FEBRUARY 2002 volume VII, issue 2

CARDIOLOGY Rounds™

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Identifying Patients for High Risk Primary Prevention

The Role of Electron Beam CT Calcium Scoring

TEJ SHETH, MD, ROBERT J. CHISHOLM, MD.

Electron beam computed tomography (EBCT) offers a non-invasive, validated assessment of the extent of atherosclerosis in the coronary tree. Elevated calcium scores identify patients at high risk for cardiac events, although the incremental prognostic value of EBCT over traditional cardiovascular risk factors remains to be established. If EBCT can improve on currently available risk stratification methods, it may allow for more effective identification of patients most likely to experience an adverse outcome. Once identified, these patients may then become the focus of the growing number of therapies available for high-risk primary prevention.

Cardiologists, internists, and family physicians routinely evaluate patients who are potentially at risk for cardiovascular disease. The use of EBCT to assess coronary calcium is growing in popularity. Although more widely available in the United States than in Canada, patients with questions about EBCT scans or who have undergone scanning are increasingly common. Consider the following patients who presented to cardiologists at St. Michael's Hospital in the past few months.

- Mr. C. is a 52-year-old, asymptomatic male smoker with hypertension (BP of 150/90 mm Hg), hypercholesterolemia (total cholesterol of 6.00 mmol/L), HDL of 0.95 mmol/L, and a normal glucose. He is concerned about his risk of CAD and wants advice about the value of an EBCT scan.
- Mr. S. is a 51-year-old, asymptomatic male with hypertension (BP of 165/105 mm Hg), mild hypercholesterolemia (total cholesterol of 4.95 mmol/L), and a positive family history. He is a non-smoker and does not have diabetes. He underwent EBCT calcium scoring at a facility in the United States and presents to your office with a report showing that his calcium score was 294.

This issue of *Cardiology Rounds* describes how EBCT calcium scoring is performed, reviews the data supporting the EBCT score as a risk predictor in asymptomatic patients, and discusses how a calcium score might contribute to an estimate of cardiac risk and patient management.

High-risk primary prevention

Patients who have sustained a cardiac event are clearly in the highest risk group for future myocardial infarction (MI) or cardiac death. In this group of patients it is now clear that secondary prevention can achieve significant success in reducing the risk of recurrent coronary events. Multiple clinical trials have established the efficacy of aspirin, beta-blockers, ACE inhibitors, and cholesterol therapy with statins in this setting.

There is also increasing evidence that in high-risk patients without prior clinical cardiovascular events, many of these therapies also produce clinically important reductions in risk.[1,2] Therefore, recent major prevention guidelines in Canada and the United States have suggested that high-risk individuals should have all CVD risk factors treated with targets identical to those

St. Michael's Hospital
30 Bond St.,
Room 9-004, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5330

The opinions expressed are only those of the Divisional members. This publication is made possible through unrestricted grants.

in secondary prevention. Since the annualized risk of cardiac events in the secondary prevention setting is 2%/year, this has been proposed as a target risk level to identify patients for high-risk primary prevention.[3]

The most common method currently used for estimating risk is the Framingham Heart Risk Equation, based on a long-term follow-up of over 5000 patients in the Framingham study. This equation incorporates age, sex, cholesterol level, smoking, diabetes, and blood pressure level to generate an estimate of CHD risk over the next 10 years.[4] The Framingham equation has been in use for many years and now effort is directed towards identifying novel methods of risk prediction that may improve on the Framingham equation. These have included new laboratory markers of risk and methods to detect subclinical atherosclerosis.[5]

Atherosclerosis as a cardiovascular risk marker

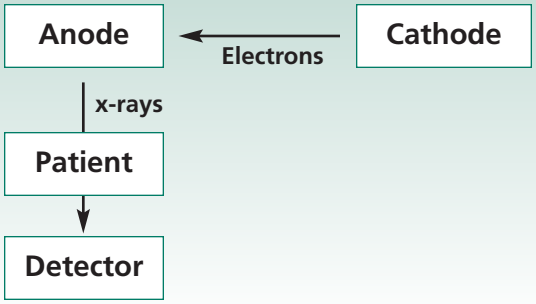
In patients with coronary artery disease, the extent of atherosclerosis is highly predictive of long-term outcome. For example, in the Coronary Artery Surgery Study (CASS), among patients not undergoing cardiac surgery, those with 3-vessel CAD had a 50% mortality at 10 years compared to 10% for those with single-vessel disease.[6] From a pathophysiologic perspective, the development of atherosclerotic lesions represents the final common pathway of the various risk factors for coronary artery disease. Current techniques for the detection of atherosclerosis, such as coronary angiography, exercise testing, and perfusion imaging are widely used in the work-up of patients with cardiac symptoms. For asymptomatic patients, several additional non-invasive methods have been proposed for the assessment of atherosclerosis, including the ankle-brachial index, carotid ultrasound, magnetic resonance imaging of carotid plaque, and computed tomography assessment of coronary calcification.

