SYNTAX Score Derived From Coronary CT Angiography for Prediction of Complex Percutaneous Coronary Interventions

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INTRODUCTION

The SYNTAX score is a comprehensive angiographic scoring system commonly used to assess the complexity of coronary artery disease (CAD) by invasive coronary angiography (ICA). The SYNTAX score combines several validated angiographic classifications of CAD complexity based on the location and morphology of obstructive coronary lesions, and allows for robust risk stratification as well as guides appropriate methods of coronary revascularization (1).

Coronary computed tomographic angiography (CCTA) has emerged as a non-invasive test that demonstrates high diagnostic accuracy compared to ICA for identification and exclusion of obstructive coronary stenosis, as well as plaque location, distribution, and extent (2–5).

To date, whether a CCTA-derived SYNTAX score compares favorably to an ICA-derived SYNTAX score has not been
well evaluated. Further, whether these non-invasive CCTA findings can be applied in the pre-procedural setting to predict the complexity of percutaneous coronary intervention (PCI) is unknown. We sought to determine the feasibility and accuracy of CCTA-derived SYNTAX score when compared to an ICA-derived SYNTAX score as a reference standard. Further, we determined the relationship of a CCTA-derived segmental SYNTAX score to the complexity of PCI.

MATERIALS AND METHODS

Study Population

We retrospectively studied consecutive patients who met the following inclusion criteria: (1) underwent CCTA and ICA within 30 days without intervening clinical cardiac event in the interscan period between CCTA and ICA; (2) were identified by CCTA as having an obstructive coronary stenosis ≥50% in non-stented segments; (3) no prior coronary artery bypass surgery (CABG). Among 170 eligible patients, 16 were excluded due to severe motion artifacts on CCTA.

Before CCTA, we prospectively collected information on the presence of CAD risk factors. Hypertension was defined as a history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus was defined by previously made diagnosis and use of insulin or hypoglycemic agents. Dyslipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. A smoking history was defined as current smoking or cessation within 3 months of testing.

The study protocol was approved by the Cedars–Sinai Institutional Review Board. All participating patients provided informed consent for the use of their clinical and imaging data.

CCTA Image Acquisition

CCTA scans were performed on a dual-source CT scanner (Somatom Definition, Siemens Medical Systems, Forchheim, Germany). The CCTA acquisition protocol is detailed in the Appendix.

CCTA Image Reconstruction and Evaluation

Reconstruction of CCTA data was routinely performed at mid-diastole and, for CCTAs acquired by retrospective electrocardiogram helical methods, at end-systole if needed. Two experienced level III equivalent readers, blinded to patient characteristics and ICA findings, visually inspected and assessed all coronary segments >1.5 mm in diameter for presence of an obstructive stenosis, defined by a ≥50% luminal diameter narrowing (6–8). Each obstructive lesion ≥50% was further assessed and scored in accordance with the previously described SYNTAX score (1). CCTA image reconstruction and evaluation protocols, as well as calculation of CCTA-derived SYNTAX scores are detailed in the Appendix. Disagreement between the two readers was resolved by means of consensus. A representative example of CCTA-based SYNTAX scoring can be seen in Figure 1.

ICA Image Acquisition and Evaluation

ICA by standard catheterization techniques was performed (Innova, GE Healthcare, Buckinghamshire, United Kingdom). ICA images were analyzed by dedicated commercially available software (AGFA Heartlab, Greenville, SC).

Two independent expert cardiologists performed image evaluation blinded to CCTA results, clinical information, and whether a PCI was performed. Each coronary segment >1.5 mm in diameter was visually inspected for presence of an obstructive lesion in a similar manner to CCTA interpretation. Each obstructive lesion ≥50% was further assessed and scored in accordance with the previously described SYNTAX score (1). Disagreement between the two readers was resolved by means of consensus, with independent adjudication of all obstructive lesions by CCTA and ICA to ensure correspondence and valid comparison of lesions between the modalities.

Complexity of PCI

There were 14 interventional cardiologists with at least 10 years of experience (range 10–25 years) who performed the PCIs in the studied population. All interventionalists were blinded appropriately to CCTA SYNTAX scores.

