Incidence, predictors and cerebrovascular consequences of leaflet thrombosis after transcatheter aortic valve implantation:

a systematic review and meta-analysis.

Fabrizio D'Ascenzo MD, Stefano Salizzoni* MD, Andrea Saglietto* MD, Martina Cortese MD, Azeem Latib MD, Anna Franzone MD, Marco Barbanti MD, Fabian Nietlispach MD, Erik W. Holy MD, Gaetano Burriesci PhD, Alessandro De Paoli MD, Paolo Fonio Prof, Francesco Atzeni MD, Leor Perl MD, Maurizio D'Amico MD, Mauro Rinaldi Prof, Federico Conrotto MD.

*these authors contributed equally to this work

Division of Cardiology, Department of Medical Sciences, Città della Salute e della Scienza, University of Turin (FDA, AS, MC, CM, MDA, FC); Division of Cardiac Surgery, Città della Salute e della Scienza, University of Turin (SS, MR, FA); Department of Cardiology, Swiss Cardiovascular Center Bern, Bern University Hospital, Freiburgstrasse 8, 3010 Bern, Switzerland (AF); University Hospital of Zurich, Zurich, Switzerland (FN,EWH); Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy (AL); Ferrarotto Hospital, University of Catania, Catania, Italy (MB); Radiology Unit, Department of Surgical Science, University of Turin, Turin, Italy (PF, AdP); UCL Mechanical Engineering, University College London, UK & Ri.MED Foundation, Palermo, Italy (GB).

Department of Cardiology, Rabin Medical Center, Petach-Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (LP).

Corresponding author: Fabrizio D'Ascenzo MD, Division of Cardiology, Department of Internal Medicine, fabrizio.dascenzo@gmail.com, telephone +39-0116336023

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Visual abstract

Key question. What are the incidence, predictors and cerebrovascular consequences of leaflet thrombosis (LT) after TAVI?

Key findings.

- Incidence rate: 0.4% per month, 4.8% per year
- **Four-fold** increased risk of stroke in patients with LT

Take home message. LT represents an infrequent event after TAVI, occurring more commonly in valve-in-valve procedures and with large valve implantation. The increased risk of stroke related to LT can be reverted by oral anticoagulant therapy.

Abstract

Objectives. We examined the incidence, the impact of subsequent cerebrovascular events and the clinical or procedural predictors of leaflet thrombosis (LT) in patients undergoing trans-catheter aortic valve implantation (TAVI).

Methods. MEDLINE/PubMed was systematically screened for studies reporting on LT in TAVI patients. Incidence (both clinical and subclinical, i.e. detected with computed tomography - CT) of LT was the primary endpoint of the study. Predictors of LT evaluated at multivariable analysis and impact of LT on stroke were the secondary ones.

Results. Eighteen studies encompassing 11,124 patients evaluating incidence of LT were included. Pooled incidence of LT was 0.43% per month (5.16% per year, 95% CI 0.21 to 0.72, I^2 = 98%). Pooled incidence of subclinical LT was 1.36% per month (16.32% per year, 95% CI 0.71 to 2.19, I2 = 94%). Clinical LT was less frequent (0.04% per month, 0.48% per year, 95% C.I. 0.00 to 0.19, I2 = 93%). LT increased the risk of stroke (OR 4.21, 95% CI 1.27 to 13.98), and was more frequent in patients with a valve diameter of 28-mm (OR 2.89: 1.55-5.8), for balloon expandable (OR 8: 2.1-9.7) or after valve-in-valve procedures (OR 17.1: 3.1-84.9). Oral anticoagulation therapy (OAT) reduced the risk of LT (**OR 0.43: 95% CI: 0.22 to 0.84, I2 = 64%)**, as well as the mean transvalvular gradient.

Conclusions. LT represents an infrequent event after TAVI, although increasing risk of stroke. Given its full reversal with warfarin, in high risk patients (those with valve in valve procedures, balloon expandable or large size devices) a protocol wich includes a control CT appears reasonable.

Keywords: transcatheter aortic valve implantation, leaflet thrombosis, stroke, cerebrovascular events.

Introduction

Transcatheter Aortic Valve Implantation (TAVI) represents an alternative to aortic valve replacement (AVR) in patients with severe aortic stenosis (AS) considered at high and intermediate surgical risk (1).

