Patients scheduled for TAVI tend to form abnormal fibrin clots more resistant to lysis: the impact of age

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ABSTRACT

Background: Fibrin accumulation within the stenotic leaflets associated with impaired fibrinolysis was observed in severe aortic stenosis (AS). Little is known about fibrin clot properties in patients scheduled for transcatheter aortic valve implantation (TAVI).

Aims: We investigated whether TAVI patients display a more prothrombotic state, including suppressed fibrinolytic capacity compared to those undergoing surgery.

Methods: We enrolled patients with advanced AS without significant atherosclerotic vascular disease scheduled for TAVI (n = 45) or surgical aortic valve replacement (*SAVR, n = 59*). Plasma fibrin clot features, including clot permeability (Ks) reflecting an average pore size, and lysis potential (Lys50), along with thrombin generation were determined off anticoagulation within 12 hours before the procedure.

Results: TAVI patients compared to SAVR had prolonged Lys50 (median 420 [IQR, interquartile range, 337–480] seconds vs 379 [337–428] seconds; $P = 0.045$) and formed denser clots, reflected by lower Ks (3.66 [3.05–4.84] vs 4.36 [3.6–5.27] $\times 10^{-9}$ cm^2; $P = 0.02$), but after adjustment for age the latter difference was no longer significant. Apart from age, concomitant diabetes mellitus, or chronic kidney disease, prolonged Lys50 was an independent predictor of indication for TAVI in AS patients on multivariate regression analysis. There was a delayed start of thrombin generation in TAVI patients (lag time, 4.5 [3.8–6.3] minutes vs 4.2 [3.3–4.7] minutes; $P = 0.035$), without other differences in thrombin generation parameters.

Conclusions: This study is the first to show that patients scheduled for TAVI are characterized by prothrombotic fibrin clot properties including denser fibrin meshwork and more resistant to lysis compared with those undergoing SAVR, which might explain in part increased thromboembolic risk following TAVI.

Key words: aortic stenosis, clot structure, fibrin, fibrinolysis, transcatheter aortic valve implantation

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INTRODUCTION

Aortic stenosis (AS) is the most common progressive valve disease and its prevalence increases with age up to 9.8% at the age of 80 years or more [1, 2]. The advanced AS is characterized by obstruction of the left ventricular (LV) outflow resulting in inadequate exercise cardiac output and death from cardiovascular causes, which affects more than half symptomatic patients during the first 2 years [1].

Involvement of blood coagulation and fibrinolysis in the progression of AS was suggested [3]. Increased valvular expression of tissue factor, tissue factor pathway inhibitor, prothrombin, factor (F) XIII, and the von Willebrand factor associated with enhanced local inflammation and calcification were described in AS [3, 4]. It was demonstrated that systemic and local imbalance between plasminogen activators and their inhibitors were involved in the progression of the valve pathology [5]. Natorska et al. [3] showed in 2013 that hypofibrinolysis as evidenced by prolonged plasma clot lysis time characterizes severe AS patients and is associated with higher maximal transvalvular gradient and larger thickness of stenotic leaflets as well as larger fibrin deposits within the stenotic aortic valves. Increased thrombin generation has also been observed in patients with moderate-to-severe AS even in the absence of clinically overt atherosclerotic vascular disease [6, 7].

WHAT'S NEW?

Fibrin accumulation within the stenotic leaflets associated with impaired fibrinolysis was observed in patients with severe aortic stenosis. The present study demonstrates for the first time that patients scheduled for transcatheter aortic valve implantation (TAVI) are characterized by prothrombotic fibrin clot properties such as denser fibrin meshwork and that the clots are more resistant to lysis in comparison to those in patients undergoing surgical aortic valve replacement (SAVR). These findings could partially explain increased thromboembolic risk following TAVI.

