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ULTRA-HIGH-RESOLUTION CT VS. CONVENTIONAL ANGIOGRAPHY FOR DETECTING HEMODYNAMICALLY SIGNIFICANT CORONARY ARTERY DISEASE--THE CORE-PRECISION MULTI-CENTER STUDY

(NCT04272060)

1. Abstract

Cardiac catheterization with invasive coronary angiography is the gold standard for determining the presence or absence of significant coronary heart disease (CHD). However, cardiac catheterization is costly and, as an invasive procedure, it is associated with some risk of adverse events, rarely even stroke, myocardial infarction, or death. It would be highly desirable if noninvasive imaging could replace cardiac catheterization for the purpose of identifying and guiding the management of patients with CHD. Recent advances in multidetector computed tomography angiography (CTA) have allowed rapid, noninvasive coronary artery imaging in patients with suspected CHD. CTA yields high accuracy for identifying patients with CHD when compared to cardiac catheterization and CTA is used now in lieu of invasive angiography in many clinical scenarios, e.g., to rule out CHD in lower risk patients prior to cardiac surgery or patients with new cardiomyopathy. CTA has also shown to be an effective goalkeeper for cardiac catheterization, leading to fewer invasive procedures and lower costs while not compromising patient outcome.

However, CTA diagnostic accuracy is reduced in the setting of severe coronary artery calcification and coronary stents due to its inferior spatial resolution compared to cardiac catheterization, which has hindered more widespread use of CTA in lieu of invasive angiography. Because high-risk patients often have severe coronary calcification or stents, the application of CTA has been particularly limited in this important patient group. Recently, an ultrahigh-resolution CT scanner was released which has shown promise to overcome the limitation of conventional CTA in the setting of severe coronary artery calcification or stents. This ultrahigh-resolution "precision" CT scanner (UHR-CT) contains detector rows with half the width than currently available systems (0.25 mm vs. 0.5 mm) resulting in approximately twice the spatial resolution.

The purpose of this investigation is to test the hypothesis that ultra-high-resolution CTA is not inferior to the current standard of cardiac catheterization for identifying significant CHD in patients with high-risk characteristics, including severe coronary artery calcification and coronary stents.

To generate the study hypothesis, we propose to enroll 200 patients over 18-24 months. Patients referred for cardiac catheterization with known CHD or severe coronary calcification and suspected obstructive coronary artery stenosis will be included. All patients will undergo both cardiac catheterization and UHR-CT for determining significant CHD as defined by coronary functional assessment. The primary end point will be the diagnostic accuracy by area-under-curve (AUC) method for identifying patients with hemodynamically significant CHD.

2. Objectives

Primary Objective

The primary objective of this study is to test the hypothesis that noninvasive UHR-CT is not inferior to invasive coronary angiography by cardiac catheterization for identifying patients with hemodynamically significant CHD.

Secondary Objectives

Secondary objectives include testing the diagnostic accuracy of UHR-CT vs. cardiac catheterization on a vessel and segment-based analysis, and comparison of adverse events and radiation doses between the CT and conventional angiography groups.

Patient-Based Hypotheses

1) Diagnostic accuracy of UHR-CT using visual assessment of coronary artery disease is non-inferior to invasive, conventional coronary angiography for identifying patients with hemodynamically significant CHD defined by an QFR-value of <0.8 in at least one vessel of 2.0 mm or larger in diameter.
2) Diagnostic accuracy of UHR-CT using quantitative assessment of coronary artery disease is non-inferior to invasive, conventional coronary angiography for identifying patients with hemodynamically significant CHD defined by an FFR-value of <0.8 in at least one vessel of 2.0 mm or larger in diameter.
3) UHR-CT coronary angiography is associated with lower radiation dose than conventional, invasive coronary angiography.
4) UHR-CT coronary angiography is associated with lower adverse effects than conventional, invasive coronary angiography.

