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Incidence, Predictors, and Prognostic Impact of Late Bleeding Complications After Transcatheter Aortic Valve Replacement

Philippe Généreux, MD,*†‡ David J. Cohen, MD, MSc,§ Michael Mack, MD,‖ Josep Rodes-Cabau, MD,¶ Mayank Yadav, MD,† Ke Xu, PhD,† Rupa Parvataneni, MS,† Rebecca Hahn, MD,*† Susheel K. Kodali, MD,*† John G. Webb, MD,# Martin B. Leon, MD*†

ABSTRACT

BACKGROUND The incidence and prognostic impact of late bleeding complications after transcatheter aortic valve replacement (TAVR) are unknown.

OBJECTIVES The aim of this study was to identify the incidence, predictors, and prognostic impact of major late bleeding complications (MLBCs) (≥30 days) after TAVR.

METHODS Clinical and echocardiographic outcomes of patients who underwent TAVR within the randomized cohorts and continued access registries in the PARTNER (Placement of Aortic Transcatheter Valves) trial were analyzed after stratifying by the occurrence of MLBCs. Predictors of MLBCs and their association with 30-day to 1-year mortality were assessed.

RESULTS Among 2,401 patients who underwent TAVR and survived to 30 days, MLBCs occurred in 142 (5.9%) at a median time of 132 days (interquartile range: 71 to 230 days) after the index procedure. Gastrointestinal complications (n = 58 [40.8%]), neurological complications (n = 22 [15.5%]), and traumatic falls (n = 11 [7.8%]) were identified as the most frequent types of MLBCs. Independent predictors of MLBCs were the presence of low hemoglobin at baseline, atrial fibrillation or flutter at baseline or 30 days, the presence of moderate or severe paravalvular leak at 30 days, and greater left ventricular mass at 30 days. MLBCs were identified as a strong independent predictor of mortality between 30 days and 1 year (adjusted hazard ratio: 3.91; 95% confidence interval: 2.67 to 5.71; $p < 0.001$).

CONCLUSIONS MLBCs after TAVR were frequent and associated with increased mortality. Better individualized and risk-adjusted antithrombotic therapy after TAVR is urgently needed in this high-risk population. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894) (J Am Coll Cardiol 2014;64:2605–15) © 2014 by the American College of Cardiology Foundation.

From the *Columbia University Medical Center/New York Presbyterian Hospital, New York, New York; †The Cardiovascular Research Foundation, New York, New York; ‡Hôpital du Sacré-Coeur de Montréal, Montreal, Quebec, Canada; §Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, Missouri; ‖Baylor Healthcare System, Plano, Texas; ¶Quebec Heart and Lung Institute, Laval University Quebec, Quebec City, Quebec, Canada; and the #St. Paul's Hospital, Vancouver, British Columbia, Canada. The PARTNER trial was funded by Edwards Lifesciences and designed collaboratively by the Steering Committee and the sponsor. Dr. Généreux has received speaker's fees from Edwards Lifesciences. Dr. Cohen has received research grant support from Medtronic, Edwards Lifesciences, Abbott Vascular, Boston Scientific, Eli Lilly, Daiichi Sankyo, AstraZeneca, and Biomet; and is a consultant for Medtronic, Eli Lilly, AstraZeneca, and Abbott Vascular. Dr. Mack has received travel reimbursements from Edwards Lifesciences related to his activities as an unpaid member of the PARTNER Executive Committee. Dr. Rodes-Cabau has received grant support from Boston Scientific Corporation and Edwards Lifesciences and has received consulting fees and honoraria from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo/Eli Lilly, GlaxoSmithKline, Janssen, Merck/Schering-Plough, and Regeneron. Dr. Hahn has received consulting fees from Edwards Lifesciences; and research support from Philips Healthcare. Dr. Kodali is a consultant for Edwards Lifesciences; is a member of the PARTNER Trial Steering Committee; is on the Steering Committee for the Portico Trial (St. Jude Medical); and is on the Scientific Advisory Board of Thubrikar Aortic Valve. Dr. Webb is a consultant for Edwards Lifesciences; and an unpaid member of the PARTNER Executive Committee. Dr. Leon has received travel reimbursements from Edwards Lifesciences related to his activities as an unpaid

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BARC = Bleeding Academic Research Consortium

GI = gastrointestinal

MLBC = major late bleeding complication

PVL = paravalvular leak

TAVR = transcatheter aortic valve replacement

Periprocedural bleeding events after transcatheter aortic valve replacement (TAVR) are frequent and have been shown to be associated with worse prognosis (1-6). Although early bleeding complications after TAVR are related mainly to procedural or technical factors (e.g., vascular complications) (7-9), the cause, nature, and impact of late bleeding (after 30 days) in this population remain unknown. Given the advanced age and the presence of multiple comorbidities, including atrial fibrillation (AF) or coronary artery disease, among the currently treated TAVR population (10-20), it is to be expected that late bleeding events, especially in the context of routine dual-antiplatelet therapy and/or anticoagulation, will be frequent and will adversely affect long-term prognosis (21). As a first

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step to better define and individualize antithrombotic therapy after TAVR (3,21,22) and to inform future trials for this population, we sought to characterize the incidence, predictors, and impact of major late bleeding complications (MLBCs; ≥30 days) on long-term prognosis after TAVR using pooled data from the multicenter, randomized PARTNER (Placement of Aortic Transcatheter Valves)-1 trial, the randomized continued-access PARTNER trial, and the nonrandomized continued-access PARTNER registry.

