Cost-Effectiveness of Drug-Eluting Stents in Elderly Patients With Coronary Artery Disease: The SENIOR Trial

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ABSTRACT

Background: Elderly patients receive bare metal stents instead of drug-eluting stents (DES) to shorten the duration of dual antiplatelet therapy (DAPT). The SENIOR trial compared outcomes between these 2 types of stents combined with a short duration of DAPT. A significant decrease in the number of patients with at least 1 major adverse cardiac and cerebrovascular event (MACCE) was noted in the DES group.

Objectives: The objective of this article was to perform an economic evaluation of the SENIOR trial.

Methods: This evaluation was performed separately in 5 participating countries using pooled patient-level data from all study patients and country-specific unit costs and utility values. Costs, MACCEs, and quality-adjusted life-years (QALYs) were calculated in both arms at 1 year, and an incremental cost-effectiveness ratio was estimated. Uncertainty was explored by probabilistic bootstrapping.

Results: A total of 1200 patients underwent randomization. The average total cost per patient was higher in the DES group. The number of MACCEs and average QALYs were not statistically different between the 2 groups. The 1-year incremental cost-effectiveness ratio for each country of reference ranged from €13 752 to €20 511/MACCE avoided and from €42 835 to €68 231/QALY gained. The scatter plots found a wide dispersion, reflecting a large uncertainty surrounding the results. But in each country studied, 90% of the bootstrap replications indicated a higher cost for greater effectiveness for the DES group. Assuming a willingness to pay of €50 000/QALY, there was between a 40% and 50% chance that the use of DES was cost-effective in 4 countries.

Conclusion: The use of DES instead of bare metal stents combined with a short duration of DAPT in elderly patients induced higher cost for greater effectiveness in each of the 5 countries studied.

Keywords: coronary artery disease, cost-effectiveness, drug-eluting stent, MACCE, QALY.

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Introduction

Patient characteristics and economic criteria determine the choice between drug-eluting stents (DES) and bare metal stents (BMS) in percutaneous coronary intervention (PCI). Elderly patients at higher risk of bleeding often receive BMS to avoid long-term dual antiplatelet therapy (DAPT) required by DES.[1,2] This choice reduces the risk of bleeding and the associated hospitalizations, which cost on average €3800 per stay in France.[3] New generations of DES allow faster healing and shorter duration of DAPT, similar to BMS.

The SENIOR international trial compared the DES Synergy® II (Boston Scientific, Marlborough, MA) with the BMS Omega® or Rebel® (Boston Scientific) in patients older than 75 years who required PCI. The same DAPT duration was applied to patients in both groups according to the initial clinical presentation. DES was more efficient (12% of patients with at least 1 major adverse cardiac and cerebrovascular event [MACCE] at 1 year in the DES group vs 16% in the BMS group; P=0.02) and tolerated as well as BMS (no statistically significant difference in bleeding complications and stent thrombosis at 1 year between the 2 groups).[4]

Given the current economic constraints, estimating the cost-effectiveness of these alternative stenting strategies is important for clinical guideline development and reimbursement policy. Our objective was to assess the efficiency of the DES Synergy II in elderly patients using data from the SENIOR trial to guide healthcare policy decisions in 5 countries (France, Belgium, Spain, England, and Switzerland).

Patients and Methods

Study Design and Patients

The design of the SENIOR trial has been reported previously and will be briefly summarized.[4,5] This prospective randomized single-blind trial conducted in 44 centers in 9 countries between 2014 and 2016 included a total of 1200 patients older than 75 years undergoing PCI for stable angina, silent ischemia, or acute coronary syndrome; 596 were randomized to the DES group and 604 to the BMS Omega or Rebel (Boston Scientific) group. Baseline characteristics, medical history, clinical indication for PCI, PCI characteristics, and DAPT and PARIS scores of the SENIOR patients are reported in Appendix 1 in Supplemental Material found at https://doi.org/10.1016/j.jval.2019.07.008. Patients in both groups received the same DAPT duration after PCI according to the initial presentation: 1 month for stable angina and silent ischemia or 6 months for acute coronary syndrome. The primary endpoint of the SENIOR trial was a composite measure of MACCEs at 1 year. Data for the economic analysis were prospectively collected during the trial in a case report form, in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[6] The study complied with the Declaration of Helsinki, and all patients eligible for enrollment provided written informed consent in accordance with the local institutional review board or ethics committee. The study was managed by the Cardiovascular European Research Center, an independent research organization.

