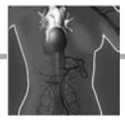
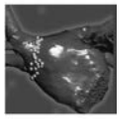
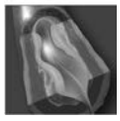

Drug-eluting stents for acute coronary syndromes: should the labeling be expanded?

"Given that the use of drug-eluting stents in the context of acute coronary syndrome was initially an off-label indication and that acute coronary syndrome has been associated with stent thrombosis, any information derived from clinical trials will be helpful to determine whether there is sufficient evidence to support expansion of the indication for the use of drug-eluting stents."

Michael Mahmoudi

Department of Internal Medicine, Division of Cardiology, Washington Hospital Center, Washington, DC 20010, USA

Ron Waksman

Author for correspondence: Department of Internal Medicine, Division of Cardiology, Washington Hospital Center, 110 Irving Street, NW, Suite 4B-1, Washington, DC 20010, USA
Tel.: +1 202 877 2812
Fax: +1 202 877 2715
ron.waksman@medstar.net

Compared with bare-metal stents (BMS), first-generation drug-eluting stents (DES), sirolimus-eluting stents and paclitaxel-eluting stents have been shown to reduce restenosis rates and target lesion revascularization following elective percutaneous coronary intervention [1–3]. However, the initial enthusiasm for DES has been dampened by concerns raised in a number of registries in which the nonrestrictive use of DES was associated with high rates of late stent thrombosis (ST; up to 0.6% per year up to 5 years). These ST rates are higher when compared with those reported for the pivotal trials and are associated with increased rates of morbidity and mortality [4,5].

"...the initial enthusiasm for drug-eluting stents has been dampened by concerns raised in a number of registries in which the nonrestrictive use of drug-eluting stents was associated with high rates of late stent thrombosis."

The rates of ST reported in studies that include ST-elevation myocardial infarction (STEMI) patients are summarized in Table 1. The question is whether these ST rates are specific to DES or are also observed with BMS. Is it the drug or the metal? A variety of risk factors that add to ST development have been identified. These include factors related to the procedure itself, such as stent malapposition and/or underexpansion, patient characteristics such as diabetes mellitus, lesion characteristics such as STEMI, non-STEMI (NSTEMI) and the thrombus burden, and factors related to the stent itself, such as delayed healing and persistent inflammation, as well as premature discontinuation of dual antiplatelet therapy [5–9]. STEMI-specific correlates for DES thrombosis could be the thrombus burden [10] and stent malapposition at implantation, which occurs at higher rates in patients with STEMI due to the tendency to undersize the stent and to avoid postdilatation, as well as the presence of a necrotic core and inflammation, which further delays healing. As these correlates can also hold true for NSTEMI, the question then arises as to whether DES implantation for patients with acute coronary syndrome (ACS) confers additional risk compared with BMS?

Restenosis and the need for repeat revascularization were never concerns for patients with STEMI who were treated with BMS. The STEMI lesions were usually located in vessels that were large in size and short in length and were associated with lower rates of restenosis. It was proven in randomized studies that DES are still associated with only a modest reduction in restenosis when compared with BMS. Thus, the risk of late ST versus the benefit of a marginally lower rate of restenosis remains a question for patients with STEMI. More importantly, and less well described in the literature, is how this risk:benefit ratio plays out for patients with NSTEMI or for patients with ACS.

Given that the use of DES in the context of ACS was initially an off-label indication and that ACS has been associated with ST, any information derived from clinical trials will be helpful to determine whether there is sufficient evidence to support expansion of the indication for the use of DES. The general consensus of the randomized clinical trials and subsequent meta-analyses comparing the first-generation DES with BMS in the context of STEMI is that the use of DES is associated with a significant reduction in the rate of reintervention [11–14]. However, there does not appear to be any difference in the rates of death or recurrent myocardial infarction. The issue of ST remains uncertain, with one meta-analysis

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Table 1. Stent thrombosis rates in major stent thrombosis-elevation myocardial infarction trials.

Trial	Stent thrombosis rate	Ref.
Randomized studies of SES versus BMS		
STRATEGY	6.9 vs 7.9%; p = 0.78 up to 5 years	[18]
TYPHOON	3.4 vs 3.6%; p = 1.0 at 12 months	[12]
SESAMI	1.2 vs 0.6%; p > 0.05 at 12 months	[19]
MISSION	1.3 vs 2%; p = 0.68 at 12 months	[20]
Randomized studies of PES versus BMS		
PASSION	1.0 vs 1.0% at 12 months	[21]
SELECTION	One subacute case in each group	[22]
HORIZONS-AMI	3.2 vs 3.4%; p = 0.77 at 12 months	[13]
Randomized studies of DES versus BMS		
DEDICATION	2.0 vs 2.6%; p = 0.72 at 8 months	[23]
PASEO	1.1 vs 2.2%; p = 0.5 at 12 months	[24]
Registry studies of DES versus BMS		
Denmark Heart Registry	0.4 vs 0.06%; p = 0.03 ≥12 months	[25]
STENT	1.0 vs 2.7%; p = 0.04 at 9 months; no difference at 2 years	[26]
Meta-analyses		
Kastrati *et al.*	HR: 0.8; p = 0.43 (DES vs BMS)	[14]
Stettler *et al.* (>30 days)	HR: 2.11; p = 0.02 (PES vs BMS) HR: 1.85; p = 0.04 (PES vs SES)	[15]

