

## Assessment of the SYNTAX score in the Syntax study

Patrick W. Serruys<sup>1\*</sup>, MD, PhD; Yoshinobu Onuma<sup>1</sup>, MD; Scot Garg<sup>1</sup>, MD, MRCP; Giovanna Sarno<sup>1</sup>, MD, PhD; Marcel van den Brand<sup>2</sup>, MD, PhD; Arie-Pieter Kappetein<sup>3</sup>, MD, PhD; Nic Van Dyck<sup>4</sup>, RN; Michael Mack<sup>5</sup>, MD; David Holmes<sup>6</sup>, MD; Ted Feldman<sup>7</sup>, MD; Marie-Claude Morice<sup>8</sup>, MD; Antonio Colombo<sup>9</sup>, MD; Eric Bass<sup>10</sup>, PhD; Katrin Leadley<sup>10</sup>, MD; Keith D Dawkins<sup>10</sup>, MD; Gerrit-Anne van Es<sup>11</sup>, PhD; Marie-Angèle M. Morel<sup>11</sup>, BSc; Friedrich W. Mohr<sup>12</sup>, MD

1. Department of Interventional Cardiology, Erasmus Medical Center, Thoraxcenter Rotterdam, The Netherlands; 2. Ouderkerk aan den IJssel, The Netherlands; 3. Department of Cardiothoracic Surgery, Erasmus Medical Center, Thoraxcenter, Rotterdam, The Netherlands; 4. Boston Scientific Corporation, Maastricht, The Netherlands; 5. Medical City Dallas Hospital, Dallas, TX, USA; 6. The Mayo Clinic, Rochester, MN, USA; 7. Evanston Hospital, Evanston, IL, USA; 8. Institut Cardiovasculaire Paris Sud, Massy, France; 9. San Raffaele Hospital, Milano, Italy; 10. Boston Scientific Corporation, Natick, MA, USA; 11. Cardialysis BV, Rotterdam, The Netherlands; 12. Herzzentrum, Leipzig, Germany

N. Van Dyck, E. Bass, K. Leadley and K. Dawkins are employees of Boston Scientific. GA. van Es, MA. Morel are employees of Cardialysis. The remaining authors have no disclosure to declare related to this investigation.

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### KEYWORDS

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### Abstract

**Aims:** The SYNTAX™ score has been designed to better anticipate the risks of percutaneous or surgical revascularisation, taking into account the functional impact of the coronary circulation with all its anatomic components including the presence of bifurcations, total occlusions, thrombus, calcification, and small vessels. The purpose of this paper is to describe the baseline assessment of the SYNTAX™ score in the Syntax randomised trial, the corelab reproducibility, the potential difference in score assessment between the investigator and the corelab, and to ascertain the impact on one-year outcome after either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) in patients with complex coronary artery disease.

**Methods and results:** To assess the reliability of Syntax™ scoring, 100 diagnostic angiograms from the Syntax trial were randomly selected and assessed independently by two observers. Intra-observer variability was assessed by analysing 91 sets of angiograms after an interval of at least eight weeks by one of the observers. Clinical outcomes in the randomised cohort of the Syntax trial up to one year are presented with stratification by tertile group of the SYNTAX™ score. The weighted kappa value for the inter-observer reproducibility on the global score was 0.45, while the intra-observer weighted kappa value was 0.59. The SYNTAX™ score as calculated by investigators consistently underscored the corelab score by 3.4 points. When the Syntax randomised cohort was stratified by tertiles of the SYNTAX™ score, there were similar or non-significantly different MACCE rates in those with low or intermediate scores; however in the top tertile the MACCE rate was greater in those receiving PCI compared to CABG.

**Conclusions:** The SYNTAX™ score is a visual coronary score with an acceptable corelab reproducibility that has an impact on the one-year outcome of those having PCI, whereas it has no effect on the one-year outcome following surgical revascularisation. The SYNTAX™ score tool is likely to be useful in a wide range of patients with complex coronary disease.

\* Corresponding author: Thoraxcenter, Ba-583a, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands

E-mail: p.w.j.c.serruys@erasmusmc.nl

## Introduction

In previously published randomised trials including 2 and 3-vessel disease, patient selection or exclusion criteria resulted in only 2-12% of the patients screened being randomised<sup>1</sup>. During the initial debate on the design of the Syntax study, it was argued that despite the fact that patients with two or three vessel disease have been included in previous randomised trials, in the "real world" surgeons were often confronted with more complex anatomy and comorbidities. Therefore, the all-comer approach became the cornerstone of the Syntax trial, reducing exclusion criteria to a minimum (previous intervention, acute myocardial infarction and concomitant cardiac surgery)<sup>2</sup>.

The anatomic heterogeneity in the patients enrolled in previous randomised trials renders their interpretation difficult. For example, a patient with 3-vessel disease and multiple lesions in each vascular territory (including long lesion, bifurcation and total chronic occlusion) was pooled together with a patient with three focal lesions in the mid-portions of each coronary artery. Both were conventionally named "3-vessel disease", despite the fact that the first patient represents a greater therapeutic challenge for the interventional cardiologist, and has a completely different prognosis compared to the second patient regardless of the revascularisation strategy. Thus the interpretation of the results of previously conducted randomised trials is severely limited by the absence of grading of the severity of coronary artery disease, and by the lack of comparison of lesion complexity based on pretreatment angiographic criteria<sup>3</sup>.

In the Syntax trial, the decision to refer the patient for either surgery or percutaneous coronary intervention (PCI) was the result of a pretreatment consensus reached between the cardiac surgeon and the interventional cardiologist. In this so called "Heart-Team Conference" the surgeon and interventional cardiologist fully assessed anginal status, comorbidities, coronary anatomy and left ventricular function. Although other scoring systems, such as the Braunwald, NYHA or CCS classification could be used to assess angina status; whilst the EuroSCORE and Parsonnet score could be used to assess the patient history, comorbidities, pulmonary and cardiovascular function<sup>4,5</sup>, there was no available comprehensive score to describe – in detail – the coronary anatomy. Therefore, the SYNTAX™ score has been designed to better anticipate the risks of percutaneous or surgical revascularisation, taking into account the functional impact of the coronary circulation with all its anatomic components, including bifurcations, total occlusions, thrombus, calcification, small vessels etc. The SYNTAX™ score was not initially devised to predict short or long term prognosis, but was a score designed to allow a detailed objective assessment, and therefore comparison of the coronary anatomy between one patient and another. During the heart-team conference, the calculation of the SYNTAX™ score became pivotal in the selection of the revascularisation strategy. As a result of the heart-team conference the population was subdivided into three groups: patients judged to be only eligible for cardiac surgery, patients eligible for PCI, and patients potentially amenable to both types of revascularisation. In designing the SYNTAX™ score, the authors' selected six pre-

existing classifications or scores to create a complex algorithm, mixing anatomical and functional characteristics that might increase the risk and complexity of percutaneous or surgical treatment. (see appendix – online as supplementary data at [www.eurointervention.org](http://www.eurointervention.org)) At the time of the design, it was not known whether the complexity of the coronary anatomy, as described by the score, would have an impact on the outcome of surgery. The purpose of the present paper is to describe the baseline assessment of the SYNTAX™ score, the corelab reproducibility, the potential difference in the score assessment between the investigator and the corelab, and to ascertain the impact of the score on the short- and long-term outcome of PCI and coronary artery bypass graft surgery (CABG). At the time it was designed it was anticipated that the prospective, blind, raw SYNTAX™ score would be retrospectively weighted, based on the short- and long-term outcomes of the Syntax trial.

