

Three-year SYNTAX results extend CABG advantage to intermediate-risk patients

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Por Shelley Wood

Geneva, Switzerland - September 13, 2010- Three-year results for the landmark [SYNTAX](#) trial are bringing some clarity to a finding just hinted at—then strenuously debated—at the two-year mark: "intermediate-risk" patients with complex coronary disease by SYNTAX score are probably better off getting open-heart surgery than PCI with a Taxus paclitaxel-eluting stent, investigators say. Cumulative event rates also point to ongoing separation of event curves for both MI and even all-cause death, although the latter by no means was statistically significant at three years.



Dr A Pieter Kappetein (Erasmus Medical Center, Rotterdam, the Netherlands), who presented the three-year results at the [European Association of Cardiothoracic Surgery 2010 Annual Meeting](#), called the findings in the intermediate-risk subgroup the "most remarkable" difference to emerge between the two- and three-year mark, although not necessarily surprising. Indeed, **Dr Manuel J Antunes** (University Hospital, Coimbra, Portugal), who discussed the two-year results after their presentation last year, predicted that between-group differences that were statistically different at year one would remain so and that differences that trended in favor of one group would reach statistical significance in due time.



Dr David Cohen (Saint Luke's Mid America Heart Institute, Kansas City, MO), commenting on the results for heartwire, said he was not "particularly concerned" by the three-year results, which, he noted, were only marginally different from the [two-year results](#) and continue to be driven by a higher revascularization rate in the Taxus/PCI-treated patients. He did single out as "interesting" the "continued gradual separation of the curves for both MI and all-cause mortality" to year three.

"These findings may relate to a variety of factors, including very late stent thrombosis, progression of disease at unstented segments, or the more complete revascularization afforded by initial CABG in these highly complex patients. Although I suspect that some of these late events might have been avoided with the current generation of drug-eluting stents [DES], which are safer than the paclitaxel-eluting stents used in SYNTAX, bypass surgery continues to set a very high standard for our patients."

The SYNTAX trial

As previously reported by heartwire, SYNTAX was an 1800-patient trial randomizing patients with left main coronary disease and/or three-vessel disease to either CABG or PCI using the Taxus DES. At one year, PCI failed to meet the prespecified margin of noninferiority against CABG, after the primary end point (major adverse cardiac and cerebral events [MACCE]) occurred significantly more often among PCI-treated patients than among CABG-treated patients, driven by repeat procedures in the PCI group. For the

"harder" end point of death/stroke/MI, rates were almost identical between the two groups; the stroke rate was higher in the CABG-treated patients. Two-year results, presented at last year's **European Society of Cardiology** meeting, showed MACCE rates continuing to diverge, still driven by higher repeat-revascularization rates and a signal of increased MI among PCI-treated patients.

At three years, 95% of the original cohort of 1800 patients was available for follow-up. Rates of the primary end point, MACCE, remained statistically lower in the CABG-treated patients, driven by the lower rates of repeat-revascularization procedures—just under 11% in the CABG-treated patients vs nearly 20% in the PCI/DES group. For the hard composite end point of all-cause death, stroke, and MI out to three years, there were no differences between groups.

Stroke, which at one year had significantly favored the DES-treated patients, was no different between the two groups by three years and nearly identical between years one and two and between two and three. MI rates, which had numerically favored the CABG-treated patients at one year and had reached statistical significance by the two-year mark, continued to be significantly lower in CABG group from year two to three and cumulatively were significantly lower in the CABG-treated patients over three years, with an absolute difference of 3.5%.

Cumulative event rates to three years

Cumulative event rate	CABG (%)	Taxus (%)	p
MACCE	20.2	28.0	<0.001
Death, stroke, MI	12.0	14.1	0.21
All-cause death	6.7	8.6	0.13
Stroke	3.4	2.0	0.07*
MI	3.6	7.1	0.002
Repeat revascularization	10.7	19.7	<0.001

*Stroke rate between one and two years 0.6% vs 0.7% and between two and three years 0.5% vs 0.6%

For the analysis of outcomes according to baseline SYNTAX score—developed to characterize complex coronary vasculature in patients with high-risk left main and/or three-vessel disease—Kappetein reminded *heartwire* that at both one and two years, the lowest-risk patients by SYNTAX score (score of 0-22) had MACCE rates that were very similar for both CABG- and DES-treated patients. By contrast, in patients with the highest SYNTAX scores (>33), reflecting the most complex disease, the SYNTAX trial clearly showed that CABG was the best option. As such, surgeons and interventionalists have largely been in agreement that PCI is a reasonable option for the lowest-risk group, while surgery is the clear winner for the highest-risk patients.

In intermediate-risk patients (23-32), the two-year results showed a trend toward improved outcomes with CABG, but no statistically significant differences, leading some to argue that PCI could still be considered for patients with an intermediate SYNTAX score—particularly if they had left main disease, but not triple-vessel disease. The three-year MACCE results in these intermediate-risk patients, however, show that the event curves have continued to

separate, reaching 27.4% for DES-treated patients and 18.9% for the CABG-treated patients, a difference that now reaches statistical significance ($p=0.02$).

What's clear from these three-year results, Kappetein told *heartwire*, is that it is only the lowest-risk patients by SYNTAX score in whom both PCI and CABG can be considered to be reasonable options.

What MI type?

According to Kappetein, the increased MACCE rate in the intermediate-risk group was driven by repeat-revascularization procedures, but also by the uptick in MIs among PCI-treated patients. But he acknowledged that it is not yet clear what kinds of MIs are driving this difference. Of note, rates of stent thrombosis (4.5%) among PCI-treated patients at three years were not statistically different from the rates of symptomatic graft occlusion (3.5%), hinting that the MIs being counted were not being caused solely by late stent thrombosis.

Asked if the bulk of these MIs were periprocedural "enzyme leaks," Kappetein said: "We don't know that yet, but we need to look deeper into that."

Cohen, for his part, stressed that the "enduring lesson" from SYNTAX is that revascularization for chronic, complex coronary disease needs to be individualized to coronary anatomy, comorbidities, and patient preferences.

"The real value of SYNTAX continues to be in helping to provide high-quality, objective information to inform these complex decisions," he commented. "I do think that is an important yet often-unappreciated aspect of SYNTAX. We often focus too much on 'winners' and 'losers.' The real winner here is the patient."