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Impact of statin therapy on mid-term mortality after transcatheter aortic valve implantation: a report from a Japanese multicentre registry

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3 **Impact of statin therapy on mid-term mortality after transcatheter aortic valve**
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5 **implantation: a report from a Japanese multicentre registry**
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10 **Short title:** Statin therapy after TAVI
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Abstract

Objectives Data on statin therapy for patients with aortic stenosis after transcatheter aortic valve implantation (TAVI) are limited. The present study aimed to evaluate the impact of statin therapy on mid-term mortality after TAVI.

Design Observational study.

Setting This study evaluated the impact of statin therapy after TAVI using data from a large patient cohort of a Japanese multicentre registry including 14 centres.

Participants The overall cohort included 2588 very elderly patients (84.4±5.2 years); the majority were women (69.3%).

Interventions Patients with severe aortic stenosis who underwent TAVI between 2013 and 2017 were classified into the statin and the non-statin group (1523 and 1065 patients, respectively) based on statin therapy at admission.

Primary and secondary outcome measures After 1:1 propensity score matching, we identified 936 matched pairs and assessed all-cause and cardiovascular mortality between the two groups. The outcomes were defined according to the Valve Academic Research Consortium-2 consensus statement.

Results The median follow-up period was 660 days. Statin therapy was associated with a significant reduction in all-cause mortality (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, $P=0.04$) and cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, $P=0.04$). In the octogenarians, statin therapy was associated with significantly lower all-cause mortality ($P=0.04$); however, the impact in the nonagenarians appeared to be lower ($P=0.25$). Comparing four groups according to previous coronary artery disease (CAD) and statin therapy, there was a significant difference in all-cause mortality ($P<0.01$). Patients who did not receive statin despite previous CAD showed the worst prognosis.

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3 **Conclusions** Statin therapy after TAVI was associated with significant reductions in all-cause
4 and cardiovascular mortality after propensity score matching. Statin therapy after TAVI will
5 be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In
6 addition, statin therapy will be essential for TAVI patients with CAD.
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14 **Keywords:** coronary artery disease, elderly, propensity score matching, statin, transcatheter
15 aortic valve implantation
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23 **Strengths and limitations of this study**

- 24 ● The present study showed that statin therapy after transcatheter aortic valve implantation
25 was associated with significant reductions in all-cause and cardiovascular mortality using
26 data from a large patient cohort of a multicentre registry.
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- 28 ● This was the first study to investigate a difference in the statin effect among
29 octogenarians and nonagenarians.
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- 31 ● The present study clearly demonstrated how the impact of statin therapy differed
32 according to the underlying coronary artery disease.
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- 34 ● Unknown and unmeasurable factors may have confounded the relationship between
35 statin therapy and mortality due to the nature of an observational study.
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- 37 ● We could not assess intolerance in patients eligible for statin treatment but who could not
38 continue treatment due to statin side effects.
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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe aortic stenosis (AS).[1, 2, 3, 4] However, long-term survival after TAVI is not satisfactory, as shown in a meta-analysis including 31 studies; 5-year and 7-year survival rates were 48% and 28%, respectively.[5] TAVI patients are very elderly and have many cardiovascular comorbidities such as coronary artery disease (CAD), stroke, and peripheral artery disease (PAD).[1, 2, 6] Therefore, adjunctive optimal medical therapy is required to improve prognosis after TAVI. Statin therapy is expected to reduce cardiovascular risk and mortality in patients who have undergone TAVI; however, data on statin therapy after TAVI are limited. A report from the Placement of Aortic Transcatheter Valve II (PARTNER II) and Sapien 3 clinical trials or associated registries showed that statin therapy was associated with a lower 2-year mortality rate compared to patients not on statin therapy.[7] However, the study did not demonstrate any differences in the statin effect among octogenarians and nonagenarians, and did not evaluate whether the impact of statin therapy would differ according to the underlying CAD. Therefore, the present study aimed to evaluate the impact of statin therapy on mid-term mortality after TAVI and its association with age and the underlying CAD, using our Japanese multicentre registry data.

METHODS

Study population and design

All patients with severe AS who underwent TAVI at 14 Japanese centres (Keio University Hospital, Teikyo University Hospital, Toyohashi Heart Centre, Nagoya Heart Centre, New Tokyo Hospital, Kokura Memorial Hospital, Saiseikai Yokohama City Eastern Hospital, Sendai Kosei Hospital, Shonan Kamakura General Hospital, Osaka City University Graduate School of Medicine, Kishiwada Tokushukai Hospital, Toyama University Hospital, Tokyo

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3 Bay Urayasu Ichikawa Medical Center, and Ogaki municipal hospital) between 2013 and
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5 2017 were prospectively included in our TAVI registry (Optimized CathEter vAlvular
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7 iNtervention [OCEAN-TAVI] registry).[8, 9, 10] Informed consent was obtained from all
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9 patients, and the institutional review boards of all 14 participating centres approved this study.
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11 Additionally, this study was conducted in accordance with the ethical guidelines of the 1975
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13 Declaration of Helsinki. The OCEAN-TAVI registry was registered with the University
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15 Hospital Medical Information Network Clinical Trial Registry and accepted by the
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17 International Committee of Medical Journal Editors (UMIN-ID: 000020423).
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21 Patients received transcatheter heart valves (THVs) via either the transfemoral,
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23 transapical, or transaortic approach. Sapien XT valves, Sapien 3 valves (Edwards
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25 Lifesciences, Irvine, CA), CoreValves, Evolut R (Medtronic, Minneapolis, MN) were used as
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27 THVs. A total of 2588 patients were treated with TAVI between 2013 and 2017. They were
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29 categorised into two groups according to statin administration at admission for TAVI
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31 procedures (Figure 1). We set the primary endpoint as mid-term all-cause mortality for up to 3
32
33 years. Secondary endpoints included mid-term cardiovascular mortality, mid-term non-
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35 cardiovascular mortality up to 3 years, and 30-day all-cause mortality. We assessed
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37 differences in the endpoints between the two groups. Furthermore, we performed propensity
38
39 score (PS) matching, as described below, and compared the endpoints between the matched
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41 groups. In addition, we categorised the matched cohort into two cohorts; an octogenarian
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43 cohort (80–89 years old) and a nonagenarian cohort (90 years or older), and investigated the
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45 differences by age in the impact of statin on mid-term all-cause mortality. Furthermore, we
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47 classified the overall cohort into four groups according to a history of CAD and statin
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49 treatment at admission and evaluated whether the impact of statin differed according to the
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51 underlying CAD condition.
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3 Clinical outcomes including all-cause mortality and cardiovascular mortality were
4 defined according to the Valve Academic Research Consortium-2 consensus document.[11]
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7 **Statistical analysis**

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10 Continuous variables are expressed as mean±standard deviation (SD), and categorical
11 variables are expressed as percentages. Continuous variables were compared using the
12 Wilcoxon rank-sum test. The chi-squared test was used to compare categorical variables.
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14 Survival curves up to 3 years were presented as Kaplan-Meier curves, and the log-rank test
15 was used for comparison of the statin and non-statin groups. Cox multivariable regression
16 analyses were performed to identify independent correlates for mid-term all-cause mortality.
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20 PS matching[12, 13] was used to account for differences in baseline characteristics. The
21 PS was calculated for each patient using a logistic regression model to predict stratification
22 into the statin group based on the following variables: age; sex; body surface area; smoking;
23 diabetes; hypertension; previous history of CAD, myocardial infarction (MI), percutaneous
24 coronary intervention, coronary artery bypass grafting, stroke, PAD; atrial fibrillation;
25 estimated glomerular filtration rate; haemoglobin level; renin-angiotensin inhibitor treatment
26 at admission; New York Heart Association (NYHA) class 3 or 4; Clinical Frailty Scale[8];
27 and Society of Thoracic Surgeons (STS) risk score. PS matching was performed using 1:1
28 matching without replacement, with the calliper width equal to 0.2 SD of the PS logit. The
29 balance between the statin and non-statin groups in the matched cohort was estimated using
30 absolute standardised difference. Multivariable cox regression analyses were performed to
31 assess the impact of statin on the clinical outcomes. In addition to the PS matching model, we
32 built a multivariable model by inverse probability of treatment weighting (IPTW) using the
33 PS.[14] Time-to-event variables were reported using Kaplan-Meier estimations. All reported
34 *P*-values were two-sided, and a *P*-value <0.05 was considered statistically significant. All
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3 statistical analyses were performed using the R software package (version 3.3.2; R
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5 Development Core Team, Vienna, Austria).
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10 11 **Patient and Public Involvement statement**

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14 Patients were first involved in the research when they underwent TAVI and registered
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16 to the OCEAN-TAVI registry through the web-based data collection system. Research
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18 questions and outcome measures were developed by the OCEAN-TAVI registry
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20 investigators. Patients were informed about the registration. They were asked to assess
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22 the burden of the intervention and time required to participate in the research.
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24 Information of the registry and the study results are available on the website of the
25
26 OCEAN-TAVI registry.
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34 35 **Results**

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37 Among the 2588 patients who underwent TAVI, 1523 and 1065 patients were classified into
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39 the statin and the non-statin group, respectively (Figure 1). The distribution of PS in the statin
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41 and non-statin groups is shown in Supplementary material online, Figure S1. After 1:1 PS
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43 matching, we identified 936 matched pairs of patients with similar PS. The patient
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45 characteristics of the statin and non-statin groups before and after matching are summarised in
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47 Table 1. The overall cohort included very elderly patients (84.4±5.2 years). The majority of
48
49 the cohort was female (69.3%). After PS matching, the two groups were well-balanced in
50
51 terms of pre-procedural patient characteristics and procedural variables. In-hospital all-cause
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53 mortality, acute kidney injury, stroke, and vascular complications did not differ between the
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55 two groups. Post-procedural echocardiography data showed no significant differences
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3 between the two groups (Table 2). The patient characteristics and in-hospital outcomes of the
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5 PS matched and unmatched groups are summarised in Supplementary material online, Tables
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7 S1 and S2. There were several differences between the two groups. The proportion of male
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9 patients was lower in the PS matched group than in the unmatched group (532 [28.4%] vs.
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11 263 [36.7%], $P<0.01$), NYHA Class 3 or 4 was less frequent in the matched group (919
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13 [49.1%] vs. 402 [56.2%], $P<0.01$), the Clinical Frailty Scale was lower in the matched group
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15 [3.8±1.2 vs. 4.2±1.4, $P<0.01$), and the STS risk score was lower in the matched group
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17 (7.7±5.7 vs 9.8±9.2, $P<0.01$). History of the previous CAD was more frequent (750 [40.1%]
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19 vs. 204 [28.5%], $P<0.01$), but previous MI was less frequent (96 [5.1%] vs. 62 [8.7%],
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21 $P<0.01$) in the PS matched group. In-hospital all-cause mortality (43 [2.3%] vs. 27 [3.8%],
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23 $P<0.01$) and bleeding (421 [22.5%] vs. 199 [27.8%], $P<0.01$) were lower in the matched
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25 group than in the unmatched group.

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30 In the overall cohort, the median follow-up period was 660 days. Statin therapy was
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32 associated with significantly lower mid-term all-cause mortality in the PS-matched cohort
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34 (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, $P=0.04$) (Figure
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36 2a), which was consistent with the IPTW model (aHR 0.80, 95% CI 0.65–0.99, $P=0.04$). The
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38 Kaplan-Meier curves relative to the mid-term outcomes additionally showed significant
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40 differences in cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, $P=0.04$) and non-
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42 cardiovascular mortality (aHR 0.86, 95% CI 0.61–1.21, $P=0.39$) between the two groups
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44 (Figure 2b and 2c). There was no significant difference in 30-day all-cause mortality ($P=0.11$)
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46 and a landmark analysis after 30 days showed a significant difference in mid-term all-cause
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48 mortality ($P=0.03$) (Figure 2d).

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53 In the octogenarian cohort (80–89 years old), statin therapy was associated with
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55 significantly lower mid-term all-cause mortality ($P=0.04$) (Figure 3a), but the impact in the
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57 nonagenarian cohort (90 years or older) appeared to be lower ($P=0.25$) (Figure 3b).

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3 Furthermore, comparing the four groups according to previous CAD and statin therapy,
4 there was a significant difference in mid-term all-cause mortality ($P<0.01$) (Figure 4).
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7 Patients who did not receive statin therapy despite a history of previous CAD showed the
8 worst prognosis. Their survival curve diverged from that of the patients without previous
9 CAD or statin after 1 year. In addition, patients with previous CAD and statin therapy seemed
10 to obtain similar risks with those who did not have previous CAD or statin therapy.
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19 DISCUSSION

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21 The present study investigated the impact of statin therapy on mid-term mortality after TAVI
22 using a Japanese multicentre registry. Statin therapy was associated with significantly lower
23 all-cause and cardiovascular mortality. It should be noted that the impact of statin therapy
24 attenuated in the nonagenarians. Furthermore, we demonstrated differences in all-cause
25 mortality according to the history of previous CAD and statin therapy. The present study
26 included the largest patient cohort (936 pairs of patients after PS matching) and the first report
27 to investigate the association of age and a history of previous CAD with the impact of statin.
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37 Few reports have assessed the impact of statin treatment on mortality after TAVI. Peri-
38 Okonny et al. demonstrated that statin therapy was associated with reductions in 2-year all-
39 cause (aHR 0.65, 95% CI 0.49–0.87, $P=0.001$), cardiovascular (aHR 0.66, 95% CI 0.46–0.96,
40 $P=0.030$), and non-cardiovascular mortality (aHR 0.64, 95% CI 0.44–0.99, $P=0.045$)
41 compared with no statin therapy, with a large cohort using PARTNER II and Sapien 3 clinical
42 trials or associated registries (626 pairs of patients after PS matching).[7] Merdler et al.
43 showed that high-intensity statin therapy was associated with a reduction in mortality after
44 TAVI (median follow-up period: 2.5 years) using data of 1238 cases from a single-centre
45 registry (aHR 0.59, 95% CI 0.37–0.96, $P=0.03$).[15] Huded et al. also showed that high-
46 intensity statin therapy was associated with a reduction in all-cause mortality (mean survival:
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3 3.9 years) based on 294 cases (aHR 0.36, 95% CI 0.14–0.90, $P=0.029$).[16] Takagi et al.
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5 reported similar results following a meta-analysis.[17] These results were consistent with our
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7 results.
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10 The mechanism through which statin therapy reduces the risks of all-cause and
11 cardiovascular mortality is thought to be associated with a reduction in ischaemic events.[7,
12 13 15, 16, 17] However, there are limited data relative to statin therapy in octogenarians and
14 nonagenarians, as are data not only on TAVI but also on statin therapy as primary and
15 secondary prevention. The PROspective Study of Pravastatin in the Elderly at Risk trial was
16 the only randomised controlled trial for elderly patients (aged 70–82 years) with a history or
17 risk factors of vascular disease. The study revealed that pravastatin led to a 3-year reduced
18 risk of CAD.[18] Recommendation of statin therapy for very elderly patients varies among
19 the guidelines.[19, 20, 21, 22, 23] Very recently, a few reports supporting statin therapy for
20 very elderly patients have been published. In the Patient and Provider Assessment of Lipid
21 Management Registry, statin therapy appeared to be similarly tolerated by patients older and
22 younger than 75 years.[24] The Cholesterol Treatment Trialists' Collaboration demonstrated
23 that statin therapy as primary and secondary prevention produced significant reductions in
24 major vascular events even in patients older than 75 years.[25] Furthermore, Romas et al.
25 revealed that statin therapy was associated with significant reductions in atherosclerotic CVD
26 and all-cause mortality for patients who were older than 74 years and had diabetes.[26]
27 Interestingly, Giral et al. demonstrated that statin discontinuation in 75-year-old primary
28 prevention patients was associated with a 33% increased risk of cardiovascular events.[27]
29 Our present study was consistent with these reports and indicated that statin therapy would be
30 effective for very elderly and atherosclerotic high-risk patients by reducing cardiovascular
31 events and mortality. Conversely, Romas et al. reported that the benefits of statin therapy
32 disappeared in nonagenarians,[26] as observed in our nonagenarian cohort.
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3 The statin effect generally appears after 1 year compared with placebo.[7, 28] Patients
4 with a history of previous CAD who did not receive statin therapy appeared to have higher
5 mortality rates after 1 year in the present study. In addition, our analysis the combining
6 history of previous CAD and statin therapy implied that TAVI patients with the previous
7 CAD might be able to achieve a similar reduction in mortality risk as those patients who had
8 no previous CAD or statin treatment.
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16
17 The present study had some limitations. First, this is an observational study, and
18 unknown and unmeasurable factors may have confounded the relationship between statin
19 therapy and mortality. However, a multicentre approach enabled us to accumulate a relatively
20 large number of patients and we used PS matching analysis and the IPTW model to confirm
21 the robustness of the results. Second, a generalisation of the present results may be slightly
22 limited due to the differences between the matched and unmatched group, but might be
23 plausible given the results of the IPTW model. Third, information on the type and doses of
24 statin therapy was not obtained. Usage of ezetimibe or proprotein convertase subtilisin/kexin
25 type 9 inhibitor was not recorded in this study. Fourth, we assessed statin use only on
26 admission and there was a possibility that statin therapy might have changed at discharge or
27 during follow-up. Finally, we could not assess intolerance in patients eligible for statin
28 treatment but who could not continue treatment due to statin side effects such as
29 rhabdomyolysis. Further studies, including a randomised controlled trial, on statin therapy
30 following TAVI are warranted to resolve these limitations.
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49 In conclusion, using data from the large multicentre registry, statin therapy after TAVI
50 was associated with significant reductions in mid-term all-cause and cardiovascular mortality.
51 Statin therapy after TAVI will be beneficial even in octogenarians, but the benefits may
52 disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients
53 with CAD.
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Conflict of interest

Drs. Yamamoto, Tada, Naganuma, Shirai, Mizutani, Tabata, Ueno, and Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Drs. Shimizu, Takagi and Hayashida are clinical proctors of Edwards Lifesciences. Dr. Inohara received a research grant from Boston Scientific. Dr. Kohsaka received lecture fees and research grants from Pfizer Japan, Bayer, Daiichi Sankyo, and Bristol-Myers Squibb. The remaining authors have nothing to disclose.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Authors' contributions

Conception or design of the work: Fumiaki Yashima, Shinichi Shirai, Toru Naganuma, Kazuki Mizutani, Motoharu Araki, Minoru Tabata, and Futoshi Yamanaka.

