Research paper

Incidence and predictors of lesion-specific ischemia by FFR$_{CT}$: Learnings from the international ADVANCE registry

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ABSTRACT

Background: To date, the clinical utility of coronary computed tomography angiography (CTA)-derived fractional flow reserve (FFRCT) has been limited to trials and single center experiences. We herein report the incidence of abnormal FFRCT (≤ 0.80) and the relationship of lesion-specific ischemia to subject demographics, symptoms, and degree of stenosis in the multicenter, prospective ADVANCE registry.

Methods: One thousand patients with suspected angina having documented coronary artery disease on coronary CTA and clinically referred for FFR$_{CT}$ were prospectively enrolled in the registry. Patient demographics, symptom status, coronary CTA and FFR$_{CT}$ findings were recorded. Univariate and multivariate analyses were performed to investigate the predictors related to abnormal FFR$_{CT}$.

Results: FFR$_{CT}$ data were analyzed in 952 patients (95.2%). Overall, 51.1% patients had a positive FFR$_{CT}$ value (≤ 0.80). Patients with ≥ 3 risk factors had a significantly higher rate of abnormal FFR$_{CT}$ than those with < 3 risk factors (60.2% vs. 43.9%, $p = 0.0001$). On multivariate analysis, baseline diabetes (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.04–2.21, $p = 0.030$) and hypertension (OR 1.56, 95%CI 1.14–2.14, $p = 0.005$) were both predictive of abnormal FFR$_{CT}$. In addition, $> 70\%$ stenosis was significantly associated with low FFR$_{CT}$ (OR 31.16, 95%CI 12.25–79.22, $p < 0.0001$) vs. $< 30\%$ stenosis. Notably, stenosis 30–49% vs. $< 30\%$ had an increased likelihood of ischemia (OR 3.74, 95%CI 1.52–9.17, $p < 0.0001$).

Conclusions: In this real-world registry, CT angiographic stenosis severity in addition to baseline cardiovascular risk factors conferred an increased likelihood of an abnormal FFR$_{CT}$. Importantly, however, mild CT

angiographic stenoses were noted to have an increased hazard for ischemia and the converse holding true for more severe stenoses as well.

1. Introduction

Previous randomized studies have shown that stable coronary artery disease (CAD) patients gain a benefit from FFR-guided treatment strategy when compared to angiography-guided treatment strategy.[1–3] Thus, currently, physiologic assessment by fractional flow reserve (FFR) at the time of invasive coronary angiography (ICA) is considered the gold standard method to identify hemodynamically significant stenosis, inducing ischemia, and justifying revascularization.[4] Anatomic assessment by coronary computed tomography angiography (CTA) has emerged as a noninvasive method for direct visualization of CAD, demonstrating high diagnostic performance.[5,6] Coronary lesions with a stenosis severity of ≥50% on visual coronary CTA are generally considered for referral to ICA.[7] Coronary CTA, however, may result in both underestimation and overestimation of a lesion's severity and is often inaccurate in identifying lesions that cause ischemia.[7,8] Thus, the ideal test for assessing suspected obstructive CAD should yield both anatomic and physiologic information regarding coronary lesions.

Recent technological advances in computational fluid dynamics and individual image-based modeling allow for the noninvasive calculation of FFR (fractional flow reserve derived by coronary computed tomography angiography [FFR_{CT}]) from standard coronary CTA datasets, without the need for additional radiation exposure or administration of hyperemic agents such as adenosine.[9] Three prospective multicenter trials have demonstrated that FFR_{CT} accurately predicts the hemodynamic significance of a coronary stenosis when compared with invasively measured FFR and the availability of FFR_{CT} data in addition to coronary CTA provides a markedly improved diagnostic performance in comparison with stenosis assessment according to coronary CTA alone.[10–12] FFR_{CT} has been shown to have strong clinical utility in recent clinical trials (PLATFORM) and multiple single center studies of patients with stable CAD.[13–15] In fact, deferring ICA in patients with an FFR_{CT} value of > 0.8 had a favorable short-term prognosis (no cardiac events during a median follow-up period of 12 months).[13–15] To date, however, the clinical utility of FFR_{CT} has been limited to trials and single center experiences.

