

# Perioperative risk of major non-cardiac surgery in patients with severe aortic stenosis: a reappraisal in contemporary practice

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## Aims

Severe aortic stenosis (SAS) is a major risk factor for death after non-cardiac surgery, but most supporting data are from studies over a decade old. We evaluated the risk of non-cardiac surgery in patients with SAS in contemporary practice.

## Methods and results

SAS patients (valve area  $\leq 1$  cm<sup>2</sup>, mean gradient  $\geq 40$  mmHg or peak aortic velocity  $\geq 4$  m/s) undergoing intermediate or high-risk surgery were identified from surgical and echo databases of 2000–2010. Controls were matched for age, sex, and year of surgery. Post-operative (30 days) death and major adverse cardiovascular events (MACE), including death, stroke, myocardial infarction, ventricular tachycardia/fibrillation, and new or worsening heart failure, and 1-year survival were determined. There were 256 SAS patients and 256 controls (age  $76 \pm 11$ , 54.3% men). There was no significant difference in 30-day mortality (5.9% vs. 3.1%,  $P = 0.13$ ). Severe aortic stenosis patients had more MACE (18.8% vs. 10.5%,  $P = 0.01$ ), mainly due to heart failure. Emergency surgery, atrial fibrillation, and serum creatinine levels of  $> 2$  mg/dL were predictors of post-operative death by multivariate analysis [area under the curve: 0.81, 95% confidence intervals: 0.71–0.91]; emergency surgery was the strongest predictor of 30-day mortality for both SAS and controls. Severe aortic stenosis was the strongest predictor of 1-year mortality.

## Conclusion

Severe aortic stenosis is associated with increased risk of MACE. In contemporary practice, perioperative mortality of patients with SAS is lower than previously reported and the difference from controls did not reach statistical significance. Emergency surgery is the strongest predictor of post-operative death. These results have implications for perioperative risk assessment and management strategies in patients with SAS.

## Keywords

Aortic stenosis • Non-cardiac surgery • Perioperative risk • Survival • Echocardiography • Valvular heart disease

## Introduction

For  $> 30$  years, severe aortic stenosis (SAS) has been recognized as a risk factor for perioperative mortality and morbidity.<sup>1,2</sup> With increasing life expectancy, the incidence of degenerative calcific aortic stenosis is rising, and many patients require non-cardiac surgery. Furthermore, widespread availability of echocardiography has led to increased recognition of asymptomatic patients with SAS.

Current European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines recommend that elective non-cardiac surgery be

postponed for symptomatic SAS patients until after aortic valve surgery.<sup>3–6</sup> In those who refuse cardiac surgery or are otherwise not candidates for aortic valve replacement, the mortality risk of non-cardiac surgery is estimated at 10%.<sup>3</sup> However, these recommendations are based primarily on studies that are now more than a decade old. Some studies included low risk or minor procedures,<sup>7</sup> whereas others included small numbers of patients with SAS.<sup>1,8–12</sup> Furthermore, echocardiographic criteria for defining SAS have changed,<sup>13</sup> and improvements in surgical and anaesthesia techniques have led to a decrease in overall surgical mortality and morbidity.<sup>14</sup> Given these changes, and the emergence of percutaneous interventions in patients

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with SAS,<sup>15,16</sup> we hypothesized that perioperative mortality of patients with SAS is lower than previously reported and set forth to re-evaluate the risk of non-cardiac surgery in the contemporary era.

## Methods

### Patient selection

The study complies with the Declaration of Helsinki, and was approved by the Institutional Review Board. In this retrospective study, patients with echocardiographic evidence of SAS undergoing intermediate or high-risk surgical interventions were identified by crossing the Mayo Clinic echocardiography and surgical databases for years 2000–2010. Severe aortic stenosis was considered to be present at the time of surgery if documented within 12 months before or 3 months after surgery. Severe aortic stenosis was defined using current echocardiographic criteria (aortic valve area  $\leq 1$  cm<sup>2</sup>, peak systolic flow velocity  $\geq 4$  m/s, or mean gradient  $\geq 40$  mmHg) in conjunction with typical 2D echocardiographic appearance of SAS.<sup>13</sup> Patients undergoing aortic valve replacement before non-cardiac surgery were excluded. Patients with high gradients or velocities attributable to increased cardiac output (anaemia, septic shock, etc.), as well as those with concomitant diseases that may have influenced Doppler indexes of SAS (hypertrophic obstructive cardiomyopathy, sub- or supravalvular aortic stenosis, coarctation of the aorta, or complex congenital heart diseases) were excluded. In SAS patients with discordant findings between the valve area and gradient or velocity, the echocardiogram was reviewed by cardiologists with expertise in assessment of valvular diseases but blinded to clinical events; only patients deemed to have true SAS were included. After defining the SAS population, controls undergoing similar interventions (and who had no aortic stenosis by echocardiography within  $\pm 12$  months of surgery) were selected to match for age, gender, and year of surgery. Baseline demographic data, type of surgical intervention, comorbidities, symptoms potentially associated with SAS (dyspnoea, angina, syncope), and functional status at the time of surgery (independent living vs. nursing home resident) were extracted from the electronic medical record.

### Echocardiography

All echocardiograms were performed as clinically indicated, and in accordance with current European and American Society of Echocardiography recommendations.<sup>13</sup> In patients with multiple echocardiograms, the study closest to the time of surgery was selected. Aortic valve parameters (valve area and valve area index, peak aortic velocity and mean aortic valve gradient), as well as left ventricular size, ejection fraction, stroke volume, cardiac output and index, parameters reflecting diastolic function (left atrial volume index, mitral peak early inflow velocity divided by peak early mitral annular diastolic velocity,  $E/e'$ ) and estimated pulmonary artery systolic pressure (based on tricuspid regurgitant velocity) were extracted from the echocardiographic database. Valvulo-arterial impedance index was calculated as previously described.<sup>17</sup> An ejection fraction of  $< 55\%$  was considered abnormal.<sup>18</sup>

### Major non-cardiac surgery

Surgical interventions were classified according to current ACC/AHA guidelines into low, intermediate, and high risk.<sup>3,4</sup> Patients undergoing intermediate (intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopaedic surgery, prostate surgery; reported cardiac risk generally 1–5%) and high-risk procedures (aortic and other major vascular surgery, peripheral vascular surgery; reported risk  $> 5\%$ )<sup>3,4</sup> under general anaesthesia were included, regardless of clinical scenario (elective vs. emergency intervention).

Low-risk procedures, ambulatory, and percutaneous interventions were excluded.

### Perioperative and long-term events

Perioperative major adverse cardiovascular events (MACE) were defined as death, myocardial infarction, stroke, ventricular tachycardia or fibrillation, and new or worsening heart failure occurring within the first 30 days of surgery. Each of these was considered present if documented as diagnoses in the patient's medical chart or identified from the electronic medical record (myocardial infarction: typical rise and fall in troponin-T with ECG changes of ischaemia; stroke: evidence of new neurological deficit and/or new intracranial event by CT or MRI). Additionally, mortality and cause of death within the first year after surgery were determined from the electronic medical record, autopsy reports, and Social Security Death Index. Certain parameters pertinent to the perioperative management of these patients (invasive haemodynamic monitoring, intraoperative cardiac events, need for blood products, and use of vasoactive agents) were obtained from the anaesthesia record. The Revised Cardiac Risk Index for non-cardiac surgery<sup>19</sup> was calculated for all patients with one point given for each of the following six predictors of events: history of ischaemic heart disease (history of myocardial infarction or a positive exercise test, current angina, use of nitrate therapy, or ECG with pathological Q waves), history of heart failure, history of cerebrovascular disease, diabetes mellitus requiring insulin, chronic kidney disease (serum creatinine  $> 2$  mg/dL), and high-risk type of surgery (intraperitoneal, intrathoracic, or suprainguinal vascular surgery).

