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Original Research

Incidence and Risk Assessment of Infolding Using Self-Expandable Devices in TAVR

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ABSTRACT

Background: Transcatheter aortic valve replacement is an evolving interventional therapy for patients with symptomatic severe aortic stenosis. Infolding (INF) as wrinkling along the valve frame is only seen in self-expandable transcatheter valves or surgical sutureless prostheses and is known to be a very rare event during delivery but probably underreported. Therefore, we aimed to (1) determine the frequency of events, (2) identify potential predictors of INF, and (3) evaluate the potential clinical impact of this adverse event.
Methods: INF cases of 2 centers were retrospectively analyzed in an all-comer cohort of 1416 patients with older- and newer-generation self-expandable (SEV) devices. The underlying functional, anatomical, and procedural conditions were evaluated by univariate analysis.
Results: INF+ was observed in 14 patients (1.0%) with the following valve size distribution: SEV-26: 14.3%, SEV-29: 28.6%, and SEV-34: 57.4%. Several dependent predictors of INF were pointed out, such as severe peripheral kinking, severe aortic calcification, resheathing maneuvers, valve-in-valve procedures, and the use of the largest valve size. INF+ patients showed a higher incidence of acute kidney injury (INF− vs. INF+: 12.3% vs. 35.7%; $p = 0.008$), of a new atrioventricular block (INF− vs. INF+: 14.8% vs. 42.9%; $p = 0.003$), and a higher need of permanent pacemaker implantation (INF− vs. INF+: 14.9% vs. 35.7%; $p = 0.031$).
Conclusions: Identifying potential predictors of INF can probably influence the implantation strategy and improve safety algorithms and clinical outcomes. Even being a rare but potentially life-threatening and underreported event, safety rules must be established when expanding transcatheter aortic valve replacement treatment to younger patients.

ABBREVIATIONS

AN, annular/annulus; AVC, aortic valve calcification; EvR, Evolut R™; INF, infolding; LVOT, left vnetricular outflow tract; SEV, self-expandable valve; TAVR, transcatheter aortic valve replacement.

Introduction

Transcatheter aortic valve replacement (TAVR) is evolving to the therapy of choice for patients with symptomatic severe aortic stenosis and appropriate anatomy with certain surgical risk profiles.[1] Initial problems of the world leading self-expandable device (Medtronic, SEV) like paravalvular leakage have been improved by technological advancements like increased radial force, retrievable valves, and new skirt techniques,[2] also including coverage of large annulus sizes. Furthermore, the supra-annular design offers convincing hemodynamic results. Based on continuous technical improvement and the worldwide growing operator experience, fatal periprocedural complications have fortunately become less frequent.[3] However, some complications or TAVR-related "side effects" still have an impact on patient outcomes and are currently a target of further improvement, especially when considering the expansion into younger low-risk patients (e.g., pacemaker

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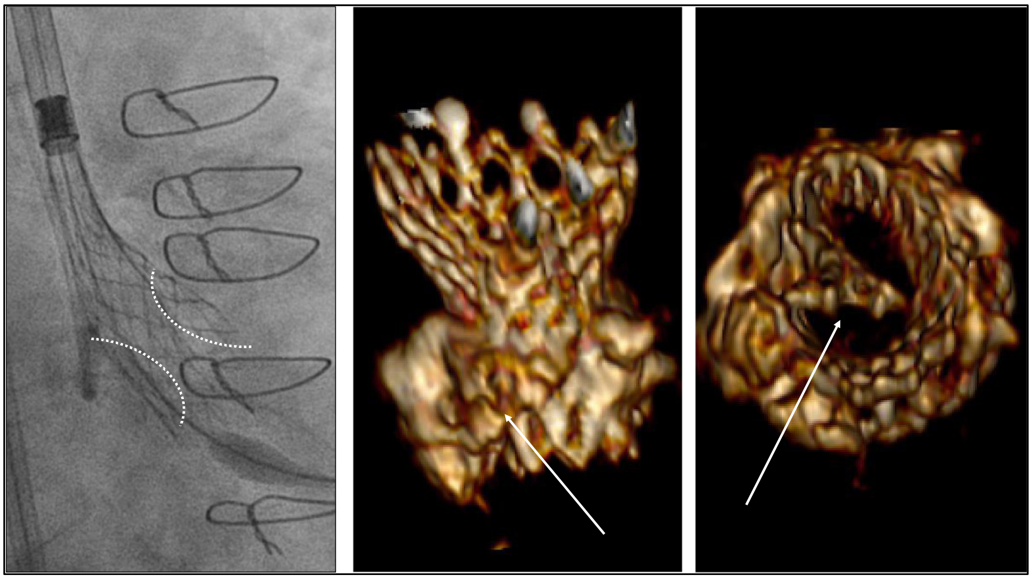

