Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial

Olivier Varenne, Stéphane Cook, Georgios Sideris, Sasko Kedev, Thomas Cuisset, Didier Carrié, Thomas Hovasse, Philippe Garot, Rami El Mahmoud, Christian Spaulding, Gérard Helft, José F Diaz Fernandez, Salvatore Brugaletta, Eduardo Pinar-Bermudez, Josepa Mauri Ferre, Philippe Commeau, Emmanuel Teiger, Kris Bogaerts, Manel Sabate, Marie-Claude Morice, Peter R Sinnaeve, for the SENIOR investigators

Summary

Background Elderly patients regularly receive bare-metal stents (BMS) instead of drug-eluting stents (DES) to shorten the duration of double antiplatelet therapy (DAPT). The aim of this study was to compare outcomes between these two types of stents with a short duration of DAPT in such patients.

Methods In this randomised single-blind trial, we recruited patients from 44 centres in nine countries. 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 of at least 70% (≥50% for the left main stem) deemed eligible for percutaneous coronary intervention (PCI). Exclusion criteria were indication for myocardial revascularisation 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 $P2Y_{12}$ inhibitors; contraindication to $P2Y_{12}$ inhibitors; and silent ischaemia of less than 10% of the left myocardium with a fractional flow reserve of 0·80 or higher. After the intended duration of DAPT was recorded (1 month for patients with stable presentation and 6 months for those with unstable presentation), patients were randomly allocated (1:1) by a central computer system (blocking used with randomly selected block sizes [two, four, eight, or 16]; stratified by site and antiplatelet agent) to either a DES or similar BMS in a single-blind fashion (ie, patients were masked), but those assessing outcomes were masked. The primary outcome was to compare major adverse cardiac and cerebrovascular events (ie, a composite of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation) between groups at 1 year in the intention-to-treat population, assessed at 30 days, 180 days, and 1 year. This trial is registered with ClinicalTrials.gov, number NCT02099617.

Findings Between May 21, 2014, and April 16, 2016, we randomly assigned 1200 patients (596 [50%] to the DES group and 604 [50%] to the BMS group). The primary endpoint occurred in 68 (12%) patients in the DES group and 98 (16%) in the BMS group (relative risk [RR] 0·71 [95% CI 0·52–0·94]; p=0·02). Bleeding complications (26 [5%] in the DES group *vs* 29 [5%] in the BMS group; RR 0·90 [0·51–1·54]; p=0·68) and stent thrombosis (three [1%] *vs* eight [1%]; RR 0·38 [0·00–1·48]; p=0·13) at 1 year were infrequent in both groups.

Interpretation Among elderly patients who have PCI, a DES and a short duration of DAPT are better than BMS and a similar duration of DAPT with respect to the occurrence of all-cause mortality, myocardial infarction, stroke, and ischaemia-driven target lesion revascularisation. A strategy of combination of a DES to reduce the risk of subsequent repeat revascularisations with a short BMS-like DAPT regimen to reduce the risk of bleeding event is an attractive option for elderly patients who have PCI.

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Hôpital Cochin, Assistance Publique—Hôpitaux de Paris, Paris, France, and Cardiology Department, Université Paris Descartes, Sorbonne Paris-Cité, Paris, France (Prof O Varenne MD); **Cardiology Department, University and Hospital Fribourg, Fribourg, Switzerland** (Prof S Cook MD); **Service de Cardiologie—Institut national de la santé et de la recherche médicale U942, Hôpital Lariboisiere, Assistance Publique - Hôpitaux de Paris, Université Paris Diderot, Paris, France** (G Sideris MD); **Cardiology Department, University St Cyril and Methodius, Skopje, Macedonia** (Prof S Kedev MD); **Département de Cardiologie, Centre hospitalier universitaire Timone, Marseille, France** (Prof T Cuisset MD); **Service de Cardiologie, Centre hospitalier universitaire Toulouse Rangueil, Université Paul Sabatier, Toulouse, France** (Prof D Carrié MD); **Institut Cardiovasculaire Paris-Sud, Ramsay Générale de Santé, Massy and Quincy, France** (T Hovasse MD, P Garot MD); **Hôpital Ambroise Paré Assistance Publique—Hôpitaux de Paris, Université Versailles-Saint Quentin en Yvelines, Versailles, France** (R El Mahmoud MD); **Service de Cardiologie, Hôpital Européen Georges Pompidou, Assistance Publique—Hôpitaux de Paris, Paris Descartes University and Sudden Death Expert Center, Institut national de la santé et de la recherche médicale U990, Paris, France** (Prof C Spaulding MD); **Institut de Cardiologie, Hôpital Pitié-Salpétrière, Assistance Publique—Hôpitaux de Paris, Université Pierre et Marie Curie**

Introduction

Elderly people represent a fast-growing segment of the population, and because of their increased risk of coronary artery disease, they are also more likely to have percutaneous coronary interventions (PCI) than are younger people.[1,2] Management of coronary artery disease in elderly patients can be challenging as they often have more extensive and complex disease and are also more prone to bleeding complications when receiving antiplatelet agents than younger patients.[3]

The optimal PCI strategy for elderly patients remains ill defined, for both the type of stent and duration of dual antiplatelet therapy (DAPT) after intervention. A Scientific Statement[4] from the American Heart Association, American College of Cardiology, and American Geriatrics Society called for closure of the gap of evidence in cardiovascular care between elderly and younger patients, recognising that current guidelines were unable to provide evidence-based recommendations for treatment of older patients.

