

Prognostic Value of CT Angiography in Coronary Bypass Patients

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OBJECTIVES We sought the incremental prognostic value of coronary computed tomography angiography (CTA) in coronary artery bypass graft (CABG) patients.

BACKGROUND Coronary CTA is a noninvasive and accurate tool for the detection of obstructive coronary artery disease, and coronary CTA appears to have prognostic value in patients without previous revascularization. However, the prognostic value of coronary CTA to predict major adverse cardiac events in CABG patients is unclear.

METHODS Consecutive CABG patients were prospectively enrolled and cardiac risk was calculated using the National Cholesterol Evaluation Program/Adult Treatment Panel III. Using the severity of native coronary artery disease and graft disease, the number of unprotected coronary territories (UCTs) (0, 1, 2, or 3) was calculated. Patients were followed for cardiac death and nonfatal myocardial infarction. All events were confirmed with death certificates or medical records and reviewed by a clinical events committee.

RESULTS Between February 2006 and March 2009, 250 consecutive patients were enrolled and followed for a mean of 20.8 ± 10.1 months. At follow-up, 23 patients (9.2%) had major adverse cardiac events (15 cardiac deaths and 8 nonfatal MI). The absence of UCTs conferred a good prognosis with an annual event rate of 2.4%. Conversely, patients with 1, 2, and 3 UCTs had annualized event rates of 5.8%, 11.1%, and 21.7%, respectively. Multivariable analysis showed that UCTs (hazard ratio: 2.08; 95% confidence interval: 1.40 to 3.10; $p < 0.001$) was a predictor of major adverse cardiac events when adjusted for clinical variables. Examining the receiver-operator characteristic curves, the area under the curve increased from 0.61 to 0.76 when UCTs was combined with clinical variables ($p = 0.001$).

CONCLUSIONS Assessing UCTs with coronary CTA appears to have prognostic value in CABG patients and is incremental to clinical variables. Coronary CTA appears to be a promising tool for risk stratification of CABG patients. Further multicenter studies using large CABG cohorts are needed to confirm our findings. (*J Am Coll Cardiol Img* 2011;4:496–502) © 2011 by the American College of Cardiology Foundation

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Manuscript received November 10, 2010; revised manuscript received January 14, 2011; accepted January 18, 2011.

Coronary computed tomography angiography (CTA) is a noninvasive diagnostic tool useful for the detection of obstructive coronary artery disease (CAD) and the assessment of coronary artery bypass grafts (CABG) (1–13). Coronary CTA has prognostic value and predicts all-cause mortality and major adverse cardiac events (MACE) such as cardiac

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death and nonfatal myocardial infarction (MI) (14–19). However, previous studies have excluded patients with a history of coronary revascularization (14–19). To further support the utility of coronary CTA in patients with CABG, the prognostic value of 64-slice coronary CTA in this population requires further investigation.

Studies using invasive coronary angiography have demonstrated that the completeness of revascularization is an important predictor of outcome and that the number of arterial territories lacking a patent graft is a key determinant of mortality (20). Although coronary CTA can assess coronary and graft disease, its ability to assess the native arteries of CABG patients has been questioned (3,21). Thus, demonstrating the prognostic value of coronary CTA in the CABG population would further support its clinical use.

The objective of this prospective cohort study is to understand the potential incremental prognostic value of coronary CTA in CABG patients.

METHODS

Between February 2006 and March 2009, 269 consecutive CABG patients undergoing coronary CTA were prospectively enrolled in a Cardiac CTA Registry and were followed for all-cause death and MACE (cardiac death and nonfatal MI) (13,14). The study was approved by the Institutional Human Research Ethics Board, and all patients provided written informed consent.

Clinical predictors. A detailed medical history and laboratory results were recorded at the time of coronary CTA. Although a validated prognostic clinical model for CABG patients is lacking, age, sex, hypertension, and diabetes appear to be predictors of late cardiac events in CABG patients (22,23). Therefore, patients' age, sex, cardiac risk factors, and symptoms were used to estimate patient risk using the National Cholesterol Education Pro-

gram/Adult Treatment Panel III (NCEP/ATP III) Guidelines and the Morise score (14,24,25).

