PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Statin therapy for patients with aortic stenosis who underwent transcatheter aortic valve implantation: a report from a Japanese multicentre registry
AUTHORS	Yashima, Fumiaki; Hara, Masahiko; Inohara, Taku; Jinzaki, Masahiro; Shimizu, Hideyuki; Fukuda, Keiichi; Tanaka, Makoto; Yamamoto, Masanori; Watanabe, Yusuke; Naganuma, Toru; Shirai, Shinichi; Yamawaki, Masahiro; Tada, Norio; Yamanaka, Futoshi; Mizutani, Kazuki; Ueno, Hiroshi; Tabata, Minoru; Takagi, Kensuke; Hayashida, Kentaro

VERSION 1 – REVIEW

REVIEWER	Łukasz Kalińczuk The Cardinal Stefan Wyszyński Institute of CardiologyDepartmentof Coronary and Structural Heart Diseases Alpejska 42 St. 04-628 Warsaw, Poland fax +48 22 34 34 516 cell 505 794 691
REVIEW RETURNED	02-Nov-2020

GENERAL COMMENTS	- in the abstract section authors should include data on the high-risk category by EuroSCORE 2/STS/frailty, - in the first point of the ‘strengths and limitations’ section authors state that ‘statin therapy after transcatheter aortic valve implantation was associated with significant reductions in all-cause and cardiovascular mortality…’ which is not true, based upon the presented data authors can only say that prior statin treatment seems to be associated with better subsequent outcome after successful TAVR, - please check the style and the grammar (e.g. stoke) = ‘Introduction. 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]’ - again, having data on the statins use on admission (PRIOR to TAVR procedure) without the knowledge of their subsequent prescription after TAVR (and not knowing the following patients' adherence to prescribed statins treatment) do not allow authors to analyze the hypothesis that there is a beneficial effect of statins when administered AFTER successful TAVR, that is the 1st major limitation of the current study, - finally, the authors did not perform relevant analyses to search for the univariate and the multivariate predictors of the long term outcome, studied separately for the prespecified endpoints and among the various subgroups, this is the 2nd major disadvantage of the current study, it is uknwn if prior statins use was associated with

	better outcome independently of the correlates?

REVIEWER	Henrik Schirmer University of Oslo, Norway I have received lecture fees from Astra Zeneca, MSD, Novartis, Sanofi Aventis and Pfizer as well as an unrestricted research grant from Astra Zeneca
REVIEW RETURNED	27-Nov-2020

GENERAL COMMENTS	This clear and well written study from a Japanese multicentre TAVI registry access the difference in survival after TAVI in propensity matched pairs of users and nonusers of statin. With 936 matched pairs, it is 50% larger than the previously published study of impact of statins on survival from the Partner II trial. This allows stratification into patients in their eighties compared to patients in their nineties as well as according to CVD comorbidity known at TAVI implantation. The propensity score matching is well described, and successfully implemented in this elderly population. The study shows a significant effect of statin treatment on both total and cardiovascular mortality of 24 and 36% respectively. Stratification into octo- and nonagenarians found a weaker and non significant effect among the oldest. The best prognosis was for those on stain with known CVD, the worst for those with known CVD not on statins. Major objection: It is stated that the significant effect of statins in octogenarians is attenuated in nonagenarians and becomes non-significant. It would be helpful to see the effect estimates with confidence intervals to be able to judge ourselves. Probably the eldest group is too small to enable interaction testing of the proposed differences but should nonetheless be reported. It is stated that participants was stratified according to statin use at admission and then followed for three years. As statin use could have changed during assessment for TAVI with detection of significant CVD and subsequent PCI, statin use at discharge would be more useful. If available please add and use. Could this explain the different trajectories for octogenarians and nonagenarians? The size of age groups differ substantially. Is this the main reason for the lack of significance among the eldest? From the difference in trajectories, one could assume that in the nonagenarians a substantial proportion of those with CVD did not receive statin and that those receiving statins had used it for a long time. It would be helpful to see the proportion with known CVD and CVD detected first during preoperative assessment as well as statin use before preop angiography and after both for octo- and nonagenarians. This could help explain why statin users without CVD fare so much better for start of follow up than all other groups. Minor comments: Introduction last sentence: as effect according age and underlying CVD was assessed in separate analyses better write: …its association with age or underlying CVD,… As approach and local anesthesia was significantly different between users and non users of statin it could impact on survival on should be considered as an adjustment variable in the cox analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Lukasz Kalinczuk, Uniwersytet Jagiellorski Collegium Medicum Instytut Kardiologii