Current drug-eluting stents (DES) limit the risk of repeat revascularisations compared with bare-metal stents (BMS) in elderly patients.[5–7] Contemporary DES are also safer than are BMS in terms of stent thrombosis.[8–11] In view of the high incidence of complex lesions in elderly patients, these DES are therefore becoming an increasingly attractive option in this population. However, elderly patients regularly receive BMS during PCI[12] since BMS require a shorter DAPT course than do DES to minimise the risk of bleeding complications associated with long antiplatelet

et Institut hospitalo-universitaire, Institute of Cardiometabolism and Nutrition, Hôpital Pitié-Salpétrière, Paris, France (Prof G Helft MD); Juan Ramón Jiménez University Hospital, Huelva, Spain (J F Diaz Fernandez MD); Cardiovascular Institute, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain (S Brugaletta MD); Hospital Universitario Virgen de la Arrixaca, Murcia, Spain (E Pinar-Bermudez MD); Hospital Universitari Germans Trias i Pujol, Badalona, Spain (J Mauri Ferre MD); Département de Cardiologie Interventionnelle, Polyclinique Les Fleurs, Ollioules, France (P Commeau MD); Service de Cardiologie, Hôpital Henri Mondor Assistance Publique—Hôpitaux de Paris, Université Paris Est Créteil, Créteil, France (Prof E Teiger MD); Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BioStat), Department of Public Health and Primary Care, Katholieke Universiteit Leuven, Leuven, Belgium, and Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BioStat), University Hasselt, Hasselt, Belgium (K Bogaerts PhD); Interventional Cardiology Unit, Cardiovascular Institute, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain (M Sabate MD); Cardiovascular European Research Center, Massy, France (M-C Morice MD); and Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium (Prof P R Sinnaeve MD)

Correspondence to: Prof Olivier Varenne, Hôpital Cochin, Assistance Publique—Hôpitaux de Paris, 75014 Paris, France
olivier.varenne@aphp.fr

Research in context

Evidence before this study

Elderly patients represent a fast-growing segment of patients having percutaneous coronary interventions (PCI). They have been largely excluded from randomised clinical trials assessing new drug-eluting stents (DES) or evaluating the optimal duration of dual antiplatelet therapy (DAPT) after PCI. As a consequence, the optimal PCI strategy for elderly patients remains poorly defined for choice of both stent type and duration of DAPT. We searched MEDLINE for articles published in English and French up to July 19, 2012, with the search terms "elderly", "octogenerians", "coronary artery disease", "percutaneous coronary intervention", and "drug eluting stents", or their abbreviations ("CAD" and "PCI"). We mainly found registries, often using outdated or obsolete DES and showing conflicting results for outcomes, and one clinical trial dedicated to patients in their eighties (XIMA) using a contemporary DES. A polymer-free drug-coated stent with 1 month DAPT has been shown to be more efficacious and safer than thick-strut bare-metal stents (BMS) in the patients at a high bleeding risk in the LEADERS-FREE trial. Still, elderly patients regularly receive BMS during PCI to minimise the risk of bleeding complications associated with long-term dual antiplatelet therapy often given after DES implantation.

Added value of this study

In all-comer patients aged older than 75 years of age receiving PCI with a short duration of DAPT on the basis of clinical presentation, a bioabsorbable polymer DES was associated with a 29% reduction in the occurrence of the composite primary endpoint of all-cause mortality, myocardial infarction, stroke, or revascularisation at 1 year compared with recipients of a similar BMS. The benefit is mainly related to a 71% reduction in ischaemia-driven target lesion revascularisation at 1 year with the DES. DAPT duration, defined before stent randomisation, was similar in both groups during the entire study period. As a consequence, bleeding complications did not differ between the two treatment arms. The rate of definite and probable stent thrombosis was low with both the DES and BMS. This study suggests that a bioabsorbable polymer DES followed by a short BMS-like DAPT duration is an attractive alternative strategy for treatment of elderly patients with coronary artery disease, regardless of their clinical presentation.

Implications of all the available evidence

Treatment of coronary artery disease in elderly patients represents specific challenges. The results of this trial show that avoidance of repeat interventions with use of a modern-era DES followed by a bleeding-averse strategy of short DAPT, traditionally reserved for BMS, can be safely and successfully implemented in this population. Taken together, the available evidence does not support use of BMS in elderly patients any longer.

therapy. Although society guidelines[13,14] recommend at least 6 months of DAPT in stable DES-treated patients and 12 months in unstable DES-treated patients, shorter durations of DAPT in patients with high bleeding risk can be considered, but no age-specific recommendations are provided.[15] DES followed by a short DAPT regimen appeared to be safe and efficacious in patients at a high bleeding risk in the LEADERS-FREE trial,[7] including in the elderly subpopulation, and in those deemed to be uncertain candidates for a DES in the ZEUS trial.[10]

Combination of a DES to reduce the risk of subsequent repeat revascularisations with a short BMS-like DAPT regimen to reduce the risk of bleeding events represents a potentially attractive option for elderly patients who have PCI. To this end, we sought to compare the composite primary endpoint of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation at 1 year and secondary endpoints, including the rate of bleeding and stent thrombosis, between the latest generations of DES and BMS in PCI patients aged 75 years or older receiving a similar short duration of DAPT in the SENIOR trial.

Methods

Study design and participants

The SENIOR trial is a randomised single-blind trial done at 44 centres in nine countries (a list of investigating centres is available in the appendix). The study design has been reported and described previously.[16] 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% (≥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. Unstable patients include patients presenting with an acute coronary syndrome—ie, unstable angina, ST-segment elevation myocardial infarction, or non ST-segment elevation myocardial infarction. Exclusion criteria were indication for myocardial revascularisation 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 $P2Y_{12}$ inhibitors; contraindication to $P2Y_{12}$ inhibitors; and silent ischaemia of less than 10% of the left myocardium with a fractional flow reserve of 0·80 or higher. Detailed inclusion and exclusion criteria are listed in the appendix.

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

See Online for appendix

was managed by the Cardiovascular European Research Center, an independent research organisation. The institutional review board at each site approved the study.

