THE CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY VISION PROTOCOL: A PROSPECTIVE OBSERVATIONAL IMAGING COHORT STUDY IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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ABSTRACT

Introduction: At present, physicians have a limited ability to predict major cardiovascular complications after noncardiac surgery and little is known about the anatomy of coronary arteries associated with perioperative myocardial infarction. We have initiated the Coronary Computed Tomographic Angiography (CTA) VISION Study to (1) establish the predictive value of coronary CTA for perioperative myocardial infarction and death, and (2) describe the coronary anatomy of patients that have a perioperative myocardial infarction.

Methods and Analysis: The Coronary CTA VISION Study is prospective observational study. Preoperative coronary CTA will be performed in 1000-1500 patients with a history of vascular disease or at least 3 cardiovascular risk factors who are undergoing major elective noncardiac surgery. Serial troponin will be measured 6-12 hours after surgery and daily for the first 3 days after surgery. Major vascular outcomes at 30 days and 1 year after surgery will be independently adjudicated.

Ethics and Dissemination: Coronary CTA results in a measurable radiation exposure that is similar to a nuclear perfusion scan (10 to 12 mSV). Treating physicians will be blinded to the CTA results until 30 days after surgery in order to provide the most unbiased assessment of its prognostic capabilities. The only exception will be the presence of a left main stenosis >50%. This approach is supported by best available current evidence that, excluding left main disease, prophylatic revascularization prior to non-cardiac surgery does not improve

outcomes. An external safety and monitoring committee is overseeing the study and will review outcome data at regular intervals. Publications describing the results of the study will be submitted to major peer-reviewed journals and presented at international medical conferences.

Key words: perioperative myocardial infarction, computed tomography, prognosis, coronary artery disease

List of Abbreviations:

CTA: computed tomographic angiography

LAD: left anterior descending

ECG: electrocardiogram

CAD: coronary artery disease

INTRODUCTION

Globally over 200 million patients undergo major noncardiac surgery annually. Despite the benefits of surgery, annually over 5 million noncardiac surgery patients will suffer a cardiovascular death or nonfatal myocardial infarction in the first 30 days after surgery[1].

Limited Capacity to Predict Major Perioperative Ischemic Events

Accurate risk estimation is important to allow patients and physicians to make informed choices about the appropriateness of surgery and to inform perioperative management (e.g,, anesthetic approach). Risk prediction based on clinical risk factors and functional capacity is suboptimal.[2] This is probably because many patients are inactive for substantial periods of time prior to their noncardiac surgery (e.g., orthopedic, vascular, and oncology patients) due to their underlying surgical condition, and as such, many patients with substantial coronary artery disease may not have experienced any suggestive symptoms.

In an attempt to improve preoperative risk prediction, some patients undergo non-invasive cardiac stress tests (e.g., stress echocardiography, nuclear scintigraphy imaging) prior to noncardiac surgery.[3] A recent meta-analyses evaluating these two tests demonstrated, however, that they have only moderate negative likelihood ratios (stress echocardiography 0.23 and stress perfusion imaging 0.44), and that more than a third of the patients who suffered a major perioperative cardiovascular event had a negative preoperative test result.[4] These data represent likely a best case scenario because most of the studies have not assessed whether these non-invasive cardiac stress tests provide independent prognostic information beyond known clinical variables. The few studies that have undertaken multivariable regression analysis provide unreliable estimates because they did not include all the known independent clinical variables or the analysis had too few events for the number of variables assessed.[5-9]

Mechanisms of Perioperative Ischemic Events

Although perioperative myocardial infarction is the most common major perioperative cardiac complication, little is known about its pathophysiology.[3] Understanding the pathophysiology of perioperative myocardial infarction is important to help inform which potential prophylactic interventions and acute management interventions should be evaluated in randomized controlled trials to improve the outcome of patients undergoing noncardiac surgery.

A commonly proposed mechanism of perioperative myocardial infarction relates to myocardial oxygen supply demand mismatch. Fluid shifts, catecholamine surges, hypotension, anemia and hypoxia can occur during and after major noncardiac surgery and transiently increase myocardial oxygen demand.[3] In coronary vessels with high grade stenoses or occlusions, the supply response may be limited, resulting in supply-demand mismatch myocardial ischemia or infarction. An additional or alternative mechanism of perioperative myocardial infarction is that the acute stress of surgery and mechanical tissue injury induces a hypercoagulable state that increases the risk of coronary thrombus formation at the site of a fissured plaque or with low coronary flow.

Rationale for use of Coronary Computed Tomographic Angiography (CTA) Prior to Noncardiac Surgery

Coronary CTA may have several advantages for risk stratification prior to noncardiac surgery. First, coronary CTA does not require exercise or pharmacologic stress to detect coronary artery disease and therefore is well suited to the vascular and orthopedic surgical populations who often cannot exercise or take the necessary pharmacological agents (e.g., patients with asthma). Second, coronary CTA can exclude obstructive coronary artery disease very reliably as it has a high sensitivity for the detection of coronary stenosis;[10-13].

Third, coronary CTA is a very sensitive modality for the detection of high-risk coronary anatomy (left main disease or three or two vessel disease including the proximal left anterior descending [LAD] artery) as coronary CTA can visualize these large proximal vessels very well.[13] Fourth, coronary CTA is the only non-invasive modality that can detect non-obstructive atherosclerosis,[14] and some of our research (e.g., POISE)[15] offers clues that non-obstructive coronary artery disease may be responsible for a substantial proportion of the perioperative myocardial infarctions that occur in the noncardiac surgery setting through plaque rupture and thrombosis.

Finally, coronary CTA can provide a comprehensive anatomic characterization of the coronary arteries prior to surgery, and this has substantial potential to shed important insight into the extent of preoperative coronary atherosclerosis in culprit vessels that are associated with perioperative myocardial infarction.

