From the Southern Association for Vascular Surgery

Diagnosis and management of silent coronary ischemia in patients undergoing carotid endarterectomy

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ABSTRACT

Background: Coronary artery disease is the primary cause of death in patients with carotid artery disease and silent ischemia is a marker for adverse coronary events. A new noninvasive cardiac diagnostic test, coronary computed tomography-derived fractional flow reserve (FFR_{CT}) can reliably identify ischemia-producing coronary stenosis in patients with coronary artery disease and help to select patients for coronary revascularization. The purpose of this study is to determine the prevalence of silent coronary ischemia in patients undergoing carotid endarterectomy (CEA) and to evaluate the usefulness of FFR_{CT} in selecting patients for coronary revascularization to decrease cardiac events and improve survival.

Methods: Patients with no cardiac history or symptoms admitted for elective CEA were enrolled in a prospective, open-label, institutional review board-approved study and underwent preoperative coronary computed tomography angiography (CTA) and FFR_{CT} with results available to physicians for patient management. Lesion-specific coronary ischemia was defined as FFR_{CT} of 0.80 or less distal to a focal coronary stenosis with an FFR_{CT} of 0.75 or less, indicating severe ischemia. Primary end point was incidence of major adverse cardiovascular events (MACE; defined as cardiovascular death, myocardial infarction, or stroke) at 30 days and 1 year.

Results: Coronary CTA and FFR_{CT} was performed in 90 CEA patients (age 67 ± 8 years; male 66%). Lesion-specific coronary ischemia was found in 51 patients (57%) with a mean FFR_{CT} of 0.71 ± 0.14. Severe coronary ischemia was present in 39 patients (43%), 26 patients had multivessel ischemia, and 5 had left main disease. CEA was performed as scheduled in all patients with no postoperative deaths or myocardial infarctions. There were no MACE events at 30 days. After recovery from surgery, 36 patients with significant lesion-specific ischemia underwent coronary angiography with coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) in 30 patients (33%). Survival at 1 year was 100% and freedom from MACE was 98%.

Conclusions: Patients undergoing CEA have a high prevalence of unsuspected (silent) coronary ischemia, which may place them at risk for coronary events. Preoperative diagnosis of silent ischemia using CTA and FFR_{CT} can identify high-risk patients and help to guide patient management. Selective postoperative coronary revascularization of patients with significant ischemia may decrease the risk of cardiac events and improve survival, but longer follow-up is needed and prospective, controlled trials are indicated. (J Vasc Surg 2020;■:1-9.)

Keywords: Carotid artery disease; Carotid endarterectomy; Preoperative cardiac evaluation; Silent myocardial ischemia; Coronary CT-derived fractional flow reserve; Coronary revascularization; Survival analysis

Coronary artery disease (CAD) is the primary cause of morbidity and mortality in patients with carotid artery disease. Patients with asymptomatic carotid stenosis have a four-fold higher risk of myocardial infarction (MI) than stroke[1] and the presence of carotid stenosis is an independent predictor of cardiac death.[2,3] Patients undergoing carotid endarterectomy (CEA) have a higher risk of MI than stroke and those with postoperative MI have a 5-year survival of only 56%.[4] Despite this high cardiac risk and the knowledge that 60% of CEA patients

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have coronary angiographic evidence of significant CAD,[5] systematic preoperative cardiac testing is not recommended for vascular surgery patients because randomized trials have shown no long-term survival benefit from preoperative coronary revascularization.[6,7] Thus, most patients undergo major vascular surgery without preoperative cardiac testing and the mortality of patients with postoperative MI remains high, despite evidence-based medical therapy.[8]

Myocardial ischemia is common in patients with CAD, is often asymptomatic (silent), and is a marker for adverse cardiac events and reduced survival.[9] Ischemic myocardial injury after vascular surgery markedly increases 30-day mortality.[10] Preoperative noninvasive testing of patients undergoing carotid or peripheral vascular surgery showed that 25%-40% of patients had silent myocardial ischemia and that silent ischemia was a predictor of adverse outcomes.[11-13] However, myocardial perfusion imaging provides no information regarding the coronary artery lesions, which may be causing ischemia and may benefit from revascularization. While coronary angiography or coronary CT angiography (CTA) can identify the location and severity of stenoses, they cannot reliably determine the hemodynamic significance of a lesion. The ischemia-producing potential of a coronary stenosis can be determined at the time of coronary angiography by measurement of fractional flow reserve (FFR). Randomized trials of CAD patients with lesion-specific coronary ischemia as demonstrated by a FFR of 0.80 or less have shown that FFR-guided coronary revascularization results in a significant reduction in death/MI at 5 years compared with best medical therapy.[14,15]

