Incomplete revascularization (ICR) has recently been shown to be a surrogate marker of a greater burden of anatomic coronary complexity and clinical comorbidity in patients undergoing percutaneous or surgical based revascularization in a post hoc analysis of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial. In addition, ICR has been linked to adverse short- and longer term morbidity and mortality. Recently, the concept of reasonable incomplete revascularization has been proposed, the underlying principle being that an acceptable burden of obstructive coronary artery disease post revascularization to be associated with similar outcomes to subjects in whom complete revascularization (CR) was achieved.

**Background**—The residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score is an objective measure of the degree and complexity of residual stenosis after percutaneous coronary intervention (PCI).

**Methods and Results**—In the randomized PCI cohort of the SYNTAX Trial (n=903), the baseline and residual SYNTAX Scores were calculated. Subjects with a residual SYNTAX Score of 0 were defined as having undergone complete revascularization (CR), and a residual SYNTAX Score >0 as incomplete revascularization (ICR). Five-year clinical outcomes were stratified by CR and ICR (tertiles of the residual SYNTAX Score: >0–4, >4–8, and >8). In the PCI cohort, the mean baseline and residual SYNTAX Scores were 28.4±11.5 and 4.5±6.9, respectively. The mean Δ SYNTAX Score (representative of the burden of disease removed by PCI) was 23.8±10.9. The residual SYNTAX Score was distributed as follows: CR, 0 (n=386, 42.7%); ICR, >0 to 4 (n=184, 20.4%), >4 to 8 (n=167, 18.5%), >8 (n=153, 16.9%). A progressively higher residual SYNTAX Score was shown to be a surrogate marker of increasing clinical comorbidity and anatomic complexity. Subjects with CR or residual SYNTAX Scores ≤8 had comparable 5-year mortality (CR, 8.5%; residual SYNTAX Score >0–4, 8.7%; >4–8, 11.4%; >8 (n=153, 16.9%). A residual SYNTAX Score >8 was associated with 35.3% all-cause mortality at 5-years (P<0.001). Stratified analyses in the predefined medical treated diabetic and left main subgroups yielded similar results.

**Conclusions**—The residual SYNTAX Score was shown to be a powerful indicator of 5-year mortality in the SYNTAX Trial. The residual SYNTAX Score may aid in determining a reasonable level of revascularization.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00114972. (Circulation. 2013;128:141-151.)

**Key Words:** coronary disease ■ drug-eluting stents ■ myocardial ischemia ■ percutaneous coronary revascularization ■ survival analysis

Incomplete revascularization (ICR) has recently been shown to be a surrogate marker of a greater burden of anatomic coronary complexity and clinical comorbidity in patients undergoing percutaneous or surgical based revascularization in a post hoc analysis of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial. In addition, ICR has been linked to adverse short- and longer term morbidity and mortality. Recently, the concept of reasonable incomplete revascularization has been proposed, the underlying principle being that an acceptable burden of obstructive coronary artery disease post revascularization to be associated with similar outcomes to subjects in whom complete revascularization (CR) was achieved.
The recently developed residual SYNTAX Score is an objective, quantitative measure of the degree and complexity of residual stenosis after percutaneous coronary intervention (PCI). In a post hoc analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial, consisting of subjects with moderate to high-risk acute coronary syndrome undergoing PCI, and substantially less complex coronary artery disease compared with the SYNTAX Trial, a residual SYNTAX Score of >8.0 after PCI was associated with adverse 1-year mortality. The purpose of this study was to assess the prognostic significance of the residual SYNTAX Score in the randomized all-comers SYNTAX Trial at the final 5-year follow-up.