Figure 1. **Typical examples of infolding.** Left: Double wrinkling along the stent frame resulting in an allover invagination of the inflow and outflow tract and a reduced diameter of the unsheathed part of the transcatheter heart valve. Middle and right: Postprocedural multislice computed tomography 3D-reconstruction with diagnosis of infolding.

dependency/conduction disturbances, paravalvular leakage, vascular closure, stroke, coronary occlusion).

Infolding (INF) as wrinkling along the valve frame is only seen in self-expandable transcatheter valves or surgical sutureless prostheses and is known to be a very rare event during delivery.[4–6] On the other hand, INF seems to be underreported in current scientific findings and has not been systematically analyzed. Therefore, we aimed to (1) determine the frequency of events, (2) identify potential predictors of INF, and (3) evaluate the potential clinical impact of this adverse event.

Materials and Methods

Study Population

In this double-center analysis (Düsseldorf, Germany; Oulu, Finland), we retrospectively analyzed INF cases in an all-comer cohort of 1416 patients with older- and newer-generation self-expandable (SEV) devices (CoreValve, Evolut R/Pro System (EvR/Pro); Medtronic Inc, Minneapolis, Minnesota) and completed data sets from 2011 until 2020. The study procedures were in accordance with the Declaration of Helsinki, and the institutional Ethics Committee of the Heinrich-Heine University approved the study protocol (4080). The study is registered at ClinicalTrials.gov (NCT01805739).

Definitions and Image Acquirement

Peripheral kinking was defined as pronounced S-form tortuosity of the aorto-iliac and femoral arteries.[7] Resheath/recapture was defined as partial retrieval of the delivered valve/complete retrieval with the intention to recross the valve.[8]

INF was defined as persisting wrinkling along the stent frame resulting in an all-over invagination of the inflow and outflow tract (in contrast to only malexpansion, i.e., distortion of only the inflow tract). The fluoroscopic sign of a dense radiopaque "vertical line" is the key diagnostic sign of an INF mechanism and is further underlined by a reduced diameter of the unsheathed part of the transcatheter heart valve.[2] This can be diagnosed by a rotational fluoroscopic view (c-arm rotational movement) or a cusp overlap technique or postprocedurally by multislice computed tomography (Figure 1).

All procedural recordings were reviewed by experienced observers and interventionalists. Computed tomography (CT) data were obtained using a 128-slice, single-source CT scanner with a temporal resolution of 150 ms and collimation of 128 × 0.6 mm ("SOMATOM Definition AS+", Siemens Healthcare, Forchheim, Germany) according to TAVR-related standardized recommendations for CT image acquisition and were transferred to a dedicated workstation for further evaluation (3mensio Structural Heart; Pie Medical Imaging BV, Maastricht, The Netherlands).

A tubular configuration of the aortic root ("tube") was considered when the mean aortic annulus and left ventricular outflow tract (LVOT) diameter matched in size toward a ratio of 0.95-1.05. A flared configuration was considered when the mean LVOT diameter was smaller than the mean annulus diameter (LVOT/AN ratio < 0.95). A tapered configuration (mean diameter of the LVOT greater than the mean annulus diameter) fulfilled the LVOT/AN ratio >1.05. The severity of aortic valve calcification (AVC) was collected in volume units for the overall and separated leaflet calcium burden assessment. Calcium originating from extravalvular structures, such as the mitral valve annulus, the ascending aorta, and the coronary arteries, was cropped. Valve oversizing was calculated as (prosthesis size–native annulus size/native annulus size) × 100.

