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FOCUS ON TRANSCATHETER AORTIC VALVE REPLACEMENT

Impact of On-Clopidogrel Platelet Reactivity on Incidence of Hypoattenuated Leaflet Thickening After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES To assess the impact of on-clopidogrel platelet reactivity (PR) on HALT, the authors prospectively tested whether patients with below-median on-clopidogrel PR have a lower incidence of HALT compared with those with above-median on-clopidogrel PR.

BACKGROUND It is unclear whether the apparent ineffectiveness of clopidogrel in preventing hypoattenuated leaflet thickening (HALT) after transcatheter aortic valve replacement (TAVR) questions the concept of $P2Y_{12}$ inhibition after TAVR or is a consequence of an inadequate response to clopidogrel in elderly patients with severe aortic stenosis.

METHODS Patients were either on long-term dual antiplatelet therapy with clopidogrel and acetylsalicylic acid or were given bolus doses of both drugs the day before TAVR. Adenosine diphosphate (ADP)–induced multielectrode impedance aggregometry was performed before TAVR. After TAVR, clopidogrel was continued in all patients. Computed tomographic angiography was performed to detect HALT.

RESULTS Of 331 patients enrolled, computed tomographic angiography was performed in 200 at 5 days (interquartile range: 4 to 6 days). Among patients with below-median ADP-induced PR (<180 AU · min), 16 were diagnosed with HALT, whereas 20 patients with above-median PR were diagnosed with HALT ($p = 0.58$). Among patients with high on-clopidogrel PR (>468 AU · min; $n = 29$), 7 (24%) displayed HALT, compared with 19 (17%) with ADP-induced PR ≤468 AU · min ($p = 0.43$). Consistently, ADP-induced PR as a continuous variable was not significantly associated with HALT ($p = 0.75$). Oral anticoagulation was associated with reduced rates of HALT (odds ratio: 0.41; 95% CI: 0.18 to 0.96; $p = 0.04$).

CONCLUSIONS On-clopidogrel ADP-induced PR was not significantly associated with the occurrence of HALT. In contrast, oral anticoagulation was associated with reduced rates of HALT. (J Am Coll Cardiol Intv 2019;12:12–8)

After the implantation of prosthetic heart valves, the goal of antithrombotic treatment is to prevent valve thrombosis that may result in valve hemodynamic deterioration and/or systemic thromboembolism. On the basis of inferences from analogy to coronary stent frames, dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and clopidogrel is the current standard

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of care after transcatheter aortic valve replacement (TAVR) (1). Nevertheless, 2 studies in which systematic computed tomographic angiography (CTA) was performed after TAVR reported similar incidences of hypoattenuated leaflet thickening (HALT), irrespective of whether the patients were treated with DAPT or with ASA alone (2,3). Although HALT as an established surrogate for leaflet thrombosis on CTA may thus not be prevented by DAPT (3,4), clopidogrel also did not confer a clinical benefit after TAVR in the recent ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) trial (5). It remains unclear, however, whether the apparent ineffectiveness of clopidogrel in preventing HALT refutes the whole concept of $P2Y_{12}$ inhibition after TAVR or is simply a consequence of an inadequate response to clopidogrel in this elderly patient subset (6). In particular, high on-treatment platelet reactivity (HTPR) has been reported in small studies with patients undergoing TAVR (7–9).

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To clarify this issue, we sought to investigate the association of HALT with the level of on-clopidogrel platelet reactivity (PR) in a cohort of consecutive patients undergoing CTA after TAVR.

METHODS

PATIENT SELECTION. For inclusion into this prospective, nonrandomized, observational single-center study, patients with severe, symptomatic aortic valve stenosis undergoing transfemoral TAVR on DAPT were consecutively included from January 2014 to August 2017. Exclusion criteria were $P2Y_{12}$ inhibitor therapy other than clopidogrel and refusal to participate in the study. The decision for TAVR was made before study inclusion by the institutional heart team. The study was approved by the ethics committee of Albert-Ludwigs-Universität Freiburg, and all patients gave written informed consent to the study.