## Methods

### The Syntax trial

The design of the Syntax trial has been described in detail elsewhere<sup>6</sup>. Between March 2005 and April 2007, 4337 patients were screened leading to randomisation of 1,800 patients with LM and/or 3VD to CABG (n=897) or PCI with TAXUS Express2 (n=903) at one of 23 sites in the US (n=245) and 62 sites in Europe (n=1555). Almost 30% of screened patients were found to be amenable for only one treatment option and were enrolled in either the CABG (n=1077) or PCI (n=198) nested registries, while 9.4% of patients were not willing to participate or had a treatment preference.

### Assessment of coronary angiograms

To assess the reliability of Syntax scoring, we randomly selected 100 diagnostic angiograms from the Syntax trial. All the angiographic variables pertinent to calculating the SYNTAX™ score were obtained by reviewing the diagnostic angiograms acquired before the procedure. Those films were assessed independently by two corelab technicians who were blinded to the clinical baseline characteristics, procedural data and clinical outcomes. In case of disagreement, the opinion of the third observer, a supervising cardiologist, was obtained and the final decision was made by consensus. To assess intra-observer variability, 91 sets of angiograms were analysed at least eight weeks later by one additional observer who remained blinded to the results of the first analysis.

### SYNTAX™ score and angiographic analysis

Each coronary lesion producing >50% luminal obstruction lumen in vessels  $\geq 1.5$  mm was separately scored and summated to provide the overall SYNTAX™ score which was calculated using dedicated software that integrates (a) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al<sup>7</sup>, and (b) the morphologic features of each single lesion, as reported in the appendix. An example of SYNTAX™ score calculation in one subject is shown in Figure 1.

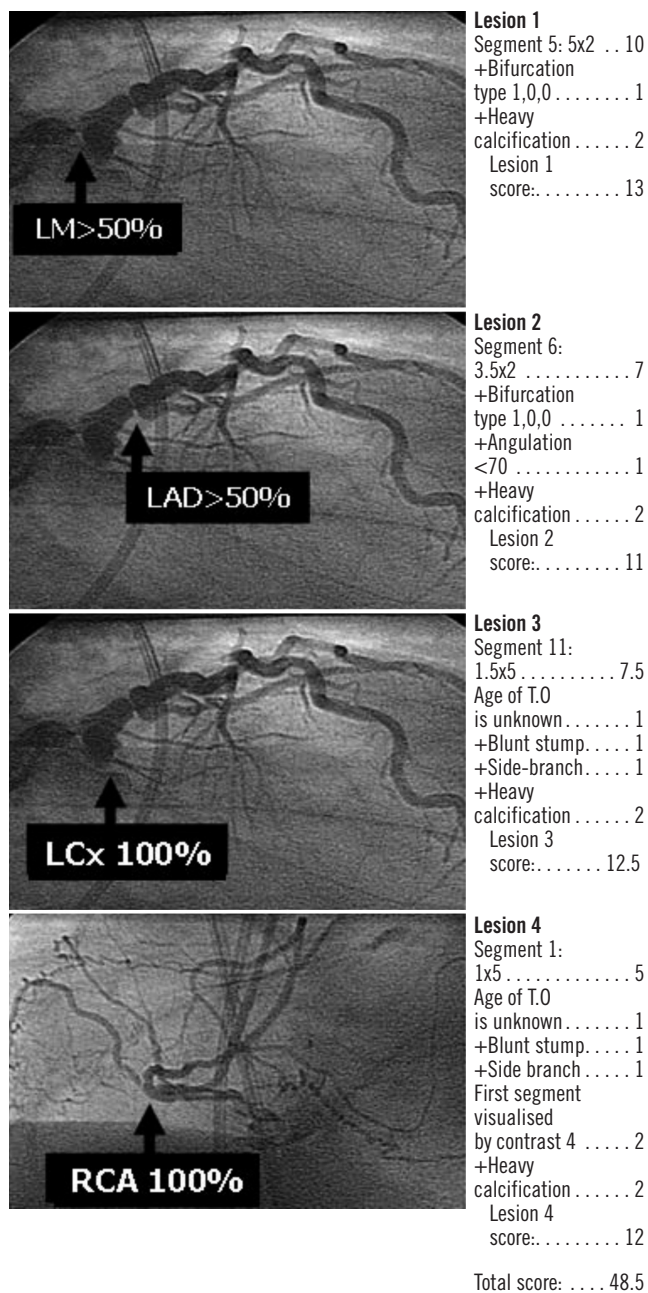


Figure 1. An example of Syntax scoring.

### Statistical analysis

The degree of agreement was measured as a weighted kappa statistics that reflect the agreement between two or more observations using weight to quantify the relative difference between categories<sup>8,12</sup>. It is usual to consider kappa values greater than 0.75 to represent excellent agreement beyond chance; values below 0.40 to represent a poor agreement beyond chance, and values between 0.40 and 0.75 to represent fair to good agreement beyond chance. The reproducibility of Syntax scoring was evaluated by calculating the intra-observer and inter-observer variability, which was defined as the difference between the corresponding measurements expressed as a percent of their mean. All variables were expressed as mean±standard deviation or median and range. A 2-tailed P value of <0.05 was considered to indicate statistical significance. The incidence of events over time was studied with the use of the Kaplan-Meier method, whilst log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

### Results

#### Corelab reproducibility

At the corelab, the value of the first measurement was, on average, 30.3 versus 29.2 for the second measurement, with an SD of 11.5 and 11.3, respectively. The mean of the differences (measure of precision) was 2.1 with a SD of 9.1 (measure of accuracy), which reflects the core laboratory inter-observer variability. As shown in Table 1, the weighted kappa value for the observations of the global score was 0.45, while the weighted kappa value for the number of lesions was 0.59. The values of weighted kappa was 0.82 for the diagnosis of total occlusions, 0.41 for bifurcation lesions and 0.63 for ostial lesions. Inconsistency in the scoring was mainly due to the presence of lesions in small vessels and at bifurcations. The weighted kappa for tertile partitioning of Syntax score (0-22, 23-32, 33-) was 0.52. Table 2 represents the weighted kappa values for intra-observer reproducibility. The weighted kappa value for the global score was 0.59, while the weighted kappa value for the number of lesions, total occlusions and bifurcation lesions was 0.71, 0.85 and 0.68, respectively. The weighted kappa for tertile partitioning of Syntax™ score (0-22, 23-32, 33-) was 0.61.

Table 1. Inter-observer reproducibility.

		Total SYNTAX™ score in classes of 10							
		Observer 2							
Observer 1	Frequency	0-10	11-20	21-30	31-40	41-50	51-60	61-70	Total
Observer 1	0-10	3	0	0	0	0	0	0	3
	11-20	0	9	2	2	0	0	0	13
	21-30	0	6	18	11	1	1	0	37
	31-40	0	1	14	9	1	2	0	27
	41-50	0	1	2	7	4	1	0	15
	51-60	0	0	1	1	1	0	0	3
	61-70	0	0	0	0	0	0	2	2
	Total	3	17	37	30	7	4	2	100

K=0.45 (SE 0.072). The inter-observer difference in SYNTAX™ score calculation at the corelab when the scores are sub-divided into categories of 10 points (0-10, 11-20).

**Table 2. Intra-observer reproducibility.**

Frequency	Total SYNTAX™ score in classes of 10							Total
	0-10	11-20	21-30	31-40	41-50	51-60	71-80	
0-10	0	1	0	0	0	0	0	1
11-20	2	24	11	2	0	0	0	39
21-30	0	6	19	4	0	0	0	29
31-40	0	1	4	5	2	0	0	12
41-50	0	1	1	1	3	2	0	8
51-60	0	0	0	0	0	1	0	1
71-80	0	0	0	0	0	0	1	1
Total	2	33	35	12	5	3	1	91

K=0.59 (SE 0.069). The intra-observer difference in SYNTAX™ score calculation at the corelab when the scores are sub-divided into categories of 10 points (0-10, 11-20)

## SYNTAX™ score – corelab scoring vs on-site scoring

Figure 2 shows the SYNTAX™ score in the CABG registry, the randomised cohorts and the PCI registry; average values as well as ranges are shown for the corelab and the site. The following observations can be made from these data: 1) the CABG registry has the highest score (37.8±13.3), the second highest group is the PCI registry with an average score of 31.6±12.3, whilst the randomised cohorts had intermediate scores of around 28-29, almost 10 points below the level of the CABG registry; 2) the investigators consistently underscored the corelab score by 3.4 points; 3) as expected by design, the score in the two randomised cohorts are comparable, (29.1±9.1 for CABG vs. 28.4± for PCI cohort, p=0.19).

