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Research article

Validation of an imaging based cardiovascular risk score in a Scottish population

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ABSTRACT

Objectives: A radiological risk score that determines 5-year cardiovascular disease (CVD) risk using routine care CT and patient information readily available to radiologists was previously developed. External validation in a Scottish population was performed to assess the applicability and validity of the risk score in other populations.
Methods: 2915 subjects aged ≥40 years who underwent routine clinical chest CT scanning for non-cardiovascular diagnostic indications were followed up until first diagnosis of, or death from, CVD. Using a case-cohort approach, all cases and a random sample of 20% of the participant's CT examinations were visually graded for cardiovascular calcifications and cardiac diameter was measured. The radiological risk score was determined using imaging findings, age, gender, and CT indication.
Results: Performance on 5-year CVD risk prediction was assessed. 384 events occurred in 2124 subjects during a mean follow-up of 4.25 years (0–6.4 years). The risk score demonstrated reasonable performance in the studied population. Calibration showed good agreement between actual and 5-year predicted risk of CVD. The c-statistic was 0.71 (95%CI:0.67-0.75).
Conclusions: The radiological CVD risk score performed adequately in the Scottish population offering a potential novel strategy for identifying patients at high risk for developing cardiovascular disease using routine care CT data.

1. Introduction

In Scotland, approximately 40% of all premature deaths are caused by cardiovascular disease (CVD) with coronary heart disease and stroke being the most prevalent [1]. Even though the cardiovascular mortality rate has dropped by more than 40% in the last 10 years it remains high compared to the rest of the UK and Western Europe [2,3]; the 2010 premature death rates for coronary heart disease in Scotland were 37% higher for men and 60% for women than in England [4]. To address the high CVD burden and identify high risk patients, several risk scores have been developed over the past few decades. Well known examples are the QRISK2[5] and ASSIGN score [6], which were developed in the UK and Scotland, respectively. These scores provide the 10 year risk of developing CVD in the general population and are based on traditional risk factors like age, gender, high blood pressure, and also social deprivation and family history.

Traditional risk scores such as QRISK2 and ASSIGN are considered moderately successful in predicting future CVD events since corresponding event rates are predominantly driven by surrogate measures of the atherosclerotic burden [7]. It is for that reason that there is substantial heterogeneity between traditional risk and actual atherosclerosis burden. In this regard, vascular calcifications, as detected on computed tomography (CT), may provide a more accurate measure of atherosclerosis burden and offer an improved assessment of

Abbreviations: DSC, descending aorta; ICD, international classification of disease; LAD, left anterior descending artery; MV, mitral valve; PROVIDI, PROgnostic Value of unrequested Information in Diagnostic Imaging

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personalized risk [8]. While the predictive qualities of these imaging markers are increasingly recognised in the medical literature [9], they do not have a defining role in CVD risk prediction in contemporary guidelines because their therapeutic consequences are still unclear.

The total number of chest CT examinations is steadily growing, due to technical developments, such as the implementation of ultra-low dose chest CT examinations [10] and new clinical indications such as population lung cancer screening [11]. As a result, information on imaging markers is increasingly available in routine care for a growing number of patients. Recently, a risk score was developed [12] for detecting subjects at increased risk for CVD using incidental findings from chest CT examinations. This score includes traditional risk factors like age and gender combined with imaging results such as cardiovascular calcifications and cardiac diameter. Although initial validation of the risk score showed promising results in a Dutch population, further validation is still required to assess whether the risk score can be applied more broadly across different (but related) patient populations. The relatively high CVD burden in Scotland provides ample opportunity, not only to validate the risk score, but the potential to provide a novel radiological method of identifying (previously undiagnosed) high-risk patients. In this study we validated whether this radiological risk score is able to detect and accurately stratify individuals from a Scottish population into clinically relevant CVD risk categories.

2. Methods

2.1. Study population

The study population (Fig. 1) consisted of 2915 subjects aged ≥ 40 years who underwent routine clinical chest CT scanning between January 2008 to July 2008 for diagnostic indications other than cardiovascular diseases in the participating hospitals (Royal Infirmary of Edinburgh, Edinburgh; Western General Hospital, Edinburgh; St John's Hospital, Livingson) in the Lothian Region, Scotland. These hospitals serve approximately 750,000 people out of a total 5.2 million population in Scotland.

