Study Protocol

Study Title: **C**omputed **T**omography-derived **F**ractional **F**low **R**eserve in the **S**ystematic **T**riage of emergency department **A**cute chest pain patients to **T**reatment. (The **CTFFR-STAT** trial).

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Principal Investigator: Gilbert Raff, MD

Co-Investigators:

Amr Abbas, MD
Neil Bilolikar, MD
Kavitha Chinnaiyan, MD
David Forst, MD
Michael Gallagher, MD
Robert Safian, MD
Mazen Shoukfeh, MD
Robert Swor, DO

Hospital Address: William Beaumont Hospital
3601 West 13 Mile Road
Royal Oak, MI. 48085
U.S.A.

The CT-STAT, ROMICAT and ACRIN randomized trials established that coronary CTA (CCTA) is safe and more efficient than alternative diagnostic strategies (such as stress testing) for low- intermediate risk acute chest pain (ACP) patients with suspected acute coronary syndromes[1-3], and current Appropriate Use Criteria consider CCTA in ACP patients with low to intermediate pre-test probability as appropriate[4,5]. Studies at Beaumont and other institutions have shown that approximately 75% of patients undergoing CCTA for ED ACP can be immediately triaged to discharge and 10% triaged to admission due to severe CAD. However, approximately 15% of patients with intermediate level stenosis (>50% but <90%) need additional testing, as this degree of anatomic narrowing does not reliably predict flow limitation as the cause of symptoms. Consequently, many such patients are admitted for stress testing or invasive coronary angiography (CATH) with subsequent negative results. An admission for chest pain diagnosis commonly incurs costs between $12-25,000. Data from the National Cardiovascular Disease Registry in nearly 400,000 patients demonstrated that only 38% of patients undergoing CATH for chronic chest pain had obstructive coronary disease in spite of routine stress testing in the majority, and recommended in a New England Journal article that "better strategies are needed to inform decisions…in routine clinical practice."

In September 2015, a new FDA-approved test became available at Beaumont, computed tomography-derived fractional flow reserve (CT-FFR, provided by HeartFlow, Inc.), that provides flow information directly from computational fluid dynamic analysis of CCTA images without further testing[7- 15].This analysis does not involve any additional imaging, contrast or medications. CT-FFR has been shown to be more accurate in predicting the presence of true ischemia on invasive fractional flow reserve testing in the invasive catheterization laboratory (CATH-FFR). Patients managed by CATH-FFR have been shown to have better outcomes than patients managed using visual inspection of CATH stenosis alone. The standard cutoff for an abnormal CATH-FFR and CT-FFR is the measurement of a blood pressure drop of ≥20% (FFR ≤0.80) across a given stenosis.

For Beaumont ED patients, CT-FFR has been in use on a research basis since September, 2015, but is not considered standard of care. Since September 2015 we have conducted a study to analyze clinical outcomes after CT-FFR, (a sub-analysis of HIC #2016-157, the Beaumont CT Registry). We have collected, analyzed data and submitted for publication, data on 147 ED patients with CCTA stenosis of 25-99% managed with CT-FFR and followed for a minimum of 90 days. These data show no evidence to date of increased risk, but do show improved prediction of the need for revascularization using CT-FFR (see Appendix, submitted for publication).

The objective of the present trial is to evaluate the CATH rate and diagnostic effectiveness of CT-FFR as compared to a standard of care diagnostic strategy (SOC) in the management of ACP patients with intermediate-to-severe stenosis on CCTA.

Hypotheses:

Primary Hypothesis:

Cardiac Catheterization Rate: Use of CT-FFR will reduce the CATH rate in ACP patients with >50% stenosis on CCTA. There will be a pre-specified subset analysis of the Intermediate (51-70%) and Severe (71-90%) stenosis groups.

Secondary Hypotheses:

1. Diagnostic Effectiveness: CT-FFR results will more accurately triage patients to CATH compared to patients triaged by SOC. True flow-limiting coronary stenosis will be defined by CATH-FFR as the gold standard in patients undergoing CATH. Accurate triage will be calculated as the proportion of patients with correct triage to CATH based on CATH-FFR results:

CT-FFR group:

True positive case: CT-FFR positive and CATH-FFR positive
True negative case: CT-FFR negative and CATH-FFR negative
Proportion of correct CT-FFR triage = (True positive + True negative)/ All CATH

SOC group:

True positive case: SOC chosen by attending physician for CATH confirmed by CATH-FFR. By definition, the clinicians' decision to CATH based on clinical evidence is considered an SOC positive case, there can be no SOC true negative cases that go to CATH.
Proportion of correct SOC triage = True positive/All CATH

2. Safety: Patients following CT-FFR-guided management will have similar MACE rates, including death, ACS and unanticipated late revascularization when compared to SOC-guided patients.

