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Comparative efficacy testing — Fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain

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ABSTRACT

Background: To evaluate diagnostic strategies in a rapid access chest pain clinic (RACPC) in the United Kingdom and to predict the economical and clinical impacts of incorporating fractional flow reserve by coronary computed tomographic angiography (FFR_{CT}) into future pathways.
Methods: A retrospective analysis of consecutive patients referred to a RACPC in the United Kingdom. All patients had an evaluation of cardiovascular risk factors and symptoms from which the pre-test likelihood (PTL) of coronary artery disease (CAD) was evaluated using the Diamond Forrester (DF) criteria. All investigative strategies and their results were recorded. For the FFR_{CT} economic evaluation of 1000 patients, standard National Health Service Tariffs were then applied and compared with a strategy that utilised FFR_{CT} for varying PTL categories.
Results: There were 410 patients with a median age of 57 (31–85) years. The DF criteria classified 39 (9.5%) patients as having a PTL of <10%, 76 (18.5%) 10–29% PTL, 117 (28.5%) 30–60% PTL, 114 (27.8%) 60–90% PTL and 64 (15.6%) >90% PTL. The concordance with the NICE recommended guidelines was <50% with the prevalence of obstructive CAD being <5% in patients with a PTL <90%. A model utilising FFR_{CT} for patients with a PTL 10–90% predicted a 48% and 49% reduction in invasive angiography and percutaneous coronary intervention, a saving of £200 per patient and a reduction in relative adverse event rates of 4%.
Conclusions: The DF algorithm overestimates the PTL of CAD supporting an extended role for coronary CTA. Strategies incorporating FFR_{CT} may confer benefits in evaluating patients with stable chest pain.

1. Introduction

It is currently estimated that up to 1.5% of visits to primary healthcare services will be for symptoms of chest pain, with only 8% of these patients being eventually diagnosed as having coronary artery disease [1]. Despite this low incidence, the adverse consequences for a missed diagnosis of CAD where early treatment can be highly effective are substantial [2]. This recognition has led to the development of rapid access chest pain clinics whereby general practitioners may refer patients with chest pain to experienced specialists with access to further basic and advanced diagnostic testing [3]. Here, it is recommended that the 2010 National Institute for Health and Clinical Excellence (NICE) guidelines for stable chest pain be followed [2]. These recommend the risk stratification of patients by the DF criteria into pre-test likelihood categories of patients having obstructive CAD [4]. For those patients with a pre-test likelihood of CAD <10% no further testing is required, 10–29% — coronary computed tomographic angiography (CTA), 30–60% — non-invasive functional imaging, 61–90% — invasive angiography and >90% — clinical judgement.

Despite these recommendations, it is recognised that there is widespread heterogeneity in RACPC practice within the United Kingdom. Although the reasons for this are complex, it is likely that this reflects local referrer preferences along with individual accessibility, availability and experiences of the various functional and anatomical imaging modalities. This variability also exposes current pathways to the risk of unnecessary layering of investigations, increased NHS costs [5] and a delay in the time to patient diagnosis.

Ideally strategies evaluating patients with chest pain should incorporate the reference standard technique for the evaluation of lesion specific ischaemia. Although fractional flow reserve (defined as the ratio between maximal blood flows achievable in a stenotic artery compared to normal maximal blood flow in the same vessel) is widely accepted as the gold standard [6–8], it has been restricted in its use owing to its inherent requirement for invasive cardiac catheterisation. Recently, a number of studies have shown a high diagnostic accuracy for fractional flow reserve by coronary CTA (FFR_{CT}) [9–11]. This new development has the potential to extend the current diagnostic capabilities of coronary CTA from an anatomical assessment of CAD in patients with a

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low pre-test risk of CAD (10–29%), to a "one-stop" anatomical and functional assessment of CAD in patients with a pre-test risk of CAD extending from 10–90%. Its use and economic viability in a RACPC however have not been evaluated before.

The aims of the current study were two fold. The primary aim was to evaluate contemporary tertiary centre RACPC practice in the United Kingdom. The secondary aim was to apply this data to a novel pathway incorporating FFR_{CT} into existing NHS RACPC pathways and to determine its economic impact.

2. Methods

We retrospectively studied all patients referred to the RACPC at our institute over a 12-month period from April 2012 through March 2013. All patients' notes were reviewed for clinical symptoms, cardiovascular risk factors and a 12-lead electrocardiogram. The pre-test likelihood of obstructive coronary artery disease was then calculated based on the recorded typicality of the chest pain, age, gender, cardiovascular risk factors and relevant 12-lead electrocardiogram findings. Patients were then subsequently grouped into the various pre-test likelihood categories indicated in the NICE guidelines (<10, 10–29%, 30–60%, 61–90% and >90%). For each category of risk, the investigations that the patients were initially referred for by the clinic practitioner were documented along with the eventual result of the test. Where patients underwent more than one test, the results of all eventual investigations were recorded along with the eventual diagnosis.