The first transcatheter aortic valve implantation (TAVI) was performed in 2002 by Alain Cribier and since then, it became an established therapeutic option in patients with symptomatic severe AS [8]. Nowadays, intervention options which include TAVI or SAVR should be based upon estimated surgical risk assessed by the Heart Team according to the current *European Society of Cardiology* (ESC) guidelines [9–11]. Changes in blood coagulation in AS patients undergoing TAVI are not well described. Sedaghat et al. [12] assessed several hemostasis-related biomarkers in 35 patients undergoing transfemoral TAVI and reported that levels of thrombin-antithrombin complex (TAT), plasmin-α2-antiplasmin complex (PAP), and D-dimer were above the reference ranges before TAVI and significantly increased after TAVI, which indicates that TAVI induces thrombin formation associated with secondary fibrinolysis. To the best of our knowledge, there are no published reports on fibrin clot properties in patients scheduled for TAVI. In this study, it was hypothesized that TAVI patients display a more prothrombotic fibrin clot phenotype, including suppressed fibrinolytic capacity, compared to those undergoing surgical treatment.

METHODS

Patients

We enrolled 104 patients with advanced symptomatic degenerative AS who were scheduled for aortic valve replacement. All patients were assessed preoperatively by a local Heart Team. Fourty-five patients were scheduled for TAVI and 59 for SAVR. Indication for TAVI was based on the current ESC guidelines [9]. Transcatheter heart valve size and approach were selected by using multidetector computed tomography angiography. Patients qualified for TAVI were older (>75 years old), had elevated surgical risk, defined as at least 4% in EuroScore II or STS score calculator, had favorable valve morphology for TAVI, did not have any indications for other cardiac surgical intervention (such as severe other valve defect, aneurysm of the ascending aorta, severe coronary artery disease requiring coronary artery bypass graft, septal hypertrophy requiring myectomy) or had geniune contraindications for SAVR such as the porcelain aorta, the presence of severe comorbidities, or frailty in accordance with ESC guidelines [9].

Inclusion criteria were: age over 18 years old, severe aortic stenosis according to the 2017 ESC and the European Association for Cardio-Thoracic Surgery defined as the peak velocity (PVel) >4 m/sec, the mean pressure gradient (MPG) >40 mm Hg and the aortic valve area (AVA) <1 cm^2 [9]. The first two parameters were directly measured with continuous wave Doppler, while the latter was calculated based on the continuity equation and measurement of the left ventricular outflow tract (LVOT) diameter, LVOT time-velocity integral (TVI) and aortic TVI.

To avoid potential confounding effects of other diseases on fibrin clot properties we excluded patients with a significant another valvular disease and epicardial or carotid artery stenosis requiring surgical or percutaneous treatment, infection, endocarditis, known cancer, autoimmune disorders, a history of thromboembolism or major bleeding during last 3 months.

Patients with abnormal glycaemia in the oral glucose tolerance test or having fasting glucose >7 mmol/l or/and receiving hypoglycemic agents were classified as having diabetes mellitus (DM). Arterial hypertension was defined according to the 2018 ESC guidelines [13]. The chronic kidney disease (CKD) was diagnosed in patients with either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for at least 3 months according to the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation. Chronic obstructive pulmonary disease (COPD) was defined on the basis of spirometry indicative of persistent airflow limitation (according to the Global Initiative for Chronic Obstructive Lung Disease).

The study was approved by Ethics Committee and the patients gave their informed written consent to participate in this study.

Laboratory investigations

Blood samples were taken after overnight fasting and 24 hours after oral anticoagulation (OAC) discontinuation. Lipid profile, fasting plasma glucose, creatinine, GFR, alanine aminotransferase (ALT) were determined by routine assays. Fibrinogen was measured by the von Clauss method (Siemens, Marburg, Germany).

Citrated venous blood samples for fibrin analysis were managed as previously described [14].

Calibrated automated thrombogram

Thrombin generation kinetics were measured with the Calibrated Automated Thrombogram (CAT) (Thrombinoscope BV, Maastricht, Netherlands) according to the manufacturer's instructions [15]. Briefly, 80 µl of plate-

let-poor plasma was diluted with 20 µl of PPP Reagent or Thrombin Calibrator, and 20 µl of FluCa solution (all from Stago, Asnieres-sur-Seine, France). Each plasma sample was analyzed in duplicate, and the intraassay variability was 7%. Lag-time is the time from the start of analysis until thrombin starts to generate. The maximum concentration of thrombin formed during the recording time is described as the thrombin peak and the area under the curve represents the endogenous thrombin potential (ETP).

