Usefulness of Clopidogrel Loading in Patients Who Underwent Transcatheter Aortic Valve Implantation (from the BRAVO-3 Randomized Trial)

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$P2Y_{12}$-inhibitor initiation with clopidogrel using a loading dose (LD) versus no LD (NLD) provides more rapid inhibition of platelet activation and reduced risk of ischemic events after coronary stenting. Whether a similar beneficial effect is achieved in the setting of transcatheter aortic valve implantation (TAVI) is unknown. We evaluate the effects of preprocedural clopidogrel LD versus no NLD on 48-hour and 30-day clinical outcomes after TAVI. In the BRAVO-3 trial, 802 patients with severe aortic stenosis who underwent transfemoral TAVI were randomized to intraprocedural anticoagulation with bivalirudin or unfractionated heparin. Administration of clopidogrel LD was left to the discretion of the treating physician. For this analysis, patients were stratified according to receiving clopidogrel LD (n = 294, 36.6%) or NLD (n = 508, 63.4%) before TAVI. LD patients more often received a self-expandable prosthesis using larger sheaths. $P2Y_{12}$-inhibitor maintenance therapy pre-TAVI was similar in patients with LD versus NLD (28.2% vs 33.1%, p = 0.16). LD versus NLD was associated with similar incidences of major adverse cardiovascular events (i e., death, myocardial infarction, or stroke) (4.1% vs 4.1%, p = 0.97) and major bleeding (8.5% vs 7.7%, p = 0.68), but a higher rate of major vascular complications (11.9% vs 7.1%, p = 0.02). Multivariable adjustment showed that clopidogrel LD did not affect any of the studied clinical events, including major vascular complications (odds ratio 0.91, 95% confidence interval 0.60 to 1.39, p = 0.67). Also patients on clopidogrel maintenance therapy and thus considered in steady state were not at reduced risk of major adverse cardiovascular events compared with patients not on clopidogrel (3.7% vs 5.2%, p = 0.36). In conclusion, in patients who underwent TAVI, use of clopidogrel LD was associated with higher vascular complications and otherwise similar clinical events compared to NLD patients. **(Am J Cardiol 2019;123:1494−1500)**

The efficacy and safety of transcatheter aortic valve implantation (TAVI) for the treatment of severe symptomatic aortic valve stenosis has been demonstrated in several randomized clinical trials in both intermediate- and high-risk patients.[1−5] Patients who underwent TAVI are at a considerable risk of both bleeding and thromboembolic complications.[6] Currently, antiplatelet therapy using a combination of acetylsalicylic acid and clopidogrel after TAVI is recommended.[7−10] Appropriate platelet inhibition is of special importance in the elderly population who underwent TAVI, given the difficulty in balancing the relative high risks of bleeding events as well as thromboembolic events such as valve thrombosis and stroke.[11−16] However, reflecting the paucity of evidence available in the

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field, the vast majority of clinicians does not treat according to the current guidelines resulting in very diverse patterns of drugs and combinations.[17] In patients who underwent coronary stenting, a preprocedural loading dose (LD) of clopidogrel provides additional platelet inhibition resulting in a reduced risk of ischemic events at the cost of bleeding.[18–21] However, evidence on preprocedural LD administration of clopidogrel in TAVI patients is lacking and loading regimens are highly variable. In the multicenter prospective, randomized controlled BRAVO-3 trial (Effect of Bivalirudin on Aortic Valve Intervention Outcomes-3),[22] 802 patients with aortic stenosis who underwent TAVI were randomized to intraprocedure anticoagulation with unfractionated heparin or bivalirudin. In the present analysis, we evaluated the effect of preprocedural clopidogrel LD versus no LD (NLD) on 48-hour and 30-day clinical outcomes.

Methods

The BRAVO-3 trial design has been described elsewhere.[23] In brief, this study was a prospective, open label, randomized controlled trial of 802 patients enrolled at 31 European and North American sites. The institutional review board or ethics committee at each center approved the study protocol. The Icahn School of Medicine at Mount Sinai coordinated the study. An independent clinical events committee blinded to treatment assignment reviewed original source documents and adjudicated all major clinical events. An independent data safety monitoring board was responsible for study oversight.