STUDY PROTOCOL AND BLOOD TESTS. If not taken chronically (clopidogrel 75 mg once daily, ASA 100 mg once daily, to be started >5 days prior to TAVR), both clopidogrel (300 or 600 mg) and ASA (400 mg) were given as an oral bolus the day before TAVR. After loading, no additional ASA doses were given to patients with an indication for oral anticoagulation. These patients were given similar loading doses but continued on a combination of clopidogrel and oral anticoagulation, either direct oral anticoagulant agents or phenprocoumon after TAVR. Oral anticoagulation with direct anticoagulant agents was stopped at least 24 h before TAVR. Anticoagulation with phenprocoumon was adjusted, aiming for a target international normalized ratio of 1.5 to 2.0 at the time of TAVR. Thereafter, it was bridged by low-molecular weight heparin or unfractionated heparin and reinstated 2 days after uncomplicated TAVR. Continuation therapy with clopidogrel was administered at a dose of 75 mg/day, at least until CTA. At the beginning of the TAVR procedure, before administration of heparin, blood was drawn from the arterial sheath into collection tubes. Within 30 min, the samples were processed for platelet function testing, as well as standard hematology and clinical chemistry assessment.

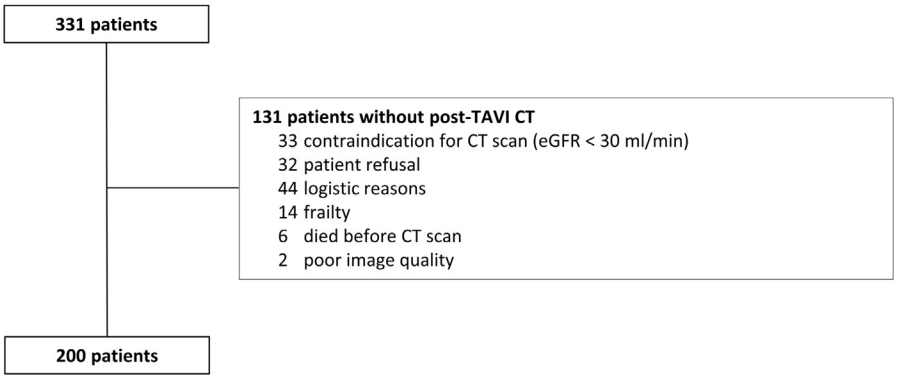
Platelet function was evaluated in recombinant-hirudin-anticoagulated blood (6.4 μM r-hirudin/ml blood) by multiple-electrode impedance aggregometry (Multiplate analyzer, Roche Diagnostics, Mannheim, Germany) using the ADPtest, ASPItest, or TRAPtest (Roche Diagnostics), as previously described (10). Standard hematologic tests were performed using a Sysmex XE-2100 (Sysmex, Norderstedt, Germany) in ethylenediaminetetraacetic acid–anticoagulated blood; clinical chemistry parameters were analyzed using a Cobas C501 (Roche Diagnostics) in heparin-anticoagulated blood.

COMPUTED TOMOGRAPHIC ANGIOGRAPHIC DATA ACQUISITION. As per local standard of care, all patients who undergo TAVR are scheduled for CTA on day 5 after TAVR, unless there are contraindications, such as poor renal function or hemodynamic compromise. Retrospectively electrocardiographically gated contrast-enhanced CTA was performed on a dual-source computed tomographic (CT) scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). The data acquisition and evaluation of the transcatheter aortic prostheses were carried out as previously described (11). In detail, computed tomographic datasets were reviewed in clinical routine. For this investigation, we also performed an independent evaluation of computed tomographic data by blinded readers. To ensure that readers were blinded to the clinical data, time point, and platelet and anticoagulation status, all datasets were deidentified. Dynamic assessment of prosthesis leaflets was executed on multiplanar reformations for the presence of HALT throughout the cardiac cycle. HALT diagnosis relies on hypoattenuated thickening with or without rigidity of 1 or more leaflet segments identifiable in at least 2 different multiplanar

ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate
ASA = acetylsalicylic acid
CI = confidence interval
CT = computed tomographic
CTA = computed tomographic angiography
DAPT = dual antiplatelet therapy
HALT = hypoattenuated leaflet thickening
HTPR = high on-treatment platelet reactivity
IQR = interquartile range
OR = odds ratio
PR = platelet reactivity
TAVR = transcatheter aortic valve replacement

FIGURE 1 Study Flowchart



eGFR = estimated glomerular filtration rate.

reformation projections and 2 different reconstruction time points.