Clot permeability

Permeation of plasma fibrin clots was determined as described [14]. Briefly, 20 mm $CaCl_2$ and 1 U/ml human thrombin (Merck KGaA, Darmstadt, Germany) were added to citrated plasma. Tubes containing the clots were connected to a reservoir of a Tris-buffered saline and its volume flowing through the gels was measured. A permeation coefficient (Ks), which indicates the pore size, was calculated from equation: $Ks = Q \times L \times \eta/t \times A \times \Delta p$, where Q is the flow rate in time t, L is the length of a fibrin gel, η is the viscosity of liquid (in poise), t is percolating time, A is the cross-sectional area (in cm^2) and Δp is a differential pressure (in dyne/cm^2).

Scanning electron microscopy (SEM)

Plasma fibrin clots from five randomly selected patients classified to SAVR or TAVI were analyzed. Fixation was performed after the permeability measurement using 2.5% glutaraldehyde in phosphate-buffered saline solution for 2 hours. Fixed clots were, washed with distilled water, and then dehydrated in graded ethanol solutions, dried by the critical point procedure, and sputter coated with gold. Samples were scanned in six different areas (microscope JEOL JCM-6000; JEOL Ltd., Tokyo, Japan). Images were analyzed in ImageJ (US National Institutes of Health, Bethesda, MD, USA).

Clot lysability

Clot lysability was assessed using a turbidimetric method by Carter et al. [16]. Briefly, citrated plasma was mixed with recombined tissue plasminogen activator (rtPA; 83.3 ng/ml, Boehringer Ingelheim, Biberach, Germany), 0.03 U/ml human thrombin (Merck KGaA), and 7.5 mmol/l $CaCl_2$. The turbidity was measured at 340 nm at 37°C (Sunrise Reader, Tecan, Maennedorf, Switzerland). Lysis time (Lys50) was calculated as the time from full clot formation to the time when absorbance was reduced by 50% (Figure 1).

Statistical analysis

Data are presented as means ± standard deviation (SD) or medians and interquartile range (IQR: 25th to 75th) for continuous variables and as frequencies and percentages for categorical variables. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Comparison between groups was performed using χ^2 test or Fisher's Exact test for categorical data and the independent t-test or the Mann-Whitney U test for continuous data as appropriate. In order to minimize the influence of age on coagulation and fibrinolysis parameters, the analysis of covariance with age as covariate was used. If appropriate, logarithmic transformation of non-normally distributed variables was performed. Univariate and multivariate logistic regression models were performed to identify variables which may influence the indication for TAVI. Demographic (age, gender, body mass index [BMI]) and clinical (comorbidities: atrial fibrillation [AF], hypertension, DM, CKD, coronary artery disease [CAD], COPD) characteristics, the severity of the defect (LV ejection fraction [EF], mean transvalvular gradient) were tested as potential explanatory variables. Variables that may influence the indication for TAVI with a significance level of $P < 0.2$ in the bivariate models were selected for possible inclusion in the multivariate logistic regression models. The multivariate model was fitted using backward stepwise regression. Results are presented as odds ratios (OR) ± 95% confidence interval (CI). A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

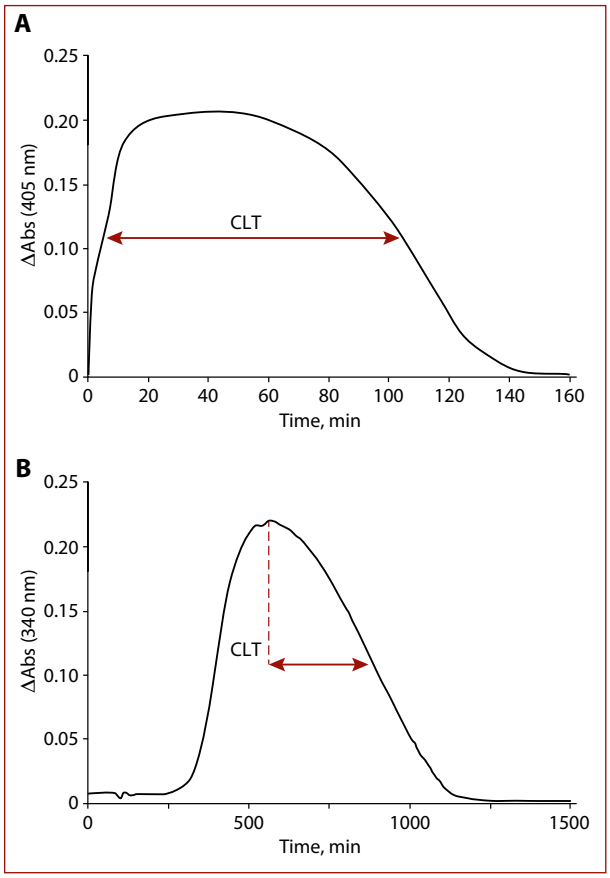

Figure 1. Representative curve of lysis time (Lys50)

