SYNTAX STUDY

# The synergy between percutaneous coronary intervention with TAXUS and cardiac surgery study: A surgical perspective

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## ABSTRACT

**The SYNTAX (The Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) study is an important study to indicate the best treatment option for patients who have three vessel coronary artery disease and/or left main stem coronary disease (LMD). CABG (coronary artery bypass grafting) is still the preferred therapy for these patient groups with proven low mortality and excellent long term survival rates. PCI-DES (percutaneous coronary intervention with drug eluting stents) is a relative non-invasive procedure with comparable short and medium term survival, but with a much higher repeat revascularisation rate.**

**The SYNTAX Study enrolled 1800 patients in a randomised arm and 1275 in a registry arm. A SYNTAX Score was developed to assess the lesion morphology. At 12 months follow-up in the randomised group there was an increased death rate (4.3% vs 3.5%), myocardial infarction rate (4.8% vs 3.2%) and repeat revascularisation rate (13.7% vs 5.9%) in the PCI-TAXUS (percutaneous coronary intervention with TAXUS stent) group compared to the CABG group. This trend continues up to 24 months with increased death rate (6.2% vs 4.9%), myocardial infarction rate (5.9% vs 3.3%), repeat procedure rate (17.4% vs 8.6%) and MACCE rate (23.4% vs 16.3%) in the PCI group compared to the CABG group.**

**The aim of the SYNTAX Study was to prove non-inferiority of PCI (percutaneous coronary intervention) compared to CABG in these patient populations. Non-inferiority of PCI-TAXUS compared to CABG in this study population could not be shown at 12 or 24 months.**

**The cerebrovascular event rate was higher in the CABG group in both study arms (2.2% vs 0.6%) in the first year, but a nearly similar CVA rate during the next 12 months.**

**The study will terminate in 2011 and will give much-needed information regarding the optimal treatment option in patients with three vessel disease and/or left main disease.**
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## INTRODUCTION

The treatment of symptomatic coronary artery disease has undergone major developmental changes in the last few decades. Coronary artery bypass surgery has become a safe procedure with in-hospital mortality that averages 1% in low risk patients and between 2-5% in all risk patient groups. New innovations like less invasive techniques (mini-bypass, off-pump surgery), arterial revascularisation, optimal cardio-protective measures, major advances in anaesthetic technique and improved peri-operative care has improved outcomes after coronary bypass surgery.[9,15,16]

Since the inception of PCI in 1977 by Gruentzig, the treatment of stenotic coronary artery disease has changed forever. The introduction of bare metal stents (BMS), then drug-eluting stents (DES) and new anti-platelet therapy has been the stimulus to treat more complex coronary artery lesions with percutaneous techniques.

Several studies of multi-vessel coronary disease have shown relative comparative mortality rates in both treatment groups, with only higher repeat revascularisation rates in the PCI groups. When reflecting on these results the question arises if CABG is still the gold standard for left main (LM) and three vessel coronary artery disease.

The SYNTAX (Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) Study was designed to show that PCI-DES is not inferior to CABG in randomised patients

with three vessel disease and/or LMD. The SYNTAX Study is the most important comparative evidence-based study to determine the best treatment option for LM and three vessel disease.

## CURRENT EVIDENCE FOR TREATMENT IN MULTI-VESSEL CORONARY ARTERY DISEASE

Multiple randomised control trials comparing PCI and CABG in the last ± 20 years have failed to address the issue of LM and three vessel disease. Fifteen RCT including RITA, ERACI I, GABI, EAST, CABRI, MASS I, BARI, AWESOME, MASS II, ARTS I and SOS trials gave inconclusive results regarding this aspect.[1-8]

In summary all of these studies included only 35% of three vessel disease, 0% had LM disease, only 43% had proximal LAD (left anterior descending artery) disease, 100% had ejection fractions of >50%, diabetes was only present in 16%. The studies exclude the bulk of patients that would benefit from CABG (Table 1).

