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Comparison of sedation and general anaesthesia for transcatheter aortic valve implantation on cerebral oxygen saturation and neurocognitive outcome†

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) is a treatment strategy for patients with severe aortic stenosis. Although general anaesthesia (TAVI-GA) and sedation (TAVI-S) have previously been described for TAVI, the difference in safety and efficacy of both methods has not been studied in a randomized trial.

Methods: The INSERT trial was a single centre, controlled parallel-group trial with balanced randomization. Sixty-six patients (68–94 yr) with acquired aortic stenosis undergoing transfemoral CoreValve™ were assigned to TAVI-GA or TAVI-S. Comparable operative risk was determined from risk-scores (EUROscore, STS-Score). Monitoring and anaesthetic drugs were standardized. Near-Infrared-Spectroscopy was used to monitor cerebral-oxymetry blinded. Primary outcome was the perioperative cumulative cerebral desaturation. As secondary outcomes, changes in neurocognitive function and respiratory and haemodynamic adverse events were evaluated.

Results: Of 66 included patients, 62 (TAVI-GA: n=31, TAVI-S: n=31) were finally analysed. Baseline characteristics were comparable. In 24 patients (39%) cerebral desaturation was observed. Cumulative cerebral desaturation was comparable (TAVI-GA:(median [IQR]) (0[0/1308] s%) vs. TAVI-S:(0[0/276] s%); P=0.505) between the groups. Neurocognitive function did not change within and between groups. Adverse events were more frequently observed in TAVI-S patients (P<0.001). Bradypnoea (n=16, 52%) and the need for airway manoeuvres (n=11, 36%) or bag-mask-ventilation (n=6, 19%) were the most common respiratory adverse events.

Conclusions: Cerebral desaturation occurred in both patient groups, but there was no significant difference between the two groups. Based on primary outcome, both methods were shown to be comparable. Neurocognitive outcome was similar.

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The higher incidence of adverse events in the sedation group suggests a potential advantage of general anaesthesia.
Clinical trial registration: NCT 01251328.

Key words: anaesthesia; aortic valve stenosis; brain; deep sedation; general; hypoxia; transcatheter aortic valve implantation

Editor's key points

- Patients undergoing Transcatheter aortic valve implantation (TAVI) can be managed using sedation techniques or general anaesthesia.
- This small study compared moderate to deep sedation using propofol and remifentanil with general anaesthesia.
- There were no differences in cerebral oxygenation or neurocognitive outcome.
- The incidence of adverse events, principally pain and respiratory depression, was much higher in the sedation group.
- Moderate to deep sedation for TAVI has potential disadvantages compared with general anaesthesia.

Since 2002 transfemoral transcatheter aortic valve implantation (TAVI)[1] has continuously evolved with different approaches and techniques,[2] for treatment of severe aortic valve stenosis. A shift from general anaesthesia (TAVI-GA) towards sedation (TAVI-S) has been increasingly described.[3–6] Simplified monitoring, shortened procedure time, less haemodynamic instability, a decreased need for catecholamine therapy and shorter intensive care unit (ICU) stays were presented as benefits.[7 8] It is noteworthy that emergency conversion to general anaesthesia for TAVI-S has been reported in up to 17% of patients.[6 8]

During procedural sedation, adverse events including hypoxemia have been reported in up to 21% of patients.[9] Cerebral oxymetry – as measured by Near-Infrared Spectroscopy (NIRS) – is a way of monitoring perfusion and oxygenation.[10 11] Induced cardiac arrest for balloon valvuloplasty and hypotension during valve release are two distinctive moments for cerebral desaturation to occur during TAVI, comparable with a decrease in cerebral saturation observed during brief cardiac arrest for ICD-testing.[12] In a different context perioperative cerebral desaturation has been linked to increased postoperative major organ morbidity and mortality.[13 14] Postoperative cognitive decline has been shown in desaturation of more than 3000 s%.[15] Neither the described benefits for TAVI-S, nor the equivalent safety of both procedures were examined in a randomized trial.

In this study we hypothesized that the cumulative perioperative cerebral desaturation is higher in patients undergoing TAVI-S because of a presumed lower Pa_{O_2} and Sa_{O_2} and as a result from a pilot study. As secondary endpoints we studied the difference in neurocognitive function, arterial blood-gas-analysis (ABG) and perioperative adverse events. In addition procedure-related time periods were evaluated.

Methods

The INSERT (Near INfrared Spectroscopy in aortic valvE ReplacemenT) trial was a single-centre, controlled, parallel-group study with balanced randomization (1:1). The trial was performed from February 2011 to April 2012 at the Institut für Anästhesiologie, Deutsches Herzzentrum München, a university-hospital specialized in cardiovascular diseases. Expert knowledge was obtained from approximately 600 previous TAVI patients. The study was approved by the medical ethics board of the Technische Universität München (Clinical trials: NCT01251328). Written informed consent was obtained from the patients before enrolment.

Patients

Inclusion criteria: patients with acquired severe aortic stenosis (age 18 yr and above), undergoing transfemoral CoreValve™ (Medtronic, Minneapolis, USA) implantation. The decision for transcatheter treatment was made by the cardiac surgeons. Patients had to be eligible to undergo the procedure using general anaesthesia or sedation and be able to undergo neurocognitive testing. Comparable operative risk was determined from comorbidities and risk-scores (EUROscore, STS-Score).

Patients with a predicted difficult airway,[16] severe pulmonary arterial hypertension (PAP_{syst}>60 mm Hg)[17] or CPAP-therapy for obstructive sleep apnoea[18] were excluded from the study. Additional exclusion criteria were former/current alcohol or drug abuse, neurocognitive/neurodegenerative disease or psychiatric disorder, and use of antidepressants/sedatives.

Secondary exclusion criteria were abortion of procedure, perioperative emergency conversion from sedation to general anaesthesia and the need for cardiopulmonary resuscitation during the observation period, as the primary endpoint could not be determined in these conditions.