Methods
The all-comers SYNTAX Trial is a randomized, prospective, multicenter trial investigating subjects with unprotected left main coronary artery (ULMCA) disease (isolated or associated with 1-, 2-, or 3-vessel disease), or de novo 3-vessel (3VD) coronary artery disease. In total, 1800 patients were recruited and randomized in PCI (n=903) and coronary artery bypass graft (CABG; n=897) arms from 85 centres in 18 countries from Europe and the United States. Exclusion criteria were limited, and consisted of subjects with prior coronary revascularization, the requirement of concomitant cardiac surgery (eg, valve surgery or resection of aortic or left ventricular aneurysm), or on-going acute myocardial infarction (MI). During the local Heart Team meeting, the interventional cardiologist and cardiac surgeon specified the number of coronary lesions requiring treatment, and their angiographic location and characteristics using the surgeon specified the number of coronary lesions requiring treatment, and their angiographic location and characteristics using the anatomic SYNTAX Score—a quantitative measure of coronary artery complexity (http://www.syntaxscore.com)—as a tool to aid in this process. All subjects considered as potentially achieving equivalent anatomic revascularization with percutaneous or surgical revascularization by the Heart Team were randomized on a 1:1 basis to either PCI with Taxus Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, MA) or CABG. Patients unsuitable for randomization were nested into registries.

Randomization of subjects was stratified by clinical site, the absence or presence of ULMCA disease, and medically treated diabetes mellitus (requiring oral medications or insulin), to ensure approximately equal allocation to the 2 revascularization methods at each site and within each stratum. The Parsonnet and EuroSCORE were assessed by the Heart Team before randomization. Baseline, peri-, and postprocedural data were prospectively collected by the individual participating centres.

Baseline, Residual, and Δ SYNTAX Scores
The calculation of the baseline SYNTAX Score was carried out by the Heart Team before randomization and corroborated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) blinded to the treatment assignment. Baseline and procedural coronary angiograms were centrally stored. The baseline and procedural coronary angiograms were analyzed side by side by a panel of 3 interventional cardiologists blinded to the clinical outcomes. The baseline SYNTAX Score and its components, including anatomic location of all lesions, recorded by the core laboratory in calculation of the original SYNTAX Score, were used to identify all coronary lesions in the baseline and procedural coronary angiogram. The residual SYNTAX Score was calculated based on the remaining obstructive coronary disease after treatment with PCI. The intraobserver variability for calculation of the residual SYNTAX Score (quartile partitioning), based on reanalyzing 50 cases at a 3-month interval, indicated a high level of agreement (κ statistic=0.89; 95% confidence interval [CI], 0.79 – 0.99; P<0.001).15,24 The high level of agreement was attributable to the panel having preknowledge of all coronary lesion locations before PCI. The Δ SYNTAX Score, representative of the burden of disease removed by PCI, was calculated by subtracting the residual from the baseline SYNTAX Score.

Clinical Outcomes
Clinical outcomes included all-cause death, all-cause death/MI/cerebrovascular accident, major adverse cardiac and cerebrovascular events (MACCE; a composite of all-cause death, MI, cerebrovascular accident, and all-cause revascularization) and its components, and stent thrombosis using the Academic Research Consortium definition. An independent Clinical Events Committee, including