### Statistical analysis

Statistical analysis was performed using the JMP software version 9.0 and SAS version 9.3 (Cary, NC, USA). Statistical significance was accepted for two-sided  $P < 0.05$ . Baseline characteristics were compared between SAS and control groups using conditional logistic regression analyses. Symptomatic vs. asymptomatic SAS groups were compared using Pearson  $\chi^2$  or two sample t-test. Survival analysis was performed by the Kaplan–Meier method. The influence of various parameters on death and MACE was analysed with a multivariate stepwise logistic regression approach; only variables with significance level of  $< 0.1$  by univariate analysis were evaluated in the multivariate step; parameters were allowed to enter and stay in the model at a  $P < 0.1$  level. Discriminatory ability of each multivariate model is summarized with area under the curve (AUC) and the associated 95% confidence intervals. With the current sample size, the study had an 80% power to detect a 9% difference in proportions. Demographic and clinical data are expressed as mean  $\pm$  SD or number (%).

## Results

From 512 852 echocardiograms performed at Mayo Clinic Rochester campus between 2000 and 2010, we identified 256 patients with SAS who underwent major non-cardiac surgery and had no exclusion criteria; of these, 25 had classical low-flow, low-gradient SAS [gradient  $< 40$  mmHg, ejection fraction (EF)  $< 55\%$ ], and 10 had paradoxical low-flow, low-gradient SAS (defined as SAS with gradient  $< 40$  mmHg and stroke volume index  $< 35$  mL/m<sup>2</sup>, EF  $\geq 55\%$ ). One hundred five (42%) SAS patients had cardiac symptoms documented prior to their surgery (angina, dyspnoea, or syncope/pre-syncope). Major characteristics of SAS patients and controls are shown in Table 1. Compared to controls, SAS patients more often had a history of coronary artery disease, hypertension, heart

**Table 1** Study population

|  | SAS                          |                                  |                                   | <i>P</i> <sup>a</sup> | Controls<br>( <i>N</i> = 256) | <i>P</i> <sup>b</sup> |
|--|------------------------------|----------------------------------|-----------------------------------|-----------------------|-------------------------------|-----------------------|
|  | Overall<br>( <i>N</i> = 256) | Symptomatic<br>( <i>N</i> = 106) | Asymptomatic<br>( <i>N</i> = 150) |                       |                               |                       |
| Demographics   |                              |                                  |                                   |                       |                               |                       |
| Age (years)  | 76 ± 11                      | 77 ± 10                          | 76 ± 12                           | 0.61                  | 76 ± 11                       | 0.92                  |
| Male gender, <i>N</i> (%)                                    | 139 (54.3)                   | 64 (60.4)                        | 75 (50.0)                         | 0.008                 | 139 (54.3)                    | 1.0                   |
| BMI (kg/m <sup>2</sup> )                                     | 28.0 ± 6.0                   | 27.8 ± 6.0                       | 28.4 ± 6.0                        | 0.43                  | 28.0 ± 6.0                    | 0.57                  |
| Nursing home resident  | 20 (7.9)                     | 12 (11.3)                        | 8 (5.3)                           | 0.08                  | 7 (2.8)                       | 0.01                  |
| Medical history, <i>N</i> (%)                                |                              |                                  |                                   |                       |                               |                       |
| Myocardial infarction  | 47 (18.4)                    | 25 (23.6)                        | 22 (14.7)                         | 0.07                  | 37 (14.5)                     | 0.25                  |
| CAD  | 140 (54.7)                   | 83 (78.3)                        | 57 (38.0)                         | <0.001                | 88 (34.4)                     | <0.001                |
| Heart failure  | 47 (18.4)                    | 33 (31.1)                        | 14 (9.3)                          | 0.003                 | 30 (11.7)                     | 0.054                 |
| Hypertension   | 218 (85.2)                   | 88 (83.0)                        | 130 (86.7)                        | 0.42                  | 171 (66.8)                    | <0.001                |
| Hyperlipidaemia  | 144 (56.3)                   | 61 (57.6)                        | 83 (55.3)                         | 0.73                  | 137 (53.5)                    | 0.53                  |
| Diabetes   | 77 (30.1)                    | 37 (34.5)                        | 40 (26.7)                         | 0.16                  | 56 (21.9)                     | 0.03                  |
| Pulmonary diseases   | 59 (23.0)                    | 39 (36.8)                        | 20 (13.3)                         | <0.001                | 40 (15.6)                     | 0.04                  |
| Peripheral vascular disease                                  | 12 (4.7)                     | 4 (3.8)                          | 8 (5.3)                           | 0.56                  | 19 (7.4)                      | 0.18                  |
| Atrial fibrillation  | 47 (18.4)                    | 26 (24.5)                        | 21 (14.0)                         | 0.033                 | 42 (16.4)                     | 0.55                  |
| NYHA class, <i>N</i> (%)                                     |                              |                                  |                                   |                       |                               |                       |
|  |                              |                                  |                                   | <0.001                |                               | 0.001                 |
| I  | 191 (70.7)                   | 41 (38.7)                        | 150 (100)                         |                       | 171 (66.8)                    |                       |
| II   | 51 (25.8)                    | 51 (48.1)                        | 0 (0)                             |                       | 81 (31.6)                     |                       |
| III/IV   | 14 (3.5)                     | 14 (13.2)                        | 0 (0)                             |                       | 4 (1.6)                       |                       |
| Surgery type, <i>N</i> (%)                                   |                              |                                  |                                   |                       |                               |                       |
| Emergency  | 24 (9.4)                     | 10 (9.4)                         | 14 (9.3)                          | 0.98                  | 21 (8.2)                      | 0.63                  |
| Vascular   | 32 (12.5)                    | 16 (15.1)                        | 16 (10.7)                         | 0.29                  | 45 (17.6)                     | 0.12                  |
| Abdominal  | 83 (32.4)                    | 23 (21.7)                        | 60 (40.0)                         | 0.002                 | 74 (28.9)                     | 0.36                  |
| Neurosurgery   | 30 (11.7)                    | 12 (11.3)                        | 18 (12.0)                         | 0.87                  | 41 (16.0)                     | 0.16                  |
| Orthopaedic  | 76 (29.7)                    | 35 (33.0)                        | 41 (27.3)                         | 0.33                  | 71 (27.7)                     | 0.62                  |
| Urologic   | 16 (6.3)                     | 10 (9.4)                         | 6 (4.0)                           | 0.08                  | 7 (2.7)                       | 0.07                  |
| Thoracic   | 10 (3.9)                     | 6 (5.7)                          | 4 (2.7)                           | 0.23                  | 13 (5.1)                      | 0.47                  |
| Gynaecologic   | 6 (2.3)                      | 3 (2.8)                          | 3 (2.0)                           | 0.47                  | 5 (2.0)                       | 0.76                  |
| Other  | 3 (1.2)                      | 2 (1.9)                          | 1 (0.7)                           | 0.38                  | 0 (0)                         | 0.98                  |
| Echo parameters (mean ± SD)                                  |                              |                                  |                                   |                       |                               |                       |
| Ejection fraction (%)  | 62 ± 10                      | 59 ± 12                          | 64 ± 9                            | <0.001                | 58 ± 10                       | <0.001                |
| Aortic valve area (cm <sup>2</sup> )                         | 0.9 ± 0.2                    | 0.88 ± 0.2                       | 0.93 ± 0.19                       | 0.039                 | 2.9 ± 0.8                     | <0.001                |
| Indexed aortic valve area (cm <sup>2</sup> /m <sup>2</sup> ) | 0.5 ± 0.1                    | 0.48 ± 0.10                      | 0.50 ± 0.09                       | 0.25                  | 1.5 ± 0.4                     | <0.001                |
| Mean gradient (mmHg)   | 40 ± 11                      | 40 ± 12                          | 40 ± 12                           | 0.93                  | 9 ± 3                         | <0.001                |
| Aortic jet velocity (m/s)                                    | 4.1 ± 0.6                    | 4.1 ± 0.6                        | 4.2 ± 0.6                         | 0.31                  | 1.5 ± 0.3                     | <0.001                |
| Stroke volume (mL)   | 88 ± 21                      | 84 ± 21                          | 90 ± 22                           | 0.048                 | 84 ± 22                       | 0.05                  |
| Cardiac output, (L/min)                                      | 6.0 ± 1.5                    | 5.9 ± 1.6                        | 6.0 ± 1.4                         | 0.59                  | 5.9 ± 1.6                     | 0.27                  |
| Right ventricular systolic pressure (mmHg)                   | 43 ± 13                      | 46 ± 15                          | 41 ± 12                           | 0.004                 | 38 ± 12                       | <0.001                |
| Left atrial volume index (mL/m <sup>2</sup> )                | 46 ± 18                      | 47 ± 18                          | 45 ± 17                           | 0.33                  | 38 ± 17                       | <0.001                |
| <i>E/e'</i>  | 17 ± 8                       | 18 ± 8                           | 17 ± 8                            | 0.17                  | 14 ± 7                        | <0.001                |
| Valvular disease, <i>N</i> (%)                               |                              |                                  |                                   |                       |                               |                       |
| Mitral regurgitation   | 39 (15.5)                    | 19 (17.8)                        | 20 (13.3)                         | 0.32                  | 33 (13.1)                     | 0.44                  |
| Aortic regurgitation   | 4 (1.6)                      | 4 (3.8)                          | 12 (8.0)                          | 0.16                  | 2 (0.8)                       | 0.42                  |
| Tricuspid regurgitation                                      | 43 (16.7)                    | 22 (20.8)                        | 21 (14.0)                         | 0.15                  | 34 (13.5)                     | 0.27                  |
| Mitral stenosis  | 10 (4.0)                     | 7 (6.6)                          | 3 (2.0)                           | 0.06                  | 5 (2.0)                       | 0.21                  |

