JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 1, 2019

Assessment of Platelet REACtivity After Transcatheter Aortic Valve Replacement

The REAC-TAVI Trial

Victor Alfonso Jimenez Diaz, MD, MPH,[a,b] Antonio Tello-Montoliu, MD, PhD,[c,d] Raul Moreno, MD,[e] Ignacio Cruz Gonzalez, MD, PhD,[d,f] Jose Antonio Baz Alonso, MD,[a] Rafael Romaguera, MD,[g] Eduardo Molina Navarro, MD,[h] Pablo Juan Salvadores, Pharma, MPH,[b,i] Emilio Paredes Galan, MD, PhD,[a] Antonio De Miguel Castro, MD,[a] Guillermo Bastos Fernandez, MD,[a] Alberto Ortiz Saez, MD,[a] Saleta Fernandez Barbeira, MD,[a] Sergio Raposeiras Roubin, MD, PhD,[a] Juan Ocampo Miguez, MD,[a] Antonio Serra Peñaranda, MD, PhD,[j] Mariano Valdes Chavarri, MD, PhD,[c,d] Angel Cequier Fillat, MD, PhD,[d,g] Francisco Calvo Iglesias, MD, PhD,[a] Andres Iñiguez Romo, MD, PhD[a,d]

ABSTRACT

OBJECTIVES The REAC-TAVI (Assessment of platelet REACtivity after Transcatheter Aortic Valve Implantation) trial enrolled patients with aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) pre-treated with aspirin + clopidogrel, aimed to compare the efficacy of clopidogrel and ticagrelor in suppressing high platelet reactivity (HPR) after TAVI.

BACKGROUND Current recommendations support short-term use of aspirin + clopidogrel for patients with severe AS undergoing TAVR despite the lack of compelling evidence.

METHODS This was a prospective, randomized, multicenter investigation. Platelet reactivity was measured at 6 different time points with the VerifyNow assay (Accriva Diagnostics, San Diego, California). HPR was defined as ($P2Y_{12}$ reaction units (PRU) ≥208. Patients with HPR before TAVR were randomized to either aspirin + ticagrelor or aspirin + clopidogrel for 3 months. Patients without HPR continued with aspirin + clopidogrel (registry cohort). The primary endpoint was non-HPR status (PRU <208) in ≥70% of patients treated with ticagrelor at 90 days post-TAVR.

RESULTS A total of 68 patients were included. Of these, 48 (71%) had HPR (PRU 273 ± 09) and were randomized to aspirin + ticagrelor (n = 24, PRU 277 ± 08) or continued with aspirin + clopidogrel (n = 24, PRU 269 ± 49). The remaining 20 patients (29%) without HPR (PRU 133 ± 12) were included in the registry. Overall, platelet reactivity across all the study time points after TAVR was lower in patients randomized to ticagrelor compared with those treated with clopidogrel, including those enrolled in the registry ($p < 0.001$). The primary endpoint was achieved in 100% of patients with ticagrelor compared with 21% with clopidogrel ($p < 0.001$). Interestingly, 33% of clopidogrel responder patients at baseline developed HPR status during the first month after TAVR.

CONCLUSIONS HPR to clopidogrel is present in a considerable number of patients with AS undergoing TAVR. Ticagrelor achieves a better and faster effect, providing sustained suppression of HPR to these patients. (Platelet Reactivity After TAVI: A Multicenter Pilot Study [REAC-TAVI]; NCT02224066) (J Am Coll Cardiol Intv 2019;12:22–32)

From the [a]Cardiology Department, Hospital Alvaro Cunqueiro, University Hospital of Vigo, Vigo, Spain; [b]Cardiovascular Research Unit, Cardiology Department, Hospital Alvaro Cunqueiro, University Hospital of Vigo, Vigo, Spain; [c]Cardiology Department, Hospital Universitario Virgen de la Arrixaca, IMIB-Arrixaca, Murcia, Spain; [d]Centro de Investigación en Red de Enfermedades Cardiovasculares (Network Research Center for Cardiovascular Diseases), CIBER-CV, Madrid, Spain; [e]Cardiology Department, Hospital Universitario La Paz, Madrid, Spain; [f]Cardiology Department, Hospital Universitario de Salamanca, Salamanca, Spain; [g]Cardiology Department, Hospital Universitario de Bellvitge, Barcelona, Spain; [h]Cardiology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain; [i]Cardiovascular Research Group, Galicia Sur Health Research Institute (IIS Galicia Sur), SERGAS-UVIGO, Vigo, Spain; and the [j]Cardiology Department, Hospital Universitario San Pau, Barcelona, Spain. This is an investigator-initiated trial, sponsored by the Spanish Society of Cardiology, and supported by AstraZeneca. Data monitoring, data

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2018.10.005

Transcatheter aortic valve replacement (TAVR) for degenerative aortic stenosis (AS), the most common valvular heart disease in the elderly (1), has become an established treatment for patients of high or intermediate surgical risk because it offers superior quality of life and similar mortality rates at 2 years follow-up, with less invasiveness than surgical aortic valve replacement (2,3). Application of this technique in younger patients and those of lower surgical risk is currently being explored.

SEE PAGE 33

In patients undergoing TAVR, thrombotic and hemorrhagic complications remain a concern, and are associated with increased mortality and morbidity (4–6). Although the immediate procedural risk relates to vascular access and valvular debris embolization, an significant percentage of thrombotic complications takes place in the first days after the procedure and during follow-up, remaining raised for up to 6 months (4–7). These are non-procedural-related events and implies the presence of a prothrombotic environment in these patients. Therefore, antiplatelet treatment plays an important role in trying to maintain the balance between the suppression of thrombotic complications without increasing the risk of bleeding.

Presently, antithrombotic therapy in patients with AS undergoing TAVR is not standardized. Various combinations of antithrombotic regimens (single-antiplatelet, dual antiplatelet therapy [DAPT], or oral anticoagulants) have been used, but evidence-based guidance is limited. Current guidelines (8,9) for the management of patients with valvular heart disease recommend DAPT combining low-dose aspirin and a thienopyridine (clopidogrel) for up to 6 months after TAVR. However, the evidence for this recommendation is weak and has no support from dedicated randomized clinical trials. Therefore, there is heterogeneity in antithrombotic treatment regimens following TAVR in real-world practice (10,11).

