Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The predictive value of coronary artery calcium (CAC) detection for the risk assessment of coronary heart disease (CHD) was compared with two global and most commonly used risk assessment tools, the Framingham Risk Score (FRS) and a combination of FRS and family history of CHD. Family history of CHD incorporated history of sudden death, myocardial infarction, coronary revascularisation in a relative before the age of 55 years (males) and 65 years (females). CAC was measured by electron-beam computed tomography (EBCT) using an Imatron C-150 LXP scanner (Imatron Corp., South San Francisco, CA). Images were taken using a 40- to 50-slice (3-mm thick) protocol with image acquisition activated to 60 to 80% of the electrocardiographic RR while the patient was holding respiration. Coronary calcium was defined as the presence of four or more adjacent pixels with more than 130 Hounsfield units. For each patient, the total CAC score was based on the sum of individual scores of the four major epicardial coronary arteries. The scan was characterised positive for CAC if the total CAC score was greater than 0.

Type of intervention
Screening and prognosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised active-duty Army personnel aged between 40 and 50 years, who were placed in the National Capital Area of the Walter Reed Health Care System. Personnel with a history of CHD were excluded from the study, as were those who demonstrated signs of a history of angina pectoris in the Rose questionnaire. No further inclusion or exclusion criteria were reported.

Setting
The setting was the Walter Reed Army Medical Center. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were collected between 26 October 1998 and 19 February 2003. Dates relating to the costs and the price year were not reported in the current study. Relevant details were given elsewhere (O'Malley et al. 2004, see 'Other Publications of Related Interest' below for bibliographic details).

Source of effectiveness data
The effectiveness data were derived from a single study, the Prospective Army Coronary Calcium (PACC) project.
Link between effectiveness and cost data
Although not explicitly reported, it seems that the costing has been carried out retrospectively on the same sample of patients as that used in effectiveness analysis.

Study sample
The authors reported that the sample size was determined in the planning phase of the study, but relevant details were published elsewhere (O'Malley et al. 1999, see 'Other Publications of Related Interest' below for bibliographic details). Retrospective sample size calculations based on the existing sample were conducted using Sample Power (version 2.0, SPSS Inc.). These demonstrated that based on the observed prevalence of CAC, hazard rates for CHD outcomes and the timeframe of the study, a total sample of 1,200 patients would ensure an 80% power to detect statistically significant results. It was reported that the power of the current study was 91%.

A sample of active-duty Army personnel aged between 40 and 50 years who met the inclusion criteria were selected for the study. Of the 2,259 individuals who were screened and were found to be eligible, only 2,000 provided written informed consent and were included in the study. It was reported that one male participant did not receive the computed tomography scan and was therefore excluded, leaving 1,999 participants in the initial sample.

Study design
The analysis was based on a prospective single-centre cohort study, the PACC project. The authors reported that the results of the EBCT scans were interpreted in a blinded manner by an experienced radiologist, based on the Agatston scoring method. However no further details of the blinding method were reported. In addition, patients were followed-up through annual structured interviews, conducted over the telephone by experienced nurse coordinators, and through a review of hospital records. Subsequently, hospital records were also reviewed by two researchers and an independent cardiologist. All the above health professionals, who reviewed hospital records, were blinded to all cardiovascular risk factors and CAC information.

The mean duration of follow-up was 3.0 (+/- 1.4) years (range: 1 - 6). It was reported that up to 26 October 2004, 16 (0.8%) patients were lost to follow-up. Five of the 16 patients withdraw their consent and refused to participate before their first follow-up assessment, one patient died, and 10 patients were lost to follow-up, although neither their death nor their admission to a military or civilian health care network could be confirmed.

Analysis of effectiveness
Although it was not explicitly stated, it appears that analysis was conducted for treatment completers only. Patient characteristics were reported for women (n=356) and men (n=1,627) separately. The mean age of the men was 42.9 (+/- 2.8) years and for women 42.8 (+/- 2.7) years. The group of patients was well-educated (82.6% college education in men and 75% in women). For men, the most common cardiac risk factor was hypertension (30.8%) and either a first- or second-degree (31.7%) family history of CHD. The metabolic syndrome was present in 6.6% of men, and 6.9% of men and 11.2% of women were current tobacco users. The mean 10-year FRS for CHD was 4.6 +/- 2.7%. Coronary artery calcification was detected in 22.4% of male participants, with a mean CAC score of 20 (+/- 111). Coronary artery calcification was detected in 7.9% of female participants, with a mean CAC score of 3 (+/- 20).