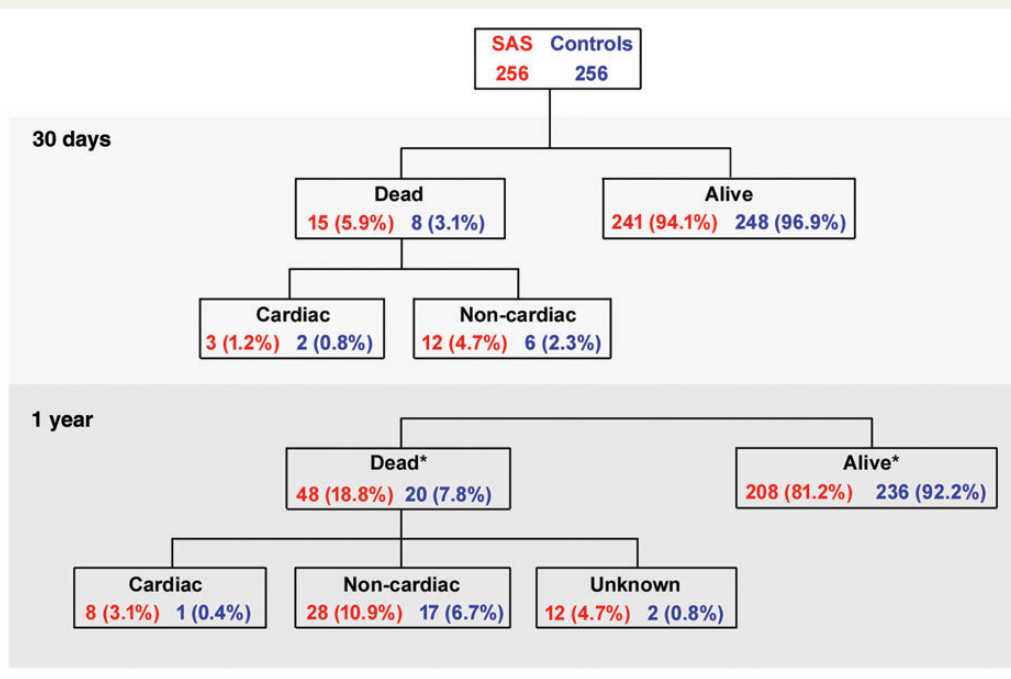
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**Table 1** Continued

|                     | SAS                  |                          |                           | <i>p</i> <sup>a</sup> | Controls<br>(N = 256) | <i>p</i> <sup>b</sup> |
|---------------------|----------------------|--------------------------|---------------------------|-----------------------|-----------------------|-----------------------|
|                     | Overall<br>(N = 256) | Symptomatic<br>(N = 106) | Asymptomatic<br>(N = 150) |                       |                       |                       |
| Medications         |                      |                          |                           |                       |                       |                       |
| Aspirin/clopidogrel | 135 (52.7)           | 61 (57.8)                | 74 (49.3)                 | 0.19                  | 140 (54.7)            | 0.66                  |
| Beta blockers       | 138 (53.9)           | 63 (59.4)                | 75 (50)                   | 0.14                  | 141 (55.1)            | 0.78                  |
| ACE-I/ARB           | 101 (39.5)           | 38 (35.9)                | 63 (42.0)                 | 0.32                  | 110 (43.0)            | 0.37                  |
| Diuretics           | 124 (48.4)           | 55 (51.9)                | 69 (46.0)                 | 0.35                  | 97 (37.9)             | 0.01                  |
| Digoxin             | 26 (10.2)            | 14 (13.2)                | 12 (8.0)                  | 0.18                  | 19 (7.4)              | 0.26                  |
| Nitrates            | 26 (10.2)            | 19 (17.8)                | 7 (4.7)                   | <0.001                | 25 (9.8)              | 0.88                  |
| Warfarin            | 57 (22.3)            | 26 (24.5)                | 31 (20.7)                 | 0.46                  | 48 (18.8)             | 0.33                  |

<sup>a</sup>Symptomatic vs. asymptomatic SAS.

<sup>b</sup>SAS vs. controls. Severe aortic stenosis patients and controls were matched for age, gender, and year of surgery. BMI, body mass index; ACE-I/ARB, ACE-inhibitor/angiotensin receptor blocker.



