Prognostic factors in primary and elective percutaneous coronary intervention

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Chapter 20

Would SYNTAX have been a positive trial if XIENCE V was used instead of TAXUS? A meta-analysis of a first vs. a next generation drug eluting stent

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Treatment options for coronary revascularisation include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). In the 'synergy between PCI with TAXUS and cardiac surgery (SYNTAX)' trial, PCI and CABG using state-of-the-art techniques (using paclitaxel-eluting stents and arterial grafts, respectively) were compared in the treatment of complex coronary artery disease. In Syntax, PCI was inferior to CABG at one year, entirely due to an increased repeat intervention rate. We hypothesised that the use of a superior drug-eluting stent system could reduce the need for repeat intervention.
Contemporary treatment options for coronary revascularisation include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Over the past decades, PCI has evolved from a treatment for single-vessel coronary artery disease into a real alternative to CABG for treatment of complex multivessel coronary artery disease. The design of coronary stent systems has improved continuously since the introduction of the first commercially available coronary stent, the Palmaz-Schatz stent. From the bare metal stent period we have moved into the present era of drug-eluting stents (DES). Many DES are currently available, all composed of similar components (a stent platform, a polymer carrying the drug and a drug). However, their clinical effectiveness differs widely.

The Synergy between PCI with TAXUS and cardiac surgery (SYNTAX) trial investigated whether PCI with DES (paclitaxel-eluting stents [PES], TAXUS, Boston Scientific, Natick, MA) was non-inferior to CABG in the treatment of complex coronary artery disease. The primary clinical endpoint was a composite of major adverse cardiac and cerebrovascular events (MACCE) consisting of death from any cause, stroke, myocardial infarction, or repeat revascularisation. In SYNTAX, PCI was inferior to CABG at one year, entirely due to an increased repeat intervention rate.

We hypothesised that the use of a superior next-generation DES could reduce the need for repeat intervention after PCI. To investigate whether the everolimus-eluting stent (EES) (XIENCE V, Abbott Vascular, Santa Clara, CA, also distributed as PROMUS, Boston Scientific, Natick, MA) is superior to the PES we performed a random-effects meta-analysis of the four randomised clinical trials comparing EES with PES for which one-year results have been published.

We studied the following safety and efficacy endpoints: death from any cause, myocardial infarction, target lesion revascularisation, and definite or probable stent thrombosis by Academic Research Consortium (ARC) definitions. In the four trials, a total of 4194 patients were randomised to EES and 2489 patients to PES. Results of the meta-analysis are shown in figure 1. At one year, patients treated with the EES had significantly lower rates of myocardial infarction (risk ratio [RR] 0.57), target lesion revascularisation (RR 0.49), and ARC definite or probable stent thrombosis (RR 0.36). These results could be explained by differences between both DES in the underlying stent platforms, differences in the drug and differences in the polymer eluting the drug (table 1).

**Table 1** Differences in stent design between the everolimus-eluting stent (EES) and the paclitaxel-eluting stent (PES).

<table>
<thead>
<tr>
<th>Underlying stent platform</th>
<th>Strut thickness</th>
<th>Polymer</th>
<th>Polymer thickness</th>
<th>Drug</th>
<th>Drug release kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilink Vision stent, made of L-605 cobalt chromium alloy</td>
<td>81 µm</td>
<td>2-layer poly n-butyl methacrylate and polyvinylidene fluoride hexafluoropropylene copolymer</td>
<td>7.8 µm</td>
<td>Everolimus (µg/mm²): an analogue of sirolimus, an antiproliferative, anti-inflammatory, and immunosuppressive agent which arrests the cell cycle by activation of the mammalian target of rapamycin</td>
<td>Releases 80% of the drug within 30 days after implantation</td>
</tr>
<tr>
<td>EXPRESS2 or Liberté, made of 316L stainless steel</td>
<td>EXPRESS2: 132 µm, Liberté: 97 µm</td>
<td>3-layer styrene-isobutylene-styrene copolymer</td>
<td>17.8 µm</td>
<td>Paclitaxel (1 µg/mm²): an antineoplastic agent which arrests the cell cycle by stabilisation of microtubules</td>
<td>Burst release in the first 48 hours after implantation, slow release over the next 10 days</td>
</tr>
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</table>
In SYNTAX, PCI would have been non-inferior to CABG if the 95% upper limit of the confidence interval (CI) for the difference in MACCE was below the prespecified delta of 6.6%. We calculated the minimal reduction in MACCE needed in the PCI group to meet the non-inferiority criterion. A hypothetical reduction of 2.2% in one-year MACCE (20 events/891 patients) would reduce the MACCE rate for PCI to 15.6% (139 events/891 patients). Assuming an unchanged MACCE rate for CABG (105 events/849 patients, 12.4%), this would have resulted in non-inferiority (absolute difference in MACCE 3.2%, 95% CI 0.0 to 6.5%).

Based on the meta-analysis, the use of EES instead of PES in SYNTAX might have led to a total reduction of approximately 81 events in the PCI group (hypothetical relative reductions of 51% in repeat intervention and 43% in myocardial infarction). This is clearly more than the needed reduction of 20 events to achieve non-inferiority between CABG and PCI in SYNTAX. However,
since patients in SYNTAX had relatively complex lesions compared with patients in the randomised trials included in our meta-analysis, these results cannot be directly extrapolated to SYNTAX. Moreover, the observed reduction in target lesion revascularisation might not directly reflect a reduction in overall repeat intervention. Finally, patients with diabetes mellitus may not benefit from EES use as a subgroup analysis from the SPIRIT IV trial showed comparable one-year results for EES and PES in diabetic patients.  

Ultimately, whether PCI with EES is non-inferior to CABG can only be determined by another large randomised controlled trial such as the recently announced Evaluation of XIENCE Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial which will randomise 2500 patients with unprotected left main disease to CABG or PCI with EES.

PCI versus CABG: It isn’t over yet!

Reference List