A sealed envelope containing the treatment assignment was allocated to the patients in the order of enrolment and opened at the patient's arrival in the operation room. The Institute of Medical Statistics and Epidemiology, Technische Universität München, provided the envelopes.

Treatment strategies

All patients received 3.75 mg of midazolam for oral premedication 30 min before arrival in the operating room. TAVI-GA and TAVI-S were performed using weight-adapted doses of propofol and remifentanil. TAVI-GA patients started with propofol 3 mg kg^{-1} h^{-1} and remifentanil 0.2 mcg kg^{-1} min^{-1}. A single dose of rocuronium (0.3 mg kg^{-1}) was administered for tracheal intubation. In TAVI-S patients propofol 1 mg kg^{-1} h^{-1} and remifentanil 0.03 mcg kg^{-1} min^{-1} were used. In TAVI-S the cardiac surgeons infiltrated the groin with 10 ml of mepivacaine 1% at the beginning of the procedure. To provide optimal implantation conditions and to avoid patient movement especially during balloon valvuloplasty and valve implantation, moderate to deep sedation (according to the ASA[19] definition) was applied.

Depth of anaesthesia/sedation was monitored by Bispectral Analysis (BIS™, Covidien, Dublin, Ireland) throughout the whole course of anaesthesia and valve implantation. Values at distinctive time-points are presented in Table 2. To achieve maximum oxygen supply, the inspiratory oxygen fraction (FI_{O_2}) was set to 1.0, and controlled ventilation was adjusted to an end-expiratory CO_2 of 4.6 kPa in TAVI-GA. TAVI-S patients received 8 Litre min^{-1} of oxygen for the same reason.

Apart from standard perioperative monitoring in accordance with ASA-guidelines, invasive arterial and central venous pressure blood pressure monitoring were applied. Perioperative transesophageal echocardiography was used in TAVI-GA patients, to monitor the result after implantation. Implantation was guided by fluoroscopy in both groups. A temporary 5-Fr pacemaker wire was inserted through the internal jugular vein for rapid ventricular pacing (RVP). Intraoperative hypotension (MAP<65 mm Hg)[20] was treated with a single i.v. norepinephrine bolus of five mcg. A continuous norepinephrine infusion was started in case five or more bolus administrations were needed. Haemodynamic parameters were documented at seven distinct perioperative time-points (at baseline, after induction, during and 60 s after RVP and valve implantation, and end of procedure). During the implantation of the self-expanding CoreValve™, two episodes of hypotension occured. The first one was during RVP-induced cardiac arrest for balloon valvuloplasty. The second episode was as a result of the temporary obstruction of the left ventricular outflow tract during valve implantation.

Two cardiac anaesthetists with experience in both procedures and perioperative care of TAVI patients (>250 patients each) were assigned to these implantations. One anaesthetist was engaged solely in study documentation, while the other anaesthetist conducted patient care. Cardiac surgeons were responsible for postoperative intensive care.

Primary endpoint

Procedure and anaesthesia-related impairment of circulation and gas-exchange may affect cerebral oxygenation[10] and initiate cerebral desaturation as demonstrated by our pilot-patients (see below). Therefore cerebral desaturation was chosen as a primary endpoint, assuming that is was greater in TAVI-S patients.

Perioperative NIRS measurement was conducted in a blinded 'study' mode. NIRS was monitored using INVOS 5100™ (Covidien, Dublin, Ireland), which has been previously described in detail.[11] Data were stored continuously in 6 s intervals, and analysed using the INVOS Monitoring-System-Analytics-Tool© (Covidien, Dublin, Ireland) after the last patient completed surgery. The room air rSO_2 baseline ($rSO_{2\text{-RA baseline}}$) parameter was defined as the average rSO_2 value in a 30 s period, during the insertion of a radial artery catheter. Neither sedative drugs nor oxygen