Eligible patients had severe symptomatic aortic stenosis, high surgical risk (defined as a European System for Cardiac Operative Risk Evaluation score of ≥18, or deemed inoperable), and were scheduled for transfemoral TAVI. The main exclusion criteria were planned surgical cut-down access; presence of a previous mechanical or mitral bioprosthetic valve; severe left ventricular dysfunction (ejection fraction <15%); minimal luminal diameter <6.5 mm for the common femoral artery; severe aortic or mitral regurgitation; concurrent percutaneous coronary intervention; recent bleeding or neurological event; and dialysis dependence. The full lists of inclusion and exclusion criteria are provided elsewhere.[22] All patients provided written informed consent before inclusion.

Patients were randomized 1:1 to either administration of intraprocedure anticoagulation with unfractionated heparin or bivalirudin (Angiomax/Angiox, The Medicines Company, Parsippany, New Jersey). Bivalirudin was administered as a 0.75 mg/kg bolus plus infusion of 1.75 mg/kg/h in patients with an estimated glomerular filtration rate (GFR) ≥60 ml/min/1.73 m^2. The infusion dose was stepwise decreased according to the underlying degree of renal impairment (i.e., 1.4 mg/kg/h in patients with a GFR of 30 to 59 ml/min/1.73 m^2, 1 mg/kg/h in patients with a GFR <30 ml/min/1.73 m^2). The infusion was stopped after successful valve implantation. The recommended target activated clotting time for patients randomized to unfractionated heparin was >250 seconds; the decision for reversal with protamine after TAVI was left to the implanters' discretion.

Before TAVI, treatment with oral anti-Xa or antithrombin agents within 48 hours and warfarin within 72 hours was not permitted. After TAVI, study recommendations were for patients to receive aspirin at a dosage of 75 to 100 mg/day for at least 1 year and clopidogrel at 75 mg/day for a period defined by institutional standard practices. Administration of clopidogrel LD was done pre-TAVI. The dosage of the clopidogrel LD was left to the investigator's discretion. Ticlopidine was permitted in case of clopidogrel allergy or unavailability. The treatment, dosage, and period of administration for the study drug and concomitant medication were documented in all patients.

The primary end point definitions have been previously described in detail.[22] Composite major adverse cardiovascular events (MACE) included death, myocardial infarction (MI), or stroke. Net adverse cardiac events (NACE) included MACE or Bleeding Academic Research Consortium (BARC) ≥3b bleeding.[24] Other secondary end points included bleeding defined according to additional bleeding scales (i.e., Thrombolysis In Myocardial Infarction,[25] Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries,[26] Acute Catheterization and Urgent Intervention Triage Strategy/Harmonizing Outcomes with Revascularisation and Stents in Acute Myocardial Infarction,[27,28] Valve Academic Research Consortium[29] and other BARC types. Other outcomes of interest included acute kidney injury, transient ischemic attacks, vascular complications, and acquired thrombocytopenia. All outcomes were assessed at 48 hours or hospital discharge, whichever occurred first.

In the current analysis, comparisons were made according to the administration of clopidogrel LD or NLD. Continuous variables are reported as mean ± standard deviation or median (interquartile range) and were tested using the Student's t test. Categorical baseline variables and binary outcomes are reported as frequencies and percentages and were tested using the chi-square test. We determined the multivariable predictors of 48-hour clinical outcomes using logistic regression analyses, generating odds ratios and 95% confidence intervals (CI) associated with baseline and procedural covariates including clopidogrel LD versus NLD. Since there were no differences between unfractionated heparin and bivalirudin in any important end point in the main study, we pooled all patients in the present analysis. To account for the possible confounding effect of preprocedural clopidogrel maintenance therapy, we performed a sensitivity analysis in clopidogrel naïve patients. In a second sensitivity analysis, we included all patients with preprocedural clopidogrel maintenance therapy considered as loaded, since they would have achieved a steady state of drug level. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Of 802 patients enrolled in the BRAVO-3 trial, 294 (36.6%) received clopidogrel LD and 508 (63.4%) NLD. Clopidogrel LD was 300 mg in 252 (85.7%) and 600 mg in 42 (14.3%) patients. All patients received their LD before TAVI, mainly within 6 hours (n = 229 [77.9%]). Baseline

