BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044319
Article Type:	Original research
Date Submitted by the Author:	08-Sep-2020
Complete List of Authors:	Yashima, Fumiaki; Saiseikai Utsunomiya Hospital; Keio University Hospital Hara, Masahiko; Shimane University Inohara, Taku; Vancouver General Hospital Jinzaki, Masahiro ; Keio University Hospital Shimizu, Hideyuki; Keio University Hospital Fukuda, Keiichi; Keio University Hospital Tanaka, Makoto; Keio University Hospital Yamamoto, Masanori; Toyohashi Heart Center Watanabe, Yusuke; Teikyo Daigaku Naganuma, Toru; Shintokyo Byoin Shirai, Shinichi; Kokura Kinen Byoin Yamawaki, Masahiro; Saiseikai Yokohamashi Tobu Hospital Tada, Norio; Sendai Kosei Byoin Yamanaka, Futoshi; Shonan Kamakura General Hospital Mizutani, Kazuki; Osaka City General Hospital Ueno, Hiroshi; Toyama Daigaku Igakubu Daigakuin Igaku Yakugaku Kyoikubu, Tabata, Minoru; Tokyo Bay Urayasu Ichikawa Iryo Center Takagi, Kensuke; Ogaki Shimin Byoin Hayashida, Kentaro; Keio University Hospital
Keywords:	Cardiology < INTERNAL MEDICINE, Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Coronary heart disease < CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Short title: Statin therapy after TAVI

Fumiaki Yashima, MD[1,2,*]; Masahiko Hara, MD, PhD[3]; Taku Inohara, MD, PhD[2,4]; Masahiro Jinzaki, MD, PhD[5]; Hideyuki Shimizu, MD, PhD[6]; Keiichi Fukuda, MD, PhD, FACC, FESC[2]; Makoto Tanaka, MD[2]; Masanori Yamamoto, MD, PhD, FESC[7,8]; Yusuke Watanabe, MD[9]; Toru Naganuma, MD, FACC, FESC[10]; Shinichi Shirai, MD[11]; Masahiro Yamawaki, MD[12]; Norio Tada, MD[13]; Futoshi Yamanaka, MD[14]; Kazuki Mizutani, MD[15]; Hiroshi Ueno, MD[16]; Minoru Tabata, MD[17]; Kensuke Takagi, MD[18]; Kentaro Hayashida, MD, PhD, FESC, FACC, FJCS[2] on behalf of the OCEAN-TAVI registry

[1]Department of Cardiology, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan

[2]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

[3]Center for Community-based Healthcare Research and Education, Shimane University, Izumo, Japan

[4]Division of Cardiology, Vancouver General Hospital, Vancouver, Canada

[5]Department of Diagnostic Radiology, Keio University School of Medicine, Tokyo, Japan

[6]Department of Cardiovascular Surgery, Keio University School of Medicine, Tokyo, Japan

[7]Department of Cardiology, Toyohashi Heart Centre, Toyohashi, Japan

[8]Department of Cardiology, Nagoya Heart Centre, Aichi, Japan

[9]Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan

[10]Department of Cardiology, New Tokyo Hospital, Matsudo, Japan

[11]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan

[12]Department of Cardiology, Saiseikai Yokohama-City Eastern Hospital, Yokohama, Japan

[13]Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan

[14]Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Japan

[15]Department of Cardiology, Osaka City General Hospital, Osaka, Japan

[16]Department of Cardiology, Toyama University Hospital, Toyama, Japan

[17]Department of Cardiovascular Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu, Japan

[18]Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan

***Corresponding author**

Fumiaki Yashima, MD, PhD

Department of Cardiology, Saiseikai Utsunomiya Hospital,

911-1 Takebayashi-cho, Utsunomiya, Tochigi, 321-0974, Japan

Phone: 81-28-626-5500; Fax: 81-28-626-5573

Email: yashima.fumiaki@gmail.com

Word count: 2591

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.

Conclusions Statin therapy after TAVI was associated with significant reductions in all-cause and cardiovascular mortality after propensity score matching. Statin therapy after TAVI will be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients with CAD.

Keywords: coronary artery disease, elderly, propensity score matching, statin, transcatheter aortic valve implantation

Strengths and limitations of this study

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

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), stoke, 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

Bay Urayasu Ichikawa Medical Center, and Ogaki municipal hospital) between 2013 and 2017 were prospectively included in our TAVI registry (Optimized CathEter vAlvular iNtervention [OCEAN-TAVI] registry).[8, 9, 10] Informed consent was obtained from all patients, and the institutional review boards of all 14 participating centres approved this study. Additionally, this study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The OCEAN-TAVI registry was registered with the University Hospital Medical Information Network Clinical Trial Registry and accepted by the International Committee of Medical Journal Editors (UMIN-ID: 000020423).

Patients received transcatheter heart valves (THVs) via either the transfemoral, transapical, or transaortic approach. Sapien XT valves, Sapien 3 valves (Edwards Lifesciences, Irvine, CA), CoreValves, Evolut R (Medtronic, Minneapolis, MN) were used as THVs. A total of 2588 patients were treated with TAVI between 2013 and 2017. They were categorised into two groups according to statin administration at admission for TAVI procedures (Figure 1). We set the primary endpoint as mid-term all-cause mortality for up to 3 years. Secondary endpoints included mid-term cardiovascular mortality, mid-term non-cardiovascular mortality up to 3 years, and 30-day all-cause mortality. We assessed differences in the endpoints between the two groups. Furthermore, we performed propensity score (PS) matching, as described below, and compared the endpoints between the matched groups. In addition, we categorised the matched cohort into two cohorts; an octogenarian cohort (80–89 years old) and a nonagenarian cohort (90 years or older), and investigated the differences by age in the impact of statin on mid-term all-cause mortality. Furthermore, we classified the overall cohort into four groups according to a history of CAD and statin treatment at admission and evaluated whether the impact of statin differed according to the underlying CAD condition.

Clinical outcomes including all-cause mortality and cardiovascular mortality were defined according to the Valve Academic Research Consortium-2 consensus document.[11]

Statistical analysis

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

PS matching[12, 13] was used to account for differences in baseline characteristics. The PS was calculated for each patient using a logistic regression model to predict stratification into the statin group based on the following variables: age; sex; body surface area; smoking; diabetes; hypertension; previous history of CAD, myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass grafting, stroke, PAD; atrial fibrillation; estimated glomerular filtration rate; haemoglobin level; renin-angiotensin inhibitor treatment at admission; New York Heart Association (NYHA) class 3 or 4; Clinical Frailty Scale[8]; and Society of Thoracic Surgeons (STS) risk score. PS matching was performed using 1:1 matching without replacement, with the calliper width equal to 0.2 SD of the PS logit. The balance between the statin and non-statin groups in the matched cohort was estimated using absolute standardised difference. Multivariable cox regression analyses were performed to assess the impact of statin on the clinical outcomes. In addition to the PS matching model, we built a multivariable model by inverse probability of treatment weighting (IPTW) using the PS.[14] Time-to-event variables were reported using Kaplan-Meier estimations. All reported *P*-values were two-sided, and a *P*-value <0.05 was considered statistically significant. All

statistical analyses were performed using the R software package (version 3.3.2; R Development Core Team, Vienna, Austria).

Patient and Public Involvement statement

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

Results

Among the 2588 patients who underwent TAVI, 1523 and 1065 patients were classified into the statin and the non-statin group, respectively (Figure 1). The distribution of PS in the statin and non-statin groups is shown in Supplementary material online, Figure S1. After 1:1 PS matching, we identified 936 matched pairs of patients with similar PS. The patient characteristics of the statin and non-statin groups before and after matching are summarised in Table 1. The overall cohort included very elderly patients (84.4±5.2 years). The majority of the cohort was female (69.3%). After PS matching, the two groups were well-balanced in terms of pre-procedural patient characteristics and procedural variables. In-hospital all-cause mortality, acute kidney injury, stroke, and vascular complications did not differ between the two groups. Post-procedural echocardiography data showed no significant differences

between the two groups (Table 2). The patient characteristics and in-hospital outcomes of the PS matched and unmatched groups are summarised in Supplementary material online, Tables S1 and S2. There were several differences between the two groups. The proportion of male patients was lower in the PS matched group than in the unmatched group (532 [28.4%] vs. 263 [36.7%], $P<0.01$), NYHA Class 3 or 4 was less frequent in the matched group (919 [49.1%] vs. 402 [56.2%], $P<0.01$), the Clinical Frailty Scale was lower in the matched group (3.8±1.2 vs. 4.2±1.4, $P<0.01$), and the STS risk score was lower in the matched group (7.7±5.7 vs 9.8±9.2, $P<0.01$). History of the previous CAD was more frequent (750 [40.1%] vs. 204 [28.5%], $P<0.01$), but previous MI was less frequent (96 [5.1%] vs. 62 [8.7%], $P<0.01$) in the PS matched group. In-hospital all-cause mortality (43 [2.3%] vs. 27 [3.8%], $P<0.01$) and bleeding (421 [22.5%] vs. 199 [27.8%], $P<0.01$) were lower in the matched group than in the unmatched group.

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

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

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

DISCUSSION

The present study investigated the impact of statin therapy on mid-term mortality after TAVI using a Japanese multicentre registry. Statin therapy was associated with significantly lower all-cause and cardiovascular mortality. It should be noted that the impact of statin therapy attenuated in the nonagenarians. Furthermore, we demonstrated differences in all-cause mortality according to the history of previous CAD and statin therapy. The present study included the largest patient cohort (936 pairs of patients after PS matching) and the first report to investigate the association of age and a history of previous CAD with the impact of statin.

Few reports have assessed the impact of statin treatment on mortality after TAVI. Peri-Okonny et al. demonstrated that statin therapy was associated with reductions in 2-year all-cause (aHR 0.65, 95% CI 0.49–0.87, P=0.001), cardiovascular (aHR 0.66, 95% CI 0.46–0.96, P=0.030), and non-cardiovascular mortality (aHR 0.64, 95% CI 0.44–0.99, P=0.045) compared with no statin therapy, with a large cohort using PARTNER II and Sapien 3 clinical trials or associated registries (626 pairs of patients after PS matching).[7] Merdler et al. showed that high-intensity statin therapy was associated with a reduction in mortality after TAVI (median follow-up period: 2.5 years) using data of 1238 cases from a single-centre registry (aHR 0.59, 95% CI 0.37–0.96, P=0.03).[15] Huded et al. also showed that high-intensity statin therapy was associated with a reduction in all-cause mortality (mean survival:

3.9 years) based on 294 cases (aHR 0.36, 95% CI 0.14–0.90, *P*=0.029).[16] Takagi et al. reported similar results following a meta-analysis.[17] These results were consistent with our results.

The mechanism through which statin therapy reduces the risks of all-cause and cardiovascular mortality is thought to be associated with a reduction in ischaemic events.[7, 15, 16, 17] However, there are limited data relative to statin therapy in octogenarians and nonagenarians, as are data not only on TAVI but also on statin therapy as primary and secondary prevention. The PROspective Study of Pravastatin in the Elderly at Risk trial was the only randomised controlled trial for elderly patients (aged 70–82 years) with a history or risk factors of vascular disease. The study revealed that pravastatin led to a 3-year reduced risk of CAD.[18] Recommendation of statin therapy for very elderly patients varies among the guidelines.[19, 20, 21, 22, 23] Very recently, a few reports supporting statin therapy for very elderly patients have been published. In the Patient and Provider Assessment of Lipid Management Registry, statin therapy appeared to be similarly tolerated by patients older and younger than 75 years.[24] The Cholesterol Treatment Trialists' Collaboration demonstrated that statin therapy as primary and secondary prevention produced significant reductions in major vascular events even in patients older than 75 years.[25] Furthermore, Romas et al. revealed that statin therapy was associated with significant reductions in atherosclerotic CVD and all-cause mortality for patients who were older than 74 years and had diabetes.[26] Interestingly, Giral et al. demonstrated that statin discontinuation in 75-year-old primary prevention patients was associated with a 33% increased risk of cardiovascular events.[27] Our present study was consistent with these reports and indicated that statin therapy would be effective for very elderly and atherosclerotic high-risk patients by reducing cardiovascular events and mortality. Conversely, Romas et al. reported that the benefits of statin therapy disappeared in nonagenarians,[26] as observed in our nonagenarian cohort.

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

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 and the IPTW 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 matched and unmatched group, but might be plausible given the results of the IPTW model. Third, information on the type and doses of statin therapy was not obtained. Usage of ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitor was not recorded in this study. Fourth, we assessed statin use only on admission and there was a possibility that statin therapy might have changed at discharge or during follow-up. Finally, we could not assess intolerance in patients eligible for statin treatment but who could not continue treatment due to statin side effects such as rhabdomyolysis. Further studies, including a randomised controlled trial, on statin therapy following TAVI are warranted to resolve these limitations.

In conclusion, using data from the large multicentre registry, statin therapy after TAVI was associated with significant reductions in mid-term all-cause and cardiovascular mortality. Statin therapy after TAVI will be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients with CAD.

Acknowledgements

We express our heartfelt gratitude to the team members at our hospital and other hospitals participating in the multicentre registry and the Japan Society of Clinical Research (http://www.japanscr.org/) for their dedicated support.

Funding

The OCEAN-TAVI registry is supported by Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Medical, and Daiichi-Sankyo Company. There are no award/grant numbers for the Funders.

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.

Data collection: Makoto Tanaka, Masahiro Jinzaki, Hideyuki Shimizu, and Keiichi Fukuda.

Data analysis and interpretation: Masahiko Hara, Taku Inohara, Kensuke Takagi, Hiroshi Ueno, and Norio Tada.

Drafting the article: Fumiaki Yashima and Taku Inohara.

Critical revision of the article: Masanori Yamamoto, Yusuke Watanabe, Kentaro Hayashida.

Final approval of the version to be published: all authors.

References

1 Mack MJ, Leon MB, Smith CR, et al. PARTNER 1 trial investigators, 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477–84.