Figure 1. Correlation between the baseline and residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score. Relationship between the baseline (x axis) and residual (y axis) SYNTAX Score, for individual patients in the randomized percutaneous coronary intervention (PCI) arm of the SYNTAX Trial. Paired data were available in 886/903 subjects (98.1%). Each point can be used to assess the baseline and residual SYNTAX Scores for individual patients from the SYNTAX Trial. Each point may represent >1 value.
Table 1. Baseline and Procedural Characteristics According to Complete (Residual SYNTAX Score 0) and Incomplete Revascularization (Tertiles of the Residual SYNTAX Score)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Residual SYNTAX Score (n=890)</th>
<th>P Value for Linear Trends*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n=386)</td>
<td>&gt;0–4 (n=184)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>64.6±9.8</td>
<td>64.8±8.7</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>72.5%</td>
<td>81.0%</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>22.0%</td>
<td>31.0%</td>
</tr>
<tr>
<td>Medically treated diabetes mellitus (oral medications or insulin)†</td>
<td>20.5%</td>
<td>26.6%</td>
</tr>
<tr>
<td><strong>HbA1c ≥7%</strong></td>
<td>13.6%</td>
<td>18.1%</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>28.0±4.7</td>
<td>28.4±5.2</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>71.5%</td>
<td>77.6%</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>77.9%</td>
<td>75.8%</td>
</tr>
<tr>
<td><strong>Peripheral vascular disease</strong></td>
<td>8.3%</td>
<td>6.0%</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>20.5%</td>
<td>15.2%</td>
</tr>
<tr>
<td><strong>Unstable angina</strong></td>
<td>25.9%</td>
<td>34.8%</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>29.8%</td>
<td>31.9%</td>
</tr>
<tr>
<td><strong>History of GI bleeding/peptic ulcer disease</strong></td>
<td>4.4%</td>
<td>1.6%</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>8.8%</td>
<td>6.0%</td>
</tr>
<tr>
<td><strong>LVEF (continuous variable), %</strong></td>
<td>60.3±12.2</td>
<td>59.8±12.9</td>
</tr>
<tr>
<td><strong>Good LVEF (≥50%)</strong></td>
<td>82.6%</td>
<td>84.2%</td>
</tr>
<tr>
<td><strong>Moderate LVEF (30%-49%)</strong></td>
<td>13.2%</td>
<td>14.1%</td>
</tr>
<tr>
<td><strong>Poor LVEF (&lt;30%)</strong></td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Creatinine clearance, ml/min‡</strong></td>
<td>87.2±32.0</td>
<td>92.4±48.2</td>
</tr>
</tbody>
</table>

**Baseline anatomical and clinical scores**

| Baseline SYNTAX Score | 23.6±10.0 | 29.0±10.2 | 31.7±9.8 | 35.9±12.4 | <0.0001 |
| Residual SYNTAX Score | 0.0±0.0 | 3.0±1.0 | 6.2±1.1 | 15.7±9.4 | <0.0001 |
| Δ SYNTAX Score¶ | 23.6±10.0 | 26.0±10.1 | 25.4±9.9 | 20.1±13.7 | 0.04 |
| **Total Parsonnet Score** | 8.2±7.1 | 7.8±5.9 | 8.6±6.8 | 10.5±7.6 | 0.002 |
| **Additive EuroSCORE** | 3.6±2.7 | 3.6±2.4 | 3.8±2.5 | 4.2±2.6 | 0.02 |
| **Logistic EuroSCORE** | 3.8±5.5 | 3.3±2.9 | 3.7±3.6 | 4.3±4.2 | 0.34 |

**Anatomical characteristics**

| Left main disease§† | 42.5% | 34.8% | 40.1% | 39.2% | 0.48 |
| De novo 3VD | 57.5% | 65.2% | 59.9% | 60.8% | 0.48 |
| Number of lesions | 3.5±1.7 | 4.1±1.6 | 4.3±1.6 | 4.5±1.6 | <0.0001 |
| Any total occlusions | 12.3% | 22.3% | 28.3% | 50.7% | <0.0001 |

**Number of total occlusions**

| 1 TO | 12.0% | 22.3% | 25.3% | 42.8% | <0.0001 |
| 2 TO | 0.3% | 0.0% | 3.0% | 7.9% | <0.0001 |
| Any bifurcation lesion | 57.3% | 66.3% | 62.9% | 70.6% | 0.0056 |
| Any trifurcation lesion | 7.3% | 6.0% | 10.2% | 6.5% | 0.77 |
| Any bifurcation or trifurcation | 62.2% | 68.5% | 70.1% | 71.9% | 0.015 |
| Diffuse or small vessel disease | 18.4% | 26.1% | 20.4% | 28.1% | 0.034 |
| Any aorto-ostial lesion | 17.3% | 13.6% | 11.5% | 17.1% | 0.48 |
| Any angiographically visible thrombus | 2.6% | 2.2% | 2.4% | 2.6% | 0.97 |
| Any heavy calcification | 42.7% | 47.3% | 53.0% | 64.5% | <0.0001 |
| Any severe tortuosity | 55.8% | 74.5% | 74.7% | 71.7% | <0.0001 |
| Left arterial dominance | 16.8% | 19.6% | 19.8% | 16.3% | 0.85 |

(Continued)
cardiologists, cardiac surgeons, and a neurologist, reviewed all the primary clinical end points.3,5 A separate independent Clinical Events Committee adjudicated the Academic Research Consortium stent thrombosis events.