Vessel Based Hypotheses

1) Diagnostic accuracy of UHR-CT using visual assessment of coronary artery disease is non-inferior to invasive, conventional coronary angiography for identifying vessels with hemodynamically significant CHD defined by an QFR-value of <0.8 in a vessel of 2.0 mm or larger in diameter.
2) Diagnostic accuracy of UHR-CT using quantitative assessment of coronary artery disease is non-inferior to invasive, conventional coronary angiography for identifying vessels with hemodynamically significant CHD defined by an FFR-value of <0.8 in a vessel of 2.0 mm or larger in diameter.

Lesion-Based Hypotheses

3) Diagnostic accuracy of UHR-CT using visual assessment of coronary artery disease is non-inferior to invasive, conventional coronary angiography for identifying lesions with hemodynamically significant CHD defined by an QFR-value of <0.8 in a vessel of 2.0 mm or larger in diameter.
4) Diagnostic accuracy of UHR-CT using quantitative assessment of coronary artery disease is non-inferior to invasive, conventional coronary angiography for identifying lesions with hemodynamically significant CHD defined by an QFR-value of <0.8 in a vessel of 2.0 mm or larger in diameter.

3. Background

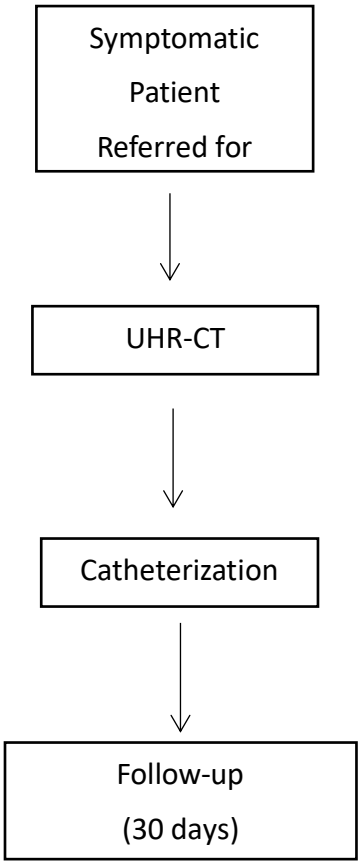
Cardiac catheterization with invasive coronary angiography has remained the gold standard for determining the presence or absence of significant coronary luminal stenosis despite its limited accuracy compared to the standard of intravascular ultrasound. Because of the inherent risks involved with this invasive procedure (e.g., stroke, myocardial infarction, death or need for emergency surgical intervention with a major complication rate of 1-2%), and considerable costs, non-invasive assessment of coronary artery disease would be preferred. Advances in multidetector computed tomography angiography (CTA) have made the non-invasive imaging of the coronary arterial lumen and wall feasible (Raff et al, J AM Coll Cardiol 2005). Numerous studies have since demonstrated good accuracy of CTA to identify patients with obstructive coronary artery disease. However, studies also demonstrated that CTA's diagnostic accuracy is only modest in patients with severe coronary artery calcification (Arbab-Zadeh et al, J Am Coll Cardiol 2012) or stents (Wykrzykowska et al, Am J Roentgenol 2010), representing a major limitation of the technology. This limitation is due to fair spatial resolution and associated image artifacts in the setting of an attenuation-based image reconstruction algorithm. In this situation, high density structures, such as calcium or metal, will disproportionally dominate information derived from an affected image voxel leading overrepresentation of these structures on image display (partial volume effect).

Recently, an ultrahigh-resolution CT scanner has been released which has shown promise to overcome the limitation of conventional CTA in the setting of severe coronary artery calcification or stents (Motoyama S et al., J Circulation 2018, Takagi H et al., Eur Radiol 2018). This ultrahigh-resolution "precision" CT scanner (UHR-CT) contains detector rows with half the width than currently available systems (0.25 mm vs. 0.5 mm) resulting in approximately twice the spatial resolution (Tanaka R et al., Clin Radiol 2018). In a pilot investigation from our laboratory in 15 patients, UHR-CT yielded high diagnostic accuracy

for detecting significant lumen obstruction despite an average calcium score of greater than 1,000 (Latina J, et al, Radiology CV Imag 2021). The purpose of this investigation is to conclusively test the hypothesis that high-resolution CTA is not inferior to the current standard of cardiac catheterization for identifying significant CHD in patients with high-risk characteristics.

