

# Percutaneous Coronary Interventions for All Patients With Complex Coronary Artery Disease: Triple Vessel Disease or Left Main Coronary Artery Disease. Yes? No? Don't Know?

Patrick Serruys and Scot Garg

Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

Coronary artery disease remains the leading cause of mortality worldwide. Coronary revascularisation, with either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG), is advocated when symptoms become uncontrolled despite optimal medical therapy.<sup>1</sup> The optimal method of revascularisation in patients with single or double vessel disease rarely needs discussion, with PCI the overwhelming choice. The optimal therapy in those patients with triple vessel disease (3VD) and/or left main stem (LMS) disease however remains subject to continuing heated debate.<sup>2,3</sup> The aim of this article is to present, and review the new data for the selection of PCI for these highly complex patients.

## Significance of LMS and 3VD Lesions

The LMS is rarely longer than 15 mm, but in view of its unique position it is a vitally important part of the coronary arterial tree. LMS lesions carry the worst prognosis of any coronary lesion, mainly because of the extensive myocardium that is put at risk. The prognosis in untreated cases has been reported at 37% at 3-years.<sup>4</sup> Similarly 3VD is associated with a worse prognosis when compared to one to two vessel disease<sup>5</sup>; however not all 3VD is the same. LMS lesions occur in approximately 6%

of diagnostic coronary angiography, and in 30% of patients having surgery.<sup>4</sup> The disease spectrum is such that it is uncommon for a LMS lesion to be present in isolation; in fact, in over 70% of cases of LMS disease additional coronary artery disease (CAD) is present, increasing the complexity of revascularisation.

## Historical Treatment and the Evidence Gap

After its introduction in the 1960s CABG became the accepted treatment for multivessel disease (MVD),<sup>6</sup> however following the advances in percutaneous treatment from balloon angioplasty (POBA) to stenting with initially bare metal stents (BMS) and now drug eluting stents (DES) PCI has become an increasingly attractive alternative.

All randomized clinical trials in patients with MVD, whether performed in the early days with POBA, or more recently with BMS or DES, show no mortality difference between PCI and CABG.<sup>7-11</sup> Of note PCI has always been associated with higher rates of re-intervention, however the advantage CABG holds over PCI in this respect has progressively narrowed with advances in stent technology.<sup>11</sup>

The improvement in outcomes with PCI with the use of DES has led to an increased confidence to tackle ever more complex disease, most of which was previously only treated by surgery. Diabetics and patients with bifurcation lesions, chronic total occlusions, and LMS disease are all increasingly undergoing PCI<sup>12</sup> as the primary method of revascularisation, despite these patients largely being excluded from the previously conducted trials.<sup>13</sup>

In 2006, 29% of patients with 3VD/LMS in Europe were being treated with PCI<sup>14</sup> despite the European Society of Cardiology's PCI guidelines stating that, "stenting for unprotected left main disease should only be considered in the absence

Correspondence: Prof. Patrick Serruys MD, PhD, Head of Interventional Cardiology, Ba583a, Thoraxcentre, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands  
E-mail: p.w.j.c.serruys@erasmusmc.nl

of other revascularization options.” In addition, the current guidelines recommend CABG as the preferred treatment for those with complex CAD and LMS lesions.<sup>15</sup>

These guidelines are perhaps not surprising, because prior to the publication of recent landmark trials there was no evidence from adequately powered randomised clinical trials comparing CABG and PCI in patients with complex CAD. This evidence gap has been addressed by the SYNTAX trial (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery), and by specific studies dedicated to patients with LMS disease.

### Emerging Data: Should We Be Changing our Practice?

#### *The SYNTAX Trial*

The SYNTAX trial<sup>16</sup> was designed specifically to identify the optimal method of revascularisation in those with complex disease. In order to ensure its results were applicable to the “real-world” it was designed as an all-comer’s trial, and only included patients with 3VD or LMS disease (isolated or with any CAD), and only excluded those who had had prior revascularisation; a recent myocardial infarction (MI); or those who required concomitant cardiac surgery. The study was a non-inferiority study comparing CABG and PCI, with a primary end point of 12-month major adverse cardiac or cerebrovascular events (MACCE); defined as death from any cause, MI, stroke, or repeat revascularisation.

