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FOR DEBATE

Screening for Asymptomatic Carotid Plaques with Ultrasound

GLOBAL BURDEN OF CARDIOVASCULAR DISEASE

Atherosclerotic cardiovascular disease (CVD), especially coronary heart disease (CHD), remains the leading cause of premature death worldwide.[1] Regrettably, CVD killed 17.5 million people in 2012, which accounts for 3 in every 10 deaths. Of these, 7.4 million people died of ischemic heart disease and 6.7 million from stroke.[2] CVD affects both men and women and of all deaths that occur before the age of 75 in Europe, 42% are caused by CVD in women and 38% in men.[1]

The total number of deaths from specific causes does not provide a good metric for informing public health priorities, hence years of life lost (YLL) has been introduced as a measure of premature mortality that takes into account both the frequency of deaths and the age at which death occurs. YLL are calculated from the number of deaths at each age multiplied by a global standard life expectancy for the age at which death occurs.[3] Ischemic heart disease and stroke were among the top three causes of YLL in 2012.[3] In 2012, global life expectancy from birth was 68.1 years for men and 72.7 years for women, which had increased by 6 years since 1990.[3] The incidence of CVD increases sharply with age, and, given the current longevity seen in the developed countries, the number of patients is expected to increase. Despite gaps in our understanding, there is ample evidence to justify intensive public health and individual preventive efforts.[1]

THE PROBLEM WITH TRADITIONAL RISK FACTORS

Risk factors for atherosclerotic CVD are well known (smoking, dyslipidemia, high blood pressure, diabetes)[4] and are used within the traditional risk factor-based approach, such as the Framingham risk scores,[5] to identify high-risk groups. However, although these equations do identify high-risk groups, in the subsequent 10 years, at best, only 40% of the heart attacks and strokes that will occur will be contained in these high-risk groups.[6] The remaining events will occur in the low-risk group, which is very large involving three-quarters of the population.[6] Thus, contrary to expectation, the risk factors causing atherosclerotic CVD are not very useful in identifying the majority of individuals who will develop CVD in the next 10 years.[7–9]

A recent study of risk prediction in 1.8 million population without CVD confirmed that the application of existing CVD risk scores (Framingham, ASSIGN, and QRISK2) may result in considerable misclassification of high-risk status as these risk scores do not predict the presence of high CVD risk well and consistently.[6] Therefore, cardiovascular risk calculated from conventional risk factors (age, gender, raised cholesterol, diabetes, elevated blood pressure, family history, smoking) using the Framingham or PROCAM equations leaves a lot to be desired, mainly because such equations are age-driven. For example, a 40-year-old female who is a heavy smoker, hypercholesterolemic, and hypertensive, has a low 10-year Framingham risk in contrast with a 70-year-old male who has no other risk factors and yet has a much higher 10-year risk because of his age.

Risk may also be higher than indicated by risk estimation charts in asymptomatic individuals with preclinical evidence of atherosclerosis, for example plaque on carotid ultrasonography and in those with moderate to severe chronic kidney disease (glomerular filtration rate [GFR] $<$60 mL/min/1.73 m^2).[1] Individuals with documented asymptomatic carotid plaque on ultrasound, peripheral arterial disease (PAD), diabetes mellitus, and severe chronic kidney disease are at very high risk.[1]

It is currently recommended that asymptomatic men over the age of 40 and women over 50 years or postmenopausal women should undergo risk factor screening including lipid profile.[10] Prevention efforts have been highly promoted in recent years and evidence shows that 50% of the reductions seen in coronary heart disease (CHD) mortality relate to changes in risk factors, and 40% to improved treatments.[1] Data from high-income countries also indicate that falls in mortality from cardiovascular diseases are the main driver of rising life expectancy at age 60 for both men and women.[3] Although women appear to be at lower CVD risk than men, this is misleading as risk is deferred by 10 years rather than avoided.[1] It is well understood that the higher the risk, the greater the benefit from preventive efforts.[1] The absolute reduction in atherosclerotic CVD events is proportional to baseline absolute atherosclerotic CVD risk.[11] The question is how best to identify high-risk groups that will contain the majority of cardiovascular events that will occur subsequently, and how to identify individuals at moderate or high risk in the absence of conventional risk factors.

