Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 21, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.08.725

STATE-OF-THE-ART PAPERS

Stent Thrombosis With Drug-Eluting Stents

Is the Paradigm Shifting?

Tullio Palmerini, MD,* Giuseppe Biondi-Zoccai, MD,† Diego Della Riva, MD,* Andrea Mariani, MD,* Philippe Genereux, MD,‡ Angelo Branzi, MD,* Gregg W. Stone, MD‡

Bologna and Latina, Italy; and New York, New York

First-generation drug-eluting stents (DES), which impart the controlled release of sirolimus or paclitaxel from durable polymers to the vessel wall, have been consistently shown to reduce the risk of restenosis and target vessel revascularization compared with bare metal stents (BMS). However, stent thrombosis (ST) emerged as a major safety concern with first-generation DES early after their adoption in clinical practice, requiring prolonged dual antiplatelet therapy. Pathological studies have shown that first-generation DES are associated with delayed arterial healing and polymer hypersensitivity reactions resulting in chronic inflammation, predisposing to late and very late ST. Second-generation DES have been developed to overcome these issues with improved stent designs and construction and the use of biocompatible and bioabsorbable polymers. Meta-analyses have shown that the thin-strut, fluoropolymer-coated cobalt-chromium everolimus-eluting stent (CoCr-EES) may be associated with lower rates of definite ST than other DES and, unexpectedly, even lower than BMS. The thin-strut structure of the stent platform, the thromboresistant properties of the fluoropolymer, and the reduced polymer and drug load may contribute to the low rate of ST with CoCr-EES. The notion of DES being safer than BMS represents a paradigm shift in the evolution of percutaneous coronary intervention. The relative safety and efficacy of fluoropolymer-coated CoCr-EES, DES with bioabsorbable polymers, and fully bioresorbable scaffolds are the subject of numerous ongoing large-scale trials.
(J Am Coll Cardiol 2013;62:1915–21) © 2013 by the American College of Cardiology Foundation

Although first-generation Cypher sirolimus-eluting stents (SES) (Cordis Corp., Miami Lakes, Florida) and Taxus paclitaxel-eluting stents (PES) (Boston Scientific, Natick, Massachusetts) significantly reduce the risk of target vessel revascularization compared with bare-metal stents (BMS) (1,2), concern has been raised over their ongoing propensity for very late stent thrombosis (ST) (3). These safety concerns prompted the development of second-generation drug-eluting stents (DES), which use different drugs, more biocompatible or bioabsorbable polymers, and different stent platforms. On their introduction, second-generation DES were most commonly compared with first-generation DES in noninferiority randomized controlled trials (RCTs) (4), which did not have sufficient statistical power to explore possible differences in ST rates between devices. In this review, we therefore analyze the relative risk of ST, death, and myocardial infarction (MI) of first-generation DES, second-generation DES, and BMS that have been extensively investigated in RCTs. We did not analyze in detail all studies enrolling patients with ST-segment elevation MI because this issue was recently addressed by a dedicated analysis (5).

From the *Dipartimento Cardiovascolare, Policlinico S. Orsola, Bologna, Italy; †Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; and the ‡Columbia University Medical Center/New York-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, New York. Dr. Palmerini has received lecture fees from Abbott Vascular. Dr. Biondi-Zoccai has served as a lecturer/consultant for Abbott Vascular, Boston Scientific, Cordis, and Medtronic. Dr. Stone is a consultant for Boston Scientific, AstraZeneca, Eli Lilly, Daiichi Sankyo, Abbott Vascular, and Medtronic. All other authors have reported that they have no relationships relevant to the content of this paper to disclose.

Manuscript received May 21, 2013; revised manuscript received August 6, 2013, accepted August 12, 2013.

ST With First-Generation DES

Although RCTs initially did not raise any safety issues with first-generation DES (1,2), a subsequent report of 4 cases of angiographically confirmed ST late after elective implantation of SES or PES raised concerns of a possible very late ST risk with DES (6). However, it was not until 2006, at the annual meeting of the European Society of Cardiology in Barcelona, that the firestorm over first-generation DES was ignited, spreading concern among the media and public as well as interventional cardiologists (7). During this congress, a meta-analysis performed on aggregate data pooled from trial programs comparing SES or PES versus BMS suggested an increased risk of mortality and MI with first generation DES compared to BMS (8). The controversy regarding the safety of DES was fueled by additional real-world studies that showed an increased risk of late ST and MI in patients treated with first-generation DES after discontinuation of dual antiplatelet therapy (DAPT) (3) and a steady accrual of ST at a rate of 0.6% per year with no evidence of plateau after 4-year follow-up (9). Pathological studies showed that the durable polymer of first-generation DES could result in chronic inflammation,

JACC Vol. 62, No. 21, 2013
November 19/26, 2013:1915–21

Abbreviations and Acronyms

ARC = Academic Research Consortium

BMS = bare-metal stent(s)

CoCr-EES = cobalt-chromium everolimus-eluting stent(s)

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

FDA = Food and Drug Administration

MI = myocardial infarction

PC-ZES = phosphorylcholine polymer-based fast-release zotarolimus-eluting stent(s)

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

PtCr-EES = platinum-chromium everolimus-eluting stent(s)

RCTs = randomized controlled trials

Re-ZES = C10/C19/PVP polymer-based slow-release zotarolimus-eluting stent(s)

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

with delayed hypersensitivity reactions, chronic fibrin deposition, and consequent poor endothelial healing of the vessel wall with increased thrombotic risk (10).