Studies have demonstrated a broad variability in individual response profiles to clopidogrel therapy resulting in adverse clinical outcomes, particularly among those who persist with high platelet reactivity (HPR) (12–14). However, most of these studies have been conducted in patients undergoing coronary stenting, and there are limited data on profiles of platelet reactivity in AS patients undergoing TAVR treated with clopidogrel. Moreover, the impact of newer generation $P2Y_{12}$ inhibitor such as ticagrelor characterized by more potent and less heterogeneous antiplatelet effects has never been prospectively tested in AS patients undergoing TAVR.

Therefore, we aimed to analyze profiles of platelet reactivity among patients with AS undergoing TAVR treated with clopidogrel, on a background of aspirin therapy, and to assess the effects of ticagrelor among patients presenting with HPR.

ABBREVIATIONS AND ACRONYMS

ARU = aspirin reaction unit(s)

AS = aortic stenosis

DAPT = dual antiplatelet therapy

HPR = high platelet reactivity

PRU = $P2Y_{12}$ reaction unit(s)

TAVR = transcatheter aortic valve replacement

METHODS

STUDY DESIGN AND PATIENT POPULATION. The REAC-TAVI trial (Assessment of platelet REACtivity after Transcatheter Aortic Valve Implantation, NCT02224066) was a prospective, open-label, investigator-initiated, randomized, multicenter, parallel-group, phase IV pharmacodynamic clinical trial, designed to investigate the incidence of HPR with aspirin and clopidogrel in patients with severe symptomatic AS undergoing TAVR and to test the hypothesis that ticagrelor is superior to clopidogrel in suppression of HPR after TAVR. An outline of the study design is provided in the Online Appendix.

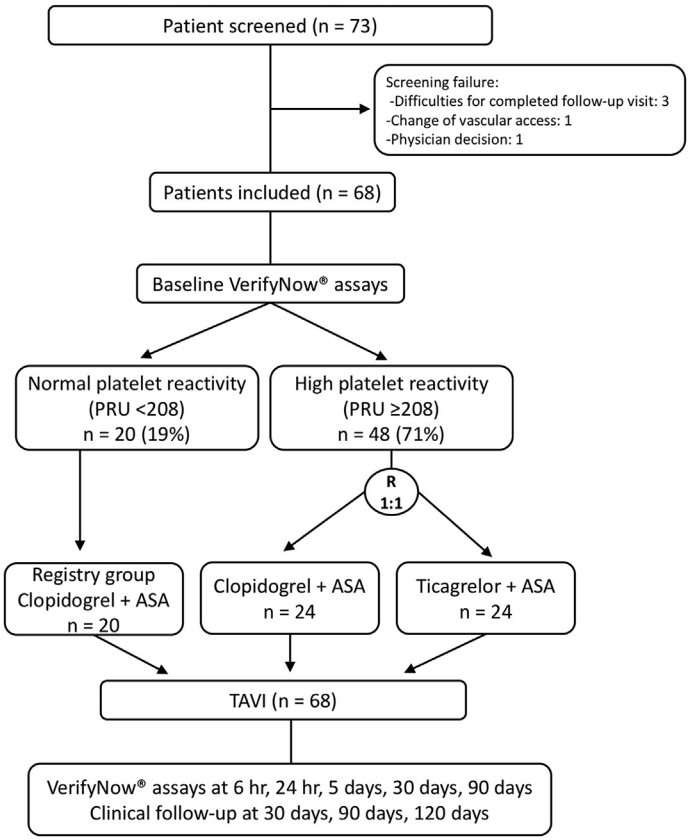
In brief, patients with severely symptomatic degenerative AS undergoing TAVR by transfemoral access were included at 7 centers in Spain (see the Online Appendix for the participating centers). Patients were excluded if they had any of the following: stroke during the 14 days before TAVR, bleeding diathesis, need for long-term oral anticoagulation treatment, contraindications to DAPT for 3 months, platelet count $<$50,000/μl, severe hepatic dysfunction, use of potent CYP3A inhibitors or inducers. All patients were on a background of aspirin (100 mg/day) in adjunct to clopidogrel. Patients need to be on clopidogrel maintenance dosing (75 mg/day) for $\geq$4 days before TAVR. Clopidogrel-naive patients were pretreated with a 300-mg loading dose.

Patients with HPR at baseline were randomized in a 1:1 ratio using computerized random-number generation in an interactive web response system by an independent investigator to either continue

entry, database maintenance, statistical analysis, and drafting and submission of the final manuscript was exclusively performed by the investigators. AstraZeneca played no role in the design of the study, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 18, 2018; revised manuscript received September 17, 2018, accepted October 2, 2018.

FIGURE 1 Study Flow Chart



ASA = acetylsalicylic acid; PRU = $P2Y_{12}$ reactivity units; TAVR = transcatheter aortic valve replacement.

clopidogrel (75 mg/day) or switch to ticagrelor (90 mg/twice daily). Patients randomized to the ticagrelor group received at least 3 maintenance doses before undergoing TAVR. Patients without HPR were included in a registry cohort and maintained on clopidogrel therapy.

The TAVR procedure was performed according to the standards of each participating center. Patients received intravenous heparin (100 U/kg), with additional doses if the activated clotting time was <250 s. Compliance to antiplatelet therapy was assessed by the 4-item Morisky Green Levine Medication Adherence Scale (15) at 30 and 90 days after TAVR and by accountability of the study drugs in both treatment arms. Onsite monitoring and source data verification were conducted by an independent contract research organization in 100% of patients and in all study procedures, with a final follow-up visit at 4 months after TAVR. Adverse events were adjudicated by an independent clinical events committee, according the Valve Academic Research Consortium-2 classification (16). The study flow chart is showed in Figure 1. The study complied with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice guidelines, and applicable regulatory requirements. Informed consent was obtained and documented for all patients before conducting any study-related procedures.

PLATELET REACTIVITY ASSESSMENT. Platelet function was assessed using the VerifyNow point-of-care assay (Accriva Diagnostics, San Diego, California). Measurements were conducted in all patients at baseline (before TAVR) and at 6 different time points following TAVR: 6 h ± 30 min, 24 ± 2 h, 5 ± 1 day, 30 ± 3 days, and 90 ± 5 days. HPR was defined as a $P2Y_{12}$ reaction unit (PRU) value ≥208, in line with consensus recommendations (17,18). Response to aspirin was also assessed; an aspirin reaction unit (ARU) value ≥550 defined patients as nonresponders to aspirin. All patients were included in the per protocol safety analysis, whereas the pharmacodynamic analysis at 30 days consisted of 61 patients: 1 patient in the registry was excluded from the analyses due to missing platelet reactivity data results; 2 patients (1 in the ticagrelor group and 1 in the clopidogrel group) were excluded due to development of new-onset atrial fibrillation during hospitalization and were switched to oral anticoagulation; and 4 patients died during hospitalization (2 in the clopidogrel group and 2 in the registry group). At 90 days, 2 patients died in the clopidogrel group. The final pharmacodynamic population at 90 days, therefore, comprised 59 patients (ticagrelor n = 23; clopidogrel n = 19; registry n = 17).