In the studies where BMS (bare metal stenting) was used, namely ERACI II, ARTS I, SOS and AWESOME the rate of repeat revascularisation was reduced significantly, but was still high. In the SOS and ARTS I trial (67% - 72% 2VD; 0% LM) the repeat revascularisation was 30% (BMS) vs 9% (CABG) in the ARTS I trial and 21% (BMS) vs 6% (CABG) in the SOS trial. The combined MACCE (death, MI, stroke, repeat revascularisation) was 41.7% in the BMS group and 21.8% in the CABG group. In the 5 year follow-up in the MASS II trial comparing CABG, PCI (BMS) and medical treatment groups, there was a 10 time higher incidence of repeat interventions in the PCI group in comparison with the CABG group (32.2% vs 3.5%). There was also a mild mortality difference over the 5 years favouring CABG (15.5% (PCI) VS 12.8% (CABG)). These studies tended to give a biased view with only a low percentage (4%) of screened patients being randomised. The trials excluded patients that would benefit from bypass surgery i.e. those with three vessel disease, left main disease, patients with diabetes mellitus and those with impaired left ventricle function (<50%). Although these studies were not representative of daily clinical practice, the results were generalised.[19] A search for "real world" evidence in registries developed from these highly selective patient trials. Hannan et al. published the 3 year outcome of coronary artery bypass grafting vs stent

**TABLE 1:** Summary of 15 randomised control trials comparing PCI vs CABG in multivessel disease

| Trial | No of patients | Stent | % Left main | % 3VD | Proximal | EF >50% LAD (%) | % DM | % IMA |
|---|---|---|---|---|---|---|---|---|
| RITA | 1 011 | - | 0 | 12 | - | - | 6 | 74 |
| ERACI | 127 | - | 0 | 45 | - | 100 | 11 | 75 |
| LAUSANNE | 134 | - | 0 | 0 | 100 | - | 12 | 100 |
| GABI | 359 | - | 0 | 18 | - | - | 10 | 37 |
| EAST | 392 | - | 0 | 40 | 70 | 100 | 25 | - |
| CABRI | 1 054 | - | 0 | 40 | - | 100 | 12 | 75 |
| MASS | 142 | - | 0 | - | 100 | 100 | 21 | 100 |
| BARI | 1 829 | - | 0 | 41 | 36 | 100 | 24 | 80 |
| TOULOSE | 152 | - | 0 | 29 | - | - | 14 | 58 |
| SIMA | 121 | - | 0 | - | 100 | 100 | 11 | 100 |
| ERACI II | 450 | + | 0 | 56 | - | - | 17 | 88 |
| AWESOME | 454 | + | 0 | 45 | - | - | - | 70 |
| MASS II | 408 | + | 0 | 41 | | | | |
| ARTS | 1 205 | + | 0 | 32 | - | 100 | 19 | 93 |
| SOS | 988 | + | 0 | 38 | 45 | 100 | 14 | 81 |
| **Summary** | **8 826** | | **0** | **35** | **41** | **100** | **16** | **79** |

*A summary of the randomised trials comparing PCI and CABG. It shows the trial, the number of patients included in the trial, stents was implanted in only the last 5 trials. The next column shows the % of LMD included in each trial. The amount of patients with three vessel disease was low in the PCI group. The LV function was good in all of these patients.*
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implantation in the New England Journal of Medicine of 26 May 2005. The New York State Cardiac Surgery and Coronary Percutaneous Intervention database was used. Thirty seven thousand two hundred and twelve (37 212) patients with multi-vessel disease underwent CABG and 22 102 patients underwent stenting between 1 January 1997 and 31 December 2000. Primary outcomes investigated were death and repeat revascularisation. In the CABG group 0.3% underwent re-CABG and 4.6% underwent PCI in the 3 year time period. In the PCI group 7.8% underwent CABG and 27.3% underwent repeated PCI. The observed rate of revascularisation in the CABG group was significantly lower (p<0,001).

When comparing the PCI and CABG group there was a survival benefit for CABG over the 3 years. There was a significant survival benefit in the group of patients who had three vessel disease and involvement of the proximal LAD (89.3% vs 84.4% survival when comparing CABG vs PCI over these 3 years).[9]

This was an observational study and not a randomised control study and was therefore criticised by Flaherty. He concluded that there are major flaws in the study and he emphasised that there was a risk-ascertainment bias between the two groups and therefore the difference in adjusted outcome in this study.[17]

Very few of these patients received drug-eluting stents (DES). Hannan et al reviewed the same databases in New York State to evaluate the influence of DES and CABG on major adverse outcomes (death, myocardial infarction) or repeat revascularisation in a patient population from 1 October 2003 to 31 December 2004. Those patients with previous revascularisation, main stem disease and those with recent myocardial infarctions were excluded. The study population included 9 963 DES patients and 7 437 CABG patients. The outcomes up to 18 months after the initial procedure were reviewed.

It was a purely observational, non-randomised, retrospective study of a "real world" situation. The revascularisation rate in the CABG group was low with 0,1% of patients requiring repeat CABG and 5.1% in the PCI group receiving repeat procedures. In the DES group 2.2% required CABG and 28.4% required repeat PCI.