Methods

Study Population

The study population will be drawn from ED ACP who have already undergone CCTA for diagnosis, and have been found to have 50% or greater stenosis but less than 90% of at least one coronary branch. Two-hundred patients meeting entry criteria will be enrolled from a sample of ED ACP patients at Beaumont Hospital (Royal Oak).These patients will be randomized 1:1 using sealed envelopes provided by the study statistician, to either standard of care (SOC) or CT-FFR management. (See Figure 1. Study Diagram)

Inclusion Criteria

1. Emergency department or inpatients admitted through the ED with chest pain suspicious for ACS based on history and physical examination.
2. At least one biomarker (troponin) and electrocardiogram with no evidence of definite ACS.
3. A completed CCTA demonstrating $\geq$50% but <90% stenosis of at least one coronary artery branch.
4. CCTA test images with sufficient diagnostic quality for CT-FFR analysis.
5. Ability and willingness to provide informed consent.

Exclusion Criteria

1. Left main coronary stenosis of 50% or greater.
2. CCTA lesions demonstrating stenosis >90% ("subtotal"), or complex, high-risk plaque characteristics resulting in an a priori recommendation for triage to CATH by CCTA interpreting physician.
3. Attending physician a priori decision for CATH.
4. Prior coronary stent, coronary bypass or prior known myocardial infarction.
5. Clinical instability, such as hypotension, signs of shock, and/or unrelieved or accelerating chest pain.
6. Pregnancy

Obtaining Consent

Consent will be obtained by a co-investigator. Patients will have at least 20 minutes to consider whether they wish to consent.

Screening Log

A screening log will be maintained by research coordinators of all patients who were considered for enrollment and their demographics, clinical characteristics and the reason for their exclusion.

Sample Size

Our primary outcome is the CATH rate at 3 months. Based on our previous analyses from our IRB 2016-157 study (the FFR-ACP study), the SOC arm had a 89.5% CATH rate in the 71-99% stenosis group and 58.3% in the 51-70% stenosis group. With the 51-70% stenosis group having twice as many patients as the 71-99% group, we anticipate 68.7% of CATHs in all SOC controls. In our previous CT-FFR negative patients, there were 65.6% CATHs in the 71-99% stenosis group and 21.3% in the 51-70% stenosis group. Again with a 2 to 1 ratio, we anticipate an overall CATH rate of 36.1% in the FFR patients. Since these are estimates for the FFR group, we calculated several possibilities. All have 90% power with a significance level of 0.05%.

We determined a sample size of 87 patients per arm are needed to detect this difference. We intend to randomize 100 patients per arm to adjust for any lost to follow-up. We used PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance
H0: P1 - P2 = 0. H1: P1 - P2 = D1 ≠ 0.

Target Power	Actual Power*	N1	N2	N	P1	P2	D1 Diff	Alpha
0.90	0.90148	44	44	88	0.6870	0.3600	0.3270	0.0500
0.90	0.90458	59	59	118	0.6870	0.4000	0.2870	0.0500

0.90	0.90155	87	87	174	0.6870	0.4500	0.2370	0.0500

* Power was computed using the normal approximation method.

Randomization

We intend to include 200 patients (100 per arm). Patients will be randomized in a 1:1 ratio to Standard of Care (SOC) or CT-FFR-guided management, in alternating block design to ensure equal groups periodically. The order of randomization will be generated using SAS for Windows 9.3, Cary, NC. Randomization envelopes will be generated by a Beaumont Research Biostatistician and will be opened in sequential order. Once the patient has met all the inclusion criteria, none of the exclusion criteria and has signed the informed consent, the next envelope will be opened which will contain a slip indicating the patients assigned study number and to which arm they are being randomized.

SOC Group Management

Attending physicians will dictate SOC management according to their own clinical judgment. This could include discharge without further testing, EKG-only stress testing, stress echocardiography, stress myocardial perfusion imaging, direct admission and further noninvasive testing or CATH. In addition to standard testing, a blinded CT-FFR will be obtained for post hoc analysis, but it will not be used for patient management. Image data from our CT workstation will be sent directly to HeartFlow, Inc. over a secure research transfer node.

If attending physicians decide that SOC Group patients should undergo CATH, the protocol will specify an invasive fractional flow reserve will be performed on all lesions over 30% stenosis severity, to confirm the presence or absence of flow-limiting stenosis. This may be waived without protocol deviation if deemed unsafe by the severity of stenosis or due to clinical circumstances, as documented in a completed Physician Study Questionnaire.

