

SYNTAX study

The SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery

History of PCI vs CABG

The first PTCA (Percutaneous Transluminal Coronary Angioplasty) or balloon angioplasty, was performed in 1977. Subsequently, the introduction of bare-metal stents (BMS) following balloon angioplasty improved the predictability and long term effect of these procedures and changed the management of coronary artery disease (CAD).


However, the Achilles heel of BMS was in-stent restenosis, or reblocking of the artery (a new phenomenon). Drug-eluting stents (DES), which are BMS coated with a drug that is released slowly to reduce restenosis, were developed to overcome this problem. The first DES were approved by the US Food and Drug Administration (FDA) in 2003. Since then, DES have been shown to reduce the need for subsequent revascularisation procedures compared with BMS, with no significant differences in the rate of death, myocardial infarction (MI), or stent thrombosis.^{1,2}

Early studies, such as the Randomised Intervention Treatment of Angina (RITAⁱ) and Bypass Angioplasty Revascularization Investigation (BARIⁱⁱ) trials, compared coronary artery bypass graft (CABG) surgery with PCI without stenting and reported lower mortality rates with CABG. However, the survival benefit of CABG over PCI disappeared with the introduction of stents, as shown in the Stenting vs Internal Mammary Artery (SIMAⁱⁱⁱ), the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass

ⁱ Sponsored by Advanced Cardiovascular Systems, Medtronic and Schneider.

ⁱⁱ Sponsored by the National Heart, Lung, and Blood Institute

ⁱⁱⁱ Sponsored by Swiss Foundation of Cardiology and Johnson & Johnson



surgery (ERACI-II^{iv}), Arterial Revascularization Therapies Study (ARTS^v), and the Stent or Surgery (SoS^{vi}) trials.³ Improvements in stent design and adjunctive pharmacological therapy in recent years have reduced the need for repeat revascularisation and improved outcomes following stenting, reducing the gap between CABG and PCI.⁴

CABG is still the gold-standard treatment for patients with left main (LM) and multivessel disease, but several studies have demonstrated the efficacy and safety of PCI with DES in patients at high risk. The ARTS-I and ARTS-II trials showed no significant difference at 1 year in the combined rate of death, MI, and stroke in PCI and CABG in patients with multivessel disease.^{5,6} Similar results were reported by the SoS trial in patients with multivessel disease.⁷ The Angina With Extremely Serious Operative Mortality Evaluation (AWESOME^{vii}) trial also showed similar long-term survival rates with CABG and PCI for patients with medically refractory myocardial ischaemia and high-risk features.⁸

However, it has been argued that the stringent exclusion criteria in these trials did not reflect the complexity normally found in daily practice and patients with different CAD severity were included in the same cohort.⁹

The SYNTAX study¹⁰

The SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study was conducted to include a more representative group of high-risk patients with 3-vessel disease (3VD^{viii}) and/or LM disease^{ix}. A local physician team – a cardiac surgeon and interventional cardiologist – assessed each patient to determine what

^{iv} Sponsored by Cook, Inc.


^v Sponsored by Cordis

^{vi} Sponsored by Bard, Guidant ACS, and Schneider

^{vii} Sponsored by The Cooperative Studies Program of the United States Department of Veterans Affairs Research and Development Service

^{viii} Revascularisation for all 3 vascular territories

^{ix} Isolated or in conjunction with 1, 2, 3 vessel disease



procedure to perform according to the patient's operative risk and the coronary vascular lesion complexity. Patients were randomised only if both physicians agreed that complete revascularisation could be performed using either procedure.

PCI was performed using the TAXUS Express^{2™} paclitaxel-eluting stent system.

Aim of the study

The aim of the study was to evaluate whether the benefits of PCI with DES could be extended to a more complex population of high-risk patients. The researchers compared the efficacy and safety of PCI with paclitaxel-eluting stents to CABG in the treatment of patients with 3VD^x and/or LM disease^{xi}.

The primary endpoint is the occurrence of major adverse cardiac and cerebral events (MACCE), including all-cause death, stroke, nonfatal MI, and revascularisation by PCI or CABG 1 year after the procedure.


Study design

The SYNTAX trial was a prospective, multinational, randomised clinical trial of patients with de novo 3VD^x and/or LM disease^{xi}. Patients were assessed to see if they were eligible for either PCI or CABG. After informed consent was obtained from patients, those who were eligible for either procedure were randomised and the remainder, only eligible for one of the revascularisation methods, were followed up in a PCI or CABG registry.

The patient's electrocardiographic data, cardiac enzymes, cardiac medications and anginal status were recorded pre-procedure and during follow-up visits at 1 and 6 months, and 1, 3 and 5 years.

^x Revascularisation for all 3 vascular territories

^{xi} Isolated or in conjunction with 1, 2, 3 vessel disease



Patients were included if they had stable or unstable angina with ischaemia, de novo lesions, with three vessel disease (at least one significant narrowing in each of the 3 coronary arteries (RCA, LAD, LCX)) and/ or LM, and vessel size of at least 1.5 mm in diameter.

