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34TH BETHESDA CONFERENCE

Executive Summary—Can Atherosclerosis Imaging Techniques Improve the Detection of Patients at Risk for Ischemic Heart Disease?

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This document presents the summary findings from the 34th Bethesda Conference: "Can Atherosclerosis Imaging Techniques Improve the Detection of Patients at Risk for Ischemic Heart Disease?" This conference, comprised of five writing groups, began the process of formulating report outlines and documents in January 2002. The conference, held October 7, 2002, at the Heart House in Bethesda, Maryland, allowed for open discussion, constructive commentary, and the formulation of summary comments resulting in the documents presented in this report. The purpose of Bethesda Conference 34 (BC 34) was to review the current status and controversies within the integration of atherosclerosis imaging into clinical cardiovascular medicine. Each Task Force was also specifically charged with developing recommendations on "Future Directions" for the field of atherosclerosis imaging, as appropriate within the scope of issues they considered.

Although it is recognized that atherosclerosis imaging, including many different emerging technologies, may enhance the detection and treatment of patients at risk for coronary heart disease (CHD), much remains unknown about these modalities despite the fact that many are rapidly moving into broad clinical use. Further consideration of these tests as clinical tools extends prior efforts such as the Prevention V Conference of the American Heart Association, and the National Cholesterol Education Program, Adult Treatment Panel III guidelines. The latter treatment guidelines focused particular attention on the relevance of diagnosing subclinical atherosclerosis for altering lipid treatment goals by designating that aortic, peripheral, and carotid artery disease were considered to represent "Coronary Heart Disease Equivalents" because the level of CHD risk and CHD event rates associated with these conditions is approximately equivalent to the level of risk seen in stable CHD. Thus, screening for atherosclerosis in other vascular regions has been considered for CHD risk evaluation.

The BC 34 brought together the multidisciplinary expertise of pathologists, epidemiologists, imaging experts, experts in disease detection and treatment, clinical trialists, and outcomes researchers to work together for the common goal of crystallizing the current science, addressing the many unanswered questions on the appropriate clinical use of the available imaging modalities, and envisioning the future of this discipline. For the purpose of this Bethesda Conference, we adhered to the use of the term "coronary heart disease" (CHD) defined as cardiac events or symptoms related to myocardial ischemia and/or injury due, in the vast majority of cases, to atherosclerosis. Such events include unstable angina, myocardial infarction (MI), and sudden death due to ischemic heart disease. It is important to recognize that coronary atherosclerosis, ischemia, and events exist as a continuum. The former need not necessarily lead to the latter, while the latter is virtually always preceded by the *presence* of the former. Thus, the challenge is not only to "detect" coronary atherosclerosis, but also to "predict" which individuals, in whom coronary atherosclerosis is detected, will progress to develop events. Finally, the use of global risk scores, such as the Framingham Risk Score, was considered as the most appropriate initial assessment of all patients undergoing coronary risk screening. Additional testing, such as imaging, must provide incremental risk-prediction information to the Framingham Risk Score. A modification to this subgrouping has recently been suggested to improve CHD risk assessment in asymptomatic people. This approach considers a less than 0.6% per year (less than 6% over 10 years) risk for coronary events as "low-risk," 0.6% to 2.0% per year (6% to 20% over 10 years) risk is termed "intermediate risk," and individuals with greater than or equal to 2.0% per year (greater than or equal to 20% over 10 years) risk are "high-risk." We have adopted these risk groupings for this Bethesda Conference.

TASK FORCE 1: IDENTIFICATION OF CORONARY HEART DISEASE RISK: IS THERE A DETECTION GAP?

Task Force 1 addressed the rationale for new methods to detect cardiovascular risk based upon limitations of current clinical screening methods within the context of primary CHD prevention. Current CHD risk-screening tools are imperfect and imperfectly applied, thus potential opportunities exist with atherosclerosis imaging for CHD risk assessment refinement. The "detection gap" may be defined as the difference between CHD cases or events currently detected and the total burden of disease or events among the population. Whether this gap may be due to current testing

not optimally detecting disease, or due to testing not being appropriately applied, is incompletely understood. Although agreed that a detection gap in CHD prognosis exists, the precise size of this gap, and thus the potential for atherosclerosis imaging to reduce cardiovascular morbidity and mortality through enhanced risk screening, is unknown, but may be substantial. The application of atherosclerosis imaging to intermediate-risk populations is theoretically "optimal" based upon the Bayes' theorem. This assumption, and the potential extension of these tests to both low- and high-risk populations, is in need of a greater body of supporting evidence in which incremental management and prognostic impact is demonstrated. Proper calibration of the results of atherosclerosis imaging modalities is necessary to avoid systematic under- or overdetection of patients as being at heightened CHD risk.

