Thrombosis of TAVI prosthesis—cause for concern or innocent bystander? A comment and review of currently available data

Stephan H. Schirmer¹ · Felix Mahfoud¹ · Peter Fries² · Bruno Scheller¹

Received: 30 November 2016 / Accepted: 1 December 2016 / Published online: 19 December 2016
© Springer-Verlag Berlin Heidelberg 2016

Transcatheter aortic valve implantation (TAVI) has become an established treatment option for severe aortic stenosis in patients at high risk of surgical aortic valve replacement [1, 2]. Recent studies, such as PARTNER-2 [3] and NOTION [4] have expanded the possible use of TAVI to patients at intermediate surgical risk. With increasing life expectancy of patients undergoing TAVI, the issue of valve durability becomes increasingly important. As yet, there is a paucity of data on the antithrombotic regimen following TAVI, although reports on many thousands TAVI procedures have been published [5], demonstrating excellent outcomes in all risk categories [6]. Until recently, much investigated safety issues in TAVI were risk of access vessel complications [7, 8], stroke, or pacemaker implantation, all of which have decreased substantially [9–12], resulting in an increasing global uptake of the approach. Changes in prosthesis leaflet morphology and function shortly after TAVI only gained interest in 2014, when a review of single case reports identified 16 clinical events of transcatheter valve thrombosis during 2002–2012 [13]. Increasing trans-valvular gradients on echocardiography (from 10 to 42 mmHg) were noted in these patients presented with dyspnea as the most common symptom.

Anticoagulation with vitamin K antagonist (warfarin) effectively restored hemodynamics within 2 months.

When considering prosthetic valve deterioration, it is important not to mix structural, hemodynamic and clinical readouts, and endpoints. According to standardized endpoint definitions on TAVI by the Valve Academic Research Consortium, valve thrombosis is defined as “Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment” [14]. To this extent, recent studies used new generation computer tomography (CT) to visualize morphological changes (such as leaflet thickening or thrombosis) not visible in echocardiography [15]. These changes do not necessarily correlate with hemodynamic changes (i.e. rise in pressure gradient) and probably even less with clinical events, such as dyspnea, heart failure or stroke, although clinical endpoints do of course need larger studies and longer follow-up.

In 2015, reduced bioprosthetic leaflet motion was incidentally observed in a patient who had a stroke in a clinical trial investigating a novel transcatheter valve system (Portico valve). Subsequent analyses of available CT scans from this trial together with two registries were published in the same year [16]. Makkar et al. [16] reported reduced leaflet motion on CT in 40% (20 of 55 patients) in the clinical trial and 13% (17 of 132 patients) in the two registries. Notably, none of the patients on warfarin showed reduced leaflet motion. Leaflet motion in patients on dual platelet inhibition (aspirin and clopidogrel, DAPT) was normalized by initiation of anticoagulation. The authors also found a hint towards more strokes or transitory ischemic attacks (TIA) in patients with reduced valve leaflet motion (3 vs. 1 in patients with normal leaflet motion). Importantly, reduced leaflet motion occurred in

✉ Stephan H. Schirmer
stephan.schirmer@uniklinikum-saarland.de

¹ Klinik für Innere Medizin III
(Kardiologie/Angiologie/Internistische Intensivmedizin),
Universitätsklinikum des Saarlandes, 66421 Homburg/Saar,
Germany

² Klinik für Diagnostische und Interventionelle Radiologie,
Universitätsklinikum des Saarlandes, 66421 Homburg/Saar,
Germany

Fig. 1 The influence of prosthetic valve type (balloon vs. self-expandable) and mode of implantation (surgical vs. transcatheter valve) (*left side*) possibly influences the course of leaflet alterations. These can most sensitively be detected by computer tomography,

while transthoracic echo offers better functional insights and transesophageal echo allows a higher temporal resolution. Antithrombotic strategies currently under prospective evaluation are depicted on the *right side*

both TAVI and surgically implanted valves and was not associated with increased transvalvular gradients as measured by echocardiography.

A recently published registry of 1521 patients after TAVI with serial echocardiographic follow-up reported the incidence of valve hemodynamic deterioration (VHD), defined as an increase of ≥ 10 mmHg in transvalvular gradient compared to discharge [17]. The authors documented VHD in 4.5% of the patients. Next to procedural issues (valve-in-valve implantation [18], small valve size), the absence of anticoagulation was a predictor of VHD, suggesting morphological changes and possibly leaflet thrombus as the underlying mechanisms. In this study, functional (echocardiography) and not structural (CT) assessments were used. During a 4-year follow-up, no difference in (cardiovascular) death or stroke was observed.