Medical management at discharge with regard to anti-aggregation and anticoagulation still represents an unresolved issue. For surgical biological prostheses, current guidelines (American College of Cardiology - ACC, European Society of Cardiology - ESC and American College of Chest Physicians - ACCP) recommend either warfarin and aspirin for the first 3 months (ACC and ESC) or aspirin alone and with warfarin and aspirin reserved only for mitral valve surgery (ACCP) (1-3).

TAVI patients, however, represent a unique population, due to extreme high risk of bleeding, especially peri-procedural, an event wich has a detrimental impact on prognosis (4, 5). Recently, in two analyses one from the ITER registry and one from the POL-TAVI, safety of single antiplatelet therapy was demonstrated, with a reduction of peri-intervention bleeding events and consequently of periprocedural mortality (6, 7). On the ather hand, some concerns have been raised about the incidence of leaflet thrombosis, both detected clinically or via a dedicated protocol using computed tomography (CT) (8, 9).

Several reports have been published on this topic, although the impact on prognosis and on subsequent cerebrovascular events, clinical and procedural predictors of the phenomenon and efficacy of reversal with warfarin remain unclear **(10,11,12).** This study presents a meta-analysis aimed at clarifying these issues and offering physicians objective indications to manage the patients at risk.

Methods

Search strategy and study selection

This work was conducted in compliance with current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, as well as recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE). The review was also registered online at its inception on metcardio.org to minimize duplicate efforts.

Pertinent articles were searched in MEDLINE/Pubmed with MeSH strategy, using the following terms: (((tavi) or (transcatheter aortic valve implantation) or (tavr) or (transcatheter aortic valve replacement)) and ((thrombosis) or (leaflet)) NOT (review[pt] OR editorial[pt] OR letter[pt]))). Research was ended on 30th April, 2018.

Two independent reviewers (A.S. and M.C.) screened the retrieved citations through the title and/or abstract, and divergences were resolved through consensus. If potentially pertinent, studies were then appraised as complete reports according to the following explicit selection criteria. Studies were included if:

(a) reporting incidence of LT in patients who underwent TAVI;

(b) specifying the follow-up.

Duplicate reporting was an exclusion criteria (in these cases, we selected the manuscript reporting the largest sample of patients).

Two independent reviewers (A.S. and F.DA) abstracted the following data on prespecified forms: authors, journal, year of publication, baseline clinical and procedural features. All potential disagreement was solved by consensus.

Incidence of LT in patients undergoing TAVI was the primary endpoint. The following were the secondary end points:

- incidence of clinical and subclinical LT appraised separately
- risk of LT according to oral anticoagulation therapy (OAT) after TAVI
- reduction of mean gradient after OAT
- risk of cerebrovascular events according to presence of LT
- independent predictors of LT at multivariable analysis evaluated in each study according to established methods (13).

Unblinded independent reviewers (A.S and F.DA.) evaluated the quality of the included studies. Risk of analytical, selection, adjudication, detection, attrition bias and incomplete reporting, quantified as low, moderate, or high risk of bias, was evaluated.

Statistical analysis

Continuous variables are presented using medians and inter-quartile ranges, categorical data are presented as counts and percentages**.** Random effect meta-analysis (inverse variance weighting) was performed due to the observational design of most of the included studies. Meta-analysis of incidence rates was performed using a **Freeman-Tukey** double arcsine transformation for the individual proportions, **with the pooled proportion calculated as the back-transformation of the weighed mean of the transformed proportions**. Meta-analysis of odds ratio (OR) was performed after logarithmic transformation, and the results with the corresponding 95% confidence interval (CI) reported after back transformation. Meta-analysis of median value of gradient was performed before and after OAT for LT. Funnel plot analysis with Egger test was used to evaluate potential publication bias, and Cochran I^2 test to investigate heterogeneity. **Using incidence rate of valve thrombosis as dependent variable, a meta-regression analysis using a general linear (mixed effects) model was performed to examine the**

impact of moderator baseline variables on the incidence of thrombosis. For meta-regression analysis we exploited https://rdrr.io/cran/meta/man/metareg.html and https://www.rdocumentation.org/packages/metafor/versions/1.9-9/topics/rma.uni which is a function to fit the meta-analytic random effects models with moderators via linear (mixed-effects) models. When reporting the independent predictors of thrombosis, we plotted the ranges of the adjusted OR of the significant predictors of thrombosis evaluated at multivariable analysis in the included studies, if available, according to the methods of Ross et al (16).