BMS: Bare-metal stent; DEDICATION: Drug-Eluting Versus Bare-Metal Stents in Patients With ST-Segment Elevation Myocardial Infarction; DES: Drug-eluting stent; HORIZONS-AMI: Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MISSION: A Prospective Randomised Controlled Trial to Evaluate the Efficacy of Drug-Eluting Stents Versus Bare-Metal Stents in the Treatment of Acute Myocardial Infarction; PASEO: Long-Term Outcome of Drug-Eluting Stents Compared With Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction: Results of the Paclitaxel or Sirolimus-Eluting Stent Versus Bare-Metal Stent in Primary Angioplasty; PASSION: Paclitaxel-Eluting Stents Versus Bare-Metal Stents in Myocardial Infarction With ST-segment Elevation Myocardial Infarction; PES: Paclitaxel-eluting stent; SELECTION: Single-Center Randomised Evaluation of Paclitaxel-Eluting Versus Conventional Stents in Acute Myocardial Infarction; SES: Sirolimus-eluting stent; SESAMI: Randomised Trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction; STENT: Strategic Transcatheter Evaluation of New Therapies; STRATEGY: Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Myocardial Infarction; TYPHOON: Trial to Assess the Use of The Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty.

demonstrating no difference between DES and BMS (HR: 0.8; 95% CI: 0.46–1.39; p = 0.43) and another demonstrating an increased risk with PES (SES, HR: 1.85; 95% CI: 1.02–3.85; p = 0.04 and BMS, HR: 2.11; 95% CI: 1.19–4.23; p = 0.02) [14,15].

> "*Compared with the wealth of data regarding the use of drug-eluting stents in ST-elevation myocardial infarction, the data regarding the performance of drug-eluting stents in non-ST-elevation myocardial infarction are very sparse and limited to a handful of registries.*"

Compared with the wealth of data regarding the use of DES in STEMI, the data regarding the performance of DES in NSTEMI are very sparse and limited to a handful of registries. The effect of DES on the composite end point of all-cause mortality, Q-wave myocardial infarction and target vessel revascularization on 3771 patients with stable angina and NSTEMI was recently reported by Li *et al.* [16]. In the NSTEMI cohort, there was no difference between DES and BMS with regard to the composite end point, whereas in patients with stable angina, the use of DES resulted in a significant reduction in the rates of target vessel revascularization. Kukreja *et al.* have also studied the risk for ST associated with DES in 3485 patients presenting with the whole spectrum of ACS and 2331 patients presenting with stable angina [17]. After a median follow-up of 3.8 years, patients with stable angina had lower rates of ST than patients with ACS, in whom both BMS and DES were found to be associated with a higher rate of ST. However, very late ST (>12 months) was found to be unique only to DES.

Some of these observed differences could be explained by anatomical differences between stable and unstable plaques. Stable plaques are characterized by thick fibrous caps, small lipid cores, a relative abundance of vascular smooth muscle cells and collagen and a sparse population of inflammatory macrophages. By contrast, unstable plaques have thin or ruptured fibrous caps, large and highly thrombogenic lipid cores and relatively large populations of macrophages

and small numbers of vascular smooth muscle cells. Therefore, it is conceivable that unstable plaques respond differently to the effects of paclitaxel and sirolimus, with persistent inflammation and delayed endothelialization mitigating the benefits of DES in patients with ACS. Indeed, the best histological predictor of very late ST have been shown to be the endothelial coverage, while the best morphometric predictor has been shown to be the ratio of uncovered to covered stent struts [6]. Furthermore, Farb *et al.* identified markedly necrotic lesions with a large lipid core as one of the pathological risk factors for ST [8].

As in the case of STEMI, the outcome of DES in the setting of NSTEMI requires further evaluation. Ideally, this will be in the setting of both randomized clinical trials as well as registries that integrate modern interventional techniques with optimal antiplatelet therapy, aggressive secondary prevention and long-term follow-up. Until such data become available, we shall continue to rely on our clinical judgement, assessment of risk scores and currently available evidence.

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