Coronary artery calcification is a good surrogate for atherosclerosis.[7] Indeed, coronary artery calcification is found exclusively in atherosclerotic arteries and is absent in the normal vessel wall. Coronary calcification occurs in small amounts in the early lesions of atherosclerosis that appear in the second and third decades of life, but it is found more frequently in advanced lesions and in older age. Calcification appears to be an organized, regulated process similar to bone formation, involving the deposition of hydroxyapatite in diseased coronary arteries.

Detecting coronary calcium

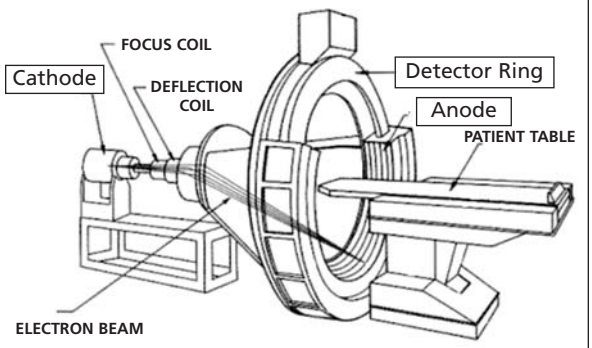
X-ray-based imaging methods are best suited for assessing calcium because of the high attenuation of the x-ray beam by calcium. In order to understand the different computed tomography (CT) technology available, it is helpful to briefly describe a basic X-ray tube. Figure 1 is a simplified schematic of an x-ray tube. In an x-ray tube, electrons travel from a cathode to strike an anode and cause the emission of x-rays. The x-rays are then transmitted through the patient and detected on the other side. In conventional CT, the x-ray tube and detector are mounted on a gantry opposite each other and both rotate around the patient. Data acquired from a single rotation about the patient are processed by computer to generate an axial image. The time for a single gantry rotation and hence, single slice acquisition is approximately 500ms. With conventional CT, cardiac imaging is challenging because both cardiac and respiratory motion blur the images. In order to control motion artifacts, the heart needs to be imaged in diastole when cardiac motion is minimized with scan acquisition times closer to 100 ms. Recently released multi-detector CT scanners have 8 or 16 detectors and gantry rotations of 250 ms or less. These are likely to very effectively image the heart and assess calcification, although validation of this technique is still ongoing.

Figure 1: Schematic representation of an x-ray tube. Electrons travel from a cathode to strike an anode and cause the emission of x-rays. The x-rays are then transmitted through the patient and detected on the other side.



The EBCT scanner is fundamentally different from the scanner used in conventional CT since it is designed for very rapid scanning. In EBCT, the cathode is separated from the anode which is comprised of a 270° ring around the patient (Figure 2). Both are stationary. Rotation is accomplished by steering the beam of electrons traveling from cathode to anode electromagnetically. Opposed stationary detectors detect the x-rays transmitted through the patient. Because there are no physically moving parts and no gantry rotation is required, EBCT is a very fast-imaging method, capable of a single slice acquisition in 100ms. In the typical EBCT protocol, the heart is imaged in 40 contiguous slices, each slice 3 mm thick. All images are acquired over a single-breath-hold with EKG gating. The presence of calcium is identified manually on each slice based on the high attenuation (bright signal) it creates. The lesions are scored and the scores are summed over all the slices using a widely accepted methodology.[8] Figure 3 shows an example of a single slice from an EBCT

Figure 2: Electron-beam CT. The cathode is at one end of the machine and the anode is comprised of a 270° ring around the patient. Rotation is accomplished by steering the beam of electrons traveling from cathode to anode electromagnetically. Opposed stationary detectors detect the x-rays transmitted through the patient.



scanner of the left main bifurcation. The bright signal in the left main, proximal left anterior descending, and circumflex arteries suggests the presence of extensive calcification.[9]