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Figure legends

Figure 1

Flowchart of patient selection for the present study.

OCEAN; Optimized CathEter vAlvular iNtervention; TAVI, transcatheter aortic valve implantation.

Figure 2

Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort. *a, b, c*:

Kaplan-Meier curves for mid-term all-cause mortality (*a*), CV mortality (*b*), and non-CV

mortality (*c*) in the matched cohort. *d*: Kaplan-Meier curve for 30-day all-cause mortality and

mid-term all-cause mortality with the landmark analysis from 30 days in the matched cohort.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Figure 3

Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.

Figure 4

Kaplan-Meier curve for all-cause mortality according to previous coronary artery disease and statin therapy in the overall cohort.

CAD, coronary artery disease.

Table 1

Patient characteristics before and after propensity score matching

	Before matching			After matching		
	Statin (+) <i>n</i> =1065	Statin (-) <i>n</i> =1523	Standardised difference	Statin (+) <i>n</i> =936	Statin (-) <i>n</i> =936	Standardised difference
Preprocedural variables						
Age, years	84.1±5.0	84.6±5.3	0.01	84.2±5.0	84.3±5.2	0.01
Men, <i>n</i> (%)	322 (30.2%)	473 (31.1%)	0.02	277 (29.6%)	255 (27.2%)	0.05
Body surface area, m ²	1.44±0.17	1.42±0.17	0.13	1.44±0.17	1.43±0.17	0.07

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4	NYHA class 3 or 4, <i>n</i> (%)	518 (48.6%)	803 (52.7%)	0.08	462 (49.4%)	457 (48.8%)	0.01
5							
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8	Clinical Frailty Scale	3.8±1.2	4.1±1.3	0.23	3.8±1.2	3.8±1.2	0.04
9							
10							
11	Diabetes mellitus, <i>n</i> (%)	264 (24.8%)	291 (19.1%)	0.14	207 (22.1%)	195 (20.8%)	0.03
12							
13							
14							
15	Smoking, <i>n</i> (%)	212 (19.9%)	260 (17.1%)	0.07	169 (18.1%)	160 (17.1%)	0.02
16							
17							
18							
19	Hypertension, <i>n</i> (%)	861 (80.9%)	1129 (74.1%)	0.16	744 (79.5%)	753 (80.5%)	0.02
20							
21							
22	Chronic kidney disease, <i>n</i> (%)	755 (70.9%)	1054 (69.2%)	0.04	651 (69.6%)	640 (68.4%)	0.03
23							
24							
25							
26	Atrial fibrillation, <i>n</i> (%)	195 (18.3%)	354 (23.2%)	0.12	181 (19.3%)	183 (19.6%)	0.01
27							
28							
29							
30	Coronary artery disease, <i>n</i> (%)	507 (47.6%)	447 (29.4%)	0.38	378 (40.4%)	372 (39.7%)	0.01
31							
32							
33	Previous myocardial infarction, <i>n</i> (%)	108 (10.1%)	50 (3.3%)	0.28	48 (5.1%)	48 (5.1%)	<0.01
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4	Previous percutaneous coronary intervention, <i>n</i>						
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8	(%)	342 (32.1%)	284 (18.7%)	0.31	249 (26.6%)	238 (25.4%)	0.03
9							
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11	Previous coronary artery bypass grafting, <i>n</i> (%)	112 (10.5%)	57 (3.7%)	0.27	60 (6.4%)	57 (6.1%)	0.01
12							
13							
14							
15	Peripheral artery disease, <i>n</i> (%)	161 (15.1%)	216 (14.2%)	0.03	136 (14.5%)	128 (13.7%)	0.02
16							
17							
18							
19	Previous stroke, <i>n</i> (%)	127 (11.9%)	174 (11.4%)	0.02	116 (12.4%)	102 (10.9%)	0.05
20							
21							
22	STS risk score	7.7±6.0	8.6±7.5	0.13	7.7±6.1	7.7±5.3	<0.01
23							
24							
25							
26	Renin-angiotensin inhibitor, <i>n</i> (%)	639 (60.0%)	748 (49.1%)	0.22	540 (57.7%)	544 (58.1%)	0.01
27							
28							
29							
30	β blocker, <i>n</i> (%)	384 (36.1%)	496 (32.6%)	0.07	334 (35.7%)	303 (32.4%)	0.07
31							
32							
33	eGFR, mL/min/1.73 m ²	51.7±18.5	51.1±20.1	0.03	52.3±18.6	51.7±19.6	0.03
34							
35							
36							
37	Haemoglobin, g/dL	11.4±1.7	11.1±1.7	0.17	11.4±1.7	11.2±1.6	0.15
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Preprocedural echocardiographic data						
Aortic valve area, cm ²	0.64±0.17	0.63±0.17	0.04	0.63±0.17	0.63±0.16	<0.01
Indexed aortic valve area, cm ² /m ²	0.44±0.12	0.44±0.12	<0.01	0.44±0.12	0.45±0.12	0.03
Mean aortic gradient, mmHg	50.0±18.1	51.0±18.4	0.05	51.0±18.2	50.8±18.2	0.01
Peak velocity, m/sec	4.5±0.8	4.6±0.8	0.07	4.6±0.8	4.6±0.8	0.02
Ejection fraction, %	59.2±12.7	59.2±12.6	<0.01	59.6±12.4	59.7±12.0	0.01
Severe aortic regurgitation, <i>n</i> (%)	12 (0.8%)	4 (0.4%)	0.05	7 (0.8%)	4 (0.4%)	0.04
Severe mitral regurgitation, <i>n</i> (%)	21 (1.4%)	12 (1.1%)	0.02	12 (1.3%)	6 (0.6%)	0.07
Pulmonary hypertension, <i>n</i> (%)	40 (3.8%)	62 (4.1%)	0.02	37 (4.0%)	33 (3.5%)	0.02
Preprocedural CT data						

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Annular area, mm ²	395.5±70.7	400.7±71.0	0.07	395.9±70.2	396.5±69.1	0.01
Procedural variables						
Transfemoral approach, <i>n</i> (%)	873 (82.0%)	1294 (85.0%)	0.08	770 (82.3%)	784 (83.8%)	0.04
Local anaesthesia, <i>n</i> (%)	799 (75.0%)	1179 (77.4%)	0.06	714 (76.3%)	734 (78.4%)	0.05
Contrast volume, mL	115.8±59.1	115.4±58	0.01	118.8±60.0	113.5±57.1	0.09
Fluoroscopy time, min	21.7±12.5	21.1±10.0	0.05	21.9±12.6	21.0±10.0	0.08
Procedure time, min	81.6±45.8	80.3±45.4	0.03	81.6±43.0	80.4±43.6	0.03

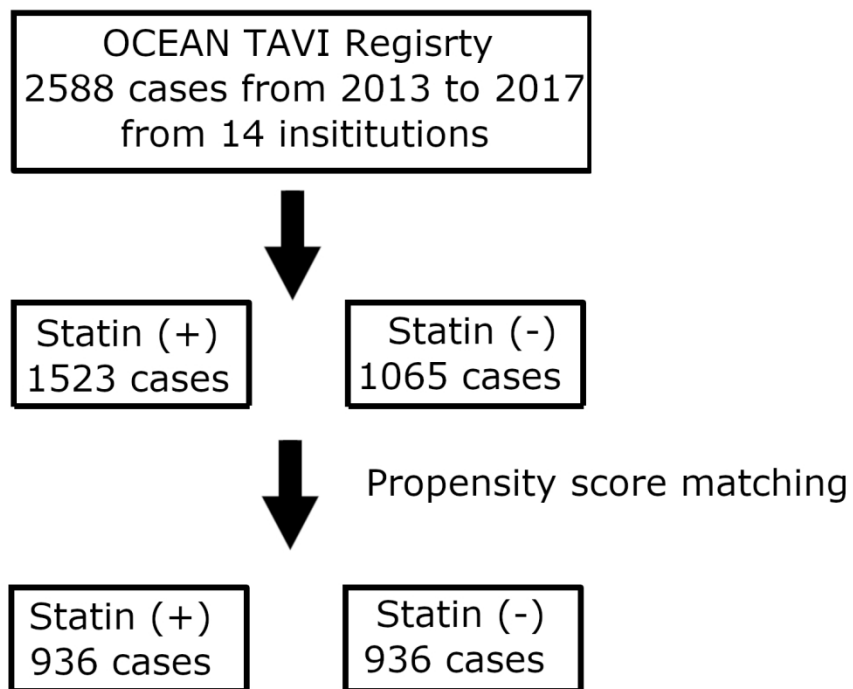
CT, computed tomography; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Table 2

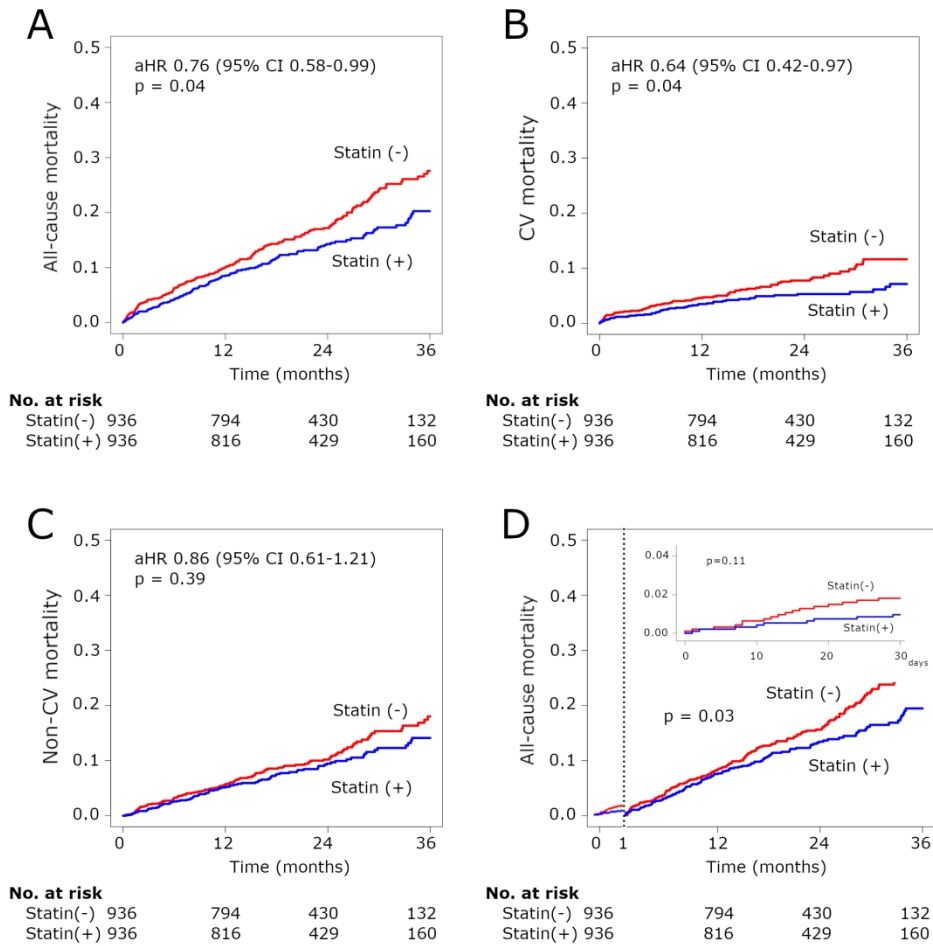
In-hospital outcomes before and after propensity score matching

	Before matching				After matching			
			Standardised				Standardised	
	Statin (+)	Statin (-)	<i>P</i> value	difference	Statin (+)	Statin (-)	<i>P</i> value	difference
	<i>n</i> =1065	<i>n</i> =1523			<i>n</i> =936	<i>n</i> =936		
All-cause mortality, <i>n</i> (%)	27 (2.5%)	43 (2.8%)	0.66	0.02	20 (2.1%)	23 (2.5%)	0.64	0.02
Acute kidney injury, <i>n</i> (%)	111 (10.4%)	178 (11.7%)	0.31	0.04	96 (10.3%)	105 (11.2%)	0.50	0.03
Stroke, <i>n</i> (%)	27 (2.5%)	34 (2.2%)	0.62	0.02	24 (2.6%)	19 (2.0%)	0.44	0.04
Vascular complication, <i>n</i> (%)	105 (9.9%)	128 (8.4%)	0.21	0.05	90 (9.6%)	78 (8.3%)	0.33	0.05

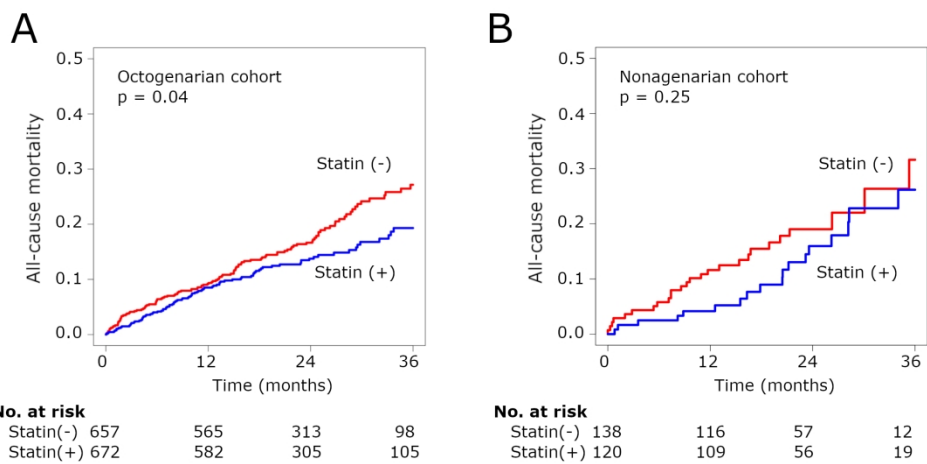
Postprocedural echocardiographic data									
Effective orifice area, cm ²	1.67±0.45	1.69±0.45	0.53	0.03	1.68±0.44	1.66±0.43	0.34	0.04	
Indexed effective orifice area, cm ² /m ²	1.17±0.32	1.20±0.31	0.02	0.10	1.18±0.32	1.18±0.30	0.99	<0.01	
Mean aortic gradient, mmHg	11.0±4.4	10.6±4.7	0.08	0.07	11.0±4.4	11.0±4.9	0.92	<0.01	
Peak velocity, m/sec	2.3±0.4	2.2±0.5	0.10	0.07	2.3±0.5	2.3±0.5	0.98	<0.01	
Moderate or severe aortic regurgitation, <i>n</i> (%)	18 (1.7%)	31 (2.1%)	0.51	0.03	17 (1.8%)	20 (2.2%)	0.61	0.02	
Moderate or severe mitral regurgitation, <i>n</i> (%)	59 (5.6%)	100 (6.6%)	0.27	0.04	45 (4.8%)	51 (5.5%)	0.52	0.03	



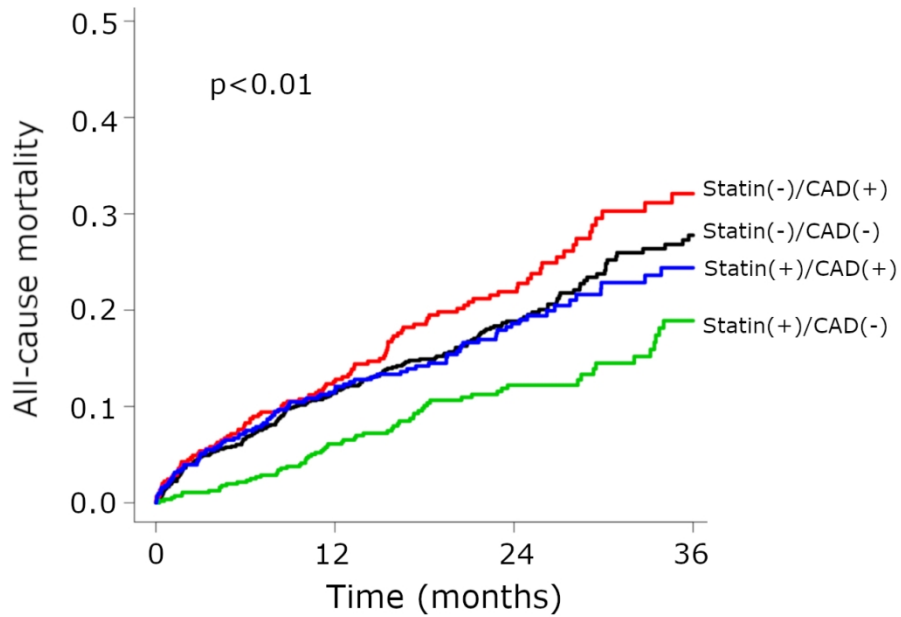
Flowchart of patient selection for the present study.



Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort.



Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.