Randomisation and masking

Randomisation was achieved through a web-based system available 24 h per day all year round, and maintained by the Data Coordinating Center (European Cardiovascular Research Center, Massy, France). Randomisation was stratified by study site and antiplatelet agent entered into the interactive web response system before randomisation to avoid inequity between the two groups on the basis of an unmasked physician's decision. Also the duration of DAPT (1–6 months) was entered into the interactive web response system before randomisation for the same reason. Each site had its own dedicated randomisation list respecting the 1:1 ratio. The randomisation list was built dynamically by the electronic data capture system whenever a new study site was declared within the system. The algorithm used when building a randomisation list was based on the standard algorithm of blocked randomisation with randomly selected block sizes (two, four, eight, or 16). Details of the randomisation procedure are provided in the appendix. We designed the study as a single-blind trial (ie, patients were masked). We maintained single-blinding by hiding any stent type reference from the medical reports; implanted stents were referenced as "SENIOR stents" instead. Importantly, all clinical events, including ischaemia-driven revascularisations, were reviewed by an independent committee masked to treatment allocation. This committee (a list of members is available in the appendix) adjudicated all components of both the primary endpoint and all secondary endpoints in a masked fashion.

Procedures

At the time of inclusion, the planned duration of DAPT was determined by the investigator before randomisation. The duration was recommended according to the patients' initial presentation: 1 month of DAPT in stable or silent cases and 6 months in unstable cases. The patients were then randomly assigned to PCI with a bioabsorbable polymer DES (Synergy; Boston Scientific, Marlborough, MA, USA) or a similar thin-strut BMS (Omega or Rebel; Boston Scientific). Details of the stent designs are provided in the appendix.

We calculated DAPT duration from the day of PCI until the day of DAPT discontinuation. We allowed staged procedures, but required them to be done within 2 weeks of the index procedure; we then calculated DAPT duration from the baseline PCI (unstable patients) or the staged procedure (stable patients). We ascertained the number of patients who adhered to a 1 month DAPT course as the number of patients discontinuing DAPT within 1 month and 1 week and the number who adhered to a 6 month DAPT course as the number discontinuing within 6 months and 2 weeks.

Outcomes

The primary endpoint was the cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE) at 365 days, assessed at 30 days, 180 days, and 365 days. We defined MACCE as a composite of all-cause mortality, myocardial infarction (defined according to the third universal definition),[17] ischaemia-driven target lesion revascularisation (IDTLR), or stroke (definitions are available in the appendix). We defined IDTLR as any target lesion revascularisation for myocardial ischaemia (clinical assessment or non-invasive assessment) under treatment. Secondary endpoints included bleeding complications according to the Bleeding Academic Research Consortium classification (BARC 2–5 and BARC 3–5 [safety outcome]);[18] definite or probable stent thrombosis as defined by the Academic Research Consortium (safety outcome);[19] all revascularisations (consisting of target vessel revascularisation, non-target vessel revascularisation, and target lesion revascularisation); all components of the primary endpoint; and cardiovascular death, at 30 days, 180 days, 365 days, and 2 years; the composite primary outcome at 30 days, 180 days, and 2 years; and complete revascularisation at baseline. We reported net clinical benefit, defined as a composite of MACCE and bleeding (BARC 2–5), at 30 days, 180 days, 365 days, and 2 years. Further secondary outcomes were major bleeding complications at 30 days, 180 days, 365 days, and 2 years; quality of life and depression at 12 months and 24 months; and cost-effectiveness. 2 year results and cost-effectiveness are not reported in this study because they are not yet available but they will be presented separately.

Statistical analysis

The study was powered to test the superiority of DES with a relative 25% reduction (ie, a hazard ratio of 0·75) in the primary endpoint compared with BMS. On the basis of previous trials,[5,20] we estimated 11% of patients to have all-cause mortality, 1·5% to have stroke, 9% to have myocardial infarction, and 10% to have target lesion revascularisation in the BMS group at 1 year, leading to a primary endpoint event proportion of 31% for BMS at 1 year. Therefore, and taking into account a minimum time to follow-up of 1 year and a constant dropout rate yielding 15% lost to follow-up at 1 year, a sample size population of 560 patients per arm will provide 80% power to show superiority with use of a χ^2 test (two-sided α=0·05) comparing the event rates at 1 year from the Kaplan-Meier curves. 1200 patients (600 in each arm) have to be randomly allocated to yield a slight increase in power to 82%. We did the sample size calculation using 10 000 simulations.

We did all analyses (including safety analyses) on an intention-to-treat (ITT) basis with a two-sided significance

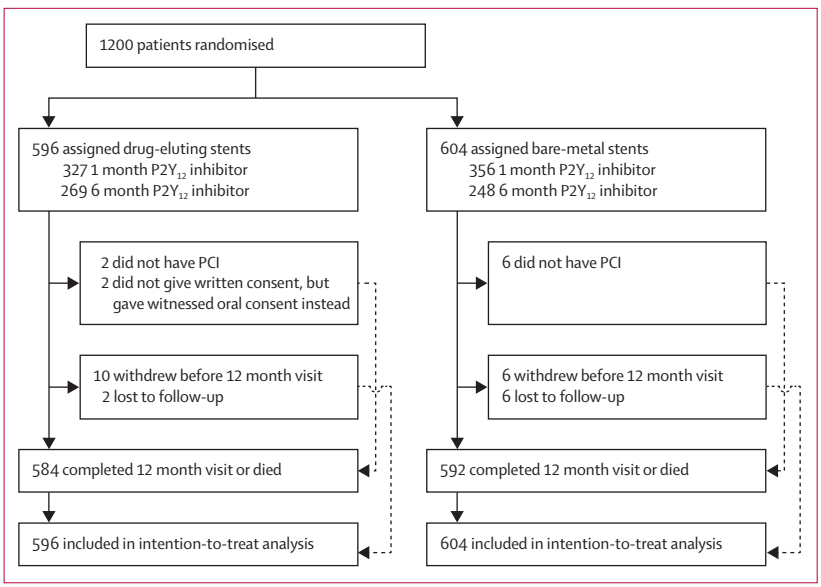

Figure 1: **Trial profile**
PCI=percutaneous coronary intervention.

level of 0·05. We did no correction for multiple testing. Hence, results other than the primary endpoint are hypothesis generating. For the primary endpoint, we also did a per-protocol (PP) analysis, excluding patients who did not receive the planned study stent or fulfil at least one inclusion criterion.