Table 1
Baseline characteristics

Variable	Loading dose (n = 294)	No loading dose (n = 508)	p value
Age (years)	82 ± 7	82 ± 6	0.64
Women	133 (45%)	258 (51%)	0.13
Logistic EuroSCORE (%)	17 ± 10	17 ± 11	0.22
Diabetes mellitus	91 (31%)	148 (29%)	0.59
Chronic kidney disease*	167 (57%)	271 (53%)	0.64
Peripheral artery disease	39 (13%)	80 (16%)	0.35
Stroke or transient ischemic attack	24 (8%)	59 (12%)	0.12
Chronic obstructive pulmonary disease	54 (18%)	101 (20%)	0.60
Left ventricular ejection fraction (%)	54 ± 13	53 ± 13	0.08
Coronary artery disease	144 (49%)	261 (52%)	0.50
Myocardial infarction	48 (17%)	68 (14%)	0.23
Atrial fibrillation	94 (32%)	203 (40%)	0.03
Coronary artery bypass graft surgery	55 (19%)	62 (12%)	0.01
Balloon aortic valvuloplasty	11 (4%)	49 (10%)	<0.01
Hemoglobin (g/dl)	13 ± 2	13 ± 2	0.66
Platelet count ($\times 10^9$/l)	239 ± 243	290 ± 395	0.23
Prior maintenance therapy			
Aspirin	214 (73%)	334 (66%)	0.05
≤160 mg	206 (96%)	326 (97%)	0.49
Clopidogrel	82 (99%)	162 (97%)	0.67
Ticagrelor	1 (1%)	0	NA
Prasugrel	0	5 (3%)	NA
Aspirin plus $P2Y_{12}$ inhibitor	71 (24%)	143 (28%)	0.20
Prior clopidogrel loading ≤6 hours	229 (78%)	0	NA
Prior clopidogrel loading dose 300 mg	252 (86%)	0	NA

Continuous values are presented as mean ± SD and categorical values as n (%). EuroSCORE = European System for Cardiac Operative Risk Evaluation.
* Defined as estimated glomerular filtration rate < 60 ml/min per 1.73 m^2.

clinical characteristics were generally well matched between the 2 groups (Table 1), except for a higher prevalence of previous coronary artery bypass graft and a lower prevalence of previous aortic valvuloplasty and atrial fibrillation in the LD group. Additionally, patients in the LD group were more likely to be treated with a self-expandable prosthesis and a larger sheath size (Table 2). Post-TAVI, patients in the LD group more frequently received a $P2Y_{12}$ inhibitor (Table 2).

Outcomes at 48 hours and 30 days are summarized in Table 3 and shown in Figure 1. Minimal change between both time points is apparent. At 48 hours, major bleeding (BARC ≥3b) occurred in 8.5% of patients who received clopidogrel LD compared with 7.7% of patients who received NLD (relative risk: 1.11; 95% CI: 0.68 to 1.79; p = 0.68). Rates of stroke, MI, acute kidney injury, or death did not differ between both groups. Rates of MACE were 4.1% in both groups. The rate of NACE was 10.5% with LD and 10.8% with NLD (relative risk: 0.97; 95% CI: 0.64 to 1.48; p = 0.91). Major vascular complications were more frequent after LD (11.9% vs 7.1%, p = 0.02; relative risk: 1.68; 95% CI 1.08 to 2.61; p = 0.02), whereas the rate of minor vascular complication did not differ. Clopidogrel LD was also not associated with thrombocytopenia post-TAVI.

The results of multivariable analysis are shown in Table 4. Clopidogrel LD did not affect MACE, major vascular complications or bleeding.

Regarding the effects of preprocedural clopidogrel maintenance therapy, sensitivity analyses in clopidogrel naïve patients showed no important differences in the primary conclusions (Supplement 1). In a secondary analysis, we compared patients with either a LD clopidogrel or maintenance therapy with clopidogrel pre-TAVI (n = 590) to those who received no clopidogrel pre-TAVI (n = 212). No significant differences were found in MACE, NACE or the individual end points (Supplement 2).

