JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 3, NO. 9, 2010

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2010.06.016

STATE-OF-THE-ART PAPER

Clinical and Angiographic Risk Assessment in Patients With Left Main Stem Lesions

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Percutaneous coronary intervention of unprotected left main stem lesions has been shown to be a suitable alternative to cardiac surgery in selected patients, emphasizing the need for appropriate risk stratification prior to selection of revascularization modality. Several risk models based on clinical and angiographic variables have been developed to guide patient selection, each of which has significant limitations. This paper reviews contemporary and newly proposed risk models for patients undergoing left main stem revascularization.
(J Am Coll Cardiol Intv 2010;3:891–901) © 2010 by the American College of Cardiology Foundation

The left main stem is rarely longer than 15 mm, but in view of its extensive myocardial distribution, it is a vitally important part of the coronary arterial tree. Unprotected left main stem (ULM) lesions carry the worst prognosis of any coronary lesion, mainly because of the extensive amount myocardium placed at jeopardy by such lesions. The mortality for nonrevascularized ULM disease has been reported to be as high as 37% at 3 years (1). The optimal therapy for patients with ULM disease remains the subject of continuing debate (2,3).

Coronary artery bypass grafting (CABG) was established as the gold standard for treatment of patients with ULM disease on the basis of trials that randomly assigned patients to CABG versus medical therapy (4). Historically, patients with ULM disease have been excluded from randomized trials comparing percutaneous coronary intervention (PCI) to CABG (5,6). Nevertheless, surveys of real-world practice have indicated that approximately one-third of patients with ULM lesions are treated by PCI (7). Percutaneous coronary intervention for ULM disease is usually "accepted" when: 1) patients require bailout ULM PCI following complications during PCI; 2) ULM disease occurs in the setting of acute myocardial infarction (MI); 3) the left main is protected by a functional coronary bypass graft; 4) patients are turned down for CABG; or 5) patients refuse surgery. Less settled are the indications for left main PCI in patients who are good candidates for CABG.

Recently, important studies have been published specifically relating to selection of revascularization modalities of the ULM (8). These data suggest that in certain groups of patients with ULM disease, such as those with ostial or shaft lesions, revascularization with PCI remains a valid alternative therapy to CABG (8–10). Consequently, in the recent focused update from the American College of Cardiology/American Heart Association (ACC/AHA), PCI for ULM lesions has been upgraded from a Class III to a Class IIb indication in those patients with "anatomical conditions which are associated with a low risk from PCI procedural complications and clinical conditions which predict adverse surgical outcomes" (11).

In view of this recommendation, there is now a clear need to appropriately identify which patients with ULM should undergo revascularization with PCI or CABG. This highly relevant topic was briefly touched upon in a recent white paper on

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Manuscript received May 24, 2010, accepted June 11, 2010.

PCI for ULM (8); however, its importance to everyday clinical practice necessitates a more detailed review. The aim of this paper is to review the currently available methods for risk stratifying those patients with ULM lesions requiring revascularization.

Does the ULM Need Revascularization?

Prior to embarking on the assessment of risk and formulation of a revascularization strategy for patients with an angiographically identified ULM lesion, it is important to determine whether the lesion is in actual need of revascularization (i.e., is hemodynamically significant). The anatomic location of the ULM, together with vessel foreshortening and overlap makes angiographic visualization and accurate lesion assessment notoriously difficult. Specifically, ostial left main lesions may appear more significant than they truly are due to catheter-induced artifacts, and the severity of distal bifurcation lesions may be notoriously difficult to accurately delineate. In part due to these reasons, lesions in the left main stem are subject to the greatest degree of angiographic intraobserver and interobserver variability compared with lesions located elsewhere in the coronary tree (12,13). Importantly, studies have shown a favorable prognosis in patients with ULM lesions that are not functionally significant (14). Conversely, bypass grafts placed to nonhemodynamically significant lesions have a high rate of early failure (15). Therefore, in practice, a suspicious or borderline ULM lesion warrants further evaluation with intravascular ultrasound, coronary computed tomography, and/or functional assessment with fractional flow reserve (12,14,16), before either suggesting the need for revascularization or dismissing the need altogether.

Abbreviations and Acronyms

ACC = American College of Cardiology
ACEF = Age, Creatinine, Ejection Fraction
AHA = American Heart Association
CABG = coronary artery bypass grafting
CSS = clinical SYNTAX score
EuroSCORE = European System for Cardiac Operative Risk Evaluation
GRC = Global Risk Classification
MACCE = major adverse cardiovascular and cerebrovascular events
MACE = major adverse cardiac events
MCRS = Mayo Clinic risk score
MI = myocardial infarction
PCI = percutaneous coronary intervention
STS = Society of Thoracic Surgery
SXscore = SYNTAX score
ULM = unprotected left main stem

Is There a Need for Risk Stratification in ULM Revascularization?

An assessment of procedural risk is imperative once the decision has been made that revascularization of the ULM is required. Technological advances, such as the availability of left ventricular assist devices during high-risk cases (17), have increased the number of patients in whom PCI is now feasible; however, the appropriateness of ULM intervention cannot be considered without a proper assessment of the risk and benefits of both PCI and CABG.