STUDY ENDPOINTS. The primary endpoint was to obtain non-HPR status (PRU <208) in ≥70% of patients treated with ticagrelor, or a net difference of ≥40% in the number of patients with PRU <208 between treatment groups at 90 ± 5 days of antiplatelet treatment following TAVR. A key secondary efficacy endpoint was the net difference in the incidence of HPR 6 h post-TAVR of ≥30% between groups.

The secondary safety endpoints are constituted by the incidence of cerebrovascular accident or hemorrhagic complications (according to Valve Academic Research Consortium-2 criteria) at 4-month follow-up following TAVR. Exploratory endpoints included the analysis of patients with HPR after 24 h, 5 days, and 30 days of antiplatelet treatment, and pre-specified subanalyses by sex, age, comorbidities (diabetes mellitus, renal failure), type of bioprosthetic valve implanted, and HPR to both antiplatelet agents.

SAMPLE-SIZE CALCULATION AND STATISTICAL METHODS. Statistical inference was based on comparison of the

incidence of the primary endpoint between treatment groups. To achieve 80% power to detect differences in the contrast of the null hypothesis H_o:p1 = p2 using a chi-square test for 2 independent samples with α = 0.05, a treatment arm allocation ratio of 1:1, under the assumption that the proportion of patients achieving adequate antiplatelet therapy at 3 months post-TAVR (PRU <208) in the aspirin + clopidogrel group is 28% and the proportion expected in the aspirin + ticagrelor group is 70%, it was necessary to enroll 21 patients in each treatment group. Given an expected dropout rate of 10%, 24 patients in each treatment group (total n = 48) would be required.

Conformity to the normal distribution was evaluated for continuous variables with the Shapiro-Wilk test. Categorical variables are expressed as frequencies and percentages. For baseline characteristics, continuous variables are expressed as mean ± SD; PRU and ARU as mean ± SE. Chi-square tests or Fisher exact tests were used, where appropriate, to compare categorical variables between 2 groups. Primary analysis of the difference between ticagrelor and clopidogrel in PRU at 90 days was analyzed using a 2-sample Student's *t*-test. Two-sample Student's *t*-tests were also used to evaluate other intergroup comparisons and to evaluate the impact of the 2 different treatments on platelet reactivity across time points.

RESULTS

PATIENT POPULATION. Between November 2015 and May 2017, of 73 patients screened, 68 patients met study entry criteria (3 patients had difficulties completing the follow-up visit, 1 patient was switched to non-transfemoral TAVR, and 1 patient was excluded due to physician decision). Most patients were on long-term use (≥4 days) of clopidogrel (84%), whereas the remaining patients received a loading dose. A total of 48 patients (71%) had HPR at baseline (PRU 273 ± 09) and were randomized to continue treatment with clopidogrel (n = 24, PRU 269 ± 49) or to switch to ticagrelor (n = 24, PRU 277 ± 08). The remaining 20 patients (29%) without HPR (PRU 133 ± 12) were included in the registry (Figure 1). Baseline ARU was 456 ± 15 in the randomized group and 451 ± 18 in the registry group; an ARU >550 was present in 9 patients (13%) (ARU 587 ± 10). Of these, 5 patients were in the registry group. Thus, 4 patients had HPR to both aspirin and clopidogrel, and were distributed equally in both randomized groups.

Baseline characteristics of the study population are displayed in Table 1. Compared with the randomized group, patients in the registry cohort had a lower prevalence of chronic kidney disease and higher hemoglobin levels. Baseline characteristics were similar between randomized groups, except for lower body mass index and mean aortic valve area, and higher STS-PROM score in the clopidogrel group compared with the ticagrelor group. The majority of patients had pre-existing cardiovascular risk factors, nearly one-half of the population were women, had diabetes, or had prior percutaneous coronary intervention, and more than one-quarter of patients had a history of myocardial infarction or chronic kidney disease.

All patients were treated by transfemoral access, with a predominance of a conscious sedation strategy in the randomized group and general anesthesia in the registry. Procedural success was achieved in >90%, and a balloon-expandable valve was used in 48% of cases (Table 2).

PHARMACODYNAMIC RESULTS. Overall, platelet reactivity across all the study time points after TAVR was lower in patients receiving ticagrelor compared with those receiving clopidogrel, including the registry group ($p < 0.001$). The primary endpoint of patients with PRU <208 was achieved in 100% of patients with ticagrelor compared with 21% with clopidogrel (PRU 240 ± 15; $p < 0.001$), with a net difference of responders between groups of 79% ($p < 0.001$) and an overall mean difference of −170 PRU in the ticagrelor group compared to clopidogrel group at the end of the treatment. Analysis of PRU levels at the different time-points also showed a significant reduction of platelet reactivity at 6 h, 24 h, 5 days, and 30 days with ticagrelor, compared with clopidogrel ($p < 0.001$) (Figure 2). The percentage of responders to ticagrelor was significantly higher throughout the entire treatment period compared with responders to clopidogrel (Figure 3). Interestingly, important variations in PRU levels throughout the treatment period was observed in the registry group, with an increase of 53 ± 26 PRU (Figure 2) and a decrease of 33% responders during the first month after TAVR (Figure 3). A total of 23 patients had at least 1 PRU value ≤70 during the treatment period: 1 in the clopidogrel group, 18 in the ticagrelor group, and 4 in the registry group. Mean ARU values were maintained in ranges of adequate response during the treatment period in the 3 groups, but significant variations in the degree of response to aspirin between groups were noticed at 5 and 30 days post-TAVR (Figure 4). The proportion of patients responding to aspirin did not vary significantly during the treatment phase.