Statistical analyses were performed with STATA 12 and R Studio 1.1.

Results

A total of 291 studies were identified after the initial search: 20 of them were appraised for possible inclusion. One study was excluded because it had evaluated only in-hospital outcomes (14), and another one because of reporting data overlapping with another study (15). Ultimately, 18 studies (one randomized clinical trial and 17 observational studies), encompassing 11,124 patients, were included according to the pre-specified selection criteria (Figure 1 and Table 1) (9-12; see ***Appendix, Web only I - XIV***). Of those, six studies reported only clinical thrombosis (clinically symptomatic), while six studies focused on subclinical thrombosis (detected with CT, in the absence of clinical symptoms). Twelve studies reported the incidence of LT according to the presence/absence of oral anticoagulation after the procedure. Moreover, six studies quantified the occurrence of stroke in patients with and without LT. Median follow up was one year.

Clinical features of the patients in the included studies are summarized in Table 2. Their median age was 82 years, 54% being women. A transfemoral approach was adopted in 96% of the patients and 87% of the patients were implanted with an Edwards valve. Median STS-PROM (predicted risk of mortality) was 5.8%.

During the follow-up, pooled LT incidence rate was 0.43% per month (5.16% per year, 95% CI 0.22 to 0.72, I^2 = 98%) (Figure 2a). Meta-regression analysis identifies diabetes ($p < 0.01$), atrial fibrillation ($p = 0.01$), STS score ($p = 0.01$) as possible sources of heterogeneity in the pooled estimated (Table 3). Considering separately subclinical and clinical LT, pooled incidence rate was 1.36% per month (16.32% per year, 95% CI 0.71 to 2.19, I2 = 94%) and 0.04% per month (0.48% per year, 95% CI 0.00 to 0.19, I2 = 93%) for subclinical and clinical LT, respectively (Figure 2b and Figure 2c). A significant reduction for LT was demonstrated in patients on OAT after TAVI, with an OR of 0.43 (95% CI 0.22

to 0.84, I^2 = 64%), as depicted in Figure 3. Pooled analysis also revealed that presence of LT was associated with a four-fold increased risk of stroke (OR 4.21, 95% CI 1.27 to 13.98, I^2 = 48%) in post-TAVI patients (Figure 4a): **moreover, after administering OAT a significant decrease in mean gradient was achieved (-21.16 mmHg [-25.86, -16.47]) (Figure 4b).**

The independent predictors of LT in the included studies (Figure 5) were: large valve diameter (>28 mm), valve-in-valve technique, single antiplatelet therapy, BMI > 30 kg/m^2 and balloon expandable prosthesis.

Discussion

In this study, we have discovered the following major outcomes:

a) Clinical and subclinical LT are rare events;

b) Despite this, it may have deleterious clinical consequences due to increased risk of stroke;

c) Patients with large valve diameter, those with balloon expandable prostheses or valve-in-valve procedures are at an increased risk of LT;

d) Patients with BMI> 30 Kg/m2 and those on SAPT have increased risk of LT

e) OAT both protects from LT and decreases mean gradient following diagnosis.

LT, especially when detected clinically, represents an infrequent event after TAVI, though it is associated with an increased risk of stroke. A recent meta-analysis evaluating only subclinical LT, after both TAVI and AVR, reported an incidence of 13.1% at three months (**17**), similar to those appraised in the present study at a mean follow-up of one year. Moreover, incidence of clinical leaflet thrombosis appears to be extremely low, stressing the need of a tailored instrumental follow-up. LT, finally, leads to a four-fold increased risk of subsequent ischemic events, due to embolization of micro-thrombus in systemic circulation. Our results differ from the more reassuring results of Ruile et al (CIYARE), in the German registry. However, the number of events was too low to drive meaningfull conclusions and a lack of association was evident at univariable but not multivariable analysis (**see *Appendix, Web only XIV***). Regarding comparison with surgical intervention, incidence estimates of SAVR thrombosis is of 0.03–0.7% per patient-year. Basra et al. recently investigated the incidence of leaflet thrombosis either in TAVI or SAVR patients (**see *Appendix, Web only XIII***). In their study incidence of LT appeared to

be similar in both groups whereas the time of LT presentation differened significantly being significantly later after SAVR than following TAVI (3.72 ys. Vs 9.6 months), as previously highlighted by Chakravarty et al(10).

