ESC European Society of Cardiology

European Journal of Heart Failure (2023)
doi:10.1002/ejhf.2969

RESEARCH ARTICLE

Quantitative fluid overload in severe aortic stenosis refines cardiac damage and associates with worse outcomes

Kseniya Halavina[1], Matthias Koschutnik[1], Carolina Donà[1], Maximilian Autherith[1], Fabian Petric[1], Anna Röckel[1], Katharina Mascherbauer[1], Gregor Heitzinger[1], Varius Dannenberg[1], Felix Hofer[1], Max-Paul Winter[1], Martin Andreas[2], Thomas A. Treibel[3,4], Georg Goliasch[1], Julia Mascherbauer[1,5], Christian Hengstenberg[1], Andreas A. Kammerlander[1], Philipp E. Bartko[1], and Christian Nitsche[1,3,4]*

[1]Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; [2]Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria; [3]Institute of Cardiovascular Science, University College London, London, UK; [4]Barts Heart Centre, St. Bartholomew's Hospital, London, UK; and [5]Karl Landsteiner University of Health Sciences, Department of Internal Medicine 3, University Hospital St. Pölten, Krems, Austria

Received 10 May 2023; revised 13 June 2023; accepted 3 July 2023

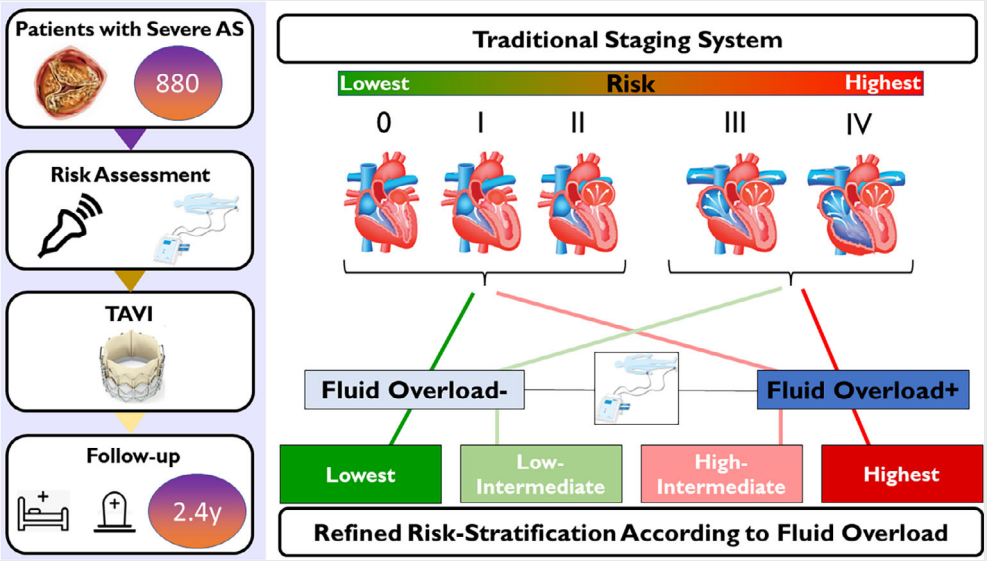
Aims Cardiac decompensation in aortic stenosis (AS) involves extra-valvular cardiac damage and progressive fluid overload (FO). FO can be objectively quantified using bioimpedance spectroscopy. We aimed to assess the prognostic value of FO beyond established damage markers to guide risk stratification.

Methods and results Consecutive patients with severe AS scheduled for transcatheter aortic valve implantation (TAVI) underwent prospective risk assessment with bioimpedance spectroscopy (BIS) and echocardiography. FO by BIS was defined as ≥1.0 L (0.0 L = euvolaemia). The extent of cardiac damage was assessed by echocardiography according to an established staging classification. Right-sided cardiac damage (rCD) was defined as pulmonary vasculature/tricuspid/right ventricular damage. Hospitalization for heart failure (HHF) and/or death served as primary endpoint. In total, 880 patients (81 ± 7 years, 47% female) undergoing TAVI were included and 360 (41%) had FO. Clinical examination in patients with FO was unremarkable for congestion signs in >50%. A quarter had FO but no rCD (FO+/rCD−). FO+/rCD+ had the highest damage markers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. After 2.4 ± 1.0 years of follow-up, 236 patients (27%) had reached the primary endpoint (29 HHF, 194 deaths, 13 both). Quantitatively, every 1.0 L increase in bioimpedance was associated with a 13% increase in event hazard (adjusted hazard ratio 1.13, 95% confidence interval 1.06−1.22, $p < 0.001$). FO provided incremental prognostic value to traditional risk markers (NT-proBNP, EuroSCORE II, damage on echocardiography). Stratification according to FO and rCD yielded worse outcomes for FO+/rCD+ and FO+/rCD−, but not FO−/rCD+, compared to FO−/rCD−.

Conclusion Quantitative FO in patients with severe AS improves risk prediction of worse post-interventional outcomes compared to traditional risk assessment.

*Corresponding author. Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Tel: +43 1 40400 46140, Fax: +43 1 40400 42160, Email: christian.nitsche@meduniwien.ac.at

Graphical Abstract



Assessment of fluid overload identifies aortic stenosis (AS) patients at high risk and treatment of fluid overload may potentially improve the post-interventional clinical course.

Keywords Volume status • Congestion • Cardiac decompensation • Transcatheter aortic valve implantation • Staging

Introduction

In aortic stenosis (AS), progressive narrowing of the aortic valve poses increased afterload on the left ventricle. Left ventricular (LV) adaptation is required to maintain cardiac output. If the afterload stimulus persists, LV compensatory mechanisms are exhausted resulting in backward failure with damage affecting the left atrium, pulmonary vasculature, and eventually the right ventricle.[1] This process of cardiac decompensation is accompanied by pulmonary and systemic congestion.[2–4] Since physical signs to assess fluid overload (FO) are not reliable,[5] more sensitive and specific measures are warranted. Bioimpedance spectroscopy (BIS) allows accurate and reproducible quantification of FO. Clinical application of this methodology initially involved patients undergoing dialysis to establish dry weight goals,[6] but it has more recently also been proven valuable in risk stratifying cardiac patients.[2,3,7]

The extent of cardiac damage – as described by a well-established staging classification – allows prognostication of clinical outcomes after aortic valve replacement.[1] However, there is concern that this staging system may be too simplistic to capture the multi-faceted nature of remodelling in severe AS and warrants refinement to achieve optimal risk stratification.[8,9] We hypothesized that FO by bioimpedance may provide incremental value in the characterization of cardiac damage and prognostication compared to traditional risk markers (N-terminal pro-B-type natriuretic peptide [NT-proBNP], EuroSCORE II, cardiac damage on echocardiography).