Baseline characteristics are reported as means and SDs or numbers and percentages, as appropriate. We did the primary analysis of the primary endpoint by calculating event rates from a Kaplan-Meier curve for each study group and comparing them using a relative risk with a 95% CI. We did a sensitivity analysis by means of a stratified Cox proportional hazards model in which we added treatment group as a covariate in the model and stratified the baseline hazard according to the type of $P2Y_{12}$ inhibitor. A second sensitivity analysis stratified the baseline hazard according to the planned duration of DAPT. Finally, we also compared Kaplan-Meier curves using a log-rank test.

We analysed the remaining efficacy and safety time-to-event endpoints by calculating event rates from either a Kaplan-Meier curve or a cumulative incidence function, with all-cause mortality as a competing risk at specific timepoints (30 days, 180 days, and 365 days) for each study group, and comparing them using relative risks with 95% CIs. We also compared the Kaplan-Meier curves between study groups using a log-rank test and compared cumulative incidence functions using a Gray's test. Complete revascularisation at baseline procedure is reported as event rates and the 95% CIs, separately for each treatment group. We report between-group comparisons using a χ^2 test and the relative risk with a 95% CI. For the primary endpoint and its components at 1 year, we also did prespecified subgroup analyses according to age (<85 years or ≥85 years), sex (male or female), atrial fibrillation (yes or no), diabetes (yes or no), DAPT score (<2 or ≥2),[21] PARIS risk score for major bleeding (0–3, 4–7, or ≥8), and PARIS risk score for coronary thrombotic events (0–2, 3–4, or ≥5).[22] We assessed the interactions between treatment and subgroups by means of a *Z* test.

We did all analyses with SAS, version 9.4. An independent data and safety monitoring board considered the data from any event analysis and assessed any safety issues. 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.

Results

Between May 21, 2014, and April 14, 2016, we randomly allocated 1200 patients (596 [50%] to DES and 604 [50%] to BMS; figure 1). The number of patients included per centre varied from one to 148. Of the 1192 (99%) patients who had PCI (594 [>99%] in the DES group and 598 [99%] in the BMS group), 1176 (99%) were followed up until death or their 1 year visit (365 days ± 2 weeks; 584 [98%] in the DES group and 592 [98%] in the BMS group). 1089 (91%) attended their 12 month visit (545 [91%] in the DES group and 544 [90%] in the BMS group).

Patients were on average 81·4 years (SD 4·3) old and predominantly male (747 [62%]; table 1); 222 (37%) patients were between 75 years and 79 years of age in the DES group versus 224 (37%) in the BMS group and 238 (40%) were between 80 years and 84 years of age versus 234 (39%), whereas 105 (18%) were between 85 years and 89 years of age in the DES group versus 126 (21%) in the BMS group and 31 (5%) were aged 90 years or older versus 20 (3%). The overall patient population had a high-risk profile typical for elderly patients, including hypertension, hypercholesterolaemia, atrial fibrillation, impaired renal function, previous myocardial infarction, and anaemia. 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. The indication for PCI was stable or silent coronary artery disease in 656 patients (55%) or an acute coronary syndrome in 544 (45%). Left main stem PCI was uncommon but more frequent in the DES group than in the BMS group. 385 (32%) patients had multivessel disease and 84 (7%) had a staged procedure. 16 (3%) patients allocated to the BMS groups with 24 lesions received a DES implantation. We observed a bifurcation

	Drug-eluting stent (n=596)	Bare-metal stent (n=604)
Baseline characteristics		
Age (years)	81·4 (4·3)	81·4 (4·2)
Male sex	368 (62%)	379 (63%)
BMI (kg/m²)	26·3 (4·3)	25·9 (3·9)
Medical history		
Diabetes	158/594 (27%)	157/603 (26%)
Current smoker	43/596 (7%)	38/604 (6%)
Renal insufficiency at screening	104/593 (18%)	99/604 (16%)
Hypercholesterolaemia	311/596 (52%)	320/604 (53%)
Hypertension	427/596 (72%)	488/604 (81%)
Previous stroke	39/593 (7%)	48/604 (8%)
History of malignancy (past 3 years)	56/593 (9%)	51/601 (8%)
Congestive heart failure	36/596 (6%)	40/603 (7%)
Previous MI	109/595 (18%)	80/602 (13%)
Previous CABG	36/596 (6%)	42/604 (7%)
Previous PCI	139/595 (23%)	143/604 (24%)
Peripheral vascular disease	87/592 (15%)	125/596 (21%)
Atrial fibrillation	103/594 (17%)	108/602 (18%)
Anaemia	77/556 (14%)	84/560 (15%)
Clinical indication for PCI		
STEMI	65 (11%)	62 (10%)
NSTEMI	152 (26%)	156 (26%)
Unstable angina	57 (10%)	52 (9%)
Stable angina	201 (34%)	215 (36%)
Silent ischaemia	121 (20%)	119 (20%)
Percutaneous coronary intervention		
Transradial approach	475/595 (80%)	490/603 (81%)
Multiple vessel disease	202/593 (34%)	183/599 (31%)
Lesion location		
LM	23/593 (4%)	8/599 (1%)
LAD	320/593 (54%)	313/599 (52%)
LCx	177/593 (30%)	159/599 (27%)
RCA	213/593 (36%)	227/599 (38%)
Intermediate ramus	11/593 (2%)	11/599 (2%)
Graft	7/593 (1%)	4/599 (1%)
At least one staged procedure	48/596 (8%)	36/604 (6%)
Bifurcation lesion	144/890 (16%)	119/875 (14%)
Chronic total occlusion	59/890 (7%)	57/875 (7%)
Number of study stents implanted per patient	1·7 (1·0)	1·6 (1·0)
Stent diameter per lesion (mm)	3·0 (0·5)	3·0 (0·5)
Stent length per lesion (mm)	19·3 (7·1)	18·3 (6·7)
Total stent length per patient (mm)	32·6 (20·8)	30·3 (20·3)
DAPT and PARIS scores		
DAPT score		
<2	562/596 (94%)	578/603 (96%)
≥2	34/596 (6%)	25/603 (4%)
PARIS coronary thrombotic event score		
Low: 0–2	287/548 (52%)	253/548 (46%)
Intermediate: 3–4	146/548 (27%)	188/548 (34%)
High: ≥5	115/548 (21%)	107/548 (20%)
PARIS bleeding score		
Low: 0–3	73/571 (13%)	51/581 (9%)
Intermediate: 4–7	287/571 (50%)	297/581 (51%)
High: ≥8	211/571 (37%)	233/581 (40%)
Planned duration of DAPT at baseline		
Patients with planned 1 month DAPT	327 (55%)	356 (59%)
Patients with planned 6 month DAPT	269 (45%)	248 (41%)