Patients with previous PCI or CABG, ongoing acute MI and cardiac enzymes more than 2 times the upper limit, patients with concomitant cardiac valve disease requiring surgical therapy and patients with single or 2VD without LM disease were excluded.

Study results

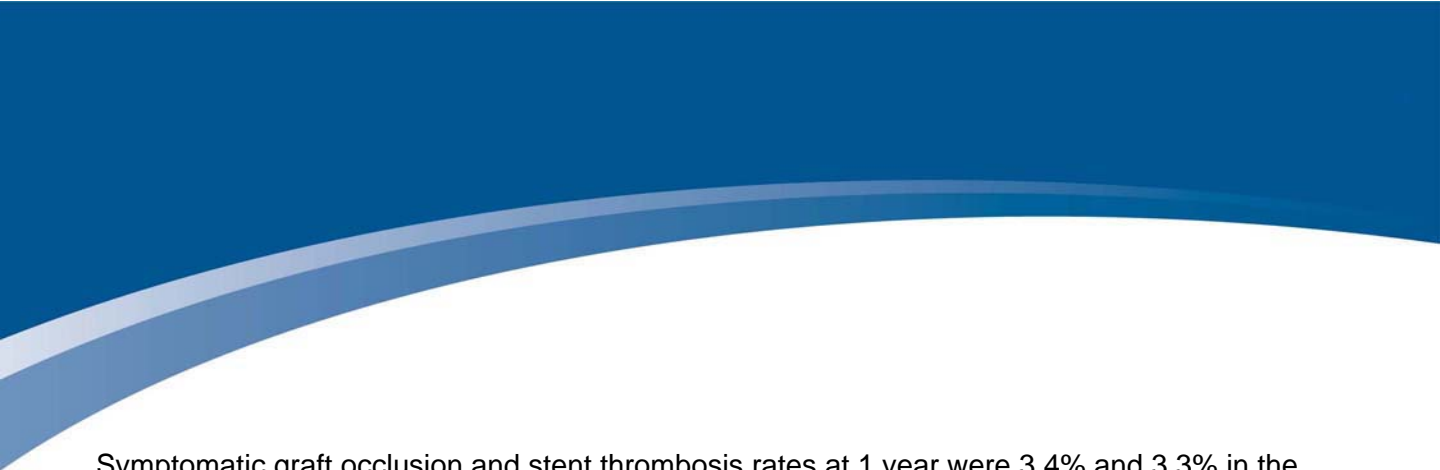
Overall, 3075 patients with de novo 3VD^{xii} and/or LM^{xiii} disease were included in the study. Of these, 1800 were randomly assigned to CABG (n=897) or PCI (n=903). Patients who were eligible for only one of the procedures were enrolled into the CABG (n=1077) or PCI (n=198) registry arms.

One year after the interventions, 849 patients in the CABG group and 891 patients in the PCI group were included in the follow-up analysis. The primary endpoint (12 month MACCE) in this non-inferiority study was not met. The composite safety endpoint (death/CVA/MI) was 7.7% for CABG and 7.6% for PCI patients respectively, indicating comparable safety for PCI and CABG in this population of high-risk patients.

All-cause death rates were similar in patients in the CABG (3.5%) and PCI groups (4.3%; p=0.37) and MI rates were also similar between the two groups (3.2% vs 4.8%, respectively, p=0.11). Stroke occurred in 0.6% of patients undergoing PCI compared with 2.2% of those in the CABG group (p=0.003).

^{xii} Revascularisation for all 3 vascular territories

^{xiii} Isolated or in conjunction with 1, 2, 3 vessel disease



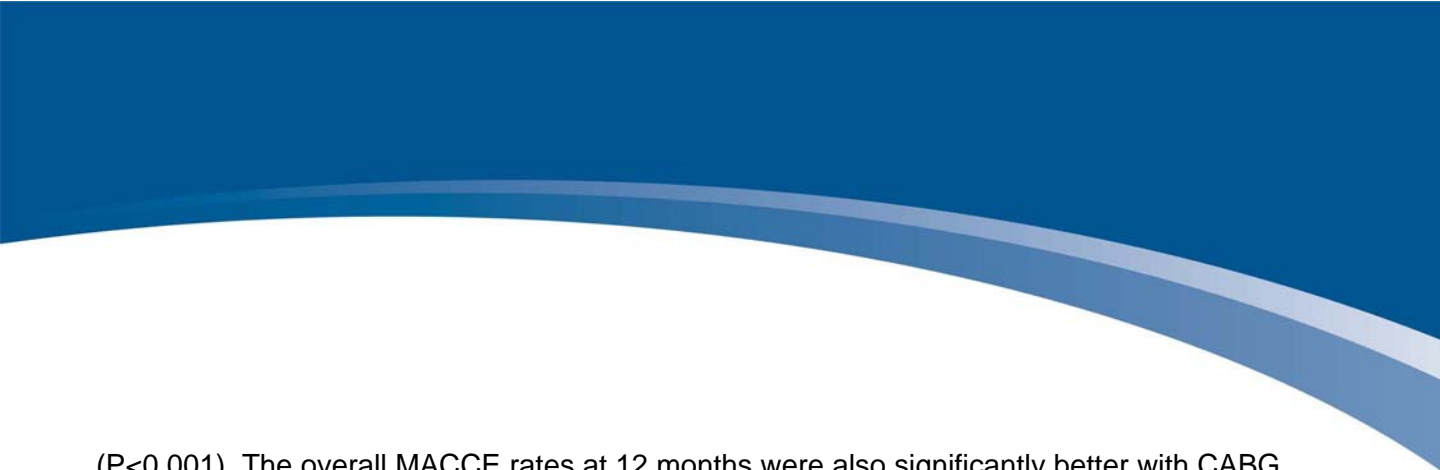
Symptomatic graft occlusion and stent thrombosis rates at 1 year were 3.4% and 3.3% in the CABG and PCI groups, respectively ($p=0.89$). Revascularisation rates were 13.7% in patients in the PCI group compared with 5.9% in the CABG group ($p<0.001$).