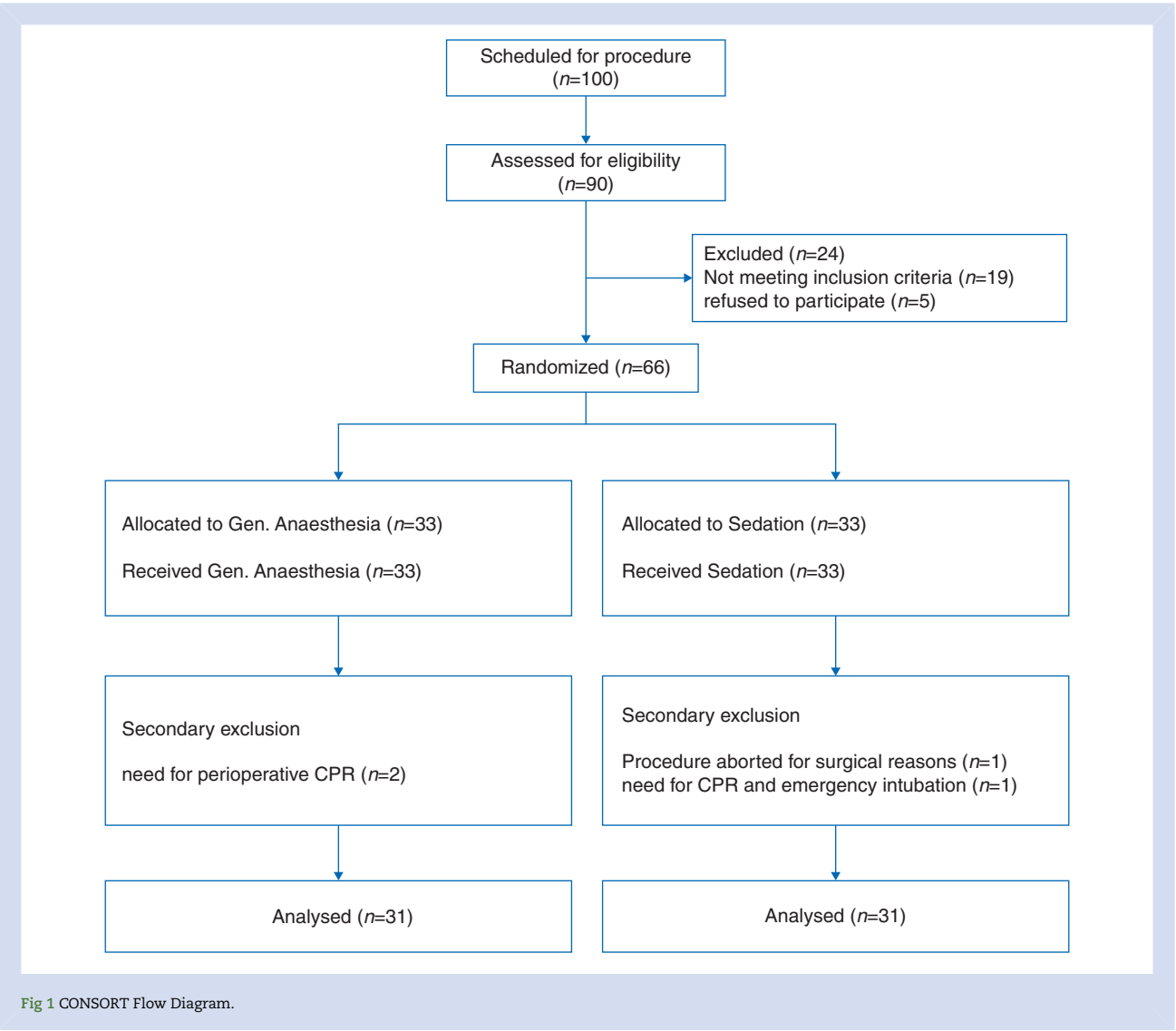

Fig 1 CONSORT Flow Diagram.

was administered before the measurement. An individual desaturation threshold ($rSO_{2\text{-DESAT}}$) was determined for each patient. The threshold was defined as a decrease of 20% below the $rSO_{2\text{-RA baseline}}$ or an absolute value below 50%, whichever was higher.[15] In case of interhemispheric rSO_2 differences ($rSO_{2\text{-}\Delta\text{interhem}}$), the lower value hemisphere was used for analysis.[21] Area-under-the curve (AUC) analysis was conducted to assess rSO_2 decreases during the entire case.[15] The AUC was calculated as

$$\text{AUC } rSO_{2\text{-DESAT}} = [rSO_{2\text{-DESAT}}(\%) - rSO_{2\text{ current}}(\%)] * \text{time (Sec)}$$

The primary endpoint (AUC $rSO_{2\ (\text{total<DESAT})}$) was defined as the calculated summation of all AUC $rSO_{2\text{-DESAT}}$.

Secondary endpoints

Neurocognitive outcome

All patients underwent neurocognitive testing the day before the intervention and on the seventh postoperative day or the day of hospital release (if earlier). The tests were provided by the Department of Psychiatry, Technische Universität München, and consisted of three parts. 'DemTect' is an age-adjusted screening test for cognitive dysfunction. The DemTect scale ranges from 0 to 18 points, with more than 13 points representing good age-based cognitive function.[22] 'Zahlenverbindungstest' (ZVT-1/2) examines the perceptual speed needed to connect 30 apparently arbitrary numbers.[23] 'Regensburger-Wortflüssigkeitstest' (RWT)[24] is an education-adjusted test to assess the formal lexical stream of speech. Patients had to name as many words with a given first letter ('P') in a period of 2 min. Speech fluency in the German language is mandatory for these tests. At the time of the preoperative testing, the randomized anaesthesia technique was unknown.

Arterial blood gas analysis (ABG)

ABG (Pa_{O_2}, Pa_{CO_2}, Sa_{O_2}, haemoglobin, pH, and lactate) was performed at baseline, after induction of anaesthesia, 60 s after RVP, and 120 s after extubation.

Adverse events and procedure-related time periods

Anaesthesia and procedure-related adverse events were predefined and documented at the time of occurrence. 'Difficult airway' was defined according to ASA guidelines as a clinical condition in which a trained anaesthetist experienced difficulty with face-mask ventilation of the upper-airway, difficulty with tracheal intubation, or both.[16] 'Difficult central venous catheter' was defined as a clinical condition in which a trained anaesthetist needed more than 2 attempts of puncturing the internal jugular vein, despite the use of ultrasound, difficulty in advancing the guidewire, or both. 'Defibrillation' was used in a clinical condition with tachyarrhythmia and hypotension. 'Jaw-thrust-manoeuvre' was used in case of upper airway obstruction because of loss of pharyngeal muscle tone. A 'nasopharyngeal airway' was inserted in situations of a permanent need of jaw-thrust-manoeuvre. 'Bag-valve mask ventilation' was used in patients with bradypnoea/apnoea and/or hypoxia. 'Bradypnoea' was defined as a respiratory rate <8 min^{-1}. 'Hypoxia' was defined as a $Sp_{O_2} < 90\%$ over 10 s.[9] 'Unrest/pain' was defined as any undesired targeted/untargeted movement from the patient or expression of pain throughout the whole anaesthetic and interventional procedure.