Large diameter prostheses represent one of the most relevant predictors of LT, being more relevant for those with a diameter > 28 mm or with those with BMI > 30 kg/m^2 which are overlapping data due to use of large prosthesis in overweight patients. These data have been previously reported in the study of Hannson et al. ***(see Appendix, Web only IV***), but also in the paper of Latib et al. (**see *Appendix, Web only I***), where more than half of the LT occurred in valves with a diameter > 26 mm. TAVI divides the Valsalva sinus into two regions, leading to a severe reduction in the flow activity in their basis, where a permanent stagnation zone is observed (**18**) with an increase in thrombogenic risk (**19**). Moreover, several studies in the field of surgical valve replacement have shown a correlation between smaller valve size and increased transvalvular flow velocity (**20-22**). Consequently, a reduced transvalvular flow more evident in large diameter valves, along with the stagnation and the substantial increase in the dynamic viscosity, may explain our findings.

Balloon expandable valves have shown an increased association with LT. The reason for this finding is not completely clear, as the implantation modality is only one of the many different features that distinguish implanted balloon-expandable from self-expanding valves. It is possible that balloon dilatation and balloon-expandable transcatheter valve insertion results in tissue fissuring and endothelial denudation. This may provide additional nests for red cells and platelets, increasing the procoagulative status. The same mechanism may justify the increased risk observed after valve-in-valve procedure. In fact, the inflow surface of the diseased surgical valve, which in this case faces the leaflets of the TAVI implant, are devoid of endothelial cells. The tissue damage in

balloon-expandable valves may also be exacerbated by the different nature of the leaflets' material employed in the most commonly implanted devices (of the SAPIEN family). These rely on the more established clinical history of bovine pericardium, which in turn comprises a greater leaflet thickness than the porcine pericardium, preferred in a number of self-expanding valves such as the CoreValve and the Symetis Acurate. Also, balloon-expandable valves are typically implanted at a lower position than self-expanding valves, the latter often released in a supraannular configuration. This may aggravate blood stagnation phenomena, contributing to platelet activation and thrombus formation. Other known mechanisms of thrombosis are incomplete prosthesis expansion which can create recesses for thrombus formation, incomplete valve apposition that can delay endotheliazation and the overlap of native leaflets and balloon-expandable systems that creates areas of diminished blood flow and stagnation (**23,24**). Interestingly, incomplete valve expansion and/or apposition have been related to larger valve size and/or larger BMI, potentially also explaining the present results (**25,26**).

Reduction of incidence of LT with OAT, which also decreases mean transvalvular gradient, may offer a solution, although the risk of bleeding should be carefully weighed against such potential benefits. The increased risk of LT with single SAPT may be the opposite side of the coin. Regarding high-risk TAVI patients, major bleeding events increase the risk of both perioperative and long-term mortality and morbidity (4,6), while impact of bleeding on intermediate risk patients still needs to be clarified. On the other hand, the attempt to expand the advantages of TAVI to low-risk patients in the future demands a safe procedure with reduced complication rate (both perioperative and at the follow-up). Consequently, in view of the present results, we suggest that in patients with high-risk features (large diameter, valve-in-valve and balloon expandable prosthesis) a CT

evaluation should be performed in the first three months, to enable tailoring a patient's specific anticoagulation therapy.

TAVI is currently the treatment of choice for patients with symptomatic severe aortic stenosis not eligible for surgical aortic valve replacement (SAVR). The present study shares some limitations. All these studies were observational and not RCTs, consequently limiting the inferential aim of our results. Moreover, adjudication of stroke was different in each study (being either appraised from dedicated physicians or evaluated by those performing the clinical follow up) and this could explain the medium risk ofadjudication bias reported in 8/15 studies.

Figure Legends

Figure 1. Flow chart.