(Table 1 continues in next column)

(Continued from previous column)

Data are mean (SD), n (%), or n/N (%). BMI=body-mass index. MI=myocardial infarction. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. NSTEMI=non-ST-segment elevation myocardial infarction. LM=left main stem. LAD=left anterior descending. LCx=left circumflex. RCA=right coronary artery. DAPT=dual antiplatelet therapy. PARIS=Patterns of Non-Adherence to Dual Anti-Platelet Regimen in Stented Patients.

Table 1: **Baseline characteristics**

lesion in 11 (46%) of the cases. In the general population, 263 (15%) of the 1765 lesions involved a bifurcation.

A 1 month DAPT regimen was planned before randomisation for 683 (57%) patients (table 1). 1 month DAPT was planned for 592 (90%) of 656 patients with stable angina or silent ischaemia, without any difference between the DES and the BMS groups. Most patients with acute coronary syndrome at baseline (453 [83%] of 544) were planned to receive 6 months of DAPT. The median aspirin dose received during the trial was 100 mg (IQR 75–100) and almost half of patients receiving prasugrel received 5 mg per day (16 [47%] of 34). Clopidogrel was the $P2Y_{12}$ inhibitor in 1057 (88%) patients. Other medications, including β-blocker agents, statins, and proton-pump inhibitors, were prescribed similarly in both groups (appendix).

At 1 year, the primary composite endpoint had occurred in 68 (12%) patients in the DES group and 98 (16%) in the BMS group (relative risk [RR] 0·71 [95% CI 0·52–0·94]; p=0·02; table 2). Time-to-event curves for the primary endpoint are shown in figure 2 and the curves for its components are shown in the appendix. All-cause mortality at 1 year was not different between the two types of stent and neither was cardiac death, whereas IDTLR occurred in a higher proportion of patients in the BMS group than in the DES group (table 2, appendix). No non-IDTLR events occurred up to 1 year in both treatment arms. We noted no significant differences in the proportion of patients with myocardial infarction or stroke at 1 year between the DES and BMS treatment groups. In the PP analysis, 63 (11%) of 585 patients reached the primary endpoint in the DES group compared with 93 (16%) of 580 in the BMS group (RR 0·67 [95% CI 0·49–0·90]; p=0·008).

Bleeding complications were not different between the two treatment arms (table 2). In the DES group,

	Drug-eluting stent (n=596)	Bare-metal stent (n=604)	Relative risk	p value
Primary endpoint				
All-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation				
1 year	68 (12%)	98 (16%)	0·71 (0·52–0·94)	0·02
Secondary endpoints				
All-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation				
30 days	23 (4%)	27 (4%)	0·86 (0·48–1·52)	0·60
180 days	45 (8%)	62 (10%)	0·75 (0·51–1·08)	0·12
All-cause mortality				
30 days	9 (2%)	15 (2%)	0·61 (0·20–1·42)	0·23
180 days	24 (4%)	30 (5%)	0·81 (0·46–1·39)	0·44
1 year	36 (6%)	48 (8%)	0·76 (0·49–1·16)	0·20
Cardiovascular death				
30 days	7 (1%)	14 (2%)	0·51 (0·13–0·26)	0·13
180 days	15 (3%)	25 (4%)	0·61 (0·29–1·14)	0·12
1 year	22 (4%)	36 (6%)	0·62 (0·34–1·04)	0·07
Myocardial infarction				
30 days	12 (2%)	11 (2%)	1·11 (0·44–2·93)	0·81
180 days	13 (2%)	17 (3%)	0·77 (0·33–1·65)	0·48
1 year	21 (4%)	22 (4%)	0·97 (0·51–1·82)	0·92
Stroke				
30 days	2 (<1%)	1 (<1%)	2·03 (0·18–22·37)	0·56
180 days	8 (1%)	1 (<1%)	8·15 (1·02–64·85)	0·02
1 year	12 (2%)	5 (1%)	2·43 (0·88–7·04)	0·08
Ischaemia-driven target lesion revascularisation				
30 days	2 (<1%)	3 (<1%)	0·67 (0·00–1·88)	0·66
180 days	7 (1%)	23 (4%)	0·31 (0·08–0·66)	0·003
1 year	10 (2%)	35 (6%)	0·29 (0·11–0·54)	0·0002
Bleeding complications*				
BARC 2–5				
30 days	11 (2%)	13 (2%)	0·85 (0·32–2·07)	0·69
180 days	20 (3%)	20 (3%)	1·01 (0·52–1·96)	0·97
1 year	26 (5%)	29 (5%)	0·90 (0·51–1·54)	0·68
BARC 3–5				
30 days	10 (2%)	8 (1%)	1·26 (0·43–4·37)	0·62
180 days	15 (3%)	14 (2%)	1·08 (0·48–2·47)	0·83
1 year	20 (3%)	21 (4%)	0·95 (0·49–1·81)	0·86
Net clinical benefit†				
30 days	32 (5%)	38 (6%)	0·85 (0·52–1·36)	0·50
180 days	60 (10%)	77 (13%)	0·79 (0·57–1·09)	0·15
1 year	85 (14%)	115 (19%)	0·75 (0·58–0·97)	0·03
Definite and probable stent thrombosis				
30 days	2 (<1%)	7 (1%)	0·28 (0·00–1·36)	0·09
180 days	3 (1%)	8 (1%)	0·38 (0·00–1·48)	0·13
1 year	3 (1%)	8 (1%)	0·38 (0·00–1·48)	0·13

Data are n (%). Percentages are Kaplan-Meier estimates (for bleeding complications, stent thrombosis, and endpoints with death as a component) or cumulative incidence function estimates (for all other endpoints) at day 365. *We defined bleeding according to the Bleeding Academic Research Consortium (BARC) definitions. BARC type 0 indicates no bleeding and BARC type 5 indicates fatal bleeding. †All-cause mortality, myocardial infarction, stroke, ischaemia-driven target lesion revascularisation, and bleeding BARC 2–5.