Statistical analysis

Categorical data are presented as absolute and relative frequencies. Group comparisons were performed using χ^2tests or Fisher's exact test depending on the expected cell counts of corresponding contingency tables. The distribution of continuous data is given by the median and interquartile range (IQR=25–75th percentile). Mann-Whitney *U*-tests and Hodges-Lehmann 95% confidence intervals were used to assess differences between groups. All statistical tests were performed using a two-sided 5% significance level. Derived from a pilot study, expected mean AUC $rSO_{2\ (\text{total<DESAT})}$ of 2000 s% (TAVI-S) and 1000 s% (TAVI-GA) with standard deviations of 1500 and 500 have been used for a conservative sample size calculation. A group size of 28 individuals was found to result in a 90% power (β=10%) for a two-sided two-sample t-test to detect such a difference of α=5% level of significance (N-Query Advisor 7.0). The application of Pitmans ARE (Asymptotic Relative Efficiency)=0.864 lead to an adjusted sample size of 28/0.864=32.4 which is approximately 33 subjects per treatment arm. SPSS Vers.21 (IBM, Germany) and SAS Enterprise Guide 4.3 (SAS Institute, Cary, USA) were used for analysis.

Results

In the study period 100 patients were undergoing transfemoral CoreValve™ implantation, 66 patients (33 TAVI-GA, 33 TAVI-S) were enrolled. Details of patient enrolment are shown in Fig. 1. Two TAVI-GA patients were excluded because of the need for perioperative cardio-pulmonary resuscitation (CPR). Both patients required CPR after valve implantation. The first one as a result of prolonged hypotension. At the end of the procedure the patient needed a second episode of resuscitation and drainage of pericardial effusion. After four days of ICU care the patient was discharged on POD 8. The other patient was resuscitated as a result of prolonged ventricular fibrillation. At the end of operation the patient was transferred awake to the ICU for a three-day stay and discharged on POD 9. One TAVI-S patient was excluded because of CPR and emergency conversion to general anaesthesia, as a result of signs of heart failure and respiratory distress at the beginning of sedation. After recompensation

Table 1 Preoperative patient characteristics. Data are given as median and 25–75th percentile for continuous variables. Categorical variables are given as percentage. BMI, Body Mass Index; NYHA, New York Heart Association classification; ASA, American Society of Anesthesiologists classification; STS, Society of Thoracic Surgeons

	TAVI-GA *n*=31	TAVI-S *n*=31
Female patients *n* (%)	18 (58)	13 (42)
Age (yr)	80 (75/84)	84 (79/86)
BMI (kg/m^2)	25 (23/30)	27 (24/29)
Aortic Valve Area (cm^2)	0.70 (0.56/0.83)	0.63 (0.60/0.80)
Left-Ventricular Ejection Fraction (%)	55 (43/60)	57 (40/62)
Pulmonary Artery Pressure (mm Hg)	43 (35/50)	47 (42/60)
Mean pressure gradient aortic valve (mm Hg)	54 (37/69)	46 (40/56)
Maximum pressure gradient aortic valve (mm Hg)	64 (45/88)	65 (45/82)
NYHA (III/IV) *n* (%)	24 (77)	22 (71)
EUROScore log (%)*	9.72 (7.01/18.26)	11.66 (10.32/21.43)
STS Mortality Score (%)	4.3 (2.8/10.2)	5.0 (3.6/7.4)
STS Morbidity Score (%)	23.3 (16.9/32.4)	25.4 (19.6/29.7)

transfemoral CoreValve™ was successfully implanted. The patient was extubated at the end of procedure and discharged home POD 13.

One additional TAVI-S patient was excluded because of difficulties with femoral vascular access and abortion of the procedure. In each group, 31 allocated patients were analysed.

Table 2 Perioperative course of rSO_2 and procedure related values. Data are given as median and 25–75th percentile for continuous variables. Categorical variables are given as percentage. rSO_2, Cerebral Saturation; ICU, Intensive Care Unit; BIS, Bispectral index; RVP, Rapid ventricular pacing. *Indicates a $P<0.05$

	TAVI-GA *n*=31	TAVI-S *n*=31	*P*-value
Procedure related timeline			
Induction time (min)	45 (40/50)	43 (35/50)	0.276
Duration of procedure (min)	72 (62/85)	75 (62/90)	0.667
Skin closure to extubation or equivalent alertness (min)	1 (−2/4)	−1 (−4/3)	0.235
Arrival of patient to handover to ICU (min)	170 (155/185)	170 (153/185)	0.983
Duration RVP (s)	22 (17/28)	21 (18/25)	0.621
Duration Valve implantation (s)	230 (170/339)	300 (179/376)	0.371
rSO_2 values			
rSO_2 at room air baseline (%)	60 (53/66)	57 (54/67)	0.916
rSO_2 interhemispheric difference (%)	0 (−3/3)	0 (−5/3)	0.789
rSO2 with oxygen after induction (%)	65 (58/70)	68 (63/78)	0.111
rSO_2 before RVP (%)	68 (60/71)	70 (64/79)	0.107
rSO_2 minimal value during RVP (%)	58 (51/64)	60 (56/67)	0.323
rSO_2 before valve implantation (%)	68 (58/72)	69 (64/78)	0.161
rSO_2 minimal value during valve impl. (%)	60 (51/66)	62 (54/71)	0.430
rSO_2 120 S after extubation (%)	73 (62/78)	72 (66/76)	0.921
Drug usage			
Remifentanil total (µg/kg)	25.3 (18.3/34.7)	4.5 (3.7/5.2)	<0.001*
Propofol total (mg/kg)	8.3 (6.1/9.9)	2.6 (2.1/3.6)	<0.001*
Norepinephrine total (µg/kg)	1.95 (1.07/4.78)	1.67 (0.62/3.13)	0.495
Depth of Anaesthesia			
BIS pre-induction	97 (92/98)	95 (89/97)	0.155
BIS at entering OR	40 (37/46)	83 (73/86)	<0.001
BIS before RVP	40 (36/43)	72 (58/81)	<0.001
BIS during RVP (minimal value)	39 (34/40)	60 (51/74)	<0.001
BIS during valve release (minimal value)	39 (31/46)	56 (50/75)	<0.001
BIS during skin closure	86 (75/95)	89 (86/92)	0.486
Postoperative			
Stay on ICU (days)	2 (1/4)	4 (1/6)	0.019*
Stay on Ward (days)	4 (3/6)	5 (2/6)	0.603
Total stay in hospital (days)	7 (6/8)	8 (7/11)	0.050
In hospital mortality *n* (%)	0	1 (3)	1.000
Adverse events			
Unrest/Pain *n* (%)	0	19 (61)	<0.001*
Bradypnoea *n* (%)	n.a.	16 (52)	n.a.
SpO_2<90% *n* (%)	0	5 (16)	0.053
Jaw-Thrust/nasopharyngeal airway *n* (%)	n.a.	11 (36)	n.a.
Bag-Mask Ventilation *n* (%)	n.a.	6 (19)	n.a.
Difficult tracheal intubation *n* (%)	3 (10)	n.a.	n.a.
Bronchospasm *n* (%)	0	1 (3)	1.000
Difficult central venous catheter *n* (%)	1 (3)	3 (10)	0.612
Defibrillation *n* (%)	0	1 (3)	1.000
Perioperative Stroke *n* (%)	0	1 (3)	1.000
Cumulative no. of patients with adverse events *n* (%)	4 (13)	29 (94)	<0.001*
Renal parameters			
Creatinine at time of admission (mg/dl)	0.91 (0.78/1.03)	0.94 (0.74/1.34)	0.205
Creatinine at time of discharge (mg/dl)	0.92 (0.81/1.10)	0.86 (0.67/1.32)	0.899
Need for dialysis *n* (%)	0	2 (6)	0.492
Procedural outcome	*n*=29	*n*=27	
Mean pressure gradient aortic valve at time of discharge (mm Hg)	11 (7/12)	12 (9/15)	0.079
Aortic Valve Area at time of discharge (cm^2)	1.55 (1.29/1.79)	1.50 (1.35/1.80)	0.975
Aortic Regurgitation at discharge	*n*=29	*n*=29	0.315
Grade 0 (%)	13 (45)	7 (26)	
Grade I (%)	14 (48)	16 (59)	
Grade II (%)	2 (7)	4 (15)	