Procedural risk stratification (for both PCI and CABG) serves several purposes. In the short term, it provides clinicians with supplementary information that can help guide treatment strategy, particularly in view of the latest guidelines "allowing," with a Class IIb recommendation, ULM PCI only in cases in which procedural success is high and procedural risk is low. In addition, and perhaps most importantly, procedural risk stratification enables patients to be more adequately informed about the risks/benefits of the alternative revascularization strategies available, allowing them to make an informed decision. Ultimately, it is the duty of a clinician to convey full and understandable information to their patients (18). Contrary to popular belief, after being offered CABG, very few patients actually refuse. In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial, the rate of refusal was 0.4% (9). Surgeons raise the valid concern that patients who refuse CABG may not have had the opportunity to discuss matters with a surgeon and may have been swayed in their decision by a relatively 1-sided discussion (1). Good clinical practice should ensure that patients with significant ULM disease have the opportunity to speak to both a cardiac surgeon and interventional cardiologist together (the "Heart Team," often with a noninvasive cardiologist) to enable an interactive discussion wherein all issues are discussed and addressed (1). With the current state of evidence, ad hoc ULM PCI should not be performed in the stable patient.

Risk stratification models, and collections of decisions resulting from patient-physician discussions, provide a vital measure of patient care and may identify future directions to further improve outcomes. In terms of clinical governance and the public reporting of results, risk stratification is imperative to enable a suitable comparison of performance between clinicians and government standards. Their significance is further enhanced as it becomes increasingly essential for clinicians to be able to justify clinical decisions to patients, peers, and regulatory bodies.

What Methods of Risk Stratification Are Available for Patients With ULM Lesions?

A variety of different methods of stratifying risk in patients undergoing ULM revascularization is available; however, each has been applied to different study populations, limiting the comparisons that can be made among different risk models. In essence, risk models can be divided into those using clinical-based variables, those using angiographic data, and those using a combination of both. Table 1

Table 1. Summary of Contemporary and Newly Developed Risk Models for Assessment of Risk in Patients Undergoing Revascularization

Risk Model	Number of Variables Used to Calculate Score		Validated in PCI/CABG		Specific Evaluation in ULM Patients?
	Clinical	Angiographic	PCI	CABG	
EuroSCORE (9,19–28)	17	0	+	+	+
Mayo Clinic Risk Score (30–32)	17	0	+	+	–
ACEF (33)	3	0	–	+	–
AHA/ACC lesion classification (36–38,40)	0	11 (per lesion)	+	–	+
SYNTAX score (6,9,24,26,34,39–48)	0	11 (per lesion)	+	+	+
Society of Thoracic Surgery score (31,49–51)	40	2	–	+	–
Clinical SYNTAX score (52)	3	11 (per lesion)	+	–	–
Global Risk Classification (54)	17	11 (per lesion)	+	+	+

AHA/ACC = American Heart Association/American College of Cardiology; ACEF = Age, Creatinine, Ejection Fraction; CABG = coronary artery bypass grafting surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; ULM = unprotected left main stem.

summarizes various contemporary risk models that are described in more detail herein.

Clinical-Based Scores

These risk scores only incorporate clinical variables and do not require any data from the angiogram. They offer the advantage of being able to be computed relatively quickly, usually at the bedside, and principally include variables that are not subject to user interpretation, thereby ensuring excellent reproducibility.

EuroSCORE. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) (19) is an additive clinical score, calculated using 17 different objective clinical variables (Table 2), which has been used since 1999 to predict in-hospital mortality in patients undergoing cardiac surgery (19). Subsequent studies have confirmed the ability of the EuroSCORE to also predict long-term mortality (20–22).

There have been no dedicated studies of the EuroSCORE (additive or logistic) in patients with isolated ULM lesions

Table 2. The Additive EuroSCORE

		Score
Patient characteristics		
Age	Per 5 years or part thereof over the age of 60 years	1
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for respiratory disease	1
Peripheral arteriopathy	*Claudication, carotid stenosis >50%, previous or planned intervention on the abdominal aorta, limb arteries, or carotids	2
Neurological dysfunction	Severely affected mobility or day-to-day function	2
Previous cardiac surgery	Previous opening of the pericardium	3
Serum creatinine	Pre-operatively >200 μmol/l	2
Active endocarditis	Antibiotic therapy at time of surgery	3
Critical pre-operative state	*Pre-operative cardiac arrest, ventilation, renal failure, inotropic support, intra-aortic balloon pump use, ventricular arrhythmia	3
Cardiac-related factors		
Unstable angina	Rest pain requiring IV nitrates	2
Left ventricular function	Moderate (30%–50%) Poor (<30%)	1 3
Recent MI	Within 90 days	2
Pulmonary hypertension	Systolic pulmonary pressure >60 mm Hg	2
Operation-related factors		
Emergency	Operation performed before the start of next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta		3
Post-infarct septal rupture		4

The additive EuroSCORE is calculated by summating the individual score from 17 different variables (19). *Any of the following.
IV = intravenous; MI = myocardial infarction; other abbreviations as in Table 1.

undergoing surgical revascularization. However, the initial validation of these scores utilized a large patient database, which included over 4,000 (22%) patients with a ULM lesion (19,23), thereby indirectly confirming the utility of the EuroSCORE in the assessment of patients undergoing CABG for ULM disease.