RESULTS

Characteristics of the patients

A total of 104 patients with severe AS, who were mostly overweight and hypertensive were included to the

Table 1. Patient characteristics

	Patients undergoing SAVR (n = 59)	Patients undergoing TAVI (n = 45)	*P*-value
Age, years, mean (SD)	74.5 (8.1)	78.5 (9.5)	0.023
Male sex, n (%)	26 (44.1)	20 (44.4)	0.569
BMI, kg/m^2, mean (SD)	27.9 (4.8)	28.8 (7.6)	0.478
Comorbidities, n (%)			
Atrial fibrillation	2 (4.4)	10 (16.9)	0.048
Hypertension	50 (84.7)	33 (73.3)	0.151
Chronic kidney disease	14 (23.7)	23 (51.1)	0.004
Diabetes mellitus	2 (3.4)	12 (26.7)	0.0006
COPD	6 (10.2)	5 (11.1)	0.999
Coronary artery disease	10 (16.9)	25 (55.6)	<0.0001
Myocardial infarction >3 months	2 (3.4)	3 (6.7)	0.650
Stroke >3 months	1 (1.7)	4 (8.9)	0.163
Laboratory parameters			
Glucose, mmol/l, median (IQR)	5.54 (5.0–5.46)	5.46 (4.94–5.61)	0.175
ALT, U/l, median (IQR)	19 (15.5–24.0)	14 (11.0–20.0)	0.014
Creatinine, µmol/l, median (IQR)	85 (71–100)	99.0 (88.4–128.0)	0.024
eGFR, ml/min, mean (SD)	65.1 (15.7)	56.0 (18.5)	0.008
LDL cholesterol, mmol/l, mean (SD)	1.75 (0.68)	2.57 (1.0)	<0.0001
Fibrinogen, g/l, mean (SD)	3.54 (0.73)	3.93 (1.02)	0.124
Echocardiographic data			
Mean transvalvular aortic gradient, mm Hg, mean (SD)	50.8 (17.0)	50.0 (17.0)	0.805
Maximal transvalvular aortic gradient, mm Hg, mean (SD)	84.6 (26.9)	82.6 (26.1)	0.699
LV EF, %	59.2 (11.2)	59.2 (11.9)	0.992
Estimated surgery risk score, mean (SD)			
Euroscore II	1.93 (1.60–3.50)	6.05 (3.38–8.49)	<0.0001
STS-risk of mortality	2.05 (1.46–2.33)	4.01 (2.71–5.54)	<0.0001

Data are given as mean (SD), median (IQR) and number (percentage).

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricle ejection fraction; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; LDL, low-density lipoproteins; SAVR, surgical aortic valve replacement; STS, short-term risk calculator; TAVI, transcatheter aortic valve implantation

study (Table 1). Forty-five patients were scheduled for TAVI and 59 for SAVR. The patients referred to the SAVR were younger (Table 1). Patients qualified for TAVI had an increased estimated risk for surgery compared to SAVR (Euroscore II: 6.05% [3.38–8.49] vs 1.93% [1.60–3.50] and STS 4.01% [2.71–5.54] vs 2.05% [1.46–2.33], both $P<0.0001$, respectively) and more often had AF, CKD, DM, CAD, and hypercholesterolemia (Table 1). Due to the diagnosed AF, 3 subjects were treated with non-vitamin K antagonist oral anticoagulants (NOAC) and 9 with vitamin K antagonists (VKA) prior to hospitalization.

Within 30 days after TAVI or SAVR, we recorded 3 ischemic cerebrovascular events, i.e. 2 ischemic stroke episodes after TAVI (4%) and one stroke after SAVR (1.6%). No other cardiovascular events were observed within the first month.

