Antithrombotic therapy – predictor of early and long-term bleeding complications after transcatheter aortic valve implantation

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Abstract

Introduction: Dual antiplatelet therapy (DAPT) – aspirin and clopidogrel – is recommended after transcatheter aortic valve implantation (TAVI) without an evidence base. The main aim of the study was to estimate the impact of antithrombotic therapy on early and late bleeding. Moreover, we assessed the impact of patients' characteristics on early bleeding and the influence of bleeding on prognosis.

Material and methods: Between 2009 and 2011, 83 consecutive TAVI patients, age 81.1 ±7.2 years, were included. Bleeding complications were defined by the Valve Academic Research Consortium (VARC) scale. The median follow-up was 12 ±15.5 months (range: 1 to 23) and included 68 (81.9%) patients.

Results: Early bleeding occurred in 51 (61.4%) patients. Vitamin K antagonists (VKA) pre-TAVI (p = 0.001) and VKA + clopidogrel early post-TAVI (p = 0.04) were the safest therapies; in comparison to the safest one, peri-procedural DAPT (p = 0.002; p = 0.05) or triple anticoagulant therapy (TAT) (p = 0.003, p = 0.05) increased the risk for early bleeding. Predictors for early bleeding were: clopidogrel pre-TAVI (OR: 4.43, 95% CI: 1.02–19.24, p = 0.04), preceding percutaneous coronary intervention (PCI) (10.08, OR: 95% CI: 1.12–90.56, p = 0.04), anemia (OR: 4.00, 95% CI: 1.32–12.15, p = 0.01), age > 85 years (OR: 5.96, 95% CI: 1.47–24.13, p = 0.01), body mass index (BMI) (OR: 0.86, 95% CI: 0.74–0.99, p = 0.04). Late bleeding occurred in 35 patients (51.4%) on combined therapy, and none on VKA or clopidogrel monotherapy (p = 0.04). Bleeding complications did not worsen the survival.

Conclusions: This study seems to suggest that advanced age, BMI, and a history of anemia increased the risk for early bleeding after TAVI. Clopidogrel pre-TAVI should be avoided; therefore, time of preceding PCI should take into account discontinuation of clopidogrel in the pre-TAVI period. Vitamin K antagonists with clopidogrel seems to be the safest therapy in the early post-TAVI period, similarly as VKA/clopidogrel monotherapy in long-term prophylaxis.

Key words: transcatheter aortic valve implantation, antithrombotic prophylaxis, bleeding complications, aortic stenosis.

Introduction

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and clopidogrel is recommended for 3–6 months after transcatheter aortic valve implantation (TAVI) in preventing thromboembolic complications [1, 2]. Although two single-center prospective analyses evaluated 3-month regimens of DAPT vs. ASA alone after TAVI [3, 4], DAPT efficacy and safety has not been the subject of any high quality randomized trials or large multicenter registries so far. Moreover, due to the concomitant atrial fibrillation (AF), thromboembolic disease or a previous surgical valve replacement, TAVI patients frequently require parallel use of vitamin K antagonists (VKA), and the real long-term antithrombotic prophylaxis often differs from the recommended one. The impact of peri-procedural and long-term antithrombotic treatment on bleeding after TAVI is still unexplained.

The main aim of the study was to estimate the impact of antithrombotic drugs on early and late bleeding due to the lack of reliable data. Moreover, we assessed the impact of patients' characteristics on early bleeding and the influence of bleeding complications on early and long-term mortality in TAVI patients.

Material and methods

Patient population and study design

We included 83 consecutive patients who underwent TAVI in our center between January 2009 and October 2011. All patients were qualified for TAVI by our heart team according to the European Society of Cardiology (ESC) Working Group consensus prepared in 2008 [2]. Transcatheter aortic valve implantation was performed via a transvascular (transfemoral/transsubclavian) or transapical route using a Medtronic CoreValve and Edwards Sapien/Sapien XT bioprostheses.

This was a single-center observational study of early and late bleeding related to TAVI. The analysis was retrospective until February 2011 then prospective from that point on.

The parameters analyzed were: (a) known bleeding risk factors such as hypertension, renal failure, previous bleeding, history of anemia, older age, female sex, body mass index (BMI); (b) the route of bioprosthesis implantation – transvascular or transapical; (c) pre- and post-procedural antithrombotic treatment.