## SYNTAX™ score according to treatment groups

Figure 3 shows the distribution of the SYNTAX™ score in the PCI registry, the CABG registry and the cohort randomised to surgery or PCI. The score distribution in these different subgroups is more or less Gaussian. The Gaussian curves of the SYNTAX™ score for patients randomised to CABG and PCI are almost superimposable. The distribution of the score for the PCI registry is shifted rightward

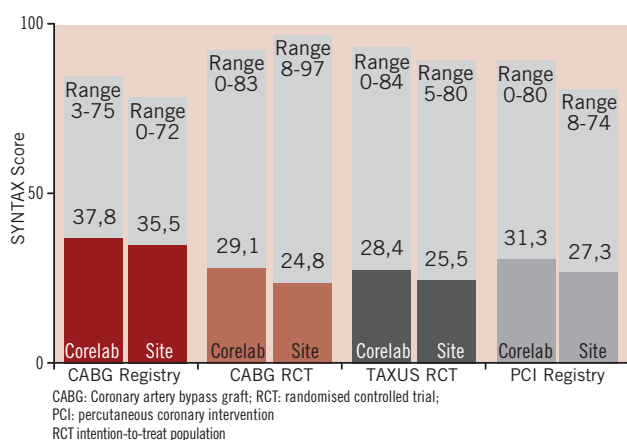


Figure 2. Bar graph of raw SYNTAX™ scores in each cohort of the Syntax trial: a comparison between Corelab assessment and site reporting. CABG: coronary artery bypass graft; RCT: randomised controlled trial; PCI: percutaneous coronary intervention.

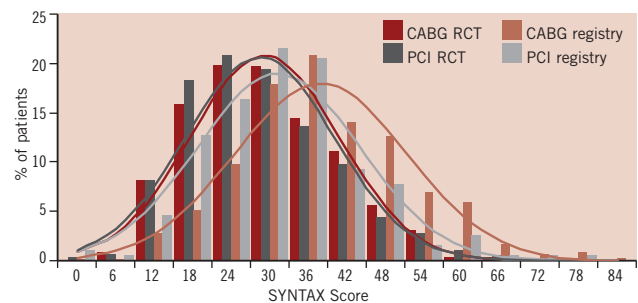


Figure 3. SYNTAX™ score distribution in the registries and in the randomised cohorts.

with a mean value of 31.6±12.3, and the distribution of the SYNTAX™ score in the CABG registry is shifted even further to the right with a peak value of 37.8±33.3. When the scores of the randomised patients were divided into tertiles, the upper boundary of the lowest tertile is 22, the second tertile ranges from 23 to 32, and the lower boundary for the highest tertile is equal or greater than 33.

## SYNTAX™ score and outcome at one year

As previously reported<sup>6</sup> – and demonstrated in Figure 4A and 4B – there was no difference in outcome amongst patients randomised to surgery between those who had low, intermediate or high scores; the major adverse cardiovascular and cerebrovascular event (MACCE) rates at one year was 14.4%, 11.7% and 10.7% for low, intermediate and high scores respectively (p=0.38). In those randomised to PCI there is a significant separation (log rank p value 0.007) of the cumulative event rate curves between patients with low, intermediate and high scores; with respective MACCE rates at 12 months of 13.5%, 16.6%, and 23.3%.

These data would suggest that patients with a low SYNTAX™ score, regardless of the presence of left main stem or 3-vessel disease, have comparable outcomes after revascularisation with PCI or CABG (Figure 5A-C); furthermore, the MACCE rate in this SYNTAX™ score cohort is not influenced by diabetic status<sup>9</sup>. Therefore, the selected revascularisation strategy in this group of patients will depend on individual patient characteristics, patient preference and the physician choice.

Patients with 3-vessel disease and intermediate SYNTAX™ scores had, irrespective of their diabetic status, a higher MACCE rate



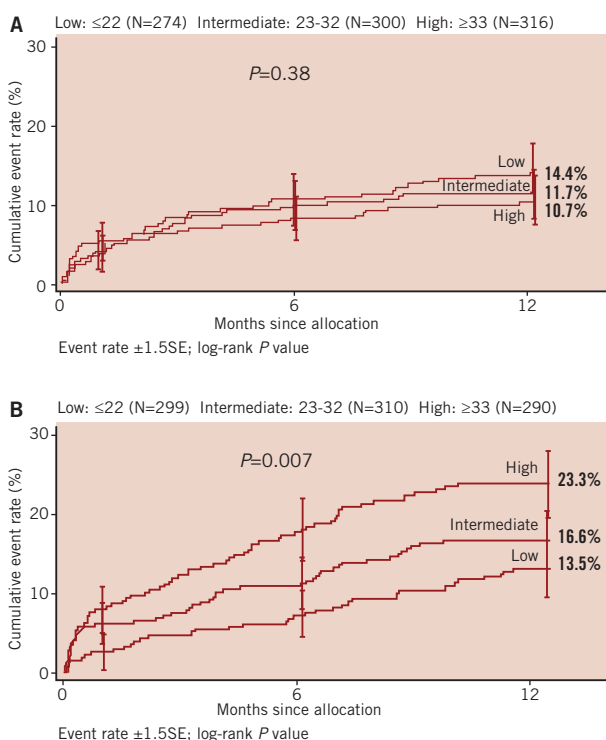


Figure 4A. Kaplan-Meier estimates of MACCE rate up to 12 months in the cohort randomised to CABG treatment stratified by tertile of SYNTAX™ score. There are no statistically significant differences between the 3 curves (p=0.38). Figure 4B. Kaplan-Meier estimates of MACCE rate to 12 months in the cohort randomised to PCI treatment stratified by tertile of SYNTAX™ score. Each curve separates at 12 months with statistical significance by log-rank test (p=0.007).

following PCI than after bypass surgery<sup>6,9</sup>. Ultimately, the final selection of treatment in this group will depend on patient characteristics and comorbidity; however, PCI remains a valid option for those patients with left main disease who do not have diabetes. (Figure 5 B and 6) The MACCE rate in patients with high scores (≥33), with or without diabetes, is significantly higher in patients having PCI compared to CABG, and therefore it is inferred that PCI typically is limited by a higher repeat revascularisation rate and might be considered as surgical candidates.(Figure 5C)

## Discussion

The present report underscores the important prognostic value of the SYNTAX™ score. When the general principles of analysis (i.e. the heart-team decision, SYNTAX™ score, and diabetic status) are applied to the entire enrolled population (n=3,075), it appears that numerically one-third of all the patients could reasonably be treated by PCI, whilst two-thirds of the patients might be referred to surgery, with the caveat that the present assessment is based on the result of one-year outcome. It has been repeatedly demonstrated that Kaplan Meier curves related to the outcome of surgery or PCI diverge with time, and based on the 5-year outcome the current partition in surgical and PCI candidates might be reviewed more conservatively in the near future<sup>3,10,11</sup>. This conclusion is based on the prospective, and thus blind and unbiased, evaluation of the

