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Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

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Aims To compare the long-term outcome after percutaneous coronary intervention with 'new-generation' drug-eluting stents (n-DES) to 'older generation' DES (o-DES), and bare-metal stents (BMS) in a real-world population.

Methods and results We evaluated 94 384 consecutive stent implantations (BMS, $n = 64\,631$; o-DES, $n = 19\,202$; n-DES, $n = 10\,551$) in Sweden from November 2006 to October 2010. All cases of definite stent thrombosis (ST) and restenosis were documented in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Older generation DES were classified as: Cypher and Cypher Select (Cordis Corporation, Miami, FL, USA), Taxus Express and Taxus Liberté (Boston Scientific Corporation), and Endeavor (Medtronic Inc.) and n-DES as: Endeavor Resolute (Medtronic Inc.), XienceV, Xience Prime (Abbott Laboratories) and Promus, Promus Element (Boston Scientific Corporation). The Cox regression analyses unadjusted and adjusted for clinical and angiographic covariates showed a statistically significant lower risk of restenosis in n-DES compared with BMS [adjusted hazard ratio (HR) 0.29; 95% confidence interval (CI): 0.25–0.33] and o-DES (HR 0.62; 95% CI: 0.53–0.72). A lower risk of definite ST was found in n-DES compared with BMS (HR 0.38; 95% CI: 0.28–0.52) and o-DES (HR, 0.57; 95% CI: 0.41–0.79). The risk of death was significantly lower in n-DES compared with o-DES (adjusted HR: 0.77; 95% CI: 0.63–0.95) and BMS (adjusted HR: 0.55; 95% CI: 0.46–0.67).

Conclusion Percutaneous coronary intervention with n-DES is associated with a 38% lower risk of clinically meaningful restenosis, a 43% lower risk of definite ST, and a 23% lower risk of death compared with o-DES in this observational study from a large real-world population.

Keywords DES • Stent thrombosis

Introduction

Although many randomized trials and studies support the overall early and long-term safety and efficacy of the first-generation drug-eluting stents (DES),[1,2] concern has been raised on long-term safety, especially regarding the potential risk of late stent thrombosis (ST).[3–5]

New-generation DES (n-DES) have been developed with an improved design that may help to overcome the current limitations of the older generation DES (o-DES). Thin, more biocompatible

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polymers, higher flexibility, conformability, and deliverability of the cobalt–chromium and platinum–chromium stent alloys associated with alternative anti-proliferative-eluting drugs may have contributed to the low late loss and thrombotic risk with their restricted use in randomized trials.[6–9] Long-term results from the unrestricted use of n-DES are limited to few clinical trials[10,11] and single-centre experiences[12] evaluating only one type of n-DES.

The purpose of our study was to compare the long-term outcome of percutaneous coronary intervention (PCI) with n-DES with o-DES and bare-metal stents (BMS), in a large unselected population from a national registry with complete consecutive enrolment, the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).

Methods

Study population

Our study included all patients in Sweden who received coronary stents from November 2006, when the first n-DES was implanted in Sweden, to October 2010. The analyses were based on the type of stent implanted at the first recorded procedure. Only DES types implanted on more than 500 occasions during the study period were assessed.

The stent types were classified as following:

Bare-metal stent group: Multilink, Multilink MiniVision, and Flexmaster (Abbott Laboratories), Driver and Micro Driver coronary (Medtronic Inc.), Liberté (Boston Scientific Corporation), Braun Coroflex Blue (B.Braun Melsungen AG, Germany), and Chrono stent (CID, Saluggia, Italy);
Older generation DES group: Cypher and Cypher Select (Cordis Corporation, Miami, FL, USA), Taxus Express and Taxus Liberté (Boston Scientific Corporation), and Endeavor (Medtronic Inc.);
New-generation DES group: Endeavor Resolute (Medtronic Inc.), XienceV, Xience Prime (Abbott Laboratories), and Promus and Promus Element (Boston Scientific Corporation).

The SCAAR data

The SCAAR has been described previously.[2–4,13,14] Briefly, this registry holds data on consecutive patients from all 29 centres that perform coronary angiography and PCI in Sweden. The registry is sponsored by the Swedish Health Authorities and is independent of commercial funding. The technology is developed and administered by the Uppsala Clinical Research Center. Since 2001, SCAAR has been Internet-based, with recording of data online through an Internet interface in the catheterization laboratory; data are transferred in an encrypted format to a central server at the Uppsala Clinical Research Center.