2 Kapadia SR, Leon MB, Makkar RR,et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2485–91.

3 Popma JJ, Deeb GM, Yakubov SJ et al.Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706–15.

4 Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–705.

5 Chakos A, Wilson-Smith A, Arora S, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. *Ann Cardiothorac Surg* 2017;6:432–43.

6 Holmes DR Jr, Brennan JM, Rumsfeld JS, et al. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 2015;313:1019–28.

7 Peri-Okonny PA, Liu Y, Malaisrie SC, et al. Association of statin use and mortality after transcatheter aortic valve replacement. *J Am Heart Assoc* 2019;8:e011529.

8 Shimura T, Yamamoto M, Kano S, et al. Impact of the Clinical Frailty Scale on outcomes after transcatheter aortic valve replacement. *Circulation* 2017;135:2013–24.

9 Yashima F, Yamamoto M, Tanaka M, et al. Transcatheter aortic valve implantation in patients with an extremely small native aortic annulus: the OCEAN-TAVI registry. *Int J Cardiol* 2017;240:126–31.

10 Kataoka A, Watanabe Y, Kozuma K, et al. Prognostic impact of low-flow severe aortic stenosis in small-body patients undergoing TAVR: the OCEAN-TAVI registry. *JACC Cardiovasc Imaging* 2018;11:659–69.

11 Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–54.

12 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.

13 Weitzen S, Lapane KL, Toledano AY, et al. Principles for modeling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiol Drug Saf* 2004;13:841–53.

14 Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med* 2013;32:2837–49.

15 Merdler I, Rozenbaum Z, Finkelstein A, et al. Effect of statin therapy and long-term mortality following transcatheter aortic valve implantation. *Am J Cardiol* 2019;123:1978–82.

16 Huded CP, Benck LR, Stone NJ, et al. Relation of intensity of statin therapy and outcomes after transcatheter aortic valve replacement. *Am J Cardiol* 2017;119:1832–38.

17 Takagi H, Hari Y, Nakashima K, et al. Meta-analysis for impact of statin on mortality after transcatheter aortic valve implantation. *Am J Cardiol* 2019;124:920–25.

18 Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–30.

19 Mortensen MB, Falk E. Primary prevention with statins in the elderly. *J Am Coll Cardiol* 2018;71:85–94.

20 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of

Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81.

21 Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2016;316:1997–2007.

22 Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2016;32:1263–82.

23 National Clinical Guideline Centre. Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London, UK: National Institute for Health and Care Excellence 2014.

24 Nanna MG, Navar AM, Wang TY, et al. Statin use and adverse effects among adults >75 years of age: insights from the Patient and Provider Assessment of Lipid Management (PALM) registry. *J Am Heart Assoc* 2018;7:e008546.

25 Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;393:407–15.

26 Ramos R, Comas-Cufi M, Marti-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ* 2018;362:k3359.

27 Giral P, Neumann A, Weill A, et al. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J* 2019;40:3516–25.

28 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–89.

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 (+) *n*=1065	Statin (-) *n*=1523	Standardised difference	Statin (+) *n*=936	Statin (-) *n*=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, *n* (%)	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

NYHA class 3 or 4, *n* (%)	518 (48.6%)	803 (52.7%)	0.08	462 (49.4%)	457 (48.8%)	0.01
Clinical Frailty Scale	3.8±1.2	4.1±1.3	0.23	3.8±1.2	3.8±1.2	0.04
Diabetes mellitus, *n* (%)	264 (24.8%)	291 (19.1%)	0.14	207 (22.1%)	195 (20.8%)	0.03
Smoking, *n* (%)	212 (19.9%)	260 (17.1%)	0.07	169 (18.1%)	160 (17.1%)	0.02
Hypertension, *n* (%)	861 (80.9%)	1129 (74.1%)	0.16	744 (79.5%)	753 (80.5%)	0.02
Chronic kidney disease, *n* (%)	755 (70.9%)	1054 (69.2%)	0.04	651 (69.6%)	640 (68.4%)	0.03
Atrial fibrillation, *n* (%)	195 (18.3%)	354 (23.2%)	0.12	181 (19.3%)	183 (19.6%)	0.01
Coronary artery disease, *n* (%)	507 (47.6%)	447 (29.4%)	0.38	378 (40.4%)	372 (39.7%)	0.01
Previous myocardial infarction, *n* (%)	108 (10.1%)	50 (3.3%)	0.28	48 (5.1%)	48 (5.1%)	<0.01

Previous percutaneous coronary intervention, *n* (%)	342 (32.1%)	284 (18.7%)	0.31	249 (26.6%)	238 (25.4%)	0.03
Previous coronary artery bypass grafting, *n* (%)	112 (10.5%)	57 (3.7%)	0.27	60 (6.4%)	57 (6.1%)	0.01
Peripheral artery disease, *n* (%)	161 (15.1%)	216 (14.2%)	0.03	136 (14.5%)	128 (13.7%)	0.02
Previous stroke, *n* (%)	127 (11.9%)	174 (11.4%)	0.02	116 (12.4%)	102 (10.9%)	0.05
STS risk score	7.7±6.0	8.6±7.5	0.13	7.7±6.1	7.7±5.3	<0.01
Renin-angiotensin inhibitor, *n* (%)	639 (60.0%)	748 (49.1%)	0.22	540 (57.7%)	544 (58.1%)	0.01
ß blocker, *n* (%)	384 (36.1%)	496 (32.6%)	0.07	334 (35.7%)	303 (32.4%)	0.07
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
Haemoglobin, g/dL	11.4±1.7	11.1±1.7	0.17	11.4±1.7	11.2±1.6	0.15

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, *n* (%)	12 (0.8%)	4 (0.4%)	0.05	7 (0.8%)	4 (0.4%)	0.04
Severe mitral regurgitation, *n* (%)	21 (1.4%)	12 (1.1%)	0.02	12 (1.3%)	6 (0.6%)	0.07
Pulmonary hypertension, *n* (%)	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, *n* (%)	873 (82.0%)	1294 (85.0%)	0.08	770 (82.3%)	784 (83.8%)	0.04
Local anaesthesia, *n* (%)	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

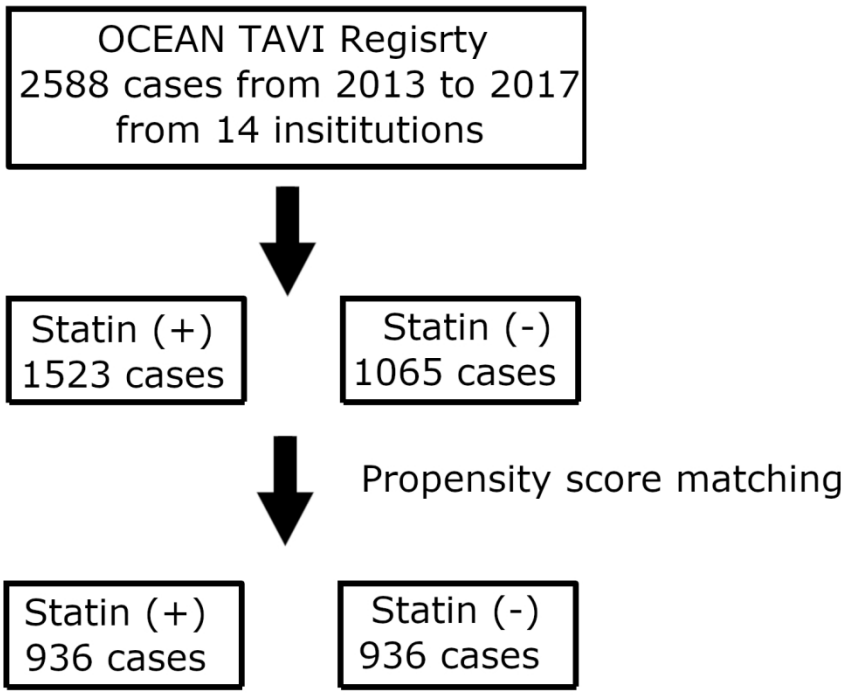
CT, computed tomography; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Table 2

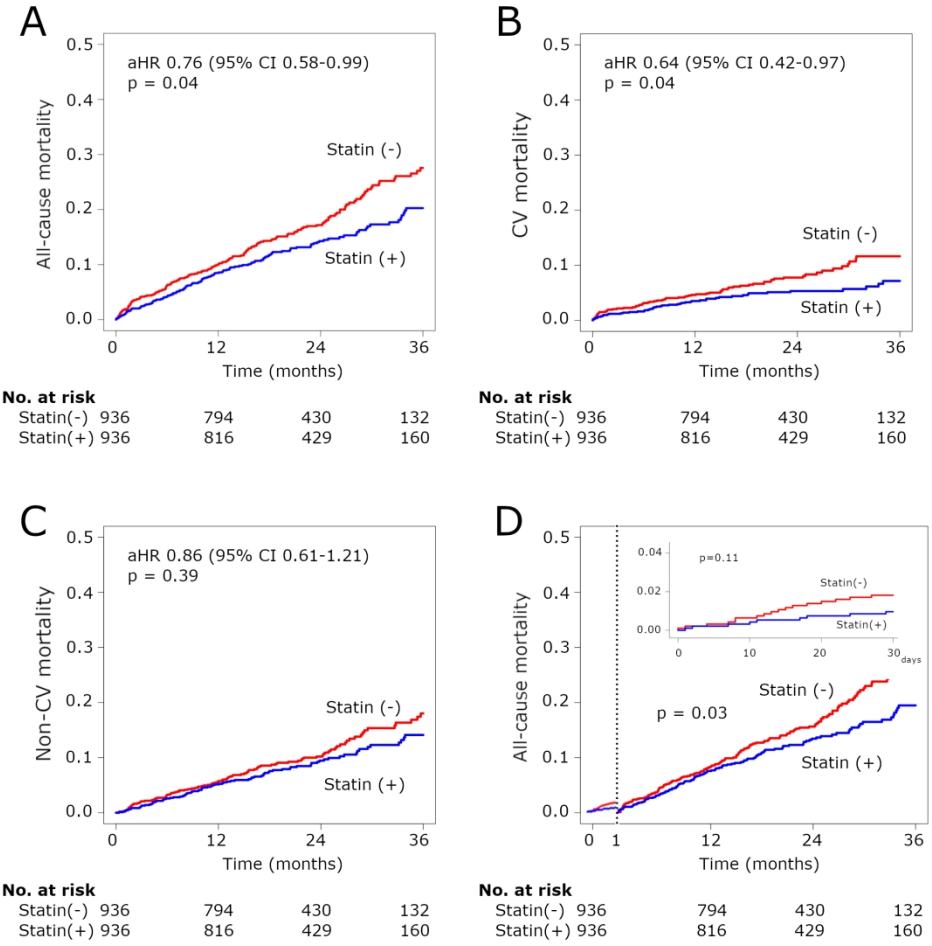
In-hospital outcomes before and after propensity score matching

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

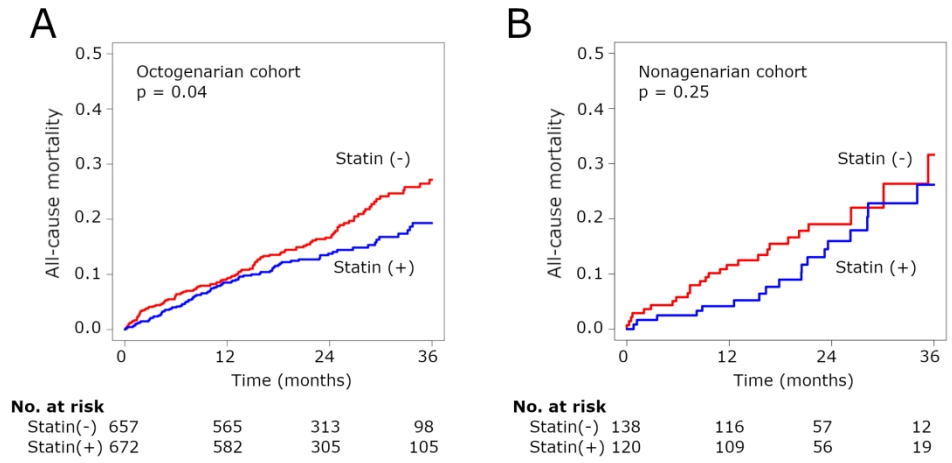
Postprocedural echocardiographic data								
Effective orifice area, cm^2	1.67±0.45	1.69±0.45	0.53	0.03	1.68±0.44	1.66±0.43	0.34	0.04
Indexed effective orifice area, cm^2/m^2	1.17±0.32	1.20±0.31	0.02	0.10	1.18±0.32	1.18±0.30	0.99	<0.01
Mean aortic gradient, mmHg	11.0±4.4	10.6±4.7	0.08	0.07	11.0±4.4	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, *n* (%)	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, *n* (%)	59 (5.6%)	100 (6.6%)	0.27	0.04	45 (4.8%)	51 (5.5%)	0.52	0.03



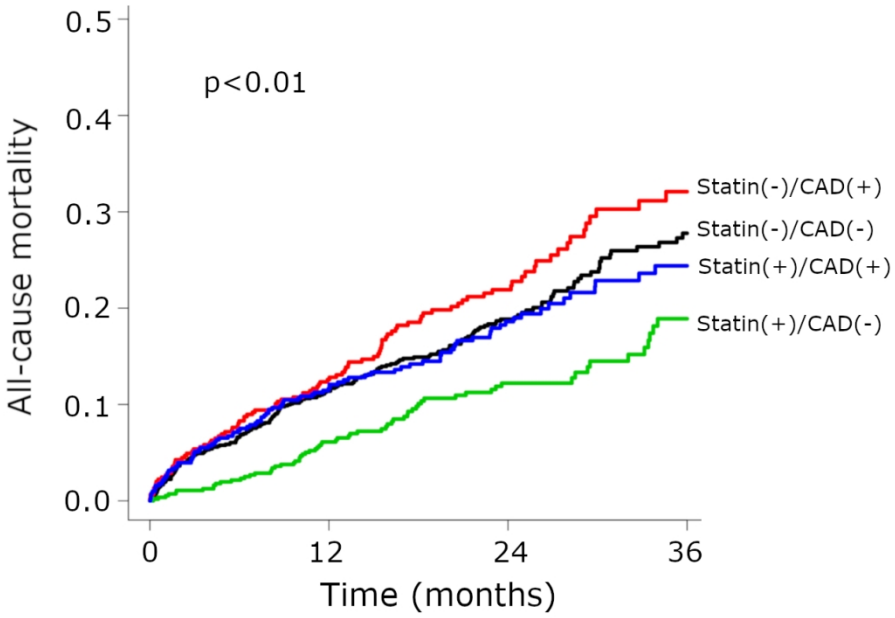
Flowchart of patient selection for the present study.