In the three vessel and two vessel disease subgroup there was an adjusted long term survival benefit in the CABG group (92.1% vs 89.7% (DES); p<0,001). Comparing subgroups of patients with diabetes, left ventricle ejection fraction <40% and patient age >80 years the conclusion was made that there was no mortality difference between the two groups but the rate of death or myocardial infarction was lower in the poor left ventricle function patients and in the patients >80 years that was treated with CABG.[10]

## THE SYNTAX STUDY

(The synergy between percutaneous coronary intervention with TAXUS and cardiac surgery).

The SYNTAX Study is a phase III multi-centre, international, randomised controlled comparison of bypass surgery and PCI with a TAXUS drug eluting stent in 1800 patients. Included were patients with three vessel disease and/or left main stem coronary artery disease. Excluded from the study were patients with acute myocardial infarction, previous coronary intervention and those who required concomitant cardiac surgery.

### The study design

Eighty five centres (62 in Europe and 23 in the USA) enrolled patients for the trial. One thousand eight hundred (1 800) patients were randomly assigned by a team of a local cardiac surgeon and an interventional cardiologist to undergo CABG or PCI with TAXUS stents in a 1:1 ratio. Patients were randomised only after both agreed that the patient can be treated by either intervention (CABG or PCI).

A non-inferiority comparison of the 2 groups was performed for the primary endpoints – a major cardiac or cerebrovascular event (death from any cause, stroke, myocardial infarction or repeat revascularisation). Patients who did not qualify were entered into a separate parallel CABG or PCI registry.

All the angiograms were reviewed by an independent group of specialists in Rotterdam, Netherlands. A SYNTAX Score was calculated for these angiograms.

### SYNTAX Score

The SYNTAX Score is an anatomical assessment score of an individual angiogram (Figure 1). It is an evaluation of coronary lesion complexity and a score is assigned to it. It includes multiple factors, eg. lesion calcification, bi-or trifurcation lesions, left main or three-vessel disease, thrombus, tortuosity, number and location of lesions. Scores are computer generated (www.syntaxscore.com).[13]

| | |
|---|---|
| A score of ≤22: | Low Syntax Score |
| A score of 23-32: | Intermediate Score |
| A score of ≥33: | High Score |

A scoring algorhythm has been developed that addresses the following twelve aspects: Coronary artery dominance; number of lesions; segments involved per lesion; total occlusion; trifurcation or bifurcation lesions; aorta-ostial lesions; severe tortuosity; lesion length >20 mm; heavy calcification; thrombus; and diffuse disease/ small vessels. It is a self-guided questionnaire and a score is assigned to the information given.

One thousand eight hundred (1 800) patients were recruited for the study in the randomised arm: 897 in the CABG group and 903 in the TAXUS group (±28.5% D.M.). One thousand two hundred and seventy-five (1 275) patients were included in the registry arm (CABG=1 077, PCI=198).

The primary clinical endpoint is the 1 and 2 year follow-up of major adverse cardiac and cerebral events (MACCE). The 24 month follow-up has just been completed. MACCE is defined as the all-cause death, myocardial infarction, any repeat revascularisation and cerebrovascular events. The study is ongoing and the study will terminate when 5 year follow-up has been completed.

A non-inferiority comparison between the two therapeutic entities was done. A zone of non-inferiority was specified between the differences of the MACCE rate of CABG vs PCI. The pre-specified value was 6.6%. A value of less than 6.6% would suggest non-inferiority for PCI compared to CABG.