SAFETY RESULTS. There was a total of 55 adverse events adjudicated by the clinical events committee

TABLE 1 Baseline Characteristics of the Study Population

	Normal Platelet Reactivity Registry (n = 20)	*p Value Registry vs. Randomized	†p Value Registry vs. Clopidogrel + Aspirin	‡p Value Registry vs. Ticagrelor + Aspirin	High On-Treatment Platelet Reactivity		§p Value
					Clopidogrel + Aspirin (n = 24)	Ticagrelor + Aspirin (n = 24)	
Demographic characteristics							
Age, yrs	75.8 ± 19.6	0.31	0.25	0.31	81.2 ± 5.5	80.3 ± 8.6	0.67
Women	9 (45.0)	0.58	0.95	0.54	11 (45.8)	13 (54.2)	0.56
BMI, kg/m^2	26.3 ± 4.5	0.10	0.48	0.004	27.3 ± 4.77	30.6 ± 4.6	0.02
Cardiovascular risk factors							
Current smokers	5 (25.0)	0.56	0.92	0.43	6 (25.0)	3 (12.5)	0.46
Hypertension	16 (80.0)	0.96	0.67	0.64	19 (79.2)	22 (91.7)	0.41
Diabetes mellitus	8 (40.0)	0.12	0.10	0.43	16 (66.7)	13 (54.2)	0.37
Insulin-treated	2 (10.0)	0.19	0.08	1.00	8 (33.3)	3 (12.5)	0.08
Dyslipidemia	11 (55.0)	0.29	0.55	0.13	16 (66.7)	19 (79.2)	0.33
History of cardiovascular disease and procedures							
PVD	0 (0.0)	0.18	0.24	1.00	3 (12.5)	1 (4.2)	0.29
CKD	2 (10.0)	0.03	0.14	0.07	8 (33.3)	9 (37.5)	0.76
COPD	2 (10.0)	0.71	0.36	0.56	5 (20.8)	4 (16.7)	0.71
Chronic liver disease	1 (5.0)	0.84	1.00	1.00	2 (8.3)	1 (4.2)	1.00
Stroke	1 (5.0)	0.63	0.61	1.00	3 (12.5)	1 (4.2)	0.29
TIA	1 (5.0)	0.89	1.00	0.45	2 (8.3)	0 (0)	0.48
Myocardial infarction	5 (25.0)	0.56	0.47	0.72	4 (16.7)	5 (20.8)	0.71
PCI	10 (50.0)	0.52	0.47	0.54	10 (41.7)	10 (41.7)	1.00
CABG	0 (0.0)	0.16	0.24	0.24	3 (12.5)	3 (12.5)	1.00
Clinical data							
Dyspnea	16 (80.0)	0.96	1.00	0.64	19 (79.2)	22 (91.7)	0.41
Angina	4 (20.0)	0.53	1.00	0.50	5 (20.8)	8 (33.3)	0.33
Syncope	3 (15.0)	0.41	0.64	0.64	2 (8.3)	2 (8.3)	1.00
NYHA II to III	14 (70.0)	0.07	0.29	0.29	22 (95.7)	23 (95.8)	1.00
Echocardiographic data							
Maximum aortic gradient, mm Hg	80.6 ± 24.5	0.42	0.94	0.33	81.1 ± 17.5	70.7 ± 23.0	0.10
Mean aortic gradient, mm Hg	51.8 ± 17.8	0.06	0.45	0.06	47.9 ± 11.6	41.1 ± 13.3	0.08
Mean aortic valve area, cm^2	0.61 ± 0.17	0.29	0.93	0.04	0.62 ± 0.20	0.73 ± 0.13	0.05
Aortic regurgitation ≥moderate	3 (15.0)	0.11	0.29	0.28	1 (5.3)	1 (4.8)	1.00
LVEF	60.5 ± 12.7	0.52	0.30	0.96	55.9 ± 12.9	60.8 ± 15.3	0.28
Systolic PAP	52.3 ± 15.6	0.08	0.29	0.04	41.7 ± 13.2	36.2 ± 8.1	0.34
Blood analysis							
Hemoglobin, mg/dl	13.4 ± 1.6	0.01	0.009	0.02	12.0 ± 1.8	12.2 ± 1.8	0.62
Platelets, 10^9/l	203.1 ± 71	0.95	0.78	0.67	197.3 ± 62	211.7 ± 60	0.42
NT-proBNP	1,901 ± 1,496	0.41	0.27	0.83	4,226 ± 5,178	2,104 ± 2,103	0.33
Risk scores							
Logistic EuroScore	8.9 ± 6.11	0.21	0.11	0.71	13.37 ± 10.37	9.52 ± 5.31	0.12
STS-PROM, %	6.36 ± 7.61	0.73	0.67	0.23	7.22 ± 5.18	4.08 ± 2.53	0.014
HAS-BLED	2.75 ± 1.30	0.63	0.87	0.34	2.69 ± 0.90	2.40 ± 0.81	0.25
CHA_2DS_2-VASC	4.00 ± 1.41	0.15	0.11	0.39	4.70 ± 1.36	4.38 ± 1.41	0.43

Values are mean ± SD or n (%). *p values of comparison between registry group and randomized group. †p values of comparison between registry group and clopidogrel + aspirin group. ‡p values of comparison between registry group and ticagrelor + aspirin group. §p values of comparison between both randomized groups.

BMI = body mass index; CABG = coronary artery bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association functional class; PAP = pulmonary arterial pressure; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

in the overall population during the entire study. There were no statistically significant differences in the incidence of major bleeding or cardiovascular death among the study groups at 4 months follow-up, as well as other adjudicated adverse events according VARC-2 definitions (Table 3). Only 1 patient had an in-hospital major bleeding related to vascular access while on a PRU value of 70 at 6 h after TAVR.