Data on patients' characteristics in relation to bleeding risk factors, peri-procedural anticoagulant treatment, early bleeding, deaths and peri-procedural hemoglobin levels were collected from interviews with patients, medical documentation and electronic databases. Data on late bleeding, long-term anticoagulant treatment and mortality during the follow-up were based on telephone interviews with patients and/or their families.

Although early bleeding included incidents of peri-procedural mechanical vessel injury and events not related to the route of bioprosthesis implantation, our main assumption was to assess only the impact of antithrombotic therapy on early bleeding, without assessing the impact of vascular complications on them. The treatment analysis was conducted with regard to therapies with the lowest frequency of bleeding.

Definitions

Early bleeding was considered as incidents which occurred within 30 days after TAVI and was defined according to the Valve Academic Research Consortium (VARC) scale, intended for TAVI complications [5]. Because of the small number of participants, major and life-threatening/disabling bleeding complications were assessed together as serious bleeding.

Late bleeding was defined as incidents which occurred more than 30 days after the procedure, and included VARC bleeding, non-previously diagnosed anemia (hemoglobin level < 12.0 g/dl) occurred in follow-up, petechiae and epistaxis.

Drug regimens

Peri-procedural and long-term antithrombotic therapy was based on an individual physician's decision which mainly took into account recommended TAVI prophylaxis, other indications for antithrombotic therapy and the risk of bleeding. Peri-procedural anticoagulant management is presented in a flow chart (Figure 1).

As preparation for the procedure, patients without other indications for antithrombotic prophylaxis received DAPT for a few days before TAVI or a loading dose of clopidogrel for a few hours prior to the procedure. Patients with coexisting coronary artery disease (CAD) received ASA or DAPT in case of preceding percutaneous coronary intervention (PCI). In all participants who received VKA bridging therapy with low molecular weight heparin (LMWH) was used in the peri-procedural period, if required. Patients with indications for chronic VKA and coexisting CAD received ASA additionally to VKA. Those ones with chronic use of VKA and preceding PCI received triple anticoagulant therapy (TAT). Each drug regimen was applied including the day before the procedure.

All patients received unfractionated heparin during TAVI under activated partial thromboplastin time control.

After TAVI, patients routinely received clopidogrel for 3–6 months plus ASA lifelong. In case of high risk of bleeding only short-term clopidogrel monotherapy was recommended. In patients with

