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Intravascular haemolysis after transcatheter aortic valve implantation with self-expandable prosthesis: incidence, severity, and impact on long-term mortality

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We aimed to determine the incidence, severity, and long-term impact of intravascular haemolysis after self-expanding transcatheter aortic valve implantation (TAVI). We believe this should be evaluated before extending the indications of TAVI to younger low-risk patients. Prospective, academic, single centre study of 94 consecutive patients treated with supra-annular self-expandable TAVI prosthesis between April 2009 and January 2014. Haemolysis at 1-year post-TAVI was defined per the published criteria based on levels of haemoglobin, reticulocyte and schistocyte count, lactate dehydrogenase (LDH), and haptoglobin. All patients had long-term clinical follow-up (6 years). The incidence of haemolysis at 1-year follow-up varied between 9% and 28%, based on different haemolysis definitions. Haemolysis was mild in all cases, no patient had markedly increased LDH levels. The presence of moderate/severe paravalvular aortic regurgitation was associated with haemolysis (7.7% vs. 23.1%, $P = 0.044$) and aortic valve area post-TAVI did not differ between groups with or without haemolysis (1.01 vs. 0.92 cm^2/m^2, $P = 0.23$) (definition including schistocyte count). The presence of haemolysis did not have any impact on patient prognosis after 6 years with log-rank test $P = 0.80$. Intravascular haemolysis after TAVI with self-expandable prosthesis is present in 9–28% of patients depending on the definition of haemolysis. The presence of haemolysis is associated with moderate/severe paravalvular aortic regurgitation but not with post-TAVI aortic valve area. Haemolysis is mild with no impact on prognosis.

Introduction

Transcatheter aortic valve implantation (TAVI) is an established treatment of severe aortic stenosis for elderly patients with high and intermediate surgical risk.[1,2] Ongoing studies aim to expand the indications for TAVI towards patients with lower risk, younger age, bicuspid anatomy, or even no symptoms. Intravascular haemolysis is found in 19–51% of patients with modern bi-leaflet mechanical prostheses and in 5% of patients with normally functioning bioprosthetic valves.[3–5] High shear stress generated by turbulent flow across prosthesis can be caused by high-velocity jets due to prosthetic valve regurgitation or small prosthesis flow area.[6] Transcatheter aortic valve implantation has so far higher incidence of paravalvular leakage (PVL) than surgical aortic valve replacement (SAVR) but better haemodynamic performance to SAVR concerning

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post-operative effective aortic valve area.[7] Two groups have studied incidence and severity of haemolysis after TAVI so far[8,9] but no systematic study of intravascular haemolysis after TAVI with supra-annular self-expandable prosthesis has been published and the impact on long-term mortality is unknown. We believe this should be evaluated before extending the indications of TAVI to low-risk and younger patients with long expected survival.

Methods

Study population

From April 2009 till January 2014, 102 consecutive patients with severe symptomatic aortic stenosis underwent TAVI in University Hospital Královské Vinohrady in Prague and agreed to participate in this study. All patients signed informed consent, data were prospectively entered into a dedicated anonymized database, the study design was academic without any industry sponsorship, in compliance with the Declaration of Helsinki, and protocol was approved by the local ethics committee. All patients were treated with supra-annular self-expandable CoreValve (Medtronic, Dublin, Ireland) prosthesis; sizes of 23, 26, 29, and 31 mm were available. Aortic regurgitation was semi-quantitatively evaluated by angiography at least 10 min post-implantation and graded according to Sellers;[10,11] grade $\geq$2 was considered as a positive finding. Eight patients did not survive till 1-year follow-up and were excluded from the analysis. The cause of death was two periprocedural complications; three cardiovascular; two non-cardiac; and one unknown. No excluded patient had clinical signs of haemolysis and only one excluded patient had moderate (or severe) aortic regurgitation post-TAVI. All remaining 94 patients represent our study cohort.