The following primary health outcomes were used in the analysis:
- cases of myocardial infarction (documented by elevated cardiac biomarkers and a clinical course of care compatible with this diagnosis);
- sudden cardiac death (defined as sudden, unexpected death occurring within one hour after onset of symptoms); and
- unstable angina pectoris (defined as acute-care hospitalisation for new-onset or rapidly progressive chest pain or another ischemic equivalent symptom with documented inducible ischaemia or obstructive coronary artery disease and a course of care in agreement with this diagnosis).
Effectiveness results
The authors reported that during the follow-up period there were 9 acute CHD events (definite myocardial infarction, unstable angina, or CHD death). Only men with a mean age of 43 years experienced CHD events. The mean age at the time of the event was 46 (+/- 2) years, compared with 46 (+/- 3) years which was the mean age during the last follow-up. The FRS was not statistically different between patients experiencing a CHD event and those who did not (5.7 +/- 2.6% versus 4.6 +/- 1.9%; p=0.19). Four events happened in men with a 10-year FRS of less than 6% and five in men with an FRS between 6 and 10%. Seventy-two men with an FRS above 10% experienced no CHD event. Five of the 9 CHD events occurred in men who had either a first- or second-degree family history of premature CHD.

The CHD events occurred in 7 of 364 men with CAC (1.95%) and 2 of 1,263 without CAC (0.16%), (p<0.0001 by log-rank).

The Cox regression analysis demonstrated that the incremental predictive value of CAC on the risk of CHD events in men was 11.8-fold (95% confidence interval, CI: 2.45 - 56.93; p=0.002) after controlling for the FRS.

In men with CAC present, the risk of CHD associated with increasing severity of CAC was incremental across CAC tertiles (hazard ratio 4.3 per quartile, 95% CI: 1.10 - 16.97; p=0.036) after controlling for the FRS.

When controlling for both the FRS and a family history of premature CHD, the incremental predictive value of CAC was 10.75 (95% CI: 2.23 - 51.84; p=0.003). In addition, the value of coronary calcium severity on the risk of CHD events in men with CAC present was incremental across tertiles (hazard ratio 4.80 per quartile, 95% CI: 1.13 - 20.44; p=0.034).

Clinical conclusions
The authors concluded that CAC presence is associated with an important, independent prognostic value in the prediction of CHD incidence in young asymptomatic men. Its predictive value is incremental to commonly used, measurable coronary risk factors.

Modelling
The authors conducted a multivariate analysis, using Cox proportional hazards modelling and stepwise methods, to estimate the independent predictive value of CAC for CHD episodes. Two models were constructed. The first model estimated the efficiency of CAC presence to predict CHD episodes, while the second model estimated how the incremental severity of CAC predicted CHD episodes. Both models were restricted to men, as women in the study sample did not experience CHD events. The second model was restricted to those patients with any measurable CAC, and CAC presence was coded in tertiles based on CAC score.

The authors also used a published decision analytic model to assess cost-effectiveness based on the CHD outcomes of the current analysis. The model, which had previously been used to assess the theoretical cost-effectiveness of atherosclerosis imaging in a low-risk population, was modified to incorporate the CHD outcomes and relative risk estimates of the current analysis. EBCT was also included in the model using Bayesian methodology, multiplying the adjusted predicted risk resulting from the FRS by the adjusted relative risk increase estimated by the CAC score. Details of the model were given elsewhere (O'Malley et al.). To calculate the marginal cost-effectiveness, the model assumed a 30% improvement in survival associated with primary prevention among at-risk men.

Measure of benefits used in the economic analysis
The authors used the health utility (quality-adjusted life-years, QALYs) as the measure of benefit. Details of the method used to assign values of health states and to derive the QALYs were not reported in the current study. The utility values were derived from another study (O'Malley et al. 2004).

Direct costs
The only cost reported in the current study was the annual cost of medications if a patient was "at risk". No discounting
was reported. No further information relating to the cost data were reported. The reader is referred to O’Malley et al. (2004) for relevant information.

**Statistical analysis of costs**
Although not explicitly stated, the costs seem to have been treated deterministically.

**Indirect Costs**
Although not explicitly stated, the indirect costs do not appear to have been included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors most probably conducted a sensitivity analysis using 95% CIs to investigate variability in the data. The parameters reported to have been tested were the estimated relative risks associated with CAC and the efficacy of primary prevention interventions (e.g. lifestyle, medications). Although not specified, a two-way sensitivity analysis appears to have been conducted.