**Statistical Analysis**

Analyses were performed by intention to treat. Binary variables are reported as counts or percentages, continuous data are expressed as means±SD. All variables were stratified according to a residual SYNTAX Score 0 (CR), and tertiles of the residual SYNTAX Score >0 (ICR). For the baseline characteristics, testing for linear trends across residual SYNTAX Score groups was performed using generalized linear models with the residual SYNTAX Score class as a covariable for continuous variables, and the Cochran-Armitage test for trends in categorical data. Prespecified patient subsets at randomization. \( \Delta \)Cockcroft and Gault formula. \( \Delta \) SYNTAX Score represents the burden of disease removed by PCI. \( \Delta \)Isolated or associated with 1, 2, or 3VD. Previously determined anatomic and clinical variables, shown to be independent predictors of long-term mortality in the SYNTAX Trial \( (P<0.1) \), were entered into the model, with no exit criteria. There was no departure from the proportionality of hazards assumption using the global proportional hazards test based on Schoenfeld residuals.27 Area under the curve for the baseline and residual SYNTAX Scores for 5-year all-cause death and 5-year MACCE were computed by logistic regression and compared using the nonparametric method of deLong et al.28 Area under the curve performed with and without censored data removed had a negligible difference. A 2-sided probability value <0.05 was considered significant for all tests. All analyses were conducted using SPSS 20.0 (SPSS Inc, Chicago IL) and SAS System Software Version 9.2 (SAS Institute, Cary, NC).

### Results

In the randomized PCI cohort \( (n=903) \), the baseline SYNTAX Score was available in 899/903 subjects (99.6%). The mean baseline SYNTAX Score was 28.4±11.5. The residual SYNTAX Score represents the burden of disease removed by PCI. 

![Figure 2. Complete (residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery [SYNTAX] Score 0) and incomplete (tertiles of the residual SYNTAX Score [residual SYNTAX Score >0]) revascularization, stratified according to tertiles of the baseline SYNTAX Score. Note the progressive increase in the frequency of a residual SYNTAX Score >8 across conventional tertiles of the baseline SYNTAX Score.](http://circ.ahajournals.org/content/144/6/144.full)
SYNTAX Score was available in 890/903 subjects (98.6%). The correlation (Spearman coefficient 0.414, P<0.001) and distribution of the baseline and residual SYNTAX Score is illustrated in Figure 1. CR (residual SYNTAX Score 0) was evident in 42.7% of the PCI arm (n=386), and ICR in 55.8% of the PCI arm (n=504) (residual SYNTAX Score: >0 to 4 (20.4% [n=184]), >4 to 8 (18.5% [n=167]), and >8 (16.9% [n=153]). The mean Δ SYNTAX Score (representative of the burden of disease removed by PCI) was 23.8±10.9. The mean residual SYNTAX Score was 4.5±6.9.

Baseline Characteristics
Baseline characteristics of CR (residual SYNTAX Score 0) and ICR (tertiles of the residual SYNTAX Score) are shown in Table 1. A higher residual SYNTAX Score was associated with progressively increasing clinical comorbidity; namely, older age (P=0.015), medically treated diabetes mellitus (P=0.0001), peripheral vascular disease (P=0.025), reduced left ventricular ejection fraction (P=0.0058), reduced creatinine clearance (P=0.059), greater Parsonnet Score (P=0.0020), and additive EuroSCORE (P=0.020). Similarly, a higher residual SYNTAX Score was associated with progressively higher baseline SYNTAX score (P=0.0001), with a residual SYNTAX Score of >8 associated with significantly more total occlusions (TO; 50.7%, P<0.0001), bifurcations (70.6%, P=0.0056), diffuse or small vessel disease (28.1%, P=0.034), heavy calcification (64.5%, P<0.0001), severe tortuosity (71.7%, P<0.0001), and long lesions (70.4%, P<0.0001). Stent length was not associated with an increase in the residual SYNTAX Score (P=0.44). Notably, the Δ SYNTAX Score was lower in subjects with a residual SYNTAX Score >8 (20.1±13.7) compared with CR (23.6±10.0, P=0.040). The correlation (Spearman coefficient 0.414, P<0.0001). Notably, the Δ SYNTAX Score was lower in subjects with a residual SYNTAX Score >8 (20.1±13.7) compared with CR (23.6±10.0, P=0.040).