Study Endpoints

The primary endpoint was to determine the frequency of INF and to identify potential predictors with the prospect of developing an algorithm for handling of self-expandable valves in risk-stratified anatomies. The secondary endpoints were defined as the impact of INF on the 30-day outcomes according to Valve Academic Research Consortium 2 definitions.[9]

Statistical Analysis

After standard testing for continuous and categorical variables, the receiver operating characteristic analysis and the c-index (area under the curve) were used to identify the sensitivity and specificity of the specific cutoff points for univariate analysis. Covariates associated with INF in the univariate analysis ($p < 0.05$) were illustrated.

The data analysis was performed using the statistical software SPSS (version 27.0.1, SPSS Inc, Chicago, Illinois), GraphPad Prism (version

Table 1
Procedural characteristics

Procedural data	Overall (n = 1416; 100%)	INF− (n = 1402; 99%)	INF+ (n = 14; 1%)	*p*-value
Valve sizes				
23 mm	17 (1.2)	17 (1.2)	0 (0.0)	0.678
26 mm	415 (29.3)	413 (29.5)	2 (14.3)	0.215
29 mm	711 (50.2)	707 (50.4)	4 (28.6)	0.104
31 mm	42 (3.0)	42 (3.0)	0 (0.0)	0.511
34 mm	231 (16.3)	223 (15.9)	8 (57.4)	<0.001*
Valve oversizing (%)	18.0 ± 7.3	18.4 ± 6.8	18.0 ± 7.3	0.776
CoreValve	134 (9.5)	134 (9.6)	0 (0.0)	0.224
CoreValve Evolut R	1193 (93.1)	1179 (93.0)	14 (100.00)	0.145
CoreValve Evolut PRO	89 (6.9)	89 (7.0)	0 (0.0)	<0.001*
Newer-generation devices (EvR/Pro)	1282 (90.5)	1268 (90.4)	14 (100.0)	0.224
Contrast, mL	99.4 ± 45.8	99.1 ± 45.6	131.6 ± 50.7	0.008*
Fluoroscopy time, min	19.8 ± 9.0	19.7 ± 8.9	28.8 ± 11.2	<0.001*
Dose area product, Gy × cm^2	4375.9 ± 3912.4	4345.7 ± 3882.2	7342.9 ± 5639.1	0.004*
Predilatation	682 (48.2)	676 (48.2)	6 (42.9)	0.792
Postdilatation	217 (15.3)	213 (15.2)	4 (28.6)	0.167
Resheath/recapture of the valve	208 (14.7)	196 (14.0)	12 (85.7)	<0.001*
Repetitive resheath/recapture	63 (4.5)	57 (4.1)	6 (43.9)	<0.001*
Functional data				
AR > mild	28 (2.0)	28 (2.0)	0 (0)	0.592
Intraprocedural complications				
Immediate stroke	3 (0.2)	3 (0.2)	0 (0)	0.862
Aortic dissection	1 (0.0)	1 (0.0)	0 (0)	0.888
Annulus rupture/LV perforation	2 (0.1)	1 (0.0)	1 (7.1)	<0.001*
Coronary obstruction	2 (0.1)	2 (0.1)	0 (0)	0.920
Vascular complications	132 (9.3)	130 (9.3)	2 (14.3)	0.521
Valve dislocation	18 (1.3)	18 (1.3)	0 (0)	0.670
Conversion to surgery	2 (0.1)	2 (0.1)	0 (0)	0.920
Immediate need of the second valve	15 (1.1)	15 (1.1)	0 (0)	0.697
Tamponade	1 (0.0)	1 (0.0)	0 (0.0)	0.888
CPR	9 (0.6)	9 (0.6)	0 (0.0)	0.764
Immediate procedural death	11 (0.8)	11 (0.8)	0 (0.0)	0.739
Disturbances of heart rhythm	62 (4.4)	60 (4.3)	2 (14.3)	0.069

Notes. Values are mean ± SD, or n (%).
Abbreviations: CPR, cardiopulmonary resuscitation; INF, infolding; LV, left ventricular.
* Indicates a significant *p*-value <0.05.