Subset analysis

One-year SYNTAX data presented at TCT 2008 was broken down into two subsets: patients with left main disease⁹ or patients with three vessel disease.¹⁰ As the SYNTAX trial did not meet its primary endpoint, the subset analyses was observational only and hypothesis generating.

A total of 705 patients were included in the left main subset analysis. Of these, 348 patients received CABG and 357 patients received TAXUS stents. At 12 months, all cause death was similar between the two groups (4.2% of TAXUS and 4.4% for CABG, $P=0.88$), however, TAXUS was associated with a significantly lower rate of stroke compared with CABG (0.3% vs. 2.7%, $P=0.009$). In addition, TAXUS showed similar results to CABG in rates of MI (4.3% vs. 4.1%, $P=0.97$), the composite of death / stroke / MI (7.0% vs. 9.1%, $P=0.29$), and symptomatic graft occlusion and stent thrombosis (2.7% vs. 3.7%, $P=0.49$). Overall MACCE was also shown to be similar with 15.8% of TAXUS patients recording an event compared with 13.6% of CABG patients ($P=0.44$). The only significant difference in favour of CABG was seen in rates of revascularisation with 6.7% of CABG patients compared with 12.0% of TAXUS patients requiring reoperation ($P=0.02$).

A total of 1095 patients (546 in the TAXUS arm and 549 in the CABG arm) were included in the three vessel disease subset analysis. At 12 months, all cause death was shown to be similar between the two groups (2.9% with CABG and 4.4% with TAXUS, $P=0.18$). There was also no significant difference seen between TAXUS and CABG with respect to stroke (0.8% vs. 1.9%, $p=0.09$), death / stroke / MI (7.9% vs. 6.4%, $P=0.39$) and symptomatic graft occlusion and stent thrombosis (3.7% vs. 3.3%, $P=0.73$). However, there were significantly more MI events in the TAXUS group compared with the CABG group (5.2% vs. 2.6%, $P=0.04$). There was also a significant difference seen in rates of revascularisation with 14.7% of TAXUS patients compared with 5.4% of CABG patients requiring reoperation



($P < 0.001$). The overall MACCE rates at 12 months were also significantly better with CABG (11.2%) compared with TAXUS (19.1%, $P < 0.001$).

SYNTAX Score^{11,12}

One of the key objectives of the SYNTAX trial is to provide guidance to physicians on which revascularisation strategy to use for patients with high risk and complex lesion morphology. The SYNTAX score was developed for this study and will be validated to prospectively identify lesion complexity and subsequent long term safety and efficacy.


The SYNTAX algorithm consists of twelve main questions that determine the dominance, the total number of lesions and segments involved per lesion, lesion characteristics, and whether the criteria for diffuse disease/small vessels is met.

The SYNTAX score is based on:

- American College of Cardiology/ American Heart Association (ACC/AHA) lesion classification system – adverse characteristics of a lesion for revascularisation
- Leaman score – importance of the affected coronary artery segment
- Duke and Institut Cardiovasculaire Paris Sud (ICPS) system classification – for bifurcation of lesions
- Total occlusion classification (J Am Coll Cardiol, 1997;30:649-56)
- Consultation of experts

Each of these classifications is focused on specific functional and anatomical parameters of the lesions. The patient's SYNTAX score is the sum of all these individual classifications and the complexity factor (additive score).

The SYNTAX score takes into account all the necessary variables to grade coronary vascular lesion complexity and select the optimal revascularisation strategy for patients with 3VD or LM disease. Higher SYNTAX scores indicate a more complex disease, a greater



therapeutic challenge and a potentially worse acute and long term outcome. The SYNTAX score was also assessed by an independent core laboratory.

Once validated and standardised, the SYNTAX score will become available online. The validated Syntax score will be presented at the EuroPCR 2009.

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