**Figure 1** Outcomes after non-cardiac surgery. 30-day and 1-year survival in severe aortic stenosis patients (red) and controls (blue). The differences in mortality at 30 days did not reach statistical significance. However, severe aortic stenosis was associated with significantly higher mortality at 1 year. \**P* < 0.001.

failure, diabetes, and pulmonary disease. Types of surgical procedures were similar between groups.

In most patients, the decision to proceed with surgical procedure without addressing the SAS first was made based on clinical grounds (patients were felt to have higher risk from delaying non-cardiac surgery than from SAS *per se*). A total of 27 patients underwent planned aortic valve replacement within 1 year after surgery (6 within first 30 days).

### Perioperative mortality and major adverse cardiovascular events

Mortality rates within first 30 days after surgery and at 1 year are summarized in *Figure 1*; other parameters pertinent to perioperative period are presented in *Table 2*. There were no deaths during the surgical procedure. While slightly higher post-operative 30-day mortality rates were observed among SAS patients than in controls, the difference did not reach statistical significance (5.9% vs. 3.1%,

**Table 2** Perioperative course

|   | SAS         |                                  |                                   | <i>P</i> <sup>a</sup> | Controls  | <i>P</i> <sup>b</sup> |
|---|-------------|----------------------------------|-----------------------------------|-----------------------|-----------|-----------------------|
|   | Overall     | Symptomatic<br>( <i>N</i> = 106) | Asymptomatic<br>( <i>N</i> = 150) |                       |           |                       |
| Major adverse cardiovascular events 30 days, <i>N</i> (%) |             |                                  |                                   |                       |           |                       |
| Total   | 48 (18.8)   | 30 (28.3)                        | 18 (12%)                          | 0.001                 | 27 (10.5) | 0.01                  |
| Death   | 15 (5.9)    | 10 (9.4)                         | 5 (3.3)                           | 0.04                  | 8 (3.1)   | 0.15                  |
| Cardiac   | 3 (1.2)     | 2 (1.9)                          | 1 (0.7)                           | 0.38                  | 2 (0.8)   | 0.66                  |
| Non-cardiac   | 12 (4.7)    | 8 (7.6)                          | 4 (2.7)                           | 0.07                  | 6 (2.3)   | 0.17                  |
| Stroke  | 2 (0.8)     | 1 (0.9)                          | 1 (0.7)                           | 0.81                  | 3 (1.2)   | 0.66                  |
| STEMI   | 2 (0.8)     | 1 (0.9)                          | 1 (0.7)                           | 0.81                  | 1 (0.4)   | 0.57                  |
| NSTEMI  | 2 (0.8)     | 1 (0.9)                          | 1 (0.7)                           | 0.81                  | 4 (1.6)   | 0.42                  |
| VT/VF   | 2 (0.8)     | 2 (1.9)                          | 0 (0)                             | 0.06                  | 3 (1.2)   | 0.66                  |
| New/worsening heart failure                               | 33 (12.9)   | 21 (19.8)                        | 12 (8)                            | 0.04                  | 13 (5.1)  | 0.004                 |
| Intra-operative course, <i>N</i> (%)                      |             |                                  |                                   |                       |           |                       |
| Use of Swan-Ganz catheter                                 | 67 (26.2)   | 22 (20.8)                        | 45 (30.0)                         | 0.09                  | 53 (20.7) | 0.14                  |
| Need for blood transfusion                                | 79 (30.9)   | 34 (32.1)                        | 45 (30.0)                         | 0.72                  | 48 (18.8) | 0.002                 |
| Use of catecholamines                                     | 63 (24.6)   | 25 (23.6)                        | 38 (25.3)                         | 0.75                  | 45 (17.6) | 0.04                  |
| Intubation and hospital stay, <i>N</i> (%)                |             |                                  |                                   |                       |           |                       |
| Intubation >24 h  | 15 (5.9)    | 9 (8.5)                          | 6 (4.0)                           | 0.13                  | 10 (3.9)  | 0.28                  |
| Need for re-intubation                                    | 4 (1.6)     | 1 (0.9)                          | 3 (2.0)                           | 0.49                  | 4 (1.6)   | 1.0                   |
| Length of stay (days)                                     | 10.3 ± 11.5 | 11.8 ± 12.9                      | 9.2 ± 10.4                        | 0.09                  | 8.5 ± 9.4 | 0.06                  |

Multiple events occurred in six patients with SAS (some with >2 events) and in five controls.

<sup>a</sup>Symptomatic vs. asymptomatic SAS.

<sup>b</sup>SAS vs. controls. Severe aortic stenosis patients and controls were matched for age, gender, and year of surgery. VT/VF, ventricular tachycardia/fibrillation; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction.

*P* = 0.13). Using more stringent criteria for SAS, the differences between SAS and their matched controls remained not significant (mortality 7.4 vs. 5.9% with valve area <0.8 cm<sup>2</sup>, *P* = 0.73; 5.9 vs. 5.9% with velocity >5 m/s, *P* = 1.0; 9.8 vs. 2.4% for mean gradient >50 mmHg, *P* = 0.20). Kaplan–Meier survival analysis yielded similar results for mortality (Figure 2A).

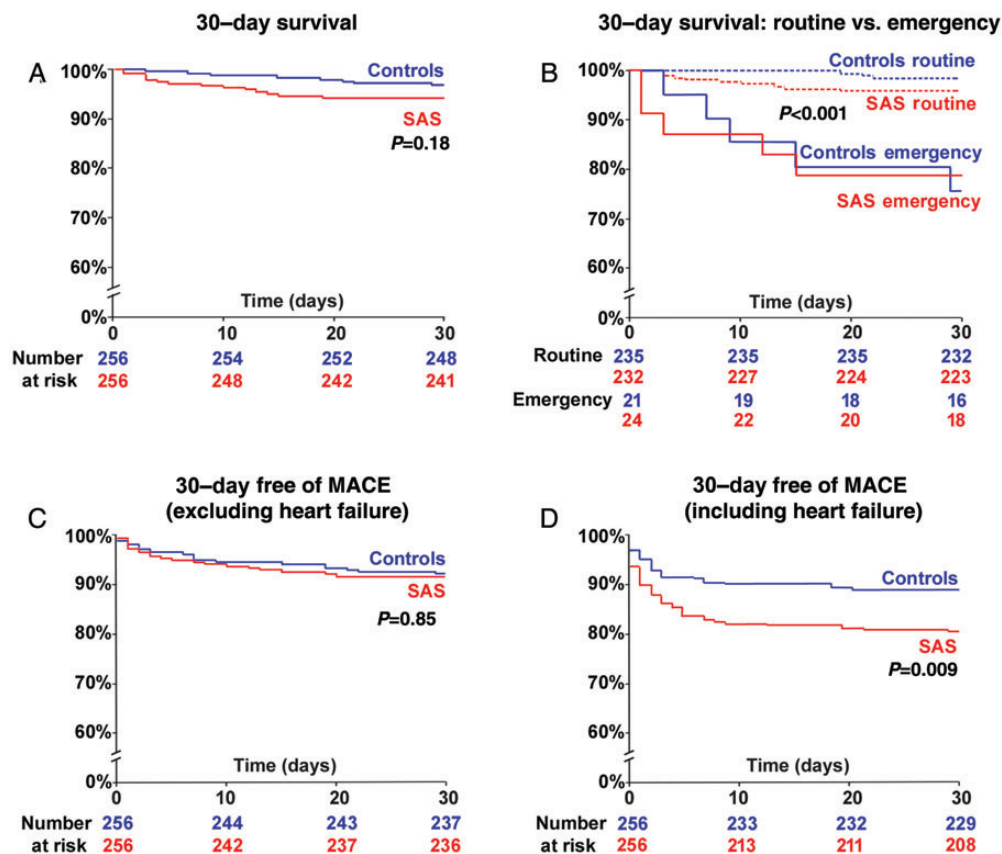
With univariate analysis, emergency surgery was the strongest predictor of 30-day mortality (Figure 3). Indeed, mortality was substantially higher with emergency interventions in both groups (25.0% in SAS vs. 23.8% in controls, *P* = 0.92). With non-emergency surgery, there was a trend for increased 30-day mortality in SAS patients (3.9 vs. 1.3%, *P* = 0.08). Other parameters associated with increased mortality with univariate analysis included pre-existing conditions (atrial fibrillation, renal failure with creatinine >2 mg/dL or dialysis, history of heart failure, more than moderate tricuspid regurgitation), baseline patient status (age, presence of symptoms, nursing home residence), echocardiographic parameters suggestive of diastolic dysfunction (increased left atrial volume index, *E/e'* ratio, and estimated pulmonary artery systolic pressure) and abdominal surgery; higher stroke volumes and aortic valve areas, and use of statins were associated with improved survival [odds ratios (OR) < 1]. With multivariate stepwise regression analysis, emergency surgery (*P* < 0.001), presence of atrial fibrillation (*P* = 0.004), and creatinine >2 mg/dL (*P* = 0.006) entered the model (AUC: 0.81, 95% confidence intervals: 0.71–0.91). The major impact of emergency