6.0, GraphPad Software, San Diego, California), and Wizard 2- Statistics & Analysis (Evan Miller). All statistical tests were 2-tailed, and a value of $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

INF+ was observed in 14 patients (1.0%). Baseline characteristics did differ according to the particular risk profile. For example, INF+ patients were predominantly male (INF− vs. INF+: 46.4% vs. 78.6%; $p = 0.016$) and had more pronounced peripheral kinking (INF− vs. INF+: 7.8% vs. 64.3%; $p < 0.001$), a narrower aortic valve area (INF− vs. INF+: 0.75 ± 0.2 cm^2 vs. 0.64 ± 0.2 cm^2; $p = 0.047$) combined with higher transvalvular gradients (INF− vs. INF+: dPmean 38.7 ± 15.4 mm Hg vs. 48.1 ± 25.9 mm Hg; $p = 0.025$), enhanced AVC (INF− vs. INF+: 393.3 [216.0-670.3] mm^3 vs. 513.8 [408.4-1.105.0] mm^3; $p = 0.003$), and larger aortic root dimensions (INF− vs. INF+: perimeter 77.1 ± 7.4 mm vs. 83.7 ± 10.6 mm; $p < 0.001$). A full overview of the baseline clinical and functional characteristics is displayed in Supplementary material–Supplemental Table 1.

Procedural Characteristics

Procedural details and clinical outcomes are displayed in Table 1. INF+ patients showed the following valve size distribution: SEV-26: 14.3%, SEV-29: 28.6%, and SEV-34: 57.4%. All these events were documented using the Evolut R system (100%).

Contrast use (INF− vs. INF+: 99.1 mL ± 45.6 vs. 131.6 mL ± 50.7; $p < 0.001$) and fluoroscopy time (INF− vs. INF+: 19.7 min ± 8.9 vs. 28.8 min ± 11.2; $p < 0.001$) were enhanced in the INF+ cohort, and repositioning maneuvers were more common (INF− vs. INF+: 14.0% vs. 85.7%; $p < 0.001$). Predilatation and postdilatation maneuvers were similar in both cohorts. Apart from one left ventricular perforation in the INF+ cohort, all intraprocedural complications were comparable.

Rescue of INF

The details are displayed in the Supplementary material–Supplemental Table 2. Two INF+ patients (14.3%) had bicuspid valve morphology; one patient (7.1%) was allocated to a valve-in-valve treatment in a previous aortic surgical prosthesis (SJM Tissue Valve ESP 100-25 mm). Postdilatation was the treatment strategy in 35.7% when the valve was already released, while one reintervention (7.1%) during the follow-up was necessary owing to severe aortic regurgitation and high gradients. In case of awareness of INF before the valve delivery, predilatation before valve release combined with retrieval and deployment of a new valve was realized in 14.3%. Prosthesis replacement with a new device without further actions (predilatation or postdilatation) was documented in 42.9% of cases.

Predictors for INF

Several dependent predictors for INF were pointed out by univariate analysis including gender distribution, a larger valve size, and specific anatomical criteria including conformation of the aortic root, AVC, and repositioning maneuvers (Table 2, model A). To better distinguish the impact of continuous parameters, thresholds were established using Youden's index (Table 2, model B).

Table 2
Univariate regression analysis of infolding

	Univariate analysis	
	OR (95% CI)	*p*-value
A) Parameters ($p < 0.05$)		
Male gender	4.23 (1.18-15.23)	0.027*
Peripheral kinking	21.57 (7.10-65.49)	<0.001*
Valve-in-valve	107.77 (6.39-1817.26)	0.001*
LVEF	0.95 (0.91-0.99)	0.027*
dPmean	1.03 (1.00-1.06)	0.024*
AVA	0.05 (0.00-0.91)	0.043*
Annulus perimeter	1.11 (1.04-1.07)	<0.001*
LVOT/AN perimeter	0.00 (0.00-0.14)	0.010*
"Flare" aortic root	3.23 (1.08-9.69)	0.037*
AVC (total)	1.00 (1.00-1.00)	0.003*
AVC (RCC)	1.00 (1.00-1.00)	0.004*
AVC (LCC)	1.00 (1.00-1.00)	<0.001*
Valve size 34 mm	7.05 (2.42-20.51)	<0.001*
Resheath/recapture	36.92 (8.2-166.21)	<0.001*
B) Subanalysis		
LVEF ≥ 40%	4.24 (1.31-13.71)	0.016*
AVA ≤ 0.65	2.15 (0.75-6.17)	0.154
LVOT/AN perimeter ≤ 0.90	3.44 (1.18-10.00)	0.023*
AVC (RCC) ≥ 130 mm^3	7.90 (1.76-35.45)	0.007*
AVC (LCC) ≥ 131 mm^3	3.78 (1.18-12.12)	0.025*
Valve size ≥ 29 mm	2.65 (0.59-11.91)	0.202
AN-EI ≥ 0.81	1.94 (0.61-6.21)	0.266