The utility of using the EuroSCORE in patients undergoing PCI has been assessed in the multicenter randomized SYNTAX study (9,24) and several additional nonrandomized studies (25–28). Four of these studies specifically evaluated the EuroSCORE in patients with ULM disease (24–27), with most except the study by Kim et al. (27) including a surgical treatment arm for the comparison of outcomes.

All studies have identified the additive EuroSCORE as an independent predictor of major adverse cardiovascular and cerebrovascular events (MACCE) in patients with ULM disease undergoing PCI (24–27). In addition, all studies that include a surgical control group have reported that the additive EuroSCORE is an independent predictor of MACCE for patients with a ULM lesion undergoing CABG (24–26). In the left main stem subgroup of the SYNTAX study, the additive EuroSCORE was shown to be an independent predictor of MACCE at 1-year follow-up irrespective of the method of revascularization (odds ratio [OR]: 1.21; 95% confidence interval [CI]: 1.12 to 1.32; $p < 0.001$) (24). Rodés-Cabau et al. (25) reported similar results among 249 octogenarians with ULM disease, with a EuroSCORE ≥ 9 identified as the best predictor of MACCE after PCI and CABG out to a mean of 23 months of follow-up (25). The C-statistic for the ability of the EuroSCORE to predict MACCE was reported as 0.65. More recently, retrospective analysis of the large MAIN COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization from Multicenter Registry), which included 1,580 patients with ULM, demonstrated that the additive EuroSCORE was an independent predictor of death/MI/stroke in patients having PCI or CABG out to 3-year follow-up (26).

In a study without a comparative surgical arm, Kim et al. (27) evaluated the potential of the EuroSCORE in 324 patients undergoing PCI for ULM disease, at a median of 26.3 months of follow-up. A EuroSCORE >5, commonly accepted as a high-risk surgical group (19), was shown to be an independent predictor of death/MI (hazard ratio [HR]: 3.4; $p = 0.02$), with a C-statistic for the ability of the EuroSCORE to predict death/MI of 0.61. In contrast, Romagnoli et al. (28) reported a C-statistic of 0.91 for the prediction of in-hospital mortality using the EuroSCORE. The superior C-statistic in this report (28) may be attributed to Romagnoli et al. limiting outcome measures to only the hard end point of mortality and restricting the period of follow-up to only in-hospital events. Of note, the C-statistic fell to 0.56 when assessing procedural failure.

Concerns that the additive EuroSCORE underestimated risk in surgical patients deemed to be at the highest risk (29) led to the development of the logistic EuroSCORE. In the setting of PCI, only Romagnoli et al. (28) have assessed the performance of the logistic EuroSCORE, which was subsequently shown to have a predictive ability that was similar to the additive EuroSCORE.

In summary, the limited studies that have assessed the additive EuroSCORE in patients with ULM disease suggest that the EuroSCORE in isolation is probably of little use in determining selection of revascularization strategy, as patients with high EuroSCORE have a high risk of adverse events following either PCI or CABG. Nevertheless, it is clear that the EuroSCORE is an effective method of identifying which patients, treated with PCI or CABG, are at high risk of mortality and/or MACCE. The role of the logistic EuroSCORE is as yet undetermined.

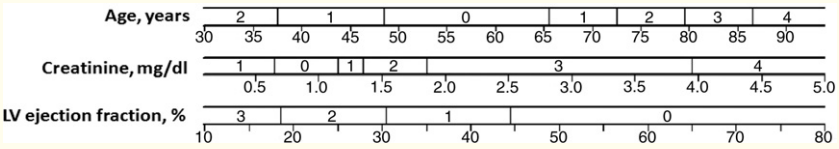
Mayo Clinic risk score. The Mayo Clinic risk score (MCRS) uses a mixture of 7 clinical variables to predict in-hospital mortality after revascularization with either PCI or CABG (Table 3). The MCRS has been validated in patients having PCI and CABG (30,31); however, no studies have been performed specifically in patients with ULM lesions. The only study to report the MCRS and specify the number of patients with a ULM lesion enrolled only 96 ULM patients, comprising 1.3% of the overall study cohort (32). This small group is clearly insufficient to allow extrapolation of the overall study results to patients with ULM disease in general. Therefore, the utility of using the MCRS for either quantifying procedural risk and/or selecting revascularization strategy in patients with ULM disease remains currently undefined.

ACEF score. The Age, Creatinine, Ejection Fraction (ACEF) score (33) is calculated using the formula [patient age ÷ ejection fraction (%)] + [1 if creatinine >2 mg/dl]. The only published data at present relate to patients undergoing elective CABG, where the ACEF score was shown to have a similar accuracy and calibration for in-hospital mortality compared with other more complicated surgical risk scores such as the EuroSCORE and the Cleveland Clinic Score. The development and validation of this score included 8,648 patients; however, the proportion of patients with a ULM lesion was not specified. Furthermore, as with the MCRS, the value of the ACEF score in either determining revascularization strategy and/or procedural risk in patients undergoing PCI is as yet undetermined by virtue of the lack of any data in PCI patients. Ultimately, the role of the ACEF score in the assessment of patients with ULM disease requires further investigation.

