

## Peri-stent contrast staining: a stain on the long-term safety of DES?

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Drug-eluting stents (DES) have contributed to lowering rates of repeat revascularisation due to a reduction in the occurrence of in-stent restenosis (ISR)<sup>1</sup>. However, the risk of stent thrombosis (ST) remains prevalent in the DES era, with several studies associating the use of DES with an increased occurrence of late and very late stent thrombosis (VLST)<sup>2,3</sup>. Delayed healing of the stented arterial segment which involves chronic inflammation with persistent fibrin deposition, and ultimately incomplete stent strut coverage, has been recognised as one of the underlying mechanisms for the late occurrence of ST<sup>4</sup>. Vessel remodelling, with a larger diameter of the stented segment, predisposes to incomplete stent apposition (ISA), a known risk factor for VLST<sup>5,6</sup>. Recently, Imai et al described the angiographic phenomenon of peri-stent contrast staining (PSS), defined as contrast staining outside the stent struts insufficient to fulfil the definition of a coronary artery aneurysm, as an angiographic correlate of ISA<sup>7</sup> that may help identify patients with higher risk of VLST.

In this issue of AsiaIntervention, Ozaki et al<sup>8</sup> investigated the impact of PSS on the occurrence of adverse events during a median clinical

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follow-up of five years in 807 patients who underwent follow-up angiography a minimum of six months after implantation of

sirolimus-eluting stents (SES). PSS was defined as contrast staining outside the stent struts of >20% of the reference diameter and was observed in 20 patients (2.48%), of whom seven had persistent and 13 late acquired PSS. The reported incidence was low and is in accord with previous studies on the occurrence of PSS after implantation of the first-generation DES<sup>7,9</sup>. However, it was nonetheless significantly associated with a higher rate of the combined primary endpoint of death, myocardial infarction (MI), ST and/or target lesion revascularisation (TLR), in the PSS versus the non-PSS group (35.0% vs. 14.9%,  $p=0.013$ , HR: 2.94,  $p=0.006$ ) and a higher rate of VLST, which occurred in three (15.0%) patients with PSS versus 13 (1.7%) in those without ( $p=0.006$ ). Current smoking, stent fracture and a larger reference vessel diameter were significantly associated with the development of PSS. Multivariable analysis, after adjusting for potential confounding variables, including stent fracture, showed PSS to be an independent predictor of MACE, along with the presence of diabetes, renal failure, saphenous vein graft, longer total stent length and unstable angina.

There seem to be two important issues when evaluating the potential of PSS to predict the occurrence of long-term adverse events after DES implantation. First, it is important to delineate

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pathophysiological mechanisms which lead to the angiographic finding of PSS. Second, the assessment of the true impact of PSS on the long-term prognosis appears to depend on the definition of the adverse events in accord with the underlying pathophysiology. The pathophysiological background of PSS may be characterised by the following three observations: the temporal nature of PSS, the lack of linear correlation with intravascular imaging of ISA, and the discrepancy in the reported incidence with different stent types. First, positive vessel remodelling after stent implantation may generate incomplete apposition of the acutely well-apposed stent struts, as evidenced by the results of several studies, showing that roughly half of observed PSS cases are late acquired and/or progressive<sup>7,8,10</sup>. In the other half of cases, PSS persists throughout the reported angiographic follow-up or is lost over time. Second, studies using intravascular ultrasound (IVUS) have shown much higher rates of ISA, as compared with the rates of angiographically detectable PSS<sup>7</sup>. Based on this finding, PSS was seen as a more severe form of ISA<sup>7</sup>. However, studies comparing the association of IVUS-defined ISA versus angiographically visible PSS with clinical outcomes are needed to support this hypothesis. Third, different stent types may account for inherent discrepancies in the pattern of arterial wall healing and thus result in different rates of PSS, as evidenced in several studies<sup>7,9,11</sup>. A study with a mixed population of patients who received BMS or paclitaxel-eluting stents (PES) documented PSS in 2.1% of patients at follow-up angiography and no difference between BMS and PES<sup>9</sup>. A more contemporary DES study reported a lower rate of PSS in patients after implantation of newer-generation everolimus-eluting stents (EES), as compared to the first-generation SES (1.2% vs. 4.5%,  $p=0.045$ )<sup>11</sup>. Of note, recent research has challenged the hypothesis that durable polymer is the premier component to provoke hypersensitivity reaction leading to delayed healing and increased risk of ST<sup>12</sup>. It seems rather that polymer, drug and scaffold all have a role in the vessel response, and the combined effect of the three produces a different healing pattern per stent type<sup>13</sup>.

When assessing the true impact of PSS on long-term DES safety, two aspects may be important. First, the combined endpoint that includes TLR might neglect the above-described pathophysiological background that PSS as an angiographic entity relies on. Second, alternative causes of ST, independent of ISA and thus potentially unrelated to PSS, should be carefully considered.

Like the pivotal study by Imai et al<sup>7</sup>, Ozaki et al use a combined primary endpoint to evaluate the association of PSS with long-term adverse events, a strategy that seems warranted in the light of the low occurrence rate of both PSS and its proposed dire consequence, VLST. Along with ST and hard clinical endpoints, such as death and MI, TLR was also included. Therefore, it appears that a distinction between the occurrence of ST and clinically relevant ISR, which appears mandated due to the different pathophysiological backgrounds, becomes neglected. Stent thrombosis has been associated with positive remodelling, incomplete stent strut apposition and coverage, while ISR is characterised by excessive proliferation of neointima. Both of these events appear to be mingled when TLR

is reported. The use of TLR additionally obscures the true impact of PSS on the long-term safety of DES, by potentially misconstruing primary PCI, an accepted treatment strategy for thrombotic stent occlusion, as an adverse event.

Importantly, other mechanisms which contribute to late occurring ST, such as neoatherosclerosis<sup>14</sup>, do not correlate with the angiographically visible PSS. Thus, the use of intravascular imaging modalities such as IVUS and optical coherence tomography (OCT) may be essential in adjudicating adverse events and establishing the relationship between PSS and late occurring ST.

In summary, PSS is a rare angiographic finding and, even though it could potentially be applicable as a marker of the delayed healing of the stented segment and thus a predictor of long-term events after DES implantation, only a thorough risk adjustment for the described distinct pathophysiological aspects of PSS can overcome the lack of a satisfactory mechanistic explanation.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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