Comments to the Author:

- in the abstract section authors should include data on the high-risk category by EuroSCORE 2/STS/frailty,

- in the first point of the 'strengths and limitations' section authors state that 'statin therapy after transcatheter aortic valve implantation was associated with significant reductions in all-cause and cardiovascular mortality…' which is not true, based upon the presented data authors can only say that prior statin treatment seems to be associated with better subsequent outcome after successful TAVR,

- please check the style and the grammar (e.g. stoke) = 'Introduction. 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]'

- again, having data on the statins use on admission (PRIOR to TAVR procedure) without the knowledge of their subsequent prescription after TAVR (and not knowing the following patients' adherence to prescribed statins treatment) do not allow authors to analyze the hypothesis that there is a beneficial effect of statins when administered AFTER successful TAVR, that is the 1st major limitation of the current study,

- finally, the authors did not perform relevant analyses to search for the univariate and the multivariate predictors of the long term outcome, studied separately for the prespecified endpoints and among the various subgroups, this is the 2nd major disadvantage of the current study, it is uknwn if prior statins use was associated with better outcome independently of the correlates?

Our responses to Reviewer: 1 (Dr. Lukasz Kalinczuk)

We appreciate the comment from Dr. Lukasz Kalinczuk.

1) We added the data on the high-risk category by EuroSCORE 2/STS/frailty to the abstract section and RESULTS.

- Abstract
  Participants The overall cohort included 2588 very elderly 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 and 3.74% (IQR 2.34-6.02%), and Clinical Frailty Scale was 3.9±1.2.
- RESULTS
  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.

2) We modified the 'strengths and limitations' section in accordance with Editor's Comments and erased the results of the present study. We changed the title of our manuscript and clarified the timing of statin therapy as below.

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

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.

3) We thank Dr. Lukasz Kalinczuk to point out our mistake. We corrected it.

- INTRODUCTION
  TAVI patients are very elderly and have many cardiovascular comorbidities such as coronary artery disease (CAD), stroke, and peripheral artery disease (PAD).

4) We specified the timing of statin therapy in METHODS and DISCUSSION, and clarified the limitation in DISCUSSION.

- METHODS
  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).
- 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.
- DISCUSSION
  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.
- DISCUSSION
  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.

5) We appreciate the precious comment. We conducted the additional analyses (univariate and multivariate Cox proportional hazards regression analyses) and added the results and a new table (Table 3).

- RESULTS
  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).

Reviewer: 2

Dr. Henrik Schirmer, University of Oslo Faculty of Medicine, Akershus University Hospital

Comments to the Author:

This clear and well written study from a Japanese multicentre TAVI registry access the difference in survival after TAVI in propensity matched pairs of users and nonusers of statin. With 936 matched pairs, it is 50% larger than the previously published study of impact of statins on survival from the Partner II trial.

This allows stratification into patients in their eighties compared to patients in their nineties as well as according to CVD comorbidity known at TAVI implantation.

The propensity score matching is well described, and successfully implemented in this elderly population. The study shows a significant effect of statin treatment on both total and cardiovascular mortality of 24 and 36% respectively. Stratification into octo- and nonagenarians found a weaker and non significant effect among the oldest. The best prognosis was for those on stain with known CVD, the worst for those with known CVD not on statins.