Effectiveness

In this economic study, the effectiveness was expressed as the difference in the number of MACCEs and the difference in quality-adjusted life-years (QALYs) between the 2 groups during the 1-year follow-up period. This choice differs from the clinical trial in which the primary clinical endpoint was the number of patients with at least 1 MACCE.[4] This can be explained by the different objectives of these 2 studies: the economic study estimated the 1-year total cost per patient including the cost of each event, whereas the clinical trial assessed the treatment efficacy for each patient.

Results were expressed in MACCE avoided and in QALY gained. MACCEs included all-cause mortality, myocardial infarction, stroke, and ischemia-driven target lesion revascularization (by PCI and coronary artery bypass grafting). QALYs represent a patient's survival time weighted by its quality of life, represented by utility. Utility values were derived from the 5-level version of the EuroQol 5-dimensional questionnaire (EQ-5D-5L) and were collected at baseline and 1 year. We applied health-related quality-of-life utility weights from the 5 countries of reference. Depending on the country, the EQ-5D-5L value set ranged from −0.6 (health condition worse than death) to 1 (best possible health).[7,8]

Estimation of Resources Used and Unit Costs

Only direct costs were taken into account in this economic study.[9] We assumed that all major events would result in a hospital admission and consequently that outpatient costs would be negligible and identical in both groups. Hospital resources included hospitalizations for index and staged procedures and rehospitalizations, whereas out-of-hospital resources such as consultations, laboratory tests, imaging, or medication were excluded. The variables used to calculate the cost of index and staged procedures were the type of hospitalizations and their duration, the type and number of stents used, and the number of days in intensive cardiac care units. We added repeat admissions when at least 1 concurrent adjudicated cardiac clinical endpoint was recorded at the same date. Severity-adjusted diagnosis related groups (DRGs) for hospitalizations were assigned based on the primary indication for hospitalization, according to the DRG classification of each country: *Manuel des GHM - Version 11d* for France, *APR-DRG (All Patient Refined Diagnosis Related Groups) version 28.0* for Belgium, *APR-GRD_V32_2016* for Spain, *Healthcare Resource Groups fourth version HRG4* for England, and *SwissDRG 6.0* for Switzerland. Hospital costs were valued using the DRGs' costs of each country.[10–14] We added to these costs an average price markup of €300 for each DES over a BMS, because these stents were not part of the hospital costs,[15] and for France an intensive care supplement of €401 per day when appropriate.[16] All costs were in 2016 Euros or inflated to 2016 using the French health-specific inflation index for France[17] or the general European inflation index for the other 4 countries.[18] British pounds and Swiss francs were converted to Euros using the Organisation for Economic Co-operation and Development purchasing power parity.[19]

Economic Evaluation

The economic evaluation was conducted from the perspective of the healthcare system with a time horizon of 1 year. It was carried out separately for the 5 main countries with higher inclusion numbers (France, England, Spain, Belgium, and Switzerland) using pooled data from all patients. The 1-way analysis of variance (ANOVA) was used to ensure that healthcare resources used to treat patients of the SENIOR trial could be pooled. The dependent variable was the length of stay, and the independent variable was the country.

Costs, MACCEs, and QALYs were assessed in both arms at 1 year and were not discounted because of the short time horizon. An incremental cost-effectiveness ratio (ICER), defined as the difference in cost between the 2 strategies divided by the difference in effectiveness, in cost per MACCE avoided and in cost per QALY gained was calculated. The uncertainty of the results was analyzed

Table 1. One-year ICER in cost per MACCE avoided and in cost per QALY gained for each of the 5 countries of reference.