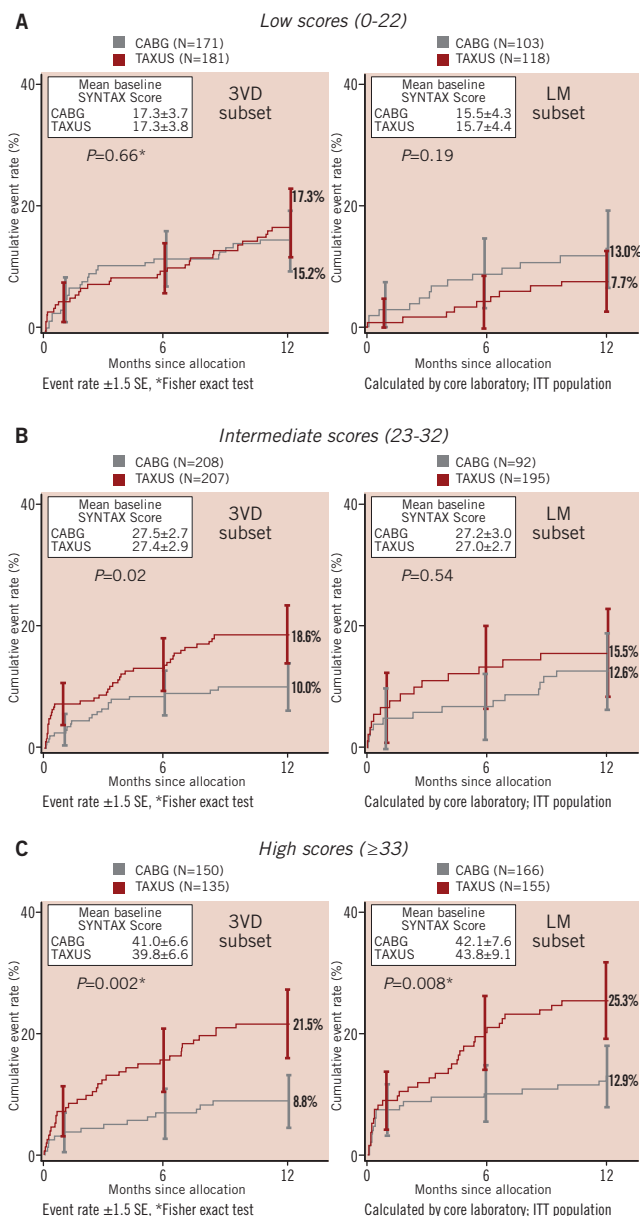


Figure 5A-C show side-by-side Kaplan-Meier curves for patients either with left main or in patients with 3-vessel disease, according to the tertiles of the SYNTAX™ score in the overall population.

SYNTAX™ score prior to randomisation by a blinded corelab who were unaware of the clinical status of the patient. Overall, in the registries and in the randomised cohorts, the evaluation of the score by the corelab was somewhat more stringent, and the score was numerically higher than those calculated by the participating site. The critical question remains as to whether this potentially powerful prognostic index, at least for PCI, is a reproducible parameter. As with any visual and categorical parameter, reproducibility should be assessed by Kappa statistics. In the present study, the Kappa parameters for inter- and intra-observer reproducibility of the global SYNTAX™ score were superior to 0.40 but inferior to 0.70, which indicate fair to good agreement<sup>8</sup>; obviously there is room for improvement. The reproducibility of the score in the future will likely improve with the quality of angiography,

the standardisation of the angiographic views acquired during diagnostic imaging, the provision of a SYNTAX™ score tutorial with examples based on real images, operator training, the use of objectively quantified parameters (e.g. stenosis, severity and length), consensus between highly qualified observers (technician or interventional cardiologist) and user-friendly software facilitating on-line correction. In addition, taking into account the fact that angiograms performed in the SYNTAX trial and registry may have been of higher quality than in the routine clinical practice, it would be very important to evaluate the reproducibility of SYNTAX score in a “real world” practice.

Kappa statistics are a generally accepted method of evaluating agreement between observers and are most useful when observations are frequent and have a Gaussian distribution (Figure 3). It is well known that visual estimates of lesion characteristics are less accurate in comparison to quantitatively derived parameters, as has been demonstrated in previously conducted variability and quality control studies. Beauman and Vogel<sup>12</sup> compared visual estimations of lesion severity, to quantitative analyses of percent diameter stenosis of coronary and phantom obstructions. Quantitatively assessed coronary arteries comprising a 50% diameter stenosis and 50% phantom stenosis recordings were visually scored in ranges from 15 to 80 percent, and 30 to 95 percent respectively. Determination of the reference diameter showed that only 41% of the estimations were within 10 % of the range of the quantitatively derived diameter.

Another study in 50 lesions<sup>13</sup> reported an inter-observer agreement of 73% for stenosis length (defined as the length of that portion of the stenosis that had a >30% reduction in luminal diameter using the adjacent normal vessel diameter as a ‘yardstick’ or unit) and 64% for lesion eccentricity (defined as asymmetrically positioning in one or more views), resulting in kappa values of respectively 0.38 and 0.25. The Cardialysis corelab in 1993 reported<sup>14</sup> the level of agreement in inter-observer observation made on 151 lesions: 79 % for lesion eccentricity, 71% for branch point involvement, 86% for location in a bend, 98% for presence of thrombus, 90% for presence of calcification and 75 % for the lesion type according to the ACC / AHA classification. These results were largely confirmed in a second evaluation reported in 1996<sup>15</sup>. Another study of 403 coronary lesions using the kappa statistics showed an excellent agreement for type C lesions ( $k=0.85$ ); good agreement for TIMI flow ( $k=0.73$ ), ABC classification ( $k=0.48$ ), angulation ( $k=0.48$ ) and side branch ( $k=0.40$ ); and poor agreement for eccentricity, tortuosity, lesion calcification, and in the distinction of discrete, diffuse and tubular lesion length. The SYNTAX™ score analysed in its constituent components largely confirmed the results previously reported.

An issue of essential relevance, which contributes to the poor agreement within and between investigators, is a clear description of the definitions of lesion characteristics being assessed. Length of lesion can be interpreted, for example, as the length of plaque related to the pre-defined size of the catheter on the image. An alternative definition is the length where the lumen diameter has a stenosis > 70%, or >50%, or >30%. This can then be expressed in absolute diameters, or in terms of normal lumen diameter ratio. Lesion length can also be defined as the calliper measurement of

the distance from the proximal to the distal shoulder of the lesion in the projection that best elongates the stenosis. For the SYNTAX™ score <10 and >20 mm were deliberately chosen as cut-off points for lesion length because these leave the least room for variation in interpretation.

A panel assessment gives a substantial improvement in inter- and intra-observer agreement. It is clear that the weighted sum of several simultaneous observations eliminates the most extreme disagreements, whereas the assessor working in isolation can develop his own interpretation and thus deviate from the original definitions. Serial observations as in pre-readings, with knowledge of the results of the first observer’s judgement, may result in higher kappa values for qualitatively assessed lesion characteristics. The mechanism of improved agreement in case of pre-reading, however, differs from improved agreement following panel assessment. In serial readings, the first assessment is dominant and respected by the second reviewer, who tends to comply, resulting in an improved outcome. So far the assessment of the SYNTAX™ score, as a prognostic index, has been only reported in the ARTS-II registry. Valgimigli et al<sup>16</sup> specifically divided the population with 3-vessel disease in tertiles according to SYNTAX™ score and reported the outcome separately. It is noticeable that the MACCE rate in the highest tertile of the ARTS-II trial (SYNTAX™ score >26) at one year is 21.5%, which is identical to the MACCE rate observed in the highest tertile of the Syntax trial (SYNTAX™ score  $\geq 33$ ) in the subgroup of the 3-vessel disease (Figure 5C).