ECHOCARDIOGRAPHY. Echocardiographic examinations were performed by experienced cardiologists using a Philips iE33 system (Philips Healthcare, Leiden, the Netherlands). Transthoracic echocardiographic evaluations were conducted before and at least once after TAVR. Quantitative assessment of the left ventricle and the aortic valve was performed following the joint European Association of Echocardiography and American Society of Echocardiography guidelines (12,13). Aortic valve area was calculated using the continuity equation with Doppler time-velocity integrals and indexed to body size.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS. To assess the impact of on-clopidogrel PR on HALT, we tested the hypothesis that patients with on-clopidogrel PR below the median have a substantially lower incidence of HALT than patients with on-clopidogrel PR above the median. On the basis of previous studies, we assumed an incidence of HALT of 15% in the entire cohort. To achieve 80% power to detect a 50% relative reduction in the risk for HALT by on-clopidogrel PR below the median versus above the median at a 2-sided alpha level of 0.05, we needed to enroll 200 patients. In addition to the median cutoff, we assessed the cutoff for high PR in the setting of coronary stenting (14,15), that is, adenosine diphosphate (ADP)-induced PR >468 AU · min. We also intended to corroborate our findings by multivariate logistic regression models with on-clopidogrel PR as a continuous variable.

If not stated otherwise, discrete variables are reported as counts (percentages) and continuous variables as medians with interquartile ranges (IQRs). For discrete variables, we tested differences between groups with the chi-square test (or the Fisher exact test when expected cell sizes were <5). The Mann-Whitney *U* test was used to compare continuous variables. Univariate and multivariate binary logistic regression models were used to test if platelet reactivity and other clinical variables were predictive of the occurrence of HALT. Clinical variables were selected if p values between groups were <0.2 and/or indicated by published research (2,4,16). Obtained odds ratios (ORs) are displayed with 95% confidence intervals (CIs).

All tests were performed as 2-sided tests with alpha = 0.05 using SPSS version 23.0.0.2 (IBM Corporation, Armonk, New York).

RESULTS

PATIENT POPULATION. The study flow is shown in **Figure 1**. Of 331 patients undergoing TAVR, 200 with interpretable CT scans were included in the analysis (**Figure 1**). Main reasons not to perform a CT scan were a contraindication to CT scan, patient refusal, and logistic reasons. Patients not undergoing CT scans were older, had higher risk scores, and more frequently had an impaired renal function (Online Table S1). CT scans were performed at a median of 5 days (IQR: 4 to 6 days), with no significant difference between patients with or without HALT.

In total, 36 patients (18%) were diagnosed with HALT. Baseline characteristics and procedural data were balanced without major differences according to occurrence of HALT (**Table 1**). Only atrial fibrillation and an indication for oral anticoagulation were less frequent in patients with HALT. All patients were on DAPT before TAVR was started. In detail, each patient

was either on long-term $P2Y_{12}$ inhibitor therapy with clopidogrel 75 mg (29%) or received a loading dose of 300 mg (56%) or 600 mg (15%) clopidogrel. Respective clopidogrel loading was given 19.9 h (IQR: 16.9 to 22.7 h) before the procedure. Long-term clopidogrel therapy was started at a median of 35 days (IQR: 10 to 51 days) prior to the TAVR procedure, mostly in the context of percutaneous coronary intervention including initial loading (48 of 58 patients). Likewise, all patients were on long-term ASA therapy (100 mg/day) or received loading doses of ASA the day before TAVR.

Regarding post-procedural oral anticoagulation, the 2 groups differed significantly ($p = 0.03$). In the group with absence of HALT, 68 patients (41.5%) had indications for oral anticoagulation. In the group with HALT, 8 patients (22.2%) had indications for anticoagulation. The indication for oral anticoagulation was mainly atrial fibrillation (88% of patients). Of the 76 patients with indications for anticoagulation, 64 (84%) were anticoagulated as described earlier, including bridging with low-molecular weight heparin. Oral anticoagulation was achieved mainly by administration of direct oral anticoagulants (73%) and less frequently with phenprocoumon (27%) (Online Tables S2 and S3). In patients taking phenprocoumon, the international normalized ratio at the time of TAVR was 1.83 (IQR: 1.66 to 2.03), with no significant differences in PR compared with the other patient groups depicted in Online Table S2 and patients with no indication for anticoagulation (data not shown).