OBJECTIVES OF THE CORONARY CTA VISION STUDY

The Coronary CTA VISION Study is a prospective cohort study that will examine patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery in order to determine: if preoperative coronary CTA has additional predictive value, beyond clinical variables, for the occurrence of major perioperative cardiac events (i.e., cardiovascular death and nonfatal myocardial infarction) at 30 days after surgery; and the underlying coronary anatomy associated with perioperative myocardial infarction. The Coronary CTA VISION Study is a sub-study of the VISION Study. The Vascular events In noncardiac Surgery patients cOhort evaluatioN (VISION) Study is a 40,000 patient international prospective cohort study that we are currently undertaking, and this study is evaluating perioperative vascular complications in patients undergoing noncardiac surgery.

METHODS

Study Design

The Coronary CTA VISION Study is a prospective observational study of coronary CTA performed in patients prior to noncardiac surgery.

Study Population

The investigators will consider all patients undergoing elective noncardiac surgery for enrollment. Tables 1 and 2 present the study's inclusion and exclusion criteria.

Clinical Data Collection

After obtaining written informed consent, research personnel will interview and examine patients and review their charts to obtain information on patient characteristics that we are evaluating in the VISION Study to determine if they have potential independent predictors of major perioperative vascular events. These variables include risk factors, co-morbidities, medications, anesthetic and surgical variables.

CTA Imaging Protocol

Once a patient is consented for the study, research personnel coordinate an appointment for the patient's preoperative coronary CTA scan. Personnel in the radiology department see patients prior to the coronary CTA scan and, when necessary, pre-treat the patients with beta-blockers (to achieve heart rate of 60 or less) and nitroglycerin (at a dose of 0.6 to 0.8 mg administered sublingually) to optimize image quality. At centres with single source scanners, patients who continue to have a heart rate 70 bpm or greater despite beta-blockade are excluded from the study (90bpm or greater with dual source scanners). In patients with asthma, personnel use a calcium channel blocker (diltazem 30 to 120 mg) is used to achieve heart rate control. A non-contrast scan is performed first. This scan is prospectively triggered at 75% of the RR interval, with 0.4 to 0.625 slice thickness (depending on scanner type) and 3mm increments. Technicians next perform a contrast scan and inject contrast agent at a rate of 5.5 to 7 ml/s depending on body habitus of the patient being scanned. For an average patient, the dose of contrast is expected to be approximately 80 ml. The contrast scan is retrospectively gated or prospectively triggered with 0.4 to 0.625 slice thickness (depending on scanner type). On scanners with the capacity for prospective triggering, studies are acquired with this technique whenever heart rate is adequately controlled (HR<65) and regular. For retrospective acquisitions, dose modulation is used to minimize radiation dose.

Standard initial reconstruction of the coronary CTA data set is performed at 75% of the R-R interval, with additional reconstructions performed as required for image interpretation. When retrospective gating is used, reconstructions for functional assessment are performed in 10 phases with 10% increments.

Participating Sites

Participating centres have a 64 detector MDCT or greater with the capacity to perform cardiac CT, an expert reader in cardiology or radiology (as defined by AHA/ACC training standards or their international equivalent) and a strong collaboration between the imaging team and the clinical peri-operative medicine service to facilitate patient recruitment. The participating sites are listed in the Appendix. Each participating site submits several scans to confirm adherence to the study imaging protocol and achievement of adequate image quality prior to initiation of study recruitment.

CTA Interpretation and Blinding

Coronary CTA is read by an expert radiologist or cardiologist. These individuals read each coronary CTA exam without knowledge of the clinical data. They report findings for each vessel, in terms of nature of plaque and extent of narrowing, and they determine whether each of the following 4 findings are present on the coronary CTA: (1) normal – no evidence of coronary atherosclerotic plaque (this excludes subsequent findings), (2) non-obstructive coronary artery disease – evidence of at least one coronary artery plaque with a <50% stenosis, (3) obstructive coronary artery disease – at least one coronary artery plaque with a ≥50% stenosis, or (4) obstructive plaque with high-risk anatomy (≥50% stenosis of the left main, ≥50% stenosis in three coronary arteries, or ≥50% stenosis in two coronary arteries including the proximal left anterior descending [LAD] artery). Where calcium and/or motion artifacts limit interpretability, the segment are identified as non-evaluable and a forced interpretation on the presence of stenosis is made. If there are more than 4 non-evaluable segments, the scan is considered non-diagnostic and excluded from the analysis.

The classification of CTA findings being used in CTA VISION predicts the risk of mortality over 1-2 years in patients with stable coronary artery disease in the non-operative setting,[16] similar to the results of the well validated prognostic classification of invasive coronary angiography that puts increased importance on the number of vessels with $\geq$50% stenoses, with particular emphasis on involvement of the proximal LAD.[17] Assessment of stenosis severity into board categories (i.e., 50-70% versus $\geq$70%) demonstrates very good agreement between coronary CTA and invasive angiography (kappa =0.74).[18] The reader calculates a calcium score using the Agatston method using the non-contrast scan.[19] This score is recorded and is available for subsequent analyses.

If a patient is discovered to have a $\geq$50% stenosis of the left main we immediately provide this test result to the patient's physicians. All other patients have their results withheld from the clinical care team until 30 days after surgery.

Patient Follow-up

After surgery, patients have a troponin measurement drawn 6 to 12 hours after surgery and on the 1st, 2nd, and 3rd days after surgery. Standard orders ensure these tests are undertaken. Orders also ensure that an electrocardiogram is undertaken immediately after an elevated troponin measurement is detected. Patients who are discovered to have an elevated troponin with or without ECG changes will usually undergo an echocardiogram or a functional evaluation such as nuclear perfusion imaging or stress MRI. Where clinically indicated, invasive coronary angiography is performed.