	ICER in €/MACCE avoided (95% CI)	ICER in cost/MACCE avoided (95% CI)	ICER in €/QALY gained (95% CI)	ICER in cost/QALY gained (95% CI)
France	20 511 (−116 932 to 160 982)	€20 511 (−116 932 to 160 982)	63 890 (30 466 to 48 260)	€63 890 (30 466 to 48 260)
England	18 169 (−107 828 to 144 507)	GBP 13 990 (−83 028 to 111 270)	68 231 (−639 902 to 720 767)	GBP 52 538 (−492 725 to 554 991)
Spain	15 826 (−123 234 to 142 879)	€15 826 (−123 234 to 142 879)	46 956 (−202 328 to 406 030)	€46 956 (−202 328 to 406 030)
Belgium	16 114 (−112 013 to 143 204)	€16 114 (−112 013 to 143 204)	50 194 (−477 715 to 562 001)	€50 194 (−477 715 to 562 001)
Switzerland	13 752 (−110 893 to 145 592)	CHF 15 127 (−121 982 to 160 151)	42 835 (−446 162 to 467 835)	CHF 47 119 (−490 778 to 514 619)

CI indicates confidence interval; ICER, incremental cost-effectiveness ratio; MACCE, major adverse cardiac and cerebrovascular event; QALY, quality-adjusted life-year.

using a nonparametric bootstrap, which provided multiple estimates of the ICER by randomly resampling the patient population 1000 times. The distribution of 596 patients in the DES group versus 604 patients in the BMS group was preserved. Results were presented as a scatter plot of 1000 ICERs on the cost-effectiveness plane and transformed into a cost-effectiveness acceptability curve based on the decision makers' willingness to pay for an additional MACCE avoided or QALY gained.

Statistical Analysis

The statistical analyses were performed on the entire intention-to-treat (ITT) population. Cost and efficacy data were described by mean (standard deviation) for quantitative data and frequency (percentage) for qualitative data. Differences in MACCEs or rehospitalizations between the 2 groups were compared with a Poisson model or by negative binomial regression depending on the variance and the mean. Difference in QALYs was compared with Student's *t* test or Mann-Whitney test depending on the distribution. The difference in costs was compared with a permutation test. A *P* value less than .05 was considered significant. Missing utility data were replaced with estimates using bootstrap resampling within the respective groups. Other missing data (duration of hospitalization, number of days spent in the intensive care unit, and number of implanted stents) were replaced by the most frequent value. SAS (version 9.3, SAS Institute, Cary, NC) was used for all analyses.

Results

Patients and Procedures

Of the 1200 patients randomized from 9 countries, 1176 (98%) were followed until death or 1-year visit. Forty-eight patients had a staged procedure in the DES group and 36 in the BMS group. Baseline characteristics at inclusion are reported in Table 1 of the clinical article.[4]

Effectiveness

Eighty-four MACCEs were observed in the DES group and 114 in the BMS group (*P* = .0649). The number of patients with at least 1 MACCE was 68 (12%) in the DES group and 98 (16%) in the BMS group (*P* = .02).

Utilities during the follow-up period for both groups and for each country are presented in Figure 1. The total QALYs in each group are represented by the area under the curves, and the difference in QALYs between the 2 groups are represented by the area between the curves. France, Belgium, and Switzerland had the same utility weights. The utility difference at 12 months between the 2 groups was statistically significant for the 5 countries of reference. Depending on the country, the average 1-year QALYs were nonsignificantly higher in the DES group, ranging from 0.73 (0.20) to 0.78 (0.17) versus 0.72 (0.22) to 0.77 (0.21) in the BMS group.

Initial Hospitalizations and Rehospitalizations

The average length of stay during the index procedure was 2.7 days (range, 0-26 days) in the DES group and 2.6 days (range, 0-63 days) in the BMS group. The average length of stay during the staged procedure was 1.4 days (range, 0-11 days) in the DES group and 0.9 days (range, 0-2 days) in the BMS group. The average number of implanted stents per patient was 1.7 (1.0) in each group. The number of rehospitalizations was 172 in the DES group and 203 in the BMS group (0.29 and 0.34 per patient, respectively; *P* = .24), and the number of patients with at least 1 rehospitalization was 122 of 596 patients (20%) in the DES group and 138 of 604 patients (23%) in the BMS group (*P* = .32).

The ANOVA showed that the length of stay was not statistically different between the countries (*P* = .07), so resources could be pooled for patients from all countries.

