# XIENCE Implantation Followed By Short Dual Antiplatelet Therapy: 'The New Normal'?

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The XIENCE family of everolimus-eluting stents ranks among the most used and most widely studied drug-eluting stents worldwide. In patients at high bleeding risk undergoing non-complex percutaneous coronary intervention with these stents, a shortened dual antiplatelet therapy (DAPT) regimen of 1–3 months appears to be associated with a reduced rate of major bleeding, a similar rate of ischaemic events and a very low incidence of stent thrombosis after DAPT discontinuation compared with DAPT up to 12 months.

**Keywords**

XIENCE stent, dual anti-platelet therapy, percutaneous coronary intervention, drug-eluting stents, high bleeding risk, aspirin, P2Y12 inhibitor

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Roughly two decades ago, drug-eluting stents (DES) replaced bare metal stents as the most popular stent type used during percutaneous coronary intervention (PCI).[1–3] However, soon after the introduction of these early-generation DES, their use was linked to an alarmingly high rate of late (>30 days) and very late (>1 year) stent thrombosis.[4] An important predictor for this phenomenon appeared to be premature discontinuation of dual antiplatelet therapy (DAPT). Consequently, an (arbitrary) extended treatment duration up to 12 months after PCI became the standard of care.[5] The advent of safer, new-generation DES has led to questions regarding the necessity of this recommendation, especially in patients at high bleeding risk (HBR).

During the late-breaking sessions of Transcatheter Cardiovascular Therapeutics Connect 2020, the XIENCE 90/28 investigators presented results from the XIENCE Short DAPT Program, which focused on short DAPT after successful PCI with the XIENCE stent in patients at HBR. The XIENCE family of everolimus-eluting stents is characterized by its cobalt–chromium alloy stent platform with thin struts (81 µm) and a biocompatible fluoropolymer, features associated with the low thrombogenicity of the stent platform.[6] The investigators studied whether a short DAPT regimen of 1 month (1,605 patients, XIENCE 28 Global Study; ClinicalTrials.gov identifier: NCT03355742) or 3 months (2,047 patients, XIENCE 90: A Safety Evaluation of 3-month DAPT After XIENCE Implantation for HBR Patients; ClinicalTrials.gov identifier: NCT03218787) was non-inferior with respect to all-cause death and myocardial infarction (MI), and superior with respect to bleeding complications, as compared with 12 months of DAPT.[7–9] Age ≥75 years, prior use of concurrent oral anticoagulant (OAC) therapy, chronic kidney disease, anaemia, haematological disorders, major bleeding in the last 12 months, and a history of stroke were considered as HBR features, much in line with international consensus.[10] Importantly, only patients without adverse events and adherent to DAPT in the first 1–3 months were ultimately included. Patients in XIENCE 90/28 were compared with propensity-score-matched controls from the XIENCE V USA trial (XIENCE V® Everolimus Eluting Coronary Stent System USA Post-Approval Study (XIENCE V® USA Long Term Follow-up Cohort) (XVU-LTF); ClinicalTrials.gov identifier: NCT01120379; n=5,054), a post-approval study evaluating the performance of the XIENCE stent in a real-world setting between 2008 and 2011.[11,12]

Three months of DAPT (XIENCE 90) was non-inferior to 12 months of DAPT between 3 and 12 months post-PCI in terms of all-cause mortality and MI (5.4% versus 5.4%, $p_{NI}$=0.0063), and there was a significant reduction in Bleeding Academic Research Consortium (BARC) type 3–5 bleeding events (2.2% versus 6.3%, p<0.0001). The rate of Academic Research Consortium (ARC)-defined definite or probable stent thrombosis between 3 and 12 months was well below the pre-specified performance goal of 1.2% (event rate 0.2%, p<0.0001). One month of DAPT (XIENCE 28) was also considered non-inferior with respect to ischaemic events compared with 12 months of DAPT between 1 and 6 months post-PCI (3.5% versus 4.3%, $p_{NI}$=0.0005). Again, the investigators found a statistically significant reduction in BARC type 3–5 bleeding events (2.2% versus 4.5%, p=0.0156). The rate of ARC-defined definite or probable stent thrombosis was 0.3%, numerically similar to the event rate in the propensity score-matched controls (0.3%), but no formal statistical testing was performed. In both XIENCE 90 and 28, there was no significant difference in BARC type 2–5 bleeding compared with XIENCE V USA, but the XIENCE V USA protocol did not mandate collection of BARC type 2 bleeding and might therefore underestimate the event rate of BARC type 2–5 bleeding.[11]