Research personnel follow patients throughout their time in hospital and personally evaluate patients and review their medical records ensuring study orders have been followed and noting any primary or secondary outcomes. The research personnel contact patients by phone at 30 days and 1 year post surgery. If patients indicate that they have experienced an outcome or hospitalization, the research personnel contact their physicians to obtain the appropriate documentation.

Study Outcomes

For our first objective (i.e., to determine if preoperative coronary CTA has additional predictive value beyond clinical variables) our primary outcome is a major cardiac event (i.e., a composite of cardiovascular death and nonfatal myocardial infarction) at 30 days post surgery. Individual secondary outcomes for our first objective at 1 year after surgery include cardiovascular death, myocardial infarction, and coronary revascularization. For our second objective (i.e., to determine the underlying coronary anatomy associated with perioperative myocardial infarction) our primary and only outcome is myocardial infarction at 30 days after surgery.

The first step in determining the underlying coronary artery anatomy associated with a perioperative myocardial infarction is to determine the region of the myocardial infarction using a combination of clinical and non-invasive tests.

Two cardiologists blinded to the CTA results will independently determine this using a pre-specified algorithm based on literature and expert opinion (Table 3). After establishing this, we then look at what the expert CTA evaluators stated was the underlying coronary artery anatomy (e.g., <50% stenosis, 50 to 69% stenosis, and ≥70% stenosis) in the coronary artery that supplied the region of the myocardial infarction.

Outcome Adjudication

A committee of clinicians who are blinded to the CTA results adjudicate the outcomes of death and myocardial infarction. We will use the decisions from the Adjudication Committee for all statistical analyses.

Sample size

Our sample size calculation is based upon our primary objective (i.e., to determine if preoperative coronary CTA has additional predictive value beyond clinical variables). Of our 2 objectives, this objective requires the largest number of patients to ensure the stability of the prediction model. The VISION Study will determine the optimal clinical risk prediction model, and we will then undertake a multivariable analysis to determine if the coronary CTA results have additional predictive value beyond the VISION clinical risk prediction model. Simulation studies demonstrate that logistic models require 12 to 15 events per predictor to produce stable estimates.[20-21.] We will evaluate 4 potential predictors in our multivariable analysis: 1 VISION clinical risk predication score, and 3 types of coronary CTA results (i.e., non-obstructive CAD, obstructive CAD, and obstructive plaque with high-risk anatomy) with 1 reference category (normal). Given our eligibility criteria, we expect that the study participants will be evenly distributed across the 4 CTA result groups.

Based upon the VISION Pilot Study and a previous non-invasive cardiac testing study that we undertook in a similar surgical population,[22] we expect a 6% event rate for major perioperative cardiac events in this study. Table 4 presents the various sample sizes needed to test 4 variables in a multivariable analysis based upon various event rates and the required number of events per variable. As the table indicates, if our event rate is 6% we will need 1000 patients to achieve stable estimates. If our event rate is 4%, we may need up to 1500 patients. We are targeting a sample size of 1500 patients but this may change depending on our event rate at 1000 patients.

Data analysis

To address our primary objective, we will undertake a multivariable logistic regression analysis in which the dependent variable is a major perioperative cardiac event at 30 days after surgery and the independent variables are the VISION clinical risk prediction score and the 4 coronary CTA results discussed above. For this logistic regression analysis we will use forced simultaneous entry (all candidate variables will remain in the model) as opposed to automated stepwise selection, because simulation studies have demonstrated a higher risk of overfitting with the latter approach.[23-24] To assess the reliability of our models we will undertake bootstrapping,[25] because this technique is superior to cross-validation and jack-knife techniques.[26] We will test the hypothesis that coronary CTA will have additional predictive value, beyond clinical variables, for the occurrence of major perioperative cardiac events in patients undergoing noncardiac surgery using the likelihood ratio (LR) test: LR test = -2ln (L1/L2) where L1 and L2 are the likelihood for the reduced model with VISION score alone, and likelihood for the full model with both VISION score and CTA variables.[27]

For the logistic model we will report the odds ratios [OR], 95% confidence intervals, and associated p-values. For all tests, we will use alpha = 0.05 level of significance. For all significant associations we will report the likelihood ratio and the 95% confidence interval.

Examination of residuals will provide an assessment of model assumptions for regression analyses. Goodness-of-fit for the models will be performed using appropriate Hosmer-Lemeshov tests. For the multivariable regression analysis, multicollinearity (correlations among predictor variables) may exist.[28] We will assess colinearity using the variance inflation factor (VIF) which measures the extent to which the variance of the model coefficients will be inflated (because of the correlation of the variable with other predictor variables) if that variable is included in the model. We will consider variables with VIF >10 colinear and we will exclude one of these variables from the analysis.[29]

For our secondary objective we will determine the proportion of patients suffering a perioperative myocardial infarction who on their coronary CTA the myocardial infarction associated artery had a coronary artery stenosis of <50%, 50-69%, ≥70-99%, 100%, or no coronary artery stenosis and the associated 95% confidence intervals. We will perform all analyses using SAS version 9.2 (Cary, North Carolina).

Ethics

Coronary CTA results in a measurable radiation exposure. Volume coverage of the whole heart using standard acquisition parameters will approximately result in an effective dose of 10 to 12 mSv if retrospectively gated CTA is performed. The dose will likely be substantially lower if prospectively triggered CTA is performed. The maximum anticipated does is similar to a nuclear perfusion scan (8 to 12 mSv), but greater than a standard chest CT (5 to 7 mSv)[30] and equals 3 to 4 years of the annual average effective dose from background radiation (3.6 mSv/year) or approximately 20 % of the annual whole body effective dose that is allowed for a radiation worker (radiologist, radiological technologist) (50 mSv/year).[31]

We feel that blinding of treating physicians to the coronary CTA findings is important to provide the most unbiased assessment of its prognostic capabilities. Thus, in keeping with prior studies that evaluated non-invasive tests in patients undergoing vascular surgery,[32-33] the attending surgeons and consultants in our study will not know the results of the pre-operative coronary CTA. The best evidence presently available from the CARP Trial[34] and DECREASE-V Trial[35] suggests that there is no benefit to prophylactic coronary revascularization prior to non-cardiac surgery and therefore, the CTA results are not required to guide treatment prior to non-cardiac surgery. In the CARP Trial one-third of the patients had 3 vessel coronary artery disease,[34] and in the DECREASE-V Trial 67% of the patients had 3 vessel coronary artery disease.[35] The only exception is hemodynamically significant left main disease which was excluded in the CARP trial. Thus, if the coronary CTA suggests significant left main disease, the results will be immediately disclosed to the treating physicians. For all patients in the study, the results of coronary CTA will be provided to all family physicians, internal medicine, and cardiology consultants involved in the care of the patients at 30 days post surgery.