Historically revascularisation trials have grouped all patients with 3VD together, however this does not allow for the complexity of an individual patient’s CAD to be taken into account—the spectrum of 3VD is wide, and so are the resulting outcomes. To assess coronary lesion complexity, and therefore enable a comparison between patients, the SYNTAX trial introduced the newly developed SYNTAX score.<sup>17</sup>

All patients that were eligible for enrolment were discussed in a “Heart Team Conference” where an interventional cardiologist and cardiac surgeon carried out a careful and thorough review of the patient in terms of anginal status, co-morbidities, coronary anatomy, using the respective Braunwald score, EuroSCORE, and SYNTAX score. The consensus reached at this conference was used to enrol 3075 patients into one of the 3 arms of the trial:

1. Randomised Group: 1800 patients (58.5%). These patients had CAD suitable for treatment by

either PCI or CABG, and they were randomised to either CABG (897) or PCI (903) with Taxus® paclitaxel DESs (Boston Scientific, Natick, USA).

2. PCI Registry: 198 patients (6.4%). These patients were deemed unsuitable for CABG, with significant co-morbidities the cited reason in over 70% of cases. Their mean EuroSCORE was 5.8, compared to 3.8 in the randomised group. Of note, these patients did not necessarily have the most complex CAD as indicated by their average SYNTAX score of 31.6, which is not markedly different from the mean SYNTAX score of 28.8 in the randomised group.

3. CABG Registry: 1077 patients (35.0%). The majority of these patients had CAD that was considered unsuitable for PCI; unsurprisingly their mean SYNTAX score was 37.8.

Overall, if all 1800 patients in the randomised group are considered en masse, as per historical trials, no significant difference in outcome was observed in terms of the rate of death, MI, or death/MI/stroke between CABG and PCI at 12 months. The rate of MACCE however was significantly higher in the PCI group (17.8% vs 12.4% CABG;  $P=.002$ ), which was largely driven by an increased rate of repeat revascularization (13.5% vs 5.9%,  $P<.001$ ); as a result, the criterion for non-inferiority was not met (Table 1).

This group analysis does not provide adequate information for the clinician, who day-to-day is faced with patients with a wide variation of CAD complexity. A more practical message is obtained by analysing patients according to their SYNTAX score tertile (<23, 23-32, >32), diabetic status, and presence/absence of LMS disease. Considering the outcomes as shown in Table 2, it is clear that PCI should not be considered in those patients in the highest tertile (SYNTAX score >32). In those patients in the lowest tertile, the final decision regarding revascularisation should be made following discussion between physician and patient. The outcomes in the remaining patients is clearer after considering the presence of diabetes and distribution of CAD (LMS and/or 3VD) as shown in Figure 1.

It follows that CABG is the preferred method of revascularisation in those patients with intermediate SYNTAX scores (23-32), who are either diabetic (LMS and/or 3VD), or those with 3VD. Post-hoc analysis has suggested that those diabetic patients treated with insulin, may have better outcomes with CABG even in those with a low SYNTAX score (<23). Unfortunately, the small numbers of patients involved makes definitive conclusions impossible.<sup>18</sup> The outcome