The results of the XIENCE Short DAPT Program are in line with previous studies evaluating short DAPT after XIENCE implantation.[13,14] The STOPDAPT-1 (Short and optimal duration of dual antiplatelet therapy after everolimus-eluting cobalt-chromium stent; ClinicalTrials.gov identifier: NCT01659034) investigators showed that stopping DAPT at 3 months was at least as safe as a 12-month (standard) DAPT regimen.[13,15] However, the patients in STOPDAPT-1 were not randomized, and the patients in the standard treatment group originated from a historical control group of RESET (Randomized evaluation of sirolimus-eluting versus everolimus-eluting stent trial; ClinicalTrials.gov identifier: NCT01035450).[13,16] In the randomized follow-up trial, STOPDAPT-2 (Short and optimal duration of dual antiplatelet therapy-2 study; ClinicalTrials.gov identifier: NCT02619760), short DAPT (1 month) followed by clopidogrel monotherapy compared with a standard DAPT regimen resulted in a reduction of the composite of major adverse cardiovascular (MACE) and bleeding events, meeting both the non-inferiority and superiority criteria.[14,17] Although promising, the STOPDAPT-2 trial had several limitations, such as its open-label design and a wide non-inferiority margin (relative margin of 50%). Importantly, STOPDAPT-1 and STOPDAPT-2 primarily included East Asian patients, who have a unique risk profile. Hence, extrapolation of these results to other ethnicities should be done with caution.

Several limitations of the XIENCE Short DAPT Program need to be acknowledged when interpreting the results. First, limitations caused by the non-randomized design cannot be fully compensated by propensity-score adjustments. For example, XIENCE V USA was completed roughly a decade before the XIENCE Short DAPT Program, so changes in clinical practice might have influenced the results. A second methodological concern is the relatively wide non-inferiority margins used for the analyses pertaining to ischaemic complications (2.8% for XIENCE 90 and 2.5% for XIENCE 28). Also, 66% of patients included in the programme had chronic coronary syndrome (CCS), for whom 6 months of DAPT is standard practice.[18] In the XIENCE Short DAPT Program, short DAPT (1–3 months) was compared with 12 months of DAPT. Extending treatment duration beyond the guideline-recommended period for patients with CCS could have led to a higher bleeding rate in the control arm, which is not representative of the true bleeding rate in clinical practice.

Importantly, approximately four out of 10 patients enrolled in XIENCE 90 and 28 were on chronic OAC therapy. Due to the excessive bleeding rate in patients on OAC therapy, the default strategy in these patients is dual antithrombotic therapy after a 1-week period of triple antithrombotic therapy, regardless of bleeding risk. Only in patients with clinical, anatomical and/or procedural high ischaemic risk features without HBR should extending triple antithrombotic therapy be considered.

Then again, the XIENCE Short DAPT Program excluded patients with several high-risk features, such as target lesions containing thrombus, PCI with overlapping stents, PCI of left main lesions, arterial or saphenous vein grafts, in-stent re-stenosis and/or chronic total occlusions, target lesions >32 mm in length and >3 target lesions with >2 target lesion vessels. Previously, multiple studies have underscored the importance of PCI complexity in determining DAPT duration.[19,20] These studies showed that complex PCI was an independent predictor of ischaemic events in the first year after PCI, and that at least 12 months of DAPT was associated with significant reductions in MACE, compared with 3 or 6 months of DAPT in patients with complex lesions. However, in patients with concurrent high bleeding and ischaemic risk, the current evidence seems to suggest that bleeding risk, rather than ischaemic risk, should guide clinical decision-making regarding optimal treatment duration.[21]