In the Syntax study, and in the subgroups of patients with 3-vessel disease and/or left main disease, the prognostic value of the SYNTAX™ score is even more significant. Irrespective of their diabetic status, the one-year outcome of all patients with left main and/ or 3-vessel disease with a SYNTAX™ score less than 22 was comparable between those randomised to PCI or surgery<sup>6</sup>. Patients with 3-vessel disease with intermediate or high scores, with or without diabetes, had significantly lower repeat revascularisation rates with surgical revascularisation than with percutaneous treatment. However, non-diabetic patients with an intermediate score and a left-main lesion (isolated or not) have an excellent outcome with PCI when compared to surgery. The take-home message is that in an all-comer population of left-main and 3-vessel disease, numerically one-third of these patients could be legitimately treated by PCI and that two thirds of patients might be referred to surgery. This initial assessment will have to be re-evaluated after medium-term follow-up out to five years. In addition, the cut-off of low, intermediate and high Syntax score classification should be further standardised and re-evaluated in the other cohort to establish robustness of this scoring system in prediction of outcomes. Finally, we should emphasise that the analysis of the outcome was related to the raw data of the score which was based on an arbitrary ranking of the complexity of the lesions. The impact of certain anatomic parameters (tortuosity, ostial lesion etc.) on predicted outcome may have been overestimated or underestimated and should be re-evaluated on the basis of the actual outcome at one year. The process of simplifying and weighting the SYNTAX™ score will be a retrospective exercise, based on complex statistical analysis, and will again need to be prospectively tested on a

different patient population. It might be more straight-forward to combine a prognostic index of mortality such as the EuroSCORE, with the descriptive coronary score of the Syntax trial, to provide more accurate risk assessment on the outcome.

The data presented in this report are the result of post-hoc subgroup analyses. It was based on a tertile division of the entire study population with the partitioning criteria being subsequently applied to subgroups of patients with either main stem or 3-vessel disease. None of the subgroup analyses (with SYNTAX™ score tertile defined a posteriori) were prespecified or statistically powered. It should be emphasised that the global hierarchical statistical hypothesis of non-inferiority of PCI as compared to surgery for treatment of left main and/ or 3-vessel disease was not confirmed; therefore, the observational data provided in the present report are hypothesis generating, and should be further validated in order to be formally incorporated in guidelines on appropriateness of revascularisation for left main or 3-vessel disease<sup>17</sup>.

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## Appendix

### Pre-existing classifications

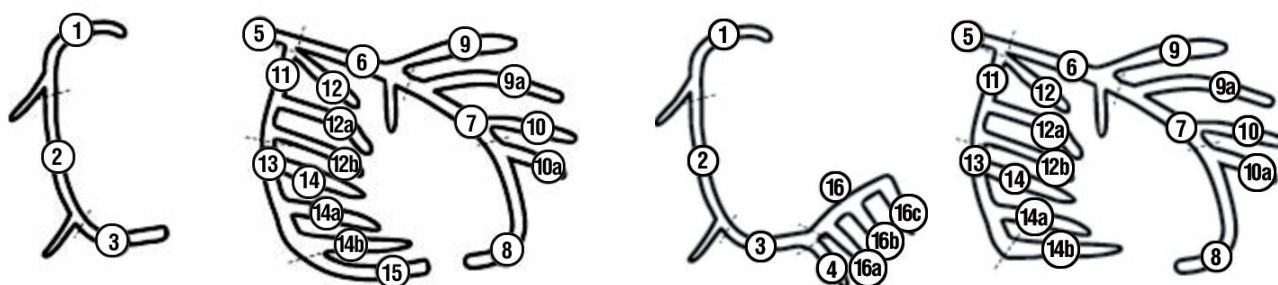
The SYNTAX score has been developed based on the following:

1. The AHA classification of the coronary tree segments modified for the ARTS study
2. The Leaman score
3. The ACC/AHA lesions classification system
4. The total occlusion classification system
5. The Medina classification bifurcation lesions
6. Consultation of experts

Each of these classifications has focused on the specific functional and anatomical parameters of the lesion. Thus it was necessary to develop a global classification system that would take into account all the variables.

### Definition of the coronary tree segments

The definition of the coronary tree segments is based on the classification proposed by the AHA and modified for the ARTS I and II trials<sup>1,2</sup>. This system divided the arterial tree into 16 segments (Figure 1) and this has been adopted in the SYNTAX score.



Left  
Figure 1.

### Leaman score<sup>3</sup>

The iLeaman score<sup>3</sup> is based on the severity of luminal diameter narrowing and weighed according to the usual blood flow to the left ventricle in each vessel or vessel segment. In a right dominant system, the right coronary artery (RCA) supplies approximately 16%, and the left coronary artery (LCA) 84% of the flow to the left ventricle (LV). This 84% is normally directed for 66% to the left anterior descending artery (LAD), and for 33% into the left circumflex coronary artery (LCX). Thus, the Left Main (LM) supplies approximately five times, the LAD approximately 3.5 times ( $84/16 \times 0.66$ ), and the circumflex 1.5 times as much blood as the RCA to the LV. In a left dominant system the RCA does not contribute to the blood supply of the ventricle. Thus the LM supplies 100% of the flow to the LV. The RCA contribution of blood flow to the LV is now supplied by the LCX. Hence the LAD provides 58% (weighing factor 3.5) and the LCX 42% (weighing factor 2.5) of the total flow to the LV. Using the same principle of relative blood supply to the LV, all coronary segments have been given a weighing factor, Table 1. The contribution of each coronary segment to the blood flow to the LV is used as a multiplication factor for the calculation of the Leaman score and as such has been transferred to the SYNTAX score.

1. RCA proximal: From the ostium to one half the distance to the acute margin of the heart.
2. RCA mid: From the end of first segment to acute margin of heart.
3. RCA distal: From the acute margin of the heart to the origin of the posterior descending artery.
4. Posterior descending artery: Running in the posterior interventricular groove.
16. Posterolateral branch from RCA: Posterolateral branch originating from the distal coronary artery distal to the crux.
- 16a. Posterolateral branch from RCA: First posterolateral branch from segment 16.
- 16b. Posterolateral branch from RCA: Second posterolateral branch from segment 16.
- 16c. Posterolateral branch from RCA: Third posterolateral branch from segment 16.
5. Left main: From the ostium of the LCA through bifurcation into left anterior descending and left circumflex branches.
6. LAD proximal: Proximal to and including first major septal branch.
7. LAD mid: LAD immediately distal to origin of first septal branch and extending to the point where LAD forms an angle (RAO view). If this angle is not identifiable this segment ends at one half the distance from the first septal to the apex of the heart.
8. LAD apical: Terminal portion of LAD, beginning at the end of previous segment and extending to or beyond the apex.
9. First diagonal: The first diagonal originating from segment 6 or 7.
- 9a. First diagonal a: Additional first diagonal originating from segment 6 or 7, before segment 8.
10. Second diagonal: Originating from segment 8 or the transition between segment 7 and 8.
- 10a. Second diagonal a: Additional second diagonal originating from segment 8.
11. Proximal circumflex artery: Main stem of circumflex from its origin of left main and including origin of first obtuse marginal branch.
12. Intermediate/anterolateral artery: Branch from trifurcating left main other than proximal LAD or LCX. It belongs to the circumflex territory.
- 12a. Obtuse marginal a: First side branch of circumflex running in general to the area of obtuse margin of the heart.
- 12b. Obtuse marginal b: Second additional branch of circumflex running in the same direction as 12.
13. Distal circumflex artery: The stem of the circumflex distal to the origin of the most distal obtuse marginal branch, and running along the posterior left atrioventricular groove. Calibre may be small or artery absent.
14. Left posterolateral: Running to the posterolateral surface of the left ventricle. May be absent or a division of obtuse marginal branch.
- 14a. Left posterolateral a: Distal from 14 and running in the same direction.
- 14b. Left posterolateral b: Distal from 14 and 14 a and running in the same direction.
15. Posterior descending: Most distal part of dominant left circumflex when present. It gives origin to septal branches. When this artery is present, segment 4 is usually absent.