Coronary CTA. Before image acquisition, metoprolol or diltiazem (oral and/or intravenous) was administered, targeting a heart rate of ≤ 65 beats/min, and nitroglycerin 0.8 mg was administered sublingually (14,26,27). A biphasic timing bolus (15 to 25 ml of contrast [Visipaque 320 or Omnipaque 350, GE Healthcare, Princeton, New Jersey; 40 ml of saline solution) was used (13,14). A triphasic protocol (100% contrast, 40%/60% contrast/saline solution [50 ml], and saline solution [40 ml]) was used to acquire the final dataset. The volume and rate of contrast were individualized according to scan time and patient body habitus (13,14).

Retrospective electrocardiogram-gated datasets were acquired with the GE Volume CT (GE Healthcare, Milwaukee, Wisconsin) (64 \times 0.625-mm slice collimation, 350-ms gantry rotation, 400 to 800 mA, kilovolt peak = 120, and pitch of 0.16 to 0.24) (14). Images were reconstructed using a slice thickness of 0.625 mm with an increment of 0.4 mm using the cardiac phase(s) with the least amount of cardiac motion (13,14).

Coronary CTA image analysis. Images were post-processed using the GE Advantage Volume Share Workstation (GE Healthcare) and interpreted by expert observers blinded to all clinical data (14). A 4-point grading score (normal, mild [$< 50\%$], moderate [50% to 69%], severe [$\geq 70\%$]) was used for the evaluation of native CAD and CABG (28). In segments that were unassessable, forced reading was performed, and readers provided their best educated guess. Cases with > 5 unassessable segments were excluded from analysis. Significant stenoses were defined as left main $\geq 50\%$ diameter stenosis, other native vessel stenosis $\geq 70\%$, or graft stenosis $\geq 70\%$.

Patients were categorized according to the number (0, 1, 2, or 3) of unprotected coronary territories (UCTs) (20). Each patient had 3 coronary territories, corresponding to each major epicardial artery (left anterior descending artery, circumflex artery or artery supplying the posterior descending artery [right coronary artery or circumflex artery]) and their corresponding branches (diagonal and marginal arteries). A coronary territory was deemed unprotected if: 1) an ungrafted native coronary artery had a significant stenosis; 2) a significant stenosis in the native artery was distal to the graft

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAD = coronary artery disease

CTA = computed tomography angiography

MACE = major adverse cardiac event(s)

MI = myocardial infarction

NCEP/ATP = III = National Cholesterol Education Program/Adult Treatment Program III

UCT = unprotected coronary territory

insertion; or 3) a native artery and its graft both had significant stenoses (20). The left main was assigned 2 coronary territories in right dominant system, but 3 coronary territories when left dominant. Similarly, the circumflex artery was assigned 2 territories when the native coronary system was left dominant.

Patient follow-up. Patient follow-up was performed (at 6-month intervals) by telephone interview by trained research staff blinded to all clinical data. All events were confirmed with death records, hospital records, or correspondence with treating physicians. A clinical events committee (blinded to the results of the coronary CTA) reviewed all events.

Outcome measures. The primary outcome measure was a composite of cardiac death and nonfatal MI. All deaths were reviewed and classified as cardiac or noncardiac. Deaths were considered cardiac when the primary cause of death was related to myocardial ischemia/infarction, heart failure or cardiac arrhythmia, and when a noncardiac cause of death could not be identified (29). Nonfatal MI was defined as myocardial ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper normal limits) (30).

Statistical analysis. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina), and statistical significance was defined as $p < 0.05$. Continuous variables were presented as means and SDs, and categorical variables were presented as frequencies with percentages.