CT-FFR-Guided Group Management

Patients in this group will be triaged using CT-FFR. Image data from our CT workstation will be sent directly to HeartFlow, Inc. over a secure Priority (STAT) transfer node. Interpreting physician will categorize CT-FFR results as follows:

1. CT-FFR >0.80. All CT-FFR segmental values are >0.80, with no indication of flow limiting ischemia. A non-binding recommendation that the patient undergo an initial trial of medical therapy will be made by the interpreting co-investigator. Attending physicians will be asked to complete a study Physician Questionnaire to determine whether they followed this recommendation or not, and if not, why not.
2. CT-FFR 0.70-0.80. These will be reported as values in the abnormal range without specific recommendations about whether CATH should be performed. Attending physicians will decide triage in consideration with other clinical data. Attending physicians will be asked to complete a study Physician Questionnaire to determine what clinical factors influenced their triage decision.

3. CT-FFR <0.70. These are abnormal values that are will be reported as high-risk. A non-binding recommendation that the patient undergo CATH will be made by the interpreting co-investigator. Attending physicians will be asked to complete a study Physician Questionnaire to determine whether they followed this recommendation or not, and if not, why not.

If attending physicians decide that study patients should undergo CATH, the protocol will specify that CATH-FFR will be performed on all lesions over 30% stenosis severity, to confirm the presence or absence of flow-limiting stenosis prior to coronary intervention or triage to medical therapy. This may be waived without protocol deviation if deemed unsafe due to the severity of stenosis or due to other clinical circumstances, as documented on the Physician Study Questionnaire.

Clinical Follow-up

Patients will be followed at 1 month, 3 month and 1 year using a chart review and structured telephone interviews. Permission will be requested from patients for examination of outside medical records including office records and hospital records related to coronary artery disease.

Risks of the Study

Both the SOC and CT-FFR management strategies are currently used routinely at Beaumont Health, where ED patients' diagnostic strategy is selected according to the preference of their individual attending physician. There is no risk from the research study associated with CCTA testing, as patients will already have completed a clinically ordered CCTA test prior to their eligibility for the study.

Both SOC and CT-FFR Group patients will undergo CATH if indicated by the results of noninvasive evaluation by CT-FFR or SOC physicians' clinical judgment. Based on the baseline year prior to CT-FFR (Sept. 2014 – Aug. 2015), the CATH rate in SOC group patients was 58%. The CATH rate in CT-FFR patients during the previous research period (IRB #2016-157) from Sept. 2015 – Dec. 2016 was similar, at 79/147 patients, or 54%. Thus, the risk from the incidence of CATH was similar in the two groups. The study protocol does require CATH-FFR in patients undergoing CATH (unless there are no lesions >30%). There is a theoretical risk of rare (<1%) vascular injury due to the CATH-FFR catheter, however, CATH-FFR is a standard clinically recommended procedure prior to revascularization in CATH patients to insure accurate diagnosis of flow-limiting stenosis. If attending physicians believe there is a clinical reason that CATH-FFR should not be done, such as a lesion that is too severe, it may be omitted without protocol deviation, as long as the reason is documented in the Physician Study Questionnaire. The additional radiation risk added by CATH-FFR is estimated at <1 mSv, equivalent to <1 year of annual background radiation from environmental sources.

Risks Associated with Heart Catheterization and Invasive Fractional Flow Reserve

Common (more than 10%)

- warm feeling or flushed feeling during adenosine infusion (which is part of the FFR study)
- lightheadedness
- nausea
- pain
- discomfort
- bruising or bleeding where the catheter is inserted in the groin
- radiation equivalent to 3-5 years of natural background radiation

Rare (less than 1%)

- contrast (dye) allergy
- diaphoresis (temporary excessive sweating)
- atrioventricular block -impaired conduction of the impulse that regulates the heartbeat (from adenosine)
- contrast induced nephropathy (deterioration of kidney function due to contrast exposure)
- hives (for those allergic to contrast dye)
- thrombosis (blood clots resulting in reduced blood flow)
- artery dissection (damage to the artery wall)
- perforation (a hole in the artery)
- stroke
- myocardial infarction (heart attack)
- death

Internal Safety Monitoring Committee

An Internal Safety Monitoring Committee will conduct regularly scheduled reviews of the safety of patients. Two physicians and a statistician who are not co-investigators will be included. Members will monitor safety outcomes, enrollment and completeness of follow-up. The Committee will meet after the first 20 patients and after each 40 subsequent patients till the study is completed. Any MACE event or major adverse outcome will be reported immediately to the Committee. The results of all Committee meetings will be provided to the IRB.