Distribution of Residual SYNTAX Score per Tertiles of the Baseline SYNTAX Score
Figure 2 illustrates the distribution of the residual SYNTAX Score per tertile of the baseline SYNTAX Score. The frequency of subjects with a residual SYNTAX Score >8 progressively increased across tertiles of the baseline SYNTAX Score (0–22: 7.1% versus 23–32: 14.3% versus ≥33: 30.9%, P value for linear trend <0.0001).

5-Year Clinical Outcomes
Figure 3 illustrates the HRs for categories of the residual SYNTAX Score for differing clinical outcomes, using CR (residual SYNTAX Score 0) as a reference. Subjects with CR or lower residual SYNTAX Scores (≤8) had comparable 5-year mortality (CR [n=386]: 8.5%, residual SYNTAX Score >0–4 [n=184]: 8.7%, >4–8 [n=167]: 11.4%, P=0.60). At 5 years, a residual SYNTAX Score >8 was associated with significantly increased all-cause mortality (35.3%, P<0.001), MACCE (59.5%, P<0.001), MI (17.0%, P<0.001), all-cause revascularization (32.0%, P<0.001), and definite/probable stent thrombosis (16.0%, P=0.005) (Figure 4).

Tertiles of the Baseline SYNTAX Score
Figure 5 demonstrates the impact of ICR (tertiles of the residual SYNTAX Score) according to the conventional tertiles of the baseline SYNTAX Score. From low (0–22), to intermediate (23–32) and high (≥33) baseline SYNTAX Scores, there was an incremental rise in the 5-year mortality impact of a residual SYNTAX Score >8 (low: 23.8%, P=0.022; intermediate: 34.1%, P<0.001; high: 39.1%, P<0.001).

Stratified Analyses
Stratified analyses (Table 2) in the subgroups of medically treated diabetes mellitus (n=231/903 [26%], P value for interaction 0.84), ULMCA disease (n=357/903 [40%], P value for interaction 0.91), and impaired left ventricular function (n=172/903 [19%], P value for interaction 0.36) indicated that a residual SYNTAX Score >8 was similarly associated with adverse 5-year mortality. In the subgroup consisting of TOS (n=217/903 [24%]), a residual SYNTAX Score of >8 was associated with a more modest effect on mortality (HR, 2.17; 95% CI, 1.21–3.87). In subjects without TOs (HR, 8.51; 95% CI, 4.64–15.62), a residual SYNTAX Score of >8 was associated with a 4-fold increased all-cause mortality (39.4%, P<0.0001; P value for interaction 0.015).

Discriminative and Predictive Value of the Baseline and Residual SYNTAX Scores
Compared with the baseline SYNTAX Score, the residual SYNTAX Score demonstrated greater discrimination for 5-year all-cause mortality (0.619 [95% CI, 0.568–0.671]...
versus 0.687 [95% CI, 0.630–0.744]; \( P = 0.024 \)) and MACCE (0.570 [95% CI, 0.531–0.610] versus 0.634 [95% CI, 0.597–0.672]; \( P = 0.0026 \)). Notably, a residual SYNTAX Score >8 was highly specific in its association with 5-year clinical outcomes (specificity: all cause death, 88%; MACCE, 90%).