EBCT calcium score and atherosclerosis

Pathologic analysis has confirmed that there is a close correlation between the extent of calcium measured by electron beam CT and the actual area of atherosclerotic plaque. Since calcification is not seen in normal arteries, the presence of calcium at EBCT (positive test) confirms the presence of atherosclerotic plaque.[10] Angiographic series have shown that a positive EBCT test is highly likely in the presence of angiographic stenosis, with reported sensitivities ranging from 85% to 100%.[7] The specificity of EBCT for angiographic stenosis is, however, lower, at around 60%. This is probably because EBCT detects atherosclerotic plaque before it is extensive enough to cause luminal stenosis detectable on an angiogram.

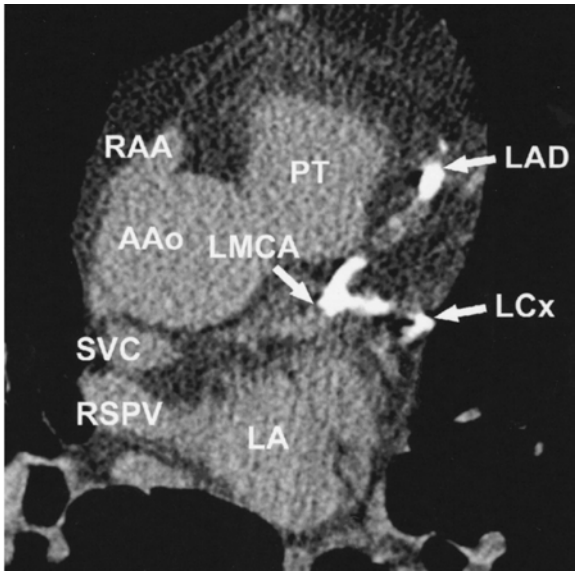
On a population level, the prevalence of the EBCT calcium score parallels that of atherosclerosis (Figure 4). Calcium scores increase exponentially with increasing age, such that a 10-fold difference exists between calcium scores in individuals aged 50-55 and 70+. For each age group, the median calcium score is higher among men than women. Women have very low calcium scores until age 55, after that they increase progressively. Most of these data are collected from white patients who obtained their EBCT scans by self-referral. The prevalence of EBCT calcium in other ethnic groups has not been extensively studied.

EBCT calcium and prognosis

The literature addressing the prognostic value of EBCT in asymptomatic patients consists of three principle studies.

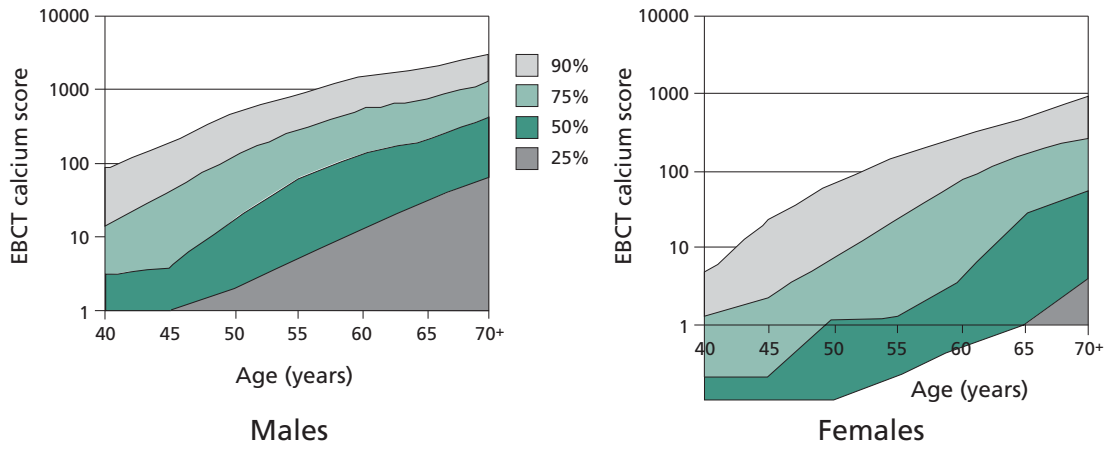
- Arad et al[11] reported the predictive value of EBCT in 1173 self-referred, asymptomatic individuals who were generally at a low-baseline risk for CAD. During a mean follow-up time of 43 months, the event rate of death and non-fatal MI was only 0.4%/year. In this study, an EBCT score >80 was associated with an odds ratio of 14.3 for clinical events (including death, MI, stroke, and need for revascularization). The use of revascularization as an endpoint in this analysis is controversial because an elevated EBCT score itself might lead treating physicians to investigate and treat patients more aggressively resulting in higher revascularization rates.
- Detrano et al[12] randomly selected 1196 high-risk individuals for EBCT scanning. In order to be included, patients had to have at least 2 risk factors for CAD and no prior coronary artery disease. Over a 41-month follow-up period, the rate of death and non-fatal MI was 1.6%/year. Using receiver-operating curve (ROC) analysis, the authors found only a modest predictive value in this group of patients from both the Framingham risk score (ROC area = 0.69) and the EBCT calcium score (ROC area = 0.64). The authors concluded that EBCT provides relatively little additional information on prognosis in high-risk patients.
- Raggi et al[13] studied 632 asymptomatic individuals who were self-referred. The authors calculated age- and sex-specific quartiles of the calcium score and compared the predictive value to the traditional Framingham risk. EBCT appeared to be the more effective risk stratifier. They found that an EBCT calcium score in the highest quartile was associated with a 21.5-fold greater risk of death or non-fatal MI than the lowest quartile. In contrast, a 7.0 times greater risk was seen in the highest Framingham risk quartile compared to the lowest.