All consecutive patients undergoing coronary angiography or PCI are included. Information with respect to restenosis and ST has been registered for patients undergoing any subsequent coronary angiography for a clinical reason since May 2005.

Study endpoints

The pre-defined endpoints were clinically driven restenosis, definite ST, and death.

Restenosis as registered in SCAAR is defined as a stenosis assessed by angiographic visual estimation (>50%) or by fractional flow reserve (FFR) ≤ 0.80[2–4,13,14] in a previously stented segment identified by coronary angiography for any clinical indication performed anywhere in the country.

The clinical relevance of restenotic lesions was detected by symptoms, routine non-invasive functional testing (exercise test, myocardial scintigraphy), and/or invasive functional evaluation by FFR.

Target lesion revascularization (TLR) by PCI was defined as any repeat percutaneous intervention of the target lesion of the target vessel performed by PCI for clinically relevant restenosis or other complication of the target lesion.

Definite ST was defined according to the Academic Research Consortium (ARC) definition.[15]

The Internet-based system provides each centre with immediate and continuous feedback on processes and quality-of-care measures. Monitoring and verification of registry data are periodically performed in at least one-third of the hospitals since 2001 by comparing 50% of the entered variables in 50% of randomly selected interventions per hospital and year with the patients' hospital records. Automatic quality control is also continuously performed on the SCAAR interface. The recording of the clinical and angiographic data is indicated as complete and the case can be closed only if all the mandatory variables have been inserted.

Vital status and date of death are monthly obtained from the National Population Registry. The merging of the registries was performed by the Epidemiologic Centre of the Swedish National Board of Health and Welfare and approved by the local Ethics Committee at the Uppsala University.

Statistical analysis

Continuous variables were expressed as means and standard deviations and discrete variables as percentages.

The primary objective was to evaluate clinical outcome up to 2 years after the implantation of n-DES, o-DES, and BMS.

The statistical analysis for restenosis and ST was performed *per stent*, while the analysis of mortality was performed *per patient*.

The adjusted cumulative risk of restenosis, ST, and death up to 2 years was calculated using the Cox proportional hazard method. All the COX analysis models were censored at 2 years.

The following clinical and procedural variables that could be potential confounders of the clinical outcome were included in the model for calculation of the adjusted relative risk: age, gender, diabetes, hypertension, dyslipidaemia, smoking status, clinical indication of the procedure, use of acetyl salicylic acid, GPIIb–IIIa and/or P2Y12 receptor inhibitors at the index procedure, treated vessel, previous myocardial infarction (MI), previous coronary artery bypass grafting (CABG), previous PCI, year of the index procedure, enrolling centre, lesion type, bifurcation lesions, restenotic lesions, chronic total occlusions (CTO), stent type, stent diameter, stent length, three-vessel/left main disease, the use of additional stents, and maximal inflation pressure. The statistical interaction between the year of the procedure and the type of stent was assessed in the COX analysis for restenosis, ST, and death.

All reported *P*-values are two-sided. All analyses were performed with the use of SPSS statistical software (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

During the study period, 94 384 stent implantations were performed (BMS, $n = 64\,631$; o-DES, $n = 19\,202$; n-DES, $n = 10\,551$) in 61 351 patients. The relative distribution of the three stent categories is shown in *Figure 1*.

Baseline characteristics are listed in *Table 1*. Bare-metal stents were more often used for patients with ST-elevation MI. The

clinical risk profile was higher in the DES groups compared with the BMS group, with no significant differences between the o-DES and n-DES groups.

Procedural characteristics are shown in *Table 2*. The stent length, the rates of restenotic lesions, and CTO at the index procedure were higher in both the DES groups compared with the BMS group, with a higher rate of restenotic lesions in the o-DES group compared with the n-DES group.