Coagulation and fibrinolysis parameters

Thrombogram analysis showed that in our patient group, thrombin peak correlated with PVel (r = –0.5; $P = 0.018$), while lag time was correlated with PVel (r = 0.51; $P = 0.015$) and AVA (r = –0.2; $P = 0.045$). Analysis of the AS patients with individual comorbidities in terms of CAT parameters showed prolonged lag time in patients with DM (4.71 [3.97–7.95] vs 4.28 [3.55–5.00] minutes; $P = 0.017$) with no other differences.

Patients with AS referred to TAVI in comparison to those qualified for SAVR were characterized by delayed thrombin generation (Table 2). There were no intergroup differences in other thrombin generation parameters, such as ETP (Figure 2, Table 2).

Among TAVI patients with or without concomitant AF, CKD, DM, CAD, or EF <40% vs ≥40% there were no differences found in thrombin generation parameters (all $P>0.05$).

Fibrin network density, reflected by Ks, was 16% lower in the TAVI group compared with the SAVR group (Table 2), but after adjustment for age the difference was not significant ($P = 0.17$; Table 2). Increased clot density in TAVI compared to SAVR patients was confirmed on SEM images (Figure 3). Image analysis showed that plasma fibrin clots from TAVI patients were composed of thinner fibrin fibers than those from SAVR patients (90.5 ± 3.3 vs 95.6 ± 4.7 nm, $P = 0.012$). Among TAVI patients, those with CKD, compared to the remainder, had Ks reduced by 13.2% (3.28 [2.71–4.36] vs 3.78 [3.56–4.87] × 10^{-9}cm^2; $P = 0.035$), while there was no impact of AF, DM, CAD, or EF <40% vs ≥40% on Ks (all $P>0.05$). After adjustment for age, the influence of CKD on Ks was no longer significant ($P = 0.36$).

In the whole cohort of AS patients , there were no associations of the AS severity measured as AVA or transvalvular gradients with Lys50 (all $P>0.05$). Of importance, the analysis of fibrinolysis capacity induced by rtPA showed 10.8%

Table 2. Coagulation and fibrinolysis parameters

	Patients undergoing SAVR (n = 59)	Patients undergoing TAVI (n = 45)	*P*-value[a]	*P*-value[b]
Lag time, min, median (IQR)	4.2 (3.3–4.7)	4.5 (3.8–6.3)	0.035	0.008
ETP, nm × min, mean (SD)	1655 (443)	1571 (573)	0.415	0.435
Peak, nm, mean (SD)	232.6 (86.6)	262.7 (120)	0.150	0.278
Ks, $\times 10^{-9}$ cm^2, median (IQR)	4.36 (3.6–5.27)	3.66 (3.05–4.84)	0.022	0.168
Lys50, s, median (IQR)	379 (337–427.5)	420 (337–480)	0.045	0.013

[a]Unadjusted for age. [b]Adjusted for age, after logarithmic measurements of right-skewed distributions.

Abbreviations: ETP, endogenous thrombin potential; Ks, a clot permeation coefficient; Lys50, lysis time; Peak, peak thrombin generated; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

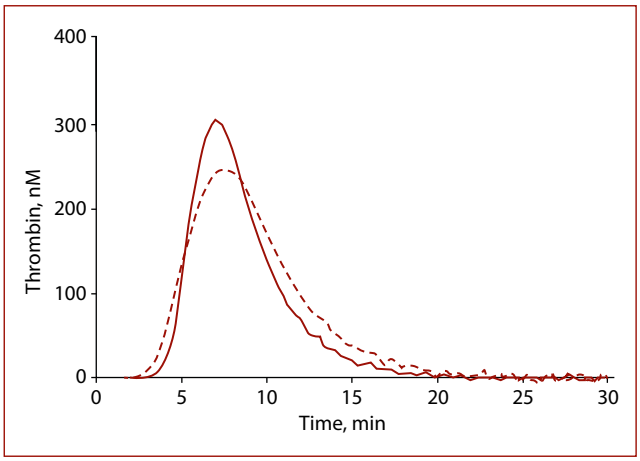

Figure 2. Representative thrombin generation curves in the calibrated automated thrombogram generated in plasma of patients scheduled for surgical aortic valve replacement (SAVR; dashed line) or those scheduled for transcatheter aortic valve implantation (TAVI; solid line)