The prognostic value of UCTs was assessed for univariable association as well as multivariable association with MACE. All unadjusted comparisons of cardiac events were performed using log-rank tests. For risk-adjusted analysis, a multivariable Cox proportional hazard model was used to assess the independent prognostic value of UCTs adjusted for clinical variables (NCEP/ATP III) and created adjusted survival curves. Model overfitting was considered, and the proportional hazards assumption was met. The incremental value of UCTs was calculated by defining the clinical variables model followed by the addition of UCTs. The area under receiver-operator characteristic curves (95% confidence intervals) was compared to evaluate the discrimination ability of UCTs over clinical variables to predict MACE.

RESULTS

Study population. Over an enrollment period of 37 months, 4,536 consecutive patients underwent cor-

onary CTA with a total of 4,508 patients (99.4%) prospectively enrolled in the University of Ottawa Heart Institute Cardiac CTA Registry. Of these, 269 had previous CABG surgery and met the inclusion criteria for this study. A total of 10 patients were excluded from analysis for >5 unassessable segments. Follow-up was available for 250 patients (96.5%) with 9 patients lost to follow-up (Table 1). The baseline characteristics of the patients lost to follow-up were similar to those with follow-up, except those lost to follow-up were younger and were more likely to have atypical chest pain or dyspnea.

Univariable analysis of baseline characteristics with MACE. Univariable analysis of baseline characteristics is summarized in Table 2. Patients with

Table 1. Characteristics of Patients With Follow-Up (n = 250)

Mean follow-up, months	20.8 ± 10.1
Age, yrs	65.4 ± 9.5
Men	200 (80.0)
Body mass index, kg/m ²	29.5 ± 5.7
Cardiac risk factors	
Smoker/ex-smoker	175 (70.0)
Hypertension	157 (62.8)
Dyslipidemia	235 (94.0)
Diabetes	87 (34.8)
Family history of CAD	136 (54.4)
Indications for study	
Chest pain	150 (60.0)
Nonanginal chest pain	22 (8.8)
Atypical angina	29 (11.6)
Typical angina	99 (39.6)
Dyspnea	55 (22.0)
Morise score	14.9 ± 2.8
NCEP/ATP III risk	
Low risk	3 (1.2)
Intermediate risk	59 (23.6)
High risk	188 (75.2)
Unprotected coronary territories	
0	128 (51.2)
1	74 (29.6)
2	37 (14.8)
3	11 (4.4)
Left ventricular ejection fraction, %*	57.9 ± 15.1
Imaging parameters	
Imaging heart rate, beats/min	57.9 ± 6.9
Contrast infusion rate, ml/s	6.2 ± 0.9
Total contrast volume, ml	125.3 ± 20.4
Effective dose, mSv†	23.2 ± 5.2

Values are mean ± SD or n (%). *Left ventricular ejection fraction could only be accurately measured in 233 patients. †Effective dose (mSv) = dose length product × 0.014.

CAD = coronary artery disease; NCEP/ATP III = National Cholesterol Education Program/Adult Treatment Program III.

MACE were older, had a higher Morise score, and a greater proportion were in the NCEP/ATP III high-risk category.

UCTs and MACE. The rates of MACE increased with the increasing number of UCTs and were observed in a total of 3.9%, 9.5%, 16.2%, and 45.5% of patients with 0, 1, 2, and 3 UCTs, respectively (Table 3). The absence of UCTs conferred a good prognosis with an annual event rate of 2.4%. Conversely, patients with 1, 2, and 3 UCTs had annualized event rates of 5.8%, 11.1%, and 21.7%, respectively.

Risk-adjusted Cox models. For the risk-adjusted analysis, the NCEP/ATP III was used as the clinical variable because it combined age, sex, and cardiac risk factors into a single measure. A multivariable Cox model demonstrated that UCTs (hazard ratio: 2.08; 95% confidence interval: 1.40 to 3.10; $p < 0.001$), was an independent predictor for MACE adjusted for the clinical variables (Fig. 1, Table 4).