Figure 2. Forest plots of leaflet thrombosis (LT) incidence rate for a) all studies, b) studies reporting clinical thrombosis, c) studies reporting subclinical thrombosis. Pooled LT incidence rate was 0.43% per month. Subclinical LT was more frequent than clinical LT (pooled incidence rate 1.36 vs 0.04% per month). [Random effect meta-analysis was performed, reporting the pooled incidence rate per person-month with the corresponding confidence interval]

Figure 3. Forest plots for the risk of leaflet thrombosis (LT) according to oral anticoagulant (OAC) status. Leaflet thrombosis was significantly less frequent in patients on OAT after TAVI. ["Random effect meta-analysis was performed, reporting the odds ratio with the corresponding confidence interval]

Figure 4. Forest plots for the risk of stroke according to the presence or absence of leaflet thrombosis (panel A) and decrease in mean gradient after oral anticoagulant (panel B). Presence of LT is associated with a four-fold increased risk of stroke. After OAT a significant decrease of mean gradient is achieved. [Random effect meta-analysis was performed, reporting the odds ratio with the corresponding confidence interval]

Figure 5. Independent predictors of leaflet thrombosis in the included studies after multivariable analysis. BMI = body mass index; SAPT = single antiplatelet therapy.

Tables

Table 1. Main features of the included studies (**18 studies**).

	Number of patients	**Follow up (months)**	**Study design**	**Multicentric**	**Kind of LT (Clinical, subclinical, both)**
Latib 2015	4,266	24	Observational retrospective	Yes	Both
Barbanti 2015	353	60	Observational prospective	Yes	Clinical
Makkar, 2015	55	6	Observational, prospective	Yes	Subclinical
Jose, 2015	638	23	Observational, retrospective	No	Clinical
Leetmaa, 2015	140	3	Observational, retrospective	No	Both
Pache, 2016	156	8	Observational retrospective	No	Subclinical
Deeb, 2016	228	36	RCT	Yes	Clinical
Hansson, 2016	405	12	Observational,	No	Both

			prospective		
Yanagisawa, 2017	70	12	Observational, prospective	No	Subclinical
Mangieri, 2017	439	6	Observational, retrospective	No	Clinical
Vollema, 2017	128	18	Observational, retrospective	No	Subclinical
Marwan, 2017	78	12	Observational, retrospective	No	Both
Holy, 2017	514	12	Observational, retrospective	No	Both
Huchet, 2017	135	1	Observational, prospective	No	Clinical
Franzone, 2017	1,396	12	Observational, prospective	No	Both
Chakravarty, 2017	**890**	**30**	**Observational, prospective**	**Yes**	**Subclinical**
Basra, 2018	**612**	**12**	**Observational, prospective**	**No**	**Clinical**
Ruile, 2018	**754**	**14**	**Observational, prospective**	**No**	**Subclinical**

219 RCT: randomized clinical trial. **LT: leaflet thrombosis.**

Table 2. Baseline and procedural features of the patients included in the study (**11,124 patients**).

	Median value (lower, upper quartile)
Age, y	82 (81, 83)
Follow-up, mo	12 (8, 14)
Female, %	54 (47, 56)
Hypertension, %	84 (78, 90)
EF, %	54 (53, 56)
Diabetes, %	27 (25, 29)
Atrial fibrillation, %	38 (23, 42)
STS score	5.8 (5, 7.3)
Transfemoral approach, %	96 (84, 98)
Edwards valve, %	87 (50, 100)

220 EF: ejection fraction; STS Society of Thoracic Surgery.

Table 3. Meta-regression analyses for the effect of different study-level covariates on the incidence rate of LT.

	Beta (95% CI)	**P value**
Study Year	0.0071 (-0.0123, 0.0266)	0.47
Age	0.0146 (-0.0005, 0.0298)	0.06
Female	0.0005 (-0.0028, 0.0038)	0.77
Hypertension	-0.0008 (-0.0041, 0.0024)	0.61
DM	0.0065 (0.0034, 0.0096)	**<0.001**
AF	0.0039 (0.0009, 0.0068)	0.010
EF	-0.0021 (-0.0087, 0.0044)	0.53
STS score	-0.0156 (-0.0281, -0.0031)	0.015
Edwards valve	-0.0006 (-0.0017, 0.0006)	0.33
Clinical thrombosis	-0.0009 (-0.0012, 0.1349)	**<0.001**
Anticoagulation	0.0009 (-0.0007, 0.0025)	0.25

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DM: diabete mellitus; AF: atrial fibrillation; EF: ejection fraction; STS Society of Thoracic Surgery.

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