METHODS

STUDY POPULATION. The PARTNER-1 trial was a multicenter, randomized clinical trial comparing TAVR with surgical aortic valve replacement for high-risk patients (cohort A) and TAVR with medical therapy for inoperable patients (cohort B) (14,15). After completion of the randomized trial and before commercial approval of the transcatheter heart valve (SAPIEN, Edwards Lifesciences, Irvine, California), additional patients were treated in a randomized continued-access trial as well as in a nonrandomized continued-access registry, with the same inclusion and exclusion criteria as in the randomized trial. All patients had severe native aortic stenosis documented on screening transthoracic echocardiography within 30 days of enrollment and were evaluated by 2 surgeons for assessment of risk with surgical aortic valve replacement. Important exclusion criteria included bicuspid aortic valve disease, ejection fraction <20%, renal failure, severe mitral regurgitation, severe aortic regurgitation, recent gastrointestinal (GI) bleeding, or a recent neurological event. Complete inclusion and exclusion criteria have been presented in the supplementary appendices to previous publications (14,15).

All patients undergoing TAVR received either a 23- or a 26-mm balloon-expandable transcatheter heart valve delivered via either the transfemoral or transapical approach on the basis of vascular access. Annular assessments to determine valve size required were site determined using transthoracic echocardiography, transesophageal echocardiography, or multislice computed tomography. All patients underwent transthoracic echocardiography before discharge and at clinical follow-up assessments, including 1 month, 6 months, and 1 year. The present analysis included all patients who actually underwent TAVR and survived up to 30 days. The institutional review board at each participating site approved the study, and all patients provided written informed consent.

STUDY ENDPOINTS. Bleeding complications were defined according to a modified version of the Valve Academic Research Consortium criteria as described in the PARTNER trial protocol and were restricted to those events that occurred at or after 30 days (14,15,23,24). Bleeding events were classified as either major or minor. MLBCs were defined as a clear site of bleeding that met any 1 of the following criteria: bleeding that caused death; bleeding that caused a new hospitalization or prolonged hospitalization ≥24 h because of treatment, bleeding that required pericardiocentesis or an open and/or endovascular procedure for repair or hemostasis, bleeding that caused permanent disability (e.g., blindness, paralysis, hearing loss), and bleeding that required transfusion of >3 U of blood within a 24-h period. Minor bleeding had to meet all of the following criteria: a bleeding event that did not meet criteria for major bleeding, clear site for bleeding, and loss of hemoglobin >3 g/dl or loss of hematocrit >9%. Adjustment for transfusions was included at 1 g/dl or 3% for each unit of blood. Only major bleeding events are reported in the present analysis.

member of the PARTNER Executive Committee. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Sanjay Kaul, MD, MPH, served as Guest Editor for this paper.
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The frequency of all-cause mortality, cardiovascular mortality, stroke, rehospitalization, and renal failure requiring dialysis between 30 days and 1 year of follow-up were reported, according to initial Valve Academic Research Consortium definitions (23) or according to a modified version of the Valve Academic Research Consortium criteria as described in the PARTNER trial protocol (14,15). An independent clinical events committee adjudicated all adverse events. Further extensive review of the source documents was performed by one of the authors (P.G.) to better characterize the causes of bleeding events. Independent core laboratories analyzed all echocardiograms and electrocardiograms. An independent academic biostatistics group performed all data analyses.

STATISTICAL ANALYSIS. Continuous variables are summarized as mean ± SD or as medians and quartiles, as appropriate, and were compared using Student *t* tests or Mann-Whitney rank sum tests accordingly. Categorical variables were compared using chi-square or Fisher exact tests. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data using Kaplan-Meier estimates, and comparisons were performed using the log-rank test.

Cox multivariate regression analysis (with a landmark analysis at 30 days for MLBCs) was performed to identify independent predictors of MLBC ($\alpha = 0.05$). The multivariate model was built by stepwise selection, with candidate variables being selected if they were of clinical interest or satisfied the entry criterion of $p < 0.10$ in the univariate analysis. To assess the association between MLBCs and all-cause mortality, Cox multivariate regression analysis (using time-updated covariates for bleeding) was performed, with variable selection performed as described above. A 2-sided α level of 0.05 was used for all statistical testing. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

An additional analysis assessing the impact of the presence of AF or atrial flutter (either at baseline or at 30 days), as determined by an independent electrocardiographic core laboratory, with the occurrence of MLBCs was performed. Although the capture of oral anticoagulation at baseline or during the course of the study was not required in the PARTNER trial, the presence of AF, given the high comorbidity of the treated population (>75 years of age, hypertension, valvular disease, prior stroke), and the high likelihood of oral anticoagulation use if AF was present among this high-risk population, could be seen as a surrogate for oral anticoagulation use.

The present analysis was carried out by academic investigators at the Cardiovascular Research Foundation.