A newly introduced cardiac diagnostic modality, coronary CT-derived FFR (FFR_{CT}) can identify ischemia-producing coronary stenoses noninvasively. FFR_{CT} analysis uses anatomic information provided by standard coronary CTA image datasets and applies computation fluid dynamics to determine hyperemic coronary blood flow and compute fractional flow values throughout the coronary tree.[16] Computed FFR_{CT} accurately reflects invasively measured FFR and reliably differentiates hemodynamically significant coronary lesions from nonfunctional stenoses.[17] Patients with ischemia-producing lesions (FFR_{CT} of $\leq$0.80) may benefit from coronary revascularization with increasing benefit for those with lower FFR_{CT} values, whereas patients with a FFR_{CT} of greater than 0.80 can be safely treated medically.[18,19] The clinical usefulness of FFR_{CT} in the evaluation of patients with symptoms of CAD is well-established[20] and FFR_{CT} analysis has been used to evaluate more than 50,000 patients with suspected CAD in the United States, Europe, Canada and Japan. The value of FFR_{CT} in patients at risk for cardiac events, such as those with peripheral vascular disease, but presenting without cardiac symptoms is unknown. The purpose of this study is to determine the prevalence of silent coronary ischemia in patients undergoing CEA using coronary CTA and FFR_{CT} and to evaluate the potential usefulness of FFR_{CT} in selecting patients for coronary revascularization to reduce cardiac events and improve survival.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, prospective cohort study
- **Key Findings:** Among 90 carotid endarterectomy patients, 51 (57%) had silent coronary ischemia by noninvasive fractional flow reserve analysis and 30 had postoperative coronary revascularization. The 1-year survival was 100%, only two patients had adverse events, one myocardial infarction and one stroke.
- **Take Home Message:** Diagnosis of silent coronary ischemia and selective coronary revascularization may improve survival of carotid endarterectomy patients.

METHODS

Study design. This prospective, single-center, open-label study was designed to determine the prevalence of ischemia-producing coronary stenosis in patients undergoing CEA using coronary CTA-derived FFR_{CT} and to assess the potential benefit of FFR_{CT} in guiding patient management to reduce cardiac complications. It is focused on the population of patients with no known cardiac disease who nonetheless are at risk of postoperative MI and death. The primary study end points are prevalence of lesion-specific coronary ischemia and incidence of major adverse cardiovascular events (MACE) consisting of cardiovascular death, MI, or stroke. The protocol was approved by the institutional ethics committee (No. 060918-1E) and all patients signed informed consent.

Patient population. The study population was composed of patients with no cardiac history or coronary symptoms who were admitted to Pauls Stradins Clinical University Hospital, Riga, Latvia, for elective CEA and who underwent preoperative cardiac evaluation with coronary CTA and FFR_{CT}. Inclusion criteria included age of 50 years or greater, symptomatic or asymptomatic carotid artery stenosis needing surgery, no cardiac history or symptoms of CAD, and no ischemic changes on preoperative electrocardiography. Exclusion criteria included a history of MI, coronary angiography, or coronary revascularization; congestive heart failure, severe arrhythmia or pacemaker, suspicion of acute coronary syndrome, chronic renal failure with a glomerular filtration rate of less than 30 mL/min, any active disease with life expectancy of more than 1 year, inability to obtain coronary CTA, and contraindication to beta-blocking agents or nitroglycerin. From September 2017 to July 2019, 96 consecutive CEA patients were enrolled in this study and underwent preoperative coronary CTA examination. In six patients, CTA image quality was unsuitable for FFR_{CT} analysis owing to excess motion, misregistration, or imaging artifacts and these patients were excluded from this report. None of the patients were excluded owing to excess calcification.

Coronary CTA. Coronary CTA was performed using a single source 64-slice scanner with standard imaging protocols in accordance with Society of Cardiovascular Computed Tomography guidelines.[21] Oral and/or intravenous beta-blockers were administered as needed for heart rate control (<60 beats/minute) and sublingual nitroglycerin was administered for coronary vasodilation. An initial nonenhanced scan was performed for calcium scoring using the Agatston method.[22] Significant coronary CT stenosis was defined as a 50% or greater diameter reduction in a major epicardial coronary artery of 2 or more mm in diameter.