Table 2: **Primary and secondary endpoints**

seven (35%) of the 20 BARC 3–5 bleeds occurred in patients receiving an anticoagulant at baseline versus seven (33%) of the 21 BARC 3–5 bleeds in the BMS group. We observed BARC 3–5 bleeding in 18 (90%) of 20 patients in the DES group receiving clopidogrel, two (5%) of 20 receiving prasugrel, and none (0%) of 20 receiving ticagrelor compared with 19 (90%) of 21 in the BMS group receiving clopidogrel, one (5%) of 21 receiving prasugrel, and one (5%) of 21 receiving ticagrelor. The net clinical benefit, a combination of the primary endpoint and BARC type 2–5 bleeding, favoured DES compared with BMS (table 2). All but one (in the BMS group) stent thrombosis occurred while patients were on DAPT. One subacute stent thrombosis occurred on day 31, the day DAPT was intentionally discontinued.

In a post-hoc analysis, time to DAPT discontinuation was similar for both treatment arms throughout the entire study period (figure 3). DAPT duration was 1 month or shorter in 429 (65%) of 656 stable patients (216 [67%] of 322 for DES *vs* 213 [64%] of 334 for BMS) and 6 months or shorter in 395 (73%) of 544 patients with acute coronary syndrome (194 [71%] of 274 *vs* 201 [74%] of 270) at baseline.

Prespecified subgroup comparisons for the primary endpoint and bleeding are shown in the appendix. These analyses show a consistent treatment effect across all predefined subgroups except for a significant effect of atrial fibrillation favouring DES compared with BMS for the primary endpoint (interaction p=0·02). We noted no significant interaction between baseline bleeding risk as assessed with the DAPT bleeding risk score and the treatment benefit of DES versus BMS. We were unable to calculate an interaction p value for the PARIS bleeding risk score, but visual inspection of the forest plot shows that an interaction did not occur. We noted no significant differences in quality of life or depression between the two treatment arms at 1 year (appendix).

Sensitivity analyses showed similar results to the primary endpoint, except that, for the sensitivity analysis in which an unstratified Cox proportional hazards model with treatment and type of ADP $P2Y_{12}$ inhibitor as covariates was used, the difference was not significant (appendix). Results of the sensitivity analyses in the PP analysis were also similar to sensitivity analyses in the ITT analysis (appendix). The hazard ratio of DES compared with BMS of 0·65 (95% CI 0·48–0·90; p=0·01) in the sensitivity analysis in which an unstratified Cox proportional hazards model with treatment as a covariate was used is very close to the one obtained in the same sensitivity analysis in the ITT set (hazard ratio 0·69 [95% CI 0·51–0·94]; p=0·02). Target vessel revascularisation, non-target vessel re-vascularisation, and all revascularisations at 1 year were not significantly different between the DES and BMS groups (appendix). All revascularisations were significantly higher in the BMS group than in the DES group. Complete revascularisation at baseline was achieved in 510 (86%) of 595 patients in the DES group versus 519 (86%) of 603 in the BMS group (RR 1·00 [0·95–1·04]; p=0·86).

Discussion

In this trial of elderly patients aged 75 years and older who had PCI for stable or unstable coronary artery disease and received a short DAPT regimen, the composite primary endpoint of all-cause mortality, myocardial infarction, stroke, or revascularisation was significantly lower in patients receiving a DES than in recipients of a BMS. The proportion of patients with bleeding complications and stent thrombosis did not differ significantly between the treatment arms.

Elderly patients are often under-represented in clinical trials and, as a consequence, current recommendations for PCI remain vague for this challenging population, despite DES having shown a clinical benefit compared with BMS more than a decade ago.[23] The absence of evidence-based guidance for optimisation of the balance between avoidance of repeat revascularisations versus minimisation of the risk of bleeding associated with extended DAPT has been identified as a key knowledge gap in the care for elderly patients with coronary artery disease.[4] We designed SENIOR as an all-comers trial, enrolling unselected elderly patients to explore the combination of two seemingly incompatible objectives, namely use of a DES to avoid repeat revascularisations and a short DAPT to limit bleeding complications.

The study population had a high prevalence of cardiovascular risk factors. Almost half of the patients presented with acute coronary syndrome and more than half had an intermediate-to-high PARIS score for a coronary thrombotic event. In this high-ischaemic risk population, the reduction in the primary composite endpoint at 1 year was mainly driven by a significant 4% absolute reduction in revascularisations in the DES group, despite a low proportion of repeat revascularisations in the BMS group. This benefit is consistent with those reported in previous randomised trials with a polymer-free, drug-coated stent in patients at high bleeding risk[7] and with a DES in patients in their eighties.[5] The reduction of the primary composite endpoint was also consistent across all subgroups studied, except for a significant treatment interaction for atrial fibrillation, which might in part have been caused by postrandomisation changes in anti-thrombotic therapies among patients with atrial fibrillation.

The proportion of patients with myocardial infarction was low overall and similar in both groups. In previous trials,[5,7] drug-coated stents and DES were associated with a significant reduction in the rate of myocardial infarction compared with BMS. In those two trials, however, the rate of myocardial infarction in patients in the BMS group at 1 year was more than twice that of patients in the BMS group in this trial. Furthermore, in the randomised Norwegian Coronary Stent Trial,[11] despite a reduction in repeated revascularisations with DES, no difference in the rates of non-fatal spontaneous myocardial infarction compared with contemporary BMS could be detected up to 6 years after PCI.