We quantitatively assessed fluid status and the extent of cardiac damage in consecutively recruited severe AS patients scheduled for transcatheter aortic valve implantation (TAVI). We aimed to investigate whether FO associates with markers of cardiac damage and provides incremental prognostic information following intervention.

Methods

Study design and population

This large-scale single-centre observational study between 2017 and 2021 prospectively enrolled consecutive adult patients with severe degenerative AS scheduled for TAVI at the Vienna General Hospital, a university-affiliated tertiary centre. A multidisciplinary heart team determined eligibility and decision for TAVI. Patients with clinical signs of overt cardiac decompensation (i.e. pulmonary oedema, haemodynamic instability), those eventually not receiving valvular treatment, and patients with insufficient BIS data quality were excluded from the final analysis (online supplementary *Figure S1*). The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Vienna (EK no. 2218/2016). All patients provided written informed consent.

Clinical measures at baseline and follow-up

Standard pre-procedural evaluation included clinical and laboratory assessment, a 12-lead electrocardiogram, and transthoracic echocardiography. EuroSCORE II was calculated. On the day preceding TAVI, volume status was assessed with bioimpedance as well as clinically (leg oedema, rales, pulmonary venous congestion/pleural effusions on chest X-ray) in all patients. Leg oedema was considered 'present' if graded at least to the level of the ankles.[3] Routine clinical follow-up was performed at 3 months, 12 months, and every 1–2 years thereafter with a minimum follow-up duration of 12 months. (Peri-)procedural complications were captured according to the Valve Academic Research Consortium-3.[10] The primary endpoint was the occurrence of hospitalization for heart failure (HHF) and/or all-cause death. HHF was determined from three sources, covering hospitalizations in all Austrian hospitals: patient records of the Medical University of Vienna, Vienna HealthAssociation database, and the nationwide electronic health records. All-cause mortality was captured from the Austrian Death Registry. Death and HHF were analysed individually as secondary study endpoints. Outcome assessment was 100% complete.

Transthoracic echocardiography

Standard echocardiograms were performed by board-certified cardiologists using commercially available equipment (Vivid E95, GE Healthcare, and Acuson Sequoia, Siemens). Cardiac morphology was assessed according to recent recommendations.[11] The extent of cardiac damage was assessed according to a previously proposed staging classification (for details see online supplementary *Table S1*), where higher stages represent increasing extra-valvular cardiac damage (stage 0: no cardiac damage; stage 1: LV damage; stage 2: left atrial [LA] or mitral damage; stage 3: pulmonary vasculature or tricuspid damage; stage 4: right ventricular damage).[1] According to this classification patients are hierarchically classified into a given stage (worst stage) if at least one of the proposed criteria is met within that stage. The present study defined right-sided cardiac damage (rCD) as the presence of either stage 3 or 4. Centralized core-lab review blinded for clinical data was done for all recorded echocardiograms to allocate a specific damage stage. Valvular stenosis and regurgitation were quantified using an integrated approach and graded as none, mild, moderate, and severe according to the respective guidelines.[12,13] AS was classified as severe when transvalvular velocity exceeded 4 m/s, mean transvalvular gradient was ≥40 mmHg, and aortic valve area was <1 cm^2. In case of low-gradient AS, dobutamine stress echocardiography and/or calcium scoring by computed tomography were applied to quantify stenosis severity.[14]

Bioimpedance spectroscopy

Patients underwent standardized evaluation of their fluid status using a portable whole-body BIS device, the Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany), as previously described.[3] The principle of BIS has been outlined by previous work,[3,15] and its reproducibility has been demonstrated.[16] In short, BIS is based on the principle that the body acts as a circuit with a given resistance (opposition of current flow through extracellular and intracellular solutions) and reactance (capacity of cells for energy storage), where the total body fluid volume is largely reflected in the resistance. The device measures impedance at 50 frequencies over a range from 5 to 1000 kHz to determine the electrical resistance of total body water and extracellular water (ECW). FO as assessed by BIS is expressed as an absolute value in litres or as a relative value in %, calculated as the ratio between FO and the content of ECW (relative FO = FO/ECW × 100). According to previously established[17] and validated[3] cut-off values, the present study defined FO as absolute FO ≥1.0 L. Patients with FO were further subclassified according to the presence of mild (1.0–3.0 L) or severe FO (>3.0 L).[3,17]

Statistical methods

Continuous data are expressed as mean ± standard deviation or as median with corresponding interquartile range (IQR) and categorical variables are presented as percentages or total numbers. Differences between groups were analysed with the Wilcoxon rank sum and Kruskal–Wallis test, as appropriate. Dunn–Bonferroni correction was used for pairwise comparisons. Chi-square tests or Fisher exact tests were used for categorical variables. Kaplan–Meier analysis (log-rank test) was applied to evaluate the discriminative power of FO and rCD, with the date of TAVI serving as the starting point. Uni- und multivariate Cox regression analyses were performed to evaluate the prognostic impact of different variables. Stepwise forward selection was used for multivariate adjustment, including all significant parameters on univariate testing. The incremental prognostic value of FO for 1-year outcomes compared to traditional risk markers and congestion signs was assessed using Harrell's C-index and integrated discrimination improvement (IDI); NT-proBNP levels, EuroSCORE II, and inferior vena cava diameter were graded according to tertiles (1st: 0 points, 2nd: 1 point, 3rd: 2 points), LV ejection fraction was graded according to established cut-off values (≥50%: 0 points, 35–49%: 1 point, <35%: 2 points), inferior vena cava collapsibility according to respiratory diameter change (≥50%: 0 points, <50%: 1 point, no change: 2 points) and then FO (no FO: 0 points, mild FO: 1 point, severe FO: 2 points) was added and the discriminatory power of the respective models was compared. Similarly, FO was added to an 'optimal clinical congestion model', determined by the scoring method yielding the highest area under the curve on receiver operating characteristic curve analysis, with consecutive comparison of discriminatory power. Furthermore, a restricted cubic spline model with knots placed at the 25th, 50th and 75th percentile was used to depict the continuous association of fluid levels and the relative event risk. A two-sided *p*-value of ≤0.05 was considered statistically significant. Statistical analyses were computed using SPSS 28 (IBM SPSS, IBM Corp., Armonk, NY, USA) and R (version 4.2.2.).