FFR_{CT} analysis. Coronary CTA image datasets were sent via secure web-based interface for off-site computational analysis of FFR (HeartFlow, Inc, Redwood City, Calif). FFR_{CT} results were returned to the hospital in less than 24 hours and were available to treating physicians for patient management decisions. Lesion-specific coronary ischemia was defined as an FFR_{CT} of 0.80 or less distal to more than 30% stenosis in a greater than 2-mm diameter coronary artery. Severe lesion-specific ischemia was defined as an FFR_{CT} of 0.75 or less distal to more than 30% stenosis in a greater than 2-mm diameter vessel.

Patient management. Patient management was at the discretion of the treating physician with guidance by a vascular team comprised of vascular surgeons, anesthesiologists, cardiologists, cardiac surgeons, and radiologists. Patients with evidence of lesion-specific ischemia were evaluated by the heart team and decisions regarding the timing and management (percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG], or optimal medical care) were based on the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization, taking into account patient preferences and comorbidities, as well as coronary anatomy specifics that may preclude use of any of the revascularization methods (eg, diffusely diseased arteries).[23] All patients received guideline-recommended optimal medical therapy and follow-up was coordinated with each patient's primary care physician.

Study end points. The primary outcome end point was the incidence of MACE rate, defined as cardiovascular death, MI, or stroke at 30 days, with follow-up at 3, 6, and 12 months. Secondary end points included cardiovascular death, MI, stroke, and all-cause mortality. Study end points were adjudicated by an interdisciplinary end points committee and defined in accord with the Academic Research Consortium-2 document[24] and fourth universal definition of MI.[25]

Statistical analysis. Continuous variables were expressed as mean ± standard deviation and categorical variables as count (percentage). Cumulative results were expressed as Kaplan-Meier estimates. Statistical analyses were performed using IBM SPSS Statistics version 23.0 with significance defined as a *P* value of less than .05.

RESULTS

Patient characteristics. The baseline characteristics of the study population of 90 CEA patients are shown in Table I. The mean age was 67 ± 8 years, 66% were men, and 34% were women. Comorbidities included hypertension in 83%, hyperlipidemia in 31%, diabetes mellitus in 9%, and smoking in 31%. All patients were free of cardiac signs or symptoms and had no ischemic changes on preoperative electrocardiography. Indications for CEA were symptoms of transient ischemic attack or stroke in 50 patients (56%) and asymptomatic carotid stenosis in 40 patients (44%). The degree of carotid stenosis was documented by Duplex ultrasound examination according to North American Symptomatic Carotid Endarterectomy Trial criteria and confirmed by carotid multidetector CTA.[26] Symptomatic patients had more than 70% diameter stenosis with Rankin scale for neurologic disability of less than 3 and asymptomatic patients had greater than 75% diameter stenosis confirmed by CTA.

Anatomic assessment of CAD: Coronary CTA. Results of preoperative coronary CTA evaluation are shown on Table II. Calcium scores ranged from 0 to 5446 with a mean of 673 ± 975 and a median of 344. Coronary stenosis 50% or greater by CTA was present 49% of patients with multivessel disease in 28%. Coronary CTA stenosis 70% or greater was present in 28% of patients and left main stenosis of 50% or greater was present in 4.4% of patients.

Functional assessment of CAD: FFR_{CT} analysis. The results of FFR_{CT} analysis are shown on Table II and Fig 1. Lesion-specific coronary ischemia was found in 51 patients (57%) with a mean FFR_{CT} value of 0.71 ± 0.12. Severe lesion-specific ischemia (FFR_{CT} of ≤0.75) was present in 43% of patients with a mean FFR_{CT} of 0.60 ± 0.09. Multivessel lesion-specific ischemia was present in 26 patients (29%), 19 patients (21%) had FFR_{CT} values of less than 0.60, and 5 patients (5.6%) had left main ischemia. No lesion-specific ischemia was found in 43% of patients (FFR_{CT} of >0.80), although some had evidence of diffuse disease with tapering FFR_{CT} values along the length of the vessel, decreasing to 0.80 or less at the distal end of one or more coronary arteries. The relationship between calcium score and lesion-specific

Table I. Characteristics (N = 90)

Characteristics	Mean ± standard deviation, range, or No. (%)
Baseline characteristics	
Age (years)	67 ± 8
Range	50-83
Male	59 (66)
Female	31 (34)
Comorbidities	
Hypertension	75 (83)
Hyperlipidemia	31 (34)
Diabetes mellitus	8 (9)
Smoking	31 (34)
Medications	
Antihypertensives	63 (70)
Statin therapy	42 (47)
Insulin	8 (9)
Antiplatelet or anticoagulants	44 (49)
Indications for CEA	
Cerebrovascular symptoms (transient ischemic attack/ stroke)	50 (56)
Asymptomatic carotid stenosis	40 (44)

CEA, Carotid endarterectomy.

ischemia is shown in Table III. Lesion-specific ischemia was present in 37% of patients with low calcium scores (0-99), in 60% of patients with moderately high calcium scores (401-1000), and in 90% of patients with very high calcium scores (>1000).