**TABLE 1. Events at 1 Year From the 1800 Patients in the Randomised Group of the SYNTAX Trial**

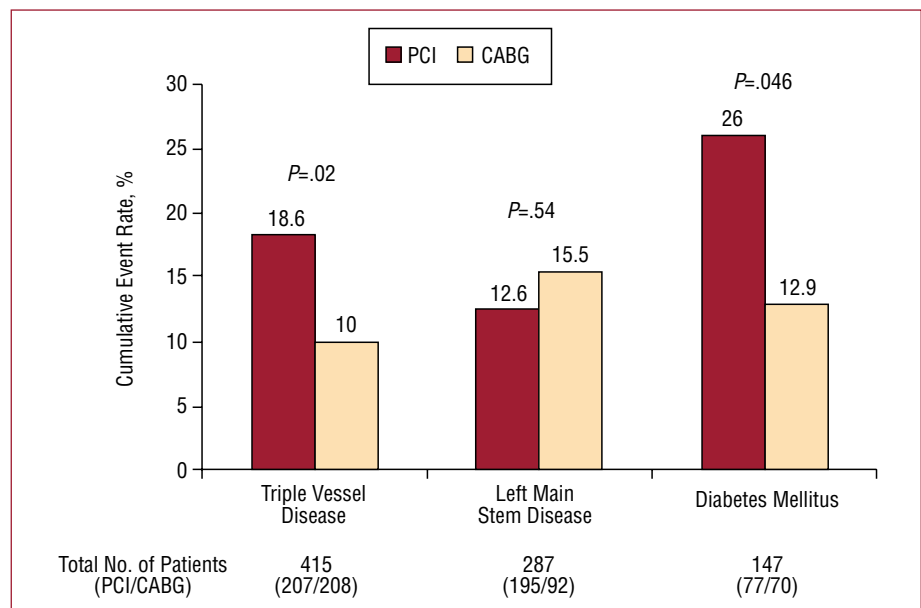
Events at 1 Year	PCI (n=903), n (%)	CABG (n=897), (%)	P
MACCE	160 (17.8)	109 (12.1)	.002
Death/CVA/MI	69 (7.6)	69 (7.7)	.98
All cause death	39 (4.3)	31 (3.5)	.37
MI	43 (4.8)	29 (3.2)	.11
CVA	5 (0.6)	20 (2.2)	.003
Repeat revascularisation	124 (13.7)	53 (5.9)	<.001

CABG indicates coronary artery bypass graft surgery; CVA, cerebrovascular accident; MACCE, major adverse cardiovascular and cerebrovascular events (all cause death, CVA, MI, and repeat revascularisation); MI, myocardial infarction; PCI, percutaneous coronary intervention.

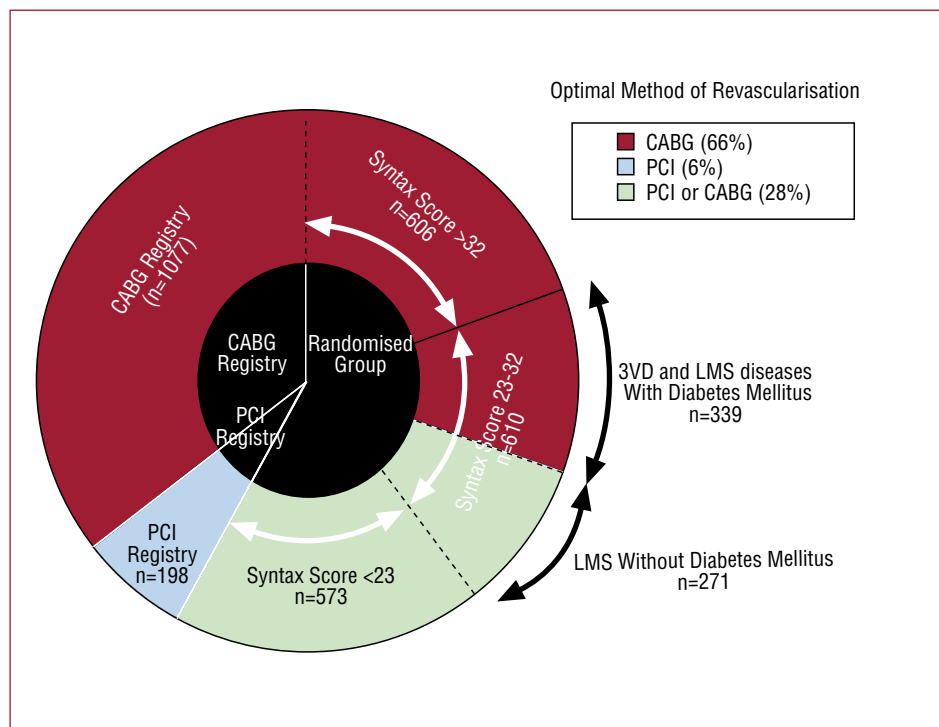
**TABLE 2. Cumulative Events in Patients From the SYNTAX Trial Grouped According to Their SYNTAX Score**