4. Study Procedures

a) Study design



The CORE-PRECISION MULTI-CENTER study is a prospective diagnostic accuracy study at three international sites comparing the diagnostic accuracy of UHR-CT to conventional, invasive coronary angiography by cardiac catheterization for the presence of hemodynamically significant CHD in 200 patients with high pretest probability of obstructive CHD. The enrollment at all centers is expected to commence in the summer of 2022: Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center, Baltimore, USA, Iwate University Medical Center, Iwate, Japan, and Einstein Medical Center, Sao Paulo, Brazil. Sites will obtain approval from their local IRB and all patients will sign informed consent prior to participation. Each study site is expected to enroll participants, with the flexibility to enroll more if other sites experience slow recruitment.

Enrollment has been ongoing since November of 2019 at JHU as part of a pilot study using the same protocol with minor variations. For each participant, it is anticipated that the Screening Evaluation Periods will last less than 2 months and will be followed by the Imaging period (less than 60 days). All patients will be followed by additional 30 days after cardiac catheterization for occurrence of adverse events.

Screening-Evaluation Period

The screening period will begin when a patient is scheduled for a clinically indicated coronary angiogram. The protocol inclusion and exclusion criteria will be reviewed for each potential participant. Patients without history of CAD may enter an extended screening period that involves the first component of the CT imaging examination, namely the coronary calcium scan. If this scan shows a calcium score <400, these patients will be considered late screen failures, will not proceed to contrast-enhanced coronary CT angiography, and will be

excluded from further participation in the trial. Patients with a calcium score of 400 or greater will proceed to coronary CT angiography and study participation.

If the patient appears to be eligible for the study based on the initial evaluation, informed consent will be obtained. To reduce in person activities, baseline information and medical history will be collected via telephone call. Blood will be obtained at the time of CTA (during IV placement) for laboratory testing of serum creatinine.

The clinically indicated coronary angiogram will not be delayed to complete the research protocol. If the CTA scan cannot be scheduled prior to the clinically indicated coronary angiogram the patient will not be enrolled in the trial. Consented patients will continue to be evaluated for participation in the trial through the imaging period.

Imaging Period

The imaging period will consist of two tests: 1) ultra-high-resolution CT (UHR-CT) angiography; 2) conventional coronary angiography (CCA). All enrolled patients referred for a clinically indicated catheterization will first receive a UHR-CT angiogram to avoid conflict with coronary artery revascularization.

UHR-CT Imaging

Patients will have one 18-20 gauge intravenous lines placed, preferably in an antecubital vein for contrast administration. The patient may be hydrated with normal saline intravenously (250 – 500 ml) prior to UHR-CT scanning, as per site practice. The patient will lie supine on the scanner table and be attached to a 3-lead system attached to the scanners monitoring system during scanning. Irregular heart rhythms will be noted and a full 12-lead ECG obtained if necessary to confirm cardiac rhythm. Patients may receive oral metoprolol and/or oral ivabradine 1-2 hours prior to the CT according to a hospital approved heart rate control algorithm. Goal for heart rate control is less than 60 bpm at the time of scan acquisition. Scout images for determining scanning range will be obtained in the anterior-posterior and lateral views. Patients with systolic blood pressure ≥100 will receive 0.4-1.2 mg sublingual nitroglycerin for vasodilation as per local practice. The adequate calcium score scan protocol will be confirmed on the scanner for each participant prior to the initiation of the calcium score scan. Patients will then be asked to hold their breath (approximately 10-15 seconds) and non-contrast CT imaging will be performed starting just cranial to the coronary ostia and extending just caudal to the apex of the heart in order to obtain a coronary calcium score. To limit radiation exposure, a coronary calcium score will only be generated for patients who

have not previously been stented as the presence of stents affects the accuracy of the calcium score. CT angiogram will then be performed to evaluate the coronaries using iodine contrast.

UHR-CT Protocol for Coronary Angiography

1) If the patient has not had prior stent placement or calcium scanning performed as part of the screening process, coronary calcium scan will be performed using the following protocol:

-No contrast.

