

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[☆]

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Abstract

Objective: Percutaneous coronary intervention with drug-eluting stents is challenging coronary artery bypass grafting (CABG) as the gold standard for treatment of three-vessel and left main coronary disease. We evaluated the current practice pattern in hospitals throughout Europe and USA. **Methods:** To qualify for participation in the SYNTAX (Synergy between PCI with TAXUS drug-eluting stent and Cardiac Surgery) study, a randomized trial comparing percutaneous coronary intervention with drug-eluting stent versus coronary artery bypass grafting for three-vessel and left main disease, 104 centers were asked to provide their case volume in 3 months in 2004. Anonymous procedural data were collected. **Results:** A total of 12,072 patients were recorded. Coronary artery bypass grafting was the most frequently performed procedure ($N = 8895$, 74%). Three-vessel disease (3VD) predominated in this population ($N = 8532$, 71%) versus left main ($N = 3540$, 29%). In the 3-month period, per center a mean of 8.3 patients with left main and 22.3 patients with three-vessel disease were treated by percutaneous coronary intervention, while 26.0 patients with left main and 60.3 patients with three-vessel disease were treated by coronary artery bypass grafting. In USA, percutaneous coronary intervention for left main and/or three-vessel disease was performed in 18% of the cases while this was performed in 29% of the cases in Europe. Of all CABG procedures, only 12% were done with total arterial grafting while 7% were treated with only venous grafts. **Conclusions:** In patients with multivessel or left main disease, still coronary artery bypass grafting remains the dominant revascularization strategy. Percutaneous coronary intervention is performed frequently without supporting data from the literature. Percutaneous coronary intervention for this indication is performed more often in Europe than in USA. Only a minority of the patients receives total arterial grafting in case of coronary artery bypass grafting. The SYNTAX trial with randomized and registry cohorts should provide guidance for selecting the preferred form of treatment.

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1. Introduction

Coronary bypass surgery remains the standard of care for patients with three-vessel disease (3VD) and left main (LM) coronary artery disease [1,2]. However, percutaneous coronary intervention (PCI) has progressed through simple balloon angioplasty, to bare metal coronary stents, and then drug-eluting stents, and is now challenging coronary artery bypass graft surgery (CABG) as an alternative for revascularization of these patients with multivessel coronary artery disease (CAD) or left main disease. Traditionally, the increased, symptom-driven need for subsequent revascularization, as a result of

restenosis, has been a major disadvantage of choosing PCI. In patients with left main disease this may result in a potential fatal complication. With the advent of drug-eluting stents, restenosis has become less of a concern [3] although the data mainly support use in more simple anatomy. Published data on the use of drug-eluting stents in the treatment of three-vessel disease and left main disease are relatively limited [4–6]. Additionally, while PCI has improved, CABG has also progressed with better perioperative management, a higher use of arterial grafting, and improved techniques with minimally invasive and off-pump surgery as options [7,8].

Due to these recent improvements in both PCI and CABG, determining the best revascularization strategy for 3VD and LM disease patients may not be straightforward.

SYNTAX (Synergy between PCI with TAXUS drug-eluting stent and Cardiac Surgery) is a prospective, randomized, multicenter trial designed to compare revascularization with either CABG or PCI with TAXUS paclitaxel-eluting stents for

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the treatment of de novo 3VD or left main disease (isolated or in association with one-, two-, or three-vessel disease). The primary objective of the SYNTAX trial is to compare the 12-month major adverse cardiac and cerebral events (MACCE) rates including death, stroke, documented nonfatal myocardial infarction, and repeat revascularization by either percutaneous intervention or bypass surgery.

The SYNTAX trial has an ‘all comers’ design to address the criticism of previous trials that did not capture the real world of clinical practice. The trial includes a randomized arm of 1500 patients: 750 assigned to PCI with a TAXUS drug-eluting stent versus 750 to coronary artery bypass graft surgery. In addition to the randomized arm, there are two nested registries, one that includes patients undergoing coronary artery bypass graft surgery who are deemed ineligible for PCI, and the other includes patients treated with PCI who are deemed ineligible for coronary artery bypass graft surgery.

As a requirement for participation in SYNTAX, all interested investigators were asked to provide anonymous information on each LM or three-vessel disease procedure performed at their site during a 3-month period. These data were used to make decisions for site entry based on case volume, case complexity, and technique. The purpose of this manuscript is to describe the findings from this unique roll in database reflecting current surgical and percutaneous revascularization patterns in Europe and North America.