CEA. CEA was performed as scheduled in all patients using general endotracheal anesthesia, radial artery blood pressure monitoring, electrocardiogram (ECG) monitoring with ST segment analysis, blood gas, and oxygen saturation monitoring. The surgical procedure consisted of eversion endarterectomy (76%) or endarterectomy with a polyester patch closure (24%). An indwelling shunt was used in 72 patients (80%). Postoperatively, patients were monitored in the intensive care unit for the first 24 hours with routine postoperative troponin measurement in all patients. There were no intraoperative or postoperative cardiovascular events and no patient had postoperative troponin elevation.

Postoperative coronary care. All patients remained free of chest pain symptoms and received optimal medical therapy including statins, antiplatelet agents, antihypertensives, and diabetes control as appropriate. Patients with significant coronary ischemia were selected for coronary angiography 1 to 3 months after CEA. Coronary angiography in 36 patients (40%) confirmed significant stenosis in each patient and coronary revascularization was performed in 30 patients (33.3%). PCI was performed in 25 patients with CABG in 5 patients. Staged PCI revascularization was required in 11 patients with multivessel ischemia. A representative patient example is shown in Fig 2. One patient with multivessel ischemia had a procedure-related MI during the second stage PCI of a left main left anterior descending stenosis. This was evidenced by transient chest pain, ST depression on the ECG, and rise and fall of troponin and creatine kinase-myocardial band. This patient recovered uneventfully and is well at 1 year. There have been no other adverse events related to coronary revascularization.

Patient outcomes. There have been no deaths in the study and no MACE events at the primary end point of 30 days. Similarly, at 3 months there were no MACE events. Two MACE events occurred in the 4-month timeframe. The first was a periprocedural MI during PCI, which is discussed elsewhere in this article. The second was a stroke related to the unoperated carotid in a patient with bilateral severe carotid stenosis. Six months of follow-up were available for 88 patients with 12 months of follow-up for 60 patients. There have been no deaths or spontaneous MIs. Cumulative results by Kaplan-Meier analysis reveals a 1-year survival of 100% and freedom from MACE of 97.8% (Fig 3).

DISCUSSION

This study shows that, among 90 patients with no symptoms of CAD undergoing CEA, 57% had unsuspected, silent coronary ischemia by preoperative coronary CTA and FFR_{CT} analysis. The extent and severity of coronary ischemia was surprisingly high with severe ischemia (FFR_{CT} of ≤0.75) in 43%, multivessel ischemia in 29%, and left main ischemia in 5.6% of patients. Despite this degree of coronary ischemia, CEA was performed safely with no complications using cardiac anesthesia, close monitoring, and optimal medical care. In a similar study of patients with no cardiac history or symptoms undergoing CEA, silent myocardial ischemia was documented in 25% by exercise ECG and concordant myocardial scintigraphy.[11] No perioperative deaths or cardiac events occurred in 106 patients, regardless of the presence of absence of myocardial ischemia. However, the presence of silent ischemia was found to strongly influence long-term outcome in that study. During 7 years of follow-up, coronary events occurred in 30% of patients with silent ischemia, but in only 1% of patients with no ischemia. Survival free from fatal and nonfatal coronary events was 51% in patients with silent ischemia compared with 98% in patients without ischemia at the time of CEA (Kaplan-Meier analysis; $P < .01$).[11] Thus, the issue of ischemic coronary disease assessment in patients undergoing CEA may not be one of ensuring the safety of the operative procedure, but rather, one of