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

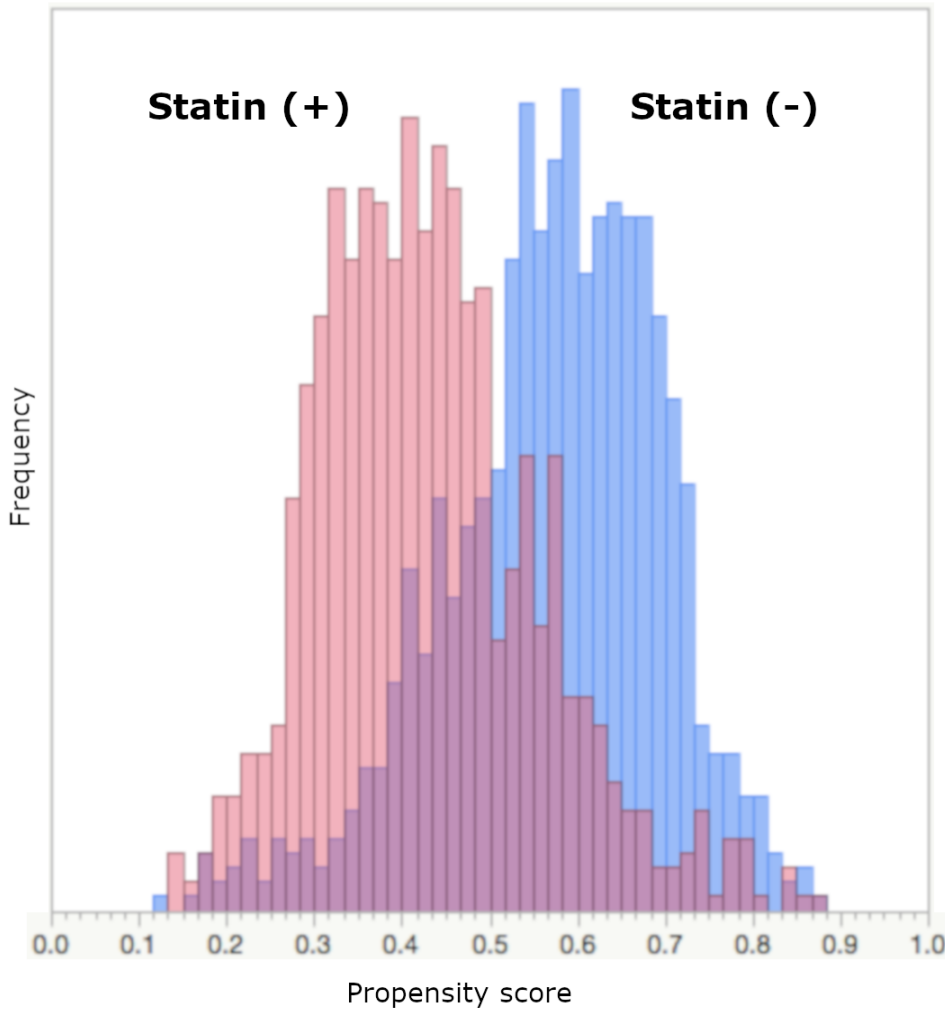
Statin(-)/CAD(+)	447	368	201	59
Statin(-)/CAD(-)	1076	895	456	142
Statin(+)/CAD(+)	507	428	231	87
Statin(+)/CAD(-)	558	497	256	93

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

	Matched group *n*=1872	Unmatched group *n*=716	*P*-value
Preprocedural variables			
Age, years	84.2±5.1	84.6±5.4	0.08
Male, n (%)	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, n (%)	919 (49.1%)	402 (56.2%)	<0.01
Clinical Frailty Scale	3.8±1.2	4.2±1.4	<0.01
Smoking, *n* (%)	364 (19.4%)	160 (22.4%)	0.10
Diabetes mellitus, *n* (%)	402 (21.5%)	153 (21.4%)	0.95
Hypertension, *n* (%)	1497 (80.0%)	493 (68.9%)	<0.01
Chronic kidney disease, *n* (%)	1291 (69.0%)	518 (72.4%)	0.09
Atrial fibrillation, *n* (%)	364 (19.4%)	185 (25.8%)	<0.01

Coronary artery disease, *n* (%)	750 (40.1%)	204 (28.5%)	<0.01
Previous myocardial infarction, *n* (%)	96 (5.1%)	62 (8.7%)	<0.01
Previous percutaneous coronary intervention, *n* (%)	487 (26.0%)	139 (19.4%)	<0.01
Previous coronary artery bypass grafting, *n* (%)	117 (6.3%)	52 (7.3%)	0.36
Peripheral artery disease, *n* (%)	264 (14.1%)	113 (15.8%)	0.28
Previous stroke, *n* (%)	9 (0.5%)	3 (0.4%)	0.98
STS risk score	7.7±5.7	9.8±9.2	<0.01
Renin-angiotensin inhibitor, *n* (%)	1084 (57.9%)	303 (42.3%)	<0.01
Beta blocker, *n* (%)	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, *n* (%)	1554 (83.0%)	613 (85.6%)	0.11

Local anaesthesia, *n* (%)	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.

Supplementary Table S2

In-hospital outcomes of the propensity score-matched and -unmatched groups

	Matched group *n*=1872	**Unmatched group** *n*=716	***P*-value**
All-cause mortality, *n* (%)	43 (2.3%)	27 (3.8%)	<0.01
Acute kidney injury, *n* (%)	201 (10.7%)	88 (12.3%)	0.27
Bleeding, *n* (%)	421 (22.5%)	199 (27.8%)	<0.01
Stroke, *n* (%)	43 (2.3%)	18 (2.5%)	0.75
Vascular complication, *n* (%)	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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044319.R1
Article Type:	Original research
Date Submitted by the Author:	17-Mar-2021
Complete List of Authors:	Yashima, Fumiaki; Saiseikai Utsunomiya Hospital; Keio University Hospital Hara, Masahiko; Shimane University Inohara, Taku; Vancouver General Hospital Jinzaki, Masahiro ; Keio University Hospital Shimizu, Hideyuki; Keio University Hospital Fukuda, Keiichi; Keio University Hospital Tanaka, Makoto; Keio University Hospital Yamamoto, Masanori; Toyohashi Heart Center Watanabe, Yusuke; Teikyo Daigaku Naganuma, Toru; Shintokyo Byoin Shirai, Shinichi; Kokura Kinen Byoin Yamawaki, Masahiro; Saiseikai Yokohamashi Tobu Hospital Tada, Norio; Sendai Kosei Byoin Yamanaka, Futoshi; Shonan Kamakura General Hospital Mizutani, Kazuki; Osaka City General Hospital Ueno, Hiroshi; Toyama Daigaku Igakubu Daigakuin Igaku Yakugaku Kyoikubu, Tabata, Minoru; Tokyo Bay Urayasu Ichikawa Iryo Center Takagi, Kensuke; Ogaki Shimin Byoin Hayashida, Kentaro; Keio University Hospital
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

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Short title: Statin therapy for TAVI patients

Fumiaki Yashima, MD, PhD[1,2,*]; Masahiko Hara, MD, PhD[3]; Taku Inohara, MD, PhD[2,4]; Masahiro Jinzaki, MD, PhD[5]; Hideyuki Shimizu, MD, PhD[6]; Keiichi Fukuda, MD, PhD, FACC, FESC[2]; Makoto Tanaka, MD[2]; Masanori Yamamoto, MD, PhD, FESC[7,8]; Yusuke Watanabe, MD[9]; Toru Naganuma, MD, FACC, FESC[10]; Shinichi Shirai, MD[11]; Masahiro Yamawaki, MD[12]; Norio Tada, MD[13]; Futoshi Yamanaka, MD[14]; Kazuki Mizutani, MD[15]; Hiroshi Ueno, MD[16]; Minoru Tabata, MD[17]; Kensuke Takagi, MD[18]; Kentaro Hayashida, MD, PhD, FESC, FACC, FJCS[2] on behalf of the OCEAN-TAVI registry

[1]Department of Cardiology, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan

[2]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

[3]Center for Community-based Healthcare Research and Education, Shimane University, Izumo, Japan

[4]Division of Cardiology, Vancouver General Hospital, Vancouver, Canada

[5]Department of Diagnostic Radiology, Keio University School of Medicine, Tokyo, Japan

[6]Department of Cardiovascular Surgery, Keio University School of Medicine, Tokyo, Japan

[7]Department of Cardiology, Toyohashi Heart Centre, Toyohashi, Japan

[8]Department of Cardiology, Nagoya Heart Centre, Aichi, Japan

[9]Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan

[10]Department of Cardiology, New Tokyo Hospital, Matsudo, Japan

[11]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan

[12]Department of Cardiology, Saiseikai Yokohama-City Eastern Hospital, Yokohama, Japan

[13]Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan

[14]Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Japan

[15]Department of Cardiology, Osaka City General Hospital, Osaka, Japan

[16]Department of Cardiology, Toyama University Hospital, Toyama, Japan

[17]Department of Cardiovascular Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu, Japan

[18]Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan

***Corresponding author**

Fumiaki Yashima, MD, PhD

Department of Cardiology, Saiseikai Utsunomiya Hospital,

911-1 Takebayashi-cho, Utsunomiya, Tochigi, 321-0974, Japan

Phone: 81-28-626-5500; Fax: 81-28-626-5573

Email: yashima.fumiaki@gmail.com

Word count: 2829

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).

Conclusions Statin for TAVI patients will be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In addition, statin will be essential for TAVI patients with CAD. Further researches are warranted to confirm and generalise our findings, since this study has inherent limitations of the observational study and included only Japanese patients.

Keywords: coronary artery disease, elderly, propensity score matching, statin, transcatheter aortic valve implantation

Strengths and limitations of this study

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

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

Bay Urayasu Ichikawa Medical Center, and Ogaki municipal hospital) between 2013 and 2017 were prospectively included in our TAVI registry (Optimized CathEter vAlvular iNtervention [OCEAN-TAVI] registry).[8, 9, 10] Informed consent was obtained from all patients, and the institutional review boards of all 14 participating centres approved this study. Additionally, this study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The OCEAN-TAVI registry was registered with the University Hospital Medical Information Network Clinical Trial Registry and accepted by the International Committee of Medical Journal Editors (UMIN-ID: 000020423).

Patients received transcatheter heart valves (THVs) via either the transfemoral, transapical, or transaortic approach. Sapien XT valves, Sapien 3 valves (Edwards Lifesciences, Irvine, CA), CoreValves, Evolut R (Medtronic, Minneapolis, MN) were used as THVs. A total of 2588 patients were treated with TAVI between 2013 and 2017. They were categorised into two groups according to statin administration at admission for TAVI procedures (Figure 1). We set the primary endpoint as mid-term all-cause mortality for up to 3 years. Secondary endpoints included mid-term cardiovascular mortality, mid-term non-cardiovascular mortality up to 3 years, and 30-day all-cause mortality.

We performed propensity score (PS) matching, as described below, and compared the endpoints between the two groups in the matched cohort. In addition, we categorised the matched cohort into two cohorts; an octogenarian cohort (80–89 years old) and a nonagenarian cohort (90 years or older), and investigated the differences by age in the impact of statin on mid-term all-cause mortality. Furthermore, we classified the overall cohort into four groups according to a history of CAD and statin treatment at admission and evaluated whether the impact of statin differed according to the underlying CAD condition. We also explored predictors of mid-term all-cause mortality in the overall cohort using multivariate analysis.

Clinical outcomes including all-cause mortality and cardiovascular mortality were defined according to the Valve Academic Research Consortium-2 consensus document.[11]

Statistical analysis

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

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

statistically significant. All statistical analyses were performed using the R software package (version 3.3.2; R Development Core Team, Vienna, Austria).

Patient and Public Involvement statement

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

RESULTS

Among the 2588 patients who underwent TAVI, 1523 and 1065 patients were classified into the statin and the non-statin group, respectively (Figure 1). The distribution of PS in the statin and non-statin groups is shown in Supplementary material online, Figure S1. After 1:1 PS matching, we identified 936 matched pairs of patients with similar PS. The patient characteristics of the statin and non-statin groups before and after matching are summarised in Table 1. The overall cohort included very elderly patients (84.4±5.2 years). The majority of the cohort was female (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.

After PS matching, the two groups were well-balanced in terms of pre-procedural patient characteristics and procedural variables. In-hospital all-cause mortality, acute kidney injury, stroke, and vascular complications did not differ between the two groups. Post-procedural

echocardiography data showed no significant differences between the two groups (Table 2). The patient characteristics and in-hospital outcomes of the PS matched and unmatched groups are summarised in Supplementary material online, Tables S1 and S2. There were several differences between the two groups. The proportion of male patients was lower in the PS matched group than in the unmatched group (532 [28.4%] vs. 263 [36.7%], *P*<0.01), NYHA Class 3 or 4 was less frequent in the matched group (919 [49.1%] vs. 402 [56.2%], *P*<0.01), the Clinical Frailty Scale was lower in the matched group (3.8±1.2 vs. 4.2±1.4, *P*<0.01), and the STS risk score was lower in the matched group (7.7±5.7 vs 9.8±9.2, *P*<0.01). History of the previous CAD was more frequent (750 [40.1%] vs. 204 [28.5%], *P*<0.01), but previous MI was less frequent (96 [5.1%] vs. 62 [8.7%], *P*<0.01) in the PS matched group. In-hospital all-cause mortality (43 [2.3%] vs. 27 [3.8%], *P*<0.01) and bleeding (421 [22.5%] vs. 199 [27.8%], *P*<0.01) were lower in the matched group than in the unmatched group.

