JACC Vol. 59, No. 15, 2012
April 10, 2012:1407–11

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Fractional Flow Reserve Estimation by Coronary Computed Tomography Angiography

We read with great interest the paper about the DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study, which compared fractional flow reserve (FFR) derived from coronary computed tomography angiography (CTA) with invasive FFR measurements (1). CTA is a reliable test to rule out coronary artery disease based on its high sensitivity and negative predictive value compared with conventional angiography as the reference (2). Considering the importance of invasive FFR as part of conventional coronary angiography for subsequent revascularization decisions (3), it would be game-changing if a reliable estimation of FFR could be performed noninvasively (4).

The DISCOVER-FLOW study is an important step in this direction. We would like to discuss 2 issues related to the study design and statistics.

1. Patients with an at least 50% diameter stenosis determined by the clinical site on CTA were studied using invasive FFR, which served as the reference in the study, but was done as clinically indicated. Thus, the final cohort of vessels that had invasive FFR measurements represents a subgroup that may be biased by the local CTA reading and a higher prevalence. This results in an overestimation of sensitivity and an underestimation of specificity. This can be seen from a different version of the Bayes formula needed to calculate sensitivity from predictive values: sensitivity = $PPV \cdot T_+/(PPV \cdot T_+ + (1 - NPV) \cdot T_-)$, where T_+ and T_- are the proportion of test positives and negatives in the study sample and PPV and NPV are the positive and negative predictive values.

The proportion of test negatives, T_- is underestimated, if T_- is calculated in the sample of verified subjects or vessels only. A very conservative estimate is to assume 3 vessels per person (i.e., 309 vessels overall). According to Koo et al. (1) 114 vessels were positive (53 true positive, 61 false positive) on CTA. Thus, we assume 195 negative vessels by CTA from which only 45 were assessed by the reference standard FFR. If we further assume that the observed negative predictive value is the true one, we can obtain corrected diagnostic performance estimates (Table 1). It is likely that the same holds true for computed tomography FFR. However, it is difficult to assess this without the correlation structure of both index tests within truly diseased and truly unaffected vessels. If both tests are conditionally independent (i.e., independent within the true positives and the true negatives), the naive estimates of sensitivity and specificity are unbiased.

Table 1 Corrected Diagnostic Performance Characteristics

	Listed Diagnostic Performance of CTA (1)	Corrected Diagnostic Performance of CTA
Sensitivity, %	91.4	71.0
Specificity, %	39.6	74.0
Negative predictive value, %	88.9	97.4

CTA = computed tomography angiography.

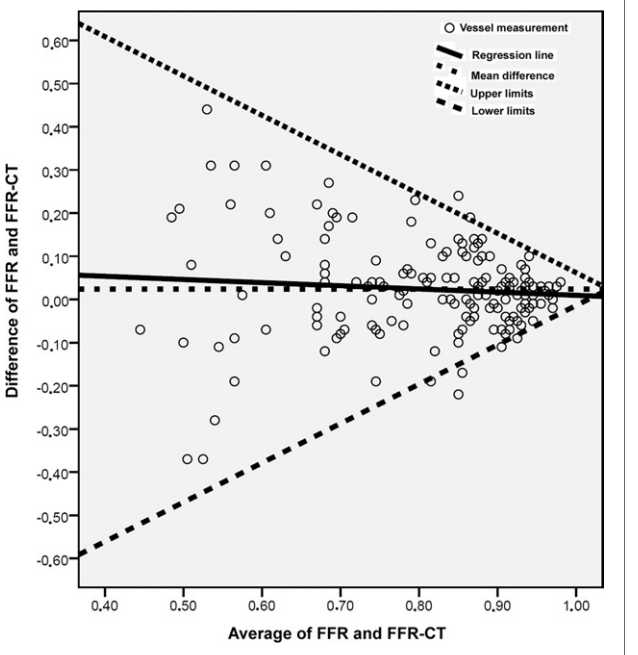

Figure 1 Bland-Altman Analysis of FFR and CT-FFR

The difference between the upper and lower limits of agreement for the comparison of fractional flow reserve (FFR) and computed tomography fractional flow reserve (CT-FFR) are not constant but increase linearly with smaller FFR results (5). Thus, the agreement between FFR and CT-FFR becomes less accurate with positive (<0.8) measurements.

2. The limits of agreement between FFR and computed tomography FFR resulting from a regression of *absolute* differences according to Altman (5) suggest that these are not constant but increase linearly with smaller FFR results (r^2 linear model = 0.335, r^2 quadratic model = 0.340, r^2 cubic model = 0.340) (Fig. 1). In other words, the more positive (lower) the FFR results become, the larger are the limits of agreement (95% confidence intervals).

These additions may be important when appraising the impressive DISCOVER-FLOW study results.

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doi:10.1016/j.jacc.2011.12.031

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Reply

We thank Dr. Martus and colleagues for their interest in DISCOVER-FLOW, a prospective multicenter study that demonstrates the high diagnostic performance of fractional flow reserve derived from typically acquired coronary computed tomography angiograms (FFR_{CT}) (1). We share their enthusiasm for this "game-changing" technology that enables noninvasive computation of coronary flow and pressure for the determination of lesion-specific ischemia.

Dr. Martus and colleagues suggest that in the DISCOVER-FLOW study, the performance of CT stenosis severity and FFR_{CT} against an invasive FFR reference standard may have been affected by workup bias because the decision to perform FFR was based on clinical indications after identification of ≥50% stenosis by CT. Dr. Martus and colleagues propose a statistical correction to account for individuals with no or mild stenoses by CT who were not subjected to FFR. This approach is certainly suitable to reduce the relative contribution of referral bias when performance measures of CT stenosis are judged against invasive angiography provoked by CT findings because the ability to identify or exclude a stenosis applies equally and universally to all patients undergoing CT. However, this approach is inappropriate for assessing the performance of FFR_{CT} because the population for whom FFR_{CT} would be expected to be applied are those with CT-identified stenoses that could both cause ischemia and be eligible for revascularization. In this regard, a >50% stenosis threshold in vessels ≥2 mm in diameter was chosen as an appropriate cutoff, given the low rates of ischemia for lesions with <50% stenosis and, more importantly, the widely accepted reluctance to revascularize nonobstructive coronary lesions. Even more fundamental, subjecting individuals who lacked any CT or invasive evidence of significant disease to FFR would have been both logistically difficult as well as questionably ethical.

Dr. Martus and colleagues note that the limits of agreement between FFR_{CT} and invasive FFR increase in a manner that is inversely proportional to the FFR values. They provide a figure that illustrates a very shallow negative slope of a regression line superimposed on a Bland-Altman plot that visually begins to diverge from the average of FFR and FFR_{CT} at values <0.75. There are numerous technological explanations for this, which are the subject of a review that we are preparing, but this negligible divergence has limited bearing on the clinical application of FFR_{CT}. Robust standards for ischemia based on FFR have been firmly established at values ≤0.80 in randomized trials, and all values ≤0.80 should thus be considered ischemia causing (2). To date, the relative impact of lesions with different values of ≤0.80 remains unexplored. Further, values >0.80, where the limits of agreement of FFR_{CT} and FFR are very close, are widely accepted as pathognomonic for those that are unquestionably *not* ischemia causing and for which revascularization can and should be safely avoided. The DISCOVER-FLOW study results support the high diagnostic performance of FFR_{CT} for both of these groups.

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doi:10.1016/j.jacc.2012.01.017

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