Abbreviations: AN, annulus; AVA, aortic valve area; AVC, aortic valve calcification; BMI, body mass index; dPmean/max, mean/max. transvalvular gradient; EI, eccentricity index; LCC, Left coronary cusp; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NCC, noncoronary cusp; OR, odds ratio; RCC, right coronary cusp.
* Indicates a significant *p*-value <0.05.

Thirty-Day Outcome and Functional Status

Although most of the outcome characteristics were comparable, INF+ patients showed a higher incidence of acute kidney injury (AKI; INF− vs. INF+: 12.3% vs. 35.7%; $p = 0.008$), of a new atrioventricular block (AVB; INF− vs. INF+: 14.8% vs. 42.9%; $p = 0.003$), and a higher need of permanent pacemaker implantation (INF− vs. INF+: 14.9% vs. 35.7%; $p = 0.031$). Transcatheter aortic valve implantation–related reintervention was only necessary in one INF case (INF− vs. INF+: 0.0% vs. 7.1%; $p < 0.001$).

Functional improvement at 30 days was observed in both groups, but with slightly enhanced flow conditions and pronounced aortic regurgitation in the INF+ cohort as evaluated by the predischarge echocardiography. Please see also Table 3.

Discussion and Limitations

Our study revealed for the first time that (1) there is a relevant incidence (1.0%) of intraprocedural INF, (2) these events are linked to specific anatomical and procedural characteristics, and (3) INF may have negative impact on the outcome.

Potential Predictors of INF

Our results confirm previous case reports, supposing that enhanced shear forces in large anatomies in combination with severe calcium burden may lead to the INF mechanism. Karrowni et al.[5] identified in their literature review particular anatomical (eccentric calcification, an elliptic annulus, a bicuspid anatomy) and procedure-related (improper loading, resheathing, and larger valve size ≥29 mm) factors (Figure 2). However, systematically derived analyses are still missing owing to the infrequency of the event and probably underreporting: Thus, the true incidence of INF is still unknown, but a recent report revealed an estimate of 3.15%.[10] INF must be distinguished from only malapposition effects by the meaning of compression of the inflow tract and is, therefore, consistently associated with a device failure and the need for further treatment. In our study, several potential anatomical and procedural influencers were identified by univariate analysis including gender distribution, larger valve sizes, and specific anatomical criteria like conformation of the aortic root, AVC burden, and repositioning maneuvers. Improper loading was not observed in any of the INF+ cases. This supposes that maybe calcification distribution in a shear-forced anatomy combined with (repetitive) resheathing maneuvers may trigger the collapse of the stent frame. Even if Ancona et al.[6] also described INF in the last-generation and the newer Evolut Pro devices, we did not see any events in our study cohort. However, the number of these valve types was limited in this study, but from a technical point of view, the risk of INF might be balanced through the pericardial wrap of the Evolut Pro device. Larger devices are known to be prone to a stent frame collapse, in particular after repetitive resheathing/recapture maneuvers, which is in line with the results of this dual center study. However, INF was also seen