Laboratory evaluation

Baseline blood samples were obtained 1 day before TAVI as part of the routine protocol and at 1-year ($\pm$2 months) follow-up. Analysis of haemoglobin, haptoglobin, lactate dehydrogenase (LDH), reticulocyte and schistocyte count, bilirubin, alanine aminotransferase, C-reactive protein (CRP) levels, and platelet count was performed at our standard hospital laboratory. We have used two definitions of haemolysis at 1-year follow-up:

(1) According to Skoularigis criteria without schistocytes (Definition 1) to enable comparison with previous studies of haemolysis after TAVI.[8,9]
(2) According to standard Skoularigis criteria (Definition 2) used in studies of haemolysis after SAVR.[3–5]

In short, Skoularigis criteria[4] for haemolysis consider patients as having haemolysis when (i) serum LDH levels are over the upper limit of normal (in our laboratory 3.67 μkat/L) and (ii) any two of the following criteria are present: (a) haemoglobin level $<$13.8 g/dL for male patients and $<$12.4 g/dL for female patients; (b) haptoglobin level $<$0.5 g/L; (c) reticulocyte count $\geq$2%; and (d) presence of schistocytes in peripheral blood smear. The severity of haemolysis was assessed by serum LDH levels.

Echocardiography and follow-up

Standard transthoracic echocardiography (TTE) was performed 1 day before TAVI and at hospital discharge. All images were analysed by experienced echocardiographer who was blind to haematologic laboratory parameters. Standard classification of aortic regurgitation as either none/trace, mild, moderate, or severe according to Valve Academic Research Consortium-2 criteria was used.[12] Aortic valve area index (AVAI) was calculated post-TAVI, and the presence and severity of patient-prosthesis mismatch (PPM) was defined as follows: no PPM—AVAI $>$0.85 cm^2/m^2; moderate PPM—AVAI $\geq$0.65 cm^2/m^2 but $<$0.85 cm^2/m^2; and severe PPM as AVAI $<$0.65 cm^2/m^2.

All patients had clinical visit 1-year ($\pm$2 months) post-TAVI and all were offered long-term clinical follow-up at our centre, but this was not mandated by the protocol and some patients were managed locally. Mortality data were obtained from both our hospital database and the central database of The Institute of Health Information and Statistics of the Czech Republic.

Statistics

Continuous variables are presented in graphs and tables as mean and standard deviation. Categorical variables are reported as counts and frequencies. Testing of differences between groups was performed by the Student's *t*-test or Mann–Whitney U test. A χ^2 test or Fisher's exact test was used to detect the difference between categorical variables. Laboratory markers of haemolysis (baseline and follow-up differences) were tested by a paired Student's test or Mann–Whitney U test. A log-rank test was used to compare survival curves. Results were considered statistically significant at a significance level of *P*-value $<$0.05. All statistical analyses were performed in IBM SPSS Statistics version 26. Graphical analyses were performed in Sigmaplot version 14.

Results

Intravascular haemolysis was present in 8 (9%) and 26 (28%) patients according to Definition 1 and Definition 2 of haemolysis, respectively. Baseline characteristics and procedural variables are described in *Table 1*, there were no significant differences between groups with and without haemolysis. No patient was treated with the CoreValve 23 mm prosthesis and no patient received two prostheses. An alternative approach was used in five patients, all from the subclavian artery. Sedation with local anaesthesia was our default approach to all patients with a transfemoral approach.

Laboratory parameters of haemolysis are summarized in *Table 2*. The difference between laboratory measurements at baseline and 1-year follow-up is shown in *Figure 1* according to the presence or absence of haemolysis; we present data based on haemolysis Definition 2 but data based on haemolysis Definition 1 are similar. Only 20 (21%) patients had normal haemoglobin levels at baseline—per the definition above. Haemoglobin levels did not decline even in the groups with haemolysis—in fact, we observed slightly higher haemoglobin values in patients with

Table 1 Baseline and procedural patient characteristics ($n = 94$)