Any bleeding occurred in 80 patients and severe bleeding in 17 patients. There was no difference in ADP-induced PR between patients with bleeding and those without bleeding, nor there was an association between the occurrence of HALT and bleeding complications (data not shown).

OCCURRENCE OF HALT IN RELATION TO ADP-INDUCED PR. Median ADP-induced PR prior to TAVR was 180 AU · min (IQR: 81 to 344 AU · min). Below-median ADP-induced PR was 82 AU · min (IQR: 37 to 122 AU · min), whereas above-median PR was 341 AU · min (IQR: 342 to 501 AU · min). Among patients with below-median ADP-induced PR, 16 (16%) were diagnosed with HALT, whereas 20 patients with above-median ADP-induced PR (20%) were diagnosed with HALT ($p = 0.58$) (**Table 2**). As shown in **Figure 2**, HALT occurred across the entire spectrum of ADP-induced PR, and ADP-induced PR did not differ significantly between patients with and without HALT (182 [IQR: 73 to 322] vs. 178 [IQR: 81 to 354], $p = 0.84$). Among patients with HTPR defined by ADP-induced PR >468 AU · min, 24% displayed HALT, whereas 17% of patients with ADP-induced PR ≤468 AU · min had HALT ($p = 0.43$).

Logistic regression analysis yielded no association between the occurrence of HALT and ADP-induced PR as continuous variable (OR: 1.00; 95% CI: 0.999 to 1.002; $p = 0.75$). In addition, neither ASA-induced

TABLE 1 Patient Characteristics

	All Patients (N = 200)	No HALT (n = 164)	HALT (n = 36)	p Value
Age (yrs)	82 (79–86)	83 (79–86)	81 (78–84)	0.34
Female	104 (52.0)	85 (51.8)	19 (52.8)	0.91
BMI (kg/m^2)	26.0 (23.9–28.8)	25.8 (23.7–28.8)	27.4 (25.0–29.4)	0.11
BMI >30 kg/m^2	38 (19.0)	30 (18.3)	8 (22.2)	0.58
EuroSCORE (%)	13.3 (8.1–21.5)	13.3 (8.4–21.9)	13.8 (6.6–19.3)	0.44
STS mortality score (%)	3.4 (2.5–4.7)	3.5 (2.6–4.7)	3.25 (2.2–4.9)	0.39
Hypertension	176 (88.0)	144 (87.8)	32 (88.9)	0.85
Diabetes mellitus	55 (27.5)	48 (29.3)	7 (19.4)	0.23
History of smoking	40 (20.0)	33 (20.1)	7 (19.4)	0.92
Coronary artery disease	153 (76.5)	124 (75.6)	29 (86.6)	0.52
History of myocardial infarction	19 (9.5)	14 (8.5)	5 (13.9)	0.32
Impaired left ventricular function	64 (32.0)	52 (31.7)	12 (33.3)	0.85
History of stroke	29 (14.5)	25 (15.2)	4 (11.1)	0.54
History of cancer	44 (22.0)	36 (21.9)	8 (22.3)	0.91
Pre-existing atrial fibrillation	67 (33.5)	61 (37.2)	6 (16.7)	0.02
Oral anticoagulation	76 (38.0)	68 (41.5)	8 (22.2)	0.03
Creatinine clearance (CKD-EPI; ml/min)	58.0 (45.6–73.4)	59.2 (45.0–76.3)	50.7 (46.0–71.9)	0.71
Previous heart surgery	22 (11.0)	19 (11.6)	3 (8.3)	0.57
Annular size (CTA; mm)	24.0 (22.4–25.4)	24.0 (22.4–25.7)	24.0 (22.5–24.8)	0.38
Mitral insufficiency				
0	40 (20.0)	31 (18.9)	9 (25.0)	0.85
1	121 (60.5)	100 (61.0)	21 (58.3)	
2	33 (16.5)	28 (17.1)	5 (13.9)	
3	6 (3.0)	5 (3.0)	1 (2.8)	
Access route (transfemoral)	200 (100)	164 (100)	36 (100)	NA
Valve type				
Balloon-expandable (SAPIEN 3/SAPIEN XT)	138 (69.0)	117 (71.3)	21 (58.3)	0.27
Self-expandable (CoreValve/Evolut R)	48 (24.0)	37 (22.6)	11 (30.6)	
Mixed group (Lotus, Portico, Symetis)	14 (7.0)	10 (6.1)	4 (11.1)	
Prosthesis size (mm)				
<29	152 (76.0)	121 (73.8)	31 (86.1)	0.14
≥29	48 (24.0)	43 (26.2)	5 (13.9)	
Postdilatation	51 (25.5)	41 (25.0)	10 (27.8)	0.73
PVL at time of CTA				
Moderate or greater	3 (1.5)	3 (1.8)	0 (0.0)	0.41
MPG after implantation (mm Hg)	11.0 (8.0–13.0)	11.0 (8.0–13.0)	10.0 (8.0–13.2)	0.72