Figure 3: EBCT images demonstrating extensive calcification in the left main, proximal left anterior descending, and circumflex arteries.



LAD = left anterior descending artery; LCx = left circumflex artery; PT = pulmonary trunk; LMCA = left main coronary artery; LA = left atrium; RSPV = right superior pulmonary vein; SVC = superior vena cava; AAo = ascending aorta; RAA = right atrial appendage

Figure 4: Prevalence of EBCT calcium scores by age and sex. Calcium scores increase exponentially with age and parallel the prevalence of atherosclerosis. Data supplied by Imatron.



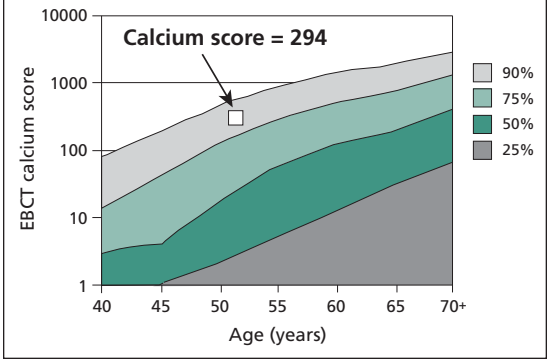
Given the limited published literature in this area, there is still a great deal of controversy over the value of EBCT in risk prediction. The studies cited above and others published thus far have primarily involved self-referred populations at the extremes of baseline risk. The sample sizes are relatively small and follow-up includes few hard clinical endpoints. Most importantly, the incremental value of EBCT over traditional multivariate risk-assessment models has not yet been established. This would require risk-adjusted statistical models that first control for risk-factor information available before EBCT, and then determine the amount of additional prognostic information obtained. It is the incremental value of EBCT that concerns the clinician since an assessment of traditional risk factors is easily made from the history, examination, and basic laboratory work that would generally be available prior to incorporating the EBCT results. Several studies addressing these issues are ongoing. The most important will be the NIH-sponsored Multi-ethnic Study of Atherosclerosis (MESA) that is evaluating the utility of EBCT calcium scoring, as well as MRI and ABI in identifying high-risk subsets. This will be performed through a planned 10-year follow-up period.

Incorporating EBCT into clinical practice

Although a definite resolution to the debate over the incremental prognostic value of EBCT must await the completion of large, prospectively-designed studies such as MESA, clinicians are increasingly confronted with patients who are either requesting EBCT calcium scoring or presenting with the results of such tests. Greenland et al[3] have proposed an approach for using and interpreting the EBCT calcium score that is based on the limited evidence currently available. They suggest that clinicians should begin with a calculation of the Framingham risk. If the patient has multiple cardiovascular risk factors or established atherosclerotic disease in other vascular beds, and the 10-year risk of CHD exceeds 2%/year, then these patients are already at high enough risk to merit aggressive risk-factor therapy as recommended by recent prevention guidelines. If the cardiovascular risk factors are absent and the Framingham risk estimate is low, no risk-factor management is indicated and the patient needs only to be periodically reassessed. In neither of these patients groups is a calcium score likely to lead to a change in management approach. In the middle, however, is a large group of patients with one or more traditional risk factors and an estimated Framingham risk of 0.6 to 2.0%/year. It is in this group of patients that additional tests such as EBCT may help to further stratify risk status.