**No. at risk**

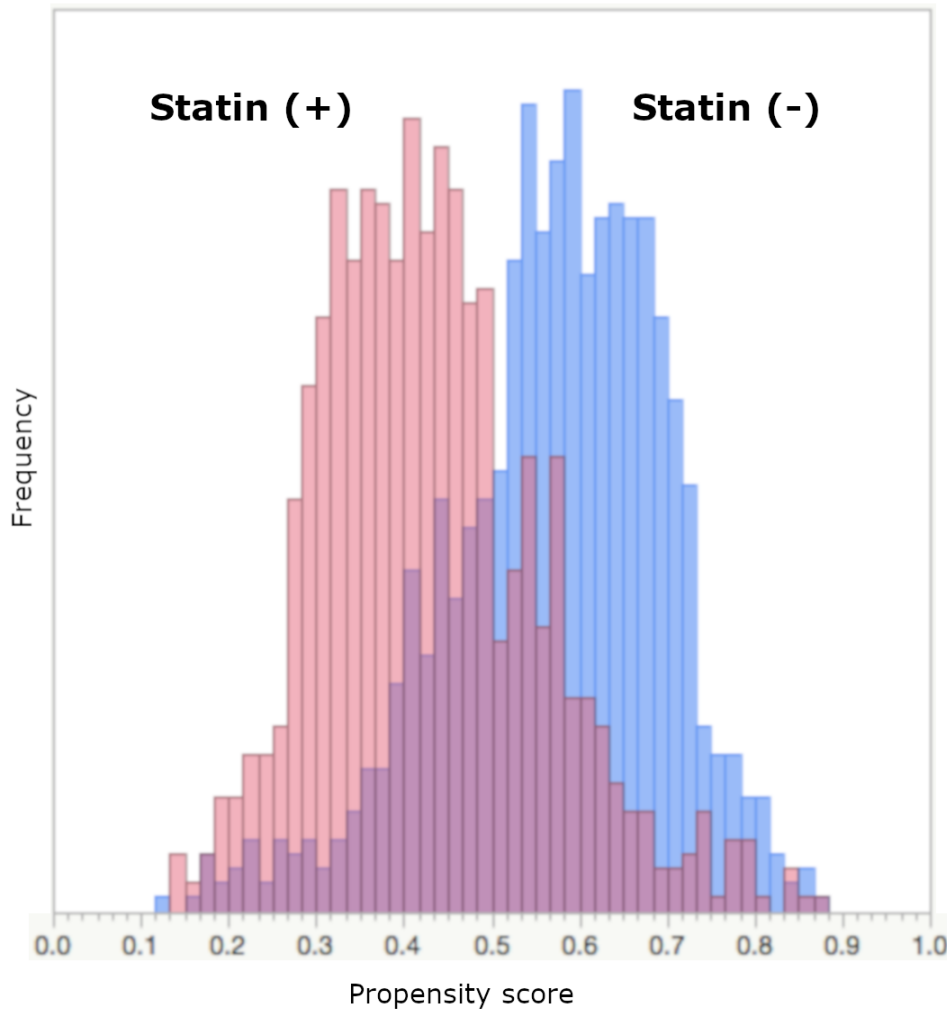
Statin(-)/CAD(+)	447	368	201	59
Statin(-)/CAD(-)	1076	895	456	142
Statin(+)/CAD(+)	507	428	231	87
Statin(+)/CAD(-)	558	497	256	93

Kaplan-Meier curve for all-cause mortality according to previous coronary artery disease and statin therapy in the overall cohort.

Supplementary material online

Supplementary Figure S1

Distribution of propensity scores between statin and non-statin groups in the overall cohort.



Supplementary Table S1

Patient characteristics of the propensity score matched and unmatched groups

	Unmatched		<i>P</i> -value
	Matched group <i>n</i> =1872	group <i>n</i> =716	
Preprocedural variables			
Age, years	84.2±5.1	84.6±5.4	0.08
Male, <i>n</i> (%)	532 (28.4%)	263 (36.7%)	<0.01
Body surface area, m ²	1.43±0.17	1.42±0.17	0.16
NYHA class 3 or 4, <i>n</i> (%)	919 (49.1%)	402 (56.2%)	<0.01
Clinical Frailty Scale	3.8±1.2	4.2±1.4	<0.01
Smoking, <i>n</i> (%)	364 (19.4%)	160 (22.4%)	0.10
Diabetes mellitus, <i>n</i> (%)	402 (21.5%)	153 (21.4%)	0.95
Hypertension, <i>n</i> (%)	1497 (80.0%)	493 (68.9%)	<0.01
Chronic kidney disease, <i>n</i> (%)	1291 (69.0%)	518 (72.4%)	0.09
Atrial fibrillation, <i>n</i> (%)	364 (19.4%)	185 (25.8%)	<0.01

Coronary artery disease, <i>n</i> (%)	750 (40.1%)	204 (28.5%)	<0.01
Previous myocardial infarction, <i>n</i> (%)	96 (5.1%)	62 (8.7%)	<0.01
Previous percutaneous coronary intervention, <i>n</i> (%)	487 (26.0%)	139 (19.4%)	<0.01
Previous coronary artery bypass grafting, <i>n</i> (%)	117 (6.3%)	52 (7.3%)	0.36
Peripheral artery disease, <i>n</i> (%)	264 (14.1%)	113 (15.8%)	0.28
Previous stroke, <i>n</i> (%)	9 (0.5%)	3 (0.4%)	0.98
STS risk score	7.7±5.7	9.8±9.2	<0.01
Renin-angiotensin inhibitor, <i>n</i> (%)	1084 (57.9%)	303 (42.3%)	<0.01
Beta blocker, <i>n</i> (%)	637 (34.0%)	243 (33.9%)	0.97
eGFR, mL/min/1.73 m ²	52.0±19.1	49.7±20.1	<0.01
Haemoglobin, g/dL	11.3±1.6	11.2±1.7	0.16
Procedural variables			
Transfemoral approach, <i>n</i> (%)	1554 (83.0%)	613 (85.6%)	0.11

Local anaesthesia, <i>n</i> (%)	1448 (77.4%)	530 (74.0%)	0.08
Contrast volume, mL	116.1±58.6	114.1±58.2	0.43
Fluoroscopy time, min	21.4±11.4	21.2±10.5	0.66
Procedure time, min	81.0±43.3	80.3±50.9	0.72

CT, computed tomography; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

1
2
3 **Supplementary Table S2**
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5 In-hospital outcomes of the propensity score-matched and -unmatched groups
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	Matched group	Unmatched group	<i>P</i>-value
	<i>n</i>=1872	<i>n</i>=716	
All-cause mortality, <i>n</i> (%)	43 (2.3%)	27 (3.8%)	<0.01
Acute kidney injury, <i>n</i> (%)	201 (10.7%)	88 (12.3%)	0.27
Bleeding, <i>n</i> (%)	421 (22.5%)	199 (27.8%)	<0.01
Stroke, <i>n</i> (%)	43 (2.3%)	18 (2.5%)	0.75
Vascular complication, <i>n</i> (%)	168 (9.0%)	65 (9.1%)	0.93

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure2-4
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Statin therapy for patients with aortic stenosis who underwent transcatheter aortic valve implantation: a report from a Japanese multicentre registry

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3 **Statin therapy for patients with aortic stenosis who underwent transcatheter aortic**
4 **valve implantation: a report from a Japanese multicentre registry**
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10 **Short title:** Statin therapy for TAVI patients
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Abstract

Objectives Data on statin for patients with aortic stenosis (AS) who underwent transcatheter aortic valve implantation (TAVI) are limited. The present study aimed to evaluate the impact of statin on mid-term mortality of TAVI patients.

Design Observational study.

Setting This study included AS patients who underwent TAVI from a Japanese multicentre registry.

Participants The overall cohort included 2588 patients (84.4±5.2 years); the majority were women (69.3%). The Society of Thoracic Surgeons risk score was 6.55% (interquartile range [IQR] 4.55-9.50%), Euro II score was 3.74% (IQR 2.34-6.02%), and Clinical Frailty Scale was 3.9±1.2.

Interventions We classified the patients based on statin at admission and identified 936 matched pairs after propensity score matching.

Primary and secondary outcome measures The outcomes were all-cause and cardiovascular mortality.

Results The median follow-up was 660 days. Statin at admission was associated with a significant reduction in all-cause mortality (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, $P=0.04$) and cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, $P=0.04$). In the octogenarians, statin was associated with significantly lower all-cause mortality (aHR 0.87, 95% CI 0.75-0.99, $P=0.04$); however, the impact in the nonagenarians appeared to be lower (aHR 0.84, 95% CI 0.62-1.13, $P=0.25$). Comparing four groups according to previous coronary artery disease (CAD) and statin, there was a significant difference in all-cause mortality and patients who did not receive statin despite previous CAD showed the worst prognosis (aHR 1.33, 95% CI 1.12-1.57 [patients who received statin without previous CAD as a reference], $P<0.01$).

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2
3 **Conclusions** Statin for TAVI patients will be beneficial even in octogenarians, but the
4
5 benefits may disappear in nonagenarians. In addition, statin will be essential for TAVI
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7 patients with CAD. Further researches are warranted to confirm and generalise our findings,
8
9 since this study has inherent limitations of the observational study and included only Japanese
10
11 patients.
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17 **Keywords:** coronary artery disease, elderly, propensity score matching, statin, transcatheter
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19 aortic valve implantation
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25 **Strengths and limitations of this study**

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27 ● The present study includes the largest number of patients with aortic stenosis who
28
29 underwent transcatheter aortic valve implantation (TAVI), assessing the impact of statin
30
31 therapy on mid-term all-cause and cardiovascular mortality.
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33
- 34 ● This was the first study to investigate a difference in the statin effect among
35
36 octogenarians and nonagenarians, and to evaluate how the impact of statin therapy
37
38 differed according to the underlying coronary artery disease.
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40
- 41 ● All-cause and cardiovascular mortality were analysed using propensity score matching
42
43 and the Cox proportional hazards regression model.
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- 46 ● Unknown and unmeasurable factors may have confounded the relationship between
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48 statin therapy at admission and mortality due to the nature of an observational study.
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- 51 ● We could not assess intolerance in patients eligible for statin treatment but who could not
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53 continue treatment due to statin side effects.
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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe aortic stenosis (AS).[1, 2, 3, 4] However, long-term survival after TAVI is not satisfactory, as shown in a meta-analysis including 31 studies; 5-year and 7-year survival rates were 48% and 28%, respectively.[5] TAVI patients are very elderly and have many cardiovascular comorbidities such as coronary artery disease (CAD), stroke, and peripheral artery disease (PAD).[1, 2, 6] Therefore, adjunctive optimal medical therapy is required to improve prognosis after TAVI. Statin therapy is expected to reduce cardiovascular risk and mortality in patients who have undergone TAVI; however, data on statin therapy for TAVI patients are limited. A report from the Placement of Aortic Transcatheter Valve II (PARTNER II) and Sapien 3 clinical trials or associated registries showed that statin therapy was associated with a lower 2-year mortality rate compared to patients not on statin therapy.[7] However, the study did not demonstrate any differences in the statin effect among octogenarians and nonagenarians, and did not evaluate whether the impact of statin therapy would differ according to the underlying CAD. Therefore, the present study aimed to evaluate the impact of statin therapy on mid-term mortality of TAVI patients and its association with age or the underlying CAD, using our Japanese multicentre registry data.

METHODS

Study population and design

All patients with severe AS who underwent TAVI at 14 Japanese centres (Keio University Hospital, Teikyo University Hospital, Toyohashi Heart Centre, Nagoya Heart Centre, New Tokyo Hospital, Kokura Memorial Hospital, Saiseikai Yokohama City Eastern Hospital, Sendai Kosei Hospital, Shonan Kamakura General Hospital, Osaka City University Graduate School of Medicine, Kishiwada Tokushukai Hospital, Toyama University Hospital, Tokyo

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3 Bay Urayasu Ichikawa Medical Center, and Ogaki municipal hospital) between 2013 and
4
5 2017 were prospectively included in our TAVI registry (Optimized Catheter Valvular
6
7 Intervention [OCEAN-TAVI] registry).[8, 9, 10] Informed consent was obtained from all
8
9 patients, and the institutional review boards of all 14 participating centres approved this study.
10
11 Additionally, this study was conducted in accordance with the ethical guidelines of the 1975
12
13 Declaration of Helsinki. The OCEAN-TAVI registry was registered with the University
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15 Hospital Medical Information Network Clinical Trial Registry and accepted by the
16
17 International Committee of Medical Journal Editors (UMIN-ID: 000020423).
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21 Patients received transcatheter heart valves (THVs) via either the transfemoral,
22
23 transapical, or transaortic approach. Sapien XT valves, Sapien 3 valves (Edwards
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25 Lifesciences, Irvine, CA), CoreValves, Evolut R (Medtronic, Minneapolis, MN) were used as
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27 THVs. A total of 2588 patients were treated with TAVI between 2013 and 2017. They were
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29 categorised into two groups according to statin administration at admission for TAVI
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31 procedures (Figure 1). We set the primary endpoint as mid-term all-cause mortality for up to 3
32
33 years. Secondary endpoints included mid-term cardiovascular mortality, mid-term non-
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35 cardiovascular mortality up to 3 years, and 30-day all-cause mortality.
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40 We performed propensity score (PS) matching, as described below, and compared the
41
42 endpoints between the two groups in the matched cohort. In addition, we categorised the
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44 matched cohort into two cohorts; an octogenarian cohort (80–89 years old) and a
45
46 nonagenarian cohort (90 years or older), and investigated the differences by age in the impact
47
48 of statin on mid-term all-cause mortality. Furthermore, we classified the overall cohort into
49
50 four groups according to a history of CAD and statin treatment at admission and evaluated
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52 whether the impact of statin differed according to the underlying CAD condition. We also
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54 explored predictors of mid-term all-cause mortality in the overall cohort using multivariate
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56 analysis.
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3 Clinical outcomes including all-cause mortality and cardiovascular mortality were
4 defined according to the Valve Academic Research Consortium-2 consensus document.[11]
5

6 7 **Statistical analysis**

8
9 Continuous variables are expressed as mean±standard deviation (SD), and categorical
10 variables are expressed as percentages. Continuous variables were compared using the
11 Wilcoxon rank-sum test. The chi-squared test was used to compare categorical variables.
12
13 Survival curves up to 3 years were presented as Kaplan-Meier curves, and the log-rank test
14 was used for comparison of the statin and non-statin groups. The Cox proportional hazards
15 regression analyses were performed to identify independent correlates for mid-term all-cause
16 mortality.
17

18
19 PS matching[12, 13] was used to account for differences in baseline characteristics. The
20 PS was calculated for each patient using a logistic regression model to predict stratification
21 into the statin group based on the following variables: age; sex; body surface area; smoking;
22 diabetes; hypertension; previous history of CAD, myocardial infarction (MI), percutaneous
23 coronary intervention, coronary artery bypass grafting, stroke, PAD; atrial fibrillation;
24 estimated glomerular filtration rate; haemoglobin level; renin-angiotensin inhibitor treatment
25 at admission; New York Heart Association (NYHA) class 3 or 4; Clinical Frailty Scale[8];
26 and Society of Thoracic Surgeons (STS) risk score. PS matching was performed using 1:1
27 matching without replacement, with the calliper width equal to 0.2 SD of the PS logit. The
28 balance between the statin and non-statin groups in the matched cohort was estimated using
29 absolute standardised difference. The Cox proportional hazards analyses were performed to
30 assess the impact of statin on the clinical outcomes. In addition to the PS matching model, we
31 built a multivariable model by inverse probability of treatment weighting (IPTW) using the
32 PS.[14] All reported *P*-values were two-sided, and a *P*-value <0.05 was considered
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3 statistically significant. All statistical analyses were performed using the R software package
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5 (version 3.3.2; R Development Core Team, Vienna, Austria).
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10 11 **Patient and Public Involvement statement**

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14 Patients were first involved in the research when they underwent TAVI and registered to the
15
16 OCEAN-TAVI registry through the web-based data collection system. Research questions
17
18 and outcome measures were developed by the OCEAN-TAVI registry investigators. Patients
19
20 were informed about the registration. They were asked to assess the burden of the intervention
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22 and time required to participate in the research. Information of the registry and the study
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24 results are available on the website of the OCEAN-TAVI registry.
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31 32 **RESULTS**

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34 Among the 2588 patients who underwent TAVI, 1523 and 1065 patients were classified into
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36 the statin and the non-statin group, respectively (Figure 1). The distribution of PS in the statin
37
38 and non-statin groups is shown in Supplementary material online, Figure S1. After 1:1 PS
39
40 matching, we identified 936 matched pairs of patients with similar PS. The patient
41
42 characteristics of the statin and non-statin groups before and after matching are summarised in
43
44 Table 1. The overall cohort included very elderly patients (84.4±5.2 years). The majority of
45
46 the cohort was female (69.3%). The Society of Thoracic Surgeons risk score was 6.55%
47
48 (interquartile range [IQR] 4.55-9.50%), Euro II score was 3.74% (IQR 2.34-6.02%), and
49
50 Clinical Frailty Scale was 3.9±1.2.
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55 After PS matching, the two groups were well-balanced in terms of pre-procedural patient
56
57 characteristics and procedural variables. In-hospital all-cause mortality, acute kidney injury,
58
59 stroke, and vascular complications did not differ between the two groups. Post-procedural
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3 echocardiography data showed no significant differences between the two groups (Table 2).
4
5 The patient characteristics and in-hospital outcomes of the PS matched and unmatched groups
6
7 are summarised in Supplementary material online, Tables S1 and S2. There were several
8
9 differences between the two groups. The proportion of male patients was lower in the PS
10
11 matched group than in the unmatched group (532 [28.4%] vs. 263 [36.7%], $P<0.01$), NYHA
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13 Class 3 or 4 was less frequent in the matched group (919 [49.1%] vs. 402 [56.2%], $P<0.01$),
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15 the Clinical Frailty Scale was lower in the matched group (3.8 ± 1.2 vs. 4.2 ± 1.4 , $P<0.01$), and
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17 the STS risk score was lower in the matched group (7.7 ± 5.7 vs 9.8 ± 9.2 , $P<0.01$). History of
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19 the previous CAD was more frequent (750 [40.1%] vs. 204 [28.5%], $P<0.01$), but previous
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21 MI was less frequent (96 [5.1%] vs. 62 [8.7%], $P<0.01$) in the PS matched group. In-hospital
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23 all-cause mortality (43 [2.3%] vs. 27 [3.8%], $P<0.01$) and bleeding (421 [22.5%] vs. 199
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25 [27.8%], $P<0.01$) were lower in the matched group than in the unmatched group.
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31 In the overall cohort, the median follow-up period was 660 days. Statin therapy was
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33 associated with significantly lower mid-term all-cause mortality in the PS-matched cohort
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35 (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, $P=0.04$) (Figure
36
37 2a), which was consistent with the IPTW model (aHR 0.80, 95% CI 0.65–0.99, $P=0.04$). The
38
39 Kaplan-Meier curves relative to the mid-term outcomes additionally showed significant
40
41 differences in cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, $P=0.04$) and non-
42
43 cardiovascular mortality (aHR 0.86, 95% CI 0.61–1.21, $P=0.39$) between the two groups
44
45 (Figure 2b and 2c). There was no significant difference in 30-day all-cause mortality (aHR
46
47 0.73, 95% CI 0.47–1.08, $P=0.11$) and a landmark analysis after 30 days showed a significant
48
49 difference in mid-term all-cause mortality (aHR 0.88, 95% CI 0.78–0.99, $P=0.03$) (Figure 2d).
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53
54 In the octogenarian cohort (80–89 years old), statin therapy was associated with
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56 significantly lower mid-term all-cause mortality (aHR 0.87, 95% CI 0.75–0.99, $P=0.04$)
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3 (Figure 3a), but the impact in the nonagenarian cohort (90 years or older) appeared to be
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5 lower (aHR 0.84, 95% CI 0.62-1.13, $P=0.25$) (Figure 3b). P for interaction was 0.90.