In summary, the different clinical-based risk scores have been found to be useful in predicting early and late mortality and MACCE in patients undergoing PCI and/or CABG.

Table 3. The Mayo Clinic Risk Score

Variable	Points
Age, yrs	See below
Creatinine, mg/dl	See below
Left ventricular ejection fraction, %	See below
Pre-procedural shock	9
Myocardial infarction <24 h	4
Congestive heart failure on presentation (without acute MI or shock)	3
Peripheral vascular disease	2



The Mayo Clinic risk score is calculated using data from 7 individual variables, each of which have their own weighted score (30).
Abbreviations as in Table 2.

However, no clinical-based score has been demonstrated to discriminate the relative early procedural risk or late survival between PCI and CABG.

Angiographic-Based Scores

Several angiographic-based scores have been proposed that are independent of patient clinical variables, being calculated using only angiographic data. This has obvious implications for the timing of risk stratification. More importantly, however, the intervariability inherent in angiographic assessment introduces a subjective element to the assessment of risk when using angiographic-based scores (34,35).

ACC/AHA lesion classification. The ACC/AHA lesion classification was 1 of the original angiographic scoring systems; it was first devised in 1986 and modified in 1990. The current scoring system uses 11 angiographic variables to categorize lesions into types A, B1, B2, and C. Historical studies prior to the arrival of drug-eluting stents indicated that that ACC/AHA lesion classification did have a prognostic impact on early and late outcomes (36,37). Data in contemporary practice using drug-eluting stents, however, are limited to retrospective registries. The German Cypher registry enrolled over 6,700 patients with approximately 8,000 lesions, 200 of which were ULM lesions. Results indicated the lack of any relationship between ACC/AHA lesion classification and clinical outcomes out to 6-month follow-up (38). In contrast to these results, a significant relationship between the ACC/AHA lesion score (derived by assigning 1, 2, 3, and 4 points to types A, B1, B2, and C lesions, respectively) and clinical outcomes has been demonstrated in patients with 3-vessel- (39) or ULM-disease (40) undergoing PCI. Specifically, Capodanno et al. (40) demonstrated that the ACC/AHA lesion score significantly predicted both cardiac death ($p = 0.001$) and major adverse cardiac events (MACE) ($p = 0.02$) at 1-year follow-up among 255 patients with ULM undergoing PCI with drug-eluting stents. Moreover, in this study, the ACC/AHA lesion score was found to be an independent predictor of cardiac death, but not MACE.

SYNTAX score. The SYNTAX score (SXscore) is a well-described anatomical scoring system that enables quantification of the complexity of coronary anatomy (34,41). Lesion location and adverse lesion characteristics are used to calculate the score using either a downloadable calculator or the SXscore website (42) (Table 4). The SXscore was first used prospectively in the SYNTAX trial and has since been calculated in a number of different clinical trials both in elective and acute patients, with simple or complex disease, followed up for between 1 and 5 years (6,9,34,39–41,43–46). In all studies, irrespective of follow-up duration, a higher SXscore tertile has consistently been associated with the poorest outcomes (6,9,39,40,43–46), whereas several studies also identified the SXscore as an independent predictor of MACE in patients undergoing PCI (6,39,40,43,44).

The value of the SXscore in patients with ULM disease has been specifically assessed in over 3,000 patients with follow-up between 12 months and 4 years in 4 separate studies: specifically, the 705-patient ULM subgroup of the SYNTAX trial (24,47), the CUSTOMIZE registry (appraise a CUSTOMIZED strategy for left main revascularization) ($n = 819$) (40,43), the MAIN COMPARE registry ($n = 1,580$) (26), and the Rotterdam LM (Rotterdam Left Main) registry ($n = 148$) (44). Importantly, a surgical arm was included in all but the Rotterdam LM registry, thereby allowing investigation as to the role of the SXscore for selecting revascularization strategy and/or determining procedural risk.

The ULM subgroup of the SYNTAX study represents the only prospectively recruited ULM patient group

Table 4. The SYNTAX Score Algorithm

1. Arterial dominance
2. Arterial segments involved per lesion
   Lesion characteristics
   3. Total occlusion
      i. Number of segments involved
      ii. Age of the total occlusion (>3 months)
      iii. Blunt stump
      iv. Bridging collaterals
      v. First segment beyond the occlusion visible by antegrade or retrograde filling
      vi. Side branch involvement
   4. Trifurcation
      i. Number of segments diseased
   5. Bifurcation
      i. Medina type
      ii. Angulation between the distal main vessel and the side branch <70°
   6. Aorto-ostial lesion
   7. Severe tortuosity
   8. Length >20 mm
   9. Heavy calcification
   10. Thrombus
   11. Diffuse disease/small vessels
      i. Number of segments with diffuse disease/small vessels

The SYNTAX score is calculated using this algorithm, which is applied to each individual coronary lesion that has a diameter stenosis greater than 50% and is located in a vessel that is larger than 1.5 mm in diameter (41). The individual lesion scores are added together to give the final SYNTAX score.

