

Plasma Neurofilament Light Chain Is Elevated after Transcatheter Aortic Valve Implantation

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Keywords

Transcatheter aortic valve implantation · Neurofilament · Silent brain infarcts · Biochemical markers · Clinical research

Abstract

Introduction: Transcatheter aortic valve implantation (TAVI) is associated with a high incidence of new silent brain infarcts (SBIs) on postprocedural neuroimaging. A venous blood sample reflecting neuronal damage following TAVI could help identify patients with potential SBIs. We aimed to investigate if a biochemical marker of neuronal injury, neurofilament light chain (NFL), is elevated after TAVI.

Methods: In this observational study, NFL was measured in plasma from 31 patients before and after TAVI. Multivariable regression analysis was performed to investigate any effect of clinical- and procedure-related factors on differences in NFL levels before and after TAVI. **Results:** Samples were collected 41 (14–81) days before and 44 (35–59) days after TAVI, median (interquartile range). Median age was 81 (77–84) years, and 35% were female. No patient had any overt procedure-related neurological complications. The geometric mean (95% confidence interval) of the NFL concentration was 30 (25–36) pg/mL before TAVI and 48 (39–61) pg/mL, after TAVI, $p < 0.001$. None of the included

variables in the multiple linear regression model were statistically significantly associated with the difference in levels before and after TAVI. **Conclusions:** NFL levels in plasma were higher after TAVI as compared with levels before, with a mean increase of 60% (18 pg/mL). Further studies including neuroimaging and cognitive outcomes are needed to understand the potential value of measuring NFL in relation to TAVI.

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Introduction

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat severe aortic stenosis and is associated with an increased risk of periprocedural stroke as well as silent brain infarcts (SBIs) on neuroimaging, due to thromboembolism, altered hemodynamics, and debris from aortic wall, valve tissue, and catheter material [1–4]. The frequency of new SBIs on magnetic resonance imaging (MRI) after TAVI is high, and two recent meta-analyses report an incidence of 74–76%, even when cerebral embolic

Trial registration: ClinicalTrials.gov NCT05629104.

protection devices are used [5, 6]. SBIs are associated with early postprocedural cognitive dysfunction, although long-term follow-up studies on association of TAVI-related SBIs and cognitive performance are scarce [6]. Even though the clinical relevance of SBI burden after TAVI is not fully understood, identification of patients with higher burden is likely to be important, e.g., to assess the need of additional cognitive follow-up evaluations. The gold standard of identifying SBIs is diffusion-weighted MRI, and higher field strength detects a higher number of SBIs after TAVI [6]. MRI is however cost- and time-consuming, and some patients have contraindications (e.g., permanent pacemaker, fever, metallic foreign bodies, claustrophobia, etc.), and it is therefore not routinely used in the follow-up of TAVI patients. A venous blood sample reflecting neuronal damage following TAVI could help identify patients with potential SBI, in need of further investigation with neuroimaging and cognitive follow-up as well as aid in evaluation of different treatment strategies, such as the use of cerebral embolic protection devices.

Neurofilaments are a critical structure of the cytoskeleton in neurons and consist of several subunits [7]. Circulating levels (in plasma or serum) of the neurofilament light chain (NFL) subunit has emerged as a reliable biochemical marker of neuronal tissue damage, regardless of cause, and correlates with size and number of both inflammatory and ischemic central nervous system lesions [8, 9]. We hypothesized that circulating levels of NFL would be elevated after TAVI, reflecting the SBIs associated with the procedure.

Materials and Methods

Study Cohort

In an ongoing clinical observational study, including consecutive non-selected patients undergoing TAVI at Uppsala University Hospital, blood samples were collected before and after TAVI. TAVI was performed according to standard procedures via femoral or subclavian access. All patients received unfractionated heparin with levels of activated clotting time >250 s and standardized protamine (50 mg) at the end of the procedure. Clinical risk factors, intervention characteristics, and short-term outcome were recorded. The first 31 patients enrolled between 2019 and 2021 were included in the present analysis. Clinical trials NCT05629104.

Biochemical Analyses

Venous blood samples were collected at study inclusion before TAVI and at a follow-up visit after TAVI and stored at -80°C until analysis. Plasma concentration of NFL was analyzed with single-molecule array (Simoa[®]) on the SR-X[™] Biomarker Detection System (Quanterix). The lower limit of quantification was 0.316 pg/mL, and the lower limit of detection was 0.0552 pg/mL.