surgery on mortality was confirmed at survival analysis; indeed, emergency surgery was associated with substantially higher death rates in both SAS and controls (Figure 2B; *P* < 0.001 for emergency vs. non-emergency surgery). Year of operation was not associated with perioperative mortality (*P* = 0.80) or MACE (*P* = 0.91).

There were no significant differences between SAS and controls in perioperative myocardial infarction (1.6 vs. 2%, *P* = 0.75), stroke (0.8 vs. 1.2%, *P* = 0.66), or ventricular tachycardia/fibrillation (0.8 vs. 1.2%; *P* = 0.66), with virtual overlap of event-free survival curves between SAS patients and controls (Figure 2C). However, when including new or worsening heart failure, we noted a significant increase in 30 days MACE in SAS patients (18.8% vs. 10.5%, *P* = 0.01; Figure 2D). Thus, excess events in SAS patients were driven mainly by heart failure episodes (12.9 vs. 5.1%, *P* = 0.004). Hospital stay tended to be longer for SAS patients (10.3 ± 11.5 days vs. 8.5 ± 9.4 days; *P* = 0.06). Univariate predictors of 30-day MACE and their OR are presented in Figure 4. With multivariate analysis, emergency surgery (*P* = 0.006), presence of peripheral arterial disease (*P* = 0.022), right ventricular systolic pressure (*P* < 0.001), and SAS (*P* = 0.06) were included in the model (AUC: 0.71, 95% confidence intervals: 0.65–0.78).

## Mortality at 1 year

Severe aortic stenosis was strongly associated with excess mortality at 1 year (18.8% vs. 7.8%, *P* < 0.001). Univariate and multivariate



**Figure 2** Kaplan–Meier analysis of perioperative outcomes. There was no significant difference in perioperative survival between severe aortic stenosis patients and controls (A), the major determinant of perioperative mortality being emergency surgery (B; log-rank  $P$ -values:  $< 0.001$  for emergency vs. non-emergency surgery, 0.073 for severe aortic stenosis vs. controls during routine surgery, 0.87 for severe aortic stenosis vs. controls during emergency surgery). Hard endpoints (death, stroke, myocardial infarction, and ventricular tachycardia/fibrillation) occurred to a similar extent in patients and controls (C). However, when new or worsening heart failure was included with major adverse cardiovascular events, severe aortic stenosis patients were significantly more likely to develop events within the first 30 days after surgery (D). Severe aortic stenosis data are in red; controls are in blue.

predictors of 1-year mortality are presented in *Figure 5*. With multivariate analysis, presence of SAS ( $P = 0.010$ ), ejection fraction  $< 55\%$  ( $P = 0.002$ ), right ventricular systolic pressure ( $P = 0.002$ ), and nursing home residence ( $P = 0.099$ ) were included in the model (AUC: 0.73, 95% confidence intervals: 0.65–0.81).

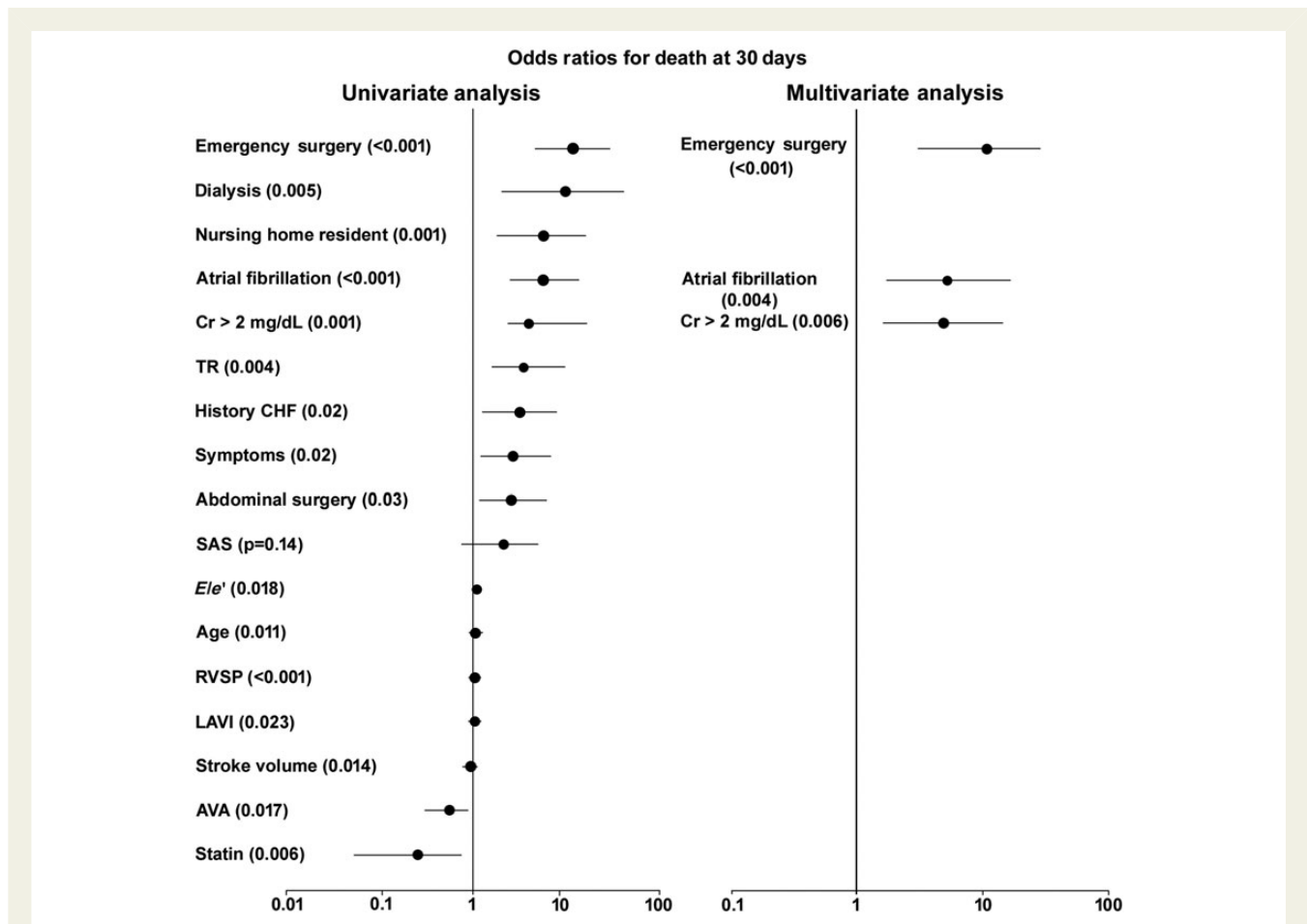
### Symptomatic vs. asymptomatic patients