Table II. Preoperative coronary assessment, per patient analysis

Coronary CTA and FFR_{CT} analysis	
Calcium score (Agatston method)	673 ± 975
Agatston score range	0-5446
Coronary CTA stenosis ≥50%	44 (49)
Left main	4 (4.4)
Single vessel	19 (21)
Two vessel	20 (22)
Three vessel	5 (5.6)
Coronary CTA stenosis ≥70%	25 (28)
Lesion-specific ischemia, FFR_{CT} ≤0.80	51 (57)
FFR_{CT} value	0.71 ± 0.14
Left main	5 (5.6)
Single vessel	25 (28)
Two vessels	16 (18)
Three vessels	10 (11)
Severe lesion-specific ischemia, FFR_{CT} ≤0.75	39 (43)
FFR_{CT} value	0.60 ± 0.09
No lesion-specific ischemia, FFR_{CT} >0.80	39 (43)
FFR_{CT} value, mean	0.88 ± 0.04
FFR_{CT} ≤0.80 at distal end of vessel	69 (77)
FFR_{CT} value	0.70 ± 0.12

CTA, Computed tomography angiography; *FFR_{CT}*, fractional flow reserve derived from coronary computed tomography angiography. Data provided as mean ± standard deviation, range or number (%).

minimizing the likelihood of postoperative cardiac events and improving long-term survival.

The low perioperative risk of CEA is well known. Operative mortality in more than 480,000 carotid endarterectomies was 0.5% and only 0.2% in low-risk patients, such as in our study.[24] However, MI or biomarker evidence of myocardial injury may occur and this can have a profound effect on the short- and long-term survival of vascular surgery patients. In a prospective study of 500 vascular surgery patients, 19% were found to have postoperative elevation of troponin and this was associated with a nine-fold increase in the 30-day mortality compared with patients without elevated troponin. Notably, 74% of patients with evidence of myocardial injury were asymptomatic.[10] The Vascular Study Group of New England registry of 16,363 patients undergoing major vascular surgery from 2003 to 2011 (including 51% carotid revascularizations) reported markedly lower survival of patients with postoperative troponin elevation (54% at 5 years) or MI (33% at 5 years) compared with patients with no ischemia (73% at 5 years; $P < .0001$).[4] A subanalysis of 8315 patients with carotid revascularization showed that patients who had postoperative troponin elevation or MI had a 1-year survival of 84% and a 5-year survival of only 56%.[27] Efforts to reduce this high mortality have been focused on aggressive medical management of atherosclerosis in vascular patients. However, the effectiveness of this strategy has been questioned by a recent report from a statewide database of 26,231 patients undergoing major vascular surgery (carotid revascularization in 52%). Postoperative MI by ECG or biomarker changes occurred in 1.6% of patients, but despite best evidence-based, guideline-directed postoperative medical therapy in almost all patients, the 1-year mortality was very high at 37%.[8] This finding suggests the need for more aggressive diagnostic and therapeutic strategies to decrease the risk of postoperative mortality in these patients.

Our study demonstrated the usefulness of preoperative cardiac risk assessment of CEA patients using CTA-FFR_{CT}. As opposed to cardiac stress testing, which only provides information on myocardial perfusion, CTA-FFR_{CT} provides a three-dimensional anatomic-functional map of the coronary tree that can readily identify coronary lesions that may benefit from revascularization. This facilitated a multidisciplinary vascular team approach to patient management, which is now strongly recommended for patients with peripheral arterial diseases.[7] High-risk patients with silent ischemia could be identified for enhanced perioperative monitoring and more intense medical care, and the map of FFR_{CT} values enabled the planning and timing of elective coronary revascularization. Noninvasive CTA-FFR_{CT} has been shown to be equivalent to invasive coronary angiography for coronary revascularization treatment planning.[28] No patient in this study had postoperative troponin elevation, which may have prompted urgent coronary revascularization. Thus, patients with left main, proximal, and multivessel ischemia could be selected for elective coronary angiography after recovery from CEA surgery. Coronary revascularization with PCI or CABG was performed in 33.3% of patients with only one PCI-related cardiac event during follow-up. This rate is similar to the 31.5% coronary revascularization rate with systematic preoperative coronary angiography.[29] Survival at 1 year was 100% and freedom from MACE was 98%, suggesting that coronary revascularization may provide benefit in decreasing the risk of coronary events.