Discussion

The present study represents the first report examining the impact of a LD of clopidogrel on early clinical outcomes in patients with a severe aortic stenosis who underwent TAVI. The major findings of the present study are that in patients who underwent TAVI, a clopidogrel LD was not associated with lower rates of mortality, stroke, MI, or the composite MACE. Additionally, clopidogrel LD was not associated with increased rates of major bleeding or thrombocytopenia. Although clopidogrel LD was associated with a higher rate of major vascular complications, this risk was attenuated after adjustment for baseline characteristics. Also patients already loaded and thus considered in steady state were not at reduced risk of MACE.

Clopidogrel is well established for use in patients with acute coronary syndromes at a LD of 300 to 600 mg followed by a maintenance dosage of 75 mg/day.[30] Clopidogrel acts by selectively and irreversibly inhibiting the $P2Y_{12}$ platelet receptor.[31] Activation of the $P2Y_{12}$ receptor leads to subsequent activation of the glycoprotein IIb/IIIa receptor, granule

Table 2
Procedural characteristics

Variable	Loading dose (n = 294)	No loading dose (n = 508)	p value
Procedural success	290 (99%)	491 (97%)	0.09
Valve type			<0.01
Balloon expandable	159 (55%)	341 (69%)	
Self-expandable	130 (45%)	152 (31%)	
Other	3 (1%)	2 (0%)	
Sheath size of valve system			<0.01
<18 French	37 (13%)	218 (24%)	
18 French	198 (69%)	226 (46%)	
>18 French	54 (19%)	40 (8%)	
Valvuloplasty performed	240 (82%)	398 (79%)	0.34
Postdilation performed	55 (19%)	144 (29%)	<0.01
Additional TAVI device used	14 (5%)	14 (3%)	0.15
Embolic protection device used	4 (1%)	7 (1%)	0.78
Closure technique used for valve implantation access site			0.78
Not attempted	3 (1%)	4 (1%)	
Successful deployment	267 (91%)	459 (93%)	
Attempted but failed	23 (8%)	33 (7%)	
Intraprocedural anticoagulation therapy			
Bivalirudin	152 (52%)	250 (50%)	0.55
Postprocedural antiplatelet therapy			
$P2Y_{12}$ inhibitor	262 (89%)	333 (66%)	<0.01
Aspirin	256 (87%)	435 (86%)	0.76
Aspirin plus $P2Y_{12}$ inhibitor	227 (77%)	299 (59%)	<0.01
Postprocedural oral ganticoagulation therapy	85 (29%)	142 (29%)	0.94

Categorical values are presented as n (%). LD indicates loading dose; NLD, no loading dose; TAVI, transcatheter aortic valve implantation.

release, amplification of platelet aggregation, and stabilization of the platelet aggregate. Clopidogrel is an inactive prodrug of which 15% is oxidized by the hepatic cytochrome P450 (CYP) system to generate an active metabolite. A LD of 300 mg is known to result in a platelet aggregation inhibition of 30% to 40%, at a time to peak effect of 4 to 6 hours.[32,33] However, the clopidogrel-induced antiplatelet effect is variable and a considerable number of patients may have poorer effects (i.e. low-responders), depending on factors at genetic, cellular, and clinical level.[34,35]

Table 3
Clinical outcomes

	48 hours			30 days		
Variable	Loading dose (n = 294)	No loading dose (n = 508)	p value	Loading dose (n = 294)	No loading dose (n = 508)	p value
Net-adverse cardiac events	31 (11%)	55 (11%)	0.90	43 (15%)	79 (16%)	0.73
Major adverse cardiovascular events	12 (4%)	21 (4%)	0.97	24 (8%)	39 (8%)	0.81
Death	3 (1%)	10 (2%)	0.39	15 (5%)	23 (5%)	0.71
Myocardial infarction	2 (1%)	3 (1%)	1.00	5 (2%)	4 (1%)	0.30
Stroke	7 (2%)	9 (2%)	0.55	8 (3%)	17 (3%)	0.62
Bleeding						
VARC (life-threatening or major)	62 (21%)	104 (21%)	0.84	74 (25%)	131 (26%)	0.70
TIMI (major)	15 (5%)	27 (5%)	0.90	18 (6%)	34 (7%)	0.75
GUSTO (severe/life-threatening)	11 (4%)	17 (3%)	0.77	14 (5%)	20 (4%)	0.58
ACUITY/HORIZONS (major)	74 (25%)	128 (25%)	0.99	86 (29%)	167 (33%)	0.29
Major bleeding (BARC ≥3b)	25 (9%)	39 (8%)	0.68	29 (10%)	49 (10%)	0.92
BARC 3a	43 (15%)	73 (14%)	0.92	52 (18%)	93 (18%)	0.83
BARC 1 and 2	63 (21%)	105 (21%)	0.80	80 (27%)	134 (26%)	0.80
TIMI minor	45 (15%)	79 (16%)	0.93	57 (19%)	106 (21%)	0.62
Acute kidney injury	26 (9%)	44 (9%)	0.93	51 (17%)	80 (16%)	0.56
Minor vascular complications	23 (8%)	53 (10%)	0.22	26 (9%)	57 (11%)	0.29
Major vascular complications	35 (12%)	36 (7%)	0.02	38 (13%)	37 (7%)	0.01
Thrombocytopenia	48 (16%)	88 (17%)	0.72	67 (23%)	122 (24%)	0.69