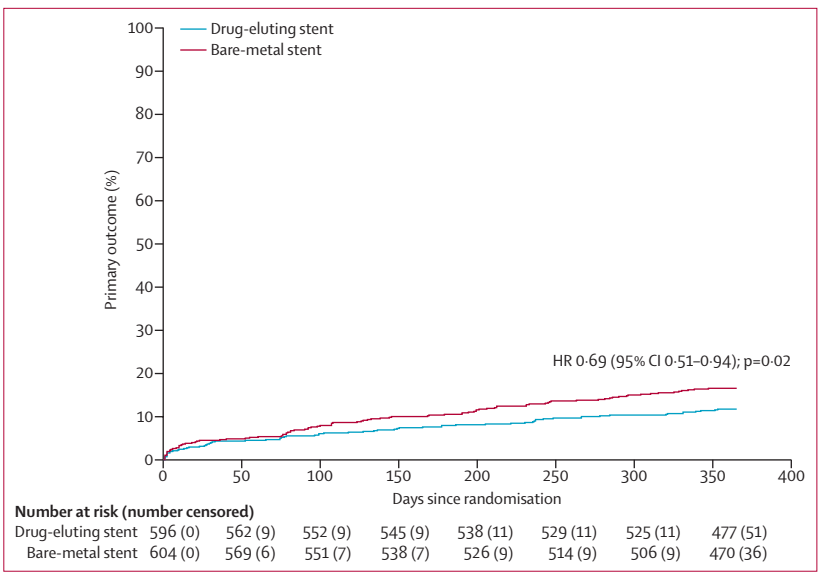

Figure 2: **Time-to-event curves for the primary endpoint**
HR=hazard ratio.

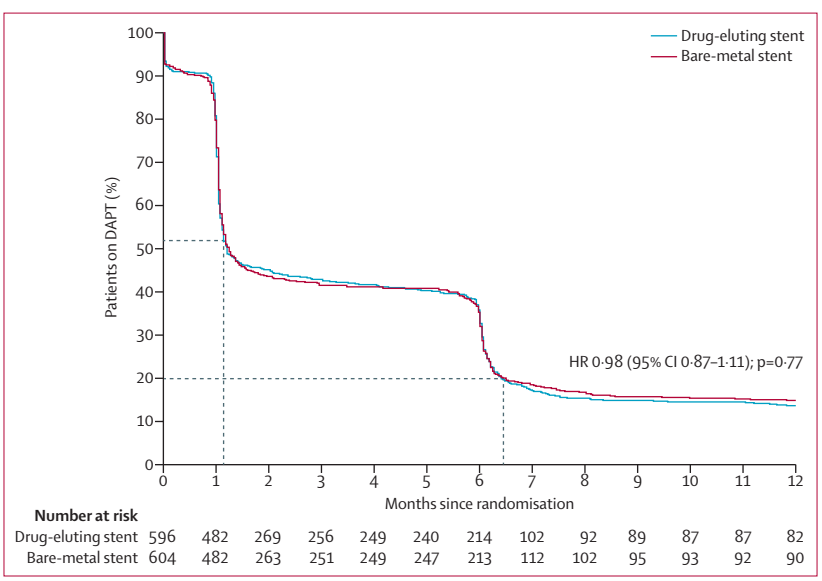

Figure 3: **Time to interruption for DAPT treatment**
No patients were censored. DAPT=dual antiplatelet therapy.

Overall, the proportion of patients with definite and probable stent thrombosis was low. All but one stent thrombosis occurred while patients were on DAPT. One subacute stent thrombosis occurred on day 31, the day DAPT was intentionally discontinued. This finding contrasts with the higher proportion of stent thrombosis (2·5%) reported with drug-coated stents in the LEADERS-FREE trial.[7] A longer DAPT duration in most patients with acute coronary syndrome in our trial (6 months *vs* 1 month) might in part explain this result, as suggested in a large network meta-analysis.[24] Another explanation might also be the thinner strut thickness (74 µm) of the

DES assessed in our study, a property associated with lower stent thrombosis rates, than the thicker struts in some studies.[25,26] Although associated with more frequent repeat revascularisations than with DES, the BMS used in our study appeared to be very safe in terms of myocardial infarction and stent thrombosis.

The elderly patients in our trial also had a high bleeding risk profile, as evidenced by a DAPT score of less than 2 and an intermediate-to-high PARIS bleeding score in most patients. Overall, the proportion of patients with bleeding complications at 1 year was not trivial, but was lower than reported in patients with a high bleeding risk in LEADERS FREE,[7] who all received a 1 month DAPT regimen. Furthermore, bleeding complications were similar in the DES and BMS groups, reflecting the identical DAPT duration in both arms. As a consequence, the net clinical benefit, including MACCE and bleeding events, significantly favoured patients in the DES group.

We selected the DAPT duration in both groups to reflect the shortest duration recommended for BMS in the guidelines:[13,14] 1 month for stable patients and 6 months for unstable patients. DAPT recommendations are not uniform across the guidelines, however. The European guidelines on DAPT[27] no longer differentiate between DES and BMS as to the duration of DAPT. These guidelines recommend a DAPT duration range of 1–12 months according to clinical presentation and bleeding risk of the patient. Until now, this strategy has never been explored prospectively. Our trial is, to our knowledge, the first randomised trial comparing contemporary DES with BMS, fully dedicated to elderly patients receiving a similar shortened DAPT course tailored to their clinical presentation.

For patients with acute coronary syndrome, both US[14] and European[15] guidelines universally recommend 12 months of DAPT irrespective of stent type, but allow regimens shorter than 12 months in patients at a high bleeding risk, without any specific age-related recommendation. A zotarolimus-eluting stent that is no longer available, together with shortened DAPT, was shown to reduce the rate of ischaemic events compared with BMS in patients who were uncertain DES candidates, two-thirds of whom presented with acute coronary syndrome at baseline.[10] In our trial, adherence to the planned, short DAPT regimens was similar for both treatment arms and was a function of clinical presentation (ie, stable *vs* unstable). More than two-thirds of patients had stopped their DAPT at the time prespecified by the investigator before randomisation, irrespective of baseline clinical presentation. Importantly, the timing of DAPT discontinuation was almost identical in the DES and BMS groups, resulting in similar bleeding proportions in both groups.

