Association between exercise habit changes and mortality following a cardiovascular event

Dong-Seon Kang,1 Jung-Hoon Sung,2 Daehoon Kim,1 Moo-Nyun Jin,3 Eunsun Jang,4 Hee Tae Yu,1 Tae-Hoon Kim,1 Hui-Nam Pak1,1 Moon-Hyung Lee1, Gregory Lip4,5 Pil-Sung Yang,1,2 Boyoung Joung1,6

ABSTRACT

Objective To investigate the associations between exercise habit changes following an incident cardiovascular event and mortality in older adults.

Methods We analysed the relationship between exercise habit change and all-cause, cardiovascular and non-cardiovascular deaths in adults aged ≥60 years between 2003 and 2012 who underwent two consecutive health examinations within 2 years before and after diagnosis of cardiovascular disease (CVD). They were categorised into four groups according to exercise habit changes: persistent non-exercisers, exercise dropouts, new exercisers and exercise maintainers. Differences in baseline characteristics were adjusted using inverse probability of treatment weighting.

Results Of 6076 participants, the median age was 72 (IQR 69–76) years and men accounted for 50.6%. Compared with persistent non-exercisers (incidence rate (IR) 4.8 per 100 person-years), new exercisers (IR 3.5, HR 0.73, 95% CI 0.58 to 0.91) and exercise maintainers (IR 2.9, HR 0.53, 95% CI 0.38 to 0.73) were associated with reduced risk of all-cause death. The rate of non-cardiovascular death was significantly lower in new exercisers (IR 2.3, HR 0.73, 95% CI 0.56 to 0.95) and exercise maintainers (IR 2.3, HR 0.61, 95% CI 0.42 to 0.90) than in persistent non-exercisers (IR 3.2). Also, trends towards reduced cardiovascular death in new exercisers and exercise maintainers were observed (p value for trend <0.001).

Conclusions More virtuous exercise trajectories in older adults with CVD are associated with lower mortality rates. Our results support public health recommendations for older adults with CVD to perform physical activity.

INTRODUCTION

Previous studies have proven that incorporating an exercise habit is inversely related to the risk of mortality.1 Current guidelines recommend regular exercise to reduce the risk of all-cause or cardiovascular death and morbidity.2 However, evidence supporting the benefits of exercise in older adults with cardiovascular diseases (CVDs) is scarce because studies on exercise and mortality have been mainly performed in healthy and middle-aged persons.3 Although some studies have attempted to demonstrate the impact of exercise habits on death in patients with CVD, the results have been inconsistent.4,5 In addition, most studies were based on a single baseline assessment of exercise with subsequent follow-up for mortality. Several studies have shown that such an assessment has time-limited predictive power and may be unable to accurately differentiate the effect of exercise per se from the influences of confounding factors such as genetic background, undetected comorbidities and changes in the variable of interest during follow-up.6 Engeseth et al described that physical fitness at inclusion was a significant predictor of early cardiovascular death but not late cardiovascular death. To overcome these limitations, some studies have suggested using change in exercise habits as a variable for evaluating long-term outcomes.7,8 Considering the lack of information on the impact of exercise in older patients with CVD, this study aimed to analyse the association between change in exercise habits after a new CVD diagnosis and risk of all-cause, cardiovascular or non-cardiovascular death.

METHODS

Data were extracted from the Korean National Health Insurance Service (NHIS)-Senior database,
Cardiac risk factors and prevention

which incorporates data of 558,147 participants recruited through a 10% simple random sampling method from a total of 5.5 million individuals aged ≥60 years in the National Health Information Database.10–11 Individuals enrolled in the insurance system undergo a general health screening examination every 2 years. The NHIS-Senior database includes information from self-report questionnaires, demographic data, anthropometric and blood pressure measurements, and information on income-based insurance status. Low income denotes income in the lowest 30% among the entire Korean population. The questionnaires collect information on participants’ medical history, family history and lifestyle factors (smoking, alcohol intake and physical activity). Current smokers and drinkers were defined as people who currently smoke cigarettes and have consumed a drink containing alcohol in the last 12 months. All variables have no missing data. The need for informed consent was waived.