The largest cohort of patients with transcatheter heart valve (THV) changes was published by the Milan group, who presented multicenter data on 4266 patients undergoing TAVI [19]. The authors defined THV dysfunction as a mean gradient of 20 mmHg on echocardiography, and THV thrombosis when according changes visualized in echo, CT, or histopathology. While patients were not systematically screened, 26 THV thromboses (0.6%) were noted, which was reported to be clinically significant (dyspnea) in two-thirds ($n = 17$). In these patients, the mean pressure gradient was described to formally fulfill the criteria of a relevant aortic stenosis (41 mmHg). Anticoagulation normalized pressure gradients in the majority of the patients (88%) within two months.

Routine multi-detector CT (MDCT) was performed in 460 consecutive patients in a Danish study 1 and 3 months following TAVI [20]. Hypo-attenuated leaflet thickening

was regarded indicative of valve thrombosis. THV thrombosis was reported in 7% of the patients, of whom the majority was asymptomatic, but 18% showed clinical symptoms. Again, THV thrombosis was more common (relative risk 6.1, confidence interval: 1.9–19.8, $p < 0.001$) in patients not on anticoagulant but antiplatelet therapy. Using MDCT and transesophageal echo showed reversal of valve thrombosis and function in 85% of patients by warfarin treatment.

In the current issue of the journal, Ruile et al. present follow-up data on TAVI prosthesis deterioration in relation to patient's antithrombotic regime [21]. A total of 51 patients with leaflet thickening as detected by MDCT were examined. Until May 2015, patients with leaflet thrombosis were treated with vitamin K antagonist (phenprocoumon) and clopidogrel for 3 months (22 out of 528 patients undergoing routine MDCT scans following TAVI). Following May 2015, in patients with leaflet thickening, anticoagulation was only initiated in an established indication for anticoagulation (e.g. atrial fibrillation, $n = 9$), the remaining 22 patients were treated with DAPT. While leaflet thickening/restriction increased in the DAPT group, it regressed significantly in the anticoagulated group. The change in CT-derived morphological valvular pathologies was significantly different between the two groups analyzed. Of note, following discontinuation of anticoagulation, leaflet pathologies relapsed, with significant recurrences of leaflet restriction and thrombus extent. Interestingly, the change in pressure gradient as measured by echocardiography correlated with the change in leaflet restriction. However, none of the patients reported clinically apparent symptoms relative to THV thrombosis. Some of the findings of the current report are confirmatory of earlier analyses by the same group and by Makkar et al.

[16] and Hansson et al. [20]. However, progression of leaflet thickening under DAPT and, particularly, possible recurrence after discontinuation of anticoagulation therapy are important novel findings. The authors published a smaller series ($n = 156$ CTs in TAVI (Sapien S3) patients) earlier this year, in which they report hypo-attenuated leaflet thickening to occur in 16 patients (10.3%) [22]. Interestingly, in that study, valve thrombosis was not linked to lack of anticoagulation therapy at baseline, while it was reversible by initiation of anticoagulation therapy.

As acknowledged also by the authors, the non-randomized and non-prospective, single-center nature of the current study represent limitations. Therapeutic decisions were left at the discretion of the treating physician; therefore, treatment bias cannot be fully excluded. The case series including follow-up does, however, provide an excellent basis for further prospective, randomized trials comparing anticoagulation (vitamin K antagonist or NOAC [23]) with antiplatelet therapy in patients with TAVI. Several of these studies are currently enrolling patients, mostly with hard clinical endpoints (death, myocardial infarction, stroke, bleeding, thrombosis) (Table 1).

The question remains if the issues described are specific for TAVI bioprostheses or occur in surgical aortic valve replacement as well. In the latter, structural valve degeneration has been reported to occur at a rate of 20–30% after 10 years of implantation [24]. Reports on valve thrombosis in surgically inserted bioprosthesis vary in the literature and reach up to 5%, but these data were acquired before MDCT became available and could, therefore, be higher. In a series of 397 explanted biological valves, Egbe et al. found bioprosthetic valve thrombosis at a rate of 11.6% [25]. Here, subtherapeutic INR was a strong predictor of valve thrombosis.