Hence, we conducted the Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care (ADVANCE) registry to observe the "real-world" utility and impact of FFR_{CT} on clinical decision-making, outcomes and resource utilization in a broad variety of healthcare settings, regions and patient subsets.[16]

We herein report the incidence and predictors of lesion-specific ischemia by FFR_{CT} from the results of the first 1000 patients enrolled in the ADVANCE registry.

2. Methods

2.1. Study design and population

The ADVANCE registry is a multicenter, prospective registry that will enroll 5000 patients with suspected stable symptomatic CAD diagnosed by coronary CTA from 38 sites in Europe, North America and Asia. Patients with prior revascularization were not included in the registry. The rationale, design and goals of this registry have previously been described.[16] The primary endpoint of the registry is the rate of reclassification between the management plan on the basis of coronary CTA alone versus coronary CTA plus FFR_{CT} data. In the present study, we report the results of the first 1000 patients enrolled from July 14th, 2015 to June 15th, 2016. CTA data sets were submitted for FFRct analysis based on the clinical decision of the interpreting physician but it required confirmation of CAD and a focal > 25% stenosis.

Clinical and demographic information, medical history, and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, body mass index [BMI] > 30 kg/m^2, current smoking, and being male) were prospectively collected.

The study protocol was designed by the steering committee and approved by the institutional review board at each site, and the subjects gave written informed consent prior to participation.

2.2. Image acquisition and analysis for CT

Coronary CTA was performed on 64- or higher detector row scanners at each site. Sublingual nitrates were administered prior to scanning in all patients. If necessary, beta-blockers were orally or intravenously administered targeting a heart rate < 60 beats per minute. The protocol for coronary CTA image acquisition was recommended to comply with the Society of Cardiovascular Computed Tomography (SCCT) guideline.[17] Assessment of luminal diameter stenosis was performed using an 18-segment coronary model[17]; the strategy of stenosis quantification was left to the discretion of the local investigator at each site. Vessel segments ≥2 mm in diameter were evaluated for luminal narrowing, and the per-vessel maximum stenosis was categorized as 0%, 1%–29%, 30%–49%, 50%–70%, 71%–90%, or > 90%. Non-evaluable (n = 8) or occluded (n = 15) vessel segments were excluded from analysis.

2.3. FFR_{CT} analysis

Standard coronary CTA datasets were submitted to HeartFlow (Redwood City, CA, USA) for analysis. The FFR_{CT} results were made available to the interpreting physician within 48 h for evaluation and treatment planning of each subject provided that coronary CTA image quality was acceptable for analysis. The scientific basis behind the computation of FFR_{CT} have been described in detail in previous reports.[9–12] FFR_{CT} was displayed for each point in the coronary tree. The lowest FFR_{CT} values in the major epicardial (left main, left anterior descending [LAD], left circumflex [LCX], and right coronary [RCA]) arteries (including side branches) > 2 mm in diameter were registered and lesion-specific ischemia was defined as $FFR_{CT} \leq 0.80$.

2.4. Statistical analysis

Data were reported as mean ± SD or number (%). Categorical variables were compared using the chi-square test. To identify independent predictors of abnormal FFR_{CT} (≤ 0.80), clinical and coronary CTA variables were entered into a multivariate logistic regression model if their univariate p value was < 0.1. Results were expressed as odds ratios with 95% confidence intervals. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

Of 1000 patients, 154 subjects (15.4%) were enrolled from North America, 377 (37.7%) from Europe, and 469 (46.9%) from Japan. Baseline patient characteristics are summarized in Table 1. The mean patient age was 66.1 ± 10.4years and 65.5% were male. The mean BMI was 25.8 ± 4.3 kg/m^2. Hypertension was present in 59.9%, diabetes in 24.0%, hyperlipidemia in 53.1%, and current smoker in 18.7%. The median heart rate at the time of CTA was 58.1 ± 7.2 beats per