Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Observational invasive

Summary

ID

NL-OMON42550

Source
ToetsingOnline

Brief title
CREDENCE

Condition

- Coronary artery disorders

Synonym
coronary artery disease, ischemic heart disease

Research involving
Human

Sponsors and support

Primary sponsor: NewYork-Presbyterian Hospital and Weill Cornell Medical College
Source(s) of monetary or material Support: National Heart Lung and Blood Institute (NHLBI)

Intervention

Keyword: Computed Tomographic (CT), Coronary Arthery Disease, Myocardial ischemia, Myocardial Perfusion Imaging

Outcome measures

Primary outcome

The primary endpoint is the diagnostic accuracy of an integrated

stenosis-APC-FFRCT metric by CT, as compared to perfusion or perfusion-MBF

stress imaging testing for vessel territory-specific ischemia as determined by

FFR (gold standard).

Secondary outcome

- To compare the accuracy of the individual components of APCs or FFRCT to MPI

vessel-specific perfusion deficits or reduced MBF against ischemia by FFR.

- To determine the accuracy of FFRCT *virtual stenting* to post-PCI FFR value

of >0.80 and determine the correlation between the FFRCT *virtual stenting* to

post-PCI FFR.

Study description

Background summary

Despite improvements in therapies targeted at reducing disease burden, coronary artery disease (CAD) continues to afflict >16 million US adults, accounting for more than 1/3 of all deaths and responsible for 1.2 million hospitalizations annually. Coronary revascularization remains a mainstay of treatment for CAD, with >1.2 million percutaneous interventions and 440,000 coronary artery bypass surgeries performed annually in the US, and occurring in more than half of hospitalizations for CAD.
In clinical practice, revascularization is often performed on an ad hoc basis from semi-quantitative measures of percent luminal diameter narrowing of the artery visualized at the time of invasive coronary angiography (ICA). This practice stems from the pioneering research of Gould et al. who elegantly

demonstrated the relationship between stenosis and ischemia*as determined by myocardial blood flow (MBF) reserve*wherein flow to the myocardium is compromised as the coronary luminal diameter progressively narrows. This diminution in flow is most evident at hyperemic states and can begin as early as 40% stenoses, with more predictable reductions in hyperemic coronary flow for stenoses *70%. Yet the relationship between coronary stenosis and ischemia is complex, with a multitude of ensuing studies demonstrating an unreliable relationship between stenosis severity and reduced MBF. One contemporary example of this was highlighted in the nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial where*for patients with *70% stenosis*only 32% exhibited severe ischemia and 40% manifested no or mild ischemia by myocardial perfusion scintigraphy. This marked disparity suggests that, even in the setting of severe coronary stenosis, other factors are operative in the regulation of MBF.

Numerous non-invasive imaging tests have thus emerged for physiologic assessment of CAD, including cardiac magnetic resonance and myocardial perfusion scintigraphy by either single photon emission CT (SPECT) or positron emission tomography (PET). These modalities identify stress-induced regional myocardial perfusion defects as a surrogate for ischemia, and serve to identify individuals who may have severe coronary stenoses. Among the non-invasive stress modalities, MPI is performed most commonly, comprising 90% of the more than 10 million stress imaging test performed in the US annually. MPI by SPECT or PET determines extent, severity and reversibility of myocardial ischemia with high performance at a per-patient level. In pooled analyses, the sensitivity and specificity of MPI to diagnose coronary stenosis is 85-90% and 70-75%, respectively. Further, the prognostic value of MPI is unsurpassed by other non-invasive tests. Despite its high reported diagnostic performance, the *real world* accuracy of MPI is less sanguine.

CT of >64-detector rows has emerged as a promising non-invasive option for coronary angiography, with significant advances in CT temporal resolution and volume coverage now allowing for acquisition of virtually motion-free images at isotropic spatial resolution between 500-750 *m. In the first prospective multicenter study of its kind, CT was performed on 230 patients prior to ICA irrespective of baseline coronary calcium score, body mass index or heart rate. For severe stenosis, CT demonstrated a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 94%, 83%, 48%, and 99%, respectively, compared to ICA. While CT excels for discriminating stenosis, stenosis by CT for identifying ischemia is poor. At present, the *gold* standard assessment of the hemodynamic significance of coronary stenoses is invasive fractional flow reserve (FFR). Recent advances in computational fluid dynamics (CFD) now enable calculation of coronary flow and pressure fields from anatomic image data. Applied to CT, these technologies enable calculation of FFR (the ratio of maximal myocardial blood flow through a diseased artery to the blood flow in the hypothetical case that the artery was normal) without additional imaging or administration of additional medications at the time of CT.

Numerous in vivo anatomic imaging techniques exist that allow for visualization

of atherosclerotic plaque characteristics (APCs) of CAD beyond stenosis severity. Of these, intravascular ultrasound (IVUS) has been most widely employed. IVUS-visualized APCs distinguish culprit lesions implicated in acute coronary events.

