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EDITORIAL COMMENT

Improvements in Coronary Stent Design Translate to Better Real-World Outcomes*

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Stent technology has evolved considerably since the initial introduction of bare metal stents to manage symptomatic coronary artery disease. Compared to balloon angioplasty, bare metal stents reduced the risk of restenosis from early arterial recoil and contraction, although 10% to 20% of patients developed excessive growth of neointima at 1 year (1-3). Drug-eluting stents (DES) for percutaneous coronary interventions (PCI) were developed in response to these high rates of in-stent restenosis and the need for repeat revascularization with bare metal stents. First-generation DES were coated with a durable polymer that was embedded with sirolimus or paclitaxel. These antistenotic drugs inhibit smooth muscle proliferation and prevent neointimal hyperplasia, but they also lead to decreased re-endothelialization, which can increase the risk of stent thrombosis (ST). Second-generation DES were developed with different antiproliferative agents, thinner stent struts, and more biocompatible polymers to reduce this risk of ST.

In an observational cohort study published in this issue of *JACC: Asia*, Yoshikawa et al (4) used a large Japanese registry of patients receiving PCI over multiple time periods to examine rates of ST and target vessel revascularization (TVR) with first-generation versus second-generation DES (4). They found that, compared with patients with first-generation DES, patients with second-generation DES had 47% lower adjusted rates of definite ST and 26% lower adjusted rates of TVR. Additionally, in a stratified analysis, patients with first-generation stents on prolonged dual antiplatelet therapy (DAPT) beyond 1 year had 58% lower rates of very late definite ST and 18% lower rates of TVR compared to patients off DAPT. The investigators highlight that there was no association with DAPT status and outcomes in the second-generation stent group. It should be noted, however, that the interaction between DAPT use and stent generation was not statistically significant, meaning that the treatment effects of extended DAPT duration observed among both first- and second-generation stents were, strictly speaking, not different from one another.

The authors should be commended for their use of a large prospective registry to detect differences between first- and second-generation stents in ST events, which are rare in clinical practice and particularly in Asian populations (5,6). A 2012 meta-analysis of 76 randomized trials found that second-generation everolimus-eluting stents had lower risk of ST compared to first-generation DES, and the risk of TVR was lower than with paclitaxel-eluting stents but similar compared with sirolimus-eluting stents (7). However, the majority of the included trials were conducted in Western populations, so it is unclear whether the results apply to the East Asian population. Notably, RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial), which was conducted in Japan, did not find evidence of lower ST in patients receiving second-generation DES compared to first-generation DES at 7 years of follow-up (8). However, the RESET trial enrolled lower-risk patients compared to the current Japanese registry study, with fewer patients with acute coronary syndrome or multivessel disease. The

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findings in this study, combined with prior published results, leave no doubt that the improvements made to stent design have led to important reductions in clinically meaningful events.

The finding in this study that the benefits of lower ST with prolonged DAPT among patients receiving first-generation stents were attenuated in patients receiving second-generation devices harmonizes with prior reports on DAPT duration after PCI. Many prior studies of extended DAPT therapy after PCI beyond 1 year, including the multicenter placebo-controlled DAPT study, suggested reduction in ischemic events at the expense of greater bleeding and were conducted during a time when both first- and second-generation DES were in use (9,10). Many newer trials of DAPT duration after PCI exclusively used second-generation DES and have found a reduction in bleeding events with shorter DAPT with no increase in ischemic endpoints, even among patients at high ischemic risk (11-15). An East Asian paradox has been described, in which East Asian patients have reduced anti-ischemic benefits and increased bleeding risk with DAPT, despite a decreased effect on platelet reactivity with clopidogrel (16). Fortunately, several of the newer trials of shorter DAPT duration after PCI have been conducted specifically in the East Asian context (12-14). However, it is important to note that none of these newer trials were powered for ischemic endpoints such as ST or TVR.

This study is an important contribution to published reports in that it provides real-world context on the reduction in ST rates with different-generation DES in the Japanese population. However, it is limited by its observational nature in making comparisons between cohorts at different periods in time. For instance, practice patterns other than stent generation, such as the use of more intravascular imaging or more potent P2Y12 inhibitors, also changed over this time and may have reduced the risk of ST and TVR in this later period. Additionally, reasons for DAPT continuation or discontinuation are unknown and could plausibly be related to unmeasured factors that could confound the analysis of DAPT duration.

In seeking answers on the effect of stent generation and DAPT duration on ST and TVR for the Japanese population, one needs to balance the results from randomized trials with those from observational cohorts such as this study, both of which have their strengths and limitations. Randomized trials may be limited by a lack of generalizability and statistical power to detect rare endpoints such as ST, whereas observational studies may have unmeasured confounding. In recent years, newer statistical methods have been developed to "transport" inferences from randomized trials to the broader populations seen in routine clinical practice (17,18). These transportability methods can take advantage of the power of randomization from trials in conjunction with the representativeness of real-world data to estimate a "real-world treatment effect," reflecting the anticipated treatment effect of a trial had a more representative study group been enrolled instead. In the future, it will be important to leverage real-world data sets such as that from the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) Registry with newer trial data to better understand how trial data can apply in clinical practice in Japan and beyond.

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REFERENCES

1. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331:496–501.

2. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med*. 1994;331:489–495.

3. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol*. 2002;40:2082–2089.

4. Yoshikawa Y, Shiomi H, Morimoto T, et al. Stent-related adverse events as related to dual antiplatelet therapy in first- versus second-generation drug-eluting stents. *JACC: Asia*. 2021;1(3):345–356.

5. Park D-W, Yun S-C, Lee S-W, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent: data from an observational cohort study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol Intv*. 2008;1:494–503.

6. Onuma Y, Kimura T, Räber L, et al. Differences in coronary risk factors, procedural characteristics, mortality and stent thrombosis between two all-comers percutaneous coronary intervention registries from Europe and Japan: a patient-level data analysis of the Bern-Rotterdam and j-Cypher registries. *EuroIntervention*. 2015;11:533–540.

7. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation*. 2012;125:2873–2891.

8. Shiomi H, Kozuma K, Morimoto T, et al. 7-Year outcomes of a randomized trial comparing the first-generation sirolimus-eluting stent versus the new-generation everolimus-eluting stent: the RESET trial. *J Am Coll Cardiol Intv*. 2019;12:637–647.

9. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166.

10. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.

11. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042.

12. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427.

13. Hahn J-Y, Song YB, Oh J-H, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428–2437.

14. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416.

15. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310:2510–2522.

16. Kim HK, Tantry US, Smith SC Jr, et al. The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. *Thromb Haemost*. 2021;121:422–432.

17. Stuart EA, Cole SR, Bradshaw CP, Leaf PJ. The use of propensity scores to assess the generalizability of results from randomized trials. *J R Stat Soc Ser A Stat Soc*. 2011;174:369–386.

18. Dahabreh IJ, Robertson SE, Steingrimsson JA, Stuart EA, Hernán MA. Extending inferences from a randomized trial to a new target population. *Stat Med*. 2020;39:1999–2014.

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