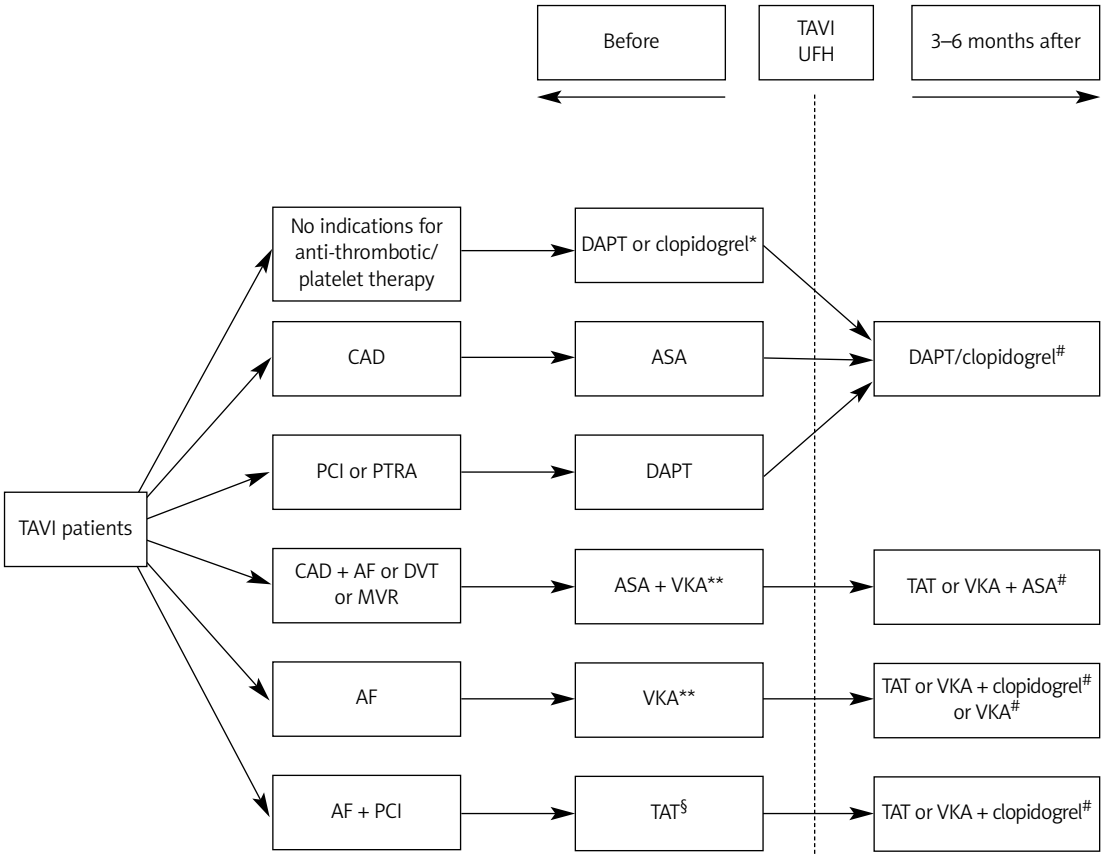

Figure 1. Antithrombotic regimens in study population according to indications for antithrombotic/antiplatelet therapy
DAPT for a few preceding days or loading dose of clopidogrel shortly before TAVI, **VKA peri-procedural replacement with LMWH, #in case of high bleeding risk, §TAT: ASA + VKA + clopidogrel. AF – atrial fibrillation, ASA – acetylsalicylic acid, CAD – coronary artery disease, DAPT – dual antiplatelet therapy, DVT – deep vein thrombosis, MVR – mitral vale replacement, PCI – percutaneous coronary intervention, PTRA – percutaneous transluminal renal angioplasty, TAT – triple anticoagulant therapy, UFH – unfractionated heparin, VKA – vitamin K antagonists*

chronic use of VKA, 3–6 months of TAT was recommended, followed by VKA monotherapy. Patients on chronic VKA therapy with high risk for bleeding received 3–6 months of VKA + clopidogrel or remained on VKA monotherapy after the procedure. Participants with chronic use of VKA and coexisting CAD received TAT for 3–6 months after TAVI and long-term VKA + ASA afterwards or remained on VKA + ASA for 3–6 months after TAVI, followed by long-term VKA in the case of high bleeding risk. If preceding PCI with stent implantation still required antiplatelet therapy, after 3–6 months of TAT, VKA + clopidogrel was administered, followed by VKA monotherapy or VKA + clopidogrel instead of TAT after the procedure was recommended, when the risk of bleeding was increased.

Acetylsalicylic acid and clopidogrel were administered at doses of 75 mg/day. The dose of VKA was adjusted to the international normalized ratio (INR) therapeutic range. In case of AF or deep vein thrombosis the therapeutic INR range was 2.0–3.0; in case of preceding mitral valve replacement INR was 2.5–3.5. Patients on VKA therapy had a properly controlled in-hospital INR range.

The study was approved by the local Research Ethics Committee and written informed consent was obtained by all patients in the prospective part of the study.

Statistical analysis

Uni- and multivariate statistical analyses were performed using SAS software. Categorical data are presented as frequencies and percentages; continuous variables are expressed as means ± SD. Comparisons were made with the χ^2 statistical test or the Fisher exact test for categorical variables and with the nonparametric Wilcoxon test for continuous variables. The multivariate analysis was performed with a multiple logistic regression analysis with estimated odds ratio (OR) and 95% confidence interval (CI) to identify independent variables predicting the risk for early bleeding. All significant variables in comparison tests were included in multivariable analysis. Predictive value of the peri-operative anticoagulant therapy was assessed with adjustment for the independent bleeding risk factors derived from clinical patient characteristics. Preceding PCI was excluded from

adjustment variables due to its significant correlation with pre-procedural clopidogrel. For all statistical tests, a significance level of $p < 0.05$ was used, which was also the p level for staying in multivariate analysis.

