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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Restenosis, Stent Thrombosis, and Bleeding Complications

Navigating Between Scylla and Charybdis

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ABSTRACT

The field of interventional cardiology has significantly evolved over 40 years by overcoming several challenges. The introduction of first-generation drug-eluting stents significantly reduced the rates of restenosis, but at the expense of an increase of late stent thrombosis. Prolonged antithrombotic therapy reduced rates of stent thrombosis, but at the cost of increased bleeding. Although the advent of second-generation drug-eluting stents subsequently reduced the incidence of late stent thrombosis, its permanent nature prevents full recovery of vascular structure and function with accordant risk of very late stent failure. In the present era of interventional cardiology, the tradeoff between stent thrombosis, restenosis, and bleeding presents as a particularly complex challenge. In this review, the authors highlight major contributors of late/very late stent thrombosis while targeting stent restenosis, and they discuss evolutionary advances in stent technology and antiplatelet therapy, to further improve upon the care of patients with coronary artery disease. (J Am Coll Cardiol 2018;71:1676–95) © 2018 by the American College of Cardiology Foundation.

Although the introduction of bare-metal stents (BMS) significantly reduced balloon angioplasty-associated complications decreasing emergency coronary artery bypass grafting surgery and restenosis, BMS were themselves related with a serious phenomenon, stent thrombosis (ST) (1,2). ST constitutes one of the most catastrophic complications of percutaneous coronary intervention (PCI), typically presenting as a large ST-segment elevation myocardial infarction (STEMI) or as sudden cardiac death, requiring emergency repeat PCI. The incorporation of dual-antiplatelet therapy (DAPT), as well as parallel improvements in stent deployment techniques, provided some relief to this complication, especially by reducing early ST events (<30 days) (2,3).

The massive utilization of BMS revealed another limitation of the device: a progressive loss of the arterial lumen inside the stent seen several months after PCI (4,5). With a more benign course, in-stent restenosis (ISR) decreased the overall efficacy of the technique leading to recurrent angina and need for additional target lesion revascularization (TLR) procedures (6). The demonstration of neointimal hyperplasia (NIH) as the main mechanism involved in ISR prompted the introduction of first-generation drug-eluting stents (1G-DES) (7). These stents provided striking results in reducing ISR, but an unexpected and worrying increase in late and very late ST (>30 days to 1 year and >1 year, respectively) was observed, triggering a reflex increase in DAPT intensity and duration (8). However, prolonged

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antithrombotic therapies introduced a new hazard in the form of serious bleeding complications (9).

A major step forward in PCI was achieved with the advent of current second-generation DES (2G-DES), incorporating more biocompatible or biodegradable polymers, different drug release formulation, stent platforms, and designs, with the associated decrease in ISR, ST, duration of DAPT, and bleeding (10,11). Novel stent technologies, however, such as fully bioresorbable scaffolds (BRS), have unfortunately not fulfilled the promise of reaching the theoretical ideal of reducing very late stent complications, and much work remains to further optimize this technology (11–13).

The story of 40 years of PCI can be illustrated as Odysseus's ship navigating through a strait, in which 2 "sea hazards" are situated close enough to each other that they posed an unavoidable threat to passing sailors: avoiding Charybdis (e.g., restenosis) could mean passing too close to Scylla (e.g., thrombosis), as well as avoiding ST could represent increasing severe bleeding. The aims of this review are first to analyze how late ST has been closely linked to the attempts to avoid restenosis, and second, to review major advances in stent technology and antiplatelet therapy to further reduce the occurrence of ST, while both maintaining a powerful antirestenosis effect and affording the lesser possible bleeding hazards.

For this review, pertinent studies were searched in PubMed/Medline (updated December 2017) using the following terms: *stent thrombosis*, *stent restenosis*, *antiplatelet therapy*, *drug-eluting stent*, *biodegradable polymer*, and *bioresorbable vascular scaffold*. Given the design of this work as a narrative review, no formal criteria for study selection or appraisal were enforced.