As shown in Table 1, the patients' preoperative baseline characteristics were comparable. Median age of TAVI-S patients was 4 yr higher leading to a higher logistic EUROscore, while other risk scores (STS) were comparable.

Primary endpoint

There was no significant difference in AUC rSO_2 (total<DESAT) (Fig. 2C) between TAVI-GA (median [IQR]) (0 [0/1308] s%) and TAVI-S (0 [0/276] s%, *P*=0.505).

Sensitivity analysis

There was no difference in rSO_2 values between the two groups (Table 2). All patients showed a decrease in rSO_2 during RVP and valve implantation (Fig. 2A and B). The baseline values of rSO_2 before these interventions were comparable (Table 2). Twenty-four patients (39%) experienced perioperative decrease in rSO_2 below the desaturation threshold (TAVI-GA: *n*=13, TAVI-S: *n*=11; *P*=0.602). Maximal calculated desaturation was 27 174 s% in TAVI-GA and 14 502 s% in TAVI-S patients. Eight of these patients (TAVI-GA: *n*=5, TAVI-S: *n*=3; *P*=0.707) experienced a cumulative perioperative desaturation of more than 3000 s% (Fig. 2C).

Secondary endpoints

Neurocognitive outcome

All three neurocognitive tests revealed no significant pre- to postoperative difference neither within nor between the two patient groups (Fig. 3). Memory function (DemTect) was comparable between TAVI-GA (0 [−2/2] points) and TAVI-S (0 [−2/2] points, *P*=0.817). Both parts of the ZVT (ZVT 1: TAVI-GA: 3 [−4/14] s, TAVI-S: −2 [−7/8] s, *P*=0.307; ZVT 2: TAVI-GA: 2 [−5/8] s, TAVI-S: 3 [−4/18] s, *P*=0.362) revealed no difference in pre- to postoperative testing. Executive function (RWT) was also similar in both groups (TAVI-GA: −1 [−3/3] s, TAVI-S: 0 [−3/2] words, *P*=0.815).

Arterial blood gas analysis

As shown in Fig. 4, baseline ABG measurements were similar in both groups. In the TAVI-S group Pa_{CO_2} increased significantly after the start of sedation (TAVI-GA: (5.2 [4.6/5.5] kPa; TAVI-S: 6.7 [6.0/7.5] kPa, *P*<0.001) and continued to stay higher perioperatively. Simultaneously, respiratory acidosis was observed (pH