In brief, determining the optimal treatment duration lies in an individualized approach based on risk stratification.[22] In patients at HBR, 1–3 months, as opposed to 12 months, of DAPT following non-complex XIENCE stent implantation seems safe and might reduce major bleeding complications. In patients on chronic OAC therapy, dual antithrombotic therapy should be preferred over triple antithrombotic therapy after 1 week. Whether short DAPT is also safe following complex PCI remains to be investigated. ❑


1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–23.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221–31.
3. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–80.
4. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation*. 2007;115:1440–55;discussion 55.
5. Farb A, Boam AB. Stent thrombosis redux--the FDA perspective. *N Engl J Med*. 2007;356:984–7.
6. Mitsis A, Valgimigli M. Device profile of the XIENCE V and XIENCE Sierra stents for the treatment of coronary artery disease: an overview of safety and efficacy. *Expert Rev Med Devices.* 2020;17:383–90.
7. ClinicalTrials.gov. XIENCE 28 Global Study. ClinicalTrials.gov Identifier: NCT03355742. Available at: https://clinicaltrials.gov/ct2/show/NCT03355742 (accessed 19 October 2021).
8. ClinicalTrials.gov. XIENCE 90: A Safety Evaluation of 3-month DAPT After XIENCE Implantation for HBR Patients. ClinicalTrials.gov Identifier: NCT03218787. Available at: https://clinicaltrials.gov/ct2/show/NCT03218787 (accessed 19 October 2021).
9. ClinicalTrials.gov. XIENCE 28 USA Study. ClinicalTrials.gov Identifier: NCT03815175. Available at: https://clinicaltrials.gov/ct2/show/NCT03815175 (accessed 19 October 2021).
10. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J.* 2019;40:2632–53.
11. Krucoff MW, Rutledge DR, Gruberg L, et al. A new era of prospective real-world safety evaluation primary report of XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System condition-of-approval post-market study). *JACC Cardiovasc Interv.* 2011;4:1298–309.
12. ClinicalTrials.gov. XIENCE V® Everolimus Eluting Coronary Stent System USA Post-Approval Study (XIENCE V® USA Long Term Follow-up Cohort) (XVU-LTF). ClinicalTrials.gov Identifier: NCT01120379. Available at: https://clinicaltrials.gov/ct2/show/NCT01120379 (accessed 19 October 2021).
13. Natsuaki M, Morimoto T, Yamamoto E, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. *Cardiovasc Interv Ther.* 2016;31:196–209.
14. 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;321:2414–27.
15. ClinicalTrials.gov. Short and Optimal Duration of Dual Antiplatelet Therapy Study (STOPDAPT). ClinicalTrials.gov Identifier: NCT01659034. Available at: https://clinicaltrials.gov/ct2/show/NCT01659034 (accessed 22 October 2021).
16. ClinicalTrials.gov. Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting Stent Trial (RESET). ClinicalTrials.gov Identifier: NCT01035450. Available at: https://clinicaltrials.gov/ct2/show/NCT01035450 (accessed 19 October 2021).
17. ClinicalTrials.gov. ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study (STOPDAPT-2). ClinicalTrials.gov Identifier: NCT02619760. Available at: https://clinicaltrials.gov/ct2/show/NCT02619760 (accessed 19 October 2021).
18. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J.* 2019;41:407–77.
19. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol.* 2016;68:1851–64.
20. Yeh RW, Kereiakes DJ, Steg PG, et al. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol*. 2017;70:2213–23.
21. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol.* 2019;73:741–54.
22. van der Sangen NMR, Rozemeijer R, Chan Pin Yin D, et al. Patient-tailored antithrombotic therapy following percutaneous coronary intervention. *Eur Heart J.* 2021;42:1038–46.