Results

Patient characteristics

In total, 945 patients were eligible for study participation, of whom 65 subjects had to be excluded for various reasons (online supplementary *Figure S1*). The remaining 880 patients with valid bioimpedance and echocardiographic data receiving TAVI were stratified according to the presence of FO. Patients with FO were further subdivided into mild and severe FO. Detailed characteristics of patients with versus without FO are displayed in *Tables 1* and *2*. Stratification according to FO and rCD is displayed in online supplementary *Tables S2* and *S3*. The median age of the study population was 81 years (IQR 78–86), 47% were female.

Table 1 Baseline characteristics according to presence of fluid overload (FO)

	FO− (*n* = 520, 59.1%)	FO+ (*n* = 360, 40.9%)	*p*-value
Demographics			
Age, years	81.1 (77.5–85.6)	80.8 (77.9–85.4)	0.912
Male sex, %	47.3	60.3	**<0.001**
BMI, kg/m^2	27.4 (24.5–30.5)	25.5 (22.9–28.7)	**<0.001**
Clinical parameters			
EuroSCORE II	4.0 (3.9–4.4)	4.1 (3.9–4.7)	**0.004**
CAD, %	51.3	53.4	0.559
Diabetes, %	25.0	29.1	0.182
Hypertension, %	61.0	57.8	0.351
COPD, %	10.0	9.5	0.805
Liver disease, %	2.9	4.7	0.148
Cancer, %	12.3	19.0	0.006
Laboratory results			
GFR, ml/min/1.73 m^2	62 (48–77)	61 (41–78)	0.314
NT-proBNP, ng/dl	1443 (642–3291)	2812 (1231–8287)	**<0.001**
CK, U/L	105 (74–165)	105 (68–194)	0.770
Haemoglobin, mg/dl	12.4 (11.1–13.5)	11.5 (10.1–12.9)	**<0.001**
C-reactive protein, mg/dl	0.5 (0.2–1.5)	0.9 (0.2–3.9)	**<0.001**
Symptoms			
Asymptomatic, %	3.3	2.8	0.678
Dyspnoea, %	94.4	93.9	0.739
Chest pain, %	24.8	23.9	0.755
Syncope, %	15.3	15.4	0.941
Medication			
Any diuretic drug, %	53.3	55.0	0.613
Loop diuretic, %	34.2	43.6	**0.005**
Thiazide diuretic, %	13.7	8.3	**0.015**
MRA, %	27.7	24.2	0.243
Xipamid, %	1.0	2.2	0.127
Clinical congestion signs			
Any sign, %	23.7	44.7	**<0.001**
Chest X-ray[a], %	12.5	28.1	**<0.001**
Leg oedema, %	19.9	33.4	**<0.001**
Rales, %	4.1	10.8	**<0.001**
FO by BIS, L	−0.1 (−1.0; 0.5)	2.1 (1.4; 3.0)	**<0.001**

Values are given as % or median (interquartile range).
BIS, bioimpedance spectroscopy; BMI, body mass index; CAD, coronary artery disease; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FO, fluid overload; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]Includes pleural effusion and/or pulmonary venous congestion.

Clinical characteristics

Quantitative fluid levels by bioimpedance in patients with versus without FO were 2.1 L (IQR 1.4–3.0) versus 0.1 L (−1.0 to 0.5) ($p < 0.001$). Patients with FO were more likely to be male (60.3% vs. 47.3%), with lower BMI values (both $p < 0.001$) and higher surgical risk (EuroSCORE II: 4.1 [3.9–4.7] vs. 4.0 [3.9–4.4], $p = 0.004$) compared to patients without FO. Cardiovascular comorbidities were evenly distributed between groups, but the prevalence of cancer was higher in patients with FO (19.0% vs. 12.3%, $p = 0.006$). Natriuretic peptide levels were significantly elevated (2812 ng/dl [1231–8287] vs. 1443 ng/dl [642–3291], $p < 0.001$), and clinical congestion signs (leg oedema, rales, and on chest X-ray; all $p < 0.001$) more prevalent in patients with FO. Accordingly, intake of loop diuretics was more frequent in patients with FO (43.6% vs. 34.2%, $p = 0.005$), whereas the prescription of any diuretic agent was comparable between groups.

Cardiac damage on echocardiography

Markers of stenosis severity were comparable between groups. Even though the distribution of cardiac damage stages according to the traditional classification did not differ significantly between patients with versus without FO (all stages $p > 0.1$), individual components of cardiac damage were more pronounced in patients with FO. This included markers of LV damage (LV mass index: 140 g/m^2 [118–161] vs. 132 g/m^2 [111–153]; E/e′: 21 [16–28]

Table 2 Echocardiographic characteristics according to presence of fluid overload

	FO− ($n = 520$, 59.1%)	FO+ ($n = 360$, 40.9%)	p-value
Valve			
AV PPG, mmHg	73.0 (64.0–88.0)	73.0 (64.0–88.0)	0.480
AV MPG, mmHg	45.0 (38.0–55.0)	47.0 (40.0–55.0)	0.362
AV Vmax, m/s	4.3 (4.0–4.7)	4.3 (4.0–4.7)	0.567
Congestion signs[a]			
IVC diameter, mm	17 (15–19)	18 (16–22)	**<0.001**
IVC collapsibility			**<0.001**
>50%	79.6	62.1	
<50%	13.3	17.3	
No change	7.0	20.6	
Cardiac damage stages and individual components			
Stage 0/1, %	34.6	30.0	0.151
LV mass index, g/m^2	132 (111–153)	140 (118–161)	**0.001**
E/e′	18 (15–24)	21 (16–28)	**0.004**
LV ejection fraction, %	58 (53–67)	56 (47–64)	**0.003**
Stage 2, %	34.2	31.4	0.378
LA volume index, ml/m^2	41 (34–48)	43 (37–54)	**<0.001**
MR ≥ moderate, %	16.2	24.2	**0.005**
Atrial fibrillation, %	27.1	33.8	**0.033**
Stage 3, %	26.9	31.9	0.106
sPAP, mmHg	52 (40–65)	53 (41–65)	0.686
TR ≥ moderate, %	14.8	24.6	**<0.001**
Stage 4, %	4.2	6.7	0.110
RV dysfunction ≥moderate, %	4.2	6.7	0.110

AV, aortic valve; FO, fluid overload; IVC, inferior vena cava; LA, left atrial; LV, left ventricular; MPG, mean pressure gradient; MR, mitral regurgitation; PPG, peak pressure gradient; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; Vmax, maximum velocity.
[a]Available in 699/880 (79.6%); in the remainder, poor echocardiographic quality did not allow for the assessment of the IVC.