RESULTS

PATIENTS AND BASELINE CHARACTERISTICS. From PARTNER trial cohort B (inoperable; n = 164), PARTNER trial cohort A (high risk but operable; n = 326), the randomized continued-access registry (n = 37), and the nonrandomized continued-access registry (n = 1,874), a total of 2,401 patients were actually treated with TAVR, survived to 30 days, and therefore were included in the present analysis. The median follow-up of the entire studied population was 1 year (365 days), with 2,323 patients (96.8%) completing 1-year follow-up. MLBCs occurred in 142 patients (5.9%) between 30 days and 1 year. The median time of occurrence was 132 days (interquartile range: 71 to 230 days) after the index procedure, with 91 (64.1%) occurring inside 6 months. The causes of major MLBCs are summarized in Table 1. GI bleeding (n = 58 [40.8%]) was the most frequent type of MLBC, with upper GI bleeding being confirmed in 22 patients (37.9%), lower GI bleeding in 13 patients (22.4%), and GI bleeding of undetermined origin in 23 patients (39.7%). Neurological bleeding occurred in 22 patients (15.5%). Importantly, mechanical falls or trauma was identified in 8 of these patients (36.4%), subsequently leading to traumatic intracranial bleeding.

Baseline, echocardiographic, and procedural characteristics of patients stratified according to the occurrence of MLBC are shown in Tables 2 and 3. Patients with MLBCs were more frequently male and hypertensive, had more baseline AF, and had lower baseline hemoglobin and white blood cell counts.

TABLE 1 Types of Major Late Bleeding (≥30 Days) After TAVR (n = 142)

Gastrointestinal	58 (40.8)
Neurological*	22 (15.5)
Trauma/fall*	11 (7.8)
Genitourinary	9 (6.3)
Chronic anemia	5 (3.5)
TAVR access-site related	3 (2.1)
Pulmonary	3 (2.1)
Other surgery†	3 (2.1)
Ears, nose, throat	2 (1.4)
Cardiac tamponade‡	1 (0.7)
Unspecified	33 (23.2)

Values are n (%). In cases of multiple bleeding events between 30 and 365 days, only the first bleeding event was counted. There were 11 patients of 142 with more than 1 late major bleeding event. *Includes 8 patients with initial falls and subsequent neurological bleeding. †Hip surgery and knee surgery. ‡At a subsequent percutaneous coronary intervention complicated by vessel perforation.

TAVR = transcatheter aortic valve replacement.

TABLE 2 Baseline Characteristics According to Occurrence of Major Late Bleeding

	Late Bleeding (n = 142)	No Late Bleeding (n = 2,259)	p Value
Age, yrs	84.32 ± 6.49	84.43 ± 7.23	0.84
Men	89/142 (62.7)	1,171/2,259 (51.8)	0.01
BMI, kg/m^2	26.02 ± 5.24	26.87 ± 6.31	0.07
Diabetes	58/141 (41.1)	832/2,258 (36.8)	0.31
Hyperlipidemia	124/141 (87.9)	1,886/2,258 (83.5)	0.17
Smoking	64/141 (45.4)	1,098/2,258 (48.6)	0.46
Hypertension	136/141 (96.5)	2,071/2,257 (91.8)	0.05
Angina	34/141 (24.1)	483/2,258 (21.4)	0.45
Stable	29/31 (93.5)	400/436 (91.7)	1.00
Unstable	2/31 (6.5)	36/436 (8.3)	1.00
CHF, NYHA class III or IV	134/142 (94.4)	2143/2259 (94.9)	0.79
Coronary artery disease	110/141 (78.0)	1,755/2,257 (77.8)	0.94
Prior myocardial infarction	35/139 (25.2)	583/2,248 (25.9)	0.84
Prior PCI	62/140 (44.3)	883/2,255 (39.2)	0.23
Prior CABG	66/141 (46.8)	960/2,257 (42.5)	0.32
Prior stroke or TIA	44/139 (31.7)	568/2,213 (25.7)	0.12
Carotid disease	33/137 (24.1)	578/2,191 (26.4)	0.55
Peripheral vascular disease	60/139 (43.2)	948/2,234 (42.4)	0.87
Porcelain aorta	4/142 (2.8)	88/2,257 (3.9)	0.51
Pulmonary hypertension	50/136 (36.8)	844/2,157 (39.1)	0.58
Frailty	15/136 (11.0)	279/2,156 (12.9)	0.52
Permanent pacemaker	39/141 (27.7)	473/2,257 (21.0)	0.06
AF	45/141 (31.9)	467/2,233 (20.9)	0.002
Atrial flutter	3/141 (2.1)	42/2,234 (1.9)	0.75
Renal disease, creatinine ≥2 mg/dl	21/141 (14.9)	372/2,256 (16.5)	0.62
Liver disease	7/141 (5.0)	54/2,255 (2.4)	0.09
COPD	67/142 (47.2)	997/2,259 (44.1)	0.48
Hemoglobin, g/dl	11.53 ± 1.41	11.78 ± 1.85	0.04
WBC, ×1,000 cells/μl	6.62 ± 1.85	7.58 ± 16.60	0.01
Platelets, cells/mm^3	186, 143-245	197 (156-246)	0.92
Creatinine clearance, ml/min	45.20 ± 20.49	45.41 ± 22.29	0.92
Albumin, g/dl	3.69 ± 0.47	4.39 ± 9.06	0.005
STS score	11.69 ± 3.94	11.37 ± 4.04	0.35
Logistic EuroSCORE	25.78 ± 15.39	26.43 ± 16.33	0.65

Values are mean ± SD, n/N (%), or median (interquartile range).

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CHF = congestive heart failure; COPD= chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack; WBC = white blood cell.

During the procedure, these patients most likely required larger valves (26 mm) and had a lower rate of successful procedures, with more frequent valve embolization.

Within 30 days, there was no difference in the rates of stroke or vascular complications, but patients with MLBCs had a slightly higher rate of major bleeding and AF than those without MLBCs. Both groups had similar lengths of hospital stay.