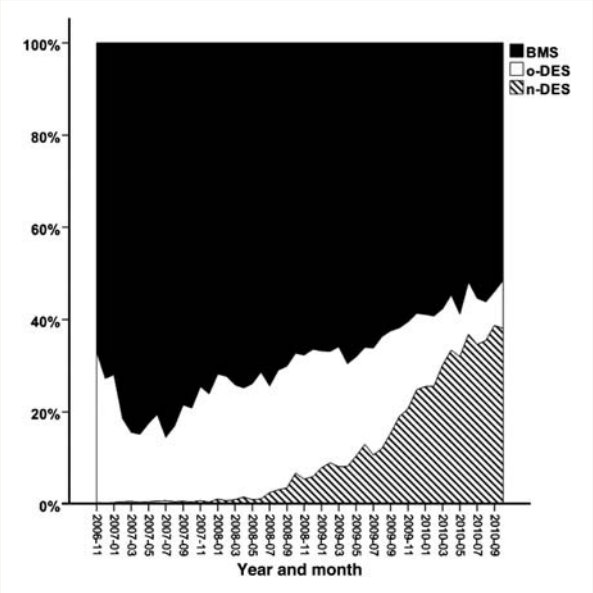


Figure 1 Relative distribution of bare-metal stents (BMS), old-generation drug-eluting stents (o-DES), and new-generation drug-eluting stents (n-DES) in the SCAAR from 2006 to 2010.

The total number of events of restenosis and definite ST up to 2 years was 5408 and 1106, respectively.

The rates of restenosis at 1 and 2 years, respectively, were 6.3 and 7.4% in the BMS group, 4.0 and 5.8% in the o-DES group, and 2.8 and 3.9% in the n-DES group (*Figure 2A*).

The rate of TLR by PCI at 1 and 2 years was 4.6 and 5.5% in the BMS group, 3.1 and 4.9% in the o-DES, and 2.2 and 3.1% in the n-DES group.

The rates of definite ST at 1 and 2 years, respectively, were 1.2 and 1.4% in the BMS group, 0.9 and 1.3% in the o-DES group, and 0.5 and 0.6% in the n-DES group (*Figure 2B*).

The adjusted cumulative risk of restenosis and definite ST up to 2-year follow-up is shown in *Figure 3A* and *B*. A statistically significant lower risk of restenosis was observed in the n-DES group compared with o-DES [adjusted hazard ratio (HR): 0.62; 95% confidence interval (CI): 0.53–0.72] and BMS (adjusted HR: 0.29; 95% CI: 0.25–0.33). Similarly, a significant lower risk of definite ST was observed in the n-DES group compared with o-DES (adjusted HR: 0.57; 95% CI: 0.41–0.79) and BMS (adjusted HR: 0.38; 95% CI: 0.28–0.52).

The adjusted cumulative risk of TLR by PCI up to 2 years was significantly lower in n-DES compared with o-DES (adjusted HR: 0.60; 95% CI: 0.51–0.70) and BMS (adjusted HR: 0.32; 95% CI: 0.28–0.38). A lower risk of restenosis (adjusted HR: 0.46; 95% CI: 0.43–0.51), definite ST (adjusted HR: 0.67; 95% CI: 0.56–0.80), and TLR by PCI (adjusted HR: 0.54; 95% CI: 0.50–0.60) was observed in the o-DES compared with BMS.

Table 1 Baseline characteristics (no. of patients = 61 351)

Variables (*n*, %) unless stated	BMS (*n* = 42 773)	o-DES (*n* = 12 153)	n-DES (*n* = 6425)
Women	11 793 (28%)	3254 (27%)	1670 (26%)
Mean body mass index (kg/m^2)	27.2 ± 5.2	27.6 ± 5.2	27.5 ± 4.7
Age (years)	67.0 ± 11.2	65.9 ± 10.4	65.8 ± 10.5
Unstable coronary artery disease	18 855 (44%)	6238 (51%)	3331 (52%)
Stable coronary artery disease	7718 (18%)	4059 (33%)	2013 (31%)
STEMI	13 981 (33%)	1422 (12%)	809 (13%)
Hypertension	21 972 (51.4%)	7459 (61.4%)	4002 (62.3%)
Diabetes mellitus	6756 (15.8%)	3315 (27.3%)	1623 (25.3%)
Insulin treatment	2861 (42.3%)	1650 (49.8%)	763 (47.0%)
Non-insulin treatment	3876 (57.3%)	1662 (50.1%)	857 (52.7%)
Unknown treatment	22 (0.3%)	3 (0.1%)	5 (0.3%)
Hypercholesterolaemia	19 505 (45.6%)	7993 (65.8%)	3983 (62.0%)
Smoking status			
Former smoker	14 279 (33.4%)	4710 (38.8%)	2517 (39.2%)
Current smoker	9181 (21.5%)	1817 (14.9%)	1101 (17.1%)
Previous MI	9698 (22.7%)	4611 (37.9%)	2334 (36.3%)
Previous CABG	3522 (8.2%)	1864 (15.3%)	885 (13.8%)
Follow-up (days, mean ± standard deviation)	607 ± 190	631 ± 166	359 ± 194