In concert with efforts to improve the accuracy of office-based CHD risk detection, a need exists for more widespread clinical use of CHD risk-scoring algorithms. Recognition of such efforts as valid and valuable clinical assessments in the form of specific reimbursement codes would further the penetrance of these tools into clinical practice. The community of cardiologists must champion CHD prevention, beginning by fully translating existing data on effective risk interventions into practice.

TASK FORCE 2: WHAT IS THE PATHOLOGIC BASIS FOR NEW ATHEROSCLEROSIS IMAGING TECHNIQUES?

Task Force 2 addressed the anatomic targets within atherosclerosis that form the basis for imaging modalities, including the relationship between plaque burden and the pathology of vulnerable atherosclerosis. Plaque burden is generally substantial in the majority of patients with acute coronary events. Ultimately, imaging individual plaque components might achieve importance in detecting both lesions and individual patients prone to plaque rupture. However, an incremental value for imaging atherosclerotic components (above and beyond assessing plaque burden) in predicting acute coronary events requires validation. A particularly rich area for exploration of vulnerable plaque detection is in younger individuals who often have relatively little plaque burden. In the future, the development of a "vulnerable plaque scoring system" could be feasible, including the characteristics of: 1) fibrous-cap thickness, 2) necrotic core size (both percent of cross-sectional plaque area and length), 3) degree of macrophage infiltration, and 4) compensatory remodeling. In comparison, coronary calcification principally reflects overall plaque burden, although it has pathology relationships to healed plaque ruptures and compensatory remodeling. Thus, indirectly, calcium measurements may reflect underlying plaque biology and propensity for future plaque rupture events.

TASK FORCE 3: WHAT IS THE SPECTRUM OF CURRENT AND EMERGING TECHNIQUES FOR THE NONINVASIVE MEASUREMENT OF ATHEROSCLEROSIS?

Task Force 3 reviewed the existing and emerging *noninvasive* technologies for atherosclerosis imaging. The imaging modalities considered within the document include carotid ultrasound for assessment of intima-media thickness (IMT), coronary calcium scanning, cardiovascular magnetic resonance imaging (CMR) for atherosclerosis, brachial artery reactivity testing, and the ankle-brachial index (ABI). Development of atherosclerosis imaging tests must be viewed as a continuum from device validation, diagnostic accuracy, prognostic accuracy, to demonstrating an independent and incremental impact on CHD risk management and CHD outcomes. The currently available atherosclerosis imaging modalities are in different phases of development. The modalities vary greatly in important parameters such as their availability, their reproducibility, and their costs. In general, the available data (although no data are available for CMR) indicate that abnormal values on atherosclerosis imaging have been associated with a three-fold or greater risk of a future CHD event. Although the supporting data for ABI and IMT most clearly show an independent prognostic impact of the test results, these technologies are also most static, with little room for further technical development. None of the available tests have yet been demonstrated to impact CHD management or outcomes. The diagnostic and prognostic effectiveness of more mature modalities as CHD risk screening tools cannot be generalized to newer modalities (e.g., plaque burden testing with CMR must be independently validated for CHD prognosis). Among all modalities, a need exists to move toward broader standardization of imaging modalities to ensure external validity of published reports, and enable cross-study comparisons. Because atherosclerosis imaging test results can be considered continuous, improved definition of "positive" versus "negative" results is warranted. There is a need for cross-modality prospective comparisons recognizing that, among important subgroups (e.g., gender and race), modalities may perform differently in detecting CHD prognosis.

TASK FORCE 4: HOW DO WE SELECT PATIENTS FOR ATHEROSCLEROSIS IMAGING?