vs. 18 [15–24]; LV ejection fraction: 56% [47–64] vs. 58% [53–67], all $p < 0.05$), LA and mitral damage (LA volume index: 43 ml/m^2 [37–54] vs. 41 ml/m^2 [34–48]; moderate or severe mitral regurgitation: 24.2% vs. 16.2%; atrial fibrillation: 33.8% vs. 27.1%; all $p < 0.05$), and tricuspid damage (moderate or severe tricuspid regurgitation: 24.6% vs. 14.8%, $p < 0.001$) (*Table 2*). Overall, higher stages of cardiac damage were associated with higher natriuretic peptide levels ($p < 0.001$) and higher fluid levels by bioimpedance ($p = 0.015$) – there was, however, considerable overlap between stages (online supplementary *Figure S2*). Finally, in patients with sufficient echocardiographic quality (n = 699/880, 79.6%), FO was associated with higher vena cava size (18 mm [16–22] vs. 17 mm [15–19]) and attenuated respiratory motion (<50% collapsibility: 37.9% vs. 20.9%; both $p < 0.001$).

Fluid overload and advanced cardiac damage

With the aim to provide new mechanistic insights into remodelling patterns in severe AS and define distinct phenotypes with specific inherent risk, we combined FO with rCD, creating four categories: FO−/rCD− ($n = 358$, 40.7%), FO−/rCD+ ($n = 162$, 18.4%), FO+/rCD− ($n = 221$, 25.1%), and FO+/rCD+ ($n = 139$, 15.8%) (*Figure 1A*). Clinically, patients with FO−/rCD+ were more likely to be female and had a higher prevalence of arterial hypertension compared to the other three categories (both $p < 0.05$). Morphologically, FO−/rCD+ was characterized by a significantly higher LV ejection fraction than all other groups ($p < 0.05$). Furthermore, in comparison to FO+/rCD+, patients with FO−/rCD+ had a lower LV mass index (131 g/m^2 [111–156] vs. 139 g/m^2 [120–172], $p = 0.01$), lower LA volume index (40 ml/m^2 [35–48] vs. 47 ml/m^2 [39–61], $p < 0.001$), less incompetent atrioventricular valves (mitral regurgitation ≥moderate: 30.1% vs. 42.1%; tricuspid regurgitation ≥moderate: 45.3% vs. 58.3%; both $p < 0.05$), but comparable levels of raised pulmonary artery pressures and right ventricular dysfunction (both $p > 0.05$). In addition, natriuretic peptide levels of FO−/rCD+ were comparable to FO−/rCD− ($p > 0.05$), and significantly lower than in FO+/rCD− and FO+/rCD+ (both $p < 0.05$). Conversely, despite the absence of advanced cardiac damage, FO+/rCD− was characterized by an intermediate phenotype with markedly elevated NT-proBNP levels – higher than FO−/rCD+ and FO−/rCD−, but lower than FO+/rCD+ – and with similar left ventricles (LV mass index and ejection fraction: both $p > 0.05$) but less pronounced LA and mitral damage compared to FO+/rCD+ (both $p < 0.05$).

Outcomes

After a median follow-up of 2.3 years (1.6–3.3), 236 patients (27%) had reached the primary endpoint (29 HHF, 194 deaths, 13 both).