SYNTAX Score	Number of Patients (PCI/CABG)	PCI	CABG	P
<23	573 (299/274)	13.5	14.4	.71
23-32	610 (310/300)	16.6	11.7	.10
>32	606 (290/316)	23.3	10.7	<.001

CABG indicates coronary artery bypass surgery; PCI, percutaneous coronary intervention.



**Figure 1.** Graph showing the outcomes of patients with a SYNTAX score between 23 and 32 at 12 months, according to the distribution of coronary artery disease, and diabetic status. CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.



**Figure 2.** A pie chart summarising the optimal method of revascularisation of all patients in the SYNTAX trial taking into account both the initial decision of the Heart team, and the SYNTAX score. The central pie chart (black) shows the distribution of patients on entry into the study, whilst the outer pie chart shows those patients in the randomised group split according to their SYNTAX score. Finally, the colours represent the preferred method of primary revascularisation for each subgroup. Reproduced with permission Garg S, Serruys PW<sup>19</sup>. CABG, coronary artery bypass surgery; LMS, left main stem; PCI, percutaneous coronary intervention; 3VD, triple vessel disease.

in those patients who are not diabetic with LMS disease is similar between CABG and PCI, and therefore individual choice and patient co-morbidities need to be considered. The distribution of the ideal method of revascularisation as indicated by the SYNTAX study is summarised in Figure 2.<sup>19</sup>

In summary, the SYNTAX trial has established that in approximately two-thirds of patients with complex CAD, CABG is the preferred method of revascularisation. Importantly, the CABG registry has indicated that over a third of patients have CAD which is so severe that CABG is the only option for revascularisation. Similarly, the PCI registry indicates that only a minority of patients have such severe co-morbidities to preclude surgery.

#### Left Main Stem PCI

In recent times additional data has become available specifically regarding treatment of LMS disease. Previously PCI in this lesion was “accepted” when: *a)* patients required bailout LMS PCI following complications during PCI; *b)* patients presented with LMS disease in the emergency setting of acute myocardial infarction; *c)* the LMS was protected by a functional coronary bypass

graft; and *d)* patients refused, or were turned down for CABG. Refusal of CABG is not common; it occurred in only 11 patients (0.4%) in the SYNTAX trial<sup>20</sup>—and some argue it is heavily influenced by the nature and quality of the discussion between patient and interventionalist.<sup>4</sup> Patients should be given the opportunity to discuss matters with a cardiac surgeon so a balanced argument is presented.<sup>4</sup>

Patient selection is of paramount importance when choosing patients for LMS PCI to ensure suitable long-term outcomes. Technical advances, including the increasing use of ventricular support devices during high-risk cases,<sup>21</sup> means that the majority of lesions can be addressed by PCI, but is this right for the patient? It has already been stated, but little discussion is needed in those patients with very complex disease that is not amenable to PCI.

Importantly to ensure an adequate risk assessment lesion parameters, such as location (ostial, shaft, distal), calcification, and involvement of the proximal left anterior descending/circumflex artery (LAD/Cx); extent of additional CAD; and patient co-morbidities must all be weighed up before making the final decision regarding whether PCI is feasible. In addition to the SYNTAX score, the EuroSCORE has also been shown to be effective

at predicting risk in these patients.<sup>22</sup> In those who are suitable for CABG or PCI, a frank discussion between all parties is then essential.