An external safety and monitoring committee (ESMC) will convene early in the study and will meet again at regular intervals. Interim analyses will be conducted when approximately 25%, 50%, and 75% of the expected events have occurred and the data are available. The analyses will be conducted on the total of adjudicated and unadjudicated events at the appropriate time points. If the ESMC decides that a definitive conclusion has been reached for the overall study population or a specific subgroup, they will immediately unblind the Co-Principal Investigators and discuss the results together.

Conclusion

Coronary CTA is a novel application of CT scanning with potentially important clinical applications. This study will evaluate the role of coronary CTA in risk stratification prior to noncardiac surgery. If we demonstrate that CTA has important additional predictive value beyond clinical information in patients undergoing elective noncardiac surgery, this finding would allow this test to facilitate informed patient decision-making about the risks of surgery and guide perioperative patient management. This study will also provide insights into the underlying coronary anatomy of coronary arteries that cause myocardial infarction in the perioperative setting. This knowledge will inform the selection of targeted prevention and management interventions to evaluate in large perioperative randomized controlled trials. Considering that over 200 million adults undergo major noncardiac surgery annually and that we know little about how to predict or manage major perioperative cardiac events, highlights the importance of the Coronary CTA VISION Study.

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Table 1. Inclusion Criteria

All patients undergoing elective noncardiac surgery are eligible if they:

• are > 45 years of age
• require at least an overnight hospital admission after surgery
• are undergoing one of the following surgeries
  ○ orthopedic (major joint arthroplasty)
  ○ vascular
  ○ thoracic surgery (pneumonectomy, lobectomy, other thoracic – wedge lung resection, mediastinal tumor resection, major chest wall resection)
  ○ major abdominal surgery (partial or total colectomy, stomach surgery, visceral resection, cytoreductive surgery, radial hysterectomy, radical prostatectomy)
  ○ major organ transplantation (kidney, liver, lung)
• have enough time prior to noncardiac surgery to obtain a coronary CTA study
• fulfill one of the following additional criteria:
  ○ history of coronary artery disease
  ○ history of peripheral vascular disease
  ○ history of stroke
  ○ history of a physician diagnosis of congestive heart failure; OR
  ○ any 3 of the following 6 risk factors: (a) diabetes and currently on an oral diabetic drug or insulin therapy, (b) age ≥70 years, (c) history of smoking within 2 years of surgery, (d) history of treatment for hypercholesterolemia, (e) history of a transient ischemic attack (TIA), or (f) a history of hypertension.

Table 2. Exclusion Criteria

All patients are excluded if they:
• are referred to invasive coronary angiography prior to noncardiac surgery (coronary CTA will not provide information incremental to an invasive angiogram) • have had a prior percutaneous coronary intervention (PCI) with stent implantation (due to limited ability of coronary CTA to evaluate stents) • have a creatinine clearance <35 ml/min (to avoid risk of contrast nephrotoxicity in patients potentially at risk) • have a known contrast reaction • are pregnant • have persistent atrial fibrillation or >2 atrial or ventricular premature beats on a preoperative 12 lead electrocardiogram (ECG) (suboptimal image quality results from irregular heart rhythms at cardiac CT due to difficulties with retrospective gating) • weight >300 lbs (obese patients have suboptimal image quality due to a poor contrast to noise ratio) • have an inability to achieve the required heart rate prior to coronary CTA despite medication (i.e., a beta-blocker or calcium channel blocker) if the patient will be scanned on a single source scanner they require a heart rate <70 beats per minute (bpm) or a heart rate <90 bpm if the patient will be scanned on a dual source scanner; or • patients who do not undergo noncardiac surgery within 6 months of their coronary CTA.

Table 3: Diagnostic confidence in determination of culprit lesion in patients who fulfill our definition of myocardial infarction

Diagnostic confidence	**Criteria**
Highly probable location of lesion	• Thrombus or features of recent plaque rupture (irregular margins, hazy appearance, dissection) coronary plaque fissure seen on invasive angiography; OR • New area of infarction on cardiac MRI
Probable location of lesion	• New perfusion abnormality identified on SPECT testing • New wall motion abnormality (as determined through comparison of pre and postoperative echocardiography or MRI; • New wall motion abnormality as determined through comparison of preoperative CTA myocardial function and postoperative echocardiography; OR • New Q waves in 2 contiguous leads on the patients ECG
Possible location of lesion	• ST segment elevation [$\geq$2 mm in leads V_1, V_2, or V_3 OR $\geq$1 mm in the other leads] in two contiguous leads; • ST segment depression [$\geq$1 mm] in two contiguous leads; • Symmetric inversion of T waves $\geq$1 mm) in at least two contiguous leads; OR • Presumed new cardiac wall motion abnormality on echocardiography • Presumed new fixed defect on SPECT testing

Table 4: Sample size needed to test 4 variables in a multivariable analysis based upon various event rates and the required number of events per variable

Required number of events per variable	Number of events needed	Sample size needed to test 4 variables in a multivariable analysis based upon various event rates	
		4%	6%
10	40	1000	667
12	48	1200	800
15	60	1500	1000

Appendix

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THE CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY VISION PROTOCOL: A PROSPECTIVE OBSERVATIONAL IMAGING COHORT STUDY IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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ABSTRACT

Introduction: At present, physicians have a limited ability to predict major cardiovascular complications after noncardiac surgery and little is known about the anatomy of coronary arteries associated with perioperative myocardial infarction. We have initiated the Coronary Computed Tomographic Angiography (CTA) VISION Study to (1) establish the predictive value of coronary CTA for perioperative myocardial infarction and death, and (2) describe the coronary anatomy of patients that have a perioperative myocardial infarction.

