Target Lesion Revascularization in the NORSTENT Trial

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Multicenter randomized clinical trials with no disclosures and an excellent design and statistic analysis such as the NORSTENT (Norwegian Coronary Stent Trial) are only sporadically found. Therefore, data coming from such a study are a helpful instrument in guiding clinical practice and shedding light on previously unclear issues.

In the NORSTENT [1], 9,013 patients were randomized to receive either drug-eluting stents (DES) or bare metal stents (BMS). At the time the trial was designed, there were major concerns regarding the safety of DES because of the potentially increased risk for stent thrombosis. After 5 years of follow-up, there were no significant differences between groups in the primary composite outcome of death from any cause or nonfatal spontaneous myocardial infarction, as well as in the individual endpoints of myocardial infarction or unstable angina. Measures of quality of life did not differ. During the 5 years of follow-up, “any repeat revascularization” occurred in 19.8% of the patients in the BMS group versus 16.5% of the patients in the DES group (3.3% absolute risk reduction; $p < 0.001$). The difference was driven by less restenosis with DES.

Due to previous criticism (the first results had total revascularization and not target lesion revascularization [TLR] as a secondary endpoint), these newly presented

data were highly anticipated. DES resulted in a stable reduction of TLR (TLR with DES: 3.5%; TLR with BMS: 7.6%; $p < 0.001$) in the first 500 days after implantation, and this effect was consistent in all clinical scenarios and among all clinical risk factors for coronary heart disease, confirming in this way the results of the first publication [1]. This effect was limited in time to the first 2 years, but there was no evidence of a later rebound during the 5-year follow-up.

Taking into account the mechanisms of in-stent restenosis (ISR) requiring TLR, these results come as no surprise. Biological, arterial, and stent-related factors are contributing to TLR following similar but not identical mechanisms after BMS and after DES implantation. Neointimal hyperplasia has been classically observed as a major factor for ISR and TLR, especially in the first 6–15 months following BMS implantation [2], which led to the development of the first generation of DES. Safety concerns were raised about these first-generation DES (regarding hypersensitivity reactions to their polymer, evidence of chronic inflammatory reactions, and early neo-atherosclerosis [2]), leading to the development of the second generation of DES with thinner struts, longer drug release, and a biocompatible/biodegradable polymer [3]. Their improved technology seems to induce a

decreased inflammatory response, but nevertheless they do not seem to protect against early neoatherosclerosis [2]. These well-known observations explain the initial reduction of TLR and the time limitation of their benefit over BMS. The current data further show that multivessel disease and longer stents also induce TLR.

At this point, the chronological discrepancy between the NORSTENT and current clinical practice should be considered. The DES used in the NORSTENT were mainly XCIENCE and Endeavour stents, and they were tested against the newest iteration of BMS (stents with no polymer and drug, and therefore potentially “safer”). Since the conduction of the NORSTENT, there has been further development of second-generation DES. Moreover, although the vast majority of trials comparing two types of second-generation DES failed to show any superiority regarding ischemic endpoints, recent data on stents with ultrathin struts show their superiority regarding TLR and stent thrombosis [4]. Since it was the reduction in strut thickness which led to the initial reduction in TLR after implantation of first-generation DES compared to BMS, it is no surprise that a further reduction in thickness yields a further clinical benefit. In addition, the decreased chronic inflammatory response [2] induces less unstable plaques such as thin-cap fibroatheroma and intimal rupture observed in ISR with first-generation DES, leading to less acute coronary syndromes.

Although in the NORSTENT, the duration of dual antiplatelet therapy (DAPT) was similar in the two groups,

there is nowadays an ongoing trend towards a reduction of DAPT for patients being treated with a DES, and this reduction is not associated with an increase in ischemic events but with a significant reduction in bleeding events. STOPDAPT-2 [5] and SMART-CHOICE [6] have proven noninferiority and superiority [5], respectively, of short DAPT to DAPT of conventional duration, leading to fewer bleeding events. Nevertheless, an advantage with regard to mortality or hospitalization could not be shown, at least for the 1-year follow-up. A very recent trial showed that major bleeding events in patients previously treated with percutaneous or surgical myocardial revascularization are related to increased mortality rates [7].

These new results of the NORSTENT also demonstrate that the reduction of TLR with the use of DES does not affect all-cause and cardiovascular mortality. On the other hand, and as already mentioned by the authors of this paper, TLR is not universally considered as being so benign, and a statistically significant association with mortality has been reported [8]. These new results of the NORSTENT demonstrate that BMS are a safe treatment option, but DES do perform better and therefore confirm daily clinical practice in catheterization laboratories worldwide.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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