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8 Furthermore, comparing the four groups according to previous CAD and statin therapy,
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10 there was a significant difference in mid-term all-cause mortality ($P<0.01$) (Figure 4).

11
12 Patients who did not receive statin therapy despite a history of previous CAD showed the
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14 worst prognosis (aHR 1.33, 95% CI 1.12-1.57 [patients who received statin without previous
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16 CAD as a reference]). Their survival curve diverged from that of the patients without previous
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18 CAD or statin after 1 year. In addition, patients with previous CAD and statin therapy (aHR
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20 1.04, 95% CI 0.87-1.23) seemed to obtain similar risks with those who did not have previous
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22 CAD or statin therapy (aHR 1.11, 95% CI 0.96-1.27 [patients who received statin without
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24 previous CAD as a reference]).

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28 The results of the univariate and multivariate Cox proportional hazards regression
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30 analyses were shown in Table 3. Statin therapy at admission was independently associated
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32 with lower all-cause mortality (aHR 0.86, 95% CI 0.77-0.95), $P<0.01$).

37 DISCUSSION

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40 The present study investigated the impact of statin therapy on mid-term mortality after TAVI
41
42 using a Japanese multicentre registry. Statin therapy at admission was associated with
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44 significantly lower all-cause and cardiovascular mortality. It should be noted that the impact
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46 of statin therapy attenuated in the nonagenarians. Furthermore, we demonstrated differences
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48 in all-cause mortality according to the history of previous CAD and statin therapy. The
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50 present study included the largest patient cohort (936 pairs of patients after PS matching) and
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52 the first report to investigate the association of age and a history of previous CAD with the
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54 impact of statin.
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3 Few reports have assessed the impact of statin treatment on mortality after TAVI. Peri-
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5 Okonny et al. demonstrated that statin therapy was associated with reductions in 2-year all-
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7 cause (aHR 0.65, 95% CI 0.49–0.87, $P=0.001$), cardiovascular (aHR 0.66, 95% CI 0.46–0.96,
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9 $P=0.030$), and non-cardiovascular mortality (aHR 0.64, 95% CI 0.44–0.99, $P=0.045$)
10
11 compared with no statin therapy, with a large cohort using PARTNER II and Sapien 3 clinical
12
13 trials or associated registries (626 pairs of patients after PS matching).[7] Merdler et al.
14
15 showed that high-intensity statin therapy was associated with a reduction in mortality after
16
17 TAVI (median follow-up period: 2.5 years) using data of 1238 cases from a single-centre
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19 registry (aHR 0.59, 95% CI 0.37–0.96, $P=0.03$).[15] Huded et al. also showed that high-
20
21 intensity statin therapy was associated with a reduction in all-cause mortality (mean survival:
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23 3.9 years) based on 294 cases (aHR 0.36, 95% CI 0.14–0.90, $P=0.029$).[16] Takagi et al.
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25 reported similar results following a meta-analysis.[17] These results were consistent with our
26
27 results.
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33 The mechanism through which statin therapy reduces the risks of all-cause and
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35 cardiovascular mortality is thought to be associated with a reduction in ischaemic events.[7,
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37 15, 16, 17] However, there are limited data relative to statin therapy in octogenarians and
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39 nonagenarians, as are data not only on TAVI but also on statin therapy as primary and
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41 secondary prevention. The PROspective Study of Pravastatin in the Elderly at Risk trial was
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43 the only randomised controlled trial for elderly patients (aged 70–82 years) with a history or
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45 risk factors of vascular disease. The study revealed that pravastatin led to a 3-year reduced
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47 risk of CAD.[18] Recommendation of statin therapy for very elderly patients varies among
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49 the guidelines.[19, 20, 21, 22, 23] Very recently, a few reports supporting statin therapy for
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51 very elderly patients have been published. In the Patient and Provider Assessment of Lipid
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53 Management Registry, statin therapy appeared to be similarly tolerated by patients older and
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55 younger than 75 years.[24] The Cholesterol Treatment Trialists' Collaboration demonstrated
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3 that statin therapy as primary and secondary prevention produced significant reductions in
4 major vascular events even in patients older than 75 years.[25] Furthermore, Romas et al.
5 revealed that statin therapy was associated with significant reductions in atherosclerotic
6 cardiovascular events and all-cause mortality for patients who were older than 74 years and
7 had diabetes.[26] Interestingly, Giral et al. demonstrated that statin discontinuation in 75-
8 year-old primary prevention patients was associated with a 33% increased risk of
9 cardiovascular events.[27] Our present study was consistent with these reports and indicated
10 that statin therapy would be effective for very elderly and atherosclerotic high-risk patients by
11 reducing cardiovascular events and mortality. Conversely, Romas et al. reported that the
12 benefits of statin therapy disappeared in nonagenarians,[26] as observed in our nonagenarian
13 cohort. However, P for interaction among the octogenarian and nonagenarian cohorts in the
14 present study was not significant, and the sizes of the cohorts and confounding regarding
15 prescribing statin to nonagenarians with CAD might skew the results.

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33 The statin effect generally appears after 1 year compared with placebo.[7, 28] Patients
34 with a history of previous CAD who did not receive statin therapy appeared to have higher
35 mortality rates after 1 year in the present study. In addition, our analysis the combining
36 history of previous CAD and statin therapy implied that TAVI patients with the previous
37 CAD might be able to achieve a similar reduction in mortality risk as those patients who had
38 no previous CAD or statin treatment.

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The present study had some limitations. First, this is an observational study, and unknown and unmeasurable factors may have confounded the relationship between statin therapy and mortality. However, a multicentre approach enabled us to accumulate a relatively large number of patients and we used PS matching analysis, the IPTW model, and the Cox proportional hazards regression model to confirm the robustness of the results. Second, a generalisation of the present results may be slightly limited due to the differences between the

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3 matched and unmatched group as it might be plausible given the results of the IPTW model.
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5 In addition, generalising our findings outside Japan also requires attention since this study
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7 included only Japanese patients. Third, information on the type and doses of statin therapy
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9 was not obtained. Usage of ezetimibe or proprotein convertase subtilisin/kexin type 9
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11 inhibitor was not recorded in this study. Fourth, we assessed statin use only on admission and
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13 there was a possibility that statin therapy might have changed at discharge or during follow-
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15 up. The duration of statin administration and the timing to start prescribing statin were not
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17 captured in the present study. Finally, we could not assess intolerance in patients eligible for
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19 statin treatment but who could not continue treatment due to statin side effects such as
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21 rhabdomyolysis. Further studies, including a randomised controlled trial, on statin therapy
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23 following TAVI are warranted to resolve these limitations.
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28 In conclusion, using data from the large multicentre registry, statin therapy at admission
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30 of TAVI was associated with significant reductions in mid-term all-cause and cardiovascular
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32 mortality. Statin therapy prior TAVI will be beneficial even in octogenarians, but the benefits
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34 may disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients
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36 with CAD. Further researches are warranted to confirm and generalise our findings, since the
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38 present study has several inherent limitations of the observational study and included only
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40 Japanese patients.
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Conflict of interest

Drs. Yamamoto, Tada, Naganuma, Shirai, Mizutani, Tabata, Ueno, and Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Drs. Shimizu, Takagi and Hayashida are clinical proctors of Edwards Lifesciences. Dr. Inohara received a research grant from Boston Scientific. Dr. Kohsaka received lecture fees and research grants from Pfizer Japan, Bayer, Daiichi Sankyo, and Bristol-Myers Squibb. The remaining authors have nothing to disclose.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Authors' contributions

Conception or design of the work: Fumiaki Yashima, Shinichi Shirai, Toru Naganuma, Kazuki Mizutani, Motoharu Araki, Minoru Tabata, and Futoshi Yamanaka.

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5 Data analysis and interpretation: Masahiko Hara, Taku Inohara, Kensuke Takagi, Hiroshi
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7 Ueno, and Norio Tada.
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10 Drafting the article: Fumiaki Yashima and Taku Inohara.
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12 Critical revision of the article: Masanori Yamamoto, Yusuke Watanabe, Kentaro Hayashida.
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14 Final approval of the version to be published: all authors.
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3 **Figure legends**
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8 **Figure 1**
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10 Flowchart of patient selection for the present study.

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12 OCEAN; Optimized CathEter vAlvular iNtervention; TAVI, transcatheter aortic valve
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14 implantation.
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19 **Figure 2**
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21 Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort. *a, b, c*:

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23 Kaplan-Meier curves for mid-term all-cause mortality (*a*), CV mortality (*b*), and non-CV

24
25 mortality (*c*) in the matched cohort. *d*: Kaplan-Meier curve for 30-day all-cause mortality and
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27 mid-term all-cause mortality with the landmark analysis from 30 days in the matched cohort.
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30 CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
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35 **Figure 3**
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37 Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.
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42 **Figure 4**
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44 Kaplan-Meier curve for all-cause mortality according to previous coronary artery disease and
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46 statin therapy in the overall cohort.
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49 CAD, coronary artery disease.
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Table 1

Patient characteristics before and after propensity score matching

	Before matching			After matching		
	Statin (+) <i>n</i> =1065	Statin (-) <i>n</i> =1523	Standardised difference	Statin (+) <i>n</i> =936	Statin (-) <i>n</i> =936	Standardised difference
Preprocedural variables						
Age, years	84.1±5.0	84.6±5.3	0.01	84.2±5.0	84.3±5.2	0.01
Men, <i>n</i> (%)	322 (30.2%)	473 (31.1%)	0.02	277 (29.6%)	255 (27.2%)	0.05
Body surface area, m ²	1.44±0.17	1.42±0.17	0.13	1.44±0.17	1.43±0.17	0.07

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4	NYHA class 3 or 4, <i>n</i> (%)	518 (48.6%)	803 (52.7%)	0.08	462 (49.4%)	457 (48.8%)	0.01
5							
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8	Clinical Frailty Scale	3.8±1.2	4.1±1.3	0.23	3.8±1.2	3.8±1.2	0.04
9							
10							
11	Diabetes mellitus, <i>n</i> (%)	264 (24.8%)	291 (19.1%)	0.14	207 (22.1%)	195 (20.8%)	0.03
12							
13							
14							
15	Smoking, <i>n</i> (%)	212 (19.9%)	260 (17.1%)	0.07	169 (18.1%)	160 (17.1%)	0.02
16							
17							
18							
19	Hypertension, <i>n</i> (%)	861 (80.9%)	1129 (74.1%)	0.16	744 (79.5%)	753 (80.5%)	0.02
20							
21							
22	Chronic kidney disease, <i>n</i> (%)	755 (70.9%)	1054 (69.2%)	0.04	651 (69.6%)	640 (68.4%)	0.03
23							
24							
25							
26	Atrial fibrillation, <i>n</i> (%)	195 (18.3%)	354 (23.2%)	0.12	181 (19.3%)	183 (19.6%)	0.01
27							
28							
29							
30	Coronary artery disease, <i>n</i> (%)	507 (47.6%)	447 (29.4%)	0.38	378 (40.4%)	372 (39.7%)	0.01
31							
32							
33	Previous myocardial infarction, <i>n</i> (%)	108 (10.1%)	50 (3.3%)	0.28	48 (5.1%)	48 (5.1%)	<0.01
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4	Previous percutaneous coronary intervention, <i>n</i>						
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7	(%)	342 (32.1%)	284 (18.7%)	0.31	249 (26.6%)	238 (25.4%)	0.03
8							
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11	Previous coronary artery bypass grafting, <i>n</i> (%)	112 (10.5%)	57 (3.7%)	0.27	60 (6.4%)	57 (6.1%)	0.01
12							
13							
14							
15	Peripheral artery disease, <i>n</i> (%)	161 (15.1%)	216 (14.2%)	0.03	136 (14.5%)	128 (13.7%)	0.02
16							
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19	Previous stroke, <i>n</i> (%)	127 (11.9%)	174 (11.4%)	0.02	116 (12.4%)	102 (10.9%)	0.05
20							
21							
22	STS risk score	7.7±6.0	8.6±7.5	0.13	7.7±6.1	7.7±5.3	<0.01
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26	Renin-angiotensin inhibitor, <i>n</i> (%)	639 (60.0%)	748 (49.1%)	0.22	540 (57.7%)	544 (58.1%)	0.01
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30	β blocker, <i>n</i> (%)	384 (36.1%)	496 (32.6%)	0.07	334 (35.7%)	303 (32.4%)	0.07
31							
32							
33	eGFR, mL/min/1.73 m ²	51.7±18.5	51.1±20.1	0.03	52.3±18.6	51.7±19.6	0.03
34							
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36							
37	Haemoglobin, g/dL	11.4±1.7	11.1±1.7	0.17	11.4±1.7	11.2±1.6	0.15
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LDL-c, mg/dL	104.3±28.9	94.2±28.0	0.35	105.9±28.2	94.8±27.8	0.4
HDL-c, mg/dL	52.9±15.8	53.6±15.0	0.04	53.5±16.3	54.3±15.0	0.05
Triglyceride, mg/dL	106.8±57.6	110.5±53.0	0.07	109.6±60.9	110.2±53.2	0.01
Preprocedural echocardiographic data						
Aortic valve area, cm ²	0.64±0.17	0.63±0.17	0.04	0.63±0.17	0.63±0.16	<0.01
Indexed aortic valve area, cm ² /m ²	0.44±0.12	0.44±0.12	<0.01	0.44±0.12	0.45±0.12	0.03
Mean aortic gradient, mmHg	50.0±18.1	51.0±18.4	0.05	51.0±18.2	50.8±18.2	0.01
Peak velocity, m/sec	4.5±0.8	4.6±0.8	0.07	4.6±0.8	4.6±0.8	0.02
Ejection fraction, %	59.2±12.7	59.2±12.6	<0.01	59.6±12.4	59.7±12.0	0.01
Severe aortic regurgitation, <i>n</i> (%)	12 (0.8%)	4 (0.4%)	0.05	7 (0.8%)	4 (0.4%)	0.04

Severe mitral regurgitation, <i>n</i> (%)	21 (1.4%)	12 (1.1%)	0.02	12 (1.3%)	6 (0.6%)	0.07
Pulmonary hypertension, <i>n</i> (%)	40 (3.8%)	62 (4.1%)	0.02	37 (4.0%)	33 (3.5%)	0.02
Preprocedural CT data						
Annular area, mm ²	395.5±70.7	400.7±71.0	0.07	395.9±70.2	396.5±69.1	0.01
Procedural variables						
Transfemoral approach, <i>n</i> (%)	873 (82.0%)	1294 (85.0%)	0.08	770 (82.3%)	784 (83.8%)	0.04
Local anaesthesia, <i>n</i> (%)	799 (75.0%)	1179 (77.4%)	0.06	714 (76.3%)	734 (78.4%)	0.05
Contrast volume, mL	115.8±59.1	115.4±58.0	0.01	118.8±60.0	113.5±57.1	0.09
Fluoroscopy time, min	21.7±12.5	21.1±10.0	0.05	21.9±12.6	21.0±10.0	0.08
Procedure time, min	81.6±45.8	80.3±45.4	0.03	81.6±43.0	80.4±43.6	0.03

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3 CT, computed tomography; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density
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5 lipoprotein cholesterol; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.
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Table 2

In-hospital outcomes before and after propensity score matching

	Before matching				After matching			
			Standardised				Standardised	
	Statin (+)	Statin (-)	<i>P</i> value	difference	Statin (+)	Statin (-)	<i>P</i> value	difference
	<i>n</i> =1065	<i>n</i> =1523			<i>n</i> =936	<i>n</i> =936		
All-cause mortality, <i>n</i> (%)	27 (2.5%)	43 (2.8%)	0.66	0.02	20 (2.1%)	23 (2.5%)	0.64	0.02
Acute kidney injury, <i>n</i> (%)	111 (10.4%)	178 (11.7%)	0.31	0.04	96 (10.3%)	105 (11.2%)	0.50	0.03
Stroke, <i>n</i> (%)	27 (2.5%)	34 (2.2%)	0.62	0.02	24 (2.6%)	19 (2.0%)	0.44	0.04
Vascular complication, <i>n</i> (%)	105 (9.9%)	128 (8.4%)	0.21	0.05	90 (9.6%)	78 (8.3%)	0.33	0.05

Postprocedural echocardiographic data									
Effective orifice area, cm ²	1.67±0.45	1.69±0.45	0.53	0.03	1.68±0.44	1.66±0.43	0.34	0.04	
Indexed effective orifice area, cm ² /m ²	1.17±0.32	1.20±0.31	0.02	0.10	1.18±0.32	1.18±0.30	0.99	<0.01	
Mean aortic gradient, mmHg	11.0±4.4	10.6±4.7	0.08	0.07	11.0±4.4	11.0±4.9	0.92	<0.01	
Peak velocity, m/sec	2.3±0.4	2.2±0.5	0.10	0.07	2.3±0.5	2.3±0.5	0.98	<0.01	
Moderate or severe aortic regurgitation, <i>n</i> (%)	18 (1.7%)	31 (2.1%)	0.51	0.03	17 (1.8%)	20 (2.2%)	0.61	0.02	
Moderate or severe mitral regurgitation, <i>n</i> (%)	59 (5.6%)	100 (6.6%)	0.27	0.04	45 (4.8%)	51 (5.5%)	0.52	0.03	

Table 3

The univariate and multivariate Cox proportional regression analyses of the all-cause mortality in the overall cohort.