Methods and Analysis: The Coronary CTA VISION Study is prospective observational study. Preoperative coronary CTA will be performed in 1000-1500 patients with a history of vascular disease or at least 3 cardiovascular risk factors who are undergoing major elective noncardiac surgery. Serial troponin will be measured 6-12 hours after surgery and daily for the first 3 days after surgery. Major vascular outcomes at 30 days and 1 year after surgery will be independently adjudicated.

Ethics and Dissemination: Coronary CTA results in a measurable radiation exposure that is similar to a nuclear perfusion scan (10 to 12 mSV). Treating physicians will be blinded to the CTA results until 30 days after surgery in order to provide the most unbiased assessment of its prognostic capabilities. The only exception will be the presence of a left main stenosis >50%. This approach is supported by best available current evidence that, excluding left main disease, prophylatic revascularization prior to non-cardiac surgery does not improve

outcomes. An external safety and monitoring committee is overseeing the study and will review outcome data at regular intervals. Publications describing the results of the study will be submitted to major peer-reviewed journals and presented at international medical conferences.

Key words: perioperative myocardial infarction, computed tomography, prognosis, coronary artery disease

List of Abbreviations:

CTA: computed tomographic angiography

LAD: left anterior descending

ECG: electrocardiogram

CAD: coronary artery disease

INTRODUCTION

Globally over 200 million patients undergo major noncardiac surgery annually. Despite the benefits of surgery, annually over 5 million noncardiac surgery patients will suffer a cardiovascular death or nonfatal myocardial infarction in the first 30 days after surgery[1].

Limited Capacity to Predict Major Perioperative Ischemic Events

Accurate risk estimation is important to allow patients and physicians to make informed choices about the appropriateness of surgery and to inform perioperative management (e.g,, anesthetic approach). Risk prediction based on clinical risk factors and functional capacity is suboptimal.[2] This is probably because many patients are inactive for substantial periods of time prior to their noncardiac surgery (e.g., orthopedic, vascular, and oncology patients) due to their underlying surgical condition, and as such, many patients with substantial coronary artery disease may not have experienced any suggestive symptoms.

In an attempt to improve preoperative risk prediction, some patients undergo non-invasive cardiac stress tests (e.g., stress echocardiography, nuclear scintigraphy imaging) prior to noncardiac surgery.[3] A recent meta-analyses evaluating these two tests demonstrated, however, that they have only moderate negative likelihood ratios (stress echocardiography 0.23 and stress perfusion imaging 0.44), and that more than a third of the patients who suffered a major perioperative cardiovascular event had a negative preoperative test result.[4] These data represent likely a best case scenario because most of the studies have not assessed whether these non-invasive cardiac stress tests provide independent prognostic information beyond known clinical variables. The few studies that have undertaken multivariable regression analysis provide unreliable estimates because they did not include all the known independent clinical variables or the analysis had too few events for the number of variables assessed.[5-9]

Mechanisms of Perioperative Ischemic Events

Although perioperative myocardial infarction is the most common major perioperative cardiac complication, little is known about its pathophysiology.[3] Understanding the pathophysiology of perioperative myocardial infarction is important to help inform which potential prophylactic interventions and acute management interventions should be evaluated in randomized controlled trials to improve the outcome of patients undergoing noncardiac surgery.

A commonly proposed mechanism of perioperative myocardial infarction relates to myocardial oxygen supply demand mismatch. Fluid shifts, catecholamine surges, hypotension, anemia and hypoxia can occur during and after major noncardiac surgery and transiently increase myocardial oxygen demand.[3] In coronary vessels with high grade stenoses or occlusions, the supply response may be limited, resulting in supply-demand mismatch myocardial ischemia or infarction. An additional or alternative mechanism of perioperative myocardial infarction is that the acute stress of surgery and mechanical tissue injury induces a hypercoagulable state that increases the risk of coronary thrombus formation at the site of a fissured plaque or with low coronary flow.

Rationale for use of Coronary Computed Tomographic Angiography (CTA) Prior to Noncardiac Surgery

Coronary CTA may have several advantages for risk stratification prior to noncardiac surgery. First, coronary CTA does not require exercise or pharmacologic stress to detect coronary artery disease and therefore is well suited to the vascular and orthopedic surgical populations who often cannot exercise or take the necessary pharmacological agents (e.g., patients with asthma). Second, coronary CTA can exclude obstructive coronary artery disease very reliably as it has a high sensitivity for the detection of coronary stenosis;[10-13].

Third, coronary CTA is a very sensitive modality for the detection of high-risk coronary anatomy (left main disease or three or two vessel disease including the proximal left anterior descending [LAD] artery) as coronary CTA can visualize these large proximal vessels very well.[13] Fourth, coronary CTA is the only non-invasive modality that can detect non-obstructive atherosclerosis,[14] and some of our research (e.g., POISE)[15] offers clues that non-obstructive coronary artery disease may be responsible for a substantial proportion of the perioperative myocardial infarctions that occur in the noncardiac surgery setting through plaque rupture and thrombosis.

Finally, coronary CTA can provide a comprehensive anatomic characterization of the coronary arteries prior to surgery, and this has substantial potential to shed important insight into the extent of preoperative coronary atherosclerosis in culprit vessels that are associated with perioperative myocardial infarction.