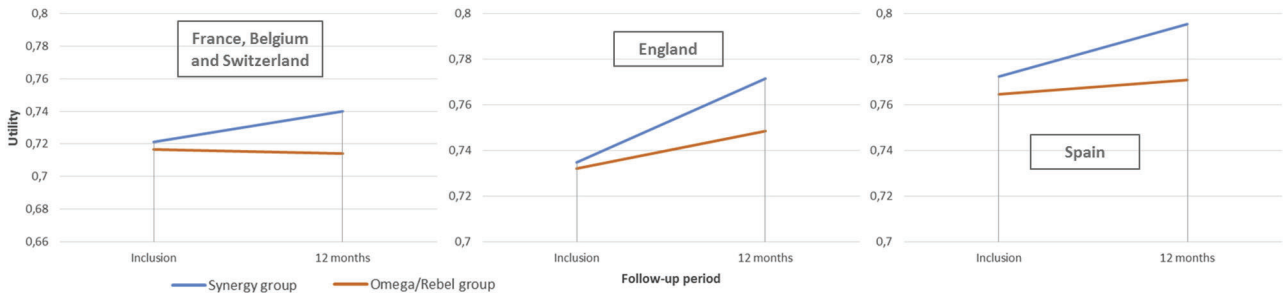
Costs

Detailed costs at 1 year for each of the 5 countries of reference are summarized in Appendix 2 in Supplemental Material found at https://doi.org/10.1016/j.jval.2019.07.008. Depending on the country, the additional cost of hospitalizations for both the index and staged procedures in the DES group (excluding stents cost) ranged from €45 to €112 (nonsignificant *P* values). Although the price of a DES was €300 higher than that of a BMS, the average cost difference of stents between the 2 groups was €480 in the ITT analysis due to the 1.7 stents implanted per patient and to the use in 34 patients of a different stent than the one determined by their randomization group. The additional cost of rehospitalizations in the BMS group ranged from €60 to €416 (nonsignificant *P* values).

Cost-effectiveness

The 1-year ICER for each of the 5 countries of reference is presented in Table 1. This ICER ranged from €13 752 to €20 511/ MACCE avoided and from €42 835 to €68 231/ QALY gained. The set of ICERs estimated by the bootstrap method is presented as a scatterplot on the cost-effectiveness plane for both effectiveness criterions. The scatter plots in €/MACCE avoided and in €/QALY found a wide dispersion, reflecting a large uncertainty surrounding the results. But regardless of the country, 96% and 90%,

Figure 1. Utilities at baseline and 1 year (connected by a straight line) for both groups and for each country. France, Belgium, and Switzerland have the same utility weights.



respectively, of the ICERs in €/MACCE avoided and in €/QALY gained were located in the top right-hand quadrant, indicating higher cost associated with better effectiveness for the DES group (Fig. 2a,b). As expected, when the difference in MACCE between the 2 groups increased, the cost difference increased as well. In addition, the acceptability curves showed that at a threshold of €20 000/MACCE avoided and €70 000/QALY gained, DES had a 50% probability of being cost-effective in all 5 countries. At a threshold of €70 000/MACCE avoided and €250 000/QALY gained, DES had an 80% probability of being cost-effective in all 5 countries (Fig.3 a,b). Finally, assuming a willingness to pay of €50 000/QALY, there was between a 40% and 50% chance that the use of DES instead of BMS was cost-effective in France, Belgium, Spain, and Switzerland.

Discussion

Our economic analysis of the SENIOR study indicated that the use of DES compared with BMS was cost-effective in all 5 countries (France, England, Spain, Belgium, and Switzerland), with ICERs ranging from €13 752 to €20 511 per MACCE avoided and from €42 835 to €68 231 per QALY gained. The cost difference between the 2 groups was driven by the DES price, which was €300 greater than the BMS price; other cost items were similar between the 2 groups. Between-country variations were mostly explained by differences in hospital costs. The scatter plots in €/MACCE avoided and in €/QALY found a wide dispersion, reflecting a large uncertainty surrounding the results. But approximately 90% of the ICERs generated by the bootstrap were located in the top right-hand quadrant, indicating a higher cost for better effectiveness for the DES group, whatever the effectiveness criterion and the country.

