The SYNTAX Trial

Expert opinions about the results and clinical implications.

EXPERT PANEL

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The 1-year results from the SYNTAX (Synergy Between Percutaneous Coronary Interventions [PCI] With Taxus and Cardiac Surgery) trial were recently presented by Patrick Serruys, MD, et al in the March 9 issue of the *New England Journal of Medicine*.[1]

SYNTAX is a randomized, controlled clinical trial comparing PCI using the Taxus Express[2] paclitaxel-eluting coronary stent system (Boston Scientific Corporation, Natick, MA) to contemporary coronary artery bypass graft (CABG) surgery in 1,800 patients with the most complex coronary artery disease (CAD), specifically left main and three-vessel disease.

The investigators reported that most of the preoperative characteristics were similar in the two groups. Rates of major adverse cardiac or cerebrovascular events (MACCE) at 12 months were significantly higher in the PCI group compared to CABG (17.8% vs 12.4%; $P = .002$), driven by an increased rate of repeat revascularization (13.5% vs 5.9%; $P < .001$); as a result, the primary combined MACCE endpoint for noninferiority was not met. At 12 months, the rates of death and myocardial infarction were similar between the two groups; stroke was significantly more likely to occur with CABG than with PCI (2.2%, vs 0.6%; $P = .003$). The investigators concluded that CABG remains the standard of care for most patients with three-vessel or left main coronary artery disease, because the use of CABG, as compared with PCI, resulted in lower rates of the combined MACCE (all-cause death, stroke, myocardial infarction, and repeat revascularization) at 1 year.

To help clarify for our readers the findings of the SYNTAX trial, we interviewed Patrick Serruys, MD, and Ted E. Feldman, MD, for their opinions on the trial and the resulting data.

WHY WAS THE SYNTAX TRIAL DONE?

Dr. Serruys: Previous trials comparing PCI with CABG were performed with stand-alone PTCA or bare-metal stents. Due to the improvements in stent technology and the development of drug-eluting stents, we had to test again bypass surgery versus PCI. However, before each of these trials, we have what we call the "Meeting of the Magnificent Seven" (surgeons and interventional cardiologists). During this meeting, Frederick Mohr, MD, a surgeon and co-PI of the trial, made it clear that there will be no other randomized trials comparing surgery versus PCI in a highly select population—if we were to work together, it would be in an all-comer population, with very few exclusions. That was a very basic concept. On the other hand, we were worried about whether we had the population to do this trial. In 2004, during preparation for the trial, we conducted a Web site survey in 100 centers in the United States and Europe, and we discovered that in a period of 3 months these 100 centers had treated more than 12,000 patients with left main and three-vessel disease. Basically, one-third of these patients were treated for main stem and two-thirds were treated for three-vessel disease. One-third of the entire population was treated by interventional car-

diologists, and the remainder was treated by a surgeon. There was a feeling that in practice, at least in Europe, physicians were already doing that without the support of evidence-based medicine.

After this meeting with the surgeons, we recognized that we needed to validate and legitimize what is actually happening in the real-world clinical setting. The surgeons also insisted that we have an all-comers format, thus there were no inclusion/exclusion criteria. What was most important was a dialogue and consensus between the surgeon and the interventional cardiologist about treatment approach.

In some cases, the interventional cardiologists determine that PCI would be too risky in the patient and those patients went on to CABG. On the other hand, in some patients it was the surgeon who said that there was too much comorbidity and those patients went on to PCI. There also was a group of patients (in this case 1,800) for whom both the surgeons and interventional cardiologists felt confident that they could treat safely and with efficacy. That was the basis for the randomized SYNTAX trial.

Dr. Feldman: Through the evolution of plain balloon angioplasty to bare-metal stents to drug-eluting stents, we have seen increasingly good outcomes from PCI in increasingly complicated patients and lesions. We felt that recent outcomes with drug-eluting stents suggested that it was a good time to test whether drug-eluting stents deliver outcomes similar to bypass surgery in the most complex coronary patients. We had good reason to believe this was so because prior to initiating the randomized trial, a survey of practices around the world showed what was being done in the drug-eluting stent era with left main and three-vessel disease. We found that most practices surveyed were treating approximately a third of their left main and three-vessel patients with drug-eluting stents rather than with bypass surgery.

WHAT PATIENT SUBSETS ARE MOST IMPACTED BY THE SYNTAX RESULTS?

Dr. Serruys: Many patients had CABG after review by the surgeon and interventionist because they were believed to be unsuitable for PCI. These were included in the registry. It is clear that the patients who went to the bypass registry did so, not through a statistical approach, but as a category that was defined through the consensus and agreement between surgeons and interventional cardiologists—looking at the patients, their anatomy, and their comorbidities. Looking back, we now see that the novel scoring system we developed for the trial to categorize disease complexity, the SYNTAX score, was higher in patients referred for CABG in the registry.

With the SYNTAX score going from 0 to 100, we start to have a common language that allows us to quantify patients. The great result of the SYNTAX trial is that in the randomized population, we realized that the patients who have a SYNTAX score below 22 do very well with PCI, even in terms of safety, mortality, and myocardial infarction. This really justifies treating these patients with PCI, at least based on the first year of follow-up. In the intermediate score group (SYNTAX score 22 to 33), multivessel disease was already doing better with surgery, but the main stem was still doing very well with PCI. In the group with a SYNTAX score above 33, there was no doubt that these patients had to be treated by surgery.