OBJECTIVES OF THE CORONARY CTA VISION STUDY

The Coronary CTA VISION Study is a prospective cohort study that will examine patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery in order to determine: if preoperative coronary CTA has additional predictive value, beyond clinical variables, for the occurrence of major perioperative cardiac events (i.e., cardiovascular death and nonfatal myocardial infarction) at 30 days after surgery; and the underlying coronary anatomy associated with perioperative myocardial infarction. The Coronary CTA VISION Study is a sub-study of the VISION Study. The Vascular events In noncardiac Surgery patients cOhort evaluatioN (VISION) Study is a 40,000 patient international prospective cohort study that we are currently undertaking, and this study is evaluating perioperative vascular complications in patients undergoing noncardiac surgery.

METHODS

Study Design

The Coronary CTA VISION Study is a prospective observational study of coronary CTA performed in patients prior to noncardiac surgery.

Study Population

The investigators will consider all patients undergoing elective noncardiac surgery for enrollment. Tables 1 and 2 present the study's inclusion and exclusion criteria.

Clinical Data Collection

After obtaining written informed consent, research personnel will interview and examine patients and review their charts to obtain information on patient characteristics that we are evaluating in the VISION Study to determine if they have potential independent predictors of major perioperative vascular events. These variables include risk factors, co-morbidities, medications, anesthetic and surgical variables.

CTA Imaging Protocol

Once a patient is consented for the study, research personnel coordinate an appointment for the patient's preoperative coronary CTA scan. Personnel in the radiology department see patients prior to the coronary CTA scan and, when necessary, pre-treat the patients with beta-blockers (to achieve heart rate of 60 or less) and nitroglycerin (at a dose of 0.6 to 0.8 mg administered sublingually) to optimize image quality. At centres with single source scanners, patients who continue to have a heart rate 70 bpm or greater despite beta-blockade are excluded from the study (90bpm or greater with dual source scanners). In patients with asthma, personnel use a calcium channel blocker (diltazem 30 to 120 mg) is used to achieve heart rate control. A non-contrast scan is performed first. This scan is prospectively triggered at 75% of the RR interval, with 0.4 to 0.625 slice thickness (depending on scanner type) and 3mm increments. Technicians next perform a contrast scan and inject contrast agent at a rate of 5.5 to 7 ml/s depending on body habitus of the patient being scanned. For an average patient, the dose of contrast is expected to be approximately 80 ml. The contrast scan is retrospectively gated or prospectively triggered with 0.4 to 0.625 slice thickness (depending on scanner type). On scanners with the capacity for prospective triggering, studies are acquired with this technique whenever heart rate is adequately controlled (HR<65) and regular. For retrospective acquisitions, dose modulation is used to minimize radiation dose.

Standard initial reconstruction of the coronary CTA data set is performed at 75% of the R-R interval, with additional reconstructions performed as required for image interpretation. When retrospective gating is used, reconstructions for functional assessment are performed in 10 phases with 10% increments.

Participating Sites

Participating centres have a 64 detector MDCT or greater with the capacity to perform cardiac CT, an expert reader in cardiology or radiology (as defined by AHA/ACC training standards or their international equivalent) and a strong collaboration between the imaging team and the clinical peri-operative medicine service to facilitate patient recruitment. The participating sites are listed in the Appendix. Each participating site submits several scans to confirm adherence to the study imaging protocol and achievement of adequate image quality prior to initiation of study recruitment.

CTA Interpretation and Blinding

Coronary CTA is read by an expert radiologist or cardiologist. These individuals read each coronary CTA exam without knowledge of the clinical data. They report findings for each vessel, in terms of nature of plaque and extent of narrowing, and they determine whether each of the following 4 findings are present on the coronary CTA: (1) normal – no evidence of coronary atherosclerotic plaque (this excludes subsequent findings), (2) non-obstructive coronary artery disease – evidence of at least one coronary artery plaque with a <50% stenosis, (3) obstructive coronary artery disease – at least one coronary artery plaque with a ≥50% stenosis, or (4) obstructive plaque with high-risk anatomy (≥50% stenosis of the left main, ≥50% stenosis in three coronary arteries, or ≥50% stenosis in two coronary arteries including the proximal left anterior descending [LAD] artery). Where calcium and/or motion artifacts limit interpretability, the segment are identified as non-evaluable and a forced interpretation on the presence of stenosis is made. If there are more than 4 non-evaluable segments, the scan is considered non-diagnostic and excluded from the analysis.

The classification of CTA findings being used in CTA VISION predicts the risk of mortality over 1-2 years in patients with stable coronary artery disease in the non-operative setting,[16] similar to the results of the well validated prognostic classification of invasive coronary angiography that puts increased importance on the number of vessels with ≥50% stenoses, with particular emphasis on involvement of the proximal LAD.[17] Assessment of stenosis severity into board categories (i.e., 50-70% versus ≥70%) demonstrates very good agreement between coronary CTA and invasive angiography (kappa =0.74).[18] The reader calculates a calcium score using the Agatston method using the non-contrast scan.[19] This score is recorded and is available for subsequent analyses.

If a patient is discovered to have a ≥50% stenosis of the left main we immediately provide this test result to the patient's physicians. All other patients have their results withheld from the clinical care team until 30 days after surgery.

Patient Follow-up

After surgery, patients have a troponin measurement drawn 6 to 12 hours after surgery and on the 1st, 2nd, and 3rd days after surgery. Standard orders ensure these tests are undertaken. Orders also ensure that an electrocardiogram is undertaken immediately after an elevated troponin measurement is detected. Patients who are discovered to have an elevated troponin with or without ECG changes will usually undergo an echocardiogram or a functional evaluation such as nuclear perfusion imaging or stress MRI. Where clinically indicated, invasive coronary angiography is performed.