**Table 1. Segment weighing factors.**

Segment No		Right dominance	Left dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	n.a.
16	Posterolateral branch from RCA	0.5	n.a.
16a	Posterolateral branch from RCA	0.5	n.a.
16b	Posterolateral branch from RCA	0.5	n.a.
16c	Posterolateral branch from RCA	0.5	n.a.
5	Left Main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9a	First diagonal	1	1
10	Second diagonal	0.5	0.5
10a	Second diagonal	0.5	0.5
11	Proximal circumflex artery	1.5	2.5
12	Intermediate/ anterolateral artery	1	1
12a	Obtuse marginal	1	1
12b	Obtuse marginal	1	1
13	Distal circumflex artery	0.5	1.5
14	Left posterolateral	0.5	1
14a	Left posterolateral	0.5	1
14b	Left posterolateral	0.5	1
15	Posterior descending	n.a.	1

### Lesion definition

A coronary lesion with a diameter stenosis >50% in a vessel  $\geq 1.5$  mm is significant, and must be scored. A lesion can involve one or more diseased segments. Less severe lesions should not be included in the SYNTAX score. The percent diameter stenosis is not considered in the algorithm. Distinction has been made only between occlusive (100% diameter stenosis) and non occlusive (50-99% diameter stenosis) disease. A multiplication factor of 2 is used for non-occlusive lesions, and 5 for occlusive lesions reflecting the difficulty of percutaneous treatment, Table 1. Importantly, all other adverse lesion characteristics considered in the SYNTAX score have an additive value, Table 2.

### Multiple stenoses

If serial stenoses are less than three reference vessel diameters apart, they should be scored as one lesion. However, stenoses at a greater distance from each other (more than three reference vessel diameters), are considered as separate lesions.

### ACC/AHA lesion classification system<sup>4,5</sup>

This lesion classification system is based on parameters, such as length, eccentricity, angulation, calcification, involvement of side branches and thrombus. Lesions are classified as Type A, (high success and low risk), Type B (moderate success and moderate risk) or Type C (low success and high risk). The majority of these individual parameters have been incorporated in the SYNTAX score (Table 2). Although the ACC/AHA system takes into account total

**Table 2. Lesions adverse characteristic scoring.**

Diameter reduction (*)		
- Total occlusion	x5	
- Significant lesion (50-99%)	x2	
Total occlusion (TO)		
- Age >3months or unknown	+1	
- Blunt stump	+1	
- Bridging	+1	
- First segment visible beyond TO (**)+1/ per non-visible segment		
- Side branch (SB) - Yes, SB <1.5 mm	+1	
- Yes, SB $\geq 1.5$ mm	+1	
Trifurcations		
- 1 diseased segment	+3	
- 2 diseased segments	+4	
- 3 diseased segments	+5	
- 4 diseased segments	+6	
Bifurcations		
- Type 100, 010, 110	+1	
- Type 111, 101, 011, 001	+2	
- Angulation <70°	+1	
Aorto-ostial stenosis		+1
Severe tortuosity		+2
Length > 20 mm		+1
Heavy calcification		+2
Thrombus		+1
"Diffuse disease"/small vessels		+1/ per segment number

x: multiplication; +: addition; (\*) In the SYNTAX algorithm there is no question for % luminal diameter reduction. The lesions are considered as significant (50-99% luminal diameter reduction) or occlusive (100%). (\*\*) Please see figure 2

occlusions and bifurcation lesions, classifying them as a high-risk, this is not considered to be detailed enough to adequately quantify their complexity.

### Total occlusion classification system<sup>6</sup>

A lesion is defined as a total occlusion when no intra-luminal antegrade flow (TIMI 0) is visible distal to the point of occlusion. Segments distal to the occlusion may be filled by bridging, ipsilateral or contra-lateral collaterals. Parameters suggested in this system such as an occlusion older than three months; the presence of a side branch at the site of the occlusion and its size; a blunt stump; the presence of bridging collaterals, and occlusion length have all been incorporated into the SYNTAX score, Table 2. The length of the obstructed segment is calculated by measuring the distance between the stump of the occlusion and the first segment beyond the occlusion, visualised by ante-grade or retrograde collateral flow, Figure 2. The age of the total occlusion is scored based on a history of previous myocardial infarction, worsening symptoms, or previous angiographic or electrocardiographic data. In cases where this information is absent the age of total occlusion is scored as unknown.

### Trifurcation lesions

Trifurcation is the division of a main branch into three branches (with a minimal diameter of 1.5 mm). In a trifurcation, one, two, three or four of the involved segments can be significantly diseased. The most common example of a trifurcation is at the division of LM

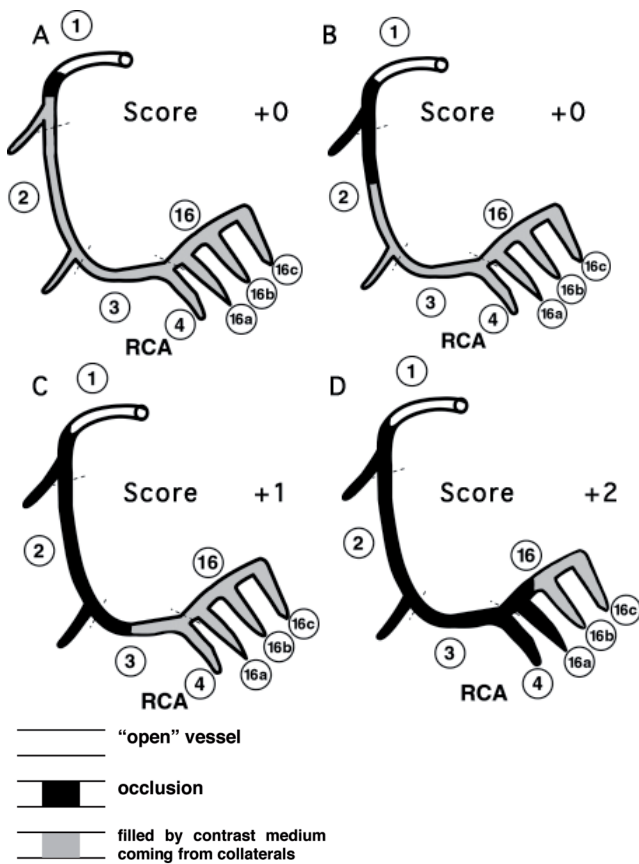


Figure 2. Total occlusion length assessment.

- A) Total occlusion involving segments 1. Segments 1, 2, 3, 4, 16, 16a, 16b, 16c are filled by antegrade or retrograde collateral flow (visualised by contrast). No points are added to the score.
- B) Total occlusion involving segments 1 and 2. Segments 2, 3, 4, 16, 16a, 16b, 16c are filled by antegrade or retrograde collateral flow (visualised by contrast). No points are added to the score.
- C) Total occlusion involving segments 1, 2 and 3. Segments 3, 4, 16, 16a, 16b, 16c are filled by antegrade or retrograde collateral flow (visualised by contrast). One point is added to the score.
- D) Total occlusion involving segments 1, 2, 3 and 4. Segments 16, 16a, 16b and 16c are visualised by antegrade or retrograde collateral flow (visualised by contrast). Three points are added to the score.

into the LAD, LCX, and an intermediate branch. Trifurcations are only scored for the following segment junctions: 3/4/16/16a, 5/6/11/12, 11/12a/12b/13, 6/7/9/9a and 7/8/10/10a, Table 2.