Physical activity level assessment

The leisure-time exercise levels at each health examination were evaluated using self-report questionnaires with a 1-week recall.12 This short form survey was developed from the International Physical Activity Questionnaire, the reliability and validity of which have been confirmed in previous studies.13–15 The questionnaire incorporated three questions that assessed the frequency (days per week) of at least 30 min/day of light-intensity exercise, at least 30 min/day of moderate-intensity exercise and at least 20 min/day of vigorous-intensity exercise. Exercise status at each health examination was dichotomised as satisfying (‘yes’) versus not satisfying (‘no’) according to the current guidelines: ≥5 day/week of moderate-intensity exercise or ≥3 day/week of vigorous-intensity exercise or an equivalent combination of moderate-intensity and vigorous-intensity exercise, regardless of any amount of light-intensity exercise. Thereafter, the participants were divided into four groups according to exercise habit change: persistent non-exercisers (no to no), exercise dropouts (yes to no), new exercisers (no to yes) and exercise maintainers (yes to yes). Figure 1A illustrates the design of the study.

Covariates, follow-up and clinical outcomes

The diagnoses of selected comorbidities were confirmed using the International Classification of Diseases 10th revision codes and prescription medications before enrolment.10–11 To ensure diagnostic accuracy, participants were considered to have comorbidities or CVD when they had a discharge diagnosis of the conditions or were confirmed to have the conditions at least twice in an outpatient setting (online supplemental table 1).10–11 13–18

The primary outcomes were all-cause, cardiovascular and non-cardiovascular deaths. The secondary outcomes were heart failure hospitalisation, ischaemic stroke, acute myocardial infarction (MI), new-onset atrial fibrillation and sudden cardiac arrest. We defined cardiovascular death if CVD was considered as the initial cause of death on death certificates.10 11 13–18 The participants were followed up from the date of the second health examination to the date of death or 31 December 2014, whichever came first. Information on death (date and causes) was confirmed from the National Population Registry of the Korea National Statistical Office, which conducts central registration of death based on death certificates. The NHIS and the National Statistical Office are national agencies covering the entire Korean population; thus, their databases allowed us to completely investigate the events.

Patient and public involvement

Patients were not invited to contribute to study design, analysis, and writing or editing this manuscript.

Statistical analysis

Categorical variables are reported as frequencies (percentages), and continuous variables are expressed as median with IQR. Baseline characteristics were compared using Pearson’s χ² test for categorical variables and Kruskal-Wallis test for continuous variables. Inverse probability of treatment weighting (IPTW) using propensity scores derived from all the baseline covariates including demographics, comorbidities, anthropometric measures, lifestyle behaviours, medications and income status was performed to correct for systematic differences among the four study groups. A standardised mean difference of <0.1 was considered to indicate acceptable differences among the study groups.19 The weighted incidence rates of all-cause, cardiovascular and non-cardiovascular deaths were estimated by dividing the number of weighted events by the sum of the follow-up duration and are presented as rates per 100 person-years. Persistent non-exercisers were defined as the reference group, and cumulative incidence curves for the outcomes were generated and compared using the log-rank test. Weighted Cox proportional hazards models with IPTW were used to compute the HR and 95% CI, considering all-cause death as a competing risk, by using the Fine and Gray method. When estimating the risk of all-cause death, the Fine and Gray method was not performed.