We will now discuss the cases that were presented at the beginning of this article. Recall that the first patient, Mr. C, is a 52-year-old, asymptomatic, male smoker with hypertension (BP of 150/90 mm Hg), hypercholesterolemia (total cholesterol of 6.00 mmol/L), HDL of 0.95 mmol/L, and normal glucose. Using the Framingham risk equation, his risk of CHD is 2.0%/year. Thus, he is already in a high-risk group and should receive aggressive risk-factor modification. Although this patient is interested in obtaining an EBCT calcium scan, the results are unlikely to change his management. Some might argue that a very high-risk calcium score might be an indication for an angiogram in this patient. Sometimes patients who have had the scanning done are the strongest advocates of this approach. However, there is no evidence

Figure 5: Calcium score for Mr. S compared to age-matched group. A score of 294 is in the highest quartile.



that a coronary angiogram, and more importantly, that revascularization of these asymptomatic patients will lead to any improvement in outcome.

The second patient, Mr. S, is a 51-year-old, asymptomatic male with hypertension (BP of 165/105), mild hypercholesterolemia (total cholesterol of 4.95mmol/L), and a positive family history. He is a lifetime non-smoker and has no diabetes. Based on the Framingham risk prediction tool, his risk of CHD is 1.0%/year. In this patient, we also have his EBCT calcium score which was 294. Figure 5 shows how this score compares to other men in the same age group and Mr. S's score is in the highest quartile. Based on the data currently available, he might, therefore, be expected to have a substantially higher risk of future CHD. Taking these results into account, a decision to treat his cholesterol and hypertension aggressively and start aspirin and an ACE inhibitor might be made.

Conclusion

Primary care physicians and specialists treating cardiovascular disease are frequently involved in the primary prevention of cardiac disease in asymptomatic patients. Several therapies have now shown clear efficacy in the primary prevention setting. Since the potential population at risk for coronary artery disease is very large, individually-based primary-prevention efforts must be targeted at those who are at highest risk. Electron beam CT offers a noninvasive, validated assessment of the extent of atherosclerosis. Although the incremental prognostic value of EBCT remains to be established, elevated calcium scores clearly identify patients at high risk of future events. When used as a screening tool in patients considered to be at intermediate risk by conventional measures, it may select those most likely to benefit from an aggressive primary prevention approach.

References

1. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-153.
2. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-1622.
3. Greenland P, Smith Jr SC, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation* 2001;104:1863-1867.
4. Grundy SM, Bazzarre T, Cleeman J, et al. Prevention conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention. *Circulation* 2000;101:E3-E11.
5. Greenland P, Abrams J, Aurigemma GP, et al. Prevention Conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: Non-invasive tests of atherosclerotic burden. *Circulation* 2000;101:E6-E22.
6. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;90:2645-2657.
7. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. *Circulation* 1996;94:1175-1192.
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15(4): 827-832.
9. Sevrukov A, Jelnin V, Kondos GT. Electron-beam CT of the coronary arteries: cross-sectional anatomy for calcium scoring. *AJR Am J Roentgenol* 2001;177(6):1437-1445.
10. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *Circulation* 2000;102:126-140.
11. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron-beam computed tomography. *J Am Coll Cardiol* 2000;36:1253-1260.
12. Detrano RC, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 1999;99:2633-2638.
13. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850-855.

Abstracts of Interest

Prognostic value of coronary calcifications for cardiovascular events in patients with diabetes mellitus.

BECKER A, KNEZ A, LEBER AW, THILO C, HABERL R, STEINBECK G. MUNICH GERMANY.

Introduction: Coronary calcifications are a highly significant marker of the early stage of atherosclerosis. We determined coronary calcifications in patients with diabetes mellitus to evaluate the possibility to predict cardiovascular events.

Patients: We examined 281 patients (174 men, 107 women, age 57.8 ± 9.1 years) without known cardiovascular diseases. All patients suffered from non insulin-dependent diabetes mellitus for 6.4 ± 3.7 years. Additional risk factors were arterial hypertension (n =189) and hyperlipidemia (n =100).