-CT Imaging: tube voltage = 120kV, tube current = 150 mA, weight adjusted, gantry rotation speed = 0.230 seconds for half rotation, slice thickness = 3 x 4 mm, range = 144 mm. Estimated radiation dose = 0.5-2.0 mSv. Standard resolution mode.

2) Coronary angiography:

Coronary arterial imaging will be performed during a 4-6 ml/sec intravenous iodinated contrast infusion for a total volume of 60-120 ml. The automated bolus tracking feature will be used to judge contrast bolus arrival and optimize image quality.

Images will be prospectively triggered using ECG gating which reduces radiation exposure to the patient compared to retrospective gating. Tube voltage and current will be adjusted according to image noise characteristics during scout imaging. A tube setting of 120 kV with 580 mA will be required for most patients in the setting of severe calcification and/or stenting. Target exposure will be 70-80% of the R-R cycle for heart rate ≤60 bpm. Heart rate of 61-70 will require a widened exposure window of 65-85% of the R-R cycle. Gantry rotation will be 350 ms with a 160 x 0.25 mm collimation in super high resolution mode, requiring approximately 6.5 second scan time. The estimated range of radiation dose for CT coronary angiography will be 4.3.0-10.7 mSv depending on patient size and weight.

Total estimated radiation dose, including calcium scoring, and CT coronary angiography, will therefore range between 4.8-12.7 mSv. For comparison, a standard nuclear stress test typically results in a radiation dose of 10-12 mSv to the patient (Einstein A, Circulation 2007). Diagnostic cardiac catheterization for conventional coronary angiography typically averages 12 mSv radiation dose (Rochitte et al., Eur Heart J 2014).

A copy of the anonymized raw data (without any patient identifiers) will be forwarded to the CT Core Laboratory for analysis within 1 week of the scan. CT raw data and reconstructed data will be saved by the site for at least 5 years after completion of the study.

Within 3 weeks of the CTA, the CTA will be reviewed for non-cardiac findings by a locally qualified, institutionally approved radiologist, and reported. The investigator will report these findings to the patient's clinical physician and patient in a timely fashion preferably prior to or during the 30-day follow-up.

A pre-catheterization serum creatinine should be obtained post CTA (per local standard, or preferably > 2 days post CTA).

Conventional Coronary Angiography

Patients will undergo their clinically indicated cardiac catheterization/coronary angiography, within 60 days of CT imaging with a recommended goal of completing all imaging within 30 days. A time window of ≥ 24-48 hours is recommended between CT imaging and conventional coronary angiography to minimize cumulative risk of contrast exposure from these two tests. Coronary angiography will be performed according to general standards to obtain optimum angles. Isocenter calibration must be performed for all studies to enable quantitative flow reserve (QFR) assessment. Intracoronary nitroglycerine will be administered (150-200 mcg) prior to first image of the left coronary artery system and right coronary artery. This is to standardize the vasomotor state of the coronary artery and eliminate any potential for catheter-induced changes (i.e., catheter induced spasm).

Fractional-flow-reserve (FFR) assessment may be performed as clinically indicated but not solely for research purposes. Coronary angiographic images will be saved in the universal DICOM format and forwarded to the Angiographic Core Laboratory for Quantitative Coronary Angiographic Analysis. Quantitative coronary analysis (QCA) will be performed using standard, validated analysis software from Medis Medical Systems (Medis QCA). QFR will be performed using a dedicated software (QFR, Medis Medical Imaging Systems).

A post-catheterization serum creatinine should be obtained per local standard, or preferably within 48-72h post invasive coronary angiogram.

Data Sharing

The data acquired for this study are owned by the study funder, Canon Medical Systems. Data sharing will require authorization by the study sponsor. The sponsor may use results and data from this study for researching, developing products or equipment, software for such product or equipment, or its enhancements or upgrades and in clinical application training. JHU shall remove any confidential information about a patient, including, without limitation, the patient's identity or other information which JHU is obligated to maintain as

confidential under applicable laws, from the reports and images before providing these to the sponsor.

