JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 5, NO. 10, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2012.08.001

EDITORIAL COMMENT

# Weighing the Risks of Target Vessel Revascularization Versus Very Late Stent Thrombosis in Primary Percutaneous Coronary Intervention*

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Compared with fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (P-PCI) reduces the risk of reinfarction and improves survival (1). Adding bare-metal stent (BMS) implantation after balloon angioplasty reduces reocclusion and restenosis rates, with drug-eluting stent (DES) implantation further decreasing the risk of restenosis and target lesion revascularization (TVR) (2). Unfortunately, there is a higher risk of very late stent thrombosis (ST) when first-generation DES (sirolimus-eluting or paclitaxel-eluting stents) are used instead of BMS, and this seems to be greater in patients with STEMI compared with stable ischemic heart disease (2,3). Stent thrombosis with DES is presumably due to delayed healing from chronic inflammation, persistent fibrin deposition, and a greater number of uncovered or malapposed stent struts compared with BMS (4,5).

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In this issue of *JACC: Cardiovascular Interventions*, Brodie et al. (6) report on their single center experience with stent thrombosis in 1,640 consecutive patients treated with P–PCI from 1995 to 2009 and a median follow-up time of 3.7 years. The frequency of ST was relatively high and progressively increased from 2.7% at 30 days to 5.2% at 1 year to 8.3% at 5 years. Early (30 day) and late (1 year) ST was predicted by STEMI due to ST, stent diameter <3 mm, Killip Class III to IV, reperfusion time <2 h, prior myocardial infarction (MI), and diabetes mellitus. Very late (>1 year) ST was only predicted by the use of DES instead of BMS.

This study is limited by including patients treated over a 15-year period, during which PCI technology and adjunctive pharmacotherapy evolved dramatically. Also, although BMS was used in the early years, first-generation DES were predominantly used in later years, so the cohorts were sequential rather than parallel. Moreover, only 410 of 1,640 patients were treated with DES, and follow-up was not equal for all patients, ranging from 1 to 15 years. Dual antiplatelet therapy (DAPT) compliance was only 60% with early ST and 52% with late ST, potentially explaining some of the events. Although this "all-comers" experience might represent a broader, more complex, and generalizable population than enrolled in randomized trials addressing this question, selection bias and unknown or unmeasured confounders might have influenced the results.

Nevertheless, several meta-analyses support the conclusion that ST progressively occurs after P–PCI with DES. Brar et al. (7) evaluated 7,352 patients from 13 randomized trials comparing BMS and DES and found reduced TVR with DES without increased risk for death, MI, or ST with up to 2-year follow-up. Additionally, 26,521 patients from 18 registry studies had similar results. However, the neutral effect on ST was due to the combination of lower ST rates with DES in the first year and higher ST rates during the second year. De Luca et al. (8) performed a patient-level meta-analysis, including 6,298 patients from 11 trials followed for a mean of 3.3 years. They also found a significant reduction in TVR without differences in cumulative mortality, reinfarction, or ST, but there was an increased risk of reinfarction and ST with DES after 2 years of follow-up. Kalesan et al. (9) evaluated 7,867 patients from 15 trials. The benefit for TVR reduction with DES was greater in the first year, compared with subsequent years, but the small risk reduction in ST during the first year with DES changed to risk increase and was doubled with DES in subsequent years. Over 5 years, the estimated number needed to treat with DES to prevent 1 TVR was 15, and the number needed to harm to cause 1 definite ST was 111. Importantly, none of the analyses have shown significant differences in late survival, perhaps because of the beneficial effects of DES in preventing the complications of restenosis (10). Note that the approximately 50% relative risk reduction in TVR rates with DES versus BMS in P–PCI randomized trials might have been exaggerated by protocols that mandated repeat angiography to evaluate for restenosis and resulted in TVR in asymptomatic patients. Clinically driven TVR rates are lower and less than seen with elective PCI, perhaps because of myocardial necrosis. Importantly, ST is

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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associated with MI and death, so reducing the incidence is an important therapeutic goal.

Therefore, the early benefit of DES in preventing ST, restenosis, and TVR in patients after P–PCI needs to be weighed against the very late risk of ST when deciding whether to implant BMS versus DES. The safety of P–PCI with DES might be improved by considering the following possible recommendations:

- Limit DES to subsets of patients at increased risk for TVR, including those with diabetes mellitus, smaller coronary arterial diameter, and longer stenosis, and use BMS in low-risk patients. By decreasing the percentage of patients with DES in P–PCI, the risk for ST due to DAPT non-adherence, future surgical procedures, or bleeding events in patients is also lowered across the population.
- Administer an upstream 4,000-U intravenous bolus of unfractionated heparin and a 600-mg (not 300-mg) loading dose of clopidogrel with bivalirudin anticoagulation (11).
- Implant newer-generation DES, with thinner, fracture-resistant stent struts and improved biocompatible polymers, because of lower ST rates than seen with first-generation DES (12).
- Prescribe prasugrel or ticagrelor instead of clopidogrel, because of lower ST rates (13,14).
- Administer at least 12 months of DAPT after P–PCI with DES, despite recent evidence that 6 months of therapy might be sufficient for other subgroups.

Proper patient selection, improved DES design, excellent stent implantation technique, improved DAPT strategies, and greater emphasis on medication adherence can maximize the benefit of P–PCI with DES. In the future, biodegradable polymers or bioresorbable vascular scaffolds might further reduce the risk of ST (15).

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## REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
2. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193–204.
3. Kukreja N, Onuma Y, Garcia-Garcia H, Daemen J, van Domburg R, Serruys PW. Primary percutaneous coronary intervention for acute myocardial infarction: long-term outcome after bare metal and drug-eluting stent implantation. Circ Cardiovasc Interv 2008;1:103–10.
4. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction: an autopsy study. Circulation 2008;118:1138–45.
5. Gonzalo N, Barlis P, Serruys PW, et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. J Am Coll Cardiol Intv 2009;2:445–52.
6. Brodie B, Pokharel Y, Garg A, et al. Predictors of early, late, and very late stent thrombosis after primary percutaneous coronary intervention with bare-metal and drug-eluting stents for ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2012;5:1043–51.
7. Brar SS, Leon MB, Stone GW, et al. Use of drug-eluting stents in acute myocardial infarction. A systematic review and meta-analysis. J Am Coll Cardiol 2009;53:1677–89.
8. De Luca G, Dirksen MT, Spaulding C, et al. Drug-eluting vs bare metal stents in primary angioplasty. A pooled patient-level meta-analysis of randomized trials. Arch Intern Med 2012;172:611–21.
9. Kalesan B, Pilgrim T, Heinimann K, et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012;33:977–87.
10. Stone GW, Ellis SG, Colombo A, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. Circulation 2007;115:2842–7.
11. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. Circulation 2011;123:1745–56.
12. Hofma SH, Brouwer J, Velders MA, et al. Second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction: 1-year results of the randomized XAMI (XienceV Stent vs. Cypher stent in primary PCI for acute myocardial infarction) trial. J Am Coll Cardiol 2012;60:381–7.
13. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–31.
14. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a platelet inhibition and patient outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131–41.
15. Navarese EP, Kubica J, Castriota F, et al. Safety and efficacy of biodegradable vs. durable polymer drug-eluting stents: evidence from a meta-analysis of randomized trials. EuroIntervention 2011;7:985–94.

**Key Words:** predictors stent thrombosis ■ primary PCI ■ STEMI ■ stent thrombosis.