Rapid Detection of Subclinical Atherosclerosis

Potential Implications for Primary Prevention in LMIC

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An ounce of prevention is worth a pound of cure.

—Benjamin Franklin

This axiom, applied to health, is as true today as it was when it was originally quoted in reference to fire safety. Acute atherothrombotic cardiovascular events such as acute coronary syndromes, ischemic stroke, and sudden death are often (nearly 50% of the time) the first clinical manifestation of occult vascular disease in subjects unaware of existence of pre-symptomatic atherosclerosis. The overall burden of cardiovascular disease worldwide is significant, and nearly two-thirds of it originates from low- and middle-income countries (LMIC) [1,2]. This very high burden of cardiovascular disease in developing nations threatens the economy of underprivileged nations because many victims tend to be young with substantial earning potential. Preventing such first and unheralded acute cardiovascular events is important because adoption of a healthy lifestyle and risk factor control can prevent such events in the asymptomatic population as well as in patients with known cardiovascular disease (primary and secondary prevention) [3,4]. In this regard, identifying seemingly healthy and asymptomatic individuals at potential risk for acute atherothrombotic events in the near term becomes relevant. At-risk individuals can be cost-effectively targeted for lifestyle modification as well as more aggressive long-term interventions including pharmacotherapy (statins, aspirin, etc.), whereas low-risk or not-at-risk individuals can be spared the expense and side effects of aggressive pharmacotherapy, and they can continue to be encouraged to adopt and maintain a healthy lifestyle [5].

The traditional approach to risk assessment is based on various risk scores (Framingham risk score, Reynold risk score, etc.) that tally risk factors associated with cardiovascular events, as defined in various epidemiologic studies. All these indirect methods suffer from the drawback that individual risk assessment is difficult; on one hand, many individuals with such risk factors never develop cardiovascular events, and on the other, a significant number develop cardiovascular events without the traditional risk factors [5,6]. Identification of subclinical atherosclerosis, the underlying basis for atherothrombosis, is an appealing target in this regard because it reflects the cumulative end result of known and unknown risk factors as well as known and unknown risk mitigators. Therefore, subclinical atherosclerosis is likely to more accurately identify high-risk as well as very-low-risk individuals [5,6]. Furthermore, in developing nations such as India where a large population of subjects lives in rural areas with limited access to medical and healthcare information, knowledge of risk factors is limited and obtaining an inventory of risk factors may be logistically more challenging than rapid and early detection of subclinical atherosclerosis would be. Atherosclerosis tends to involve multiple arterial beds in the body with the coronary bed and cerebrovascular bed contributing most to the life-threatening cardiovascular events. Because imaging of 1 bed may predict disease and events related to another vascular bed, carotid imaging with ultrasound and/or coronary imaging, mostly using computed tomography (CT) calcium scores, are the 2 most commonly employed modalities for the detection of subclinical atherosclerosis.

In this issue of *Global Heart,* Singh et al. [7] provide preliminary data from a cross-sectional study that supports the potential feasibility of such an approach in a rural community in Northern India [7]. This study is part of a much larger multinational effort involving mass screening and mass community education for prevention of cardiovascular disease and promotion of cardiovascular health (HAPPY [Heart Attack Prevention Program for You] Study) [8]. The study was conducted in less than a week in January 2012, taking advantage of the fact that nearly 10 million followers of a local spiritual leader congregate in the northern Indian town of Sirsa annually during this time. The investigators used B-mode ultrasound imaging of both carotid arteries to detect carotid plaque (defined as protrusion of 1.5 mm or more) and measured intima-media thickness (IMT) in 771 asymptomatic volunteer subjects (626 men and 145 women) with each test taking an average of 3 min. Rapid imaging was made possible by a semiautomatic system [7]. A simple questionnaire collected some basic demographic information, and no blood tests were required. The imaging was performed by physicians (radiology and cardiology trainees) who had received 4 h of on-site training prior to implementation of the screening program. One or more carotid plaques were detected in nearly 9% of the cohort (10% of men and 4% of women) who were relatively young (mean age of 40 years), but the prevalence clearly increased with increasing age [7]. The average IMT was 0.55 ± 0.13 mm, which also increased with increasing age. The investigators rightly focused on carotid plaque rather than simply an IMT, because several studies have shown improved prognostic ability of plaque versus IMT [9,10]. It is of interest to note that this rural Northern Indian community practices

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a largely healthy lifestyle (vegetarian diet, low prevalence of current smoking, and moderate physical activity). The overall prevalence of carotid plaque (about 9%) was lower than what was recently reported in another cross-sectional study (78%), but the patients included in that study were on an average 28 years older (mean age of 68 years) and the methodology involved a manual sweep and 3-dimensional (3D) ultrasound technology to measure plaque and plaque burden [11]. The 3D ultrasound technique is likely to be more reliable in identifying carotid plaque [11].

The potential advantages of carotid ultrasound to detect subclinical atherosclerosis include: its risk-free nature; relative technical simplicity in completing the assessment with relatively modest training requirements for performance and interpretation of the test; rapid data acquisition; and known association of carotid plaque with coronary atherosclerosis and cardiovascular outcomes, especially when plaque area, plaque volume, or plaque burden are considered [11—14]. Furthermore, serial carotid ultrasound examinations are feasible, and changes in carotid plaque burden may be quantifiable, allowing assessment of changes in plaque burden with time and/or therapy [15].

Although the report by Singh et al. [7] demonstrates the feasibility of rapid screening for carotid plaque, several important questions remain to be answered:

1. Does subclinical atherosclerosis detection by carotid ultrasound ultimately lead to better adoption of and compliance with risk-mitigating interventions and, above all, improved clinical outcome compared with standard risk factor—based assessment and treatment?
2. Does absence of carotid plaque identify a low-risk population that is unlikely to benefit from aggressive risk-mitigating pharmacotherapy? This is particularly important because nearly 30% of subjects without a carotid plaque may have subclinical coronary atherosclerosis as detected by coronary calcium scanning by CT [16]. The improved sensitivity of carotid plaque detection using plaque area/volume measurement with use of 3D ultrasound may further improve sensitivity and specificity of carotid ultrasound to predict coronary atherosclerosis.
3. Could serial carotid ultrasound examinations at intervals identify a larger proportion of subjects with subclinical atherosclerosis who are likely to benefit from aggressive interventions?
4. Can the methodology adopted by Singh et al. [7] in their study be applied in other populations and in other countries?
5. Will this approach be cost-effective compared with population-based widespread low-cost preventive interventions such as a polypill [17] or possibly in the future, a vaccine against atherosclerosis [18]?

Some but not all observational studies have suggested that screening for subclinical atherosclerosis (mostly using coronary CT) may improve the use of risk-mitigating interventions among at-risk subjects, but randomized trials are clearly needed to prove the impact on outcomes [19—21].

Notwithstanding these limitations of the study by Singh et al. [7], the investigators deserve to be congratulated on demonstrating the feasibility of a noninvasive risk-free approach to rapid detection of subclinical carotid atherosclerosis in a rural setting, paving the way for feasibility of initiating intervention based on the identification of subclinical atherosclerosis and beginning to address the many unanswered but important questions outlined here.

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