When analysing the entire population (SAS and controls combined), presence of symptoms (dyspnoea, angina, or syncope) was associated with significantly higher 30-day mortality. Compared to controls, SAS patients more often had angina (1.2% vs. 9.4%,  $P < 0.001$ ), but dyspnoea (33.2% vs. 36.6%,  $P = 0.42$ ) and pre-syncope/syncope (2.3% vs. 3.9%,  $P = 0.30$ ) were similar in both groups. We further compared symptomatic and asymptomatic SAS patients with their matched controls. Death and MACE at 30 days were virtually identical for SAS patients without symptoms and controls (30-day mortality 3.3% vs. 2.7%,  $P = 0.73$ , and MACE 12.0% vs. 12.0%,  $P = 1.0$ ). On the contrary, symptomatic SAS patients had significantly higher MACE at 30 days when compared to their controls

(28.3% vs. 8.5%,  $P < 0.001$ ); mortality was higher, but the difference did not reach statistical significance (9.4% vs. 3.8%,  $P = 0.097$ ). At 1 year, SAS was strongly associated with excess mortality in symptomatic patients (16.0% vs. 6.6%,  $P < 0.001$ ); in the absence of symptoms, SAS patients had higher mortality, but the difference was not statistically significant (14.0% vs. 8.7%,  $P = 0.14$ ).

### Mortality and major adverse cardiovascular events by Revised Cardiac Risk Index

Increasing Revised Cardiac Risk Index values were associated with higher mortality (1.6, 8.8, and 12.1% in SAS vs. 2.2, 5.2, and 2.5% in controls at risk index values of 0, 1, and  $\geq 2$ , respectively; *Figure 6*). No significant differences were observed between SAS and controls for risk scores of 0 or 1. Separation between SAS and controls became more apparent for risk scores  $\geq 2$ , with significant difference in MACE rates ( $P = 0.018$ ) and a trend for 30-day mortality ( $P = 0.067$ ) in SAS patients (*Figure 6*).



**Figure 3** Odds ratios for 30-day mortality. Results of univariate and multivariate logistic regression analysis. Data presented as odds ratios and 95% confidence intervals; P-values in parentheses. For continuous variables, odds ratios are given per unit change in the regressor. TR, more than moderate tricuspid regurgitation; Cr, creatinine; AVA, aortic valve area; RVSP, right ventricular systolic pressure; LAVI, left atrial volume index. Severe aortic stenosis was not a significant univariate predictor, but is presented for reference.

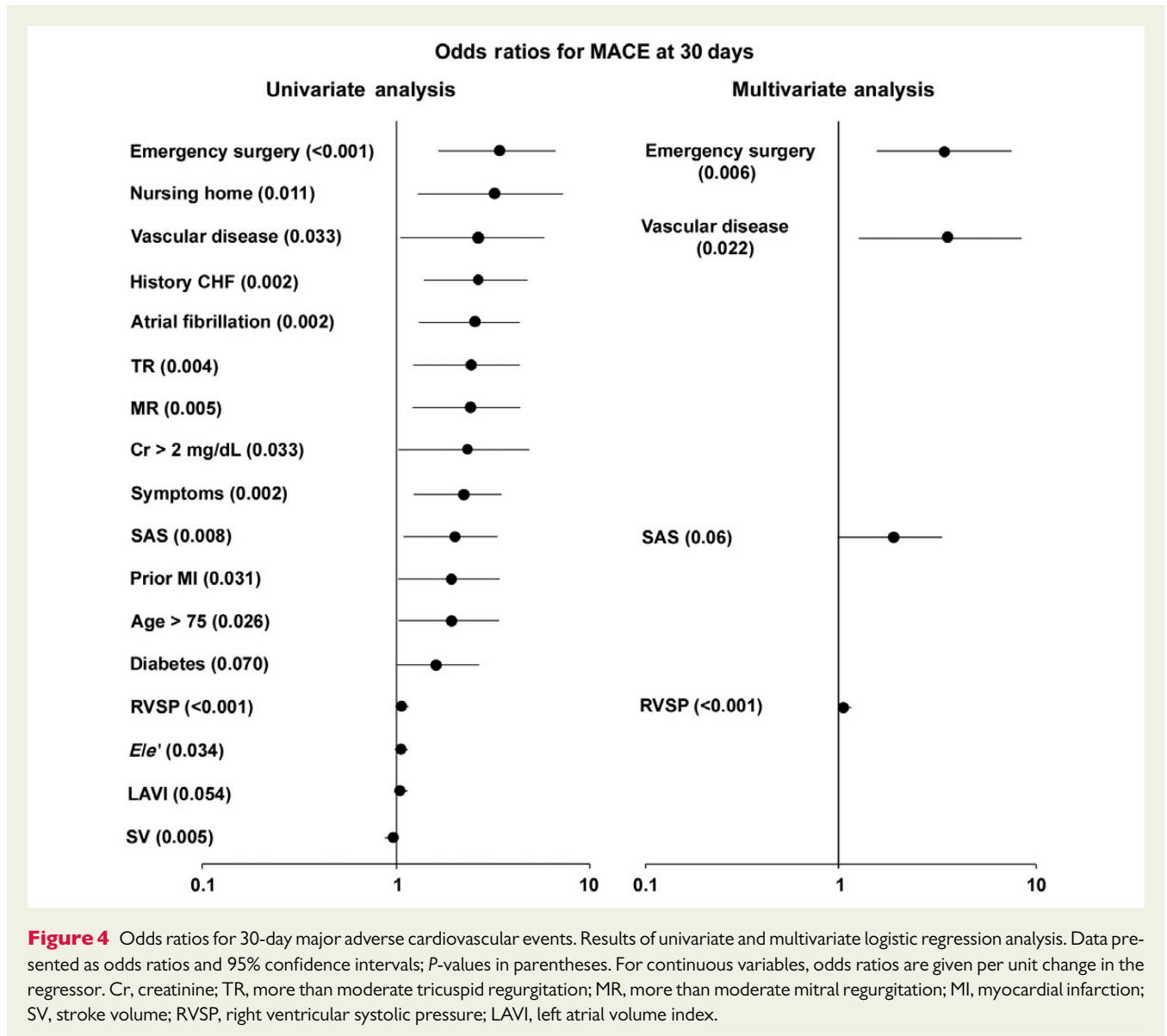
## Discussion

This is a large contemporary study addressing the risk associated with non-cardiac surgery in patients with SAS. Only patients undergoing intermediate or high-risk intervention under general anaesthesia were included, as it is in these patients that the risk attributable to SAS is presumably greatest. The major findings of our study are that (i) perioperative mortality in SAS patients is significantly lower than previously reported, (ii) emergency surgery was the major determinant of perioperative death irrespective of SAS, and (iii) presence of symptoms was important in perioperative risk stratification of SAS patients.

