporting the means, SDs, and a threshold value does not adequately characterize the data for the clinician caring for an individual patient.

We propose that a more useful way to report continuous variables that impact patient care is to give at least 3 reference values: 1) the point where an individual patient is just as likely as not to belong to group 1 as to group 2; 2) the odds of belonging to group 1 at X1; and 3) the odds of belonging to group 2 at X2. In some situations, additional reference values may be useful. For the MIBG WR data, the CP = 33.5%. This is the point at which the odds are 50/50 in regard to whether the patient is in the high-risk or in the low-risk group. The formula to determine this point is given in the preceding text.

When a patient's MIBG WR is 39.9% or greater, the odds are at least 2.6 to 1 that the patient is in the high-risk group. This is calculated by finding the *z*-score of the absolute value of $(X1 - X2)/SD2$, then dividing 0.5 by the area under the curve to the right of this *z*-score. When a patient's MIBG WR is 27.6% or less, the odds are at least 2.4 to 1 that the patient is in the low-risk group. This is calculated by finding the *z*-score of the absolute value of $(X1 - X2)/SD1$, then dividing 0.5 by the area under the curve to the right of this *z*-score.

This type of numerical summary helps clinicians reasonably apply and explain the MIBG WR to individual patients with stable CHF. When a patient's MIBG WR is around 33%, the test does not help categorize the patient into a low- or high-risk category (a coin flip is just as accurate). However, when the MIBG WR is 27% or less, the odds are greater than 2:1 that the patient is at low risk. When the MIBG WR is 40% or higher, the odds are greater than 2:1 that the patient is at high risk. Basing medical management upon MIBG WR values between 30% and 36% is basically just guessing, and will lead to suboptimal care in a high percentage of patients.

***Thomas F. Heston, MD**
Richard L. Wahl, MD

*Johns Hopkins University
Johns Hopkins Nuclear Medicine
600 North Caroline Street, Suite 3223
Baltimore, Maryland 21287
E-mail: theston1@jhmi.edu

doi:10.1016/j.jacc.2009.02.082

REFERENCES

1. Tamaki S, Hamada T, Okuyama Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. J Am Coll Cardiol 2009;53:426–35.
2. Jacobson NS, Traux P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991;59:12–9.