This study population provided an overall comparable Caucasian population with a slightly increased cardiovascular risk profile as compared to the Dutch cohort in which the radiological cardiovascular score was developed [4]. Patients with a previous diagnosis of primary lung cancer (including mesothelioma or distant metastatic disease from other types of cancer (excluding hematologic malignancies) at baseline were excluded (n = 740). These patients were excluded because it is highly unlikely that detection of unexpected image findings will alter clinical decision making in patients with such a poor prognosis. Also excluded were patients yielding prior history of CVD or subjects with a CT referral indication directly related to (suspected) cardiovascular pathology (n = 51), to ensure that the evaluated imaging findings were truly "incidental". After exclusion, the full baseline validation cohort consisted of 2124 subjects who were considered for analyses.

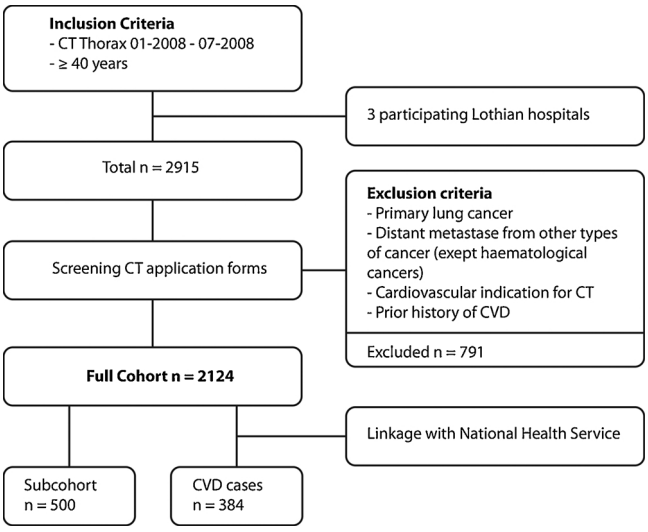

Fig. 1. Flowchart of study design. CVD = Cardiovascular Disease.

The study was approved by the Research Ethics Committee of the Royal Infirmary of Edinburgh (Ref: NR/1404AB6). Written informed consent was waived for all patients because of the retrospective design and absence of intervention of the study. This study is in compliance with the declaration of Helsinki and was performed in accordance with relevant guidelines and regulations.

2.2. Cardiovascular events and follow-up

Subjects who developed a CVD event during follow-up were identified as cases. CVD events were defined, using the international classification of disease (ICD) 10 definitions, as all diagnosis of coronary artery disease (Angina, (sub)acute myocardial infarction, acute or chronic ischaemic heart diseases), cerebrovascular events (ischemic stroke, haemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure [13]. Data on fatal and non-fatal CVD events were obtained from the National Health Service (NHS) registry using ICD 10 codes (Supplementary Table S1). The Information and Statistics Division (ISD) of the NHS in Scotland has linked information on all Scottish hospital inpatient discharges (1981–2015) and death records (1981–2015) using probability matching.

For all patients we determined the entry date, which was the date subjects underwent chest CT examination. The censor date was determined as the date on which they developed an event as specified above, the date the study period ended (April 1 st 2014) or date of death, whichever occurred first.

2.3. Sample selection and study design

We used a case-cohort approach as introduced by Prentice using all cases and a subcohort resembling an approximately 20% random sample from the full validation cohort (n = 2124) at the beginning of the study [14]. The cases together with the subcohort define the study population. A major advantage of this design is that it enables survival analyses without the need to score the chest CT scans for the full cohort. Because this implies that cases are inherently overrepresented, we adjusted all analyses for the sampling fraction such that estimates of model performance are applicable to the full cohort. Previous studies have suggested that case-cohorts with sampling fractions above 10% yield similar to the full cohort analysis [15].

2.4. CT scanning and scoring of CT characteristics

All chest CT examinations were obtained using multi-detector CT of different vendors according to the prevailing routine clinical protocols of the participating hospitals. When study subjects underwent multiple chest CT examination during follow-up, the findings from the first examination were used. All types of CT (including non-contrast) were considered eligible. Slice thicknesses had a range of 1.25 mm to 8 mm and varied according to the chest CT indication and corresponding protocol.

CT examinations were graded by a qualified medical practitioner with 2 years of chest CT experience who was trained on using the radiological risk score under the supervision of an experienced chest radiologist. The training consisted of scoring 50 randomly selected patients who were not part of the study population. Weighted kappa for inter-observer reliability regarding calcifications in the training set was 0.90.

CT examinations were graded for calcifications in the Left Anterior