Incremental value analysis. The discrimination ability of UCTs over NCEP/ATP III was evaluated using receiver-operator characteristic curves (Fig. 2). The area under the curve for the clinical variable only was 0.61 (95% confidence interval: 0.56 to 0.66), with a significant increase to 0.76 (95% confidence interval: 0.66 to 0.86) when UCTs was added ($p = 0.001$).

DISCUSSION

To our knowledge, the prognostic value of coronary CTA in CABG patients has not been previously reported. The results of our study suggest that coronary CTA assessment of UCTs is of prognostic value and is incremental to clinical measures.

Prognostic value of coronary CTA. The diagnostic accuracy and prognostic value of coronary CTA have been well studied but have focused on patients with suspected CAD and those without a history of coronary revascularization (1,14-16,31,32). Because these studies excluded CABG patients, the prognostic value of coronary CTA in the CABG population is unknown.

Conversely, the prognostic value of invasive coronary angiography in CABG patients has been well studied. Liao et al. (20) developed a prognostic model for CABG patients and showed that the graft index and number of protected coronary territories predicted all-cause death.

Table 2. Univariable Analysis of Clinical Characteristics for MACE

	No MACE (n = 227)	MACE (n = 23)	Hazard Ratio (95% CI)	p Value
Age, yrs	64.9 ± 9.5	70.3 ± 8.9	1.06 (1.01-1.11)	0.012
Male	180 (79.3)	20 (87.0)	1.72 (0.51-5.78)	0.384
BMI, kg/m ²	29.6 ± 5.7	28.0 ± 4.8	0.94 (0.87-1.02)	0.159
Cardiac risk factors				
Diabetes	78 (34.4)	9 (39.1)	1.21 (0.52-2.80)	0.656
Dyslipidemia	213 (93.8)	22 (95.7)	2.07 (0.28-15.51)	0.479
Hypertension	142 (62.6)	15 (65.2)	1.09 (0.46-2.57)	0.846
Family history of CAD	121 (53.3)	15 (65.2)	1.75 (0.74-4.13)	0.205
Smoker/ex-smoker	156 (68.7)	19 (82.6)	2.13 (0.72-6.26)	0.170
Morise score	14.8 ± 3.4	16.1 ± 3.0	1.12 (0.99-1.28)	0.081
NCEP/ATP III risk				
Low	3 (1.3)	0 (0.0)		
Intermediate	58 (25.6)	1 (4.3)		
High	166 (73.1)	22 (95.7)		

Values are mean ± SD or n (%), unless otherwise indicated.
BMI = body mass index; CI = confidence interval; MACE = major adverse cardiac events; other abbreviations as in Table 1.

