Evidence Table

Clinical Area: Coronary artery calcium scoring.

Study Type: Prospective cohort
Study Aim: To determine the prognostic accuracy of electron beam computed tomographic scanning of the coronary arteries and the relationship of coronary calcification in the prediction of atherosclerotic cardiovascular disease (ASCVD) events in apparently healthy middle aged-individuals.

Outcomes:
Primary: Increase in the incremental prognostic value with the addition of coronary artery calcium (CAC) to the to standard coronary artery disease (CAD) risk factors. The endpoints were coronary death, nonfatal MI, surgical or percutaneous coronary revascularization, nonhemorrhagic stroke and peripheral vascular surgery.

Design
- Number of subjects: N=4,903 in the cohort study.
- Description of study population: Men and women 50-70 years old with a mean age of 59 years, 88% Caucasians, 35% women, 34% a history of hypertension, 6% diabetes, 10% smoking, and 21% a family history of premature CAD. Mean total cholesterol 224 mg/dL, LDL-C 143 mm/dL, HDL-C 52 mg/dL, and triglycerides 141 mg/dL.
- Setting: Office based.
- Inclusion criteria: Men and women 50-70 years of age with no history, symptoms or sings of ASCVD.
- Exclusion criteria: Indication for risk factor modification (insulin dependent diabetes, triglycerides >500mg/dl, and in men LDL-C >175 mg/DL, or conditions that might interfere with the conduct or conclusions of a natural history study.
- Intervention: All participants underwent a baseline EBCT scanning, using C-150 XP scanner (Imatron, South San Francisco, CA). 40 3-mm slices were scanned during a single breath hold. Medical history, and Rose questionnaire were obtained for all participants, but only but only those who were included in the embedded randomized trial (subjects with coronary calcium score (CCS) >80th percentile for age and gender) underwent a physical exam, ECG, and lab tests including lipid levels, and CRP level. Thus risk factors were measured for only 1,357 (27.7%) subjects. All subjects with CCS >80th percentile were given 81 mg of aspirin daily.
- Source of outcome data (e.g. patient self-report, doctor report, lab results): Not discussed but apparently from doctors and hospital records.
- Length of follow-up: Mean of 4.3 years.
- Completeness of follow-up: 94% complete.

Validity

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- **Is the study type appropriate for the question(s) being asked?** Yes.
- **Patients followed from a well-defined point in the course of disease?** Yes.
- **Likelihood of selection bias?** Recruitment letters were sent out to 300,000 individuals, and only 20,000 responded.
- **If human judgment required to determine outcome, was the assessor blinded to prognostic factors?** The investigators who ascertained the endpoint events were blinded to the coronary calcium scores.

**Conclusions regarding validity of methods:**

This was prospective population based study, however only around 2% of those eligible were enrolled, and the majority were Caucasians, which may limit generalization of the results. Moreover, risk factors were measured for only 28% of the participants. The study had a relatively short duration and a small number of events, and those lost to follow-up were younger subjects with lower LDL-c levels.

**Results:**

Median calcium score was 10 (range 0-105) for all participants, 30 (range 1-174) for men and 0.5 (range 0-20) for women.

119 of the 4,903 participants (2.4%) experienced ASCVD events, only 34% of these events were hard CHD events (MI plus coronary death).

At the beginning of the study those with CAC score >80th percentile for age and gender, underwent Framingham risk scoring to determine their 10-year risk for hard CHD events. 654 had a projected 10 year risk <10%, 506 had a risk of 10-20%, and 86 a risk >20%.

<table>
<thead>
<tr>
<th>CAC score</th>
<th>n† (weighted)</th>
<th>Event rate %</th>
<th>Relative risk ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0**</td>
<td>1504</td>
<td>1.0</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>1-99</td>
<td>1973</td>
<td>2.6</td>
<td>1.9 (0.8-4.2)</td>
</tr>
<tr>
<td>100-399</td>
<td>686</td>
<td>3.8††</td>
<td>10.2 (4.8-21.6)</td>
</tr>
<tr>
<td>&gt;400</td>
<td>450</td>
<td>6.3</td>
<td>26.2 (12.6-53.7)</td>
</tr>
</tbody>
</table>

* Included coronary death, nonfatal MI, coronary bypass surgery and percutaneous coronary angioplasty.
† n=4,613 subjects with follow-up data
†† 1.3%/year for total CHD events, .58%/year for hard CHD events (nonfatal MI and coronary death)
**33% of the participants had a score of 0

Test performance in all patients and for the subgroup where risk factors were measured

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A multivariate regression analysis showed that CCS was strongly predicted by age, male gender, and family history of premature coronary disease.

The CCS predicted CAD events independently of standard risk factors* (p=0.01)

*Age, gender, LDL, and HDL cholesterol, hypertension< DM, Smoking, family history, BMI, and triglycerides.

ROC curve analysis (for n=1,293):

The area under ROC curve

<table>
<thead>
<tr>
<th></th>
<th>Framingham risk score</th>
<th>Coronary calcium score</th>
<th>P for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS</td>
<td>0.68 ± 0.03</td>
<td>0.79 ± 0.03</td>
<td>=0.0006</td>
</tr>
</tbody>
</table>

Authors’ Conclusions:

The authors concluded that coronary calcium score predicts CAD events independent of and more accurate than standard risk factors and refines the Framingham risk stratification.

Reviewer’s Conclusions:

The study was prospective, and population based. However it had some limitations which are potential sources of selection and observation bias. The study enrolled only 2% of the eligible subjects, who were 88% White, and risk factors were measured for less than one third of the participants. These were participants with coronary calcium scoring >80th percentile for age and gender, i.e. comparing the predictive value of coronary calcium vs. Framingham risk scoring was only made patients with high calcium scores. Moreover, not all participants were managed equally e.g. only those with high calcium scores were treated with aspirin.

Overall the results of the study show that initially healthy men and women 50-70 years of age who developed an ASCVD event had higher baseline coronary calcium scores than those without events. The events rates were found to increase with higher coronary calcium scores. The multivariate analysis indicated that coronary calcium score predicted
CAD events independently of standard risk factors. It was also found to be strongly predicted by age, male gender, and family history of premature coronary disease. The AUC curve for a subgroup of patients with high CCS was 0.79 compared to 0.68 for FRS.

These results may only be generalized to a similar population i.e. White participants with a high level of coronary calcium.