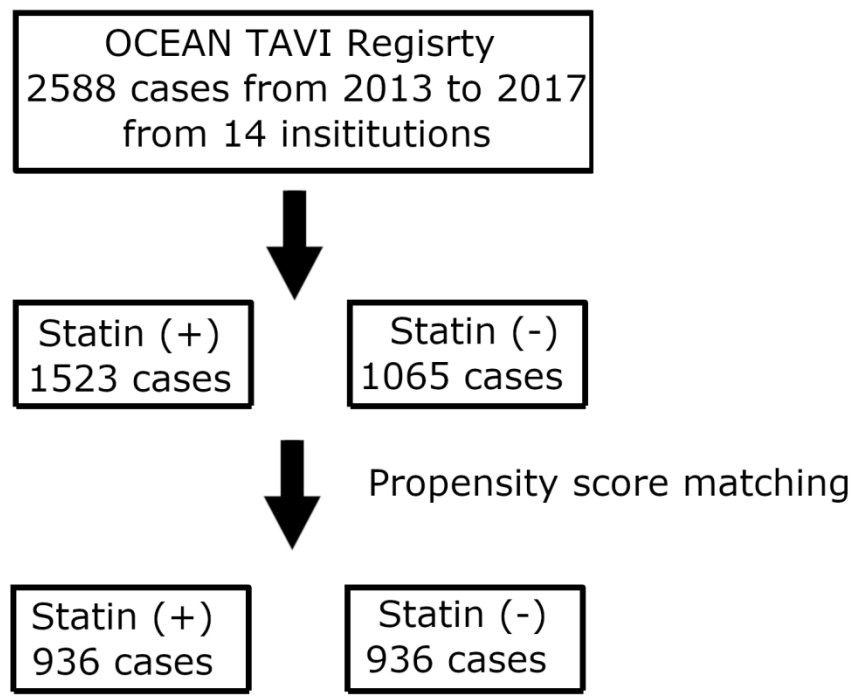
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	adjusted HR (95% CI)	P value
Men	1.30 (1.18-1.42)	<0.01	1.40 (1.25-1.57)	<0.01
Age	1.01 (0.99-1.03)	0.13	0.99 (0.97-1.01)	0.31
Clinical Frailty Scale 1-3	0.77 (0.70-0.85)	<0.01	0.81 (0.73-0.90)	<0.01
NYHA class 3 or 4	1.33 (1.21-1.46)	<0.01	1.18 (1.07-1.31)	<0.01
Smoking	1.20 (1.08-1.33)	<0.01	1.02 (0.90-1.15)	0.74
Diabetes mellitus	1.12 (1.00-1.24)	0.04	0.99 (0.89-1.11)	0.87
Hypertension	0.97 (0.88-1.09)	0.63	0.97 (0.86-1.08)	0.54
Previous myocardial infarction	1.32 (1.13-1.52)	<0.01	1.14 (0.96-1.35)	0.14

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4	Previous coronary artery bypass grafting	1.21 (1.02-1.40)	0.03	1.05 (0.88-1.24)	0.60
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7	Peripheral artery disease	1.35 (1.21-1.50)	<0.01	1.08 (0.95-1.22)	0.24
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10	Previous stroke	1.14 (0.99-1.30)	0.06	1.04 (0.90-1.19)	0.62
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13	Atrial fibrillation	1.19 (1.07-1.32)	<0.01	1.00 (0.90-1.12)	0.98
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16	STS risk score	1.04 (1.03-1.04)	<0.01	1.02 (1.01-1.03)	<0.01
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20	eGFR, mL/min/1.73 m ²	0.98 (0.98-0.99)	<0.01	0.99 (0.99-1.00)	<0.01
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23	Haemoglobin, g/dL	0.83 (0.78-0.88)	<0.01	0.85 (0.80-0.91)	<0.01
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26	Medication at admission				
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29	Statin	0.84 (0.77-0.93)	<0.01	0.86 (0.77-0.95)	<0.01
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32	Renin-angiotensin inhibitor	0.92 (0.84-1.01)	0.08	0.88 (0.80-0.97)	0.01
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35	β blocker	1.09 (0.99-1.20)	0.08	1.06 (0.96-1.16)	0.28
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38	Preprocedural echocardiographic data				
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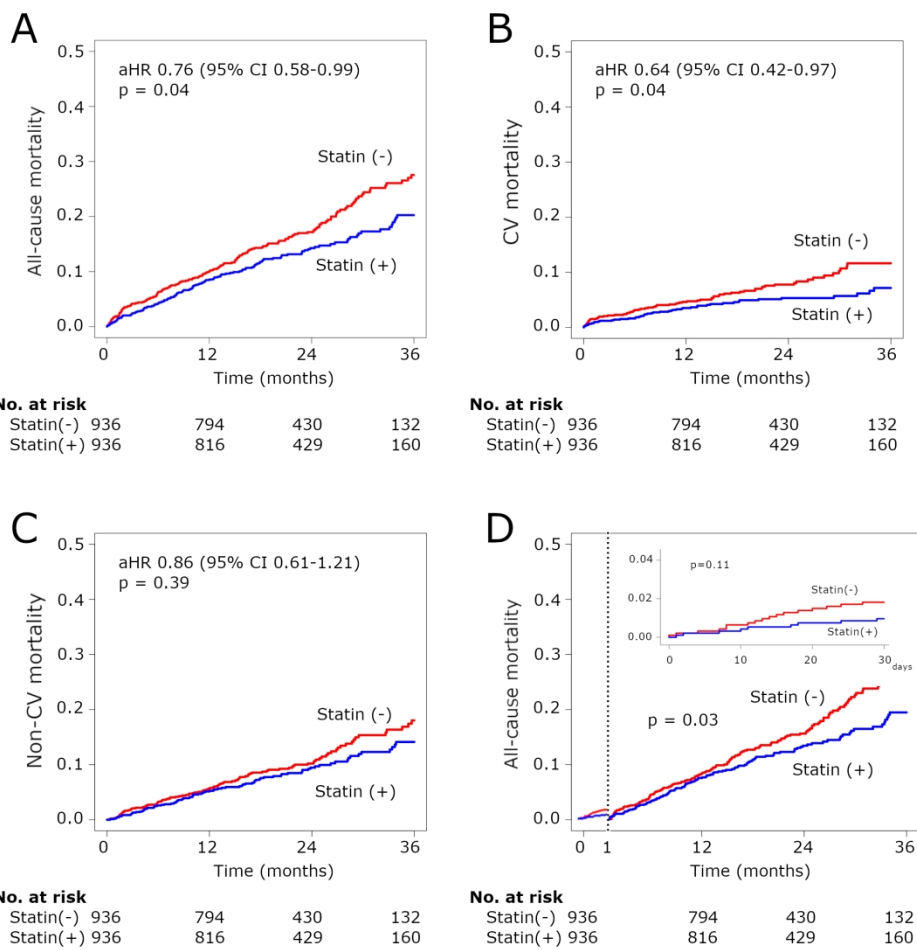
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4	Aortic valve area, cm ² /m ²	1.29 (0.76-2.20)	0.35	1.23 (0.63-2.38)	0.54
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7	Peak velocity, mmHg	0.75 (0.67-0.85)	<0.01	0.76 (0.66-0.88)	<0.01
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10	Ejection fraction, %	0.99 (0.98-0.99)	0.03	1.01 (1.00-1.02)	0.02
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13	Pulmonary hypertension	1.50 (1.25-1.78)	<0.01	1.27 (1.05-1.53)	0.01
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16	Severe aortic regurgitation	0.56 (0.13-1.19)	0.16	0.57 (0.21-1.51)	0.26
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19	Severe mitral regurgitation	1.34 (0.93-1.81)	0.11	0.99 (0.70-1.40)	0.96
20					
21					
22	Procedural variables				
23					
24					
25	Transfemoral approach	0.81 (0.73-0.91)	<0.01	0.87 (0.77-0.98)	0.03
26					
27					
28	Local anaesthesia	0.89 (0.79-1.01)	0.07	0.92 (0.81-1.05)	0.22
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33 CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; STS, Society of
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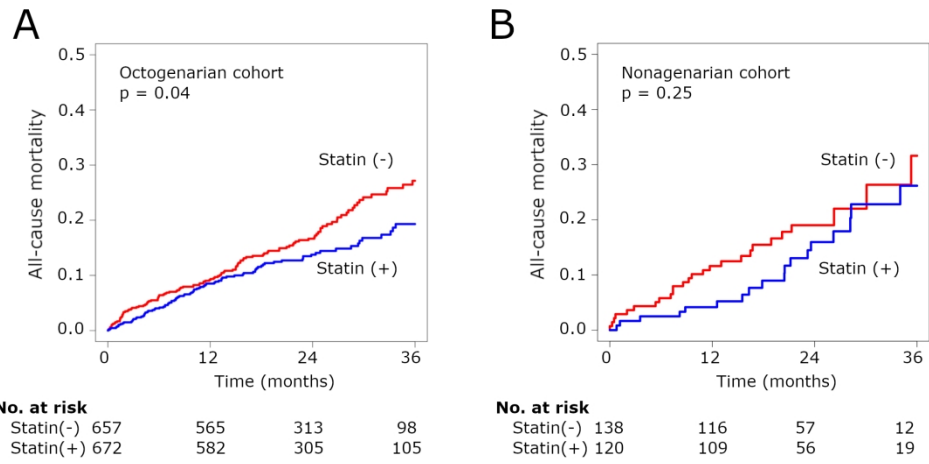


Flowchart of patient selection for the present study.

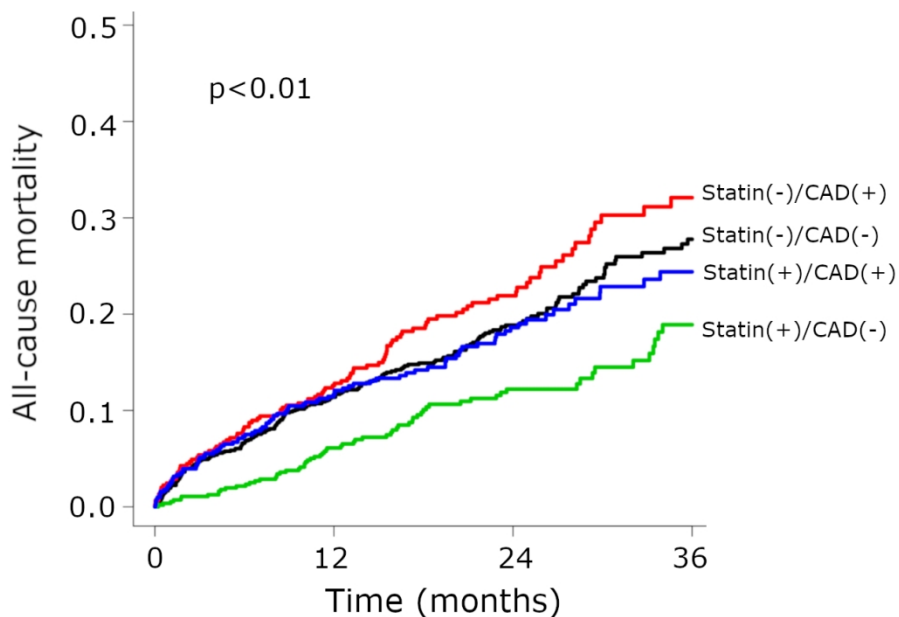


Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort.

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Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.



No. at risk				
Statin(-)/CAD(+)	447	368	201	59
Statin(-)/CAD(-)	1076	895	456	142
Statin(+)/CAD(+)	507	428	231	87
Statin(+)/CAD(-)	558	497	256	93

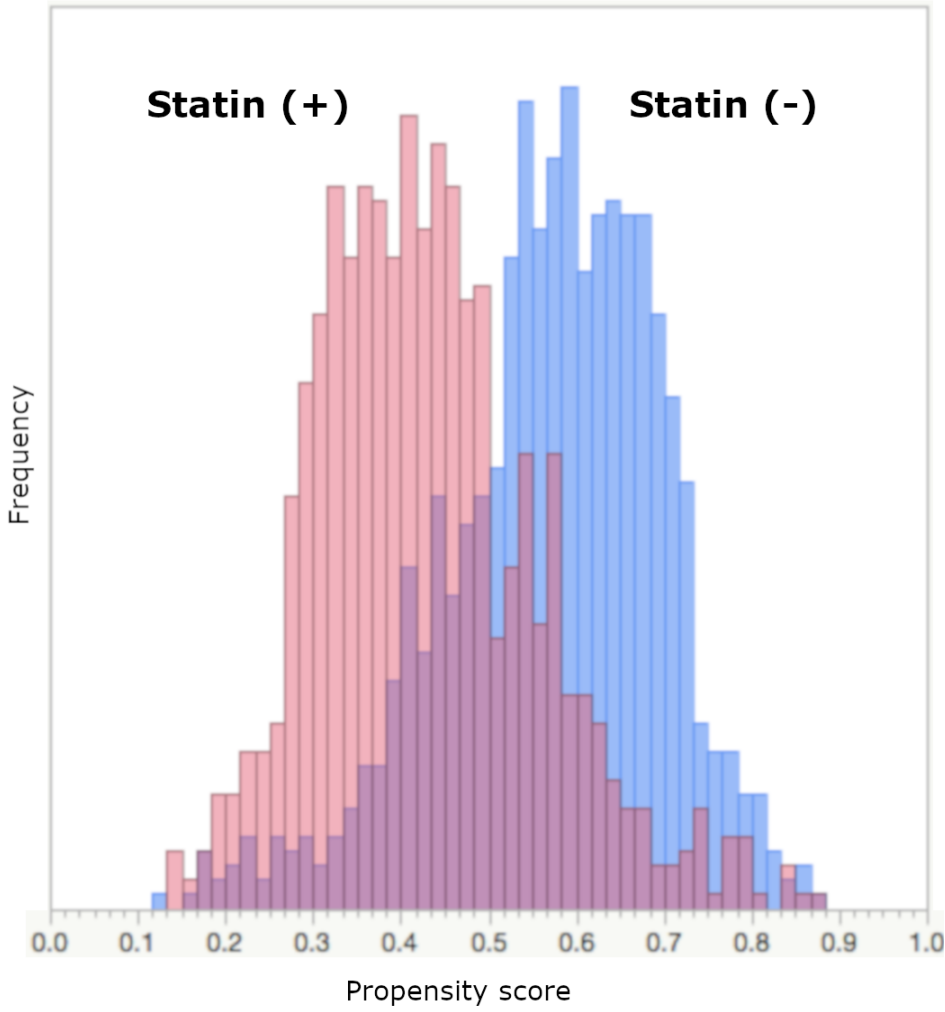
Kaplan-Meier curve for all-cause mortality according to previous coronary artery disease and statin therapy in the overall cohort.

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Supplementary material online

Supplementary Figure S1

Distribution of propensity scores between statin and non-statin groups in the overall cohort.