Results

Early bleeding complications

The characteristics of 83 study participants are presented in Table I. Fifty-one (61.4%) patients had serious early bleeding. Life-threatening/disabling and major bleeding were noted in 19 (37.2 %) and 32 (62.7%) patients respectively. Forty-four (86.2%) serious bleeding events were related to vascular complications, 10 (19.6%) incidents were not related to the route of bioprosthesis implantation, but 3 of them occurred in patients with vascular complications (Table II).

Table I. Baseline characteristics of the 83 patients

Parameter	Results
Age, mean ± SD [years]	81.1 ±7.2
> 85-year, *n* (%)	31 (37.3)
Female sex, *n* (%)	54 (65.1)
Logistic EuroSCORE %, range (mean ± SD)	2.9–59 (24.9 ±12.7)
Implantation	
TF-AVI/TSC-AVI, *n* (%)	59/8 (71.1%/9.6%)
TA-AVI, *n* (%)	16 (19.2)
NYHA class, *n* (%)	
II	16 (19.2)
III	52 (62.6)
IV	15 (18.1)
Coronary artery disease, *n* (%)	62 (74.7)
Previous myocardial infarction, *n* (%)	20 (24.1)
Previous coronary intervention, *n* (%)	38 (45.8)
PCI	26 (31.3)
≤ 6 months pre-TAVI	18 (21.7)
CABG	12 (14.5)
COPD, *n* (%)	25 (30.1)
Atrial fibrillation, *n* (%)	32 (38.5)
Permanent pacemaker – pre/post TAVI, *n* (%)	12/26 (14.4%/31.3%)
Pulmonary hypertension, *n* (%)	47 (56.6)
Extensively calcified aorta, *n* (%)	7 (8.4)
Osteoporosis, *n* (%)	23 (27.7)
BMI, mean ± SD [kg/m^2]	25.5 ±4.0

BMI – body mass index, CABG – coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease, NYHA – New York Heart Association, TA-AVI – transapical aortic valve implantation, PCI – percutaneous coronary intervention, TF-AVI – transfemoral aortic valve implantation, TSC-AVI – transsubclavian aortic valve implantation

Univariate analysis demonstrated that a history of anemia ($p = 0.03$), age ($p = 0.01$), especially above 85 years ($p = 0.008$), BMI ($p = 0.02$), and preceding PCI ($p = 0.001$) significantly increased the risk for early bleeding (Table III).

The analysis of peri-procedural treatment demonstrated that the use of clopidogrel or DAPT before TAVI significantly increased the risk for early bleeding (respectively $p = 0.005$ and $p = 0.02$). No bleeding was observed only in the patients on VKA monotherapy before TAVI ($p = 0.001$). Moreover, the smallest number of bleeding events was noted in patients receiving VKA with clopidogrel in the early post-procedural period ($p = 0.04$) (Table IV). In comparison to the safest therapy, peri-procedural use of DAPT and TAT significantly increased the risk for early bleeding (Table V).

The use of clopidogrel before TAVI was significantly related to PCI ($p = 0.001$) performed between 8 and 161 (57 ±48) preceding days as preparation for TAVI (Table VI).

In multivariate analysis, age above 85 years, BMI, history of anemia, and preceding PCI were independent predictors of early bleeding (Table III). Most importantly, clopidogrel used before TAVI, irrespective of its combination with other drugs, was an independent predictor of 30-day bleeding (Table IV).

We noted one incident of early ischemic stroke. It occurred in a patient with advanced atherosclerosis of the ascending aorta shortly after transfemoral bioprosthesis implantation.

There were 6 (7.2%) early deaths: 3 of them were caused by bleeding. Early bleeding did not significantly increase the risk of early mortality ($p = 0.57$) (Table II).

