

# Platelet Function Testing after Transcatheter Aortic Valve Implantation

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Thromb Haemost 2018;118:1681–1685.

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Transcatheter aortic valve implantation (TAVI) is the standard of care for patients with severe aortic stenosis who are inoperable, and a valid alternative to surgery for patients at high or intermediate surgical risk.<sup>1</sup> Current candidates to TAVI are typically octogenarians, which makes their propensity to thrombus formation or bleeding higher at baseline compared with younger individuals.<sup>2</sup> It is of no surprise that TAVI itself further contributes to increase the risk of ischaemic and haemorrhagic complications in this population.<sup>3</sup>

Despite numerous technical innovations over the years, cerebrovascular events are still detected in 4 to 6% of intermediate-risk patients at 30 days, typically as the consequence of procedural factors.<sup>4</sup> Subsequently, the risk of cerebrovascular events peaks at 8 to 10% at 1 year and 10 to 12% at 2 years, with late events mostly explained by concurrent patient-related (e.g. atrial fibrillation) and valve-related (e.g. stent surface exposure, leaflet thrombosis) conditions.<sup>4</sup> Leaflet thrombosis is an emerging concern of uncertain clinical significance, more frequently observed with transcatheter valves rather than surgical bioprostheses, which is more likely to resolve with anti-coagulants rather than anti-platelets.<sup>5,6</sup>

Bleeding in TAVI patients is approximately 31% at 5 years, with similar proportions of access-site and non-access site-related events, and a well-known detrimental impact on prognosis.<sup>7,8</sup> Of non-access-site bleeding, approximately 40% of the episodes (mostly neurological and gastrointestinal) accrue beyond 30 days.<sup>4,8</sup> The incidence and timing of bleeding and ischaemic complications after TAVI call into question the net benefit of using adjuvant anti-thrombotic therapies in this setting. Current guidelines from the European Society of Cardiology recommend clopidogrel in addition to aspirin for 3 to 6 months after TAVI in patients who are not candidates to oral anti-coagulation, followed by single anti-platelet therapy lifelong (class IIa).<sup>9</sup> Patients at high risk of bleeding may be considered eligible upfront for anti-platelet monotherapy (class IIb). In the United States, joint guidelines from the American College of Cardiology and

American Heart Association recommend dual-anti-platelet therapy (DAPT) for 6 months (class IIb).<sup>10</sup> Therefore, anti-platelet therapy with aspirin and/or clopidogrel is the current anti-thrombotic standard for non-anti-coagulated patients undergoing TAVI.

Investigations from the field of percutaneous coronary intervention (PCI) have consistently demonstrated some degree of inter-individual variability in the platelet response to clopidogrel,<sup>11</sup> and high on-treatment platelet reactivity may have prognostic implications.<sup>12–15</sup> Several platelet function assays (e.g., light transmission aggregometry, VerifyNow, multiple electrode aggregometry) allow distinguishing patients with on-clopidogrel high platelet reactivity (HPR) or low platelet reactivity (LPL) based on standardized cut-off values.<sup>16,17</sup> PCI studies suggest that HPR and LPR denote a status of impaired or undue response to clopidogrel, and carry a higher risk of thrombosis and bleeding, respectively.<sup>11</sup>

Nonetheless, the impact of tailoring anti-platelet therapy based on platelet function profiles is controversial. In elderly patients from the ANTARCTIC study—a population that resembles but does not necessarily match the population of patients undergoing TAVI—platelet function monitoring with treatment adjustment did not improve the clinical outcomes of PCI.<sup>18</sup> In the TAVI field, the association of platelet reactivity and clinical outcomes has been investigated in small studies correlating on-treatment LPR and bleeding<sup>19–23</sup> (→ **Table 1**).

In this issue of *Thrombosis and Haemostasis*, Gross et al add to this evidence with another instructive investigation.<sup>24</sup> The authors studied platelet reactivity by using the Multiplate analyzer<sup>25</sup> in 136 consecutive TAVI patients on DAPT with aspirin plus a P2Y<sub>12</sub> inhibitor (mostly clopidogrel). Bleedings were assessed according to the Valve Academic Research Consortium-2 (VARC-2) definition.<sup>26</sup> At 30 days post-TAVI, there was a significant association between LPR and VARC-2 bleeding both in unadjusted (hazard ratio [HR], 2.10, 95% confidence interval [CI], 1.17–3.79;  $p = 0.01$ ) and age-adjusted (HR<sub>adj</sub>, 2.06, 95% CI, 1.14–3.71;  $p = 0.02$ )

received  
September 4, 2018  
accepted  
September 4, 2018

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Stuttgart · New York

DOI <https://doi.org/10.1055/s-0038-1672215>.  
ISSN 0340-6245.