Study objective

The present proposal seeks to integrate the entirety of anatomic and physiologic information measurable by CT to optimize the precise identification of coronary vessels that manifest ischemia. These determinations will take place in the largest cohort of patients undergoing CT, MPI, ICA and FFR, and on a background of comprehensive core laboratory-interpreted image assessment and clinical data collection; thus rendering this proposal the most thorough effort to date to determine the utility of a novel integrated anatomic-physiologic approach to diagnosing vessel-specific ischemia. In doing so, this proposal aims to establish the rationale for a novel diagnostic paradigm that is more accurate than conventional stress imaging testing for not only identifying patients who manifest ischemia but also pinpointing the coronary lesions that are the cause; thus, allowing for better selection of individuals for revascularization and eliminating unnecessary invasive procedures.
To date, the relative performance of traditional stress imaging testing compared to the entirety of information proffered by CT (e.g., FFRCT and APCs) has not been assessed compared to an unbiased gold standard. The study proposed herein will directly address this unmet need.

Study design

The CREDENCE trial will be a prospective multicenter cross-sectional study of 618 individuals (n=309 [derivation cohort]; n=309 [validation cohort]) who will undergo MPI, CT, ICA and FFR. For the purposes of the study, either MPI or CT will have been performed for clinical purposes, with the other test being performed as part of trial procedure. Study analyses will focus on the diagnostic performance of the information derived by MPI versus CT against an invasive gold standard of ICA + FFR for an endpoint of vessel territory-specific ischemia. In keeping with prior studies, vessel territories will be comprised of the left anterior descending artery [LAD] (and diagonal branches), the left circumflex artery [LCx] (and obtuse marginal branches) and the right coronary artery [RCA] (and posterolateral branch and posterior descending artery).
The targeted population will be those for whom CT and MPI testing confer the largest potential benefit; that is, for those with suspected CAD who are being referred for non-emergent clinically indicated ICA based upon an imaging study (either MPI or CT). The study is considered non-significant risk because all subjects will undergo clinically-indicated ICA as planned, with FFR performed in vessel territories with >50% stenosis. Additional study procedures will include only one additional non-invasive procedure with a very low rate of

complications (<1%).

Study burden and risks

MPI can be performed by a variety of methods, including SPECT, PET and CMR. These test are routinely and commonly employed for evaluation of patients with suspected CAD in the clinical setting. Risks associated with stress testing are very low. For pharmacologic stress testing using adenosine, there may be a low incidence of wheezing or shortness of breath. These symptoms may require treatment in the low frequency of patients for which they occur, but most commonly dissipate very quickly after cessation of adenosine. MPI performed by SPECT or PET exposes patients to small amounts of radiation. For the CREDENCE study, the MPIs will comprise the majority of tests that have been performed for clinical purposes and will thus not represent any additional radiation exposure. The estimated radiation dose for the SPECT or PET examination is estimated to range between 3-12 milliSieverts (mSv). In comparison, the estimated annual radiation exposure from background radiation is approximately 3 mSv for an adult individual living at sea level.
CCTA exposes patients to small amounts of ionizing radiation, the estimated effective biological radiation dose for the CCTA examination is estimated to range between 2-8 mSv. In comparison, the average yearly effective dose of natural background radiation is ~3 mSv, the allowed annual exposure of radiation workers is 50 mSv, the allowed exposure in five years is 100 mSv. CCTA performance necessitates use of iodinated contrast. Minor reactions to x-ray contrast material can occur such as itching or hives with an incidence of approximately 1 in 200 subjects. These reactions are treated with intravenous Benadryl (antihistamine). More severe reactions that are very infrequent include hypotension, laryngospasm and bronchospasm. The incidence of these reactions is estimated at about 1 in 5,000 and is treated with intravenous epinephrine. Contrast-induced nephropathy (CIN) is expected to be a very rare event among this patient population because patients with already impaired renal function will not be enrolled.
All ICAs will be performed as part of routine clinical care. No ICA will be performed for non-clinically indicated research purposes. Cardiac catheterization procedures, including ICA, carry a very low risk of complications that is less than 1% for ICA. If FFR is not performed as a part of clinical care, it will be done for the purpose of this research study. FFR is a short and painless procedure that will take approximately 10-15 minutes. FFR requires the use of a very thin wire to measure the pressures in the coronary arteries. This procedure is very safe but can result in similar potential complications of ICA. Risk of coronary dissection from FFR is 0.6%. In addition, FFR measurements require the use of intravenous adenosine. The administration of adenosine is routine in clinical practice and in the performance of FFR. Side effects of adenosine, however, include facial flushing, a temporary rash on the chest, lightheadedness, diaphoresis, nausea or a metallic taste after administration. These symptoms are almost always

temporary, and generally last less than a minute.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age *18 years
Scheduled to undergo clinically-indicated non-emergent invasive coronary angiography

Exclusion criteria

1) Known CAD (myocardial infarction [MI], percutaneous coronary interventions [PCIs], coronary artery bypass graft [CABG],)

2) Hemodynamic instability
3) Inability to provide written informed consent
4) Concomitant participation in another clinical trial in which subject is subject to investigational drug or device
5) Pregnant state
6) Absolute contraindication to iodinated contrast due to prior near-fatal anaphylactoid reaction (laryngospasm, bronchospasm, cardiorespiratory collapse, or equivalent)
7) Serum creatinine *1.7 mg/dl or Glomerular Filtration Rate <30 ml/min
8) Baseline irregular heart rhythm (e.g., atrial fibrillation, etc.)
9) Heart rate *100 beats per minute
10) Systolic blood pressure *90 mm Hg
11) Contraindications to * blockers or nitroglycerin or adenosine
12) BMI >40 kg/m2
13) <3 maanden geleden straling gekregen

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-07-2016
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	09-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL53928.029.15