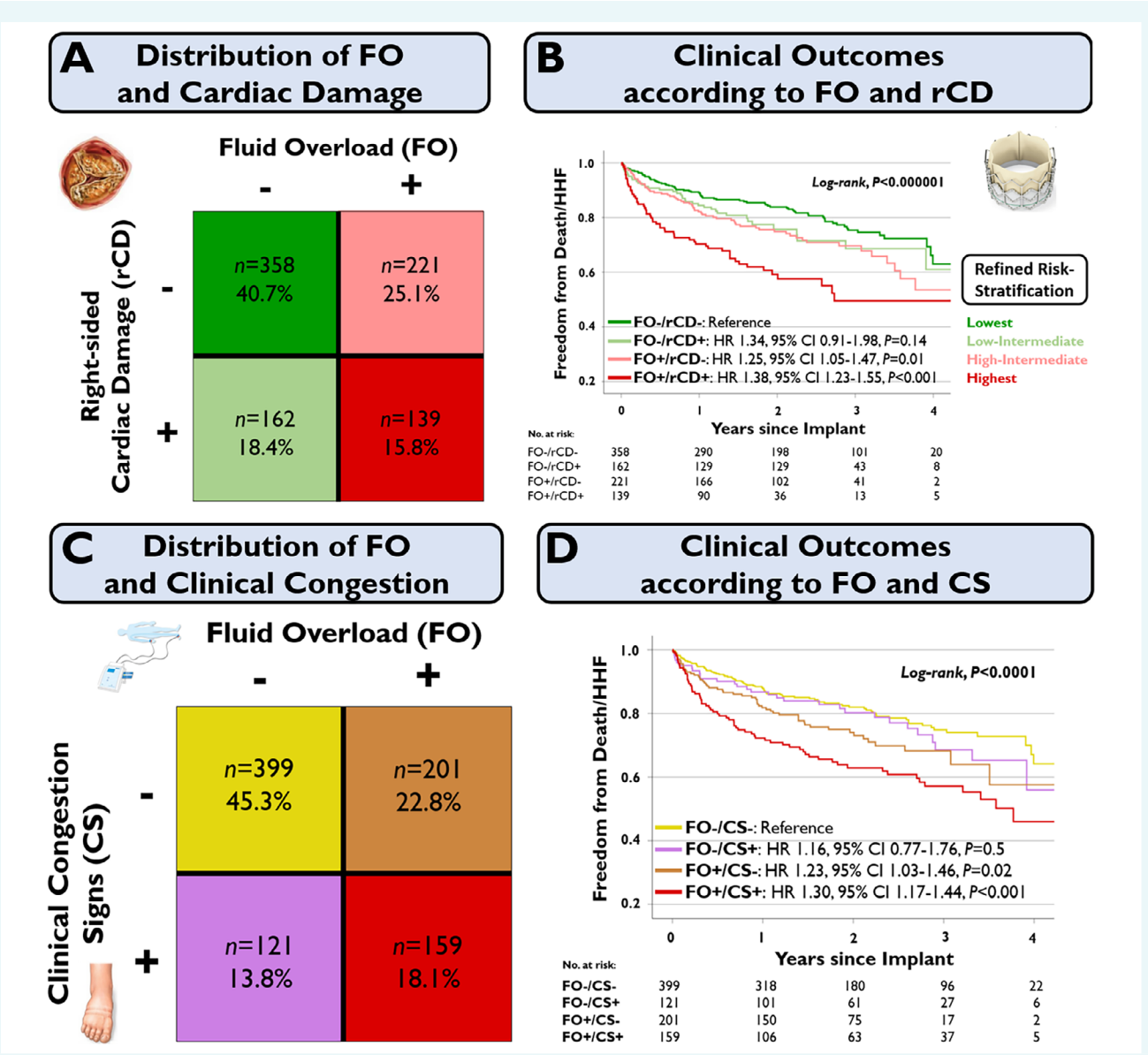


Figure 1 Risk refinement using fluid overload. Bioimpedance spectroscopy combined with the traditional staging system yielded different categories defined by the presence of fluid overload (FO) and right-sided cardiac damage (rCD) (*A*). Only patients with FO (FO+/rCD− and FO+/rCD+), but not FO−/rCD+ had higher cumulative event rates than FO−/rCD− (*B*). Similarly, when combined with the presence of clinical congestion signs (CS) (*C*), only FO+/CS− and FO+/CS+, but not FO−/CS+ had worse outcomes than FO−/CS− (*D*). CI, confidence interval; HR, hazard ratio.

A stepwise increase in risk was observed from mild FO (vs. no FO: adjusted hazard ratio [adjHR] 1.40, 95% confidence interval [CI] 1.03–1.90) to severe FO (vs. no FO: adjHR 1.39, 95% CI 1.13–1.71; vs. mild FO: adjHR 1.58, 95% CI 1.04–2.41; log-rank: $p < 0.0001$) (*Figure 2A*). Quantitatively, every 1 L increase in fluid levels was associated with a 20% increase in event hazard (HR 1.20, 95% CI 1.12–1.27, $p < 0.001$). This effect was consistent across all studied subgroups, including cardiac damage stages and NT-proBNP levels (online supplementary *Figure S3*). Restricted cubic spline curves best depict the continuous effect of ascending fluid levels on increased event hazard (online supplementary *Figure S4*). The significant prognostic effect of fluid levels persisted after multivariate adjustment (adjHR 1.13, 95% CI 1.06–1.22, $p < 0.001$; *Table 3*). Landmark analysis demonstrated consistent relationship between fluid levels and the occurrence of death or HHF (*Figure 2B*) beyond 30 days. Results remained virtually unchanged when death was analysed separately (adjHR 1.15, 95% CI 1.07–1.24, $p < 0.001$; log-rank: $p < 0.001$) (online supplementary *Figure S5*), and when additional parameters of significant MR (online supplementary *Table S4*), and severe renal failure and daily furosemide equivalent dose (online supplementary *Table S5*) were entered into the model. Also, fluid levels were

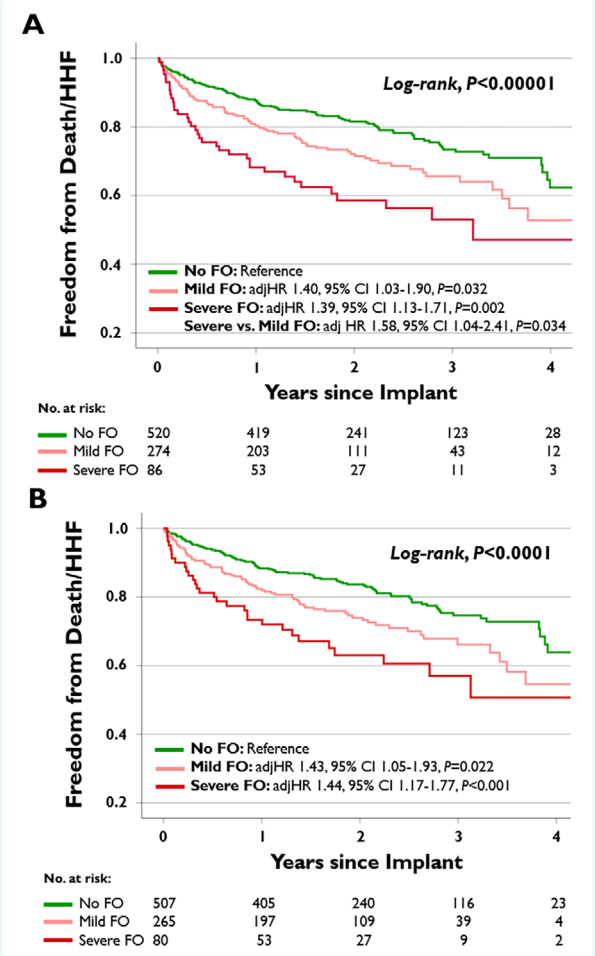


Figure 2 Kaplan–Meier curves stratified according to the presence of fluid overload. A stepwise increase of risk was observed for patients with no fluid overload (FO) to mild FO to severe FO after adjustment for age, sex, and EuroSCORE II. (*A*) All-cause death and/or hospitalization for heart failure (HHF). (*B*) All-cause death and/or HHF with 30-day landmark analysis. adjHR, adjusted hazard ratio; CI, confidence interval.

significantly associated with the occurrence of HHF (HR 1.18, 95% CI 1.01–1.37, $p = 0.04$) – the relatively low number of events precluded multivariate adjustment for this secondary endpoint. In an outcome model containing all congestion parameters performed in patients with available vena cava measurements, fluid levels remained significantly associated with worse prognosis (adjHR 1.11, 95% CI 1.03–1.21, $p = 0.01$) (online supplementary *Table S6*). Finally, peri-procedural outcomes were comparable between groups apart from slightly lower mean trans-prosthetic gradients in patients with FO (online supplementary *Table S7*).

Fluid overload and refinement of risk stratification

Using the traditional classification, higher stages of cardiac damage on average had higher cumulative event rates (log-rank, $p = 0.001$) – an effect driven by stages 3 (vs. stage 0/1: HR 1.30, 95% CI 1.10–1.54) and 4 (vs. stage 0/1: HR 1.33, 95% CI 1.12–1.59), but not stage 2 (vs. stage 0/1: HR 1.26, 95% CI 0.90–1.76) (online supplementary *Figure S6*). The combination of bioimpedance results with the traditional staging system yielded different categories defined by the presence of FO and rCD, which showed significantly different inherent risk for adverse outcomes (log-rank: $p < 0.000001$, *Figure 1B*). When compared to FO–/rCD– as a reference, there was a stepwise increase in hazard from FO+/rCD– (HR 1.25, 95% CI 1.05–1.47) to FO+/rCD+ (HR 1.38, 95% CI 1.23–1.55). Conversely, outcomes of FO–/rCD+ did not differ significantly from those of FO–/rCD– (HR 1.34, 95% CI 0.91–1.98). Combining FO by bioimpedance with clinical congestion signs (CS) yielded four categories, where FO+/CS+ ($p < 0.001$) and FO+/CS– ($p = 0.02$), but not FO–/CS+ ($p = 0.5$) had worse outcomes compared to FO–/CS– as a reference, which conveyed the best prognosis (*Figure 1C, D*). The addition of FO to traditional risk markers significantly improved the discriminatory power of the respective models including an additive clinical congestion score (area under the curve 0.632 vs. 0.673, $p = 0.027$) (*Table 4*).