Comparability

From an economic point of view, other international economic studies compared DES with BMS in the general population or in different subgroups of patients.[20-26] The BASKET economic study in Switzerland found an 18-month ICER of €39 641/QALY in the general population and of €300/QALY in the elderly subgroup. The 1-year Swiss ICER of the SENIOR study was €42 835/QALY gained and was closer to the 18-month general population ICER of the BASKET study, although the SENIOR study focused on elderly patients.[20] Moreover, the RESEARCH economic study found a decrease of the ICER between 1 and 2 years from €29 373/repeat revascularization avoided to €22 627/repeat revascularization avoided.[21] We can therefore assume that the higher cost of the DES could be offset in part by a longer follow-up period, which would reduce the rate of MACCEs. A sustained QALY gain for the DES group could further reduce the ICER. But these 2 studies used a first-generation DES, whereas the SENIOR study used a new-generation DES.

The LEADERS FREE economic study compared DES with BMS in patients at high risk of bleeding who underwent PCI in 6 countries. In this study, the cost of rehospitalization was significantly higher in the BMS group for 2 reasons: the number of predefined rehospitalizations was significantly lower in the DES group and only the costs of these rehospitalizations were considered for calculation. Hence, the higher cost of DES was offset by the lower cost of adverse events in the DES group. This might in part explain why the probability that DES dominated BMS was >50% in the LEADERS FREE study but not in the SENIOR study.[24] Ferko et al[25] also showed that DES dominated BMS over a 2-year time horizon from the US Medicare perspective with a Markov state transition model.

Finally, Schur et al[26] used a modeling approach and combined nonparametric bootstrapping with probabilistic sensitivity analyses to estimate an average ICER over a lifetime horizon from a Spanish health service perspective. The difference in stent cost was €600, and the average ICER over all simulations was €3948 per QALY gained, which was below the willingness-to-pay threshold of €25 000 per QALY gained in 87% of the simulations, indicating cost-effectiveness of DES over BMS.[26]

In addition, from a clinical point of view, the SENIOR study compared the latest-generation DES with thin struts, bioabsorbable polymer, and everolimus, which represented the best device available at the time of the trial, capable of rapid endothelialization and thus allowing a short DAPT regimen. Nowadays, there are many more DES on the market with comparable or slightly better features (thinner struts), which may therefore produce slightly different results. Based on our results, we cannot conclude a class effect and would suggest caution in applying the conclusions of the SENIOR study to other stents.[4]