In the overall cohort, the median follow-up period was 660 days. Statin therapy was associated with significantly lower mid-term all-cause mortality in the PS-matched cohort (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, *P*=0.04) (Figure 2a), which was consistent with the IPTW model (aHR 0.80, 95% CI 0.65–0.99, *P*=0.04). The Kaplan-Meier curves relative to the mid-term outcomes additionally showed significant differences in cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, *P*=0.04) and non-cardiovascular mortality (aHR 0.86, 95% CI 0.61–1.21, *P*=0.39) between the two groups (Figure 2b and 2c). There was no significant difference in 30-day all-cause mortality (aHR 0.73, 95% CI 0.47-1.08, *P*=0.11) and a landmark analysis after 30 days showed a significant difference in mid-term all-cause mortality (aHR 0.88, 95% CI 0.78-0.99, *P*=0.03) (Figure 2d).

In the octogenarian cohort (80–89 years old), statin therapy was associated with significantly lower mid-term all-cause mortality (aHR 0.87, 95% CI 0.75-0.99, *P*=0.04)

(Figure 3a), but the impact in the nonagenarian cohort (90 years or older) appeared to be lower (aHR 0.84, 95% CI 0.62-1.13, *P*=0.25) (Figure 3b). P for interaction was 0.90.

Furthermore, comparing the four groups according to previous CAD and statin therapy, there was a significant difference in mid-term all-cause mortality (*P*<0.01) (Figure 4). Patients who did not receive statin therapy despite a history of 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]). Their survival curve diverged from that of the patients without previous CAD or statin after 1 year. In addition, patients with previous CAD and statin therapy (aHR 1.04, 95% CI 0.87-1.23) seemed to obtain similar risks with those who did not have previous CAD or statin therapy (aHR 1.11, 95% CI 0.96-1.27 [patients who received statin without previous CAD as a reference]).

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

DISCUSSION

The present study investigated the impact of statin therapy on mid-term mortality after TAVI using a Japanese multicentre registry. Statin therapy at admission was associated with significantly lower all-cause and cardiovascular mortality. It should be noted that the impact of statin therapy attenuated in the nonagenarians. Furthermore, we demonstrated differences in all-cause mortality according to the history of previous CAD and statin therapy. The present study included the largest patient cohort (936 pairs of patients after PS matching) and the first report to investigate the association of age and a history of previous CAD with the impact of statin.

Few reports have assessed the impact of statin treatment on mortality after TAVI. Peri-Okonny et al. demonstrated that statin therapy was associated with reductions in 2-year all-cause (aHR 0.65, 95% CI 0.49–0.87, *P*=0.001), cardiovascular (aHR 0.66, 95% CI 0.46–0.96, *P*=0.030), and non-cardiovascular mortality (aHR 0.64, 95% CI 0.44–0.99, *P*=0.045) compared with no statin therapy, with a large cohort using PARTNER II and Sapien 3 clinical trials or associated registries (626 pairs of patients after PS matching).[7] Merdler et al. showed that high-intensity statin therapy was associated with a reduction in mortality after TAVI (median follow-up period: 2.5 years) using data of 1238 cases from a single-centre registry (aHR 0.59, 95% CI 0.37–0.96, *P*=0.03).[15] Huded et al. also showed that high-intensity statin therapy was associated with a reduction in all-cause mortality (mean survival: 3.9 years) based on 294 cases (aHR 0.36, 95% CI 0.14–0.90, *P*=0.029).[16] Takagi et al. reported similar results following a meta-analysis.[17] These results were consistent with our results.

The mechanism through which statin therapy reduces the risks of all-cause and cardiovascular mortality is thought to be associated with a reduction in ischaemic events.[7, 15, 16, 17] However, there are limited data relative to statin therapy in octogenarians and nonagenarians, as are data not only on TAVI but also on statin therapy as primary and secondary prevention. The PROspective Study of Pravastatin in the Elderly at Risk trial was the only randomised controlled trial for elderly patients (aged 70–82 years) with a history or risk factors of vascular disease. The study revealed that pravastatin led to a 3-year reduced risk of CAD.[18] Recommendation of statin therapy for very elderly patients varies among the guidelines.[19, 20, 21, 22, 23] Very recently, a few reports supporting statin therapy for very elderly patients have been published. In the Patient and Provider Assessment of Lipid Management Registry, statin therapy appeared to be similarly tolerated by patients older and younger than 75 years.[24] The Cholesterol Treatment Trialists' Collaboration demonstrated

that statin therapy as primary and secondary prevention produced significant reductions in major vascular events even in patients older than 75 years.[25] Furthermore, Romas et al. revealed that statin therapy was associated with significant reductions in atherosclerotic cardiovascular events and all-cause mortality for patients who were older than 74 years and had diabetes.[26] Interestingly, Giral et al. demonstrated that statin discontinuation in 75-year-old primary prevention patients was associated with a 33% increased risk of cardiovascular events.[27] Our present study was consistent with these reports and indicated that statin therapy would be effective for very elderly and atherosclerotic high-risk patients by reducing cardiovascular events and mortality. Conversely, Romas et al. reported that the benefits of statin therapy disappeared in nonagenarians,[26] as observed in our nonagenarian cohort. However , P for interaction among the octogenarian and nonagenarian cohorts in the present study was not significant, and the sizes of the cohorts and confounding regarding prescribing statin to nonagenarians with CAD might skew the results.

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

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

matched and unmatched group as it might be plausible given the results of the IPTW model. In addition, generalising our findings outside Japan also requires attention since this study included only Japanese patients. Third, information on the type and doses of statin therapy was not obtained. Usage of ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitor was not recorded in this study. Fourth, we assessed statin use only on admission and there was a possibility that statin therapy might have changed at discharge or during follow-up. The duration of statin administration and the timing to start prescribing statin were not captured in the present study. Finally, we could not assess intolerance in patients eligible for statin treatment but who could not continue treatment due to statin side effects such as rhabdomyolysis. Further studies, including a randomised controlled trial, on statin therapy following TAVI are warranted to resolve these limitations.

In conclusion, using data from the large multicentre registry, statin therapy at admission of TAVI was associated with significant reductions in mid-term all-cause and cardiovascular mortality. Statin therapy prior TAVI will be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients with CAD. Further researches are warranted to confirm and generalise our findings, since the present study has several inherent limitations of the observational study and included only Japanese patients.

Acknowledgements

We express our heartfelt gratitude to the team members at our hospital and other hospitals participating in the multicentre registry and the Japan Society of Clinical Research (http://www.japanscr.org/) for their dedicated support.

Funding

The OCEAN-TAVI registry is supported by Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Medical, and Daiichi-Sankyo Company. There are no award/grant numbers for the Funders.

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.

Data collection: Makoto Tanaka, Masahiro Jinzaki, Hideyuki Shimizu, and Keiichi Fukuda.

Data analysis and interpretation: Masahiko Hara, Taku Inohara, Kensuke Takagi, Hiroshi Ueno, and Norio Tada.

Drafting the article: Fumiaki Yashima and Taku Inohara.

Critical revision of the article: Masanori Yamamoto, Yusuke Watanabe, Kentaro Hayashida.

Final approval of the version to be published: all authors.

References

1 Mack MJ, Leon MB, Smith CR, et al. PARTNER 1 trial investigators, 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477–84.

2 Kapadia SR, Leon MB, Makkar RR,et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2485–91.

3 Popma JJ, Deeb GM, Yakubov SJ et al.Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706–15.

4 Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–705.

5 Chakos A, Wilson-Smith A, Arora S, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. *Ann Cardiothorac Surg* 2017;6:432–43.

6 Holmes DR Jr, Brennan JM, Rumsfeld JS, et al. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 2015;313:1019–28.

7 Peri-Okonny PA, Liu Y, Malaisrie SC, et al. Association of statin use and mortality after transcatheter aortic valve replacement. *J Am Heart Assoc* 2019;8:e011529.

8 Shimura T, Yamamoto M, Kano S, et al. Impact of the Clinical Frailty Scale on outcomes after transcatheter aortic valve replacement. *Circulation* 2017;135:2013–24.

9 Yashima F, Yamamoto M, Tanaka M, et al. Transcatheter aortic valve implantation in patients with an extremely small native aortic annulus: the OCEAN-TAVI registry. *Int J Cardiol* 2017;240:126–31.

10 Kataoka A, Watanabe Y, Kozuma K, et al. Prognostic impact of low-flow severe aortic stenosis in small-body patients undergoing TAVR: the OCEAN-TAVI registry. *JACC Cardiovasc Imaging* 2018;11:659–69.

11 Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–54.

12 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.

13 Weitzen S, Lapane KL, Toledano AY, et al. Principles for modeling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiol Drug Saf* 2004;13:841–53.

14 Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med* 2013;32:2837–49.

15 Merdler I, Rozenbaum Z, Finkelstein A, et al. Effect of statin therapy and long-term mortality following transcatheter aortic valve implantation. *Am J Cardiol* 2019;123:1978–82.

16 Huded CP, Benck LR, Stone NJ, et al. Relation of intensity of statin therapy and outcomes after transcatheter aortic valve replacement. *Am J Cardiol* 2017;119:1832–38.

17 Takagi H, Hari Y, Nakashima K, et al. Meta-analysis for impact of statin on mortality after transcatheter aortic valve implantation. *Am J Cardiol* 2019;124:920–25.

18 Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–30.

19 Mortensen MB, Falk E. Primary prevention with statins in the elderly. *J Am Coll Cardiol* 2018;71:85–94.

20 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of

Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81.

21 Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2016;316:1997–2007.

22 Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2016;32:1263–82.

23 National Clinical Guideline Centre. Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London, UK: National Institute for Health and Care Excellence 2014.

24 Nanna MG, Navar AM, Wang TY, et al. Statin use and adverse effects among adults >75 years of age: insights from the Patient and Provider Assessment of Lipid Management (PALM) registry. *J Am Heart Assoc* 2018;7:e008546.

25 Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;393:407–15.

26 Ramos R, Comas-Cufi M, Marti-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ* 2018;362:k3359.

27 Giral P, Neumann A, Weill A, et al. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J* 2019;40:3516–25.

28 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–89.

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 (+) ***n*=1065**	**Statin (-)** ***n*=1523**	**Standardised difference**	**Statin (+)** ***n*=936**	**Statin (-)** ***n*=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, *n* (%)	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

NYHA class 3 or 4, *n* (%)	518 (48.6%)	803 (52.7%)	0.08	462 (49.4%)	457 (48.8%)	0.01
Clinical Frailty Scale	3.8±1.2	4.1±1.3	0.23	3.8±1.2	3.8±1.2	0.04
Diabetes mellitus, *n* (%)	264 (24.8%)	291 (19.1%)	0.14	207 (22.1%)	195 (20.8%)	0.03
Smoking, *n* (%)	212 (19.9%)	260 (17.1%)	0.07	169 (18.1%)	160 (17.1%)	0.02
Hypertension, *n* (%)	861 (80.9%)	1129 (74.1%)	0.16	744 (79.5%)	753 (80.5%)	0.02
Chronic kidney disease, *n* (%)	755 (70.9%)	1054 (69.2%)	0.04	651 (69.6%)	640 (68.4%)	0.03
Atrial fibrillation, *n* (%)	195 (18.3%)	354 (23.2%)	0.12	181 (19.3%)	183 (19.6%)	0.01
Coronary artery disease, *n* (%)	507 (47.6%)	447 (29.4%)	0.38	378 (40.4%)	372 (39.7%)	0.01
Previous myocardial infarction, *n* (%)	108 (10.1%)	50 (3.3%)	0.28	48 (5.1%)	48 (5.1%)	<0.01

Previous percutaneous coronary intervention, *n* (%)	342 (32.1%)	284 (18.7%)	0.31	249 (26.6%)	238 (25.4%)	0.03
Previous coronary artery bypass grafting, *n* (%)	112 (10.5%)	57 (3.7%)	0.27	60 (6.4%)	57 (6.1%)	0.01
Peripheral artery disease, *n* (%)	161 (15.1%)	216 (14.2%)	0.03	136 (14.5%)	128 (13.7%)	0.02
Previous stroke, *n* (%)	127 (11.9%)	174 (11.4%)	0.02	116 (12.4%)	102 (10.9%)	0.05
STS risk score	7.7±6.0	8.6±7.5	0.13	7.7±6.1	7.7±5.3	<0.01
Renin-angiotensin inhibitor, *n* (%)	639 (60.0%)	748 (49.1%)	0.22	540 (57.7%)	544 (58.1%)	0.01
ß blocker, *n* (%)	384 (36.1%)	496 (32.6%)	0.07	334 (35.7%)	303 (32.4%)	0.07
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
Haemoglobin, g/dL	11.4±1.7	11.1±1.7	0.17	11.4±1.7	11.2±1.6	0.15

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, *n* (%)	12 (0.8%)	4 (0.4%)	0.05	7 (0.8%)	4 (0.4%)	0.04

Severe mitral regurgitation, *n* (%)	21 (1.4%)	12 (1.1%)	0.02	12 (1.3%)	6 (0.6%)	0.07
Pulmonary hypertension, *n* (%)	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, *n* (%)	873 (82.0%)	1294 (85.0%)	0.08	770 (82.3%)	784 (83.8%)	0.04
Local anaesthesia, *n* (%)	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