Discussion

The present large-scale prospective study evaluated the role of quantitative FO in risk stratifying patients with severe AS. Overall, increasing fluid levels indicated higher stages of cardiac damage and conveyed incremental hazard of death and heart failure events post-TAVI – an effect consistent across all subgroups, including patients without clinical congestion signs. However, the incorporation of FO re-allocated patients into lower and higher risk categories, respectively, compared to the traditional staging classification, thereby refining cardiac damage and prognostication in severe AS.

Congestion is common in patients with heart failure and carries worse outcomes.[18] Clinical signs of FO, however, have limited reliability[5,19] and hence great interest has accrued to develop congestion monitoring devices that would ideally detect imminent heart failure and enable early treatment initiation.[20–22] In the present study, we used a portable whole-body BIS device to assess FO, which is an established tool in dialysis and has lately gained importance in the risk assessment of cardiac patient populations.[2,3,7] Measurements are performed with the patient in supine position and take ~2 min. There are no reported adverse events and given its good reproducibility one measurement is sufficient for accurate assessment of volume status.[16] Here, half of patients with FO on bioimpedance had an unremarkable physical examination for congestion signs, yet suffering worse outcomes (*Figure 1D*), backing previous reports.[3,5,19] We also assessed vena cava size and respiratory motion on echocardiography. Patients with FO on average had a larger vena cava size with attenuated respiratory motion. However, poor echocardiographic quality (precluding assessment in approximately one-fifth of patients in our study) and the lack of standardized sex-specific and prognostic cut-off values may limit the broad applicability of vena

Table 3 Uni- and multivariate Cox regression analyses assessing the association of parameters with mortality/hospitalization for heart failure

Parameter	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age, per year increase	1.038 (1.017–1.060)	<0.001	1.049 (1.026–1.072)	<0.001
Male sex	1.529 (1.178–1.986)	0.001	1.546 (1.164–2.053)	0.003
BMI, per kg/m^2 increase	0.974 (0.948–1.002)	0.065		
EuroSCORE II, per point increase	1.156 (1.108–1.206)	<0.001	1.116 (1.050–1.185)	<0.001
CAD	1.330 (1.027–1.722)	0.031		
Diabetes	1.250 (0.945–1.653)	0.118		
Hypertension	0.989 (0.761–1.285)	0.932		
COPD	1.753 (1.229–2.500)	0.002		
Liver disease	2.954 (1.824–4.783)	<0.001	2.608 (1.552–4.384)	<0.001
Cancer	1.506 (1.102–2.058)	0.010		
GFR, per ml/min increase	0.988 (0.983–0.994)	<0.001		
NT-proBNP, per quartile increase	1.454 (1.288–1.640)	<0.001	1.197 (1.044–1.373)	0.010
Haemoglobin, per mg/dl increase	0.854 (0.797–0.915)	<0.001		
C-reactive protein, per mg/dl increase	1.040 (1.021–1.059)	<0.001	1.026 (1.003–1.049)	0.027
CK, per quartile increase	1.041 (0.928–1.167)	0.498		
Diuretic drug use	1.465 (1.123–1.912)	0.005		
Clinical signs of congestion	1.532 (1.178–1.992)	0.001		
Stage of cardiac damage, per stage increase	1.253 (1.107–1.418)	<0.001		
AV PPG, per mmHg increase	0.987 (0.980–0.993)	<0.001		
AV MPG, per mmHg increase	0.979 (0.970–0.988)	<0.001	0.987 (0.978–0.996)	0.006
AV Vmax, per m/s increase	1.016 (0.979–1.054)	0.411		
PPM implantation	1.812 (1.201–2.731)	0.005	1.544 (1.007–2.367)	0.046
FO by BIS, per L increase	1.196 (1.122–1.274)	<0.001	1.134 (1.055–1.218)	<0.001

AV, aortic valve; BIS, bioimpedance spectroscopy; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FO, fluid overload; GFR, glomerular filtration rate; MPG, mean pressure gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PPG, peak pressure gradient; PPM, permanent pacemaker; Vmax, maximum velocity.

cava assessment for outcome prediction in AS. In line with the concept of worse cardiac decompensation with higher degrees of congestion,[23] ascending fluid levels were strongly associated with worse outcomes. We observed a 13% increase in the risk of heart failure or death after TAVI with every 1 L increase in fluid levels. This effect was independent of other well-established markers of poor outcome and FO provided incremental prognostic value to clinical and echocardiographic signs of congestion, natriuretic peptide levels, EuroSCORE II, and cardiac damage on echocardiography. This unfavourable impact of FO on post-procedural outcomes was consistent across all subgroups, including patients in different cardiac damage stages according to the traditional classification.

This concept of sequential backward failure in (severe) AS is intriguing as it is physiologically intuitive and easily comprehensible. However, remodelling in AS may be highly heterogeneous.[24] Hence, when the sequential staging classification was initially proposed, authors already acknowledged that a significant proportion of patients displayed rCD (stages 3 or 4) without cumulated damage from earlier stages.[1] These discrepancies in the evolution of extra-valvular cardiac damage may be related to various factors, such as ventricular interdependence, hormonal response to LV pressure overload and individual patient susceptibility and may potentially bear prognostic implications. Mechanistic insights into rCD in AS are of particular interest, as worse outcomes following intervention are mainly driven by stages 3 and 4.[1,25,26] Indeed, in the present study, the incorporation of quantitative FO into risk stratification allowed subdividing patients in advanced cardiac damage stages into a lower and higher risk category, respectively. Only patients with both rCD and FO (FO+/rCD+) had significantly worse outcomes after TAVI, but not patients with isolated rCD but no FO (FO−/rCD+, *Figure 1B*). On comparison of remodelling types, FO−/rCD+, which made up approximately one-fifth of the study population, resembled a more benign 'heart failure with preserved ejection fraction' phenotype characterized by a higher prevalence of females and hypertension, better LV function, less hypertrophy and lower NT-proBNP levels compared to FO+/rCD+ and FO+/rCD−. Conversely, the presence of FO was linked to significantly worse outcomes despite the absence of rCD (FO+/rCD−). Pulmonary venous congestion/lung water accumulation can be detected in patients with left-sided heart damage,[4,27] has been linked to worse prognosis,[4,27] and may have been responsible for the unfavourable clinical course in this subgroup. Of note, these patients would have been assigned to a lower risk category based on the traditional staging classification.