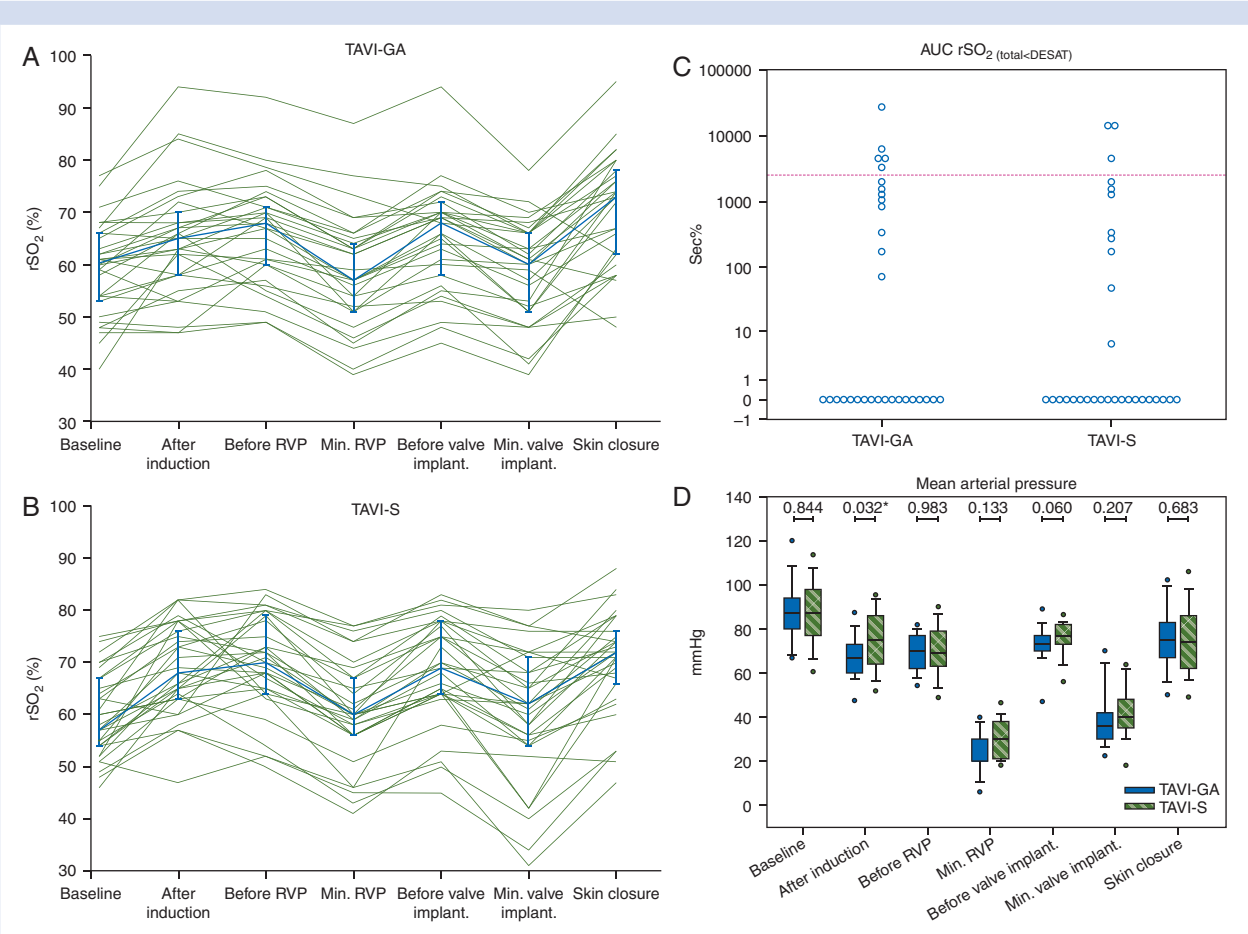

Fig 2 Perioperative evolution rSO_2. (A and B) Green lines show the individual perioperative rSO_2 values. The blue line shows the Median and the 25–75th percentile. (C) Cummulative Area under the curve (AUC) for individual patients in both groups below the desaturation (DESAT) threshold. The pink line indicates 3000 s% (D) Perioperative mean arterial pressure. Boxplots show Median, 25–75th percentile, Minimum, Maximum and outliers within 5–95th percentile. TAVI-GA – general anaesthesia, TAVI-S sedation, RVP – Rapid Ventricular Pacing for balloon valvuloplasty.