TABLE 2 Procedural Characteristics and In-Hospital Outcome

	Normal Platelet Reactivity Registry (n = 20)	*p Value Registry vs. Randomized	†p Value Registry vs. Clopidogrel + Aspirin	‡p Value Registry vs. Ticagrelor + Aspirin	High On-Treatment Platelet Reactivity		§p Value
					Clopidogrel + Aspirin (n = 24)	Ticagrelor + Aspirin (n = 24)	
Procedural data							
Local anesthesia only	3 (15.0)	0.003	0.10	<0.001	3 (12.5)	1 (4.2)	0.07
Conscious sedation	5 (25.0)				14 (58.3)	21 (87.5)	
General anesthesia	12 (60.0)				7 (29.2)	2 (8.3)	
Transfemoral access	20 (100.0)	1.00	1.00	1.00	24 (100)	24 (100.0)	1.00
Balloon pre-dilation	4 (20.0)	1.00	1.00	1.00	5 (20.8)	5 (20.8)	1.00
Balloon size, mm	23.3 ± 1.5	0.01	0.17	0.008	20.7 ± 2.3	19.8 ± 1.1	0.48
Valve type, size, and post-dilation							
Balloon-expandable valve	6 (30.0)				9 (37.5)	14 (58.3)	
Self-expandable valve	9 (45.0)				11 (45.8)	9 (37.5)	
Other type of valve	5 (25.0)	0.37	0.86	0.11	4 (16.7)	1 (4.2)	0.21
≤23-mm valve	0 (0.0)	0.10	0.10	0.11	7 (29.2)	7 (29.2)	0.83
25- to 29-mm valve	18 (90.0)				15 (62.5)	16 (66.7)	
>29-mm valve	2 (10.0)				2 (8.3)	1 (4.1)	
Balloon post-dilation	5 (25.0)	0.70	1.00	0.64	6 (25.0)	3 (12.5)	0.46
Balloon size, mm	24.3 ± 0.96	0.38	0.38	0.49	22.7 ± 2.3	23.3 ± 2.3	0.76
Vascular closure							
2 ProGlides	13 (65.0)	0.66	0.63	0.71	19 (79.2)	16 (66.7)	0.58
Prostar	5 (25.0)				3 (12.5)	4 (16.7)	
Surgical closure	2 (10.0)				2 (8.3)	4 (16.7)	
Procedural outcome							
Procedural success	18 (90.0)	1.00	NA	1.00	23 (96)	23 (87.5)	1.00
Final maximum gradient, mm Hg	17.9 ± 15.8	0.37	0.26	0.29	7.0 ± 4.6	11.4 ± 8.1	0.17
Final mean gradient, mm Hg	8.7 ± 8.1	0.75	0.35	0.78	4.8 ± 3.7	9.8 ± 5.5	0.11
Final AR ≥moderate	2 (10.0)	0.13	0.08	0.35	1 (4.1)	3 (12.5)	0.35
Total dose of UFH, UI	5,090 ± 2,634	0.02	0.06	0.03	6,904 ± 2,462	7,000 ± 2,161	0.89
Need of valve recapture and reposition	2 (10.0)	0.59	0.60	0.60	2 (8.3)	2 (8.3)	1.00
Need for a second valve	0 (0.0)	NA	NA	NA	0 (0)	0 (0.0)	NA
Conversion to open-heart surgery	0 (0.0)	NA	NA	NA	0 (0)	0 (0.0)	NA
Need of permanent pacemaker implantation	3 (15.0)	0.71	1.00	1.00	5 (20.8)	5 (20.8)	1.00
Hospital stay, days	7.9 ± 3.6	0.86	0.88	0.85	7.7 ± 4.0	7.6 ± 5.6	0.93

Values are n (%), or mean ± SD. *p values of comparison between the registry group and the randomized group. †p values of comparison between the registry group and the clopidogrel + aspirin group. ‡p values of comparison between the registry group and the ticagrelor + aspirin group. §p values of comparison between both randomized groups. Other type of valve includes Lotus valve and Direct Flow valve.

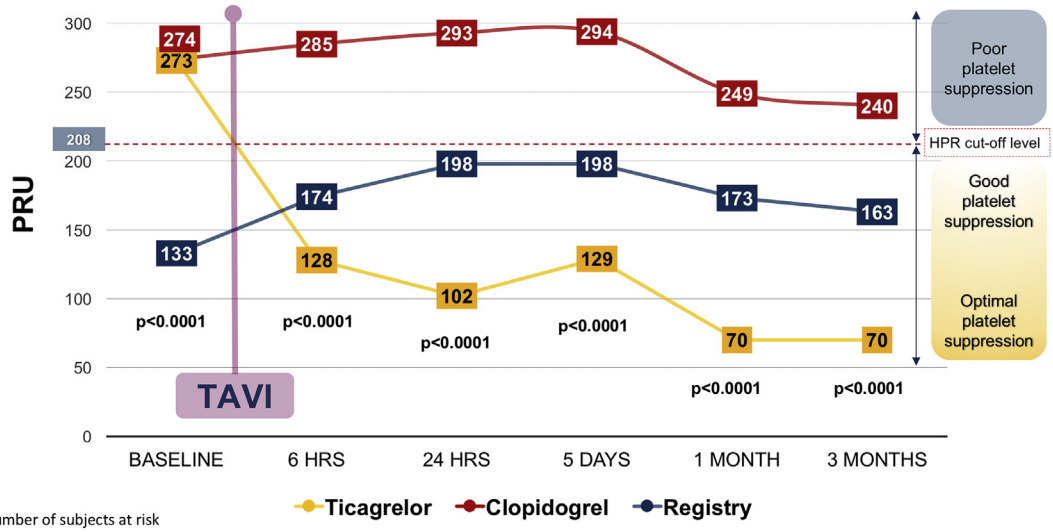
AR = aortic regurgitation; UFH = unfractionated heparin.

DISCUSSION

To date, there are limited studies evaluating profiles of platelet reactivity in patients with severe AS undergoing TAVR (19-21). The present study is the first to our knowledge to prospectively evaluate profiles of platelet reactivity of patients with AS undergoing TAVR treated with aspirin plus clopidogrel therapy and to evaluate the effects of ticagrelor among patients with HPR. The main results of our study are as follows: 1) HPR to clopidogrel is present in more than two-thirds of patients with AS undergoing TAVR; 2) more than one-third of patients who were identified to be responders to clopidogrel developed HPR status during the first month after TAVR; and 3) ticagrelor is highly effective for the suppression of HPR to clopidogrel after TAVR with reduced rates of HPR observed already a few hours after valve implantation and with consistent effects throughout the treatment period.

Previous studies have demonstrated that platelet reactivity is abnormally increased in patients with valvular heart disease, generating deposition of platelets and formation of thrombi on the surface of altered or diseased, natural heart valves (22). This may act as a nidus for microthrombi formation in vivo. Increased platelet activation and the thrombogenic environment in patients with severe AS undergoing aortic bioprosthesis implantation might be related to: 1) high transvalvular gradient leading to