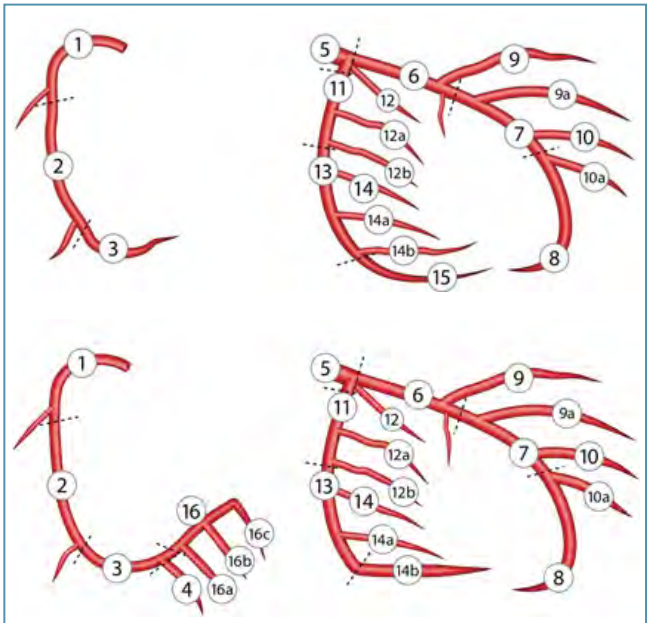


**FIGURE 1:** Morphology of coronary artery segments for description in the SYNTAX Score (www.syntax.net)

## Randomised cohort of the SYNTAX Study

Demographics between the CABG and TAXUS groups were nearly similar. Twenty eight % of patients were diabetic and the Euroscore and Parsonnet scores were 3.8 and 8.4 respectively in both groups.

SYNTAX Score in the CABG group was 29.1 and 28.4 in the TAXUS group. Subgroups of left main (LM) disease and three vessel disease were identical in both groups (65% and 34%). In the TAXUS group a mean of 3.6 lesions was treated and 4.6 stents was implanted/patient. Total length of stents implanted was 86.1 ± 47.9 mm and in 33.2% of patients stenting of >100 mm was performed.

In the CABG group 15% of patients were off-pump cases, 97.3% received at least one arterial graft, 95.6% received an arterial graft to LAD, 27.6% received double arterial grafts (RIMA/LIMA). Only 2.6% of patients received only venous grafts (Table 2).

**Primary endpoint for 12 month MACCE (The non-inferiority analysis):**

Difference in MACCE = 8.3%, therefore the non-inferiority comparison was not met for the primary outcome at 12 months.[11]

**Subgroup MACCE rate:**

Non-inferiority was not proven in this randomised cohort, therefore information for each subgroup is of an observational nature and is hypothesis generating.

At 12 months there was an equivocal MACCE rate in the isolated left main group. In the LM+one vessel disease group there was an increase MACCE rate for CABG (13.2%) vs 7.5% for TAXUS. For LM+two vessel disease and LM+three vessel disease there was a preference for CABG. LM+two vessel disease: CABG= 14.4%, TAXUS=19.8%; LM+three vessel disease: CABG=15.4%, TAXUS=19.3%. For three vessel disease there was a better MACCE for CABG (11.5% vs 19.2% for TAXUS). In the diabetes group the MACCE rate was substantially higher in the TAXUS group than in the CABG group (CABG=14.2%, TAXUS=26.0%).

At 24 months the MACCE rate in the three vessel disease subgroup was 23.8% in the PCI group and 14.4% in the CABG group ($p<0.001$). In the left main subgroup the MACCE rate was 22.9% in the PCI group and 19.3% in the CABG group ($p=0.27$).

**TABLE 2:** Results of the randomised cohort

| | Twelve month results | | | Twenty-four month results | | |
|---|---|---|---|---|---|---|
| | CABG | TAXUS | P-value | CABG | TAXUS | P-value |
| All-cause death | 3.5% | 4.3% | 0.37 | 4.9% | 6.2% | 0.53 |
| CVA rate | 2.2% | 0.6% | 0.003 | 2.8%* | 1.4% | 0.82 |
| Myocardial infarction rate | 3.2% | 4.8% | 0.11 | 3.3% | 5.9% | 0.01# |
| Symptomatic graft closure or Stent trombosis | 3.4% | 3.3% | 0.89 | | | |
| Repeat revascularisation | 5.9% | 13.7% | <0.0001 | 8.6% | 17.4% | <0.001+ |
| MACCE(Myocardial infarction/ CVA/all-cause death/repeat revascularisation) | 12.1% | 17.8% | 0.0015 | 16.3% | 23.4% | <0.001~ |

*After 1 year the increase in CVA for CABG was 0.7% and 0.6% for TAXUS. #After 1 year myocardial infarction rate increased by 1.2% for TAXUS 0.1% for CABG(0.008).
+After 1 year the increase of repeat revascularisation was 3.7% for CABG and 5.6% for TAXUS (p=0.06). ~After 1 year the increase in MACCE was 5.7% for CABG and 8.3% for TAXUS (p=0.03).

## RESULTS IN THE PCI AND CABG REGISTRIES

One hundred and ninety-eight (198) patients were enrolled in the PCI registry and 1 077 in the CABG registry. The CABG group had a higher SYNTAX Score than the PCI group and was therefore ineligible for PCI. The PCI group had a higher Euroscore, because of more co-morbidities (Table 3).[12]

## DISCUSSION

The SYNTAX Study is a landmark study in the treatment of three vessel and left mainstem coronary artery disease. The all-comer design will make it possible to evaluate the proper treatment option for any given clinical situation. However it should be noted that 1 077 (35%) of all the patients screened (n = 3 075) were not eligible for PCI. One hundred and ninety-eight (6.4%) patients were not suitable for CABG, due to a high logistic Euroscore.