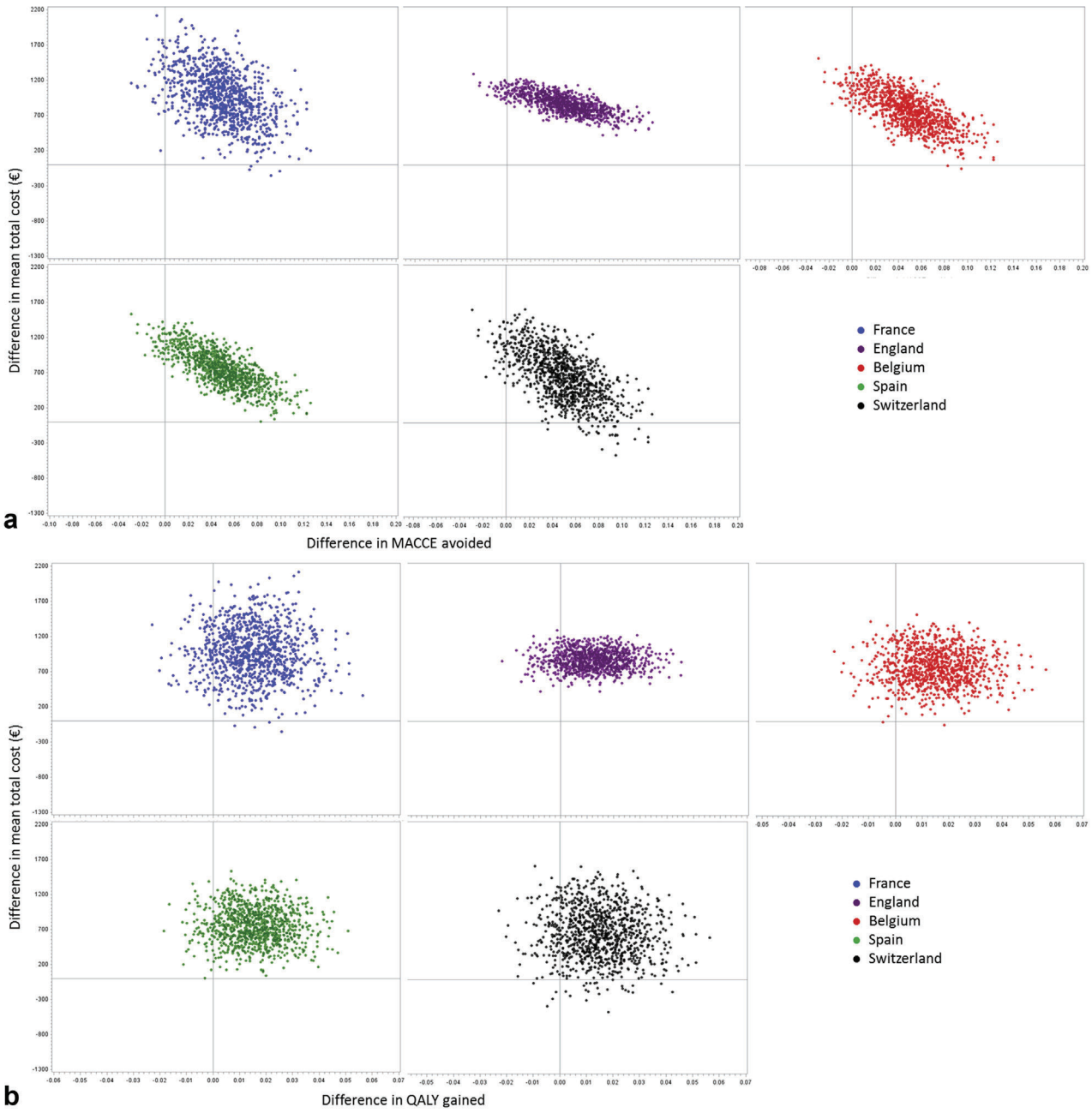
Study Limitations

This economic study had several limitations.

The study was conducted in only 5 of 9 countries included. Nevertheless, these 5 countries represented more than 80% of the enrolled study population, and the ANOVA showed that the length of hospitalization did not differ in the 9 countries of the study, which allowed us to pool patients.

Another limitation of the SENIOR economic study was that the EQ-5D-5L questionnaire was completed only twice during the follow-up period, at the beginning and at 1 year. Additional utility

Figure 2. (a) Scatter plot of incremental cost and effectiveness in Euros per major adverse cardiac and cerebrovascular event (MACCE) avoided for each of the 5 countries of reference. (b) Scatter plot of incremental cost and effectiveness in Euros per quality-adjusted life-year (QALY) gained for each of the 5 countries of reference.