	Haemolysis Definition 1 (Skoularigis without schistocytes)			Haemolysis Definition 2 (standard Skoularigis)		
	No (86) Count (%) or mean ± SD	Yes (8)	*P*-value	No (68) Count (%) or mean ± SD	Yes (26)	*P*-value
Age (years)	80.5 ± 7.1	78.3 ± 10	0.674	80.1 ± 7.3	80.8 ± 7.5	0.457
Men	43 (50)	6 (80)	0.163	34 (50)	15 (57.7)	0.332
Women	43 (50)	2 (20)	0.163	34 (50)	11 (42.3)	0.332
NYHA I + II	36 (41.9)	1 (12.5)	0.103	26 (38.2)	11 (43.2)	0.447
NYHA III + IV	50 (58.1)	7 (87.5)	0.103	42 (61.8)	15 (57.7)	0.447
Diabetes mellitus	44 (51.2)	6 (75)	0.179	38 (55.9)	12 (46.2)	0.269
Smoking	30 (34.9)	4 (50)	0.313	25 (36.8)	9 (34.6)	0.522
Hypertension	72 (83.7)	7 (87.5)	0.625	56 (82.4)	23 (88.5)	0.353
Sinus rhythm	59 (68.6)	6 (75)	0.528	47 (69.1)	18 (69.2)	0.6
GFR (mL/min/m^2)	44.4 ± 20.3	45.9 ± 24.2	0.924	43.8 ± 20.1	46.5 ± 21.7	0.597
LV ejection fraction (%)	52.6 ± 12	56.8 ± 9.2	0.331	52.4 ± 11.6	54.4 ± 12.2	0.26
Mean aortic gradient (mmHg)	44 ± 14.4	51.5 ± 19	0.408	43.7 ± 14.4	47.1 ± 16.2	0.285
Aortic valve area (cm^2)	0.75 ± 0.2	0.7 ± 0.1	0.715	0.7 ± ± 0.2	0.7 ± 0.1	0.405
Pulmonary hypertension[a]	12 (14)	1 (12.5)	0.695	10 (14.7)	3 (11.5)	0.49
EuroSCORE I logistical (%)	20.6 ± 13.4	19.8 ± 15.1	0.73	19.8 ± 13.1	22.3 ± 14.7	0.486
Prosthesis size (mm)						
26	45 (52.3)	6 (75)	0.445	38 (55.9)	13 (50)	0.715
29	39 (45.3)	2 (25)	0.445	29 (42.6)	12 (46.2)	0.715
31	2 (2.3)	0 (0)	0.445	1 (1.5)	1 (3.8)	0.715
Transfemoral approach	82 (95.3)	7 (87.5)	0.268	65 (95.6)	24 (92.3)	0.417

GFR, glomerular filtration rate; LV, left ventricle; NYHA, New York Heart Association; SD, standard deviation.
[a]Pulmonary artery systolic pressure over 50 mmHg.

haemolysis (*Figure 1A*). Levels of LDH increased in both groups, but no patient had LDH levels above double the upper limit of normal value; in other words, all detected haemolyses were mild. Low levels of CRP at 1-year follow-up were demonstrated and prove that haptoglobin levels were not influenced by the acute-phase reaction. All other measured laboratory parameters did not change from baseline to 1-year follow-up.

Post-implantation haemodynamic parameters are described in *Table 3*. Aortic regurgitation assessed by angiography in the operating room occurred in 12 (13%) patients and did not predict haemolysis. Moderate or severe aortic regurgitation (all paravalvular—no central regurgitation was detected) was diagnosed by TTE at discharge from hospital in 11 (12%) patients and was associated with a higher incidence of haemolysis—38% vs. 9% in patients with vs. without per Definition 1, $P = 0.049$ (similar results for Definition 2, see *Table 2*). Markedly higher incidence (approximately seven times) of haemolysis in patients with moderate or severe aortic regurgitation diagnosed by TTE at discharge is shown in *Figure 2A*. We detected a trend towards higher mean prosthetic aortic valve gradient and smaller prosthetic aortic valve area in patients with haemolysis, but this finding did not reach statistical significance and the more appropriate AVAI values were very similar at 0.99 ± 0.34 vs. 0.92 ± 0.39, $P = 0.408$ in patients without vs. with Haemolysis Definition 1 (for all values see *Table 3*). Similarly, neither the severe PPM nor moderate or severe PPM was associated with the presence of haemolysis. *Figure 2B* summarizes the frequency of moderate and severe form of PPM in our cohort and illustrates a similar incidence of haemolysis in these patients.