THE VALUE OF DETECTING SUBCLINICAL ATHEROSCLEROSIS

Early detection of arterial disease in apparently healthy individuals has focused on the peripheral arterial territory and especially on the carotid arteries as they are easily accessible and because atherosclerosis in one arterial

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territory is often associated with involvement of other territories.[12] Ultrasound imaging of the carotid bifurcations is a non-invasive means of assessing subclinical atherosclerosis. Carotid plaques are related to both coronary obstructive disease[13] and the risk of cerebrovascular events.[1]

It has recently been demonstrated that screening with ultrasound is particularly useful in the absence of risk factors.[14] Thus, the detection of subclinical carotid or coronary atherosclerosis improves risk predictions and reclassification compared with conventional risk factors, with comparable results for either modality.[14] In one study, 47% of asymptomatic individuals at low 10-year Framingham risk (<10%) screened with ultrasound had carotid plaques.[15] Such individuals should be reclassified as intermediate (10—20%) or high risk (>20%) according to plaque number and area present. In the CAFES-CAVE study, 10,000 asymptomatic, non-diabetic, normotensive individuals with total cholesterol <5.2 mmol/L had both carotid and common femoral bifurcations scanned with ultrasound and followed-up for 10 years.[16] In the absence of plaques (90% of the population), the average annual event rate was 0.1%. In the presence of at least one plaque, the annual event rate was 5% (mainly myocardial infarction). The annual event rate was 3% if the plaque produced <50% stenosis and 8% in the presence of >50% stenosis. Subsequent studies have substantiated these findings and have demonstrated that the presence of carotid plaques, however small, place an individual in a high-risk group.[13,16—18] In addition, the bigger the plaque as measured by thickness and preferably area, the higher is the risk.[13,18] High cardiovascular mortality in patients with asymptomatic carotid stenosis >50% was consistently reported in recent publications (2006—2014) in which only some patients were on statins.[19—23] In these publications, the average annual mortality was 5—6%. When causes of death were reported, 67% of deaths were from cardiac ischemic events.[24—27]

The above findings indicate that the presence of a carotid plaque, however small, places an asymptomatic individual in a high-risk group (10-year cardiac event rate >20% or annual rate of >2%).

In future three-dimensional ultrasound may provide better characterization of carotid atheroma with the assistance of computer-based software, and thus may prove a more accurate tool in the detection of early atherosclerosis.

SCREENING GUIDELINES: RESOLVING THE CONFUSION

The 2014 update of the 2007 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for carotid artery stenosis recommends against screening for asymptomatic carotid artery stenosis in the general adult population.[28] This recommendation is centered on asymptomatic carotid artery disease producing 60—99% stenosis, which has been traditionally considered as a criterion for carotid surgery. Although the recommendation against screening to identify those with >60% stenosis with the view to offer surgery to non-selected patients is relevant, the statement significantly fails to address asymptomatic carotid stenosis as subclinical atherosclerotic disease which is a marker for all cardiovascular events and could enable better targeting of intensive medical therapy.

The latest ACC/AHA guidelines published in November 2013 recommend that non-diabetic individuals without clinical (i.e. asymptomatic) atherosclerotic cardiovascular disease (ASCVD) and an LDL-C of 70—189 mg/dL (1.8—4.9 mmol/L) should be treated aggressively with statins in addition to other risk factor modifications when the 10-year risk of ASCVD is >7.5% (average annual risk >0.75%).[11] This is because randomized controlled trials (RCTs) have demonstrated that in such individuals the reduction in ASCVD risk by statin therapy occurs regardless of risk factor characteristics in both primary and secondary prevention and outweighs potential harm from side effects. Thus, the high incidence of myocardial infarction and mortality in patients with asymptomatic carotid atherosclerotic plaques as outlined above, and by the latest ACC/AHA guidelines (2013), has resulted in a new concept of the value of screening with ultrasound.

NEW CONCEPT OF SCREENING FOR ASYMPTOMATIC CAROTID ATHEROSCLEROSIS WITH ULTRASOUND

Screening for asymptomatic carotid stenosis (ACS) in the past was based on the belief that it was possible to prevent strokes by operating or stenting the majority of moderate to severe stenotic lesions. This practice, which is a legacy of the ACAS[29] and ACST[30] trials, is now outmoded. This is because recent reviews of cohort studies on the outcomes of patients with ACS given medical intervention alone (including the medical arms of randomized carotid endarterectomy trials) indicate that the average annual risk of ipsilateral stroke has fallen to approximately 1% or less.[31—33] With the current annual stroke risk of ≤1%, carotid endarterectomy or stenting is likely to produce more strokes than it can prevent,[34,35] unless it becomes possible to identify a minority of patients at high risk for ipsilateral stroke[36,37] despite optimal medical therapy.

Screening for the presence of asymptomatic atherosclerotic carotid plaques is a relatively new concept.[38,39] The presence of plaques, however small or large, is a marker of high risk for myocardial infarction and death indicating the need for optimal medical therapy (cessation of smoking, lifestyle changes, adequate control of diabetes, BP control to predefined targets, antiplatelet therapy, and high-intensity statin therapy) according to current guidelines for high-risk individuals. This need is supported by a wealth of compelling evidence. Admittedly this evidence is not from RCT, but it is unlikely that a RCT with a control group receiving suboptimal medical therapy will ever be considered in such high-risk individuals for ethical reasons. In addition, it indicates that such patients who are often considered to be healthy or at low risk need a full cardiac assessment with appropriate management. This is a unique opportunity that may never again occur in their lifetime. The cost-effectiveness of such screening programs should