CABG, coronary artery bypass grafting; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 2 Procedural characteristics

Variables (*n*, %) unless stated	BMS (*n* = 64 631)	o-DES (*n* = 19 202)	n-DES (*n* = 10 551)
Number of stents per procedure, mean ± SD	1.45 ± 0.77	1.59 ± 0.92	1.63 ± 0.93
Stent diameter (mm), mean ± SD	3.14 ± 0.50	2.97 ± 0.48	2.93 ± 0.45
Stent length (mm), mean ± SD	24.26 ± 14.33	30.67 ± 19.66	31.76 ± 20.65
Restenotic lesions, *n* (%)	693 (1.6)	1879 (15.5)	664 (10.3)
Chronic total occlusions, *n* (%)	577 (1.3)	707 (5.8)	406 (6.3)
Bifurcations, *n* (%)	5015 (7.8)	2644 (13.7)	1605 (15.2)
1-vessel disease, *n* (%)	20 760 (48.5)	4701 (37.5)	2546 (39.6)
2-vessel disease, *n* (%)	12 274 (28.7)	2897 (23.8)	1591 (24.8)
3-vessel disease, *n* (%)	7239 (16.9)	1911 (15.7)	1017 (15.8)
Left Main disease, *n* (%)	154 (0.4)	93 (0.8)	52 (0.8)
Treated vessel, *n* (%)			
RCA	15 188 (35.5)	2667 (21.9)	1427 (22.2)
Left main	671 (1.6)	492 (4.0)	216 (3.4)
LAD	17 641 (41.2)	4817 (39.6)	2669 (41.5)
LCX	7996 (18.7)	1896 (15.6)	1076 (16.7)
CABG	1277 (2.9)	597 (4.9)	231 (3.6)
Lesion classification, *n* (%)			
Type A	5396 (12.6)	767 (6.3)	372 (5.8)
Type B1	16 854 (39.4)	3402 (27.9)	1790 (27.8)
Type B2	14 199 (33.2)	3640 (29.9)	2044 (31.8)
Type C	6324 (14.8)	2660 (21.9)	1413 (22.0)
ASA, *n* (%)	63 304 (98.0)	19 079 (99.1)	10 428 (98.5)
Clopidogrel, *n* (%)	62 189 (96.3)	18 838 (97.9)	10 143 (96.1)
GPIIb–IIIa, *n* (%)	18 197 (28.1)	2736 (14.2)	1368 (12.9)

ASA, acetyl-salicylic acid; CABG, coronary artery bypass grafting; GPIIb–IIIa, glycoprotein IIb–IIIa inhibitors; LAD, left anterior descending; LCX, left circumflex.

A significantly higher adjusted cumulative risk of restenosis up to 2 years was observed with the Endeavor stent when compared with the Cypher stent (adjusted HR: 1.86; 95% CI: 1.50–2.25) and with the Taxus stent (adjusted HR: 1.86; 95% CI: 1.51–2.28), while no difference was observed between the Taxus and Cypher stents (HR: 1.00, 95% CI: 0.82–1.22).

The adjusted cumulative risk of ST was not significantly different with the Endeavor stent when compared with Cypher (adjusted HR: 1.07; 95% CI: 0.66–1.66) and with the Taxus stent (adjusted HR: 1.08; 95% CI: 0.66–1.77).

The adjusted cumulative risk of restenosis (adjusted HR: 0.68, 95% CI: 0.59–0.80) and ST (adjusted HR: 0.59, 95% CI: 0.42–0.83) up to 2 years was significantly higher even after the removal of the Endeavor stent from the o-DES group.

The mortality up to 2 years in all 61 351 patients was 5.6%. Mortality was 6.8% in the BMS group, 3.4% in the o-DES group, and 1.9% in the n-DES group. The cumulative risk of death is shown in *Figure 4*. The risk of death was significantly lower in the n-DES group compared with the o-DES (adjusted HR: 0.77; 95% CI: 0.63–0.95) and BMS (adjusted HR: 0.55; 95% CI: 0.46–0.67) groups. Older generation DES showed a significantly lower mortality (adjusted HR: 0.72; 95% CI: 0.64–0.81) compared with BMS.