**Estimated benefits used in the economic analysis**
The estimated benefits used in the economic analysis were not reported separately in the current study.

**Cost results**
The total costs were not reported separately.

**Synthesis of costs and benefits**
The authors reported that the marginal cost of including EBCT into a conventional risk prediction assessment was $37,633/QALY. This ranged from $31,500/QALY when the upper adjusted relative risk of 60 was used, to $500,000/QALY when the lower adjusted relative risk limit of 2 was used.

The sensitivity analysis demonstrated that the results were sensitive to the efficacy of primary prevention at improving survival. In particular, when the relative improvement in overall survival due to primary preventive measures (i.e. unique measures according to patients needs, such as aspirin, statins, lower goals for blood pressure and cholesterol) was assumed to be 25%, the marginal cost-effectiveness was approximately $100,000/QALY (ranging from $1,000,000/QALY in the upper CI of relative risk estimates to $79,000/QALY in the lower CI of relative risk estimates). When the efficacy of primary prevention was estimated to result in a 45% overall survival improvement, the marginal cost effectiveness was approximately $13,000/QALY (range: 11,500 - 22,000).

**Authors’ conclusions**
In young, asymptomatic men, the presence of coronary artery calcification provides a substantial, cost-effective, independent prognostic value for the prediction of incident coronary heart disease (CHD) that is incremental to measured coronary risk factors. However, although the analysis proved that coronary artery calcium (CAC) has an incremental predictive value in comparison with conventional risk factors for premature CHD outcomes, its cost-effectiveness was not clearly demonstrated.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparators was explicitly justified. The CAC measurement conducted by EBCT was compared with
the FRS and family history of CHD, which seem to have represented commonly used risk assessments for premature CHD outcomes in the authors' setting. You should decide if this represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a prospective cohort study, which seems to have been appropriate given the study question. The study sample was representative of the study population, but the analysis was conducted on treatment completers only, excluding individuals who were lost to follow-up. No analysis was undertaken to account for the characteristics of those lost to follow-up. It is not possible to comment on the internal validity of the effectiveness results since the authors referred to a separate clinical paper for details of the clinical study. Extensive statistical analyses were, however, undertaken to take potential biases and confounding factors into consideration. Power calculations were reported and an appropriate sample size was used for men. The authors acknowledged that the analysis was underpowered to exclude a relationship between CAC and CHD events in women.

**Validity of estimate of measure of benefit**
The summary measure of benefit was the health utility (QALYs). It is not possible to comment on the method of derivation of health utilities since the authors referred to a separate paper for relevant details.

**Validity of estimate of costs**
The authors did not specify the perspective for the study. It could not be societal since the indirect costs were not included in the analysis. The authors included only the costs of the drugs used in patients at risk. It is not possible to comment on the validity of the cost estimates used since relevant details were reported in a separate paper. For example, the costs and the quantities were not reported separately, which would not enable the analysis to be easily reworked for other settings. In addition, the sources of the quantities and price data were not stated, nor was the price year. This may affect the generalisability of the study results in other countries. Although the costs were incurred during more than two years, discounting does not appear to have been performed. Finally, the costs were treated deterministically and no sensitivity analyses were conducted to assess the robustness of the results when the estimated costs were modified.

**Other issues**
The authors compared the findings of their study with those from other studies. The differences spotted were mainly attributed to the different measurement tools used to assess risk factors, the different health outcomes used in the analysis, and the inclusion of women in the cohort. The issue of generalisability of the results was directly addressed. The cost results and estimated benefits used in the economic analysis were not reported separately, thus impeding the reproducibility of the results to other settings. The study enrolled non-referred individuals aged between 40 to 50 years and this was reflected in the authors' conclusions.

The authors reported a number of limitations to their study. For example, the low event rate that was observed in the selected cohort makes it difficult to control for variables other than the FRS and may limit the accuracy of the risk estimates of the current study. In addition, the sample size was not sufficiently powered to exclude an association between CAC and a CHD event in women.

**Implications of the study**
The authors did not make explicit recommendations for changes in policy or practice. However, they stressed the need for further research. Specifically, studies that include larger female cohorts and are sufficiently powered to demonstrate statistically significant results for ethic minorities as well. Prospective clinical trials with accurate cost measurements are also necessary to achieve more robust cost-effectiveness results.

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Other publications of related interest


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