**Table 1** Relation between platelet function measurement and bleedings in TAVI population

Trial	Polzin et al	Orvin et al	Watanabe et al	Czerwińska-Jelonkiewicz et al	Kibler et al	Gross et al
Year of publication	2015	2016	2016	2018	2018	2018
Journal	European Journal of Pharmacology	Journal of Thrombosis and Thrombolysis	International Heart Journal	Archives of Cardiovascular Diseases	Thrombosis and Haemostasis	Thrombosis and Haemostasis
Patients, N°	140	39	32	100	219	146
Age, median ± SD	83 ± 6	81.7 ± 6.5	84.2 ± 5.0	78.3 ± 9.9 <sup>a</sup> and 79.5 ± 7.1 <sup>a</sup>	82.8 ± 6.5 <sup>b</sup> and 83.4 ± 6.9 <sup>b</sup>	81 ± 8.4
Coronary artery disease, n (%)	98 (70)	NA	13 (40.6)	96 (96)	NA	133 (91.1)
Anti-coagulant intake, n (%)	25 (18)	12 (30.8)	6 (18.8)	34 (34)	85 (38.8)	NA
Platelet function assessment method	VASP, LTA	VerifyNow, Multiplate analyser	LTA, VASP, VerifyNow	VerifyNow	PFA-100	Multiplate analyser
Platelet function assessment timing	During hospital stay	1–3 days before TAVI, at 3–5 days and at 30 days	At 7 and 30 days	24 hours before TAVI and at 6 days	Post-procedural	Along with the TAVI procedure
Primary outcome	Ischaemic and bleeding complications	Platelet reactivity	Platelet function parameters	In-hospital bleeding and vascular complications	PVAR	Association between platelet reactivity and bleedings
Secondary outcomes	None	None	In-hospital thrombotic or bleedings events	NA	Bleeding or its composite with PVAR	None
Anti-thrombotic therapy	Aspirin + Clopidogrel	Clopidogrel + Aspirin or OAC	Aspirin ± Clopidogrel	Aspirin + Clopidogrel or OAC + Aspirin or Clopidogrel	Aspirin + Clopidogrel	Aspirin + P2Y <sub>12</sub> inhibitor (mostly Clopidogrel)
Bleeding definition	VARC-2	NA	VARC-2	VARC-2	VARC-2	VARC-2
Conclusion	No correlations between platelet reactivity and ischaemic or bleeding events	TAVI patients treated with DAPT have high rates of residual platelet reactivity	A hyper-response to clopidogrel is associated with bleeding	Platelet reactivity to clopidogrel seems to predict TAVI-related bleeding	CT-ADP (vWf-dependent platelet function) predict PVAR and bleedings	LPR is associated with bleeding in TAVI patients

Abbreviations: CT-ADP, closure time adenosine diphosphate; DAPT, dual-anti-platelet therapy; LPR, low platelet reactivity; LTA, light transmittance aggregometry; NA, not available; OAC, oral anti-coagulant; PFA, platelet function analyser; PVAR, paravalvular aortic regurgitation; TAVI, transcatheter aortic valve implantation; VARC-2, valve academic research consortium-2 consensus document; VASP, vasodilator stimulated phosphoprotein phosphorylation; vWf, von Willebrand factor.

<sup>a</sup>In the bleedings and no bleedings group, respectively. Comprehensive data are not reported.

<sup>b</sup>In the PVAR and no PVAR group, respectively. Comprehensive data are not reported.

analyses. In contrast, HPR was not significantly associated with the risk of ischaemic events. Although these results were obtained in a relatively small sample of patients, the study shows some admirable methodological aspects. Bleeding assessment was based on the broadly accepted VARC-2 definition,<sup>26</sup> which is context-specific, and HPR and LPR were defined according to the cut-off values that were previously shown to link with adverse events in the PCI setting.<sup>27</sup> In addition, the study population reflects contemporary TAVI practice in intermediate- to high-risk patients treated with either balloon-expandable or self-expandable bioprostheses, and the follow-up rate was complete.