(24,47). The rate of MACCE out to 2-year follow-up, together with the individual components of death, stroke, MI, and repeat revascularization in patients randomly assigned to treatment with PCI or CABG, stratified according to SXscore tertiles are shown in Table 5. Of note, whereas the SXscore was an independent predictor of MACCE for patients undergoing PCI, the same was not true for those undergoing CABG. This is not surprising considering the bypass anastomosis occurs distal to the complex disease. Moreover, the relatively "flat" relationship between MACCE and SXscore in patients undergoing CABG, which contrasts with the positive relationship between MACCE and SXscore in patients undergoing PCI (Fig. 1), indicates how the SXscore, in addition to its ability to predict outcomes, is able to aid revascularization decisions in these patients. In those patients in the low and intermediate SXscore tertiles, the rates of MACCE between PCI and CABG are comparable (Table 5), whereas in those patients in the highest SXscore tertile, outcomes are significantly worse in those receiving PCI.

Similar findings have been demonstrated in retrospective registries of patients undergoing ULM PCI who have reported outcomes from 1 to 4 years of follow-up.

At 1-year follow-up, among 255 patients in the CUSTOMIZE registry, the SXscore was identified as an independent predictor of MACE (adjusted HR: 1.06; 95% CI: 1.02 to 1.10; p = 0.005) and cardiac death (adjusted HR: 1.15; 95% CI: 1.05 to 1.26; p = 0.003), with respective C-statistics of 0.64 and 0.83 (40). At 2-year follow-up, further analysis of the same registry (expanded to 819 patients) reaffirmed the ability of the SXscore to aid revascularization decisions (43). The rate of MACE among patients treated with PCI and CABG for those with an SXscore ≤34 was 8.1% and 6.2% (p = 0.46), respectively, compared with 32.7% and 8.5% (p < 0.001) for those with SXscore >34.

At 3-year follow-up in the MAIN COMPARE registry, the rate of death/stroke/MI after ULM PCI increased from 4.6%, to 9.4% and 11.4% with increasing SXscore tertile (p = 0.01) (26). A significant trend was not present, however, when rates of MACCE (composite of death, stroke, MI, and repeat revascularization) were stratified according to SXscore; of note, this population included patients treated with bare-metal stents, which may in part explain this finding. Finally, data from the Rotterdam LM registry indicate that the ability of the SXscore to identify those at high risk of adverse outcomes following ULM PCI is sustained out to at least the 4-year follow-up (44).

In contrast to these studies, which have all consistently demonstrated no interaction between the SXscore and those

Table 5. 2-Year Outcomes in the Left Main Subgroup of the SYNTAX Trial Stratified by SYNTAX Score Tertiles

2-Year Outcomes (47)	Treatment Modality: PCI (%)	Treatment Modality: CABG (%)	p Value
Low SYNTAX score tertile (0–22)	n = 118	n = 104	
Major adverse cardiovascular events	15.5	18.8	0.45
Death	0.9	4.9	0.07
Stroke	0.9	4.1	0.12
MI	3.6	2.0	0.53
Death/stroke/MI	4.5	9.9	0.10
Repeat revascularization	14.7	10.1	0.37
Intermediate SYNTAX score tertile (23–32)	n = 103	n = 92	
Major adverse cardiovascular events	22.4	22.4	0.91
Death	4.9	11.3	0.10
Stroke	1.0	2.3	0.46
MI	4.0	3.3	0.86
Death/stroke/MI	9.8	14.5	0.28
Repeat revascularization	14.9	12.8	0.72
High SYNTAX score tertile (≥33)	n = 135	n = 150	
Major adverse cardiovascular events	29.7	17.8	0.02
Death	10.4	4.1	0.04
Stroke	0.8	4.2	0.08
MI	8.4	6.1	0.48
Death/stroke/MI	15.6	11.5	0.32
Repeat revascularization	21.8	9.2	0.003

Abbreviations as in Tables 1 and 2.

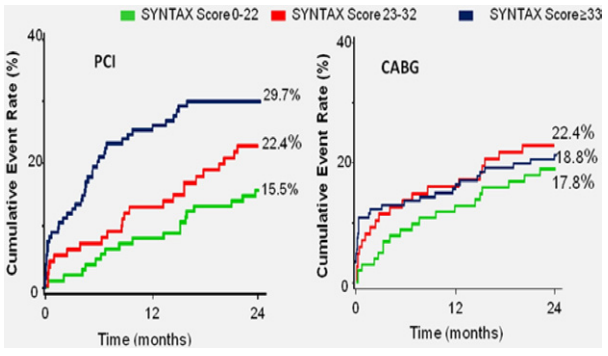


Figure 1. Clinical Outcomes (Composite of Death, Stroke, MI and Repeat Revascularization) Stratified by SYNTAX Score Tertile

Clinical outcomes (composite of death, stroke, myocardial infarction, and repeat revascularization) stratified by SYNTAX score tertile among the 705 patients randomized to treatment with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery in the unprotect left main subgroup of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) study (47). There is an increasing event rate among patients treated with percutaneous coronary intervention with increasing SYNTAX score tertile. Conversely, there is relatively little difference between outcomes in the coronary artery bypass grafting group. These results illustrate the utility of the SYNTAX score in determining revascularization strategy. CABG = coronary artery bypass grafting; MI = myocardial infarction.

undergoing CABG, are the results of a study by Birim et al. (48) who reported surgical outcomes in 148 patients with ULM disease stratified according to tertiles. The study, which only used 1 investigator to score all angiograms, demonstrated that the SXscore was an independent predictor of MACCE at 1-year follow-up after CABG. The small sample size and retrospective design may have influenced the results, which have not yet been repeated, or fully explained (48).