Table II. The cause of serious early bleeding and its influence on in-hospital mortality in 51 patients

Serious early bleeding after TAVI	*N* (%)	No. of deaths
Implantation related bleeding:		
TF-AVI/TSC-AVI	35 (68.6)	3
TA-AVI (pleural hemorrhage)	9 (17.6)	
Gastrointestinal hemorrhage	2 (3.9)	
Pericardial tamponade	2 (3.9)	
Hematuria	1 (1.9)	
Mediastinal hemorrhage	2 (3.9)	
Hemoptysis	1 (1.9)	
Intramuscular hematoma[a]	2 (3.9)	
Total	51* (100)	3

*[a]Hemorrhage in quadriceps, not caused by injury, confirmed in CT, without fascial compartment syndrome, *3 patients with parallel vascular complications and not vascular related bleeding, TA-AVI – transapical aortic valve implantation, TF-AVI – transfemoral aortic valve implantation, TSC-AVI – transsubclavian aortic valve implantation*

Table III. The predictive value of known bleeding risk factors in uni- and multivariate analysis

Risk factors	Bleeding complications *n* (%)		Value of *p*	Univariate analysis OR (95% CI); value of *p*	Multivariate analysis OR (95% CI); value of *p*
	Yes (*n* = 51)	No (*n* = 32)			
Hypertension	39 (76.5)	29 (90.6)	0.1	–	–
Renal failure[a]	32 (62.7)	17 (53.1)	0.38	–	–
History of bleeding	6 (11.7)	6 (18.7)	0.37	–	–
Anemia[b]	31 (60.8)	12 (37.5)	0.03	2.58 (1.040–6.416); 0.04	4.00 (1.32–12.15); 0.01
Age, mean ± SD [years]	82.8 ±6.3	78.6 ±7.9	0.01	1.08 (1.014–1.163); 0.018	–
Age > 85-year	26 (50.9)	5 (15.6)	0.008	5.75 (1.760–18.782); 0.003	5.96 (1.47–24.13); 0.01*
Female sex	36 (70.6)	18 (56.2)	0.18	–	–
Diabetes mellitus	19 (37.2)	14 (43.7)	0.55	–	–
Stroke/TIA	6 (11.7)	7 (21.9)	0.21	–	–
BMI, mean ± SD [kg/m^2]	25.6 ±3.0	26.9 ±4.7	0.02	0.84 (0.742–0.964); 0.0119	0.86 (0.74–0.99); 0.04
PCI ≤ 6 months	17 (33.3)	1 (3.1)	0.001	15.49 (1.947–123.291); 0.009	10.08 (1.12–90.57); 0.04
Implantation:					
TF-AVI + TSC-AVI/	33 + 6 (76.5)/	26 + 2 (87.5)/	0.27	–	–
TA-AVI	12 (23.5)	4 (12.5)			

*[a]Serum creatinine ≥ 200 µmol/l or GFR < 60 ml/min/1.73 m^2, [b]history of anemia and/or hemoglobin < 12.0 g/dl day before TAVI, *age > 85-year old was used in multivariate analysis because of its stronger predictive value than mean age, BMI – body mass index, PCI – percutaneous coronary intervention, TA-AVI – transapical aortic valve implantation, TF-AVI – transfemoral aortic valve implantation, TIA – transient ischemic attack, TSC-AVI – transsubclavian aortic valve implantation*

Table IV. The impact of peri-procedural antithrombotic therapy on early bleeding complications in univariate and multivariate logistic regression analysis

Antithrombotic therapy before TAVI	Patients on treatment before TAVI, *n* (%) *N* = 75[a]	Value of *p*	Univariate analysis OR (95% CI); value of *p*	Multivariate analysis* OR (95% CI); value of *p*
Clopidogrel[b]	22 (29.3)	0.005	5.737 (1.537–21.415); 0.009	4.43 (1.023–19.249); 0.04
DAPT	15 (20)	0.02	5.129 (1.074–24.495); 0.04	3.75 (0.668–21.136); 0.13
TAT	6 (8)	0.25	–	–
ASA	42 (56)	0.71	–	–
VKA	6 (8)	0.001	< 0.001 (< 0.001 – > 999.999); 0.96	< 0.001 (< 0.001 – > 999.999); 0.96
VKA + ASA	5 (6.6)	0.3	–	–
Antithrombotic therapy before TAVI	**Patients on treatment before TAVI, *n* (%) *N* = 80[c]**	**Value of *p***	**Univariate analysis OR (95% CI); value of *p***	**Multivariate analysis OR (95% CI); value of *p***
Clopidogrel	4 (5)	0.56	–	–
DAPT	48 (60)	0.49	–	–
TAT	8 (10)	0.40	–	–
VKA + ASA	15 (18.7)	0.33	–	–
VKA + clopidogrel	5 (6.2)	0.04	0.140 (0.015–1.315); 0.08	0.26 (0.024–2.688); 0.25