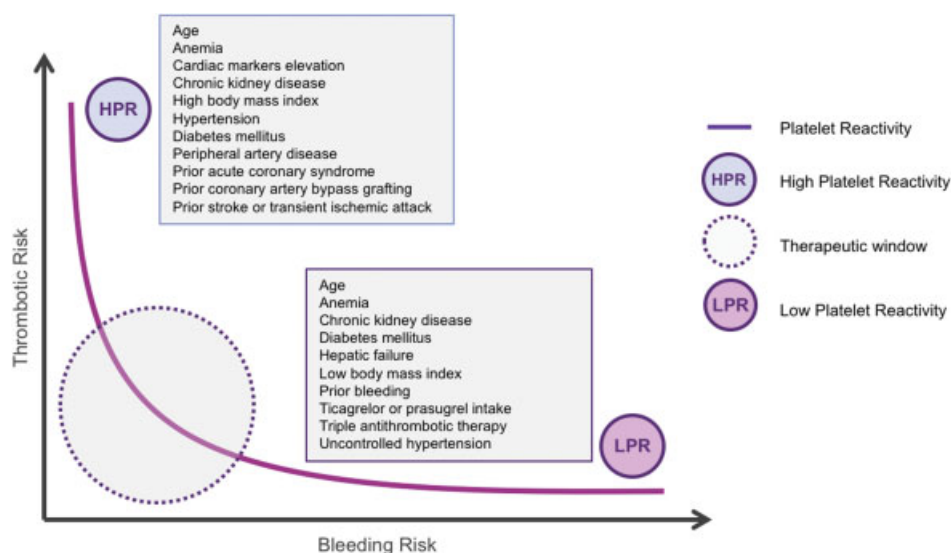
Unfortunately, some caveats of this study should also be underlined. First, the conclusion that HPR was not associated with thrombotic events is undermined by the small number of ischaemic events at 30 days and resulting low power. Bleeding events were more frequent, which makes the inference about the association between LPR and haemorrhagic complications more statistically robust. Of interest, as eloquently shown by the Kaplan–Meier analysis, the higher propensity of LPR patients to bleed was mostly confined to the first 5 days from the procedure. Yet, the comparison between LPR and non-LPR patients was adjusted only by age and suffers from residual confounding, possibly including identifiable risk factors, because the result of univariate analyses for many variables of interest (e.g. demographic, clinical, procedural) was not reported. It would have been also valuable to know how many of the bleeding events occurring in LPR patients were life-threatening, major, or minor. The cut-off value of LPR identified for bleeding suffered from relatively low positive (53.6%) and negative (75.6%) predictive values, which is consistent with the multifactorial nature of bleeding. Other limitations include the availability of a single platelet function measurement, the lack of confirmation from other point-of-care assays and

the inclusion of patients with different backgrounds of loading and maintenance P2Y<sub>12</sub> inhibitor doses.

The net benefit of DAPT after TAVI has been recently questioned by a patient-level meta-analysis of three small randomized trials comparing DAPT with aspirin.<sup>28</sup> Over a total of 421 patients, life-threatening VARC-2 bleeding at 30 days were significantly increased with DAPT (6.8% vs. 2.4%,  $p = 0.036$ ), corresponding to a 2.68-fold relative increase compared with aspirin. No differences in stroke and all-cause death were reported, but numbers were small. Further evidence on the merits of DAPT in the TAVI setting is expected from the on-going POPular-TAVI and CLOE trials.<sup>29</sup> If DAPT will not be ultimately shown to be more beneficial than aspirin alone, speculating on HPR and LPR will become a sterile exercise in the TAVI scenario.

Another field of intense investigation is the role of anti-coagulation in TAVI patients with no baseline indication for vitamin K antagonists or non-vitamin K antagonist oral anticoagulants. The joint American College of Cardiology and American Heart Association guideline for valvular heart disease affirms that a short term of anti-coagulation may be considered in these patients (class IIb), although it remains unclear if this regimen should be stacked on top of anti-platelet therapy.<sup>10</sup> As expected, dual-pathway inhibition increases the risk of bleeding in the elderly population currently referred to TAVI.<sup>30</sup> Also notably, the seminal GALILEO study, comparing a rivaroxaban-based with an antiplatelet-based strategy in TAVI patients, has been recently stopped due to an increase in safety events in the rivaroxaban arm (NCT02556203). Further insight on the comparison between anti-coagulants and anti-platelets in TAVI will come from the ATLANTIS trial of apixaban.<sup>31</sup>

Concomitant coronary artery disease is frequently discovered during the clinical work-up prior to TAVI and requires treatment in 20 to 40% of patients.<sup>32</sup> Mostly based



**Fig. 1** Spectrum of potential platelet reactivity profiles in patients undergoing transcatheter aortic valve implantation (TAVI), ranging from high platelet reactivity (HPR) to low platelet reactivity (LPR). An area of “sweet spot” for the optimal use of anti-thrombotic medications is envisaged. Risk factors for HPR and LPR are proposed based on lessons from the field of percutaneous coronary intervention.<sup>11</sup>

on empiric considerations, guidance on the use of anti-thrombotic therapy after TAVI for these patients is given by two recent joint European consensus documents.<sup>33,34</sup> TAVI patients who are already taking oral anti-coagulants and have recent PCI or an acute coronary syndrome should be treated similarly to patients receiving a stent without TAVI. Conversely, waiting for the results of on-going studies, patients undergoing TAVI without concomitant need for oral anti-coagulation should receive an anti-platelet regimen consisting of lifelong aspirin monotherapy or aspirin and clopidogrel for 3 to 6 months followed by aspirin monotherapy, depending on the bleeding risk, and concomitant treated or untreated coronary artery disease.

In conclusion, accruing evidences suggest that LPR may be one of the predisposing factors for bleeding in the TAVI setting, particularly early after the procedure. While this argument is not a call for guiding anti-platelet therapy by means of platelet function testing, it voices about the risk of anti-thrombotic over-treatment if one-size-fits-all strategies are implemented. Because the boundary between tailored therapy and under-treatment is equally thin, further evidence is needed to find the sweet spot of optimal pharmacotherapy in the TAVI setting (►Fig. 1). These investigations must take into account the ever-changing nature of TAVI in the context of improved safety and extension towards individuals at lower risk.

#### Conflict of Interest

None.

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