ST AS AN "ADVERSE EFFECT" OF ANTIRESTENOSIS THERAPIES

FROM STAND-ALONE BALLOON ANGIOPLASTY TO BMS. The first balloon angioplasty (BA) of a coronary atherosclerotic plaque performed by Andreas Grüntzig in 1977 (14) marked the birth of the field of interventional cardiology. However, at present, with few exceptions, BA is rarely preferred as a stand-alone treatment (**Figure 1**).

In 1986, BMS were introduced into the therapeutic arsenal representing the second turning point in the history of interventional cardiology (15). However, the success of BMS was initially eclipsed with the occurrence of serious ST episodes. In fact, ST was optimally circumvented more than a decade later only after 2 paramount advances were simultaneously achieved. First, old antithrombotic regimens (including heparin, dextran, warfarin, and dipyridamole) were replaced by a safer DAPT regimen (including aspirin and a $P2Y_{12}$ receptor inhibitor) (9,16). Second, the understanding of the concept of "adequate" stent deployment technique, with optimal implantation strategy aiming at an absolutely perfect primary result with no residual narrowing, absence of dissections, and complete stent expansion and apposition (2,3,17).

Initially, stents were considered a "bail-out procedure" in the case of abrupt or threatened artery closure post-BA, reducing the need of emergent coronary artery bypass grafting (17). However, several years later, the BENESTENT (BElgian NEtherlands STENT study) and STRESS (Stent Restenosis Study) trials demonstrated that routine elective placement of a Palmaz-Schatz stent significantly reduced the rates of angiographic restenosis as compared with BA (1,18). Although, current BMS offer improved geometric structure, thinner struts [<120 μm]) and stronger alloys, the risk of NIH and TLR have relegated BMS to second-line therapy (7).

LATE/VERY LATE ST WHILE PREVENTING NIH. NIH is a complex and time-dependent phenomenon that occurs in response to deep vascular injury after BA and stenting. It is characterized by inflammation, smooth muscle cells migration, proliferation, and production of collagen fibers in the extracellular matrix (5,19).

Early efforts to reduce NIH included intracoronary brachytherapy, which despite promising data for reducing NIH over midterm follow-up, were limited by a "late catch-up phenomenon" and an increase in late ST (20). Indeed, late ST rates of ~10% have been observed, depending on the use of DAPT (20,21).

A major breakthrough in interventional cardiology was the introduction of 1G-DES. DES while maintaining the mechanical advantages of BMS are able to effectively deliver an antiproliferative therapy locally to the arterial wall. In fact, 1G-DES rapidly became the standard of care resulting in angiographic restenosis rates of a "single digit number" at 6 to 12 months follow-up (4). Unfortunately, like prior advances in PCI, there are 2 sides to the 1G-DES story: on the one hand, 1G-DES reduced the need for TLR by at least 50% to 70% (7), but on the

ABBREVIATIONS AND ACRONYMS

1G-DES = first-generation drug-eluting stent(s)

2G-DES = second-generation drug-eluting stent(s)

ACS = acute coronary syndrome(s)

BA = balloon angioplasty

BES = biolimus-eluting stent(s)

BMS = bare-metal stent(s)

BP-DES = biodegradable polymer-based drug-eluting stent(s)

BRS = bioresorbable scaffold(s)

BVS = bioresorbable vascular scaffold(s)

CI = confidence interval

CoCr = cobalt chromium

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

DT = device thrombosis

EES = everolimus-eluting stent(s)

HR = hazard ratio

ISR = in-stent restenosis

LST = late stent thrombosis

NA = neoatherosclerosis

NIH = neointimal hyperplasia

OCT = optical coherence tomography

OR = odds ratio

PCI = percutaneous coronary intervention

PtCr = platinum chromium

RCT = randomized controlled trial

Re-ZES = Resolute zotarolimus-eluting stent(s)

SES = sirolimus-eluting stent(s)

SM = stent malapposition

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TLF = target lesion failure

TLR = target lesion revascularization

VLST = very late stent thrombosis