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# **Two-year outcomes after percutaneous coronary intervention with drug-eluting stents or bare-metal stents in elderly patients with coronary artery disease.**

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Word count: 3986

## **(1) Abstract**

### **Background**

Patients above 75 years of age represent a fast-growing population in the cathlab. In the SENIOR trial, patients treated by percutaneous coronary intervention (PCI) with drug eluting stent (DES) and a short duration of P2Y12 inhibitor (1 month and 6 months for stable and unstable coronary syndromes respectively) compared to bare metal stents (BMS) was associated with a 29% reduction in the rate of all-cause mortality, myocardial infarction (MI), stroke, and ischaemia-driven target lesion revascularization (ID-TLR) at 1 year. The results at 2 years are reported here.

### **Methods and results**

We randomly assigned 1200 patients (596[50%] to the DES group and 604[50%] to the BMS group). At 2 years, the composite endpoint of all-cause mortality, MI, stroke and ID-TLR had occurred in 116(20%) patients in the DES group and 131(22%) patients in the BMS group (RR 0.90 (95%CI 0.72-1.13),  $p=0.37$ ). IDTLR occurred in 14(2%) patients in the DES group and 41(7%) patients in the BMS group (RR 0.35 (95%CI 0.16-0.60),  $p=0.0002$ ). Major bleedings (BARC 3-5) occurred in 27(5%) patients in both groups (RR 1.00, (95%CI 0.58-1.75),  $p=0.99$ ). Stent thrombosis rates were low and similar between DES and BMS (0.8% vs 1.3%, (RR 0.52 (95%CI 0.01-1.95),  $p=0.27$ ).

### **Conclusions**

Among elderly PCI patients, a strategy combining a DES together with a short duration of DAPT is associated with a reduction in revascularization up to 2 years compared to BMS with very few late events and without any increased in bleeding complications or stent thrombosis.

## **(2) Introduction**

Elderly patients used to receive bare-metal stents (BMS) instead of drug-eluting stents (DES) during percutaneous coronary interventions (PCI) to shorten the duration of double antiplatelet therapy (DAPT) and minimize the risk of bleeding complications<sup>1-4</sup>. They have been largely excluded, or highly selected, from randomized clinical trials, and long-term outcomes in this population are scarce.

In the randomized SENIOR trial, a DES (SYNERGY stent, Boston Scientific, Marlborough, MA, USA) was compared to a BMS (REBEL or OMEGA, Boston Scientific) in elderly patients ( $\geq 75$  years old) with coronary artery disease at 1 year receiving a similar short duration of DAPT. DES reduced the occurrence of the primary endpoint, a composite of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularization (IDTLR) by 29% (Relative Risk 0.71 (95%CI 0.52-0.94),  $p=0.02$ ), largely driven by a substantial decrease in ischemia-driven revascularization (2% vs 6%, RR 0.29, CI 95% 0.11-0.54,  $p=0.0002$ )<sup>5</sup>. Secondary endpoints which included bleeding complications and stent thrombosis were similar and low in both groups<sup>5</sup>.

To further characterize the long-term outcomes of PCI with DES versus BMS in this elderly population, we report here the final outcomes of the trial at 2-year after the intervention.

## **(3) Materials and Methods**

### **Study design and participants**

The trial design has been reported and described previously<sup>6</sup>. Briefly, SENIOR is a randomized single-blind trial. Patients were eligible if they were aged 75 years or older; had stable angina, silent ischaemia, or an acute coronary syndrome, and had at least one coronary artery with a stenosis with a visual diameter of at least 70% ( $\geq 50\%$  for left main stem) deemed eligible for

PCI. We required patients with silent ischaemia to have a left ventricular myocardial perfusion defect of at least 10% or a fractional flow reserve of lower than 0.80 for the lesion to be considered for PCI. Exclusion criteria were indication for myocardial revascularization by coronary artery bypass grafting; inability to tolerate, obtain, or comply with DAPT; requirement for additional surgery; non-cardiac comorbidities with a life expectancy of less than 1 year; previous haemorrhagic stroke; allergy to aspirin or P2Y12 inhibitors; contraindication to P2Y12 inhibitors. The study complied with the Declaration of Helsinki and all patients eligible for enrolment provided written informed consent in accordance with the local institutional review board or ethics committee. The study was managed by CERC (Cardiovascular European Research Center), an independent research organization. The institutional review board at each site approved the study.

#### Randomization and masking

Randomization was achieved through a web-based system available 24 h per day all year round, and maintained by the Data Coordinating Center (CERC, Massy, France). The duration of DAPT (1–6 months) was decided and entered into the interactive web response system before randomization. Importantly, all clinical events, including ischaemia-driven revascularizations, were reviewed by an independent committee masked to treatment allocation. This committee adjudicated all components of both the primary endpoint and all secondary endpoints in a masked fashion.