From the total population referred to the surgeon and interventional cardiologist, in an all-comers decision, 66% are better treated by surgery, and 33% can legitimately be treated by PCI, with the big caveat being 1-year follow-up.

Dr. Feldman: The group studied in SYNTAX was the overall population of left main and three-vessel disease. The patient population we randomized is, by definition, those who the surgeon and interventional cardiologist agreed could be treated with either therapy. Thus, there is still a large group of patients in whom we, as interventional cardiologists, will look at the anatomy and determine that it is not realistic to achieve revascularization percutaneously. From analysis of subgroups in SYNTAX, we are seeing that among the left main and three-vessel disease patients, those with anatomy in first tertile SYNTAX scores have outcomes that are at least as good as bypass, and in the second tertile of SYNTAX score, the left main patients also do very well with PCI.

WHAT IS THE MAJOR TAKE-HOME MESSAGE FROM THE TRIAL FOR PRACTITIONERS?

Dr. Serruys: I think for the practitioner, the message is that they should no longer rely on a simplistic description of patients with three-vessel disease. They should have a very careful assessment of the coronary circulation, with the SYNTAX score telling the expert surgeon/interventional cardiologist that with that type of score, it is better to undergo PCI or CABG. The practitioner needs to understand that there is a score that helps to clarify the indication.

Dr. Feldman: One very powerful message is that, particularly in patients with left main disease in whom surgery has been the only alternative for many years, things have really changed. Clearly, we have good results in the

lower two tertiles of SYNTAX score with left main disease, with a high expectations of success and a very clear proof of procedure safety.

HOW IS THE SYNTAX TRIAL DIFFERENT FROM PREVIOUS TRIALS COMPARING PCI AND CABG?

Dr. Serruys: There are a few differences. First, it was an all-comers design. There was no "cherry picking" of patients or selection process. Second, there was the concept of a heart team. That is, both a surgeon and an interventional cardiologist were involved together in assessing patients. Together, they came to a consensus about the patient.

Dr. Feldman: Previous trials, such as BARI and COURAGE (which compared PCI and medical therapy), screened large numbers of patients and randomized only a few percent of the screened population. SYNTAX was designed as an all-comers trial, with very few exclusions (prior revascularization, acute MI, and need for other cardiac operation were the only exclusions). With those very liberal inclusion criteria, 71% of the screened patients were enrolled in either the randomized trial or the registry. SYNTAX differs in that it really does apply to the broad target population. That is, it is a real world experience.

HOW DO YOU FORESEE THE RESULTS FROM SYNTAX AFFECTING PRACTICE?

Dr. Serruys: I think an important point is that the idea of the main stem being only treatable by surgery is now part of evidence-based medicine. We now know what types of main stem disease can be reasonably approached by PCI. This is a very important message for the future.

It is the same story for three-vessel disease. We now know which patients, and with what type of quantified score, can be approached using PCI.

Dr. Feldman: The hope is that a growing proportion of patients with left main and three-vessel disease who have the lower two tertiles of anatomic complexity based on SYNTAX score will be able to have revascularization without having to recover from a sternotomy. That would be a huge impact. Also, the stroke risk in the PCI arm of the trial was substantially less than that of the surgical arm.

IS THE SYNTAX SCORE A USEFUL CLINICAL SCORING SYSTEM?

Dr. Serruys: Yes. It is actually a combination scoring system. There is the SYNTAX score, which is a score that quantifies the coronary anatomy, and then there is the classical general clinical score aspect (ie, Euroscore and Parsonnet).

Dr. Feldman: We have demonstrated that it is, based on the trial results. We have previously never had a systematic way to decide if a given patient with complex coronary disease will have a better outcome with bypass or PCI. The data we are seeing from analyses of outcomes by SYNTAX score have reinforced that it is a useable tool.

WHAT QUESTIONS DOES THE SYNTAX TRIAL FAIL TO ANSWER?

Dr. Serruys: When we designed the trial, we had to have a general hypothesis. The question was, if you take together the left main and the three-vessel as one package, is PCI noninferior with respect to CABG? It was basically a test of noninferiority. We could not afford to have a difference greater than 6.8% between the two groups and still meet the noninferiority. As a matter of fact, the difference between the two groups is 5.5%, but you have to include the standard deviation in the noninferiority test. PCI failed the test of noninferiority. Therefore, in left main and three-vessel disease globally, PCI is inferior to CABG. It is only when we separately analyze three-vessel and left main disease, and only when we start to look at the SYNTAX score, that we start to be able to delineate situations in which PCI can actually be used as a method of treatment.

Dr. Feldman: One of the largest unanswered questions is that the trial endpoint is a 1-year endpoint. We will only know about later outcomes as time passes. I think people are concerned that the mortality rates between surgery and PCI might begin to diverge after 1 year (and as late as after 3 years). We will, of course, eventually have 5-year results from the SYNTAX trial. What is also important to remember is that we have several meta-analyses of all of the existing PCI and surgery experiences that suggest no differences in mortality at 5 years or later. Although there has been a mortality difference in some trials, it has been primarily with plain balloon angioplasty in the pre-stent era. Also, in previous trials, there was less good medical therapy and less developed surgical and PCI techniques and technology. I am very optimistic that the long-term results are going to be similar to the acute results. ■

1. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360:1024-1026.