All patients had mortality data at 6 years post-implantation (5 years post-evaluation for haemolysis) available. Overall, 67 (71%) patients died during 6 years of follow-up, 70% of cardiovascular and 30% of other causes. No patient expired due to haemolytic anaemia. Presence or absence of haemolysis had no impact on long-term patient survival, this is expressed as Kaplan-Meier survival curves in *Take-home figure*. The presence of moderate or severe aortic regurgitation post-TAVI was not associated with worse long-term prognosis in our population—mortality at 6 years was 72% in patients with trace or mild aortic regurgitation and 64% in patients with moderate or severe regurgitation, $P = 0.46$.

Discussion

In this study, we provide the first data on intravascular haemolysis after implantation of supra-annular self-expandable transcatheter aortic prosthesis. The major findings of this study are the following: (i) incidence of intravascular haemolysis depends on the definition used, (ii) intravascular haemolysis is associated with turbulent blood flow and this is in the case of supra-annular self-expanding TAVI prosthesis associated with paravalvular aortic regurgitation but not with PPM, and (iii) intravascular haemolysis was mild in all diagnosed cases and did not have any prognostic impact till 6 years post-implantation.

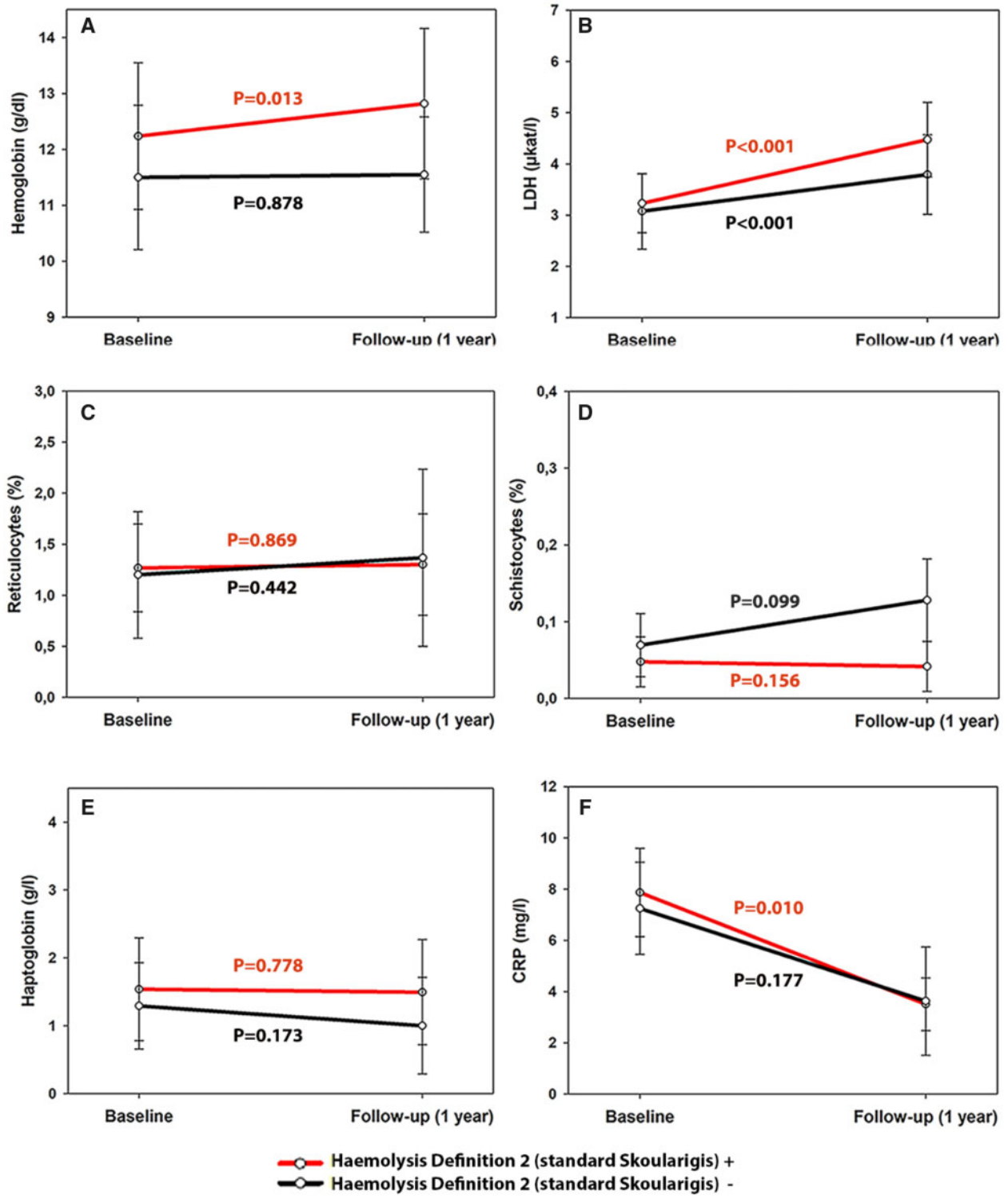


Figure 1 The comparison of laboratory parameters of haemolysis at baseline (before transcatheter aortic valve implantation) and 1-year follow-up (*A*) Haemoglobin; (*B*) Lactatedehydrogenase (LDH); (*C*) Reticulocytes; (*D*) Schistocytes; (*E*) Haptoglobin; (*F*) C-reactive protein (CRP).

During the 1960s aortic valve replacement surgery was introduced with a mechanical prosthesis[13] or bioprosthetic xenograft[14] and the first report of haemolytic anaemia of mechanical origin followed shortly afterward,[15] interestingly with authors correctly recognizing the role of turbulent blood flow. Since then, the incidence of clinical, symptomatic haemolysis decreased and became rare with reported rates under 1% with modern prosthetic

valves.[3,4,16,17] However, mild subclinical haemolysis is commonly detected even with contemporary prostheses use, the reported incidence ranges from 18% to 51% and 5% to 10% in mechanical and biological prostheses, respectively. The wide range reflects the non-uniform diagnostic criteria used, this issue is covered in detail in two review articles.[18,19] Our results confirm this matter as a simple omission of one diagnostic parameter (schistocyte count) from standard Skoularigis criteria results in a three-times lower rate of haemolysis diagnosis (28% vs. 9%). Red blood cell survival analysis has been used in a small study and this approach might be more reliable in mild intravascular haemolysis detection and quantification.[20]