Values are median (interquartile range) or n (%).

BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CTA = computed tomographic angiography; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HALT = hypoattenuated leaflet thickening; MPG = mean pressure gradient; NA = not applicable; PVL = paravalvular leakage; STS = Society of Thoracic Surgeons.

TABLE 2 Adenosine Diphosphate-Induced Platelet Reactivity and Hypoattenuated Leaflet Thickening

	No HALT	HALT	p Value
ADPtest below median	84	16	0.58
ADPtest above median	80	20	
ADPtest ≤468 AU · min	142	29	0.43
ADPtest >468 AU · min	22	7	

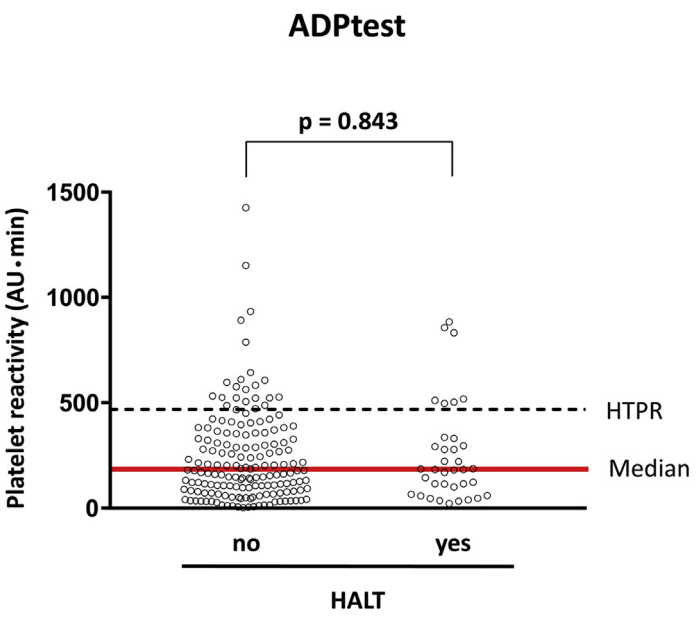
Numbers of patients within respective groups. ADPtest median: cutoff 180 AU · min. The p values were calculated using chi-square tests.

(OR: 0.999; 95% CI: 0.997 to 1.001; p = 0.33) nor thrombin receptor-activated peptide-induced (OR: 0.984; 95% CI: 0.999 to 1.001; p = 0.89) PR was predictive of the occurrence of HALT. Platelet counts were not associated with the occurrence of HALT (OR: 0.999; 95% CI: 0.993 to 1.005; p = 0.66).

SENSITIVITY ANALYSES EXCLUDING PATIENTS WITH ORAL ANTICOAGULATION. Presence of oral anticoagulation might mask an association between PR and the occurrence of HALT. Therefore, sensitivity analyses were performed with restriction to patients without oral anticoagulation (n = 124). Here, 13 patients (20%) with ADP-induced PR <180 AU · min were diagnosed with HALT, whereas 15 patients (25%) with ADP-induced PR ≥180 AU · min were diagnosed with HALT (p = 0.47). Using the median of patients without oral anticoagulation, similar results were obtained (12 patients with HALT and PR <168 AU · min and 16 patients with HALT and PR ≥168 AU · min, p = 0.39). In the patient stratum with HTPR defined by ADP-induced PR >468 AU · min, 29% of patients displayed HALT, whereas 21% of patients with ADP-induced PR ≤468 AU · min had HALT (p = 0.47). Again, logistic regression analysis with ADP-induced PR as a continuous variable showed no association to occurrence of HALT (OR: 1.00; 95% CI: 0.998 to 1.002; p = 0.86).