2.1. Rapid access chest pain clinic investigations

The standard practice within the RACPC was to conduct a detailed clinical history and examination of all patients referred to the service along with a 12-lead electrocardiogram. Following the integration of this information, a clinical decision as to subsequent testing was required was made by an experienced cardiologist who had access to all of the data. The choices included no testing, coronary calcium scoring, coronary calcium scoring + coronary CTA, myocardial perfusion scintigraphy (MPS), contrast enhanced dobutamine stress echocardiography (DSE), cardiac magnetic resonance (CMR) perfusion scans and invasive coronary angiography (ICA). All diagnostic imaging tests were performed by experienced practitioners in a high-volume centre using standardised protocols that were in routine clinical use at the time.

2.2. Economic evaluation — incorporation of FFR_{CT}

A number of studies have demonstrated a high diagnostic accuracy of coronary CTA for the exclusion of obstructive coronary artery disease [12–14]. However, the use of coronary CTA is currently restricted to the exclusion of CAD in patients at a low/low-intermediate risk of likelihood of coronary disease owing to its modest positive predictive accuracy, and inability to measure the functional significance of coronary stenoses. Recently, a number of studies have demonstrated that by applying the bioengineering principles of computational fluid dynamics, lesion specific ischaemia by fractional flow reserve [15] can now be measured from standard coronary CTA [16]. In the recent HeartFlow NXT trial, Nørgaard et al. showed in 254 patients that FFR_{CT} gave a sensitivity and specificity for detecting myocardial ischaemia by invasive FFR of 86% and 79% vs. 94% and 34% by coronary CTA alone [11]. This and other studies suggest the capability of FFR_{CT} to assess anatomical and functional coronary disease simultaneously that may confer significant advantages to the evaluation of patients with stable chest pain. To test this hypothesis, we utilised the data derived from our RACPC to evaluate the economic costs of our RACPC investigative strategy and also the impact of incorporating FFR_{CT} into future clinical pathways.

2.3. Statistical analysis

For ease of cost analysis the 410 patients were scaled to a total of 1000 patients. This was applied to the frequency of patients in each pre-test likelihood category from the RACPC data. A standardised unit cost for each diagnostic investigation and procedure was applied that was derived from the NHS National Tariff 2013/2014 (Table 1). The unit price for the FFR_{CT} evaluation was £888 (HeartFlow, Redwood City, CA, USA). The total price for each patient pathway was calculated as well as the per-patient cost for each pre-test likelihood category. A comparison of costs between the current NICE proposed algorithm and one incorporating FFR_{CT} was made. In order to be able to generate a functional economic model we applied a number of assumptions to the data. These included an assumption that the calcium score would be 0 Agatston units in 15%, 1–400 AU in 80% and >400 in 5% of patients. In addition we used published rates for sensitivity and specificity for the MPS [17] and coronary CTA scans [13]. In order to ensure the robustness of the current model we mandated the use of MPS for functional testing since this had the lowest associated NHS tariff. A per-patient cost analysis was performed across each pre-test likelihood category and the entire patient cohort. Where patients underwent coronary angiography alone, predicted rates of further angiography and invasive FFR requirements were made based on prior published studies.

3. Results

3.1. Rapid access chest pain clinic

There were 410 patients with a median age of 57 (31–85) years of whom 217 (53%) were women. The majority presented with atypical chest pain (77%), with 21% presenting with typical chest pain and 2% non-cardiac chest pain. The commonest cardiovascular risk factors were hypercholesterolaemia in 54%, hypertension in 52% and current tobacco smoking in 35%. Only 22% of the population had diabetes mellitus and 19% a positive family history of premature cardiovascular disease. Table 2 gives the initial and subsequent investigations for the entire group of patients. Where coronary CTA was used as the primary investigation, no further investigations were required in 97% of patients. This compared with 83% for MPS and 88% for DSE.

The actual investigative strategy used for each PTL category is given for the 410 patients in Table 3. In patients with a PTL < 10% there was an apparent reluctance to not perform any investigative test with 92% of patients receiving at least one form of diagnostic test. In patients with a PTL ranging from 10–29%, functional imaging was used (43%) as well as the recommended coronary CTA in 38%. In patients deemed to be at an intermediate PTL of CAD, functional testing was used more

Table 1
Unit cost per investigation based on NHS Tariffs 2013–2014.

Diagnostic investigation	Unit cost (£)	Code
DSE	292	EA45Z
ETT	172	EA47Z
CTA	166	RA14Z
CAC	98	RA08Z
CMR-contrast	213	RA03Z
CMR-perfusion	279	RA05Z
MPS	249	RA37Z
ICA	1259	EA36A
PCI		
≤2 stents	2742	EA31Z
≥3 stents	3262	EA49Z
Invasive FFR	3262	EA49Z

Abbreviations.
DSE — dobutamine stress echocardiography, ETT — exercise treadmill testing, CTA — computed tomographic angiography, CAC — coronary artery calcium scoring, CMR — cardiac magnetic resonance imaging, MPS — myocardial perfusion scintigraphy, ICA — invasive coronary angiography, PCI — percutaneous coronary intervention, FFR — fractional flow reserve.