The benefit of selective coronary revascularization to improve survival of CEA patients with asymptomatic CAD was shown in a recent randomized trial published by Illuminati et al.[29] In this trial, 426 CEA patients with no cardiac history or clinical symptoms of CAD were randomized to systematic preoperative coronary angiography followed by selective coronary revascularization (n = 216) or CEA without coronary angiography (n = 210). All patients had normal functional capacity (as determined by a median Metabolic Equivalent Task Score of 5.8), normal resting ECG, and normal transthoracic echocardiography with a left ventricular ejection fraction of greater than 50%. Preoperative angiography revealed more than 70% coronary stenosis in 68 patients

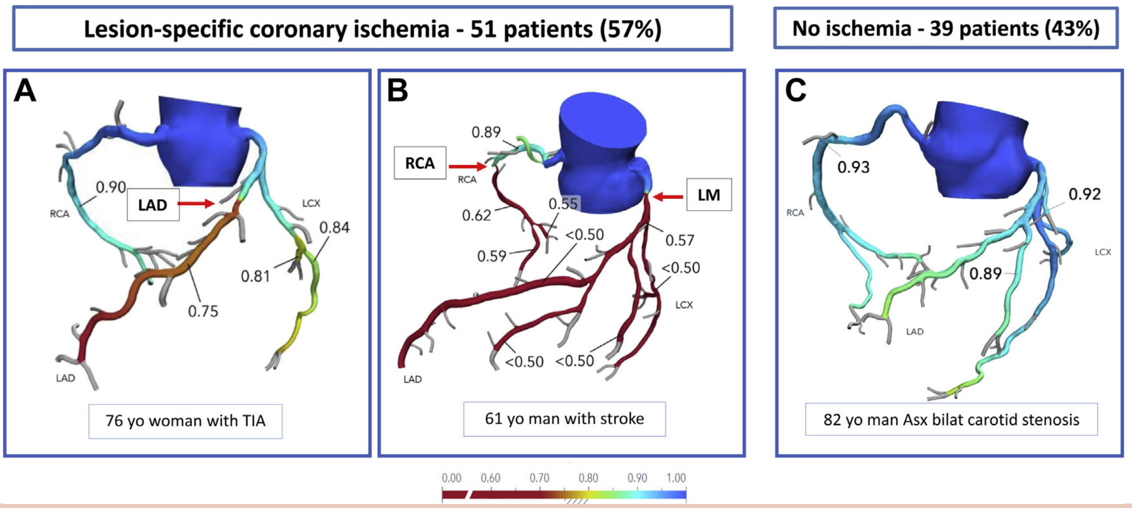

Fig 1. Results of preoperative fractional flow reserve derived from coronary computed tomography angiography (FFR_{CT}) analysis in patients with no cardiac history or coronary symptoms undergoing carotid endarterectomy (CEA). Unsuspected, lesion-specific coronary ischemia (FFR_{CT} of ≤0.80) was found in 57% of patients of which 47% had single vessel ischemia as seen in **(A)** and 51% had multivessel ischemia as seen in **(B)**. Severe coronary ischemia, as evidenced by FFR_{CT} values of 0.75 or less was present in 43% of patients and 5.6% had left main (LM) ischemia as seen in **(B)**. No ischemia was found in 43% of patients. *Asx,* Asymptomatic; *LAD,* left anterior descending; *LM,* left main; *RCA,* right coronary artery; *TIA,* transient ischemic attack.

(31.5%) and these were revascularized with PCI in 66 patients and combined CEA and CABG in 2 patients. CEA was performed in all patients with a median delay of 4 days (range. 1-8 days) with no complications. In the angiography group, there were no postoperative deaths or MIs whereas six MIs occurred in the no angiography group, one of which was fatal ($P = .01$). During 6 years of follow-up, 3 MIs (1.4%) occurred in the angiography group and 33 were observed in the no angiography group (15.7%; $P < .001$), of which 6 were fatal. Survival at 6 years was improved in the angiography group compared with the no angiography group (95.6% vs 89.7%; Kaplan-Meier estimate; log rank test, $P = .01$).[29] Based on the results of this trial, the 2017 European Society of Cardiology/European Society for Vascular Surgery Guidelines on the Diagnosis and Treatment of Peripheral Vascular Diseases provided a new recommendation: "in patients undergoing elective CEA, preoperative CAD screening, including coronary angiography, may be considered" (Evidence IIb).[7] Our study shows that, in patients undergoing CEA, effective preoperative CAD evaluation can be done noninvasively using CTA and FFR_{CT} and that this can be used to help guide revascularization decisions. A randomized trial of heart team decision making and treatment planning for PCI or CABG in patients with multivessel coronary disease found high agreement between noninvasive CTA-based decisions and invasive angiography-based decisions[28] and showed that the physiologic assessment provided by FFR_{CT} changed the heart team's treatment decision and procedural plan in one-fifth of patients.[30]

Table III. Relationship of calcium score to lesion-specific ischemia

Calcium score range	Patients with calcium score	Lesion-specific ischemia, FFR_{CT} ≤0.80
0-99	27 (30)	10 (37)
100-400	22 (25)	11 (50)
401-1000	20 (23)	12 (60)
>1000	19 (22)	17 (90)

FFR_{CT}, Fractional flow reserve derived from coronary computed tomography angiography.
Values are number (%).

