

## EDITORIAL COMMENT

# The Continuing Diabetic Drug-Eluting Stents Saga

## From Very-Late Stent Thrombosis to Very-Late Late Loss\*

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Unlike various atherosclerotic risk factors in which the population attributable to risk fell marginally from the period 1952 to 1974 to the period 1975 to 1998, it rose for diabetes (1). This adverse trend is worrisome as the prevalence of diabetes is rapidly growing worldwide, rising from 171 million in 2000 to a projected 366 million in 2030 (2). The increase may potentially reverse the decline in cardiovascular disease, a condition that accounts for 58% of diabetic deaths (3). Furthermore, management of patients with diabetes is costly. In the U.S., the 2002 expenditure for diabetes care was estimated to be \$132 billion (3). From 2009 to 2034, the cost is expected to double (4), and a substantial component of that is related to hospitalization (3), including the use of various investigative and therapeutic procedures.

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Several early clinical studies have shown outcomes following coronary revascularization among patients with diabetes were consistently poorer than for patients without diabetes (5). Undoubtedly, coronary stents and potent antiplatelet agents have improved results with percutaneous coronary intervention. A collaborative meta-analysis has shown that although there was no overall difference in mortality between patients with multivessel disease undergoing bare-metal stenting (BMS) versus coronary artery bypass grafting (CABG), surgery afforded better survival for those with diabetes (6).

The advent of drug-eluting stents (DES) was likened to an interventional cardiologist entering the Promised Land,

bestowed with a device without fear of restenosis (7). However, the euphoria for treating diabetes patients with DES was cut short by an early meta-analysis comparing sirolimus-eluting stents (SES) with BMS (8). After 4 years, the risk of dying was roughly 3 times higher among diabetic patients receiving SES. A subsequent, more comprehensive study involving 3,852 individuals with and 10,947 without diabetes found that there was no difference in the frequency of death, myocardial infarction, or both events among those receiving DES or BMS (9). Notably, the stent thrombosis rate was comparable between both treatment groups. These findings were also observed in contemporary large angioplasty registries (10–12). In this issue of *JACC: Cardiovascular Interventions*, the investigators of the ARTS (Arterial Revascularization Therapies Study), parts I and II (13) provided additional evidence for the long-term safety of DES compared with BMS among patients with diabetes and multivessel disease, with similar death and stent thrombosis rates. However, a favorable and important finding was that myocardial infarction occurred >2.5 times less frequently among diabetics treated with DES versus BMS (10.7% vs. 4.4%;  $p = 0.048$ ). Not only was this benefit (13.8% vs. 16.9%) observed in the separate Massachusetts Data Analysis Center Registry (14), but also the 3-year mortality rate (17.5% vs. 20.7%) was significantly lower for patients with diabetes treated with DES versus BMS.

Notably in ARTS, there was no difference in mortality and myocardial infarction rates between patients with diabetes undergoing CABG or receiving SES. Taken together with similar findings from recent studies (15,16), DES implantation in diabetic patients is likely to be safe compared with cardiac surgery. However, the reason for the outcome improvement among studies over time is uncertain. Although it was shown that use of dual antiplatelet agents >6 months was associated with superior outcome (9), most patients in ARTS II receiving SES were treated with dual therapy for only 3 months. Despite coronary lesions being more complex in ARTS II, perhaps greater care in stent deployment and a return to the high-pressure post-dilation technique (14.9 vs. 16.2 atm,  $p < 0.01$ ) played a role in improving outcome.

A principal limitation of DES compared with CABG among patients with diabetes and multivessel disease is the need for repeat revascularization procedures. At 5 years, the ARTS investigators reported this rate to be 31.4% and 10.4% for the SES and CABG groups, respectively. Although diabetic patients treated with SES were ~40% less likely to require another revascularization procedure than those treated with BMS, the investigators described a disturbing “catch-up” phenomenon. After the second year, the rate of increase of repeat revascularization procedures accelerated, and the superiority provided by SES over BMS

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diminished. The underlying mechanism for this unfavorable trend was unclear. Although the risk of acquired late malapposition was higher among diabetic patients treated with SES versus BMS (14.7% vs. 0%;  $p = 0.001$ ) at 9 months (17), no patient in that study suffered from stent thrombosis. However, a subsequent meta-analysis (18) suggested that acquired late malapposition may be associated with >6 times higher risk for late stent thrombosis. However, its relationship with the need for late revascularization procedure is unknown. Conversely, this delayed rise in revascularization procedure among diabetic patients treated with DES was not observed in large registries with follow-up periods of 2.5 years (12) and 3 years (14).

Nonetheless, most patients requiring repeat procedures underwent percutaneous coronary intervention. Generally, individuals tend to have a natural distaste for surgery and concerns regarding cognitive decline (19). Although the figures were not available for 5 years for ARTS, the numbers undergoing cardiac surgery at 3 years were 6 (3.8%) and 2 (2.1%) for SES and CABG patients, respectively (20). In other words, DES treatment may have avoided CABG in 96.2% of patients with diabetes and multivessel disease.

For 12 years, Hercules used his strength, ingenuity, and, sometimes, assistance from some helpful individuals to complete task after task for King Eurystheus. It has been almost 15 years since the Bypass Angioplasty Revascularization Investigation (21) alert raised concern for treating diabetic patients with angioplasty. The field of interventional cardiology has progressed substantially since then, developing ideas from engineering and drug delivery. The investigators of ARTS and other studies have shown that coronary stenting in patients with diabetes and multivessel disease is relatively safe. Because of the superiority over BMS, DES is probably the preferred device for percutaneous coronary intervention. Novel pharmacological agents may further improve outcomes among patients with diabetes undergoing coronary stenting (22). Although newer generations of DES (23,24) have not been shown to be fully comparable to CABG regarding the need for repeat revascularization, continuous innovation will narrow the efficacy gap further for patients with diabetes.

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