**Adjusted to the independent predictors for early bleeding: BMI, anemia, age > 85 years, [a]8 patients without anticoagulation before TAVI, [b]1 patient on clopidogrel monotherapy + DAPT + TAT, [c]2 early deaths, 1 patient on VKA monotherapy, ASA – acetylsalicylic acid, DAPT – dual antiplatelet therapy, TAT – triple anticoagulant therapy, VKA – vitamin K antagonists*

Late bleeding complications

Initially, long-term observation included 77 (92.7%) patients; 2 (2.4%) patients were lost in follow-up; 10 (12.9%) patients died after discharge, and 7 of them were excluded due to a lack of reliable data. The median follow-up was 12 ±15.5 months (range: 1 to 23) and included 68 (81.9%) patients.

Antithrombotic therapy at discharge and late bleeding are presented in Table VII. We noted 35 (51.4%) late bleeding events and 29 (82.8%) of them

Table V. Early bleeding complications – comparison of peri-procedural antithrombotic therapy to the safest regimens

Anticoagulation before TAVI vs. VKA (no. of bleeding events/no. of patients) (51/68[a]) vs. (0/6)	Value of *p*	Anticoagulation after TAVI vs. VKA + clop. (no. of bleeding events/no. of patients) (51/75[b]) vs. (1/5)	Value of *p*
ASA (25/42)	0.006	Clopidogrel (3/4)	0.09
DAPT (14/15)	0.002	DAPT (31/48)	0.05
TAT (5/6)	0.003	TAT (6/8)	0.05
VKA + ASA (2/5)	0.19	VKA + ASA (7/15)	0.24

[a]1 patient clopidogrel monotherapy, 8 patients without pre-TAVI treatment, [b]2 early deaths, 1 patient VKA monotherapy, ASA – acetylsalicylic acid, DAPT – dual antiplatelet therapy, TAT – triple anticoagulant therapy, VKA – vitamin K antagonists

Table VI. Indication for antithrombotic therapy pre-TAVI and correlation with early bleeding in 75 patients

Indication for pre-TAVI anticoagulant therapy	ASA (bleeding)	VKA (bleeding)	DAPT (bleeding)	VKA + ASA (bleeding)	TAT (bleeding)
CAD	42 (25)				
CAD + AF				3 (2)	
CAD + DVT				1	
CAD + MVR				1 (1)	
PCI preparation for TAVI			**12 (12)***		
PTRA pre TAVI			1		
Preparation for TAVI			3 (2)[a]		
PCI preparation for TAVI+AF					**6 (5)***
AF		6 (0)			

**p = 0.001 the difference in early bleeding between patients with preceding PCI (PCI pre TAVI, PCI pre TAVI + AF) vs. patients without PCI, [a]1 patient clopidogrel monotherapy, AF – atrial fibrillation, ASA – acetylsalicylic acid, CAD – coronary artery disease, DAPT – dual antiplatelet therapy, DVT – deep vein thrombosis, MVR – mitral vale replacement, PCI – percutaneous coronary intervention, PTRA – percutaneous transluminal renal angioplasty, TAT – triple anticoagulant therapy, TAT – triple anticoagulant therapy, VKA – vitamin K antagonists*

Table VII. Antithrombotic therapy and late bleeding during first 6 months of follow-up

Late bleeding	Combined therapy[a], *n* (%), *N* = 64	Monotherapy[b], *n* (%), *N* = 4
Gastrointestinal tract	6 (9.4)[c]	0
Epistaxis	5 (7.8)[d]	0
Petechiae	11 (17.2)[e]	0
Anemia (hemoglobin < 12.0 g/dl)	13 (20.3)[f]	0
Total	**35 (54.7)***	**0**

**p = 0.04 the difference in late bleeding between patients with long-term combined prophylaxis vs. patients on antithrombotic monotherapy, [a]DAPT (n = 43), VKA + ASA (n = 12), Clop + VKA (n = 6), TAT (n = 3), [b]Clop (n = 2), VKA (n = 2), [c]VKA + ASA (n = 3) (breaching the therapeutic INR range), DAPT (n = 3), [d]VKA + ASA (n = 3), DAPT (n = 1), TAT (n = 1), [e]DAPT (n = 7), TAT (n = 2), VKA + Clop (n = 1), VKA + ASA (n = 1), [f]DAPT (n = 9), VKA + ASA (n = 3), VKA + Clop (n = 1)*

occurred during the first 6 months after TAVI. There were no incidents of bleeding in the VKA/clopidogrel monotherapy group. The difference between the number of late bleeding events in the combined therapy compared to monotherapy group was significant ($p = 0.04$).