#### Procedures

The duration of DAPT was determined according to the patients' initial presentation: 1 month in stable patients and 6 months in unstable patients; these durations were recommended per

protocol for all patients but the intended duration was left to the discretion of the physician. The patients were then randomly assigned to PCI with a bioabsorbable polymer DES (Synergy stent) or a similar thin-strut BMS (Omega or Rebel stent). Staged procedures were allowed if performed within 2 weeks of the index procedure using the same stent.

## Outcomes

The primary endpoint in the SENIOR trial was the cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE) at 365 days. MACCE were defined as a composite of all-cause mortality, myocardial infarction, IDTLR, or stroke. Secondary endpoints included BARC 2-5 and BARC 3-5 bleeding complications according to the Bleeding Academic Research Consortium classification (BARC)<sup>7</sup>; definite or probable stent thrombosis as defined by the Academic Research Consortium<sup>8</sup> (safety outcome); all revascularizations (consisting of target vessel revascularization, non-target vessel revascularization, and target lesion revascularization); all components of the primary endpoint; and cardiovascular death, at 30 days, 180 days, 365 days, and 2 years. SENIOR 2-year results outcomes are reported here.

## Statistical analysis

Statistical analysis has been precisely described earlier<sup>5</sup>. Briefly, the study was powered to test the superiority of DES with a relative 25% reduction in the primary endpoint compared with BMS at one year. All analyses (including safety analyses) were performed on an intention-to-treat (ITT) basis with a two-sided significance level of 0.05. We did not correct for multiple testing. Hence, results presented here are only hypothesis generating.

The SENIOR trial is registered with ClinicalTrials.gov, number NCT02099617.



## Role of the funding source

The funder had no role in study design, data collection, site monitoring, data analysis, data interpretation, or writing of the report. Members of the Scientific Committee had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

## **(4) Results**

Between May 21, 2014, and April 14, 2016, we randomly allocated 1200 patients (596 [50%] to DES and 604 [50%] to BMS). Patients were on average 81.4 years (SD 4.3) old and predominantly male (747 [62%]). The overall patient population had a high-ischaemic and high bleeding profile typical for elderly patients including hypertension, hypercholesterolaemia, atrial fibrillation, impaired renal function, previous myocardial infarction, and anaemia (Table 1). The two groups were well balanced except for an excess of previous myocardial infarction in the DES group and more patients with hypertension and peripheral vascular disease in the group receiving a BMS than in those receiving a DES. Two thirds of the two populations were treated with beta-blocker agents and RAS inhibitors, 80% were on statins<sup>5</sup>. The indication for PCI was stable or silent coronary artery disease in 656 patients (55%) or an acute coronary syndrome in 544 (45%) patients (Table 1). Radial access approach was largely predominant (80% in each group)<sup>5</sup>.

A 1-month DAPT regimen was planned before randomization for 683 (57%) patients (Table 2). Less than 50% of the patients received 6-month DAPT irrespective of stent type. Importantly, the duration of DAPT was similar between both groups<sup>5</sup>. Clopidogrel was the P2Y12 inhibitor in 1057 (88%) patients after PCI. At 2 years, only a minority (<10%) of patients was still receiving DAPT (Table 2).

At 2 years, the composite endpoint had occurred in 116 (20%) patients in the DES group and 131 (22%) patients in the BMS group (relative risk (RR) 0.90 (95% CI 0.72-1.13),  $p=0.37$ ) (Table 3, Figure 1). Between 1 and 2 years all-cause mortality occurred in 39 (7%) and 17 patients (3%) in DES and BMS groups respectively, while cardiac mortality occurred in 20 (3%) and 8 (1%) patients in these respective groups. However, all-cause mortality at 2 years was not different between the two types of stents: 13% in the DES group and 11% in the BMS group (RR 1.18 (95% CI 0.86-1.62),  $p=0.31$ ), and neither was cardiac mortality (RR 0.98, (95% CI 0.64-1.49),  $p=0.90$ ) (Table 3, Figure 1). Myocardial infarction was rare between 1 and 2 years and the occurrence of an MI at 2 years was similar between DES and BMS (RR 0.86, 95% CI 0.51-1.42) (Table 3).

IDTLR at two years occurred in fewer patients in the DES group than in the BMS group, respectively 14 (2%) patients and 41 (7%) patients (RR 0.35 (95% CI 0.16-0.60),  $p=0.0002$ ). Similarly, the rate of all- revascularizations was lower in DES patients ( $n=40$ , 7%) than in the BMS group ( $n=66$ , 11%) (RR 0.61 (95% CI 0.41-0.89),  $p=0.01$ ) (Table 3, Figure 1).

Bleeding complications were not different between the two treatment arms. At 2 years, major bleedings (BARC 3-5) occurred in 27 (5%) patients in DES and BMS groups with only 6 patients reporting bleeding between 1 and 2 years in both groups (Table 4). Definite and probable stent thrombosis were similar and low in both groups, respectively 4 (0.7%) patients in the DES group and 8 (1.3%) patients in the BMS group. Only 1 episode of ST between 1 and 2 years in the entire population (Table 4).