Research personnel follow patients throughout their time in hospital and personally evaluate patients and review their medical records ensuring study orders have been followed and noting any primary or secondary outcomes. The research personnel contact patients by phone at 30 days and 1 year post surgery. If patients indicate that they have experienced an outcome or hospitalization, the research personnel contact their physicians to obtain the appropriate documentation.

Study Outcomes

For our first objective (i.e., to determine if preoperative coronary CTA has additional predictive value beyond clinical variables) our primary outcome is a major cardiac event (i.e., a composite of cardiovascular death and nonfatal myocardial infarction) at 30 days post surgery. Individual secondary outcomes for our first objective at 1 year after surgery include cardiovascular death, myocardial infarction, and coronary revascularization. For our second objective (i.e., to determine the underlying coronary anatomy associated with perioperative myocardial infarction) our primary and only outcome is myocardial infarction at 30 days after surgery.

The first step in determining the underlying coronary artery anatomy associated with a perioperative myocardial infarction is to determine the region of the myocardial infarction using a combination of clinical and non-invasive tests.

Two cardiologists blinded to the CTA results will independently determine this using a pre-specified algorithm based on literature and expert opinion (Table 3). After establishing this, we then look at what the expert CTA evaluators stated was the underlying coronary artery anatomy (e.g., <50% stenosis, 50 to 69% stenosis, and ≥70% stenosis) in the coronary artery that supplied the region of the myocardial infarction.

Outcome Adjudication

A committee of clinicians who are blinded to the CTA results adjudicate the outcomes of death and myocardial infarction. We will use the decisions from the Adjudication Committee for all statistical analyses.

Sample size

Our sample size calculation is based upon our primary objective (i.e., to determine if preoperative coronary CTA has additional predictive value beyond clinical variables). Of our 2 objectives, this objective requires the largest number of patients to ensure the stability of the prediction model. The VISION Study will determine the optimal clinical risk prediction model, and we will then undertake a multivariable analysis to determine if the coronary CTA results have additional predictive value beyond the VISION clinical risk prediction model. Simulation studies demonstrate that logistic models require 12 to 15 events per predictor to produce stable estimates.[20-21.] We will evaluate 4 potential predictors in our multivariable analysis: 1 VISION clinical risk predication score, and 3 types of coronary CTA results (i.e., non-obstructive CAD, obstructive CAD, and obstructive plaque with high-risk anatomy) with 1 reference category (normal). Given our eligibility criteria, we expect that the study participants will be evenly distributed across the 4 CTA result groups.

Based upon the VISION Pilot Study and a previous non-invasive cardiac testing study that we undertook in a similar surgical population,[22] we expect a 6% event rate for major perioperative cardiac events in this study. Table 4 presents the various sample sizes needed to test 4 variables in a multivariable analysis based upon various event rates and the required number of events per variable. As the table indicates, if our event rate is 6% we will need 1000 patients to achieve stable estimates. If our event rate is 4%, we may need up to 1500 patients. We are targeting a sample size of 1500 patients but this may change depending on our event rate at 1000 patients.

Data analysis

To address our primary objective, we will undertake a multivariable logistic regression analysis in which the dependent variable is a major perioperative cardiac event at 30 days after surgery and the independent variables are the VISION clinical risk prediction score and the 4 coronary CTA results discussed above. For this logistic regression analysis we will use forced simultaneous entry (all candidate variables will remain in the model) as opposed to automated stepwise selection, because simulation studies have demonstrated a higher risk of overfitting with the latter approach.[23-24] To assess the reliability of our models we will undertake bootstrapping,[25] because this technique is superior to cross-validation and jack-knife techniques.[26] We will test the hypothesis that coronary CTA will have additional predictive value, beyond clinical variables, for the occurrence of major perioperative cardiac events in patients undergoing noncardiac surgery using the likelihood ratio (LR) test: LR test = -2ln (L1/L2) where L1 and L2 are the likelihood for the reduced model with VISION score alone, and likelihood for the full model with both VISION score and CTA variables.[27]

For the logistic model we will report the odds ratios [OR], 95% confidence intervals, and associated p-values. For all tests, we will use alpha = 0.05 level of significance. For all significant associations we will report the likelihood ratio and the 95% confidence interval.

Examination of residuals will provide an assessment of model assumptions for regression analyses. Goodness-of-fit for the models will be performed using appropriate Hosmer-Lemeshov tests. For the multivariable regression analysis, multicollinearity (correlations among predictor variables) may exist.[28] We will assess colinearity using the variance inflation factor (VIF) which measures the extent to which the variance of the model coefficients will be inflated (because of the correlation of the variable with other predictor variables) if that variable is included in the model. We will consider variables with VIF >10 colinear and we will exclude one of these variables from the analysis.[29]

For our secondary objective we will determine the proportion of patients suffering a perioperative myocardial infarction who on their coronary CTA the myocardial infarction associated artery had a coronary artery stenosis of <50%, 50-69%, ≥70-99%, 100%, or no coronary artery stenosis and the associated 95% confidence intervals. We will perform all analyses using SAS version 9.2 (Cary, North Carolina).

Ethics

Coronary CTA results in a measurable radiation exposure. Volume coverage of the whole heart using standard acquisition parameters will approximately result in an effective dose of 10 to 12 mSv if retrospectively gated CTA is performed. The dose will likely be substantially lower if prospectively triggered CTA is performed. The maximum anticipated does is similar to a nuclear perfusion scan (8 to 12 mSv), but greater than a standard chest CT (5 to 7 mSv)[30] and equals 3 to 4 years of the annual average effective dose from background radiation (3.6 mSv/year) or approximately 20 % of the annual whole body effective dose that is allowed for a radiation worker (radiologist, radiological technologist) (50 mSv/year).[31]

We feel that blinding of treating physicians to the coronary CTA findings is important to provide the most unbiased assessment of its prognostic capabilities. Thus, in keeping with prior studies that evaluated non-invasive tests in patients undergoing vascular surgery,[32-33] the attending surgeons and consultants in our study will not know the results of the pre-operative coronary CTA. The best evidence presently available from the CARP Trial[34] and DECREASE-V Trial[35] suggests that there is no benefit to prophylactic coronary revascularization prior to non-cardiac surgery and therefore, the CTA results are not required to guide treatment prior to non-cardiac surgery. In the CARP Trial one-third of the patients had 3 vessel coronary artery disease,[34] and in the DECREASE-V Trial 67% of the patients had 3 vessel coronary artery disease.[35] The only exception is hemodynamically significant left main disease which was excluded in the CARP trial. Thus, if the coronary CTA suggests significant left main disease, the results will be immediately disclosed to the treating physicians. For all patients in the study, the results of coronary CTA will be provided to all family physicians, internal medicine, and cardiology consultants involved in the care of the patients at 30 days post surgery.