Data Analysis

Descriptive statistics will be given for all variables collected including indications for the test, demographics, patient history, CTA tech information, details from the physicians reading form, and from the CT-FFR. Missing data will remain missing and will not be replaced by substitutions or interpolation. Categorical variables will be summarized as counts and percentages. All continuous variables will be

summarized as means+/- the standard deviation where normal or median and 25th, 75th percentiles if not normal. The minimum and maximum will also be provided.

Catheterization Rate: The primary outcome will be examined between the 2 randomization arms using Pearson's Chi-square test. The Odds ratio and 95% confidence interval will also be reported.

Diagnostic Effectiveness: The secondary outcome will be defined as the proportion of accurate triage using CATH-FFR as the gold standard among all patients triaged to CATH by each strategy.

The SOC group will be analyzed according to actual triage decisions, as well as the hypothetical results of triage using a blinded CT-FFR analysis collected on those patients. The accuracy of triage between these two methods will then be compared.

Safety: The secondary outcome will be safety, as defined by the incidence of death, ACS or late unscheduled revascularization in each group.

Additional data analysis:

The Total length of stay, with sub-analysis of ED and inpatient length of stay will be reported as medians, 25th and 75th percentiles and minimum to maximum. The 2 randomization arms will be examined for each of these using Wilcoxon rank sum tests.

The hospital admission rate, the proportion of patients going to CATH in either arm who are found to have significant coronary stenosis (>50 stenosis), proportion of patients going to CATH who have a positive invasive FFR, percentage of patients undergoing PCI or CABG within 3 months, secondary diagnostic testing during index visit or within 3 months follow-up, including: recurrent ED visits, inpatient admissions for suspected acute coronary syndromes and/or CATH, outpatient or inpatient evaluation with cardiac CCTA or stress testing, cardiac surgery or PCI and MACE events (including all cause death, acute myocardial infarction, acute coronary syndromes, unscheduled revascularization after index visit) will be examined between the 2 arms using Pearson's Chi-square test where appropriate (Expected frequency>5 in all cells), otherwise Fisher's Exact tests will be used. The Odds ratios and 95% confidence intervals will also be reported.

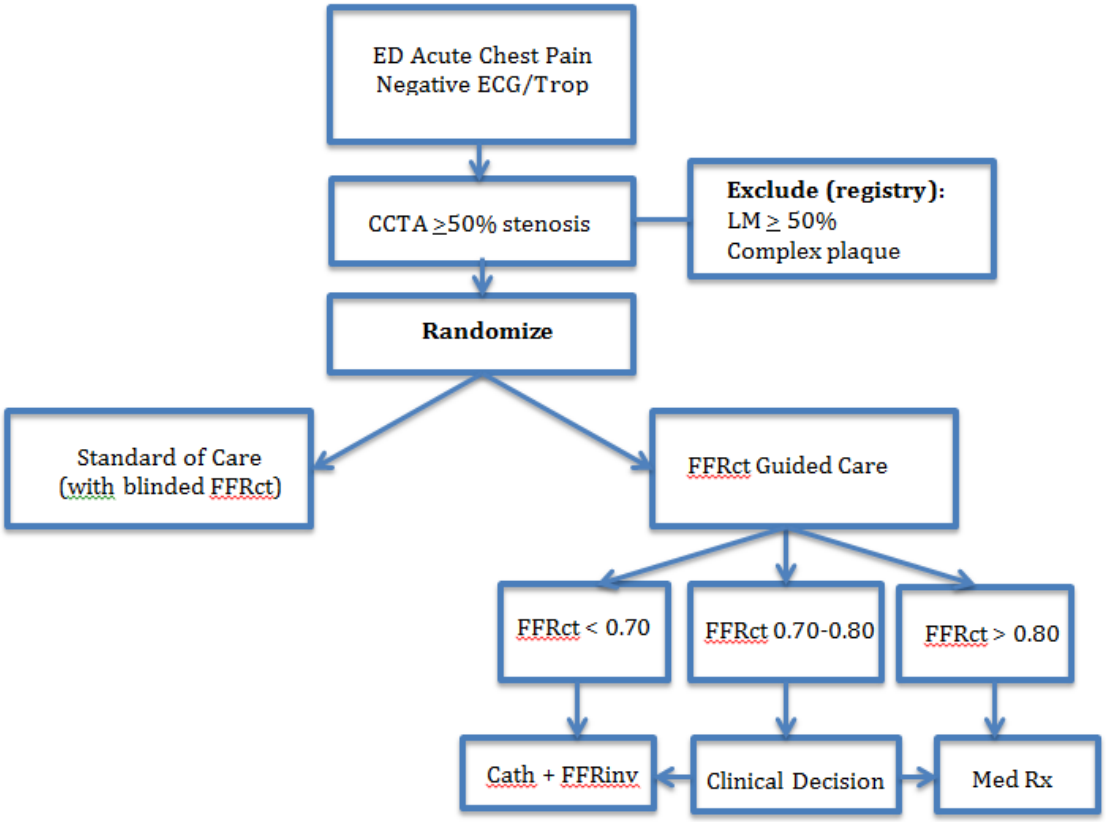
Estimated costs of care: including all estimated charges based on Beaumont hospital analysis multiplied by the standard Medicare cost/charge ratio will be reported as medians, 25th and 75th percentiles and minimum to maximum. The 2 randomization arms will be examined using Wilcoxon rank sum tests.