FIGURE 2 Mean PRU Values During 3 Months of Treatment Following TAVR

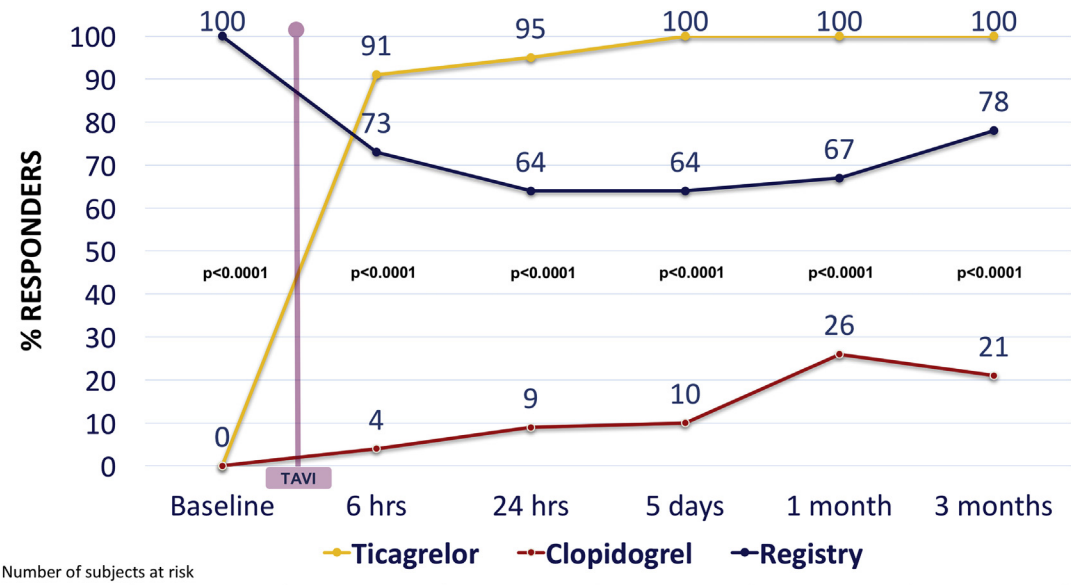


Number of subjects at risk

Ticagrelor	24	24	24	24	23	23
Clopidogrel	24	24	24	23	21	19
Registry	20	19	19	19	17	17

HPR = high platelet reactivity; other abbreviations as in Figure 1.

FIGURE 3 Responders to $P2Y_{12}$ Inhibitors

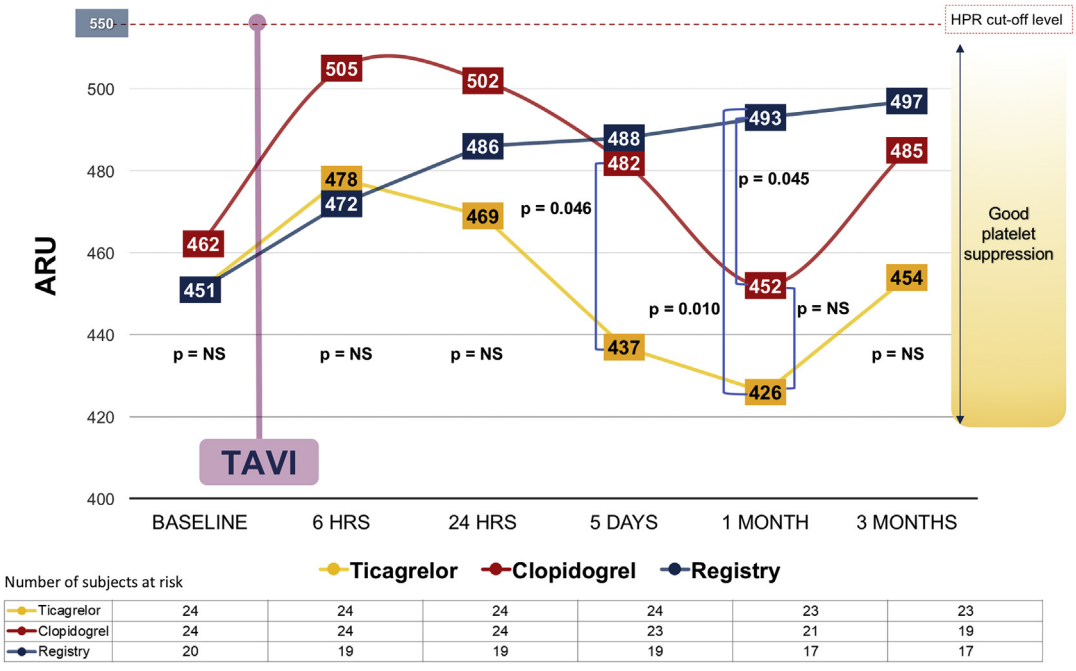


Number of subjects at risk

Ticagrelor	24	24	24	24	23	23
Clopidogrel	24	24	24	23	21	19
Registry	20	19	19	19	17	17

TAVR = transcatheter aortic valve replacement.

FIGURE 4 Mean ARU Values During 3 Months of Treatment Following TAVR



Number of subjects at risk

Ticagrelor	24	24	24	24	23	23
Clopidogrel	24	24	24	23	21	19
Registry	20	19	19	19	17	17

ARU = aspirin reactivity units; NS, nonsignificant; other abbreviations as in Figures 1 and 2.

increased shear stress and endothelial injury, thereby promoting platelet adhesion and activation; 2) altered aortic blood flow and activation of various prothrombotic factors (23-26) (von Willebrand factor, factor VIII); 3) exposure of subendothelial thrombus-producing materials and release of activated thrombotic factors, such as tissue factor and thrombin, from degenerated native aortic valve leaflets (27) into the circulation generating microthromboemboli (28); and 4) poor antiplatelet effects leading to accumulation of fibrin in the stent valve and microthrombi formation on the nonendothelialized surface of the bovine pericardial tissue leaflets, due to microfissures (potentially produced during crimping) prone to platelet adhesion (**Figure 5**).

Also, abnormal functional characteristics of platelets in patients with valvular heart disease have been documented, compared with normal subjects, consisting of morphological alterations and with subendothelial components, such as collagen fibers, exposed to the circulating blood with platelet aggregates adhering to collagen fibers. Moreover, abnormally increased thromboplastic activity and decreased fibrinolytic capacity in histopathology analysis of rheumatic mitral valves have been described (29). These features may explain the hyperactive platelet response found in these patients sustaining a thrombogenic environment.

