Assembling Evidence to Justify Prevention of Atherosclerosis Beginning in Youth

Samuel S. Gidding, MD

Atherosclerosis begins in youth when the earliest lesions, fatty streaks, can be identified in the arterial beds of most adolescents. Rapid progression of these early lesions to fibrous plaques occurs in the third and fourth decades of life, with the rate of progression directly associated with the number of cardiovascular risk factors. The presence of atherosclerosis early in life, its relationship at a young age to the major cardiovascular risk factors, and its steady progression toward cardiovascular events later in life have suggested to many that the optimal age to begin atherosclerosis prevention is as young as possible.

However, the various strategies proposed to achieve early prevention remain highly controversial. What is the best age to begin (the range considered in the literature is from conception to young adulthood)? Should efforts be limited to those at the highest risk (eg, patients with familial hypercholesterolemia or youth onset diabetes) or directed toward the entire population? Is there evidence that any such strategies are effective, and, most importantly, what are the legitimate study designs and end points to establish that evidence? Are randomized trials the only strategy to establish that evidence base, and are the only appropriate endpoints prevention of cardiovascular events, or is the demonstration of the prevention of atherosclerosis sufficient?

Certain to be cited as support for every possible stance in the youth prevention debate is the paper by Juonala et al in this issue of Circulation, in which results from 4 different longitudinal studies from the United States, Finland, and Australia are pooled to demonstrate the relationship among risk factors measured in youth and carotid intima-media thickness (IMT) measured in young adulthood. Because atherosclerotic fibrous plaques are raised lesions, carotid artery ultrasound has been used to measure IMT as a surrogate measure for the detection of atherosclerosis. Despite significant limitations (only vessel diameter is measured, and the measurements are of tiny diameters, the predictors of carotid atherosclerosis are not exactly identical with coronary atherosclerosis, and carotid atherosclerosis probably develops later than coronary atherosclerosis), higher carotid IMT in adults has been consistently associated with future cardiovascular morbidity in adults. By inference, if risk factors present in childhood predict higher IMT in young adults, they must also be implicated in future myocardial infarction, stroke, and other hard cardiovascular outcomes.

The key findings of the study by Juonala et al are (1) high levels of specific cardiovascular risk factors relative to the population studied and measured in youth (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure, body mass index, and perhaps triglycerides) are highly predictive of having higher carotid IMT as an adult, (2) the more of these risk factors one has the higher the likelihood of having high IMT (Table 2 presents the odds for having a single risk factor), (3) the age at which this effect becomes statistically significant is 9 years, and (4) with minor exceptions, these results are consistent across all 4 cohorts. Most important for youth prevention today is an extrapolation of these findings to the contemporary obesity epidemic; a 9-year-old obese child with 2 other risk factors would be twice as likely as a child with no cardiovascular risk factors to have a carotid IMT measurement in the top decile of the young adult distribution.

The most unambiguous interpretation of these findings is support for a population-wide approach to cardiovascular risk reduction beginning in youth. These studies were conducted around the world, in whites and blacks, and in generally healthy children selected from the general community. Without strategies (particularly for obesity prevention) that can be implemented population-wide, the limitation of atherosclerosis development cannot be achieved.

A second contribution of this study is the identification of an age, 9 years, at which the presence of a cardiovascular risk factor has definite implications for future something (disease if you believe in subclinical atherosclerosis as an end point, or surrogate if you do not). The rationale for screening fasting lipids in late childhood or early adolescence is supported by these data, as is caution in assuming that elevated levels of cardiovascular risk factors obtained earlier in childhood imply a heart attack is just over the horizon. It is important to recognize that these data do not preclude the noninvasive assessment of body mass index and blood pressure in younger children as a preventive strategy to limit the worsening of these traits, the screening of children at high risk for genetic defects in lipid metabolism, or the management of cardiovascular risk in other high-risk situations such as end-stage renal disease or type 1 diabetes mellitus.

How strong is the evidence in this article for making recommendations concerning youth prevention? Consistency

© 2010 American Heart Association, Inc. Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.110.992123
is the article’s most important virtue. There is internal consistency in the findings across the 4 component studies conducted around the world and there is external consistency with studies of atherosclerosis in young adults, basic science studies of the relationship of risk factors to atherosclerosis, and epidemiological findings from other populations. The methodology of the 4 component studies is strong, so despite differences in protocol, the results are likely reproducible.

Missing from this study are 3 critical evidence assessments: calibration of the severity of the problem, information on other major cardiovascular risk factors that might influence results (tobacco use and diabetes), and an assessment of associated traits in these populations that either improve or worsen risk. Regardless of the cardiovascular disease rate, high or low, in a population, it is likely that those at risk extremes will have higher IMT than those not at the extremes. What is missing is knowledge of a threshold level of IMT for which an event can be considered imminent. The investigators have compensated for this in 2 ways: (1) by repeating analyses using accepted thresholds for cardiovascular risk in children instead of quintiles of the population distribution and showing similar findings, and (2) (indirectly) by conducting the studies in countries with high cardiovascular disease rates. The absence of data on tobacco use and diabetes most likely lowers the odds ratios observed in this study as some of those without dyslipidemia, hypertension, or obesity would use tobacco or develop type 1 diabetes. With regard to the role of change in risk over time, our group has conducted studies in young cohorts, evaluating both baseline risk and change in risk over time, which an event can be considered imminent. The investigation of risk factors to atherosclerosis, with studies of atherosclerosis in young adults, basic science research. Studies have already shown that health behaviors such as the acquisition of obesity, low physical fitness, and tobacco use are associated with worsening of risk.

Because clinical trials of risk intervention in youth with cardiovascular outcomes measured 5 to 6 decades later will never be conducted because longitudinal studies such as those included in the work of Juonala et al are no longer being performed, is the evidence in this article as good as it’s going to get? And if so, what have we learned? Perhaps the most important lesson is indirect. A consistent finding across all subclinical atherosclerosis studies conducted in any age group is that the absence of cardiovascular risk factors is associated with low likelihood of subclinical atherosclerosis. Thus, the traits that keep risk factors low, that is, things that healthy people do to maintain the low-risk state, can be firmly advocated and also be the subject of future prevention research. Studies have already shown that health behaviors such as the acquisition of obesity, low physical fitness, and tobacco use are associated with worsening of risk.11–13

What remains unknown is how to select those individuals who would most benefit from more aggressive, pharmacological intervention to lower risk. For this, clinical trials in high-risk individuals such as those with familial hypercholesterolemia, diabetes mellitus, severe hypertension, and other multiple risk states will be needed. And to conduct these trials, the field will have to decide if the only appropriate end point for studies conducted in youth is prevention of hard events or if evaluations of subclinical atherosclerosis or other measures of target organ injury are sufficient.

Disclosures

None.

References


Key Words: Editorials · hypertension (high blood pressure) · lipids · pediatrics · prevention · risk factors
Assembling Evidence to Justify Prevention of Atherosclerosis Beginning in Youth
Samuel S. Gidding

Circulation. 2010;122:2493-2494; originally published online November 29, 2010;
doi: 10.1161/CIRCULATIONAHA.110.992123
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/122/24/2493

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/