As far as the comparison of our results to published data:

(1) There is only one report on haemolysis after surgical bioprosthetic valve in the aortic position. The study by Mecozzi *et al.*[3] reported 3% incidence of haemolysis after stented surgical bioprosthesis in the aortic position. This is numerically clearly lower than our 28% incidence using the same Haemolysis Definition 2 criteria but should still be interpreted with caution as patient populations are quite different too; for example, age differs by 13 years. The majority of our patients (80%) had haemoglobin levels below the cut-off value per Skoularigis criteria even before TAVI. Hypothetically, replacing the absolute values of haemoglobin levels by drop of 1 g/dL or more from baseline would result in a dramatic reduction of haemolysis incidence to 9% in the old and high-risk TAVI patients.

(2) There are two reports on haemolysis after TAVI and both have used our haemolysis Definition 1 criteria. Laflamme *et al.*[8] have reported subclinical haemolysis in 15% of 122 patients following TAVI with mostly balloon-expandable prostheses; PVL had no impact on haemolysis but novel association between PPM and haemolysis was found. Ko *et al.*[9] have reported subclinical haemolysis in 38% of 64 patients following TAVI with a mix of several prostheses used; moderate PVL and bicuspid aortic valve predicted haemolysis. These published data seem to report a numerically higher rate of haemolysis than our results (15–38% vs. 9%) but this comparison should be interpreted with caution as numbers are small.

Table 2 Laboratory parameters at baseline and at 1-year follow-up

	Baseline	1 Year	*P*-value
Haemoglobin (g/dL)	12.03 ± 1.34	12.45 ± 1.38	0.034
Platelet count (10^9/L)	192 ± 68	202 ± 71	0.177
Schistocyte count (%)	0.05 ± 0.06	0.06 ± 0.1	0.950
Retikulocyte count (%)	1.24 ± 0.49	1.31 ± 0.6	0.530
LDH (μkat/L)	3.12 ± 0.68	3.98 ± 0.82	<0.001
ALT (μkat/L)	0.4 ± 0.23	0.43 ± 0.27	0.711
Bilirubin (μkat/L)	11.49 ± 6.98	10.76 ± 5.43	0.818
Haptoglobin (g/L)	1.45 ± 0.72	1.35 ± 0.78	0.441
CRP (mg/L)	7.7 ± 9.44	3.53 ± 2.81	0.004

Values are presented as mean ± SD.
ALT, alanine aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; SD, standard deviation.