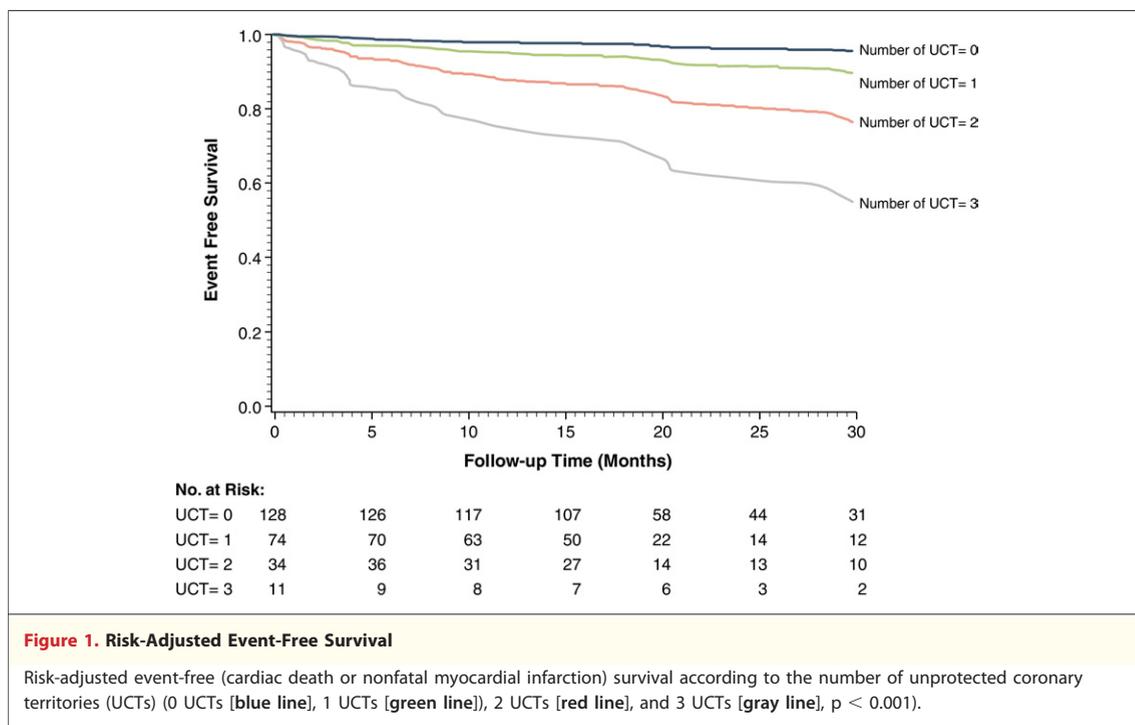
The ability to translate this model to coronary CTA is less certain. Because CABG patients typically have severe native CAD and coronary calcification, the diagnostic accuracy of coronary CTA may be suboptimal (3,21). Such a reduction in diagnostic accuracy may negatively affect the ability of coronary CTA to determine prognosis and limit its utility in the CABG population. Confirming the prognostic value of coronary CTA would support its potential use in patients with previous CABG.

Although more complex invasive coronary angiography models have significant prognostic power (20), our UCTs model appears to be feasible with coronary CTA and simple to adopt into clinical practice. A simple UCTs score (0, 1, 2, 3) predicts annual MACE (2.4%, 5.8%, 11.1%, and 21.7%, respectively).

Table 3. Number of UCTs and Adverse Cardiac Events (n = 250)

# of UCTs	n	MACE			
		Cardiac Death	Nonfatal MI	Cardiac Death, Nonfatal MI	Annual Event Rate, %
0	128	2 (1.6)	3 (2.3)	5 (3.9)	2.35
1	74	5 (6.8)	4 (5.4)	7 (9.5)	5.80
2	37	4 (10.8)	3 (8.1)	6 (16.2)	11.1
3	11	4 (36.4)	3 (27.3)	5 (45.5)	21.7
Log-rank p value		<0.001	0.003	<0.001	

Values are n (%).
MI = myocardial infarction; UCTs = unprotected coronary territories; other abbreviation as in Table 2.



Previous coronary CTA prognosis studies have used different outcome measures. Some have used all-cause mortality, whereas others have combined softer endpoints such as unstable angina and coronary revascularization (15–19). One strength of our study, although small, is the use of hard cardiac endpoints (cardiac death and nonfatal MI). Although all-cause mortality is an important and valuable outcome measure, coronary CTA alone cannot accurately predict deaths caused by cancer, sepsis, or trauma. Chow et al. (14) demonstrated that 59% of deaths in a low-risk coronary CTA population were noncardiac; therefore, using cardiac endpoints may often be

preferred. Our results expand on previous literature by studying a novel population and demonstrating that coronary CTA may have merit beyond diagnosis and may be used to risk stratify symptomatic CABG patients.

Predictors of MACE in CABG patients. The NCEP/ATP III was initially designed and validated in patients without known CAD; therefore, its utility in the CABG population is unclear (25). Although the CABG population is traditionally considered at high risk of future cardiovascular events, each individual's risk may vary. Because studies have shown that CABG surgery reduces cardiac mortality (22), CABG patients may not be uniformly at high risk of cardiac events, especially when cardiac death is used as one of the outcome measures. Previous work has identified that age, sex, hypertension, and diabetes are clinical predictors of late cardiac events in CABG patients (22,23). Because the NCEP/ATP III combines these risk factors, it was selected as the primary clinical model for comparison.