Table 3
Postprocedural and functional outcome

Postprocedural outcome	Overall (n = 1416; 100%)	INF− (n = 1402; 99%)	INF+ (n = 14; 1%)	*p*-value
30-d mortality	22 (1.6)	21 (1.5)	1 (7.1)	0.089
Disabling bleeding	25 (1.8)	25 (1.8)	0 (0.0)	0.614
Major bleeding	129 (9.1)	128 (9.1)	1 (7.1)	0.797
Major vascular complications	136 (9.6)	135 (9.6)	1 (7.1)	0.753
CPR	25 (1.8)	24 (1.7)	1 (7.1)	0.125
Stroke	44 (3.1)	44 (3.1)	0 (0.0)	0.501
AKI I–III	177 (12.5)	171 (12.3)	5 (35.7)	0.008*
New RRT	27 (1.9)	27 (1.9)	0 (0.0)	0.600
New AVB (I–III°)	213 (15.0)	207 (14.8)	6 (42.9)	0.003*
New LBBB/RBBB	201 (14.2)	200 (14.3)	1 (7.1)	0.447
New PPI	214 (15.1)	209 (14.9)	5 (35.7)	0.031*
TAVR-related reintervention	1 (0.1)	0 (0.0)	1 (7.1)	<0.001*
In-hospital stay, d	11.1 [5.7-13.6]	11.1 [10.6-11.5]	9.6 [5.7-13.6]	0.544
ICU stay, d	2.8 [0.5-3.6]	2.8 [2.6-3.1]	2.0 [0.5-3.6]	0.510
Vmax	1.8 ± 0.3	1.8 ± 0.3	2.0 ± 0.4	0.016*
dPmean	7.4 ± 3.5	7.3 ± 3.5	8.7 ± 3.6	0.151
AR > mild	49 (3.5)	48 (3.6)	1 (7.1)	<0.001*

Notes. Values are mean ± SD, median [interquartile range], or n (%).
Abbreviations: AKI, acute kidney injury; AR, aortic regurgitation; AVB, atrioventricular block; ICU, intensive care unit; INF, infolding; LBBB, left-bundle branch block; PPI, permanent pacemaker implantation; RBBB, right-bundle branch block; RRT, renal replacement therapy; TAVR, transcatheter aortic valve replacement.
* Indicates a significant *p*-value <0.05.

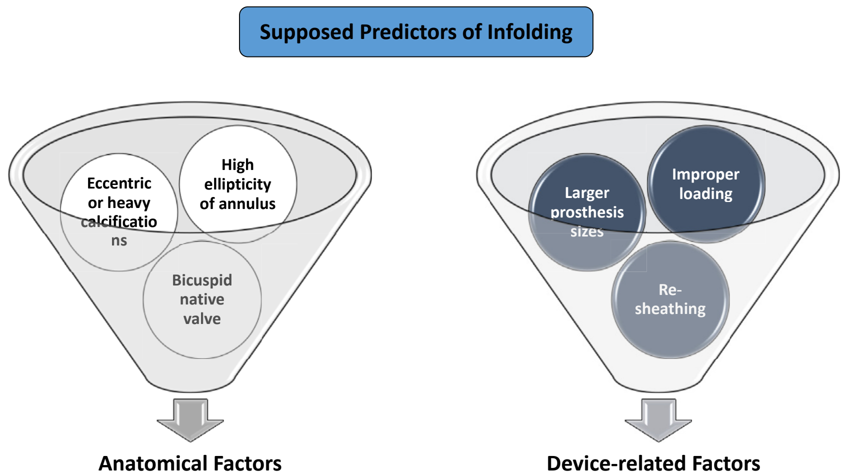

Figure 2. **Supposed anatomical and device-related factors of infolding (according to Karrowni et al.).**

in valve sizes 26 and 29, but more frequently using the valve size 34 (SEV-26: 14.3%, SEV-29: 28.6%, and SEV-34: 57.4%).

Outcome Aspects

It is known that INF can cause severe paravalvular leakage and hemodynamic collapse and was also reported to be associated with an increased risk of periprocedural stroke[11,12] and is, therefore, considered to be a rare but life-threatening adverse event. In our study, INF prolonged procedure time and caused enhanced contrast use. INF was associated with a higher incidence of acute kidney injury and new atrioventricular blocks with a consecutive higher need of permanent pacemaker implantation when compared to a large control cohort. Furthermore, the need for a contemporary reintervention as valve-in-valve treatment was only necessary for the INF cohort owing to severe aortic regurgitation. This has to be taken into consideration when expanding TAVR treatment to younger patients.

Diagnosis and Treatment of INF

According to Abdelghani et al.,[4] we recommend first

- to fluoroscopically inspect the loaded valve before any implantation to ensure a proper loading and
- to look carefully for the fluoroscopic “vertical line” sign before the final release of the valve, in particular when the risk factors—as mentioned above—are fulfilled.