Complexity of PCI was determined by two metrics: (1) assessment of total fluoroscopy time of ICA and PCI; (2) volume of contrast use, inclusive of both the diagnostic and interventional portions of the procedure.

Importantly, total fluoroscopy time was employed as a surrogate for overall radiation dose as no reliable metric exists for calculation of effective radiation dose from clinically performed ICA or PCI. Similarly, volume of contrast use was employed as a surrogate marker for risk of contrast-induced nephropathy (CIN). We performed analyses for individuals undergoing serial serum creatinine measurements. Creatinine levels before and within 96 hours after PCI were employed for evaluation. Baseline glomerular filtration rate was calculated by the Modification of Diet in Renal Disease formula (9). CIN was classified as grades 0, 1, and 2, as previously described in the literature (10).

For metric (1) and (2), we assessed the impact of SYNTAX score among all patients who underwent PCI, as well as reserved analysis to cases that involved only a single lesion percutaneous revascularization (n = 85 patients). This was done to adequately estimate the impact of a segmental SYNTAX score on fluoroscopy time and contrast use. In exploratory analyses, procedure failure was also evaluated and defined as an inability to successfully cross an obstructive lesion with an intracoronary wire or post-procedural thrombolysis in myocardial infarction flow <3. Procedure-related complications included any serious adverse event, including occurrence of coronary dissection or perforation.
CCTA- and ICA-derived SYNTAX scores were compared for lesions considered anatomically obstructive by both modalities. Continuous variables are presented as means ± SD or medians and interquartile ranges for skewed variable values. Categorical variables were assessed using Pearson chi-square test or Fisher exact test for cell counts less than 6, and for ordered comparisons across >2 groups using the chi-square test for trend. Continuous variables were compared using 2-sample t test or one-way analysis of variance test across >2 groups. Cuzick test for trend was used for >2 ordered groups. Inter-observer and intra-observer variability studies were performed on CCTAs or ICAs, and assessed by kappa tests. Strength of agreement with kappa values was defined as follows: <0 none, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, 0.81–1.00 excellent. Agreement and correlations between ICA and CCTA were determined with Bland-Altman plots and Pearson correlation coefficients, respectively. Logistic regression was employed to assess the ability of SYNTAX tertiles to predict complex PCI. In addition, we performed a post hoc power analysis for the comparison of SYNTAX scores on a per-patient basis. The post hoc analysis to detect a difference for a dichotomous classification of complex vs non-complex PCI on a per-patient basis yielded a power of 0.8 for CCTA. Two-tailed P < 0.05 was considered statistically significant. All data were analyzed using Stata version 11 (Stata Corp., College Station, TX).

RESULTS

Patient Characteristics

There were 154 patients (66% males, mean age 66 ± 12 years) who had CCTA and ICA within 30 days, with baseline characteristics summarized in Table 1. In total, 6% of patients did not have obstructive CAD, as evidenced by ICA, whereas 45%, 38%, and 11% had 1-, 2-, and 3-vessel CAD, respectively. CAD distribution included left main (8%), left anterior descending (70%), left circumflex (34%), and right (37%) coronary arteries. Calcified plaques accounted for 13% of obstructive lesions, whereas mixed-calcified and non-calcified plaques were encountered in 37% and 30% of lesions, respectively.
There were 302 obstructive lesions detected by ICA and CCTA, with excellent agreement between CCTA and ICA for the number of obstructive lesions ($\kappa = 0.91$; 95% confidence interval 0.88–0.93). Inter- and intra-observer variability for each modality showed significant agreement for number of obstructive lesions, bifurcation lesions, total occlusions, and SYNTAX tertiles (Table 2). The average length of totally occluded segments by CCTA was $17.7 \pm 5.2$ mm vs $15.8 \pm 4.9$ mm by ICA ($P = 0.14$).