Notwithstanding the clinical relevance of the current findings, it is important to note that mid- to long-term clinical outcomes following TAVI have been excellent. Recent reports (presented at EuroPCR 2016 by Danny Dvir) on long-term follow-up of patients undergoing balloon-expandable first-generation valves, provide hints of valve degeneration (more regurgitation than stenosis) that were, interestingly, not linked to anticoagulant therapy but to the presence of comorbidities, such as chronic kidney disease. The authors reported a better than 90% valve patency up to 5 years followed by accelerated valve degeneration between 5 and 7 years. However, these findings have been questioned due to methodological flaws of the Kaplan–Meier analysis used including limited patient numbers at risk at the later time points [26].

As demonstrated in the long-term follow-up analysis of the PARTNER trial, 5-year function of TAVI prosthesis ($n = 3105$ patients) is good (i.e. no structural valve

deterioration requiring surgery), providing reassurance about the long-term durability [27]. Particularly, there was no difference in transvalvular pressure gradient between the TAVI and the surgical group (mean gradient 10.7 vs. 10.6 mmHg). In the intermediate risk PARTNER 2 trial, pressure gradients were even lower following TAVI than after conventional surgery (2-year follow-up data available) [3].

What do the different outcome measures yielded by different diagnostic strategies tell us? To reliably detect leaflet thickening and valve thrombosis, CT would have to be performed on a routine basis in all patients. Transesophageal echocardiography is, however, superior in terms of temporal resolution. Because of the discrepancy between clinical outcomes and rate of leaflet thickening, functional analysis, i.e. (transthoracic) echocardiography, might be sufficient to identify those patients with hemodynamically relevant valve obstruction by thrombotic material. If currently ongoing studies provide evidence that anticoagulant therapy is indeed necessary, valve morphological and functional deterioration might (again) become rare. In the meantime, prescribing anticoagulant instead of antiplatelet therapy not only in patients with concomitant atrial fibrillation but in all patients following TAVI at low or intermediate bleeding risk might become an option (Fig. 1). Weighing the benefits for anticoagulation using the CHA₂DS₂-Vasc score may also be an option in TAVI patients without atrial fibrillation [28]. In patients with concomitant atrial fibrillation, combination of antiplatelet with anticoagulation therapy seems not to reduce ischemic events, but increases bleeding complications, as suggested by a recent retrospective analysis in 621 patients [29], indicating that the combination of anticoagulant with antiplatelet therapy may worsen outcome. Of note, relying on CT for a diagnosis of valve deterioration might be misleading in the end, owing to its morphological rather than functional character. The few clinical events demonstrated in currently available reports are in contrast to the apparent frequency of valve alterations. Regression of the parameters described following initiation of anticoagulation will also have to be scrutinized in a prospective fashion.

Findings on bioprosthetic valve deterioration are increasingly important when intermediate or low risk patients undergo TAVI and also surgical bioprosthesis implantation. Both, the ESC 2012 [30] and AHA 2014 [31] guidelines assign anticoagulation therapy only a class IIb indication following surgical aortic bioprosthesis implantation. Given the data on both transcatheter but also surgical valve deterioration, opting for a more aggressive strategy here might be necessary.

Table 1 Ongoing studies comparing different antithrombotic regimes following TAVI

Study	Acronym	NCT-number	Study arms	Primary endpoint	Planned pat. number	Sponsor	Timeline
Global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes	GALILEO	NCT02556203	Rivaroxaban + aspirin vs. DAPT	Death/MI/stroke/embolism/prosthesis thrombus/major bleeding	1520	Bayer	Estimated completion 01/2018
Comparison of a rivaroxaban-based strategy with an antiplatelet-based strategy following successful TAVR for the prevention of leaflet thickening and reduced leaflet motion as evaluated by four-dimensional, volume-rendered computed tomography (4DCT)	GALILEO substudy	NCT02833948	As above	Leaflet thickening and motion	300	ECRI/Bayer	Estimated completion 11/2017
Anti-thrombotic strategy after trans-aortic valve implantation for aortic stenosis	ATLANTIS	NCT02664649	Apixaban vs. DAPT or VKA	Death/MI/stroke/embolism/prosthesis thrombus/major bleeding	1509	Pfizer/BMS	Estimated completion 09/2018
Edoxaban compared to standard care after heart valve replacement using a catheter in patients with atrial fibrillation	ENVISAGE-TAVI AF	NCT02943785	Edoxaban vs. VKA	Death/MI/stroke/embolism/prosthesis thrombus/major bleeding	1400	Daiichi Sankyo	Estimated completion 11/2020
Antiplatelet therapy for patients undergoing transcatheter aortic valve implantation (POPular-TAVI)	POPular-TAVI	NCT02247128	Aspirin vs. DAPT vs. OAC vs. OAC + clopidogrel	Bleeding	1000	St. Antonius Hospital, Netherlands	Estimated primary completion 08/2016
Dual antiplatelet therapy versus oral anticoagulation for a short time to prevent cerebral embolism after TAVI	AUREA	NCT01642134	DAPT vs. acenocoumarol	Cerebral thromboembolism (MRI)	–	Hospital de Meixoeiro, Spain	Estimated completion 04/2017
Anticoagulation alone versus anticoagulation and aspirin following transcatheter aortic valve interventions (1:1)	AVATAR	NCT02735902	Aspirin vs. aspirin + VKA	Death/MI/stroke/valve thrombosis major bleeding	170	Nîmes university Medtronic	Estimated start 04/2017
Aspirin versus aspirin + clopidogrel following transcatheter aortic valve implantation: the ARTE Trial	ARTE	NCT01559298	Aspirin vs. DAPT	Death/MI/stroke/major bleeding	155	University Quebec/Edwards Lifesciences	Estimated completion 01/2017