Both Valgimigli et al. (39) and Capodanno et al. (40) have reported a significant correlation between the SXscore with the ACC/AHA lesion score. However, the SXscore has been shown to have superior discriminative ability compared with the ACC/AHA lesion score for both cardiac death (SXscore 0.83 vs. 0.76 ACC/AHA) (40) and MACCE (SXscore 0.73 vs. ACC/AHA 0.56) (39).

Overall, these multiple studies indicate that the SXscore has a role to play in both stratifying clinical outcomes and assisting important revascularization decisions in those patients undergoing revascularization of ULM disease.

Combined Risk Scores

The clinical and angiographic-based scores assess completely different, but equally important, variables. Importantly, clinical and angiographic risk models may be better suited to predict different outcomes. For example, Singh et al. (32) reported that the MCRS was superior to the ACC/AHA lesion classification in the prediction of death/stroke/MI/emergent CABG, but inferior for the prediction of angiographic failure. This observation supports the notion of a model combining clinical and angiographic variables, which intuitively would be able to provide a more complete assessment of risk. In view of this, several combined clinical and angiographic risk scores have been developed. However, validation of these scores is at an early stage, such that outcome data are currently confined to small, retrospective studies, with limited follow-up. The most prominent combined risk scores include: Society of Thoracic Surgery (STS) Score, clinical SYNTAX score (CSS), and combined EuroSCORE and SYNTAX.

STS Score. The STS score is considered a combined risk score, although it only incorporates 2 angiographic variables (presence of ULM lesion and number of vessels diseased) together with 40 clinical variables. The STS risk model predicts the risk of operative mortality and morbidity after adult cardiac surgery (49,50) such that it is used exclusively by cardiac surgeons; at present, no data exist regarding the utility of the STS score in patients undergoing PCI. Previous data have indicated the STS score to be superior to the MCRS in patients having CABG (31), whereas comparisons between the EuroSCORE and STS score indicate only a slight improvement in mortality prediction with the STS score (51). There appears to be little role of the STS score in the assessment of patients with ULM disease prior to the selection of a strategy of surgical revascularization.

Clinical SYNTAX score. The notion of adding a clinical-based component to the angiographic SXscore led to the development of the CSS (52). This score incorporates, as its clinical component, the ACEF score, which is modified to include the creatinine clearance as opposed to the serum creatinine as originally described by Ranucci et al. (33). This was performed to improve the discrimination of risk as previously observed when a similar modification was incorporated into the EuroSCORE (53). The CSS is calculated by multiplying the SXscore with this modified ACEF score (Table 6). The evaluation of the CSS has only been performed thus far in 1 patient study cohort, which included

Table 6. The Clinical SYNTAX Score

$$\text{Clinical SYNTAX Score} = \text{SYNTAX Score} \times \left(\frac{\text{Age}}{\text{LV ejection fraction (\%)}} + 1 \text{ point for each 10-ml creatinine clearance}^{*} < 60 \text{ ml/min/1.73 mm}^2 \right)$$

The clinical SYNTAX score is calculated using the patient's age, left ventricular ejection fraction, serum creatinine clearance, and SYNTAX score (52). *Calculated using the Cockcroft/Gault equation.
LV = left ventricular; other abbreviations as in Table 1.