**Bifurcation lesions and the Medina classification system<sup>7</sup>**

A bifurcation is defined as the division of a main, parent, branch into two daughter branches (each with a minimal diameter of 1.5mm). Bifurcation lesions may involve the proximal main vessel, the distal main vessel and the side branch and are classified according to the Medina classification. The smaller of the two daughter branches should be designated as the 'side branch'. In cases of a left main stem lesion, either the LCX or the LAD can be designated as the side branch, depending on their respective calibres. Only those lesions in direct contact with the bifurcation should be scored.

Bifurcation lesions not involving the ostium of the side branch are classified as type 1,0,0 if the lesion in the main vessel is proximal to the

bifurcation; type 0,1,0 if the lesion in the main branch is distal to the bifurcation, and type 1,1,0 if the lesion in the main branch lies both proximal and distal to the side branch. Bifurcation lesions involving the ostium of the side branch are classified as type 1,0,1 if the lesion in the main branch is proximal to the bifurcation; type 0,1,1 if the lesion in the main branch is distal to the bifurcation, and type 1,1,1 if the main branch lesion lies both proximal and distal to the side branch. As plaque shift can occur even when only the ostium of a side branch is narrowed, such a lesion is also considered as a bifurcation (type 0,0,1) (Figure 3). Bifurcations are only considered for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a and 3/4/16 and 13/14/15 in case of left dominance.

One lesion characteristic added to the bifurcation lesion classification is an angulation between the side branch and the distal main vessel of less than 70 degrees. Despite the fact that this represents a less technical challenge, it is regarded as an adverse lesion characteristic due to the fact that the smaller this angle is the more difficult it will be to cover the ostium of the side branch when stenting is necessary, Figure 4.

**Aorto-ostial lesions**

A lesion is classified as aorto-ostial when it is located immediately at the origin of the coronary arteries from the aorta. It applies only to segments 1 and 5. In case of an absent LM (double ostium of the Left Coronary Artery), segment 6 of the LAD and 11 of the LCX originate directly from the aorta, and consequently may also involve aorto-ostial lesions. An aorto-ostial location is regarded as an adverse characteristic because the treatment of such lesions is technically more challenging.

**Diffuse disease/small vessels**

This characteristic is present when at least 75% of the length of any segment(s) proximal to the lesion, at the site of the lesion or distal to the lesion has a vessel diameter of  $\leq 2$  mm.

Diffuse disease/small vessels is the last question of the algorithm and is the only non-lesion specific question. This question pertains to all the segments of that targeted vascular territory (either LAD and its branches, or LCX and its branches, or RCA and its branches) provided

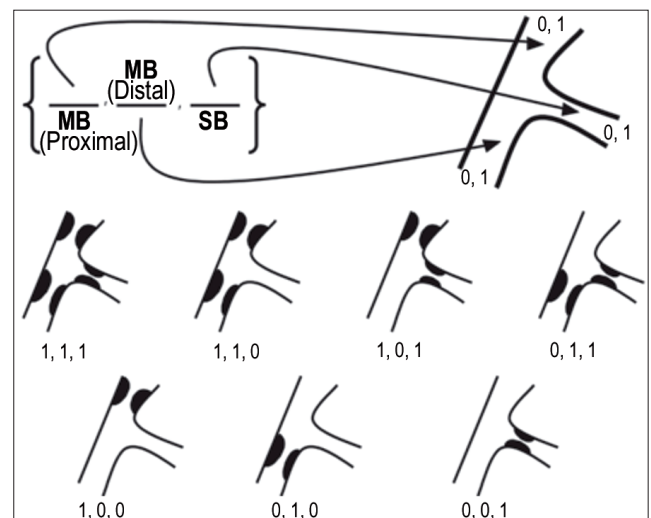
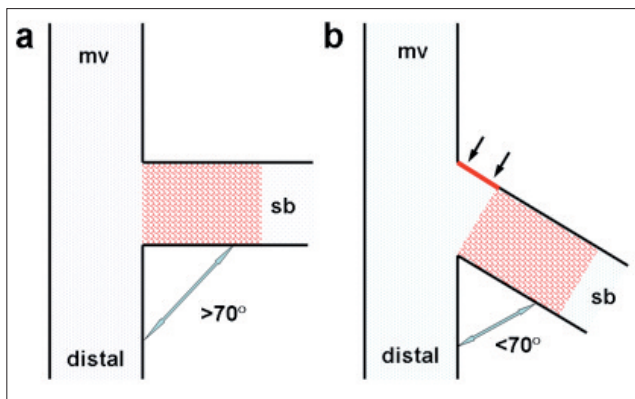


Figure 3. Bifurcation classification (according to MEDINA classification).



**Figure 4.** a) An example of a bifurcation lesion with a wide angle ( $>70$  degrees) between the side branch and the distal main vessel. Although technically challenging sometimes, the stent can fully cover both the proximal and distal rims of the side branch ostium. b) An example of a bifurcation with a steep angle ( $<70$  degrees) between the side branch and the distal main vessel. Side branch stenting might be technically less challenging compared to the previous anatomy but when the stent is placed to cover the distal rim of the ostium the proximal rim will remain uncovered (red line with arrows). If the stent is placed to cover the proximal rim it will protrude into the main vessel distally. mv denotes main vessel, sb denotes side branch

this vascular territory exhibits at least one lesion. This question will appear only once per vascular territory after the assessor has described for the final time a stenotic lesion in that vascular territory. For example, if a patient has a lesion in the RCA located in segment 1 the assessor will be asked to characterise the diffuse/small appearance of all the segments of the RCA vascular territory (1, 2, 3, 4, 16, 16a, 16b, 16c). This will occur only after indicating that no other coronary lesions need to be scored within the RCA vascular territory.

### The SYNTAX score algorithm (Table 3)

The SYNTAX score is calculated by a computer program consisting of sequential and interactive self-guided questions. The algorithm consists of twelve main questions. They can be divided in two groups: The first three determine the dominance, the total number of lesions and the vessel segments diseased per lesion and they appear once. The maximum number of lesions allowed is twelve and each lesion is characterised by a number, 1 to 12. Each lesion can involve one or more diseased segments. In this case each vessel segment involved contributes to the lesion scoring. There is no limit in the number of segments involved per lesion. The last nine questions refer to adverse lesion characteristics and are repeated for each lesion. The question referring to a total occlusion is the first one. If a total occlusion is scored, answers must be given to detailed sub-questions. The last of these sub-questions refers to the presence or absence of side branches and their size. If there are no side branches or if their diameter is  $<1.5$  mm then the questions related to the trifurcation and bifurcation lesions will be automatically skipped since vessels  $<1.5$  mm are not considered large enough for treatment either with PCI or CABG. If side branches with diameter  $\geq 1.5$  mm are involved then the lesion is considered as both total occlusion and bifurcation lesion and the algorithm will continue with all the questions. The same is the case for non-occlusive lesions.

**Table 3. The SYNTAX score algorithm.**

1. Dominance	
2. Number of lesions	
3. Segments involved per lesion	
Lesion characteristics	
4. 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
5. Trifurcation	i. Number of segments diseased
6. Bifurcation	i. Type ii. Angulation between the distal main vessel and the side branch $<70^\circ$
7. Aorto-ostial lesion	
8. Severe tortuosity	
9. Length $>20$ mm	
10. Heavy calcification	
11. Thrombus	
12. Diffuse disease/ small vessels	i. Number of segments with diffuse disease/small vessels

The SYNTAX score is calculated by a computer program consisting of sequential and interactive self-guided questions. All the below mentioned definitions are projected in a side window when the signal (i) indicating information, available for each question, is pointed to with the cursor.

#### Definitions

**Dominance.** a) Right dominance: the posterior descending coronary artery is a branch of the right coronary artery (segment 4). b) Left dominance: the posterior descending artery is a branch of the left coronary artery (segment 15). Co-dominance does not exist as an option at the SYNTAX score.