Table 4 Assessment of additional prognostic value of fluid overload compared to traditional risk markers and congestion signs alone by Cox regression, Harrell's C-index and integrated discrimination improvement

Model	Cox regression analysis		Harrell's C-index		IDI	
	Hazard ratio (95% CI)[a]	*p*-value		*p* for comparison		*p* for comparison
Right-sided CD	1.297 (1.110–1.516)	<0.001	0.570		–	—
Right-sided CD + FO[b]	1.525 (1.314–1.771)	<0.001	0.622	0.010	0.023	<0.001
LVEF[c]	1.312 (1.148–1.499)	<0.001	0.569		–	–
LVEF + FO	1.519 (1.321–1.746)	<0.001	0.622	0.007	0.021	<0.001
NT-proBNP[d]	1.537 (1.259–1.876)	<0.001	0.605		–	–
NT-proBNP + FO	1.638 (1.385–1.938)	<0.001	0.645	0.011	0.017	<0.001
EuroSCORE II[d]	1.542 (1.298–1.834)	<0.001	0.623		–	–
EuroSCORE II + FO	1.736 (1.482–2.035)	<0.001	0.662	0.012	0.026	<0.001
IVC diameter[d]	1.554 (1.267–1.905)	<0.001	0.621		–	–
IVC diameter + FO	1.734 (1.441–2.087)	<0.001	0.663	0.013	0.023	<0.001
IVC collapsibility[e]	1.536 (1.332–1.783)	<0.001	0.624		—	—
IVC collapsibility + FO	1.708 (1.462–1.996)	<0.001	0.663	0.043	0.021	0.001
Clinical congestion	1.258 (1.076–1.471)	0.004	0.561		—	—
Clinical congestion + FO	1.487 (1.279–1.728)	<0.001	0.617	0.004	0.023	<0.001
Congestion score[f]	1.603 (1.367–1.879)	<0.001	0.632		–	–
Congestion score + FO	1.597 (1.414–1.804)	<0.001	0.673	0.027	0.041	<0.001

CD, cardiac damage; CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FO, fluid overload; IDI, integrated discrimination improvement; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]Shown as scaled hazard ratios (Z-scores).
[b]FO was graded into no FO, mild FO, and severe FO.
[c]LVEF was graded into ≥50%, 35–49%, and <35%.
[d]NT-proBNP, EuroSCORE II, and IVC diameter were graded into tertiles.
[e]IVC collapsibility was graded into ≥50%, <50%, and no respiratory change.
[f]Additive score composed of IVC collapsibility (≥50%: 0 points, <50%: 1 point, no respiratory change: 2 points), rales (absence: 0 points, presence: 1 point), leg oedema (absence: 0 points, presence: 1 point).

The present study provides evidence that measures of FO should be included in the risk stratification of patients with severe AS. Patients may be assigned to a specific risk category based on the presence or absence of FO and the extent of cardiac damage on echocardiography (*Graphical Abstract*). Importantly, the presence of FO should always indicate elevated risk (intermediate-high or highest), emphasizing the essential prognostic value of FO.

The clinical applicability of FO assessment may potentially go beyond risk stratification. Reducing congestion has yielded improved outcomes in patients with heart failure.[18,22] We may speculate that, in severe AS with volume overload, reverse remodelling following afterload removal may theoretically support decongestion, whereas failure to recover from cumulated cardiac damage may lead to persistent FO. Heart failure across the spectrum of LV ejection fraction is frequent after left-sided valve surgery and conveys impaired prognosis,[28] which highlights that patients with AS are not 'cured' once the diseased valve has been replaced. Inclusion of quantitative FO in the assessment of AS/heart failure patients is intriguing because it represents a potentially modifiable risk factor as opposed to other markers of poor prognosis (EuroSCORE II, NT-proBNP). Weighing the device costs (~8000 to 10 000$) against the economic burden of HHF (~10 000–18 000$ per HHF) demonstrates that prevention of one single HHF through bioimpedance-guided decongestion would already make this intervention cost-effective. The hypothesis that decongestive treatment tailored to the patient's individual dry weight may improve outcomes and alleviate the symptomatic burden after valve replacement is currently being tested in a randomized controlled trial (EASE-TAVR, NCT04556123).

Strengths and limitations

The current report has several strengths. We performed a comprehensive, multi-parametric risk assessment in a substantial number of patients with severe AS. For the first time, we present quantitative FO in a large-scale format as a powerful predictor of post-interventional heart failure admissions and death. The incorporation of FO allowed to refine cardiac damage, defining less and more vulnerable categories as opposed to the traditional staging classification alone. Furthermore, contrary to previous reports on the prognostic value of staging cardiac damage,[1,8,9,26] the present study had a prospective design with a dedicated a priori defined research aim. Potential research and clinical utility outside the current study include: (i) improvement of risk stratification of AS patients prior to valve replacement with implications on patient information and expectations; (ii) support for the enhanced scientific implementation of quantitative FO as a risk assessment tool in cardiac patients; and (iii) definition of FO as a potential treatment target to further improve prognosis following valve replacement.

Several limitations of the present report merit comment. This was a single-centre study with possible inherent selection and referral bias. Nevertheless, the study design allowed us to follow an identical protocol for FO and echocardiographic assessment as well as TAVI throughout the entire study, enabling thorough data acquisition and data consistency. The study population consisted of (primarily symptomatic) patients with severe AS awaiting intervention. Therefore, the applicability of bioimpedance to detect patients with moderate AS or severe asymptomatic AS at increased risk, who may potentially benefit from early intervention, remains speculative. Efficacy of timely valve replacement in these patient populations is currently being investigated by other trials (EASY-AS, EVOLVED, EARLY TAVR, TAVR UNLOAD). Also, results of the present TAVI population with a mean age of 81 years may not be transferrable to younger, less vulnerable patients undergoing surgical aortic valve replacement.