**Multivariable Analysis**

Multivariable analysis (Table 3) demonstrated the residual SYNTAX Score to be an independent predictor of 5-year all-cause death (HR, 1.65; 95% CI, 1.41–1.92; \( P < 0.001 \)).
Discussion

The main findings of this study are the following, at 5 years: (1) A progressively higher residual SYNTAX Score was shown to be a surrogate marker of increasing clinical comorbidity and more anatomically complex disease; (2) a residual SYNTAX Score of ≤8 was associated with long-term mortality comparable with subjects with CR; (3) a residual SYNTAX Score of >8 was associated with progressively increasing adverse long-term clinical outcomes, including mortality—an effect that remained consistent across all conventional tertiles of the baseline SYNTAX Score; (4) The findings of a residual SYNTAX Score >8 to be associated with adverse long-term mortality were equally applicable in the predefined subgroups of ULMCA disease and medically treated diabetes mellitus, and the subgroup with impaired left ventricular ejection function; (5) In the TO subgroup, a residual SYNTAX Score >8 was associated with a more modest effect on long-term mortality, compared with a pronounced effect in subjects without TOs; and (6) the residual SYNTAX Score was shown to be a powerful indicator of long-term mortality and other clinical outcomes in subjects with ULMCA disease or de novo 3VD.

Previous predominantly registry studies investigating the clinical impact of CR and ICR have lacked standardized definitions. These studies have for example used the number of treated vessels/treated important vessels based on varying degrees of stenosis, and have analyzed IR with or without the presence of TOs, or on revascularization of all vessels with a size ≥1.5 mm.1,6–14,29 Such varying definitions of ICR have made comparisons between studies problematic. In addition, the unavoidable selection bias inherent to all registries has added to the difficulties in interpreting these studies.7,8 Even using multivariate and propensity score adjustments of baseline characteristics to control for selection bias would be potentially misleading, because ICR was...
demonstrated to be a surrogate marker of sicker patients with more anatomically complex baseline coronary artery disease. Conversely, the residual SYNTAX Score allowed for an objective, quantitative assessment of the extent of ICR in PCI treated subjects in the randomized all-comers population of the SYNTAX Trial, in which selection bias would have been minimal. Furthermore, the residual SYNTAX Score allowed for a threshold value of ICR to be determined that would not have a negative impact on long-term mortality (ie, the concept of reasonable incomplete revascularization). This concept, using the residual SYNTAX Score, has recently been described in the ACUITY Trial, the main differences being that the ACUITY Trial recruited subjects solely presenting with non-ST elevation acute coronary syndrome, followed up for 1-year, and importantly, with substantially lesser complex coronary artery disease (primarily single or double vessel disease, median SYNTAX Score 9.0, interquartile range 5.0–16.0). Comparatively, the SYNTAX Trial recruited subjects with substantially more complex coronary artery disease (left main or de novo 3VD, median SYNTAX Score 28, interquartile range 20.0–36.0), and validated the findings of a residual SYNTAX Score >8 to be associated with adverse outcomes at up to 5 years, in an all-comers randomized population, and in several clinical and anatomic subgroups.

Reducing the Ischemia Burden

The residual SYNTAX Score is principally a marker of the residual ischemia burden, dependent on the location of the coronary lesion and the anatomic complexity (eg, calcification, bifurcation, long lesion, etc) associated with the obstructive disease. This is attributable to the fact that most of the points of the SYNTAX Score are accrued from the severity of luminal diameter narrowing and its weighting according to the usual blood flow to the left ventricle in each vessel or vessel segment. More proximal coronary artery disease therefore scores more highly on the SYNTAX Score, particularly if the obstructive disease is more complex. From a prognostic perspective this is important because MIs have been shown to cluster in the proximal third of major epicardial vessels, and a large plaque burden and small luminal area have both been linked to the highest risk of future cardiac events. Reducing the ischemia burden of the patient would undoubtedly improve long-term prognosis, as exemplified by previous studies associating a short- and long-term survival benefit in

Table 3. Univariable and Multivariable Cox Regression Analyses, Incorporating the Residual SYNTAX Score, Using Clinical Variables Previously Shown to be Independent Predictors of Long-Term Mortality in the SYNTAX Trial