Information provided as provided on <http://www.clinicaltrials.gov>

DAPT dual antiplatelet therapy (i.e. aspirin + clopidogrel), OAC oral anticoagulation, VKA vitamin K antagonist, MI myocardial infarction, MRI magnetic resonance imaging

References

- Haussig S, Schuler G, Linke A (2014) Worldwide TAVI registries: what have we learned? *Clin Res Cardiol* 103(8):603–612
- Seiffert M, Sinning JM, Meyer A, Wilde S, Conradi L, Vasa-Nicotera M, Ghanem A, Kempfert J, Hammerstingl C, Ojeda FM, Kim WK, Koschky DH, Schirmer J, Baldus S, Grube E, Mollmann H, Reichenspurner H, Nickenig G, Blankenberg S, Diemert P, Treede H, Walther T, Werner N, Schnabel RB (2014) Development of a risk score for outcome after transcatheter aortic valve implantation. *Clin Res Cardiol* 103(8):631–640
- Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG (2016) Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 374(17):1609–1620
- Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Sondergaard L (2015) Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol* 65(20):2184–2194
- Mollmann H, Bestehorn M, Bestehorn M, Papoutsis K, Fleck E, Ertl G, Kuck KH, Hamm C (2016) In-hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: complete dataset of patients treated in 2013 in Germany. *Clin Res Cardiol* 105(6):553–559
- Biermann J, Horack M, Kahlert P, Schneider S, Nickenig G, Zahn R, Senges J, Erbel R, Wasem J, Neumann T (2015) The impact of transcatheter aortic valve implantation on quality of life: results from the German transcatheter aortic valve interventions registry. *Clin Res Cardiol* 104(10):877–886
- Geis NA, Chorianopoulos E, Kallenbach K, Andre F, Pleger ST, Karck M, Katus HA, Bekerredjian R (2014) Feasibility of sheathless transfemoral aortic valve implantation in patients with small access vessel diameters. *Clin Res Cardiol* 103(10):775–780
- Seidler T, Hunlich M, Puls M, Hasenfuss G, Jacobshagen C (2016) Feasibility and outcomes of interventional treatment for vascular access site complications following transfemoral aortic valve implantation. *Clin Res Cardiol*. doi:10.1007/s00392-016-1038-1
- Abdul-Jawad Altisent O, Ferreira-Gonzalez I, Marsal JR, Ribera A, Auger C, Ortega G, Cascant P, Urena M, Del Blanco BG, Serra V, Sureda C, Igual A, Rovira A, Gonzalez-Alujas MT, Gonzalez A, Puri R, Cuellar H, Tornos P, Rodes-Cabau J, Garcia-Dorado D (2016) Neurological damage after transcatheter aortic valve implantation compared with surgical aortic valve replacement in intermediate risk patients. *Clin Res Cardiol* 105(6):508–517
- Kim WK, Liebetrau C, van Linden A, Blumenstein J, Gaede L, Hamm CW, Walther T, Mollmann H (2016) Myocardial injury associated with transcatheter aortic valve implantation (TAVI). *Clin Res Cardiol* 105(5):379–387
- Samim M, Hendrikse J, van der Worp HB, Agostoni P, Nijhoff F, Doevendans PA, Stella PR (2015) Silent ischemic brain lesions after transcatheter aortic valve replacement: lesion distribution and predictors. *Clin Res Cardiol* 104(5):430–438
- Weber M, Bruggemann E, Schueler R, Momcilovic D, Sinning JM, Ghanem A, Werner N, Grube E, Schiller W, Mellert F, Welz A, Nickenig G, Hammerstingl C (2015) Impact of left ventricular conduction defect with or without need for permanent right ventricular pacing on functional and clinical recovery after TAVR. *Clin Res Cardiol* 104(11):964–974
- Cordoba-Soriano JG, Puri R, Amat-Santos I, Ribeiro HB, Abdul-Jawad Altisent O, del Trigo M, Paradis JM, Dumont E, Urena M, Rodes-Cabau J (2015) Valve thrombosis following transcatheter aortic valve implantation: a systematic review. *Revista espanola de cardiologia (English ed)* 68(3):198–204
- Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB (2012) Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 42(5):S45–S60
- Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, Jensen JM, Webb J, Blanke P, Tang M, Norgaard BL (2015) Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. *Circ Cardiovasc Interv* 8(4):e001596
- Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, de Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelnin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB, Sondergaard L (2015) Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 373(21):2015–2024
- Del Trigo M, Munoz-Garcia AJ, Wijeyesundera HC, Nombela-Franco L, Cheema AN, Gutierrez E, Serra V, Kefer J, Amat-Santos IJ, Benitez LM, Mewa J, Jimenez-Quevedo P, Alnasser S, Garcia Del Blanco B, Dager A, Abdul-Jawad Altisent O, Puri R, Campelo-Parada F, Dahou A, Paradis JM, Dumont E, Pibarot P, Rodes-Cabau J (2016) Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. *J Am Coll Cardiol* 67(6):644–655
- Milburn K, Bapat V, Thomas M (2014) Valve-in-valve implantations: is this the new standard for degenerated bioprostheses? Review of the literature. *Clin Res Cardiol* 103(6):417–429
- Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, Baumgartner H, Finkelstein A, Legrand V, de Lezo JS, Kefer J, Messika-Zeitoun D, Richardt G, Stabile E, Kaleschke G, Vahanian A, Laborde JC, Leon MB, Webb JG, Panoulas VF, Maisano F, Alfieri O, Colombo A (2015) Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv* 8(4):e001779
- Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, Jensen KT, Blanke P, Leetmaa T, Tang M, Krusell LR, Klaaborg KE, Christiansen EH, Terp K, Terkelsen CJ, Poulsen SH, Webb J, Botker HE, Norgaard BL (2016) Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *J Am Coll Cardiol* 68(19):2059–2069
- Ruile P, Jander N, Blanke P, Schoechlin S, Reinohl J, Gick M, Rothe J, Langer M, Leipsic J, Buettner HJ, Neumann FJ, Pache G (2016) Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. *Clin Res Cardiol*. doi:10.1007/s00392-016-1052-3
- Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, Gick M, Buettner HJ, Leipsic J, Langer M, Neumann FJ, Ruile P (2016) Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J* 37(28):2263–2271
- Yadlapati A, Groh C, Malaisrie SC, Gajjar M, Kruse J, Meyers S, Passman R (2016) Efficacy and safety of novel oral