Statistical Analyses

Baseline characteristics are presented as median with interquartile range (IQR) for continuous variables and as percent and number for discrete and categorical variables. The distributions of NFL concentrations before and after TAVI were approximately lognormal and are presented as geometric mean with 95% confidence interval. NFL levels before and after TAVI were compared using paired T-test, after log transformation using the natural logarithm. Multiple linear regression analysis was used to assess the effect of clinical- and procedure-related variables on the difference in NFL levels before and after TAVI. A pre-specified model was fitted with level of NFL after TAVI as the dependent variable, and level of NFL before TAVI, time interval between TAVI and collection of follow-up sample, age, sex, diabetes, and renal function (eGFR) as explanatory variables as they have previously been associated with both circulating NFL levels and SBI frequency [6, 10]. All NFL values were log transformed before statistical analysis but are reported back-transformed. All tests were two sided, and a statement of statistical significance implies a p value <0.05 . R version 4.2.1 and GraphPad Prism version 9.5.0 were used for statistical analyses and graphical presentation.

Results

Patient characteristics are presented in Table 1. Median age was 81 years (77–84, IQR), and 35% were females. Comorbidities were common: hypertension 87%, atrial fibrillation 45%, diabetes and congestive heart failure 39%, previous stroke or transient ischemic attack 19%. Two (6.5%) of the patients had a high-risk aorta (defined as severe circumferential calcification or calcified plaques throughout the ascending aorta), whereas four (13%) had a bicuspid valve. The access route was femoral in 28 (90%) and subclavian in 3 (9.7%) of the patients. Pre dilation was performed in 24 (77%) of the patients, and the most frequently used TAVI prosthesis was Medtronic Evolut R (61%). No cerebral embolic protection device was used, and no patient had any overt procedure-related neurological complications (neurological complication at laboratory or peri- or postprocedural stroke). One patient suffered a stroke after collection of the first blood sample but before TAVI was performed. Almost all patients (90%) were treated with antiplatelet therapy after intervention (45% single, 45% dual), whereas 42% were treated with oral anticoagulants (35% on direct acting oral anticoagulants and 6.5% on warfarin). Only one of the patients was treated with dual antiplatelets as well as an oral anticoagulant.

Blood samples were collected 41 (14–81) days before and 44 (35–59) days after TAVI, median (IQR). The NFL concentration was 30 (25–36) pg/mL before and 48

Table 1. Patient characteristics

Clinical characteristics	<i>n</i> = 31
Age, median (IQR), years	81 (77–84)
Female sex, <i>n</i> (%)	11 (35)
BMI, median (IQR), kg/m ²	27 (24–28)
Hypertension, <i>n</i> (%)	27 (87)
Diabetes, <i>n</i> (%)	12 (39)
Congestive heart failure, <i>n</i> (%)	12 (39)
Coronary heart disease, <i>n</i> (%)	10 (32)
Atrial fibrillation, <i>n</i> (%)	14 (45)
Peripheral artery disease, <i>n</i> (%)	3 (9.7)
Previous stroke or TIA, <i>n</i> (%)	6 (19)
eGFR, median (IQR), mL/min/1.73 m ²	60 (51–70)
LVEF%, median (IQR) (<i>n</i> = 27)	55 (55–63)
High-risk aorta*, <i>n</i> (%)	2 (6.5)
Bicuspid aortic valve, <i>n</i> (%)	4 (13)
Annulus diameter, median (IQR), mm	26 (23–27)
Valve area, median (IQR), cm ²	0.8 (0.7–0.9)
Max velocity, median (IQR), m/s (<i>n</i> = 28)	4.2 (3.9–4.3)
Mean gradient, median (IQR), mm Hg	40 (35–44)
Interventional characteristics	
Access route, <i>n</i> (%)	
Femoral	28 (90)
Subclavian	3 (9.7)
Pre dilation, <i>n</i> (%)	24 (77)
Post dilation, <i>n</i> (%)	5 (16)
Type of prosthesis, <i>n</i> (%)	
Medtronic Evolut R	19 (61)
Medtronic Evolut PRO	6 (19)
Edwards SAPIEN 3 Ultra	5 (16)
Edwards SAPIEN 3	1 (3.2)
Cerebral embolic protection device used, <i>n</i> (%)	0 (0)
Procedure time, median (IQR), minutes (<i>n</i> = 24)	70 (60–89)
General anesthesia, <i>n</i> (%)	3 (9.7)
Neurological complication at laboratory, <i>n</i> (%)	0 (0)
Peri- or postprocedural stroke, <i>n</i> (%)	0 (0)
Oral anticoagulation after intervention, <i>n</i> (%)	
DOAC	11 (35)
Warfarin	2 (6.5)
Antiplatelet therapy after intervention, <i>n</i> (%)	
Single	14 (45)
Dual	14 (45)

Median (interquartile range) is used for continuous variables and number (percent) for discrete and categorical variables. DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF%, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation; TIA, transient ischaemic attack.
*High risk aorta was defined as severe circumferential calcification or calcified plaques throughout the ascending aorta.