<table>
<thead>
<tr>
<th></th>
<th>Univariable Analyses</th>
<th>Multivariable Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Residual SYNTAX Score (4 groups)*</td>
<td>1.76 (1.50, 2.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline SYNTAX Score (tertiles)†</td>
<td>1.50 (1.20, 1.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preprocedural (&lt;30%) LVEF</td>
<td>5.60 (2.61, 12.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3.31 (2.15, 5.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of GI bleeding or peptic ulcer disease</td>
<td>2.08 (1.05, 4.09)</td>
<td>0.035</td>
</tr>
<tr>
<td>Age per increase in 10 yr</td>
<td>1.79 (1.46, 2.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.70 (1.17, 2.47)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Four groups comprising CR (residual SYNTAX Score 0) and ICR (tertiles of the residual SYNTAX Score >0 to 4, >4 to 8, >8).
†Conventional tertiles of the baseline SYNTAX Score (low 0–22, intermediate 23–32, high ≥33).
patients with moderate to large amounts of inducible ischemia who were revascularized.\textsuperscript{34–36} Specifically, in the nuclear sub-study of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial,\textsuperscript{35} ≥10% reversible ischemia was associated with adverse 5-year mortality if treated medically.

Strikingly, the frequency of a high residual SYNTAX Score (ie, >8), and its association with more severe baseline anatomic complexity such as calcification, bifurcations, TOs, and tortuosity (Table 1), was shown to progressively increase across the conventional tertiles of the baseline SYNTAX Score (Figure 2), which in turn was linked to an incremental rise in 5-year all-cause mortality (Figure 5). In addition, the most pronounced effect of the long-term adverse prognostic effects of a residual SYNTAX Score >8 were in subjects without TOs (Table 2). These findings perhaps epitomize the need for appropriate myocardial viability testing to ensure that revascularization of the TO is clinically justified.\textsuperscript{37–42}

Notably, in the high baseline SYNTAX Scores, despite the greater anatomic complexity, the Δ SYNTAX Score (representative of burden of coronary disease removed by PCI) was less than that seen in subjects with CR. These results suggest the potential difficulties the interventional cardiologist may face in the treatment of highly complex coronary artery disease. Advances in PCI technology, with more deliverable newer generation drug-eluting stents, adjunctive devices to aid stent delivery, crossing and re-entry systems to aid TO revascularization, functional assessment of lesions, intravascular ultrasound guidance to ensure adequate stent expansion, and dedicated specialists for specific anatomic subsets, may improve long-term prognosis by ensuring major epicardial vessels are fully revascularized.\textsuperscript{43–47}

**Surrogate Marker of Anatomic Complexity and Clinical Comorbidity**

The findings associating ICR with sicker patients, more anatomic complexity coronary artery disease, and consequent poorer long-term clinical outcomes, are supported by the historical data as detailed below.

First, that very long term follow-up data (≥10 years) of CABG treated patients in 2 separate registries,\textsuperscript{49,50} have associated more extensive baseline preoperative disease with adverse mortality. Second, in the Bypass Angioplasty Revascularization Investigation (BARI) Trial,\textsuperscript{50} where jeopardized myocardium and recurrence of angina were shown to occur more frequently secondary to native coronary artery disease progression, a reflection of the clinical risk profile of the patient, compared with failed revascularization in both PCI- and CABG-treated subjects at 5 year follow-up. Findings that have also been observed in other studies,\textsuperscript{51,52} with baseline comorbidities, such as diabetes mellitus, having been shown to be a predictor of native coronary disease progression. Third, that coronary artery calcification has been linked to adverse all-cause mortality at 10 years, independent of other risk factors.\textsuperscript{53,54} Notably, heavy calcification was present in almost two-thirds (64.5%) of subjects with a residual SYNTAX Score >8 (Table 1).