Task Force 4 addressed the application of atherosclerosis imaging tests to patients, including the selection of patients within categories of clinically predicted heart disease risk, matching patients to specific imaging modalities, and management of the results. A valuable screening test should: a) identify both high- and low-risk groups (e.g., a low proportion of false negative and false positives) more accurately; b) enhance the identification of high-risk individuals, c) result in a favorable impact on disease outcomes; d) be relatively

free of risk; e) be cost-effective when compared to the current screening modalities; and f) educate the public concerning atherosclerosis and vascular disease risk. Selecting intermediate-risk patients for screening with plaque-burden assessment has potential theoretical advantages within a Bayesian approach to screening. More study is needed in low- and high-risk patients. Once a modality is shown to incrementally *and to a clinically important extent* predict cardiovascular risk, then effectiveness studies are appropriate to establish threshold values (indicating a shift to increased intensity of risk-factor treatments) and to determine their impact on management and CHD outcomes. Until such effectiveness studies are complete, the appropriateness of shifting individual patients to more intense risk-reduction therapies based on atherosclerosis imaging modalities requires clinical judgment.

Limitations of modalities within specific patient populations are beginning to emerge. Currently, coronary calcium detection and the ABI, abnormal primarily in the setting of advanced atherosclerosis, have limited application to young patients. A specific ethnic-based imaging limitation appears to be present for coronary calcium, particularly in African-Americans. The outcome of efforts to better detect CHD risk is ultimately dependent upon the effectiveness of the risk-reduction therapies that ensue. A policy of self-referral to atherosclerosis imaging tests remains premature and should be the subject of formal effectiveness study prior to widespread adoption of this practice.

TASK FORCE 5: IS ATHEROSCLEROSIS IMAGING COST-EFFECTIVE?

Task Force 5 addressed the role of cost-effectiveness considerations in atherosclerosis imaging. Cost-effectiveness data are increasingly being applied to the evaluation of imaging technology, and optimally it should be considered in parallel with the development of imaging modalities. The aim of cost-effectiveness analysis is to guide health care payers and regulators in the evaluation of new therapies and technology for the setting of standards for use, reimbursement, and for approving use. A requisite amount of high-quality clinical effectiveness data is necessary for the determination of an added economic benefit. Thus, an important need exists for high-quality, long-term outcome data to be developed for all of the newer imaging modalities so as to inform potential models of cost-effectiveness. Standards for defining cost-effectiveness include the amount of resources or costs required to achieve a given clinical benefit. Such standards, developed from therapeutic intervention data and models, may not be directly applicable to the use and application of imaging modalities to detect subclinical atherosclerosis. As such, professional societies and stakeholder government agencies as well as senior leaders in health care economic analysis should convene to create and define standards for evaluating imaging procedures with regard to costs and outcomes. Current clinical and economic effectiveness analysis are hampered by a lack of clinical algorithms with noted inputs for serial testing, post-test treatment strategies, resultant proportional risk reduction, as well as induced resource consumption levels with a variety of atherosclerosis imaging modalities. Future research in the area of atherosclerosis imaging must provide more definitive data regarding the links between the initial imaging procedure and results and subsequent downstream testing and treatment effectiveness. Substantial additional data are needed for virtually all currently available and developing modalities of atherosclerosis imaging prior to the support of any techniques being considered as cost-effective.

CALL FOR CLINICAL TRIALS

Observational data are key to improving management of cardiovascular disease, but diagnostic imaging utility should also be tested with randomized clinical trials. Undertaking an experimental design, including blinding the involved patients and their physicians, would allow rigorous testing of the utility of the new procedures. Appropriate exclusion criteria within such an experimental design would be necessary to address concerns over withholding information for individuals with very "abnormal" test results. Alternatively, rigorous analysis of testing strategies in this situation might be undertaken by randomizing patients to testing or no testing, then prospectively assessing outcomes. Important design elements include demonstrating incremental diagnostic and management impact beyond that achieved with global risk scoring algorithms, and inclusion of emerging markers of CHD risk. Such studies would also serve the valuable purpose of determining appropriate thresholds for the results of atherosclerosis imaging and providing input data for cost-effectiveness models.

Finally, an important concept worthy of testing is the value of a "negative" test—for example, toward reducing the post-test probability of disease and validating therapeutic avoidance. As with all clinical trials, both the presence and magnitude of clinically relevant results are important interpretive considerations. Funding support for such initiatives from both the private and public sector is strongly encouraged.