There seems to be a suggestion of a different predominant mechanism causing haemolysis: PPM for balloon-expandable TAVI prosthesis and PVL for supra-annular self-expandable TAVI prosthesis. Our results reflect a high rate (12%) of moderate or severe PVL after implantation of the first generation of a self-expandable prosthesis. This has improved considerably, recent data from a low-risk trial with 74% of patients treated with Evolut R prosthesis show moderate or severe PVL rate of 3.5% at 30 days post-implantation.[7] Further improvement can be expected with Evolut PRO device use. On the other side, the rates of PVL

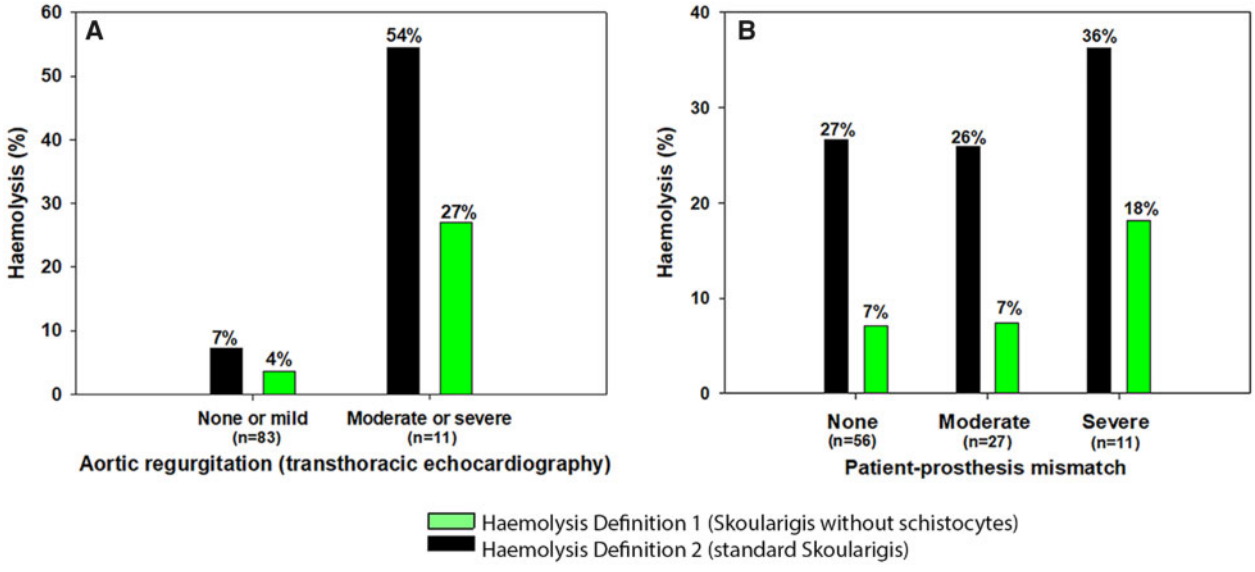
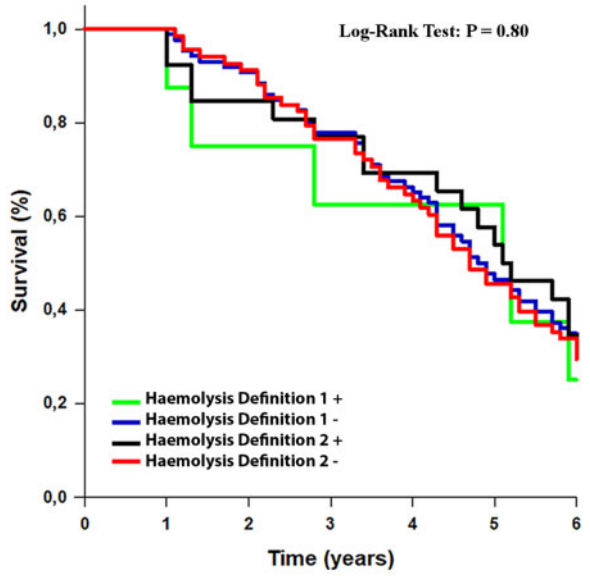


Figure 2 The incidence of intravascular haemolysis according to the severity of (*A*) aortic regurgitation and (*B*) patient-prosthesis mismatch; both determined by transthoracic echocardiography at discharge.