OTHER PREDICTORS OF HALT. To test for other predictors of HALT, binary logistic regression models of the entire cohort (n = 200), with ADP-induced PR stratified according to the median of 180 AU · min, were constructed (Table 3). Likewise, ADP-induced PR showed no significant predictive value. Among other clinical parameters, only oral anticoagulation remained significantly associated with reduced rates of HALT (Table 3).

FIGURE 2 Platelet Reactivity by Multiple-Electrode Aggregometry



The **dashed black line** indicates the high on-treatment platelet reactivity (HTPR) cutoff of 468 AU · min; the **continuous red line** indicates the median platelet reactivity of 180 AU · min within the entire cohort (n = 200). Statistical testing was performed using the Mann-Whitney *U* test. ADP = adenosine diphosphate; AU = arbitrary units; HALT = hypoattenuated leaflet thickening.

DISCUSSION

The $P2Y_{12}$ inhibitor clopidogrel is widely used after TAVR. Current guidelines recommend a combination of ASA and clopidogrel for 3 to 6 months after TAVR on the basis of expert opinion (17,18). HALT as an emerging phenomenon associated with TAVR has underlined the need to reassess the concept of antithrombotic therapy after TAVR. Previous studies failed to show an appreciable effect of clopidogrel administration on the incidence of leaflet thrombosis after TAVR, as evidenced by HALT. Here, we demonstrate that the inability of clopidogrel to prevent early HALT is not linked to the subset of patients with a residual $P2Y_{12}$-dependent PR in the higher range of the variable clopidogrel response.

The incidence of HALT was not significantly different irrespective of whether residual $P2Y_{12}$-dependent PR was above or below the median of the entire cohort. Applying the more strict threshold of HTPR derived from studies with coronary stents (14), most of the cases of HALT occurred at a residual $P2Y_{12}$-dependent PR that was well below the critical threshold. Furthermore, it is noteworthy that levels of ADP-induced PR in the present study were comparable with ranges known from patients with coronary artery disease without aortic stenosis (14).

Thus, we cannot confirm previously reported high rates of HTPR in patients undergoing TAVR (7–9).

In this context, it must be noted that HALT was initially detected by chance (19) or because of prespecified imaging analysis within clinical trials (4). Although anticoagulation has been reported to be effective in therapy or prevention of HALT (4,11,16), the clinical significance of HALT has only recently been outlined. In 2017, Chakravarty et al. (2) showed in a large dataset that HALT is associated with an increased rate of transient ischemic attacks. Again, oral anticoagulation but not DAPT was protective regarding the incidence of HALT (2). Yet it was not demonstrated that antiplatelet therapy was effective, and computed tomography was performed a median of 83 days after TAVR.

In the present study, only 14% of patients receiving clopidogrel displayed HTPR. Still, this overall effective platelet inhibition was not protective with regard to HALT. Therefore, inadequate platelet inhibition cannot be maintained as a major predisposing factor for HALT. Yet a minor effect (but small compared with the clear preventive effect of anticoagulation) cannot be excluded. Although the rationale for DAPT is justified on the basis of an assumed prevention of atherothrombotic events, anticoagulation is seen as a preventive strategy for thrombus formation secondary to stasis and flow conditions.

Neither the discussed studies nor the present study were randomized controlled trials. Thus, the results of several currently recruiting multicenter trials might shed additional light on the occurrence of HALT and its possible progression to valve hemodynamic deterioration (20). Comparing antiplatelet therapy with anticoagulation after TAVR, the POPULAR TAVI, ATLANTIS, and GALILEO trials are focused on clinical endpoints such as mortality and stroke. Only a substudy of the GALILEO trial evaluates whether anticoagulation compared with current DAPT after TAVR can reduce the risk for leaflet thrombosis. Upon publication of these results, the current standard with DAPT may be questioned. This study underlines that, in the setting of TAVR, clopidogrel should not be seen as an inappropriate $P2Y_{12}$ inhibitor because of its variable response. Rather, the whole concept of $P2Y_{12}$ inhibition after TAVR needs to be reevaluated.