Late bleeding was not a direct cause of any of the 10 (12.9%) late deaths. There were no incidents of late thromboembolic complications.

Discussion

Early bleeding is one of the most common TAVI complications, affecting from 30% to more than 70% of the TAVI population [6–15]. A high proportion of late bleeding is also observed at 1–2 years after the procedure (14.7–28.6%) [6–11]. This is probably a result of special characteristics of the TAVI population. Transcatheter aortic valve implantation patients are mainly elderly people who due to advanced age, a high prevalence of anemia, renal failure and low body mass, are subjected to high risk for bleeding [9–14]. Similarly, our analysis showed that early bleeding affected more than 60% of the study population and more than 50% of participants had bleeding during the long-term follow-up. Moreover, we confirmed that pre-procedural

anemia, BMI and advanced age were independent predictors of early bleeding after the procedure.

Despite the high prevalence of TAVI bleeding, the impact of peri-procedural and long-term antithrombotic regimens on them has never been investigated so far. Therefore, the analysis of the correlation between anticoagulation and TAVI bleeding is the main advantage of our study.

Firstly, we showed that long-term combined antithrombotic prophylaxis correlated significantly with late bleeding. Nearly 60% of late bleeding concerned patients on DAPT, and over 80% of late bleeding occurred in the first 6 months after TAVI, when combined therapy is recommended. We suggest that the safest prophylaxis after TAVI seems to be antithrombotic or antiplatelet monotherapy, instead of the currently recommended DAPT.

This finding is consistent with numerous data which proved that use of DAPT for the secondary prevention of acute coronary syndrome is associated with a more than 3-fold and 5-fold increase in bleeding and vascular complications respectively, in comparison to ASA alone [16]. Similarly, TAT is an independent risk factor for late bleeding and worsens the 1-year prognosis. The ratio of bleeding increases especially in the elderly on TAT, and almost all incidents occur within the first 6 months of treatment [17–19]. Furthermore, the results of the Danish Registry concur with our finding that combined therapy in comparison to VKA monotherapy significantly increased the risk for late bleeding in patients with AF, without any advantages in thromboembolic risk reduction [20]. Therefore, chronic VKA monotherapy is considered as one of the safest in elderly patients with AF and stable CAD [21–24].

Moreover, with regard to early post-TAVI prophylaxis, we found that only participants on VKA + clopidogrel had the fewest bleeding events. Similar results derived from the randomized prospective WOEST trial, which confirmed that the combination of VKA with clopidogrel was the safest early antithrombotic prophylaxis in patients with chronic VKA therapy undergoing PCI [25]. This statement was also confirmed by Karjalainen *et al*., who suggested that this combination was the safest antithrombotic therapy in elderly patients with a high risk for bleeding who underwent PCI [17].

Secondly, our study is the first to assess the impact of pre-procedural antithrombotic therapy on 30-day risk for bleeding after TAVI. We found that over 90% of participants had already received various antithrombotic regimens before TAVI; of those 20% chronically used VKA due to AF and nearly 30% received DAPT or TAT because of prior PCI. Nearly 90% of patients with a preceding use of DAPT and over 80% with TAT experienced early bleeding and only the patients on preceding VKA monotherapy, prepared for the procedure as recommended [21, 24], had no bleeding within 30 days after TAVI.

These results are consistent with numerous studies and registries dedicated to invasive procedures performed during the use of VKA or combined therapy. These data showed increased rates of bleeding, blood transfusions, early mortality and prolonged hospitalization after coronary artery bypass grafting (CABG) or PCI performed during DAPT or TAT [17, 18, 26]; meanwhile short peri-procedural discontinuation of VKA or its replacement with LMWH is safe [21, 24]. Therefore the EACTS statement recommends at least 5-day discontinuation of clopidogrel before planned CABG or other surgery connected with a high bleeding risk [24].

