Editorial Comment

Which DES for Diabetics? Round 1: A Draw. Round 2: Everolimus Leading?

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The bypass angioplasty revascularization in type 2 diabetes trial (BARI-2D) demonstrates improved quality of life and functional status in type II diabetics undergoing an initial strategy of mechanical revascularization including percutaneous coronary intervention (PCI) compared with an initial strategy of medical therapy alone for stable CAD [1]. There was no short-term improvement in "hard endpoints" such as mortality with PCI. Across the spectrum of acute coronary syndromes, PCI has been demonstrated to have incremental benefit in diabetics over medical therapy alone similar to the broader population. In an individual diabetic patient capable of taking dual antiplatelet therapy (DAPT), once it is determined to pursue PCI, what is the optimal stent to place?

When compared with bare metal stents (BMS), randomized trials demonstrate a markedly reduced risk of restenosis with drug-eluting stents (DES) in diabetics. A meta-analysis of six sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) versus BMS trials in 2,491 diabetics documented an 84% reduction in the odds of restenosis with DES compared with BMS [2]. In the DECODE and DIABETES studies, DES reduced angiographic restenosis from 50 to 10% and target vessel revascularization from 30% to single digits compared with BMS in diabetics, with particular advantage in reference vessel diameters <3.0 mm [3,4].

Given different mechanisms of cell cycle inhibition, is sirolimus or paclitaxel superior in the proliferative diabetic milieu? SES has less late loss than PES, 0.2 versus 0.5 mm on average. However, impaired phosphatidylinositol-3 kinase activity in diabetics might reduce conversion of sirolimus to its active metabolite that inhibits mammalian target of rapamycin. Head-to-head trials of SES and PES have generally had angiographic endpoints, which demonstrate that the late loss in the diabetic subgroup is less with SES than PES and not dissimilar to nondiabetics. The seven SES versus PES comparative trials have had limited power to detect differences in clinical outcome in the diabetic subgroup.

In this issue of *Catheterization and Cardiovascular Interventions*, Akin et al. present compelling evidence comparing clinical outcomes with these first-generation DES [5]. In a large prospective consecutive real world registry in Germany, 1,526 diabetics receiving SES or PES are examined at 1-year follow-up. Although not randomized, baseline differences between the groups are negligible. Mortality, target vessel revascularization, stent thrombosis (ST), and overall major adverse cardiovascular and cerebrovascular events are without statistical or appreciable clinical difference at 1 year (11.4% with SES and 10.3% with PES.)

However, US practice has widely adopted the second-generation everolimus-eluting stents (EES) due to low restenosis rates similar to SES, greater ease of delivery, and evidence supporting more complete endothelialization compared with first-generation DES. The hope is that we will observe a lower risk of late and very late stent thrombosis. In the SPIRIT IV trial, comparing EES with PES, clinical outcomes were better with EES than PES in the overall study population [6]. However, diabetics were the only prespecified subgroup that did not enjoy a significantly lower restenosis rate with EES (6.4%) than PES (6.9%). In the 1,800 patient COMPARE study of EES versus PES, stent thrombosis and restenosis were reduced with EES in nondiabetics. Test for interaction suggested not dissimilar results for diabetics (interaction $P = 0.22$) [7]. Given restenosis equipoise between EES and PES in diabetics in the larger SPIRIT IV trial, it seems reasonable to favor EES given the overall lower stent thrombosis rate with EES. Indirectly, Akin et al.'s data imply that we might anticipate

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similar results with SES versus EES. We await the results of the ESSENCE-DM trial that randomized 380 Korean diabetics to EES versus SES.

In Akin et al.'s registry, definite stent thrombosis is not significantly different between SES and PES at 0.7% versus 0.7% at 1 year. Definite, probable, and possible stent thrombosis was also not statistically different at 5.6% with SES and 4.6% with PES. A high definite stent thrombosis rate (4.3% with multivessel disease and 2.3% with single vessel disease) was observed in 356 diabetics (compared with 3.0 and 0.8% in nondiabetics) in the EVASTENT registry in France [8]. Insulin requirement was an independent significant risk factor for ST. Hence, if the lower overall relative stent thrombosis rate observed with EES than PES in SPIRIT IV can be proportionally extrapolated to diabetics, then it would appear logical that EES is presently the optimal stent in diabetic patients able to take DAPT for at least 6 months and ideally 1 year or longer. While we seem to have a better stent to offer to diabetics, we almost certainly have better adjunctive medicines as well. Given the higher baseline and on-treatment (aspirin/clopidogrel) platelet reactivity and prothrombotic state observed in diabetics, the TIMI-38 and PLATO trials provide compelling data that the more consistent and potent platelet inhibitors prasugrel and ticagrelor will further improve outcomes in our diabetic patients without an appreciable bleeding penalty.

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