Supplementary Table S1

Patient characteristics of the propensity score matched and unmatched groups

	Unmatched		<i>P</i> -value
	Matched group <i>n</i> =1872	group <i>n</i> =716	
Preprocedural variables			
Age, years	84.2±5.1	84.6±5.4	0.08
Male, <i>n</i> (%)	532 (28.4%)	263 (36.7%)	<0.01
Body surface area, m ²	1.43±0.17	1.42±0.17	0.16
NYHA class 3 or 4, <i>n</i> (%)	919 (49.1%)	402 (56.2%)	<0.01
Clinical Frailty Scale	3.8±1.2	4.2±1.4	<0.01
Smoking, <i>n</i> (%)	364 (19.4%)	160 (22.4%)	0.10
Diabetes mellitus, <i>n</i> (%)	402 (21.5%)	153 (21.4%)	0.95
Hypertension, <i>n</i> (%)	1497 (80.0%)	493 (68.9%)	<0.01
Chronic kidney disease, <i>n</i> (%)	1291 (69.0%)	518 (72.4%)	0.09
Atrial fibrillation, <i>n</i> (%)	364 (19.4%)	185 (25.8%)	<0.01

Coronary artery disease, <i>n</i> (%)	750 (40.1%)	204 (28.5%)	<0.01
Previous myocardial infarction, <i>n</i> (%)	96 (5.1%)	62 (8.7%)	<0.01
Previous percutaneous coronary intervention, <i>n</i> (%)	487 (26.0%)	139 (19.4%)	<0.01
Previous coronary artery bypass grafting, <i>n</i> (%)	117 (6.3%)	52 (7.3%)	0.36
Peripheral artery disease, <i>n</i> (%)	264 (14.1%)	113 (15.8%)	0.28
Previous stroke, <i>n</i> (%)	9 (0.5%)	3 (0.4%)	0.98
STS risk score	7.7±5.7	9.8±9.2	<0.01
Renin-angiotensin inhibitor, <i>n</i> (%)	1084 (57.9%)	303 (42.3%)	<0.01
Beta blocker, <i>n</i> (%)	637 (34.0%)	243 (33.9%)	0.97
eGFR, mL/min/1.73 m ²	52.0±19.1	49.7±20.1	<0.01
Haemoglobin, g/dL	11.3±1.6	11.2±1.7	0.16
Procedural variables			
Transfemoral approach, <i>n</i> (%)	1554 (83.0%)	613 (85.6%)	0.11

Local anaesthesia, <i>n</i> (%)	1448 (77.4%)	530 (74.0%)	0.08
Contrast volume, mL	116.1±58.6	114.1±58.2	0.43
Fluoroscopy time, min	21.4±11.4	21.2±10.5	0.66
Procedure time, min	81.0±43.3	80.3±50.9	0.72

CT, computed tomography; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

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3 **Supplementary Table S2**
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5 In-hospital outcomes of the propensity score-matched and -unmatched groups
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	Matched group	Unmatched group	P-value
	n=1872	n=716	
All-cause mortality, <i>n</i> (%)	43 (2.3%)	27 (3.8%)	<0.01
Acute kidney injury, <i>n</i> (%)	201 (10.7%)	88 (12.3%)	0.27
Bleeding, <i>n</i> (%)	421 (22.5%)	199 (27.8%)	<0.01
Stroke, <i>n</i> (%)	43 (2.3%)	18 (2.5%)	0.75
Vascular complication, <i>n</i> (%)	168 (9.0%)	65 (9.1%)	0.93

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure2-4
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Statin therapy for patients with aortic stenosis who underwent transcatheter aortic valve implantation: a report from a Japanese multicentre registry

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical management
Keywords:	Cardiology < INTERNAL MEDICINE, Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Coronary heart disease < CARDIOLOGY

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3 **Statin therapy for patients with aortic stenosis who underwent transcatheter aortic**
4 **valve implantation: a report from a Japanese multicentre registry**
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10 **Short title:** Statin therapy for TAVI patients
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Abstract

Objectives Data on statin for patients with aortic stenosis (AS) who underwent transcatheter aortic valve implantation (TAVI) are limited. The present study aimed to evaluate the impact of statin on mid-term mortality of TAVI patients.

Design Observational study.

Setting This study included AS patients who underwent TAVI from a Japanese multicentre registry.

Participants The overall cohort included 2588 patients (84.4±5.2 years); the majority were women (69.3%). The Society of Thoracic Surgeons risk score was 6.55% (interquartile range [IQR] 4.55-9.50%), Euro II score was 3.74% (IQR 2.34-6.02%), and Clinical Frailty Scale was 3.9±1.2.

Interventions We classified the patients based on statin at admission and identified 936 matched pairs after propensity score matching.

Primary and secondary outcome measures The outcomes were all-cause and cardiovascular mortality.

Results The median follow-up was 660 days. Statin at admission was associated with a significant reduction in all-cause mortality (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, $P=0.04$) and cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, $P=0.04$). In the octogenarians, statin was associated with significantly lower all-cause mortality (aHR 0.87, 95% CI 0.75-0.99, $P=0.04$); however, the impact in the nonagenarians appeared to be lower (aHR 0.84, 95% CI 0.62-1.13, $P=0.25$). Comparing four groups according to previous coronary artery disease (CAD) and statin, there was a significant difference in all-cause mortality and patients who did not receive statin despite previous CAD showed the worst prognosis (aHR 1.33, 95% CI 1.12-1.57 [patients who received statin without previous CAD as a reference], $P<0.01$).

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3 **Conclusions** Statin for TAVI patients will be beneficial even in octogenarians, but the
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5 benefits may disappear in nonagenarians. In addition, statin will be essential for TAVI
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7 patients with CAD. Further researches are warranted to confirm and generalise our findings,
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9 since this study has inherent limitations of the observational study and included only Japanese
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11 patients.
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17 **Keywords:** coronary artery disease, elderly, propensity score matching, statin, transcatheter
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19 aortic valve implantation
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25 **Strengths and limitations of this study**

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27 ● The present study includes the largest number of patients with aortic stenosis who
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29 underwent transcatheter aortic valve implantation (TAVI), assessing the impact of statin
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31 therapy on mid-term all-cause and cardiovascular mortality.
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- 34 ● This was the first study to investigate a difference in the statin effect among
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36 octogenarians and nonagenarians, and to evaluate how the impact of statin therapy
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38 differed according to the underlying coronary artery disease.
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- 41 ● All-cause and cardiovascular mortality were analysed using propensity score matching
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43 and the Cox proportional hazards regression model.
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- 46 ● Unknown and unmeasurable factors may have confounded the relationship between
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48 statin therapy at admission and mortality due to the nature of an observational study.
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- 51 ● We could not assess intolerance in patients eligible for statin treatment but who could not
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53 continue treatment due to statin side effects.
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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe aortic stenosis (AS).[1, 2, 3, 4] However, long-term survival after TAVI is not satisfactory, as shown in a meta-analysis including 31 studies; 5-year and 7-year survival rates were 48% and 28%, respectively.[5] TAVI patients are very elderly and have many cardiovascular comorbidities such as coronary artery disease (CAD), stroke, and peripheral artery disease (PAD).[1, 2, 6] Therefore, adjunctive optimal medical therapy is required to improve prognosis after TAVI. Statin therapy is expected to reduce cardiovascular risk and mortality in patients who have undergone TAVI; however, data on statin therapy for TAVI patients are limited. A report from the Placement of Aortic Transcatheter Valve II (PARTNER II) and Sapien 3 clinical trials or associated registries showed that statin therapy was associated with a lower 2-year mortality rate compared to patients not on statin therapy.[7] However, the study did not demonstrate any differences in the statin effect among octogenarians and nonagenarians, and did not evaluate whether the impact of statin therapy would differ according to the underlying CAD. Therefore, the present study aimed to evaluate the impact of statin therapy on mid-term mortality of TAVI patients and its association with age or the underlying CAD, using our Japanese multicentre registry data.

METHODS

Study population and design

All patients with severe AS who underwent TAVI at 14 Japanese centres (Keio University Hospital, Teikyo University Hospital, Toyohashi Heart Centre, Nagoya Heart Centre, New Tokyo Hospital, Kokura Memorial Hospital, Saiseikai Yokohama City Eastern Hospital, Sendai Kosei Hospital, Shonan Kamakura General Hospital, Osaka City University Graduate School of Medicine, Kishiwada Tokushukai Hospital, Toyama University Hospital, Tokyo

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3 Bay Urayasu Ichikawa Medical Center, and Ogaki municipal hospital) between 2013 and
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5 2017 were prospectively included in our TAVI registry (Optimized Catheter valvular
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7 intervention [OCEAN-TAVI] registry).[8, 9, 10] Informed consent was obtained from all
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9 patients, and the institutional review boards of all 14 participating centres approved this study.
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11 Additionally, this study was conducted in accordance with the ethical guidelines of the 1975
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13 Declaration of Helsinki. The OCEAN-TAVI registry was registered with the University
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15 Hospital Medical Information Network Clinical Trial Registry and accepted by the
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17 International Committee of Medical Journal Editors (UMIN-ID: 000020423).
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21 Patients received transcatheter heart valves (THVs) via either the transfemoral,
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23 transapical, or transaortic approach. Sapien XT valves, Sapien 3 valves (Edwards
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25 Lifesciences, Irvine, CA), CoreValves, Evolut R (Medtronic, Minneapolis, MN) were used as
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27 THVs. A total of 2588 patients were treated with TAVI between 2013 and 2017. They were
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29 categorised into two groups according to statin administration at admission for TAVI
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31 procedures (Figure 1). We set the primary endpoint as mid-term all-cause mortality for up to 3
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33 years. Secondary endpoints included mid-term cardiovascular mortality, mid-term non-
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35 cardiovascular mortality up to 3 years, and 30-day all-cause mortality.
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40 We performed propensity score (PS) matching, as described below, and compared the
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42 endpoints between the two groups in the matched cohort. In addition, we categorised the
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44 matched cohort into two cohorts; an octogenarian cohort (80–89 years old) and a
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46 nonagenarian cohort (90 years or older), and investigated the differences by age in the impact
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48 of statin on mid-term all-cause mortality. Furthermore, we classified the overall cohort into
49
50 four groups according to a history of CAD and statin treatment at admission and evaluated
51
52 whether the impact of statin differed according to the underlying CAD condition. We also
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54 explored predictors of mid-term all-cause mortality in the overall cohort using multivariate
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56 analysis.
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3 Clinical outcomes including all-cause mortality and cardiovascular mortality were
4 defined according to the Valve Academic Research Consortium-2 consensus document.[11]
5

6 7 **Statistical analysis**

8
9 Continuous variables are expressed as mean±standard deviation (SD), and categorical
10 variables are expressed as percentages. Continuous variables were compared using the
11 Wilcoxon rank-sum test. The chi-squared test was used to compare categorical variables.
12
13 Survival curves up to 3 years were presented as Kaplan-Meier curves, and the log-rank test
14 was used for comparison of the statin and non-statin groups. The Cox proportional hazards
15 regression analyses were performed to identify independent correlates for mid-term all-cause
16 mortality.
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19 PS matching[12, 13] was used to account for differences in baseline characteristics. The
20 PS was calculated for each patient using a logistic regression model to predict stratification
21 into the statin group based on the following variables: age; sex; body surface area; smoking;
22 diabetes; hypertension; previous history of CAD, myocardial infarction (MI), percutaneous
23 coronary intervention, coronary artery bypass grafting, stroke, PAD; atrial fibrillation;
24 estimated glomerular filtration rate; haemoglobin level; renin-angiotensin inhibitor treatment
25 at admission; New York Heart Association (NYHA) class 3 or 4; Clinical Frailty Scale[8];
26 and Society of Thoracic Surgeons (STS) risk score. PS matching was performed using 1:1
27 matching without replacement, with the calliper width equal to 0.2 SD of the PS logit. The
28 balance between the statin and non-statin groups in the matched cohort was estimated using
29 absolute standardised difference. The Cox proportional hazards analyses were performed to
30 assess the impact of statin on the clinical outcomes. In addition to the PS matching model, we
31 built a multivariable model by inverse probability of treatment weighting (IPTW) using the
32 PS.[14] All reported *P*-values were two-sided, and a *P*-value <0.05 was considered
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3 statistically significant. All statistical analyses were performed using the R software package
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5 (version 3.3.2; R Development Core Team, Vienna, Austria).
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10 11 **Patient and Public Involvement statement**

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14 Patients were first involved in the research when they underwent TAVI and registered to the
15
16 OCEAN-TAVI registry through the web-based data collection system. Research questions
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18 and outcome measures were developed by the OCEAN-TAVI registry investigators. Patients
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20 were informed about the registration. They were asked to assess the burden of the intervention
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22 and time required to participate in the research. Information of the registry and the study
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24 results are available on the website of the OCEAN-TAVI registry.
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31 32 **RESULTS**

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34 Among the 2588 patients who underwent TAVI, 1523 and 1065 patients were classified into
35
36 the statin and the non-statin group, respectively (Figure 1). The distribution of PS in the statin
37
38 and non-statin groups is shown in Supplementary material online, Figure S1. After 1:1 PS
39
40 matching, we identified 936 matched pairs of patients with similar PS. The patient
41
42 characteristics of the statin and non-statin groups before and after matching are summarised in
43
44 Table 1. The overall cohort included very elderly patients (84.4±5.2 years). The majority of
45
46 the cohort was female (69.3%). The Society of Thoracic Surgeons risk score was 6.55%
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48 (interquartile range [IQR] 4.55-9.50%), Euro II score was 3.74% (IQR 2.34-6.02%), and
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50 Clinical Frailty Scale was 3.9±1.2.
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55 After PS matching, the two groups were well-balanced in terms of pre-procedural patient
56
57 characteristics and procedural variables. In-hospital all-cause mortality, acute kidney injury,
58
59 stroke, and vascular complications did not differ between the two groups. Post-procedural
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3 echocardiography data showed no significant differences between the two groups (Table 2).
4
5 The patient characteristics and in-hospital outcomes of the PS matched and unmatched groups
6
7 are summarised in Supplementary material online, Tables S1 and S2. There were several
8
9 differences between the two groups. The proportion of male patients was lower in the PS
10
11 matched group than in the unmatched group (532 [28.4%] vs. 263 [36.7%], $P<0.01$), NYHA
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13 Class 3 or 4 was less frequent in the matched group (919 [49.1%] vs. 402 [56.2%], $P<0.01$),
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15 the Clinical Frailty Scale was lower in the matched group (3.8 ± 1.2 vs. 4.2 ± 1.4 , $P<0.01$), and
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17 the STS risk score was lower in the matched group (7.7 ± 5.7 vs 9.8 ± 9.2 , $P<0.01$). History of
18
19 the previous CAD was more frequent (750 [40.1%] vs. 204 [28.5%], $P<0.01$), but previous
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21 MI was less frequent (96 [5.1%] vs. 62 [8.7%], $P<0.01$) in the PS matched group. In-hospital
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23 all-cause mortality (43 [2.3%] vs. 27 [3.8%], $P<0.01$) and bleeding (421 [22.5%] vs. 199
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25 [27.8%], $P<0.01$) were lower in the matched group than in the unmatched group.
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31 In the overall cohort, the median follow-up period was 660 days. Statin therapy was
32
33 associated with significantly lower mid-term all-cause mortality in the PS-matched cohort
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35 (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, $P=0.04$) (Figure
36
37 2a), which was consistent with the IPTW model (aHR 0.80, 95% CI 0.65–0.99, $P=0.04$). The
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39 Kaplan-Meier curves relative to the mid-term outcomes additionally showed a significant
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41 difference in cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, $P=0.04$) and an
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43 insignificant difference in non-cardiovascular mortality (aHR 0.86, 95% CI 0.61–1.21,
44
45 $P=0.39$) between the two groups (Figure 2b and 2c). There was no significant difference in
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47 30-day all-cause mortality (aHR 0.73, 95% CI 0.47–1.08, $P=0.11$) and a landmark analysis
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49 after 30 days showed a significant difference in mid-term all-cause mortality (aHR 0.88, 95%
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51 CI 0.78–0.99, $P=0.03$) (Figure 2d).
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56 In the octogenarian cohort (80–89 years old), statin therapy was associated with
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58 significantly lower mid-term all-cause mortality (aHR 0.87, 95% CI 0.75–0.99, $P=0.04$)
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3 (Figure 3a), but the impact in the nonagenarian cohort (90 years or older) appeared to be
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5 lower (aHR 0.84, 95% CI 0.62-1.13, $P=0.25$) (Figure 3b). P for interaction was 0.90.

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8 Furthermore, comparing the four groups according to previous CAD and statin therapy,
9
10 there was a significant difference in mid-term all-cause mortality ($P<0.01$) (Figure 4).