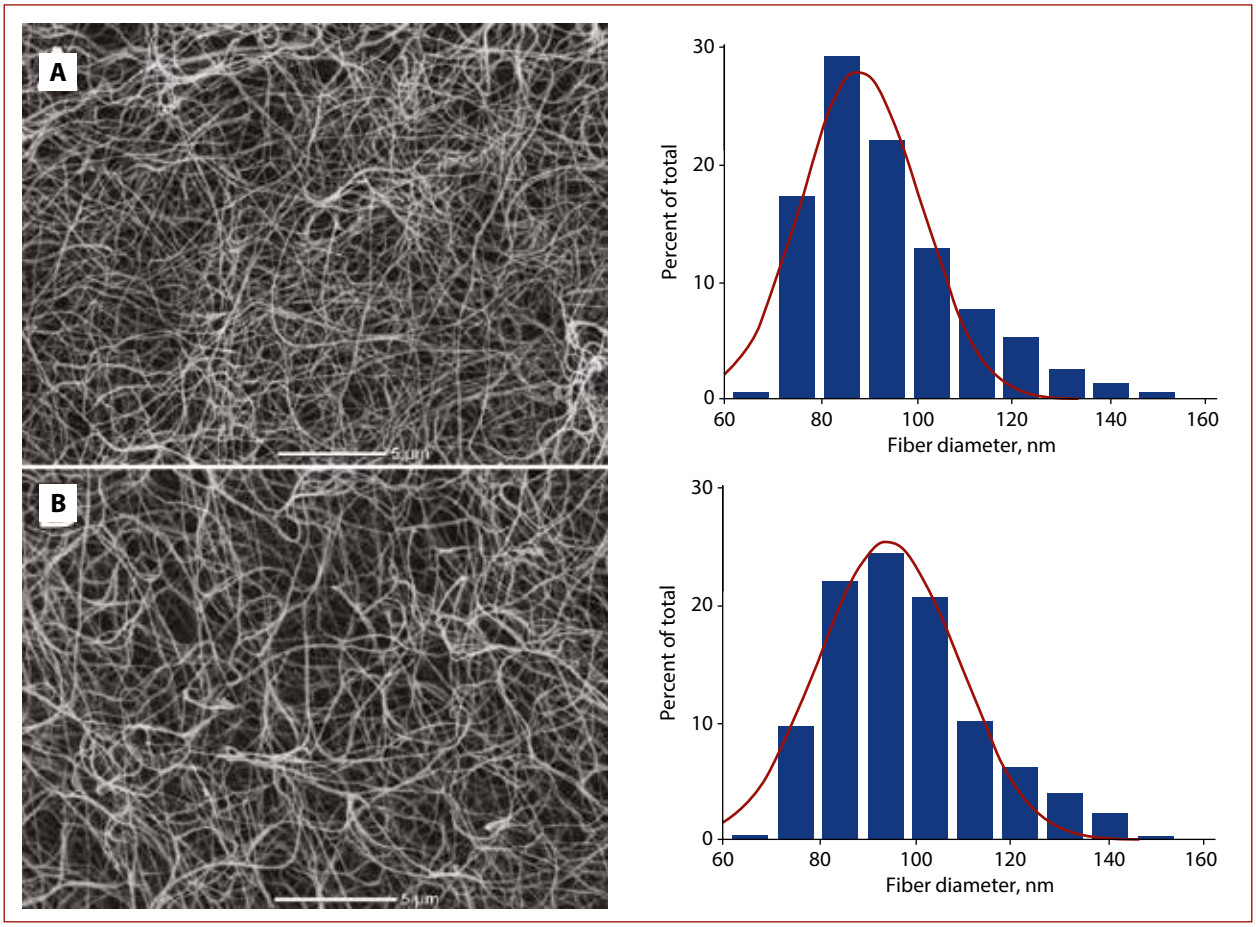

Figure 3. Representative scanning electron micrographs showing morphology of fibrin clots prepared from plasma of patients with similar fibrinogen levels scheduled for transcatheter aortic valve implantation (**A**) or surgical aortic valve replacement (**B**), along with histograms for fibrin diameter. Magnification, 5000×; scale bar, 5 µm

Table 3. Logistic regression models for *tr*anscatheter aortic valve implantation indication