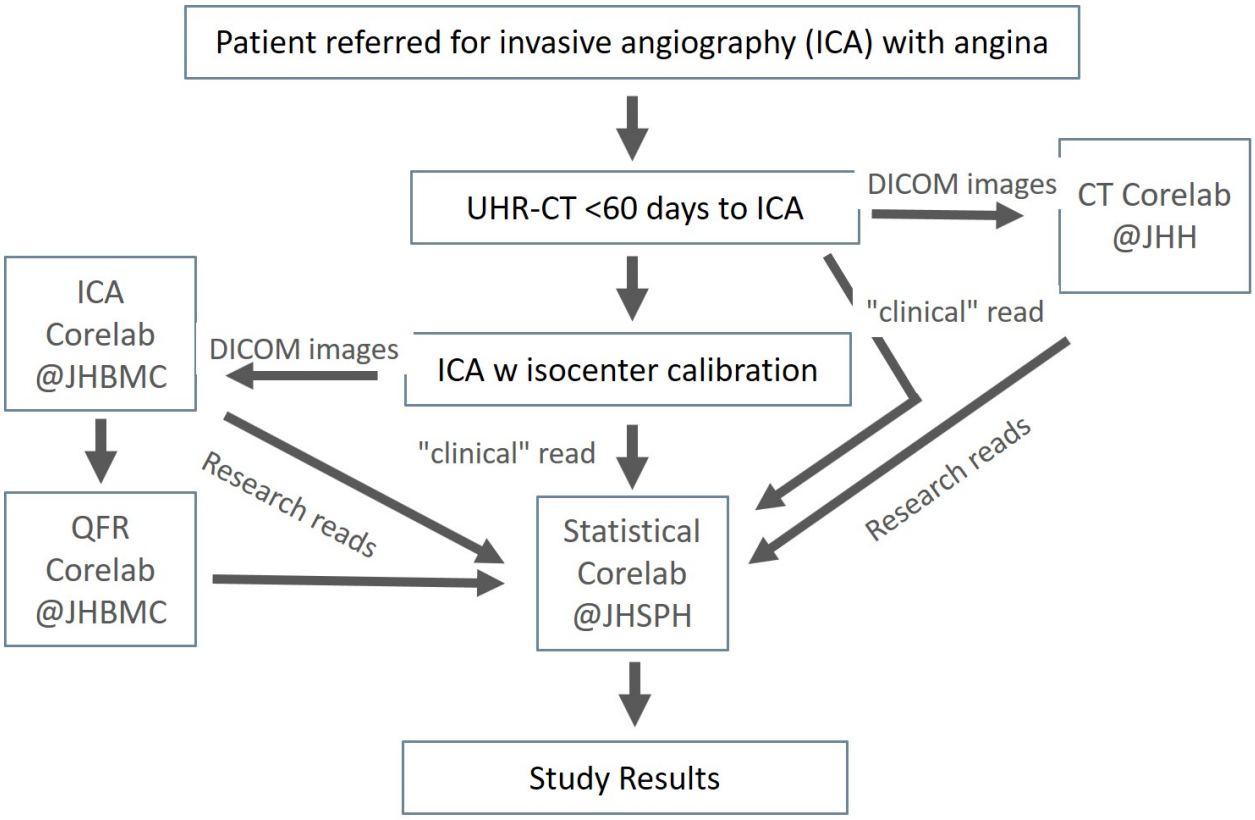
Follow-Up Period

Assessment of cardiovascular events will be performed post CTA, at the time of coronary angiography, and 30 days post conventional coronary angiography via telephone contact and review of electronic health records.

Study Organization

JHU will serve as the study and data coordinating center. The three sites will obtain individual authorization for patient enrollment at their respective institutional review boards using the same protocol. No central IRB will be utilized. However, the coordinating center at JHU will monitor all research activities at the three participating sites and will assure compliance with the approved protocol.

Data will be sent from the three study sites to the respective core laboratories at JHU. An overview of the dataflow is shown below.