No significant statistical interaction between the year of the procedure and the type of stent was observed on the outcomes.

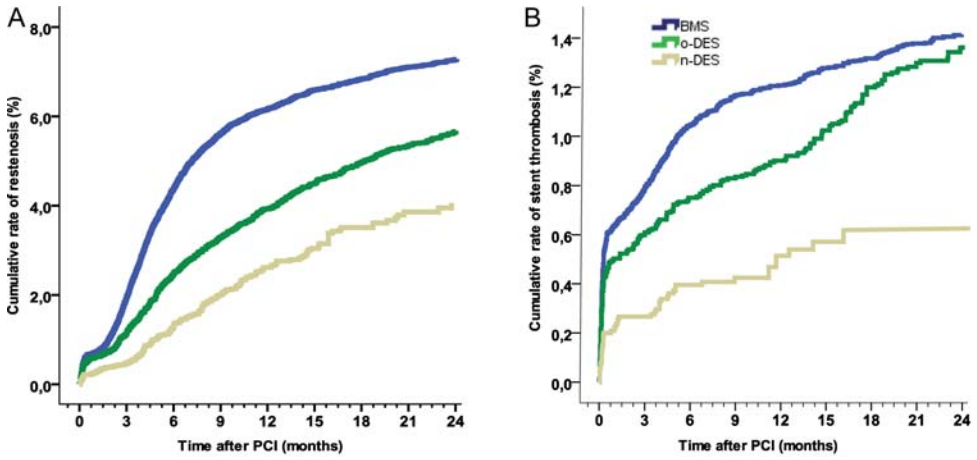
Discussion

A main finding of this study is that n-DES are associated with a 38% lower risk of clinically relevant restenosis and a 43% lower risk of definite ST up to 2 years compared with o-DES in a large real-world population.

Although the first clinical trials with o-DES showed low rates of ST,[16–19] a consistent increase has been shown when implantation was broadened from simple lesions to unselected and more complex lesions.[14]

Previous studies[20–24] have reported heterogeneous results for ST and restenosis within o-DES. In this study population, there were no significant differences in ST rates between individual stents in the o-DES group, while the restenosis rate was significantly higher with the Endeavor stent, as described already in previous SCAAR reports.[13]

A continuous increased risk of late ST with sirolimus- and paclitaxel-eluting DES has been reported in registry studies with a 0.4–0.6% increment per year.[25–27] In the present study, o-DES were associated with a relative risk reduction in restenosis and definite ST by 54 and 35% at 2 years, respectively, compared with BMS. However, the ST rate after 1 year increased by 0.4% per year in the o-DES group in consistence with the results reported by previous studies.[25–27] Although many factors such



N at risk	0 months	6 months	12 months	18 months	24 months
BMS	64631	56070	47968	40539	32698
o-DES	19202	17862	16014	13517	10533
n-DES	10551	8092	4188	2005	847

Figure 2 Cumulative rate of restenosis (*A*) and definite stent thrombosis (*B*) up to 2 years in bare-metal stents (BMS), old-generation drug-eluting stents (o-DES), and new-generation drug-eluting stents (n-DES).