Variable	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age (per 10 years)	1.57 (1.060–11.12)	0.028	1.82 (1.20–11.49)	0.010
Chronic kidney disease	3.62 (1.55–8.47)	0.003	—	
Diabetes mellitus	10.18 (2.15–48.34)	0.004	9.30 (1.76–49.03)	0.009
Coronary artery disease	6.81 (2.71–17.12)	<0.0001	—	
Lys50 (per 10 s)	1.06 (1.01–1.11)	0.029	1.05 (1.01–1.11)	0.041

Abbreviations: CI, confidence interval; OR, odds ratio

longer Lys50 in TAVI patients compared to SAVR (Table 1). There were no differences in Lys50 between TAVI patients with or without concomitant AF, CKD, DM, CAD, or EF <40% vs ≥40% (all $P > 0.05$).

In the univariate regression models predictors of indication for TAVI were: older age, concomitant CKD, DM, CAD, and prolonged Lys50 (all $P < 0.05$), but not BMI, AF, hypertension, COPD, EF, or mean transvalvular gradient (all $P > 0.05$).

The multivariate logistic regression analysis revealed that age, concomitant DM, CKD and prolonged Lys50 were independently associated with indication for TAVI in AS patients (Table 3).

DISCUSSION

The present study demonstrates for the first time that the impact of advanced age on prothrombotic fibrin clot properties in patients undergoing TAVI in comparison to those undergoing SAVR. We found a trend toward greater risk of the formation of denser fibrin networks in patients undergoing TAVI. It was identified that hypofibrinolysis is a key feature of the prothrombotic clot phenotype in patients scheduled for TAVI. The current study increases our knowledge on potential new mechanisms which might contribute to the risk of valve thrombosis as well as ischemic cerebrovascular events following TAVI. Our results provide a rationale for further studies assessing a predictive value of fibrin variables in AS patients. Furthermore, it is unknown whether any antithrombotic therapy after TAVI might reduce the prothrombotic tendency and this issue remains to be established.

Previous reports showed that hypofibrinolysis is implicated in the pathophysiology of severe AS [3]. A key novel finding is a longer Lys50 in the TAVI group compared to SAVR also after adjustment for age, indicating that patients scheduled for TAVI are characterized by impaired global fibrinolysis. In the Lys50 assay α2-antiplasmin as a fibrinolysis inhibitor and plasma fibrinogen concentration have a major contribution [16]. In our study, there were no differences in fibrinogen concentrations between the SAVR and TAVI groups, thus it might be speculated that α2-antiplasmin may contribute to ,impairment of fibrinolysis in patients undergoing TAVI given a typical increase in antiplasmin levels observed with increasing age [17]. Lys50 has been considered as the most suitable plasma-based lysis variable for analysis in clinical studies [16] as evidenced by a sub-analysis of the large randomized clinical trial with ticagrelor, PLATO, which showed that each 50% increase in Lys50 was associated with cardiovascular death or spontaneous myocardial infarction during one-year follow-up after acute coronary syndrome [18]. Interestingly, the multivariate regression analysis showed that besides age and other factors previously reported to be more frequent, i.e. comorbidities, and associated with the indication for TAVI such as DM [19] and CKD [20, 21], also prolonged Lys50 was identified as an independent predictor of indication for TAVI. This highlights the role of fibrinolytic capacity in advanced AS.

It was found that patients with AS scheduled for TAVI compared to SAVR had lower Ks, indicating a smaller average size of pores in the fibrin network and thinner fibrin fibers in TAVI patients, which was confirmed by SEM analysis. More compact clots, relatively resistant to lysis are mostly composed of thin fibrin fibers and are usually formed at higher concentrations of fibrinogen or thrombin in both purified and plasma-based assays [22]. However, after adjustment for age the differences in Ks were no more significant. This observation highlights the impact of age and associated comorbidities known to unfavorably modify fibrin clot features. On the other hand, impaired clot lysability, at a relatively high dose of tPA used in the assay by Carter et al. [16], remained significant even after adjustment for age or multiple coexisting comorbidities such as DM, AF, CAD, or CKD which are known to be associated with prolonged Lys50 [13, 16]. This observation suggests that the contribution of hypolysability to a prothrombotic state in patients scheduled for TAVI is substantial. Thus, lower susceptibility to enzymatic degradation of fibrin in TAVI patients is an important and previously unknown prothrombotic marker, which might be useful in everyday clinical practice given positive results of future studies. Further studies are needed to elucidate whether impaired fibrin clot properties, assessed before TAVI, may be predictive of thrombotic complications after the TAVI procedure. Since such fibrin features cannot be markedly improved by antiplatelet therapy with inconsistent data on a beneficial effect of aspirin on fibrin variables [23], our study might support clinical data suggesting suboptimal thromboprotection in a subset of TAVI patients, who receive dual antiplatelet therapy (DAPT), which is usually recommended for 3 or