Data will be anonymized according to an algorithm determined by the data coordinating center before transfer to JHU for analysis. Data include imaging data, patient characteristics, including age, sex, medical history, risk factors for CHD, medications, results from laboratory testing. Data will be sent via electronic transfer in DICOM format for images while raw data and hard copies will be maintained at the study sites. Other participant data will be entered by each site directly using online data entry forms (REDCAP). Data analysis will be performed at the data coordinating center at the JH School of Public Health.

b) Study duration and number of required visits by research participants

The study duration is 3 years, including 18-24 months of enrollment and up to 12 months data analysis. Only up to one visit is required by participants for research purposes (if CTA is being performed for research). No other visits are required.

c) Blinding and justification for blinding or not blinding

Healthcare providers and investigators caring for enrolled patients will be blinded to data acquired for research purposes only, e.g., CTA results if they were solely acquired for research. Investigators evaluating CTA, ICA, or QFR images, will be blinded to the results of the other imaging data. Core laboratories will be located on JHU campus but in distinct locations on the Johns Hopkins Medical Campus to avoid cross-talk.

d) Justification of why participants will not receive standard care or will have current therapy stopped.

All participants will receive standard care. No current therapy will be stopped because of this research.

e) Justification for inclusion of a placebo or non-treatment groups

Not Applicable. No therapy will be given as part of research.

f) Definition of treatment failure or participant removal criteria

This study does not involve treatment. Subject removal will occur in the event that a participant experiences a previously unknown allergic reaction to iodinated contrast. Patients also may be removed if they are not able to follow instructions necessary to complete the study, or request withdrawal from the study.

g) Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

No treatment will be given as part of research. If the participant's participation ends prematurely, there will be no impact on clinical care. Research information will be utilized as feasible.

5. Inclusion Exclusion Criteria

Inclusion Criteria

A. Patients aged 45-85 years with history of CHD will be asked to participate. History of CHD is defined as history of coronary artery revascularization by percutaneous coronary intervention (PCI), stenosis of 50% or greater on prior angiogram (CTA or invasive), or a calcium score of 400 or greater. Women of child bearing potential must demonstrate a negative pregnancy test within 24 hours of the study CTA.

AND

B. Suspected obstructive coronary artery stenosis based on clinical history and/or noninvasive testing, prompting a clinical referral for invasive coronary angiography; and/or planned PCI within the next 60 days.

AND

C. Ability to understand and willingness to sign the Informed Consent Form.

Exclusion Criteria

A. Known allergy to iodinated contrast media

B. History of multiple myeloma or previous organ transplantation

C. Renal failure (defined as estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) with the exception of patients with documented end stage renal disease on chronic dialysis who may participate

D. Atrial fibrillation or uncontrolled tachyarrhythmia, or advanced atrioventricular block (second or third degree heart block) at the time of imaging.

E. Evidence of severe symptomatic heart failure (NYHA Class III or IV) at the time of imaging;

F. Known or suspected severe aortic stenosis

G. Previous coronary artery bypass or other cardiac surgery

H. Patients without history of CHD who had no or only mild coronary calcification on chest CT imaging within the past 5 years or had their most recent coronary calcium scan with a score <400.

I. . The presence of any other history or condition that the investigator feels would be problematic

6. Study Statistics

a. Primary outcome variable

The primary analysis will be a comparison of the diagnostic capability of the UHR-CT angiography to conventional coronary angiography at the patient level with the reference standard being quantitative flow reserve (QFR). A positive patient will be defined as having at least one vessel with a flow reserve <0.8.

b. Secondary outcome variables

A secondary analysis will be performed at the vessel level. Similar to the primary analysis, a comparison of the diagnostic capability of UHR-CT angiography and conventional coronary angiography will be performed. A positive vessel will be defined as having at least stenosis with a flow reserve <0.8. In addition, study groups will be compared for occurrence of adverse effects, radiation doses, contrast volume, and costs.

c. Statistical Plan including sample size justification and interim data analysis

In order to assess the diagnostic accuracy of UHR-CT angiography compared with invasive angiography to flow reserve we will consider the result from CT angiography as continuous measures on a patient, vessel, and segment level. The analysis will be based on the area under the receiver operating characteristic (ROC) curve (AUC). The gold standard will be coronary flow reserve estimations by either FFR, iFR, or QFR. Construction of the ROC curves using the CT and ICA measures will be based on the well-known result that the curve based on the risk score has the same ROC curve as the optimal curve based on the likelihood ratio (Pepe, 2003, Result 9.4). The risk score will be estimated by logistic regression analysis with CT angiography and ICA as independent predictor variables. The resulting risk score (the linear predictor from the logistic regression) will be used to construct the ROC curve. The AUC and its standard error will be estimated nonparemetrically using standard methods (Pepe, 2003).