Overall, SYNTAX score elements for CCTA and ICA were compared for 285 lesions in 230 vessels considered obstructive by both (Table 3). Of note, the prevalence of intracoronary thrombus by ICA was extremely low in our patient population (two cases) and was undetected by CCTA. Incorporating intracoronary thrombi in the SYNTAX score results in minimal change (1 point) of the total SYNTAX score and did not affect the average SYNTAX score.

Agreement and Reproducibility of CCTA- and ICA-Derived SYNTAX Scores

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The majority of lesions were estimated to cause $\geq 70\%$ luminal narrowing ($76\%$ of lesions by CCTA vs $70\%$ by ICA, $P = 0.09$; $\kappa = 0.62$, 95% confidence interval 0.52–0.72). Mean per-patient SYNTAX score derived from ICA was lower in comparison to mean CCTA-derived per-patient SYNTAX score ($10.2 \pm 8.0$ vs $10.9 \pm 8.3$, $P = 0.001$). The SYNTAX tertiles for CCTA and ICA, on a per-patient basis, were coincidentally identical and defined as low-$\text{SYNTAX} \leq 7$, intermediate-$\text{SYNTAX} > 7$ < intermediate-$\text{SYNTAX} \leq 12$, and high-$\text{SYNTAX} > 12$. Correlation and agreement between CCTA- and ICA-derived SYNTAX

<table>
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<th>TABLE 1. Baseline Characteristics</th>
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<td>$n = 154$</td>
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<td>Age (years)*</td>
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<td>Male gender</td>
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<tr>
<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Current cigarette smoking</td>
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<td>Family history of premature CAD</td>
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<td>BMI (Kg/m$^2$)†</td>
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<td>Baseline creatinine (mg/dL)*</td>
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<td>Baseline glomerular filtration rate*</td>
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<td>Agatston coronary calcium score (n = 127)†</td>
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<td>BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention. * mean ± SD, † median (interquartile range).</td>
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<th>TABLE 2. Reproducibility Analyses—Inter-Observer Variability Between ICA Readers, CCTA Readers, as Well as Intra-observer Variability for Each of the CCTA Readers</th>
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<tr>
<td>SYNTAX Score Tertiles*</td>
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<td>Inter-observer variability</td>
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CCTA, coronary computed tomographic angiography; ICA, invasive coronary angiography. * Data presented as weighted kappa values (95% confidence intervals).
scores, on per-patient, per-vessel, and per-segment basis, are presented in Figures 2 and 3a, respectively.

Comparison Between Patients Referred to PCI vs CABG or Medical Therapy

The therapeutic decision was taken ad hoc by the operator and was based upon visual assessment of stenosis severity or functional assessment by prior nuclear myocardial perfusion imaging or functional flow reserve at the time of diagnostic angiography or intravascular ultrasound assessment.

CCTA, ICA, and PCI were performed in 113 patients for 154 lesions in 131 vessels within less than 30 days between CCTA and PCI. Diagnostic ICA and PCI were performed on the same day for the majority of the patients (95%). Visual assessment of stenosis severity was associated with coronary intervention in 130 (84%) obstructive lesions, whereas functional assessment accounted for the remainder of interventions.

There were 15 patients referred for CABG for 48 lesions. Diffuse obstructive disease was associated with the decision to operate in 13 patients, whereas 2 patients underwent concomitant valve replacement and CABG.

Within each therapeutic approach group, the per-patient CCTA- and ICA-derived SYNTAX scores, as well as segmental SYNTAX scores, were similar (Table 4). As expected, the per-patient SYNTAX scores in patients who were referred to surgery were significantly higher in comparison to patients that were referred to PCI or medical management. The segmental SYNTAX scores of CABG lesions were higher in comparison to lesions that were designated to medical management but were similar in comparison PCI lesions (Table 4).