(39–61) pg/mL after TAVI, geometric mean (95% confidence interval), *p* < 0.001 (Fig. 1). One patient had a very high concentration of NFL (507 pg/mL) after TAVI, however not the same patient who suffered a stroke between first sample and TAVI (this patient had an NFL

level of 68 pg/mL after TAVI and is indicated with a thick blue line in Fig. 1).

The result of the multivariable linear regression analysis is presented in Table 2. None of the variables included were statistically significantly associated with

Fig. 1. Plasma levels of NFL before and after transcatheter aortic valve implantation (TAVI). Geometric mean (95% CI) of NFL was 30 (25–36) pg/mL before TAVI versus 48 (39–61) pg/mL after TAVI, $p < 0.001$ and is visualized by black points (geometric mean) and whiskers (95% CI) to the left and right. Connected points represent the individual patients, and x-axis indicates the time line for sample collection in relation to TAVI. Blue lines denote patients where femoral access was used, and red lines denote patients where subclavian access was used. The thick blue line represents the patient who suffered a stroke between first sample and TAVI. CI, confidence interval.

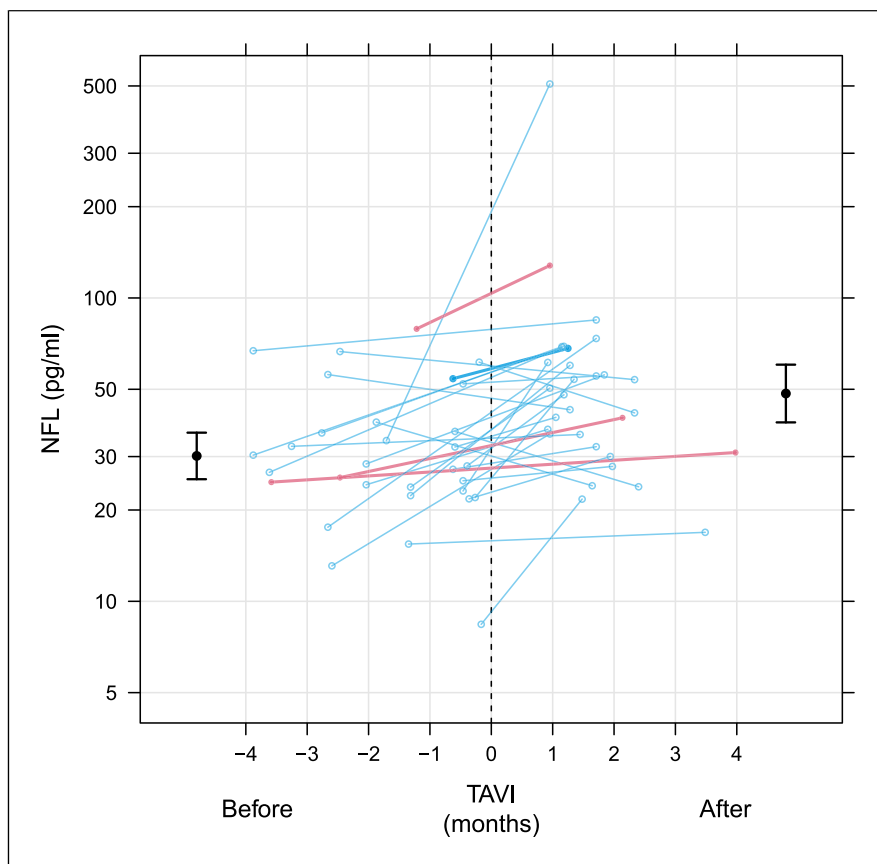


Table 2. Association between characteristics and NFL levels after TAVI in multiple linear regression analysis

Variable	N = 31	
	e ^{Beta} (95%CI)	p value
Age (per 10 years)	1.4 (0.96–2.2)	0.08
Female sex	0.93 (0.55–1.6)	0.78
Diabetes	0.87 (0.55–1.4)	0.53
eGFR (per 10 mL/min/1.73 m ²)	0.93 (0.77–1.1)	0.42
NFL before TAVI (per doubling)	1.1 (0.69–1.8)	0.64
Interval between TAVI and follow-up sample (per week)	0.94 (0.87–1.0)	0.05
Pre dilation	1.2 (0.69–2.0)	0.56

Association between characteristics and NFL levels after TAVI analysed by multiple linear regression analysis. One model was fitted and prior to analysis, NFL was log-transformed using the natural logarithm. The beta-values were then retransformed for easier interpretation (e^{Beta}). e^{Beta} corresponds to the proportional change in geometric mean of NFL. eGFR, estimated glomerular filtration rate; CI, confidence interval; NFL neurofilament light chain; TAVI, transcatheter aortic valve implantation.