STUDY LIMITATIONS. This study had distinct limitations. First, it was observational, but patients were included prospectively.

TABLE 3 Platelet Reactivity, Clinical Characteristics, and Hypoattenuated Leaflet Thickening

	Univariate Model			Multivariate Model		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Platelet reactivity (median)	0.762	0.369–1.573	0.462			
Oral anticoagulation	0.403	0.173–0.939	0.035	0.409	0.175–0.957	0.039
Body mass index	1.032	0.957–1.114	0.412			
Prosthesis ≥29 mm	0.454	0.166–1.242	0.124	0.465	0.168–1.283	0.139
Age, yrs	0.983	0.919–1.051	0.615			
Impaired LV function	0.929	0.431–2.000	0.850			

Platelet reactivity stratified according to median ADPtest (180 AU · min).
CI = confidence interval; LV = left ventricular.

Second, the sample size of 200 patients was too small to detect differences in hard clinical endpoints such as mortality and stroke. For the same reason, we cannot exclude a minor effect of clopidogrel on HALT. Nevertheless, HALT occurred across the entire spectrum of on-clopidogrel PR. Accordingly, the risk for HALT remained substantial even in patients with adequate clopidogrel response. We therefore exclude a clinically relevant preventive effect of lower levels of on-clopidogrel PR.

Third, this study only delivers insights into the post-interventional phase with, compared with other studies, an earlier assessment of HALT.

Finally, it should be noted that only 1 method to assess PR was applied. Other aspects of platelet activation, such as expression of surface markers, were therefore not addressed. However, we aimed to test for efficacy of antiplatelet therapy in the setting of TAVR. Here, impedance aggregometry was selected because of its wide use and the large amount of data confirming clinical relevance of its results (15).

CONCLUSIONS

On-clopidogrel ADP-induced PR was not significantly associated with the occurrence of HALT. In contrast, oral anticoagulation was associated with reduced rates of HALT.

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PERSPECTIVES

WHAT IS KNOWN? $P2Y_{12}$ inhibition with clopidogrel is the current standard of care after TAVR.

WHAT IS NEW? The level of residual ADP-induced PR is not associated with the risk for early HALT as a sensitive marker of emerging valve thrombosis. The present findings question whether $P2Y_{12}$ inhibition is sufficiently effective in preventing valve thrombosis to justify the increased risk for bleeding associated with it.

WHAT IS NEXT? The concept of $P2Y_{12}$ inhibition to prevent HALT after TAVR needs to be reevaluated.

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438–88.

2. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383–92.

3. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J 2016;37:2263–71.

4. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015–24.

5. Rodes-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. J Am Coll Cardiol Intv 2017;10:1357–65.

6. Hochholzer W, Trenk D, Fromm MF, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol 2010;55:2427–34.

7. Orvin K, Eisen A, Perl L, et al. Platelet reactivity in patients undergoing transcatheter aortic valve implantation. J Thromb Thrombolysis 2016;42:11–8.

8. Tousek P, Kocka V, Sulzenko J, Bednar F, Linkova H, Widimsky P. Pharmacodynamic effect of clopidogrel in patients undergoing transcatheter aortic valve implantation. Biomed Res Int 2013;2013:386074.

9. Polzin A, Schleicher M, Seidel H, et al. High on-treatment platelet reactivity in transcatheter aortic valve implantation patients. Eur J Pharmacol 2015;751:24–7.

10. Hochholzer W, Amann M, Titov A, et al. Randomized comparison of different thienopyridine loading strategies in patients undergoing elective coronary intervention: the ExcelsiorLOAD trial. J Am Coll Cardiol Intv 2016;9:219–27.

11. Ruile P, Jander N, Blanke P, et al. Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. Clin Res Cardiol 2017;106:85–95.

12. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1–25.

13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

14. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009;53:849–56.

15. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.

16. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol 2016;68:2059–69.

17. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

18. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2017;69:1313–46.

19. Pache G, Blanke P, Zeh W, Jander N. Cusp thrombosis after transcatheter aortic valve replacement detected by computed tomography and echocardiography. Eur Heart J 2013;34:3546.

20. Del Trigo M, Munoz-Garcia AJ, Wijeysundera HC, et al. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. J Am Coll Cardiol 2016;67:644–55.

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APPENDIX For supplemental tables, please see the online version of this paper.