In view of the rare incidence of ST and the conflicting evidence, several pooled analyses and meta-analyses were performed to address the safety of first-generation DES (11–14). As shown in Table 1, these studies collectively established no significant differences in the risk of death or MI between first-generation DES and BMS but an increased risk of very late ST with both SES and PES compared with BMS. On the basis of this mounting evidence regarding the ongoing propensity of DES ST over time, the Food and Drug Administration (FDA) assigned an expert panel to review the available evidence. Eventually, the advisory panel released a statement acknowledging a small but significant increased risk of very late ST with DES while recognized them as safe and effective for on-label indications (15). The absence of a significant difference in mortality or MI between first-generation DES and BMS despite the increased risk of very late ST with DES may be explained by the fact that in-stent restenosis is not always a benign phenomenon, presenting as acute MI in 3.5% to 19.4% of patients (16). Thus, a small increase in a low-frequency event (late or very late ST) with frequent, serious, life-threatening consequences may be offset by a large reduction of a more common event (restenosis), which is occasionally but less frequently associated with serious clinical consequences (17).

Nonetheless, responding to the general concerns of increased ST with DES, the FDA and societies recommended lengthening the requirement for DAPT after DES from 3 to 6 months (as studied in the pivotal approval trials) to 1 year, although little data supported this extension.

The Academic Research Consortium Definition of ST

The lack of a uniform definition of ST provided significant uncertainty in the comparative interpretation of the results of clinical trials and meta-analyses. To standardize definitions for patients enrolled in cardiovascular trials, a formal collaboration between academic research organizations in the United States and Europe, the Academic Research Consortium (ARC), was established (18). Using ARC criteria, ST is defined according to various levels of certainty, depending on whether the level of evidence needs to be more or less restrictive (18). ST is also classified relative to the timing of occurrence after stent implantation as early (within 30 days), late (between 30 days and 1 year) and very late (beyond 1 year). Mauri et al. (19) were the first to analyze the risk of ST using both the trial protocol definitions of ST and the ARC criteria in a meta-analysis. At 4-year follow-up, there were no significant differences in the risk of ST between either SES or PES and BMS, but a different temporal trend in the risk of ST was apparent depending on whether the protocol definition or the ARC criteria were used to define ST. In the Stettler meta-analysis, using mixed treatment comparisons and comparing outcomes of PES, SES, and BMS, the authors reported that mortality was similar in the 3 groups, SES was associated with significantly lower rates of MI than both BMS and PES, and PES was associated with significantly higher rates of late plus very late definite ST than both SES and BMS.

ST With Second-Generation DES

Second-generation DES have been developed with advanced design features, specifically thinner strut stent platforms (most commonly using a cobalt-chromium alloy) and more biocompatible polymers or bioabsorbable polymers. FDA-approved second-generation DES currently in use include Xience V, Xience Prime, and Xience Expedition (Abbott Vascular, Santa Clara, California), which are cobalt-chromium everolimus-eluting stents (CoCr-EES); Promus Element (Boston Scientific, Natick, Massachusetts), a platinum-chromium everolimus-eluting stent (PtCr-EES); Endeavor (Medtronic, Santa Rosa, California), a phosphorylcholine polymer-based fast-release zotarolimus-eluting stent (PC-ZES); and Resolute (Medtronic), a C10/C19/PVP polymer-based slow-release zotarolimus-eluting stent (Re-ZES) (Table 2).

CoCr-EES have undergone the most extensive clinical investigation. RCTs and observational studies have consistently shown low rates of ST with CoCr-EES, with some studies showing significantly lower rates of ST with CoCr-EES than with PES or SES (4,20,21). However, all these studies were insufficiently powered to reliably detect differences in ST, and therefore several meta-analyses have been performed to address this issue (Table 1). In the meta-analysis by Baber at al. in which 13 RCTs with 17,101 patients were included, CoCr-EES significantly reduced definite/probable ST and MI compared with pooled PES, SES, and Re-ZES after a median follow-up of 21 months (22). However, treatment effects for each endpoint varied by DES comparator, with the largest difference apparent for CoCr-EES versus PES, intermediate for CoCr-EES versus Re-ZES, and smallest for CoCr-EES versus SES. In the meta-analysis by de Waha et al. (23) in which CoCr-EES were compared with SES in 5 RCTs with 7,370 patients,