For patients without thrombotic or bleeding events during the first year after PCI, prolongation of the DAPT duration up to 30 months reduces the rate of myocardial infarction and stent thrombosis.[28] In the DAPT study,[28] for patients without thrombotic or bleeding events during the first year after PCI, extension of the DAPT duration up to 30 months reduces the rate of myocardial infarction and stent thrombosis. However, the rates of death, myocardial infarction, and stroke were similar in the subgroup of patients aged 75 years and older. Since a longer DAPT duration than in the DAPT study was not tested in this trial, the optimal duration of DAPT cannot be derived from our trial. Nevertheless, in a retrospective analysis[29] of the DAPT study, patients with low DAPT scores (<2) receiving extended DAPT were not protected from recurrent ischaemic events, but more frequently had major bleeding complications than did those with high DAPT scores (≥2). Because of their age, most patients in our trial had a low DAPT score at baseline (<2), suggesting that they might derive more harm than benefit from extended DAPT.

Most of the patients in our trial received clopidogrel instead of prasugrel and ticagrelor. Although these more potent than clopidogrel $P2Y_{12}$ inhibitors are not indicated after PCI in stable patients, the predominance of patients with acute coronary syndrome receiving clopidogrel in this trial probably reflects the perceived bleeding risk in these patients and reluctance of physicians to use ticagrelor or prasugrel in elderly patients. We cannot exclude the possibility that this risk-aversive strategy is particular to the setting of a clinical trial and might not reflect real-world practices. The observed primary endpoint occurred in 16% of patients in the BMS group, a lower proportion than anticipated in the sample size calculation (31%) of this understudied population. However, the study maintained its intended power as we also observed lower than anticipated dropouts at 1 year (2% *vs* 15%) and a larger-than-anticipated treatment effect (hazard ratio of 0·69 *vs* 0·75).

A 2015 European Society of Cardiology task force for assessment of coronary stents advocates use of study device-oriented endpoints, listing the composite of cardiac death, myocardial infarction, and target lesion revascularisation as the recommended primary endpoint for clinically oriented stent trials, but leaving room for other composite endpoints capturing broader cardiovascular outcomes than the one suggested.[9] Given the advanced age and comorbidities of our intended study population, as well as allowing patients with an indication for oral anticoagulation to be randomly allocated, we chose all-cause mortality rather than cardiac death and added stroke to the primary composite endpoint. The advantage of DES compared with BMS in the primary combined endpoint was driven by a significant difference in ischaemia-driven revascularisation, an expected and known advantage of DES. We did not observe significant differences in the other individual components of the primary endpoint. We also noted some imbalances in baseline and procedural characteristics, including an excess number of left main procedures in the DES group. Although this difference is due to chance, as the

treatment allocation occurred via randomisation and in view of the intention-to-treat analyses, we cannot exclude that imbalances might have affected postrandomisation clinical decisions, including the length to DAPT.

The number of patients included per centre varied considerably and might not be perfectly related to the size of the centre, which could have affected the study results. The duration of DAPT was intended to be uniform, reflecting the shortest duration recommended by guidelines per baseline presentation. The intended DAPT duration was recommended to be 1 month for stable patients and 6 months for unstable patients and required to be specified by the investigator before randomisation. The study was not designed to evaluate the optimal duration of DAPT. The safety profile of a short DAPT regimen after DES implantation therefore needs to be interpreted cautiously and might not necessarily apply to other patient populations. It did, however, show that a short duration of DAPT was as safe with the assessed DES as with the BMS.

Indices of frailty were not collected in this trial. The baseline comorbidities suggest that few frail patients were randomly allocated in the trial, however. Additionally, all patients with non-ST segment elevation-acute coronary syndrome were managed invasively, as per the trial design and conforming to guideline recommendations.[15] However, the safety-benefit balance of an early invasive management in non-ST segment elevation-acute coronary syndrome has been less well established for very elderly or frail patients than for young patients. These biases warrant some caution for application of our findings to very old and frail patients. The findings of this study apply to a specific DES platform and cannot, therefore, be extrapolated to other bioabsorbable or durable polymer DES platforms.

Contributors

OV, PRS, M-CM, TC, and MS designed the study, analysed and interpreted data, and wrote and revised the manuscript. SC, GS, SK, DC, TH, PG, REM, CS, GH, JFDF, SB, EP-B, JMF, PC, and ET implemented the study, enrolled patients, interpreted data, and wrote the manuscript. KB analysed data, did the statistical analyses, and wrote the manuscript. OV and PRS wrote the first draft and submitted the final version of the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

OV reports personal fees from Boston Scientific, Abbott Vascular, AstraZeneca, and Servier. SC reports grants and personal fees from Boston Scientific, Abbott Vascular, St Jude Medical, AstraZeneca, and Medtronic, and grants from Biotronik and Novartis, all outside the submitted work. TC reports personal fees from Sanofi, Eli Lilly, AstraZeneca, Medtronic, Terumo, and Biosensors outside the submitted work. CS reports grants from the French Ministry of Health and personal fees from Zoll, Medtronic, Abiomed, Stentys, AstraZeneca, Cordis, Servier, Lead-Up, Bayer Medicine, and Eli Lilly, all outside the submitted work. GH reports personal fees from Boston Scientific, grants from Terumo and Biotronik, and personal fees from AstraZeneca, Abbott Vascular, Bristol-Myers Squibb, Boehringer Ingelheim, and Bayer, all outside the submitted work. SB reports grants from AstraZeneca and personal fees from Abbott Vascular, all outside the submitted work. PC reports personal fees from Boston Scientific. KB reports consulting fees to his institution (Katholieke Universiteit Leuven) from the Cardiovascular European Research Center for the statistical analysis. MS reports grants from Abbott Vascular outside the submitted work. M-CM reports grants from Boston Scientific. PRS reports grants from AstraZeneca and Daïchi-Sankyo, institutional fees from Bristol-Myers Squibb, Sanofi, AstraZeneca, Daïchi-Sankyo, and Boston Scientific, and institutional fees from Abbott Vascular, Pfizer, and Boehringer Ingelheim, all outside the submitted work. All other authors report no competing interests.

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