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12 Patients who did not receive statin therapy despite a history of previous CAD showed the
13
14 worst prognosis (aHR 1.33, 95% CI 1.12-1.57 [patients who received statin without previous
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16 CAD as a reference]). Their survival curve diverged from that of the patients without previous
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18 CAD or statin after 1 year. In addition, patients with previous CAD and statin therapy (aHR
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20 1.04, 95% CI 0.87-1.23) seemed to obtain similar risks with those who did not have previous
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22 CAD or statin therapy (aHR 1.11, 95% CI 0.96-1.27 [patients who received statin without
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24 previous CAD as a reference]).
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29 The results of the univariate and multivariate Cox proportional hazards regression
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31 analyses were shown in Table 3. Statin therapy at admission was independently associated
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33 with lower all-cause mortality (aHR 0.86, 95% CI 0.77-0.95), $P<0.01$).
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38 DISCUSSION

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40 The present study investigated the impact of statin therapy on mid-term mortality after TAVI
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42 using a Japanese multicentre registry. Statin therapy at admission was associated with
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44 significantly lower all-cause and cardiovascular mortality. It should be noted that the impact
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46 of statin therapy attenuated in the nonagenarians. Furthermore, we demonstrated differences
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48 in all-cause mortality according to the history of previous CAD and statin therapy. The
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50 present study included the largest patient cohort (936 pairs of patients after PS matching) and
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52 the first report to investigate the association of age and a history of previous CAD with the
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54 impact of statin.
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3 Few reports have assessed the impact of statin treatment on mortality after TAVI. Peri-
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5 Okonny et al. demonstrated that statin therapy was associated with reductions in 2-year all-
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7 cause (aHR 0.65, 95% CI 0.49–0.87, $P=0.001$), cardiovascular (aHR 0.66, 95% CI 0.46–0.96,
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9 $P=0.030$), and non-cardiovascular mortality (aHR 0.64, 95% CI 0.44–0.99, $P=0.045$)
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11 compared with no statin therapy, with a large cohort using PARTNER II and Sapien 3 clinical
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13 trials or associated registries (626 pairs of patients after PS matching).[7] Merdler et al.
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15 showed that high-intensity statin therapy was associated with a reduction in mortality after
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17 TAVI (median follow-up period: 2.5 years) using data of 1238 cases from a single-centre
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19 registry (aHR 0.59, 95% CI 0.37–0.96, $P=0.03$).[15] Huded et al. also showed that high-
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21 intensity statin therapy was associated with a reduction in all-cause mortality (mean survival:
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23 3.9 years) based on 294 cases (aHR 0.36, 95% CI 0.14–0.90, $P=0.029$).[16] Takagi et al.
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25 reported similar results following a meta-analysis.[17] These results were consistent with our
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27 results.
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33 The mechanism through which statin therapy reduces the risks of all-cause and
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35 cardiovascular mortality is thought to be associated with a reduction in ischaemic events.[7,
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37 15, 16, 17] However, there are limited data relative to statin therapy in octogenarians and
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39 nonagenarians, as are data not only on TAVI but also on statin therapy as primary and
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41 secondary prevention. The PROspective Study of Pravastatin in the Elderly at Risk trial was
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43 the only randomised controlled trial for elderly patients (aged 70–82 years) with a history or
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45 risk factors of vascular disease. The study revealed that pravastatin led to a 3-year reduced
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47 risk of CAD.[18] Recommendation of statin therapy for very elderly patients varies among
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49 the guidelines.[19, 20, 21, 22, 23] Very recently, a few reports supporting statin therapy for
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51 very elderly patients have been published. In the Patient and Provider Assessment of Lipid
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53 Management Registry, statin therapy appeared to be similarly tolerated by patients older and
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55 younger than 75 years.[24] The Cholesterol Treatment Trialists' Collaboration demonstrated
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3 that statin therapy as primary and secondary prevention produced significant reductions in
4 major vascular events even in patients older than 75 years.[25] Furthermore, Romas et al.
5 revealed that statin therapy was associated with significant reductions in atherosclerotic
6 cardiovascular events and all-cause mortality for patients who were older than 74 years and
7 had diabetes.[26] Interestingly, Giral et al. demonstrated that statin discontinuation in 75-
8 year-old primary prevention patients was associated with a 33% increased risk of
9 cardiovascular events.[27] Our present study was consistent with these reports and indicated
10 that statin therapy would be effective for very elderly and atherosclerotic high-risk patients by
11 reducing cardiovascular events and mortality. Conversely, Romas et al. reported that the
12 benefits of statin therapy disappeared in nonagenarians,[26] as observed in our nonagenarian
13 cohort. However, P for interaction among the octogenarian and nonagenarian cohorts in the
14 present study was not significant. There seemed to be a difference among the two cohorts
15 during 12-24 months after TAVI but then the curves converged. The insignificance might be
16 due to low life expectancy in nonagenarians after 24 months. Besides, the sizes of the cohorts
17 and confounding regarding prescribing statin to nonagenarians with CAD might skew the
18 results.

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40 The statin effect generally appears after 1 year compared with placebo.[7, 28] Patients
41 with a history of previous CAD who did not receive statin therapy appeared to have higher
42 mortality rates after 1 year in the present study. In addition, our analysis the combining
43 history of previous CAD and statin therapy implied that TAVI patients with the previous
44 CAD might be able to achieve a similar reduction in mortality risk as those patients who had
45 no previous CAD or statin treatment.

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The present study had some limitations. First, this is an observational study, and
unknown and unmeasurable factors may have confounded the relationship between statin
therapy and mortality. However, a multicentre approach enabled us to accumulate a relatively

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3 large number of patients and we used PS matching analysis, the IPTW model, and the Cox
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5 proportional hazards regression model to confirm the robustness of the results. Second, a
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7 generalisation of the present results may be slightly limited due to the differences between the
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9 matched and unmatched group as it might be plausible given the results of the IPTW model.
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11 In addition, generalising our findings outside Japan also requires attention since this study
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13 included only Japanese patients. Third, information on the type and doses of statin therapy
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15 was not obtained. Usage of ezetimibe or proprotein convertase subtilisin/kexin type 9
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17 inhibitor was not recorded in this study. Fourth, we assessed statin use only on admission and
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19 there was a possibility that statin therapy might have changed at discharge or during follow-
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21 up. The duration of statin administration and the timing to start prescribing statin were not
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23 captured in the present study. Finally, we could not assess intolerance in patients eligible for
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25 statin treatment but who could not continue treatment due to statin side effects such as
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27 rhabdomyolysis. Further studies, including a randomised controlled trial, on statin therapy
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29 following TAVI are warranted to resolve these limitations.
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35 In conclusion, using data from the large multicentre registry, statin therapy at admission
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37 of TAVI was associated with significant reductions in mid-term all-cause and cardiovascular
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39 mortality. Statin therapy prior TAVI will be beneficial even in octogenarians, but the benefits
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41 may disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients
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43 with CAD. Further researches are warranted to confirm and generalise our findings, since the
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45 present study has several inherent limitations of the observational study and included only
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47 Japanese patients.
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Conflict of interest

Drs. Yamamoto, Tada, Naganuma, Shirai, Mizutani, Tabata, Ueno, and Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Drs. Shimizu, Takagi and Hayashida are clinical proctors of Edwards Lifesciences. Dr. Inohara received a research grant from Boston Scientific. Dr. Kohsaka received lecture fees and research grants from Pfizer Japan, Bayer, Daiichi Sankyo, and Bristol-Myers Squibb. The remaining authors have nothing to disclose.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Authors' contributions

Conception or design of the work: Fumiaki Yashima, Shinichi Shirai, Toru Naganuma, Kazuki Mizutani, Masahiro Yamawaki, Minoru Tabata, and Futoshi Yamanaka.

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3 Data collection: Makoto Tanaka, Masahiro Jinzaki, Hideyuki Shimizu, and Keiichi Fukuda.
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7 Ueno, and Norio Tada.
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10 Drafting the article: Fumiaki Yashima and Taku Inohara.
11

12 Critical revision of the article: Masanori Yamamoto, Yusuke Watanabe, Kentaro Hayashida.
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14 Final approval of the version to be published: all authors.
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19 **Ethics Statement**

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21 The OCEAN-TAVI registry was registered with the University Hospital Medical Information
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23 Network Clinical Trial Registry and accepted by the International Committee of Medical
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25 Journal Editors (UMIN-ID: 000020423). The institutional review boards of all the
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27 participating centres approved this study. Informed consent was obtained from all patients.
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For peer review only

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3 **Figure legends**
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8 **Figure 1**
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10 Flowchart of patient selection for the present study.

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12 OCEAN; Optimized CathEter vAlvular iNtervention; TAVI, transcatheter aortic valve
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14 implantation.
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19 **Figure 2**
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21 Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort. *a, b, c*:

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23 Kaplan-Meier curves for mid-term all-cause mortality (*a*), CV mortality (*b*), and non-CV

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25 mortality (*c*) in the matched cohort. *d*: Kaplan-Meier curve for 30-day all-cause mortality and
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27 mid-term all-cause mortality with the landmark analysis from 30 days in the matched cohort.
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30 CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
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35 **Figure 3**
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37 Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.
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42 **Figure 4**
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44 Kaplan-Meier curve for all-cause mortality according to previous coronary artery disease and
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46 statin therapy in the overall cohort.
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49 CAD, coronary artery disease.
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Table 1

Patient characteristics before and after propensity score matching

	Before matching			After matching		
	Statin (+) <i>n</i> =1065	Statin (-) <i>n</i> =1523	Standardised difference	Statin (+) <i>n</i> =936	Statin (-) <i>n</i> =936	Standardised difference
Preprocedural variables						
Age, years	84.1±5.0	84.6±5.3	0.01	84.2±5.0	84.3±5.2	0.01
Men, <i>n</i> (%)	322 (30.2%)	473 (31.1%)	0.02	277 (29.6%)	255 (27.2%)	0.05
Body surface area, m ²	1.44±0.17	1.42±0.17	0.13	1.44±0.17	1.43±0.17	0.07

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4	NYHA class 3 or 4, <i>n</i> (%)	518 (48.6%)	803 (52.7%)	0.08	462 (49.4%)	457 (48.8%)	0.01
5							
6							
7							
8	Clinical Frailty Scale	3.8±1.2	4.1±1.3	0.23	3.8±1.2	3.8±1.2	0.04
9							
10							
11	Diabetes mellitus, <i>n</i> (%)	264 (24.8%)	291 (19.1%)	0.14	207 (22.1%)	195 (20.8%)	0.03
12							
13							
14							
15	Smoking, <i>n</i> (%)	212 (19.9%)	260 (17.1%)	0.07	169 (18.1%)	160 (17.1%)	0.02
16							
17							
18							
19	Hypertension, <i>n</i> (%)	861 (80.9%)	1129 (74.1%)	0.16	744 (79.5%)	753 (80.5%)	0.02
20							
21							
22	Chronic kidney disease, <i>n</i> (%)	755 (70.9%)	1054 (69.2%)	0.04	651 (69.6%)	640 (68.4%)	0.03
23							
24							
25							
26	Atrial fibrillation, <i>n</i> (%)	195 (18.3%)	354 (23.2%)	0.12	181 (19.3%)	183 (19.6%)	0.01
27							
28							
29							
30	Coronary artery disease, <i>n</i> (%)	507 (47.6%)	447 (29.4%)	0.38	378 (40.4%)	372 (39.7%)	0.01
31							
32							
33	Previous myocardial infarction, <i>n</i> (%)	108 (10.1%)	50 (3.3%)	0.28	48 (5.1%)	48 (5.1%)	<0.01
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4	Previous percutaneous coronary intervention, <i>n</i>						
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6							
7	(%)	342 (32.1%)	284 (18.7%)	0.31	249 (26.6%)	238 (25.4%)	0.03
8							
9							
10							
11	Previous coronary artery bypass grafting, <i>n</i> (%)	112 (10.5%)	57 (3.7%)	0.27	60 (6.4%)	57 (6.1%)	0.01
12							
13							
14							
15	Peripheral artery disease, <i>n</i> (%)	161 (15.1%)	216 (14.2%)	0.03	136 (14.5%)	128 (13.7%)	0.02
16							
17							
18							
19	Previous stroke, <i>n</i> (%)	127 (11.9%)	174 (11.4%)	0.02	116 (12.4%)	102 (10.9%)	0.05
20							
21							
22	STS risk score	7.7±6.0	8.6±7.5	0.13	7.7±6.1	7.7±5.3	<0.01
23							
24							
25							
26	Renin-angiotensin inhibitor, <i>n</i> (%)	639 (60.0%)	748 (49.1%)	0.22	540 (57.7%)	544 (58.1%)	0.01
27							
28							
29							
30	β blocker, <i>n</i> (%)	384 (36.1%)	496 (32.6%)	0.07	334 (35.7%)	303 (32.4%)	0.07
31							
32							
33	eGFR, mL/min/1.73 m ²	51.7±18.5	51.1±20.1	0.03	52.3±18.6	51.7±19.6	0.03
34							
35							
36							
37	Haemoglobin, g/dL	11.4±1.7	11.1±1.7	0.17	11.4±1.7	11.2±1.6	0.15
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LDL-c, mg/dL	104.3±28.9	94.2±28.0	0.35	105.9±28.2	94.8±27.8	0.4
HDL-c, mg/dL	52.9±15.8	53.6±15.0	0.04	53.5±16.3	54.3±15.0	0.05
Triglyceride, mg/dL	106.8±57.6	110.5±53.0	0.07	109.6±60.9	110.2±53.2	0.01
Preprocedural echocardiographic data						
Aortic valve area, cm ²	0.64±0.17	0.63±0.17	0.04	0.63±0.17	0.63±0.16	<0.01
Indexed aortic valve area, cm ² /m ²	0.44±0.12	0.44±0.12	<0.01	0.44±0.12	0.45±0.12	0.03
Mean aortic gradient, mmHg	50.0±18.1	51.0±18.4	0.05	51.0±18.2	50.8±18.2	0.01
Peak velocity, m/sec	4.5±0.8	4.6±0.8	0.07	4.6±0.8	4.6±0.8	0.02
Ejection fraction, %	59.2±12.7	59.2±12.6	<0.01	59.6±12.4	59.7±12.0	0.01
Severe aortic regurgitation, <i>n</i> (%)	12 (0.8%)	4 (0.4%)	0.05	7 (0.8%)	4 (0.4%)	0.04

Severe mitral regurgitation, <i>n</i> (%)	21 (1.4%)	12 (1.1%)	0.02	12 (1.3%)	6 (0.6%)	0.07
Pulmonary hypertension, <i>n</i> (%)	40 (3.8%)	62 (4.1%)	0.02	37 (4.0%)	33 (3.5%)	0.02
Preprocedural CT data						
Annular area, mm ²	395.5±70.7	400.7±71.0	0.07	395.9±70.2	396.5±69.1	0.01
Procedural variables						
Transfemoral approach, <i>n</i> (%)	873 (82.0%)	1294 (85.0%)	0.08	770 (82.3%)	784 (83.8%)	0.04
Local anaesthesia, <i>n</i> (%)	799 (75.0%)	1179 (77.4%)	0.06	714 (76.3%)	734 (78.4%)	0.05
Contrast volume, mL	115.8±59.1	115.4±58.0	0.01	118.8±60.0	113.5±57.1	0.09
Fluoroscopy time, min	21.7±12.5	21.1±10.0	0.05	21.9±12.6	21.0±10.0	0.08
Procedure time, min	81.6±45.8	80.3±45.4	0.03	81.6±43.0	80.4±43.6	0.03

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3 CT, computed tomography; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density
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5 lipoprotein cholesterol; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.
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For peer review only

Table 2

In-hospital outcomes before and after propensity score matching

	Before matching				After matching			
	Statin (+) <i>n</i> =1065	Statin (-) <i>n</i> =1523	<i>P</i> value	Standardised difference	Statin (+) <i>n</i> =936	Statin (-) <i>n</i> =936	<i>P</i> value	Standardised difference
All-cause mortality, <i>n</i> (%)	27 (2.5%)	43 (2.8%)	0.66	0.02	20 (2.1%)	23 (2.5%)	0.64	0.02
Acute kidney injury, <i>n</i> (%)	111 (10.4%)	178 (11.7%)	0.31	0.04	96 (10.3%)	105 (11.2%)	0.50	0.03
Stroke, <i>n</i> (%)	27 (2.5%)	34 (2.2%)	0.62	0.02	24 (2.6%)	19 (2.0%)	0.44	0.04
Vascular complication, <i>n</i> (%)	105 (9.9%)	128 (8.4%)	0.21	0.05	90 (9.6%)	78 (8.3%)	0.33	0.05

Postprocedural echocardiographic data									
Effective orifice area, cm ²	1.67±0.45	1.69±0.45	0.53	0.03	1.68±0.44	1.66±0.43	0.34	0.04	
Indexed effective orifice area, cm ² /m ²	1.17±0.32	1.20±0.31	0.02	0.10	1.18±0.32	1.18±0.30	0.99	<0.01	
Mean aortic gradient, mmHg	11.0±4.4	10.6±4.7	0.08	0.07	11.0±4.4	11.0±4.9	0.92	<0.01	
Peak velocity, m/sec	2.3±0.4	2.2±0.5	0.10	0.07	2.3±0.5	2.3±0.5	0.98	<0.01	
Moderate or severe aortic regurgitation, <i>n</i> (%)	18 (1.7%)	31 (2.1%)	0.51	0.03	17 (1.8%)	20 (2.2%)	0.61	0.02	
Moderate or severe mitral regurgitation, <i>n</i> (%)	59 (5.6%)	100 (6.6%)	0.27	0.04	45 (4.8%)	51 (5.5%)	0.52	0.03	

Table 3

The univariate and multivariate Cox proportional regression analyses of the all-cause mortality in the overall cohort.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	adjusted HR (95% CI)	P value
Men	1.30 (1.18-1.42)	<0.01	1.40 (1.25-1.57)	<0.01
Age	1.01 (0.99-1.03)	0.13	0.99 (0.97-1.01)	0.31
Clinical Frailty Scale 1-3	0.77 (0.70-0.85)	<0.01	0.81 (0.73-0.90)	<0.01
NYHA class 3 or 4	1.33 (1.21-1.46)	<0.01	1.18 (1.07-1.31)	<0.01
Smoking	1.20 (1.08-1.33)	<0.01	1.02 (0.90-1.15)	0.74
Diabetes mellitus	1.12 (1.00-1.24)	0.04	0.99 (0.89-1.11)	0.87
Hypertension	0.97 (0.88-1.09)	0.63	0.97 (0.86-1.08)	0.54
Previous myocardial infarction	1.32 (1.13-1.52)	<0.01	1.14 (0.96-1.35)	0.14

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4	Previous coronary artery bypass grafting	1.21 (1.02-1.40)	0.03	1.05 (0.88-1.24)	0.60
5					
6					
7	Peripheral artery disease	1.35 (1.21-1.50)	<0.01	1.08 (0.95-1.22)	0.24
8					
9					
10	Previous stroke	1.14 (0.99-1.30)	0.06	1.04 (0.90-1.19)	0.62
11					
12					
13	Atrial fibrillation	1.19 (1.07-1.32)	<0.01	1.00 (0.90-1.12)	0.98
14					
15					
16	STS risk score	1.04 (1.03-1.04)	<0.01	1.02 (1.01-1.03)	<0.01
17					
18					
19					
20	eGFR, mL/min/1.73 m ²	0.98 (0.98-0.99)	<0.01	0.99 (0.99-1.00)	<0.01
21					
22					
23	Haemoglobin, g/dL	0.83 (0.78-0.88)	<0.01	0.85 (0.80-0.91)	<0.01
24					
25					
26	Medication at admission				
27					
28					
29	Statin	0.84 (0.77-0.93)	<0.01	0.86 (0.77-0.95)	<0.01
30					
31					
32	Renin-angiotensin inhibitor	0.92 (0.84-1.01)	0.08	0.88 (0.80-0.97)	0.01
33					
34					
35	β blocker	1.09 (0.99-1.20)	0.08	1.06 (0.96-1.16)	0.28
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38	Preprocedural echocardiographic data				
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4	Aortic valve area, cm ² /m ²	1.29 (0.76-2.20)	0.35	1.23 (0.63-2.38)	0.54
5					
6					
7	Peak velocity, mmHg	0.75 (0.67-0.85)	<0.01	0.76 (0.66-0.88)	<0.01
8					
9					
10	Ejection fraction, %	0.99 (0.98-0.99)	0.03	1.01 (1.00-1.02)	0.02
11					
12					
13	Pulmonary hypertension	1.50 (1.25-1.78)	<0.01	1.27 (1.05-1.53)	0.01
14					
15					
16	Severe aortic regurgitation	0.56 (0.13-1.19)	0.16	0.57 (0.21-1.51)	0.26
17					
18					
19	Severe mitral regurgitation	1.34 (0.93-1.81)	0.11	0.99 (0.70-1.40)	0.96
20					
21					
22	Procedural variables				
23					
24					
25	Transfemoral approach	0.81 (0.73-0.91)	<0.01	0.87 (0.77-0.98)	0.03
26					
27					
28	Local anaesthesia	0.89 (0.79-1.01)	0.07	0.92 (0.81-1.05)	0.22
29					
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33 CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; STS, Society of
 34 Thoracic Surgeons.