**Decision-Making Between CABG and PCI**

The recently developed and validated SYNTAX Score II\textsuperscript{55} combines anatomic (including the SYNTAX Score) and clinical variables that directly affect decision making between CABG and PCI. This is based on the provision that the cardiologist and cardiac surgeon agree, before revascularization, that equivalent anatomic revascularization could be achieved. Incorporation of quantitative factors of completeness of revascularization in the SYNTAX Score II would however have a limited role in decision-making between CABG and PCI, because this is a clinical outcome. This is typified in the SYNTAX Trial, where, despite the mandatory requirement of the interventional cardiologist and cardiac surgeon to agree that equivalent anatomic revascularization could be achieved to allow the patient to be randomized, CR was realized in 56.7% and 63.2% of the PCI and CABG arms, respectively.\textsuperscript{39}

**Study Limitations**

The present study represents a post hoc analysis of the SYNTAX Trial, and the results should be considered as hypothesis-generating. Although a core laboratory undertook baseline SYNTAX Scores prospectively, the residual SYNTAX Score was retrospectively assessed by a panel of 3 interventional cardiologists. Despite this limitation, analyses were performed with the identification of the lesions recorded by the core-laboratory, with consequent excellent reproducibility (κ statistic 0.89). It is entirely plausible that the residual SYNTAX Score could be improved through enhanced identification of functionally significant lesions with fractional flow reserve\textsuperscript{47,56} or viability assessment of the supplied myocardium.\textsuperscript{37–42} Although multivariable adjustments were performed for significant confounders (P≤0.1), the possibility of other unmeasured confounders to have affected the results cannot be excluded. Although the SYNTAX Trial was based on contemporary revascularization practice at the time, improvements in technology in PCI and CABG may yield differences in clinical outcomes in future trials.

**Conclusions**

The residual SYNTAX Score was shown to be a powerful indicator of 5-year clinical outcomes, including mortality, after PCI with drug-eluting stents in subjects with left main or de novo 3VD. The residual SYNTAX Score may aid determining a reasonable level of revascularization.

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**Disclosures**

Drs Dawkins and Huang are all full-time employees in Boston Scientific. Dr Mack holds stock in Boston Scientific. Dr Mack has served on the Speaker’s Bureau of Boston Scientific, Cordis, and Medtronic. Dr Feldman reported serving on the Speaker’s Bureau of Boston Scientific, receiving grant support from Abbott, Atritech, BSC, Edwards, and Evalve, and consulting for Abbott, Coherex, Intervalse, Square One, and...
WL Gore. Dr Morice reported that her institution received a research grant from Boston Scientific. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Interpreting the long-term prognostic impact of incomplete revascularization (ICR) in patients with complex coronary artery disease has historically remained difficult. The lack of standardized definitions of ICR, lack of randomized data, unavoidable selection bias inherent to all registry studies, and quality of monitoring and adjudication of outcomes, have led to conflicting results in the literature. The residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score is based on the principle of being a measure of the myocardial ischemia burden, dependent on the location of the coronary disease, its importance in supplying blood to the myocardium, and the anatomic complexity associated with the obstructive disease. Importantly, the residual SYNTAX Score allowed for the determination of an objective level of reasonable ICR, whereby a threshold value of ICR could be determined (≤ 8) that would not have a negative impact on long-term mortality and other clinical outcomes. The residual SYNTAX Score was validated in a randomized, all-comers population, consisting of subjects with complex coronary artery disease (unprotected left main coronary artery or de novo 3-vessel disease) who had undergone 5-year follow-up. Notably, progressively higher residual SYNTAX Scores were shown to be a surrogate marker of sicker patients, with greater baseline clinical comorbidity and anatomic complexity, with consequent adverse long-term clinical outcomes, including all-cause mortality. Results that were equally applicable in subjects with unprotected left main coronary artery disease and medically-treated diabetes mellitus. Such findings are of value in guiding the clinician to reduce the level of reversible myocardial ischemia by treating obstructive lesions to stay within the threshold of reasonable ICR.
Quantification of Incomplete Revascularization and its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score
Vasim Farooq, Patrick W. Serruys, Christos V. Bourantas, Yaojun Zhang, Takashi Muramatsu, Ted Feldman, David R. Holmes, Michael Mack, Marie Claude Morice, Elisabeth Ståhle, Antonio Colombo, Ton de Vries, Marie-angèle Morel, Keith D. Dawkins, Arie-Pieter Kappetein and Friedrich W. Mohr

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