**Total occlusion.** No intra-luminal antegrade flow (TIMI 0) beyond the point of occlusion.

**Bridging collaterals.** Small channels running in parallel to the vessel and connecting the proximal vessel to the distal vessel, and being responsible for the ipsilateral collateralisation.

**Trifurcation.** A division of a main branch into three branches.

Trifurcations are only scored for the following segment junctions: 3/4/16/16a, 5/6/11/12, 11/12a/12b/13, 6/7/9/9a and 7/8/10/10a.

**Bifurcation.** A bifurcation is defined as the division of a main, parent, branch into two daughter branches (with a minimal diameter of 1.5mm). Bifurcations are only considered for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a and 3/4/16 and in case of left dominance 13/14/15.

**Aorto ostial.** A lesion is classified as aorto-ostial when it is located immediately at the origin of the coronary vessels from the aorta (applies only to segments 1, 5, 6 and 11).

**Severe tortuosity.** One or more bends of  $90^\circ$  or more, or three or more bends of  $45^\circ$  to  $90^\circ$  proximal to the diseased segment.

**Length  $>20$  mm.** Estimation of the length of that portion of the stenosis that has  $\geq 50\%$  reduction in luminal diameter in the projection where the lesion appears to be the longest. (In case of a bifurcation lesion at least one of the branches has a lesion length of  $>20$  mm).

**Heavy calcification.** Multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion.

**Thrombus.** Spherical, ovoid or irregular intraluminal filling defect or lucency surrounded on three sides by contrast medium seen just distal or within the coronary stenosis in multiple projections, or a visible embolisation of intraluminal material downstream.

**Diffuse disease/small vessels.** More than 75% of the length of any segment(s) proximal to the lesion, at the site of the lesion or distal to the lesion that has a vessel diameter of  $<2$  mm.



With the exception of the selection of the type in case of a bifurcation or a trifurcation lesion all the other questions of the algorithm can be answered by selecting “yes” or “no”.

An important characteristic of the SYNTAX score is that it is lesion based. For each lesion a separate score is calculated. The total SYNTAX score is derived from the summation of these individual scores. After the completion of the algorithm a report is automatically generated summarising all the adverse characteristics, and the individual scoring of each lesion as well as the total SYNTAX score. Two examples of the SYNTAX score calculation are presented in Figures 5 and 6. Both patients have significant stenosis in all three coronary arteries with four lesions each but the calculated SYNTAX score differs greatly (54.5 versus 19) reflecting the more complex pattern of coronary artery disease in the patient with the higher score.

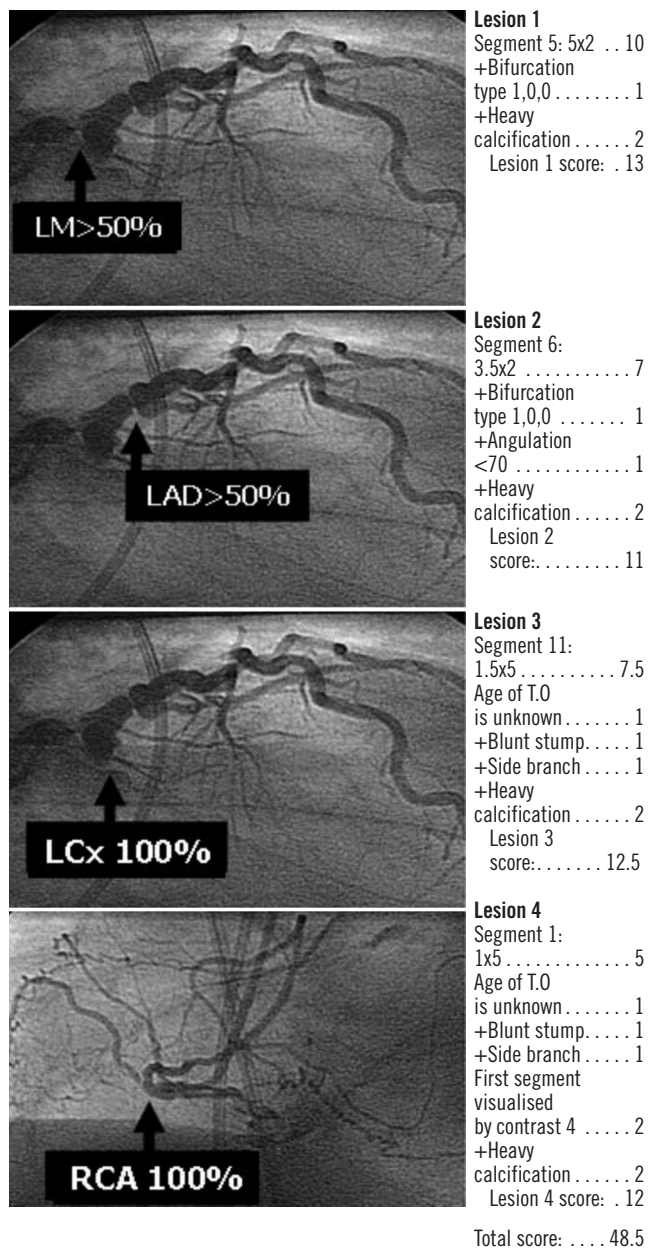


Figure 5. First example of the Syntax score calculation.

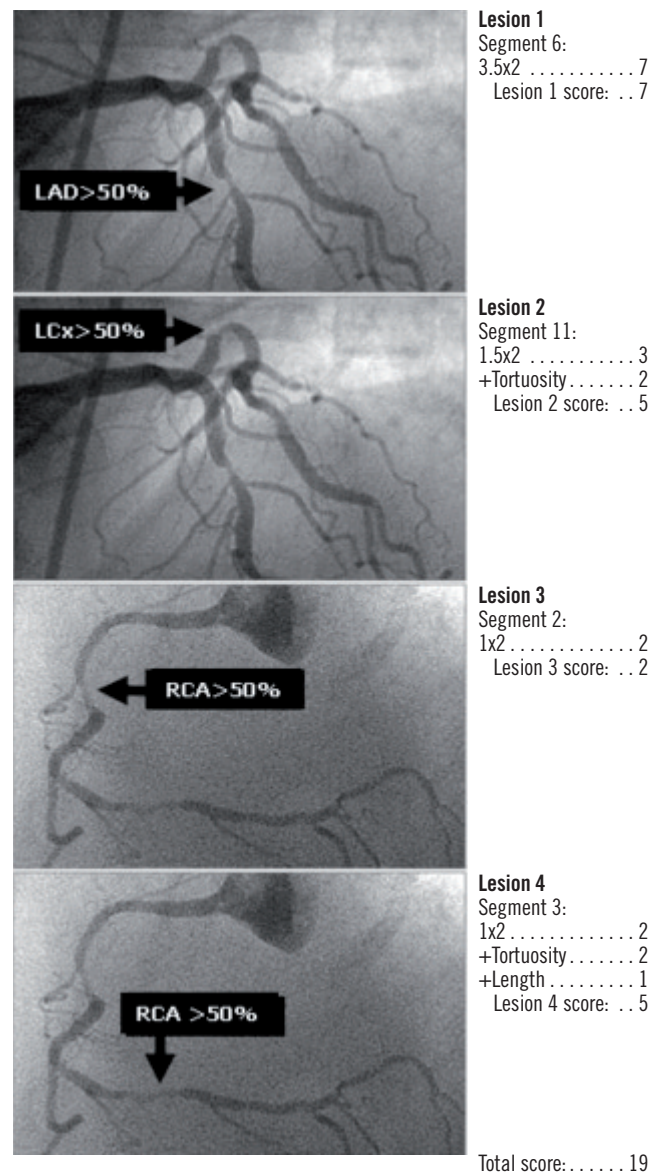


Figure 6. Second example of the Syntax score calculation.

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