Concusions

In conclusion, quantitative FO in patients with severe AS has a strong association with worse post-interventional clinical outcomes, refines risk stratification compared to the traditional staging classification and clinical congestion signs, and provides incremental prognostic information to common risk markers. Future studies should clarify whether FO persists after valve replacement and may serve as a potential therapeutic target to improve prognosis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: V.D.: proctor/speaker (Edwards, Abbott). M.A.: Proctor/consultant/speaker (Edwards, Abbott, Medtronic, Boston, Zoll, Abbvie), institutional research grants (Edwards, Abbott, Medtronic, LSI). C.H.: proctoring/speaker (Edwards Lifesciences, Boston Scientific), institutional research grants (Abbott, Boston Scientific, Edwards Lifesciences, Medtronic). A.A.K: research grants (Pfizer), speaker fees (Bayer, Boehringer Ingelheim), advisory board honoraria (Boehringer Ingelheim). C.N.: speaker, institutional research grants (Pfizer), advisory board honoraria (Prothena). All other authors have nothing to disclose.

References

1. Genereux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, *et al.* Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;**38**:3351–3358. https://doi.org/10.1093/eurheartj/ehx381
2. Nitsche C, Kammerlander AA, Koschutnik M, Donà C, Aschauer S, Sinnhuber L, *et al.* Volume status impacts CMR-extracellular volume measurements and outcome in AS undergoing TAVR. *JACC Cardiovasc Imaging* 2021;**14**:516–518. https://doi.org/10.1016/j.jcmg.2020.08.010
3. Nitsche C, Kammerlander AA, Koschutnik M, Sinnhuber L, Forutan N, Eidenberger A, *et al.* Fluid overload in patients undergoing TAVR: What we can learn from the nephrologists. *ESC Heart Fail* 2021;**8**:1408–1416. https://doi.org/10.1002/ehf2.13226
4. Thompson RB, Chow K, Pagano JJ, Sekowski V, Michelakis ED, Tymchak W, *et al.* Quantification of lung water in heart failure using cardiovascular magnetic resonance imaging. *J Cardiovasc Magn Reson* 2019;**21**:58. https://doi.org/10.1186/s12968-019-0567-y
5. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;**261**:884–888. https://doi.org/10.1001/jama.1989.03420060100040
6. Hur E, Usta M, Toz H, Asci G, Wabel P, Kahvecioglu S, *et al.* Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: A randomized controlled trial. *Am J Kidney Dis* 2013;**61**:957–965. https://doi.org/10.1053/j.ajkd.2012.12.017
7. Koell B, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, Dalos D, *et al.* Fluid status and outcome in patients with heart failure and preserved ejection fraction. *Int J Cardiol* 2017;**230**:476–481. https://doi.org/10.1016/j.ijcard.2016.12.080
8. Vollema EM, Amanullah MR, Prihadi EA, Ng ACT, van der Bijl P, Sin YK, *et al.* Incremental value of left ventricular global longitudinal strain in a newly proposed staging classification based on cardiac damage in patients with severe aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1248–1258. https://doi.org/10.1093/ehjci/jeaa220
9. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, *et al.* Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:550–563. https://doi.org/10.1016/j.jacc.2019.04.065
10. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, *et al.* Valve Academic Research Consortium 3: Updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol* 2021;**77**:2717–2746. https://doi.org/10.1016/j.jacc.2021.02.038
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270. https://doi.org/10.1093/ehjci/jev014
12. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, *et al.* Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–644. https://doi.org/10.1093/ehjci/jet105
13. Baumgartner HC, Hung JCC, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, *et al.* Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2017;**18**:254–275. https://doi.org/10.1093/ehjci/jew335
14. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.* 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632.
15. Kushner RF. Bioelectrical impedance analysis: A review of principles and applications. *J Am Coll Nutr* 1992;**11**:199–209. https://doi.org/10.1080/07315724.1992.12098245
16. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, *et al.* Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006;**27**:921–933. https://doi.org/10.1088/0967-3334/27/9/012
17. Wabel P, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009;**27**:75–80. https://doi.org/10.1159/000167013
18. Selvaraj S, Claggett B, Pozzi A, McMurray JJV, Jhund PS, Packer M, *et al.* Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. *Circulation* 2019;**140**:1369–1379. https://doi.org/10.1161/CIRCULATIONAHA.119.039920
19. Stein JH, Neumann A, Marcus RH. Comparison of estimates of right atrial pressure by physical examination and echocardiography in patients with congestive heart failure and reasons for discrepancies. *J Am Coll Cardiol* 1997;**80**:1615–1618. https://doi.org/10.1016/s0002-9149(97)00776-5
20. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, *et al.*; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *Lancet* 2011;**377**:658–666. https://doi.org/10.1016/S0140-6736(11)60101-3
21. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, *et al.* Haemodynamic-guided management of heart failure (GUIDE-HF): A randomised controlled trial. *Lancet* 2021;**398**:991–1001. https://doi.org/10.1016/S0140-6736(21)01754-2
22. Kleiner Shochat M, Fudim M, Kapustin D, Kazatsker M, Kleiner I, Weinstein JM, *et al.* Early impedance-guided intervention improves long-term outcome in patients with heart failure. *J Am Coll Cardiol* 2021;**78**:1751–1752. https://doi.org/10.1016/j.jacc.2021.08.036

23. Donà C, Nitsche C, Anegg O, Poschner T, Koschutnik M, Duca F, *et al.* Bioimpedance spectroscopy reveals important association of fluid status and T_1-mapping by cardiovascular magnetic resonance. *J Magn Reson Imaging* 2022;**56**:1671–1679. https://doi.org/10.1002/jmri.28159
24. Treibel TA, Kozor R, Fontana M, Torlasco C, Reant P, Badiani S, *et al.* Sex dimorphism in the myocardial response to aortic stenosis. *JACC Cardiovasc Imaging* 2018;**11**:962–973. https://doi.org/10.1016/j.jcmg.2017.08.025
25. Koschutnik M, Dannenberg V, Nitsche C, Dona C, Siller-Matula J, Winter MP, *et al.* Right ventricular function and outcome in patients undergoing transcatheter aortic valve replacement. *Eur Heart J Cardiovasc Imaging* 2021;**22**:1295–1303. https://doi.org/10.1093/ehjci/jeaa342
26. Vollema EM, Amanullah MR, Ng ACT, van der Bijl P, Prevedello F, Sin YK, *et al.* Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:538–549. https://doi.org/10.1016/j.jacc.2019.05.048
27. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, *et al.* Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. *Eur Heart J* 2016;**37**:1244–1251. https://doi.org/10.1093/eurheartj/ehv745
28. Kammerlander AA, Nitsche C, Donà C, Koschutnik M, Dannenberg V, Mascherbauer K, *et al.* Heart failure with preserved ejection fraction after left-sided valve surgery: Prevalent and relevant. *Eur J Heart Fail* 2021;**23**:2008–2016. https://doi.org/10.1002/ejhf.2345