We estimated the primary and secondary outcomes using unweighted and various multivariable Cox models to verify the robustness of the results. Model 1 included age and sex. Model 2 was adjusted for body mass index, waist circumference, drinking, smoking, low income, Charlson comorbidity index,
hypertension, diabetes mellitus and dyslipidaemia, in addition to variables in model 1. Model 3 incorporated peripheral artery disease, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, sleep apnoea, CHA2DS2-VASc score, use of aspirin, use of P2Y12 inhibitors, use of statins and use of oral anticoagulation, in addition to variables in model 2. In addition, we analysed the outcomes in prespecified subgroups, divided according to age (<75 or ≥75 years), sex, severity of comorbidities (Charlson comorbidity index <4 or ≥4) and each component of newly diagnosed CVD. We calculated the p value for interaction to examine the consistency of the patterns in the main results. All tests were two-tailed, with p<0.05 considered to indicate statistical significance. All analyses were performed using R programming (V4.1.0; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population
From the Korean NHIS-Senior database, we identified 312736 patients who underwent a health screening examination between 2003 and 2012. We defined CVD as a composite of acute MI, ischaemic stroke or hospitalisation for heart failure (online supplemental table 1). We excluded participants diagnosed with CVD before enrolment and those free from CVD between 2003 and 2012. Among the remaining participants, 6076 participants who had data from two consecutive health examinations within 2 years before and after the CVD diagnosis were finally included in this study (figure 1B).

Baseline characteristics
Table 1 shows the baseline characteristics of the 6076 study participants. The median age was 72 (IQR 69–76) years and men accounted for 50.6%. There were 2871 persistent non-exercisers (47.3%), 754 exercise dropouts (12.4%), 1363 new exercisers (22.4%) and 1088 exercise maintainers (17.9%). New exercisers and exercise maintainers were predominantly men. All variables were well balanced after IPTW (table 1, online supplemental figure 1).

Risks of all-cause, cardiovascular and non-cardiovascular deaths according to exercise habit change
Before estimating the risk of primary and secondary outcomes, the Cox proportionality assumption was tested based on the Schoenfeld residuals. No relevant violations were found. During the median follow-up of 3.8 years (IQR 2.2–5.7 years), the weighted all-cause mortality rate was 4.8, 4.6, 3.5 and 2.9 per 100 person-years in the persistent non-exerciser, exercise dropout, new exerciser and exercise maintainer groups, respectively. New exercisers (HR 0.73, 95% CI 0.58 to 0.91) and exercise maintainers (HR 0.53, 95% CI 0.38 to 0.73) had a lower risk of all-cause death than persistent non-exercisers. Exercise maintainers also had a lower risk of cardiovascular death (HR 0.34, 95% CI 0.17 to 0.64). New exercisers exhibited a numerically improved survival with respect to cardiovascular death, although it was not statistically significant (HR 0.76, 95% CI 0.49 to 1.17, p=0.21). The risk of non-cardiovascular death was lower in both new exercisers (HR 0.73, 95% CI 0.56 to 0.93) and exercise maintainers (HR 0.61, 95% CI 0.42 to 0.90) than in persistent non-exercisers. Exercise dropouts showed similar risks of the three mortality outcomes compared with the reference group (table 2, figure 2). The cumulative incidence curves of all-cause, cardiovascular and non-cardiovascular deaths are shown in online supplemental figure 2, with the concordant results of the log-rank test. Trends towards a reduced risk of primary outcomes in patients with favourable exercise changes were observed (p value for trend <0.001 in all-cause death, p<0.001 in cardiovascular death, p=0.006 in non-cardiovascular death).

Risks of other outcomes according to exercise habit change
The incidence rates and risks of other outcomes, including heart failure hospitalisation, ischaemic stroke, acute MI, new-onset atrial fibrillation and sudden cardiac death, are presented in online supplemental table 2 and online supplemental figure 3. No significant associations between exercise changes and these outcomes were observed. The risk of acute MI could not be estimated due to the small number of events.