Methods: For determination of coronary calcifications we acquired 40 slices with the Imatron C-150 EBCT (acquisition time 100 ms, slice thickness 3 mm) in the high resolution mode beginning 1 cm below the carina covering the whole heart. Examination was carried out in breathhold inspiration and prospective ECG-gating at 80% of the RR-interval. For calcium quantification, we calculated the Agatston and the volume score. The patients were divided into group I, Agatston score below 100, and group II, score above 100. Evaluation of cardiovascular events took place 35 months after initial examination.

Results: The average score in group I was 62 ± 34, n =119 and 231 ± 87 in group II, n = 162. There was no significant difference in risk factor distribution between group I and II. During the observation period, the number of patients with unstable angina pectoris was 10 (8.4%) in group I compared to 38 (23.4%) in group II, 6 patients (5.0%) underwent coronary angioplasty in group I, 25 (15.4%) in group II. One patient (0.8%) suffered from myocardial infarction in group I, 10 in group II (6.2%). There was a highly significant difference between group I and II for all cardiovascular events ($p \leq 0.01$).

Conclusion: The number of cardiovascular events was significantly higher in patients with calcium scores above 100. The determination of coronary calcifications allows the identification of patients at high risk for future cardiovascular events in a group of initial asymptomatic patients with diabetes mellitus.

Abstract #110366 presented at the American Heart Association Meeting, November 13, 2001, Anaheim, CA.

What is the marginal cost of scanning for coronary calcium? A decision analysis of screening EBCT's downstream costs

O'MALLEY PG, GREENBERG BA, TAYLOR AJ. WASHINGTON, DC.

Background: The cost implications of coronary calcium scanning in asymptomatic patients are undefined. The "tradeoff" between the incremental accuracy of EBCT, leading to wider identification of patients at risk for coronary heart disease, and costs associated with incidental scan findings are important components driving the cost/benefit equation.

Methods: We used data from a consecutive sample of 1,000 asymptomatic 40-45 year old Army personnel presenting for a screening physical and EBCT to develop a decision analysis comparing the costs associated with a screening strategy of risk assessment with the Framingham Risk Index (FRI) +/- EBCT. All costs associated with EBCT (including the test cost and the induced costs of further testing, treatment, and incidental scan findings) were included. The primary outcome was the marginal cost per additional patient diagnosed with increased cardiovascular risk. Chosen risk thresholds included either a FRI of 1%/yr or a calcium score in the upper quartile for age/gender.

Results: Using FRI+EBCT increased the detection of "at risk" cases from 7.2% (FRI alone) to 22.4%. Incidental findings were seen in 8%, of which 19% were considered major findings. The cost associated with using EBCT+FRI was ten-fold that of FRI alone. The marginal cost per additional "at risk" case identified by EBCT+FRI was $2,994. Marginal cost was sensitive to the cost of EBCT and to its relative value for identifying "at risk" cases. The cost per additional case identified by combined EBCT+FRI ranged from $1800 to $15,000 as the absolute gain in case identification decreased from 23% to 3%. Multiway sensitivity analysis defined a threshold of approximately 10% for the absolute increase in case identification by EBCT+FRI, below which the cost per additional case identified rose exponentially. The cost per additional case identified was not sensitive to the incidence of incidental findings.

Conclusion: Adding EBCT to conventional risk prediction methods is expensive, particularly when the percentage of additional cases identified as "at risk" falls below an absolute difference of 10%. Incidental scan findings affect an important minority of screened individuals, but do not appear to appreciably affect the cost per additional case identified.

Abstract # 115115 presented at the American Heart Association Meeting, November 12, 2001 in Anaheim, CA.

Upcoming Scientific Meetings

15-18 May, 2002
17th Scientific Meeting of the American Society of Hypertension
New York, NY
CONTACT: Phone: 212 644-0650
Fax: 212 644-0656
Email: ash@ash-us.org

26-30 October, 2002
Canadian Cardiovascular Congress 2002
Edmonton, Alberta
CONTACT: Ms. Stephanie Mutschler
Phone: 613 569-3407 ext. 402
Email: meetings@ccs.ca
Website: www.cardiocongress.org

13-20 November, 2002
American Heart Association Scientific Sessions 2002
Chicago, IL
CONTACT: Phone: 214 706-1543
Fax: 214 706-5262
Email: sessions@heart.org

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.