Secondary Analysis of Patients Undergoing PCI

CCTA- and ICA-derived per-patient and per-vessel SYNTAX scores demonstrated excellent agreement (Fig 3b) and correlation (Pearson correlation coefficients were 0.99, 0.95, 0.9, and 0.93 for left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA), respectively; P < 0.05 for all), with CCTA correctly detecting...
Figure 3. Bland-Altman plots for agreement for the (a) entire study cohort and (b) patients undergoing PCI.
The contrast volume administered at each of the per-patient or segmental SYNTAX score tertiles was not significantly different between CCTA- or ICA-derived SYNTAX tertiles. Ten patients had baseline glomerular filtration rate >0 and <60 mL/min and none developed CIN. Overall CIN grades 1 or 2 were observed in three patients and one patient, respectively. CCTA- and ICA-derived segmental SYNTAX score as a function of contrast media volume was similar among patients who developed CIN as compared to patients who did not (270 ± 95 mL vs 190 ± 93 mL, \( P = 0.2 \)).

### Total Fluoroscopy Time

Total fluoroscopy time was moderately correlated with CCTA- and ICA-derived segmental SYNTAX score tertiles (\( r = 0.42, P < 0.05 \) and \( r = 0.43, P < 0.05 \), respectively). Distribution of total fluoroscopy time is presented in Table 5.

Of note, there was no correlation between operators’ expertise and metrics of contrast volume utilization or fluoroscopy time.

### Procedure Failure or Complication

PCI was unsuccessful in four totally occluded lesions (3%). The mean CCTA-derived segmental SYNTAX score for lesions with unsuccessful interventions was significantly higher than for lesions with successful interventions (13 ± 8 vs 5.3 ± 3.2, \( P < 0.001 \)), a finding in accord with ICA-derived segmental SYNTAX scores. Dissection occurred in additional three lesions (2%) with mean CCTA- and ICA-derived segmental SYNTAX scores of 3.0 ± 1.0 and 3.3 ± 1.1, respectively (\( P = 0.7 \)).

## DISCUSSION

In the present study we assessed the feasibility and accuracy of a CCTA-derived SYNTAX score to predict complex PCI.

### Total Contrast Volume

Total contrast volume was moderately correlated with CCTA- and ICA-derived segmental SYNTAX score tertiles (\( r = 0.50, P < 0.05 \) and \( r = 0.51, P < 0.05 \), respectively). Distribution of contrast volumes by SYNTAX tertiles is presented in Table 5.

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### Total Contrast Volume

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Within the study population, we noted generally high concordance and diagnostic accuracy of the CCTA-derived SYNTAX score as compared to an ICA-derived SYNTAX score reference standard. Further, higher CCTA-derived SYNTAX scores were associated with increasing complexity of coronary revascularization, with higher volumes of iodinated contrast, longer fluoroscopy times, and greater use of advanced devices and procedures.

The SYNTAX score is a useful ICA score that incorporates anatomical and morphological lesion characteristics that can be used to reliably determine the complexity of CAD (1,8). SYNTAX score is well-validated, highly reproducible (11,12), and predictive of adverse cardiovascular events in a myriad of scenarios concerning PCI in multivessel and left main CAD (13–15). The SYNTAX score provides greater discriminatory ability compared to the modified American College of Cardiology/American Heart Association lesion classification system (13).

CCTA has been established as a non-invasive anatomic test that offers high diagnostic performance for detection and exclusion of high-grade coronary stenosis when compared to traditional ICA. Moreover, CCTA allows for direct visualization of additional CAD features beyond stenosis severity, including measures of lesion length, lesion location (eg, bifurcations of coronary vessels), and a multitude of other variables commonly used in the ICA SYNTAX (16). Several of these findings of CAD extent, severity, location, and morphology manifest important prognostic implications, and are associated with future death and major adverse cardiovascular events across numerous patient populations (17–22). As previously demonstrated by our investigative group, proximal LAD stenosis, coronary plaque distribution, weighted segmental stenosis scores, and number of vessels with ≥50% and ≥70% stenosis strongly predict mortality (17). Papadopoulou et al. have studied the application of CCTA-derived SYNTAX score in a group of 80 patients, and concluded that CCTA-derived score is feasible, reproducible, and comparable to ICA-derived SYNTAX score (23). Our present study is both in accordance with as well as advances these findings and, to our knowledge, represents the largest study to date to assess the reliability and applicability of a CCTA-derived SYNTAX score.