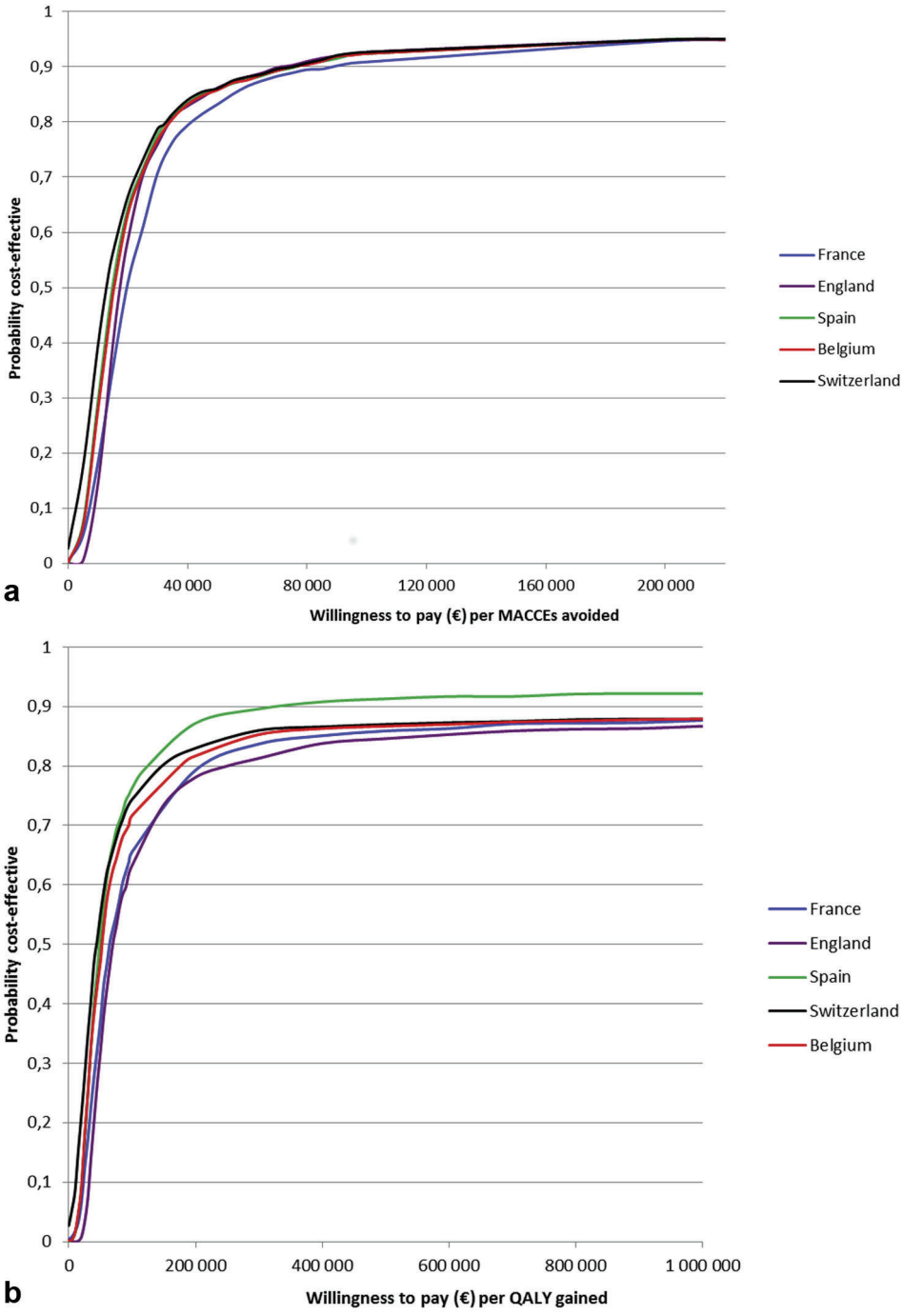


measures at 4 and 8 months would have limited the loss of information related to the utility decline after each MACCE and thus refine the calculation of QALYs. Moreover, the low sensitivity of the EQ-5D-5L to detect quality-of-life improvements in coronary patients over a 1-year period could explain the less striking results for QALYs than for MACCEs.

The short time horizon of 1 year of the SENIOR economic study was clinically driven, as the trial investigators assumed that MACCEs related to the procedure or the characteristics of the stent occur during the first year after PCI. Moreover, economic evaluations of stents that use MACCEs (and QALYs) as the effectiveness criteria and are trial based usually have a 6- to 18-month time horizon.[20,27] Two-year results are collected and will be reported.[4]

Finally, we took into account only hospitalizations for index and staged procedures and rehospitalizations costs. Outpatient resources (consultations, laboratory tests, imaging, or medication) were not included in the cost calculations because patients had an identical antiplatelet regimen and follow-up. Moreover, we assumed that all significant events would be severe enough, especially in this elderly population, to result in a hospital admission. The overall 1-year cost in each group was therefore probably underestimated by our calculation but balanced in the 2 groups.

Figure 3. (a) Acceptability curve in Euros per major adverse cardiac and cerebrovascular event (MACCE) avoided for each of the 5 countries of reference. (b) Acceptability curve in Euros per quality-adjusted life-year (QALY) gained for each of the 5 countries of reference.



Conclusion

The use of DES instead of BMS combined with a short duration of DAPT in elderly patients induces higher cost for greater effectiveness in each of the 5 countries studied (France, England, Spain, Belgium, and Switzerland), with a 1-year ICER ranging from €13 752 to €20 511/MACCE avoided and from €42 835 to €68 231/QALY gained. Finally, assuming a willingness to pay of €50 000/QALY, there was between a 40% and 50% chance that the use of DES instead of BMS was cost-effective in France, Belgium, Spain, and Switzerland.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.07.008.

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