## **(5) Discussion**

In SENIOR, the use of DES together with a short duration of DAPT is associated with a lower risk of MACCE at 1 year, mainly driven a reduction in revascularizations with similar bleeding and stent thrombosis compared to BMS in a all-comers elderly population<sup>5</sup>.

The results reported here show a preserved benefit up to 2 years, with a significant reduction in ID TLR ( $p<0.0002$ ) although the MACCE benefit did not remain statistically significant.

In our trial, the occurrence of myocardial infarction did not differ between the two groups at 2 years and was low in both groups. Importantly, the incidence of myocardial infarction in our BMS population was more than two times lower than with BMS in similar studies who did show a significant reduction in its incidence after DES<sup>9,10</sup>. Furthermore, a recent meta-analysis of randomized trials which compared DES with BMS in elderly patients showed that the use of a DES was associated with a lower incidence of myocardial infarction<sup>11</sup>. In an individual patient data meta-analysis of randomized clinical trials to compared outcomes after implantation of DES or BMS during PCI, Piccolo et al reported a reduction in the risk of myocardial infarction and non-significant cardiac mortality benefit<sup>12</sup>. The choice of a thin-struts BMS in our control arm is potentially a key factor in these diverging findings.

Not surprisingly, PCI with a DES did not alter 2 years all-cause mortality in this elderly population, possibly because of the unpredictable nature of non-cardiac mortality, which was higher in our DES aged population at 2 years. All-cause mortality, a component of our MACCE primary endpoint, was numerically higher in DES- compared to BMS-treated patients between 1 and 2 years and might explain the absence of statistical significance in MACCE events at 2 years between the two groups. One potential explanation for this observation is the play of chance in this elderly population with severe comorbidities, although we cannot exclude a catch-up of late non-cardiac events related to our interventions. It is important to note, however, that cardiac mortality at 2 years was similar in both groups.

The benefit in terms of IDTLR, which implies not only a reintervention but also often a rehospitalization and re- introduction of a potentially harmful DAPT regimen, remains important because it is not trivial for older patients, a fast-growing population in the cathlabs. It is also important to note that the benefit of DES on IDTLR is maintained at 2 years despite the excellent results of the BMS in this specific outcome with only 6% and 7% IDTLR at 1 and 2 years, respectively. The choice of the stent for the control group is clearly of pivotal importance when dealing with reintervention and could have been more pronounced with another BMS. The use of DES with short duration of DAPT represents the default strategy for PCI in elderly patients now and is recommended by the current European and American guidelines<sup>13,14</sup>.

Indeed, since the publication of the 1 year results of the SENIOR trial, European Society of Cardiology guidelines recommend a 6 month regimen of DAPT for stable coronary artery disease and a 12 month regimen of DAPT for unstable patients, which can respectively be reduced to 1 month for stable presentation and 6 months for unstable presentation for patients with high bleeding risk<sup>13</sup>.

Importantly, the benefit of DES in terms of revascularization in SENIOR was accompanied with a similarly low rate of BARC 2-5 and BARC 3-5 bleeding complications and stent thrombosis between the two treatment arms. In a sub-study of the LEADERS FREE trial, HBR patients over 75 years (63%), were treated with drug coated stents or BMS with a very short DAPT of 1 month<sup>9</sup>. At one year, major bleedings were high in this population with more than one HBR criteria, although still similar (7.3% vs 8.2%,  $p=0.55$ ) between the two groups. Bleeding complications in SENIOR are closer to those observed in the ONYX ONE trial, where a DES was compared with polymer-free drug coated-stents in HBR patients (patients were over 75 years old in two thirds of the cases)<sup>15</sup>.

These findings should be interpreted in view of a few limitations. First this trial was single-blinded. Second, the absence of a significant reduction in MACCE at 2 years might be related to non-significant differences in all-cause mortality, due to a higher incidence of non-cardiac mortality, an interfering factor which typically remains difficult to interpret in this elderly population. Furthermore, the trial was powered to show a difference in MACCE at 1 but not at 2 years. Third, the findings of this study apply to a specific thin strut DES platform and cannot, therefore, be extrapolated to other bio-absorbable or durable polymer DES platforms. Fourth, in selected high thrombotic risk patients, a longer duration of DAPT might still be beneficial, especially if the elderly patient does not have other high bleeding risk features. Finally, most of our patients were predominantly treated with clopidogrel, and these results should be interpreted with caution for other P2Y<sub>12</sub> inhibitors.

## **(6) Conclusion**

Among elderly patients to be treated by PCI, a strategy combining a DES together with a short duration of DAPT is associated with a reduction in revascularization up to 2 years compared to BMS with very few late events and without any increased bleeding complications or stent thrombosis. The potential benefit of DES on IDTLR persists up to 2 years, deserving further clinical studies in the growing population of patients 75 years old and above.

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**Figure 1.** Time-to-event curves for the Major adverse Cardiovascular and Cerebrovascular events (Upper Left Corner), all-cause mortality (Upper Right Corner), cardiac mortality (Lower Left Corner) and ischemia driven target lesion revascularization (Lower Right Corner).