Table 3 Post-implantation haemodynamic parameters according to the presence of haemolysis at 1-year follow-up

	Haemolysis Definition 1 (Skoularigis without schistocytes)			Haemolysis Definition 2 (standard Skoularigis)		
	No (86) Count (%) or mean ± SD	Yes (8) Count (%) or mean ± SD	*P*-value	No (68) Count (%) or mean ± SD	Yes (26) Count (%) or mean ± SD	*P*-value
Moderate or severe AoReg by angiography	11 (12.8)	1 (14.3)	0.73	9 (13.2)	3 (11.5)	0.565
Echocardiography at discharge						
Moderate or severe AoReg	8 (9.3)	3 (37.5)	0.049	5 (7.4)	6 (23.1)	0.044
Mean aortic gradient (mmHg)	7.7 ± 3.5	13.2 ± 9	0.081	7.6 ± 3.5	10 ± 6.3	0.191
Aortic valve area (cm^2)	1.83 ± 0.61	1.67 ± 0.79	0.153	1.88 ± 0.64	1.64 ± 0.55	0.064
Aortic valve area index (cm^2/m^2)	0.99 ± 0.34	0.92 ± 0.39	0.408	1.01 ± 0.35	0.92 ± 0.31	0.228
Severe PPM	9 (11.6)	2 (33.3)	0.275	7 (11.3)	4 (17.3)	0.339
Moderate or severe PPM	34 (44.1)	4 (50)	0.518	27 (43.5)	11 (47.8)	0.456

AoReg, aortic regurgitation; PPM, patient-prosthesis mismatch; SD, standard deviation.



Take-home figure Kaplan–Meier survival analysis according to the presence or absence of intravascular haemolysis at 1-year follow-up.

might be higher in patients with bicuspid anatomy who will be more frequent in younger patients.

Similarly to previously mentioned reports, all intravascular haemolysis was mild in severity in our study and no patient had severe symptomatic haemolysis. Levels of LDH can be falsely increased by other causes than haemolysis[19] but mild elevations reliably rule-out severe haemolysis. As far as the clinical impact of subclinical haemolysis is concerned, Perek *et al.*[21] reported a single-centre study with a possible negative impact of subclinical haemolysis on functional status at follow-up. Ko *et al.* found that mild haemolysis after TAVI was associated with an increased cardiovascular readmission rate at 1-year follow-up. We have not found any drop in haemoglobin levels even in patients with haemolysis at 1-year post-TAVI, but the development of anaemia in longer follow-up is possible. Turbulent blood flow does not only affect red blood cells but platelet activation might be linked to the same flow-induced mechanism as haemolysis.[22]

Our study provides the longest reported follow-up and did not find any impact of mild intravascular haemolysis (irrespective of the definition used) on patient mortality as a hard clinical endpoint.

Limitations

This study has important limitations. The small number of patients precludes multivariate analysis and does not allow us to draw any definitive conclusions. The intravascular haemolysis detection requires prospective laboratory testing of specific parameters that are not routinely clinically required, and this makes *post hoc* efforts to enlarge the number of patients by including other centres impossible. However, both our sample size and univariate data analysis are similar to most published literature on this topic. Selection bias due to eight excluded patients is unlikely but cannot be ruled out. All patients have received first-generation self-expandable TAVI device and our results should not be extrapolated to newer generations or different designs of valve prostheses. Mortality data reflect the high risk of enrolled patients and a small effect on mortality might be missed in our analysis.

Conclusion

No severe symptomatic haemolysis was found after TAVI with self-expandable prosthesis. Mild subclinical intravascular haemolysis is present in 9–28% of patients depending on the definition of haemolysis. The presence of haemolysis is associated with moderate or severe aortic regurgitation but not with post-TAVI aortic valve area, this finding might be specific for the supra-annular self-expandable type of TAVI prosthesis. Subclinical haemolysis seems to be a benign condition with no detected impact on patient mortality at a 6-year follow-up. This topic warrants further study in younger low-risk patients and a more exact definition of intravascular haemolysis is needed.

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