CT, computed tomography; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; 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			
	Statin (+) *n*=1065	Statin (-) *n*=1523	*P* value	Standardised difference	Statin (+) *n*=936	Statin (-) *n*=936	*P* value	Standardised difference
All-cause mortality, *n* (%)	27 (2.5%)	43 (2.8%)	0.66	0.02	20 (2.1%)	23 (2.5%)	0.64	0.02
Acute kidney injury, *n* (%)	111 (10.4%)	178 (11.7%)	0.31	0.04	96 (10.3%)	105 (11.2%)	0.50	0.03
Stroke, *n* (%)	27 (2.5%)	34 (2.2%)	0.62	0.02	24 (2.6%)	19 (2.0%)	0.44	0.04
Vascular complication, *n* (%)	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, *n* (%)	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, *n* (%)	59 (5.6%)	100 (6.6%)	0.27	0.04	45 (4.8%)	51 (5.5%)	0.52	0.03

Table 3

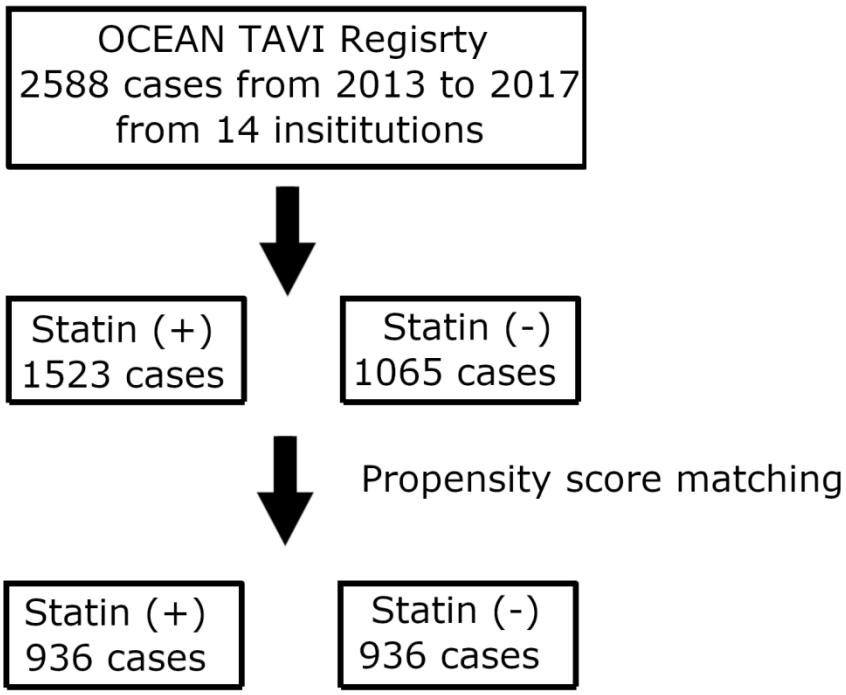
The univariate and multivariate Cox proportional regression analyses of the all-cause mortality in the overall cohort.

	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

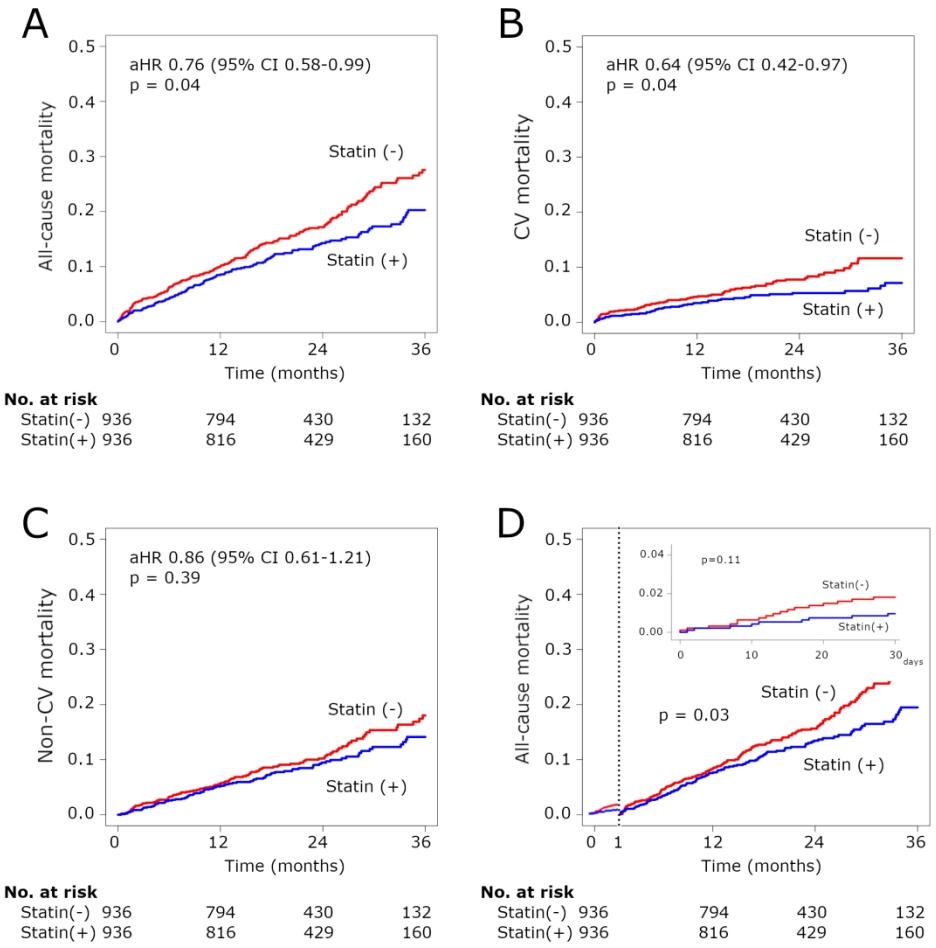
Previous coronary artery bypass grafting	1.21 (1.02-1.40)	0.03	1.05 (0.88-1.24)	0.60
Peripheral artery disease	1.35 (1.21-1.50)	<0.01	1.08 (0.95-1.22)	0.24
Previous stroke	1.14 (0.99-1.30)	0.06	1.04 (0.90-1.19)	0.62
Atrial fibrillation	1.19 (1.07-1.32)	<0.01	1.00 (0.90-1.12)	0.98
STS risk score	1.04 (1.03-1.04)	<0.01	1.02 (1.01-1.03)	<0.01
eGFR, mL/min/1.73 m^2	0.98 (0.98-0.99)	<0.01	0.99 (0.99-1.00)	<0.01
Haemoglobin, g/dL	0.83 (0.78-0.88)	<0.01	0.85 (0.80-0.91)	<0.01
Medication at admission				
Statin	0.84 (0.77-0.93)	<0.01	0.86 (0.77-0.95)	<0.01
Renin-angiotensin inhibitor	0.92 (0.84-1.01)	0.08	0.88 (0.80-0.97)	0.01
ß blocker	1.09 (0.99-1.20)	0.08	1.06 (0.96-1.16)	0.28
Preprocedural echocardiographic data				

Aortic valve area, cm^2/m^2	1.29 (0.76-2.20)	0.35	1.23 (0.63-2.38)	0.54
Peak velocity, mmHg	0.75 (0.67-0.85)	<0.01	0.76 (0.66-0.88)	<0.01
Ejection fraction, %	0.99 (0.98-0.99)	0.03	1.01 (1.00-1.02)	0.02
Pulmonary hypertension	1.50 (1.25-1.78)	<0.01	1.27 (1.05-1.53)	0.01
Severe aortic regurgitation	0.56 (0.13-1.19)	0.16	0.57 (0.21-1.51)	0.26
Severe mitral regurgitation	1.34 (0.93-1.81)	0.11	0.99 (0.70-1.40)	0.96
Procedural variables				
Transfemoral approach	0.81 (0.73-0.91)	<0.01	0.87 (0.77-0.98)	0.03
Local anaesthesia	0.89 (0.79-1.01)	0.07	0.92 (0.81-1.05)	0.22

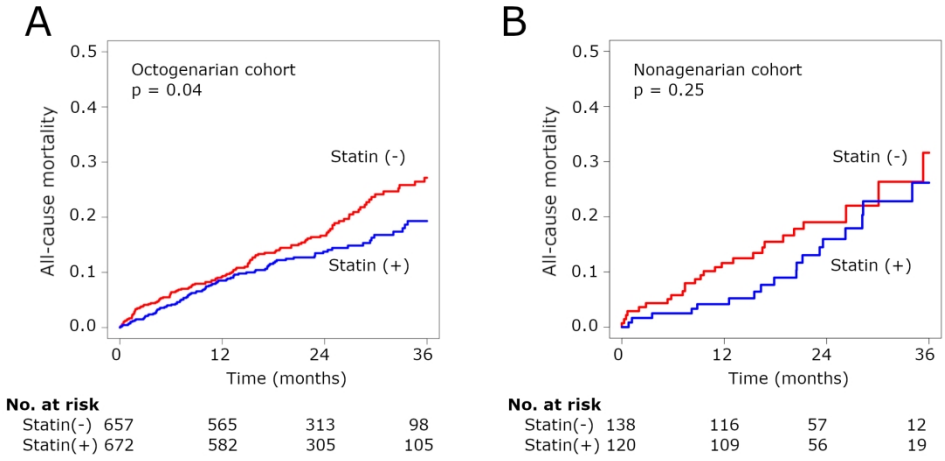
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.



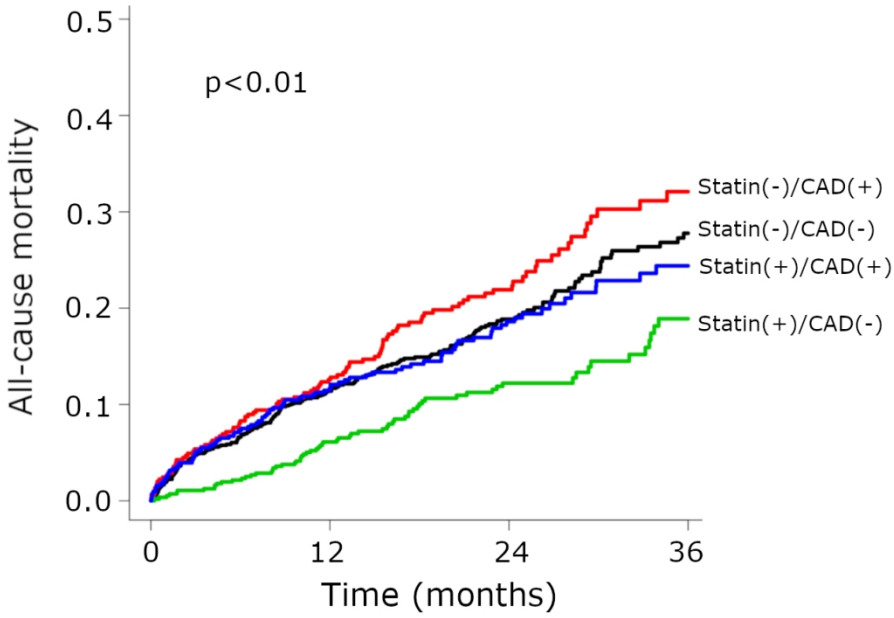
Flowchart of patient selection for the present study.



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

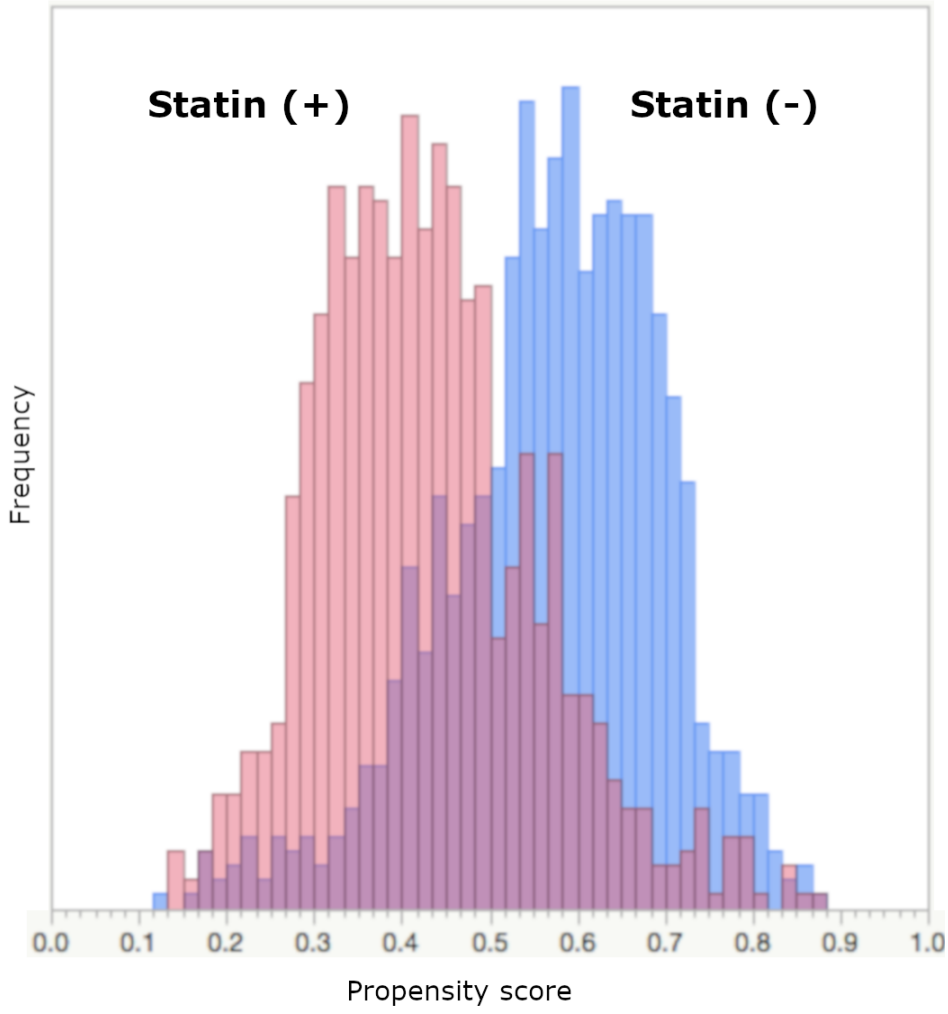
Statin(-)/CAD(+)	447	368	201	59
Statin(-)/CAD(-)	1076	895	456	142
Statin(+)/CAD(+)	507	428	231	87
Statin(+)/CAD(-)	558	497	256	93