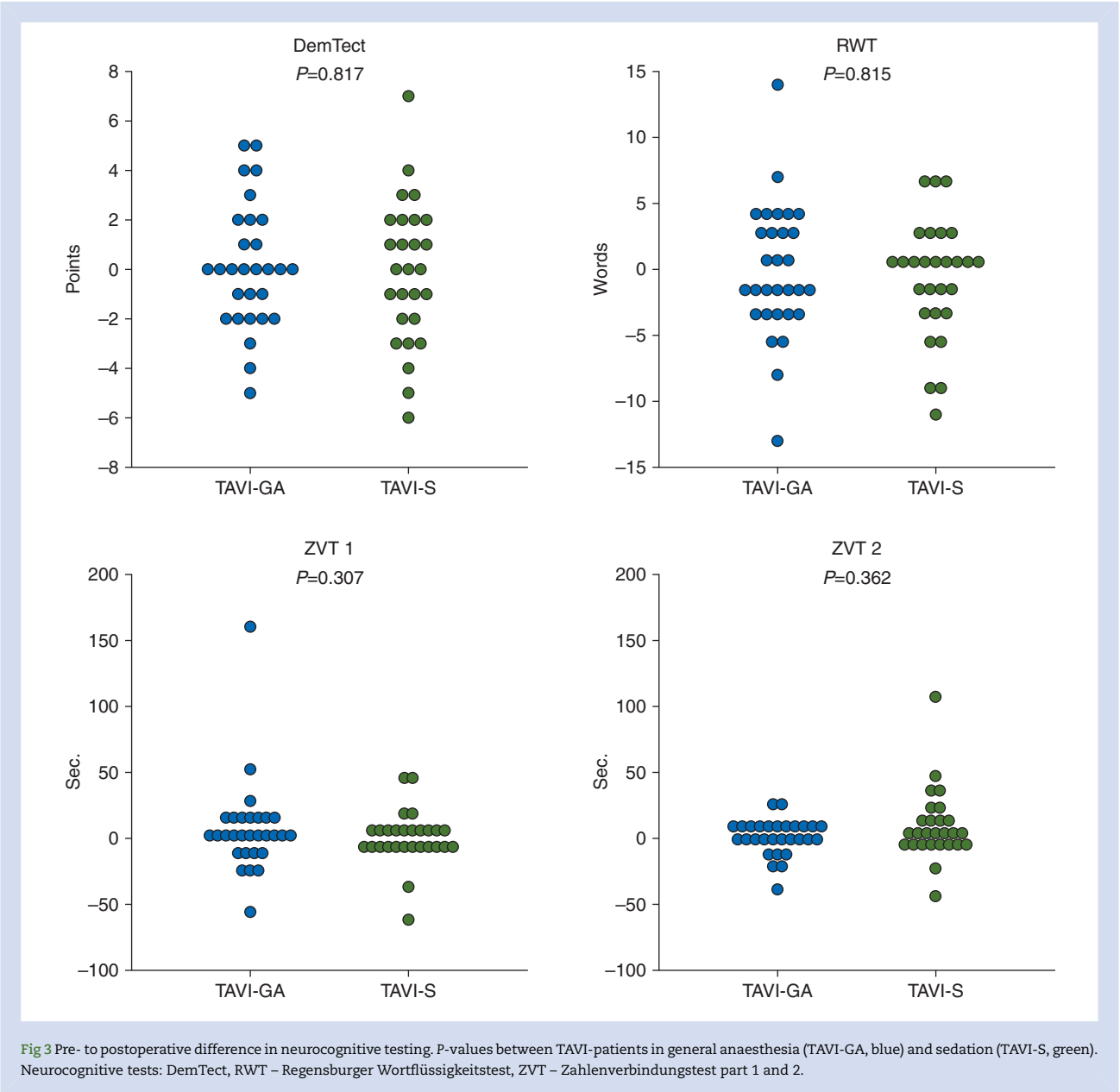

Fig 3 Pre- to postoperative difference in neurocognitive testing. P-values between TAVI-patients in general anaesthesia (TAVI-GA, blue) and sedation (TAVI-S, green). Neurocognitive tests: DemTect, RWT – Regensburger Wortflüssigkeitstest, ZVT – Zahlenverbindungstest part 1 and 2.

TAVI-GA: (7.45 [7.41/7.48]; pH TAVI-S: 7.35 [7.31/7.42], $P<0.001$). Pa_{O_2} was significantly higher in TAVI-GA patients during this period (TAVI-GA: (48 [39.3/53.3] kPa; TAVI-S: 22.8 [16.3/27.2] kPa, $P<0.001$). At the end of the procedure, ABG values were similar in both groups. Haemoglobin values remained comparable during the procedure (Fig. 4).

Adverse events and procedure-related time periods

Several perioperative adverse events occurred during the study, as shown in Table 2. In 29 of 31 (94%) TAVI-S and in 4 of 31 TAVI-GA patients (13%) ($P<0.001$) adverse events were observed. One TAVI-S suffered a perioperative severe stroke (confirmed by neuroimaging) without signs of cerebral desaturation. This patient was transferred to an external ICU and died on POD 19. A second TAVI-S patient was re-admitted to ICU on POD 8 and died on POD 22 from septic multi-organ failure.

Induction time, procedure time, and time from arrival of the patient until handover to the ICU were comparable as shown in Table 2. The anaesthetic drug dosage was higher in TAVI-GA patients. As to be expected, perioperative BIS values were lower in TAVI-GA (Table 2) during the operation. There was no statistically significant difference in catecholamine use. The ICU stay was statistically significantly shorter in TAVI-GA patients (TAVI-GA: 2 [1/4] days; TAVI-S: 4 [1/6] days; $P=0.019$)).

Procedural outcome and postoperative kidney injury

Procedural outcome defined as aortic regurgitation, mean pressure gradient and aortic valve area at discharge were comparable in TAVI-GA and TAVI-S patients (Table 2). Two TAVI-S patients required temporary postoperative dialysis. Pre- and postoperative creatinine values did not differ between TAVI-GA and TAVI-S patients (Table 2).