Echocardiographic findings at baseline and 30 days are shown in Table 3. The rate of moderate or severe aortic regurgitation (total and paravalvular leak [PVL]) was significantly higher among patients with subsequent MLBCs. Also, moderate or severe mitral regurgitation, left ventricular mass, and diastolic and stroke volumes were more elevated among patients with MLBCs.

No major differences were seen in antiplatelet therapy (aspirin and/or clopidogrel) regimens between the 2 groups at 30-day and 6-month follow-up (Online Appendix).

PREDICTORS OF MLBCS. Variables associated with MLBCs are summarized in Table 4. After multivariate analysis, moderate or severe aortic PVL (at 30 days), AF or atrial flutter at baseline or 30 days, greater left ventricular mass, and low baseline hemoglobin were identified as independent predictors of MLBCs after TAVR.

CLINICAL OUTCOMES. Between 30 days and 1 year, the occurrence of MLBC was associated with significantly higher rates of death, cardiac death, major stroke, and rehospitalization (Figures 1A to 1D), with a consistent impact among major patient subgroups (Figure 2). MLBCs also were associated with an increased risk for renal failure needing dialysis (3.9% vs. 1.5%; p = 0.02). After multivariate analysis adjusting for clinical, echocardiographic, and procedural characteristics, as well as outcomes, the occurrence of MLBCs was identified as a strong predictor of mortality between 30 days and 1 year (adjusted hazard ratio: 3.83; 95% confidence interval: 2.62 to 5.61; p < 0.001) (Table 5).

IMPACT OF AF OR ATRIAL FLUTTER. Among patients with AF, 8.6% (58 of 671) had MLBCs, compared with 4.8% (84 of 1,730) of those with no AF. No interaction was demonstrated between the presence of AF and MLBCs with regard to the occurrence of mortality (p for interaction = 0.83). The presence of AF, especially when MLBCs occurred, was associated with a poor prognosis and high rate of mortality (Central Illustration, Online Appendix).

DISCUSSION

This study is the first to specifically evaluate and assess the incidence, predictors, and impact of MLBCs on long-term prognosis after TAVR. The main results of the present study are as follows: 1) among patients treated with TAVR, MLBCs (≥30 days) were relatively frequent, occurring in approximately 6% of patients; 2) GI and neurological origin were the most frequent identifiable sites of bleeding; 3) independent predictors of MLBCs after TAVR included the presence of AF, residual moderate or severe

TABLE 3 Procedural and Echocardiographic Characteristics According to the Occurrence of Major Late Bleeding

	Late Bleeding (n = 142)	No Late Bleeding (n = 2,259)	p Value
Procedural characteristics			
Approach			
Transfemoral	87/142 (61.3)	1,324/2,259 (58.6)	0.53
Transapical	55/142 (38.7)	935/2,259 (41.4)	0.53
Valve size			
23-mm	62/141 (44.0)	1,156/2,215 (52.2)	0.058
26-mm	79/141 (56.0)	1,058/2,215 (47.8)	0.057
Successful valve implantation	136/140 (97.1)	2,197/2,247 (97.8)	0.56
Migration or embolization	4/56 (7.1)	11/839 (1.3)	0.01
Artery closure			
Surgical cutdown	47/140 (33.6)	784/2,252 (34.8)	0.76
Closure device	38/140 (27.1)	546/2,252 (24.2)	0.44
Device success	113/142 (79.6)	1,928/2,258 (85.4)	0.06
Procedure success	106/142 (74.6)	1,858/2,258 (82.3)	0.02
Post-procedure			
Aortic valve area, cm	2.13 ± 0.93	2.19 ± 2.79	0.69
Mean AV gradient, mm Hg	6.40 ± 5.31	7.31 ± 8.67	0.16
Peak AV gradient, mm Hg	6.11 ± 6.27	8.12 ± 12.14	0.02
Vascular complications, <30 days	19 (13.4)	273 (12.1)	0.64
Major	10 (7.0)	141 (6.2)	0.70
Bleeding, <30 days	19 (13.4)	208 (9.2)	0.11
Major	19 (13.4)	158 (7.0)	0.005
Stroke or TIA, <30 days	8 (5.6)	76 (3.4)	0.16
Major	5 (3.5)	48 (2.1)	0.28
Minor	2 (1.4)	18 (0.8)	0.44
TIA	1 (0.7)	10 (0.4)	0.65
AF, at 30 days	46/129 (35.7)	446/2,074 (21.5)	0.0002
Atrial flutter, at 30 days	3/129 (2.3)	40/2,074 (1.9)	0.74
Days in hospital, post-procedure	6.29 ± 3.18	6.26 ± 2.68	0.93
Echocardiographic characteristics			
Baseline			
AV peak gradient, mm Hg	67.30 ± 21.12	71.78 ± 22.29	0.02
AV mean gradient, mm Hg	41.08 ± 13.53	44.41 ± 14.25	0.008
AV area (EOA), cm^2	0.67 ± 0.20	0.65 ± 0.19	0.11
AV annular diameter, cm	1.97 ± 0.28	1.90 ± 0.27	0.01
Total aortic regurgitation moderate or severe	18/140 (12.9)	234/2,207 (10.6)	0.40
Mitral regurgitation moderate or severe	40/138 (29.0)	475/2,204 (21.6)	0.04
LVEDV, ml	149.31 ± 54.21	132.70 ± 49.68	0.007
LVESV, ml	75.93 ± 43.47	67.09 ± 41.19	0.08
LV ejection fraction, %	52.62 ± 12.78	52.46 ± 12.92	0.89
Stroke volume, ml	73.25 ± 23.08	65.62 ± 20.62	0.003
LV mass, g	266.40 ± 75.48	249.03 ± 76.25	0.01
30 days			
AV peak gradient, mm Hg	17.18 ± 6.78	17.78 ± 7.77	0.35
AV mean gradient, mm Hg	8.94 ± 3.81	9.33 ± 4.29	0.27
AV area (EOA), cm^2	1.77 ± 0.48	1.70 ± 0.49	0.16
Total AR moderate or severe	29/124 (23.4)	244/2,083 (11.7)	0.0001
Paravalvular AR moderate or severe	26/123 (21.1)	204/2,072 (9.8)	<0.0001
Mitral regurgitation moderate to severe	32/124 (25.8)	366/2,077 (17.6)	0.02
LVEDV, ml	149.70 ± 54.56	134.24 ± 49.34	0.04
LVESV, ml	72.26 ± 45.30	64.28 ± 37.26	0.25
LV ejection fraction, %	54.54 ± 10.72	54.20 ± 11.17	0.74
Stroke volume, ml	77.22 ± 20.35	69.92 ± 22.08	0.03
LV mass, g	259.64 ± 77.66	232.44 ± 73.89	0.0001