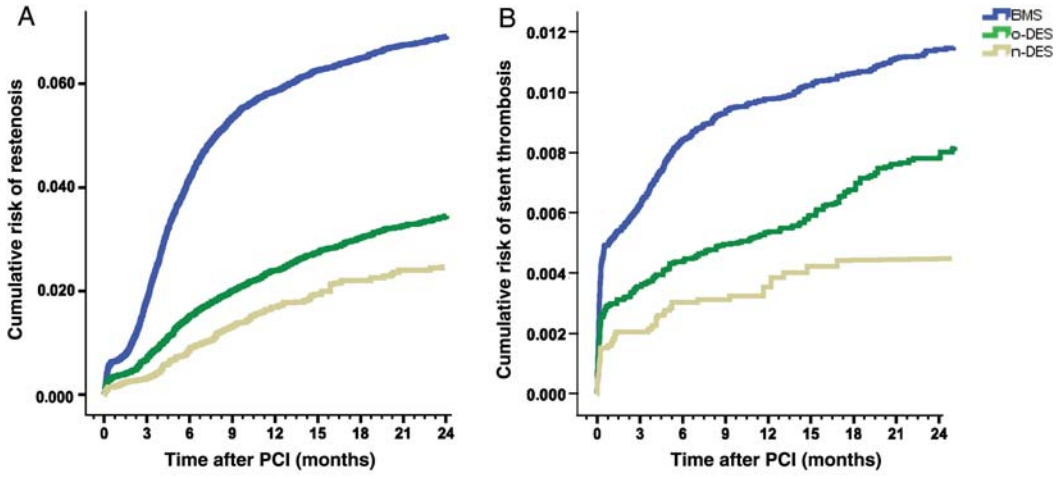


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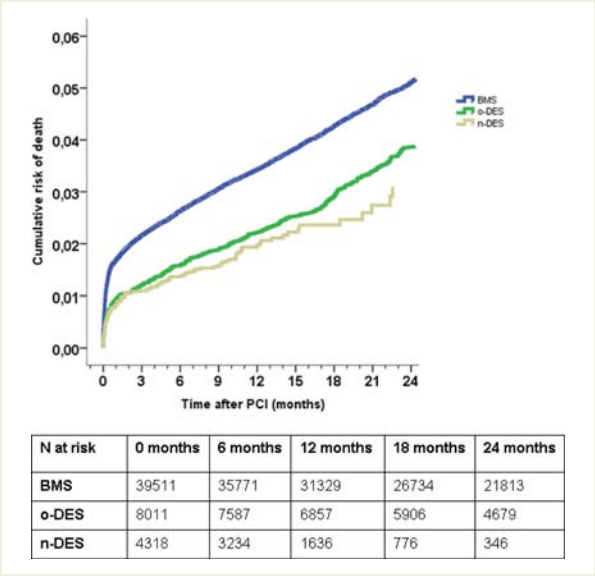
Figure 3 Adjusted cumulative risk of restenosis (*A*) and definite stent thrombosis (*B*) up to 2 years in bare-metal stents (BMS), old-generation drug-eluting stents (o-DES), and new-generation drug-eluting stents (n-DES).

as patient, lesion, and procedural characteristics may be contributing, delayed arterial healing and reduced re-endothelialization may play a role in the pathogenesis of late ST in o-DES.[28,29] Delayed arterial healing could be related to a toxic effect from the eluting drug and/or a hypersensitivity reaction from the polymer and/or drug.[29,30]



N at risk	0 months	6 months	12 months	18 months	24 months
BMS	39511	35771	31329	26734	21813
o-DES	8011	7587	6857	5906	4679
n-DES	4318	3234	1636	776	346

Figure 4 Adjusted cumulative risk of death up to 2 years in bare-metal stents (BMS), old-generation drug-eluting stents (o-DES), and new-generation drug-eluting stents (n-DES).

Improved stent designs with thinner struts and more biocompatible polymers may have an important impact on drug elution profiles, endothelial coverage, and functional recovery.[31,32]

Previous randomized studies are limited to comparisons between one type of n-DES and o-DES, mainly the everolimus-eluting stent (EES) vs. paclitaxel-eluting stent (PES).[6,7,33–36] The ST rates reported from a 3-year pooled analysis of the SPIRIT II and III studies, with restrictive enrolment criteria, showed a significant reduction in the rate of probable or definite ST with EES compared with PES (1.2 vs. 1.9%).[37]

In the COMPARE study, the ST rate was 0.9% with EES at 2 years in all-comers patients with a relative risk reduction by 79% compared with PES. Target lesion revascularization and target vessel revascularization were both significantly lower for EES compared with PES at 2 years, with a relative risk reduction of 55 and 60%, respectively.[38]

Recently, the RESOLUTE all-comers[39] study reported TLR rates of 4.4% with the new zotarolimus-eluting stent (ZES) resolute and 4.0% with EES in complex lesions; no significant differences in TLR rates were reported between ZES and EES in simple lesions (3.0% ZES vs. 2.1% EES, $P = NS$). Stent thrombosis rates in the RESOLUTE all-comers study ranged from 0 to 1.2% with no significant differences between complex and simple lesions.

However, the sample sizes of these studies were limited and the statistical power to detect potential differences between stent types was inadequate.