Subgroup and sensitivity analyses
Sensitivity analyses were conducted to examine whether unweighted (online supplemental table 3) and various weighted (online supplemental table 4) Cox proportional hazards models showed consistent results. As shown in online supplemental table 3, new exercisers tended to experience a reduced risk of cardiovascular death (HR 0.63, 95% CI 0.42 to 0.93). Except for this, other results were consistent with the main results. As seen in online supplemental table 4, all estimates of model 1 and model 2 were comparable with the main results (model 3).

We performed subgroup analysis according to age. The incidence rate of cardiovascular death showed significant interactions with an increased risk thereof in exercise dropouts (HR 1.99, 95% CI 1.04 to 3.82) and increased benefits in exercise maintainers (HR 0.15, 95% CI 0.05 to 0.45) among those aged <75 years (p value for interaction=0.017; online supplemental table 5). Subgroup analysis according to sex, severity of comorbidities and type of CVD showed no significant interactions (online supplemental tables 6–8).

Compared with enrolled patients, patients who did not receive the second health examination were older with more comorbidities (online supplemental table 9). However, compared with non-exercisers at the first examination, exercisers also tended to have significantly lower all-cause, cardiovascular and non-cardiovascular death rates (online supplemental table 10).

DISCUSSION
The principal findings of this nationwide population-based cohort study that categorised patients according to changes in exercise habits after a first incident CVD event are summarised in figure 3. First, exercise maintenance was associated with a reduced risk of all-cause, non-cardiovascular or cardiovascular death. Second, a trend of progressively lower mortality rates was observed with an increase of exercise from persistent non-exercisers to exercise maintainers. Finally, among patients aged <75 years, those who were physically inactive tended to have a higher risk of cardiovascular death and those with a regular exercise habit tended to obtain greater benefits from exercise than their counterparts among patients aged ≥75 years.

Single assessment of exercise habit versus assessment of exercise habit change
Most studies on exercise relied on long-term follow-up of a single baseline assessment of physical activity. However, temporal changes in exercise habits could affect the risk of mortality during a long follow-up period. Moreover, previous studies have already described not only that a single assessment of exercise habits has limited predictive power in estimating the
Table 1  Baseline characteristics of the total study population according to exercise habit change

<table>
<thead>
<tr>
<th></th>
<th>Before IPTW</th>
<th>After IPTW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Persistent non-exerciser (n=2871)</td>
<td>Exercise dropouts (n=1363)</td>
</tr>
<tr>
<td>Age</td>
<td>73 (69, 77)</td>
<td>72 (69, 76)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1271 (44.3)</td>
<td>384 (50.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 (21.5, 25.8)</td>
<td>23.5 (21.5, 25.6)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.0 (78.0, 90.0)</td>
<td>83.0 (78.0, 89.9)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>130 (120, 140)</td>
<td>130 (120, 140)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 (70, 85)</td>
<td>80 (70, 85)</td>
</tr>
<tr>
<td>Economic status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>688 (24.0)</td>
<td>150 (19.9)</td>
</tr>
<tr>
<td>Middle</td>
<td>654 (22.8)</td>
<td>179 (23.7)</td>
</tr>
<tr>
<td>High</td>
<td>1529 (53.3)</td>
<td>425 (56.4)</td>
</tr>
<tr>
<td>Current drinker</td>
<td>380 (13.2)</td>
<td>90 (11.9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>236 (8.2)</td>
<td>46 (6.1)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>5 (3.7)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>66.7 (53.0, 82.7)</td>
<td>69.1 (56.2, 84.2)</td>
</tr>
<tr>
<td>Newly diagnosed CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalisation</td>
<td>811 (28.2)</td>
<td>212 (28.1)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1991 (69.3)</td>
<td>518 (68.7)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>69 (2.4)</td>
<td>24 (3.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1957 (68.2)</td>
<td>564 (74.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>660 (23.0)</td>
<td>231 (30.6)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1755 (61.8)</td>
<td>545 (72.3)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>267 (9.3)</td>
<td>99 (13.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>1019 (35.5)</td>
<td>267 (35.4)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>536 (18.7)</td>
<td>153 (20.4)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>98 (3.4)</td>
<td>41 (5.4)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3 quartiles; 25th and 75th percentiles) or n (%).