Continued in the next column

Values are n/N (%) or mean ± SD.

AR = aortic regurgitation; AV = aortoventricular; EOA = effective orifice area; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; TIA = transient ischemic attack.

PVL, baseline hemoglobin, and increased left ventricular mass; and 4) MLBCs were associated with an increased rate of mortality and morbidity between 30 days and 1 year.

To the best of our knowledge, the present study is the first to specifically examine bleeding events after TAVR beyond the periprocedural period (≥30 days) and to demonstrate their strong association with increased mortality. Indeed, MLBCs were associated with a 4-fold increase in late mortality among the TAVR population enrolled in the PARTNER trial. Several groups have previously described the negative impact of periprocedural bleeding and red blood cell transfusions after TAVR procedures (2,4-6,8). The present study reinforces and extends beyond the periprocedural period the detrimental effect of major bleeding events and identifies a potential area for improved patient care. Although much attention initially focused on the improvement of acute outcomes (advances in device technologies, optimization of implantation

TABLE 4 Multivariate Predictors of Major Late Bleeding

	HR (95% CI)	p Value
Moderate to severe PVL*	2.14 (1.26–3.63)	0.005
AF/atrial flutter†	1.87 (1.28–2.73)	0.001
LV mass (per 10-g increase)*	1.04 (1.01–1.06)	0.002
Baseline hemoglobin (g/dl)	0.85 (0.75–0.95)	0.006

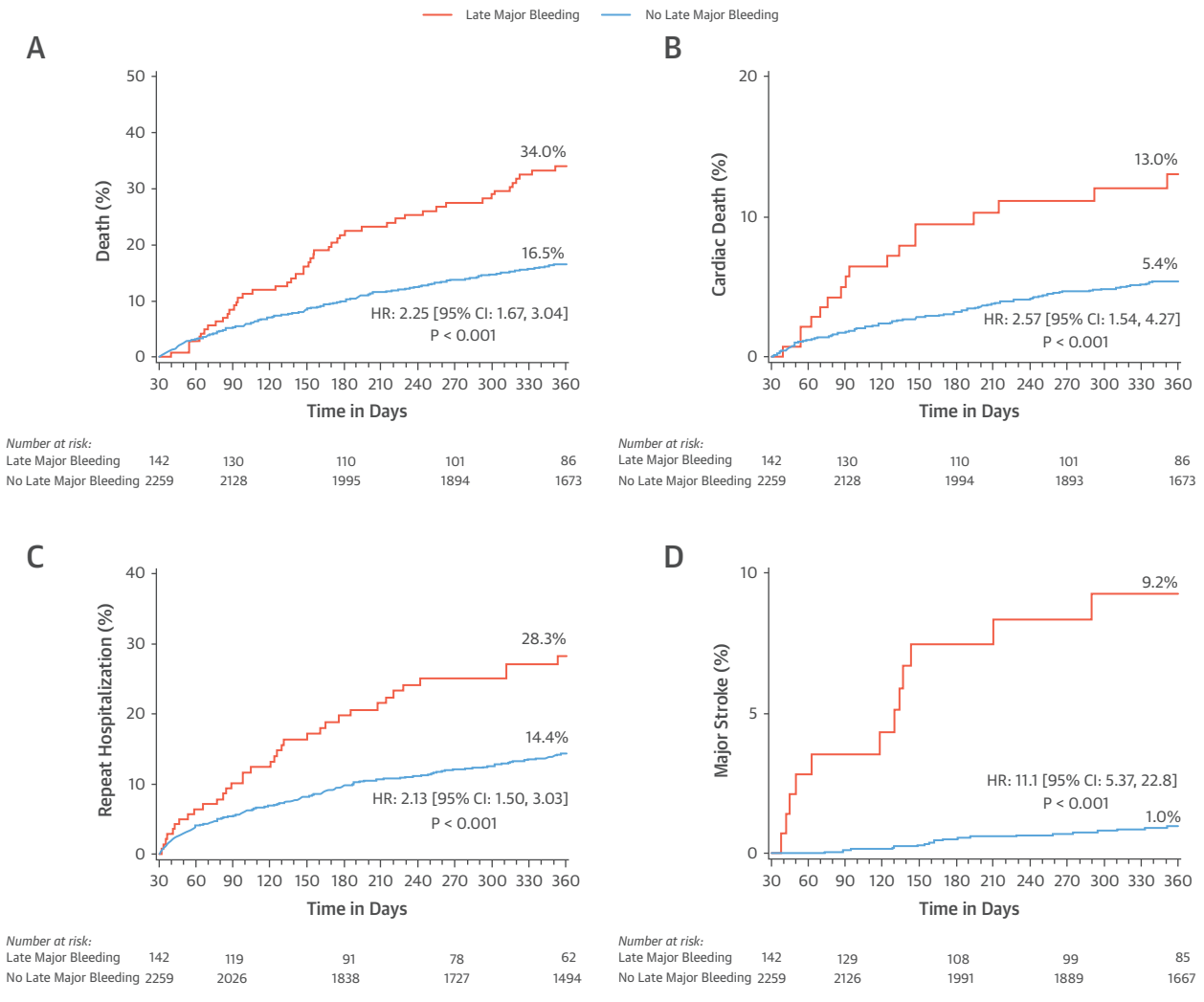
Candidate variables for the model were age, sex, AF or atrial flutter at baseline or at 30 days, procedural success, moderate or severe PVL at 30 days, renal insufficiency at baseline (creatinine >2 mg/dl), body mass index, Society of Thoracic Surgeons score, hypertension, baseline hemoglobin, LV end-diastolic dimension at 30 days, aortoventricular annulus at baseline, LV mass at 30 days, and moderate to severe mitral regurgitation at 30 days. *At 30 days. †At baseline or 30 days.

