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Long-term Effects of Carotid Screening on Patient Outcomes and Behaviors

There have been conflicting reports regarding the effects of carotid ultrasonographic screening (CUS) on health-related behaviors¹⁻³; however, long-term studies have not evaluated the effects of CUS on clinical outcomes.⁴ This study's objectives were to determine if patients with advanced subclinical atherosclerosis (AdvAthero) on CUS are more likely to achieve guideline-based risk factor goals and improve their long-term cardiovascular disease (CVD) health-related behaviors.

Methods. This study was approved by our institutional review board. Potential subjects were 40- to 70-year-old patients with 1 or more risk factor and no history of CVD, who were referred by their physician to the University of Wisconsin Vascular Health Screening Program for CUS from January 2002 through December 2006. We performed CUS using the carotid intima-media thickness (CIMT) protocol from the Atherosclerosis Risk in Communities Study.⁵ AdvAthero was defined as the presence of CIMT greater than 75th percentile for age, sex, and race, or carotid plaque presence.^{4,5} All subjects had a primary care provider in the University of Wisconsin Health medical practice and insurance coverage for CUS. Qualifying patients were invited to participate by mail. To reduce selection bias, a waiver of consent for electronic medical record review was obtained for subjects who could not be contacted.

A patient questionnaire evaluated health-related behaviors and adherence to lifestyle and pharmacotherapy recommendations. The electronic medical record was re-

viewed for achievement of low-density lipoprotein cholesterol (LDL-C)⁶ and systolic blood pressure (SBP)⁷ goals. Multivariable logistic regression models evaluated predictors of correct recall of CUS results and recommendations and achievement of LDL-C and SBP goals. For each outcome, a multivariable model was created that included age, sex, and presence of AdvAthero. Baseline variables were added to each model, including LDL-C level, high-density lipoprotein cholesterol level, SBP, Framingham Risk Score, family history of premature CVD, body mass index, hypertension history, dyslipidemia history, educational level, and length of follow-up.

Results. Of 1165 patients who had CUS examinations, 602 met inclusion criteria and were invited to participate; only 73 declined. Of the 529 subjects (**Table**), electronic medical records were abstracted for 100% and questionnaires were returned by 59.6%. AdvAthero was identified in 58.6%.

One year after CUS, LDL-C goal achievement increased from 62.1% to 84.1% ($P < .001$) in all subjects. Among subjects with AdvAthero, only 61.2% were at the LDL-C goal at baseline, but 86.7% were at goal 1 year after CUS ($P < .001$). Similarly, among subjects without AdvAthero, 63.2% were at the LDL-C goal at baseline, whereas 80.2% were at goal after CUS ($P < .001$). The presence of AdvAthero (odds ratio [OR], 2.15 [95% confidence interval {CI}, 1.38-3.34]; $P < .001$), but not baseline LDL-C level ($P = .99$), independently predicted prescription of lipid-lowering medication after CUS, but the interaction between prescription of lipid-lowering therapy and presence of AdvAthero on achieving the LDL-C goal was not significant (P value for interaction, .10). Thus, having AdvAthero on CUS did not influence the use of lipid-lowering therapy to achieve LDL-C goals.

One year after CUS, subjects with AdvAthero had a lower mean LDL-C level ($\Delta = 12$ mg/dL; $P < .001$) compared with subjects with normal scan results; however, 32.7% of subjects that started a lipid-lowering medication after CUS did not have AdvAthero. There was no significant change in SBP. AdvAthero ($P = .81$) did not predict SBP goal achievement or prescription of antihypertensives ($P = .20$). AdvAthero predicted prescription of aspirin (OR, 2.25 [95% CI, 1.43-3.54]; $P < .001$).

Survey follow-up was a mean (SD) 55.6 (19.1) months after CUS. AdvAthero presence did not increase subjects' perceived risk of current ($P = .15$) or future ($P = .21$) CVD. Subjects accurately recalled 83.0% of prevention recommendations; however, the AdvAthero presence only modestly predicted correct recall of CUS results (OR, 3.20 [95% CI, 0.01-2.31]; $P = .047$). With longer follow-up after CUS, subjects were less likely to remember their results ($P = .01$), or post-CUS dietary ($P = .005$) and exercise ($P = .008$) recommendations. AdvAthero did not predict changes in diet, exercise frequency, or long-term health-related behaviors.

Comment. To our knowledge, this is the first study to evaluate long-term clinical outcomes after patients undergo CUS for measurement of CIMT and carotid plaque

Table. Baseline Characteristics for 529 Patients Who Underwent Carotid Ultrasonographic Screening for Whom Electronic Medical Records Were Abstracted