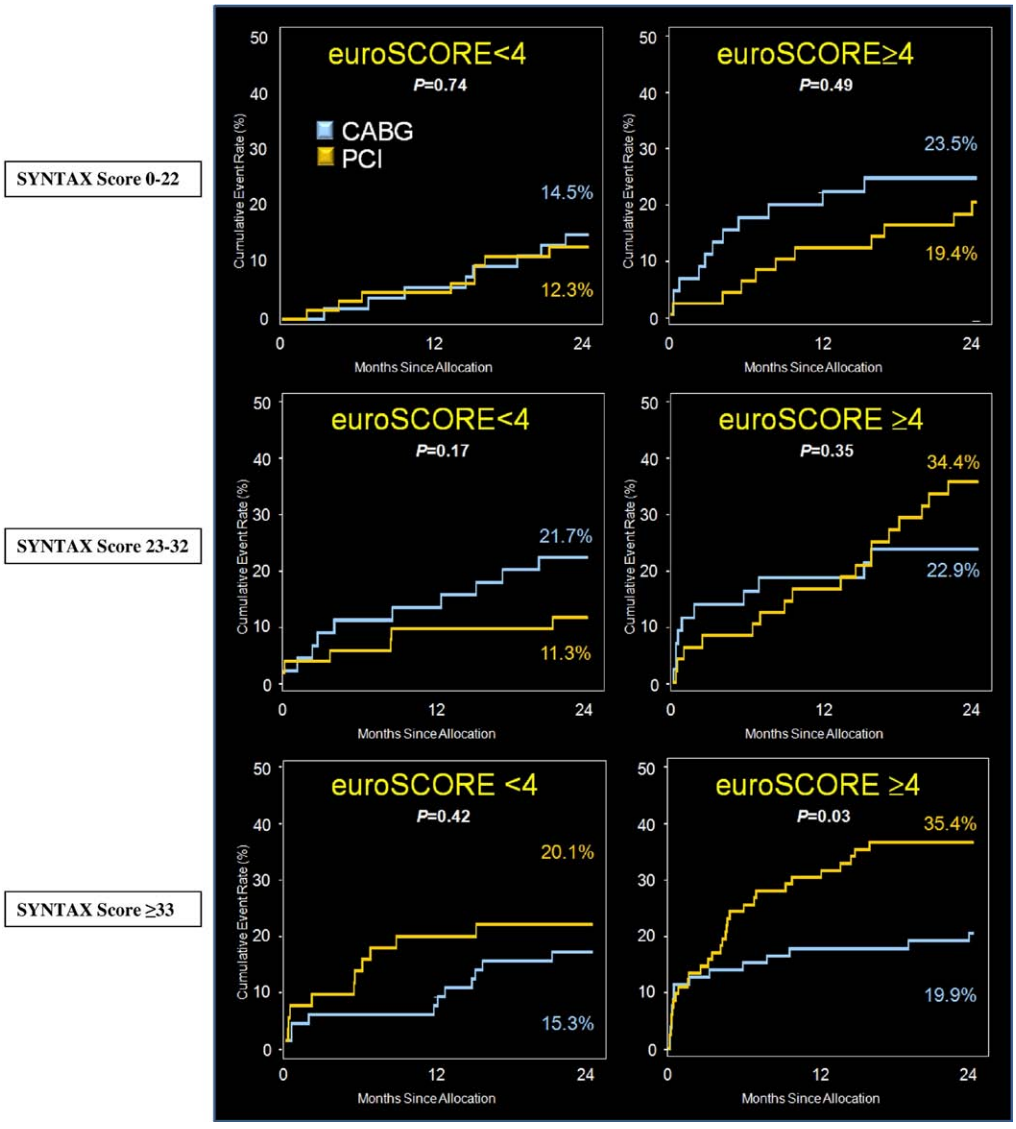


Figure 2. The Relationship Between the EuroSCORE and the SYNTAX Score as Assessed in the ULM Population Enrolled in the SYNTAX Study

All patients with a EuroSCORE (European System for Cardiac Operative Risk Evaluation) ≥4 have a greater event rate than patients with a EuroSCORE <4 irrespective of the treatment modality or their SYNTAX score tertile. Furthermore, the largest absolute difference in event rate between patients with a EuroSCORE above and below 4 occurs in patients in the intermediate SYNTAX score tertile when treated with percutaneous coronary intervention, and in the lowest SYNTAX score tertile when treated with coronary artery bypass grafting. ULM = unprotected left main stem; other abbreviations as in Figure 1.

patients with multivessel disease but excluded those with ULM lesions. At 5-year follow-up, among patients with triple-vessel disease, the CSS was shown to have a superior discriminative ability compared with the SXscore and ACEF score in the prediction of both mortality (CSS 0.80 vs. SXscore 0.70 vs. ACEF 0.73) and MACCE (CSS 0.67 vs. SXscore 0.64 vs. ACEF 0.59) (52). Further evaluation of this score is required, particularly in patients with ULM disease.

EuroSCORE and SYNTAX. The previous discussion has indicated that the EuroSCORE and SXscore are the most validated tools for risk assessing patients undergoing coronary revascularization and in particular those with ULM disease. The combination of these 2 scores appears particularly attractive given the ability of the EuroSCORE to identify patients at high risk of adverse events irrespective of treatment modality and the ability of the SXscore to assist in establishing optimal revascularization strategy.

The 2 scores have a somewhat complex relationship that is highlighted by the confusing results seen in the SYNTAX study, when patients in low, intermediate, and high SXscore tertiles were further subdivided by a EuroSCORE above or below the median of 4 (Fig. 2). The EuroSCORE was an

Table 7. The Global Risk Classification

	SYNTAX Score Tertile		
EuroSCORE	**LOW**	**INTERMEDIATE**	**HIGH**
LOW	Low	Low	Intermediate
MEDIUM	Low	Low	Intermediate
HIGH	Intermediate	Intermediate	High

The Global Risk Classification uses the patient's EuroSCORE and SYNTAX score in combination to classify patients as low, intermediate, or high risk (54). It is derived using this matrix.
Abbreviations as in Table 1.

independent predictor of MACCE for both revascularization strategies; therefore it would have been expected that outcomes in those with a high EuroSCORE were worse than those with a low EuroSCORE irrespective of the SXscore tertile. However, as is clearly seen, in the low SXscore tertile the division by EuroSCORE identified those patients at highest risk of events from surgery and had little effect on PCI outcomes. In the high SXscore tertile group the opposite was observed: whereas surgical outcomes in patients with a EuroSCORE above or below 4 were similar, PCI outcomes varied from 20% to 35%. The small number of patients in these subgroups may certainly have played its part in these observations, which therefore require further investigation with subsequent larger studies.