First, proper valve loading is crucial, avoiding a nonconcentric loading or uneven crimping of the inflow end into the inflow cone. The newer self-expandable device requires an in-depth evaluation of the correct crimping process owing to the larger sealing cuff, which might—theoretically—increase the risk of INF given the greater compression of the device. The potentially resulting fold is typically resolved during deployment but may persist in case of a higher annular restriction (e.g., high-grade calcification, bicuspid anatomy).[10] We recommend filming the fluoro load inspection in a 360-degree rotation of the loaded valve, also ensuring that both paddles appear simultaneously in the pocket, that the node bands are aligned, and that there is no severe crown overlap (although the latter case means no valve misload but can be a risk factor in a certain anatomy). Second, a rotational c-arm movement[13] can reliably reveal the signs of INF along with the valve frame during the procedure. When INF is

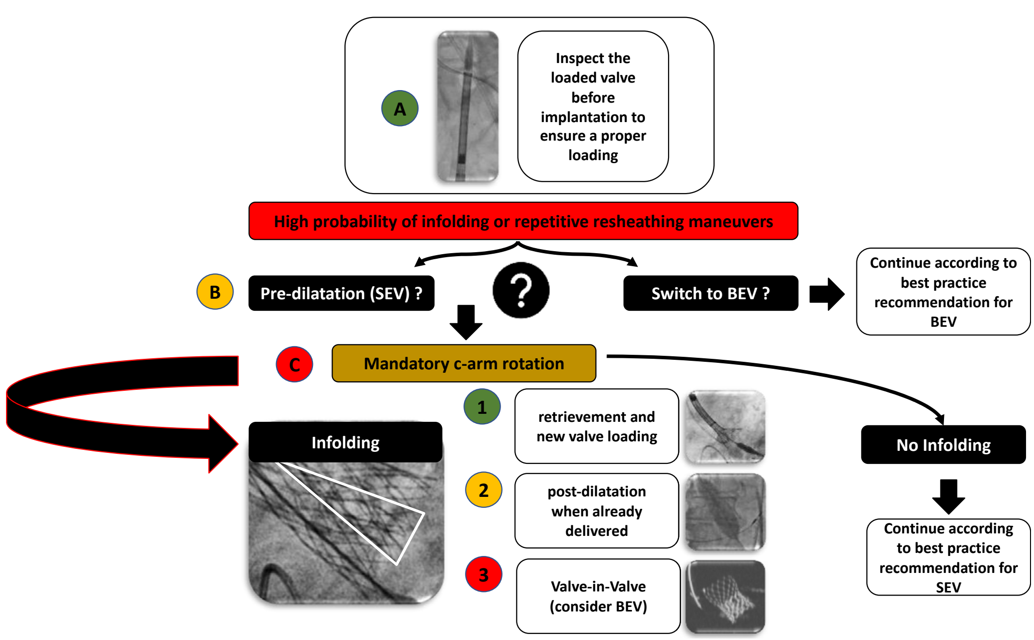

Figure 3. **Commonly used techniques that may prevent or resolve infolding.**

intraprocedurally observed, retrieval and new valve loading are recommended by the manufacturer before delivery; postdilatation is the primary rescue tool if the valve is already released, followed by valve-in-valve implantation with a balloon-expandable device in case of insufficient postdilatation effects (Figure 3). If the probability of INF is high along specific anatomical and procedural criteria, interventionalists may also consider a direct switch to the use of a balloon-expandable device instead, which must be balanced against other potential risks (e.g., annular rupture). It has to be pronounced that these are commonly used techniques believed to prevent or treat valve INF, but they are not proven nor are they known to be superior to other techniques such as withdrawing the device into the ascending aorta, followed by a complete recapture of the valve, and a new recross and deployment of the valve.

Limitations

Some limitations should be mentioned: (i) this is a retrospective study so that some cases of INF might have been undetected, (ii) the number of events is limited, and (iii) there is a lack of impact evaluation in the longer term (e.g., durability, reinterventions).

Conclusion

Identifying potential predictors of INF can probably influence the implantation strategy and improve safety algorithms and clinical outcomes. Even being a rare but potentially life-threatening and underreported event, safety rules must be established when expanding TAVR treatment to younger patients.

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Ethics Statement

The research reported was conducted in accordance with the Declaration of Helsinki and all relevant ethical guidelines. The Institutional Ethics Committee of the Heinrich Heine University approved the study protocol (4080).

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Disclosure statement

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Supplementary Material

Supplemental data for this article can be accessed on the publisher's website.

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