Current ACC/AHA<sup>3</sup> and ESC guidelines<sup>4</sup> on perioperative cardiovascular evaluation for non-cardiac surgery emphasize the increased surgical risk of patients with SAS. The ESC recommends proceeding with surgery only in asymptomatic SAS patients and only for low- or intermediate-risk interventions, while ACC/AHA suggest postponing intervention in asymptomatic patients who have not had a valvular evaluation within 1 year. Both American and European societies advise against elective surgical procedures in symptomatic SAS

before correcting SAS by surgical or percutaneous interventions. Our results demonstrate that perioperative mortality of patients with SAS is significantly lower than previously reported,<sup>1,8–11,20</sup> and in our study, it is similar to that of age- and gender-matched controls without SAS undergoing similar surgical procedures.

The strongest predictor of perioperative death in both SAS and controls was emergency surgery. Indeed, once its effects were taken into account, subsequent parameters entering the multivariate model added little to explain variability. Perioperative mortality was <5% for both SAS patients and controls when undergoing routine (non-emergency) surgery (Figure 2B), and in line with what is expected with intermediate and high-risk procedures (1–5% in intermediate risk surgery, >5% in aortic and major vascular surgery).<sup>3</sup> Increasing Revised Cardiac Risk Index was associated with higher mortality. Surprisingly, non-cardiac rather than cardiac deaths were more common in SAS patients, perhaps reflecting an increased awareness of SAS haemodynamic consequences at time of surgery, and improvements in anaesthesia and surgical techniques. Indeed, SAS patients more often received blood transfusions intra-operatively ( $P = 0.002$ ); catecholamine use was also higher ( $P = 0.04$ ).



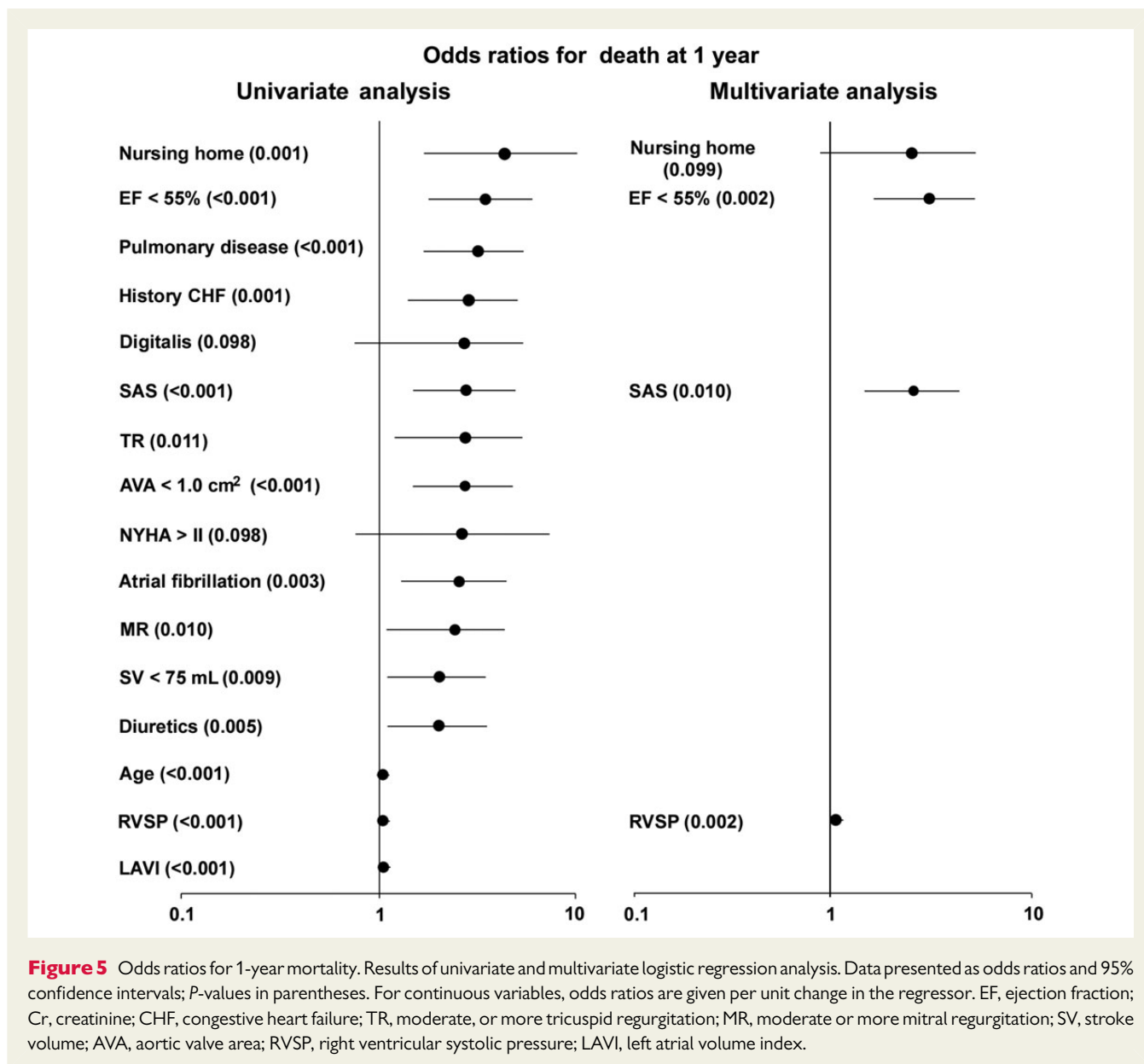
We noted slightly higher 30-day mortality rates in the SAS group, but these differences did not reach statistical significance. The slight excess seems to be isolated to patients with symptomatic SAS, as asymptomatic SAS patients and their controls had similar death rates at 30 days. These findings confirm other reports showing SAS patients have no significant increase in mortality at the time of non-cardiac surgery.<sup>12,20</sup> Our combined MACE endpoint reached statistical significance mainly due to more frequent episodes of new or worsening heart failure in SAS patients; hard endpoints (post-operative myocardial infarction, stroke, malignant ventricular arrhythmias) were virtually identical between groups. Heart failure was more common in symptomatic patients with SAS.

Agarwal and colleagues have recently reported a large centre experience with non-cardiac surgery in aortic stenosis patients<sup>20</sup> specifically referred for pre-operative clearance, where 18.9% were minor surgeries, and emergency surgery cases were excluded. Similarities between our study and that reported by Agarwal *et al.* include use

of the current definition of SAS, systematic search of echocardiographic and surgical databases, and use of contemporary anaesthesia techniques. On the other hand, our study reduced potential referral bias by selecting SAS patients solely from the combined analysis of echocardiographic and surgical databases. Ours was the first study to systematically include *all* patients undergoing emergency surgery (8.9% of the patients in our study), and with *all* procedures carried out under general anaesthesia, thereby eliminating the confounding effect of minor surgery. These differences likely account for the higher perioperative mortality in our study compared with that reported by Agarwal and colleagues (5.9% vs. 2.1%).