2. Material and methods

The SYNTAX trial Steering Committee identified recruiting sites for this trial in Europe, United States, and Canada based on procedural volume and expertise, participation in prior scientific trials, and personal knowledge of the specific centers and operators. To project expected enrolment, a ‘run-in phase’ was performed to gather anonymous information on patients treated at the potential sites during a 3-month period between January and March 2004. Parameters evaluated included the number of three-vessel disease and left main disease patients undergoing revascularization with either coronary artery bypass graft surgery or PCI. Additional information was collected to identify isolated left main coronary artery disease, left main disease in conjunction with one-, two-, or three-vessel disease, and protected or unprotected left main coronary artery disease. Information was also gathered to determine whether CABG procedures utilized arterial grafts only, venous grafts only, or a combination of both. This survey included 104 sites, with 77 in Europe and 27 in North America. Detailed information on CABG patients was missing from one North American site.

3. Statistical analysis

Data summaries primarily consisted of descriptive tabulations of overall and subgroup procedural data collected. Descriptive statistics included sample size (*N*), mean, median, standard deviation, and minimum and maximum values for continuous variables. Sample size (*N*), number of subjects, and percent of subjects were used to summarize the categorical variables.

4. Results

A total of 12,072 patients were entered in the database (Table 1). There were 8895 patients (74%) who underwent CABG and 3177 patients (26%) who underwent PCI. Three-vessel disease patients predominated with 8532 (71%) versus 3540 (29%) left main patients. A total of 6215 (70%) patients in the CABG group and 2317 (73%) patients in the PCI group had three-vessel disease. The mean number of left main disease patients treated per center with PCI was 8.3 and with CABG was 26.0. The ratio of PCI to CABG for both three-vessel disease and left main disease was 1:3.

Of the 3540 patients treated for LM coronary artery disease, 459 (13%) had isolated left main disease (Table 2). In these cases, PCI was performed more often (274, 60%) than CABG (185, 40%). However, among the 1645 patients with both LM coronary artery disease and three-vessel disease, CABG was used 10 times more frequently than PCI (1492, 91% vs 153, 9%).

There were important differences between the European and North American sites (Table 3). In all three-vessel and left main disease patients, PCI was performed more often in Europe than in North America (2638, 29% vs 539, 18%). This difference was more pronounced for three-vessel disease (1990, 30% in Europe vs 327, 17% in North America) than for left main disease (648, 26% in Europe vs 212, 21% in North America). With respect to PCI treatments of left main disease, unprotected left main coronary artery interventions were performed three times more often in Europe (429, 66%) than in North America (48, 23%). PCI for left main stenosis in conjunction with three-vessel disease was also performed more often in Europe with a mean number of patients per site of 1.8 versus 0.7 in North America.

Differences in CABG and PCI practice patterns were observed between individual European countries (Figs. 1 and 2). CABG revascularization for either three-vessel or left main disease ranged from 50% in France to 87% in the United Kingdom. For LM coronary artery disease as a whole, CABG revascularization was lowest in the Netherlands at 59% and

Table 1
Overall results

	PCI (N = 3177)	CABG (N = 8895)	Total (N = 12,072)
Number of sites	104	103	
Patients/site	30.5	86.4	
Three-vessel disease	2317 (27%)	6215 (73%)	8532
Three-vessel disease/site	22.3	60.3	
Total left main disease	860 (24%)	2680 (76%)	3540
Left main disease/site	8.3	26.0	

Table 2
PCI and CABG treatment for left main coronary artery disease

	PCI (N = 860)	CABG (N = 2680)	Total (N = 3540)
Isolated left main	274 (32%)	185 (7%)	459 (13%)
Mean isolated left main/site	2.6	1.8	
Left main + one-vessel disease	240 (28%)	274 (10%)	514 (15%)
Mean left main + one-vessel/site	2.3	2.7	
Left main + two-vessel disease	193 (22%)	729 (27%)	922 (26%)
Mean left main + two-vessel/site	1.9	7.1	
Left main + three-vessel disease	153 (18%)	1492 (56%)	1645 (46%)
Mean left main + three-vessel/site	1.5	14.5	

Table 3
Differences between Europe and North America for treatment of left main and three-vessel disease

	Europe		North America	
	PCI	CABG	PCI	CABG
Number of sites	77	77	27	26
Number of patients	2638 (29%)	6490 (71%)	539 (18%)	2405 (82%)
Patients/site	34	84	20	93
Three-vessel disease	1990 (30%)	4623 (70%)	327 (17%)	1592 (83%)
Patients/site	26	60	12	61
Left main disease	648 (26%)	1867 (74%)	212 (21%)	813 (79%)
Patients/site	8	24	8	31
Unprotected left main/site	6	—	1.8	—

highest in Belgium at 87%. The Netherlands (85%) was more likely to perform unprotected left main PCI procedures than the rest of Europe (66%), while Germany was less likely (55%). For three-vessel disease, CABG revascularization was lowest in France at 42% and highest in the United Kingdom at 90%.