Platelets are well known to play a major role in coronary stent thrombosis and adequate antiplatelet therapy protects against this phenomenon (17,18,30-34). However, the role of platelets and thus that of antiplatelet therapy in the development of clinical (transient ischemic attack, stroke, valve thrombosis) or subclinical (hypoattenuated leaflet thickening and reduced leaflet motion) thrombotic events after a percutaneous or surgical implant of an aortic bioprosthesis (35-37) is less established. Theoretically, poor antiplatelet response (i.e., presence of HPR) after bioprosthesis implantation could promote fibrin deposition and platelet aggregation, favoring the thickening of valvular leaflets and bioprosthetic structures, a phenomenon that would end with the formation of thrombotic material. Symptomatic increased pressure gradients with thickened leaflet tips, leaflet adhesion, and impairing proper opening but with no evidence of thrombi have been described after early discontinuation of DAPT, with complete resolution after DAPT resume (38). Also, acute cerebral occlusion by a fresh thrombus consisting mainly of accumulations of fibrin and platelets during TAVR, have been reported (39). Ongoing clinical trials are

TABLE 3 Clinical Events at 4-Month Follow-Up

	Normal Platelet Reactivity Registry (n = 20)	*p Value Registry vs. Randomized	†p Value Registry vs. Clopidogrel + Aspirin	‡p Value Registry vs. Ticagrelor + Aspirin	High On-Treatment Platelet Reactivity		§p Value
					Clopidogrel + Aspirin (n = 24)	Ticagrelor + Aspirin (n = 24)	
Death	2 (10.0)	1.00	0.67	0.20	4 (16.7)	0 (0.0)	0.10
Stroke	1 (5.0)	0.50	1.00	0.45	1 (4.2)	0 (0.0)	1.00
Myocardial infarction	1 (5.0)	0.29	0.45	0.45	0 (0.0)	0 (0.0)	NA
Major bleeding	1 (5.0)	0.15	0.54	0.61	7 (29.2)	3 (12.5)	0.28
MACE	3 (15.0)	0.68	0.71	0.08	5 (20.8)	0 (0.0)	0.05
NACE	4 (20.0)	0.43	0.07	0.68	11 (45.8)	3 (12.5)	0.01
All bleeding events	1 (5.0)	0.09	0.05	0.35	7 (29.2)	4 (16.7)	0.49
Acute renal failure	0 (0.0)	1.00	NA	1.00	0 (0.0)	1 (4.2)	1.00
Vascular complication	0 (0.0)	0.55	0.49	1.00	2 (8.3)	1 (4.2)	1.00
Vascular closure device failure	0 (0.0)	0.55	1.00	0.49	1 (4.2)	2 (8.3)	1.00
Arrhythmias and conduction disturbances	2 (10.0)	0.19	0.15	0.25	7 (29.2)	6 (25.0)	1.00

Values are n (%). *p values of comparison between the registry group and the randomized group. †p values of comparison between the registry group and the clopidogrel + aspirin group. ‡p values of comparison between the registry group and the ticagrelor + aspirin group. §p values of comparison between both randomized groups. All events are according Valve Academic Research Consortium-2 criteria. MACE includes death, stroke, and myocardial infarction. NACE includes death, stroke, myocardial infarction, and major bleeding.

MACE = major adverse cardiovascular event(s); NACE = net adverse clinical event(s).

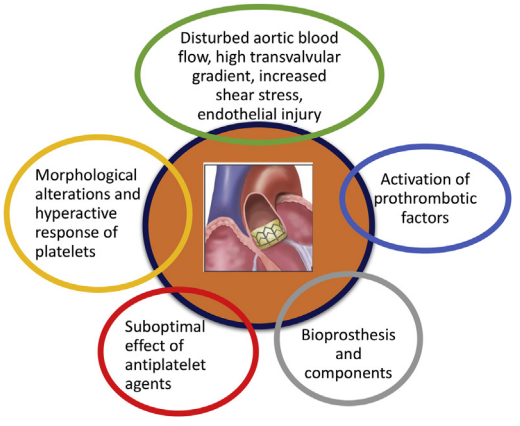
evaluating oral anticoagulation and DAPT in TAVR patients without atrial fibrillation and will help to define the role of platelets and thrombin on thrombotic events after TAVR (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes [GALILEO], NCT02556203; Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI [AUREA], NCT01642134).

The TAVR population is continuously increasing and poses unique challenges on implementing the optimal antithrombotic regimen. Overall, our results confirm the superior potency of ticagrelor over clopidogrel to achieve prompt and potent platelet inhibitory effects in a new challenging scenario, comparable to what has been described in prior investigations conducted in other clinical settings (40,41). Notably, by the 6-h time point after TAVR, <10% of ticagrelor-treated patients still had HPR. The suppression of HPR with ticagrelor was reached in 100% at 5 days post-TAVR, remaining unchanged during follow-up in all patients. Furthermore, the fact that over 30% of patients initially responding to clopidogrel became nonresponders during the first month after valve implantation, highlights the significant increase in platelet reactivity induced by the bioprosthetic valve implantation procedures and its components at an early stage (use of large-bore catheters and stiff guidewire in the left ventricle, pre-/post-dilation with disruption of native aortic valve leaflets, and calcifications of the aortic valve annulus and aortic arch), as well as the poor efficacy of clopidogrel to maintain adequate platelet inhibition during the following 3 months after TAVR.

Therefore, ticagrelor represent an attractive alternative to clopidogrel, not only to treat HPR, but also to prevent this from occurring in patients who may present with optimal response to clopidogrel before TAVR.

Platelet reactivity seems to be a dynamic phenomenon, giving relevance to the effect of the timing of measurement on the level of reactivity. Also, interindividual variability in the platelet inhibitory response

FIGURE 5 Potential Factors Leading to Increased Platelet Activation and Prothrombotic Environment in Patients With AS Undergoing TAVR



AS = aortic stenosis; TAVR = transcatheter aortic valve replacement.

to clopidogrel has been demonstrated in patients undergoing elective coronary stenting. Gurbel et al. (42), found that the maximum inhibitory response to a 300-mg loading dose of clopidogrel occurs within 24 h. In GRAVITAS (Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety) trial (43), HPR measured 12 to 24 h after percutaneous coronary intervention resolved at the 30-day follow-up in 38% of the patients randomly assigned to standard-dose clopidogrel. In our study, 79% of patients were on long-term (>30 days) use of clopidogrel, and the remaining 29% clopidogrel-naive patients received a 300-mg loading dose, with evaluation of platelet reactivity 24 h after the loading dose. This heterogeneity to timing of baseline platelet function assessment with relationship to timing of clopidogrel intake may explain why 21% of patients initially identified to be nonresponders became responders after TAVR. Furthermore, the Hawthorne effect could also have a role in this change. Hence, the clinical, procedural, and genetic predictors of the early resolution of HPR after TAVR deserve further evaluation.

STUDY LIMITATIONS. The HPR cutoff point used in our study was the cutoff recommended for the evaluation of thrombotic events in patients with coronary artery disease. But, the HPR cutoff for assessing thrombotic events in the TAVR population is still unclear. Given the pharmacodynamic design of the study, it was underpowered for clinical endpoints warranted by adequately powered studies for this purpose.