An external safety and monitoring committee (ESMC) will convene early in the study and will meet again at regular intervals. Interim analyses will be conducted when approximately 25%, 50%, and 75% of the expected events have occurred and the data are available. The analyses will be conducted on the total of adjudicated and unadjudicated events at the appropriate time points. If the ESMC decides that a definitive conclusion has been reached for the overall study population or a specific subgroup, they will immediately unblind the Co-Principal Investigators and discuss the results together.

Conclusion

Coronary CTA is a novel application of CT scanning with potentially important clinical applications. This study will evaluate the role of coronary CTA in risk stratification prior to noncardiac surgery. If we demonstrate that CTA has important additional predictive value beyond clinical information in patients undergoing elective noncardiac surgery, this finding would allow this test to facilitate informed patient decision-making about the risks of surgery and guide perioperative patient management. This study will also provide insights into the underlying coronary anatomy of coronary arteries that cause myocardial infarction in the perioperative setting. This knowledge will inform the selection of targeted prevention and management interventions to evaluate in large perioperative randomized controlled trials. Considering that over 200 million adults undergo major noncardiac surgery annually and that we know little about how to predict or manage major perioperative cardiac events, highlights the importance of the Coronary CTA VISION Study.

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Table 1. Inclusion Criteria

All patients undergoing elective noncardiac surgery are eligible if they:

• are ≥ 45 years of age
• require at least an overnight hospital admission after surgery
• are undergoing one of the following surgeries
    ○ orthopedic (major joint arthroplasty)
    ○ vascular
    ○ thoracic surgery (pneumonectomy, lobectomy, other thoracic – wedge lung resection, mediastinal tumor resection, major chest wall resection)
    ○ major abdominal surgery (partial or total colectomy, stomach surgery, visceral resection, cytoreductive surgery, radial hysterectomy, radical prostatectomy)
    ○ major organ transplantation (kidney, liver, lung)
• have enough time prior to noncardiac surgery to obtain a coronary CTA study
• fulfill one of the following additional criteria:
    ○ history of coronary artery disease
    ○ history of peripheral vascular disease
    ○ history of stroke
    ○ history of a physician diagnosis of congestive heart failure; OR
    ○ any 3 of the following 6 risk factors: (a) diabetes and currently on an oral diabetic drug or insulin therapy, (b) age ≥70 years, (c) history of smoking within 2 years of surgery, (d) history of treatment for hypercholesterolemia, (e) history of a transient ischemic attack (TIA), or (f) a history of hypertension.

Table 2. Exclusion Criteria

All patients are excluded if they:

- are referred to invasive coronary angiography prior to noncardiac surgery (coronary CTA will not provide information incremental to an invasive angiogram)
- have had a prior percutaneous coronary intervention (PCI) with stent implantation (due to limited ability of coronary CTA to evaluate stents)
- have a creatinine clearance <35 ml/min (to avoid risk of contrast nephrotoxicity in patients potentially at risk)
- have a known contrast reaction
- are pregnant
- have persistent atrial fibrillation or >2 atrial or ventricular premature beats on a preoperative 12 lead electrocardiogram (ECG) (suboptimal image quality results from irregular heart rhythms at cardiac CT due to difficulties with retrospective gating)
- weight >300 lbs (obese patients have suboptimal image quality due to a poor contrast to noise ratio)
- have an inability to achieve the required heart rate prior to coronary CTA despite medication (i.e., a beta-blocker or calcium channel blocker) if the patient will be scanned on a single source scanner they require a heart rate <70 beats per minute (bpm) or a heart rate <90 bpm if the patient will be scanned on a dual source scanner; or
- patients who do not undergo noncardiac surgery within 6 months of their coronary CTA.

Table 3: Diagnostic confidence in determination of culprit lesion in patients who fulfill our definition of myocardial infarction

Diagnostic confidence	Criteria
Highly probable location of lesion	• Thrombus or features of recent plaque rupture (irregular margins, hazy appearance, dissection) coronary plaque fissure seen on invasive angiography; OR • New area of infarction on cardiac MRI
Probable location of lesion	• New perfusion abnormality identified on SPECT testing • New wall motion abnormality (as determined through comparison of pre and postoperative echocardiography or MRI; • New wall motion abnormality as determined through comparison of preoperative CTA myocardial function and postoperative echocardiography; OR • New Q waves in 2 contiguous leads on the patients ECG
Possible location of lesion	• ST segment elevation [$\geq$2 mm in leads V_1, V_2, or V_3 OR $\geq$1 mm in the other leads] in two contiguous leads; • ST segment depression [$\geq$1 mm] in two contiguous leads; • Symmetric inversion of T waves $\geq$1 mm) in at least two contiguous leads; OR • Presumed new cardiac wall motion abnormality on echocardiography • Presumed new fixed defect on SPECT testing

Table 4: Sample size needed to test 4 variables in a multivariable analysis based upon various event rates and the required number of events per variable

Required number of events per variable	Number of events needed	Sample size needed to test 4 variables in a multivariable analysis based upon various event rates	
		4%	6%
10	40	1000	667
12	48	1200	800
15	60	1500	1000

Appendix

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