The crucial achievement of our study is the evidence that the use of clopidogrel before TAVI related to preceding PCI is an independent bleeding risk factor.

Of note, the current position of ESC regarding TAVI recommends that the diagnosis and treatment of CAD should be performed before TAVI [1]. Moreover, untreated CAD is a contraindication for TAVI [1]. However, the term of prior PCI, the type of stents and the duration of DAPT remain undefined. In view of our results, it seems reasonable to extrapolate EACTS recommendations on pre-procedural clopidogrel discontinuation for TAVI preparation [24].

We believe that if PCI before TAVI is required, coronary angioplasty or bare metal stent implantation should be favored with the use of only 4 weeks of DAPT, so that patients can return to ASA alone before TAVI. Thus, PCI should be performed to allow for at least 5 days of clopidogrel discontinuation before TAVI. In patients undergoing PCI and using VKA, in order to reduce the risk for bleeding, TAT should be limited to 2 weeks after PCI. The soonest return to VKA with one antiplatelet agent followed by VKA monotherapy before TAVI should be recommended.

Post-TAVI anticoagulation should be individualized. In light of promising reports, in patients where VKA is used chronically, we may attempt to use only VKA in combination with one antiplatelet agent during the first 3–6 months after TAVI, followed by long-term VKA monotherapy. The TAT after TAVI should depend only on prior PCI. Since TAVI patients are a group with a high risk for bleeding, if the time that elapsed from PCI still requires that TAT be used after TAVI, such patients' TAT should be ceased as soon as possible, and they must start VKA with one antiplatelet agent with subsequent VKA monotherapy. Similarly, in patients with CAD and no indications for chronic VKA, DAPT should be used after TAVI only when the time that has elapsed since PCI still requires that, followed by the chronic use of one antiplatelet agent. Finally, in patients with no other indications for anticoagulation, in view of the

presumed low thrombogenicity of bioprostheses and high bleeding risk in the TAVI population, we are convinced that 3–6 month antiplatelet monotherapy is sufficient.

Finally, despite the fact that early bleeding caused 50% of in-hospital deaths, we were not able to prove its impact on prognosis. This finding is contrary to other reports which clearly stated that early post-procedural bleeding is a predictor of 30-day mortality and worsens long-term survival after TAVI [5–14]. This is probably due to a high number of all noted early incidents and the small size of our study population.

Our study is the first known report on the impact of peri-procedural and long-term antithrombotic therapy on bleeding complications after TAVI. We managed to prove that the peri-procedural use of DAPT or TAT had a direct impact on early bleeding and combined long-term prophylaxis increased the risk for late bleeding. Moreover, the analysis proved that TAVI patients had a high risk for bleeding complications, which significantly exceeds the risk for thromboembolic events. Although this report describes initial, one-center results when peri-procedural antithrombotic therapy was mostly based on an individual physician's decision, it can be valuable guidance for TAVI care until the results of multi-center prospective studies appear.

The partially retrospective nature and the number of patients involved were the obvious limitations of the present study. Moreover, the analysis regarding anticoagulation was not based on randomized treatment, which causes a basic bias of our analysis. Because of the small number of participants we could not assess separately either the risk for major and life-threatening bleeding or the risk for bleeding in patients with transvascular and transapical bioprosthesis implantation. We could not fully estimate the impact of variable drug regimens on late bleeding for the same reason. A larger number of patients and treatment randomization would allow more accurate statistical modeling and give greater power to the results. In the end, the definitions of bleeding differ between early and long-term follow-ups mainly because of data collection before VARC end points standardization. Neither did we fully evaluate the impact of preceding PCI on early bleeding because of its strong correlation with use of clopidogrel. Further studies on antithrombotic treatment and preceding interventions with respect to early and late bleeding, in larger TAVI populations, are required.

In conclusion, advanced age, BMI, and a history of anemia increased the risk for early bleeding after TAVI. Pre-TAVI clopidogrel should be avoided; therefore when deciding about the time of PCI and stent type, discontinuation of clopidogrel in the pre-operative period must be taken into account. Vitamin K anatagonists with clopidogrel seems to be the safest therapy in the early post-TAVI period. Clopidogrel or VKA monotherapy seems to be the safest long-term prophylaxis.

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