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

	Matched group *n*=1872	Unmatched group *n*=716	*P*-value
Preprocedural variables			
Age, years	84.2±5.1	84.6±5.4	0.08
Male, n (%)	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, n (%)	919 (49.1%)	402 (56.2%)	<0.01
Clinical Frailty Scale	3.8±1.2	4.2±1.4	<0.01
Smoking, *n* (%)	364 (19.4%)	160 (22.4%)	0.10
Diabetes mellitus, *n* (%)	402 (21.5%)	153 (21.4%)	0.95
Hypertension, *n* (%)	1497 (80.0%)	493 (68.9%)	<0.01
Chronic kidney disease, *n* (%)	1291 (69.0%)	518 (72.4%)	0.09
Atrial fibrillation, *n* (%)	364 (19.4%)	185 (25.8%)	<0.01

Coronary artery disease, *n* (%)	750 (40.1%)	204 (28.5%)	<0.01
Previous myocardial infarction, *n* (%)	96 (5.1%)	62 (8.7%)	<0.01
Previous percutaneous coronary intervention, *n* (%)	487 (26.0%)	139 (19.4%)	<0.01
Previous coronary artery bypass grafting, *n* (%)	117 (6.3%)	52 (7.3%)	0.36
Peripheral artery disease, *n* (%)	264 (14.1%)	113 (15.8%)	0.28
Previous stroke, *n* (%)	9 (0.5%)	3 (0.4%)	0.98
STS risk score	7.7±5.7	9.8±9.2	<0.01
Renin-angiotensin inhibitor, *n* (%)	1084 (57.9%)	303 (42.3%)	<0.01
Beta blocker, *n* (%)	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, *n* (%)	1554 (83.0%)	613 (85.6%)	0.11

Local anaesthesia, *n* (%)	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.

Supplementary Table S2

In-hospital outcomes of the propensity score-matched and -unmatched groups

	Matched group ***n*=1872**	**Unmatched group** ***n*=716**	***P*-value**
All-cause mortality, *n* (%)	43 (2.3%)	27 (3.8%)	<0.01
Acute kidney injury, *n* (%)	201 (10.7%)	88 (12.3%)	0.27
Bleeding, *n* (%)	421 (22.5%)	199 (27.8%)	<0.01
Stroke, *n* (%)	43 (2.3%)	18 (2.5%)	0.75
Vascular complication, *n* (%)	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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044319.R2
Article Type:	Original research
Date Submitted by the Author:	26-Apr-2021
Complete List of Authors:	Yashima, Fumiaki; Saiseikai Utsunomiya Hospital; Keio University Hospital Hara, Masahiko; Shimane University Inohara, Taku; Vancouver General Hospital Jinzaki, Masahiro ; Keio University Hospital Shimizu, Hideyuki; Keio University Hospital Fukuda, Keiichi; Keio University Hospital Tanaka, Makoto; Keio University Hospital Yamamoto, Masanori; Toyohashi Heart Center Watanabe, Yusuke; Teikyo Daigaku Naganuma, Toru; Shintokyo Byoin Shirai, Shinichi; Kokura Kinen Byoin Yamawaki, Masahiro; Saiseikai Yokohamashi Tobu Hospital Tada, Norio; Sendai Kosei Byoin Yamanaka, Futoshi; Shonan Kamakura General Hospital Mizutani, Kazuki; Osaka City General Hospital Ueno, Hiroshi; Toyama Daigaku Igakubu Daigakuin Igaku Yakugaku Kyoikubu, Tabata, Minoru; Tokyo Bay Urayasu Ichikawa Iryo Center Takagi, Kensuke; Ogaki Shimin Byoin Hayashida, Kentaro; Keio University Hospital
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

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Short title: Statin therapy for TAVI patients

Fumiaki Yashima, MD, PhD[1,2,*]; Masahiko Hara, MD, PhD[3]; Taku Inohara, MD, PhD[2,4]; Masahiro Jinzaki, MD, PhD[5]; Hideyuki Shimizu, MD, PhD[6]; Keiichi Fukuda, MD, PhD, FACC, FESC[2]; Makoto Tanaka, MD[2]; Masanori Yamamoto, MD, PhD, FESC[7,8]; Yusuke Watanabe, MD[9]; Toru Naganuma, MD, FACC, FESC[10]; Shinichi Shirai, MD[11]; Masahiro Yamawaki, MD[12]; Norio Tada, MD[13]; Futoshi Yamanaka, MD[14]; Kazuki Mizutani, MD[15]; Hiroshi Ueno, MD[16]; Minoru Tabata, MD[17]; Kensuke Takagi, MD[18]; Kentaro Hayashida, MD, PhD, FESC, FACC, FJCS[2] on behalf of the OCEAN-TAVI registry

[1]Department of Cardiology, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan

[2]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

[3]Center for Community-based Healthcare Research and Education, Shimane University, Izumo, Japan

[4]Division of Cardiology, Vancouver General Hospital, Vancouver, Canada

[5]Department of Diagnostic Radiology, Keio University School of Medicine, Tokyo, Japan

[6]Department of Cardiovascular Surgery, Keio University School of Medicine, Tokyo, Japan

[7]Department of Cardiology, Toyohashi Heart Centre, Toyohashi, Japan

[8]Department of Cardiology, Nagoya Heart Centre, Aichi, Japan

[9]Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan

[10]Department of Cardiology, New Tokyo Hospital, Matsudo, Japan

[11]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan

[12]Department of Cardiology, Saiseikai Yokohama-City Eastern Hospital, Yokohama, Japan

[13]Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan

[14]Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Japan

[15]Department of Cardiology, Osaka City General Hospital, Osaka, Japan

[16]Department of Cardiology, Toyama University Hospital, Toyama, Japan

[17]Department of Cardiovascular Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu, Japan

[18]Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan

***Corresponding author**

Fumiaki Yashima, MD, PhD

Department of Cardiology, Saiseikai Utsunomiya Hospital,

911-1 Takebayashi-cho, Utsunomiya, Tochigi, 321-0974, Japan

Phone: 81-28-626-5500; Fax: 81-28-626-5573

Email: yashima.fumiaki@gmail.com

Word count: 3087

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).

Conclusions Statin for TAVI patients will be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In addition, statin will be essential for TAVI patients with CAD. Further researches are warranted to confirm and generalise our findings, since this study has inherent limitations of the observational study and included only Japanese patients.

Keywords: coronary artery disease, elderly, propensity score matching, statin, transcatheter aortic valve implantation

Strengths and limitations of this study

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

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

Bay Urayasu Ichikawa Medical Center, and Ogaki municipal hospital) between 2013 and 2017 were prospectively included in our TAVI registry (Optimized CathEter vAlvular iNtervention [OCEAN-TAVI] registry).[8, 9, 10] Informed consent was obtained from all patients, and the institutional review boards of all 14 participating centres approved this study. Additionally, this study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The OCEAN-TAVI registry was registered with the University Hospital Medical Information Network Clinical Trial Registry and accepted by the International Committee of Medical Journal Editors (UMIN-ID: 000020423).

Patients received transcatheter heart valves (THVs) via either the transfemoral, transapical, or transaortic approach. Sapien XT valves, Sapien 3 valves (Edwards Lifesciences, Irvine, CA), CoreValves, Evolut R (Medtronic, Minneapolis, MN) were used as THVs. A total of 2588 patients were treated with TAVI between 2013 and 2017. They were categorised into two groups according to statin administration at admission for TAVI procedures (Figure 1). We set the primary endpoint as mid-term all-cause mortality for up to 3 years. Secondary endpoints included mid-term cardiovascular mortality, mid-term non-cardiovascular mortality up to 3 years, and 30-day all-cause mortality.

We performed propensity score (PS) matching, as described below, and compared the endpoints between the two groups in the matched cohort. In addition, we categorised the matched cohort into two cohorts; an octogenarian cohort (80–89 years old) and a nonagenarian cohort (90 years or older), and investigated the differences by age in the impact of statin on mid-term all-cause mortality. Furthermore, we classified the overall cohort into four groups according to a history of CAD and statin treatment at admission and evaluated whether the impact of statin differed according to the underlying CAD condition. We also explored predictors of mid-term all-cause mortality in the overall cohort using multivariate analysis.

Clinical outcomes including all-cause mortality and cardiovascular mortality were defined according to the Valve Academic Research Consortium-2 consensus document.[11]

Statistical analysis

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

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

statistically significant. All statistical analyses were performed using the R software package (version 3.3.2; R Development Core Team, Vienna, Austria).

Patient and Public Involvement statement

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

RESULTS

Among the 2588 patients who underwent TAVI, 1523 and 1065 patients were classified into the statin and the non-statin group, respectively (Figure 1). The distribution of PS in the statin and non-statin groups is shown in Supplementary material online, Figure S1. After 1:1 PS matching, we identified 936 matched pairs of patients with similar PS. The patient characteristics of the statin and non-statin groups before and after matching are summarised in Table 1. The overall cohort included very elderly patients (84.4±5.2 years). The majority of the cohort was female (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.

After PS matching, the two groups were well-balanced in terms of pre-procedural patient characteristics and procedural variables. In-hospital all-cause mortality, acute kidney injury, stroke, and vascular complications did not differ between the two groups. Post-procedural

echocardiography data showed no significant differences between the two groups (Table 2). The patient characteristics and in-hospital outcomes of the PS matched and unmatched groups are summarised in Supplementary material online, Tables S1 and S2. There were several differences between the two groups. The proportion of male patients was lower in the PS matched group than in the unmatched group (532 [28.4%] vs. 263 [36.7%], *P*<0.01), NYHA Class 3 or 4 was less frequent in the matched group (919 [49.1%] vs. 402 [56.2%], *P*<0.01), the Clinical Frailty Scale was lower in the matched group (3.8±1.2 vs. 4.2±1.4, *P*<0.01), and the STS risk score was lower in the matched group (7.7±5.7 vs 9.8±9.2, *P*<0.01). History of the previous CAD was more frequent (750 [40.1%] vs. 204 [28.5%], *P*<0.01), but previous MI was less frequent (96 [5.1%] vs. 62 [8.7%], *P*<0.01) in the PS matched group. In-hospital all-cause mortality (43 [2.3%] vs. 27 [3.8%], *P*<0.01) and bleeding (421 [22.5%] vs. 199 [27.8%], *P*<0.01) were lower in the matched group than in the unmatched group.

In the overall cohort, the median follow-up period was 660 days. Statin therapy was associated with significantly lower mid-term all-cause mortality in the PS-matched cohort (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.58–0.99, *P*=0.04) (Figure 2a), which was consistent with the IPTW model (aHR 0.80, 95% CI 0.65–0.99, *P*=0.04). The Kaplan-Meier curves relative to the mid-term outcomes additionally showed a significant difference in cardiovascular mortality (aHR 0.64, 95% CI 0.42–0.97, *P*=0.04) and an insignificant difference in non-cardiovascular mortality (aHR 0.86, 95% CI 0.61–1.21, *P*=0.39) between the two groups (Figure 2b and 2c). There was no significant difference in 30-day all-cause mortality (aHR 0.73, 95% CI 0.47-1.08, *P*=0.11) and a landmark analysis after 30 days showed a significant difference in mid-term all-cause mortality (aHR 0.88, 95% CI 0.78-0.99, *P*=0.03) (Figure 2d).

In the octogenarian cohort (80–89 years old), statin therapy was associated with significantly lower mid-term all-cause mortality (aHR 0.87, 95% CI 0.75-0.99, *P*=0.04)

(Figure 3a), but the impact in the nonagenarian cohort (90 years or older) appeared to be lower (aHR 0.84, 95% CI 0.62-1.13, *P*=0.25) (Figure 3b). P for interaction was 0.90.

Furthermore, comparing the four groups according to previous CAD and statin therapy, there was a significant difference in mid-term all-cause mortality (*P*<0.01) (Figure 4). Patients who did not receive statin therapy despite a history of 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]). Their survival curve diverged from that of the patients without previous CAD or statin after 1 year. In addition, patients with previous CAD and statin therapy (aHR 1.04, 95% CI 0.87-1.23) seemed to obtain similar risks with those who did not have previous CAD or statin therapy (aHR 1.11, 95% CI 0.96-1.27 [patients who received statin without previous CAD as a reference]).

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

DISCUSSION

The present study investigated the impact of statin therapy on mid-term mortality after TAVI using a Japanese multicentre registry. Statin therapy at admission was associated with significantly lower all-cause and cardiovascular mortality. It should be noted that the impact of statin therapy attenuated in the nonagenarians. Furthermore, we demonstrated differences in all-cause mortality according to the history of previous CAD and statin therapy. The present study included the largest patient cohort (936 pairs of patients after PS matching) and the first report to investigate the association of age and a history of previous CAD with the impact of statin.

Few reports have assessed the impact of statin treatment on mortality after TAVI. Peri-Okonny et al. demonstrated that statin therapy was associated with reductions in 2-year all-cause (aHR 0.65, 95% CI 0.49–0.87, *P*=0.001), cardiovascular (aHR 0.66, 95% CI 0.46–0.96, *P*=0.030), and non-cardiovascular mortality (aHR 0.64, 95% CI 0.44–0.99, *P*=0.045) compared with no statin therapy, with a large cohort using PARTNER II and Sapien 3 clinical trials or associated registries (626 pairs of patients after PS matching).[7] Merdler et al. showed that high-intensity statin therapy was associated with a reduction in mortality after TAVI (median follow-up period: 2.5 years) using data of 1238 cases from a single-centre registry (aHR 0.59, 95% CI 0.37–0.96, *P*=0.03).[15] Huded et al. also showed that high-intensity statin therapy was associated with a reduction in all-cause mortality (mean survival: 3.9 years) based on 294 cases (aHR 0.36, 95% CI 0.14–0.90, *P*=0.029).[16] Takagi et al. reported similar results following a meta-analysis.[17] These results were consistent with our results.