*Low-income and high-income denote income in the lowest and highest 30% among the entire Korean population; individuals with low income are supported by the medical aid programme.

BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; OAC, oral anticoagulant; SMD, standardised mean difference.
long-term cardiovascular risk but also that the change in exercise habits between the time of inclusion and the second assessment remains an independent predictor of death. In addition, the impact of selection bias on the association between exercise habits and death in large prospective cohort studies, which were mainly based on contemporary exercise guidelines, should be considered. For these reasons, we classified the participants into four groups according to exercise habit change. This may have allowed discriminating the benefits of exercise by itself from the influence of other confounding risk factors that have been improved by the accumulated gains from exercise. Thus, the present study confirms the benefits of exercise in preventing death, especially when considering the results among exercise maintainers.

Exercise habit change after CVD diagnosis and death

Physical inactivity is a well-known risk factor for all-cause and cardiovascular deaths in adults. Contemporary physical activity guidelines recommend substituting physical inactivity with regular exercise and establishing a target exercise level to improve life expectancy. However, most previous studies cited in these guidelines were based on results in healthy adults or patients with hypertension, diabetes mellitus or HIV infection. Guidelines for CVD management have also supported the benefits of exercise training, although uncertainty remains about its effects on mortality because the evidence was mainly based on small-sized randomised trials or non-randomised subgroup analyses of prospective cohort studies. A recent cohort study found that a higher level of exercise not only tended to reduce the risk of all-cause death among patients with CVD but also resulted in greater survival benefit than in individuals without CVD. Our results were consistent with these findings and were robust even after adjusting for covariates in the Cox regression models and after analysing the outcomes in subgroups divided according to age, sex, degree of comorbidities and type of CVD.

Exercise habit change and death in older adults

The WHO guideline describes the impact of regular moderate-intensity exercise on all-cause and cardiovascular deaths in

<table>
<thead>
<tr>
<th>Table 2</th>
<th>HR with 95% CI for all-cause, cardiovascular and non-cardiovascular deaths according to exercise habit change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individuals (n)</td>
</tr>
<tr>
<td>All-cause death†</td>
<td>Persistent non-exercisers</td>
</tr>
<tr>
<td></td>
<td>Exercise dropouts</td>
</tr>
<tr>
<td></td>
<td>New exercisers</td>
</tr>
<tr>
<td></td>
<td>Exercise maintainers</td>
</tr>
<tr>
<td>CV death</td>
<td>Persistent non-exercisers</td>
</tr>
<tr>
<td></td>
<td>Exercise dropouts</td>
</tr>
<tr>
<td></td>
<td>New exercisers</td>
</tr>
<tr>
<td></td>
<td>Exercise maintainers</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>Persistent non-exercisers</td>
</tr>
<tr>
<td></td>
<td>Exercise dropouts</td>
</tr>
<tr>
<td></td>
<td>New exercisers</td>
</tr>
<tr>
<td></td>
<td>Exercise maintainers</td>
</tr>
</tbody>
</table>

P values were evaluated by the likelihood ratio test.
*Weighted incidence rates were computed after inverse probability of treatment weighting.
†The Fine and Gray method was not used when calculating the risk of all-cause death.
CV, cardiovascular; IR, incidence rate; PY, person-years.
older adults. However, it merely extrapolates the conclusion of studies that showed the benefits in middle-aged adults because no upper age limit criterion was set. Few studies to date have investigated a specific old-age group, and some studies failed to prove that exercise improves prognosis.27 28 Our current study showed that starting or maintaining regular exercise was associated with a lower risk of all-cause, cardiovascular or non-cardiovascular death. Although the results among new exercisers were not statistically significant for cardiovascular death, they were consistent with the tendency observed in the main analysis regardless of various sensitivity and subgroup analyses. A recently published study examined physical activity trajectories in the elderly with incident CVD and overall mortality.7 Some results across more virtuous trajectories of physical activity when considering cardiovascular outcomes and overall mortality go in the same direction as those found in the present paper. In our study, although patients aged ≥75 years had reduced benefits with respect to preventing death compared with those aged <75 years, the benefits were still statistically significant. Barbiellini et al8 showed comparable results that interaction with age goes in support of a stronger effect of physical activity early in late-life rather than late in late-life. Therefore, our results suggest that the adoption and maintenance of regular exercise should not be ignored in older patients, even considering the reduced benefits obtained from exercise.