Based on the literature (Rochitte et al, Eur Heart J 2014, Budoff et al, Jacc-Img 2015, Stuijezand et al, JAMA Cardiol 2020) we are assuming an AUC of 0.83 for CT vs. 0.77 for ICA. Results will be compared using AUC analysis and 95% CI interval. We determined 6% as an acceptable noninferiority margin. For achieving 80% power with an alpha error of 5%, we require 180 patients. Given the complexity of the imaging protocol, we anticipate a 10% drop out rate which brings the **total required sample size to 200 patients.**

d. Early stopping rules

For any individual patient if an adverse reaction to intravenous contrast noted, if the clinical course changes or an intercurrent illness is noted in a patient; consideration will be given immediately for study withdrawal. There is no plan for early termination of study for efficacy.

However, a blinded interim analysis is planned after 12 months of enrollment to assess if enrollment goals should be adjusted to meet statistical requirements for executing the main outcome analysis. Enrollment may be shortened or extended accordingly.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

CT Imaging

Risks of CTA imaging could include contrast related risks, radiation related risks, and symptoms of claustrophobia.

Contrast related: Patients may experience allergic reactions of CT contrast, even if previously unknown. These may include mild reactions (itching, hives, flushing, and nausea) to serious reactions including anaphylactic allergic reactions that can potentially lead to death. Medical personnel are always available to administer necessary medical care in the event of allergic reactions. Contrast may also cause contrast-induced nephropathy and renal damage. Hence patients with renal insufficiency are excluded from the study.

Radiation related: Short term risks of high doses of radiation (far higher than used in this study) include skin burns, gastrointestinal symptoms. Long-term risks of radiation include damage to cells and reduction in fertility. Women of childbearing age will have a lead apron placed over their abdomen and pelvis in order to reduce the radiation exposure to the ovaries. The estimated radiation dose for the entire cardiac computed protocol will be 4.8 mSv to 12.7 mSv depending on patient size and weight. A radiation dose of 10 mSv is commonly associated with a 0.1% increased risk of cancer (Einstein A, Circulation 2007).

The risks from a single blood draw and the placement of intravenous lines are minimal, but include: bleeding at the site, bruising, infection, cellulitis, and fainting (vasovagal reaction).

Fast Acting, Short lasting Nitrates (i.e., sublingual nitroglycerine)

Nitroglycerin is a FDA approved drug used as a vasodilator to treat heart conditions, such as angina and chronic heart failure. The side effects include Headache (most common; 50% to 63%), lightheadedness (6%), syncope (4%), dizziness. Allergic reactions, application, cardiovascular collapse, exfoliative dermatitis, methemoglobinemia (rare; overdose), pallor, palpitation, rash, rebound hypertension, restlessness, shock, vertigo, weakness reported in extremely rare instances (<1%).

Beta-Blocker (Metoprolol)

Metoprolol is an FDA approved selective β_1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. The side-effects include tiredness and dizziness (10%). depression (5%), rash (5%), diarrhea (5%) shortness of breath (3%), chest pain (1%), wheezing (1%). Palpitations, congestive heart failure, peripheral edema, syncope, chest pain, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, heartburn, hypotension, mental confusion, short-term memory loss, headache, somnolence, nightmares, and insomnia reported in very rare instances (<1%).

Ivabradine

Ivabradine is an FDA approved selective blocker of the "funny channel" in the sinus node, leading to slowing of the sinus impulse and associated lowering of heart rate. Ivabradine was approved in the US for the treatment of heart failure with reduced ejection fraction but has been used "off-label" for the purpose of heart rate control. The drug is available in oral form and has an onset of 60-120 minutes. Precautions include a history of atrial fibrillation and severe hypotension. Common side effects may include bradycardia (10%), hypertension (8.9%), atrial fibrillation (8.3%), and visual brightness (2.8%).

b. Steps taken to minimize the risks.