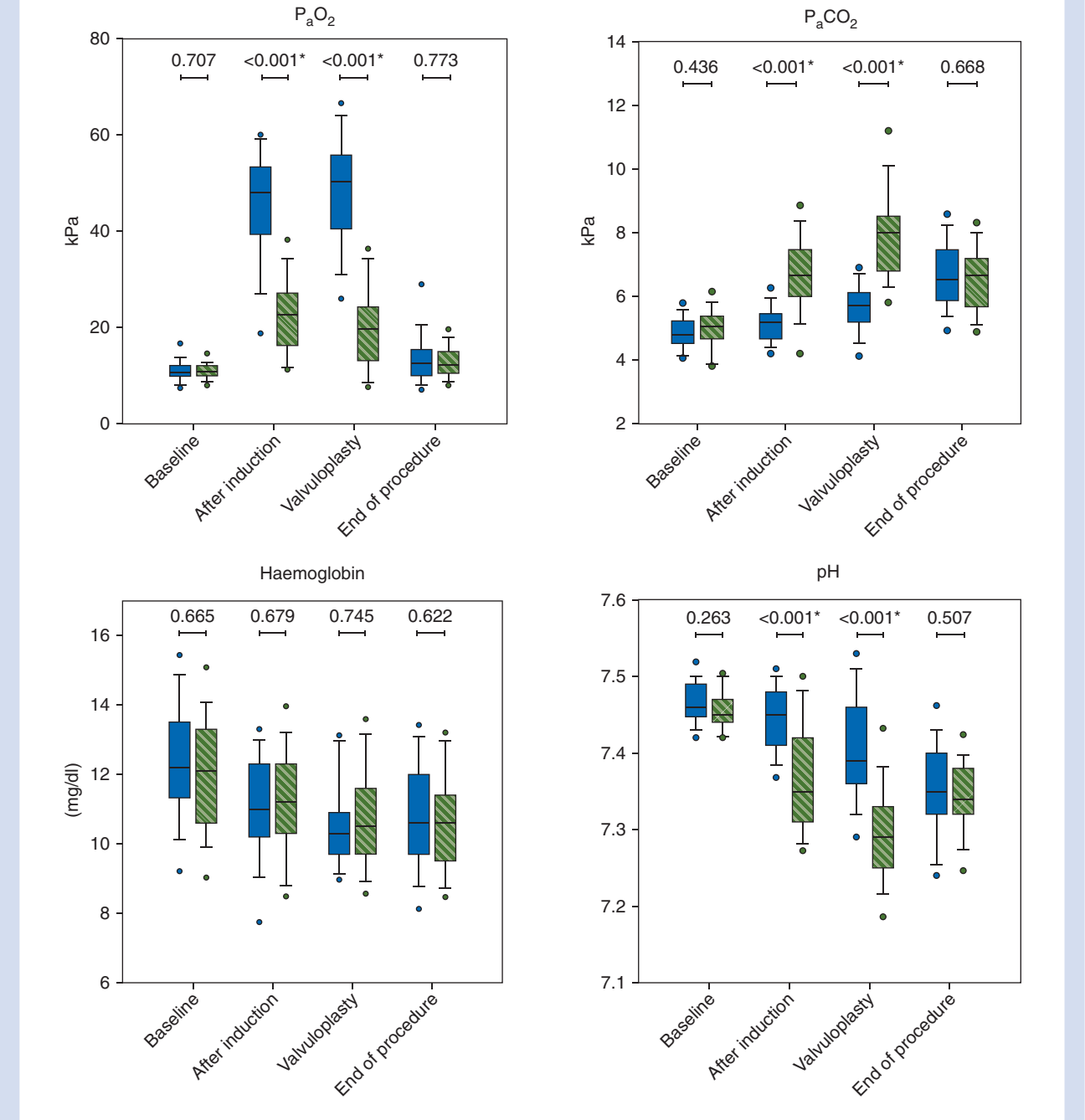

Fig 4 Blood gas analysis of arterial blood samples. TAVI-GA – general anaesthesia (blue), TAVI-S – Sedation (green). Boxplots show Median, 25–75th percentile, Minimum, Maximum and outliers within 5–95th percentile.

Discussion

The results of this study show that cerebral desaturation occurred both during general anaesthesia and sedation without a statistically significant and clinical difference in primary outcome (Table 2, Fig. 2). Sedation was associated with more adverse events, such as respiratory events. Longer periods of cerebral desaturations are associated with adverse outcome. In this study episodes of perioperative cerebral desaturation were monitored especially during balloon valvuloplasty and valve implantation, but were too short to produce desaturation to a larger extend. Our data are comparable with those recently published in a cohort of patients undergoing cardiac surgery[21] and baseline values described in patients undergoing transapical TAVI.[25] Although NIRS is a localized trend monitoring and only parts of the frontal lobe are monitored for signs of hypoperfusion and/or desaturation, it is the best available method to monitor the common

endpoint of cerebral perfusion and oxygenation. In addition the chosen desaturation threshold complies with the current consensus.[15] Although extracranial contamination has been described, with INVOS™ we used the technique that has been used in most trials.[14 15 21]

Three neurocognitive tests examining different types of cognitive function did not reveal any significant difference between pre- and postoperative testing. These data are in accordance with results recently published,[26] showing that more than 90% of sedated TAVI patients had no signs of cognitive deficit. From our point of view, neither general anaesthesia nor sedation impairs postoperative neurocognitive function in this specific group of patients (Fig. 3).

Perioperative Pa_{CO_2} was significantly higher in TAVI-S patients with consecutive respiratory acidosis. In moderate to deep sedation Pa_{CO_2} is often difficult to control as most sedatives and opioids affect respiration to a certain degree.[25] Respiratory depression, hypercarbia, and acidosis may increase pulmonary artery pressure (PAP) and may lead to right ventricular failure.[27] Pulmonary hypertension (PH) has been described in TAVI patients in up to 50%.[28] As PAP is easier to control, we consider general anaesthesia as favourable in patients with pre-existing PH.

Shorter procedure times for TAVI-S have been described[7 29] but these studies were not randomized. In addition different ways of haemodynamic monitoring, different techniques for femoral access and different periods of the learning curve were compared. Our study was performed with an experienced team, and the same haemodynamic monitoring was used, showing no time-benefit for sedation. On the contrary, ICU stay was significantly shorter in TAVI-GA patients. The reason for this difference remains unclear.

Several adverse events were observed in our study. A high rate of respiratory events and the need for bag-valve mask ventilation in 19% of TAVI-S patients, occurred even in the presence of experienced anaesthetists (Table 2). This number is in agreement with a previously described rate of unplanned perioperative intubations of 17%.[6] Unrest and pain may not be considered severe adverse events but are disturbing for the surgeon. Movement of the legs may also cause injury to the femoral vessels. Despite moderate to deep sedation and infiltration of local anaesthesia, unrest and pain were common during sedation. These adverse events in TAVI-S patients expose the potential risks of moderate to deep sedation for this procedure. There was no significant impact of anaesthesia to the implantation result. The tendency towards more aortic regurgitation in TAVI-S is in accordance with the recent published FRANCE-2 registry.[30] With the introduction of novel devices and the reduction of the diameter of the delivery system to 14 French, unrest and pain may be less problematic. As the experience with these new devices is rapidly growing, moderate or even minimal sedation might be sufficient and decrease the rate of respiratory events.[16] Further studies are needed to prove this concept.

Limitations

This study was powered for the primary endpoint of cerebral desaturation and not for the secondary outcome parameters of neurocognitive outcome and adverse events. This might be a limitation for these results. As we did not measure PAP, the effect of hypercapnia on the right ventricular function and PAP in our TAVI-S patients remains unclear. Although the study was blinded for most parts, the anaesthesia technique could not be blinded for obvious reasons.

Conclusion

In summary, TAVI in sedation did not offer an advantage with respect to cerebral desaturation and neurocognitive outcome compared with general anaesthesia. Moreover sedation was associated with more adverse events, such as respiratory events, and ICU longer stays. Therefore these data suggest an advantage of general anaesthesia *vs* moderate to deep sedation.

Authors' contributions

Study design/planning: N.P.M., A.H., A.K., B.B.
Study conduct: N.P.M.
Data analysis: N.P.M., A.H.
Writing paper: N.P.M., A.H.
Revising paper: all authors

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Declaration of interest

None declared.

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