Study limitations

Our study suffered several limitations. First, as the CVD diagnosis was confirmed using claims data, errors due to incorrect coding may be present. To minimise this problem, previously verified definitions used in cohort studies based on the Korean NHIS database were applied. Second, recall bias is a major limitation because information about exercise habits relied on self-report questionnaires asking about lifestyle behaviours during the previous week. Third, physical activity level before and after the CVD diagnosis was evaluated using a questionnaire with a 1-week recall, assessing the physical activity over a period of 7 days rather than the entire period before and after the cardiovascular event. Therefore, the level of exercise could not be precisely defined. Additionally, while the validity of the International Physical Activity Questionnaire Short Form has been proven, its reliability has been shown to be low. Fourth, various types of physical activities, including light-intensity exercise, household tasks, occupational activities and transportation-related physical activities, were not included or analysed.29 Fifth, multivariable Cox models were used to adjust results with potential confounders. However, the severity of CVD was not included. In fact, the severity of CVD could have both a prognostic value in terms of mortality risk and an impact on the physical activity level. Sixth, as only the Korean population could be enrolled in the study, ethnic differences might limit the external generalisability of the results. Seventh, the inclusion of patients who had two consecutive health examinations could introduce a selection bias. Information on individuals who did not undergo health examinations was not available; however, we found that the primary outcomes in patients who did not undergo a second health examination were consistent with the main results. Lastly, this was a nationwide cohort study and the causality between exercise habits and mortality cannot be proven.

CONCLUSION

Initiation or maintenance of at least 5 days of moderate-intensity activity or 3 days of vigorous-intensity activity a week is associated with reduced risk of all-cause, cardiovascular and non-cardiovascular deaths in older adults with newly diagnosed CVD. Exercise is important and should be recommended to older adults with CVD.

Author affiliations

1 Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
2 Division of Cardiology, CHA Bundang Medical Center, Seongnam, Korea
3 Division of Cardiology, Inje University College of Medicine, Busan, Korea
4 Cardiology, Yonsei University College of Medicine, Seodaemun-gu, Korea
5 Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK
6 Department of Internal Medicine, Yonsei University College of Medicine, Seodaemun-gu, Korea

Acknowledgements

The NHS of Korea provided the database used in this study. The authors would like to thank the NHS for their cooperation.

Contributors

D-SK, J-HS, P-SY and BJ participated in designing the work and statistical analysis and drafted the manuscript. EJ, DK and P-SY contributed to data collection. BJ, the guarantor of this article, critically reviewed the study proposal and controlled the decision to publish. All authors were involved in interpretation of the results. All authors read and approved the manuscript before its submission.

Funding

This research was supported by a grant from the Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HC19C0130).

Competing interests

BJ has served as a speaker for Bayer, BMS/Pfizer, Medtronic and Daiichi Sankyo and received research funds from Medtronic and Abbott.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0179). The study complied with the requirements of the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request.

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Daehoon Kim http://orcid.org/0000-0002-9736-450X
Hui-Nam Pak http://orcid.org/0000-0002-3256-3620
Gregory Lip http://orcid.org/0000-0002-7566-1626
Pil-Sung Yang http://orcid.org/0000-0002-6552-1742
Boyong Joungh http://orcid.org/0000-0001-9036-7225

REFERENCES