Although the subdivision of patients into 2 groups according to their EuroSCORE produced puzzling results, more promising results have been reported by Capodanno et al. (54) when subdividing the EuroSCORE into the historically defined groups of low (0 to 2), intermediate (3 to 5), and high risk (≥6) and combining this in a Global Risk Classification (GRC) with SXscores in low, intermediate, and high tertiles (Table 7). This GRC has so far only been applied to a population of 255 patients undergoing ULM revascularization, for which SXscores were calculated retrospectively. At 2-year follow-up, the rates of cardiac death in patients in low, intermediate, and high SXscores tertiles were 3.9%, 5.4%, and 21.9%, whereas with the GRC, rates of 1.6%, 16.0%, and 31.4% were seen in low, intermediate, and high GRC groups. Additional results indicated that the GRC had a greater discriminatory ability when compared with other risk scores, including the EuroSCORE and the SXscore, for the prediction of in-hospital and 2-year mortality. In essence, the study reiterated the importance of considering both clinical and angiographic variables in the assessment of overall risk and provided a combined scoring system that appears to hold promise; however, validation in a large patient group is required.

Limitations of Risk Models

There are numerous other variables such as diabetic status and body mass index, which have been shown to influence clinical outcomes but have not been included in most risk models. Importantly, the number of variables included in the risk model must be sufficient, on one hand, to ensure the model adequately predicts risk, but, on the other hand, the number must not be excessive to inhibit user uptake. Furthermore, inclusion of numerous variables increases the chances of colinearity between independent variables resulting in redundant information being collected (33), whereas also increasing the chances of overfitting the model, thereby reducing the overall accuracy of the results (55). Overall, it must be acknowledged that all risk scores lack the sensitivity to accurately predict events in an individual patient who may have comorbidities not accounted for in the risk model. The purpose of risk scores therefore is to report the risk of the population being studied; in a good risk model the variables selected will account for interpatient variation in comorbidities.

The accuracy of risk models can also be improved with the inclusion of treatment-specific procedural factors, such as the number of stents implanted and the stenting technique employed in patients having PCI, and the cardiopulmonary bypass time and use of off-pump surgery in patients having CABG. For example, Chen et al. (56) incorporated 4 procedural variables together with 17 clinical and 33 angiographic variables to produce a risk model that had a greater predictive accuracy than the SXscore alone in 337 patients with ULM disease treated with PCI. Despite the improved accuracy, it is important to remember that these variables cannot be reliably predicted prior to undertaking PCI or CABG, and therefore their inclusion unfortunately moves the ability to accurately calculate risk to a time point after the procedure has been completed.

Table 8. Comparison of the Different Predictive Ability of Risk Models When Assessing Hard and Soft Clinical End Points

Risk Score	Study	Hard End Point (Follow-Up)	C-Statistic	Soft End Point (Follow-Up)	C-Statistic
EuroSCORE	Romagnoli et al. (28)	Mortality (In-hospital)	0.91	Procedural failure (In-hospital)	0.56
Mayo Clinic Risk Score	Singh et al. (32)	Death/stroke/MI/emergent CABG (In-hospital)	0.78	Angiographic success (In-hospital)	0.67
AHA/ACC lesion score	Capodanno et al. (40)	Cardiac death (12 months)	0.76	Cardiac death, MI, TLR (12 months)	0.64
SYNTAX score	Capodanno et al. (40)	Cardiac death (12 months)	0.83	Cardiac death, MI, TLR (12 months)	0.64
Clinical SYNTAX score	Garg et al. (52)	All-cause death (60 months)	0.80	Death, stroke, MI, repeat revascularization (60 months)	0.67

TLR = target lesion revascularization; other abbreviations as in Table 1.

Finally, data indicate that overall ability of clinical or angiographic models to predict hard end points (such as mortality) is superior to their ability to predict softer outcomes such as angiographic failure and repeat revascularization. As shown in Table 8, this trend appears consistent with all risk models, with recent data from Garg et al. (52) indicating that combined scores such as the CSS are not exempt from this phenomenon.

Conclusions

There is a clear need for adequate risk stratification in patients undergoing revascularization of the ULM. Although numerous different risk models are available for the assessment of these patients, each has been evaluated in a different patient population and has measured different outcome end points at varying follow-up time periods. This heterogeneity identifies an important gap in the current evidence base. As a result, identification of a single best risk score for use as a day-to-day clinical tool is presently not possible. Assessment of prospectively and carefully collected data from a large ULM population undergoing long-term follow-up is required to provide the substrate from which a useful risk stratification model can be developed that is capable of optimally discriminating between PCI and CABG in patients with ULM disease requiring revascularization.

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Key Words: ACEF score ■ clinical SYNTAX score ■ coronary artery bypass grafting ■ EuroSCORE ■ global risk classification ■ percutaneous coronary intervention ■ stenting ■ SYNTAX score ■ unprotected left main stem.