- anticoagulants in patients with bioprosthetic valves. *Clin Res Cardiol* 105(3):268–272
24. Pibarot P, Dumesnil JG (2009) Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation* 119(7):1034–1048
  25. Egbe AC, Pislaru SV, Pellicka PA, Poterucha JT, Schaff HV, Maleszewski JJ, Connolly HM (2015) Bioprosthetic valve thrombosis versus structural failure: clinical and echocardiographic predictors. *J Am Coll Cardiol* 66(21):2285–2294
  26. Capodanno D (2016) Transcatheter aortic valve durability and the dark side of Kaplan–Meier analysis. *EuroIntervention* 12(7):821–822
  27. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG (2015) 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 385(9986):2477–2484
  28. Cerit L (2016) Transcatheter Aortic Matryoshka Doll. *Thrombosis*. *Clin Res Cardiol*. doi:[10.1007/s00392-016-1057-y](https://doi.org/10.1007/s00392-016-1057-y)
  29. Abdul-Jawad Altisent O, Durand E, Munoz-Garcia AJ, Nombela-Franco L, Cheema A, Kefer J, Gutierrez E, Benitez LM, Amat-Santos IJ, Serra V, Eltchaninoff H, Alnasser SM, Elizaga J, Dager A, Garcia Del Blanco B, Ortas-Nadal Mdel R, Marsal JR, Campelo-Parada F, Regueiro A, Del Trigo M, Dumont E, Puri R, Rodes-Cabau J (2016) Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 9(16):1706–1717
  30. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M (2012) Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 33(19):2451–2496
  31. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD (2014) 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 63(22):2438–2488