So what is the state of current evidence for PCI in LMS disease? In terms of short-term outcomes, registries and randomised trials indicated that PCI offers reduced rates of peri-procedural MI, and stroke, however repeat revascularisation is consistently higher with PCI<sup>4,16,23</sup>; unfortunately, data on long-term outcomes compared with CABG are limited. The recent multi-centre DELFT (Drug Eluting stent for LeFT main) registry of 358 patients undergoing unprotected LMS PCI with drug eluting stents (DES) showed encouraging levels of MACCE out to 3 years follow up.<sup>24</sup> The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) registry comprising 2240 patients (1138 CABG and 1102 who had PCI: bare metal stent =318, DES=784) had similar results. At 3 years, outcomes were comparable between those undergoing PCI or CABG in terms of death (HR=1.18 for PCI; 95% CI, 0.77-1.80;  $P=.45$ ), and MACCE (HR=1.10 for PCI; 95% CI, 0.75-1.62;  $P=.61$ ). Repeat revascularisation was significantly higher in the PCI group (HR=4.76; 95% CI, 2.80-8.11;  $P<.001$ ), with DES performing much better than BMS.<sup>25</sup>

Randomised data is confined to that from the SYNTAX trial, and the considerably smaller Study of Unprotected Left Main Stenting Versus Bypass Surgery (LeMANS study) which recruited 105 patients who were randomised to either PCI (52 patients) or CABG (53 patients).<sup>23</sup> Factors which should be considered in interpreting the results were the low use of DES (35% vs 100% SYNTAX randomised group), and arterial graft conduits (72% LeMANS vs 97% in SYNTAX randomised group). Overall survival and MACCE, which were secondary end-points, at over 2 years follow up were comparable between both groups.

The complexities and technical challenges of LMS PCI are beyond the scope of this discussion; however, the recent ISAR-LEFT MAIN study deserves consideration because it is the largest randomised trial to date of PCI in LMS disease, and the first comparing 2 different DES.<sup>26</sup> The study in 607 patients randomised 305 patients to receive paclitaxel DES (PES), and 302 patients to receive sirolimus DES (SES). At 1-year follow-up there was no significant difference in MACCE ( $P=.44$ ), and mortality was similar at 2 years (PES 10.7% vs SES 8.7%;  $P=.64$ ). Unfortunately the absence of a surgical control arm is an

inherent limitation of the study, however the safety of DES in PCI for LMS lesions was further emphasised.

A comprehensive evaluation of PCI in LMS lesions necessitates long-term outcome data from randomised trials; unfortunately, this will still take several years to materialise, and until then the current guidelines are unlikely to change. Data currently available suggests that in the short term, in the appropriate patient, PCI is comparable to CABG.

## Conclusions

Evidence from the SYNTAX study indicates that CABG remains the standard of care for those with complex CAD; however, in selected patients PCI can be performed not only safely, but with comparable outcomes to CABG.

Patient selection as highlighted above is very important, and the SYNTAX trial has essentially formalised what interventional cardiologists informally already practice.<sup>14</sup> There is no debate that 2/3 of complex patients should have CABG as the preferred method of treatment, either because they have anatomy not suitable for PCI, or due to co-morbidities, such as diabetes mellitus, that ensure that outcomes are better with CABG. For the remaining patients, PCI offers a suitable alternative.

The importance of a detailed discussion of complex patients between the cardiologist and cardiac surgeon cannot be over emphasised. The two should not consider themselves on opposing teams, but rather on the same team—"Team Patient." Those patients who have been identified to have comparable outcomes between PCI or CABG should be fully involved in the decision making process—or at least granted the opportunity of discussing matters with both cardiologist and surgeon. Cardiologists and surgeons must ensure on their part that patients are able to weigh the individual benefits and risks of each procedure, and thereby come to an informed decision.<sup>27</sup>

Common in all aspects of medicine, risk assessment is vitally important to enable appropriate decisions to be made, which are justifiable to patients, colleagues, and regulators. The SYNTAX trial has shown the importance of risk assessment using a coronary anatomy based scoring system, however a patient based risk assessment, such as the EuroSCORE, may also offer additional potential in helping stratifying these complex patients. Whatever the case PCI or CABG should not be undertaken before a comprehensive risk assessment.