Major objection:

It is stated that the significant effect of statins in octogenarians is attenuated in nonagenarians and becomes non-significant. It would be helpful to see the effect estimates with confidence intervals to be able to judge ourselves. Probably the eldest group is too small to enable interaction testing of the proposed differences but should nonetheless be reported.

It is stated that participants was stratified according to statin use at admission and then followed for three years. As statin use could have changed during assessment for TAVI with detection of significant CVD and subsequent PCI, statin use at discharge would be more useful. If available please add and use.

Could this explain the different trajectories for octogenarians and nonagenarians?

The size of age groups differ substantially. Is this the main reason for the lack of significance among the eldest? From the difference in trajectories, one could assume that in the nonagenarians a substantial proportion of those with CVD did not receive statin and that those receiving statins had used it for a long time.

It would be helpful to see the proportion with known CVD and CVD detected first during preoperative assessment as well as statin use before preop angiography and after both for octo- and nonagenarians.

This could help explain why statin users without CVD fare so much better for start of follow up than all other groups.

Minor comments:

Introduction last sentence: as effect according age and underlying CVD was assessed in separate analyses better write: …its association with age or underlying CVD,…

As approach and local anesthesia was significantly different between users and non users of statin it could impact on survival on should be considered as an adjustment variable in the cox analysis.

Our responses to Reviewer: 2 (Dr. Henrik Schirmer)

We appreciate the comment from Dr. Henrik Schirmer.

Major objection:

1) We added the effect estimates with confidence intervals and conducted the additional analyses (P for interaction).

- RESULTS
  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.

2) We are afraid that the data on statin use at discharge was not available in the present study. This is one of the limitations of this study as we described.

- DISCUSSION
  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.

3) We really appreciate the precious comment. We made additional comments to DISCUSSION according to it.

- DISCUSSION

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.

4) We thank Dr. Henrik Schirmer for the important comment. We are afraid that the information was unavailable on known CVD and CVD detected first during preoperative assessment and statin use before preop angiography and after both for octo- and nonagenarians. We added the limitation to DISCUSSION.

- DISCUSSION
  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.

Minor comments:

1) We really appreciate the kind comment. We modified it.

- its association with age or the underlying CAD, using our Japanese multicentre registry data.

2) We appreciate the precious comment. We conducted the additional analyses (univariate and multivariate Cox proportional hazards regression analyses) including approaches and local anaesthesia as covariables and added a new table (Table 3).

VERSION 2 – REVIEW

REVIEWER	Henrik Schirmer University of Oslo, Norway I have received lecture fees from Astra Zeneca, MSD, Novartis, Sanofi Aventis and Pfizer as well as an unrestricted research grant from Astra Zeneca
REVIEW RETURNED	06-Apr-2021

GENERAL COMMENTS	The data are now more clearly presented and differences between groups are comparable. There is a mistake in reporting of results on page 52 line 45 where differences in non cardiac mortality is reported as significant despite a CI overlapping 1 and a p value of 0.39 (aHR 0.86 95% CI 0.61-1.21). As there is no interaction between age group and statin on survival (p=0.9) the seemingly different effect could be due to overall low life expectancy as there is an effect in nonagenarians after 12-24 months but then the curves converge.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Henrik Schirmer, University of Oslo Faculty of Medicine, Akershus University Hospital

Comments to the Author:

The data are now more clearly presented and differences between groups are comparable. There is a mistake in reporting of results on page 52 line 45 where differences in non cardiac mortality is reported as significant despite a CI overlapping 1 and a p value of 0.39 (aHR 0.86 95% CI 0.61-1.21).

As there is no interaction between age group and statin on survival (p=0.9) the seemingly different effect could be due to overall low life expectancy as there is an effect in nonagenarians after 12-24 months but then the curves converge.

Our responses to Reviewer: 2 (Dr. Henrik Schirmer)

We really appreciate the comments from Dr. Henrik Schirmer.

5) We corrected the text regarding the result as below.

- RESULTS
  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).

6) We made additional comments to DISCUSSION according to the comment from Dr. Henrik Schirmer.

- DISCUSSION
  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.