6 months to prevent device-related thromboembolic complications [9]. Thromboembolic events after TAVI, mostly ischemic cerebrovascular episodes, occur in up to 7% of the patients within the first years of TAVI and are associated with considerable morbidity and mortality [24–27]. Subclinical leaflet thrombosis following TAVI may affect up to 11.5% of patients within months after the procedure, which increases the risk of stroke or transient ischemic attack [24, 25, 28]. OAC, including VKA or NOAC, was shown to prevent and treat this complication [24, 26], and OAC was demonstrated to favorably affect fibrin clot characteristics [29]. Therefore, given robust data linking abnormal fibrin clot structure with arterial thromboembolism and AS, it is possible that the prothrombotic fibrin clot phenotype can be observed in TAVI patients being an additional risk factor for thromboembolic complications. On the other hand, AS has repeatedly been reported to be associated with bleeding tendency in approximately 20% of patients [30]. The main mechanism of bleeding observed in severe AS patients free of anticoagulation is acquired type 2A von Willebrand syndrome (vWS), which is correlated with the severity of valve stenosis and disappears after correction of the valve defect. The type 2A vWS detected using various laboratory assays in up to 80% of patients with severe AS is characterized by a selective deficiency of high molecular weight multimers of vWF involved among others in platelet adhesion [30]. Interestingly, clinically relevant bleeds are less common in AS patients despite the features of this deficiency measured in plasma and this may suggest the existence of the mechanisms promoting efficient hemostasis such as enhanced thrombin formation [7, 30]. In the TAVI cohort, vWS occurs with incidence of 1.7%, and it increases the periprocedural bleeding risk [31]. It remains to be established whether fibrin clot properties show any association with vWS in TAVI patients.

Of note, this study showed that TAVI patients generated similar amounts of thrombin, i.e. peak thrombin and ETP, to those found in SAVR. However, the former group had slightly prolonged lag time in the CAT profiles than SAVR patients, indicating delayed onset of the propagation phase in thrombin generation capacity curves in TAVI patients. It might be concluded that patients with severe AS scheduled for TAVI had delayed prothrombin conversion to thrombin, but the final amount of thrombin generated is similar in TAVI and SAVT patients.

An increased in vivo thrombin generation as reflected by elevated TAT complexes has been found in patients before the TAVI procedure by Sedaghat et al. [12], which might in part counterbalance the primary hemostasis impairment, i.e. by potentiating platelet activation and aggregation. The actual formation of thrombin and its influence on the prothrombotic clot phenotype in TAVI patients remain to be established.

The study has several limitations. First, this was a preliminary study of a small sample size, thus the presented data should be interpreted with caution and perceived as the hypothesis-generating study. Second, several fibrinolysis and coagulation proteins which are involved in thrombin generation, fibrin formation, and fibrinolysis, including prothrombin, antiplasmin, plasminogen, and platelet-derived proteins, have not been evaluated [22, 29, 32]. Genetic modifiers of fibrin clot properties have not been assessed by us [33]. However, the mechanisms underlying the observed differences between two groups of patients were beyond the scope of the current research. Our findings on global tests strongly suggest that prothrombotic fibrin-related abnormalities are detectable in severe AS patients, which might be clinically relevant. To elucidate the role of blood prothrombotic alterations and their therapeutic implications after TAVI larger follow-up studies are needed.

CONCLUSIONS

Patients who were scheduled for TAVI demonstrated preoperatively a prothrombotic fibrin clot phenotype characterized by impaired lysis of denser fibrin networks composed of thinner fibers. Our results suggest that prothrombotic clot features may have an impact on increased risk of thromboembolic episodes associated with TAVI in AS patients, providing the rationale for further research to optimize the effectiveness of antithrombotic treatment after TAVI.

Article information

Conflict of interest: None declared.

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