We may explore possible associations between patient characteristics demographics, prior history or testing indications and the randomization groups, safety outcomes,

or events using contingency table methods, t tests or Wilcoxon Rank Sum, as appropriate. Associations between radiation dose/efficiency and patient characteristics may be explored with nonparametric methods. We may also explore possible relationships between the CTA stenosis categories (0%, 1-49%, 50- 100%) and the CT-FFR final test results categories and CATH and revascularization results. The occurrence of clinical events recorded at the 3 month chart review and structured patient questionnaire will be related to the category of final noninvasive results (Normal, Probably Normal, Equivocal, Probably Abnormal and Abnormal) using methods for contingency tables which incorporate the natural ordering of test categories. Odds ratios (ORs) with associated 95% confidence intervals (CIs) may be shown relating the occurrence of safety outcomes to test response categories with the normal category as the reference point.

Analysis will be completed by a Beaumont Research Institute biostatistician using The SAS System for Windows version 9.3 (or higher).

Figure 1 - Study Diagram



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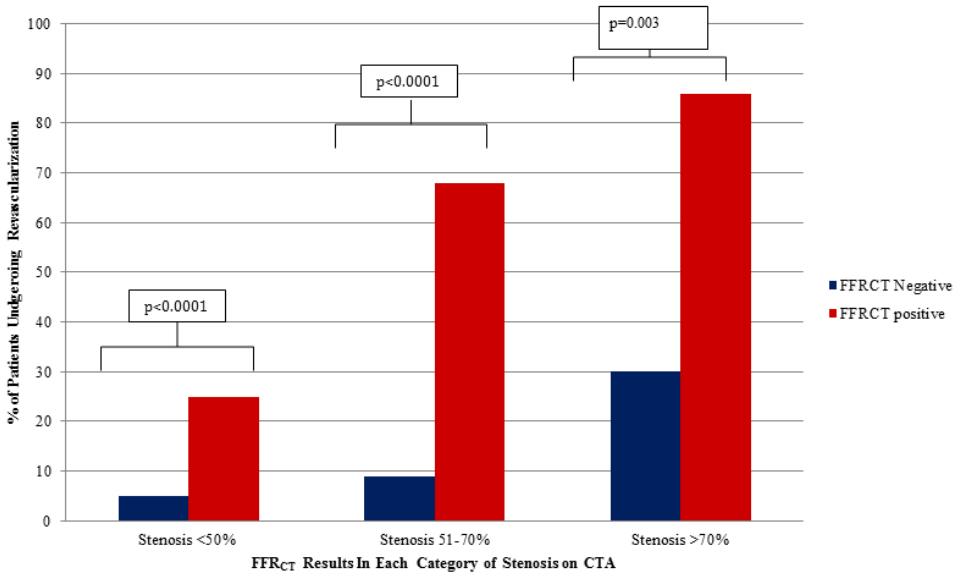
Appendix: Graph of Revascularization Rate by CT-FFR Results

From: Utility of Fractional Flow Reserve by Coronary CT Angiography in Acute Chest Pain. Chinnaiyan, Raff, et al. Submitted to Journal American College of Cardiology, July 2017



The relationship between cumulative revascularization with CT-FFR results among the three stenosis categories. In stenosis <50%, two patients underwent PCI, of which one had positive FFR_{CT}. Among patients with 50-70% and >70% stenosis, those with positive CT-FFR had higher revascularization (68.2% vs. 9.1%, p<0.0001 and 86.4% vs. 30%, p=0.003). The low rate of revascularization in CT-FFR negative patients suggests that a trial of medical therapy in such patients will be safe.