The strategy of systematic preoperative coronary angiography followed by selective coronary revascularization to improve survival has also been tested in a population of 208 consecutive patients with medium to high risk undergoing major vascular surgery. Patients were randomized to selective preoperative coronary angiography based on the results of noninvasive cardiac stress tests or to a systematic strategy of preoperative coronary angiography in all patients. Patients in the routine preoperative coronary angiography group had a higher coronary revascularization rate and at 58 months had significantly better survival ($P = .01$) and freedom from death/cardiovascular events ($P = .003$).[31]

The prevailing opinion that preoperative coronary revascularization provides no survival benefit to patients undergoing is major vascular surgery is largely based on the prospective, randomized Coronary Artery Revascularization Prophylaxis (CARP) trial.[6] This trial screened 1048 patients with coronary angiography and randomized

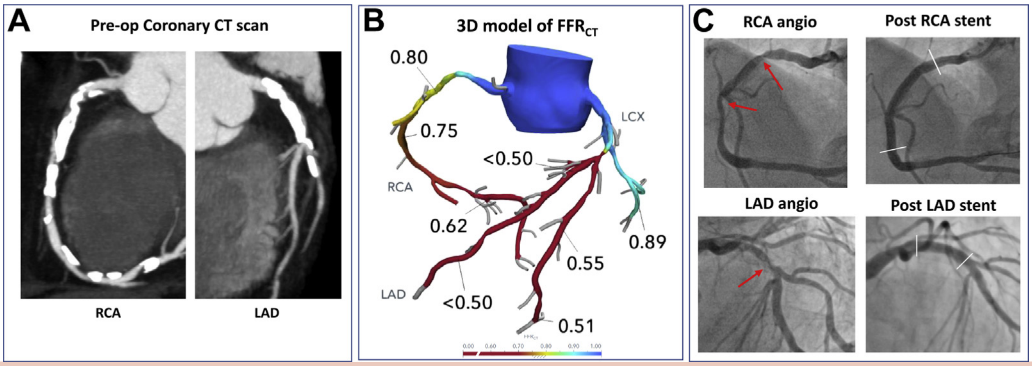

Fig 2. Case example. A 73-year-old man admitted with a left hemispheric transient ischemic attack. The patient had no cardiac history or symptoms of coronary artery disease (CAD). **A,** Preoperative coronary computed tomography (*CT*) angiography showed extensive coronary calcification (Agatston score 2585) with 70% left anterior descending (*LAD*) and 60% right coronary artery (*RCA*) stenosis. **B,** fractional flow reserve derived from coronary computed tomography angiography (*FFR_{CT}*) analysis revealed tandem lesions in the RCA with lowest FFR_{CT} distal to stenosis of 0.62 and proximal LAD stenosis with FFR_{CT} of less than 0.50 distal to the lesion. **C,** Coronary angiography performed one month after uneventful left carotid endarterectomy (CEA) revealed greater than 75% stenoses in both RCA and LAD (arrows). The RCA lesions were treated with two drug-eluting stents at the time of coronary angiography. The left coronary lesion was treated with a drug eluting stent 6 weeks later. The patient is asymptomatic and doing well at 1 year of follow-up.

510 patients to coronary revascularization or no revascularization prior to elective vascular surgery. Among patients excluded from the randomized trial were patients with left main stenosis (4.6% of patients). A subsequent reanalysis that included all patients screened for the CARP trial showed that the only subgroup to benefit from preoperative revascularization were those with left main disease. Survival of left main patients with revascularization was significantly improved at 2.5 years compared with patients with no revascularization (84% vs 52%; $P < .01$).[32] The high risk of patients with left main stenosis is well-known and these patients are appropriately excluded from prospective clinical trials. However, their exclusion may limit the generalizability of trial results. We found unsuspected left main disease in five patients (5.6%) undergoing CEA. This is consistent with the 5% to 7% rate of finding left main disease when angiography or CTA is used to screen patients prior to randomization in large multicenter clinical trials.[6,33,34]