The low rates of ST and restenosis with n-DES have been confirmed in the Platinum trial[9] that showed a rate of TLR of 1.9% and ST of 0.4% at 1 year with both the platinum–chromium and cobalt–chromium EES in selected low-risk patients, excluding those with acute or recent MI or visible thrombus, true bifurcations, left main coronary artery stenosis, CTO, and saphenous vein graft stenoses.

Our study evaluated the performance up to 2 years of different types of n-DES in an unselected large real-world population—including patients with MI, three-vessel and/or left main disease, bifurcation lesions, graft disease, restenotic lesions, and CTO.

Another main finding of this study is a significantly lower mortality in both the DES groups compared with BMS. The risk of death was 28% lower with o-DES and 45% lower with n-DES, when compared with BMS; n-DES were associated with a 23% lower risk of death at 2 years compared with o-DES. No mortality reduction in DES vs. BMS has been shown in previous randomized studies[7,11,39–41] or reports from the SCAAR registry[2,3] including patients from earlier time periods. However, similarly to our current results, in observational studies, the unrestricted use of DES was associated with a significant reduction (22%) in death compared with BMS.[41]

Our results need to be interpreted with caution. Despite our use of appropriate statistical adjustments, differences in baseline characteristics or selection criteria that might not have been recorded could remain. On the other side, it could also be argued that the larger sample size of our study could provide more power to detect differences in low-frequency events such as death.

The SCAAR is a continuously evolving registry and differences in the mortality between the current and previous analysis[2] could be explained by a possible change in the outcome over time. The sample size in this current study is more than 50% larger than the previous analysis that included 28 953 patients who received one BMS or one DES between 2003 and 2006 and followed-up up to 5 years. Patients enrolled in the SCAAR before November 2006, when the first n-DES was introduced, were excluded from the current analysis in order to reduce time-dependent changes that could affect the outcome.

Although the large sample size of our study allowed for adjustments for angiographic, clinical characteristics, enrolling centre, and date of the index procedure, the absence of randomization for the stent selection could also affect the outcome. The use of DES in Sweden has progressively increased during the study period and their use has been more frequent in patients at higher risk for restenosis; while BMS have been still more often used in patients with ST elevation MI. Although ST appears to occur with a low frequency, it is possible that the 43 and 62% lower risk of definite ST in n-DES compared with o-DES and with BMS is a possible explanation for the differences in mortality. Further studies are needed in order to attempt to discriminate whether one of the three components of the new-generation DES—the polymer, the stent alloy, the eluting drug—or a synergic effect between them is mainly involved in improving the outcomes.

Study limitations

There are intrinsic limitations to registry data such as differences in baseline characteristics and/or selection bias that might not have been recorded as well as time-dependent changes of outcome. The inclusion of the year of the procedure in the COX model can only partially address this issue. An additional analysis has been performed only in patients undergoing PCI from 2008 until 2010 in order to evaluate whether time-dependent changes and

the different distribution in the type of stent used in this time frame could affect the outcome. The results of this analysis are very similar to the present data and they are reported in the Supplementary material online, Appendix, *Figures S1–S3*). In the Supplementary material online, Appendix, the odds ratios for 1-year mortality in DES vs. BMS from the SCAAR are reported per each year from 2003 to 2010 (*Figure S4*).

There is no mandatory angiographic follow-up in the SCAAR registry. However, the design of this national registry with a binding control of every previously implanted stent ensures identification of cases of restenosis and ST in patients undergoing a subsequent coronary angiogram in all over the country. Our definition of TLR includes only clinical need for repeat revascularization by PCI, while restenosis includes the restenotic lesions treated by PCI, CABG, or medical therapy.

Another limitation of the present study is the lack of information about the medical therapy during the follow-up and the duration and doses of P2Y12 receptor inhibition treatment in individual patients. The longer duration of dual antiplatelet therapy prescribed with DES may reduce long-term adverse event rates independently of stent selection. However, this limitation does not apply to the comparison between old and new DES for which the recommended duration of dual antiplatelet therapy was the same.

Conclusions

This study shows that patients treated with PCI with n-DES have a lower risk of restenosis, ST, and death at 2 years compared with o-DES in a large real-world population. A significantly lower mortality was observed in both the DES groups compared with BMS in this study.

Large-scale randomized studies are needed to confirm these findings that can be useful for the management of patients with a high-risk profile for ST and restenosis.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: S.J. has received institutional research grants from Terumo Inc., Medtronic Inc., and Vascular Solutions.

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