CONCLUSIONS

Our data suggest that patients undergoing TAVR for severe AS and treated with clopidogrel have high rates of residual platelet reactivity during the periprocedural period, with a significant increase in platelet reactivity during the first month after TAVR and that may last for up to 3 months thereafter, casting doubts of its efficacy in this setting. Ticagrelor achieves a better and faster effect, providing sustained benefit to these patients over the course of the treatment period without safety concerns. Larger studies are urgently needed to define its clinical benefit in this setting.

ADDRESS FOR CORRESPONDENCE: Dr. Victor A. Jimenez Diaz, Cardiology Department, Hospital Alvaro Cunqueiro, University Hospital of Vigo, Estrada Clara Campoamor 341, Vigo 36312, Spain. E-mail: victor.alfonso.jimenez.diaz@sergas.es.

PERSPECTIVES

WHAT IS KNOWN? Lack of compelling evidence exists on the efficacy of aspirin + clopidogrel as antithrombotic treatment in patients with severe AS undergoing TAVR.

WHAT IS NEW? HPR to clopidogrel is present in a considerable number of patients with AS undergoing TAVR and more than one third of patients initially responders to clopidogrel become nonresponder during the treatment period. Ticagrelor achieves a better and faster effect providing sustained suppression of HPR to these patients.

WHAT IS NEXT? Larger clinical trials are needed to assess the clinical implications of these findings.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.

2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

3. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.

4. Kapadia S, Agarwal S, Miller DC, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the PARTNER trial (Placement of Aortic Transcatheter Valves). Circ Cardiovasc Interv 2016;9:e002981.

5. Rodes-Cabau J, Dauerman HL, Cohen MG, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. J Am Coll Cardiol 2013;62:2349–59.

6. Piccolo R, Pilgrim T, Franzone A, et al. Frequency, timing, and impact of access-site and non-access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2017;10:1436–46.

7. Tay EL, Gurvitch R, Wijesinghe N, et al. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2011;4:1290–7.

8. 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.

9. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

10. Cerrato E, Nombela-Franco L, Nazif TM, et al. Evaluation of current practices in transcatheter aortic valve implantation: the WRITTEN (WoRld-wIde TAVI ExperieNce) survey. Int J Cardiol 2017;228:640–7.

11. Ahmad Y, Demir O, Rajkumar C, et al. Optimal antiplatelet strategy after transcatheter aortic valve implantation: a meta-analysis. Open Heart 2017;5:e000748.

12. Angiolillo DJ. Variability in responsiveness to oral antiplatelet therapy. Am J Cardiol 2009;103:27A–34A.

13. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response

to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429–36.

14. Neubauer H, Kaiser A, Busse B, et al. Identification, evaluation and treatment of prasugrel low-response after coronary stent implantation—a preliminary study. Thromb Res 2010;126:e389–91.

15. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67–74.

16. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

17. Tantry US, Bonello L, Aradi D, et al., for the Working Group on On-Treatment Platelet Reactivity. 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.

18. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12 inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015;36:1762–71.

19. Tousek P, Kocka V, Sulzenko J, et al. Pharmacodynamic effect of clopidogrel in patients undergoing transcatheter aortic valve implantation. Biomed Res Int 2013;2013:386074.

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

21. 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.

22. Riddle JM, Stein PD, Magilligan DJ Jr., McElroy HH. Evaluation of platelet reactivity in patients with valvular heart disease. J Am Coll Cardiol 1983;1:1381–4.

23. Jaffer IH, Fredenburgh JC, Hirsh J, et al. Medical device-induced thrombosis: what causes it and how can we prevent it? J Thromb Haemost 2015;13 Suppl 1:S72–81.

24. Kopanidis A, Pantos I, Alexopoulos N, et al. Aortic flow patterns after simulated implantation of transcatheter aortic valves. Hellenic J Cardiol 2015;56:418–28.

25. Spiel AO, Gilbert JC, Jilma B. von Willebrand factor in cardiovascular disease: focus on acute coronary syndromes. Circulation 2008;117:1449–59.

26. Van Belle E, Rauch A, Vincent F, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. N Engl J Med 2016;375:335–44.

27. Otto CM, Prendergast B. Aortic-valve stenosis—from patients at risk to severe valve obstruction. N Engl J Med 2014;371:744–56.

28. Van Mieghem NM, Schipper ME, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. Circulation 2013;127:2194–201.

29. Homma T, Okudaira S, Iida Y. Studies on thromboplastic and fibrinolytic activities of valvular tissue in rheumatic valvular disease. Res Exp Med (Berl) 1980;176:193–200.

30. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614–23.

31. Aradi D, Storey RF, Komocsi A, et al. Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. Eur Heart J 2014;35:209–15.

32. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING study. J Am Coll Cardiol 2005;46:1820–6.

33. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST study. J Am Coll Cardiol 2005;46:1827–32.

34. Wenaweser P, Dorffler-Melly J, Imboden K, et al. Stent thrombosis is associated with an impaired response to antiplatelet therapy. J Am Coll Cardiol 2005;45:1748–52.

35. 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.

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

37. 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.

38. Al-Rashid F, Konorza TFM, Plicht B, et al. Transient increase in pressure gradients after termination of dual antiplatelet therapy in a patient after transfemoral aortic valve implantation. Circ Cardiovasc Interv 2012;5:318–20.

39. Jimenez Diaz VA, Baz Alonso JA, Estevez Ojea O, Serantes Combo A, Rodriguez Paz CM, Iñiguez Romo A. Real-time detection of an acute cerebral thrombotic occlusion during a transcatheter valve intervention. J Am Coll Cardiol Intv 2018;11:e103–4.

40. Bliden KP, Tantry US, Storey RF, et al. The effect of ticagrelor versus clopidogrel on high on-treatment platelet reactivity: combined analysis of the ONSET/OFFSET and RESPOND studies. Am Heart J 2011;162:160–5.

41. Alexopoulos D, Galati A, Xanthopoulou I, et al. Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. J Am Coll Cardiol 2012;60:193–9.

42. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.

43. Price MJ, Berger PB, Teirstein PS, et al., for the GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention. The GRAVITAS randomized trial. JAMA 2011;305:1097–105.

KEY WORDS antithrombotic therapy, aortic stenosis, high platelet reactivity, transcatheter aortic valve replacement, VerifyNow

APPENDIX For supplemental methods and a list of the trial investigators, coordinators, committees, and study sites, please see the online version of this paper.