Although revascularization in asymptomatic patients with high-risk coronary disease such as left main stenosis and multivessel disease is considered appropriate, coronary revascularization of patients with stable obstructive CAD and no symptoms is unsettled. A recent population-based study from Ontario, Canada, found that 10% of all coronary angiograms performed from 2008 to 2013 were in in patients with no coronary symptoms. Almost 10,000 asymptomatic patients had angiographic evidence of 50% or greater left main or 70% or greater coronary stenosis, 53% underwent coronary revascularization, and 47% were treated medically. During a median follow-up of 4.6 years, revascularized patients had a 19% decrease in death (11.9% vs 18.6%; $P < .001$) and a 42% decrease in MI (3.8% vs 6.5%; $P < .001$) compared with patients treated medically.[35]

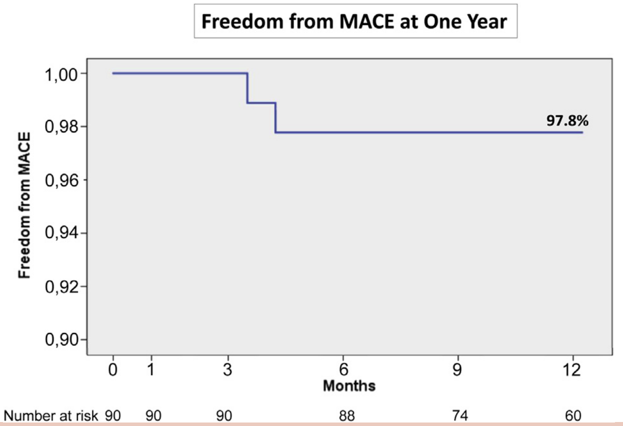

Fig 3. Kaplan-Meier survival curve showing 97.8% freedom from major adverse cardiovascular events (*MACE*) at 1 year. Two events have occurred in the 4-month time frame: (1) a periprocedural myocardial infarction (MI) during stenting of left main left anterior descending (LAD) stenosis and (2) a stroke in the distribution of the unoperated carotid in a patients with bilateral subocclusive carotid stenoses.

The FAME 2 trial of 888 patients with at least one hemodynamically significant coronary stenosis (FFR of ≤0.80) randomized to PCI or medical therapy included 99 patients (11%) who were asymptomatic (had silent ischemia).[33] In a subanalysis of patients who were randomized to the medical treatment arm, the 5-year outcomes of asymptomatic patients were compared with symptomatic patients. The rate of death or MI was found to be more than two times higher in asymptomatic patients than in symptomatic patients (31.1% vs 14.4%; hazard ratio 2.47; $P = .002$).[36] The rate of MI alone was twice as high in asymptomatic patients than in symptomatic patients (24.4% vs 10.6%; $P = .004$). The authors concluded that, in patients with hemodynamically significant stenosis in large coronaries, FFR-guided coronary revascularization should be considered, even in the absence of symptoms.[36] The functional significance of coronary stenosis can now be evaluated noninvasively using coronary FFR_{CT}. Preoperative assessment of high-risk patients, such as those undergoing CEA, can identify patients who have hemodynamically significant stenosis and who may benefit from invasive coronary angiography and revascularization.

This single-center observational study of preoperative cardiac assessment of CEA patients with CTA and FFR_{CT} is limited by the absence of a control group undergoing CEA with standard preoperative cardiac evaluation. This study is further limited by the small number of patients and short duration of follow-up. Thus, no firm conclusions can be drawn from these preliminary observations. Nonetheless, this is the first study to demonstrate the high prevalence of unsuspected, hemodynamically significant coronary artery stenosis using the new cardiac diagnostic modality of CTA-FFR_{CT} in patients undergoing elective CEA. This study also demonstrates the feasibility of multidisciplinary care in the perioperative period with selective postoperative coronary revascularization. Longer term follow-up and controlled studies are needed to determine the value of this approach.

In summary, this study found that 57% of patients undergoing elective CEA had unsuspected (silent) coronary ischemia which may put them at risk of death or MI. Preoperative diagnosis of ischemia-producing coronary stenosis using FFR_{CT} identified high-risk patients and helped to guide interdisciplinary patient management. Selective postoperative coronary revascularization was performed in 33% of patients with silent coronary ischemia with 100% survival and only 2.2% adverse cardiovascular events at 1 year. These results are consistent with longer term results reported from a prospective, randomized, controlled trial showing that selective coronary revascularization of asymptomatic CAD improved long-term survival of CEA patients.[29] Prospective, controlled trials are needed to further define the role of CTA-FFR_{CT} in the evaluation and treatment of patients undergoing CEA.

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AUTHOR CONTRIBUTIONS

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