Revascularization, with arterial grafts only, was performed in 12% of the CABG procedures while 7% were treated with venous grafts only. The majority (81%) was treated with a combination of venous and arterial grafts. There were no differences in graft use between Europe and North America. However, within Europe, France (39%), the Netherlands (15%), and Germany (14%) had a higher rate of total arterial grafting compared to the rest of Europe (mean 12%).

5. Discussion

PCI and CABG have both proven to be effective in improving symptoms from myocardial ischemia; however, the two techniques were initially used in very different populations. Technical challenges limited PCI applicability to chronic totally occluded vessels and there was concern in treating complex anatomical subsets because of the high risk of restenosis. With the advent of drug-eluting stents the practice of interventional cardiology has changed dramatically and also, to a lesser extent, there have been parallel improvements in cardiac surgery. The progress in both specialties not only depends on major advances in technique and equipment, such as the introduction of

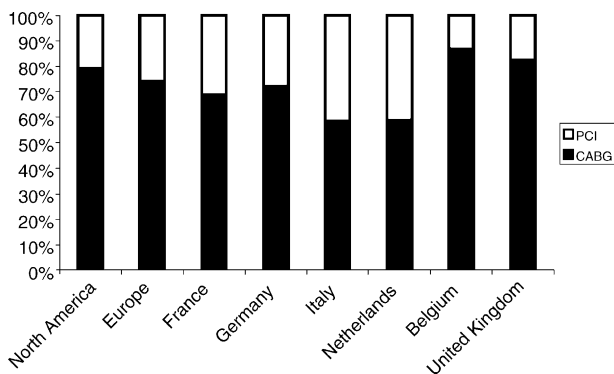


Fig. 1. Procedures by region or country for three-vessel disease.

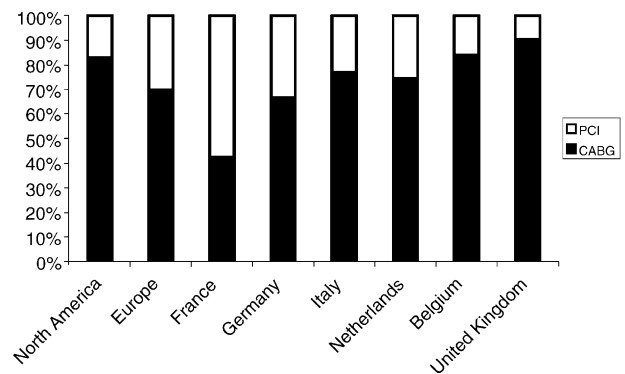


Fig. 2. Procedure by region or country for left main disease.

drug-eluting stents for PCI and off-pump or minimally invasive surgery, but also on the implementation of more aggressive adjunctive pharmacology such as aspirin, clopidogrel, IIb/IIIa inhibitors and statins, better control of risk factors, and improving operator experience. The contribution of each of these factors to changing practice patterns may vary between institutions, regions, and countries. As documented in this study, there is substantial variability in the selection of specific revascularization strategies chosen for patients with multivessel and left main coronary artery disease.

With technical advances, more challenging anatomical subsets become amenable to treatment with PCI. Patients with three-vessel disease and left main coronary artery disease are being treated with increasing frequency with PCI, due to findings that in selected patients who could have either procedure, both survival and survival free of myocardial infarction are equivalent between PCI and CABG [1,2]. The introduction of drug-eluting stents may also have a major impact on the need for repeat revascularization in diabetic patients, and the difference between PCI and coronary surgery may also narrow considerably in this higher risk patient population [9].

Despite the increasing age and concomitant increased comorbidity of patients presenting for CABG, clinical outcomes have continued to improve [8]. This trend was evident from the 5-year results of the ARTS study [2] with a lower mortality seen in the CABG arm compared with older studies. The off-pump coronary bypass technique, developed to minimize the invasiveness of CABG, has demonstrated a reduction in morbidity and mortality in several large, retrospective studies when compared with CABG [10,11]. Conversely, aside from improvements in atrial fibrillation, randomized, controlled trials did not show the same statistically significant reductions in short-term mortality or morbidity that were demonstrated by observational studies [12]. These discrepancies might be due to differing patient-selection and study methodologies. Larger randomized trials focusing on long-term outcomes are necessary to definitively address this issue [13].