CI = confidence interval; HR = hazard ratio; PVL = paravalvular leak; other abbreviations as in Tables 2 and 3.

techniques, and enhanced operator experience), leading to a dramatic reduction in periprocedural complications (25–27), this study demonstrates that reducing later adverse events (such as MLBCs) is also crucial if long-term prognosis is to be improved. Fortunately, prospective studies are ongoing (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation [NCT01559298]) and are expected to provide some answers to this important question.

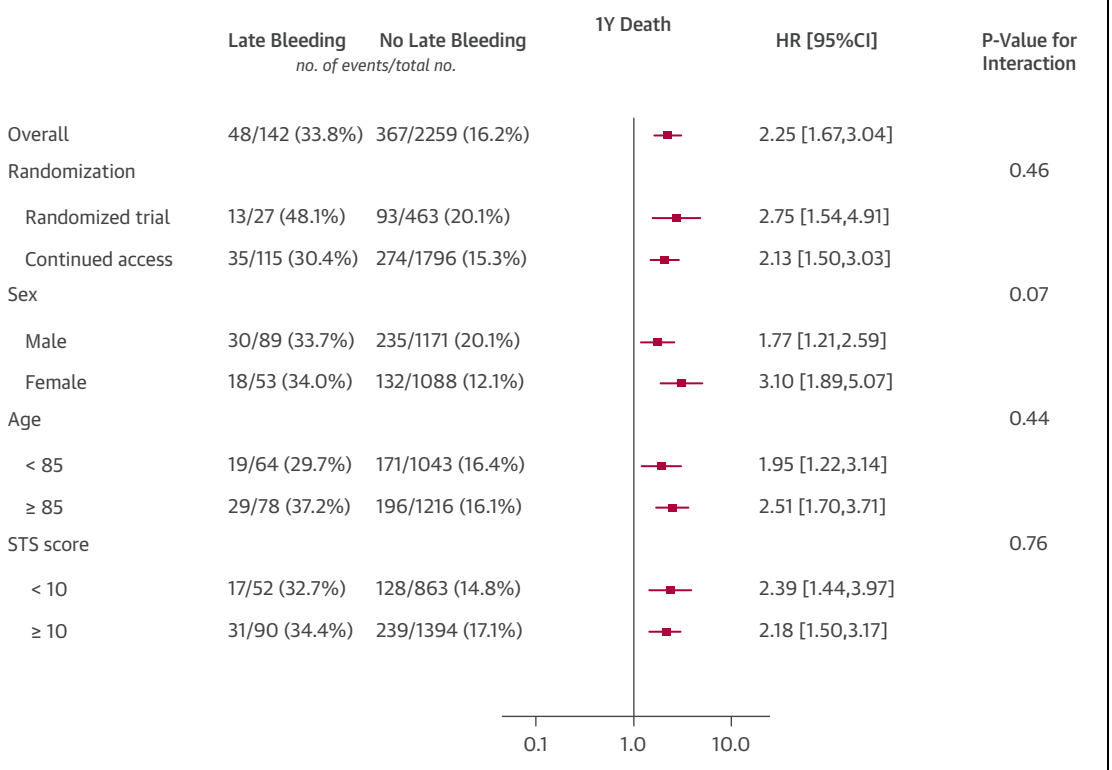
Previous reports demonstrated that periprocedural bleeding was driven mainly by anatomical and technical considerations (2,7–9). However, MLBCs

FIGURE 1 Kaplan-Meier Curves Showing Cumulative Adverse Event Rates Through 1 Year Between Patients With Late Bleeding Compared With No Late Bleeding Complications



Comparison of cumulative adverse event rates through 1 year in patients with late bleeding compared with patients with no late bleeding. **(A)** All-cause mortality, **(B)** cardiac mortality, **(C)** rehospitalization, and **(D)** major stroke. CI = confidence interval; HR = hazard ratio.