NFL levels after TAVI. There was a tendency of association between higher NFL after TAVI and older age, as well as shorter interval between TAVI and collection of follow-up sample, although these associations did not meet the pre-specified significance level.

Discussion

In this small observational, proof-of-concept study, plasma NFL was increased with 60% (18 pg/mL) at a median of 44 days after TAVI as compared with levels before TAVI.

In face of the previous literature on NFL and cerebral injury, these findings are novel but not unexpected. Using data from a previous study on NFL in serum and ischemic stroke, an increase of NFL of 18 pg/mL corresponds to 1–2 cm³ infarcted brain tissue, which is similar to the reported mean lesion size of SBI on MRI after TAVI [6, 11, 12]. However, the exact origin of the observed increase of NFL in the present study remains uncertain, as no neuroimaging was available, preventing any firm conclusions regarding the relationship between SBI after TAVI and NFL.

The incidence of SBIs is much higher than clinically overt stroke after TAVI, a feature likely to be explained not only by differences in lesion size but also location as many brain areas are non-eloquent (not associated with focal neurological deficits when injured) [5, 6, 13]. However, both stroke and SBIs are associated with increased risk of cognitive impairment and dementia [14, 15]. NFL has the potential to reflect ischemic lesions independent of clinical symptoms, which may be of interest when evaluating the effect of different interventional strategies, such as the use of cerebral embolic protection devices. In a recent large multicentre randomized clinical trial, a trend of benefit from the use of a cerebral embolic protection device was noted in both primary and secondary outcomes, however not statistically significant [16]. It is possible that the use of a sensitive molecular biomarker of neuronal damage such as NFL could have supported the use of cerebral embolic protection devices.

NFL has previously been evaluated in a small study of 25 patients in relation to cardiac surgery with a rise of NFL (1090%, $p < 0.0001$) 7 days after surgery [17]. No prior study as far as we know has investigated NFL levels in relation to TAVI, although one ongoing randomized clinical trial on TAVI has included change in NFL within 3 months as an outcome in their protocol (ClinicalTrials.gov NCT05145283). Other circulating biomarkers of neuroglial injury, such as neuron-specific enolase, glial fibrillary acidic protein, and S100 calcium-binding protein B, have been studied in relation to TAVI with conflicting results [3, 18–20]. This may be explained by difference in the timing of blood sample as the protein levels peak at different time points for different proteins. One advantage of NFL is the relatively slow turnover, making the time point less important. Serum levels stay elevated for several months after an ischemic stroke, and probably peaks between 2 and 3 weeks, although the precise half-life and mechanisms of elimination of NFL in blood is currently unknown [21, 22]. Due to practical reasons, the median interval between TAVI and collection of follow-up sample was 44 days as sample collection coincided with a post-TAVI revisit. This may be 3–4 weeks past the assumed peak of NFL, which is

somewhat reinforced by the multivariable regression analysis, where a tendency of association was seen between lower NFL levels and longer interval between TAVI and collection of follow-up sample, although not significant. A larger sample size might have altered this finding. Nevertheless, a significant difference was still demonstrated between NFL levels before and after TAVI. A sampling 2–3 weeks after TAVI may have shown an even greater difference. In future studies, it is important to consider the timing of blood sampling, which ideally should capture peak levels of NFL while at the same time accommodate to practical circumstances, such as outpatient return visits.

Major limitations of this study include the lack of a control group, and the lack of neuroimaging, which prohibited examination of the correlation between NFL concentrations and SBI frequency and size. Another limitation was the small sample size, limiting analysis of how patient characteristics and procedure-related variables affect NFL in relation to TAVI. Nevertheless, given the magnitude of difference noted in NFL before and after TAVI, a larger sample size would probably not change the main result of this study, i.e., plasma NFL is elevated after TAVI.

Conclusion

NFL levels in plasma were higher after TAVI as compared with levels before. More research based on larger patient populations, preferably with MRI data together with detailed clinical and functional patient evaluation and outcomes, including a control group without SBI, are needed to understand the potential value of NFL as a marker for periprocedural SBI that can be used to identify patients in need of additional cognitive follow-up as well as to evaluate the benefit of different treatment strategies, such as the use of cerebral embolic protection devices, different valve types, and anti-thrombotic strategies peri- and postprocedurally.

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Statement of Ethics

This study was performed according to the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Uppsala, Sweden (DNr 2017/194). All included patients provided written informed consent.

Conflict of Interest Statement

S.J. reports personal proctoring fees from Medtronic relating to aortic valves. K.S., C.C., J.L., S.Å., and J.B. report no conflict of interests in connection with the submitted article.

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Author Contributions

K.S., C.C., S.J., S.Å., and J.B. planned and designed the study. K.S. and J.L. performed the statistical analyses. K.S. drafted the first version of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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