## REFERENCES

1. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-16.
2. Taggart D. The DELFT (Drug Eluting stent for LeFT main) Registry: The Unknowns. *J Am Coll Cardiol*. 2008;52:1680-1.
3. Meliga E, Maree AO, García-García HM, Serruys PW. Reply. *J Am Coll Cardiol*. 2008;52:1681.
4. Taggart DP, Kaul S, Boden WE, Ferguson TB, Jr., Guyton RA, Mack MJ, et al. Revascularization for unprotected left main stem coronary artery stenosis stenting or surgery. *J Am Coll Cardiol*. 2008;51:885-92.
5. Lopes NH, Paulitsch FdS, Gois AF, Pereira AC, Stolf NA, Dallan LO, et al. Impact of number of vessels disease on outcome of patients with stable coronary artery disease: 5-year follow-up of the Medical, Angioplasty, and bypass Surgery Study (MASS). *Eur J Cardiothorac Surg*. 2008;33:349-54.
6. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117-24.
7. Sim I, Gupta M, McDonald K, Bourassa MG, Hlatky MA. A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. *Am J Cardiol*. 1995;76:1025-9.
8. Pocock SJ, Henderson RA, Rickards AF, Hampton JR, King SB, 3rd, Hamm CW, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet*. 1995;346:1184-9.
9. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodríguez A, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation*. 2008;118:1146-54.
10. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373:1190-7.
11. Serruys PW, Ong ATL, Morice MC, de Bruyne B, Colombo A, Macaya C, et al. Arterial Revascularisation Therapies Study Part II-Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention*. 2005;1:147-56.
12. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoyer A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation*. 2004;109:190-5.
13. Brodie BR, Stuckey T, Downey W, Humphrey A, Bradshaw B, Metzger C, et al. Outcomes and Complications With Off-Label Use of Drug-Eluting Stents: Results From the STENT (Strategic Transcatheter Evaluation of New Therapies) Group. *J Am Coll Cardiol Interv*. 2008;1:405-14.
14. Kappetein AP, Dawkins KD, Mohr FW, Morice MC, Mack MJ, Russell ME, et al. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. *Eur J Cardiothorac Surg*. 2006;29:486-91.
15. Smith SC, Feldman TE, Hirshfeld JW, Jacobs AK, Kern MJ, King SB, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation*. 2006;113:e166-286.
16. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-72.
17. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219-27.
18. Banning A. Revascularisation with cardiac surgery versus paclitaxel eluting stents in patients with diabetes and metabolic syndrome. One year results from the SYNTAX study. *J Am Coll Cardiol*. 2009;53 Suppl A:A3.
19. Garg S, Serruys PW. Secondary revascularisation, mediations following the SYNTAX trial, Eurointervention 2009;5(Suppl D):D14-20.
20. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Supplementary appendix-Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease *N Engl J Med*. 2009;360:961-72.
21. Vranckx P, Meliga E, de Jaegere PP, van den Ent M, Regar ES, Serruys PW. The TandemHeart, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience. *EuroIntervention*. 2008;4:331.
22. Kim YH, Ahn JM, Park DW, Lee BK, Lee CW, Hong MK, et al. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol*. 2006;98:1567-70.
23. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538-45.
24. Meliga E, García-García HM, Valgimigli M, Chieffo A, Biondi-Zoccai G, Maree AO, et al. Longest Available Clinical Outcomes After Drug-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Disease: The DELFT (Drug Eluting stent for LeFT main) Registry. *J Am Coll Cardiol*. 2008;51:2212-9.

25. Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med.* 2008;358:1781-92.
26. Mehilli J, Kastrati A, Byrne RA, Bruskina O, Iijima R, Schulz S, et al. Paclitaxel-Versus Sirolimus-Eluting Stents for Unprotected Left Main Coronary Artery Disease. *J Am Coll Cardiol.* 2009;53:1760-8.
27. Federspiel J, Stearns S, van Domburg R, Sheridan B, Lund J, Serruys P. Risk-Benefit Trade-offs in Revascularization Choices. *Med Decis Making.* 2009 [in press].