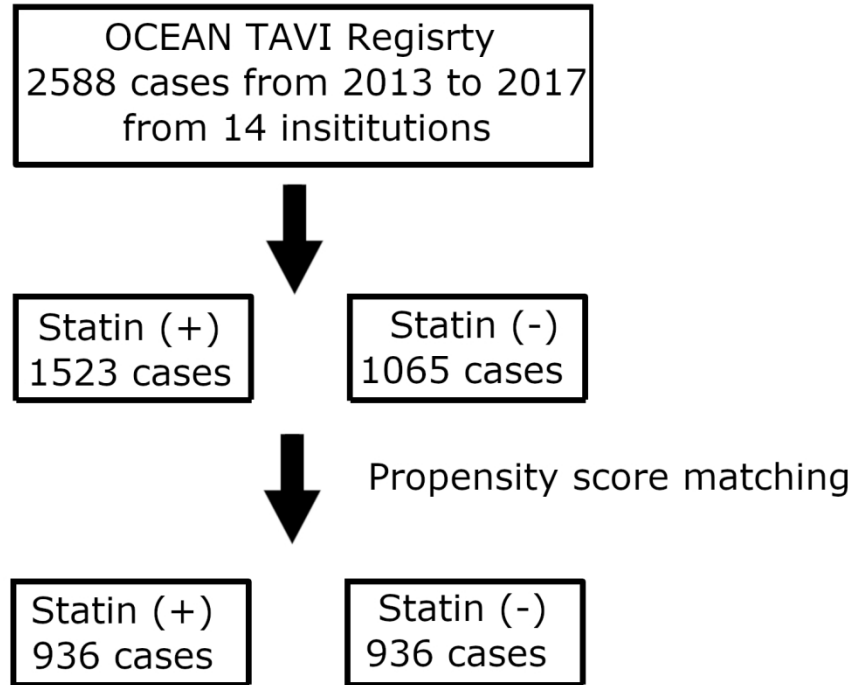


Figure 1

Flowchart of patient selection for the present study.
OCEAN; Optimized CathEter vAlvular iNtervention; TAVI, transcatheter aortic valve implantation.

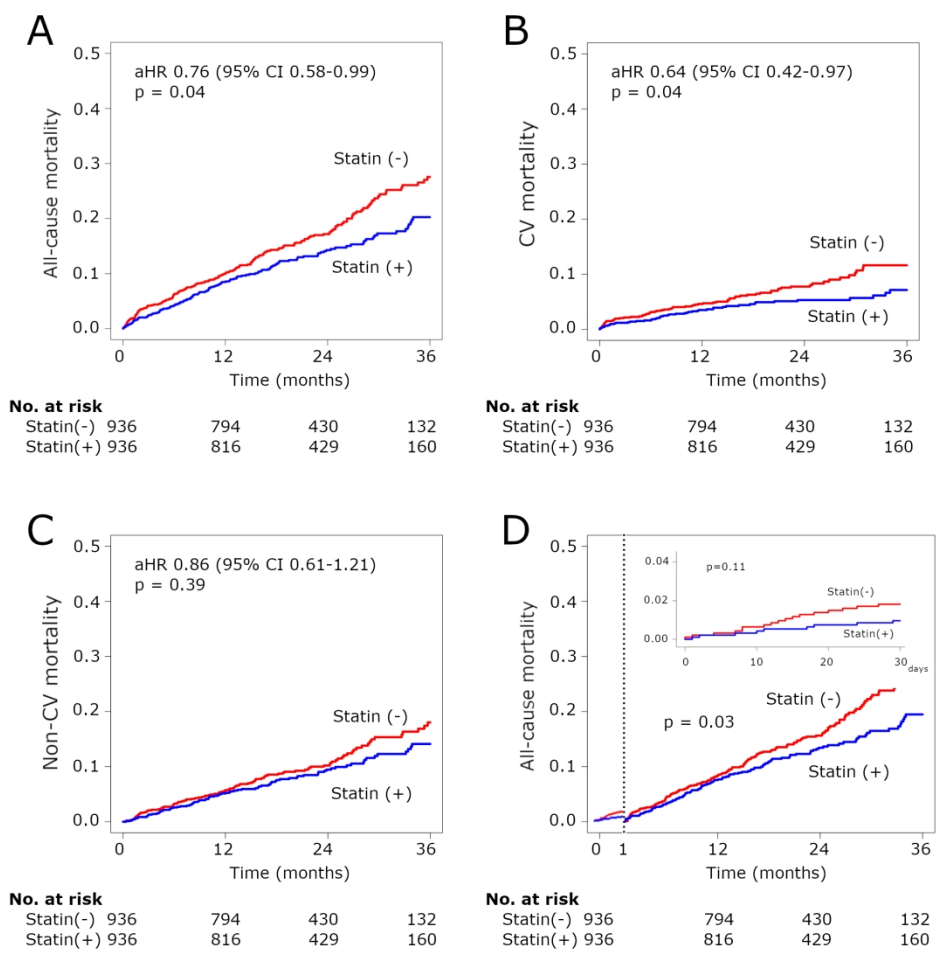


Figure 2

Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort. a, b, c: Kaplan-Meier curves for mid-term all-cause mortality (a), CV mortality (b), and non-CV mortality (c) in the matched cohort. d: Kaplan-Meier curve for 30-day all-cause mortality and mid-term all-cause mortality with the landmark analysis from 30 days in the matched cohort. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

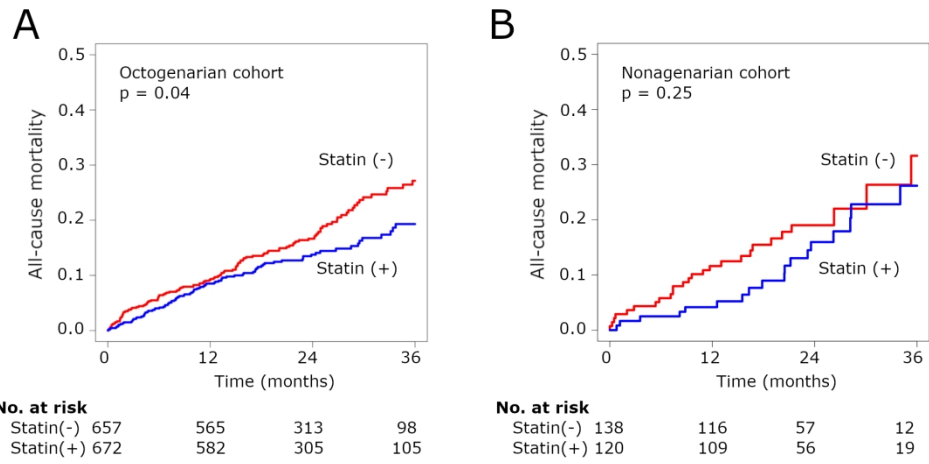
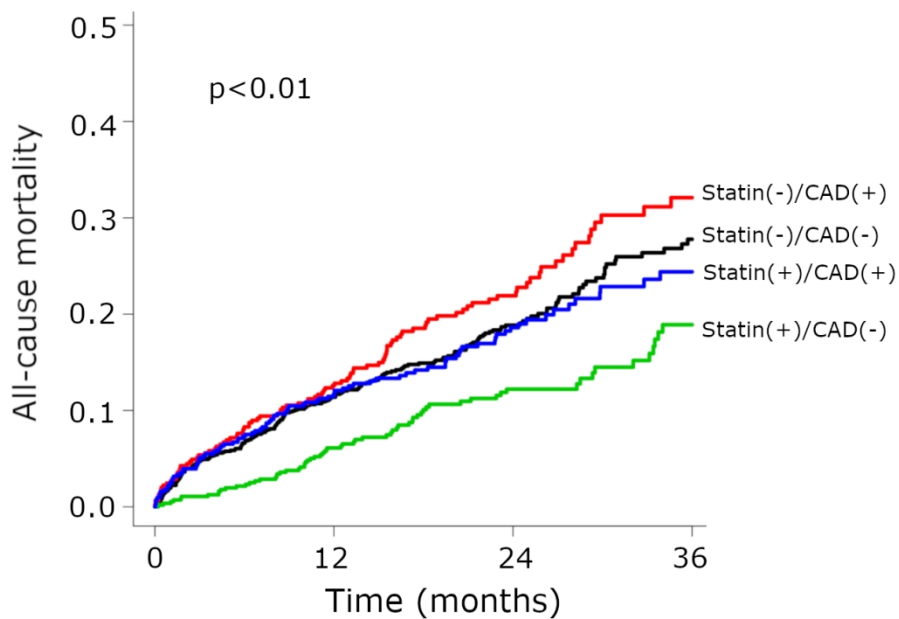


Figure 3

Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.



No. at risk				
Statin(-)/CAD(+)	447	368	201	59
Statin(-)/CAD(-)	1076	895	456	142
Statin(+)/CAD(+)	507	428	231	87
Statin(+)/CAD(-)	558	497	256	93

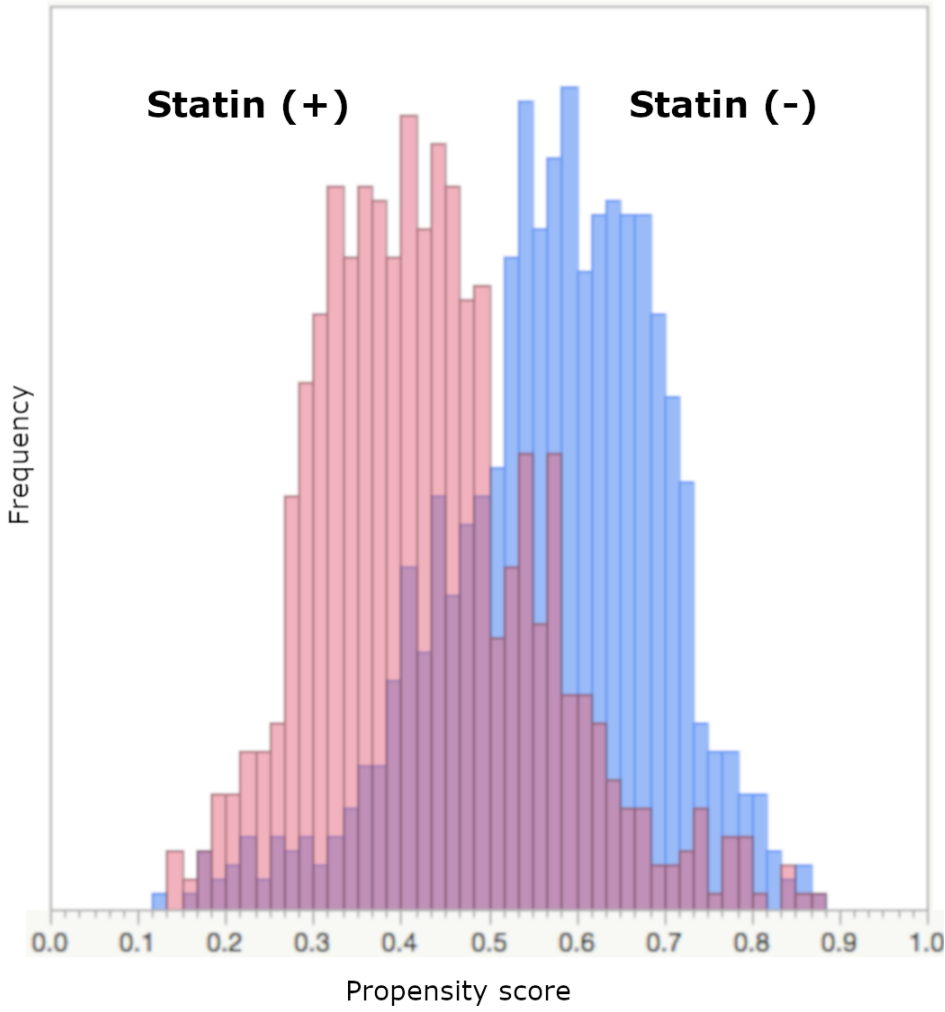
Figure 4
Kaplan-Meier curve for all-cause mortality according to previous coronary artery disease and statin therapy in the overall cohort.
CAD, coronary artery disease.

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Supplementary material online

Supplementary Figure S1

Distribution of propensity scores between statin and non-statin groups in the overall cohort.



Supplementary Table S1

Patient characteristics of the propensity score matched and unmatched groups

	Unmatched		<i>P</i> -value
	Matched group <i>n</i> =1872	group <i>n</i> =716	
Preprocedural variables			
Age, years	84.2±5.1	84.6±5.4	0.08
Male, <i>n</i> (%)	532 (28.4%)	263 (36.7%)	<0.01
Body surface area, m ²	1.43±0.17	1.42±0.17	0.16
NYHA class 3 or 4, <i>n</i> (%)	919 (49.1%)	402 (56.2%)	<0.01
Clinical Frailty Scale	3.8±1.2	4.2±1.4	<0.01
Smoking, <i>n</i> (%)	364 (19.4%)	160 (22.4%)	0.10
Diabetes mellitus, <i>n</i> (%)	402 (21.5%)	153 (21.4%)	0.95
Hypertension, <i>n</i> (%)	1497 (80.0%)	493 (68.9%)	<0.01
Chronic kidney disease, <i>n</i> (%)	1291 (69.0%)	518 (72.4%)	0.09
Atrial fibrillation, <i>n</i> (%)	364 (19.4%)	185 (25.8%)	<0.01

Coronary artery disease, <i>n</i> (%)	750 (40.1%)	204 (28.5%)	<0.01
Previous myocardial infarction, <i>n</i> (%)	96 (5.1%)	62 (8.7%)	<0.01
Previous percutaneous coronary intervention, <i>n</i> (%)	487 (26.0%)	139 (19.4%)	<0.01
Previous coronary artery bypass grafting, <i>n</i> (%)	117 (6.3%)	52 (7.3%)	0.36
Peripheral artery disease, <i>n</i> (%)	264 (14.1%)	113 (15.8%)	0.28
Previous stroke, <i>n</i> (%)	9 (0.5%)	3 (0.4%)	0.98
STS risk score	7.7±5.7	9.8±9.2	<0.01
Renin-angiotensin inhibitor, <i>n</i> (%)	1084 (57.9%)	303 (42.3%)	<0.01
Beta blocker, <i>n</i> (%)	637 (34.0%)	243 (33.9%)	0.97
eGFR, mL/min/1.73 m ²	52.0±19.1	49.7±20.1	<0.01
Haemoglobin, g/dL	11.3±1.6	11.2±1.7	0.16
Procedural variables			
Transfemoral approach, <i>n</i> (%)	1554 (83.0%)	613 (85.6%)	0.11

Local anaesthesia, <i>n</i> (%)	1448 (77.4%)	530 (74.0%)	0.08
Contrast volume, mL	116.1±58.6	114.1±58.2	0.43
Fluoroscopy time, min	21.4±11.4	21.2±10.5	0.66
Procedure time, min	81.0±43.3	80.3±50.9	0.72

CT, computed tomography; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

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3 **Supplementary Table S2**
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5 In-hospital outcomes of the propensity score-matched and -unmatched groups
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	Matched group	Unmatched group	P-value
	n=1872	n=716	
All-cause mortality, <i>n</i> (%)	43 (2.3%)	27 (3.8%)	<0.01
Acute kidney injury, <i>n</i> (%)	201 (10.7%)	88 (12.3%)	0.27
Bleeding, <i>n</i> (%)	421 (22.5%)	199 (27.8%)	<0.01
Stroke, <i>n</i> (%)	43 (2.3%)	18 (2.5%)	0.75
Vascular complication, <i>n</i> (%)	168 (9.0%)	65 (9.1%)	0.93

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure2-4
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.