Despite the growing evidence in the literature that arterial-only grafts in CABG achieve significantly better long-term survival than the combined use of arterial and vein grafts [7,14], the 12% rate of total arterial grafting in this study was low. In comparison with PCI, the strength of coronary surgery may ultimately lie in better long-term outcomes, and therefore, the use of arterial grafts should be further advocated.

In this current run-in phase, patients with multivessel disease are frequently treated with PCI. Of interest is the fact that PCI is performed 1.5 times more often in these selected centers in Europe as compared with North America. When isolated three-vessel disease patients are considered, the frequency of PCI performance is 1.8 times higher in Europe compared to North American centers. PCI for unprotected left main coronary artery disease showed the most striking difference with three times as many procedures in Europe. There was also a considerable variability within Europe with the United Kingdom using CABG for three-vessel disease almost twice as often as France. There was less variability between North American and European centers for left main coronary

artery disease. However, there were noticeable differences between European countries, with 60% CABG revascularization for left main disease in the Netherlands compared to 87% CABG revascularization in Belgium. This regional variability may reflect differences in reimbursement policies, local practice guidelines, or more conservative approaches to novel technologies due to a lack of evidence-based medicine.

Earlier data from randomized trials indicated an advantage of CABG over PCI for left main and three-vessel coronary artery disease, and surgery remained the standard of care for these patients. However, as the data from this run-in phase show, the introduction of drug-eluting stents has changed practice patterns, and many patients are now being treated with PCI. Nevertheless, drug-eluting stents may also be associated with complications, particularly stent thrombosis [15–17], and it has yet to be proven in a randomized trial that the hard end points of death, repeat revascularization, cerebrovascular accidents and myocardial infarction are the same with both revascularization techniques. The SYNTAX trial will provide a solid dataset to assess the various issues in left main and multivessel disease and will set new guidelines for our patients in the future.

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Appendix A. Conference discussion

Dr P. Kolh (Liege, Belgium): As you know, we are participating in the trial and happy to do so. I would like to ask you a couple of questions. First, do you have any idea why PCI is less used in the US as compared to Europe? I understand why there could be regional differences within Europe but I don't see why there would be a between-continent difference.

The second is that most of us should be surprised by the rather low use of full arterial revascularization. Do you think that because of this trial and because of the long-term importance of arterial revascularization, the surgeons would change their practice during the ongoing trial and, furthermore, are we going to encourage them to do so?

Dr Kappetein: Very important questions you raise. I think that an important reason why there is a difference in PCI rate between Europe and North America is that because PCI treatment for three-vessel disease and left main is not evidence-based medicine yet, the interventional cardiologists in the United States are more reluctant to perform PCI for this indication, because if something goes wrong they might be eligible for a lawsuit. If you look at the difference between the United Kingdom and the rest of Europe, it might be due to the reason that drug-eluting stents in the UK are not reimbursed. It is not that the interventional cardiologists are not so skilful as in the rest of Europe.

And coming back to your question about arterial grafting, yes, indeed we think it is very important. We have seen a lot of papers in the literature that arterial grafting is important, especially in the younger patient population. So we encourage the surgeons who participate in the trial to perform as much

arterial grafting as they can, hopefully without increasing the risk for the patient. So if they are used to perform arterial grafting we encourage them to do so.

Whether we will be able to answer the question whether complete arterial grafting is better, I have my doubts, because, as you know, cardiac surgeons look at the long-term outcome while interventional cardiologists look at a much shorter term. The primary end point of this trial will be at one year and the secondary end point at five years and then it will stop. Therefore, the follow-up might be too short.

Dr R. Mohr (Tel Aviv, Israel): What is the meaning of all-comer study and how do you make sure that it is an all-comer?

Dr Kappetein: Like I said before, in the former trials only about 5% of the patients were included in the studies, so we wanted to have this all-comer design to be sure that we capture the real practice. Therefore, we asked the centers, to capture all patients that enter their hospital, when they start the trial. When they think that the patient is eligible for PCI and coronary bypass surgery, the patient will be randomized. When they think that coronary bypass surgery is not possible because the patient has a lot of co-morbidities, the patient will be entered into a database, what we call the PCI registry, and when the interventional cardiologist says, well, I cannot do a PCI on this patient because he has two chronic total occlusions and he has a very bad left main stem, then the patient will be sent to surgery and he will be entered in a CABG registry. In this way the surgeon and the cardiologist are forced to sit down to discuss the patient. So the surgeon and the cardiologist together decide whether the patient is randomizable or whether he has to go into one of the registries.