Similar to previous reports, MACE were more common in SAS patients.<sup>1,7–12,20</sup> In order to capture any significant effects of SAS, we included both traditional hard endpoints (death, myocardial infarction, and stroke) and cardiac complications relevant to presence of aortic stenosis (new or worsening heart failure, ventricular tachycardia/fibrillation). The incidence of MACE in our study was lower





than that reported by Kertai *et al.*<sup>11</sup> (18.8% vs. 31%); similarly, the incremental risk of SAS patients over controls was lower (twofold vs. fivefold increased risk), even if our definition of MACE was more inclusive. We believe these differences are related to matching for age and gender in our study (patients with SAS were significantly older than controls in the Kertai study) and for time-related technological advances (Kertai *et al.* included patients undergoing surgery one decade earlier than our study).

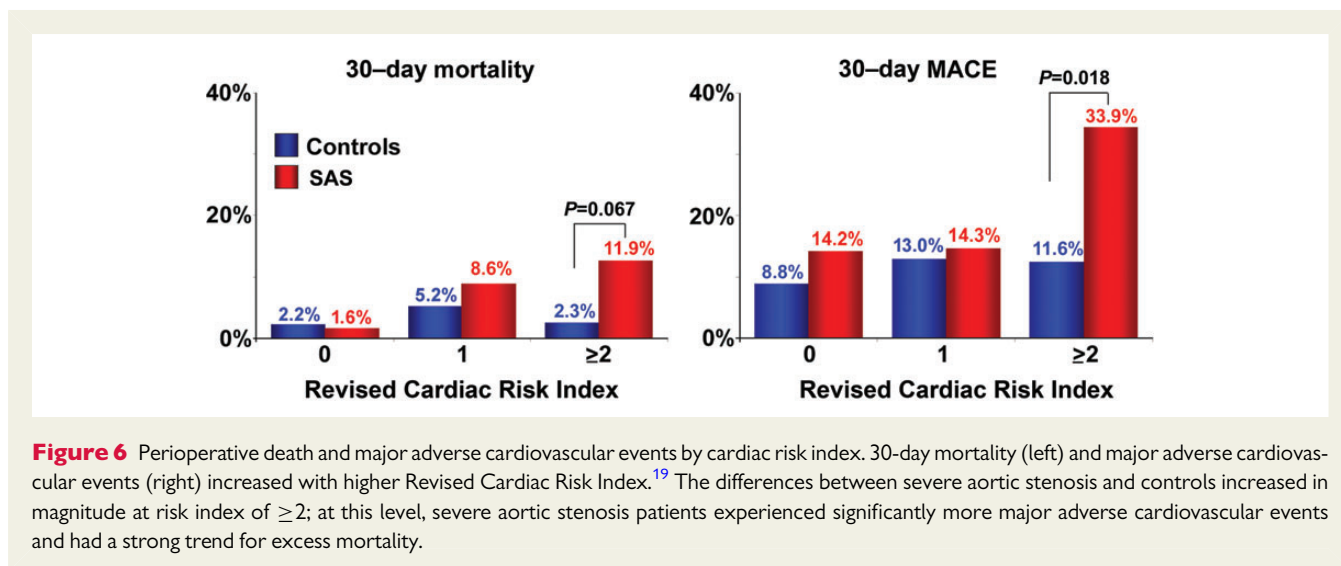
Echocardiographic parameters related to severity of aortic stenosis are known to predict long-term outcomes in SAS.<sup>21,22</sup> In our study, valve area, mean gradient, and peak aortic velocity were all associated in various degrees with perioperative MACE by univariate analysis; none retained prognostic value in multivariate models. For 1-year mortality, among parameters of SAS, an aortic valve area of <1.0 cm<sup>2</sup> was associated with the highest OR of death (OR: 2.7 vs. 1.02 and 1.4 for gradient >40 mmHg and velocity >4 m/s,

respectively). These findings are consistent with the recent emphasis of valve area as the main determinant of long-term outcomes in patients with SAS.<sup>23</sup>

Interestingly, right ventricular systolic pressure as estimated by Doppler echocardiography was a predictor of 30-day MACE and 1-year mortality. Pulmonary hypertension may be associated with increased events due to both a reflection of more advanced left ventricular disease and by increasing the occurrence of right-sided heart failure with its known deleterious consequences.

### Clinical implications

The two most important findings from this study were the substantially lower perioperative death rates in SAS patients compared with historical reports, and that emergency surgery rather than SAS was the principal determinant of perioperative mortality. Our results support a reconsideration of current guidelines of



pre-operative risk assessment and management for non-cardiac surgery in patients with SAS. In the proper clinical settings (cooperation between surgical and anaesthesia teams with input from cardiac anaesthesiologists; Revised Cardiac Risk Index  $\leq 1$ ; asymptomatic status), elective intermediate and high-risk non-cardiac interventions in SAS patients can be undertaken at  $< 5\%$  mortality risk. Under these particular circumstances, the current recommendation of postponing surgical intervention until SAS is corrected seems to be overly conservative, and may delay necessary non-cardiac surgery. On the other hand, symptomatic patients, those with left ventricular dysfunction, or Revised Cardiac Risk Index  $\geq 2$  should be considered for correction of SAS prior to non-cardiac surgery. Emergence of catheter-based aortic valve replacement may simplify management, allowing correction of SAS in high-risk patients before elective non-cardiac surgery.

However, importantly, new or worsening heart failure is increased after surgery in patients with SAS, and may contribute to increased length of hospital stay in patients with SAS. Aggressive perioperative management of heart failure is warranted.

## Limitations

The study was retrospective, and initial selection was based on echocardiographic presence of indexes of SAS. It is possible that we missed other patients with severe SAS undergoing surgical procedures, as echocardiography was not systematically performed prior to surgery. Similarly, presence of SAS was recognized after surgical intervention in 10 patients and, therefore, SAS guided anaesthesia management was not used; however, none of these patients had perioperative death or myocardial infarction. As some patients had follow-up outside of Mayo Clinic, we may have missed some MACE other than mortality (ascertained using the Social Security Death Index) that occurred after hospital dismissal. It may be that sicker patients were more likely to be evaluated with echocardiography, therefore introducing a selection bias and sicker controls. Differences between patients and controls other than presence of SAS may have contributed to differences in outcomes. Six SAS patients underwent aortic valve replacement within 30 days after non-cardiac

surgery. While this is a small number compared with the total population (and none had events within 30 days), it is possible that they may have influenced the results in SAS group. It is not possible to ascertain the role of aortic valve replacement prior to non-cardiac surgery from the current study because cases were selected on the basis of native aortic valve disease at the time of index non-cardiac surgery. Statistical power was limited by the sample size, and some significant effects may have been missed. Finally, these results reflect the experience of a large tertiary centre with greater proportion of complicated patients but also with expertise in complex case management.

## Conclusions

Severe aortic stenosis is associated with increased risk of MACE after non-cardiac surgery. In contemporary practice, perioperative mortality of patients with SAS was lower than previously reported, and was similar to that of patients without SAS. Emergency surgery was the strongest predictor of post-operative death. For SAS patients without symptoms, death and MACE at 30 days were virtually identical to those of controls matched for age, sex, and year of surgery. Our results suggest that current guidelines on perioperative risk assessment and management strategies in patients with SAS should be revisited.

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