The mechanism through which statin therapy reduces the risks of all-cause and cardiovascular mortality is thought to be associated with a reduction in ischaemic events.[7, 15, 16, 17] However, there are limited data relative to statin therapy in octogenarians and nonagenarians, as are data not only on TAVI but also on statin therapy as primary and secondary prevention. The PROspective Study of Pravastatin in the Elderly at Risk trial was the only randomised controlled trial for elderly patients (aged 70–82 years) with a history or risk factors of vascular disease. The study revealed that pravastatin led to a 3-year reduced risk of CAD.[18] Recommendation of statin therapy for very elderly patients varies among the guidelines.[19, 20, 21, 22, 23] Very recently, a few reports supporting statin therapy for very elderly patients have been published. In the Patient and Provider Assessment of Lipid Management Registry, statin therapy appeared to be similarly tolerated by patients older and younger than 75 years.[24] The Cholesterol Treatment Trialists' Collaboration demonstrated

that statin therapy as primary and secondary prevention produced significant reductions in major vascular events even in patients older than 75 years.[25] Furthermore, Romas et al. revealed that statin therapy was associated with significant reductions in atherosclerotic cardiovascular events and all-cause mortality for patients who were older than 74 years and had diabetes.[26] Interestingly, Giral et al. demonstrated that statin discontinuation in 75-year-old primary prevention patients was associated with a 33% increased risk of cardiovascular events.[27] Our present study was consistent with these reports and indicated that statin therapy would be effective for very elderly and atherosclerotic high-risk patients by reducing cardiovascular events and mortality. Conversely, Romas et al. reported that the benefits of statin therapy disappeared in nonagenarians,[26] as observed in our nonagenarian cohort. However, P for interaction among the octogenarian and nonagenarian cohorts in the present study was not significant. There seemed to be a difference among the two cohorts during 12-24 months after TAVI but then the curves converged. The insignificance might be due to low life expectancy in nonagenarians after 24 months. Besides, the sizes of the cohorts and confounding regarding prescribing statin to nonagenarians with CAD might skew the results.

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

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 matched and unmatched group as it might be plausible given the results of the IPTW model. In addition, generalising our findings outside Japan also requires attention since this study included only Japanese patients. Third, information on the type and doses of statin therapy was not obtained. Usage of ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitor was not recorded in this study. Fourth, we assessed statin use only on admission and there was a possibility that statin therapy might have changed at discharge or during follow-up. The duration of statin administration and the timing to start prescribing statin were not captured in the present study. Finally, we could not assess intolerance in patients eligible for statin treatment but who could not continue treatment due to statin side effects such as rhabdomyolysis. Further studies, including a randomised controlled trial, on statin therapy following TAVI are warranted to resolve these limitations.

In conclusion, using data from the large multicentre registry, statin therapy at admission of TAVI was associated with significant reductions in mid-term all-cause and cardiovascular mortality. Statin therapy prior TAVI will be beneficial even in octogenarians, but the benefits may disappear in nonagenarians. In addition, statin therapy will be essential for TAVI patients with CAD. Further researches are warranted to confirm and generalise our findings, since the present study has several inherent limitations of the observational study and included only Japanese patients.

Acknowledgements

We express our heartfelt gratitude to the team members at our hospital and other hospitals participating in the multicentre registry and the Japan Society of Clinical Research (http://www.japanscr.org/) for their dedicated support.

Funding

The OCEAN-TAVI registry is supported by Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Medical, and Daiichi-Sankyo Company. There are no award/grant numbers for the Funders.

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.

Data collection: Makoto Tanaka, Masahiro Jinzaki, Hideyuki Shimizu, and Keiichi Fukuda.

Data analysis and interpretation: Masahiko Hara, Taku Inohara, Kensuke Takagi, Hiroshi Ueno, and Norio Tada.

Drafting the article: Fumiaki Yashima and Taku Inohara.

Critical revision of the article: Masanori Yamamoto, Yusuke Watanabe, Kentaro Hayashida.

Final approval of the version to be published: all authors.

Ethics Statement

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

References

1 Mack MJ, Leon MB, Smith CR, et al. PARTNER 1 trial investigators, 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477–84.

2 Kapadia SR, Leon MB, Makkar RR,et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2485–91.

3 Popma JJ, Deeb GM, Yakubov SJ et al.Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706–15.

4 Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–705.

5 Chakos A, Wilson-Smith A, Arora S, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. *Ann Cardiothorac Surg* 2017;6:432–43.

6 Holmes DR Jr, Brennan JM, Rumsfeld JS, et al. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 2015;313:1019–28.

7 Peri-Okonny PA, Liu Y, Malaisrie SC, et al. Association of statin use and mortality after transcatheter aortic valve replacement. *J Am Heart Assoc* 2019;8:e011529.

8 Shimura T, Yamamoto M, Kano S, et al. Impact of the Clinical Frailty Scale on outcomes after transcatheter aortic valve replacement. *Circulation* 2017;135:2013–24.

9 Yashima F, Yamamoto M, Tanaka M, et al. Transcatheter aortic valve implantation in patients with an extremely small native aortic annulus: the OCEAN-TAVI registry. *Int J Cardiol* 2017;240:126–31.

10 Kataoka A, Watanabe Y, Kozuma K, et al. Prognostic impact of low-flow severe aortic stenosis in small-body patients undergoing TAVR: the OCEAN-TAVI registry. *JACC Cardiovasc Imaging* 2018;11:659–69.

11 Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–54.

12 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.

13 Weitzen S, Lapane KL, Toledano AY, et al. Principles for modeling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiol Drug Saf* 2004;13:841–53.

14 Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med* 2013;32:2837–49.

15 Merdler I, Rozenbaum Z, Finkelstein A, et al. Effect of statin therapy and long-term mortality following transcatheter aortic valve implantation. *Am J Cardiol* 2019;123:1978–82.

16 Huded CP, Benck LR, Stone NJ, et al. Relation of intensity of statin therapy and outcomes after transcatheter aortic valve replacement. *Am J Cardiol* 2017;119:1832–38.

17 Takagi H, Hari Y, Nakashima K, et al. Meta-analysis for impact of statin on mortality after transcatheter aortic valve implantation. *Am J Cardiol* 2019;124:920–25.

18 Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–30.

19 Mortensen MB, Falk E. Primary prevention with statins in the elderly. *J Am Coll Cardiol* 2018;71:85–94.

20 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of

Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81.

21 Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2016;316:1997–2007.

22 Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2016;32:1263–82.

23 National Clinical Guideline Centre. Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London, UK: National Institute for Health and Care Excellence 2014.

24 Nanna MG, Navar AM, Wang TY, et al. Statin use and adverse effects among adults >75 years of age: insights from the Patient and Provider Assessment of Lipid Management (PALM) registry. *J Am Heart Assoc* 2018;7:e008546.

25 Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;393:407–15.

26 Ramos R, Comas-Cufi M, Marti-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ* 2018;362:k3359.

27 Giral P, Neumann A, Weill A, et al. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J* 2019;40:3516–25.

28 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–89.

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 (+) ***n*=1065**	**Statin (-)** ***n*=1523**	**Standardised difference**	**Statin (+)** ***n*=936**	**Statin (-)** ***n*=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, *n* (%)	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

NYHA class 3 or 4, *n* (%)	518 (48.6%)	803 (52.7%)	0.08	462 (49.4%)	457 (48.8%)	0.01
Clinical Frailty Scale	3.8±1.2	4.1±1.3	0.23	3.8±1.2	3.8±1.2	0.04
Diabetes mellitus, *n* (%)	264 (24.8%)	291 (19.1%)	0.14	207 (22.1%)	195 (20.8%)	0.03
Smoking, *n* (%)	212 (19.9%)	260 (17.1%)	0.07	169 (18.1%)	160 (17.1%)	0.02
Hypertension, *n* (%)	861 (80.9%)	1129 (74.1%)	0.16	744 (79.5%)	753 (80.5%)	0.02
Chronic kidney disease, *n* (%)	755 (70.9%)	1054 (69.2%)	0.04	651 (69.6%)	640 (68.4%)	0.03
Atrial fibrillation, *n* (%)	195 (18.3%)	354 (23.2%)	0.12	181 (19.3%)	183 (19.6%)	0.01
Coronary artery disease, *n* (%)	507 (47.6%)	447 (29.4%)	0.38	378 (40.4%)	372 (39.7%)	0.01
Previous myocardial infarction, *n* (%)	108 (10.1%)	50 (3.3%)	0.28	48 (5.1%)	48 (5.1%)	<0.01

Previous percutaneous coronary intervention, *n* (%)	342 (32.1%)	284 (18.7%)	0.31	249 (26.6%)	238 (25.4%)	0.03
Previous coronary artery bypass grafting, *n* (%)	112 (10.5%)	57 (3.7%)	0.27	60 (6.4%)	57 (6.1%)	0.01
Peripheral artery disease, *n* (%)	161 (15.1%)	216 (14.2%)	0.03	136 (14.5%)	128 (13.7%)	0.02
Previous stroke, *n* (%)	127 (11.9%)	174 (11.4%)	0.02	116 (12.4%)	102 (10.9%)	0.05
STS risk score	7.7±6.0	8.6±7.5	0.13	7.7±6.1	7.7±5.3	<0.01
Renin-angiotensin inhibitor, *n* (%)	639 (60.0%)	748 (49.1%)	0.22	540 (57.7%)	544 (58.1%)	0.01
ß blocker, *n* (%)	384 (36.1%)	496 (32.6%)	0.07	334 (35.7%)	303 (32.4%)	0.07
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
Haemoglobin, g/dL	11.4±1.7	11.1±1.7	0.17	11.4±1.7	11.2±1.6	0.15

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, *n* (%)	12 (0.8%)	4 (0.4%)	0.05	7 (0.8%)	4 (0.4%)	0.04

Severe mitral regurgitation, *n* (%)	21 (1.4%)	12 (1.1%)	0.02	12 (1.3%)	6 (0.6%)	0.07
Pulmonary hypertension, *n* (%)	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, *n* (%)	873 (82.0%)	1294 (85.0%)	0.08	770 (82.3%)	784 (83.8%)	0.04
Local anaesthesia, *n* (%)	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

CT, computed tomography; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; 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			
	Statin (+) *n*=1065	Statin (-) *n*=1523	*P* value	Standardised difference	Statin (+) *n*=936	Statin (-) *n*=936	*P* value	Standardised difference
All-cause mortality, *n* (%)	27 (2.5%)	43 (2.8%)	0.66	0.02	20 (2.1%)	23 (2.5%)	0.64	0.02
Acute kidney injury, *n* (%)	111 (10.4%)	178 (11.7%)	0.31	0.04	96 (10.3%)	105 (11.2%)	0.50	0.03
Stroke, *n* (%)	27 (2.5%)	34 (2.2%)	0.62	0.02	24 (2.6%)	19 (2.0%)	0.44	0.04
Vascular complication, *n* (%)	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, *n* (%)	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, *n* (%)	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

Previous coronary artery bypass grafting	1.21 (1.02-1.40)	0.03	1.05 (0.88-1.24)	0.60
Peripheral artery disease	1.35 (1.21-1.50)	<0.01	1.08 (0.95-1.22)	0.24
Previous stroke	1.14 (0.99-1.30)	0.06	1.04 (0.90-1.19)	0.62
Atrial fibrillation	1.19 (1.07-1.32)	<0.01	1.00 (0.90-1.12)	0.98
STS risk score	1.04 (1.03-1.04)	<0.01	1.02 (1.01-1.03)	<0.01
eGFR, mL/min/1.73 m^2	0.98 (0.98-0.99)	<0.01	0.99 (0.99-1.00)	<0.01
Haemoglobin, g/dL	0.83 (0.78-0.88)	<0.01	0.85 (0.80-0.91)	<0.01
Medication at admission				
Statin	0.84 (0.77-0.93)	<0.01	0.86 (0.77-0.95)	<0.01
Renin-angiotensin inhibitor	0.92 (0.84-1.01)	0.08	0.88 (0.80-0.97)	0.01
ß blocker	1.09 (0.99-1.20)	0.08	1.06 (0.96-1.16)	0.28
Preprocedural echocardiographic data				

Aortic valve area, cm^2/m^2	1.29 (0.76-2.20)	0.35	1.23 (0.63-2.38)	0.54
Peak velocity, mmHg	0.75 (0.67-0.85)	<0.01	0.76 (0.66-0.88)	<0.01
Ejection fraction, %	0.99 (0.98-0.99)	0.03	1.01 (1.00-1.02)	0.02
Pulmonary hypertension	1.50 (1.25-1.78)	<0.01	1.27 (1.05-1.53)	0.01
Severe aortic regurgitation	0.56 (0.13-1.19)	0.16	0.57 (0.21-1.51)	0.26
Severe mitral regurgitation	1.34 (0.93-1.81)	0.11	0.99 (0.70-1.40)	0.96
Procedural variables				
Transfemoral approach	0.81 (0.73-0.91)	<0.01	0.87 (0.77-0.98)	0.03
Local anaesthesia	0.89 (0.79-1.01)	0.07	0.92 (0.81-1.05)	0.22

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

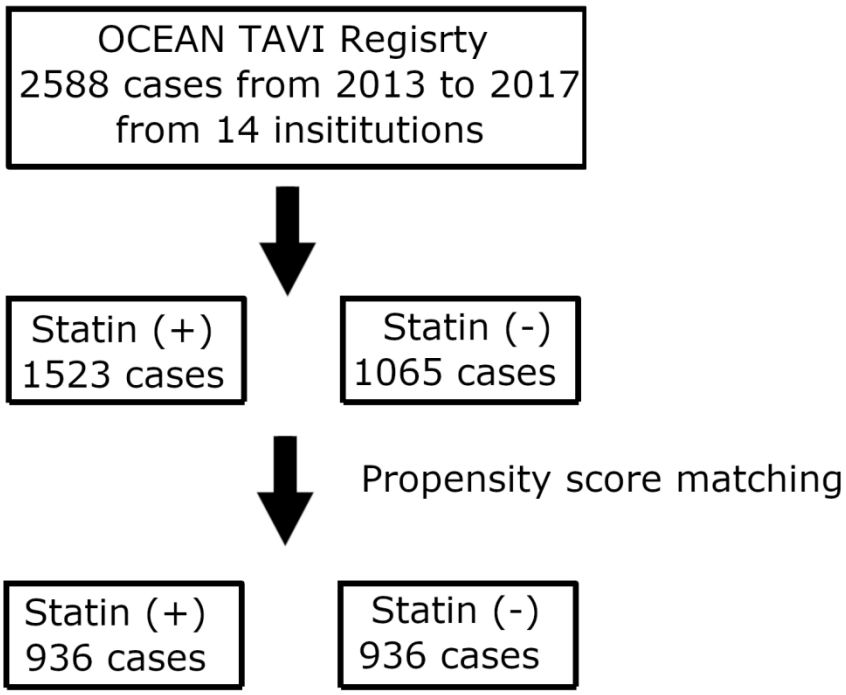


Figure 1
Flowchart of patient selection for the present study.
OCEAN; Optimized CathEter vAlvular iNtervention; TAVI, transcatheter aortic valve implantation.