Continuous values are presented as mean ± SD and categorical values as n (%). ACUITY/HORIZONS = Acute Catheterisation and Urgent Intervention Triage Strategy/Harmonizing Outcomes with Revascularisation and Stents in Acute Myocardial Infarction[27,28]; BARC = Bleeding Academic Research Consortium[24]; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries[26]; TIMI = Thrombolysis In Myocardial Infarction[25]; VARC = Valve Academic Research Consortium.[29]

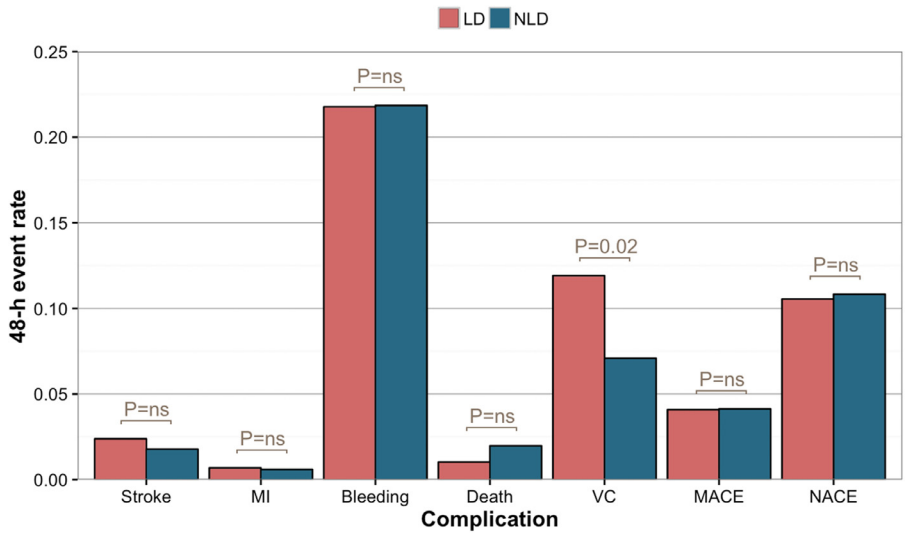

Figure 1. Clinical outcomes after transcatheter aortic valve implantation according to administration of clopidogrel loading dose (LD) or no loading dose (NLD). Bleeding represents bleeding according to the Bleeding Academic Research Consortium (BARC) ≥3. MACE = major adverse cardiac events; MI = myocardial infarction; NACE = net adverse cardiac events; ns = nonsignificant; VC = major vascular complication.

This is the first study investigating the role of a clopidogrel LD in patients who underwent TAVI. Current guidelines recommend to administer clopidogrel for 1 to 6 months after TAVI using a LD of 300 mg followed by a maintenance dosage of 75 mg/day.[8,36] This regimen is mainly based upon our understanding of platelet based ischemic events after coronary stent implantation, the time needed for endothelialization of the prosthesis, as well as the Siegburg first-in-man CoreValve study.[37] In the latter study, more severe thrombocytopenia was found in those who did not receive clopidogrel compared with those who did. However, in the present study, we found that the rate of thrombocytopenia between LD and NLD patients did not differ. This is in line with other data showing that persistent thrombocytopenia is similar in patients treated with and without clopidogrel.[38]