CCTA- and ICA-derived SYNTAX scores demonstrated generally high concordance on a per-segment, per-vessel, and per-patient basis, as well as substantial agreement for the majority of the SYNTAX score variables. CCTA and ICA were in excellent agreement for detection of obstructive lesions and total occlusions, but only in moderate agreement for lesion length. The potential reasons for this are manifold. Given the ability of CCTA to define atherosclerosis in three dimensions rather than two, it is possible that multiplanar reconstructions of coronary vessels by CCTA may provide slightly different measures over ICA which may be susceptible to foreshortening and vessel overlap. Although determination of heavy calcification by CCTA was in good agreement with ICA, severe coronary calcification was prominently visualized and noted as a limitation of current-generation CCTA for measures of stenosis severity; as such, this may have led to overestimation by CCTA. Blunt stumps and intracoronary thrombi were completely undetected by CCTA. These disparities may stem from the superior spatial and temporal resolution of ICA over CCTA, and may suggest a need for improved methods of CCTA interpretation. Finally, additional elements of the SYNTAX score, ie, tortuous vessels, were rarely encountered in the study population, were therefore not compared between CCTA and ICA, and underscore the need for future larger studies.

Perhaps more important than the demonstration that CCTA-derived SYNTAX scores are accurate and concordant with ICA-derived scores is the finding that this non-invasive method is associated with PCI complexity. Although prior studies have reported the usefulness of CCTA to identify chronic total occlusions that are amenable to revascularization (24–27), these investigations are limited in number and scope, have not evaluated the totality of SYNTAX CAD variables, and have not systematically examined the utility of CCTA to identify complex PCI across a range of CAD states, as was done in this study.

Stähli et al. have reported their experience with applying a CCTA-derived SYNTAX score for assessment of 66 lesions deemed eligible for intervention (28). The CCTA- and ICA-derived SYNTAX scores were comparable and predictive of failed PCI, but not for PCI complexity. Our study directly extends these important observations by providing a comprehensive assessment of PCI complexity by an array of metrics that indicate heightened complexity of PCI. These factors may allow for pre-procedural assessment and planning in a more refined manner, and may allow for enhanced physician-patient interactions for maximizing informed consent.

As complex CAD is often accompanied by baseline chronic kidney disease, concerns regarding a heightened incidence of CIN exist. Further, radiation dose is an important consideration even within an aging population, and the stochastic risk of radiation-induced cancer remains of non-negligible concern. Complex procedures entail higher contrast volume and radiation exposure, as has been reported in an array of prior studies (29) and corroborated by the present study findings. In the present study, CCTA- and ICA-derived segmental SYNTAX scores correlated well between patients with and without CIN. This finding may be largely explained by the relatively low CIN incidence and thus, whether SYNTAX score can predict development of CIN in larger cohorts remains to be determined.

This study is not without limitations. While all patients undergoing CCTA were prospectively identified and enrolled, examination of the ICA and PCI of these generally low-intermediate risk patients was performed in a retrospective fashion, and potentially affected by selection or referral bias. Moreover, the study population represented low-intermediate risk individuals who underwent ICA based upon CCTA and thus, whether these findings are applicable to higher risk patients requires further study. As CCTA is prone to overestimation of stenosis severity, the overall accuracy of the CCTA-derived scores may be reduced (3–5,30,31). Further, prior fractional flow reserve
studies have proven the prognostic utility of a “functional” SYNTAX score, and this was not addressed in the current investigation (32). As radiation dose by ICA is difficult to quantify, we relied upon estimates based upon total fluoroscopy time as a surrogate for total effective radiation dose. Finally, as PCIs are primarily performed in an ad hoc manner by interventionalists of potentially different skill levels for patients with various comorbidities, CCTA-based SYNTAX scores cannot alone serve as the definitive guide for prediction of individuals who may experience complex coronary interventions.

In conclusion, SYNTAX scores derived from CCTA are concordant with those derived from ICA, and correspond well with complex PCI.

REFERENCES


SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.acra.2016.07.003.