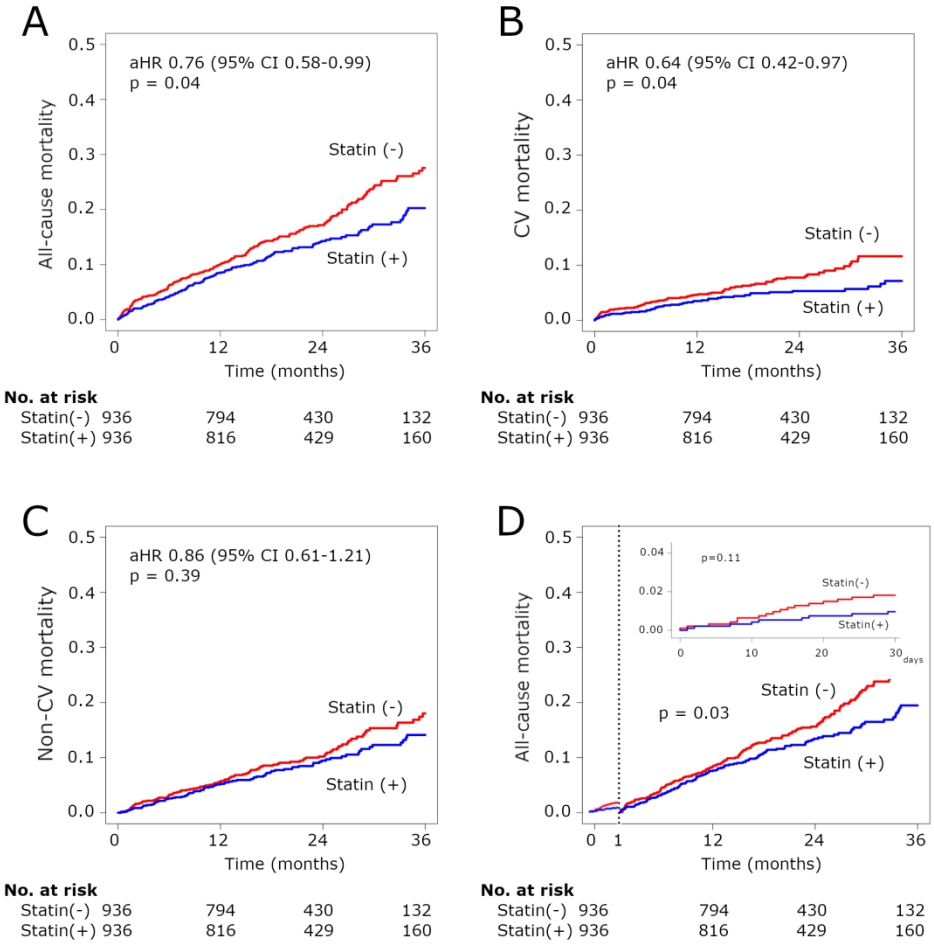


Figure 2
Kaplan-Meier curves for mid-term and 30-day mortality in the matched cohort. a, b, c: Kaplan-Meier curves for mid-term all-cause mortality (a), CV mortality (b), and non-CV mortality (c) in the matched cohort. d: Kaplan-Meier curve for 30-day all-cause mortality and mid-term all-cause mortality with the landmark analysis from 30 days in the matched cohort. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

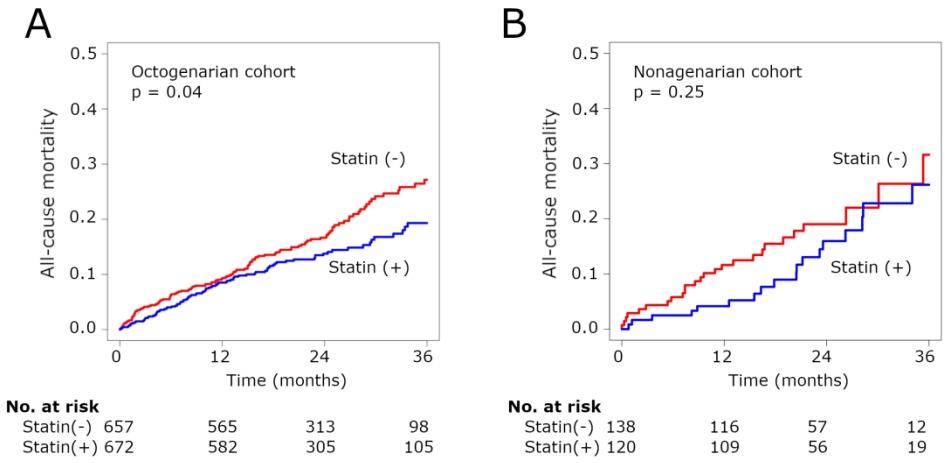
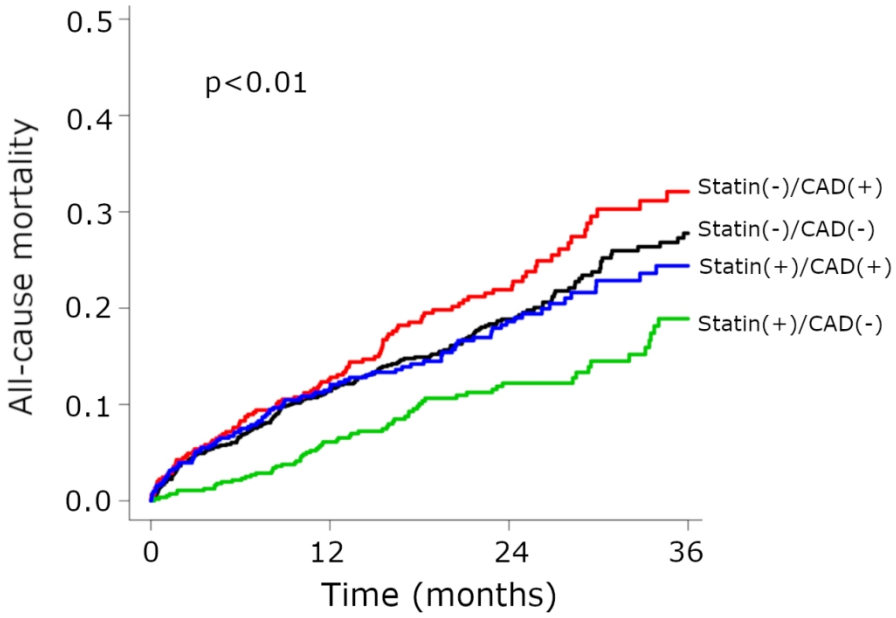


Figure 3
Kaplan-Meier curves for all-cause mortality in the octogenarian and nonagenarian cohort.



No. at risk

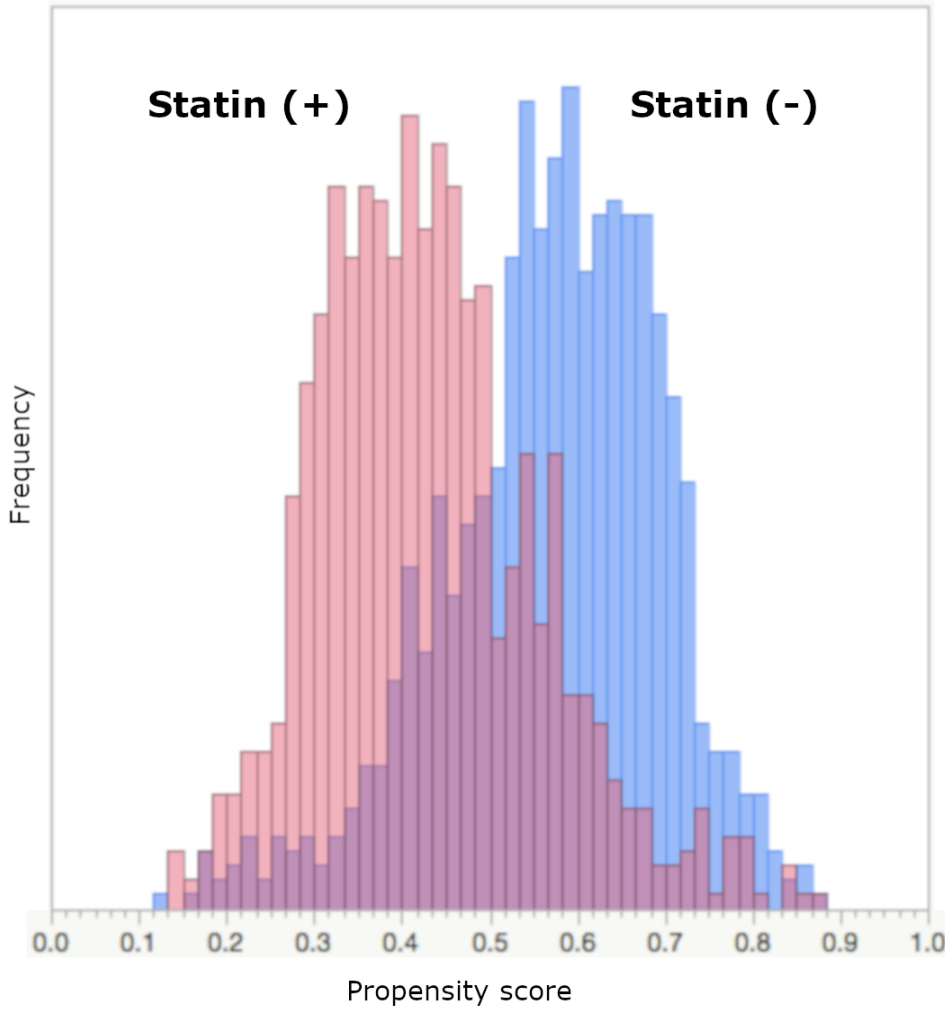
Statin(-)/CAD(+)	447	368	201	59
Statin(-)/CAD(-)	1076	895	456	142
Statin(+)/CAD(+)	507	428	231	87
Statin(+)/CAD(-)	558	497	256	93

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.

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

	Matched group *n*=1872	Unmatched group *n*=716	*P*-value
Preprocedural variables			
Age, years	84.2±5.1	84.6±5.4	0.08
Male, n (%)	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, n (%)	919 (49.1%)	402 (56.2%)	<0.01
Clinical Frailty Scale	3.8±1.2	4.2±1.4	<0.01
Smoking, *n* (%)	364 (19.4%)	160 (22.4%)	0.10
Diabetes mellitus, *n* (%)	402 (21.5%)	153 (21.4%)	0.95
Hypertension, *n* (%)	1497 (80.0%)	493 (68.9%)	<0.01
Chronic kidney disease, *n* (%)	1291 (69.0%)	518 (72.4%)	0.09
Atrial fibrillation, *n* (%)	364 (19.4%)	185 (25.8%)	<0.01

Coronary artery disease, *n* (%)	750 (40.1%)	204 (28.5%)	<0.01
Previous myocardial infarction, *n* (%)	96 (5.1%)	62 (8.7%)	<0.01
Previous percutaneous coronary intervention, *n* (%)	487 (26.0%)	139 (19.4%)	<0.01
Previous coronary artery bypass grafting, *n* (%)	117 (6.3%)	52 (7.3%)	0.36
Peripheral artery disease, *n* (%)	264 (14.1%)	113 (15.8%)	0.28
Previous stroke, *n* (%)	9 (0.5%)	3 (0.4%)	0.98
STS risk score	7.7±5.7	9.8±9.2	<0.01
Renin-angiotensin inhibitor, *n* (%)	1084 (57.9%)	303 (42.3%)	<0.01
Beta blocker, *n* (%)	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, *n* (%)	1554 (83.0%)	613 (85.6%)	0.11

Local anaesthesia, *n* (%)	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.

Supplementary Table S2

In-hospital outcomes of the propensity score-matched and -unmatched groups

	Matched group ***n*=1872**	**Unmatched group** ***n*=716**	***P*-value**
All-cause mortality, *n* (%)	43 (2.3%)	27 (3.8%)	<0.01
Acute kidney injury, *n* (%)	201 (10.7%)	88 (12.3%)	0.27
Bleeding, *n* (%)	421 (22.5%)	199 (27.8%)	<0.01
Stroke, *n* (%)	43 (2.3%)	18 (2.5%)	0.75
Vascular complication, *n* (%)	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.