We observed no differences in the rate of ischemic complications after TAVI such as stroke and MI between clopidogrel LD and NLD. Three small randomized studies explored the role of clopidogrel maintenance after TAVI and compared dual antiplatelet therapy (DAPT) with aspirin monotherapy.[39–41] Ussia et al showed no significant differences between DAPT and aspirin monotherapy with respect to MACE up to 6 months in 79 patients.[40] In the Single Antiplatelet Therapy for TAVI (SAT-TAVI) trial (N = 120), the rate MACE did not differ between DAPT and aspirin monotherapy at 30 days, but the rate of vascular access site related complications was lower for aspirin monotherapy.[41] In the Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation trial, randomization to DAPT versus aspirin monotherapy in 222 patients resulted in an increased risk of major or life-threatening bleeding events while not reducing the risk of MI or stroke at 3 months.[39]

Table 4
Multivariable regression results for 48-hour outcomes

Variable	Odds ratio	95% Confidence interval	p value
Major adverse cardiovascular events	0.75	[0.32-1.74]	0.501
Major vascular complication	0.91	[0.60-1.39]	0.669
Bleeding ≥ BARC 3b	0.87	[0.48-1.58]	0.648

Values are provided as odd ratio (OR) with their corresponding confidence intervals (CI) for clinical outcomes at 48 hours after transcatheter aortic valve implantation (TAVI) according to the administration of a clopidogrel loading dose. Values are adjusted for: age >80, gender, left ventricular ejection fraction <50%, no aspirin post-TAVI, no clopidogrel post-TAVI, clopidogrel maintenance pre-TAVI, self-expanding prosthesis, sheath size ≥18 French, procedural Bivalirudin, and postprocedural oral anticoagulation. BARC = Bleeding Academic Research Consortium.[24]

In the present study, the LD clopidogrel did not increase the rate of bleeding or reduce MACE after TAVI. Clopidogrel LD was not associated with a higher rate of major vascular complications after multivariable adjustment for baseline and procedural variables including sheath size and postprocedural anticoagulation. Whether this holds for clopidogrel maintenance therapy at longer term post-TAVI will be clarified by the currently recruiting Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial.[42]

Although we found no effects of clopidogrel LD in the reduction of MACE, the strength of the clopidogrel LD may matter. In the present study, the majority of patients (86%) received 300 mg LD. Increasing the dosage to 600 mg increases platelet aggregation inhibition to over 40%, at a time to peak effect of approximately 2 hours (vs 4 to 6 hours), and significantly reduces the incidence of clopidogrel hyporesponsiveness.[32,33] This is associated with a reduced risk of ischemic events in patients who underwent percutaneous coronary intervention.[21,43] However, patients who underwent TAVI widely differ from these populations, with numerous potential factors interfering with clopidogrel pharmacokinetics and pharmacodynamics, such as poor absorption, polypharmacy with drug-drug interactions involving CYP3a4, insulin-dependent diabetes mellitus, and compliance issues. Previous studies suggested that the

majority of patients who underwent TAVI are low-responders to clopidogrel and that these patients also showed a higher decrease in platelet number versus normal-responders.[11,44] Although increasing the LD to 600 mg reduces the incidence of hyporesponsiveness, we did not find any difference in clinical outcomes between both dosages. Furthermore, in a sensitivity analysis including patients on clopidogrel maintenance therapy and thus considered in steady state showed that these patients were not at reduced risk of MACE. Therefore, the possible advantages of clopidogrel LD at 300 mg or 600 mg before TAVI seem not clinically relevant and do not outweigh the potential risks.

Although this was a prespecified analysis of the BRAVO-3 trial, outcomes were not powered according to clopidogrel LD and results may be affected by a selection bias by the treating physician. The exact timing of clopidogrel LD administration was not registered and platelet reactivity testing was not performed, therefore we could not consider the time to peak effect. In the present study, no cases of clinical valve thrombosis were encountered, but follow-up was limited to 30-days; further post-TAVI computed tomographic imaging was not mandated by the study protocol. Therefore, this issue remains to be further investigated.

In conclusion, in this analysis from the BRAVO-3 trial, clopidogrel LD versus NLD was not associated with any significant differences in ischemic or bleeding events, except for a higher incidence vascular complications that was no longer present after multivariate adjustment. Therefore, the potential advantages of clopidogrel LD do not seem clinically relevant for early outcomes.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.049.

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