Characteristic	Value
Age, mean (SD) [range], y	53.7 (6.81) [33-73]
Female, %	43.3
Framingham risk score, mean (SD) [range], %/10 y	5.5 (4.78) [1-25]
History of hypertension, %	37.4
On antihypertensive medication, %	35.3
Systolic blood pressure, mean (SD) [range], mm Hg	124.0 (15.2) [80-177]
Diastolic blood pressure, mean (SD) [range], mm Hg	75.0 (9.02) [56-108]
History of dyslipidemia, %	52.2
Lipid-lowering medication use, %	42.0
Total cholesterol, mean (SD) [range], mg/dL	201.6 (42.98) [101-392]
Triglycerides, mean (SD) [range], mg/dL	133.9 (187.3) [21-2761]
High-density lipoprotein cholesterol, mean (SD) [range], mg/dL	56.3 (16.69) [23-115]
Low-density lipoprotein cholesterol, mean (SD) [range], mg/dL	119.9 (34.9) [41-223]
History of diabetes mellitus, %	5.5
Receiving aspirin therapy, %	25.3
Cigarette use in the past year, %	7.6
Family history of premature CVD, %	51.8
BMI, mean (SD) [range]	27.6 (5.41) [17-52]
Screening referral source, %	100.0
Internal medicine or family practice	95.8
General cardiology	4.2
Composite common carotid artery CIMT, mean (SD) [range], mm	0.784 (0.184) [0.420-1.688]
CIMT >75th percentile, %	58.4
Carotid plaque present, %	43.7
Presence of advanced atherosclerosis, %	58.6
Carotid plaque and increased CIMT, %	21.4

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIMT, carotid intima-media thickness; CVD, cardiovascular disease.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

detection. Major limitations include retrospective electronic medical record abstraction, use of questionnaires that relied on recall and self-report, and referral bias. However, all subjects were part of an academic health network and had medical insurance coverage that paid for the test. AdvAthero did not predict LDL-C goal achievement. Nearly one-third of subjects prescribed lipid-lowering therapy after CUS did not have AdvAthero. This suggests that achievement of LDL-C goals after CUS was not primarily because of abnormal screening results. It may be that physicians who ordered the test were predisposed to prescribe lipid-lowering medication, regardless of the results, and LDL-C improvements were from the screening and management process and not the results. Over time, CVD risk perception among those with AdvAthero decreased. Despite intensive counseling about their CUS results and recommendations, our subjects had inappropriate risk perception, decay in recall over time, and poor adoption of lifestyle changes. These observations support the importance of recurring CVD risk education and counseling and emphasize the lack of long-term effectiveness of 1-time interventions, even if they are as powerful as arterial imaging.⁸

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HEALTH CARE REFORM

The FDA Drug Safety Surveillance Program: Adverse Event Reporting Trends

The Adverse Event Reporting System (AERS) of the US Food and Drug Association (FDA) is the largest repository of passively reported adverse drug events in the world.¹ Approximately one-half million reports are received by the FDA annually. Designed as a safety net, allowing the FDA to monitor all marketed drugs and quickly detect serious safety problems, AERS reports have served as the basis for numerous regulatory actions.² In an 8-year period (1998-2005), the number of serious event reports increased 2.6-fold and reports of deaths increased 2.7-fold.³ Given the dramatic increase in adverse event reporting following the last major revision of the AERS database in 1997, we sought to characterize current reporting patterns.

Methods. Adverse event reports received by the FDA from January 1, 2000, through December 31, 2009, were identified in the public release of AERS. Each report is classified by report type. Reports that come through the product sponsors are either expedited (serious and unexpected or unlabeled events), which must be reported within 15 days of learning of the event, or periodic (all other serious events). The frequency of submitting periodic summary reports to the FDA and the need to supply individual event reports varies by the time since approval and the existence of a report waiver.⁴ Direct reports come to the FDA from health care professionals and the public through their MedWatch program.

The absolute minimum information that constitutes a report is an identifiable reporter, a unique patient, an adverse event, and a drug that is suspected by the reporter to have caused or contributed to the event. Adverse events are classified using the Medical Dictionary for Regulatory Activities (MedDRA).⁵ Possible outcomes include death; life-threatening condition; hospitalization (initial or prolonged); required intervention to prevent harm, disability, or permanent damage; and congenital anomaly.

We used QSCAN-FDA (DrugLogic, Reston, Virginia) to identify the cohort from the publically released AERS data and conduct analyses. Original and follow-up reports of the same event were consolidated. Rates of reporting were calculated by dividing the total reports received annually by the FDA⁶ by the estimated number of visits to physician offices during which drugs were prescribed, ordered, or provided (drug visits) in the United States from the National Ambulatory Medical Care Survey.^{7,8}

Results. One-half (2.2 million [54.8%]) of the reports in the AERS database, from its inception in 1969 through the end of 2009, were received in just the past 10 years. This represents a 1.65-fold increase from the prior decade. Report volume increased from 2000 to 2010 at a mean annual rate of 11.3%. Report rates, as a proportion of drug visits at physician offices, increased from 4.90 reports per 10 000 visits in 2000 to 6.83 reports per 10 000 visits in 2005.

There was a slight preponderance of adverse event reports for women (55.3%), which is consistent with the distribution of drug visits by sex (58.5% female in 2005). In AERS, one-third (32.8%) of reports were among adults aged 30 to 64 years, and an even higher percentage (37.4%) were missing age. Just 4.4% of reports were among patients younger than 18 years and 20.1% among patients 65 years and older. Among 1 635 014 reports in which an outcome was reported, patients were hospitalized in 687 442 (42.0%), and in 247 171 reports (15.1%) the patient died. There remain significant limitations in the completeness and quality of reports. Reports missing data on age (37.4%) and sex (7.5%) have implications in the interpretation of studies limited to a particular subset and these key variables in the identification of duplicate reports. While not technically considered missing, the outcome of "other" was checked in 48% of reports.

Recombinant DNA products predominated among the most frequently reported suspect brand name drugs. The tumor necrosis factor (TNF) blockers Enbrel (etanercept; Immunex Corp, Seattle, Washington; approved No-