It has been recognized that left ventricular ejection fraction has prognostic and incremental value over CAD severity (14). Although left ventricular ejection fraction measures were available for our population, our small sample size limited our ability to assess the incremental value of ejection fraction over UCTs and clinical predictors. Future studies

Table 4. Cox Models for MACE

Models	Hazard Ratio (95% CI)	p Value
Clinical variables		
NCEP/ATP III	6.66 (0.92–48.35)	0.061
Clinical + UCTs		
NCEP/ATP III	4.81 (0.66–35.22)	0.122
Unprotected coronary territories	2.08 (1.40–3.10)	<0.001
0	1.0	—
1	2.57 (0.81–8.12)	0.108
2	3.57 (1.09–11.77)	0.036
3	10.89 (3.12–37.99)	<0.001

Abbreviations as in Tables 2 and 3.

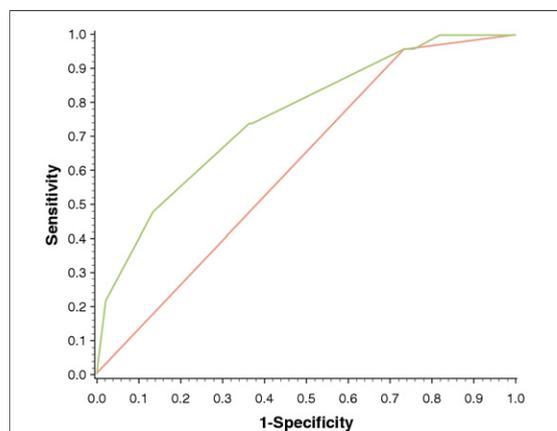


Figure 2. Receiver-Operator Characteristic Curves

Significant differences in the area under the receiver-operator characteristic curves confirm the incremental value of unprotected coronary territories (area under the curve: 0.76; 95% confidence interval: 0.66 to 0.86) (green line) over clinical variables (area under the curve: 0.61; 95% confidence interval: 0.56 to 0.66) (red line) ($p = 0.001$).

are needed to understand the incremental value of left ventricular ejection fraction in this patient population.

The estimated patient radiation dose in our study (23.2 ± 5.2 mSv) was higher than that in previous coronary CTA studies. This likely relates to the greater scan length needed to ensure coverage of bypass grafts. In addition, many of the patients were recruited before the availability of prospective electrocardiogram-gated acquisition at our institution. Understanding the potential harm of radiation exposure, the authors stress the importance of radiation reduction techniques and that such techniques should be used whenever possible.

Study limitations. This was a single-center, prospective study of patients referred for coronary CTA,

and the results of our study may not necessarily be translatable to the general CABG population or to populations at other centers. Although prospectively enrolled, the CABG population was small with relatively few events, thus potentially subjecting our analysis to overfitting.

Patient follow-up in our study was excellent (96.5%) and similar to previous prognostic studies (33). However, the authors recognize that incomplete follow-up ($n = 9$) may result in the underreporting of MACE, which could affect our findings. In addition, the small numbers of MACE restricted our ability to assess the incremental value of left ventricular ejection fraction and arterial and venous grafts. Further multicenter studies using larger CABG cohorts with extended follow-up are required.

CONCLUSIONS

The assessment of native CAD, CABG, and UCTs with coronary CTA appears to have independent and incremental prognostic value over clinical predictors. Coronary CTA appears to be a promising tool for risk stratification of CABG patients. Further multicenter studies using large CABG cohorts are needed to confirm our findings.

Acknowledgments

The authors extend their gratitude to Kathryn Calladine, Nancy Chow, Debbie Gauthier, Patricia Grant, Sandina Jamieson, and Richard Tessier for their expertise and dedication to cardiac research.

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Key Words: cardiac death ■
 computed tomography ■
 coronary angiography ■
 coronary artery bypass graft ■
 major adverse cardiac events ■
 myocardial infarction ■
 prognosis.