Patients with known allergic reactions to CT contrast or to iodine will be excluded from participation. At least 1 investigator (Physician) will be present during the study in the case of the need to treat a previously unknown contrast allergy and during saline infusion to monitor for adverse reactions. Patients with a reduced glomerular filtration rate (<60) or history of contrast induced nephropathy will be excluded. All patients will be required to have a minimum of 24 hours (recommended at least 48 hours) between their CTA scan and any other procedure requiring iodinated contrast administration, i.e., cardiac catheterization. All patients will have a creatinine repeated prior to their cardiac catheterization. A follow-up creatinine is strongly recommended within 72 hours after catheterization procedure. Patients will be hydrated with normal saline prior to and following their CTA scan. Menstruating women must have a negative pregnancy test within 24 hours of CTA and angiographic imaging. Pregnant women are excluded. Women of childbearing age will have a lead apron placed over their abdomen and pelvis in order to reduce the radiation exposure to the ovaries. Prospective scan triggering will be applied to all patients to reduce radiation dose compared to retrospective gating.

Intravenous catheters will be inserted by a nurse/technician who is well trained in that procedure.

All patients will be carefully screened for the presence of any contraindications prior to them signing the consent form.

It is recommended that nitroglycerin will **not** be administered to subjects who have used phosphodiesterase V inhibitors in the past 72h, i.e., treatment for erectile dysfunction. It is recommended that NSAIDS will be held prior to contrast media administration.

c. Plan for reporting adverse events unanticipated problems or study deviations.

Notification of events occurring within 30 days of study enrollment (CTA imaging) will be transmitted within 24 hours of occurrence electronically to the Study Coordinator and Johns Hopkins Hospital respectively. Safety monitoring of the study will be performed by the study team biannually. A data and safety monitoring board (DSMB) will be appointed for specifically monitoring the safety of participants and data. The DSMB will be outside JHU.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Individual patient medical information obtained as a result of this study it is considered confidential. The patient will be identified by an assigned unique identifier code (number and letter code), that will be used on all films/study binders. The data will be stored in a secure area. The principal investigator/study coordinator will maintain documents that identify the patient in strict confidence, except to the extent necessary to allow auditing by the JCCI and FDA. No participants in the study will be identified by name in any report, publication, or presentation of this study or its results. Confidentiality will be maintained by removing all identifying information from films prior to their being transmitted and read by the independent core labs. No genetic testing will be performed.

9. Benefits

Individual participant

We expect no direct benefit to patients participating in this study. All patients will receive a CTA examination of the heart at no cost. All CTA examinations will be reviewed locally by a cardiologist and radiologist. Alert incidental findings that need further medical follow-up will be communicated to the patient's treating physician within 7-14 days of procedures. Alert incidental findings include, but are not limited to: pulmonary emboli, aortic dissection, pulmonary masses, three vessel coronary disease, left main coronary disease.

Society

This research will benefit society by helping healthcare professionals to evaluate this new technology which has the potential to become a routine non-invasive diagnostic tool for evaluation of coronary artery disease.

10. Payment and Remuneration

Patients will not be compensated for their participation in the study. Patients will receive a parking coupon ($20 value) to cover parking expenses at the Johns Hopkins Hospital. If a patient requires alternate transportation, the patient will receive reimbursement for the cost of the transportation in lieu of the parking coupon. Participants will also receive $100 upon completion of the CT scan and an additional $150 for completing the CT coronary angiogram (total of $250 for both scans).

11. Costs

The CTA study will cost approximately $500 for the scan plus approximately $200 for contrast, laboratory testing, and medications. If the CTA is being performed for research purposes, the sponsor will cover the costs. If the CTA is being performed for clinical purposes, the patient will be responsible for its costs. The patient and / or insurance company will not be charged for procedures specifically done for research purposes.

12. Transfer of Materials

No biospecimen will be transferred to JHU for this research