FIGURE 2 **Major Subgroups Analysis**



The detrimental impact of major late bleeding is constant among all major subgroups. STS = Society of Thoracic Surgeons; other abbreviations as in Figure 1.

appear to be related mainly to patients' bleeding susceptibility, which is often "triggered" by the antithrombotic agent used. Unsurprisingly, GI bleeding was the most frequently identifiable source of major bleeding after 30 days. Bleeding from arteriovenous malformation distributed throughout the GI tract is a well-described syndrome (Heyde's syndrome) associated with severe aortic stenosis, accounting for a significant proportion of GI bleeding in this population (28,29). Similarly, benign and malignant tumors are frequent in this group of patients. Appropriate screening, such as gastroscopy, colonoscopy (either before or soon after the TAVR procedure), and the use of gastroprotection (i.e., proton pump inhibition), could be considered during the high-risk period and may help prevent a proportion of these GI bleeds. Further studies are needed to evaluate the risk and benefits of these strategies.

The association between MLBCs and moderate or severe PVL is previously unrecognized and may represent a mechanism underlying the excess mortality and morbidity associated with residual moderate or severe PVL among patients surviving beyond 30 days post-TAVR. Indeed, several groups have previously noted that high shear stress and flow - turbulence may lead to the loss (cleavage) of essential proaggregation proteins (high-molecular weight von Willebrand factor), leading to an increased susceptibility to bleeding (acquired von Willebrand disease type 2A) (28-31). This hematologic disturbance has been shown to rapidly resolve with treatment of the aortic stenosis or any anatomic situation causing high-flow turbulence (28-32). Our findings, in which patients with underlying high-risk bleeding profiles, combined with highly turbulent flow through "crushed" heavily calcified native valve leaflets and underexpanded leaking prostheses, suggest that post-TAVR paravalvular aortic regurgitation may represent the perfect storm for acquired thrombophilia, ultimately leading to major bleeding events. This biological phenomenon may be amplified

TABLE 5 Independent Predictors of 30-Day to 1-Year Mortality

Predictor	Adjusted HR (95% CI)	p Value
Major stroke within 1 yr	5.44 (3.33–8.90)	<0.0001
Major late bleeding*	3.83 (2.62–5.61)	<0.0001
AF/atrial flutter†	2.03 (1.60–2.58)	<0.0001
Moderate to severe PVL†	1.70 (1.27–2.27)	0.0004
Hemodynamic support use (CPB or IABP)	1.63 (1.10–2.39)	0.01
Renal insufficiency (creatinine ≥2 mg/dl)	1.61 (1.23–2.10)	0.0006
Severe pulmonary hypertension	1.40 (1.11–1.77)	0.005
Liver disease	1.78 (1.00–3.19)	0.051
Moderate to severe MR†	1.30 (1.00–1.70)	0.051
Platelet count at baseline	1.00 (1.00–1.00)	0.02
AV mean gradient at baseline	0.99 (0.98–0.99)	0.002
Dual-antiplatelet therapy†	0.76 (0.60–0.98)	0.03

Candidate variables for the model were male sex, bleeding <30 days, BMI, Society of Thoracic Surgeons score, pulmonary hypertension, renal insufficiency (creatinine ≥2 mg/dl), liver disease, chronic obstructive pulmonary disease (oxygen dependent), migration or valve embolization, hemodynamic support use (CPB or IABP), albumin at baseline, platelet count at baseline, hemoglobin at baseline, dual-antiplatelet therapy at 30 days, baseline left ventricular ejection fraction, AV mean gradient at baseline, moderate to severe PVL at 30 days, moderate to severe MR at 30 days, AF at baseline or 30 days, and unplanned arterial vascular procedure. One-year major stroke was the time-dependent covariable. *Between 30 days and 1 year. †At 30 days.

CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pulsation; MR = mitral regurgitation; other abbreviations as in Tables 2 and 4.

by using aggressive antiplatelet therapy and/or anticoagulation therapy (21). This finding reinforces the importance of optimizing valve implantation to minimize the presence of significant residual PVL (33–37), not only to avoid its detrimental hemodynamic effect on the left ventricle but also to restore a normal "biological-hematological" homeostasis and decrease the risk for subsequent major bleeding events. The association of increased left ventricular mass with future MLBCs is intriguing and interesting. Although this association is most likely multifactorial, the hypothesis of increased flow turbulence leading to increased bleeding tendency may also be an explanation. That said, given the retrospective nature of our analysis and the presence of potential residual confounders despite a well-conducted multivariate analysis, this finding can only be identified as hypothesis generating at this point.