**TABLE 3:** Results for the PCI and CABG registries

| | Twelve month results | | Twenty-four month results | |
|---|---|---|---|---|
| | CABG | TAXUS | CABG | TAXUS |
| All-cause death | 2.5% | 7.3% | | |
| Cerebrovascular accidents(CVA) | 2.2% | 0% | | |
| Death / CVA / Myocardial infarction | 6.6% | 10.5% | | |
| Repeat re-vascularisation | 3.0% | 12% | | |
| Myocardial infarction | 2.5% | 4.2% | | |
| Total MACCE | 8.8% | 20.4% | 12.9% | 28.6% |

The higher MACCE for PCI in the randomised control cohort and registry was due to higher repeat procedures as well as higher myocardial infarction rates. There was also a high incidence of staged procedures in the PCI group (14.1% in TAXUS RCT and 13.0% PCI registry). The economic implications will be significant. The myocardial infarction rate continues to rise in the PCI group, but stayed static in the CABG group (5.9% in PCI group compared to 3.3% in the CABG group). This increase of myocardial infarction in the PCI group is most probably due to stent trombosis as well as coronary territories not completely revascularised by PCI.

Symptomatic graft closure/stent thrombosis in RCT was similar in the two groups at 12 months. (CABG = 3.4% vs TAXUS = 3.3%). Stent thrombosis is associated with a higher incidence of malignant sequelae if compared to graft closure: the reported incidence of acute myocardial infarction is 65 – 70% and the mortality is 25 – 45% post stent thrombosis. (JAMA 2005, 293: 2126-2130. Ann Int Med 2006; 144: 913 – 919; Circulation 2007; 15: 1440 – 5). The peri-procedure rate of myocardial infarction after CABG is

**TABLE 4:** MACCE rates with reference to the SYNTAX score at 24 months

| | TAXUS | CABG | |
|---|---|---|---|
| Low SYNTAX score (0-22) | 19.4% | 17.4% | P=0.63 |
| Intermediate SYNTAX score (23-32) | 22.8% | 16.4% | P=0.06 |
| High SYNTAX score (>32) | 28.2% | 15.4% | P=0.001 |

3-6%. In patients with angiographic defined post-procedure graft closure and acute myocardial infarction the mortality is 9.3% if treated with PCI and 39% if treated with re-CABG.[18]

A significant difference in mortality and repeat procedure in especially the three vessel disease/LM+two vessel disease/LM+three vessel disease groups favouring CABG. The reason for this increase in cardiac-related deaths in the PCI group is most probably due to the fact that CABG led to more complete revascularisation compared to PCI. This is more pronounced in the registry co-hort (CABG=2.5%, TAXUS=7.3%).

An increased cerebrovascular event rate in the CABG group of 1.6%. That amounts to a 3 times higher CVA rate in the CABG group. The CVA rate during the second 12 months shows an equivocal increase in both goups.

The SYNTAX score will be an important scoring system to decide on the best treatment option. In the CABG group the MACCE rate in all the SYNTAX Score levels was similar. (0 -22: 14.7%; 23 -32: 12%; ≥33: 10.9%), but MACCE events increased in the PCI group as the SYNTAX Score increased (0 - 22%: 13.6%; 23-32: 16.9%; ≥33: 23.4%). This is amplified in the second year with a significant increase in MACCE in the high SYNTAX Score PCI group. Therefore the higher the SYNTAX Score the higher the cardiac-related complications in the PCI treated group.

SYNTAX will therefore identify the best treatment option for the specific coronary pathology (SYNTAX Score).

Collaboration between surgeon and interventional cardiologist will be important in the future to optimise the best treatment option. Complexity of coronary artery anatomy, the patient's risk for a specific procedure (Euroscore, Parsonnet) and the economic implications should be considered before embarking on a specific procedure.[14]

The 5 year follow-up will be completed in 2011 and will give us much-needed information about the ideal therapy for a specific coronary artery profile.

The treatment of complex coronary artery disease should ideally be managed by a team approach. The SYNTAX Study emphasises the benefits of surgery in this patient population at two year follow up. CABG is known to have good long term results and we need to determine if the same results can be achieved by stenting. At present CABG remains the preferred treatment for complex coronary artery disease based on the two year follow up data from the SYNTAX Trial.

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