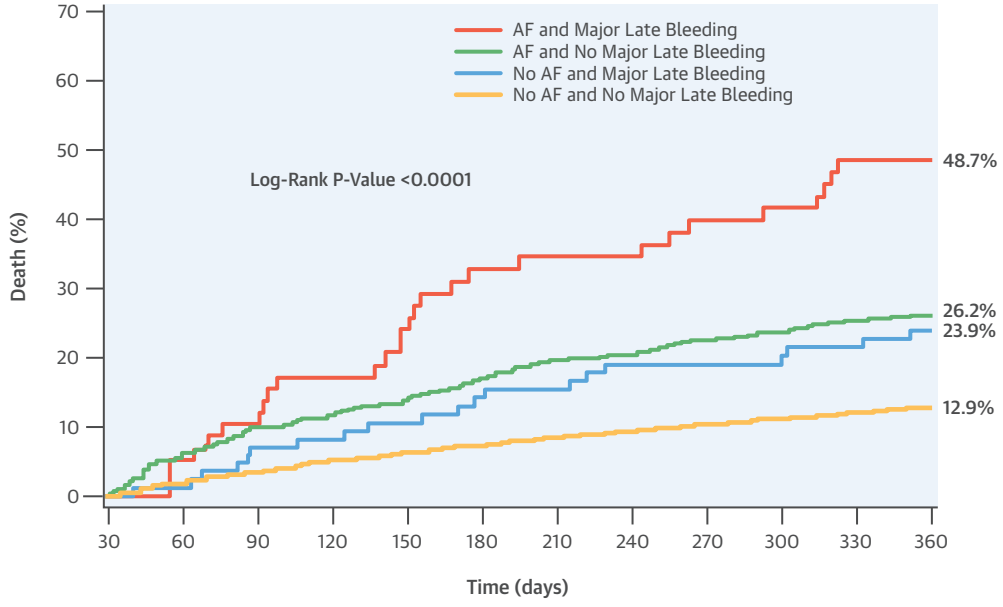
Patients with AF, at either baseline or post-procedurally, have been shown to represent a high-risk population with worse outcomes and increased mortality after TAVR (38–41). Our report reinforces these previous results, showing that patients with AF have a higher rate of death, because of a higher occurrence of MLBCs or thromboembolic events. Further studies may help determine the best strategies to manage AF among this group of high-risk patients.

STUDY STRENGTHS AND LIMITATIONS. This study has some important strengths. It is the largest study to use both an independent echocardiographic core laboratory and an independent clinical events committee, providing extensive analysis and allowing the identification of a meaningful association between specific echocardiographic parameters (e.g., PVL) and important clinical findings (e.g., bleeding). Nonetheless, several important limitations of the present analysis should be acknowledged. First and foremost, systematic capture of anticoagulation regimens (e.g., with warfarin) was not performed during the different PARTNER studies. Although we acknowledge the central importance of such information when appraising causes and correlates of major bleeding events, our report still brings meaningful insight regarding the incidence and impact of MLBCs after TAVR and raises awareness of the importance and urgency to better define the safest and most effective post-procedural antithrombotic therapy, particularly among patients with AF. That said, given the high thromboembolic risk profile of this population, most of the TAVR patients diagnosed with AF were on, or should have received, anticoagulation therapy. It is likely that the strong association between AF and bleeding, as well as AF and mortality, in the TAVR population represents the effect of oral anticoagulation either alone or in combination with antiplatelet therapy in such patients. This finding clearly illustrates the extreme challenge of treated AF in the TAVR population and the need to better define the optimal antithrombotic regimens in such patients.

Second, patients with recent GI bleeding or neurological events (ischemic or hemorrhagic) were excluded from the PARTNER trial. The inclusion of such patients (as in real-world practice) would have likely resulted in an even higher rate of MLBCs.

Third, the definition of major bleeding used in the present report lies at the extreme range of bleeding severity, particularly in the outpatient setting. It is possible that a more refined, detailed bleeding classification, such as that proposed by the Bleeding Academic Research Consortium (BARC), could have been used and may have led to different findings (42). The bleeding definitions used in the present report correspond approximately to BARC classes 3 and 5, depending on the severity (leading to death or not). However, BARC classification has not been validated in the TAVR space, and data collection unfortunately does not allow BARC bleeding readjudication. Finally,

CENTRAL ILLUSTRATION **Kaplan-Meier Curves Showing Cumulative Death Rates Through 1 Year, According to Bleeding and AF Status**



Number at Risk:

AF and MLB	58	52	38	34	26
AF and No MLB	613	551	498	459	394
No AF and MLB	84	78	72	67	60
No AF and No MLB	1,646	1,577	1,497	1,435	1,279

Généreux, P. et al. J Am Coll Cardiol. 2014; 64(24):2605–15.

The presence of atrial fibrillation (AF) or atrial flutter and bleeding was associated with a significant increase in mortality rates between 30 days and 1 year compared with patients with no AF and/or no late bleeding (LB) events. MLB = major late bleeding.

although we adjusted for imbalances in a number of important covariates, potential unmeasured confounders may still be present. The results of this observational post hoc analysis should therefore be considered hypothesis generating.

CONCLUSIONS

MLBCs (between 30 days and 1 year) after TAVR were frequent and associated with increased mortality. The observed association between moderate or severe PVL and the occurrence of MLBCs is interesting and deserves further investigation. Better individualized and risk adjusted antithrombotic therapy after TAVR is urgently needed in this high-risk population.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Martin B. Leon, Columbia University Medical Center, New York-Presbyterian Hospital, 161 Fort Washington Avenue, 6th Floor, New York, New York 10032. E-mail: ml2398@columbia.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among high-risk or inoperable patients undergoing TAVR, those who develop major bleeding complications more than 30 days after the procedure exhibit more than twice the mortality rate of those without late post-procedural bleeding.

TRANSLATIONAL OUTLOOK: Future studies are needed to define predictors of late bleeding complications and tailored antithrombotic therapy strategies for patients undergoing TAVR.

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KEY WORDS aortic stenosis, bleeding, paravalvular leak, TAVR

APPENDIX For supplemental material, please see the online version of this article.